TITLE: Phase II study to test Pembrolizumab (MK-3475) in first line treatment of advanced NSCLC patients with PD-L1 low tumors (<50%)_ PEOPLE TRIAL (Pembrolizumab in Pd-L1 low Expressors)

EudraCT number: 2017-002841-31

Version: 3.0 _ 22.02.2021

Sponsor: National Cancer Institute, Milan, Italy

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Lo Russo G, *et al. J Immunother Cancer* 2023; 11:e006833. doi: 10.1136/jitc-2023-006833

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1.0 TRIAL SUMMARY

Abbreviated Title	**PEOPLE TRIAL (Pembrolizumab in Pd-L1 mild Expressors)**
Trial Phase	II
Clinical Indication	Non-Small Cell Lung Cancer
Trial Type	Interventional
Type of control	No control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	1
Number of trial subjects	Approximately 65 subjects will be enrolled.
Estimated enrollment period	One year
Estimated duration of trial	Three years
Duration of Participation	Three years

2.0 TRIAL DESIGN

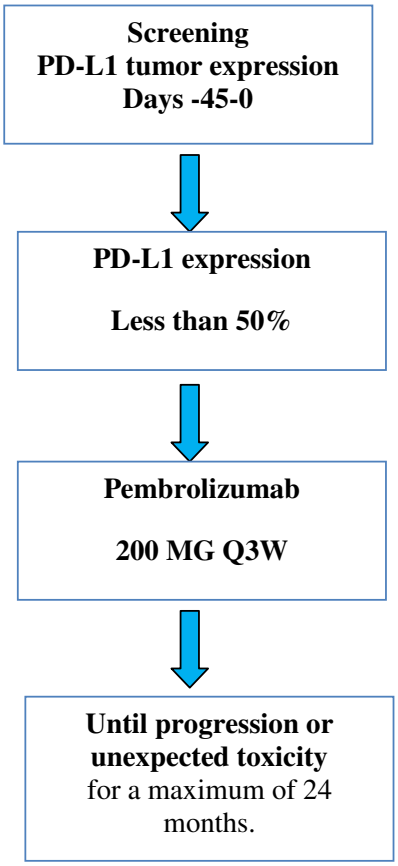
2.1 Trial Design

This is a prospective, monocentric, open label, phase II trial of intravenous (IV) Pembrolizumab monotherapy in subjects previously untreated for their stage IIIB-IV, PD-L1 low non small cell lung cancer (NSCLC). Approximately 65 subjects with PD-L1 low (PD-$L1^{Lo}$), EGFR wt, EML4/ALK fusion negative NSCLC will be enrolled in this trial for examination of the biological characteristics associated to efficacy and safety of Pembrolizumab. Subjects will receive Pembrolizumab iv at dose of 200 mg every three weeks. Subjects will be evaluated every 9 weeks (63 +/- 3 days) with radiographic imaging to assess response to treatment. Subjects will continue with the assigned study treatment until RECIST-defined progression of disease, unacceptable toxicity or consent withdrawal. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with Pembrolizumab will continue until two years of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Pembrolizumab treated subjects who obtain a confirmed Complete Response (CR) per RECIST 1.1 may consider stopping trial treatment. These subjects may be eligible for re-treatment with Pembrolizumab after they have experienced radiographic disease progression at the discretion of the investigator, this re-treatment will be the Second Course Phase. Response or

progression in the Second Course Phase will not count towards the primary endpoint in this trial.

After the end of treatment, each subject will be followed for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

2.2 Trial Diagram



3.0 HYPOTHESIS(ES) & OBJECTIVE(S)

3.1 Hypotheses:

3.1.1 Role of tumor infiltrating lymphocytes in NSCLC and relationship with PD-L1 expression in the tumor tissue.

Several recent studies have addressed the relationship between the immune profile of the lesions and PD-L1 expression in neoplastic tissues from NSCLC patients. The results of such studies may provide clues as to the type of biomarkers that may be investigated when looking for association with response/resistance to Pembrolizumab in patients whose tumors have been classified as "not strong" for PD-L1 expression (PD-L1^{NS}). Veklcheti et al., in 458 NSCLC cases, found that PD-L1 expression was significantly associated with presence of tumor-infiltrating lymphocytes. Moreover, patients with PD-L1 expression showed a significantly better outcome, independently of histology. Taube et al. investigated PD-L1, PD-L2 and PD-1 expression in pre-therapy lesions from a cohort of 41 cancer patients with tumors of different histology, including NSCLC, treated with the anti-PD-1 mAb Nivolumab. They found that PD-L1 expression was associated with PD-L2, the second ligand for PD-1, as well as with expression of PD-1 on infiltrating lymphocytes. However, interestingly, PD-L1 expression on neoplastic cells was associated with immune cell infiltrates mainly in melanoma and RCC, whereas in NSCLC it was constitutive or out of proportion to infiltrating immune cells. They also found that expression of the PD-1 receptor on TILs had only a borderline association with clinical response.

More recent studies have investigated the predictive correlates of response to targeting of the PD-1/PD-L1 axis in different tumor types, including NSCLC. As shown by Tumeh et al. in pre-therapy lesions of patients treated with anti-PD-1 antibody, response to therapy is associated with presence, at the invasive tumor margin, of CD8$^+$ lymphocytes expressing PD-1, in close proximity with PD-L1$^+$ cells, and with proliferation of intratumoral CD8$^+$ T cells during treatment. By targeting of PD-L1, in different tumor types, including melanoma and NSCLC, an unexpected association has been found by Herbst et al. between response and expression, in pre-therapy lesions, of PD-L1 on tumor infiltrating immune cells. Specifically, in NSCLC patients treated with an anti-PD-L1 antibody, a significant association has been reported between response to treatment and PD-L1 expression on tumor infiltrating immune cells, but not between response an PD-L1 on tumor cells. Moreover, post-therapy lesions from responding patients showed enhanced infiltration of PD-L1$^+$ immune cells, while progressing lesions showed defective immune cell infiltration, or lack of PD-L1 upregulation on intra- tumoral immune cells.

These findings suggest that presence of PD-L1$^+$ infiltrating immune cells, in neoplastic tissues, reflects a condition of pre-existing immune activation that is associated with subsequent response to immune checkpoint blockade.

Further evidence indicates that the number, type and location of tumor-infiltrating lymphocytes (TILs) in neoplastic lesions has a strong prognostic value, as shown by studies by Galon and colleagues. Based on these results, the "immunoscore" (density and location of $CD8^+$ T cells with a memory phenotype) is being proposed as a prognostic tool. Additional evidence indicates that the pattern and phenotype of the lymphocytic infiltrate, found in biopsies taken during treatment with antibodies targeting the PD-1/PD-L1 axis, can be associated with the type of response to therapy. Herbst et al. have found that tumors from progressing patients are characterized by one of three patterns: absence of lymphocyte infiltration ("immunological ignorance"), or presence of infiltrating lymphocytes that lack PD-L1 ("non functional immune response"), or presence of immune cells only at the edge of the tumor mass ("excluded infiltrate").

