Protocol Title: A Four Arm Randomized Phase II Study Comparing Single-Agent Olaparib, Single Agent Cediranib, the Combination of Cediranib/Olaparib and the Combination of Olaparib/Wee1 Inhibitor AZD1775 in Women with Recurrent, Persistent or Metastatic Endometrial Cancer (EEC)

Target Population: Stage IVA – IVB Endometrial Cancer that is recurrent, persistent, or metastatic

Summary: This randomized phase II trial studies how well Olaparib, Cediranib maleate, and Wee1 Inhibitor AZD1775 work in treating patients with Endometrial Cancer that has come back, does not respond to treatment, or has spread to other places in the body.

Key Inclusion Criteria:
- Recurrent or persistent Endometrial Carcinoma, which is refractory to curative therapy or established treatments.
  - Histologic confirmation of the original primary tumor is required.
  - The following histologic epithelial cell types are eligible:
    - Endometrioid Adenocarcinoma
    - Serous Adenocarcinoma
    - Undifferentiated Carcinoma
    - Mixed Epithelial Carcinoma
    - Adenocarcinoma not otherwise specified (N.O.S.)
  - NOTE: Clear Cell histology is EXCLUDED
- Evaluable disease as defined by RECIST 1.1.
  - All patients must have measurable disease.
- Received 1 prior chemotherapeutic regimen for management of Endometrial Carcinoma.
  - Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy.
  - Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.
- Allowed to receive, but are not required to receive, 1 additional cytotoxic regimen for management of recurrent or persistent disease according to the following definition: cytotoxic regimens include any agent that targets the genetic and/or mitotic apparatus of dividing cells, resulting in dose-limiting toxicity to the bone marrow and/or gastrointestinal mucosa.
  - Note: Patients on this non-cytotoxic study are allowed to receive 1 additional cytotoxic chemotherapy regimen for management of recurrent or persistent disease, as defined above; however, patients are encouraged to enroll on second-line non-cytotoxic studies prior to receiving additional cytotoxic therapy.
- NOT received any non-cytotoxic chemotherapy for management of recurrent or persistent disease.
  - Prior hormonal therapy is allowed.
  - Hormonal therapy for grade 1 endometrial cancers with low volume or indolent disease is encouraged.
- ECOG Performance Status of 0, 1 or 2 (Karnofsky ≥ 60%) within 7 days prior to registration.
- Adequate baseline organ function.
- Adequately controlled blood pressure (BP), with a BP no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility.
  - Hypertension may be managed with up to a maximum of 3 antihypertensive medications; it is strongly recommended that patients who are on 3 antihypertensive medications be followed by a cardiologist or blood pressure specialist for management of blood pressure while on protocol.
  - Patients must be willing and able to check and record daily blood pressure reading.
- Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and Thyroid-Stimulating Hormone (TSH) within normal limits.
Key Exclusion Criteria:

- Prior enrollment into a clinical trial including Cediranib, Olaparib, or AZD1775.
- Prior chemotherapy, endocrine therapy, radiotherapy, or investigational agents within 4 weeks.
- Current signs/symptoms of bowel obstruction and/or signs/symptoms of bowel obstruction within the preceding 3 months.
- History of gastrointestinal perforation.
  - Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired or has healed, there has been no evidence of fistula for at least 6 months, and patient is deemed to be at low risk of recurrent fistula.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Participants receiving any medications or substances that are strong inhibitors or inducers of CYP3A4 are ineligible.
  - Strong inhibitors and inducers of UGT/PgP should be used with caution.
- Known HIV-positive individuals are ineligible.
  - In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy.
- Prior history of stroke or transient ischemic attack within the last 6 months.
- Prior history of hypertensive crisis or hypertensive encephalopathy.
- Major surgical procedure, trauma or open biopsy within 28 days of starting Cediranib.
- Patients may not use any complementary or alternative medicines including natural herbal products or folk remedies as they may interfere with the effectiveness of the study treatments.
- No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT).
- No features suggestive of Myelodysplastic Syndrome (MDS) or Acute Myelogenous Leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.
- Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on CT or MRI scans should not be included on this study.
  - Screening imaging to rule out brain metastases is not required for screening but should be performed prior to study enrollment if clinically indicated.
  - Patients with treated brain metastases and resolution of any associated symptoms must demonstrate stable post-therapeutic imaging for at least 6 months prior to starting study drug.
- Any concomitant or prior invasive malignancies with the following curatively treated exceptions:
  - Treated limited stage basal cell or squamous cell
  - Carcinoma in situ of the breast or cervix
  - Prior cancer treated with a curative intent with no evidence of recurrent disease 3 years following diagnosis and judged by the investigator to be at low risk of recurrence
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to Cediranib, AZD1775 or Olaparib.

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For additional information: [https://clinicaltrials.gov/ct2/show/NCT03660826](https://clinicaltrials.gov/ct2/show/NCT03660826)