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A Phase II, Single-Arm Study of RAD001 (Everolimus), Letrozole, and Metformin in Patients with Advanced or Recurrent Endometrial Carcinoma

RAD001CUS195T

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List of abbreviations

4E-BP1	4E-binding protein
Ab	Antibodies
ADR	Adverse Drug Reaction
AE	adverse event
ANC	Absolute neutrophil count
ALT/SGPT	alanine aminotransferase/glutamic pyruvic transaminase/Serum glutamic-pyruvic transaminase
AST/SGOT	aspartate aminotransferase/glutamic oxaloacetic transaminase/Serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma-concentration time curve
BAC	Bronchoalveolar carcinoma
BUN	Blood urea nitrogen
Cmax	Maximum plasma concentration
CR	Complete Response/Complete Remission
CRF	Case report/Record form
CRO	Contract Research Organization
CT	Computer tomography
CTC	Common toxicity criteria
CV	Coefficient of Variation
CYP3A4	CytochromeP450 3A4 isoenzyme
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety and Epidimology
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EGF	Epidermal growth factor

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EGFR	Epidermal growth factor receptor
eIF-4E	Eucariotic Initiation Factor 4E
EPR	Early progression rate
EU	European Union
FDG-PET	Fluorine-18-2-fluoro-Deoxy-D-Glucose Positron Emission Tomography
FKBP-12	FK506-binding protein 12
GF	Growth factor
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibodies
HBs Ab	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL	High-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
LDL	Low-density lypoproteins
LFTs	liver function tests
LLOQ	Lower limit of quantification
MAPK	Mitogen Activated Protein Kinase
mRNA	messenger Ribonucleic acid
mTOR	mammalian Target of Rapamycin
NIH/NCI	National Institutes of Health/National Cancer Institute
nM	nano-molar
NSCLC	Non-small cell lung cancer
OS	overall survival
P-AKT	phosphor-AKT
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PET	Proton emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PK/PD model	Pharmacokinetic/pharmacodynamic model

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PT/PTT	prothrombin time
PTEN	Phosphatase and Tensin homolog deleted on chromosome 10
RBC	red blood cell count
REB	Research Ethics Board
RNA	Ribonucleic acid
RR	response rate
RT	Radiation therapy
S6K1	S6 kinase 1
SAE	serious adverse event
s.c.	subcutaneous
SCLC	Small cell lung cancer
STAT3	Signal Transducer and Activator of Transcription 3
TK	Tyrosine kinase
TSC2	Tuberous Sclerosis Complex 2
TUNNEL	Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin Nick End Labeling
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	total white blood cell count
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	For efficacy evaluations, the baseline assessment will be the last available assessment before or on the date of randomization. For safety evaluations (i.e. laboratory assessments and vital signs), the baseline assessment will be the last available assessment before or on the start date of study treatment. The value obtained at baseline assessments, referred to as “baseline value” will be used as reference for the patient.

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Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival

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Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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1 Introduction

1.1 Endometrial Cancer

1.1.1 Epidemiology

Endometrial cancer is the most common gynecologic malignancy in the United States. An estimated 46,470 women will have been diagnosed with uterine cancer in 2011, and it is estimated that 8,120 of these women will die of the disease (Siegel, et al. 2011). Endometrial adenocarcinoma is most frequently diagnosed in women between the ages of 50 and 65 years. Women have an overall lifetime risk of 2.53% (1 in 40) of developing endometrial cancer (Jemal, et al. 2010). Of the endometrial carcinomas, 80% are endometrioid adenocarcinomas and 15-20% are more rare subtypes: papillary serous, clear cell, mucinous, or mixed carcinomas (Prat, 2004). While the majority of women are diagnosed at an early stage and are often cured, patients with advanced or recurrent disease continue to have a poor long-term prognosis.

1.1.2 Endometrial Cancer Biology

Based on epidemiological, molecular, and prognostic factors, endometrial cancer can be subdivided broadly into two types. Type I carcinomas account for approximately 80% of cases and are classically of endometrioid histology. Type II carcinomas are often of non-endometrioid histology (serous and clear cell) and typically arise in a background of atrophic endometrium. These lesions appear to be unrelated to estrogen stimulation and have a worse prognosis.

Type I and type II lesions exhibit distinct molecular alterations. The most frequent genetic alteration associated with type I lesions is a loss of function of the tumor suppressor PTEN. In contrast, PTEN inactivation is uncommon in Type II lesions. PTEN loss of function can be seen in up to 83% of endometrioid carcinomas and 55% of precancerous lesions (Mutter, et al. 2000). Mutations in PTEN have been documented in endometrial hyperplasia with and without atypia and, thus, have been postulated to be an early event in the endometrial tumorigenesis process (Maxwell, et al. 1998). In addition to PTEN gene mutations, PTEN inactivation may also occur as a result of epigenetic silencing through promoter hypermethylation. PTEN most notably plays a role in the regulation of the phosphatidylinositol 3-kinase (PI3K)/AKT pathway by inhibiting the downstream phosphorylation of AKT. Recent studies have identified AKT as a potential mediator of tumorigenesis in endometrial cancer cell lines through the upregulation of signaling through mammalian target of rapamycin (mTOR) which is downstream of AKT and is involved in cellular proliferation and

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mRNA translation. Thus, the PI3K-AKT-mTOR pathway is a logical target in the treatment of endometrial cancer.

1.1.3 Endometrial Cancer Treatment

Advanced stage endometrial cancer is treated primarily with surgical resection, when feasible, and chemotherapy. Radiation therapy has a role in local control and in treating patients with positive lymph nodes. However, long-term outcomes in patients with advanced, recurrent endometrial cancer remain poor. There have been several randomized studies in this group of patients in an attempt to identify optimal therapy. In a randomized prospective study of 281 patients, comparing doxorubin and cisplatin (AP) with doxorubicin alone, the combination regimen produced an overall response rate that was significantly higher than doxorubicin alone (42% vs 25%, p=0.004) (Thigpen, et al. 2004). However, there was no significant difference in overall survival and increased response rates were at the expense of greater toxicities. Later, in GOG-177 a three drug regimen of paclitaxel, doxorubicin, and cisplatin (TAP) was shown to significantly improve the objective response rate (57% vs 35%, p<0.01), PFS (median 8.3 vs 5.3 months, p<0.01), and OS (median 15.3 vs 12.3 months, p =0.037) when compared with AP in patients with Stage III-IV recurrent endometrial cancer (Fleming, et al. 2004). However, the improved response came at the expense of worse grade 3 neurotoxicity (12% vs 1%). The GOG has recently completed accrual to a phase III trial comparing TAP to the more tolerable regimen of carboplatin and paclitaxel. Despite improvements in response rates, more effective systemic agents with longer response durations and improved tolerability are needed. Hormonal therapies have been used, but have produced low response rates of short duration.

Recently, several classes of drugs have been developed that target specific aberrations in tumorigenic pathways for endometrial carcinoma (Dedes, et al. 2011). Unfortunately, the response rates to these agents have been modest. One promising target has been the mTOR pathway through the use of rapamycin analogs. Several “in class” agents have been developed and studied in endometrial cancer including RAD001 (everolimus) In one phase II study of 28 patients with advanced or recurrent Type I endometrial carcinoma, RAD001 produced no complete or partial responses, but did demonstrate prolonged stable disease in 12 patients (43%) at 8 weeks evaluation and in 6 patients (21%) at 20 weeks evaluation (Slomovitz, et al. 2010). A similar result was achieved with ridaforolimus in a phase II study of recurrent endometrial cancer patients who were previously exposed to chemotherapy. In this small cohort, no responders were recorded. However, response to mTOR inhibitors in the absence of prior chemotherapy have produced single-agent objective responses, including a 25% response rate with in one single arm multi-institutional

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study of temsirolimus and 9% response in another with ridaforolimus. In a randomized phase II study of ridaforolimus versus investigators choice of either hormones or chemotherapy in recurrent/advanced endometrial cancer patients previously treated with up to 2 prior lines of therapy, response was similar (8% vs 4%) but CBR and PFS was improved for those taking ridaforolimus (64% vs 32%, and 5.6 months vs 1.9 months, both P< 0.01). The need remains to identify targeted-agents that may result in improvement in response rates and/or added clinical benefit.

1.1.4 Obesity, Type II Diabetes Mellitus, and Endometrial Cancer

Obesity is associated with Type I ECs in up to 90% of cases. The relative risk of uterine cancer-related death for women considered obese is 2.53, while for morbidly obese women it is 6.25. Furthermore, the association between obesity and other medical co-morbidities, such as diabetes mellitus and insulin resistance, also contributes to mortality. The prevalence of diabetes in the general population is approximately 7% to 8% and continues to rise.

1.2 Investigational Agents

1.2.1 Everolimus (RAD001)

Everolimus (Afinitor®/Votubia®; RAD001) is a signal transduction inhibitor (STI) targeting mTOR (mammalian target of rapamycin), or more specifically, mTORC1 (mammalian 'target of rapamycin' complex 1). mTOR is a key serine-threonine kinase playing a central role in the regulation of cell growth, proliferation and survival. The regulation of mTORC1 signaling is complex, being modulated by mitogens, growth factors, energy and nutrient availability. mTORC1 is an essential regulator of global protein synthesis downstream on the PI3K/AKT/mTOR pathway, which is dysregulated in the majority of human cancers (Boulay and Lane 2007). Consistent with the known activity of mTORC1, its inhibition by everolimus has been shown to reduce cell proliferation, glycolysis and angiogenesis in solid tumors in vivo, both through direct antitumor cell activity and inhibition of the tumor stromal compartment.

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 HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

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At weekly and daily schedules and at various doses explored, RAD001 is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible. (everolimus IB)

mTOR Pathway and Mechanism of Action

The target of everolimus, mTOR (mammalian target of rapamycin), is a serine-threonine kinase implicated in the PI3/AKT pathway and is known to be active in numerous neoplastic conditions.

The main known functions of mTOR include the following (Bjornsti and Houghton 2004; Boulay and Lane, 2007):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.
- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates translation of important massages, including those encoding the HIF-1 proteins, c-myc, ornithine decarboxylase, and cyclin D1, as well as ribosomal proteins themselves.
- The activation of mTOR pathway leads to the increased production of pro-angiogenic factors (i.e., VEGF) in tumors and to tumor, endothelial and smooth muscle cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

Preclinical studies

Everolimus acts as an inhibitor of interleukin and growth-factor-dependent proliferation of cells. The only currently known target of everolimus is mTOR, a key regulatory protein affecting cell growth (Boulay and Lane, 2007). Everolimus exerts its activity through high affinity interaction with an intracellular receptor protein, the immunophilin FKBP12. The FKBP12/everolimus complex subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1 to S-phase transition.

The main known functions of mTOR include:

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- Function as a sensor of mitogens, growth factors, energy and nutrient levels, facilitating cell-cycle progression from G1 - S phase in appropriate growth conditions.
- Regulation of protein synthesis important for tumor cell proliferation and angiogenesis through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (e.g. p70S6K1). For example, activation of the mTOR pathway leads to a) increased production of pro-angiogenic factors (e.g. VEGF) in tumors b) tumor, endothelial and smooth muscle cell growth and proliferation.

The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors. The regulation of mTOR signaling is complex and involves positive regulators such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2). In summary, mTOR has pleiotropic functions; hence, the activities of everolimus may vary depending upon cell type.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in breast cancer. Various signal transduction pathways are activated to escape the effect of endocrine therapy. One pathway is the PI3K/Akt/mTOR pathway, which is constitutively activated in aromatase inhibitor (AI)-resistant and long-term estrogen-deprived breast cancer cells. In breast cancer cells, resistance to AIs due to Akt activation can be reversed by coadministration with everolimus.

The mTOR inhibitory activities presumably contribute to the antiproliferative activity of everolimus against tumor cell lines. However, everolimus may also exert an antitumor effect through the inhibition of angiogenesis. Indeed, both rapamycin and everolimus potently inhibit proliferation of endothelial cells (Francesc 1999, Yu 1999, Lane et al 2009) and have antiangiogenic activity in vivo (Guba 2002, Tsutsumi 2004, Mabuchi et al 2007, Lane et al 2009).

Exactly which molecular determinants predict responsiveness of tumor cells to everolimus is still unclear. Currently, the activation status of the PI3K/AKT/mTOR/p70 S6K pathway may be indicative of responsiveness to rapamycins. For example, preclinically, loss of PTEN or constitutive/hyper-activation of AKT has been suggested to sensitize tumors to the effects of inhibition of mTOR (Reviewed in Boulay and Lane, 2007, Mabuchi et al 2007). Also, clinically, it has been suggested that high p70S6K activation in baseline GBM tumor samples may predict a patient population more likely to derive benefit from mTOR inhibition (Galanis, et al 2005).

Everolimus is a highly specific inhibitor of mTOR, which is afforded by high-affinity binding to the protein FKBP-12 (IC_{50} of 5.3 nM) similar to that of rapamycin. Similar potency of rapamycin and everolimus was also demonstrated at forming the mTOR / FKBP-12 tertiary complex *in vitro*. Specificity was demonstrated by a lack of inhibitory activity against 10 other protein kinases at concentrations up to 10 μM.

The antiproliferative effects of everolimus were investigated in a mixed panel of 48 different tumor cell lines (including breast, colon, epidermoid, glioblastoma, lung,

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melanoma, prostate and renal). The majority of tumor cell lines were highly sensitive to the anti-proliferative effects of everolimus while a few others appeared intrinsically insensitive, or 'resistant' (IC_{50} range 0.2 to 4125 nM) (O'Reilly and McSheehy, 2009). The median IC_{50} value of the 48 cell lines was 0.5 nM. Similar findings have been observed for rapamycin (Huang and Houghton 2002). Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported (Zitzmann, et al 2007), as well as in acute myeloid leukemia cells (Zeng, et al 2007), mantle cell lymphoma cells (Haritunians, et al 2007), adult T-cell leukemia cells (Ikezoe, et al 2007), diffuse large B cell lymphoma cells (Wanner, et al 2006), pancreatic tumor cells (Tuncyurek, et al 2007), ovarian cancer cells (Treeck, et al 2006, Mabuchi, et al 2007) and hepatocellular carcinoma cells (Sieghart, et al 2007).

Everolimus was also evaluated in a clonogenic assay using cells derived from 81 patient derived tumor xenografts never cultured in vitro (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC, SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma). Everolimus inhibited colony formation in a concentration-dependent manner (mean IC_{50}: 175 nM). In addition, normal hematopoetic stem cells were found to be relatively insensitive to everolimus, with an IC_{50} about 15 fold higher than the tumor lines.

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Everolimus was effective and well tolerated against subcutaneous (s.c.) tumors established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, and epidermoid), including a PgP170-overexpressing,

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multi-drug resistant tumor line. Typically, the antitumor activity of everolimus was that of reduction of tumor growth rates rather than producing regressions or stable disease although, in the case of A549 and NCI-H596 lung and ARJ42 pancreatic tumors, regressions could be obtained. These effects occurred within the dose range of 2.5 to 10 mg/kg, p.o., once per day. The change in tumor volume of the treated mice divided by the change in tumor volume of control mice (T/C) typically ranged from approximately 15 to 50% at optimal doses. A marked loss of antitumor activity occurred when tumor-bearing mice were treated with everolimus once per week, but improved moderately with twice per week dosing. Antitumor activity of everolimus has also been demonstrated in mouse models of ovarian (Mabuchi, et al 2007), breast (Lu, et al 2007, Torres-Arzayus, et al 2007) and gastrointestinal stromal tumors (Rossi, et al 2006).

Pre-clinical safety

In safety pharmacology studies, everolimus was devoid of relevant effects on vital organ functions including the cardiovascular, respiratory and nervous systems. Everolimus had no effects on QT interval. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000 mg/kg or after repeated administration at up to 40 mg/kg/day.

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys, and rabbits. Effects secondary to immunosuppression were evident at higher doses in all species, and indicated a potential of everolimus to exacerbate infectious background diseases. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species and consequentially, infertility is considered a potential risk for young adult subjects; lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in rats and mice up to the highest doses, corresponding respectively to 0.2 and 4.0 times the estimated clinical exposure.

In reproduction studies, everolimus was toxic to the conceptus in rats and rabbits, and was considered potentially teratogenic in rats. It is therefore recommended that women of childbearing potential should use effective contraceptive measures during the entire treatment period and for up to 8 weeks after ending treatment. Additionally, delay of growth and development, and reduced fertility are considered potential risks for younger population such as SEGA subjects.

More pre-clinical information is provided in the everolimus IB

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Clinical Experience

Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median tmax of 1-2 hours. The steady-state AUC0-τ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Steady-state was achieved within two weeks with the daily dosing regimen. Cmax is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in Cmax is less than dose proportional.

In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment.

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of PgP. Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity. No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces.

There was a significant correlation between AUC0-τ and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Table 3-6 (Section 3.3.3) lists examples of clinically relevant CYP3A inhibitors and inducers.

Please refer to Section 3.3.3 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

More information on everolimus pharmacokinetics is provided in the everolimus IB.

Everolimus Pharmacodynamic Studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained

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target inhibition ([Study C2101] / [Study 2102], Lane, et al 2003). Molecular changes in tumors were evaluated through serial biopsying before and during treatment. Biopsying on treatment took place in week 4 (pharmacokinetic steady-state). All patients underwent a 24-hour post-dose biopsy. Patients following the weekly regimen had a further biopsy on Day 4 or 5 of the same week. Molecular activity was measured by immunohistochemistry. In the absence of a reliable technique for measuring mTOR phosphorylation, the phosphorylation status of downstream markers S6 and eIF4G, for which reliable antibodies exist, was selected as reflecting the immediate pharmacodynamic effect of everolimus. Also measured were changes in the phosphorylation status of upstream AKT and the proliferation index Ki67. Fifty-five patients were treated and the results revealed a dose and schedule dependent inhibition of the mTOR pathway with a near complete inhibition of pS6 and peIF-4G at the 10 mg/day and 50 mg/wk schedules. In addition, pAKT was upregulated in 50% of the treated tumors. In the daily schedule, there was a correlation between everolimus plasma trough concentrations and inhibition of peIF4G and p4E-BP1. There was good concordance of mTOR pathway inhibition between skin and tumor. ([Study C2107], Tabernero, 2008)

More information is provided in the everolimus IB.

Clinical Experience with Everolimus

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and was approved in Europe in 2003 under the trade name Certican®, for the prevention of organ rejection in patients with renal and cardiac transplantation. Approval was granted in the United States in 2010 under the trade name of Zortress® for the prevention of organ rejection in adults receiving kidney transplants who are at a low to moderate immunologic risk. Clinical experience of everolimus in the transplant indication is summarized in the everolimus IB.

In oncology, everolimus has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with antitumor agents. Please note that safety pharmacology and toxicology studies as well as some human pharmacology studies which have been conducted in support of the transplant indication, are described in the oncology IB due to the relevance of these data for the oncology indication. Malignancies that are currently being evaluated in Novartis sponsored studies include the following: metastatic renal cell carcinoma (mRCC), breast cancer, gastroenteropancreatic neuroendocrine tumors (GEP-NET), mantle cell lymphoma (MCL) and diffuse large B cell lymphoma (DLBCL), hepatocellular cancer (HCC), gastric cancer, and lung cancer. In addition, treatment of patients with Tuberous Sclerosis Complex (TSC) associated subependymal giant cell astrocytoma (SEGA) and Angiomyolypoma are also being evaluated. Colorectal cancer (CRC) and lung cancer are no longer being evaluated.

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Phase I dose escalating studies, exploratory Phase I/II studies with everolimus as single agent or in combination with other anti-cancer agents, Phase II/III studies of everolimus in indications, and Phase III double-blind studies are contributing to the extensive database. Approximately 35,982 cancer patients have been treated with everolimus as of 31-Mar-2014:

- 19,668 patients in Novartis-sponsored clinical trials
- 2,394 patients in the individual patient supply program
- 13,930 in investigator-sponsored studies.
- In addition, healthy volunteer subjects and non-oncology hepatically impaired subjects have participated in the clinical pharmacology studies as described in Section 7.2.

As of 30-Sep-2011, there are a total of 11 Phase III trials ongoing in the indications mRCC (1), advanced NET (2), breast cancer (3), TSC (2), DLBCL (1), gastric cancer (1) and hepatocellular carcinoma (1).

Everolimus was approved by the United States (US) Food and Drug Administration (FDA) under the trade name Afinitor® ® for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib, and for the treatment of progressive neuroendocrine tumors of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease. The European Commission approved Afinitor® ® for the treatment of patients with advanced RCC, whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy, and for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors (NET) of pancreatic origin in adults with progressive disease.

More recently, an application was submitted for Afinitor® in the treatment of patients with hormone receptor-positive advanced breast cancer in combination with an aromatase inhibitor, in postmenopausal women previously treated with endocrine therapy. On 21-Jan-2012, Afinitor® was approved in Argentina for this indication.

In addition, everolimus received accelerated approval for the treatment of patients with tuberous sclerosis (TSC) who have subependymal giant cell astrocytoma (SEGA) who require therapeutic intervention but are not candidates for curative surgical resection (as Afinitor®) in the US, and received conditional approval in the EU (as Votubia®) for the treatment of patients aged 3 years and older with TSC who have SEGA who require therapeutic intervention but are not amenable to surgery.

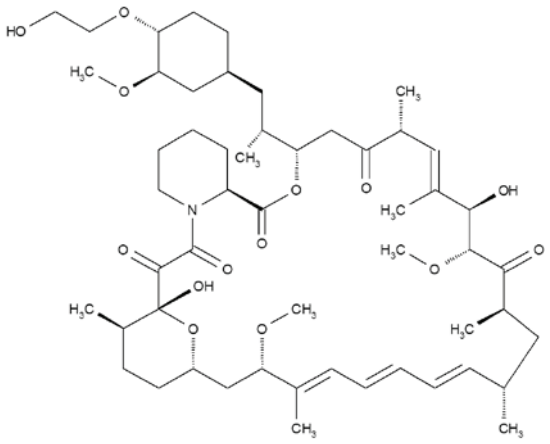
Furthermore, marketing authorization applications have been submitted for Afinitor® /Votubia® in the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

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Table 1-1 Everolimus – Drug Substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1 Chemical Structure of Everolimus



Further detailed information regarding everolimus clinical development, safety and efficacy is provided in the everolimus IB.

1.2.2 Letrozole (Femara)

Letrozole is a highly potent, orally active non-steroidal competitive inhibitor of the aromatase enzyme system. It effectively inhibits the conversion of androgens to estrogens both *in vitro* and *in vivo*. It is indicated both as first-line treatment of postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer as well as for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.

Letrozole was initially studied at doses of 0.1mg to 5.0mg daily in six non-comparative Phase I/II trials in 181 postmenopausal estrogen/progesterone receptor positive or unknown advanced breast cancer patients previously treated with at least antiestrogen therapy. Patients had received other hormonal therapies and also may have received cytotoxic therapy. Eight (20%) of forty patients treated with letrozole

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2.5mg daily in Phase I/II trials achieved objective tumor response (complete or partial response).

A randomized, double-blinded, multinational trial compared Letrozole 2.5mg with tamoxifen 20mg in 916 postmenopausal patients with locally advanced (Stage IIIB or loco-regional recurrence not amenable to treatment with surgery or radiation) or metastatic breast cancer. Time to progression (TTP) was the primary endpoint of the trial. Letrozole was superior to tamoxifen in TTP and rate of objective tumor response.

Letrozole has been investigated to a limited degree in patients with advanced/recurrent endometrial cancer. In one study of 32 patients not previously exposed to chemotherapy (28 evaluable) 1 CR and 2 PR's were recorded (Ma, et al. 2004). The median PFS and OS was 3.9 and 8.8 months, respectively.

1.2.3 Metformin

Metformin was discovered during the 1920s in a search for a guanidine-containing compound with anti-diabetic properties. This biguanide was introduced clinically in Europe in the 1950s and in the United States in 1995. It is FDA-approved for the treatment of non-insulin dependent diabetes mellitus (type 2). It is often the first drug of choice used to treat newly diagnosed type 2 diabetic patients. In 2006, it accounted for 37% of the non-insulin diabetic prescriptions in the United States. Non-FDA approved indications include treatment of gestational diabetes, hyperinsulinar obesity, hypersecretion of ovarian androgens, and polycystic ovarian syndrome (PCOS).

Metformin tablets contain 500mg, 850mg, or 1000mg of metformin hydrochloride. The tablets are freely soluble in water. Metformin is stored in light-resistant containers at temperatures of 20-25^{0}C. Metformin is taken orally. There is no fixed dose regimen for the management of hyperglycemia in patients with type 2 diabetes with metformin. It should be given in divided doses with meals. It should be started at a low dose, with gradual escalation to reduce gastrointestinal side effects and determine the minimal effective amount. In general, clinically significant responses are not seen at doses below 1500mg per day. The usual starting dose is 500mg twice a day or 850mg once a day.

Contraindications

Metformin is contraindicated in patients with: renal disease or renal dysfunction (serum creatinine level >60); congestive heart failure requiring pharmacologic treatment; known hypersensitivity to metformin hydrochloride; acute or chronic metabolic acidosis, including diabetic ketoacidosis. Metformin should be temporarily

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discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials.

Drug Interactions

Metformin has been shown to interact with the following drugs:

- Cephalexin: May increase the serum concentration of metformin.
- Cimetidine: May decrease the excretion of metformin. Other cationic drugs have the same theoretical potential (amiloride, digoxin, morphine, procainamide, quinidine, quinine, raniditine, triamterence, thrimethoprim, or vancomycin).
- Iodinated contrast agents: May enhance the adverse/toxic effect of metformin. Renal dysfunction that may be caused by iodinated contrast agents may lead to metformin-associated lactic acidosis.
- Furosemide: The plasma and blood concentrations of metformin were increased with administration of furosemide, and the concentration of furosemide was slightly decreased.
- Nifedipine: Appears to enhance the absorption of metformin and increase plasma concentrations of metformin.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control/diminish hypoglycemic effect of metformin (thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimietics, calcium channel blocking agents and isoniazid).

Preclinical Efficacy and Tolerability

It is now understood that metformin functions, at least in part, as an activator of LKB1 and subsequently AMPK. In the liver, this results in inhibition of gluconeogenesis and hepatic glucose output, which in turn reduces circulating glucose levels. This results in a secondary decrease in insulin levels. Thus, it is suspected to have dual anti-neoplastic activity by (1) directly activating the growth-inhibitory AMPK pathway and (2) indirectly decreasing levels of the growth hormone insulin.

Antineoplastic actions of metformin are more complex than simply lowering insulin levels. Because metformin activates AMPK through LKB1, it appears that at least one functioning allele of LKB1 would be necessary for the drug to be active. There is evidence to suggest that metformin might be less active in cancers with wild-type p53. There are still important knowledge gaps in our understanding of the pharmacology of metformin.

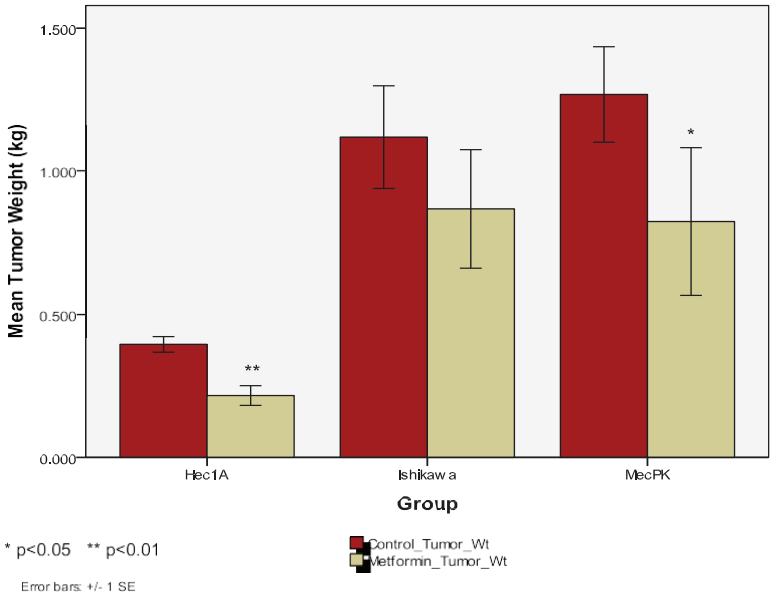
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Metformin has been studied extensively preclinically in breast and endometrial cancer cells, and these studies confirmed an AMPK-mediated growth inhibitory effect. Metformin has also been studied in other cancer cell types with similar findings. Preliminary evidence from our laboratory, as well as others, verified phosphorylation and activation of AMPK in PTEN wild-type and PTEN null endometrial cancer cell lines as well as decreased cell viability. However, cell lines with an activating K-Ras mutation were most sensitive to metformin treatment compared to cell lines with wild-type K-Ras. Preliminary evaluation of human endometrial cancers suggest K-Ras activating mutations may be present alone or in the context of other mutations in the PI3K pathway in up to 30% of type I cancers. This may implicate the Ras pathway as another potential target of metformin.

Our group recently completed an orthotopic mouse model in which mice were inoculated with endometrial cancer cells and then treated with orally administered metformin at a concentration of 5 mg/mL dissolved in drinking water compared to control over a period of 29-60 days. Metformin treatment was well tolerated with no significant changes in mean mouse weights (a surrogate for toxicity) at the completion of treatment. Also, serum levels of hepatic transaminases were within normal levels and not significantly different than in control treated mice. Mice inoculated with endometrial cancer cell lines with activating K-Ras mutations (Hec1A and MecPK) and treated with metformin were found to have significant reductions in mean tumor volume at necropsy compared to control treated mice (Figure 1-2). In contrast, consistent with our *in vitro* data, mice inoculated with an endometrial cancer cell line with wild-type K-Ras (Ishikawa) and treated with metformin did not demonstrate a significant reduction in mean tumor volume when compared to control-treated mice.

Figure 1-2 - Metformin treatment in nude mouse xenografts inoculated with various endometrial cancer cell lines

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Clinical Experience with Metformin

Clinical Pharmacology of Metformin

Metformin lowers both basal and postprandial glucose levels through several mechanisms including decreasing hepatic glucose production, decreasing intestinal absorption and increasing peripheral glucose uptake and utilization by improving insulin sensitivity. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects except in special circumstances. The molecular target of metformin was not known when it entered clinical use, and the exact mechanism of action remains unclear but, as described above, is in part believed to involve the enzyme AMPK.

The absolute bioavailability of a 500mg tablet given under fasting conditions is approximately 50-60%. There is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve (AUC), and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850mg tablet of metformin with food, compared to the same tablet strength administered fasting.

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The apparent volume of distribution (V/F) of metformin following a single oral dose of 850 mg averages 654 +/- 358 L. Metformin is negligibly bound to plasma proteins. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations are reached within 24-48 hours and are generally < 1 g/mL.

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism or biliary excretion. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.

Special Populations

Patients with Type 2 Diabetes: In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects.

Renal insufficiency: In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Geriatrics: Limited data in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased compared to healthy young subjects. This change is primarily accounted for by a change in renal function.

There are no adequate and well-controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600mg/kg/day. It is classified as a Pregnancy Catergory B drug. Metformin is excreted into milk in rat studies at levels comparable to those in plasma. This may pose a risk for hypoglycemia in an infant.

Clinical Safety and Toxicities

Adverse reactions observed in >10% of patients include: gastrointestinal (diarrhea 10-53%, nausea/vomiting 7-26%, and flatulence 12%), and neuromuscular (weakness 9%).

Adverse reactions observed in 1-10% of patients include: chest discomfort, flushing, palpitations, headache (6%), chills, dizziness, lightheadedness, rash, hypoglycemia,

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indigestion (7%), abdominal discomfort (6%), abdominal distension, abnormal stools, constipation, dyspepsia/heartburn, taste disorder, myalgia, dyspnea, upper respirtatory infection, diaphoresis, vitamin B12 decreased levels (7%), flu-like syndrome, nail disorder.

Rare adverse reactions (<1%) include lactic acidosis, leukoclastic vasculitis, megaloblastic anemia, and pneumonitis.

Lactic acidosis is a rare, but potentially severe consequence of therapy with metformin. Lactic acidosis should be suspected in any patient receiving metformin who has evidence of acidosis when evidence of ketoacidosis is lacking. Lactic acidosis, when it occurs, is fatal in 50% of cases. The reported incidence is ~0.03 cases/1000 patient-years. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. The onset of lactic acidosis is often subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and no specific abdominal distress. The patient and patient's physician must be aware of the possible importance of such symptoms.

In cases of overdose, hypoglycemia with metformin alone has not been reported, although lactic acidosis has occurred in such cases. Metformin is dialyzable with a clearance of up to 170mL/min under good hemodynamic conditions.

Patients should be instructed to avoid excessive or chronic alcohol use as alcohol may potentiate metformin's effect on lactate metabolism. Therapy should be suspended for any surgical procedures and resumed only after normal intake and renal function are verified.

Metformin should be used with caution in patients with heart failure requiring pharmacologic management as the risk of lactic acidosis may be increased secondary to hypoperfusion. Metformin use should also be avoided in patients with impaired liver function due to potential for lactic acidosis. Metformin should be withheld in patients with dehydration and/or prerenal azotemia, in patients with renal dysfunction, and use should be monitored in patients taking concomitant medications that may affect renal function. Patients taking herbal supplements of garlic, chromium, and gymnema may have increased risk of hypoglycemia.

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Non-Oncology Experience

There is extensive safety and efficacy data for the FDA-approved use of metformin in the treatment of type 2 diabetes. In a double-blind, placebo-controlled multicenter U.S clinical trial involving obese patients with type 2 diabetes whose hyperglycemia was not adequately controlled with dietary management alone, treatment with metformin (up to 2550 mg/day) for 29 weeks resulted in significant mean net reduction in fasting and postprandial plasma glucose and hemoglobin A_{1c}. In clinical studies, metformin alone or in combination with a sulfonylurea lowered mean fasting serum triglycerides, total cholesterol, and LDL cholesterol levels and had no adverse effects on other lipid levels. In contrast to sulfonylureas, body weight on metformin tended to remain stable or even decrease somewhat. There are also multiple randomized clinical trials of metformin in combination with other antidiabetic agents including sulfonylureas and insulin. In these studies, patients that were poorly controlled on single-agent non-metformin therapy had improved glycemic control with the addition of metformin.

There have also been many large, randomized clinical trials for the treatment of non-FDA approved, benign indications. The treatment of polycystic ovarian syndrome and associated hypersecretion of ovarian androgens and infertility with metformin, alone and in combination, has been studied extensively. The most notable recent trial was a randomized, placebo controlled trial comparing metformin alone vs clomiphene citrate vs the combination in the treatment of infertility in women with polycystic ovary syndrome. Live birth rate and conception rates were significantly lower in the metformin treated group than either the clomiphene group or combination group. However, with the exception of pregnancy complications, adverse-event rates were similar in all groups. Another recent clinical trial randomized pregnant women with gestational diabetes to metformin or insulin. The rate of neonatal complications was similar for both groups, but more women in the metformin group stated they would choose to receive their assigned treatment again. Glycemic control was also similar in both groups.

Oncology Experience

Evidence from retrospective epidemiologic studies indicates that metformin may have both preventive and therapeutic potential in the management of cancer. A retrospective case-control study demonstrated a reduced incidence of cancer in diabetic patients taking metformin compared to diabetics using other hypoglycemic agents (Evans, et al. 2005). Another retrospective cohort study demonstrated an increased risk of cancer-related mortality in diabetic patients treated with sulfonylureas alone or with any combination of insulin, compared to those treated with some combination of metformin (Bowker, et al. 2006). Similarly, diabetic breast

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cancer patients receiving neoadjuvant systemic therapy treated with metformin had improved pathologic complete response than diabetic not on metformin (Jiralerspong, et al. 2009). DeCensi and colleagues completed a meta-analysis of five observational studies of all cancer types and found that metformin was associated with a 31% decrease in CA risk (SRR 0.69, 95%CI 0.61-0.79) (DeCensi, et al. 2010). A recent retrospective review of patients with stage I-IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma stratified into subgroups based on metformin use found that the 5-year overall survival was 63%, 37%, and 23% for the diabetic patients who used metformin, the nondiabetic patients, and the diabetic patients who did not use metformin, respectively (p=.03) (Romero, et al. 2012).

In an on-going single-arm, open-label phase II trial of RAD001 (10 mg daily) in combination with letrozole (2.5 mg daily), 9 of the 35 evaluable patients on trial were also using metformin (4 were on metformin prior to study entry for diabetes, 5 started metformin while on trial for RAD001-induced hyperglycemia). Interestingly, metformin users had a substantially improved CBR and ORR (78% and 44%) compared to the 26 metformin non-users on the study, with a CBR and ORR of 39% and 12% in that group. Furthermore, of the 4 complete responders on trial thus far, 3 occurred in the metformin group. Toxicities in patients taking metformin were not significantly different to those not taking metformin. A summary of the outcome data can be found in Table 1-2.

Table 1-2 – Summary of patient outcomes in Phase II Trial of RAD001 + Letrozole in patients with recurrent or progressive endometrial cancer stratified by metformin use

	Metformin Non-Users (n=26)	**Metformin Users (n=9)**
Progressive Disease	16	2
Clinical Benefit		
CR	1	3
PR	2	1
SD	7	3
Overall		
RR	11.5%	44.4%
CBR	38.5%	77.8%

An on-going randomized Phase II, double blind, trial in women with metastatic breast cancer (NCT01310231) is comparing standard chemotherapy with metformin versus

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standard chemotherapy with placebo. The metformin dose used in this trial is 850 mg orally twice daily which is the proposed dose in our present study.

1.3 Study Rationale and Purpose

1.3.1 Rationale for Use of RAD001 in Endometrial Cancer

Given the frequency of PTEN loss of function and other aberrations of the PI3K/AKT/mTOR pathway in Type I endometrial tumors, the discovery of rapamycin and its analogs, which target and inhibit mTOR, have drawn interest as potential therapeutic agents in endometrial cancer. Preclinical data using RAD001 and other mTOR inhibitors in endometrial cancer have been compelling. In a preclinical, PTEN heterozygous transgenic mouse model, RAD001 decreased the progression of endometrial hyperplasia by increasing the rate of apoptosis and decreasing cell proliferation (Milam, et al. 2007). The decrease in phospho-p70 S6 kinase in the treated group compared to the untreated group also suggested a target specific down regulation of the mTOR pathway with the treatment of RAD001.

