MD Anderson IND Sponsor Cover Sheet

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TITLE: Single-arm, phase II trial of **Im**munotherapy with **P**emb**r**ol**i**zumab for the Preve**nt**ion of **Lung** Cancer **(IMPRINT-Lung)**

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1.0 TRIAL SUMMARY

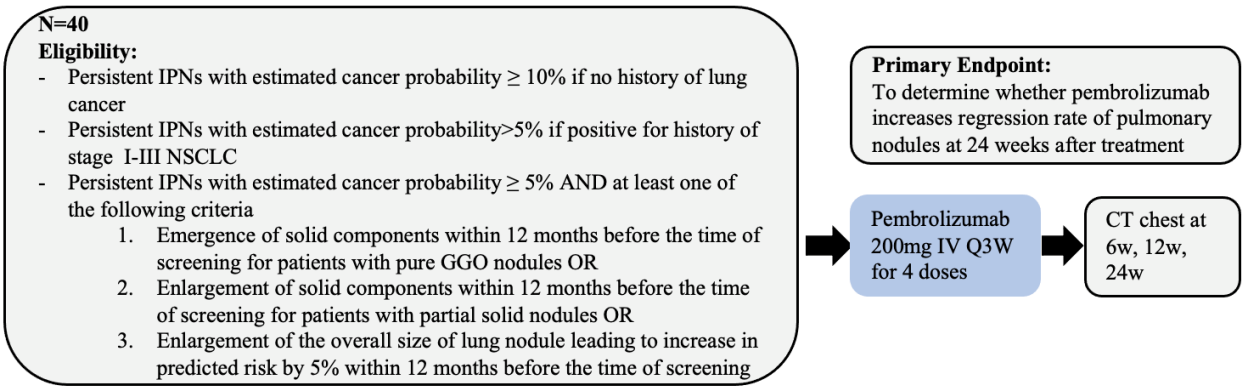
Abbreviated Title	Pembrolizumab for high risk IPN
Trial Phase	II
Clinical Indication	High-risk indeterminate pulmonary nodules
Trial Type	Single arm
Type of control	Standard of care: histological control
Route of administration	Intravenous
Trial Blinding	Open label
Treatment Groups	Pembrolizumab
Number of trial participants	60
Estimated enrollment period	42 months
Estimated duration of trial	48 months
Duration of Participation	8 months
Estimated average length of treatment per patient	12 weeks

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single arm, multi-center, phase 2 study of pembrolizumab in immunotherapy-naïve patients with high-risk indeterminate pulmonary nodules.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine whether immune checkpoint blockade using pembrolizumab eliminates persistent (on two CT scans at least 3 months apart with no evidence of shrinkage or regression) high-risk indeterminate pulmonary nodules (IPNs) at 6 months after initiation of treatment.

Hypothesis: Immune evasion contributes to malignant transformation of pre-neoplastic lung lesions into invasive lung cancers and modulation of immune checkpoint pathways augments immunosurveillance and prevents or delays the development of invasive lung cancers.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine whether immune checkpoint blockade using pembrolizumab decreases the incidence of lung cancers confirmed by histology (biopsy or resection).

(2) To determine whether immune checkpoint blockade using pembrolizumab prolongs cancer free survival (DFS) in patients with high-risk IPNs.
(3) To determine whether immune checkpoint blockade using pembrolizumab prolongs lung cancer-specific survival in patients with high-risk IPNs.
(4) To determine whether immune checkpoint blockade using pembrolizumab prolongs overall survival (OS) in patients with high-risk IPNs.
(5) To assess the safety and tolerability of pembrolizumab in patients with high-risk IPNs.
(6) To assess quality of life patient reported outcomes in patients treated with pembrolizumab.
(7) To determine whether immune checkpoint blockade using pembrolizumab decreases the solid component of high-risk IPNs.
(8) To assess the health-related quality of life (QoL) on subjects enrolled in the study.

3.3 Exploratory Objective

(1) **Objective:** An important aspect of this trial is to identify novel prognostic and predictive markers present at diagnosis, and to determine modulation of markers by immunotherapy in order to inform future translational studies. As such, radiographic data as well as blood and tissues (from either biopsy or surgical resection) will be collected throughout the study period (at MD Anderson and New York University). The markers to be assessed will be determined according to the best scientific knowledge and technology available. Correlative studies will be interpreted as hypothesis-generating data, to be validated in subsequent trials. Candidate markers to be evaluated may include (depending on tissue availability):

1. To explore the radiographic (including radiomic features) evolution of high-risk IPNs with and without treatment of pembrolizumab and to assess their association with risks of risk of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

2. To explore the germline DNA profile and genomic evolution of circulating tumor DNA (ctDNA) of patients with high-risk IPNs and assess their association with risks of risk of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

3. To explore the TCR repertoire evolution of patients with high-risk IPNs and assess their association with risks of risks of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

4. To explore the evolution of serum soluble factors, such as IFN-gamma and interferon inducible factors (such as CXCL9 and CXCL10), IL-12, TNFα, IL-10, TGF-β, VEGF, IL-6, IL-8, IL-17, IL-18, C-reactive protein etc. and assess their association with risks of risks of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

5. To explore the evolution of immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types and assess their association with risks of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

6. To explore the evolution of microbiome and assess their association with risks of lung cancer as well as their association with clinical benefit/toxicities in patients treated with pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including

autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in lung cancer.

The role of Pembrolizumab in treatment of lung cancers: Immune surveillance is an important host protection process inhibiting carcinogenesis and controlling the outgrowth of cancer [1]. The interactions between the host immune system and cancer cells are governed by a complex network of biological pathways. Despite the expectations that the host immune system should automatically attack and eliminate cancer cells as 'foreign,' the molecular evolution of cancer cells can often lead to tolerance, representing a natural balance between the immune system and cancer, which is maintained by regulatory immune cells, immunosuppressive cytokines and chemokines, and immune checkpoint pathways. The programmed cell death protein 1 (PD1) – PD1 ligand 1 (PDL1) receptor–ligand pair is a dominant immune checkpoint pathway that can be induced in cancer cells to suppress host anti-tumor immune functions and evade immune attack [2,3]. Monoclonal antibodies (mAbs) that block this pathway have shown great clinical benefit to patients with various cancer types including NSCLC [4-10].

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 demonstrated significant improvement in overall survival in patients with metastatic NSCLC with progression on or after platinum-based chemotherapy as compared with standard of care second-line chemotherapy agent docetaxel and was approved in the United States for the treatment of patients with metastatic NSCLC in the second-line setting [11]. Most recently, the results from KEYNOTE-024 have shown Keytruda was associated with longer progression-free and overall survival than platinum-based combination chemotherapy in patients with previously untreated advanced NSCLC and a PD-L1 tumor proportion score of 50% or greater, and has become the only PD-1 inhibitor approved for the treatment of advanced NSCLC in the first line setting. Pembrolizumab is very well tolerated and has shown favorable toxicity profiles in multiple studies [11-14].

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Indeterminate pulmonary nodules and preinvasive neoplastic lung lesions: Despite advances in its management, lung cancer remains the leading cause of cancer-related deaths worldwide. One major problem is that most lung cancer patients are diagnosed at an advanced stage of disease, when cure is less feasible. Low-dose helical CT screening (LDCT) was demonstrated to result in a reduction in lung-cancer mortality of 20% in former and current heavy smokers compared to chest x-rays, advocating the importance of early detection and early intervention [15].

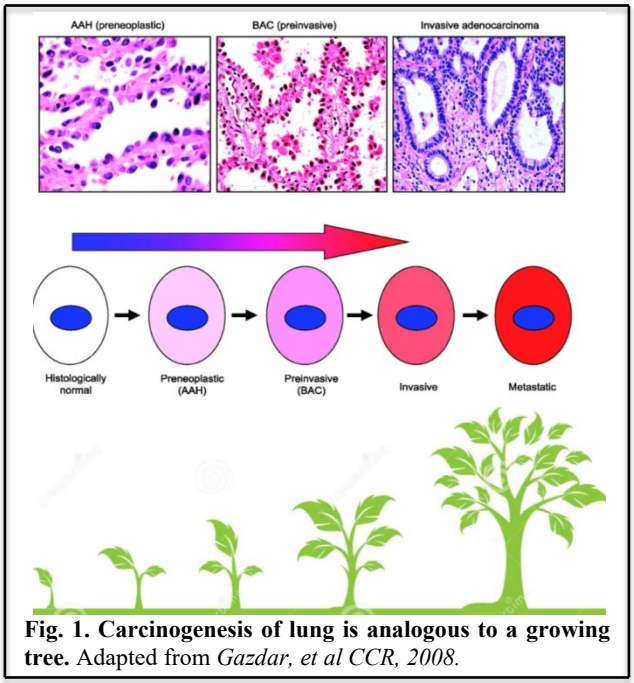


Fig. 1. Carcinogenesis of lung is analogous to a growing tree. Adapted from *Gazdar, et al CCR, 2008.*

Furthermore, growing implementation of LDCT-guided screening and the advent of high resolution CT for diagnostic imaging have resulted in a dramatic increase in the number of indeterminate pulmonary nodules (IPN) identified, most of which present as ground glass opacities (GGOs) [15]. As reported in the initial LDCT screening study, nearly 30% of subjects were found to have pulmonary nodules, the majority of which were IPNs [15]. Clinicians have encountered a tremendous increase in number of patients with IPNs. While many of these lesions may be resected with minimal morbidity, the cost and relevance of surgical resection have been called into question [16]. In addition, multifocality is a relatively common occurrence, with up to 25% of the patients harboring multiple IPNs [17,18], which makes surgical resection more challenging. Chemoprevention is a theoretically appealing approach to reduce lung cancer incidence and mortality. However, randomized trials have produced only disappointing results to date [19-27]. This may be due to the constellation of many factors including the lack of reliable molecular biomarkers to identify high-risk patients, the lack of appropriate molecular targets, and the lack of appropriate drugs based on our rudimentary knowledge on early carcinogenesis of lung cancers.

Over the past decade, progress has been made in our understanding of early non-small cell lung cancer (NSCLC) [28]. Historically, GGOs have been the most common type of IPNs that were thought to correlate with the fairly imprecise category of bronchioloaveolar carcinomas (BAC) if they persisted or grew. In early 2011, the IASLC/ATS/ERS jointly proposed a reclassification of BAC to highlight the spectrum of invasiveness that may be delineated within this group of lesions. It has been postulated that atypical adenomatous hyperplasia (AAH) represents a preneoplastic lung lesion that can progress to adenocarcinoma in situ (AIS), to minimally invasive adenocarcinoma (MIA), and further to frankly invasive adenocarcinoma [29]. However, the biological nature of these lesions is poorly understood and the definition and management of these lesions remain controversial [30].

Investigations into the early carcinogenesis of lung cancer are difficult due to the unpredictable clinical course of these preinvasive lesions, lack of specimens to study due to the small size of

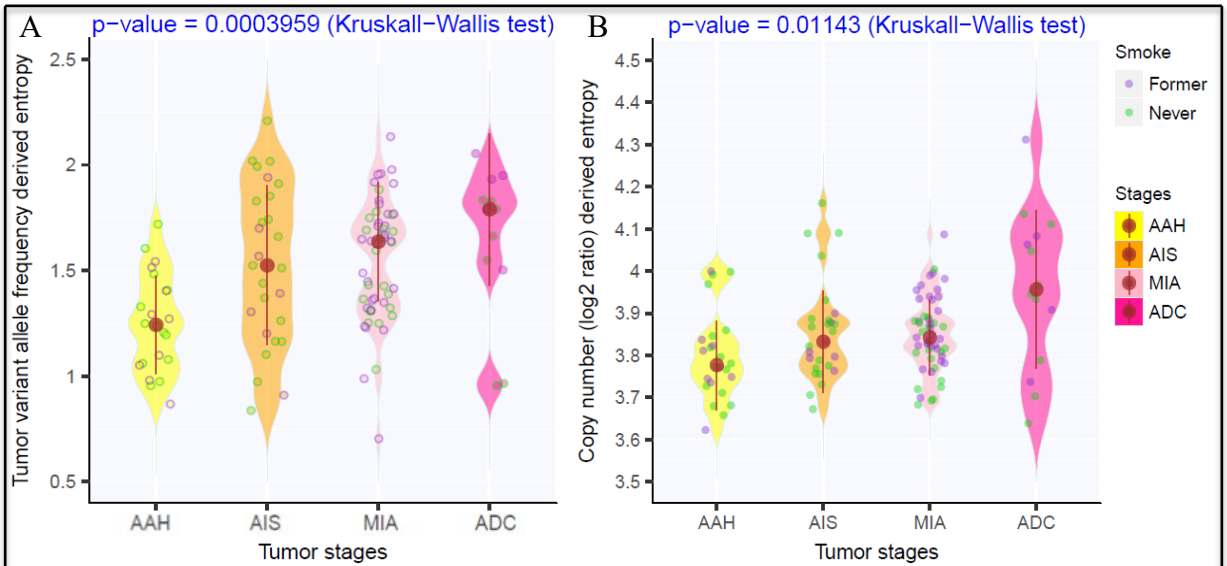


Fig. 3. Genomic heterogeneity evolution during early carcinogenesis of lung adenocarcinoma. A. Progressive increase of somatic mutation heterogeneity with disease evolution. Median tumor variant frequency derived entropy (Shannon index) in the AAH, AIS, MIA and ADC stages was labeled by solid brown dots. **B. Progressive increase of copy number aberration heterogeneity with disease evolution**. The median log2 ratio of segments derived entropy in the AAH, AIS, MIA and ADC stages was labeled by solid brown dots, each small dot represent entropy in one lesion Hu, *et al*, *WCLC, 2017*.

these lesions, and the challenge in obtaining longitudinal samples at different time points of disease progression.

It has been proposed that carcinogenesis results from accumulation of molecular events in a branched evolutionary model like a growing tree (**Fig. 1**) [31-34]. The trunk harbors early founder mutations, while the branches represent subsequent mutations acquired later during carcinogenesis. Multi-region sequencing can depict genomic events to their relative molecular time with early trunk mutations ubiquitously present in every tumor region and late branch mutations confined to spatially separated tumor regions (**Fig. 2**). Using this approach, our recent work has delineated the genomic evolution of 11 early stage lung adenocarcinomas (8 stage I, 2 stage II and 1 stage III) and demonstrated that 20/21 known cancer gene mutations were early genetic events (**Fig. 2**). In addition, our results suggested that complex genomic heterogeneity is associated with inferior survival in patients with early stage lung cancers[35]. With the intent to delineate the pivotal molecular events driving early carcinogenesis of lung cancer, we have collected 154 resected GGOs and matched normal lung tissues. The pathology of these GGOs ranges from preneoplastic lesions (AAH) to preinvasive cancers (AIS) to early invasive cancers (MIA) and invasive lung cancers. Using the same multi-region exome sequencing approach, our prelim data have demonstrated that with disease evolution from AAH, to AIS, MIA and ADC, genomic landscape has become progressively more complex including mutation burden, APOBEC signature and genomic heterogeneity (**Fig. 3**)[36].

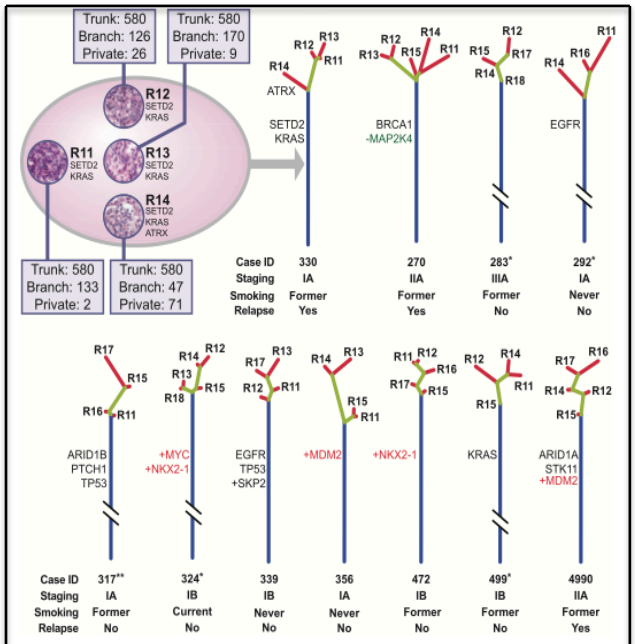


Fig. 2. Phylogenetic trees of 11 localized lung adenocarcinomas. The lengths of trunks and branches are proportional to the numbers of mutations acquired on the corresponding trunks or branches. Known cancer gene mutations are mapped to the trunks/branches: point mutation, amplification (+) and deletion (-). *Patients who have had relapse. Adapted from Zhang, *et al*, *Science 2014*.

The rationale of using pembrolizumab for immunoprevention of NSCLC: Although immune checkpoint blockade therapy has demonstrated unprecedented rates of durable clinical benefits in patients with various cancer types, the response rate is only modest for patients with advanced NSCLC[4-10]. While tremendous efforts are being made to increase the response rate in patients with advanced disease, there has been increasing enthusiasm for the use of immune checkpoint blockade to treat early-stage NSCLC in the adjuvant or preoperative setting [37] because early-stage cancers theoretically have less "immunoediting" capacity than cancers of advanced stages, thus may potentially respond better to immunotherapy than advanced diseases [38]. Immunoediting is a dynamic interaction between the host immune system and evolving tumor cells. It is made up of three phases: elimination, equilibrium, and escape. The elimination phase refers to the phase when host innate and adaptive immune responses are able to eradicate tumor cells of early carcinogenesis when the cancer cell molecular architectures are relatively simple. With selection and evolution, cancer cells become molecularly more complex and cancer immunoediting enters the next phase, equilibrium, during which tumor cells that have escaped elimination and have a non-immunogenic phenotype are selected for growth. During this phase, new tumor cell variants emerge with various mutations that further increase overall resistance to immune attack. The last phase of immunoediting is the escape phase when tumor cell variants selected in the equilibrium phase have breached the host immune defenses, with various genetic and epigenetic changes conferring further resistance to immune detection[39]. Our recent work has demonstrated that heterogeneous T cell

repertoire is associated with heterogeneous genomic landscape and increased risks of postsurgical recurrence in patients with early stage lung adenocarcinomas (**Fig. 4**) suggesting the complex interaction between evolving tumors and host immune surveillance[40].

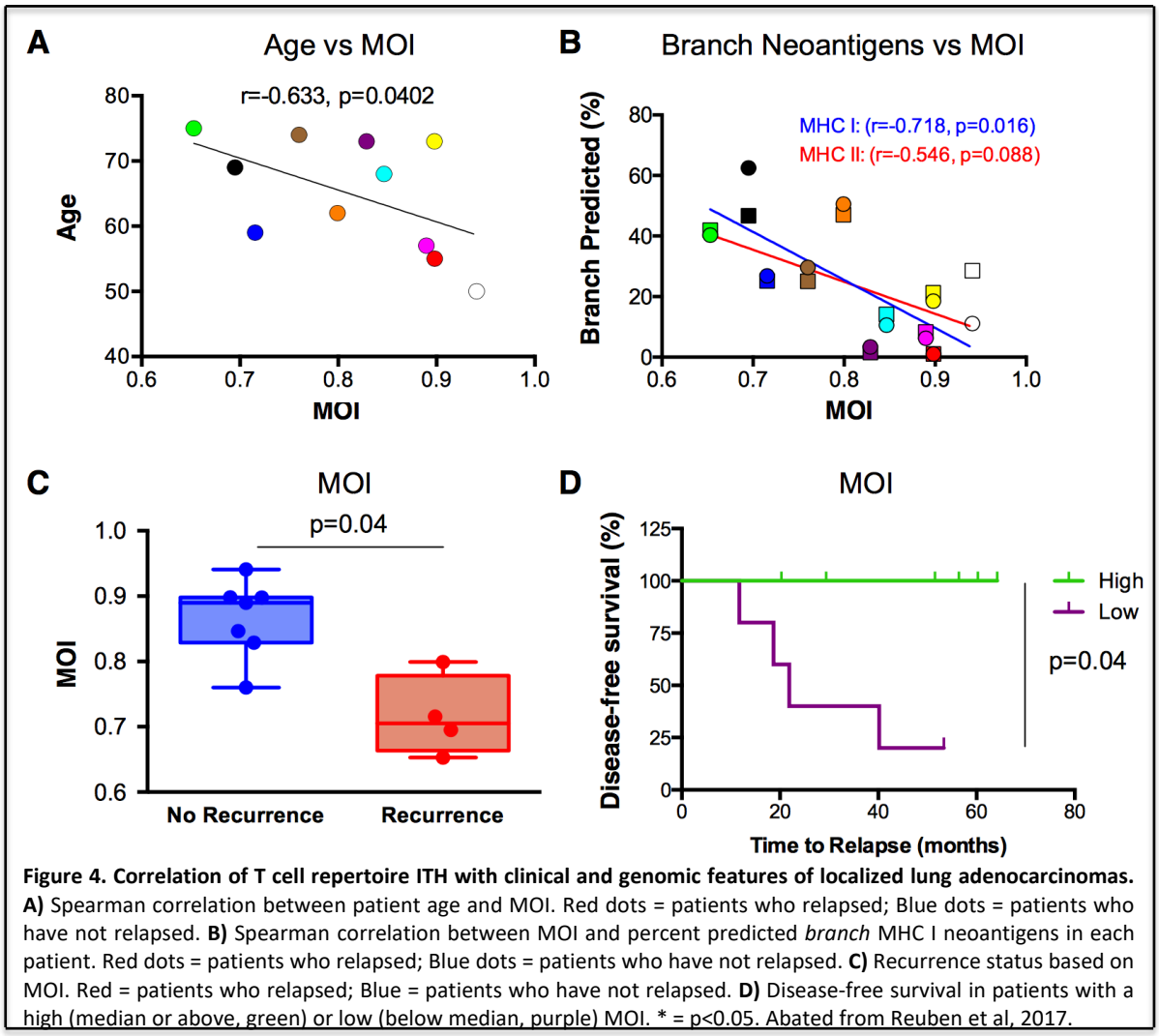


Figure 4. Correlation of T cell repertoire ITH with clinical and genomic features of localized lung adenocarcinomas. **A)** Spearman correlation between patient age and MOI. Red dots = patients who relapsed; Blue dots = patients who have not relapsed. **B)** Spearman correlation between MOI and percent predicted *branch* MHC I neoantigens in each patient. Red dots = patients who relapsed; Blue dots = patients who have not relapsed. **C)** Recurrence status based on MOI. Red = patients who relapsed; Blue = patients who have not relapsed. **D)** Disease-free survival in patients with a high (median or above, green) or low (below median, purple) MOI. * = p<0.05. Abated from Reuben et al, 2017.

Evidence has started to emerge suggesting that late stage cancer may have more prominent "immunosuppressive" microenvironment than early stage cancers. A large meta-analysis study on the prognostic influence of tumor infiltrating lymphocytes (TIL) has demonstrated TIL density was associated with survival across different cancer types, supporting the protective role of host anti-tumor immune response. However, the protective impact of TILs faded away in later stage cancers, suggesting a more immunosuppressive tumor microenvironment may have developed in advanced cancers [41]. Our analyses on gene expression profiles of TCGA lung adenocarcinoma cohorts revealed significantly higher immune scores in early stage cancers than later stage cancers (**Fig. 5A.**). Given the important role of T cells in anti-tumor immune response, we have recently investigated the T cell receptor repertoire of resected NSCLC. Our data has demonstrated that T cell infiltration is significantly prominent in smaller tumors than larger tumors (**Fig. 5B.**). Taken together, these findings suggest that early-stage lung cancers may have less immunosuppressive microenvironment, thus may respond better to immune checkpoint blockade. At the 2016 ESMO Congress in Copenhagen, Forde et al. reported data from 16 patients with Stage I-IIIA NSCLC who received two doses of nivolumab, an PD1 mAB, at four and two weeks prior to surgical resection. The investigators found that 11 of 15 patients (73%) had regression of their tumors, including 6 of 15 patients (40%) demonstrating major pathological regression, defined as either a complete pathologic response or isolated remaining tumor cells (less than 10% viable tumor cells) following treatment with nivolumab. Although the sample size was small, the response rate is very encouraging compared to the 20% response rate to nivolumab in patients with advanced NSCLC [4-10].

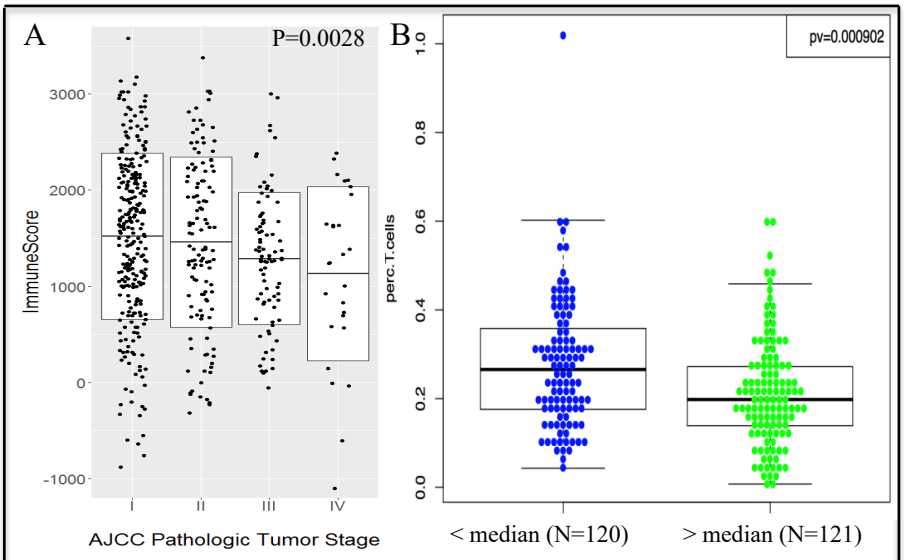


Fig. 5. Advanced cancers may have more immune suppressive microenvironment. A. Different tumor infiltrating immune scores in TCGA lung adenocarcinomas by staging. Immune scores are derived from gene expression profiles using ESTIMATE algorithm. **B. Different T cell density in resected NSCLC by tumor size.** T cell density is measured by T cell receptor sequencing and presented as percent nucleated cells in each resected NSCLC tumor.

According to the concept of immunoediting, preneoplastic lesions (such as AAH) and preinvasive lung cancers (such as AIS) may have even less suppressive immune microenvironment and thus may respond even more favorable than localized lung cancers. However, because of the challenge of obtaining study materials, the immune landscape of preneoplastic lesions (AAH), preinvasive (AIS) and minimally invasive lung cancer (MIA) has not been systemically studied. Our preliminary data leveraging the large cohort of resected GGOs has suggested more active immune microenvironment in preneoplastic and preinvasive stages. With disease evolution from AAH to AIS, MIA and ADC, there progressive decrease in infiltrating T cell density, progressive decrease in TCR clonality, an indicator for T cell expansion and activation as well as progressive increase in TCR inverse Simpson evenness suggesting progressive immunosuppressive microenvironment with disease evolution (Fig. 6)[36].

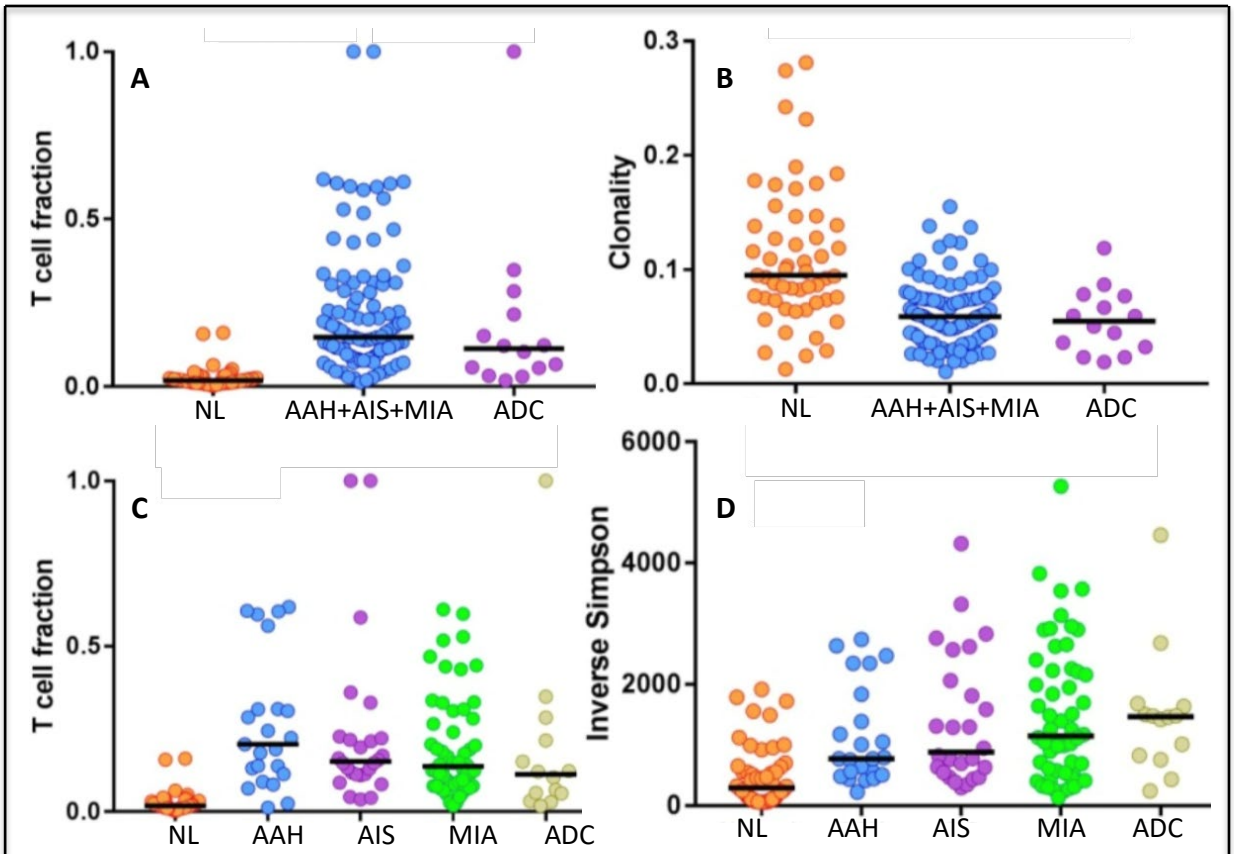


Figure 6. Progressive TCR repertoire evolution from preneopalstic stage to invasive lung adenocarcinoma. A) Infiltrating T cell density is higher in invasive lung adenocarcinomas (ADC) compared to normal lung, but numerically lower than neoplastic lesions of earlier stages. **B)** TCR clonality is lower in invasive lung adenocarcinomas (ADC) compared to neoplastic lesions of earlier stages. **C)** Progressive decrease in T cell density from AAH, to AIS, to MIA and ADC. **D)**. Progressive increase in T cell inverse Simpson evenness from AAH, to AIS, to MIA and ADC. Abated from Hu et al, WCLC, 2017.

The efficacy of immune checkpoint blockade in the treatment of human preneoplastic disease is unknown. Our most recent data in 4-Nitroquinoline-1- oxide (4-NQO) mouse model and Kras-mutant genetically engineered murine lung cancer model has demonstrated that PD1 blockade increases CD4+ and CD8+ T cell infiltration preneoplastic diseases and prevents progression of preneoplasia into invasive cancers (**Fig. 7**)[42].

Taken together, the above findings provide the basis for our primary hypothesis that **immune evasion contributes to malignant transformation of pre-neoplastic lung lesions into invasive lung cancers and that modulation of immune checkpoint pathways augments immunosurveillance and prevents or delays the development of invasive lung cancers.** We therefore propose the single-arm, phase II trial of immunotherapy for the prevention of non-small cell lung cancers using pembrolizumab.

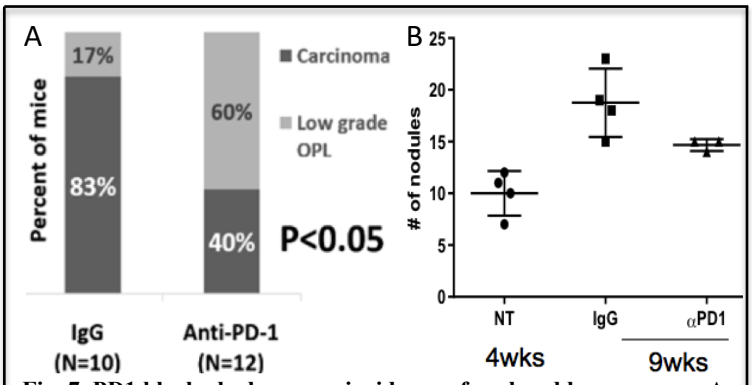


Fig. 7. PD1 blockade decreases incidence of oral and lung cancers. A. Treatment with PD1 blockade significantly decreases incidence of severe dysplasia and oral cancer compared to IgG control in 4-Nitroquinoline-1-oxide mouse model. Adapted from Wang et al, 2017. B. Treatment with PD1 blockade decreases incidence of lung adenocarcinoma in KRAS mutant genetically engineered murine model. NT: no treatment. Heymach Lab, unpublished data.

4.2.2 Justification for Dose, Schedule, and Treatment Duration

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). KN10 dosing was q 3 weeks for both 2 and 10 mg /kg. All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

The treatment duration of 4 doses was chosen to balance the therapeutic efficacy and risks of adverse effects. Currently, metastatic NSCLC patients receive pembrolizumab treatment for up to 2 years[11,12]. In neoadjuvant clinical trials, early stage NSCLC patients typically receive 2 to 3 doses of immune checkpoint blockade agents to avoid delay of surgical resection (the definitive treatment), and have shown promising anti-tumor activity and safety profiles[43-45]. The current study is the first clinical trial using an immune checkpoint blockade agent for lung cancer prevention, thus, there is no concern for delay of definitive treatment. On the other hand, since the study subjects will be patients without definitive cancer diagnosis, we want to limit the treatment doses to avoid accumulative toxicities. Therefore, we have designed this study using 4 doses of pembrolizumab. In patients with metastatic non-small cell lung cancer treated with pembrolizumab in the second-line setting for up to 2 years, the rate of toxicity leading to discontinuation of treatment is only 8%. Although these patients do not have a diagnosis of cancer, they are at a high risk (at least 15%) of developing cancer. An ongoing cancer prevention trial for high-risk oral intra-epithelial neoplasias titled "Personalized, randomized, phase 2 study of pembrolizumab for high risk oral intra-epithelial neoplasias"[46] also uses 4 doses of pembrolizumab.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Surrogate markers to assess efficacy of treatment in individuals with high-risk IPNs are yet to be developed. As a "signal-finding" study, we selected "regression of high-risk IPNs" based on modified RECIST criteria detailed below in Table 1 at 6 months after initiation of treatment as the primary efficacy endpoint to have an early readout. Although there is the concern that response rates would inaccurately ascertain the efficacy of the agent, we believe that regression of high-risk IPNs will be translated into preventing invasive cancers in a good number of patients because a high-risk population is targeted for this study. In the meanwhile, in order to truly evaluate the possible effects of pembrolizumab in reducing development of invasive cancer, decreasing the solid component of high-risk IPNs, reduction of incidence of histologically proven cancer, prolongation of cancer free survival and overall survival have been selected as secondary endpoints.