Recent technical developments (digital quantitative pathology) also provide effective means for objective measurement of number and localization within the neoplastic tissue of TIL and this approach has indicated a significant association of high CD3 and CD8 values and survival in NSCLC as shown by Schalper et al. These tools of quantitative digital pathology will be used in this project aiming at assessing whether the immunoscore, as described by Galon and colleagues, and assessed in pre-therapy lesions, is a predictive marker of response to therapy.

In this project we will also take advantage of evidence indicating that tumor-reactive T lymphocytes at tumor site can be recognized by specific traits. A recent study by Gros et al. has shown that tumor-specific T cells, associated with the neoplastic tissue, are characterized by an effector memory-like phenotype, and by frequent co-expression of several inhibitory receptors (as PD-1, LAG-3, TIM-3), or of the costimulatory molecule 4-1BB (CD137). In NSCLC, as shown by Djenidi et al., tumor-specific tissue-resident memory T cells, whose presence correlates with improved survival, can be identified by CD103 expression and by upregulation of inhibitory receptors PD-1 and TIM-3. Recently, a new co-inhibitory receptor (TIGIT) has been shown by Johnston et al. to be upregulated on $CD8^+$ T cells in several tumor types.

Taken together these results suggest that:

a) tumor infiltrating lymphocytes may be found not only in patients whose tumors have strong PD-L1 expression, but even in patients with a $PD\text{-}L1^{Lo}$ tumor and these cells may contribute to response to Pembrolizumab, depending on their phenotype and functional differentiation; thus, assessing the immunoscore by quantitative pathology tools, in pre-therapy lesions from $PD\text{-}L1^{Lo}$ patients, may allow to test the potential association of this parameter with reponse to therapy.

b) presence of infiltrating T cells that upregulate PD-1 and/or additional inhibitory receptors (such as TIM-3, LAG-3 and TIGIT) may signal for an ongoing immune response even in lesions with a $PD\text{-}L1^{Lo}$ scoring and may represent a predictive biomarker of response;

c) response to therapy may be associated not only with the level of expression of PD-L1, but also with the type of cells being positive for this marker (neoplastic cells vs infiltrating immune cells).

Based on this rationale, we will verify whether presence and phenotype of tumor-infiltrating lymphocytes (TILs) in the pre-therapy lesions of patients with PD-L1^{Lo} tumors is associated with responsiveness to Pembrolizumab. To this end, we intend to use semi-quantitative immunohistochemistry and digital pathology instruments (Vectra) to assess and quantitate extent of neoplastic tissue infiltration by:

a) CD3$^+$, CD4$^+$ and CD8$^+$ lymphocytes;

b) expression, in TIL, of markers of functional differentiation to cytolytic stage such as granzyme B and TIA-1, or of maturation to memory stage (CD45RO);

c) expression of PD1$^+$ by TIL;

d) expression of inhibitory receptors as LAG-3, TIM-3 and TIGIT by tumor-associated lymphocytes;

e) expression of PD-L1 on neoplastic cells vs immune cells.

In addition, the efficacy of the anti-tumor immune response occurring at tumor site or re-activated by immune checkpoint-targeted therapy, is thought to be heavily influenced by powerful immunosuppressive mechanisms, including regulatory T cells (Treg) and myeloid derived suppressor cells (MDSCs). Thus, we will assess whether a high frequency of Tregs and of MDSCs in pre-therapy lesions may be a predicting factor of resistance to Pembrolizumab. To this end, we will evaluate the frequency of FOXP3$^+$ lymphocytes, as well as of CD11b$^+$ CD33$^+$ MDSCs by immunohistochemistry in pre-therapy lesions. We will also take into account the possibility that mechanisms of tumor immune escape may prevent responsiveness to Pembrolizumab in patients with PD-L1^{Lo} tumors. To this end, we will assess, by immunohistochemistry in pre-therapy lesions, the extent of loss of expression of HLA class I and II molecules in the neoplastic tissues. The hypothesis will be that lack of expression of HLA molecules by the tumor cells may be associated with lack of responsiveness to Pembrolizumab.

3.1.2. Immune profiling in peripheral blood of patients treated with immune checkpoint-directed immunotherapy.

Initial information on relevant immunological parameters affected by immune checkpoint-directed therapy has been obtained from studies based on the administration of anti-CTLA-4 mAb Ipilimumab. Relevant findings include the absolute lymphocyte counts, whose increase correlates with clinical benefit and OS. Reduction of Tregs (CD4$^+$ FOXP3$^+$ T cells), development of tumor-antigen-associated (NY-ESO-1) humoral and CD8$^+$-mediated responses and pre-treatment levels of Ki-67$^+$ EOMES$^+$ CD8$^+$ T cells, are all positively correlated with clinical outcome. A low pre-treatment level of CD14$^+$/HLA-DR$^-$ myeloid-derived suppressor cells (MDSC), may also correlate with response. Additional evidence have provided evidence for increased frequency of ICOS$^+$ CD4$^+$ T cells and for reduction in MDSCs as pharmacodynamic biomarkers in anti-CTLA-4 therapy. In a different study a greater decrease in circulating MDSC (Lin1-/HLA-DR-/CD33$^+$ /CD11b$^+$) was associated with improved PFS. Recent studies have looked at peripheral blood immune profiles in cancer patients, including NSCLC patients, treated with antibodies targeting the PD-1/PD-L1 axis. Increase in IL-18 and CXCL11 levels as well as in frequency of activated CD8$^+$ HLA-

DR^+ $Ki\text{-}67^+$ lymphocytes has been described by Hebst et al. during the first cycle of therapy, but these changes were not associated with responsiveness to treatment. A more recent study by Twyman-Saint Victor et al. has provided evidence that a specific subset of circulating T cells can be associated with response to radiation plus immune checkpoint blockade. Specifically, these authors found that exhausted T cells, defined as $CD3^+$ $CD8^+$ $PD\text{-}1^+$ $Eomes^+$ lymphocytes, remain high post-treatment in non responding patients, while in responding patients this subset has lower frequency and shows a phenotypic change associated with reversal of exhaustion (a process defined as "reinvigoration") and characterized by increase expression of Ki67 and Granzyme B. Intriguingly, reinvigoration of exhausted T cells in blood was observed only in patients whose neoplastic cells where scored as $PD\text{-}L1^{Lo}$, and not in those scored as $PD\text{-}L1^{Hi}$, and whose circulating T cells retained an exhausted profile.

