Confidential

TITLE: A phase Ib /II trial of pembrolizumab and idelalisib in patients with non-small cell lung cancer (NSCLC) who have failed immune checkpoint inhibitor.

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PROTOCOL NUMBER: CC-16053

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Investigational Agent(s):

Drug Name:	Pembrolizumab	Idelalisib
Other Identifier:	MK-3475, Keytruda®	GS-1101, Zydelig®
IND Number:	123,482	101254
Manufacturer:	Merck	Gilead

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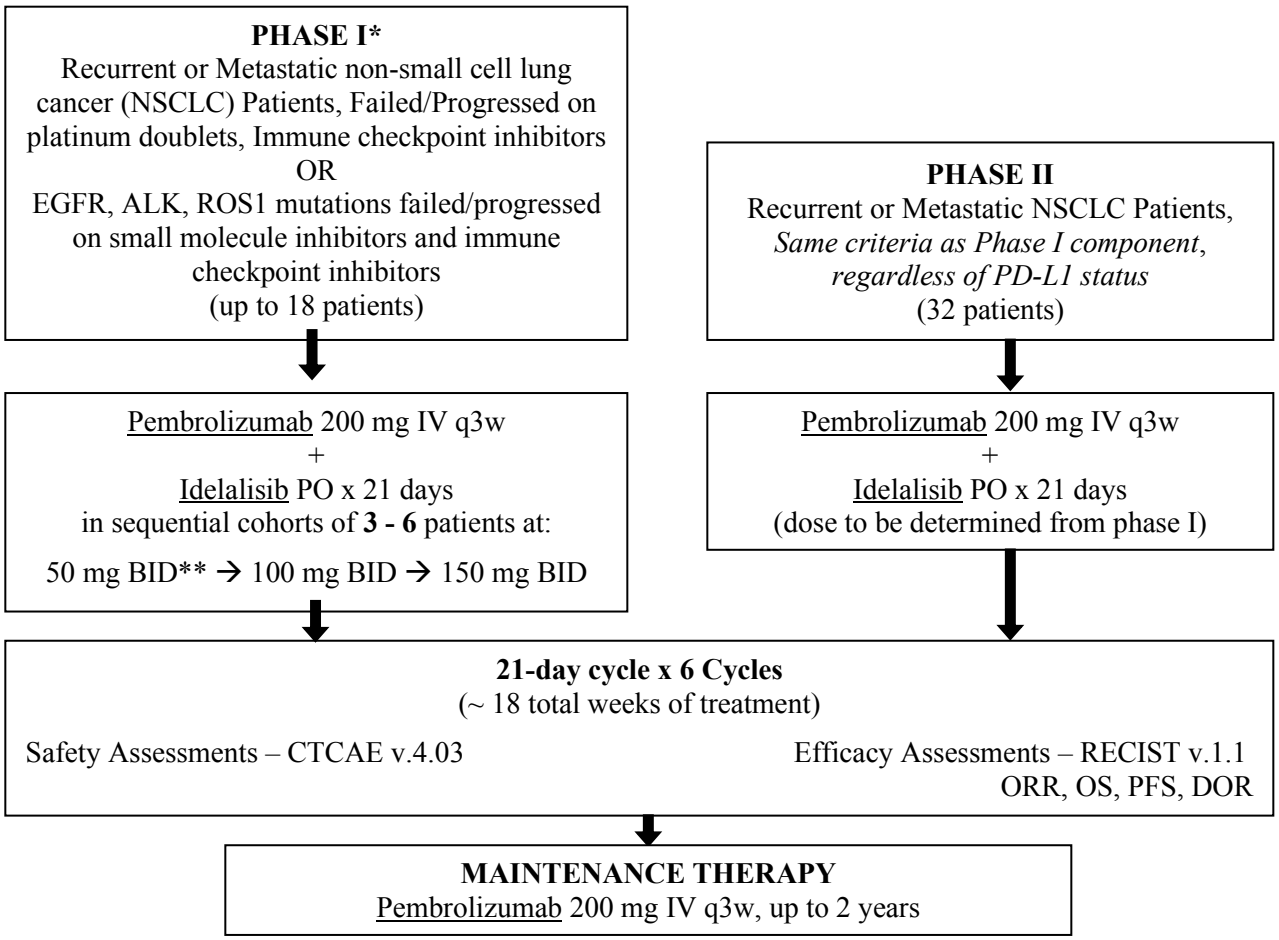
1.0 TRIAL SUMMARY

Abbreviated Title	**pembrolizumab and idelalisib for NSCLC**
Trial Phase	Ib/II
Clinical Indication	NSCLC
Trial Type	Therapeutic intervention
Type of control	Historical
Route of administration	Intravenous/oral
Trial Blinding	None
Treatment Groups	Pembrolizumab (Keytruda) and idelalisib (Zydelig)
Number of trial subjects	40 to 50 (6-18 + 32)
Estimated enrollment period	*1/2017-06/2019M*
Estimated duration of trial	*3 years*
Duration of Participation	30 months

Study Schema



*In Phase 1, DLT's will be defined from toxicities observed during the first 9 weeks of combined treatment for each dose level.
**If DLT is found at 50 mg PO BID daily, dose may be reduced to 50 mg PO daily, or reduced further to 50 mg PO every other day.

2.0 TRIAL DESIGN

2.1 Trial Design

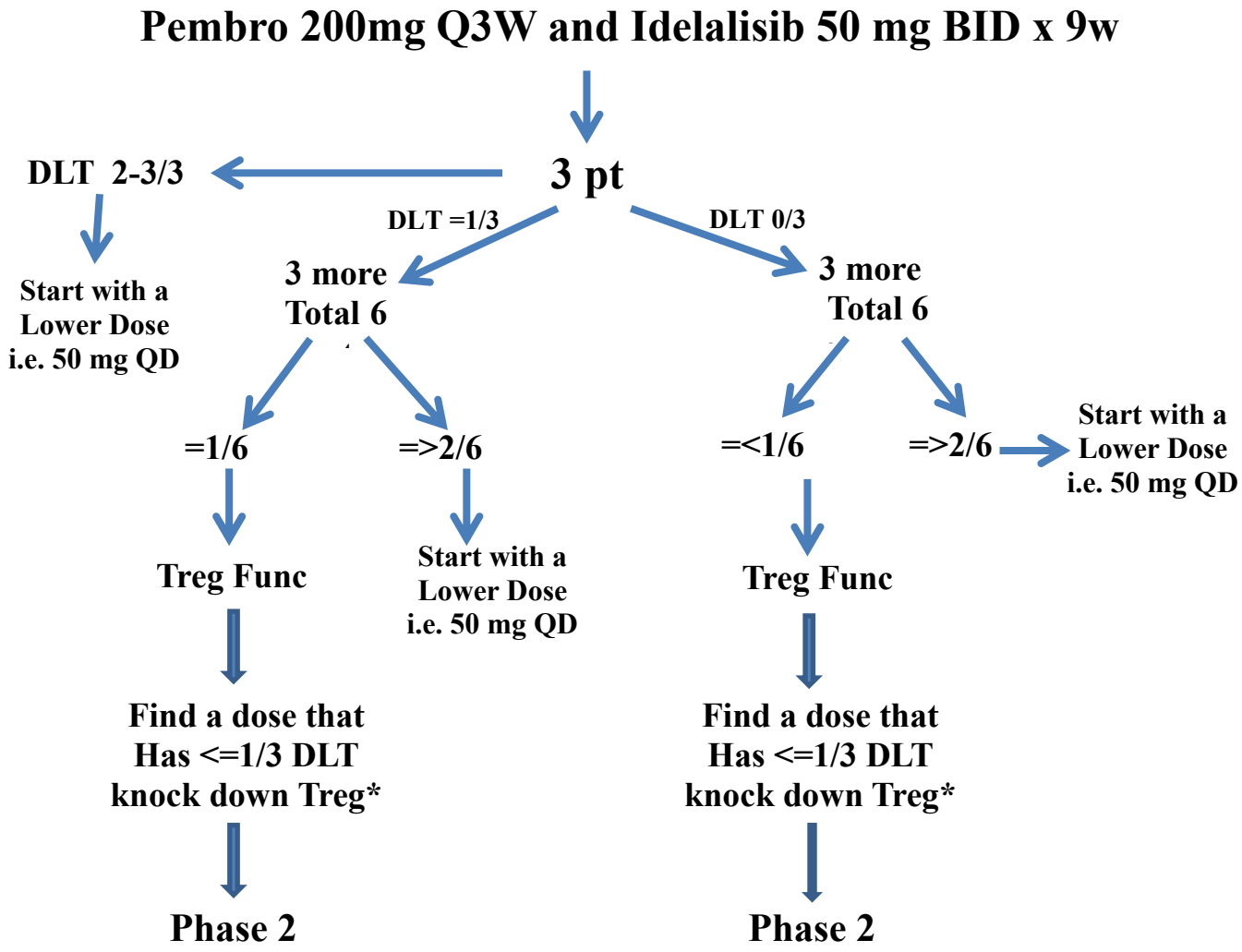
This is an open labeled, single arm, interventional study combining two drugs: pembrolizumab (MK-3475, trade name: Keytruda) and idelalisib (trade name: Zydelig) in non-small cell lung cancer (NSCLC). Subjects with metastatic (stage IV, AJCC 7th edition) or recurrent (after radiation or chemo/radiation) NSCLC of all histologies (squamous or non-squamous cell) will be eligible to enroll. They will have failed or progressed on immune checkpoint inhibitor such as nivolumab or pembrolizumab after failing or intolerant to the standard-of-care (SOC) platinum-based chemotherapy. Patients with EGFR, ALK or ROS mutated tumors must have failed treatment with appropriate small molecule inhibitors followed by failure or progression while on the immune checkpoint inhibitor to be eligible.

The study will enroll patients regardless of their PD-L1 status in two phases: a dose finding/tolerability assessment phase and an efficacy assessment phase. In the dose finding/ tolerability assessment phase, the safe dose of idelalisib in combination with pembrolizumab, that down-regulates the activity of T-regulatory function (Treg) by more than 80% of baseline in at least 80% of patients (5 out of 6 or more) will be determined. If we cannot find a safe dose that suppresses Treg by 80%, the safe dose that offers the highest Treg suppression will be chosen. Initially, 3 NSCLC patients will be evaluated at 50 mg twice daily of idelalisib (in combination with pembrolizumab, 200 mg every three weeks). If there is 0/3 or 1/3 dose-limiting toxicity (DLT), another 3 will be enrolled. If no more than 1/6 has DLT, Treg will be determined. If at this dose level 80% patients have reduction of Treg function of >=80% of baseline level, this dose will be the phase 2 recommended dose (P2RD). If dose limiting toxicity occurs in equal to 2/3 in the initial 3 patients or more than 1/6 patients after another 3 patients, then lower doses of idelalisib will be investigated in cohorts with similar number of patients until a dose that causes no more than 1/6 DLT is found before functional analysis of Treg. Other idelalisib doses that will be evaluated may include 100 mg twice daily, 150 mg twice daily or 50 mg once daily and 50 mg every other day.

In the efficacy assessment phase, patients will be enrolled to detect whether idelalisib added to pembrolizumab at the P2RD will result in further objective response. All subjects in the efficacy assessment phase will be treated with pembrolizumab (200 mg IV Q3W) in combination with idelalisib (dose not exceeding 150 mg BID per the tolerability assessment phase) for 18 weeks before maintenance with pembrolizumab 200 mg IV Q3W for up to 2 years, until disease progression or unacceptable toxicity. The primary end point will be objective response rate (ORR), based on RECIST 1.1. Patients will be managed using immune response RECIST (irRECIST) criteria[2]. The secondary endpoint will be duration of response (DOR).

2.2 Trial Diagram

Metastatic NSCLC
Failed/Progressed on platinum doublets, Immune checkpoint inhibitors
OR EGFR, ALK, ROS1 mutations ailed/progressed on small molecule inhibitors and immune checkpoint inhibitors



* Successful knock down is defined as a decrease of >80% of baseline Treg activity in =>80% of patients tested (n=>6). Or the safe dose that offers the highest Treg suppression activity. Doses to be tested: 50 mg QOD, 50mg QD, 50mg BID, 100mg BID, and 150 mg BID

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective(s) & Hypotheses

(1) Objective: To determine whether addition of idelalisib at the P2RD to pembrolizumab is safe in checkpoint inhibitor refractory NSCLC patients.

Hypothesis (1): addition of idelalisib at the P2RD to pembrolizumab is safe in NSCLC patients

(2) Objective: To determine the P2RD of idelalisib used in combination with pembrolizumab in patients with checkpoint inhibitor refractory NSCLC.

Hypothesis (2): Combination of pembrolizumab (200 mg IV Q3W) with idelalisib can down-regulate Treg cell function by 80% in 80% patients at a dose lower than the current FDA approved dose of 150 mg BID PO in patients with NSCLC.

(3) Objective: To determine whether addition of idelalisib to pembrolizumab in NSCLC improves ORR over that seen with pembrolizumab or other immune checkpoint inhibitors alone in treatment of NSCLC.

Hypothesis (3): In NSCLC patients previously treated with anti-PD-1/PD-L1 therapies the ORR for the combination of idelalisib and pembrolizumab is 10% (it is nearly 0% for the refractory patients).

3.2 Secondary Objective

Objective: To evaluate DOR in NSCLC treated with idelalisib at P2RD in combination with pembrolizumab

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

PD-1

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector

T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control.[3,4] The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-regulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28/CTLA-4. PD-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[5,6] 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. 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. PD-1 has been shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as on subsets of macrophages and dendritic cells.

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. 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 on T-cells inhibits 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 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 T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers have been found to express abundant levels of this T-cell inhibitor. 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 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. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.

Keytruda has also been approved for the treatment of patients with unresectable or metastatic melanoma and lately head and neck squamous cell cancer.

In addition to pembrolizumab, nivolumab has also been approved by the US FDA for treatment of NSCLC in the second line settings after failing platinum based chemotherapy. Despite all the excitement, ORR associated with the immune checkpoint inhibitors in NSCLC was only ~20% in all comers and the response is often short-lived. Although PD-L1 positive patients tended to respond more, PD-L1 negative patients also responded. It was postulated that other immune suppressive mechanisms such as upregulation of Treg and MDSC function in the tumor microenvironment play important role in blunting the immune response. Therefore, downregulation of such mechanism holds promise of boosting response to immune checkpoint inhibitor therapy.

Phosphatidylinositol 3-kinases

Phosphatidylinositol 3-kinases (PI3Ks) are lipid kinases that play central role in regulation of a number of important cellular processes such as cell cycle, apoptosis, DNA repair, senescence, angiogenesis, and cellular metabolism.[7] PI3Ks transmit signals from transmembrane receptors such as activated receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) to the cytoplasm by generating phosphorylated phosphatidylinositols as second messengers.

In human, there are three distinct classes of PI3Ks (I – III). They are different in terms of their structural characteristics, substrate specificities, and nature of lipid end-products. Class I PI3Ks are heterodimers that can be further divided into 2 subfamilies, IA and IB. Class IA PI3Ks are the most well studied and frequently implicated in cancer. [8] Structurally, class IA PI3Ks are comprised of a catalytic p110 subunit complexed with a regulatory p85 subunit. The catalytic p110 isoforms (α, β, and δ) are encoded by the PIK3CA, PIK3CB, and PIK3CD gene respectively, whereas the regulatory p85 subunits– p85, p55, and p50 isoforms – are encoded by PIK3R1, PIK3R2, and PIK3R3 genes, respectively.

The N-terminus of class IA p110 (α, β, and δ) enzymes carries the p85- binding domain (PI3K-ABD), which constitutively interacts with the SH2 domain of the regulatory subunit. It also contains the Ras-binding domain (PI3K-RBD), which mediates interaction with Ras-GTPases. The central region is comprised of the C2 PI3K-type and PIK helical domains, whereas the C-terminus contains the catalytic domain. The PI3K-RBD domain is the most divergent region of the class IA kinase.

P110α and p100β are ubiquitously expressed in all tissues whereas p110δ expression is primarily confined to hematopoietic cells. p110δ plays an important role in B-cell homeostasis and function. PI3Ks integrate signals from RTKs and GPCRs. p110γ, which is predominantly expressed in the pancreas, skeletal muscles, liver and heart, mediates signaling downstream of GPCRs.[9]

In response to signaling from the growth factors, tyrosine phosphate motifs of activated receptors recruit PI3Ks to the plasma membrane by direct interaction with the SH2 domains of the

regulatory subunit.[10] This interaction changes the conformation of the regulatory subunit. As a result, the inhibitory activity is abrogated, and the enzymatic activity of the catalytic subunit is fully liberated and become activated[11]. PI3Ks can also be stimulated by activated Ras-GTPases that form complex with phosphorylated adapter proteins (e.g. GRB2, SOS).[12,13] The activated PI3Ks catalyze the generation of second messengers – phosphorylated phosphatidylinositols (PI). PIs in turn activate multiple downstream signaling pathways.

Upon generation of second messengers (PIP3, PI 3,4-bisphosphate), the PI3K signaling indirectly triggers a cascade of events that culminates in activation of multiple effector kinase pathways, including the mTOR, ERK1/2, p38 MAPK, NF-kappa-B, and JNK/SAPK pathways[7,14,15]. Recent studies suggest that activated AKT has a direct effect on the apoptosis pathway by targeting and down-regulating the pro-apoptotic activity of Bcl-2 family members BAD and BAX resulting in cell survival. PI3K-AKT signaling also controls cell death and survival through NF-kappa-B regulation of pro- and anti-apoptotic genes.[16] In addition, AKT also signals to other proteins, such as mammalian target of rapamycin–containing protein complex (mTORC1) and the forkhead family of transcription factors (FOXOs) and regulates cell proliferation.

It has been recognized that deregulation of the PI3K signaling pathway is associated with development in one-third of human cancers,[17,18] although the mechanism of PI3K activation may vary. For example, it is estimated that ~30% of breast cancers are associated with activating missense mutations of PIK3CA, the gene encoding the catalytic p110α subunit of class IA PI3K, which provides cells with a growth advantage and promotes tumor progression[19]. Somatic loss of PTEN activity, resulting in upregulated PI3K, by gene mutation, epigenetic silencing or deletion is also associated with significantly greater Gleason score, poorer prognosis, and higher rate of metastasis in prostate cancer[20]. Lastly, activating mutations of RTKs such as EGFR and HER2 has also been implicated in PI3K activation.[21,22] Importantly, dysregulated PI3K pathway signaling has also been implicated in conferring resistance to therapies in breast cancer, and non-small cell lung cancer.[23,24] The PI3K-BTK signaling also plays an essential role in B-cell development, proliferation and survival through recruitment and activation by CD19.[25] In response to CD28 costimulation, PI3K upregulates BCL-XL expression in T-cells, and confers resistance to apoptosis during their activation.[26]

Idelalisib (Zydelig, marketed by Gilead Sciences Inc), the first-in-class oral PI3K p110-δ inhibitor, has recently been approved by the FDA for the treatment of relapsed/ refractory chronic lymphocytic leukemia (CLL) in combination with rituximab. It is also approved as monotherapy for the treatment of small lymphocytic lymphoma and follicular lymphoma. As discussed below, recent work also suggests that PI3K-δ inhibition may promote anti-tumor immune responses.

4.1.2 Preclinical and Clinical Trial Data

Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor

rejection, either as a monotherapy or in combination with other treatment modalities. Anti–mouse PD-1 and anti–mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function *in vivo*. In addition, the combination of gemcitabine and anti–PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors. In-house experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

PI3K-δ knockout mice have reduced numbers of Treg in the periphery, although Treg numbers are increased in the thymus.[27] Treg cells from these mice have attenuated suppressor function, fail to secrete IL-10 *in vitro*, and fail to protect mice from experimentally induced colitis in adoptive transfer experiments. PI3K-δ deficiency is associated with an increased sensitivity to autoimmune diseases and protects these mice against a broad range of tumors.[27,28] PI3K is also critical for clonal expansion and differentiation of the T cells. In mice, inhibitors of PI3K-δ deplete Treg, alter myeloid derived suppressor cell (MDSC) function and can protect against tumor challenge. Treatment with a PI3K-δ inhibitor also disrupts the protective microenvironment essential for the survival of malignant B cells in B cell malignancies, causing rapid shrinkage of lymphadenopathy and transient lymphocytosis.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Immune checkpoint inhibitors (Anti PD-1) are effective in treating NSCLC as single agent, but overall response is still not optimal.

PD-L1 / PD-1 signaling is one immune checkpoint mechanism thought to maintain tolerance to self-antigens and prevent autoimmune disease. However, this mechanism appears to have been hijacked by numerous types of cancer cells to promote immune escape.[3,4] NSCLC is among the several solid tumors that utilize this mechanism for immune escape. Early studies found that pembrolizumab is effective in treating NSCLC in the Keynote 001 trial,[29] with an objective response rate of 19.4%, a median duration of response of 12.5 months, and a median overall survival of 12 months. Although patients whose tumors expressed higher levels (≥50%) of PD-L1 had higher response rates (40% ORR) than those will tumors expressing lower levels of PD-L1 (15% ORR), low levels (<1%) of tumor PD-L1 expression did not completely preclude response. For nivolumab, the same was true. Nivolumab is currently approved by the US FDA for treatment of advanced NSCLC patients who have failed or progressed on platinum based chemotherapy regardless of PD-L1 status. Taking PD-L1 status out of the picture, both pembrolizumab and nivolumab induce ~20% ORR. Current hypothesis holds that other immunosuppressive mechanisms are involved. Combination therapy with additional immune modulators has the potential to increase these response rates seen with pembrolizumab or nivolumab monotherapy.

Treg inhibition may boost the efficacy of immune checkpoint inhibitors

Increased numbers of T regulatory cells (Treg) in the peripheral blood and T regulatory cell infiltration in the tumor has been observed in murine tumor models and in patients with cancer.[30,31] Treg depletion dramatically enhances the effect of immunotherapy in murine tumor models.[32] Treg inhibit the function of tumor specific T cells, particularly in the tumor microenvironment, and their elimination allows antigen-specific T cells to proliferate more robustly. Treg-mediated immune suppression may in part explain the poor clinical response of some cancer patients undergoing immunotherapy. There is a positive correlation in murine models and in patients treated with ipilimumab between the CD8 effector to Treg cell ratio in the tumor microenvironment and tumor response.[33-36] Agents that increase this ratio are associated with improved tumor control.

Research using lung cancer models and patient studies support the concept that Treg-targeted intervention has the potential to improve lung cancer control.

In three models of lung cancer (a Kras mutation, a carcinogen-driven and a transgenic model), depletion of Treg with rapamycin, or antibody or genetic ablation, reduced lung tumorigenesis by 90%, 80% and 75% respectively.[37] It was observed that Treg exhibited high suppressive activity and this activity increased with tumor stage with NSCLC.[38] In a retrospective analysis of 87 surgically resected NSCLC specimens, it was found that patients with high Treg counts had significantly worse prognosis in terms of relapse free survival (RFS) and overall survival (OS).[39] In another animal model, depletion of Treg by repeated injection of CD25 antibody was able to reduce the number of malignant lesions induced by peritoneal injection of chemicals coupled with a constitutive active NF-kB.[40] Compared with healthy individuals, NSCLC patients have increased number of Treg in their peripheral blood. The increase in Treg number correlates with stage, with higher levels of Treg observed in more advanced stages (IV>III>II).[41] Following chemotherapy, a greater increase in CD8+ T cell/Treg was predictive of better prognosis in advanced thoracic malignancies including NSCLC and mesothelioma.[42] Compared with squamous cell lung cancer, immune tolerance seems to be more pronounced in adenocarcinomas.[43] Immunosuppressive Treg increased significantly in adenocarcinoma of the lung. Treg depletion using anti-CD25 with cytotoxic chemotherapy significantly extended survival in these lung adenocarcinoma patients.[44] Inhibition of mTOR signaling enhances antitumor memory lymphocytes. However, pharmacologic mTOR inhibition also enhances Treg activity. When anti-CD4 antibody was used for Treg control in this mTOR inhibition preclinical model, depletion of Treg combined with a pharmacological mTOR inhibitor led to successful control of tumor lung metastasis in a syngeneic model.[45] Here, depletion of the CD4+ FoxP3+ cells (Treg) was responsible for the immunosuppression since adding back the CD4+FoxP3+ cells completely negated the effects. Finally, the drop of Treg during neoadjuvant chemo-immunotherapy with cisplatin, docetaxel and cetuximab in NSCLC significantly correlated with clinical response.[46]

Idelalisib, a newly approved PI3K–δ inhibitor, may provide clinically applicable approach for Treg inhibition

By using the PC61 monoclonal antibody that targets murine CD25, mice can be depleted of Treg, but attempts to deplete Treg in humans have not been highly successful despite multiple attempts. Rosenberg has used three reagents to deplete Treg including denileukin difitox, an IL-2 diphtheria toxin construct approved for the treatment of cutaneous T cell lymphoma,[47] LMB-2, a CD25 antibody-pseudomonas immunotoxin,[48,49] and the CD25 directed immunotoxin RFT5-SMPT-dgA.[50] Although cells expressing high levels of CD25 are depleted by these strategies, Treg, which express lower levels of CD25, are not as well targeted and these approaches have not been associated with significant clinical tumor responses. In addition, CD25 is upregulated on activated T cells, raising the possibility that depletion of CD25+ cells will deplete effector T cells as well as Treg.

We and others have shown that inhibition of PI3K-δ in mice alters T regulatory cell numbers and function and has the potential to enhance the effects of tumor immunotherapy. The PI3K-δ knockout mouse has reduced numbers of Treg in the periphery although Treg numbers are increased in the thymus.[27] PI3K-δ deficiency is associated with an increased sensitivity to autoimmune diseases and protects these mice against a broad range of tumors.[27,28] The pharmacologic inhibitor of PI3K-δ idelalisib has been approved by the FDA for the treatment of chronic lymphocytic leukemia (when given in combination with rituximab), small lymphocytic lymphomas and follicular lymphomas. In mice, inhibitors of PI3K-δ deplete Treg, alter myeloid derived suppressor cell (MDSC) function, and can protect against tumor challenge. Combining PI3K-δ inhibition with immune checkpoint blockade has the potential to further increase the response rate of these agents by relieving Treg-mediated suppression of tumor antigen-specific T cells and thus allowing tumors that are not responsive to immune checkpoint blockade alone to respond.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab

The selection of the 200 mg IV Q3W fixed dosing for pembrolizumab is based on extensive analyses performed using population PK modeling showing that the fixed dose of 200 mg every 3 weeks will provide exposures that (1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks (the FDA-approved dose for the treatment of metastatic melanoma), (2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and (3) will maintain individual patient exposure in the exposure range established in melanoma that is well tolerated and safe.

This fixed dose simplifies the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Idelalisib in combination with pembrolizumab

Idelalisib has been approved for use in CLL (in combination with rituximab), SLL and follicular lymphoma at a recommended dose of 150 mg PO BID. At this dose, the most common side effects greater or equal to grade 3 were diarrhea (due to colitis), which was reported in 13% patients (16/120), transaminitis (13%, 16/120) and neutropenia (27%, 34/120).[51,52]

Similarly, in the KEYNOTE-001 trial treating NSCLC with single agent pembrolizumab, the most common grade 3 or higher side effects were dyspnea (3.8%), pneumonitis (1.8%) and decreased appetite (1%). Diarrhea occurred in0.6% and increased alanine transaminase in 0.4% of patients. Noted here, many of these significant toxicity are immune mediated and are overlapping in nature. These include but are not limited to colitis with diarrhea, hepatotoxicity and pneumonitis, hence we favor a cautionary approach in testing the combination (see below).

In March 2016, six clinical trials exploring idelalisib (Zydelig) in combination with other therapies were halted due to reports of an increased rate of adverse events, including death, for patients with hematologic malignancies, according to an alert issued by the FDA. The clinical trials involved untreated CLL or SLL and indolent NHL patients. Pneumocystis pneumonia (PCP) was the cause of mortality in these patients. However detailed analysis did not show significant increase of incidence in idelalisib group compared to placebo. In the end, PCP/pneumonia was added to the FDA approval for idelalisib Black Boxed Warning for fatal and serious side effects which included previously liver toxicity, diarrhea, colitis, pneumonitis, and intestinal perforation associated with the first-in-class PI3K-delta inhibitor. Therefore, the autoimmune related side effects will be closely monitored. Since mandatory PCP prophylaxis would have prevented death from PCP/pneumonia, we will implement strict PCP prophylaxis in patients receiving idelalisib throughout the study and continued for 6 months after the study. TMP 160 mg, QD, PO, 3 times per week, on alternative day Monday, Wednesday and Friday will be implemented. Dapsone 100 mg once daily PO will be the alternative in case of sulfa allergy. More importantly, we will start the idelalisib combo at a lower dose (i.e 50 mg BID) and going up until a dose that causes no more than 1/6 DLT and meets the functional criteria is found. The highest idelalisib dose we will go for the combination will be 150 mg BID PO. The functional criteria require down-regulation of the Treg function by 80% in more than 80% of patient tested. In case we still do not have 80% down-regulation of Treg function, we will pick the safe idelalisib dose that offers the highest suppression of Treg function. All patients will be observed for 18 weeks or >4 months before proceeding to the phase 2 study.

Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

We will use objective response rate (ORR) as the primary end point. Since responses seen in the immune therapy trials correlate with clinical benefit, we believe that ORR will translate into survival benefit. Therefore, ORR is a surrogate marker for survival (PFS and possibly OS). Because loss of response is common in cancer patients, DOR will be assessed as the secondary efficacy endpoint.

4.2.2.2 Efficacy in Patients That Have Progressed During PD-1/PD-L1 Blockade

For patients with NSCLC who have progressed during PD-1/PD-L1 blockade, further treatment with pembrolizumab or other immune checkpoint inhibitors would be expected to have limited efficacy. Intratumoral Tregs and/or MDSCs are hypothesized to be a factor that may limit the effectiveness of PD-1/PD-L1 blockade. As such, treating patients with tumors that have progressed during PD-1/PD-L1 blockade with idelalisib+pembrolizumab may lead to tumor responses.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

All subjects to be screened must have documented tissue diagnosis of NSCLC from biopsy, either metastatic or recurrent. They must have failed or progressed on platinum-based chemotherapy (e.g. cisplatin, carboplatin) as well as immune checkpoint inhibitor (e.g nivolumab or pembrolizumab). Patients with EGFR/ALK mutations/translocations must have failed or progressed on small molecule inhibitor therapies (e.g. erlotinib, afatinib, etc.).

Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Expected life expectancy of more than 6 months.
4. Have at least one measurable lesion based on RECIST 1.1.
5. Have a performance status of 1 or less on the ECOG Performance Scale.
6. Demonstrate adequate organ function as defined in Table **1**. All screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /µL
Platelets	≥100,000 / µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR**	≤1.5 X upper limit of normal (ULN) **OR**

Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≥60 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
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

7. If a female subject of childbearing potential, have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

8. If a female subject of childbearing potential, be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

9. If a male subject, agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study drugs.

5.1.2 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study drug or has participated in a study of an investigational agent and received study drug or used an investigational device within 3 weeks of the first dose of treatment.
2. Is within 3 weeks of most recent chemotherapy.
3. Patients who are currently taking steroid must come off 7 days before come on the trial
4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
5. Has a known history of active TB (Bacillus Tuberculosis)
6. Has a history of hypersensitivity to pembrolizumab or any of its excipients.
7. Has a history of hypersensitivity to idelalisib or any of its excipients.

8. Has had a prior anti-PD-1 or anti-PD-L1 monoclonal antibody, who discontinued such treatment due to adverse events. Discontinuation of such therapy due to disease progression is not grounds for exclusion. Has had prior chemotherapy, targeted small molecule therapy, radiation therapy, or other anti-tumor mAb treatment within 3 weeks prior to study Day 1 or has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

9. Note: If subject received major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention prior to starting therapy (routinely 6-8 weeks after surgery). Has a known additional malignancy that is progressing or requires active treatment in the past 2 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging over a period of at least 4 weeks, with a brain imaging study documenting stability of such brain metastasis(es) within 4 weeks of the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
11. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
12. Has known history of non-infectious pneumonitis that required steroid use or has current pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has a 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.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
17. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy. Note: Seasonal influenza inactivated vaccines for injection are allowed; however live attenuated influenza vaccines (e.g., Flu-Mist®) are not allowed.

5.2 Trial Treatments, Mandatory Prophylaxis of Pneumocystis pneumonia (PCP)

The treatment and prophylaxis to be used in this trial is outlined below in Table 2.

Table 2. Trial Treatment and Prophylaxis of PCP Pneumonia

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg*	Q3W*	IV infusion	Day 1 of each 3 week cycle*	Experimental
Idelalisib	50 mg†	BID†	PO	Every Day†	Experimental
Bactrim DS#	160mg/800mg	QD	PO	M, W, Friday 3/W	Prophylaxis
*Pembrolizumab doses may be withheld due to toxicity as described in Section 5.2.1.2. †May be administered at a higher or lower dose and frequency based on results of the tolerability assessment/dose finding phase of the study. #Dapsone will be used in case of sulfa allergy, 100 mg once daily PO.					

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

Pembrolizumab will be administered at a dose of 200 mg IV Q3W. The rationale for this dosing is provided in Section 4.0 – Background and Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in Section 5.2.2., Drug Preparation and Administration.

The planned dose of idelalisib to be utilized in combination with pembrolizumab in this trial is ≤150 mg PO BID. If in the tolerability assessment phase of the study this dose is not tolerated in the combination with pembrolizumab, a tolerable lower dose will be identified and then used for the efficacy assessment phase of the study in combination with pembrolizumab.

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab and idelalisib must be

withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

For idelalisib, the blackbox warning cites fatal and serious hepatotoxicity, severe diarrhea or colitis occurring in 14% of the patients taking the drug. Pneumonitis is also life threatening. Patients participating in this study will be closely monitored during treatment for signs of toxicity. In the tolerability assessment phase of the study, if significant toxicity occurs with a given dose regimen of idelalisib, either a lower dose of idelalisib and/or less frequent dosing of idelalisib in combination with pembrolizumab may be evaluated in cohorts of additional patients.

During concurrent administration of idelalisib and pembrolizumab, it will not be possible to definitely ascribe any toxicities and severe or life-threatening AEs to one of the two agents. Should such toxicities or AEs occur, the guidance for managing pembrolizumab-related AEs should be followed, with the additional caveat that idelalisib should be held and then restarted concurrently with pembrolizumab.

Table 3. Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Neutropenia	3	Normalize to above 1,500/mm3	Grade 4
Thrombocytopenia	3	Once above 100,000/mm3	Bleeding occurred or grade 4
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1, Idelalisib will start at a lower dose level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia or Hypertriglyceridemia or Hypoglycemia	T1DM or 3-4	Hold pembrolizumab and idelalisib for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. Hold idelalisib if grade 3-4 hypoglycemia or hypertriglyceridemia	Resume pembrolizumab and idelalisib when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab and idelalisib can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab and idelalisib can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Pneumonitis	1	Toxicity resolves to Grade 0, idelalisib to start at a lower dose level	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	2-4	Permanently discontinue	Permanently discontinue
CMV infection or viremia	Any evidence	Interrupt idelalisib in patients with evidence of CMV infection of any grade or viremia (positive PCR or antigen test) until the infection has resolved. If idelalisib is resumed, continue PCR or antigen testing on day 1 of each remaining cycle.	If toxicity does not resolve, permanently discontinue.
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity including rash[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

5.2.1.3 Selection for Idelalisib Dosing When Administered in Combination with Pembrolizumab

Table 4: Dose Levels of Idelalisib*

Pembrolizumab	Idelalisib dose level	Idelalisib Dose (mg)	Idelalisib Frequency
200mg Q3W	-2	50	QOD
	-1	50	QD
	1*	**50**	**BID**
	2	100	BID
	3	150	BID

**Note: Trial will be started at dose level 1 (in bold) and may go up or down. Pembrolizumab is given at a constant dose and frequency intravenously whereas idelalisib will be given orally at the dose and frequency specified in the table.*

The rules for modifying the selected idelalisib dose used in combination with pembrolizumab treatment (dose finding and tolerability assessment phase of the study) are as follows (all dose adjustments are made only to idelalisib):

An initial cohort of 3 subjects are enrolled, receiving both pembrolizumab (200 mg Q3W, IV) and idelalisib at 50 mg PO BID:

- If none of the three patients develop a DLT, we will enroll another 3 patients. If no more than 1/6 patient develops a DLT, we will test the suppression of Treg function by 80% in more than 80% patients. If meeting these criteria, we will declare this dose as the P2RD and will proceed to the phase II part using this dose. If more than 1/6 subjects develops a DLT, we will follow the dose reduction scheme highlighted below. If the functional criteria are not met, then a higher dose will be tested from the beginning.
- If one of the 3 subjects develops a DLT, an additional 3 will be enrolled. If no more than 1/6 has a DLT, Treg function test will begin as above. If ≥2/6 subjects with a DLT at this dose level, this dose will not be administered to any additional subjects, and the next lower dosing regimen for idelalisib 50 mg PO QD) will be studied, in 3 new subjects, following this same algorithm.
- If ≥2/3 subjects develop a DLT, this dose will not be administered to any additional subjects, and the next lower dosing regimen for idelalisib (50 mg PO QD) will be studied, in 3 new subjects, following this same algorithm.

It is conceptually acceptable to de-escalate to a lower, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the subsequent efficacy assessment phase of the study. If this approach is taken, 3 new subjects should be enrolled at the new lower dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

DLT's will be defined from toxicities observed during the first 9 weeks of idelalisib treatment for each dose level. See Section 5.2.4 for rules on replacement of subjects in the tolerability assessment phase of the trial. The occurrence of any of the following toxicities during the initial 9 weeks of idelalisib treatment, if assessed by the Investigator to be possibly, probably or definitely related to idelalisib will be considered a DLT:

1. Grade 4 non-hematologic toxicity (not laboratory)
2. Grade 4 hematologic toxicity lasting ≥ 7 days, except thrombocytopenia
    a. Grade 4 thrombocytopenia of any duration
    b. Grade 3 thrombocytopenia is a DLT if associated with bleeding:
3. Grade 3 non-hematologic toxicity (not laboratory) lasting > 3 days despite optimal supportive care. Grade 3 nausea or vomiting will be considered a DLT if lasting more than 3 days despite optimal supportive care.

4. Any Grade 3 or Grade 4 non-hematologic laboratory abnormality, if
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for > 1 week
5. Febrile neutropenia Grade 3 or Grade 4
6. Any drug-related AE which caused subject to discontinue treatment
7. Grade 5 toxicity

5.2.2 Drug Preparation and Administration

5.2.2.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion on an outpatient basis every 3 weeks. 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 from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Preparation and administration of the investigational agent, pembrolizumab, will follow the same guidelines as for the FDA-approved agent, pembrolizumab, known commercially as Keytruda.

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solutions

The product does not contain a preservative. Store the diluted solution of pembrolizumab either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not freeze.

Administration

- Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- The patient will be monitored for at least 30 minutes including a determination of blood pressure, heart rate, and respiratory rate before and after each infusion.
- After the patient is monitored for 30 minutes following the first pembrolizumab infusion, the patient will be given the first oral dose of idelalisib. On day 1 of all following cycles, idelalisib will be taken by the patient at home, prior to infusion appointments.

5.2.3 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 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion duration to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Patients will be given idelalisib for oral self-administration at home. This drug should be taken at fixed times of the day, with or without food. Patients will be required to record oral drug intake in a pill diary that is provided by the study site. Diet restrictions apply.

5.2.4 Trial Blinding/Masking

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

5.2.5 Subject Replacement During the Tolerability Assessment Phase of the Trial

In order to determine safety, all subjects selected must meet the criteria for evaluability for the initial 9 weeks of treatment during the tolerability assessment phase of the study. Subjects during the tolerability assessment phase of the study are considered non-evaluable and will be replaced if:

- They are enrolled but not treated
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related adverse events
- They receive less than 9 weeks of treatment with idelalisib and did not experience a DLT

Non-evaluable subjects will not be counted toward the cohort total for DLT evaluation.

If a subject experiences a DLT during the initial 9 weeks of the tolerability assessment phase of the trial, treatment may be discontinued at the discretion of the Investigator. However, if the subject is deriving clinical benefit from the trial treatment, the subject may be allowed to continue.

5.3 Randomization or Treatment Allocation

This is a single arm study comparing with historical controls. No randomization is needed.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the 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 final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 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 medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days but within 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications and Drug Interactions to Watch

5.5.2.1 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and idelalisib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Dexamethasone affects the idelalisib levels and should be avoided while taking idelalisib.
- Subjects who, in the assessment by the investigator, require the use of any of the contraindicated treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.
- Drugs metabolized by CYP3A, including some commonly used drugs such as cisapride, simvastatin, are contraindicated while taking idelalisib; see section 5.5.2.2 for drug interactions with idelalisib).
- The following drugs will be prohibited while taking idelalisib in this trial: Alfuzocin, carbamazepine, cisapride, cobimetinib, conivaptan, cyclosporine, dihydroergotamine, eliglustat, ergotamine, fentanyl**,** flibanserin, ivabradine, ketoconazole, lovastatin, lurasidone, midazolam, naloxegol, phenytoin, pimozide, quinidine, rifampin, simvastatin, sirolimus, St.John's Wort tacrolimus, venetoclax, warfarin.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.2.2 Potential drug interactions with idelalisib

Idelalisib is metabolized primarily via aldehyde oxidase, and to a lesser extent via CYP3A and glucuronidation (UGT1A4). Its primary metabolite is GS-563117. Idelalisib is not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6, or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2. GS-563117 is a mechanism-based inhibitor of CYP3A (KI = 0.18 μM, Kinact = 0.033 min-1). GS-563117 is not an inhibitor of the metabolizing enzymes CYP1A2, CYP2B6, CYP2C, CYP2D6 or UGT1A1, or of the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

A clinical drug interaction study found that co-administration of idelalisib with rifampin (a strong CYP3A inducer) resulted in a ~75% reduction in idelalisib plasma AUCinf. Co-administration of idelalisib with strong CYP3A inducers such as **rifampin, phenytoin, St. John's Wort, or carbamazepine** should be avoided.

A clinical drug interaction study found that co-administration of idelalisib with **ketoconazole** (a strong CYP3A inhibitor) resulted in a 26% increase in idelalisib Cmax and a 79% increase in AUCinf, indicating that ZYDELIG is not a sensitive CYP3A substrate.

A clinical drug interaction study found that co-administration of idelalisib with **midazolam** (a sensitive CYP3A substrate) resulted in a ~140% increase in Cmax and a ~440% increase in AUCinf of midazolam due to the CYP3A inhibition by GS-563117. Accordingly, idelalisib is considered to be a strong CYP3A inhibitor. Coadministration of idelalisib with CYP3A substrates (e.g., certain **antiarrhythmics**, **calcium channel blockers, benzodiazepines, HMGCoA reductase inhibitors, phosphodiesterase-5 (PDE5) inhibitors, and warfarin**) may increase their systemic exposures, stop the drug or close monitoring is advised. Avoid coadministration of idelalisib with narrow therapeutic index CYP3A substrates (e.g**. alfentanil, cyclosporine, sirolimus, tacrolimus, cisapride, pimozide, fentanyl, quinidine, ergotamine, dihydroergotamine**).

Table 5. Known CYP3A Substrates:

CYP3A Inhibitors	CYP3A Inducers
Amiodarone	• Ethosuximide
Anastrazole	• Glucocorticoids
• Azithromzcin	• Griseofulvin
• Cannabinoids	• Primidone
• Cimetidine	• Progesterone
• Clarithromycin	• Rifabutin
• Clotrimazole	• Rifampin
• Danazol	• Nafcillin
• Delavirdine	• Nelfinavir
• Diethyldithiocarbamate	• Oxcarbazepine
• Diltiazem	• Phenobarbital
• Dirithyromycin	• Phenylbutazone
• Disulfiram	• Rofecoxib (mild)
• Entacapone (high dose)	• Sulfadimidine
• Erythromycin	• Sulfinpyrazone

• Ethinyl estradiol	• Troglitazone
• Fluconazole	
• Fluoxetine	
• Fluvoxamine	
• Gestodene	
• Grapefruit juice	
• Indinavir	
• Isoniazid	
• Metronidazole	
• Mibefradil	
• Miconazole	
• Nefazodone	
• Nelfinavir	
• Nevirapine	
• Norfloxacin	
• Norfluoxetine	
• Omeprazole	
• Oxiconazole	
• Paroxetine (weak)	
• Propoxyphene	
• Quinine	
• Quinupristine and dalfopristin	
• Ranitidine	
• Ritonavir	
• Saquinavir	
• Sertindole	
• Sertraline	
• Troglitazone	
• Troleandomycin	
• Valproic acid	

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab and/or idelalisib.

Note: if after the evaluation the event is determined to be not related to pembrolizumab or idelalisib, the investigator should follow the adverse event reporting guidance in section 7.2 of this document. Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Study drug administration will be held during any ongoing investigation of the cause of an ECI/AE.

The following supportive care guidelines should be utilized for management of subjects participating in this trial who experience these specific AEs/ECIs:

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events and **Grade 2-4** hypothyroidism:
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
  Fatal and/or serious hepatotoxicity occurred in 11% of patients treated with idelalisib in combination trials. Elevations in ALT or AST greater than 5 times the upper limit of normal (ULN) have occurred. These findings were generally observed within the first 12 weeks of treatment and were reversible with dose interruption. Monitor ALT and AST in **all patients** every 2 weeks for the first 3 months of treatment, every 4 weeks for the next 3 months, then every 1 to 3 months thereafter.
  - For **Grade 2** events (>3-5 x ULN), monitor liver function tests weekly until resolved (<1 x ULN), maintaining idelalisib dose, but holding pembrolizumab dose.
    - If treating with IV or oral corticosteroids, hold both idelalisib and pembrolizumab.
  - For **Grade 3-4** events (>5 x ULN), monitor liver function tests at least weekly and treat with intravenous corticosteroids for 24 to 48 hours (withhold idelalisib and pembrolizumab).

- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks. Study treatment may be restarted if toxicity resolves in less than 4 weeks off steroids.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Hypoglycemia:**
  - For grade 2 events, corticosteroid should be given
  - For Grade 3-4 events, glucagon should be given.
  - When symptoms improve to grade 1 or less steroid should be taper down and dose should be reduced
- **Neutropenia and neutropenic fever:**

  Neutropenia (decreased ANC) and neutopenic fever may occur while receiving idelalisib
  - For grade 1 and 2 (ANC>1000/mm3), no intervention needed.
  - For grade 3, hold idelalisib until ANC > 500/mm3 and start at a lower dose.
  - For Grade 4 or neutropenic fever, hold idelalisib and manage per neutropenic fever with antibiotics and growth factor at the discretion of the investigator. Discontinue idelalisib permanently.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after pembrolizumab infusion and generally resolve completely within 24 hours of completion of infusion.

- **Table 6** below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	Subject may be pre-medicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with:

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
for < =24 hrs	Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Grapefruit, grapefruit juice, pomegranate and Seville oranges should be excluded from the diet due to their effects on idelalisib.

5.7.2 Contraception

Pembrolizumab or idelalisib may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab or idelalisib has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and

has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. 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 study Visit 1 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).

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 (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor. 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.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or idelalisib, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours to the Sponsor and within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab or idelalisib is 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.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial

plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4---Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression

  Note: Subjects should be managed by irRECIST, with PD confirmed as outlined in Section 5.8.1.

  Note: For unconfirmed radiographic disease progression, please see Section 5.8.1

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 5.8.1 and Table 5.
- Unacceptable adverse experiences as described in Section 5.2.1.2 under Dose Modification section in Table 3.
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- The subject has completed 35 administrations of pembrolizumab (approximately 2 years of treatment) during the trial

  Note: Subjects who discontinue pembrolizumab after 35 administrations may be eligible for up to 17 administrations (approximately one year) of additional study treatment if

they progress after discontinuing study treatment provided they meet additional criteria. Subjects who discontinue trial treatment before receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or who attain a CR and discontinue trial treatment may also be eligible for up to 17 administrations (approximately one year of retreatment (Second Course)) after experiencing disease progression. The decision to retreat will be at the discretion of the investigator, provided that such a subject meets the criteria for treatment and the trial is ongoing.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease (PD) will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Treatment after Initial Radiologic Progression (irRECIST-based Management)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial apparent increase in tumor burden (i.e., pseudoprogression) or even the appearance of new lesions. Standard RECIST-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab. For this reason, irRECIST has been developed to help guide treatment decisions during tumor immunotherapy.

For subjects who have initial radiological evidence of radiological PD by RECIST 1.1 as determined by the site, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained (irRECIST-based subject management) (see **Table 7 below**). This clinical judgment decision by the investigator should only be made if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such subjects may continue to receive study treatment and a tumor assessment should be repeated ≥ 4 weeks later in order to reassess PD by RECIST 1.1 per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status

- Absence of rapid progression of disease
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (e.g., CNS metastasis with potential for cord compression)

  NOTE: Subjects exhibiting toxicity from trial therapy as outlined in Section 5.2.1.2 and 7.2 may NOT continue to receive trial therapy.

NOTE: Any subject deemed **clinically unstable** should be discontinued from trial treatment at investigator-assessed 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Upon repeat imaging, PD will be confirmed if ANY of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is worse (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is worse (qualitative assessment)
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from trial therapy.

Upon repeat imaging, PD will have failed to be confirmed if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- New lesion resulting in initial diagnosis of PD is stable or improved (qualitative assessment)
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

Table 7. Imaging and Treatment after First Radiologic Evidence of PD (irRESIST-based Management)

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable at investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

If repeat local site imaging fails to confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flares include any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

5.8.2 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 27 weeks with pembrolizumab and 9 weeks of idelalisib and have had at least three treatments with pembrolizumab and 9 weeks of idelalisib beyond the date when the initial CR was declared. However, such subjects with a CR may continue treatment (up

to a total of 2 years of treatment with pembrolizumab) as long as they are still deriving clinical benefit. If such subjects subsequently experience radiographic disease progression, they may be eligible for up to one more additional treatment with idelalisib for 18 Weeks and pembrolizumab for 2 years via the Second Course Phase, at the discretion of the investigator, if no cancer treatment has been administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open. Such subjects will resume therapy at the same dose and schedule as they received at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

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

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

In the event the drug manufacturer(s) decides to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

Table 8. Study Schedule of events

Trial Period:	**Screening**	**Main Study Treatment Period[a]**						**Maintenance Period[b]**	**End of Treatment**	**Post-Treatment**	
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	Q3W	Discon	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks
Administrative Procedures											
Informed Consent	x										
Inclusion/Exclusion Criteria	x										
Demographics and Medical History	x	x	x	x	x	x	x		x	x	
Prior and Concomitant Medication Review	x	x	x	x	x	x	x		x	x	
Post-study Survival and cancer therapy status									x	x	x
Clinical Procedures/Assessments											
Review Adverse Events		x	x	x	x	x	x	x	x	x	x
Full Physical Examination	x								x		
Directed Physical Examination		x	x	x	x	x	x	x		x	
Vital Signs and Weight	x	x	x	x	x	x	x		x	x	
ECOG Performance Status	x	x	x	x	x	x	x		x	x	
Combination Treatment Administration		x	x	x	x	x	x				
Maintenance Treatment Administration								x			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG	x										
PT/INR and aPTT	x			x							
CBC with Differential	x	x	x	x	x	x	x		x	x	x
Comprehensive Serum Chemistry Panel	x	x	x	x	x	x	x		x	x	x
Urinalysis	x										
T3, FT4 and TSH	x	x	x	x	x	x	x	?	x	x	x

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Trial Period:	Screening	Main Study Treatment Period[a]						Maintenance Period[b]	End of Treatment	Post-Treatment	
Treatment Cycle/Title:	Study Screening	1	2	3	4	5	6	Q3W	Discon	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks
CMV serology (IgG and IgM antibody) [d]			x	x	x	x	x				
Efficacy Measurements											
Tumor Imaging [c]	x			9W			18W	Q9W		x	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood											
Archival or Newly Obtained Tissue Collection	x		x								
Correlative Studies Blood Collection (T-reg assay)	x			x			x	x			

a: Each treatment cycle is comprised of one infusion of pembrolizumab 200 mg IV on Day 1 in combination with 21 days of idelalisib BID PO in 3 weeks at P2RD or test dose BID PO.

b: Following 6 cycles (18 weeks) of combination treatment, subjects will receive maintenance therapy consisting of one infusion of pembrolizumab 200 mg IV every 21 days, for up to 2 years.

c: The first scheduled tumor imaging after treatment initiation occurs at week 9+/- 3 days and then every 9 weeks for the first year of therapy, then every 12 weeks for the duration of treatment.

d: Prophylactic screening for cytomegalovirus CMV infection should begin following the first cycle of idelalisib, and should be performed at the beginning (day 1) of each cycle of treatment with idelalisib).

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 some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. 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.

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.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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 investigator or qualified designee 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 medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

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. The details will be extracted from prior office visit/hospitalization documents including but not limited to office visit notes, hospital discharge summaries, radiology reports, pathology reports, mutational analysis etc.

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 all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30

days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Study Number

Once the informed consent is signed, the subject to be screened will be assigned a number. The number will be designated **PILxxazzz**: where **PIL** stands for **P**embrolizumab and **I**delalisib **L**ung cancer study; **xx** is the site number and a is the cohort number and **zzz** is the subject screening number. For example, the first subject screened in site 05 in cohort A is designated PIL05A001.

7.1.1.7 Assignment of Randomization Number

This is a non-randomized trial. Therefore, a randomization number will not be assigned.

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 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab and idelalisib, all AEs of unknown etiology should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history.

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.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, blood pressure, pulse, respiratory rate, body weight and O_2 saturation. 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 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging should be performed by computed tomography (CT) (preferred). Magnetic resonance imaging (MRI) should be used only when CT is contraindicated or for imaging of the CNS. The same imaging technique with respect to the modality and use of contrast should be used for a given subject throughout the trial to optimize the visualization of existing and new tumor burden.

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. Determination of measurable disease based on RECIST 1.1 will be conducted by the local site investigator during screening for initial assessment of subject eligibility. Only subjects with confirmation of measurable disease by RECIST 1.1 will be eligible to participate in the trial.

The first imaging assessment during treatment should be performed at 9 weeks (63 days ±7 days) from Cycle 1, Day 1. Subsequent imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After the first 12 months on therapy, the imaging interval should be increased to every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression (unless the investigator elects to continue treatment and follow irRECIST) (see Section 5.8.1), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

Per RECIST 1.1, PRs and CRs should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 9-12 weeks later). Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmatory scan do not need to undergo the next scheduled

tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Imaging should continue to be performed until PD is documented by local investigator assessment (or in cases were the investigator elects to continue treatment and follow irRECIST (see Section 5.8.1), confirmed by local investigator assessment of a repeat imaging study ≥ 4 weeks later), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

When archival tissue is available, no new tumor biopsy during the screening period, prior to receiving the first dose of study drug is necessary. When needed, image-guided biopsy should be used for tissue collection. Tissue collected by fine needle aspiration during bronchoscopy or EBUS is not sufficient.

At each biopsy, a minimum of three 18 gauge cores (or an equivalent volume) of tumor tissue should be collected and placed in formalin. These cores will be embedded in a single, paraffin block and sectioned per standard histological procedures. Tumor tissue sections will subsequently be used for H&E staining and IHC.

One additional tube of blood will be drawn for correlative studies every 9 weeks throughout the treatment period.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial for hematology, chemistry, urinalysis, and others are specified in **Table 9**.

Table 9. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		Pharmacodynamics (PD)[#]
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. 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.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial 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 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

No blinding necessary since this is an open labeled study.

7.1.5 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.

7.1.5.1 Screening Period

Prior to signing the consent, outlines of the current clinical trial and a copy of the informed consent may be given to the patient to read at home and record any questions they might have. The screening period starts from the day the informed consent is signed by both the patient and the principal investigator or his/her designee, and ends when the trial or treatment begins. Patients are given the opportunity to ask all questions and consent to be screened for the current clinical trial. Screening may last up to 4 weeks. They are screened at this period per inclusion and exclusion again carefully. Labs, procedures, biopsies when needed are ordered promptly so that patients can be started on treatment in a timely fashion. A full history and physical is due at this period. Target lesion(s) are determined after the imaging (CT with contrast). If archived tissue is available, it can be sent in the place of a fresh biopsy for confirmation in Augusta University Medical Center Pathology Department.

7.1.5.2 Treatment Period

Pembrolizumab (200 mg) will be infused intravenously in 30 min at day 1 and repeated every 3 weeks. Idelalisib will be given at 150 mg PO BID (or possibly at a lesser dose based on results from the tolerability assessment phase of the trial) throughout the study starting on the day of the first dose of pembrolizumab. Patients will be given a pill diary to complete at home.

A history is obtained, a focused physical examination is performed, and blood samples for all scheduled labs are drawn at each visit, prior to pembrolizumab dose administration (unless otherwise indicated in the study flow chart).

The first scheduled tumor imaging after treatment initiation occurs at week 9+/- 7 days, and will follow the schedule specified in section 7.1.2.6.

Treatment period will continue until either disease progression per irRECIST 1.1 criteria, or the treating physician determines that the subject is no longer deriving clinical benefit, or the subject withdraws from the trial, or the subject receives 2 years of treatment.

7.1.5.3 Post-Treatment Visits

Post-treatment visits include a safety follow up visit, routine follow up visit and survival visits listed below.

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab and idelalisib (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (84 ± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section

7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab and idelalisib according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab and idelalisib with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab and idelalisib after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 12 weeks with pembrolizumab and idelalisib before discontinuing therapy.
        - Received at least two treatments with pembrolizumab and idelalisib beyond the date when the initial CR was declared.

OR

    - Had SD, PR or CR and stopped pembrolizumab and idelalisib treatment after 24 months of study therapy for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab and idelalisib.
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab and idelalisib.

- Has a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrates adequate organ function as detailed in Section 5.1.2.
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication.
- Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab and idelalisib. Treatment will be administered for up to one additional year.

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Adverse events may occur within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck and Gilead Sciences Inc.

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). If an adverse event(s) is associated with ("results from") an overdose of pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

For idelalisib, overdose is not well-defined. However, if it happened that an individual has accidentally taken more than 400 mg a day, the patient should be monitored closely for side effects. Bone marrow suppression causing neutropenia, diarrhea or liver failure and pneumonitis may ensue in case of idelalisib overdose. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided as clinically indicated. The incident should be promptly communicated to the local PI and the Sponsor.

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX (215) 993-1220) and Gilead Sciences Inc (1-800-445-3235, option #2).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant

must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX (215) 993-1220) and Gilead Sciences Inc (1-800-445-3235, option #2).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck and Gilead Sciences Inc.

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck and Gilead Sciences Inc.'s product that:

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

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck and Gilead Sciences Inc product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety and Gilead Sciences Inc.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1 (215) 993-1220 and Gilead Sciences Inc (1-800-445-3235, option #2).

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by the FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX: (215) 993-1220) at the time of submission to FDA.

The current study uses both pembrolizumab and idelalisib to treat patients. Although the two agents seemingly have different mechanism of action, it is not always easy to distinguish. Drugs may have overlapping adverse effects. Sites should report all adverse drug effects to both Merck and Gilead Science Inc.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX (215) 993-1220) and Gilead Sciences Inc (1-800-445-3235, option #2).

Events of clinical interest for this trial include:

1. An overdose, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

Additional adverse events:

ECIs (both non-serious and serious adverse events) identified in this protocol from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX (215) 993-1220) and Gilead Sciences Inc (1-800-445-3235, option #2) regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness (See Table 8 below).

Table 10. Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

7.2.6 Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

7.2.7 Protocol Violation

Any change, divergence, or departure from the study procedures in an IRB-approved research protocol that has a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy or reliability of the study data.

7.2.8 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3 AU IRB Adverse Event Reporting

7.3.1 AU IRB Expedited Reporting of Adverse Events and Deaths

The Protocol PI will report to the AU IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to PD
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the AU IRB within 24 hours of PI awareness via the IRBNet system.

7.3.2 AU IRB Requirements for PI Reporting of Adverse Events at Continuing Review

The protocol PI will report to the AU IRB:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.4 IND PI-Sponsor Reporting Criteria

7.4.1 Expedited reporting to the FDA

The PI-Sponsor will notify FDA via phone, fax, or email of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible but no later than 7 calendar days of initial receipt of the information. This will be followed with a written report within 15 days using the MedWatch Form 3500a.

The PI-Sponsor will notify FDA in writing of any suspected adverse reaction that is both serious and unexpected as soon as possible but no later than 15 calendar days after initial receipt of the information using the MedWatch Form 3500a. If FDA requests any additional data or information, the sponsor must submit it to the FDA as soon as possible, but no later than 15 calendars days after receiving the request.

The PI-Sponsor will also report expeditiously as above:

- any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

7.4.2 FDA Annual Reports

The study Sponsor will submit a brief report annually of the progress of the trial within 60 days of the anniversary date that the IND went into effect.

The Annual Report will include:

- A summary of the status of the trial, including the title of the study, protocol number, purpose (objectives), a description of the patient population, and a statement as to whether the study has been completed or is ongoing.
- The accrual ceiling and the number enrolled, tabulated by age group, gender, and race. The number whose participation in the study was completed as planned and the number who withdrew from the study for any reason.
- Once the study is completed, a brief description of the results should be reported.
- A narrative or tabular summary of the most frequent and most serious adverse experiences by body system.
- A summary of all IND Safety Reports
- A list of subjects who died during participation with the cause of death for each subject.
- A list of subjects who withdrew prematurely during the course of the study in association with any adverse experience, whether or not it was thought to be associated to the Sponsor.
- A description of any protocol modifications during the past year if not previously reported.
- A description of the general investigation plan for the coming year.

8.0 STATISTICAL CONSIDERATIONS

This study has two parts:

- Phase I dose finding/tolerability part to determine the safe dose of idelalisib in combination with pembrolizumab that down regulate the activity of Treg by more than 80% of baseline in at least 80% of the treated NSCLC patients.
- Phase 2 assessment of preliminary efficacy of the treatment combination in terms of objective response rate (ORR).

8.1 General consideration

Descriptive statistics will be presented for primary and secondary endpoints. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages; and time-to-event variables will be summarized by Kaplan-Meier medians and survival plots. Data listings will be created to support each table and to present all data. The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, for primary efficacy and safety measures per study part (Phase I, II), and on a per dose level for phase I part. The primary efficacy analysis will be conducted on the efficacy evaluable population and safety analysis will be performed on the safety evaluable population. A safe dose below the maximum tolerated dose of idelalisib when used in combination with pembrolizumab will be estimated based on the data from modified 3+3 dose escalation. RP2D will then be determined based on the dual DLT and functional criteria, which should not exceed 1/6 of patients with DLT where at least 80% of

patients have down regulated the activity of Treg by at least 80% of baseline. SAS 9.4 software, or higher will be used for data analysis.

8.2 Study Objectives

8.2.1 Primary Objective(s) & Hypotheses

1. To determine whether addition of idelalisib at the P2RD to pembrolizumab is safe in checkpoint inhibitor refractory NSCLC patients.

2. To determine the P2RD of idelalisib used in combination with pembrolizumab in patients with checkpoint inhibitor refractory NSCLC. Our hypothesis is the combination of pembrolizumab (200 mg IV Q3W) with idelalisib can down-regulate Treg cell function by 80% in 80% patients at a dose lower than the current FDA approved dose of 150 mg BID PO in patients with NSCLC.

3. To determine whether addition of idelalisib to pembrolizumab in NSCLC improves ORR over that seen with pembrolizumab or other immune checkpoint inhibitors alone in treatment of NSCLC. Our hypothesis is that in NSCLC patients previously treated with anti-PD-1/PD-L1 therapies the ORR for the combination of idelalisib and pembrolizumab is 10% (it is nearly 0% for the refractory patients).

8.2.2 Secondary Objective

To evaluate DOR in NSCLC treated with idelalisib at P2RD in combination with pembrolizumab

8.3 Study Design/Endpoints

Phase I: A modified 3+3 design will be employed and will include dose escalation to determine the P2RD of idelalisib in combination with the approved dose of pembrolizumab. The starting dose is 50 mg BID and will be de-escalated in case of DLT in more than 1/6 patients.

Phase II: The ORR will be used as the preliminary efficacy endpoint, and DOR will be used as a secondary endpoint.

8.4 Sample Size/Accrual Rate

For part 1: 6 to 18 patients will be used for the dose escalation part. The actual number of patients will depend on the DLT and functional studies of Treg. We are expecting 3 to 4 patients per month.

For Part 2: We assume the ORR without the treatment combination to be 1% and expect an ORR increase with the proposed treatment combination (using P2RD from the phase

1). The minimum sample size required for achieving 80% power at one-sided alpha=0.05 (0.10) depends on the expected improvement of the ORR. The following table provides sample size estimation based on one year (3-4 patients per month) accrual and 24 month of follow-up using single stage design. We will follow the one stage design in this study (32 patients to achieve an 80% power at alpha=0.05).

Table 11. Sample Size Estimation

ORR under H0	ORR under H1	alpha	Sample size (n) One-Stage Design	Sample size (n) Two-Stage Design
0.01	0.05	0.05	99	50+50=100
0.01	0.05	0.10	72	50+37=77
0.01	0.10	0.05	32	20 +15=35
0.01	0.10	0.10	23	15+10=25

If we consider ORR to increase from 1% to 10% for the proposed combination, the sample size would be as follows:

a. For a one-stage trial, we need a minimum of 23 patients to maintain an 80% power at alpha=0.10 OR 32 patients to achieve an 80% power at alpha=0.05.

b. (Included for reference, not implementation in this trial) For two-stage design, would need a minimum of 35 patients with 20 patients at stage 1 and 15 patients at the second stage for testing the hypothesis (when alpha=0.05 or 25 (15 and 10 patients for alpha=0.10.

Statistical References

Simon, Richard. *'Optimal Two-Stage Designs for Phase II Clinical Trials'*, Controlled Clinical Trials, 1989, Volume 10, pages 1-10.

A'Hern, R. P. A. 2001. *'Sample size tables for exact single-stage phase II designs.'* Statistics in Medicine, Volume 20, pages 859-866.

Fleming, T. R. 1982. *'One-sample multiple testing procedure for Phase II clinical trials*.' Biometrics, Volume 38, pages 143-151.

8.5 Analysis of Primary Endpoints

<u>For dose de-escalation and determination of P2RD:</u>

Modified 3+3 design will be used to determine the P2RD with escalation mechanism. The starting dose of idelalisib is 50 mg BID in addition to an approved dose of pembrolizumab 200 mg Q3W, which will be a fixed dose for all patients.

Each dose will be administered to a cohort of 3 patients. If 0 out of 3 patients experienced a DLT at the starting level, 3 additional patients will be assigned to the same dose. If we still have a ratio of patients with DLT of less than or equal to 1/6, we declare the first (highest dose) to be the P2RD. Otherwise the idelalisib dose will be reduced to the lower dose (100mg). See graph in page 4. Section 2.1

Functional studies of Treg will be performed. The P2RD is at most 1 out of 6 patients experiences a DLT. The P2RD will down regulate Treg function by 80% from baseline in more than 80% of the patients.

For Part 2:
To assess preliminary evidence of efficacy, the ORR will be calculated and along with the associated exact 95% Confidence interval.

8.6 Analysis Datasets

Analysis will be conducted on the modified intent-to-treat set (mITT), which Includes all enrolled subjects treated with at least 1 dose (or partial dose) of the study medications. The mITT set will be used for all safety and preliminary efficacy analysis.

8.7 Randomization

There will be no randomization for this study.

8.6 Interim Analysis

No interim analysis is applicable for the proposed study

This section outlines the statistical analysis strategy and procedures for the study. Post hoc exploratory analyses will be clearly identified in the Clinical Study Report (CSR).

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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.

Clinical Supplies will be provided by Merck and Gilead Sciences as summarized in Table 10.

Table 12. Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection (Merck)
Idelalisib 50 mg,100mg or 150 mg tab	Pill (Gilead Sciences)

9.1.1 Pembrolizumab (MK-3475, Keytruda®)

Pembrolizumab will be provided by Merck for use in this investigational setting. Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2 to 8°C).

The lyophilized drug product after reconstitution with sterile water for injection, and the liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-3475 solutions in the IV bags. For each individual trial, clinical supplies are to be stored in accordance with specific instructions on the label.

9.1.2 Idelalisib (GS-1101, Zydelig®)

Idelalisib oral tablets will be supplied by Gilead Sciences for use in this investigational setting. Idelalisib supply details, including how it will be supplied, how it should be stored, how it will be ordered, will be appended to the main protocol document when those details become available.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or Gilead Sciences Inc., 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 at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality and Privacy

Confidentiality: Only the investigator, the members of the research team, the sponsor, authorized officials from state and federal governments such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), and authorized representatives of the AU Institutional Review Board and the Augusta University will have access to confidential data which would identify participants, unless specifically required to be disclosed by state or federal law. Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this study may be presented at meetings or in publications. However, participants will not be identified in any

reports or publications resulting from the study. All reasonable steps will be taken to ensure confidentiality.

Protection of patient privacy: Following enrollment patients will be assigned a patient protocol number. All data derived from patient visits, laboratory, radiological and other examinations will be coded with this number. Research samples (such as blood samples), patient demographic data, and results or images from imaging studies will be encoded with this number to insure patient anonymity. The key relating patient identifiers to patient protocol number will be kept in a single secure location under control of the PI. Demographic data will be securely stored in a location separate from the encoding key.

10.2 Compliance with Financial Disclosure Requirements

Investigators participating in the study will comply with federal and Augusta University financial disclosure requirements.

10.3 Compliance with Law, Audit and Debarment

Investigators will comply with federal and state laws. This study will be audited by the Augusta University/Georgia Cancer Center auditing team. Investigators who have been debarred from clinical trial participation by the FDA may not participate in this trial.

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to Merck Global Safety or Gilead Sciences Inc., and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed consent form(s) will be given to every subject, and the original(s) will be maintained with the subject's records.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.0 DATA MANAGEMENT

The DM (Data Monitor) Console is OnCore's data management tool and is the validation and management workspace for online forms in OnCore.

11.1 Forms Design

Electronic case report forms (eCRFs) are created in the eCRFs Console, and attached to specific protocol calendar visits for completion by the coordinator.

11.2 Data Entry

11.2.1 Recording and handling data

In OnCore, when a subject visit as occurred, forms that need to be completed are listed on the Forms by Status > To Do Forms tab. Data is recorded specific to each form/visit. By opening the form, it becomes "Active," and the coordinator can continue to work on the form until the "Complete" button is selected. In declaring a form as complete, coordinators are in effect stating that the form is completely filled-out and is ready for a data monitor (DM) to validate the data.

11.2.2 Subject documents (questionnaires, diaries)

Subject documents, such as questionnaires and diaries, completed by the subject on paper, is then manually transcribed and entered into OnCore by the research staff.

11.3 Study Data Flow

Validation
As online forms are declared as Completed, the data monitor validates the data and either raise a query or locks the form. If the data is accurate and the monitor has no questions, the form can be Validated by clicking the Validate button (shown for Completed and Amended forms) in the DM Console. After all queries have been resolved, the form and be **Locked**.

Queries

Raising a query sends the form and a question back to the person who entered the data within OnCore. A queried form can be amended and then validated and locked. The process of querying and amending a form may have multiple iterations.

Database lock
In OnCore, individual validated forms are locked, preventing further edits. After all forms are validated, the database is essentially locked.

11.4 Data Export & Reporting

Data export formats

OnCore's Biostat Console is used to extract data from OnCore for use in statistical analysis tools. The subject's full name is never included in the export. The Biostat Console can also be used to view the current progress of protocols related to accruals, forms, and adverse events. From the Data Export page, selected data can be exported into Excel spreadsheets or files formatted for easier import into SAS.

12.0 APPENDICES

Table 13. ECOG Performance

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.

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

12.2 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.

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

12.3 Immune Related Response Criteria

Responses will be evaluated in the expanded cohorts only. Because of direct clinical observations of immune cell influx into tumor causing enlargement in some patients prior to sustained response, recently it has been suggested that clinical trials involving the use of immunotherapy use alternative guidelines, called immune related response criteria (irRC) to determine radiographic response or progression after therapy. The criteria for evaluation of response are those defined in Wolchok JD, Hoos A, O'Day S, et al#. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 2009; 15:7412-7420. These recommendations have been used in recent clinical trials. One study of 227 subjects with metastatic melanoma showed that the approximately 10% of patients who had PD by modified WHO criteria but either CR, PR or SD by irRC had a similar overall survival as those patients who had SD, PR or CR by both criteria. The irRC was created using bi-dimensional measurements (as previously widely used in the WHO criteria). We have taken the concepts of the irRC and combined them with the recently revised RECIST 1.1* to come up with the modified irRC used in this protocol. Consistent with the irRC, the main changes from RECIST 1.1 are (a) a requirement for confirmation of both progression and response by imagining at least 4 weeks after initial imaging and (b) not automatically calling the appearance of new lesions PD if the total measurable tumor burden has not met criteria for PD.

For immune-related response criteria (irRC), only index and measurable new lesions are taken into account. At baseline tumor assessment on this trial, target lesions will be measured along the longest axis and the measurements will be summed, called sum of largest diameter (SLD). These lesions must be a minimum of 10mm per lesion, maximum of 5 target lesions, maximum of 2 per organ system. At each subsequent tumor assessment, the uni-dimensional measurement of target lesions and of new measureable lesions are added together to provide the total tumor burden: As per the modified definitions below, all responses and progression except stable disease (SD) required confirmation on a consecutive scan at least 4 weeks from the initial observation). See Table 12 for definition for irRC.

Table 14. Definitions of irRC:

Response	**irRC**
New measurable lesions	**Incorporated into tumor burden**
New non-measurable lesions	**Do not define progression (but precludes irCR)**
Non-index lesions	Contributes to defining irCR (complete disappearance required)

Overall irCR	100% disappearance of all lesions, whether measurable or not, and no new lesions, in two consecutive observations not less than 4 wks from the date first documented. All measurable lymph nodes also must have reduction in short axis to <10mm.
Overall irPR	≥ 30% decrease in SLD compared with baseline confirmed by a consecutive assessment at least 4 wk after first documentation
Overall irSD	Not meeting criteria for irCR or irPR, in absence of irPD: 30% decrease in SLD compared with baseline cannot be established nor 20% increase compared with nadir.
Overall irPD	At least 20% increase in SLD compared with nadir (minimum recorded tumor burden) and an increase of at least 5mm over the nadir, confirmed by a repeat, consecutive observation at least 4 wk from the date first documented.

Overall responses derived from changes in index, non-index and new lesions as demonstrated in the following (Table 13):

Table 15. Definition of Response per irRC

Measurable response	**Non-measurable response**		**Overall response using irRC**
Index and new, measurable lesions	**Non-index lesions**	**New, non-measurable lesions**	

(tumor burden)* %			
Decrease 100%	Absent	Absent	irCR[&]
Decrease 100%	Stable	Any	irPR[&]
Decrease 100%	Unequivocal progression	Any	irPR[&]
Decrease ≥ 30%	Absent / Stable	Any	irPR[&]
Decrease ≥ 30%	Unequivocal progression	Any	irPR[&]
Decrease < 30% to increase < 20%	Absent / Stable	Any	irSD
Decrease < 30% to increase < 20%	Unequivocal progression	Any	irSD
Decrease ≥ 20%	Any	Any	irPD

- * Decreases assessed relative to baseline
  [&] Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

12.4 References

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12.5 Abbreviations

Table 16. Abbreviations used in the text

Abbreviation	Definition
AE	Adverse Event
AJCC	American Joint Committee for Cancer
ALK	ALK gene
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Alanine Aspartate Aminotransferase
BID	Twice daily
CBC	Complete Blood Count
CLL	Chronic Lymphocytic Leukemia
CLL	Chronic Lymphocytic Leukemia
CMP	Complete Metabolic Profile
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Effects
CTLA-4	Cytotoxic T Lymphocyte Associated Protein-4
DKA	Diabetic Ketoacidosis
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECI	Events of Clinical Interests
ECOG	East Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
eIRB	electronic Institutional Review Board
EPO	Erythropoietin
ERC	Ethical Review Committee
FDA	Food and Drug Administration
FOXO	Forkhead Box 3
FT4	Free Thyroid Hormone T4
GCC	Georgia Cancer Center (at Augusta University)
GCP	Good Clinical Practice
GPCR	G-Protein Coupled Receptor
GRU	Georgia Regents University
HIV	Human Immune Deficiency Virus
ICH	International Conference on Harmonization
IHC	Immunohistochemistry

Abbreviation	Definition
IND	Investigational New Drug
IRB	Institutional Review Board
irRECIST	immune related Response Evaluation Criteria in Solid Tumor
IV	Intravenous
mAb	Monoclonal Antibody
MDSC	Myeloid Derived Suppressor Cells
MRI	Magnetic Resonance Imaging
mTORC1	(mammalian) Target Of Rapamycin Complex 1
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-small cell lung cancer
OHRP	Office for Human Research Protection
ORR	Objective response rate
OS	Overall Survival
OTC	Over the Counter
PCP	Pneumocystis pneumonia
PD	Progression Disease
PD-1	Programmed Death-1 (receptor)
PD-L1	Programmed Death Ligand-1
PI	Principal Investigator
PI3K	Phosphatidylinositol 3-kinases
PI3K-RBD	Phosphatidylinositol 3-kinases Ras Binding Domain
PI3KCA	Phosphatidylinositol 3-kinases Catalytic (subunit) Alpha
PI3KCB	Phosphatidylinositol 3-kinases Catalytic (subunit) Beta
PI3KCC	Phosphatidylinositol 3-kinases Catalytic (subunit) Gamma
PI3KCD	Phosphatidylinositol 3-kinases Catalytic (subunit) Delta
PI3KR1	Phosphatidylinositol 3-kinases Receptor 1
PO	Per Os or orally
PR	Partial Response
QD	Once daily
RECIST	Response Evaluation Criteria In Solid Tumor
RFS	Relapse Free Survival
ROS	Reactive Oxygen Species
RTK	Receptor Tyrosine Kinase
SD	Stable Disease
SLD	Sum of Largest Diameter
SOC	Standard of care
T1DM	Type 1 Diabetes Mellitus
TB	Bacillus Tuberculosis
TIL	Tumor Infiltrating Lymphocytes

Abbreviation	Definition
Treg	T regulatory cell
ULN	Upper Limit Normal
WHO	World Health Organization

Participant's Name: _____
Participant's Medical Record Number: _____

APPROVED
AS MODIFIED
Dec 05, 2017
WIRB®

Augusta University
Research Informed Consent Document

TITLE: A phase Ib /II trial of pembrolizumab and idelalisib in patients with non-small cell lung cancer (NSCLC) who have failed immune checkpoint inhibitor.

PROTOCOL NO.: CC-16053
WIRB® Protocol #20170581
1031896

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706-721-2505 (24 hours)

INVITATION TO TAKE PART IN RESEARCH

You are being asked to take part in this research study about the safety and effectiveness of combining two drugs, pembrolizumab and idelalisib, on patients with non-small cell lung cancer (NSCLC). This study is being offered to you because you have a type of lung cancer that has not responded to previous standard treatment.

The purpose of this document is to:

- Explain your rights and responsibilities
- Explain the purpose of the study
- Describe what will happen if you decide to take part in this study
- Explain the potential risks and benefits of taking part in the study

Participation in research studies is voluntary. Please read this consent form carefully and take your time making your decision. As the study staff discusses this consent form with you, please ask them to explain any words or information that you do not clearly understand. You are encouraged to talk with your family and friends before you decide to take part in this study.

Please tell the study staff if you are taking part in another study.

Why is this study being done?
The purpose of this study is to determine the safety and effectiveness of the combination of pembrolizumab and idelalisib in NSCLC patients whose disease has stopped responding to immune therapy with a drug that blocks the interaction of the T cell molecule PD-1 and its ligand PD-L1. Drugs that block the interaction of these molecules prevent immune cells from being "turned off" by cancer cells; this allows the immune system to better fight cancer cells.

Pembrolizumab is an antibody that is made in the laboratory. An antibody is a natural protein made by our immune system that binds other proteins or molecules to fight infection and its ill effects. Pembrolizumab has been approved by the Food and Drug Association (FDA) for melanoma skin cancer, head and neck cancer, Hodgkin's lymphoma and lung cancer. Pembrolizumab is an experimental drug therapy for many other types of cancer and has shown outstanding effects in certain tumor types like microsatellite repair insufficient tumors particularly of the large bowel. Pembrolizumab binds to PD-1 on T cells and may prevent cancer growth by helping certain blood cells of the immune system eliminate the tumor.

Idelalisib belongs to a group of drugs called kinase inhibitors. These drugs act by blocking certain cellular pathways so that cancer cells cannot reproduce and grow. Idelalisib is FDA approved for the treatment of some leukemias and lymphomas (blood cancers). Like pembrolizumab, it is also being investigated as possible therapy for other cancers.

