Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775])

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
Eisai Inc.

Collaborator:
Merck Sharp & Dohme Corp.

Information provided by (Responsible Party):
Eisai Inc.
Brief Summary:
This is a study of pembrolizumab (MK-3475, KEYTRUDA®) in combination with lenvatinib (E7080) versus treatment of physician's choice (doxorubicin or paclitaxel) for the treatment of advanced endometrial cancer. Participants will be randomly assigned to receive either pembrolizumab and lenvatinib or treatment of physician's choice. The primary study hypothesis is that pembrolizumab in combination with lenvatinib prolongs progression free survival (PFS) and overall survival (OS) when compared to treatment of physician's choice.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Endometrial Neoplasms</td>
<td>Drug: Pembrolizumab</td>
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<tr>
<td></td>
<td>Drug: Lenvatinib</td>
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<td></td>
<td>Drug: Paclitaxel</td>
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<td>Drug: Doxorubicin</td>
<td>Phase 3</td>
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Study Design

- Study Type: Interventional (Clinical Trial)
- Estimated Enrollment: 780 participants
- Allocation: Randomized
- Intervention Model: Parallel Assignment
- Masking: None (Open Label)
- Primary Purpose: Treatment
- Official Title: A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer

- Actual Study Start Date: June 11, 2018
- Estimated Primary Completion Date: February 24, 2022
- Estimated Study Completion Date: January 25, 2023

Resource links provided by the National Library of Medicine

Drug Information available for: Lenvatinib Pembrolizumab

U.S. FDA Resources

Arms and Interventions

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intervention/treatment</th>
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<tbody>
<tr>
<td>Experimental: Lenvatinib 20 mg + Pembrolizumab 200 mg</td>
<td>Drug: Pembrolizumab</td>
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</table>
### Participants will receive pembrolizumab 200 milligram (mg) administered by intravenous (IV) infusion on Day 1 of each 21-day cycle plus lenvatinib 20 mg administered orally (PO) once daily (QD) during each 21-day cycle for up to 35 cycles.

**Other Names:**
- **KEYTRUDA®**
- **MK-3475**

**Drug:** Lenvatinib  
20 mg administered orally (PO) QD during each 21-day cycle.  
**Other Name:**  
LENVIMA®

### Active Comparator: Treatment of Physician's Choice

Participants will receive either of the following treatments: doxorubicin 60 milligram per square meter (mg/m^2) administered by IV on Day 1 of each 21-day cycle for up to a maximum cumulative dose of 500 mg/m^2 OR paclitaxel 80 mg/m^2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.

**Other Names:**
- **DOXIL®**
- **ADRIAMYCIN®**

**Drug:** Doxorubicin  
60 mg/m^2 administered by IV on Day 1 of each 21-day cycle.  
**Other Names:**  
- **DOXIL®**  
- **ADRIAMYCIN®**

**Drug:** Paclitaxel  
80 mg/m^2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.  
**Other Names:**  
- **TAXOL®**  
- **ABRAXANE®**
Primary Outcome Measures:

1. Progression Free Survival (PFS) [Time Frame: Up to approximately 24 months]
   PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as determined by Blinded Independent Central Review (BICR) or death due to any cause, whichever occurred first.

2. Overall Survival (OS) [Time Frame: Up to approximately 27 months]
   OS is defined as the time from date of randomization to date of death from any cause.

Secondary Outcome Measures:

1. Objective Response Rate (ORR) [Time Frame: Up to approximately 24 months]
   ORR is defined as the percentage of participants who have best overall response of either complete response (CR) or partial response (PR), as determined by BICR per RECIST 1.1.

2. Health-Related Quality of Life (HRQoL) Score Using the European Organization for Research and Treatment (EORTC) Quality of Life (QoL) Questionnaire (QLQ-C30) Version 3.0 [Time Frame: Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and at the end of follow-up (up to approximately 27 months)]
   Change from baseline in HRQoL using the global score of EORTC QLQ-C30 will be determined. EORTC QLQ-C30 is a cancer specific health-related quality-of-life (QoL) questionnaire, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale. The score for each item and the overall score ranges from 0 to 100. A high overall scale and subscale scores represent improved health status. However, in case of individual symptoms, higher scores suggest increased perception of these symptoms of life.

3. Number of Participants With Adverse Events (AE) [Time Frame: Up to approximately 27 months]
   The number of participants experiencing an AE will be assessed. An AE is defined as any unfavorable and unintended sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.

4. Number of Participants With Serious Adverse Events (SAE) [Time Frame: Up to approximately 27 months]
   The number of participants experiencing an SAE will be assessed. A SAE is an AE that results in death, is life threatening, results in persistent or significant disability/incapacity, results in or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is associated with an overdose, or is another important medical event.
5. Number of Participants With Immune-related Adverse Events (irAE) [ Time Frame: Up to approximately 27 months ]

The number of participants experiencing an irAE will be assessed. An irAE is defined as any unfavorable and unintended immune-related sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.

6. Number of Participants With Treatment Discontinuations Due to AEs [ Time Frame: Up to approximately 27 months ]

The number of participants who discontinue study treatment due to an AE will be assessed.

7. Time to Treatment Failure (TTF) Due to Treatment Emergent AEs [ Time Frame: Up to approximately 27 months ]

Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a participant discontinues study treatment due to AEs.

8. Area Under the Concentration time Curve of Lenvatinib From Time 0 to Infinity (AUC 0-∞) [ Time Frame: Cycle 1 Day 1: 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 15: predose and 2-12 hours postdose; Cycle 2 Day 1: predose and 0.5 - 4 hours and 6-10 hours postdose; Cycle length = 21 days ]

9. Apparent Total Body Clearance (Cl/F) of Lenvatinib [ Time Frame: Cycle 1 Day 1: 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 15: predose and 2-12 hours postdose; Cycle 2 Day 1: predose and 0.5 - 4 hours and 6-10 hours postdose; Cycle length = 21 days ]

10. Apparent Total Body Volume of Distribution (Vd/F) of Lenvatinib [ Time Frame: Cycle 1 Day 1: 0.5-4 hours and 6-10 hours postdose; Cycle 1 Day 15: predose and 2-12 hours postdose; Cycle 2 Day 1: predose and 0.5 - 4 hours and 6-10 hours postdose; Cycle length = 21 days ]

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

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

Criteria

Inclusion Criteria:

1. Has a histologically confirmed diagnosis of endometrial carcinoma (EC)
2. Documented evidence of advanced, recurrent or metastatic EC.
3. Has radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting.
   Note: There is no restriction regarding prior hormonal therapy.
4. Has historical or fresh tumor biopsy specimen for determination of mismatch repair (MMR) status.
5. Has at least 1 measurable target lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and confirmed by Blinded Independent Central Review BICR.
6. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of starting study treatment.
7. Is not pregnant, breastfeeding, and agrees to use a highly effective method of contraception during the treatment period and for at least 120 days (for participants treated with lenvatinib plus pembrolizumab) or at least 180 days (for participants treated with treatment of physician's choice [TPC]) after the last dose of study treatment.

Exclusion Criteria:

1. Has carcinosarcoma (malignant mixed mullerian tumor), endometrial leiomyosarcoma and endometrial stromal sarcomas.
2. Has unstable central nervous system (CNS) metastases.
3. Has active malignancy (except for endometrial cancer, definitively treated in-situ carcinomas [e.g. breast, cervix, bladder], or basal or squamous cell carcinoma of the skin) within 24 months of study start.
4. Has gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
5. Has a pre-existing greater than or equal (\(\geq\)) Grade 3 gastrointestinal or non-gastrointestinal fistula.
6. Has radiographic evidence of major blood vessel invasion/infiltration.
7. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study treatment.
8. Has a history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident (CVA) stroke, or cardiac arrhythmia associated with hemodynamic instability within 12 months of the first dose of study treatment.
10. Has not recovered adequately from any toxicity and/or complications from major surgery prior to
11. Is positive for Human Immunodeficiency Virus (HIV).

12. Has active Hepatitis B or C.

13. Has a history of (non-infectious) pneumonitis that required treatment with steroids, or has current pneumonitis.

14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

15. 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 study start -Has an active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years.

16. Is pregnant or breastfeeding.

17. Has had an allogenic tissue/solid organ transplant.

18. Has received >1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for Endometrial Cancer. Participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as one is given in the neoadjuvant or adjuvant treatment setting.

19. Has received prior anticancer treatment within 28 days of study start. All acute toxicities related to prior treatments must be resolved to Grade ≤1, except for alopecia and Grade ≤2 peripheral neuropathy.

20. Has received prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

21. Has received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor other than an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, and who has discontinued from that treatment due to a Grade 3 or higher immune-related adverse event.

22. Has received prior radiation therapy within 21 days of study start with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks of study start. Participants must have recovered from all radiation-related toxicities and/or complications prior to randomization.

23. Has received a live vaccine within 30 days of study start.

24. Has a known intolerance to study treatment (or any of the excipients).

25. Prior enrollment on a clinical study evaluating pembrolizumab and lenvatinib for endometrial carcinoma, regardless of treatment received.

26. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of study start.

27. Participants with urine protein ≥1 gram (g)/24 hour.

28. Prolongation of corrected QT (QTc) interval to >480 milliseconds (ms).

29. Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).
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