Table 1 Evaluation of Target and Non-target Lesions by Response Evaluation Criteria in Indeterminate Pulmonary Nodules

Response Assessment	Modified RECIST Guideline***
Evaluation of target lesions*	
CR	Disappearance of all target lesions
PR	≥ 30% decrease in the sum of the longest diameters of target lesions compared with baseline
PD	≥ 20% increase in the sum of the longest diameter of target lesions compared with baseline or the appearance of one or more new lesions with predicted cancer risk > 15% by Brock criteria
SD	Neither PR or PD
Evaluation of non-target lesions**	
CR	Disappearance of all non-target lesions
Incomplete response, SD	Persistence of one or more non-target lesions
PD	Appearance of one or more new lesions with predicted cancer risk > 15% by Brock criteria regardless of shrinkage or disappearance of existing IPNs

Note—CR = complete response, PR = partial response, PD = progressive disease, SD = stable disease.
* Target lesions: Each pulmonary nodule will be identified and assessed using Brock University criteria described above. Pulmonary nodules with predicted cancer risk > 5% for patients with no history of lung cancer or >10% for patients with history of stage I-III NSCLC who complete surgery and standard adjuvant chemotherapy if indicated will be identified as the targeted lesions. Patients with IPNs that are difficult to uniquely identify or follow will be excluded.
** Nontarget lesions: Other pulmonary nodules that can be uniquely identified and followed, but do not meet the criteria for target lesions will be identified as nontarget lesions.
*** Ground-glass nodules/opacities will be evaluated and measured on CT lung window setting (WL -600, WW 1500).

4.2.3.2 Biomarker Research

There is substantial interest in identifying biomarkers predictive of response to immune checkpoint inhibitors in invasive solid tumors and the same principles apply to the setting of preinvasive lung neoplastic lesions. Furthermore, the interactions of non-invasive lesions with the immune system, microbiome, and genetic and epigenetic changes in the epithelium, and how they are influenced by PD-1 blockade are largely unknown. As such, the biomarkers to be evaluated on this study aim at:

(1) understanding the risk of malignant transformation in individuals exposed or not to pembrolizumab, thus providing novel prognostic markers for risk assessment
(2) identifying the population more likely to benefit from pembrolizumab
(3) characterizing the immune response in the setting of non-invasive lesions, before and after treatment
(4) evaluating the interplay between the immune system, the microbiome, the non-invasive epithelial lesions, and their genetic, epigenetic, transcriptomic and phenotypic changes before and after treatment with pembrolizumab.

Because the biomarker research embedded in this protocol is exploratory, a broad panel of markers will be studied, utilizing the most updated knowledge from other clinical and pre-clinical studies related to the biology of high-risk IPNs and immune checkpoint blockade at the time of the analysis.

4.2.4 Rationale to make updated the current IMPRINT-Lung protocol

IMPRINT-Lung was initiated in November 2018. As a novel trial in this space, it has raised a lot of interest in the medical community and patients. It has been showing very good safety profile, but there are a couple of issues. 1) The enrollment has been slow. One major reason was that many motivated patients declined the trial because it is a randomized trial. Therefore we propose to change it to a single arm study based on histologic data and patients in our database. In our database, if IPNs are persistent (2 CT scans, 3 months apart), the predicted risk score is >3%, the spontaneous regression rate is 0. 2) The current inclusion criteria miss some real high-risk IPNs. The current risk score based on Brock algorithm gives one snapshot of the disease course while it is well known the change of property of nodules (emergence of solid component in pure GGO IPNs or enlargement of solid component in partial solid IPNs even the size of the IPNs does not increase) is associated with risk of lung cancer development. ~~Therefore, we add additional inclusion criteria listed below to increase the predicted risk and lower the spontaneous regression rate.~~ 3) In this high risk yet non-cancer population, more safety measures, particularly pulmonary functions, should be incorporated when enrolling patients. Therefore, we propose the following changes.

1. Change IMPRINT-lung to a single arm study without observation arm.
2. Add exclusion criteria:
    a. Patient has lung diseases requiring oxygen supplement.
    b. ~~Patient with lung diseases requiring steroids treatment.~~ Patients has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

    c. Patient has other lung diseases requiring steroids treatment (10mg of prednisone or equivalent) within 4 weeks at the time of screening.

3. Add the following inclusion criteria.
    a. With or without personal history of lung cancer AND
    b. Predicted risk > 5% at the time of screening AND
    c. Emergence of solid components within 12 months before the time of screening for patients with pure GGO nodules OR
    d. Enlargement of solid components within 12 months before the time of screening for patients with partial solid nodules OR
    e. Enlargement of the overall size of lung nodule leading to increase in predicted risk by 5% within 12 months before the time of screening

Patients who are currently on the observation arm will continue tumor imaging, survival status, SAEs and QLQ-C30 and EORTC QLQ-LC29 at 3 and 6 months as previously planned. These patients who completed 6 months on observation arm can have the option to receive pembrolizumab.

4.2.5 Risk/Benefit Ratio

This protocol has been carefully designed to optimize the risk / benefit ratio, as outlined below:

(a) Selection of a high-risk patient population. The patients enrolled in this study are at high risk for developing invasive lung cancers. For patients with no personal history of lung cancer, we choose patients detected with IPNs of cancer probability 10% at least using validated predicting algorithms. We will also enroll patients with IPNs and a history of lung cancer and patients with progressing IPNs (emergence of solid component, enlargement of solid component or enlargement of overall size of IPNs). For these patients, there is no reliable predicting algorithms, but are known to be at high risk of developing into cancer. Therefore, a big portion of the study population will develop into invasive cancer if untreated and the current standard of care is observation.

(b) Selection of regression of high-risk IPNs as the primary endpoint. The widespread use of CT for lung cancer screening and other reasons has resulted in a dramatic increase in the number of IPNs. While many of IPNs can be resected with minimal morbidity, the cost has been called into question. Furthermore, multifocality is a relatively common, which makes decisions on extent of surgical resection and potential benefit less clear. Treatment of diagnosed lung cancers on the other hand entails surgery, radiation and systemic, that may result in treatment-related complications (e.g., infections, pneumonias, radiation-induced pulmonary fibrosis, cisplatin-induced neuropathies, renal failure and ototoxicity). As such, a reduction in high-risk of IPNs and potentially the incidence of lung cancer may lead to lesser need for morbid therapeutic interventions, possibly improving functional outcomes.

(c) Selection of an immunotherapy drug with a favorable adverse event profile. In contrast to anti-CTLA4 drug ipilimumab, the anti-PD-1 antibody pembrolizumab has been shown to have a more favorable adverse event profile.[15] In randomized studies comparing pembrolizumab to docetaxel, pembrolizumab was also found to have a lower incidence of toxic effects[16]. The tables below outline the incidence of adverse events associated with pembrolizumab single agent in a clinical trial including 550 NSCLC patients (an FDA-approved indication for the drug). The overall incidence of grade 3-5 adverse events was 9.5%. While severe immune mediated adverse events may occur, the incidence was low (3.8% grade 3-5), fatalities were extremely rare (0.2%), and the vast majority of patients (69.3%) exhibited complete resolution of toxicities to grade 0.

Table 2 Immune-Mediated AE Summary in patients with metastatic non-small cell lung cancer treated with pembrolizumab in the KEYNOTE-001 study

Category	Total N-550
Any, n (%)	80 (14.5)
Grade ≥3, n (%)	21 (3.8)

Led to death[a], n (%)	1 (0.2)
Let to discontinuation, n (%)	15 (2.7)
Events resolved [b,c], %	69.3

[a]Pneumonitis. [b]Includes all events of any grade, excluding hypothyroidism. [c]Resolution is defined as a return to grade 0 or baseline. Data cutoff date: January 23, 2015

Table 3 Adverse Events in patients with NSCLC treated with pembrolizumab in KEYNOTE-001*

Adverse Events	Any Grade	Grade 3-5
	no. of patients (%) N=495 total patients	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

* Listed are events that were considered to be related to treatment by the investigator and were reported in at least 2% of patients.
† Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.

(d) Selection of a short treatment course. The three-month treatment period utilized within this protocol is likely to reduce the incidence of adverse events and/or limit their duration.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Patients with no history of lung cancer who are identified with IPNs detected by lung cancer screening or imaging studies for any reason (incidentolomas) with cancer probability at least 10% will be screened for the study. For patients who have a history of lung cancer status post treatments with curative intent who presented with persistent IPNs will also be screened for this study.

