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SUMMARY OF CHANGES

For Protocol Revision #9 to:

NCI Protocol #: GOG-0248
Local Protocol #: GOG-0248

NCI Version Date: December 22, 2014
Protocol Date: December 22, 2014

#	Section	Page(s)	Change
1.	Title Page	1-2	NCI version date has been updated. Includes Revisions #1-9. Lead Organization has been added. Revised footer has been added.
	ICD		NCI version date has been update on the Informed Consent

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PROTOCOL GOG-0248

A RANDOMIZED PHASE II TRIAL OF TEMSIROLIMUS (NCI-SUPPLIED AGENT,
NSC # 683864, IND # 61010) OR THE COMBINATION OF HORMONAL THERAPY PLUS
TEMSIROLIMUS IN WOMEN WITH ADVANCED, PERSISTENT, OR RECURRENT
ENDOMETRIAL CARCINOMA

NCI Version Date: December 22, 2014

(Includes Revisions # 1-9)

POINTS:

PER CAPITA – 10

MEMBERSHIP – 3

TRANSLATIONAL RESEARCH PER CAPITA – Award based on specimen submissions. Distribution: 1.0 point for a block or 20 unstained slides of formalin-fixed and paraffin-embedded (FFPE) primary (1st choice), metastatic (2nd choice), and/or recurrent tumor (3rd choice), and 0.5 point for a frozen blood specimen.

Lead Organization: NRG/NRG Oncology

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*NCI Version Date: December 22, 2014
(Includes Revisions # 1-9)*

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SCHEMA*

Arm 1: Temsirolimus IV 25 mg (flat dose) weekly

Arm 2: **CLOSED TO ACCRUAL AS OF 12/21/09** Megestrol Acetate (MA) 80 mg bid for three weeks alternating with Tamoxifen (T) 20 mg bid for 3 weeks PLUS Temsirolimus IV 25 mg (flat dose) weekly

*One cycle = 6 weeks

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SUGGESTED PATIENT INFORMATION/INFORMED CONSENT

APPENDIX I – Clinical Staging (FIGO)

APPENDIX II – Medications Interacting with CYP3A4 and CYP2D6

APPENDIX III – CRADA/CTA Language

APPENDIX IV – Specimen Procedures for GOG-0248

APPENDIX V – Patient Pill Calendar

1.0 OBJECTIVES

1.1 Clinical Objectives

- 1.11 The primary objective is to determine the response rate of patients with advanced, persistent, or recurrent endometrial cancer when treated with each of the arms of the trial. The proposed arms are:
- Arm #1 Temozolomide IV weekly
 - Arm #2 Megestrol Acetate/Tamoxifen plus Temozolomide IV weekly
- 1.12 Time to progression and number of patients remaining on study therapy at 24 weeks will also be collected.
- 1.13 A secondary objective is to describe the toxicities of each of the arms of the trial when used for patients with advanced/metastatic endometrial cancer.

1.2 Translational Research Objectives

- 1.21 Explore whether immunohistochemical expression of hormone receptors (estrogen receptor-alpha, estrogen receptor-beta, progesterone receptors-A, progesterone receptor-B and the alternative estrogen receptor, GPR-30) or components of the mTOR signaling pathway (normal and mutant PTEN, total and phosphorylated Akt as well as total and phosphorylated p70S6 kinase) are associated with treatment, outcome or clinical characteristics.
- 1.22 Explore whether single nucleotide polymorphisms (SNPs) in the *FRAP1* and *RAPTOR* genes, mutations in *PIK3CA*, *PTEN* and *paxillin* or copy number abnormalities in *PTEN* and *paxillin* are associated with treatment, outcome or clinical characteristics.

2.0 BACKGROUND AND RATIONALE

2.1 Hormonal Therapy

The Gynecologic Oncology Group (GOG) has a long history of studying hormonal therapy in women with advanced/recurrent endometrial carcinoma. Although such regimens are generally well tolerated, and may produce responses of long duration in selected patients, the overall response rates and progression free survival (PFS) have been disappointing. Among the more active hormonal regimens tested by the GOG has been the sequential use of Megestrol Acetate (MA) at 80 mg bid for 3 weeks alternating with Tamoxifen (T) 20 mg bid for 3 weeks. This regimen produced a response rate of 27% in 56 eligible women with no prior chemotherapy or hormonal therapy.¹ Median PFS was 2.7 months and median overall survival was 14.0 months. This trial will combine this hormonal therapy with a generally well-tolerated biologic agent that has the potential to increase the benefits of hormonal therapy.

2.2 Temsirolimus

Temsirolimus (CCI-779, sirolimus 42-ester with 2,2-bis(hydroxymethyl) propionic-acid) is a specific inhibitor of mTOR (mammalian target of rapamycin).² mTOR is a member of the phosphatidylinositol kinase-related kinases. Its catalytic activity is regulated by the mitogen-activated phosphatidylinositol 3 kinase (PI3K)/Akt pathway. Its downstream targets, p70s6 kinase and 4E-Binding Protein 1, are involved in controlling translation. Another of mTOR's downstream targets, eukaryotic initiation factor 4e, can induce transformation when overexpressed in experimental models.³

Rapamycin prevents cyclin-dependent kinase activation and retinoblastoma protein phosphorylation, which accelerates turnover of cyclin D1 expression, resulting in a decrease cdk 2 complexes inhibiting cell cycle progression. Temsirolimus is a more water soluble ester analog of rapamycin with a broad range of anti-proliferative activity. It has more favorable pharmacokinetic properties and toxicity profile compared with Rapamycin.⁴ Temsirolimus was well tolerated with observed activity in various tumor types in two Phase I trials evaluating a weekly or a daily x 5 schedule.^{5,6} Preliminary clinical evidence of antitumor activity for temsirolimus has been observed in a number of tumor types, including breast cancer,⁷ renal cell cancer⁸, and mantle cell lymphoma.⁹ A randomized Phase III trial reported at ASCO 2006 reported a 3.6 month median survival advantage for patients with poor-risk metastatic renal cell carcinoma treated with temsirolimus 25 mg IV weekly versus those treated with interferon.¹⁰ Temsirolimus has received FDA approval for the treatment of renal cell carcinoma.

Activation of the PI3K/Akt pathway in general predicts for response to mTOR inhibitors *in vitro*. This includes two specific mechanisms of PI3K/Akt pathway activation that have been well described in endometrial carcinomas: PTEN loss,¹¹ which is very common in endometrioid endometrial carcinomas, and *PIK3CA* gene mutations.¹² Interestingly, while in breast cancers *PTEN* mutations and *PIK3CA* mutations appear to be mutually exclusive, they have been reported to co-exist at a high frequency in endometrial carcinoma.^{13,14}

Thirty to 50% of sporadic endometrial carcinomas carry somatically acquired inactivating mutations and/or deletions of the PTEN tumor suppressor gene.^{15,16} A recent study reports PTEN inactivation in up to 83% of endometrioid endometrial adenocarcinomas.¹⁷ Because inactivation of the PTEN gene is accompanied by complete absence of the protein (truncated proteins are extremely rare), immunohistochemistry of paraffin-embedded tissues with anti-PTEN antibody 6h2.1 is a sensitive, inexpensive, and rapid means of classifying tumor tissues by PTEN status.^{17,18} PTEN is a dual specificity phosphatase that negatively regulates the PI3K/Akt signaling pathway. In samples where PTEN expression was depressed, phosphorylated Akt levels were inversely elevated. Further proof that PTEN inactivation is important to the pathogenesis of endometrial carcinoma was garnered using mutant PTEN endometrial carcinoma cell lines. The expression of exogenous PTEN resulted in decreased levels of activated Akt and cell growth inhibition in mutant but not wild-type PTEN-containing endometrial carcinoma cell lines.¹⁹ Thus, endometrial carcinoma represents a rational target for temsirolimus (CCI-779) therapy.

The single agent activity of temsirolimus in endometrial carcinoma has been explored in two small, uncontrolled Phase II trials.³⁹ In the first, 33 chemotherapy-naïve patients with recurrent or metastatic endometrial cancer were treated. There were 7 PRs in 28 evaluable patients. Response rate was 25.0% (95% CI: 10.7-44.9%) and 16 patients had SD. Median duration of response was 5.6 months (95% CI 3.7- 18.7 months) and of stable disease was 8.4 months (95% CI 3.1- 10.5 months). Median PFS was 8 months.²⁰

In the second, 27 chemotherapy-treated women with recurrent or metastatic endometrial cancer were treated at a dose of 25 mg i.v. weekly. Thirteen had received prior radiation and 10 had received prior hormonal therapy. Twenty five patients had adenocarcinoma (8 serous carcinoma) and 2 had adeno-squamous carcinoma; 20 patients had grade 2/3 disease, 5 unknown grade, and 2 grade 1. Two patients have had a confirmed partial response (PR) (7.4%; 95% CI 0.9-24.3%) and 12 patients had stable disease (SD) (44%), median duration 3.5 months (2.4-7.2m) and 10 patients had progressive disease (41.7%). Five of the 8 patients with serous disease had SD and of the 17 with Grade 3 disease, 1 had a PR and 7 SD. Median PFS was 3.25 months (95% CI 2-3.88 months), 6 month PFS was 8% (95% CI 1-23%). There was no correlation between PTEN and response.

2.3 Rationale for the Combination of Hormones and Temsirolimus

In addition to predicting for sensitivity to mTOR inhibitors, PTEN loss and *PI3K* activating mutations can confer *in vitro* resistance to a variety of therapies, including chemotherapy, trastuzumab, growth factor receptor TKIs, and hormonal therapy.^{21,22} In many models, this resistance can be overcome by use of an mTOR inhibitor such as sirolimus or temsirolimus.^{23,24} Some of the most elegant work has been by Wendel et al.^{25,26} They demonstrated that a reduced dosage of PTEN (loss of even one PTEN allele) which was only modestly tumorigenic in their mouse lymphoma model, resulted in lymphomas that were relatively resistant to chemotherapy and only modestly sensitive to sirolimus. However the combination produced a dramatic improvement in outcomes, outperforming doxorubicin alone in control tumors (which did not have any improvement in outcomes with the addition of rapamycin to chemotherapy).

There is cross-talk between hormone receptor signalling pathways and the PI3K/Akt pathway at multiple levels.²⁷⁻²⁹ PTEN loss activates ER-alpha. Activation of the PI3K/AKT pathway is associated with resistance to tamoxifen or estrogen deprivation in breast cancer models.²⁸⁻³⁰ This resistance can be overcome by temsirolimus *in vitro*.³¹⁻³² A randomized Phase III trial of oral temsirolimus plus letrozole versus letrozole alone in women with advanced breast cancer was prematurely stopped for lack of benefit; this may be related to variability of absorption of the oral compound.

2.4 Translational Research

The G₁ to S cell cycle checkpoint plays a critical role in controlling endometrial cancer cell proliferation.³³ Progesterone, the principal hormonal inhibitor of endometrial cell growth, inhibits cyclin D1 and is a strong inducer of the tumor suppressors PTEN and p53, and the cyclin dependent kinase inhibitors p21 and p27. When expressed at high levels, p53, p21, and p27 prevent cell cycle progression at this checkpoint, and PTEN inhibits activation of Akt and mammalian target of rapamycin (mTOR). Unfortunately, the growth-limiting effects of progesterone are often lost in endometrial cancers due to down-regulation of estrogen and progesterone receptors (ER and PR).

The GOG attempted to use sequential hormonal treatment to maintain ER and PR expression in a Phase II trial of women with persistent or recurrent endometrial carcinoma (GOG-0119). The rationale for sequential hormone treatment in this trial was based on the thought that tamoxifen, an estrogen surrogate in the uterus, would upregulate PR expression and allow the medroxyprogesterone acetate to inhibit G₁ to S transition (block cell proliferation) and induce cell differentiation by binding to and activating PR.³⁴ Treatment with the medroxyprogesterone acetate would then be expected to stimulate a negative feedback loop and down regulate PR expression. Discontinuation of the medroxyprogesterone acetate and re-exposure to tamoxifen would then counteract the negative feedback loop and provide signals to upregulate PR expression and responsiveness. The response rate to sequential hormonal therapy in GOG 119 was an impressive 33% with an additional 35% of the patients having stable disease.

Immunohistochemistry studies, performed in tumor tissue from women on GOG-0119, demonstrated that tumor response to sequential hormonal therapy in GOG-0119 was linked to the expression of ER-alpha.³⁵ Baseline expression of ER-alpha in the recurrent tumor specimens was correlated with the immunohistochemical expression of PR, but tumor response was not associated with PR.³⁵ Unfortunately, regardless of the robust initial response, all patients eventually failed treatment. We hypothesize that treatment failure to sequential hormonal therapy in endometrial cancer is related to the prevalent constitutive activation of PI3K, Akt and mTOR in endometrial carcinoma, which eventually overcomes the growth-limiting effects of progestin.

The PI3K/Akt pathway has been shown to regulate the catalytic activity of mTOR, a PIK-related kinase, and to activate other downstream targets including p70S6 kinase which controls translation. PTEN is a dual specificity phosphatase that negatively regulates the PI3K/Akt signaling pathway. Endometrial cancers with low or no PTEN expression often express high levels of phosphorylated Akt. Constitutive activation of the PI3K/Akt pathway results from inactivating mutations and/or deletions of the *PTEN* tumor suppressor gene (*PTEN* loss) and mutations in the *PIK3CA* gene.^{11, 12, 15-17}

Endometrial cancers often exhibit *PTEN* loss and mutations in *PIK3CA*.¹⁵⁻¹⁷ The finding that activation of the PI3K/Akt pathway is associated with response to mTOR inhibitors *in vitro* coupled with the data indicating that endometrial cancers often exhibit *PTEN* loss and mutations in *PIK3CA*¹⁵⁻¹⁷ provide strong rationale for evaluating mTOR inhibitors in advanced or recurrent endometrial cancer.

To test these hypotheses in a Cooperative Group setting, the expression of hormone receptors (ER-alpha, ER-beta, PR-A, PR-B and the alternative estrogen receptor, GPR-30) and components of the mTOR pathway (normal and mutant *PTEN*, total and phosphorylated Akt as well as phosphorylated p70S6 kinase) will be examined by immunohistochemistry in archival formalin-fixed and paraffin-embedded (FFPE) tumor tissue from women in this cohort. The associations between the immunohistochemical expression of these biomarkers and between these biomarkers and treatment, outcome or clinical characteristics will be explored.

FRAP1 and *RAPTOR* are the genes that encode mTOR and the regulatory associated protein of mTOR (RAPTOR), respectively. Natural variations, such as single nucleotide polymorphisms (SNPs), have been described for both of these genes. The mTOR and RAPTOR proteins form a complex that is inhibited by mTOR inhibitors and, therefore, are strong candidates for variation in response to temsirolimus treatment. Genotyping of normal DNA using the Sequenom iPLEX Gold technology will capture the genetic variations in up to 167 tag SNPs and 11 tag SNPs in the *RAPTOR* and *FRAP1* genes, respectively. SNPs in other genes in the mTOR pathway may also be genotyped if initial results are promising. Genotypes at the tag SNPs will be compared with treatment, outcome or clinical characteristics in the patients in this clinical trial. Normal DNA will be extracted from a buffy coat prepared from whole blood drawn from women in this cohort.

Mutation analysis and copy number abnormalities will also be determined in genes involved in mTOR signaling (*PIK3CA*, *PTEN* and *paxillin*). As indicated above, loss of *PTEN* (due to an inactivating mutation or deletion) and mutation of *PIK3CA* are common mechanisms for activation of the PI3K/Akt pathway in endometrial cancers. *Paxillin* is another gene involved in mTOR signaling that has been implicated in the regulation of cell growth and invasion. In lung cancer tissues, *paxillin* was highly expressed compared with normal lung, amplified (12.1%, 8 of 66) or mutated (somatic mutation rate of 9.4%, 18 of 191); *paxillin* mutations (90.5%, 19 of 21) were clustered between the functional LD motifs 1 and 2 and the LIM domains.³⁸ We hypothesize that similar defects exist in endometrial cancer and contribute to the dysregulation in cell growth and invasion observed in this disease. In this Phase II trial, DNA will be extracted from archival FFPE tumor tissue to examine mutations and/or copy number abnormalities in genes involved in mTOR signaling. The associations between mutations in *PIK3CA*, *PTEN* and *paxillin* or copy number abnormalities in *PTEN* and *paxillin* and treatment, outcome or clinical characteristics will be examined in this cohort.

2.5 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire endometrial cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 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.

3.12 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.

3.13 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. **(06/22/09)**

3.14 Patient must be able to take p.o. medications.

3.15 Performance status must be 0-2.

3.16 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, v 3.0 (≤ 5 times ULN for subjects with liver metastases)
- creatinine ≤ 1.5 x normal institutional upper limit of normal,
- cholesterol ≤ 350 mg/dL (fasting)
- triglycerides ≤ 400 mg/dL (fasting)
- albumin ≥ 3.0 mg/dL

- 3.17 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).
- 3.18 Patients who have met the pre-entry requirements specified in Section 7.0.
- 3.19 Patients must have signed an approved informed consent including HIPAA authorization.

3.2 Ineligible Patients

- 3.21 Patients with GOG Performance status of 3 or 4.
- 3.22 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 selected list of drugs that may have potential interactions with CYP2D6 is found in Appendix II. The following website can also be consulted:
www.medicine.iupui.edu/flockhart/table.htm (11/24/08)

All concomitant medications **must** be recorded at baseline.

- 3.23 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).
- 3.24 Patients known to have congestive heart failure. Patients with baseline requirement for oxygen. Patients with serious concomitant illness that, in the opinion of the treating physician, will place patient at unreasonable risk from therapy on this protocol.
- 3.25 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.”
- 3.26 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.

- 3.27 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.
- 3.28 Patients who have received hormonal therapy or biologic therapy as treatment for endometrial carcinoma.
- 3.29 Patients who have received chemotherapy directed at metastatic or recurrent endometrial carcinoma, except as noted in Section 3.13. **(06/22/09)**

4.0 STUDY MODALITIES

4.1 Megestrol Acetate (Megace®)

4.11 Formulation: Tablets of 40 mg megestrol acetate

4.12 Storage: Room temperature protected from heat and light.

4.13 Adverse Effects: Weight gain, thromboembolic phenomena, nausea and vomiting, edema, break through bleeding, dyspnea, tumor flare, hyperglycemia, carpal tunnel syndrome, and rash.

4.14 Supplier: Commercially available. See package insert for further information.

4.15 Administration: See section 5.2

4.2 Tamoxifen Citrate (Nolvadex®) (NSC #180973)

4.21 Formulation: Tablets of 10 and 20 mg of tamoxifen.

4.22 Storage: Room temperature protected from heat and light.

4.23 Adverse Effects: Transient thrombocytopenia and leukopenia, menopause-like reactions (hot flushes, nausea), skin rashes/changes, pruritus vulvae, dizziness, headaches, depression, lassitude, muscle pain, fluid retention, anorexia, menstrual irregularities, vaginal bleeding, vaginal discharge, food distaste and thromboembolic events. Of note also is a report of a few cases of severe retinopathy associated with decreased visual acuity in patients on high doses (>200 mg/day) for prolonged periods over a year. Dose modifications or cessation of drug because of adverse effects are seldom necessary. See package insert for complete list of adverse effects.

4.24 Supplier: Commercially available. See package insert for further information.

4.25 Administration: See Section 5.2.

4.3 Temsirolimus [COMMERCIAL Torisel (NSC # 683864, IND #61010) will be distributed by the NCI for this study]

4.31 Formulation: Chemical Name: Sirolimus 42-ester with 2,2-bis (hydroxymethyl)-propionic acid

Other Names: CCI-779, Torisel®, rapamycin analog, WAY-130779

Classification: Cell cycle inhibitor

Molecular Formula: C₅₆H₈₇NO₁₆ M.W.: 1030.30 daltons

Mode of Action: Temsirolimus (an ester of the immunosuppressive compound sirolimus [rapamycin, Rapamune[®]]) blocks cell cycle progression from the G1 to the S phase by binding to the intracellular cytoplasmic protein, FK506 binding protein (FKBP)12. This complex inhibits activity of the enzyme mTOR (mammalian target of rapamycin), inhibiting translation of several key proteins that regulate progression through the G1 phase in response to growth factors. Sirolimus, temsirolimus' major metabolite, also binds to FKBP12.

4.32 How Supplied: TORISEL (temsirolimus) is supplied by the NCI as a commercially labeled kit consisting of the following:

- TORISEL (temsirolimus) injection (25 mg/ml). The TORISEL vial includes an overfill of 0.2 mL. Inert ingredients in the drug vial include dehydrated alcohol, d,l-alpha-tocopherol, propylene glycol, and anhydrous citric acid.
- DILUENT for TORISEL. The DILUENT vial includes a deliverable volume of 1.8 mL. The diluent vial contains polysorbate 80 NF, polyethylene glycol 400 NF, and absolute alcohol USP.

TORISEL will be supplied by the Division of Cancer Treatment and Diagnosis, (DCTD), NCI. Please do not obtain commercially available TORISEL through any other mechanism. (Please see Section 4.311)

4.33 Preparation: These mixing instructions apply to commercial TORISEL only; commercial drug will be supplied by the NCI for this study.

Protect from excessive room light and sunlight during preparation.

Follow this two step dilution process (TORISEL should only be diluted with the supplied diluent):

Step 1

Inject 1.8 mL of DILUENT for TORISEL into the vial of TORISEL injection (25 mg/mL). Due to the intentional 0.2 mL overfill in the TORISEL injection vial, the resulting drug concentration will be 10 mg/mL. A total volume of 3 mL will be obtained. Mix well by gentle inversion of the vial. DO NOT SHAKE. Allow sufficient time for air bubbles to subside.

Step 2

Withdraw the required amount of TORISEL from the 10 mg/mL drug solution/diluent mixture prepared in Step 1. Further dilute with 0.9% sodium chloride injection immediately in glass or polyolefin containers to a final concentration between 0.04 mg/mL and 1 mg/mL.

TORISEL will be supplied by the Division of Cancer Treatment and Diagnosis, (DCTD), NCI. Please do not obtain commercially available TORISEL through any other mechanism. (Please see Section 4.311)

- 4.34 Storage: Refrigerate intact TORISEL kit at 2°-8°C and protect from light.
- 4.35 Stability: The 10 mg/mL drug solution/diluent mixture is stable for 24 hours at room temperature.

Administer within 6 hours of the final dilution in 0.9% NaCl. Store at room temperature (20°-25°C) and protect from light.

