SPONSOR: Mehmet Asim Bilen, MD

TITLE: *Neoadjuvant Lenvatinib with pembrolizumab in Patients with Locally Advanced Nonmetastatic Clear Cell Renal Cell Carcinoma*

IND NUMBER: 147484

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Supplied Agent: *pembrolizumab (Merck), lenvatinib (Merck)*

1.0 TRIAL SUMMARY

Abbreviated Title	Neoadjuvant Lenvatinib Plus Pembrolizumab in Locally Advanced, Non-Metastatic Clear Cell Renal Cell Carcinoma
Trial Phase	Phase 2
Clinical Indication	Neoadjuvant therapy
Trial Type	Single-Arm
Type of control	N/A
Route of administration	PO (lenvatinib) and IV (pembrolizumab)
Trial Blinding	N/A
Treatment Groups	Single-Arm
Number of trial participants	17
Estimated enrollment period	1 year
Estimated duration of trial	3 years
Estimated average length of treatment per patient	12 weeks

2.0 TRIAL DESIGN

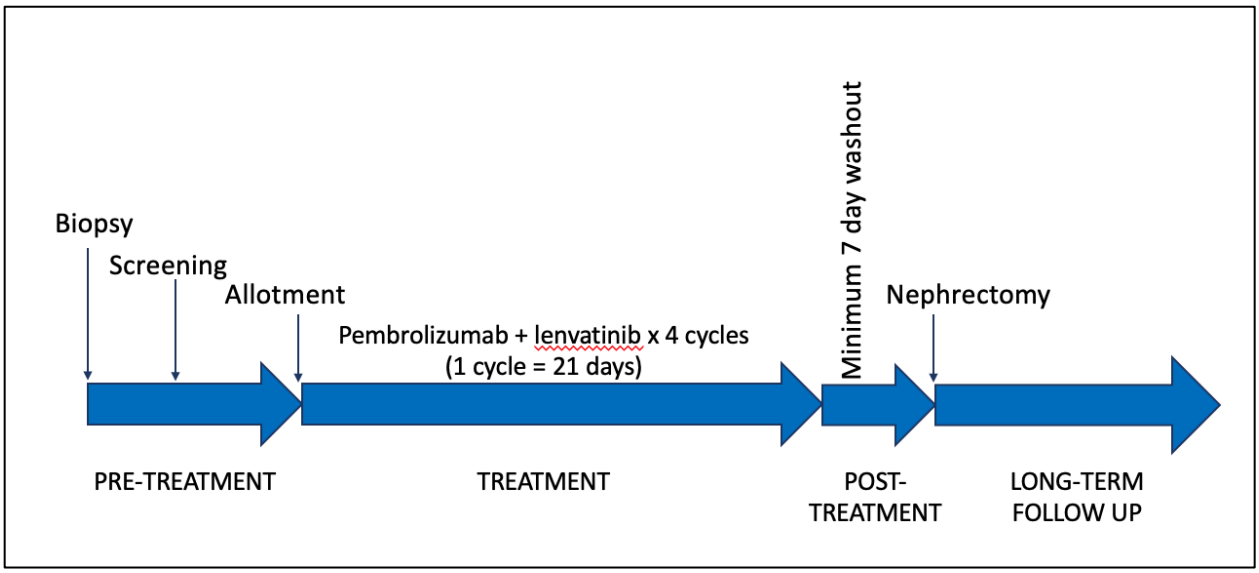
2.1 Trial Design

Patients with locally advanced, non-metastatic clear cell renal cell carcinoma (T3Nx or TanyN+) will be enrolled to receive neoadjuvant lenvatinib plus pembrolizumab for 4 cycles (12 weeks) before surgical resection.

Each subject's course will consist of four periods, all of which are depicted in the Trial Flow Chart (Section 6.0):

- A Pre-Treatment Period in which subjects are consented and undergo screening assessments to be qualified for the study.
- A Treatment Period in which subjects receive study treatment and undergo study assessments. This period will end at the time of completion of lenvatinib plus pembrolizumab, or when the patient withdraws consent or experiences unacceptable toxicity.
- A Post-Treatment Period in which subjects no longer receive study treatment and undergo kidney surgery. This period also includes intraoperative and post-operative period.
- A Long-Term Follow-up Period in which subjects will be followed after surgery until the patient's withdrawal of consent or loss to follow up, death, or study termination

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective & Hypothesis

(1) **Objective:** To assess the objective response rate (complete and partial responses), following the administration of lenvatinib and pembrolizumab for a total of 4 cycles (12 weeks) in patients with locally-advanced, biopsy-proven non-metastatic ccRCC prior to undergoing nephrectomy (partial or radical).

(2) **Hypothesis:** Patients with non-metastatic ccRCC who are treated with 12 weeks of neoadjuvant lenvatinib with pembrolizumab will achieve an objective response rate >= 25%.

3.2 Secondary Objectives

(1) **Objectives**:

- To assess the safety and tolerability of neoadjuvant lenvatinib plus pembrolizumab in apresurgical population.
- To determine the clinical outcomes including disease-free survival (DFS) and overall survival (OS) of patients with non-metastatic ccRCC treated with neoadjuvant lenvatinib and pembrolizumab.
- To evaluate surgery-related complications and outcomes as per the Clavien-Dindo classification system [1]

3.3 Exploratory Objectives

(1) Objectives:

- To evaluate changes in biomarkers of immune activation and gene expression before, during and after treatment
- To assess the quality of life, frailty and sarcopenia of patients before and after treatment

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Introduction

In the United States in 2018, there were approximately 65,340 new cases of kidney or renal pelvis cancer diagnosed with 14,970 deaths attributable to the disease [2]. Renal cell carcinomas (RCC) arising from the renal cortex make up about 85% of kidney cancers in adults with clear cell histology making up as many as 85% of RCC [3]. Tumor pathogenesis in clear cell renal cell carcinoma (ccRCC) is most often related to deletion, mutation or silencing of the von Hippel-Lindau (VHL) tumor suppressor gene, either through spontaneous deletion of chromosome 3p (on which VHL lies) or in the autosomal dominant VHL disease [4]. When VHL is defective, this leads to the accumulation of hypoxia inducible factors (HIFs) which in turn induces the production of multiple factors implicated in RCC tumorigenesis including vascular endothelial growth factor (VEGF), a main driver of angiogenesis. VEGF is a major molecular target in the treatment of RCC in those with unresectable disease or poor surgical candidates for nephrectomy [5-9].

4.1.2 Lenvatinib in RCC

Lenvatinib is an oral multi-kinase inhibitor of the vascular endothelial growth factor receptor (VEGFR 1-3), fibroblast growth factor receptor (FGFR1-4), platelet growth factor receptor α (PDGFR α), RET and KIT. Lenvatinib was approved by the FDA in May 2016 in combination with the mTOR inhibitor everolimus in the treatment of advanced RCC based on the randomized, open-label phase II trial investigating lenvatinib, everolimus or the combination of the two agents (in a 1:1:1 ratio) in patients with metastatic disease who had previously received at least one VEGFR inhibitor. Lenvatinib plus everolimus produced a significantly higher progression-free survival (PFS) compared to everolimus alone (median 14.6 months versus 5.5 months). Even lenvatinib alone prolonged PFS to 7.4 months compared to everolimus alone, although the difference was not as robust as when compared to the combination [10]. Overall survival (OS) was a secondary endpoint and was 25.5 months for lenvatinib plus everolimus, 18.4 months for single agent lenvatinib and 17.5 months for single agent everolimus; these differences were not significant at the time of primary data cutoff. Of note, lenvatinib has an acceptable safety profile and is also indicated as a single agent in the first line treatment of unresectable hepatocellular carcinoma as well as differentiated thyroid carcinoma that has progressed despite radioactive iodine therapy [11, 12]. Recently, combination of lenvatinib and

pembrolizumab is approved by FDA for patients with advanced endometrial carcinoma [13]. For more details on specific indications refer to the Investigator Brochure and prescribing information from Eisai.

4.1.3 Checkpoint inhibitors in RCC

Other than molecularly targeted agents such as anti-VEGF agents, the other primary therapeutic approach to RCC lies in immunotherapy with checkpoint inhibitors. Such an approach evolved after observation that removal of primary kidney lesion could result in spontaneous regression of metastatic lesions and demonstration that immunologic agents such as interferon gamma-1b and interleukin-2 (IL-2) have the capacity to induce relatively rare but durable complete responses in RCC [14-16]. RCC has been shown to demonstrate a penchant for attracting both tumor infiltrating lymphocytes (TILs) and NK cells to the tumor [17]. The goal of checkpoint inhibition is to counteract the T-cell exhaustion that happens at the tumor bed by disrupting the immunosuppressive interactions between programmed cell death receptor-1 (PD-1), a coinhibitory molecule expressed on activated B and T cells, and its ligand (PD-L1) on the tumor cell surface [18]. RCC also relatively highly expresses PD-L1 at tumor bed, also making it an attractive target for checkpoint inhibition [19]. Motzer, et al. (2018) on behalf of the CheckMate 214 investigators conducted an open-label, phase III trial investigating the combination of ipilimumab, a humanized monoclonal antibody (mAb) against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and the anti-programmed cell death 1 (PD-1) monoclonal antibody nivolumab compared to standard-of-care sunitinib in the first line setting for intermediate and poor risk unresectable RCC. They showed an overall survival advantage with nivolumab plus ipilimumab vs sunitinib in patients with previously untreated advanced renal cell carcinoma. In an intent-to-treat analysis of all 1,096 randomized patients, the 30-month overall survival rate was 64% with the immunotherapy combination vs 56% with sunitinib (P = .0003). The objective response rates in the intent-to-treat population was 41% vs 34% (P = .015), respectively, including complete response rates of 11% vs 2%. Based on the primary CheckMate 214 data analysis, the U.S. Food and Drug Administration approved the combination of nivolumab and ipilimumab in April 2018 as front-line treatment for intermediate- and poor-risk patients with advanced renal cell carcinoma [20].

