TITLE: A multicenter phase 2 trial to evaluate intracranial response to pembrolizumab and lenvatinib in patients with brain metastases from melanoma or renal cell carcinoma who are anti-PD1/PD-L1 experienced

Sponsor Investigator: Harriet Kluger, MD
Professor of Medicine Section of Medical Oncology
Yale Cancer Center
333 Cedar Street, WWW-213 New Haven, CT 06520
Tel: (203) 737-2572
Harriet.Kluger@yale.edu

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab plus lenvatinib in patients with untreated brain metastases from melanoma or renal cell carcinoma
Trial Phase	2
Clinical Indication	Patients with metastatic melanoma or renal cell carcinoma and untreated brain metastases who are anti-PD-1/PD-L1 experienced
Trial Type	Prospective, non-randomized
Type of control	Historical
Route of administration	Intravenous and oral
Trial Blinding	Unblinded
Treatment Groups	2
Number of trial participants	Total: 56 (up to 62 total when accounting for anticipated unevaluable patients) Cohort 1: Melanoma (PD-1/PD-L1-experienced): 27 evaluable patients + 3 extra to replace unevaluable patients = 30 Cohort 2: RCC (PD-1/PD-L1 experienced): 29 evaluable patients + up to 3 extra to replaced unevaluable patients = 32
Estimated enrollment period	36 months
Estimated duration of trial	4-5 years
Duration of Participation	2 years
Estimated average length of treatment per patient	1 year

2.0 TRIAL DESIGN

2.1 Trial Design

This is a phase 2, Simon's 2-stage designed study with 2 cohorts of anti-PD-1/PD-L1 experienced patients with untreated brain metastases: 1) melanoma and 2) renal cell carcinoma (RCC). The primary endpoint of this study is to determine the best intracranial response of combined pembrolizumab and lenvatinib in patients with untreated brain metastases from melanoma or RCC who are anti-PD-1/PD-L1--experienced. Secondary endpoints include best overall objective response (combined intracranial and extracranial response), progression-free survival (PFS), overall survival (OS), duration of intracranial response, and rate of adverse events. Exploratory/correlative endpoints will include evaluation of pre-treatment tumor tissue (either intracranial or extracranial) for immunohistochemical markers (PDL-1, tumor infiltrating lymphocytes, and angiogenic factors) and genetic analysis of tumor mutations or mutational burden. Pre-treatment and on-treatment blood samples will be collected and evaluated for biomarkers of response by cytokine profiling and transcriptomic analysis.

Patients must have at least one evaluable asymptomatic intracranial lesion, no smaller than 5mm and no larger than 3 cm. Patients may have prior radiation to or surgical resection of a symptomatic brain metastasis as long as at least one untreated lesion or unequivocally growing lesion is present for response assessment. Pembrolizumab 200mg IV every 3 weeks will be administered in combination with lenvatinib 20 mg PO daily for up to 2 years.

Patients must have received at least 2 doses of an anti-PD-1/PD-L1 mAb at some point in their treatment course and must have unequivocal intracranial progression. Intracranial progression in patients who are anti-PD-1/PD-L1 experienced is defined as either development of a new brain lesion(s) or unequivocal progression in a previously irradiated or resected brain lesion(s) site. Patients can be deemed to have progression after discussion and group consensus of the case at tumor board. Secondary imaging assessments to confirm intracranial progression are not required.

Archival tissue from extracranial and/or CNS metastases will be obtained, if available, for correlative studies. A baseline pre-treatment fresh biopsy will also be required from an accessible metastasis unless there is not an easily accessible site to biopsy or if a biopsy is determined to be unfeasible by the treating physician after discussion with the study PI. The tumor tissue will be studied retrospectively for PD-L1 expression, TIL characteristics, and other immune and angiogenic markers that may predict sensitivity to this drug combination.

First response assessment will be performed at 6 weeks and will include MRI of the brain and CT body scans (or other clinically indicated body imaging such as MRI or PET CT) to assess systemic disease. Brain metastasis response will be determined using modified RECIST (mRECIST) 1.1 criteria, and extracranial disease response will be determined using RECIST 1.1. Responses will be confirmed with repeat imaging done at 12 weeks. Subsequent imaging will be performed at 12-week intervals thereafter and include an MRI of the brain along with body imaging, which may include CT, MRI, or PET/CT, as clinically indicated. Patients will discontinue treatment for disease progression,

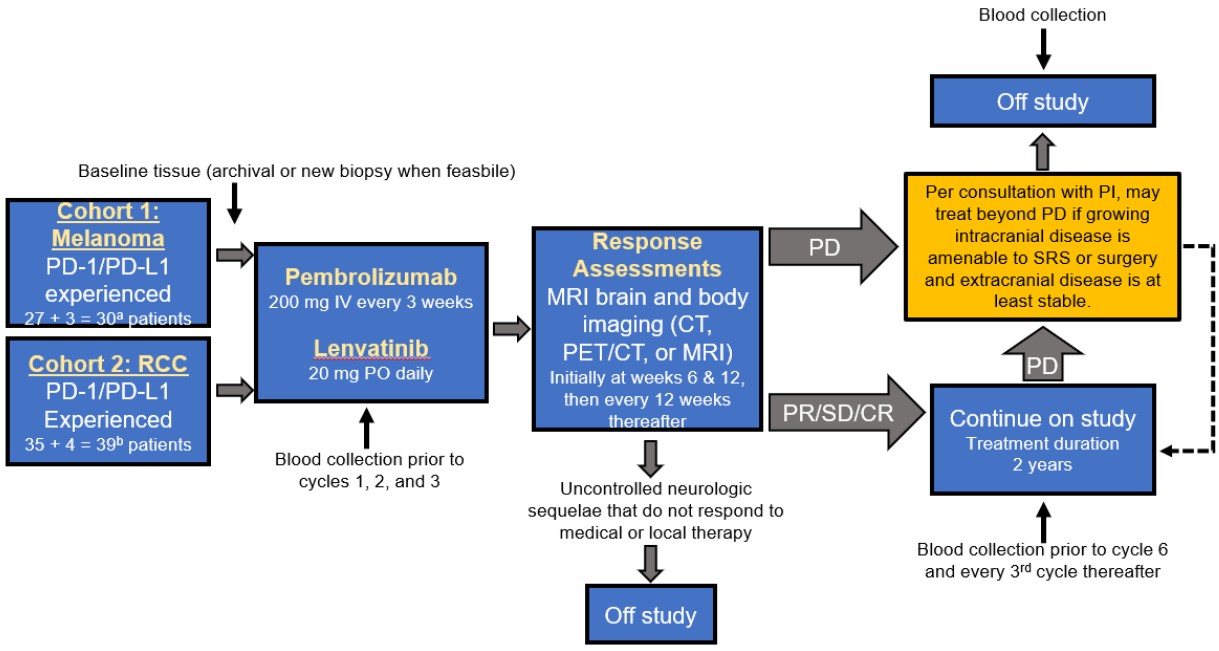
unacceptable toxicity, patient withdrawal from the study, termination of study, or death. Patients may be treated beyond progression of intracranial metastases after consultation with the study PI, provided symptomatic lesions are treated with stereotactic radiosurgery (SRS) or surgery. Dose reduction of pembrolizumab for immune-related toxicities is not permitted. Dose-reduction of lenvatinib for related toxicities is permitted.

Number of Patients:

A total of up to 62 eligible patients will be enrolled (27 patients with melanoma with allowance for 3 additional patients if any are unevaluable and 29 patients with RCC with allowance for 3 additional patients if any are unevaluable). Either cohort can be stopped for futility according to Simon's two-stage design. The study will accrue for approximately 36 months and will be open for approximately 24 additional months as patients on study are followed.

2.2 Trial Schema

The study schedule is depicted in Figure 1.



a. Plan for a total of 30 patients in order to have 27 evaluable patients given an estimated 10% drop-out rate (3 patients) due to being unevaluable in the brain. Unevaluable is defined as patients who do not make it to the first 6-week scan, unless they had clear clinical CNS progression.

b. Plan for a total of 32 patients in order to have 29 evaluable patients given an estimated 10% drop-out rate (3 patients) due to being unevaluable in the brain.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective & Hypothesis

(1) Objective: To determine the best brain metastasis response rate (BMRR) of pembrolizumab in combination with lenvatinib in previously untreated melanoma or RCC brain metastases by modified RECIST 1.1 criteria in patients who are PD-1/PD-L1 experienced.

Hypothesis: The combination of pembrolizumab and lenvatinib will demonstrate intracranial anti-tumor activity in patients who are anti-PD-1/PD-L1- experienced.

3.2 Secondary Objectives & Hypotheses

(1) Objective: To determine the best overall objective response rate of pembrolizumab in combination with lenvatinib by RECIST 1.1.

Hypothesis: The combination of pembrolizumab and lenvatinib will demonstrate both intracranial and extracranial anti-tumor activity in patients who are anti-PD-1/PD-L1-experienced.

(2) Objective: To assess PFS and OS of patients with untreated melanoma or RCC brain metastases on pembrolizumab in combination with lenvatinib.

Hypothesis: The combination of pembrolizumab and lenvatinib will improve PFS and OS in patients who are anti-PD-1/PD-L1- experienced.

(3) Objective: To determine the duration of brain metastasis response to pembrolizumab in combination with lenvatinib.

Hypothesis: The combination of pembrolizumab and lenvatinib will prolong the duration of intracranial response in patients who are anti-PD-1/PD-L1 inhibitor- experienced.

(4) Objective: To determine the safety and rate of adverse events of pembrolizumab in combination with lenvatinib.

Hypothesis: The combination of pembrolizumab and lenvatinib will result in an improved CNS toxicity profile compared to the historical CNS toxicity profile seen with pembrolizumab monotherapy, including a decreased incidence of perilesional edema and radionecrosis.

3.3 Exploratory Objective

(1) Objective: To identify predictive biomarkers to pembrolizumab and lenvatinib which correlate with intracranial and extracranial responses and toxicity via a combination of immunohistochemical, transcriptional, protein, and genetic assays using pre-treatment tumor and pre- and on-treatment blood samples.

Hypothesis: Analysis of patient samples will identify useful biomarkers to help determine, at baseline, patients who will respond or who will experience toxicity from combination pembrolizumab and lenvatinib.

4.0 BACKGROUND & RATIONALE

4.1 Background

Melanoma

Melanoma is the most serious form of skin cancer and affects adults of all ages. Melanoma accounts for approximately 5% of all new cases of cancer in the United States (US). The incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9,000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1, respectively (R. Siegel, Naishadham, & Jemal, 2012).

High-dose interleukin-2 was the first treatment to modify the natural history of patients with metastatic melanoma and may be curative for a small fraction of patients. However, its severe toxicity limited its application to carefully selected patients treated at centers with experience in managing the side effects of treatment. More recent research led to the development of immunotherapy using checkpoint inhibitors such as anti-PD-1 antibodies, pembrolizumab and nivolumab, and the anti-CTLA-4 antibody (ipilimumab) and to targeted therapy such as BRAF and/or MEK inhibition (dabrafenib and/or trametinib, respectively). Both of these approaches prolong progression-free survival (PFS) and overall survival (OS) compared with chemotherapy (Sosman, 2019), thus, they are standard therapeutic options for patients with melanoma.