1. Participants are eligible to be included in the study **only if one** of the following criteria applies:

    a. Patients with no history of lung cancer, who have IPNs detected by LDCT-guided lung cancer screening or imaging studies for other reasons (incidentalomas) with 10 - 30% cancer probability by Brock University cancer prediction equation as following[47]. This is one of the most frequently utilized cancer risk prediction equations and has been confirmed to be highly effective in catching the disease in its very early stages by large national studies[48].
    b. Patients with no history of lung cancer, who have IPNs detected by LDCT-guided lung cancer screening or imaging studies for other reasons (incidentalomas) with > 30% cancer probability by Brock University cancer prediction equation as following, but biopsy reveals no clear evidence of malignancy.
    c. Patients with history of Stage I-III NSCLC, who have completed curative treatment (surgery and/or radiation) with or without chemotherapy, who have persistent IPNs (on two CT scans at least 3 months apart with no evidence of shrinkage or regression) with 5-30% cancer probability by Brock University cancer prediction equation as following.
    d. Patients with history of Stage I-III NSCLC, who have completed curative treatment (surgery and/or radiation) with or without chemotherapy, who have persistent IPNs (on two CT scans at least 3 months apart with no evidence of shrinkage or regression) with > 30% cancer probability by Brock University cancer prediction equation as following, but biopsy reveals no clear evidence of malignancy.
    e. Persistent IPNs with estimated cancer probability $\geqslant$ 5% AND at least one of the following criteria
        i. Emergence of solid components within 12 months before the time of screening for patients with pure GGO nodules OR
        ii. Enlargement of solid components within 12 months before the time of screening for patients with partial solid nodules OR
        iii. Enlargement of the overall size of lung nodule leading to increase in predicted risk by 5% within 12 months before the time of screening

Log odds = (0.0287 * (Age - 62)) + Sex (female= +0.6011; male = 0) + Family History Lung Cancer (yes= + 0.2961; no=0) + Emphysema - (5.3854* ((Nodule size/10)$^{-0.5}$ - 1.58113883)) + Nodule type + Nodule Upper Lung - (0.0824 * (Nodule count - 4)) + Spiculation - 6.7892.

Cancer probability = 100 * ($e^{(Log\ odds)}$ / (1 + $e^{(Log\ odds)}$))

Brock University cancer prediction equation. This calculator estimates the probability that a lung nodule described above will be diagnosed as cancer within a two to four year follow-up period. Equation parameters, such as Sex, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, eg, (0.6011), represent the values that will be used[47].

2. Male/female participants who are at least 18 years of age on the day of signing informed consent with diagnosis of high-risk IPNs as defined below will be enrolled in this study.

3. A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 12 weeks while receiving pembrolizumab plus an additional 120 days (a spermatogenesis cycle) for study treatments with evidence of genotoxicity at any dose after the last dose of study treatment and refrain from donating sperm during this period.

4. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3 OR
   b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days for study treatments with risk of genotoxicity after the last dose of study treatment.

5. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of study enrollment.

7. Have adequate organ function as defined in the following table (Table **4**). Specimens must be collected within 10 days prior to the start of study treatment.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	

Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation[c]	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

[c] PT(INR),aPTT only required for patients having a biopsy and/or if clinically indicated

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study **if any** of the following criteria apply:

1. Patient has lung diseases currently requiring oxygen supplement.
2. Patients has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
3. Patient has other lung diseases requiring steroids treatment (10mg of prednisone or equivalent) within 4 weeks at the time of screening.
4. A WOCBP who has a positive urine pregnancy test within 72 hours prior to treatment (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: in the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
6. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks [could consider shorter interval for kinase inhibitors or other short half-life drugs] prior to treatment.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

7. Has received prior chest radiotherapy and the radiation field overlaps with IPNs.
   Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.
   Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

9. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

10. Has a known additional metastatic malignancy that is progressing or requiring active treatment. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ), or potentially curable early-stage malignancies including localized NSCLC, head and neck squamous carcinoma, breast cancer, bladder cancer etc., that have undergone potentially curative therapy (surgery and/or radiation with or without chemotherapy) are not excluded.

11. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

12. 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has an active infection requiring systemic therapy.

14. Has a known history of Human Immunodeficiency Virus (HIV).

15. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

16. Has a known history of active TB (Bacillus Tuberculosis).

17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the

full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

18. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

19. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, 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 Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 Use in Nursing Women

It is unknown whether pembrolizumab 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, participants who are breast-feeding are not eligible for enrollment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table **5**.

Table 5 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 weeks cycle for 4 cycles	Experimental

5.2.1 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 7 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 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).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.2 Dose Modification and toxicity management <u>for immune-related AEs associated with pembrolizumab</u>

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table **6**.

5.2.3 General description on the assessment of health-related quality of life (QoL)

To assess the health-related quality of life (QoL) of subjects enrolled in the study, we will apply two validated instruments, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire (EORTC QLQ-C30) as well as the Quality of Life Lung Cancer 29 Module (EORTC QLQ-LC29) (it will be used in conjunction with EORTC QLQ-C30), to all enrolled subjects. These two questionnaire will be given at three time points: (1) at baseline (screening visit 2) after signing the informed consent form but prior to the first dose treatment , (2) at completion of treatments, i.e., end of cycle 4 (approximately 3 months after the

first dose of treatment) or at time of treatment termination, and (3) at 6 months follow-up after treatment initiation. The goal is to assess the QoL of patients treated with pembrolizumab.

The QLQ-C30 consists of 30 items covering five function subscales (physical, role, emotional, cognitive and social), nine symptom subscales/items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties) and a global health/QoL subscale.

EORTC QLQ-LC29 provides 29 items, retained 12 of the 13 original EORTC QLQ-LC13 items to access cough, short of breath, sore mouth/tongue, swallowing, tingling in hands or feet, hair loss, pain, etc; supplemented with 17 items to primarily assess side effects of targeted therapy, radio-chemotherapy, and thoracic surgery etc. Several studies have validated and applied these two QoL instruments in both healthy populations and lung cancer patients.[49-53]

Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver

Increased bilirubin	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of		

		event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table **7**.

Table 7 Pembrolizumab Infusion Reaction Dose modification and 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
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: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants 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.

5.3 Treatment Allocation

Patients seeking treatment at one of treatment sites will be screened for this trial. Subjects may also be identified at the multidisciplinary planning conferences, or through databases maintained by the Thoracic Program or other departments. Patients in these databases who have a diagnosis of IPN may be contacted by phone or mail or during their clinic visits at one of the treatment sites to offer participation in the study.

Study-related procedures must not commence before obtaining consent. However, results from assessments performed before obtaining informed consent that are considered "routine standard of care" (e.g., laboratory results, CT scans, etc.) may be used to determine eligibility.

This will be a single arm study of 40 eligible patients. No randomization will be performed. To account for 8 patients enrolled in the early phase of the study who did not receive treatment, the total enrollment was set at 48 patients. The sample size will be increased to 60 patients to yield the 40 eligible patients. The sample size of 60 randomized patients will not change the preplanned analysis of 40 eligible patients as it is recommended for screen failures and early drop outs/therapy discontinuation during or at response.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participants' primary physician.

5.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Clinical data capture called DMI (Data Management Initiative) will be the electronic database used for this study's electronic case report forms. 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 may 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 after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

Participants 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
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- 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 study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

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

5.4.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, [Table **4**]. Where appropriate, these guidelines include the use of oral or IV 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.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table **6** in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **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 liothyroinine, 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**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **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.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table **8** below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8 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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS 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 premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: 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.		

5.5 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose.

- Administrative reasons

5.6 Participant Replacement Strategy

MD Anderson is well suited to identify patients with high-risk IPNs. The MDA Lung Cancer Screening Trial (MST; PI Hanash, a collaborator of this trial), a multi-site trial will be the major source for high-risk IPN patients without personal history of lung cancer. More than 1,000 individuals have enrolled thus far. In addition, chest CTs are routinely applied for imaging surveillance of cancer patients at MD Anderson that will provide a big cohort of patients with high-risk IPNs with or without personal history of lung cancer. Dr. Antonoff, a collaborator of this trial has identified 35,386 MD Anderson patients with GGOs on chest CT scans and 1,491 patients have had at least two chest CT scans[54]. In addition, IPNs have become a very common clinical entity that is frequently encountered in the clinic. We are therefore very confident that we will be able to successfully accrue patients as planned.

5.7 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 participants

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

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase		Treatment Cycles				After the first dose of treatment					
Treatment Cycle/Title:		Main Study Screening	1	2	3	4	(± 1 Month)					
Scheduling Window (Days):		-28 to -1	± 7d	± 7d	± 7d	± 7d			3m	6m		
Treatment/Pembrolizumab			X	X	X	X						
Administrative Procedures												
Inclusion/Exclusion Criteria		X										
Demographics and Medical History		X										
Prior and Concomitant Medication Review		X	X	X	X	X			X	X		
Trial Treatment Administration			X	X	X	X						
Survival Status [q]			X	X	X	X			X	X		
Clinical Procedures/Assessments												
Review Adverse Events [a]				X	X	X			X	X		
Physical Examination [b]		X							X	X		
Directed Physical Examination [c]			X	X	X	X			X	X		
Vital Signs and Weight [d]		X	X	X	X	X			X	X		
ECOG Performance Status [e]		X	X	X	X	X			X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG [f]		X										
CBC with Differential [g],PT(INR)[g,n],aPTT [g,n]		X	X	X	X	X			X	X		
Comprehensive Serum Chemistry Panel [h]		X	X	X	X	X			X	X		
Urinalysis [i]		X										

Trial Period:	Screening Phase		Treatment Cycles				After the first dose of treatment					
Treatment Cycle/Title:		Main Study Screening	1	2	3	4	(± 1 Month)					
Scheduling Window (Days):		-28 to -1	± 7d	± 7d	± 7d	± 7d			3m	6m		
Treatment/Pembrolizumab			X	X	X	X						
T3, FT4 and TSH [j]		X			X				X	X		
Efficacy Measurements												
Tumor Imaging [k]		X			X				X	X		
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival or Newly Obtained Tissue Collection [l]		X										
Correlative Studies Blood Collection [m,p]		X	X	X	X	X			X	X		
Correlative Studies for Stool Collection [m]		X		X						X		
Health-related quality of life (QoL) EORTC QLQ-C30 and EORTC QLQ-LC29 .		X							X	X		

[a, b, c, d, e, g, h, k, m] After 6 months on trial, these will be performed as the standard of care. Imaging, cancer diagnosis and survival data will be collected beyond the trial duration as standard of care. Please refer to Table 9 Laboratory Tests for the required lab assessments.

[f, i, j] Pregnancy test must be performed <72 hours prior to the first dose of study medication.

[l] Pre-treatment tissue will be obtained as indicated (estimated cancer probability ⩾ 30%) post-enrollment tissue will be obtained as indicated if cancer probability increase ≥15% over baseline or when patients develop lung cancer as the standard of care. All archival tissue will be collected by site and sent to MDA as per the lab manual excluding UC/Rocky Mountain Regional VA Medical Center.

[m]**Microbiome** Stool samples will be collected at screening, before Cycle 2 and 6 months after the first dose of treatment. Samples will be sent directly to sites ambient and shipped to MDACC ITB lab as per lab manual excluding UC/ Mountain Regional VA Medical Center.

[n] PT(INR), aPTT only to be performed prior to biopsy and/or if clinically indicated.

Trial Period:	Screening Phase		Treatment Cycles				After the first dose of treatment					
Treatment Cycle/Title:		Main Study Screening	1	2	3	4	(± 1 Month)					
Scheduling Window (Days):		-28 to -1	± 7d	± 7d	± 7d	± 7d			3m	6m		
Treatment/Pembrolizumab			X	X	X	X						

[p] Correlative study blood samples will be collected at Screening; Day 1 of Cycles 1,2, 3, 4; 3 and 6 after the first dose of treatment at all sites and be shipped/stored in batches at MDACC ITB lab as per attached manual excluding UC/Rocky Mountain Regional VA Medical Center.

[q] Participants who experience confirmed disease progression or start a new anticancer therapy will be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 7.1 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 and/or Merck for reasons related to participant 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 participant. 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 participant prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant'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 participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant'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 participant's dated signature or by the participant'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 participant 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 participant 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 participant within 28 days before starting the trial. Treatment for the disease for which the participant 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 participant 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.

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 participant 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 participant will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All subjects must be registered through an electronic data capture (EDC) system (CORe). A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy.

Data collection for this trial will be via means of electronic data capture through the Data Management Initiative (DMI) database. The DMI is a secured password protected system. Access to the system is restricted to the PI, study coordinators, data coordinators, database analyst, and other members of the team who require needed access.

Electronic Case Report Forms (eCRFs) will be completed in the DMI. Data collected in the eCRFs will be abstracted from the electronic health record and other available source documentation.

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

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant 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 Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.2 Physical Exam

The investigator or qualified designee will perform a physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Physical exam during screening will include vitals, weight, ECOG status, and an examination of skin, HEENT (head, eyes, ears, nose, and throat), lymph nodes, heart, chest, lungs, abdomen, extremities, and neurological system.

7.1.2.3 Directed Physical Exam

For cycles that do not require a 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 and weight at: 1) screening, 2) prior to the administration of each dose of trial treatment and 3) at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 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 Lung Lesion Measurements

Chest CT scans will be used to monitor the IPNs and recorded in the patient's electronic medical record for assessment of clinical response to treatment. If IPNs disappear, this will also be recorded in the patient's record.

7.1.2.7 Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood/Stool

Biospecimens collected (including archival and newly obtained biopsied and resected tissues) will be used for evaluation of histological response to treatment as well as correlative studies. As part of the study, a biospecimen repository will be created. The objective of this repository will be to provide material for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. All samples will be stored at the Institutional Tissue Bank and de-identified and logged using Tissue Station. A written informed consent will be obtained from patients enrolled in this study so that these samples may be analyzed in the future for biomarkers not described in this protocol. Biopsies when clinically indicated will be performed as standard of care. Archival tissue will be collected by site and be shipped in batches to MDACC lab as per the attached manual.

Microbiome stool samples will be shipped ambient to MDACC ITB lab excluding UC/Rocky Mountain VA Regional Medical Center).

Correlative blood specimens will be collected at sites and stored/shipped in batches as per the attached lab manual excluding UC/Rocky Mountain VA Regional Medical Center.

The correlative studies to be evaluated in the biospecimens include (but are not limited to):

- expression of PD-L1, PD-L2, B7-H3, B7-x/H4, PD-1, LAG-3, 2B4, BTLA, Tim3 in neoplastic cells, immune cells and epithelium
- expression of CD3, CD4, FoxP3, CD8, CD68, CD57, CD45RO in immune cells
- T cell receptor profiling by massive parallel sequencing, and/or T cell receptor

expression assay (DTEA)

- whole exome sequencing to determine presence of neo-antigens
- genomic analysis (including genome sequencing and SNP analysis)
- proteomic analysis
- phosphorylation status of multiple kinases (using antibody arrays when appropriate)
- non-coding-RNA and messenger-RNA levels, including the expression signatures interferon gamma, TCR signaling, expanded-immune, de novo.
- identification of sub-populations of T-cells (e.g. CD4+ helper T-cells, CD8+ cytotoxic T-cells, CD4+ CD25+ regulatory T-cells, FOXP3) and myeloid derived suppressor cells (CD19-, CD3-, CD14-, HLADR-, CD11b+, CD33+, CD45+) as well as immune phenotypic markers including ICOS/ICOSL; OX40/OX40-L; 41BB/41BB-L; PD-1/PD-L1 and PD-L2; CD69, and HLA-DR (activation markers that affect T cell function)
- Cytokine profiling

7.1.2.8 Stool-based biomarkers

Patients will provide their stool samples as detailed in the tables above. Stool collection will be performed with commercially available collection kits from DNA Genotek company. These kits will be provided to patients at no cost and shipped to their respective sites for data analysis.

Other biomarkers that may emerge to be important related to the biology of lung cancer and/or pembrolizumab therapy

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

Laboratory tests 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 tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		Stool Sample for microbiome analysis for correlative Studies
	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.

* Only to be performed prior to biopsy and/or if clinically indicated.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant 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. Participants who complete 12 weeks of treatment with pembrolizumab may discontinue treatment. After discontinuing treatment, these participants 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 7.1.5.3.2).

7.1.4.2 Blinding/Unblinding

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

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

7.1.5.1.1 Screening Period

We anticipate to complete enrollment within 4 years.

7.1.5.2 Treatment Period

The treatment will be complete in 12 weeks - 4 cycles of pembrolizumab every 3 weeks. Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.3 Post-Treatment Visits

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 study 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. Participants 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-cancer 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.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed accordingly as outlined in Section 6.0 - Trial Flow Chart by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and will be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant 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 Merck's product, is also an adverse event. Clinical data capture called DMI (Data Management Initiative) will be the electronic database used for this study's electronic case report forms.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

● All AEs from the time of treatment through 90 days following cessation of study treatment or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

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.

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 participant, 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 to the Sponsor and to Merck within 2 working days..	
	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 participant 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 Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to 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 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 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 Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to 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) Sponsor's 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR 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 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 Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

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

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Table 11 Recommended adverse event recording guidelines

Recommended Adverse Event Recording Guidelines					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices".

The MD Anderson Lead-site will utilize the electronic SAE application (eSAE) for reporting SAEs to the IND office & IRB

Reporting for all sites:

- A written report should be submitted to the Institutional Review Board (IRB) according to the requirements of the assigned IRB for patients enrolled at each site.
- Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, *within 5 working days of knowledge of the event* regardless of attribution.
- **Death** or **life-threatening events,** that are unexpected, possibly, probably or definitely related to drug, must be reported within **24 hours** of knowledge of the event.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

- All events reported to the supporting company must also be reported to IND Office.

Reporting for Non-Lead site:

- SAEs will be reported to the IND Office (sponsor) on a template form that will be provided to each non-lead site. If available, a copy of all relevant examinations that have been carried out and the dates on which these examinations were performed should be attached. For laboratory results, normal ranges should be included. Patient name should be marked out and initials and study number included on all attachments.

- In case of a serious adverse event, the following actions must be undertaken by the non-lead site principal investigator: (Please note that these are in addition to the reporting that is required by the local IRB and supporting company). Complete the SAE form and upload it to the MD Anderson Box system or through secure electronic submission of SAE report(s) via e-mail to the MD Anderson IND Office safety inbox: MDACCSafetyReports@mdanderson.org

- The non-lead site will receive an electronic confirmation of receipt, and approval of the SAE report and it should be filed in the study regulatory binder at the non-lead site.

- The University of Texas M.D. Anderson Cancer Center IND Office Medical Affairs & Safety Contact Information:

Carla Tuttle, Medical Monitor
7007 Bertner, 1MC12.2225
Houston, Texas 77030
Tel no.: 713-563-5466
Fax no.: 713-792-8987
e-mail: mdaccsafetyreports@mdanderson.org

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

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

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a pre-treatment procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment initiation through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies 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 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

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'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 another important medical event;

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table **10** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until initiation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a pre-treatment procedure.

For the time period beginning at treatment initiation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by 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 215-661-6229) at the time of submission to FDA.

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 reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment initiation, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a pre-treatment procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, 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.

8.0 STATISTICAL CONSIDERATIONS

8.1 Sample Size Calculation

In this single-arm phase II study, eligible patients will receive pembrolizumab for 4 doses every 3 weeks with a total treatment duration of 12 weeks. The primary efficacy endpoint of the study is regression (CR or PR by modified RECIST criteria, Table 1) of high-risk IPNs by 6 months after the initiation of treatment. Assuming the spontaneous regression of high-risk IPNs occurs in 5% of patients based on histological control (estimated based on the analysis of NELSON study[55] and our own cohort), the regression (CR or PR by modified RECIST criteria, Table 1) rate increases to 20% in the pembrolizumab group and 10% patients may not be evaluable for the primary endpoint, we will need to enroll 40 patients to detect the difference with 87% power and one-sided 5% type I error rate with the one-sample exact binomial test.

Details of the assumptions used for the sample size calculation are listed below.

1. The study has a 39 months period to accrue 40 patients with high-risk IPNs, with an additional 9 months of follow-up after last patient is enrolled. The total study duration was 48 months (4 years). The sample size will be increased to 60 patients to yield the 40 eligible patients. The sample size of 60 randomized patients will not change the preplanned analysis of 40 eligible patients as it is recommended for screen failures and early drop-outs/therapy discontinuation during or at response.
2. Based on the NELSON study, the spontaneous regression rate of any IPNs was 8% by 3 months[55]. Based on own study, for persistent IPNs (at least 2 CT scans, 3 months apart, no evidence of regression) with estimated risk score ≥5%, the regression rate was 0% without treatment. We chose 5% spontaneous regression rate to be conservative.
3. The majority of high-risk IPNs are preneoplastic lesions or pre-invasive lung neoplasms. The response rate of these lesions to checkpoint blockade agent including is unknown. In metastatic NSCLC, the response rate to checkpoint blockade agent including pembrolizumab, is ~20%. We therefore chose 20% as the regression (CR or PR by modified RECIST criteria, Table 1) rate in the pembrolizumab treated arm.
4. One-sample exact binomial test is used to compare the regression rate between the pembrolizumab group and the spontaneous regression rate obtained from the historical data.

Based on the above assumptions, a total of 40 eligible and treated patients will be enrolled to yield 36 evaluable patients in order to reach 87% power with a one-sided 5% type I error rate by applying the one-sample exact binomial test. To account for 8 patients enrolled in the early phase of the study who did not receive treatment, the total enrollment was set at 48 patients. The sample size will be increased to 60 patients to yield the 40 eligible patients. The sample size of 60 randomized patients will not change the preplanned analysis of 40 eligible patients as it is recommended for screen failures and early drop-outs/therapy discontinuation during or at response.

8.2 Statistical Analysis Plan

Our understanding of biology and clinical course of high-risk IPNs is rudimentary. Although decrease the incidence of histologically-confirmed cancer, prolongation of cancer-free survival and overall survival may be the ultimate goal of immune prevention. Very large sample size

and long follow up are needed to provide the definitive answers to these questions. Therefore, as a "signal finding" study, this single-arm phase 2 trial focuses on the rate of regression (CR or PR by modified RECIST criteria, Table 1) of high-risk IPNs.

The study population is a high-risk population with at least ≥15% risk of being diagnosed with lung cancer within 2-4 years of follow up period. A big proportion of this study population are patients who have had personal history of lung cancer and/or progressing IPNs, a very high-risk group for second primary lung cancer but there are no reliable prediction tools available. Therefore, regression (CR or PR by modified RECIST criteria, Table 1) of these very-high risk IPNs will lead to decrease of incidence of invasive cancers. The advantages of selecting a high risk group as the eligible population include: (1) avoidance of exposure of low-risk individuals to the drug, who are unlikely to develop lung cancer and therefore, unlikely to benefit from prevention interventions; (2) improvement of benefit/risk rations and benefit/cost ratios, justifying further use of the drug if positive effects are identified.

The proposed study will be an open-label single-arm study to evaluate the effect of pembrolizumab in a high-risk group of IPN patients.

Study Duration: We expect to accrue 1-2 patients per month. The trial period is 48 months (4 years) with 39 months of accrual and 9 additional months of follow-up after last patient's enrollment. Patient will be followed and data will be collected as standard of care.

Study Endpoints: The primary endpoint is regression of IPNs (CR or PR by modified RECIST criteria, Table 1) at 6 month after treatment in patients receiving pembrolizumab. Multiple secondary and/or exploratory endpoints will be assessed as outlined in Section 3.2 and 3.3.

Treatment Group: This is a single-arm open-label Phase II multi-center trial of pembrolizumab in patients with high-risk IPNs. The trial will enroll 40 eligible patients to receive pembrolizumab.

The 95% exact confidence interval for the regression rate of high-risk IPNs by 6 months after treatment will be computed. Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as frequency distribution, mean (± s.d.) and median (range) accompanied by graphical analysis. Student t-test/Wilcoxon test and ANOVA/Kruskal-Wallis test will be used to compare continuous variables between different groups. The chi- square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

Time-to-event endpoints will be computed using the Kaplan-Meier method.

CONSORT diagram will be used to summarize the conduct of the trial.[17]

The primary endpoint of the study Is regression (CR or PR by modified RECIST criteria, Table 1) rate of high-risk IPNs at 6 months after treatment. The primary endpoint will be analyzed by the one-sample exact binomial test as described in the above Section 8.1. For events that have not occurred by the time of data analysis, times will be censored at the last contact at which

the patient was known to be lung cancer- free. The distribution of time to lung cancer development will be estimated by the Kaplan-Meier method. One-sample log-rank test[18] will be used to compare cancer-free survival of the treatment group with the prespecified target. The Cox (proportional hazards) regression model will be used to incorporate potential prognostic factors as covariates.

The Investigator is responsible for completing efficacy/safety summary reports and submitting them to the IND Office Medical Affairs and Safety Group for review and approval. These should be submitted after the first 9 evaluable patients who initiated pembrolizumab treatment, complete 6 months of study treatment, and every 9 evaluable patients thereafter. Toxicity assessment must include the first cycle of study therapy, and response assessment the first six months.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.3 Statistical consideration on the assessment of health-related quality of life (QoL)

In this study, the eligible subjects have persistent IPNs with or without prior lung cancer but without active disease. We expect that the general QoL for study subjects at baseline is good. We expect that QoL may decline slightly due to the drug's side effect during treatment period but will recover at 6-month follow-up. The overall QoL scores and subscales for both instruments will be estimated at the three specified time points (baseline, 3-month, and 6-months after first dose of treatment. Descriptive statistics such as mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum will be calculated. Histogram, boxplot, and change-over-timeline plot will be generated to characterize the distribution. The changes from baseline to 3-month after first dose of treatment and from baseline to 6-month after first dose of treatment will be computed. The primary QoL endpoint is the global health/QoL of EORTC QLQ-C30. The primary objective is to assess the change of the global health/QoL of EORTC QLQ-C30 from baseline to 6-months after initiation of treatment. Exploratory analysis will be applied to compare the difference of change in QoL from baseline to 3 months and from baseline to 6 months after the first dose of treatment in the subscales of EORTC QLQ-C30 and all the measures of EORTC QLQ-LC29. No multiple comparison adjustments will be applied in these exploratory analyses.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES AND SAMPLES

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.

Pembrolizumab will be provided by Merck as summarized in Table **12**.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, 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 Shipping and Handling of Biospecimen Samples

Sites (excluding UC/Rocky Mountain Regional VA Medical Center) will be responsible for sending biospecimen (blood correlative and tissue) samples to MDACC. Microbiome (stool) samples will be sent to sites and then shipped ambient to MDACC ITB lab as per lab manual. Data will include the following: protocol ID + the patient study ID + date of collection + study visit/time point. All patient health information will be de-identified. Subjects will be provided shipping packages, stool kits and labels to return directly to MDACC ITB Lab.

9.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the participants 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

The University of Texas MD Anderson Cancer Center IND Office will monitor the study investigators to assure satisfactory enrollment rate, data recording, and protocol adherence. The site principal investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. MD Anderson Cancer Center will monitor and/or audit the other participating sites to assure satisfactory protocol adherence and enrollment.

The site will be visited on a regular basis by the Clinical Study Monitor, who will check completed source documentation, discuss the progress of the study and monitor drug according to good clinical practice (GCP). The monitoring will also include source data verification (SDV).

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12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 2: 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)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in section 5.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table **10** when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table **13** during the protocol-defined time frame in Section 5.1.1.

Table 13 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).

b) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.