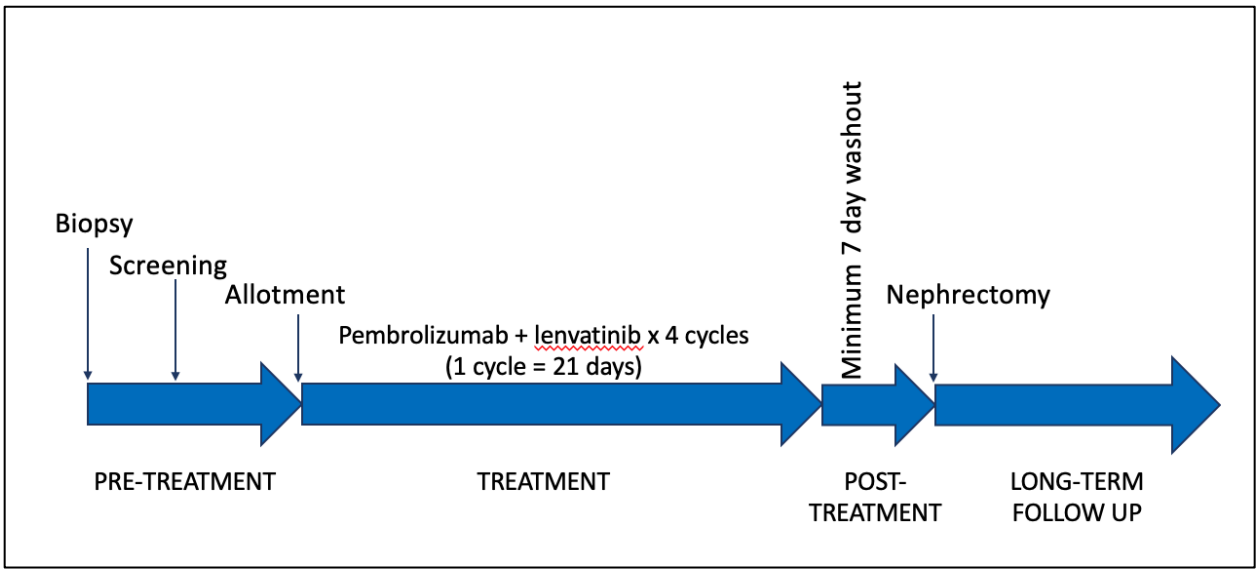
2.2 Trial Diagram



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

- **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

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

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

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.

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.

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

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

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.

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**	

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.

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

- 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

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)

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.

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

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

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.

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

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

	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

- 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.