In endometrial cancer cell lines, rapamycin demonstrated a growth-inhibitory effect through induction of cell cycle arrest (Zhou, et al. 2003). This effect, however, was independent of PTEN status because PTEN-positive cells were as sensitive to rapamycin as PTEN-null cells. This suggested that rapamycin may be effective against a broad range of endometrial cancers. In addition, rapamycin inhibited phosphorylation of downstream targets of mTOR (S6K and 4E-BP1). In a mouse model, tumors from PTEN deficient mice had elevated levels of phosphorylated AKT and S6K (Podsypanina, et al. 2001). In this model, inactivation of mTOR using an mTOR inhibitor reduced neoplastic proliferation, tumor size, and S6K activity, but did not alter the status of AKT.

Our group has previously found a relatively high rate of activated mTOR and its downstream effector protein, S6 kinase in a series of endometrial cancers. These data support the current investigations of mTOR inhibition for the treatment of patients with this disease. Future studies will further evaluate markers in this pathway and possibly identify molecular factors that may predict response to therapy.

Clinical trials of mTOR inhibitors in various cancers are in progress. CCI-779, an intravenous analog of rapamycin, has been evaluated in a phase II trial in patients with metastatic or recurrent endometrial cancer. In this study there was a 25% partial response rate (median duration 5.1 months) and a 57% stable disease rate (median

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duration 8.7 months). None of these patients received prior chemotherapy (Oza, et al. 2006).

As described above we completed a phase II study of 28 patients with advanced or recurrent Type I endometrial carcinoma who were treated the rapamycin analog RAD001 (Slomovitz, et al. 2010). While no complete or partial responses were produced, treatment with RAD001 alone did result in prolonged stable disease in 12 patients (43%) at 8 weeks evaluation and in 6 patients (21%) at 20 weeks evaluation. The median duration of stable disease observed was 4 cycles (months). Immunohistochemistry translational endpoints demonstrated 76% overexpression of mTOR and 41% overexpression of phospho-mTOR. No relationship of CBR was seen with PTEN mutation (66% of samples).

As expected based on studies of other targeted agents in the setting of recurrent endometrial cancer, measurable clinical responses were uncommon; however, the stable disease rate seen in this study was promising. Although toxicity (mostly hyperlipidemia) has been seen, clinically significant side effects were not problematic. In a preliminary analysis of translational endpoints and response, patients who had tumors harboring PTEN mutations were more likely to experience a clinical benefit (i.e., stable disease) than patients whose tumors had wild-type PTEN. We believe that this single agent activity in pretreated patients suggest that RAD001 will have clinical applications in the treatment of this disease. However, we felt that combination therapies would be needed to improve response rates.

1.3.2 Rationale for Combination of RAD001 with Letrozole in Endometrial Cancer

The combination of RAD001 and letrozole was first evaluated as part of a neoadjuvant breast cancer trial (Baselga, et al. 2009). The biologic rationale for the combination arose from preclinical observations that treatment with RAD001 caused reduced progesterone receptor levels resulting in loss of the antiproliferative effects associated with progesterone. Addition of aromatase inhibitors was suggested to counter the pro-proliferative effects of estrogen by reducing serum estrogen levels. In this phase II trial, RAD001 was found to significantly increase the efficacy of letrozole (ORR 68%) in patients with estrogen receptor-positive breast cancer compared to letrozole alone (ORR 59%). Furthermore, the safety profile of the combination was consistent with historical results of RAD001 used as monotherapy. The frequent expression of hormonal receptors in endometrial cancer, particularly in

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low grade lesions, was felt to be another setting in which this combination therapy may be effective.

To answer this question, a single-arm, open-label phase II trial of RAD001 (10 mg daily) in combination with letrozole (2.5 mg daily) was initiated. This regimen was given to 35 patients and demonstrated a clinical benefit rate of 48.6% and an overall response rate of 20.0% (including 4 complete responses). The median duration of response was 8 months (range, 3-17+). While these results are still preliminary and patient follow-up continues, the responses observed in this trial show significant promise to combined therapy with RAD001 and letrozole. Furthermore, this combination was well tolerated with the most common grade 3 toxicities being: fatigue (n=3), diarrhea (n=2), and thrombocytopenia (n=2). Interestingly, as mentioned above several patients (n=9) were either on metformin upon study entry for management of diabetes or metformin was added during the trial following the development of hyperglycemia. These patients who were treated with metformin while on trial were noted to have an increased clinical benefit rate (77.8%) compared to metformin non-users (CBR 38.5%). Of the 4 complete responses observed, 3 have been in patients also treated with metformin. Based on the preliminary findings of this phase II trial with RAD001 and letrozole, we believe that the addition of metformin to this regimen may provide some added benefit.

1.3.3 Rationale for Combination of RAD001, Letrozole, and Metformin in Endometrial Cancer

The oral biguanide, metformin, is one of the most commonly used hypoglycemic agents in the management of type II diabetes mellitus and the polycystic ovarian syndrome (PCOS) which are both associated with insulin resistance and an increased risk for the development of endometrial cancer. Several epidemiological studies have demonstrated that diabetic patients being treated with metformin have a reduced cancer incidence compared to diabetic patients receiving insulin or other oral hypoglycemic agents (Jiralerspong, 2009; DeCensi, 2010; Romero, 2012).

The principle mechanisms of action of metformin in the management of diabetes mellitus include reducing hepatic gluconeogenesis, increasing insulin sensitivity in target tissues, and improving glucose uptake by skeletal muscles and adipocytes. This ultimately leads to decreased circulating glucose and insulin levels. Specifically, metformin has been shown to inhibit mitochondrial adenosine-5'-triphosphate (ATP) production which results in activation of the cellular energy-sensing liver kinase B1 (LKB1)/AMPK pathway that downregulates energy-consuming processes such as lipid and protein synthesis in response to energy depletion. In the case of

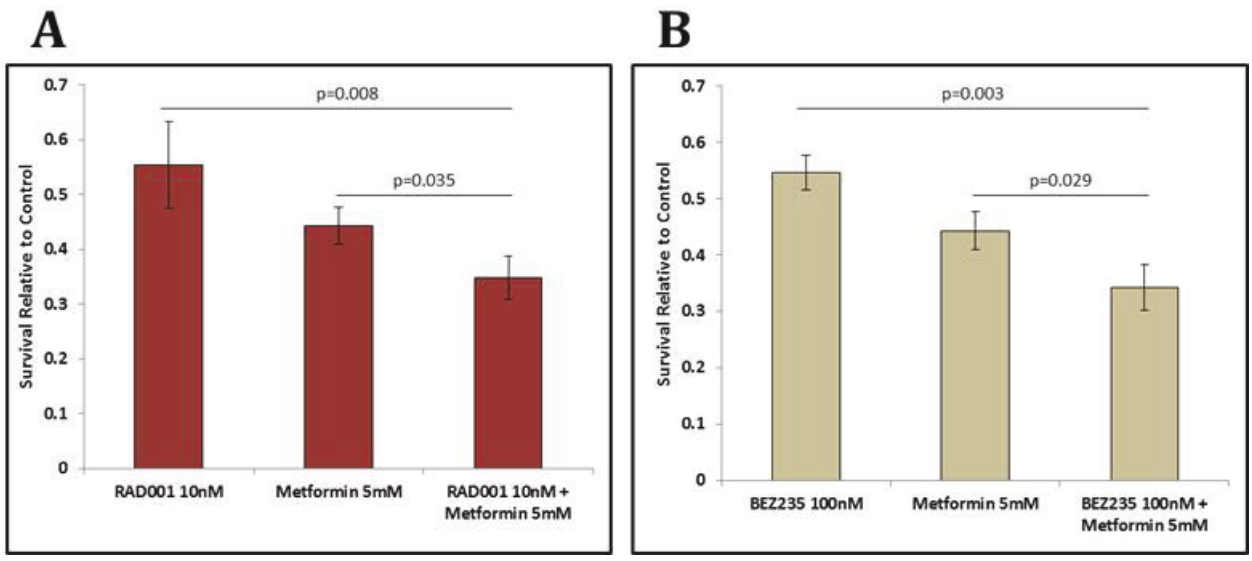
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hepatocytes, this results in a decrease in gluconeogenesis and ultimately to decreased circulating insulin levels. However, following the observations that insulin acts as a mitogen in a subset of cancer cells (Pollak, et al. 2008) and that AMPK activation also down regulates mTOR signaling, there has been increasing interest in evaluating the potential anti-neoplastic effects of metformin. As discussed above, aberrations in mTOR signaling have been implicated in the development of endometrial cancer. In a study evaluating the pre-clinical effects of metformin, Cantrell and colleagues, using two endometrial cancer cell lines expressing PTEN, demonstrated that metformin was a potent inhibitor of endometrial cancer cell proliferation that was partially mediated by activation of AMPK with a subsequent decrease in mTOR signaling (Cantrell, et al. 2010). However, in our lab, we have demonstrated that metformin may also produce anti-neoplastic effects through alternative mechanisms, such as disruption of Ras signaling. Given that Ras mutations are the second most common molecular alteration associated with Type I endometrial cancer – occuring in ~20-30% of cases – this may have significant implications in designing novel therapeutic strategies to target endometrial cancer.

We have found that metformin treatment results in a concentration-dependent decrease in relative cell viability compared to control in endometrial cancer cell lines with activation K-Ras mutations. Western blot analysis demonstrated decreased signaling through the PI3K pathway with decreased phospho-S6 protein expression and decreased signaling through the Ras pathway with decreased phospho-ERK1/2 expression. These effects were less pronounced in cells with wild-type K-Ras with significance only at high metformin concentrations. These results were confirmed *in vivo* using a xenograft mouse model which demonstrated that oral metformin treatment significantly decreased mean tumor weights in mice inoculated with endometrial cancer cells harboring an activating K-Ras mutation, but not in mice inoculated with endometrial cancer cells with wild-type K-Ras. Furthermore, using endometrial cancer cells characterized by loss of PTEN expression and an activating K-Ras mutation, treatment with the combination of RAD001 plus metformin or BEZ235 (a dual inhibitor of PI3K and mTOR) plus metformin resulted in a significant decrease in relative cell survival than either agent alone (Figure 1-3, A and B).

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Figure 1-3: Relative survival of MecPK cells after 48 h of treatment with RAD001 (A) or BEZ235 (B) and metformin each as monotherapy and the combination.



A: The combination of RAD001 and metformin resulted in a significant decrease in relative survival compared to either therapy alone. **B:** The combination of BEZ235 and metformin resulted in a significant decrease in relative survival compared to either therapy alone.

In a preclinical study of PTEN loss and activation of K-Ras, Kim and colleagues generated a transgenic mouse model of conditional PTEN ablation and an oncogenic K-Ras mutation in progesterone receptor positive cells (Kim, et al. 2010). These double mutant mice experienced dramatic acceleration in the development of endometrial cancer compared to a single mutation of either gene. Histological analysis showed that all of the double mutant female mice developed endometrial cancer with myometrial invasion. The expression of progesterone receptor was downregulated in these mice compared to a single mutation of either gene which resulted in decreased suppression of estrogen signaling.

Based in part on these findings, the preliminary results of the phase II trial of RAD001 and letrozole and our previous preclinical work, we hypothesize that the combination of RAD001 which targets the PI3K pathway and metformin which targets both the PI3K and Ras pathways would provide added benefit in the treatment of endometrial cancer. Furthermore, addition of letrozole would counter the pro-proliferative effects

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of estrogen that go unchecked as a result of decreased progesterone expression in endometrial tumors with loss of PTEN and mutant K-Ras.

1.3.4 Rationale for Study Design

This is an open-label, Phase II, single-arm trial to evaluate the clinical efficacy combination therapy with RAD001, letrozole, and metformin in recurrent or progressive endometrial carcinoma. This will follow a two-stage design. This study design allows for limiting patient exposure to an inactive agent.

1.3.5 Background and Rationale for Correlative Studies

A second objective of this study is to evaluate whether there is a correlation between PTEN loss of function or K-Ras mutational activation and response to the combination of RAD001, letrozole, and metformin. PTEN loss of function occurs in up to 70-80% of Type I endometrial cancers. PTEN gene mutation or deletion is the most common mechanism and occurs in up to 50% of cases (Risinger, 1997; Tashiro, 1997). PTEN promoter hypermethylation is an alternative mechanism of PTEN inactivation which occurs in 19% of patients and is associated with metastatic disease (Salvesen, 2001). Meanwhile, K-Ras mutations are the second most common molecular alteration seen in Type I endometrial cancers – occurring in up to 20-30% of cases. Identifying a subgroup of patients who are more likely (or less likely) to respond to therapy would be clinically useful in counseling patients regarding their treatment options.

We will evaluate pre-treatment tissue for molecular profiles that may predict which patients have a response to therapy. In particular we will look at the mTOR pathway, as well as K-Ras and other clinically relevant genetic mutations. Where available, immunohistochemical analysis of different markers (LKB1, phosphorylated AKT, S6K, ribosomal protein S6, 4E-BP1, and OCT-1) pre and post treatment with RAD001, letrozole, and metformin as well as in the original tumor tissue will be analyzed to determine whether the drug combination resulted in molecular changes at the level of the target tissue. Identification of patterns of change in these biomarkers could be correlated to response and provide prognostic information.

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2 Study Objectives

2.1 Overview

This is an open-label, phase II, single-arm trial to evaluate the clinical efficacy of the combination of RAD001 (Everolimus), letrozole, and metformin in the treatment of advanced or recurrent endometrial carcinoma. Pre-clinical data has demonstrated that the combination of metformin and RAD001 produces a decrease in endometrial cancer cell proliferation that is greater than either agent alone. This may be the result of targeting different pro-proliferative pathways to produce an additive effect. Further, in a recently completed phase II trial of combination RAD001 with letrozole, of nine patients who were also taking metformin for management of diabetes mellitus or initiated on metformin for the management of treatment-related hyperglycemia, seven achieved clinical benefit with a clinical benefit rate (CBR, defined as objective response or delay in clinical progression of 8 weeks or greater) of 78% (with 4 total responders, including 3 complete responses) in this subgroup compared to a CBR of 39% for patients were did not use metformin. As patients with recurrent endometrial cancer often have limited effective treatment options, development and evaluation of novel therapies is needed. We hypothesize that addition of metformin to RAD001 and letrozole will be effective in the treatment of patients with advanced or recurrent endometrial carcinoma than RAD001 and letrozole alone.

2.2 Primary Objective

To determine the efficacy of RAD001 in combination with letrozole and metformin in patients with recurrent or progressive endometrial carcinoma.

2.3 Secondary Objectives

1. To determine the median duration of progression-free survival and overall survival in patients with recurrent or progressive endometrial adenocarcinoma treated with RAD001, letrozole, and metformin.
2. To determine the frequency and severity of toxicities associated with RAD001, letrozole, and metformin in this cohort of patients.
3. To determine the effects of RAD001, letrozole, and metformin on tissue DNA biomarkers of women with endometrial cancer and to determine response to treatment based on PTEN expression and/or KRAS and other gene mutation status.

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2.4 Primary Endpoint

The proportion of patients demonstrating a clinical benefit (CBR: complete response + partial response + stable disease rates) based on RECIST v1.1.

2.5 Secondary Endpoints

1. Six month progression free survival (PFS), median duration of survival from time of study entry (first treatment) to progression (PFS) or death (OS).
2. Frequency and severity of toxicities as assessed by CTCAE v4.0.
3. Correlative endpoints: Binary outcomes (present vs. absent) of KRAS and other gene mutation status and PTEN expression status of the primary surgical specimen or most recent tumor biopsy using he SMS 50 panel will be correlated with response to RAD001, letrozole, and metformin. Biomarkers (LKB1, phosphorylated AKT, S6K, ribosomal protein S6, ERK1/2, and OCT-1) will be evaluated and compared from pre-treatment and post-treatment (after 2 cycles) tumor biopsies from patients who consent to this optional second biopsy.

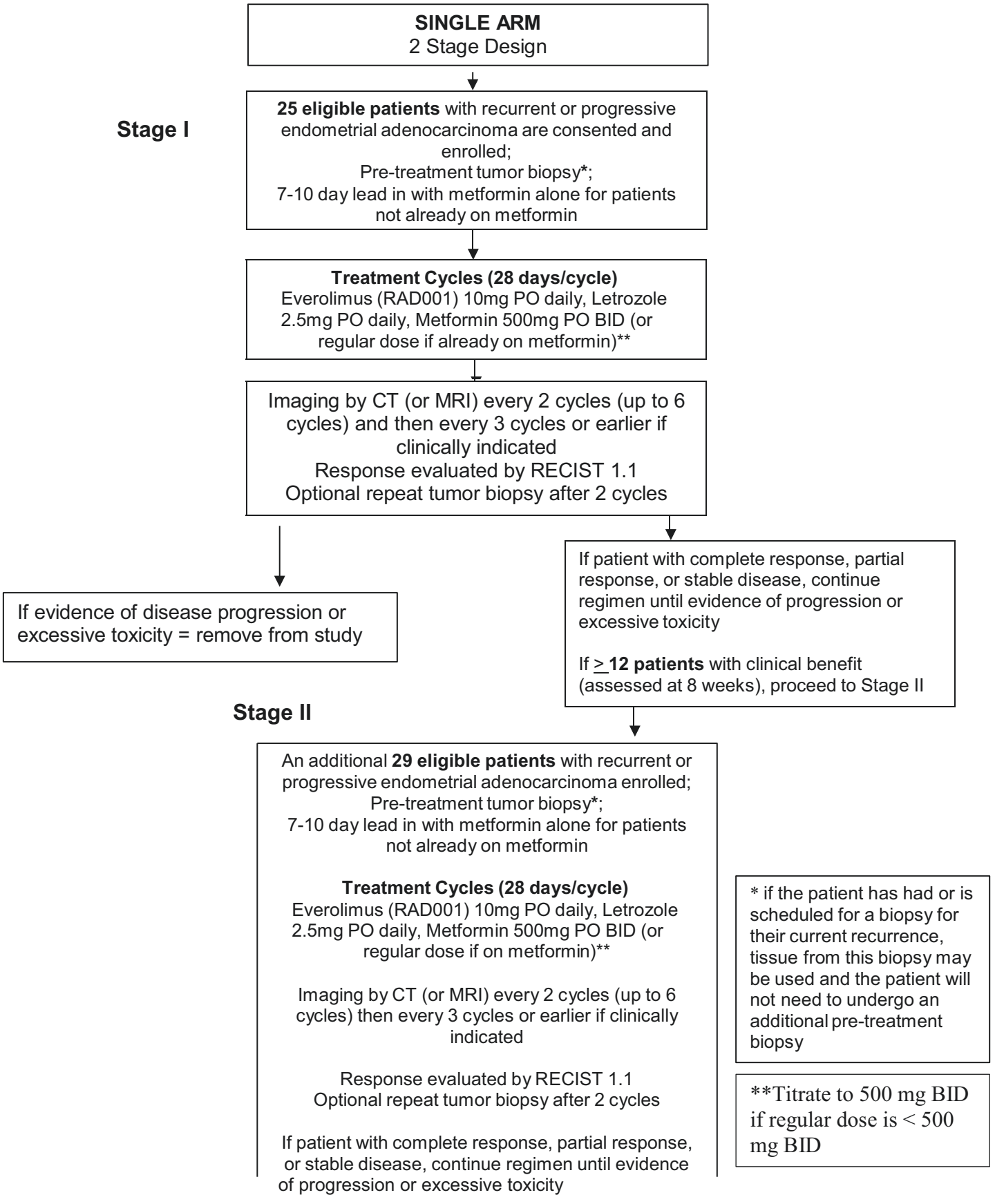
3 Investigational Plan

3.1 Overall Study Design

This is an open-label, Phase II, single-arm trial to evaluate the clinical efficacy combination therapy with RAD001, letrozole, and metformin in recurrent or progressive endometrial carcinoma. This will follow a two-stage design. This study design allows for limiting patient exposure to an inactive agent.

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3.1.1 Schema



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3.2 Study Population

The target population is women who are ≥ 18 years of age with recurrent or progressive endometrial cancer who have not received more than 2 regimens of systemic chemotherapy for recurrence. This does not include chemo-sensitizing radiation. Females under the age of 18 are excluded as the safety and efficacy of letrozole has not been established in children.

3.2.1 Patient Population

A two-staged design will be employed with 25 patients evaluable for efficacy (2 cycles) in the first stage. If there are at least 12 patients with an objective response or stable disease (confirmed at 8 weeks), an additional 29 evaluable patients will be enrolled in the second stage for a total of 54 evaluable patients. Thus, we will accrue a minimum of 25 evaluable patients and a maximum of 54 evaluable patients at a rate of 2 patients per month. We estimate that 10 patients may be inevaluable and thus need to be replaced. Therefore, our total number of patients will not exceed 64.

3.2.2 Inclusion and Exclusion Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion criteria. Results of all baseline evaluations must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment.

The MDACC CORe system will be utilized for registration and will be a two-step process. Pre-enrollment registration will be completed once the informed consent is signed for screening (step one). After eligibility is confirmed, registration will be completed (step two).

Inclusion Criteria

1. Patients must have histologically-confirmed advanced or recurrent endometrial carcinoma (endometrioid and mixed tumors, any grade) that is refractory to curative therapy or established treatments.
2. Patients must have had no more than two prior chemotherapeutic regimens for recurrent management of endometrial carcinoma. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer is not counted as a prior treatment for recurrent or advanced disease.
3. Prior radiation therapy of any kind is allowed.

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4. All patients must have measurable disease per RECIST version 1.1 defined as at least one "target lesion" that can be accurately measured in at least one dimension (>/= 10 mm longest dimension to be recorded; Lymph nodes must be >/= 15 mm per short axis). Each lesion must be > 20 mm when measured by palpation or conventional imaging techniques (CT or MRI – based on primary physician preference) or >10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in millimeters. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented. Ascites and pleural effusions are not considered measurable disease. If the measurable disease is confined to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
5. Patients must not be of child-bearing potential. Patients are considered not of child-bearing potential if they are surgically sterile (they have undergone a total hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are postmenopausal for greater than 12 months. Patients in whom ovaries are present and were not previously menopausal at the time of hysterectomy, should have a serum estradiol <10 pm/mL to confirm ovarian senescence.
6. Patients must be off all other anti-tumor therapies (including immunologic or hormonal agents) for at least four weeks prior to study registration.
7. Age ≥ 18 years
8. GOG performance status < 2 (Appendix A)
9. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hb >9 g/dL
10. Adequate liver function as shown by:
    a. serum bilirubin ≤ 1.5 x ULN
    b. ALT and AST ≤ 2.5 x ULN (≤ 5x ULN in patients with liver metastases)
    c. Adequate renal function: serum creatinine < 1.4mg/dl. (per manufacturer, metformin is contraindicated in the prescence of renal dysfunction defined as a serum creatinine > 1.4mg/dL in females and in patients with abnormal clearance.
    d. Fasting serum cholesterol ≤240 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
11. Signed informed consent
12. Prior treatment with letrozole is allowed.

Exclusion Criteria

1. Patients who have uterine sarcomas, carcinosarcomas, any serous histology or pure clear cell carcinomas.

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2. Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of study drug (including chemotherapy, radiation therapy, antibody based therapy, etc.)
3. Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study
4. Prior treatment with any investigational drug within the preceding 4 weeks
5. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
6. Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period. Close contact with those who have received attenuated live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.
7. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases
8. Other malignancies within the past 3 years except for basal or squamous cell carcinomas of the skin.
9. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

   a. Symptomatic congestive heart failure of New York heart Association Class III or IV

   b. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease

   c. Severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 02 saturation that is 88% or less at rest on room air.

   d. Active (acute or chronic) or uncontrolled severe infections

   e. Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).

      Note: A detailed assessment of Hepatitis B/C medical history and risk factors (see 3.5.1) must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection.

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f. A known history of HIV seropositivity

g. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea or malabsorption syndrome)

h. Patients with an active, bleeding diathesis

10. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Adequate contraception must be used throughout the trial and for 8 weeks after the last dose of study drug, by both sexes. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of everolimus)
11. Patients who have received prior treatment with an mTOR inhibitor (e.g., sirolimus, temsirolimus, everolimus).
12. Patients with a known hypersensitivity to everolimus or other rapamycins (e.g., sirolimus, temsirolimus) or to its excipients
13. History of noncompliance to medical regimens
14. Patients unwilling to or unable to comply with the protocol.
15. Patients with isolated recurrences (vaginal, pelvic, or paraaortic) that are amenable to potentially curative treatment with radiation therapy or surgery.
16. Patients with acute or chronic metabolic acidosis, lactic acidosis, or ketoacidosis. Note: during the study, metformin must be discontinued for 24 hours before and 48 hours after imaging involving IV contrast to minimize risk of lactic acidosis.
17. Patients who have hypoglycemia with a value of </= 50 mg/dL

Inclusion of Women and Minorities

Women of all racial and ethnic groups are eligible for this trial.

3.2.3 Interruption or Discontinuation of Treatment

For enrolled patients that undergo a pre-treatment biopsy but we are unable to obtain adequate amount of tissue for molecular testing, the patients will be allowed to continue on treatment as outlined in the protocol.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug (Table 3-0). If administration of everolimus must be interrupted because of unacceptable toxicity,

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drug dosing will be interrupted or modified according to rules described in Table 3-1. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for AdverseEvents v4.0

(CTCAEv4.0,http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf).

Table 3-0. For the purposes of dose reduction, the following dose levels will be utilized:

Dose Level	RAD001 Dose	Letrozole Dose	Metformin Dose*
-3	Off Study	Off Study	Off Study
-2	2.5 mg daily	2.5 mg daily	500 mg BID
-1	5mg daily	2.5mg daily	500mg BID
0	10mg daily	2.5mg daily	500mg BID

*Or regular dose of metformin if patient already taking greater than 1000mg of metformin per day. If a patient is taking less than 1000mg/day, their dose will be titrated up to 500mg BID per trial dose.

- Prior to starting each cycle, non-hematologic toxicities should have resolved to Grade 1 or may be grade 2 if tolerable to the patient (electrolyte abnormalities should resolve to at least Grade 2) and hematologic toxicities to Grade 1 (Table 3.1)
- If the toxicity is felt to be related to the metformin (including but not limited to weight loss, diarrhea, dehydration, etc…), The metformin can be reduced at the discretion of the primary physician or the PI of the study. The first dose reduction would be to 500 mg QD. If the metformin-related toxicity continues, the patient may continue on the everolimus and letrozole alone assuming there are no toxicities related to the other drugs. If a patient is on more than 1000mg/day of metformin due to diabetes, the dose can be reduced by 500mg at each reduction.
- If a patient develops treatment related diabetes, the dose of metformin will be titrated up to gain glucose control prior to adding any additional hypoglycemic agents.

Patients will be removed from study for any:

- Grade 4 treatment-related non-hematologic toxicity (assuming that appropriate preventive therapy has been give where possible), or

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- Hematologic or non-hematologic toxicity requiring interruption of drug therapy for more than 3 weeks, or
- Recurrent/persistent hematologic or non-hematologic toxicities resulting in greater than 2 dose reductions
- If a patient has grade 3 anemia with a hemoglobin less than 8.0 /dL, a blood transfusion is required and the study medication may be continued.

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Table 3-1 Criteria for dose-modification in case of suspected "treatment related" toxicity

Non-hematological toxicity	
Toxicity	Actions
Grade 1	
Hyperglycemia >150	No dose adjustment for everolimus is required.
Serum creatinine	No dose adjustment for metformin required.
Grade 2 (except hyperlipidemia*) (except pneumonitis- refer to table 3-5)	
• If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt the likely causative agent until recovery to grade ≤1. Then reintroduce that agent at same dose. • If event recurs (return to grade 2), interrupt everolimus letrazole or metformin until recovery to grade ≤ 1. If resolution occurs≤ 7 days. Everolimus, metformin and letrozole 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, and letrozole until recovery to grade ≤ 1 or baseline grade / value and reintroduce the medication s at one dose level lower, if available.	
Hyperglycemia >160-250 mg/dL	For hyperglycemia no dose adjustment for everolimus is required, manage with appropriate medical therapy and monitor
Elevated creatinine	Temporary metformin dose interruption until recovery to < grade 1 or baseline grade value and reintroduce metformin at dose level prior to interruption. If grade 2 toxicity in more than one occasion reduce metformin by one dose level
Grade 3 (except hyperlipidemia*) (except pneumonitis – refer to Table 3-5)	
• For the first occurrence, interrupt everolimus, metformin and letrozole until recovery to grade ≤ 1. If resolution occurs ≤ 7 days, Everolimus, metformin, and letrazole 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, metformin, and letrozole until recovery to ≤ grade 1 or baseline grade / value and reintroduce the medications at one dose level lower, if available. • Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days	
Hyperglycemia >300-500 mg/dL	Temporary dose interruption of everolimus until recovery to grade < 1 and reintroduce at a lower dose. Manage with appropriate medical therapy.
Elevated creatinine	Temporary dose interruption of metformin to grade < 1 or baseline grade value and reintroduce metformin at dose level prior to interruption. If grade 3 toxicity in more than one occasion reduce metformin dose to 500mg QD.
Grade 4	
Hold everolimus, metformin, and letrozole until recovery to ≤ grade 1 or baseline grade/ value and reintroduce the medications at one dose level lower, if available.	
Hyperglycemia> 500 mg/dL	Discontinue everolimus and treat with appropriate medical therapy

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Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	No action
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Hold Everolimus until recovery to ≤ grade 1 (platelets ≥ 75 x10^9/L). 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 the medications at one dose level lower, if available.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Hold Everolimus and letrozole until recovery to ≤ grade 1 (platelets ≥ 75 x10^9/L) then reintroduce the medications at one dose level lower, if available.
Grade 3 Neutropenia (neturophils <, ≥0.5 x 10^9/L)	Hold Everolimus until recovery to ≤ grade 1 (neutrophils ≥ 1.5 x 10^9/L). 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 the medications at one dose level lower, if available.
Grade 4 Neutropenia (neutrophis < 0.5x 10^9/L)	Hold Everolimus until recovery to ≤ grade 1 (neutrophils ≥ 1.5 x 10^9/L) then reintroduce the medications at one dose level lower, if available.
Grade 3 febrile neutropenia (not life-threatening)	Hold Everolimus until resolution of fever and recovery to ≤ grade 1 (neutrophils ≥ 1.5 x 10^9/L). 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 the medications at one dose level lower, if available.
Grade 4 febrile neutropenia (life-threatening)	Remove from study.
Any hematological or non-hematological toxicity requiring interruption for ≥ 21 days	Discontinue the drug that is causing the side effect.

***Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 3.2.5.5).**

3.2.4 Monitoring of Everolimus Suspected Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to everolimus must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

3.2.5 Known Undesirable Side Effects of Everolimus

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose

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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 rash, stomatitis /oral mucositis, non-infectious pneumonitis (see Table 3-5), fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections.

Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2). Refer to recommendations for dose adjustments, should any of these treatment-related adverse events occur, in Table 3-1. Everolimus has immunosuppressive properties and may predispose patients to infections, especially 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 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, be vigilant for symptoms and signs of infection, and initiate appropriate treatment promptly. Pre-existing invasive infections prior to starting treatment with everolimus should be treated. 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, treatment with study drug should be discontinued and appropriate antifungal therapy inititated. Cases of pneumocystis jirovecii 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.

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. (See Table 3-3)

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 (see section 3.5) must be done for all patients at screening, with testing performed prior to the first dose of everolimus, as indicated by medical history.

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.

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Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on everolimus. See table 3.1 for hyperglycemia parameters.

Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with everolimus. In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter. If the serum creatinine increases to > 1.4mg/dL, metformin must be held. Metformin may be restarted once serum creatinine improves to grade ≤ 1or baseline value.

Decreased hemoglobin, lymphocytes, platelets and neutrophils have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of everolimus therapy and periodically thereafter.

Everolimus is not recommended in patients with severe hepatic impairment, (Child- Pugh class C).

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus.

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

Table 3-1 provides general recommendations for the management of patients, with suspected drug toxicities while on treatment with everolimus.

More detailed information regarding everolimus reported suspected toxicities and individual cases is provided in the everolimus IB.

3.2.5.1 Management of Hepatitis Reactivation/flare

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality (Loomba et al. 2008).

Monitoring and Prophylactic Treatment for Hepatitis B Reactivation

Table 3-2 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

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Table 3-2 Action to be taken for positive baseline hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-

Test	Result Result	Result	Result	Result	
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 study drug Monitor HBV-DNA approximately every 6 weeks		No prophylaxis Monitor HBV-DNA approximately every 3 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For HBV reactivation definition and management guidelines, see Table 3-3.

Table 3-3 Guidelines for 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** study drug administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days,** study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug 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 study drug. **If resolution occurs > 28 days**, patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.

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For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** [Positive HBs Ab (with no prior history of vaccination against HBV), **OR** positive HBc Ab] --- **reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat :** Start first antiviral medication **AND** **Interrupt** study drug administration until resolution: ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days** study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug 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 study drug. **If resolution occurs > 28 days**, patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which **both** DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

Monitoring for Hepatitis C Flare

The following two categories of patients should be monitored every 6 weeks for HCV reactivation:

- Patients with detectable HCV RNA-PCR test at baseline.
- 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')

For definition of hepatitis C reactivation and the management guidelines, see Table 3-4 Guidelines for management of hepatitis C.

Table 3-4 Guidelines for management of hepatitis C

HCV flare*	
For patients with baseline results: Detectable HCV-RNA, HCV flare is defined as: 2 log10 IU/mL increase in HCV-RNA AND ALT elevation x 5 ULN or 3 baseline level, whichever is higher	Discontinue study drug

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For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, HCV flare is defined as: New appearance of detectable HCV-RNA **AND** ALT elevation x 5 ULN or 3 baseline level, whichever is higher	Discontinue study drug

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* All flares of hepatitis C are to be recorded as grade 3 (CTCAE v4.0 Metabolic Laboratory/Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Flare).

3.2.5.2 Management of Stomatitis/Oral Mucositis/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. gastroesophageal 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.

Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must 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. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 4.0.

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3.2.5.3 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.

3.2.5.4 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.

3.2.5.5 Management of Hyperlipidemia and Hyperglycemia

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 (>2.5x upper normal limit) 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.

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 creatine 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 clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. **Optimal glycemic control should be achieved before starting a patient on study drug. If patients develop poor glycemic control while on study, their dose of metformin will be titrated up to achieve glycemic control prior to adding another hypoglycemic agent. See table 3.1**

3.2.5.6 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

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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 pneumonititis, prophylaxis for pneumocystis jirovecii 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.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus 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. Everolimus may be reintroduced at a reduced dose until recovery to Grade 1 or better.

For cases where symptoms of non-infectious pneumonitis are severe (Grade 3), everolimus therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with everolimus may be re-initiated at a reduced dose depending on the individual clinical circumstances.

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

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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).

Table 3-5 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	everolimus Dose Adjustment
Grade 1	CT scans with lung windows	No specific therapy is required	Administer 100% of everolimus dose.
Grade 2	CT scan with lung windows and consider pulmonary function testing including: spirometry, D_LCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *	Symptomatic only. Consider corticosteroids if cough is troublesome.	Rule out infection and consider interruption of Everolimus until recovery to ≤ Grade 1. Re-initiate Everolimus at one dose level lower if available. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, D_LCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to ≤ Grade 1 . Bronchoscopy is recommended *	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and consider interruption of Everolimus until recovery to ≤ Grade 1. Re-initiate Everolimus at one dose level lower if available. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 28 days..
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue treatment.

***A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.**

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded.

Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

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1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. Determination by the physician it is in the best interest of the patient to stop treatment.
5. disease progression
6. protocol violation
7. patient withdrew consent
8. Non-compliance by the patient with protocol requirements.
9. lost to follow-up
10. termination of the study by the investigator or Sponsor
11. Patient becomes pregnant
12. death

3.3 Treatments

3.3.1 Everolimus, Letrozole and Metformin Administration

The study drugs everolimus, letrozole and metformin will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Everolimus should be administered orally once daily at the same time every day either consistently with or consistently without food. Everolimus tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed and grapefruit or citrus juices should be avoided.

- Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.
- All drugs will be dispensed by the pharmacy. Study medication will be supplied in an open label fashion.
- All patients not already on metformin will have a 7 (up to 10 days to allow for holidays and important life events) day lead in period (Cycle 0) where they take Metformin alone. The starting dose will be 500mg PO daily for days 1-4 of cycle 0 and then increased to 500mg PO BID. If a patient is already on metformin they will continue their regular dose and start Cycle 1 day #1. If they are on metformin but their dose is less than 1000mg/day, their dose will be titrated up to the study dose and then they will start Cycle #1.
- The Everolimus and Letrozole will be added to Metformin on day 7 (up to 10 days to allow for holidays and important life events) and this will be considered the start of Cycle #1.
- Everolimus will be administered orally as once daily dose of 10 mg.
- Letrozole is formulated as tablets of 2.5mg strength and supplied in bottles. One tablet should be taken orally once daily. The oral dose of Everolimus should be taken together with the daily dose of letrozole.

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- Metformin is formulated as tablets of 500 mg strength and supplied in bottles. One 500 mg tablet should be taken orally twice each day (12 hours apart) OR patients should continue their usual dosing if already on metformin. As metformin may cause GI upset, patients are advised to take following a light, fat-free meal.

The oral dose of everolimus should be taken together with letrozole and one of the daily metformin doses (ex: morning dose). The evening dose of metformin should be taken alone following a light, fat-free meal. All medications should be taken continuously as directed by the study team from study day 1 until progression of disease or unacceptable toxicity. Metformin may be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials.

- If vomiting occurs, no attempt should be made to replace the vomited dose.

- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

- Each cycle (except cycle 0) consists of 28 days (4 weeks) of therapy. Patients will have labs drawn (CBC and serum chemistries) and be evaluated in clinic prior to each cycle. To allow for holidays, vacations, and other important life events, patients may be seen +/- 10 days of their return visit date. Any other schedule modifications must be approved by the study chair. In these circumstances, patients may be dispensed additional medication in order not to interrupt treatment.

Medication labels will comply with US legal requirements and 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.

Everolimus is manufactured and provided by Novartis. Everolimus is formulated as tablets for oral administration of 2.5mg, 5mg, and 10mg strength. Tablets are blister-packed under aluminum foil in units of 7 tablets (4 blisters per box), which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

3.3.2 Treatment Assignment

Not applicable. This is an open-label, single-arm study.

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3.3.3 Concomitant therapy

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug and blood transfusions should be recorded.

The following restrictions apply during the entire duration of the study:

a. No other investigational therapy should be given to patients.

b. No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.

c. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug (see Section 3.2).

d. The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.

e. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule.

f. Oral contraceptives in preclinical and clinical data have shown everolimus to have CYP3A4 inhibitory activity rather than induction activity, induction of metabolism of contraceptive hormones by everolimus is unlikely. Consequently, administration of everolimus should not reduce the efficacy of oral contraceptives.

Inhibitors of CYP3A4 and/or PgP

g. Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided.

h. Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. **If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus to 2.5 mg daily**. 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.

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Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.

Inducers of CYP3A4 and/or PgP

i. Avoid the use of strong CYP3A4 inducers for at least 7 days prior to starting on trial. **If patient requires co-administration of strong CYP3A4 inducers** (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort)**, an increase in the dose of everolimus from 10mg daily to 20mg daily, using 5mg increments**. When the strong CYP3A4 inducer is discontinued, everolimus dose will be reduced to prior dose level. Enzyme induction usually occurs within 7-10 days, therefore everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily 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.

Table 3-6 Clinically relevant drug interactions: substrates, inducers, and inhibitors of isoenzyme CYP3A

SUBSTRATES	
Antibiotics: Clarithromycin, erythromycin, telithromycin	**Calcium channel blockers:** Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil
Anti-arrhythmics: Quinidine	**HMG CoA reductase inhibitors:** Cerivastatin, lovastatin, simvastatin
Benzodiazepines: Alprazolam, diazepam, midazolam, triazolam	**Steroid 6beta-OH:** estradiol, hydrocortisone, progesterone, testosterone
Immune modulators: Cyclosporine, tacrolimus (FK506)	**Miscellaneous:** Alfentanil, aprepitant, aripirazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine-N-demethylation,
HIV Antivirals: Indinavir, nelfinavir, ritonavir, saquinavir	

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Prokinetic: Cisapride	dapsone, dexamethasone, dextromethorphan, docetaxel domperidone, eplerenone, fentanyl, finasteride, Gleevec/imatinib, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, risperidone, salmeterol, sildenafil, sirolimus, sorafenib, sunitinib, tamoxifen, taxol, terfenadine, torisel, trazodone, vincristine, zaleplon, ziprasidone, zolpidem
Antihistamines: Astemizole, chlorpheniramine, terfenadine	

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, cobicistat, conivaptan, elvitegravir, indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole,ketoconazole, lopinavir, mibefradil, nefazodone, saquinavir, telaprevir,telithromycin, tipranavir, troleandamycin, voriconazole

Posaconazole (Krishna et al, 2009)

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

Weak inhibitors:

Cimetidine,

Seville orange (Malhotra et al, 2001)

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Unclassified as per the Indiana University DDI listing:

Delaviridine, amiodarone, chloramphenicol, diethyldithiocarbamate, fluvoxamine, starfruit, gestodene, mifepristone, norfloxacin, norfluoxetine, voriconazole*,

Based on http://medicine.iupui.edu/clinpharm/ddis/table.asp as of December 01, 2009 * Voriconazole (unclassified as per the Indiana University DDI table)
Strong inhibitor according to the following reference:
(http://www.nature.com/clpt/journal/v80/n5/pdf/clpt2006438a.pdf)

Table 3-7 Clinically relevant drug interactions mediated by PgP

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, talinolol, topotecan, paclitaxel, everolimus	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	rifampin, St John's wort

Reference:

Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated 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. "

NOTES:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

*****This list of clinically relevant drug interactions is updated as of October, 2012*****

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j. grapefruit or citrus juices affect P450 and PgP activity. Concomitant use should be avoided

k. No chronic treatment with systemic steroids (at a dose equivalent of greater than 20 mg prednisone per day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

l. The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The coadministration of everolimus and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

Examples are provided in Table 3-6 (CYP3A4 inhibitors/inducers) and Table 3-7 (Drug interactions mediated by P-glycoprotein). A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

3.4 Correlative Studies

3.4.1 Correlation of KRAS mutation, PTEN expression, and/or PI3K pathway signaling with response to RAD001, letrozole, and metformin.

Collection of Specimens

M.D. Anderson Cancer Center maintains a tumor bank that collects tumor samples from all surgical cases following the patient's informed consent. Once enrolled, patients will undergo a pre-treatment biopsy with interventional radiology or have an office biopsy if their recurrent tumor is accessible. If a patient has had or is scheduled for a biopsy for their current recurrence, the tissue from this biopsy may be used and the patient will not need to undergo an additional pre-treatment biopsy. Part of this sample will be sent to pathology for routine testing. An

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additional sample will be obtained for the study. The study tissue specimens will be formalin-fixed and paraffin embedded into blocks. Molecular testing will be performed on all pre-treatment samples including CMS 50 panel testing. Pre-treatment samples will be sequenced to analyze the mutational status of KRAS and other genes as this may be a marker of response.

We will evaluate the immunohistochemical expression of PTEN, mTOR, AKT, p70S6K, and ERK1/2 using commercially available antibodies. We will evaluate the difference in expression of these proteins between the pre-treatment biopsy and post-treatment biopsy after 2-cycles in the same patients (for those who consent to post-treatment biopsy) to determine if there are any alterations of the expression of these biomarkers during the progression of disease.

Handling of Specimens

Paraffin-embedded unstained slides or blocks from the primary surgery may be requested from pathology. Pre-and post-treatment samples will be collected by the research staff and stored in the tumor bank. Routine handling of unstained slides and tumor blocks will be employed. Shipping of specimens will be via courier services in secure containers when specimens are not available at the study center (if tissue specimen was not obtained at MD Anderson).

Site Performing the Correlative Study

All assays will be performed at The University of Texas MD Anderson Cancer Center. The MD Anderson Molecular Diagnostics Laboratory will be performing the CMS 50 Panel testing which will include the KRAS gene sequencing and mutation analysis.

3.5 Visit Schedule and Assessments

3.5.1 HBV/HCV Assessments

A detailed assessment of hepatitis B/C medical history and risk factors must be done for all patients at screening. Patients with positive hepatitis B and/or hepatitis C test

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results must begin a course of antivirals 1-2 weeks prior to the first dose of everolimus (as outlined in section 3.2.5).

Testing for hepatitis B viral load and serologic markers: HBV-DNA, HBsAg, HBsAb, and HBc Ab and HCV RNA PCR are required at screening for all patients in the following risk categories:

- 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/2010/chapter-2/hepatitis-b.aspx#849]
- 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,
  - 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

Testing for hepatitis C should be performed using quantitative RNA-PCR at screening for all patients in the following risk categories:

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

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3.5.2 Visit Schedule

Table 3-8 Evaluation and visit schedule

Assessments	Screening/ baseline	Cycle 0[v]	Every Cycle	Every 2nd or 3rd cycle[d]	End of treatment[i]	Follow-up[h]
Medical history	X[a]					
Physical examination	X[b, c]		X		X	X
Vital signs	X[b]		X		X	X
GOG Performance status	X[b]	X	X	X	X	
Weight	X[b]	X	X		X	X
CBC with differential	X[b]		X[r]		X	
Hepatitis screening/monitoring	X[k,m]		X[l,n,q]			
HIV blood test	X[s]					
Serum chemistries (Mg+, SGPT, SGOT, total bilirubin, BUN, serum, creatinine/creatinine clearance) and electrolytes, glucose	X[b,o]		X[q]		X	
Lipid panel (Triglycerides, LDL,HDL)	X[b]			X	X	
Urine or Serum blood Pregnancy Test, if able to become pregnant	X[b]					
Tumor staging (baseline tumor measurements)	X[a]					
O2 sats on room air	X					
CT/MRI of chest, abdomen and pelvis and/or appropriate imaging	X[a]			X[f,r,e]	X[f,r,e]	X
Toxicity	X[a]		X[g]		X	X
Tumor response				X		
Serum estradiol[j]	X[a]					
Medication compliance/pill count			X[p]			
Biopsy	X[t]			X[u]		
Everolimus, Letrozole and Metformin		X[V]	X			

a Within 4 weeks prior to of study registration as defined in section 3 2.2
b Within 7 days of initiation of therapy
c Pelvic exam is done at baseline, after 2 cycles for the first 6 cycles and then every 3rd cycle thereafter (if disease is palpated at baseline the exam is repeated with each restaging, i.e. at the time of CT scan)
d Obtained after cycle #2 (~8 weeks), cycle #4 (~16 weeks), cycle #6 (~20 weeks) and then every three cycles (approximately 12 weeks) thereafter.
e CT/MRI of chest only in patients with chest disease.
f Using the same imaging technique used during the initial evaluation.
g Toxicity will be assessed on an ongoing basis.
h Follow-up time interval at the physician's discretion.

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i Within 4 weeks of the last dose of study drug.
j Documentation of a serum estradiol < 10 pg/mL is required only for patients in whom hysterectomy was performed pre-menopausally and in whom bilateral oophorectomy was not completed. Estradiol is not required for women known to be menopausal or surgically castrated.
k Hepatitis B Virus testing the categories of patients listed in Section 3.5.1 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.
l HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 3.2 and 3.3.
m 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 Table 3-4 Follow-up testing will be performed, as per the visit schedule, only if the patient has a history or is positive at baseline, or both.
n 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
o Creatinine: Patients must have an adequate renal function serum creatinine of < 1.4 mg/dL.
p Patients are requested to bring their unused medication, to the clinic at each visit. Compliance should be verified by a patient pill diary and counting the number of tablets consumed between visits using pill count clarification document.
q Laboratory within 2 days of scheduled clinic visit each cycle. Lipids do not need to be repeated if they have been done 14 days prior to starting Cycle 1. Lipid to be done every other cycle.
r Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials.
s An HIV blood test will be performed if the physician feels the patient is high risk.
t If a patient has had within three months or is scheduled for a biopsy for their current recurrence, the tissue from this biopsy may be used and the patient will not need to undergo an additional pre-treatment biopsy.
u optional: patients will have a tumor biopsy after two cycles if they consent to this optional biopsy
v Patient not already on metformin will have a 7-10 day lead in period when they will only be taking Metformin.

* All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral (i.e. Lamivudine) for 1-2 weeks prior to receiving study drug (see Section 3.2.5.1). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR.

** Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for re-activation. If re-activation is confirmed, everolimus must be interrupted or discontinued according to the guidance in Table 3-3. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered ‘cured’) should have HCV RNA-PCR testing performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for reactivation. everolimus must be discontinued if HCV reactivation is confirmed according to the guidance in Table 3-4.

3.5.3 Screening Procedures

To be completed within four weeks prior to study registration.

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1. Medical history including list of current medications and dosing schedules, history of previous therapies for current disease; and any residual toxicity from prior therapies should be recorded by using the grading schema in CTCAE, v4.0.
2. GOG performance status.
3. Baseline tumor measurements
4. Oxygen Saturation level on Room Air
5. CT/MRI of chest, abdomen and pelvis and/or appropriate imaging.
6. Hepatitis screening as indicated
7. HIV blood test as indicated
8. Pre-treatment, image-guided tumor biopsy. If a patient has had a biopsy for their current recurrence prior to enrolling on this study, the tissue from this previous biopsy may be used and the patient will not need to undergo a pre-treatment biopsy.

Screening/Baseline procedures to be completed within seven days of initiation of therapy. (Cycle 0)

Physical exam including pelvic exam

1. Weight
2. Vital signs (blood pressure, pulse, respiratory rate, temperature)
3. GOG performance status
4. Complete blood count with leukocyte differential and platelet count
5. Serum chemistries (magnesium, SGPT, SGOT total bilirubin, BUN, serum creatinine, glucose and electrolytes).
6. Lipid panel (Triglycerides, LDL, HDL)
7. A urine or blood serum pregnancy test, if patient is able to become pregnant

3.5.4 Treatment Evaluations (Cycle 1 initiation of 3 study drugs)

<u>To be obtained every cycle (4 weeks+/- 10 days):</u>

1. Weight
2. Complete blood count, serum chemistries (magnesium, SGPT, SGOT total bilirubin, BUN, serum creatinine), glucose and electrolytes.
3. Vital Signs (blood pressure, pulse, respiratory rate, temperature)

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4. Physical exam, pelvic exam needed only if disease is palpable in the pelvis.
5. GOG performance status
6. Assessment of treatment related toxicities
7. Hepatitis monitoring, if indicated
8. Medication compliance, pill count

To be obtained after cycle # 2, 4 , and 6 (+/- 10 days):

1. Evaluation of measurable tumor
2. Physical exam Pelvic exam to be done on the same schedule as CT scan, only if disease is palpable in the pelvis.
3. CT/MRI scan of chest, abdomen and pelvis and/or appropriate imaging (the same imaging technique used during the initial evaluation will be performed). Chest imaging (only in patients with chest disease)
4. Assessment of treatment related toxicities
5. Repeat image-guided tumor biopsy (after 2 cycles of treatment) in patients who consented to this optional procedure
6. Lipid panel (Triglcerides, LDL, HDL)

After this first evaluation, patients with progressive disease will be taken off study. To be assigned a status of PR or CR according to RECIST 1.1, tumor measurements must be confirmed by repeat studies (i.e., evaluation of measurable tumor, physical exam, and imaging) that should be performed no less than 4 weeks after the criteria for disease control are first met. To be assigned a status SD, tumor measurements must be confirmed by repeat studies (i.e., evaluation of measurable tumor, physical exam, and imaging) that should be performed no less than 8 weeks after the criteria for disease control are first met.

After these confirmatory studies, to be obtained every 3 cycles (12 weeks +/- 10 days):

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1. Pelvic exam
2. CT/MRI scan and/or appropriate imaging (the same imaging technique used during the initial evaluation will be performed)
3. Chest imaging (only in patients with chest disease)

3.5.5 End of Treatment

To be obtained at the end of treatment (within 4 weeks of the last dose of study drug)

1. Physical exam including pelvic exam
2. Vital signs
3. GOG performance status
4. Weight
5. Complete blood count with differential and platelets, serum chemistries (magnesium, SGPT, SGOT total bilirubin, BUN, serum creatinine, glucose and electrolytes.
6. Lipid panel (Triglycerides, LDL, HDL)
7. CT/MRI scan of chest, abdomen and pelvis and/or appropriate imaging (the same imaging technique used during the initial evaluation will be performed). Chest imaging (only in patients with chest disease)
8. Assessment of treatment related toxicities
9. Medication compliance/pill count and return of unused medication

3.5.6 Follow-Up

Follow-up will be at the discretion of the patient's primary physician. Subjects may come for a clinic visit or may be contacted by telephone.

To be obtained during follow-up visits:

- Physical exam
- Vital signs (blood pressure, pulse, respiratory rate, temperature, weight)
- GOG Performance status
- CT/MRI scan of chest, abdomen and pelvis and/or appropriate imaging (the same imaging technique used during the initial evaluation will be

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performed). Chest imaging (only in patients with chest disease). **The frequency of imaging will be determined by the physician.**

- Toxicity assessment

3.5.7 Efficacy Assessments

Antitumor Effect – Solid Tumors
For the purposes of this study, patients should be re-evaluated for response after the first 2 cycles (8 weeks). In addition to a baseline scan, confirmatory scans should also be obtained after cycle # 4 and 6 and then every 3 cycles (12 weeks) following initial documentation of objective response.

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) Committee guidelines (version 1.1) [*Eur J Ca* 45:228-47, 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.

Definitions
Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with RAD001, Letrozole, and Metformin.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable, but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

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 ≥20 mm

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with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. 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.

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 <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

> Note: 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

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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 or absence of each should be noted throughout follow-up.

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 when both methods have been used to assess the antitumor effect of a treatment.

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. 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 5mm 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. 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.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between

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response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathologic 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 longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum LD must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only 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).

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires*:
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should

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be reported as "*symptomatic deterioration*". Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* '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		

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 recurrent 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 the treatment started, including the baseline measurements.

Patients achieving a complete response, once confirmed, are permitted to stop study medication. Subsequent follow-up will be at the discretion of the treating physician.

Other Efficacy Parameters

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Duration of disease control, time to disease progression, 6 month progression free survival and overall survival will be evaluated.

3.5.8 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry, and regular measurement of vital signs and the performance of physical examinations. See Table 3-8 evaluation and visit schedule

Safety and tolerability will be assessed according to the NIH/NCI CTC http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of

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assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Laboratory Evaluations

Pregnancy Test

A urine or serum pregnancy test is required for all women of child-bearing potential at screening, within 7 days prior to the first dose of everolimus.

Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

Blood chemistry

Blood chemistry must include sodium, potassium, chloride, bicarbonate, magnesium, glucose, creatinine, blood urea nitrogen SGPT(ALT), SGOT(AST), total bilirubin, serum lipid profile (triglycerides, total cholesterol, HDL and LDL).

Because accurate serum glucose and lipid measurements are required, patients should be fasting at the time of the blood sampling.

Hepatitis B Virus testing

The categories of patients listed in Section 3.5 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.

HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 3-3.

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 3.5

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Follow-up testing will be performed, as per the visit schedule, only if the patient has a history or is positive at baseline, or both.

Vital Signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position.

Physical Examination

Physical examination will be performed which must comprise a total body examination.

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

Performance Status

Performance status will be assessed using the GOG performance status scale.

3.5.9 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

3.5.10 Drug Levels and Pharmacokinetic Assessments

No pharmacokinetic measurements will be taken.

3.6 Safety Monitoring

3.6.1 Serious Adverse Events

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug

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- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring:

- after the patient has provided informed consent and until 4 weeks (28 days) after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks (28 days) after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 4 weeks (28 days) after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week (28 days) period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax (877-778-9739) within 24 hours to the Novartis Drug Safety and Epidemiology Department.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should

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describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the everolimus IB or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

3.6.2 Novartis Instructions for Rapid Notification of Serious Adverse Events

The principal investigator has the obligation to report all serious adverse events perM. D. Anderson Cancer Center policy to the IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (877-778-9739)to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks (28 days) after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks (28 days) after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

3.6.3 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine

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outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications

4 Protocol Amendments, or Changes in Study Conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at the study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

5 Data Management

5.1 Data Collection

5.1.1 Registration

MDACC will serve as the only site for this study. All patients enrolled in the study will be registered in the Clinical Oncology Research System (CORe) at MDACC following procedures describedin section 3.2.2

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Patient data will be collected and entered in the MDACC's Protocol Data Monitoring System (PDMS and CORe for adverse events). Data to be entered to include baseline data, study medications by course including, drug holds and reductions, laboratory and diagnostic test results, clinic visit data, involved disease sites and response, adverse events, and off study date.

Investigators must record the information required by the protocol.

5.1.2 Confidentiality Procedures

All pathology specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient or the patient's guardian, except as necessary for monitoring by regulatory authorities, or the IRB.

The investigators and all employees and co-workers involved with this study shall not disclose or use for any purpose, other than performance of the study, any data, records or other unpublished, confidential information disclosed to those individuals for the purpose of the study. No patient identifiers will be used when analyzing or reporting the results.

6 Statistical Methods

6.1 Definition of Primary Endpoint

Clinical benefit rate (CBR) will be determined by combining the complete response rate, partial response rate, and stable disease rate. Response will be evaluated by repeat imaging (CT or MRI) using RECIST 1.1 at the completion of the second cycle (8 weeks $\pm$ 7 days of treatment).

6.2 Definition of Secondary Endpoints

- Survival will be determined by measuring the time from study entry (1st treatment) to progression (PFS) or death (OS)
- Frequency and severity of toxicities as assessed by CTCAE v.4.0
- Correlative Studies: Binary outcomes (present vs. absent) of KRAS gene and other mutation status and PTEN expression status of the primary surgical specimen or most recent tumor biopsy using the CMS 50 panel will be correlated with response to RAD001, letrozole, and metformin.

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6.3 Analytic Plan for Primary Objective

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients. We will estimate the clinical benefit rate with exact 95% binomial confidence intervals.

6.4 Analytic Plan for Secondary Objectives

- We will estimate PFS and OS with the Kaplan-Meier product-limit estimator.
- Toxicities will be tabulated by type and grade according to CTCAE v4.0.
- Correlative Studies: In an exploratory analysis, KRAS and other gene mutation status and PTEN expression status will be correlated with response to therapy using univariate analyses; two-tailed Fisher Exact tests. Response rates with exact 95% confidence intervals will be reported for the binary outcomes of KRAS and other mutation present/absent and PTEN expression present/absent.

6.5 Definition of Populations for Analyses

Patients who are withdrawn from the study before being assessed for response will be counted as treatment failures.

6.6 Sample Size Justification

A two-stage design will be employed with 25 patients evaluable for efficacy (2 cycles) in the first stage. If there are at least 12 patients with clinical benefit (i.e., an objective response or stable disease) (confirmed at 8 weeks), an additional 29 evaluable patients will be enrolled in the second stage for a total of 54 evaluable patients. Thus, we will accrue a minimum of 25 evaluable patients and a maximum of 54 evaluable patients at a rate of 2 patients per month. We estimate that 10 patients may be in-evaluable and thus need to be replaced. Therefore, our total number of patients will not exceed 64. This study design has 91% power with a 10% significance level to reject a clinical benefit rate (CBR) of 40% (the CBR in metformin non-users in a previous RAD001+Letrozole phase II trial) in favor of a CBR of 60% (alternate hypothesis). Thus, we must observe at least 26 patients with clinical benefit among the 54 patients to reject the null hypothesis in favor of the alternate hypothesis. If we observe 12 patients with clinical benefit in the first stage before enrolling all 25 patients in the first stage we will open the second stage to accrual. Otherwise, we will suspend accrual after enrolling the 25 patients in the first stage until we observe 12 patients with clinical benefit allowing us to open the second stage to accrual. This design has a 0.73 probability of stopping after the first stage if the CBR rate is actually 40%, and a 0.08 probability of stopping after the first stage if the CBR rate is actually 60%. Once the study is completed we will estimate the CBR rate with a 95%

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confidence interval. We will enroll 18 patients with KRAS mutation and 36 patients without KRAS mutation. We will use Fisher's exact test to compare patients with/without KRAS mutation with respect to CBR. With 1/3 of patients with KRAS mutation we will have 80% power with a 1-sided significance level of 0.10 to detect a difference in CBR rates of 0.33 for patients without KRAS mutation and 0.67 for patients with KRAS mutation.

Toxicity Monitoring

We will monitor the rate of unacceptable toxicity. Grade 3+ non-hematologic toxicity and grade 4 hematologic toxicity will be considered unacceptable. We will use the methods of Thall et al. (1995) to monitor the unacceptable toxicity rate, and we will consider a rate > 33% too high. We will enroll at least 5 patients, and we will monitor unacceptable toxicity in cohorts of 5 patients.

We will stop the trial early if P(unacceptable toxicity rate > 33% | data from the trial) > 0.95. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than a 95% chance that the unacceptable toxicity rate is more than 33% we will stop the trial. This decision rule gives the following stopping rule. We assume a uniform prior distribution for the unacceptable toxicity rate. Stop the trial if [# of pts with unacceptable toxicity / # of pts evaluated]

≥ 4/5, 6/10, 8/15, 11/20, 13/25, 15/30, 17/35, 19/40, 21/45, 22/50.

The operating characteristics of this study design are shown in Table 1.

Table 1. Operating Characteristics of Toxicity Monitoring Rule

Unacceptable Toxicity Rate	Probability of Stopping Early	Sample Size P_{25}	P_{50}	P_{75}
0.20	0.0135	54	54	54
0.25	0.0410	54	54	54
0.30	0.1097	54	54	54
0.33	0.1800	54	54	54
0.35	0.2479	54	54	54
0.40	0.4795	15	54	54
0.45	0.7121	10	30	54

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0.50	0.8862	10	15	54

Once we have completed the study we will estimate the unacceptable toxicity rate with a 90% credible interval. If we find unacceptable toxicity in 11 of the 54 patients, then our 90% credible interval for the unacceptable toxicity rate will be 13% to 31%. We will also report the posterior probability that the unacceptable toxicity rate is more than 33% (Thall, et al. 1995).

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8 Procedures and instructions

8.1 Publication of Results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

8.2 Disclosure and Confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

8.3 Discontinuation of Study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

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8.4 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

8.5 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

8.6 Informed Consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

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The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

8.7 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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9 Appendices:

9.1 APPENDIX A – GOG Performance Status

GOG Score	Karnofsky Score	Activity Level
0	90-100	Fully active, unrestricted activities of daily living
1	70-80	Ambulatory, but restricted in strenuous activity
2	50-60	Ambulatory, and capable of self care. Unable to work. Out of bed for >50% of waking hours
3	30-40	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance
4	10-20	Completely disabled, and no self care
5	0	Dead