4.1.4 Immunotherapy and targeted therapy combinations in RCC

Pembrolizumab is also 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 ligands 1 and 2 (PD-L1/2). Pembrolizumab has an acceptable preclinical safety profile and is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell and reduce tumor-induced immunosuppression. For more details on specific indications refer to the Investigator Brochure from Merck.

There is data to suggest that combining immunotherapy with targeted therapy has the potential to create synergy in its anti-tumor effect. Angiogenesis as a mechanism for tumor development requires immune tolerance and the antiangiogenic effects of targeted therapy in RCC may also be immunomodulatory; pazopanib, axitinib and sunitinib have all been shown to reduce the *in* vitro

expression of myeloid-derived suppressive macrophages [21] and pazopanib was shown to increase the expression of PD-1 and PD-L1, potentially increasing concurrent or future responsiveness to checkpoint inhibition [22]. More recently, Kimura, et al. showed that lenatinib combined with an anti-PD-1 antibody in a pre-clinical mouse model showed an increased response rate compared to either single treatment and that lenvatinib regardless of the presence of the anti-PD-1 agent led to decreased monocyte/macrophage populations and increased CD8+ T cells at the tumor in a hepatocellular carcinoma model [23]. With these mechanisms in mind, pembrolizumab was recently FDA approved in combination with axitinib, another multi-kinase inhibitor of VEGFR 1-3, in April 2019 for metastatic RCC for *all* risk groups. This was based on the phase III data comparing this combination to sunitinib and showing a median PFS of 15.1 months in the combination cohort versus 11.1 months in the sunitinib group; the median OS was not reached in either group but death-related hazard ratio was 0.53 (95% CI 0.38-0.74; P<0.0001) for the combination compared to sunitinib [24]. These data were the first leading to FDA approval of an immunotherapy and targeted therapy combination in RCC but have not been the last. Since that time, the FDA approved the combination of axitinib and avelumab (a mAb against PD-L1) in May 2019 based on a phase III trial showing improved PFS in patients with PD-L1 positive tumors of 13.8 months compared to 7.2 months with sunitinib (HR 0.61, CI 0.47-0.79, P<0.001) [25]. In 2018, Lee, et al. published RCC-specific data from a phase 1b/2 trial of lenvatinib plus pembrolizumab in selected solid tumors in the metastatic setting and of the 30 patients with RCC enrolled, overall response rate at 24 weeks of 66.7% and only 4 patients (13%) discontinued the treatment due to adverse events [26]. The phase III CLEAR clinical trial investigating lenvatinib combined with either everolimus or pembrolizumab compared to sunitinib in metastatic RCC is currently underway [27]. Thus, combination therapy represents a new horizon in the treatment of RCC.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

The above discussion involves the application of targeted and immunotherapy agents in the metastatic setting. This is because as of June 2019, the NCCN Clinical Practice Guidelines in Oncology have no recommendation for kidney cancer neoadjuvant therapy in stage I through III disease and only a category 3 recommendation for sunitinib as an adjuvant treatment in stage III disease [28, 29]. However, potential advantages of neoadjuvant therapy include downsizing and/or downstaging tumors with the goal of allowing resection of previously unresectable tumors or minimally-invasive approaches, decreasing surgical morbidity (e.g. decreasing blood loss, recovery time, need to resect continguous structures), and treating micrometastatic disease if present. Phase II data on molecularly targeted agents in the neoadjuvant setting have been accumulating. Lane, et al. reported presurgical sunitinib in 72 patients with RCC [30]. Median tumor size decreased from 7.2 cm to 5.3 post treatment, downsizing occurred in 65 tumors (83%) with 15 partial responses (19%). Rini, et al. reported a phase II study of pazopanib in patients with localized RCC in which 6 of 13 patients for whom partial nephrectomy was not possible pre-treatment proceeded to successful partial nephrectomy [31]. Karam, et al. showed that 12 weeks of neoadjuvant axitinib in 24 patients with locally advanced RCC led to 11 partial responses and 13 with stable disease (and no disease progression) [32]. In terms of neoadjuvant immunotherapy in RCC, there is currently an ongoing phase III randomized clinical trial

investigating perioperative nivolumab in at least T2 disease with two doses given prior to nephrectomy and 9 months of therapy following surgery [33]. Pembrolizumab itself has been applied in the neoadjuvant setting in bladder cancer but not yet RCC. Necchi, et al. recently published data investigating the use of pembrolizumab in the neoadjuvant setting in patients with muscle-invasive bladder carcinoma. Fifty patients received 3 cycles of pembrolizumab prior to radical cystectomy (RC). 23 patients achieved a complete pathologic response (42%) at the time of RC and 27 patients (54%) who had a PD-L1 combined positive score of ≥ 10% achieved the same [34].

Taken together, there is ample data to support the use of immunotherapy in the management of mRCC and the combination of immunotherapy and targeted therapy has recently begun and represents a promising new approach by attacking two mechanisms of tumorigenesis simultaneously: immunosuppression and angiogenesis. However, this combination has yet to be applied in the neoadjuvant setting and there remains gaps in our knowledge of how to best approach the management of patients with locally advanced RCC. We have phase Ib/II data on the combination of pembrolizumab and lenvatinib in the mRCC with promising response rates and manageable adverse events. Thus, we propose the novel application of this combination in the neoadjuvant setting for locally advanced RCC.

4.2.2 Justification for Dose

The planned dose of lenvatinib for this study is 20 mg daily. In the phase 1b/II trial of these two therapeutics together in selected metastatic solid tumors including RCC, patients received one of three lenvatinib dose levels including 24 mg, 20 mg and 14 mg daily. The maximum tolerated dose was determined to be 20 mg daily in combination with pembrolizumab [26]. This is the dose of lenvatinib applied in the currently enrolling phase III CLEAR triple-arm trial which examines the efficacy of lenvatinib 20 mg daily plus pembrolizumab versus lenvatinib 18 mg daily plus everolimus versus sunitinib in metastatic RCC [27].

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings

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

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

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

Recently, pembrolizumab 200 mg intravenously every three weeks in combination with lenvatinib 20 mg orally once daily is approved by FDA for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation [13].

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

- **Primary endpoint:**

Objective response rate was chosen as the primary endpoint to allow us to assess the proportion of patients with a reduction in overall tumor burden from baseline after 12 weeks of treatment with neoadjuvant lenvatinib and pembrolizumab. This endpoint can be assessed after just 12 weeks of treatment and has immediate implications on surgical planning and potentially long-term effects on DFS and OS.

- **Secondary endpoints:**

The safety and tolerability of lenvatinib in combination with pembrolizumab have been assessed in the Phase 2 and now Phase 3 trial of these drugs in tandem in metastatic RCC. However, we are seeking to assess their tolerability in the neoadjuvant setting where a patient is being treated with curative intent with the goal of nephrectomy after the completion of study treatment.

We hypothesized that the downsizing/downstaging of primary after neoadjuvant treatment has the potential to allow for conversion from radical to partial nephrectomy. Thus, the assessment of any perioperative adverse events such as anemia, bleeding, wound dehiscence, or post-operative pneumonia or pulmonary embolism, among many others, will be important to understand the potential impact this neoadjuvant therapy may have on decreasing surgical morbidity [1].

In addition, if tumor burden can be reduced significantly prior to surgery, it is possible that patients may ultimately experience improved DFS and OS as a result. We seek to address outcomes in our Long-Term Follow-up period.

- **Exploratory endpoints:**

Given that patients enrolled in this trial are being treated with curative intent, it is important to assess how experimental neoadjuvant therapy affects their quality of life, frailty and degree of sarcopenia. Thus, we will be assessing quality of life will be studied using the Functional Assessment of Cancer Therapy-Kidney Specific Index-19 (FKSI-19) questionnaire (Appendix 4), frailty using the Fried Frailty score (Appendix 5), and degree of sarcopenia by assessment of pre-and post-treatment imaging via SliceOmatic v5.0 by TomoVision program.

