ENGOT-en9 / MK-7902-001

Study name: Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for Endometrial Carcinoma (ENGOT-en9 / MK-7902-001) (LEAP-001)

Estimated Enrollment:	720 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)
Actual Study Start Date:	April 11, 2019
Estimated Primary Completion Date:	April 10, 2023
Estimated Study Completion Date:	April 10, 2023

Arm	Intervention/treatment
Experimental: Lenvatinib + Pembrolizumab Participants receive lenvatinib daily and pembrolizumab once at the start of each 3-week treatment cycle.	Drug: Lenvatinib Lenvatinib 4 mg or 10 mg capsules at a total daily dose of 20 mg taken by mouth once per day. Other Name: E7080, MK-7902, LENVIMA® Biological: Pembrolizumab Pembrolizumab 200 mg IV infusion given on Day 1 of each cycle. Other Name: MK-3475, KEYTRUDA®
Active Comparator: Paclitaxel + Carboplatin Participants receive paclitaxel and carboplatin once at the start of each 3-week treatment cycle.	Drug: Paclitaxel Paclitaxel 175 mg/m^2 IV infusion given on Day 1 of each cycle. Other Name: TAXOL®, ONXAL® Drug: Carboplatin Carboplatin 10 mg/mL IV infusion at a total dose of are-under-the-curve (AUC) 6 (per Calvert's formula) given on Day 1 of each cycle. Other Name: PARAPLATIN®

Outcome Measures

Primary Outcome Measures:

1 Progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR) [Time Frame: Up to approximately 31 months]Progression-free survival based on RECIST 1.1 as assessed by BICR. Progression-free survival is measured from the time of randomization to the first documented disease progression or death due to any cause, whichever occurs first.

2 Overall Survival (OS) [Time Frame: Up to approximately 45 months]Overall survival is

measured from the time of randomization up to death due to any cause.

Secondary Outcome Measures:

1 Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent review (BICR) [Time Frame: Up to approximately 31 months]The ORR (either confirmed complete response [CR] or partial response [PR]) based on RECIST 1.1 and assessed by BICR will be determined in mismatch repair proficient (pMMR) participants and in all-comer participants who have measurable disease at study entry.

2 Change from baseline in the global score of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) in pMMR and in all-comer participants [Time Frame: Baseline and designated time points up to 27 months]The EORTC QLQ-C30 was developed to assess the quality of life of patients with cancer. It contains 30 questions (items), 24 of which aggregate into nine multi-item scales representing various aspects, or dimensions, of quality of life (QoL): one global scale, five functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain), and six additional single-symptom items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhea) and perceived financial impact of the disease. Individual items are scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Raw scores for each scale are standardized into a range of 0 to 100 by linear transformation; a higher score on the global and functional scales represents a higher ("better") level of functioning, and a higher score on the symptom scale represents a higher ("worse") level of symptoms.

3 Percentage of participants experiencing an adverse event (AE) [Time Frame: Up to approximately 27 months (through 90 days after the last dose of study treatment)]An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

4 Percentage of participants experiencing a serious adverse event (SAE) [Time Frame: Up to approximately 28 months (through 120 days after the last dose of study treatment)] An SAE is an AE that results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability, is a congenital birth defect, or is another important medical event.

5 Percentage of participants experiencing an immune-related AE (irAE) [Time Frame: Up to approximately 27 months (through 90 days after the last dose of study treatment)]Immune-related AEs will be monitored in both arms.

6 Percentage of participants discontinuing from study treatment due to an AE(s) [Time Frame: Up to approximately 24 months (through the last dose of study treatment)]Discontinuations related to AEs will be monitored in both arms.

Eligibility Criteria

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	Female
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Has Stage III, Stage IV, or recurrent, histologically-confirmed endometrial carcinoma with disease that is either measurable or non-measurable but radiographically apparent, per RECIST 1.1 as assessed by BICR (note: may have received prior chemotherapy only if administered concurrently with radiation; may have received prior radiation without concurrent chemotherapy; may have received prior hormonal therapy for treatment of endometrial carcinoma, provided that it was discontinued ≥1 week prior to randomization; and may have received 1 prior line of systemic platinum-based adjuvant and/or neoadjuvant chemotherapy)
- Has provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion that was not previously irradiated, for determination of mismatch repair (MMR) status
- Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 7 days prior to the first dose of study intervention
- Is not pregnant or breastfeeding, and is either not a woman of childbearing potential (WOCBP) or is a WOCBP who agrees to use contraception during the study and for ≥120 days after pembrolizumab, ≥30 days after lenvatinib, or ≥196 days after (chemotherapy) [if a WOCBP, a pregnancy test will be required within 24 hours of first dose of study drug]
- Has adequately controlled blood pressure within 7 days prior to randomization
- Has adequate organ function based on assessment within 7 days prior to the first dose of study intervention

Exclusion Criteria:

- Has carcinosarcoma (malignant mixed Műllerian tumor), endometrial leiomyosarcoma or other high grade sarcomas, or endometrial stromal sarcomas
- Has a central nervous system (CNS) metastasis, unless local therapy (e.g., whole brain radiation therapy, surgery, or radiosurgery) has been completed and have discontinued use of corticosteroids for this indication for ≥4 weeks prior to starting study medication (major surgery within 3 weeks of the first dose of study drug will be exclusionary)
- Has a known additional malignancy (other than endometrial carcinoma) that is progressing or has required active treatment in the last 3 years
- Has gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib
- Has a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula
- Has radiographic evidence of major blood vessel invasion/infiltration
- Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to randomization
- Has significant cardiovascular impairment within 12 months of the first dose of study intervention such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident (CVA) stroke, or cardiac arrhythmia associated with hemodynamic instability
- Has any infection requiring systemic treatment
- Has not recovered adequately from any toxicity and/or complications from major surgery prior to randomization
- Has a known history of human immunodeficiency virus (HIV) infection (HIV test is required

at screening)
- Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (Hepatitis B and C testing is required at screening)
- Has a history of (non-infectious) pneumonitis that required treatment with steroids, or has current pneumonitis
- Has a known history of active tuberculosis (tuberculosis test is required at screening)
- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator
- Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study
- 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 randomization
- Has an active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs)
- Has received prior systemic chemotherapy in any setting for the treatment of endometrial carcinoma (note: prior chemotherapy administered concurrently with radiation is permitted)
- Has received prior radiotherapy within 4 weeks prior to randomization (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 to non-CNS disease and vaginal brachytherapy)
- Has received prior hormonal therapy for the treatment of endometrial carcinoma within 1 week of randomization
- Has received prior therapy with any treatment targeting vascular endothelial growth factor (VEGF)-directed angiogenesis, an anti-programmed cell death (PD)-1, anti-PD ligand (L)1, or anti-PD L2 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137)
- Has received a live vaccine within 30 days prior to the first dose of study intervention
- Has known intolerance to study intervention (or any of the excipients)
- Has had an allogenic tissue/solid organ transplant
- Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization