

GOG 0248: A Randomized Phase II Trial of Temsirolimus or the Combination of Hormonal Therapy Plus Temsirolimus in Women With Advanced, Persistent, or Recurrent Endometrial Carcinoma

Fast Facts

Eligibility Criteria

1. Patients must have histologically confirmed advanced (FIGO stage III or IV), persistent, or recurrent endometrial carcinoma, which is not likely to be curable by surgery or radiotherapy. Histologic documentation of the recurrence is not required.
2. All patients must have measurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.
-Patients must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST (Section 8.1). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented.
3. Prior chemoradiotherapy for a pelvic recurrence is permitted. Prior chemotherapy in the adjuvant setting for Stage I, II, or III disease is permitted.
Note: No prior chemotherapy in the setting of Stage IV disease is permitted unless the patient was without evidence of disease at the completion of chemotherapy and had at least six months of progression-free survival since the completion of chemotherapy.
Regardless of circumstances, no more than one prior chemotherapy regimen (including chemoradiotherapy) is permitted.
4. Patient must be able to take p.o. medications.
5. Performance status must 0 - 2.
6. Patients must have adequate organ and marrow function as defined below:
 - absolute neutrophil count $\geq 1,500/\text{mcl}$
 - platelets $\geq 100,000/\text{mcl}$
 - total bilirubin within normal institutional limits
 - AST(SGOT) and alkaline phosphatase ≤ 2.5 times institutional upper limit of normal, grade 1 per CTCAE v 3.0 (≤ 5 times ULN for subjects with liver metastases)
 - creatinine ≤ 1.5 x normal institutional upper limit of normal, grade 1 per CTCAE v 3.0
 - cholesterol ≤ 350 mg/dL (fasting)
 - triglycerides ≤ 400 mg/dL, (fasting)
 - albumin ≥ 3.0 mg/dL
7. At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: hysterectomy, resection of a lung nodule - minor: a port-a-cath placement).
8. Patients who have met the pre-entry requirements specified in Section 7.0.
9. Patients must have signed an approved informed consent including HIPAA authorization.

Ineligibility Criteria

1. Patients with GOG Performance status of 3 or 4.
2. Temsirolimus is primarily metabolized by CYP3A4. Patients cannot be receiving enzyme-inducing antiepileptic drugs (EIAEDs; e.g., phenytoin, carbamazepine, phenobarbital) nor any other CYP3A4 inducer such as rifampin or St. John's wort, as these may decrease temsirolimus levels. A partial list of agents which interact with cytochrome P450 (CYP3A) is found in Appendix II. All medications in the inducer section of Appendix II may be considered potent. Use of agents that potently inhibit CYP3A (and hence may raise temsirolimus levels), such as ketoconazole, is discouraged, but not specifically prohibited. Temsirolimus can inhibit CYP2D6, and may decrease metabolism (and increase drug levels) of drugs that are substrates for CYP2D6. The appropriateness of use of such agents is left to physician discretion. A list of drugs that may have potential interactions with CYP2D6 is found in Appendix II. All concomitant medications **must** be recorded at baseline.

3. Because of the theoretical risk of immunosuppression from mTOR inhibitors, patients on maintenance corticosteroids are ineligible with the exception of short term use (fewer than 5 days).
4. Patients known to have congestive heart failure. Patients with baseline requirement for oxygen. Patients with serious concomitant illness which, in the opinion of the treating physician, will place patient at unreasonable risk from therapy on this protocol.
5. Patients with a history of unprovoked DVT or PE, unless patient is maintained on anticoagulation for the duration of the trial. While the exact definition of "provoked" is left to the treating physician, a DVT in the setting of pelvic surgery or trauma would be considered "provoked."
6. Women of child-bearing potential must have a negative pregnancy test prior to treatment on study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with temsirolimus, breastfeeding should be discontinued if the mother is treated with temsirolimus. The effects of temsirolimus on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because mTOR inhibitors may have antiangiogenic activity, and other antiangiogenic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception [barrier method of birth control or abstinence; oral contraceptives (also known as "the pill") are not acceptable] prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
7. Patients with a concomitant invasive malignancy or a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the past five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
8. Patients who have received hormonal therapy or biologic therapy as treatment for endometrial carcinoma.
9. Patients who have received chemotherapy directed at metastatic or recurrent endometrial carcinoma, except as noted above.

Pre-study Parameters

1. History and physical including vital signs, height, weight, performance status, list of concomitant meds
2. CBC with differential, CMP, serum cholesterol and triglycerides (fasting), β -HCG (when applicable), INR for pts on warfarin
3. Tumor measurement, chest imaging using CXR, CT or MRI, and CT or MRI abdomen and pelvis

Treatment

Arm 1:

Temsirolimus IV 25 mg weekly

Arm 2:

Megestrol Acetate 80 mg bid for 3 weeks alternating with Tamoxifen 20 mg bid for 3 weeks
Temsirolimus IV 25 mg weekly

Therapy will continue until progression.

Temsirolimus provided.