ID: UMCC 2017.057	Pembrolizumab in Combination With Platinum-Based Chemotherapy in Non-Small Cell Lung Cancer (NSCLC) Patients With Targetable Genetic Alterations, Previously Treated With Appropriate Targeted Agents, With Progressive Disease	NCT03242915

TITLE: UMCC 2017. 057: Phase II multi-center study of pembrolizumab in combination with platinum-based doublet chemotherapy in NSCLC (non-small cell lung cancer) patients with targetable genetic alterations in their tumor previously treated with appropriate targeted agents with progressive disease

IND NUMBER: IND Exempt

Principal Investigator

Gregory Kalemkerian, MD
1500 E. Medical Center Drive
C350 Med Inn Building – SPC 5848
Ann Arbor, MI 48109
Tel: (734) 647-8921
Fax: (734) 647-8792
email: kalemker@med.umich.edu

Coordinating Center
University of Michigan

Statistician

Thomas Braun, PhD
University of Michigan
Cancer Center Biostatistics, Analytics and Bioinformatics Core, M4063 SPH II
Ann Arbor, MI 48109
P: (734) 936-9844
Email: tombraun@umich.edu

Version: 05/03/2021

NOTE: The study was amended to address protocol-required items that the COVID-19 pandemic may temporarily affect. The potential changes are listed in Section 15.0 (COVID-19 Addendum).

Index

1.0 Trial Summary	3
2.0 Trial Diagram	5
3.0 Objectives and Hypothesis	5
4.0 Background and Rationale	6
5.0 Methodology (Inclusion & Exclusion Criteria)	16
6.0 Trial Treatments	19
7.0 Trial Flow Chart	34
8.0 Trial Procedures	37
9.0 Correlative Studies	48
10.0 Statistical Analysis Plan	51
11.0 Labeling, Packaging, Storage and Return of Clinical Supplies	54
12.0 Administrative & Regulatory Details	55
13.0 References	59
14.0 Appendices	63
15.0 Addendum	65

1.0 TRIAL SUMMARY

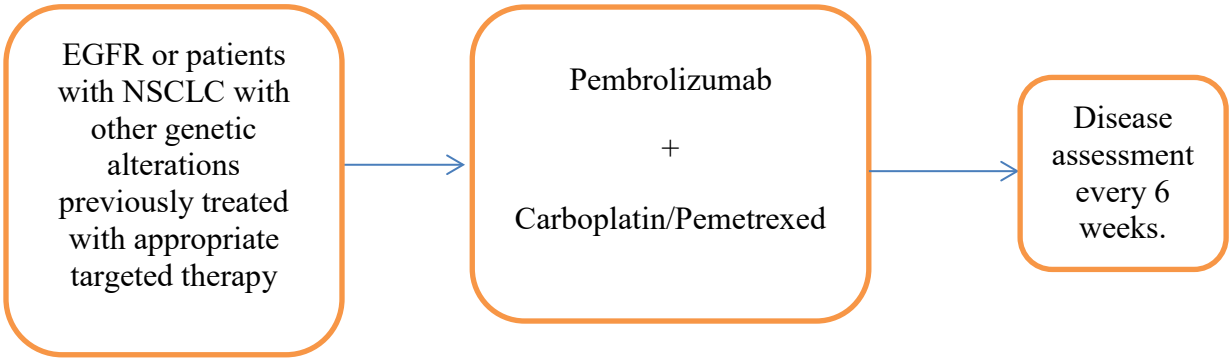
Abbreviated Title	A multi-center study of pembrolizumab with platinum-based chemotherapy in patients in NSCLC patients with targetable genetic alterations, previously treated with appropriate targeted agents with progressive disease
Trial Phase	*II*
Clinical Indication	Non-Small Cell Lung Cancer (NSCLC)
Trial Type	Single Arm Open Label Phase II with 2 cohorts
Type of control	N/A
Treatment and Route of administration	Pembrolizumab 200 mg with carboplatin at AUC 5 and pemetrexed at 500 mg/m^2 administered intravenously every 3 weeks
Duration of Therapy	All drugs will be administered for a maximum of 4 cycles followed by maintenance pemetrexed and pembrolizumab for a maximum of 24 months.
Trial Blinding	N/A
Treatment Groups	Single Group
Number of trial subjects	31 EGFR and 31 NSCLC patients with other targetable genetic alterations
Study Centers	6 including University of Michigan as the lead site.
Estimated enrollment period	*24 months*
Estimated duration of trial	*48 months*
Duration of Participation	24 months
Estimated average length of treatment per patient	7 months
Primary Objective	To assess the response rate (RR) of the combination of pembrolizumab and chemotherapy in EGFR mutation or patients with NSCLC patients with other targetable genetic alterations, who have progressive disease following appropriate targeted therapy.
Key Inclusion Criteria	1. Cohort 1-Patients with EGFR mutation positive NSCLC previously treated with appropriate targeted therapy with measurable and progressive disease. Cohort 2- Other genetically altered NSCLC patients, previously treated with appropriate targeted therapy with measurable and progressive disease. Patients could have received more than one targeted therapy. Patients taken off an appropriate targeted therapy due to intolerance are eligible. 2. Tumor to assess PD-L1 status should be available unless PD-L1 status of the tumor is known. 3. ECOG PS of 0,1 4. Defined hepatic, renal and hematologic laboratory results

Key Exclusion Criteria	1. Has a diagnosis of immunodeficiency. Patient should not be on any immunosuppressive therapy or steroids > prednisone 10mg/day or its equivalent on the day of the start of therapy. 2. Has had targeted small molecule therapy, or palliative radiation therapy within 1 week 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. Some exceptions are allowed. 3. Has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with **asymptomatic** brain metastases may participate provided they are clinically stable and are not using steroids equivalent to >10mg of prednisone day prior to trial treatment. 4. 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. 5. Has known history of non-infectious pneumonitis that required steroids or has current pneumonitis. Has known history of interstitial lung disease.
Statistical Design	The study design is a multi-site, single arm phase II trial with 2 parallel cohorts. To minimize the number of patients required the single arm two-stage minimax Simon's design will be used for each cohort. The study will be conducted in two separate cohorts; EGFR mutation positive NSCLC cohort and NSCLC patients with other genetic alterations, previously treated with appropriate targeted therapy. The primary objective is to assess the treatment efficacy based on the response rate (RR), of combination pembrolizumab and platinum-based doublet in EGFR mutation positive or NSCLC patients with other genetic alterations patients who have progressed in the two study cohorts. The primary endpoint is RR defined by RECIST 1.1. For each cohort the sample size calculation is the same as we chose the same parameter settings. Sample size calculation: The combination treatment would be of clinical interest if the RR is > 0.55 and will not if the RR is <0.3. With 14 pts in stage I and 28 total pts, the 2-stage Simon's minimax design has a 5% type I error and 85% power and a probability of early termination of 0.58. The cohort is to be terminated at stage I if ≤ 4 pts respond. If the cohort goes on to stage II and total number of responses is ≤ 12, the treatment is rejected. Thus, if both cohorts go to stage II then each of the cohorts will require 28 evaluable patients. To be evaluable for efficacy, the patient has to have received at least one dose of pembrolizumab and doublet chemotherapy. **We assume an ineligibility rate of 10% so we plan to enroll 31 patients in each cohort of the trial.**

	Due to slow enrollment on the study and changes in study personnel, the study enrollment will be terminated on December 31, 2020. We anticipate that we will enroll approximately 25 patients in Cohort 1 and approximately 7 in Cohort 2.

2.0 TRIAL DIAGRAM

Trial Diagram



The primary end point of the study is to assess response rate (RR) by RECIST 1.1.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective: To assess the response rate (RR) by RECIST 1.1 (Appendix 14.3) of the combination of pembrolizumab and chemotherapy in EGFR mutation or patients with NSCLC with other genetic alterations, who have progressive disease following appropriate targeted therapy.

Hypothesis: We hypothesize that addition of pembrolizumab will enhance the efficacy of carboplatin and pemetrexed in EGFR mutation and patients with NSCLC with other genetic alterations who have disease progression following appropriate targeted therapy.

3.2 Secondary Objective(s)

1. To assess the PFS (progression free survival defined by RECIST 1.1) (Appendix 14.3), OS (Overall Survival) in these patients.

