

TITLE: Phase II study with safety lead-in of lenvatinib, pembrolizumab, and weeklypaclitaxel for recurrent endometrial, epithelial ovarian, fallopian tube and primary peritoneal cancer

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LOCAL PROTOCOL: OSU-20172

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1.0 TRIAL SUMMARY

Abbreviated Title	Lenvatinib, pembrolizumab, and weekly paclitaxel for recurrent endometrial, epithelial ovarian, fallopian tube and primary peritoneal cancer
Trial Phase	2 (with safety lead in)
Clinical Indication	recurrent endometrial, epithelial ovarian, fallopian tube and primary peritoneal cancer
Trial Type	Single arm, open label
Type of control	n/a
Route of administration	PO lenvatinib, IV paclitaxel, IV pembrolizumab
Trial Blinding	n/a
Treatment Groups	n/a
Number of trial participants	29-47
Estimated enrollment period	18 months
Estimated duration of trial	24 months

Duration of Participation	12 months
Estimated average length of treatment per patient	12 months

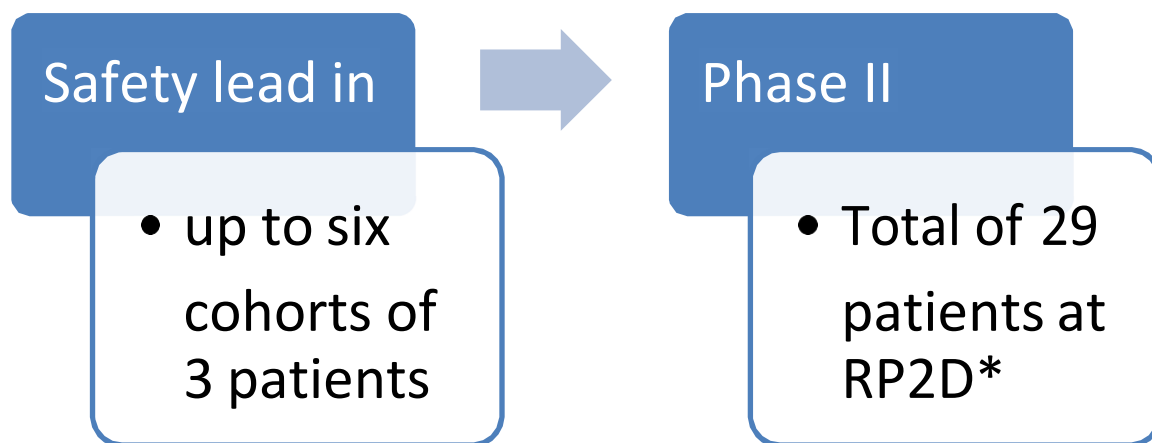
2.0 TRIAL DESIGN

2.1 Trial Design

The trial starts with a safety lead-in stage of up to 18 recurrent endometrial and/or ovarian cancer patients. Once the safety of the treatment is shown, accrual will open to the Phase II studies. Patients treated at the recommended phase 2 dose (RP2D) from the safety lead-in will be included in the Phase II accruals.

The Phase II stage is designed as an open label, basket trial to assess the efficacy and confirm the safety of lenvatinib, pembrolizumab, and weekly paclitaxel for treatment of recurrent endometrial and recurrent platinum resistant ovarian cancer.

2.2 Trial Diagram



Note: *Patients from safety lead in treated at RP2D will be included in phase II enrollment.

3.0 OBJECTIVES & HYPOTHESIS(ES)

Hypothesis: Combination pembrolizumab, lenvatinib, and weekly paclitaxel has an acceptable safety profile and is highly effective in patients with recurrent endometrial cancer and recurrent platinum resistant ovarian, fallopian tube, and primary peritoneal cancer

3.1 Primary Objective

- (1) To determine objective antitumor activity (complete and partial response) of lenvatinib, pembrolizumab, and weekly paclitaxel as measured by RECIST criteria in recurrent endometrial and platinum resistant ovarian cancer.

3.2 Secondary Objectives

- (1) To determine the safety and tolerability weekly paclitaxel, lenvatinib, and pembrolizumabin study patients.
- (2) To measure the progression free survival in the study population.
- (3) To measure the overall survival in the study population

3.3 Exploratory Objective

To explore the baseline tumor genetic and microenvironment parameters predictive of clinical benefit or resistance to the treatment combination and potential mechanisms of resistance.

4.0 BACKGROUND AND RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab

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

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

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

Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. The angiogenesis process begins with local degradation of the basement membrane surrounding capillaries, followed by invasion of the surrounding stroma by underlying endothelial cells in the direction of the angiogenic stimulus. Endothelial cell migration is accompanied by the proliferation of endothelial cells and their organization into three-dimensional structures that join with other similar structures to form a network of new blood vessels. This process involves an alteration in the balance between proangiogenic and antiangiogenic molecules.

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFR α , KIT, and RET. Co-crystal structural analysis demonstrated that lenvatinib has a distinct mode of the interaction with VEGFR2 or FGFR1, termed Type V, while most of the known kinase inhibitors on market are categorized as Type I or II (Okamoto, et al., 2015). Lenvatinib binds to ATP-binding site and the neighboring allosteric region in the kinase domain adopting the DFG-in conformation. Most of the known kinase inhibitors are categorized as Type I,

binding these kinases in the DFG-in configuration and only binding to the ATP-binding site, or Type II binding to the kinase in the DFG-out conformation and binding to both the ATP-binding site and the neighboring regions. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis. Lenvatinib inhibited cell free kinase activities for VEGFR1 – 3 and FGFR1 – 3 with K_i values around 1 nmol/L, and 8 – 22 nmol/L, respectively.

In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and MTC), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone. Considering the roles of VEGFR1-3, FGFR1 – 4, KIT, PDGFR α , and RET in tumor malignancy, the antitumor activity of lenvatinib may be the result of inhibition of VEGF- and FGF-driven angiogenesis, lymphangiogenesis, and a direct antitumor effect for some tumors. Therefore, lenvatinib is being developed as an anticancer therapy for use either as a single agent or in combination with other anticancer agents for the treatment of malignancies including thyroid cancer, RCC, HCC, and endometrial cancer.

Paclitaxel

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Paclitaxel given weekly demonstrated a 27% objective response rate in patients with recurrent endometrial cancer (1). In patients with platinum-taxane refractory ovarian cancer, retreatment with paclitaxel using a weekly schedule has demonstrated activity, possibly through anti-angiogenic as well as direct cytotoxic mechanisms. GOG-0126N demonstrated a 21% objective response rate (and a 46% rate of stable disease) in this population (2). A retrospective study of weekly paclitaxel combined with every two-week bevacizumab resulted in an improved progression free survival (3-5). A randomized phase III (Aurelia) trial showed that when weekly paclitaxel was combined with bevacizumab (monoclonal antibody against VEGF) the response rate and progression free survival were significantly improved compared to weekly paclitaxel alone (hazard ratios (HRs) 0.46 (95% confidence interval [95% CI], 0.30 to 0.71; median PFS 10.4

v 3.9 months; objective response rate (ORR) 53.3% v 30.2%, 95% CI, 1.7% to 44.5%)(6, 7). Furthermore, in first line treatment of ovarian cancer weekly paclitaxel combined with carboplatin versus every three-week paclitaxel and carboplatin significantly improved progression free and overall survival (PFS 17 mos vs 28 mos, P = 0.0014)(8).

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Population

There is an urgent need for new and improved treatment strategies for recurrent endometrial and ovarian cancer, and methods to identify which patients will benefit from these therapies. Survival of patients who develop recurrent endometrial cancer is short(9). Chemotherapy and/or hormonal or targeted therapy may provide disease control but response rates have generally been less than 15%(9). Similarly, recurrent platinum resistant ovarian cancer has very limited active treatment options and survival is also typically short (10).

Pembrolizumab has been approved for patients with mismatch repair deficient (MSI-H or dMMR). Although response rates were very promising in the mismatch repair deficient population (56%)(11-13) (13), in patients with microsatellite stable recurrent endometrial cancer response rates were only 13% (14). Similarly, single agent lenvatinib did not demonstrate significant activity in recurrent endometrial cancer (15), however, this agent appears very promising in combination with other therapy.

On September 17 2019, the (FDA) granted FDA approval for lenvatinib (20 mg PO daily), in combination with pembrolizumab (200 mg IV every 3 weeks) for the potential treatment of patients with advanced and/or metastatic non-microsatellite instability high (MSI-H)/proficient mismatch repair (pMMR) endometrial carcinoma (EC) who have progressed following at least one prior systemic therapy. In the study by Makker et al 108 patients were enrolled (16, 17); 94 (87%) were non-MSI-H/proficient MMR (MMRp). The objective response rate (ORR) was 38.3% (95% CI, 29–49%). The median PFS was 7.4 months (95% CI, 5.0–NE); 69% had a response duration

≥6 months(17). The toxicity profile was favorable. Grade 3 treatment-related adverse events (TRAEs) occurred in 37 (70%) pts; there were no Grade 4 TRAEs. 5 (9%) pts discontinued treatment due to a TRAE. The most common TRAEs were hypertension (59%), fatigue (55%), diarrhea (51%), hypothyroidism (47%), decreased appetite (40%), nausea (38%), stomatitis (34%), and palmar-plantar erythrodysesthesia (32%)(16).

While pembrolizumab is FDA approved for recurrent mismatch repair deficient

endometrial cancer, activity has also been seen in recurrent ovarian cancer (ORR 11.5%). Data from the KEYNOTE-028 study suggested that pembrolizumab has clinical activity in patients with PD-L1+advanced ovarian cancer. Phase II data from the KEYNOTE-100 study showed an 8% response rate in all-comers with 8.2 months duration of response (18). Of note, in patients with a PD-L1 expression level measured by combined positive score (CPS) ≥ 1 the ORR was 10.2% and for CPS ≥ 10 the ORR was 17.1%, including 8.5% complete responders(18). Although single agent activity is relatively low, combination therapy with other agents is promising. For example, combination pembrolizumab and niraparib (TOPACIO/KEYNOTE-162) showed an ORR 18% with a clinical benefit rate of 65%, and this was similar across patients with platinum resistant ovarian cancer, with and without tumor BRCA mutations, HRD positive and negative (19). However, in a phase III trial (JAVELIN Ovarian 200) avelumab alone or in combination with pegylated liposomal doxorubicin (PLD), compared with PLD, did not meet the prespecified primary endpoints of overall survival (OS) or progression-free survival (PFS) in patients with platinum-resistant or -refractory ovarian cancer. Objective response rates were 13.3% [95% CI 8.8, 19.0] for avelumab + PLD; 3.7% [95% CI 1.5, 7.5] for avelumab alone; and 4.2% [95% CI 1.8, 8.1] for PLD alone)(20). Thus, other combinations have to be explored to improve outcomes for patients with recurrent platinum resistant ovarian cancer and recurrent endometrial cancer.

Taxanes have significant single agent activity in ovarian (7, 21, 22), and endometrial cancer (1). Our group conducted a phase I study of weekly paclitaxel with lenvatinib in recurrent endometrial cancer and recurrent platinum resistant ovarian cancer. Preliminary data suggest very promising activity in both recurrent endometrial and recurrent platinum resistant ovarian cancer patients with a favorable side effect profile. The ORR was 71% in ovarian cancer (1/19 CR, 17/19 PR) and 50% in endometrial cancer (3/6 with PR) with a median duration of response of 10.9 months and median PFS of 14 months (23). In order to further improve response rates and survival, we propose adding pembrolizumab to weekly paclitaxel and lenvatinib. We believe that this may provide synergy as taxanes have been demonstrated to upregulate PD-1 and PD-L1 in preclinical studies (24, 25). In an ovarian cancer mouse model, treatment with paclitaxel increased CD8+ tumor infiltrating lymphocytes, PD-L1 expression and activated NF-kB signaling(26). Furthermore, mice treated with paclitaxel and PD-1/PD-L1 blockade survived longer compared paclitaxel alone. Recent results of pembrolizumab with weekly paclitaxel in platinum resistant ovarian cancer demonstrated a partial response in 51% of patients with a median PFS of 7.6 months (4.8-12 months)(27). Furthermore, pembrolizumab is also FDA approved in combination with paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC). Therefore, we hypothesize that the addition of pembrolizumab to weekly paclitaxel and lenvatinib (or weekly paclitaxel to pembrolizumab and lenvatinib) is highly effective and safe with manageable toxicities in both recurrent endometrial and platinum resistant ovarian cancer.

4.2.2 Justification for Dose

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the

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

Lenvatinib

A global Phase 1/1b program, in subjects with solid tumors, has been conducted to explore the safety, tolerability, pharmacokinetics (PK), pharmacodynamic biomarkers, and antitumor efficacy of lenvatinib at a wide range of dose levels and with 4 different dosing schedules: once a day (QD) continuous dosing in Study E7080-E044-101, twice daily (BID) interrupted dosing (Schedule 1 [abandoned before reaching a maximum tolerated dose MTD]), BID continuous dosing (Schedule 2), and QD dosing (Schedule 3, melanoma combination cohort) in Study E7080-A001-102, and BID interrupted dosing in Study E7080-J081-103. Modeling of PK data in Studies E7080-E044-101 and E7080-A001-102 demonstrated that progression-free survival (PFS) and response (partial response [PR] and durable stable disease [SD]) significantly increased with higher lenvatinib exposure (based on C_{max} and AUC(0-24,ss)). The MTD from Study E7080-E044-101 (25 mg QD) was correlated with higher drug exposure compared with the MTD from Study E7080-A001-102 (10 mg BID). Consequently, 25 mg QD was selected for the future studies, as it was determined to be the safest dose that provides the highest efficacy. To simplify the dose reduction scheme, a dosage of 24 mg QD (two 10 mg capsules + one 4 mg capsule) was selected for continued lenvatinib development.

In a mass balance study (Study E7080-E044-104), in which subjects received 22 to 24 mg of ¹⁴C-E7080, analysis showed that 25% of the dose was eliminated in urine and 64% was eliminated in feces. E7080-J081-105 was a dose escalation Phase 1b study to investigate the tolerability and safety of lenvatinib up to 24 mg, orally, QD on a continuous dose schedule in Japanese subjects with solid tumors that are resistant to standard therapies, or for which no appropriate treatment is available. The 24-mg dose of lenvatinib was determined to be tolerable when administered orally on a once daily continuous dose schedule in Japanese subjects with solid tumor. The adverse events (AEs) observed are consistent with the VEGF targeted therapy profile and are manageable with dose reductions and interruptions.

A Phase 1b study (Study E7080-J081-110) of lenvatinib administered by BID continuous dosing, in combination with carboplatin and paclitaxel, was conducted in subjects with non-small cell lung cancer (NSCLC). The MTD observed for lenvatinib administered by

continuous BID dosing when given in combination with carboplatin and paclitaxel was 4 mg BID. An open-label Phase 1b trial of lenvatinib plus pembrolizumab in subjects with selected solid tumors (E7080-J081-115) is being conducted in Japan. Studies of lenvatinib in combination with pembrolizumab in subjects with HCC (E7080-J081-116) and lenvatinib in combination with nivolumab in subjects with HCC (E7080-J081-117) are ongoing.

In a phase I study (Backes et al) doses were escalated from 8, 12, 16, to 20 mg in combination with weekly paclitaxel 80 mg/m². Two patients developed a dose limiting toxicity (DLT) on dose level 4, thus lenvatinib 16 mg daily with weekly paclitaxel 80 mg/m² (day 1, 8, 15 on a 28-day cycle) was determined to be the recommended phase 2 dose. PK analysis are pending. Encouraging antitumor activity was seen at all dose levels.

We believe the addition of pembrolizumab to weekly paclitaxel will have limited overlapping toxicities. Therefore, we have chosen a starting dose of weekly paclitaxel 80 mg/m², lenvatinib 16 mg daily and pembrolizumab 200 mg every 3 weeks on a 21-day cycle.

4.2.3 Rationale for Endpoints

Primary Endpoint:

Objective tumor response assessed by RECIST v1.1 criteria will be reported as a percentage and will be calculated by the number of patients with a complete or partial response divided by the total number of patients. The percentage of patients with stable disease and progressive disease will be calculated in a similar fashion.

Secondary Endpoints:

1. Safety and toxicity:

Toxicity as assessed by Common Terminology for Adverse Events (CTCAE) v5.0 will be evaluated descriptively using frequencies and percentages and will be reported using tables. All patients who receive treatment, regardless of eligibility, will be evaluated for toxicity. Toxicities by type and maximum grade over the course of treatment and follow up will be summarized and by date of occurrence.

2. Progression free survival

Progression free survival will be calculated as the time from first therapy to the time of cancer progression, death or lost to follow up. Patients who do not progress will be censored at the last day of follow up.

3. Overall survival:

This endpoint is not expected to have sufficient power for a definitive test and will therefore be treated as supportive evidence.

Exploratory Endpoints:

Objective response rate and progression-free survival by tumor microenvironment, MMR status and PD-L1 and other protein expression. Measures of T cell receptor (TCR) and clinical benefit such as ORR, PFS and OS.

Evaluations of circulating tumor DNA with treatment and clinical outcomes; parameters derived from the ctDNA assay, such as relative ctDNA titers, tumor mutational burden, and specific genetic alterations will be explored as prognostic and predictive biomarkers in this study

4.2.3.1 Biomarker Research

T Cell Receptor

Analysis

Serial tumor biopsies in responders to immune checkpoint blockers have shown longitudinal increase in T cell infiltration over time thus suggesting that tumor eradication in these patients is mediated by reactivation and expansion of pre-existing tumor infiltrating T cells. The recent development of next generation T cell receptor sequencing has now provided the opportunity to identify, quantify, and longitudinally track each individual T cell clone thus providing an unprecedented insight into mechanisms of tumor eradication by these agents and also serving as a tool to study the mechanism through which the immune system prevents tumor recurrence.

We hypothesize that patients who respond to treatment will have peripheral persistence or expansion of the T cell clones present in tumors at baseline.

We plan to define T cell clones present in the tumor and establish their concordance with peripheral blood T cell clones at baseline and will then track the persistence of these T cell clones in peripheral blood longitudinally during the surveillance period. In addition, we will compare and contrast the overall clonal dynamics of the TCR repertoire in order to define the parameters suggestive of response to treatment, and furthermore establish the correlation between clonal expansion/persistence of tumor infiltrating T cell clones and progression free survival.

Archival tumor blocks will need to be submitted for T cell receptor sequencing.

Research blood samples will be collected at baseline (screening, during and after treatment).

Circulating tumor DNA analysis

CtDNA is tumor-derived fragmented DNA that is detectable in the bloodstream but not associated with tumor cells. This is different from cell-free DNA (cfDNA), which is a broader term describing freely circulating DNA in the blood stream that is not

necessarily of tumor origin. There is interest in utilizing circulating tumor DNA (ctDNA) as a surrogate to predict clinical outcomes more rapidly and less invasively than traditional imaging and biopsy-based methods.(28) Small studies in endometrial and ovarian cancers suggest that ctDNA may be a reliable biomarker of disease, identify disease at an earlier stage than imaging, and independently predict survival.(29, 30) However, further studies are needed to validate the clinical use of ctDNA in this population.(31)

In this study, we will plan to collect plasma followed by cfDNA isolation prior to therapy initiation, after cycle 1 and 2 (prior to cycle 2 and 3) and then at the time of first imaging (after cycle 3). We will use the ctDNA assay to assess the predictive value of ctDNA pre-treatment, after the first cycle and at the time of first imaging. In addition, other parameters derived from the ctDNA assay, such as relative ctDNA titers, tumor mutational burden, and specific genetic alterations will be explored as prognostic and predictive biomarkers in this study.

Immune cell population analysis

Evaluation of immune populations pre- and post-immunotherapy has resulted in differences between responders and non-responders in tumor types such as melanoma. The fusion of two technologies termed mass spectrometry (i.e. Cytometry of Time-Of-flight, CyTOF) provides measurements of over 40 simultaneous cellular parameters at single-cell resolution. Mass cytometry uniquely enables investigation of not only cell identity but also behavior at the level of proteins. Given we have shown differences in peripheral blood immune populations between pre- and post-pembrolizumab treatment advanced stage endometrial cancers, **we hypothesize that** patients who respond to paclitaxel, lenvatinib, and pembrolizumab will have a unique immune signature prior to treatment compared to those who do not respond to treatment.

We plan to define the myeloid and lymphoid cell signature in the peripheral blood prior to treatment for those who respond to treatment. In addition, we will compare and contrast the myeloid and lymphoid signature before and after treatment for those who respond and those who do not respond. Research blood samples will be collected at baseline at screening and after the second cycle of treatment. The CyTOF analysis will be complementary to TCR sequencing currently in the protocol.

Tumor Microenvironment

Multi-parameter immunohistochemistry will be used to analyze the tumor microenvironment (e.g., T cells, macrophages, etc.).

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Female participants who are at least 18 years of age on the day of signing informed consent will be enrolled in this study.
2. Women with histologically confirmed (epithelial) endometrial cancer, epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (all histological subtypes)
3. Patients must have received prior treatment with a platinum containing regimen and may have received 1-3 prior regimens. Hormonal therapy and maintenance therapy (with bevacizumab or PARP inhibitor) does not count towards the number of prior treatments.
4. Patients with ovarian, fallopian tube or primary peritoneal cancer must be platinum resistant (progression < 6 months after completion of a platinum containing regimen) or not a candidate for further platinum treatment.
5. Patients with and without mismatch repair deficiency are allowed.
6. Prior PD-1/PD-L1 inhibitors are allowed as long as this was not the most recent regimen and treatment was not discontinued due to side effects/toxicity.
Prior weekly paclitaxel is allowed as long as this was not the most recent regimen and treatment was not discontinued due to side effects/toxicity.
7. Prior targeted therapy targeting angiogenesis is allowed as long as treatment was not discontinued due to side effects/toxicity
8. Have measurable disease based on RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
9. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

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

- A WOCBP who agrees to follow the contraceptive during the treatment period and for at least 4 months

(corresponding to time needed to eliminate any study treatment(s) (MK and or any active comparator/combination) plus 30 days (a menstruation cycle) after the last dose of study treatment. Refer to Appendix 3.

10. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
11. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
12. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Evaluation of ECOG is to be performed within 14 days prior to the date of starting study treatment
13. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 14 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

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

International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. ^a Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. ^b Creatinine clearance (CrCl) should be calculated per institutional standard. Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.	

5.1.2 Participant Exclusion Criteria

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

1. A WOCBP who has a positive urine pregnancy test within 14 days prior to registration (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Note: in the event that 14 days have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication.

2. Has received prior systemic anti-cancer therapy including investigational agents within 4weeks or 5 half-lives whichever is shorter prior to study entry. Patients may not have received biologics, targeted therapy or immunotherapy for 4 weeks (6 weeks for nitrosoureas or mitomycin C). Hormonal therapy is not considered anti-neoplastic therapy.

Note: Participants must have recovered from all clinically significant treatment related AEs due to previous therapies to $\leq$ Grade 1 or baseline, except grade 2 alopecia or fatigue.

3. Has received prior radiotherapy within 3 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 2-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
4. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox),

yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are liveattenuated vaccines and are not allowed.

5. Is currently participating in or has participated in a study of an investigational agent orhas used an investigational device within 4 weeks prior to the first dose of study treatment.
Note: Participants who have entered the follow-up phase of an investigational study mayparticipate as long as it has been 4 weeks after the last dose of the previous investigational agent.
6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
7. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. Note: Participants with basal cell carcinoma of the skin, squamouscell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
8. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and withoutrequirement of steroid treatment for at least 14 days prior to first dose of study treatment.
9. Has severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab, lenvatinib, or paclitaxel and/orany of its excipients. Note, patients with paclitaxel hypersensitivity are eligible if the if infusion can safely be completed with reduced infusion rates and premedication.
10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e.with use of disease modifying agents, corticosteroids or immunosuppressive drugs).Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has a history of (non-infectious) pneumonitis or interstitial lung disease that required steroids or has current pneumonitis.

12. Has a known history of Hepatitis B that is still active (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected)infection. Note: no testing for Hepatitis B and Hepatitis C is required unless the patient is at risk for, or has symptoms or signs of, hepatitis
13. Known HIV-positive patients on combination antiretroviral therapy are ineligible becauseof the potential for pharmacokinetic interactions with pembrolizumab, lenvatinib and paclitaxel. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
14. Significant cardiovascular disease, including:
 - a. If the patient has a known history of decreased LVEF on imaging or clinical suggestion of heart failure, an ECHO or MUGA should be completed. Symptomatic left ventricular dysfunction or baseline left ventricular ejection fraction (LVEF) by multigated acquisition scan (MUGA) or echocardiogram (ECHO) of < lower limit of institutional normal (LVEF<50%) will exclude the patient.
 - b. Patients with marked Baseline prolongation of QT/QTc interval (QTc interval > 480 msec)
 - c. Uncontrolled hypertension: systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg documented on 2 consecutive measurements taken at least 24 hours apart.
 - d. Myocardial infarction, severe angina, or unstable angina within 6 months prior to administration of first dose of study drug.
 - e. History of serious ventricular arrhythmia (ie, ventricular tachycardia or ventricular fibrillation).
 - f. Cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with anti-arrhythmic medication).
 - g. Coronary or peripheral artery bypass graft within 6 months of screening.
 - h. History of Class III or IV congestive heart failure, as defined by the New York Heart Association.
15. Major surgical procedure (e.g. laparotomy, bowel resection) 4 weeks prior to start of the study drug. Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

16. Neuropathy grade >1
17. Non-healing wound, bone fracture, or skin ulcer
18. Active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to administration of first dose of study drug
19. Patients who have a history of a small or large bowel obstruction within 2 weeks of screening or who have an active partial small bowel obstruction or PEG-tube.
20. Serious/active infection or infection requiring parenteral antibiotics
21. Significant arterial or venous thromboembolic disease or vascular disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
 - a. Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
 - b. Peripheral ischemia > Grade 2 (per CTCAE Version 5.0)
 - c. Arterial thrombotic event
 - d. Patients who have a history of deep vein thrombosis or pulmonary embolus < 3 months prior to enrollment must be excluded. However, if patients are on therapeutic anticoagulation, and the DVT/PE has been clinically stable or improved on anticoagulation for >3 months, patients are eligible.
 - e. Patients with a history of clotting disorders must be excluded
22. Significant bleeding disorders within 6 months prior to administration of first dose of study drug, including but not limited to:
 - a. Hematemesis, hematochezia, melena or other gastrointestinal bleeding $\geq$ Grade 2 (per CTCAE Version 5.0)
 - b. Hemoptysis, laryngeal hemorrhage, or other pulmonary bleeding $\geq$ Grade 2 (per CTCAE Version 5.0)
 - c. Hematuria or other genitourinary bleeding $\geq$ Grade 2 (per CTCAE Version 5.0)
23. Inability to swallow pills, malabsorption syndrome or gastrointestinal disease that severely affects the absorption of study drugs, major resection of the stomach or small bowel, or gastric bypass procedure.

24. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
25. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
26. Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment. Pregnant women are excluded from this study because the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lenvatinib, breastfeeding should be discontinued if the mother is treated lenvatinib. These potential risks may also apply to other agents used in this study.

5.1.3 Lifestyle Restrictions

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

Concomitant use of cytochrome P450 (CYP3A4) inhibitors or inducers is allowed but should be monitored closely for the use of strong inhibitors and/or inducers. Patient is strongly advised to avoid grapefruit or grapefruit juice and herbal supplements with high risk of interaction with CYP3A4 or CYP2C8, such as St. John's Wort while on study

5.1.3.2 Contraception

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

5.1.4 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, lenvatinib and paclitaxel, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck within 2 working days if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every

effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to Merck. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.2.

5.1.5 Use in Nursing Women

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

5.1.6 Dental health and oral hygiene

Events of osteonecrosis of the jaw (ONJ) have been observed with lenvatinib. Invasive dental procedures are an identified risk factor for the development of ONJ. An oral dental examination and appropriate preventive dentistry should be considered prior to initiation of lenvatinib. Patients should be advised regarding periodic dental examinations and oral hygiene practice during lenvatinib therapy. Avoid invasive dental procedures during lenvatinib treatment, if possible.

5.2 Trial Treatments

Study Design

The trial starts with a safety lead-in stage of up to 18 patients (six cohorts of 3) with recurrent endometrial and/or ovarian cancer patients using the Time-to-Event Bayesian optimal interval (TITE-BOIN) design (see Section 8). Once the safety of the treatment is shown and the optimal starting dose has been confirmed or established (see Table 2 and section on Safety lead-in), accrual will open to the Phase II study. Patients treated at the RP2D in the safety lead-in cohort will be included towards the phase II accrual.

Safety lead-in

Patients will be closely monitored for toxicity according to CTCAE v5.0 during cycle 1. The trial starts with a safety lead-in stage of up to 18 patients with recurrent endometrial and/or ovarian cancer using the Time-to-Event Bayesian optimal interval (TITE-BOIN) design. Each cohort will consist of 3 patients. The first 3 patients will be treated at dose level 1. To assign a dose to the next cohort of patients, we will count the number of patients, the number of patients who experienced DLT, and the number of pending patients and their weighted standardized total follow-up time at the current dose (following approval of protocol version 4 dated 01/27/2022). To assign a dose to the next cohort of patients, we conduct dose escalation/de-escalation according to the rule displayed in Table 9. If a cohort of patients is determined to be enrolled at DL-2 (Table 2),

the schedule will be reconsidered before going to DL-2. **Dose escalation and de-escalation in the safety cohort will be decided by the study statistician and the study PI.**

Before enrolling to each next cohort the study team will evaluate, based on the type and severity of toxicities seen in cohort 1 (DL1). Decisions about the dose level for each cohort in the safety lead in phase will be decided by the study PI in conjunction with the study statistician.

Otherwise, the regimen will be considered sufficiently safe to continue onto the phase II part of the trial.

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

Table 2. Dose levels for the safety lead-in to establish the recommended phase 2 dose

Dose level	Lenvatinib (mg, PO, daily)	Pembrolizumab (mg, IV, every 3 weeks)	Paclitaxel (mg/m2, IV, weekly)
-2	14	200	60
-1	16	200	60
1 (starting dose)	16	200	80

Addendum 7/11/2022: after reviewing toxicities on DL1 and DL-1 with 2/4 DLTs on DL1 and no DLTs on DL-1 (0/4), the study team including treating providers, PI, and statistician, decided not to dose re-escalate but to assign the RP2D at DL-1 due to improved tolerance. Safety lead in completed and all next patients will be enrolled at DL-1.

Table 11. Dose level for Phase 2

Dose level	Lenvatinib (mg, PO, daily)	Pembrolizumab (mg, IV, every 3 weeks)	Paclitaxel (mg/m2, IV, weekly)
-1	16	200	60

DLT definitions:

DLT will be defined as adverse events which occur in association with the first cycle of treatment and meets the criteria below, as evaluated by the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, **unless clearly related to disease progression, or other extraneous causes**. If unexpected toxicity or greater than expected toxicity commonly seen with IO is noted, we will consider making adjustments to doses and/or dosing schedules as indicated after discussion with the study team.

DLT is defined as either hematologic or non-hematologic toxicity (assessed in accordance with the CTCAE Version 5.0), which cause any of the following:

1. *Hematologic Toxicity:*

- Dose delay of greater than 3 weeks due to failure to recover counts.
- Febrile neutropenia.
- Grade 4 neutropenia lasting > 7 days.
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with clinically significant bleeding requiring transfusion.

2. *Non-Hematologic Toxicity:*

- Failure to administer more than 25 of the 35 planned doses of lenvatinib during cycle 1 due to toxicity
- Grade 3 hypertension that is not controlled on antihypertensive medication to Grade 2 or less within 72 hours.
- $\geq$ CTCAE Grade 3 noninfectious pneumonitis
- $\geq$ CTCAE Grade 3 fatigue for $\geq$ 1 week
- Clinically significant electrolyte abnormalities $\geq$ Grade 3 that do not resolve with adequate supplementation in $\leq$ 72 hours
- Any Grade 4 immune related adverse event
- Any $\geq$ grade 3 colitis
- Any Grade 2 noninfectious pneumonitis that does not resolve to $\leq$ grade 1 within 7 days of the initiation of maximal supportive care
- Liver transaminase elevation $> 8 \times$ ULN or total bilirubin $> 5 \times$ ULN
- $\geq$ CTCAE Grade 2 ALT/AST elevation with concurrently elevated bilirubin $\geq 2 \times$ ULN, and without elevated alkaline phosphatase, or other reason for combined elevation of ALT/AST/bilirubin
- Any $\geq$ grade 3 non immune related adverse event except for the exclusion list below

Note: For any dose limiting hepatic toxicity, evaluations should be performed to determine the underlying etiology and rule out drug-induced liver injury (Hy's Law) per investigator discretion.

<https://www.fda.gov/media/116737/download>

3. *Any non-hematologic Grade 3 or 4 adverse event will be a DLT except:*

- AEs related to underlying disease or pre-existing condition, or other extraneous causes
- Isolated, asymptomatic CTCAE Grade 3 abnormalities in biochemistry laboratory values that last for ≤ 3 days (or < 72 hours). This includes electrolyte abnormalities that respond to medical intervention.
 - Grade 3 or 4 neutropenia (that is not associated with fever or infection) lasting ≤ 7 days
 - Grade 3 or 4 lymphopenia
 - Grade 3 thrombocytopenia that is not associated with clinically significant bleeding
- Grade 3 anorexia (unless > 1 week)
 - Grade 3 nausea and/or vomiting (unless > 48 hours)

hours despite maximal medical management, and related to study drug)

- Grade 3 dehydration as a result of nausea and vomiting (unless > 48 hours)
- Grade 3 constipation
 - Grade 3-4 hypersensitivity reaction that cannot be managed with safely desensitization protocol and/or supportive medications
 - Grade 3 hypertension that is controlled on antihypertensive medication to Grade 2 or less within 72 hours.
 - Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic

4. *Any death (unless clearly due to the underlying disease or extraneous causes)*
5. *Delay of initiation of cycle 2 of greater than 3 weeks due to failure to recover AE/failure to meet protocol directed treatment parameters for restart after management of AE*

5.2.1 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Day 8 and Day 15 paclitaxel doses may be administered up to ± 1 day window. If the day 8 or day 15 paclitaxel dose is missed, it should be omitted. Patients will be permitted to have a treatment day delayed up to 7 days (for a new cycle of chemotherapy/day 1) or omitted (day 8 or 15) without this being considered to be a protocol violation for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

All trial treatments will be administered on an outpatient basis.

Due to the possible negative effect of corticosteroid administration, required for prevention of hypersensitivity reactions to paclitaxel, and potential diarrhea associated with pembrolizumab and lenvatinib, we will start treatment with paclitaxel and lenvatinib only, for 2 weeks prior to cycle 1 day 1 (cycle 1 day -15 and day -8). Pembrolizumab will start with cycle 1 day 1.

Thus, during cycle 1 treatment will start with 2 weekly doses of paclitaxel (cycle 1 day -15 and day -8) and daily oral lenvatinib to ensure the patient does not develop a hypersensitivity reaction to paclitaxel and that pretreatment steroids can safely be omitted. Lenvatinib will start on the day of first paclitaxel infusion. Pembrolizumab will start Cycle 1 day 1, after 2 weeks of weekly paclitaxel and oral daily lenvatinib.

Each cycle is 3 weeks (except cycle 1 as above) and will continue indefinitely until disease progression, unacceptable toxicity, or patient withdrawal.

Pembrolizumab will be given for a maximum of 2 years, paclitaxel and/or lenvatinib may be continued indefinitely.

Paclitaxel

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP. Paclitaxel will be prepared in accordance to institutional standards by the site pharmacy.

All patients should be premedicated with corticosteroids (Cycle 1 day -15 and day -8 only), diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to drug may need to repeat the premedication and to be re-challenged with a dilute solution and slow infusion. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a re-challenge. The management of infusion reaction and hypersensitivity reaction will be based on institutional standards. If the patient does not experience a hypersensitivity reaction during cycle 1 day -15 or day -8, steroids will be omitted on cycle 1 day 1 and further cycles to avoid interference with pembrolizumab treatment.

Paclitaxel should be given after pembrolizumab when given on the same day.

Lenvatinib

Lenvatinib should be taken at the same time each day with or without food starting at cycle 1. The lenvatinib capsules should be swallowed whole with water.

Lenvatinib can be taken on an empty stomach, with fluid, or with food according to patient preference. Alternatively, add the lenvatinib capsules to a tablespoon of water or apple juice in a small glass to produce a suspension. Leave the capsules in the liquid for at least 10 minutes. Stir for at least 3 minutes. Drink the mixture. After drinking, add the same amount of water or apple juice (one tablespoon) to the glass. Swirl the contents of the glass a few times and swallow the additional liquid.

If the patient misses a dose, and it cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Lenvatinib may be taken before or after infusion with pembrolizumab and/or

paclitaxel when given on the same day (keeping the same time of day as much as possible).

Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks starting with cycle 1 day 1 (after 2 weeks of paclitaxel/lenvatinib). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). When administering pembrolizumab in combination with chemotherapy, administer pembrolizumab prior to paclitaxel when given on the same day.

Pembrolizumab will be prepared in accordance to institutional standards by the site pharmacy.

Table 3: Regimen Description

Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Paclitaxel	Premedicate with dexamethasone 10* mg IV, diphenhydramine 50 ^{##} mg IV and famotidine 20 ^{##} mg IV 30 minutes prior to infusion	60 mg/m ² (updated with amendment #16) in 250 mL NS, 5DW, or LR	IV over 1 hour	Days 1,8,15 (starting at cycle 1 day -15)	21 days (3 weeks)
Lenvatinib	Take with or without food	16 mg (four 4 mg capsules)	PO at the same time each day	Daily Starting at cycle 1 day -15	
Pembrolizumab		200 mg	IV over 30 min	Day 1 (starting at cycle 1 day 1)	

*If the patient does not develop a hypersensitivity reaction to paclitaxel the dexamethasone dose will be omitted for cycle 1 day 1 and further treatment days.

Diphenhydramine, Dexamethasone, and famotidine may be modified or held at the investigator discretion.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

5.2.2 Dose Modifications and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care.

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Please also review dose modifications for paclitaxel and lenvatinib in section 5.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Adverse events will be graded using NCI CTCAE Version v5.0. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, lenvatinib and pembrolizumab and paclitaxel interventions should be held according to recommended dose modifications (as described in section 5.2). Investigators will then decide

the probability of the event being related to one or the combination of drugs as to whether dose modification of one or all drugs is required.

Participants who interrupt or discontinue one drug in the lenvatinib-pembrolizumab combination due to toxicity can continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression). Also see section 5.2.2 and 5.2.3.

If the participant is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 4.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 4, the combination of paclitaxel, lenvatinib, and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to paclitaxel or lenvatinib alone, re-initiation of pembrolizumab, lenvatinib, or paclitaxel as a monotherapy or as a dual therapy may be considered at the principal investigator's discretion.

Table 4: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab monotherapy and IO combinations

General instructions:				
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If study intervention has been withheld, study intervention may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up

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Version 8: 07/03/2024

General instructions:				
- Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. - Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. - The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. - If study intervention b has been withheld, study intervention may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of pneumonitis - Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue	Add prophylactic antibiotics for opportunistic infections	
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)
	Recurrent Grade 3 or Grade 4	Permanently discontinue		- Participants with $\geq$ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis - Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 ^a	Withhold	Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 ^b or 4 ^c	Permanently discontinue	Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	

OSU-20172 (MISP Protocol)
Version 8: 07/03/2024

General instructions:				
- Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. - Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. - The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. - If study intervention b has been withheld, study intervention may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold ^d	- Initiate insulin replacement therapy for participants with T1DM - Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ^d	hormonal replacements as clinically indicated	
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue ^d		
Hypothyroidism	Grade 2, 3, 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
Neurological Conditions	Grade 2	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 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		

General instructions:				
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If study intervention b has been withheld, study intervention may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				
All Other immune-related AEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
^a AST/ALT: $>3.0 - 5.0 \times$ ULN if baseline normal; $>3.0 - 5.0 \times$ baseline, if baseline abnormal; bilirubin: $>1.5 - 3.0 \times$ ULN if baseline normal; $>1.5 - 3.0 \times$ baseline if baseline abnormal ^b AST/ALT: >5.0 to $20.0 \times$ ULN, if baseline normal; $>5.0 - 20.0 \times$ baseline, if baseline abnormal; bilirubin: $>3.0 - 10.0 \times$ ULN if baseline normal; $>3.0 - 10.0 \times$ baseline if baseline abnormal ^c AST/ALT: $>20.0 \times$ ULN, if baseline normal; $>20.0 \times$ baseline, if baseline abnormal; bilirubin: $>10.0 \times$ ULN if baseline normal; $>10.0 \times$ baseline if baseline abnormal ^d The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or $\leq$ Grade 2, pembrolizumab may be resumed. ^e Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis. Note: Non-irAE will be managed as appropriate. following clinical practice recommendations				

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at <http://ctep.cancer.gov>

Criteria to Resume Treatment with MK-3475 (Pembrolizumab)

For non-autoimmune or inflammatory events, patients may resume treatment with MK-3475 (pembrolizumab) when the drug-related AE(s) resolve to $\leq$ Grade 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Patients with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Patients with combined Grade 2 AST/ALT AND total bilirubin value $> 2 \times$ ULN or INR > 1.5 should have treatment (all three drugs) permanently discontinued.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Patients with drug-related endocrinopathies (not including drug-related adrenal insufficiency or hypophysitis) adequately controlled with only physiologic hormone replacement may resume treatment after replacement correction and clinically stable regimen.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the treatment should resume at the earliest convenient point that is within the 12-week delay period.

If treatment is delayed > 12 weeks, the patient must be permanently discontinued from study therapy, except as specified in Section 5.4 (Duration of Therapy).

Other allowed dose interruption for pembrolizumab

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

5.2.3 Dose modifications for lenvatinib and paclitaxel

Dose Modification	<i>Lenvatinib</i> Dose (4 mg and 10 mg capsules)
Starting dose	<i>16 mg</i>
First dose reduction	<i>14 mg</i>
Second dose reduction	<i>10 mg</i>

Dose Modification	<i>Paclitaxel</i> Dose
Starting dose	<i>60 mg/m²</i>
First dose reduction	<i>50 mg/m²</i>
Second dose reduction	<i>40 mg/m²</i>

Note: dose modification table updated with Amendment #16

There are no dose reductions for pembrolizumab. Withhold or discontinue pembrolizumab to manage adverse reactions as described in Table 4.

Please note all CTCAE grading below refers to the CTCAE version 5.0.

If the patient is experiencing unacceptable toxicity from one agent (for example neuropathy or immune mediated pancreatitis) despite dose modification/reduction, but is: 1) deriving clinical benefit for at least 6 months before experiencing significant toxicity from treatment (despite dose modifications and dose reductions); and 2) the patient would like to continue on study; the investigator may consider discontinuing one of the offending agents after 3) discussion with the PI and study team. For example, a patient has a sustained partial or complete response(>6 months) to treatment but experiences neuropathy grade 2 or greater from paclitaxel that does not improve despite dose modifications and reductions. This patient is allowed to discontinue paclitaxel, but may continue lenvatinib and pembrolizumab, as long as the patient desires to stay on trial and it is deemed safe and in the best interest of the patient by the investigator and PI.

5.2.4 Hematologic toxicity

5.2.4.1 Neutropenia

Dose limiting neutropenia is defined as febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days.

Uncomplicated (absence of sepsis or fever) neutropenia of any grade and <7 days does not require dose modification. Patients who require a delay of dosing for three weeks or more beyond when a cycle is due to start (6 weeks from day 1, 4 weeks from day 15), or who experience fever and/or sepsis while neutropenic, are at risk for subsequent severe myelosuppression. Patients who require a cycle delay of three weeks or greater (6 weeks from the previous day 1) or experience fever and/or sepsis while neutropenic on the reduced dosage will possibly be taken off study after consultation with the Principal investigator. Follow-up will continue for any patient taken off study.

Patients who are hospitalized for fever with either grade 3 or 4 neutropenia may be treated with growth factors during the episode at the discretion of the treating physician. At least two days should elapse between the discontinuation of growth factors and the initiation of another cycle of chemotherapy in order to allow bone marrow progenitors to cease cell cycling. Growth factors will not be used between doses of chemotherapy in the absence of febrile neutropenia.

If febrile neutropenia occurs despite a one dose level reduction, then with subsequent courses the patient will receive filgrastim 5 mcg/kg/d SQ (weight ≤ 80 kg: filgrastim 300mcg; weight >80 kg: filgrastim 480mcg) starting 24 hours after the completion of the subsequent course of chemotherapy and continuing for 3 days per institutional standards.

5.2.4.2 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

a. Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

b. Patients will NOT receive prophylactic thrombopoietic agents. Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
<http://www.fda.gov/Medwatch/safety/2007/safety07.htm>

c. Patients may NOT receive amifostine or other protective reagents.

5.2.4.3 Treatment decisions will be based on the absolute neutrophil count (ANC) rather

than the total white cell count (WBC).

5.2.4.4 Subsequent cycles of therapy will not begin until the ANC is 1000 cells/mcl and the platelet count is 75,000 cells/mcl on day 1 of each cycle. Day 1 of the cycle (pembrolizumab and paclitaxel) will be delayed for a maximum of three weeks until these values are achieved. Lenvatinib will be held until counts recover to grade ≤ 2 . Lenvatinib should be held for grade 3 or higher neutropenia and for grade 2 or higher thrombocytopenia. Lenvatinib may be resumed when neutropenia grade 2 or less and thrombocytopenia grade 1 or less. Patients who fail to recover adequate counts within a three week delay will be removed from study.

Day 1	Neutropenia First occurrence	Neutropenia Second occurrence	Neutropenia Third Occurrence
Grade 1 ANC >1500-LLN	No interventions needed		
Grade 2 ANC 1000-1500	No interventions needed		
Grade 3 ANC 500-1000	Delay	Reduce paclitaxel and lenvatinib by 1 dose level	Reduce lenvatinib by 1 dose level
Grade 4 ANC <500	Delay and reduce paclitaxel and lenvatinib by 1 dose level	Reduce lenvatinib by 1 dose level	Reduce lenvatinib by 1 dose level and omit paclitaxel day 15

Delay Day 1	Modification
1-7 days	none
8-14 days	Decrease paclitaxel and lenvatinib by 1 dose level
> 21 days	Off study

The day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 1000 cells/mcl and the platelet count is at least 75,000/mcl. If not given, these doses are omitted and not made up or delayed.

For the second occurrence of neutropenia on day 8 or 15 requiring omission of the day 8 or day 15 dose, paclitaxel will be reduced by 1 dose level with the start of the subsequent cycle. There will be no paclitaxel dose modifications for a third occurrence or neutropenia on any subsequent

day 8 or day 15 if treatment criteria are not met and the patient is already on the lowest dose of paclitaxel. In case treatment criteria for paclitaxel are not met, day 8 and/or 15 doses are omitted. Patients should continue to hold Lenvatinib for Grade 3 or greater neutropenia until recovered to grade 2 or better.

5.2.4.5 For the first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting >7 days, reduce lenvatinib and paclitaxel by one dose level on subsequent cycles.

5.2.4.6 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting > 7 days (after initial lenvatinib and paclitaxel dose reduction), add prophylactic growth factors (filgrastim can be used according to institutional standard). In this circumstance, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24 hours after paclitaxel chemotherapy. Administration of filgrastim on the same day as chemotherapy is not recommended.

5.2.4.7 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

5.2.4.8 Thrombocytopenia

Patients with grade 4 thrombocytopenia on day 1 will have a 1 level dose reduction of lenvatinib and paclitaxel. For the second occurrence of grade 4 thrombocytopenia reduce lenvatinib by 1 dose level. All study drugs on day 1 will be held until platelets recover to $\geq 75,000/\text{mm}^3$

Delay Day 1	Modification
1-7 days	none
8-14 days	Decrease paclitaxel and lenvatinib by 1 dose level
> 21 days	Off study

5.2.4.9 Anemia

Anemia is not an indication for dose reduction in any patient; however, a record of transfusions required should be detailed on the D2R Form.

For Grade 3 / 4 anemia due to any cause including paclitaxel or lenvatinib therapy, hold both lenvatinib and paclitaxel until Hgb > 8 g/dL. For Grade 3/ 4 anemia due to hemorrhage or bleeding, all therapy should be held until bleeding/hemorrhage has ceased or is mild and intermittent (< Grade 1) and hemoglobin is stable at > Hgb 8 gm/dl.

5.2.5 Non-hematologic toxicity

Treatment Modification for Clinically Significant Toxicities Deemed Related to Lenvatinib and/or Paclitaxel		
<u>Non-hematologic Toxicities</u>	Management/Next Dose for <i>Lenvatinib</i>^{a, c}	Management/Next Dose for <i>Paclitaxel</i>^{a, c}
Grade ≤1	No change in dose	No change in dose
Grade 2 (First occurrence) ^b	Hold* until grade ≤1. Resume at same dose level.	Hold until grade ≤1. Resume at same dose level.
Grade 2 (Second and subsequent occurrence) ^{b, c}	Hold* until grade ≤1. Resume at one dose level lower.**	Hold* until grade ≤1. Resume at one dose level lower.**
Grade 3 (First occurrence) ^b	Hold* until grade ≤1. * Resume at one dose level lower.**	Hold* until grade ≤1. * Resume at one dose level lower.**
Grade 3 (Second occurrence) ^b	Off protocol therapy	Off protocol therapy.
Grade 4	Off protocol therapy	Off protocol therapy
^aDose reduction applies only to the agent that is deemed to be the cause of the adverse event based on treating physician's opinion. If the attribution of the adverse event to either agent is not clear, both drugs should be held. ^bPatients who develop grade 2 fatigue may continue treatment without dose reduction per discretion of treating physician. ^cTreatment modification for clinically significant toxicities deemed related to lenvatinib and/or paclitaxel *Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions of the same agent should go off protocol therapy.		

5.2.5.1 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level for paclitaxel and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. If no recovery after 2 weeks, patient should be removed from study.

5.2.5.2 Grade 3 (or greater) renal toxicity as a result from lenvatinib or paclitaxel requires reduction of one dose level for paclitaxel and lenvatinib and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be removed from study. A biopsy may be required to determine if renal toxicity is due to lenvatinib or immune related to determine appropriate treatment.

- 5.2.5.3** Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin that are not immune related requires reduction of one dose level of paclitaxel and lenvatinib and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If no recovery after 3 weeks, patient should be removed from study. A biopsy may be required to determine if hepatic toxicity is due to lenvatinib or immune related to determine appropriate treatment. For Grade 2 elevations of ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5); Although Table 4 advises pembrolizumab to be withheld (interrupted), all three drugs must be permanently discontinued immediately (also see section 5.2.2).
- 5.2.5.4** There will be no dose modifications for alopecia or fatigue grade ≤ 2 .
- 5.2.5.5** It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 24 hours) grade 3 (or greater) toxicity in spite of optimal medical management require reduction of one dose level of paclitaxel and lenvatinib and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.
- 5.2.5.6** Other non-hematologic toxicities with an impact on organ function of grade 2 (or greater) that are clinically significant and related to study drug require reduction of one dose level of paclitaxel and/or lenvatinib (depending on the etiology and offending drug) and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1, or pre-therapy baseline. If no recovery after 3 weeks, patient should be removed from study.
- 5.2.5.7** Heart failure grade 4 will result in removal from study. All other cardiac toxicity > grade 3 will result in removal from study. All other cardiac toxicity, grade 3, can result in delay of subsequent therapy for a maximum of three weeks and one level dose reduction of paclitaxel and lenvatinib.
- 5.2.5.8** Decrease of left ventricular ejection fraction (LVEF) to < 50% or decrease of LVEF by $\geq 10\%$ from baseline will result in removal from the study (grade 3 or greater, CTCAE v5.0 Investigations, Ejection fraction decreased).
- 5.2.5.9** Impaired thyroid function should be treated with thyroid replacement medication as needed and does not require holding study treatment.
- 5.2.5.10** Any patient who had CNS toxicity including an intracranial hemorrhage > Grade 2, stroke, or Reversible Posterior Leukoencephalopathy > Grade 2 will be discontinued from treatment and removed from study.
- 5.2.5.11** Patients requiring greater than two dose reductions for any cause will result in removal from study.
- 5.2.5.12** Discontinue lenvatinib and paclitaxel in patients who develop gastrointestinal perforation or life-threatening fistula.

5.2.5.13 QT Interval Prolongation: Monitor and correct electrolyte abnormalities in all patients. Withhold lenvatinib for QT interval prolongation >500 msec or greater than 60 msec increase from baseline. Lenvatinib may be resumed at one dose level lower once QTc interval $\leq$ 480 ms.

5.2.5.14 Discontinue lenvatinib following an arterial thrombotic event

5.2.5.15 Gastrointestinal disorders:

<u>Nausea</u>	Management/Next Dose for <i>lenvatinib</i> and <i>paclitaxel</i>
$\leq$ Grade 1	No change in dose
Grade 2	Hold until $\leq$ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
**Patients requiring > two dose reductions despite adequate anti-emesis management should go off protocol therapy.	
Recommended management: anti-emetics (e.g. ondansetron, olanzapine, haloperidol, prochlorperazine, Promethazine). Note that lenvatinib has interaction with Olanzapine/Haloperidol/Ondansetron and can increase risk of QT prolongation. Check EKG periodically with use of these agents as clinically indicated.	
<i>Avoid corticosteroids as antiemetics since these may diminish the effect of Pembrolizumab</i>	

<u>Vomiting</u>	Management/Next Dose for <i>lenvatinib</i> and <i>paclitaxel</i>
$\leq$ Grade 1	No change in dose
Grade 2	Hold until $\leq$ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy.	
**Patients requiring > two dose reductions despite adequate antiemesis management should go off protocol therapy.	
Recommended management: antiemetics (e.g. ondansetron, olanzapine, haloperidol, prochlorperazine, Promethazine). Note that lenvatinib has interaction with Olanzapine/Haloperidol/Ondansetron and can increase risk of QT prolongation. Check EKG periodically with use of these agents as clinically indicated.	

Avoid corticosteroids as antiemetics since these may diminish the effect of Pembrolizumab

<u>Diarrhea</u>	Management/Next Dose for <i>lenvatinib</i> and <i>paclitaxel</i>
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level. If no improvement after 24 hours of holding lenvatinib, rule out C. Diff. If C diff negative take lomotil or immodium. <i>If no improvement with lomotil or worsening at any time after holding lenvatinib, consider immune related diarrhea/colitis and see table 4 for pembrolizumab immune related toxicities for management.</i>
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy if diarrhea is thought to be caused by lenvatinib or paclitaxel. **Patients requiring > two dose reductions despite adequate antidiarrheal management should go off protocol therapy. *** Also see Table 4 for management of immunotherapy induced diarrhea and/or colitis	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy (lomotil®/diphenoxylate hydrochloride and atropine sulfate tablets) is permitted and should be recorded when used.	

<u>Mucositis</u>	Management/Next Dose for <i>lenvatinib</i>	Management/Next Dose for <i>paclitaxel</i>
≤ Grade 1	No change in dose ^a	No change in dose

Grade 2	Maintain dose level if tolerable and intensify oral care; if toxicity is or becomes intolerable omit dose until resolved to Grade ≤ 1 , then restart at the same dose level. At the second occurrence and intolerable, resume at 1 dose level lower.	No change in dose
Grade 3	Hold* until $\leq$ Grade 1. Resume at 1 dose level lower. Pembrolizumab may be held if mucositis does not improve with holding paclitaxel and lenvatinib	Hold* until $\leq$ Grade 1. Resume at 1 dose level lower.
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
To reduce and/or prevent the incidence of mucositis all patients will receive 10 mL of alcohol-free dexamethasone 0.5 mg/5 mL oral solution. Patients are encouraged to start the mouthwash on the first day of their treatment and to swish for 2 minutes and spit 4 times per day for 9 weeks and not to eat for 1 hour after using the mouthwash. After 9 weeks, dexamethasone mouthwash may be continued for up to 9 additional weeks at the discretion of the clinician and patient and subsequently as needed. ^aPatients with grade 1 stomatitis any time during the study are advised to swish 10 mL of a 0.9% saltwater solution and spit or other rinses, followed by the same regimen of dexamethasone mouthwash 10–15 min later. Patients are allowed to take oral nystatin suspension or other topical antifungal agents after the dexamethasone mouthwash according to clinician preference based on the protocols of individual institutions and practices. <i>Adapted from: Rugo HS, Seneviratne L, Beck JT, Glaspy JA, Peguero JA, Pluard TJ, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. The Lancet Oncology. 2017 Mar 14</i>		

Lenvatinib

Treatment with lenvatinib will be interrupted for clinically significant grade ≥ 2 drug-related

toxicity, excluding alopecia, anemia and lymphopenia, and re-commenced following resolution to grade ≤ 1 or baseline levels. Dose reductions of lenvatinib will be allowed for subjects with $\geq$ Grade 3 drug-related adverse events. The exception is hypertension, which must be treated with anti-hypertensive drugs prior to dose reduction.

5.2.6 Management of Hypertension:

Hypertension (HTN) that occurs during study treatment must be treated with anti-hypertensive drugs prior to any dose reduction. Recommended management of HTN for subjects receiving study drug is presented in Figure 2 (Appendix 5). Control blood pressure prior to treatment with lenvatinib. Withhold lenvatinib for Grade 3 hypertension despite optimal anti-hypertensive therapy until it resolves to Grade 2 or less. Discontinue for life-threatening (grade 4) hypertension.

While subjects are receiving treatment with lenvatinib, the early initiation of anti-hypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 AE.

Persistent HTN is defined as 2 consecutive elevated blood pressure (BP) measurements preferably taken in the clinic and obtained at least 1 hour apart. It is recommended that 24-48 hours should elapse between the decision steps. For a listing of recommended DHP (dihydropyridine) calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers, see Appendix 5, Recommended Anti-hypertensive Medications. BP-lowering drugs should be individualized to the patient's clinical circumstances; ACE inhibitors or ARA should be preferred for those patients with proteinuria, chronic kidney disease risks, or metabolic syndrome; nondihydropyridine CCB should be avoided in treating patients receiving CYP450 inhibitors. Dihydropyridine CCB should be preferred in elderly or black patients. Angiogenic inhibitors should be withheld only from patients who experienced hypertensive crisis (32). Nondihydropyridine CCBs, such as verapamil and diltiazem, are CYP3A4 inhibitors and nifedipine (a dihydropyridine CCB) has been shown to induce VEGF secretion and should be avoided if possible.

Note: If a subject has controlled HTN on an anti-hypertensive regimen at baseline and then develops a worsening of HTN requiring more intensive therapy than the previous regimen, this would be considered Grade 3 HTN.

Blood Pressure Level	Recommended Action
Systolic BP ≥ 140 mmHg up to 160 mmHg or diastolic BP ≥ 90 mmHg up to 100 mmHg	Continue lenvatinib and initiate anti-hypertensive therapy, if not already receiving OR

	Continue lenvatinib and increase the dose of the current antihypertensive therapy or initiate additional antihypertensive therapy
Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg despite optimal antihypertensive therapy	• Withhold lenvatinib • When systolic BP ≤ 150 mmHg, diastolic BP ≤ 95 mmHg, and patient has been on a stable dose of antihypertensive therapy for at least 48 hours, resume lenvatinib at a reduced dose
Life-threatening consequences (malignant hypertension, neurological deficit, or hypertensive crisis)	Urgent intervention is indicated. Discontinue lenvatinib and institute appropriate medical management

5.2.7 Management of Proteinuria:

Management of proteinuria	
Dipstick 2+	Check 24h urine for 2+ (do not need to hold) or urine protein creatinine ratio
Dipstick 3+ or greater	Hold lenvatinib and obtain 24 hour urine or urine protein creatinine ratio
If 24-hour urine protein or urine protein creatinine ratio < 2 grams	Continue lenvatinib
If 24-hour urine protein or urine protein creatinine ratio is greater than or equal to 2 grams	Step 1: Interrupt lenvatinib treatment Step 2: Monitor urine protein (weekly) until 24 hour urine protein or urine protein creatinine ratio is < 2 grams, then restart lenvatinib dose-reduced by one dose level.
If 24-hour urine protein or urine protein creatinine ratio is greater than or equal to 2 grams after 3 weeks of lenvatinib interruption / nephrotic syndrome	Discontinue lenvatinib Obtain nephrology consultation

5.2.8 Once a subject's dose of lenvatinib or paclitaxel is reduced, it may not be re-escalated through the remainder of the subject's participation in the study. If a subject is unable to tolerate a reduced dose due to toxicities thought to be related to treatment, treatment should be discontinued.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

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

Because there is a potential for interaction of lenvatinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. However, lenvatinib is not considered a strong inducer or inhibitor of cytochrome P450 or uridine 5'-diphosphoglucuronosyl transferase (UGT) enzymes. Interactions have not been found to be clinically significant and thus CYP3A4 inducers and inhibitors are allowed.

Lenvatinib may be co-administered without dose adjustment with CYP3A and P-gp inducers or P-gp inhibitors. Patients are allowed to take agents that increase the gastric pH (H₂ receptor blockers, proton pump inhibitors, antacids) as it does not have a significant effect on lenvatinib exposure.

Use caution in patients receiving agents associated with osteonecrosis of the jaw (ONJ), such as bisphosphonates and denosumab. Events of osteonecrosis of the jaw (ONJ) have been observed with lenvatinib. Invasive dental procedures are an identified risk factor for the development of ONJ. An oral dental examination and appropriate preventive dentistry should be considered prior to initiation of lenvatinib. Patients should be advised regarding periodic dental examinations and oral hygiene practice during lenvatinib therapy. Avoid invasive dental procedures during lenvatinib treatment, if possible.

Paclitaxel is metabolized by CYP3A4 and CYP2C8. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8. Potential interactions between paclitaxel, a substrate of CYP3A4, and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4, have not been evaluated in clinical trials. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified in section 5.2.4.

Patients will NOT receive prophylactic thrombopoietic agents. Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing

information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted. <http://www.fda.gov/Medwatch/safety/2007/safety07.htm>

Patients may NOT receive amifostine or other protective reagents.

To reduce and/or prevent the incidence of mucositis all patients will receive 10 mL of alcohol-free dexamethasone 0.5 mg/5 mL oral solution. Patients are instructed to start the mouthwash on the first day of their treatment and to swish for 2 minutes and spit 4 times per day for 9 weeks and not to eat for 1 hour after using the mouthwash. After 9 weeks, dexamethasone mouthwash may be continued for up to 9 additional weeks at the discretion of the clinician and patient and subsequently as needed.

Patients are allowed to take oral nystatin suspension or other topical antifungal agents after the dexamethasone mouthwash according to clinician preference based on the protocols of individual institutions and practices.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs only as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab, paclitaxel, lenvatinib
- Radiation therapy

- Note: Radiation therapy to a symptomatic solitary lesion or to the brain maybe allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed (flu vaccine and COVID vaccine); however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.3.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2 and Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin

photography as part of evaluation of the event.

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

5.4 Participant Withdrawal/Discontinuation Criteria:

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

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

- The participant or participant's legally acceptable representative requests to discontinue study treatment
- Confirmed radiographic disease progression
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Unacceptable adverse experiences
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The participant is lost to follow-up
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

Note: The number of treatments is calculated starting with the first dose.

- Administrative reasons

5.5 Participant Replacement Strategy:

Patients in the safety lead-in cohort who go off trial prior to completing the first cycle will be

replaced. Patients treated at the RP2D who do not complete 2 full cycles will be replaced for efficacy evaluation.

5.6 Clinical Criteria for Early Trial Termination:

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Schedule/Tests	Screening*		Cycle 1 ^a					Cycle 2 ^a			Cycles 3+ ^a			EOT ^p	Follow Up ^{q,r}		
			Day -15	Day -8	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 day Safety	90 day Safety	Survival ^{h,o}
Scheduling Window (Days)	-28 to -1	-14 to -1	± 1	± 1	± 3	± 1	± 1	± 3	± 1	± 1	± 3	± 3	± 3	± 7	± 7	±7	±7
Informed Consent	X																
Inclusion/Exclusion	X																
Demographics and Medical History		X															
Concomitant Medication Review		X															
Full Physical Examination		X															
Directed Physical Examination					X			X			X			X	X		
Weight, Height, and BSA		X	X	X	X	X	X	X	X	X	X	X	X		X		
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X		X		
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X		X		
Review Adverse Events		X	X		X			X			X			X	X	X	
CBC with Differential ^b		X		X	X	X	X	X	X	X	X	X	X		X		
Comprehensive Serum Chemistry Panel ^b		X			X			X			X				X		
Urinalysis ^b		X			X			X			X				X		
TSH with reflex to free T4 ^{b, c}		X ^c									X ^c				X ^c		
PT/INR and aPTT ^b		X													X		
CA-125 ^{b, d}		X ^d			X ^d			X ^d			X ^d				X ^d		
Pregnancy Test (Urine or Serum β-HCG) ^{b, e}		X ^e													X ^e		

Schedule/Tests	Screening*		Cycle 1 ^a					Cycle 2 ^a			Cycles 3+ ^a			EOT ^p	Follow Up ^{q,r}		
			Day -15	Day -8	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		30 day Safety	90 day Safety	Survival ^{h, o}
Scheduling Window (Days)	-28 to -1	-14 to -1	± 1	± 1	± 3	± 1	± 1	± 3	± 1	± 1	± 3	± 3	± 3	± 7	± 7	± 7	± 7
Echocardiogram/MUGA ^f	X																
Electrocardiogram ^g		X ^g						X ^g			X ^g				X ^g		
Tumor Imaging ^h	X ^h										X ^h				X ^{h, o}	X ^{h, o}	X ^{h, o}
Pre-medications ⁱ			X	X	X	X	X	X	X	X	X	X	X				
Paclitaxel Administration ^j			X	X	X	X	X	X	X	X	X	X	X				
Lenvatinib Administration ^j			X	X	X	X	X	X	X	X	X	X	X				
Pembrolizumab Administration ^j					X			X			X						
Lenvatinib Dosing Diary			X		X			X			X						
Blood Pressure Monitoring ^k		X	X	X	X	X	X	X	X	X	X	X	X				
Archival and Newly Obtained Tissue Collection ^l		X ^l												X ^l			
PBMC ^m			X ^m					X ^m			X ^m			X ^m			
ctDNA ^{m, s}			X ^{m, s}					X ^{m, s}			X ^{m, s}			X ^{m, s}			
cyTOF ^m			X ^m					X ^m			X ^m			X ^m			
Matched normal blood sample			X ⁿ														
Post-study anti-cancer therapies															X ^{h, o}	X ^{h, o}	X ^{h, o}
Survival status															X ^{h, o}	X ^{h, o}	X ^{h, n}

*Screening visits and procedures are to be collected within 28 days or 14 days prior to starting protocol treatment.

- A cycle of treatment is defined as every 21 days. Treatment should be started within 14 days following registration/enrollment. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Paclitaxel dosing visits on day 8 and day 15 have a 1 day window and otherwise should be omitted. Patients will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life

events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided. (see section 5.2.1)

- b. Refer to Table 7 for details on required laboratory evaluations
- c. T4 only required if TSH abnormal. Thyroid function labs should be evaluated at baseline/screening, cycle 3, and then every other cycle (i.e. cycles 5, 7, 9, etc.), and at the 30 day safety follow up visit
- d. CA-125 required for subject's with ovarian, fallopian tube, primary peritoneal cancers and for subjects with endometrial cancer if previously elevated and/or followed.
- e. Pregnancy test is only required in women of child bearing potential
- f. Echocardiogram or MUGA evaluation is required at screening if the patient has a known history of decreased LVEF on imaging or clinical suggestion of heart failure. Echocardiogram or MUGA will only be evaluated when clinically indicated.
- g. Electrocardiogram should be collected at screening, cycle 2 day 1, cycle 4 day 1, and at the 30 day safety visit.
- h. Tumor imaging every 9 weeks (approximately every 3 cycles). First on-study imaging assessment should be performed at 8 weeks (56 days $\pm$ 7 days) from the date of starting study treatment (after 2 full cycles). Subsequent tumor imaging should be performed every 9 weeks (63 days $\pm$ 7 days) or more frequently if clinically indicated. After 52 weeks (365 days $\pm$ 7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days $\pm$ 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator. See Section 7.1.2.6 for details. Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.
- i. Pre medications are outlined in Table 3 and will be given prior to Paclitaxel administration
- j. Pembrolizumab will be given for a maximum of two years. Paclitaxel and lenvatinib may be continued indefinitely
- k. Blood pressures at screening require two readings $>$ 24 hours appointment to determine eligibility. Blood pressures will be monitored at each clinic visit and via patient monitoring at home.
- l. Fresh biopsy should be obtained at screening (within 14 days prior to starting treatment). Archival tumor tissue may be submitted in subjects that cannot safely undergo biopsy. Patient who progress while on protocol therapy are required to have a fresh biopsy at the end of treatment ($<$ 30 days from last dose and before starting a new treatment regimen). If a biopsy cannot be scheduled within 14 days a delay to start protocol treatment of an additional 7 days (21 days total) is allowed. Note, if the patient has had a recent biopsy for diagnostic purposes (i.e. to confirm cancer recurrence) and has not received other cancer targeted treatment between the biopsy and starting protocol treatment, this biopsy may be used for research as the baseline/pre-treatment biopsy provided that an adequate sample is available for research purposes.

- m. PBMC and ctDNA must be collected prior to treatment on cycle 1 day -15, cycle 2 day 1, cycle 3 day 1, cycle 6 day 1, and at progression/end of treatment visit. cyTOF must be collected prior to treatment on cycle 1 day -15, cycle 2 day 1, cycle 6 day 1, and at progression/end of treatment visit. Patients should not have a transfusion within 90 days of the collection of a ctDNA sample. If a patient has had a transfusion within 90 days of the ctDNA timepoint, the collection of this sample will be deferred until the patient is > 90 days following transfusion.
- n. Matched normal blood sample must be collected at baseline prior to dosing. Patients should not have a transfusion within 90 days of the collection of a matched normal sample. If a patient has had a transfusion within 90 days of the matched normal timepoint, the collection of this sample will be deferred until the patient is > 90 days following transfusion.
- o. Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase. Patient who do not start other anti-cancer treatment should be assessed every 12 weeks (84 ± 7 days) for 1 year by radiologic imaging to monitor disease status if the patient agrees to this (not mandatory) and should be followed at the discretion of the treating physician. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and may be contacted periodically by telephone to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.
- p. End of treatment visit is defined as the visit protocol treatment is discontinued. In the event that this visit coincides with the 30 day follow up visit, requirements may be obtained at the same visit.
- q. Follow up visits should be timed from last dose of protocol therapy (whichever drug was discontinued last)
- r. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the participant will move into survival follow-up.
- s. ctDNA and matched normal samples are only required to be collected and analyzed for the first 30 subjects enrolled onto the study. These samples will be collected on OSU subjects only

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria:

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the trial. Treatment for the disease for which the participant enrolled in this study will be recorded separately and

not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

- An approved consent form and authorization permitting release of personal health information must be signed by the patient or guardian. Current FDA, NCI and Institutional regulations concerning informed consent will be followed.
- All eligibility requirements indicated in Section 5.1.1 and 5.1.2 must be satisfied and verified by the PI or sub -I
- Research staff \ must register the patient in OnCore.
- The patient will be assigned a study identification number.
- The Study Statistician and PI will assign the patient a dose at the current dose level

The inclusion and exclusion criteria will be assessed during screening (within 28 days prior to the first dose of any study drug on Cycle 1, Day 1). All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. A screening log will be maintained to record details of all participants screened and to confirm eligibility or reasons for screening failure, as applicable. Procedures conducted as part of the patient's routine clinical management and obtained before signing an informed consent form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the Schedule of Clinical/Study Assessments.

A patient is considered enrolled when deemed eligible by the investigator and registered into OnCore.

General Guidelines

Eligible patients will be entered on study by the Study Coordinator. Following registration, patients should begin protocol treatment within 14 days. If a biopsy cannot be scheduled within 14 days a delay to start protocol treatment of an additional 7 days (21 days total) is allowed. Archival tissue may be used in cases in which a biopsy cannot safely be done. Other issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

7.1.2 Clinical Procedures/Assessments

Baseline and Pre-treatment evaluations

Patients will be required to have imaging to document recurrent measurable disease within 28 days of starting protocol. Within 14 days of starting protocol treatment all patients will have a history and physical exam, toxicity assessment and laboratory evaluation (including CA-125 for patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer or endometrial cancer if initially elevated). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the first cycle of therapy. Laboratory evaluations should be done within 3 days of each IV chemotherapy treatment, except for C1D-15 as mentioned above.

Evaluations during Treatment

During therapy all patients will have to have laboratory evaluation within 3 days of treatment documenting adequate bone marrow and organ function. After the first 2 full cycles (8 weeks) patients will be evaluated with CT scans to assess target and non-target lesions. After that imaging will be performed every 3 cycles (~9 weeks) +/- 1 week. If there is concern for progressive disease at any time, either by symptoms, clinical exam, or CA-125, imaging will be performed at the discretion of the treating physician and/or PI.

Per iRECIST, disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.4/ Table 6.

Post-treatment Evaluations

After discontinuation of treatment patients will have a follow up visit approximately 30 +/- 7 days after the last dose (safety/end of treatment visit). Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase. Patient who do not start other anti-cancer treatment should be assessed every 12 weeks (84 ± 7 days) for 1 year by radiologic imaging to monitor disease status if the patient agrees to this (not mandatory) and should be followed at the discretion of the treating physician. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and may be contacted periodically by telephone to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first

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

7.1.2.1 Adverse Event (AE Monitoring)

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

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

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Expedited confirmation of measurable disease based on RECIST 1.1 at Screening should be used to determine participant eligibility and will be used as a baseline to monitor response to treatment. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required.

Participant eligibility will be determined using local assessment (Investigator assessment) based on RECIST 1.1. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be used to determine progression.

When the Investigator identifies radiographic progression per RECIST 1.1, efforts should be made to verify radiologic PD. Treatment should continue until PD has been verified.

Regardless of whether PD is verified, if the Investigator considers the participant has progressed, but elects to implement iRECIST, the Investigator will assess for confirmation of progression by iRECIST at subsequent time points.

7.1.2.6.1 Initial Tumor Imaging

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

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

Baseline imaging should include chest, abdomen and pelvis.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

7.1.2.6.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 8 weeks (56 days $\pm$ 7 days) from the date of starting study treatment (after 2 full cycles). Subsequent tumor imaging should be performed every 9 weeks (63 days $\pm$ 7 days) or more frequently if clinically indicated. After 52 weeks (365 days $\pm$ 7 days), participants who remain on treatment will have imaging performed every 12 weeks (84 days $\pm$ 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Imaging should always include abdomen and pelvis. If there is chest disease at baseline, all future imaging should include chest imaging to monitor response to treatment. If there is no chest disease at baseline, CT chest may be replaced by chest X-ray or omitted. If the patient has symptoms suggestive of any kind of possible chest pathology, chest imaging has to be included.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm

PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Appendix 4), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the Investigator until progression is confirmed by the site provided they have met the conditions detailed in Appendix 4. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Appendix 4.

7.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 -week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the Investigator elects not to implement iRECIST, this is the final required tumor imaging.

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase. Patients who do not start other anti-cancer treatment should be assessed every 12 weeks (84 ± 7 days) for 1 year by radiologic imaging to monitor disease status if the patient agrees to this (not mandatory) and should be followed at the discretion of the treating physician. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and may be contacted periodically by telephone to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

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

7.1.2.6.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules below. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response.

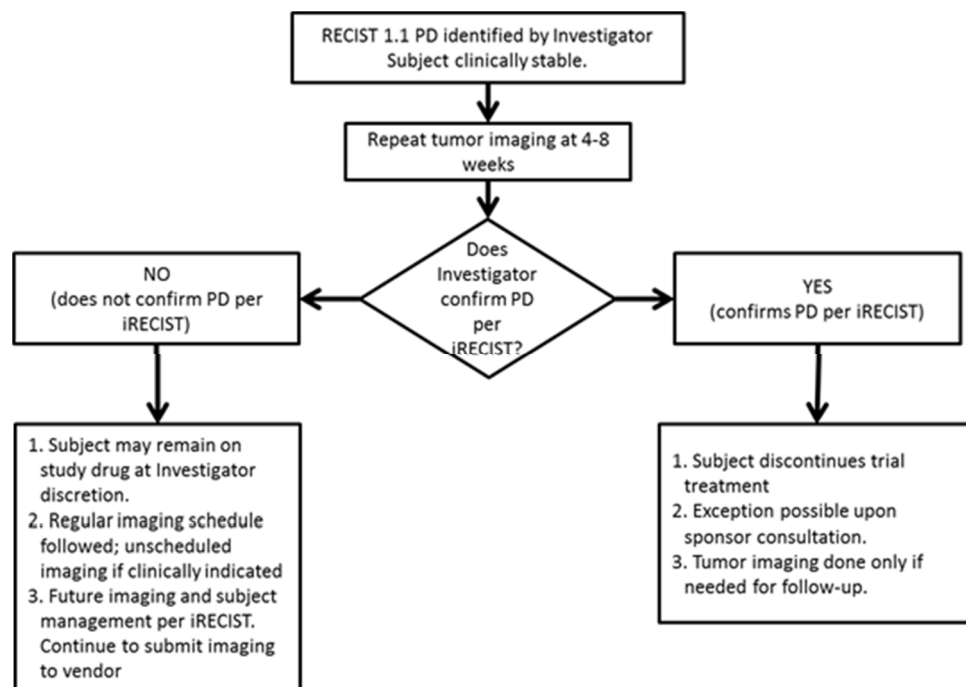
A description of the adaptations and iRECIST process is provided in Appendix 4, with additional detail in the iRECIST publication [Seymour et al, 2017]. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions.

Table 6 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1..

Figure 1: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



Other Response Parameters

Patients with ovarian and endometrial cancer (if initially elevated) will have CA125 measured every cycle and at approximately the same time they undergo radiologic assessment. Patients will have a CA125 measured 14 days prior to Cycle 1 Day 1. Patients with measurable lesions should be assessed using CT or MRI scan after cycle 3 and then every three cycles, from the date of first dose until the 30-day Follow-up visit. Although progression may be determined by the investigator based upon clinical deterioration, every effort should be made to document progression using radiographic methods. The basis for determination of progression per clinical deterioration should be documented.

Patients experiencing CA125 response must have a confirmatory test performed at least 21 days after initial response is documented. In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks. Progression must be documented by imaging and cannot be determined solely by CA-125 increase.

On the basis of the available data and extensive discussions among the cooperative groups within the GCIG, it is recommended that the following definition of response be used in ovarian cancer trials so that response can be measured by either RECIST 1.1 or CA 125 criteria. If the response is evaluable by both criteria, then the date of response will be the date of the earlier of the two events.

Definition of response:

- $\geq 50\%$ reduction in CA 125 levels from baseline

- the response must be confirmed and maintained for at least 21 days
- the pretreatment sample must be ≥ 2.0 times the UNL and within 2 weeks prior to starting treatment
- the date of response corresponds to the date when the CA 125 level is first reduced by 50%

7.1.2.7 Tumor Tissue Collection and Correlative Studies in Blood Sampling

Shipping, storage, and handling of blood, archival tumor, fresh tumor, and leftover tumor tissue for the assessment of biomarkers will be managed and ordered by the CTO processes. Refer to the laboratory manual for instructions and applicable laboratories (Good fellow, Raval, and Signatera labs).

Tumor biopsies collection time points (up to 2 time points):

1. Archival tumor tissues (formalin-fixed paraffin-embedded block)
2. Fresh biopsy within 14 days prior to starting treatment. Note, if the patient has had a recent biopsy for diagnostic purposes (i.e. to confirm cancer recurrence) and has not received other cancer targeted treatment between the biopsy and starting protocol treatment, this biopsy may be used for research as the baseline/pre-treatment biopsy provided that an adequate sample is available for research purposes.
3. Biopsies will also be taken for the patients who have confirmed disease progression during the study.

Immune correlates/biomarkers to be assessed with immunohistochemistry (IHC):

Processing tissue samples: Formalin fixed tissue samples will be sent to pathology through clinical trial tissue procurement, then paraffin embedded, cut, and stained with desired antibodies at the IHC Core (OSU).

Biomarkers to be studied (include but not limited to): PD-1, PD-L1, CTLA-4, CD3, CD4, CD8, IDO-1, Tregs (CD4⁺FoxP3⁺), and MDSCs (CD11b⁺CD33⁺). MLH1, PMS2, MLH2, MSH6.

TCR sequencing (from tissue):

RNA Extraction: RNA will be extracted from paraffinized tissue sections by RecoverAll Total Nucleic Acid Isolation Kit (Ambion) following manufacturer's protocol. Isolated RNA will be sent to OSU Genomics Core for TCR sequencing. Prior to sequencing RNA quality will be analyzed by determining RNA Integrity Number (RIN).

RNA Sequencing: T cell clonal diversity at each time point will be assessed by identifying TCR RNA sequences within the tumor and compared between responders and non-responders.

Determining immune correlates/biomarkers by flow cytometry from blood:

Isolation of peripheral blood mononuclear cells (PBMCs):

Peripheral blood mononuclear cells (PBMCs) will be isolated from blood

Biomarkers to be assessed (but not limited to): PD-1, PD-L1, CTLA-4, CD3, CD4, CD8, IDO-1, Tregs

(CD4+FoxP3+), and MDSCs (CD11b+CD33+)

TCR Sequencing (from blood):

RNA Extraction: PBMCs isolated from peripheral blood will be selected for CD3 expressing T cells by Human CD3 Microbeads Isolation Kit (Miltenyi Biotech) or other kits according to manufacturer's protocol. RNA will be extracted from T cells using Trizol reagent. Isolated RNA will be sent to the OSU Genomics Core for TCR sequencing. Prior to sequencing RNA quality will be analyzed by determining RNA Integrity Number (RIN).

RNA Sequencing: T cell clonal diversity at each time point will be assessed by identifying TCR RNA sequences within the tumor and compared between responders and non-responders.

Circulating tumor DNA (ctDNA) testing

We will ship cell-free DNA (ctDNA) and matched normal to a CLIA-certified laboratory running assays that are capable of reliably identifying genomic alterations in plasma at or below a minimum allele frequency of 0.2%. Examples of tests that meet this requirement include Foundation ACT (Foundation Medicine), PlasmaSelect (Personal Genome Diagnostics), Guardant 360 (Guardant), and MSK-ACCESS (MSKCC).

CyTOF (Cytometry of Time Of Flight) Analysis

A next generation of single-cell analysis technology called mass cytometry overcomes the limitations of flow cytometry (i.e., measuring a maximum of ten markers per panel). The CyTOF is a mass spectrometer-flow cytometer hybrid instrument that uses stable isotopes instead of fluorophores as reporters. Due to the discrete read-outs of mass cytometry, use of isotopes as reporters enables a significant increase in the number of measurable parameters per cell.

Upon subsequent review and approval, CyTOF will be used to detect changes in immune populations and markers between responders and non-responders in blood samples will be collected as outlined in section 6 of the study flow chart. 10.1200/JCO.2019.37.15_suppl.5590 *Journal of Clinical Oncology* 37, no. 15_suppl (May 20 2019) 5590-5590]. Additionally, panels can be designed with up to 45 antibodies focused completely on surface markers to delineate cellular hierarchy and intracellular signaling molecules. This will be done in the lab of Katherine Fuh at University of California, San Francisco. A panel of myeloid and lymphoid markers will be utilized for this analysis.

Mailing address for specimens:

Sirirak Buarpung, DVM, PhD

Katherine Fuh Lab

513 Parnassus Avenue, HSE 1645

San Francisco, CA 94143

7.1.3 Laboratory Procedures/Assessments

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

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β -human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β -hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam (<i>If abnormal</i>)	Free tyroxine (T4) (only if TSH abnormal)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Thyroid stimulating hormone (TSH) with reflex
Absolute Lymphocyte Count	(<i>CO₂ or biocarbonate</i>)	Urine pregnancy test †	
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		CA-125 if this is a marker for the patient (SOC)
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		
	Blood Urea Nitrogen		
† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.			
‡ If considered standard of care in your region.			

Laboratory tests for screening do not need to be repeated prior to cycle 1 day -15 if they were performed within 14 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a participant discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Participants who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 5.2.3. After discontinuing treatment following assessment of CR, these participants should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study (described in Section 7.1.5).

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. AEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Monitoring for AEs will continue for 90 days after study treatment cessation or at the time of initiation of new anti-cancer treatment, whichever comes first.

7.1.5.2 Follow Up Visit

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-Up Phase. Patient who do not start other anti-cancer treatment should be assessed every 12 weeks (84 ± 7 days) for 1 year by radiologic imaging to monitor disease status if the patient agrees to this (not mandatory) and should be followed at the discretion of the treating physician. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

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

AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Drug interactions
- Events related to or possibly related to concomitant medications
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, and weight.

Note that progressive disease should not be reported as an AE unless the outcome is fatal within the safety reporting period.

- All AEs from the time of treatment allocation through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

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

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

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

For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000mg or greater (≥ 5 times the indicated dose) and for lenvatinib 100 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and infant exposure during breast-feeding are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a participant (spontaneously reported to them) that occurs during the study.

Pregnancies and infant exposures during breastfeeding that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the participant to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- Is a congenital anomaly/birth defect;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.
- Note that hospitalization is defined as admission to treat a clinical adverse event.

The following events would not be considered hospitalizations for SAE reporting purposes:

- <24-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (e.g., a homeless patient) or admission not associated with a precipitating clinical adverse event (e.g., elective or pre-planned surgery, or in-patient administration of subsequent chemotherapy, etc.).
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an important medical event and as a SAE with CTC Grade 5 (fatal outcome) indicated.

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

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

SAE Reporting

Our standard process for IIT studies is to use Oncore for SAE reporting. SAEs will be reported to the sponsor using the Oncore system. SAEs will be reported to Merck using the Merck Global Safety Intake Form. Per our institutional SOP for reporting SAEs the MW form will only be used when an event is

unexpected & related that requires 15-day reporting to the FDA.

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

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

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

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

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

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

All SAEs and AESIs, regardless of relationship to study drug, must be reported to Merck **within 24 hours** of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below. After the 30-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

The Sponsor-Investigator's study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

The Sponsor-Investigator is responsible for submitting IND safety reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32 .

Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the

definitions:

- *Suspected adverse reaction* (The sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a *suspected adverse reaction*)
- *Serious*
- *Unexpected*

Not Related To Study Drug	An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) It does not follow a reasonable temporal sequence from administration of the study drug. It does not follow a known pattern of response to study drug It does not reappear or worsen when study drug is restarted. An alternative explanation is likely, but not clearly identifiable.
Related To Study Drug	An AE that is difficult to assign to alternative causes. It follows a strong or reasonable temporal sequence from administration of study drug. It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. It follows a known response pattern to study drug It is confirmed with a positive re-challenge or supporting laboratory data.

The Sponsor-Investigator will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

For SAE the completed study SAE form or the fully assessed case on MW or CIOMS will be submitted to Merck.

For expedited SAE/SUSAR the MW/CIOMS will be provided to Merck as submitted to FDA.

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up

to an ECI, that occurs to any participant must be reported within 2 workingdays to Merck Global Safety if it causes the participant to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Adverse Events

Please refer to the most recent Investigator Brochure for the comprehensive list of adverse events. For lenvatinib Section 8, Table 19 of the IB shows the expected SADR for regulatory reporting purposes. The listed events are included on the basis of SADR reported from lenvatinib clinical trials and post marketing experience. While these events are considered expected, any reaction with a fatal outcome will be considered unexpected.

Please refer to the most recent Investigator Brochure for the comprehensive list of adverse events. For pembrolizumab Section 7.2 Table 47 of the IB shows the expected SADR for regulatory reporting purposes. The listed events are included on the basis of SADR reported from pembrolizumab clinical trials and post marketing experience. While these events are considered expected, any reaction with a fatal outcome will be considered unexpected. Fatal and life-threatening reactions are considered unexpected for purposes of expedited reporting unless noted in product labeling and specifically annotated in Table 47.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 8 Evaluating Adverse Events

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

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The trial starts with a safety lead-in stage of up to 18 recurrent endometrial and ovarian cancer patients. Once the safety of the treatment is shown, accrual will open to the Phase II study. Patients treated at the RP2D from the safety lead-in will be included in the Phase II accruals.

The Phase II stage is designed as an open label, non-comparative basket trial to assess the efficacy and confirm the safety of lenvatinib+pembrolizumab+paclitaxel for treatment of recurrent endometrial or ovarian cancer. The efficacy will be evaluated against its relevant historical controls.

8.2 Statistical Analysis Plan

Sample size calculations assumptions

For sample size calculations we used the following assumptions.

Summarizing the data from patients treated with weekly paclitaxel on 5 prospective NCI- funded clinical trials in recurrent platinum resistant ovarian cancer, an overall response was seen in 53/230 (23%), with response rates in the individual studies ranging from 20 to 28%(14).

The ORR of weekly paclitaxel with in recurrent platinum resistant ovarian cancer is 27-31% based on phase II data from weekly paclitaxel with bevacizumab or pazopanib (AURELIA trial (13) and Richardson (12)). Expected PFS is 6-7 months and median OS is approximately 13-23 months.

For recurrent endometrial cancer on pembrolizumab and lenvatinib the objective response rate (ORR) at week 24 and overall was 39.6% (95% CI, 26.5–54.0), and this was similar for MMRd and MMRp patients. The median PFS was 7.4 months (95% CI, 5.0–NE); 83% had a response duration ≥ 6 months and 64.5% ≥ 12 months (7).

Design for safety lead-in stage

We will use the Time-to-event Bayesian Optimal Interval Design (TITE-BOIN) design developed by Yuan et al. [Yuan, Y., Lin, R., Li, D., Nie, L. and Warren, K.E. (2018). Time-to-event Bayesian Optimal Interval Design to Accelerate Phase I Trials. Clinical Cancer Research, DOI: 10.1158/1078-0432.CCR-18-0246.] for this phase I study, where the target toxicity rate for the RP2D is 30%, cohort size is 3 and the maximum sample size is 18 DLT evaluable patients. Considering DLT evaluation period is 5 weeks, the TITE-BOIN escalation and de-escalation design will be used to allow for real-time dose assignment decisions for new patients while some enrolled patients' toxicity data are still pending. This

shortens the trial duration and reduces the logistic difficulties caused by repeatedly suspending accrual. The TITE-BOIN works by predicting the dose-limiting toxicity (DLT) outcome for patients whose DLT data are pending based on their follow-up time. The first cohort of 3 patients will be treated at dose level 1. To assign a dose to the next cohort of patients, we will count the number of patients (“No. treated”), the number of patients who experienced DLT (“No. DLTs”), and the number of pending patients (“No. data pending”) and their weighted standardized total follow-up time (“WSTFT”) at the current dose, and then make the decision of dose de-escalation to dose level -1 or staying at the current dose level 1 according to the rule displayed in Table 1 below, which minimizes the probability of incorrect dose assignment. The trial continues until the maximum sample size of 18 patients is exhausted or the number of patients treated at the current dose reaches 6. During the trial conduct, the TITE-BOIN design also imposes a dose elimination rule to avoid assigning too many patients to the overly toxic dose. The trial will be terminated if the lowest dose is eliminated. In this case, no dose should be selected as the MTD. At the end, MTD will be determined based on isotonic regression as specified. Specifically, we select the MTD as the dose for which the isotonic estimate of the toxicity rate is closest to the targeted DLT (i.e. 30%) via “TITE-BOIN” software (MD Anderson).

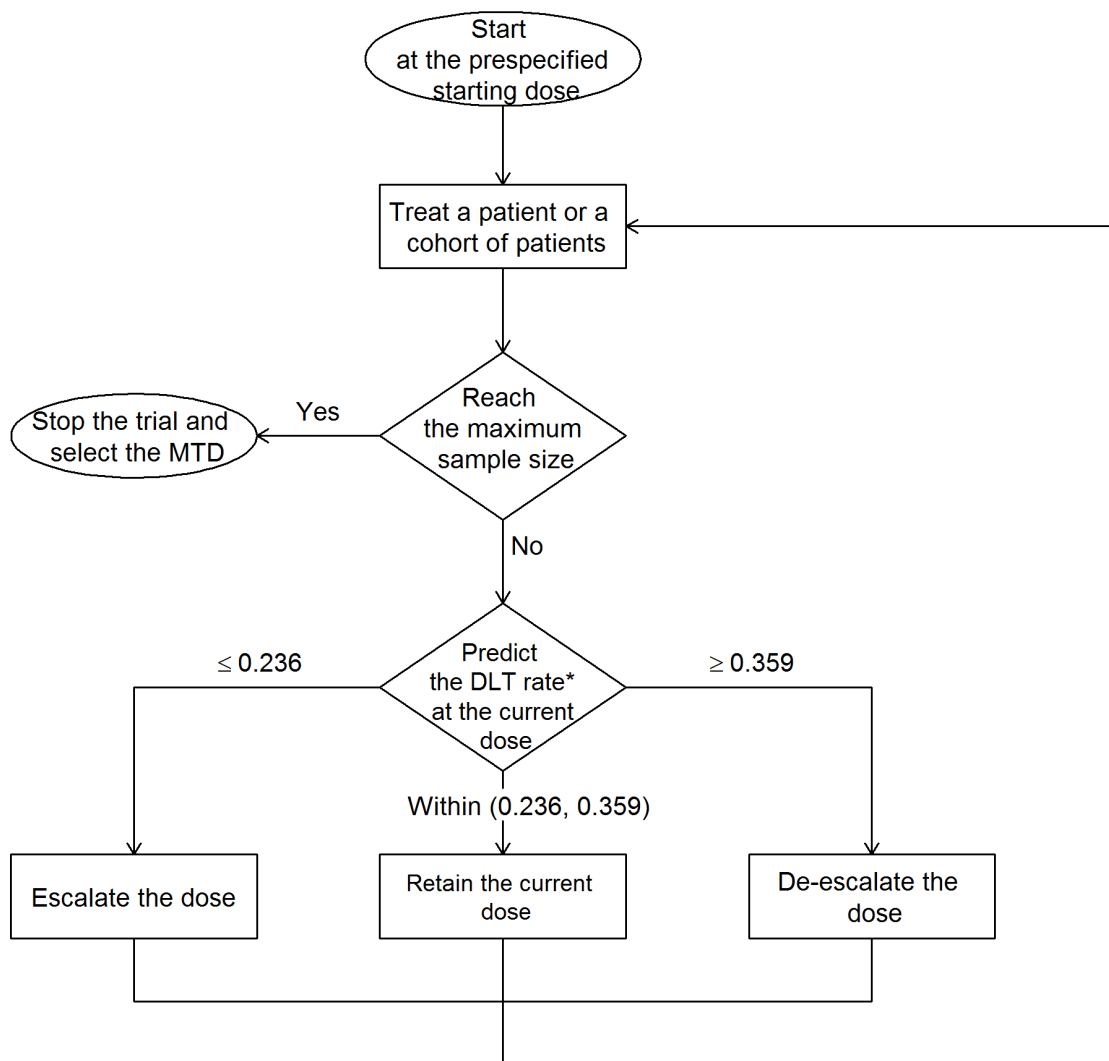
Addendum 7/11/2022: after reviewing toxicities on DL1 and DL-1 with 2/4 DLTs on DL1 and no DLTs on DL-1 (0/4), the study team including treating providers, PI, and statistician, decided not to dose re-escalate but to assign the RP2D at DL-1 due to improved tolerance. Safety lead in completed and all next patients will be enrolled at DL-1.

Table 9. Dose escalation/de-escalation rule for the TITE-BOIN design. NOTE: If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose.

No. treated	No. DLTs	No. data pending	WSTFT		
			Escalate	Stay	De- escalate
3	0	≤ 1	Y		
3	0	≥ 2		Suspend	
3	1	0		Y	
3	1	1		>0.88	≤ 0.88
3	1	≥ 2		Suspend	
3	2	≤ 1			Y
3	3	0	Y&Elim		

6	0	≤ 3	Y		
6	0	≥ 4		Suspend	
6	1	≤ 1	Y		
6	1	2	≥ 0.60	< 0.60	
6	1	3	≥ 1.96	< 1.96	
6	1	≥ 4		Suspend	
6	2	0		Y	
6	2	1		> 0.73	≤ 0.73
6	2	2		> 1.80	≤ 1.80
6	2	3		> 2.87	≤ 2.87
6	2	≥ 4		Suspend	
6	3	≤ 3			Y
6	≥ 4	≤ 2	Y&Elim		

Note: “No. treated” is the total number of patients treated at the current dose level, “No. DLTs” is the number of patients who experienced DLT at the current dose level, “No. data pending” denotes the number of patients whose DLT data are pending at the current dose level, “WSTFT” is the standardized total follow-up time for the patients with data pending. “Y” represents “Yes”, and “Y&Elim” represents “Yes and Eliminate”. When a dose is eliminated, all higher doses should also be eliminated.



* Predicted DLT rate = $\frac{\text{Predicted total number of patients who will experience DLT at the current dose}}{\text{Total number of patients treated at the current dose}}$

Figure 2. Flowchart for trial conduct using the TITE-BOIN design. NOTE: If the current dose is the highest dose and the rule indicates dose escalation, we will treat the new patients at the highest dose.

Table 10 demonstrates operating characteristics of the proposed TITE-BOIN design with the target DLT probability of 30% and the maximum sample size of 18. The time to toxicity is simulated from a uniform distribution $\text{Unif}(0, T)$, and the patient accrual follows a Poisson process at the rate of 3 patient per month.

Table 10. Operating characteristics of the proposed TITE-BOIN design with the target DLT probability of 30% and the sample size of 18 for 3 scenarios.

Operating Characteristics

	Dose Level			Number of Patients	% Early Stopping
	-2	-1	1		
Scenario 1					
True DLT Rate	0.05	0.15	0.30	9.8	0.2
Selection %	0.5	20.7	78.6		
# Pts Treated	4.3	30.7	65.0		
Scenario 2					
True DLT Rate	0.20	0.30	0.40	11.3	1.5
Selection %	16.8	36.3	45.4		
# Pts Treated	16.4	35.3	48.3		
Scenario 3					
True DLT Rate	0.30	0.40	0.50	12.1	4.5
Selection %	36.7	33.8	25.0		
# Pts Treated	24.4	36.4	39.3		

Design for Phase II stage

For the Phase II stage, the primary efficacy objective is overall response rate (ORR). The ORR will be quantified as the binomial proportion of evaluable patients with Best Overall Response (BOR) of complete or partial response per RECIST 1.1. This design tests the null hypothesis that the experimental treatment has an ORR at-most equal to the standard of care, against an alternative that it is greater. The primary statistical hypothesis is:

$$H_0: \pi \leq \pi_0 \text{ vs } H_A: \pi > \pi_0$$

where (π, π_0) is the true and null hypothesis ORR, respectively.

Accrual and Study Duration

$n =$	29
1-sided $\alpha =$	0.10
$\pi_{0(k)} =$	0.35

$\Delta =$	0.20
$\pi_{(k)} =$	0.55
Efficacy (r/n)	14/29
Power	0.80

The accrual target is 29 patients at the RP2D. Patients in the safety lead-in treated at the RP2D will be included in the Phase II accruals. Accounting for 10% attrition and if multiple dose levels or schedules are needed for the safety lead-in, the maximum accrual number would be 41 (29+3+9). At an expected accrual rate of 3 patients per month across all sites, enrollment of 47 patients (accounting for additional screen failures) should take about 18 months. The accrual period may be shortened if only one safety lead-in cohort is needed or if attrition is lower than expected. It would be longer if an alternative dosing schedule will need to be explored, or if attrition is higher than expected. We expect that accrual time will be no longer than 18 months regardless.

Primary Analyses

For each arm, the ORR estimate and its 2-sided Wilson Score confidence interval will be obtained using all evaluable patients. The Wilson Score interval will be interpreted as the plausible range for the true (unobserved) ORR that is supported by the data.

Measured outcome variables will be summarized overall and by relevant demographic and baseline variables. Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data, ex. histograms, boxplots, scatterplots, etc.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab and lenvatinib will be provided by Merck as summarized in below. Paclitaxel is commercially supplied.

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL	Solution for Injection
Lenvatinib 4 and 10 mg capsules	4 and 10 mg capsules
Paclitaxel 6 mg/mL	

9.2 Packaging and Labeling Information

Supplies will be labeled in accordance with regulatory requirements.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor-investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

Attribution of the AE:

- 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.

Responsibility for Data Submission

This study will be monitored by the Ohio State University/James Comprehensive CancerCenter Data Safety Monitoring Board (DSMB).

The clinical research coordinator and/or investigator will be responsible for collecting and recording all relevant data for the protocol. As these results are collected, all toxicities and adverse events will be identified, recorded and reported to the principal investigator. Adverse events and unanticipated problems will be reported as described above. The principal investigator will determine the relationship of the adverse event(s) to the intervention(s), procedure(s), and/or agent(s) of the protocol and decide the appropriate course of action for the study participant(s).

The Principal Investigator will meet with the study team at least monthly to discuss safety, data quality and data timeliness, and will conduct continuous review of data and patient safety. During the safety lead in, this trial will be discussed during the weekly GynOnc Phase I meetings (Mondays at 4:30 pm) and we will review safety, dose escalation and monitoring. DLTs will also be discussed with the statistician to make decisions to escalate/de-escalate during the safety lead in portion of the trial. The Phase I team consists of the PI, 2 additional gynecologic oncologists leading the Phase I team (David O'Malley and John Hays), research manager, nurses lead, phase I study nurses, nurse practitioners and research coordinators. Serious adverse events and responses will also be reviewed by the OSUCCC – James Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report of the trial semi-annually that will be reviewed by the committee per the DSMC plan. All reportable serious adverse events will also be reported to the Institutional Review Board (IRB) of record as per the policies of the IRB as well as to Merck

and the FDA.

Mandatory safety and trial review teleconferences will be scheduled and moderated by the Multi-Center Trial Program (MCTP). All sites involved in the study are expected to have a representative present for every call to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the MCTP protocol files. Teleconferences must minimally be held quarterly and may be held more frequently, as needed.

For details on the monitoring plan, see separate multi-site monitoring document.

Compliance will be achieved via IRB Continuing Review, and conscientious conduct by members of the study team, adhering to relevant regulations and the principles of the ethical conduct of human subject research. Sub-sites will send to OSU IRB.

11.0 REFERENCES

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12.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in <i>Am. J. Clin. Oncol.</i> : Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: <i>Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group</i> . <i>Am J Clin Oncol</i> 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP:

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

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

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

Contraception Requirements

Female Participants:

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

Contraception should be used during study treatment and until 6 months after the last dose of paclitaxel.

Table 10 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
• Progestogen- only contraceptive implant ^{a, b} • Intrauterine hormone-releasing system (IUS) ^b • Intrauterine device (IUD) • Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 6 months after the last dose of study treatment.

Pregnancy Testing

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

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

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

Appendix 4: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 6 and Figures 1). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. I

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to $\geq 20\%$ and ≥ 5 mm from nadir
 - Please note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

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New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
 - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
 - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
 - For new lesions, worsening is any of these:
 - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
 - Visible growth of new non-target lesions
 - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1 Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the scan on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
 - Sum of diameters reaches the PD threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression.
The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
 - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
 - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
 - New lesions appear for the first time
 - Additional new lesions appear
 - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
 - Previously identified non-target lesions show any significant growth

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If any of the events above occur, the overall response for that visit is iUPD, and the iUPDevaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

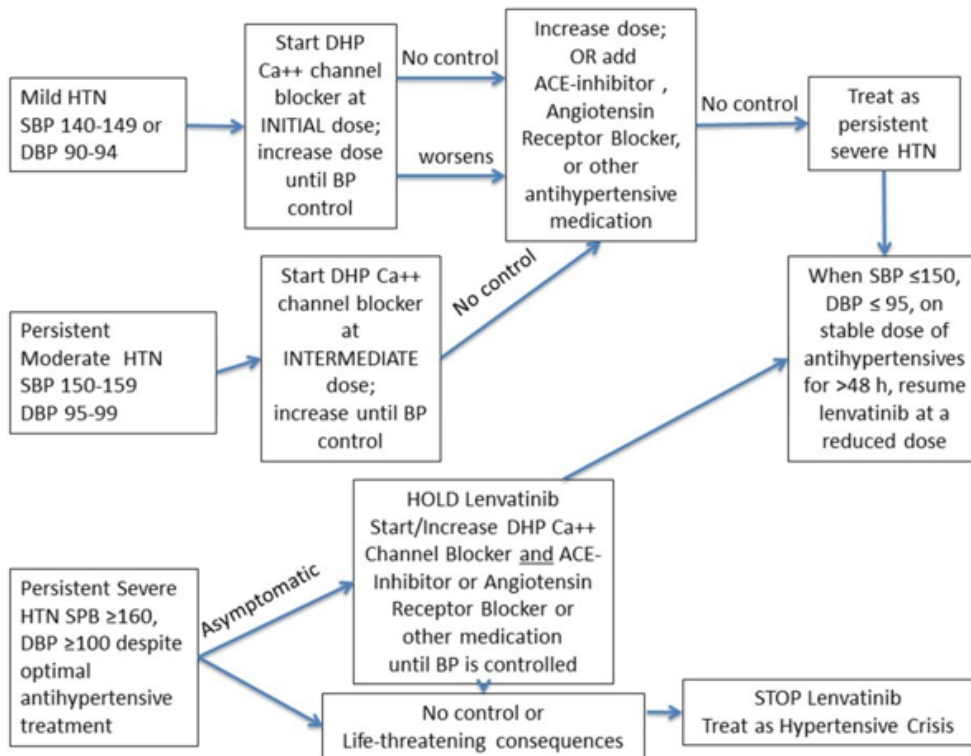
The decision process is identical to the iUPD confirmation process for the initial PD, except in one respect. If new lesions occurred at a prior instance of iUPD, and at the confirmatory scan the burden of new lesions has increased from its smallest value (for new target lesions, their sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al,2017].

APPENDIX 5 MANAGEMENT OF HYPERTENSION

RECOMMENDED MANAGEMENT FOR LENVATINIB-RELATED HYPERTENSION

Figure 1 provides a guideline for treatment of hypertension (HTN); however, changes may be made at the discretion of the treating physician.



RECOMMENDED ANTI-HYPERTENSIVE MEDICATIONS

Agent	Initial Dose	Intermediate Dose	Maximum Dose
<i>Dihydropyridine (DHP) Calcium Channel Blockers</i>			
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
Felodipine	2.5 mg po qd	5 mg po qd	10 mg po qd
Nifedipine XL (avoid if possible as it is VEGF secretion inducer)			
<i>Angiotensin Converting Enzyme (ACE) Inhibitors</i>			
Captopril	12.5 mg po tid	25 mg po tid	50 mg po tid
Enalapril	5 mg po qd	10–20 mg po qd	40 mg po qd
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd
Lisinopril	5 mg po qd	10–20 mg po qd	40 mg po qd
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd
Perindopril	4 mg po qd	None	8 mg po qd
Quinapril	10 mg po qd	20 mg po qd	20 mg po qd
<i>Angiotensin II Receptor Blockers</i>			
Losartan	25 mg po qd	50 mg po qd	100 mg po qd
Candesartan	4 mg po qd	8–16 mg po qd	32 mg po qd
Ibuprofen	75 mg po qd	150 mg po qd	300 mg po qd

Telmisartan	40 mg po qd	None	80 mg po qd
Valsartan	80 mg po qd	None	160 mg po qd

po = oral administration; qd = once daily; tid = three times daily

Adapted from Kollmannsberger C, et al, *CUAJ*. 2007;Vol 1 (Issue 2 Suppl):S41–54.

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