- 4.36 Route of Administration: Intravenous with an appropriate in-line filter (i.e. 0.2 to 5 micron) for all temsirolimus doses equal to or greater than 10 mg. Do not use an inline filter for temsirolimus doses less than 10 mg. Protect from light during administration.
- 4.37 Patient Care Implications: For hypersensitivity prophylaxis, give diphenhydramine 25-50 mg I.V. (or comparable antihistamine) approximately 30 minutes before starting temsirolimus infusion. Infuse over 30 minutes.

If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. The manufacturer recommends famotidine 20 mg IV, rather than cimetidine, because it lacks reported drug interactions. If famotidine is unavailable, administer ranitidine 50 mg IV. Re-attempt infusion at a slower rate, possibly over one hour. (Please see Section 5.3 for temsirolimus administration and management of hypersensitivity reactions)

- 4.38 Incompatibilities: Avoid contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)phthalate (DEHP) to prevent DEHP leaching. Store diluted temsirolimus solutions in bottles (glass) or plastic bags (polyolefin or polypropylene).

Temsirolimus is compatible with most infusion sets that are acceptable with paclitaxel. Infusion sets which have been qualified for use with temsirolimus include the following:

- Baxter vented paclitaxel set
- Baxter unvented paclitaxel set
- Abbott #11947 tubing set
- Alaris #72953 tubing set

Other non-PVC tubings can be used with the following in-line filters:

- IV 6200 Disposable I.V. Filter 0.2 micron by EPS®, Inc
- IV 6120 Disposable I.V. Filter 1.2 micron by EPS®, Inc
- LV 5000 Large Volume 5 micron Conical Filter by B.Braun
- Baxter Paclitaxel IV 0.2 micron filter set (2C7555)
- Codan 5 micron monofilter
- Alaris extension filter set #20350E

Other polyethersulfone filters may be used.

4.39 Potential Drug Interactions: Temsirolimus is a CYP3A4 substrate. Avoid concomitant treatment of temsirolimus with potent CYP3A4 inhibitors and agents that have CYP3A4 induction potential.

The combination of temsirolimus and sunitinib resulted in dose limiting toxicity at low doses of both agents. Avoid concomitant sunitinib during temsirolimus treatment.

Temsirolimus and warfarin may interact to increase INR. Monitor warfarin patient's PT/INR after starting and stopping temsirolimus.

4.310 Reported Adverse Events and Potential Risks: (05/24/10)

**Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Temsirolimus (CCI-779, NSC 683864)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 1288 patients.* Below is the CAEPR for temsirolimus (CCI-779).

Version 2.2, January 22, 2010¹

Adverse Events with Possible Relationship to Temsirolimus (CCI-779) (CTCAE 4.0 Term) [n= 1288]			EXPECTED AEs FOR ADEERS REPORTING
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Agent Specific Adverse Event List (ASAEL)
			<i>Expected</i>
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			<i>Anemia</i>
	Febrile neutropenia		<i>Febrile neutropenia</i>
ENDOCRINE DISORDERS			
	Endocrine disorders - Other (decreased testosterone)		<i>Endocrine disorders - Other (decreased testosterone)</i>
GASTROINTESTINAL DISORDERS			
	Abdominal distension		<i>Abdominal distension</i>
	Abdominal pain		<i>Abdominal pain</i>
	Constipation		<i>Constipation</i>
Diarrhea			<i>Diarrhea</i>
Gastrointestinal disorders – Other (Mucositis/stomatitis – Select) ²			<i>Gastrointestinal disorders – Other (Mucositis/stomatitis – Select)²</i>
		Gastrointestinal disorders – Other (Perforation, GI – Select) ³	<i>Gastrointestinal disorders – Other (Perforation, GI – Select)³</i>
Nausea			<i>Nausea</i>
	Vomiting		<i>Vomiting</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		<i>Chills</i>

	Edema face		<i>Edema face</i>
	Edema limbs		<i>Edema limbs</i>
Fatigue			<i>Fatigue</i>
	Fever		<i>Fever</i>
	Flu like symptoms		<i>Flu like symptoms</i>
	Non-cardiac chest pain		<i>Non-cardiac chest pain</i>
IMMUNE SYSTEM DISORDERS			
	Allergic reaction ⁴		<i>Allergic reaction⁴</i>
INFECTIONS AND INFESTATIONS⁵			
	Infections and infestations – Other (Infection – Select)		<i>Infections and infestations – Other (Infection – Select)</i>
	Infections and infestations - Other (Opportunistic infection associated with \geq Grade 2 Lymphopenia)		<i>Infections and infestations - Other (Opportunistic infection associated with \geqGrade 2 Lymphopenia)</i>
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Wound dehiscence ⁶		<i>Wound dehiscence⁶</i>
INVESTIGATIONS			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased</i>
	Alkaline phosphatase increased		<i>Alkaline phosphatase increased</i>
	Aspartate aminotransferase increased		<i>Aspartate aminotransferase increased</i>
Cholesterol high ⁷			<i>Cholesterol high⁷</i>
	Creatinine increased		<i>Creatinine increased</i>
	Fibrinogen decreased		<i>Fibrinogen decreased</i>
	GGT increased		<i>GGT increased</i>
	Lymphocyte count decreased		<i>Lymphocyte count decreased</i>
	Neutrophil count decreased ⁸		<i>Neutrophil count decreased⁸</i>
Platelet count decreased ⁸			<i>Platelet count decreased⁸</i>
	Weight loss		<i>Weight loss</i>
	White blood cell decreased		<i>White blood cell decreased</i>
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		<i>Acidosis</i>
Anorexia			<i>Anorexia</i>
	Glucose intolerance ⁹		<i>Glucose intolerance⁹</i>
	Hyperglycemia ⁹		<i>Hyperglycemia⁹</i>
	Hypertriglyceridemia ⁷		<i>Hypertriglyceridemia⁷</i>
	Hypocalcemia		<i>Hypocalcemia</i>
	Hypokalemia		<i>Hypokalemia</i>
	Hypophosphatemia		<i>Hypophosphatemia</i>
	Metabolism and nutrition disorders- Other (hyperlipidemia) ⁷		<i>Metabolism and nutrition disorders- Other (hyperlipidemia)⁷</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia</i>
	Back pain		<i>Back pain</i>
	Myalgia		<i>Myalgia</i>
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		<i>Depressed level of consciousness</i>
	Dysgeusia		<i>Dysgeusia</i>
	Headache		<i>Headache</i>
PSYCHIATRIC DISORDERS			
	Depression		<i>Depression</i>
	Insomnia		<i>Insomnia</i>
	Libido decreased		<i>Libido decreased</i>
RENAL AND URINARY DISORDERS			

		Acute kidney injury ¹⁰	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
	Erectile dysfunction		<i>Erectile dysfunction</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		
	Cough		<i>Cough</i>
	Dyspnea		<i>Dyspnea</i>
	Epistaxis		<i>Epistaxis</i>
	Pleural effusion		<i>Pleural effusion</i>
	Pneumonitis ¹¹		<i>Pneumonitis¹¹</i>
	Sinus disorder		<i>Sinus disorder</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		<i>Dry skin</i>
	Nail loss		<i>Nail loss</i>
	Pruritus		<i>Pruritus</i>
	Rash acneiform		<i>Rash acneiform</i>
Rash maculo-papular			<i>Rash maculo-papular</i>
	Urticaria		<i>Urticaria</i>
VASCULAR DISORDERS			
	Hypertension		<i>Hypertension</i>
	Hypotension		<i>Hypotension</i>
		Thromboembolic event	<i>Thromboembolic event</i>

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Mucositis/stomatitis: Gingivitis, mucositis/stomatitis, ulcers in mouth and throat, pharyngitis, and dysphagia have been reported in subjects receiving temsirolimus.

³Perforation, GI - Select: GI perforation (including fatal outcome) has been observed in subjects who received temsirolimus.

⁴Hypersensitivity /infusion reactions (including some life threatening and rare fatal reactions), including and not limited to flushing, chest pain, dyspnea, hypotension, apnea, loss of consciousness, hypersensitivity, and anaphylaxis, have been associated with the administration of temsirolimus. These reactions can occur very early in the first infusion, but may also occur with subsequent infusions. Patients should be monitored early during infusion and appropriate supportive care should be available. Temsirolimus infusion should be interrupted in all patients with severe infusion reactions and appropriate medical care administered. A risk-benefit assessment should be done prior to the continuation of temsirolimus therapy in patients with severe life-threatening reactions.

⁵Infections: Bacterial and viral infections including opportunistic infections have been reported in subjects. Infections may originate in a variety of organ systems/body regions and may be associated with normal or grade 3-4 neutropenia. Bacterial and viral infections have included cellulitis, herpes zoster, herpes simplex, bronchitis, abscess, pharyngitis, urinary tract infection (including dysuria hematuria, cystitis, and urinary frequency), rhinitis folliculitis, pneumonia, and upper respiratory tract infection.

⁶Wound Dehiscence: The use of temsirolimus has been associated with abnormal wound healing. Therefore, caution should be exercised with the use of temsirolimus in the perisurgical period.

⁷Cholesterol High: The use of temsirolimus in subjects has been associated with increases in serum levels of triglycerides and cholesterol. This may require initiation of or increase in the dose of lipid-lowering agents.

⁸Thrombocytopenia and Neutropenia: Grades 3 and 4 thrombocytopenia and/or neutropenia have been observed at higher frequency in subjects with mantle cell lymphoma (MCL).

⁹Hyperglycemia/Glucose Intolerance: The use of temsirolimus in subjects was associated with increases in serum glucose level. This may result in the need for an increase in the dose of, or initiation of, insulin and/or oral hypoglycemic agent therapy.

¹⁰Acute Kidney Injury: Renal failure (including fatal outcome) has been observed in subjects receiving temsirolimus for advanced RCC and/or with pre-existing renal insufficiency.

¹¹Interstitial Lung Disease: There have been cases of nonspecific interstitial pneumonitis, including rare fatal reports. Some subjects were asymptomatic with pneumonitis detected on computed tomography scan or chest radiograph. Others presented with symptoms such as dyspnea, cough, and fever. Some subjects required discontinuation of temsirolimus or treatment with corticosteroids and/or antibiotics, while some subjects continued treatment without additional intervention.

Also reported on temsirolimus (CCI-779) trials but with the relationship to temsirolimus (CCI-779) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis

CARDIAC DISORDERS - Left ventricular systolic dysfunction; Pericardial effusion; Right ventricular dysfunction; Sinus tachycardia

EYE DISORDERS - Blurred vision; Conjunctivitis

GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Enterocolitis; Esophagitis; Gastritis; Gastrointestinal disorders – Other (Hemorrhage, GI – Select); Oral pain; Pancreatitis; Periodontal disease; Rectal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance

HEPATOBIILIARY DISORDERS - Hepatic failure

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture

INVESTIGATIONS – Activated partial thromboplastin time prolonged; Blood bilirubin increased; INR increased (potential interaction with Coumadin); Investigations - Other (lactic dehydrogenase increased)

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (bursitis)

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Intracranial hemorrhage; Ischemia cerebrovascular; Peripheral sensory neuropathy; Seizure; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Personality change; Psychosis

RENAL AND URINARY DISORDERS – Cystitis noninfective⁵; Proteinuria; Renal and urinary disorders – Other (Hemorrhage, GU – Select); Urinary frequency; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Pleuritic pain; Pulmonary hypertension; Respiratory failure

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis

Note: Intracerebral Bleeding: Subjects with central nervous system (CNS) tumors (primary CNS tumors or metastases) and/or receiving anticoagulation therapy may be at an increased risk of intracerebral bleeding (including fatal outcomes) while receiving therapy with temsirolimus.

Note: Temsirolimus (CCI-779) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Note: Temsirolimus (CCI-779) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent. During the first phase of the combination arm of this trial a clot rate of at least 7/22 was observed in the combination arm. (05/24/10)

4.311 Availability:

Temsirolimus is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. In this trial a commercial supply of Temsirolimus is provided, but the agent is used in an investigational way.

Temsirolimus is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Wyeth Pharmaceuticals, Inc. and the DCTD, NCI. (Please see Appendix III).

4.312 Drug Ordering and Accountability: NCI-supplied agents may be requested by the Principal Investigator or their authorized designee at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is being treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD, through an annual submission of FDA Form 1572, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form. If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by completing a Clinical Drug Request (CDR [NIH-986]) (print from the CTEP website at <http://ctep.cancer.gov/requisition/>) and mailing it to the Pharmaceutical Management Branch, DCTD, NCI, EPN, Room 7149, Bethesda, MD 20892 or faxing it to (301) 480-4612. Beginning 11/10/03, all CDR's for PMB-distributed agents sent to the PMB must be signed by the investigator in whose name the agent is ordered OR by the shipping designee OR by an ordering designee whom the investigator has listed on their most recent IDF on file with the PMB.

If the investigator has not designated the individual signing the CDR as a shipping or ordering designee, or if the shipping or ordering designees at a clinical site change, the first two pages of the IDF should be updated to reflect the current designees, the IDF should be signed and dated by the investigator and returned to the PMB by fax at (301) 402-4870. For questions (on the first two pages of the investigator's current IDF) call the PMB at (301) 496-5725 Monday through Friday from 8:30 am to 4:30 pm Eastern Time.

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from the PMB using the NCI Drug Accountability Record Form (DARF). See the CTEP web site for Policy and Guidelines for Accountability and Storage of Investigational Drugs at <http://ctep.cancer.gov/requisition/>

Requests for Investigator's Brochures (IB) should be e-mailed to ibcoordinator@mail.nih.gov or you may call the IB coordinator at 301-496-5725.

4.4 Pathology Requirements

- 4.41 Eligible disease characteristics: Patients must have histologically confirmed, advanced (FIGO stage III or IV), persistent, or recurrent endometrial carcinoma. All histologic cell types and grades of endometrial carcinoma of the uterine corpus are allowed.
- 4.42 Ineligible disease characteristics: Patients with a sarcoma, carcinosarcoma (MMMT), or leiomyosarcoma of the uterine corpus are not eligible. Patients with early stage (FIGO stage I or II) endometrial carcinoma are also not eligible.
- 4.43 Requirements: Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type and grade will be required. At least one representative H&E stained slide documenting the most advanced stage of disease will be required if the most advanced stage is documented by histology or cytology. If the patient is enrolled with recurrent disease, at least one representative H&E stained slide demonstrating recurrent disease will be required if recurrent disease is documented by histology. See Sections 7.2 and 10.2 for additional instructions for submitting the stained pathology slides to the GOG Statistical and Data Center in Buffalo, NY.
- 4.44 See Section 7.3 and Appendix IV for information and instructions regarding the specimen requirements for Translational Research. **(05/24/10)**

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

All initial and continuing reviews must be submitted to the CTSU Regulatory Office. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsuo.org/public/rss2_page.aspx). IRB submissions can be faxed or mailed to:

**CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
1-888-823-5923
FAX 215-569-0206 (05/24/10)**

5.1 Patient Entry and Registration

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

- 5.11 Patient must have signed an approved informed consent and authorization permitting release of personal health information. Current FDA, NCI and institutional regulations concerning informed consent will be followed.
- 5.12 All eligibility requirements indicated in Section 3.0 must be satisfied.
- 5.13 The Fast Fact Sheet data must be gathered.
- 5.14 The institution must register the patient using the web-based registration application or by phone if necessary (800-523-2917). Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page.
- 5.15 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan

Stage I Accrual (Patients enrolled prior to 12/21/09): (05/24/10)

Treatment randomization will be stratified into two levels based on previous treatment for endometrial cancer:

- Level 1. Patients who have received adjuvant chemotherapy or chemoradiation either at time of initial diagnosis or for a pelvic recurrence
- Level 2. Patients who have never received adjuvant chemotherapy or chemoradiation for pelvic recurrence. **(05/24/10)**

Prior radiotherapy in the absence of chemotherapy is not considered in this stratification.

Study therapy will be randomized between:

Arm 1: Temozolomide IV 25 mg (flat dose) weekly
and

Arm 2: Megestrol Acetate (MA) 80 mg bid for 3 weeks alternating with Tamoxifen (T) 20 mg bid for 3 weeks PLUS Temozolomide IV 25 mg (flat dose) weekly.

Therapy is to be continued until tumor progression or undue toxicity. For purposes of evaluation, a cycle will be considered six weeks. Re-evaluation for disease response and status will be every six weeks for the first 24 weeks of therapy, then every 12 weeks for patients who are receiving protocol therapy longer than 24 weeks.

Stage II accrual (Patients enrolled after 12/21/09): (05/24/10)

As of December 18, 2009, there have been seven venous-thrombosis-related events reported among the 22 women assigned to the megestrol acetate/tamoxifen/temozolomide arm of this study and none among the 21 women on the temozolomide alone arm. The combination arm was therefore permanently closed to new accrual. The single agent temozolomide arm has met the criteria to proceed with the second stage and will be reopened to accrual.

Patients will be stratified into two levels based on previous treatment for endometrial cancer:

Level 1. Patients who have received adjuvant chemotherapy or chemoradiation either at time of initial diagnosis or for a pelvic recurrence

Level 2. Patients who have never received adjuvant chemotherapy or chemoradiation for pelvic recurrence. **(05/24/10)**

Prior radiotherapy in the absence of chemotherapy is not considered in this stratification.

All patients enrolled after 12/21/2009 will receive

Arm 1: Temozolomide IV 25 mg (flat dose) weekly

Therapy is to be continued until tumor progression or undue toxicity. For purposes of evaluation, a cycle will be considered six weeks. Re-evaluation for disease response and status will be every six weeks for the first 24 weeks of therapy, then every 12 weeks for patients who are receiving protocol therapy longer than 24 weeks.

5.3 Temozolomide Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 4.3.10. Appropriate dose modifications for temozolomide are described in Section 6.0. Patients receiving temozolomide on this protocol may not receive any other investigational agents either for the treatment of the patient's cancer or for any other indication. Patients on this protocol may not be treated with any other anti-cancer therapy.

Patients will receive temsirolimus at their assigned dose administered over 30 minutes IV weekly continuously. It may be given up to 2 days early or late due to holiday or scheduling reasons.

Temsirolimus is incompatible with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl) pthalate (DEHP). Please see Section 4.38 (Incompatibilities) for a list of compatible tubings and filings.

Patients should be premedicated with diphenhydramine 25 – 50 mg IV or PO (or a similar antihistamine) approximately 30 minutes before the start of the temsirolimus infusion. If the subject begins to develop a hypersensitivity reaction despite pretreatment with diphenhydramine, the infusion should be stopped for at least 30 – 60 minutes, depending upon the severity of the reaction. The infusion may be resumed by administering a histamine H₂-receptor antagonist approximately 30 minutes before restarting the temsirolimus infusion. Famotidine 20 mg IV or ranitidine 50 mg IV are recommended rather than cimetidine because of the lack of likely metabolic/pharmacologic interactions with the former drugs. The rate of the temsirolimus infusion may also be slowed from 30 minutes to over an hour. All subjects should be monitored while receiving the temsirolimus infusion and emergency medical equipment and health care personnel must be readily available to respond to hypersensitivity reactions or other medical emergencies.

5.4 Megestrol Acetate and Tamoxifen Compliance

The use of a patient pill calendar (See Appendix V) during study therapy will be utilized by the patient and the treating clinic to help promote and monitor compliance with Megestrol Acetate and Tamoxifen.

5.5 Concomitant Medications

In vitro studies with temsirolimus in human liver microsomes indicate that CYP3A4 may be the primary enzyme responsible for the agent's metabolism, suggesting that compounds known to modulate CYP3A4 activity may therefore affect the metabolism of temsirolimus. Inhibitors of CYP3A4 may decrease the metabolism and increase temsirolimus levels, while inducers of CYP3A4 may increase the metabolism and decrease temsirolimus levels. Temsirolimus or its metabolites may also interact with the CYP450 enzyme system by inhibiting CYP2D6. While caution is indicated in many circumstances, the only medications prohibited on this protocol are the potent CYP3A4 inducers. A selected list is included in 3.22 and Appendix II. The following website can also be consulted: www.medicine.iupui.edu/flockhart/table.htm. (11/24/08)

Therapeutic anticoagulation: Patients on warfarin should have PT/INR monitored closely during warfarin therapy (*e.g.*, at baseline, weekly for the first three weeks of the first cycle, weekly for the first three weeks of any cycle following a dose reduction, and for a minimum of two weeks after stopping temsirolimus.). Temsirolimus therapy should be held if the coagulation parameters are meaningfully higher than the intended therapeutic range as defined by the treating physician.

5.6 Supportive Care Guidelines

Nausea/vomiting: Nausea induced by study agents should be treated initially with a phenothiazine (prochlorperazine 10 mg q8h PO prn or promethazine 12.5-25 mg IV q6h prn). If this is inadequate, a serotonin type-3 (5-HT(3)) antagonist or benzodiazepine should be added until acute nausea is controlled. Should this prove inadequate acutely, a corticosteroid may be added (*e.g.*, dexamethasone 4 mg q6h prn). Treatment with corticosteroids should be limited to fewer than 5 days.

After acute nausea has resolved, consideration should be given to initiation of prophylactic antiemetic therapy. If nausea recurs despite reasonable medical intervention (as outlined above), dose reduction will be needed as described in Section 6.

Routine supportive measures for cancer patients such as analgesics, blood transfusions, antibiotics, bisphosphonates, and erythropoietic colony stimulating factors for treatment of anemia (according to national guidelines) are permitted. However, given emerging data about adverse outcomes in a number of cancer types with erythropoietic colony stimulating factors, these should be used with caution, and only to avoid transfusion.

The administration of anticancer therapies, other investigational agents, or prophylactic use of granulocyte colony stimulating factors are not permitted. Use of granulocyte colony stimulating factors for neutropenic fever is permitted.

6.0 TREATMENT MODIFICATIONS

6.1 Tamoxifen/Megestrol Acetate

There are no dose modifications for the tamoxifen/megestrol acetate. However, because of the risk of DVT, subjects not already on anticoagulation who require major abdominal or pelvic surgery or fracture a femur or pelvis should have drug held from one week prior to the procedure (if it is a planned procedure) till they are ambulatory again. Patients receiving both tamoxifen/megestrol acetate and temsirolimus should have their temsirolimus held during the same time period during which the tamoxifen/megestrol acetate is held. However, in general, if temsirolimus is held for any reason on Arm # 2, the tamoxifen/megestrol acetate should still continue. Suspected severe and unusual toxicities from either agent (e.g. hives from tamoxifen) should be discussed with the study chair.

6.2 Temsirolimus (CCI-779)

Additional cycles of therapy may be administered provided that the patient meets the following criteria before each dose (counts done up to 24 hours ahead of time are acceptable):

- ANC \geq 1,000/mcl
- Platelets \geq 100,000/mcl
- Non-hematologic toxicity recovered to \leq grade 1 (or tolerable grade 2)
- No evidence of progressive disease

In the event of toxicity, the doses of temsirolimus will be adjusted according to the guidelines shown in the Dose Delays/Dose Modifications tables that follow. If an adverse event is not covered in the table, doses may be reduced or held at the discretion of the investigator for the subject's safety. Dose adjustments for hematological toxicity are based on the blood counts obtained in preparation for the day of treatment.

Patients requiring dose reductions should not have the dose re-escalated with subsequent treatments.

Subjects with toxicities that are manageable with supportive therapy may not require dose reductions (e.g., hyperlipidemia may be treated with statins, nausea/vomiting may be treated with antiemetics, diarrhea with loperamide rather than by dose reduction).

Loperamide should be started for diarrhea as follows: 4 mg at first onset, then 2 mg every 2-4 hours until diarrhea is controlled (maximum = 16 mg loperamide/day).

When triglyceride and cholesterol lowering is desired, use pravastatin, fluvastatin, or atorvastatin with the addition of a fibrate if necessary. Pravastatin and fluvastatin are not metabolized by CYP3A4 and are preferred. Fenofibrate is preferred in combination with statins. Avoid nicotinic acid as it may exacerbate hyperglycemia. Anti-lipid therapy should not be started without fasting lipid values.

When ONLY triglyceride lowering is desired, use a fibrate (fenofibrate or gemfibrozil). Please note that only very high triglyceride levels (>500 mg/kL) have been definitively associated with increased morbidity while moderate triglyceride increases (200-499 mg/dL) have only been associated with increased cardiac events in patients with risk factors for atherosclerotic cardiac disease or with high LDL.

Subjects with glucose elevation who are already on antidiabetic medications should have such medications cautiously adjusted if they are to stay on protocol, with a planned decrease in dosage at the time the patients comes off temsirolimus therapy. If the glucose is over 400, they should be instructed to call their doctor. Those who are not on antidiabetic medication, but with blood glucose levels over 200, should have dietary instruction (avoid concentrated sugars); if the glucose is persistently over 200 and it is the judgment of their physician that they are benefiting from temsirolimus therapy, oral hypoglycemics with appropriate monitoring can be used. Again, these must be stopped with cessation of temsirolimus therapy. (11/24/08)

Subjects who experience a clot may, at the discretion of the investigator, be continued on study with the addition of anticoagulation. If warfarin is chosen as the method of anticoagulation, INR must be in-range (target as determined by investigator, usually 2.0-3.0) prior to re-initiation of therapy. (05/24/10)

Weight loss, in the absence of other toxicity, does not require treatment to be held. (05/24/10)

For laboratory abnormalities other than hematologic parameters, study therapy should be discontinued in subjects who fail to recover to CTCAE Grade 0-1 or tolerable grade 2 (or within 1 grade of starting values for pre-existing laboratory abnormalities other than as described above) from a treatment-related toxicity within 14 days OR they experience agent related adverse events requiring dose modification despite two previous dose reductions (i.e. would require a 3rd dose reduction) unless the treating physician, study chair, and CTEP monitor agree that the subject should remain in the study because of evidence that the patient is/may continue deriving benefit from continuing study treatment. The appropriate reduced dose will be determined after discussion between the treating physician, study chair, and CTEP monitor.

Adverse Event	Agent	Treatment Modifications
Blood/Bone Marrow²		
Neutrophils ANC 500-999 Platelets 50,000-99,999	Temsirolimus	<ul style="list-style-type: none"> Delay temsirolimus until recovery to ANC $\geq 1,000$ and plt $\geq 100,000$ Retreat at a one dose level reduction If recovery requires > 14 days,¹ discontinue all study treatment.
Neutrophils ANC <500 Platelets $<50,000$		<ul style="list-style-type: none"> Delay temsirolimus until recovery to ANC $\geq 1,000$ and plt $\geq 100,000$ Retreat at two dose levels reduction If recovery requires > 14 days,¹ discontinue all study treatment.
Pulmonary/Upper Respiratory		
Grade 2 or higher Pneumonitis (cough, dyspnea, fever)	Temsirolimus	Discontinue temsirolimus pending investigation. If diagnosis is confirmed and events are considered at least possibly due to temsirolimus, the agent is discontinued.

Adverse Event	Agent	Treatment Modifications
All other non-hematologic adverse events		
<u>Grade 0-2</u>	Temsirolimus	Grade 2 toxicities that are persistent and intolerable (i.e. stomatitis) can result in dose delays and dose reductions to the next lower dose level
<u>Grade 3-4</u>		Hold dose. <ul style="list-style-type: none"> Re-evaluate until AE resolved to ≤ 1 or tolerable grade 2. Re-treat at a one dose level reduction If recovery requires > 14 days, discontinue all study treatment. Patients with grade 4 AEs related to agent may discontinue study therapy at investigator's discretion.

1. 14 days from when the dose was due, or 21 days from the previous dose.

2. Hold the study drug if coagulation parameters are meaningfully higher than the intended therapeutic range, as determined by the treating physician for patients on warfarin (See Section 5.5). Conduct INR testing weekly for the first three weeks of any cycle following a dose reduction.

Dose Reductions for Temsirolimus-related Toxicity

Dose Level	Temsirolimus Dose (mg)
Starting dose	25
-1	20
-2	15

7.0 STUDY PARAMETERS

7.1 The following observations and tests are to be performed and recorded on the appropriate form(s): See Section 7.3 for the specimen requirements for translational research for this study. Stained pathology slides will be required for central review by the GOG Pathology Committee to confirm eligibility (see Sections 7.2 and 10.2):

Observations and Tests	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study treatment ^f
Temsirolimus ⁱ		X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent meds ^a	X	X-----X												
Physical exam ^b	X**	X	X	X	X			X						
Vital signs ^b	X**	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X**													
Weight ^b	X**	X	X	X	X			X						
Performance status ^b	X	X			X			X						
CBC w/diff, plts ^{i,c}	X*	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry ^{j,c}	X*	X			X			X			X			
Serum lipid levels ^{b,d,c}	X***				X			X			X			
INR ^h	X													
Toxicity Assessment ^k		X-----X												X
Tumor measurements	X***	Tumor measurements are repeated every six weeks for 24 weeks, and then repeated every 12 weeks for patients on study therapy longer than 24 weeks.												X
Radiologic evaluation ^e	X***	Radiologic evaluation should be performed every six weeks for the first 24 weeks and then repeated every 12 weeks for patients on study therapy longer than 24 weeks.												X
B-HCG	X ^c													

* Within 7 days prior to initiating protocol therapy.
 ** Within 14 days prior to initiating protocol therapy.
 *** Within 28 days prior to initiating protocol therapy.
 a: Document in patient’s medical chart at each scheduled visit with special attention to drugs that interact with CYP3A4 and CYP2D6.
 b: Physical exam weekly for the first 4 doses, with dose 7, then every 6 weeks. Physical exam includes weight, and assessment of PS and toxicity; pelvic exam is not required except for tumor measurement or as clinically indicated. Vital signs (temperature, pulse, and blood pressure) should be taken with each infusion. Full physician or nurse practitioner physical exam should be at least every three weeks for cycle one, then at least six weeks for subsequent cycles; weeks 1, 2, and 3 require only a brief assessment to include vital signs and blood tests.
 c: Pre-treatment labs for subsequent cycles can be obtained up to 24 hours ahead of treatment.
 d: Serum cholesterol and triglycerides should be collected every 3 weeks for the first 2 cycles, then every 6 weeks.
 e: Serum or urine pregnancy test (women of childbearing potential). To be done within 48 hours before starting treatment.
 f: If patient comes off study treatment prior to progression, continue tumor measurements and radiologic evaluations on schedule until progression.. Toxicity assessments will be continued until resolution. Patients will be followed after last drug dose until toxicity resolution, until progression if patient withdraws before progressive disease, and for one year after the end of treatment for survival, or until study withdrawal if it occurs before this time. **(05/24/10)**
 g: Baseline assessment must include an evaluation of the chest by x-ray, CT scan, or MRI, and an evaluation of the abdomen and pelvis by MRI or CT scan); repeat assessments must include areas with target and non-target lesions found at baseline. Radiologic tumor evaluations are repeated every six weeks for the first 24 weeks and then repeated every 12 weeks. Repeat after treatment discontinuation if patient was taken off study for reasons other than progressive disease as seen in radiologic imaging.
 h. Only for patients on warfarin. This is to be done at baseline, weekly for the first three weeks, weekly for the first three weeks of any cycle following a dose reduction, and for a minimum of two weeks after stopping temsirolimus (See Section 5.5).
 i. Continuing weekly while patient is on therapy.
 j. Serum chemistry includes albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose,

phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium. Continuing every 3 weeks while on study.
k. Weekly for the first four weeks, then with dose 7, then continuing every 6 weeks while on study; when patient is taken off study, continue about once a month until toxicity resolution. If appropriate, toxicity assessments can be conducted by telephone. **(05/24/10)**

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Protocol Eligibility (05/24/10)

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site histologic cell type and grade will be required for ALL patients, with additional slides documenting most advanced stage or recurrence if documented by histology or cytology. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date.

Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, two copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports to the GOG Statistical and Data Center. **Please see Sections 4.4 and 10.2 for additional requirements and instructions.**

7.3 Translational Research

7.31 Specimen Requirements

Please see below for a summary of the specimen requirements for GOG-0248 if the patient gives permission for her specimens to be submitted and used for this research study. Patients may participate in this treatment protocol even if they don't give permission for their specimens to be submitted and used for this research study. **If this is the case, indicate "patient refused" as the reason in Item 5 on the SP Form.**

Refer to Appendix IV for a description of the Specimen Procedures for this protocol including instructions for obtaining a GOG Bank ID, ordering

Specimen Kits for GOG-0248, submitting SP Forms as well as preparing, shipping, banking and distributing the GOG-0248 specimens.

Quick Scan Summary of the Specimen Requirements for GOG-0248 (05/24/10)

Required Specimens (Specimen Codes) ¹	Form SP Label in Forms Tracking System ²	Collection Time Points and Requirements	Deadlines and Recommendations ²
Archival Formalin-Fixed and Paraffin-Embedded (FFPE) Primary, Metastatic, and/or Recurrent Tumor (FT01): ³ 1 st choice: Block 2 nd choice: 20 Unstained Slide - 15 unstained 5 micrometer sections on charged slides for immunohistochemistry assays - 5 unstained 10 micrometer sections on clean glass slides suitable for laser capture microdissection and/or nucleic acid extractions	SP-FT01-0248 (05/24/10)	Tumor must have been removed prior to starting treatment on this phase II trial	Ship FT01 to the <u>GOG Tissue Bank</u> using your own shipping container via US Postal Mail at your own expense within 8 weeks of study entry. ³ Form SP for FT01 will need to be submitted to the GOG Statistical and Data Center (SDC) online using the SDC Electronic Data Entry System (SEDES) within 8 weeks of study entry.
Room Temperature Blood (WB01) for immediate submission and DNA extraction by the Bank ⁴ (05/24/10) Draw 10 ml blood into your own purple-top Vacutainer® tube(s) with EDTA	SP-WB01-0248	Collect prior to starting treatment on this phase II trial	Ship WB01 to the GOG Tissue Bank at ambient temperature the day the blood is collected in your own shipping container. ⁴ Form SP for WB01 will need to be submitted to the SDC online using SEDES the day the blood is collected.
Frozen Blood (WB02) ⁵ (05/24/10) Draw 10 ml blood into your own purple-top Vacutainer® tubes with EDTA	SP-WB02-0248	Collect prior to starting treatment on this Phase II trial	Ship WB02 to the GOG Tissue Bank using a Single Chamber Kit provided for this trial within 1 week of starting treatment. ⁵ Form SP for WB02 will need to be submitted to the SDC online using SEDES within 1 week of treatment start.

- ¹ Label each specimen with the protocol number (GOG-0248), a GOG Bank ID (##### - ## - G ###), a specimen code (see above) and the collection date (mm/dd/yyyy).
- ² Please complete Form SP for EACH specimen and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix IV.
- ³ The unstained slides or block of primary, metastatic, and/or recurrent tumor will need to be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0248, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org. Primary tumor is the 1st choice, metastatic tumor is the 2nd choice and recurrent tumor is the 3rd choice. We strongly encourage the submission of more than one type of tumor tissue whenever possible. In this situation, please label the tumor specimens sequentially using FT01 for primary tumor tissue, FT02 for metastatic tumor and FT03 for recurrent tumor, and contact the GOG Statistical and Data Center to have the additional “**optional**” SP Forms for FT02 and FT03 added to the patient form schedule. In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient

refused or referring site won't release tumor). If the quantity of FFPE tumor is limited, please call a GOG Translational Research Scientist for advice (716-845-5702). **(05/24/10)**

- 4 Room temperature. whole blood specimen for GOG-0248 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. This blood specimen must be shipped at ambient temperature the day the blood is collected as it will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank *FedEx Priority Overnight* on a Monday through Friday schedule for Tuesday through Saturday delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0). Refer to Section V and Section VII in Appendix IV for instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0248 as the GOG Tissue Bank cannot provide Shipping Kits for submitting the room temperature whole blood specimen for this protocol. In the event that it is not possible to submit the whole blood specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood, non-US site, logistically infeasible or IRB refused). **(05/24/10)**
- 5 Frozen whole blood specimen for GOG-0248 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB02 via Federal Express for next morning delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0) on a Monday through Thursday schedule for Tuesday through Friday delivery. Please store the blood in an ultra-cold freezer or in an appropriate container/cooler surrounded by excess dry ice until the blood can be shipped to the GOG Tissue Bank. In the event that it is not possible to submit the whole blood specimens, submit the SP form via SEDES with the reason the specimen was not collected in Item 5 (see above for examples). **(05/24/10)**

7.32 Laboratory Testing

Staff at the GOG Tissue Bank will coordinate with the Chairs of the GOG Committee for Experimental Medicine and the Tissue Utilization Subcommittee as well as staff in the GOG Statistical and Data Center to distribute appropriate specimens to approved investigators for testing for this trial (see below for details). **The translational research component of this Phase II protocol does involve genetic testing** to study genetic changes that are inherited and passed on in families. **(11/24/08)**

7.321 Immunohistochemistry Assays

Staff at the GOG Tissue Bank will prepare and distribute fifteen unstained sections 5 micrometers in thickness on charged slides suitable for standard immunohistochemistry assays to Dr. Kimberly Leslie at the University of Iowa Hospitals and Clinics. **(05/24/10)**

Validated immunohistochemistry assays will be performed and evaluated for ER-alpha, ER-beta, PR-A, PR-B, GPR-30, normal and mutant PTEN, total and phosphorylated Akt as well as total and phosphorylated p70S6 kinase in the GOG Receptor Core Laboratory under the supervision of Dr. Leslie and her designee. **(05/24/10)**

The following is a general description of the immunohistochemistry procedure to evaluate steroid receptor isoform expression. Appropriate unstained slides will be baked at 60°C for 20 minutes and then deparaffinized through three changes of xylene and graded alcohols to water. Sections will then be treated with 3% H₂O₂ to inactivate the endogenous peroxidase activity. Antigen retrieval will be performed in a Decloaking chamber in which the slides will be immersed in 10 mM Citrate solution (pH 6.0) and boiled for 20 minutes at 120°C (20-25 p.s.i). The slides will then be cooled in buffer for 20 minutes and rinsed

in three changes of deionized water and phosphate buffered saline (PBS). Non-specific binding will be minimized by incubating the sections with 5% normal goat serum, in PBS, for 30 min. PBS will be used to rinse and wash the sections between each of the subsequent incubations. Slides will be incubated overnight at 4°C with optimal concentrations of primary antibodies, with an appropriate secondary antibody for 1 hour and then with 3,3-diaminobenzidine solution, the chromogen substrate, for 10 minutes. Slides will then be rinsed with deionized water and PBS and counterstained with hematoxylin, dehydrated through graded alcohols and permounted. Positive and negative controls will be included in each run. For the negative control sections, the primary antibody will be substituted with immune serum.

PTEN will be detected and evaluated using an immunohistochemistry assay optimized by Dr. George Mutter at Brigham and Womens Hospital in Boston, MA. Total and phosphorylated Akt and p70S6K will be detected using commercially available antibodies. The assays to detect total and phosphorylated Akt and p70S6K will be optimized with respect to antibody concentration as well as antigen retrieval method and time by the GOG Receptor Core Laboratory. Appropriate positive and negative controls will be included in each run.

Immunohistochemical staining for each biomarker will be evaluated by approved reviewers in a blinded manner. The H-score will be used to evaluate the immunohistochemical expression of the steroid receptor isoforms. The H-score is calculated based on estimates of percentages of positive stained epithelial and stromal cells in each of 5 intensity categories (0, 1+, 2+, 3+, and 4+). The H-score represents the sum of each of the percentages multiplied by the weighted intensity of staining, as follows: $H\text{-score} = \sum_{i=1}^4 (i+1)P_i$, where $i=1,2,3,4$, and P_i varies from 0 to 100%. Another more quantitative method involves the use of computer program imaging to quantify immunohistochemical expression of steroid receptors. We are currently testing such a program at the GOG Tissue Bank and have the opportunity to incorporate this methodology in the future. **(05/24/10)**

The criteria for evaluating the immunohistochemical expression of normal and mutant PTEN, total and phosphorylated Akt and total and phosphorylated p70S6K will be documented and reviewed by appropriate staff in the GOG Statistical and Data Center prior to initiating the review of the stained slides for this trial.

Dr Leslie will be responsible for providing an electronic copy of the consensus immunohistochemical data for this phase II trial linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical and Data Center for analysis. Dr. Leslie will also be responsible to returning any residual unstained slides with accurate identifiers to the GOG Tissue Bank.

7.322 Genotyping for Single Nucleotide Polymorphisms (SNPs)

Staff at the GOG Tissue Bank will extract DNA from room temperature blood specimens submitted for this protocol on the day the blood is received at the Bank, and will distribute approved aliquots of DNA and banked frozen blood specimens for this trial to Dr. Anna Di Rienzo in the Department of Human Genetics at the University of Chicago. Dr. Di Rienzo will supervise the extraction of genomic DNA and the SNP analysis for *FRAP1* and *RAPTOR*. Genomic DNA will be extracted from each frozen blood sample using the Blood & Cell Culture midi kit from Qiagen, which yields 160-200 µg of DNA from 10 ml of blood. Genotyping of normal DNA using the Sequenom iPLEX Gold technology will capture the genetic variations in up to 11 tag SNPs and 167 tag SNPs in the *FRAP1* and *RAPTOR* genes, respectively. SNPs in other genes in the mTOR pathway may also be genotyped if initial results are promising. **(05/24/10)**

Dr. Di Rienzo will also be responsible for the following: (1) providing an appropriate aliquot of normal DNA to Drs. Rajani Kanteti and Ravi Salgia for the mutation analysis described in Section 7.223, (2) submitting an electronic copy of the SNP data for this phase II trial linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical and Data Center for analysis, and (3) shipping the residual DNA for this trial with appropriate identifiers and documentation regarding DNA concentration and quality to the GOG Tissue Bank.

7.323 DNA Sequencing and Mutational Analysis, and Quantitative Real-Time Polymerase Chain Reaction (PCR)

Staff at the GOG Tissue Bank will distribute 5 unstained sections 10 micrometers in thickness on clean glass slides suitable for laser capture microdissection and/or nucleic acid extractions to Drs. Rajani Kanteti and Ravi Salgia in the Section of Hematology / Oncology at the University of Chicago to perform the genomic assessments for *PTEN*, *PI3KCA*, and *paxillin*.

Drs. Kanteti and Salgia will supervise the DNA extractions as well as the analysis of somatic mutations in *PTEN*, *PI3KCA*, and *paxillin* and the assessment of copy number abnormalities in *PTEN* and *paxillin*.

Once the unstained thick sections for this trial are distributed to the laboratory, the DNA extraction will be carried out according to Sato (Sato, Y et al., Diagnostic Molecular Pathology 10: 265-271, 2001) with minor modifications. The tissue sections will be re-suspended in 0.3 ml of digestion buffer (50mM Tris/HCl, pH 8.5, 1 mM EDTA and 1% Tween 20). The tube will be tightly capped with a pinhole at the center.

High power microwave irradiation will be carried out for 1 to 1.5 min with irradiation time split into 15 seconds segment to prevent over boiling. The tubes will be centrifuged while they are warm, at 12000 x g for 10 minutes and placed on ice. Using a sterile tooth pick the solid paraffin wax ring that forms above the buffer will be removed. Proteinase K will be added to each sample to get the final concentration of 0.5 mg/ml and the tubes will be incubated at 55°C in a water bath for 48 hours with constant shaking. After two days of digestion with proteinase K, Chelex -100 (BioRad) will be added to each sample to final concentration of 5% and the mixture will be vortexed and heated at 95°C for 10 minutes to inactivate the proteinase K. The samples will then be centrifuged for 5 minutes at 12,000 x g and the supernatant containing DNA will be transferred to a new tube and stored at -20°C or 4°C. The amount of DNA extracted will be quantified by running an aliquot on 0.8% agarose gel. The above steps will ensure the suitability of extracted DNA for amplification of specific genes.

Appropriate PCR primers covering the exons spanning the entire coding region of *PTEN*, *PI3KCA* and *paxillin* will be used and sequenced. Aliquots of normal DNA will also be obtained from Dr. Di Rienzo (see Section 7.222) for sequencing. All mutations will be confirmed by sequencing in both directions.

Quantitative real-time PCR will be performed for gene copy number measurement of *PTEN* and *paxillin* using DNA extracted from the FFPE tumor specimens using the Stratagene Mx3000P system and the iQ SYBR green PCR kit (Bio-Rad Laboratories). Relative gene copy number for *PTEN* or *paxillin* was calculated from the real-time PCR efficiencies for each individual run and based on the deviations of the target gene and reference gene (LINE-1) in the a test sample versus a control. LINE-1 is a repetitive element and copy numbers per diploid genome are similar in healthy and malignant human cells. Reactions will be performed in triplicate under standard thermocycling conditions and the mean threshold cycle number will be used.

Drs. Kanteti and Salgia will be responsible for the following: (1) submitting an electronic copy of the mutation analysis in *PTEN*, *PI3KCA*, and *paxillin*, and the assessment of copy number abnormalities in *PTEN* and *paxillin* for this phase II trial linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical and Data Center for analysis, and (2) shipping any residual DNA and unused unstained slides for this trial with appropriate identifiers and documentation regarding DNA concentration and quality to the GOG Tissue Bank.

7.33 Future Research

See Section X in Appendix IV for important details regarding the banking and distribution of residual FFPE tumor tissue, DNA and whole blood specimens for future research. **(05/24/10)**

7.4 Quality of Life (05/24/10)

This protocol does not include quality of life research.

8.0 EVALUATION CRITERIA

8.1 Parameters of Response – GOG RECIST Criteria

8.11 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.

8.12 Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present” or “absent”.

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

8.13 Best Response

Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline. *Reporting of these changes in an individual case should be in terms of the **best response** achieved by that case since entering the study.*

8.131 Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart.

- 8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.
- 8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 6 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 6 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.
- 8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.
- 8.135 Stable Disease is any condition not meeting the above criteria.
- 8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.
- 8.14 Progression (measurable disease studies) is defined as ANY of the following:
- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
 - In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
 - The appearance of one or more new lesions
 - Death due to disease without prior objective documentation of progression
 - Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression

- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)
- 8.15 Recurrence (non-measurable disease studies) is defined as increasing clinical, radiological or histological evidence of disease since study entry.
- 8.16 Survival is the observed length of life from entry into the study to death or the date of last contact.
- 8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.
- 8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.
- 8.19 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v3.0.

9.0 DURATION OF STUDY

9.1 In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study,
- Patient non-compliance with the protocol, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

9.2 Patients will be followed after last drug dose until toxicity resolution and for one year after the end of treatment, or until study withdrawal if it occurs before this time.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent

Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system. **(9/26/2011)**

Beginning October 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG

member web site (<https://gogmember.gog.org> under MANUALS).
(9/26/2011)

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected With Hospitalization	Unexpected Without Hospitalization	Expected With Hospitalization	Expected Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
 AdEERS 24-hour notification followed by complete report within 3 calendar days for:
 • Grade 4 and Grade 5 unexpected events
 AdEERS 7 calendar day report:
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization
 • Grade 5 expected events

² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled “Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND.”

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
 - “24 hours; 3 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - “7 calendar days” - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial

registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- There are no additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at <http://ctep.cancer.gov>. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: “Secondary malignancy-Other (specify)”. **(9/26/2011)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. **(9/26/2011)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted. **(9/26/2011)**

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AEs within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP’s clinical experience with this agent and defines “expected” Grade 2 and 3 AEs not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com. The CAEPR for temsirolimus is located in Section 4.310.

10.15 Automated CDUS reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The

AEs reported through AdeERS will also be included with the quarterly CDUS data submissions.

As of 10/1/2011, this study will cease using CTCAE v3 and switch to CTCAE v4 for the purposes of reporting through AdeERS and/or CDUS. The GOG Statistical and Data Center will internally convert the adverse event terms and grades reported through AdeERS for this study from April 1, 2011 onward from version 4 to version 3. Additionally, the Statistical and Data Center will map all CTCAE v3 data reported for this study on GOG case report forms to CTCAE v4 defined terms and grades for CDUS reporting purposes. This will allow use of a consistently defined set of criteria for reporting adverse events throughout the study with minimal impact on the participating sites. **(9/26/2011)**

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. **Note: Pathology materials (Form F, path report, and stained path slides** to confirm eligibility) should be submitted together via postal mail. The Upload feature in SEDES is an alternate method for submitting Form F and Pathology reports (not applicable for slides). (05/24/10)**

Form [±]	Due within		Copies*	Comments
	Weeks	Event		
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Specimen Consent Application	1	Registration	N/A	Complete online
Form OSR (Recurrent Gynecologic Cancer On-Study Form)	2	Registration	1	Mandatory Submission via SEDES
Form DR (Pre-Treatment Summary Form)	2	Registration	1	Mandatory Submission via SEDES
Form CONM (Concomitant Medication Form) - baseline	2	Registration	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) - baseline	2	Registration	1	Mandatory Submission via SEDES

Primary/Advanced Disease: Form F (Pathology Form)	6	Registration	2	Available in SEDES for print only
Pathology Report**	6	Registration	2	Submit via postal mail to GOG SDC in Buffalo, New York**
Stained Path Slides to confirm eligibility and advanced disease	6	Registration	**	
Persistent or Recurrent Disease: Form F	6	Registration	2**	
Pathology Report	6	Registration	2**	Submit via postal mail to GOG SDC in Buffalo, New York**
Stained Path Slides to confirm eligibility, if documented by histology or cytology	6	Registration	**	
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	1	
Form D2M (Solid Tumor Evaluation Form)	2	Tumor response or progression assessment	1	Mandatory Submission via SEDES
Form SP-FT01-0248† for archival formalin-fixed and paraffin-embedded (FFPE) primary, metastatic and/or recurrent tumor (block or unstained slides) (05/24/10)	8	Registration	1	Submit via SEDES <i>f</i> Ship block or unstained slides for translational research with a copy of the SP Form for FT01 to the GOG Tissue Bank in Columbus Ohio †
Form SP-WB01-0248‡ for room temperature blood for immediate submission and DNA extraction by the Bank (05/24/10)	1	Start of treatment	1	Submit via SEDES <i>f</i> Ship WB01 blood for translational research at ambient temperature the day the blood is collected with a copy of the SP Form for WB01 to the GOG Tissue Bank in Columbus Ohio ‡ (05/24/10)
Form SP-WB02-0248‡‡ for frozen blood (05/24/10)	1	Start of treatment	1	Submit via SEDES <i>f</i> Ship WB02 frozen blood for translational research with a copy of the SP Form for WB02 to the GOG Tissue Bank in Columbus Ohio ‡‡
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle	1	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory Submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up; change in treatment	1	Submit via SEDES for one year from end of treatment

* The number of required copies including the original form which must be sent to the Statistical and Data Center.

** Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. See Sections 4.4 and 7.2 for additional requirements and instructions. If F form and path reports are uploaded, only one copy of the F form should be submitted with slides. **(05/24/10)**

f Form SP **must be submitted online** to the GOG SDC using SEDES regardless of whether the specimen is submitted for research.

- † See Footnote 3 in the Quick Scan Summary in Section 7.31 of the protocol and Appendix IV for important details about submitting up to three tumor specimens (FT01, FT02 and FT03), loading optional SP Forms for FT02 (second type of FFPE tumor) and FT03 (third type of FFPE tumor), and instructions for shipping the block or unstained sections of primary, metastatic and/or recurrent tumor in your own shipping container to the GOG Tissue Bank and for completing the corresponding SP Form(s). **(05/24/10)**
- ‡ See Footnote 4 in the Quick Scan Summary in Section 7.31 of the protocol and Appendix IV for important details for preparing and shipping the room temperature blood (WB01) the day the blood is collected in your own shipping container to the GOG Tissue Bank, and for completing the corresponding SP Form. **(05/24/10)**
- ‡‡ See Footnote 5 in the Quick Scan Summary in Section 7.31 of the protocol and Appendix IV for important details for preparing and shipping the frozen blood (WB02) in a Single Chamber Kit provided for this trial to the GOG Tissue Bank within 1 week of starting treatment, and for completing the corresponding SP Form. **(05/24/10)**

This study will be monitored by the **Complete** Clinical Data Update System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site (<http://www.gog.org> under MANUALS) and can be mailed to the institution registering a patient to this study if requested. **(9/26/2011)**

11.0 STATISTICAL CONSIDERATIONS

Overview, Study Registration and Randomization: This study is a two-stage, open-label randomized phase II clinical trial. The intent of this study is to screen regimens for activity. The two regimens will be assessed separately to estimate the probability of response. If both regimens are deemed active following completion of stage II, one regimen will be selected for further investigation as a means of prioritization in the event that resources are limited. All patients on this study will be registered and receive a random treatment assignment centrally at the GOG Statistical and Data Center. Prior to registration, eligibility will be reviewed via Fast Fact Sheet verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. A procedure will be used that tends to allocate the two regimens in the ratio of 1:1 within the strata defined by 1) Patients who have received adjuvant chemotherapy or chemoradiation either at time of initial diagnosis or for a pelvic recurrence of endometrial cancer and 2) Patients who have never received adjuvant chemotherapy or chemoradiation for treatment of endometrial cancer or its subsequent recurrence. Study reports will include a complete accounting of all patients registered to this protocol.

11.1 **Data Collection:** The principal parameters to be collected, analyzed and reported to evaluate the activity level of these treatment regimens are:

- 11.11 **Outcome Variables:** the primary outcome variable is the frequency of complete and partial clinical response among all eligible patients; survival time and progression-free survival time distributions will also be estimated.
- 11.12 **Tumor Characteristics:** FIGO stage, recurrence status, sites of measurable disease, tumor grade, histological cell type, estrogen and progesterone receptor status.
- 11.13 **Patient Characteristics:** age at entry, performance status, race, and prior therapy.
- 11.14 **Adverse Effects:** frequency and severity of adverse effects in patients who received any amount of study drug graded according to CTCAE v3.0.
- 11.15 **Treatment:** the total dose of each study drug administered, the number of cycles of study therapy administered, the reason for discontinuing study therapy.
- 11.16 **Laboratory Testing Results:** immunohistochemical expression of estrogen receptor-alpha, estrogen receptor-beta, progesterone receptor-A, progesterone receptor-B and GPR30 (H-Score); immunohistochemical expression of , total Akt, phosphorylated Akt, total p70S6 kinase and phosphorylated p70S6 kinase (scoring criteria to be defined); genotype for 11 tag SNPs for *FRAP1* and 167 tag SNPs for *RAPTOR*; type and localization of mutations in *PTEN*, *PI3KCA*, and *paxillin*; the ratio of the number of copies of *PTEN* to *LINE-1* and *paxillin* to *LINE-1*.

11.2 **Accrual Rate:** Previous GOG phase II studies of hormonal agents differed in their requirement for biopsied tissue which had an impact on the accrual rate. This study does not require sampling metastatic tumor for the purposes of testing the receptor status but does require a tissue block from either primary, metastatic or recurrent tumor. Accrual to previous phase II studies of hormonal agents that did not require biopsied tissue and did not select for receptor positive patients ranged from 36 to 62 patients annually.

The accrual rate of the most recently completed phase II study requiring biopsied tumor averaged 10 patients per year among the patients with estrogen receptor positive metastatic tumor. The accrual rate on the currently active phase II study among those with receptor positive metastatic tumors is now 44 patients per year (based on 1st and 2nd quarters of 2007).

The accrual rate on this study is expected to be higher than the previous study given that it does not require a biopsy (primary uterine tissue can be tested for receptors) and the fact that this study incorporates a new targeted biologic agent. The accrual rate for this study is based upon that observed in GOG 153 (49) and current accrual on GOG 188 (44), 46 patients per year.

- 11.3 **Study Design and Sample Size:** This study will implement a two-stage design with early stopping guidelines intended to limit the accrual of patients to inactive regimens. Additionally, if at the end of stage II, both regimens are deemed to have sufficient activity, a selection procedure will be employed to prioritize the regimens for further investigation.

Hormonal agents studied by the GOG have yielded response rates ranging from 11% to 33%. Within estrogen receptor positive subgroups, response rates of hormonal agents studied varied from 0% to 50%. The response rate for a standard hormonal therapy studied by the GOG (Protocol 81 MPA: 200 mg PO daily) is 25% overall.

Data describing response to temsirolimus were provided by Janet Dancey (IDB/CTEP/DCTD/NCI) suggest that response may differ depending on whether or not a patient has received previous chemotherapy (alone or in combination with radiation) for endometrial carcinoma. The observed proportions of endometrial cancer patients responding were 25% (7) of 33 patient without a history of chemotherapy and 7.5% (2) of 27 patients who had previously been treated with chemotherapy. Patients with or without a history of chemotherapy or chemoradiation are eligible for this study. Sixty percent of patients enrolled on GOG 188 in 2007 had received adjuvant chemotherapy. Accrual trends observed on GOG 188 and the increasing use of adjuvant chemotherapy for endometrial carcinoma suggest that the proportion of patients receiving prior chemotherapy is increasing over time. A simple (i.e. single) binomial distribution approximating

the marginal number of responses over both populations may not be adequate. Furthermore, splitting the patient population by prior chemotherapy to create two separate trials is not feasible due to the length of time it would take to get sufficient patients in each trial. Therefore, a two-stage conditional stratified phase II trial as proposed by London and Chang³⁶ will be used which utilizes the marginal number of responses across all populations while factoring differing probabilities of response within each population. Conditioned on the realized sample size in each stratum, the probability mass function for R_1 and R_2 corresponding to the responses produced in stages 1 and 2 can be found with:

$$P(R_j = r_j) = \sum_{r_{1j} + \dots + r_{kj} = r_j} \prod_{i=1}^2 \binom{n_{ij}}{r_{ij}} p_i^{r_{ij}} (1 - p_i)^{n_{ij} - r_{ij}}, j = 1, 2.$$

Where i indexes the number of important stratification levels under consideration and j indexes the stage of accrual. The distribution of R_j depends on the probabilities of response, p_i , within each stratum. Stratum 1 will correspond with those patients who have never been treated with chemotherapy whereas stratum 2 will correspond with those patients who have had prior chemotherapy. A response rate of 20% or less in those patients who have not had previous chemotherapy and a response rate of 10% or less in those patients who have received previous chemotherapy would be considered not worthy of further study. The null hypothesis of no treatment effect is $H_0: p_1 = 0.20$ and $p_2 = 0.10$. Under the alternative hypothesis of $H_1: p_1 = 0.40$ and $p_2 = 0.30$, the following design will limit the probability of type I error to 0.06 and type II to 0.10. According to London and Chang³⁶, the first stage rejection boundary, a_1 , is found with the following equation:

$$P(R_1 < a_1 | p_i = p_{i0} + \Delta_i) \approx \gamma\beta$$

where $p_{10} = 0.20$, $\Delta_1 = 0.20$, $p_{20} = 0.10$, $\Delta_2 = 0.20$, and β is the probability of a type II error. There is interest in spending 50% of the total beta in the first stage, so $\gamma = 0.50$. Since it is important to maintain the original design parameters for this study, a_1 is found with

$$P(R_1 < a_1 | p_i = p_{i0} + \Delta_i) \approx 0.5 \times 0.10 = 0.05$$

For each treatment arm we will target 21 patients during each stage of accrual and expect $n_{11} = 8$ without previous chemotherapy and $n_{21} = 13$ who have received chemotherapy in the past. Approximating the equation above gives $a_1 = 4$ (note: \approx means ‘less than and as close as possible’). According to the decision rule provided by this method, if there were 3 or fewer responses, the agent would have been deemed clinically uninteresting. Accordingly, the probability of early termination under the null hypothesis would be 67%. If the proportions in each stratum differ from those expected, the rules above will be recalculated for the observed proportion of patients in each stratum while maintaining probability of type I and type II error limits as closely as possible.

For a given total sample size, the rejection boundary, b_2 , is found by searching for the smallest marginal total across all strata (over both stages) such that the following equation is satisfied:

$$P(a_1 \leq R_1, R > b_2 | p_i = p_{i0}) < \alpha$$

where $R = R_1 + R_2$. The decision rule at the end of the study is to recommend further study (if medical judgment indicates) when $R > b_2$. Otherwise, the agent is deemed clinically uninteresting. Power of the study is determined by looking at the probability:

$$1 - P(R_1 < a_1 | p_i = p_{i0} + \Delta_i) - P(a_1 \leq R_1, R \leq b_2 | p_i = p_{i0} + \Delta_i).$$

The cumulative targeted accrual for the second stage will be 42 patients. Because the rejection boundary depends on the realized sample size and the proportion of patients from each stratum, it is difficult to present an exhaustive list of rejection boundaries that could be used to determine the worthiness of the agent to undergo further investigation, however, Table 11.1 is provided here to give examples of the properties of the design where n_1 is the sample size for stage 1, n_{11} is the number of patients in the first stage that are from stratum 1 (no prior chemotherapy), n_{21} is the number of patients in the first stage that are from stratum 2 (prior chemotherapy), n_{Tot} is the cumulative sample size, n_{12} is the number of patients in the second stage that are from stratum 1 (no prior chemotherapy), n_{22} is the number of patients in the second stage that are from stratum 2 (prior chemotherapy), α is the probability of a type I error, and β is the probability of a type II error:

Table 11.1

Stage I				Stage 2					
n_1	n_{11}	n_{21}	a_1	n_{Tot}	n_{12}	n_{22}	b_2	α	β
20	8	12	3	41	14	27	9	0.039	0.083
20	8	12	3	41	15	26	9	0.043	0.079
20	8	12	3	41	16	25	9	0.047	0.074
20	8	12	3	41	17	24	9	0.052	0.070
20	8	12	3	41	18	23	9	0.058	0.067
21	8	13	4	42	14	28	9	0.041	0.087
21	8	13	4	42	15	27	9	0.045	0.083
21	8	13	4	42	16	26	9	0.049	0.080
21	8	13	4	42	17	25	9	0.053	0.077
21	8	13	4	42	18	24	9	0.058	0.075
22	9	13	4	43	6	15	9	0.051	0.067
22	9	13	4	43	7	14	9	0.056	0.064
22	9	13	4	43	8	13	10	0.028	0.900
22	9	13	4	43	9	12	10	0.031	0.096
22	9	13	4	34	10	11	10	0.034	0.091

Table 11.2 displays the operating characteristics for the highlighted design and decision rule in Table 11.1 under different alternative hypotheses.

Table 11.2

π_A	π_{A+B}	Pr(neither A nor A+B are deemed active π_A, π_{A+B})	Pr(both A and A+B are deemed active π_A, π_{A+B})	Pr(A is deemed active and A+B is not deemed active π_A, π_{A+B})	Pr(A+B is deemed active and A is not deemed active π_A, π_{A+B})
0.1,0.2	0.1,0.2	0.905	0.002	0.046	0.046
0.1,0.2	0.3,0.4	0.076	0.045	0.004	0.874
0.1,0.2	0.5,0.6	<0.001	0.049	<0.001	0.951
0.3,0.4	0.1,0.2	0.076	0.045	0.874	0.004
0.3,0.4	0.3,0.4	0.006	0.846	0.074	0.074
0.3,0.4	0.5,0.6	<0.001	0.919	<0.001	0.080
0.5,0.6	0.1,0.2	<0.001	0.049	0.951	<0.001
0.5,0.6	0.3,0.4	<0.001	0.919	0.080	<0.001
0.5,0.6	0.5,0.6	<0.001	>0.999	<0.001	<0.001

π_A = probabilities of response on regimen A (stratum 2, stratum 1); π_{A+B} = probabilities of response on regimen A+B (stratum 2, stratum 1)

Sum the last three columns in each row to get the probability of declaring at least one of the regimens active.

Selection

In the event that both regimens are found to have sufficient activity following completion of stage II of accrual, the following rule will be used to select one of the two regimens for prioritized further investigation. The combination regimen will be chosen for further study if the difference in proportion responding weighted by stratum size is at least 0.07 (3 more responses among 42 patients per arm) favoring the combination arm. Otherwise the single agent regimen will be selected for further study. Table 11.3 displays the operating characteristics for this selection rule.

Table 11.3

π_A	π_{A+B}	Pr(selecting A+B A and A+B were deemed active, π_A, π_{A+B})*
0.1,0.2	0.1,0.2	0.077
0.1,0.2	0.3,0.4	0.512
0.1,0.2	0.5,0.6	0.996
0.3,0.4	0.1,0.2	0.000
0.3,0.4	0.3,0.4	0.152
0.3,0.4	0.5,0.6	0.825
0.5,0.6	0.1,0.2	0.000
0.5,0.6	0.3,0.4	0.003
0.5,0.6	0.5,0.6	0.188

*based upon simulation of 10,000 samples; *Pr(selecting A| A and A+B were found active, π_A, π_{A+B}) =

1- Pr(selecting A+B| A and A+B were found active, π_A, π_{A+B})

95% Confidence intervals for proportion responding to each regimen will be calculated with adjustment for interim analyses.³⁷

11.4 **Study Monitoring:** In general, data sheets from patients on this protocol will be reviewed semi-annually and will also be reviewed by the Study Chair annually or at the discretion of the Statistical and Data Center. In particular, adverse events on the combination arm will be closely monitored by the Study Chair by review of patient summaries every two to three months during the first stage of accrual. In some instances because of unexpectedly severe toxicity, the Statistical and Data Center may elect to suspend accrual and, after consultation with the Study Chair and the committee responsible for monitoring the safety data for phase II trials, recommend early closure of a study.

The frequency and severity of all toxicities will be tabulated from submitted case report forms and summarized for review by the study chairperson and GOG Data and Safety Monitoring Board (DSMB) in conjunction with each semi-annual GOG meeting. For studies sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB). An overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity.

All AdEERS reports of serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) for consideration of investigator notification, amendment, or immediate study suspension. When immediate suspension is warranted, all participating institutions will then receive notification of the

toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the committee responsible for monitoring the safety data for phase II trials. However, in some instances patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

- 11.5 **Study Duration:** The anticipated duration of accrual is 12 months for Stage I (42 patients) and 12 months for Stage II (42 additional patients) if necessary. Six months or less will be necessary to observe the results of Stage I in order to make a decision to continue or discontinue accrual.
- 11.6 **Translational Research Analysis:** The expression of candidate markers will be determined by standard semi-quantitative methods for IHC evaluation of estrogen and progesterone receptors; GPR30; normal and mutant PTEN; total and phosphorylated Akt and p70S6 kinase. Additionally, genotypes for 11 tag SNPs for *FRAP1* and 167 tag SNPs for *RAPTOR*; type and localization of mutations in *PTEN*, *PI3KCA*, and *paxillin*; the number of copies of *PTEN* to *LINE-1* and *paxillin* to *LINE-1* will also be determined. These data will be transmitted to the GOG Statistical Office, Buffalo, NY. The levels of expression of the candidate markers measured prior to study treatment will be tabulated/described. Associations between markers, other baseline data and clinical outcome will be assessed in an exploratory manner. Methods such as logistic or proportional hazards regression will likely be used for these analyses when response, PFS or survival is the dependent variable when necessary model assumptions are appropriate. Exploratory analyses utilizing methods appropriate to the type of data will be conducted to examine the associations between markers and between markers and clinical characteristics.

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