

Neoadjuvant Lenvatinib plus Pembrolizumab in Resectable Merkel Cell Carcinoma

MCC 20773

TITLE: Neoadjuvant lenvatinib plus pembrolizumab in resectable merkel cell carcinoma

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Statement of Compliance

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Supporting Agency Terms. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator:

Print/Type Name

Signed: _____ Date: _____

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1.0 TRIAL SUMMARY

Abbreviated Title	Neoadjuvant lenvatinib plus pembrolizumab in merkel cell carcinoma
Trial Phase	II
Clinical Indication	Resectable merkel cell carcinoma
Trial Type	interventional
Type of control	n/a
Route of administration	IV/PO
Trial Blinding	none
Treatment Groups	Single arm
Number of trial participants	12 to 26
Estimated enrollment period	2 years
Estimated duration of trial	5 years
Duration of Participation	3 years
Estimated average length of treatment per patient	1 year

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single arm, phase 2 trial with a planned interim analysis for futility. The first stage will enroll 12 patients and expansion to 26 patients total will occur if efficacy criteria are met.

Patients with Merkel cell carcinoma amenable to complete resection will receive two cycles (6 weeks) of therapy with the combination of lenvatinib plus pembrolizumab and then proceed to planned resection within 2-4 weeks following completion of cycle 2. Following surgical recovery and completion of adjuvant radiation therapy (if indicated), treatment will resume with pembrolizumab monotherapy with intent to complete 17 cycles total of pembrolizumab.

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2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Objective: Assess the pathological complete response rate for resectable Merkel cell carcinoma treated with the combination of pembrolizumab and lenvatinib in the neoadjuvant setting.

Hypothesis: Treatment with pembrolizumab plus lenvatinib will lead to a higher pathological complete response rate compared to that expected by anti-PD1 therapy alone.

3.2 Secondary Objective(s) & Hypothesis(es)

- (1) **Objective:** Assess the progression free survival of resectable Merkel cell carcinoma treated with neoadjuvant pembrolizumab and lenvatinib
- (2) **Objective:** Assess the feasibility of neoadjuvant therapy with pembrolizumab and lenvatinib for potentially resectable Merkel cell carcinoma

3.3 Exploratory Objective

- (1) **Objective:** Biobanking for post-hoc exploratory translational immunological endpoints

4.0 BACKGROUND & RATIONALE

4.1 Background

Merkel cell carcinoma (MCC) is a relatively rare, aggressive cutaneous malignancy. There are approximately 1600 cases of Merkel cell carcinoma in the United States each year [Lemos and Nghiem, 2007]. The reported incidence of MCC has almost tripled in the past 20 years, rising from 0.15 cases per 100,000 in 1986 to 0.44 cases per 100,000 in 2001 [Heath et al., 2008; Hodgson et al., 2005].

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

[Keytruda®](#) (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure.

Lenvatinib 4-[3-Chloro-4-(*N*'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate (lenvatinib mesilate) is an oral, potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptor FGFR1-4, platelet-derived growth factor (PDGF) receptor PDGFR α , KIT, and RET. Lenvatinib has an acceptable preclinical safety profile and is in clinical development as an oral therapy for advanced malignancies. [Lenvima®](#) (lenvatinib) is indicated for the treatment of patients across several indications. For more details on specific indications refer to the Investigator brochure.

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including

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autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

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

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. The angiogenesis process begins with local degradation of the basement membrane surrounding capillaries, followed by invasion of the surrounding stroma by underlying endothelial cells in the direction of the angiogenic stimulus. Endothelial cell migration is accompanied by the proliferation of endothelial cells and their organization into three-dimensional structures that join with other similar structures to form a network of new blood vessels. This process involves an alteration in the balance between proangiogenic and antiangiogenic molecules. In Merkel cell carcinoma, increased expression of proangiogenic vascular endothelial growth factor receptors (VEGFRs) has been correlated with poor prognosis and inhibition of this pathway has been proposed as a rationale target for therapy in this disease [Fernandez-Figueras, et al., 2007; Kervarrec, et al., 2019].

Recent evidence suggests that proangiogenic signaling, especially VEGFR signaling have an important immunosuppressive role in the tumor microenvironment (TME), where immunosuppressive tumor associated macrophages (TAMs) and regulatory T cells are increased, while differentiation/maturation of dendritic cells (antigen-presenting cells) is impaired, and CD8⁺ T cells are depleted. FGF / FGFR signaling also support migration and survival of TAM in the TME. Accumulation of TAMs in the TME predicts poor prognosis in patients with many types of cancers [Joyce and Pollard, 2009; Ding, et al., 2009; Heusinkveld and van der Burg, 2011; Takase, et al., 2006]. TAMs produce a variety of cytokines/chemokines such as transforming growth factor β , interleukin- 10, VEGF, and basic FGF, and could inhibit the attack of tumor killing CD8⁺ T cells on cancer cells, as well as promoting tumor angiogenesis [Pollard, 2004; Riabov, et al., 2014; Noy and Pollard, 2014]. Endothelial cells in the TME, under a constitutive proangiogenic signaling could have an immunosuppressive function upregulating immune checkpoint molecules, prevent

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extravasation of CD8⁺ T cells, and expressing Fas-ligands leading to Fas- mediated apoptosis of CD8⁺ T cells. Therefore, blocking both immune checkpoint signals and proangiogenic signaling should be not only a combination of immune therapy and antiangiogenesis therapy, but also a new strategy for accelerated anticancer immune therapy [Lantis et al, 2015; Ott, et al., 2015; Yang, et al., 2018].

Lenvatinib and lenvatinib in combination with immune checkpoint inhibitor, rat anti-murine PD-1 mAb showed significant tumor growth inhibition against various murine tumor isografts in immunocompetent mice including RCC, lung carcinoma, HCC, and colon carcinoma [Kato et al, 2019]. The antitumor activity of the combination was greater than each monotherapy in all isograft models tested. Results of recent in vivo nonclinical pharmacodynamics studies suggest that in addition to its antiangiogenesis activity, lenvatinib has an immunomodulatory activity probably due to its inhibitory activity against VEGF/VEGFR and involving the decrease of immunosuppressive TAMs, increase of activated cytotoxic T cells, and an activation of IFN- γ signaling in tumor microenvironment that contributes to its antitumor activity. Since the mode of immunomodulatory activity of lenvatinib is complementary to that of an immune checkpoint inhibitor, anti-PD-1 mAb, these nonclinical pharmacodynamics results suggest that the combination of lenvatinib and pembrolizumab may provide an effective therapeutic option for many cancers.

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

Merkel cell carcinoma is an aggressive cutaneous malignancy. The historically reported 5-year relative survival (estimate of MCC-specific survival) for patients with local, nodal and metastatic disease is 64%, 39% and 18% respectively [Lemos et al., 2010]. Therefore even patients with potentially surgically resectable disease are at high risk for recurrence and disease-related mortality.

For resectable MCC, standard care is directed towards the primary tumor and/or regional lymphatics. This is typically a wide excision of the primary lesion as well as surgical evaluation of the regional lymphatics. Since MCC has a high propensity for regional spread via the lymphatics, regional lymph nodes are generally evaluated clinically and when indicated, pathologically (via sentinel lymph node biopsy and/or lymphadenectomy)[Gupta et al., 2006]. For patients with confirmed metastasis in the regional lymph nodes, definitive management is usually directed at the regional lymphatics. Such treatment may include either a therapeutic lymph node dissection or radiation therapy (RT). Adjuvant RT is commonly used to reduce the risk of loco-regional recurrence, but does not appear to have a significant effect on overall survival (OS) [Bhatia et al., 2016]. Adjuvant chemotherapy is offered at some centers to reduce the risk of systemic recurrence, but does not appear to have a significant impact on OS [Bhatia et

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al., 2016] and is not routinely recommended by current guidelines [NCCN version 2.2019]. Furthermore, adjuvant chemotherapy can be associated with considerable morbidity in this relatively elder population. **There is therefore a strong unmet need for effective neoadjuvant or adjuvant systemic therapy in MCC patients at high-risk of recurrence.**

Checkpoint inhibitor immunotherapy has recently become standard initial treatment for patients with advanced disease based on high response rates as well as response durability in this setting [Nghiem et al, 2019; D'Angelo et al, 2018]. Anti-PD-1 therapy therefore makes an attractive therapeutic target in the adjuvant or neoadjuvant setting and several of these agents are in ongoing single-agent adjuvant clinical trials for high risk disease. Regarding neoadjuvant therapy, in the CheckMate 358 trial of nivolumab in virus-associated cancers, patients with resectable Merkel cell carcinoma were treated with two neoadjuvant doses of the anti-PD-1 agent nivolumab. In preliminary reports from this study presented at ASCO 2018, this approach was highly feasible and induced a pathological complete response in 47% of tumors that underwent central review [Topalian, et al, 2018]. Further study of neoadjuvant immunotherapy in this disease was therefore highly encouraged by the authors of this study.

Single agent anti-PD-1 checkpoint inhibitor therapy, while highly effective in advanced MCC, still only benefits approximately half of the population. Combination therapies adding to an anti-PD-1 backbone in hopes of increased efficacy is therefore a high priority for study in this disease. Targeting the angiogenic pathway as an addition to anti-PD-1 immunotherapy has a strong scientific rationale in MCC and in malignancy more generally (see 4.1.1 for details). Specifically, the combination of pembrolizumab and lenvatinib has strong preclinical rationale for use and this combination is already in clinical study in several non-MCC cancer histologies.

In summary, we have compelling rationale for combining pembrolizumab and lenvatinib in resectable MCC. This is a high area of unmet clinical need and the combination proposed is supported by strong preclinical rationale across malignancies as well as in MCC specifically.

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 Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

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

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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.