Through this study, the researchers are trying to determine the dose of idelalisib that is safe and tolerable when it is combined with pembrolizumab in patients with lung tumors. This study will also evaluate how the combination of pembrolizumab and idelalisib activates your immune system in your blood and inside the tumor and how it affects the size and number of tumor(s) in your body.

The use of pembrolizumab and idelalisib in combination is investigational in this study. The information learned in this study may be helpful in the further development of combining immune stimulating agents such as idelalisib and pembrolizumab in patients with specific types of tumors that benefit from immunological treatments.

This study will enroll patients into two separate phases: Phase 1 will determine the best tolerated dose of idelalisib in combination with pembrolizumab, and Phase 2 will assess the effectiveness

of this combination in patients with lung cancer. Georgia Cancer Center/Augusta University Health System will enroll up to 18 participants in the Phase 1 period, and up to 32 participants in the Phase 2 period, for a total of 50 patients.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

How long will I be in this study?
Your active participation in this study is expected to take up to 28 months (about 2 ½ years). This will include approximately 18 weeks of combination idelalisib and pembrolizumab treatment, followed by 2 years of maintenance therapy with pembrolizumab alone.

You can choose not to be in the study or stop participating at any time without penalty or loss of any rights or benefits you are entitled to. Please talk to the study staff first before you stop participating in the study.

What will happen to me in the study?
*(See also the **Summary of Assessments** later in this document.)*

Screening Period
During the screening period, we will see if you are eligible (qualify) for and can safely participate in this study. The study will be explained to you by the study doctor and study staff, and you will be asked to sign this consent form before any tests for the study are done. This does not commit you to being in the study. It is simply to show that you understand what the study is about and that you are willing to participate, if eligible. You are free to withdraw from the study any time.

We will conduct several routine screening procedures that include a physical examination, reviewing your current medications, and recording your medical history. In addition, you will have one blood draw of approximately 11.5 tablespoons of which two and a half tablespoons will be used to measure your blood chemistry, kidney/liver function and blood counts. The remaining 9 tablespoons of blood will be used to evaluate your immune responses (how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body such as tumors).

You will also have standard urine tests to assess organ function, and an electrocardiogram (ECG) to measure and record the electrical activity (heart beat) of your heart. Your doctor may review a tissue sample from the original biopsy that was done to confirm your cancer diagnosis.

You will have a CT-scan of the chest/abdomen/pelvis and a CT scan of any extremity affected by your tumor, or a brain MRI or CT scan of the brain. In some cases, you may have a PET/CT scan performed. You may have an ultrasound performed of the lesions to determine whether they can be biopsied under ultrasound guidance. The scanning imaging tests have to be done within 4 weeks of your first study treatment.

If you are a female who is able to become pregnant, you will have a pregnancy test taken to determine if you are pregnant. Pregnant women are not allowed to participate in this study because the risks of the study for an unborn fetus are unknown. If you are not pregnant and could become pregnant you must use contraceptives during the course of this study, and for 3 months after going off study (completion or involuntary). If you are a male you must use contraceptives (abstinence, condoms, etc.) while on study and for 3 months after going off study (completion or involuntary).

After we complete all of the screening assessments, we will contact you to let you whether you are eligible to participate in the study. If you decide to take part in the study, you will be asked to return to the clinic to begin study treatment.

Treatment Period (6 Cycles)

Phase 1: The first phase of the study will enroll in groups, or cohorts, of three to six patients for each dose level: Cohort A for 50 mg twice daily, followed by Cohort B for 100 mg twice daily, and then Cohort C for 150 mg twice daily. Treatments will be given in 21-day cycles. All patients will receive the standard dose of pembrolizumab as a single infusion of 200 milligrams by vein on Day 1 of each cycle, followed by oral idelalisib tablets at their designated Cohort dose, every day of the cycle. All patients will be closely monitored for any possible drug reactions.

After 3 cycles (9 weeks), Cohort A patients will have blood drawn again to check their body's immune response to the treatment (T-regulatory function). If these patients haven't experienced any dose limiting toxicities (DLTs) or only one out of the three has a DLT, another three patients will be enrolled in Cohort A. After another 3 cycles, T-regulatory function will be determined. If at this dose level, 80% of patients (5 out of 6) have significant reduction of T-reg function from their baseline levels, this dose will be the phase 2 recommended dose (P2RD). Otherwise, Cohort B will begin enrollment to test patients' T-regulatory responses to the idelalisib 100 mg twice daily dose.

If DLTs occur in 2 of the initial 3 patients or more than 1/6 patients after another 3 patients, then lower doses of idelalisib may be investigated in cohorts with similar number of patients until a dose that causes no more than 1/6 DLT is found before functional analysis of Treg. If dose limiting toxicity occurs in more than two of the six tested at the lowest dose level of 50 mg twice daily, then lower doses of idelalisib may be investigated in 6 newly enrolled patients. Other

idelalisib doses that may be evaluated may include 50 mg once daily and 50 mg every other day.

Phase 2: After the phase 2 recommended dose (P2RD) of idelalisib is determined, the efficacy assessment phase (phase 2) of the study will begin, enrolling up to 32 patients. The designated dose of idelalisib in combination with the standard dose of 200 mg pembrolizumab on Day 1 of each cycle will be given for six 21-day cycles. Following the treatment period, patients will receive maintenance therapy with 200 mg pembrolizumab intravenously every 3 weeks, for up to 2 years, or until disease progression or unacceptable toxicity

You will have a biopsy taken from the tumor before receiving the 2nd cycle of treatment. The biopsy is done under local anesthesia with the guide of CT scan or ultrasound. During the maintenance period, tumors might need a repeated biopsy if they show progression or appearance of new lesions. Biopsy samples are taken by special needles that can produce a minimal scar of a few millimeters.

Maintenance Period
During the maintenance period you will receive pembrolizumab at a dose of 200 mg every three weeks for up to two years.

Summary of Assessments

Normal clinical care procedures	**Research procedures done ONLY because of study**
• Pregnancy test (during screening; otherwise only as indicated) • Blood tests (before each cycle) • Thyroid tests (before each cycle, at the same time as other standard blood tests) • Urine tests (only during screening; otherwise as clinically indicated) • ECG (only during screening; otherwise as clinically indicated) • Tumor imaging (CT, PET/CT and/or MRI; During screening, and then every 9 weeks)	• CMV screening blood tests (At screening and on day 1 of each treatment cycle) • T-regulatory cell blood tests (One additional tube of blood, drawn at the same time as standard blood tests; during screening, and then every 9 weeks) • Biopsy (during screening, if no archival tissue is available; and before receiving the third cycle of treatment)

What additional responsibilities will I have if I take part in this study?
If you decide to take part in this research study you will be responsible for the following things:

- Tell the study doctor how you feel and about any side effects.
- Tell the study doctor about any medication, over-the-counter products, herbal remedies, or alternative therapies that you use while you are in this study. Certain medications

cannot be taken while you are in this study. The study doctor will explain what these medications are. If you need treatment with any medications that are not allowed during this study, you must tell the study doctor or the study staff. You will not be denied medications required to treat an illness you may have, but you may be required to stop taking the study medication. This is for your safety, since some medications may not work well with idelalisib and you might have physical problems. You must check with the study doctor first if you need to take any new over-the- counter medications or herbal supplements, or if you need to change your usual prescription medications during this study.

- You should not have any immunizations (vaccinations) without the study doctor's approval.
- Tell the study doctor about any medical treatments that you will have to get during the study (such as elective surgery).
- If you decide to take part in the study, it is important that you follow the instructions and advice given to you by the study doctor.
- You should not donate blood for 3 months following the last dose of study treatment.
- You may be able to return to work or stay home at the time you receive your study drug. Normal daily activities need not to be changed unless you experience drug related serious adverse events or your study physician recommends you limited activities or special considerations.

What are the risks of being in this study?
Possible risks that could result from being in this study are listed below. You should discuss these with your study doctor and your regular health care provider if you choose to participate in this study.

Some possible adverse events include those associated with venipuncture, study drug administrations, and tumor biopsies. Imaging studies with CT scan as well as electrocardiography (ECG) may also show their own adverse reactions. Certain of the expected events listed below are also due to activation of the patient's own immune system against the tumor, with potentially beneficial inflammation and tumor necrosis.

<u>Possible Risks Associated with Pembrolizumab:</u>
Most of the possible side effects listed below are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. Some patients may need to delay doses of pembrolizumab to allow the side effects to get better. The most important possible side effects, which are listed below, may occur because of the way pembrolizumab works on the immune system and they have been seen in patients treated with pembrolizumab in clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to pembrolizumab.

Very Common side effects seen in >20% of patients treated with pembrolizumab/KEYTRUDA® include the following:
•Itching of the skin
•Loose or watery stools
•Cough

Common side effects seen in >10% to <20% of patients treated with pembrolizumab/KEYTRUDA® include the following:
•Joint pain
•Fever
•Back pain
•Rash

Common side effects seen in >1% to <10% of patients treated with pembrolizumab/KEYTRUDA® include the following:
•Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, sweat, tired, have loose and watery stools
•Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to death.
•Inflammation of the bowels/gut that may cause pain in your belly with loose or watery stools
•Inflammation of the skin so you may have peeling of the skin, itching, skin redness
•Pain in your belly
•Loss of skin color
•Low level of salt in the blood that may cause you to feel tired, confused, headache, muscle cramps or sick to your stomach
•Dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

Common serious side effects seen in 1% to 4% of patients treated with pembrolizumab/KEYTRUDA® include the following:
•Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to death
•Inflammation of the bowels/gut that can cause pain in your belly with loose or watery stools
•Fever

Immune-mediated serious side effects seen in <1.0% of patients treated with pembrolizumab/KEYTRUDA® include the following:

•Inflammation of the skin so you may have widespread peeling of the skin, itching, and skin redness. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. Rarely these reactions lead to death.

•Inflammation of the liver that may cause a poor appetite, feeling tired, mild fever, muscle or joint aches, sick to your stomach and vomiting, pain in your belly, yellow eyes and skin, and dark urine

•Inflammation of the pituitary gland (a gland in the head), which may cause headaches, sick to your stomach, changes in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting

•Adrenal glands (glands on top of the kidneys) may not make enough hormone causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan

•Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, increased sweating, weight loss, hair loss, tired, have loose and watery stools

•Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have in frequent or hard bowel movements

•Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain

•Inflammation of the muscles so you may feel weak or pain in the muscles

•Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to the back, sick to your stomach, and vomiting that gets worse when you eat

•Inflammation of the eye so you may have redness of the eye, blurred vision, sensitive to light, have eye pain, see floaters or have headaches

•Too much sugar in your blood (diabetes), so you may feel thirsty, and are likely to need regular insulin shots

•Inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis

•Inflammation of the middle layer of your heart wall (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death

Possible Risks Associated with Idelalisib:
Medical problems, or side effects, that have been reported in clinical studies and are believed to be caused by idelalisib are described below. You should tell your study doctor about any medical problems that you notice while you are on the study, even if they are not mentioned below. A side effect is considered "common" if there is between a 1% (one in a hundred) and a 10% (one in ten) chance, and "very common" if there is a greater than 10% chance that it will happen to you during treatment with idelalisib.

Very Common Side Effects (more than 10%):

- **Severe diarrhea or colitis:** Some people treated with idelalisib have experienced severe diarrhea. This could happen to you at any time during treatment. It is important that you tell your study doctor if you have any diarrhea, providing an estimated number of loose stools per day, even if you do not consider it severe. This way your study doctor can determine if you need treatment. Your doctor may decide to perform a procedure called a colonoscopy. During this procedure a biopsy is usually taken, which may show a condition called colitis. The complications of severe diarrhea could become life-threatening if not appropriately treated. If you develop severe diarrhea or colitis, your idelalisib treatment will be stopped. It is sometimes possible to resume idelalisib after improvement. If you do restart idelalisib, your doctor may use a lower dose.
- **Liver injury:** Some people taking idelalisib have had blood tests that showed reversible liver injury during the first few months of treatment. If this happens, it is almost always without any symptoms. Your study doctor will closely watch your blood liver test results for signs of liver injury, especially when you first start taking the drug. If necessary, your idelalisib treatment may be temporarily stopped. Most patients are able to resume idelalisib after improvement in the blood tests. If you do restart idelalisib, your doctor may use a lower dose.
- **Rash:** Various type rashes may occur in some people who take idelalisib. Although usually mild, rashes may sometimes be severe and rarely life threatening. If you notice any rash or itching, tell your study doctor right away.
- **Neutropenia and Fever:** People who take idelalisib have often experienced a decrease in a certain type of white blood cell that helps fight infections, called the neutrophil. A low neutrophil count results in a condition called neutropenia. If this happens to you, you may be at increased risk of infection. An important early sign of infection can be fever, however you may also develop a fever without neutropenia or infection. If you do experience a fever, or otherwise think that you have an infection, it is important to contact your study doctor immediately.

Common Side Effects (from 1% up to 10%)

- **Pneumonitis:** Inflammation of the lungs, known as pneumonitis, has been reported in some people receiving treatment with idelalisib, either alone or with other study medication. In some cases, people needed oxygen or help from a machine to breathe and a few have died. Because this is a serious condition, it is very important that you tell your study doctor if you experience any new or worsening shortness of breath or difficulty breathing, so that your doctor can treat you as soon as possible.

Rare medical problems that have occurred in clinical studies with idelalisib
Some serious medical problems have occurred in less than 1% (one in a hundred) of people taking idelalisib in clinical studies. It is not known whether idelalisib caused these problems to happen, because in most cases other conditions were present that could have been responsible.

Serious or fatal pneumocystis pneumonia (PCP) or cytomegalovirus (CMV) has occurred in less than 1% of patients treated with idelalisib. CMV infection is common in healthy people and it's usually not serious. Many people have this virus in their bodies and don't even know it. But when the immune system is weakened, CMV can cause things like serious pneumonia, intestinal infection (enteritis), liver infection (hepatitis), and a serious eye infection that can lead to blindness if not treated (retinitis).

CMV infection can be very hard to treat in people with low white blood cell (WBC) counts, because the drugs used to fight the virus also lower the number of WBCs. This makes it hard for the body to fight the infection. Often, the best thing to do for patients with weak immune systems is try to prevent the infection from flaring up. This is done by giving patients certain anti-viral drugs before any symptoms begin. Since most people with CMV don't know they have it, blood tests are used to check for it. Your physician will order lab tests to detect these possible rare infections each cycle that you are receiving idelalisib, as well as for 6 months following treatment.

There is also risk of a severe, life threatening allergic reaction to a medication or food, called anaphylaxis. The symptoms of anaphylaxis include swelling in the mouth and throat or other areas of the body, difficulty breathing, low blood pressure, and hives and other kinds of rashes. If this occurs to you outside of a medical facility, an ambulance must be called immediately.

Another condition is called intestinal perforation, which describes a small hole that develops in the small or large intestine allowing bacteria to enter the abdominal cavity. Intestinal perforation usually requires emergency surgery. If you develop severe abdominal pain or hardness of the abdomen you must seek medical attention immediately.

There is also risk of developing an extremely severe blistering rash that is also associated with inflammation and blistering of the lining of the mouth, the eyelids and outer surface of the eye. If you develop such symptoms, you must seek medical attention immediately.

Possibility of interaction with other medications
Idelalisib may affect your body's reaction to other drugs. In particular, one of the by-products of idelalisib may block the ability of an enzyme in the liver, called CYP3A, to inactivate other drugs. The result of taking idelalisib at the same time as drugs that are usually inactivated by this enzyme can cause your blood levels of these drugs to be significantly higher than expected and, depending on those drugs, could result in undesirable side effects.

Just as idelalisib may affect the blood levels of certain drugs, idelalisib may itself be affected by other drugs. Some drugs increase the activity of the CYP3A enzyme, and these drugs are called CYP3A inducers. Taking a CYP3A inducer with idelalisib could lead to lower blood levels of idelalisib, and this can decrease the potential anti-cancer benefit to you. In addition to certain prescription drugs (which will be evaluated by your doctor). The herbal preparation known as St. John's Wort are CYP3A inducers and should not be taken during your treatment with idelalisib.

Because of these potential drug-drug interactions, it is important that you tell the research doctor about all prescription and non-prescription drugs, vitamins, herbal preparations, nutritional supplements, health foods, street drugs, and birth control methods that you are taking or are planning to take. You should tell any doctor who prescribes medication to you that you are taking idelalisib so that they are aware of these possible interactions. If you are prescribed medication by a doctor who is not part of the study staff, you should tell the study staff what drug you were prescribed before you take it.

If you are not sure, or if you take something you worry that you should not have taken, it is safest to be honest with the study clinic staff. The study clinic staff needs to know what you are taking to protect your health. They can help decide if any of the drugs you are taking need to be stopped or adjusted, or if idelalisib needs to be stopped or adjusted.

Other Medical Problems
Tell your study doctor about any medical problems you have even if you do not think they are caused by the study drug. Ask your study doctor for more information if you have questions or concerns. There may be more risks that are not known or not expected as this is the first time this combination of drugs is being administered. These risks may be new, more severe, or long lasting than seen when these drugs are used alone. These risks may include death.

The study staff will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Biopsy: If you have easily accessible tumors, you will have biopsy samples taken before beginning treatment and before receiving the third cycle of the treatment. There will also be a repeated biopsy of the tumor if relapse in encountered during the follow up period. The biopsies are done under the guidance of either ultrasound or CT scan and up to 3 core needle biopsies less than 1mm in width will be taken of each lesion. These procedures are done to evaluate how your body recognizes and defends itself against cancer. A biopsy is a relatively safe surgical procedure. As with any surgical procedure, you may experience side effects that include pain, infection, temporary swelling/bleeding, tenderness, scarring at the surgical site and allergic reaction to the drugs. The study doctor will give you specific instructions on how to care for your biopsy site and contact information in case of an emergency.

Blood Draw: Symptoms may include bleeding, fainting, injection site infection and/or anemia (low red blood cell levels that could result in tiredness, dizziness, sleeplessness, shortness of breath, leg cramps). Fainting can occur during or after a blood draw in some individuals. Your red blood cell level will be monitored periodically during the study. You may be asked to take iron supplements if your level decreases.

Radiation Exposure: If you take part in this research, you will have a number of radiation procedures or examinations that are part of the regular medical care for your condition and you would have them whether or not you participate in this research. You will not be exposed to any additional radiation because you are participating in this research.

These tests include X-rays, CT scans, and or PET scans, all of which are used routinely to follow up on your condition. The study doctor will decide which test you have, and when you have it, based upon your disease, where it is located, and your progress. You may also have MRI scans, but these do not involve radiation exposure.

Some of the scans could involve “contrast”, which is like a dye injected into the bloodstream, which makes things appear more clearly on the test. Since some of the contrast dyes contain iodine, it is important that you tell the study doctor if you are allergic to iodine.

The study doctors will always try to keep radiation exposure as low as reasonably achievable by choosing tests and procedures that involve the lowest possible exposure while providing the necessary information about your condition.

Women of Childbearing Potential
You cannot participate in this study if you are or plan to become pregnant, or if you are breastfeeding. There may be unknown risks to you, the embryo/fetus or nursing infant if you become pregnant during the study.

You must be using adequate contraception for the duration of the study and for 120 days following your participation. If you become pregnant, suspect pregnancy, if you have a change in your menstrual cycle, or in your contraception method you should immediately contact the study doctor. Should you become pregnant during the study, you will be withdrawn from the study immediately and should seek care from a doctor who specializes in pregnant women (an OB/GYN, or obstetrics and gynecologist physician). The study doctor or any investigator on this study, or Merck and Gilead (the manufacturers of the study drugs), are **not** responsible for any financial aspects of obstetrical, child or related care.

Psycho/Social/Economic Risks: Risks and discomforts not only include physical injury, but also possible psychological, social or economic harm, discomfort or inconvenience, or breach of confidentiality.

Privacy Risk: There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

Unknown Risks: It is possible that the study treatment or procedures may involve risks to you that are not currently known or foreseeable. It is important that you should consult with the treating physician regarding any questions or concerns you may have about the study treatments.

As well as the important possible risks described above patients with different types of cancer who have been treated with pembrolizumab in clinical trials have very commonly (i.e., more than 10% of patients) reported: feeling tired, nausea, vomiting, decreased appetite, shortness of breath, cough, fever and pain in muscles and joints.

Will I benefit from this study?
The possible benefits of this study are: Your tumor may decrease in size or there may be improvement in your symptoms. The likelihood of your benefitting from this study is low.

What are my other choices if I do not take part in this study?
You are not required to take place in this study. Some other options for you are:

- You may participate in other clinical trials

You may receive comfort measures to control symptoms of your disease but without any therapy for your tumor(s). Comfort care includes pain medication and other supportive measures. It aims to maintain your comfort and dignity rather than cure disease. This care may be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

The study staff will discuss these other options with you.

Who will see my study information?
Study team members, the sponsor of the study, and their representatives will be able to see your study information. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include the Augusta University Institutional Review Board (the committee who oversees safety of volunteers in research studies), institutional officials, and outside agencies, such as the Food and Drug Administration (FDA) and the Western Institutional Review Board (WIRB).

Whenever possible, your identifying information will be protected; for example, your name replaced by a study number. Absolute confidentiality cannot be guaranteed because of the need to give information that identifies you to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

How will you keep my study information confidential?
Study records that identify you will be kept confidential except as required by law. You will not be identified in study records or publications disclosed outside Augusta University.

What are my costs (what will it cost me) for taking part in the study?
If you agree to participate in this study, you and/or your insurance will not be billed for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. You will be responsible for all co-pays, deductibles and denied claims.

You have the right to specifically ask what it will cost you to take part in this study. You have the right to contact your insurance company to discuss the costs of your routine care and whether these will be covered if you participate in this study. You may choose not to be in this study if your insurance does not pay for your routine care. In that case, your doctor will discuss other treatment plans with you.

Will I be paid for participation in this study?
You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you think that you have suffered a research related injury seek medical care right away and contact the study team as soon as possible at (706) 721-2505. In the event that this research related activity results in an injury, treatment will be made available including first aid, emergency treatment, and follow-up care as needed. Cost for such care will be billed in the ordinary manner to you or your insurance company. No reimbursement, compensation, or free medical care is offered by Augusta University (AU), AU Medical Center, AU Medical

Associates, AU Dental Associates, AU Nursing Associates, Inc., AU Health Professions Associates, Inc. collectively designated AU Affiliates, or any other facility involved with this study. You do not give up your legal rights by participating in this study.

Who can answer my questions about this study?
You can ask questions about this study at any time. Please contact the study staff listed on page 1 of this document if you have questions about:

- Study procedures or treatments
- Reporting an illness, injury or other problem
- Leaving the study before it is finished
- Expressing a concern about the study
- Any other questions you may have about the study

If you have questions or concerns about the privacy of your information please contact the Enterprise Privacy Officer at 706 721-5631, or through our Toll Free Hotline, 1-800-576-6623. Written inquiries or complaints may be emailed to: privacy@augusta.edu or mailed to the: Enterprise Privacy Officer, Augusta University, C/O Augusta University IRB Office, Pavilion III, CJ-2103, 1120 15th Street, Augusta, Georgia, 30912.

Who can I contact to discuss my rights, problems, concerns, questions, or complaints I have as a study participant?

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who perform independent review of research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Could there be any harm to me if I decide to stop participating in the study before it's finished?
If you decide to stop taking part in the study, the study staff will discuss ways to safely remove you from the study. You should follow the instructions the study staff gives you.

Can I be removed from the study?
Yes, you may be removed from the study if:

- The drug manufacturers or study doctors decide to stop the study.
- Your study doctor stops your taking part in the study for your safety.
- You are not eligible to take part in the study.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow the instructions from the study staff.

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study
If you sign this document, you give permission to Augusta University and AU Affiliates to use or release your health information that identifies you for the study described earlier in this document.

The health information Augusta University and AU Affiliates may use or release for this study includes information in your medical record, results of physical exams, medical history, lab tests or certain health information indicating or relating to your condition.

The health information listed above may be used by and/or released to the following, as applicable:

- Researchers and their staff;
- The sponsor of the study including its agents such as data storage banks or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Health insurers or payers in order to secure payment for covered treatment;
- Parents/Guardians of children younger than 18 years
- Federal/state agencies and Augusta University and AU Affiliates committees having authority over the study. These may include, but are not limited to:
    - The Institutional Review Board (IRB) overseeing this study;
    - Committees with quality improvement responsibilities;
    - Office of Human Research Protections;
    - Food and Drug Administration;
    - National Institutes of Health;
    - Other governmental offices as required by law.

Augusta University and AU Affiliates are required by law to protect your health information. By signing this document, you authorize Augusta University and AU Affiliates to use and/or release your health information for this research.

Once your information has been released outside Augusta University and AU Affiliates, it may no longer be protected by federal laws and regulations and might be disclosed by the persons or institutions receiving the information.

Please note that:

You cannot receive this research-related treatment if you do not sign this Authorization.

Augusta University and AU Affiliates may not withhold treatment whether or not you sign this Authorization.

You may change your mind and take back (revoke) this Authorization at any time. If you revoke this Authorization, Augusta University and AU Affiliates may still use or release health information and any data and/or specimens already obtained about you as necessary for this study. If you revoke this Authorization, you cannot continue to participate in this study. To revoke this Authorization, you must write to the Principal Investigator listed on page 1 of this document.

You may not be allowed to see or copy the study information described on this Authorization as long as the study is in progress. Feel free to ask the study staff if this applies to this study. When the study is complete, you have a right to request a copy of your personal health information collected for the study.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and for conducting public health surveillance, investigations or interventions. No publication or public presentation about the study will reveal your identity without another signed authorization from you.

You will be given a copy of this Authorization. This Authorization does not have an expiration date. If you have questions or concerns about this Authorization or your privacy rights, please contact the Augusta University and AU Affiliates Privacy Officer at 706-721-0900.

Regulations require that you be given a copy of the Augusta University and AU Affiliates Notice of Privacy Practices describing the practices of Augusta University and AU Affiliates regarding your health.

APPROVED
AS MODIFIED
Dec 05, 2017
WIRB®

STATEMENT OF CONSENT

I have read this form and the information in it was explained to me. All of my questions were answered. I agree to take part in this research study. My taking part in the study is voluntary. I will receive a copy of this form for my records. **I am not giving up my legal rights by signing this form.**

_____
Participant's Name (print)

_____ _____ /_____
Participant's Signature Date Time (00:00)

_____
Witness' name (print)

_____ _____ /_____
My signature indicates that I was present during the informed consent process and that informed consent was given freely by the subject. My signature also indicates that I was present when the subject signed the form. Date Time (00:00)

INVESTIGATOR STATEMENT

I acknowledge that I have discussed the above study with this participant and answered all of his/her questions. They have voluntarily agreed to participate. I have documented this action in the participant's medical record source documents or research chart source documents, as applicable. A copy of this signed document will be placed in the participant's medical record or research chart, as applicable. A copy of this document will be given to the participant or the participant's legally authorized representative.

_____
Printed name of Investigator obtaining consent

_____ _____ /_____
Signature of Investigator obtaining consent Date Time (00:00)