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A PHASE IB TRIAL OF PEMBROLIZUMAB (MK-3475) AND TRAMETINIB FOCUSED ON ADVANCED KRAS MUTANT NON-SMALL CELL LUNG CANCER

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Protocol Number: UCDCC#259

Protocol Title: A Phase Ib Trial of Pembrolizumab (MK-3475) and Trametinib Focused on Advanced KRAS Mutant Non-Small Cell Lung Cancer

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

_____
Investigator Name (print)

_____
Investigator Signature

_____
Date

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LIST OF ABBREVIATIONS

AE	adverse event
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BAL	bronchoalveolar lavage
β-HCG3	β-human chorionic gonadotropin
BID	twice daily
CBC	complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR	complete response
CRF	case report form (paper or electronic as appropriate for this study)
CSR	central serous retinopathy
CT	computed tomography
DKA	diabetic ketoacidosis
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSMB	UCDCC Data and Safety Monitoring Board
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C
H&E	hematoxylin & eosin
HIV	Human Immunodeficiency Virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
IHC	immunohistochemistry
INR	international normalized ratio
IRB	institutional review board
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	intraveinous
LDH	lactate dehydrogenase
LLN	lower limit of normal
mAb	monoclonal antibody
MEK	mitogen-activated extracellular signal-regulated kinase
MK-3475	pembrolizumab
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology for Adverse Events
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer

NYHA	New York Heart Association
OCR	Office of Clinical Research
ORR	overall response rate
OTC	over-the-counter
PI	principal investigator
PD	progressive disease
PD-1	Programmed cell Death protein 1
PD-L1	Programmed Death-Ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PBMC	peripheral blood mononuclear cell
Pt	platinum
PT	prothrombin time
PTT	partial thromboplastin time
QTc	QT interval on electrocardiogram
RNA	ribonucleic acid
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended phase II dose
RPED	retinal pigment epithelial detachment
RPPA	Reverse Phase Protein Assays
RVO	retinal vein occlusion
SAE	serious advese event
SPF	sun protection factor
SRC	Scientific Review Committee
SU2C	Stand Up to Cancer
T3	total thriiodothyronine
T4	free thyroxine
T1DM	Type 1 diabetes mellitus
TB	Bacillus tuberculosis
TIL	tumor-infiltrating lymphocytes
TKI	tyrosine kinase inhibitors
TSH	thyroid stimulating hormone
UCD	University of California, Davis; UC Davis
UCDCC	UC Davis Comprehensive Cancer Center
ULN	upper limit of normal

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase Ib Trial of Pembrolizumab and Trametinib Focused on Advanced KRAS mutant Non-Small Cell Lung Cancer
Trial Phase	Ib
Clinical Indication	Advanced Non-Small Cell Lung Cancer Harboring a KRAS mutation
Trial Type	Phase Ib with Expansion Cohorts
Route of administration	Pembrolizumab (MK-3475) (Intravenous) Trametinib (Oral)
Trial Blinding	Unblinded Open-label
Treatment Groups	Phase I dose escalation of combination Pembrolizumab and Trametinib with lead in trametinib (cohort A) or lead in pembrolizumab (cohort B) in advanced NSCLC patients to determine the MTD and expansion phase dose. At the MTD, there are two Expansion Cohorts in KRAS Mutant NSCLC as follows: Cohort A: Lead in intermittent Trametinib for 1 cycle (3 weeks) followed by intermittent Trametinib and Pembrolizumab Cohort B: Lead in Pembrolizumab for 1 cycle (3 weeks) followed by intermittent Trametinib and Pembrolizumab
Number of trial subjects	We estimate 42 evaluable patients total (9 in each dose escalation cohort and 24 patients total for the dose expansion cohorts. A minimum of 12 patients (i.e., only 6 in each dose escalation arm if trial is terminated early due to unacceptable toxicity) and a maximum of 62 patients (18 patients in each dose escalation cohort and 24 patients total for the dose expansion cohorts.)
Estimated enrollment period	2 years
Estimated duration of trial	3 years
Duration of Participation	3 years

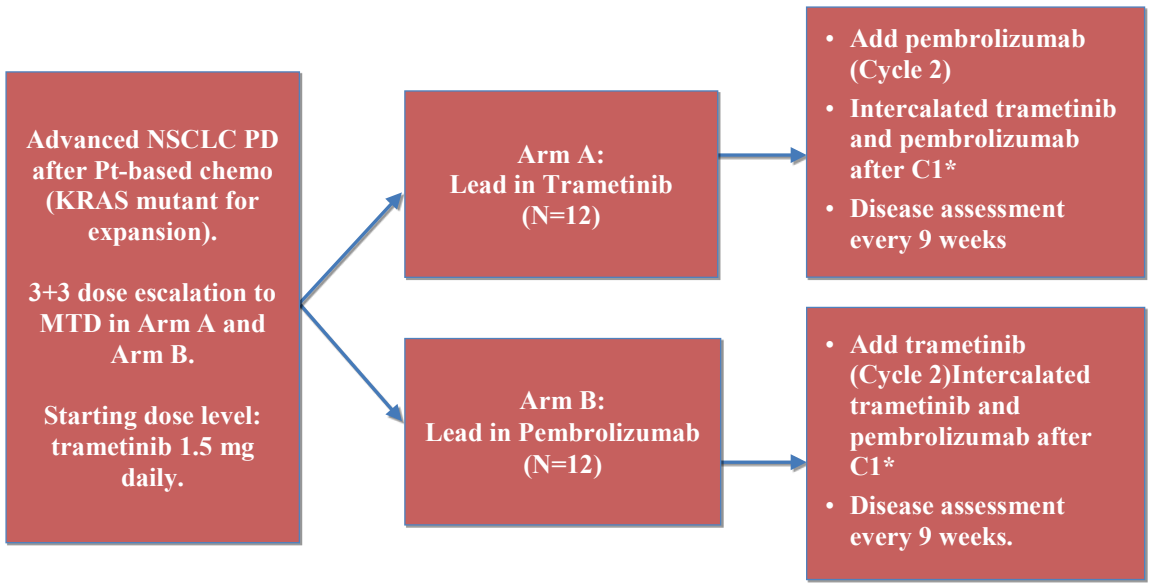
2.0 TRIAL DESIGN

2.1 Trial Design

This is a trial for patients with advanced or metastatic non-small cell lung cancer patients with KRAS mutations who have progressed on prior platinum-based frontline therapy. After the initial dose escalation with two different sequencing schemes (lead in trametinib and lead in pembrolizumab), in the expansion cohorts patients will be allocated to one of these two different arms: a) lead in trametinib followed by the intermittent trametinib/pembrolizumab and b) lead in pembrolizumab followed by intermittent pembrolizumab and trametinib to further define toxicities at the MTD, to determine the RP2D, to assess initial estimates of efficacy and to examine in the tumor and immune microenvironment changes in PD-L1 expression and T-cell subsets) across these two different sequencing schemes. Safety findings and preliminary efficacy will be employed as primary criteria for whether one or both treatment sequences may warrant further study. Exploratory immune correlates will be examined as secondary criteria to inform further development of this approach in future studies. The treatment arm that provides the better RR, PFS, safety profile and enhanced tumor immune microenvironment at rebiopsy will be recommended for further development. It is anticipated that ORR ≥ 50% or a median PFS ≥ 8 months would be sufficient to recommend further development, provided safety and tolerability are acceptable. Patients will be treated until progression per RECIST 1.1 guidelines or intolerable toxicity.

2.2 Trial Diagram

Intercalated Trametinib and Pembrolizumab in Advanced KRAS Mutant NSCLC



* Dose escalation in Arm A and Arm B followed by dose expansion (see 8.0 Statistical Analysis Plan).
Trametinib starting 10 days on and 11 days off. Starting dose level 1.5 mg daily.
Paired biopsy baseline, D11, and at progression (optional).
Pt=platinum, PD=progressive disease, MTD=maximum tolerated dose, NSCLC=non-small cell lung cancer

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypotheses

Objective: To evaluate the safety and tolerability of pembrolizumab (MK-3475) when given in combination with trametinib in the proposed sequencing schemes in patients with advanced or metastatic non-small cell lung cancer with KRAS mutations.

Hypothesis: We hypothesize that pembrolizumab in combination with trametinib given with our lead in and intermittent sequencing schemes will be safe and tolerable.

3.2 Secondary Objective & Hypotheses

Objective: To assess in a preliminary manner the clinical efficacy of these combinations with the proposed sequencing schemes outlined above including overall response rate and progression free survival.

Hypothesis for Secondary Objective: We hypothesize that the combination of trametinib and pembrolizumab will be efficacious.

3.3 Exploratory Objective

Objective: To determine in an exploratory manner changes in PD-L1 expression as well as other immune correlates induced by MEK inhibition.

Hypothesis for Exploratory Objective: We hypothesize that lead in trametinib will demonstrate the most promise for preliminary efficacy based on clinical outcome and changes in immune micro-environment.

4.0 BACKGROUND & RATIONALE

4.1 Pembrolizumab (MK-3475)

4.1.1 Background

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

4.1.2 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of 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 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.3 Preclinical and Clinical Trial Data

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

4.2 Trametinib

4.2.1 Background

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

4.2.2 Pharmaceutical and Therapeutic Background

Trametinib is a reversible and highly selective allosteric inhibitor of mitogen-activated extracellular signal-regulated kinase (MEK1 and MEK2 activation and kinase activity). MEK proteins are critical components of the extracellular signal-regulated kinase (ERK) pathway which is commonly hyperactivated in tumor cells. Oncogenic mutations in both BRAF (a member of the RAF kinases) and RAS signal through MEK1 or MEK2.

Trametinib is administered with doses up to 2 mg once daily. Subjects should take trametinib under fasting conditions, at least 1 hour prior to or 2 hours after a meal.

Trametinib is being developed for the treatment of a variety of cancers and is currently approved in the United States, Canada, Australia, and the EU as a monotherapy treatment for the treatment of subjects with unresectable or metastatic melanoma with BRAF V600 E/K mutation (approval was also granted in Chile on 22 September 2014). It is also approved in combination with dabrafenib for the same indication in the US and Australia.

4.2.3 Preclinical and Clinical Trial Data

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

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

Recent advances such as targeted therapy with EGFR and ALK tyrosine kinase inhibitors (TKIs) for patients harboring EGFR mutations and ALK translocations have dramatically improved patient outcomes and quality of life. However, no therapies targeting KRAS, the most common oncogenic driver mutation in NSCLC (~25%) are FDA approved.

Discovery of new therapeutic combinations that can alter the natural history of KRAS mutant lung cancer addresses a major unmet medical need.

KRAS was the first oncogenic driver mutation identified in NSCLC patients over a quarter of a century ago. Ras is a GTP-binding membrane-associated protein that typically modulates cell cycling and survival in response to external stimuli. Oncogenic KRAS mutations lock KRAS in a persistently activated state that triggers three main downstream signaling pathways to varying degrees (Ral, MEK/ERK and PI3K/AKT/MTOR)[1].

Though no approved clinical therapies exist specifically for KRAS mutant lung cancer, there are several promising clinical trials targeting MEK in KRAS mutated lung cancer. MEK inhibition alone appears insufficient to have meaningful clinical activity in KRAS positive NSCLC, but preclinical and early clinical trial data suggest that combination therapy with MEK inhibitors can be a highly effective treatment option in advanced NSCLC. In particular, preclinical data suggests that taxanes such as docetaxel are synergistic with MEK inhibitors [2] and in a randomized phase II clinical trial of 97 patients with KRAS mutated lung cancer, patients who received the MEK inhibitor selumetinib with docetaxel versus patients who received docetaxel alone had a significant improvement in progression free survival (PFS) and a trend towards increased overall survival (OS). In a recently presented single-arm phase I clinical trial from UC Davis and others at ASCO, a 28% response rate to docetaxel combined with the MEK inhibitor trametinib was observed in KRAS mutant patients (single agent docetaxel response rates ~7%)9. A signal towards preferential activity in KRAS G12C mutant patients was observed (40% vs. 20%), though sample size was small [3].

In several tumor types, in preclinical and translational studies the MEK-ERK pathway modulates PD-L1 expression, though different studies come to different conclusions regarding the degree and direction of this immunomodulation. In one preclinical study, PD-L1 expression is upregulated in melanoma cells resistant to BRAF inhibition and reversed by MEK inhibition with downregulation of PD-L1 and induction of apoptosis [4].

In a recently published clinical study, patient samples with metastatic melanoma BRAF inhibition increased PD-L1 expression while also enhancing markers of T-cell toxicity and providing a more favorable tumor immune microenvironment [5]. In other tumor types, studies suggest PD-L1 is also dependent on MEK/ERK and suppressed by MEK/ERK inhibition including Hodgkin's and Non-Hodgkin's Lymphoma and restores anti-immune activity [6].

Though there are somewhat discrepant conclusions regarding pre-clinical and clinical/translational data with MEKi and PD1/PDL1 inhibition in several tumor types, the weight of the evidence suggests that MEKi can potentiate the immune response and modulate PD-L1 expression. In KRAS mutant NSCLC treatment with selumetinib led to upregulation of PD-1 on CD8 T-cells and depletion of Treg with increase in PD-1 and CTLA-4 providing some rationale for integrating PD-1 blockade with MEK inhibition and highlighting the need to biopsy tissue on treatment to examine the tumor immune microenvironment[7]. Examination of immune correlates in tissue and blood in this early phase trial (including modulation of PD-L1 expression and T-cell subsets) are required to determine optimal sequencing of MEKi and PD1 antibody for maximum clinical impact.

This proposal builds a foundation for the study of pembrolizumab (MK-3475) with targeted therapeutic combinations incorporating MEK inhibitors in KRAS mutant NSCLC (a major unmet clinical need) and data regarding safety and tolerability from this proposal can be extended to other tumor types where MEK inhibition and PD1/PD-L1 blockade may be utilized.

Higher response rates with PD-1 blockade in tumors known to be highly mutated such as melanoma and NSCLC have been noted and we have observed higher responses in NSCLC

tumors with KRAS mutations (28% vs. 19%) suggesting potential roles for both KRAS and overall mutation burden in driving an adaptive immune escape phenotype (Figure 1).

Figure 1. Response rates to pembrolizumab according to mutation status

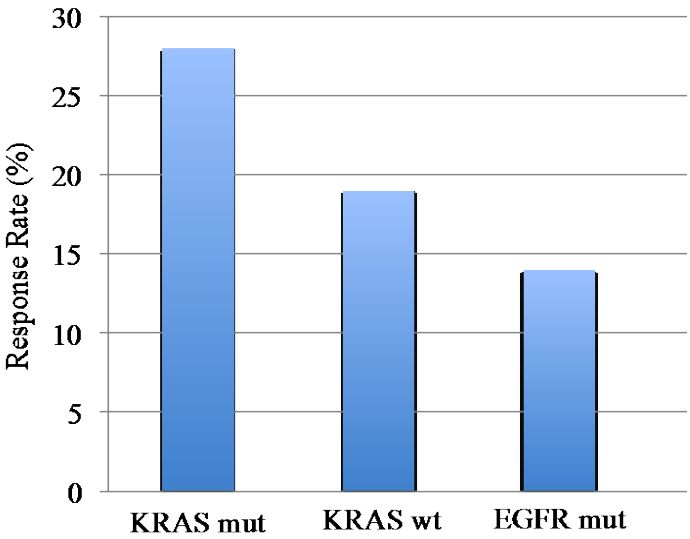
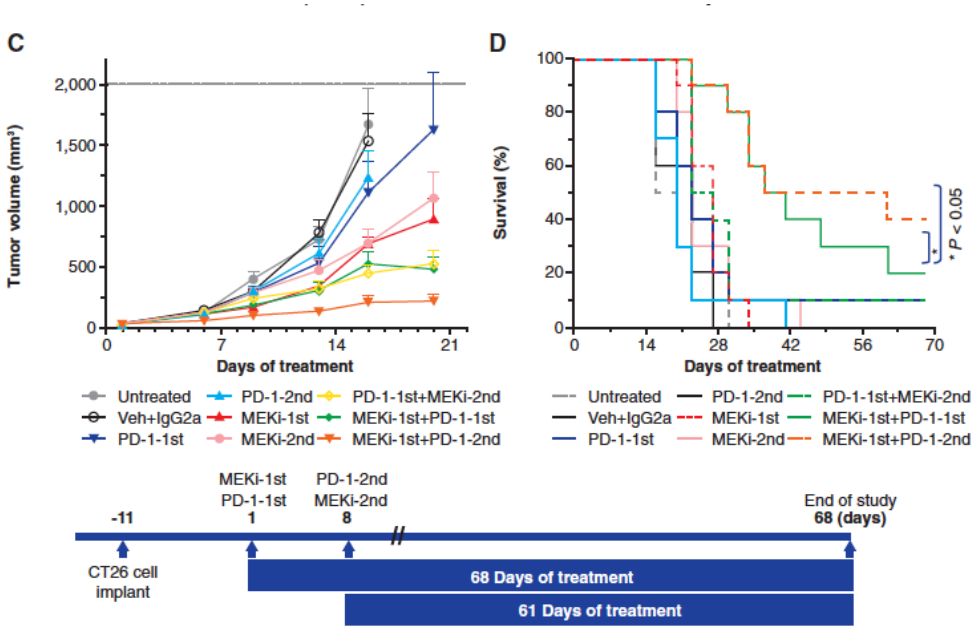


Figure 2. In vivo antitumor activity in CT26 Mouse Model dependent on sequencing of MEK inhibition with trametinib and PD-1 blockade (Liu et al, Clinical Cancer Research 2015)



Rationale for sequencing of combined therapy with MEK inhibitors and PD-1/PD-L1 blockade[8]. The combination of trametinib (a MEKi) and anti-PD1 antibodies (RMP1-14 clone, rat IgG2a, Bioxcell) was studied in the CT26 murine syngeneic tumor model, which is homozygous for the KRAS (G12D) mutation, and contains amplification of MAPK1 and MET genes, in immune competent mice. Three combination regimens were evaluated: (1) trametinib and anti-PD1 antibody given concurrently starting week; (2) trametinib in week 1 as a single agent with anti-PD-1 added in week 2; and (3) anti-PD-1 in week 1 with addition of trametinib in week 2 (Figure 2). All three combinations were found to inhibit tumor growth more effectively than the single agents during the initial 2-3 weeks of treatment (Figure 2). However, schedule mattered as the combination in which anti-PD-1 was administered first did not lead to a profound effect on tumor growth (Figure 2, C). These findings reinforce the view that a detailed understanding of dose and schedule will likely have a profound impact on efficacy. Furthermore, the combination of trametinib and anti-PD-1 antibody increased tumor infiltrating CD8+ T cells in vivo compared to anti-PD-1 alone (data not shown), demonstrating the importance of concurrent immune monitoring for optimization of targeted therapy combinations. Similar in vivo anti-tumor activity was observed in the CT26 model using a different mouse anti-PD1 antibody (mDX400), supporting the validity of the observations.

4.3.2 Rationale for Dose Selection/Regimen/Modification

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established

exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

The FDA approved starting dose of trametinib is 2 mg administered orally daily. This fixed dose of pembrolizumab is combined with trametinib starting a dose reduction of 1.5 mg daily and then escalated to trametinib 2 mg daily if the combination is well tolerated. Pembrolizumab is approved for the treatment of advanced NSCLC with positive PD-L1 expression. Intermittent and dose reduced schedule is designed to manage potential toxicities seen in KEYNOTE-022 trial in phase 1 dose escalation of continuous 2 mg of trametinib with pembrolizumab. Intermittent dosing also may be more favorable for reducing depletion of T-cells in response to prolonged MEK inhibition.

4.3.3 Rationale for Endpoints

This is a phase I 3+3 dose escalation study followed by expansion cohorts for safety and correlative studies. Therefore, the endpoints include determination of MTD, and recommended phase II dose (RP2D) correlative endpoints and secondary efficacy endpoints. MTD and RP2D are standard endpoints for phase I dose escalation studies.

- The recommended dose expansion and recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD and toxicities observed in the dose escalation portion of this study.

4.3.3.1 Efficacy Endpoints

- Overall response rate (ORR). ORR is an acceptable measure of clinical benefit in early phase clinical trials to provide a preliminary signal of activity to consider later phase trials.

- Progression-free survival (PFS). PFS is an acceptable measure of assessing benefit in NSCLC clinical trials.

As this is a phase I study, our goal is a preliminary assessment of a signal of efficacy as defined in the statistical plan.

4.3.3.2 Biomarker Research

4.3.3.2.1 Immunology Correlates

Immunology correlates will be performed by collaborators at the Translational Immuno-Oncology Laboratory Yale University and/or by the Human Immune Monitoring Core at UC Davis as defined in the protocol. The Human Immune Monitoring Core at UC Davis is under the supervision of Emanual Maverakis, MD. Dr. Maverakis' laboratory is a world renowned immunology laboratory and has the equipment and expertise to conduct the proposed studies. The Translational Immuno-Oncology Laboratory at Yale University is under the direction of David Rimm MD, Ph.D and Kurt Schalper, MD, Ph.D and has been a leader in the translational immuno-oncology of immune checkpoint inhibitors.

a. Biopsy (Biopsy at Baseline, C1D11-13 and at progression (optional)

- PD-L1 expression by immunohistochemistry at baseline and in repeat biopsy specimens to assess for changes in PD-L1 expression in response to treatment will be conducted by Yale Immuno-Oncology under the direction of Kurt Schalper using the approved DAKO 22C3 antibody and in addition quantitative IHC assays for PD-L1 if tissue permits. UC Davis may also perform IHC for PD-L1 using the standard DAKO 22C3 antibody.

- Enumeration and changes in immune cell subsets by immunohistochemistry in repeat biopsy specimens in response to treatment will be conducted by Yale Translational Immuno-Oncology.

