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Pembrolizumab and Lenvatinib in Advanced/Metastatic Neuroendocrine Prostate Cancer

Phase II trial of Pembrolizumab and Lenvatinib in Advanced/metastatic Neuroendocrine Prostate Cancer [PLANE-PC]

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PROTOCOL SIGNATURE PAGE

Phase II trial of Pembrolizumab and Lenvatinib in Advanced/metastatic Neuroendocrine Prostate Cancer [PLANE-PC]

VERSION DATE: 30JUN2022

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____

Signature of Site Investigator Date

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Site Investigator Name (printed)

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Site Investigator Title

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Name of Facility

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Location of Facility (City and State)

PLEASE COMPLETE AND EMAIL A COPY TO HCRN

SYNOPSIS

TITLE	Phase II trial of Pembrolizumab and Lenvatinib in Advanced/metastatic Neuroendocrine Prostate Cancer [PLANE-PC]
SHORT TITLE	Pembrolizumab and lenvatinib in neuroendocrine prostate cancer
PHASE	II
OBJECTIVES	**Primary Objective** Evaluate 6 month radiographic progression free survival (rPFS) rate with lenvatinib and pembrolizumab combination therapy in metastatic neuroendocrine prostate cancer (NEPC). **Secondary Objectives** • Assess the safety of pembrolizumab and lenvatinib combination therapy in metastatic neuroendocrine prostate cancer (NEPC). • Assess overall survival (OS). • Assess objective response rate (ORR). • Assess duration of response (DoR).
STUDY DESIGN	An open label phase II study design of lenvatinib and pembrolizumab in metastatic NEPC is planned with primary endpoint of 6- month radiologic progression-free survival (rPFS) rate.
STATISTICAL CONSIDERATIONS	A 2-stage Simon near optimal statistical study design will be used for the binary primary endpoint of 6-month rPFS (yes/no). The design uses these input parameters: p0 = 0.10; p1 = 0.25; alpha = 0.125; and power = 0.90. If there are at least 3 successes in the 27 patients in Stage 1 the study will proceed to Stage 2, otherwise it will terminate early due to insufficient efficacy. If there are at least 7 successes in the final total of 40 patients, the treatment will be considered promising. To allow for up to 20% of registered patients becoming non evaluable, up to 50 patients will need to be enrolled to yield 40 evaluable patients. It may become necessary to temporarily suspend accrual at or near the completion of Stage 1 of the study in order to evaluate the 6-month rPFS (primary endpoint) of the last few Stage 1 patients.
TOTAL NUMBER OF SUBJECTS	N = 40 evaluable, Up to 50 total accrual

ESTIMATED ENROLLMENT PERIOD	Estimated 38 months of accrual.
ESTIMATED STUDY DURATION	Estimated 44 months to meet primary endpoint.

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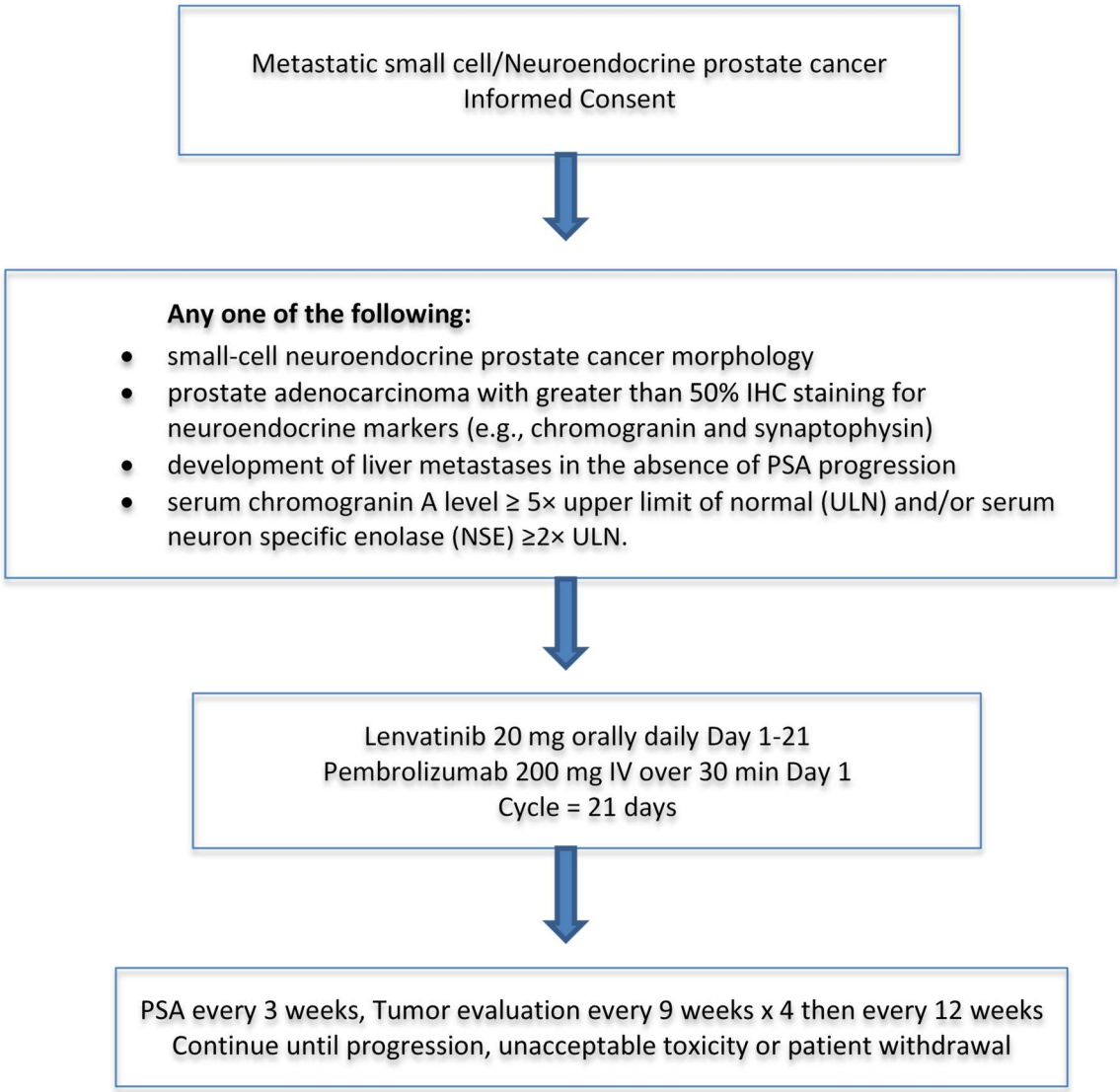
SCHEMA