3.3 Other Objectives

1. To assess the toxicity of the combination.
2. To correlate the RR with PD-L1 status of the tumor and the mutational load of the tumor.
3. To assess the numerical changes in the CTCs (circulating tumor cells) count before the 1st and before 3rd cycles of therapy and correlate it with response to study therapy.
4. To assess the ability to analyze PDL1 expression and assess the expression of EMT markers in CTCs.
5. To assess the ability to extract tumor DNA from CTCs and conduct analysis of EGFR and other gene alterations.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 EGFR mutation positive NSCLC

EGFR tyrosine kinase inhibitors (TKIs) are the standard first line therapy for advanced NSCLC patients (pts) with tumors that harbor activating EGFR mutations (1). For pts progressing on first line TKIs, the most common mechanism of resistance is presence of T790M mutation (2). Recently, T790M inhibitors, like osimertinib, have shown clinical benefit in these pts. However, almost all patients develop tumor progression even on these drugs (3,4). In addition, there are no approved targeted treatments for pts who have other mechanisms of resistance. Many of these patients will be considered for chemotherapy. The IMPRESS trial showed that continuation of gefitinib, an EGFR TKI, after disease progression did not prolong PFS in pts who received platinum-based doublet chemotherapy as subsequent therapy. Thus, platinum-based doublet chemotherapy remains a treatment option for patients with EGFR mutation positive cancer who have disease progression on a T790M inhibitor or have progression of disease following front line EGFR-TKI and don't have the T790M mutation in their tumor. In the IMPRESS trial, the response rate (RR) to chemotherapy was 33% (5). Another combination evaluated in a similar population is the combination of afatinib and cetuximab. In a single arm multi-institutional study the response rate with this combination was 29% (6).

4.1.2 Other genetically altered NSCLC

Several ALK inhibitors are currently approved as front line therapy for ALK positive NSCLC (7). The median progression free survival with these drugs can range from about 11 months to 34 months. Two drugs are currently approved for the treatment of crizotinib resistant/refractory ALK positive NSCLC, ceritinib and alectinib (8, 9). The response

rate with these agents is about 50% and the median PFS is about 6-9 months. There are other agents, such as lorlatinib, that have shown activity in ALK positive patients following treatment with 2 prior ALK inhibitors (10). However, many patients eventually require chemotherapy. Though the response rate with chemotherapy in ALK positive patients who have received 2 prior ALK inhibitors is not known, it is expected to be around the same as observed in EGFR mutation positive NSCLC patients in the IMPRESS trial.

Over the last few years targeted drugs for other genetically altered NSCLC have also received FDA approval. Crizotinib and entrectinib are now approved for the treatment of ROS1 positive NSCLC (11.12). Similarly, the combination of dabrafenib and trametinib is approved for the treatment of Braf mutation positive NSCLC and recently larotrecinib was approved for the treatment of NTRK gene rearranged cancers (13, 14). In addition, NCCN guidelines include treatment with crizotinib for patients with cMET amplification and exon 14 skip mutation and RET inhibitors for the treatment of RET altered NSCLC (15). Despite clinical efficacy of these agents, almost all patients eventually experience disease progression. Many of these patients are treated with platinum based chemotherapy. The efficacy of platinum based chemotherapy following targeted therapy in these patients is not well defined but is not expected to be any better than the efficacy of chemotherapy in EGFR or ALK positive patients.

4.2 Immune Surveillance and PD-1 axis

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (16). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (17,18,19). 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 (20,21,22,23,24). 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 either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. 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 (Keytruda®) 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. In the case of pembrolizumab the use is restricted to patients whose tumors express PD-L1. More recently pembrolizumab was approved for front line use in advanced NSCLC patients with tumors that have high PD-L1 expression. This approval was based on the results of the Keynote-24 trial (25). In this trial patients with tumors that had ≥ 50% tumor proportion score (TPS score) for PD-L1 expression were randomized to pembrolizumab or platinum based chemotherapy. Patients with EGFR mutation and ALK positive NSCLC were excluded. The results of this study showed that pembrolizumab significantly improved survival and progression free survival compared to chemotherapy. Thus currently single agent pembrolizumab is approved for advanced NSCLC patients as front line therapy if their tumors have high PD-L1 expression and for patients who have had prior chemotherapy or targeted therapy if their tumor has any level of PD-L1 expression.

4.2.1 Anti-PD-1 Therapy in patients with NSCLC with gene alterations

PD1 inhibitors, such as pembrolizumab and nivolumab and PD-L1 inhibitor atezolizumab have been FDA approved for second line therapy in NSCLC (26,27,28). Activity of single agent anti-PD-1/PD-L1 drugs has been modest in EGFR mutated/ALK positive patients. Retrospective subset analysis of Checkmate 057 and atezolizumab trials showed that never

smokers and EGFR mutated pts did not derive greater benefit from these agents compared to docetaxel . Recently, Gainor, et al published the results of a retrospective analysis of the use of these agents in 28 patients with EGFR mutation (n=22 patients) or ALK translocations (n=6 patients) (29). Of these patients, only 1 EGFR mutation positive patient had tumor response to a PD-1 directed agent. This response rate was far lower than the response rate of 23% among 30 patients, treated at the same institution, who were EGFR and ALK wild type or ALK unknown. Similar results have been reported in patients with other gene altered NSCLC (29).

Previous studies have suggested that tumors with higher number of somatic mutations such as melanoma and lung cancer had higher RR to PD1-blockade (30, 32). This was also supported by the observation that in lung cancer cohorts, pts with smoking history had higher RR to PD1 inhibition (31). In addition, anti-PD-1 drugs have shown clinical benefit in mismatch repair-deficient colorectal cancer which are known to have 10 to 100 times as many somatic mutations as mismatch repair-proficient (34). The relative lack of benefit with anti-PD-1 agents in EGFR mutated or ALK positive patients may be a result of low mutation load, since most are never/light smokers.

4.2.2 Combination of Pembrolizumab and Chemotherapy

Since recurrent tumors are likely to have greater mutational load, it can be speculated that anti-PD-1 drugs may be more beneficial in EGFR mutation and ALK positive NSCLC pts following recurrence, as compared to front line therapy. With the recognition that anti-PD-1 drugs have only modest activity in recurrent EGFR mutated and ALK positive patients, these drugs may have to be combined with other drugs in such patients. Chemotherapy is thought to cause release of tumor antigens through cell necrosis and activate the anti-tumor T cell response which can be further potentiated with the addition of anti-PD-1 drugs. Initial results evaluating the combination of pembrolizumab with chemotherapy have shown promising results (29).

In the Keynote 021 trial (35), 74 advanced NSCLC patients were treated with one of 3 different chemotherapy regimens in combination with pembrolizumab. In cohort A, patients received carboplatin and paclitaxel; in cohort B, patients received carboplatin paclitaxel and bevacizumab and in cohort C patients received carboplatin (Parapatin®) and pemetrexed (Alimta®). The overall response rate was 57% (RR varied from 48%-71%). The response rate did not vary according to the PD-L1 status. The median PFS (progression free survival) was 10.2 months in cohorts A and C and had not been reached at the time of analysis in cohort B. No unusual toxicities were reported. Immune related AEs were reported in 16%-38% of the patients.

Subsequently over 120 patients with advanced non-squamous histology were randomized to carboplatin pemetrexed with or without pembrolizumab (36). The results of this randomized cohort demonstrated that the progression free survival (median 13mo vs. 8.9mo, HR- 0.53, p=0.0102) and response rate (55% vs. 29%) were significantly improved with the addition of pembrolizumab. These data suggest that the addition of pembrolizumab can enhance the

efficacy of chemotherapy regimens and this study also showed that the increase in efficacy can occur irrespective of tumor PD-L1 expression. Based on these data a randomized double blind phase III study Keynote 189 was initiated and reported similar results (37) initiated (NCT02578680). In this study treatment naïve advanced non-squamous NSCLC patients, that are EGFR and ALK negative were randomized in 2:1 fashion to chemotherapy and pembrolizumab. Based on the improved survival observed with combination of pembrolizumab and chemotherapy, the FDA has now approved the regimen for advanced NSCLC patients without EGFR or ALK gene alterations in their tumors.

4.3 Preclinical and Clinical Trial Data

Refer to the investigator's brochure and package insert for preclinical and clinical data of pembrolizumab. Also please refer to package inserts of carboplatin (paraplatin®) and pemetrexed (Alimta®) for details of these drugs.

4.4 Rationale

4.4.1 Rationale for the Trial and Selected Subject Population

EGFR tyrosine kinase inhibitors (TKIs) are the standard first line therapy for advanced NSCLC patients (pts) with tumors that harbor activating EGFR mutations. The most common mechanism of resistance in pts progressing on first line TKIs is presence of T790M mutation. T790M inhibitors, like osimertinib, have shown clinical benefit in these pts. However, almost all patients eventually develop tumor progression. In addition, there are no approved targeted treatments for pts who have mechanisms of resistance, other than T790M. All such patients will be considered for chemotherapy. The most commonly considered chemotherapy for such patients is the combination of carboplatin and pemetrexed.