- Whole exome DNA/RNA next generation sequencing and assessment of mutational load will be performed by the Broad Institute in Boston. The Broad Institute is a world leader in genomic sequencing and analysis.

- Tissue banked for RPPA (Reverse Phase Protein Assays) for on-target EGFR pathway inhibition will be performed by Theranostics in collaboration with the Mack lab at UC Davis.

b. Plasma PD-L1 DNA/RNA levels will be assayed by Liquid Genomics in a CLIA certified laboratory.

Additional peripheral blood will be collected and banked at relevant time points for enumeration of immune cell subsets and changes in cytokine expression in response to treatment with methods including Flow Cytometry and Luminex Cytokine Assays by the Human Immune Monitoring Core at UC Davis.

4.3.3.2.2 Molecular Correlates

a. Biopsy

Whole exome DNA/RNA next generation sequencing including KRAS aminio acid substitution, p53 and LKB1 mutations, and assessment of mutational load will be performed by the Broad Institute in Boston. The Broad Institute is a world leader in genomic sequencing and analysis.

b. Plasma KRAS-mutant DNA/RNA Levels

Changes in plasma KRAS-mutant DNA/RNA in patients with KRAS-mutant NSCLC may be prognostic for recurrence, the development of resistance to existing therapies and may track response or lack of benefit to existing treatment. Determination of plasma KRAS-mutant DNA/RNA levels will be conducted at Liquid Genomics in a CLIA certified laboratory.

c. If tissue permits, analysis for pharmacodynamic markers of on-target MEK-ERK inhibition with RPPA will be performed by Theranostics and the Mack lab at UC Davis.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Stage IV or Metastatic/Recurrent Non-Small Cell Lung Cancer. For expansion cohorts, patient's tumor must also harbor a KRAS mutation detected in a CLIA certified laboratory.

5.1.2 Subject Inclusion Criteria

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

1. Have histologically or cytologically confirmed non-small cell lung cancer.
2. Have stage IV, metastatic or recurrent non-squamous NSCLC with progressive disease after platinum containing chemotherapy (EGFR mutant, ALK, or ROS-1 rearranged NSCLC must have progressed on prior approved TKI's).

3. For phase I dose expansion cohorts the patient's tumor must harbor a KRAS mutation detected by a CLIA certified laboratory.
4. Be willing and able to provide written informed consent/assent for the trial.
5. Be ≥ 18 years of age on day of signing informed consent.
6. Have measurable disease based on RECIST 1.1.
7. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. In the opinion of the investigator, the patient must have tumor accessible by CT or ultrasound guided core biopsy. Subjects for whom newly-obtained samples cannot be provided may submit an archived specimen provided it was obtained after last systemic treatment, within 6 months of signing consent and that tissue is available for either 2 cell blocks or 20 uncut slides (core or excisional biopsy required, fine needle aspirate is not acceptable).
8. Have a performance status of 0 or 1 on the ECOG Performance Scale.
9. Able to swallow and retain orally administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
10. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Values
Absolute neutrophil count	≥1.5 × 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥100 × 10^9/L
PT/INR and PTT	≤1.5 x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 x ULN
AST and ALT	≤ 2.5× ULN
Renal	
Creatinine or	≤ 1.5 ULN
Calculated creatinine clearance[a]	≥ 50 mL/min
Cardiac	
Left Ventricular Ejection fraction (LVEF)	≥ LLN by ECHO or MUGA[b]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal; LLN=lower limit of normal

[a] Calculated by the Cockcroft-Gault formula.

[b] Same method as used at baseline must be use throughout the study, ECHO is the preferred method

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

12. Female subjects of childbearing potential (Section 5.8.2) must be willing to use an adequate method of contraception as outlined in Section 5.8.2 – 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 for the subject.

13. Male subjects of childbearing potential (Section 5.8.1) must agree to use an adequate method of contraception as outlined in Section 5.8.1- 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.

5.1.3 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 3 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Inhaled or topical steroids are allowed.
3. Has a known history of active TB (Bacillus Tuberculosis).
4. Hypersensitivity to pembrolizumab or any of its excipients.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 3 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 3 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.
    - 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. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
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, or any evidence of active, non-infectious pneumonitis. History of radiation pneumonitis is allowed provided that it is not active and no corticosteroids were required for pneumonitis management.
11. Evidence of interstitial lung disease.
12. Has an active infection requiring systemic therapy.
13. Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to trametinib, or excipients or to dimethyl sulfoxide (DMSO).
14. History of retinal vein occlusion (RVO).
15. 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.
16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
17. 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.
18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent for dose expansion. (Patients in dose escalation may have received an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent).
19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
21. History or evidence of cardiovascular risk including any of the following:

- LVEF<LLN on screening exam.
- A QT interval corrected for heart rate using the Fridericia's formula (QTcF; Appendix X) ≥470 msec (Appendix 11.2) on screening exam.
- History or evidence of current clinically significant uncontrolled arrhythmias.
- **Clarification:** Subjects with atrial fibrillation controlled for >30 days prior to dosing are eligible.
- History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
- History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA; Appendix 11.5).
- Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy;
- Patients with intra-cardiac defibrillators.

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

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

5.2 Trial Treatments

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

Table 2. Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Trametinib	x mg†	Daily†	PO	Daily starting D1	Experimental
† See dose escalation schema. RP2D for expansion cohorts.					

Dose Escalation Cohort (Arm A): Trametinib will be adminstered starting C1D1 and continued as per Table 3, until determination of the MTD. Pembrolizumab will be added to trametinib starting C2D1.

Dose Escalation Cohort (Arm B): Pembrolizumab will be administered starting C1D1 and trametinib will be added to pembrolizumab starting C2D1.

Expansion Cohort (Arm) A: Trametinib will be administered starting C1D1 and pembrolizumab will be added to trametinib starting C2D1 at the MTD of the combination as determined from the dose escalation portion of the study.

Expansion Cohort (Arm) B: Pembrolizumab will be administered starting C1D1 and trametinib will be added to pembrolizumab starting C2D1 at the MTD of the combination as determined from the dose escalation portion of the study.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

The dose of pembrolizumab is fixed at 200 mg IV Q3W.

The dose escalation schema of trametinib is as follows. Each cycle is Q3W (21 days).

Table 3. Dose Escalation Schema for Trametinib

Dose Level	Trametinib dose (PO Daily) Q3W	Pembrolizumab (MK-3475) dose IV Q3W
-1	1.5 mg (D1-D7)	200 mg
*1	1.5 mg (D1-D10)	200 mg
2	2.0 mg (D1-D10)	200 mg
* Dose level 1 is the starting dose. For each cohort, trametinib dose will be the same for lead in and for concurrent trametinib + pembrolizumab administration.		

For Cohort A: Lead in trametinib will precede combination trametinib and pembrolizumab, which will commence for C2.

For Cohort B: Lead in pembrolizumab will precede combination trametinib and pembrolizumab, which will commence for C2.

The recommended dose expansion and recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD (the maximum dose level where 6 patients have been treated in the dose escalation portion of the study) and toxicities observed in the dose escalation portion of this study.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 5 below. See dose modification and supportive care guideline sections, including use of corticosteroids. There are no dose reductions for pembrolizumab.

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. The reason for interruption should be documented in the patient's medical record.

Table 4. Dose Modification for Trametinib. Lowest permitted Trametinib dose will be 1.5 mg daily.

Dose Level	**Trametinib Dose (QD) (D1-D10 administration unless otherwise specified)**		
For Starting Dose	2 mg	1.5 mg	1.5 mg (dosed from D1-D7)
1st Does Reduction	1.5 mg	1.5 mg (dosed from D1-D7)	Discontinue Trametinib
2nd Dose Reduction	1.5 mg (dosed from D1-D7)	Discontinue trametinib	-

Table 5. Dose Modification Guidelines for Pembrolizumab (MK-3475) for Drug-Related Adverse Events

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia	Resume pembrolizumab when patients are clinically and metabolically stable

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Hyperglycemia		associated with evidence of beta cell failure	
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 3 – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor Investigator. Subjects who require corticosteroids to manage drug-related adverse events must be at an equivalent dose of ≤10mg per day of prednisone to resume dosing with pembrolizumab. Furthermore, an inability to reduce

the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤10 mg prednisone per day within 12 weeks of last pembrolizumab dose should result in permanent discontinuation from pembrolizumab. With investigator and Sponsor 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. For information on the management of adverse events, see Section 5.7.2.

In subjects who continue on pembrolizumab having experienced a Grade 3, Grade 4, or persistent (> 4 weeks) Grade 2 drug-related AE, once the subject has recovered from the AE to Grade 0-1, the dosing interval in subsequent cycles may be increased by 1 week (e.g., to every 4 week dosing in subjects who were on an every 3 week schedule). However, in subjects who experience Grade 3 or 4 pneumonitis, or recurrent persistent (>4 weeks) Grade 2 drug - related pneumonitis after rechallenge from a prior episode of persistent (> 4 weeks)Grade 2 drug-related pneumonitis, pembrolizumab must be permanently discontinued.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, a consultation between the Sponsor Investigator and investigator should occur to determine whether the subject should continue in the trial. However, for a subject who experiences a recurrence of the same serious adverse event at the same grade or greater with rechallenge of pembrolizumab, the subject must discontinue pembrolizumab.

Table 6 Dose Modification Guidelines for Trametinib for Drug-Related Adverse Events (Unless Otherwise Specified)

Grade (CTC-AE)*	Dose Modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0-1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

Please follow Table 5 and Table 6 for dose modifications unless specified below.

For Grade ≥ 3 drug related adverse events attributed to trametinib both pembrolizumab and trametinib should be simultaneously interrupted with the exceptions shown below.

Except for Grade ≥ 3 lymphopenia

Exceptions where dose modifications are necessary for only trametinib:

- LVEF reduction
- Retinal Vein Occlusion (RVO) and Retinal Pigment Epithelial Detachment (RPED)

Table 7. Trametinib Dose Modification Guidelines and Stopping Criteria for LVEF Decrease

Clinical Evaluation	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt trametinib and repeat ECHO/MUGA within 2 weeks.[a] • If the LVEF recovers within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Consult with the Novartis trametinib medical monitor and request approval for restart. – Restart treatment with trametinib at reduced dose by one dose level. – Repeat ECHO/MUGA 2, 4, 8, and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – **Permanently discontinue trametinib.** – **Report as SAE** – Repeat ECHO after 2, 4, 8, 12, and 16 weeks or until resolution.
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue trametinib.** • **Report as SAE.** • **Consult with cardiologist.** • Repeat ECHO/MUGA after 2, 4, 8, 12, and 16 weeks or until resolution.

[a] If ECHO/MUGA does not show LVEF recovery after 2 weeks, repeat ECHO/MUGA 2 weeks later.
[b] Symptoms may include: dyspnea, orthopenea, and other signs and symptoms of pulmonary congestion and edema.

Table 8. Trametinib Withholding and Stopping Criteria for QTc Prolongation

Prolongation*	Action and Dose Modification
• QTc ≥501 msec, or • Uncorrected QT >600 msec, or • QTc >530 msec for subjects with bundle branch block	• Interrupt study treatment until QTc prolongation resolves to grade 1 or baseline. • Test serum potassium, calcium, phosphorus, and magnesium. If abnormal, correct per routine clinical practice to within normal limits. • If the QTc prolongation resolves to grade 1 or baseline, trametinib may be resumed if the investigator and study chair agree that the subject will benefit from further treatment. • **If the event does not resolve, permanently discontinue study treatment.** • **If the event recurs, permanently discontinue study treatment.**
Abbreviations: msec = milliseconds; QTc = QT interval on electrocardiogram * Based on average QTcF value of triplicate ECGs. For example, if an ECG demonstrates a prolonged QT interval, obtain two or more ECGs over a brief period, and then use the averaged QTcF values of the three ECGs to determine if study treatments should be interrupted or discontinued. (See Appendix 11.4 for QTcF calculation).	

Table 9. Trametinib Dose Modification Guidelines for Hypertension

Toxicity Grade	Dose Modification
2: Asymptomatic	Maintain dose level
3: Asymptomatic	Hold until blood pressure is well controlled. Restart at reduced dose level.
3: Symptomatic	Hold until blood pressure is well controlled. Restart at reduced dose level.
4	Permanent discontinuation of treatment.

Eye Disorders

Visual changes have been observed in patients receiving trametinib, and can be caused by central serous retinopathy (CSR) with retinal pigment epithelial detachments (RPED), or Retinal Vein Occlusion (RVO). Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and any time patients report visual disturbance. The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy. Special attention should be given to retinal (e.g., CSR, RPED) or retinal vein abnormalities (e.g., RVO).

Table 10. Management and Trametinib Dose Modification for Visual Changes and/or Ophthalmic Examination Findings

Event CTCAE Grade	Management Guideline	Dose Modification
Grade 1*	• Consult ophthalmologist within 7 days of onset.	• If dilated fundus examination cannot be performed within 7 days of onset, hold trametinib until RPED and RVO can be excluded by retina specialist/ophthalmologist. • If RPED and RVO excluded, continue/or restart trametinib at same dose level. • If RPED suspected/diagnosed: See RPED dose modification table below (following this table); **report as SAE**. • If RVO diagnosed: **Permanently discontinue trametinib and report as SAE.**
Grade 2 and Grade 3	• Consult ophthalmologist immediately.	• Hold trametinib • If RPED or RVO excluded, restart trametinib at same dose level after visual AE is ≤ grade 1. If no recovery within 3 weeks, discontinue trametinib • If RPED diagnosed: See RPED dose modification table below; **report as SAE**. • If RVO: **Permanently discontinue trametinib and report as SAE.**
Grade 4	• Consult ophthalmologist immediately. • Report as SAE.	• Hold Trametinib • If RPED/RVO excluded, may restart trametinib at same or reduced dose after discussion with the Principal Investigator • **If RVO or RPED, permanently discontinue trametinib.**
Abbreviations: RPED=retinal pigment epithelial detachments; RVO=retinal vein occlusion; SAE=serious adverse event * If visual changes are clearly unrelated to study treatment (e.g., allergic conjunctivitis), monitor closely but ophthalmic examination is not required.		

Table 11. Trametinib Dose Modification for RPED

Event CTCAE Grade	Action and Dose Modification
Grade 1 RPED (Asymptomatic; clinical or diagnostic observations only)	• Continue treatment with retinal evaluation monthly until resolution. If RPED worsens, follow instructions below.
Grade 2-3 RPED (Symptomatic with mild to moderate decrease in visual acuity; limiting instrumental ADL)	• Interrupt trametinib. • Retinal evaluation monthly. • If improved to ≤ Grade 1, restart trametinib with one dose level reduction (reduced by • 0.5 mg) or discontinue in patients taking trametinib 1 mg daily. • If no recovery within 4 weeks permanently discontinue trametinib

Table 12. Management and Dose Modification Guidelines for Diarrhea

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Uncomplicated Diarrhea,[1] Grade 1 or 2	• Diet: Stop all lactose containing products; eat small meals, BRAT-diet (banana, rice, apples, toast) recommended. • Hydration: 8-10 large glasses of clear liquids per day (*e.g.*, Gatorade or broth). • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea- free for 12 hours. • Diarrhea >24 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Consider adding oral antibiotics. • Diarrhea >48 hours: Loperamide 2 mg every 2 hours; maximum 16 mg/day. Add budesonide or other second-line therapies (otreotide, or tincture of opium) and oral antibiotics.	• Continue trametinib. • If diarrhea is grade 2 for > 48h, interrupt trametinib until diarrhea resolves to grade ≤1. • Restart trametinib at the same dose level • If treatment delay is > 28 days, discontinue trametinib.
Uncomplicated Diarrhea,[1] Grade 3 or 4 **Any Complicated Diarrhea2**	• Clinical evaluation mandatory. • Loperamide[3]: Initially 4 mg, followed by 2 mg every 4 hours or after every unformed stool; maximum 16 mg/day. Continue until diarrhea- free for 12 hours. • Oral antibiotics and second-line therapies if clinically indicated • Hydration: Intravenous fluids if clinically indicated. • Antibiotics (oral or intravenous) if clinically indicated. • Intervention should be continued until the subject is diarrhea-free for ≥24 hours. • Intervention may require hospitalization for subjects at risk of life- threatening complications.	• Interrupt trametinib and pembrolizumab until diarrhea resolves to ≤ grade 1. Then restart pembrolizumab and trametinib reduced by one dose level.[4] • If 3 dose reductions of study treatment are clinically indicated, **permanently discontinue trametinib**. • If treatment delay is >28 days, discontinue trametinib and pembrolizumab.

[1] **Uncomplicated diarrhea** defined by the absence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution.

[2] **Complicated diarrhea** defined by the presence of symptoms such as cramping, nausea/vomiting, ≥ grade 2, decreased performance status, pyrexia, sepsis, neutropenia ≥ grade 3, frank bleeding, and/or dehydration requiring intravenous fluid substitution. Patients with complicated diarrhea should be evaluated for pembrolizumab mediated autoimmune colitis with additional management as specified for pembrolizumab.

[3] Loperamide should be made available prior to start of study treatment so loperamide administration can begin at the first signs of diarrhea.

[4] Escalation of trametinib to previous dose level is allowed after consultation with the study chair and in the absence of another episode of complicated or severe diarrhea in the 4 weeks subsequent to dose reduction.

Table 13. Dose Modification Guidelines and Management for Rash

Rash Severity	Management Guideline	Dose Modification
Grade 1	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• Continue trametinib. • If rash does not recover to baseline within 2 weeks despite best supportive care, **reduce trametinib by one dose level**.[3]
Grade 2	• Initiate prophylactic and symptomatic treatment measures.[1] • Use moderate strength topical steroid.[2] • Reassess after 2 weeks.	• **Reduce trametinib by one dose level.** • If rash recovers to ≤ grade 1 within 2 weeks, increase dose to previous dose level. • If no recovery to ≤ grade 1 within 2 weeks, interrupt trametinib until recovery to ≤ grade 1. • **Restart trametinib at reduced dose level.**
Grade ≥3	• Use moderate strength topical steroids. Consider oral methyl-prednisolone dose pack.[2] • Consider consulting dermatologist.	• Interrupt trametinib until rash recovers to ≤ grade 1. Then restart pembrolizumab and trametinib (reduced by one dose level).[3] • If no recovery to ≤ grade 2 within 4 weeks, **permanently discontinue trametinib and pembrolizumab.**

[1] Rash prophylaxis is recommended for the first 6 weeks of study treatment.
[2] Moderate-strength topical steroids: Hydrocortisone 2.5% cream or fluticasone priopionate 0.5% cream.
[3] Trametinib may be escalated to previous dose level if no rash is evident 4 weeks after restarting study treatment.

Table 14. Pneumonitis Guidelines

CTCAE Grade	Adverse Event Management	Action and Dose Modification
Grade 1	• CT scan (high-resolution with lung windows) recommended. • Work-up for infection. • Monitoring of oxygenation via pulse- oximetry recommended. • Consultation with pulmonologist recommended.	• Continue trametinib at current dose.
Grade 2	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests: If < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL recommended. • Symptomatic therapy including corticosteroids if clinically indicated.	• Interrupt trametinib and pembrolizumab until recovery to grade ≤1. • If AE resolved to Grade ≤1 and relationship to trametinib and or pembrolizumab is equivocal, restarting pembrolizumab and trametinib (with dose reduction at investigators discretion) may be considered, after discussion with the study chair. • If treatment delay is > 4 weeks, permanently discontinue trametinib and pembrolizumab.
Grade 3	• CT scan (high-resolution with lung windows). • Work-up for infection. • Consult pulmonologist. • Pulmonary function tests-if < normal, repeat every 8 weeks until ≥ normal. • Bronchoscopy with biopsy and/or BAL if possible. • Symptomatic therapy including corticosteroids as clinically indicated.	• Permanently discontinue trametinib and pembrolizumab.
Grade 4	• Same as grade 3.	• Permanently discontinue trametinib and pembrolizumab.
Abbreviations: BAL = bronchoalveolar lavage; CT = computed tomography.		

Dose Reduction Scheme for Trametinib

No dose reductions for trametinib are permitted below 1.5 mg PO daily.

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion 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).

5.3 Treatment

The dose escalation portion of the trial will determine the MTD. Once the dose escalation portion is complete, patients will enroll sequentially (see Statistical Analysis Plan section for further details) into one of two expansion cohorts as noted below. Enrollment into Expansion Cohorts A and B are pre-planned in regards to sequence and timing. Arm A (lead in trametinib) will open first to dose escalation and will accrue 3 patients. Once 3 patients are accrued for Arm A, Arm B will open and accrue 3 patients.

Expansion Cohort (Arm)	Regimen	Number of patients
A	Lead in trametinib for 1 cycle (Q3W) followed by intercalated Trametinib and Pembrolizumab.	12
B	Lead in pembrolizumab for 1 cycle (Q3W) followed by intercalated Trametinib and Pembrolizumab.	12

5.4 Definition of Dose Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0. The occurrence of any of the following toxicities during the first two cycles (i.e. after completion of the lead in cycle and the first cycle where both pembrolizumab and trametinib are administered) will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration. The goal of the dose escalation portion of the study is to assess the safety of the combination after pembrolizumab or trametinib lead in, therefore, patients must have completed the lead in phase and also have received both trametinib and pembrolizumab concurrently to be evaluable for a DLT.

A DLT evaluable subject is defined as a subject who receives treatment for the 6 week dose-limiting toxicity (DLT) observation period and who receives at least 80% of all planned treatments. A subject who does not receive at least 80% of planned treatment due to AEs that are unrelated to study treatment will not be considered evaluable for DLTs and may be replaced as

needed during dose escalation or dose confirmation. More than 3 or 6 subjects may be enrolled to a given dose level if needed to replace subjects who are not evaluable for DLT or to ensure a thorough evaluation of a given dose level during the dose escalation part of the study. An event will be considered a dose-limiting toxicity (DLT) if it occurs during the first two cycles of treatment (first 6 weeks after initiating treatment) and meets at least one of the following criteria:

- Clinically significant hematologic toxicity (e.g. grade 4 neutropenia lasting more than 7 days or accompanied by neutropenic fever, or Grade 4 thrombocytopenia of any duration)
- Clinically significant Grade ≥3 non-hematologic toxicity that has not been previously identified for either pembrolizumab or dabrafenib/trametinib and cannot be controlled with routine supportive measures (e.g. anti-emetics)
- Clinically significant Grade ≥3 non-hematologic toxicities that are known to occur with either pembrolizumab or trametinib but that cannot be controlled using the recommended product-specific supportive measures (e.g. steroids for pembrolizumab -related immune toxicities)
- Drug-related toxicity, regardless of CTCAE grade, that results in an interruption of any component of study therapy during Cycle 1 for more than 21 consecutive days and cannot be controlled within 2 weeks from its onset
- Any other Grade 2 or greater non-hematological toxicity that in the judgment of the investigator and Sponsor Investigator is dose limiting, with the exception of mild or moderate immune -mediated adverse reactions or symptomatic endocrinopathy attributable to pembrolizumab
- For Liver Function Tests
    - ALT or AST ≥8x ULN
    - ALT or AST ≥5x ULN but <8x ULN persists for ≥2 weeks
    - ALT or AST ≥3x ULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash or eosinophilia.

The following will NOT be considered a DLT for the purposes of this protocol:

- Clinically insignificant laboratory values of any grade (i.e. asymptomatic amylase, lipase elevations).

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

The MTD is the highest dose tested in which ≤ 1 out of 6 patients has experienced a DLT.

Table 15: Dose Escalation Decision Rule Summary

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximum administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximum administered dose (unless ≤1 out of 6 patients have DLT's at Dose Level 2 – in which case this is also the MTD).	This is the maximum tolerated dose (MTD), and generally the recommended phase 2 dose (RP2D). At least 6 patients must be entered at the RP2D.

If ≤1 out of 6 patients treated at Dose Level 2 have DLT, this will be declared the maximum administered dose and the presumptive RP2D. The RP2D may be less than the MTD or the maximum administered dose, depending on toxicities in later cycles and the extent of toxicities not qualifying as DLT.

5.5 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 Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded in the subject's 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 subject's medical record.

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

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Investigator.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

5.6.2 Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events

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

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

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

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

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 colitis,** treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or Grade ≥3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

    - For **T1DM** or **Grade 3-4** Hyperglycemia

        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

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

- **Hypophysitis**:

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

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

- **Hyperthyroidism or Hypothyroidism**:

    Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):

        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

    - **Grade 3-4** hyperthyroidism

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

- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 16 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475). May follow institutional guidelines.

Table 16. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator, or per institutional policies.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms**. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (±30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion**. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration**.	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.3 Supportive Care for Trametinib

Rash is a frequent AE observed in subjects receiving trametinib (see the Investigator Brochures for more information). Recommendations for supportive care and guidelines for dose modifications for rash are based on experience with other MEK inhibitors[9] and EGFR inhibitors[10] and are provided in the table below and in the dose modification section for rash. Additional supportive care guidelines for trametinib and pembrolizumab are included in the dose modification guidelines in section 5.2.

Table 17. Guidelines for Supportive Care of Rash from Trametinib

Type of Care	Action
Prevention /Prophylaxis[a]	• Avoid unnecessary exposure to sunlight • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (e.g., glycerine and cetomacrogol cream) on dry areas of the body at least twice daily. • Topical steroids and antibiotics should be applied at least twice daily starting on Day 1 of study treatment, to body areas such as face, chest, and upper back. Use mild-strength topical steroid (hydrocortisone 1% cream) or topical antibiotic (e.g., clindamycin) or oral antibiotics (e.g., doxycycline 100 mg BID, minocycline 100 mg BID)
Symptomatic Care[b]	• Pruritic lesions: cool compresses and oral antihistamine therapies • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream • Desquamation: thick emollients and mild soap • Paronychia: antiseptic bath, local potent corticosteroids in addition to oral antibiotics; if no improvement, consult dermatologist or surgeon • Infected lesions: appropriate bacterial/fungal culture-driven systemic or topical antibiotics

Abbreviations: BID = twice daily; SPF = sun protection factor
a Rash prophylaxis is recommended for the first 6 weeks of study treatment
b Subjects who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or trametinib, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor Investigator and to Merck and to Novartis without delay and within 24 hours to the Sponsor Investigator and within 2 working days to Merck and Novartis 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 Investigator, Merck and Novartis. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor Investigator and to Merck and to Novartis and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor Investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.3 – 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: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- 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. Trametinib may be continued longer.

  Note: 24 months of pembrolizumab is calculated from the date of first dose.
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Study Calendar) and Section 7.1.4 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

5.9 Subject Replacement Strategy

N/A

5.10 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's or Novartis' decision to no longer supply study drugs, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 STUDY CALENDAR

Time Period:	**Screening Phase**	**Treatment Cycle[1]**								**End of Treatment**		**Post-Treatment**	
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles				Discontinuation Visit	Safety Follow-up 30 days Post Discontinuation[14]	Follow-up[15]	Survival Follow-up[16]
						5	6	7	8				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discontinuation			
Administrative Procedures													
Informed Consent	X												X
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X												
Trial Treatment Administration[8]		X	X	X	X	X	X	X	X				
Survival Status		X	----------Ongoing----------							X	X	X	X
Clinical Procedures/Assessments[1,2]													
Review Adverse Events		X	----------Ongoing----------							X	X		
Full Physical Examination	X												
Directed Physical Examination		X[1]	X	X	X	X	X	X	X	X	X		
Vital Signs, Weight and Height (height only at screening).	X	X[1]	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		
Ophthalmology Exam[11]	X	As clinically indicated											
ECG[13]	X	X	X	X					X				
ECHO/MUGA[12]	X				X				X				
Laboratory Procedures/Assessments[5,6]	-10 to -1												
Pregnancy Test – Urine or Serum β-HCG[3]	X												
PT/INR and aPTT[4]	X												
CBC with Differential	X		X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X		X	X	X	X	X	X	X	X	X		
Urinalysis	X												
T3, FT4 and TSH	X		X		X		X		X	X	X		
Efficacy Measurements													
Tumor Imaging[7]	X	Every 9 weeks while on treatment								X	X	X	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection[9]	X	X								X			
Correlative Studies Blood Collection[10]	X	X	X	X	X	X	X	X	X	X			

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days); however the pembrolizumab (MK-3475) treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided. If treatment cycles are increased all procedures except imaging will be completed according to the Cycle number and not weeks on treatment, imaging will be performed every 9 weeks (± 3 days) from the first dose of trial treatment regardless of any treatment delays. Weekly visits will also occur for the first cycle when starting trametinib (when trametinib is added (Cohort A C1D1, Cohort B C2D1). The first cycle where both drugs are given requires weekly clinic visits for review of adverse events, vital signs, ECOG performance status, directed physical exam and CBC and CMP.
2. In general, the window for each visit is ± 3 days unless otherwise specified.
3. For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
4. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Table 19 for a list of specific laboratory procedures/assessments to be performed in this study.
6. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.
7. The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging will be performed every 9 weeks (63 ±7 days) after the first dose of trial treatment or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab /trametinib cycle frequencies. The same imaging technique should be used in a subject throughout the trial. CT including the chest, abdomen and pelvis or PET-CT is required for the baseline assessment. Patients who discontinue for reasons other than progression will be followed by imaging every 9 weeks.
8. Pembrolizumab (MK-3475) can be administered for up to 2 years. For the dose escalation and expansion Cohort (Arm) A (concurrent trametinib and pembrolizumab (MK-3475) both drugs will be administered as outlined in this protocol starting with cycle #1. For cohort B. trametinib will be initiated with cycle #1 and pembrolizumab (MK-3475) will commence in combination with trametinib starting with cycle #2, for Cohort C pembrolizumab (MK-3475) will be given for cycle 1 with concurrent trametinib added on C2D1.
9. Tumor biopsy for immune and molecular biomarker analysis will be performed prior to Cycle 1 of treatment either on archival tissue or fresh biopsy (within 6 months– no intervening treatment). Repeat biopsy will be performed on cycle 1 D11-13 or within 2 days after the last dose of trametinib for Arm A) and an optional end of study biopsy (within 28 days after progression).
10. Correlative blood draws for immune correlates will be performed prior to cycle 1 (- 3 days), prior to cycle 4 (-3 days), prior to cycle 7 (-3 days) and at discontinuation visit (± 5 days). Correlative blood draws for plasma DNA/RNA will be performed at baseline (cycle 1, day 1 prior to dosing or prior during screening), prior to each cycle of treatment (prior to concurrent administration of trametinib and pembrolizumab), and at progression (± 5 days).
11. Ophthalmology Exam: Indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy within 6 weeks prior to registration.
12. ECHO/MUGA will be performed every 12-16 weeks unless clinically indicated. The same study should be used for follows that was done for the baseline exam.
13. EKG at baseline, C1D1, C2D1, C3D1. Then every 12-16 weeks unless clinically indicated.
14. 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.15. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up phase and should be assessed every 9 weeks (63 ±7 days) by radiologic imaging to monitor disease status.
16. Once a patient has progression, they will be followed every 12 weeks until death or withdraw from follow-up.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.5) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Study Calendar.

7.1.2.6 Tumor Imaging and Assessment of Disease

This will be performed using RECIST 1.1 Criteria.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Molecular Studies Blood

- Plasma DNA/RNA detection of KRAS and PD-L1

- Prior to each cycle of treatment two tubes of blood (1 for RNA and 1 for DNA) will be collected for KRAS and PD-L1 DNA and RNA quantification. Tubes will be provided in a collection kit from Liquid Genomics. The assay will be performed by Liquid Genomics, which has validated DNA and RNA assays for KRAS and PD-L1. Please see appendix for tube collection and shipping instructions.Immune studies blood - Peripheral blood will be collected prior to cycle 1 (-3 days), prior to cycle 4 (-3 days), prior to cycle 7 (-3 days), and at progression (± 5 days) for flow cytometry for immune cell subsets, DNA sequencing for T-cell repertoire, Luminex Assay for measurement of cytokines (25 plea) in plasma and supernatant after activation with CD3+ CD28 or PMA+Ionomycine will also be performed in the HIMC at UC Davis at select time points. These studies will be performed by the Human Immune Monitoring Core at UC Davis.

From each patient, at the relevant time points indicated in the study calendar, for the immune studies blood will be withdrawn directly into two 10 mL lavender-topped (EDTA coated) tubes. Samples will be banked and stored and assays run at the Human Immune Monitoring Core (Director: Emanual Maverakis laboratory at UC Davis).

Contact information: Human Immune Monitoring Core (Maverakis Laboratory)
UC Davis School of Medicine
IRC Bldg., Room 1630
2921 Stockton Blvd. Sacramento CA 95817
LAB: 916-734-2156

The HIMC laboratory (Director: Emanual Maverakis, MD) is a research laboratory at UC Davis with both immunology expertise and the appropriate equipment to carry out the proposed studies. These studies may include: Luminex Cytokine Assays to determine changes in cytokine profiles in response to treatment and Flow Cytometry to detect changes in immune cell subsets.

The tubes should be centrifuged as soon as possible at approximately 800 x g for 10 minutes. Plasma should be transferred to a 15 mL conical tube and centrifuged a second time at 1000 – 1500 x g for 10 minutes. After the second centrifugation, aliquot plasma in 500 ul aliquots into labeled cryovials. For peripheral blood mononuclear cell (PBMC) preparation, replace the plasma removed with an equal amount of PBS (Ca and Mg free) in the original lavender-top tubes, and then slowly layer it on top of the 15ml of Ficoll in a 50ml conical tube, followed by centrifugation at 800 x g for 20 minutes with the break off. The buffy coat, a whitish layer of cells between the PBS and Ficoll layers above the red blood cell layer, should be collected and transferred into a new 50ml tube, washed once with 50ml of PBS, re-suspended in an appropriate volume of freezing medium and then transferred into labeled cryovials (10^7/ml/vial). All cryovials are then to be frozen as rapidly as possible, and stored in a -70 degree freezer until batch analysis is feasible by the HIMC.

Molecular correlates tissue – whole exome sequencing, determination of mutational load and RNA sequencing will be performed by the Broad Institute as part of the SU2C Team. A tube of blood will be collected for germline DNA comparison. Kits will be provided by the Broad Institute.

Immune Studies Tissue

Tumor biopsy at three time points with a biopsy prior to treatment, cycle 1, day 11 (+/- 2 days) and within 28 days post-treatment upon progression for immune correlates (optional), anti-apoptotic proteins, p-ERK by multiplexed immunofluorescence. Next generation sequencing on baseline and post-progression biopsies will also be conducted by the Broad Institute, conducted by the Stand Up to Cancer Core Facility, the Broad institution (NGS), the Mack lab and Theranostics. Studies performed at SU2C Core (Yale and Broad) are part of the the SU2C Lung Cancer Dream Team.

Table 18.Tissue Summary

Order Priority[a]	Tissue Correlative Study	Baseline	C1D11-13	Progression	Slides[c]	Cell Blocks[b]	Institution
1	IHC and QIF of PD-L1 and other Immune Proteins and Tumor Infiltrating Immune Cells	X	X	X	5 minimum (10 ideal)	1	SU2C Immune Core
2	Next Generation Sequencing (tissue + blood for germline DNA comparison)	X		X	20	1	Broad Institute (SU2C Core)
3	RPPA and Multiplex Immunofluorescence for MEK-ERK pathway	X	X	X	4 minimum (10 ideal)	1	Mack Lab UC Davis, Theranostics
5	YAP1/TAZ IHC	X	-	X	2	1	Bivona Lab, UCSF
6	PDX	X	-	X	Fresh Tissue	N/A	Jackson Laboratory West

a. Prioritization of tissue use and correlates in order from #1 to #5 for baseline biopsy. Biopsy on or around C1D11-D13 will be sent for Multiplex Immunofluorescence for p-MEK, DUSP6 and Immune IHC/QIF.
b. Paraffin embedded cell block(s) may be substituted for slides.
c. Unstained slides total cut from FFPE blocks at 5 microns thickness. The sample must contain a minimum of 20% tumor tissue. Slides must be positively charged. 1 H&E slide should also be made for IHC and NGS.
Please see the relevant correlative study sections below for further details regarding proper collection, shipping and handling of specimens.

Tissue Collection

Tumor tissue obtained at each biopsy time point will be collected by a representative of the study team. At the first biopsy, one of the cores will be submitted directly to Pathology for clinical interpretation and report as well as standard of care molecular studies. The remaining cores will be delivered to UC Davis Research Pathology, Pavilion Room 2P524 (or corresponding local research lab at other trial sites) and divided into 2 components.

At least two core biopsies not less than 22 gauge in diameter and 1cm in length or tissue the equivalent of core biopsies sufficient to generate at least 20 cut slides should be paraffin embedded and stored in research pathology until ready for processing and shipping. Ideally, 6 cores per biopsy timepoint should be obtained. At the first timepoint 2 cores should be used for histologic confirmation and standard molecular testing. 2 cores should be paraffin embedded for IHC of PD-L1 and other markers of the tumor immune microenvironment. At UC Davis, this FFPE specimen may also be stored in the laboratory of Dr. Philip Mack or the UC Davis HIMC for storage until sent for further testing.

If available, two additional cores should be immediately stored in 2ml of RNAlater solution (Life Technologies) (the tissue portion should be processed into pieces, each less than 0.5cm^3) for comprehensive DNA/RNA sequencing at the Broad Institute. The Samples in RNAlater solution should be kept refrigerated until processed at HIMC. This should be delivered to the Human Immune Monitoring Core with the contact information listed below. If not enough cores are obtained DNA/RNA sequencing can be sent of the initial FFPE tissue

Specimens in RNA Later should be shipped on cool packs (Monday – Thursday only) to:

Human Immune Monitoring Core (Maverakis Laboratory)
Department of Dermatology
UC Davis School of Medicine
IRC Bldg., Room 1630
2921 Stockton Blvd.
Sacramento CA 95817
LAB: 916-734-2156

Tissue from the second biopsy time point will be divided into the 2 research components with the procedures outlined above. Component 1: at least 2 cores or enough tissue for 20 cut slides as specified for initial biopsy for FFPE for PD-L1 and additional IHC quantification by UC Davis or Yale and 2: remaining cores in RNA later solution then FFPE for DNA/RNA sequencing. (**If no cores were available for processing with RNA later in the initial biopsy, the repeat biopsy should all go through FFPE and not through an RNA later step**). A research H&E slide will also be generated and reviewed by a research pathologist to confirm presence of tumor.

If there is limited tissue for all biopsy timepoints priority should be given to immunofluorescence panel and PD-L1 testing by SU2C Core Facility at Yale or UC Davis HIMC.

Molecular Studies Tissue

For the baseline biopsy, archival tissue is acceptable if a core or surgical was performed after last systemic treatment and within 6 months of consent for this study and if at least 20 unstained slides or 2 cell block is available for analyses (Fine needle specimens or cell blocks from cytology specimens are not acceptable).

Next Generation Sequencing (DNA and RNA (if enough tissue available) of a Customized SU2C Gene Panel will be performed at the Broad Institute as part of the SU2C Collaboration. This will be performed at baseline biopsy and post-progression biopsy. When requested the Broad Institute Samples lab will ship sample collection kits to research site. A companion blood collection tube will also be provided and should be collected at baseline.

Kits are specific for Material Type collected

i. Labels – FFPE or Frozen Tumors

ii. Labels – Blood or Buffy Coat Samples

iii. Matrix Kits – DNA or RNA analytes

1. Researcher fill kit & provides Sample Kit Metadata spreadsheet (example provided).
2. Kits are shipped back to the Broad Institute Samples lab per instructions provided in the kits. (See Attached Documents). Specimens should be coded with a unique identifier (ie. patient number and biopsy number in sequence (ie. for patient 1, 001-01 (baseline biopsy), 001-02 (on-treatment biopsy), 001-03 (post progression biopsy).
3. Sample Processing & Data Generation will proceed.

(Turnaround Time is expected to be 5-6 weeks for Exome runs). RNA sequencing will be batched into runs of 96 samples across the project so timeline will be more variable.

Quantitative Immunofluorescence

To demonstrate on target knockdown of MEK inhibition with trametinib, the Mack lab at UC Davis and Theranostics Health (Gaithersburg, MD) will bank tissue to perform multiplexed immunofluorescence and RPPA for phospho-MEK, DUSP6 and associated pathway proteins on FFPE.

The Mack laboratory at UC Davis has extensive experience in the multiplexed immunofluorescence assay including incorporation into NCI sponsored studies such as SWOG 0931 Everest study of the mTOR inhibitor everolimus as adjuvant therapy in Renal Cell Carcinoma and FGF/FGFR.

Up to 10 unstained slides (minimum 4) or 1 FFPE block will be sent to the Mack lab.

Dr. Philip Mack
UC Davis Comprehensive Cancer Center
4501 X Street, Suite 1009
Sacramento, CA 95817
Phone: 916-734-6447
Email: pcmack@ucdavis.edu

Patient-Derived Xenotransplants

Collection of Specimen(s)

Tissue for PDX should only be obtained at procedures performed on a Monday, Tuesday, Wednesday, or Thursday. The fresh specimen will be submitted directly and immediately to The Jackson Laboratory using the following procedures.

a. The physician should obtain the maximum amount of tumor that is prudent at the time of biopsy or resection. Minimum sample size is a core measuring 8mm x 3mm. Please approximate these dimensions.

b. The specimen should be collected following Institution Universal precautions SOPs for maintaining tissue integrity. Please remind all personnel that are involved in processing the sample that it will be implanted in profoundly immune deficient mice, which is why it is imperative that extra care be taken in sample collection to minimize the risk of transferring human bacteria to the mice.

Handling of Specimens(s)

The tumor sample should be placed in a 50 ml screw cap conical tube containing 40 ml RPMI buffer (without fetal calf serum); preferably within 30 minutes of tumor removal. Seal cap tightly with Parafilm. Sample should be refrigerated at 4°C until packed for shipping on the same day as procurement.

Shipping of Specimen(s)

The sealed conical tube containing RPMI & the tumor specimen must be wrapped in absorbent material (i.e. paper towels) and placed in an airtight plastic bag (i.e. a ziplock bag). Pack the specimen into an insulated Styrofoam shipper with a refrigerated (4° C) cool pack (not frozen) to protect specimen from temperature fluctuations. All paperwork pertaining to the patient should be placed in a plastic bag, sealed tightly, and packed with the tissue shipment. Include the Jackson Laboratory Sample Submission Form.

Ship by Fed Ex for overnight delivery to:

The Jackson Laboratory
In Vivo Services
c/o Margaret Bundy or James Keck
1650 Santa Ana Ave.
Sacramento, CA 95838

Prior to shipping, contact for sample coordination: Margaret Bundy 916-469-2609.

Creation of PDX is funded under a UC Davis – Jackson Laboratory Collaboration.

Immune Studies Tissue

Immunohistochemistry and Quantitative Immunofluorescence

PD-L1 and Evaluation of TILS

The PD-L1 immunohistochemistry will be performed in 3-5 μm-thick histology preparations obtained from conventional biopsy formalin-fixed, paraffin-embedded (FFPE) tissue samples. The tumor PD-L1 protein will be tested using the FDA-approved Dako 22C3 assay using chromogenic immunohistochemistry in the Yale Pathology Labs or UC Davis under CLIA laboratory conditions. The scoring procedure will include the determination of the percentage of positive cells in the tumor by a surgical pathologist using bright field microscopy. The score will be semi-quantitative and determined based on the percentage of positive cells.

