Ramucirumab and atezolizumab after progression on any immune checkpoint blocker in NSCLC (RamAtezo-1)

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8056
St. Louis, MO 63110

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Principal Investigator: **Daniel Morgensztern, M.D.**
Phone: (314) 747-7948
E-mail: danielmorgensztern@wustl.edu

Sub-Investigators	**Modality**
Brett Herzog, M.D., Ph.D.	Medical Oncology
Maria Baggstrom, M.D.	Medical Oncology
Siddhartha Devarakonda, M.D.	Medical Oncology
Ramaswamy Govindan, M.D.	Medical Oncology
Peter Oppelt, M.D.	Medical Oncology
Timothy Rearden, M.D.	Medical Oncology
Caron Rigden, M.D.	Medical Oncology
Anna Roshal, M.D.	Medical Oncology
Saiama Waqar, MBBS	Medical Oncology
Jeff Ward, M.D., Ph.D.	Medical Oncology
Feng Gao, Ph.D.	Biostatistics

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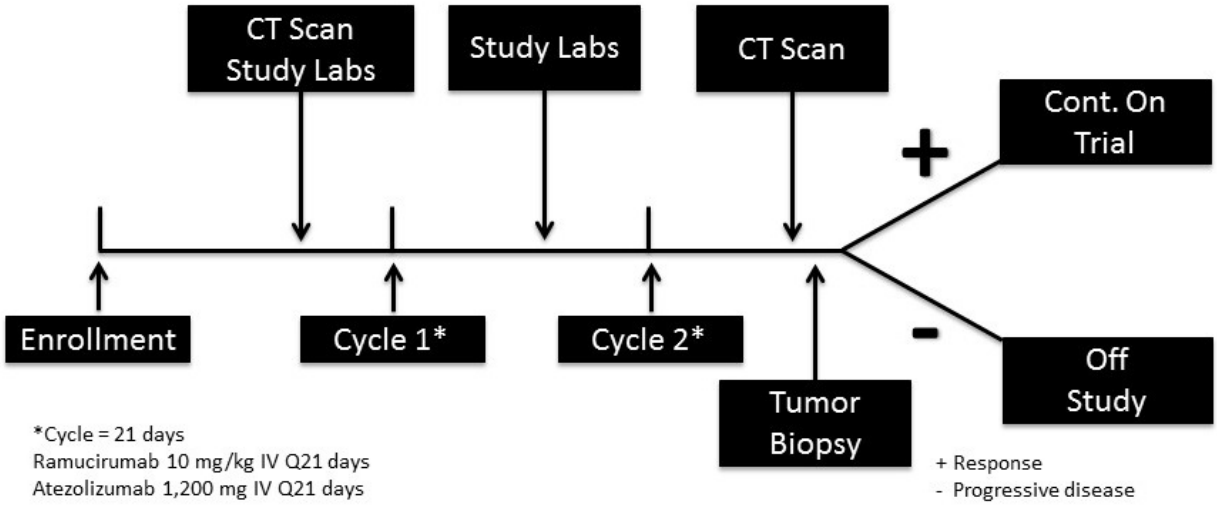
SCHEMA



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1.0 BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer (NSCLC)

Lung cancer remains the leading cause of cancer-related death, with an estimated 1.6 million deaths per year [1]. In the United States, the American Cancer Society estimates that there will be approximately 250,000 new cases of lung cancer and 158,000 deaths in 2018 [2]. Approximately 85% of patients with lung cancer have a group of histological subtypes, collectively known as non-small cell lung cancer (NSCLC) [3]. The majority of patients with NSCLC present with stage IV disease due to distant metastases or malignant pleural effusion and are treated with palliative intent [4]. Even among patients undergoing surgery with curative intent, a high percentage of tumors recur, with 5-year overall survival (OS) ranging from 83% in stage IA to 36% in stage IIIA [5]. Patients with metastatic NSCLC and no targetable oncogenic alterations usually have a poor prognosis, with low responses to the initial platinum-based chemotherapy and virtually universal relapse [6]. Immune checkpoint blockers (ICBs) have revolutionized the treatment of NSCLC, with the three approved drugs (nivolumab, pembrolizumab and atezolizumab) being more effective than docetaxel in randomized clinical trials [7-10]. Nevertheless, the benefit is restricted to a small percentage of patients, with objective response rates of less than 20% and median progression-free survival (PFS) ranging from 2.3 to 3.9 months.

1.2 Atezolizumab

Under normal physiologic conditions, the immune checkpoint molecules maintain self-tolerance preventing autoimmunity and limiting collateral damage to the normal tissues during response to infections [11,12]. Cancer cells however, may co-opt these molecules to evade immune destruction. Programmed death 1 (PD-1), one of the key checkpoint molecules, may bind to two ligands, PD-L1/PD-L2. PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer [13,14]. Binding of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production [15,16]. Overexpression of PD-L1 on tumor cells and the tumor microenvironment has been reported to prevent anti-tumor immunity, resulting in immune evasion [17]. Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. Atezolizumab is a humanized IgG1 monoclonal antibody against PD-L1 [18]. Direct targeting of PD-L1 leaves the PD-L2-PD-1 interaction intact, potentially avoiding effects on immune homoeostasis. Atezolizumab is approved in the United States metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen.

1.3 Ramucirumab

Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2)-mediated signaling and angiogenesis contribute to the pathogenesis of lung cancer. In patients with lung cancer, circulating VEGF levels are associated with increased tumor aggressiveness and reduced survival [19]. Furthermore, high levels of VEGF in preclinical models reduced the T cell progenitors in the thymus [20], and exposure to VEGF led to decreased number, activity and cytotoxic activity of T cells ex vivo in a VEGFR-2 dependent mechanism [21]. Blocking VEGF receptor-mediated signaling abrogated VEGF's suppressive effects on T-cells in preclinical models and VEGFR-2 inhibition reduced tumor growth in lung adenocarcinoma animal studies [22,23]. Ramucirumab, a human IgG1 monoclonal antibody against VEGFR-2, prevents ligand binding and receptor-mediated pathway activation in endothelial cells and is currently indicated for the treatment of multiple malignancies including gastric and gastric-esophageal adenocarcinomas progressing after platinum-containing therapy and in combination with docetaxel in metastatic NSCLC with disease progression on or after platinum-based chemotherapy [24]. Ramucirumab in combination with docetaxel has demonstrated improved response rates and PFS in NSCLC patients compared to docetaxel alone [25]. In early phase studies, ramucirumab in combination with ICBs has shown promising results in ICB-naïve patients [26].

1.4 Rationale

Although ICBs have changed advanced NSCLC treatment, only a small percentage achieve a sustained benefit. Furthermore, efficacy from additional therapy is limited [27]. While the lack of response to ICBs is likely multifactorial, an important factor in achieving a response with anti-PD-1/PD-L1 blockade is the presence of T cells entering the tumor to kill the tumor cells once their defense is removed. Unfortunately, tumors often inhibit T-cell trafficking to the tumor via vascular endothelial growth factor (VEGF)-mediated down-regulation of important adhesion molecules on tumor-associated blood vessels and failure to respond to ICBs has been associated with decreased tumor-infiltrating immune cells [28] [29]. Inhibition of VEGF-VEGFR-2 signaling results in increased T-cell invasion into the tumor [28,30,31], and preclinical models have demonstrated a synergistic effect of blocking both tumor-associated immunosuppression and angiogenesis [30,32,33]. Furthermore, inhibition of VEGF receptor mediated signaling decreased PD-1 expression on cytotoxic T-cells, suggesting that inhibition of this pathway may enhance T-cell function in the tumor microenvironment [34]. Indeed, use of immunotherapy and anti-angiogenesis therapy in melanoma also increased CD8+ T-cell infiltration in tumors [31]. Together, this data suggests that combining ramucirumab with immunotherapy in NSCLC patients who have previously received ICBs may be more effective than traditional therapy. We propose a pilot study to test the combination of ramucirumab and atezolizumab in patients with advanced-stage NSCLC patients previously treated with ICB.

1.5 Correlative Studies Background

Despite the widespread use of PD-1/PD-L1 antagonists for patients with NSCLC, the exact molecular mechanisms that mediate disease response remain poorly understood [35]. It is clear that PD-1-directed therapies induce proliferation and increase the functional activity

of CD8+ T-cells in the periphery of patients [36-38], but despite this, the majority of patients will not derive meaningful benefit from this class of agents, and responses are often not durable. Blunting tumor angiogenesis in order to remodel the tumor microenvironment is an attractive combinatorial approach to synergize with standard immunoncology agents [39]. Increased VEGF expression is known to suppress the maturation of antigen-presenting dendritic cells and inhibit lymphocyte tracking into tumor tissues, which can limit the effectiveness of an antitumor adaptive immune response [40]. We hypothesize that the addition of ramucirumab will augment the clinical activity of atezolizumab, and in order to evaluate the exact mechanism of action of the combination, we propose a comprehensive analysis of paired peripheral blood samples collected longitudinally during this study. We will evaluate whether the combination of atezolizumab and ramucirumab (a) alters populations of circulating monocytes and myeloid derived suppressor cells, (b) increases the number and affects the phenotype of circulating NK cells, effector CD8+ and effector CD4+ T-cell subsets, (c) results in the generation of durable populations of memory CD8+ and CD4+ T-cells and (d) alters the ratio of circulating regulatory T-cells to effector CD8+ cells. We will utilize mass cytometry (CyTOF) for these analyses, a high dimensional technique that allows the assessment of ~40 individual markers using metal labeled antibodies to enable deep profiling of selected phenotypic and functional makers on individual cells as well as unique statistical analyses to simplify the interpretation of complex relationships of large numbers of cells [41-43]. We will collect and cryopreserve peripheral blood mononuclear cells prior to combination atezolizumab/ramucirumab therapy and again at the time of first radiographic assessment. Analyses will be completed in a batched fashion using an established mass cytometry panel at the The Andrew M. and Jane M. Bursky Center for Human Immunology & Immunotherapy Programs (CHiiPs) at Washington University School of Medicine at the conclusion of study procedures to correlate immune profiles with clinical response. Patients will also undergo repeated biopsy to evaluate the differences in immune cell infiltrates between baseline and after two cycles of treatment.

1.6 Amendment #3 Study Continuation

1.6.1 Synopsis

The primary objective of the RamAtezo trial is to determine the overall response rate for the combination of ramucirumab and atezolizumab in patients with NSCLC previously treated with immune checkpoint blocker. This is an unmet need where there are few treatment options for patients after tumor progression on immune checkpoint blockers, particularly when used in combination with platinum-based doublet in the first-line setting.

The study design uses a Simon's two-stager MiniMax design where 12 patients are enrolled into the stage I. In case of one or more responses, the study will accrue 9 more patients, with a total of 4 responders indicating the preliminary evidence of efficacy.

Although there were no responses among the initial 12 patients, 8 patients had tumor reduction from baseline, including patient reaching 27% reduction, only 3% below the threshold for the RECIST criteria for response. Furthermore, the treatment has been well tolerated and 3 out of the 12 patients (25%) are still on treatment with progression-free survival higher than 6 months.

Therefore, we believe that the study should continue with the accrual of the additional 9 patients with the primary endpoint remaining the overall response rate. In this case, the Minimax design will be replaced by a simple enrollment of 21 patients.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the overall response rate (ORR) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.

2.2 Secondary Objectives

1. To determine the overall survival (OS) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.
2. To determine the progression-free survival (PFS) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.
3. To determine clinical benefit rate (CBR) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB. CBR is defined as the percentage of patients who have achieved responses or stable disease.
4. To evaluate toxicity and tolerability of this combination as measured by NCI-CTCAE version 5.0.

2.3 Exploratory Objectives

1. To explore the relationship of the immunophenotype of peripheral blood immune cells and response to combined therapy.
2. To explore the changes in tumor immune cell infiltrate after treatment and relationship with response.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed squamous or non-squamous non-small cell lung cancer. Patients with known EGFR or ALK mutations are eligible only if they have received at least one line of targeted therapy for these mutations.

2. Availability of archival biopsy tissue or willingness to undergo a "baseline" biopsy prior to initiation of the trial for biomarker analysis, including PD-L1 by IHC.

   Note: Results of PD-L1 testing are not required for enrollment.

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

4. Prior use of an immune checkpoint blocker alone or in combination therapy.

5. At least 18 years of age.

6. ECOG performance status ≤ 1 (see Appendix A)

7. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500 /cumm
   b. Platelets ≥ 100,000 /cumm
   c. Hemoglobin ≥ 9.0 g/dL
   d. Total bilirubin ≤ 1.5 x ULN
   e. AST(SGOT)/ALT(SGPT) ≤ 3.0 x ULN or 5.0 x ULN in the setting of liver metastasis
   f. Serum creatinine ≤ 1.5 x ULN or CrCl ≥ 40 mL/min. if serum creatinine is >1.5 times the ULN, a 24-hour urine collection to calculate creatinine clearance must be performed

8. Adequate coagulation function as defined by:
   a. INR ≤ 1.5
   b. PTT/aPTT < 1.5 x ULN

   Note: 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).

9. Urinary protein ≤ 1+ on dipstick or routine urinalysis; if urine dipstick or routine analysis is ≥ 2+, a 24-hour urine collection for protein must demonstrate < 1 g of protein in 24 hours to allow participation

10. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

11. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Treatment with cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

   Note: Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea or premedication for contrast dye allergy) are eligible. The use of inhaled corticosteroids for chronic obstructive pulmonary disease (COPD) and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

2. A history of other malignancy ≤ 3 years previous with the exception of patients with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per SOC management (e.g., Rai Stage 0 chronic lymphocytic leukemia, prostate cancer with Gleason score ≤ 6 and prostate-specific antigen (PSA ≤ 10 ng/mL, etc.).

3. Currently receiving any other investigational agents.

4. Symptomatic or untreated asymptomatic brain metastases. Patients with treated brain metastases are eligible if they are 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 randomization, or after surgical resection performed at least 28 days prior to randomization. The patient may have no evidence of Grade ≥1 CNS hemorrhage based on pretreatment MRI or IV contrast CT scan (performed within 21 days before randomization).

5. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab, ramucirumab, any other immune checkpoint blockade, chimeric or humanized antibodies, fusion proteins, or other agents used in the study.

6. Receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

7. Arterial or venous thromboembolic event, including but not limited to myocardial infarction, transient ischemic attack, cerebrovascular accident, or unstable angina, within 6 months prior to enrollment.

8. Uncontrolled or poorly controlled hypertension (> 160 mmHg systolic or > 100 mmHg diastolic for > 4 weeks) despite standard medical management.

9. Gastrointestinal perforation, and/or fistula, or risk factors for perforation within 6 months prior to enrollment.

10. Grade 3 or 4 gastrointestinal bleeding within 3 months prior to enrollment.

11. History of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

    Note: Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible. Patients with controlled type 1 diabetes mellitus on a stable insulin regimen are eligible.

12. History of idiopathic pulmonary fibrosis, pneumonitis (including drug-induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan.

13. Hemoptysis (defined as bright red blood or ≥ ½ teaspoon) within 2 months prior to Cycle 1 Day 1 or with radiographic evidence of intratumor cavitation or radiologically documented evidence of major blood vessel invasion or encasement by cancer.

14. Serious or non-healing would, ulcer, or bone fracture within 28 days prior to Cycle 1 Day 1.

15. Undergone major surgery within 28 days prior to Cycle 1 Day 1, or minor surgery/subcutaneous venous access device placement within 7 days prior to Cycle 1 Day 1, or has elective or planned major surgery to be performed during the course of the clinical trial.

16. Known clinically significant liver disease, including cirrhosis at a level of Child-Pugh B or worse, cirrhosis (any degree) with a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis (defined as ascites from cirrhosis requiring diuretics or paracentesis), fatty liver, and inherited liver disease.

17. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as, HBV surface antigen (HBsAg) positive and HBV core antibody (HbcAb) positive with reflex positive HBV DNA. Note: Patients with past or resolved hepatitis B infection (defined as having a negative HBsAg test and a positive HBcAb test or treated HCV with negative HCV RNA are eligible.

18. Active tuberculosis.

19. Administration of a live, attenuated influenza vaccine within 4 weeks before Cycle 1 Day 1 or at any time during the study.

20. Severe infections within 2 weeks prior to Cycle 1 Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia. Received oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1 Day 1. Note: Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

21. History of deep venous thrombosis, pulmonary embolism, or any other significant thromboembolism (venous port or catheter thrombosis or superficial venous thrombosis are not considered "significant") during the 3 months prior to Cycle 1 Day 1.

22. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test within 7 days of study entry.

23. Known HIV-positivity.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Agent Administration

Ramucirumab will be given intravenously over the course of an hour on an outpatient basis on Day 1 of each 21-day cycle at a dose of 10 mg/kg.

Atezolizumab will be given intravenously on an outpatient basis on Day 1 of each 21-day cycle at a dose of 1200 mg. The initial dose will be administered over 60 minutes (+/- 15 minutes). If the first infusion is tolerated without infusion-associated events, the second infusion may be delivered over 30 minutes (+/- 10 minutes).

Ramucirumab and atezolizumab may be given in any order on treatment days.

5.2 Toxicity and Response Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of Cycle 2 and have not had any disease assessment.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Ramucirumab

Patients may not be receiving chronic antiplatelet therapy, including aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs, including ibuprofen, naproxen, and others), dipyridamole or clopidogrel, or similar agents. Once-daily aspirin use (maximum dose 325 mg/day) is permitted.

Patients who experience infusion-associated symptoms may be treated symptomatically with diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice).

In the event of additional reaction, systemic hydrocortisone or another corticosteroid may be administered at the discretion of the treating physician.

Montelukast will be administered daily for 7 days, starting 6 days prior to treatment with the final dose on Day 7, per the treating physician's discretion.

5.3.2 Atezolizumab

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (*e.g.*, supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles $\geq$2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use. Females of reproductive potential should use highly effective means of contraception.

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity.
- The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab.

Patients are not allowed to receive immunostimulatory agents, including, but not limited to, IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 7 days prior to the first day of study treatment.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 6 months following the last day of study treatment.

If a patient is suspected to be pregnant, both study drugs should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 6 months after the last day of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed every 3 months for 2 years or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for Ramucirumab

Treatment modifications for toxicities not listed below will be made at the discretion of the PI. Treatment may be held for a maximum of 6 weeks before a patient must be removed from study treatment. Patients who discontinue ramucirumab must come off study but may continue to receive atezolizumab as standard of care.

6.1.1 Infusion-Related Reactions

Reduce the infusion rate of ramucirumab by 50% for grade 1 or 2 infusion-related reactions. Permanently discontinue ramucirumab for grade 3 or 4 infusion-related reactions.

6.1.2 Hypertension

Interrupt ramucirumab for grade 3 hypertension until controlled with medical management. Permanently discontinue ramucirumab for severe hypertension that cannot be controlled with antihypertensive therapy or any grade 4 hypertension.

6.1.3 Proteinuria

Interrupt ramucirumab for urine protein levels ≥ 2 g/24 hours. Reinitiate treatment

at a reduced dose once the urine protein level returns to < 2 g/24 hours. If the protein level ≥ 2 g/24 hours reoccurs, interrupt ramucirumab and reduce the dose again once the urine protein level returns to < 2 g/24 hours. Permanently, discontinue ramucirumab for urine protein level > 3 g/24 hours, if there is a third occurrence of > 2 g/24 hours, if the protein level does not return to < 2 g/24 hours within 2 weeks, or in the setting of nephrotic syndrome.

6.1.4 Venous and Arterial Thromboembolic Events, Gastrointestinal Perforation, Fistula, or Grade 3 or 4 Bleeding

Ramucirumab should be permanently discontinued in the event of a gastrointestinal perforation or fistula formation.

Patients with who develop grade 3 or 4 venous thromboembolism may receive anticoagulation and continue ramucirumab therapy provided that the tumor does not confer an excessive bleeding risk, in the opinion of the patient's physician.

Grade 3 or 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 SAE mechanism.

6.1.5 Hepatic Encephalopathy or Other Serious Signs of Liver Impairment

For grade 2 liver test elevations, hold ramucirumab. Permanently discontinue ramucirumab for grade 3 or 4 liver test elevations or other signs of serious liver impairment. Signs of serious liver impairment include hepatorenal syndrome or other signs as determined by the treating physician.

6.1.6 Reversible Posterior Leukoencephalopathy Syndrome

If RPLS is diagnosed, ramucirumab must be permanently discontinued. All cases of RPLS must be reported via the SAE mechanism.

6.1.7 Other Non-Hematologic Adverse Events

If any other grade 3 non-hematologic adverse event occurs, hold the dose of ramucirumab and consult with the PI.

If any other grade 4 non-hematologic adverse event occurs, discontinue treatment with ramucirumab.

6.2 Dose Modifications for Atezolizumab

Atezolizumab dose reduction is not allowed. However, study treatment may be temporarily

suspended in patients experiencing toxicity considered to be related to study treatment for up to 60 days after the last dose if they experience toxicity that require a dose to be withheld. If atezolizumab is withheld because of toxicity for > 60 days after the last dose, then the patient will be discontinued from atezolizumab treatment and will be followed for safety and efficacy.

Recommendations for dosage modifications are provided in the table below:

Adverse Reaction	Severity (by CTCAE Grade)	Dosage Modifications
Pneumonitis	2	Withhold dose until grade 1 or resolved and corticosteroid dose ≤ 10 mg/day (or equivalent)
	3 or 4	Permanently discontinue
Hepatitis	AST or ALT 3-5 x ULN or total bilirubin 1.5-3 x ULN	Withhold dose until grade 1 or resolved and corticosteroid dose ≤ 10 mg/day (or equivalent)
	AST or ALT > 5 x ULN or total bilirubin > 3 x ULN	Permanently discontinue
Colitis or diarrhea	2 or 3	Withhold dose until grade 1 or resolved and corticosteroid dose ≤ 10 mg/day (or equivalent)
	4	Permanently discontinue
Endocrinopathies (including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus)	2, 3, or 4	Withhold dose until grade 1 or resolved and clinically stable on hormone replacement therapy
Other immune-mediated adverse reactions involving a major organ	3	Withhold dose until grade 1 or resolved and corticosteroid dose ≤ 10 mg/day (or equivalent)
	4	Permanently discontinue
Infections	3 or 4	Withhold dose until grade 1 or resolved
Infusion-related reactions	1 or 2	Interrupt or slow the rate of infusion
	3 or 4	Permanently discontinue
Persistent grade 2 or 3 adverse reaction (excluding endocrinopathies)	2 or 3 that does not recover to 0 or 1 within 60 days after last dose	Permanently discontinue
Inability to taper	Inability to	Permanently discontinue

corticosteroid	reduce to ≤ 10 mg/day (or equivalent) within 60 days after last dose	
Recurrent grade 3 or 4 adverse reaction	Recurrent grade 3 or 4	Permanently discontinue

Dose interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed, with PI approval. The PI will determine the acceptable length of interruption.

Patients who discontinue atezolizumab must come off study.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix B for definitions and Appendix C for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 30 days after the last administration of study drug. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Laboratory adverse events that are not clinically significant

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

7.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that have been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.3 Reporting to Eli Lilly

Eli Lilly must be notified within 24 hours 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.

All instances of reversible posterior leukoencephalopathy must be reported to Eli Lilly via the SAE mechanism.
Any venous or arterial event leading to discontinuation of ramucirumab therapy will be considered serious and should be reported to Eli Lilly via the SAE mechanism

7.4 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Ramucirumab (Cyramza)

8.1.1 Ramucirumab Description

Ramucirumab is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor receptor 2. Ramucirumab has an approximate molecular weight of 147 kDa. Ramucirumab is produced in genetically engineered mammalian NS0 cells.

8.1.2 Clinical Pharmacology

Ramucirumab is a vascular endothelial growth factor receptor 2 antagonist that specifically binds VEGF Receptor 2 and blocks binding of VEGFR ligands, VEGF-

A, VEGF-C, and VEGF-D. As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2, thereby inhibiting ligand-induced proliferation, and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an in vivo animal model.

8.1.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetic (PK) characteristics of ramucirumab are similar for patients with gastric cancer, NSCLC, and mCRC based on a population PK analysis. The mean (% coefficient of variation [CV%]) clearance for ramucirumab was 0.015 L/hour (30%) and the mean terminal half-life was 14 days (20%).

8.1.4 Supplier

Ramucirumab is an investigational agent for this trial and will be supplied by Lilly Oncology, free of charge to the patient.

8.1.5 Dosage Form and Preparation

Ramucirumab is available in two dose strengths:

- 100 mg/10 mL (10 mg per mL) solution, single dose vial
- 500 mg/50 mL (10 mg per mL) solution, single dose vial

8.1.6 Storage and Stability

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.

8.1.7 Administration

Calculate the dose and the required volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg/10 mL or 500 mg/50 mL at a concentration of 10 mg/mL solution of ramucirumab.

Withdraw the required volume of ramucirumab and further dilute with only 0.9% Sodium Chloride Injection in an intravenous infusion container to a final volume of 250 mL. Do not use dextrose containing solutions.

Gently invert the container to ensure adequate mixing.

DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

Store diluted infusion for no more than 24 hours at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature (below 25°C [77°F]).

Discard vial with any unused portion of ramucirumab.

Visually inspect the diluted solution for particulate matter and discoloration prior to administration. If particulate matter or discolorations are identified, discard the solution.

Administer diluted ramucirumab infusion via infusion pump over 60 minutes through a separate infusion line. Use of a protein sparing 0.22 micron filter is recommended. Flush the line with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

8.2 Atezolizumab (Tecentriq)

8.2.1 Description

Atezolizumab is a human monoclonal antibody based on a human IgG1 framework containing heavy chain VHIII and light chain VκI subgroup sequences. The recombinant antibody consists of two heavy chains (448 amino acid residues each) and two light chains (214 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG1 antibodies. Atezolizumab incorporates an amino acid substitution (asparagine to alanine) at position 298 in the CH2 domain of each heavy chain resulting in a non-glycosylated antibody that has minimal binding to Fcγ receptors and, consequently, prevents Fc-effector function and depletion of cells expressing PD-L1 at expected concentrations in humans. Therefore, atezolizumab lacks the N-linked oligosaccharides typically observed on other CHO-derived monoclonal antibodies.

8.2.2 Pharmacokinetics and Drug Metabolism

On the basis of available preliminary PK data (0.03−20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent CL and the mean Vss had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

8.2.3 Supplier(s)

Atezolizumab will be commercially available.

8.2.4 Dosage Form and Preparation

The atezolizumab drug product is provided in the following configurations:

(1) The atezolizumab drug product produced using the Phase I manufacturing process is provided in a single-use, 2-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 1.2 mL (150

mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 1.2 mL volume. The atezolizumab drug product is formulated as 125 mg/mL atezolizumab in 20 mM histidine acetate, 240 mM sucrose, 0.02% polysorbate 20, pH 5.5 (Phase I formulation).

(2) The atezolizumab drug product produced using the Phase III manufacturing process is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8 (Phase III formulation).

8.2.5 Storage and Stability

Atezolizumab must be refrigerated at 2°C−8°C (36°F−46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in atezolizumab drug product; therefore, the vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

8.2.6 Administration

Atezolizumab will be given intravenously at a dose of 1200 mg.

9.0 CORRELATIVE STUDIES

9.1 Peripheral Blood

Patients will have up to 40 mL of blood collected in 4 pink top EDTA tubes at baseline and Cycle 2 Day 1. Patients with hemoglobin below 10 mg/dL will only have 30 mL. 3 EDTA tubes collected.

9.2 Biopsy Samples

When available, archival biopsy tissue will be used for a baseline biopsy. If baseline tissue is not available, the patient will undergo a baseline biopsy prior to initiation of the trial.

When feasible, a repeated tumor biopsy will be obtained between Cycles 2 and 3 after the scheduled CT scan.

9.3 Processing and Storage

Tissue samples will be sent to Siteman Cancer Center Tissue Procurement Core (TPC) and processed according to TPC standard operating procedures. Biospecimens will be cryopreserved and stored for future analysis.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done no more than 4 weeks prior to the start of the protocol therapy. Cycles are 21 days long. There is a +/- 3 day window for all assessments and procedures.

	Screening	**Baseline**	**C1 D1**	**C2 D1**	**After Cycle 2**	**D1 of subsequent cycles**	**End of every 2 cycles**	**EOT**	**F/U[3]**
Informed consent	X								
H&P, ECOG PS	X			X		X		X	
CBC	X		X	X		X			
CMP	X		X	X		X			
PTT/aPTT, INR	X								
TSH[6]	X		X						
Hepatitis B and C test	X								
Pregnancy test[1]	X								
Urinalysis	X		X	X		X			
CT scan	X						X		
Ramucirumab			X	X		X			
Atezolizumab			X	X		X			
Research blood		X		X					
Archival tumor	X[5]								
Fresh biopsy	X[5]				X[4]				
Survival									X
AE assessment		X ----------							X[2]

