Protocol Template for Investigator-Initiated Studies

Template Instructions

Sections will expand to fit your responses.

Keep an electronic copy to modify when making changes either as directed by the IRB, or for amendments/modifications.

Mark sections NA if they are not applicable to your research.

Please use lay language, avoid professional jargon and define all abbreviations when they first appear.

Dr. Keresztes

PROTOCOL TITLE:

Response: Phase-II Trial of Platinum-Based Chemotherapy Plus Ramucirumab in Patients with advanced NSCLC who have Progressed on First line anti-PD-1 Immunotherapy

PROTOCOL VERSION/AMENDMENT # AND DATE

Response: 06/04/2020Version 5

PRINCIPAL INVESTIGATOR:

Response: Roger Keresztes, MD, Amna Sher, MD. John Haley, PhD.

DATE:

Response: 06/04/2020

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives of this research. Specifically, explain why it is important to do the study.

Response:

Primary Objective

1) To assess the objective response rate to a three-drug regimen (a platinum doublet plus an anti-angiogenic agent) in patients with non-small cell lung cancer who fail to respond, or progress after an initial response, to primary therapy with an immune checkpoint inhibitor.
2) To assess the toxicity profile of the three-drug regimen in this population compared to historical treatment-naïve population (as published in literature)

Exploratory Objective

1) To investigate the role of peripheral blood immune cell cytokines and absolute eosinophil count (AEC) as biomarkers of response to salvage chemotherapy after primary immunotherapy
2) To investigate the role of plasma carbonic anhydrase IX level as predictive biomarker of response to Ramucirumab.

1.2 State the hypothesis to be tested, if applicable.
NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.

Response: We hypothesize that immune therapy acts as a chemo-sensitizer by altering the tumor immune milieu and improves response rate to salvage chemotherapy in advanced NSCLC.

2.0 Scientific/Safety Endpoints

2.1 Describe the scientific endpoint(s), the main result or occurrence under study. NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should not be a date.

Response:

1. Objective Response Per RECIST 1.1 as assessed by Stony Brook Radiologist [Time Frame: ≥18 weeks, up to maximum of 12 months]

- Objective response (OR) is the occurrence of CR or PR as the best overall response. OR will be based on responses confirmed using the subsequent 6-weekly scan.

2. Toxicity - Treatment related dose delay or Treatment Discontinuation [Time Frame: Through study completion, up to a maximum of 12 months. Serious AEs: Up to 90 days after last dose of study treatment, Other AEs: Up to 30 days after last dose of study treatment]

- Adverse events will be recorded in relation to each cycle of treatment and graded according to CTCAE criteria. The toxicity co-primary outcome measure for the trial is defined as the occurrence of a treatment-related dose delay or treatment discontinuation due to toxicity

3.0 Background

3.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute/fill in gaps to existing knowledge.

Response: Lung cancer remains the leading cause of cancer mortality for both men and women in the United States, and despite a trend towards decreased tobacco use, the frequency of the disease is not expected to decline for some time [1]. Unfortunately, the majority of patients are diagnosed at an advanced stage, hence conventional treatments are unlikely to be curative.

For many years, the mainstay of treatment for patients with stage IV NSCLC has been "doublet" chemotherapy with a platinum compound (cisplatin or carboplatin) and one of several chemotherapy agents. Both platinum-based and non-platinum based two drug regimens have been shown to be efficacious in the first line treatment of advanced NSCLC. Numerous studies have failed to show clear superiority of one doublet over another, and most have shown comparable efficacy with different toxicity profile [2].

In 2006, a landmark study by the Eastern Cooperative Oncology Group was published, demonstrating improved survival with the addition of an anti-angiogenic agent, bevacizumab, to a standard platinum doublet, paclitaxel and carboplatin [3]. It is generally considered that the added benefit of anti-angiogenic therapy is independent of the chemotherapy doublet used. Unfortunately, the use of bevacizumab is limited by demonstration of an increased risk of fatal hemorrhage in patients with squamous cell carcinoma, and by retrospective analysis which suggests that the anti-tumor benefit of bevacizumab is offset by the increased risk of serious side effects in patients over age 70[4] [5].

Ramucirumab, another anti-angiogenic antibody which binds to VEGFR-2, was evaluated in combination with docetaxel in a double-blind randomized phase III trial, in NSCLC patients who had disease progression after primary platinum-based chemotherapy. The combination conferred a modest but significant survival benefit over docetaxel alone in this population which has limited treatment options[6]. Based on these findings, FDA approved ramucirumab in combination with docetaxel as second line treatment of stage IV NSCLC after progression on platinum based therapy. Importantly, this study did not exclude patients with squamous cell carcinoma, and the benefit in that subset was comparable to that of the group as a whole. In addition, about 35% of patients in each arm of the study were over age 65, and again the benefit in that subset was comparable to that of the group as a whole. Promising results were observed in a single-arm phase II trial of ramucirumab in combination with carboplatin and paclitaxel as first line therapy in stage IV NSCLC patients[7].The effects of ramucirumab on survival and PFS were consistent with the ECOG 4599 study of bevacizumab. Another randomized phase II trial compared the addition of ramucirumab to pemetrexed-cisplatin or pemetrexed-carboplatin followed by maintenance pemetrexed, with chemotherapy alone[8] In both these studies there were no new or unexpected safety findings.

With advancements in Immuno-oncology, the treatment paradigm for advanced lung cancer has greatly changed. Immune checkpoint inhibitors, especially PD-1 and PD-L1 inhibitors, have emerged as novel treatments for NSCLC patients. Nivolumab was the first immune check point inhibitor approved for the treatment of advanced lung cancer in 2015. CheckMate 017 and CheckMate 057 trials demonstrated that nivolumab significantly improved OS compared to docetaxel, in patients with NSCLC who had progressed on prior platinum based chemotherapy[9, 10]. A number of these agents have been shown to improve survival (compared to a standard

second-line chemotherapy drug) in patients whose disease has progressed on or after platinum-based chemotherapy [11, 12].

Pembrolizumab, a PD-1 blocking antibody has also shown to significantly improve PFS (10.3 vs 6.0 months) and overall response rates (ORR) (45% vs 28%) in untreated patients whose tumors express high levels of PD-L1 , compared to platinum based doublet chemotherapy [13] . Immunotherapy has now become the new standard of care treatment for patients with stage IV NSCLC with high PDL-1 expressing tumors. In the phase I/II KEYNOTE-021 study, addition of Pembrolizumab to platinum-doublet chemotherapy was associated with significant improvement in ORR and PFS in treatment-naïve advanced non-squamous NSCLC, compared to chemotherapy alone [14].

Durvalumab, a PD-L1 inhibitor has recently shown a remarkable improvement in PFS compared to placebo (16.8 months vs 5.8 months, $p < 0.001$), in un-resectable locally advanced NSCLC patients who had not progressed following concurrent chemo-radiation[15]. Consolidation durvalumab is a major advancement in the treatment of stage III NSCLC patients in decades.

Despite success, only about 20-30% of patients with NSCLC respond to immune checkpoint inhibitors. Most patients will ultimately fail to respond or stop responding, and will require treatment with traditional cytotoxic therapy. There is no consensus on how to treat patients after failure of primary immunotherapy, nor is there data on response rates or patients' ability to tolerate aggressive treatments in this context. As per National Cancer Comprehensive Network (NCCN) guidelines, treatment options for these patients include systemic therapy FDA approved for first line treatment of metastatic lung cancer. This includes platinum-doublet chemotherapy with or without anti-angiogenic agent depending on performance status (PS) and histology [2, 3, 16]. Most commonly used doublets are carboplatin plus paclitaxel or docetaxel, and carboplatin plus pemetrexed.

The benefit of ramucirumab combined with platinum doublet chemotherapy for first line metastatic NSCLC, seems to be comparable to that seen with bevacizumab [7].The rationale for using ramucirumab is that , it can be used for both squamous and non-squamous histologies, as opposed to bevacizumab which is restricted to adenocarcinoma only. Also the benefit was seen in elderly population as well.

We propose to conduct a Phase II trial in patients with advanced NSCLC who have progressed on primary Immunotherapy, to evaluate the efficacy and safety of a three-drug regimen (platinum doublet plus anti-angiogenic agent).

This is a novel patient population which did not exist in the pre-immunotherapy era. The proposed drug regimens have demonstrated clinical efficacy and safety in earlier trials, before

immunotherapy became widely used for NSCLC. All these chemotherapy agents are approved for treatment of advanced lung cancer.

With the advent of immunotherapy for the treatment of advanced lung cancer, determining the optimal treatment sequence for cytotoxic chemotherapy and antiangiogenic agents has become a complex clinical question. Although, historically chemotherapy has been considered as immune suppressive, several mechanisms have been proposed by which chemotherapy modulates the tumor immune biology. These include increased neo-antigen presentation, upregulation of co-stimulatory molecules (B7-1), or down-regulation of co-inhibitory molecules (PD-L1/B7-H1 or B7-H4) expressed on the tumor cell surface, thus promoting anti- tumor CD4+ T-cell activity[19].

In a preclinical study, activated CD4+T cells were used as chemo-sensitizer prior to administration of chemotherapy. This was associated with significant enhancement of cytotoxic effects of chemotherapy drugs in both in vitro and in vivo tumor xenograft models [17].