The level of major TIL subtypes, TIL activation/proliferation and expression of major immune inhibitory receptors will be evaluated using multiplexed quantitative immunofluorescence (QIF) performed in 3-5 μm-thick histology preparations obtained from formalin-fixed, paraffin-embedded (FFPE) tissue samples, as previously reported [11]. We will perform three multiplexed QIF panels containing the following markers: Panel #1: DAPI/CD4/CD8/CD20; Panel #2: DAPI/CD3/Granzyme-B/Ki-67; and Panel #3: DAPI/CD3/PD-1/TIM-3/LAG-3. The Yale group has already performed validation of the antibodies and combined these markers into multiplexed QIF panels. Simultaneous measurements of the targets will be performed using multispectral imaging and the AQUA® method providing continuous fluorescence marker scores. Eventually, quantification of positive cells for each marker will also be performed using the Vectra multispectral imaging platform with the cell phenotyping tool of the InForm®

software; and reported as cell density (number of cells/area unit).See section 7.2.4 for processing and shipping information for the PD-L1 and QIF samples.

Immune correlates will be performed by Yale University Translational Immuno-Oncology or the Human Immune Monitoring Core (HIMC) at UC Davis as outlined below.

PD-L1 expression will be assayed using Merck's proprietary 22C3 antibody that is FDA approved as a companion diagnostic for pembrolizumab for quantifying PD-L1 expression for MK-3475 trials in NSCLC and melanoma including [12].

Biopsied tumor for PD-L1 Quantification

PD-L1 expression by immunohistochemistry at baseline and in repeat biopsy specimens to assess for changes in PD-L1 expression in response to treatment will be conducted by UC Davis or Yale Translational Immuno-Oncology using the FDA approved DAKO 22C3 antibody and by quantitative IHC.

If there is not enough tissue for entire DNA/RNA sequencing panel at the Broad Institute biopsied tumor for Tumor Infiltrating Lymphocytes and Subsets and RT-PCR for Immune Markers Real time-PCR for immune markers (if tissue size permits) including CD3, PD-1, GranzB, Perforin, IL-2, IFNg, Tim3, LAG3, CTLA-4, Foxp3 will be performed if adequate tissue is available.

Processing Instructions for Immunohistochemistry and Quantitative Immunofluorescence

Immunohistochemistry and Quantitative Immunofluorescence: Staining for PD-L1, relevant immunoproteins and tumor infiltrating immune cells will be performed by the SU2C Immune Core at Yale University as outlined below. Tissue samples will be collected from participants who have been properly consented and who have agreed to participate in the research study. Tumor tissues are optimally suitable for IHC/QIF studies if fixed in 10% neutral buffered formalin (NBF) for 16-24 hours and processed into paraffin blocks using clinical-grade pathology laboratory conditions.

1. Select the tumor block and obtain one Hematoxylin & Eosin (H&E) stained slide for review by site pathologist to confirm diagnosis and ensure presence of tumor cells. For in situ analyses, there is no lower limit in the amount of tumor cell content.

    a. Samples with few tumor cells (<100-200 cells) may be insufficient for PD-L1 immunostaining but should still be submitted for the QIF studies of TILs and other stromal markers.

2. If pathologist review is not possible or available at the site, the H&E slides or a digital version may be sent directly to Yale Pathology for initial assessment.

3. Obtain 5 additional serial 4-5µm thick sections from the reviewed paraffin block and place each section in a positively-charged glass histology slide. Tissues should be cut

and processed using conventional, clinical-grade in-house histology protocols. Paraffin dipping of slides after sectioning is not recommended.

4. Collect 5 freshly cut (<5 days) unstained serial section slides from each case, label each preparation using the SU2C coding system and place them in a conventional plastic histology slidebox. Make sure slides are in a firm position to avoid damage during transportation and cover with paper towel prior to packing to prevent movement within the box. If possible, also include the sectioning order on the label for each slide.

   a. Whenever feasible, blocks should be processed in batches, and shipped together within a 5-day period after sectioning.

5. Include H&E stained preparation together with the 5 unstained sections in the slidebox. This slide will be digitalized and become available for review within the SU2C group. Specimens should be coded with a unique identifier (ie. institution, trial number, patient number and biopsy number in sequence (ie. for UC Davis patient 1, UCD250-001-01 (baseline biopsy), UCD250-001-02 (on-treatment biopsy), UCD250-001-03 (post progression biopsy).

6. Seal the slidebox using Parafilm and/or a plastic envelope and wrap with bubble wrap prior to shipping. Include detailed sender information (with email) and ship using overnight service to:

   Attention to: Nikita Mani (nikita.mani@yale.edu).
   Backup contact should Nikita be out is Ila Datar (ila.datar@yale.edu)
   Address: BML112/BML113
   Department of Pathology
   Yale School of Medicine
   310 Cedar Street
   New Haven, CT 06510
   Phone 1: 203-737-4205
   Phone 2: 203-785-3588

A confirmation of sample reception will be sent via email to the sender within 72 hours.

7. Slides will be stained for IHC and the QIF panels within 5 working days from reception in the lab or stored in appropriately until use and batched to accommodate projects in single experimental runs (whenever possible).

8. Results of the analyzed markers will be provided as continuous scores using fluorescence intensity scores and/or phenotype cell counts. The turnaround time will depend on the amount of slides and project volume.

YAP1/TAZ Immunohistochemistry

We will collect pre- and post- treatment tissues as available. Formalin-fixed, paraffin-embedded (FFPE) slides will be applied for immunohistochemistry (IHC) staining with YAP and TAZ antibody separately. YAP1 antibody will be purchased from Santa Cruz Biotechnology (sc-15407). And TAZ antibody will be purchased from Sigma (HPA007415). The nuclear and cytosol YAP/TAZ expression will be quantified and scored by board-certificated pathologists. The scores of YAP/TAZ expression in pre- and post- treatment will be compared to explore up regulation of YAP/TAZ as a biomarker of resistance to trametinib + pembrolizumab treatment. These studies will be funded by the Addario Lung Cancer Foundation and Van Auken Foundation Young Innovators Team Award.

Collection of Specimen(s)

Completion of both assays requires a total of 2 unstained slides cut from FFPE blocks at 5 microns thickness on positively charged (+) slides.

Shipping of Specimen(s): Bivona Laboratory
Room N216R, Genentech Hall
600 16th Street, San Francisco, CA 94158
Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified below.

Table 19. Laboratory Tests

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

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

Laboratory tests for screening should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 3 days prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the discontinuation visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment. Trametinib may be continued after 24 months. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.4.4) and then proceed to the Follow-Up Period of the study (described in Section 7.1.4.5).

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Study Calendar. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.4.1 Screening

Screening should be completed within 28 days of the patient signing consent.

7.1.4.2 Treatment Period

Please see study calendar for treatment period details.

7.1.4.3 Post-Treatment Visits

Only safety follow up period required.

7.1.4.4 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.4.5 Follow-up Visits

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

7.1.4.5.1 Survival Follow-up

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be

excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

7.2.1 Definition of an Overdose for this Protocol and Reporting of Overdose to the Sponsor 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

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

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

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Merck product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the

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

Such events must be reported within 24 hours to the Sponsor Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event
- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table **20** for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study

whether or not related to the Merck product, must be reported within 24 hours to the Sponsor Investigator and within 2 working days to Merck Global Safety.

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

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

- **SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220**

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor Investigator and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor Investigator and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

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

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor Investigator and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor Investigator within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor Investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

Hospitalization related to convenience (e.g., transportation issues, etc.) will not be considered a SAE.

Reporting Adverse Events to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report

Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739). The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Warnings and Precautions

Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which

changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 20. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor Investigator within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor Investigator and to Merck within 2 working days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	

Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR INVESTIGATOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Investigator Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

The initial dose escalation will follow a standard 3+3 design, starting at dose level 1. The decision to escalate to the next dose level will be determined by the rate of dose-limiting toxicity (DLT) observed during Cycle 2, with a cycle length defined as 3 weeks. Up to 3 patients will be initially enrolled in a dose cohort, starting at dose level 1. If 1 of 3 patients were to experience DLT, 3 additional patients will be enrolled at same dose level. If 0 of 3 patients or 1 of 6 patients enrolled at a dose level were to experience DLT, enrollment to next dose level will be opened. If >1 of 3 patients or >1 of 6 patients enrolled at a dose level were to experience DLT, the maximum tolerated dose (MTD) will have been exceeded. Adverse events will be collected and described for the expansion cohorts. Enrollment to dose level 1 will be expanded to 6 patients if applicable, or enrollment to dose level -1 will be opened if dose level 1 were to exceed the MTD. The highest dose level at which 0 of 3 patients or 1 of 6 patients experience DLT will be declared the MTD. A minimum of 6 patients and maximum of 18 patients will be enrolled for each cohort (Arm A: Lead in Trametinib and Arm B: Lead in Pembrolizumab) in this dose escalation portion of the study.

Enrollment into Cohorts A and B are pre-planned in regards to sequence and timing. Arm A (lead in trametinib) will open 1st to dose escalation and will accrue 3 patients. Once 3 patients are accrued for Arm A, Arm B will open and accrue 3 patients. This is to ensure cohorts remain open for accrual given the 6-week DLT period; these cohorts will alternate in opening in this fashion until the MTD is achieved for both Arm A and Arm B. Once the MTD is achieved for both Arms A and B, Arm A will open to dose expansion at the MTD and complete accrual, followed by Arm B. If one Arm is delayed in opening additional dose levels due to toxicity, the alternate cohort may open at additional dose levels if approved by the Primary Investigator in consultation with Novartis and Merck.

The recommended dose expansion and recommended phase II dose (RP2D) will be determined by the overall assessment of the MTD and toxicities observed in the study.

All patients who receive a dose of pembrolizumab and trametinib will be analyzed for safety and efficacy. Subjects who discontinue from study participation prior to receiving the combination of trametinib and pembrolizumab will be replaced. Subjects in dose escalation who discontinue from study and are not evaluable for dose limiting toxicities will be replaced. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to grade 2 or lower. However, they will not be replaced.

A group of 12 patients will be enrolled in each of the 2 expansion cohorts at the MTD. Patients will enroll into the next subsequent cohort upon completion of the previous cohort (Arm A then Arm B). A sequencing scheme will be considered as promising if at least 5 of 12 patients were to achieve a complete or partial response per RECIST 1.1. The decision rule is associated with 80% exact power with an exact alpha of 0.16 if the underlying response rate associated with a sequencing scheme were truly at least 50% compared to current expectation of 25% ORR with single agent pembrolizumab. A median PFS of 8 months in 12 patients per cohort will provide 81 power to detect a difference compared to historical PFS of about 4 months with single agent pembrolizumab with an alpha of 0.1 based on accrual time of 24 months and follow up of 12 months. A sequencing scheme will be recommended for further development based on a combination of promising efficacy (response rate, PFS) and favorable changes in the tumor immune microenvironment at rebiopsy, provided the safety and tolerability profiles are acceptable.

