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Multicenter, Open-Label Phase 2 Study to Evaluate the Safety and Efficacy of Lenvatinib in Combination with Pembrolizumab in Black Participants with Mismatch Repair-Proficient Recurrent Endometrial Cancer

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Virginia Commonwealth University Massey Cancer Center

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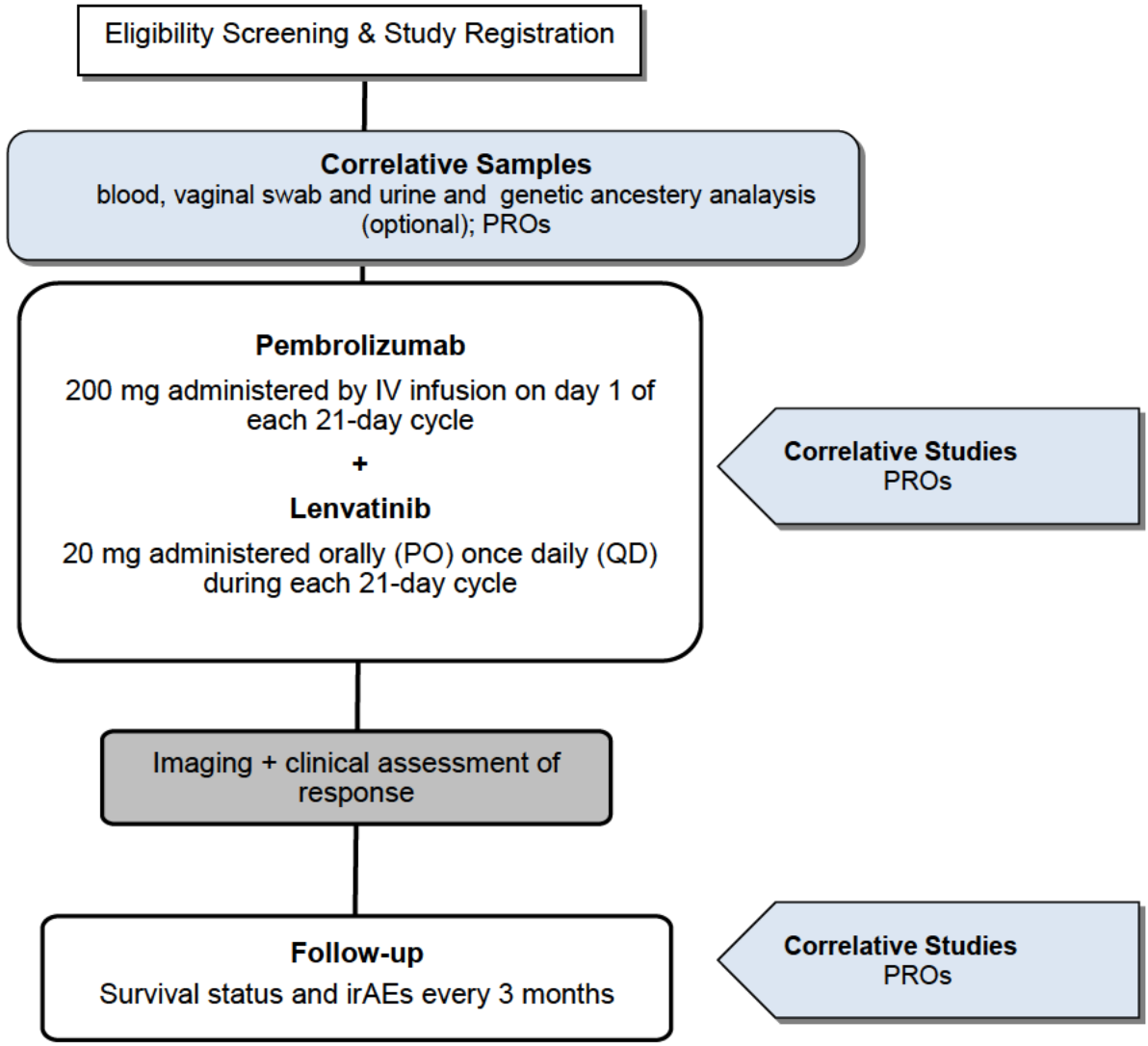
SCHEMA


Eligibility Screening & Study Registration
Correlative Samples
blood, vaginal swab and urine and genetic ancestery analysis (optional); PROs
Pembrolizumab
200 mg administered by IV infusion on day 1 of each 21-day cycle
+
Lenvatinib
20 mg administered orally (PO) once daily (QD) during each 21-day cycle
Correlative Studies
PROs
Imaging + clinical assessment of response
Follow-up
Survival status and irAEs every 3 months
Correlative Studies
PROs

REVISION HISTORY

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
CAR-T	chimeric antigen receptor-modified T cells
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CR	complete response
dMMR	deficient mismatch repair
DOR	duration of response
DSMC	data and safety monitoring committee
DSMP	data and safety monitoring plan
ECOG	Eastern Cooperative Oncology Group
EPD	Early Phase Development
eCRF	electronic case report form
FDA	Food and Drug Administration
HADS-D	hospital anxiety and depression scale-depression subscale
HADS-A	hospital anxiety and depression scale-anxiety subscale
HIV	human immunodeficiency virus
Ig	immunoglobulin
IHC	immunohistochemistry
irAE	immune-related adverse event
IRB	Institutional Review Board
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCC	Massey Cancer Center
MOE	margin of errors
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death-1
Pdcd1	programmed cell death protein 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PRO	patient-reported outcomes
PR	partial response
SD	stable disease
SAE	serious adverse event
UP	unanticipated problem
VCU	Virginia Commonwealth University
WCBP	woman of child-bearing potential

1 BACKGROUND

1.1 Cancer Immunotherapy – Promise and Limitations

Over the past 4 decades, the promise of immunotherapy for treating cancer has waxed and waned, but has recently enjoyed a dramatic renaissance of enthusiasm. For many years, the successes of manipulating the immune response to induce regression of cancers were largely limited to murine models, human melanoma, and renal cell carcinoma, with little cause for optimism in the treatment of epithelial malignancies, which are the most common causes of cancer death (1-3).

Immunotherapeutic approaches can be roughly divided into 2 main categories—active and passive. Active immune therapies are aimed at stimulating and activating the host's own immune system to recognize and destroy cancer cells. This category includes vaccines, infusion of immunologically active cytokines, and altering the tumor itself to make it more immunogenic. Passive immunotherapy refers to treatments that involve infusing antigen-targeted molecules or cells into the host, which then attack the tumor directly, either causing tumor cell destruction or inhibition of tumor growth. These passive approaches include adoptive cellular therapy, such as infusion of T lymphocytes which have been removed from the patient, manipulated and expanded in vitro, and then reinfused into the host, sometimes in combination with recombinant cytokines that encourage expansion of the cells and increase their activity (4). For example, tumor-infiltrating lymphocytes grown from biopsy samples of melanoma tumors have induced dramatic regression in patients with metastatic disease. More recently, T cells genetically modified to express chimeric antigen receptors (CAR-T cells) created from antibody-antigen combining regions and T-cell signaling molecules have been used successfully to treat hematologic malignancies (5-7). Monoclonal antibodies, either alone or linked to cytotoxic molecules, are another example of passive immunotherapy that has had considerable success (8). To a varying degree, monoclonal antibodies that recognize cancer cell surface targets may be both passive and active, in the sense that antibodies bound to cancer cells can directly inhibit signaling by the target molecule and can also trigger host immune cells (e.g., natural killer [NK] cells) to attack and kill the cancer cells (9) (10).

The most recent wave of excitement about immunotherapy has been generated by what may be considered a "hybrid" form of therapy that is both passive and active. This approach, termed "immune checkpoint inhibition", uses monoclonal antibodies to inhibit mechanisms that suppress T-cell activation and function, and led to the 2018 Nobel Prize in Physiology or Medicine (11).

1.2 Proposed Immunotherapy Regimen

1.2.1 Pembrolizumab (Keytruda)

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 Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins

containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B cells, Tregs, and NK cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Examples of additional indications include non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, and gastric/gastroesophageal junction cancer.