The planned dose of lenvatinib is 20mg orally once daily. This dose was selected as the recommended phase 2 dose when used in combination with pembrolizumab on the basis of results from a dose-finding phase 1b study [Taylor et al, 2016]. Of note this same dose combination is in use in several ongoing studies of this drug combination across several disease histologies. In advanced endometrial carcinoma, interim analysis of an ongoing study of pembrolizumab plus lenvatinib reported this dose combination to have a manageable toxicity profile [Makker et al, 2019].

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The study design is a phase II with a primary efficacy endpoint of pathological response. Generally, response rate is a well-accepted endpoint for phase II study of oncologic therapies. As an example, in a recent review of 87 phase II checkpoint inhibitor trials response rate was identified as the most common endpoint [Ritchie, et al., 2018]. Pathological response rate is a

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potentially more sensitive endpoint to the more typical clinical/radiographic response rate and has been well validated in neoadjuvant trials more generally. Specifically in MCC with checkpoint inhibitor treatment, in the preliminary report from the CheckMate 358 trial of neoadjuvant nivolumab pathological response rate was higher than radiographic response rate [Topalian, et al, 2018]. In advanced MCC, responses to checkpoint inhibitor therapy are often durable and correlate strongly with overall survival [Knepper, et al, 2019]. Therefore, we propose pathological response rate as an appropriate primary efficacy endpoint for study. Additional efficacy endpoints include progression free survival and feasibility of surgery after study therapy.

4.2.3.2 Biomarker Research

The trial includes a significant biobanking initiative for the purposes of post-hoc biomarker research.

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 Merkel cell carcinoma will be enrolled in this study. The clinical stage of the patient must be stage II, III, or IV (AJCC 8th edition) at the time of enrollment.

Male participants:

2. A male participant must agree to use contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 6 days after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

3. 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 3OR
 - b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 30 days after the last dose of study treatment.

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4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
5. Have clinically or radiographically detectable disease that is felt by the treating physician to be amenable to complete surgical resection.
6. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Be willing and able to perform home blood pressure monitoring
9. Have adequate organ function as defined in the following table (Table 1).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1500/\mu\text{L}$
Platelets	$\geq 100\,000/\mu\text{L}$
Hemoglobin	$\geq 9.0\text{ g/dL}$ or $\geq 5.6\text{ mmol/L}^a$
Renal	
Creatinine <u>OR</u> Measured or calculated ^b creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times \text{ULN}$ <u>OR</u> $\geq 30\text{ mL/min}$ for participant with creatinine levels $> 1.5 \times \text{institutional ULN}$
Hepatic	
Total bilirubin	$\leq 1.5 \times \text{ULN}$ OR direct bilirubin $\leq \text{ULN}$ for participants with total bilirubin levels $> 1.5 \times \text{ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for participants with liver metastases)

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Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
<p>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.</p> <p>^a Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.</p> <p>^b Creatinine clearance (CrCl) should be calculated per institutional standard.</p> <p>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.</p>	

5.1.2 Participant Exclusion Criteria

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

1. A WOCBP who has a positive urine pregnancy test (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
3. Has receive prior therapy with a systemic anti-VEGFR inhibitor for oncologic purposes
4. Uncontrolled blood pressure (Systolic BP>140 mmHg or diastolic BP >90 mmHg) in spite of an optimized regimen of antihypertensive medication.
5. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment at Screening.
6. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (e.g. carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
7. Subjects having > 1+ proteinuria on urine dipstick testing unless a 24-hour urine collection for quantitative assessment indicates that the urine protein is ≤ 1 g/24 hours.

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8. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks [could consider shorter interval for kinase inhibitors or other short half-life drugs] prior to [randomization /allocation].

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

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

9. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (\leq 2 weeks of radiotherapy) to non-CNS disease.
10. 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.
11. 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.
12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
13. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, chronic lymphocytic leukemia or other indolent malignancy not requiring therapy and not expected to require therapy during the study treatment period, carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

14. Has known active CNS metastases and/or carcinomatous meningitis.

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15. Has severe hypersensitivity (\geq Grade 3) to pembrolizumab and/or any of its excipients.
16. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
17. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
18. Has an active infection requiring systemic therapy.
19. Has a known history of Human Immunodeficiency Virus (HIV).
20. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [[qualitative](#)] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
21. 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.
22. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
23. 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.

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

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

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

5.1.4 Pregnancy

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

5.1.5 Use in Nursing Women

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

5.1.6 Screen Failures

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

Screen failure individuals who do not meet the criteria for participation in this trial because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

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
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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	20mg	Daily	PO	Day 1-21 of each 3 week cycle (i.e. continuous) for cycles #1 and #2 only (neoadjuvant)	Experimental

5.2.1 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

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).

Lenvatinib will be self-administered on a once-daily basis.

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

5.2.2 Study intervention compliance

To assess compliance to oral medication, patient daily drug diaries will be utilizing. This participant drug log will be used to calculate study intervention compliance of the self-administered oral study medication.

To assess compliance of home BP monitoring, a daily blood pressure diary will be utilized.

5.2.3 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 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

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interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

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

General instructions: <ol style="list-style-type: none"> 1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. 2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks. 3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. 				
Immune-related AEs	Toxicity grade or conditions (CTCAEv5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with \geq Grade 2 diarrhea

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	Grade 4	Permanently discontinue		<p>suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</p> <ul style="list-style-type: none"> 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 / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold	<ul style="list-style-type: none"> Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia 	<ul style="list-style-type: none"> Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.

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			liothyroinine) per standard of care	
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none">Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	<ul style="list-style-type: none">Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none">Based on severity of AE administer corticosteroids	<ul style="list-style-type: none">Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none">Based on type and severity of AE administer corticosteroids	<ul style="list-style-type: none">Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.				
NOTE:				
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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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.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

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

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<p>Grades 3 or 4</p> <p>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)</p> <p>Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p>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.</p> <p>Participant is permanently discontinued from further study drug treatment.</p>	<p>No subsequent dosing</p>
<p>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</p>		

Other allowed dose interruption for pembrolizumab

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

5.2.4 Dose Modifications for lenvatinib associated toxicities

For intolerable grade 2 toxicities and for all grade 3 toxicities attributable to lenvatinib, therapy should be interrupted until resolved to Grade 0-1 or baseline at which point treatment can be reinitiated at dose reduction (Table 5). For hematologic toxicity or proteinuria, treatment can restart when resolved to Grade 2 at the discretion of the treating investigator.

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

Table 5: Lenvatinib dose modifications

Dose Level	Daily Dose	Number of Capsules
Starting dose	20 mg orally once daily	Two 10 mg capsules
First dose reduction	14 mg orally once daily	One 10 mg capsule plus one 4 mg capsule
Second dose reduction	10 mg orally once daily	One 10 mg capsule
Third dose reduction	8 mg orally once daily	Two 4 mg capsules

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications

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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.

5.3.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy, with the exception of adjuvant radiation therapy as per the overall treatment schema (see section 2.2)
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.3.3 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.

5.4 Participant Withdrawal/Discontinuation Criteria

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed disease progression outlined in Section 7.1.2.6
- Unable to undergo complete surgical resection following the neoadjuvant portion of protocol therapy
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences as described in Section 5.2.2.

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- 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
- The participant is lost to follow-up
- Administrative reasons

5.5 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and if study site staff are unable to contact the participant.

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

- The site will attempt to contact the participant and reschedule the missed visit within a one month time frame and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, by making 3 telephone calls and, if necessary, by sending a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- A minimum of 2 years should be spent attempting to locate the patient. If after that period of time the coordinator has sufficiently documented all failed attempts to locate the patient, including sending a certified letter with no response, then he or she will be considered to have withdrawn from the study for the primary reason of being lost to follow-up.

5.6 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

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4. Plans to modify or discontinue the development of the study drug

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

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6.0 TRIAL FLOW CHART

Trial Period:	Screening Phase	Treatment Cycles^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening Visit	1	2	Pre-operati ve evaluat ion	Post-operati ve evaluat ion	3	4	5-17 (odd)	6-16 (even)	Discontinue	Safety Follow- up	Follow Up Visits ^b	Survival Follow- Up ^b
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 7	± 7	± 3	± 3	± 3	± 3	At time of Discontinue	30±7 days post disconuat ion	Every 3 months± 14 days	Every 6 months
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Trial Treatment Administration		X	X			X	X	X	X				
Post-study anticancer therapy status													X
Survival Status										X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight ^c	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG	X					X		X		X	X		
PT/INR and aPTT	X			X									
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X	X	X										

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Trial Period:	Screening Phase	Treatment Cycles^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening Visit	1	2	Pre-operati ve evaluat ion	Post-operati ve evaluat ion	3	4	5-17 (odd)	6-16 (even)	Discontinue	Safety Follow- up	Follow Up Visits ^b	Survival Follow- Up ^b
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 7	± 7	± 3	± 3	± 3	± 3	At time of Discontinue	30±7 days post disconuat ion	Every 3 months± 14 days	Every 6 months
T3, FT4 and TSH	X	X	X	X	X	X	X	X	X	X	X		
	Efficacy Measurements												
Tumor Imaging/Surveillance Imaging ^d	X			X		X						X	
	Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival or Newly Obtained Tissue Collection ^e	X												
Correlative Studies Blood Collection ^f	X		X	X	X		X			X			