Similarly, in mouse models Immunogene therapy followed by chemotherapy was associated with enhanced antitumor activity. Intratumoral injection of adenovirus expressing interferon alfa (Ad–IFN-a) in mice bearing lung cancer tumors, followed by intravenous chemotherapy with gemcitabine and cisplatin, resulted in the greatest tumor shrinkage compared to Ad–IFN-a alone, chemotherapy alone, and chemotherapy followed by Ad–IFN-a[20].

Schvartsman, G et al demonstrated in a retrospective analysis, that ORR to third line single agent chemotherapy following immunotherapy was 39%, which almost equaled the ORR with first line-platinum based chemotherapy [21].Similarly, in another retrospective analysis the ORR to salvage chemotherapy after immunotherapy (SCAI), was greater than that of last chemotherapy given before immunotherapy (LCBI)[22] .

Biomarkers

Checkpoint inhibitors might enhance the effects of chemotherapy by immune activation and the increased number of activated T cells following treatment with these agents might result in improved response rate to salvage chemotherapy.

Kamphorst AO, et al 2017 evaluated changes in peripheral blood T cells, in NSCLC patients receiving anti-PD1 therapy. In this analysis they demonstrated that early proliferation of PD-1+ CD8 T cells was seen in majority of the patients and co-related with positive clinical outcome [23].

To explore this we will measure peripheral blood immune cell cytokines and absolute eosinophil count (AEC) prior to initiation of chemotherapy and during the course of treatment and correlate with response.

Currently there are no validated biomarkers for predicting response to antiangiogenic agents, which may be partly due to dynamic changes in biomarker expression induced by VEGF targeted therapy. Carbonic anhydrase IX (CAIX) is a hypoxia regulated transmembrane protein, which helps maintain intracellular pH. In RCC, studies have shown that CAIX protein expression increased following VEGF targeted therapy and was associated with improved outcomes [24].Elevated circulating plasma CAIX levels have been associated with poor outcomes in breast cancer patients and have also been shown to correlate with response to anti-angiogenic agents [25]. In our study we will investigate the role of plasma carbonic anhydrase IX (CAIX) as potential biomarker of response to ramucirumab.

3.2 Include complete citations or references:

Response:

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer Statistics, 2017.* CA Cancer J Clin, 2017. **67**(1): p. 7-30.
2. Schiller, J.H., et al., *Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.* N Engl J Med, 2002. **346**(2): p. 92-8.
3. Sandler, A., et al., *Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.* N Engl J Med, 2006. **355**(24): p. 2542-50.
4. Sandler, A.B., et al., *Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non-small-cell lung cancer treated with Carboplatin and Paclitaxel plus bevacizumab.* J Clin Oncol, 2009. **27**(9): p. 1405-12.
5. Ramalingam, S.S., et al., *Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599.* J Clin Oncol, 2008. **26**(1): p. 60-5.
6. Garon, E.B., et al., *Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial.* Lancet, 2014. **384**(9944): p. 665-73.
7. Camidge, D.R., et al., *A phase II, open-label study of ramucirumab in combination with paclitaxel and carboplatin as first-line therapy in patients with stage IIIB/IV non-small-cell lung cancer.* J Thorac Oncol, 2014. **9**(10): p. 1532-9.
8. Doebele, R.C., et al., *Phase 2, randomized, open-label study of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic non-small cell lung cancer.* Cancer, 2015. **121**(6): p. 883-92.
9. Brahmer, J., et al., *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(2): p. 123-35.
10. Borghaei, H., et al., *Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer.* N Engl J Med, 2015. **373**(17): p. 1627-39.
11. Herbst, R.S., et al., *Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial.* Lancet, 2016. **387**(10027): p. 1540-50.

12. Rittmeyer, A., et al., *Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial.* Lancet, 2017. **389**(10066): p. 255-265.
13. Reck, M., et al., *Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer.* N Engl J Med, 2016.
14. Langer, C.J., et al., *Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study.* Lancet Oncol, 2016. **17**(11): p. 1497-1508.
15. Antonia, S.J., et al., *Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer.* N Engl J Med, 2017. **377**(20): p. 1919-1929.
16. Patel, J.D., et al., *PointBreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer.* J Clin Oncol, 2013. **31**(34): p. 4349-57.
17. Radfar, S., Y. Wang, and H.T. Khong, *Activated CD4+ T cells dramatically enhance chemotherapeutic tumor responses in vitro and in vivo.* J Immunol, 2009. **183**(10): p. 6800-7.
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20. Fridlender, Z.G., et al., *Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms.* Mol Ther, 2010. **18**(11): p. 1947-59.
21. Schvartsman, G., et al., *Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer.* Lung Cancer, 2017. **112**: p. 90-95.
22. Park, S.E., et al., *Increased Response Rates to Salvage Chemotherapy Administered after PD-1/PD-L1 Inhibitors in Patients with Non-Small Cell Lung Cancer.* J Thorac Oncol, 2017.
23. Kamphorst, A.O., et al., *Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients.* Proc Natl Acad Sci U S A, 2017. **114**(19): p. 4993-4998.
24. Stewart, G.D., et al., *Carbonic anhydrase 9 expression increases with vascular endothelial growth factor-targeted therapy and is predictive of outcome in metastatic clear cell renal cancer.* Eur Urol, 2014. **66**(5): p. 956-63.
25. Brown-Glaberman, U., et al., *Circulating Carbonic Anhydrase IX and Antiangiogenic Therapy in Breast Cancer.* Dis Markers, 2016. **2016**: p. 9810383.

4.0 Study Design

4.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, and observational). Indicate if

there is randomization, blinding, control group, etc. If randomizing, explain how this will be achieved.

Response: This is a non-randomized, phase-II study of platinum doublet chemotherapy plus ramucirumab in patients with advanced NSCLC who have progressed on first line anti-PD-1 Immunotherapy. Up to 25 evaluable participants will be enrolled over a period of 2 years. Seven patients will be recruited at the first stage .Eligible patients would include those treated with a PD-1 inhibitor as primary therapy and exhibit evidence of disease progression, but maintain a good performance status.

Patients who meet the eligibility criteria will be screened, and if eligible will receive the investigator's choice of one of the platinum doublets plus ramucirumab as listed below:

1. Paclitaxel 200 mg/m2 IV Q3W and Carboplatin AUC 6 on day 1 Q3W and Ramucirumab 10 mg/kg IV day 1 Q3W for 4 cycles.
2. Docetaxel 75mg/m2 IV Q3W and Carboplatin AUC 5 or 6 on day 1 Q3W and Ramucirumab 10 mg/kg IV day 1 Q3W for 4 cycles.
3. Pemetrexed 500 mg/m2 Q3W and Carboplatin AUC 5 day 1 Q3W and Ramucirumab 10 mg/kg IV day 1 Q3W for 4 cycles.

The investigator will determine the specific three drug regimen based on tumor histology, individual patients' co-morbidities and after discussing risks/benefits of each regimen with the patient.

Initial response assessment will be done after 2 cycles of treatment. If 0 or 1 response is seen in first 6 patients, no more patients will be enrolled till the seventh patient has been assessed for treatment response. If zero or one patient responds to the treatment at the end of the first stage, the study will stop early for futility. If the number of responders is two or more, the study will continue recruiting to the second stage. If six or fewer responders are observed by the end of stage two, then no further investigation of the treatment is warranted. The probability of early stop will be 72% if the true response rate is lower than 10%.

If three or more, grade 3 non-hematologic toxicities are observed in the first 7 patients, the study will stop early due to high toxicity. Patients who withdraw for toxicity or disease progression before the first planned evaluation for treatment response, will be considered non-responders. Patients who come off study before the initial response evaluation for reasons OTHER THAN toxicity or disease progression (e.g, withdrawal of consent, lost to follow up) will be replaced. We expect less than 10% of patients to discontinue treatment before the first assessment.

Expected toxicities include myelosuppression, alopecia, nausea, vomiting, fatigue, neurotoxicity, and thrombotic or hemorrhagic events. The toxicity profile varied based on the platinum-doublet

chemotherapy regimen used. More grade 3 or 4 anemia (14.5% *v* 2.7%), thrombocytopenia (23.3% *v* 5.6%) and fatigue (10.9% *v* 5.0%) occurred with pemetrexed containing regimen. Whereas, more grade 3 or 4 neutropenia (40.6% *v* 25.8%) , febrile neutropenia, (4.1% *v* 1.4%) sensory neuropathy (4.1% *v* 0%), and alopecia (grade 1 or 2; 36.8% *v* 6.6%) occurred with taxane-based regimen [16]. In previous studies with ramucirumab, only grade 3-4 neutropenia was seen in a significant proportion of patients up to 40%. Incidence of grade 3-4 febrile neutropenia was also higher in the ramucirumab group 16% versus 10%. Hypertension (any grade 11 % *v* 5%), and bleeding(any grade 29 % *v* 15%) were more common with ramucirumab There was no other grade 3-4 toxicity with a frequency of greater than 10% [6]

Specifically data for patients treated with combination of carboplatin , bevacizumab and paclitaxel or pemetrexed in the first line setting (the ECOG 4599 and PointBreak trials) and in those treated with docetaxel and ramucirumab in the second line setting (the REVEL trial) will be used for comparison[3, 6, 16]

Response will be assessed by the investigator according to RECIST 1.1.
Treatment will continue until RECIST 1.1-defined progression, unacceptable toxicity, withdrawal of consent, or until start of new therapy.