Based on this evidence, and on the mechanism of action of immune checkpoint blockade targeting the PD-1/PD-L1 axis, treatment with Pembrolizumab may be expected to reverse the condition of immune dysfunction, generally associated with advanced cancers. This effect may be more pronounced in responders than in non responders to therapy, and may be associated with measurable shifts in the frequency/phenotype of distinct immune cell subsets in peripheral blood. Based on this rationale, we plan to compare frequency/phenotype of main immune cell subsets (such as T cells, Treg, and MDSCs) in pre- and post-therapy blood samples and to test whether some of these immune parameters are associated with clinical response to treatment. To this end, we will use multiparametric flow cytometry to look at:

a) absolute count, frequency, phenotype, maturation stage, polarization and expression of markers of proliferation, cytotoxicity, activation, exhaustion and anergy of main T cell subsets, including $CD4^+$ and , $CD8^+$ lymphocytes. Specifically we will look at: 1. activation/maturation of circulating T cells by staining peripheral blood lymphocytes for CD3, CD4, CD8, CD45RA, Ki67, Granzyme B, CCR7, CD69. 2. Costimulatory receptor expression by circulating T cells by staining for CD3, CD4, CD8, PD-1 (the latter only in pre-therapy samples), PD-L1, TIM-3, LAG-3, TIGIT. 3. Exhaustion/reinvigoration of peripheral blood T cells by staining for: CD3, CD4, CD8, PD-1, Eomes, Ki67, Granzyme B.
b) Frequency of $CD3^+$ $CD4^+$ $FOXP3^+$ regulatory T cells by staining perypheral blood lymphocytes for CD3, CD4, CD127, FOXP3 and CD25;
c) frequency and phenotype of myeloid and plasmacytoid dendritic cell subsets by staining peripheral blood cells for CD45, Lin-1, CD34, HLA-DR, CD11c, CD123, PD-L1, CD86;
d) frequency and phenotype of MDSCs by staining for: CD45, Lin, CD14, CD15, HLA-DR, CD11b, CD33.

The main aims of this extensive peripheral blood immune profiling are to test whether: a) responding and progressing patients show significant differences in frequency/phenotype of

any of the above mentioned immune cell subsets in their pre-therapy blood samples; b) any of the above mentioned immune cell subsets show differential changes in frequency/phenotype in responding vs progressing patients when comparing pre- and on-therapy blood samples. Specifically, on-therapy samples will be obtained and assessed at 6-weeks intervals.

3.1.3 ***T-NGS analysis of PD-L1 low tumors regarding either responders or non-responders*** (at the beginning of the therapy).

Also tumor patients, for whom post-treatment tumor tissue will be available upon re-biopsy and liquid samples, will be subjected to mutation analysis. The rationale is that recurrent mutations could underline response profiles, taking into account the likelihood that some somatic gene mutations (e.g. BRAF) may modify the expression of major histocompatibility complex –type I molecule, affecting the capability of be recognized and killed by immune response. To this purpose, a next generation sequencer - PGM IonTorrent (Life Technologies, US)- will be exploited according to the IonAmpliseq technology by assaying a large panel of 50 oncogenes and tumor suppressor genes (IonAmpliseq Cancer HotSpot Panel, v.2) recurrently altered by mutation in human cancers, including NSCLC, with wide coverage for EGFR, KRAS and BRAF.

3.1.4 ***Gut microbiota profiling of patients treated with immune checkpoint-directed immunotherapy.***

Bacteria inhabiting the gut, collectively named as gut microbiota, maintain host physiology and health by exerting fundamental functions, spanning from metabolic to immunomodulatory properties. It was recently demonstrated that gut microbiota affect the response to chemotherapeutic and immunotherapeutic drugs, through its ability to regulate the immune response. Indeed, works in mouse models clearly showed the cause-effect relationship between the gut microbiota composition and the efficacy of both chemotherapy and immunotherapies. In details, Sivan et al demonstrated the importance of *Bifidobacterium* in altering dendritic cell activity and improving tumor infiltration of tumor specific CD8+ T cells and anti PD-L1 efficacy in a mouse model of melanoma. Vetiziou et al described the importance of *Bacteroides* species for the activity of CTLA-4 blockade in mice and patients.

Recent studies evaluated the association between gut microbiota composition and response to immunotherapies in human cancer patients. Matson et al. found a significant association between commensal microbial composition and clinical response to anti PD-1 therapies in melanoma patients. Gopalakrishnan et al. found differences in the composition of gut microbiome of responders versus nonresponders to anti– PD-1 immunotherapy. Moreover, immune profiling suggested enhanced systemic and antitumor immunity in responding patients with a favorable gut microbiome as well as in germ-free mice receiving fecal transplants from responding patients. Routy et al. demonstrated correlation between metagenomic profiles of non–small cell lung cancer and renal cell carcinoma patient stool samples at diagnosis and clinical response to immunotherapies. Moreover, the fecal microbiota transplantation (FMT) from patients who responded to immunotherapies into

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mice depleted from their flora ameliorated the antitumor effects of PD-1 blockade, whereas FMT from nonresponding patients failed to do so.
Based on this evidence, we plan to compare metagenomic profiles in pre- and post-therapy fecal samples and to test their association with immune profiles and response to Pembrolizumab.

3.2 Primary Objective

- To identify immune biomarkers associated with Progression-free-survival (PFS); refer to subparagraph 4.2.3.3 for details about predictor variables.

3.3 Secondary Objectives

- To detect differences in immune biomarkers distribution between pre and post Pembrolizumab treatment
- To estimate the activity of Pembrolizumab treatment; Objective Response Rate (ORR), Response Duration (DoR) and Disease Control Rate (DCR) will be used as activity endpoints
- To estimate the effectiveness of Pembrolizumab treatment; Overall Survival (OS) will be used as effectiveness endpoint
- To estimate the safety of Pembrolizumab treatment. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. A particular attention will be placed in the evaluation of potential Immune related adverse events (IrAE).
- To estimate patient–reported health status for physical, mental, and social well–being at pre-specified time points while on treatment and after treatment discontinuation; the Patient Reported Outcomes Measurement Information System (PROMIS) will be used as Multi-item scale
- To identify metagenomic profiles associated with PFS, and their association with patient immune phenotype.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Pembrolizumab .

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway

plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.
Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (Pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure

4.1.3 Current approvals for Pembrolizumab

On the basis of clinical trial results Pembrolizumab received approval in the following indications.

Table 1 Approved Pembrolizumab Indications in the US, EU, and Japan (from IB Ed.18 10 March 2020)

Cancer Type	**US**	**EU**	**Japan**
Melanoma	• Unresectable or metastatic melanoma • As adjuvant tretment of patients with melanoma with involvement of lymph node(s) following complete resection	• As monotherapy for advanced (unresectable or metastatic) melanoma in adults. • As monotherapy for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection	• Malignant melanoma

