PROTOCOL NUMBER: OSU-19132

CLINICAL STUDY PROTOCOL

AN INVESTIGATOR-SPONSORED PHASE 2 SINGLE ARM TRIAL OF RAMUCIRUMAB AND PEMBROLIZUMAB IN PATIENTS WITH EGFR MUTANT NON-SMALL CELL LUNG CANCER

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SPONSORING PRINCIPAL INVESTIGATOR:	ASRAR ALAHMADI, MBBS
DRUG PRODUCT SUPPLIER:	LILLY MERCK
STATISTICIAN:	SARAH JANSE, PHD

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SYNOPSIS

Study Title	A Phase II Single Arm Trial of Ramucirumab with Pembrolizumab in EGFR Mutant Non-Small Cell Lung Cancer
Study Rationale	Non-small cell lung cancer (NSCLC) is one of the most common and lethal cancers in the United States. Fifteen percent of these NSCLC patients have epidermal growth factor receptor (EGFR) driver mutations, which are associated with high response rates (>70%) to tyrosine kinase inhibitors (TKI) but low response rates (10%) to single agent immune checkpoint inhibitors (ICI) such as pembrolizumab (anti-PD1 monoclonal antibody (mAb)).[1-5] In addition, responses to TKIs are not durable due to acquired resistance.[6] Vascular endothelial growth factor (VEGF) has emerged as a potential pathway of interest for treatment in this patient population because EGFR mutant NSCLC is associated with increased VEGF expression.[7] Notably, VEGF induces tumor related angiogenesis and also has immune dysregulatory effects that impact dendritic cell (DC) maturation, myeloid derived suppressor cells (MDSC) proliferation, and T cell PD-1 expression.[8-11] In clinical and preclinical studies, VEGFR inhibitors reverse this immune dysregulation and may work in synergy with ICI to enhance immune response.[12-14] Given the lack of durable responses to first line therapy in EGFR mutant NSCLC, development of tolerable and effective second line therapies is imperative. Two phase 3 trials demonstrated potential clinical importance of VEGF inhibitors for EGFR mutant patients receiving ICI. IMPower150 demonstrated progression-free survival advantage for carboplatin and paclitaxel with bevacizumab (anti-VEGF mAb) and atezolizumab (anti-PDL1 mAb) whereas IMPower130 demonstrated no survival difference for carboplatin, nab-paclitaxel, and atezolizumab without the addition of bevacizumab.[15-17] These results suggest a key role of anti-VEGF in combination with ICI in the EGFR mutant population and this combination may obviate the need for chemotherapy. Chemotherapy toxicity was significant in both IMPower trials – up to 55% of patients experienced grade 3-4 toxicity, most of which was attributable to carboplatin and paclitaxel (neuropathy, nausea, and pancytopenia).[16]

	To evaluate the clinical efficacy of this combination, we propose a phase II single arm trial of ramucirumab (anti-VEGFR mAb) and pembrolizumab (anti-PD1 mAb) for EGFR mutant NSCLC patients who have progressed on at least one EGFR TKI. The primary endpoint will be response rate and the secondary endpoints will be safety, tolerability, and survival. We anticipate that the combination of ramucirumab and pembrolizumab will be associated with a higher response rate (≥ 25%) than observed responses with single agent ICI (~ 10%). We will perform exploratory correlative studies to evaluate the immune cell activation profiles with combination therapy.
Primary Objective	To evaluate response rate of the combination of ramucirumab and pembrolizumab in EGFR mutant NSCLC.
Secondary Objectives **Correlative Studies**	To evaluate safety, tolerability, and survival for patients receiving ramucirumab and pembrolizumab. **Exploratory objectives:** To characterize predictive immunologic biomarkers of response in tissue and peripheral blood of patients receiving R+P combination therapy **Exploratory Correlative Endpoints:** 1) Baseline tumor immunoprofile by IHC, including tumor infiltrating lymphocytes and T cell receptor (TCR) immunosequencing (immunoSEQ) and relationship to clinical outcomes, including response rate. 2) Circulating immune cell profiles in response to treatment and in relation to clinical response using 10-color 65 marker multiplex CyTOF profile on peripheral blood samples. 3) Circulating VEGF at baseline, after treatment and at progression to evaluate correlation with clinical response.
Sample Size	Minimum 13 patients, maximum 34 patients
Study Design	**Agents:** Ramucirumab, Pembrolizumab

	Tumor type: EGFR mutation positive NSCLC The proposed study will be an open-label single arm phase II trial of ramucirumab and pembrolizumab (R+P) in EGFR mutant NSCLC after progression on tyrosine kinase inhibitors (TKIs). Patients are required to receive at least one TKI (erlotinib, gefitinib, afatinib or osimertinib). Post-TKI chemotherapy is also permitted. Each treatment cycle will be 21 days; patients will receive ramucirumab 10 mg/kg IV and pembrolizumab 200 mg IV and on day 1. Dosing of ramucirumab and pembrolizumab is based on prior phase 1 testing of the combination. A two-stage design will be utilized to minimize exposure to combination therapy if there is limited efficacy. The initial stage will enroll 13 patients; if ≥ 1 patient has a confirmed response, the study will continue and enroll an additional 21 patients for a total of 34 patients. Response will be assessed using RECIST (RECIST 1.1 and iRECIST). Imaging will be performed every 6 weeks/2 cycles to assess response. Patients with clinical benefit may continue therapy beyond progression for up to 2 cycles – if progressive disease confirmed on repeat imaging, therapy would be discontinued. Toxicity will be assessed using CTCAE v5.0. Progression free survival will be assessed using RECIST and will be assessed starting from date of study enrollment. Blood samples tissue will be collected at baseline (day 1, cycle 1), cycle 3 day1 (approx. 6 weeks), and at study discontinuation (or progression). Archival tissue will be requested at enrollment for correlative studies.
Duration of Treatment	Patients may continue to receive study treatment (R+P) until radiographic documentation of disease progression, the occurrence of unacceptable toxicity or of the occurrence of other withdrawal criteria. If either drug is discontinued due to toxicity, the other drug may be continued.
Inclusion /Exclusion Criteria	**Inclusion Criteria:** 1. Adult patients aged ≥18 years

	2. Histologically confirmed recurrent or metastatic non-small cell carcinoma of the lung with sensitizing EGFR mutations. Exon 20 resistance mutations will not be permitted but uncommon sensitizing mutations are allowed. 3. Prior Systemic Anticancer Therapy: Neo/adjuvant therapy or prior therapy for locally advanced disease will be permitted. Patients with prior exposure to PD/PD-L1 inhibitors will be excluded. No limit on prior EGFR TKIs (erlotinib, gefitinib, afatinib, dacomitinib or osimertinib). Prior chemotherapy for metastatic disease is permitted only. A 7 day washout period or four half-lives after the last treatment dose, whichever is longer, is required for TKI. A 4 week washout is required for cytotoxic chemotherapy. 4. Measurable disease per RECIST criteria 5. ECOG performance status of 0-1 6. Adequate organ function, hematologic, hepatic, renal and coagulation parameters as defined in the protocol. 7. Because the teratogenicity of ramucirumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods). 8. Female patients of childbearing potential must have a negative serum pregnancy test within 72 hours prior to first dose of protocol therapy. **Exclusion Criteria** 1. 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. 2. Known active chronic infections – HIV/AIDS, known active Hepatitis B or C. Known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no

	testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. 3. Cirrhosis (Child-Pugh B or worse) or cirrhosis with history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. 4. Prior exposure to ramucirumab. 5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137). 6. Any Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy. 7. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy. 8. Patients receiving dipyridamole, clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted. 9. Uncontrolled CNS metastases. Patients with treated brain metastases are eligible if they were clinically stable with regard to neurologic function, off steroids after cranial irradiation (whole brain radiation therapy, focal radiation therapy, and stereotactic radiosurgery) ending at least 2 weeks prior to first dose of study treatment, or after surgical resection performed at least 28 days prior to first dose of study treatment. The patient must have no evidence of Grade ≥1 CNS hemorrhage based on pretreatment MRI or IV contrast CT scan (performed within 28 days before first dose of study treatment). Note: Patients who received systemic therapy that adequately and appropriately treated CNS metastases, including tyrosine kinase inhibitors, are eligible provided that CNS disease control is confirmed by pretreatment MRI within 28 days of receiving first dose of study treatment. 10. Hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to first dose of protocol therapy or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.

	11. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management. 12. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy. 13. Major surgery within 28 days or device placement within 7 days prior to the first dose of protocol therapy. Patient has elective or planned major surgery to be performed during the course of the clinical trial. 14. Serious or non-healing wound, ulcer, or bone fracture within 28 days of study treatment. 15. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation. 16. Small cell or mixed (small cell/non-small cell) lung cancer 17. Pregnancy or breastfeeding. 18. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. 19. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis. 20. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. 21. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 22. Severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients. 23. Active infection requiring systemic therapy. 24. Known history of active TB (Bacillus Tuberculosis).