1. For women of childbearing potential only
2. For 30 days after end of treatment
3. Every 3 months for 2 years; may be done by phone.
4. When feasible, the biopsy will follow CT scan performed between Cycles 2 and 3
5. When available, archival biopsy tissue will be used for a baseline biopsy. If baseline tissue is not available, the patient will undergo a baseline biopsy prior to initiation of the trial.
6. Reflex to free T3, free T4.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form Concomitant Medications Form	Continuous. See Section 7.0 for reporting requirements
Research Tissue Form	Baseline, after Cycle 2/before Cycle 3
Research Blood Form	Baseline, C2D1
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months for 2 years
Death Form	Time of death
RECIST Form	Baseline, end of every even numbered cycle, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 1.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes

reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

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

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

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed in 4-6 weeksby the Principal Investigator.

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD***	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD****	Yes or No	PD	
Any	Any	Yes	PD	
*	See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.			
**	Only for non-randomized trials with response as primary endpoint.			

*** If the patient is clinically stable, treatment may continue with repeated scans in 4 weeks to rule out pseudoprogression
**** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

12.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Endpoints

The primary objective of this study is to determine the overall response rate (ORR) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.

The secondary objectives include

- To determine the overall survival (OS) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.
- To determine the progression-free survival (PFS) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB.
- To determine clinical benefit rate (CBR) for the combination of ramucirumab and atezolizumab in patients with NSCLC who have previously received an ICB. CBR is defined as the percentage of patients who have achieved responses or stable disease.
- To evaluate toxicity and tolerability of this combination as measured by NCI-CTCAE version 5.0.

The exploratory objectives include

- To explore the relationship of the immunophenotype of peripheral blood immune cells and response to combined therapy.
- To explore the changes in tumor immune cell infiltrate after treatment and relationship with response.

14.2 Study Design

This single institution study will be designed using Simon's two-stage MiniMax design. We plan to enroll twenty-one (21) advanced-stage NSCLC patients.

Assuming a null hypothesis of ORR less than 5% in this setting, we hypothesize that ORR of 20% or higher warrants further investigation. A total number of 21 patients allows an 80% power at 1-sided alpha of 0.1 to detect the expected difference. If 4 or more responders are observed at the end of the trial, we would conclude that there is preliminary evidence for efficacy warranting further investigation.

14.3 Data Analysis

Demographic and clinical characteristics of the sample, as well as toxicity by grade and loss to follow up will be summarized using descriptive statistics. Overall response rate (ORR) and clinical benefit rate (CBR) will be evaluated using the RECIST 1.1 criteria according to investigator's assessment, and their 1-side 90% confidence intervals will also be calculated. Kaplan-Meier product limit estimator will be used to describe the distribution of overall survival (OS) and progression free survival (PFS). The association between response and the immunophenotype of peripheral blood immune cells will be summarized using descriptive statistics. Although data analysis will be primarily descriptive, permutation test will be used to rank the strength of association. Specifically, we first compute the observed test statistics for the differences between responders and non-responders. Then the null distribution of the test statistics will be generated by simulating 10,000 datasets where the status of response was randomly shuffled. The permutation p-values equal the proportion of simulations from the null distribution that exceed the observed test statistics. Similar analysis will be performed for the association between response and the changes in tumor immune cell infiltrate after treatment.

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APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

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

- Death
- A life-threatening adverse event

- 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
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

For the purposes of this protocol, the following events are also defined as a SAE:

- Any venous or arterial event leading to discontinuation of ramucirumab therapy
- Reversible posterior leukoencephalopathy syndrome of any grade

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX C: Reporting Timelines

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Eli Lilly**
Serious AND unexpected suspected adverse reaction			Report within 24 hours
Unexpected fatal or life-threatening suspected adverse reaction			Report within 24 hours
Reversible posterior leukoencephalophathy (any grade)			Report within 24 hours
Any venous or arterial event leading to discontinuation of ramucirumab therapy			Report within 24 hours
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment	
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.		
Protocol exception	Approval must be obtained prior to implementing the change		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1		

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Eli Lilly**
	working day. Otherwise, report at the time of continuing review.		
Breach of confidentiality	Within 10 working days.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	