NSCLC	• In combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations • In combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC • As a single agent for the first-line treatment of patients with Stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations. • As a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR	• In combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumors have no EGFR or ALK positive mutations • In combination with carbolatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults • As monotherapy for the first-line treatment of metastatic NSCLC in adults whose tumors express PD-L1 with a ≥ 50% TPS with no EGFR-or ALK-positive tumor mutations • As monotherapy for locally advanced or metastatic NSCLC in adults whose tumors express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR- or ALK-positive tumor mutations should also have received targeted therapy before receiving KEYTRUDA	• Unresectable, advanced or recurrent NSCLC

	or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.		
HNSCC	• Patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.	• As monotherapy for recurrent or metastatic HNSCC in adults whose tumors express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy	N/A
cHL	• Adult and pedriatic patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy	• Adult patients with relapsed or refractory cHL who have failed ASCT and BV, or who are transplant-ineligible and have failed BV	• Relapsed or refractory cHL
PMBCL	• Adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy • Limitations o fuse: Not recommended for treatment of patints who require urgent cytoreductive therapy	N/A	N/A
UC	• Patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test, or in patients who	• As monotherapy for locally advanced or metastatic UC in adults who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a CPS ≥ 10	• Radically unresectable UC that progressed after cancer chemotherapy

	are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. • Patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	• As monotherapy for locally advanced or metastatic UC in adults who have received prior platinum-containing chemotherapy	
MSI-High	• Adult and pediatric patients with unresectable or metastatic, MSI-H or mismatch repair deficient -Solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or -Colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan. • Limitations of use: The safety and effectiveness in pediatric patients with MSI-H central nervous system cancers have not been established.	N/A	MSI-H solid tumors that have advanced or relapsed after chemotherapy (limited to use when difficult to tret with standard of care
Gastric/GEJ	• Patients with recurrent locally advanced or metastatic gastric or	N/A	N/A

	GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test, with disease progressionon or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy		
Cervical	• Patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test	N/A	N/A
HCC	• Patients with HCC who have been previously treated with sorafenib	N/A	N/A
MCC	• Adult and pediatric patients with recurrent locally advanced or metastatic MCC	N/A	N/A
RCC	• In combination with abitini, for the first-line treatment of patients with advanced RCC	N/A	N/A

ALK=anaplastic lymphoma kinase; ASCT= autologous stem cell transplant; BV=brentuximab vedotin; cHL= classical Hodgkin lymphoma; CPS=combined positive score; EGFR=epidermal growth factor receptor; EU= European Union; FDA0food and Drug Administration; GEJ= gastroesophageal junction; HCC= hepatocellular carcinoma; HNSCC= head and neck squamous cell carcinoma; MCC=merkel cell carcinoma; MSI-H= microsatellite instability-high; N/A=not applicable; nab-paclitaxel=nanoparticle albumin-bound paclitaxel; NSCLC=non-small cell lung cancer; PD-L1= programmed cell death 1; PMBCL= primary mediastinal large B-cell lymphoma; RCC=renal cell carcinoma; TPS= tumor proportion score; UC=urothelial carcinoma; US=United States (of America).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for the selection of PD-L1 low NSCLC patients

Lung cancer is the leading cause of cancer-related mortality worldwide. During the last three decades, platinum based chemotherapy has become the standard treatment for metastatic NSCLC in unselected patient populations. Although combination platinum-based regimens have been associated with improved survival compared with best supportive care, the median OS remains about one year and almost no patients are alive at 5 years.

Newly developed immune checkpoint inhibitors are challenging current treatment paradigms. Immune checkpoint inhibitors have been demonstrated to modulate the interactions of T cells and either antigen presenting cells (APCs) or tumor cells. In contrast to conventional chemotherapy, these agents appear to have potential for effecting durable responses and possibly long-term survival.

PD-L1 (B7-H1) is widely expressed in non-small cell lung cancers, both in adenocarcinomas and in squamous cell carcinomas (approximately 30-50% in each subtype), and may be associated with a poor prognosis. Anti-PD-1 directed agents block the interaction of PD-1 to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), activating previously functionally exhausted immune responses. Tumor expression of PD-L1 by immunohistochemistry (IHC) is a promising predictive biomarker of response to anti-PD-1/PD-L1, although its role in treatment decision making is still being clarified. The dynamic nature of PD-L1 expression may limit its use. At least three distinct PD-L1 antibodies have been developed as potential companion diagnostics to each agent (nivolumab, Pembrolizumab and MPDL3280A), each with its own performance specifications and thresholds for positivity. The definition of "positive" PD-L1 expression, therefore, is variable across studies and may impact on trial results.

In detail, for nivolumab the ORR was 17.1% and appeared similar between squamous (16.7%; nine of 54) and non-squamous histology (17.6%; 13 of 74). One year after starting therapy, 42% of patients were alive. While patients with PD-L1 expression achieved a response rate (36%), none of the patients with PD-L1 negative had a response. A phase I (Garon et al) study included 450 patients with NSCLC who had received prior chemotherapy, 305 patients (67.7%) were eligible for Pembrolizumab based on PD-L1 tumor expression. Strong PD-L1 expression was defined as staining ≥50% of tumor cells, weak PD-L1 expression was <50% of tumor cells. Approximately 25% of samples were classified as strong staining. In preliminary data reported on the 159 patients with tumors that were positive for expression of PD-L1, the response rate was 23%, median time to response was 9 weeks, and duration of response was 31 weeks. In 35 patients with tumors that were PD-L1 negative (-) the response rate was 9%, median time to response was longer at 14 weeks and duration has not been reported. Among all patients, current/former smokers appeared to have a higher response rate compared with never smokers (26% vs 8%). Several studies are

ongoing or planned for Pembrolizumab all requiring biopsies and enrolling patients with tumors that are positive for expression of PD-L1.
Response data, presented at the 2014 annual ASCO meeting, and including 262 patients with untreated (n=45) and previously treated (n=217) advanced NSCLC, enrolled in the expansion cohort of the KEYNOTE-001 study, have provided evidence for an ORR of 37% in patients with strongly PD-L1 positive tumors, but also of 10% in cases with a PD-L1 negative tumor. This evidence suggests that expression of PD-L1 on neoplastic cells is associated with response to PD-1 blockade, but lack of expression of the PD-1 ligand does not necessarily prevent clinical efficacy, at least in a subset of patients.
Finally, differently from anti CTLA4 compounds, responses have been achieved in the first six-nine weeks of treatment and responders are those patients long survivors.
Results on the activity of anti PD-1 agents in patients without expression of PD-L1 or with low expression of PD-L1 is controversial and it must be clarified in a proper prospective trial.

4.2.1.2 Rationale for the selection of EGFR wild type and EML4-ALK fusion negative NSCLC patients

Lung cancer had the highest incidence of malignancies globally in 2008 with more than 1.6 million cases. Mortality from lung cancer in 2008 was similar with over 1.4 million deaths from lung cancer globally. NSCLC counts for approximately 85% of all lung cancer cases. Progress has been made in the clinical management early stage NSCLC by establishing comprehensive, multi-modality treatment regimens; however, the prognosis or advanced disease has not improved substantially. With an overall 5-year survival rate of 9% to 13%, the treatment of NSCLC remains a highly unmet medical need. Cytotoxic chemotherapy as single agents or in combination have served as the mainstay of treatment for decades with platinum containing doublets and maintenance strategies conferring the greatest advances in overall survival gains. Platinum-based combination chemotherapy prolongs survival, improves quality-of-life, and controls disease related symptoms. Platinum chemotherapy, thus, is the backbone treatment or initial (first line) treatment of patients not candidates for treatment with tyrosine kinase inhibitors (TKIs) and who have an ECOG PS of 0 or 1 . Cytotoxic agents such as gemcitabine or docetaxel are considered SOC for patients with an ECOG PS of 2. Approved therapies for EGFR wt and EML4-ALK fusion negative NSCLC in previously untreated patients with advanced or metastatic settings in Europe include paclitaxel, gemcitabine, docetaxel, pemetrexed and bevacizumab, all in combination with platinum based chemotherapy. While ECOG 1594 demonstrated that the four platinum-doublets tested (cisplatin combined with either paclitaxel, gemcitabine or docetaxel, and carboplatin and paclitaxel) have equivalent activity in the first-line setting, either pemetrexed nor bevacizumab is appropriate for patients with squamous histology. Recently, targeted therapies for specific tumor genetic alterations have resulted in higher response rates in specific subpopulations of NSCLC patients. Examples include inhibitors against the epidermal growth factor receptor (EGFR) family and the anaplastic lymphoma kinase

(ALK). Because of the highly significant demonstration of clinical benefit in these molecularly defined sub-populations, ESMO and NCCN guidelines indicate that first-line treatment with an approved TKI, should be prescribed to patients with tumors bearing an activating sensitizing epidermal growth factor receptor (EGFR) mutation because of significantly higher response rate (RR), longer Progression Free Survival (PFS), and better quality of life (QoL) (ESMO) when compared with first-line chemotherapy. Recently, a third EGFR inhibitor, afatinib, was approved for the treatment of EGFR inhibitor (TKI) naïve patients with advanced or metastatic NSCLC who bear EGFR activating mutations on the basis of a significantly improved PFS and acceptable safety, as compared to a SOC platinum doublet of cisplatin + pemetrexed. The composite of data demonstrated a favorable benefit-risk ratio and thus contributes to the arsenal of options or NSCLC patients who harbor EGFR activating mutations. Furthermore, recent retrospective analyses indicate that continuation of TKI treatment beyond RECIST defined progression is associated with a significantly improved overall survival as compared to subjects who were switched to cytotoxic chemotherapies at the time of RECIST defined PD .The ongoing single arm, Phase II ASPIRATION trial (NCT01310036) aims to prospectively determine if continuation of erlotinib beyond RECIST defined progression in Asian subjects with EGFR mutations confers clinical benefit. To our knowledge, no randomized studies comparing treatment beyond progression to the traditional paradigm in which cytotoxic chemotherapy is initiated at the time of progression have been performed. Despite these definitive data, the NCCN guidelines recommend that EGFR inhibitors be continued despite PD in asymptomatic patients who arbor EGFR sensitizing mutations, further underscoring the potential to slow the rate progression and ultimately provide clinical benefit in a patient population with limited therapeutic options in the 2L and beyond. Patients with previously treated NSCLC harboring an anaplastic lymphoma kinase (ALK) translocation should be considered for crizotinib (Xalkori). Despite the development of these targeted therapies, most patients relapse and die from their lung cancer; therefore, advanced and metastatic NSCLC remain a major unmet medical need. Patients who harbor EGFR mutations and/or ALK translocations will be excluded from this study. Significant preclinical and clinical data indicate that activation of these respective pathways fundamentally alter the natural history of tumors that bear these mutations as compared to tumors that do not, which ultimately affect sensitivity to standard of care chemotherapies including pemetrexed in the case of ALK rearrangements. In addition, EGFR activating mutations confer significant prognostic implications as illustrated by the improved PFS to the platinum doublet, carboplatin and paclitaxel, and overall survival in the EGFR mutant population .These mutations also potentially alter PD-L1 expression, likely due to yet undefined interactions between the PD-1/PD-L1/2, EGFR and EML4/ALK pathways .These observations indicate that tumors that bear EGFR mutations or ALK rearrangements may be fundamentally different from tumors that do not bear these mutations and may have different safety and efficacy profile with Pembrolizumab as compared to tumors that do not bear these mutations. Given that little data exist regarding the safety and/or efficacy implications of Pembrolizumab on these tumors. Tumors that bear these mutations will be excluded from this study.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of Pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of Pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for Pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of Pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of Pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of Pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of Pembrolizumab (as assessed by the population PK model) and 4) the assumption

that the dynamics of Pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of Pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.
A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.3 Rationale for Endpoints

4.2.3.1 Primary Efficacy Endpoints

- **Progression-free survival (PFS)**

Progression-free-survival is defined as the time from enrolement to the first documented disease progression per RECIST 1.1 based on radiologists' review or death due to any cause, whichever occurs first. Progression free survival is an acceptable measure of clinical benefit , especially if the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for 1L NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors afatinib and erlotinib.

4.2.3.2 Secondary Efficacy Endpoints

- **Overall Survival (OS)**

Overall Survival (OS) is defined as the time from errollement to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

- **Overall Response Rate (ORR)**

Overall response rate (ORR) is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon radiologists' review per RECIST 1.1.

- **Response Duration (DoR)**

The Duration of Response (DoR) is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest

measurements recorded since the treatment started). It measures the length of the response in those patients who responded. The patients who don't respond aren't included.

- **Disease Control Rate(DCR)**

The Disease Control Rate (DCR) is defined as the percentage of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention. The DCR is the sum of complete responses (CR) + partial responses (PR) + stable disease (SD).

4.2.3.3 Biomarker Research

4.2.3.3.1-Tumor expression of PD-L1.
Results of the Keynote 001 study have indicated that progression-free and overall survival were shorter among patients with a proportion score (PS) of 1 to 49%, or a score of less than 1%, compared to patients with a score of at least 50%. However, ORR were observed even in patients' subsets with a score<50%. Specifically, ORR were 8.1%, 12.9% and 19.4% in patients wit a PS<1%, between 1 and 24%, and between 25 and 49%, respectively, indicating that even a fraction of patients with a PD-L1 "low" expression can respond to this type of therapy.

4.2.3.3.2-Tumor-associated leukocyte subsets.
Based on the available evidence described in the section 3.1, patients responding to therapy with antibodies targeting the PD-1/PD-L1 axis are expected to have either a pre-existing condition of active T cell –mediated anti-tumor immunity, or to develop anti-tumor immunity during therapy. Presence at tumor site of tumor-infiltrating T lymphocytes, often of the $CD8^+$ subset and that upregulate PD-1, or increased frequency of $CD8^+$ T cells, in the existing lesions, as result of therapy, have been shown to predict responsiveness to immune checkpoint blockade. Several additional T cell activation/functional differentiation markers can be evaluated on lymphocytes found in the neoplastic lesions and can reveal whether there is an ongoing immune response at tumor site. These markers include those associated with maturation to cytolytic stage (as granzyme b and TIA1) as well as those associated with chronic antigen stimulation (as PD-1, LAG-3, TIGIT). Moreover, response to immune checkpoint blockade requires the downmodulation of immunosuppressive mechanisms. This means that for response to take place, cells with immunoregulatory functions, such as regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) are expected to be excluded from the lesion or be present at very low frequency. Based on this rationale, responding and progressing patients are expected to show significant differences in the frequency of at least some of the following tumor-associated leukocyte subsets, as determiend by immunohistochemistry in pre-therapy lesions, including:
a) $CD3^+$, $CD4^+$ and $CD8^+$ lymphocytes;
b) T cells expressing markers of functional differentiation to cytolytic stage such as granzyme B and TIA-1, or of maturation to memory stage (CD45RO);

c) T cells expressing PD1;
d) T cells expressing inhibitory receptors as LAG-3, TIM-3 and TIGIT;
e) T cells expressing PD-L1.
f) Cells with immunosuppressive functions including Tregs and MDSCc.

4.2.3.3.3-Peripheral blood immune profiling.
As mentioned in section 3.1, evidence based on peripheral immune profiling of patients treated with antibodies that block immune checkpoints, indicates that this type of therapy can promote several different systemic effects including: changes in absolute leukocyte subsets counts, changes in frequency of cells with immunosuppressive function, as well as functional activation or rescue of the function of exhausted T cells (reinvigoration). Based on this evidence, responding and progressing patients are expected to show significant differences, for at least some of the following immune cell subsets, based on:
a) comparison for frequency/phenotype in pre-therapy blood samples;
b) comparison for changes in frequency/phenotype in pre- vs on-therapy samples.
Immune cell subsets to be characterized:
-Dendritic cell subsets (mDCs, pDCS and iDCs), by staining for: CD45, Lin, CD34, HLA-DR, CD11c, CD123, PD-L1, CD86.
-Myeloid-derived suppressor cells (MDSCs) subsets by staining for: CD45, Lin, CD14, CD15, HLA-DR, CD11b, CD33.
-Regulatory T cells by staining for CD3, CD4, CD8, CD127, FOXP3, CD25.
-T cell activation/maturation by staining for: CD3, CD4, CD8, CD45RA, Ki67, GranzymeB, CCR7, CD69.
-Inhibitory receptor expression on T cells by staining for : CD3, CD4, CD8, PD-1, PD-L1, TIM-3, LAG-3, TIGIT.
-T cell exhaustion/reinvigoration by staining for : CD3, CD4, CD8, PD-1, EOMES, Ki67, GranzymeB.

4.2.3.4 PROMIS questionnaires

The Patient Reported Outcomes Measurement Information System (PROMIS®) provides clinicians and researchers access to reliable, valid, and flexible measures of health status that assess physical, mental, and social well–being from the patient perspective. PROMIS measures are standardized, allowing for assessment of many patient-reported outcome domains—including pain, fatigue, emotional distress, physical functioning and social role participation—based on common metrics that allow for comparisons across domains, across chronic diseases, and with the general population. Further, PROMIS® tools allow for computer adaptive testing, efficiently achieving precise measurement of health status domains with few items. There are PROMIS measures for both adults and children. PROMIS® was established in 2004 with funding from the National Institutes of Health (NIH) as one of the initiatives of the NIH Roadmap for Medical Research. The PROMIS questionnaires develops and evaluates standard measures for key patient-reported health

indicators and symptoms. Patient-reported measures such as pain, fatigue, emotional distress, and physical functioning complement clinical measures by providing healthcare providers with information about what patients are able to do and how they feel.

4.2.3.3.4-Stool sample profiling

Based on the available evidence described in the section 3.1 patients responding to therapy with antibodies targeting the PD-1/PD-L1 axis are expected to have a peculiar gut microbiota composition.

16S rRNA gene profiling of pre-therapy and on-therapy stool samples will be performed and compared in responders vs non responders.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with EGFR wt and EML4/ALK fusion negative NCSLC whose tumors demonstrate PD-L1 "low" expression as determined by immunohistochemistry with anti-PD-L1 mAb 22C3 (DAKO) who have received no prior systemic chemotherapy treatment for their advanced NSCLC, and are ≥ 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Have a confirmed diagnosis of NSCLC in stage IIIB/ IV. Do not have an EGFR sensitizing (activating) mutation or ALK translocation and have a PD-L1 "low" (<50%) tumor as determined by immunohistochemistry with anti-PD-L1 antibody (DAKO 22C3). Have not received prior systemic chemotherapy treatment for advanced NSCLC. Subjects with non-squamous histologies will not be enrolled until the EGFR mutation status and/or ALK translocation status is available. For patients enrolled who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR and ALK translocation will not be required .

2. Be willing and able to provide written informed consent/assent for the trial.

3. Be ≥ 18 years of age on day of signing informed consent.

4. Have measurable disease based on RECIST 1.1.
5. Be willing to provide tissue from archived histological specimen or newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 45 days prior to initiation of treatment on Day 1.
6. Have a performance status of 0-2 on the ECOG Performance Scale.
7. Demonstrate adequate organ function as defined in.
8.
9. Table , all screening labs should be performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

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

12. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

13. No history of active malignancy requiring treatment

5.1.3 Subject Exclusion Criteria

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

1. Has an EGFR sensitizing mutation and/or an ALK translocation.
2. Has a PD-L1 expression assessed as "high" by the central laboratory
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
4. Has a known history of active TB (Bacillus Tuberculosis).
5. Hypersensitivity to Pembrolizumab or any of its excipients.
6. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

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

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

9. 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.

10. Has a history of non-infectious pneumonitis that required steroids or has current pneumonitis.

11. Has an active infection requiring systemic therapy.

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

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

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

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

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

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

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

Table 3 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg TOT	Q3W	IV infusion	Day 1 of each 3 weeks cycle	Experimental

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

Details on preparation and administration of Pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose modification and toxicity management guidelines for pembrolizumab

5.2.1.2.1 Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

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 trial 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.
The important identified risks of immune-mediated nature for pembrolizumab included : pneumonitis; colitis; encephalitis";"sarcoidosis"; hepatitis; nephritis; endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), and Type I diabetes mellitus; uveitis; myositis; Guillain-Barré syndrome; pancreatitis; myocarditis; severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with

fatal outcome; and "solid organ transplant rejection" following pembrolizumab treatment in donor organ recipients. The risk profile for pembrolizumab also included 2 other important potential risks – i.e. myasthenic syndrome or worsening of "myasthenic syndrome" and increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

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 4.

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. Pembrolizumab is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Table 4 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 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 pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 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 Increased bilirubin	Grade 2 or 3	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 enzyme value returned to baseline or is stable
	Grade 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

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 or 3	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 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		
Severe skin reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)	Any grade	Permanently discontinue	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper	• Monitor subjects for signs and symptoms of severe skin reactions • Add prophylactic antibiotics for opportunistic infections in Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN)
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).

For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

5.2.1.2.2 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 4.

Table 5 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 subject 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 subject 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject 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		

5.2.1.2.3 Other allowed dose interruption for pembrolizumab

Pembrolizumab maybe interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. The site should make every effort to target infusion timing to be as close to 30 minutes as possible. However 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.

5.2.3 Trial Blinding/Masking

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

5.3 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 subject's primary physician.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications

and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date 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.