Screening Assessments	Signed written informed consent Inclusion/Exclusion Criteria Demographics and medical history Pregnancy test (if applicable) Physical examination, ECOG, and vital signs Urine analysis Hematology (CBC, coagulation studies) Complete serum chemistry Assessment of disease status Concomitant medication
Treatment and Post-Treatment Assessments	**Cycle 1 , Day 1** Physical examination and vital signs Complete blood count with differential Complete clinical chemistry (including liver function tests) TSH - free T3 and T4 if abnormal Adverse events and concomitant medication Cycle 1, Day 8 Physical examination and vital signs Complete clinical chemistry (including liver function tests) Urinalysis **Cycle 2 and Beyond** Physical examination and vital signs Complete blood count with differential Complete clinical chemistry (including liver function tests) TSH - free T3 and T4 if abnormal – repeat every 3rd cycle Urine analysis Pregnancy test (if applicable) Assessment of disease status: • CT scans (disease evaluation will be done according to irRECIST and RECIST 1.1) Adverse events and concomitant medication

	Final Visit Physical examination and vital signs Complete blood count with differential Complete clinical chemistry (including liver function tests) Assessment of disease status Adverse events and concomitant medication
Response	CT scans will be used for tumor assessment, at baseline and then at 6 week intervals. Patients who achieve stable disease, partial response (PR), or complete response (CR) per RECIST v.1.1 criteria will continue therapy until disease progression. Patients with confirmed disease progression by RECIST will be discontinued.
Safety Variables & Analysis	The safety and tolerability of ramucirumab and pembrolizumab will be evaluated by assessment of drug related toxicities, adverse event (AE) reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used for grading of AEs. Investigators will provide their assessment of causality as 1) unrelated, 2) possibly related, or 3) probably or definitely related for all AEs.
Statistical Analysis	The primary study objective is to assess the overall response rate (ORR) of ramucirumab and pembrolizumab. The study will use Simon's two-stage design. Response rate with single agent IO is around 10% and we would consider a response rate of at least 25% to be interesting for further study. The initial stage will include 13 patients; the trial will be terminated if there are no responses. If the trial goes on to the second stage, an additional 21 patients will be included for a total of 34 patients studied. Secondary objectives involve evaluating safety and tolerability and estimating PFS and overall survival. Descriptive statistics will be calculated for these outcomes and Kaplan-Meier curves will be calculated to estimate PFS and OS. Patients who have reached the end of the study but not progressed will be considered censored at the last documented date of contact. Estimates from this analysis will be used as preliminary data to inform future research.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Adenomatous polyposis coli
API	Active pharmaceutical ingredient
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
BW	Body weight
CBC	Complete blood count
CI	Confidence interval
CK	Creatine kinase
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organisation
CTCAE	Common terminology criteria for adverse events
CT Scan	Computed Tomography Scan
CYP450	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Desoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of treatment
FU	Follow-up
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good laboratory practice
h	Hour
HR	Hazard ratio
IA	Interim analysis
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
i.v.	Intravenous
KRAS	Kirsten Rat sarcoma
LDH	Lactate dehydrogenase
m^2	Square metre (body surface area)

mg	Milligram
min	Minute
mL	Millilitre
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PO	Per oral
PR	Partial response
PTT	Partial thromboplastin time
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SADR	Serious adverse drug reaction
SUSAR	Suspected unexpected serious adverse reaction
TSH	Thyroid Stimulating Hormone
TTP	Time to progression
UNL	Upper normal limit
WBC	White blood cell count

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1. INTRODUCTION

1.1 Overview

Non-small cell lung cancer (NSCLC) is one of the most common and lethal cancers in the United States. Fifteen percent of these NSCLC patients have epidermal growth factor receptor (EGFR) driver mutations, which are associated with high response rates (>70%) to tyrosine kinase inhibitors (TKI) but low response rates (10%) to single agent immune checkpoint inhibitors (ICI) such as pembrolizumab (anti-PD1 monoclonal antibody (mAb)).[1-5] In addition, responses to TKIs are not durable due to acquired resistance.[6] Vascular endothelial growth factor (VEGF) has emerged as a potential pathway of interest for treatment in this patient population because EGFR mutant NSCLC is associated with increased VEGF expression.[7] Notably, VEGF induces tumor related angiogenesis and also has immune dysregulatory effects that impact dendritic cell (DC) maturation, myeloid derived suppressor cells (MDSC) proliferation, and T cell PD-1 expression.[8-11] In clinical and preclinical studies, VEGFR inhibitors reverse this immune dysregulation and may work in synergy with ICI to enhance immune response.[12-14]

Given the lack of durable responses to first line therapy in EGFR mutant NSCLC, development of tolerable and effective second line therapies is imperative. Two phase 3 trials demonstrated potential clinical importance of VEGF inhibitors for EGFR mutant patients receiving ICI. IMPower150 demonstrated progression-free survival advantage for carboplatin and paclitaxel with bevacizumab (anti-VEGF mAb) and atezolizumab (anti-PDL1 mAb) whereas IMPower130 demonstrated no survival difference for carboplatin, nab-paclitaxel, and atezolizumab without the addition of bevacizumab.[15-17] These results suggest a key role of anti-VEGF in combination with ICI in the EGFR mutant population and this combination may obviate the need for chemotherapy. Chemotherapy toxicity was significant in both IMPower trials – up to 55% of patients experienced grade 3-4 toxicity, most of which was attributable to carboplatin and paclitaxel (neuropathy, nausea, and pancytopenia).[16]

To evaluate the clinical efficacy of this combination, we propose a phase II single arm trial of ramucirumab (anti-VEGFR mAb) and pembrolizumab (anti-PD1 mAb) for EGFR mutant NSCLC patients who have progressed on at least one EGFR TKI. The primary endpoint will be response rate and the secondary endpoints will be safety, tolerability, and survival. We anticipate that the combination of ramucirumab and pembrolizumab will be associated with a higher response rate (≥ 25%) than observed responses with single agent ICI (~ 10%). We will perform exploratory correlative studies to evaluate the immune cell activation profiles with combination therapy.

1.2 Ramucirumab: Mechanism of Action

Ramucirumab is an anti-VEGFR-2 monoclonal antibody (mAb); it inhibits angiogenesis by binding specifically to the extracellular domain of VEGFR-2 inhibiting binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. Clinical studies support the activity of ramucirumab in altering the tumor microenvironment; among other changes, PD-L1 expression and CD8+ T cell infiltration was increased with ramucirumab.[14] The relationship between tumor VEGF and PD-1 presents a critical therapeutic opportunity to target both pathways to enhance clinical response.

1.3 Pembrolizumab: Mechanism of Action

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

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades.[18] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.[19, 20]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[21, 22]

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.[22-25] The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.[26, 27] As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC.

1.3.1 Clinical Experience

Ramucirumab and pembrolizumab both have clinical activity in NSCLC.

Ramucirumab is approved in combination with docetaxel for NSCLC. The phase III REVEL trial evaluated second line docetaxel + ramucirumab/placebo, including EGFR mutant patients (n=33, 5%). The addition of ramucirumab improved median OS (10.5 months vs 9.1 months, p=0.023) as well as RR (23% vs 14%, p<0.0001) for the overall NSCLC population. [28, 29]

Pembrolizumab, an anti-PD-1 mAb, is approved for treatment of patients with metastatic non-mutant NSCLC both as first line and second line therapy. [30-32] In non-mutated NSCLC, pembrolizumab – as a single agent or with chemotherapy - is associated with response rates ≥ 20%.[30] The use of checkpoint inhibitors in patients with EGFR mutations has been more nuanced. A recent phase II study of pembrolizumab in TKI-naïve EGFR mutant lung cancer was stopped early (only 11 patients were enrolled) due to futility. A retrospective cohort study confirmed these findings; the cohort included 110 EGFR mutant patients with response rate of 12% to ICI.[5] These results suggest low efficacy for single agent checkpoint inhibitors but do not exclude potential synergy of combination therapies. [20, 21]

A recent phase I study evaluated ramucirumab (R) and pembrolizumab (P) in multiple tumor types, including EGFR *wild type* NSCLC (n=22). The primary objective of the study was to assess safety and tolerability of R+P (R 10 mg/kg and P 200 mg on day 1 of 21 day cycle). The study concluded that there were no new concerning safety signals at full doses of each mAb; it also demonstrated encouraging antitumor activity in previously treated *EGFR wild type* NSCLC (RR – 18-45% when stratified by PDL1).

1.4 Clinical Safety

Pembrolizumab and ramucirumab are both approved by the Food and Drug Administration (FDA) for commercial use in NSCLC but have not been approved in combination. Measures will be taken to ensure the safety of the patients participating in this trial including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with NCI CTCAE, Version 5.0. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and SAEs will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

1.5 Phase II Single Arm Trial of Ramucirumab and Pembrolizumab in EGFR mutant Non-Small Cell Lung Cancer

1.5.1 Rationale for the Study

Non-small cell lung cancer (NSCLC) is among the most common and most lethal cancer in the United States. Of these patients, approximately 15% have tumors with sensitizing EGFR driver mutations. Sensitizing mutations, in particular exon 19 and exon 21, are associated with first line response rates of > 70% with tyrosine kinase inhibitors (TKI).[3] Although these drugs are highly effective, responses are not durable and most patients will develop progressive disease. After first or second generation TKI, osimertinib is available for patients with T790M mutation. Current therapies after TKI are limited primarily to cytotoxic chemotherapy. Immunotherapy appears to

have an evolving role in this population. Single agent immunotherapy (PDL1 inhibitors) have been associated with low response rates in these patients. Given the synergistic activity of pembrolizumab (P) and ramuciramab (R) in phase 1 trials, we propose a single arm phase II trial of R+P in EGFR mutant NSCLC patients who have progressed on EGFR TKI.

EGFR Mutations in NSCLC

EGFR driver mutations are associated with sensitivity to EGFR inhibition with tyrosine kinase inhibitors. The first and second generation EGFR inhibitors – gefitinib, erlotinib, and afatinib – demonstrated dramatic improvements in response rates and progression free survival (PFS) in EGFR mutant patients when compared to first line chemotherapy.[2, 33-35] Despite these successes, patients ultimately progress. Up to 60% of patients receiving erlotinib, afatinib, or gefitinib develop T790M resistance mutation and can be salvaged with osimertinib, a third generation EGFR inhibitor.[36] The FLAURA trial then compared first line osimertinib to erlotinib and demonstrated a significant improvement in PFS, moving osimertinib into first line as the preferred agent.[4]

When osimertinib is used in the first line setting, the mechanisms of resistance are yet to be fully characterized and no cases of T790M mutation were reported in the phase 1 study in nine patients with previously untreated EGFR mutation–positive advanced NSCLC who received osimertinib.[37] Some reported mechanisms in patients with T790M-positive NSCLC after EGFR-TKI treatment include acquired EGFR mutations (C797S), MET and HER2 amplification, and small-cell transformation.[38-41] Second line options after osimertinib currently include cytotoxic chemotherapy, immunotherapy, or chemoimmunotherapy.