Ipilimumab, an anti-CTLA-4 blocking antibody, and vemurafenib, a BRAF inhibitor, were the initial agents to demonstrate OS benefit in randomized, comparative Phase 3 studies. In the Phase 3 study MDX010-20, ipilimumab monotherapy demonstrated a hazard ratio of 0.66 and a 4-month median OS benefit compared to gp100 in pretreated advanced melanoma subjects (Hodi et al., 2010). Grade 3 to 4 immune-related adverse events (AEs) included colitis (3.2%), diarrhea (4.5%), endocrinopathies (1.1%), and rash (1.3%). In the US, 3 mg/kg of ipilimumab was approved for advanced melanoma based on data from MDX010-20 and without restriction to line of therapy.

Approximately 50% of cutaneous melanoma cases are BRAF V600E mutation positive (Larkin et al., 2014). Vemurafenib was initially approved in the US and in the EU for the treatment of BRAF V600E mutation-positive advanced melanoma subjects regardless of line of therapy (U.S. Prescribing Information: ZELBORAF (vemurafenib) tablet for oral use, 2017). In the BRIM-3 Phase 3 study, vemurafenib demonstrated a 48% response rate and an increased OS benefit compared to dacarbazine with a hazard ratio (HR) of 0.37, but with inadequate follow-up. More recently, the combination of a BRAF inhibitor plus a MEK inhibitor demonstrated an increased efficacy and a better safety profile compared to BRAF inhibition alone as first line therapy in patients with advanced melanoma. Both the combinations of dabrafenib and trametinib, vemurafenib and cobimetinib, and encorafenib and

binimetinib are approved as first-line therapy in BRAF V600E mutation positive melanoma patients (Dummer et al., 2018; Larkin et al., 2014; Robert, Karaszewska, et al., 2015).

KEYNOTE-006 Phase III trial demonstrated superior efficacy of pembrolizumab compared to ipilimumab in PFS, OS and objective response rate (ORR). The ORR was 32.9% for pembrolizumab versus 11.9% for ipilimumab. Median PFS were 4.1 months for pembrolizumab versus 2.8 months for ipilimumab. The hazard ratio for the disease progression for pembrolizumab every 3 weeks (Q3W) versus ipilimumab was 0.58 (95% confidence interval [CI], 0.46 to 0.72; $p<0.001$). One-year estimates of survival for subjects receiving pembrolizumab Q3W were 68.4% as compared with ipilimumab at 58.2% (hazard ratio for death as compared with ipilimumab group 0.69; 95% CI, 0.52 to 0.90; $p=0.0036$). Because the OS results were superior to those for the ipilimumab group, the Data Monitor Committee (DMC) recommended stopping the study early to allow patients in the ipilimumab group the option of receiving pembrolizumab (Robert, Schachter, et al., 2015).

Similarly, nivolumab was studied in subjects with previously untreated advanced melanoma compared to dacarbazine and resulted in a 5.1 month median PFS compared to 2.2 months for the dacarbazine group. The ORR was 40% in the nivolumab group and 13.9% in the dacarbazine group. At 1 year, the overall rate of survival was 72.9% for the nivolumab group compared to 42.1% in the dacarbazine group. Nivolumab showed significant improvements in PFS and OS compared with dacarbazine among previously untreated patients who had metastatic melanoma without BRAF mutation (Robert, Long, et al., 2015). Estimated 3-year overall survival (OS) rates are 58% for combination therapy and 40-50% for single agent anti-PD-1 therapy (Caroline Robert, 2016; Wolchok et al., 2017).

In 2014, the FDA approved both nivolumab and pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600E mutation positive, a BRAF inhibitor. In October 2015, the combination of ipilimumab and nivolumab was granted accelerated approved by the FDA based on the phase II trial CheckMate-069 in patients with previously untreated advanced melanoma that were BRAF V600 wild-type (Postow et al., 2015). In November 2015, nivolumab received approval for first-line treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. In December 2015, the pembrolizumab label was expanded to include first-line treatment of patients with advanced melanoma regardless of BRAF status. The European Commission has also approved pembrolizumab and nivolumab, for both first-line and previously-treated patients with advanced melanoma.

RCC

In 2020, there will be an estimated 73,000 new cases of kidney cancer and over 14,000 deaths in the U.S. Kidney cancer is the 8th most common cancer diagnosed in the U.S. and accounts for 4.1% of all new cancer cases (R. L. Siegel, Miller, & Jemal, 2020). Approximately 1.7% of the population will develop kidney cancer at some point in their lifetime. The majority of kidney cancers present as localized disease and later metastasize but up to 16% of cases are metastatic upon presentation. Kidney cancer is the 12th leading cause of cancer death in the U.S. (National Cancer Institute. Bethesda). The majority of kidney tumors are RCC and the most common histologic subtype is clear

cell carcinoma. Less common histologic subtypes include papillary, chromophobe, collecting duct, and medullary tumors.

Systemic therapy options for advanced RCC include immune checkpoint inhibitors, targeted therapy using tyrosine kinase inhibitors (TKIs) or anti-VEGF antibodies, or combinations of these drugs including ipilimumab + nivolumab and pembrolizumab + axitinib. The phase III Checkmate 214 trial compared nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab monotherapy compared to sunitinib 50 mg (4 weeks on, 2 weeks off) in patients with previously untreated advanced RCC. In intermediate and poor risk patients, 18-month OS rate was 75% with ipilimumab plus nivolumab and 60% with sunitinib. Median OS was not reached for ipilimumab plus nivolumab and was 26 months with sunitinib. ORR was 42% for the immunotherapy arm compared to 27% for sunitinib (Motzer et al., 2018).

In another phase III trial, patients with previously untreated advanced RCC were randomized to pembrolizumab 200 mg IV every 3 weeks plus axitinib 5 mg PO bid versus sunitinib 50 mg daily (4 weeks on, 2 weeks off). Twelve month OS was 89.9% in the pembro-axitinib group and 78.3 in the sunitinib group. ORR was 59.3% in the pembro-axitinib group and 35.7% in the sunitinib group (Rini et al., 2019).

The choice of frontline treatment for advanced RCC is based upon prognostic risk groups, patient performance status, pathologic information from the tumor, and/or clinical trial availability. Subsequent therapy at time of disease progression may include immune checkpoint inhibitors and/or antiangiogenic therapy depending on what was utilized in the frontline setting. Nivolumab monotherapy has shown an OS benefit in RCC patients who have progressed on antiangiogenic therapy (Motzer, Escudier, et al., 2015). Pembrolizumab plus lenvatinib yielded week 24 ORR of 63% in a mix of front-line and second-line patients in a phase Ib/2 trial (Taylor et al., 2020). In RCC patients who had progressed on prior immune checkpoint inhibitors, pembrolizumab plus lenvatinib yielded a ORR of 51% (Lee et al., 2020). Second-line pembrolizumab plus bevacizumab has yielded similar ORR of 61% (Dudek et al., 2020). While these trials enrolled small numbers of patients, the combination of anti-PD-1 plus anti-VEGF therapy in patients resistant to prior therapy warrants further study.

Brain Metastases

Brain metastases are a common cause of morbidity and mortality in patients with advanced solid tumors and develop in up to 40% of patients with metastatic melanoma, with an incidence of 30% in de novo metastatic melanoma and up to 75% at autopsy (Cagney et al., 2017; Sloan, Nock, & Einstein, 2009). Brain metastases occur in 4-17% of cases of RCC (Saitoh, Shimbo, Tasaka, Iida, & Hara, 1982; Sheehan, Sun, Kondziolka, Flickinger, & Lunsford, 2003). Melanoma and RCC brain metastases are typically managed with local therapy including SRS or surgical resection depending on the size and number of lesions and presence of neurologic deficits. While local therapy can be effective, it does not prevent local or distant recurrence and does not impact extracranial disease.

Although monoclonal antibodies targeting the immune checkpoint molecules CTLA-4 (ipilimumab) and PD-1 (nivolumab, pembrolizumab) are FDA-approved for front-line treatment of advanced melanoma, the efficacy of these drugs for untreated melanoma brain metastases was not established until very recently because this patient population was historically excluded from clinical trials. Studies in previously untreated melanoma brain metastasis show that intracranial response can range from 16% with ipilimumab (Margolin et al., 2012), 26% with pembrolizumab (Kluger et al., 2019), 20% with nivolumab (Georgina V. Long et al., 2017), and 55% with combination ipilimumab and nivolumab (Tawbi et al., 2018). Although intracranial response rates are the highest with ipilimumab and nivolumab therapy, 60% of patients had grade 3-4 toxicities, and 36% had neurologic toxicity of any grade (Tawbi et al., 2018). Furthermore, the increase in multimodality therapy with combination immune therapy and radiation therapy has increased the incidence of long-term complications for treatment, evident by rising rates of radiation necrosis (Kluger et al., 2019). Additionally, concerns over worsening peritumoral edema have limited therapy in symptomatic patients.

Less is known regarding therapy for untreated brain metastases in RCC. Sunitinib has been shown to have limited efficacy for patients with untreated RCC brain metastases (Chevreau et al., 2014). The intracranial response rate of nivolumab in the second-line setting after disease progression on antiangiogenic or cytokine therapy was also low at 12% (Flippot et al., 2019). Better success with anti-PD-1 therapies combined with antiangiogenic therapy in the second-line setting have been demonstrated, however these combinations have not been tested in a dedicated population of patients with RCC and untreated brain metastases (Dudek et al., 2020; Lee et al., 2020; Taylor et al., 2020).

Anti-VEGF therapies have been used to treat steroid-refractory edema and radiation necrosis (Banks et al., 2019; Levin et al., 2011). VEGF is a well-known driver for tumor-associated neo-angiogenesis, and elevated circulating levels are associated with worse disease-free survival in melanoma patients (Ascierto et al., 2004). Therefore, there is scientific rationale to combine immune therapy with treatments targeting the angiogenesis pathway for create anti-tumor synergy and to decrease neurologic treatment toxicity.

We propose combining pembrolizumab, a potent humanized immunoglobulin (Ig) G4 monoclonal antibody with high specificity of binding to the programmed cell death 1 (PD-1) receptor, with lenvatinib, a potent multiple-receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors. Pembrolizumab inhibits the interaction between PD-1 and the programmed cell death ligands 1 (PD-L1) and 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable safety profile and is used clinically as an intravenous (IV) immunotherapy for advanced malignancies. Lenvatinib is a potent multiple-receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1 [FLT1], VEGFR2 [KDR], VEGFR3 [FLT4]) in addition to other pro-angiogenic and oncogenic pathway-related receptor tyrosine kinases, including fibroblast growth factor (FGF) receptors FGFR1-4, platelet-derived growth factor (PDGF) receptor α, KIT, and RET.

Refer to the respective Investigator's Brochures (IB)/approved labeling for detailed background information on pembrolizumab and lenvatinib.

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab

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

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

The structure of murine PD-1 has been resolved (Zhang et al., 2017). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Chemnitz, Parry, Nichols, June, & Riley, 2004; Okazaki et al., 2001; Riley, 2009; Sheppard et al., 2004). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Francisco, Sage, & Sharpe, 2010; Parry et al., 2005). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma.