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Trial Period:	Screening Phase	Treatment Cycles ^a								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening Visit	1	2	Pre-operative evaluation	Post-operative evaluation	3	4	5-17 (odd)	6-16 (even)	Discontinue	Safety Follow-up	Follow Up Visits ^b	Survival Follow-Up ^b
Scheduling Window (Days):	-28 to -1	± 3	± 3	± 7	± 7	± 3	± 3	± 3	± 3	At time of Discontinue	30±7 days post discontinuation	Every 3 months± 14 days	Every 6 months
<p>^aTreatment consists of 21 day cycles. Cycle #1 and #2 are to be administered with neoadjuvant intent. A pre-operative evaluation will be undertaken at the completion of cycle #2 and surgery will be planned 2-4 weeks following completion of cycle #2 unless delays are clinically necessary for toxicity or administrative concerns. A post-operative study evaluation will take place 2 weeks ± 7 days after surgical resection. Adjuvant radiation therapy may then be administered as per standard of care of the treating institution if indicated. Cycles 3-17 will take place in the adjuvant setting and after completion of radiation therapy (if administered). Cycle #3 can be scheduled once adequate surgical recovery has been achieved as per treating physician and after radiation therapy is complete (if administered) and radiation associated toxicities have resolved to Grade 1 or less (if applicable) but must be started within 12 weeks of completion of locally directed therapies (surgery ± radiation). For treatment cycle related laboratories and ECOG assessment, these may be completed up to 72 hours prior to dosing.</p> <p>^bPost-treatment study follow-up visits will be conducted for a 3 year period starting from the date of surgery. The follow-up visits should be scheduled to be concurrent with timing of surveillance imaging (see ^d) ± 14 days. Survival Follow-up will continue to complete 5 years total starting from the date of surgery.</p> <p>^cIn addition to vital sign monitoring during study visits, patients will be instructed to conduct daily home monitoring of blood pressure while on active therapy and to contact the study team if BP increases to >140 systolic or >90 diastolic. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height should be measured at screening visit only.</p> <p>^dComputed tomography (CT) scan of any known sites of measureable disease are required at the time of screening and pre-operative evaluations, with the exception of clinically measureable cutaneous disease. For clinically measurable cutaneous disease, clinical measurements may instead be substituted at these timepoints. For surveillance for metastatic disease, either CT scan including chest, abdomen and pelvis or positron emission tomography/computed tomography (PET/CT) scans may be utilized as per standard of care of the treating institution. Surveillance imaging for metastatic disease should be performed at the time of screening, prior to the start of adjuvant systemic therapy (cycle #3) and every 3 months (90 days ± 14 days) thereafter, including both during the treatment and post-treatment follow-up timeframe.</p> <p>^eIn addition to tissue collected during the screening phase, tissue from the surgical resection performed will also be collected for assessment of pathological response as well as for correlative studies. New biopsy is not required at the time of screening if archival tissue is available.</p> <p>^fCorrelative blood will include collection of 40mL of blood in green top tubes at all marked timepoints. This will be separated for PBMC and plasma and banked for later use. At screening, Cycle #2, pre-operative, post-operative, Cycle #4 and end of treatment timepoints correlative studies will also include anti merkel cell panel (AMERK) testing if the screening sample has detectable level of merkel cell oncoprotein. If the screening AMERK timepoint has no detectable merkel cell oncoprotein, then this test is not repeated.</p>													

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7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

An optional informed consent to allow for biobanking of collected specimens for future unspecified studies will also be presented to the patient.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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 ECIs 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.

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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 Registration Procedure

All subjects must be registered with the Moffitt Clinical Research Network (MCRN) at Moffitt Cancer Center to be able to participate in the trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Once documents are received, the MCRN research coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility will not be registered and will be unable to participate in the trial.

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.

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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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment, at discontinuation of trial treatment, and at the 30 day safety follow-up visit as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease Progression

Tumor imaging is strongly preferred to be acquired by computed tomography (CT) with iodinated contrast unless the contrast is contraindicated. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

For patients with measurable disease (not required for study entry) tumor response to neoadjuvant therapy will be assessed per RECIST 1.1 comparing the screening and pre-operative imaging.

Progressive disease will be defined by the detection (clinically or radiographically) of any recurrent disease following complete surgical resection or by progression of disease that is not amenable to complete surgical resection prior to planned surgery. Of note, RECIST 1.1 will NOT be utilized to define disease progression during the neoadjuvant period to account for the unique tumor response seen with immunotherapeutic drugs (i.e. possibility of pseudoprogression during this 6 week period). When clinically stable, participants should not be discontinued from the trial at this timepoint but instead be allowed to proceed with complete surgical resection as planned. Completion of planned adjuvant trial therapy will be allowed at the discretion of the treating physician in this scenario provided that disease recurrence is not noted in the post-surgery period. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

7.1.2.6.1 Initial Tumor Imaging

Initial screening tumor imaging is required of the chest, abdomen and pelvis as well as any other known sites of disease with the exception of clinically measureable cutaneous disease. For clinically measurable cutaneous disease, clinical measurements may instead be substituted for these areas.

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Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation and can be assessed by the central imaging vendor.

7.1.2.6.1 Tumor Imaging During the Study

For patients with measurable disease, the first and only follow-up on-study imaging assessment should be performed at the time of the pre-operative evaluation, i.e. 6 weeks (42 days \pm 7 days) from the date of C1D1, and should include all known sites of disease with the exception of clinically measurable cutaneous disease. For clinically measurable cutaneous disease, clinical measurements may instead be substituted for these areas. For patients without measurable disease at baseline, tumor imaging is not required at this time point but may be implemented at the discretion of the treating physician. Following the pre-operative restaging scan, patients who continue on study will have undergone complete surgical resection and therefore be followed only with surveillance imaging.

7.1.2.6.2 Surveillance Imaging

Surveillance imaging should first be performed prior to the start of adjuvant systemic therapy. This first post-surgical surveillance imaging should be performed within 28 days of the start of the first adjuvant systemic therapy cycle (Cycle #3). Subsequent surveillance imaging should be performed every 3 months (90 days \pm 14 days) including during the follow-up period.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Correlative blood will include collection of 40mL of blood in green top tubes at serial timepoints (see section 6.1). This collection will be separated for PBMC and plasma and banked for later use with the Kenneth Tsai laboratory at Moffitt Cancer Center. At screening, Cycle #2, post-operative, Cycle #4 and end of treatment timepoints correlative studies will also include anti merkel cell panel (AMERK) testing if the screening AMERK test has detectable levels of Merkel cell polyomavirus oncoprotein.

Tumor tissue will be collected either archival or newly obtained at the time of screening and will be collected as well as from the surgical specimen when the patient undergoes complete surgical resection.

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.

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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 (<i>If abnormal</i>)	Total triiodothyronine (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 (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	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.			

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For treatment cycles laboratories, 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 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following completion of study therapy, 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 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.

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 3 months (90 ± 14 days) by radiologic imaging to monitor disease status. After 3 years of follow-up (starting post complete resection), patients will be transitioned to survival follow-up. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

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7.1.5.3.3 Survival Follow-up

Participants who complete the planned follow-up interval, or those who experience disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 6 months (180 days \pm 14 days) 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. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use. For the purposes of this study both pembrolizumab and lenvatinib are considered Merck products.

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/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, 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/randomization through 30 days following cessation of study treatment must be reported by the investigator.

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- All AEs meeting serious criteria, from the time of treatment allocation/randomization 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/randomization 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 Merck.

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

For purposes of this study, an overdose of lenvatinib will be defined as any dose of 40 mg or greater (≥ 2 times the indicated dose). No specific information is available on the treatment of overdose of lenvatinib. In the event of overdose, the participant should be observed closely for signs of toxicity and subsequent dose(s) may be held at the discretion of the treating physician. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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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/randomization must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Such events must be reported within 24 hours to the 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 the Sponsor and 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.

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to

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be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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.

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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 mild 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 of 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		

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	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	<p>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.</p> <p>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):</p> <table border="1"> <tr> <td>Exposure</td><td>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?</td></tr> <tr> <td>Time Course</td><td>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)?</td></tr> <tr> <td>Likely Cause</td><td>Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr> </table>	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
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						

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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	<p>Was Merck product discontinued or dose/exposure/frequency reduced?</p> <p>If yes, did the AE resolve or improve?</p> <p>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.</p> <p>(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.)</p>
	Rechallenge	<p>Was the participant re-exposed to Merck product in this study?</p> <p>If yes, did the AE recur or worsen?</p> <p>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.</p> <p>(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).</p> <p>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.</p>
	Consistency with Trial Treatment Profile	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?</p>
<p>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.</p>		
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.	<p>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.</p>	
No, there is not a reasonable possibility of Merck product relationship	<p>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.)</p>	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The study will follow a Simon's two-stage minimax design following the primary outcome of pathologic complete response rate with 12 patients in the first stage with expansion to 26 total patients in the second stage.

8.2 Sample Size Determination and Accrual

The primary endpoint is pathological complete response (CR). The null hypothesis is that the CR is 40% and the alternative hypothesis is that the CR is 65%. The assumptions for the response rate are based on the study conducted by Topalian et al (2018). Using a Minimax design with alpha 0.05 and 80% power yields a 12 patient in first stage with expansion to 26 total patients in stage II if at least 6 patients achieve pathologic complete response in the first stage. Assuming the second stage is completed, if 15 or more patients achieve pathologic CR the drug will be considered worthy of further study in this patient population.

8.3 Population for Analyses

For purposes of analysis, the following populations are defined.

Population	Description
Enrolled	All participants who sign the informed consent form.
Per-Protocol	All participants who have completed a minimum of disease evaluations and who do not have any major deviations, including but not limited to efficacy assessments or compliance. This data will be used to analyze the primary endpoint.
Safety	All participants assigned to study treatment and who take at least one dose of study treatment

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8.4 Data Analysis Plan

For this phase 2 study, the primary endpoint is pathological complete response in the per-protocol population. It will be summarized with the point estimate and corresponding exact 2-sided 95% confidence interval.

The secondary endpoint of progression free survival (PFS) will be assessed by Kaplan-Meier method utilizing the definition for progression defined in section 7.2.1.6. Participants who do not meet the criteria for progression will be censored at the last follow-up date. The median PFS will be estimated along with the corresponding 95% confidence interval.

Feasibility of treatment will be defined by the percentage of patients able to complete both neoadjuvant cycles of trial therapy and be able to complete surgical resection as planned.

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.

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.

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1. Internal Monitoring

Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

10.2 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3 Data Collection and Management Responsibilities

Data will be captured in OnCore and/or Moffitt's electronic Clinical Trials Management System. For each subject enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Clinical data will be entered directly from the source documents. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those subjects who fail to complete the study. If a subject stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a subject terminates from the study because of a DLT, thorough efforts should be made to clearly document the outcome.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

10.4 Study Records Retention

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when there is no longer a need for these documents to be retained. Permission must be acquired from the State of Florida for document destruction after the 10-year minimum record-retention period described above has elapsed.

10.5 Protocol Monitoring Committee

Protocol Monitoring Committee (PMC): The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

10.6 External Sites

10.6.1. Compliance to the Protocol and Adherence to Moffitt External Site Coordination Handbook

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Moffitt is responsible for monitoring each sites compliance to adherence to applicable Moffitt External Site Coordination Handbook. In coordination with the Monitoring office, the ESC Office assists to monitor compliance to the protocol.

10.6.2. External Site Access to Clinical Trial Database

To obtain access to OnCore, the External Site Coordinator will supply forms required to be completed by the site staff. Once the completed forms are received, the site coordinator will receive VPN access, logon/password, and information on how to access OnCore. The ESC office will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

10.6.3. Registration Procedures for External Sites

All external enrolled subjects must be registered with the External Site Coordination (ESC) office to be able to participate in a trial. The participating site must email the completed current eligibility checklist, registration form, all supporting documents, and signed, unredacted informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the ESC Coordinator will review them to confirm eligibility and complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the ESC Coordinator will provide the participating site with the study sequence number and, when applicable, randomization information. Within 48 hours after registration, it is the site's responsibility to:

Enter the on-study patient information into the Oncore database

Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with the patient registration form and supporting documentation to the ESC via email at ESC_Partnerships@Moffitt.org, Monday through Friday between 8:00AM and 5:00PM (EST). If a short turnaround time is required between registration and first treatment, please consider discussing this with you ESC Coordinator and, if possible, submit a partial submission.

10.6.4. Required Documentation for External Sites

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Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the External Site Coordination (ESC) office at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the ESC office for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the ESC staff for review and approval prior to resubmission to the IRB.

The ESC office must receive the following trial specific documents either by hardcopy or email before a site can be activated for any trial. All corresponding updates to these documents are required to be submitted to the ESC office throughout the trial:

- IRB Approval Letter that includes the protocol version and date
- FDA Form 1572 Protocol Signature Page
- Investigator Brochure (or Package Insert) Signature Page(s)
- IRB Approved Consent Form
- Site Delegation of Authority Log
- Signed Financial Interest Disclosure Forms (For all individuals listed on the 1572)
- Investigator/Personnel documents (CVs, licenses, GCP and HSP training certificates, etc.) as needed
- Laboratory Documents (certifications, normal ranges, etc.) as needed
- Signed Clinical Trial Agreement
- Protocol specific documentation as needed

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

The site PI and appropriate research staff

Moffitt PI and ESC Coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The ESC utilizes the EDC system, OnCore. OnCore training will be scheduled, if indicated, with the appropriate staff from the site.

External sites are required to send updated documentation to the ESC Office at ESC_Partnerships@Moffitt.org within 10 business days of updating.

10.6.5. SAE Reporting *Special Language for External Sites*

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to the sponsor expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE Report

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from OnCore must be signed and reported by email (ESC_Partnerships@moffitt.org) to the External Site Coordination (ESC) office within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to Financial Sponsors and government agencies.

10.6.6. External Site Monitoring and Reporting

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management. All monitoring efforts will occur based on the protocol specific monitoring plan.

Following each monitoring visit, a monitoring follow-up report will be provided to the Participating Site (i.e. Site PI and Coordinator). The monitoring report will summarize any issued queries or data clarification requests, identify any reportable events or required follow-up on prior events and will specify details of any non-compliance. Participating Sites are requested to respond to all queries and data clarifications requests within 20 business days. The Moffitt Cancer Center Protocol Monitoring Committee will review all monitoring reports and issue resolution. This Committee reserves the right to close accrual for non-compliance to monitoring.

11.0 REFERENCES

Bhatia S, Storer BE, Iyer JG, et al. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: survival analysis of 6098 cases from the National Cancer Database. *J Natl Cancer Inst.* 2016; 108(9)

Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol* 2004;173:945-54

D'Angelo SP, Russell J, Lebbe C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic merkel cell carcinoma: a preplanned interim analysis of a clinical trial. *JAMA Onc.* 2018; 4(9):e1800077

Ding T, Xu J, Wang F, Shi M, Zhang Y, Li SP, et al. High tumor-infiltrating macrophage density predicts poor prognosis in patients with primary hepatocellular carcinoma after resection. *Hum Pathol.* 2009;40:381-9.

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Disis ML. Immune regulation of cancer. *J Clin Oncol* 2010;28(29):4531-8.

Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. *J Clin Oncol* 2005;23(10):2346-57.

Fernandez-Figueras MT, Puig L, Musulen E, et al. Expression profiles associated with aggressive behavior in Merkel cell carcinoma. *Mod Pathol*. 2007;20(1):90-101.

Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. *Immunol Rev* 2010;236:219-42

Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol* 2005;23:515-48.

Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana-Farber experience and meta-analysis of the literature. *Arch Dermatol*. 2006; 142(6):685-90

Hodgson NC. Merkel cell carcinoma: changing incidence trends. *J Surg Oncol*. 2005; 89(1): 1-4.

Heusinkveld M, van der Burg SH. Identification and manipulation of tumor associated macrophages in human cancers. *J Transl Med*. 2011;9:216. doi: 10.1186/1479-5876-9-216. eCollection 2016.

Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. *N Engl J Med* 2008;358(25):2698-703.

Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. *Nat Rev Cancer*. 2009;9(4):239-52.

Kato Y, Tabata K, Kimura T, et al. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8+ T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. *Plos One*. 2019; 14(2): e0212513.

Knepper TC, Montesion M, Russell JS, et al. The genomic landscape of Merkel cell carcinoma and clinicogenomic biomarkers of response to immune checkpoint inhibitor therapy. *Clin Cancer Res*. 2019; epub.

Lantis E, Irving M, Coukos G. Targeting the tumor vasculature to enhance T cell activity.

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Curr Opin Immunol. 2015;33:55-63.

Lemos B, Nghiem P. Merkel cell carcinoma: more deaths but still no pathway to blame. *J Invest Dermatol.* 2007. 127(9):2100-3.

Makker V, Rasco D, Vogelzang NJ, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicenter, open-label, single arm, phase 2 trial. *Lancet Oncol.* 2019; 20(5):711-718.

Nghiem P, Bhatia S, Lipson EJ, et al. Durable tumor regression and overall survival in patients with advanced merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol.* 2019; 37(9):693-702.

Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity.* 2014;41(1):49-61.

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proc Natl Acad Sci U S A* 2001;98(24):13866-71.
Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. *Nature Rev Cancer* 2004;4:71-8.

Ott PA, Hodi FS, Buchbinder EI. Inhibition of immune checkpoints and vascular endothelial growth factor as combination therapy for metastatic melanoma: an overview of rationale, preclinical evidence, and initial clinical data. *Front Oncol.* 2015;5:202. doi: 10.3389/fonc.2015.00202. eCollection 2015.

Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 2005;25(21):9543-53.

Riabov V, Gudima A, Wang N, Mickley A, Orekhov A, Kzhyshkowska J. Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis. *Front Physiol.* 2014;5:75. doi: 10.3389/fphys.2014.00075.eCollection 2014.

Riley JL. PD-1 signaling in primary T cells. *Immunol Rev* 2009;229:114-25.

Ritchie G, Gasper H, Man J, et al. Defining the most appropriate primary end point in phase 2 trials of immune checkpoint inhibitors for advanced solid cancers: a systemic review and meta-analysis. *JAMA Oncol.* 2018; 4(4): 522-528.

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017;18(3):e143-e152. Epub 2017 Mar 2.

Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits

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T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett.* 2004;574:37-41.

Takase N, Koma Y, Urakawa N, Nishio M, Arai N, Akiyama H, et al. NCAM- and FGF-2- mediated FGFR1 signaling in the tumor microenvironment of esophageal cancer regulates the survival and migration of tumor-associated macrophages and cancer cells. *Cancer Lett.*;380(1):47-58.

Taylor M, Dutcus CE, Schmidt E, et al. A phase Ib trial of lenvatinib plus pembrolizumab in patients with selected solid tumors. *Ann Oncol*, 27 (2016) p776PD

Topalian SL, Bhatia S, Kudchadkar RR, et al. Nivolumab as neoadjuvant therapy in patients with resectable Merkel cell carcinoma in CheckMate 358. *J Clin Oncol.* 2018; 36(15_suppl):9505

Yang J, Yan J, Liu B. Targeting VEGF/VEGFR to modulate antitumor immunity. *Front Immunol.* 2018;9:978. doi: 10.3389/fimmu.2018.00978. eCollection 2018.

Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity* 2004;20:337-47.

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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.: <i>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.</i>	

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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 in section X:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 9 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.

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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 in Section X.

Table 10 Highly Effective Contraception Methods

<p>Highly Effective Contraceptive Methods That Are User Dependent ^a <i>Failure rate of <1% per year when used consistently and correctly.</i></p>
<ul style="list-style-type: none"> Combined (estrogen- and progestogen- containing) hormonal contraception ^{b, c} <ul style="list-style-type: none"> Oral Intravaginal Transdermal Injectable
<ul style="list-style-type: none"> Progestogen-only hormonal contraception ^{b, c} <ul style="list-style-type: none"> Oral Injectable
<p>Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i></p>
<ul style="list-style-type: none"> Progestogen- only contraceptive implant ^{b, c} Intrauterine hormone-releasing system (IUS) ^b Intrauterine device (IUD) Bilateral tubal occlusion
<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> 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.)
<p>Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.</p> <p>a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly).</p>

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- 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 30 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 and in accordance with local requirements. When applicable this test should be repeated a maximum of 24-hours before the first dose/vaccination.

Following initiation of treatment additional pregnancy testing will be performed at monthly intervals during the treatment period and at 30 days after the last dose of study treatment and as required locally.

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