Immunotherapy in NSCLC

Immunotherapy (IO), specifically PD/PDL1 inhibition, has emerged as an important option for management of NSCLC. The immune system plays a role in prevention/treatment of cancer through surveillance and cytotoxic killing of tumor cells. Tumor growth may occur due to immune dysregulation; immunotherapy by checkpoint inhibition helps restore the immune system to recognize, stimulate immune response and eliminate tumor cells by overcoming mechanisms used for immune evasion. Pembrolizumab is a selective humanized IgG4 kappa monoclonal antibody that inhibits the pPD-1 receptor, an integral component of immune checkpoint regulation in the tumor microenvironment. In lung cancer, pembrolizumab is approved for treatment of patients with metastatic NSCLC both as first line and second line therapy. For first line therapy, it is utilized either in patients with tumor PD-L1 expression ≥ 50 % as a single agent or in combination with chemotherapy (regardless of PD-L1 expression).[30, 31] For second line (or later), pembrolizumab is approved for patients with tumor PD-L1 ≥1.[32] Across these trials, pembrolizumab – as a single agent or with chemotherapy - is safe and effective in NSCLC with response rates ≥ 20%. Specifically in patients with high PD-L1 expression (≥ 50 %), response rate to single agent pembrolizumab is 44.8% (compared to 27.8% with chemotherapy doublet).[30]

The use of checkpoint inhibitors in patients with EGFR mutations has been more nuanced. Many of the early trials either excluded EGFR mutant patients or included limited numbers of EGFR patients. BIRCH (phase II trial of single agent atezolizumab) included 45 EGFR mutant patients

who progressed or did not tolerate TKI therapy. Response rates were similar for "first line" EGFR mutant (compared to wild-type) but lower for patients in second/third line.[42] Two other single agent atezolizumab trials also included EGFR mutant patients (POPLAR and OAK).[43, 44] OAK included 85 EGFR mutant patients; a subgroup analysis of EGFR-mutant patients favored chemotherapy over atezolizumab (HR, 1.24; 95% CI, 0.21- 2.18), suggesting a lack of benefit for these patients.[44] The phase 3 IMpower150 trial (carboplatin, paclitaxel, bevacizumab and atezolizumab) also included EGFR mutant patients. As in the BIRCH trial, "first line" EGFR mutant patients were required to have received at least 1 TKI prior to enrollment. A total of 80 EGFR mutant patients were included – 35 received atezolizumab, 45 received chemotherapy alone. There was a benefit with the addition of atezolizumab in PFS (9.7 months vs 6.1 months).[16] Notably, EGFR mutants have been excluded from most trials with pembrolizumab. A recent phase II study of pembrolizumab in TKI-naïve EGFR mutant lung cancer was stopped early (only 11 patients were enrolled) due to futility. These results suggest low efficacy for single agent checkpoint inhibitors but do not exclude potential synergy of combination therapies.

Anti-Angiogenic Agents in NSCLC

Anti-angiogenic agents, particularly VEGF inhibitors, have demonstrated activity in EGFR mutant NSCLC. Ramucirumab is a human monoclonal antibody that targets the VEGF receptor-2, an important key receptor implicated in angiogenesis and for tumor growth. It inhibits angiogenesis by binding specifically to the extracellular domain of VEGFR-2 inhibiting binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D. The phase III REVEL trial evaluated second line docetaxel + ramucirumab or placebo. It has been approved as second-line for patients with advanced or metastatic non-small cell lung cancer (NSCLC) in combination with docetaxel. EGFR mutant patients were permitted if they had received both TKI and platinum-based chemotherapy, although there were only 33 EGFR mutant patients on the trial (≤ 3% of overall study population). The addition of ramucirumab improved median OS (10.5 months vs 9.1 months, p=0.023) as well as RR (23% vs 14%, p<0.0001). Primary toxicities related to ramucirumab included hypertension and bleeding. Results were similar across histologic subgroups.[28, 29] Ramucirumab is currently approved as second-line therapy for patients with advanced/metastatic NSCLC in combination with docetaxel.

Based on these findings of activity of anti-VEGF therapy in EGFR mutant NSCLC and synergy between P+R, we propose a phase II single arm trial to evaluate the efficacy of R+P in EGFR mutant NSCLC patients.

1.5.2 Rationale for Starting Dose and Dosing Schedule

A phase I study evaluated ramucirumab (R) plus pembrolizumab (P) in patients with multiple tumor types, including a NSCLC cohort (n=27). One dosing regimen was evaluated in a phase 1a for NSCLC: R 10 mg/kg and P 200 mg on day 1 of 21 day cycle. The primary objective of the study was to assess safety and tolerability of R+P. The study concluded that there were no new concerning safety signals; it also demonstrated encouraging antitumor activity in previously treated NSCLC - RR 30%, median PFS 9.7 months.[45]

Based on this phase 1 data, our study will use the same dose and doing schedule.

1.5.3 Assessment for Response

CT scan will be used for objective tumor assessment at baseline and then at 6 week/2 cycle intervals. Patients who achieve stable disease, PR, or CR per RECIST v.1.1 criteria will continue therapy until disease progression. Immune RECIST criteria will also be assessed (Table 1). For patients with progressive disease by RECIST, treatment may be continued for up to 2 additional cycles if the primary physician feels there is clinical benefit (Figure 1). If progression is confirmed on second scan, treatment will be discontinued.

1.5.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

1.5.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

A description of the adaptations and iRECIST process is provided in Appendix 2, with additional detail in the iRECIST publication.[46] iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Table 1: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment

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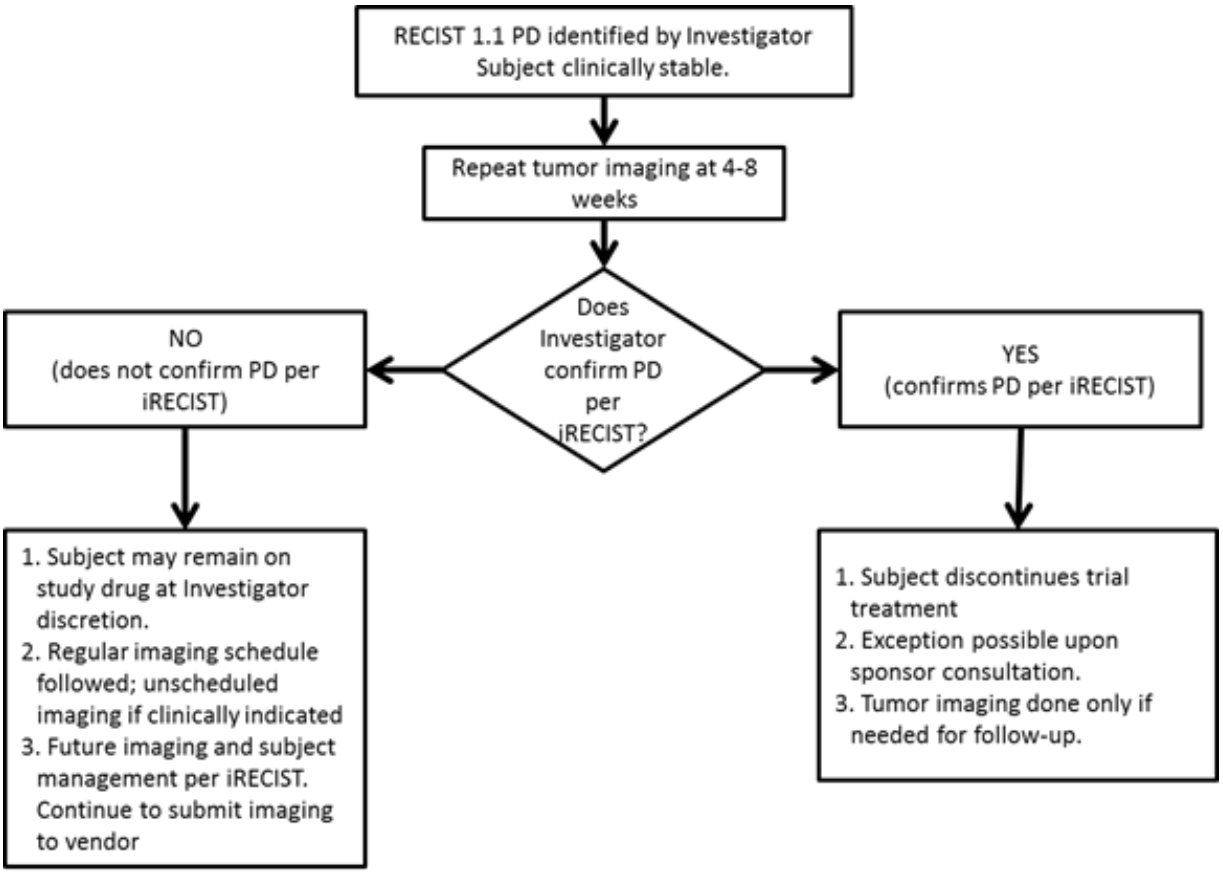
	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

To evaluate response rate of the combination of ramucirumab and pembrolizumab in EGFR mutant NSCLC.

Primary Endpoint: Overall response rate (ORR): Response rate will be evaluated with CT scans every 2 cycles and tumor measurements using RECIST 1.1 criteria. Immune RECIST (iRECIST) will also be assessed (see Appendices 1 and 2 for details).

2.2 Secondary Objectives

To evaluate safety, tolerability, and survival for patients receiving pembrolizumab and ramucirumab.

Secondary Endpoints: Safety, tolerability, clinical benefit rate (responses + stable disease), progression-free and overall survival.

2.3 Exploratory objectives

To characterize predictive immunologic biomarkers of response in tissue and peripheral blood of patients receiving ramucirumab and pembrolizumab combination therapy

Exploratory Endpoints: 1) Baseline tumor immunoprofile by IHC, including tumor infiltrating lymphocytes and T cell receptor (TCR) immunosequencing (immunoSEQ) and relationship to clinical outcomes, including response rate. 2) Circulating immune cell profiles in response to treatment and in relation to clinical response using CyTOF profile on peripheral blood samples. 3) Circulating VEGF at baseline, after treatment and at progression to evaluate correlation with clinical response

3. INVESTIGATIONAL PLAN

3.1 Overview of Study Design and Dosing Regimen

The clinical trial will be an open-label, two-stage, single arm phase II trial of ramucirumab and pembrolizumab in EGFR mutant NSCLC after progression on at least one EGFR TKI.

Each treatment cycle will be 21 days. Patients will receive ramucirumab 10 mg/kg and pembrolizumab 200 mg IV on day 1. Dosing of pembrolizumab and ramucirumab is based on prior phase 1 testing of the combination.

All trial treatments will be administered on an outpatient basis.

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

Table 2: Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Ramucirumab	10 mg/kg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Tumor tissue will be collected at baseline. Peripheral blood samples will be collected at baseline, cycle 3 day 1, and at progression (or study discontinuation).

During the treatment period, patients will undergo physical examination monthly and CT scans at baseline and then approximately every 6 weeks (2 cycles) thereafter. The disease status will be assessed per RECIST v.1.1 and iRECIST (immune RECIST) criteria (Appendices 1 and 2).

Patients will be treated for up to 35 cycles or until confirmed progression of disease or the development of unacceptable toxicities. All patients will then undergo a final visit (end of treatment visit).

3.1.1 Definition of Treatment Cycle and Duration

Ramucirumab and pembrolizumab will be administered on day 1 of each cycle. One cycle is defined as 21 days.

3.1.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.3). 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. Ramucirumab will be administered first followed by pembrolizumab.

Ramucirumab 10 mg/kg will be administered as an IV infusion every 3 weeks. Administer initial infusion over 60 minutes; if tolerated, may administer subsequent infusions over 30 minutes starting with cycle 2. 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).

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

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

3.1.3 Treatment Phase

Treatment will be continued for up to 35 cycles until confirmed progression of disease is demonstrated by CT scan, unacceptable toxicities occur in individual subjects, or consent is withdrawn.

3.1.4 End of Treatment Visit

Patients that discontinue from treatment will undergo an end of treatment visit, regardless of the reason of discontinuation, 30 (+/- 14) days after the last dose of study medication.

This study to be conducted at The Ohio State University Wexner Medical Center. If the protocol meets criteria to proceed with enrollment after initial futility analysis, we will consider expansion to include additional sites.

3.2 Study Duration

Patients will receive pembrolizumab and ramucirumab day 1 during each 21-day cycle. Patient may continue on study drugs until disease progression or for up to 35 cycles. Objective assessment of disease progression will be performed every six weeks.

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The study enrolled first patient in Summer 2020 with respect to first patient in (FPI). With an expected accrual rate of 1 patients every 2months, and a total number of 34 patients planned (if trial proceeds to second stage), the anticipated enrollment period is 60 months with the last patient enrolled by Summer2025. The anticipated length of treatment period will be approximately 3-6 months, leading to the last patient off study treatment in November-December 2025. The primary endpoint analysis will be done after the last accrued patient has been followed for at least 6 weeks.

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3.3 Study Schema

Figure 2: Study Schema

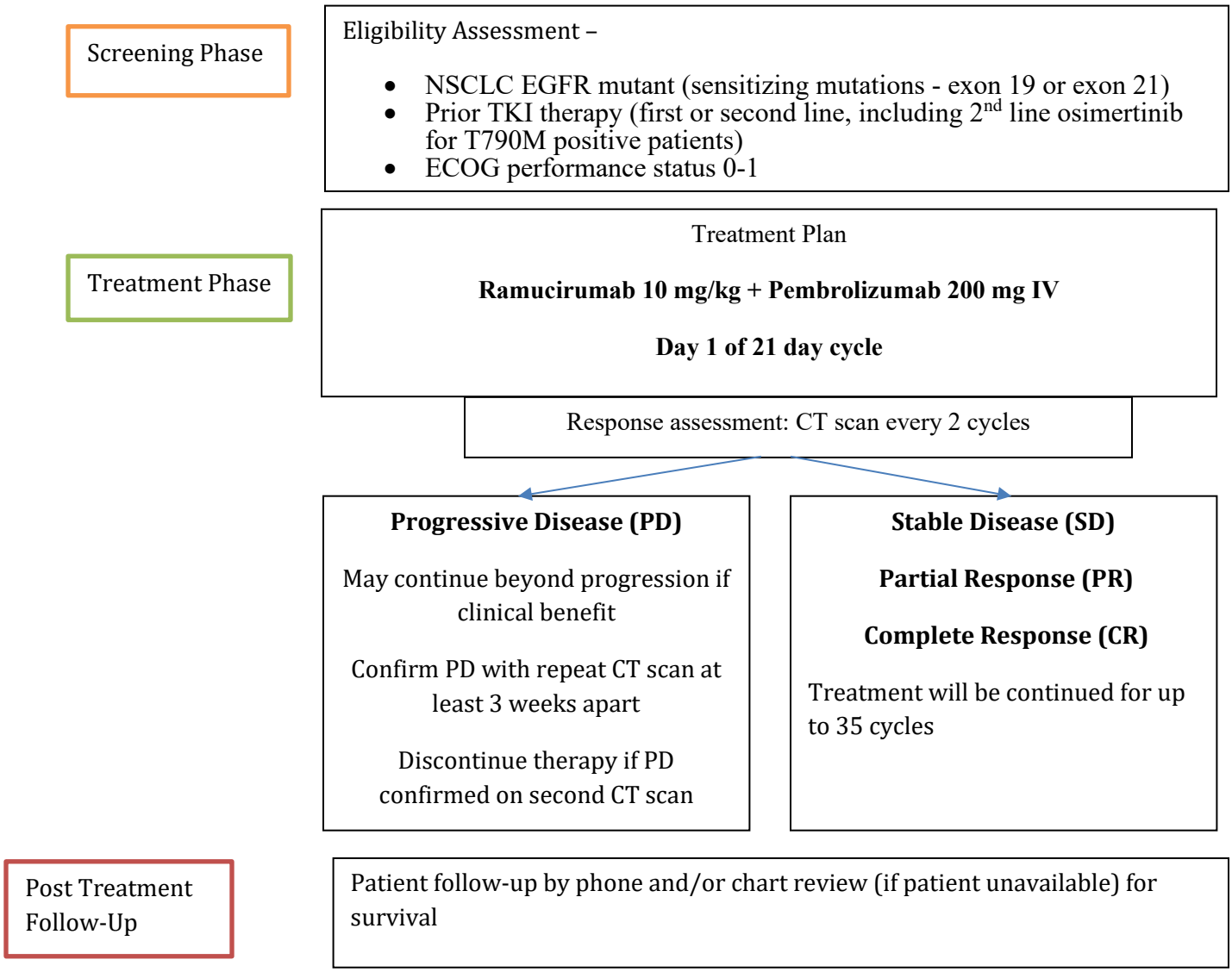
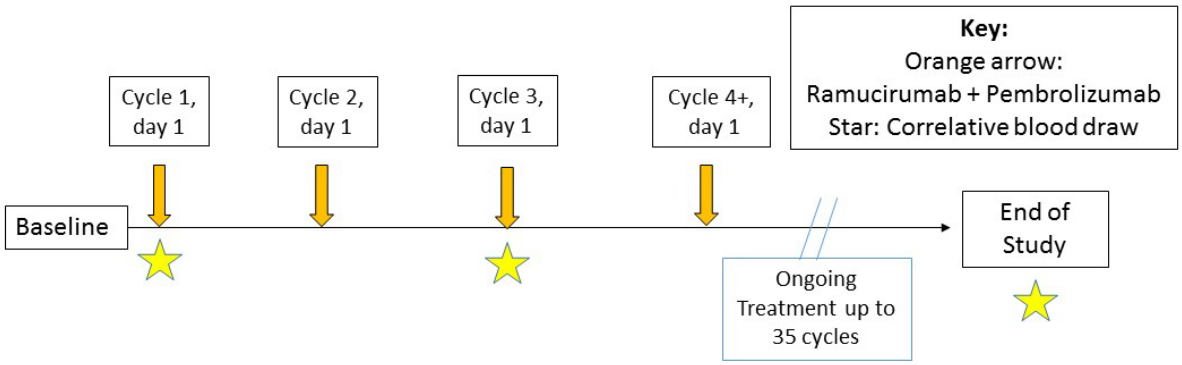


Figure 3: Correlative Study Schedule



4. PATIENT SELECTION

This Investigator Initiated Trial will be conducted in compliance with the protocol, GCP and all applicable regulations.

4.1 Study Population and Sample Size

This trial will be open to non-small cell lung cancer (NSCLC) patients with sensitizing EGFR mutations who have received first or second line therapy with tyrosine kinase inhibitor (TKI). These are most commonly lung adenocarcinoma but there are no restrictions for histology.

Planned enrollment is up to 34 patients. There will be a 2 stage design with a planned interim analysis for futility planned after the initial 13 patients (stage 1) have been followed for at least 6 weeks.

4.2 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible to enroll in this study.

1. Male/female participants who are at least 18 years of age on the day of signing informed consent in accordance with federal, local, and institutional guidelines
2. Histologically confirmed recurrent or metastatic non-small cell carcinoma of the lung with sensitizing EGFR mutations. Exon 20 resistance mutations will not be permitted but uncommon sensitizing mutations are allowed.
3. Prior Systemic Anticancer Therapy: Neo/adjuvant therapy or prior therapy for locally advanced disease will be permitted. Patients with prior exposure to PD/PD-L1 inhibitors will be excluded. No limit on prior EGFR TKIs (erlotinib, gefitinib, afatinib, dacomitinib or osimertinib). Patients who develop progressive disease after erlotinib, gefitinib, afatinib, or dacomitinib must either receive osimerintib (T790M positive) or be T790M negative. Prior chemotherapy for metastatic disease is permitted. A 7 day washout period or four half-lives after the last treatment dose, whichever is longer, is required after TKI therapy. A 4 week washout period is required for cytotoxic chemotherapy.
4. Measurable disease per RECIST criteria.

