A single arm, multicenter, phase 2 trial to evaluate the efficacy of lenvatinib (LEN) in combination with pembrolizumab (KEYtruda) in subjects with locally advanced or metastatic Non-clear cell renal cell carcinoma (The LENKYN Trial)

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Study Drugs: Lenvatinib
Pembrolizumab (MK-3475, Keytruda)

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Protocol Revision History

Initial Approval Version	**24-Mar-2020**
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Amendment #2 Version	**10-Mar-2022**

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Glossary of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
BCG	Bacillus Calmette-Guérin
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate
ccRCC	Clear cell RCC
CFR	Code of Federal Regulations
chRCC	Chromophobe RCC
CL	Clearance
CONSORT	Consolidated standards of reporting trials
CR	Complete response
CTFG	Clinical trial facilitation group
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DCR	Disease control rate
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DOB	Date of birth
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EBRT	External beam radiotherapy
ECG (or EKG)	Electrocardiogram
ECI	Events of Clinical Interest
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose - positron emission tomography
FFPE	Formalin-fixed paraffin-embedded
FGFR1–3	Fibroblast growth factor receptor 1
FSH	Follicle stimulating hormone
FWA	Federal wide assurance

GCP	Good Clinical Practice
GI	Gastrointestinal
H&P	History & Physical
HDPE	High-density polyethylene
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
HRT	Hormonal replacement therapy
KEY	Keytruda (Pembrolizumab)
KM	Kaplan-Meier
IND	Investigational New Drug
IgG4	Immunoglobulin G4
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
LEN	Lenvatinib
mAb	monoclonal antibody
mTOR	mammalian target of rapamycin
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network
nccRCC	Non-clear cell renal cell carcinoma
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PDGF	Platelet-derived growth factor
PDGFRα	Platelet-derived growth factor receptor α
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PEM	Pembrolizumab
PFS	Progression-free survival
PI	Principal investigator
PMDA	Pharmaceutical and Medical Devices agency
PR	Partial response

PRES	Posterior reversible encephalopathy syndrome
PS	Performance status
PSA	Prostate-specific antigen
QASMC	Quality Assurance and Safety Monitoring Committee
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RET	Rearranged during transfection
RF	Radiofrequency
RFS	Relapse free survival
RNA	Ribonucleic acid
RR	Response rate
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
T1DM	Type 1 diabetes mellitus
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UPN	Unique patient number
uRCC	Unclassified RCC
US	Ultrasound
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell (count)
WOCBP	Women of childbearing potential

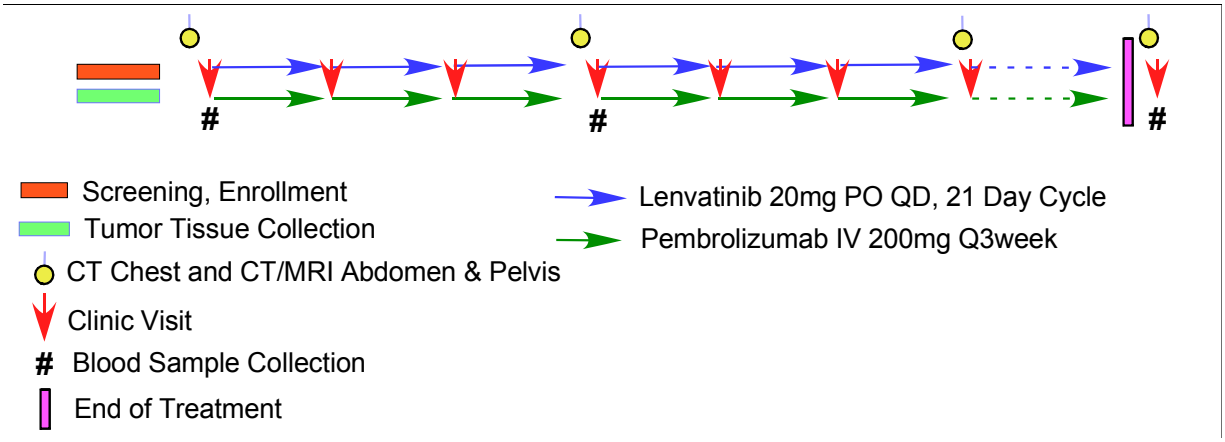
Table of Contents

PROTOCOL SUMMARY

Synopsis

Title:	A single arm, multicenter, phase 2 trial to evaluate the efficacy of lenvatinib (LEN) in combination with pembrolizumab (KEYtruda) in subjects with locally advanced or metastatic Non-clear cell renal cell carcinoma (The LENKYN Trial)
Study Description:	This is a single-arm, multicenter, phase 2 study of lenvatinib 20 mg QD in combination with pembrolizumab 200mg q3weeks in subjects with locally advanced or metastatic nccRCC who have not received any systemic therapy for advanced disease.
Objectives:	**Primary Objective:** To evaluate objective response rate (ORR) of lenvatinib in combination with pembrolizumab in subjects with locally advanced or metastatic nccRCC. **Secondary Objectives** ▪ To assess safety and tolerability of lenvatinib in combination with pembrolizumab in nccRCC patients ▪ To evaluate progression-free survival (PFS) ▪ To evaluate overall survival (OS)
Endpoints:	**Primary Endpoint:** The primary efficacy endpoint is ORR defined as the proportion of subjects who have a best overall response (BOR) of CR or PR. **Secondary Endpoints:** ▪ Safety and tolerability – by CTCAE v 5.0 ▪ Progression-Free Survival (PFS) – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first. ▪ Overall Survival (OS) – defined as the time from the date of first dose of study drug until date of death from any cause.
Study Population:	The study population includes patients 18 years or older with locally advanced or metastatic histologically confirmed nccRCC who have not received any systemic therapy for advanced disease.
Phase:	Phase II
Description of Sites / Facilities Enrolling:	This is a multicenter trial with the intention of activating a total of four sites within the US.
Description of Study Intervention:	Lenvatinib (20 mg/day) administered orally in combination with pembrolizumab (200mg) infused every 3 weeks
Study Duration:	36 months
Participant Duration:	24 months

SCHEMA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Screening, Enrollment
Tumor Tissue Collection
CT Chest and CT/MRI Abdomen & Pelvis
Clinic Visit
Blood Sample Collection
End of Treatment
Lenvatinib 20mg PO QD, 21 Day Cycle
Pembrolizumab IV 200mg Q3week

1.0 SCHEDULE OF ACTIVITIES

Screening tests may take place no more than 21 days prior to the first day of study treatment. Window for study visits during treatment is +/- 7 days.

	Screening	C1D1	D1 of each subsequent cycle	Q9 wks	EOT	FU[4]
Informed consent	X					
H&P, PS	X					
Vital signs	X		X			
CBC	X	X	X		X	
Blood chemistry[9]	X		X			
Pregnancy test[1]	X[3]					
TSH	X		X			
INR	X		X			
Urinalysis	X					
UPCR		X	X			
ECG	X					
CT or MRI[8]	X			X	X	
Pembrolizumab		X	X			
Lenvatinib[2]		X----------X[2]				
Research tissue collection[7]	X					
Research blood collection	X[5]	X[5]	X[6]		X	
Adverse events	X---------- X					
Progression and survival						X

1. Women of childbearing potential only
2. Lenvatinib is to be self-administered daily on each day of every 21-day cycle
3. Within 72 hours prior to first dose
4. After coming off treatment, patients will be followed every 12 weeks +/- 1 week until death for survival. If patients discontinue treatment prior to progression, patients will continue to be followed by scans approximately every 9 weeks until progression or the start of another anti-cancer therapy.
5. To be drawn at screening or C1D1 (up to 14 days prior to the start of treatment)
6. C4D1 only
7. Archival from within 3 months (preferred), up to 6 months acceptable; if no biopsy has been performed in the 6 months prior to treatment start then an SOC biopsy should take place after a patient has been determined to be eligible for the trial, if safe and feasible. See section 10.0 for more details.
8. Scans should continue every 9 weeks regardless of cycle length. See Section 12 for further instructions of timelines for obtaining confirmatory scans. For responses, or progression, a confirmatory scan should be performed at least 4 weeks after the initial scan showing progression or response.
9. Albumin, alkaline phosphatase, total bilirubin (and direct bilirubin if total bilirubin is above ULN), bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, AST, ALT, sodium

2.0 BACKGROUND AND RATIONALE

2.1 Renal Cell Carcinoma

Kidney cancer accounts for approximately 2% of all cancer diagnoses and cancer deaths worldwide, with incidence rates generally higher in developed countries. Annually, approximately 295,000 new kidney cancer cases are diagnosed and approximately 134,000 deaths are recorded worldwide (1). Men are more affected than women (a 2:1 ratio of new diagnoses). Renal cell carcinoma (RCC) denotes cancer originated from renal epithelium and accounts for more than 90% of cancers in the kidney (2). The disease encompasses more than 10 histological and molecular subtypes, of which clear cell RCC (ccRCC) is most common and accounts for the most (~80%) kidney cancer-related deaths.