Lenvatinib

Lenvatinib is a potent multiple-receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors (VEGFR1 [FLT1], VEGFR2 [KDR], VEGFR3 [FLT4]) in addition to other pro-angiogenic and oncogenic pathway-related receptor tyrosine kinases, including fibroblast growth factor (FGF) receptors FGFR1-4, platelet-derived growth factor (PDGF) receptor α, KIT, and RET. Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors

(VEGRs 1through 3) play a major role in tumor angiogenesis (Ellis & Hicklin, 2008; Ferrara, Gerber, & LeCouter, 2003; Tammela & Alitalo, 2010). Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR, also play important roles for tumor angiogenesis (Cross & Claesson-Welsh, 2001; Lieu, Heymach, Overman, Tran, & Kopetz, 2011; Limaverde-Sousa, Sternberg, & Ferreira, 2014). Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to very important for tumor angiogenesis. In addition to lenvatinib's role in inhibiting tumor angiogenesis, it also has been shown to decrease the tumor-associated macrophage (TAM) population in pre-clinical models. TAMs are known as an immune-regulators in the tumor microenvironment. By decreasing TAMs, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation, thus potentially boosting anti-cancer responses.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

Pembrolizumab Rationale:

We previously demonstrated the activity and safety of pembrolizumab in a phase 2 trial for patients with untreated melanoma brain metastases whose lesions were larger than 0.5 cm but less than 2 cm in diameter and did not require corticosteroids for symptom control (Goldberg et al., 2016; Kluger et al., 2019). Most patients had been heavily pre-treated. The brain metastasis response rate was 26%, median OS was 17 months, and 48% of patients were still alive after 2 years (Kluger et al., 2019). Although nivolumab and ipilimumab in combination yielded superior brain metastasis response rates, in excess of 40%, the toxicity of the combination was higher, as seen in patients with extracerebral disease (G. V. Long et al., 2018; Tawbi et al., 2018). Of note, the pembrolizumab monotherapy trial and the two studies of ipilimumab and nivolumab demonstrated consistent concordance between intracranial and extracranial responses.

Immune checkpoint inhibitors are a standard of care therapy for advanced RCC however these studies excluded patients with untreated brain metastases (Motzer, Escudier, et al., 2015; Motzer et al., 2018). The management of brain metastases from RCC remains a therapeutic challenge. Flippot et al. conducted the first prospective study of nivolumab in patients with RCC brain metastases who had progressed on at least one prior treatment with an antiangiogenic agent (Flippot et al., 2019). Single agent nivolumab had limited efficacy against RCC brain metastases with an intracranial response rate of 12% which was about half that of the extracranial response rate. The addition of antiangiogenic therapies to anti-PD-1 in this setting may improve the anti-tumor immune response and increase tumor sensitivity to anti-PD-1 however this has not been studied prospectively in this population.

Lenvatinib Rationale:

Based on our institutional experience with the aforementioned trial of pembrolizumab in patients with brain metastases, perilesional cerebral edema can limit the ability to administer the drug (Kluger et al., 2019). Moreover, it can require steroid administration, theoretically hampering the activity of immune therapy. Additionally, prior local therapy with SRS can be complicated by radiation necrosis, particularly in patients receiving immune checkpoint inhibitors (Colaco, Martin, Kluger, Yu, & Chiang, 2016). Bevacizumab, an antibody to vascular endothelial growth factor (VEGF), has been shown to reduce cerebral perilesional edema (Torcuator et al., 2009). Additionally, single agent antiangiogenic therapy has minimal activity in melanoma; cabozantinib (Daud et al., 2017), ramucirumab (Carvajal et al., 2014), and aflibercept (Tarhini et al., 2011) have had modest activity in phase 2 trials. A number of lines of pre-clinical evidence support synergistic effects of immune checkpoint inhibitors combined with inhibitors of the VEGF pathway. VEGF decreases dendritic cell function and subsequently antigen presentation and T cell activation while promoting the development of myeloid-derived suppressor cells (Gabrilovich, Ishida, Nadaf, Ohm, & Carbone, 1999; Ohm & Carbone, 2001). VEGF is commonly found in the tumor microenvironment where it functions in immune evasion by altering the tumor vasculature to reduce lymphocyte adhesion to vessel walls, thus contributing to decreased trafficking across endothelium into tumor deposits (Bouzin, Brouet, De Vriese, Dewever, & Feron, 2007; Kandalaft, Motz, Busch, & Coukos, 2011; Ozao-Choy et al., 2009). Restoration of dendritic cell and T cell function may improve the T cell response and result in overall improved clinical activity (Hodi et al., 2014; Kandalaft et al., 2011).

Lenvatinib has shown clinical activity in RCC in the TKI refractory setting in combination with everolimus (Motzer, Hutson, et al., 2015) and in an early phase clinical trial in combination with pembrolizumab (Taylor et al., 2020), and thus makes the combination of pembrolizumab plus lenvatinib worthy of study for RCC brain metastases.

We are currently conducting a phase 2 trial of pembrolizumab in combination with 4 doses of bevacizumab in patients with untreated melanoma brain metastases (NCT02681549) for which enrollment of 20 patients is complete. Preliminary results thus far confirm our hypothesis that bevacizumab can both decrease rates of cerebral edema and radionecrosis and boost antitumor efficacy in melanoma patients with untreated brain metastases. The mechanism for these effects is yet to be determined. The primary endpoint of this trial (cerebral response rate of >25%) has been met. In fact, the response rate to date is in excess of 50%. Moreover, toxicity of the combination is minimal, and our results to date strongly suggest the combination of pembrolizumab and VEGF pathway inhibitors should be further studied.

Combination Pembrolizumab and Lenvatinib Rationale:

As lenvatinib is able to decrease TAM populations in pre-clinical models, the immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with anti-PD-1/PD-L1 monoclonal antibodies has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 monoclonal antibody) as well as the LL/2 lung cancer syngeneic model (anti-PD-1 monoclonal antibody). Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 monoclonal antibody showed significant and

superior antitumor effects compared with either compound alone in these 2 syngeneic models (Kato et al., 2019).

Based on these results, an open-label, Phase 1b/2 study (Study E7080-A001-111 [Study 111]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the maximum tolerated dose (MTD) and recommended phase 2 dose as 20 mg lenvatinib once daily (QD) in combination with 200 mg of pembrolizumab given IV Q3W. The safety and efficacy of the combination at the lenvatinib recommended phase 2 dose was assessed in the Phase 2 portion of the study which included 6 cohorts (ie, non-small cell lung cancer [NSCLC], RCC, esophageal cancer, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck). The cohort of melanoma patients treated with this combination showed encouraging clinical activity and tolerability (Taylor MH, 2019). Out of 103 patients with metastatic melanoma who progressed on anti-PD-1, confirmed ORR for pembrolizumab plus lenvatinib was 21% overall and 31% for patients who had progressed on anti-PD-1 plus anti-CTLA-4. The melanoma patient population was also quite advanced in that 67% had stage M1c/M1d disease, 55.3% had LDH >ULN (20.4% ≥2 × ULN), and 61.2% received ≥2 prior therapies, including 28.2% who had disease progression on prior anti–PD-1/L1 + anti–CTLA-4 (A.M. Arance Fernandez, 2020). Out of 104 patients with RCC who progressed on anti-PD-1, ORR to pembrolizumab plus lenvatinib was 51%. Median PFS was 11.7 months and median duration of response (DOR) was 9.9 months (Lee et al., 2020).

LEAP-003 is an ongoing Phase 3 randomized, placebo-controlled trial evaluating the safety and efficacy of pembrolizumab and lenvatinib versus pembrolizumab alone as first-line therapy in advanced melanoma. This study is actively recruiting and no results have been published to date. LEAP-003 does allow patients with asymptomatic, untreated brain metastases but limits these lesions to ≤3, and all must be <1 cm. The study fails to address patients with >4 brain metastases and lesions of a larger size, which are common features of patients with melanoma brain metastases.

This trial will specifically target this vulnerable population. It will enroll two patient cohorts: (1) anti-PD-1/PD-L1 naïve and (2) anti-PD-1/PD-L1 experienced. The second cohort will address the up to 50% of patients who develop primary or acquired resistance to PD-1 inhibitors, specifically with progression in the brain. Successful immune cell migration into tumor is dependent upon the cells' ability to traverse the vascular endothelium, the integrity of which may be compromised by angiogenic factors in the tumor microenvironment such as FGF (Lieu et al., 2011) and VEGF (Kandalaft et al., 2011; Ott, Hodi, & Buchbinder, 2015), whose overexpression is associated with worse clinical outcomes (Gorski, Leal, & Goydos, 2003; Yuan et al., 2014). Furthermore, immunotherapy itself can induce an immune-mediated vasculopathy, in which granulocytic and lymphocytic infiltration of the vascular endothelium leads to its destruction, creating a barrier against immune cell migration (Hodi et al., 2003). To our knowledge there are currently no clinical trials available to treat brain metastases after progression on anti-PD-1/PD-L1 therapy. Multiple levels of evidence thus support use of lenvatinib in combination with pembrolizumab.

4.2.2 Justification for Dose

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

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

E7080-A001-111/KEYNOTE-146 is an ongoing multi-cohort Phase 2 study to assess the efficacy and safety of lenvatinib in combination with pembrolizumab in six types of biomarker-unselected metastatic solid tumors, including melanoma (excluding uveal melanoma) and renal cell carcinoma, that have progressed after treatment with approved therapies or for which there are no standard effective therapies available. The study enrolled 103 melanoma patients and 104 RCC patients.

Eligible patients were aged 18 years or older and had histologically confirmed non-uveal melanoma, 0 to 2 prior systemic anticancer regimens and ECOG 0 or 1. The primary endpoint is ORR at Week 24 based on Response Evaluation Criteria in Solid Tumors 1.1 for Immune-based Therapeutics (iRECIST), as determined by investigator-read tumor assessments performed at baseline, every 6 weeks until Week 24, and then every 9 weeks thereafter. Secondary endpoints include ORR, duration of response (DOR), PFS, OS, and safety and tolerability of the combination. All patients received lenvatinib 20 mg daily in combination with 200 mg pembrolizumab IV Q3W. At data cutoff (01-Mar-2018), 21 metastatic melanoma patients were enrolled, and 38% of patients had 1 or more prior anticancer therapy.

For all enrolled subjects (N=21), the ORRWeek24 was 47.6% (95% CI: 25.7, 70.2) using iRECIST by investigator review. Of the 10 confirmed responses, 9 (42.9%) were partial response (PR), and 1 (4.8%) was complete response (CR). Stable disease was observed in 7 (33.3%) patients, and 3 (14.3%) experienced progressive disease (PD). One patient had an unknown response. Median duration of objective response was 12.5 months (95% CI, 2.7 months, not estimable [NE]). Median PFS observed was 7.6 months (95% CI: 2.6 months, 15.8 months).

All patients experienced ≥1 treatment-related adverse event (TRAE). There were no fatal TRAEs. The most common any-grade TRAEs were fatigue (52%), decreased appetite (48%), diarrhea (48%), hypertension (48%), dysphonia (43%), and nausea (43%). Dose reduction and interruption due to TRAEs occurred in 13 (62%) and 10 (47.6%) patients, respectively. The safety profile of lenvatinib in combination with pembrolizumab appears manageable in patients with malignant melanoma and other tumor types and is consistent with each agent's safety profile when administered as monotherapy.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary endpoint:

Best brain metastasis response rate (BMRR), defined as PR and CR per modified RECIST 1.1.

Secondary endpoints:

Best overall objective response rate, defined as PR and CR per RECIST 1.1.

PFS, defined as the time from start of study drug administration to the date of the first documentation of disease progression or death from any cause, whichever occurs first.

OS, defined as the time from start of study drug administration to date of death from any cause.

Duration of brain metastasis response, defined as the time from response to the time of the first documentation of intracranial disease progression.

Safety and rate of adverse events, particularly neurologic adverse effects, which include worsening of edema and development of radiation necrosis.

4.2.3.2 Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies, including novel combinations with anti-angiogenesis therapy, is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive or prognostic biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs.

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components and other circulating molecules will be collected from participants as specified:

- Tumor (formalin-fixed paraffin-embedded blocks from archival CNS or extracranial metastatic tumor tissue, or both) and fresh tumor tissue from extracranial or intracranial sites (unless deemed unfeasible)

  Note: Tumor samples can be from formalin-fixed, paraffin-embedded tumor tissue sample of a tumor lesion not previously irradiated. Tumor samples must be provided in the form of a tissue block. Subjects with an archival sample considered not adequate may obtain a new biopsy. Subjects with a newly obtained biopsy considered not adequate may undergo re-biopsy at the discretion of the investigator. Subjects undergoing a fresh biopsy will have tissue stored in two methods, when possible: (1) formalin-fixed and embedded in a paraffin block and (2) fresh tissue for harvesting tumor infiltrating immune cells, endothelial cells, and tumor cells. If limited tissue is available, emphasis will be placed on collecting tissue for paraffin embedding. Cranial tumor tissues are not required but, if available, preferred to extracranial tissue.

- Blood for collection of plasma and peripheral blood mononuclear cells (PBMCs)

<u>Tumor immune and angiogenic signature</u>

Pretreatment tumor samples (extracerebral and/or cerebral) will retrospectively be assessed for PD-L1 staining, TIL characteristics, and other immune and angiogenic factors that may predict tumor sensitivity to this drug combination. We will use in situ mass cytometry or a method of quantitative immunofluorescence developed at Yale to determine expression levels of immune checkpoint mediators and quantify and characterize infiltration of T-cells. Tumor vessel area will be studied using this method as previously described by Kluger et al. (Kluger et al., 2008). For pre-treatment tumor specimens which are freshly obtained, tumor infiltrating lymphocytes will be isolated from and

subjected to immunophenotyping studies to characterize T and B cells using single-cell RNA-sequencing.

Tumor and blood RNA and DNA analyses

We will evaluate whether genetic or transcriptional variation within a clinical study population correlates with response to the combination of pembrolizumab and lenvatinib. If variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population.

The application of new technologies, such as next generation sequencing, RNA-sequencing and methylation profiling has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability) contributing towards the development/progression of cancer and/or driving response to therapy. Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in PBMCs may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab and lenvatinib. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene expression sets (i.e., those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual gene expression related to the immune system and growth factor signaling pathways (e.g., VEGF and FGF) may also be evaluated and be predictors of response to combined therapy with lenvatinib. MicroRNA profiling may also be pursued as well as exosomal profiling.

Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Evaluation of molecular targets and signaling pathways including angiogenesis and growth factor related signaling pathways related to pembrolizumab and lenvatinib may also be explored. Thus, genome-wide and single cell approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome.

Peripheral cytokine analysis

Peripheral blood samples will be collected before cycles 1, 2, and 3 and every 3 cycles thereafter. Based on when clinical responses are detected in the majority of patients, blood from one later time point will be compared to baseline samples and studied for a panel of cytokines.

Circulating immune cell signature

PBMCs will be obtained from blood samples collected before cycles 1, 2, and 3 and every 3 cycles thereafter. Based on when clinical responses are detected in the majority of patients, blood from one later time point will be compared to baseline samples. Cells will be assayed for immune markers to profile circulating cells and determine their population changes due to treatment. Cells will be analyzed either by mass cytometry or by flow cytometry.

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. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of melanoma or RCC and untreated metastatic brain disease will be enrolled in this study.

   Male participants: A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

   Female participants: A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3

   OR

   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 120 days after the last dose of study treatment.
2. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.

3. Have histologic or cytologic confirmation from any body site of metastatic melanoma irrespective of BRAF mutation status or renal cell carcinoma irrespective of histologic subtype.

4. Patients who have had prior resection or biopsy of a CNS and/or extracranial metastasis will be required to provide a formalin-fixed, paraffin embedded (FFPE) specimen from tumor taken at the time of surgery, if available. Fresh biopsies of a metastatic lesion should be performed if clinically able.

   Note: Participants are not required to have new or repeat brain metastasis biopsies for enrollment on the trial.

Note: For those who have never had CNS brain metastasis biopsies, tissue of an accessible extracranial lesion will be obtained pre-treatment, unless deemed not possible by the treating physician and upon discussion with PI. In this case, archival extracranial metastatic tissue will be suitable.

5. Have at least one brain metastasis that is at least 5 mm AND twice the MRI slice thickness, but less than or equal to 3 cm, which is asymptomatic, has not been previously radiated, and is not requiring immediate local therapy or steroids. Lesions situated in a previously irradiated area are considered allowed if measurable per the aforementioned criteria and if progression has been demonstrated. Patients with any lesion(s) >3 cm can be enrolled provided the following: (1) the lesion must receive local treatment prior to initiation of study drugs (either by stereotactic radiosurgery or resection), (2) the patient is not symptomatic from the lesion(s) once local therapy has been administered, and (3) at least one additional, non-treated lesion between 5 mm and 3 cm is still present.

6. Prior treatment for either the Melanoma or RCC cohorts may include:
   Patients must have received at least 2 doses of an anti-PD-1/PD-L1 drug at some point in their treatment course. Any number of prior treatments including PD-1/PD-L1 inhibitors are allowed. Anti-PD-1/PD-L1 does not have to be the most recent therapy. Patients with melanoma who developed brain metastasis within 6 months of the last dose of adjuvant anti-PD-1 can be enrolled.

7. Life expectancy of at least 3 months.

8. A history of radiotherapy for brain metastases is allowed up to 1 week before study treatment provided that neurologic sequelae are resolved, and that measurable untreated target lesion(s) remain.

9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 7 days prior to the date of allocation.

10. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as a systolic BP ≤150 or a diastolic BP ≤90 mmHg at screening and on Cycle 1 Day 1.

    Note: Eligibility of a participant that is receiving ≥3 antihypertensive medications prior to study entry will require PI approval.

11. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to the start of study treatment.

12. Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min 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 (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
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

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.2 Participant Exclusion Criteria

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

1. Symptomatic melanoma or RCC brain metastases at the time of therapy initiation.

2. Active use of corticosteroids to control CNS symptoms, unless steroid requirement has been decreasing and currently on ≤10 mg of prednisone or its equivalent without CNS symptoms for 7 days or more.

3. Overt hemorrhage from CNS metastases.

4. Presence of leptomeningeal disease.

5. Unable to undergo MRI imaging (either due to such conditions as inability to lie flat for the scan duration, incompatible medical devices at risk for malfunction, and foreign metal objects that pose a safety risk for imaging).
6. A WOCBP who has a positive urine pregnancy test within 72 hours prior to allocation (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
7. Has received anti-cancer therapy including investigational agents within 14 days prior to allocation or less than 4 weeks from prior immunomodulating antibody (excluding anti-PD1/PD-L1).

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

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

8. Has received prior CNS radiotherapy within 1 week of start of study treatment. Participants must have recovered from all radiation-related toxicities and not require corticosteroids.

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

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

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

11. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in doses 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.

12. Has a known additional malignancy that is progressing or is requiring active treatment.

13. Has active autoimmune disease that has required systemic treatment in the past 3 months or a documented history of clinical severe autoimmune disease, or a syndrome that requires chronic systemic steroids or immunosuppressive agents. Replacement therapy (eg., thyroxine,

insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency with prednisone ≤ 10 mg or the equivalent, etc.) is not considered a form of systemic treatment. Subjects with thyroid disease or vitiligo will not be excluded from the study.

14. Has presence of gastrointestinal condition including malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.

15. Has a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.

16. Serious non-healing or dehiscing wound.

17. Has radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

18. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

19. Has clinically significant cardiovascular disease within 6 months of the first dose of study intervention including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

    Note: Medically controlled arrhythmia is permitted.

20. Has prolongation of QTc interval (calculated using Fridericia's formula) to >480 msec.

21. 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.

22. Has urine protein ≥2 g/24-hour.

    Note: Participants with >1+ proteinuria on urine dipstick will undergo 24-hour urine collection for quantitative assessment of proteinuria.

23. Evidence of a bleeding diathesis, risk for severe hemorrhage, or clinically significant coagulopathy.

24. Uncontrolled hypertension (systolic BP >150 mmHg or diastolic BP >90 mmHg) in spite of an optimized regimen of antihypertensive medication.

25. Has a history of (non-infectious, non-radiation-induced) pneumonitis not responsive to steroids or has current pneumonitis. Patients will also be excluded if there are respiratory issues including active infection or require supplemental oxygen for activities of daily living.

26. Has an active infection requiring systemic therapy.

27. Has a known history of Human Immunodeficiency Virus (HIV).

28. Has a known history of Hepatitis B or known active Hepatitis C virus infection.

    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

29. 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.

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

31. 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.

32. Women of child-bearing potential who are unwilling to or unable to use an acceptable method of contraception to avoid pregnancy for the entire study and for at least 5 months after cessation of study drug or have a positive pregnancy test at screening or baseline, or who are pregnant or breast feeding.

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.

Based on its mechanism of action, lenvatinib can cause fetal harm when administered to a pregnant woman. Lenvatinib may also result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. In animal reproduction studies, oral administration of lenvatinib during organogenesis at doses below the recommended human dose resulted in embryo toxicity and teratogenicity in rats and rabbits.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 3) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with lenvatinib or pembrolizumab, the participant will be immediately discontinued from study intervention.

5.1.5 Use in Nursing Women

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

5.2 Trial Treatments

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

Table 2 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	Experimental
Lenvatinib	20 mg	Daily	Oral	Day 1-21 of each 3 week cycle	Experimental

Trial treatment should begin on the day of allocation or as close as possible to the date on which treatment is allocated/assigned.

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.

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

Lenvatinib 20 mg will be provided for the patient to take orally once daily for 3 weeks. The patient will maintain a pill diary, and all pills will be counted to ensure proper home self-administration. The patient will be instructed to take lenvatinib every 24 hours, as close to the exact hour as possible. If a dose of lenvatinib is missed and cannot be taken within 12 hours from the scheduled administration, the participant should skip this dose and take the next dose at the scheduled time the next day.

5.2.2 Dose Modification and toxicity management

5.2.2.1 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one 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/combination treatment, 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 3.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to lenvatinib alone or to pembrolizumab alone, for adverse events listed in Table 3, both interventions must be held according to the criteria in Table 3: Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 3.

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.
- If the toxicities do resolve and conditions are aligned with what is defined in Table 3, the combination of lenvatinib and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to lenvatinib alone, re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .]

Table 3. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		• 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
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b]	Withhold; discontinue only if not improving on steroids within 7 days	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
	Grade 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	associated with evidence of β-cell failure		• Administer antihyperglycemic in participants with hyperglycemia	
Hypophysitis	Grade 2-3	Continue unless clinically unstable	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 4	Withhold	• The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.	
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold	• The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2-3	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

5.2.2.2 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 4.