5. ECOG performance status of 0-1. Evaluation of ECOG is to be performed within 7 days prior to the date of first dose of study treatment.

6. Have adequate organ function as defined in the following table (Table 3). Specimens must be collected within 10 days prior to the start of study treatment

Table 3: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥40 mL/min for participant with creatinine levels >1.5 × institutional ULN
Urine protein	≤1+ on dipstick or routine urinalysis (UA; if urine dipstick or routine analysis is ≥2+, a 24-hour urine collection for protein must demonstrate <1000 mg of protein in 24 hours to allow participation in this protocol).
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants[c]

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

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

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

[c] Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin (LMWH). If receiving warfarin, the patient must have an INR ≤3.0. For heparin and LMWH there should be no active bleeding (that is, no bleeding within 14 days prior to first dose of protocol therapy) or pathological condition present that carries a high risk of bleeding (for example, tumor involving major vessels or known varices).

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

7. Because the teratogenicity of ramucirumab is not known, patients who are sexually active, must be either postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods).
    - A male participant must agree to use a contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 3 months after the last dose of study treatment and refrain from donating sperm during this period.
    - A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:
      a) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5
      OR
      b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 3 months after the last dose of study treatment.
8. For female patients of childbearing potential, a negative serum pregnancy test within 72 hours prior to first dose of protocol therapy is required.

4.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible to enroll in this study.

1. 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.

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2. Known active chronic infections – HIV/AIDS, known active Hepatitis B or C. Known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

3. Cirrhosis (Child-Pugh B or worse) or cirrhosis with history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites from cirrhosis requiring diuretics or paracentesis.
4. Prior exposure to ramucirumab.
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
6. Any Grade 3-4 GI bleeding within 3 months prior to first dose of protocol therapy.
7. History of deep vein thrombosis (DVT), pulmonary embolism (PE), or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to first dose of protocol therapy.
8. Patients receiving dipyridamole, clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
9. Uncontrolled CNS metastases. Patients with treated brain metastases are eligible if they were clinically stable with regard to neurologic function, off steroids after cranial irradiation (whole brain radiation therapy, focal radiation therapy, and stereotactic radiosurgery) ending at least 2 weeks prior to first dose of study treatment, or after surgical resection performed at least 28 days prior to first dose of study treatment. The patient must have no evidence of Grade ≥1 CNS hemorrhage based on pretreatment MRI or IV contrast CT scan (performed within 28 days before first dose of study treatment). Note: Patients who received systemic therapy that adequately and appropriately treated CNS metastases, including tyrosine kinase inhibitors, are eligible provided that CNS disease control is confirmed by pretreatment MRI within 28 days of receiving first dose of study treatment.
10. Hemoptysis (defined as bright red blood or ≥ 1/2 teaspoon) within 2 months prior to first dose of protocol therapy or with radiographic evidence of intratumor cavitation or has radiologically documented evidence of major blood vessel invasion or encasement by cancer.
11. Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) despite standard medical management.
12. Any arterial thromboembolic events, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to first dose of protocol therapy.
13. Major surgery within 28 days or device placement within 7 days prior to the first dose of protocol therapy. Patient has elective or planned major surgery to be performed during the course of the clinical trial.
14. Serious or non-healing wound, ulcer, or bone fracture within 28 days of study treatment.
15. Prior history of GI perforation/fistula (within 6 months of first dose of protocol therapy) or risk factors for perforation.
16. Small cell or mixed (small cell/non-small cell) lung cancer
17. Pregnancy or breastfeeding.

18. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
19. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
20. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
21. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
22. Severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
23. Active infection requiring systemic therapy.
24. Known history of active TB (Bacillus Tuberculosis).

4.4 Lifestyle Restrictions

4.4.1.1 Meals and Dietary Restrictions

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

4.4.1.2 Contraception

Ramuricumab and/or Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception.

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

Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

Use in Nursing Women

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

4.5 Patient Removal from Study Treatment

Patients may be removed from the study treatment at any time for the following reasons:

- Disease progression
- Noncompliance with study procedures
- Need of treatment with medications not allowed by the study protocol
- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Intercurrent illness that interferes with study assessments
- Incidence or severity of AEs in this study indicates a potential health hazard to the patient (Investigator discretion)
- Pregnancy
- At the discretion of the treating investigator after discussion with principal investigator
- Termination of the study by the Investigator or pharmaceutical company
- Ramucirumab specific criteria for end of study treatment:
    - Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
    - Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.
    - The patient will have ramucirumab permanently discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks.
    - Patients with grade 4 hypertension must not receive further treatment with Ramucirumab. Patients with grade 3 or 4 infusion-related reactions must not receive further treatment with ramucirumab.
    - Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation.
    - If Reversible Posterior Leukoencephalopathy (RPLS) is diagnosed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

  - Completion of 35 treatments (approximately 2 years) with ramucirumab.
- Pembrolizumab specific criteria for end of study treatment (detailed in Table 5):
  - Recurrent grade 3 toxicity
  - Recurrent Grade 2 pneumonitis
  - Grade 4 toxicity, except for endocrinopathies (as detailed in Table 5)
  - Completion of 35 treatments (approximately 2 years) with pembrolizumab
- Patients who complete 35 cycles of either pembrolizumab or ramucirumab will discontinue study treatment but will continue to be followed for survival and toxicity unless the patient withdraws consent. Likewise, patients who are removed for other reasons listed above may still be followed for survival and toxicity unless study consent is withdrawn.

5. INVESTIGATIONAL MEDICINAL PRODUCTS AND TREATMENT PLAN

5.1 Ramucirumab Formulation and Administration

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.

Product Name & Potency	Dosage Form
Ramucirumab 10 mg/1 ml	Solution for Injection

Premedication: Diphenhydramine 50 mg intravenous (IV) 30 minutes prior to infusion.

For patients with infusion reaction (grade 1 or 2), premedication should also include dexamethasone 10 mg IV and acetaminophen 650 mg oral (PO).

5.2 Ramucirumab Storage and Stability

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.

5.3 Ramucirumab Labelling

Supplies will be labeled in accordance with regulatory requirements.

5.4 Ramucirumab Dosing Information

The planned dose of ramucirumab is 10 mg/kg IV every 3 weeks (Q3W). This is the FDA approved dose for non-small cell lung cancer. This is also the dose that was utilized in phase 1 combination testing of ramucirumab and pembrolizumab.[45]

5.5 Pembrolizumab Formulation and Administration

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

Pembrolizumab will be provided by Merck as summarized below.

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

5.6 Pembrolizumab Storage and Stability

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.

5.7 Pembrolizumab Labelling

Supplies will be labeled in accordance with regulatory requirements.

5.8 Pembrolizumab Dosing Information

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

As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also

observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

5.9 Handling – Ramucirumab and Pembrolizumab

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

5.10 Drug Product Accountability

Study drug for the study are provided by Lilly and Merck and will be labeled as per the applicable regulations. Sites must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The Investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during each monitoring visit and at the close out visit.

All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

The Investigational medicinal product should not be used for any purpose outside the scope of this protocol, nor can Investigational medicinal product be transferred or licensed to any party not participating in the clinical study. Data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the Investigators.

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of unused material.

All clinical drug supplies must be kept in an appropriate, limited access, secure place until used or returned to Lilly or Merck or designee for destruction. After study drug is reconciled, drug

may be destroyed as per Institutional Policy, or returned to Lilly or Merck respectively. The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents.

6. STUDY PROCEDURES

Data will be collected via the completion of a Case Report Form (CRF) for each eligible patient. The investigator should confirm eligibility of the patient according to the inclusion and exclusion criteria of the study. All patients have to provide written Informed Consent before any study specific assessment is performed. A study specific assessment is defined as a procedure that is not part of the routine assessments performed for diagnostic purposes or standard care. Screening assessments should occur within 10 days of the first administration of study drug.

Patients not meeting the eligibility criteria will not be enrolled into the study. Patients should receive their first dose of study treatment as soon as possible after registration, but not later than 7 days after registration.

6.1 Study Assessments

6.1.1 Efficacy Assessments

Primary Endpoint: The response rate of R+P will be evaluated using RECIST 1.1 as well as iRECIST. Disease status will be measured by CT scan at baseline and then once every two cycles and as clinically indicated. Radiographic response per RECIST v.1.1 and iRECIST criteria (Appendices 1 and 2) will be determined by comparison to the tumor measurement obtained at baseline. Tumor progression will be determined by comparison to the smallest tumor measurement at either baseline or after initiation of therapy. The baseline disease assessment must be recorded and measured within 28 days prior to treatment start. During the treatment period, disease assessments will be performed every 6 weeks, i.e. once every two cycles, and as clinically indicated.

Secondary Endpoints: Safety and tolerability will be assessed with adverse event (AE) assessments at each study visit. CTCAE v5.0 will be used for adverse event grading. Attributions of causality will be assessed by the primary treating physician. Clinical benefit rate (stable disease + responses) will be assessed using the same criteria as response rate and on the same schedule. Survival will be measured from the date of study registration to the date of event (i.e., death or progressive disease) or the date of last follow-up if no event has occurred at their last evaluation.

6.1.2 Laboratory Assessments

Safety blood samples include complete blood count, clinical chemistry, including liver function test, and coagulation.

6.1.3 Summary Table for Specimen Collection

Biomarker Name	Collection Time Point	Specimen and Quantity	Send Specimens to:
Baseline			
TCR immunoSEQ/multiplex IHC		Formalin-Fixed-Paraffin-Embedded (FFPE) tumor tissue (archival or fresh biopsy), 5-10 slides per patient	Ohio State University – Carbone lab
Cycle 1, Day 1			
CyTOF panel	Pre-treatment	Blood (1x heparin tubes, 10 ml)	Ohio State University Carbone Lab/Li lab (PIIO)
TCR immunoSEQ	Pre-treatment	Blood (1x heparin tubes, 10 ml[a])	Ohio State University Carbone lab/Li lab (PIIO)
VEGF Elisa	Pre-treatment	Blood (1x heparin tubes, 10 ml[a])	Ohio State University – Carbone lab/Li lab (PIIO)
Cycle 3, Day 1			
CyTOF panel	Pre-treatment	Blood ((1x heparin tubes, 10 ml*)	Ohio State University – Carbone lab/Li lab (PIIO)
TCR immunoSEQ	Pre-treatment	Blood (1x heparin tubes, 10 ml[a])	Ohio State University – Carbone lab/Li lab (PIIO)
VEGF Elisa	Pre-treatment	Blood (1x heparin tubes, 10 ml[a])	Ohio State University – Carbone lab/Li lab (PIIO)
End of Treatment or Progressive Disease			

CyTOF panel		Blood ((1x heparin tubes, 10 ml)	Ohio State University – Carbone lab/Li lab (PIIO)
TCR immunoSEQ		Blood (1x heparin tubes, 10 ml[a])	Ohio State University – Carbone lab/Li lab (PIIO)
VEGF Elisa		Blood (1x heparin tubes, 10 ml[a])	Ohio State University – Carbone lab/Li lab (PIIO)
TCR immunoSEQ Molecular testing/multiplex IHC	Optional at progression	Formalin-Fixed Paraffin-Embedded (FFPE) tumor tissue (archival or fresh biopsy), 5-10 slides per patient	Ohio State University – Carbone lab/Li lab (PIIO)

a – Same tube will be used for TCR and VEGF

Sample Collection for translational/correlative analyses

Correlative study assessments will be included:

Tumor biopsies: Archival or fresh biopsy will be utilized. For archival tissue, we will request a minimum of 5 slides (FFPE). Tissue will be tested for expression of biomarkers of response including TCR immunoSEQ and cancer specific markers to the tumor by immunohistochemistry. Tumor tissue will be kept with the intention to perform tests as new techniques, research tools, and biomarkers become available.

Blood (2 tubes x 10 ML): BD Vacutainer (heparin tubes) will be used for blood collection. Peripheral blood will be analyzed for circulating immune cell profiles in relation to clinical response using CyTOF profile at baseline and prior to cycle 3. Peripheral blood analysis will also include TCR immunosequencing (immunoSEQ) and VEGF (ELISA) at baseline, during treatment and at progression.

Peripheral blood for CyTOF profile will be collected at 3 time points (baseline and cycle 2, day 1 at progression/end of treatment) for the initial 13 patients (stage 1). If a patient discontinues treatment after cycle 2, EOT samples will be collected at that time. Peripheral blood mononuclear cells (PBMC) and plasma for remaining correlative studies (TCR immunoSEQ and VEGF) will be preserved from collected blood samples at 3 time points: baseline (pre-treatment day 1), prior to cycle 3, and at study discontinuation or disease progression. Correlative studies will be collected as scheduled even if one of the two drugs is held/discontinued.

Samples will be stored for batching of correlative studies (TCR immunoSEQ and VEGF).

6.2 Data Safety and Monitoring Plan

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular disease group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease group meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the investigators, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (biannually for Phase II and quarterly for Phase I) that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will also be reported to the IRB of record as per the policies of the IRB.

Throughout the treatment period until one month after the last dose of study medication, patients will be assessed for all adverse events. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v 5.0) will be used for grading. If necessary, the patient may be withdrawn from the study treatment.

6.3 Schedule of Study Events

The Schedule of Study Events is shown in Table 4**Table 4.**

Table 4. Schedule of Study Events

Assessments	Screening/ Baseline			Cycle 1*	Cycle 1	Cycle 2	Cycle 2	Cycle 3 +	End of Treatment
Visit window [days]	Within 28 days	Within 10 days	Within 7 days	Day 1	Day 8	Day 1 +/- 3 days	Day 8	Day 1 +/- 3 days	30 days ± 14 days
Informed consent[1]	X								
Inclusion and exclusion criteria		X							
Demographics		X							
Medical History[2]		X							X
Pregnancy test (if applicable)[3]		X						X	
Vital signs and weight[5]		X		X	X	X	X	X	X
Physical examination and ECOG			X	X	X	X	X	X	X
Urine analysis[6]		X		X	X	X	X	X	X
Hematology[7]		X		X				X	X
Coagulation studies[8]		X						X[7]	
Complete Serum chemistry[9]		X		X	X	X	X	X	X
TSH [10]		X						X[9]	
Peripheral blood correlative studies[11]				X				X[11]	X
Tumor biopsy[11]	X								X
Assessment of disease status[12]	X							X	X
Ramucirumab dosing				X		X		X	
Pembrolizumab dosing				X		X		X	
Adverse event assessment				X		X		X	X
Concomitant Medication		X		X		X		X	X

Study Assessment Footnotes

* Each treatment cycle is 21 days
[1] Prior to the first study-specific assessments
[2] Medical history includes baseline symptoms as well as a detailed history of prior cancer therapies including start and stop dates, disease progression during or after therapy, as well as discontinuations due to intolerability or any other serious illness.
[3] Applicable for women of childbearing potential. Serum β-HCG test within 14 days before the first dose of study drug.
[4] Urine pregnancy test on day 1 of cycle 1 to confirm pregnancy status prior to treatment. Repeat urine pregnancy testing for women of childbearing potential every 9 weeks or if pregnancy is suspected. Positive urine pregnancy testing will require confirmation with serum pregnancy testing.
[5] Vital signs: Weight, blood pressure, pulse and temperature
[6] Urine analysis will include appearance, color, glucose, hemoglobin, ketones, pH, and protein. Microscopy will only be performed if clinically indicated. Urine dipstick protein > 1+ will require 24 hour urine collection for urine protein assessment. 24 urine collection will include measurement of both protein and creatinine.
[7] Hematology: Complete blood count including differential is required. WBC differential may be automated or manual as per institutional standards.
[8] Coagulation studies will include PT/INR and PTT. These studies will be repeated every 3rd cycle or as needed (for patients on active anti-coagulation).
[9] Complete Serum Chemistry includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin.
[10] TSH will be performed at baseline - free T3/free T4 to be checked if TSH is out of the normal range.
[11] Correlative studies (peripheral blood) will be drawn pre-treatment on cycle 1 day 1; cycle 3 day 1, and at final study visit. Tumor biopsy sample (archival) will be collected at study enrollment. Optional tumor biopsy at progression if clinically indicated.
[12] Disease status will be measured by CT scan every 6 weeks (+/- 7 days) for the first 6 months and then every 12 weeks and as clinically indicated. Baseline imaging within 28 days of study initiation.

6.3.1 Screening Assessments

All patients will be screened and screening procedures performed within 10 days (unless otherwise noted) prior to the start of induction treatment. These include the following:

Signed written informed consent	Obtained prior to any study specific assessments
Inclusion/Exclusion Criteria (Day -28 to 1)	• Age • Tumor diagnosis • Prior therapies • Comorbid conditions
Demographics and Medical History	• Age, gender, ethnic background • Previous and concurrent relevant diseases • Current symptoms and/ or residual toxicities from prior therapies • Details on prior cancer therapy, including start and stop dates, disease progression during or after therapy, as well as discontinuation due to toxicities
Concomitant medication	Concomitant medication currently used will be documented.
Pregnancy test (if applicable)	A serum pregnancy test will be performed in women of child-bearing potential: pre-menopausal women and women who are post-menopausal for < 2 years.
Physical examination and vital signs (Day -7 to 1)	• Body height and weight • Vital signs: Blood pressure, pulse, temperature • Physical examination • ECOG performance status (Appendix 3)
Urine analysis	Appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen.
Hematology (CBC)	Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards.

Complete Serum Chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
Assessment of disease status (Day -28 to 1)	The disease status will be measured by CT scan (Chest/Abdomen/Pelvis). MRI brain will be done as clinically indicated.
Tumor biopsy - archival	Archival tumor biopsy material (paraffin embedded and formalin fixed) will be collected, if available. If standard of care biopsy is performed, fresh tumor cells will be collected for study.

6.3.2 Treatment Phase

During the treatment phase the following assessments are to be performed (see Schedule of Study Events in Table 4 for timing of assessments in each cycle).

Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination (symptom directed)
Urine analysis (every other cycle)	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards.
Complete clinical chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
TSH	If TSH is abnormal, free T3 and free T4 will also be measured. Repeat TSH every 3rd cycle
Pregnancy test (if applicable)	A urine pregnancy test will be performed on cycle 1 day 1 and every 3rd cycle **or** if pregnancy is suspected in women of child-bearing potential: pre-

	menopausal women and women who are post-menopausal for < 2 years.
Adverse events and concomitant medication	Assessed on an ongoing basis

6.3.3 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Expedited confirmation of measurable disease based on RECIST 1.1 at Screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to participant enrollment.

6.3.4 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the start of study treatment The site study team must review screening images to confirm the participant has measurable disease per RECIST 1.1 prior to first dose of study treatment.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

6.3.5 Tumor Imaging on Study

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days]) from the date of allocation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 6 months, participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 6 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Appendix 2), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants as defined by Appendix 2 (Note- if patient is receiving clinical benefit, oligoprogressive CNS disease that can be controlled with local therapy such as stereotactic radiation, may continue on treatment beyond progression with PI approval. Ramucirumab should be held for 2 weeks prior to radiation. Patient can have radiation for CNS oligoprogression as long as ramucirumab is held for 4-6 weeks afterwards. Ramucirumab can be restarted after this time if the patient is asymptomatic, clinically stable and this is considered appropriate by the investigator.). Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 9.2.1.6. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment.

6.3.6 End of Treatment and Follow-up Tumor Imaging

Patients who discontinue therapy for any reason must have and end of treatment (EOT) visit completed 30 days (± 14 days) after the last application of study drug.

At the EOT visit, the patients will undergo the following assessments:

Physical examination and vital signs	• Body weight • Blood pressure, pulse, temperature • Physical examination
Urine analysis	Urine bilirubin, glucose, hemoglobin, ketones, pH, protein
Hematology	Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. WBC differential may be automated or manual as per institutional standards.
Complete serum chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin
Assessment of disease status	CT scan (if not performed within the last 28 days)
Adverse events and concomitant medication	Assessed on an ongoing basis

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 12 weeks in Year 1 or every 24 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.3.7 Post-treatment follow-up

Patient status will continue to be evaluated post-study. Patients will be contacted via telephone every 3 months for the first year after study completion. Beyond 1 year post-treatment, patients will be contacted every 6 months to obtain information for post-study survival data. Patients will be asked to supply the name and addresses of two contact people who the site may contact to assist with phone follow-up. Post-study survival data may alternatively be obtained during patient visits to site or source documents from other medical visits.

6.4 End of Study

The primary statistical analysis will be performed when 80% of the events for the secondary analysis of PFS have occurred. This will ensure appropriate follow-up time for the primary endpoint of ORR and for the secondary endpoints of PFS and OS.

6.5 Planned Treatment of the Patients after End of Treatment Phase

After completion of the study at routine follow-up (EOT), patients will generally be treated at the discretion of the investigator according to medical routine.

6.6 Removal of Patients from Treatment

Subjects will be free to discontinue treatment or withdraw from the study at any time, for any reason, or they may be withdrawn/ removed if necessary in order to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects should be avoided.

If there is a medical reason for withdrawal of treatment, the patient will remain under the supervision of the investigator until the AEs have been resolved or declined to baseline values.

If a patient has failed to attend scheduled assessments in the study, the investigator must determine the reasons and circumstances as completely and accurately as possible.

In case of premature discontinuation of the study treatment, the investigations scheduled for the EOT should be performed, if possible. The CRF section entitled “End of Treatment” must be completed in all cases. Should a patient decide to withdraw, every effort will be made to complete and report the observations as thoroughly as possible. The investigator should contact

the patient to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the case report form.

6.7 Study Discontinuation

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

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

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

7. TOXICITIES, RISKS AND AE-RELATED DOSE MODIFICATIONS

7.1 Ramucirumab Toxicity Overview

Ramucirumab is currently approved by the Food and Drug Administration (FDA) for commercial use in combination with docetaxel in non-small cell lung cancer. The combination of pembrolizumab with ramucirumab is investigational. The entire safety profile of the combination therapy is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with NCI CTCAE version 5.0. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

7.1.1 Risks Associated with Ramucirumab

Potential risks and toxicities of ramucirumab are detailed in the manufacturer's package insert (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125477s002lbl.pdf).

7.1.2 Dose Modification for Ramucirumab

<u>Infusion-Related Reactions (IRR):</u>

- Reduce infusion rate by 50% of grade 1 or 2 IRR.
- Grade 1 or 2 IRR should receive pre-medication with dexamethasone and acetaminophen prior to subsequent infusions.
- Grade 3 or 4 IRR: Discontinue ramucirumab.

<u>Hypertension</u>

- Hold ramucirumab for severe hypertension (Uncontrolled or poorly-controlled hypertension (>160 mmHg systolic or > 100 mmHg diastolic) until controlled with medical management.
- Discontinue ramucirumab for severe hypertension (>160 mmHg systolic or > 100 mmHg diastolic for >4 weeks) that cannot be controlled with antihypertensive therapy.

Proteinuria:

- If a patient has proteinuria with 24 hour urine protein ≥ 2 g, ramucirumab should be held. When level returns to less than 2 g/24 hr, may resume at a reduced dose of 8 mg/kg every 3 weeks. If level 2 g/24 hr or greater recurs, interrupt therapy again, and when level returns to less than 2 g/24 hr, resume at a reduced dose of 6 mg/kg every 3 weeks.
- For nephrotic syndrome or urine protein > 3 g/24 hr, ramucirumab should be permanently discontinued.

Wound Healing:

- Hold ramucirumab prior to surgery and until the wound is fully healed.

Indications for permanent discontinuation of Ramucirumab

- IRR: Patients with grade 3 or 4 infusion-related reactions must not receive further treatment with ramucirumab.
- Hypertension: Patients with grade 4 hypertension must not receive further treatment with Ramucirumab.
- Proteinuria: The patient will have ramucirumab permanently discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 2 weeks.
- Thromboembolism: Grade 3 and 4 arterial thromboembolic events, or any PE/DVT occurring or worsening during anticoagulant therapy, require permanent discontinuation of ramucirumab therapy. Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported via the serious adverse event (SAE) mechanism.
- Hepatic disease: Any patient who experiences signs of hepatic encephalopathy or other serious signs of liver impairment such as hepatorenal syndrome must be permanently discontinued from ramucirumab therapy.
- Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation.
- If Reversible Posterior Leukoencephalopathy (RPLS) is diagnosed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

For all other toxicities, ramucirumab may be held for up to 42 days. If toxicity does not improve to grade 1 or better within 21 days, discontinue ramucirumab.

7.1.3 Reproductive risks

Because the teratogenicity of ramucirumab and pembrolizumab is not known, the patient, if sexually active, must be postmenopausal, surgically sterile, or using effective contraception (hormonal or barrier methods).

Patients should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important patients understand the need to use birth control while on this study. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening (≤ 14 days prior to first dose) and negative urine pregnancy test on day 1 of study drug. Male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. Total (true) abstinence (when this is in line with the preferred and usual lifestyle of the patient), is an acceptable method of contraception. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post- ovulation methods) and withdrawal are not acceptable methods of contraception. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

7.2 Pembrolizumab Toxicity Overview

Pembrolizumab is currently approved by the Food and Drug Administration (FDA) for commercial use as a single agent and in combination with cytotoxic chemotherapy for non-small cell lung cancer. The combination of pembrolizumab with ramucirumab is investigational. The entire safety profile of the combination therapy is not known at this time. Measures will be taken to ensure the safety of the patients participating in this trial, including the use of stringent inclusion and exclusion criteria and close monitoring. Toxicity grading will be performed in accordance with NCI CTCAE version 5.0. If more than one different type of toxicity occurs concurrently, the most severe grade will determine the modification.

If toxicities are encountered, adjustments will be made to the study treatment as detailed in the sections below. All AEs and SAEs will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first.

7.2.1 Risks Associated with Pembrolizumab

Potential risks and toxicities associated with Pembrolizumab are detailed in the Investigator's Brochure.

7.2.2 Dose Modifications for Pembrolizumab

Pembrolizumab may be held up to 12 weeks for immune-related toxicity. If a patient has an immune-related toxicity that does not resolve within 12 weeks, pembrolizumab will be discontinued

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided below in Table 5.

7.3 Study Drug Discontinuation

If either ramucirumab or pembrolizumab is held or discontinued for toxicity, the remaining drug may be continued as maintenance therapy for up to 35 cycles or disease progression or unacceptable toxicity.

Table 5. Dose modifications and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv5.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Table 6. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement;	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors	No subsequent dosing

hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 6.

7.3.2 Other allowed dose interruption for pembrolizumab

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

8. SUPPORTIVE CARE GUIDELINES

8.1 Concomitant Medications

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

8.2 Permitted Concomitant Medication

Patients will receive concomitant medications to treat symptoms, AEs and intercurrent illnesses that are medically necessary as standard care. Medications to treat concomitant diseases like diabetes, hypertension, etc., are allowed.

8.3 Glucocorticoid therapy

Glucocorticoids ($\leq$ 20 mg oral prednisone or equivalent) per day are permitted at baseline and during the study for non-malignant conditions (i.e., asthma, irritable bowel disease, etc.,) as needed, but patients should preferably have been on a stable dose for at least two weeks before study entry.

8.4 Prohibited Medication

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents is not permitted. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.
- Radiation therapy
    - Note: Radiation therapy to the brain may be allowed after consultation with the PI for patients receiving clinical benefit. See section 6.3.5. . Ramucirumab therapy should be temporarily discontinued for 2 weeks prior to starting radiation. However,

starting radiation sooner is permissible if the investigator considers that the benefits outweigh the risks for the patient. Patient can have radiation for CNS oligoprogression as long as ramucirumab is held for 4-6 weeks afterwards. Ramucirumab can be restarted after this time if the patient is asymptomatic, clinically stable and this is considered appropriate by the investigator.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

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

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

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

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

8.5 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.2 [Table 5]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

8.6 Dose Adjustments for Weight

Ramucirumab dose will be adjusted if patient has > 10% change in weight from weight used to calculate previous dose. No weight based dose adjustment is required for pembrolizumab.

9. STATISTICAL CONSIDERATIONS

9.1 Endpoints

9.1.1 Primary Endpoint

Overall response rate will be evaluated using both RECIST and iRECIST criteria. Patients will have repeat imaging every 6 weeks to assess response.

9.1.2 Secondary Endpoints

- Safety and tolerability as measured by adverse events
- Clinical benefit rate – CR+PR+SD
- Survival – progression-free and overall

9.1.3 Exploratory Endpoints (Correlative Studies)

To characterize predictive immunologic biomarkers of response in tissue and peripheral blood

- T cell receptor (TCR) immunosequencing in peripheral blood (before and after treatment) and tumor tissue (at baseline) with clinical response.
- CyTOF from peripheral blood and infiltrating immune cells in tissue at baseline and after treatment
- Circulating VEGF in peripheral blood at baseline and after treatment with clinical response

9.2 Sample Size Justification

Response rate with single agent IO is around 10% and we would consider a response rate of at least 25% to be interesting for further study. The optimal two-stage design to test the null hypothesis that $P \leq 0.10$ versus the alternative that $P \geq 0.25$ will include 13 patients in the first stage. After testing the drug on 13 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, an additional 21 patients will be included for a total of 34 patients studied.

9.3 Planned Interim Analysis

After testing the drug on 13 patients in the first stage, the trial will be terminated if no patients respond. If the trial goes on to the second stage, an additional 21 patients will be included for a total of 34 patients studied.

9.4 Analysis Plan

9.4.1 Primary endpoint analysis:

The primary study objective is to assess the overall response rate (ORR) of ramucirumab plus pembrolizumab. To do so, we will use Simon's two-stage design.[20] This design is implemented by first enrolling a small group of patients and then enrolling a second group of patients in the second stage conditional on an adequate number of responses in the first group. Response rate with single agent IO is around 10% and we would consider a response rate of at least 25% to be interesting for further study. The optimal two-stage design to test the null hypothesis that $P \leq 0.10$ versus the alternative that $P \geq 0.25$ will include 13 patients in the first stage. After testing the drug on 13 patients in the first stage, the trial will be terminated if 1 or fewer respond. If the trial goes on to the second stage, an additional 21 patients will be included for a total of 34 patients studied. If the

total number responding is less than or equal to 5, the drug is rejected. This design has an expected sample size of 20.95 and a probability of early termination of 0.621.The sample size was calculated using PASS 16 and assuming $\alpha = 0.10$ with a desired power of 80%.

Overall survival and progression-free survival as continuous time-to-event outcomes: All evaluable patients will be used for this analysis. Kaplan-Meier curves will be used to estimate overall survival, measured from the date of study registration to the date of event (i.e., death) or the date of last follow-up if no event has occurred at their last evaluation. We will further consider Cox proportional hazards models to explore a limited set of confounding factors.

9.4.2 Analysis of secondary endpoints:

Secondary objectives involve evaluating safety and tolerability and estimating PFS and overall survival. Descriptive statistics will be calculated for these outcomes and Kaplan-Meier curves will be calculated to estimate PFS and OS. Patients who have reached the end of the study but not progressed will be considered censored at the last documented date of contact. Estimates from this analysis will be used as preliminary data to inform future research.

Overall response. All evaluable patients (i.e. eligible patients who have received at least one dose of the treatment) will be assessed in terms of their best response to therapy. Those who achieve a partial response (PR) or complete response (CR) will be considered responses and the overall response rate will be calculated as the number of PRs and CRs divided by the total number of evaluable patients. We will also perform analysis of disease control rate (CR + PR + SD). These estimates will be accompanied by exact binomial confidence intervals as well.

Safety and Tolerability. Frequency and severity of adverse events and tolerability of the regimen will be collected and summarized by descriptive statistics for each of the disease cohorts. As per NCI CTCAE v 5.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatments. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described. We will also assess tolerability of the regimens through assessing the number of patients who required dose modifications and/or dose delays. In addition, we will also capture the proportion of patients who go off treatment due to adverse reactions or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. All patients who have received at least one dose of the therapeutic agent in this study will be evaluable for toxicity and tolerability. This is detailed in Table 7.

Table 7: Evaluating Adverse Events

V5.0 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 investigational product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of the investigational products and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours, to Merck within 2 working days and to Lilly within 15 days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days and to Lilly within 15 days.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon	

	appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause investigational agent to be discontinued?	
Relationship to Investigational Product	Did investigational agent cause the adverse event? The determination of the likelihood that investigational agent 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 investigational agent and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely investigational agent caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to investigational agent 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 investigational agent? 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

9.5 Analysis of Exploratory Endpoints - Correlative studies:

Several correlative markers will be explored in this trial in relation to clinical outcomes of interest, and in particular in relation to the primary endpoint of response rate. Statistical analysis corresponding to the correlative studies will be descriptive and exploratory in nature.

For immune cell subpopulation data by flow cytometry, we will identify differences between the paired PBMC samples from the same patients. TCR immunoSEQ data will be summarized for each patient for T-cell clonality difference, descriptive statistics and confidence interval will be obtained across patients.

To study the association of immune cell subpopulations among blood and the tumor microenvironment, we will use linear mixed-effects models for repeated measurements within patients. A bivariate plot will be used to describe the relationship between response rate and peak VEGF via ELISA over time. Results will be summarized using descriptive statistics (i.e. means, medians, standard deviations, 95% confidence intervals for continuous variables, and frequencies for discrete data). The limited sample will not provide sufficient power for formal hypothesis testing (except to detect very large differences in these markers), but the preliminary data will be used to explore potential relationships and differences using graphical analyses and quantitative summaries of these markers. These results and exploratory analyses will also be used in planning a future randomized study of this combination treatment regimen in this patient population.

10. DATA MANAGEMENT

10.1 Clinical Data

A Research Study Manager will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team and coordination with the study statistician. The data collected for this study will be entered into a secure database (Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

10.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

11. PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and serial cardiac monitoring. Specific guidelines for symptom management are in place to protect the study participant.

11.1 Human Subjects Involvement and Characteristics:

All patients who meet the all of the inclusion and none of the exclusion criteria will be eligible. Eligible patients will be 18 years of age or older with a ECOG performance status ≤ 1 and a diagnosis of EGFR mutant NSCLC. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This

protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

11.2 Consent process:

All patients at the OSU Thoracic Oncology clinic who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

11.3 Possible Toxicities/Side-Effects:

There are risks associated with treatment as described in Section 7; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

11.3.1 Benefits

It is unknown if the combination of ramucirumab and pembrolizumab can benefit patients with EGFR mutant lung cancers. The goal of this study is to assess if combination therapy has the potential to demonstrate objective response in patients with lung cancer.

11.3.2 Costs

Patients will be charged for physician visits, routine laboratory tests, and radiologic studies required for monitoring their condition.

The cost of research only biopsies, research related testing/screening, study drugs, as well as correlative analyses will be covered by research funds.

11.3.3 Alternatives

For patients considering this trial as second or third-line therapy or beyond, standard chemotherapy or chemo-immunotherapy may be treatment alternatives.

11.3.4 Confidentiality

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (eg. qualified monitors) and external personnel (e.g. qualified monitors from Lilly or Merck), its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

11.3.5 Patient safety

Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

11.3.6 Monitoring of data to ensure safety

This study is to be monitored by the institutional IRB and Ohio State University Comprehensive Cancer Center Data and Safety Monitoring Committee (DSMC). This incorporates an independent data and safety monitoring board established by arrangement with the National Cancer Institute. The analysis of safety will include all patients. Adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

11.3.7 Privacy

The use and disclosure of protected health information pursuant to a completed and signed Research Authorization form may be allowed. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

12. INFORMED CONSENT

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

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

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

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

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

13. REPORTING REQUIREMENTS

13.1 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTC Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

13.2 Serious Adverse Event Reporting (SAE)

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

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

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

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB within 10 days of the investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of study activities by the investigator, sponsor, or DSMB to avoid potential harm to subjects should be reported within 48 hours. Events that may represent unanticipated problems involving risks to subjects or others should be promptly reported, regardless of whether they occur during or after the study, or involve a subject who has withdrawn from or completed study participation. If changes to the research or consent process are proposed as a result of the event, or if additional information will be provided to current and/or past participants, an amendment request must also be submitted for IRB review

Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- A description of the AE in medical terms
- The severity grade as assessed by the investigator according to the definitions in NCI-CTCAE Version 5.0

- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and chemotherapy and any action taken
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

If in any one subject the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

The investigator is required to submit SAE Follow-up reports until the SAE has resolved or stabilized and all queries have been answered.

13.3 Reporting to FDA:

Serious adverse events will be forwarded to FDA by the Investigator according to 21 CFR 312.32.

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

13.4 Reporting to the Drug Provider (Lilly)

Responsibilities of the Principal Investigator and Institution also include:

- to comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;

- to notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

- to notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" and/or "unexpected" adverse event experienced by a patient participating in the Study and receiving Study Drug that is possibly related, based on Investigator's assessment, to the Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such

records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug;

Lilly Adverse Event Reporting:

- Local fax number: 866-644-1697

  Local telephone number: 317-453-3402

13.5 Reporting to the Drug Provider (Merck)

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

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

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

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

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of

study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

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

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

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."
All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

Although pregnancy and infant exposure during breast feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study. Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.
Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of investigational 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.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, 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 participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

All participants with serious adverse events must be followed up for outcome.
SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

13.5.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, 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 participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.
Events of clinical interest for this trial include:
1. an overdose of Merck product, as defined in Section 13.5.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

13.6 Sponsor Responsibility for Reporting Adverse Events

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

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APPENDIX 1 RECIST 1.1 CRITERIA

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum LD.

Stable Disease (SD)

Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD)

At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions will also constitute progressive disease.

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since the treatment started.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

APPENDIX 2: DESCRIPTION OF THE IRECIST PROCESS FOR ASSESSMENT OF DISEASE PROGRESSION

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 1 and Figure 1). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
    - Please note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
        - Visible growth of new non-target lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The

assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined above.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold ($\geq$ 20% and $\geq$ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.[46]

APPENDIX 3: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS SCALE ASSESSMENT

ECOG Performance Status Scale	
Grade	Descriptions
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 hr.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hr.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-655	

APPENDIX 4: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

APPENDIX 5: CONTRACEPTIVE GUIDANCE AND PREGNANCY TESTING

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Male Participants:

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

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

Female participants:

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 8 during the protocol-defined time frame.

Table 8 : Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]
  • Oral
  • Intravaginal
  • Transdermal
  • Injectable

Progestogen-only hormonal contraception [b, c]
  • Oral
  • Injectable

Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen- only contraceptive implant [b, c] • Intrauterine hormone-releasing system (IUS) [b] • Intrauterine device (IUD) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 3 months after the last dose of study treatment.

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

Pregnancy Testing

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

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

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