5.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Thoracic Radiation therapy
    - Note: Radiation therapy to a symptomatic lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AEs of suspected immunologic etiology. Steroids required to prevent allergic reactions due to Imaging (CT scan or MRI contrast) are allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

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

5.4 Diet/Activity/Other Considerations

5.4.1 Diet

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

5.4.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if Pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects 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).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.4.3 Use in Pregnancy

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

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

5.4.4 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, subjects who are breast-feeding are not eligible for enrollment.

5.5 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

- Confirmed radiographic disease progression
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with Pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop Pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment.

- Administrative reasons

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

5.5.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with Pembrolizumab and had at least two treatments with Pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with Pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of

Pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation.

5.6 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Treatment Cycles[a]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-45 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Informed Consent	x												
Inclusion/Exclusion Criteria	x												
Demographics and Medical History	x												
Prior and Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x	x	x	
Trial Treatment Administration		x	x	x	x	x	x	x	x				
Post-study anticancer therapy status											x	x	x
Survival Status	x	x	x	x	x	x	x	x	x	x	x	x	x
Review Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x
Full Physical Examination	x	x	x	x	x	x	x	x	x	x	x	x	
Directed Physical Examination	x	x	x	x	x	x	x	x	x	x	x	x	
Vital Signs and Weight	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x	
PROMIS questionnaires 1	x	X		X		x		x		X	X	x	
Pregnancy Test – Urine or Serum β-HCG	x												
PT/INR and aPTT	x												
CBC with Differential	x	x	x	x	x	x	x	x	x	x	x	x	

Trial Period:	**Treatment Cycles[a]**									**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-Up
						5	6	7	8				
Scheduling Window (Days):	-45 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel	x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis	x				x				x	x	x	x	
T3, FT4 and TSH	x		x		x		x		x	x	x	x	
Tumor Imaging	x			x			x					x	
Archival or Newly Obtained Tissue Collection	x												
Correlative Studies Blood Collection	x		x		x		x		x	x			
Correlative studies stool collection	x		x							x			

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before participation in the trial.
The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.
Specifics about a trial and the trial population will be added to the consent form template at the protocol level.
The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded .

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 subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before

the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to enrollment. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

7.1.1.7 Assignment of allocation Number

All eligible subjects will be enrolled and will receive a allocation number. The allocation number identifies the subject for all procedures occurring after allocation. Once a allocation number is assigned to a subject, it can never be re - assigned to another subject. A single subject cannot be assigned more than 1 allocation number.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between Pembrolizumab doses due to toxicity require consultation with the Sponsor and written documentation of the collaborative decision on subject management. Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 . Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with Pembrolizumab all AEs of unknown etiology associated with Pembrolizumab exposure should be evaluated to determine if it is possibly a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Disease assessments are to be performed as scheduled according to the calendar days regardless of treatment delays. On-study tumor assessments for subjects enrolled (CT scan of brain, chest, abdomen and pelvis) are to be performed every 9 weeks (63 +/- 3 days) from the date of enrollment until radiographic PD has been established and documented. If study drug is discontinued in the absence of confirmed RECIST 1.1 defined disease progression, subjects should remain on study until confirmation is received (section 7.1.5.4). Subjects may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. CT scan of brain, chest, abdomen and pelvis is required for the baseline assessment in the screening phase. For subjects with previously unidentified brain metastases, a screening brain MRI will not need to be obtained. If brain metastases are identified brain MRI will be necessary instead of the brain CT.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood and Stool Sampling

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion must be provided in the form of a tissue block or at least ten unstained slides. Only subjects whose tumors demonstrate "low" PD-L1 expression are enrolled. Low PD-L1 expression is defined as <50% neoplastic cells showing membranous staining of PD-L1 (i.e. proportion score <50% as described by Garon et al in N Engl J Med 2015;372:2018-28). Tumor PD-L1 expression will be evaluated, at Istituto Nazionale Tumori of Milan, by immunohistochemistry, on either a contemporaneous biopsy sample or on archival pre-therapy lesion with anti-PD-L1 antibody (DAKO 22C3). In addition to expression of PD-L1, neoplastic samples will be characterized by immunohictochemistry for the following markers: CD3, CD4, CD8, CD45RO, Granzyme B, TIA-1, PD-1, TIM-3, LAG-3, TIGIT, FOXP3, HLA-I and II, CD11b, CD33. A fine needle aspirate or cytologic specimen will not be acceptable. Needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are encouraged. Older biopsy material or surgical specimens may be used to assess EGFR mutation status and ALK translocation status, if not already known when the subject signs informed consent.

Correlative Studies. Blood sampling will be performed in the screening phase, every two cycles in the treatment phase and at the end of treatment visit. Blood samples will be characterized by multiparametric flow cytometry for the following parameters/cell subsets:
-Quantitative determination, by BD Trucount Beads method, of main cellular subsets including: T, B, monocytes, by staining for: CD45, CD3, CD4, CD8, CD14, CD19, HLA-DR, PD-1 (latter marker only in pre-therapy sample).
-Dendritic cell subsets (mDCs, pDCS and iDCs), by staining for: CD45, Lin, CD34, HLA-DR, CD11c, CD123, PD-L1, CD86.
-Myeloid-derived suppressor cells (MDSCs) subsets by staining for: CD45, Lin, CD14, CD15, HLA-DR, CD11b, CD33.
-Regulatory T cells by staining for CD3, CD4, CD8, CD127, FOXP3, CD25.
-T cell activation/maturation by staining for: CD3, CD4, CD8, CD45RA, Ki67, GranzymeB, CCR7, CD69.
-Inhibitory receptor expression on T cells by staining for : CD3, CD4, CD8, PD-1, PD-L1, TIM-3, LAG-3, TIGIT.
-T cell exhaustion/reinvigoration by staining for : CD3, CD4, CD8, PD-1, EOMES, Ki67, GranzymeB.
Stool sampling will be performed in the screening phase, before the second cycle in the treatment phase and at the end of treatment. Stool samples will be characterized by 16S rRNA gene profiling.

7.1.2.8 Patient Reported Outcomes (PROs)

The Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires will be administered by qualified site personnel as specified in the Trial Flow Chart. If the subject discontinues from the study for reasons other than PD then the PRO assessments will be collected until the subject experiences disease progression.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 6 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 thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine		
	Gamma-glutamyl Transpeptidase (GGT)		
	trigliceridi		
	Colesterolo totale		

Hematology	Chemistry	Urinalysis	Other
	Colesterolo HDL		
	Colesterolo LDL		

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements. Subjects who a)obtain a CR or b) complete 24 months of treatment with Pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

7.1.5.1.1 Screening Period

Visit requirements are outlined in Trial Flow Chart. Approximately 45 days prior to enrollement, potential subjects will be evaluated to determine that they fulfill the entry requirements.
Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 45 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu

of repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

7.1.5.2 Treatment Period

Visit requirements are outlined in Trial Flow Chart.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 End of treatment visit

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated.