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.	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. For Grade 4 reaction, participant is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.2.2.3 Other allowed dose interruption for pembrolizumab

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

5.2.2.4 Management of AEs associated with lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib- related toxicity that are not considered irAEs will be in accordance with the dose modification guidelines described in Table 5. An interruption of study treatment for more than 28 days will require PI consultation and approval before treatment can be resumed.

Adverse events will be graded using NCI CTCAE v5.0. For presumed non irAEs,,investigators will decide the probability of the event being related to lenvatinib and whether dose modification or interruption/discontinuation, as applicable, of one or both drugs is required. The starting dose of lenvatinib is 20 mg/day for participants enrolled. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the PI. Once the study drug dose has been reduced, it may not be increased at a later date, unless the dose was mistakenly decreased; in this situation, PI's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 5.2.2.6), proteinuria(Section 5.2.2.7), diarrhea (Section 5.2.2.8), hepatotoxicity (Section 5.2.2.9), thromboembolic events (Section 5.2.2.10), posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 5.2.2.11), hypocalcemia (Section 5.2.2.12), and hemorrhage (Section 5.2.2.13), as appropriate, before consulting the dose modification table (Table 5).

- BP should be well-controlled prior to the start of lenvatinib. Blood pressure should be monitored after 1 week of treatment with lenvatinib, then every 2 weeks for the first 2 months and at the beginning of each cycle thereafter while on treatment. If a patient develops systolic BP ≥150 mmHg or diastolic BP ≥90 mmHg active management is indicated.
- Urine protein should be monitored regularly. If urine dipstick ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary. Discontinue in the event of nephrotic syndrome.
- Monitor and correct all electrolyte abnormalities in all patients.
- Liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. In the case of hepatotoxicity, dose interruptions, adjustments, or discontinuation may be necessary.

- Thyroid function, T3, T4 and TSH should be monitored before initiation of, and periodically throughout treatment with lenvatinib. Hypothyroidism should be treated according to standard medical practice to maintain euthyroid state.
- Monitor patients for clinical symptoms or signs of cardiac dysfunction as dose interruptions, adjustments, or discontinuation may be necessary.
- Gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure. Dose interruptions, adjustments, or discontinuation may be necessary.

5.2.2.5 Dose Reductions/ Interruptions for non-immune related Adverse Events attributed to Lenvatinib

Table 5 Dose Modification Guidelines for Lenvatinib-related Adverse Events

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c] or Grade 3[d]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with PI
Grade 4[e]: Discontinue Study Treatment		

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).
a An interruption of study treatment for more than 28 days will require Sponsor's approval before treatment can be resumed.
b Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
d For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with PI.
e Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events

Other allowed dose interruptions for lenvatinib

Lenvatinib 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.

Indications for discontinuation of lenvatinib

Treatment should be discontinued in case of life-threatening reactions (e.g., Grade 4) with the exception of laboratory abnormality judged to be non-life-threatening, in which case they should be managed as severe reactions (e.g., Grade 3).

5.2.2.6 Management of Hypertension

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

Regular assessment of BP should be as detailed in the Study Flow Chart (Section 6.1). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications). If the participant's initial BP measurement is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later.

One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

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

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm

Hg for 2 consecutive treatment cycles. Participants will have the option of having BP measurements between visits obtained locally by a health care professional. A diary will be provided as a tool to aid the participant in collecting blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

- Continue study drug and institute antihypertensive therapy for participants not already receiving antihypertensive therapy. Note: Eligibility of a participant that is receiving ≥3 antihypertensive medications prior to study entry will require PI approval.

- For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.

    - Additional dose reduction should be discussed with the study PI.

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

    - Institute appropriate medical management

- Discontinue study drug

5.2.2.7 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the Study Flow Chart (Section 6.0). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

- Perform urine dipstick testing per the Study Flow Chart (Section 6.0)

- A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:

    - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while on study drug

    - 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+.

    - A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria:

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained.

Management of lenvatinib administration will be based on the grade of proteinuria according to Table 5:

- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Monitoring:

- Urine dipstick testing for participants with proteinuria ≥2+ should be performed on D15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles.

5.2.2.8 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 5 should be

followed. If diarrhea does not improve, pembrolizumab-induced diarrhea should be considered and managed with corticosteroids as detailed in Table 3.

5.2.2.9 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the Study Flow Chart (Section 6.1) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued. It might not be possible to determine whether LFT abnormalities are due to pembrolizumab or lenvatinib. Therefore, both drugs should be held and if no improvement is seen, corticosteroids should be initiated.

5.2.2.10 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, and deep vein thrombosis signs including lower-extremity swelling and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, the study drug must be discontinued. Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

5.2.2.11 Management of Posterior Reversible Encephalopathy Syndrome/Reversible

<u>Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome</u>
PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 5 should be followed.

5.2.2.12 Management of Hypocalcemia

Serum calcium should be monitored per the Study Flow Chart (Section 6.1). Corrected serum calcium should be used to assess the grade of hypocalcemia per NCI CTCAE v5.0, using the following formula: Corrected calcium = ([4 − serum albumin in g/dL] × 0.8 + serum calcium). The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead. Hypocalcemia should be

treated per institutional guidelines (e.g., using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

5.2.2.13 Management of Hemorrhage

Instructions in Table 5 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

5.2.2.14 Dose Modifications for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to one or both drugs, it is recommended to hold both drugs, and initiate management per Dose Modification Guidelines for Lenvatinib-Related Adverse Events. If toxicity does not improve within 1 to 2 days or worsens, management per Dose Modification Guidelines for Pembrolizumab-Related Adverse Events should be followed.

Participants who experience an unacceptable toxicity that is attributed to lenvatinib in the opinion of the investigator and the PI, may permanently discontinue lenvatinib, but may continue with pembrolizumab, upon resolution of toxicity to Grade 0 or 1 or baseline, until unacceptable toxicity or progression. Participants who discontinue pembrolizumab due to untoward toxicities may not continue on the trial receiving only lenvatinib.

5.2.2.15 Other Allowed Dose Interruptions for Lenvatinib and Pembrolizumab

If a participant requires surgery during active treatment on the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 3 days before the procedure and restart it at least 1 week after once there is evidence of adequate healing and no risk of bleeding. SRS is considered a minor procedure but does not requiring holding of lenvatinib.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after once there is evidence of adequate healing and no risk of bleeding.

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 participant's study record.

Intervention After the End of the Study
There is no study-specified intervention following the end of the study.

5.2.3 Second Course *

All participants who stop study treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab and lenvatinib treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 cycles of pembrolizumab and lenvatinib beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped study treatment after completion of 35 cycles (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
    - No new anticancer treatment was administered after the last dose of study treatment, and
    - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
    - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

*Note: patients must have measurable disease at the start of protocol treatment to be eligible for this provision.

5.3 Treatment Allocation

This is a phase 2, non-randomized study with 2 cohorts of anti-PD-1/PD-L1 experienced patients with untreated brain metastases: 1) melanoma and 2) RCC. After establishing eligibility, patients will undergo fresh biopsy of a metastatic site, if feasible. The biopsy requirement can be waived

if there is not an easily accessible site to biopsy or if a biopsy is determined to be unfeasible by the treating physician after discussion with the study PI. Archived metastatic tumor tissue, including prior CNS tumor tissue, should also be submitted, if available. The tumor tissue will be studied retrospectively for PD-L1 expression, TIL characteristics, and other immune and angiogenic markers that may predict sensitivity to this drug combination. Pembrolizumab 200mg IV every 3 weeks will be administered in combination with lenvatinib 20 mg PO daily.

MRI of the brain will be obtained after 6 weeks of therapy for initial assessment of efficacy by mRECIST, and a confirmation scan will be performed at 12 weeks. CT body scans (and/or MRI or PET CT as clinically indicated) will also be done at these times to evaluate for extracranial response by RECIST. The next MRI brain or body imaging will be done every 12 weeks thereafter. Patients will continue on study until they have overall disease progression in either their clinically evaluable CNS lesions or in their systemic metastases, toxicities that preclude continuing the study drug, withdrawal from study, termination of study, or death. Dose reductions for immune-related toxicities will not be allowed.

5.4 Stratification

A total of up to 62 eligible patients will be enrolled on this trial (up to 30 melanoma patients who are anti-PD-1/PD-L1-experienced and up to 32 RCC patients who are anti-PD-1/PD-L1-experienced). Individual cohorts of the study can be stopped for futility according to a Simon two-stage design. The study will accrue for approximately 36 months and will be open for approximately 24 additional months as patients on study are treated and followed.

5.5 Concomitant Medications/Vaccinations/Therapies (allowed & prohibited)

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

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.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and lenvatinib
- Radiation therapy
    - Note: Radiation therapy to a progressing, symptomatic solitary intracranial or extracranial lesion may be allowed after consultation with the study PI. Radiation to an intracranial lesion must be given at least 7 days prior to the initiation of study drugs. Palliative radiation to other sites may be administered at any time.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids (doses ≤10 mg prednisone daily or equivalent) is approved.

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 study PI and the participant.

There are no prohibited therapies during the Post-Treatment 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 5.2.2, (Table 3). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to (Table 3) in Section 5.2.2 for guidelines regarding dose modification and supportive care.

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

5.5.4 Local Therapy and Treatment Beyond Disease Progression

Local therapy for brain metastases:

Local therapy in the form of craniotomy, LITT, or SRS can be performed on symptomatic brain lesions prior to assessment for study eligibility, provided all neurologic side effects from the procedure have resolved and all other eligibility criteria are met. At any time point throughout the study, local therapy (surgery, LITT, or SRS) will be administered to a lesion that becomes clinically concerning if deemed necessary by the investigators. This can be followed by continuation on pembrolizumab and lenvatinib, provided that the patient is otherwise benefiting from therapy and has stable disease or disease shrinkage in other lesions by RECIST criteria. Approval from the study PI or co-PIs is required to continue treating the patient on pembrolizumab and lenvatinib. Craniotomy and LITT are considered major procedures and require temporary holding of lenvatinib as detailed in Section 5.2.2.15. SRS is considered a minor procedure and does not requiring holding of lenvatinib. Further details for holding lenvatinib are detailed in Section 5.2.2.15.

A brain metastasis that has been treated locally will not be considered evaluable for response and will not be included when calculating the sum of largest dimensions. If the treated lesion constitutes >25% of the target lesions (for example, if one of three target lesions is treated locally), this will be considered progressive disease. If >75% of the baseline lesions are not treated with local therapy and evaluable by imaging, the patient will be considered evaluable, and response for the primary endpoint analysis will be assessed based on the remaining lesions. Additional response evaluation will be performed which will consider those patients who require local therapy while on study as having PD at the time of local therapy.

Local therapy for extra-cerebral metastases:

Local surgery or radiation therapy (if indicated for palliative measures only after discussion with the study PI or co-PIs) may be permitted and the patient can continue to receive pembrolizumab and lenvatinib provided there is otherwise evidence of clinical benefit from treatment (i.e. stable disease or response in measurable lesions). The criteria applied for assessing response is detailed in Section 7.1.2.9.

5.6 Participant Withdrawal/Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 7.1.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the study PI if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 7.1.5.3.

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 7.1.2.9. Patients who are believed to be deriving benefit based on the discretion of the investigator and PI are allowed to continue.

- Any progression or recurrence of any malignancy, or any occurrence of secondary malignancy that requires active treatment. Exceptions to secondary malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new non-ulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the study PI prior to continuing therapy or remaining in follow-up.

- Unacceptable adverse experiences as described in Section 5.2.2.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test.
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis, and other AEs that may require treatment discontinuation per Section 5.2.2 (Dose Modification).
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of lenvatinib beyond the date when the initial CR was declared. These participants may be eligible for second course treatment described in Section 5.2.3.
- The participant is lost to follow-up
- Completion of 35 treatment cycles (approximately 2 years) with pembrolizumab and lenvatinib. Note: Participants experiencing a clinical benefit may continue on lenvatinib alone beyond this time point until unacceptable toxicity or disease progression upon study PI consultation and approval (See Section 5.2.3 for additional details).

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination after receiving 2 years of treatment may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 5.2.3. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Administrative reasons

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

- Discontinuation of trial treatment with pembrolizumab and lenvatinib may be considered for participants who have attained a confirmed CR and have been treated for at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

  Note: The number of treatments is calculated starting with the first dose of pembrolizumab.
- Progressive disease and/or lack of clinical benefit.

Note: Participants will be permitted to continue treatment beyond RECIST 1.1-defined progression provided investigator-assessed clinical stability is observed, and the participant is tolerating study drug (Section 5.5.4). Treatment beyond PD may be permitted upon study PI consultation and approval.

Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 7.1.4. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined below.

Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

5.7 Participant Replacement Strategy

A participant who discontinues from study intervention, withdraws, or is unevaluable due to inability to reach first intracranial assessment scan will be replaced. An anticipated 10% drop-out rate was accounted for in the sample size calculations for Cohort 1/Melanoma and Cohort 2/RCC. An extra 3 patients were estimated to obtain at least 27 analyzable patients in Cohort 1/Melanoma.

An extra 3 patients were estimated to obtain at least 29 analyzable patients in Cohort 2/RCC.

5.8 Clinical Criteria for Early Trial Termination

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

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

In the event of Merck's 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 Period:		Treatment Cycles[a]								EOT[b]	Post-Treatment			Notes
Treatment Cycle/Title:	Main Study Screening Visit	1	2	3	4	To be repeated beyond 8 cycles				Discon	Safety FU[b,c]	FU Visits	Survival Follow-Up	
						5	6	7	8					
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 and 90 days post discon	Every 12 weeks post discon	Every 12 weeks	
Administrative Procedures														
Informed Consent	X													Consent form can be signed at any time prior to any protocol-specific screening procedures being performed. Additional consent is required at initial disease progression per RECIST 1.1.
Inclusion/Exclusion Criteria	X													
Demographics and Medical/Surgical History	X													Significant medical/surgical history will be captured for last 10 years.
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		Concomitant medications will be recorded for 90d after last dose (or for up to 120d after last dose for SAEs).
Pembrolizumab and Lenvatinib Administration		X	X	X	X	X	X	X	X					Pembrolizumab 200 mg Q3W with lenvatinib 20 mg QD; 21-d cycle
Post-study anticancer therapy status											X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow up information may be obtained via telephone or email.
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures/Assessments														

Review Adverse Events		X	X	X	X	X	X	X	X	X	X			AEs: monitored up to 90d after last dose. SAEs and pregnancy: monitored up to 120d after last dose, or 30d after last dose if participant starts a new anticancer therapy, whichever is sooner
Full Physical Examination	X													To be performed within 7d of C1D1.
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight[d]	X	X	X	X	X	X	X	X	X	X				BP and HR will be measured after the participant has been resting for 5 minutes. See Section 5.2.2.6 for management of hypertension and Section 7.1.2.4 for vital signs. Height is measured at Screening only.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X				
12-lead ECG	X													Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. Additional assessments may be performed if clinically indicated.
Laboratory Procedures/Assessments: analysis performed by LOCAL Lab[g]														
Pregnancy Test – Urine or Serum β-HCG	X	X	X	X	X	X	X	X	X	X	X			Performed within 10 days of C1D1 and prior to all subsequent scheduled visits. Every effort should be made to collect samples at the same time of day. LDH is only required at screening. Urine protein ≥2 requires 24-hour urine collection and D15 re-evaluation per Section 5.2.2.7. Pregnancy test for WOCP to be done within 72 hours days of C1D1.
PT/INR and aPTT	X													
CBC with Differential	X		X	X	X	X	X	X	X	X	X			
Comprehensive Serum Chemistry Panel	X		X	X	X	X	X	X	X	X	X			
Urinalysis	X		X	X	X	X	X	X	X	X	X			
T3, FT4 and TSH	X		X	X	X	X	X	X	X	X	X			
Efficacy Measurements														
Tumor Imaging (MRI brain[e] and CT Chest, Abdomen, Pelvis)	X		X		X				X	X		X	X	Prior scans performed within the screening period but before signing informed consent may be

														used. All imaging visits have a scheduling window of ±7d. Intracranial disease progression will be assessed by mRECIST 1.1. Extracranial disease will be assessed by RECIST 1.1. For participants who DC for reasons other than PD, imaging should be performed Q12W. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit. Imaging of any anatomy that shows disease either at screening or in subsequent evaluations will be required and should be submitted.
Tumor Biopsies/Archival Tissue Collection/Correlative Studies														
Archival or Newly Obtained Tissue Collection	X													New tissue will be collected if the patient has a biopsy or resection for any reason while on study; a new consent will be obtained from the subject for use of part of the collected tissue for research.
Correlative Studies Blood Collection[f]		X	X	X			X			X				

a. Participants who continue treatment with lenvatinib beyond approximately 2 years (only if they experience clinical benefit until unacceptable toxicity or disease progression and upon Sponsor consultation and approval) will follow the same SOA except that thyroid labs beyond approximately 2 years will be performed per SOC or as clinically indicated.

b. If EOT visit occurs ~30 days from last dose of study treatment, a 30-day safety follow-up visit is not required. In this situation, all procedures required at the 30-day Safety Visit and EOT are performed once and entered into the EOT visit only. End of treatment will be defined as the date when the participant discontinues all trial treatments.

c. Safety FU will occur during 2 separate visits: 30 days AND 90 days after last dose. If the 90 day-safety FU visit falls within the same window as an imaging FU visit, these visits may be combined. All procedures required at the Safety FU visit at 90 days will be performed at the imaging FU.

d. BP should also be obtained 1 week after starting lenvatinib (can be done at home or by a community health care provider), then every 2 weeks for the first 2 months. BP can be then followed at least once monthly thereafter and may coincide with treatment visits.

e. Brain MRI must be performed at screening. Brain MRI should then be performed at week 6, 12, and Q12W thereafter; following Week 102, imaging should be performed every Q24W, or sooner if clinically indicated. Brain CT scan should only be used when MRI is contraindicated. The same imaging technique regarding modality and the use of contrast should be used in a participant throughout the trial to optimize the visualization of existing and new tumors.

f. Blood for correlative studies will be collected prior to C1, C2, and C3 as well at every 3rd cycle thereafter (ie. prior to C6, C9, C12, etc.).

g. Review requirements in Table 6 when scheduling lab assessments

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; CT = computed tomography; D1 = Day; DC = discontinue/discontinuing; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; FU = follow-up;; INR = international normalized ratio; LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PE = physical examination; PT = prothrombin time; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; Q24W= every 24 weeks; QD = once daily; mRECIST = modified Response Evaluation Criteria in Solid Tumors; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid stimulating hormone; UPCR=urine protein-to-creatinine; WOCBP = women of childbearing potential.

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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

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/ approval/. 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 by the Project Manager/sponsor team.

The informed consent will adhere to IRB/ 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 Medical History

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

the participant has enrolled in this study will be recorded separately and not listed as medical history.

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 events of clinical interests should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Study ID

All consented participants will be given a unique study ID that will be used to identify the participant for all procedures that occur. Each participant will be assigned only 1 study ID. Screening numbers must not be re-used for different participants.

7.1.1.7 Assignment of Allocation Number

The study ID as described above will be used throughout the length of participation.

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

Lenvatinib: Lenvatinib 20 mg (two 10-mg capsules) once daily will be taken orally with water (with or without food) at approximately the same time each day in 21-day cycles. If a lenvatinib dose is missed and cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

Pembrolizumab: Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. 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 (ie, infusion time is 30 minutes [−5 min/+10 min]).

After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

Administration of pembrolizumab will be witnessed by the investigator and/or qualified designee. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

7.1.2 Clinical Procedures/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 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 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 screening,

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. BP reading should be obtained 1 week after starting lenvatinib. Patients can either purchase a blood pressure cuff and the study team will train the subject on obtaining a BP at home, or it can be done by community health provider, as long as values are reported) and anti-hypertensives started if the systolic is ≥140 or diastolic is ≥90 or drug held per Section 5.2.2.6. The treating physician will prescribe anti-hypertensives.

7.1.2.5 Electrocardiograms

Electrocardiograms will be obtained as specified in the Trial Flow Chart (Section 6.0). 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. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG.

7.1.2.7 Urine Dipstick

Urine dipstick testing will be performed locally within 3 days prior to start of treatment. Participants with >1+ proteinuria on urine dipstick during screening will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24-hour will not be eligible.

Once participants are allocated, urine dipstick testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed at the investigational site. If a new event of proteinuria ≥2+ occurs, the participant must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles.

For participants with proteinuria ≥2+, see Section 5.2.2.7.

7.1.2.8 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.9 Tumor Imaging and Assessment of Disease

Extracranial tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. Brain imaging is required for all participants. Brain imaging will be done by MRI only. Patients unable to undergo brain MRI are not eligible. The same imaging technique and modality, ideally the same scanner type, 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 mRECIST 1.1 at screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 intracranial, previously untreated lesion that is appropriate for selection as a target lesion per mRECIST 1.1 is required prior to participant allocation.

7.1.2.9.1 Initial Tumor Imaging

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

The screening images will be reviewed by local radiology at the trial institution per mRECIST 1.1 for eligibility prior to allocation. Brain imaging should be by MRI. Additional CT screening images must also be submitted for evaluation of extracranial disease and must include at least the chest, abdomen, and pelvis. MRI or PET/CT may be substituted for CT scans of these extracranial areas when appropriate.

7.1.2.9.2 Tumor Imaging During the Study

The first on-study imaging assessment for best BMRR by brain MRI should be performed at 6 weeks (42 days ±7 days) from the date first study dose. Response assessment will be confirmed at 12 weeks. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Best overall objective response should be confirmed by repeat imaging assessment. Initial best overall response assessment will be done by CT scans (preferred) performed at 6 weeks (42 days ±7 days) from the date first study dose. Response assessment will be confirmed at 12 weeks. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

Participants who have disease progression may continue on treatment at the discretion of the Investigator and study PI provided they have met the conditions detailed in Sections 5.5.4.

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory.

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

7.1.2.9.3 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab and lenvatinib. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility.

The first on-study imaging assessment should be performed at 6 weeks (28 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

Per RECIST 1.1 (Section 7.1.2.9), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 12 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed 4 to 12 weeks after the first tumor imaging indicating PD, by the Investigator using RECIST, in clinically stable participants.

