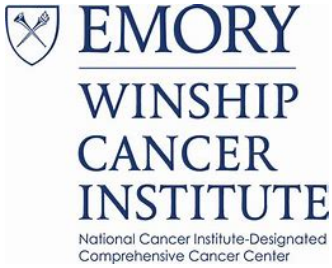

PROTOCOL TITLE: A phase 2 study of docetaxel, ramucirumab, and pembrolizumab for patients with metastatic or recurrent non-small cell lung cancer who progressed on platinum-doublet and PD-1/PD-L1 blockade

WINSHIP PROTOCOL #: WINSHIP4950-20

COORDINATING CENTER: Winship Cancer Institute, Emory University

PRINCIPAL INVESTIGATOR:

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VERSION: (Version 4.0; 3/7/2025)

FUNDING SOURCE: Merck

INVESTIGATIONAL PRODUCT (IP): pembrolizumab (supplied by Merck)
OTHER AGENT(S): docetaxel and ramucirumab (commercially available)

IND #:
X **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Section Number	Section Title	Description of Change(s)	Rationale
Header	Header	**Correction:** version and date updated throughout the document	New Version
Cover page	Cover page	**Correction**: statistician name, address, and telephone	Previous statistician left institution
4.1.1	Participant Inclusion Criteria	**Deletion:** 12. Human immunodeficiency virus (HIV) infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial	To be consistent program wide requirement (including Company Sponsored and MISP studies) and align with exclusion criteria #18
		Deletion: 13. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated, cured and have an undetectable HCV viral load.	To be consistent with program wide requirement (including Company Sponsored and MISP studies) and align with exclusion criteria #19
4.1.2	Participant Exclusion Criteria	**Insertion:** 18. … Note: no HIV testing is required unless mandated by local health authority.	To align with pembrolizumab program standard version 11 protocol template
		Insertion: 19. … Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.	
4.2.3	Dose modification and toxicity management	**Correction:** Table 4. Aligned left instead of justified some of the contents	Alignment correction
5.1	Study Flow Chart (Table)	**Deletion:** ":" after **Trial Period,** Treatment Cycle/Title, Scheduling window (Days)	Typo correction
		Correction: Follow-Up (use dash and capital U throughout table); Discon (capital D throughout table)	Typo correction

		Correction: blood tests that will be ordered if clinically indicated were moved and placed after mandatory tests	Better organized
		Correction: mandatory imaging (CT) moved and placed ahead of the imaging that will only be ordered if clinically indicated	Better organized
		Deletion: PET/CT and MRI chest/Abdomen	List only the strongly preferred imaging in calendar
		Correction: interval of imaging	Align with primary endpoint 6-month PFS
		Insertion: Every 12 weeks and at end of treatment	Clarify timing of MRI Brain and Bone Scan if clinically indicated
		Insertion: [e] and [f] next to X	Clarify correlative studies blood collection
5.1	Study Flow Chart (Legend and footnotes)	**Correction:** Font in the mid of the legend	Font correction
		Deletion: "End of Treatment" from a:	Typo correction
		Insertion: Subsequent tumor imaging will be performed every 6 weeks (42 days ±7 days) from Cycle 1 Day 1 during first 6 months, then every 9 weeks (63 days ±7 days) between 6 months and 1year, then every 12 weeks (84 days ±7 days) after 1 year. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Every effort should be made to continue tumor imaging using same interval for participants who discontinue study treatment without documented disease progression.	Provided specifics for interval of imaging to align with primary endpoint 6-month PFS and clarification for spacing interval of imaging
		Deletion: footnote g	Not needed

		Deletion: footnote h	Not needed; clarification added to footnote c
		Insertion: End of Treatment	Clarify acronym
6.1.2.6.1	Initial Tumor Imaging	**Change:** Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated.	Provided specifics for interval of imaging to align with primary endpoint 6-month PFS
		Change and insertion: After 6 months, participants who remain on treatment will have imaging performed every 9 weeks (63 days ±7 days) until 1 year, and every 12 weeks (84 days ±7 days) thereafter.	Clarified spacing interval of imaging; since 6 months is a fixed period, it is not necessary to place equivalent in days
6.1.2.6.2	Tumor imaging during the study	**Correction: (**Section 9.2.1.6) will be replaced by (Table 7, Figure 3)	Section 9.2.1.6 does not exist on current template; reference updated throughout iRECIST text
		Correction: Section 9.2.1.6 will be replaced by Appendix 4	
		Insertion and correction: Exceptions are possible upon consultation with Merck; (Section 9.2.1.6) will be replaced by (Table 7, Figure 3, and Appendix 4)	
6.1.2.6.4	Figure	**Correction:** Figure 1 was corrected to Figure 3	Keep with succession of figures in the text
6.1.5.3.2	Follow-up Visits	**Correction:** After 1 year, the imaging time point will occur every 12 weeks (± 7 days).	Typo correction; align with interval of imaging plan
Template		**Change:** using new Emory IRB protocol template	Align with Emory IRB new template
Table 5	4.2.3	**Change:** Table 5 updated from MISP v.12 template	Align with updated dose modification guidelines on MISP v.12
Version 2.0 revisions			
Cover page	Cover page	**Deletion:** co-investigator name and contact	One co-investigator left institution

3.1.2	Preclinical and Clinical Trial Data	**Correction:** EHFR changed to EGFR	Typo correction
4.2	Trial Treatments	**Insertion:** "following the sequence"	Align to match with the approved and established treatment order sequence for this study
4.2.1	Timing of Dose Administration	**Insertion:** "We are not aware of any clinical concern of administering docetaxel prior to ramucirumab. To maximize the clinical benefit of this study treatment in patients who have already progressed on PD-1/PD-L1 blockade, we will give chemotherapy with docetaxel upfront in an attempt to enhance tumor anti-genecity and tumor mutation burden. This will be followed by an anti-angiogenic agent, ramucirumab, in an attempt to modulate the tumor immune microenvironment. And last, we will administer pembrolizumab." **Insertion:** "However, in this study, we will administer docetaxel prior to ramucirumab based on the rational provided above."	Added rational and clarification for the treatment sequence
5.1	Study Flow Chart (Legend and footnotes)	**Change:** footnotes d and e **Insertion:** footnotes f and g **Insertion:** footnotes d, f, and g in table	Clarified timepoints for tissue collection and for correlative studies blood collection
5.1	Study Flow Chart	**Deletion:** Pre-screening Consent line	This study does not have a pre-screening consent
6.1.4.2	Treatment period	**Correction:** Docetaxel, Ramucirumab, and Pembrolizumab	Align to match with the approved and established treatment order sequence for this study

6.2.3	Immediate Reporting of Adverse Events to the Principal Investigator and to Merck	**Deletion:** IND language	IND language is not required for this IND-exempt study
		Correction: 90 days instead of 30 days "For the time period beginning at treatment allocation through 90 days following cessation of treatment"	Align with MISP protocol guidance
		Insertion: "(or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier)"	Align with MISP protocol guidance
Table 3	4.2	**Change:** Pembrolizumab moved to 3rd row in Table 3	Align to match with the approved and established treatment order sequence for this study
Table 10	8.1	**Change:** Ramucirumab moved to 2nd row and pembrolizumab moved to 3rd row	Align to match with the approved and established treatment order sequence for this study
Version 2.1 revisions			
Cover page	Cover page	**Insertion:** co-investigators names and contact information	Two co-investigators added to the study
		Deletion: co-investigator name and contact, VA institution	Co-investigator is moving to another institution
Study summary, 1.1, 4.3, 7.1, 7.3	Study summary Study design Treatment allocation Trial design Statistical analysis plan	**Insertion:** We estimate to enroll 60 participants to account for screen failures in order to have 41 evaluable patients (study summary) **Insertion:** evaluable (1.1, 4.3, 7.1, 7.3) **Insertion:** We estimate to enroll 60 participants to account for screen failures (7.3)	To clarify the total number of patients accounting for screen failures and evaluable patients for analysis

Version 2.2 revisions			
Study summary, 7.3	Study summary Statistical analysis plan	**Correction:** We estimate to enroll 45 participants to account for screen failures in order to have 41 evaluable patients (study summary) **Correction:** We estimate to enroll 45 participants to account for screen failures (7.3)	To clarify the total number of patients including screen failures to account 10% above target. Should this prove insufficient as the study proceeds, we will discuss any change that might prove necessary with the funding source
Table 4	4.2.3	**Insertion:** (defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg)	Added definition of severe hypertension
Version 2.3 revisions			
3.2.4.2, 5.1, 6.1.2.7, 6.1.4.2	Biomarker Research Study Flow Chart Tumor Tissue Collection and Correlative Studies Blood Sampling Treatment Period	**Change:** 2nd timepoint blood collection was moved from cycle 1 between day 8 and 15 to cycle 2 day 1 prior to drug administration	To eliminate the inconvenience of an extra visit for blood draw on participants and improve accrual on correlative studies
2.3, 3.2.4.2, 6.1.2.7	Exploratory Objective(s) Biomarker Research Tumor Tissue Collection and	**Change:** RNA sequencing replaced by mass cytometry on tumor	To clarify the technology used on tumor infiltrating immune cells collected from fresh biopsy specimen and align with current budget
		Change: "after treatment" to "at end of treatment"	To align 2nd biopsy timing throughout protocol

	Correlative Studies Blood		
3.2.4.2, 5.1, 6.1.2.7	Biomarker Research Tumor Tissue Collection and Correlative Studies Blood	**Insertion:** We will use Winship Cancer Tissue and Pathology (CTP) Shared Resource to ensure specimens for the study are properly tracked for reporting purposes and stored prior to distributing them to the recipient lab (Winship Immune Monitoring Shared Resource at the end of the study for analysis. Winship CTP will follow their standard biorepository processes as described in IRB00045796 (PI: Schneider, Storage & Research Use of Tissue & Information). **Deletion:** Address: HSRB E330 – phone: 404-727-3701)	To clarify the need for Winship Cancer Tissue and Pathology (CTP) Shared Resource
		Insertion: tube for each timepoint	To clarify that the amount of blood collected refer to each time timepoint
		Insertion: Blood tubes will be delivered at room temperature, on same day if possible, or overnight, to Winship Cancer Tissue and Pathology (CTP) Shared Resource (1365B Clifton Road, 3rd Floor, 3200 – phone: 404-778-5108). Winship CTP standard process is to aliquot plasma into 4 x 0.5ml aliquots and 4 x 1.0ml aliquots before storage at -80. PBMC are cryopreserved at ~5x10^6 cells/aliquot and stored long-term in LN2. Blood collected outside of the windows indicated below or missed blood collections will not constitute protocol deviations. Blood collection timing may vary because appointments may not be scheduled solely for this study.	To clarify delivery, processing, and storage of the research blood samples and include language to eliminate protocol deviations if samples are not collected or are collected outside these timepoints

		Insertion: Freshly obtained biopsies will be logged and de-identified by Winship CTP (Address: B3200) before distribution to the recipient lab (Address: B3204). Tumor tissue collected outside of the windows indicated above or missed tumor tissue collections will not constitute protocol deviations. Tumor tissue collection timing may vary because appointments may not be scheduled solely for this study.	To clarify delivery of the research tumor samples with new room address and include language to eliminate protocol deviations if samples are not collected or are collected outside these timepoints
		Insertion: in coordination with the recipient lab (Address: B3204 – phone 404-727-3701) and Winship CTP (Address: B3200 – phone: 404-778-5108). Tumor studies will only be offered to participants accrued at Emory. **Insertion:** foot note h: Tissue collection will only be offered to participants accrued at Emory. Biopsies will be coordinated with the recipient lab (Address: B3204 – phone 404-727-3701) and Winship CTP (Address: B3200 – phone: 404-778-5108). **Deletion:** Address: HSRB E330. We can also arrange for pickup if main lab number is called: 404-727-3701.	To clarify coordination of arranging fresh biopsies for analysis and to limit this option to the main research site for logistical reasons
Version 3.0 revisions			
Cover page	Cover page	**Insertion:** Ascension Sacred Heart Pensacola	Emory required multi-site language
Study Summary	Description of Sites/Facilities Enrolling	**Insertion:** Winship Cancer Institute of Emory University (Atlanta, GA)	Emory required multi-site language

	Participants:	Ascension Sacred Heart (Pensacola, FL)	
Section 3.2	Section 3.2	**Insertion:** We propose a prospective multicenter (Emory and Ascension Sacred Heart Pensacola) phase II clinical trial to study this combination.	Emory required multi-site language
Section 8.5	Returns and Reconciliation	**Insertion:** The IDS (Investigational Drug Service) personnel at Winship and Ascension Sacred Heart Pensacola will account for all study drugs.	Emory required multi-site language
Section 4.1	Study Population	**Insertion:** We plan to have 41 participants complete the protocol required research procedures and estimate to enroll 45 participants across all sites to account for screen failures. Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, multidisciplinary tumor board at Emory University and Ascension Sacred Heart Pensacola. Emory: The number of participants who are expected to be enrolled and screened at Winship is 33, and the number of participants needed to complete the research procedures (i.e., number of participants excluding screen failures) is 35. Ascension Sacred Heart Pensacola: The number of participants who are expected to be enrolled and screened at Mayo Clinic is 8, and the number of participants needed to complete the research procedures (i.e., number of participants excluding screen failures) is 10.	Emory required multi-site language