7.1.5.3.2 Safety Follow-Up Visit

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

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Pembrolizumab. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with Pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.4.1 Survival Follow-up

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

7.1.5.5 Second Course Phase (Retreatment Period)

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

- **Either**
  - Stopped initial treatment with Pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with Pembrolizumab before discontinuing therapy
    - Received at least two treatments with Pembrolizumab beyond the date when the initial CR was declared

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with Pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of Pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

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

- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have 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.
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, teething, typical crying in infants and children and 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 placebo or 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 adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject 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, placebo treatment or a procedure.

From the time of treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

For purposes of this trial, an overdose of Pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of Pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided 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 AE 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 215 993-1220).

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

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject 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, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject 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 215 993-1220)

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 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event,

including death due to any cause that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject 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 24 hours to the Sponsor and 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 the Sponsor and to Merck Global Safety.

All subjects 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: +1-215-993-1220

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 215 993-1220) 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 recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 7 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization 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 subject 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause 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 subject 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 subject 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 SUBJECT, 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	Subject 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 subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Using a clustering procedure specific subsets of immune biomarkers showing association with PFS will be identified; for each cluster one or more representative predictors (PDTs) will be selected and their association with PFS will be estimated using a univariate Cox regression model. The point and 95% confidence interval estimates will be provided for each activity and effectiveness endpoint; the assessment of safety will be based on the frequency and nature of AEs; maximum and average grade experienced by each patient for each specific PROMIS item and for each specific dimension associated with PROMIS (e.g. functional ability, emotional well-being, sexuality/intimacy, family well-being, treatment satisfaction, and social functioning) will be used as summary statistics.

8.2 Statistical Analysis Plan

8.2.1 Primary analysis

The primary analysis is aimed to identify immune biomarkers associated with PFS (PDTs); univariate analysis of individual PDTs requires a multiple testing correction to control the type I error rate, but also results in a loss of power; multivariate regression models to identify a smaller subset of biomarkers that contains the interesting predictors can suffer from low power and inability to find out the correct relationships between the dependent and independent variables; more clearly with many variables evaluated in a multivariate regression model the following statistical problems could be encountered: 1. Overfitting the data 2. Destabilizing the parameter estimates when PDTs are highly correlated between each other or there are missing data 3. Confounding the model interpretation when PDTs are highly correlated between each other or there are missing data; in order to reduce the number of PDTs to a smaller set of independent variables a variable clustering procedure will be applied; variable clustering provides groups of variables where variables in a groups are similar to other variables in the same group and as dissimilar as possible to variables in another group; an orthoblique principal components-based clustering (OPCC)[†] approach will be applied; the OPCC goal is to define a subset of clusters that explains a large proportion of total variance, such that those clusters can then be directly tested for association with PFS; in order to preserve the statistical power of the OPCC global association test a 60% explained variance threshold will be applied to identify PDTs clusters; the SAS VARCLUS[††] procedure will take PDTs data as input and output PDTs cluster correlations and cluster component scores, by number of clusters; each cluster score will be tested for association with PFS in a univariate Cox regression model; p-value from 1 d.f. Wald χ^2 for association with outcome, corrected for multiple testing with Bonferroni for number of clusters will be reported; because this study is exploratory (i.e. no specific prestated hypothesis was stated in advance)

no formal threshold for the p-value will be applied to reject the absence of statistical association.

After testing the statistical association between PDT clusters and PFS the following statistical properties of each cluster will be estimated:

1. the Correlation matrix; in order to detect non-linear correlation the Spearman's rank correlation coefficient will be used
2. the Squared correlation coefficient between a given PDT and its own cluster (R_o^2); each PDT should have a high correlation ($R_o^2 \approx 1$) with its cluster
3. the Next highest squared correlation coefficient (R_N^2) between a given PDT and any other cluster; each PDT should have a low correlation ($R_N^2 \approx 0$) with the other clusters
4. The 1-R^2 index used to identify the most representative PDT of the cluster; 1-R^2 index is defined as the ratio between 1- (R_o^2 index) and 1- (R_N^2 index); the PDT with the lowest 1- R^2 index (1-$R^2 \approx 0$) will be the most representative PDT of the cluster

For each cluster one or two most representative PDTs will be selected and their association with PFS will be estimated using a univariate Cox regression model; this procedure will permit to identify the strength and the direction of statistical association (i.e. HR < 1 or HR > 1) not only for the single PDT but also for the PDT cluster; because the purpose of these univariate analysis is merely exploratory after having identified interesting PDTs clusters no correction for multiple testing will be applied to p-values.

8.2.2 Secondary analysis

Median and range statistics will be used to estimate follow-up duration; median follow-up will be estimated using the inverse Kaplan-Meier method; the patient alive with the shorter follow-up will be considered to compute the minimum follow-up time; the number of patients lost-to follow-up and the Clark's C index[†††] will be computed in order to quantify the completeness of follow-up.

Survival functions and median survival times will be non-parametrically estimated using the Kaplan-Meier estimator; a 95% confidence interval will be associated to each median survival time in order to control sampling error.

Each binomial parameter (e.g. ORR, DCR endpoints) will be accompanied by an exact 95%CI in order to control sampling error.

All safety parameters will be analyzed and presented in terms of listings and summary tables; the assessment of safety will be based on the frequency and nature of AEs.

Maximum and average grade experienced by each patient for each specific PROMIS item and for each specific dimension associated with PROMIS (e.g. functional ability, emotional well-being, sexuality/intimacy, family well-being, treatment satisfaction, and social functioning) will be computed and summarized by descriptive statistics (median and range).

Baseline covariate distributions will be summarized using descriptive statistics (median and range for continuous variables, and absolute and percentage frequencies for categorical variables).

Primary and secondary analyses will be performed using SAS software (SAS Institute, Cary, NC, USA), version 9.2 or later.

Further details regarding statistical analysis will be provided in the SAP.

8.3 Sample size

The sample size for clinical trials such as this are not normally based on formal statistical considerations, as there are no primary hypotheses being tested; there was therefore no need to formally power this trial. A lower limit on the number of patients that would be included in the trial was set at 65; this limit was based on pragmatic considerations that included the planned study duration and a worthwhile clinically relevant effect; considering an enrollment period of one year at least 65 patients are expected to be enrolled; in order to provide 80% power to detect a relative hazard per standard deviation unit equal to 1.50 using a two-sided test at the 0.05 level, the number of events required will be 48; assuming a proportion of events at analysis time greater or equal to 75% the sample size will be 64 patients. Final analysis is expected to occur after 1 year from the closure of enrollment.

† Back M.H., Watanabe R.M. A principal Components-Based Clustering Method to Identify Variants Associated with Complex Traits Hum Hered 2011;71:50-58
†† SAS/STAT 9.2 User's Guide, Chapter 93
††† Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. Lancet. 2002 Apr 13;359(9314):1309-10

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor. By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures. If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and

all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor. Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms. The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed. The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this trial. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened. In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

The Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must

be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases. These timelines may be extended if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement.

When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures,

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.
For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.
Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.
The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation.
Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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11.0 APPENDICES

11.1 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.	

11.2 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)

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

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

* As published in the European Journal of Cancer:

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

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