Subjects who respond to 4 cycles of the initial regimen and maintain a good performance status with minimal toxicity, will receive maintenance therapy with Docetaxel 75mg/m2 and Ramucirumab 10 mg/kg Q3W until disease progression or unacceptable toxicity.

Physical examinations, vital sign measurements, and clinical laboratory evaluations will be performed at selected times throughout the treatment period. Participants will be closely monitored for adverse events throughout the study.

During treatment peripheral blood samples, will also be collected for exploratory biomarker analysis.

5.0 Local Number of Subjects

5.1 Indicate the total number of subjects who will be enrolled or records that will be reviewed through Stony Brook.

Response: Up to 25 evaluable participants will be enrolled over a period of 2 years.

5.2 If this study is only being conducted through Stony Brook, provide statistical justification (i.e. power analysis) for the number of subjects provided in 5.1 above. If

qualitative research, so state, and provide general justification for the total number of subjects proposed.

Response: We plan to use a Simon's two-stage design to test the efficacy for this study. If a response rate lower than 15% is a failure and a response rate over 40% is promising, we will need a sample size up to 25 for 80% power and 5% alpha using the Simon's two-stage optimum method. Up to 25 evaluable participants will be recruited for two years. Seven patients will be recruited at the first stage. Initial response assessment will be done after 2 cycles of treatment. If zero or one patient responds to the treatment at the end of the first stage, the study will stop early for futility. If the number of responders is two or more, the study will continue recruiting to the second stage. If six or fewer responders are observed by the end of stage two, then no further investigation of the treatment is warranted. The probability of early stop will be 72% if the true response rate is lower than 10%.

If three or more, grade 3 non-hematologic toxicities are observed in the first 7 patients, the study will stop early due to high toxicity.

Expected toxicities include myelosuppression, alopecia, nausea, vomiting, fatigue, neurotoxicity, and thrombotic or hemorrhagic events. In previous studies with ramucirumab, only grade 3-4 neutropenia was seen in a significant proportion of patients up to 40%. Incidence of grade 3-4 febrile neutropenia was also higher in the ramucirumab group 16% versus 10%. There was no other grade 3-4 toxicity with a frequency of greater than 10% [6].

For primary objectives, binomial exact tests will be used to compare response rate and toxicity to historical response rates and toxicity, as reported in the literature for similar treatment regimens. Specifically data for patients treated with paclitaxel, carboplatin and bevacizumab in the first line setting (the ECOG 4599 and PointBreak trials) and in those treated with docetaxel and ramucirumab in the second line setting (the REVEL trial) will be used for comparison[3, 6, 16].

The exploratory analysis is mainly descriptive and non-parametric methods will be used for the small sample size and possible normality violation. Immune cell cytokines and AEC will be measured at baseline and every treatment cycle. Additionally, if one patient is a responder, those outcomes will be measured every three weeks during maintenance. A non-responder may have a minimum of three measures (baseline + 2 treatment cycles) and a responder may have more than 30 measures over 6 months of follow-up.

Descriptive statistics (e.g. mean, sd, median and etc) will be presented for baseline, available treatment cycles, and for follow-up for responders. If the study stops early due to futility, there will be no comparison group. Due to the small sample size (n=7), a non-parametric Friedman test will be used to compare the outcomes over time.

If the respond rate is 40% under the alternative hypothesis (10 vs 15), Wilcoxon rank sum test will be used to compare changes in outcomes between responders and non-responders. In addition, Wilcoxon rank sum test will be used to compare plasma carbonic anhydrase IX level between responders and non-responders. For the exploratory purpose, p value will not be adjusted for multiple tests in order to show trends.

5.3 If applicable, indicate your screen failure rate, i.e., how many subjects you expect to screen to reach your target sample.

Response: N/A

5.4 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit? Response:

6.0 Inclusion and Exclusion Criteria

NOTE: If your study is more than minimal risk, you must also upload a copy of your inclusion/exclusion checklist (with space for specific subject values) to be completed at time of enrollment of each subject.

6.1 Describe, in bullet points, the criteria that define who will be included in this study:

Response: For entry into the study, the following criteria MUST be met.

1. Histologically or cytologically confirmed stage IV NSCLC per 8th IASCL of squamous and non–squamous histology, with progression on first line anti-PD1 immunotherapy.
   OR

Oligo-metastatic stage IV patients who received concurrent chemotherapy with thoracic radiation, followed by durvalumab consolidation and had progression of disease OR
Locally advanced un-resectable NSCLC patients who received concurrent chemotherapy with thoracic radiation, followed by durvalumab consolidation and had progression of disease.

2. Males or females at least 18 years of age.
3. ECOG PS of 0 or 1.
4. Measureable disease by CT or MRI per RECIST 1.1 criteria.
5. Life expectancy of at least 3 months.
6. Resolution of all clinically significant toxic effects of prior anticancer therapy to Grade ≤1 by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.
7. The participant must have adequate organ function, defined as:

- Total bilirubin less than or equal to the upper limit of normal value (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, or ≤5 x ULN if the transferase elevation was due to liver metastases.
- Serum creatinine ≤1.5 x ULN or calculated creatinine clearance ≥50 mL/min (per the Cockcroft-Gault formula or equivalent and/or 24-hour urine collection [Cockcroft-Gault glomerular filtration rate = (140-age) * (Wt in kg) * (0.85 if female) / (72 * Cr) where "Cr" is serum creatinine]).
- Absolute neutrophil count (ANC) ≥1.5 x 103/μL (≥1.5 x 109/L), hemoglobin ≥10.0 g/dL (≥ 6.2 mmol/L), and platelets ≥100 x 103/μL (≥100 x 109/L).

- International Normalized Ratio (INR) less than or equal to 1.5, or prothrombin time and partial thromboplastin time less than or equal to 1.5 x ULN.

The participant does not have cirrhosis at a level of Child-Pugh B (or worse) or cirrhosis (any degree) and a history of hepatic encephalopathy or clinically meaningful ascites resulting from cirrhosis. Clinically meaningful ascites is defined as ascites resulting from cirrhosis and requiring ongoing treatment with diuretics and/or paracentesis.

8. Urinary protein is ≤1+ on dipstick or routine urinalysis (UA). If urine dipstick or routine analysis indicated proteinuria ≥2+, then a 24-hour urine must be collected and must demonstrate <1000 mg of protein in 24 hours to allow participation in the study.
9. Woman of child bearing potential (WOCBP) must have a negative urine or serum pregnancy test at screening AND within 72 hours of first dose of study medication.
10. Woman of childbearing potential (WOCBP) must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 180 days after last dose of chemotherapeutic agents.
    Note: Abstinence is acceptable if this is the established and preferred contraception.
11. Male subjects with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods throughout the trial starting with the screening visit through 180 days after the last dose of chemotherapy. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.
12. The participant has voluntarily agreed to participate by giving written informed consent for the trial.

6.2 Describe, in bullet points, the criteria that define who will be excluded from this study: **Response:** Participant will be excluded from the study if:

1. Participant has received prior cytotoxic therapy or targeted oral agents for the treatment of their stage IV NSCLC. Participants with oligo-metastatic stage IV disease who

received concurrent chemotherapy with thoracic radiation, followed by durvalumab consolidation with disease progression were eligible.

2. Participant has any known gene mutation as part of standard of care prior to study treatment.
3. Participant has undergone major surgery within 28 days prior to screening, or subcutaneous venous access device placement within 7 days prior to screening. Furthermore, any participant with postoperative bleeding complications or wound complications from a surgical procedure performed in the last 2 months will be excluded.
4. Participant has untreated CNS metastases. Participants 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 study treatment, or after surgical resection performed at least 28 days prior to screening. No evidence of Grade ≥1 CNS hemorrhage based on pretreatment MRI or IV contrast CT scan (performed within 21 days before screening).
5. There is radiologically documented evidence of major blood vessel invasion or encasement by cancer.
6. There is radiographic evidence of intra-tumor cavitation, regardless of tumor histology.
7. Participant has a history of uncontrolled hereditary or acquired thrombotic disorder.
8. Participant has a history of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months prior to screening.
9. Participant has clinically relevant congestive heart failure (CHF; NYHA II-IV) or symptomatic or poorly controlled cardiac arrhythmia.
10. Participant has experienced any arterial thrombotic event, including myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack, within 6 months prior to screening.
11. Participant has uncontrolled arterial hypertension ≥150 / ≥90 mm Hg despite standard medical management.
12. Participant has a serious or non-healing wound, ulcer, or bone fracture within 28 days prior to screening.
13. Participant has significant bleeding disorders, vasculitis, or experienced Grade 3-4 gastrointestinal (GI) bleeding within 3 months prior to screening.
14. History of GI perforation and/or fistulae within 6 months prior to screening.
15. Participant has bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection (hemicolectomy or extensive small intestine resection with chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.
16. Participant has peripheral neuropathy ≥Grade 2 (NCI-CTCAE v 4.0).
17. Participant has a serious illness or medical condition(s) including, but not limited to, the following:

- Known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related illness based on medical history.
- Active or uncontrolled clinically serious infection.
- Previous or concurrent malignancy except for basal or squamous cell skin cancer and/or in situ carcinoma of the cervix, or other solid tumors treated curatively and without evidence of recurrence for at least 3 years prior to screening.
- Uncontrolled metabolic disorders or other nonmalignant organ or systemic diseases or secondary effects of cancer that induced a high medical risk and/or made assessment of survival uncertain.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might increase the risk associated with study participation or study drug administration, or might interfere with the interpretation of study results, and in the judgment of the investigator made the patient ineligible for entry into this study.
- Participant has significant third-space fluid retention (for example, ascites or pleural effusion), and is not amenable for required repeated drainage.
- Known allergy or hypersensitivity reaction to any of the treatment components.
- Participant has a known history of active drug abuse.

6.3 Describe how individuals will be screened for eligibility. Upload all relevant screening documents with your submission (screening protocol, script, questionnaire). Identify who will certify that subjects meet eligibility requirements.

Response: Patients will be screened from the population of lung cancer patients seen by the co-PI's at the Stony Brook University Cancer Center.

6.4 Indicate whether you are specifically recruiting or targeting any of the following special populations in your study using the checkboxes below. (You will be asked for additional information in Section 7 if you check any of these boxes)

Response: N/A

☐ Adults unable to consent
☐ Minors (under 18 years old)
☐ Pregnant women
☐ Prisoners

6.5 Indicate if you will include minorities (American Indians, Alaskan Native, Asian, Native Hawaiian, Pacific Islander, Black [not of Hispanic origin] and Hispanic) as Federal mandates require that you include minorities unless you can justify their exclusion

Response:

☒ Yes

☐ No, Justify:

6.6 Indicate whether you will include non-English speaking individuals in your study. Provide justification if you will specifically exclude non-English speaking individuals. Review http://research.stonybrook.edu/human-subjects-standard-operating-procedures/policy-non-english-speakers-research-subjects for SBU policy on inclusion of non-English speakers. Upload any translated materials (consent, questionnaires, etc).

Response: Non-English speaking subjects will be included if, in the investigator's opinion, adequate translation resources are available to obtain informed consent

7.0 Vulnerable Populations

7.1 For research that involves pregnant women, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed

☒ N/A: This research does not involve pregnant women.

7.2 For research that involves neonates of uncertain viability or non-viable neonates, review, complete and upload Supplemental Form A: Pregnant Women, Fetuses, Non-Viable Neonates, or Neonates of Uncertain Viability.

☐ Confirmed

☒ N/A: This research does not involve non-viable neonates or neonates of uncertain viability.

7.3 For research that involves prisoners, review, complete and upload Supplemental Form H: Prisoners

☐ Confirmed

☒ N/A: This research does not involve prisoners.

7.4 For research that involves minors (under 18 years), review, complete and upload Supplemental Form F: Minors

☐ Confirmed

PROTOCOL TITLE: *Phase-II Trial of Platinum-Based Chemotherapy Plus Ramucirumab in Patients with advanced NSCLC who have Progressed on First line anti-PD-1 Immunotherapy*

☒ N/A: This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

7.5 For research that involves adults who cannot consent for themselves, you will be asked additional information in Section 25 ("Informed Consent")

☐ Confirmed

☒ N/A: This research does not involve this population

7.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.

Safeguards include:

☒ N/A

8.0 Eligibility Screening

8.1 Describe screening procedures for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.

📎 Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaires) as attachments.

Response: Patients will have had all relevant screening procedures as part of their "standard of care" evaluation for lung cancer.

☐ N/A: There is no screening as part of this protocol.

9.0 Recruitment Methods

☐ N/A: This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections, including date range for records that will be reviewed.

9.1 Describe source of subjects: When, where, and how potential subjects will be recruited.
NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. These may include, but are not limited to: ResearchMatch.org, physician referral, Office of Clinical Trials database, West Campus

departmental pools, reviewing medical charts, Research Participant Groups/help groups, ***advertising companies, call centers, in person announcements / presentations***

Response: Potential participants will be identified from the existing lung cancer patient population at the Stony Brook University Cancer Center by the Co-PI's.

9.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.
NOTE: Privacy refers to an individual's right to control access to him or herself. This is NOT asking about confidentiality of data.

Response: The study is introduced to patients during a clinic visit with the PI or sub-Is in a private setting, such as a consultation room. If the patient is interested, the study is explained.

9.3 Identify/describe any materials that will be used to screen/recruit subjects and upload copies of these documents with the application. They may include, but are not limited to Telephone scripts for calling, flyers, Questionnaires, Posters, Letters or written material to be sent or emailed, pamphlets, posted advertisements, email invitations.

Response: None

10.0 Research Procedures

Provide a detailed description of all research procedures or activities being performed on the research subjects. **This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research.** For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response. Be sure to include:

- Procedures being performed to monitor subjects for safety or to minimize risks.
- All drugs and devices used in the research and the purpose of their use, and their regulatory status

The treatments to be used in this trial are outlined below in Table 1. The choice of platinum doublet and the respective dose of each chemotherapeutic agent must be made at the screening visit. Pemetrexed is not permitted as a treatment for subjects with squamous histology.

TABLE 1.

Drug	Dose	Dose	Route of	Treatment

		frequency	**administration**	**regimen**
Carboplatin	AUC 5 or 6	Q3Wk	IV	Day 1 of each 21 day Cycle
Paclitaxel	200mg/m^2	Q3Wk	IV	Day 1 of each 21 day Cycle
Docetaxel	75 mg/m^2	Q3Wk	IV	Day 1 of each 21 day Cycle
Pemetrexed	500mg/m^2	Q3Wk	IV	Day 1 of each 21 day Cycle
Ramucirumab	10mg/kg	Q3Wk	IV	Day 1 of each 21 day Cycle

Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT3 receptor antagonist (type per investigator discretion and local standards-of-care). Additional use of antiemetic premedication may be employed at the discretion of the Investigator.

Premedication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, the day of, and the day after the administration of pemetrexed. Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered In the 7 days prior to the first dose. Oral folic acid should be continued daily throughout the treatment with pemetrexed and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be given approximately one week prior to the first dose of pemetrexed and repeated every 3 cycles thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Premedications for use with paclitaxel: Oral or IV corticosteroid should be given prior to paclitaxel according to local standard. Such premedication may consist of oral dexamethasone 20 mg, 12 hours and 6 hours prior to paclitaxel administration. Oral or IV diphenydramine 50 mg (or its equivalent) and an H2-blocker (per local standards) should be administered 30 to 60 minutes prior to paclitaxel infusion. All participants should be carefully monitored for infusion reactions during the paclitaxel administration. Participants should be treated in a facility with the necessary

medical-resuscitation equipment and medications on hand to manage serious acute infusion reactions.

Premedications for use with docetaxel:
All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

Growth factor prophylaxis: Primary prophylaxis for febrile neutropenia should be considered based on individual risk factors such as patients who have undergone radiation to a significant volume of blood-forming bone marrow (pelvis or spine), bone marrow involvement, liver or kidney dysfunction, age >65 receiving full intensity chemotherapy. Secondary prophylaxis is required for all subsequent cycles for subjects who experience grade 4 neutropenia or febrile neutropenia.

a. Dose Selection:
Carboplatin, paclitaxel, docetaxel, pemetrexed and ramucirumab will be prepared and administered as per the approved product label OR at prescribing investigators discretion within acceptable standard of care provisions +/- 10% of the calculated dose.

b. Dose modification:

Dose Delay: Dosing of both drugs in the platinum doublet chemotherapy regimen should be delayed for any of the following on the Day 1 of each cycle:

- Presence of febrile neutropenia or neutropenia < 1500 cells/mm3 for greater than one week despite the use of growth factors
- Any Grade ≥ 2 non-skin, drug-related adverse event, except for alopecia, fatigue or laboratory abnormalities
- Any Grade 3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay
  - Delay if total bilirubin >1x ULN or if AST and/or ALT > 1.5 x ULN occurs concomitant with alkaline phosphatase > 2.5x ULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants skipping the dose of study medication

A dose of chemotherapy given more than 3 days after the intended dose date will be considered a dose delay. A maximum delay of 8 weeks between doses is allowed.

Dose reductions:

Dose reductions of chemotherapy may be required, and will be performed according to Table 2. Chemotherapy dose reductions are permanent, once the dose of any chemotherapy agent is reduced, it may not be re-escalated in subsequent cycles, except as noted when starting pemetrexed maintenance therapy.

TABLE 2

Dose level	Carboplatin	Carboplatin	Paclitaxel	Docetaxel	Pemetrexed
Starting dose	AUC 5 or 6 with pemetrexed	AUC 6 with paclitaxel	200 mg/m2	75mg/m^2	500mg/m^2
First dose reduction	AUC 4 or 5 with pemetrexed	AUC 5 with paclitaxel	150 mg/m2	65mg/m^2	375mg/m^2
Second dose reduction	AUC 3 or 4 with pemetrexed	AUC 4 with paclitaxel	100 mg/m2	50mg/m^2	250mg/m^2
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

Dose modifications for Ramucirumab:

Dose modifications were permitted for ramucirumab in the setting of non-life-threatening, reversible Grade 3 AEs i.e (fatigue, anorexia, or Grade 3 or 4 fever) that resolved to Grade ≤ 1 within one treatment cycle (approximately three weeks). In this setting, investigational product could be re-administered.

If a second instance of such an event occurred, ramucirumab was subsequently re-administered at a dose of 8mg/kg every 3 weeks.

A second dose reduction to 6 mg/kg every 3 weeks was permitted for this level of event (non-life-threatening, reversible Grade 3 event). If the dose of ramucirumab was reduced because of potentially related AEs, subsequent dose increases were not permitted.