Metastatic small cell/Neuroendocrine prostate cancer
Informed Consent
Any one of the following:
small-cell neuroendocrine prostate cancer morphology
prostate adenocarcinoma with greater than 50% IHC staining for neuroendocrine markers (e.g., chromogranin and synaptophysin)
development of liver metastases in the absence of PSA progression
serum chromogranin A level ≥ 5× upper limit of normal (ULN) and/or serum neuron specific enolase (NSE) ≥2× ULN.
Lenvatinib 20 mg orally daily Day 1-21
Pembrolizumab 200 mg IV over 30 min Day 1
Cycle = 21 days
PSA every 3 weeks, Tumor evaluation every 9 weeks x 4 then every 12 weeks
Continue until progression, unacceptable toxicity or patient withdrawal

1. BACKGROUND AND RATIONALE

1.1 Disease Background

Metastatic prostate cancer remains an incurable, terminal prognosis and within this, small cell type is a particularly lethal and aggressive form with few therapeutic options [1]. Recent advances in advanced prostate adenocarcinoma have not benefitted patients with small cell/neuroendocrine prostate cancer (NEPC) whether de novo small cell or treatment induced. As resistance develops, the neuroendocrine component emerges as the predominant driver of metastases. Abiraterone or enzalutamide treatment induced neuroendocrine prostate cancer has been reported. The morphologic and molecular features of NEPC are quite distinct from adenocarcinoma of the prostate. NMYC amplification can elicit transformation of the prostate epithelium to NEPC. Aurora kinase overexpression is frequently noted, but an aurora kinase inhibitor that was evaluated revealed only modest efficacy [2]. Overall a critical unmet need exists for the development of effective therapies in NEPC.

NEPC is typically resistant to hormone therapies and to standard taxane based chemotherapy regimens used in advanced prostate adenocarcinoma. One of the reasons is that lineage plasticity is noted with conversion from luminal epithelial cells to basal androgen independent cells. Sox 2 overexpression and Rb and p53 loss have been reported to create this lineage plasticity. N-Myc overexpression has also been attributed to neuroendocrine differentiation of prostate cancer. A review of clinical characteristics and outcomes of either de novo small cell prostate cancer or high-grade neuroendocrine transformation from prostate adenocarcinoma are that prognosis is poor and median survival is about 15 months. The front line therapy is platinum and etoposide chemotherapy which was noted to have a 48% objective response rate and median PFS of 6.5 months [3] The results of second line therapy demonstrated limited efficacy and clinical impact.

Pembrolizumab has been evaluated in small cell lung cancer and demonstrated efficacy [4]. In a study conducted in 107 patients with extensive small cell lung cancer who had failed standard therapy, the overall response rate was 18.7% (20/107; 95% CI, 11.8–27.4) with 35.7% response rate in pts with PD-L1–positive tumors, and 6.0% (3/50; 95% CI, 1.3–16.5) in PD-L1–negative tumors. 77% had durable remissions at 9 months or greater.

Lenvatinib is a multitargeted kinase that is currently FDA approved in hepatocellular cancer and advanced endometrial cancer. It is also approved in combination with everolimus for advanced kidney cancer. The agent has demonstrated promising tumor regression effects in a small cell lung cancer tumor model; H 146. The tumor shrinkage was affected through stem cell factor (SCF) induced angiogenesis inhibition. In a murine immunocompetent model of anaplastic thyroid cancer, lenvatinib monotherapy increased tumor-infiltrating macrophages, CD8+ T-cells, regulatory T-cells, and most notably, polymorphonuclear myeloid derived suppressor cells (PMN-MDSCs). While combination with other therapies led to increases in CD8+ T-cells, only the lenvatinib and anti-PD-1 combination decreased PMN-MDSCs [5]. Increased tumor shrinkage and longer survival was noted with the combination as compared to lenvatinib monotherapy. Similar results were noted in hepatocellular carcinoma xenograft model. Lenvatinib has immunomodulatory activity that contributes to the antitumor activity enhanced by treatment with anti-PD-1 antibody which results in increased CD8+ve lymphocytes and depleted monocytes and MDSC. Lenvatinib demonstrated single agent activity in pancreas and

gastrointestinal neuroendocrine tumors. The preliminary efficacy showed disease stabilization rates of 55.7% and 76% with median progression free survival of 16.5 months [6]. Phase I/II studies of lenvatinib and pembrolizumab have been conducted in multiple malignancies. The results revealed predominant toxicities of decreased appetite (67%), fatigue (62%), hypothyroidism (43%), diarrhea (43%), proteinuria (43%), arthralgia (33%) and hypertension (33%). Tolerability and promising efficacy were noted in metastatic melanoma, renal cancer and urothelial cancer cohorts regardless of PD-L1 status. A large randomized trial in advanced renal cancer contained the lenvatinib and pembrolizumab combination as one of the arms. Since this trial recently completed accrual without interruption, the tolerability of the combination is noted in a multicenter setting. These preclinical and clinical trial results provide robust rationale for the proposed phase II trial in NEPC.

1.2 Current Standard of Care

No standard of care exists at present for this disease after platinum and etoposide combination.

1.3 Lenvatinib (E7080); LENVIMA; KISPLYX

1.3.1 Therapeutic Indications

Lenvatinib is indicated for the treatment of patients with progressive, RAI-RDTC and for the treatment of patients with HCC. Lenvatinib is indicated in combination with everolimus for the treatment of patients with advanced RCC in the EU following one prior anti-angiogenic therapy. It has also received recent FDA approval in combination with pembrolizumab for treatment of advanced endometrial cancer.

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Co-crystal structural analysis demonstrated that lenvatinib has a distinct mode of the interaction with VEGFR2 or FGFR1, termed Type V, while most of the known kinase inhibitors on market are categorized as Type I or II (Okamoto, et al., 2015). Lenvatinib binds to ATP-binding site and the neighboring allosteric region in the kinase domain adopting the DFG-in conformation. Most of the known kinase inhibitors are categorized as Type I, binding these kinases in the DFG-in configuration and only binding to the ATP-binding site, or Type II binding to the kinase in the DFG-out conformation and binding to both the ATP-binding site and the neighboring regions. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to very important for tumor angiogenesis. Lenvatinib inhibited cell free kinase activities for VEGFR1 – 3 and FGFR1 – 3 with Ki values around 1 nmol/L, and 8 – 22 nmol/L, respectively. In cell based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC50 values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model (Yamamoto, et al., 2014). In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and MTC), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and

osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone. Therefore, lenvatinib is being developed as an anticancer therapy for use either as a single agent or in combination with other anticancer agents for the treatment of malignancies including thyroid cancer, RCC, HCC, and endometrial cancer. The results of the cell-based assays, as well as the results of various murine in vivo models (Yamamoto, et al., 2014; Tohyama et al., 2014) suggest that in most tumors, the mode of action for lenvatinib antitumor activity is primarily related to the inhibition of both VEGF and FGF- dependent angiogenesis. For several thyroid cancers where RET kinase is constitutively activated, direct antitumor activity of lenvatinib is postulated to be important in the model of action. In subjects with RCC, our Study E7080-G000-205 demonstrated that the combination of lenvatinib and everolimus, an mTOR targeting agent improved PFS compared to everolimus alone (Motzer, et al., 2015). This clinical evidence is supported by the nonclinical in vitro and in vivo studies, which suggested a dual targeting of mTOR-S6KS6 pathway by lenvatinib and everolimus. The malignancies for which treatment with lenvatinib will be investigated are those in which lenvatinib has demonstrated nonclinical or clinical antitumor activity. An effective oral, QD outpatient treatment regimen that is well tolerated, with toxicities that are easily managed with standard therapies or dose reduction/interruption, would be an important advancement in the treatment of patients with thyroid cancer (Schlumberger, et al., 2014; Dunn and Fagín, 2015; Cully, 2015), RCC (Motzer, et al., 2015), HCC, endometrial cancer, melanoma, glioblastoma, ovarian cancer, and nonsquamous NSCLC.

1.3.2 Lenvatinib (Lenvima) Dose Justification

A variety of doses have been used for the different clinical uses of lenvatinib [7]. The starting dose utilized for single agent lenvatinib was 24 mg once daily in thyroid cancer trials and 12 mg and 8 mg once daily respectively for patients with advanced hepatic cancers with body weight >60 kg and < 60 kg. In renal cancer lenvatinib 18 mg oral daily dose in combination with everolimus 5 mg daily demonstrated improved efficacy and received FDA approval. Keynote 146 was a phase IB/II trial conducted in metastatic endometrial cancer that used a combination of lenvatinib 20 mg oral daily dose and pembrolizumab 200 mg IV every 21 days. The combination received accelerated FDA approval in 2019 and safety is well established in this trial. Since the same combination is being evaluated in the current proposed trial the starting dose of lenvatinib in this trial is 20 mg orally daily.

1.4 Pembrolizumab

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

1.4.1 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 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 (CD3ζ), protein kinase C-theta (PKCθ), 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 neuroendocrine metastatic prostate cancer.

1.4.2 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 in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells. Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

1.5 Hypothesis

The clinical hypothesis is that the combination of lenvatinib and pembrolizumab will provide at least an absolute 15% improvement in 6 month radiologic PFS as compared to historical controls or as noted in contemporary phase II studies conducted in this patient population.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Evaluate 6 month radiographic progression free survival (rPFS) with lenvatinib and pembrolizumab combination therapy in metastatic neuroendocrine prostate cancer (NEPC).

2.1.2 Secondary Objectives

- Assess the safety of pembrolizumab and lenvatinib combination therapy in metastatic neuroendocrine prostate cancer (NEPC).
- Assess overall survival (OS).
- Assess objective response rate (ORR).
- Assess duration of response (DoR).

2.1.3 Correlative/Exploratory Objectives

- Correlate genomic sequencing results with clinical outcomes in the study population.
- Correlate PDL-1 status and tumor mutation burden with clinical outcomes.
- Correlate gut microbiome data with clinical outcomes.

2.2 Endpoints

2.2.1 Primary Endpoint

- Evaluate the clinical efficacy as defined by 6-month radiologic progression free survival rate (rPFS).
    - For soft tissue lesions, rPFS is defined as the date of Cycle 1 Day 1 to date of radiologic progression of soft tissue lesions per RECIST 1.1 or death whichever occurs first.
    - For bone lesions, rPFS is defined as the date of Cycle 1 Day 1 to date of progression of bone lesions per PCWG3 criteria or death whichever occurs first.

  NOTE: the "date of progression" is the earlier date of either of those two possible types of progression.

2.2.2 Secondary Endpoints

- Safety of the combination will be assessed based on Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Overall survival (OS) will be measured from date of registration to date of death from any cause.
- ORR will be the proportion of patients achieving either a complete response or a partial response, among all patients meeting the criteria of Section 12.6, as well as among all patients enrolled.
- DOR will be measured from the start date of the best response achieved until the date of relapse (i.e., progression).

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information prior to registration. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days prior to the date of registration.

4. The subject has histologically proven prostate cancer with radiologic evidence of metastases and at least one of the following:
    - Small-cell or NEPC morphology (determined by the enrolling center) on the basis of tissue sample.
    - Prostate adenocarcinoma with IHC staining for neuroendocrine markers (e.g., chromogranin and synaptophysin).
    - Presence of visceral metastases or high volume disease (> 4 sites of metastases) with a PSA ≤ 5.
    - Serum chromogranin A level ≥ 5× upper limit of normal (ULN) and/or serum neuron specific enolase (NSE) ≥ 2× ULN.
    - RB1 deletions or mutations noted on genomic testing
    - Trans-differentiated carcinoma or poorly-differentiated carcinoma

5. Subject has adequate organ function as defined in the table below; all screening labs to be obtained within 10 days prior to Cycle 1 Day 1.
    - Absolute neutrophil count (ANC) ≥ 1500/mm^{3}without colony stimulating factor support
    - Platelets ≥ 100,000/mm^3
    - Hemoglobin ≥ 9 g/dL. Transfusions are allowed as needed.
    - Serum creatinine ≤ 1.5 × ULN or creatinine clearance (CrCl) ≥ 30 mL/min. For creatinine clearance estimation, the Cockcroft and Gault equation should be used.
    - Bilirubin ≤ 1.5 × the upper limit of normal (ULN) OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN. For subjects with known Gilbert's disease, bilirubin ≤ 3.0 mg/dL
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN if no liver involvement, or ≤ 5 × ULN with liver involvement
    - International normalized ratio (INR) OR prothrombin time (PT), Activated partial thromboplastin time (aPTT) ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
    - Urine protein < 2+ by urine dipstick

6. A male participant must agree to use of contraception during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period.

7. Projected life expectancy of at least 6 months as determined by treating physician.

8. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.2 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Received prior therapy with VEGF-TKI, immune checkpoint inhibitor, 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).

2. Received prior systemic anti-cancer therapy including investigational agents within 3 weeks prior to registration. **NOTE:** Participants must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Participants with ≤ 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.

3. Received more than two prior chemotherapy regimens for metastatic prostate cancer. Prior therapy with androgen receptor axis targeted agents is allowed but needs to be discontinued at least 2 weeks prior to study therapy. Prior therapy with Rad-223 or other radiopharmaceuticals is permitted but study therapy should be started at least 4 weeks after the last dose.

4. Concurrent treatment with anti-androgen medications. **NOTE:** LHRH agonists and GNRH antagonists may be continued. All oral anti androgens should be discontinued.

5. 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 (≤ 2 weeks of radiotherapy) to non-CNS disease.

6. Currently participating in or has participated in a study of an investigational agent or has used an investigational device within 3 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 3 weeks after the last dose of the previous investigational agent.

7. Uncontrolled blood pressure (Systolic BP>140 mmHg or diastolic BP >90 mmHg) despite an optimized regimen of antihypertensive medication.

8. Presence of non-healing wounds after surgical procedures.
9. Known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.

10. Received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed viruses are allowed. All COVID-19 vaccines are permitted at any time before or during the study.

11. 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.

12. 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.

13. 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.

14. 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.

15. Severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.

16. Severe hypersensitivity (≥ Grade 3) to lenvatinib and/or any of its excipients.

17. 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. Replacement steroids for adrenal insufficiency or daily dose equivalent of 10 mg prednisone are allowed.

18. History of severe (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.

19. Active uncontrolled infection.

20. 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 or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Subjects with other solid tumors treated curatively and without evidence of recurrence for at least 2 years prior to enrollment may be eligible for study after discussion with the sponsor-investigator.

21. Known history of Human Immunodeficiency Virus (HIV). **NOTE:** HIV testing is not required unless mandated by a local health authority.

22. 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:** Hepatitis B and Hepatitis C testing is not required unless clinical history indicates that this is likely.

23. Known history of active TB (Bacillus Tuberculosis).

4. SUBJECT REGISTRATION

All subjects must be registered through HCRN's electronic data capture (EDC) system. A subject is considered registered when an "On Study" date is entered into the EDC system. Subjects must be registered prior to starting protocol therapy. Protocol therapy must begin **within 5 business days** of study registration.

5. TREATMENT PLAN

Eligible patients will be treated with the combination of lenvatinib and pembrolizumab. A cycle equals 21 days and therapy will continue until radiographic progression, intolerable toxicity, or patient/physician wishes to discontinue protocol therapy. A maximum of 35 cycles may be administered. On Day 1, when both pembrolizumab and lenvatinib are administered, patients should take the lenvatinib per their normal routine.

If measurable disease is present, response will be assessed by RECIST 1.1 criteria. For bone only metastases at least 2 new areas of metastases will qualify as progression, and PSA response will be also reported per Prostate Cancer working Group 3 guidelines. Section 7 calendar outlines the schedule for assessments.

5.1 Study Treatment Administration

Drug	Dose	Route	Schedule	Cycle Length
Lenvatinib	20 mg	Orally	Day 1-21	3 weeks (21 days)
Pembrolizumab	200 mg	Intravenously (IV) over 30 minutes	Day 1	

A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2 Lenvatinib

Lenvatinib can be taken orally with or without food once daily. For subjects that cannot swallow the capsule: Use a medicine cup to measure about one tablespoon of water or apple juice and place into a small glass. Place the lenvatinib capsules into the small glass without breaking or crushing them. Leave the capsules in the liquid for at least 10 minutes. Stir the contents of the glass for at least 3 minutes. Drink the mixture. After drinking, rinse the glass with a small amount of additional water or apple juice and swallow the liquid. If a dose is missed and cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Optimal medical management for nausea, vomiting, and/or diarrhea should be initiated prior to any lenvatinib therapy interruption or dose reduction; however, gastrointestinal toxicity should be actively managed in order to reduce the risk of development of renal impairment or renal failure.

NOTE: Diaries will be provided to subjects for completion of oral medication administration. Subjects will be asked to bring the diary and medication container to each clinic visit. Dose modification guidelines can be found in Section 6.

5.3 Pembrolizumab

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).

5.4 Concomitant Medications

5.4.1 Allowed 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. Bisphosphonate therapy can be continued. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded if associated with SAEs and ECIs as defined in Section 11.

5.4.2 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 and lenvatinib
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (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-investigator.

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

5.5 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. 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 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.

5.6 Reproductive Information

5.6.1 Male Recipients

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 3.1:

- 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 above 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.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Modifications for Lenvatinib

Management of some adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib therapy. Upon resolution/improvement of an adverse reaction, treatment should be resumed at a reduced dose. Mild to moderate adverse reactions (eg, Grade 1 or 2) generally do not warrant interruption of lenvatinib or of the combination, unless intolerable to the patient despite optimal management. Severe and clinically relevant (eg, Grade 3 or 4) or intolerable adverse reactions that are considered to be possibly, probably or definitely related to lenvatinib, pembrolizumab or both require interruption of lenvatinib or the combination until improvement of the reaction to Grade 0-1 or baseline.

For lenvatinib-related toxicities, upon resolution/improvement of an adverse reaction to Grade 0-1 or baseline, treatment of lenvatinib should be resumed with one level dose reduction as outlined in the Table below. For patients deriving clinical benefit and persistent toxicities at the lowest (-3) dose of lenvatinib, please contact the sponsor-investigator and HCRN for consideration of lowering the dose further. No dose re-escalation is allowed unless discussion with the sponsor-investigator and HCRN occurs and approval is obtained.

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

6.1.1 Dose Levels for Dose Reductions of Lenvatinib

Dose level	Dose of Lenvatinib
Starting Dose	20 mg
Dose level (-1)	14 mg
Dose level (-2)	10 mg
Dose level (-3)	8 mg

6.2 Dose Modifications for Pembrolizumab

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, 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/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 1.

Table 1: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO Combinations

General instructions:

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

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
				• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	Grade 3 or 4	Withhold or permanently discontinue [d]	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

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

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

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

6.3 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 reactions are provided below.

Table 2: Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	No subsequent dosing

	Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

6.3 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset
   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:
   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

   If the subject recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE
   If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:
   - ALT or AST >5 X ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per the Table above, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
   - ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
     Although the Table above advises pembrolizumab to be withheld (interrupted), and advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.4 Protocol Therapy Discontinuation

In addition to discontinuation from therapy related to toxicities as outlined above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF)

- Completion of maximum of 35 cycles of study treatment.
- Documented disease progression per RECIST 1.1 (subjects with measurable disease) or PCWG (subjects without measurable disease). If a subject is receiving clinical benefit (as determined by treating physician), treatment can continue after discussion with sponsor-investigator.
- Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy, whether due to unacceptable toxicity or for other reasons
    - In a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- If protocol therapy (both drugs) is interrupted for ≥ 42 days from the expected day of the next treatment. If one drug is permanently discontinued, treatment with the other drug may continue at investigator discretion.