Localized ccRCC can be successfully managed with surgery, whereas metastatic ccRCC is refractory to conventional chemotherapy (1). However, over the past two decades, marked advances in treatment of metastatic ccRCC have been made, with targeted agents (including sorafenib, sunitinib, bevacizumab, pazopanib and axitinib that inhibit vascular endothelial growth factor (VEGF) and its receptor (VEGFR)) and everolimus and temsirolimus, which inhibit mTOR complex 1, being approved (3). Since 2015, agents with additional targets aside from VEGFR have been approved, such as cabozantinib and lenvatinib; immunotherapies such as nivolumab, avelumab, pembrolizumab, and ipilimumab have also been added to the armamentarium for metastatic ccRCC (1, 4-6).

2.2 Non-Clear Cell Renal Cell Carcinoma (nccRCC)

Patients with non-clear cell renal cell carcinoma (nccRCC) constitute 25-30% of RCC patients. nccRCC includes papillary RCC (pRCC, ~15%), chromophobe RCC (chRCC, ~5%), rare molecular subtypes (<1%, e.g. TFE3 fusion kidney cancer), and unclassified RCC (uRCC, ~4%)(2, 7, 8). Due to rarity, advanced nccRCC patients have generally been excluded from most RCC clinical trials that focus on ccRCC (9). Hence, there is no first-line standard of care for RCC patients with non-clear cell histology (9, 10). Accordingly, the choice of therapy in this patient population is challenging and is often extrapolated from the ccRCC patients and from retrospective studies. The National Comprehensive Cancer Network (NCCN) guidelines recommend sunitinib as the preferred regimen, with everolimus and cabozantinib being the alternative regimens (10). Sunitinib and everolimus offers first line PFS of 8.1 and 5.6 months respectively (11, 12), while PFS on any line of cabozantinib is 6.7 months (13). Similarly, ORR on first line sunitinib and everolimus as well as any line cabozantinib are 18%, 9% and 27%, respectively (3, 11, 13). Hence, it is crucial to develop more effective therapies in the patient population. Of note, a recent 2019 GU ASCO meeting abstract of KEYNOTE Arm B reported 25% response rate of nccRCC treated with single agent Keytruda (14).

2.3 Pembrolizumab

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. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications (15).

2.4 Lenvatinib

Lenvatinib is an oral, multi–tyrosine kinase inhibitor active against RET, VEGFR1–3, FGFR1–3, KIT, and PDGFRα (16, 17). It is approved in the US in combination with everolimus for patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy (18).

2.5 Lenvatinib and Pembrolizumab

The effect of combining lenvatinib with pembrolizumab has been evaluated in a multicenter, open-label phase Ib/II trial in patients with metastatic tumors, including clear cell renal cell carcinoma (ccRCC) (NCT02501096). Patients received oral lenvatinib 20 mg daily in combination with pembrolizumab 200 mg IV every 3 weeks. Out of the 30 patients enrolled, 12 (40%) were treatment-naive and 18 (60%) had at least one prior anticancer therapy. Objective response rate (ORR) at week 24 was 63.3% (95% CI, 43.9–80.1) by investigator review, per immune related RECIST. ORR by IRR using RECIST 1.1 was 66.7% (95% CI, 47.2–82.7), and median PFS was 17.7 mos (95% CI, 9.6–NE). Grade 3 or 4 adverse events (AEs) occurred in 21 (70%) pts; however, 4 (13%) discontinued treatment due to AE. The most common AEs were diarrhea (83%), fatigue (70%), hypothyroidism (67%), stomatitis (63%), and nausea (60%). The current treatment paradigm in RCC is shifting towards combination therapies, as they are more promising in overcoming the different mechanisms of resistance implicated. Lenvatinib and pembrolizumab have shown promising efficacy results in a phase Ib/IIb study of patients with metastatic ccRCC (19). Therefore, we propose a consortium-based phase II trial of lenvatinib and pembrolizumab in patients with locally advanced or metastatic nccRCC. The LENKYN trial is the first to test this combination in advanced nccRCC patients.

2.6 Study Design

2.6.1 Overall Design

This is a single-arm, multicenter, phase 2 study of lenvatinib in combination with pembrolizumab (lenvatinib 20 mg/day + pembrolizumab 200mg q3weeks) in subjects with unresectable advanced or metastatic nccRCC who have not received any chemotherapy for advanced disease.

A Simon's Two-Stage Design will be implemented in approximately 34 enrolled subjects. Nine subjects will be enrolled in Stage 1. If there are at least 2 responders

as assessed by ORR, the study will proceed to Stage 2 in which 25 more subjects may be enrolled. Otherwise, the study will stop early for futility. In the final analysis of 34 subjects, at least 9 responders are required to show a statistically significant improvement of ORR over historical control in the same patient population (one-sided type I error of 5% and targeting for 80% power).

This study consists of 3 phases:

1. Pre-treatment phase (Screening Periods)
2. Treatment phase (starting Cycle 1 Day 1)
3. Post-treatment phase (End of Treatment Visit and survival follow-up)

The pre-treatment phase is planned to last no longer than 21 days and will include a screening period to establish protocol eligibility.

The treatment phase will begin at the time of study drug administration on Day 1 of Cycle 1 and continue in 21-day (3-week) cycles until completion of the off-treatment assessments (within 30 days after the last study drug administration). Lenvatinib 20 mg/day will be administered orally on a daily basis and pembrolizumab 200 mg will be infused once every 3 weeks. Subjects will undergo safety and efficacy assessments. Toxicity will be managed by treatment interruption, dose reduction and/or treatment discontinuation. Subjects who discontinue one of the study drugs due to its toxicities may continue to receive the other study drug as long as they demonstrate clinical benefit. Subjects will discontinue both study drugs at the time of confirmed disease progression, development of unacceptable toxicity, withdrawal of consent, or study termination. Subjects may be treated with pembrolizumab for a maximum of 35 cycles or approximately 2 years, but treatment with lenvatinib can continue beyond 2 years if the subject does not meet other treatment discontinuation criteria.

The post-treatment phase will start at the End of Treatment Visit and will continue as long as the subject is alive or until the study subject withdraws consent. Subjects who discontinue study treatment before disease progression will continue to undergo tumor assessment every 9 weeks ±1 week until documentation of disease progression or start of another anticancer therapy. Follow-up assessment for survival will be performed every 12 weeks ±1 week until death.

A total of approximately 34 subjects will be enrolled.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To evaluate objective response rate (ORR) of lenvatinib in combination	The primary efficacy endpoint is ORR defined as the proportion of subjects	There is no standard of care for locally advanced unresectable or metastatic nccRCC. This trial

with pembrolizumab in subjects with locally advanced or metastatic nccRCC.	who have a best overall response (BOR) of CR or PR.	wishes to establish effective treatment regimen for nccRCC at the first line setting. Hence, BOR of CR or PR is chosen as the primary endpoint.
Secondary		
To assess safety and tolerability of lenvatinib in combination with pembrolizumab	CTCAE v 5.0	Although the safety profile of combining lenvatinib at 20mg daily and pembrolizumab 200mg Q3weeks was reported to be tolerable and is currently being investigated in a large phase III first-line trial for ccRCC, there is no safety and tolerability data of this combination in nccRCC.
To evaluate progression-free survival (PFS)	Progression-Free Survival (PFS) – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first.	Progression free survival has been shown to be a good surrogate endpoint for survival benefit demonstrated in RCC.
To evaluate overall survival (OS)	Overall Survival (OS) – defined as the time from the date of first dose of study drug until date of death from any cause.	Although the overall survival data takes a long time to mature and is with many confounding factors, it remains as the final proof of cancer treatment benefit.
Tertiary/Exploratory		
To explore clinical benefit rate (CBR)	Clinical benefit rate (CBR) is the proportion of subjects who have a BOR of CR or PR or durable stable disease (SD). Stable disease must be achieved at ≥ 23 weeks after first lenvatinib administration to be considered durable SD.	There is no standard of care for nccRCC and no established biomarkers to predict treatment response of nccRCC to combined targeted and immune therapies. Blood and tissue biomarkers correlated with treatment outcome of nccRCC will be explored in this trial.
To explore disease control rate (DCR)	Disease control rate (DCR) is the proportion of subjects who have a BOR of CR, PR or SD.	
To explore duration of response (DOR)	Duration of response (DOR) is defined as the time from the date that the criteria are	

	met for CR or PR (whichever is recorded first) to the date that progressive disease (PD) is objectively documented or death, whichever occurs first.	
To identify and explore tumor and blood biomarkers that correlate with clinical outcomes, including efficacy	Blood immune cell CyTOF panel, plasma ProcartaPlex cytokine/chemokine/growth factor panel, and tissue MxIF tumor-immune interface panel will be performed on respective enrolled patient specimens.	
To explore the relationship of biomarkers, safety, and efficacy data using a model-based approach	Potential biomarkers derived from this study will include DNA, RNA, protein, immune profiles, and tumor-immune interactions.	

4.0 STUDY POPULATION

4.1 Inclusion Criteria

1. Locally advanced or metastatic histologically confirmed nccRCC (2, 7). Must have one of the following subtypes of nccRCC:
   a. papillary RCC
   b. chromophobe RCC
   c. TFE-3/B translocation RCC
   d. SDHB-loss RCC
   e. TSC1-loss RCC
   f. sarcomatoid RCC without clear cell component
   g. unclassified RCC

2. Has not received any prior lines of systemic therapy except adjuvant or neoadjuvant treatments.

3. Radiologically measurable disease meeting the following criteria:
   a. At least 1 lesion of ≥ 10 mm in the longest diameter for a non-lymph node or ≥ 15 mm in the short axis diameter for a lymph node which is serially measurable according to iRECIST (Section 12) using computerized tomography (CT) or magnetic resonance imaging (MRI).
   b. Lesions that have had external beam radiotherapy (EBRT) or locoregional therapies such as radiofrequency (RF) ablation must show evidence of subsequent

progressive disease (substantial size increase of ≥20%) to be deemed a target lesion. Patients who received EBRT must be at least 2 weeks out from last RT treatment.

4. At least 18 years of age.

5. Karnofsky performance status ≥ 70% (see Appendix A)

6. Blood pressure (BP) ≤ 150/90 mmHg at screening with or without antihypertensive medications and no change in antihypertensive medications within 1 week prior to Cycle 1 Day 1.

7. Adequate renal function defined as creatinine <1.5 x ULN or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5 x ULN.

8. Adequate bone marrow function:
   a. Absolute neutrophil count (ANC) ≥1500/mm3 (≥1.5 x 103/□L)
   b. Platelets ≥100,000/mm3 (≥100 x 109/L)
   c. Hemoglobin ≥9.0 g/dL

9. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5

10. Adequate liver function as evidenced by:
    a. bilirubin ≤1.5 times the upper limit of normal (ULN)
    b. alkaline phosphatase (ALP) ≤3×ULN (in the case of liver metastases ≤5×ULN)
    c. alanine aminotransferase (ALT) ≤3×ULN (in the case of liver metastases ≤5×ULN)
    d. aspartate aminotransferase (AST) ≤3×ULN (in the case of liver metastases ≤5×ULN).

    In case ALP is >3×ULN (in the absence of liver metastases) or >5×ULN (in the presence of liver metastases) AND the subject also is known to have bone metastases, the liver specific ALP isoenzyme must be separated from the total and used to assess the liver function instead of the total ALP.

11. Subjects with known brain metastases will be eligible if they have completed the primary brain therapy (such as whole brain radiotherapy, stereotactic radiosurgery, or complete surgical resection) and if they have remained clinically stable, asymptomatic, and off steroids for at least 2 months before starting study treatment.

12. All females of childbearing potential (please refer to Section 6.4) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of beta-human chorionic gonadotropin [β-hCG]) at the screening visit. Females of childbearing potential* must agree to use a highly effective method of contraception (please refer to Section 6.5) for the entire study period and for 120 days after study

discontinuation

13. Male subjects who are partners of women of childbearing potential must follow one of the methods of contraception described in Section 6.5 beginning at least 1 menstrual cycle prior to starting study drugs, throughout the entire study period, and for 120 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile.

14. Archival tumor tissue from within 3 months (preferred) or up to 6 months (acceptable)must be available prior to the first dose of study drug for biomarker analysis. If no biopsy has been performed in the prior 6 months, an SOC biopsy is requested if safe and feasible. In the case tissue cannot be provided, patients can be enrolled upon consultation and agreement by the trial PI.

    Note: In case of submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut.

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

4.2 Exclusion Criteria

1. Predominant clear cell renal cell carcinoma (RCC)

2. Uncontrolled or untreated brain metastasis

3. Major surgery performed within 4 weeks prior to the first dose of study drugs or scheduled for major surgery during the study. Subjects must have recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.

4. Subjects having >1+ proteinuria on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein ≥1 g/24-hour will be ineligible.

5. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.

6. New York Heart Association congestive heart failure of grade II or above, unstable angina, myocardial infarction within the past 6 months, or serious cardiac arrhythmia associated with significant cardiovascular impairment within the past 6 months.

7. Prolongation of QTc interval to >480 msec.

8. Active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to

the first dose of study drug.

9. Clinically significant active infection (any infection requiring systemic treatment).

10. Subject is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C

11. Serious nonhealing wound, ulcer, or bone fracture.

12. Known intolerance to either of the study drugs (or any of the excipients).

13. History of organ allograft (subject has had an allogenic tissue/solid organ transplant), or allogeneic stem cell transplant (subject has received blood-forming stem cells from a donor).

14. Biologic response modifiers (e.g., granulocyte colony-stimulating factor) within 4 weeks before study entry. Chronic erythropoietin therapy is permitted provided that no dose adjustments were made within 2 months before first dose of study treatment.

15. Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial.

16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment. If the required urine pregnancy test is positive (or cannot be confirmed as negative) within 72 hours prior to the start of treatment, a serum pregnancy test will be required.

17. Excluding the primary tumor leading to enrollment in this study, any other active malignancy (except for definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the bladder or cervix) within the past 36 months.

18. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. The use of up to 10 mg/day of prednisone or equivalent is approved and does not exclude the patient from the trial.

19. Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, > 10 mg of prednisone per day, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. The use of up to 10 mg/day of prednisone or equivalent is approved and does not exclude the patient from the trial.

20. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required

maintenance steroids (>10 mg of prednisone) or current pneumonitis/interstitial lung disease.

21. Has received a live-virus vaccination or live-attenuated vaccine within 30 days of planned treatment start. Administration of killed vaccines is allowed.

4.3 Inclusion of Women and Minorities

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

5.0 REGISTRATION PROCEDURES

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

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

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

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

5.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least two business days prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

5.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT.

Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within two business days. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

5.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

6.0 TREATMENT PLAN

6.1 Study Intervention Administration

Lenvatinib 20 mg will be administered with water orally once a day (with or without food) in 21-day cycles at approximately the same time each day. Treatment cycles will be counted continuously regardless of dose interruptions (meaning that cycles will not last for more than 21 days regardless of the number of lenvatinib doses a patient receives during that cycle). On Day 1 (D1) of each cycle, it will be administered approximately within 1 hour after completion of pembrolizumab administration.

Pembrolizumab will be administered as a dose of 200 mg as a 30-minute IV infusion, Q3W (25 minutes to 40 minutes are acceptable), for a maximum of 35 cycles.

6.2 Definitions of Evaluability

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

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable).

6.3 Concomitant Medications/Vaccinations

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 subject's primary physician.

6.3.1 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.

6.3.2 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 lenvatinib and 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 PI.

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.

Lenvatinib can prolong the QT interval, so providers must use caution with coadministration of QT-prolonging agents.

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 and the participant.

There are no prohibited therapies during the post-treatment follow-up phase.

6.3.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.0. 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 pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Section 7.0 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.

6.4 Women 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.

6.5 Contraception Requirements

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

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below 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 consistently and correctly as described in the table below during the protocol-defined time frame.

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 120 days 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.

6.6 Pregnancy Testing

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

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

6.7 Duration of Therapy

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

In the absence of treatment delays due to adverse events, treatment with pembrolizumab may continue for a maximum of 35 cycles (approximately 2 years) and treatment with lenvatinib may continue indefinitely or until one of the following criteria applies:

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

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

6.8 Duration of Follow-up

After coming off treatment, patients will be followed approximately every 12 weeks until death for survival. Patients who discontinue prior to progression will continue scans approximately every 9 weeks until progression or the start of another anti-cancer therapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.9 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.0 DOSE DELAYS/DOSE MODIFICATIONS

Other holds and modifications beyond those described below may be made at the discretion of the PI. Dose holds of modifications for lenvatinib and pembrolizumab can occur independently of each other provided the toxicity is clearly attributable to the individual therapy, with the exception of toxicities that fall under the guidance in Section 7.2.

7.1 Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-related toxicity will be in accordance with the dose reduction instructions shown in the tables below. Any dose reduction below 4 mg/day must be discussed with the trial PI. Once the dose has been reduced, it cannot be increased at a later date.

Dose Reduction Recommendations for Lenvatinib Treatment-Related Toxicity

Initial Lenvatinib Dose	**Adjusted Dose To Be Administered**			
	Reduction 1	**Reduction 2**	**Reduction 3**	**Reduction 4**
20 mg QD	14 mg QD	10 mg QD	8 mg QD	4[a] mg QD

a. Consult trial PI for further dose reduction recommendations.

Occurrence of Lenvatinib Treatment-related Toxicity[a,b]	**During Therapy**	**Adjusted Dose[f]**
Grade 1, Tolerable Grade 2		
Any occurrence	Continue treatment	No change
Intolerable Grade 2[c,d] and Grade 3[g]		
First occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 dose level

Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to tolerable Grade 2, or Grade 0-1	Reduce lenvatinib by 1 more dose level
Grade 4[e,g]		
Any occurrence	Discontinue lenvatinib	

a. An interruption of lenvatinib treatment for more than 21 days (due to lenvatinib treatment-related toxicities) will require a discussion with the Sponsor before treatment can be resumed.
b. Excluding alopecia. Initiate optimal medical management for nausea, vomiting, hypothyroidism, hypertension, and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c. Applicable only to Grade 2 toxicities judged by subject and/or physician to be intolerable.
d. Obese subjects with weight loss do not need to return to the baseline weight or 10% of baseline weight (i.e. grade 1 weight loss). These subjects will restart the study drugs at a lower dose once their weight remains stable for at least 1 week and they reached the normal BMI (if the weight loss occurred but it is still above normal BMI, they can restart the study treatment at a lower dose once the weight has been stable for at least 1 week). Normal BMI should be used as the new baseline for further dose reductions.
e. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
f. Refer to table above for adjusted dose.
g. For asymptomatic Grade ≥3 elevations of amylase and lipase, the trial PI should be consulted to obtain permission to continue treatment.

7.1.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before Cycle 1/Day 1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments a minimum of 1 hour apart. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments a minimum of 1 hour apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists. For subjects with hypertension and proteinuria, appropriate therapy, eg, angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist, is preferred (Kilfoy, et al., 2009).

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the subject has been on the same hypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

During the Treatment Period, subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 or more frequently as clinical indicated until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on repeat measurements after 1 hour:

1. Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication
2. For those subjects already on antihypertensive medication, dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted. It should be restarted at one lower dose level as specified in Table 3 only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of restarted at an additional dose reduction as specified in Table 3 only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted. It should be restarted at a third dose reduction as specified in Table 3 only when systolic BP ≤150 mmHg and diastolic BP ≤95 mmHg

and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

- Institute appropriate medical management
- Discontinue study drug

7.1.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the study calendar. Guidelines for assessment and management of proteinuria:

1. Grading will be based on the 24-hour urinary protein result. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained the table above, "Dose Modifications for Lenvatinib Treatment-Related Toxicity."
2. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation is required in the following situations:
    a. The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug
    b. A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
    c. When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is 2+, 3+, or 4+
3. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 3 consecutive months.

Grading of proteinuria should be performed according to CTCAE v 5 but will be based on the 24-hour urine collection for total protein result, if a 24-hour urine was performed at that time point.

For subjects with lenvatinib-related toxicity, the dose reduction and/or interruption instructions provided in the table above, "Dose Modifications for Lenvatinib Treatment-Related Toxicity," should be followed.

7.1.3 Management of Hepatotoxicity

Regular monitoring of liver function tests (eg, alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the study calendar and as clinically indicated. If signs occur indicating a decrease in liver function by 1 grade or more from baseline, the instructions contained in the table above, "Dose Modifications for Lenvatinib Treatment-Related Toxicity," should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

7.1.4 Management of Thromboembolic Events

Subjects should be advised to pay attention to the symptoms suggestive of venous thromboembolic events, which include acute onset of dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, redness and warmth to touch or tenderness. In case any of these signs or symptoms appear, subjects should be instructed to report such signs and symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in the table above, "Dose Modifications for Lenvatinib Treatment-Related Toxicity," should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

7.1.5 Management of Posterior Reversible Encephalopathy Syndrome (PRES)

In clinical studies with lenvatinib, events of posterior reversible encephalopathy syndrome (PRES) were reported in less than 1% of lenvatinib-treated subjects. PRES is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure. In subjects with signs or symptoms of PRES, dose interruptions, reductions, or discontinuation may be required per instructions included in the table above, "Dose Modifications for Lenvatinib Treatment-Related Toxicity." Please refer to Section 7 of the Investigator's Brochure for further information on lenvatinib, including the full set of special warnings and precautions for use (Section 7.4.4).

7.1.6 Management of Hypocalcemia

Serum calcium should be monitored every 3 weeks per the study calendar. Hypocalcemia should be treated per institutional guidelines (e.g., using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution.

7.2 Pembrolizumab

Pembrolizumab dose interruption for subjects who experience pembrolizumab-related toxicity will be in accordance with the table below. Adverse events (both nonserious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per the table below.

Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab and Combination Therapy

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 0 or 1 and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has improved to Grade 0 or 1 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.

***For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated irAEs cannot be controlled by corticosteroids.**

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE V5.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and 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. Add prophylactic antibiotics for opportunistic infections.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	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. Subjects 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.	Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Subjects with Grade ≥2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2[a]	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[b] or 4[c]	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[d]	Initiate insulin replacement therapy for subjects with T1DM. Administer antihyperglycemic in subjects with hyperglycemia.	Monitor subjects 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[d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate.	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
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: grading according to increased creatinine or acute kidney injury	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		
Neurological Toxicities	Grade 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		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids.	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	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[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.
Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal
b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal
c AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
d The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
e Events that require discontinuation include but are not limited to: encephalitis, and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis)

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

7.2.1 Supportive Care Guidelines for Infusion Reactions

Pembrolizumab may cause severe or life-threatening 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 the table below.

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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one 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 subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. ** In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. *For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov*		

7.2.2 Combination Therapy with Pembrolizumab

Attribution of Toxicity: When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to lenvatinib alone or to pembrolizumab alone, for adverse events listed in the table in Section 7.2 above, both interventions must be held.
.

Restarting Study Interventions:
Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in the table in sSection 7.2 above. If pembrolizumab is to be held for a related toxicity, the dose will be skipped and restarted at the next cycle if resolved.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions, unless the toxicity can be clearly attributed to only one of the study therapies.
- If the toxicities do resolve and conditions are aligned with what is defined in the table in Section 7.2 above, the combination of lenvatinib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to lenvatinib alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion.

8.0 REGULATORY AND REPORTING REQUIREMENTS

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

Adverse events will be tracked from start of treatment through 120 days after last day of study treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

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

Reporting requirements for Washington University study team may be found in Section 8.1. Reporting requirements for secondary site study teams participating in Washington University-coordinated research may be found in Section 8.2.

8.1 Washington University PI Reporting Requirements

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

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

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

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

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

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

For events that occur at secondary sites, the Washington University PI (or designee) is required to notify the QASMC within 10 days of Washington University notification via email to qasmc@wustl.edu. Submission to QASMC must include either the myIRB form and supporting documentation or (if not submitted to myIRB) the date of occurrence, description of the event, whether the event is described in the currently IRB approved materials, the event outcome, determination of relatedness, whether currently enrolled participants will be notified, and whether the informed consent document and/or any study procedures will be modified as a result of this event.

8.1.3 Reporting to Merck

8.1.3.1 Overdose

If an adverse event(s) is associated with ("results from") the overdose of a Merck product (either pembrolizumab or lenvatinib), 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 Washington University PI and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

8.1.3.2 Pregnancy and Lactation

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

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor’s product, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

8.1.3.3 Serious Adverse Events

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Washington University PI and within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or

discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Washington University PI and within 2 working days to Merck Global Safety.

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

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

8.1.3.4 Events of Clinical Interest (ECI)

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

8.1.4 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all unanticipated problems involving risks to participants or others that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable. Refer to Section 16.0 (Multicenter Management) for more information.

8.2 Secondary Site Reporting Requirements

The research team at each secondary site is required to promptly notify the Washington University PI and designee of all serious adverse events (refer to Appendix C, Section D) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using an FDA Form 3500a (MedWatch) and Washington University's cover sheet (Appendix E)). A formal written report must be sent to the Washington University PI and designee within **4 calendar days** (for fatal or life-threatening suspected adverse reactions) or **11 calendar days** (for serious unexpected adverse reactions) of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to Merck as needed.

Washington University pre-approval of all protocol exceptions must be obtained prior to implementing the change. Local IRB approval must be obtained as per local guidelines. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

8.3 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 8.1 include:

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

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

9.0 PHARMACEUTICAL INFORMATION

9.1 Lenvatinib

9.1.1 Lenvatinib Description

Lenvatinib 4-[3-Chloro-4-(N'-cyclopropylureido)phenoxyl]- 7-methoxyquinoline-6-carboxamide methanesulfonate (lenvatinib mesilate) is an oral, potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptor FGFR1-4, platelet-derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. Nonclinical studies showed lenvatinib to be a potent antiangiogenesis agent with antitumor activity versus various human cancer xenograft models in athymic mice. Lenvatinib drug substance is a white to pale yellow powder that is being used in the capsuleformulation for the clinical studies evaluating lenvatinib. It is slightly soluble in water and has a molecular weight of 522.96 and a pKa of 5.27 (mesilate salt).

9.1.2 Clinical Pharmacology

Please refer to Section 2.2.1 of the Lenvatinib IB.

9.1.3 Pharmacokinetics and Drug Metabolism

Please refer to Section 2.2.1 of the Lenvatinib IB.

9.1.4 Supplier(s)

Lenvatinib will be provided by Merck.

9.1.5 Dosage Form and Preparation

E7080 drug products used in clinical studies are hard capsules containing 1, 4, or 10 mg E7080 as anhydrous free base. The size of the capsules is No. 4 for all strengths with an average length of 14.3 mm. The color of the cap is yellowish-red for all strengths. The colors of the body are white, yellowish-red, and yellow for the 1-mg, 4-mg, and 10-mg strengths, respectively (capsules with or without markings in black ink might be used).

9.1.6 Storage and Stability

E7080 capsules are packaged in cold form blisters or high-density polyethylene (HDPE) bottles with a polypropylene cap and desiccant. The blisters and bottles should be stored under room temperature.

9.1.7 Administration

Lenvatinib will be given at a dose of 20 mg (two 10 mg capsules) once daily. The daily dose of lenvatinib is to be modified as needed according to the dose/toxicity management plan.

Lenvatinib is to be taken at the same time each day with or without food.

9.1.8 Special Handling Instructions

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not open the capsule. Avoid repeat exposure to contents of the capsule.

9.2 Pembrolizumab

Pembrolizumab may be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab.

9.2.1 Investigational Product – Pembrolizumab

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

Pembrolizumab will be provided by Merck as summarized in the table below:

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

9.2.2 Clinical Pharmacology

The PK profile of pembrolizumab, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Exposure to pembrolizumab is approximately linear in the dose range of clinical relevance (1 to 10 mg/kg and at 200 mg). Furthermore, pembrolizumab has a low potential of eliciting the formation of ADAs.

9.2.3 Pharmacokinetics and Drug Metabolism

Pembrolizumab is administered intravenously and is therefore immediately and completely bioavailable.

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; CV%: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Pembrolizumab is catabolized through nonspecific pathways; metabolism does not contribute to its CL.

Pembrolizumab CL is approximately 23% lower (geometric mean, 195 mL/day [CV%: 40%]) after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32%) at steady-state.

9.2.4 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.2.5 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, 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.

9.2.6 Supplier

Merck will provide pembrolizumab as a liquid drug product.

9.2.7 Dosage Form and Preparation

Merck will provide pembrolizumab as a 100 mg/vial liquid drug product.

The liquid drug product is clear to opalescent, essentially free of visible particles. The liquid product is intended for IV administration. The liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in IV containers made of PVC or non-PVC material. The infusion solution should be administered immediately.

9.2.8 Administration

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30

minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

9.2.9 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.

9.2.10 Storage and Stability

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6-hour countdown begins when the vial is pierced and includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6-hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

If refrigerated, allow the IV bags to come to room temperature prior to use.

9.2.11 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 subjects and the amount remaining at the conclusion of the trial.

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.

10.0 CORRELATIVE STUDIES

Biomarker discovery and/or validation will be performed to identify blood or tumor biomarkers that may be useful to predict subject response to lenvatinib and/or pembrolizumab, as determined by evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development. Blood samples from subjects receiving lenvatinib and pembrolizumab may be analyzed using global proteomic methods, enzyme-linked immunosorbent assay (ELISA), multiplex bead-based immunoassay, or other assays/methods or new technology. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of this study and/or the signals observed in other clinical studies or other information available at that time.

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to lenvatinib, pembrolizumab, cancer and/or for potential diagnostic development.

10.1 Blood Collection

10.1.1 Collection of Specimen

Blood samples for the development of exploratory predictive biomarkers will be collected within 2 weeks prior to the first dose of study drug, on Cycle 4 Day 1, and at the Off-Tx assessment. A blood sample for peripheral blood mononuclear cells (PBMC) and plasma isolation will be collected from consented subjects for potential analysis. Plasma will be used for protein biomarkers analysis. PBMCs will be used for immune cell profiling (e.g. tumor infiltrating lymphocytes, T-cell repertoire, and immune cell types). At each blood collection time point, two 10ml EDTA tubes (purple preferred, pink acceptable) will be filled and transferred to the Tissue Procurement Core (TPC) at Washington University (coordinating site) or processed according to the instructions in Appendix H (secondary sites).

10.1.2 Handling and Shipping of Specimen(s)

Blood tubes collected will be either taken to the TPC immediately following draw for processing (coordinating site) or processed according to instructions in Appendix H (secondary sites). Secondary sites must bulk ship frozen samples at a minimum of every 2 months to the address provided below in protected shipment container.

Hannah Black, Washington University School of Medicine
660 South Euclid CB 8056-29-10200
St. Louis, MO 63110, USA
Phone: 314-747-2089, 314-362-9913 or 314-273-2696

Samples should only be shipped Monday through Wednesday. If Thursday shipping is required, please contact the study team at LENKYN@wustl.edu to assess availability or recommended storage conditions. Blood cannot be shipped on a Friday. See Appendix G for further shipping instructions.

10.2 Tumor Tissue

10.2.1 Collection of Specimen(s)

Subjects will be required to provide an archival tumor tissue sample before treatment for biomarker analyses (patients without archival tissue can be enrolled upon consultation and agreement by the trial PI). Archived, formalin-fixed paraffin-embedded (FFPE) tissue or an OCT embedded frozen tissue block will be collected from all subjects for potential assessment of protein biomarkers which may be important in the development and progression of cancer as well as for potential use in diagnostic development. Appropriate technology/methodologies will be used based on the amount of tumor tissue available.

10.2.2 Handling of Specimens

Sufficient tumor tissue specimens, preferably collected within 3 months but no more than 24 months prior to enrollment with an associated pathology report, will be required in the form of an OCT embedded frozen tissue block (preferred), formalin-fixed paraffin-embedded block or 20 unstained slides. A minimum of 10 slides will be acceptable if tumor tissue is limited. In these situations, it is recommended to consult with the protocol team to discuss the specifics of the case.

10.2.3 Shipping of Specimens

Tumor samples will be either taken to the TPC upon obtaining tissue slides/block (coordinating site), or shipped on the same day the samples are obtained to the address provided below in protected shipment container (secondary sites).

Hannah Black, Washington University School of Medicine
660 South Euclid CB 8056-29-10200
St. Louis, MO 63110, USA
Phone: 314-747-2089, 314-362-9913 or 314-273-2696

Samples should only be shipped Monday through Wednesday. If Thursday shipping is required, please contact the study team at LENKYN@wustl.edu to assess availability or recommended storage conditions. Tissue cannot be shipped on a Friday. See Appendix F for further shipping instructions.

11.0 DATA SUBMISSION SCHEDULE

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

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 12 weeks until death
iRECIST Form	Baseline, every 9 weeks, end of treatment
Blood Form	Baseline, C4D1, end of treatment
Tissue Form	Baseline
Progression Form	Time of progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 8.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

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

12.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans may also be obtained in accordance with the guidance below following either initial documentation of objective response or initial documentation of progression.

12.1 Antitumor Effect – Immune-Related RECIST (iRECIST) Criteria

12.1.1 Definitions

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (RECIST version 1.1) proposed by the RECIST committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment. 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 4 to 8 weeks later is obtained using iRECIST for participant management. 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.

12.1.2 RECIST 1.1 Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an

identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

12.1.3 Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [*Eur J Ca* 45:228-247, 2009]) before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of target, non-target, and new lesions into response assessment

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response For This Category Also Requires**
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/non-PD	No	PR	Normalization of tumor markers, tumor nodes <10 mm
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline

Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment. *Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.				

12.1.4 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming progression: Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
  - Continued unequivocal progression in non-target disease with an increase in tumor burden.
  - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD (*Lancet Oncol* 18:e143-e152, 2017 - Table 2).

New lesions:

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**, ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD).
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD.
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and/or

Time-point (TP) iResponse

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	**Prior iUPD**, *****
				• previously identified NT lesion iUPD (need not be unequivocal) and/or • size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified.
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
Table assumes a randomized study where confirmation of CR or PR is not required. • NE = not evaluable that cycle. • Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation. • For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.					

12.1.5 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

12.1.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.*, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion."

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (*e.g.*, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case (*Eur J Ca* 45:228-247, 2009). For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

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

Tumor Markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR.

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

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also

be disclosed.

Until such a time as the first secondary site enrolls its first patient, a semi-annual DSM report to be prepared by the study team will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after study activation at Washington University (if at least one patient has been enrolled) or one year after study activation (if no patients have been enrolled at the six-month mark).

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after enrollment of the first patient at a secondary site, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

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

Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 8.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study design

This is a single arm, multicenter, phase II study of of lenvatinib in combination with pembrolizumab (lenvatinib 20 mg/day + pembrolizumab 200mg q3weeks) in subjects with locally advanced or metastatic nccRCC who have not received any systemic therapy for stage IV RCC.

15.2 Endpoints

The primary endpoint is ORR, defined as the proportion of response-evaluable patients who have a best overall response (BOR) of either CR or PR, as graded by RECIST V1.1.

The secondary endpoints include:

1) Toxicity profiles and adverse events. The severity of AEs will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
2) Progression-Free Survival (PFS): defined as the time from date of first dose of study drugs to date of first documented disease progression or death to any cause or latest follow up, whichever occurs first.

If the disease recurrence/progression assessment involves more than one date, the earliest date will be used as the event date. A patient will be censored at the date of the last radiographic disease assessment indicating a lack of recurrence, if any of the following occurs before documented disease progression:

- Patient is alive and progression free at the time of analysis data cut-off.
- Disease progression or death occurs right after missing data for a scheduled radiographic disease assessment (including missing the assessment or assessment results in an in-evaluable status for overall response per RECIST 1.1).
- Patient receives non-protocol systemic anticancer treatment.
- Patients missing baseline disease assessment will be censored at date of receiving first drugs.
- For equivocal findings of progression (*e.g.,* very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

3) Overall Survival (OS), defined as the time from the date of first dose of study drugs until date of death from any cause or latest follow up.

15.3 Statistical Hypotheses

In this population, ORR in first line treatment in locally advanced or metastatic non-clear cell RCC (nccRCC) is assumed to be 15%. Most published ORR prior to 2019 was at ~8%. However, the most recently reported data in Feb, 2019, on Keynote 427 cohort B nccRCC, a phase II study, was 24.8% Hence, the ORR in this study is estimated ≥ 35%, which is deemed a clinical meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR≤15% versus H_a: ORR ≥35%

15.4 Sample Size Determination

The Simon's Two-Stage optimal design was adopted to design the study with a one-sided type I error rate of 5% and targeting for 80% power. Approximately 34 efficacy evaluable subjects will be enrolled. During the 1st stage, 9 subjects will be enrolled and if there are ≥2 responders as assessed by ORR, the study will proceed to Stage 2 in which 25 new subjects will be enrolled; otherwise, the study will stop early for futility. In the final analysis of 34 efficacy evaluable subjects, ≥9 responders are required to claim preliminary efficacy of the treatment combination over historical control in the same patient population.

The actual alpha level was 0.047 and the actual power was 0.811. The early termination probability is estimated at 0.5995 if null is true and the average sample size is around 19.

15.5 Population for Analyses

- Safety Analysis set: refers to the set of participants who take at least one dose of the study interventions and will be used for safety analysis.
- Efficacy Analysis set: refers to the participants who take at least two cycles of the combined study interventions and have baseline and at least one tumor assessment after receiving treatments unless discontinued due to disease progression, death or toxicity. Subjects received less than 2 cycles of combination treatments will be replaced with additional participants. Efficacy analysis set will be used as the primary set for ORR and other efficacy endpoints.
- Per-Protocol Analysis set: refers to the participants who follows the protocol without major violation and have received at least 80% of the targeted dosage. This set will be used for sensitivity analyses of the efficacy endpoints.

15.6 Statistical Analyses

15.6.1 General Approach

Descriptive statistics will be used to summarize all data including mean, median, standard deviation, inter-quartile range etc. for continuous data and count and percentages for categorical data. Data will be analyzed as observed and no data imputation will be performed. Statistical significance is set at 5% level.

15.6.2 Analysis of the Primary Endpoint(s)

The primary endpoint ORR assessed by investigator review will be analyzed using the efficacy analysis set. ORR will be calculated as the proportion of patients who achieves the BOR of either CR or PR per RECISIST v1.1 and the 95% Clopper-Pearson exact CI will be derived.

The right-side one-sample binomial exact test will be conducted to test the hypothesis testing as follows:

$$H_0: ORR \leq 15\% \text{ vs. } H_a: ORR \geq 35\%.$$

15.6.3 Analysis of Secondary Endpoint(s)

PFS and OS will be analyzed using Kaplan–Meier product-limit estimates. Median PFS and OS and the cumulative probability of PFS at 3, 6, and 12 months and cumulative probability of OS at 6, 12, and 18 months will be presented with two-sided 95% confidence interval (CI) if estimable. PFS censoring rules will follow Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). The KM

estimates of cumulative PFS and OS will be plotted over time with 95% CI if estimable.

15.6.4 Safety Analyses

Safety analyses will be performed using the Safety Analysis set. Safety data include adverse events and lab data will be summarized using descriptive statistics. AE and Severe AE will be summarized by count and percentages by relationship to study drugs, by grade and by patient characteristics. Categorical lab data will be summarized by number and percentage. Continuous lab data will be summarized using n (number of subjects with available data), mean, standard deviation (SD), median, and range (minimum and maximum) unless otherwise specified. General safety will be assessed by the monitoring and recording of all AEs and serious adverse events (SAEs), regular monitoring of hematology and blood chemistry, regular measurement of vital signs, ECG, and the performance of physical examinations (PE) and other safety assessments in line with local regulations governing a study of this nature. Laboratory test results will be summarized using 3 categories, hematology, liver and renal, and other clinical chemistry. Hematology and clinical chemistry parameters that are graded by CTCAE v 4.03 will be summarized by CTCAE grade. Shifts from baseline to the worst CTCAE grade will be tabulated.

Progression of nccRCC and signs and symptoms clearly related to the disease progression should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

In case of life-threatening bleeding, the investigator should discontinue lenvatinib per Synopsis Table for Grade 4 toxicity and treat the subject based on the institution's standard practice. Clinically significant bleeding will be considered as study-specific events and should always be considered as serious important medical events, which will be entered on the adverse event CRF and reported using the procedures for reporting SAEs, even if the study-specific event does not meet other serious criteria.

15.6.5 Planned Interim Analysis

An interim analysis for futility will be performed based on the Simon's 2-stage optimal design when 9 efficacy evaluable patients are evaluable for ORR. The study will stop early if 2 or fewer responders are observed. If 3 or more responders are confirmed before the planned interim analysis and the safety profiles of both drugs are acceptable, the study will continue to Stage 2 and a normal interim analysis may be waived. There will be no enrollment gap for the interim analysis.

At the final analysis with 34 efficacy evaluable patients, the study will claim preliminary efficacy to warrant further study if 9 or more responders are observed.

	Threshold
Interim Analysis	Continue to enroll if ≥2 responders among the first 9 efficacy evaluable patients
Final Analysis	Reject H_0 if ≥9 responders among n=34 patients

15.6.6 Planned subset Analyses

Exploratory subset analysis on efficacy endpoints may be performed, for example, by race, by sex, by histological subtype.

15.6.7 Exploratory endpoint Analyses

A 2-sided 95% Clopper–Pearson CI will be constructed for CBR and DCR. DOR will be analyzed using the KM method described above.

15.7 Continuous monitoring for toxicity using a Pocock-type boundary

We will monitor the occurrence of intolerable toxicities (as defined below) in the 34 efficacy evaluable patients using a Pocock-type boundary for repeated testing for toxicity (20). This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.25, using a one-sided alpha level 0.016 test. The accrual will be halted if excessive numbers of intolerable toxicities are seen, that is, if the number of intolerable toxicities is equal to or exceeds boundary (b_n) out of a total of n patients treated and with full follow-up (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary ≤0.05 when the rate of intolerable toxicities is equal to the acceptable rate of 0.25.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	-	4	5	5	5	6	6	7	7	7	8	8	9	9	9	10	10	10
Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30	31	32	33	34						
Boundary, b_n	11	11	11	12	12	12	13	13	14	14	14	15	15	15						

Intolerable toxicities include severe treatment-emergent adverse events which can't be resolved within 7 days, including

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: _____

Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take 20 mg (2 capsules) of lenvatinib daily at approximately the same time each day. Take the lenvatinib with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your lenvatinib dose and it cannot be taken within 12 hours of the normal dosing time within the same day, then do not take a dose that day. Restart taking the lenvatinib the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.
6. Avoid St. John's Wort, Seville oranges, grapefruit, grapefruit juice, grapefruit hybrids, pummelos, and exotic citrus fruits from 7 days before you start taking lenvatinib and throughout the entire study.

Day	Date	What time was dose taken?	# of tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

APPENDIX C: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

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

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

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

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

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

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

As defined in 21 CFR 312.32:

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

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

As defined in 21 CFR 312.32:

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

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- A new cancer (that is not a condition of the study
- Associated with an overdose
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

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

F. Deviation

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

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

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

G. Overdose

Definition: For purposes of this trial, 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 subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

An overdose of lenvatinib will be defined as any dose of 120 mg or greater (≥ 6 times the indicated dose). There is no specific antidote for overdose with lenvatinib. In case of suspected overdose, lenvatinib should be withheld and supportive care initiated.

H. Events of Clinical Interest

Events of clinical interest for this trial include:

1. an overdose of Merck product (either pembrolizumab or lenvatinib), as defined in Section 8.6.1 - 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.

APPENDIX D: Reporting Timelines

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Merck**
Serious adverse event			Report within 2 working days.
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment	
Overdose			If an AE is associated with overdose of either pembrolizumab or lenvatinib, report as a serious adverse event within 2 working days. If an overdose is taken without any associated AE, report as a non-serious Event of Clinical Interest to Merck within 2 working days.
Pregnancy and infant exposure during breastfeeding			Report within 2 working days.
Event of Clinical Interest			Report within 2 working days.
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.		
Protocol exception	Approval must be obtained prior to implementing the change		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days.		

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**Merck**
	If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Breach of confidentiality	Within 10 working days.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

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

Expedited Reporting Timelines for Secondary Sites			
Event	**WU (Coordinating Center)**	**Local IRB**	**Merck**
Serious AND unexpected suspected adverse reaction	Report no later than 11 calendar days after it is determined that the information qualifies for reporting.	Report all applicable events to local IRB according to local institutional guidelines.	The research team at Washington University is responsible for reporting all applicable events to Merck as needed.
Unexpected fatal or life-threatening suspected adverse reaction	Report no later than 4 calendar days after initial receipt of the information.		
Unanticipated problem involving risk to participants or others	Report no later than 4 calendar days after initial receipt of the information.		
Overdose	Report within 24 hours.		
Event of Clinical Interest	Report within 24 hours.		
Pregnancy and infant exposure during breastfeeding	Report within 24 hours.		
Adverse event or SAE that does not require expedited reporting	As per routine data entry expectations		
Protocol exception	Approval must be obtained prior to implementing the change.		

APPENDIX E: Washington University Unanticipated Problem Reporting Cover Sheet

SAE COVER SHEET- Secondary Site Assessment

Washington University HRPO#:	Washington University PI:
Subject Initials:	Subject ID:
Treating MD:	Treating Site:
EVENT TERM:	Admission Date:
EVENT GRADE:	Date of site's first notification:

Treating MD Event Assessment:

Is this event **possibly, probably, or definitely** related study treatment?

☐ yes ☐ no

If yes, please list which drug (if more than one)_____

Explain _____

_____

_____ _____ _____

Physician's Name **Physician's Signature** **Date**

APPENDIX F: TUMOR TISSUE SUBMISSION FORM

Submitter Name: _____ **Submitter's Phone #:** _____

STUDY ID#: 202003148 **Subject ID:** _____

Participant Initials: (first, middle, last) _____ **DOB:**_____

Collection Site (*select one*):

☐ Washington University School of Med ☐ Cornell University
☐ Stanford University ☐ Tulane University

Specimen(s) Submitted: *Please label tissue block or slides with Study ID, Subject ID, Date of Collection, and type of sample (ie, FFPE or OCT block).*

Specimen Type	Timepoint	Date Collected (MM/DD/YY)	Number of Slides/Specimens	Site of Tissue
☐Fixed tissue block ☐tissue slides ☐OCT embedded frozen tissue	Pre-treatment			

Shipping directions: Samples should only be shipped Monday through Wednesday. If Thursday shipping is required, please contact the study team at LENKYN@wustl.edu to assess availability or recommended storage conditions. Tissue cannot be shipped on a Friday. Samples to be shipped same day obtained when possible in protected shipment container for overnight delivery by FEDEX. In case of submitting unstained cut slides, freshly cut slides should be shipped **within 14 days from when the slides are cut**. FFPE samples can be sent at room temperature, on cool packs if ambient temperature requires. OCT tissue should be shipped on dry ice.

Pathology Report: redact PHI and include with tumor specimen shipment (required)

Shipment Address:
Hannah Black, Washington University School of Medicine
660 South Euclid Campus Box 8056-29-10200
St. Louis, MO 63110, USA
Phone: 314-747-2089, 314-362-9913 or 314-273-2696

Sample tracking number: _____
Please send the original requisition with the samples. Retain a copy for the research chart.

Please send email notification of shipment, along with a copy of this submission form and the FedEx tracking number to: LENKYN@wustl.edu

APPENDIX G: PBMC & PLASMA CORRELATIVE BLOOD SUBMISSION FORM

Submitter Name: _____Submitter's Phone #: _____

STUDY ID#: 202003148 **Subject ID: _____**

Participant Initials: (first, middle, last) **_____ DOB:_____**

Collection Site (*select one*):

☐ Washington University School of Med ☐ Cornell University
☐ Stanford University ☐ Tulane University

Specimen(s) Submitted: *Please label tubes with Study ID, Subject ID, Date of Collection, and type of specimen (ie, plasma or PBMC). Requisition can be used for multiple timepoints but only one patient.*

Specimen Type	Timepoint	Number of Cryovials	Date Collected (MM/DD/YY)	Time collected (__:__)
☐ PBMCs ☐ double spun plasma	☐ Pre-treatment ☐ Cycle 4 ☐ Off treatment			
☐ PBMCs ☐ double spun plasma	☐ Pre-treatment ☐ Cycle 4 ☐ Off treatment			
☐ PBMCs ☐ double spun plasma	☐ Pre-treatment ☐ Cycle 4 ☐ Off treatment			
☐ PBMCs ☐ double spun plasma	☐ Pre-treatment ☐ Cycle 4 ☐ Off treatment			

Shipping directions: Samples should only be shipped Monday through Wednesday. If Thursday shipping is required, please contact the study team at LENKYN@wustl.edu to assess availability or recommended storage conditions. Blood cannot be shipped on a Friday. Samples to be bulk shipped frozen at a minimum of every 2 months in protected shipment container for overnight delivery by FEDEX.

Shipment Address:
Hannah Black, Washington University School of Medicine
660 South Euclid Campus Box 8056-29-10200
St. Louis, MO 63110, USA
Phone: 314-747-2089, 314-362-9913 or 314-273-2696

Sample tracking number: _____
Please send the original requisition with the samples. Retain a copy for the research chart.

Please send email notification of shipment, along with a copy of this submission form and the FedEx tracking number to: LENKYN@wustl.edu

APPENDIX H: RECOMMENDED BLOOD PROCESSING INSTRUCTIONS

It is requested that secondary sites process two 10mL tubes of EDTA blood (purple top preferred, pink acceptable) to double spun plasma and PBMCs prior to shipping in order to ensure samples are viable for analyses. If the secondary site is unable to process according to the instructions below or if the processing SOPs differ, contact LENKYN@wustl.edu for alternate arrangements or approval of the SOP.

ISOLATION OF PLASMA FROM PERIPHERAL BLOOD

(adopted from SOP-200 from TPC, v3.1, dated 7/20/2020)

Safety

Use universal safety precautions and don appropriate personal protective equipment when handling human samples.

Materials

- Clinical centrifuge with swinging bucket rotor
- Microcentrifuge (4°C)
- Cryovials (2.0mL)
- Microcentrifuge tubes (5.0mL)
- Transfer pipette
- Dry ice and container

Procedure

Platelet Poor Plasma (PPP) Isolation (also known as Double Spun Plasma): Whole Blood EDTA BCTs

1. Centrifuge two 10mL EDTA BCTs at 1,600 × g for 10 minutes at room temperature.
2. The specimen will separate into three layers: plasma, buffy coat and RBCs
3. Carefully transfer plasma into 5 mL flip-top microcentrifuge tube.
   3.1. Do not disturb white blood cell/platelet or red blood cell layers.
4. Pellet residual cells/platelets via centrifugation at 13,000 rpm (16,000 × g) for 10 minutes at 4°C.
5. Aliquot 1.5 mL plasma into labeled cryovials (up to 6 cryos) and immediately store at -80°C.

ISOLATING PBMCS FROM PERIPHERAL BLOOD USING Ficoll-Paque™ Plus REAGENT

(adopted from SOP-203 from TPC, v2.2, dated 5/21/2021)

Safety

Use universal safety precautions and don appropriate personal protective equipment when handling human samples.

Materials

- Clinical Centrifuge with swinging bucket rotor
- Microcentrifuge (4°C)
- Cryovials (2 mL)
- Microcentrifuge Tubes with O-ring lid (1.5 mL)
- 15 mL Conical Tubes
- 50 mL Conical Tubes
- RBC Lyse Solution, Qiagen or equivalent
- Phosphate Buffered Saline (PBS)

- Ficoll-Paque PlusTM (Ficoll)
- Leucosep™ or SepMate™ Tubes
- Freezing Medium (90% FBS + 10% DMSO)
- Rocker (Gyro Mini Nutating Mixer)
- Control-rate freezing container
- Cool Box™ insert, Cool Box™ and frozen ice pack
- Serological pipette
- Serological pipettes
- Transfer pipette (5.8 mL)
- Fine-tip transfer pipette (1.5 mL)
- Blood Bloc absorbent wipes, or equivalent
- Wet ice and container
- Dry ice and container

For preparation of cryopreserved cells the following materials are required:

- Prepare Freezing Media by adding 55.5 mL of DMSO to a 500 mL thawed FBS container, mix thoroughly and pour into eleven 50 mL conical tubes.

Procedure

1. Plasma Collection
   1.1. Perform plasma isolation as described above. Once complete, combine the fractionated sample (erythrocytes, granulocytes and lymphocytes, platelets) with the remaining whole blood or whole bone marrow into a 50 mL conical tube.
2. Preparation of Whole Blood
   2.1. Dilute one 10mL EDTA BCT of whole blood 1:1 with PBS in a labeled 50 mL conical tube depending on starting volume of whole blood.
   Example: if processing 20 mL whole blood, combine 20 mL whole blood and 20 mL PBS in a 50 mL conical tube.
3. Isolation of Mononuclear Cells from Whole Blood using Leucosep^{TM} Tubes
   3.1. Leucosep tubes cannot be used if granulocyte isolation is required. If the processing ntoes requires the collection of granulocytes, proceed to Step 6.
   3.2. Prepare the Leucosep tubes by filling the 50 mL Luecosep tube with 15 mL of room temperature Ficoll and centrifuge at 1000 x g for 2 minutes at room temperature.
      3.2.1. The Ficoll is now located below the porous barrier of the Leucosep tube.
      3.2.2. Leucosep tubes can be prepped in advance of use and stored for 3 months. Prepped Leucosep tubes must be stored at room temperature and away from direct exposure to light.
   3.3. Transfer 15-30 mL of diluted blood directly into the Leucosep tube and centrifuge at 800 x g for 15 minutes at room temperature. Set rotor brake to 6 and allow the centrifuge to come to a complete stop before removing the tubes.
   3.4. Aspirate the Plasma/PBS layer fraction with a serological or transfer pipette and discard. Leave behind 5 to 10 mm of Plasma/PBS above the Mononuclear Cell layer in order to reduce presence of platelets in the cell isolate.
      3.4.1. Alternatively, this step can be skipped if there is a small amount of original suspension and the MC layer is indistinct.

3.5. Harvest the supernatant containing the Mononuclear Cells by pouring the supernatant directly into 50 mL conical tubes.
    3.5.1. The Mononuclear Cell isolate from two Leucosep™ Tubes can be pooled into a single 50 mL conical tube.
3.6. Bring the volume in the conical tube to 50 mL using PBS and mix 5 times by gentle inversion.
3.7. Pellet the Mononuclear Cells using centrifugation at 400 x g for 10 minutes at room temperature.
3.8. Remove the supernatant and turn the tube upside down and briefly place on a Blood bloc to allow the remaining supernatant to drain.
3.9. Suspend the pellet in 1-5 mL of PBS; gently pipette up and down.
3.10. Proceed to Step 6--Cell Suspension Quantitation.

4. Isolation of Mononuclear Cells from Whole Blood or Bone Marrow using SepMate™ Tubes
4.1. SepMate tubes cannot be used if granulocyte isolation is required. If the processing notes requires the collection of granulocytes, proceed to Step 6.
4.2. SepMate tubes can be prepared in advance and stored for 3 months. Pipet 15 mL of room temperature Ficoll onto the SepMate insert.
    4.2.1. Centrifuge at 1000 x g for 2 minutes at room temperature.
    4.2.2. The top of the density gradient medium will be above the insert.
    4.2.3. Prepped SepMate tubes must be stored vertically at room temperature and away from direct exposure to light.
4.3. Keeping the tube vertical, add the diluted whole blood sample by pouring down the side of the tube. Take care not to pour the diluted sample directly through the central hole.
4.4. Centrifuge at 1200 x g for 10 minutes, with the brake on.
    4.4.1. If it appears that separation did not occur (sample appears dark red), centrifuge at 1200 x g for an additional 10 minutes.
4.5. Pour off the top layer into a new 50 mL conical tube. **Do not invert tube for longer than 2 seconds.**
    4.5.1. If samples from two or more tubes will be pooled, carefully aspirate the Plasma/PBS layer without disturbing the MC layer before pouring into a new 50 mL conical tube.
4.6. Bring the volume in the conical tube to 50 mL using PBS and mix 5 times by gentle inversion.
4.7. Pellet the Mononuclear Cells using centrifugation at 400 x g for 10 minutes at room temperature.
4.8. Remove the supernatant and turn the tube upside down and briefly place on a Blood bloc to allow the remaining supernatant to drain.
4.9. Suspend the pellet in 1-5 mL of PBS; gently pipette up and down.
4.10. Proceed to Step 6--Cell Suspension Quantitation.

5. Isolation of Mononuclear Cells and Granulocytes using Ficoll Layering in Conical Tubes
5.1. This procedure must be used if Mononuclear Cell and Granulocyte isolation is required from peripheral whole blood.
5.2. Prepare the Ficoll reagent.
    5.2.1. Ensure the Ficoll reagent is at room temperature.
    5.2.2. To an empty 15 mL, add 4 mL of Ficoll reagent for every 10 mL of diluted whole blood sample intended for processing.

5.2.3. Carefully layer the diluted whole blood sample onto the Ficoll reagent using a serological or transfer pipette.
5.2.3.1. Tilt the conical tube and touch the pipette tip to the inside of the tube and allow the sample to slowly slide down the side of the tube. Do not submerge the pipette tip below the Ficoll reagent layer.
5.2.4. Disengage the rotor break and centrifuge the tubes at 400 × g for 25 minutes at room temperature. Allow the centrifuge to come to a complete stop before removing the tubes.
5.2.5. Centrifugation will separate the sample into 4 distinct layers (top to bottom): plasma/PBS layer, Mononuclear cells, Ficoll, Granulocytes and Erythrocytes.

5.3. Isolation of Mononuclear Cells
5.3.1. Remove and discard the upper Plasma/PBS layer.
5.3.1.1. Alternatively, pierce through the upper Plasma/PBS layer to reach the white interface layer using a transfer pipette.
5.3.2. Transfer the white interface layer containing the Mononuclear Cells to a new 50 mL conical tube. Prolonged contact with Ficoll is toxic to cells. Remove and wash cells as quickly as possible.
5.3.3. Pellet the Mononuclear Cells with centrifugation at 400 × g for 10 minutes at room temperature.
5.3.4. Remove supernatant and discard.
5.3.5. Add 1 to 5 mL of PBS to the cell pellet and gently pipette up and down to avoid aerosolizing the solution while resuspending the cells.
5.3.6. Proceed to Step 6--Cell Suspension Quantitation.

5.4. Isolation of Granulocytes
5.4.1. Insert a transfer pipette through the Ficoll layer to the granulocyte and erythrocyte layer. Transfer the layer into a new 50 mL conical tube.
5.4.1.1. The granulocyte and erythrocyte layers from multiple tubes, with total layer volume not exceeding 10ml, may be pooled together in a single 50 mL conical tube.
5.4.2. Add enough RBC Lyse Solution to bring the total volume to 40 mL, mix 5 times with gentle inversion and place on the rocker for 10 minutes at room temperature.
5.4.3. Pellet the Granulocytes with centrifugation at 400 × g for 10 minutes at room temperature.
5.4.4. Pour off the supernatant. Turn the tube upside down and briefly place on a Blood bloc to allow the remaining supernatant to drain.
5.4.5. Add 1 – 5 mL of PBS to the cell pellet and gently pipette up and down to resuspend the cells.
5.4.6. Proceed to Step 6--Cell Suspension Quantitation.

6. Cell Suspension Quantitation
6.1. To establish total cell count, concentration and viability of cell suspensions, analyze the samples and record cell count.

7. Frozen Cell Pellet Derivative
7.1. Based on the measured total cell count, add enough PBS to the cell suspension to achieve 1×10^7 cells/mL; gently mix the cell suspension by pipetting up and down and transfer 1 mL (1×10^7 cells/mL) into separate, labeled 1.5 mL microcentrifuge tubes.

7.1.1. If quantitation measures less than 1×10^7 isolated cells, pellet the cell suspension via centrifugation at 400 × g for 10 minutes at room temperature. Pour off the PBS, turn the tube upside down and briefly place on a Blood Bloc to drain. Suspend the pellet in 1 mL of PBS and transfer the entire cell suspension to a single 1.5 mL microcentrifuge tube.

7.1.2. If quantitation measures more than what is required by the collection protocol, the cell suspension is aliquoted to 5 microcentrifuge tubes, and the excess is discarded.

7.1.3. If quantitation was not required by the collection protocol, but a pre-determined number of cell pellets will be generated, suspend the cell pellet in a total volume of PBS equal to the volume needed to deliver 1 mL of cell suspension into each 1.5 mL microcentrifuge tube equal to the number of desired cell pellets.

7.2. Centrifuge the cells at 1500 × g for 5 minutes at 4°C; remove supernatant using a fine-tip transfer pipette and discard.

7.3. Specimen is snap frozen in LN2, EtOH/dry ice bath, or crushed dry ice.

8. Cryopreserved Cell Derivative

8.1. Pre-chill labeled cryovials in a Cool Box™.

8.2. Centrifuge counted cell suspension at 400 × g for 10 minutes at room temperature to pellet the sample. Pour off the PBS, turn the tube upside down and briefly place on a Blood Bloc to drain.

8.2.1. Alternatively, using a fine tip pipette, pull off the supernatant while being careful not to disturb the cell pellet and discard pipette.

8.3. Based on the measured total cell count, add enough Freezing Medium to the cell pellet to achieve 1×10^7 cells/mL or as indicated on BSF; gently mix the cell suspension by pipetting up and down and transfer 1mL into separate, labeled cryovials.

8.3.1. If quantitation measures less than 1×10^7 isolated cells or amount specified on BSF, suspend the pellet in 1mL of freezing medium and transfer the entire cell suspension to a single cryovial.

8.3.2. If quantitation measures more than what is required by the collection protocol, the cell suspension is aliquoted to 5 cryovials at $1x10^7$ /mL and the excess is discarded.

8.3.3. If quantitation was not required by the collection protocol, or a pre-determined number of aliquots will be generated at an unspecified cell count, suspend the cell pellet in a total volume of Freezing Medium equal to the volume needed to deliver 1 mL of cell suspension to each cryovial aliquot needed.

8.4. Transfer the aliquots from the Cool Box™ into a controlled-rate freezing container and immediately store the container at -80°C. Allow the aliquots to freeze at -80°C for a minimum of 8 hours before transferring to long-term storage.