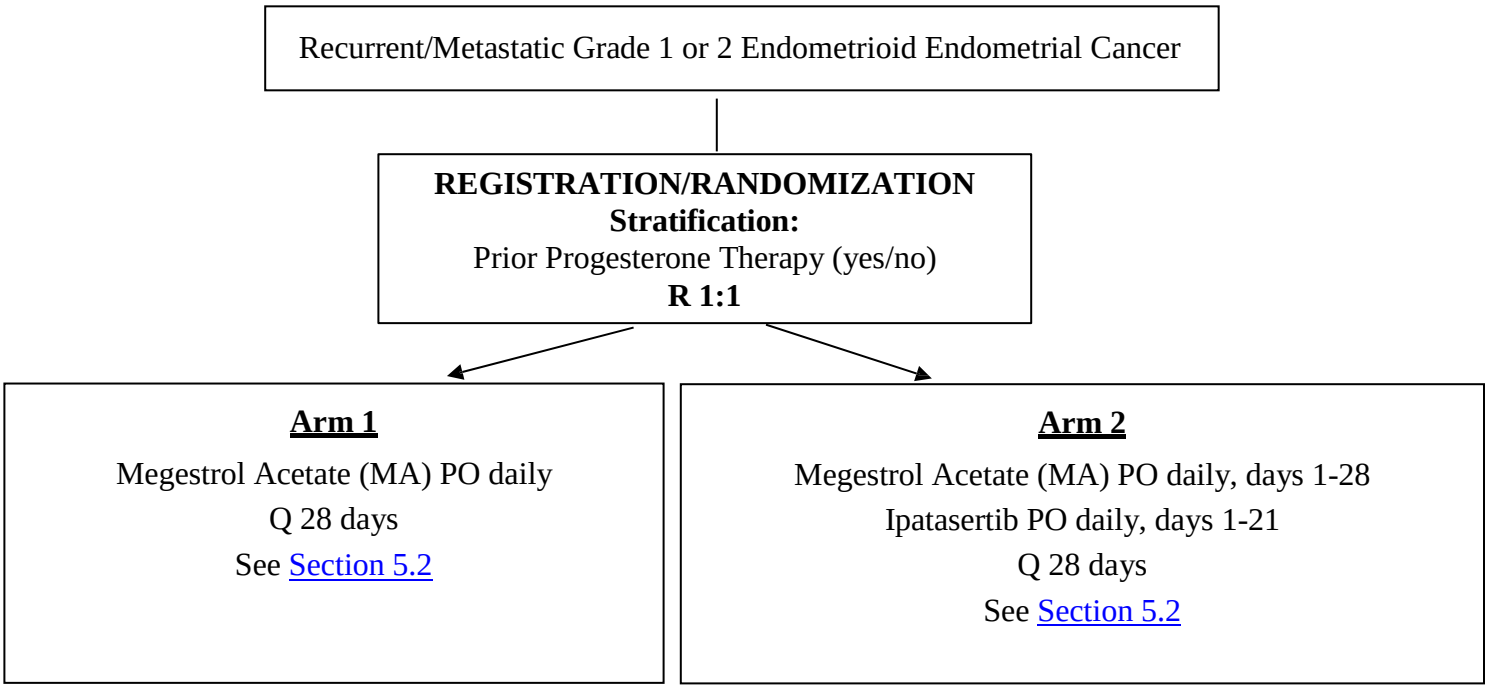
PHASE II COMPONENT—Accruing as of PVD 11-JAN-2024



3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, see protocol cover page.

Submission of tissue is required. Investigators should check with their pathology department regarding release of tissue before approaching patients about participation in the trial (see Section 10 for details).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Patients must have grade 1 or 2 recurrent or metastatic endometrioid endometrial cancer. See Appendix I.

3.1.2 Patients must have measurable disease according to RECIST v1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI. Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

3.1.3 Patients may have received unlimited prior lines of therapy. If patient received prior hormonal therapy (e.g., megestrol acetate, medroxyprogesterone acetate, aromatase inhibitor, tamoxifen, fulvestrant) it must have completed at least 6 months prior to registration.

3.1.4 Age ≥ 18.

3.1.5 ECOG Performance Status of 0, 1 or 2. See Appendix II.

3.1.6 Adequate hematologic function within 14 days prior to registration defined as follows:

- Platelets ≥ 100,000/mcl
- Absolute neutrophil count (ANC) ≥ 1,500/mcl
- Hemoglobin ≥ 9g/dL

3.1.7 Adequate renal function within 14 days prior to registration defined as follows: GFR ≥60 mL/min/1.73m^2 measured using Cockcroft-Gault equation or the estimated glomerular filtration rate from the Modification of Diet in Renal Disease Study.

3.1.8 Adequate hepatic function within 14 days prior to registration defined as follows:

- Total bilirubin ≤ 1.5 x the upper limit of normal (ULN).
    - Patients with known Gilbert syndrome who have bilirubin ≤3 x ULN may be enrolled.
- AST (SGOT)/ALT (SGPT) ≤ 3 x institutional ULN

- Albumin ≥ 3 g/dL

3.1.9 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. See Appendix III.

3.1.10 The effects of ipatasertib on the developing human fetus are unknown. For this reason and because AKT inhibitor agents as well as other therapeutic agents used in this trial are known to be teratogenic, participants of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) during study therapy and for 28 days following the last dose of study therapy. Should a participant become pregnant or suspect pregnancy while participating in this study, they should inform their treating physician immediately.

3.1.11 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.12 For patients with known HIV, HBV, and/or HCV infection:

- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.

- Patients with evidence of chronic hepatitis B virus (HBV) infection must have an undetectable HBV viral load on suppressive therapy, if indicated.

- Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.13 Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.

3.1.14 Patients must be able to swallow and retain oral medications and not have gastrointestinal illnesses that would preclude absorption of megestrol acetate or ipatasertib as judged by the treating physician.

3.1.15 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Patients who have had prior treatment with an AKT inhibitor. (Prior treatment with PI3K or mTOR inhibitors is allowed.)

3.2.2 Patients who have received treatment with strong CYP3A inhibitors or inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to study registration.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference (e.g., https://drug-interactions.medicine.iu.edu/MainTable.aspx. *As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Please see Appendix IX for drug interactions handout.*

3.2.3 Patients with diabetes either requiring insulin therapy or with a baseline fasting glucose >160 mg/dL and/or high HbA1c (>8), suggesting poorly controlled diabetes. Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

3.2.4 Patients who require chronic corticosteroid therapy of >10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressant agents for a chronic disease.

3.2.5 Patients with Grade 2 or greater uncontrolled or untreated hypercholesterolemia (>300 mg/dL) or hypertriglyceridemia (>300 mg/dL).

3.2.6 Patients with a history of known or active inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis).

3.2.7 Patients with a history of or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction).

3.2.8 Patients with known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis, current drug or alcohol abuse, or cirrhosis.

3.2.9 Patients with lung disease: Grade 2 or greater pneumonitis, Grade 2 or greater interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia) within the past 6 months.

3.2.10 No active infection requiring parenteral antibiotics.

3.2.11 Women who are pregnant or unwilling to discontinue nursing.