6.5 Protocol Discontinuation

If a subject decides to discontinue from the protocol (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. A complete final evaluation at the time of the subject's protocol withdrawal should be made with an explanation of why the subject is withdrawing from the protocol. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

6.6 Safety Follow Up

The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. 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. The Day 90 assessment may be performed via phone call, email or other avenues as appropriate.

6.7 Long Term Follow Up

For subjects who discontinue for reasons other than progressive disease, radiographic disease assessment should be performed per discretion of the site investigator per standard of care for disease assessment. The scan interval may be reset if scans were done sooner for clinical reasons and the type of scan may be left to discretion of the site investigator. This imaging may be done locally. Follow up for these subjects will occur every 6 months until progression. Once disease progression is documented, subjects will be followed for survival every 6 months for 5 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone

call, or other avenues as appropriate. A window of ± 14 days will be applied to long term follow up.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening[10]	Cycle 1	Cycle 2+	Safety follow up visit[8]	Long-term Follow up[9]
	-28 days from C1D1	Day 1 ± 3 days	Day 1 ± 3 days	30/90 days post last dose + 7 days	Every 6 months (±14 days)
REQUIRED ASSESSMENTS					
Informed Consent	X				
Medical History and Disease Staging[1]	X				
Physical Exam	X	X	X	D30	
Vital signs and ECOG Performance Status[2]	X	X[2]	X[2]	D30	
ECG[2]	X	X[2]	X[2]		
AEs & concomitant medications	X	X	X	X	
LABORATORY ASSESSMENTS					
Complete Blood Cell Count with diff (CBC)[3]	X	X[10]	X	D30	
Comprehensive Metabolic Profile (CMP)[3]	X	X[10]	X[3]	D30	
PT/INR and aPTT[3]	X				
Thyroid Function Testing[3]	X		X[3]		
Urine protein[3]	X		X[3]		
Chromogranin A, neuron specific enolase and urine NTx[4]	X		X[4]	D30	
Prostate-specific antigen (PSA)[4]	X		X	D30	X[4]
Testosterone[4]	X			D30	
DISEASE ASSESSMENT					
CT of chest[5]	X		X[5]	D30[5]	X[5]
CT or MRI of abdomen and pelvis[5]	X		X[5]	D30[5]	X[5]
MRI Brain[5]	X		X[5]	D30[5]	X[5]
Bone scan[5]	X		X[5]	D30[5]	X[5]
TREATMENT EXPOSURE					
Lenvatinib		D1-21	D1-21		
Pembrolizumab		X	X		
SPECIMEN COLLECTION					
Archival Tumor Tissue[6]	X[6]				
Blood for somatic baseline		X			
Blood for plasma[7]		X[7]		D30[7]	
Stool for microbiome[7]		X[7]			
FOLLOW-UP					
Survival Status, Subsequent Therapy					X

Key to Footnotes

1: Medical History; other data to obtained during this assessment includes a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. Prior genomic sequencing and PD-L1 results are required if available. Diagnosis and staging to include pathology report and imaging reports.

2: Vital signs to include temperature, pulse, respirations, blood pressure, weight, and height (screening only) and ECOG performance status. Blood pressure should be monitored after 1 week of treatment with lenvatinib (around C1D7), then every 2 weeks for the first 2 months (C2D1 at clinic visit and C2D14) and Day 1 of every cycle thereafter while on treatment. If a subject develops systolic BP ≥140 mmHg or diastolic BP ≥ 90 mmHg active management is indicated. Monitoring may be done locally by clinic visit, at home BP monitoring or similar. Subjects will be asked to maintain a record of BP readings and communicate results to research staff at timepoints as outlined above. ECG to be performed at screening then as clinically indicated during study treatment per investigator discretion.

3: CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; calcium, albumin, and liver function tests (LFTs). LFTs to include AST, ALT, total bilirubin, and alkaline phosphatase; LFTs will be monitored every 2 weeks for 2 months (C1D14, C2D1, C2D14, C3D1). PT/INR and PTT should be obtained at screening then at site investigator discretion. Thyroid Function testing should be performed at screening then every 4 cycles (12 weeks). TSH should be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. Urine protein should be obtained at screening then every 3 cycles (9 weeks). If urine dipstick ≥2+ is detected, dose interruptions, adjustments, or discontinuation may be necessary.

4: Chromogranin A, neuron specific enolase and urine NTx (optional) will be performed at screening/day 1 then prior to treatment every other Cycle starting at Cycle 3 Day 1 then at the D30 safety visit. PSA should be obtained at screening then prior to treatment every Cycle then at the D30 safety visit. Subjects that come off study without progression should have PSA obtained per investigator discretion. Testosterone will be performed at screening and at the D30 safety visit.

5: Tumor response assessment will consist of evaluation by CT scans of chest and MRI or CT of abdomen and pelvis. If a PET/CT is done for tumor assessment and if tumor/s are visible on the CT, this may be used for tumor evaluation. A bone scan will be obtained at screening and with other radiology imaging at the frequency as outlined below. An MRI of the brain should be performed at screening if there is a concern for the presence of brain metastases. Tumor imaging will be done at screening and every 3 cycles (9 weeks) for the first 12 cycles (36 weeks) and then every 4 cycles (12 weeks) until the patient is off study therapy (window of ± 1 week). Tumor imaging should follow week intervals in the case of study treatment delays due to toxicities. During follow up after completion of study treatment, imaging frequency is at the discretion of the site investigator. Imaging selected for each subject should remain the same throughout the study. Tumor imaging to be done at treatment discontinuation/safety follow up visit is at discretion of site investigator. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated.

6: Archival tissue obtained within 12 months of registration is required if available. Archival tissue should be identified at screening and shipped prior to Cycle 2 Day 1 treatment. If not available, the patient may still be eligible after discussion with the sponsor-investigator. These samples will be stored for correlative analysis which may include PD-1/PD-L1 expression, tumor mutation burden, and next generation sequencing to evaluate genomic markers once funding is available. Subjects will also be consented for optional storage of any remaining tissue/blood samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered "banking samples". See Correlative Laboratory Manual (CLM) for additional details regarding correlative samples.

7: Peripheral blood samples will be collected prior to treatment (1) Cycle 1 Day 1, (2) Cycle 3 Day 1 (9 weeks) and (3) at progression. For subjects that discontinue treatment for progression, these samples may be collected at the D30 safety visit. Plasma will be stored for circulating tumor DNA (ctDNA) and miRNA analysis once funding is available. Whole blood samples will also be collected prior to treatment (1) Cycle 1 Day 1 and stored for somatic baseline testing once funding is available. Stool for microbiome will be collected prior to (1) Cycle 1 Day 1 treatment and stored for correlative analysis once funding is available. Subjects will be provided instructions after consent during screening and asked to bring the sample back prior to C1D1 treatment. Subjects will also be consented for optional storage of any remaining tissue/blood/stool samples after protocol-specified studies are complete. These samples will be stored for future unspecified cancer-related research and are considered "banking samples". See Correlative Laboratory Manual (CLM) for additional details regarding correlative samples.