ALK inhibitors are now consistently utilized as front line and second line treatments for ALK positive NSCLC patients. Though there are ALK inhibitors in development that may have activity after patients that have received 2 ALK inhibitors, chemotherapy will be considered for many of these patients. As with EGFR mutated NSCLC patients, carboplatin and pemetrexed is the most commonly considered chemotherapy combination for ALK positive NSCLC patients who have progressed on 2 or more ALK inhibitors.

Similarly, though targeted agents are used for other gene altered NSCLC patients such as Braf, ROS1 or RET, chemotherapy is considered in patients who have disease progression following targeted therapy.

Anti-PD-1 drugs may be more beneficial in EGFR mutation, ALK positive NSCLC and other gene altered NSCLC pts following recurrence, as compared to front line therapy, since recurrent tumors are likely to have greater mutational load. However, single agent anti-PD-1 drugs have not shown significant activity in these patients. Chemotherapy is thought to cause release of tumor antigens through cell necrosis and activate the anti-tumor T cell response which can be further potentiated with the addition of anti-PD-1 drugs. The trial Keynote 189 showed that the addition of pembrolizumab to the combination of carboplatin/pemetrexed enhanced the efficacy of chemotherapy in advanced NSCLC patients, irrespective of PD-L1 status of the patient's tumor.

Based on the above data, we hypothesize that the addition of pembrolizumab to the combination of carboplatin and pemetrexed will increase the response rate in EGFR mutation and other gene altered NSCLC patients who have had disease progression on appropriate targeted therapy. To test this hypothesis we propose to conduct a phase II clinical trial evaluating the addition of pembrolizumab to standard platinum based doublet chemotherapy in EGFR mutation and other gene altered NSCLC patients who have disease progression following treatment with appropriate targeted therapy.

For this exploratory study, we believe that a single arm study with 2 cohorts one (EGFR mutated and other gene altered NSCLC cohorts) is acceptable design since efficacy of chemotherapy in these patients is well defined. If the results of the proposed trial demonstrate sufficient efficacy then a randomized study will be conducted in the future.

4.4.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) has reported safety and clinical activity of single agent MK-3475 (20). 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 MK-3475 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 MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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.

Finally, in the Keynote 021 trial, cohort G this flat dose of 200mg of pembrolizumab administered every 3 weeks when combined with carboplatin/pemetrexed was found to be well tolerated and efficacious. So consistent with the schedule tested in cohort G of trial Keynote 021, in this trial all eligible patients will be treated with pembrolizumab at a dose of 200mg in

combination with carboplatin AUC 5 and pemetrexed 500 mg/m^2 every 3 weeks. Patients will receive combination chemotherapy for a maximum of 4 cycles. Following 4 cycles patients will receive maintenance therapy with pemetrexed and pembrolizumab for a maximum of 24 months (from the start of trial therapy).

4.4.3 Rationale for Endpoints

4.4.3.1 Efficacy Endpoints

We have selected Response Rates (RR) as defined by RECIST 1.1 criteria as the primary endpoint. RR with the combination of a platinum analogue and pemetrexed in a similar patient population, as being studied in this study, was found to be 33% in the recently reported IMPRESS trial. Another combination of afatinib+cetuximab examined in a similar population showed a RR of 29%. These two datasets provide the benchmark for EGFR mutation positive NSCLC patients. The response rate with second line and third line ALK inhibitors in ALK positive NSCLC is about 50% and this establishes the benchmark of ALK positive NSCLC patients. Though data with platinum based chemotherapy in other gene altered NSCLC patients is not well defined we speculate that efficacy will be no better than what has been observed in EGFR mutation positive NSCLC patients. We also wanted to select a relatively early endpoint for this exploratory trial.

It is well recognized that in minority of patients treated with immune therapy may have pseudo progression or can have delayed response. In addition, there are patients who have isolated areas of progression, with control in other areas. Therefore, patients can continue on study therapy beyond progression, if felt to be in the best interest of the patient.

In this trial we will also assess PFS by RECIST criteria and we will assess overall survival as well.

4.4.3.2 Biomarker Research

Response rates to PD-1 and PD-L1 targeted agents indicate that a subset of patients derive greater benefit from this treatment strategy, whereas some patients have no benefit. To complement this study and increase its scientific yield, we are proposing scientific correlates in an attempt to identify potentially predictive biomarkers for pembrolizumab combined with chemotherapy. While these are unlikely to be definitive, based on the relatively small numbers of patients involved, the data collected will help guide the development of potential biomarkers in future studies as well as identify patients most

likely to benefit or not benefit from the combination of pembrolizumab and chemotherapy in these specific NSCLC patients.

PD-L1 expression

Emerging data suggests that expression of PD-L1 on the tumor may predict for benefit from pembrolizumab and other anti-PD-1. Benefit has also been observed in patients whose tumors don't express PD-L1 but the percentage of such patients who benefit is far less. This difference in efficacy with anti- PD-1 drugs has been observed across tumor types.

Preliminary data suggest that tumor PD-L1 expression is a predictive marker for pembrolizumab (20). In patients with recurrent NSCLC the drug is only approved in patients whose tumors have some level of tumor PD-L1 expression. In addition, recently the results of trial Keynote 024 showed that in patients with tumors that have high level of PDL1 expression (tumor proportion score of ≥ 50%) pembrolizumab demonstrated significantly greater response rate, PFS and overall survival compared to platinum based combination chemotherapy (22). Based on these data pembrolizumab is currently approved for front line treatment of advanced NSCLC patients whose tumors have high PDL1 expression. However, the relevance of PD-L1 expression in determining efficacy of the combination of pembrolizumab with chemotherapy is unclear. In Keynote-021 PD-L1 expression did not correlate with response rate. Also what is not known is if PDL1 expression defines activity of these agents in EGFR, ALK positive and other gene altered NSCLC patients. In an effort to characterize PD-L1 expression in tumors of these patients with progressive disease, **we will analyze tumor specimens, for PD-L1 expression. PD-L1 expression will be correlated with response rate**.

Assessing PD-LI expression in NSCLC patients is considered standard of care and this information will be collected.

Mutational Load

In addition to PD-L1 expression, recent data has also shown that mutational load of tumors can correlate with efficacy from pembrolizumab (26). Mutational load in EGFR mutation positive and other gene altered NSCLCs is not well defined. We therefore propose to analyze the mutational load of the tumors of patients enrolling on the trial. This analysis will also be conducted on tumor tissue obtained via tumor biopsy following tumor progression on prior targeted therapy. This analysis will be conducted by Genomic Core of University of Michigan.

Resistant mutation status

All available gene analysis data on the patient will be collected. An attempt will be made to assess efficacy of the study regimen in patients with specific resistant gene alterations.

Circulating Tumor Cells

Obtaining tumor tissue in advanced NSCLC can prove to be challenging. In addition, the tumor sample obtained can be small and this can limit the biomarkers that can be analyzed. Therefore, in recent years 'liquid biopsies' are being used increasingly both in clinical practice and in clinical research. One avenue that holds promise in developing accurate predictive tools and pharmacodynamic biomarker information is the analysis of circulating tumor cells (CTCs) (38). CTCs describe the subset of tumor cells that have genetically acquired the ability to disseminate from primary and metastatic sites and intravasate to the circulatory system. The full clinical potential of CTCs is not yet realized due to the limitation of existing technologies to measure and study these cells in patient blood samples.

Dr. Sunitha Nagrath from the Department of Chemical Engineering at University of Michigan has developed the GO Chip technology which we propose to use in the current study (39). This technology takes the advantage of the novel nanomaterial graphene oxide for the sensitive capture of CTCs using the self-assembly of GO nano-arms on a flat substrate. Some researchers have used circular patterns to capture rare cells in microfluidic devices. However, to enhance the surface area and the hydrodynamic interactions, we used a flower-shaped architecture pattern instead of regular circular structures. Dr. Nagrath and her colleagues have evaluated this technology and the resulting CTC capture in early stage NSCLC patients and found that presence of CTCs can have prognostic import (40).

In addition, her group has demonstrated the ability to assess PD-L1 expression in CTCs and also evaluate markers for epithelial mesenchymal transition (EMT) in CTCs. As previously mentioned PD-L1 expression does correlate with clinical efficacy with PD-1 and PD-L1 inhibitors. In addition, EMT is a known resistance mechanism to EGFR-TKIs and ALK inhibitors. Recently tissue based data has suggested that presence of EMT features maybe associated with increased benefit from PD-1/PD-L1 inhibitors (42, 42).

We therefore propose to collect and bank blood on all patients enrolled on the trial before the first cycle and before the third cycle. Apart from quantifying CTCs, we will also assess PD-L1 expression and presence of EMT markers. We will attempt to correlate CTC count, PD-L1 expression and presence of EMT markers to response rate from the study therapy. We also propose to isolate tumor DNA from the circulating tumor cells and analyze for EGFR and ALK gene alterations.