Assays will be performed at the SU2C Lung Cancer Dream Team Immune Monitoring Core, Yale University, The Broad Institute, UCSF and at UC Davis Comprehensive Cancer Center as part of the SU2C Dream Team Lung Cancer Collaboration. Next generation sequencing by the Broad Institute will perform whole exome DNA/RNA sequencing to confirm KRAS amino acid substitution and examine mutational load and other co-mutations of interest and well as changes in RNA expression of relevant gene in the tumor immune microenvironment. A subset analysis will explore clinical outcome by KRAS amino acid substitution (G12C vs. non-G12C). The immune correlative studies performed in baseline and repeat biopsy specimens include: (in order of priority) 1) IHC and IF to determine PD-L1 expression, MEK target inhibition 2) additional immunophenotyping, and functional assessment of tumor infiltrating immune cells 3) Luminex evaluation of local tumor cytokine / chemokine signatures. In blood, FACS for quantification, immunophenotyping, and functional assessment of PBMCs will also be performed.

Adverse events will be summarized descriptively by type and by severity, with number and relative frequency calculated for all non-zero occurrences. With 16 patients treated at the MTD for either regimen, we will have an at least an 81% chance of seeing one or more cases of any adverse event that occurs in 10% or more patients.

All molecular and immune correlates will be assessed in exploratory analyses. Due to the limited sample size and exploratory framework, any such analysis will be stated carefully as hypothesis-generating with the reported p-values not adjusted for multiple comparisons. Standard descriptive and graphical methods will be used to summarize the baseline levels and post-treatment changes for comparison of the three MEKi and pembrolizumab sequencing schemes, which will allow us to examine whether observed patterns are consistent with hypothesized mechanisms. The quantitative immune studies will be compared using a t-test to further inform the decision. Multiplicity of testing will not be considered since this considered an exploratory analysis. Association with response rate will be summarized descriptively by presenting the mean, SD, and other characteristics of molecular and immune measures, stratified by response status. Associations of molecular and immune measures with PFS will be summarized descriptively by stratified Kaplan-Meier curves and, if numbers permit, by proportional hazards models with molecular and immune responses as predictors. If the MEKi and pembrolizumab combination were not found to have sufficient activity, the molecular and immune patterns may

help explain the lack of activity. If sufficient activity were observed, then the correlates will be compared between patients who experience an objective response and those who did not. Results of these correlative studies including biopsies at pre-treatment and week 1 on treatment will be analyzed in conjunction with the Battle-Immunotherapy trial (with its later biopsy correlative timepoints) to inform the optimal dosing and sequencing of pembrolizumab with trametinib.

Decisions for whether to pursue one of these strategies in a larger trial will incorporate ORR, toxicity and immune correlative endpoints in collaboration with the company sponsors and SU2C Dream Team. The primary considerations will be ORR and toxicity, with immune and genomic correlative studies used as supplementary criteria.

If only one arm meets safety criteria and preliminary efficacy criteria (ORR $\geq$ 50% or a median PFS $\geq$ 8 months), then that treatment will be considered for future study. Immune and genomic correlative studies will be examined for the potential to inform future study design for that arm.

If both arms A and B meet the safety criteria and preliminary efficacy criteria and give comparable response rates and toxicities, we will carry out two additional sets of analyses to inform the decision process of which treatment to pursue for further study. First, we will use regression models to assess whether one arm might have superior performance after accounting for key patient differences (PD-L1 status, KRAS amino acid substitution (G12C vs. non-G12C), smoking status). We will assess whether one arm has superior ORR, using logistic regression analysis to control for clinical covariates, and whether one arm has superior PFS, using proportional hazards models to control for clinical covariates. Second we Second, we will examine biomarkers that might shed light on the impact of the treatments. We will compare exploratory immune correlates (enhanced tumor immune microenvironment). The final decision will be based on best clinical judgment of all investigators.

We expect that the distribution of PD-L1 expression in Arm A and Arm B to be comparable. Based on the current indication for first line pembrolizumab in PD-L1 high (>50%) NSCLC, the majority of patients accrued into this second line trial will likely contain tumors with lower PD-L1 expression. At completion of Arm A we will review baseline characteristics and current clinical practice at that time to assess whether it is anticipated there would be a shift in biomarker distribution in Arm B.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Pembrolizumab

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

Clinical Supplies will be provided by Merck as summarized in Table 21.

Table 21. Product Descriptions

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

9.2 Trametinib

Trametinib tablets are provided as immediate release tablets for oral administration containing trametinib dimethyl sulfoxide (GSK1120212B) equivalent to 0.125 mg, 0.5 mg or 2 mg of trametinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the trametinib Investigator's Brochure for a list of excipients.

The trametinib tablets are packaged in high-density polyethylene bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

Classification

Cytotoxic drug: molecular targeted cytotoxic drug

Mechanism of Action

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 256 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are 257 upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes 258 cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF 259 pathway which includes MEK1 and MEK2. Trametinib inhibits BRAF V600 mutation-positive 260 melanoma cell growth in vitro and in vivo.

Metabolism

Trametinib is metabolized predominantly via deacetylation alone or with mono282 oxygenation or in combination with glucuronidation biotransformation pathways in vitro. 283 Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases. 284 Following a single dose of [14C]-trametinib, approximately 50% of circulating radioactivity is 285 represented as the parent compound. However, based on metabolite profiling after repeat dosing 286 of trametinib, > 75% of drug-related material in plasma is the parent compound.

Contraindications

None.

Availability

Trametinib will be supplied by Novartis.

Storage and Handling

Trametinib tablets should be stored refrigerated at 2° to 8°C (36° to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

Side Effects

Complete and updated adverse event information is available in the Investigational Drug Brochure and/or product package insert.

9.3 Packaging and Labeling Information

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

9.4 Clinical Supplies Disclosure

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

9.5 Storage and Handling Requirements

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

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

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

9.6 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD Office of Clinical Research. Medical records of patients will be maintained in strict confidence according to legal requirements. The investigator will grant monitor(s) and auditor(s) from Merck or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.2 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information

Management for inclusion in the participant's UCD Health System Medical Record or per participating site's policies.

10.4 Records and Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

10.5 Data and Safety Monitoring

In addition to the requirements for adverse event reporting this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Office of Clinical Research (OCR) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable. Because this is a phase I study, a meeting and/or conference call will take place when the last subject on each cohort completes DLT (dose-limiting toxicity) assessment. The meeting and/or call will update the attendees of the current status of the study and will include investigators from all participating centers, and, if necessary, representatives from the drug provider or financial supporter. All serious adverse events experienced by study subjects will be discussed and appropriate action taken. If serious adverse events occur between these meetings and/or calls, all investigators will be informed by email.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

10.6 Compliance with Law and Regulations

This study will be conducted in accordance with current US Food and Drug Administration (FDA) Good Clinical Practices (GCPs), International Conference on Harmonization (ICH) guidelines and local ethical and legal requirements. Specifically, the study will be conducted under a protocol reviewed by an IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed. All patients will have signed an informed consent for participation in research activities in accord with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights.

10.7 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor 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.

10.8 Quality Management System

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Comprehensive Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

11.0 APPENDICES

11.1 Multisite Patient Registration

A. Before registration, the site study coordinator should check to make sure that the corresponding Investigational Drug Service or equivalent has investigational product(s) in stock.

B. Registrations must be made through the Office of Clinical Research (OCR) of the University of California, Davis Comprehensive Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol must be on file prior to registration of patients.

C. Slot reservation. Prior to consenting, email the UCD team the following information: patient initials and anticipated start date. Confirmation of slot reservation will be emailed back to the site within 3 hours. Enrollment is competitive. Confirmed slots are only valid for 2 weeks. Should enrollment take longer than 2 weeks you must contact UC Davis to request additional time, otherwise you will be notified that the slot will be released.

D. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

E. Patients may be registered up to 72 hours prior to treatment initiation. The signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays (where applicable) must be faxed to UC Davis Study Coordinator in order to register the patient. These documents are to be redacted and the "patient initials" or "a participating site subject identifier" will be written on the documents until the Study Subject ID is issued. The UC Davis Study Coordinator will review these documents and fax and/or email a registration confirmation (which includes a subject ID number).

F. Reminder: Confirm eligibility of ancillary studies and willingness to participate at the same time as eligibility for the treatment study.

G. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax 24 hours prior to proposed treatment start date that the site has a patient to register.

I. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

11.2 Data Management

All data will be collected using UC Davis data collection forms. Any and all source documentation should be maintained.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form
- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)
- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form
- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event-Drug Relationship Form
- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)
- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation
- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)
- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL

11.3 ECOG Performance Status

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

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

11.4 FRIDERICIA'S CRITERIA FOR QTC CALCULATION

Fridericia's formula QTcF = (QT/RR^0.33). RR is the time from the interval of 1 QRS complex to the next measured in seconds and is commonly calculated as (60/HR) (Hosmane et al, Journal of Applied Research 2006).

11.5 New York Heart Association Classification of Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

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

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

11.7 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.

11.8 Drug Diary

D1-10 DOSING

Protocol Number: UCDCC#259

Patient Name: _____ **Medical Record #:** _____

Cycle #: _____ **Start Date:** _____ **Dose:** _____

Instructions: Please record the time that you take your study medications. Return this diary, the medication bottles (even if empty or unopened), and any unused tablets at your next clinic visit and make sure you are given another diary.

Store your study medication in the original bottle in the refrigerator (2°C to 8°C). Temperature excursions should be limited to the time it takes for you to transport your study medication from the clinic/hospital to your home refrigerator.

Trametinib comes in a tablet form and should be taken by mouth every day for the first 10 days of each 21 day cycle. You should take trametinib at least 1 hour before or 2 hours after a meal.

D1-10 Dosing				
Day	**Date (mm/dd/yy)**	**Dose (mg)**	**Time Taken**	**Notes**
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

Signature of Participant: _____ **Date:** _____

D1-7 DOSING

Protocol Number: UCDCC#259

Patient Name: _____ **Medical Record #:** _____

Cycle #: _____ **Start Date:** _____ **Dose:** _____

Insructions: Please record the time that you take your study medications. Return this diary, the medication bottles (even if empty or unopened), and any unused tablets at your next clinic visit and make sure you are given another diary.

Store your study medication in the original bottle in the refrigerator (2°C to 8°C). Temperature excursions should be limited to the time it takes for you to transport your study medication from the clinic/hospital to your home refrigerator.

Trametinib comes in a tablet form and should be taken by mouth every day for the first 7 days of each 21 day cycle. You should take trametinib at least 1 hour before or 2 hours after a meal.

D1-7 Dosing				
Day	**Date (mm/dd/yy)**	**Dose (mg)**	**Time Taken**	**Notes**
1				
2				
3				
4				
5				
6				
7				

Signature of Participant: _____ **Date:** _____

11.9 References

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