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PROTOCOL GOG-3007
(ClinicalTrials.gov NCT02228681)

A RANDOMIZED PHASE II TRIAL OF EVEROLIMUS AND LETROZOLE OR HORMONAL THERAPY (TAMOXIFEN/MEDROXYPROGESTERONE ACETATE) IN WOMEN WITH ADVANCED, PERSISTENT, OR RECURRENT ENDOMETRIAL CARCINOMA

SPONSOR: GOG FOUNDATION, INC.
IND EXEMPT
Version Date: June 25, 2015

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SCHEMA (6/25/15)
Arm 1: Everolimus 10 mg daily and Letrozole 2.5 mg PO daily

Arm 2: Tamoxifen 20 mg PO BID (days 1-28); Medroxyprogesterone Acetate 200mg PO (once a day days 8-14 and 22-28)

Continue until disease progression or adverse events prohibit further therapy
Cycle Length = 28 days

GOG-3007
PARTICIPATING INSTITUTIONS (03/10/2015, 6/25/15)

601-01	Abington Memorial Hospital
602-01	Barbara Ann Karmanos Cancer Institute
603-01	St. Dominic-Jackson Memorial Hospital
604-01	University of Colorado
605-01	Huntsman Cancer Institute
606-01	Johns Hopkins
607-01	UNC Chapel Hill
608-01	Magee Women's Hospital of UPMC
609-01	SUNY Downstate Medical Center
610-01	New Mexico Cancer Alliance
611-01	Women's Cancer Care Associates, LLC
612-01	St. Vincent Hospital and Health Care Center, Inc.
614-01	The Ohio State University Wexner Medical Center
615-01	University of Texas MD Anderson Cancer Center
616-01	University of Massachusetts Memorial Medical Center
617-01	Women's Cancer Center of Nevada
618-01	University of Oklahoma
619-01	Sylvester Comprehensive Cancer Center, University of Miami
620-01	University of Chicago
621-01	University Hospital Case Medical Center
622-01	Women & Infants Hospital of Rhode Island
623-01	Maine Medical Center
624-01	Memorial Health University Medical Center
625-01	John B. Amos Cancer Center
626-01	St. Joseph's Hospital & Medical Center
629-01	Metro MN CCOP
630-01	Sanford Medical Center – Sioux Falls
631-01	Shivers Cancer Center at University Medical Center Brackenridge
632-01	University of Mississippi Medical Center
638-01	The University of Pennsylvania
639-01	Memorial Center – Las Cruces
640-01	Southwest Gynecologic Oncology Associates

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1.0 OBJECTIVES

1.1 Objectives

Primary Objectives: (6/25/15)

1.1.1 To determine the objective 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 everolimus 10 mg daily and Letrozole 2.5 mg PO daily
- Arm #2 Tamoxifen 20 mg PO BID; on alternating weeks (even numbered) weeks, Medroxyprogesterone Acetate 200 mg PO once daily with Tamoxifen 20 mg PO BID

Secondary Objectives:

1.1.2 To estimate the time to disease progression for each arm

1.1.3 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:

1.2.1 To determine if relevant biomarkers correlate with response to treatment in each of the two arms. Three panels of biomarkers are proposed.

- immunohistochemical expression of hormone receptors (estrogen receptor-alpha, estrogen receptor-beta, progesterone receptor-A, progesterone receptor B and the G protein-coupled estrogen receptor, GPR-30),
- immunohistochemical evaluation of components of the mTOR pathway and related proteins, including phosphorylated S6 ribosomal protein, PTEN, total and phosphorylated AKT, total and phosphorylated mTOR, and phospho-ERK1/2
- mutational analysis including PTEN, PIK3CA, KRAS, and CTNNB1 (beta-catenin) performed using a sequencing panel assay.

2.0 BACKGROUND AND RATIONALE

The identification of novel targets in malignant tumors has led to the development of inhibitors for the treatment of a wide range of cancers. The rationale for targeting dysregulated pathways has led to the development and testing of several targeted agents. The challenges of developing rational targets for therapeutic intervention in specific solid tumors remain an area of intense research. The current study will evaluate the impact targeting two dominant pathways, hormonal regulation and mTOR, has on endometrial cancer growth in women with recurrent and progressive disease.

2.1 Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in the United States with 53,630 new cases and 8,590 deaths estimated for 2014 (Siegel, 2014). The standard treatment for primary endometrial cancer consists of a total hysterectomy with bilateral salpingo-oophorectomy and possible lymph node dissection. This may be followed by radiation therapy depending on tumor factors and stage. Treatment failure in low-risk patients is rare. Tumor recurrence is most common in women with advanced-stage disease or those with high risk features. Women with isolated pelvic recurrences can potentially be salvaged with radiation therapy or surgery. However, in women with distant recurrent disease, treatment is largely systemic.

2.2 Treatment of Recurrent or Advanced Endometrial Cancer

Several chemotherapeutic agents or combinations of agents have been studied in the treatment of women with advanced or recurrent endometrial cancer. Paclitaxel and carboplatin has been established as the usual initial chemotherapy for endometrial cancer (Miller, 2012). Initial chemotherapy with paclitaxel and carboplatin is given either in the adjuvant or advanced/recurrent disease setting.

In addition, some endometrial cancers are hormonally sensitive. Treatment of recurrent and progressive tumors with progestins and progestins in combination with tamoxifen (a selective estrogen receptor modulator) has been evaluated (Lentz, 1996; Thigpen, 1999; Whitney, 2004; Fiorica, 2004). In GOG 81, medroxyprogesterone acetate at 200 mg daily resulted in an objective response rate of 25% (36/145 patients) (Thigpen, 1999). Median duration of response was short (3.2 months). In GOG 119, single arm phase II trial of medroxyprogesterone acetate plus tamoxifen (tamoxifen 20 mg BID with medroxyprogesterone acetate 100 mg BID given on alternating weeks) showed a 33% (19/58 patients) objective response rate (Whitney, 2004). Again, median progression free survival was short (3 months). In a phase II study by the Gynecologic Oncology Group, an aromatase inhibitor (anastrozole) had limited activity as a single agent against recurrent and progressive endometrial cancer (Rose, 2000). In this study, of the 23 patients enrolled, two had partial responses (9%) and two had short-term stable disease.

More effective systemic agents with longer durations of response are needed. Prognosis remains poor for patients who recur following first-line chemotherapy (generally paclitaxel/carboplatin) given in either the adjuvant or advanced/recurrent disease setting.

2.3 PTEN/AKT/mTOR Pathway

PTEN, a tumor suppressor gene, has been shown to play several roles in tumor suppression, including cell cycle arrest and promotion of apoptosis. Inactivating mutations in PTEN occur frequently in many human cancers. In particular, mutations in PTEN are frequent in endometrial carcinomas (TCGA, 2013).

Tumor cells lacking PTEN contain high levels of activated AKT. This suggests that PTEN is necessary for the appropriate regulation of the phosphatidylinositol 3-kinase/AKT pathway. Recent studies have identified the AKT kinase as a potential mediator of tumorigenesis in endometrial cancer cell lines. The finding of PTEN mutations in the majority of endometrial cancer suggests that the loss of PTEN function may be one mechanism by which AKT activity is increased in this disease. Because PTEN-deficient cancer cells may have upregulated activity of the mammalian target of rapamycin (mTOR), which is downstream of AKT, these cells may be sensitive to mTOR inhibition.

2.4 Everolimus

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection in kidney transplant patients. Afinitor® was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Approximately 30,582 cancer patients have been treated with everolimus as of 30-Sep-2013

- 16,671 patients in Novartis-sponsored clinical trials
- 1,911 patients in the individual patient supply program
- More than 12,000 patients in investigator-sponsored studies.
- In addition, healthy volunteer subjects and non-oncology hepatically impaired subjects have participated in the clinical pharmacology studies.

The following is a brief summary of the main characteristics of everolimus. More complete information can be obtained from the everolimus Investigator's Brochure (IB).

2.41 Overview of Everolimus

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (Boulay, 2007).

Everolimus is being investigated as an anticancer agent based on its potential to act

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation;
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

2.42 mTOR pathway and cancer

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development (Cohen, 2005).

The main known functions of mTOR include the following (Bjornsti, 2004):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels;
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers (Frattini 2005, Velho 2005);
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers (Goel, 2004);
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

2.43 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to μM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to everolimus *in vitro*.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and

"relatively resistant" *in vitro*. In general, everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 ribosomal protein (p-S6rp) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

In vitro genotoxicity studies covering relevant genotoxicity end-points showed no evidence of clastogenic or mutagenic activity.

In male fertility studies in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg which corresponded to 0.7 times the estimated clinical exposure at 10 mg/day, and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus caused an increase of pre-implantation loss in female rats at doses > 0.1 mg/kg, suggesting it could also potentially impact fertility in females. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the planned therapeutic level comprising mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryo toxicity was evident by an increase in late resorptions. Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥0.1 mg/kg, and did not indicate a specific toxic potential.

The potential reproductive risk for humans is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the fetus. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore women who are taking everolimus should not breastfeed.

Further details can be found in the everolimus Investigator's Brochure.

2.5 mTOR inhibition and endometrial cancer

Recent molecular profiling has shown that increased PI3K/AKT/mTOR signaling is associated with aggressive disease and poor prognosis, irrespective of endometrial cancer histology.

Clinically available mTOR inhibitors target either mTORC1 alone, or mTORC1/2. Others in development target multiple nodes of the PI3K pathway including PI3K. mTORC1 inhibitor currently in clinical development include everolimus, temsirolimus and ridaforolimus.

Recently, everolimus and temsirolimus showed antitumor activity in endometrial cancer cell lines, with greatest sensitivity in cells with *PIK3CA* and/or *PTEN* mutations. Furthermore, everolimus reduced progression of endometrial hyperplasia in a *PTEN* heterozygous mouse model, and repressed tumor growth in mouse xenograft models harboring endometrial cancer cells with loss of PTEN and/or *PIK3CA* mutations. Consistent with these findings, ridaforolimus also showed antitumor activity in endometrial cancer cells and a mouse xenograft model, with greatest sensitivity observed in cells with loss of PTEN or increased phosphorylated or total AKT.

In patients with recurrent and/or metastatic endometrial cancer, single-agent treatment with everolimus, temsirolimus, and ridaforolimus has led to clinical benefit rates of 21%, 52% to 83%, and 33% to 66%, respectively (Slomovitz, 2010; Oza, 2011; Colombo, 2013). For both temsirolimus and ridaforolimus, the best responses were seen in patients with no prior chemotherapy. Furthermore, ridaforolimus was also shown to significantly improve progression-free survival (PFS) in patients with no further approved treatment options. Common adverse events in these studies included fatigue, nausea, mucositis, diarrhea, and rash. Hypertriglyceridemia was also reported in 2 studies, and pneumonitis was common in 1 study (37%). In addition, hyperglycemia, a possible “on target” effect of PI3K/AKT/mTOR pathway inhibition, was observed in 2 studies (27% and 19%, respectively).

2.6 Hormonal Therapy and endometrial cancer

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 (Fiorica, 2004). This regimen produced a response rate of 27% in 56 eligible women with no prior chemotherapy or hormonal therapy. Median PFS was 2.7 months and median overall survival was 14.0 months. This trial was closed to patient entry in November 1995. Another study (GOG-0119), evaluated the efficacy of tamoxifen citrate plus intermittent administration of medroxyprogesterone acetate in patients with recurrent or metastatic endometrial carcinoma (Whitney, 2004). This regimen produced a response rate of 33% in 58 eligible patients with no prior chemotherapy or hormonal therapy. Median PFS was 3 months and the median overall survival as 13.0 months. This study will evaluate this hormonal therapy in a contemporary cohort including patients who have received prior adjuvant chemotherapy.

2.7 Rationale for the combination of hormones and everolimus

Given the importance of ER signaling in type I endometrial cancer, and the cross-regulation between the ER and PI3K/AKT/mTOR pathways, combining agents that disrupt ER signaling

with PI3K/AKT/mTOR pathway inhibitors may also result in synergistic antitumor responses. The combination of everolimus with the aromatase inhibitor exemestane significantly improved PFS in patients with aromatase inhibitor-refractory breast cancer, thus demonstrating proof-of-concept that PI3K/AKT/mTOR pathway inhibitors may reverse resistance to aromatase inhibitors.

The GOG-0248 evaluated the combination of temsirolimus and megestrol acetate compared to temsirolimus alone (Fleming, 2014). In this study, the temsirolimus/hormonal arm was closed secondary to a high rate of thromboembolic events.

In patients with advanced breast cancer, the combination of everolimus 10 mg/day and letrozole 2.5 mg/day was tolerable. Efficacy data in patients with advanced breast cancer have demonstrated some activity in some patients that do not respond to letrozole alone.

Our group recently completed a single arm phase II activity trial of everolimus in combination with letrozole for patients with recurrent endometrial cancer (Slomovitz, 2011). Of the 35 evaluable patients, the response rate was 31% (11/35). There were 8 patients who achieved a complete remission and 3 patients with a partial remission.

The safety profile of everolimus was acceptable in the context of heavily pretreated patients with endometrial cancer. Compared to a previous phase 2 single agent everolimus trial showing no objective responses, the addition of letrozole likely blocks the bypass of PI3K/AKT/mTOR pathway and thus resulted in better treatment response.

2.8 Translational Research

The translational research component for this study will be performed in collaboration with the MD Anderson Uterine Cancer SPORE. This group has been studying biomarkers to predict responsiveness to mTOR inhibitors alone and in combination with aromatase inhibitors. These biomarker studies have developed from two SPORE-sponsored completed clinical trials: the first was a single agent everolimus study (Slomovitz, 2010) and the second was a dual everolimus and letrozole study (Slomovitz, 2011).

Biomarkers to predict responsiveness to mTOR inhibitors have been examined in a number of different cancers, including renal cell carcinoma, neuroendocrine cancers, sarcoma, glioblastoma and endometrial cancer. To date, no single biomarker predictive of response to an mTOR inhibitor has been identified and validated. In a Phase II study of temsirolimus in renal cell carcinoma, high phospho-S6rp levels were correlated to response, with phospho-AKT levels demonstrating a trend toward positive response. In endometrial cancer, neither we, nor the Canadian NCIC group found an obvious correlation between PTEN status, phospho-AKT, phospho-S6rp or phospho-mTOR levels and response to temsirolimus or everolimus (Oza, 2011). Although our numbers were small, our study showed that the combination of high phospho-S6rp levels with an activating KRAS mutation was predictive of non-response to these agents in endometrial tumors. Therefore, identifying biomarkers that predict non-response to mTOR inhibitors may be a more clinically achievable goal, and will contribute to the development of personalized treatment regimens for endometrial cancer.

With the positive report of BOLERO 2 demonstrating the efficacy of the combination of everolimus with the aromatase inhibitor exemestane in metastatic breast cancer (BOLERO 2 study; Baselga 2012), there is increasing clinical and pre-clinical evidence of the close interaction between the PI3K/AKT/mTOR pathway and ER ligand-independent signaling. More specifically, studies have demonstrated that S6 kinase is involved in phosphorylation of estrogen receptor for ligand-independent receptor activation (phospho-ERalpha-S167 and phospho-ERalpha-S118) (Yamnik, 2010; Yamnik, 2009, de Leeuw, 2011). With the

availability of phosphorylation site specific antibodies, we are currently evaluating these markers in pre-and post-treatment samples.

i) Tissue Analysis

For the GOG trial, biomarkers will be performed from formalin-fixed paraffin embedded samples. Three panels of biomarkers are proposed.

- First, immunohistochemical expression of hormone receptors (estrogen receptor-alpha, phospho-ERalpha-S167, phospho-ERalpha-S118, estrogen receptor-beta, progesterone receptor-A, progesterone receptor B and the G protein-coupled estrogen receptor, GPR-30) will be quantified.
- Second, immunohistochemical evaluation of components of the mTOR-signaling pathway and related proteins, including phospho- S6rp, PTEN, total and phospho-AKT, and phospho-ERK1/2 will be performed.
- Third, mutational analysis including PTEN, PIK3CA, KRAS, and CTNNB1 will be performed. Mutations in PIK3CA have been demonstrated to be a marker for response to everolimus and letrozole. Mutations in KRAS have been implicated in non-response to everolimus. Using endometrial cancer TCGA data, we have recently identified beta-catenin (CTNNB1) as a predictor of poor outcome for patients with endometrioid endometrial cancer (unpublished data). Hotspot mutations for these genes will be analyzed using a CLIA-certified next-generation sequencing panel including 42 additional cancer-related genes (Singh, 2013*)*. This assay has been validated for use with FFPE samples. In addition, because of the low somatic mutation rate of KRAS we observed in previous phase II trials, it is possible that rather than the KRAS mutation, the KRAS expression level may play a role in response to everolimus. Quantitive PCR analysis of mRNA extracted from patient tissue will be used an alternative method to study KRAS as a biomarker.

ii) Blood collection

We plan to collect pre-treatment blood from patients enrolled in this study. DNA extracted from peripheral blood mononuclear cells (PBMC) can be used as control to identify somatic mutations in tumor tissue samples. Approximately 10ml of blood should be collected at the time of study entry.

2.9 Inclusion of Women and Minorities

The GOG Partners 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 by RECIST version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be greater than or equal to 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or greater than or equal to 20 mm when measured by chest x-ray. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT or MRI (See section 8).

Patients must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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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 chemo-radiotherapy) is permitted.

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

3.15 Performance status must be 0-1.

3.16 Patients must have adequate organ and marrow function as defined below:
NOTE: Institutional/laboratory upper limit of normal = ULN
Institutional/laboratory lower limit of normal = LLN

3.161 Bone marrow function:
- Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl
- Platelets greater than or equal to 100,000 cells/mcl
- Hemoglobin greater than or equal to 9 g/dL

3.162 Renal function:
- Creatinine less than or equal to 1.5 x ULN

3.163 Hepatic function:
- Bilirubin less than or equal to 1.5 x ULN
- ALT *and* AST less than or equal to 3 x ULN
- Alkaline phosphatase less than or equal to 2.5 x ULN

- Albumin greater than or equal to 2.8 g/dL

3.164 Lipid panel:
- Fasting serum cholesterol less than or equal to 300 mg/dL
- Fasting triglycerides less than or equal to 300 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: central venous access catheter placement).

3.18 At least 4 weeks must have elapsed since the patient received any radiation therapy.

3.19 Patients who have met the pre-entry requirements specified in Section 7.0.

3.20 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.21 All patients must be at least 18 years of age

3.22 Patients of childbearing potential must have a negative serum pregnancy test prior to the study entry and be practicing a highly effective form of contraception.

During the study treatment and for 8 weeks after stopping the treatment. Highly effective contraception methods include combination of any two of the following:

a. Use of oral, injected or implanted hormonal methods of contraception or;
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
d. Total abstinence or;
e. Male/female sterilization.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

3.2 Ineligible Patients

3.21 Patients who have previously received everolimus, any another mTOR inhibitor or any agent targeting the PI3K/AKT/mTOR pathway.

3.22 Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus)

3.23 Patients who have previously received hormonal therapy for endometrial cancer.

3.24 Patients with 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.

3.25 Patients receiving chronic treatment with systemic steroids or another immunosuppressive agent.

3.26 Patients with active or uncontrolled systemic infection.

3.27 Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and anti-diabetic treatment must be monitored closely throughout the trial and adjusted as necessary.

3.28 Known severely impaired lung function, including:

- CTCAE grade 2 (or greater) hypoxia (decreased oxygen saturation with exercise [e.g., pulse oximeter <88%]; intermittent supplemental oxygen)

3.29 Patients with a known history of cardiac disease. This includes:

3.291 Uncontrolled hypertension, defined as systolic greater than 150 mm Hg or diastolic greater than 90 mm Hg despite antihypertensive medications.

3.292 Myocardial infarction or unstable angina within 6 months prior to registration.

3.293 New York Heart Association (NYHA) Class II or greater congestive heart failure.

3.294 History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication. This does not include asymptomatic atrial fibrillation with controlled ventricular rate.

3.295 Cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) within 6 months prior to the first date of study therapy.

3.210 Patients who are pregnant or breast-feeding.

3.211 Patients with known central nervous system metastases.

3.212 Patients with known human immunodeficiency virus (HIV) infection.

3.213 Patients with an impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease; uncontrolled nausea, vomiting and/or diarrhea; malabsorption syndrome; clinical signs and symptoms of gastrointestinal obstruction; and/or patients who require parenteral hydration and/or nutrition).

3.214 Patients who plan to receive live attenuated vaccines within 1 week of start of everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

3.215 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder or coagulopathy.

3.216 Patients with history of unprovoked venous thrombosis unless taking anticoagulation treatment for duration of trial.

3.217 Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 30 days prior to dosing.

3.218 Patients must be able to follow concomitant medication restrictions:

- Avoid the use of strong CYP3A/PgP inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole).
- Use caution when co-administered with moderate CYP3A4/PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem).
- Grapefruit, grapefruit juice, and other foods known to inhibit cytochrome P450 and PgP activity may increase everolimus exposures and should be avoided during treatment.
- Avoid the use of concomitant strong CYP3A4/PgP inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital).
- St. John's Wort may decrease everolimus exposure unpredictably and should be avoided.

3.219 Patients with active hepatitis B or C.

Screening for hepatitis B

Prior to randomization/start of everolimus, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBsAg, HBcAb, HBsAb and quantitative hepatitis B DNA PCR (HBV-DNA):

- All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece. [http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm]
- Patients with any of the following risk factors:
  - known or suspected past hepatitis B infection,
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - household contact with hepatitis B infected patient(s),
  - current or prior high-risk sexual activity,
  - body piercing or tattoos,
  - mother known to have hepatitis B
  - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
- Additional patients at the discretion of the investigator

The management guidelines, in Section 6, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos.

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

The management guidelines, in Section 6 are provided according to the results of the baseline assessment of hepatitis C viral load.

4.0 STUDY MODALITIES

4.1 Medroxyprogesterone Acetate (Provera®) (06/25/15)

4.1.1 Formulation: Tablets of 10 mg medroxyprogesterone acetate

4.1.2 Storage: Room temperature protected from heat and light.

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

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

4.2 Tamoxifen Citrate (Nolvadex®)

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.

4.3 Everolimus (Afinitor®) (6/25/15)

4.31 Other Names: RAD001

4.32 Description: Everolimus is a novel oral derivative of rapamycin.

4.33 Investigator Brochure (IB): All participating institutions must obtain an IB. Each site must have an executed CDA (Confidential Disclosure Agreement) or CTSA (Clinical Trial Site Agreement) before the IB can be distributed. Upon execution of a CDA or CTSA, an IB may be requested.

Please submit a request to GOG3007ib@gog.org and include:

- Institution Name
- Institution Number
- Institution Principal Investigator

4.34 Supplier: Everolimus will be supplied by Novartis.

4.35 How Supplied: Everolimus is formulated as tablets for oral administration. For everolimus, each patient is started with 10 mg tablets. Patients who require dose de-escalation will be given 5mg and 2.5mg tablets as needed. Tablets are blister- packed

under aluminum foil in units of 7 tablets, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Refer to label for expiration date and storage conditions.

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of Afinitor Tablets. Wash hands thoroughly before and after preparation of either suspension.

Medication labels will comply with US legal requirements and will be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

4.36 Stability/Storage: Everolimus must be stored below 30◦ C in the original double-side aluminum blister packaging and protected from light and moisture. The expiration date of the supply will be provided with the drug shipment.

4.37 Drug Distribution: Everolimus will be supplied by Novartis Pharmaceuticals and distributed by Fisher Clinical Services.

Novartis must do an initial regulatory review before an initial shipment of everolimus can be shipped to the institution. The GOG Regulatory Department will e-mail the institution-specific 1572, IRB approval, informed consent form (ICF – must match the draft that was reviewed by Novartis prior to IRB submission (see Section 5.0)), PI CV, PI medical license and Pharmacy Information Form to Novartis for review. Please be sure to include the pharmacy shipping address in box 3 of the 1572. Novartis will do a review for accuracy and completeness. **Please allow 10-14 days for this review process before screening your first patient.**

For all subsequent shipments, Novartis will ensure that the institutions' regulatory documents are not expired. If any documents are expired, updated documents must be submitted to GOG and Novartis prior to drug shipment. Please allow 5 days for this review when requesting a subsequent shipment of drug.

4.371 Initial Supply **(02/19/2015)**
To request an initial supply of everolimus, please complete the "Everolimus-RAD001 Drug Order Form" and email to: **john.sabo@novartis.com**

Novartis requires a 10-day window for initial drug delivery to the institution.

Novartis will notify Fisher Clinical Services of when to ship drug. Drug is only shipped Monday through Thursday and any orders received on Fridays will be shipped on Monday. Fisher Clinical Services does not deliver during major holidays.

4.372 Subsequent Supply Requests **(02/19/2015)**
To receive subsequent drug, please complete the "Everolimus-RAD001 Drug Order Form" and email to: **john.sabo@novartis.com**

Novartis requires a 5-day window for subsequent drug delivery to the institution.

Novartis will notify Fisher Clinical Services of when to ship drug. Drug is only shipped Monday through Thursday and any orders received on Fridays will be

shipped on Monday. Fisher Clinical Services does not deliver during major holidays.

4.38 Drug Accountability: All study drug supplies must be kept in a locked room with limited access. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Novartis.

The pharmacist will maintain a complete drug accountability record on the GOG Investigational Agent Drug Accountability Record Form (on GOG-3007 web site) for each capsule strength with lot numbers of each drug received, including the number of bottles dispensed to each patient, the date's drug was dispensed, and the daily dose of everolimus or placebo the patient received. The prescribed dose should also be recorded in the patient's medical records.

4.39 Drug Disposition: All used, unused or expired drug should be destroyed according to the institution's standard operating procedures, and their disposition should be recorded on a GOG Investigational Agent Drug Accountability Record Form.

4.40 Adverse Effects: Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, and diarrhea. Infections have not been notably frequent or severe. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts, hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia.

Stomatitis (grade 3) was the principal DLT in Phase 1 trials.

Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting so that this aspect must be verified when interpreting results.
Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results.

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic.

In oncology studies with everolimus, severe pneumonitis suspected as drug- related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveoloar hemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug- related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting everolimus. Cytology for both the pleural and

pericardial fluids were positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug. Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung.

Serious opportunistic infections have also been reported in cancer patients treated with RAD001: mycobacterium, Aspergillus, and fatal candidal sepsis, and fatal pneumocystis carinii in particular. Because everolimus, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with everolimus must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co- medications. Outcome may be fatal in case of serious infections.

Cytopenias. A reduction in blood cell counts is frequent when everolimus therapy is initiated. Without clinical significance and infrequently, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, everolimus should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug-related thrombocytopenia.

Liver Transaminase Elevation. Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with everolimus in oncology clinical studies, and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminases (AST and ALT) generally appears after four weeks of treatment. In all but a few cases it does not exceed Grade 1 ($\leq$ 2.5 x ULN). Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer. Fatal reactivation of hepatitis B and C have been reported.

Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest of the patients had concurrent morbidities, which might have contributed to the reported events.

Electrolyte Abnormalities. Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with everolimus.

Consult the package insert for the most current and complete information.
Please reference the everolimus Investigator Brochures for complete information regarding adverse effects for everolimus.

4.4 Letrozole (Femara®)

4.41 Description: Letrozole is a highly potent, orally active non-steroidal competitive inhibitor of the aromatase enzyme system.

4.42 Formulation: Tablets of 2.5 mg of letrozole

4.43 Storage: Room temperature protected from heat and light.

4.44 Adverse Effects: The most common side effects are sweating, hot flashes, arthralgia (joint pain), and fatigue. Generally, side effects include signs and symptoms of hypoestrogenism. Dose modifications or cessation of drug because of adverse effects are seldom necessary. See package insert for complete list of adverse effects.

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

4.5 Pathology Requirements

4.51 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.

4.52 Ineligible disease characteristics: Patients with a sarcoma, carcinosarcoma (MMMT), or leiomyosarcoma of the uterine corpus are not eligible.

4.53 Requirements: Pathology report for histologic confirmation of primary tumor. Pathology report for histologic confirmation of recurrent or persistent disease is not required for this protocol. Stained slides to confirm eligibility by Central Pathology Committee Review are not required for this protocol.

4.54 See Section 7.2 and Appendix IV for information and instructions regarding the specimen requirements for Translational Research.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before a patient can be screened and enrolled, each institution must have an executed CTSA and approval of the required regulatory documents.

To obtain regulatory approval, please submit the following regulatory documents to the GOG Administrative Office via e-mail to GOG3007Regulatory@gog.org.

Sites must submit the draft informed consent (initial and amendments) for review by GOG and Novartis prior to IRB submission.

- IRB approval*
- IRB-approved informed consent
- IRB approved site-specific HIPAA consent
- IRB Membership list or FWA assurance letter
- Study-specific signed FDA Form 1572 for institution PI**
- Current CV (signed and dated within two-years) for institution PI
- Medical license for institution PI
- Signed GOG Investigator Signature Page for PI**
- Signed GOG Financial Disclosure Form for all investigators listed on FDA Form 1572**
- Pharmacy Information Form**

Please allow 10-14 days for processing of regulatory documents before screening the first patient. All copies of the above should be filed into a study-specific regulatory binder at your institution.

*All initial, continuing and amendment reviews must be sent to the GOG Administrative Office.

** Please see GOG-3007 protocol documentation page to download forms by clicking on the "Regulatory Forms" link.

The GOG Administrative Office will forward these documents to Novartis for review and approval. Novartis will notify the GOG Administrative Office when the documents have been approved (see Section 4.37).

When an institution has an executed CTSA and has received regulatory approval, an institution will be notified, via e-mail, from GOG, that patients may be screened and enrollment can begin.

5.1 Patient Entry and Registration

This trial is open to U.S. GOG Member Institutions. The GOG Statistical and Data Center (SDC) utilizes a web-based patient registration system (available at the GOG web menu page). When a suitable candidate has been identified for protocol entry, the following steps should be taken:

5.11 An IRB-approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. Current FDA, 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 patient identification number, and date of registration in the appropriate place in their Log Book to document the patient's entry.

5.2 Treatment Plan

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.

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

Study therapy will be randomized between:
Arm 1: Everolimus 10 mg PO daily and Letrozole 2.5 mg PO daily
Arm 2: Tamoxifen 20 mg PO BID; on alternating weeks (even numbered) weeks, medroxyprogesterone acetate 200 mg PO daily with Tamoxifen 20 mg PO BID.

Therapy is to be continued until tumor progression or undue toxicity. Tumor assessments will be performed per Appendix V (excel tool for calculating dates).

See Appendix II for General Chemotherapy Guidelines.

5.3 Everolimus and letrozole administration

5.31 Everolimus will be provided and dispensed by the pharmacy. Letrozole is commercially available and will be prescribed. Study medication will be supplied in an open label fashion. Patients will self-administer the both medications at home.

5.32 Patients will be instructed to take the study medication at an approximately consistent time each day.

5.33 Everolimus is formulated as tablets of 2.5, 5 and 10 mg strength and supplied in blister packs under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Tablets should be taken orally once daily in a fasting state or after no more than a light, fat-free meal. Avoid grapefruit-containing products during the treatment period.

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day.

5.34 Letrozole is formulated as tablets of 2.5 mg and supplied in bottles. The dose of letrozole is one 2.5 mg tablet administered orally once daily. The oral single dose of everolimus should be taken together with the daily dose of letrozole 2.5 mg.

5.35 The use of a patient pill calendar (See Appendix III) during study therapy will be utilized by the patient and the treating clinic to help promote and monitor compliance with everolimus and letrozole.

5.4 Tamoxifen and medroxyprogesterone acetate administration

5.41 Tamoxifen and medroxyprogesterone acetate are commercially available and will be prescribed. Patients will self-administer both medications at home.

5.42 Patients will be instructed to take the study medication at an approximately consistent time each day.

5.43 Tamoxifen is formulated as tablets of 20 mg strength and supplied in bottles.

5.44 Medroxyprogesterone acetate is formulated in tablets of 10 mg strength and supplied in bottles. The dose of medroxyprogesterone acetate is 20, 10 mg tablets (200mg total) administered orally once daily. (6/25/15)

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

6.0 TREATMENT MODIFICATIONS

Toxicity will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

6.1 Tamoxifen/ medroxyprogesterone acetate

There are no dose modifications for the tamoxifen/ medroxyprogesterone 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) until they are ambulatory again. Suspected severe and unusual toxicities from either agent (e.g. hives from tamoxifen) should be discussed with the study chair.

6.2 Everolimus/Letrozole

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Details of study treatment schedule adjustments and dose levels are provided in Table 6-1.

Table 6-1. Dose Levels

Dose level	**-2**	**-1**	**0**
Everolimus	**2.5 mg daily**	**5 mg daily**	**10 mg daily**
Letrozole	**Not applicable**	**Not applicable**	**2.5 mg daily**

6.21 **Algorithm for interpretation and dose modification due to suspected treatment related toxicity:**

Table 6-2. Dosing guidelines for everolimus-related non-hematologic toxicities

Toxicity	**Action**
Non-Infectious Pneumonitis	Please refer to 6-4
Reactivation of HBV or HCV flare	Please refer to Table 6-6 and Table 6-7
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)* Recurrence of grade 4 after dose reduction or toxicity requiring everolimus interruption for > 28 days	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes > 7 days, discontinue everolimus. Discontinue everolimus.
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 6.2.2.5)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study treatment if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other grade 4	Hold everolimus until recovery to grade ≤ 1 or baseline value Reintroduce everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue everolimus
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation.
Recurrence of grade 4 after dose reduction	Discontinue everolimus
Any non-hematologic toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus
* Should HCV flare be confirmed, the guidelines for flare must take precedence(Table 6-7)	

Table 6-3. Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	**Action**
Grade 2 thrombocytopenia (platelets <75, ≥ 50x109/L)	No action
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x109/L)	Interrupt everolimus until recovery to grade ≤ 1. Then reintroduce everolimus at one dose level lower, if available.
Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x109/L)	Interrupt everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Interrupt everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.*
Febrile neutropenia (grade≥2)	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued.
***Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction**	**Discontinue everolimus**
***Any hematologic toxicity requiring everolimus interruption for > 28 days**	**Discontinue everolimus**

If discontinuation of everolimus is required, patients should continue on single agent letrozole until progression or unacceptable toxicity.

6.22 Management of specific toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are stomatitis, rash, diarrhea, fatigue, infections, asthenia, nausea, peripheral edema, decreased appetite, headache, dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting, pruritus, cough, dyspnea, dry skin, nail disorder, and pyrexia. . Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters

including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia).; increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium.. The majority of these AEs have been of mild to moderate severity (CTCAE grade 1-2).

6.221 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus Some of these infections have been severe (e.g., leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Cases of pneumocystis jiroveci pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

6.222 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.223 Management of Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

6.224 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

6.224 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should

be monitored particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

6.225 Management of stomatitis / oral mucositis / mouth ulcers

Adverse Drug Reaction	**Severity**	**Everolimus Dose Adjustment and Management Recommendations**
Stomatitis	Grade 1 (Minimal symptoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day until resolution.
	Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
	Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*
	Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue everolimus and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis is discouraged as they may worsen mouth ulcers.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastro esophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. These agents should be avoided. Antifungal agents should be avoided unless a fungal infection is diagnosed. In

particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6.226 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

6.227 Management of hyperlipidemia and hyperglycemia

Adverse Drug Reaction	**Severity**	**Everolimus Dose Adjustment and Management Recommendations**
Metabolic events (e.g., hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate everolimus at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue everolimus and treat with appropriate medical therapy.

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>300 mg/dl or 3.42 mmol/L should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatinine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on everolimus.

6.228 Management of non-infectious pneumonitis`

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in

patients taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration.
If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt Afinitor until resolution to less than or equal to grade 1. Afinitor may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of Afinitor. For cases of grade 4 non-infectious pneumonitis, Afinitor therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jiroveci pneumonia (PJP) may be considered. The two compounds studied most extensively for prophylaxis against PJP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

If non-infectious pneumonitis develops, the guidelines in Table 6-4 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 6-4. Management of non-infectious pneumonitis

Worst grade pneumonitis	**Suggested investigations**	**Management of pneumonitis**	**Everolimus dose adjustment**
Grade 1 (Asymptomatic, radiologic findings only)	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 3 (Symptomatic, interfering with Activities of Daily Living, O2 indicated)	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt Everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating Everolimus at one dose level lower (approximately 50% lower than the dose previously administered depending on individual clinical circumstances) Discontinue Everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation
Grade 4 (Life threatening, ventilatory support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue everolimus.

6.229 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been

seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6-5 provides detail of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 6-5. Action to be taken based on screening hepatitis B results

Test	**Result**	**Result**	**Result**	**Result**	**Result**
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of everolimus Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of everolimus. For HBV reactivation definition and management guidelines, see Table 6-6.

Table 6-6 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA **OR** positive HBsAg ---------- **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	**Treat**: Start a second antiviral medication AND Interrupt everolimus administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days**, everolimus should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days** Patients should discontinue everolimus but continue both antiviral therapies at least 4 weeks after last dose of everolimus.
For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** **[**Positive HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb**]** ---------- **Reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat :** Start first antiviral medication AND **Interrupt** everolimus administration until resolution: • ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days**, everolimus should be re-started at one dose lower, if available (see 6-1 for dose levels available). If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days** Patients should discontinue everolimus but continue antiviral therapy at least 4 weeks after last dose of everolimus.
* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.	

Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 4–8 weeks for HCV flare:

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')
- For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 6-7.

Table 6-7 Guidelines for the management of hepatitis C flare

Baseline results	**HCV flare definition***	**HCV flare management**
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus
* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).		

6.230 Hepatic impairment dose modifications

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 5 mg daily.
- Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.
- Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.
- Afinitor is not recommended for patients with hepatic impairment who require doses below 2 mg every other day or 2.5 every other day. Everolimus exposure was increased in patients with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment (see Section 5.2.3). Everolimus is not recommended for use in postmenopausal women with hormone receptor positive advanced breast cancer, or in patients with advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin or advanced renal cell carcinoma with severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk.

6.231 Special Populations

Geriatrics (≥ 65 years):

No dosage adjustment is required.

Renal impairment:

No dosage adjustment is required.

Ethnicity:

Pharmacokinetic characteristics are similar for Caucasian and Japanese subjects. Pharmacokinetic studies in Black transplant patients have shown an average 20% higher clearance.

6.232 Concomitant therapy
Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be recorded.

Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates
Co-administration with strong inhibitors of CYP3A4 or PgP should be avoided; and may cause increased everolimus concentrations. For a current table of Substrates, Inhibitors and Inducers please access the following website:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus by approximately 50%. . Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.
- Grapefruit, Seville oranges and star fruit juices effect P450 and PgP activity. Concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of everolimus (based on pharmacokinetic data), using increments of 5 mg or less. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 6-8 listing relevant inducers and inhibitors of CYP3A and Table 6-9 for a list of relevant substrates, inducers, and inhibitors of PgP.

Everolimus and drugs influencing CYP3A4 enzyme
Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Refer to Table 6-2 in section 6 for a comprehensive list of inducers and inhibitors of CYP3A4 and Table 6-3]for a list of relevant

substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins).

Table 6-8. Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
Moderate inducers: bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir
Weak inducers: amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine
Inhibitors
Strong inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole
Moderate inhibitors: Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil

Table 6-9. Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Vaccinations
Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

7.0 STUDY PARAMETERS

Assessments	Pre-Therapy	Prior to Each Cycle	Every other Cycle	Every 8 weeks x 2, then every 12 weeks	Off All Study Therapy
Medical history & Physical	1	X			
Review of Medications **	1	X			
Vital Status					2
Vital signs	1	X			
Pulse oximeter	1				
Weight	1	X			
Performance Status	1	X			
Toxicity Assessment	1	X			2, 4
CBC with differential and platelets	3	5			
Electrolytes, glucose, BUN, Creatinine	3	5			
Bilirubin, AST, ALT, Alkaline Phosphatase, Albumin	3	5			
Fasting Lipid panel	1		5		
HbA1C	1				
HBV-DNA	8				
HBsAg	8				
HBcAb	8				
HBsAb	8				
HCV RNA-PCR	9				
Pregnancy Test (if childbearing potential exists)	3				
Chest imaging (x-ray or CT of chest)	1			6	6
CT of abdomen and pelvis	1				
Radiographic tumor measurement	1			7	7
ECG	1				

ONE CYCLE = 28 days

Notes:

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Follow-up every 3 months from the last dose of study drug (+/- 2 weeks) for 2 years and then every 6 months (+/- 2 weeks) for 3 years. Follow-up forms (Form Q) are collected for the 5-year follow-up period or until study termination.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Report all adverse events that occur within 30 days of last protocol treatment on the T form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 10.1.
5. Labs must be obtained within 4 days of re-treatment with protocol therapy.
6. Repeat chest imaging every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) x 2; then every 12 weeks (+/- 7 days) thereafter, if required to monitor tumor response; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. A tool is provided to calculate dates of re-imaging (Appendix V).
7. CT scan or MRI of the abdomen and pelvis if used to follow lesion for measurable disease every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) x 2; then every 12 weeks (+/- 7 days) thereafter until disease progression is confirmed; also repeat at any other time if

clinically indicated based on symptoms or physical signs suggestive of progressive disease. A tool is provided to calculate dates of re-imaging (Appendix V).

8. Hepatitis B Virus testing: Prior to randomization, the categories of patients listed in Section 3.215 should be tested for hepatitis B serologic markers and viral load: HBV-DNA, HBsAg, HBcAb, and HBsAb. HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Tables 6-5 and 6-6.
9. Hepatitis C Virus testing: Patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be tested for HCV RNA-PCR test at baseline. For a list of hepatitis C risk factors, refer to Section 3.215. Patients with detectable HCV RNA-PCR (determined at baseline) and patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered "cured") should be monitored every 4 weeks for HCV reactivation. See Table 6-7.

** Whether or not patient is taking metformin should be noted and if she starts to take it while on protocol that should be noted as well.

7.2 Pathology Requirements

7.21 Pathology report for histologic confirmation of primary tumor.

7.22 Pathology report for histologic confirmation of recurrent or persistent disease is not required for this protocol.

7.3 Translational Research

7.31 Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions are required to submit the patient's translational research specimens as outlined below (unless otherwise specified).

A detailed description of the translational research specimen procedures can be found in Appendix IV.

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *(Preferred FFPE)*	Biopathology Center within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *(Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FPP01, or FPM01 is submitted)*	

FFPE **Persistent Primary** Tumor (**FPP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPM01 is submitted)*	
FFPE **Persistent Metastatic** Tumor (**FPM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted)*	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	Biopathology Center the day the specimen is collected[1]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the Biopathology Center.

1 Biopathology Center / Protocol GOG-3007, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

7.32 Laboratory Testing

7.321 Hormone Receptor Immunohistochemistry

Unstained sections of formalin-fixed, paraffin-embedded (FFPE) tumor will be used for hormone receptor (e.g., estrogen receptor [ER]-alpha, ER-beta, progesterone receptor [PR]-alpha, PR-beta, G protein-coupled ER [GPR-30]) immunohistochemistry (IHC).

7.322 mTOR Pathway Immunohistochemistry

Unstained sections of FFPE tumor will be used for mTOR pathway (e.g., phosphorylated S6 ribosomal protein, PTEN, total and phosphorylated AKT, total and phosphorylated mTOR, phosphor-ERK1/2) IHC.

7.323 Mutation Analysis

Unstained sections and DNA extracted from whole blood will be used for mutational analysis (e.g., PTEN, PIK3CA, KRAS, CTNNB1 [beta-catenin]).

7.33 Future Research

Details regarding the banking and use of translational research specimens for future research can be found in Appendix IV.

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eisenhauer, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.11 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated

and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.12 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In

addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. **For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.**

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A "positive" FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases, e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.13 Response Criteria

Determination of response should take into consideration all target (See 8.131) and non-target lesions (See 8.132) and, if appropriate, biomarkers (See 8.133).

8.131 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.132 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)
Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.133 Evaluation of Biomarkers

Biomarker measurements are not used to determine response or progression on this study.

8.134 Evaluation of Best Overall (unconfirmed) Response

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions		New Lesions*	Time Point Response
CR	CR		No	CR
CR	Non-CR/Non-PD		No	PR
CR	NE		No	PR
PR	Non-PD or NE		No	PR
SD	Non-PD or NE		No	SD
NE	Non-PD		No	NE
PD	Any		Yes or No	PD
Any	PD**		Yes or No	PD
Any	Any		Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions		New Lesions*	Time Point Response
CR		No	CR
CR		No	Non-CR/non-PD*
Non-CR/non-PD		No	Non-CR/non-PD*
NE		No	NE
Unequivocal PD		Yes or No	PD
Any		Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.135 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*

CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8.14 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since date of study entry, including the baseline measurements.

8.15 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.16 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

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 withdraws consent for 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 If patient comes off study treatment prior to progression, continue tumor measurements and radiologic evaluations on schedule until progression or initiation of a subsequent cancer therapy. Toxicity assessments will be continued until resolution or return to baseline. Patients will be followed after last drug dose until toxicity resolution or return to baseline, until progression if patient withdraws before progressive disease, or until study withdrawal if it occurs before this time.

9.3 All patients will be treated (with completion of all required case report forms) until disease progression or study withdrawal. Patients will then be followed every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Follow-Up Forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. Follow-Up Forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.

9.4 A patient is considered off study therapy when the patient has progressed or died, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Report all treatment received on Cycle Drug Information Forms and adverse events on Adverse Event Forms up until the patient qualifies as being off study therapy.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

Sponsor: GOG

10.1 ADVERSE EVENT REPORTING

10.11 Definitions

10.111 Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

10.112 Suspected Adverse Reaction (SAR): Adverse event for which there is a reasonable possibility that the investigational drug caused the adverse event (i.e., attribution to study drug of possible, probable, or definite).

10.113 Serious Adverse Event (SAE): An adverse event or suspected adverse reaction is considered "serious" if in the view of either the Investigator or sponsor, it results in any of the following outcomes:

1) Death,
2) A life-threatening adverse event,
3) Inpatient hospitalization or prolongation or existing hospitalization,
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
5) A congenital anomaly/birth defect.
6) Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.114 Unexpected Adverse Event: An adverse event is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

10.12 Reporting Requirements: All investigators and ultimately the protocol Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the study drug. It is the responsibility of the investigator to supply the medical documentation needed to support expedited AE reports in a timely manner. Investigators **MUST** immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is reasonable possibility that the drug caused the event (21 CFR 312.64(b)). Please refer to Section 10.15 for reporting procedures.

Information regarding AEs and SAEs will be collected from the time of the first dose of study drug until 30 days from the last dose administered.

When possible, adverse events should be described in terms of a change in the baseline status or with a diagnosis or summary term rather than as individual symptoms.

The Investigator is responsible for reporting SAEs to the appropriate Institutional Review Board (IRB) or other committees in accordance with local institutional and IRB policies.

10.13 Criteria for Determining Adverse Event Severity: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

10.14 Criteria for Determining Adverse Event Causality: The following attribution categories will be used in assessing the relationship between the AE and the study drug:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

10.15 Procedures for SAE Reporting: The investigator must report to GOG any serious adverse event, including pregnancy, whether or not considered drug-related, within 24 hours of any site personnel becoming aware of the event.

All SAE reports (both initial and follow-up) are to be submitted using the GOG SAE Portal within SEDES. Instructions for using the GOG SAE Portal can be found at (GOG username and password is required): https://gogmember.gog.org/gog/sae_portal/using%20the%20sae%20portal%20-%20site%20user.pdf

The GOG Regulatory Compliance Department will forward all SAE reports to usdrugsafety.operations@novartis.com within 24 hours of first awareness.

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 report should be submitted via postal mail. The Upload feature in SEDES is an alternate method for submitting Pathology reports.**

Form±	Due within		Copies*	Comments
	Weeks	Event		
Form R (Registration Form)	2	Registration	N/A	Mandatory Submission via SEDES
Specimen Consent	1	Registration	N/A	Mandatory Submission via SEDES
Form OSR (Recurrent Gynecologic Cancer On-Study Form)	2	Registration	N/A	Mandatory Submission via SEDES
Form DR (Pre-Treatment Summary Form)	2	Registration	N/A	Mandatory Submission via SEDES
Form CONM (Concomitant Medication Form) - baseline	2	Registration	N/A	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) - baseline	2	Registration	N/A	Mandatory Submission via SEDES
Primary/Advanced Disease: Pathology Report** Persistent or Recurrent Disease: Pathology Report (only if histologically documented)	6 6	Registration Registration	1 1	Submit pathology reports via postal mail to SDC in Buffalo, New York or via report uploader
Form D2R_TREAT (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	N/A	Mandatory Submission via SEDES
Form LABSPG1 (Labs and Chemistries Form Page 1)	2	Completion of each cycle of therapy	N/A	Mandatory Submission via SEDES
Form LABSPG2 (Labs and Chemistries Form Page 2)	2	Completion of each cycle of therapy	N/A	Mandatory Submission via SEDES
Form VITALSV2 (Vital Signs Form)	2	Completion of each cycle of therapy	N/A	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	Tumor response or progression assessment	N/A	Mandatory Submission via SEDES
Form TR-FP01-3007*** FFPE primary tumor	8	Registration	N/A	Mandatory submission via SEDES*f*
Form TR-FM01-3007*** FFPE metastatic tumor (optional)	8	Registration	N/A	Mandatory submission via SEDES*f*
Form TR-FRP01-3007*** FFPE recurrent primary tumor (optional)	8	Registration	N/A	Mandatory submission via SEDES*f*
Form TR-FRM01-3007*** FFPE recurrent metastatic tumor (optional)	8	Registration	N/A	Mandatory submission via SEDES*f*
Form TR-FPP01-3007*** FFPE persistent primary tumor (optional)	8	Registration	N/A	Mandatory submission via SEDES*f*

Form TR-FPM01-3007*** FFPE persistent metastatic tumor (optional)	8	Registration	N/A	Mandatory submission via SEDES*f*
Form TR-WB01-3007 whole blood	26	Registration	N/A	Mandatory submission via SEDES*f*
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle	N/A	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	N/A	Mandatory Submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up; change in treatment	N/A	Submit via SEDES quarterly for 2 years, semi-annually for 3 more years, annually thereafter

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

** Pathology slides for central Pathology Committee review are not required on this study.

*** A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the Biopathology Center.

f Form TR must be submitted regardless of whether the specimen is submitted for research.

This study utilizes the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) for defining and grading adverse events to be reported on GOG case report forms.

11.0 STATISTICAL CONSIDERATIONS (06/25/15)

Overview, Study Registration and Randomization: This study is a single 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. 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 any chemoradiation for treatment of endometrial cancer and 2) Patients who have never received adjuvant chemotherapy or chemoradiation for treatment of endometrial cancer. 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 and sizes/status of target and non-target lesions, tumor grade, histological cell type and estrogen 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, regardless of attribution, in patients who received any amount of study drug categorized and graded according to CTCAE v4.0.
- 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 the G protein-coupled estrogen receptor, GPR-30, phosphorylated S6rp, PTEN, total and phosphorylated AKT, total and phosphorylated mTOR, mutational analysis for PTEN, PIK3CA and K-ras, and mutational analysis of K-ras in circulating tumor cells

11.2 **Accrual Rate:** 5 per month based on accrual to GOG-0248

11.3 **Study Design and Sample Size:** This study will implement a single stage stratified statistical design. There is no planned statistical test to compare the regimens with respect to response.

Hormonal agents studied by the GOG have yielded response rates ranging from 11% to 33% in chemo-naïve patients. 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.

Response rates are expected to differ based on a history of previous chemotherapy (alone or in combination with radiation) for endometrial carcinoma. Patients with or without a history of chemotherapy or chemoradiation are eligible for this study.

Fifty-five percent of patients enrolled on GOG-0248 in 2010-2011 had received adjuvant chemotherapy. The increasing use of adjuvant chemotherapy for endometrial carcinoma suggests 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 conditional stratified phase II trial as proposed by London and Chang 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 can be found with:

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

Where *i* indexes the number of important stratification levels under consideration and *j* indexes the stage of accrual, in this case there is only one stage. 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 been treated with chemotherapy whereas stratum 2 will correspond with those patients who have never 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: $p_1 = 0.10$ and $p_2 = 0.20$. Under the alternative hypothesis of H_1: $p_1 = 0.30$ and $p_2 = 0.40$, the following design will limit the probability of type I error to 0.06 and type II to 0.10. According to London and Chang[A], the rejection boundary, a_1, is found with the following equation:

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

where $p_{10} = 0.20$, $\Delta_1 = 0.20$, $p_{20} = 0.10$, $\Delta_2 = 0.20$, and $\gamma\beta$ is the probability of a type II error. Since it is important to maintain the original design parameters for this study, a_1 is found with

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

The cumulative targeted accrual will be set at 36 patients for each treatment arm or a total of 72 patients. Each regimen will be assessed separately. 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 α is the probability of a type I error, and β is the probability of a type II error:

Table 11.1 Rejection boundaries for various scenarios for an individual treatment arm

Proportion in stratum 1	Proportion in stratum 2	Number in stratum 1	Number in stratum 2	Sample Size	Rejection boundary a_1	α	1- β
0.4	0.6	15	22	37	9	.058	.907
0.5	0.5	19	19	38	9	.048	.906
0.6	**0.4**	**22**	**14**	**36**	**8**	**.052**	**.908**
0.7	0.3	26	11	37	8	.042	.906
0.8	0.2	28	7	35	7	.050	.914

Proportion in stratum 1	Proportion in stratum 2	Number in stratum 1	Number in stratum 2	Sample Size	Rejection boundary a_1	α	1- β
0.9	0.1	29	3	32	6	.053	.907

If the number of responses reported for an individual regimen is less than the value in the column labeled as "Rejection Boundary a1" then the regimen will be deemed unworthy of further investigation.

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

Table 11.2 Operating characteristics

π_A	π_B	Pr(neither A nor B are deemed active $\|\pi_A, \pi_B$)	Pr(both A and B are deemed active $\|\pi_A, \pi_B$)	Pr(A is deemed active and B is not deemed active$\|\pi_A, \pi_B$)	Pr(B is deemed active and A is not deemed active$\|\pi_A, \pi_B$)
0.1,0.2	0.1,0.2	0.899	0.003	0.049	0.049
0.1,0.2	0.3,0.4	0.087	0.047	0.005	0.861
0.1,0.2	0.4,0.5	0.006	0.052	<0.001	0.942
0.3,0.4	0.1,0.2	0.087	0.047	0.861	0.005
0.3,0.4	0.3,0.4	0.008	0.824	0.084	0.084
0.3,0.4	0.4,0.5	<0.001	0.903	0.005	0.091
0.4,0.5	0.1,0.2	0.006	0.052	0.942	<0.001
0.4,0.5	0.3,0.4	<0.001	0.903	0.091	0.005
0.4,0.5	0.4,0.5	<0.001	0.988	0.006	0.006

π_A =probabilities of response on regimen A (stratum 2, stratum 1);
π_B =probabilities of response on regimen 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.

95% Confidence intervals for proportion responding to each regimen will be calculated.

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 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 Safety Review Committee (SRC) in conjunction with each semi-annual Group meeting.

All reports of serious and/or unexpected adverse 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 17 months. An additional 6-18 months may be necessary for data maturity, laboratory and statistical analysis.

11.6 **Secondary Objectives:** Progression-free survival (PFS) will be estimated using the Kaplan-Meier product limit estimator and graphed by treatment arm. Median PFS will be reported with a 95% confidence interval for each treatment arm. The frequency and severity of adverse events will be tabulated without regard to attribution by treatment arm using adverse event terms and grades defined in CTCAE version 4.

11.7 **Translational Research Analysis:**

The expression of candidate markers will be determined by standard semi-quantitative methods for IHC evaluation of hormone receptors (estrogen receptor-alpha, estrogen receptor-beta, progesterone receptor-A, progesterone receptor B and the G protein-coupled estrogen receptor, GPR-30) and components of the mTOR signaling pathway (phosphorylated S6rp, as well as PTEN, total and phosphorylated AKT, phospho-ERK1/2). Additionally, mutational analysis, including PTEN, PIK3CA, KRAS, and CTNNB1 will be performed. 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 and 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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APPENDIX I - Clinical Staging (FIGO)

CARCINOMA OF THE ENDOMETRIUM
FIGO CLASSIFICATION
2009

Stage I*	Tumor confined to the corpus uteri.
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae[#]
IIIB*	Vaginal and/or parametrial involvement[#]
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes[#]
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

*Either G1, G2, or G3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#]Positive cytology has to be reported separately without changing the stage.

APPENDIX II - General Chemotherapy Guidelines

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
  Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

APPENDIX III - PATIENT PILL CALENDAR: ARM I

Patient Name: _____Date of first dose on calendar: _____
Patient Study ID: _____ Cycle #:_____

- Complete one form for each cycle of treatment
- You will take Letrozole and Everolimus once a day
- Please bring this form and your bottles of Letrozole and Everolimus each time you return for an appointment

Day	Date	Time of Letrozole Dose	Dose taken	Time of Everolimus Dose	Dose taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
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26						
27						
28						

APPENDIX III - PATIENT PILL CALENDAR: ARM II

Patient Name: _____ Date of first dose on calendar: _____
Patient Study ID: _____ Cycle #:_____

- Complete one form for each cycle of treatment
- You will take Tamoxifen (20 mg) twice a day
- On alternating weeks (even numbered weeks) you will take Medroxyprogesterone Acetate (200 mg) once daily with Tamoxifen (20 mg) twice a day
- Please bring this form and your bottles of Tamoxifen and Medroxyprogesterone each time you return for an appointment

Day	Date	Time of Tamoxifen Dose AM	Time of Tamoxifen Dose PM	Dose taken	Time of Medroxyprogesterone Dose	Dose taken	Comments
1					[redacted]		
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15					[redacted]		
16							
17							
18							
19							
20							
21							
22							
23							
24							
25							
26							
27							
28							

APPENDIX IV - Translational Research Specimen Procedures (03/10/2015)

I. Summary of Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions are required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimen (Specimen Code)	Collection Time Point	Ship To
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *(Preferred FFPE)*	Biopathology Center within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to all treatment *(Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FPP01, or FPM01 is submitted)*	
FFPE **Persistent Primary** Tumor (**FPP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPM01 is submitted)*	
FFPE **Persistent Metastatic** Tumor (**FPM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (10 charged, 5µm & 10 uncharged, 10µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted)*	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	Biopathology Center the day the specimen is collected[1]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the Biopathology Center.

1 Biopathology Center / Protocol GOG-3007, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

II. Obtaining a Biopathology Center Number for Translational Research Specimens

Only one GOG **F**oundation BPC # (# # # # - # # - **F** # # #) is assigned per patient. **Note: GOG Foundation BPC # includes the letter "F."** All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A BPC # can be obtained online via the Tissue Bank Portal (under Tools on the Web Menu page).

Obtain the patient's study ID before requesting a BPC # from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous** study ID **when registering.**

Please contact Support if you need assistance or have assigned more than one BPC # to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

III. Requesting Translational Research Specimen Kits

Kits are not provided for this protocol. A pre-paid FedEx air bill is provided for the submission of whole blood.

IV. Labeling Translational Research Specimens

A waterproof permanent marker or printed label should be used to label each translational research specimen with:

BPC # (# # # # - # # - **F** # # #) **Note: GOG Foundation BPC # includes the letter "F."**
GOG protocol number (GOG-3007)
specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent). **Primary** and **metastatic** tumor should be collected prior to all treatment. **Recurrent** and **persistent** tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary** or **persistent primary**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic** or **persistent metastatic**, respectively. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (10 charged, 5µm and 10 uncharged, 10 µm) should be submitted. All tissue sections should be cut sequentially from the same block.

The type of specimen (block or slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.

2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.

3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the Biopathology Center the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

VII. Submitting Form TR

Form TR must be submitted via SEDES for each required specimen regardless of whether the specimen is submitted for research.

A copy of the SEDES-completed Form TR must accompany each specimen shipped to the Biopathology Center (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent if the specimen is not collected.

Retain a printout of the completed form for your records.

Please contact Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

VIII. Shipping Translational Research Specimens

A SEDES-completed copy of Form TR must be included for each translational research specimen.

A. FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

Biopathology Center / Protocol GOG-3007
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood

Whole blood specimens should be shipped to the Biopathology Center (address above).

Whole blood specimens can be shipped to the Biopathology Center **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the Biopathology Center at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).

5. Insert a copy of Form SP for each specimen.

6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

IX. Distributing Translational Research Specimens

The GOG Statistical and Data Center and Biopathology Center (or alternate laboratory) will coordinate the distribution of specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring laboratory data to the statistics center.

At the discretion of the Committee on Experimental Medicine Chair and Director of the Biopathology Center, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the Biopathology Center.

A. FFPE

FFPE will be batch shipped upon trial completion to:

Dr. Karen Lu
ATTN: Joseph Celestino
MD Anderson Cancer Center
Gyn Onc & Reproductive Med-Rsch
1515 Holcombe Blvd.
Houston, TX 77030
Phone: 713-745-8902
Email: khlu@mdanderson.org

B. Whole Blood

The Biopathology Center will extract DNA form whole blood. Aliquots of DNA will be batch shipped upon trial completion to Dr. Karen Lu (address above).

X. Banking Translational Research Specimens for Future Research

Specimens will remain in the Biopathology Center and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via the specimen consent form. At the time of specimen selection for project distribution, the most recent consent information will be used.

Institutions can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the Biopathology Center will destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the institution's expense.

APPENDIX V – CT Scan Date Calculator

Please refer to separate spreadsheet for CT Scan Date Calculator.