Section 11	Section 11	**Insertion:** Multi-Site language	Adding Ascension Sacred Heart Pensacola to the study and needing to insert multi-site language
Version 4.0 revisions			
Cover page	Cover page	**Deletion:** Ascension Sacred Heart Pensacola Insertion: non-Emory collaborating site	Non-Emory collaborating site will be determined if necessary to complete accrual
Study Summary	Description of Sites/Facilities Enrolling Participants		
Section 3.2	Section 3.2		
Section 8.5	Returns and Reconciliation		
Section 4.1	Study Population		
Section 11	Section 11		
Study summary, 1.1, 4.1, 4.3, 7.1, 7.3	Study summary Study Design Study Population Treatment Allocation Trial Design Sample size	**Change:** We estimate to consent up to 45 patients to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study in order to have 21 evaluable patients for the primary endpoint (Study Summary). **Change:** We will include 21 evaluable patients to assess the safety of the combination treatment and its efficacy in terms of 6-month progression free survival (PFS) targeting a 25% increase (1.7-fold) over the historic PFS on REVEL study (i.e. from 37% to 62%) (Study Design)	To clarify the total number of patients accounting for screen failures, dropout prior to 6 months, and evaluable patients for analysis

		Change: We plan to have 21 participants complete the protocol required research procedures for the primary endpoint and estimate to consent up to 45 patients across all sites to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study (Study Population) **Deletion:** Emory: The number of participants who are expected to be enrolled and screened at Winship is 33, and the number of participants needed to complete the research procedures (i.e., number of participants excluding screen failures) is 35. Ascension Sacred Heart Pensacola: The number of participants who are expected to be enrolled and screened at Mayo Clinic is 8, and the number of participants needed to complete the research procedures (i.e., number of participants excluding screen failures) is 10 (Study Population) **Change:** In the first stage, 10 evaluable patients will be accrued. If there are 4 or fewer patients with free of progression at 6-month among these 10 patients, the study will be stopped for futility. Otherwise, 11 additional evaluable patients will be accrued for a total of 21 (Treatment Allocation)	

		Change: Simon's two-stage optimum design will be used. The null hypothesis that the 6-month PFS rate is 37% will be tested against one-sided alternative hypothesis that the actual 6-month PFS rate is higher than 62%. In the first stage, 10 evaluable patients will be accrued. If there are 5 or more patients who progressed or died prior to 6 months among these 10 patients, the study will be stopped early for futility. Otherwise, 11 additional evaluable patients will be accrued for a total of 21 patients. The null hypothesis will be rejected if 11 or more remain free of progression or death by 6 months among 21 evaluable patients. This design yields a type I error of 0.10 and power of 80% when the actual 6-month PFS rate is 62%. To account for early dropout prior to 6 months on study, we plan to enroll up to 30 patients. The calculation is based on current enrollment status including early dropout (among 23 enrolled, 5 dropouts without progression at 6 months and 2 did not complete cycle 1 of study treatment). (Trial Design) **Change:** We will include 21 evaluable patients to assess the safety of the combination treatment and its efficacy in term of 6-month PFS rate as defined by 25% increase (1.7-fold) from the historic 6-month PFS rate on REVEL study (37% to 62%). We estimate to consent up to 45 patients to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study (Sample size)	

4.1	Table 3	**Insertion:** infusion timing for each agent **Insertion:** Sites should make every effort to target infusion duration of each administered agent to be as close as possible to the recommended infusion duration of each agent. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes will be permitted.	To clarify the infusion duration for each agent and add a time window to allow technical variabilities
4.1	Table 4	**Insertion:** Resume ramucirumab no sooner than 2 weeks after surgery and until adequate wound healing. **Deletion:** no sooner than 28 days after surgery and until the surgical wound is fully healed. Discontinue ramucirumab for wound healing complications that require medical intervention.	To align with ramucirumab package insert 3/2022
5.1	Study Flow Chart	**Insertion:** +3 days under column 1 of 21-day treatment cycle	To allow flexibility similar to other cycles for sites who can't bill for provider and infusion chair on same day.
Page 3		Updated IRB approved pending status	

Table of Contents

STUDY SUMMARY

Abbreviated Title	**Docetaxel, ramucirumab, and pembrolizumab in metastatic or recurrent NSCLC**
Trial Phase	*Phase 2*
Clinical Indication	NSCLC
Trial Type	Prospective, single arm, open-label
Type of control	N/A
Route of administration	Intravenously
Trial Blinding	N/A
Treatment Groups	Single arm: NSCLC patients who progressed on platinum-based and any of the FDA-approved PD-1 or PD-L1 immune checkpoint inhibitors, when given sequentially or in combination, and who were not previously exposed to docetaxel or ramucirumab.
Number of trial participants	We estimate to consent up to 45 patients to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study in order to have 21 evaluable patients for the primary endpoint.
Estimated enrollment period	24 months
Estimated duration of trial	24 months
Duration of Participation	Until progression of the disease confirmed on 2 consecutive scans obtained at least 4 weeks apart, or occurrence of severe side effects, or if the patient or the treating physician believes that continuing on the study treatment is not in the best interest of the patient.
Estimated average length of treatment per patient	6 months
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA) Non-Emory collaborating site (TBD)

1.0 STUDY DESIGN

1.1 Study Design

This is a prospective, single arm, open-label, phase 2 study of the combination of docetaxel, ramucirumab, and pembrolizumab for adult patients with metastatic or recurrent NSCLC that progressed after receiving concomitantly or sequentially a platinum-doublet chemotherapy and a PD-1 or PD-L1 checkpoint inhibitor. The combination will be administered every 21 days until confirmed disease progression defined as progression on 2 consecutive scans at least 4 weeks apart, or occurrence of severe side effects, withdrawal of consent by the patient or if in the opinion of the treating physician continuing on the study treatment is not in the best interest of the patient.

We will include 21 evaluable patients to assess the safety of the combination treatment and its efficacy in terms of 6-month progression free survival (PFS) targeting a 25% increase (1.7-fold) over the historic PFS on REVEL study (i.e. from 37% to 62%). We will first evaluate safety of the 3-drug regimen in an initial run-in of six patients. If less than 2 of 6 patients experience dose limiting toxicity, we will continue with the efficacy assessment of the combination. If safety signals are noted, we will consider dose reduction, when clinically appropriate, for the subsequent group of patients.

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the 28-day screening period. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s). Rescreening after screen failure will be allowed.

Treatment will continue until unacceptable toxicity, death, disease progression per RECIST 1.1, Investigator's decision to discontinue treatment, patient withdraws consent, lost to follow-up, or Institution decides to terminate the trial. Patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator; see Section "Treatment beyond progression". Patients with a PR or SD will continue to receive treatment until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR.

2.0 OBJECTIVE(S) & HYPOTHESIS(ES)

2.1 Primary Objective(s) & Hypothesis(es)

Objective: To determine the anti-tumor efficacy of the combination treatment using the 6-month progression free survival rate (6-month PFS rate) by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Hypothesis: We hypothesize that the combination of docetaxel, ramucirumab, and pembrolizumab is safe and more effective than docetaxel and ramucirumab in patients with metastatic or recurrent NSCLC who have progressed on platinum-based chemotherapy given concomitantly or sequentially with a PD-1 or PD-L1 immune checkpoint inhibitor.

2.2 Secondary Objective(s) & Hypothesis(es)

Objectives:

(1) To determine the safety profile and tolerability of docetaxel and ramucirumab in combination with pembrolizumab in patients who progressed on platinum-based chemotherapy and PD-1 or PD-L1 checkpoint inhibitor given sequentially or in combination.

(2) To determine immune related adverse events of the combination docetaxel, ramucirumab, and pembrolizumab.

(3) To assess the overall response rate (ORR) of the combination docetaxel, ramucirumab, and pembrolizumab.

(4) To assess the overall survival (OS) of the combination docetaxel, ramucirumab, and pembrolizumab.

2.3 Exploratory Objective(s)

Objectives:

(1) To correlate treatment response with PD-L1 22C3 expression, STK11 and KRAS mutation status.

(2) To correlate treatment response with the doublet tumor mutation burden (TMB) and PD-L1 22C3 expression.

(3) To perform an immunophenotypic analysis of circulating immune cells by mass cytometry before and after treatment and EOT.

(4) To analyze the tumor infiltrating immune cells by mass cytometry coupled to blood mass cytometry, in paired biopsies before and at end of after treatment.

3.0 BACKGROUND & RATIONALE

3.1 Background

Immunotherapy in cancer

The development of therapeutic agents that binds to the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) is one of the major advances in the treatment of lung cancer in the last decade. In particular, pembrolizumab (formerly MK-3475 and lambrolizumab, trade name Keytruda®), was the first FDA-approved anti-PD-1 therapy in oncology. Immunotherapy is an established modality for the treatment of lung cancer. Inflammation and immune escape play crucial roles in the progression of disease while on immune checkpoint inhibitors.

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

In September 2014, the US Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab as treatment of relapsed or refractory melanoma. This designation was granted based on early findings of efficacy and unmet medical need for melanoma patients. Since then, pembrolizumab and other PD-1/PD-L1 inhibitors have received FDA-approval for the treatment of a variety of solid tumors including lung cancer. Most pembrolizumab's approved indications are based on the companion diagnostic test PD-L1 22C3 expression. In addition, pembrolizumab is the only tissue-agnostic immune checkpoint inhibitor (ICI) that is FDA-approved for any unresectable or metastatic solid tumor with mismatch repair deficiency (dMMR) or microsatellite instability (MSI high).

3.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in lung cancer.

Non-Small Cell Lung Cancer (NSCLC) current treatments

NSCLC represents a heterogeneous cancer, with different biology and clinical behavior. For wild type NSCLC, chemotherapy with platinum-doublet and PD-1 or PD-L1 checkpoint inhibitor, given in combination or sequentially, are the main 2 effective treatment approaches. For mutant type metastatic NSCLC, an oral tyrosine kinase inhibitor targeting the appropriate mutation is the preferred upfront treatment for these patients.

To overcome therapeutic limitations of chemotherapy, investigators have explored the use of anti-angiogenic agents prior to immune therapy. The development of hypoxia within a growing tumor activates the hypoxia-inducible factors (HIF-1a and HIF-2a) that in turn activate multiple intracellular signaling pathways leading to the generation and release of pro-angiogenic factor from within the tumor and stroma responsible of the formation of new capillaries and blood vessels. Thus, inhibition of the angiogenesis pathway by targeting VEGF-A and VEGFR-2 lead to new treatment options for NSCLC: the two monoclonal antibodies, bevacizumab (1st line) and ramucirumab (2nd line and beyond), are FDA-approved therapies when administered in combination with chemotherapy.

After progression on platinum doublets, docetaxel with or without ramucirumab, a human IgG1 monoclonal antibody that targets the extracellular domain of VEGFR-2, was the preferred 2nd line

therapy before the immune therapy era with checkpoint inhibitors. The combination resulted in a modest improvement in overall survival (OS) compared to docetaxel alone. The REVEL study [Garon E.B. *et al*., 2014] is a randomized, double-blind, placebo-controlled, multicenter phase 3 study of to treat patients with NSCLC that progressed on platinum doublet. 624 patients received docetaxel 75 mg/m^2 with ramucirumab 10 mg/kg every 3 weeks and 621 patients received docetaxel 75 mg/m^2 with placebo every 3 weeks until disease progression, unacceptable toxicity, withdrawal, or death. OS was the primary endpoint. Median OS was 10.5 vs. 9.1 months (HR 0.86; 95% CI: 0.75, 0.98; *p* =0.023) and median PFS was 4.5 vs. 3 months (HR 0.76; 95% CI: 0.68, 0.86; *p* <0.0001) in the combination and control arms, respectively.

The investigator-assess overall response rate (ORR) was 23% vs. 14% (odds ratio [OR] 1.89, 95% CI: 1.41, 2.54; *p* <0.0001) and the disease control rate (DCR) in 64% vs. 53% (OR 1.60, 95%CI: 1.28, 2.01; *p* <0.0001) in combination and control arms, respectively. Non-squamous and squamous subgroups had the same response rate benefit.

TRAE of any grade were noted in 98% of the treatment arm and 95% in the control arm. The most common severe TRAE were neutropenia 49% vs. 40%, febrile neutropenia 16% vs. 10%, fatigue 14% vs. 10%, leukopenia 14% vs. 12%, fatigue 14% vs. 10%, hypertension 6% vs. 2%, and diarrhea 5% vs. 3% in the treatment and control arms, respectively. Toxicities were manageable with appropriate dose reductions and supportive care. Grade ≥3 pulmonary hemorrhage (1%) and death from adverse events (5% vs. 6%) were not significantly different between both arms.

3.1.2 Preclinical and Clinical Trial Data

Immune therapy has changed the paradigm of how we treat lung cancer. It is now a standard of care treatment for lung cancer patients in 1st line and beyond in the metastatic space and in consolidation after definitive therapy with concurrent chemoradiation for locally advanced, non-metastatic, unresectable disease.

Pembrolizumab was initially approved as monotherapy for 2nd line treatment of NSCLC patients with PD-L1 ≥1% in the metastatic setting [Herbst, R.S., *et al.*, 2016] In Keynote-010, 354 patients were assigned to pembrolizumab 2mg/kg, 346 to pembrolizumab 10 mg/kg, and 343 to docetaxel. The primary endpoints were overall survival (OS) and progression free survival (PFS). OS was longer with pembrolizumab 10.4 (hazard ratio 0.71; 95% CI: 0.58, 0.88; *p*= 0.0008) and12.7 (hazard ratio 0.61; 95% CI: 0.49, 0.75; *p*< 0.0001) months, compared to 8.5 months with docetaxel. Similarly, PFS was significantly longer with pembrolizumab than with docetaxel (5, 5.2, and 4.1 months respectively). Severe treatment-related adverse events (TRAE) were less common with pembrolizumab than with docetaxel (13%, 16%, and 35% in the 3 arms, respectively).

Similarly, nivolumab was approved as monotherapy for 2nd line treatment of NSCLC patients disregards their PD-L1 status in the metastatic setting [Brahmer, J. *et al.,*2015]. In CheckMate 017, 272 patients were randomized to receive either nivolumab or docetaxel. The primary endpoint was OS. Median OS was 9.2 vs. 6 months (HR 0.59; 95% CI: 0.44, 0.79; *p*<0.001) and 1-

year OS was 42% vs. 24% with nivolumab and docetaxel, respectively. Median PFS was 3.5 vs. 2.8 months (HR 0.62; 95% CI: 0.47,0.81; *p* <0.001) with nivolumab and docetaxel, respectively. Grade 3-4 TRAE were reported by patients in 7% in the nivolumab arm and 55% in the docetaxel arm.

Later on, pembrolizumab was approved as monotherapy in the 1st line setting for wild type, NSCLC patients with PD-L1 ≥50% in the metastatic setting [Reck, M. *et al*., 2016]. In Keynote-024, 305 previously untreated patients were randomly assigned to receive pembrolizumab 200 mg every 3 weeks or the investigator's choice of platinum-based systemic therapy. Crossover was allowed on progression. The median PFS, primary endpoint, was longer in the pembrolizumab arm (10.3 months) compared to chemotherapy (6 months); (hazard ratio 0.50; 95% CI: 0.37, 0.68; *p*< 0.001). Response rate was higher in the pembrolizumab arm (44.8 vs. 27.8%). The median duration of response was longer in pembrolizumab arm (not reached; range, 1.9+ to 14.5+ months) vs. 6.3 months (range, 2.1+ to 12.6+) in the chemotherapy arm. TRAE of any grad were less frequent (73.4% vs. 90%) as were the severe TRAE (26.6% vs. 53.3%). Median OS was significantly longer in the pembrolizumab arm (30 months) compared to 14.2 months in the chemotherapy arm. In an updated follow up analysis, pembrolizumab continued to show significant OS benefit (over chemotherapy n this population despite crossover to pembrolizumab on progression [Reck, M., et al.,2019].

Pembrolizumab has also demonstrated superiority when given in combination with platinum-based chemotherapy regardless of PD-L1 expression in NSCLC of nonsquamous [Gandhi, L., et al., 2018] and squamous cell carcinoma [Paz-Ares, L., et al. 2018] histology (KeyNote-189 and -407).

The ICI indications in the lung cancer patients are in adjuvant[8] (PACIFIC) and metastatic settings: in monotherapy [Reck, M. *et al* 2016; Mok, T.S.K. *et al.* 2019; Herbst, R.S., *et al.*, 2016; Brahmer, J. *et al.,* 2015] (KeyNote-024, -042, -010, and CheckMate 017) or, in combination with chemotherapy [13, 14] [Gandhi, L. *et al.*, 2018; Paz-Ares, L. *et al.,* 2018] (KeyNote-189 and -407) or with another monoclonal antibody targeting angiogenesis [Socinski, M.A. *et al.*, 2018] (IMpower 150). Studies using ICI with radiation therapy, immune therapies with different mechanism of action, tyrosine kinase inhibitor, or with surgery are in current development. Pembrolizumab's approved indications in monotherapy are based on the companion diagnostic test PD-L1 22C3 expression (in 1st line, ≥50% in first line per KeyNote-024 and ≥1% per KeyNote-042; in 2nd line, ≥1% per KeyNote-010). In addition, pembrolizumab is the only tissue-agnostic ICI that is FDA-approved for any unresectable or metastatic solid tumor with mismatch repair deficiency or microsatellite instability [Le, D.T. *et al.*, 2015] (KeyNote-016).

Recently, the combination of anti-PD-L1, anti-angiogenic and chemotherapy: Atezolizumab with Bevacizumab, Carboplatin, and Paclitaxel was approved in the 1st line setting in metastatic NSCLC patients with no EGFR or ALK genomic tumor aberrations disregard their PD-L1 expression [Socinski, M.A. *et al.*, 2018]. In IMpower 150, 356 patients were assigned in the ABCP arm and 336 to the BCP arm. The estimated median PFS, primary endpoint, was 8.3 months for patients receiving the 4-drug regimen and 6.8 months for those receiving the 3-drug regimen (hazard ratio 0.62; 95% CI 0.52, 0.74; *p* <0.001). This was consistent across all clinical subgroups analyzed with notable benefit in the small subgroup with EGFR and ALK genetic alterations. The 1-year PFS was

36.5 vs. 18%, respectively. The estimated median OS was 19.2 months for patients receiving the 4-drug regimen and 14.7 months for those receiving carboplatin, paclitaxel, and bevacizumab (hazard ratio 0.78; 95% CI: 0.64, 0.96; *p*= 0.02). The overall response rates were 63.5% in the 4-drug arm and 48% in the control arm. 3 patients (0.8%) had a grade 5 febrile neutropenia related to the 4-drug regimen. No new safety signals were identified with the combination and TRAE frequency was similar to that reported in previous trials with chemotherapy and ICI combination.

3.2 Rationale

Currently, the treatment options for NSCLC after progression on platinum-based chemotherapy and immunotherapy are relatively limited; docetaxel monotherapy [Fossella, F.V., et al., 2000] or in combination [Garon, E.B., et al., 2014] with ramucirumab remain the best available standard salvage treatment with a modest increase in median PFS of 3 and 4.5 months, respectively, when used in 2nd line prior to immune therapy era. Thus, there is an urgent and unmet need for innovative therapies in this population. The role of chemotherapy in combination with PD-1 inhibition after progression on prior PD-1 or PD-L1 based regimens is not known. Anecdotal reports in patients progressing on ICI suggest a higher response rate to docetaxel compared to historical experience. Furthermore, pathologic tumor related angiogenesis promotes tumor growth and may also contribute to immune escape in patients treated with ICI.

We hypothesize that the combination of **docetaxel**, **ramucirumab**, and **pembrolizumab** is safe and more effective than docetaxel and ramucirumab in patients with metastatic or recurrent NSCLC who progressed on platinum-based chemotherapy given concomitantly or sequentially with a PD-1 or PD-L1 immune checkpoint inhibitor. We propose a prospective multicenter (Emory and non-Emory collaborating site) phase II clinical trial to study this combination.

Rationale for combining pembrolizumab with docetaxel and ramucirumab:

Angiogenesis and immunosuppression are two hallmarks of tumor growth. VEGF is important in modulating the tumor immune microenvironment [Rivera, L.B. and G. Bergers 2015; Terme, M., E. et al. 2013; Yang, J. et al. 2018]. It induces PD-1 expression, impedes T cell extravasation, inhibits the proliferation and cytotoxicity of cytotoxic T lymphocytes, impairs the differentiation, maturation, and activation of dendritic cells, stimulates the proliferation of T regulatory (T_{reg}) cells, stimulates the accumulation and activity of myeloid-derived suppressor cells (MDSCs). The abnormal tumor vasculature promotes immune suppression in the tumor microenvironment. This effect can be reversed with anti-VEGF therapy. Furthermore, antiangiogenic therapies and immune checkpoint inhibitors have independently demonstrated clinical efficacy in NSCLC.

In addition, chemotherapy enhances antigenicity of the tumor, increases tumor mutation burden (TMB), enhances T cell activation, PD-L1 expression, and response rate.

Therefore, combining pembrolizumab with docetaxel and ramucirumab is therefore a rational next step for this population with unmet need.

- Preclinical experience for combining anti angio-genesis and immune stimulation:
  The potential of increased efficacy of combining both strategies is supported by preclinical findings *in vivo* NSCLC models where the combination significantly inhibited tumor growth whereas neither treatment alone had a significant effect [Shi, S., et al., 2013]: by normalizing tumor vasculature and decreasing hypoxic tumor microenvironment, there was increase in cytokine-induced killer cells' proliferation, cytotoxicity and migration as well decreased accumulation in suppressive immune cells in the tumor tissue. In addition, there was increased tumor-infiltration lymphocytes compared with other treatments. Ziogas *et al.* [Ziogas A.C., et al., 2012] found that T cells secrete VEGF and express VEGFR-2 upon activation and that VEGF directly suppress T cell activation from ovarian cancer patients and healthy individuals is mediated by VEGFR-2.

- Clinical experience for combining anti angio-genesis and immune stimulation:
  Multiple trials investigating anti-angiogenic agents in combination with immunotherapy in NSCLC are ongoing.

  Previously treated: (presented at 2018 ASCO Annual Meeting)

  Herbst et al presented the phase 1 clinical trial findings of the combination of ramucirumab and pembrolizumab at the 2018 ASCO Annual Meeting [Herbst, R.S., *et al.*, 2019]. 92 previously treated cancer patients with NSCLC (n= 27), gastric and gastro-esophageal junction (n= 17) and urothelial (n= 48) cancers were treated with the combination of ramucirumab and pembrolizumab (Figures 1 and 2). The safety profile was consistent with that of each individual drug. There were no additive toxicities. The NSCLC cohort was treated with ramucirumab 10 mg/kg and pembrolizumab 200 mg on Day 1 every 3 weeks after 1-3 prior lines of therapy. Median follow-up for this cohort was 32.8 months. ORR was observed in 8 (30%) patients and stable disease was observed in 56% of patients with NSCLC. Fatigue (36%) was the most common treatment-related adverse event (TRAE) of any grade. Grade 3 or 4 TRAE occurred in 26% of patients with the most common being hypertension (7%). One (1%) patient on the gastro-esophageal adenocarcinoma had a Grade 5 TRAE; none on NSCLC cohort. This combination was safe and active. It will be tested in a larger, randomized trials within LUNGMAP (S1800A).

Table 1: Adverse events of the combination ramucirumab and pembrolizumab.

	G/GEJ (2nd-3rd line) n=41		NSCLC (2nd-4th line) n=27		UC (2nd-4th line) n=24		Total, n=92		
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3	Grade 4
Any	34 (83)	12 (29)	26 (96)	7 (26)	15 (63)	4 (17)	75 (82)	19 (21)	4 (4)[b]
Fatigue[a]	18 (44)	2 (5)	9 (33)	1 (4)	6 (25)	0	33 (36)	3 (3)	0
Hypertension	5 (12)	3 (7)	8 (30)	2 (7)	3 (13)	1 (4)	16 (17)	6 (7)	0
Hypothyroidism	4 (10)	0	7 (26)	0	2 (8)	0	13 (14)	0	0
Decreased appetite	5 (12)	0	4 (15)	1 (4)	1 (4)	0	10 (11)	1 (1)	0
Nausea	3 (7)	0	4 (15)	0	4 (17)	0	11 (12)	0	0
Diarrhea	2 (5)	1 (2)	5 (19)	0	2 (8)	1 (4)	9 (10)	2 (2)	0
Infusion related reaction	6 (15)	1 (2)	2 (7)	1 (4)	1 (4)	0	9 (10)	2 (2)	0
Rash[a]	8 (20)	0	1 (4)	0	0	0	9 (10)	0	0
Pruritus	5 (12)	0	2 (7)	0	1 (4)	0	8 (9)	0	0
AST increased	2 (5)	0	2 (7)	0	3 (13)	0	7 (8)	0	0
Proteinuria	1 (2)	0	3 (11)	1 (4)	3 (13)	0	7 (8)	1 (1)	0
Epistaxis	3 (7)	0	4 (15)	0	0	0	7 (8)	0	0
ALT increased	1 (2)	0	2 (7)	0	3 (13)	0	6 (7)	0	0
Headache	1 (2)	0	3 (11)	0	2 (8)	0	6 (7)	0	0
Pyrexia	2 (5)	0	0	0	4 (17)	0	6 (7)	0	0
Anemia	2 (5)	1 (2)	3 (11)	0	1 (4)	0	6 (7)	0	1 (1)
Vomiting	1 (2)	0	3 (11)	0	2 (8)	0	6 (7)	0	0
Abdominal pain[a]	3 (7)	3 (7)	2 (7)	0	1 (4)	0	6 (7)	3 (7)	0
Stomatitis	2 (5)	1 (2)	4 (15)	0	0	0	6 (7)	1 (1)	0
Thrombocytopenia[a]	1 (2)	0	3 (11)	0	1 (4)	0	5 (5)	0	0
Colitis	3 (7)	3 (7)	0	0	2 (8)	2 (8)	5 (5)	5 (5)	0

Data are number (%). The table shows treatment-related adverse events according to preferred term or [a]consolidated categories; [b]A total of 4 patients experienced Grade 4 treatment-related AEs: anemia (G/GEJ), cholestasis (G/GEJ), pneumocystic jirovecii pneumonia (G/GEJ), pulmonary sepsis (G/GEJ), and hypokalemia (NSCLC). One patient died due to pulmonary sepsis, deemed related to treatment by the investigator.

Signs of Efficacy	PD-L1 <1 % (n = 11)	PD-L1 ≥1 % (n = 11)
ORR, % (95% CI)	18% (2.3-51.8)	45% (16.7-76.6)
PFS, months (95% CI)	9.7 (2.1-13.9)	6.9 (2.8-NR)
OS, months (95% CI)	17.0 (10.5-NR)	NR (4.0-NR)

Figure 1. NSCLC Cohort tumour response assessment per RECIST v1.1 by investigator review. (A): Treatment duration and response; (B): Change in tumour size over time.

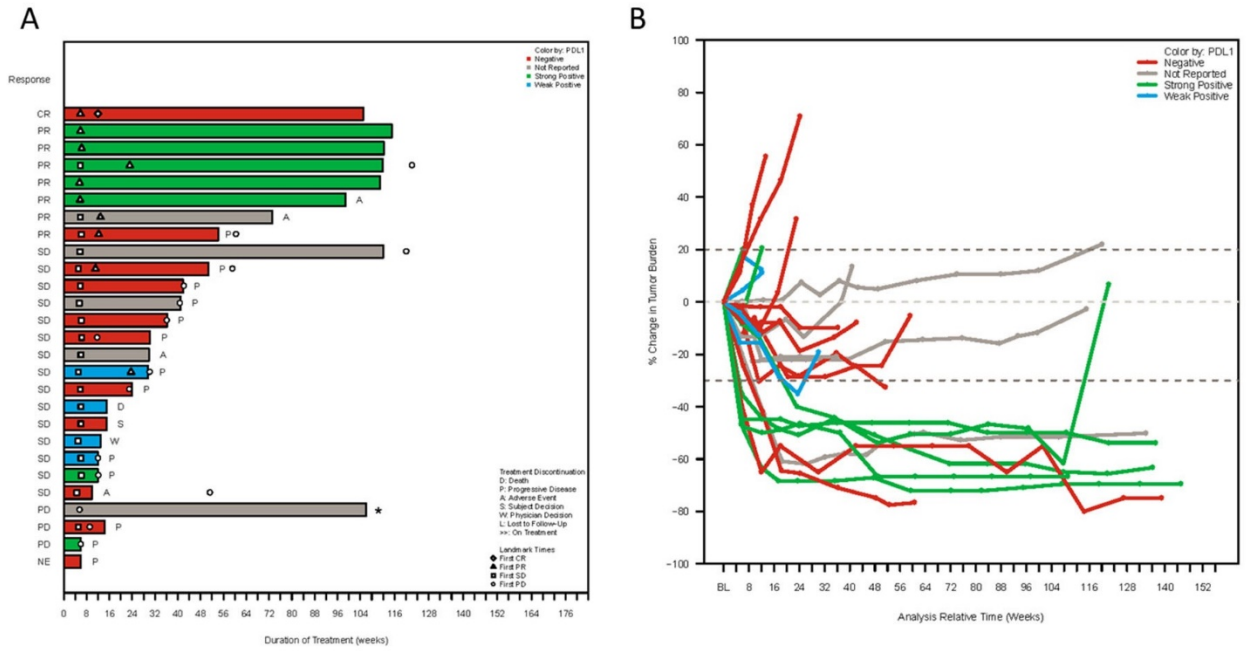
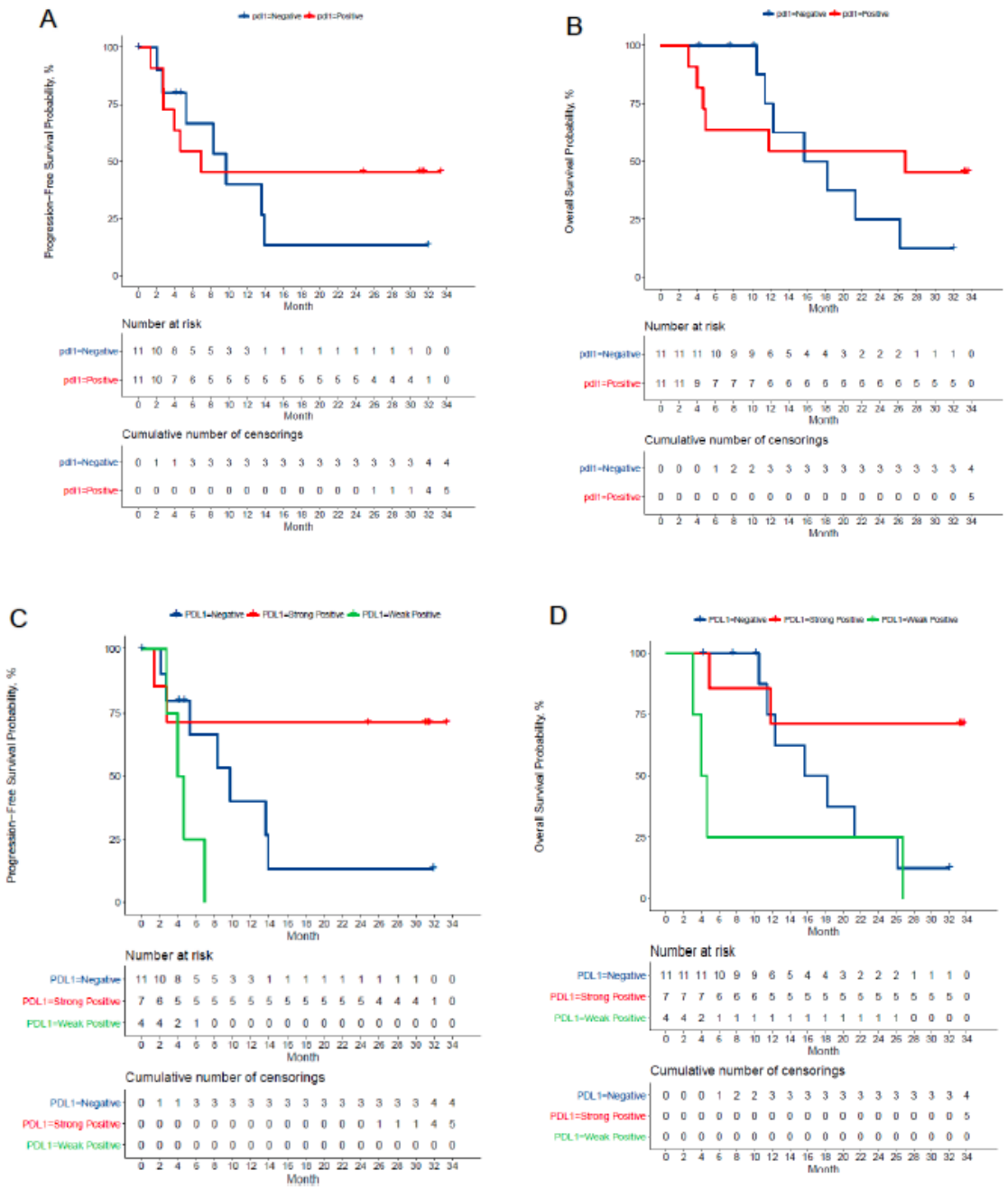


Figure 2. NSCLC Cohort. (A) Progression-free survival, (B) Overall survival by PD-L1 status (negative/positive) (C) Progression-free survival, (D) Overall survival by PD-L1 status (negative <1% / strong positive ≥50% / weak positive 1-49%).



Treatment Naïve: (presented at 2019 ESMO Annual Meeting)

In a phase 1 expansion cohort of ramucirumab and pembrolizumab in 26 advanced treatment-naïve patients with NSCLC with PD-L1 22C3 ≥1%, Herbst et al found that the combination has a manageable safety profile with no additive toxicities and was active. 11 (42.3%) patients had Grade ≥3 TRAEs, most commonly hypertension (15.4%) and myocardial infarction (7.7%). No patients discontinued because of TRAEs.

Signs of Efficacy	PD-L1 1-49 % (n = 9)	PD-L1 ≥50 % (n = 16)
ORR, % (95% CI)	22.2% (2.8-60.0)	56.3% (29.9-80.2)
PFS, 12-month (95% CI)	33.3% (7.8-62.3)	56.2% (26.9-77.6)
OS, 12-month (95% CI)	66.7% (28.2-87.7)	75.0% (46.3-89.8)

Based on above, ramucirumab plus pembrolizumab should be further explored with chemotherapy.

3.2.1 Rationale for the Trial and Selected Population

The combination of docetaxel plus ramucirumab is recommended after progression on platinum-doublet chemotherapy for patients with metastatic or recurrent NSCLC. While taxane containing doublet chemotherapy has been safely combined with pembrolizumab, there is no data on the combination of docetaxel, ramucirumab and pembrolizumab. However, we expect that the proposed combination to be safe, with manageable safety profile and with no additive toxicity. Our expectation is based on the encouraging facts that there was no additive toxicity with the combination docetaxel / ramucirumab, the combination pembrolizumab / ramucirumab, and the combination of Atezolizumab / Bevacizumab / Carboplatin / Paclitaxel. Therefore, the study combination of docetaxel, ramucirumab, and pembrolizumab would not pose a significant risk and would not require an IND.

This study design addresses safety concerns and accommodates this patient population by providing access to this novel combination therapy and will allow us to understand the mechanism of tackling three hallmarks of cancer by combining immunotherapy, chemotherapy, and anti-angiogenic in NSCLC patients exposed to immunotherapy.

3.2.2 Comprehensive Adverse Events and Potential Risks List

The Adverse Event and Potential Risks list provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system.

Refer to the package inserts for the comprehensive list of adverse events.

Ramucirumab

The following adverse events, associated with the use of ramucirumab as single agent, have been reported:

- Cardiovascular: Hypertension, arterial thrombosis.
- Hematologic: neutropenia, anemia, hemorrhage.
- Respiratory: Epistaxis
- Gastrointestinal: Diarrhea (14%), intestinal obstruction (2%)
- Genitourinary: Proteinuria
- Endocrine & metabolic: Hyponatremia
- Central nervous system: Headache
- Immunologic: Antibody development
- Dermatologic: Skin rash
- Miscellaneous: Infusion related reaction
- Thyroid Dysfunction: Hypothyroidism (2.6%)

Toxicity of ramucirumab in combination with docetaxel:
In the REVEL clinical trial, patients received either ramucirumab 10 mg/kg or placebo intravenously in combination with docetaxel.

The most common serious adverse reactions in patients who received **ramucirumab with docetaxel** were febrile neutropenia (14%), pneumonia (6%), and neutropenia (5%). The use of granulocyte colony-stimulating factors was 42% in ramucirumab with docetaxel-treated patients versus 37% in patients who received placebo with docetaxel.

The most common adverse reactions leading to treatment discontinuation of ramucirumab were infusion-related reaction (IRR) (0.5%) and epistaxis (0.3%).

The most common adverse reactions (all grades) observed in ramucirumab with docetaxel-treated patients at a rate of ≥30% and ≥2% higher than placebo with docetaxel were neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation.

Clinically relevant adverse drug reactions reported in ≥1% and <5% of ramucirumab with docetaxel-treated patients in REVEL were:

- Hyponatremia (4.8%)
- Proteinuria (3.3%)

Warning and Precautions:

Hemorrhage: ramucirumab increased the risk of hemorrhage and gastrointestinal hemorrhage, including Grade ≥3 hemorrhagic events.

Gastrointestinal Perforations: ramucirumab can increase the risk of gastrointestinal perforation, a potentially fatal event.

Impaired Wound Healing: Impaired wound healing can occur in patients who receive drugs that inhibit the VEGF or VEGFR pathway. Ramucirumab, a VEGFR2 antagonist, has the potential to adversely affect wound healing. Ramucirumab has not been studied in patients with serious or non-healing wounds.

Arterial Thromboembolic Events: Serious, sometimes fatal, arterial thromboembolic events (ATEs), including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia, occurred across clinical trials.

Hypertension: An increased incidence of severe hypertension occurred in patients receiving ramucirumab. Control hypertension prior to initiating treatment with ramucirumab. Monitor blood pressure every two weeks or more frequently as indicated during treatment.

Infusion-Related Reactions: Prior to the institution of premedication recommendations across clinical trials of ramucirumab, IRRs occurred in 6 out of 37 patients (16%), including two severe events. The majority of IRRs across trials occurred during or following a first or second ramucirumab infusion. Symptoms of IRRs included rigors/tremors, back pain/spasms, chest pain and/or tightness, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.

Worsening of Pre-existing Hepatic Impairment: Clinical deterioration, manifested by new onset or worsening encephalopathy, ascites, or hepatorenal syndrome, was reported in patients with Child-Pugh B or C cirrhosis who received single agent ramucirumab.

Reversible Posterior Leukoencephalopathy Syndrome: Reversible Posterior Leukoencephalopathy Syndrome (RPLS) has been reported in <0.1% of 1916 patients enrolled in five clinical studies with ramucirumab.

Proteinuria Including Nephrotic Syndrome: Across five clinical studies in 1916 patients with various cancers treated with ramucirumab, the incidence of all Grade proteinuria ranged from 3-20%. Grade ≥3 proteinuria (including 4 patients with nephrotic syndrome) incidence ranged from <1-3%.

Thyroid Dysfunction: Across five clinical studies in 1916 patients with various cancers treated with ramucirumab, the incidence of Grade 1-2 hypothyroidism ranged from <1-3%; no grade 3-5 reported.

Embryo-fetal toxicity: Based on its mechanism of action, ramucirumab can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF and VEGFR2 to critical aspects of female reproduction, embryo-fetal development, and postnatal development.

Docetaxel

The most **serious adverse reactions** from docetaxel are: toxic deaths, hepatotoxicity, neutropenia, hypersensitivity, and fluid retention.

The most common **adverse reactions** across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

Pembrolizumab
Most common adverse reactions (reported in ≥20% of patients) were:

Pembrolizumab as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

Pembrolizumab in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis.

Pembrolizumab in combination with ramucirumab: diarrhea, fatigue, hypertension, hypothyroidism.

3.2.3 Justification for Dose

Ramucirumab is approved for metastatic NSCLC. The recommended dose is 10 mg/Kg administered intravenously every 3 weeks over 60 minutes infusion time.

Docetaxel is approved for metastatic NSCLC. For treatment after failure of prior platinum-based chemotherapy, docetaxel was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks.

Pembrolizumab (anti-PD-1): the planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

3.2.4 Rationale for Endpoints

We will study the efficacy and safety profile of the study combination in patients with NSCLC who progressed on platinum doublet and immune therapy. We chose the 6-month PFS as primary endpoint because it is a more reliable endpoint to quantify the impact of ICI and efficient to

assess in the context of a single institution study. The safety profile will be studied because there is no study that has tested the combination yet. The correlative studies will help us find predictive biomarkers for efficacy and impact of this combination on the immune system cells.

3.2.4.1 Efficacy Endpoints

Primary Endpoint:

6-month Progression-free Survival (PFS) rate as determined by RECIST 1.1.

Secondary Endpoints:

- Toxicity will be evaluated according to NCI CTCAE Version 5.0.
- ORR will be determined per RECIST 1.1 and iRECIST
- OS is defined from treatment start date to date of death for any cause.

3.2.4.2 Biomarker Research

Various factors that could potentially affect clinical response to treatment with Pembrolizumab in combination with Docetaxel and Ramucirumab will be investigated in peripheral blood in pre-treatment, after treatment and upon progression as well on tumor specimens (optional).

Data from these investigations will be evaluated for associations with clinical efficacy data. All samples collected may also be used for exploratory analyses to assess biomarkers associated immunotherapy treatment.

We will use Winship Cancer Tissue and Pathology (CTP) Shared Resource to ensure specimens for the study are properly tracked for reporting purposes and stored prior to distributing them to the recipient lab (Winship Immune Monitoring Shared Resource at the end of the study for analysis. Winship CTP will follow their standard biorepository processes as described in IRB00045796 (PI: Schneider, Storage & Research Use of Tissue & Information).

Peripheral blood samples

Blood samples will be collected for immunophenotypic analysis of circulating immune cells by mass cytometry before and after treatment and EOT. The goal is to characterize treatment emergent changes in immune cells (T, B, myeloid cells) using a 35-marker panel. For this, we would collect 30 ml of blood in green top (heparin) tube for each timepoint. Blood tubes will be delivered at room temperature, on same day if possible, or overnight, to Winship Cancer Tissue and Pathology (CTP) Shared Resource (1365B Clifton Road, 3rd Floor, 3200 – phone: 404-778-5108). Winship CTP standard process is to aliquot plasma into 4 x 0.5ml aliquots and 4 x 1.0ml

aliquots before storage at -80. PBMC are cryopreserved at ~5x10^6 cells/aliquot and stored long-term in LN2. Blood collected outside of the windows indicated below or missed blood collections will not constitute protocol deviations. Blood collection timing may vary because appointments may not be scheduled solely for this study.

- At Baseline, on cycle 1 day 1 prior to drug administration (if no planned optional biopsy); otherwise, same day of the optional biopsy
- On Cycle 2 day 1 prior to drug administration
- At the EOT discontinuation visit (if no planned EOT optional biopsy); otherwise, same day of EOT optional biopsy.

Tumor Tissue

Tissue biopsies will be collected for analysis of tumor infiltrating immune cells mass cytometry coupled to blood mass cytometry, in paired biopsies before (within 28 days prior to C1D1) and at end of treatment in coordination with the recipient lab (Address: B3204 – phone 404-727-3701) and Winship CTP (Address: B3200 – phone: 404-778-5108). Tumor studies will only be offered to participants accrued at Emory. The goal is to evaluate treatment emergent changes in tumor microenvironment in diverse immune cell subsets. Freshly obtained biopsies will need to be logged and de-identified by Winship CTP (Address: B3200) before distribution to the recipient lab (Address: B3204). Tumor tissue collected outside of the windows indicated above or missed tumor tissue collections will not constitute protocol deviations. Tumor tissue collection timing may vary because appointments may not be scheduled solely for this study.

If the information is already known, tissue will be evaluated to measure TMB, PDL-1 22C3 expression, STK11 and KRAS mutations (if known).

When sufficient quantities of fresh tissue is available, it will be preserved for future exploratory studies including genomic profiling.

4.0 METHODOLOGY

4.1 Study Population

We plan to have 21 participants complete the protocol required research procedures for the primary endpoint and consent up to 45 participants across all sites to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study. Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, multidisciplinary tumor board at Emory University and non-Emory collaborating site.

4.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of non-small cell lung cancer will be enrolled in this study.
2. Patients must have progressed on a platinum-based chemotherapy and any of the FDA-approved PD-1 or PD-L1 immune checkpoint inhibitors, either given sequentially or in combination.
3. A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period plus an additional 120 days after the last dose of study treatment and refrain from donating sperm during this period.
4. A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:
   a.) Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
   OR
   b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days plus 30 days (a menstruation cycle) after the last dose of study treatment.
5. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
6. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
8. Life expectancy > 12 weeks as determined by the Investigator.
9. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected within 10 days prior to the start of study treatment.

Table 2: Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine

clearance (GFR can also be used in place of creatinine or CrCl)	levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. [a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. [b] Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

10. Palliative radiotherapy (to bone or soft tissue lesions) must be completed >1 week prior to start of study drug (exception: palliative radiotherapy for pain may be used any time prior to first dose).
11. Clinically significant toxic effect(s) of the most recent prior anti-cancer therapy must be Grade 1 or resolved (except alopecia and sensory neuropathy); patients with Grade 2 adrenal insufficiency related to prior anti-cancer therapy (defined as requiring medical intervention, such as concomitant steroids) or Grade 2 hypothyroidism (defined as requiring hormone replacement therapy) may be enrolled provided that clinical symptoms are adequately controlled and the daily dose is 10 mg or less of prednisone or equivalent. If the patient received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
12. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
13. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association (NYHA) Functional Classification (Appendix 1 B). To be eligible for this trial, patients should be class 2B or better.

4.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. A WOCBP with a positive urine pregnancy test within 72 hours prior of the planned treatment on Day 1 of each cycle (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

2. Patients have prior exposure to docetaxel or ramucirumab.

3. Patients with proteinuria of ≥2+ on dipsticks or urine protein/creatinine ratio of >1 g/24-hour.

4. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks or 5 times the half-life time, whichever is shorter [could consider shorter interval for kinase inhibitors or other short half-life drugs] prior to allocation.

   Note: Participants must have recovered from all AEs due to previous therapies to Grade ≤1 or baseline. Participants with Grade ≤2 neuropathy may be eligible.

   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

5. Has received prior radiotherapy within 1 week of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

6. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

7. Is currently participating in or has participated in a study of an investigational device within 4 weeks prior to the first dose of study treatment.

8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

9. Patients with symptomatic brain metastasis (patients with treated brain metastasis without symptoms and not requiring steroid are allowed to participate).

10. Has severe hypersensitivity (Grade ≥3) to pembrolizumab and/or any of its excipients.

11. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

12. Patients with significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 6 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association (Appendix 1B) Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy.

13. Patients with any major hemorrhage or thromboembolic events within 3 months prior to start on this study.

14. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis or established interstitial lung disease.

16. Patients who had prior history of immune-related adverse event (irAE) that required treatment with steroids and permanent ICI discontinuation per NCCN guidelines.

17. Has an active infection requiring systemic therapy.

18. Has a known history of Human Immunodeficiency Virus (HIV). Note: no HIV testing is required unless mandated by local health authority.

19. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

20. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.

4.1.3 Lifestyle Restrictions

4.1.3.1 Meals and Dietary Restrictions

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

4.1.3.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception.

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

4.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 6.2.2.

4.1.5 Use in Nursing Women

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

4.2 Trial Treatments

The treatment to be used in this trial is outlined below following the sequence in Table .

Table 3: Trial Treatment Sequence

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Docetaxel	75 mg/m^2	Q3W	IV infusion over 60 minutes	Day 1 of each 3-week cycle	Standard of Care
Ramucirumab	10 mg/kg	Q3W	IV infusion over 60 minutes	Day 1 of each 3-week cycle	Standard of Care
Pembrolizumab	200 mg	Q3W	IV infusion over 60 minutes	Day 1 of each 3-week cycle	Experimental

Trial treatment should begin on the day of allocation or as close as possible to the date on which treatment is allocated. Sites should make every effort to target infusion duration of each administered agent to be as close as possible to the recommended infusion duration of each agent. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes will be permitted.

4.2.1 Timing of Dose Administration

We are not aware of any clinical concern of administering docetaxel prior to ramucirumab. To maximize the clinical benefit of this study treatment in patients who have already progressed on PD-1/PD-L1 blockade, we will give chemotherapy with docetaxel upfront in an attempt to enhance tumor anti-genecity and tumor mutation burden. This will be followed by an anti-angiogenic agent, ramucirumab, in an attempt to modulate the tumor immune microenvironment. And last, we will administer pembrolizumab.

Ramucirumab

Prior to each Ramucirumab infusion, premedicate all patients with an intravenous histamine-1 receptor antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 IRR, premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each Ramucirumab infusion.

The recommended dosage of Ramucirumab is 10 mg/kg administered by intravenous infusion over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion. However, in this study, we will administer docetaxel prior to ramucirumab based on the rational provided above.

Injection: 100 mg/10 mL (10 mg/mL) or 500 mg/50 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

Docetaxel

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

For treatment after failure of prior platinum-based chemotherapy, Docetaxel was evaluated as monotherapy, and the recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks (-5 minutes and +10 minutes).

Pembrolizumab

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 5.0). Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

All trial treatments will be administered on an outpatient basis. All trial treatments may be administered up to 3 days before or after the scheduled Day 1 of each cycle.

4.2.2 Definition of dose-limiting toxicities (DLT)

A DLT is defined as one of the following AEs that occur within the first 4 weeks of the study treatment (DLT observation period), if considered to be definitely, probably, or possibly related to the study regimen by the investigator; and fulfills any one of the following criteria using NCI CTCAE Version 5.0:

1. Nonhematologic toxicity as follows:
    a) Grade 4 nonlaboratory toxicity
    b) Grade 3 nonlaboratory toxicity (for example, nausea, vomiting, and diarrhea) lasting
        >3 days despite optimal supportive care
    c) Any Grade 3 or Grade 4 laboratory value if:
        i) Medical intervention is required to treat the patient, or
        ii) The abnormality persists for >1 week.

    Note: Liver function abnormality: For patients with liver metastasis who begin treatment with Grade 2 aspartate aminotransferase (AST) or alanine amino transferase (ALT), if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 7 days.

2. Hematologic toxicity, as follows:
    a) Grade 4 toxicity lasting ≥ 7 days, or
    b) Grade 3 thrombocytopenia if associated with bleeding and requires platelet transfusion, or

c) Febrile neutropenia Grade 3 or Grade 4

3. Grade 5 toxicity (that is, death)

4. Any other significant toxicity deemed by the primary investigator and Merck clinical research personnel to be dose limiting, for example:

a) Any toxicity that is possibly related to study treatment that requires the withdrawal of the patient from the study during Cycle 1, or

b) A delay of > 14 days due to persistent Grade ≥ 2 toxicities in initiating Cycle 2, with the exception of Grade 2 fatigue

Any infusion or hypersensitivity reactions occurring during the infusion of the drug are not considered dose-related and therefore will NOT be considered to be a DLT.

After each of the 3 patients in a dose schedule completes the observation period, a safety analysis will occur; the data will be reviewed by study investigators and Merck, and the findings documented, indicating whether each dose schedule is or is not well tolerated. The results will inform the decision whether or not to move onto Phase 2.

4.2.3 Dose Modification and toxicity management

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drugs is required per the guidance below.

Ramucirumab

Prior to each **Ramucirumab** infusion, premedicate all patients with an intravenous histamine-1 receptor antagonist (e.g., diphenhydramine hydrochloride). For patients who have experienced a Grade 1 or 2 infusion-related reaction (IRR), premedicate with a histamine-1 receptor antagonist, dexamethasone (or equivalent), and acetaminophen prior to each **Ramucirumab** infusion.

Reduce dose, withhold dose, or discontinue **Ramucirumab** to manage adverse reactions as described in Table 4 and are based on criteria in the **Ramucirumab** package insert.

Table 4: Dose Modification for Immune-related Adverse Events Associated with Ramucirumab**.**

Adverse Event	Dose Modification
Infusion-related reactions	• Reduce infusion rate by 50% for grade 1 or 2 • Permanently discontinue for grade 3 or 4

Hypertension	• Interrupt infusion for severe hypertension (defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg) until controlled with medical management • Permanently discontinue if severe hypertension cannot be controlled with antihypertensive therapy
Proteinuria	• Interrupt ramucirumab for urine protein levels ≥2g/24h (first occurrence). Reinitiate treatment at a reduced dose of 8 mg/Kg every 3 weeks once the protein level returns to <2g/24h. • If the urine protein level ≥2g/24h reoccurs, interrupt ramucirumab and reduce the dose to 6 mg/Kg every 3 weeks once the urine protein level returns to <2g/24h. • Permanently discontinue if urine protein levels >3g/24h or in the setting of nephrotic syndrome.
Wound healing complications (all grades)	Withhold ramucirumab for 28 days prior to elective surgery. Resume ramucirumab no sooner than 2 weeks after surgery and until adequate wound healing.
Arterial thromboembolic events (all grades)	Permanently discontinue ramucirumab
Gastrointestinal perforation (all grades)	Permanently discontinue ramucirumab
Grade 3 or 4 bleeding	Permanently discontinue ramucirumab
Reversible posterior leukoencephalopathy syndrome	Permanently discontinue ramucirumab for confirmed diagnosis

Docetaxel

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3/4 non-hematological toxicities during Docetaxel Injection treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop grade ≥3 peripheral neuropathy should have Docetaxel Injection treatment discontinued entirely.

Pembrolizumab

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

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

Table 5: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

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

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

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

	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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

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

Table 6: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _Pembrolizumab____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

4.3 Treatment Allocation

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements will receive Docetaxel and Ramucirumab in combination with pembrolizumab.

Subjects will be enrolled sequentially: 6 patients will be enrolled and evaluated for safety data. If less than 2 patients experience dose limiting toxicity (DLT), we will continue with the efficacy assessment of the combination.

In the first stage, 10 evaluable patients will be accrued. If there are 4 or fewer patients with free of progression at 6-month among these 10 patients, the study will be stopped for futility. Otherwise, 11 additional evaluable patients will be accrued for a total of 21.

Patient will be considered evaluable for safety data if the patient has received at least 1 infusion of (agent) and had safety assessments for a minimum of 4 weeks or have had a DLT during the first 4 weeks of treatment.

4.4 Stratification

N/A.

4.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

4.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant’s welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF)

including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 6.2.

4.5.2 Prohibited Concomitant Medications

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

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

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

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the Investigator, the Sponsor and the participant.

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

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.
In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of Docetaxel Injection and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with Docetaxel Injection, close monitoring for toxicity and a Docetaxel Injection dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided.

Avoid coadministration of study drugs with strong CYP3A4 inducers, strong CYP3A inhibitor or a sensitive CYP3A4 substrate.

4.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 4.2.3, [Table 4 and 5]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to study treatment, the Investigator does not need to follow the treatment guidance. Refer to [Table 4-5] in Section 4.2.3 for guidelines regarding dose modification and supportive care.

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

4.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 6.1.4 – Other Procedures.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 6.1.2.6
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 4.2.2 and 4.2.3.
- If both docetaxel and ramucirumab are discontinued, patients will be allowed to continue on pembrolizumab only
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of Ramucirumab and Docetaxel beyond the date when the initial CR was declared.
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 4.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Administrative reasons

4.7 Participant Replacement Strategy

Patients who are not evaluable for toxicity during the safety period will be replaced. Similarly, patients who are not evaluable for efficacy will be replaced.

4.8 Clinical Criteria for Early Trial Termination

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

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

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

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period	**Screening Phase**	**21- day Treatment Cycles**			**End of Treatment[a]**	**Post-Treatment**		
Treatment Cycle/Title	Main Study Screening (Visit 1)	1	Subsequent cycles		Discon	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
			Even	Odd				
Scheduling Window (Days)	-28 to -1	+3	± 3	± 3	At time of Discon	30 days post Discon	Every 8 weeks post Discon	Every 12 weeks
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographics, Height and Medical History	X							
Prior and Concomitant Medication Review	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X				
Post-study anticancer therapy status						X	X	X
Survival Status							X	X
Clinical Procedures/Assessments								
Review Adverse Events	X	X	X	X	X	X	X	

Trial Period	**Screening Phase**	**21- day Treatment Cycles**			**End of Treatment[a]**	**Post-Treatment**		
Treatment Cycle/Title	Main Study Screening (Visit 1)	1	Subsequent cycles		Discon	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
			Even	Odd				
Scheduling Window (Days)	-28 to -1	+3	± 3	± 3	At time of Discon	30 days post Discon	Every 8 weeks post Discon	Every 12 weeks
Full Physical Examination	X				X	X		
Directed Physical Examination		X	X	X				
ECOG Performance Status	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory								
Pregnancy Test – Urine or Serum β-HCG[b]	X	X	X	X				
PT/INR and aPTT (prior to optional biopsies)	X				X			
CBC with Differential	X	X	X	X	X			
Comprehensive Serum Chemistry Panel	X	X	X	X	X			
FT3, FT4 and TSH	X			X	X			
Urinalysis	X		X	X	X			
Spot urine for protein / creatinine	X		X	X	X			

Trial Period	**Screening Phase**	**21- day Treatment Cycles**			**End of Treatment[a]**	**Post-Treatment**		
Treatment Cycle/Title	Main Study Screening (Visit 1)	1	Subsequent cycles		Discon	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
			Even	Odd				
Scheduling Window (Days)	-28 to -1	+3	± 3	± 3	At time of Discon	30 days post Discon	Every 8 weeks post Discon	Every 12 weeks
HBs Ag, HCV Ab, HCV viral load, and HIV serology *(if clinically indicated)*	X							
Lipase, Amylase, LDH, CK, Hb A1c, ACTH, Cortisol, Prolactin, FSH, LH, testosterone *(if clinically indicated)*	X				X			
Radiology/Efficacy Measurements								
CT scan Chest / Abdomen	X	Every 6 weeks first 6 months; then, every 9 weeks between 6-12 months; and every 12 weeks thereafter [c]			X			
MRI Brain *(if clinically indicated)*	X	Every 12 weeks			X			
Bone Scan *(if clinically indicated)*	X	Every 12 weeks			X			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood								
Archival or Newly Obtained Tissue Collection *(Optional)*	X[d]				X[g]			

Trial Period	**Screening Phase**	**21- day Treatment Cycles**			**End of Treatment[a]**	**Post-Treatment**		
Treatment Cycle/Title	Main Study Screening (Visit 1)	1	Subsequent cycles		Discon	Safety Follow-Up	Follow-Up Visits	Survival Follow-Up
			Even	Odd				
Scheduling Window (Days)	-28 to -1	+3	± 3	± 3	At time of Discon	30 days post Discon	Every 8 weeks post Discon	Every 12 weeks
Correlative Studies: Blood and Tissue[h] Collection *(Optional)*	X[d, h]	X[e]		X[f]	X[g, h]			

Abbreviations: ACTH: adrenocorticotropic hormone; CK: Creatinine kinase; ECOG = Eastern Cooperative Oncology Group; FSH: Follicle-stimulating hormone; HBs Ag = hepatitis B surface antigen; HIV = human immunodeficiency virus; LDH: Lactate Dehydrogenase; LH: Luteinizing Hormone; PT = prothrombin time; PTT = partial thromboplastin time; TSH = thyroid stimulating hormone; FT4 = free thyroxin; FT3 = free triiodothyronine; HCV Ab = Hepatitis C virus antibody.

a: 30 days (+10 days) after the last dose of study drug.

b: for women of childbearing potential.

c: All known sites of metastases should be evaluated at each time point. Baseline imaging will be done within 28 days from starting cycle 1. Subsequent tumor imaging will be performed every 6 weeks (42 days ±7 days) from Cycle 1 Day 1 during first 6 months, then every 9 weeks (63 days ±7 days) between 6 months and 1year, then every 12 weeks (84 days ±7 days) after 1 year. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Every effort should be made to continue tumor imaging using same interval for participants who discontinue study treatment without documented disease progression.

d: The 1st time point of peripheral blood will be collected the same day of the 1st optional biopsy.

e: If no optional biopsy is planned, the 1st time point of peripheral blood will be collected on Cycle 1 Day 1 prior to treatment administration.

f: The 2nd time point of peripheral blood will be collected on Cycle 2 Day 1 prior to drug administration.

g: The 3rd time point of peripheral blood will be collected the same day of the End of Treatment (EOT) 2nd optional biopsy; if no plan for EOT optional biopsy, peripheral blood will be collected at the EOT visit.

h: Tissue collection will only be offered to participants accrued at Emory. Biopsies will be coordinated with the recipient lab (Address: B3204 – phone 404-727-3701) and Winship CTP (Address: B3200 – phone: 404-778-5108).

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Trial Flow Chart - Section 5.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

6.1.1.1.1 General Informed Consent

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

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

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

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

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

6.1.1.2 Inclusion/Exclusion Criteria

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

Patients will be registered after meeting all entry requirements and signing of the informed consent document.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.
Enrolling a subject requires careful screening and determination of eligibility.
Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.
When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. OnCore and ERMS must be updated to reflect eligibility and on treatment status.

6.1.1.3 Medical History

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

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the

participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

6.1.1.6 Trial Compliance (Medication/Diet/Activity/Other)

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured. Dose changes and interruptions of study drug must be specifically documented in the patient's CRF.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be

characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

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

6.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 5.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

On infusion days, patients receiving treatment will be monitored during and after infusion:

- A 1-hour observation period is required after the first infusion. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each infusion).

The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. ECOG classification groups are referenced in Appendix 1.

6.1.2.6 Tumor Imaging and Assessment of Disease

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

Brain imaging at screening will be performed in patients who have symptoms concerning for brain metastases or have prior history of brain metastases. MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

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

6.1.2.6.1 Initial Tumor Imaging

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

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

6.1.2.6.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) from the date of allocation. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 6 months, participants who remain on treatment will have imaging performed every 9 weeks (63 days ±7 days) until 1 year, and every 12 weeks (84 days ±7 days) thereafter. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 6 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for

confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Table 7, Figure 3), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Appendix 4. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are are possible upon consultation with Merck (Table 7, Figure 3 and Appendix 4).

6.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

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

In participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 6-12 weeks in Year 1 or every 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.2.6.4 RECIST 1.1 Assessment of Disease

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

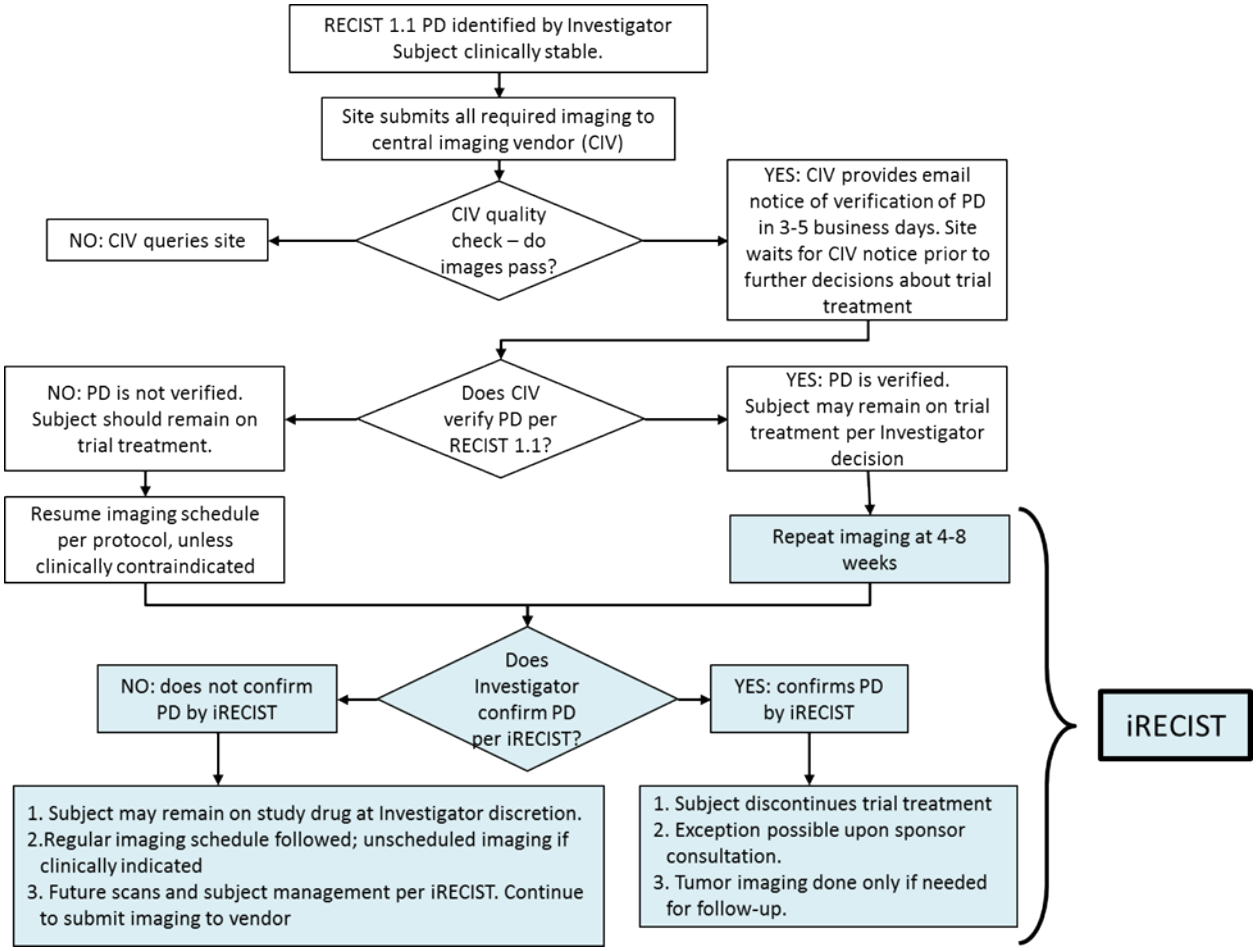
Table 7: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**

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

Figure 3. Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Various factors that could potentially affect clinical response to treatment with Pembrolizumab in combination with Docetaxel and Ramucirumab will be investigated in peripheral blood in pre-treatment, after treatment and upon progression as well on tumor specimens (optional).

Data from these investigations will be evaluated for associations with clinical efficacy data. All samples collected may also be used for exploratory analyses to assess biomarkers associated immunotherapy treatment.

Peripheral blood samples

Blood samples will be collected for immunophenotypic analysis of circulating immune cells by mass cytometry before and after treatment and EOT. The goal is to characterize treatment emergent changes in immune cells (T, B, myeloid cells) using a 35-marker panel. For this, we would collect 30 ml of blood in green top (heparin) tube for each timepoint. Blood tubes will be delivered at room temperature, on same day if possible, or overnight, to Winship Cancer Tissue and Pathology (CTP) Shared Resource (1365B Clifton Road, 3rd Floor, 3200 – phone: 404-778-5108). Winship CTP standard process is to aliquot plasma into 4 x 0.5ml aliquots and 4 x 1.0ml aliquots before storage at -80. PBMC are cryopreserved at ~5x10^6 cells/aliquot and stored long-term in LN2. Blood collected outside of the windows indicated below or missed blood collections will not constitute protocol deviations. Blood collection timing may vary because appointments may not be scheduled solely for this study.

- At Baseline, on cycle 1 day 1 prior to drug administration (if no planned optional biopsy); otherwise, same day of the optional biopsy
- On Cycle 2 day 1 prior to drug administration
- At the EOT discontinuation visit (if no planned EOT optional biopsy); otherwise, same day of EOT optional biopsy.

Tumor Tissue

Tissue biopsies will be collected for analysis of tumor infiltrating immune cells by mass cytometry coupled to blood mass cytometry, in paired biopsies before (within 28 days prior to C1D1) and at end of treatment in coordination with the recipient lab (Address: B3204 – phone 404-727-3701) and Winship CTP (Address: B3200 – phone: 404-778-5108). Tumor studies will only be offered to participants accrued at Emory. The goal is to evaluate treatment emergent changes in tumor microenvironment in diverse immune cell subsets. Freshly obtained biopsies will be logged and de-identified by Winship CTP (Address: B3200) before distribution to the recipient lab (Address: B3204). Tumor tissue collected outside of the windows indicated above or missed tumor tissue collections will not constitute protocol deviations. Tumor tissue collection timing may vary because appointments may not be scheduled solely for this study.

If the information is already known, tissue will be evaluated to measure TMB, PDL-1 22C3 expression, STK11 and KRAS mutations (if known).

When sufficient quantities of fresh tissue is available, it will be preserved for future exploratory studies including genomic profiling.

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

The schedule regarding specific laboratory procedures/assessments to be performed in this trial are noted in the Study Flow Chart.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Clinical laboratory assessments during the treatment period may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol. In these instances, the AE corresponding to the laboratory abnormality will be recorded.
Laboratory tests for hematology, chemistry, urinalysis, and others are specified below and in Table 8.

- Hematology (hemoglobin, hematocrit, white blood cell count with differential and platelet count)
- Clinical Chemistry (sodium, potassium, chloride, bicarbonate, magnesium, calcium, blood urea nitrogen, creatinine, glucose (random), total bilirubin, total protein, ALP, ALT, AST, and albumin)
- LDH, CK, amylase, lipase (if clinically indicated)
- Urinalysis and spot urine for protein / creatinine
- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed prior to optional biopsies
- Pregnancy test (only in women of childbearing potential)
    - Urine human chorionic gonadotropin, or
    - Serum beta-human chorionic gonadotropin
- Endocrine test
    - TSH, free T3, and free T4
    - Hb A1c, ACTH, cortisol, FSH, LH, Prolactin, and testosterone (if clinically indicated)
- Other laboratory tests (if clinically indicated)
    - Hepatitis B surface antigen
    - Hepatitis C antibody
    - Hepatitis C viral load
    - HIV antibody

Table 8: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Free thriiodothyronine (FT3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (FT4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Blood Urea Nitrogen	24h urine protein	CK
	Creatinine		Hb A1c
	Calcium		Blood for correlative studies
	Chloride		ACTH
	Glucose		FSH
	Potassium		LH
	Sodium		Prolactin
	Magnesium		Testosterone
	Total Bilirubin		Cortisol
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		Hepatitis B surface antigen

Hematology	Chemistry	Urinalysis	Other
	Total protein		Hepatitis C antibody
	Amylase		HIV antibody
	Lipase		Hepatitis C viral load

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

6.1.3.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 4.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 6.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 6.1.5.3.2).

6.1.4 Visit Requirements

Visit requirements are outlined in Section 5.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations will be performed. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

6.1.4.1 Screening

Screening procedures will be performed up to 28 days prior initiation of treatment, except for baseline imaging (up to 28 days allowed) unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs [temperature, heart rate (HR), blood pressure (BP) and respiratory rate (RR), oxygen saturation], height and weight
- Optional

a. Tumor tissue from diagnostic biopsy, if available, is provided for biomarker analysis
b. Peripheral blood samples for correlative studies at the time of the planned pre-treatment optional biopsy

- Review of prior/concomitant medications
- Radiologic imaging studies to evaluate tumor status: computed tomography (CT) of the chest and abdomen, PET/CT, or MRI of chest and abdomen. Additional imaging may be obtained as clinically indicated. Baseline scans may be done within 4 weeks prior to the first dose of study drug.

Clinical laboratory tests for:

a. Hematology
b. Clinical chemistry
c. TSH, free T3, and free T4
d. Serum or urine pregnancy test (for women of childbearing potential)
e. Urinalysis and spot urine for protein / creatinine
f. Optional:
    - Peripheral blood samples for correlative studies at the time of the planned pre-treatment optional biopsy
g. If clinically indicated:
    - Hb A1c, ACTH, cortisol, FSH, LH, Prolactin, and testosterone
    - LDH, CK, amylase, lipase
    - Coagulation (PT, PTT, INR) if plan for biopsy
    - Hepatitis B, Hepatitis C antibody and viral load, and HIV serologies

6.1.4.2 Treatment Period

Procedures to be conducted during the treatment phase of the study are presented in the Trial Flow Chart (Section 5.1). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Brief medical history
- Symptom-directed physical exam
- ECOG Performance Status
- Vitals signs and weight
- Review of prior/concomitant medications
- Record AEs
- Treatment with Docetaxel, Ramucirumab, and Pembrolizumab
- Clinical laboratory tests for:
    a. Hematology
    b. Clinical chemistry
    c. TSH, free T3, free T4 (odd cycles)

d. Serum or urine pregnancy test (for women of childbearing potential)
e. Urinalysis and spot urine for protein / creatinine
f. Optional peripheral blood samples for correlative studies:
    - on Cycle 1 Day 1 prior to drug administration (if no plan for the optional biopsy)
    - on Cycle 2 Day 1 prior to drug administration
    - At EOT visit (if no plan for the optional EOT biopsy); otherwise, will be collected at the same day of the planned optional EOT biopsy
g. If clinically indicated:
    - Hb A1c, ACTH, cortisol, FSH, LH, Prolactin, and testosterone
    - LDH, CK, amylase, lipase

6.1.4.3 Post-Treatment Visits

End of treatment is defined as the last planned dosing visit within the dosing period. For patients who discontinue drug treatment, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for patients who have completed treatment and achieved disease control or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until end of the study.

6.1.5.3.1 Safety Follow-Up Visit

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

6.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding

disease status until the start of new anti-cancer therapy, disease progression, death, end of the study Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

6.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks (± 3 weeks) for 2 years, then every 6 months for next 3 years, then annually until the subject's death or until the subject is lost to follow-up up to 10 years to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

The following information will be collected:

- Disease status as:
  - No evidence of disease on treatment (document treatment type if available)
  - No evidence of disease on follow-up
  - Active disease on treatment (document treatment type if available)
  - Active disease not on treatment
- The patient's survival status, and if deceased, the date of death. If known, cause of death.
- The method by which the survival status was assessed and the date it was assessed.
- Any subsequent anti-cancer therapy received, or imaging performed after completion of study.

6.2 Assessing and Recording Adverse Events

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

All adverse events, that begin or worsen after informed consent through 30 days following cessation of treatment, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

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

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1-5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)

2. Its duration (Start and end dates)

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)

4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 6.2 and which seriousness criteria have been met (include for NCDS trials)

Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

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

event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

6.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Principal Investigator and to Merck

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

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Principal Investigator and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

6.2.2 Reporting of Pregnancy and Lactation to the Principal Investigator and to Merck

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

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious

events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Principal Investigator and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

6.2.3 Immediate Reporting of Adverse Events to the Principal Investigator and to Merck

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

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Important medical events 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 participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

For the time period beginning at treatment allocation through 90 days following cessation of treatment (or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier), any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on a Winship SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA and/or Merck.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study PI and should be provided as soon as possible.

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

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB and/or Merck if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (Pembrolizumab and/or Ramucirumab and/or Docetaxel), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph must be reported immediately (within 2 working days) to Merck Global Safety.

Global Safety facsimile number: +1-215-661-6229

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

6.2.3.1 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through **30** days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 6.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

6.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 9: Evaluating Adverse Events

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

V5.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is	

	considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the participant was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.	

No, there is not a reasonable possibility of Merck product relationship	Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

6.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Trial Design

Simon's two-stage optimum design will be used. The null hypothesis that the 6-month PFS rate is 37% will be tested against one-sided alternative hypothesis that the actual 6-month PFS rate is higher than 62%. In the first stage, 10 evaluable patients will be accrued. If there are 5 or more patients who progressed or died prior to 6 months among these 10 patients, the study will be stopped early for futility. Otherwise, 11 additional evaluable patients will be accrued for a total of 21 patients.

The null hypothesis will be rejected if 11 or more remain free of progression or death by 6 months among 21 evaluable patients. This design yields a type I error of 0.10 and power of 80% when the actual 6-month PFS rate is 62%. To account for early dropout prior to 6 months on study, we plan to enroll up to 30 patients. The calculation is based on current enrollment status including early dropout (among 23 enrolled, 5 dropouts without progression at 6 months and 2 did not complete cycle 1 of study treatment).

7.2 Statistical Analysis Plan

Descriptive statistics will be provided for collected demographic data, safety, dosage, clinical factors, etc. as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses. Proportion of acute and late toxicity will be reported, and 95% confidence intervals will be estimated using the Clopper-Pearson method.

The treatment response (6-month PFS rate) will be reported, and its 95% confidence intervals will be estimated using the Clopper-Pearson method. Chi-square test will be used to compare the efficacy in term of treatment response between the two groups stratified by binary biomarker (PD-L1 and KRAS status), respectively. Two sample t-test will be used to compare the tumor mutation burden (TMB) if known, and PD-L1 22C3 expression, changes of circulating immune cells in peripheral blood (pre-treatment, after treatment and on progression) between treatment responders and non-responders,

respectively. Logistics regression model will be further employed to test the adjusted effect of PD-L1 22C3, STK11, KRAS, TMB (if known), immunophenotypic analysis of circulating immune cells on the treatment response after adjusting for other clinical factors and demographic factors.

For progression free survival, progression or death from any cause will be defined as the event. Patients will be censored at time of last follow-up. For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. Overall survival (OS) and progression free survival (PFS) rates of two patient groups stratified by binary biomarker (PD-L1 and KRAS status), respectively will be estimated with the Kaplan-Meier method and compared using the log-rank test, respectively. Cox proportional hazards models will be further used in the multivariable analyses to assess adjusted effect of PD-L1 and KRAS status on the patients' OS and PFS after adjusting for other factors. Interaction terms between these factors will also be tested for statistical significance. The proportional hazards assumption will be evaluated graphically and analytically with regression diagnostics. Violations of the proportional hazard's assumptions will be addressed by use of time-dependent covariates or extended Cox regression models.

7.3 Sample size

We will include 21 evaluable patients to assess the safety of the combination treatment and its efficacy in term of 6-month PFS rate as defined by 25% increase (1.7-fold) from the historic 6-month PFS rate on REVEL study (37% to 62%). We estimate to consent up to 45 patients to account for screen failures and enroll up to 30 patients to account for early dropout prior to 6 months on study.

We will evaluate the first six patients for safety data. If less than 2 patients experience dose limiting toxicity, we will continue with the efficacy assessment of the combination.

7.4 Analysis sets

All subjects who receive any amount of study drug will be included in the evaluation of safety, except for patients who take less than 80% of their prescribed doses of study drugs since they will be considered unevaluable for the primary endpoint.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

Ramucirumab (CYRAMZA®)

Ramucirumab is a human monoclonal antibody (IgG1) against vascular endothelial growth factor receptor 2 (VEGFR2), a type II trans-membrane tyrosine kinase receptor expressed on endothelial cells. By binding to VEGFR2, ramucirumab prevents binding of its ligands (VEGF-A, VEGF-C, and VEGF-D), thereby preventing VEGF-stimulated receptor phosphorylation and downstream ligand-induced

proliferation, permeability, and migration of human endothelial cells. VEGFR stimulation also mediates downstream signalling required for angiogenesis and is postulated to be heavily involved in cancer progression, making it a highly likely drug target. In contrast to other agents directed against VEGFR-2, ramucirumab binds a specific epitope on the extracellular domain of VEGFR-2, thereby blocking all VEGF ligands from binding to it.
Ramucirumab is a recombinant human IgG1 monoclonal antibody, it has an approximate molecular weight of 147 kDa. And it is produced in genetically engineered mammalian NS0 cells.

Docetaxel (TAXOTERE®)
Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

Pembrolizumab (KEYTRUDA®)
Pembrolizumab is an immunoglobulin IgG4, with a variable region against the human PD-1 receptor, a humanized mouse monoclonal [228-L-proline (H10-S>P)]γ4 heavy chain (134-218') disulfide and a humanized mouse monoclonal κ light chain dimer (226-226:229-229)-bisdisulfide. It is recombinantly manufactured in Chinese hamster ovary (CHO) cells.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.
Pembrolizumab will be provided by Merck, the commercially available **Docetaxel** and **Ramucirumab** will be prescribed and administered per local laws and prescribing information as summarized in Table 10.

Table 10: Product Descriptions

Product Name & Potency	Dosage Form
Docetaxel (20 mg/2 mL or 80 mg/8 mL or 160 mg/16 mL).	Solution for Injection
Ramucirumab 100 mg/10 mL or 500 mg/50 mL)	Solution for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

8.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

Ramucirumab

Ramucirumab injection is a clear to slightly opalescent and colorless to slightly yellow, preservative-free solution supplied in single-dose vials.
Injection: 100 mg/10 mL (10 mg/mL) or 500 mg/50 mL (10 mg/mL) in a single-dose vial

- NDC 0002-7669-01: 100 mg/10 mL (10 mg/mL), individually packaged in a carton
- NDC 0002-7678-01: 500 mg/50 mL (10 mg/mL), individually packaged in a carton

Docetaxel

Docetaxel Injection is supplied in a multiple dose vial as a sterile, pyrogen-free solution. Docetaxel Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution. Docetaxel Injection 10 mg/mL is supplied as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.
Each mL of Docetaxel Injection contains 10 mg docetaxel; 80 mg polysorbate 80; 648 mg polyethylene glycol 300; 275.9 mg alcohol 96% (v/v), and 4 mg citric acid.
Refer to the latest package insert for complete details.

Pembrolizumab

Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion.

- Pembrolizumab solution is provided in single-dose vials containing 100 mg/4 mL (25 mg/mL). Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.
- The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of the infusion solution. An infusion of pembrolizumab in this study will require 2 vials of solution.

Pembrolizumab will be supplied in commercial packaging, which includes the package insert or patient information leaflet. Refer to the latest package insert for complete details.

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

Ramucirumab
Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze or shake the vial.
Docetaxel

Store between 2°C and 25°C (36°F and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.
After initial puncture, Docetaxel Injection multiple dose vials are stable for 28 days when stored between 2ºC to 8ºC and at room temperature, with or without protection from light. Docetaxel Injection infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours in either 0.9% Sodium Chloride solution or 5% Dextrose solution. Use within 4 hours including storage and administration. Do not freeze infusion solution.

Pembrolizumab

Storage of Reconstituted and Diluted Solutions The product does not contain a preservative. Store the reconstituted and diluted solution from the pembrolizumab 50 mg vial either:

At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the diluted solution, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.

Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

8.5 Returns and Reconciliation

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

The study drug provided for this study will be used only as directed in the study protocol.
The IDS (Investigational Drug Service) personnel at Winship and non-Emory collaborating site will account for all study drugs.

Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.

Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.

The Drug Accountability Log may record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

The study drug supply will be disposed of as per Winship's Investigational Pharmacy (IDS) SOP.

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver. This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

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

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Data Reporting / Regulatory Requirements

Data Reporting

Study participants are responsible for submitting data and/or data forms in the clinical management system - Online Collaborative Research Environment (ONCORE) - per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may

temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.

Queries will be resolved by the research staff within the time frame specified by the protocol, not to exceed 2 weeks.

Source data and documents

In accord with section 1.51 of the ICH E6 document all information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

Protocol Adherence

By signing the Form FDA 1572, the Investigator agrees to conduct the study according to the protocol and the FDA regulations set forth in 21 CFR Parts 50, 54, 56, and 312.

Retention of Study Documents

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. Since this study is deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal

Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

10.0 ETHICS AND PROTECTION OF HUMAN SUBJECTS

10.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research, and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements patient data protection.

10.2 Institutional review board

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

10.3 Informed consent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants

will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.4 Participant and data confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.5 Research use of stored samples, specimens, or data

Samples and data collected under this protocol may be used for future exploratory studies including genomic profiling. Access to stored samples will be limited to IRB-approved investigations. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

11.0 Multi-Site or Collaborative Research

The research will be conducted at Emory University and non-Emory collaborating site.
All sites will have the current protocol document and each IRB will review each site's consent form and all required approvals will be obtained at each site. Any protocol modifications will be communicated to all sites with the appropriate regulatory agencies notified for their respective reviews and approvals. All engaged participating sites will safeguard date, including secure transmission of data, as required by local information security policies. All local site investigators will conduct the study in accordance with applicable federal regulations and local laws. All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Site initiation at subsites
At the time of study initiation at a subsite, the coordinating center multi-site coordinator (with additional staff as needed) will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance.

Subsite data collection
Subsite data must be submitted to the coordinating center multi-site coordinator as outlined in the protocol-specific monitoring plan. The protocol-specific monitoring plan will be provided by the coordinating center multi-site coordinator to external participating prior to site activation. Access to the coordinating center OnCore database will be provided to external participating sites for direct electronic data entry. All data submitted must be accompanied by supporting source documents, where applicable and as outlined in the protocol-specific monitoring plan. All data must be entered in the timeframe required at each site, but no later than 14 days following registration and each visit completion. All queries are to be resolved within 4 weeks of issue. The coordinating center multi-site coordinator will provide OnCore training and request access to the appropriate staff at the participating site.

Monthly investigator conference calls
The subsite research coordinators will maintain a spreadsheet which will be de-identified and will summarize patient data for subjects actively being treated on the trial well as a roadmap detailing pending tests/treatments for each individual subject. The spreadsheet will be shared with the coordinating center PI (or designee) via e-mail. Teleconferences will be conducted at least once monthly between the PI (or designee) at Emory and the research team at the participating site(s).

The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy. The coordinating center (or designee) will communicate with participating sites via monthly email as needed.

The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition, electronic copies will be sent via email to the research teams at subsite.

Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial follows the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

Subsite self-monitoring: The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator (or designee), the clinical research coordinator and the regulatory affairs coordinator as applicable, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. Chart reviews will be performed on selected cases by participating site staff to confirm that the data collection is accurate regarding study conduct, data collection, documentation and completion.

Central monitoring: Study-specific monitoring plans are specified per site, with the only difference between sites whether the site submits source data on paper or provides the coordinating center multi-site team remote access to that site's local electronic medical record. Centralized monitoring will occur minimally quarterly, no more frequently than monthly. Monitoring will be centralized, including data reporting and research sample acquisition. The coordinating center multi-site coordinator will perform on-site and/or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (on site up to once per year and at least three times remotely) until subject follow-up is terminated. Monthly reviews of data will be conducted to ensure compliance or identify discrepancies; specifically, to assess compliance with the protocol, verify informed consent forms, verify compliance with SAE reporting procedures, monitor the tracking of study drug (pharmacy visit, storage and accounting of study drug), retrieve regulatory documentation, and perform quality control by comparing data from the CRF to the source documents of the center.

Auditing

For sites with an auditing mechanism in place that are able to share documentation of their auditing standards and processes followed, an agreement may be requested for the site to perform local auditing and provide formal audit reports to the coordinating center.

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13.0 APPENDICES

Appendix 1:

A) ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
*As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

B) The New York Heart Association (NYHA) functional classification of heart failure

Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heartbeat), dyspnea (shortness of breath), or anginal pain (chest pain)
Class II (Mild)	Patients with card iac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix 2: Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Male Participants:

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

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 10 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 11 during the protocol-defined time frame.

Table 11: Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 6 months after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at least 120 days plus 30 days (a menstruation cycle) after the last dose of study treatment and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression
Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression
In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 5 and Figures 1 and 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

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

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

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

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

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

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

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions

total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 5.

Detection of Progression at Visits After Pseudo-progression Resolves

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

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear

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

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

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

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al, 2017].

APPENDIX 5 Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BP	Blood pressure
CL	Clearance
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
FT3	Free thriiodothyronine
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICI	immune checkpoint inhibitor
DMSC	Data Monitoring Safety Committee
IgG	Immunoglobulin G
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	Explanation
IV	Intravenous
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
Q3W	Every 3 weeks
QT	QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
SAE	Serious adverse event
SD	Stable disease
T_3	Triiodothyronine
T_4	Thyroxine
TMB	Tumor mutation burden
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential