SPONSOR CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Title

A phase II study of PCSK9 inhibitor Alirocumab and PD-1 inhibitor Cemiplimab in patients with metastatic, refractory to prior anti PD-1 non-small cell lung cancer (NSCLC)

Study Description

Preclinical models have shown that PCSK9 mediates immune checkpoint blockade resistance by downregulating tumor cell surface MHC class 1 molecules. This study will evaluate if combining the anti-PCSK9 antibody alirocumab with the anti-PD-1 antibody cemiplimab can generate anti-tumor activity and clinical responses in patients with metastatic lung cancer who have progressed on first line immune checkpoint blockade therapy.

Primary Objective

To assess the clinical activity (response rate) of alirocumab in combination with cemiplimab

Study Population

Patients with metastatic NSCLC after progression on frontline immune checkpoint blockade therapy.

Number of Subjects

60

Study Intervention

Alirocumab and cemiplimab

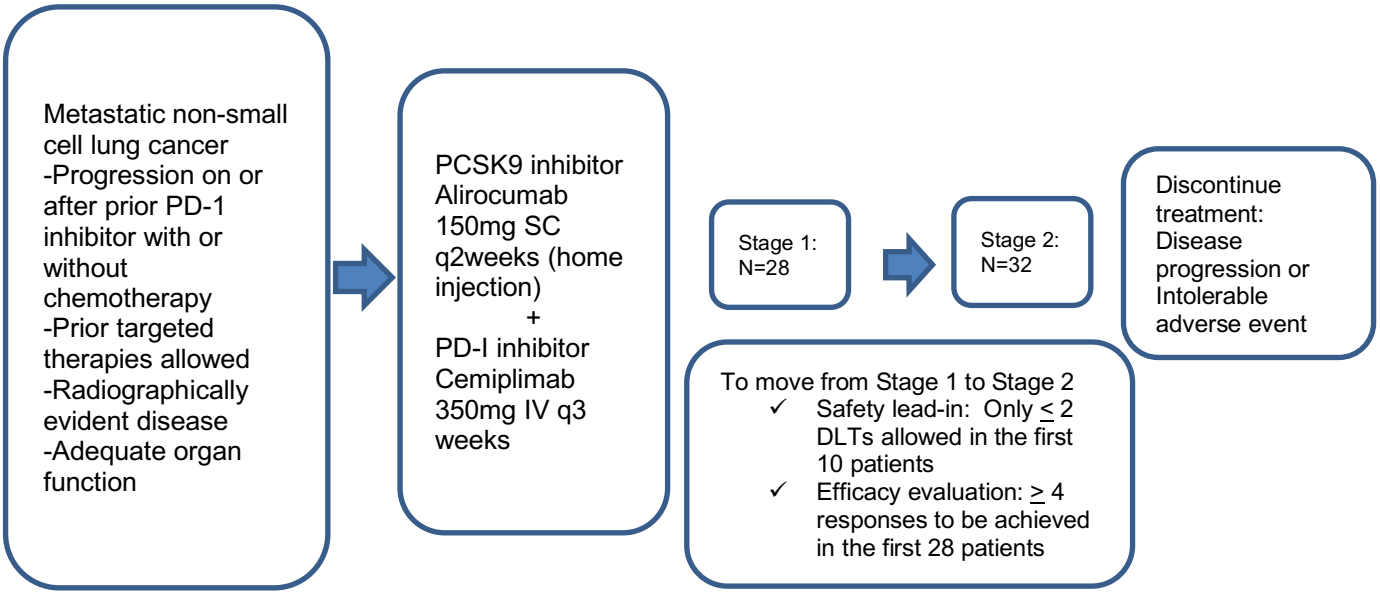
Duration of Subject Participation

Up to two years of therapy, or until disease progression

Duration of Study

6 years, 3.0 years of enrollment with potential for 3.0 years of patient follow up

STUDY SCHEMA



SCHEDULE OF EVENTS

Cycle = 6 weeks	Screening [A]	Cycle 1 Day 1	Cycle 1 Day 22	Cycle 2+ Day 1	Cycle 2 + Day 22	Restaging	End of Treatment Follow-Up	Long Term Follow-Up
	Baseline							
General Evaluations								
Informed Consent	X							
Eligibility Criteria	X							
Demographics	X							
Medical History	X							
Smoking History	X							
Oncology Treatment History	X							
Physical Exam	X	X	X	X	X		X	
Height	X							
Weight	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X		X	
Performance Status (ECOG)	X	X	X	X	X		X	
Concomitant Medications	X	X	X	X	X		X	
Adverse Events Assessment (NCI CTCAE Version 5.0)	X	X	X	X	X		X	
Survival Status								X[M]
Laboratory Evaluations (performed by local clinical laboratories)								
CBC with Differential	X[B]	X	X	X	X		X	
Complete Metabolic Panel [C]	X[B]	X	X	X	X		X	
HbA1c	X							
Thyroid Profile (TSH, free T4) [D]		X		X[D]				
Pregnancy Test [E]	X	X	X	X	X			
Low Density Lipoprotein (LDL) Cholesterol[J]		X		X[J]			X[J]	
Cardiac Evaluations								
ECG (single, 12-lead)	X							
Disease Evaluations								
MRI of brain [F]	X							
Radiographic Imaging [G]	X			X		X		X[H]
Tumor Measurements (RECIST 1.1) [I]	X			X		X		
Study Treatment								
Alirocumab 150 mg SC every 2 weeks [K]		X			Patient self-administers every 2 weeks at home. [K]			
Cemiplimab 350 mg IV every 3 weeks [L]		X	X	X	X			

To allow for patient and investigator schedules, holidays, weather or other emergencies requiring facilities to be closed, visits/evaluations after Cycle 1 Day 1 can be performed ±7 days. (This does not apply to study treatment. See footnotes K and L for those windows pertaining to Alirocumab and Cemiplimab.)

A. Screening (baseline) assessments are to be performed within 30 days prior to Cycle 1 Day 1 unless otherwise specified. Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day 1.
B. Must be within 14 days prior to Cycle 1 Day 1, day 1 and day 22 of every cycle and end of treatment.
C. Complete metabolic panel (CMP) to include sodium, potassium, chloride, total protein, albumin, calcium, glucose, BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT. Must be within 14 days prior to Cycle 1 Day 1, day 1 and day 22 of every cycle and end of treatment.
D. Thyroid profile to be assessed every 6 weeks regardless of treatment cycle.
E. All women of child bearing potential MUST test negative for pregnancy (serum or urine) within 48 hours prior to any initial study procedures. Pregnancy test must be completed every 3 weeks prior to cemiplimab dosing. If the pregnancy test is positive, the subject must not receive cemiplimab or alirocumab and must not be enrolled in the study, or will be removed from treatment.
F. MRI of Brain required at baseline (CT is allowed if there is a reason the subject cannot have an MRI). Subjects with a history of brain metastasis to have surveillance MRI per routine standard of care. If all known brain metastasis are treated, the screening brain MRI would not need to be repeated until 4 weeks after treatment date completion.
G. Baseline imaging will be performed with the relevant images to include CT scan (or MRI) of chest/abdomen with or without contrast and all known or suspected sites of disease. Restaging scans CT of chest and known sites of disease (e.g., abdomen with or without pelvis) required for subjects with metastasis in those areas identified at baseline will be performed every 6 weeks after the start of treatment for the first 48 weeks and then every 12 weeks thereafter. The same method for tumor assessment is to be employed at every assessment.
H. Subjects who discontinue study treatment for any reason (e.g., toxicity) other than disease progression will have disease status followed per routine care until disease progression is reported or start of new anti-cancer regimen.
I. Tumor measurements and response assessment will follow RECIST 1.1 criteria.
J. Obtain blood for LDL cholesterol (for safety) at the following time points: prior to start of study treatment; Cycle 2 Day 1, and at disease progression or at discontinuation of study treatment. Additional labs can be drawn per PI discretion. LDL will be performed by local clinical lab. The preference is for this to be a fasting lab. Should the subject not be fasting at the draw time, please draw the lab anyway and document the fasting status at the time of draw.
K. Patients will receive alirocumab 150mg sub-cutaneous (SC) every 2 weeks until disease progression, unacceptable toxicity, or completing 2 years of treatment. First dose of alirocumab will be administered in clinic. Subsequent dose of alirocumab will be self-administered by patient at home using the injector pen. For the 2nd and 3rd doses of alirocumab, the study coordinator/provider designee will contact the patient by phone to remind them to self-administer dose of alirocumab. Reminders for the injections given at home by phone contact can be the first cycle then as needed per provider's discretion. Patients will complete a drug diary card to document the date, time and injection location of alirocumab and return drug diary card for review by study coordinator at every clinic visit.
   For missed doses of Alirocumab: If a dose is missed:
   - Within 7 days from the missed dose, administer Alirocumab and resume the subject's original schedule.
   - More than 7 days after the missed dose, instruct the subject to wait until the next dose on the original schedule.
L. Patients will receive cemiplimab 350 mg IV every 3 weeks on day 1 and day 22 of each cycle until disease progression, unacceptable toxicity, or completing 2 years of treatment. Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3-day window is allowed to accommodate scheduling problems.
M. Subjects are followed for survival every 3 months starting from off treatment for up to 2.5 years after the last patient is enrolled or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records.

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1.0 BACKGROUND AND RATIONALE

1.1 Non-small cell Lung Cancer

Incidence, Prevalence, and Mortality

Lung cancer is the leading cause of cancer mortality in the United States with an estimated 228,820 new cases in 2020 and approximately 135,720 deaths annually in the US. Non-small cell lung cancer (NSCLC) encompasses the vast majority of new lung cancer diagnoses. More than half of patients have distant metastases at time of initial diagnosis, indicating stage IV disease which is considered to be incurable in the vast majority of cases[1].

Current Standard of Care

Immune checkpoint blockade has significantly improved outcomes in subset of patients with metastatic NSCLC. Anti-PD-1 agents have emerged as the standard of care for frontline treatment, given as monotherapy or in combination with chemotherapy, anti-CTLA4 or anti-VEGF agents[2-4]. However, even with combination therapy, over 60% of patients will have progressive disease within the first year of therapy[5]. Additionally, five-year survival for the original cohort of patients treated with anti-PD-1 therapies for metastatic NSCLC, while significantly improved, is only 16% [6]. Thus, novel therapies are needed in order to improve outcomes for patients with both primary and secondary resistance to immune checkpoint blockade.

1.2 Mechanisms of Response and Resistance to Immune Checkpoint Blockade

Certain factors have been correlated with responses to immune checkpoint blockade in NSCLC. Patients with evidence of a pre-existing immune response, reflected through high PD-L1 expression (measured by immunohistochemistry, IHC) or a T cell inflamed gene signature (measured by RNA seq) have been shown to achieve the most clinical benefit from immune checkpoint blockade[7]. Patients with a high tumor mutational burden also have superior outcomes, suggesting that tumor specific neoantigens drive anti-tumor T cell responses[8]. In order for T-cells to recognize tumor specific antigens, they must be presented by MHC molecules on the tumor cell surface. Translational studies in human NSCLC biopsies have shown that tumor cell surface MHC expression (measured by IHC) correlates with T lymphocyte infiltration, and MHC expression also correlates with overall survival in early-stage NSCLC[9, 10]. For patients receiving immune checkpoint blockade, MHC downregulation has been identified as one mediator of treatment resistance. This has included loss of heterozygosity at the HLA locus (loss of one genomic regions of the gene expressing MHC), and beta 2 microglobulin mutations (a protein forming part of the MHC complex)[11, 12]. Thus, MHC expression and antigen presentation by tumor cells drive CD8 T cell responses, and loss of MHC expression is one mechanism of immune checkpoint blockade resistance.

1.3 PCSK9 Inhibition

Pre-clinical Rationale

The lab of Dr. Chuan-Yuan Li at Duke University has recently shown that the cholesterol regulating protein, PCSK9, drives checkpoint blockade resistance through posttranslational downregulation of MHC class 1 molecules on tumor cells[13]. They used a CRISPR platform to knockout PCSK9 in murine melanoma, breast and colon cancer cell lines. After implanting the tumors in syngeneic mice, PCSK9 knockout tumors were observed to have suppressed tumor growth in comparison to PCSK9 wild type tumors. The administration of an anti-PD1 antibody to the mice with PCSK9 knockout tumors further delayed tumor growth, with long-term survival of some host mice. Examination of the tumor microenvironment showed that PCSK9 knockout tumors had increased infiltration of CD8 T-cells, CD4 T-cells, and NK cells. There was also an increase in the total and unique number of TCR sequences represented in CD8 T cells in the microenvironment. Antibody depletion of CD8 T cells completely abolished the anti-tumor effects in the PCSK9 knockout mice, proving an immune mediated mechanism.

As mentioned above, PCSK9 has previously been characterized due to its regulation of cholesterol metabolism, where it targets the LDL receptor for degradation in the lysosome. Dr. Li hypothesized that through a similar mechanism, PCSK9 may downregulate MHC molecules on tumor cells. Indeed, MHC class 1 expression in the murine tumor models, as well as the MDA-MB-231 human breast cancer cell lines, were increased in PCSK9 knockout tumors. They also showed that knockout of H2-K1, an MHC class 1 gene in the B16 melanoma cell line abolished the anti-tumor effects of PCSK9 knockout. Finally, through immunofluorescence co-staining they demonstrated that PCSK9 knockout cells had MHC localization on the cell membrane, while MHC molecules were localized in the lysosome in wildtype cells. In summary, these studies show that PCSK9 promotes immune escape through downregulation of MHC class 1 molecules on tumor cells.

Clinical Rationale

Anti-PCSK9 antibodies alirocumab and evolocumab have been FDA approved as treatment for hypercholesterolemia and patients at increased risk of cardiovascular disease, and are currently in clinical use. Dr. Li has also shown in the murine models that evolocumab mediates the same immune modulatory effects and tumor control when administered to mice with PCSK9 wild type tumor cells in comparison to the PCSK9 knockout tumors. Additionally, analysis of The Cancer Genome Atlas (TCGA) showed that PCSK9 mRNA expression was inversely correlated with CD8a expression in human tumors. Patients with higher levels of PCSK9 tumor secretion also have inferior overall survival across 9 tumor subtypes in TCGA, including lung adenocarcinoma. Thus, these data support that PCSK9 is a clinically relevant protein expressed by human tumor cells, with negative immunomodulatory effects that may be inhibited by clinically available anti-PCSK9 antibodies.

1.4 Cemiplimab

Cemiplimab is a human IgG4 monoclonal antibody targeting the PD-1 receptor and inhibiting its interactions with PD-L1 and PD-L2. This has been shown to reactivate T-cells that had previously lacked effector function due to inhibition mediated by the PD-1 pathway. Cemiplimab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspensions.

1.4.1 Clinical Trial Summary

Cemiplimab was FDA approved in September 2018 for metastatic or locally advanced cutaneous squamous cell carcinoma. It was initially evaluated in a phase 1 dose escalation study (NCT02383212), with an expansion cohort as well as a phase II trial (NCT02760498) evaluating activity in cutaneous squamous cell carcinoma. Among 59 patients in the phase II trial, the overall response rate was 47%, with progression free survival of 53% at 12 months, and median overall survival not reached[14].

Cemiplimab has also been evaluated in a randomized phase 3 trial (NCT03088540) for advanced NSCLC with PD-L1 expression > 50%. The cemiplimab arm in this trial had a response rate of 36.5%, PFS of 6.2 months and OS of 22.1 months, superior to the chemotherapy arm (Response rate 20.6%, PFS 5.6 months, OS 14.3 months)[15]. Based on the results of this trial, cemiplimab monotherapy was FDA approved on February 22, 2021 for patients with first-line advanced NSCLC with PD-L1 expression of $\geq$ 50%.

1.4.2 Safety Profile

Cemiplimab is well tolerated and carries a similar safety profile to other anti-PD-1 agents. Among 219 patients with advanced cutaneous squamous cell carcinoma evaluated in the FDA label, the most common adverse events were fatigue (34%), rash (31%), diarrhea (25%), musculoskeletal pain (24%) and nausea (21%). Grade 3-4 events were uncommon and included anemia (4%), fatigue (3%), musculoskeletal pain (3%), rash (1%), arthralgia (1%), diarrhea (0.5%), constipation (0.5%), and vomiting (0.5%)[16].

The phase 3 trial evaluating cemiplimab in patients with NSCLC and PD-L1 expression >50% also showed a similar safety profile. In this trial among 355 patients who received cemiplimab, only 5.1% discontinued therapy due to treatment related adverse events. The most common treatment-emergent adverse events (which may not have been directly related to cemiplimab) included anemia (14.6%), decreased appetite (11.8%), fatigue (10.1%). Grade 3-5 treatment-emergent adverse events occurring in more than 1% of patients included pneumonia (4.8%), anemia (3.4%), and fatigue (1.1%).

The safety of cemiplimab was evaluated in 132 patients with advanced BCC (mBCC N=48, laBCC N=84) in an open-label, single-arm trial (Study 1620). The most common adverse reactions reported in at least 15% of patients were fatigue, musculoskeletal pain, diarrhea, rash, pruritus, and upper respiratory tract infection. The most common Grade 3 or 4 adverse reactions (> 2%) were hypertension, colitis, fatigue, urinary tract infection, pneumonia, increased blood pressure,

hypokalemia and visual impairment. The most common (> 3%) laboratory abnormality worsening from baseline to Grade 3 or 4 was hyponatremia [16].

1.4.3 Dose Selection

In the initial phase 1 trial, cemiplimab was tested at dose levels of 1 mg/kg every 2 weeks, 3 mg/kg every 2 weeks and 10 mg/kg every 2 weeks. Cemiplimab concentrations in serum increased in a close to dose-proportional manner, however there was no increase in toxicity (no DLT reached) or efficacy at higher doses. The first cohort of patients in the phase II cutaneous squamous cell carcinoma were dosed at 3 mg/kg every 2 weeks, however a fixed dose of 350 mg every 3 weeks was found to have comparable steady-state drug exposure and is the current dosing on the FDA label. A subsequent cohort in the phase II cutaneous squamous cell carcinoma trial has shown similar efficacy and safety at the set dose of 350 mg IV every 3 weeks dose, and this is also the dose used in the phase III NSCLC trial[16, 17]. Therefore, for this trial, the cemiplimab dose will be 350mg IV every 3 weeks.

1.5 Alirocumab

Alirocumab is a human IgG1 antibody targeting and inhibiting the PCSK9 protein. It is produced through recombinant DNA technology in Chinese hamster ovaries. PCSK9 targets the LDL receptor for degradation in the lysosome. This reduces cell surface expression of the LDL receptor and ultimately increases serum LDL concentrations. By inhibiting PCSK9, alirocumab increases LDL receptor expression on the surface of hepatic cells, leading to a decrease in serum cholesterol levels.

1.5.1 Clinical Trial Summary

Alirocumab has been extensively studied to evaluate the effect of lowering LDL cholesterol levels and reducing cardiovascular events in patients with familial hypercholesterolemia or patients with cardiovascular disease. At the time of initial FDA approval for efficacy review, there were six randomized controlled trials enrolling 4,046 patients.

In the Odyssey Long Term Study, 2,341 patients at high risk for cardiovascular events who had an LDL cholesterol level of 70 mg per deciliter or more and were on a maximally tolerated statin were randomized in a 2:1 ratio to alirocumab 150 mg every two weeks or placebo. At 24 weeks, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in LDL level was -62 percentage points (P<.0001)[18].

In the Odyssey Outcomes study, 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had an LDL level of at least 70 mg per deciliter and were receiving a statin were randomized to alirocumab 75 mg every 2 weeks or matching placebo. After a median duration of follow up of 2.8 years, the composite primary end-point (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) occurred in 9.5% of patients in the alirocumab group and 11.1% of patients in the placebo group (HR .85 CI .78 to .93; p<.0001)[19].

1.5.2 Safety Profile

At the time of FDA label review, the safety of alirocumab was evaluated in 9 placebo-controlled trials that included 2,476 patients dosed at 75 mg or 150 mg every two weeks. The most common adverse reactions with alirocumab occurring more frequently than placebo include injection site reactions (7.2% vs 5.1%), nasopharyngitis (11.3% vs 11.1%), influenza (5.7% vs 4.6%), and myalgia (4.2% vs 3.4%). Liver enzyme abnormalities were noted in 2.5% of patients receiving alirocumab and 1.8% of patients receiving placebo. Overall, alirocumab had tolerable side effect profile as 5.3% of patients had adverse reactions leading to discontinuation compared to 5.1% of patients in the placebo group[20]. Of note, none of these common AEs from alirocumab are expected to overlap with immune-mediated AEs from cemiplimab.

There were initial concerns for effects of very low LDL levels on neurocognitive function, with the Odyssey Long term study showing a trend to increasing neurocognitive disorder related adverse events (1.2% vs .5%). However, a meta-analysis of 3,340 patients from 14 randomized phase 2 or 3 trials found a similar rate of treatment related neurocognitive adverse events with alirocumab (.9%) vs placebo treated patients (.7%) (HR 1.24 CI .57-2.68)[21]. Additionally, neuropsychological tests were prospectively conducted in a randomized trial of a different PCSK9 inhibitor, evolocumab. In this trial 1,204 patients were followed for a median of 19 months and there was no difference in executive function, working memory, episodic memory or psychomotor speed between the evolocumab and placebo groups. There were also no associations between LDL cholesterol levels and cognitive changes [22].

1.5.3 Dose Selection

The recommended starting dose for lipid management on the FDA label is 75 mg subcutaneous once every 2 weeks, since the majority of patients achieve sufficient LDL reduction at this dose. The dosage can be increased to 150 mg subcutaneous every 2 weeks if there is insufficient LDL response. Alternative dosing for patients who prefer less frequent dosing is 300 mg every 4 weeks.

After subcutaneous administration of 75 mg to 300 mg of alirocumab the median times to maximum serum concentrations were 3-7 days, with a half-life at steady state of 17 to 20 days. A slightly greater than dose proportional increase is seen, with 2.1 to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg every 2 weeks to 150 mg every 2 weeks. In phase 1 trials, the 150 mg dose of alirocumab was shown to decrease the serum concentration of free PCSK9 to below the lower limit of quantification. The 150 mg of alirocumab every 2 week dose was administered to 1530 patients in the Odyssey Long Term trial, with a comparable safety profile to 75 mg every 2 week dosing used in other trials. Thus, for the purposes of this current trial, alirocumab will be dosed at 150 mg subcutaneously every 2 weeks, in order to maximize the reduction in free PCSK9 levels.

1.6 Study Rationale

The substantial pre-clinical evidence that PCSK9 contributes to an immune excluded microenvironment (in part due to MHC downregulation on tumor cells) and the preclinical data

showing the combined effect of PCSK9 and PD-1 inhibition, lead us to translate this concept into a study of clinical feasibility. Defects in antigen presentation are commonly implicated in immunotherapy resistance. Thus, PCSK9 inhibition in combination with anti-PD1 may be one mechanism to overcome resistance in primary or secondary refractory patients. PCSK9 inhibitors such as alirocumab are already FDA approved to lower lipid levels in cardiovascular disease and carry a favorable and non-overlapping toxicity profile with ICB. We have designed this trial to evaluate preliminary efficacy of alirocumab (anti-PCSK9) and cemiplimab (anti-PD-1) in an immunotherapy-refractory population of patients with non-small cell lung cancer.

2.0 OBJECTIVES

2.1 Primary Objective

1. To study the clinical activity (response rate as assessed by RECIST 1.1) of PCSK-9 inhibitor alirocumab in combination with cemiplimab in patients with locally advanced or metastatic non-small cell lung cancer who have progressed on prior therapy with an anti-PD1/L1 agent.

2.2 Secondary Objectives

1. To evaluate the safety and tolerability of the combination regimen.
2. To evaluate secondary efficacy endpoints of the combination regimen.
    a. Disease control rate (SD, PR and CR)
    b. Complete response rates
    c. Progression Free Survival per RECIST 1.1 criteria
    d. Overall Survival
    e. Duration of responses

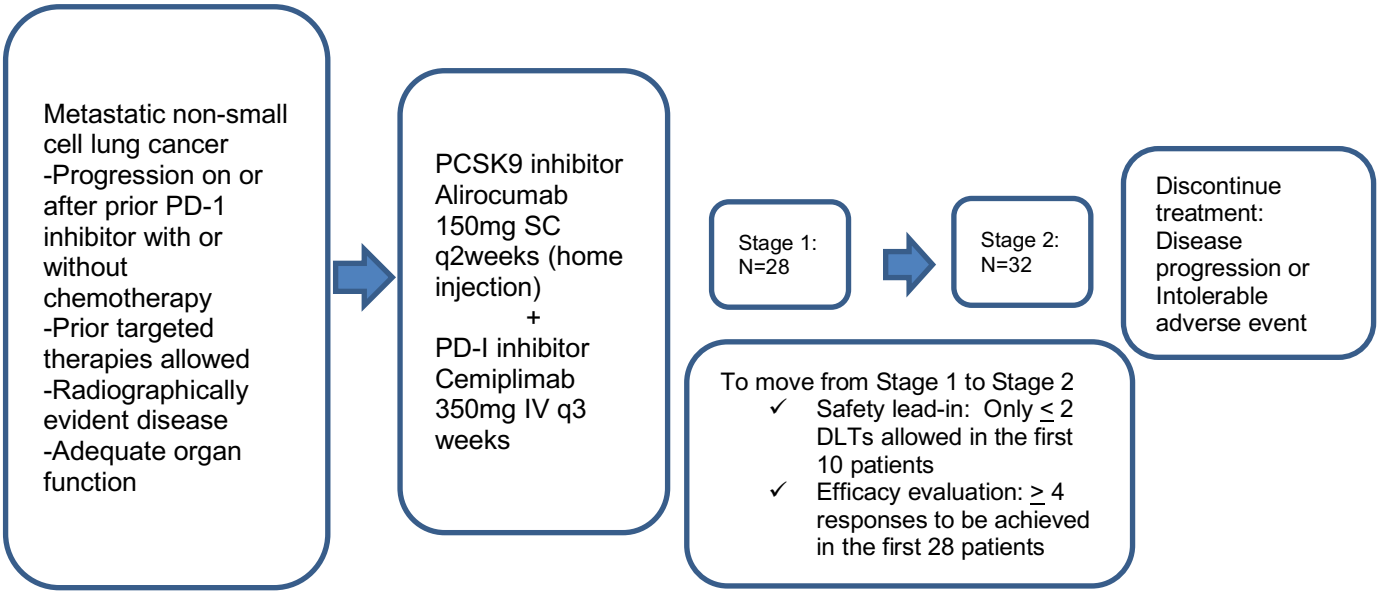
2.3 Exploratory Objectives

1. To evaluate the pharmacodynamic marker of the change in LDL cholesterol levels measured in serial plasma collections while on treatment with alirocumab.

3.0 STUDY DESIGN

3.1 Study Description

This is an open label, single-arm, phase II trial of alirocumab in combination with cemiplimab in patients with metastatic or locally advanced NSCLC who have disease progression on or after prior checkpoint monotherapy or in combination with chemotherapy, or anti-CTLA4. Patients with genomic driver alteration positive NSCLC must have progressed on at least one targeted therapy.



3.2 Stage 1 Cohort

In the first stage, 28 patients will be accrued. In one cycle, patients will receive 2 doses of cemiplimab 350 mg IV every 3 weeks along with 3 doses of alirocumab 150 mg SC every 2 weeks. DLT's will be collected for the first 10 patients only. Enrollment will be held for 30 days after the 10th patient has been enrolled for an initial safety evaluation. If 3 DLTs within the first 10 patients enrolled are observed during that time, then enrollment will be stopped for safety.

Enrollment will then be held after the 28th patient has been enrolled until 4 or more responders are observed. If there are 3 or less responses in these 28 patients, then enrollment will be stopped. Response will be achieved if a patient experiences a PR or CR as their best response.

3.2.1 Definition of Dose-Limiting Toxicity (DLT)

Toxicities will be graded according to the NCI CTCAE version 5.0 criteria. A subject will be considered evaluable for DLT if they have received at least one dose of cemiplimab and alirocumab. DLTs will be assessed for 30 days after the first dose of study therapy. 'If a treatment emergent AE is considered to be related to disease, it will not be considered a DLT.

The following criteria will define a DLT:

Non-Hematologic Toxicity

1. Grade ≥ 2 uveitis (considered as a potential immune-related adverse event [irAE]).
2. Any Grade ≥ 3 non-hematologic toxicity; with the exception of:

a. Grade 3 nausea, vomiting or diarrhea unless persistent (>7 days duration) despite maximal supportive care measures as prescribed by the treating physician.
b. Grade ≥ 3 laboratory abnormalities that are considered clinically insignificant and do not meet criteria for an AE.
c. Grade 3 infusion-related reactions that respond to medical management.
d. Grade 3 immune-related AE other than uveitis that improves within 7 to 14 days to Grade 2 or lower with medical management (including treatment with steroids).

Hematologic Toxicity

1. Grade 4 neutropenia lasting more than 7 days
2. Grade 4 thrombocytopenia
3. Grade 3 thrombocytopenia with bleeding
4. Grade ≥3 febrile neutropenia (fever ≥ 38.5°C with absolute neutrophil count [ANC] < 1.0 × 10^9/L), or Grade ≥ 3 neutropenia with documented infection

3.3 Stage 2 Cohort (Expansion)

If there are 4 or more objective responses in the first 28 patient cohort, then an expansion cohort with an additional 32 patients will be accrued. This cohort will receive the same regimen of cemiplimab 350 mg IV every 3 weeks along with alirocumab 150 mg SC every 2 weeks.

4.0 SUBJECT SELECTION AND REGISTRATION

4.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the criteria below apply.

1) Histologically and/or cytologically documented recurrent and/or metastatic stage IV non-small cell lung cancer (NSCLC).
2) Progression after prior PD-1/PDL1 directed therapy (as monotherapy or in combination with chemotherapy and/or anti-CTLA4, or anti-VEGF agents) – defined as investigator assessed progression from prior treatment.
3) If molecularly altered NSCLC including EGFR, ALK, ROS1, MET exon 14, RET, BRAF, NTRK, progression on prior targeted therapy is required.
4) Measurable disease by RECIST 1.1 (see Appendix A). Tumor lesions in a previously irradiated area are considered measurable **IF** progression has been demonstrated in such lesions after radiation.
5) ECOG Performance Status 0 or 1 (see Appendix B).
6) Minimum of 4 weeks from any anti-cancer therapies or prior PD-1 treatment.

7) Age > 18 years.
8) Signed written informed consent including HIPAA according to institutional guidelines.
9) Patients are eligible to be included in the study only if they meet **all** the following laboratory criteria:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500 per uL
Platelets	≥ 100,000 per uL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine	≤ 1.5 X upper limit of normal (ULN) **OR** creatinine clearance using Cockcroft-Gault formula (see Appendix C) ≥ 40 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** bilirubin < 3.0 mg/dL and direct bilirubin ≤ ULN for subject with Gilbert's syndrome with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subject with documented liver metastases

4.2 Exclusion Criteria

Participants are excluded from the study if any of the criteria below apply.

1) Prior treatment with PCSK9 inhibitors.
2) Myocardial infarction having occurred less than 6 months prior to study enrollment, any known uncontrolled arrhythmia, symptomatic angina pectoris, active ischemia, or cardiac failure not controlled by medications. Patients with CAD recently treated with surgery and/or stent greater than 6 months prior to enrollment, and if stable without symptomatic angina pectoris, or active ischemia are eligible.
3) Uncontrolled diabetes mellitus, defined as HbA1c > 8.5.
4) Major surgery less than 4 weeks prior to study enrollment.
5) Known history of HIV seropositivity or known acquired immunodeficiency syndrome (AIDS).

6) Another malignant condition diagnosed within 3 years of study enrollment. Exceptions include non-invasive superficial cancers including squamous cell in situ of skin, Stage 0 ductal carcinoma in situ of the breast, and Gleason 6 prostate adenocarcinoma with very low or low risk prostate cancer intact; or definitively treated prostate cancer determined to be in remission.
7) Pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
8) Extracranial palliative radiation within 2 weeks of study enrollment.
9) Receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent with the following exceptions:
    a. Intermittent steroids (not to exceed prednisone 10 mg every day or equivalent dosing) may be used on an as-needed basis (e.g., treatment for chemotherapy-related nausea, anorexia, and fatigue.)
    b. Physiologic replacement doses of steroids due to adrenal insufficiency for any reason.
    c. Topical, inhaled, or intra-articular corticosteroids.
10) Known autoimmune conditions requiring systemic immune suppressive therapy other than prednisone less than or equal to 10 mg.
11) Symptomatic brain or leptomeningeal metastases, including patients who continue to require glucocorticoids and/or anti-seizure therapy for brain or leptomeningeal metastases. Treated, asymptomatic metastases are permitted provided the patient has completed radiation at least 2 weeks prior to day 1 and has been off steroids for at least 1 week prior to day 1 of study drug. Stable (MRI or CT with contrast performed >4 weeks apart), untreated brain metastases are permitted if patient does not require steroids or anti-seizure therapy.
12) History of interstitial pneumonitis from any cause.
13) Severe chronic obstructive or other pulmonary disease with hypoxemia (requires supplementary oxygen, or in the opinion of the investigator any physiological state likely to cause systemic or regional hypoxemia).
14) Intolerance to prior PD-1/L1 treatment including discontinuation for severe or recurrent severe toxicity (including myocarditis or other myocardiotoxicity, encephalitis, colitis, diarrhea, pancreatitis, hypo/hyperthyroidism, hypopituitarism, adrenal insufficiency, rash, autonomic neuropathy, myasthenia gravis, Guillain-Barre, myositis/polymyositis, hepatitis, Type 1 Diabetes, thrombocytopenia) or known anaphylaxis/allergy or severe hypersensitivity to CHO products or developed an immune checkpoint blockade related immune adverse event that was refractory to steroids and required additional systemic immunosuppressive medication. Prior topical steroids for rashes and oral steroids with control of prior immune-mediated adverse event are permitted.

4.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this trial.

4.4 Protocol Eligibility Waivers

No waivers of inclusion or exclusion criteria will be granted. All prospective patients must meet all entry criteria. If there are any questions regarding the interpretation of a criterion for a potential patient, contact the principal investigator to discuss.

4.5 Patient Registration

Patient registration for all patients signing informed consent will be completed through the Duke Cancer Institute (DCI) Clinical Research Unit (CRU) into EPIC and ONCORE systems within 1 business day of obtaining consent. Patients will be enrolled only after all pre-treatment evaluations are completed and all eligibility criteria are met.

4.6 Patient Registration for External Sites

All patients signing informed consent at external sites must be registered with the DCI MiSTiC (Multisite Trials Service Center), the central coordinating center at Duke. For screen failures- indicate screen failure status on last page of eligibility checklist. The following documents are to be completed by the investigator and/or designee and forwarded to the MiSTiC as per instructions provided during training. All supporting source documents should be sent de-identified.

- TOP 2201 Eligibility Checklist with supporting source documents
- Signed Informed Consent

5.0 STUDY ASSESSMENTS

The Study Calendar summarizes the study procedures to be performed at each clinic visit. Refer to Schedule of Events for Study Calendar. For this study, a cycle is 6 weeks.

For all study assessments, every effort is to be made to comply with the study schedule. However, it is known that scheduling issues may occur. For all scheduling issues other than management of treatment toxicities, intercurrent illness, etc., a 7-day window is allowed after Cycle 1. Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3-day window is allowed to accommodate scheduling problems. For scheduling changes that occur outside of these windows, particularly those due to toxicity, the Principal Investigator or designee should be notified (in advance, if feasible) and provide approval (or acknowledgement).

Furthermore, additional evaluations/testing may be deemed necessary by the Principal Investigator for reasons related to subject safety.

5.1 Screening Period

During the Screening Period, subjects are consented and screened for the study. Informed consent must be obtained before initiation of any screening procedure that is performed solely for the purpose of determining eligibility for this study. Evaluations performed as part of routine care before informed consent can be considered as screening evaluations if done within the defined screening period, and if permitted by the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) policies. Study eligibility is based on meeting all the inclusion criteria and none of the exclusion criteria (refer to Section 4.0) before the first dose of study drug on Cycle 1 Day 1.

The following study procedures must be done within **30 days prior to Cycle 1 Day 1** (unless otherwise specified). Baseline and Cycle 1 Day 1 procedures may be completed on the same day, however, screening assessment(s) to confirm eligibility **MUST** have already been determined.

- Demographics
- Medical and cancer history
- Smoking history
- Concomitant medications
- Height
- Radiographic imaging (CT and/or MRI scans) of chest and abdomen, and all known or suspected sites of disease
- MRI or CT of brain
- HbA1c

The following study procedures must be done within **14 days prior to Cycle 1 Day 1**:

- Physical examination
- Vital signs and weight
- ECOG performance status
- CBC with differential
- Complete metabolic panel

- Pregnancy test (only for women of childbearing potential)
- ECG
- Low density lipoprotein (LDL) cholesterol (may also obtain prior to receipt of study treatment on Cycle 1 Day 1)
- Adverse event assessment (review of baseline symptoms)

Subject eligibility is determined using lab results obtained prior to receipt of study treatment on Cycle 1 Day 1. Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study.

5.2 Treatment Period

During the Treatment Period, subjects will receive 150 mg of alirocumab SC every 2 weeks as well as 350 mg of cemiplimab IV every 3 weeks. Subjects will continue to receive alirocumab and cemiplimab until either: 1) disease progression; 2) the occurrence of unacceptable treatment-related toxicity (As outlined in section 7.0 or per patient or investigator discretion); 3) completion of 24 months of study treatment; or 4) other reason(s) for subject discontinuation as described in Section 5.8. There will be no toxicity-related dose modifications, but treatment delays are allowed if immune related adverse event occurs. If clinically indicated, additional visits and/or safety assessments may be warranted.

Each cycle is 6 weeks long administering 2 infusions of cemiplimab every 3 weeks and 3 injections of alirocumab every 2 weeks. The following study procedures must be completed **every 3 weeks** prior to cemiplimab. A -2-day window is allowed for C1D1 study assessments. A 7-day window is allowed for study assessments after Cycle 1. Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3-day window is allowed to accommodate scheduling problems.

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Complete metabolic panel
- Pregnancy test (only for women of childbearing potential)

The following study procedures are to be completed **every 6 weeks**:

- Thyroid profile
- Radiographic imaging (CT and/or MRI scans) of chest and abdomen and all known or suspected sites of disease

Blood for standard of care LDL cholesterol (through local clinical laboratory) must be obtained at Cycle 2 Day 1, with the first restaging (i.e. after first 2 cycles of study treatment) and at disease progression or discontinuation of study treatment.

The Treatment Period ends when a subject receives his or her last dose of study treatment; the subject then enters the Follow-up Period.

5.3 Follow-up Period

The end of treatment follow-up visit is of critical importance and is essential to preserving subject safety and integrity of the study. Subjects are to return 28 days after their last dose of study drug (±7 days) or \Subjects complete the following study procedures at the post treatment visit:

- Physical examination
- Vital signs and weight
- Concomitant medications
- ECOG performance status
- Adverse event assessment
- CBC with differential
- Complete metabolic panel
- Blood for correlative studies including LDL cholesterol (if not already obtained at disease progression or discontinuation of study treatment)

Additional follow-up for 90 days will occur for subjects with adverse events (AEs) related to study drug that are ongoing at the time of this end of treatment follow-up visit unless AE is deemed unresolvable or subject has started a new anti-cancer treatment regimen.

For subjects that are discontinued from study treatment for reasons other than disease progression, subjects will have restaging scans per standard of care schedule followed until disease progression or start of new anti-cancer treatment regimen, at the discretion of the treating physician. Disease status may be collected by personal interviews or review of medical records.

Subjects are followed for survival every 3 months starting from off treatment for up to 2.5 years after the last patient is enrolled or until the study is closed (whichever comes first). Survival status may be collected by personal interviews or review of medical or public records.

5.4 Laboratory Assessments

Local laboratories will perform all clinical laboratory tests using standard procedures, and results will be provided to the Investigator. Abnormalities in clinical laboratory tests that lead to a change in subject management (e.g., dose modification, requirement for additional medication, treatment or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the case report form (CRF). If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as a serious adverse event (SAE).

5.5 Adverse Event Assessment

AE definition is described in Section 10.1. AEs will be documented throughout the study. AE seriousness, grade, and relationship to study drug will be assessed by the Investigator using NCI-CTCAE version 5.0 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

SAE definitions and reporting requirements are described in Section 10.2.

Other safety related events must be recorded and reported as described in Section 10.3.

5.6 Concomitant Medications

Concomitant medications will be documented in the subject record throughout the study. Subjects will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the subject about any new medications he/she is taking or has taken after the start of the study drug. Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The Investigator should discuss any questions regarding this with the Lead PI.

5.6.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care.

5.6.2 Contraception

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. Non-pregnant, non-breast feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal women (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal). The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Non-pregnant, non-breast feeding women must agree to use two highly effective birth control methods after informed consent is signed through 4 months after the last dose of study drug.

The following are considered adequate barrier methods of contraception:

- stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
- intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
- bilateral tubal ligation

- vasectomized partner (provided that partner is the sole sexual partner of the WOCBP patient and that the vasectomized partner has received medical assessment of the surgical success)

- and/or sexual abstinence†,‡.

  † *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.*

  ‡ *Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.*

Women of child bearing potential is defined as women who are fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion. In addition, male participants must be willing to refrain from sperm donation during this time.

Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this protocol.

Investigators shall counsel WOCBP, and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception which have a failure rate of < 1 % when used consistently and correctly.

5.6.3 Prohibited and/or Restricted Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Period of this study:

- Other investigational therapy.
- Anticancer agents other than the study medication should not be given to subjects, including chemotherapy, biological therapy, and immunotherapy. If such agents are required, then the subject must first be withdrawn from the study.
- Chronic treatment with systemic steroids or other immunosuppressive agents.
    - Intermittent steroids (not to exceed prednisone 10 mg every day or equivalent dosing) may be used on an as-needed basis (e.g., treatment for chemotherapy-related nausea, anorexia or fatigue).
    - Patients on physiologic replacement doses of steroids due to adrenal insufficiency for any reason may remain on those medications.
    - Topical, inhaled, or intra-articular corticosteroids are allowed.
- Palliative radiotherapy is not allowed to target lesions used to assess disease response. However, palliative radiotherapy to a single metastatic non-target lesions may be allowed with the approval of the PI in subjects who do not require immediate initiation of other systemic anti-cancer therapy.

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

There are no prohibited therapies during the Follow-up Period.

5.7 Tumor Assessments

Radiographic imaging will be performed with the relevant imaging to include CT scan of chest/abdomen with or without contrast and/or MRI scan of chest/abdomen and all known or suspected sites of disease. Restaging scans will be performed every 6 weeks after the start of study treatment. The same method for tumor assessment should be employed at every assessment.

MRI (or CT) of brain is required at baseline. Subjects with a history of brain metastasis to have surveillance MRI/CT per routine standard of care.

Tumor response will be assessed using RECIST 1.1 (see Appendix A).

Treatment Beyond UPD (Unconfirmed Progressive Disease)

At the time of initial UPD, patients must be clinically stable by investigator assessment in order to continue immunotherapy-based treatments. Clinical stability to continue treatment in light of UPD is defined as absence of any of the following:

- worsening of performance status,
- clinically relevant increase in disease-related symptoms such as pain or dyspnea that are associated with disease progression, and
- increased management/treatments of disease-related symptoms (including increased analgesic agents, radiation, or other palliative treatments).

Subjects will be permitted to continue on cemiplimab and alirocumab for treatment beyond initial UPD as long as they are clinically stable (as defined above) and meet the following criteria:

- Clinical benefit and no rapid disease progression (as assessed by Investigator)
- Tolerating study treatment
- Treatment beyond UPD will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

Imaging findings and recommendation to continue with treatment should be discussed with the patient before the decision to continue. Patients with UPD and who are clinically unstable should be designated as clinically unstable in the CRF and removed from study.

Confirmatory Scans

RECIST 1.1 guidelines also recommend that confirmation of progression be obtained between 4 to 8 weeks of the initial UPD scan date. For purposes of this trial, confirmatory scans may be obtained after 6 weeks, and no more than 13 weeks after initial UPD scans (as standard of care, depending on insurance coverage, as scans will not be billable to this study).

For subjects who continue study therapy beyond initial UPD, further progression is defined as per RECIST 1.1 guidelines (see Appendix A). Study treatments should be discontinued permanently upon documentation of further progression.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

Refer to Appendix A for definitions and guidelines of RECIST 1.1. The Principal Investigator or designee should be consulted if assistance is needed to adjudicate response/progression.

5.8 Treatment Discontinuation

Subjects will receive study drug up to 24 months, or treatment is discontinued for one of the reasons listed below. Subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. All reasons for discontinuation or withdrawal from trial will be recorded.

- Death
- Disease progression/treatment failure. Subjects felt to be clinically benefiting from treatment (e.g., mixed response, symptom improvement, demonstrable slowing of progression, e.g., progression rate of less than 20% over 6 months) may be continued on treatment with the agreement of the treating physician and study PI.
- Significant noncompliance by subject or treating physician
- Persistent (>8 weeks) NCI-CTCAE v5.0 grade 3 or 4 AE related to alirocumab or cemiplimab or any significant AE that compromises the subject's ability to safely continue to participate in the study. AE resulting in dosing delay for >8 weeks.
- Investigator or Lead PI determination that it is no longer safe and/or no longer in the subject's best interest to continue participation
- Withdrawal of consent
- Lost to follow-up
- Necessity for treatment with other anticancer treatment prohibited by protocol
- Sexually active subjects who refuse to use medically accepted methods of contraception during the course of the study and for 6 months following the last dose of study drug
- Women who become pregnant or are breast feeding
- Request by regulatory agencies for termination of treatment of an individual subject or all subjects under the protocol
- Concurrent illness that prevents further administration of treatment
- The investigator for any reason, stops the study
- The compulsory detention for the treatment of either a psychiatric or physical (e.g., infectious disease) illness

6.0 STUDY DRUGS

6.1 Treatment Compliance and Study Drug Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory

requirements regarding drug accountability, all unused study drug will be reconciled and destroyed in accordance with applicable state and federal regulations.

6.2 Cemiplimab

This will be provided by Regeneron. The following information is taken from the FDA label: Cemiplimab-rwlc injection is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles.

Drug Name: cemiplimab-rwlc

Dosage Form and Strengths:
Cemiplimab will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label.

- Each vial will contain a withdrawable volume 7 mL of cemiplimab (REGN2810) at a concentration of 50 mg/mL.
- The recommended dose of cemiplimab is 350 mg as an intravenous infusion over 30 minutes every 3 weeks.

6.2.1 Storage and Handling

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Protect from light. Do not freeze or shake.

After infusion preparation, store at room temperature up to 25°C (77°F) for no more than 8 hours from the time of preparation to the end of the infusion or at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of preparation to the end of infusion.

Allow the diluted solution to come to room temperature prior to administration.

Do not freeze.

6.2.2 Administration

Preparation

Do not shake. Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection.

Mix diluted solution by gentle inversion. Do not shake.

Discard any unused medicinal product or waste material.

Administration

Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter.

6.3 Alirocumab

This will be provided by Regeneron. The following information is taken from the FDA label:

Alirocumab is a clear, colorless to pale yellow solution, supplied in single-dose pre-filled pens and single-dose pre-filled glass syringes. Each pre-filled pen or pre-filled syringe of alirocumab is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution.

Alirocumab is available in cartons containing 1 or 2, pre-filled pens.

6.3.1 Storage and Handling

Do not freeze. Do not expose to extreme heat. Do not shake.

Pharmacy: Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton in order to protect from light.

Patient/Caregiver: Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton in order to protect from light. If needed, alirocumab may be kept at room temperature up to 77°F (25°C) for a maximum of 30 days in original carton to protect from light. Do not store above 77°F (25°C). After removal from the refrigerator, alirocumab must be used within 30 days or discarded.

6.3.2 Administration

Store alirocumab in the refrigerator. Allow alirocumab to warm to room temperature for 30 to 40 minutes prior to use. If needed, alirocumab may be kept at room temperature up to 77°F (25°C) for a maximum of 30 days in original carton to protect from light. Do not store above 77°F (25°C). After removal from the refrigerator, alirocumab must be used within 30 days or discarded.

Alirocumab should be inspected visually for particulate matter and discoloration prior to administration. If the solution is discolored or contains visible particulate matter, the solution should not be used.

Follow aseptic injection technique every time alirocumab is administered.

Administer alirocumab by subcutaneous injection into the thigh, abdomen, or upper arm using a single-dose pre-filled pen or single-dose pre-filled syringe.

Rotate the injection site with each injection.

Do not inject alirocumab into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

Do not co-administer alirocumab with other injectable drugs at the same injection site.

7.0 DOSE MODIFICATION AND TOXICITY MANAGEMENT

Subjects will be monitored continuously for AEs throughout the study and for 28 days after the last dose of study drug. Additional follow-up for 90 days may occur for subjects with AEs related to study drug that are ongoing at the time of this end of off-treatment follow-up visit unless AE is deemed unresolvable or subject has started a new anti-cancer treatment regimen.

Subjects will be instructed to notify their treating physician of any and all AEs. Toxicity will be graded according to NCI-CTCAE version 5.0.

All AEs should also be managed with supportive care at the earliest signs of toxicity considered related to study drug(s).

7.1 Dose Modifications and Dose Delay

Subjects experiencing one or more AEs of grade 2 or higher due to the study drug(s) may have doses withheld until the toxicity has resolved to Grade 1 or less as described in Section 7.2.1. As alirocumab and cemiplimab are given at fixed doses in this trial, no dose modifications will be made.

Subjects may need to be followed at least weekly when any study drug is held for toxicity until the toxicity returns to Grade ≤ 1 or is determined to be chronic or irreversible.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 4 weeks of the scheduled interruption, unless otherwise discussed with the PI. The reason for interruption should be documented in the patient's study record.

All reasons for modification to the dosing schedule must be recorded in the CRF.

7.2 Toxicity Management

Subjects should receive appropriate supportive care measures as deemed necessary by the Investigator.

7.2.1 Dose Modification

Adverse events (both non-serious and serious) associated with cemiplimab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose

or several months after the last dose of treatment. Both cemiplimab and alirocumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 7.2** below.

Table 7.2 Toxicity Criteria and Dose Modification Scheme

Adverse Reaction	Severity	Dosage Modification
Pneumonitis	Grade 2	Withhold
	Grades 3 or 4	Permanently discontinue
Colitis	Grades 2 or 3	Withhold
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times the ULN	Withhold
	AST or ALT increases to more than 8 times the ULN or Total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grades 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN or DRESS	Withhold
	Confirmed SJS, TEN or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3 or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold
	Grades 3 or 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

7.3 Supportive Care Guidelines

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

7.3.1 Pulmonary Adverse Events

Rule out non-inflammatory causes. If a non-inflammatory cause, treat accordingly and follow modifications in Section 7.2.1. Evaluate with imaging and pulmonary consultation.

- For **Grade 1 events**, consider delay of therapy. Monitor for symptoms every 2-3 days, consider pulmonary and ID consults. Re-image at least every 3 weeks.
- For recurrent **Grade 2 events**, hold therapy. Consider bronchoscopy, lung biopsy, and pulmonary and ID consults. Monitor symptoms daily, consider hospitalization. 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Re-image every 1-3 days. If symptoms return to near baseline, taper steroids over at least 1 month and then resume therapy per protocol and consider prophylactic antibiotics.
- For **Grade 3-4 events**, discontinue therapy. Recommend hospitalization, and consulting pulmonary and infectious disease services. Give 2-4 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consider bronchoscopy as well as lung biopsy. If symptoms return to baseline, taper steroids over at least 6 weeks. If not improving after 48 hours or worsening, add additional immunosuppression.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.2 GI Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and follow modifications in Section 7.2.1. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

- For **Grade 1** diarrhea/colitis, continue therapy per protocol and administer symptomatic treatment. Monitor closely for worsening symptoms and educate patient to report worsening immediately.
- For **Grade 2** diarrhea/colitis, hold therapy and administer symptomatic treatment. If it improves to grade 1, resume therapy per protocol. If it persists > 3-5 days or recurs, give 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent. When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.
- For **Grade 3** diarrhea/colitis, hold therapy. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections, consider lower endoscopy. If it improves, continue steroids until grade 1, then taper over at least 1 month. If it persists > 3-5 days or recurs after improvement, add infliximab 5 mg/kg (if no contraindication).
- For **Grade 4 diarrhea/colitis**, discontinue therapy. Supportive management as outlined above for grade 3 diarrhea/colitis.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.3 Renal Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and follow modifications in Section 7.2.1.

- For **Grade 1** events, continue therapy per protocol, monitor creatinine weekly. If it returns to baseline, resume routine creatinine monitoring per protocol.
- For **Grade 2-3** events, hold therapy, and monitor creatinine every 2-3 days. Administer 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Consider a renal biopsy with nephrology consult. If it returns to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy and routine creatinine monitoring per protocol.
- For **Grade 4** events, discontinue therapy per protocol, and monitor creatinine daily. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Consult a nephrologist and renal biopsy. If it returns to grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.4 Hepatic Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and follow modifications in Section 7.2.1. Consider imaging for obstruction.

Hepatitis with no tumor involvement of the liver

- For **Grade 1** events, continue therapy per protocol, and continue LFT monitoring per protocol.
- **For AST or ALT increases more than 3 to 8 times ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN**, hold therapy and increase frequency of monitoring to every 3 days. If symptoms return to baseline, resume routine monitoring and resume therapy per protocol. If elevations persist > 5-7 days or worsen, administer 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.
- **For AST or ALT increase to more than 8 times ULN or total bilirubin increase more than 3 times ULN,** discontinue therapy and increase frequency of monitoring to every 1-2 days. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent (recommended starting dose for grade 4 hepatitis is 2 mg/kg/day IV). Add prophylactic antibiotics for opportunistic infections and consult a gastroenterologist. If symptoms do not improve in >3-5 days, worsen or rebound, add mycophenolate mofetil 1 g BID. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.

Hepatitis with tumor involvement of the liver

- For **Grade 1** events, continue therapy per protocol, and continue LFT monitoring per protocol.
- **For baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT that is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN**, hold therapy and increase frequency of monitoring to every 3 days. If symptoms return to baseline, resume routine monitoring and resume therapy per protocol. If elevations persist > 5-7 days or worsen, administer 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.
- **For AST or ALT increase to more than 10 times ULN or total bilirubin more than 3 times ULN ,** discontinue therapy and increase frequency of monitoring to every 1-2 days. Administer 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent (recommended starting dose for grade 4 hepatitis is 2 mg/kg/day IV). Add prophylactic antibiotics for opportunistic infections and consult a gastroenterologist. If symptoms do not improve in >3-5 days, worsen or rebound, add mycophenolate mofetil 1 g BID. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.5 Endocrinopathy Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and follow modifications in Section 7.2.1. Consider visual field testing, endocrinology consultation, and imaging.

- For **Asymptomatic TSH Elevation,** continue therapy per protocol. If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated; consider endocrinology consult.
- For **Symptomatic Endocrinopathy,** hold therapy, evaluate endocrine function and consider a pituitary scan. For subjects who are symptomatic with abnormal labs or pituitary scan, administer 1-2 mg/kg/day methylprednisolone IV or PO equivalent, and initiate appropriate hormone therapy. If there are no abnormal labs or pituitary MRI scan, but symptoms persist, repeat labs in 1-3 weeks and repeat MRI in 1 month. If the symptoms improve with or without hormone replacement, taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections. Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
- **Suspicion of Adrenal Crisis** – hold therapy and rule out sepsis. Administer stress dose of IV steroids with mineralocorticoid activity and IV fluids. Consult endocrinologist. If adrenal crisis is ruled out, then treat as above for symptomatic endocrinopathy.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Patients on sufficient hormone replacement therapy may be re-challenged with study treatments after steroid taper. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.6 Skin Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue follow modifications in Section 7.2.1.

- For **Grade 1-2** events, continue study treatments and administer symptomatic therapy. If symptoms persist > 1-2 weeks or recur, consider a skin biopsy and delay therapy per protocol. Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper the steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume therapy per protocol.
- For **Grade 3-4** events, hold therapy see guidance on SJS (Stevens-Johnson Syndrome), TEN (toxic epidermal necrolysis) or DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) below. Get a dermatology consult and consider a skin biopsy. Administer 1.0-2.0 mg/kg/day

IV methylprednisolone IV or IV equivalent. If signs improve to grade 1 and not SJS, TEN, or DRESS taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids. If SJS/TEN/DRESS is suspected, withhold therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue therapy.

7.3.7 Neurologic Adverse Events

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and follow modifications in Section 7.2.1.

- For **Grade 1** events, continue therapy per protocol. Continue to monitor the patient.
- For **Grade 2** events, hold therapy. Treat symptoms per local guidelines. Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent. If signs improve to baseline, resume therapy per protocol.
- For **Grade 3-4** events, discontinue therapy, and obtain neurology consult. Treat symptoms per local guidelines. Administer 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent and add prophylactic antibiotics for opportunistic infections. If signs improve to grade 2, taper steroids over at least 1 month. If they worsen, or atypical presentation, consider IVIG or other immunosuppressive therapies per local guidelines.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

7.3.8 Infusion Reactions

An infusion reaction for cemiplimab may manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (Version 5.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

For Grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50

mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.

For <u>Grade 2</u> symptoms (moderate reaction that requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

- Stop the study drug infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further study drug will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the CRF.
- For future infusions, the following prophylactic premedication are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000mg should be administered at least 30 minutes before study drug infusions. If necessary, corticosteroids (up to 25 mg of Solucortef or equivalent) may be used.

For <u>Grade 3</u> or 4 symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. <u>Grade 4</u>: Life threatening; pressor or ventilator support indicated)

- Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drugs will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

7.4 Criteria for Restarting Treatment after Resolved Toxicity

Participants may resume treatment when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Participants may resume treatment in the presence of Grade 2 fatigue.
- Drug-related pulmonary toxicity must have resolved to baseline before treatment is resumed. Participants with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the PI.
- Participants who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. Steroid doses equivalent to prednisone ≥ 10 mg/day are permissible if needed for physiologic hormone replacement.
- Participants who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator, may resume study treatments when the amylase or lipase abnormality has resolved to Grade 1 or baseline.

Treatment should be restarted by administering one cycle of cemiplimab at 350 mg without administration of alirocumab. If toxicity has not recurred after three weeks of cemiplimab alone then subsequent cycles will include both cemiplimab and alirocumab. If treatment cannot be resumed within nine weeks of the last dose of cemiplimab, study treatments must be permanently discontinued.

8.0 CORRELATIVES

N/A

8.1 Low Density Lipoprotein (LDL) Cholesterol Levels

<u>Mean/median plasma LDL cholesterol levels at baseline and changes from baseline to on-treatment levels</u>

We will measure LDL cholesterol levels at baseline, additional on-treatment time points, and at disease progression or study treatment discontinuation to evaluate changes in level of LDL in the blood.

9.0 STATISTICAL ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

9.1 Sample Size Justification

An admissible two-stage design (Jung et al. 2004) will be used. We will not be interested in the study therapy if its true overall response (=PR+CR) rate (ORR) is 10% or lower, and will be highly interested if the true ORR is 25% or higher. In the first stage, 28 patients will be accrued. If there are 3 or fewer responders in these 28 patients, the study will be stopped by rejecting the study therapy. Otherwise (# of responders is 4 or more), an additional 32 patients will be accrued during the second stage for a total of 60. The null hypothesis will be rejected (or the study therapy will be accepted for further investigation) if 10 or more responders are observed from the cumulative 60 patients. This design assumes a one-sided alpha of 5% and a power of 90%.

If the final sample size after the second stage is different from 60, then we will calculate the 1-sided p-value based on the observed sample size (Jung et al. 2006), and reject the null hypothesis if the p-value is smaller than 0.05. ORR will be estimated using the two-stage design (Jung and Kim, 2004). A Jennison-Turnbull (1983) 90% confidence interval for ORR will be estimated.
Accounting for about 5% of attrition due to ineligibility or drop out, a maximum of 60 patients will be enrolled.

9.2 Study Endpoints

9.2.1 Primary Endpoint

The primary objective is to describe the response rate associated with alirocumab and cemiplimab, with 90% 2-sided (or 95% 1-sided) confidence intervals. Response rate is defined as the proportion of treated subjects with a complete or partial response per RECIST 1.1 criteria.

All patients who receive at least one dose of alirocumab and cemiplimab will be considered for the primary endpoint analysis. The initial imaging assessment of response will be performed approximately 6 weeks after Cycle 1 Day 1. If patients are unable to continue on trial and complete the initial treatment response assessment at 6 weeks due to death, toxicity, or any other reason they will be considered as progressive disease.

9.2.2 Secondary Endpoints

<u>Safety Endpoints</u>

The first 10 patients in Stage 1 will be considered as part of the safety lead. DLT will be evaluated within 30 days of Cycle 1 Day 1. Please see Section 3.2.1 for definition of a DLT. Enrollment will be held for 30 days after the 10th patient in Stage 1as been enrolled. If 3/10 DLTs are observed during that time in each cohort, enrollment will be halted for that cohort.

In addition to the safety lead in, safety will be recorded throughout the duration of the protocol, up to 90 days after the last dose of trial agent. Adverse events will be characterized by type, incidence, severity, timing, and study treatment attribution of adverse events and laboratory abnormalities.

Toxicity data will be summarized by attribution and grade using a contingency table.

Efficacy Endpoints

Disease control rate (SD, PR, and CR) will be estimated by the sample proportion. Progression-free survival by RECIST 1.1 criteria (the time from the first dose of treatment to the time of progressive disease or death in all patients eligible for efficacy analysis), overall survival, and duration of response (time from first treatment to the time of progressive disease, or death among patients who have a documented treatment response) will be estimated by Kaplan-Meier curves.

9.2.3 Exploratory Endpoints

Refer to Section 8.0 for discussion of correlative studies.

1) Mean/median plasma LDL cholesterol levels at baseline and changes from baseline to on-treatment levels: We will conduct a paired t-test to test if plasma LDL cholesterol levels decreases on-treatment compared to baseline. The sample size for this experiment will be 25.

10.0 SAFETY Monitoring and Reporting

All patients who receive at least one dose of alirocumab, and/or one dose of cemiplimab will be considered evaluable for safety parameters. Additionally, any occurrence of non-SAE or SAE from time of consent forward, up to and including follow-up visits will be reported as per Adverse Event Reporting sections below. Safety will be evaluated for all treated patients using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests.

The Investigator is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the Investigator or designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an adverse event (AE) or serious adverse event (SAE) has occurred.

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to use of the study drug. Abnormal laboratory findings without clinical significance (based on the Investigator's judgment) should not be recorded as AEs. But laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

From the time the subject signs the informed consent form through 28 days after the last dose of study treatment, all AEs must be recorded in the subject medical record and adverse events CRF. If an event that starts post the defined safety, follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

The Investigator is responsible for following all treatment related AEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the study treatment(s)
- Action taken with regard to study treatment(s)
- Administration of treatment for the AE
- Outcome

AEs will be assessed according to the CTCAE version 5.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- **Definite:** The AE is clearly related to the study drug
- **Probably:** The AE is likely related to the study drug
- **Possible:** The AE may be related to the study drug
- **Unlikely:** The AE is doubtfully related to the study drug
- **Unrelated:** The AE is clearly NOT related to the study drug

Progression of the cancer under study is not considered an AE unless it is considered to be drug related by the Investigator.

10.2 Serious Adverse Events

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

1. Results in death.
2. Is immediately life threatening (I.e., in the opinion of the Investigator, the AE places the subject at immediate risk of death; it does not include a reaction that, had it occurred in a more severe form, might have caused death).
3. Requires inpatient hospitalization or results in prolongation of an existing hospitalization.
4. Results in persistent or significant disability or incapacity. (Note: The term “disability” refers to events that result in a substantial disruption of a subject’s ability to conduct normal life function.)
5. Is a congenital anomaly or birth defect.
6. Is an important medical event (Note: The term “important medical event” refers to an event that, based upon appropriate medical judgment, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require intervention to prevent one of the other serious outcomes listed under the definition of SAE. Examples of important medical events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of product dependency or product abuse.)

SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from time of informed consent through 90 days after discontinuation of the Regeneron product., whether or not related to study drug(s), must be recorded on the adverse events CRF.

All SAEs must be followed until resolution, return to baseline condition, or stabilization. Any SAEs that are ongoing at the time the clinical database is closed will be reported to supporting companies as unresolved.

10.2.1 SAE Reporting

SAEs as defined in Section 10.2 are subject to this reporting provision are those that occur from time of informed consent through 90 days after discontinuation of the Regeneron product. SAEs that occur more than 90 days after discontinuation of the Regeneron product will be reported only if the investigator believes the study drug caused the AE/SAE.

SAE Reporting Procedure for Investigators:

Immediately upon awareness of a SAE, the Investigator (or designee) completes and submits the **DCI Serious Adverse Event Report Form – Investigator-Initiated Trials (IITs)** within 24 hours of knowledge of the event via email:

- **TO:** eziafa.oduah@duke.edu (Dr. Eziafa Oduah, PI)

CC (copy):

- MiSTiC (Multisite Trials Service Center) at DCI-MultiSiteStudies@duke.edu

Note: It is imperative that initial SAE reports are submitted as soon as possible (within 24 hours of knowledge of the event) with available information to the PI and MiSTiC. Missing and/or clarified event information may be provided in a follow-up report.

De-identified source documentation (i.e. admission notes, discharge notes, applicable laboratory results, radiology/diagnostic testing results, etc.) must be sent with the DCI SAE Report Form. Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to MiSTiC as soon as possible using the same forms mentioned above.

In accordance with applicable regulations, Investigators must report SAEs according to their institutional guidelines.

SAE Reporting Procedure for PI and MiSTiC (Multisite Trials Service Center)

Upon receipt, the PI will review the submitted DCI SAE Report Form with available source documents and complete the PI's Medical Review Assessment on the DCI SAE Report Form. MiSTiC will report SAEs to Regeneron at medical.safety@regeneron.com within twenty-four **(24) hours** of awareness(or 3 calendar Days if weekend/holiday), collected/recorded on the FDA MedWatch Form or other safety reporting form as applicable:

1) **All Serious Adverse Events ("SAEs")** (regardless of causality) including but not limited to:

SAEs as defined by FDA 21 CFR 312.32 and ICH E2A and ICH E6 and/or by applicable local laws and regulations which includes, for the avoidance of doubt, adverse events that: : (i) are life-threatening, and/or (ii) result in (A) death, (B) in-patient hospitalization or prolongation of existing hospitalization, (C) persistent or significant disability or incapacity, (D) a congenital anomaly or birth defect, or (E) An Important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of SAE. ; and all serious and/or nonserious reports of: (i) overdose, (ii) abuse, (iii) misuse, (iv) medication error (defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the Study subject (for example, issues related to dispensing and administration which either (A) reach the Study subject or (B) are intercepted and never reached a Study subject, but had the potential to cause harm), (v) occupational exposure and/or (vi) lack of therapeutic efficacy.

If cemiplimab is being given in combination with another investigational product (not chemotherapy), Adverse Events of Special Interest (AESIs) are to be reported:

- Grade ≥2 infusion related reactions (IRR)
- Grade ≥2 allergic/hypersensitivity reactions
- Grade ≥3 immune-mediated AEs
- Grade 2 or greater injection site reactions (applicable to intralesional or SC administration)

2) **Pregnancy**

a) Any pregnancy occurring in a female Study subject or female partner of a male Study subject, during the Study or within **120 days** of the last dose of the Cemiplimab.
b) Any complication of pregnancy affecting a female Study subject or female partner of a male Study subject, and/or fetus and/or newborn that meets the SAE criteria.
c) Outcomes for all such pregnancies.

If the event meets the Duke University Health System (DUHS) IRB reporting requirements, MiSTiC will submit information about the SAE including the PI's Medical Review Assessment as a safety event to the DUHS IRB.

In accordance with applicable regulations, Investigators must report SAEs according to their institutional guidelines.

10.2.2 Reporting to the FDA

The Sponsor-Investigator is responsible for reporting SAEs to the FDA in accordance with 21CFR 312.32. Any SAE that is possibly related and unexpected must be submitted to the FDA.

If the SAE meets criteria for reporting to the FDA, MiSTiC will complete the Form FDA 3500A (MedWatch) and send to the PI and the supporting companies that are noted in Section 10.2.1. This submission of the Form FDA 3500A to the FDA will be completed by the PI or designee.

- All unexpected, drug related SAEs that are fatal or life-threatening will be reported to the FDA by phone or fax within 7 calendar days of initial receipt of the information and will provide a complete report within 8 days of the initial report submission (by calendar day 15).
- All unexpected, treatment-related SAEs that are not fatal or life-threatening will be reported in a written report to the FDA within 15 days of initial receipt of the information.

MiSTiC will forward all expedited reports to participating Investigators in the form of an Investigator Alert.

All reports to the FDA or local health authority shall also be reported to Regeneron at **Safety Reporting Mailbox:** medical.safety@regeneron.com. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided on the MedWatch Form or other reporting form. Specific or estimated dates of event onset, treatment, and resolution should be included, when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Information not available at the time of the initial report must be documented in a follow-up report. Source documents (including hospital or medical records, diagnostic reports, etc.) shall be summarized in the narrative on the FDA MedWatch Form or other reporting form as may be provided by Regeneron retained by the Principal Investigator and shall be available upon request.

10.3 Other Safety Considerations

The Investigator must also report in the same timelines as SAEs any incidence of pregnancy or overdose. Refer to SAE reporting procedures in Section 10.2.1.

10.3.1 Pregnancy

Pregnancy occurring in a female patient or female partner of a male patient during the study or within 120 days of the last dose of study drug must be reported to Regeneron within 24 hours of identification.

During the course of the trial and within 120 days of last dose of study drug, all female subjects of childbearing potential or female partner of a male subject should be instructed to contact the treating physician immediately if they suspect that they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female subject, or an investigator, suspects a pregnancy prior to the administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study. Regeneron must be informed if a pregnancy occurs.

Throughout the entire pregnancy, additional contact should be made with the subject, and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.
If a male subject is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the possible risk to the fetus. In addition, the

treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

All serious AE reports relating to the pregnancy, including spontaneous abortion, elective abortion and congenital anomalies should also be reported
Such events must be reported in the same procedure as an SAE. Refer to SAE reporting procedures in Section 10.2.1

10.3.2 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

In the event of an overdose, the investigator/treating physician should:

1. Contact PI and Regeneron
2. Closely monitor the participant for AEs/SAEs and laboratory abnormalities
3. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

11.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable federal, state, and local regulations.

11.1 Institutional Review Board and Scientific Review Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the Duke University Health System (DUHS) Institutional Review Board (IRB) and Duke Cancer Institute Protocol Review and Monitoring Committee (PRMC) for review. The study may be initiated only after the PI has received written and dated approval from the PRMC and IRB.

The PI must obtain protocol re-approval from the IRB within one year of the most recent IRB approval. The PI must also obtain protocol re-approval from the PRMC within one year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

11.2 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

11.3 Protocol Amendments

The PI must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the PI must inform the IRB and all other applicable regulatory agencies of such action immediately.

The PRMC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

11.4 Protocol Deviations and Violations

A protocol deviation is non-adherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

A protocol violation is any significant divergence from the protocol such as non-adherence on the part of the subject, the Investigator, or the Sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines.

As a matter of policy, the PI (I.e. Sponsor) will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If it is found that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), the PI and/or designee must be informed immediately. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the PI and the IRB.

Protocol deviations and violations must be reported according to IRB policy.

11.5 Safety Oversight Committee

The Duke Cancer Institute Safety Oversight Committee (SOC) is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent data and safety monitoring board.

The primary focus of the SOC is review of safety data, toxicities and new information that may affect subject safety or efficacy. Annual safety reviews includes but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the Duke Cancer Institute Monitoring Team (see Section 11.7 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator, greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements.

11.6 Data and Safety Monitoring Board

There is no independent data and safety monitoring board (DSMB) for this study.

11.7 Monitoring and Audits/Inspections

This study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute.

In terms of internal review, the PI and/or designee(s) will continuously monitor and tabulate adverse events. Appropriate reporting to the IRB will be made. If an unexpected frequency of Grade 3 or 4 adverse events occurs, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled (if applicable);
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately recorded on the CRF in a reasonably timely manner.

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and to ensure that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, GCP, and applicable regulatory requirements. This study has been assigned as “High Risk” by DCI Protocol Review and Monitoring Committee

(PRMC). The “Frequency of Regulatory and Participant Review” is: “Every 6 months based on Open to Accrual CTMS Date”. And, the “Monitoring Level” is: “100% Regulatory and Participant data/chart review of the first 3 subjects enrolled; For ongoing subject chart review, a minimum of 10% of records to be reviewed every 6 months” as specified in the DCI Data and Safety Monitoring Plan, until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. All the participating sites will be monitored at the same time during the biannual monitoring visits.

MiSTiC’s Data Management Plan addendum describes data management and monitoring at participating sites.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Protocol Review and Monitoring Committee (PRMC), the DCI Safety Oversight Committee (SOC), the sponsor, the PI, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including but not limited to the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

11.8 Source and Study Documentation

Source documents include all original recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports (including normal and abnormal results), radiology reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original certified document. For paper source documents, errors will crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary).

When clinical observations are entered directly into an electronic medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has must be validated to meet the FDA requirements for electronic records and signatures (i.e. meets 21 CFR Part 11 compliant).

Regulations require that Investigators maintain information in the study subject’s medical records which corroborate data recorded on the CRF.

Study documentation includes but is not limited to source documents, CRFs, monitoring logs, correspondence with sponsors or regulatory bodies/committees, and regulatory documents maintained in the 'regulatory binder', which includes but is not limited to approved protocols, approved and signed informed consent forms, FDA Form 1572, laboratory certifications, and clinical supplies receipts and distribution records.

11.9 Case Report Forms

The case report form (CRF) will be the primary data collection document for the study. Subject data will be entered (i.e. CRFs completed) and an audit trail maintained into an electronic data capture (EDC) system. The EDC system is maintained on a secure Duke University server.

The CRFs will be updated within two weeks of acquisition of new source data. Only authorized key personnel are permitted to make entries, changes, or corrections in the CRF. In the event of discrepant data, the study monitor or designee will request data clarification from the Investigator or authorized key personnel for which may be resolved electronically in the EDC system.

11.10 Privacy, Confidentiality, and Data Storage

The PI will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated web-access secure database, which is housed in an encrypted and password-protected server behind the Duke firewall. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the Duke Cancer Institute and/or Duke Medicine.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

11.11 Records Retention

Upon completion of the study, research records will be retained and stored per DUHS Human Research Protection Program (HRPP) policies.

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Appendix A.

Appendix A: RECIST 1.1*

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Definitions
Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Non-measurable Disease
All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions
All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more

details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

Guidelines for Evaluation of Measurable Disease
All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate

cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria
Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived

from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-target Lesions
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow- up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best

overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Appendix B. ECOG Performance Status

The ECOG Scale of Performance Status, developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair*, describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.).

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

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

Appendix C. Cockcroft-Gault Formula

Cockcroft-Gault Formula* for Calculated Creatinine Clearance (CrCl)

*Cockcroft, D. W., & Gault, H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, *16*(1), 31-41.

Using serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

If female, multiply result x 0.85

Using serum creatinine concentration in mol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{0.81 \times \text{serum creatinine (mol/L)}}$$

If female, multiply result x 0.85

Appendix D: Guidelines for Management of Immune-Related Adverse Events

Select immune-related adverse events (irAEs) and their management are described in this appendix. The following general principles apply to management of irAEs, if they are not otherwise specifically described in this appendix:

Grade 1: Continue study treatment with close monitoring and provide symptomatic management.

Grade 2: Consider withholding study treatment

Grade 3: Withhold study treatment

Grade 4: Discontinue study treatment.

Temporary hold and resumption. Except as described for select irAEs, if cemiplimab is withheld for grade ≤3 irAE, consider resuming cemiplimab when the irAE improves to baseline or grade 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.

Permanent discontinuation. Except as described for select irAEs, give an initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and permanently discontinue study treatment for:

- Grade 4 adverse reactions (excluding endocrinopathies)
- Recurrent grade 3 irAEs
- Grade 2 or 3 irAEs persisting for ≥12 weeks after the last study treatment
- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment.

For additional guidance to that provided here, please refer to regional irAE management guidelines such as those provided by NCCN or ESMO. In countries where cemiplimab has a marketing authorisation the local product information may be consulted. Note that local and regional treatment guidelines and cemiplimab product information may be updated periodically and the latest version should always be reviewed.

Recommended Adverse Event Management for Colitis/Diarrhea

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 • **Colitis**: Asymptomatic; clinical or diagnostic observations only; intervention not indicated • **Diarrhea**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• No change	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consider consultation with gastroenterologist for prolonged symptoms • If symptoms are persistent, consider endoscopic evaluation • If persists for >2 weeks, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or viral

Grade 2 • **Colitis**: Abdominal pain; mucus or blood in stool • **Diarrhea**: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent •	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least a month • If no improvement within 2 to 3 days, treat as grade 3	gastroenteritis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 • **Colitis:** Severe abdominal pain; peritoneal signs • **Diarrhea**: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of grade 3 colitis or diarrhea upon re-challenge	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Inpatient care for close monitoring and supportive care • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least 1 month • If no improvement with corticosteroid within 2 to 3 days, consider additional immunosuppressive therapy ie, mycophenolate 0.5 to 1g BID, infliximab 5 mg/kg IV	
Grade 4 or Recurrent Grade 3 • **Colitis**: Life-threatening consequences: urgent intervention indicated • **Diarrhea**: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue study treatment	• Same as above • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections	

Recommended Adverse Events Management for Dermatologic Toxicities

Immune-related skin toxicities include maculopapular rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction. **Guidance here is provided for maculopapular rash**.

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 or **Grade 2** lasting 1 week or less	• No change	• Treatment with mild to moderate potency topical steroids • Treatment with oral antihistamine	• All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease
Grade 2 lasting longer than 1 week or **Grade 3** or **Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug rash with eosinophilia and systemic symptoms (DRESS)**	• Withhold study treatment until skin reaction improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month • Consider treatment with medium to high potency topical steroids • Treatment with oral antihistamine	
Grade 4 or **Confirmed SJS, TEN, or DRESS**	• Permanently discontinue study treatment	• Consultation with dermatologist and skin biopsy • Treatment with high potency topical steroids and with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month	

Recommended Adverse Events Management for Endocrine Events: Hypothyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 3 to 6 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	
Grade 3 or 4	• Withhold study treatment until hypothyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	

Recommended Adverse Events Management for Endocrine Events: Hyperthyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 2 to 3 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines • Consider β-blocker for symptomatic relief • For persistent hyperthyroidism (> 6weeks), consider work up for Graves disease and refer to endocrinology for Graves disease	
Grade 3 or 4	• Withhold study treatment until hyperthyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Same as above • For severe symptoms, inpatient care and consider systemic corticosteroids treatment (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over 1-2 weeks in consultation with endocrinology • Consider use of saturated solution of potassium idodide (SSKI) or thioanmide	

Recommended Adverse Events Management for Endocrine Events: Hypophysitis or Adrenal Insufficiency

CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grades 2 to 4	• Withhold study treatment until hypophysitis or adrenal insufficiency improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper • Replacement of relevant hormone(s) as indicated	

Recommended Adverse Events Management for Endocrine Events: Type I Diabetes Mellitus

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor glucose level more frequently until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary until glucose control is obtained	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines	
Grade 3 or 4 (hyperglycemia)	• Withhold study treatment until diabetes mellitus returns to grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initiate treatment with anti-hyperglycemics as clinically indicated	

Recommended Adverse Events Management for Hepatitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor liver function tests (LFT) more frequently until resolution to baseline values	• All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis
Grade 2 with: Elevated ALT & AST >3 and ≤5x ULN Or total bilirubin >1.5x and ≤3x ULN	• Withhold study treatment until hepatitis improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	• Monitor liver function tests (LFT) more frequently until resolution to baseline values • Consider appropriate consultation with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary • Consider inpatient monitoring for patients with ALT/AST >8x ULN and or elevated total bilirubin >3x ULN • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 1 month • If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	
Grade 3 or 4 with: Elevated ALT & AST >5x ULN or total bilirubin >3x ULN	• Permanently discontinue study treatment	• Same as above	

Recommended Adverse Events Management for Neurotoxicity

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Closely monitor the patient • If worsening, treat as grade 2 or 3 to 4, as clinically appropriate	• If immune-mediated encephalitis is suspected, consider radiologic assessment and, if possible, CSF assessment for auto-immune antibodies
Grade 2	• Withhold study treatment until improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Treat symptoms per local guidelines, eg 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent • If worsening, treat as grades 3 to 4 • Consider neurology consult	
Grade 3 or 4	• Permanently discontinue study treatment	• Neurology consult required • Treat symptoms per local guidelines AND give 1 to 2 mg/kg/day methylprednisolone IV • If improves to grade 2: taper with corticosteroids over at least 4 weeks • Consider adding prophylactic antibiotics for opportunistic infections • If worsening or atypical presentation, consider IVIG or other immunosuppressive therapies per local guidelines	

Recommended Adverse Events Management for Pneumonitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Consider withholding study treatment	• Monitor symptoms every 2 to 3 days • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • May resume study treatment upon improvement or resolution. If no improvement, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	• Withhold study treatment until pneumonitis improves and remains at grade 0-1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of ≥ grade 2 pneumonitis upon re-challenge	• Monitor symptoms daily; consider hospitalization • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider pulmonary function tests and laboratory work up for infections • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, treat as grade 3 • Consider empiric antibiotics if infection has not yet been fully excluded	

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 or 4 or Recurrent Grade 2 **Grade 3:** Severe symptoms; limiting selfcare ADL; oxygen indicated **Grade 4:** Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	• Permanently discontinue study treatment	• Inpatient care • Consultation with pulmonologist and infectious disease specialties • Treatment with systemic corticosteroids (2 to 4 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 6 weeks • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, consider additional immunosuppressive treatment ie, mycophenolate mofetil 1 to 1.5 g BID, infliximab 5 mg/kg IV • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Empiric antibiotics if infection has not yet been fully excluded • Consider adding prophylactic antibiotics for opportunistic infections	

Recommended Adverse Events Management for Renal Events

Immune-Mediated Nephritis with renal dysfunction CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	• All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents
Grade 2 Blood creatine increased > 1.5 – 3.0 X baseline or ULN	• Withhold study treatment until nephritis improves and remains at grade 0-1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consultation with nephrologist • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • Consider prophylactic antibiotics for opportunistic infections • Consider renal biopsy • If elevations persist >7 days or worsen, treat as severe AE	
Grade 3 Blood creatinine increased > 3.0 X baseline or > 3.0 – 6.0 x ULN **Grade 4 Blood creatine increased > 6.0 X ULN**	• Permanently discontinue study treatment	• Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate • Consider inpatient care and monitor creatinine daily • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If no improvement within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID	

Recommended Adverse Events Management for Uveitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Consultation with ophthalmologist within 1 week • Treatment with artificial tears	• All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (eg, glaucoma or cataracts)
Grade 2	• Withhold study treatment	• Urgent consultation with ophthalmologist • Treatment with topical/periocular/intravitreal corticosteroids and/or systemic corticosteroids guided by ophthalmologist • May resume study treatment if resolved to ≤ grade 1 and systemic steroid is reduced to ≤10 mg. Topical/ocular steroids are permitted during study treatment	
Grade 3 or 4	• Permanently discontinue study treatment	• Same as above • If severe or refractory to steroid treatment, consider infliximab	

Recommended Adverse Events Management for Myocarditis or Pericarditis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 - 2 **Grade 2**	• Consider withholding study treatment	• Immediate consultation with cardiologist • Inpatient care • Consider ECG, telemetry monitoring, cardiac MRI • Consider cardiac biomarker assessment (creatine kinase and troponin) or inflammatory biomarkers (ESR, CRP, WBC count, etc) • May offer immediate transfer to a coronary care unit for patient with elevated troponin or conduction abnormalities • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) initiated rapidly (oral or IV depending on symptoms) until resolution to baseline and taper over 4-6 weeks • Manage cardiac symptoms according to American College of Cardiology (ACC)/AHA guidelines and with guidance from cardiology	• All attempts should be made to rule out other causes such as metastatic disease and viral infection
Grade 3 - 4	• Permanently discontinue study treatment	• Same as above • Consider 1 g methylprednisolone pulse dose • If severe or refractory to steroid treatment, consider additional immunosuppressive agents	

Appendix E. Summary of Protocol Changes

Summary of Changes from version 5.1_dated 08.03.2023 to version 6.0_dated 11.20.2023
(This includes information from Admin Letters/Protocol Clarifications dated 8/29/2023 and 11/10/2023)

Section:	Original:	As amended:	Rationale:
Protocol Synopsis Number of Subjects	25	60	Increase to enrollment
Protocol Synopsis Duration of Study	4 years, 1.5 years of enrollment with potential for 2.5 years of patient follow up	6 years, 3.0 years of enrollment with potential for 3.0 years of patient follow up	Increase to duration of study
Study Schema	Stage 1: N=15 Stage 2: N=10 Efficacy evaluation: ≥ 2 responses to be achieved in the first 15 patients	Stage 1: N=28 Stage 2: N=32 Efficacy evaluation: ≥ 4 responses to be achieved in the first 28 patients	Increase to numbers in stages due to number of subjects increased
Schedule of Events	To allow for patient and investigator schedules, holidays, weather or other emergencies requiring facilities to be closed, visits after Cycle 1 Day 1 can be performed ±7 days.	To allow for patient and investigator schedules, holidays, weather or other emergencies requiring facilities to be closed, visits/evaluations after Cycle 1 Day 1 can be performed ±7 days. (This does not apply to study treatment. See footnotes L and L for those windows pertaining to Alirocumab and Cemiplimab.)	Added as per Protocol clarification letter dated 11/10/2023 for clarity
Schedule of Events Footnote J	J. Obtain blood for LDL and cholesterol (for safety) at the following time points: prior to start of study treatment; Cycle 2 Day 1, and at disease progression or at discontinuation of study treatment. Additional labs can be drawn per PI discretion. LDL will be performed by local clinical lab	J. Obtain blood for LDL cholesterol (for safety) at the following time points: prior to start of study treatment; Cycle 2 Day 1, and at disease progression or at discontinuation of study treatment. Additional labs can be drawn per PI discretion. LDL will be performed by local clinical lab. The preference is for this to be a fasting lab. Should the subject not be fasting at the draw time, please draw the lab anyway and document the fasting status at the time of draw.	Added as per Protocol clarification letter dated 8/29/2023 for clarity
Schedule of Events Footnote K	K. Patients will receive alirocumab 150mg sub-cutaneous (SC) every 2 weeks until disease progression, unacceptable toxicity, or completing 2 years of treatment. First dose of alirocumab will be administered in clinic. Subsequent dose of alirocumab will be self-administered by patient at home using the injector pen. For the 2nd and 3rd doses of alirocumab, the study coordinator will contact the patient by phone to remind them to self-administer dose of alirocumab. Patients will complete a drug diary card to document the date, time and injection location of alirocumab and return drug diary card for review by study coordinator at every clinic visit.	K. Patients will receive alirocumab 150mg sub-cutaneous (SC) every 2 weeks until disease progression, unacceptable toxicity, or completing 2 years of treatment. First dose of alirocumab will be administered in clinic. Subsequent dose of alirocumab will be self-administered by patient at home using the injector pen. For the 2nd and 3rd doses of alirocumab, the study coordinator/provider designee will contact the patient by phone to remind them to self-administer dose of alirocumab. Reminders for the injections given at home by phone contact can be the first cycle then as needed per provider's discretion. Patients will complete a drug diary card to document the date, time and injection location of alirocumab and return drug diary card for review by study coordinator at every clinic visit. For missed doses of Alirocumab: If a dose is missed: o Within 7 days from the missed dose, administer Alirocumab and resume the subject's original schedule. o More than 7 days after the missed dose, instruct the subject to wait until the next dose on the original schedule.	Added as per Protocol clarification letter dated 11/10/2023 for clarity

Section 3.2 Stage 1 Cohort	N/A	Changed as in study schema for first stage to be 28 patients and enrollment held after 28th patient to confirm 4 or more responders. If 3 or less responders in the 28 patients, then enrollment will be stopped	To account for increase in enrollment
Section 3.3 Stage 2 Cohort (Expansion)	N/A	Changed that if there are 4 or more objective responses in the first 28 patient cohort, then an expansion cohort with an additional 32 patients will be accrued	To account for increase in enrollment
Section 9.1 Sample Size Justification	N/A	An admissible two-stage design (Jung et al. 2004) will be used. We will not be interested in the study therapy if its true overall response (=PR+CR) rate (ORR) is 10% or lower, and will be highly interested if the true ORR is 25% or higher. In the first stage, 28 patients will be accrued. If there are 3 or fewer responders in these 28 patients, the study will be stopped by rejecting the study therapy. Otherwise (# of responders is 4 or more), an additional 32 patients will be accrued during the second stage for a total of 60. The null hypothesis will be rejected (or the study therapy will be accepted for further investigation) if 10 or more responders are observed from the cumulative 60 patients. This design assumes a one-sided alpha of 5% and a power of 90%. Accounting for about 5% of attrition due to ineligibility or drop out, a maximum of 60 patients will be enrolled.	Updated for increased # of patients
Section 9.2.1 Primary Endpoint	The primary objective is to describe the response rate associated with alirocumab and cemiplimab, with 95% confidence intervals.	The primary objective is to describe the response rate associated with alirocumab and cemiplimab, with 90% 2-sided (or 95% 1-sided) confidence intervals.	Updated to account for increase in enrollment
Section 5.6.1 Acceptable Concomitant Medications	All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care. All concomitant medication received from the date of signed informed consent through 30 days after the last dose of study drug should be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and intravenous medications	All treatments that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the local standards of medical care.	The need to add all concomitant medication in CRF has been removed as not needed
Section 5.6.2 Contraception	Non-pregnant, non-breast-feeding women must agree to use two highly effective birth control methods after informed consent is signed through 3 months after the last dose of study drug.	Non-pregnant, non-breast-feeding women must agree to use two highly effective birth control methods after informed consent is signed through 4 months after the last dose of study drug.	Updated contraception from 3 to 4 months to match IB and ICF
Section 4.1 Inclusion Criteria #9	Hepatic Serum total bilirubin ≤ 1.5 X ULN OR bilirubin < 3.0 ml/dL and direct bilirubin ≤ ULN for subject with Gilbert's syndrome with total bilirubin levels > 1.5 ULN	Hepatic Serum total bilirubin ≤ 1.5 X ULN OR bilirubin < 3.0 mg/dL and direct bilirubin ≤ ULN for subject with Gilbert's syndrome with total bilirubin levels > 1.5 ULN	Updated to correct ml/dL to mg/dL
Section 5.2 Treatment Period	N/A	Added "A -2 day window is allowed for C1D1 study assessments	Clarification that a -2 day window is allowed for C1D1 study assessments.

Appendix D: Summary of Protocol Changes	Changed to Appendix E	Changed to Appendix E: Summary of Protocol Changes	Changed Appendix D Summary of Protocol Changes to Appendix E so it is last appendix in protocol and added irAE management guidelines as Appendix D
Added new Appendix D: Guidelines for Management of Immune-Related Adverse Events			Appendix Section added at request of funding source, Regeneron

Summary of Changes from version 5.0 dated 1.24.2023 to version 5.1_dated 08.03.2023

(This includes information from Admin Letters/Protocol Clarifications dated 3/21/2023, 5/19/2023, 6/9/2023, and 7/31/2023)

Section:	Original:	As amended:	Rationale:
Footnote G – Schedule of Events	Baseline imaging will be performed with the relevant images to include CT scan (or MRI) of chest/abdomen/pelvis with or without contrast and all known or suspected sites of disease.	Baseline imaging will be performed with the relevant images to include CT scan (or MRI) of chest/abdomen with or without contrast and all known or suspected sites of disease.	Pelvic CT scan is not required
Table of Contents (TOC)	8.1 PCSK9 Levels	8.1 Low Density Lipoprotein (LDL) Cholesterol Levels	PCSK 9 level biomarkers were removed as biomarker study was removed
Table of Contents (TOC)	8.3 Future Use of Patient Samples	N/A	Removed from TOC as removed from protocol and TOC was not updated
Table of Contents (TOC)	N/A	Added Appendix D: Summary of Protocol Changes to TOC	Added Appendix D to have a list of protocol changes per version listed in the protocol
Schedule of Events	Footnote A: Screening (baseline) assessments are to be performed within 30 days prior to Cycle 1 Day 1 unless otherwise specified. Footnote B Footnote L: Patients will receive cemiplimab 350 mg IV every 3 weeks on day 1 and day 22 of each cycle until disease progression, unacceptable toxicity, or completing 2 years of treatment.	Footnote A: Screening (baseline) assessments are to be performed within 30 days prior to Cycle 1 Day 1 unless otherwise specified. Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day 1. Disregard Footnote B (X^B) at Thyroid Profile Cycle 1 Day 1 as it is incorrect Footnote L: Patients will receive cemiplimab 350 mg IV every 3 weeks on day 1 and day 22 of each cycle until disease progression, unacceptable toxicity, or completing 2 years of treatment. Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3 day window is allowed to accommodate scheduling problems.	Added "Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day 1" for clarity Correction Added infusion window for clarity
4.1 Inclusion Criteria #2	Progression after prior PD-1 directed therapy (as monotherapy or in combination with chemotherapy and/or anti-CTLA4, or anti-VEGF agents) – defined as investigator assessed progression from prior treatment.	Progression after prior PD-1/PDL1 directed therapy (as monotherapy or in combination with chemotherapy and/or anti-CTLA4, or anti-VEGF	Added PDL1

		agents) – defined as investigator assessed progression from prior treatment.	
4.1 Inclusion Criteria #6	Minimum of 4 weeks from any other experimental anti-cancer therapies or prior PD-1 treatment	Minimum of 4 weeks from any anti-cancer therapies or prior PD-1 treatment.	Minimum of 4 weeks for any anti-cancer therapies, not just experimental
Section 5.0 Study Assessments and Section 5.2 Treatment Period	Infusions may be delayed up to 7 days for Cycle 2 and beyond (but may not be given early).	Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3 day window is allowed to accommodate scheduling problems.	Added "Infusions may be delayed up to 7 days for Cycle 2 and beyond. A -3 day window is allowed to accommodate scheduling problems" as correction
5.1 Screening Period	Radiographic imaging (CT and/or MRI scans) of chest, abdomen, and pelvis and all known or suspected sites of disease Subject eligibility is determined using lab results obtained prior to receipt of study treatment on Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study. Thyroid profile	Radiographic imaging (CT and/or MRI scans) of chest and abdomen, and all known or suspected sites of disease Subject eligibility is determined using lab results obtained prior to receipt of study treatment on Cycle 1 Day 1. Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day 1. Any laboratory assessments repeated on Cycle 1 Day 1 must meet eligibility requirements. The Screening Period ends upon receipt of the first dose of study drug or final determination that the subject is ineligible for the study. Thyroid profile removed from under Section 5.1, "The following study procedures must be done within 14 days prior to Cycle 1 Day 1."	Removed scan of pelvis as not required Added "Screening labs done within 7 days prior to treatment initiation do not have to be repeated on Cycle 1 Day1" to last paragraph in Section 5.1 for clarity Remove thyroid profile from screening as incorrect
5.7 Tumor Assessments	Radiographic imaging will be performed with the relevant imaging to include CT scan of chest/abdomen/pelvis with or without contrast and/or MRI scan of abdomen/pelvis and all known or suspected sites of disease.	Radiographic imaging will be performed with the relevant imaging to include CT scan of chest/abdomen with or without contrast and/or MRI scan of chest/abdomen and all known or suspected sites of disease.	Removed scan of pelvis as not required
8.0 Correlatives	Blood-based biomarker studies will be performed to better understand the role of factors that may be associated with efficacy or toxicity from study treatment and/or cancer biology. Additional markers related to efficacy, toxicity, and/or cancer biology may be analyzed.	Removed the whole paragraph about biomarker studies	Biomarker studies are not being performed

	Anticipated analyses are listed below and focus on factors associated with inflammation, immunity, and tumor growth. However, final analyte lists and technology platforms will be based upon best science and available funding at the time of analysis. External vendors and collaborators may conduct or participate in these analyses, provided samples are de-identified. All collaborations will be subject to Duke Policies on sample and data sharing.		
10.2 Serious Adverse Events	SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs from the date of the first dose of study drug through 28 days following the last dose of study drug, whether or not related to study drug(s), must be recorded on the adverse events CRF.	SAEs and/or follow up to SAEs including death due to any cause other than progression of the cancer under study, that occurs **from time of informed consent through 90 days after discontinuation of the Regeneron product**, whether or not related to study drug(s), must be recorded on the adverse events CRF.	Updated so that section 10.2 and 10.2.1 agree. SAEs should be recorded **from time of informed consent through 90 days after discontinuation of the drug**