7.1.2.9.4 Modified RECIST 1.1 Assessment of CNS Disease

Modified RECIST 1.1 will be used as the primary measure for assessment of intracranial tumor response, date of intracranial disease progression, and as a basis for all protocol guidelines related

to intracranial disease status (eg, discontinuation of study treatment). Up to 5 intracranial, previously untreated target lesion in the brain will be followed for response and progression. Size is considered the tumor's largest diameter. Measurements from multiple lesions are summed to calculate the sum of the diameters (SD). The SD calculated on a baseline scan performed within 28 days of study drug initiation will be used as a reference to determine the objective response of the clinically evaluable lesions. All responses must be confirmed at 12 weeks with an equivalent or better response. Please refer to the original RECIST criteria if further reference is necessary. Please see section 7.1.2.9 for response assessment in patients requiring local therapy while on study.

Measurable disease

Specification of a minimal lesion diameter for measurable lesions reduces the potential for variation in the measurement of smaller lesions due to slice selection and volume averaging. The minimal lesion diameter should be greater than or equal to 2 times the section thickness and a minimum of 5mm. A previously irradiated lesion will not be measured as a target lesion unless it is documented to have progressed since treatment.

Non-measurable disease

Non-measurable lesions at baseline are important in clinical trials because tumor progression may occur at these sites. Non-measurable lesions include enhancing lesions that are less than the specified smallest measurable diameter (5mm when slice thickness is 2.5mm or twice the slice thickness), hemorrhagic or predominantly cystic or necrotic lesions that are difficult to accurately measure and track, and lesions that are indeterminate for metastatic disease. Intrinsic T1- hyperintensity is noted within hemorrhagic lesions that may be misinterpreted as enhancing tumor, and for this reason, the precontrast T1-weighted image must be examined at baseline to prevent this error. Non-measurable lesions should be briefly described on the imaging case report form for each study {Henson, 2008 #303}.

RECIST 1.1 limits the number of lesions measured to 5 in total, with 2 per organ. For our purposes, even if there are multiple measurable lesions in the brain, the sum of diameters of up to a maximum of 5 of the largest lesions will be considered for response assessment.

Modified response criteria for brain metastases

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded since the treatment started or the appearance of one or more new lesions (new lesions must be greater than slice thickness).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters since the treatment started. Please refer to RECIST v1.1 for additional details regarding response criteria.

7.1.2.9.5 RECIST Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of overall systemic tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment).

RECIST 1.1 stipulates that the number of lesions required to assess tumor burden for response determination has been reduced to a maximum of five total lesions (two lesions maximum per organ). Briefly, measurable lesions must have a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) in at least one dimension. Lesions with a longest diameter of <10 mm are considered non-measurable lesions and will be tracked as non-target disease. Tumor lesions in a previously irradiated area, or in an area subject to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion. For complete definitions of measurable and non-measurable disease, please refer to the RECIST v1.1 criteria.

7.1.2.9.6 Evaluation of Best Overall Response

The Best Overall Response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The best response will take into consideration both the clinically evaluable brain metastases and systemic metastases, and therefore will include measurements from both mRECIST criteria (in the brain) and RECIST criteria (in the body) as follows:

Complete Response (CR): Disappearance of all target lesions in the brain and systemic disease.

Partial Response (PR): Partial response in both the brain and the systemic disease, or if there is PR at one site and SD at the other, the sum of diameters from the brain and systemic disease will be added and the best overall response will be considered PR if there is at least a 30% decrease, taking as reference the baseline sum diameters.

Progressive Disease (PD): Progressive disease in either the brain or the systemic disease will qualify as PD as the best overall response.

Stable Disease (SD): Stable disease in both the brain and systemic disease, or if the sum of diameters from the brain and systemic disease does not qualify for PR or PD (at least a 20% increase in the sum of diameters of target lesions), taking as reference the smallest sum diameters since the treatment started.

7.1.2.9.7 Duration of Response

Duration of overall response: The duration of overall response is measured from the time that measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented. Please note that objective documentation implies confirmation of response by imaging.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. The duration of stable disease is determined by the interval at which images are obtained (initially at weeks 6 and 12, and then every 12 weeks thereafter).

7.1.2.9.8 Progression-Free Survival (PFS)

PFS is defined as the time from initiation of study drug until the first documented, confirmed progression of clinically evaluable brain metastases based on mRECIST criteria, systemic disease based on RECIST criteria, or death. If there is progression of disease that is then confirmed on a follow up scan at least 4 weeks later, the initial date of documented progression should be used in the PFS analysis.

7.1.2.10 Tumor Tissue Collection and Correlative Studies

7.1.2.10.1 Collection and Shipment of Specimen(s):

Before initiation of systemic therapy, surgical specimens of brain tumor or extracranial tumor will be obtained (either archival or as a new biopsy). Archival tissue must have been formalin fixed and embedded in paraffin. If fresh tissue from a new biopsy site is obtained, tissue will be prioritized for formalin fixation and embedding in paraffin, but effort will be made to flash freeze a portion of tissue in liquid nitrogen, and SNAP frozen tissue will be stored for further studies. Please see the Procedures Manual for tissue requirements and handling of tissue.

7.1.2.10.2 Site(s) Performing Correlative Study:

The stored tissue specimens will be analyzed at Yale University. Please see Section 8.3 on Statistical Analysis for information on how results will be analyzed.

7.1.2.10.3 Correlative Studies

Correlative studies will be conducted on the pre-treatment tissue specimen. A number of additional biomarkers will be studied for their potential predictive value in pre-treatment CNS specimens taken at the time of surgery or LITT and/or on tumor tissue from a systemic site. These exploratory studies include (but are not limited to):

1) Markers to be studied on tumor cells: B7H1, PDL2, B7H4, Galactin-9.

2) Percent of tumor sample that constitutes CD4 and CD8 cells

3) Markers on T cells: LAG-3 on CD4 cells, PD1-H (PD-1 homologue) on T cells, CTLA4 on T cells TIM3 on T cells

Patients who undergo surgical procedures (either of the CNS or peripheral) while on systemic treatment will also be asked to provide a research specimen to determine changes in the above markers in the context of response or resistance to therapy.

Levels of all of the above markers will be measured by a method of Automated Quantitative Analysis (AQUA) of in situ protein levels in Dr. Kluger's laboratory at Yale University. This method has been validated for epithelial cancers and melanoma and has shown to be more precise than pathologist-based scoring of 3,3′-diaminobenzidine stain. AQUA is highly reproducible and quantitative, as reviewed (Jilaveanu et al., 2009). Tumors will be stained with a number of fluorophores: A tumor mask for melanoma will be made using a cocktail of anti-S100 and anti-Melan-A. The methods for masking tumor have been described in the literature (Berger et al., 2004; Camp, Chung, & Rimm, 2002; Kluger et al., 2008). The mask will by conjugated to Cy-3, and will be differentiated from the target antigen, which will be conjugated to Cy-5. After fluorescent staining is completed, images are taken at the different wavelengths, and the images will be analyzed using algorithms that have been extensively described 58. A monochromatic, high-resolution images of each histospot will be obtained using the 10Å~ objective of an Olympus AX-51 epifluorescence microscope (Olympus) with automated microscope stage and digital image acquisition driven by a custom program and macrobased interfaces with IPLabs software (Scanalytics, Inc.). Tumor will be distinguished from stromal elements by the tumor mask signal. The signal intensity of the target biomarker will be scored on a scale of 0-255 (the AQUA score). This will provide quantitative results.

Biomarker analysis will be conducted using standard methods. Associations between continuous AQUA scores and binarized outcome variables (such as response) will be done by ANOVA. Cox univariate analysis will be used to study the associations between the survival endpoints and biomarker expression; Kaplan Meier curves will be generated to depict the association between binarized biomarker levels and survival endpoints. Multivariable models will be generated to predict response.

Immune monitoring will be performed as a part of this study. Peripheral blood lymphocytes (PBLs) and plasma (approximately 40cc) will be collected before cycles 1, 2, and 3, and subsequent to that, before every 3rd cycle thereafter, until patients come off of study. PBMCs will be separated and cryopreserved for T and B cell studies. Samples will be stored for immunophenotyping studies and serological profiling to be done using the Yale Cy-TOF core facility, or flow cytometry and by Eve Technologies.

7.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (If abnormal)	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free tyroxine (T4)
Absolute Lymphocyte Count	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (If total bilirubin is elevated above the upper limit of normal)		
	Total protein		
	Blood Urea Nitrogen		

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 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. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab and lenvatinib may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.3.2).

7.1.5 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.

7.1.5.1 Screening

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

7.1.5.1.1 Screening Period

28 days prior to treatment allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 5.1.1 and 5.2.1. Screening procedures may be repeated after consultation with the Sponsor. Screening procedures are to be completed within 28 days prior to the first dose of study treatment except for the following:

- Laboratory tests are to be performed within 10 days of Cycle 1 Day 1. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.
- Evaluation of ECOG is to be performed within 3 days of Cycle 1 Day 1.
- Full physical examination to be performed within 7 days of Cycle 1 Day 1.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 3 days prior to Cycle 1 Day 1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

- Tumor tissue must have been obtained prior to treatment allocation.

7.1.5.2 Treatment Period

Visit requirements are outlined in the Study Flow Chart (Section 6.0). Assessments/procedures are to be performed prior to the administration of study treatment.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Participants who are eligible for retreatment with pembrolizumab and lenvatinib (as described in Section 5.2.3) may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the participant begins retreatment with pembrolizumab and lenvatinib as detailed in Section 5.2.3. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Participants who are eligible to receive retreatment with pembrolizumab and lenvatinib according to the criteria in Section 5.2.3 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

7.1.5.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

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 the Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation must be reported by the investigator if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

● All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.

● All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

● All pregnancies and exposure during breastfeeding, from the time of treatment allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.

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 the Sponsor.

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

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 1000 mg or greater (≥5 times the indicated dose). An overdose of lenvatinib will be defined as any dose ≥20% over the prescribed dose described in the protocol that the participant is receiving at the time of the overdose. No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib. In the event of overdose, the specific treatment should be withheld and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest, 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 Sponsor 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 Sponsor 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 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, or a procedure.

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

Such events must be reported within 24 hours to the Sponsor 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 Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is another important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation, any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any participant must be reported within 24 hours to the Project Manager who will report 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, 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 serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Project Manager who will report within 2 working days to Merck Global Safety.

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

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

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 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 7 Evaluating Adverse Events

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

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

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

Relationship to Merck Product (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the participant re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Participant did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a participant with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

The site investigator must report any expected Serious Adverse Event (SAE-E) or unexpected Serious Adverse Event (SAE-U) that occurs during the treatment period starting at the time the consent is signed, through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, regardless of whether it is attributable to the study drug. Events must be reported to the Yale Project Manager and Sponsor PI within 24 hours of becoming aware of such events.

Sites are responsible for reporting to their IRB per local policy. All events will be forwarded by the Yale Project Manager to Merck as required following the method and timeline outlined below.

All SAEs should be entered into the EDC system within 24 hours of the site becoming aware of the event.

Any delayed serious adverse event (occurring after the 90-day period) that may reasonably be considered related to the treatment(s) described in the protocol or to the study must be reported, and no time limit applies to such adverse events. For each event, the investigator shall complete the SAE reporting form. SAEs will be followed until resolution or until clinically relevant improvement or stabilization.

The study site should send the SAE form to the Yale Project Manager and Sponsor PI as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Yale Project Manager and Sponsor PI are informed of an SAE with preliminary information obtained, the study site will be instructed to update the SAE form with additional information, as per the following guidelines.

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Yale Project Manager and Sponsor PI for review. Each Site PI is responsible for following up on completion of the SAE form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Yale Project Manager and Sponsor PI. In the case of fatality, autopsy reports will be furnished to the Yale Project Manager and Sponsor PI as soon as available. During the initial communication, the Yale Project Manager will require the following information about the patient and the reported SAE:

- patient identification including patient number, initials, and date of birth
- date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose;
- date of last dose of study drugs (i.e., prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose)

• medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event)
• date of onset of the AE
• date of resolution of the AE (or confirmation ongoing)
• severity of the AE
• assessment of the attribution of the AE to the study drug
• reason AE is considered serious
• whether the AE is expected
• action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the patient was discontinued from the study); all concomitant medications (including doses, routes, regimens, and indications)
• pertinent clinical laboratory testing data
• medical history

The Sponsor PI will review each SAE report and evaluate the relationship of the adverse reaction to the study drug and to the underlying disease. Based on the Investigator's and Sponsor PI assessment of the adverse experience, a decision will be made concerning further actions. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor PI will take immediate steps to notify the regulatory authorities.

7.2.7 Reporting to the IRB

Sites are responsible for reporting to their IRB per local policy.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized here.

Study Design Overview	A non-randomized phase 2, Simon's 2-stage designed trial to evaluate intracranial response to pembrolizumab and lenvatinib in anti-PD-1/PD-L1 experienced patients with untreated brain metastases evaluated in 2 cohorts: 1) melanoma and 2) RCC
Treatment Assignment	Approximately 62 participants will be allocated between 2 groups: cohort 1/melanoma (PD-1/PD-L1-experienced) will have 30 participants, and cohort 2/RCC (PD-1/PD-L1 experienced) will have 32 participants.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	Best brain metastasis response per mRECIST 1.1, up to 5 previously untreated or progressing intracranial tumors will be followed.
Key Secondary Endpoints	1) Best overall response rates per RECIST 1.1 2) PFS and OS 3) Duration of intracranial response 4) Adverse events

Statistical Methods for Secondary Endpoints	1) A Chi-squared analysis and 95% confidence interval will be employed to evaluate the overall response rate. 2) PFS and OS will be evaluated using the Kaplan-Meier method. 3) Duration of intracranial response will be evaluated by the Kaplan-Meier method. 4) Adverse events will be assessed tabulated by frequency with descriptive statistics such as grade, attribution, and type.

8.2 Sample Size Considerations

Cohort 1: Melanoma

A second-line immunotherapy option for patients who have progressed on anti-PD-1/PD-L1 may be ipilimumab, which has an estimated response rate of approximately 10% in the second-line setting in extracerebral melanoma (Bowyer et al., 2016; Long GV, 2016). An immune therapy regimen which is modestly active in patients with melanoma brain metastases whose disease had progressed on PD-1/PD-L1 inhibitors would be expected to have a brain metastasis response rate of an estimated 5%, as this represents a sicker patient population. Pembrolizumab combined with lenvatinib will be considered worthy of further study in patients with untreated brain metastases who are PD-1/PD-L1 inhibitor-experienced if the true brain response rate is 20%. Simon's two-stage design will be used, with 80% power and a one-sided level of significance equal to 0.05. In the first stage, 13 patients will be accrued. If there are 0 responses in these 13 patients, this cohort will be stopped for futility. Otherwise, 14 additional patients will be accrued for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. Due to an anticipated drop-out of 10% either due to being unevaluable in the brain due to loss to follow-up or death due to extracranial disease prior to initial response evaluation, we anticipate enrolling 30 patients for at least 27 evaluable.

Cohort 2: Renal cell carcinoma

Frontline standard of care therapies for metastatic renal cell carcinoma (RCC) are variable and may include anti-PD-1/PD-L1 +/- anti-CTLA-4, pembrolizumab + axitinib, or an antiangiogenic TKI. There are very limited data on the efficacy of second-line systemic therapy for untreated brain metastases in patients with RCC. Nivolumab as a second-line immunotherapy option for patients with untreated RCC brain metastases who have progressed on antiangiogenic or cytokine therapy has an intracranial response rate of 12% (Flippot et al., 2019). This is the same as the objective response rate reported for sunitinib in patients with RCC brain metastases (Gore et al., 2011). Checkpoint inhibitors combined with antiangiogenic therapies such as pembrolizumab plus

lenvatinib and pembrolizumab plus bevacizumab have demonstrated activity against RCC in the second-line setting, with ORR of 51% and 61%, respectively, in small early phase trials (Dudek et al., 2020; Lee et al., 2020; Taylor et al., 2020), but there is no data for these combinations in RCC brain metastases which represents a sicker patient population. Therefore, we propose that pembrolizumab combined with lenvatinib will be considered worthy of further study in RCC patients with untreated brain metastases who are PD-1/PD-L1 inhibitor-experienced if the true brain response rate is 30%. Simon's two-stage design will be used, with 80% power and a type I error rate of 0.05. In the first stage, 18 patients will be accrued. If there are 2 or fewer responses in these 18 patients, this cohort will be stopped for futility. Otherwise, 11 additional patients will be accrued for a total of 29 patients. The null hypothesis will be rejected if 7 or more responses are observed in 29 patients. Conservatively estimating for a 10% drop out rate accounting for patients who may be unevaluable due to inability to reach the first intracranial assessment scan, an additional 3 patients may be enrolled if needed, for a total of 32 patients.

8.3 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9).

All baseline patient demographics and clinical characteristics will be summarized by mean/standard deviations and count/frequency for continuous and categorical variables respectively. All analyses will be completed as intent to treat.

Intracranial and Objective Response Rate

The primary endpoint is the best brain metastasis response rate of pembrolizumab in combination with lenvatinib. For the primary objective, the proportion of patients that experienced an intracranial response in each cohort will be estimated with corresponding 95% confidence interval.

The combination will be deemed worthy of further study as outlined in the Simon 2-stage designs in Section 8.2.

For objective response rate, the proportion of patients experience an objective response in each cohort will be estimated with corresponding 95% confidence interval.

PFS and OS

The non-parametric Kaplan-Meier method will be used to estimate median survival, along with survival at 1 year and 2 years.

Participants without documented event at the time of analysis will be censored at the date of last clinical evaluation for each outcome.

Duration of Intracranial Response Analysis

Duration of intracranial response will be evaluated by the Kaplan-Meier method. Intracranial responses will be analyzed separately from extracranial responses. If the patient has SD/PR/CR in the brain but PD in the body, then the patient will still be considered to have an ongoing intracranial response.

Statistical Methods for Safety Analyses

AEs will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and grouped system organ class. AEs will be graded by the investigator according to the NCI CTCAE, v5.0.

All subjects will be included in the safety analysis. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawals and incidence of serious adverse events. Listing of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal.

Exploratory Objectives

Biomarker Studies

Immunohistochemical evaluation of baseline tumor PD-L1 staining, TIL populations, and other immune and angiogenic factors that may predict tumor sensitivity to this drug combination will be compared between non-responders (SD and PD) versus responders (PR and CR) using a mixed methods approach, that adjusts for repeated measures over time and response as defined above. If there are differences by time, pairwise contrasts will be utilized to assess for specific differences at various time points, adjusting for multiple comparisons using the Tukey method.

For patients who have on-treatment tumor samples, comparison will be made to pre-treatment tissue for PD-L1 staining, TIL populations, and other immune and angiogenic factors that may predict tumor sensitivity. Differences in these markers by response will be assessed using two-sample t-test.

Blood samples collected before and on treatment will be analyzed for cytokines and by flow cytometry. Data will be analyzed by a repeated measures ANOVA and adjusted for multiple comparisons via Tukey method.

TIL will be extracted from resected pre-treatment specimens and subjected to immunophenotyping studies to characterize T and B cells using single-cell RNA-sequencing. Data will be analyzed by a repeated measures ANOVA and adjusted for multiple comparisons via Tukey method.

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 9.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Lenvatinib 20 mg	Tablet for oral dosing

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

Multicenter Management and Coordination

The YCCI MCU will support the Sponsor-Investigator with the multi-site management aspects of this trial. This includes, but is not limited to, study start-up, regulatory assistance (IRB submissions, amendments, and renewals), provision of template study forms (tracking and eligibility checklists, etc.), site qualification and activation, training, and overall project management. The MCU will provide tools to assist the study teams in conducting the trial appropriately and according to Good Clinical Practice Standards.

The MCU will ensure that all participating sites undergo remote training in which all key study personnel will be instructed study procedures, informed consent, source documentation requirements, safety and adverse event reporting, Good Clinical Practice guidelines and additional study related topics. This training will be conducted by the YCCI Study Monitor and/or MCU staff and documentation of completion will be required for all personnel.

Data and Safety Monitoring Committee

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

Study Site Monitoring

Study site monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted.

The Sponsor-Investigator-designated monitor(s) conducts monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits and/or remote interim monitoring visits while subjects are on study, and a site close-out visit at all participating sites. Following each site visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of informed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- GCP compliance
- If applicable, include: Investigational Drug/ Device Storage and Accountability (including quantity and disposal procedures)
- If applicable, include: Laboratory Facilities
- If applicable, include: Equipment maintenance and calibration
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Sponsor-Investigator and YCCI will define the required study monitoring activities in a Study Monitoring Plan.

DATA HANDLING AND RECORD KEEPING

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. In most cases, the source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. The investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Forte EDC will be the designated electronic data capture tool. All data should be entered onto the EDC System within 1 week of study entry. AEs need to be entered within 72 hours and SAEs need to be entered within 24 hours of the site becoming aware of the event.

CONFIDENTIALITY & SECURITY OF DATA

Data will be entered into the Electronic Data Capture (EDC) System. De-identified data will then be downloaded in Excel format for statistical analysis, which will be done on a HIPAA compatible, password protected encrypted laptop computer. All data entry will be performed by the local study site personnel. All source documentation will be retained at the local study site per local site regulations and monitored during regularly scheduled monitoring visits.

Record Retention

To enable evaluations and/or audits from regulatory authorities or Yale, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g. CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to International Conference on Harmonization (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Yale should be prospectively notified.

ETHICS

This study will be conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki; applicable Good Clinical Practice (GCP) Guidelines published by the International Conference on Harmonisation; and applicable US laws and regulations including those found in 21 CFR Parts 50, 54, 56, and 312.

Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, e.g. recruitment advertisements, if applicable, from the IRB. All correspondence with the IRB should be retained in the investigator file. Copies of IRB approvals should be forwarded to the Project Manager.

The only circumstance in which an amendment may be initiated prior to IRB approval is where the change is necessary to eliminate apparent immediate hazards to the patients.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor PI with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

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

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Male Participants:

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

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

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

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 during the protocol-defined time frame.

Table 10 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] Failure rate of <1% per year when used consistently and correctly.
● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) a non-hormonal IUD (copper) can be used as an alternative for patients who may be ineligible for hormonal contraception ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

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

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally. A pregnancy test will be performed at the end of the period of systemic exposure.