4.2.3.2 Biomarker Research

- Tumor tissue from prior to trial allotment (in the form of archival tissue or new biopsy if archival tissue is not available) compared to post-treatment nephrectomy specimen will be evaluated for assessment of mutations and/or immune markers including PD-1/PD-L1 and other relevant biomarkers (e.g. tumor infiltrating lymphocytes, T- cell repertoire, RNA signature profiles). We will also use flow cytometry to assess the phenotypic characteristics of cell populations in the tumor microenvironment and changes occurring throughout the course of neoadjuvant VEGF inhibition and immunotherapy. Tissue will be preserved for future exploratory studies including genomic profiling. Stool sample will be collected for microbiome analysis.

Correlative peripheral blood samples will be collected prior to study drug allotment, throughout treatment and post-treatment (both before and after nephrectomy). These samples will be assessed for

- Circulating tumor DNA (ctDNA) to explore genetic alterations that are present are baseline and/or emerge during treatment
- Analysis of peripheral blood mononuclear cells (PBMCs) to assess for phenotypic/functional changes in T-cells or myeloid markers during and after treatment
- Nuclear acid analysis for gene expression profiling

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

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

1. Patients with a renal mass consistent with a clinical stage ≥ T3Nx or TanyN+ or deemed unresectable by surgeon
2. Renal cell carcinoma with clear cell component on pre-treatment biopsy of the primary tumor
3. The subject is ≥ 18 years of age on the day of signing informed consent
4. The participant (or legally acceptable representative if applicable) provides written informed consent and the willingness and ability to comply with all aspects of the protocol
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
6. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 72 hours prior to the start of study treatment.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological/Coagulation	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL[a]
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Renal	
Serum creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥ 40 mL/min (≥ 0.67 mL/sec) for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST and ALT	≤3 × ULN (≤5 × ULN for participants with liver metastases)

ALT = alanine aminotransferase; AST =aspartate aminotransferase; GFR=glomerular filtration rate; ULN=upper limit of normal

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 4 weeks.

[b] Creatinine clearance (CrCl) calculated per the Cockcroft and Gault formula

- Males: (140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)
- Females: [(140 – age) x weight (kg)/(serum creatinine [mg/dL] × 72)] × 0.85

7. Female participants:

    a. All females 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 and the Baseline Visit. A pregnancy test needs to be performed within 72 hours of the first dose of study drug. Women of childbearing potential (WOCBP) must agree to use a highly effective method of contraception for the entire study period and for 120 days after study discontinuation as described in Appendix 3.

8. Male participants:

    a. Male subjects who are partners of women of childbearing potential must use a condom and their female partners of childbearing potential must use a highly effective method of contraception 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 (Appendix 3).

5.1.2 Participant Exclusion Criteria

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

1. Evidence of metastatic disease on pre-treatment imaging

2. The subject has received of any type of cytotoxic, biologic or other systemic anticancer therapy for kidney cancer

3. The subject has received any other type of investigational agent within 28 days before the first dose of study treatment

4. Excluding the primary tumor leading to enrollment in this study, any other active malignancy (except for localized prostate cancer, 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 24 months;

5. Prior treatment with lenvatinib or any agent directed against PD-1, PD-L1 or PD-L2, or another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137)

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

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

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

9. The subject has uncontrolled, significant intercurrent or recent illness including, but not limited to, the following conditions:

a. Cardiovascular disorders:

   i. 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

   ii. Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90 mm Hg diastolic despite optimal antihypertensive treatment

   iii. Prolongation of QTc interval to >480 msec per electrocardiogram (ECG)

within 28 days before first dose of study treatment.

b. Clinically significant hematemesis, or hemoptysis of > 0.5 teaspoon (2.5 ml) of red blood, or other history of significant bleeding (e.g. pulmonary hemorrhage) within 3 weeks prior to the first dose of study drug

c. Serious non-healing wound/ulcer/bone fracture

d. History of organ allograft (subject has had an allogenic tissue/solid organ transplant)

10. 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.

11. Subjects must have recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.

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

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

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

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

16. Has an active infection requiring systemic therapy.

17. Has a known history of active Hepatitis B (e.g., hepatitis B surface antigen [HBsAg]) or hepatitis C (e.g., HCV RNA qualitative is detected)

18. Has uncontrolled HIV defined by a CD4+ count < 350 cells/uL, an AIDS-defining opportunistic infection within the last 12 months prior to study enrollment or documented multidrug resistance that prevents effective HIV therapy

19. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

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

5.1.3.2 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 3 for approved methods of contraception for WOCBP and men with WOCBP as sexual partners.

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab and lenvatinib, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 Use in Nursing Women

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

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 1. Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle x 4 cycles	Experimental

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Lenvatinib	20 mg	Daily	PO with water	QD in 21 day cycles x 4 cycles	Experimental

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

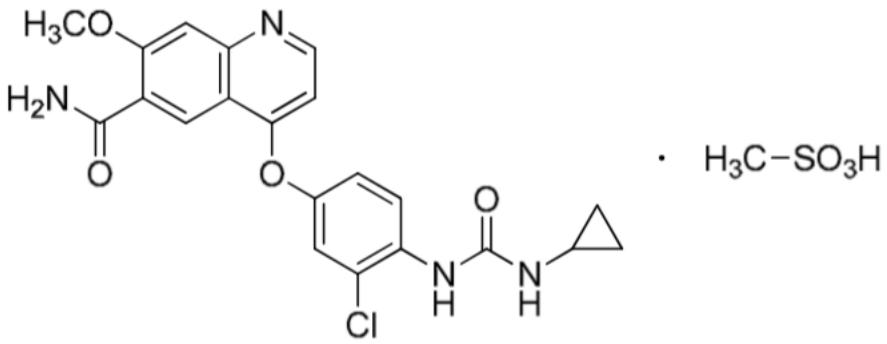
All trial treatments will be administered on an outpatient basis.

5.2.2 Lenvatinib

Lenvatinib 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. On Day 1 of each cycle, it will be administered approximately 1 hour after completion of pembrolizumab administration.

Lenvatinib will be provided as 4 mg and 10 mg capsules. Lenvatinib is formulated with calcium carbonate, mannitol, microcrystalline cellulose, hydroxypropylcellulose, low-substituted hydroxypropylcellulose, and talc.

Lenvima is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6 carboxamide methanesulfonate. The molecular formula is $C_{21}H_{19}ClN_4O_4 \bullet CH_4O_3S$ and the molecular weight is 522.96. The chemical structure of lenvatinib mesylate is:



5.2.2.1 Criteria for Interruption of Treatment, Dose Reduction and Resumption of Treatment

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib-related toxicity will be in accordance with the guidelines provided in Table 3. Once the dose has been reduced, it may not be increased at a later date.

As this is a neoadjuvant study culminating in the potentially curative surgery, we will allow no more than one dose-limiting toxicity for each drug including lenvatinib and pembrolizumab. The lenvatinib dose may be lowered once to 14 mg. If the patient has a 2nd occurrence (same or new toxicity) of an intolerable grade 2 or any grade 3-4 event, the patient should stop both study drugs immediately and proceed with nephrectomy at least 7 days after the last dose of lenvatinib. Those patients will be in-evaluable and be replaced.

For management of hypertension and proteinuria, refer to main protocol text for instructions before consulting the table below, as appropriate.

Table 3. Dose Modifications for Lenvatinib Treatment-Related Toxicity

Lenvatinib Treatment-Related Toxicity[a,b]	**During Therapy**	**Adjusted Dose[f]**
Grade 1, Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c,d] and Grade 3[g]		
1st occurrence	Interrupt lenvatinib until resolved to tolerable Grade 2 or Grade 0-1	Reduce lenvatinib dose to 14mg
2nd occurrence (same toxicity or new toxicity)	Discontinue lenvatinib and pembrolizumab and proceed to nephrectomy at least 7 days after the last dose of lenvatinib	
Grade 4:[e,f]		
Discontinue lenvatinib and pembrolizumab and proceed to nephrectomy at least 7 days after the last dose of 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. For treatment-related hypertension, refer to Management of Hypertension (Section 5.2.2.2.1) for dose modification guidelines.
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 drug(s) 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. For asymptomatic Grade ≥3 elevations of amylase and lipase, treatment may resume per investigator discretion.
g. Refer to Table 4 for dose adjustments

General guidelines for holding periods of lenvatinib due to procedures:

For minor procedures, lenvatinib should be stopped 2 days before the procedure and restarted 2 days after, once there is evidence of adequate healing and no risk of bleeding. Needle biopsies (fine needle aspirations and core needle aspiration) are usually considered minor procedures.

For major procedures, lenvatinib should be stopped 1 week (5 half-lives) before the procedure and then restarted once there is clear wound healing and no risk of bleeding, but at least 1 week after the procedure. It is up to the investigator to determine if it is a major or minor procedure. Usually a major procedure implies general anesthesia.

5.2.2.2 Management of Potential Adverse Events Associated with Lenvatinib

5.2.2.2.1 Management of Hypertension

Hypertension is a potential adverse event when using any drug active against the VEGF pathway, including lenvatinib. To minimize the need for lenvatinib dose interruptions and reduction, a blood pressure of ≤ 150/90 is required at the time of enrollment and subjects known to be hypertensive should be on a stable dose of antihypertensive therapy for at least 1 week before receiving Cycle 1 Day 1. The management of hypertension occurring during trial is outlined below in Table 5.

Table 4. Recommendations for management of hypertension during trial

Blood pressure level	Management
Systolic BP ≥140 mmHg up to 160 mmHg or diastolic BP ≥90 mmHg up to 100 mmHg[a,b]	Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication[c,d] OR 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[c,d]
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg and not on optimal antihypertensive therapy	Continue lenvatinib and institute antihypertensive therapy for subjects not already receiving antihypertensive medication[c,d] OR 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[c,d]
Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg *despite optimal antihypertensive therapy*	1. Withhold lenvatinib 2. When systolic BP ≤150 mmHg, diastolic BP ≤95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at reduced dose[e]
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management.

a. Confirmed on 2 assessments a minimum of 1 hour apart

b. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart

c. Choice of antihypertensive treatment should be individualized to the subjects' clinical circumstances and follow standard medical practice.

d. For subjects with hypertension and proteinuria, management with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor antagonist is preferred [35]

e. During the treatment period, subjects with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored every 2 weeks or more frequently as clinically 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 evaluation every 2 weeks until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months.
BP = blood pressure

5.2.2.2.2 Management of Proteinuria

Proteinuria has been reported in patients receiving lenvatinib. Regular assessment of proteinuria should be conducted as detailed in the Trial Flow Chart (Section 6.0) and as clinically indicated. Guidelines for the assessment and management of proteinuria:

1. If urine dipstick of ≥2+ proteinuria is detected, a 24-hour urine collection should be completed within 72 hours for protein quantitation in the following situations:
    - The initial occurrence of ≥2+ proteinuria on urine dipstick while receiving lenvatinib
    - A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
    - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+
2. Grading of proteinuria will be performed according to CTCAE 4.0 (Appendix 2) and based on the 24-hour urine collection for total protein if available from that time point.
3. Urine dipstick testing for subjects with proteinuria ≥2+ should be performed every 2 weeks or more frequently as clinically indicated until the results have been 1+ or negative for 3 consecutive months.
4. Management of lenvatinib administration will be based on the grade of proteinuria according to instructions contained in Table 3 (Dose Modifications for Lenvatinib Treatment-Related Toxicity).

5.2.2.2.3 Management of QT interval prolongation

The effect of a single 32 mg dose of lenvatinib on the QT/QTc interval was evaluated in a thorough QT study in healthy subjects (E7080-A001-002). In this study lenvatinib did not prolong the QT/QTc interval. QT/QTc interval prolongation has been reported at a higher rate in patients treated with lenvatinib. Monitor ECG in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, and drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Monitor and correct electrolyte abnormalities in all patients as per the Trial Flow Sheet (Section 6.0). If QTc prolongation is noted, withhold drug and resume at reduce dose of lenvatinib as per Table 3 (Dose Modifications for Lenvatinib Treatment-Related Toxicity).

5.2.2.2.4 Management of hepatotoxicity

The most commonly reported liver-related adverse reactions in patients treated with lenvatinib are increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum bilirubin. Liver-related adverse reactions were reported at a high frequency in lenvatinib-treated

patients with HCC than with RCC. Across clinical studies enrolling 1327 LENVIMA-treated patients with malignancies other than HCC, serious hepatic adverse reactions occurred in 1.4% of patients. Fatal events, including hepatic failure, acute hepatitis and hepatorenal syndrome, occurred in 0.5% of patients. Patients with worse hepatic impairment and/or greater liver tumor burden at baseline had a higher risk of developing hepatic encephalopathy and hepatic failure. Hepatic encephalopathy also occurred more frequently in patients aged 75 years and older. Approximately half of the events of hepatic failure were reported in patients with disease progression.

Regular monitoring of liver function should be monitored as per the Trial Flow Chart (Section 6.0). As per standard of care, we plan to monitor liver enzymes (including AST and ALT) every 2 weeks for the first 2 months of lenvatinib administration.

Any change in liver function should be graded according to CTCAE v4.0 (Appendix 2). In the case of a decrease in liver function by 1 grade or more from baseline, Table 3 (Dose Modifications for Lenvatinib Treatment-Related Toxicity) should be followed. If hepatic failure occurs, the study drug must be discontinued.

5.2.2.2.5 Management of Thromboembolic Events

Both venous and arterial thromboembolism have been reported at an increased frequency in patients receiving lenvatinib. Study participants should be advised to self-assess for any symptoms consistent with venous thromboembolism (VTE) including symptoms of acute onset of dyspnea, chest pain, tachycardia, tachypnea, fever, hemoptysis, and cough and symptoms of lower extremity deep venous thrombosis (DVT) such as unilateral swelling, tenderness, erythema or warmth. If a thromboembolic event is diagnosed, appropriate supportive care should be provided together with close monitoring. The instructions for managing study drug described in Table 3 (Dose Modifications for Lenvatinib Treatment-Related Toxicity) should be followed. If a subject experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued.

5.2.2.2.6 Management of Hemorrhagic Events

Serious hemorrhagic events have been reported in patients treated with lenvatinib. History, physical exam and complete blood count (CBC) measurements should be serially assessed as per the Trial Flow Chart (Section 6.0). Lenvatinib should be discontinued in subjects with serious and life-threatening bleeding events or recent hemoptysis ($\geq$ 2.5 mL of red blood).

5.2.2.2.7 Management of Wound Healing Complications

No formal studies of the effect of lenvatinib on wound healing have been conducted but impaired wound healing has been reported in patients receiving lenvatinib. To prevent difficulty with wound healing, lenvatinib should be held for 2 days prior to a minor procedure (e.g. needle biopsy) and restarted 2 days after given evidence of adequate healing and hemostasis. For major procedures (e.g. requiring general anesthesia), lenvatinib should be stopped 1 week (5 half-lives)

before the procedure and then restarted once there is clear wound healing and adequate hemostasis (at least 1 week after the procedure). Any wounds should be monitored for wound dehiscence, wound infection and other signs of impaired wound healing after lenvatinib is resumed. If dehiscence occurs, lenvatinib should be interrupted until complete healing has taken place.

5.2.2.2.8 Management of Gastrointestinal (GI) Disorders

5.2.2.2.8.1 Fistula Formation and GI Perforation

Events of fistula formation or gastrointestinal perforation and their sequelae have been reported in patients treated with lenvatinib. Fistulas (e.g. gastrointestinal, bronchopleural, trachea-esophageal, cutaneous, pharyngeal, female genital tract fistula) have been reported in lenvatinib clinical trials and in post-marketing experience. In addition, pneumothorax has been reported with and without clear evidence of a bronchopleural fistula. Some reports of gastrointestinal perforation, fistula and pneumothorax occurred in association with tumor regression or necrosis. In most cases of fistula formation or gastrointestinal perforation, risk factors such as prior surgery or radiotherapy were present.

Discontinue treatment with lenvatinib and initiate appropriate management in subjects who have been diagnosed with GI perforation or fistula.

5.2.2.2.8.2 Diarrhea

Diarrhea is one of the most common AEs noted during lenvatinib treatment and should be managed as per Table 6.

Table 5. Management of Diarrhea Associated with Lenvatinib

Status	Management
Tolerable Grade 1-2 (duration < 48 h)	• Continue lenvatinib and consider dose reduction • Initiate treatment with an antidiarrheal agent (e.g. loperamide 4 mg followed by 2 mg after each episode of diarrhea with maximum 16 mg loperamide per day) • Dietary modifications (e.g. small, bland meals such as the BRAT diet [bananas, rice, applies, toast]) • Increase intake of isotonic fluids (1-1.5 L/day orally) • Reassess after 24 hours: o Resolving to baseline: advance diet and decrease antidiarrheal treatment after 12 h without diarrhea o Not resolving: Continue/resume antidiarrheal treatment
Intolerable Grade 2, Grade 2 > 48 h, or ≥ Grade 3	• Interrupt study treatment • Evaluation participant in clinic • Rule out infection (e.g. C. difficile toxin, stool culture) o Administer antibiotics as needed (e.g. if fever or evidence of neutropenic enterocolitis) • Administer fluids (1-1.5 L/day orally or IV) for hydration • Correct electrolyte abnormalities if present • Consider hospitalization and IV hydration for grade 3-4 diarrhea • Re-assess after 24 h o Resolving to baseline or Grade ≤ 1: consider restarting study treatment at reduced dose o Not resolving: Start and or continue antidiarrheal treatment. Consider starting or adding second line antidiarrheal or referral to gastroenterologist

5.2.2.2.8.3 Nausea and Vomiting

Treat with antiemetic agents as clinically appropriate. Administer supportive care including PO or IV fluids and electrolyte supplementation as indicated.

5.2.2.2.9 Management of Thyroid Dysfunction

Hypothyroidism has been reported in patients treated with lenvatinib. Thyroid function, T3, T4 and TSH should be monitored serially as per the Trial Flow Chart (Section 6.0). Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.

5.2.2.2.10 Management of Posterior Reversible Encephalopathy Syndrome (PRES)

Events of reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome (PRES), have been reported (<1%) in patients treated with lenvatinib. 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. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Appropriate measures should be taken to control blood pressure.

In patients with signs or symptoms of PRES, dose interruptions, adjustments, or discontinuation may be necessary as per Table 3 (Dose Modifications for Lenvatinib Treatment-Related Toxicity).

5.2.2.2.11 Management of Hypocalcemia

Hypocalcemia has been reported in patients taking lenvatinib. Calcium is to be monitored regularly as per the Trial Flow Chart (Section 6.0) and more frequently if clinically necessary. Hypocalcemia should be treated per institutional guidelines (e.g., using, as appropriate, calcium, magnesium, and Vitamin D supplementation) until resolution. Interrupt and adjust lenvatinib dosing as necessary depending on severity, presence of ECG changes, and persistence of hypocalcemia.

5.2.3 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks (+/- 3 days). 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). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Pembrolizumab may be provided as a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial will be reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate-80 (0.4 mg), sucrose (140 mg). The solution may contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

Pembrolizumab will be provided as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection.

5.2.3.1 Dose Modification and Toxicity Management for Immune-Related AEs Associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue

pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

As this is a neoadjuvant study culminating in the potentially curative surgery, we will allow no more than one dose-limiting toxicity for each drug including lenvatinib and pembrolizumab. Any more than one dose-limiting toxicity for each drug will result in discontinuation of both study drugs and early nephrectomy at least 7 days after the last dose of lenvatinib. Those patients will be in-evaluable and be replaced.

Table 6. Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

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

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

5.2.3.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

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

Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.2.3.3 Other Allowed Dose Interruptions for Pembrolizumab

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

5.3 Randomization or Treatment Allocation

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements will receive lenvatinib in combination with pembrolizumab. There is no randomization in this study.

5.4 Stratification

There will be no stratification as this is a single-arm trial.

5.5 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.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with lenvatinib or pembrolizumab may be continued during the study.

For clarification, the following concomitant medications are also allowed:

- Antiemetics and antidiarrheal medications are allowed according to standard clinical practice if indicated

- Granulocyte colony-stimulating factors (G-CSF or GM-CSF) are allowed if used per clinical guidelines (e.g. ASCO guidelines)

- Erythropoietin (e.g. epoetin alfa and darbepoetin alfa) is allowed if used per clinical guidelines (e.g. ASCO guidelines) but the subject should be carefully monitored for increases in red blood cell (RBC) counts

- Transfusions if clinically indicated
- Thyroid hormone suppressive therapy (including therapy to treat hypothyroidism and hyperthyroidism)
- Adjuvant hormonal therapy for history of definitively treated breast cancer or localized prostate cancer
- Low-molecular-weight heparin
- Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulants including low-molecular-weight heparin, warfarin, anti-Xa agents or direct thrombin inhibitors are permissible but should be used with caution
- Bisphosphonates or denosumab
- Medications for treatment of infusion reaction associated with pembrolizumab (see Section 5.2.3.2)
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the patient has been enrolled)

5.5.1.1 Drug-Drug Interactions

Lenvatinib's weak in vitro inhibitory and induction potential on cytochrome P450 (CYP P450) enzymes (Study No. XT063020) suggests a low risk of lenvatinib interference with the PK of other drugs metabolized by CYP P450 enzymes which are co-administered in usual clinic practice. Nonclinical studies identify CYP3A4 as an important enzyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted to test these findings showed that co-administration of lenvatinib with CYP3A4/P-glycoprotein (P-gp) inhibitors or inducers is not of clinical concern.

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. Pembrolizumab is a monoclonal antibody; pharmacokinetic interactions with lenvatinib (and vice-versa) are not expected.

5.5.2 Prohibited Concomitant Medications

Participants are *prohibited* from receiving the following therapies during the Pre-Treatment and Treatment Phases of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy

- 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 (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

    - Note: Inhaled steroids are allowed for management of asthma or seasonal allergies.

Participants *should avoid* drugs that are known to prolong the QTc interval until the study treatment has been discontinued, although these agents are not specifically prohibited if there is a clinical indication for their use as long as the QTc has been < 480 ms as per monitoring based on the Trial Flow Chart (Section 6.0).

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

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

There are no prohibited therapies during the Long-Term Follow-Up Phase.

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.3.1, [Table 6]. 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.

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

5.6 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.5.1 (Other Procedures).

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression outlined in Section 7.1.4.1.4.
- Any progression of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in 5.2.2.2 (lenvatinib) and 5.2.3.1 (pembrolizumab).
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Sexually active subjects of childbearing potential who refuse to use medically accepted barrier methods of contraception (e.g. male condom) during the course of the study and for 4 months after discontinuation of study treatment
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The participant is lost to follow-up

- Administrative reasons

5.7 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Phase:	**Pre-treatment Phase**		**Treatment Phase[b]**												**Post-Treatment Phase**	**Long-term Follow-up Phase**
Treatment Cycle/Title:	Screening (Visit 1)[a,b]	Baseline (Visit 2)[a,b]	1			2			3			4				
Day:	-28 to 1	-3 to 1	1	8	15	22	29	36	43	50	57	64	71	78	Within 14 days of last dose of lenvatinib	Every 12 weeks +/- 14 days[c]
Administrative Procedures																
Informed Consent	X															
Inclusion/Exclusion Criteria	X	X														
Demographics and Medical History	X															
Prior and Concomitant Medication Review	X	X				X			X			X			X[d]	
Assessment of Trial Compliance		X				X			X			X			X	
Lenvatinib Administration			Throughout (daily)													
Pembrolizumab Administration			X			X			X			X				
Clinical Procedures/Assessments																
Review Adverse Events			X (throughout)												X	X
Full Physical Examination	X															
Focused Physical Exam		X				X			X			X			X	
Vital Signs, Height and Weight[e]	X	X	X	X		X			X			X				
ECOG Performance Status[f]	X	X				X			X			X			X	
MUGA or echocardiogram	X		X[g]												X[g]	
12-lead EKG	X	X				X			X			X			X	
Sarcopenia Assessment[h]	X														X	
Quality of Life Assessment[i]		X							X						X	
Frailty Assessment[j]		X							X						X	

Trial Phase:	Pre-treatment Phase		Treatment Phase[b]												Post-Treatment Phase	Long-term Follow-up Phase
Treatment Cycle/Title:	Screening (Visit 1)[a,b]	Baseline (Visit 2)[a,b]	1			2			3			4				
Day:	-28 to 1	-3 to 1	1	8	15	22	29	36	43	50	57	64	71	78	Within 14 days of last dose of lenvatinib	Every 12 weeks +/- 14 days[c]
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																
Pregnancy Test – Urine or serum β-HCG[k]	X	X	X						X						X	
PT/INR and aPTT	X	X	X			X			X			X			X	
Clinical laboratory tests[l]	X	X	X			X			X			X			X	
Liver enzymes[m]				X			X			X						
Urinalysis[n,o]	X	X	X			X			X			X			X	
T3, FT4 and TSH	X	X	X			X			X			X			X	
Efficacy Measurements																
Tumor Imaging																
MRI brain[p]	X															
CT chest[q]	X														X	
CT or MRI abdomen/pelvis[r]	X														X	X
Survival			X (throughout)												X	X[c]
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																
Archival or Newly Obtained Tissue Collection[s]	X															
Nephrectomy															X[t,u]	
Correlative Studies Blood Collection		X	X	X		X			X			X			X[v]	
Stool sample for microbiome		X													X	

a. The screening period extends from Day -28 to Day 1 Subjects must be screened within 28 days prior to Cycle 1/Day 1. The screening assessment can serve as the baseline assessment, if performed within 72 h before Cycle 1/Day 1. The baseline assessment can be performed from Day -3 to Cycle 1/Day 1 (prior to the first dose of study drug). Informed consent may be obtained up to 8 weeks prior to the start of study drug.

b. Efforts should be made to conduct study visits on the day scheduled (±3 days). Treatment cycles will be counted continuously regardless of dose interruptions. Clinical laboratory assessments may be conducted anytime within 72 h prior to the scheduled visit, unless otherwise specified.

Trial Phase:	Pre-treatment Phase		Treatment Phase[b]												Post-Treatment Phase	Long-term Follow-up Phase
Treatment Cycle/Title:	Screening (Visit 1)[a,b]	Baseline (Visit 2)[a,b]	1			2			3			4				
Day:	-28 to 1	-3 to 1	1	8	15	22	29	36	43	50	57	64	71	78	Within 14 days of last dose of lenvatinib	Every 12 weeks +/- 14 days[c]

c. Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination. Patients in long term follow-up can be seen by medical oncology or urology team, have chart reviewed, or phone call to determine current status every 12 weeks.

d. Concomitant meds are recorded for 30 days after last dose

e. Assessments will include vital signs (resting BP, HR, RR, and body temperature), weight, and height. Height will be measured at the Screening Visit only. Elevated BP assessment (i.e., systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg) should be confirmed by a repeat assessment after a minimum of 1 hour. One BP assessment is defined as the mean value of 3 measurements at least 5 minutes apart. Subjects with systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg must have their BP monitored every 2 weeks until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months. If a new event of systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg occurs, the subject must resume the evaluation every 2 weeks until systolic BP has been ≤150 mmHg and diastolic BP has been ≤95 mmHg for 3 consecutive months.

f. Appendix 1

g. If clinically indicated

h. Sarcopenia assessment will be completed using baseline and post-week 12 archival scans via SliceOmatic v5.0 by TomoVision program after completion of study.

i. Appendix 4

j. Appendix 5

k. Only necessary in women of child bearing potential

l. Clinical laboratory tests include a standard hematology panel (WBC with differential [including absolute count of neutrophils, basophils, eosinophils, lymphocytes, monocytes at minimum], hemoglobin/hematocrit, platelet count), chemistry panel (albumin, alkaline phosphatase, ALT, amylase, AST, bicarbonate, bilirubin, blood urea nitrogen, calcium, chloride, creatinine, γ-glutamyltransferase [GGT], glucose, lactate dehydrogenase, lipase, magnesium, phosphorus, potassium, sodium, total protein, uric acid), and CRP

m. As per standard of care while initiating lenvatinib, transaminases including AST and ALT need to be monitored every 2 weeks for the first 2 months of treatment. For this reason, the patient will have these checked at the time of each cycle start but also between days 8 and 15, days 29 and 36, and days 50 and 57 (This test can be done by locally if patient is traveling).

n. Urinalysis includes appearance, color, pH, specific gravity, ketones, protein, UPCR, glucose bilirubin, nitrite, creatinine, urobilinogen, occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)

o. If urine dipstick has ≥2+ proteinuria, a 24-hour urine collection will be collected for protein quantification and adverse effect grading

Trial Phase:	**Pre-treatment Phase**		**Treatment Phase[b]**												**Post-Treatment Phase**	**Long-term Follow-up Phase**
Treatment Cycle/Title:	Screening (Visit 1)[a,b]	Baseline (Visit 2)[a,b]	1			2			3			4				
Day:	-28 to 1	-3 to 1	1	8	15	22	29	36	43	50	57	64	71	78	Within 14 days of last dose of lenvatinib	Every 12 weeks +/- 14 days[c]

p. Screening brain scans will be performed by MRI pre- and post- gadolinium within 28 days prior to C1D1. During the Treatment Phase, CT/MRI of the brain will be performed if clinically indicated

q. Screening tumor assessments using CT of the chest can be done with or without IV iodinated contrast

r. Screening and post-treatment tumor assessments of the abdomen pelvis can be done with MRI or CT. CT should be performed with iodinated IV contrast and MRI scans should be done with IV gadolinium chelate unless there is a medical contraindication to contrast.

s. An archival tumor tissue sample must be available prior to first dose. If an archival tumor sample for biomarker analysis is not available, then a newly obtained tumor biopsy must be obtained prior to the first dose. Subjects must have recovered adequately from the biopsy prior to starting therapy.

t. Patients will undergo kidney surgery a minimum 7 days after the last dose of lenvatinib

u. Analysis of intraoperative and post-operative complications using the universally used Clavien-Dindo perioperative classification of adverse events [1]

v. Blood for correlative studies will be collected in the post-treatment phase both before and after nephrectomy

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart (Section 6.0) summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant prior to participating in a clinical trial. This must be done within 8 weeks of Cycle 1 Day 1.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Demographics and Medical History

Patient demographics and medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Trial compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form (Appendix 6). This information must be captured in the source document at each patient visit. Dose changes and interruptions of study drug must be specifically documented in the patient's CRF.

7.1.1.6 Lenvatinib Administration

Lenvatinib will be administrated daily during each 21-day cycle and the initiation of Cycle 1 Day 1 should align with the first pembrolizumab administration +/- 3 days.

7.1.1.7 Pembrolizumab Administration

Pembrolizumab will be administered on the 1st day of each 21-day cycle for a total of four cycles.

7.1.2 Clinical Procedures and Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

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

7.1.2.3 Focused Physical Exam

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

7.1.2.4 Vital Signs, Height and Weight

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.6 Multigated acquisition scan (MUGA) or echocardiogram

A MUGA scan (using technetium-99m-pertechnetate) or an echocardiogram to assess left ventricular ejection fraction (LVEF) will be performed as designated in the Study Flow Chart. MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject.

All scans performed during the study should be archived in accordance with the standard local practice. They must be accessible in the event of a sponsor request to submit them for central review.

7.1.2.7 12-lead Electrocardiogram (EKG)

Electrocardiograms will be obtained as designated in the Study Flow Chart. Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position or sitting for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 7.2). In these instances, the AE corresponding to the ECG abnormality will be recorded as an Adverse Event.

7.1.2.8 Sarcopenia Assessment

Sarcopenia assessment will be completed using baseline and post-week 12 scans via SliceOmatic v5.0 by TomoVision program after completion of study.

7.1.2.9 Frailty Assessment

Frailty assessment will be studies using the Fried Frailty score (Appendix 5), which will be obtained at baseline, halfway through treatment (Cycle 3 Day 1) and after 12 weeks of treatment at the post-treatment assessment.

7.1.2.10 Quality of Life Assessment

Quality of life will be studied using the Functional Assessment of Cancer Therapy-Kidney Specific Index-19 (FKSI-19) questionnaire (Appendix 4), which will be filled out at baseline, halfway through treatment (Cycle 3 Day 1) and after 12 weeks of treatment at the post-treatment assessment.

7.1.3 Laboratory Procedures and Assessments

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

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

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 7.2). In these instances, the AE corresponding to the laboratory abnormality will be recorded.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7. Trial-Related Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Appearance	β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Color	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	pH	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Ketones	Free thyroxine (T4)
Absolute Neutrophil Count	Bicarbonate	Protein	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid	UPCR	CRP
Absolute Monocyte Count	Calcium	Glucose	
Absolute Eosinophil Count	Chloride	Bilirubin	Blood for correlative studies
Absolute Basophil Count	Glucose	Nitrite	
	Phosphorus	Creatinine	
	Potassium	Urobilinogen	
	Sodium	Occult blood	
	Magnesium	(microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)	
	Bilirubin	Urine pregnancy test †	
	Total protein		
	Blood Urea Nitrogen		
	Amylase		
	Lipase		
	γ-glutamyltransferase (GGT)		

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

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates

it. MRI is the strongly preferred modality for imaging the brain. CT of the brain with IV iodinated contrast is acceptable only if MRI is medically contraindicated. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

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

7.1.4.1.1 Initial Tumor Imaging

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

Brain imaging is required to rule out radiographically detectable brain metastases. Magnetic resonance imaging is preferred; however, CT imaging will be acceptable if MRI is medically contraindicated.

7.1.4.1.2 Tumor Imaging During the Study

Imaging assessment during the study can be performed as clinically indicated but there is no scheduled time for assessment within the 12 weeks between Cycle 1 Day 1 and the completion of 12 weeks of study treatment.

7.1.4.1.3 End of Treatment and Follow-up Tumor Imaging

In participants who complete the 12 weeks of neoadjuvant treatment, tumor imaging should be performed within 14 days of treatment completion such that it is after the last dose of lenvatinib but before surgical resection. If they prematurely discontinue study treatment prior to the 12 weeks, tumor imaging should be performed within 2 weeks of treatment discontinuation if that is ≥ 4 weeks from Cycle 1 Day 1 of the study. As study enrollment requires localized, non-metastatic disease, abdominal/pelvic imaging is sufficient to assess the extent of the target lesion.

Post-nephrectomy and in the long-term follow-up period, every effort should be made to continue monitoring subjects disease status by tumor imaging as per NCCN guidelines for stage III RCC [29]. This includes abdominal imaging within 3 to 6 months of

nephrectomy followed by surveillance imaging every 3 to 6 months for at least 3 years and then annually for up to 5 years. Imaging beyond 5 years should be performed as clinically indicated.

7.1.4.1.4 RECIST 1.1

Objective response rate (ORR) is the primary endpoint for this study which will be evaluated. ORR will be based on the tumor assessment performed by the investigators using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. This assessment will be made based on the imaging obtained after the completion of 12 weeks of therapy but before nephrectomy as per the Trial Flow Chart.

- Target lesions:

All tumor measurements will be recorded in centimeters. RECIST references a maximum of 5 lesions in total and 2 per organ that should be identified as target lesions and recorded and measured at baseline. Non-lymph nodes must be at least 10mm in the longest diameter and lymph nodes must be at least 15mm in short axis to be included as a target lesion. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum of longest diameters will be used as the reference by which the objective tumor response is characterized. Given that inclusion criteria for this study specifies that participants must have T3Nx or TanyN1 disease, it is likely that only target lesion assessment will be required.

- Non-target lesions:

All other lesions (or sites of disease) should also be recorded at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline. This may include lesions that are felt to represent neoplastic tissue but are difficult to measure in a reproducible manner (e.g. bone metastases, leptomeningeal metastasis, ascites) although these are not expected as this is a trial of locally advanced and not metastatic disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

- New lesions:

Any lesion that was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment may be used by the investigator. A new lesion should be unequivocal and not due to differences in scanning technique.

Target and non-target lesions will be evaluated after treatment as per Table 8.

Table 8. RECIST 1.1 evaluation of target and non-target lesions

Type of response	**Definition**
Complete response (CR)	Complete disappearance of all measurable and non-measurable lesions (from baseline) and there are no unequivocal new lesions. Lymph nodes must decrease to <10 mm in short axis.
Partial response (PR)	$SOD_{post\text{-}treatment}$ of target lesions (TLs) decreases by ≥30 % compared to $SOD_{baseline}$ and there are no unequivocal new lesions, and no progression of nontarget disease.
Stable disease (SD)	Failure to meet criteria for CR or PR in the absence of PD. If the sum of the TLs and the status of the nontarget lesions do not reach the criteria to meet PR or PD (increase ≥20% and at least 5 mm absolute increase in SOD compared to baseline), the response is SD. **SD = neither 30% decrease compared to $SOD_{baseline}$ or 20% increase and at least 5 mm absolute change compared to nadir.**
Progressive disease (PD)	Minimum 20% increase and a minimum 5 mm absolute increase in SOD compared to nadir, or PD for nontarget lesion(s) or unequivocal new lesion(s).
Not evaluable (NE)	Used in exceptional cases where insufficient data exists due to poor quality of scans or missed scans or procedure
$SOD_{baseline}$ = Sum of diameters at baseline = longest diameter of all non-nodal + shortest diameter of all nodal target lesions	

Best overall response after the completion of treatment will be evaluated as per Table 9.

Table 9. Evaluation of Best Overall Response per RECIST 1.1

Target Lesions (% change in SOD)[a]	**Non-Target Lesions Status**	**New Lesions Status**	**Overall Response (RECIST)**
↓ 100	Absent	Absent	CR
↓ 100	Present/NE	Absent	PR
↓ ≥ 30	Present/Absent/NE	Absent	PR
↓ 100 ↓ ≥ 30	Present/Absent/NE	Present	PD

↓ < 30 to ↑ < 20 NE			
↓ 100 ↓ ≥ 30 ↓ < 30 to ↑ < 20 NE	Unequivocal progression[b]	Any	PD
↑ ≥ 20 from nadir	Any	Any	PD
NE	Present/Absent/NE	Absent	NE

a. Decreases assessed relative to baseline, including measurable lesions only

b. In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

7.1.4.2 Survival

Survival will be assessed throughout treatment as well as in the post-treatment period and long-term follow-up period until the patient's withdrawal of consent or loss to follow up, death, or study termination.

7.1.4.3 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.4.3.1 Tumor Tissue Collection

Tumor tissue will be collected prior to trial enrollment and allotment in the form of archival tissue. If archival tissue is not available, tumor biopsy must be obtained prior to the first dose. Subjects must have recovered adequately from the biopsy prior to starting therapy. Tissue will be obtained during nephrectomy and will serve as the post-treatment specimen. Any obtained tissues will be handled as follows:

- RNAlater for RNA stabilization and tissue storage
- Formalin-fixed paraffin-embedded (FFPE) block with one cut H&E stained slide
- Liquid nitrogen frozen tissue in cryo-preservation vials

All collected tissues are stabilized and stored in -80°C freezers (RNAlater stabilized, OCT embedded, short term storage) or the vapor phase of a liquid nitrogen freezer (long term storage) in single use aliquots. All FFPE tissue blocks are stored in a climate-controlled storage room that is temperature (less than 27ºC) and humidity controlled.

Tissue will be evaluated for assessment of mutations and/or immune markers including PD-1/PD-L1 and other relevant biomarkers (e.g. tumor infiltrating lymphocytes, T- cell repertoire, RNA signature profiles). When sufficient quantities of fresh tissue are available, it will also be dissociated and flow cytometry will be used to determine the phenotypic characteristics of cell populations in the tumor microenvironment. Tissue will be preserved for future exploratory studies including genomic profiling.

7.1.4.3.2 Correlative Studies Blood Sampling

Correlative peripheral blood samples will be collected prior to study drug allotment, on Cycle 1 Day 1 of each cycle, on Cycle 1 Day 8 to assess for any immune-related changes occurring in the immediate period following checkpoint inhibitor exposure, and in the post-treatment period (both pre- and post-nephrectomy) as expanded in the Trial Flow Chart. Approximately 60 mL of peripheral blood will be collected at each time point. The samples will be stored in -80°C freezers until analysis. Stool sample for microbiome analysis will be collected at baseline, and post-treatment phase within the 14 days after the last dose of lenvatinib. Analysis may include but is not limited to:

- Circulating tumor DNA (ctDNA) to explore genetic alterations that are present are baseline and/or emerge during treatment
- Analysis of peripheral blood mononuclear cells (PBMCs) to assess for phenotypic/functional changes in T-cells or myeloid markers during and after treatment
- Nuclear acid analysis for gene expression profiling
- Stool sample for microbiome analysis

Shipping and handling instructions

After appropriate processing, the blood samples, tissue blocks, slides or frozen tissue samples will be sent to:

Kissick Laboratory

1462 Clifton Rd, Room 420

Atlanta, Georgia, 30322

ph: 617 259 8364

email: haydn.kissick@emory.edu

On the day that the specimens are to be shipped, notify Dr. Haydn Kissick of the pending specimen shipments. Include the Fed-Ex tracking number in the email.

Research blood contact Information:

Kissick Laboratory

ph: 617 259 8364

email: haydn.kissick@emory.edu

7.1.5 Other Procedures

7.1.5.1 Local Registration/Enrollment Procedures

7.1.5.1.1 Registration

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial. Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

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

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

7.1.5.1.2 Enrollment

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study at Winship Cancer Institute by the Study Coordinator. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

7.1.5.2 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment, these participants should return to the site for a Safety Follow-up Visit (Section 7.1.6.3.1) and then proceed to nephrectomy and then the Follow-Up Period of the study (Section 7.1.5.4).

7.1.5.3 Blinding/Unblinding

Not applicable to this unblinded study.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening Period

The screening period extends from Day -28 to Day 1. Subjects must be screened at a visit within 28 days prior to Cycle 1/Day 1. The screening assessment can serve as the baseline assessment, if performed within 72 h before Cycle 1/Day 1. The baseline assessment must be performed at a visit and can be performed anywhere between Day -3 to Cycle 1/Day 1 (prior to the first dose of study drug). Informed consent may be obtained up to 8 weeks prior to the start of study drug.

7.1.6.2 Treatment Period

A visit is required at the start of each cycle of treatment beginning with Cycle 1 Day 1. Efforts should be made to conduct study visits on the day scheduled (±3 days). Treatment cycles will be counted continuously regardless of dose interruptions.

7.1.6.3 Post-Treatment Period

7.1.6.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted within approximately 14 days after the last dose of study treatment and before nephrectomy. Laboratory and physical examinations will be performed including peripheral blood collection for correlative studies. Remaining study treatment will be returned by the subject, and treatment compliance will be assessed and documented. Additional follow-up will occur for subjects with AEs related to study treatment that are ongoing at the time of this visit, and for subjects with SAEs related to study treatment that occur after the time of this visit.

7.1.6.3.2 Nephrectomy

The post-treatment period includes the intraoperative and post-operative period of the subjects' nephrectomies. Patients will wait at least 7 days from the last dose of lenvatinib before undergoing nephrectomy. Patients will be analyzed for intraoperative and post-operative complications using the Clavien-Dindo perioperative classification of adverse events [1]. Our documentation will include but not be limited to complications such as anemia, chylous ascites, pulmonary embolism, ileus, bleeding, superficial wound dehiscence, fascial dehiscence, pleural effusion, pneumonia, urinary retention, gastroparesis, and post-operative delirium. We will also collect data regarding the details of the surgical procedure (e.g. extent of nephrectomy).

7.1.6.4 Long Term Follow-Up Period

After their nephrectomy, patients enter the long-term follow-up period. During this time, they can be seen by the medical oncology or urology team via clinic visit, chart review, or phone call to determine current status every 12 weeks (+/- 14 days) until disease recurrence, initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination.

7.1.6.4.1 Loss to Follow-Up

A study participant will be considered lost to follow-up if he/she does not present for three scheduled visits and is unable to be contacted by the trial team after three attempts at contact by phone.

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

- The study team will attempt to contact the subject and reschedule the missed visit. They will counsel the subject on the importance of keeping scheduled visits and determine whether the subject wishes to or should remain in the study.

- Before being labeled as lost to follow-up, the investigator or study designee with make every effort to regain contact with the subject including 3 telephone calls and, if necessary, a certified letter to their last known mailing address. These attempts will be recorded in the subject's file.

- If these attempts are unsuccessful, the subject will be considered to have withdrawn from the study with the reason of lost to follow-up.

7.2 Assessing and Recording Adverse Events

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

From the time of treatment allocation through 90 days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

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

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

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.

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

laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

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

2. Its duration (Start and end dates)

3. Its relationship to the study treatment (Definitely Related, Probably Related, Potentially Related, Unlikely to be related, Not Related)

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

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

6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials)

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

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

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

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

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

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

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

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

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

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

Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of lenvatinib 120mg orally.

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

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

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

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

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

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of Supporter`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 PI and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

7.2.3.1 Serious Adverse Events

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

For the time period beginning 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:

- **submitted on a Winship SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities
- 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 through **90** days following cessation of treatment, or **30** days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be:

- **submitted on a Winship SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities,.
- reported within 2 working days to Merck Global Safety

Both lenvatinib and pembrolizumab are Merck products. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor-Investigator will be responsible for notifying FDA and Merck of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the PI's initial receipt of the information..

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

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be **submitted on a new Winship SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, (IRB, DSMC, FDA) and submitted to Merck as follow-up to the original episode.

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

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

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

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

All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

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

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

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

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.

7.2.3.2 Events of Clinical Interest

Both lenvatinib and pembrolizumab are Merck products. Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported

within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

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

For the time period beginning at treatment allocation 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.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Supporter, 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.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 10. Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the participant, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of participant taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	

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

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

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The primary outcome is objective response rate (complete and partial responses) at week 12 after the administration of lenvatinib and pembrolizumab. The Simon's two-stage design will be adopted for a possible early termination for futility. The null hypothesis that the true response is 5% will be tested against a one-sided alternative. In the first stage, 9 patients will be accrued, and if there is no responses among them, the study will be stopped for futility. Otherwise, additional 8 patients will be accrued for a total of 17 patients (This does not include screen failures and in-evaluable patients). The null hypothesis will be rejected if there are 3 or more responses in 17 patients. The design yields a type I error rate of 0.05 and power of 80% when the true response rate is 25%. The final response rate will be estimated with 95% confidence interval by binomial test. The power calculation was from web-base calculation developed by UNC Lineberger Comprehensive Cancer Center [36].

For the secondary objectives, the safety profile of the treatment will be documented and summarized by summary statistics as frequency and percentage for each AE. Disease free survival (DFS), which was defined as the interval between time of surgery and the first tumor recurrence, or death. For overall survival, death from any cause will be defined as the event. Patients will be censored at time of last follow-up. OS and DFS will be estimated with the Kaplan-Meier method. The DFS and OS of each patient group at specific time points such as 6 months, 1 year, 3 years, etc. and will be also estimated alone with 95% CI.

For the exploratory endpoint, paired t-test or Wilcoxon singed-rank test will be used to compare the biomarkers change before, during, and after treatment. Summary statistics will be applied to all items in the measurements for quality of life, frailty, and degree of sarcopenia.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 and lenvatinib will be provided by Merck as summarized in Table 11.

Table 11. Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Lenvatinib 10 mg and 4 mg	Capsule

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

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

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 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Data Reporting

Study staff are responsible for submitting data and/or data forms in the clinical management system - Online Collaborative Research Environment (ONCORE) - per Winship SOP 4.2 Data Completion Metrics. Data completion will be reviewed monthly. In situations where there are significant delays of data completion, the Associate Director of Clinical Research or the Director of Clinical Trials may temporarily suspend enrollment. Data entry is to be completed within the designated timeframe, not to exceed 30 days of the subject visit.

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

10.1.1 Source Data and Documents

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

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

Protocol Adherence

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

Retention of Study Documents

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

10.2 Data and Safety Monitoring Plan

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within

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

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

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

The PI and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet to review and discuss study data to ensure subject safety. During the meetings the PI or co-I will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, random checks of case report form completion and roadmap for each patient on the trial. All study personnel will be trained on the protocol by the PI or co-I. Study personnel will sign training log prior to being included on delegation of authority log. All AE and SAE will be handled according to Section 7.2 which provides detailed instructions on reporting requirements.

10.3 Ethical Aspects

10.3.1 Ethical standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, as well as the federal regulations pertaining to ICH E6.

10.3.2 Informed Consent

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

Informed consent is a process that is initiated prior to the individual consent to participate in the study and continues throughout the individual's participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

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

10.3.3 Institutional Review Board/Ethics Committee

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

10.3.4 Participant and data confidentiality

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

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

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

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

10.3.5 Research use of stored samples, specimens, or data

Samples and data collected under this protocol may be used to study RCC. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

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

10.4 Conditions for Modifying the Protocol

Protocol modifications (including protocol amendments) may be made and will be prepared, reviewed, and approved by representatives of the principal investigator. Protocol modifications or amendments must be reviewed and approved by Merck prior to implementation.

All protocol modifications must be submitted to the IRB/EC for information and approval in accordance with local requirements and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects or those that involve only logistical or administrative aspects of the trial (e.g. change in monitor or change of telephone number).

10.5 Conditions for Terminating the Study

At any time, the study may be terminated by the investigator, the IRB, or by Merck. Should this be necessary, Merck and the investigator will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Merck and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. Upon study termination, the investigator(s) shall cease enrolling subjects into the study, and shall discontinue conduct of the study as soon as is medically practical.

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12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Oken, et al (1982) [37]	

Appendix 2: Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

(1) Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

(2) Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following 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:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 14 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 13 during the entire study period and for 120 days after the last dose of study drug:

Table 13 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b] ● 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.)
a. Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. c. Must be on a stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study.

(3) Pregnancy Testing

WOCBP 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 and the Baseline Visit. A pregnancy test needs to be performed within 72 hours of the first dose of study drug. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

Following initiation of treatment, pregnancy testing will be performed at the time points specified in the Trial Flow Chart.

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

Appendix 4: Quality of Life Assessment (NCCN-FACT FKSI-19 V2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to you <u>the past 7 days.</u>**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
RCC2	I have had blood in my urine	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4

DRS-

DRS-F	GF5	I am sleeping well	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix 5: Frailty Assessment

Fried frailty score	Explanation
Shrinking	Self-reported unintentional weight loss ≥10 lb in the last year.
Weakness	Measured by having the patient squeeze a hand-held dynamometer (Jamar). Three serial tests of maximum grip strength with the dominant hand were performed, and a mean of the 3 values was adjusted by sex and BMI. Men met the criteria for weakness if their BMI and grip strength were ≤24 kg/m^2 and ≤29 kg of force; 24.1 to 26 and ≤30 kg; 26.1 to 28 and ≤31 kg; >28 and ≤32 kg, respectively. Women met the criteria for weakness if their BMI and grip strength were ≤23 kg/m^2 and ≤17 kg; 23.1 to 26 and ≤17.3 kg; 26.1 to 29 and ≤18; and >29 and ≤21 kg, respectively.
Exhaustion	Measured by responses to questions about effort and motivation. The following 2 statements were used from the modified 10-item Center for Epidemiological Studies-Depression scale: "I felt that everything I did was an effort" and "I could not get going." Subjects were asked, "How often in the last week did you feel this way?" Potential responses were 0 = rarely or none of the time (<1 day); 1 = some or little of the time (1 to 2 days); 2 = a moderate amount of the time (3 to 4 days); and 3 = most of the time. Subjects answering either statement with a response of 2 or 3 met the criteria for exhaustion.
Low activity	Determined by inquiring about leisure time activities. Physical activities were ascertained for the previous 2 weeks using the short version of the Minnesota Leisure Time Activities Questionnaire, and included frequency and duration. Weekly tasks were converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure below the following criteria were classified as having low physical activity: men, <383 kcal/wk; women, <270 kcal/wk.
Slow walking speed	Measured by the speed at which a patient walks 15 feet. The final time was taken by averaging 3 trials of walking the 15 feet at a normal pace. Men met the slowness criteria if height and walk time were ≤173 cm and ≥7 seconds, or >173 cm and ≥6 seconds, respectively. Women met criteria if height and walk time were ≤159 cm and ≥7 seconds, or >159 cm and ≥6 seconds, respectively.

*Each domain yields a dichotomous score of 0 or 1, based on the criteria provided. Score classified patients as not frail (0 to 1), intermediate frail (2 to 3), and frail (4 to 5).

Appendix 6: Lenvatinib Pill Diary

Lenvatinib Pill Diary

Subject Initials:_____ Subject ID: _____ Cycle: _____ Current Dose:_____

Instruction:

1. Take ___ of the 4mg capsules once per day. Take___ of the 10 mg capsules once per day.
2. Caregivers should not open the capsule, in order to avoid repeated exposure to the contents of the capsule.
3. You should take your dose at approximately the same time every day.
4. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at usual time of administration.
5. Please return any empty packaging and unused product at your next visit. Do not throw away any medicines via wastewater or household waste.

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

Patient Signature: _____ **Date:** _____

This section to be completed by a Research Nurse / Research Coordinator: _____

Dosing Cycle Start Date: _____ Dosing Cycle End Date:_____
Lot Number: _____ # of Tablets Dispensed:_____
Any Interruptions? □ Yes □ No Any Dose reduction? □ YES □ NO