5. METHODOLOGY

5.1 Inclusion Criteria

1. Cohort 1- EGFR mutation positive NSCLC patients previously treated with appropriate targeted therapy with progressive and measurable disease per RECIST 1.1 criteria tumor. Cohort 2- Other genetically altered NSCLC patients previously treated with appropriate targeted therapy with progressive and measurable tumor. Patients could have received more than 1 targeted therapy. Patients taken off an appropriate targeted therapy due to intolerance are eligible.
2. Tumor tissue for PD-L1 assessment should be available unless PD-L1 assessment results are already available.
3. Patients should not have received any systemic chemotherapy for advanced NSCLC Patients who received 1 cycle of systemic chemotherapy for advanced NSCLC while awaiting the results of tumor molecular analysis and subsequently were switched to appropriate targeted therapy will be eligible. Patients who have received neoadjuvant, adjuvant or as part of concurrent chemotherapy and radiation are eligible if they received the chemotherapy 12 months or more before the start of study therapy.
4. ECOG PS 0-1 (Appendix 14.1).
5. Patients should have recovered to ≤ grade 1 from clinically meaningful (example alopecia is not considered clinically meaningful) adverse events related to prior treatments.
6. Patients should be willing and able to provide written informed consent for the trial.
7. Be ≥ 18 years of age on day of signing informed consent.
8. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 14 days of treatment initiation.

Table 1 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	≤1.5 X upper limit of normal (ULN) **OR** ≥45 mL/min for subject with creatinine levels > 1.5 X institutional ULN

(GFR can also be used in place of creatinine or CrCl)	
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
[a]Creatinine clearance should be calculated per institutional standard.	

9. Female subject of childbearing potential should have a negative urine or serum pregnancy within 1 week of enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Patients may need the pregnancy test repeated if the test done prior to enrollment is more than 1 week prior to receiving the first dose of study medication.

10. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlines in section 6.3.2. Contraception for the course of the study through 120 days after the last dose of study medication. Note- Abstinence is acceptable if this is the usual lifestyle and preferred contraception of the subject.

11. Male subjects of child bearing potential must agree to use an adequate method of contraception as outlined in Section 6.3.2. Contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.2 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. If the half-life of the drug is known then starting therapy 5 half-lives after the end of the last therapy is acceptable.

2. Has a diagnosis of immunodeficiency. Patient should not be on any immunosuppressive therapy or steroids > prednisone 10mg/day or its equivalent on the day of the start of therapy.

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

4. Hypersensitivity to pembrolizumab, carboplatin or pemetrexed or any of its excipients.

5. 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.

6. Has had targeted small molecule therapy, or palliative radiation therapy within 1 week 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. **Patients who received stereotactic radiotherapy can start on therapy without any delay as long as they have recovered from any adverse events to ≤ grade 1. Also, it is well recognized that some EGFR and ALK patients after discontinuing their TKI can develop tumor flare. Therefore, if it is felt that in the best interest of the patient the prior TKI should be continued until the day prior to start of this study therapy it is acceptable.**

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

    - Patients with grade 2 or greater toxicities from prior therapy, such as alopecia, that are not considered clinically meaningful and not likely to impact administration of study therapy may start study therapy. An approval from the Principal Investigator of the study is required for AEs related to prior therapies other than alopecia that are not grade 1.

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

7. Has a known additional malignancy that is progressing or requires active treatment or the treating physician believes will require therapy within 1 year. Discussion with Principal Investigator is required before enrolling a patient with known history of another malignancy.

8. Has symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with **asymptomatic** brain metastases may participate provided they are clinically stable and are not using steroids equivalent to >10mg of prednisone day prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of whether it is symptomatic or not.

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 known history of non-infectious pneumonitis that required steroids or has current pneumonitis. Has known history of interstitial lung disease.

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.

6. TRIAL TREATMENTS

All patients deemed eligible and registered by the Multi-Site Coordinator of the Clinical Trials Support Unit (CTSU) at University of Michigan, will initiate study therapy within 5 days of registration. Due to logistical and administrative issues therapy maybe started within 48 hours of the 5 days limit. Please see section 7.0 for all required tests and assessments prior to registration. This is a single arm study so all eligible patients will receive the study treatment.

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration
Pembrolizumab	**200 mg**	Every 3 weeks	IV infusion
Carboplatin	**AUC 5**	Every 3 weeks	IV infusion
Pemetrexed	**500 mg/m^2**	Every 3 weeks	IV infusion

Patients will receive combination chemotherapy for a maximum of 4 cycles. Following 4 cycles patients will receive maintenance therapy with pemetrexed and pembrolizumab for a maximum of 24 months (from the start of trial therapy). Patients may receive carboplatin for a shorter number of cycles if felt to be in the best interest of the patient by the treating physician or if the patient so desires**.**

Patients will continue therapy for maximum of 24 months as long as the patient is deriving clinical benefit and is not experiencing unacceptable adverse events and patients wants to continue therapy. Patients can continue therapy beyond progression if the treating physician believes that continuing therapy is in the best interest of the patient and patient is agreeable with it. See Section 6.4.

6.1 Dose Selection/Modification/Timing of Administration

6.1.1 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.

6.1.2 Dose Modification

The Common Terminology Criteria for Adverse Events version 4.0 (CTC AE 4.0) will utilized to grade toxicities.

Appropriate dose and schedule modification should be considered for carboplatin and pemetrexed according to package inserts of both drugs and institutional guidelines. Guidelines for dose modification for hematologic toxicities are provided in Table 3 below. **For grade 3-4 non-hematologic toxicities both chemotherapy drugs should be held till the toxicity**

recovers to ≤ grade 1 and then restarted at next lower dose as in the table for hematologic toxicities (Table 3). If grade 3 toxicity is not felt to related to chemotherapy drugs and will not worsen with chemotherapy drugs (eg- serum sodium of 129mmol/L) chemotherapy treatment maybe continued after discussion with the PI. For grade 2 non-hematologic adverse events chemotherapy drugs maybe continued without dose modification as long as the treating physician considers the toxicities not related to the chemotherapy drugs.

Reduction in the dose of one chemotherapy drug does not require the reduction in the dose of the other chemotherapy drug if the other drug is not felt to be the cause of the toxicity that led to the dose reduction. Discontinuation of one of the chemotherapy drugs at any point during the therapy is acceptable if the treating physician considers it to be in the best interest of the patient or the patient so desires. If chemotherapy drugs are held for longer than 3 weeks for pembrolizumab related toxicities or for toxicities that cannot be definitively attributed to chemotherapy drugs, chemotherapy drugs could be restarted after a discussion with the PI (Principal Investigator).

Table 3 Suggested dose modifications for chemotherapy drugs for hematologic toxicities[1]

		Pemetrexed	Carboplatin
Nadir Platelet count	Nadir Neutrophil count	Dose	Dose
≥50 AND	≥0.5	500 mg/m^2	AUC 5
≥50 AND	≤ 0.5	400 mg/m^2	AUC 3.75
≤ 50 without bleeding AND	≥0.5	400 mg/m^2	AUC 3.75
≤ 50 with bleeding AND	ANY	400 mg/m^2	Don't give
≤ 25	ANY	400 mg/m^2	Don't give
ANY	≤ 1.0 with fever of > 38.3 degrees C once or sustained ≥ 38 degrees C	400 mg/m^2	Don't give

1. A treating physician may decide to reduce the dose of the chemotherapy drugs (one or both) more than suggested in the table above or not give one of the

chemotherapy drugs. Dosages different than the suggested doses may be used if consistent with local guidelines. If a physician wants to give doses higher than recommended or wants to give both drugs in situations where it is recommended to only give pemetrexed, a discussion with and permission from the PI is required.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab/combination treatment must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 4 below.

There is no dose reduction allowed for pembrolizumab on the protocol. If the schedule of concomitant chemotherapy is changed to every 4 weeks due to tolerability issues then pembrolizumab will be administered on the day of the chemotherapy. Patients should be monitored closely to maintain the schedule as close to every 3 weeks as possible.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 4 below. **In addition, the drug can be held for any grade of toxicity by the treating physician if it is felt that it is in the best interest of the patient.**

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, or to pembrolizumab alone, for adverse events listed in Table 4, both interventions must be held according to the criteria in Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 4.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 4, the combination of chemotherapy and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to chemotherapy alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

Table 4. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab monotherapy and IP Combinations

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 study intervention has been withheld, study intervention can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Study intervention should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 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)
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				• 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
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic 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 [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[l]		
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 – grading	Grade 2	Withhold	• Administer corticosteroids	• Monitor changes of renal function

according to increased creatinine or acute kidney injury	Grade 3 or 4	Permanently discontinue	(prednisone 1-2 mg/kg or equivalent) followed by taper.	
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	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 [e].		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

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

With investigator and Principal Investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. **A patient who requires longer than 12 weeks but less than 24 weeks to recover from an adverse event that led to the withholding of pemetrexed and/or pembrolizumab and is still grade 2, the patient could be restarted on the drug/drugs IF the treating physician believes that it is in the best interest of the patient to restart the drug and the patient is agreeable. This has to be discussed with the Principal Investigator before restarting the drugs. This does not apply to toxicities that require discontinuation of one or more study drugs.**

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of study therapy drugs should be discontinue trial treatment.

6.1.3 Timing of Dose Administration

Subjects will receive pembrolizumab 200 mg together with pemetrexed 500mg/m^2 (with vitamin supplementation) + carboplatin AUC 5 all on Day 1 Q3W for 4 cycles followed by pembrolizumab 200 mg together with pemetrexed 500 mg/m2 Q3W until progression/completion. Patients should receive appropriate nausea and emesis prophylaxis.

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 7.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons, including patient's desire. It is understood that patients on a study with a planned therapy for 2 years may desire to take short breaks or travel. For patient's desire, therapy may be delayed for up to 3 weeks. Such delays should not be done in the first 6 cycles. The number of such delays should be minimized.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered at least 30 minutes prior to premedication for chemotherapy (pemetrexed with or without carboplatin).

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

Merck will provide Pharmacy Manual which contains specific instructions for pembrolizumab dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Carboplatin and pemetrexed will be administered according to package insert and institutional guidelines.

Pemetrexed 500 mg/m2 will be administered as an IV infusion over approximately 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive appropriate supplementation with vitamin B12 and folic acid and corticosteroid prophylaxis.

Carboplatin AUC 5 mg/mL/min will be administered as an IV infusion over approximately 15-60 minutes Q3W for 4 cycles immediately after pemetrexed as per local practice and labels.

All patients should have CBC with differential and a multiphasic profile before each cycle of therapy. Patients can only receive chemotherapy (carboplatin and/or pemetrexed) if

Neutrophil count ≥1,500 /mcL

Platelets ≥ 100,000/mcL

In addition patients should meet criteria mentioned in tables 3 and 4 and should be dosed accordingly.

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

6.1.4 Trial Blinding/Masking

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

6.2 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 investigator should discuss any questions regarding this with the PI and/or Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary treating physician.

6.2.1 Acceptable Concomitant Medications

Patients **will** receive vitamin B12 (1000 mcg intramuscularly) and folic acid (1 mg orally daily) supplementation at least 5 days before starting therapy with pemetrexed and continue to receive it at frequencies mentioned in the package insert or according to institutional guidelines. All patients should receive anti-nausea and other supportive measures according to institutional guidelines.

Patients should receive appropriate anti-nausea medications and dexamethasone for management of chemotherapy related adverse events as per institutional guidelines and package insert. All treatments that the investigator considers necessary for patient'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 in the medical record 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 in the medical record.

6.2.2 Prohibited Concomitant Medications

Patients should not receive any other systemic therapy for cancer unless specified in the protocol. If a patient needs palliative radiation therapy or other such local therapy for the treatment of limited areas of symptomatic disease or limited areas of progression, such as painful bone lesions, study therapy will have to be interrupted. Study therapy may be re-initiated after completion of such palliative therapy after **discussion with the Principal Investigator (PI). Following are the prohibited medications.**

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the investigator's discretion. This has to be discussed with the PI. It is

important that at least one target lesion remains untreated with treatment other than study therapy.

- 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 immune related adverse event or for use as a pre-medication before chemotherapy or to treat contrast related allergy or for treatment of COPD/asthma exacerbation. The use of replacement doses of corticosteroids while on study is allowed.

Subjects may receive other medications that the investigator deems to be medically necessary to manage the patient's cancer such as bone modifying agents in patients with bone metastases and growth factors for management of neutropenia.

The Exclusion Criteria section 5.2 describes other medications which are prohibited in this trial.

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

6.3 Contraception/Pregnancy/Nursing

6.3.1 Contraception

Pembrolizumab and chemotherapy 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 that 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.

6.3.2 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and chemotherapy drugs, 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 PI 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 PI and to Merck and followed as described above and in Section 8.2.2.

6.3.3 Use in Nursing Women

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

6.4 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 PI 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 8.1.4 – 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
    - *Note*: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved. **It is well recognized that in some patients despite radiologic evidence of disease progression the treating physician may want to continue therapy since the progression may not be clinically relevant. In addition certain patients may develop isolated areas of progression. The treating physician may consider treating such isolated areas of progression with local treatments such as radiation or surgery, as long as at least one target lesion is not treated with any other treatment than the study therapy. The patient may continue on study therapy after the patient has recovered to ≤ grade 1 adverse events from such local treatments, as long as the treating physician considers that patient is still deriving clinical benefit from study therapy. CONTINUATION of study therapy in patients who have disease progression or after local therapy for limited areas of progression can only be done after discussing with the PRINCIPAL INVESTIGATOR.**
- 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 provided they meet the requirements detailed in Section 8.1.5.2

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Protocol Flow Chart) and Section 8.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 8.2.3). 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.

Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 24 weeks, receiving two cycles of combination including 2 doses of pembrolizumab and at least 80% of the planned dose beyond the date when the initial CR was declared. The decision to continue or discontinue pemetrexed in such patients is to be decided by the treating physician. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab with or without pemetrexed via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, other than pemetrexed, 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. Additional details are provided in Section 8.1.5.2.

6.5 Subject Replacement Strategy

Patients will only be replaced if the patient withdraws consent before the first dose of study therapy.

6.6 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

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

7 TRIAL FLOW CHART

Trial Period:	Main Study Screening (Visit 2)	**Treatment Cycles** ***(for initial combination treatment and retreatment phase start at cycle 1)***										
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles				Safety Follow-Up/ EOT	Progression Free Follow-Up Phase	Survival Follow-Up
						5	6	7	8			
Scheduling Window (Days):	-28 to -0		±3	±3	±3	±3	±3	±3	±3	30 days (+/- 7 days) after last dose/ before initiation of new tx	Every 12 weeks +/- 2 weeks	Every 12 weeks +/- 2 weeks
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Medical History[1]	X	X	X	X	X	X	X					
Medication Review[2]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[3]		X	X	X	X	X	X	X	X			
Survival Status												X
Review Adverse Events		X	X	X	X	X	X	X	X	X		
Physical Examination[1]	X											
Directed Physical Examination[1]		X	X	X	X	X	X		X	X		
ECOG Performance Status[4]	X	X	X	X	X	X	X		X	X		
Pregnancy Test – Urine or Serum β-HCG[5]	X											
CBC with Differential[6]	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[6]	X	X	X	X	X	X	X	X	X	X		

Trial Period:	Main Study Screening (Visit 2)	**Treatment Cycles** ***(for initial combination treatment and retreatment phase start at cycle 1)***										
Treatment Cycle/Title:		1	2	3	4	To be repeated beyond 8 cycles				Safety Follow-Up/ EOT	Progression Free Follow-Up Phase	Survival Follow-Up
						5	6	7	8			
Scheduling Window (Days):	-28 to -0		±3	±3	±3	±3	±3	±3	±3	30 days (+/- 7 days) after last dose/ before initiation of new tx	Every 12 weeks +/- 2 weeks	Every 12 weeks +/- 2 weeks
Urinalysis (See Table 6)	X											
T3, FT4 and TSH[7]	X				X				X			
Tumor Imaging[8]	X		X		X		X				X	
Research Blood Collection (CTC)[10]		X		X								
Research Blood (Mutational Load)[11]		X										
Tissue Collection[9]	X											

1. Patients should undergo a detailed history and physical examination during screening. A full examination, to be performed to determine eligibility, means detailed medical history is obtained and all relevant systems have been examined, include height at baseline and weight. All patients should undergo a focused (at the discretion of the managing health care provider) history and physical examination during each treatment day for the first 6 cycles. After the first 6 cycles history and physical examination can be performed every other cycle as per the discretion of the managing health care provider.

2. All medications need to be reviewed at screening visit. During follow up visits any changes in medications should be documented.

3. Pembrolizumab will be administered at a dose of 200 mg IV every 3 weeks for a maximum of 2 years. For the first 4 cycles patients will receive carboplatin AUC 5 and pemetrexed 500 mg/m^2. After first 4 cycles patients will receive maintenance pemetrexed. Prior to each administration vital signs- heart rate, blood pressure, temperature, weight, respiratory rate should be

documented. Cycles can be administered +/- 3 days around the scheduled day of therapy. Please also see section 6.1.2. Patients can be retreated with pembrolizumab with or without pemetrexed. Please see section 8.1.5.2

4. Performance status needs to be documented on the day of study drug administration for the first 6 doses. After the first 6 doses it should be documented as deemed appropriate by the treating physician.

5. Pregnancy test should be performed within 1 week of the first dose of study therapy in appropriate women.

6. Patients should undergo CBC with differential count, a multiphasic profile consisting of serum electrolytes, BUN, serum creatinine, AST, ALT, serum bilirubin, alkaline phosphatase, and calcium with each treatment. Baseline labs should be done within 2 weeks of the first dose of study therapy, unless patient was undergoing any cancer therapy within a week of starting study therapy. In that case patient should have repeat labs after the completion of such cancer therapy. During the trial, laboratory tests can be done within 72 hours of the administration of study therapy.

7. Patients should undergo Thyroid tests within 2 weeks of the first dose. These should be repeated at least every 4 cycles.

8. Patients should undergo appropriate scans, including brain scan, during screening, to document the status of the patient's cancer. The screening scans should be done within 4 weeks before the first dose of study therapy. Patients should undergo appropriate scans to restage the patient after every 2 cycles for the first 6 cycles. For the first 6 cycles the re-staging scans should be performed within 1 week of the next cycle. After the first 6 cycles, the scans can be done as often as necessary by the treating physician but should be done at least every 4 cycles. Brain imaging does not have to be repeated if patient does not have known brain metastases at baseline or has had prior treatment to brain metastases and is stable at baseline.

9. Tumor tissue will be retrieved to assess tumor PD-L1 status and mutational load. If PD-L1 status is not known and no archival tumor tissue is available to conduct such analysis a new tumor biopsy is necessary. Mutational load will be assessed on any tumor tissue available, with preference for the tissue from the most recent biopsy. See Section 9.0.

10. Blood will be collected ***prior*** to the start of study therapy and ***before*** the third cycle in patients enrolled in this trial to identify and quantify CTCs. Samples will not need to be re-drawn if a patient comes back on study for the re-treatment phase. See Section 9.0.

11. Blood for mutational load should be collected on all patients who undergo a biopsy or who have archival tissue. The blood sample can be taken at any time while the patient is on study, however it is preferred to be taken prior to treatment on C1D1.

8 TRIAL PROCEDURES

8.1 Trial Procedures

Patient registration for this trial will be centrally managed by the Coordinating Center of The Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

Once registration has occurred patient has to be treated within 5 days. If patient does not start therapy within 5 days of registration, the reasons for delay should be communicated to the Principal Investigator. He will then decide if the patient can continue on study therapy.

The Trial Flow Chart - Section 7.0 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 PI and/or Merck 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.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial or conducting any testing specifically to assess eligibility.

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.

8.1.1.2 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.

8.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition that are considered to be clinically significant by the Investigator.

8.1.1.4 Concomitant Medications Review

8.1.1.4.1 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial in the medical record. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 8.2.

8.1.1.5 Disease Details and Treatments

8.1.1.5.1 Disease Details

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

8.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries. The number of prior treatments for the lung cancer will be recorded. Details of any radiation administered will be recorded. This will include site radiated, dose and dates.

8.1.1.5.3 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.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 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 (Appendix 14.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 8.2 for detailed information regarding the assessment and recording of AEs.

8.1.2.2 Physical Exam/Vital Signs/Eastern Cooperative Oncology Group Performance Scale (ECOG PS)

The investigator or qualified designee will perform physical exam, including vital signs (temperature, pulse, respiratory rate, weight and blood pressure) and assess ECOG PS during the screening period and subsequent visits as mentioned in Trial Flow Chart section 7.0. Clinically significant abnormal findings should be recorded. A full physical exam should be performed during screening.

8.1.2.3 Tumor Imaging and Assessment of Disease

Patients will undergo scans to assess the status of the cancer within 4 weeks before the first dose of study therapy. All known areas of metastases should be imaged. Patients will undergo restaging scans every 2 cycles for the first 6 cycles. Subsequently they can be done as often as necessary, but should be done at least every 4 cycles. See section 7.0

The treating physician will decide which scans need to be done to appropriately assess the status of the cancer.

8.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

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

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

‡ If considered standard of care in your region.

α These tests are to be conducted at baseline. Once the patient is on trial therapy tests to be conducted at least every 4 cycles.

Baseline labs should be done within 2 weeks of the first dose of study therapy, unless patient was undergoing any cancer therapy within a week of starting study therapy. In that case patient should have repeat labs after the completion of such cancer therapy. 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 to proceed with treatment.

8.1.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 8.1.5.2. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.1.5.1) and then proceed to the Follow-Up Period of the study (described in Section 8.1.5.1).

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

8.1.5.1 Follow-up Visits Including Safety Follow Up Visit

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed at least every 12 weeks (by radiologic imaging) to monitor disease status. 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 with or without pemetrexed as detailed in Section 8.1.5.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

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. It is recognized that in some NSCLC patients such a visit may not be possible and inability to conduct such a visit will not be considered a protocol deviation. 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. If the investigator or a member of the study team becomes aware of SAEs that occurred 90 days after end of treatment and they were considered to be treatment related then they should be recorded as the other SAEs. Subjects who are eligible for retreatment (as described in Section 8.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Subjects who are eligible to receive retreatment according to the criteria in Section 8.1.5.2 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

8.1.5.1.1 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 or other mode of communication every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.1.5.2 Second Course Phase (Retreatment Period)

Subjects who stop therapy with SD or better may be eligible for up to one year of additional pembrolizumab therapy with or without pemetrexed 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 after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab with or without either of the chemotherapy drugs before discontinuing therapy
        - Received at least two treatments with pembrolizumab with or without chemotherapy 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
    - Patients who stopped therapy earlier than 24 months and had SD, PR or CR can also be considered for re-treatment after discussion with the PI.

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

- 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 5.2). 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. The investigator can decide to either start pembrolizumab alone or with pemetrexed. For the retreatment patients will not receive carboplatin again. Treatment will be administered for up to one additional year. Therapy beyond one year may be considered after discussing with the PI.

Visit requirements will be the same as done with the first treatment on the study. See section 7.0 – Trial Flow Chart.

8.2 Assessing and Recording Adverse Events

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

Adverse events may occur during the course of the use of any of the study therapy drugs 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 start of study treatment allocation must be reported by the investigator

From the time of treatment start through 90 days following cessation of treatment, or 30 days after the cessation of treatment if the patient starts on another therapy, whichever is earlier, 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 reporting timeframe for adverse events meeting any serious criteria is described in section 8.2.3.1 The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

8.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the PI (Principal Investigator) 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 pembrolizumab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the PI and Coordinating Center. The Coordinating Center within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Overdose of carboplatin and pemetrexed should be addressed according to institutional guidelines and should be documented in patient's study records.

8.2.2 Reporting of Pregnancy and Lactation to the PI 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. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of any study therapy, 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 PI and Coordinating Center. The Coordinating Center will report within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

8.2.3.1 Serious Adverse Events (SAEs)

A serious adverse event is any adverse event occurring during study therapy that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization; Hospitalization related to patient convenience (eg. Transportation issues) will not be considered a SAE.
- Is a congenital anomaly/birth defect;
- Is any other 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.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen, or that is required per protocol
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care
- Death due to disease progression unless attributable to the study drug(s)
- A hospitalization due to an expected adverse event (e.g., hospitalization due to expected febrile neutropenia).

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Study Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of

first awareness of the event. Events should be reported using the Coordinating Center SAE form as available in the study database. A copy of the Coordinating Center SAE form should be sent to the Coordinating Center via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs should be reported to the local IRBs per current local institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and Merck, as appropriate (outlined below).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to study therapy 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 PI, the Coordinating Center and to Merck Global Safety.

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

In this trial, serious unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

The Coordinating Center will be responsible for sending SAE reports and any other relevant safety information 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, 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 the Coordinating Center 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.

8.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the PI and within 2 working days after the University of Michigan Multi-Site Coordinator becomes aware of the event to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning at start of study therapy through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to study therapy, must be reported within 72 hours to the PI and within 2 working days after the University of Michigan Multi-Site Coordinator becomes aware of the event to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 8.2.1 - 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.*This is not required if the elevation is deemed to be related to progression of underlying cancer.

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

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician or an appropriate designee will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. The investigator or sub-investigator will assess the grade, duration of the AE, management of the AE and the relatedness to the study therapy. 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.

8.2.5 Responsibility for Reporting Adverse Events

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

8.3 Study Closure

At this amendment (dated 10/27/2020) the enrollment rate has been significantly slower than anticipated when this study was developed. We therefore may close the study earlier than planned since planned enrollment is not feasible. The current plan is to close the study to enrollment on December 31st 2020. Based on current enrollment, we anticipate that we will enroll approximately 25 patients in the EGFR cohort (Cohort 1) and 7 patients in the other cohort (Cohort 2).

9 CORRELATIVE STUDIES

Response rates to PD-1 and PD-L1 targeted agents indicate that a subset of patients derive greater benefit from this treatment strategy, whereas some patients have no benefit. To complement this study and increase its scientific yield, we are proposing scientific correlates in an attempt to identify potentially predictive biomarkers for the study therapy. While these are unlikely to be definitive, based on the relatively small numbers of patients involved, the data collected will help guide the development of potential biomarkers in future studies as well as identify patients most likely to benefit or not benefit from the study therapy.

PD-L1 expression

The available data suggests that NSCLC patients with tumors that express PD-L1, particularly at a high level, have a greater probability of deriving benefit from anti-PD-1 drugs such as pembrolizumab (20,22). In addition, the FDA has recently approved the use of pembrolizumab as single agent for upfront therapy in patients with advanced NSCLC with high PD-L1 expressing tumors (22).

Although the predictive relevance of tumor PD-L1 expression in patients receiving pembrolizumab in combination with chemotherapy is unclear, the data from Keynote-021 trial suggests that benefit with the addition of pembrolizumab to chemotherapy maybe irrespective of tumor PD-L1 expression (30,31). In an effort to characterize PD-L1 expression in tumors of EGFR mutation or other genetically altered NSCLC patients with progressive disease, we will analyze tumor specimens, for PD-L1 expression analyses, unless these results are already available. If these results are not available and there is no tumor tissue available, then a fresh tumor biopsy will have to be obtained.

PD-L1 expression can be conducted locally and the results and methodology reported to the Coordinating Site. It is highly encouraged that the test be performed on the tumor tissue obtained with the most recent biopsy procedure.

Mutational Load

In addition to PD-L1 expression, recent data has also shown that mutational load of tumors can correlate with efficacy from checkpoint inhibitors (26). Mutational load is higher in tumors of patients who have a history of smoking for many years. It is speculated that lung cancers that arise in patients with chronic smoking history are a result of chronic exposure to carcinogens that leads to accumulation of several genetic changes and higher mutational load in such tumors. It is also suggested that higher mutational load may cause more neo-antigens to be expressed on the surface of cancer cells and therefore these cancers maybe more susceptible to immunogenic attack. It is possible that one of the reasons single agent anti-PD-1 and anti-PD-L1 agents are not very effective in patients with EGFR/ALK NSCLCs is that almost all of

these patients are never or light smokers and therefore the tumors in these patients have a low mutational load.

We therefore propose to analyze the mutational load of the tumors of patients enrolling on the trial, as reported by Rizvi, et al and classify tumors as high or low mutational load tumors (a blood sample will be utilized to conduct genomic analysis in order to assess if the mutations identified in the tumor are somatic or germline. We will then attempt to correlate mutational load of the tumor with the response rate observed with the study therapy. This analysis will be conducted by Genomic Core of University of Michigan. It is recognized that tissue for both PD-L1 expression and mutational load may not be available. PD-L1 expression is considered mandatory and mutational load will only be assessed if tissue remains available.

T790M Status

All eligible EGFR mutation positive NSCLC patients' tumors will be analyzed for EGFR mutations in exons 18-21, including T790M. About 60% of the EGFR mutation positive NSCLC patients have T790M as the primary mechanism of resistance to EGFR-TKIs. We propose to evaluate the efficacy of pembrolizumab administered with chemotherapy in these patients based on presence or absence of T790M mutation. This assessment will be considered standard of care. If patients have a positive T790M result from a circulating cell free tumor DNA test, then a tissue test will not be mandatory.

Circulating Tumor Cells (CTCs)

Dr. Nagrath, et al at University of Michigan have developed a unique technique of identifying and quantifying CTCs. In addition, they can assess several biomarkers including PDL1 and markers associated with EMT (epithelial mesenchymal transition). Dr. Nagrath has demonstrated that CTCs can provide prognostic information in NSCLC patients.

We propose to collect and bank blood from prior to the start of study therapy and before the third cycle in patients enrolled in this trial to identify and quantify CTCs by the method developed by Dr. Nagrath. In addition, we propose to assess PD-L1 expression and correlate it with tumor tissue PD-L1 expression where possible. We also plan on assessing markers for EMT in the isolated CTCs. EMT has been recognized as a resistance mechanism to both EGFR-TKIs in EGFR mutation positive NSCLC patients and to ALK TKIs in ALK positive NSCLC patients. We also propose to isolate tumor DNA from the CTCs to conduct EGFR and other gene analysis.

We also propose to correlate the number of CTCs at baseline and the change in the CTC count before and after 2 cycles with response rate from the study therapy.

Blood sample collection

Whole blood will be obtained for the CTC analysis. All samples will be labeled with a unique specimen ID. The specimen ID will not contain names, MRN, or other identifiers.

Circulating tumor cell isolation

Circulating tumor cells will be isolated from whole blood using a CTC chip as previously described (Nagrath 2007). Isolated tumor cells will be confirmed by morphology using microscopy and/or immunostaining for tumor cell and nucleated blood cell surface markers.

CTC quantification protocol

Patient blood will be run over the CTC chip. The chips containing bound CTCs are then washed with PBS and fixed with PFA. Fixed chips can be stored in a refrigerator. The number of tumor cells is determined by microscopy.

CTC RNA and DNA isolation

DNA and RNA will be extracted from the isolated CTCs.

CTC staining protocol

The CTC-chip containing patient sample is treated with buffer then washed with PBS. The CTC-chip is then incubated with serum and the appropriate antibodies are added (e.g. CK, CD45) for a specific period of time. CTC-chips are then washed with PBS and the appropriate secondary antibody are added.

9.1. Shipping of tissues and blood samples to University of Michigan

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or at least ten unstained slides. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, then only new biopsies will be acceptable for determination of PD-L1 status. 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. Refer to the Laboratory Manual for details.

Blood samples for CTC and mutational load analysis should collected, handled and shipped to the University of Michigan as outlined in the Laboratory Manual.

10 STATISTICAL ANALYSIS PLAN

10.1 Definition of Endpoints

Primary Endpoint

As cited in Appendix 14.3, RECIST 1.1 will be used to define response rates as:

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

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

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

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

Secondary Endpoints-

RECIST 1.1 defined Progression Free Survival (PFS)- PFS is defined as the duration of time from registration to time of progression. Patients who die without reported prior progression will be considered to have progressed on the day of their death. Patients who did not progress will be censored at the day of last tumor assessment.

Overall Survival- Overall survival is defined as the time from registration to time of death. If the patient is lost to follow-up, survival will be censored on the last date the patient was known to be alive.

10.2 Statistical Analysis Plan

10.2.1 Study Design and Primary Endpoint

The study design is a multi-site, single arm phase II trial with 2 parallel cohorts. To minimize the number of patients required the single arm two-stage minimax Simon's design will be used for each cohort. The study will be conducted in two separate cohorts; EGFR mutation positive NSCLC cohort and other genetically altered NSCLC cohort. The primary objective is to assess the treatment efficacy based on the response rate (RR), of combination pembrolizumab and platinum-based doublet in EGFR mutation positive or ALK positive NSCLC patients who have progressed on prior TKIs. The primary endpoint is RR defined by RECIST 1.1.

Secondary objectives include the evaluation of toxicity, overall survival (OS) duration, and Progression Free Survival (PFS). OS is defined as the time from the initiation of study therapy to death from any cause, see 10.2. PFS is defined as the time from the initiation of pembrolizumab to disease progression or death due to any cause, whichever occurs first. PFS as defined by RECIST 1.1 (Section 10.1).

Exploratory endpoints include correlating tumor PD-L1 expression positive or negative and tumor mutational load as high or low with the primary endpoint of response rate. In addition, the study will assess toxicity from the study therapy.

10.2.2 Sample Size and Accrual Rate:

With chemotherapy in these patients, both EGFR mutation positive NSCLC patients and other genetically altered NSCLC patients are expected to demonstrate a response rate of about 30%. We hypothesize that the study regimen will be higher than 30% in both cohorts. A RR of 55% with the study regimen for this patient population will be considered of interest in both cohorts. The accrual rate of both cohorts should be similar.

For each cohort, the combination treatment would be of clinical interest if the RR is > 0.55 and will not if the RR is <0.3. With 14 pts in stage I and 28 total pts, the 2-stage Simon's minimax design has a 5% type I error and 85% power and a probability of early termination of 0.58. The cohort is to be terminated at stage I if ≤ 4 pts respond. If the cohort goes on to stage II and total number of responses is ≤ 12, the treatment is rejected.

Thus, if both cohorts go to stage II then each of the cohorts will require 28 evaluable patients. To be evaluable for efficacy, the patient has to receive at least one dose of pembrolizumab and doublet chemotherapy. **We assume an ineligibility rate of 10% so we plan to enroll 31 patients in each cohort of the trial.**

Assuming accrual duration of 12-24 months and minimum follow up of 12 months for OS, the duration of this trial will be 24-36 months. Although the accrual rate will not affect the primary endpoint RR, the total study duration might be different for each cohort.

For each cohort, once the 14th patient has been enrolled, further enrollment for that cohort will be halted until a decision has been reached from the interim analysis. The interim analysis for each cohort will be done after the first 14 patients in the cohort have all completed at least six weeks of follow-up and have been assessed for CR/PR.

10.2.3 Analysis plan for primary and secondary endpoints

The primary analysis is response rate and will include reporting the response count and proportion with the associated exact 95% binomial confidence interval in the response evaluable population in each cohort. If stage 2 is initiated for a cohort then the efficacy analysis methods will be as described by Koyama and Chen (43).

Secondary endpoint analysis will include Kaplan-Meier methods to describe OS and PFS. Descriptive analysis including counts and proportions will be used to describe toxicity. Expression of PD-L1 by IHC will be categorized into positive (≥1% of cells) or negative. Mutation load will be high/low (Rizvi, et al) (32). A description of the association of each with the response rate will be described using counts and percentages and tested using fisher's exact chi-square test.

Counts of CTC before the first cycle and before the third cycle will be summarized across all patients with sample means and standard deviations, or sample medians and ranges if the distribution of CTC levels is skewed. We will also summarize counts of CTC before the first cycle and before the third cycle separately for responders and non-responders. All other data collected from the blood samples, such as EGFR and ALK expression, will be summarized in similar fashion and Pearson's correlation coefficient will be used to summarize the association of PD-L1 expression in CTCs and in tumor tissue.

11 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

11.1 Investigational Product

Each of the site investigators shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of pembrolizumab in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 7. Carboplatin and pemetrexed will sourced from commercial sources.

Table 7 Product Descriptions

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

11.2 Packaging and Labeling Information

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

11.3 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.

11.4 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.

11.5 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.

12 ADMINISTRATIVE AND REGULATORY DETAILS

12.1 Confidentiality

All efforts will be made at each participating site to maintain the confidentiality of patients enrolled on the trial according to institutional, local and federal guidelines.

12.2 Compliance with Financial Disclosure Requirements

All participating staff will disclose any financial conflicts of interest to respective institutional review boards or applicable compliance authorities.

12.3 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 Principal Investigator 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.

12.4 Data Safety Monitoring

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the sites data manager or study coordinator and the site principal investigator or co-investigator. These reports are to be sent to the University of Michigan Coordinating Center within 7 calendar days of awareness of the event.

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

12.4.1 Quality Assurance and Audits

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

12.4.2 Clinical Monitoring Procedures

Clinical studies coordinated by The Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes first treatment cycle**.** The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol

- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

12.5 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
    - Subject entry into EDC
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. [Information on dose limiting toxicity events must be entered within one

business day.] Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.2.3 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

13 REFERENCES

1. Mok T, Yang JJ, Lam KC. Treating patients with EGFR-sensitizing mutations: first line or second line- is there a difference? J Clin Oncol:2013;31:1081-88.

2. Jackman D, Pao W, Reily GJ, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol 2010;28:357-60.

3. Sequist LV, Soria JC, Goldman JW, et al. Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer. N Engl J Med 2015;372:1700-9.

4. Jänne PA, Chih-Hsin Yang JC, Kim D, et al. AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer. N Engl J Med 2015;372:1689-99.

5. Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015;16:990-98.

6. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discov:2014;9:1036-45.

7. Peters S, Camidge R, Shaw A, et al. , et al. Alectinib versus crizotinib in intreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829-38.

8. Kim DW, Mehra R, Tan D, et al. Activity and safety of ceritinib in patients with ALK rearranged non-small cell lung cancer (ASCEND-1): updated results from the multicenter, open label, phase I trial. Lancet Oncol 2016;17:452-63.

9. Ou S, Ahn JS, Petris LD, et al. Alectinib in crizotinib refractory ALK rearranged non-small cell lung cancer: A phase II global study. J Clin Oncol 2016;34:661-8.

10. Solomon BJ, Bauer TM, Felip E, et al. Safety and efficacy of lorlatinib (PF-06463922) from the dose escalation component of a study in patients with advanced ALK + or ROS1+ non-small cell lung cancer (NSCLC). J Clin Oncol 2016;34(supplement, abstract 9009).

11. Shaw AT, Ou SI, Bang Y, et al. Crizotinib in ROS-1 rearranged non-small-cell lung cancer. N Engl J Med 2019;371:1963-71.

12. Doebele RC, Ahn MJ, Siena S, et al. Efficacy and safety of entrectinib in locally advanced or metastatic ROS-1 positive non-small cell lung cancer; Abstract presented

at World Conference of Lung Cancer, September 2018; abstract 13903.

13. Planchard D, Smit EF, Groen HJ, et al. Dabrafenib plus trametinib in patients with previously untreated Braf V600E mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol 2017;18:1307-16.

14. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-39.

15. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf, MS-66; accessed October 27th , 2019.

16. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

17. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

18. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

19. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

20. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

21. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

22. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

23. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

24. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-d

25. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375:1823-33.

26. Garon E, Leighl NB, Rizvi NA, et al. Safety and clinical activity of MK-3475 in previously treated patients with non-small cell lung cancer. N Engl J Med 2015;372:2018-28.

27. Borghaei H, Paz‑Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.

28. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small cell lung cancer (OAK): a phase 3, open-label, multicenter randomised controlled trial. Lancet 2017;389:255-65.

29. Gainor J, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: A retrospective analysis. Clin Cancer Res 2016;22:4585-93.

30. Mazieres J, Drilon AE, Mhanna L, et al. Efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients harboring activating molecular alterations. J Clin Oncol 2018;36:15 suppl, abstract 9010.

31. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med 2012;366:2443-54.

32. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology: mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124-8.

33. Cancer Genome Atlas Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature 2012; 487: 330-7.

34. Timmermann B, Kerick M, Roehr C, et al. Somatic mutation profiles of MSI and MSS colorectal cancer identified by whole exome next generation sequencing and bioinformatics analysis. PLoS One 2010; 5(12): e15661.

35. Gadgeel SM, Stevenson J, Langer CJ, et al. Pembrolizumab plus chemotherapy as front-line therapy for advanced NSCLC: Keynote-021 cohorts A-C. J Clin Oncol 2016;34:abstract 9016.

36. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label Keynote-021 study. Lancet Oncol 2016;17:1497-1508.

37. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cll lung cancer. N Engl J Med 2018;378:2078092.

38. Gallo M, DeLuca A, Maiello MR, et al. Clinical utility of circulating tumor cells in patients with non-small cell lung cancer. Transl Lung Cancer Res 2017;6:486-98.

39. Yoon HJ, Kim TH, Zhang Z, et al. Sensitive capture of circulating tumour cells by functionalized graphene oxide nanosheets. Nat Nanotechnology 2013;8:735-741

40. Murlidhar, V, Reddy RM, Fouladdel S, et al. Poor Prognosis Indicated by Venous Circulating Tumor Cell Clusters in Early-Stage Lung Cancers. Cancer Res 2017;77:5194-5206.

41. Zhang Z, Shiratsuchi H, Palanisamy N, et al. Expanded Circulating Tumor Cells from a Patient with ALK-Positive Lung Cancer Present with EML4-ALK Rearrangement Along with Resistance Mutation and Enable Drug Sensitivity Testing: A Case Study. J Thorac Oncol 2017;12:397-402.

42. Zhang Z, Shiratsuchi H, Lin J, et al. Expansion of CTCs from early stage lung cancer patients using a microfluidic co-culture model. Oncotarget 2014;5:12383-97.

43. Koyama T, Chen H. Proper inference from Simon's two-stage designs. Statistics in Medicine 2008;27:3145-54.

14 APPENDICES

14.1 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.	

14.2 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)

14.3 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.

15.0 COVID-19 Addendum

Purpose

The purpose of this addendum is to address protocol-required items that the COVID-19 pandemic may temporarily affect.

A. Study Visit Schedule:
   - Visits: Where participants cannot be seen at the site, the use of telemedicine and adaptation of schedule of assessments will be implemented, where feasible to ensure patient safety.
   - Treatment: Per physician discretion, 1-2 cycles of treatment may be omitted once a patient completes 4 cycles of therapy.

B. Correlative Samples:
   - PD-L1 testing: Per physician discretion, a new biopsy is not required if a patient does not have PD-L1 results or archival tissue
   - CTC samples: Samples will not be collected while the lab is closed due to COVID-19.
   - Mutational Analysis samples: Blood and tissue will not be collected or shipped while the lab is closed due to COVID-19.