1.2.2 Lenvatinib (Lenvima, Eisai)

Lenvatinib is an oral, multi–tyrosine kinase inhibitor active against RET, VEGFR1–3, FGFR1–3, KIT, and PDGFRα (12-16). It is approved in the US for the treatment of (1) patients with locally recurrent or metastatic, progressive, radioactive iodine refractory differentiated thyroid cancer, (2) in combination with everolimus for patients with advanced renal cell carcinoma following 1 prior antiangiogenic therapy, (3) for the first-line treatment of patients with unresectable hepatocellular carcinoma, and (4) in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR who have disease

progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. Data from Phase 2 clinical studies showed lenvatinib has antitumor activity in multiple other tumors.

1.3 Study Rationale

Until recently, microsatellite stable (MSS) recurrent endometrial cancer was a disease of high unmet medical need. In 2018, the US Food and Drug Administration (FDA) granted a breakthrough designation and, in 2019, an accelerated approval to the combination of the immune checkpoint inhibitor, pembrolizumab, and the oral anti-angiogenic agent, lenvatinib.

With an objective response rate (ORR) at 24 weeks of 36.2% (95% CI, 26.5% to 46.7%) in patients with MSS tumors (n = 94), and a median duration of response (DOR) of 21.2 months (95% CI, 7.6 months to not estimable), compared to historical ORR of 12-15% and DOR of 3-6 months, these results were exciting and led to widespread adoption of the combination in clinical practice. This enthusiasm was despite the incidence of grade 3 or 4 treatment-related adverse events (AEs) in 83/124 (66.9%) patients--most commonly hypertension and diarrhea—a 33% discontinuation rate for toxicity, and absence of quality of life data. A confirmatory phase 3 trial of lenvatinib/pembrolizumab versus standard chemotherapy in the second-line setting recently reported a progression-free survival (PFS) and overall survival (OS) advantage for the lenvatinib/pembrolizumab combination but again with significant AEs and treatment discontinuation (33% vs 8% for chemotherapy). On July 21, 2021, the FDA approved pembrolizumab in combination with lenvatinib for patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

1.3.1 Rationale for Version 3 Changes

In patients with advanced or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer progression-free survival than with chemotherapy alone. In the mismatch repair-proficient cohort, median progression-free survival was 13.1 months with pembrolizumab and 8.7 months with placebo (hazard ratio, 0.54; 95% CI, 0.41 to 0.71; P<0.001 (17)

Dostarlimab plus carboplatin–paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer In the overall population, progression-free survival at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (hazard ratio for death, 0.64; 95% CI, 0.46 to 0.87).(18)

1.4 Correlative Studies

1.4.1 Patient-Reported Outcomes (PROs)

PROs provide unique information on the impact of a medical condition and its treatment from the patient's perspective and help ensure the impact of a trial intervention is comprehensively assessed. PROs to be measured include health related quality of life (HRQOL), financial toxicity and depression and anxiety.

EORTC-QLQ-C30+EN24 is a PRO measurement system developed to assess the health related quality of life of cancer patients. It has been translated and validated (19) (into over 100 languages and is used each year in more than 5,000 studies worldwide. Subscales include assessments of physical, role, cognitive, emotional, and social function; physical symptoms; and overall QOL. Scores are linearly transformed to a 0-100 scale, where higher scores for the functional subscales represent healthier level of functioning. Higher scores on the symptom subscales represents higher level of symptomatology. Symptoms specific to endometrial cancer are assessed including lymphoedema, urological symptoms, gastrointestinal, body image, and sexual/vaginal symptoms; and single items assess back/pelvic pain, tingling/numbness, muscular/joint pain, hair loss, taste change, sexual interest, sexual activity, and sexual enjoyment.

EQ-5D-5L is a self-assessed, health related, quality of life questionnaire. The scale measures quality of life on a 5-component scale including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each level is rated on scale that describes the degree of problems in that area (i.e. I have no problems walking about, slight problems, moderate problems, severe problems, or unable to walk). This tool also has an overall health scale where the rater selects a number between 1-100 to describe the condition of their health, 100 being the best imaginable. Convergent validity was demonstrated by a correlation between EQ-5D-5L and the dimensions of WHO 5, (r=.43, P<.001) . (20).The EuroQuol approach is reliable, average test-re-test reliability using inter-class coefficients with mean of .78 and .73 (20-23).

FACIT-COST is a 12-item PRO of financial distress experienced by cancer patients. It is both a reliable and valid measure of financial stress. Item response options are on a 5-point Likert scale (24).

HADS is a 14-item measure used to identify depression and anxiety for patients in a hospital outpatient clinic setting and has commonly been used for cancer patients. The subscales for depression (HADS-D) and anxiety (HADS-A) may be used separately and have good mean internal consistency: HADS-A (Cronbach's α: 0.83) and HADS-D (Cronbach's α: 0.82) (25). Item response options are on a 4-point Likert scale (26).

Gendered Racial Microaggressions Scale (GRMS) (27, 28) is an intersectional measure to assess the frequency and stress appraisal of subtle gender racism. It is a 26-item measure assessing nonverbal, verbal, and behavioral negative racial and gender slights experienced by Black women. Frequency is assessed on a 6-point Likert-type scale, ranging from 0 (*never*) to 5 (*once a week or more*). Stress Appraisal is assessed on a 6-point Likert-type scale, ranging from 0 (*not at all stressful*) to 5 (*extremely stressful*). The measures are broken into 4 subscales: Assumptions of Beauty and Sexual Objectification (1-11), Silenced and marginalized (12-18), Strong Black Woman Sterotype (19-23), and Angry Black Woman Sterotype (24-26). Higher total mean scores indicate a greater frequency and stress appraisal of gendered racial microaggressions.

In-group Identificaion Scale:Centrality Subscale (27, 28) is a hiearchal and multidimensional model that consists of 14 items in 5 distinct components of in-group identification: *self-stereotyping (2 items)*, *in-group homogeneity (2 items)*, *solidarity (3 items)*, *satisfaction (4 items)*, and *centrality (3 items)*. The centrality component of in-group identification makes individuals perceive a great threat to their group, whether real or symbolic. Since this perception of threat tends to encourage active coping, centrality may lead individuals to defend their in-group against a perceived threat. Thus, the more central the in-group, the more individuals defend this group against threats. An unimportant in-group is not worth defending. Mean scoresare calculated with higher scores indicating higher levels of identity centrality.

Please see Section 12 for collection timepoints.

1.4 [redacted]

1.4 

2 OBJECTIVES

2.1 Primary Objective

To determine the efficacy of the combination of lenvatinib and pembrolizumab in Black participants.

2.2 Secondary Objectives

2.2.1 Determine median PFS in the study population

2.2.2 Determine the incidence of treatment-related AEs in the study population

2.2.3 Determine the number of patients who discontinue treatment due to treatment-related AEs

2.3 Exploratory Objectives

2.3.1 Explore patient-reported outcomes of health related quality of life (EORTC-QLQ-C30+EN24), anxiety and depression (HADS), and financial toxicity (FACIT COST) in the study population

2.3.2 Explore ancestral markers and microbiome and cytokine/growth factor levels in blood, urine, and vaginal samples in Black patients with recurrent endometrial cancer undergoing treatment with lenvatinib and pembrolizumab

3 STUDY DESIGN

3.1 General Description

This study is a single-arm, open-label, multicenter phase 2 trial designed to prospectively evaluate the safety and efficacy of lenvatinib in combination with pembrolizumab for mismatch repair-proficient recurrent endometrial cancer in Black patients (a population under-represented on 2 FDA registration trials). Up to 100 patients will be treated at up to 10 sites throughout the United States. All patients will receive lenvatinib and pembrolizumab while participating in the study. Patients will continue to receive lenvatinib and pembrolizumab until their disease progresses or they experience unacceptable toxicity.

3.2 Primary Endpoint

ORR at 24 weeks in Black patients with recurrent endometrial cancer treated with lenvatinib 20 mg orally daily in combination with pembrolizumab 200 mg IV every 3 weeks

3.3 Secondary Endpoints

3.3.1 Proportion of patients who are alive and have not had disease progression or relapse following last dose of study treatment

3.3.2 Using criteria in the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0), all AEs captured as described in Section 8.4.

3.3.3 Number of patients who discontinue treatment due to treatment-related AEs.

3.4 Exploratory Endpoints

3.4.1 Effects of lenvatinib and pembrolizumab on patient-reported outcomes of health related quality of life (EORTC-QLQ-C30+EN24), anxiety and depression (HADS), and financial toxicity (FACIT COST) in the study population

3.4.2 Genetic ancestry analysis, microbiome analysis, and levels of cytokines/growth factors in blood, and urine

3.4.3 Quantify patient-reported gendered racial microaggressions, in-group identification scale, and Africultural coping systems inventory and compare with allostatic load scores, inflammatory markers and treatment response.

3.5 Multicenter Site Participation

This study will be conducted at up to 10 sites across the United States. The VCU MCC Early Phase Development Department serves as the Coordinating Team.

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to participate in the study:

		Yes	No	N/A
4.1.1	Histologically and/or cytologically confirmed endometrioid, serous, clear cell, carcinosarcoma, or de-differentiated or undifferentiated endometrial cancer with radiographic and/or clinical evidence of disease progression			
4.1.2	Documented microsatellite stable disease as tested by either MSI PCR or DNA mismatch repair (MMR) by IHC			
4.1.3	Self-identify as being of predominantly (>50%) Black race, inclusive of Black, African-American, Black Hispanic (Afro-Latinx), African, or Afro-Caribbean ancestry			
4.1.4	Received, ineligible for (by investigator determination), or declined platinum containing chemotherapy			
4.1.5	Received no greater than 2 prior lines of therapy. Maintenance therapies and hormonal therapies will NOT count as a line of therapy. Patients may have received prior immune checkpoint inhibitor therapy or bevacizumab in one of the 2 prior lines of therapy.			
4.1.6	Measurable disease as determined by RECIST v1.1: ● At least one lesion of ≥10 mm in the longest diameter for a non-lymph node, or ≥15 mm in the short-axis diameter for a lymph node that is serially measurable using computerized tomography/magnetic resonance imaging (CT/MRI) ● Target lesions limited to a radiated field must show evidence of substantial size increase according to previous scans to be deemed a target lesion			
4.1.7	Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 1)			
4.1.8	Age ≥ 18 years			
4.1.9	Ability to swallow oral medications			

		Yes	No	N/A
4.1.10	Patients who are not postmenopausal or have not undergone hysterectomy must have a documented negative serum pregnancy test within 72 hours prior to initiating study treatment Note: Postmenopausal is defined as any of the following: • Age ≥ 60 years • Age < 60 years and amenorrheic for at least 1 year with follicle-stimulating hormone (FSH) and plasma estradiol levels in the postmenopausal range • Bilateral oophorectomy			
4.1.11	Patients of child-bearing potential must agree to use a medically accepted method for preventing pregnancy during and for a minimum of 4 months following the last dose of lenvatinib or pembrolizumab			
4.1.12	Patients with known brain metastases will be eligible if they have completed primary brain therapy (such as whole brain radiotherapy, stereotactic radiosurgery, or complete surgical resection) and if they have remained clinically stable, asymptomatic, and off of steroids for at least 28 days before starting study treatment			
4.1.13	Toxicities from previous cancer therapies resolved to grade ≤1 unless specified otherwise (exceptions: chronic residual toxicities that in the opinion of the investigator are not clinically relevant, given the known safety/toxicity profiles of Lenvatinib and pembrolizumab, such as alopecia, grade ≤2 anemia; neuropathy related to previous chemotherapy must be resolved to grade ≤2)			
4.1.14	Ability to understand and the willingness to sign a written informed consent document			

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is ineligible to participate in the study:

		Yes	No	N/A
4.2.1	Endometrial leiomyosarcoma or endometrial stromal sarcoma			

		Yes	No	N/A
4.2.2	Unstable central nervous system (CNS) metastases			
4.2.3	Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib			
4.2.4	Pre-existing grade ≥3 gastrointestinal or non-gastrointestinal fistula			
4.2.5	Radiographic evidence of major blood vessel invasion/infiltration			
4.2.6	Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study treatment			
4.2.7	History of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident, stroke, or cardiac arrhythmia associated with hemodynamic instability within 12 months of the first dose of study treatment			
4.2.8	Known history or evidence of interstitial lung disease or active, non-infectious pneumonitis			
4.2.9	Administration of or condition requiring administration of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to initiating study treatment Exception: Patients with conditions that can be managed with steroids equivalent to or less than an oral prednisone dose of 10 mg daily are not excluded from the study			
4.2.10	Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs) or a documented history of clinically severe autoimmune disease or a syndrome that requires systemic steroids or immunosuppressive agents Note: Patients with the conditions or medical history listed below are not excluded from the study. • Vitiligo • Resolved childhood asthma/atopy • Requirement for intermittent use of bronchodilators or local steroid injections or topical steroids			

		Yes	No	N/A
	• Hypothyroidism stable on hormone replacement • Sjogren's Syndrome			
4.2.11	Has received >2 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for endometrial cancer; participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as one is given in the neoadjuvant or adjuvant treatment setting			
4.2.12	Prior anticancer treatment within 28 14 days of study start			
4.2.13	Has received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor other than an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, and who has discontinued from that treatment due to a grade 3 or higher immune-related adverse event (irAE)			
4.2.14	Has received prior radiation therapy within 21 days of study start with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks before study start; participants must have recovered from all radiation-related toxicities and/or complications prior to randomization			
4.2.15	Participants with urine protein ≥3.5 gram (g)/24 hour			
4.2.16	Administration of a live vaccine within 30 days prior to initiating study treatment Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are permitted; however, intranasal influenza vaccines (e.g., Flu-Mist) are live attenuated vaccines, and are not allowed. COVID-19 vaccines are allowed and encouraged			
4.2.17	Administration of any investigational agent within 4 weeks prior to initiating study treatment			
4.2.18	History of solid organ or allogeneic stem cell transplant			
4.2.19	Known intolerance to either of the study drugs (or any of the excipients)			
4.2.20	Known immunodeficiency, eg, human immunodeficiency virus (HIV) Note: HIV testing is not required for eligibility screening			
4.2.21	Known active hepatitis B or C			

		Yes	No	N/A
	Note: hepatitis B and C testing is not required for eligibility screening			
4.2.22	Serious (ie, grade ≥3) uncontrolled infection			
4.2.23	Pregnancy or breastfeeding			
4.2.24	Diagnosis or treatment for another malignancy within 2 years prior to study registration, with the following exceptions: complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, and any in situ malignancy.			
4.2.25	Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk or limit the patient's adherence with study requirements			

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Required Pre-Registration Screening Tests and Procedures

Refer to the study calendar in Section 12 for the screening tests and procedures that are required prior to registration and for the timing of these events relative to the start of treatment.

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently registered in the study. Demographics and consent data for these patients are entered into OnCore.

5.1.2 Registration Process

After informed consent has been obtained, the following documents are submitted to the VCU MCC Coordinating Center [redacted] for study registration:

- Completed registration cover sheet or request form as provided by the coordinating center
- Attestation of patient eligibility
- Signed and dated consent form

The Coordinating Center will complete the registration process by assigning a study identification (ID) number and returning a Confirmation of Registration to the registering study team. Study treatment may not begin until the Confirmation of Registration

assigning a study ID number has been received from the registrar. The registering study team will enter the patient's initial enrollment data (eg, demographics, consent, eligibility, on-study, treatment assignment) into the OnCore database within 24 hours following study registration (before treatment begins).

5.2 Study Withdrawal

A patient may decide to withdraw from the study at any time. Patients must be withdrawn from the study when any of the following occurs:

- The patient has withdrawn consent for study treatment and study procedures.
- If, in the investigator's opinion, continuation of the study requirements would be harmful to the patient's well-being.
- The patient is lost to follow-up. (See Sction 5.3)

The reason for withdrawal from the study and the date the patient was removed from the study must be documented in the source documents and OnCore database.

5.3 Lost to Follow-Up

A participant is identified as lost-to-follow-up (LTFU) if all of the following criteria are met:

- The last contact date for a participant has exceeded 2 consecutive years.
- Since the last contact date, documentation of at least 3 attempts to contact the participant by telephone and a certified letter to the last known address has either been returned or not answered within 7 days of confirmation that the letter was received or undeliverable.
- A Social Security Death Index (SSDI) search has been completed with negative results. If a participant is determined to be LTFU, the certified letter receipt will be filed in the participant's research record with a copy of the letter sent, a thorough explanation of the contact attempts will be documented in the participant's research record, and the participant's status will be changed/confirmed in OnCore.

6 STUDY TREATMENT

6.1 Baseline Tests and Procedures

Refer to the study calendar in Section 12 for requirements prior to initiation of therapy.

6.2 Investigational Agent Administration

Participants will receive pembrolizumab 200 mg administered by IV infusion on day 1 of each 21-day cycle plus lenvatinib 20 mg administered orally (PO) once daily (QD) during each 21-day cycle.

6.2.1 Premedications for Pembrolizumab

- Patients may be premedicated for nausea and vomiting. Choice of antiemetic is at the treating physician'sdiscretion with the exception that steroids are NOT permitted for this purpose.
- Refer to Table 1 for management of infusion reactions.

6.2.2 Administration of Pembrolizumab

Refer to Section 9.2.5 for preparation instructions.

- Administer reconstituted pembrolizumab in intravenous infusion bag of either 0.9% Sodium Chloride Injection or 5% Dextrose Injection.
- Administer infusion solution over 30 minutes through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. (Do not co-administer other drugs through the same infusion line.)
- Every effort should be made to plan for administration as close to 30 minutes as possible. However, a window of -5 minutes and +10 minutes is permitted.

6.2.3 Pembrolizumab Infusion Reaction Treatment Guidelines

Severe infusion reactions have been reported in 2 (0.1%) of 1562 patients receiving pembrolizumab in clinical trials. Management of a pembrolizumab infusion reaction is outlined in Table 1.

Table 1. Management of Pembrolizumab Infusion-related Reaction

Grade (NCI CTCAE v5.0)	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating physician.	None
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop infusion and monitor symptoms.** 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 patient is deemed medically stable in the opinion of the treating physician. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hour to 50 mL/hour). Otherwise dosing will be held until symptoms resolve; the patient should be premedicated for the next scheduled dose. **Pembrolizumab should be permanently discontinued for patients who develop grade 2 toxicity despite adequate premedication.**	Patient may be premedicated 1.5 hour (± 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 antipyretic).
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4** Life-threatening consequences; urgent intervention indicated; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the treating physician. Hospitalization may be indicated. **Permanently discontinue pembrolizumab.**	No subsequent dosing
Note: Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

6.3 General Concomitant Medication and Supportive Care Guidelines

- Patients should receive appropriate supportive care measures as deemed necessary by the treating physician and according to the current prescribing information for each agent.
- Patients may be premedicated for nausea and vomiting. Choice of antiemetic is at the treating physician's discretion with the exception that steroids are NOT permitted.
- Refer to Table 1 for management of infusion reactions.

6.3.1 Supportive Care

- Patients should receive appropriate supportive care measures as deemed necessary by the treating physician
- Supportive care measures for the management of AEs with potential immunologic etiology, ie, irAEs, are outlined in Appendix 2.

6.3.2 Prohibited Medications and Treatments

6.3.2.1 Cancer Treatment

Cancer treatment (e.g., chemotherapy, biological therapy, immunotherapy, radiation therapy) other than the treatment specified in the protocol for this study is not permitted during study treatment.

6.3.2.2 Other Medications

- Live vaccines (examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine) are prohibited.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology are prohibited. Exception: Steroids equivalent to or less than an oral prednisone dose of 10 mg daily are permitted and steroids are allowed without limitation
- Any investigational agent not specified in the protocol for this study is not permitted.

6.4 Duration of Therapy

Study treatment will be administered per schema unless one of the following occurs (also see study withdrawal criteria in Section 5.2):

- AE that requires discontinuation of study treatment (see Section 8)
- Pregnancy
- Determination by the investigator that discontinuation is in the patient's best medical interest

- Patient decision to discontinue study treatment
- Withdrawal of study sponsor support

The reason for discontinuation of study treatment must be documented in the source documents and in the OnCore database.

6.5 Duration of Follow-Up

6.5.1 Initial AE Evaluation Period after Discontinuation of Treatment

Patients who discontinue treatment **for any reason other than death or their choice to withdraw from all study follow-up** remain on study in follow-up status for an initial 30-day AE evaluation period following the last dose of study treatment. This 30-day post-treatment follow-up period is meant to capture resolution or stabilization of ongoing treatment-related AEs or evolution of new treatment-related AEs.

The initial AE follow-up period may be extended if new or worsening treatment-related AEs require longer observation. Similarly, the initial AE follow-up period may end early in the event of death, patient request to withdraw from follow-up, or initiation of new anticancer therapy.

6.5.2 Ongoing Follow-up

Patients who discontinue treatment with ongoing SD, PR, or CR (see Section 10) remain in follow-up status for PFS by reported clinical status every 3 months until one of the following occurs: disease progression, relapse, or death.

All patients will be followed for OS status every 3 months, until death or off-study.

The primary reason(s) for a patient's discontinuation from study treatment and from follow-up status are to be recorded in the source documents and the OnCore database.

6.6 Study Pocket Card for Patients

A pocket card identifying the name of the study, the names of the study medications, and contact information including the study team and a 24-hour on-call study physician will be provided to each patient. The purpose of this card is to facilitate communication between the study team and the patient's health care providers not involved with the study. Patients will be encouraged to carry the card with them at all times and to show it to their health care providers so that potential interactions with the study medications can be identified before initiating new medications.

6.7 Monitoring Patient Adherence

Patients will be instructed to record their lenvatinib doses in the drug diary that will be provided.

Adherence will be assessed at time points per Study Calendar. Patient reports of self-administration, review of the study drug diary, and lenvatinib pill counts will be used to

assess the patient's adherence with the oral study treatment regimen. Adherence is defined as taking ≥ 80% of planned lenvatinib doses in a cycle. Doses omitted due to AE management will not count towards nonadherence. Patients who are not adherent will be re-instructed.

7 DOSING DELAYS/DOSE MODIFICATIONS

7.1 Recording Dose Delays and Omissions

All dosing delays and omissions will be recorded in the source documents and captured in the OnCore database.

7.2 Toxicity Grading

AEs will be characterized and graded according to NCI CTCAE v5.0.

7.3 Lenvatinib Treatment Modification

Dose modifications for lenvatinib are based on current prescribing information.

Recommendations for lenvatinib dose interruption, reduction and discontinuation for adverse reactions are listed in Table 2. Table 3 lists the recommended dosage reductions of lenvatinib for adverse reactions.

Table 2: Recommended Dosage Modifications for Lenvatinib

Adverse Reaction	Severity	Dosage Modifications for Lenvatinib
Hypertension	Grade 3	• Withhold for grade 3 that persists despite optimal antihypertensive therapy. • Resume at reduced dose when hypertension is controlled at less than or equal to grade 2.
	Grade 4	• Permanently discontinue.
Cardiac Dysfunction	Grade 3	• Withhold until improves to grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on the severity and persistence of adverse reaction.
	Grade 4	• Permanently discontinue.
Arterial Thromboembolic Event	Any Grade	• Permanently discontinue.
Hepatotoxicity	Grade 3 or 4	• Withhold until improves to grade 0 to 1 or baseline. • Either resume at a reduced dose or discontinue depending on severity and persistence of hepatotoxicity. • Permanently discontinue for hepatic failure.
Renal Failure or Impairment	Grade 3 or 4	• Withhold until improves to grade 0 to 1 or baseline. • Resume at a reduced dose or discontinue depending on severity and persistence of renal impairment.

Table 3: Recommended Dosage Reduction Steps for Lenvatinib

First Dosage Reduction	Second Dosage Reduction	Third Dosage Reduction
14 mg once daily	10 mg once daily	8 mg once daily

7.3.1 Dosage Modifications for Severe Renal Impairment

The recommended dosage of lenvatinib for patients with endometrial carcinoma and severe renal impairment (creatinine clearance less than 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is 10 mg orally once daily.

7.3.2 Dosage Modifications for Severe Hepatic Impairment

The recommended dosage of lenvatinib for patients with endometrial carcinoma and severe hepatic impairment (Child-Pugh C) is 10 mg taken orally once daily.

7.3.3 General Guidelines for Holding Periods of Lenvatinib due to Procedures

For minor procedures, lenvatinib should be stopped 2 days before the procedure and restarted 2 days after, once there is evidence of adequate healing and no risk of

bleeding. Needle biopsies (fine needle aspirations and core needle aspiration) are usually considered minor procedures.

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

7.4 Pembrolizumab Treatment Modification

Dose modifications for pembrolizumab are based on current prescribing information.

No dose reduction for pembrolizumab is recommended. In general, withhold pembrolizumab for severe (grade 3) immune-mediated adverse reactions. Permanently discontinue pembrolizumab for life-threatening (grade 4) immune-mediated adverse reactions, recurrent severe (grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for pembrolizumab for adverse reactions that require management different from these general guidelines are summarized in Table 4.

Table 4: Recommended Dosage Modifications for Pembrolizumab		
Adverse Reaction	**Severity***	**Dosage Modification**
Immune-Mediated Adverse Reactions		
Pneumonitis	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold†
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold†
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver‡	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold†
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold†
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold†
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold†
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
Other Adverse Reactions		
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

† Resume in patients with complete or partial resolution (grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.

‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue pembrolizumab based on recommendations for hepatitis with no liver involvement.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens-Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Serious AE (SAE)

An AE is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the

IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.4 AE Description and Grade

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting.

8.1.5 AE Expectedness

AEs can be 'Unexpected' or 'Expected'.

Expected AEs are listed in Section 8.2 below.

Unexpected AEs are those AEs occurring in one or more subjects participating in the research protocol, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

8.1.6 AE Attribution

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Known AEs List

See Section 9.2.11

8.3 Time Period and Grade of AE Capture

All AEs, SAEs, and UPs will be captured as follows and recorded in the study database.

All AEs, SAEs, and UPs will be evaluated from the time the informed consent form is signed through the follow-up visit 30 ±15 days after the last administered component of study regimen (see Section 6.5.1). The AE safety follow-up period may be truncated if the patient begins other antineoplastic therapy during that time. Collection of irAEs will continue at survival status assessment time points (every 3 months ±15 days) as long as survival status assessment continues.

8.4 Procedures for Recording AEs, SAEs, and UPs

- AEs, SAEs, UPs, and other reportable events will be recorded in MCC's OnCore Clinical Trials Management System.
- In most cases, it is acceptable to record in OnCore only the highest grade of a toxicity occurring during a particular study segment when an event has serial fluctuations in grade over time.
- SAEs will be entered into the OnCore SAE domain. UPs will be entered into the OnCore Deviations domain. An SAE that is both an SAE and a UP will be entered in both domains.
- AEs requiring expedited reporting must also be recorded by routine AE capture (i.e., in AE eCRFs).

8.5 Expedited Reporting Procedures

Table 5. Expedited Reporting Requirements for Participating Sites

SAEs	UPs	Qualifying Toxicities
Principal Investigator[1] Chelsea Salyer, MD [redacted]	**Principal Investigator**[1] Chelsea Sayler, MD [redacted]	**Principal Investigator**[1] Chelsea Sayler, MD [redacted]
Coordinating Center[1] Investigator-Initiated Trials Research Operations (IITRO) [redacted]	**Coordinating Center**[1] Investigator-Initiated Trials Research Operations (IITRO) [redacted]	**Coordinating Center**[1] Investigator-Initiated Trials Research Operations (IITRO) [redacted]
IRB (if applicable)[2]	**IRB**[2]	

[1] Report event within 1 business days of becoming aware of the occurrence. A PDF of a de-identified Oncore Deviation record may be used for expedited event reporting purposes.

[2] Report SAEs and UPs to the IRB of record according to local institutional guidelines.

Table 6. Expedited Reporting Requirements for Coordinating Center

UPs
DSMC[1] [redacted]
IRB[2]

[1] Report to DSMC within 2 business days of becoming aware of the occurrence. A PDF of a de-identified Oncore Deviation record may be used for expedited event reporting purposes.

[2] Report to the VCU IRB within 5 business days of becoming aware of the occurrence.

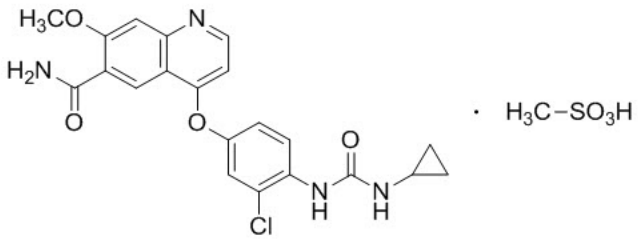
9 PHARMACEUTICAL INFORMATION

9.1 Lenvatinib (Lenvima)

The following information is based on the Prescribing Information for Lenvima (lenvatinib) dated July 2021.

9.1.1 Product Description

Lenvatinib, a kinase inhibitor, is the mesylate salt of lenvatinib. Its chemical name is 4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide methanesulfonate. The molecular formula is C21H19ClN4O4 • CH4O3S, and the molecular weight of the mesylate salt is 522.96. The chemical structure of lenvatinib mesylate is:



Lenvatinib mesylate is a white to pale reddish yellow powder. It is slightly soluble in water and practically insoluble in ethanol (dehydrated). The dissociation constant (pKa value) of lenvatinib mesylate is 5.05 at 25°C. The partition coefficient (log P value) is 3.3.

Lenvima capsules for oral administration contain 4 mg or 10 mg of lenvatinib, equivalent to 4.90 mg or 12.25 mg of lenvatinib mesylate, respectively. The inactive ingredients are: calcium carbonate, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and talc.

In addition, the capsule shell contains ferric oxide red, ferric oxide yellow, hypromellose, and titanium dioxide. The printing ink contains black iron oxide, potassium hydroxide, propylene glycol, and shellac.

9.1.2 Mechanism of Action

Lenvatinib is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and

VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in hepatocellular carcinoma cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α (FRS2α) phosphorylation.

In syngeneic mouse tumor models, lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and demonstrated greater antitumor activity in combination with an anti-PD-1 monoclonal antibody compared to either treatment alone.

9.1.3 Storage and Handling Requirements

Lenvatinib 4-mg capsules are supplied as hard hypromellose capsules with yellowish-red body and yellowish-red cap, marked in black ink with “Є” on the cap and “LENV 4 mg” on the body.

Lenvatinib 10 mg capsules are supplied as hard hypromellose capsules with yellow body and yellowish-red cap, marked in black ink with “Є” on the cap and “LENV 10 mg” on the body.

Lenvatinib capsules are supplied in cartons of 6 cards.

Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F)

9.1.4 Administration

Oral.

Reduce the dose for certain patients with renal or hepatic impairment.

Take lenvatinib once daily, with or without food, at the same time each day. If a dose is missed and cannot be taken within 12 hours, skip that dose and take the next dose at the usual time of administration.

The recommended dosage of lenvatinib is 20 mg orally once daily, in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks, until unacceptable toxicity or disease progression.

9.1.5 Availability and Ordering

Lenvatinib is commercially available and administration is standard of care for patients with endometrial cancer. The costs of lenvatinib and its administration will be the responsibility of the patient and/or the patient’s 3rd party payor.

9.1.6 Contraindications

No contraindications have been identified.

9.1.7 Pharmacokinetics

In patients with solid tumors administered single and multiple doses of lenvatinib once daily, the maximum lenvatinib plasma concentration (Cmax) and the area under the concentration-time curve (AUC) increased proportionally over the dose range of 3.2 mg (0.1 times the recommended clinical dose of 24 mg) to 32 mg (1.33 times the recommended clinical dose of 24 mg) with a median accumulation index of 0.96 (20 mg) to 1.54 (6.4 mg).

Absorption

The time to peak plasma concentration (Tmax) typically occurred from 1 to 4 hours post-dose.

Food Effect: Administration with a high fat meal (approximately 900 calories of which approximately 55% were from fat, 15% from protein, and 30% from carbohydrates) did not affect the extent of absorption, but decreased the rate of absorption and delayed the median Tmax from 2 hours to 4 hours.

Distribution

In vitro binding of lenvatinib to human plasma proteins ranged from 98% to 99% at concentrations of 0.3 to 30 µg/mL. The blood-to-plasmconcentration ratio ranged from 0.59 to 0.61 at concentrations of 0.1 to 10 µg/mL in vitro.

Elimination

The terminal elimination half-life of lenvatinib was approximately 28 hours.

Metabolism: The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes.

Excretion: Ten days after a single administration of radiolabeled lenvatinib, approximately 64% and 25% of the radiolabel were eliminated in the feces and urine, respectively.

9.1.8 Drug Interactions

Effect of Other Drugs on Lenvatinib

CYP3A, P-gp, and BCRP Inhibitors: Ketoconazole (400 mg daily for 18 days) increased lenvatinib (administered as a single 5 mg dose on Day 5) AUC by 15% and Cmax by 19%. P-gp Inhibitor: Rifampicin (600 mg as a single dose) increased lenvatinib (24 mg as a single dose) AUC by 31% and Cmax by 33%.

CYP3A and P-gp Inducers: Rifampicin (600 mg daily for 21 days) decreased lenvatinib (24 mg as a single dose on Day 15) AUC by 18%. The Cmax was unchanged.

In Vitro Studies with Transporters: Lenvatinib is a substrate of P-gp and BCRP but not a substrate for organic anion transporter (OAT) 1, OAT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, multidrug and toxin extrusion (MATE) 1, MATE2-K, or the bile salt export pump (BSEP).

Effect of Lenvatinib on Other Drugs

Clinical Studies with Substrates of CYP3A4 or CYP2C8: There is no projected significant drug-drug interaction risk between lenvatinib and midazolam (a CYP3A4 substrate) or repaglinide (a CYP2C8 substrate).

In Vitro Studies with Substrates of CYP or UDP-glucuronosyltransferase (UGT): Lenvatinib inhibits CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Lenvatinib does not inhibit CYP2A6 and CYP2E1. Lenvatinib induces CYP3A, but it does not induce CYP1A1, CYP1A2, CYP2B6, and CYP2C9.

Lenvatinib inhibits UGT1A1, UGT1A4, and UGT1A9 in vitro, but likely only inhibits UGT1A1 in vivo in the gastrointestinal tract based on the expression of the enzyme in tissues. Lenvatinib does not inhibit UGT1A6, UGT2B7 or aldehyde oxidase. Lenvatinib does not induce UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.

In Vitro Studies with Substrates of Transporters: Lenvatinib does not have the potential to inhibit MATE1, MATE2-K, OCT1, OCT2, OAT1, OAT3, BSEP, OATP1B1, or OATP1B3 in vivo.

Lenvatinib has been reported to prolong the QT/QTc interval. Avoid coadministration of lenvatinib with medicinal products with a known potential to prolong the QT/QTc interval.

9.1.9 Warnings and Precautions

Hypertension: Serious complications of poorly controlled hypertension have been reported. Control blood pressure prior to initiating lenvatinib. Monitor blood pressure after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment. Withhold or discontinue for grade 3 hypertension despite optimal antihypertensive therapy. At treating physician's discretion, resume at a reduced dose when hypertension is controlled or permanently discontinue lenvatinib based on severity. Discontinue for grade 4 hypertension.

Cardiac Dysfunction: Serious and fatal cardiac dysfunction can occur with lenvatinib. Monitor patients for clinical symptoms or signs of cardiac dysfunction. Withhold or discontinue for grade 3 cardiac dysfunction. At treating physician's discretion, resume at a reduced dose upon recovery. Discontinue for grade 4 cardiac dysfunction.

Arterial Thromboembolic Events: Discontinue following an arterial thromboembolic event.

Hepatotoxicity: Monitor liver function prior to treatment and periodically (every 2 weeks for the first 2 months, and at least monthly thereafter) during treatment. Withhold or discontinue for grade 3 or 4 hepatotoxicity. Discontinue for hepatic failure.

Renal Failure or Impairment Serious including fatal renal failure or impairment can occur with lenvatinib. Initiate prompt management of diarrhea or dehydration/hypovolemia. Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib for renal failure or impairment based on severity.

Proteinuria: Monitor for proteinuria prior to treatment and periodically during treatment. Withhold for 2 or more grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome.

Diarrhea: May be severe and recurrent. Promptly initiate management for severe diarrhea. Withhold and resume at a reduced dose upon recovery or permanently discontinue based on severity.

Fistula Formation and Gastrointestinal Perforation: Permanently discontinue in patients who develop grade 3 or 4 fistula or any grade gastrointestinal perforation.

QT Interval Prolongation: Monitor and correct electrolyte abnormalities. Withhold and resume at reduced dose of lenvatinib upon recovery based on severity for QT interval greater than 500 ms or for 60 ms or greater increase in baseline QT interval.

Hypocalcemia: Monitor blood calcium levels at least monthly and replace calcium as necessary. Withhold and resume at reduced dose upon recovery or permanently discontinue lenvatinib depending on severity.

Reversible Posterior Leukoencephalopathy Syndrome: Withhold and resume at a reduced dose upon recovery or permanently discontinue lenvatinib depending on severity and persistence of neurologic symptoms.

Hemorrhagic Events: Serious including fatal hemorrhagic events can occur with lenvatinib. Consider the risk of severe or fatal hemorrhage associated with tumor invasion or infiltration of major blood vessels (e.g., carotid artery). Withhold and resume at reduced dose upon recovery or permanently discontinue lenvatinib based on the severity.

Impairment of Thyroid Stimulating Hormone Suppression/Thyroid Dysfunction: Lenvatinib impairs exogenous thyroid suppression. Monitor thyroid function prior to initiating lenvatinib and at least monthly during treatment. Treat hypothyroidism according to standard medical practice.

Impaired Wound Healing: Impaired wound healing has been reported in patients who received lenvatinib. Withhold lenvatinib for at least 1 week prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of lenvatinib after resolution of wound healing complications has not been established.

Osteonecrosis of the Jaw Osteonecrosis of the Jaw (ONJ): ONJ has been reported in patients receiving lenvatinib. Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Consider preventive dentistry prior to treatment with lenvatinib. Avoid invasive dental procedures, if possible, particularly in patients at higher risk. Withhold lenvatinib for at least 1 week prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution.

Embryofetal Toxicity: Lenvatinib can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception during treatment and for at least 30 days after the last dose.

9.1.10 Adverse Events

See Section 9.2.11

9.2 Pembrolizumab (Keytruda)

The following information is based on the Prescribing Information for Keytruda (pembrolizumab; MK-3475) dated July 2021.

9.2.1 Product Description

Pembrolizumab is a programmed death-receptor-1 (PD 1)-blocking antibody. Pembrolizumab is a humanized monoclonal IgG4 kappa antibody with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA (pembrolizumab) injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

9.2.2 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

9.2.3 Storage and Handling Requirements

Store vials of solution under refrigeration at 2-8°C (36-46°F) in original carton to protect from light. Do not freeze. Do not shake.

9.2.4 Administration

Pembrolizumab is administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.

No other drugs should be co-administered through the same infusion line.

9.2.5 Preparation and Storage Following Dilution

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute pembrolizumab (solution) prior to intravenous administration.

- Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution

The product does not contain a preservative. Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

9.2.6 Availability and Ordering

Pembrolizumab is commercially available and administration is standard of care for patients with endometrial cancer. The costs of pembrolizumab and its administration will be the responsibility of the patient and/or the patient's 3rd party payor.

9.2.7 Contraindications

No contraindications have been identified.

9.2.8 Pharmacokinetics

The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (Cmax), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

9.2.9 Drug Interactions

As pembrolizumab is an IgG4 antibody that is administered parentally and cleared by catabolism, food and drug-drug interactions are not anticipated to affect exposure. Therefore, no dedicated drug-drug interaction studies have been performed. However, as systemic corticosteroids may be used to treat immune-

mediated adverse reactions concomitant with pembrolizumab, the potential for a PK drug-drug interaction with pembrolizumab as a victim was assessed. No relationship was observed between prolonged use of systemic corticosteroids and pembrolizumab exposure. Similarly, the potential of drug-drug interaction between pembrolizumab and chemotherapy agents as well as other small molecules is expected to be low.

9.2.10 Warnings and Precautions

Severe and Fatal Immune-Mediated Adverse Reactions

Pembrolizumab is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue pembrolizumab depending on severity. In general, if pembrolizumab requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to grade 1 or less. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

- Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated adverse reactions can occur after discontinuation of treatment. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions in pembrolizumab, administration of corticosteroids and/or supportive care. For additional information, refer to the current version of the Prescribing Information for pembrolizumab.
  - Immune-mediated pneumonitis

- Immune-mediated colitis
- Immune-mediated hepatitis
- Immune-mediated hypophysitis
- Adrenal insufficiency
- Immune-mediated hyperthyroidism and hypothyroidism
- Renal failure and immune-mediated nephritis
- Immune-mediated Type 1 diabetes mellitus
- The following additional clinically significant, immune-mediated adverse reactions occurred: severe skin reactions (including exfoliative dermatitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis), uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, adrenal insufficiency, myasthenic syndrome, optic neuritis, rhabdomyolysis, myocarditis, and myelitis

- Other immune-mediated adverse reactions:

  The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received pembrolizumab or were reported with the use of other PD 1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

  - *Cardiac/Vascular*: Myocarditis, pericarditis, vasculitis .
  - *Nervous System*: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.
  - *Ocular*: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
  - *Gastrointestinal*: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis.
  - *Musculoskeletal and Connective Tissue*: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica.
  - *Endocrine*: Hypoparathyroidism Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

- Transplant-related adverse reactions
  - Solid organ transplant rejection
  - Acute graft versus host disease (GVHD), including fatal GVHD, in patients with history of allogeneic hematopoietic stem cell transplant
- Increased mortality in patients with multiple myeloma when pembrolizumab is added to a thalidomide analogue and dexamethasone
- Infusion-related reactions, including hypersensitivity and anaphylaxis
- Embryofetal toxicity:

  Pembrolizumab may cause fetal harm when administered to a pregnant woman. Highly effective contraception must be used during treatment with pembrolizumab and for 4 months after the last dose.

9.2.11 Adverse Events

The safety of pembrolizumab in combination with lenvatinib (20 mg orally once daily) was investigated in KEYNOTE-146, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). The median duration of exposure to pembrolizumab was 6 months (range: 0.03 to 23.8 months).

Pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Fatal adverse reactions occurred in 3% of patients receiving pembrolizumab and lenvatinib, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage. Serious adverse reactions occurred in 52% of patients receiving pembrolizumab and lenvatinib.

Serious adverse reactions in ≥ 3% of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%). Pembrolizumab was discontinued for adverse reactions (grade 1-4) in 19% of patients, regardless of action taken with lenvatinib.

The most common adverse reactions (≥ 2%) leading to discontinuation of pembrolizumab were adrenal insufficiency (2%), colitis (2%), pancreatitis (2%), and muscular weakness (2%).

Adverse reactions leading to interruption of pembrolizumab occurred in 49% of patients; the most common adverse reactions leading to interruption of pembrolizumab (≥2%) were: fatigue (14%), diarrhea (6%), decreased appetite (6%), rash (5%), renal impairment (4%), vomiting (4%), increased lipase (4%), weight loss (4%), nausea (3%), increased blood alkaline phosphatase (3%), skin ulcer (3%), adrenal insufficiency (2%), increased amylase (2%), hypocalcemia (2%), hypomagnesemia (2%), hyponatremia (2%), peripheral edema (2%), musculoskeletal pain (2%), pancreatitis (2%), and syncope (2%). Table 7 and

Table 8 summarize adverse reactions and laboratory abnormalities, respectively, in patients on pembrolizumab in combination with lenvatinib.

Table 7. Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-146

Adverse Reaction	Pembrolizumab 200 mg every 3 weeks with Lenvatinib (n=94)	
	All Grades (%)	Grades 3-4 (%)
General		
Fatigue*	65	17
Musculoskeletal and Connective tissue		
Musculoskeletal pain†	65	3
Vascular		
Hypertension‡	65	38
Hemorrhagic events§	28	4
Gastrointestinal		
Diarrhea¶	64	4
Nausea	48	5
Stomatitis#	43	0
Vomiting	39	0
Abdominal painÞ	33	6
Constipation	32	0
Metabolism		
Decreased appetiteß	52	0
Anemia	27	3
Endocrine		
Hypothyroidismà	51	1
Investigations		
Decreased weight	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infectionè	31	4
Respiratory, Thoracic, and Mediastinal		
Dysphonia	29	0
Dyspneað	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rashø	21	3

* Includes asthenia, fatigue, and malaise
† Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity
‡ Includes essential hypertension, hypertension, and hypertensive encephalopathy
§ Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, hemorrhage intracranial, injection site hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage
¶ Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea
# Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis
Þ Includes abdominal discomfort, abdominal pain, lower abdominal pain, and upper abdominal pain
ß Includes decreased appetite and early satiety
à Includes increased blood thyroid stimulating hormone and hypothyroidism
è Includes cystitis and urinary tract infection

ð Includes dyspnea and exertional dyspnea
ø Includes rash, rash generalized, rash macular, and rash maculo-papular

Table 8. Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-146

Laboratory Test*	Pembrolizumab 200 mg every 3 weeks with Lenvatinib (n=94)	
	All Grades (%)†	Grades 3-4 (%)†
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alanine phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3

* With at least 1 grade increase from baseline
† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter (range: 71 to 92 patients).

10 MEASUREMENT OF EFFECT

10.1 Evaluation Criteria for Tumor Response

Tumor response will be evaluated and recorded according to RECIST v1.1.

In the event of a PR or CR, the imaging used when the response was first documented must be repeated at the time of the next scheduled imaging to confirm tumor response. At the treating physician's discretion, confirmatory scans can be performed sooner, but no less than 4 weeks following the imaging indicating the PR or CR.

10.2 Imaging

Only imaging of the initial sites of disease is required at subsequent time points to provide tumor measurements for assessment of antitumor effect. History of brain metastases should prompt brain imaging at baseline and periodically after initiation of study therapy.

The same type of imaging used at baseline should be used at each scheduled assessment. At the treating physician's discretion, additional imaging may be performed when clinically indicated.

10.3 Centralized Radiology Review

Radiologic images to determine response status (baseline and subsequent exams) will be transmitted to the Coordinating Center for centralized, independent review and confirmation of response assessment when a patient goes off treatment.

11 CORRELATIVE STUDIES

11.1 Participation in Correlative Studies

Section 1.4 outlines the plans and rationale for the correlative studies. Participation in the correlative studies is a study requirement. Samples for correlative studies will be collected at the participating study site.

[redacted]

11.4.1 [redacted]

[redacted]

[redacted]

11.6 Tracking and Collection of Samples

Collection and distribution of all samples will be logged by the study team at the participating site in OnCore.

12 STUDY CALENDAR

Assessments and other Requirements	Baseline (Prior to registration)[A]	Treatment	
		Every Cycle Day 1[B] (±3 days, except Cycle 1)	End of study therapy (±3 days)
Informed consent[D]	X		
History, physical exam	X	X	X
Height	X		
Weight, Vital Signs	X	X	X
Performance status[E]	X	X	X
Concurrent medications[F]	X	X	X
Baseline conditions and symptoms	X		
AEs assessment[G]	X	X	X
CBC, differential platelet count	X	X	X
Blood chemistry[H]	X	X	X
TSH, 3T4, cortisol	X	X[I]	X
Serum pregnancy test[J]	X	X	
Urinalysis	X		
Diary review/pill count		X	
Tumor assessment and measurement[K]	X	X[L]	
Patient-reported outcomes			
EORTC-QLQ-C30+EN24[M]	X	X	X
EQ-5D-DL[M]	X	X	X
FACIT/HADS[N]	X	X	X
Gendered Racial Microagressions and Africultural Coping Systems	X		
Correlative whole blood samples[O]	X[P]		X[Q]
Urine and vaginal swab samples[O]	X		
Survival status			X[R]
Lenvatinib administration		X[S]	
Pembrolizumab administration		X[T]	

A. Unless otherwise noted, eligibility evaluations within 28 days prior to initiation of study treatment

B. Day 1 assessments do not need to be repeated if done within 72 hours prior to initiation of study treatment. Assessments are to be completed every 21 ±3 days even if study drug is held.

C. See Section 6.5. All patients who initiate treatment on study will proceed to 30-day follow-up and extended follow-up after the initial 30-day period.

D. If a patient has been consented but not registered within 4 weeks, reconsenting is not required unless a new IRB-approved version of the consent form is available.

E. See Appendix 1 for ECOG criteria.

F. Include over-the-counter medications.

G. Assessment and reporting based on the NCI CTCAE v5.0. Refer to Section 8 regarding expedited reporting. Assessment will be performed by the study team using telemedicine when treatment is received at a non-study site.

H. Chemistry includes the following: basic metabolic panel (sodium, potassium, carbonate, chloride, glucose, calcium, BUN, creatinine) and hepatic panel (ALT, AST, ALP, total bilirubin, direct bilirubin, albumin, total protein).

I. Every 6 weeks (± 1 week).

J. Only required for WCBP (see SectionInclusion Criteria for definitions and related requirements). In addition, review pregnancy risks and offer pregnancy test as clinically indicated.

K. Brain imaging only required for patients with brain metastasis diagnosed and treated prior to initiation of study treatment. The imaging used at baseline should be used at each subsequent imaging time point.

L. Counting from C1D1, for the first 24 weeks, during Week 6, 12, 18, and 24 (±1 week), or sooner, if clinically indicated, until documentation of confirmed progression. After 24 weeks, tumor assessments must be performed every 9 weeks counting from C1D1 (during Week 33, 42, 51, 60, etc.) (±1 week), or sooner if clinically indicated, until documentation of confirmed PD. Responses and PD must be confirmed at least 4 weeks later (usually at the next tumor assessment).

M. PROs will be administered every day 1 of every cycle starting at C1D1 and 30 days after last dose of study drug until patient enters the extended follow-up period. During the extended follow-up period PROs will be administered every 3 months (see Section 1.4.1).

N. FACIT/HADS questionnaire will be administered at baseline, C1D1, C2D1, C3D1, then every other cycle beginning at C5 and beyond, end of study, and the first extended follow-up visit (see Section 1.4.1)..

O. Collect correlative whole blood urine, and vaginal swab samples any time after consent and before C1D1 prior to the initiation of any study treatment. See also Section 11.

P. An optional additional blood sample will be collected for DNA ancestrial analysis. See Section 11.3.1

Q. Collect correlative whole blood at the conclusion of therapy if prior to 90 days. See also Section 11

R. Capture survival status approximately every 3 months during the extended follow-up period. During the extended follow-up period, data may be obtained by record review or patients may be contacted by phone for report of disease status, new treatment and/or survival status approximately every 3 months.

S. Lenvatinib administered orally (PO) once daily (QD) during each 21-day cycle For lenvatinib instructions refer to Sections 6.2, 7.3, and 9.1.

T. Pembrolizumab administered by IV infusion on day 1 of each 21-day cycle. For pembrolizumab instructions refer to Sections 6.2, 7.4, and 9.2.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design and Analysis

Primary Analysis: The binary outcome ORR: will be estimated with a sample proportion and 95% Wilson confidence intervals. The ORR will be estimated in unadjusted and adjusted manners, where in the latter case we use logistic regressioin to model the outcome against fixed effects for patient characteristics and disease biomarkers, using a Bernoulli distribution and logit link function, including a set of measurements that minimize the Bayesian Information Criterion.

Secondary Analyses: OS is calculated as the time between treatment start date until date of death from any cause or until censoring. PFS is calculated as the time between treatment start date until occurrence of disease progression or until censoring. The Kaplan-Meier product limit approach will be used to estimate step functions for OS and PFS. Proportional hazard modeling will be used to estimate mean survival time in both unadjusted and adjusted manners, where in the latter case we account for patient characteristics and disease biomarkers.

Safety Analyses: Times to toxicity, dose reduction, or drug discontinuation will be used as safety outcomes. Each measure is calculated as the time between treatment start date until event occurrence or until censoring. These measures will be summarized using proportional hazards regression, and visually present the event curves with cumulative incidence curves.

13.2 Sample Size/Accrual Rates

As the goal of this proposal is to estimate ORR, we will not formally power for hypothesis testing. With 100 subjects (and conservativiely assuming a 0.5 ORR for maximum variability), we would be able to estimate the ORR with a margin of error of ±0.1.

This study is expected to be open to accrual at a total of 10 sites across the US within 24 months of its initial approval at the coordinating site, VCU Massey Cancer Center. Each site is anticipated to accrue an average of 1 patient every 2 to 3 months. The total period of study recruitment is therefore anticipated to occur over a period of 25 to 42 months, with recruitment complete by July 1, 2025.

14 DATA AND SAFETY MONITORING PLAN (DSMP)

While patients are on treatment, the principal investigator, study team members (e.g., site investigators, research nurses, clinical research associates) and Coordinating Center staff will meet at least monthly to review study status. The biostatistician will review data with the principal investigator and Coordinating Center staff at least quarterly. This review will include, but not be limited to, reportable events and an update of the ongoing study summary that describes study progress in terms of the study schema. All meetings, including attendance, are documented.

14.1 Monitoring and Auditing

14.1.1 MCC Compliance Office

Compliance specialists in the MCC Compliance Office will provide monitoring and auditing for this study.

14.1.2 Data Safety and Monitoring Committee

The study will be reviewed by the MCC DSMC initially according to the risk level specified by the MCC Protocol Review and Monitoring Committee (PRMC) and then according to a schedule based on study status and quality indicators. The DSMC will review reports provided by the principal investigator/study team and the MCC Compliance Office focusing on data integrity and patient safety.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with the clinical trial protocol and with federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Patients/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children).

15.3 Institutional Review Board

The VCU IRB, which is registered with the Office for Human Research Protections (OHRP), must review and approve the protocol, the associated informed consent document, and recruitment material (if any). Any amendments to the protocol or consent form must also be approved.

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of this therapy will be provided to patients and their families. Consent forms describing the study interventions, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to

the patient and answer any questions that may arise. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to patients for their records; the original consent form will be maintained in the research records.

15.5 Patient Confidentiality

Patient confidentiality is strictly held in trust by the principal investigator, participating investigators, staff, and the sponsor and its agents. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The participating site will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections. Source documents provided to the Coordinating Center for the purpose of auditing or monitoring will be de-identified and labeled with the study number, patient ID number, and patient initials.

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

16 DATA COLLECTION AND MANAGEMENT

16.1 Data Management Responsibilities

The principal investigator is responsible for: (i) the overall conduct of the investigation, (ii) ongoing review of trial data including all safety reports, and (iii) reporting SAEs and UPs as required in Section 8.

16.2 Case Report Forms and Data Collection

MCC will provide standard electronic CRFs (eCRFs) and create study-specific eCRFs to be able to capture all information required by the protocol. The eCRFs will be approved by the Coordinating Center to ensure the most effective data acquisition.

The investigator(s) and study coordinator(s) must maintain source documents for each patient in the study. All information on eCRFs will be traceable to these source documents, which are generally maintained in the patient's file.

All eCRFs should be completed and available for collection within a timely manner, preferably no more than 5 days after the patient's visit.

16.3 OnCore Data Entry

Data will be entered into MCC's OnCore database on an ongoing basis by all participating centers via remote access. Sites are responsible for updating data to allow for data compilation and review. Electronic data submissions will be reviewed periodically for data timeliness and accuracy. Sites will be queried periodically and significant problems with delinquency or accuracy may result in suspension of enrollment at a site.

16.4 Study Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond the publication of any abstract or manuscript reporting the results of the protocol or submission of a final report to clinicaltrials.gov.

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APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Description**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self; unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about > 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair > 50% of waking hours.	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX 2. DOSE MODIFICATION AND TOXICITY MANAGEMENT FOR IMMUNE-RELATED ADVERSE EVENTS (irAEs) ASSOCIATED WITH PEMBROLIZUMAB

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
General instructions: Corticosteroid taper should be initiated upon AE improving to Grade 0 or 1 and continue to taper over at least 4 weeks. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has improved to grade 0 or 1 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. **For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.**				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics for opportunistic infections.	Monitor for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment.
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Patients 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.	Monitor subjects for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Patients with grade ≥ 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.
	Grade 4	Permanently discontinue		
AST / ALT elevation or increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable).
	Grade 3 or 4	Permanently discontinue		
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or grade 3 or 4 hyperglycemia associated with evidence of β-cell	Withhold	Initiate insulin replacement therapy for patients with T1DM. Administer anti-hyperglycemic in patients with hyperglycemia.	Monitor patients for hyperglycemia or other signs and symptoms of diabetes.

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
	failure			
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include but are not limited to: Gullain-Barre Syndrome, encephalitis		

Immune-related Adverse Event	Toxicity Grade or Conditions (CTCAE v4.0)	Action Taken with Pembrolizumab	irAE Management with Corticosteroids and Other Therapies	Monitor and Follow-up
	Grade 4 or recurrent grade 3	Permanently discontinue		

Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.

For patients with grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when the AE improves to grade ≤ 2 and is controlled with hormonal replacement therapy or metabolic control is achieved (in the case of T1DM).

AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GI = gastrointestinal, irAE = immune-related adverse event, IV = intravenous, T1DM = Type 1 diabetes mellitus.