Infusion-Related Reactions (IRR):

- Reduce the infusion rate of ramucriumab by 50% for Grade 1 or 2 IRRs.
- Permanently discontinue ramucriumab for Grade 3 or 4 IRRs

Hypertension:

- Interrupt ramucriumab for severe hypertension until controlled with medical management.
- Permanently discontinue ramucriumab for severe hypertension that cannot be controlled with antihypertensive therapy.

Proteinuria

• Interrupt ramucriumab for urine protein levels ≥2 g/24 hours. Reinitiate treatment at a reduced dose of 8 mg/kg every 2 weeks 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 to 6 mg/kg every 2 weeks once the urine protein level returns to <2 g/24 hours.

- Permanently discontinue ramucirumab for urine protein level >3 g/24 hours or in the setting of nephrotic syndrome.

Permanently discontinue ramucirumab for Arterial Thromboembolic Events, Gastrointestinal Perforation, or Grade 3 or 4 Bleeding.

Dose Modifications Not Related to Toxicity:
The prescribing investigator may make dose adjustments for non-toxicity reasons (ex: weight, medical history) within acceptable standard of care provisions +/- 10% of the calculated dose.

Recommended Chemotherapy Dose Reductions for Hematologic Toxicity:

TABLE 3

Toxicity	Carboplatin	Paclitaxel	Docetaxel	Pemetrexed
Neutrophils Count Decreased				
Grade 4 (<500/mm3 or < 0.5 x 109/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Platelet count Decreased				
Grade 3 (25,000 - <50,000/mm3; 25.0 < 50.0 x 109/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level
Grade 4 (<25,000/mm3; < 25.0 x 109/L)	Reduce one dose level	Reduce one dose level	Reduce one dose level	Reduce one dose level

Recommended Chemotherapy Dose Reductions for Non- Hematologic Toxicity:

TABLE 4

Toxicity	Carboplatin	Paclitaxel	Docetaxel	Pemetrexed
Febrile	Reduce one	Reduce one	Reduce one	Reduce one

neutropenia Grade>3	dose level	dose level	dose level	dose level
Neuropathy Grade 2	No change	Reduce one dose level	Reduce one dose level	No change
Neuropathy Grade 3	Discontinue	Discontinue	Discontinue	Discontinue
Other Grade 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

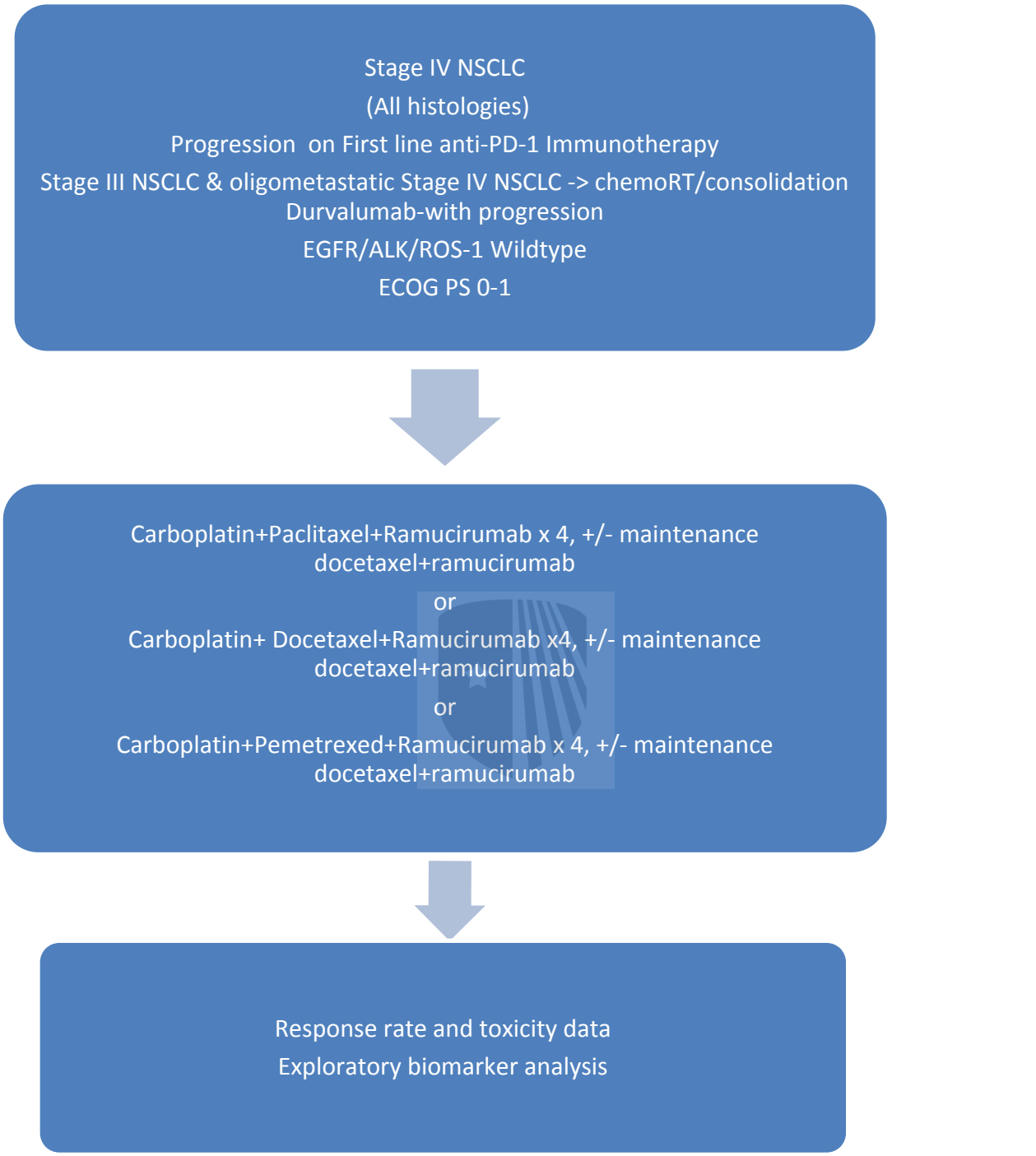
Criteria to Resume Treatment with Chemotherapy

- Participants may resume treatment with chemotherapy when the ANC returns to 1500/µl, the platelet count returns to 100,000/mm3, and all other drug-related toxicities have returned to baseline or Grade 1 (or Grade 2 for alopecia and fatigue).
- If a participant fails to meet criteria for re-treatment, then re-treatment should be delayed, and the participant should be re-evaluated weekly or more frequently as clinically indicated. Any participant who fails to recover from toxicity attributable to chemotherapy to baseline or Grade 1 (except Grade 2 alopecia and fatigue) within 8 weeks from the last dose given should discontinue the drug(s) that caused the delay.

c. Maintenance treatment:

Subjects who respond to 4 cycles of the initial regimen and maintain a good performance status with minimal toxicity, will receive maintenance therapy with Docetaxel 75mg/m^2 and Ramucirumab 10 mg/kg Q3W until disease progression or unacceptable toxicity.

Study Schema:



10.1 Describe what data, including long-term follow-up, will be collected.
NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.

PROTOCOL TITLE: *Phase-II Trial of Platinum-Based Chemotherapy Plus Ramucirumab in Patients with advanced NSCLC who have Progressed on First line anti-PD-1 Immunotherapy*

Response: TRIAL FLOW CHART

	Screen (Visit 1)	**Treatment Cycle**					**End of Treatment Phase**		**Follow up[a]**
Treatment Cycle	-42 to -1 day	1	2	3	4	Maintenance every 3 weeks	Discontinuation Visit	Safety Follow Up Visit	
Scheduling window (days)		+/7	+/7	+/7	+/7	+/7	At study Drug Discontinuation +/-7	30 days from Last Dose +/-7	
Administrative procedures									
Informed Consent	x								
Inclusion/ Exclusion Criteria	x								
Demographics and Medical History	x								
Review Prior and Concomitant Medications	x	x	x	x	x	x	x	x	
NSCLC Disease Details and Prior Treatment	x								
Survival Status								x	
Clinical Procedures /Assessments									
Review Adverse Events	x	x	x	x	x	x	x	x	
Full Physical Examination (progress note)	x						x		
Directed Physical Examination (progress note)		x	x	x	x	x		x	
	Screen (Visit 1)	**Treatment Cycle**					**End of Treatment Phase**		

Treatment Cycle	-42 to -1 day	1	2	3	4	Maintenance every 3 weeks	Discontinuation Visit	Safety Follow Up Visit	
Scheduling window (days)		+/7	+/7	+/7	+/7	+/7	At study Drug Discontinuation +/-7	30 days from Last Dose +/-7	
Clinical Procedures /Assessments (continued)									
Vital Signs including Height (only at screening) and Weight	x	x	x	x	x	x	x	x	
ECG	x								
ECOG Performance Status	x	x	x	x	x	x	x	x	
Laboratory Procedures/Assessments									
Pregnancy test urine or serum HCG	x	x	x	x	x	x	x	x	
PT/INR and aPTT	x								
CBC with Differential[#]	x	x	x	x	x	x	x	x	
Comprehensive Chemistry Panel	x	x	x	x	x	x	x	x	
Urinalysis for protein[#]	X[*#]		x		x		x	x	
[***#]No known mutation as part of SOC prior to study treatment	x								
Peripheral Blood Biomarkers		x	x	x	x	x	x	x	
Efficacy Measurements									
Tumor Imaging[***#]	x			x		x	x	x	
Brain Imaging	x								

[#]cbc/diff will be monitored for nadir counts between 10-12 days of each cycle. If ANC <1000 then cbc/diff will be monitored weekly until ANC recovered.

[*#]If screen urine protein ≥2+ a 24 hour urine must be collected and results must be <1000 mg of protein for study participation.

[*#]Mutation Testing must be performed as standard of care prior to first treatment cycle[***#]Baseline tumor assessment within 28 days of study enrollment. During maintenance subsequent tumor assessments will be every 6 weeks (+/-1 week) up to 24 weeks, then every 12 weeks until disease progression**

a After the safety follow up patients will be followed via a phone call every 3 months.

Study assessments at screening: As routine medical care

- Medical history including demographics (race, ethnicity, age, etc.)
- Review concomitant medication use
- Vital signs (Blood pressure, temperature, pulse and pulse oximetry)
- Height (screening only) and weight
- Laboratory testing at baseline: CBC/differential, LFT (AST,ALT, total bilirubin, alkaline phosphatase, Chemistry panel (BUN, Creatinine, Na, K, Cl, glucose)
- Urine analysis for protein
- ECOG PS
- Electrocardiogram
- A urine or serum pregnancy test is required for females subjects of child bearing potential AND within 72 hours of first dose of study medication
- Baseline tumor assessment within 28 days of study enrollment

Study assessments during protocol treatment: As routine medical care

- Focused medical history and directed physical exam
- Review concomitant medication use
- Vital signs (Blood pressure, temperature, pulse and pulse oximetry)
- Weight
- Laboratory testing prior to each dose: CBC/differential, LFT(AST,ALT, total bilirubin, alkaline phosphatase, Chemistry panel (BUN, Creatinine, Na, K, Cl, glucose)
- ECOG PS
- Tumor assessments: First tumor assessment will be performed at 6 weeks (+/-1 week) following screening. During maintenance subsequent tumor assessments will be every 6 weeks (+/-1 week) up to 24 weeks, then every 12 weeks until disease progression
- About 10 ml of extra peripheral blood will be collected for research related biomarker analysis

Biomarker Analysis

- Cytokines will be measured by Luminex bead-based elisa, using the Genomics core facility.
- Carbonic anhydrase IX will be measured by widely used enzyme-linked immunosorbent assays (ELISA) kit in the Pathology department.

List, and upload, any instruments or measurement tools used to collect data (e.g. survey, scripts, questionnaire, interview guide, validated instrument, data collection form).

Response: N/A

10.2 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records) and include the date range for records that will be accessed.

Response: Electronic medical records will be accessed from initial presentation until death or withdrawal of informed consent.

10.3 Indicate whether or not the results for individual subjects, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.

Response: Results for individual subjects will not be shared with others unless, in the opinion of the treating physician/PI such results are critical to the appropriate medical care of the subject.

10.4 Indicate whether or not generalized study results will be shared with subjects or others, and if so, describe how these will be shared.

Response: Once tabulated and de-identified, study results will be shared with subject at their request, and study results may be published in peer-reviewed publications and/or presented at scientific conferences.

11.0 Study Timelines

11.1 Describe the anticipated duration of the study needed to enroll all study subjects.

Response: We hope to complete enrollment in a period of two years.

11.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.

Response: Total length of time on the study, including the screening, study treatment, and follow-up periods, will vary depending on how the treatment works but is expected to be about 1 year

11.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).

Response: 5 years

12.0 Research Setting

12.1 Describe all facilities/sites/locations where you will be screening and conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.

Example: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Stony Brook University Hospital, a fully accredited tertiary care institution within New York State with badge access,"

Response: The Stony Brook University Cancer Center is an ambulatory evaluation and treatment center which provides a full range of services for cancer patients and others.

12.2 For research procedures being conducted, for this study, external to SBU and its affiliates (e.g., in schools, out-of-state, internationally, etc.) describe:

- *Site-specific regulations or customs affecting the research*
- *The composition and involvement of any community advisory board*
- *Local scientific and ethical review structure outside the organization.*
- *Local issues affecting the research and rights of research subjects.*

NOTE: This question is not referring to multi-center research. If this research is being conducted internationally, Supplemental Form C must be completed and uploaded.

Response:

☒ N/A: This study is not conducted outside of SBU or its affiliates.

13.0 Resources and Qualifications

13.1 The Principal Investigator (PI) must confirm, in consultation with Chair and Dean as applicable, that adequate resources are present to conduct and complete the study compliantly and safely. Specifically:

☐ **NO** ☒**YES** *The proposed subject population(s) are available in sufficient numbers to meet the study requirements*

☐ **NO** ☒**YES** *Sufficient funds are available to conduct and complete the study compliantly and safely*

☐ **NO** ☒**YES** *The PI and study team have sufficient time to conduct and complete the study compliantly and safely*

☐ **NO** ☒**YES** *The PI has determined that the named study team is qualified to conduct the research compliantly and to monitor the safety and welfare of the enrolled research subjects effectively.*

☐ **NO** ☒**YES** *The PI ensures that the study team is fully aware of his/her involvement in this study and the details of the study protocol*

☐ **NO** ☒**YES** *The PI ensures that the study teams will only be involved in research procedures for which they have been trained, and are currently certified and/or licensed, if required..*

13.2 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable. (e.g, "on-call availability of a counselor or psychologist for a study that screens subjects for depression").

Response: An oncology attending is on call to respond to medical problems 24 hours a day, 7 days a week.

13.3 Describe your process to ensure that all study team members are updated on the progress of the research and the regulatory requirements (including enrolled subjects, unanticipated problems etc.)

Response: The study team meets regularly on a monthly basis as part of the Thoracic Oncology Clinical Research Team (CRT), at which time the status of all prospective and enrolled patients is reviewed.

14.0 Other Approvals

14. List approvals that will be obtained prior to commencing the research (e.g., University Hospital sign-offs per the UH Application, Cancer Center Scientific review, school, external site, funding agency, laboratory, Radiation Safety, IBC, SCRO, IACUC, RDRC).

Response: CRT, RAFTR, Cancer Center PRMC, Radiology, University Hospital, Privacy Officer, Security Officer, Department Chair.

☐ N/A: This study does not require any other approvals.

15.0 Provisions to Protect the Privacy Interests of Subjects

15.1 Describe how you will protect subjects' privacy interests during the course of this research and any steps you will take to make the subject feel at ease.
NOTE: Privacy refers to an individual's desire/right to control access to or to place limits on whom they interact with or whom they provide personal information. Privacy

applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.
Examples of appropriate responses include: "participant only meets with a study coordinator in a private office setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."

Response: Participants only meets with the PI/Sub-Is and/or study coordinator in a private office setting where no one can overhear

16.0 Data Management and Analysis

16.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.

Response: Up to 25 evaluable participants will be recruited for two years. Seven patients will be recruited at the first stage. Initial response assessment will be done after 2 cycles of treatment. If zero or one patient responds to the treatment at the end of the first stage, the study will stop early for futility. If the number of responders is two or more, the study will continue recruiting to the second stage. If six or fewer responders are observed by the end of stage two, then no further investigation of the treatment is warranted. The probability of early stop will be 72% if the true response rate is lower than 10%. If three or more, grade 3 non-hematologic toxicities are observed in the first 7 patients, the study will stop early due to high toxicity.

Expected toxicities include myelosuppression, alopecia, nausea, vomiting, fatigue, neurotoxicity, and thrombotic or hemorrhagic events. In previous studies with ramucirumab, only grade 3-4 neutropenia was seen in a significant proportion of patients up to 40%. Incidence of grade 3-4 febrile neutropenia was also higher in the ramucirumab group 16% versus 10%. There was no other grade 3-4 toxicity with a frequency of greater than 10% [6].

For primary objectives, binomial exact tests will be used to compare response rate and toxicity to historical response rates and toxicity, as reported in the literature for similar treatment regimens. Specifically data for patients treated with paclitaxel, carboplatin and bevacizumab in the first line setting (the ECOG 4599 and PointBreak trials) and in those treated with docetaxel and ramucirumab in the second line setting (the REVEL trial) will be used for comparison[3, 6, 16].

The exploratory analysis is mainly descriptive and non-parametric methods will be used for the small sample size and possible normality violation. Immune cell cytokines and AEC will be measured at baseline and every treatment cycle. Additionally, if one patient is a responder, those outcomes will be measured every three weeks during maintenance. A non-responder may have a

minimum of three measures (baseline + 2 treatment cycles) and a responder may have more than 30 measures over 6 months of follow-up.

Descriptive statistics (e.g. mean, sd, median and etc) will be presented for baseline, available treatment cycles, and for follow-up for responders. If the study stops early due to futility, there will be no comparison group. Due to the small sample size (n=7), a non-parametric Friedman test will be used to compare the outcomes over time.

If the respond rate is 40% under the alternative hypothesis (10 vs 15), Wilcoxon rank sum test will be used to compare changes in outcomes between responders and non-responders. In addition, Wilcoxon rank sum test will be used to compare plasma carbonic anhydrase IX level between responders and non-responders. For the exploratory purpose, p value will not be adjusted for multiple tests in order to show trends.

16.2 If applicable, provide a power analysis.
NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.

Response: We plan to use a Simon's two-stage design to test the efficacy for this study. If a response rate lower than 15% is a failure and a response rate over 40% is promising, we will need a sample size up to 25 for 80% power and 5% alpha using the Simon's two-stage optimum method

17.0 Confidentiality

A. Confidentiality/Security of Study Data

Describe the local procedures for maintenance of security and confidentiality of **study data and any records that will be reviewed for data collection.**

17.1 Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, certificates of confidentiality, and separation of identifiers and data, as applicable. Include physical (e.g. paper) and electronic files.

Response: Data will be entered into a password protected study site database. The data access will be password-protected and role-based. The Principal Investigator and Co-PI will ensure the accuracy, completeness, legibility and timeliness of the data reported in CRF.

17.2 How long will the data be stored?

Response: For a period of 6 years after completion of all study-related treatment by the last patient enrolled.

17.3 Who will have access to the data?

Response: The Principal Investigators and the study personnel

17.4 Who is responsible for receipt or transmission of the data?

Response: The Principal Investigators and the study personnel

17.5 How will the data be transported/transmitted?

Response: Data will be stored in a password protected electronic database used by the CCCTO as well as paper shadow charts that are stored in a locked records room.

B. Confidentiality of Study Specimens

Describe the local procedures for maintenance of confidentiality of study specimens.

☐ **N/A:** No specimens will be collected or analyzed in this research.
(Skip to Section 18.0)

17.6 Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.

Response:
Blood will be collected for biomarker analysis but will not be stored for future research.

17.7 How long will the specimens be stored?

Response: The blood samples will be stored until biomarker analysis completed and study results have been reported

17.8 Who will have access to the specimens?

Response: The PI, sub-investigators and study personnel

17.9 Who is responsible for receipt or transmission of the specimens?

Response: The PI, sub-investigators and approved study coordinators.

17.10 How will the specimens be transported?

Response:
The specimens will be transported in biohazard bags to the pathology department by the CCTO staff

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

☐ **N/A:** This study is not enrolling subjects OR is limited to records review procedures only OR is a minimal risk study

18.1 Describe the plan to evaluate the data periodically regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

Response: All Investigator-Initiated studies require continuous monitoring by the PI of the study. However, the determination of how often a study will be reviewed at a DSMC meeting is dependent of its level of risk that was assigned by the Protocol Review & Monitoring Committee (PRMC).

Level of Risk	**Frequency of DSMC Review**
Low Risk	Once a year
Moderate Risk	Every 6 months
High Risk	Quarterly

The PI is ultimately responsible for monitoring compliance at all participating sites and has the authority to suspend and/or close a participating site based on lack of compliance.

Cancer-related Stony Brook investigator-initiated studies will adhere to the policies and processes described in the SBCC DSMP, and the Stony Brook DSMC will serve as the protocol's DSMC unless an external DSMB is approved by the PRMC. These trials are subject to quarterly auditing by the Stony Brook QIU and the SBCC DSMC will require copies of external DSMB monitoring reports.

All investigator-initiated interventional therapeutic studies are audited by an external independent quality assurance audit or once they have achieved ten percent of target accrual. The audit will be conducted in accordance with internal policies and the NCI Clinical Trials Monitoring Branch audit guidelines to ensure the accuracy of data, adherence to the protocol and the protection of human subjects.

18.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response:
Safety data, AE/SAEs, efficacy, procedure compliance, case records etc.

18.3 Describe any primary or secondary safety endpoints.

Response:
N/A

18.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: The safety information will be collected by the PI at study visit and tabulated in case report forms, adverse event log. etc

18.5 Describe the frequency of safety data collection, including when safety data collection starts.

Response:
Once they have achieved ten percent of target accrual.

18.6 Describe who will review the safety data.

Response:
The PI and DSMC if applicable

18.7 Describe the frequency or periodicity of review of cumulative safety data.

Response:
The PI will review the cumulative safety data at each study visit .DSMC will review the safety data every 6months

18.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: We plan to use a Simon's two-stage design to test the efficacy for this study. If a response rate lower than 15% is a failure and a response rate over 40% is promising, we will need a sample size up to 25 for 80% power and 5% alpha using the Simon's two-stage optimum method. Up to 25 evaluable participants will be recruited for two years. Seven patients will be recruited at the first stage. Initial response assessment will be done after 2 cycles of treatment. If zero or one patient responds to the treatment at the end of the first stage, the study will stop early for futility. If three or more, grade 3 non-hematologic toxicities are observed in the first 7 patients, the study will stop early due to high toxicity.

18.9 Describe any conditions that trigger an immediate suspension of the research.

Response:

19.0 Withdrawal of Subjects

☐ N/A: This study is not enrolling subjects. This section does not apply.

19.1 Describe anticipated circumstances under which subjects may be withdrawn from the research without their consent.

Response: A subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative, the study doctor decide that the study participant is no longer benefiting from treatment, the study participant failed to adequately follow instructions or procedures, the study participant needs treatment that is not allowed by the study, the study has been cancelled, and/or other safety reasons. Disease progression by RECIST 1.1 as determined by Stony Brook Radiologist unless the subject is considered to be deriving clinical benefit by the investigator and is clinically stable.

19.2 Describe any procedures for orderly termination.
NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.

Response: In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Discontinuation from treatment is permanent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin treatment again.

19.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.

Response: If a study participant withdraws, the data already collected will be retained for data analysis.

19.4 Describe what will happen to data already collected.

Response: The data will be used for data analysis.

20.0 Risks to Subjects

20.1 In your opinion, what is the overall risk (physical and nonphysical) to research subjects in this study (minimal, greater than minimal or unknown)

Response: This trial has been designated as a medium risk study. Medium risk studies are intended to include all trials involving therapeutic intervention(s), which are not designated as high risk per NCI and the IND is not held by the investigator

20.2 Describe if any subjects are withdrawn from therapeutic procedures or drugs (e.g., washout periods) prior to, or during, their participation in the study.

Response: N/A

20.3 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.
NOTE: Breach of confidentiality is always a risk for identifiable subject data.

Response: Study participants may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Many side effects go away soon after the study participant stops what is causing them. In some cases, side effects can be serious and may be long lasting or may never go away. There also is a rare risk of death.
Expected toxicities include myelosuppression, alopecia, nausea, vomiting, fatigue, neurotoxicity, and thrombotic or hemorrhagic events. The toxicity profile varied based on the platinum-doublet chemotherapy regimen used. More grade 3 or 4 anemia (14.5% *v* 2.7%), thrombocytopenia (23.3% *v* 5.6%) and fatigue (10.9% *v* 5.0%) occured with pemetrexed containing regimen. Whereas, more grade 3 or 4 neutropenia (40.6% *v* 25.8%) , febrile neutropenia, (4.1% *v* 1.4%) sensory neuropathy (4.1% *v* 0%), and alopecia (grade 1 or 2; 36.8% *v* 6.6%) occurred with taxane-based regimen [16]. In previous studies with ramucirumab, only grade 3-4 neutropenia was seen in a significant proportion of patients up to 40%. Incidence of grade 3-4 febrile neutropenia was also higher in the ramucirumab group 16% versus 10%. Hypertension (any grade 11 % *v* 5%), and bleeding(any grade 29 % *v* 15%) were more common with ramucirumab There was no other grade 3-4 toxicity with a frequency of greater than 10% [6]

There may be risks associated with breach of confidentiality, which are the same as those associated with breach of confidentiality of any medical information.

20.4 Describe procedures performed to minimize the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.

Response: Patients will be monitored by their treating physician (who will be one of the Co-PI's) on a regular basis to assess for toxicities, as per the study schema.

20.5 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Response: Treatment with any chemotherapeutic agent has inherent risks, both foreseen and unforeseeable. Study participants may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Many side effects go away soon after the study participant stops what is causing them. In some cases, side effects can be serious and may be long lasting or may never go away. There also is a rare risk of death.

20.6 Indicate which research procedures, if any, may have risks to an embryo or fetus should the subject be or become pregnant.

Response: All anti-cancer treatment carries some degree of risk to an embryo or fetus, and therefore pregnancy is an exclusion criterion, and subjects must agree to use two adequate barrier methods of contraception throughout the trial starting with the screening visit through 180 days after last dose of chemotherapeutic agents.

☐ **N/A**

20.7 If you responded to 20.6 that there are such risks, how will you minimize the risk of a pregnancy occurring during the course of the study? (Select all that apply)

☐ Counseling on birth control and /or abstinence

☐ Pregnancy test during the study

☐ Pregnancy test prior to initiation of the study

☒ Other pregnancy is an exclusion criterion, and subjects must agree to use two adequate barrier methods of contraception throughout the trial.

☐ **N/A**

20.8 If applicable, describe possible risks to others who are not subjects.

Response: N/A

21.0 Potential Benefits to Subjects

21.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits.

Response: Currently there is no defined optimal treatment for patients who have progressed on primary immunotherapy, and there is lack of data on response rates to cytotoxic chemotherapy and anti-angiogenic agents after progression on immunotherapy. This trial would help address those important clinical questions, and could potentially result in control of the patient's cancer for a longer period of time than other treatment schemas currently in use.

21.2 Indicate if there is no direct benefit.
NOTE: Compensation cannot be stated as a benefit.

Response:

There is no direct benefit expected as a result of being in this study, but participating in the study may or may not cause health improvement in study participants.

Indicate if there is a potential benefit to others, future science or society.

Response: If promising results are seen, it could form the basis for a multi-institutional study comparing single agent therapy to platinum based doublets, +/- ramucirumab. This could potentially impact the care of all patients with metastatic non-small cell lung cancer.

22.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury. This section does not apply.

22.1 If the research procedures carry a risk of research related injury, describe the available compensation to subjects in the event that such injury should occur.

Response: There is no direct benefit expected as a result of being in this study, but participating in the study may or may not cause health improvement in study participants.

22.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.
NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with different language regarding

research related injury, you must modify your response here and submit an amendment to the IRB for review and approval.

Response: N/A

23.0 Economic Burden to Subjects

23.1 Describe any costs that subjects may be responsible for because of participation in the research.
NOTE: Some examples include transportation or parking.

Response: The study participant and his/her health plan will be billed for the routine cost of medical care provided during this study. The study participant and his/her health plan will need to pay for medicines and clinic, hospital and doctors services that are part of your regular medical care.

All procedures that are required only for this study, and that are not part of regular medical care will be provided to the study participant at no charge. This includes the extra blood sample (approximately 2 tablespoons) drawn at screening and prior to each cycle for study related analysis.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

24.0 Compensation for Participation

☒ **N/A:** There is no compensation for participation. This section does not apply.

24.1 Describe the amount/nature and timing/scheduling of any compensation to subjects, including monetary, course credit, or gift card compensation. Describe any prorated payments based on participation.

Response:

24.2 Justify the amount and scheduling of payments described above to ensure that they are reasonable and commensurate with the expected contributions of the participant. If multiple visits are involved payments should be prorated.
Note: If using West Campus Departmental pools, participation in studies may be offered for credit in class but students MUST be given other options for fulfilling the research component that are comparable in terms of time, effort, and education benefit. Please list alternative activities

Response:

N/A

25.0 Informed Consent

25.1 Will you be obtaining consent from subjects?

☒ ***Yes*** *(If yes, Provide responses to each question in this Section, and upload your consent documents where indicated in the electronic submission system)*

☐ ***No*** *(If no, Skip to next section)*

25.2 Describe how the capacity to consent will be assessed for all subjects. Review for guidance http://research.stonybrook.edu/human-subjects-standard-operating-procedures/determining-potential-adult-subjects-ability-consent:

Response:

25.3 Describe the consent process that will be conducted to ensure that subject is fully informed regarding study details and subject rights. Include where the consent process will take place, with consideration of the need to protect the subject's right to privacy. Investigators or the study coordinators must:

• Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
• Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
• Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
• Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
• Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.
• Protect the confidentiality of the subject's records, respect the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

25.4 Describe how you will ensure that subjects are provided with sufficient time to consider taking part in the research study. Detail if there is there any time period expected between informing the prospective subject and obtaining the consent.
NOTE: It is respectful to the prospective subject to ensure that sufficient time is given to have their questions answered and to consider their participation

Response: After the PI/Sub-I/study coordinator explains the study the patient is asked if they have any questions; if they need to think about whether they would like to participate or not; and asked if he/she would like to take the consent form home to discuss with family or friends before agreeing to participate or not. The patient is given the study personnel's phone number to call with any questions. The study personnel also explain that participation is voluntary and that their participation or choosing not to participate will not affect their care. It is also explained that he/she can choose to withdraw at any time.

25.5 Describe the process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.

Response: The study personnel review the study activities at each visit and the study participant is asked if he/she has any questions. The study participants are reminded that the investigator's and study coordinator's can be contacted by phone at anytime if any questions arise and the contact information is given to the study participant if needed.

Non-English Speaking Subjects

☐ *N/A: This study will not enroll Non-English speaking subjects.*

25.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: Patients who do not speak English will not be excluded. An amendment to use a short form will be submitted for review then the long consent form will be translated into the study participant's (patient's) language to re-consent.

25.7 If subjects who do not speak English will be enrolled, describe the process to consent the subjects, as well as the process to be used to ensure their understanding of research procedures throughout the conduct of the study. Review SOP's section 17.8 for important policies in this regard: http://research.stonybrook.edu/human-subjects-standard-operating-procedures/policy-non-english-speakers-research-subjects for SBU policy on inclusion of non-English speakers.

Response:

1. The oral presentation will either conducted by either a study investigator who certifies to the IRB that she/he is fluent in English and the language of the subject, or a study investigator who is assisted by either a qualified translator unrelated to the study, or a recognized interpreter service, and
2. There will be a witness to the oral presentation who is fluent in both English and the language of the subject. Note: If an unaffiliated, qualified interpreter or service is used in the oral presentation as above, that individual may serve as the witness, to a family member may not serve as the witness, and
3. The IRB must approve a written summary of what is to be read to the subject.
Note: the IRB approved English consent form will serve as the summary, and
4. The witness will sign both the short form and a copy of the summary; and
5. The person actually obtaining consent must sign a copy of the summary; and
6. A copy of the summary will be given to the subject or representative, in addition to a copy of the short form.

Adults Unable to Consent

☒ **N/A:** This study will not enroll adults unable to consent.

25.8 Justify why it is necessary to include adult subjects who are unable to consent.

Response:

25.9 Describe how you will identify Legally Authorized Representatives (LAR) for the subjects that will be consistent with the NYS Family Health Care Decisions Act (FHCDA; see http://research.stonybrook.edu/human-subjects-standard-operating-procedures/definitions-2). Indicate why it is necessary to include subjects who are unable to consent.
Note: For research conducted outside of New York State, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research.

Response:
N/A

25.10 Describe the process for obtaining assent from the adult subjects
Indicate whether assent will be obtained from all, some, or none of the subjects. If some, indicate which adults will be required to assent and which will not.

Response:
N/A

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Response:
N/A

25.11 Describe whether assent of the adult subjects will be documented and the process to document assent.

Response:
N/A

25.12 Describe how you will obtain consent from a subject to use their data if they later become capable of consent. How will competence be assessed and by whom?

Response:
N/A

26.0 Waiver or Alteration of Consent Process

Complete this section if:

- Informed consent will not be obtained at all
- Informed consent will be obtained, but not documented, or
- consent will be obtained, but not all required information will be disclosed (e.g., in deception research)

☒ **N/A:** A waiver or alteration of consent is not being requested.

26.1 Review, complete, and upload SUPPLEMENTAL FORM G: Consent Waivers

☐ Confirmed

26.2 If the research involves a waiver of the consent process for planned emergency research, please contact the Office of Research Compliance for guidance regarding assistance in complying with federal regulations governing this activity (see: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24)

27.0 Multi-Site Research (Multisite/Multicenter Only)

☒ **N/A:** This study is not an investigator-initiated, multi-site study. This section does not apply.

27.1 If this is a multi-site study where SBU is the lead site and/or the IRB of record, describe the processes to ensure communication among sites. Include:

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*

- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

27.2 Describe the method for communicating to engaged participating sites:

- *Problems*
- *Interim results*
- *Study closure*

Response:

*27.3 Indicate and statistically justify the total number of subjects that will be enrolled or records that will be reviewed **across all sites**.*

Response:

28.0 Banking Data or Specimens for Future Unspecified Use

☒ **N/A:** This study is not storing data or specimens for research outside the scope of the present protocol. This section does not apply.

IMPORTANT: If you are proposing to bank specimens for future use, you may be subject to licensure requirements under the NYS Department of Health, and must be covered under the SBU license. See SOPs at http://research.stonybrook.edu/human-subjects-standard-operating-procedures/data-tissue-registries-banks

28.1 If data will be banked for research outside of the scope of the present protocol, describe where the data will be stored, how long they will be stored, how will they be accessed, and who will have access to the data
NOTE: Your response here must be consistent with the information provided to subjects in your Consent Documents

Response:

28.2 If specimens will be banked (stored) for research outside of the scope of the present protocol, describe where the specimens will be stored, how long they will be

stored, identifiers that will be associated with each specimen, how will they be accessed, and who will have access to the specimens

NOTE: Your response here must be consistent with the information provided to subjects in your
Consent Documents

Response:

28.3 Describe the procedures to release banked data and/or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response:

29.0 Drugs and Devices

☐ **N/A:** This study does not involve drugs or devices. This section does not apply.

29.1 Does this study involve use of radiopharmaceuticals? ☐ Yes ☒ No

29.2 For investigational devices (including marketed devices being used off label), Provide the following information below:
Where will the device(s) be stored? Note that the storage area must be within an area under the PI's control
Describe the security of the storage unit/facility
Provide full detail regarding how the dispensing of the device(s) will be controlled (accountability of removal/return of used devices, and disposition of remaining devices at the conclusion of the investigation) and documented (accounting records/logs)

Response:

29.3 For investigational drugs (including marketed drugs being used off label), will the services of the Investigational Drug Pharmacy be used for storage, dispensing, accounting the drug (required for research conducted at UH, HSC, Cancer Center, and Ambulatory Surgery Center)?

☒ **Yes**

☐ **No** →PI Provide the following information below:

- *Where will the drugs/biologics be stored? Note that the storage area must be within an area under the PI's control*

- *Describe the security of the storage unit/facility:*
- *Provide full detail regarding dispensing of the drugs(s), how labeled, controlled (accountability, disposition of unused drug at the conclusion of the investigation) and documented (accounting records/logs):*

Response: N/A- All drugs being used are FDA approved

30.0 Sharing of Results with Subjects

30.1 Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response: