A Phase II Study of Letrozole and RAD001 (Everolimus) in Patients with Advanced or Recurrent Endometrial Cancer

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1 INTRODUCTION

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

1.1 Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in the United States with 40,100 new cases and 7,470 deaths estimated for 2008.[1] The standard treatment for primary endometrial cancer consists of a total hysterectomy with bilateral salpingo-oophorectomy and possible lymph node dissection. This may be followed by radiation therapy depending on tumor histology, grade and stage. Treatment failure in low-risk patients is exceedingly rare [2]. Tumor recurrence is most common in women with advanced-stage disease or those with high risk features in their primary tumor [3]. The patterns of recurrence depend on the initial disease distribution. Women with advanced primary disease tend to have abdominal or systemic failure. In women whose primary disease was limited to the uterus, one third tend to have recurrences limited to the pelvis and two thirds have distant failure. Women with isolated pelvic recurrences can potentially be salvaged with radiation therapy or radical surgery. However, in women with distant recurrent disease, treatment is largely palliative.

1.2 Treatment of Recurrent or Advanced Endometrial Cancer

Several chemotherapeutic agents or combinations of agents have been studied in the treatment of women with recurrent or advanced endometrial cancer. Doxorubicin was one of the first agents identified to have activity in endometrial cancer and treated patients had a 22% response rate and a progression free survival of 3.2 months [4]. Single agent cisplatin and carboplatin when used as first-line agents have also been shown to have anti-tumor activity, with response rates of 20-42% and progression free survival rates of 3-5 months [3,5,6]. A phase III study combining cisplatin with doxorubicin showed improved progression-free survival but no difference in overall survival [7]. Paclitaxel has also been shown to have activity in endometrial cancer and has been incorporated into combination therapy regimens. The Gynecologic Oncology Group (GOG) is currently performing a phase III study comparing doxorubicin/cisplatin/paclitaxel to carboplatin/paclitaxel.

In addition, some endometrial cancers are hormonally sensitive. Treating recurrent and progressive tumors with progestins and progestins in combination with tamoxifen (a selective estrogen receptor modulator) has had limited results. In a phase II study by the Gynecologic Oncology Group, an aromatase inhibitor (anastrozole) had limited activity as a single agent against recurrent and progressive endometrial cancer. In this study, of the 23 patients enrolled, 2 had partial responses and 2 had short-term stable disease.

Although response rates have improved, more effective systemic agents with longer durations of response are needed. Prognosis remains very poor for patients who fail first-line chemotherapy for progressive or recurrent endometrial cancer [3,8].

1.3 PTEN/AKT/mTOR Pathway:

PTEN, a tumor suppressor gene, has been shown to play several roles in tumor suppression, including cell cycle arrest and promotion of apoptosis. Inactivating mutations in PTEN occur frequently in many human cancers. In particular, mutations in PTEN occur in 80% of endometrial carcinomas.[3]

Tumor cells lacking PTEN contain high levels of activated Akt. This suggests that PTEN is necessary for the appropriate regulation of the phosphatidylinositol 3-kinase/Akt pathway. Recent studies have identified the AKT kinase as a potential mediator of tumorigenesis in endometrial cancer cell lines.[3,9] The finding of PTEN mutations in the majority of endometrial cancer suggests that the loss of PTEN function may be one mechanism by which AKT activity is increased in this disease. Because PTEN-deficient cancer cells may have upregulated activity of the mammalian target of rapamycin (mTOR), which is downstream of AKT, these cells may be sensitive to mTOR inhibition.[10,11]

1.4 RAD001 (everolimus)

RAD001 (everolimus) has been in clinical development since 1996 in solid organ transplantation. Since 2003, the drug is approved in several countries, including the majority of European Union states, as prophylaxis of rejection in renal and cardiac transplantation in combination with cyclosporin A and glucocorticosteroids. Its first commercialization (as Certican) dates from March 2004 in Germany.

Everolimus 5mg and 10mg tablets were recently approved under the trade name Afinitor® for patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide.

The following is a brief summary of the main characteristics of RAD001. Fuller information can be obtained from the [Investigator's Brochure].

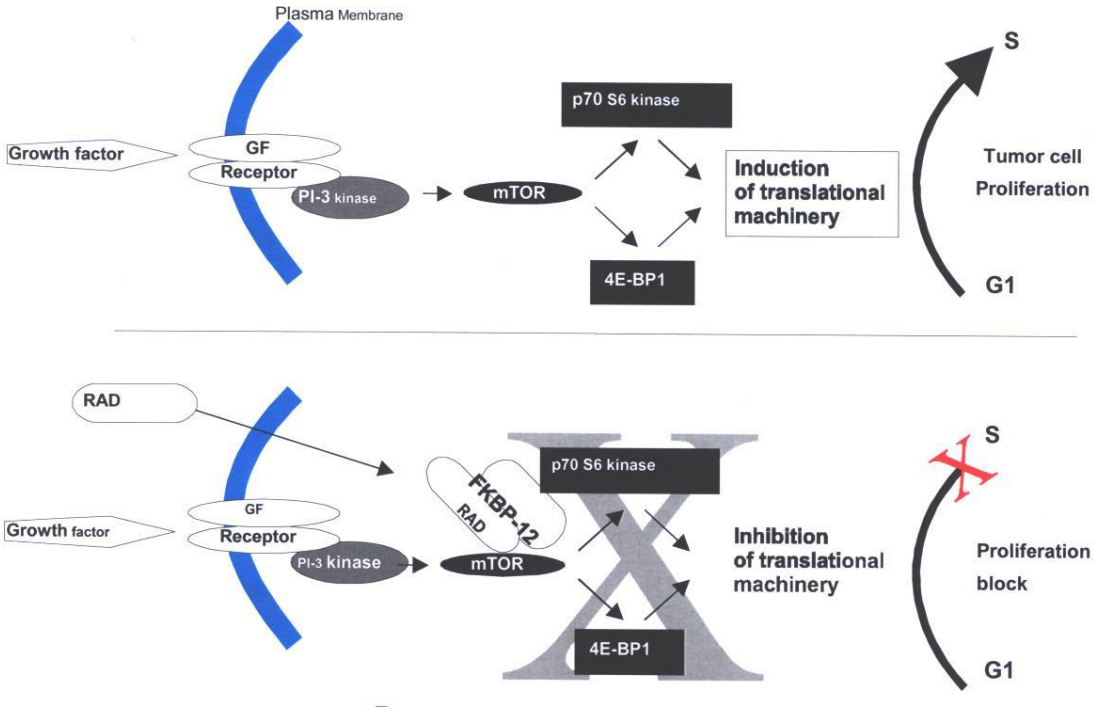
1.4.1 Pharmacology of RAD001

RAD001 (INN: everolimus) is a novel macrolide formulated for oral administration, which is being developed as an antiproliferative drug with applications as an immunosuppressant and anticancer agent.

At the cellular and molecular level, RAD001 has the same mechanism of action as an immunosuppressant and as an anti-tumor agent. It acts by selectively inhibiting mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation of activated T-lymphocytes or neoplastic cells. TOR is a ubiquitous protein kinase implicated in cell cycle control and specifically in the progression of cells from the G1 to S phase. TOR is considered to be a downstream

component of the PI3/Akt pathway, its own primary downstream substrates being the eIF-4E-binding protein (4E-BP1) and p70 S6 kinase 1 (S6K1) which both play a role in the translational regulation of mRNAs encoding proteins involved in G1-phase progression (see Figure 1-1).

Figure 1 RAD001 as an inhibitor of cellular proliferation



GF: Growth factor; PI-3 kinase: Phosphoinositide 3-kinase; FKBP-12: FK506-binding protein 12; 4E-BP1: eIF-4E binding protein 1; mTOR: mammalian "Target of Rapamycin". Upper Panel: situation in presence of growth factors (mTOR pathway and translational machinery are induced; cells proliferate). Lower Panel: situation in presence of RAD001 (mTOR pathway is inhibited by RAD001/FKBP-12 complex [large X]; translational machinery is inhibited and cells are blocked or delayed in G1 resulting in a block/reduction of proliferation [small X]).

RAD001 acts on interleukin and growth-factor-dependent proliferation of cells through high affinity for an intracellular receptor protein, the immunophilin FKBP-12. The resulting FKBP-12/RAD001 complex then binds with mTOR to inhibit downstream signaling events.

In vitro studies have shown that RAD001 can inhibit the proliferation of numerous cell lines originating from solid tumors, including breast cancer, with the most sensitive cell lines having IC50's at the sub nanomolar/low nanomolar level. In addition, experiments in vitro with human umbilical endothelial cells (HUVECS) and in animal models of angiogenesis suggest an additional anti-angiogenic effect, presumably through mTOR

inhibition in proliferating endothelial cells.

In vivo studies in rodent models have shown orally administered RAD001 to be a potent inhibitor of tumor growth at well-tolerated doses. This has included several different mouse xenograft models, including pancreatic, colon, epidermoid (including a Pgp-170 over expressing, cytotoxic-resistant variant) and two syngeneic models (CA20948 rat pancreatic, B16/BL6 mouse melanoma). In general, RAD001 was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e. doxorubicin and 5-fluorouracil), while possessing similar antitumor activity. Only one instance of in vivo resistance has been observed (MAXF 401 mammary xenograft model), otherwise the activity of RAD001 was general inhibition of tumor growth (persistent regressions in one tumor model, T/C values of 9 to 45% in 12 tumor models). Xenograft models sensitive to RAD001 treatment included tumors derived from cell lines exhibiting comparative resistance in vitro (KB-31 and HCT116).

The preclinical studies also demonstrated that inhibition of p70S6kinase 1 (S6K1), downstream of mTOR, was a marker of drug activity. In vitro, short-term exposure to RAD001 led to S6K1 inactivation for as long as 120 hours. In vivo, in the rat syngeneic setting, a single dose of RAD001 led to S6K1 inhibition for up to 72 hours in tumors and skin and for up to seven days in peripheral blood mononuclear cells (PBMCs).

1.4.2 Clinical pharmacology of RAD001

RAD001 is administered orally, its bioavailability being estimated at approximately 11%. Absorption is intestinal. Absorption is delayed moderately by food (60% reduction in Cmax and 16% reduction in AUC when drug administration follows a fat-rich meal). The AUC is consistently dose-linear with moderate inter-patient variability (CV approx 50%). Cmax is dose-linear until 20mg increasing in a non-linear manner thereafter. The terminal half- life is 30-35 hours. The main elimination route for RAD001 is by hepatic metabolism, mainly hydroxylation. The parent compound is the major component in the blood. Metabolism to rapamycin is of minor importance. The main metabolites are not bioactive. Excretion is (>80%) through the bile and the intestinal tract.

RAD001 is a substrate of the CYP3A4 isoenzyme and P-gp and its metabolism is sensitive to 3A4 inhibitors/inducers. In combination with microemulsion cyclosporine A (Neoral®), a 3A4 and P-gp inhibitor, the bioavailability of RAD001 is significantly increased: for AUC by a mean of 168% (range: 46-365%); for Cmax by 82% (range: 25-158%). RAD001 itself does not appear to have an enzyme-inducing/inhibiting effect at the levels achieved in solid organ transplantation and current oncology studies. Mild-moderate hepatic impairment will increase exposure. Ethnic differences exist with clearance in blacks approximately 20% higher than that in Caucasians and Japanese patients who appear to be similar as regards clearance. Renal function has only marginal influence on the clearance of RAD001 so that no dosage adjustment is necessary in patients with renal failure.

1.4.3 Clinical experience with RAD001 in non-oncology indications

There is extensive safety data on RAD001 because of the advanced stage of its development in solid organ transplantation. Safety data includes animal testing, single-dose studies in non-transplant patients, and short- and long-term studies in transplant patients where RAD001 was administered daily as a part of an immunosuppressant, multi-drug regimen consistently including cyclosporin A and glucocorticoids, and other drugs (azathioprine, basiliximab) on occasions. Controlled studies in the transplant setting consisted of dosage comparisons and comparisons between RAD001 and mycophenolate mofetil or azathioprine, but never placebo, as additions to cyclosporin and steroids.

The tolerability of RAD001, when used alone and given daily, appeared to be good with only mild to moderate suspected adverse drug reactions, mostly headache. Treatment with RAD001, given daily, has been associated with a decrease in absolute neutrophil counts and platelet counts. This is most likely due to a pharmacodynamic action on hematopoiesis. This rarely led to severe leucopenia or thrombocytopenia, defined in the transplant setting as CTC grade 2. Chronic treatment with RAD001, given daily is associated with an increase in serum lipid levels. Hyperlipidemia responded to lipid-lowering drugs. Long-term treatment with RAD001 was associated with reduced testosterone levels, probably the result of interference with sterol metabolism. This did not appear to translate into increased sexual dysfunction. Long-term RAD001 treatment of renal transplant patients with RAD001 and cyclosporin A was associated with an increase in renal dysfunction in comparison with comparator drugs (azathioprine, mycophenolate mofetil) combined with cyclosporin A. The preclinical findings and effects observed on reducing cyclosporin levels suggest this to be a potentiation of cyclosporin nephrotoxicity rather than an effect of RAD001 itself.

1.4.4 Phase 1 study in oncology (Protocols 2101, 2102)

Clinical studies of RAD001 in Oncology have been ongoing since 2002.
Because of the anticipated long pharmacodynamic (PD) effect (as shown in preclinical studies by the prolonged inhibition of downstream markers in tumor and other tissues) the first phase 1 study investigated RAD001 administered weekly. For reasons described below the phase 1 program has been extended to explore daily dosing also. The phase 1 program investigates the effects of dose and schedule on safety and pharmacokinetics as well as the pharmacodynamic effects in order to identify an optimal biological dosage (OBD). The OBD is defined as the minimum dosage of RAD001 resulting in target inhibition and which is satisfactorily safe. This program is still ongoing. A certain number of combination studies have also been initiated, and are summarized in the [Investigator's Brochure].

RAD001C: Protocols 2101/2: Steady-state pharmacokinetics (whole blood)

Parameter	5 mg/week	10 mg/week	20 mg/week	30 mg/week
N	4	4	2[2]	5
tmax (h)	1 (1-2)	1 (1)	1 (1)	2 (1-2)
C_{max}^{ss} (ng/ml)	32.3 ± 15.4	69.0 ± 8.1	93.5 ± 0.4	80.0 ± 19.7[1]
C_{max}^{ss}/Dose (ng/ml/mg)	6.5 ± 3.1	6.9 ± 0.8	4.7 ± 0.0	2.7 ± 0.71
$AUC\tau^{ss}$ (ng·h/ml)	283 ± 48	573 ± 258	1001 ± 301	1798 ± 827
$AUC\tau^{ss}$/Dose (ng·h/ml/mg)	56.6 ± 9.7	57.3 ± 25.8	50.1 ± 15.1	59.9 ± 27.6
$t_{1/2}$ (h)	26.3 ± 2.9	37.9 ± 13.6	30.5 ± 12.0	36.8 ± 6.1

Values are median (range) for tmax and mean ± standard deviation for all others.
1. Two values above the upper assay quantification limit of 100 ng/ml were omitted.
2. samples for PK measurement of 2 patients lost in transport.

1.4.4.1 Phase 1 single agent studies (protocols 2101/2102, 2106 and 2107)

Two phase 1 studies (2101/2102 and 2107) are being conducted in patients with advanced solid cancers in whom the treatment may prove therapeutic. Study 2106 investigates the PD activity of RAD001 in a setting (4 weeks treatment pre-resection of newly diagnosed prostate cancer) in which the treatment cannot be expected to be therapeutic. The studies are open-label, sequential cohort studies in which the dosage of RAD001 is escalated from one cohort to the next according to the presence or absence of patients with dose-limiting toxicity (DLT). More details on these studies are included in the [Investigator's Brochure].

1.4.4.2 Safety findings

All adverse events occurring in more than 10% of patients in studies 2101/2, 2106 and 2107 are summarized by schedule and dosage (according to the NCI Common Terminology Criteria, version 3) in Table 1-2.

Suspected adverse drug reactions (ADR) occurring in ≥10% of patients are summarized in Table 1-3. In order of frequency these include: rashes (37%), stomatitis/mucositis (27%), fatigue (26%), headache (19%), nausea (12%), diarrhea (10%) and vomiting (10%). The majority of suspected ADRs were of mild to moderate severity (CTC grade 1-2) with only isolated grade 3 events. The data suggest dose-relationship for rash, stomatitis/mucositis and fatigue.

The most frequently-reported ADR was rash &/or erythema. Mostly the nature of the rash was not specified. Descriptions were given for 7 patients: macular &/or papular (n=4), erythematous (n=2), acneiforme (n=1), pustular (n=1), pruritic (n=4), associated with dry skin in 3 cases. Rash was always grade 1-2. The localization was given for 16 patients, this involved: face/neck (n=9), upper limbs (n=6), lower limbs (n=6), trunk/back/buttocks (n=4). In 4 patients the rash was generalized (≥3 zones involved). Events reported as mucositis, stomatitis or mouth ulceration, were grade 1-2 in all but four patients. Grade 3 stomatitis occurred in 2 patients at 70mg/wk and in one patient

each at 50mg/wk and 10mg/d. It is the main dose-limiting toxicity.

Table 1-2 All adverse events in greater than or equal 10% of patients (grade 3-4 in brackets) Phase 1 monotherapy studies (June 04)

Weekly regimen							Daily regimen		Total
No of patients	5mg	10mg	20mg	30mg	50mg	70mg	5mg	10mg	
Study 2101/2	4	4	5	5	6	7	4	6	41
Study 2107	0	0	8	0	6	7	6	6	33
Study 2106	0	0	0	4	1	0	4	1	10
Total	4	4	13	9	13	14	14	13	84
Weekly regimen							Daily regimen		Total
Reported events									
Rash (all)[1]	0	0	1	3	7	7	8	8	34
Fatigue	1	0	7(1)	4	6(1)	4(1)	4(1)	6	32(4)
Headache	1	2	3	3(1)	6	4	5	3	25(1)
Stomatitis/mucositis	0	0	2	3	4(1)	5(2)	4	5(1)	24(4)
Nausea	3(1)	2	2	2	3	4(1)	2	2	20(2)
Anorexia	3	0	1	1	4	2	1	3	15
Constipation	2	0	2	1	1	2	4	2	14
Diarrhea	2	0	0	1	7	0	1	2	13
Vomiting	3	0	1	1	4	2	0	2	13
Cough	0	1	2	2	3	2	1	2	13
Dyspnea NOS	2	0	2	2(1)	3(1)	2(1)	1(1)	1(1)	13(5)
Abdominal pain NOS	3	0	1	0	1	0	2	2	9
Pruritus	0	1	1	2	1	0	3	1	9
Pyrexia	1	1	1	2	1	0	1	2	9
Back pain	1	1	0	1	3	0	1	1	8
Abdominal distension	0	0	0	0	3	1	1	3	8

1. Rash (all) includes: all types of reported rash & erythema

Table 1-3 Suspected adverse drug reactions[1] in greater than or equal 10% of patients (grade 3-4 in brackets) Phase 1 monotherapy studies (June 04)

	Weekly Regimen						Daily Regimen		Total
No of patients	**5mg**	**10mg**	**20mg**	**30mg**	**50mg**	**70mg**	**5mg**	**10mg**	**Total**
Study 2101/2	4	4	5	5	6	7	4	6	41
Study 2107	0	0	8	0	6	7	6	6	33
Study 2106	0	0	0	4	1	0	4	1	10
Total	4	4	13	9	13	14	14	13	84
Reported events									
Rash (all)[2]	0	0	2	2	5	7	7	8	31
Stomatitis/mucositis	0	0	2	3	3(1)	5(2)	3	5(1)	23(4)
Fatigue	1	0	2	4	5	4	0	6	22(1)
Headache	0	0	1	3	3	2	5	2	16
Nausea	2	1	1	1	2	1	1	1	10
Diarrhea NOS	0	0	0	1	5	0	0	2	8
Vomiting NOS	2	0	1	1	2	1	0	1	8

1 Suspected drug-causality according to investigators.

2 Rash (all) includes: all types of reported rash & erythema

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomized phase III study for the treatment of metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The median age of patients was 61 years (range 27 to 85). The most common adverse reactions (incidence ≥10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnoea. The most common grade 3-4 adverse reactions (incidence ≥2%) were infections, stomatitis, fatigue, and pneumonitis.

The median duration of blinded study treatment was 141 days (range 19 to 451) for patients receiving everolimus and 60 days (range 21 to 295) for those receiving placebo. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups,

respectively. Most treatment-emergent adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 39% versus 7% of patients receiving everolimus and placebo, respectively. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm.

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

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

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

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.

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. 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

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.

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.

1.4.4.3 Laboratory findings

Blood cell counts were monitored regularly because of the known myelosuppressive effect of rapamycins. Abnormal counts were reported as adverse events in only four patients (grade 1 thrombocytopenia in 3 patients at 20 mg/wk, 70 mg/wk, 5 mg/d respectively) in study 2101/2, and a transient grade 3 neutropenia in patients at 70 mg/wk in study 2107 which was dose-limiting. Preliminary evaluation of the recorded values indicate that in a significant fraction (approx 50%) of patients, the platelet count falls with initiation of treatment but that this is generally limited to the normal range, occasionally grade 1, not worsening with continuing therapy nor requiring therapeutic intervention. In some patients a similar decrease of the neutrophil count, within the normal range, was also observed. The occurrence of a grade 3 thrombocytopenia in a patient receiving RAD001 and letrozole (Section 1.5.3) does suggest that some individuals may be particularly sensitive to the myelosuppressive effects of RAD001 (a pharmacodynamic interaction with letrozole being unlikely as letrozole is not believed to influence hematopoiesis).

Serum lipid levels were monitored because of the known hyperlipidemic effect of rapamycins. Hyperlipidemia was reported as an adverse event in 8 patients (hypercholesterolemia in n=7, hypertriglyceridemia in n=1). Preliminary evaluations of recorded laboratory values suggest that approximately 23% of patients acquire grade 1-2 hyperlipidemia on treatment of which 19% have raised cholesterol, 10% raised triglycerides, and 6% have both. Only one grade 3 value was recorded.

Five patients have received lipid-lowering drugs concomitantly with RAD001:

- 1 pt for gr.3 hypertriglyceridemia at 5mg/d
- 4 pts for gr.1-2 hypercholesterolemia at 5mg/d (n=2), 10mg/d (n=1), 50mg/wk (n=1).

Non-hematological laboratory abnormalities other than hyperlipidemia have not been recorded as suspected adverse events.

Infections

RAD001 has immunosuppressive properties because of its ability to inhibit the proliferation of activated T-lymphocytes. In the 84 patients treated in the mono-agent studies, infectious events have been recorded on 26 occasions. These have been mostly common infections, half of them bronchopulmonary (n=6) and urinary tract (n=7). Herpes simplex or zoster infections were not particularly frequent (n=5) and were not severe. Oral candidiasis was reported on 3 occasions, but this may represent under-reporting, as it may have been a component of the frequently reported oral stomatitis. The only serious and only grade 3 infection recorded was that of pneumonia in a patient with advanced NSCLC.

1.4.4.4 Efficacy findings

Efficacy assessment was not the primary purpose of phase 1. However, in studies 2101/2 and 2107 patients undergo regular clinical and CT appraisal for assessment according to RECIST. No complete responses have been observed. The numbers of patients with partial response (PR) or prolonged stable disease (SD) as of June 2004 are summarized in Table 1-4.

Table 1-4 RAD001 monotherapy. Summary of patients with PR or prolonged SD in studies 2101/2 & 2107 (June04)

		N treated	PR	SD (6mo)	SD (4mo)
RAD001 Weekly	≤30mg	n=26	2 NSCLC (30mg)[1] CRC (20mg)[2]	3 HCC, CRC, fibrosarcoma (10mg)[1]	2 CRC(20mg)[1] NSCLC (30mg)[1]
	50mg	n=12			Adeno ca. unknown primary[1]
RAD001 Daily	5mg	n=10		Oesophago-gastric[1] CRC[1]	Breast[2] cholangiocarcinoma[2]
	10mg	n=12			

CRC: Colorectal carcinoma HCC: hepatocellular carcinoma NSCLC: non small cell lung cancer
[1]Study 2101/2
[2] Study 2107

1.4.4.5 Pharmacodynamic findings

In part 1 of study 2101/2102, 16 patients (4 pts in each dosage cohort) could be assessed for changes in S6K1 activity in PBMC by radioimmunoassay.

There was variation in activity as shown by the differences in the two baseline (pre-treatment) values obtained for each patient. However, there was striking inhibition of activity in all patients at the 24 hr post-dose assessment. The dose influenced the duration of inhibition. At steady state, the duration of total S6K1 inhibition was from 3-5 days in patients at doses of 510mg and for ≥7 days in patients at 20-30mg.

PK/PD modeling to predict intratumoral inhibition in patients

Subsequent modeling has been carried out, combining the pharmacokinetic (PK) and pharmacodynamic (PD) data from this study with preclinical data.

Preclinical studies showed that RAD001 has an antiproliferative effect on tumor cells *in vitro* and in tumor-bearing rodents, including CA20948 pancreatic tumor-bearing rats (Section 1.2.1). Inhibition of S6K1 by RAD001 was shown in tumor, skin and PBMC. The *in vivo* relationship between unbound drug levels and S6K1 inhibition was assessed in the rat CA20948 tumor setting in order to build a basic concentration-effect model in PBMC, skin and tumor. In rats, the unbound drug level at 50 % S6K1 inhibition (IC_{50}) in tumor was 0.05 ng/g, similar to that in skin, while IC_{50} in PBMC was 0.01 ng/mL.

Unbound drug levels estimated from the rodent PK model were scaled up to humans. In patients, S6K1 inhibitions in PBMC, predicted by the PK/PD model derived from the rat

in vivo study, were comparable to values measured in the clinical studies. Model-derived intratumoral PK/PD values for patients were compared to those in rats.

Assuming that to be efficacious, the drug should achieve target inhibition at least as great as that associated with efficacy in the rat experiment, and that a similar PK/PD relationship for tumor exists in patients as in rats, 20mg in patients was predicted to be the minimum effective dose. Hence, 20mg was taken as the initial weekly dose to take forward into the subsequent phase 1 study (2107) in which the PD effect of RAD001 is being investigated in tumor itself obtained by biopsy.

The PK/PD model also suggests that a greater degree of sustained inhibition should result from daily administration compared to an increase in the weekly dosage above 20mg, for the same total drug consumption (i.e. 10mg/d compared to 70mg weekly). These results are summarized in Figure 1-2 and Figure 1-3.

Figure 1-2 **Syngeneic pancreatic tumor-bearing rats. Pharmacodynamic response (S6K1inhibition) with various regimens**

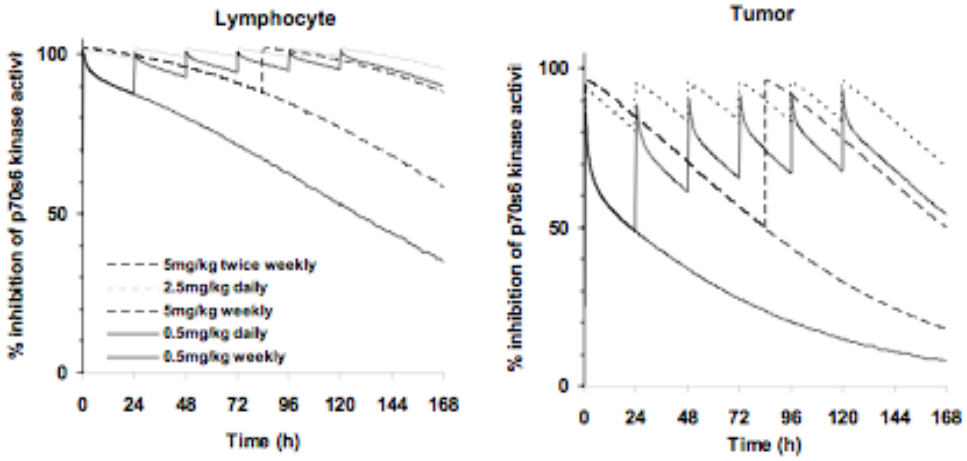
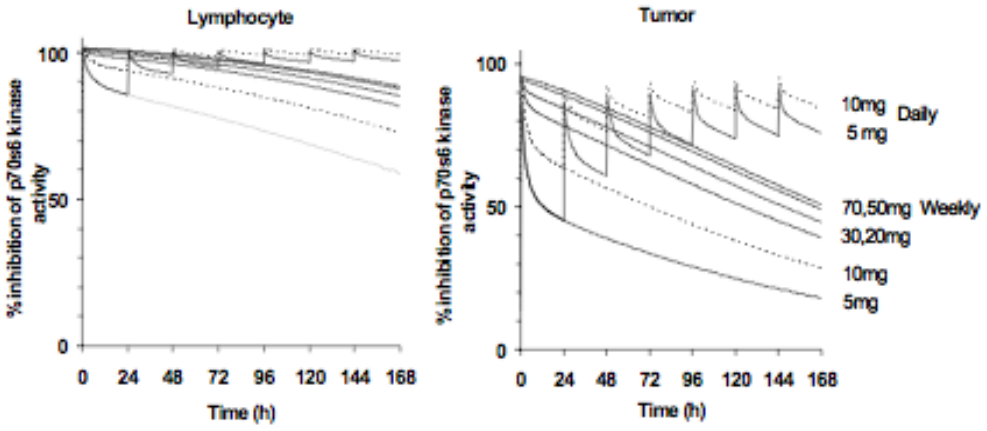


Figure 1-3 **Predicted PD changes in patients at 6 different weekly dosages (5,10,20,30,50,70mg) and 2 different daily dosages of RAD001 (5, 10mg).**



1.5 RAD001 – Rationale for use in endometrial cancer

Our group recently found that RAD001 decreased the progression of endometrial hyperplasia in the Pten heterozygote murine model by increasing the rate of apoptosis and decreasing cell proliferation. The decrease in phospho-p70 S6 Kinase in the treated group compared to the untreated group also suggests 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[12]. 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[13]. In this model, inactivation of mTOR using an mTOR inhibitor reduced neoplastic proliferation, tumor size, and S6K kinase 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 to 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 duration 8.7 months). None of these patients received prior chemotherapy[14].

We recently completed a phase II single-agent clinical trial of RAD001 in 35 women with recurrent, chemotherapy-refractory measurable disease. The median age of the cohort was 58 years. All grade toxicity was infrequent and most commonly represented by fatigue (51% any grade, 20% grade 3), pain (375 any grade, 0% Grade 3), nausea (34% any grade, 11% grade 3) and stomatitis (26% any grade, 0% grade 3). The most common hematological toxicity was anemia (46% any grade), neutropenia (40% any grade) and lymphopenia (34% any grade). Dose reduction was required in 17 patients – predominately (10 of 17) from stomatitis. Efficacy was measured by clinical benefit rate (CBR) which consisted of complete and partial response as well as stable disease. No objective responses were observed however, stable disease was observed in 12 or 28 evaluable patients (CBR: 43%). 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, measurable clinical responses are uncommon; however, the current rate of observed stable disease cases is excellent. Although chemical toxicity (mostly

hyperlipidemia) has been seen, clinically significant side effects have not been problematic. In a preliminary analysis of translational endpoints and response, we are finding that patients who have tumors that have PTEN mutations are more likely to experience a clinical benefit (i.e., stable disease) than in patients whose tumors do not have PTEN mutations. We believe that this single agent activity in pretreated patients suggest that RAD001 will have clinical applications in the treatment of this disease. In our institution, we plan on evaluating RAD001 in combination with a hormonal agent as a first line treatment for patients with recurrent endometrial cancer. Continued evaluations of tissue biomarkers will allow us to potential predict response and to screen patients based on the molecular profile of their tumors.

1.6 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 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.

For further information on letrozole, see Femara Prescribing Information, Appendix F.

1.7 Combination of letrozole and RAD001

There is evidence that an enhanced PI3K/Akt/mTOR pathway may be one of the key adaptive changes accounting for endocrine-resistant growth in breast cancer. Inhibition of this pathway might therefore prevent or delay the onset of resistance to anti-endocrine therapy.

1.7.1 Pharmacology

An in-vitro study of the effects of RAD001, letrozole and combinations of both compounds has been carried out in aromatase-expressing breast tumor cells (MCF-7 cell-line transfected with the aromatase gene) which are stimulated not only by estradiol but by androstenedione, the precursor of estradiol and substrate of aromatase. The concentration-dependent antiproliferative activity of both compounds given individually was enhanced by the combination (Rudloff, et al 2004). Subsequent analysis has established the antiproliferative enhancement to be accompanied by a clear increase in apoptosis normally associated only minimally with each compound alone (Novartis data on file).

1.7.2 Potential for drug-drug interaction

Pharmacokinetic interaction between letrozole and RAD001 is not expected. The two drugs follow different metabolic routes (RAD001: CYP3A-mediated metabolism and hepato-intestinal elimination; letrozole: CYP2A6 mediated metabolism and renal elimination).

1.7.3 Combination Phase 1b study

An ongoing interaction study (Protocol CRAD001C2108) investigates the combination of letrozole (2.5mg/d) with RAD001 at escalating doses in patients receiving letrozole as first-line therapy for advanced HR+ breast cancer. To be eligible, patients have to have received letrozole already for a minimum of 4 months with sub optimal response, defined as: stable disease or progressive disease without urgent indication to go to chemotherapy (e.g. bulky or symptomatic disease). All patients continue to receive letrozole 2.5 mg once daily, to which RAD001 is added. Successive cohorts are defined by the dosage of RAD001: 5mg and then 10mg/d. Assessed over the first 28 days of the combined therapy, DLT is defined as any grade 3-4 toxicity with the exception of grade 3 hypercholesterolemia, hypertriglyceridemia, or lymphopenia as well as any toxicity requiring interruption of treatment for more than two weeks.

The main safety events are summarized in Table 1-5. One patient (RAD001 at 10mg/d) has been reported with a DLT, this being a grade 3 thrombocytopenia, the nadir (48x109/L) of a progressive decline in the platelet count over 3 weeks treatment. Recovery followed interruption of treatment. No other DLT or grade 3-4 adverse events have been reported. Suspected ADRs occurring in more than 10% of patients (i.e. ≥2/11 patients documented so far) include: fatigue/asthenia (n=8), stomatitis/mucositis (n=5), headache, rash/skin reaction (n=3 each), diarrhea, nausea (n=2 each). A patient with coexisting chronic viral hepatitis was discontinued when her serum transaminase activity increased from grade 1 to grade 2.

Table 1-5. Study 2108 (RAD001 + letrozole) Main safety events (July 04)

Letrozole 2.5 mg/d + RAD 001	RAD001 5 mg/day N=6	RAD001 10mg/day N=9
DLT	0/6	1/9
Pts with Gr 3/4 suspected ADR	0	1[2]
Discontinuations / Death	0	0
Progressive disease	2	2
Adverse events	1[1]	1
Withdrew consent	0	0
Suspected drug-related SAEs	0	1[3]

DLT: dose-limiting toxicity in first 4 weeks (# of pts with DLT/mo of those evaluable for DLT)
ADR: adverse drug reaction
SAE: serious adverse event (death or potentially fatal; requiring or prolonging hospitalization)

1. discontinuation for raised serum transaminase activity (patient with chronic viral hepatitis)
2. grade 3 thrombocytopenia
3. hospitalization of the patient who developed grade 3 thrombocytopenia

Pharmacokinetic profiles of letrozole were investigated before addition of RAD001 and after RAD001 reached steady state (day 15). Currently available data in 6 patients for letrozole and 3 patients for RAD001 suggested that co-administration of RAD001 with 2.5 mg/day letrozole does not influence letrozole pharmacokinetics and that exposure to RAD001 in the presence of letrozole dose not exceed historical exposure data obtained from study 2101.

2 STUDY OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

2.2.1 To determine the duration of disease control, time to disease progression, and survival of this cohort of patients.

2.2.2 To determine the nature and degree of toxicity of RAD001 and letrozole in this cohort of patients.

3 INVESTIGATIONAL PLAN

This is a phase II activity trial of RAD001 in combination with letrozole for patients with recurrent or progressive endometrial cancer. We will enroll a minimum of 10 patients and a maximum of 35 patients. Patients will be enrolled at M.D. Anderson Cancer Center and at Morristown Memorial Hospital, Women's Cancer Center. Our goal is to obtain a response rate or stable disease rate of greater than 20 % in patients with recurrent or progressive endometrial cancer. For the purposes of this study, response rate will be defined as stable disease, partial response or complete response. Early stopping points have been incorporated to stop the trial if there is limited disease control. We will also evaluate the toxicity profile of letrozole and RAD001 in this cohort of patients with endometrial cancer. Patients will be evaluated for response rate, duration of response rate, time to disease progression, and survival.

4 SELECTION OF PATIENTS

4.1 Patient 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. 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.

4.2 Inclusion Criteria

To be eligible for the study, patients must fulfill all of the following criteria:

1. Patients must have signed an approved informed consent.
2. Histologically confirmed endometrial cancer (endometrioid, serous, or clear cell, or mixed histology; any grade) which is considered progressive or recurrent.
3. Patients may have failed no more than two prior chemotherapeutic regimens for recurrent or advanced disease (including adjuvant therapy). Chemotherapy administered in conjunction with radiation as a radio-sensitizer is not counted as a prior treatment for recurrent or advanced disease.
4. All patients must have measurable disease as defined by RECIST 1.1 (See section 7.1)
5. Patients must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST (Section 7.1). Tumors within a previously irradiated field will be designated as "non-target" lesions, unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
6. Patients must have a Zubrod performance status of 0, 1, or 2 (Appendix E).

7. 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 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.
8. Patients must have a pretreatment granulocyte count (i.e., segmented neutrophils + bands) of >1,500/Fl, a hemoglobin level of ≥9gm/dL and a platelet count of >100,000/Fl. 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.
9. Patients must have an adequate renal function of >50cc/min as documented by the Cockcroft Gault creatinine clearance formula:

   $$\frac{(140 - \text{age}) \times (\text{weight kg})}{}$$

   Estimated GFR = 72 x serum Creatinine (non-IDMS) x 0.85 (female)
10. Patients must have adequate hepatic function as documented by a serum bilirubin ≤2.5 mg/dL, regardless of whether patients have liver involvement secondary to tumor. Note: A detailed assessment of Hepatitis B/C medical history and risk factors 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.
11. Alanine aminotransferase (SGPT) must be ≤3x institutional upper limit of normal unless the liver is involved with tumor, in that case, the alanine aminotransferase must be ≤5 x institutional upper limit of normal..
12. Prior to beginning therapy, at least 4 weeks must have elapsed since prior chemotherapy, surgery, radiation therapy, hormonal therapy or investigational therapy. Patients receiving palliative radiation therapy are exempt from the 4 week waiting period.
13. Baseline lipid levels (triglycerides, cholesterol) must be ≤ grade 1. Patients are allowed to be on lipid lowering drugs.
14. Patients must be >/= 18 years of age.

4.3 Exclusion Criteria

Patients meeting any of the following criteria will be ineligible to participate in this study:

1. Patients with intact ovarian function.

2. Patients who have previously received RAD001 or another mTOR inhibitor or letrozole or another aromotase inhibitor. Use of progestational or other hormonal agents are permitted provided they have not been administered within the previous 4 weeks.
3. Patients who have uterine sarcomas or mixed malignant mullerian tumors.
4. Patients who have isolated recurrences (vaginal, pelvic, or paraaortic) that are amenable to potentially curative treatment with radiation therapy or surgery.
5. Patients with any other severe concurrent disease, which would make the patient inappropriate for entry into this study, including significant hepatic, renal, or gastrointestinal diseases.
6. Patients currently receiving chemotherapy or radiotherapy or those in whom anti-cancer treatment has occurred within the preceding 4 weeks.
7. Chronic treatment with systemic steroids or another immunosuppressive agent. Patients on systemic steroids or another immuosuppresive agent for greater than 3 months.
8. Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period.
9. Patients with a history of prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for at least five years.
10. Patients with an active infection that requires systemic antibiotics.
11. Patients with a known history of cardiac disease; i.e., uncontrolled hypertension (systolic B/P >/= 140 mm Hg and/or diastolic B/P >/= 90 mm Hg) or unstable angina. Patients with a history of myocardial infarct within 6 months before enrollment, New York Heart Association (NYHA) Class II or greater heart failure, or symptoms suspicious for congestive heart failure are not eligible unless a left ventricular ejection fraction in the past 6 months is documented to be 50% or greater. Patients who have had a LVEF (performed for any reason) of less than 50% in the past 6 months are ineligible.
12. Patients with a known history severely impaired lung function (patients who are oxygen dependent).
13. Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
14. Patients who are pregnant or breast-feeding.
15. Presence of clinically apparent untreated central nervous system metastases.
16. Patients with carcinomatous meningitis.
17. Patients with deep venous or arterial thrombosis (including pulmonary embolism) within 6 weeks of study entry. Patients may be on maintenance anticoagulation therapy.

18. Patients with previously documented human immunodeficiency virus (HIV) infection.
19. Patients with an impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).

MDACC and Morristown Memorial Hospital will not exclude any potential subject from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol.

4.4 Withdrawal of Patients from Treatment

Patients should be removed from therapy if any of the following occurs:

- Disease progression. Every effort should be made to document objective evidence of tumor progression.
- The occurrence of unacceptable toxicity indicating the need for cessation of treatment.
- The physician feels it is in the best interest of the patient to stop treatment.
- Patient refusal to continue with therapy.
- Non-compliance by the patient with protocol requirements.
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome, if possible.
- Patient becomes pregnant.
- Termination of the study by investigator or Sponsor – M. D. Anderson Cancer Center.

5.0 TREATMENT PLAN

This is a Phase II open label study of combination therapy with RAD001 and letrozole in patients with progressive or recurrent endometrial cancer. The initial dose of RAD001 is 10 mg daily and the dose of letrozole is 2.5 mg daily, both given orally.

5.1 Multi-Center Patient Registration Procedures: All patients from Morristown and M. D. Anderson will be registered in CORe at University of Texas, MD Anderson Cancer Center.

Centralized Registration Requirements: Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients must be registered both locally and centrally with MDACC.

Before an institution may begin participating in a MDACC sponsored protocol that is coordinated by MDACC, they must complete the following steps:

- Submit the following required regulatory documents to the MDACC Office of Multicenter Clinical Research (OMCR)
- Participate in a site initiation visit, webcast, or conference call
- Receive training regarding study specific CRF's and/or databases
- Execute study specific contractual agreements

After these requirements have been fulfilled, the participating institution will receive by fax, e-mail, or hard copy memo a Site Activation Notification. Once the Site Activation Notification has been received, the participating institution may begin to register patients to the protocol.

<u>Required Regulatory Documents include</u>:

- ✓ FDA 1572
- ✓ Curriculum Vitae (CV) or Biosketch. The CV/Biosketch must be submitted with the individual's signature and date.
- ✓ Delegation of Authority Log (DAL)
- ✓ Approval Letter signed by the Chairman of the institution's IRB (must be updated annually. Patient registrations will be suspended for expired IRB approvals)
  - An Expedited IRB first approval is NOT acceptable
  - IRB Approval for amendments

Informed Consent/Authorization

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an Institutional Review Board (IRB) approved consent form.

Patient Registration Procedures

M. D. Anderson Cancer Center (MDACC) patients will be registered in The Clinical Oncology Research System (CORe) by department of Gynecology staff. Participating institutions must register patients via phone, fax, and/or email with the MDACC Office of Multicenter Clinical Research at:

Fax: (713) 563-4317
Phone: (713) 792-8519
Email: OMCR_GYN@mdanderson.org

Registration hours are 8:00 a.m. to 5:00 p.m. Central Standard Time, Monday through Friday, except holidays.

Registration is a 2-step process. Step 1 - Initial registration must be completed:

- After the patient has signed the informed consent and has been determined to be eligible by the local investigator.

Once eligibility has been determined, Step 2 is treatment assignment -

- Before study related treatment is initiated.

At the time of registration the following information will be requested by the MDACC Office of Multicenter Clinical Research (OMCR):

- A faxed or emailed copy of a completed and signed, protocol specific, eligibility checklist form
- One copy of a Pathology report from the patient's most recent surgery or biopsy
- One copy of the signed and dated Informed Consent/Authorization.

The eligibility checklist should be prepared and signed prior to faxing or emailing to the MDACC OMCR. The fax/email should be followed by a phone call to the MDACC OMCR to verify receipt.

If the patient fails eligibility screening do not proceed to the MDACC registration process.

Patient Number for Participating Institutions

Once eligibility has been established during Registration, the patient from the participating institution is assigned a six character MDACC OMCR patient number. This number is unique to the patient and must be written on all data and correspondence for the patient.

Verification of Registration

For participating institutions, a Registration Verification Letter for patients registered will be faxed or emailed to the registering institution within one working day after registration.

Initiation of Therapy

Treatment may not be initiated until the participating institution receives a faxed or emailed copy of the patient's Registration Verification Letter from the MDACC OMCR. Patients must initiate treatment within 10 calendar days after the registration is completed.

The MDACC OMCR must be notified in writing of any exceptions to this policy.

Eligibility Exceptions: Eligibility Exceptions will not be granted**.**

Confidentiality: All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the MDACC OMCR must have the patient's full name & social security number "blacked out" and the assigned MDACC patient ID number and protocol number written in. Patient initials may be included or retained for cross verification of identification.

5.2 RAD001 and letrozole administration

5.2.1 Both study medications will be dispensed by the pharmacy. Study medication will be supplied in an open label fashion. Patients will self administer the both medications at home.

5.2.2 Patients will be instructed to take the study medication at a consistent time each day.

5.2.3 RAD001 is formulated as tablets of 5 mg strength and supplied in blister packs under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Two 5 mg tablets should be taken orally once daily in a fasting state or after no more than a light, fat-free meal. Avoid grapefruit-containing products during the treatment period.

5.2.4 Letrozole is formulated as tablets of 2.5 mg and supplied in bottles. The dose of letrozole is one 2.5 mg tablet administered orally once daily. The oral single dose of RAD001 should be taken together with the daily dose of letrozole 2.5 mg.

5.2.5 Each cycle will consist of 4 weeks of therapy. Patients will be seen prior to each cycle. To allow for holidays, vacations and other important life events, patients may be seen +/- 7 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.

5.2.6 After the second cycle (8 weeks ±7 days), patients will undergo a radiologic evaluation using the same imaging technique that was used during the initial evaluation (i.e., CT or MRI) unless clinical suspicion warrants earlier evaluation.

5.2.7 For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each physician visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

5.3 Dose modifications / Management of Adverse Reactions

Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, (http://ctep.cancer.gov/forms/CTCAEv3.pdf)).

Dose Modification Table:

Dose level	-2	-1	0
RAD001	Off study	5 mg daily	10 mg daily
Letrozole	Off study	2.5 mg daily	2.5 mg daily

Patients will be removed from study for any:

- grade 4 treatment-related toxicity (assuming that appropriate preventive therapy has been given where possible – e.g. antiemetic therapy in case of vomiting, lipid-lowering drug in case of hyperlipidemia), or
- hematologic or non-hematologic toxicity requiring interruption of one or both drugs for > 3 weeks. For detailed recommendations on dose interruption and modification due to suspected toxicity, please refer to the following table.

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

Treatment-related toxicity	Actions
Non-hematological toxicity	
Grade 2 (except fatigue, hyperlipidemia, and non-infectious pneumonitis – see Dose Modification Table, page 30)	For first occurrence, interrupt RAD001 (continue letrozole) until recovery to grade ≤1 then reintroduce RAD001 (no dose reduction). If the event recurs, interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤1 then reintroduce therapy at -1 dose level. If the event recurs a 3rd time, remove patient from study.
Grade 3 (except hyperlipidemia and non-infectious pneumonitis)	For first occurrence, interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤ 1. Then reintroduce therapy at -1 dose level. If the event recurs remove from study. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Remove from study.

Lipid-lowering drugs
Increased lipid levels are a known adverse effect of treatment with both RAD001 and aromatase inhibitors. In case of hyperlipidemia (≥grade 1 hypercholesterolemia with or without hypertriglyceridemia), in addition to dietary advice to patients, an HMG-CoA reductase inhibitor such as atorvastatin, pravastatin or fluvastatin may be associated with study treatment.

Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤1 (>75 x10^9/L) then resume study treatment (no dose reduction). If the grade 2 thrombocytopenia recurs, interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤1 then reintroduce therapy at -1 dose level. If the event recurs a 3rd time, remove patient from study.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x$10^9$1/L)	Interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤1 (platelets ≥ 75 x10^9/L) then resume study treatment at the -1 dose level. If grade 3 thrombocytopenia recurs, remove from study.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Remove from study
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤ 1 then resume study treatment (no dose reduction). If ANC again returns to Grade 3, hold study treatment (Letrozole and RAD001) until the ANC ≥ 1.5 x 10^9/L then resume study treatment (Letrozole and RAD001) at the -1 dose level. Remove from study for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt study treatment (Letrozole and RAD001) until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L) then resume study treatment (Letrozole and RAD001) at the -1 dose level. Remove from study if grade 4 neutropenia reoccurs despite this dose reduction.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt study treatment (Letrozole and RAD001) until resolution of fever and neutropenia to grade ≤ 1 and hold further study treatment (Letrozole and RAD001) until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume study treatment (Letrozole and RAD001) at the -1 dose level. If febrile neutropenia recurs, remove from study.
Grade 4 febrile neutropenia (life-threatening)	Remove from study
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Remove from study

5.3.1 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 (see Section 5 Adverse drug reactions). Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. 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 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.

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1	**CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.**	**No specific therapy is required**	**Administer 100% of everolimus dose.**
Grade 2	**CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy***	**Symptomatic only. Prescribe corticosteroids if cough is troublesome.**	**Reduce everolimus dose until recovery to ≤ Grade 1. Everolimus may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.**
Grade 3	**CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended***	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 2 weeks.**
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*.**	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Discontinue treatment.**

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

5.3.2 Management of Hepatitis reactivation

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.

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

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4 weeks		No prophylaxis Monitor HBV-DNA approximately every 4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug.

For patients who have already received study drug prior to the approval of the amendment, the same process should be followed at the patient's next visit. The first HBV-DNA result would be regarded as baseline.

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

Table 3-3 Guidelines for management of hepatitis B

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] AND ALT elevation x 5 ULN	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ grade 1 ALT (or baseline ALT, if > grade 1) and ≤ 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.
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 3.0 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 3.0 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).

5.3.3 Monitoring for hepatitis C

The following two categories of patients should be monitored every 4 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 reactivation*	
For patients with baseline results: Detectable HCV-RNA, --- reactivation is defined as: ALT elevation x 5 ULN	Discontinue study drug
For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, --- reactivation is defined as: New appearance of detectable HCV-RNA	Discontinue study drug

* All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v3.0 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 3.0 Metabolic Laboratory/Other: Viral Re-activation).

5.3.4 Concomitant therapy

<u>Lipid-lowering drugs</u>
Increased lipid levels are a known adverse effect of treatment with both RAD001 and aromatase inhibitors. In case of hyperlipidemia (≥grade 1 hypercholesterolemia with or without hypertriglyceridemia), in addition to dietary advice to patients, an HMG-CoA reductase inhibitor such as atorvastatin, pravastatin or fluvastatin may be associated with study treatment.

- 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).
- The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule.

- 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.

- Patients will be provided a list of all drugs/substances to avoid when entered on the study (Appendix E).

5.3.5 INDUCERS & INHIBITORS OF CYP3A4 AND/OR PgP and OTHER RELEVANT DRUG INTERACTIONS

Table 3-5 Inducers/Inhibitors of CYP3A4 and/or PgP

Inhibitors of CYP3A4 and/or PgP Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided. 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 half the currently used dose e.g., 10mg daily would be reduced to 5mg 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. Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.
Inducers of CYP3A4 and/or PgP Avoid the use of strong CYP3A4 inducers. 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 up to twice the currently used daily dose should be considered, using 5mg increments. 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

<table>
<tr><th colspan="2">SUBSTRATES</th></tr>
<tr><td>Antibiotics:
Clarithromycin, erythromycin, telithromycin</td><td>Calcium channel blockers:
Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil</td></tr>
<tr><td>Anti-arrhythmics:
Quinidine</td><td>HMG CoA reductase inhibitors:
Cerivastatin, lovastatin, simvastatin</td></tr>
<tr><td>Benzodiazepines:
Alprazolam, diazepam, midazolam, triazolam</td><td>Steroid 6beta-OH:
estradiol, hydrocortisone, progesterone, testosterone</td></tr>
<tr><td>Immune modulators:
Cyclosporine, tacrolimus (FK506)</td><td rowspan="4">Miscellaneous:
Alfentanil, aprepitant, aripirazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine-N-demethylation, 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</td></tr>
<tr><td>HIV Antivirals:
Indinavir, nelfinavir, ritonavir, saquinavir</td></tr>
<tr><td>Prokinetic:
Cisapride</td></tr>
<tr><td>Antihistamines:
Astemizole, chlorpheniramine, terfenadine</td></tr>
<tr><th colspan="2">INDUCERS</th></tr>
<tr><td colspan="2">Barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John’s wort, troglitazone, efavirenz, nevirapine</td></tr>
<tr><th colspan="2">INHIBITORS</th></tr>
<tr><td colspan="2">Strong inhibitors:
indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, Posaconazole (Krishna et al, 2009)
Moderate inhibitors:
aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil,
Weak inhibitors:
Cimetidine, Seville orange (Malhotra et al, 2001)
Unclassified as per the Indiana University DDI listing:
Ciprofloxacin, delaviridine, troleandamycin, mibefradil, amiodarone, chloramphenicol, diethyldithiocarbamate, fluvoxamine, starfruit, gestodene, imatinib, mifepristone, norfloxacin, norfluoxetine, voriconazole*,</td></tr>
</table>

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, topotecan, paclitaxel	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole, ketocoanzole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	rifampin, St John's wort

- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided
- 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.
- 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 3-5 (CYP3A4 inhibitors/inducers) and Table 3-6 (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.

Patients will be provided a list of all drugs/substances to avoid when entered on the study (Appendix E).

5.4 Treatment compliance

Novartis will distribute agents direct to sites under individually negotiated contracts. M. D. Anderson Cancer Center (MDACC) will collect and manage regulatory and monitor /audit sites. RAD001 and letrozole will be dispensed from the sites investigational pharmacy. Patients will be provided with an adequate supply (1 cycle plus 1 week) of letrozole plus RAD001 for self-administration at home. Patients are requested to bring their unused medication, including the empty blister packs, to the clinic at each visit. Compliance should be verified by a patient pill diary (Appendix G) and counting the number of tablets consumed between visits.

Records of study medication used, dosages administered, and intervals between visits will be kept during the study, during site visits and at the completion of the trial. Patients

will be asked to return all unused medication at the end of treatment. All unused medication will be returned to the investigational pharmacy.

The site must maintain an overall drug accountability log for the study, as well as individual accountability records (pill diaries) for each patient. The dose, amount dispensed, amount received, and amount unused must be recorded in the source documents for each patient. To avoid waste, leftover medications at the end of each cycle may be used in the subsequent cycle.

5.5 Supportive Care Guidelines/Concomitant Medications

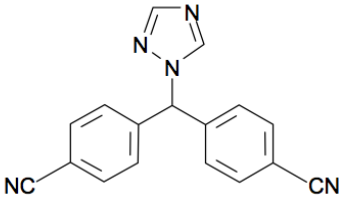
5.5.1 Growth Factors: Routine prophylactic use of growth factors is not permitted. However, therapeutic use in patients with serious hematologic complications such as sepsis may be considered at the investigator's discretion.

5.5.2 Antiemetics: The use of antiemetics will be left to the investigator's discretion.

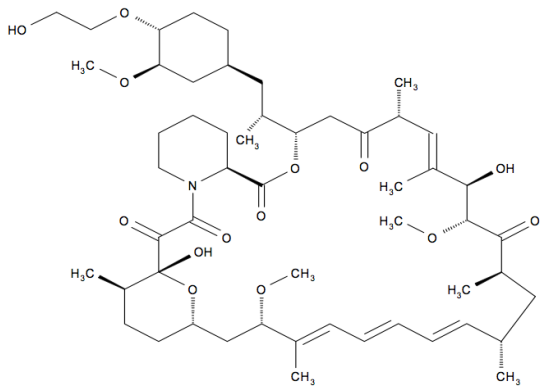
5.5.3 Other Concomitant Medications: In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient record. The administration of any other anticancer agents including chemotherapy and biologic agents is NOT permitted. Similarly, the use of other concurrent investigational drugs is not allowed.

5.6 Drug Information

5.6.1 Physical, Chemical and Pharmaceutical Properties of Letrozole

Chemical name:	4,4'-[(1H-1,2,4-triazol-1-yl)methylene]bisbenzonitrile
Generic name:	Letrozole
Proprietary name	Femara®
Laboratory code:	CGS 20267
Structural formula:	
Molecular formula:	$C_{17}H_{11}N_5$
Molecular weight:	285.31
Appearance:	White to yellowish, crystalline powder
Melting range:	184-185°C
Hygroscopicity:	Not hygroscopic
Stability:	Very stable
Route of administration:	Oral
Storage conditions:	Do not store above 30°C, protect from moisture.
Shelf life:	5 years

5.6.2 Physical, Chemical and Pharmaceutical Properties of Everolimus



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
Chemical abstracts registry number	159351-69-6
International non-proprietary name	Everolimus
Molecular formula:	$C_{53}H_{83}NO_{14}$
Molecular weight:	958.2
Physical form:	White to faintly yellow powder. Everolimus stabilized with butylated hydroxytoluene (BHT) is amorphous, and contains 0.2% BHT as an antioxidant.
Chirality:	The drug substance, everolimus, contains 15 asymmetric carbon atoms and 4 substituted double bonds. The configuration of the asymmetric carbon atoms and the double bonds are guaranteed by the microbial origin of rapamycin, the starting material of the synthesis, and by the X-ray analysis performed on crystalline everolimus. The configuration at carbon 40 is not changed by the chemical derivatization that converts rapamycin into everolimus.
Formulation:	All formulations are based on an everolimus solid dispersion intermediate that was selected on the basis of the chemical stability of the active ingredient and properties allowing for a good *in vivo* performance.
Dosage forms:	Tablets: 2.5 mg, 5 mg and 10 mg
Composition/excipients:	Tablets: butylhyroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose monohydrate, hypromellose/hydroxypropyl methylcellulose, crospovidone, lactose anhydrous The excipients comply with the requirements of the applicable compendial monographs (Ph. Eur., USP/NF).
Stability:	Current stability data permit a shelf life of either 36 months (for 5 mg tablet variants based on solid dispersion dried by evaporation/drying oven) or 24 months (for 2.5 mg, 5 mg and 10 mg tablet variants based on solid dispersion dried by paddle dryer), assuming correct storage below 30°C in the original double sided aluminium blister and protected from light and moisture.

6 STUDY PROCEDURES

Patients will be seen by a physician at the start of treatment and then prior to initiating subsequent cycles, i.e., every four weeks. In order to more precisely determine time of progression, the investigator is encouraged to obtain radiologic assessments earlier if there is a strong clinical suspicion of progression of disease to either confirm or refute the clinical impression. Adverse events will be discussed in detail with each patient and assessed on a continuing basis.

6.1 Schedule of Assessments

Assessments	Screening / baseline	Weekly	Every cycle	Every 2nd / 3rd cycle[d]	End of treatment [j]	Follow-up[h]
Medical history	X[a]					
Physical examination	X[b,c]		X[c]		X	X
Vital signs	X[b]		X		X	X
Zubrod Performance Status	X[b]		X[b]		X	X
Weight	X[b]		X		X	X
CBC with differential and platelets	X[b]		X		X	
Hepatitis screening/monitoring	X[l,n]		X[m,o]			
Serum chemistries (Mg+, SGPT, total bilirubin, BUN, serum creatinine/creatinine clearance) and electrolytes, glucose	X[b,p]		X		X	
Lipid panel (Triglycerides, LDL, HDL)	X[b]		X		X	
Tumor staging (baseline tumor measurements)	X[a,e]					
Chest x-ray	X[a]			X[i]	X[i]	
CT/MRI of chest, abdomen and pelvis and/or appropriate imaging	X[a,e]			X[f]	X[f]	X
Toxicity	X[a]	X[g]	X		X	X
Tumor response				X		
Serum estradiol[k]	X[a]					
Medication compliance/pill count			X[q]			

a Within 4 weeks prior to Step 2 of study registration (treatment assignment)
b Within 7 days of initiation of therapy
c Pelvic exam every cycle if disease is in the pelvis. Otherwise, pelvic exam is done at baseline, after 2 cycles, and then every 3rd cycle thereafter.
d Obtained after the first two cycles (approximately 8 weeks), after four cycles (approximately 16 weeks) for confirmation, 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. Follow up begins after the patient stops study medication.
i Only in patients with chest disease
j Within 4 weeks of the last dose of study drug.
k Documentation of a serum estradiol < 10 pg/mL is required only for patients in whom hysterectomy was performed premenopausally and in whom bilateral oophorectomy was not completed. Estradiol is not required for women known to be menopausal or surgically castrated.
l Hepatitis B Virus testing: Prior to randomization (or starting study drug in non-randomized trials), the categories of patients listed in Section 3.2 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.
m HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 3-3.
n 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 3-2. 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.
o 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 arae considered "cured") should be monitored every 4 weeks for HCV reactivation
p Creatine clearance: Patients must have an adequate renal function of >50cc/min as documented by the Cockcroft Gault formula:

$$\text{Estimated GFR} = \frac{(140 - \text{age}) \times (\text{weight kg})}{72 \times \text{serum Creatinine (non-IDMS)} \times 0.85 \text{ (female)}}$$

q Patients are requested to bring their unused medication, including the empty blister packs, to the clinic at each visit. Compliance should be verified by a patient pill diary (Appendix G) and counting the number of tablets consumed between visits.

6.2 Screening/Baseline

To be completed within four weeks prior to Step 2 of study registration (treatment assignment):

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, v3.0.
2. Zubrod performance status.
3. Baseline tumor measurements
4. Chest x-ray
5. CT/MRI of chest, abdomen and pelvis and/or appropriate imaging. Chest imaging (only in patients with chest disease)
6. Hepatitis screening

To be completed within seven days of initiation of therapy. Therapy must be initiated within 10 calendar days after Step 2 of registration (treatment assignment):

1. Physical exam including pelvic exam
2. Weight
3. Vital signs (blood pressure, pulse, respiratory rate, temperature)
4. Zubrod performance status
5. Complete blood count with leukocyte differential and platelet count
6. Serum chemistries (magnesium, SGPT, total bilirubin, BUN, serum creatinine, glucose and electrolytes).
7. Lipid panel (Triglycerides, LDL, HDL)

6.3 Treatment Evaluations To be obtained every cycle (4 weeks):

1. Weight
2. Complete blood count, serum chemistries (magnesium, SGPT, total bilirubin, BUN, serum creatinine), glucose and electrolytes.
3. Lipid panel (Triglycerides, LDL, HDL)
4. Vital Signs (blood pressure, pulse, respiratory rate, temperature)
5. Physical exam including pelvic exam every cycle if disease is in the pelvis. Otherwise pelvic exam is performed at baseline, after 2 cycles (8 weeks), and then every 3 cycles (12 weeks) thereafter.
6. Zubrod performance status

7. Assessment of treatment related toxicities
8. Hepatitis monitoring, if indicated
9. Medication compliance, pill count

To be obtained after the first 2 cycles (8 weeks):

1. Evaluation of measurable tumor
2. Physical exam (including pelvic exam)
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

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):

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)

6.4 End of Treatment: To be obtained at the end of treatment:

1. Physical exam including pelvic exam
2. Vital signs
3. Zubrod performance status
4. Weight
5. Complete blood count with differential and platelets, serum chemistries (magnesium, SGPT, 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

6.5 Follow-up

Follow-up will be at the discretion of the patient's primary physician. However, follow-up data will be due to M. D. Anderson OMCR every 6 months.

To be obtained during follow-up visits:

- Physical exam including pelvic exam
- Vital signs (blood pressure, pulse, respiratory rate, temperature, weight)
- 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 performed). Chest imaging (only in patients with chest disease). The frequency of imaging will be determined by the physician.
- Toxicity assessment

6.6 Correlative Studies

When available, we will collect paraffin embedded tumors from the original tumor at the time of hysterectomy, pretreatment biopsy, and post-treatment biopsy. We will evaluate the immunohistochemical expression of PTEN, mTOR, AKT, p70S6K, and E4-BP1 using commercially available antibodies. We will also evaluate the difference in expression of these proteins between the primary tumors and the recurrences (pre- and post- treatment) in the same patients to determine if there are any alterations of the expression of these biomarkers during the progression of disease. Paraffin blocks will be requested from all study participants (both responders and non-responders). If paraffin blocks are not available, at least 5 slides each (pre- and post-treatment) will be requested. Pre-treatment samples will be sequenced to analyze the mutational status of K-Ras as this may also be a marker of response.

7 Efficacy and Safety Assessments – RECIST 1.1

7.1 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 the next two cycles (8 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) guideline (version 1.1) [*Eur J Ca* 45:228-247, 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.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Letrozole (Evirolimus) and RAD001.

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.

7.1.2 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 by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. 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 <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be

identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body
scans should be performed with breath-hold scanning techniques, if possible.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

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

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

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

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

7.1.4.2 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

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

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).

7.1.4.3 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 Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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 1.1 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 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

7.1.5 Duration of Response

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

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

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

7.1.6 Other efficacy parameters

Duration of disease control, time to disease progression, and survival will be evaluated.

7.1.7 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 urine values, regular measurement of vital signs and the performance of physical examinations.

7.1.7.1 Adverse events

Adverse events will be recorded and collected in the in accordance with the Adverse Event Recording Guidelines (Described in the Data Quality Management Plan (DQMP) Appendix L.

8 STUDY MONITORING

Study Monitoring procedures are described in the Data Quality Management Plan (DQMP) Appendix L.

9 DATA MANAGEMENT

9.1 Registration: MDACC will serve as the primary site for this study. All patients enrolled in the study from each of the participating sites will be registered in the Clinical Oncology Research System (CORe) at MDACC following procedures described in section 5.1. Patient data will be collected and entered in the MDACC's Protocol Data Monitoring System (PDMS).

9.2 Confidentiality Procedures:
All pathology specimens, evaluations 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 the OMCR or its representative, 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 the data or reporting the results.

9.3 Data Safety and Monitoring Committee: The MDACC Data Safety and Monitoring Committee will monitor the overall conduct of the study.

10 STATISTICAL METHODOLOGY

This is a phase II activity trial. We will accrue a minimum of 10 patients and a maximum of 35 evaluable patients at a rate of 2 patients per month. We estimate 7 patients will be inevaluable and thus need to be replaced. Therefore our total number of patients will not exceed 42. The primary outcome for this trial is the objective response or stable disease rate (CR + PR + SD), which is evaluated within approximately 8 weeks of treatment. A confirmatory evaluation will be made no sooner than 4 weeks from this event (8 weeks, if SD). Once a response category is confirmed, evaluation for objective responses will be made every 12 weeks as outlined in Sections 6 and 7.1.3. Our target objective response or stable disease rate is 20%. We will monitor the objective response or stable disease rate as patients accrue and are evaluated following the example of Thall and Simon.[17] We will stop the trial if we have evidence that the target objective response or stable disease rate cannot be met.

We will stop the trial early if P(objective response or stable disease rate ≥ 20% | data from the trial) < 0.10. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is less than a 10% chance that the objective response or stable disease rate is 20% or more, we will stop the trial. This decision rule gives the following stopping rule. We assume a uniform prior distribution for the rate of objective response or stable disease. Stop the trial if: [# of patients with objective response or stable disease / # of patients evaluated] < 1/10, 2/17, 3/24, 4/31.

The operating characteristics of this study design are shown in the following table.

Operating Characteristics of Monitoring Rule				
Rate of CR + PR + SD	Probability of Stopping Early	P_{25}	P_{50}	P_{75}
0.05	0.956	10	10	17
0.10	0.725	10	17	35
0.15	0.436	17	35	35
0.20	0.220	35	35	35
0.25	0.097	35	35	35

We will estimate the rate OF CR + PR + SD with a 90% credible interval once the study is complete. If we complete the study with 11 patients with treatment success (CR or PR or SD) among 35 patients total (31%), then our 90% credible interval for the success rate would be 20.5 to 45.5%.

We will also estimate the overall survival and progression free survival for patients on study with the product-limit estimator of Kaplan and Meier (1958). [18]

10.1 Definition of Populations for Analyses

Patients who are removed from the study during the first course because of progression are considered evaluable for efficacy only if progression can be documented per RECIST **1.1** criteria. Patients who come off

treatment for reasons other than progression (and prior to establishing response) are evaluable for toxicity only.

10.2 Efficacy Analyses

10.2.1 Definitions of Endpoints

Survival: The observed length of life from study entry (1st treatment) to death or, for living patients, date of last contact.

Time to tumor progression: The time from date of initial treatment

Progression-free survival: The observed time from study entry (1st treatment) to date of tumor progression, date of death, or, for patients alive without tumor progression, date of last follow-up.

10.3 Safety Analyses

All eligible patients who receive therapy on this study will be considered evaluable for safety. Patients who are removed from the study during the first course because of progression, serious drug related adverse events, or for other reasons (e.g. patient request or non-drug related toxicity) will also be evaluable for safety.

Descriptive statistics and tabulations will be used to summarize adverse events and laboratory data. Transition tables will be used to describe changes in laboratory values from baseline to follow-up.

11 Special safety-related procedures

11.1 Instructions for rapid notification of serious adverse events

The principle investigator has the obligation to report all serious adverse events per M. D. Anderson Cancer Center policy to the IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E). Procedures for reporting Serious Adverse Event's are described in the Data Quality Management Plan (DQMP) (Appendix L).

In addition, any serious adverse event occurring in a patient after providing informed consent, while receiving study drug, and until four weeks after stopping study drug must be reported by FAX (888-299-4565) to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of its occurrence, even if it is not felt to be drug related (Appendix H). The OMCR will forward SAE's to Novartis.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

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