8: Safety Follow Up: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of treatment. 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. The Day 90 assessment may be performed via phone call, email or other avenues as appropriate.

9: Long Term Follow Up: For subjects who discontinue for reasons other than progressive disease, radiographic disease assessment should be performed per discretion of the site investigator per standard of care for disease assessment. The scan interval may be reset if scans were done sooner for clinical reasons and the type of scan may be left to discretion of the site investigator. This imaging may be done locally. Follow up for these subjects will occur every 6 months until progression. Once disease progression is documented, subjects will be followed for survival every 6 months for 5 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate. A window of ± 14 days will be applied to long term follow up.

10: Screening labs as outlined in Section 3 of the inclusion criteria must be performed within 10 days of C1D1. If screening (baseline) CBC and CMP were performed within 7 days of Day 1 of treatment, these do not need to be repeated. All laboratory assessments should be done prior to treatment.

8. BIOSPECIMEN STUDIES AND PROCEDURES

Please refer to the Correlative Laboratory Manual (CLM) for all sample collection, processing, labeling, and shipping instructions of samples outlined below.

8.1 Tissue

Tissue samples will be stored for future correlative analysis which may include PD-1/PD-L1 expression, tumor mutation burden, RNA and next generation sequencing to evaluate genomic markers once funding is available.

8.1.1 Archival Tissue

Archival tissue is required if available. Archival tissue should be identified at screening and shipped prior to Cycle 2 Day 1 treatment.

8.2 Peripheral Blood Samples

8.2.1 Plasma for Circulating Tumor DNA and miRNA

Peripheral blood samples will be collected prior to treatment Cycle 1 Day 1, prior to Cycle 3 Day 1 and at progression. For subjects that discontinue treatment for progression, these samples may be collected at the D30 safety visit. Plasma will be stored for possible ctDNA and miRNA analysis once funding is available.

8.2.2 Whole Blood for Somatic Baseline

Whole blood samples will be collected prior to treatment Cycle 1 Day 1 and stored for future correlative analysis once funding is available.

8.3 Stool for Microbiome

Stool for microbiome will be collected prior to Cycle 1 Day 1 treatment and stored for correlative analysis once funding is available.

8.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. Hoosier Cancer Research Network (HCRN) will manage the banked samples. Samples will be coded and banked indefinitely in the Hoosier Cancer Research Network Biorepository and used for future unspecified cancer-related research.

8.5 Confidentiality of Biospecimens

Samples will be identified by the subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

RECIST 1.1 criteria will apply to subjects with measurable disease. For patients with non-measurable disease the PCWG3 criteria will be utilized for response assessment. PSA response and progression will also be evaluated per PCWG3 criteria. [9]

9.1 Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

9.1.1 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

9.2 Non-measurable Lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.4 Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1[8] (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

9.8 Definitions for Response and Survival Evaluation

9.8.1 Time to Response (TTR)

The time between initiation of therapy and first documentation of PR or CR.

9.8.2 Radiologic Progression Free Survival (rPFS)

rPFS has two components to its definition. For soft tissue lesions, rPFS will be measured from Cycle 1 Day 1 to date of radiologic progression per RECIST 1.1 or death from any cause, whichever occurs first. For bone lesions (non-measurable disease), rPFS will be measured from Cycle 1 Day 1 to date of progression per PCWG3 criteria [9] or death from any cause, whichever occurs first. Thus, the "date of progression" is the earlier date of either of those two possible types of progression. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

9.8.3 Overall survival

Overall survival (OS) will be measured from Cycle 1 Day 1 to date of death from any cause. Patients still alive will be right-censored as of the most recent date on which they were last confirmed (by any of the methods listed) to be alive.

9.8.4 Duration of Response (DoR)

DOR will be measured from the start date of the best response achieved until the date of relapse (i.e., progression). Continuing responders will be right-censored as of the most recent date on which their response status had been assessed. DoR applies to only the patients who achieve either a complete response (CR) or a partial response (PR).

10. DRUG INFORMATION

10.1 Pembrolizumab

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

10.1.1 Supplier/How Supplied

Merck will supply pembrolizumab from commercial stock at no charge to subjects participating in this clinical trial.

The investigator at each site 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.

10.1.1 Preparation

The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution, which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 24 hours from time of dilution. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion. Please refer to the investigator's brochure for additional information.

10.1.2 Storage and Stability

Clinical supplies must be stored in a secure, limited-access location. Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake. 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.

10.1.3 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

After final drug reconciliation, unused pembrolizumab vials should be disposed at the site following procedures for the disposal of anticancer drugs.

10.1.4 Dispensing

Pembrolizumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Pembrolizumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.5 Adverse Events Associated with Pembrolizumab

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies that include hypophysitis (including hypopituitarism and secondary adrenal insufficiency), thyroid disorder (hypothyroidism, hyperthyroidism, thyroiditis), Type I diabetes mellitis, uveitis, myositis, Guillain-Barré syndrome, pancreatitis, myocarditis, myasthenic syndrome, encephalitis, sarcoidosis, severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome; and “solid organ transplant rejection following pembrolizumab treatment in donor organ recipients” (risk applicable primarily to post-marketing setting only, as such patients are currently excluded from Merck-sponsored clinical studies with pembrolizumab).

The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy.

Further details regarding immune-related adverse events (irAEs) can be found in the current version of the Investigator’s Brochure.

10.2 Lenvatinib

Lenvatinib (lenvatinib mesilate) is an oral, potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other pro-angiogenic and oncogenic pathway-related RTKs including fibroblast growth factor (FGF) receptor FGFR1-4, platelet-derived growth factor (PDGF) receptor PDGFRα, KIT, and RET. Nonclinical studies showed lenvatinib to be a potent antiangiogenesis agent with antitumor activity versus various human cancer xenograft models in athymic mice.

10.2.1 Supplier/How Supplied

Lenvatinib may be supplied in a 8 mg, 10 mg, 14 mg or 20 mg capsule. Lenvatinib drug substance is a white to pale yellow powder that is being used in the capsule formulation for the clinical studies evaluating lenvatinib. It is slightly soluble in water and has a molecular weight of 522.96 and a pKa of 5.27 (mesilate salt).

Merck will supply lenvatinib from clinical lots at no charge to subjects participating in this clinical trial.

The investigator at each site 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.

10.1.2 Storage and Stability

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

10.1.3 Handling and Disposal

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

10.1.4 Dispensing

Lenvatinib must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Lenvatinib should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.5 Adverse Events Associated with Lenvatinib

The most common adverse reactions include fatigue, arthralgia/myalgia, vomiting, nausea, stomatitis/oral inflammation, hypertension, headache, decreased appetite, stomach pain, hoarseness and rash, redness, itching or peeling of your skin on your hands and feet.

Further details around frequency, reporting, and management of adverse events (AEs) can be found in the current version of the Investigator's Brochure.

11. ADVERSE EVENTS

The descriptions and grading scales found in the NCI CTCAE v5 will be utilized for AE assessment. A copy of the CTCAE v5 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the EDC system (Documents and Information Tab).

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

11.1.3 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.4 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)
Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.1.5 Definition and Reporting of a Pembrolizumab and Lenvatinib Overdose

For purposes of this trial, an overdose 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 or lenvatinib. In the event of overdose, subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an AE (s) is associated with ("results from") the overdose of pembrolizumab or lenvatinib, the AE(s) is reported as a SAE, even if no other seriousness criteria are met.

If a dose of pembrolizumab or lenvatinib 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 ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an AE (and other Reportable Events) must be reported on a HCRN Serious Adverse Event Submission Form **within 1 business day** to HCRN safety via email: safety@Hoosiercancer.org. HCRN will report the event **within 1 business day** to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229).

11.1.6 Reporting of Pregnancy

Although pregnancy is not considered an adverse event, it is the responsibility of investigators or their designees to report any pregnancy of a participant's partner (spontaneously reported to them) that occurs from the time of treatment initiation through 120 days following cessation of study drugs. 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.

All reports of pregnancy with and without an AE must be reported **within 1 business day** to SAFETY@hoosiercancer.org on appropriate Pregnancy Reporting form.. HCRN will report the event **within 1 business day** to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229).

11.1.7 Definition and Reporting of Events of Clinical Interest (ECI)

Selected non-serious and SAEs are also known as ECI and must be recorded as such on the Adverse Event case report forms/worksheets and reported to HCRN **within 1 business day** of the event.

ECI for this trial include:

1. An overdose of pembrolizumab or lenvatinib, as defined above, 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 3 × the upper limit of normal, **and** an elevated total bilirubin lab value that is greater than or equal to 2 × the upper limit of normal, **and**, at the same time, an alkaline phosphatase lab value that is less than 2 × 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.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates a new anticancer therapy, whichever is earlier, whether or not related to pembrolizumab or lenvatinib, must be reported **within 1 business day** to SAFETY@hoosiercancer.org. HCRN will report the event **within 1 business day** to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-661-6229).

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to HCRN

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.

The site will submit the completed SAE Submission Form to HCRN **within 1 business day** of discovery of the event**.** The form will be submitted to HCRN electronically to safety@hoosiercancer.org. The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved, sites must submit a follow-up SAE Submission Form within a reasonable timeframe to HCRN electronically to safety@hoosiercancer.org.

11.2.2.2 HCRN Requirements for Reporting SAEs to Merck

HCRN will report all SAEs to Merck **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to Merck as it is received from site.

11.3 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.4 IND Exempted Protocols

For protocols exempt from the requirements of an IND, HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.5 IND Safety Reports Unrelated to this Trial

Merck will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). Any changes made to the protocol and/or informed consent document will be submitted to the FDA by MICHR-MIAP. All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12. STATISTICAL METHODS

12.1 Objectives

12.1.1 Primary Objective

Evaluate 6 month radiographic progression free survival (rPFS) rate with lenvatinib and pembrolizumab combination therapy in metastatic NEPC.

12.1.2 Secondary Objectives

- Assess the safety of pembrolizumab and lenvatinib combination therapy in metastatic neuroendocrine prostate cancer (NEPC).
- Assess overall survival (OS).
- Assess objective response rate (ORR).
- Assess duration of response (DoR).

12.1.3 Correlative / Exploratory Objectives

- Correlate genomic sequencing results with clinical outcomes in the study population.
- Correlate PDL-1 status and tumor mutation burden with clinical outcomes.
- Correlate gut microbiome data with clinical outcomes.

12.2 Endpoints

12.2.1 Definition of Primary Endpoint

rPFS is defined as the date of Cycle 1 Day 1 to date of radiologic progression of soft tissue lesions per RECIST 1.1 or death whichever occurs first. rPFS is defined as the date of Cycle 1 Day 1 to date of progression of bone lesions (non-measurable disease) per PCWG3 criteria or death whichever occurs first. Censoring of rPFS is described in Section 9.8.2.

12.2.2 Definition of Secondary Endpoints

- Safety of the combination will be assessed based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
- Overall survival (OS) will be measured from Cycle 1 Day 1 to date of death from any cause. OS is further defined (including its censoring) in Section 9.8.3.
- ORR will be the proportion of patients achieving either a complete response (CR) or a partial response (PR), among all patients meeting the criteria of Section 12.6, as well as among all patients enrolled.
- DoR will be measured from the start date of the best response achieved until the date of relapse (i.e., progression). DoR is further defined (including its censoring) in Section 9.8.4. DoR applies to only the CR or PR patients.

12.2.3 Correlative/Exploratory Endpoints

- Genomic sequencing results will be either categorical variables (e.g, if from DNA sequencing), or continuous variables (e.g., if from RNA sequencing).
- PDL-1 status will be a binary variable (either positive or negative). Tumor mutation burden (TMB) is a continuous variable (e.g., the number of mutations per megabase [Mb] of the genome coding area (as per the Caris Life Sciences website).
- Gut microbiome data will consist of continuous variables (i.e., diversity measures and composition measures). Common diversity measures are the α-diversity and the Shannon diversity index. One composition measure is the between-community diversity (the β-diversity).

12.3 Study Design and Interim Analyses

An open label phase II study design of lenvatinib and pembrolizumab in metastatic NEPC is planned with primary endpoint of 6- month radiologic progression-free survival (rPFS), yes/no. For this binary endpoint, a 2-stage Simon near optimal design will be used, with these input parameters: p0 = 0.10; p1 = 0.25; alpha = 0.125; and power = 0.90. This results in the following design features: N1 = 27; R1 = 2; N = 40; R = 6; PET = 0.485; and ASN = 33.70.

Hence, if there are at least 3 successes (patients who have had ≥ 6.00 months of rPFS) in the 27 patients in Stage 1 then the study will proceed to Stage 2, otherwise it will terminate early. If there are at least 7 successes in the final total of 40 patients, then the treatment will be considered promising. To allow for up to 20% of registered patients becoming non evaluable, up to 50 patients will need to be enrolled to yield 40 evaluable patients.

It may become necessary to temporarily suspend accrual at or near the completion of Stage 1 of the study in order to evaluate the 6-month rPFS (primary endpoint) of the last few Stage 1 patients. If Stage 1 accrual is at say, 24 patients and there have been no successes (i.e., no patients who have had ≥ 6.00 months of rPFS), then Stage 2 of accrual could not begin until up to 3 more patients are enrolled in Stage 1 and their rPFS outcome (success or not) has been determined.

Conversely, if ≥ 3 successes have been observed within the first 24 or fewer patients, then the interim analysis can be omitted, and accrual could continue into Stage 2 without interruption. There would be no need for a temporary suspension of accrual.

The study design operational characteristics were calculated using the "Two Stage Phase II Clinical Trials" program in the PASS (2019) software [10]. PET is the probability of early termination under the null hypothesis that p = 0.10. ASN is the average sample number, which is what is minimized in a Simon optimal (or near optimal) design. ASN is the mean number of patients required to complete a given Simon optimal (or near optimal) design after many hypothetical replications of the trial, wherein some trials terminated early (i.e., after Stage 1, with only N1 patients) and the others did not (i.e., went on to Stage 2, using a total of N patients).

12.4 Analysis

12.4.1 Primary Objective

For the Primary objective (efficacy assessment), the binary endpoint (rPFS ≥ 6.00 months, yes/no) will be summarized with its point estimate (an occurrence rate), and 2-sided Wilson type 95% confidence interval (CI).

The duration of censored rPFS will be estimated with standard Kaplan-Meier (K-M) methodology. Point and CI estimates of the median and various timepoint-specific rPFS rates will be derived from the K-M life table (e.g., 6 month rate, 12 month rate, etc.), each with its own respective CI. A graph of the K-M curve for rPFS will be generated along with the Hall-Wellner 95% confidence band, and a display of the number of patients at risk at several time points, below the X-axis.

12.4.2 Secondary Objective

For the first Secondary objective (safety assessment), the analysis of toxicity rates will be performed using only the toxicity-evaluable (t-e) patients. All patients receiving at least one dose of study medication will be t-e.

The grade of each type of toxicity (an ordinal categorical variable) will be summarized with 1-way frequency distributions. Dichotomized versions (e.g., the occurrence rate of Grade 3-4 fatigue) will be summarized as described in Section 12.4.1 for a binary endpoint.

For the second Secondary objective (follow up for survival), OS will be analyzed in the same fashion as rPFS. See Section 12.4.1.

For the third Secondary objective (ORR assessment), ORR will be analyzed in the same fashion as 6-month rPFS rate. See Section 12.4.1, first paragraph.
For the fourth Secondary objective (DoR assessment), DoR will be analyzed in the same fashion as rPFS. See Section 12.4.1, second paragraph.

12.4.3 Exploratory Objectives

For the Exploratory objectives, all categorical variables will be summarized as described in Section 12.4.1. All continuous variables (e.g., number of mutations, or TMB, or gut microbiome diversity or composition measures) will be summarized with descriptive statistics including the point estimate of the mean, its associated 95% CI, standard deviation, median, inter-quartile range (IQR), minimum, and maximum.

The association of Exploratory correlative markers (whether binary, or ordinal categorical, or continuous) with a binary clinical outcome (e.g., the primary endpoint of achievement of rPFS ≥ 6.00 months, yes/no) will be explored using logistic regression models. Point and CI estimates of the odds ratio (OR) will be calculated, but the statistical interpretation will be limited to only the direction, magnitude, and precision of the association (i.e., the OR) as these are only exploratory analyses.

The same approach will be used to model clinical response (defined in Section 9.0) as a function of a given Exploratory correlative marker (e.g, TMB).

The association of Exploratory correlative markers (whether binary, or ordinal categorical, or continuous) with rPFS (or OS) will be explored using Cox proportional hazards (PH) regression models. Point and CI estimates of the hazard ratio (HR) will be calculated, but the statistical interpretation will be limited to only the direction, magnitude, and precision of the association (i.e., the HR) as these are only exploratory analyses.

12.5 Assessment of Safety

All patients receiving one dose of study medication (lenvatinib or pembrolizumab) will be evaluable for safety assessment. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE 5.0 will be used to evaluate toxicity.

12.6 Assessment of Efficacy

All patients receiving 1 cycle of study treatment (any amount of pembrolizumab and lenvatinib) and having had radiology imaging for disease assessment will be evaluable for efficacy.

12.7 Expected Accrual Rate, Accrual Duration, and Total Study Duration

The expected combined accrual rate for this multi-center trial would be 16-30 patients per year. Thus, to enroll up to 50 patients is expected to take 24-38 months of accrual. Allowing another 6 months to obtain the primary endpoint (6-month rPFS), all biomarkers, and all genomic endpoints on all patients, the expected total study duration is 30-44 months.

Patients who discontinue study treatment for reasons other than progression, should have disease assessment performed per investigator discretion. Follow up for these subjects will be every 6 months until progression. Once disease progression is documented, patients will be followed for survival every 6 months for 5 years from the time of documented progression.

13. TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by HCRN and the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

HCRN oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Coordinate monthly study team meetings that include each accruing site's principal investigator, clinical research specialist and/or research nurse (other members per site principal investigator's discretion). On a quarterly basis, the study team meetings will also discuss matters related to:

  - Enrollment rate relative to expectations, characteristics of participants
  - Safety of study participants (Serious Adverse Event reporting, unanticipated problems)
  - Adherence to protocol (protocol deviations)
  - Completeness, validity and integrity of study data
  - Retention of study participants
- Submit a comprehensive Protocol Specific Data and Safety Monitoring Report (DSMR) form to the Rogel Cancer Center DSMC on a quarterly basis. The form will document the study team meeting and include data from all participating sites, signed by the sponsor-investigator.

13.2 University of Michigan Data and Safety Monitoring Committee

The Rogel Cancer Center DSMC will review the information included on the DSMR from the first subject enrolled until the last subject has completed the study drug interventions and is outside the SAE reporting window.

Documentation of DSMC reviews will be provided to the sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

The DSMC will provide the sponsor-investigator and HCRN with evidence of its review. HCRN will distribute this information to the participating sites for submission to their respective IRB per the local IRB's policies and procedures.

13.4 Data Quality Oversight Activities

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

13.4.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

Participating sites may also be subject to quality assurance audits by Merck or its designee as well as inspection by appropriate regulatory agencies.

13.5 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the

requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. MICHR-MIAP will be responsible for submitting FDA Form 3674 to the FDA. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Merck, IRB, or government agencies, like the FDA, may

inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB to HCRN before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

16 REFERENCES

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