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Phase I/II Study of Weekly Abraxane and RAD001 in Women with Locally Advanced or Metastatic Breast Cancer

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Drug(s) Under Investigation:	**Company**	**IND #**	**Drug Supply**
RAD001 (Everolimus)	Novartis Pharmaceuticals	105009	Yes
Abraxane (*nab* paclitaxel)	Abraxis Oncology	NA	No

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
BUN	Blood urea nitrogen
CBC	Complete blood count
CINJOG	Cancer Institute of New Jersey Oncology Group
CT	Computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
dl	Deciliter
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony Stimulating Factor
HHS	Department of Health and Human Services
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenously
kg	Kilograms
L	Liter
mg	Milligram
mL	Milliliters
mmol	Millimolar
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ULN	Upper limit of normal
USP	United States Pharmacopeia

1. Purpose/Specific Objectives

1.1 Primary Endpoint

Phase I:

- To determine the MTD of RAD001 in combination of weekly Abraxane and determine the Phase II dose of RAD001.

Phase II:

- To determine the anti-tumor activity, as measured by clinical tumor response according to RECIST criteria, of the combination of RAD001 and Abraxane at the Phase II dose in patients with advanced breast cancer.

1.2 Secondary Endpoint(s)

- To determine the safety and tolerability of weekly RAD001 administered at the Phase II determined dose in combination with Abraxane at 150 mg/m^2 weekly for 3 of 4 weeks on a 28-day cycle.

2. Background and Significance

Approximately 215,000 new cases of breast cancer were diagnosed in the United States in 2005 and ~43,000 died from this disease. Single agent or combination chemotherapy produces response rates of 40-70% in the treatment of advanced breast cancer. Although numerous regimens are effective in palliating symptoms and inducing tumor regression, the complete response rate is less than 20%. Moreover, the median duration of response is nine months with a median survival of 12-24 months. Thus, most responses are of limited duration and nearly all patients with stage IV disease eventually die of disease progression. Similarly, the prognosis for inflammatory or locally advanced breast cancer is dismal, with fewer than 25% of diagnosed patients alive at five years (1). Therefore, the treatment of patients with metastatic and locally advanced breast cancer warrants investigation of novel therapeutic strategies including more rationale design and sequencing of combination chemotherapy regimens.

The choice of cancer chemotherapy is usually empirical, based more on the histological appearance of the tumor than on an understanding of the molecular determinants of drug sensitivity. This may account for the suboptimal response rates in many treated patients. Recently, important gene products have been discovered that affect the action of cancer chemotherapeutic agents. These drug-resistance genes appear to be selected for the survival advantage they impart to tumors. We now appreciate that activation of several oncogenes and loss of tumor suppresser gene products increase cellular viability and lead to resistance to radiation and chemotherapy (2). Recently, new molecularly-targeted, non-cytotoxic therapies have emerged as an option for treatment of a select set of malignancies, whereby inhibition of a pathologically-significant molecular target is thought to be responsible for disease regression. Given the comparatively non-toxic characteristics of these molecularly-targeted pharmacotherapeutic agents, a logical next step in the search for more effective

chemotherapeutic regimens is their combination with standard cytotoxics. Additionally, the use of molecularly targeted therapies in combination with cytotoxic agents may maximize the antitumorigenic properties of the latter.

Genes in the PI3K/AKT pathway are key to the regulation of cell growth, cell viability, cell motility, and resistance to chemotherapeutic and hormonal agents. Deregulation of these genes is found in many tumor types, including breast cancer in which pathway activation is felt to be an early event in carcinogenesis. The serine-threonine kinase Akt plays a vital role in stimulation of cell growth, cell proliferation, and tumor transformation. It acts as a signal transducer for growth factor-controlled processes. Transformation, e.g. such as that associated with amplification of Her2/*neu*, occurs due to activation of the PI3-K/Akt pathway (1, 2). Tumor cells also have altered metabolism with a shift to glycolysis. Akt, a direct regulator of glucose metabolism and protein translation, produces its effects on nutrient transport and protein production through its action on the downstream mediator: mammalian target of resistance (mTOR). In turn, there is potential positive feedback from phosphorylation of Akt by mTOR (Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science 2005, 307: 1098-101). Previous work shows correlation between activated Akt and mTOR levels. Preclinical studies on cells with chemotherapy-, trastuzumab-, tamoxifen-, and radiation-resistant phenotypes secondary to up-regulation of Akt indicate that Akt-pathway inhibitors and mTOR inhibitors can modify this resistance (3-5). In vitro resistance to paclitaxel can occur through up-regulation of Akt and mTOR activityVanderWeele et al. (6) have shown that this resistance that can be abrogated by concomitant use of paclitaxel and an mTOR inhibitor. Elevated phosphorylation of Akt and mTOR are highly associated with invasive breast tumors. Phosphorylated mTOR is found in 25-45% of breast cancers at moderate to high levels, consistent with studies on breast cancer cell lines, while activated mTOR is nearly undetectable in normal primary mammary epithelial cell lines. 38-80% of invasive breast tumors demonstrate moderate to high levels of phosphorylated Akt (8,9). Akt-1 levels are enriched in Stage III/IV invasive breast cancers with 80% demonstrating protein overexpression (1,7). Paclitaxel is a standard cytotoxic agent used in stage IV disease. Inhibition of mTOR activity may represent a target for increasing sensitivity of advanced breast cancers to paclitaxel. We, therefore, propose to study the combination of the mTOR inhibitor RAD001 with Abraxane in women with advanced breast cancer. We anticipate that RAD001 will enhance the effect of Abraxane by targeting the PI3K/Akt/mTOR pathway.

2.1 Supporting Data and Rationale

2.1.1 RAD001 (everolimus)

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

The following is a brief summary of the main characteristics of RAD001. More complete information can be obtained from the Investigators' Brochure (10).

2.1.1.1 Pharmacology of RAD001

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

At the cellular or molecular level, RAD001 has the same mechanism of action as an immunosuppressant or 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. In this context, there is an increasing body of evidence suggesting that AKT regulates mTOR activity (11, 12, 13), and that the activation status of the PI3K/AKT pathway may be indicative of responsiveness to rapamycins such as RAD001.

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 lung cancer, with the most sensitive cell lines having IC50's at the sub nanomolar/low nanomolar level. All of the four investigated lung cancer cell lines were sensitive to RAD001 with A549 human lung carcinoma being the most sensitive cell line overall (IC50 ~2nM). On the other hand, rapamycin has shown to be a potent inhibitor of proliferation of NSCLC and SCLC cell lines *in vitro* (IC50 range 2-40 nM) with sensitivity linked to higher levels of phosphorylated AKT and PTEN status (14, 15). In addition, rapamycin inhibited growth and metastatic progression in 3 different NSCLC animal models (16).

Experiments *in vitro* with human umbilical endothelial cells (HUVECs) and in animal models of angiogenesis suggest an additional antiangiogenic effect of RAD001, 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 included several different mouse models, including lung xenograft models (NCI-H596, NCI-H520 and A549), and was associated with no animal deaths or significant body weight loss. Moreover, persistent tumor regressions (41%) were seen in A549 tumors [Investigators' Brochure-Section 4.1.2.6]. 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. In

combination experiments *in vitro* with conventional cytotoxic agents, RAD001 potentiate the induction of A549 lung carcinoma cell death at sub-optimal gemcitabine concentrations with little effect of drug schedule on the antiproliferative effect. *In vivo* experiments involved combination of RAD001 with suboptimal doses of paclitaxel, cisplatinum, gemcitabine and doxorubicin using NCI-H596 lung xenograft model, showing weak increased antitumor effect. In addition, a mouse model bearing a ras codon 12 mutation, ras mutations being frequent in adenocarcinoma with BAC features (17, 18, 19, 20) bears a striking resemblance to adenocarcinoma with BAC features and has been shown in extensive studies to manifest p-AKT and p-S6R expression in the progression of lesions to adenocarcinoma. The tumors formed in these mice are sensitive to mTOR inhibition both in terms of numbers and tumor volume (J.Kurie personal communication).

Molecular Determinants of Sensitivity to RAD001

The molecular determinants predicting responsiveness of tumor cells to RAD001 are only now becoming evident. The mTOR pathway is downstream of the PI3K/AKT/TSC pathway, a signalling module known to be heavily deregulated in many human cancers (21, 11). In this context, there is an increasing body of evidence suggesting that AKT regulates mTOR activity (11, 12), and that the activation status of the PI3K/AKT pathway may be indicative of responsiveness to rapamycins such as RAD001. Specifically, loss of PTEN or constitutive/hyper-activation of AKT has been suggested to sensitize tumors to the effects of inhibition of mTOR (12, 13, 22). Indeed, RAD001 preferentially inhibits the proliferation of tumor cells displaying high AKT activity [Investigators' Brochure-Section 4.1.2] and totally reverses AKT-driven prostate intraepithelial neoplasia in a mouse transgenic model (13). Moreover, a correlation between increased RAD001 sensitivity and high levels of S6 ribosomal protein phosphorylation has also been observed *in vitro*.

Preclinical studies also demonstrated that inhibition of p70S6kinase 1 (S6K1) activity and 4E-BP1 phosphorylation, downstream effectors of the mTOR pathway, are markers of drug activity. In terms of the S6K1, *in vitro*, short-term exposure to RAD001 led to S6K1 inactivation for as long as 120 hours. *In vivo*, in a syngeneic rat pancreatic tumor model, 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). Dramatically, inhibition of PBMC-derived S6K1 for ≥7 days correlated with the antitumor activity of weekly administration schedules. Moreover, in tumor, this inhibition of S6K1 correlated with a dramatic dephosphorylation of the ribosomal protein S6 (23). Hence, analysis of molecular determinants predicting predisposition for response (such as these and perhaps others yet to be identified) may aid patient selection in oncology.

2.1.1.2 Clinical Background Information

In oncology, clinical experience with RAD001 is based on ongoing Phase 1 studies of single-agent RAD001 and Phase 1b studies of RAD001 in combination with systemic anticancer agents (imatinib, paclitaxel, gemcitabine and letrozole). Clinical experience in non-oncology indications comes from single-dose studies in healthy volunteers, studies in solid organ

transplant patients, where RAD001 is co-administered with other immunosuppressive drugs, and a study in patients with severe rheumatoid arthritis.

2.1.1.3 Clinical Pharmacology of RAD001

RAD001 is administered orally, its bioavailability being estimated at approximately 11%. Absorption is intestinal and is delayed moderately by food (60% reduction in C_{max} 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%). The C_{max} 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 through the bile and the intestinal tract (>80%).

RAD001 is a substrate of the CYP3A4 isoenzyme and P-gp and its metabolism is sensitive to 3A4 inhibitors/inducers. In combination with micro-emulsion cyclosporin 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 C_{max} 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 to moderate hepatic impairment will increase exposure to RAD001. Caucasians and Japanese patients appear to be similar as regards clearance, while clearance in blacks is approximately 20% higher.

Renal function has only marginal influence on the clearance of RAD001 so that no dosage adjustment is necessary in patients with renal failure.

2.1.1.4 Clinical Studies in Oncology

Since 2002, RAD001 has been used in Phase 1 in cancer patients both as monotherapy and in combination with a number of other anticancer agents (10). Phase 1 clinical studies of RAD001 as a single agent are ongoing and explore two regimens: weekly dosing (range 5-70 mg) and daily dosing (5-10 mg). Preliminary data are available for 84 patients, 74 advanced cancer patients, and 10 patients with newly-diagnosed prostate carcinoma. At the weekly schedule, dose-limiting toxicity (DLT) in the first four weeks of treatment has been observed at 50mg (1/12) and 70 mg (3/14). At the daily dosage, DLT has been observed at 10 mg only (1/12). DLT was principally Grade 3 stomatitis, but also Grade 3 fatigue and neutropenia.

Apparent adverse drug reactions (ADR) include mild-moderate rash (approx. 40%), stomatitis/mucositis and fatigue (30% each), headache (20%), nausea, vomiting, diarrhea (10% each).

Reduced blood cell counts at the initiation of treatment are frequent but remain mostly within normal range or limited to Grade 1 although a Grade 3 neutropenia was dose-limiting in one patient (as was a Grade 3 thrombocytopenia in a patient receiving RAD001 with letrozole where a pharmacodynamic interaction is unlikely). This suggests that some patients may be particularly sensitive to the myelosuppressive effect of RAD001 making it necessary to monitor carefully blood cell counts at initiation of treatment.

Hyperlipidemia has been reported as ADR in 10% of patients although review of the laboratory values suggests that as many as a quarter of patients develop Grade 1-2 hyperlipidemia on treatment, mostly hypercholesterolemia.

Infectious episodes have not been more frequent than might have been expected. Herpes infections (zoster, labialis), observed in 5 patients on the monotherapy were not severe.

Pharmacokinetic-pharmacodynamic modeling based on inhibition of a peripheral molecular marker (S6 kinase 1 activity in peripheral blood mononuclear cells) suggests that 5-10 mg daily should be an adequate dose to produce a high degree of sustained target inhibition. Pharmacodynamic studies are underway to investigate this by investigating changes in the molecular pathology of biopsied tumor by immunohistochemistry in treated patients. Preliminary indications from these studies are that treatment with RAD001 at 5 and 10mg daily is associated with dephosphorylation of protein effectors known to be immediately downstream of mTOR. This inhibition is quasi-total in patients as regards S6 and partial as regards 4EBP1, a picture similar to that observed preclinically in *in vivo* models in which RAD001 demonstrated clear anti-tumor activity.

Four Phase 1B oncology studies are ongoing to investigate the feasibility of combining RAD001 with imatinib (Glivec®/Gleevec™), gemcitabine, paclitaxel or letrozole in patients with various types of cancer (10).

2.1.1.5 RAD001 Safety

The most frequent adverse drug reactions in the context of renal and cardiac transplantation are highly specific to the transplant context. However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels.

Phase 1 studies with RAD001 alone, as both weekly regimen (up to 70 mg/week) and daily regimen (10 mg/day) have explored the drug's activity in 147 patients with advanced cancers [RAD001C Investigators' brochure, Section 5]. Pre- and on-treatment molecular pharmacodynamic studies on the tumor of patients, by immunohistochemistry assay, have shown target inhibition at both daily dosage (5-10mg) and weekly dosage (50-70mg) with satisfactory tolerability in most patients. The 10mg/d dosage is proposed for further studies in similar patient populations. The most frequent adverse effects have been rash, stomatitis, fatigue and, to a lesser extent, gastrointestinal disorders (nausea, anorexia, diarrhea, vomiting) and headache. The adverse events are mild-moderate (CTC Grade 1-2) in majority

of patients. Severe (Grade 3), suspected drug-related, dose-limiting events occurred in 19% of patients, these being mainly stomatitis, and occasionally severe fatigue, hyperglycemia and neutropenia. Reduced blood counts, hyperlipidemia (mainly hypercholesterolemia) and hyperglycemia are relatively frequent laboratory findings. Infections have not been notably frequent or severe. Preliminary indications of anti-tumor activity are encouraging.

2.1.2 Abraxane (*nab* paclitaxel) (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) Abraxane is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentration of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell wall, thereby breaching the blood/tumor interface. This albumin-specific receptor mediated process involves the binding of a specific receptor (gp60) on the endothelial cell wall, resulting in activation of a protein caveolin-1, which initiates an opening in the endothelial wall with formation of a little caves or caveolae, with transport of the albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium (24). A protein specifically secreted by the tumor (SPARC) binds and entraps the albumin, allowing release of the hydrophobic drug to the tumor cell membrane (24). Abraxane is the first biologically interactive nanoparticle leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic drug in normal tissue.

Preclinical Studies with Abraxane

Preclinical studies comparing Abraxane to Taxol demonstrated lower toxicities, with a MTD approximately 50% higher for Abraxane compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, Abraxane was found to be markedly more efficacious than Taxol (25).

Clinical Studies with Abraxane

Every 3 Weeks Schedule

In a Phase I study, the maximum tolerated dose (MTD) of Abraxane was determined to be 300 mg/m^2 by 30 minute infusion every 3 weeks, without premedication or G-CSF support (26). No severe hypersensitivity reactions occurred with Abraxane despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2. Two multicenter Phase II studies have evaluated 2 dose levels of Abraxane (300 mg/m^2, n=63, and 175 mg/m^2, n=43) in patients with metastatic breast cancer (26,27). The overall response rates in these 2 Phase II trials were 40% (95% CI 25-54%) for the 175 mg/m^2 dose, and 48% (95% CI 35-60%) for the 300 mg/m^2 dose. Of 39 patients receiving 300 mg/m^2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared Abraxane 260 mg/m^2 to Taxol 175 mg/m^2 given every 3 weeks (28). Significantly higher efficacy for Abraxane vs Taxol was demonstrated as measured by overall response rates (33% vs 19%, p<0.001) and time to tumor progression (5.8 vs 4.2 months, p=0.006). The Overall Response Rate (ORR) was superior for all patients, patients who received Abraxane as first-line therapy, patients who received Abraxane as second- or greater-line therapy, patients with prior anthracycline exposure, elderly patients, and patients with poor prognostic factors, including visceral tumor involvement. The overall median survival was 65.0 weeks for the Abraxane group and 55.7 weeks for the Taxol group (p = 0.374). In second line or greater patients, median survival in the Abraxane group was significantly improved (56.4 weeks vs 46.7 weeks, p=0.024; HR = 0.73). Despite the 49% higher dose of paclitaxel administered to patients in the Abraxane group compared to the Taxol group, the incidence of treatment-related Grade 4 neutropenia was significantly less (9% vs 22%; p = <0.001). The Abraxane group also had a higher mean neutrophil nadir (1.67 vs 1.31 x 10^9/L; p = 0.046) suggesting that Cremophor® may have contributed to this toxicity. Grade 3 sensory neuropathy occurred in 10% of Abraxane treated patients compared with 2% of those treated with Taxol. Of the patients who developed Grade 3 sensory neuropathy while on Abraxane, 58% had documented rapid improvement in symptoms after a median of 22 days and 42% of patients were able to resume treatment at a reduced dose. Only 3% of patients that received Abraxane discontinued treatment due to peripheral neuropathy.

Weekly for 3 Weeks, Every 4 Weeks Schedule

A Phase I study of Abraxane administered weekly for 3 weeks followed by a 1 week rest in patients with advanced solid tumors has recently been completed (29). The MTDs for heavily and lightly pre-treated patients were 100 and 150 mg/m^2 respectively. Dose limiting toxicities included Grade 4 neutropenia and Grade 3 sensory neuropathy. Premedication was not required, and unexpected, non-taxane associated toxicities were not observed. In a Phase II trial in heavily pretreated patients with taxane-refractory metastatic breast cancer, objective antitumor responses occurred in 15% of women treated with Abraxane 100 mg/m^2 on this schedule (30). Abraxane weekly regimen was well tolerated. 91% of patients were treated at the full dose of 100 mg/m^2 of Abraxane without dose reductions. Based on the activity and low toxicity documented with the Abraxane 100 mg/m^2 weekly regimen, this study was expanded to evaluate the efficacy and safety/tolerability of a higher dose of Abraxane 125 mg/m^2 weekly regimen in 75 additional patients. Results of this dose-finding study confirm the dose of Abraxane 100 mg/m^2 as the appropriate dose for further study in this patient population (31). A phase II study examined the efficacy of Abraxane 125 mg/m^2 in women with previously untreated metastatic breast cancer or locally advanced disease (32). Twenty-seven patients received 285 cycles of therapy. Grade 3 neutropenia occurred in 7.4% of the patients treated. No grade 4 non-hematologic toxicities occurred, thus confirming the safety of this dose for first-line therapy.

2.1.3 Rationale for Combination of Abraxane and RAD001

As a key role in the PI3-K/AKT pathway, the serine-threonine kinase Akt plays a vital role in stimulation of cell growth, cell proliferation, and tumor transformation. Transformation, e.g.

such as that associated with amplification of Her2/*neu*, occurs due to activation of the PI3-K/Akt pathway (1, 2). Tumor cells also have altered metabolism with a shift to glycolysis. Akt, a direct regulator of glucose metabolism, produces its effects on nutrient transport through its action on the downstream mediator: mammalian target of rapamycin (mTOR). Preclinical studies on cells with chemotherapy-, trastuzumab-, tamoxifen-, and radiation-resistant phenotypes secondary to up-regulation of Akt indicate that Akt-pathway inhibitors and mTOR inhibitors can modify this resistance (3-5). In vitro resistance to paclitaxel can occur through up-regulation of Akt and mTOR activity. VanderWeele et al. (6) have shown that this resistance that can be abrogated by concomitant use of paclitaxel and an mTOR inhibitor. Because increased Akt-1 activity is found in approximately 38% of all breast cancers but 80% of Stage III/IV (1,7), inhibition of mTOR activity may represent a target for increasing sensitivity of advanced breast cancers to paclitaxel. An additional mechanism of drug resistance pertinent to the PI3-K/AKT pathways has been studied by Drs. Arnold Levine and Shengkan Jin. Autophagy is a novel tumor suppression mechanism whereby damaged organelles are eliminated or entire cells undergo self-digestion. Inhibition of mTOR results in autophagy in MCF-7 breast cancer cell lines (33). Beclin 1 is a gene product that functions in and is essential to the process of autophagy. Mono-allelic deletion of beclin-1 in human breast tumors and other tumors has been demonstrated and in mouse models, is associated with reduction of autophagy levels. As autophagy is negatively regulated by mTOR, Jin postulates that the use of mTOR inhibitors will reactivate autophagy in beclin-deficient tumors. RAD001 (INN: everolimus), an orally active derivative of rapamycin, can be considered a signal transduction modifier. After forming a complex with FKBP-12, this complex subsequently interacts with the mTOR protein kinase. We, therefore, propose to study the combination of RAD001 with Abraxane in women with advanced breast cancer. We anticipate that RAD001 will enhance the effect of Abraxane by targeting the PI3K/Akt/mTOR pathway. Importantly, working in collaboration with the laboratories of Drs. Levine and Jin, we propose to measure potential molecular predictors of response, including AKT over-expression and Beclin 1 gene expression in the primary breast tumor. This will also be correlated with germline determination of gene haplotype in both Akt and beclin 1.

There is increasing evidence that the effectiveness of small molecular protein-inhibitors can be highly dependent on intratumoral molecular characteristics. Therefore, there is the possibility that only a subpopulation might benefit from the addition of RAD001 to Abraxane. Consequently, this study places particular emphasis on the assessment of the molecular characterization of the tumor to allow correlative analyses (see Section 11 for details).

Rationale for starting doses:
Based on non-overlapping non-hematological toxicities, it is expected that when administered together, both drugs will be able to be given safely at full single-agent doses. However, as described in Section 7.4, a reduction in doses of both drugs will be implemented if more than 1 of the first 6 patients experiences a Grade 3 non-hematological toxicity (with

the exception of increased transaminases, or nausea in the absence of aggressive anti-emetics), or Grade 4 neutropenia with fever.

3. Participating Institutions

The Rutgers Cancer Institute of New Jersey, Robert Wood Johnson University Hospital and the Cancer Institute of New Jersey Oncology Group (CINJOG) affiliate hospitals.

4. Experimental Design and Methods

This is an open label Phase I/II study of RAD001 in combination with Abraxane. Initially, six patients will be accrued and evaluated for toxicity at Cancer Institute of New Jersey. PK data will be collected. It is not anticipated that RAD001 will modify the DLT of Abraxane. If the toxicity data suggests increased toxicity (any related ≥ Grade 3 non-hematologic toxicity), a dose de-escalation schema will be implemented (See Sections 7.3 and 7.4) and toxicity data reassessed. After a Phase II dose is established, 39 to 72 total patients will be accrued to assess for response.

This study will require approximately 15 to 24 months to complete accrual of 39 to 72 total patients onto this study.

5. Patient Selection Criteria

5.1 Inclusion Criteria

A patient is eligible for enrollment if all of the following inclusion criteria are met.

5.1.1 Adult women (≥ 18 years of age) with metastatic or locally recurrent breast cancer, not amenable to treatment by surgery or radiotherapy

5.1.2 Histological confirmation of breast cancer that is Her2/neu negative

5.1.3 Patients may not have received prior chemotherapy for metastatic breast cancer. Prior adjuvant chemotherapy is allowed.

5.1.4 Patients may have received prior systemic endocrine treatment for advanced breast cancer (i.e. metastatic or locally recurrent breast cancer, not amenable to treatment by surgery or radiotherapy).

5.1.5 Patients must have at least one measurable lesion. Measurable disease documented and defined as by RECIST criteria (see Section 9). Baseline measurements must be obtained within 4 weeks prior to enrollment.

- As the only exception regarding the requirement for at least one measurable lesion, patients with bone metastases as the sole site of disease can be included, provided they have at least 2 lytic bone lesions, detected by either X-Ray, CT scan or MRI.

5.1.6 Prior radiation therapy allowed to < 25% of the bone marrow and patients must have recovered from the toxic effects of the treatment prior to study enrollment (except for alopecia). Prior radiotherapy must be completed 30 days before study entry. Lesions that have been radiated in the advanced setting cannot be included as sites of measurable disease unless clear tumor progression has been documented in these lesions since the end of radiation therapy.

5.1.7 Patients must have an ECOG performance status ≤ 2 (Appendix A).
5.1.8 Patients on antiangiogenic agents are not excluded from this study.
5.1.9 Patients must have normal organ and marrow function as defined below:
- ANC ≥ 1.5 x 10^9 cells/L,
- Platelets ≥ 100 x 10^9 cells/L,
- Hb >9 g/dL,
- Serum Bilirubin ≤ 1.5 x ULN,
- Absence of ascites and encephalopathy due to liver disease,
- INR < 1.5 x ULN,
- ALT and AST, ≤ 2.5x ULN (≤ 5x ULN in patients with liver metastases).
- Serum Creatinine ≤ 1.5 mg/dL
- Fasting serum cholesterol ≤ 300 mg/dl or 7.75 mmol/L and fasting triglycerides ≤ 2.5 x ULN
    - In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy.

5.1.10 Estimated life expectancy of at least 3 months.
5.1.11 Give written informed consent.

5.2 Exclusion Criteria

A patient will not be eligible for this study if any of the following exclusion criteria are met.

5.2.1 Grade ≥ 2 neuropathy.
5.2.2 Prior chemotherapy for advanced breast cancer.
5.2.3 Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites etc.)
5.2.4 Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
5.2.5 Patients with an active, bleeding diathesis or on oral anti-vitamin K medication (except low dose coumadin).
5.2.6 CNS metastases (except patients with stable CNS metastases are allowed on this study), bilateral diffuse lymphangitis carcinomatosa of the lung (>50% of lung involvement), evidence of metastases estimated as more than a third of the liver as defined by sonogram and/or CT scan.
5.2.7 Patients in whom localized radiotherapy (for analgesic purposes) is considered an actual requirement (inclusion should be delayed until radiation therapy has been completed and the patient's condition stabilized).
5.2.8 Patients with a known history of HIV seropositivity.
5.2.9 History of other malignancies with exception of:
- in-situ carcinoma of the cervix or non-melanomatous skin cancer which have received curative therapy
- cancer treated ≥5 years previously and considered as cured.

5.2.10 Known hypersensitivity to everolimus or sirolimus (rapamycin), to Abraxane or lactose (contained in formulations of RAD001)

5.2.11 Patients with a history of noncompliance to medical regimens.
5.2.12 Patients who received any other investigational drugs within the preceding 30 days.
5.2.13 Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itroconazole, Voriconazole, Ritinavir, Telithromycin) within the last 5 days from randomization (please also refer to Section 7.5 for prohibited concomitant medications).
5.2.14 Women who are pregnant or breast feeding, or women able to conceive and unwilling to practice an effective method of birth control. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of RAD001 and Abraxane). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study.
5.2.15 Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene) are prohibited.
5.2.16 Require chronic treatment with systemic steroids or another immunosuppressive agent.
5.2.17 Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period.
5.2.18 Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction $\leq$ 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia
- severely impaired lung function
- any active (acute or chronic) or uncontrolled infection/ disorders
- nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
- liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis

5.3 Inclusion of Women and Minorities

Women from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Males will not be eligible for this study. Breast cancer in men is rare and the efficacy of chemotherapy combinations in males is limited.

5.4 Participation of Children

Patients under the age of 18 will be excluded from study participation.

5.5 Sources or Methods of Recruitment

Referrals from within the Cancer Institute of New Jersey and from community oncologists will be encouraged. Patients will also be recruited through participating CINJOG affiliate hospitals.

5.6 Study Enrollment Procedures

A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients. The participating institution's consent form must be reviewed and approved by the OHRS Regulatory Affairs Manager and all documents must be received (i.e., IRB approved documentation, IRB approved consent form, See Section 15.2 for a complete list of regulatory items).

To register eligible patients on this study, each site will contact the Cancer Institute of New Jersey's OHRS Registration Desk (732) 235-7251 and fax (732) 235-6404 the signed and dated eligibility checklist, the signed consent form, a copy of the pathology report and additional source documents if requested by OHRS. Once the OHRS Registration Desk verifies eligibility, a treatment assignment and unique patient study number will be issued. This is the point that the patient is considered on study. **Patients must <u>not</u> start protocol treatment prior to registration.**

If a patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the "follow-up eCRF". Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.

6. Study Parameters

The tests and evaluations will be performed according to the schedule below. Baseline (i.e. pre-study) evaluations must be performed ≤ 4 weeks (+/- 3 days) of enrollment, unless otherwise indicated below.

Evaluations	Pre-study		Prior to each cycle	Every 2 Cycles	After Cycle 1	Off study
	within 4 weeks of enrollment	within 2 weeks of enrollment				
Initial history and physical		x				
Interim history and physical			x			x
Weight and height	x[(a)]		x			x
ECOG Performance Status	x		x			x
Toxicity assessment			x			x
CBC with differential		x	x[(g)]			x
Prothrombin time (INR)	x					
Serum electrolytes[(b)(h)]		x	x			x
Fasting lipid profile[(h)]	x			x		
Hepatic panel[(c) (h)]		x	x			x
Pregnancy test[(h)]		x[(f)]				
ECG	x					
Radiographic assessments[(d)]	x			x		x
Compliance assessment			x			x
Archived tumor tissue	x[(e)]					

[(a)] Height to be measured only at baseline.

[(b)] Serum electrolytes include: sodium, potassium, chloride, bicarbonate, phosphorus, fasting glucose, BUN and creatinine.

[(c)] Hepatic panel includes: ALT/SGPT, AST/SGOT, alkaline phosphatase, and total bilirubin.

[(d)] Radiographic assessments will be selected by the attending physician as clinically indicated and in accordance with the criteria for tumor measurement assessments. Confirmatory scans should be obtained ≤ 4 weeks following initial documentation of response. Response will be evaluated every 2 cycles

[(e)] Obtain archived tumor tissue (from time of original diagnosis) for immunohistochemical analysis; can be obtained at anytime after enrollment.

[(f)] Women of childbearing potential must have a negative pregnancy test within 7 days prior to treatment.

[(g)] CBC will be checked prior to each weekly treatment.

[(h)] Within 7 days.

7. Treatment Plan

7.1 General Considerations

A cycle is defined as an interval of 28 days (delays due to holidays, weekends and bad weather will be permitted and will not be counted as a protocol violation). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. Patients will receive treatment until disease progression, unacceptable toxicity or withdrawal of consent. Patients may discontinue therapy at any time for any reason.

7.2 Dose Calculation

Doses of Abraxane will be calculated on Day 1 of each cycle using the patient's actual weight in the determination of body surface area. A variance of 5% of the calculated total dose will be allowed.

BSA (m^2) =

$$\sqrt{\frac{height(in)xweight(lbs)}{3131}} \quad \text{or} \quad \sqrt{\frac{height(cm)xweight(kg)}{3600}}$$

7.3 Treatment Administration

7.3.1 Phase I

Abraxane will be initially administered at 80 mg/m^2 without premedication as a 30 minute intravenous infusion weekly for the first 3 of the 4 weeks of a 28 day cycle (Day 1, Day 8, and Day 15 of each cycle).

Orally administered RAD001 will be initiated at 5 mg daily. Each cohort administration will proceed based on escalation criteria. RAD001 will be given initially once every day. Doses will be adjusted per the dosing regimen (Section 7.3.1.1) for each cohort throughout the Phase I portion of the study. RAD001 may be taken with or without food. Patients will be advised to take their tablets at the same time of the day and at the same time in relation to meals. Tablets must be swallowed whole with a glass of water.

Abraxane Premedication

Patients do not require premedication prior to Abraxane administration, as hypersensitivity reactions are not expected. However, during post market surveillance, rare occurrences of severe hypersensitivity reactions have been reported.

Patients who experience a severe hypersensitivity reaction to Abraxane should not be rechallenged with the drug.

In the rare event of a severe hypersensitivity reaction, discontinue Abraxane.

7.3.1.1 Dosing Regimen

Dose Level	Abraxane (mg/m^2)	RAD001 (mg)
-2	60	5 every other day
-1	60	5 daily
0	80	5 daily
1	100	5 daily
2	125	5 daily
3	125	10 daily

For the Phase I portion of the study, patients will be enrolled according to the following with the first 3 patients starting at Dose Level 0.

Dose Level 0:

- If 0 patients treated at Level 0 are observed with dose limiting toxicity (DLT) during Cycle 1, then the dose will be escalated to the next dose level.
- If 1 of 3 patients experience DLT in Cycle 1, then 3 more patients will be treated at this dose level for a total of 6 patients.
- If 1 of these 6 patients experiences DLT in Cycle 1, the dose will be escalated.
- If 2 or more patients at this dose level experience DLT in Cycle 1, then we will have exceeded the maximum tolerated dose (MTD) and will de-escalate to Level -1 and enroll as outlined in the table.

Dose Level 1:

- If 0 patients experience DLT in Cycle 1, the dose will be escalated to the next dose level.
- If 1 of 3 patients experience DLT in Cycle 1, then 3 more patients will be treated at this dose level for a total of 6 patients.
- If 1 of these 6 patients experiences DLT in Cycle 1, the dose will be escalated.
- If 2 or more patients experience DLT in Cycle 1, we will have exceeded the MTD and Level 0 will be the recommended dose.

Dose Level 2:

- If 0 patients experience DLT in Cycle 1, the dose will be escalated to the next dose level.
- If 1 of 3 patients experience DLT in Cycle 1, then 3 more patients will be treated at this dose level for a total of 6 patients.
- If 1 of these 6 patients experiences DLT in Cycle 1, the dose will be escalated.
- If 2 or more patients experience DLT in Cycle 1, we will have exceeded the MTD and Level 1 will be the recommended dose.

Dose Level 3:

- If 0 patients experience DLT in Cycle 1, then this will be the recommended dose.
- If 1 of 3 patients experience DLT in Cycle 1, then 3 more patients will be treated at this dose level for a total of 6 patients.
- If 1 of these 6 patients experiences DLT in Cycle 1, this will be our recommended dose.
- If 2 or more patients experience DLT in Cycle 1, we will have exceeded the MTD and Level 2 will be the recommended dose.

DLT will be evaluated in the first cycle of therapy and defined as: Any ≥Grade 3 non-hematologic toxicity (except alopecia, nausea, emesis that resolves to ≤ Grade 1 with symptomatic treatment) or ≥ Grade 4 hematologic toxicity that is definitely, probably or possibly related to study drug. All adverse events are considered related to study drug unless proven to be unlikely or definitely unrelated to study drug.

7.3.2 Phase II Treatment Administration

The Phase II treatment schedule will continue following the same 28 day cycle schedule as Phase I.

Abraxane will be administered without premedication as a 30 minute intravenous infusion weekly for the first 3 of the 4 weeks of a 28 day cycle (Day 1, Day 8, and Day 15 of each cycle). The dose of Abraxane to be used in the Phase II portion of the trial will be based upon the MTD established in the Phase I portion of this trial.

RAD001 will be administered on the schedule and at the maximum tolerated dose as determined by the Phase I results. RAD001 may be taken with or without food. Patients will be advised to take their tablets at the same time of the day and at the same time in relation to meals. Tablets must be swallowed whole with a glass of water

ADDENDUM TO DEFINE PHASE II DOSE: Two of 6 participants enrolled to this study experienced dose-limiting toxicities at dose level 2; therefore, as specified in section 7.3.1.1 above, the Phase II portion of this study will be initiated and patients enrolled to the Phase II portion will receive Abraxane 100 mg/m^2 in combination with RAD001, 5 mg daily.

7.4 Dose Modifications or Escalations

To address the safety concerns of these drugs being given in combination, a toxicity analysis will be performed after all of the first 6 patients complete the first cycle of therapy. In the event that more than one patient experiences a ≥ Grade 3 non-hematologic toxicity (with the exception of alopecia, nausea or vomiting in the absence of aggressive anti-emetics), they will cease to receive further study drug. The subsequent dose cohort enrolled will be at a reduced intermediate dose.

Chemotherapy dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities/adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.

- All dose reductions will be permanent.
- No more than 2 dose reductions are allowed. Patients requiring >2 dose reductions will be removed from the study.
- If the starting dose is reduced to Dose Level –1 no further dose reductions will be made below Dose Level –2.
- Unless specified in the following sections, adverse events that do not resolve to ≤ Grade 1 within 4 weeks of maximum toxicity grade will require discontinuation of further treatment.
- Starting dose (Dose Level 0) will be determined by the Phase I part of this study.

Phase II - Modifications

Dose Level	Abraxane (mg/m^2)	RAD001 (mg)
-2	60	5 daily
-1	80	5 daily
0	100	5 daily

- All dose reductions will be permanent.
- No more than 2 dose reductions are allowed. Patients requiring >2 dose reductions will be removed from the study.
- Unless specified in the following sections, adverse events that do not resolve to ≤ Grade 1 within 4 weeks of maximum toxicity grade will require discontinuation of further treatment.

7.4.1 Hematologic Toxicity - Abraxane

Abraxane dosing should not be administered at the start of each cycle until the absolute neutrophil count returns to ≥ 1.5 x 10^9 cells/L and the platelet count returns to >100 x 10^9 cells/L. For each subsequent dose of Abraxane within a cycle (Days 8 and 15), patients must have an ANC ≥ 1.0 x 10^9 cells/L and platelets > 75 x 10^9 cells/L. If the ANC and platelets are not adequate for treatment on Day 8 and/or 15, the dose is to be omitted and the total cycle length remains 28 days. A guideline for implementing dose reductions and growth factor treatment for hematologic toxicity is presented in Table 7.4.1.1.

7.4.1.1 Dose Reductions for Abraxane and Use of Growth Factors for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC < 0.5 x 10^9 cells/L (nadir count) with neutropenic fever > 38°C OR Delay of next cycle due to persistent neutropenia (ANC < 1.5 x 10^9 cells/L) OR For patients on weekly treatment whose next treatment within the cycle (Day 8 or Day 15) is omitted due to persistent neutropenia (ANC < 1 x 10^9 cells/L). OR Neutropenia < 0.5 x 10^9 cells/L for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF is given as outlined in 7.4.1.2. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction of Abraxane to the next lower level will be required for subsequent cycles once ANC is ≥ 1.5 x 10^9 cells/L (see Section 7.4). If G-CSF is given concurrently with weekly Abraxane, administration may begin the day after Abraxane is given and should stop at least 48 hours prior to when Abraxane is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

*Refer to NCI CTCAE Version 3 for definition of Grade 3 and Grade 4 events.

7.4.1.2 G-CSF Administration

For weekly study drug administration (Days 1, 8, 15) administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per Investigator/Institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose s.c. on Days 2-5, 9-12, and 16-19.

For patients who are receiving RAD001 on a dose level lower than 5 mg daily, for example, every other day, the treating physician in consultation with the principal investigator may opt to omit G-CSF from the regimen.

7.4.2 Non-Hematologic Toxicity - Abraxane

7.4.2.1 Hepatotoxicity

Abraxane should not be administered at the beginning of a cycle if hepatic function parameters are out of the range that was established for entry into the study.

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

7.4.2.2 Sensory Neuropathy

Abraxane should be withheld in patients who experience ≥ Grade 2 sensory neuropathy. Treatment may be resumed at the next lower dose level in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduced dose in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. Patients in whom neuropathy does not resolve to ≤ Grade 1 in 4 weeks should be removed from further treatment.

7.4.2.3 Hypersensitivity Reactions

Hypersensitivity reactions may occur with either study drug. In the event of Grade 1 or Grade 2 hypersensitivity reactions, temporary discontinuation of the study drug may be required. In the event of any Grade 1 or 2 hypersensitivity reaction which does not abate with supportive measures or any ≥ Grade 3 hypersensitivity reactions, immediately discontinue the administration of study drug. Patients who develop severe hypersensitivity reactions to Abraxane should not be re-challenged.

7.4.2.4 Other Toxicities

If toxicities are ≤ Grade 2, manage symptomatically if possible, and retreat without dose reduction. If toxicities are ≥ Grade 3, except for anemia, treatment should be withheld until resolution to ≤ Grade 1 or baseline if baseline was greater than Grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 7.4.1.1 above).

7.4.3 RAD001 Toxicity

Table 7.4.3 – Criteria for Dose-Modification in Case of Suspected RAD001 Toxicity and Re-Initiation of RAD001 Treatment

Toxicity	Actions
Non-hematological toxicity **Grade 2 (except pneumonitis, refer to section 7.4.3.5)**	**If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 until recovery to Grade ≤ 1. Then reintroduce RAD001 at same dose.** **If event returns to Grade 2, interrupt RAD001 until recovery to Grade ≤ 1. Then reintroduce RAD001 at the lower dose level.**
Grade 3 **(except hyperlipidemia)**	**Interrupt RAD001 until recovery to Grade ≤1. Then reintroduce RAD001 at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.**
Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia)	**Should be managed using standard medical therapies.**
Grade 4	**Discontinue RAD001.**

Hematological toxicity **Grade 2 Thrombocytopenia (platelets < 75, ≥ 50x10^9/L)**	**Interrupt RAD001 until recovery to Grade ≤ 1 (>75 x10^9 cells/L). Then reintroduce RAD001 at initial dose.** **If thrombocytopenia again returns to Grade 2, interrupt RAD001 until recovery to Grade ≤ 1. Then reintroduce RAD001 at the lower dose level.**
Grade 3 Thrombocytopenia (platelets < 50, ≥ 25 x10^9/L)	**Interrupt RAD001 until recovery to Grade ≤ 1 (platelets ≥ 75 x10^9 cells/L). Then resume RAD001 at one dose level lower. If Grade 3 thrombocytopenia recurs, discontinue RAD001.**
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	**Discontinue RAD001.**
Grade 3 Neutropenia (neutrophils (<1, ≥0.5 x10^9/L)	**Interrupt RAD001 until recovery to Grade ≤1 (neutrophils ≥ 1.5 x 10^9 cells/L). Then resume RAD001 at the initial dose. If ANC again returns to Grade 3, hold RAD001 until the ANC ≥ 1.5 x 10^9/L. Then resume RAD001 dosing at the lower dose level. Discontinue patient from study therapy for a third episode of Grade 3 neutropenia.**
Grade 4 Neutropenia (neutrophils (< 0.5 x10^9/L)	**Interrupt RAD001 until recovery to Grade ≤ 1 (neutrophils ≥ 1.5 x 10^9 cells/L). Then resume RAD001 at the lower dose level. If Grade 3 or Grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001.**
Grade 3 febrile neutropenia (not life-threatening)	**Interrupt RAD001 until resolution of fever and neutropenia to Grade ≤ 1. Hold further RAD001 until the ANC ≥ 1.5 x 10^9 cells/L and fever has resolved. Then resume RAD001 at the lower dose level. If febrile neutropenia recurs, discontinue RAD001.**
Grade 4 febrile neutropenia (life-threatening)	**Discontinue RAD001.**
Any hematological or non-hematological toxicity requiring interruption for ≥ 4 weeks	**Discontinue RAD001**

7.4.3.1 Known Undesirable Side Effects of RAD001

Adverse events most frequently observed with RAD001 are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, ocular toxicity and infections. Non-infectious pneumonitis has also been observed. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (Grade 1-2).

7.4.3.2 Monitoring of RAD001 Suspected Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to Grade 1. If a patient requires a dose delay > 28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

7.4.3.3 Management of Stomatitis/Oral Mucositis/Mouth Ulcers

Stomatitis/oral mucositis/mouth ulcers due to RAD001 should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with RAD001 as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

- For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouthwash several times a day until resolution.
- For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
- Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
- Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, therefore leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

7.4.3.4 Management of Hyperlipidemia and Hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or Grade 2 or higher hypertriglyceridemia (>2.5 x upper normal limit) should be treated with a statin or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

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

Grade 3 hyperglycemia has been observed in patients receiving RAD001 therapy. In many cases the affected patients had an abnormal fasting glucose at baseline. Based on this finding, it is recommended that optimal glucose control is achieved before starting a patient on RAD001. Study patients should have their glucose levels monitored during RAD001 therapy.

7.4.3.5 Management of Non-infectious Pneumonitis

Both asymptomatic radiological changes (Grade 1) and symptomatic non-infectious pneumonitis (Grade 2 = not interfering with activities of daily living or Grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis has been associated with RAD001 and other mTOR inhibitors [34]. In order to monitor for asymptomatic (Grade 1) non-infectious pneumonitis, a chest X-ray or CT scan is required in addition to the by-monthly CT or MRI tumor examinations. Additional chest X-rays or CT scans may be performed, when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops Grade 3 pneumonitis, treatment with RAD001 should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc). Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modifications instructions are provided in Tables 7.4.3 and 7.4.3.5

Table 7.4.3.5 Management of Non-infectious Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	CT scans with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat a chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required	Administer 100% of RAD001 dose.
Grade 2	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider a bronchoscopy	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce RAD001 dose until recovery to ≤Grade 1. RAD001 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 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.	Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 3 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 3 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.

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

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

7.5 Concomitant Medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the study without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics +/- steroids), with the following exceptions:

- no other investigational therapy should be given to patients
- no chronic treatment with systemic steroids or another immunosuppressive agent
- no anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- No live vaccines should be administered to patient due to immunosuppressant potential of RAD001.
- Concurrent treatment with bisphosphonates is allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form.
- For patients with radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended according to the ASCO guidelines on the use of bisphosphonates in women with breast cancer (35).
- leukocyte growth factors (e.g. G-CSF and GM-CSF) are not to be administered prophylactically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
- drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided in association with RAD001 as these can alter metabolism. Strong inhibitors

or inducers of the isoenzyme CYP3A should not be administered as systemic therapy (see Appendix B).

- Lipid-lowering drugs may be given in case of hyperlipidemia, a known side-effect of RAD001. Treatment should be for ≥ Grade 1 hypercholesterolemia with or without hypertriglyceridemia in addition to, and ideally after failure of, dietary advice to patients. HMG-CoA reductase inhibitors (e.g. atorvastatin, pravastatin, fluvastatin) are the preferred therapy. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events.
- Prolonged systemic corticosteroid treatment, except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) should not be given. A short duration (< 2 weeks) of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease).

The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug/s) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug/s must be recorded.

7.6 Supportive Care Guidelines

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Erythropoietin may be administered at the discretion of the Investigator, consistent with Institutional guidelines. G-CSF should be administered according to the guidelines in this protocol.

Symptomatic anemia should be treated with appropriate red blood cell support and transfusion is recommended if the hemoglobin falls below 8 g/dl. Alternately recombinant erythropoietin may be used if desired by the patient's physician.

Thrombocytopenia should be treated conservatively. In the absence of bleeding or a planned invasive procedure, platelet transfusions should only be given for a platelet count below 10 x 10^9 cells/L. If invasive procedures are planned or the patient develops bleeding, platelet transfusions should be administered in accordance with the Institution's standard of practice, usually maintaining a platelet count greater than 50 x 10^9 cells/L.

Nutritional assessment and psychological support: Refractory neoplasms are commonly complicated by malnutrition. Patients with weight loss or evidence of wasting syndrome should have a nutritional consult. Patients who are having emotional difficulties dealing with their treatment, and disease, or those patient's who request assistance, will be referred to a Social Worker for evaluation and support.

7.7 Adherence/Compliance

Patient compliance in daily self-administration of the oral tablets will be assessed at each clinic visit. They will be given a medication diary and instructed to fill out how many tablets were taken each day and the time of day the drug was taken. At the end of each cycle of treatment, the actual amount of unused drug will be compared to the anticipated amount of unused drug and the patient's medication diary.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician or their designee will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. Toxicities (including laboratory abnormalities) will be reported as outlined in the data capture plan.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

The Investigator will follow all patients who experienced an adverse event until there is a return to the patient's baseline condition or until a clinically satisfactory resolution is achieved.

8.1 Adverse Event Reporting Requirements

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

All "unexpected" (see Section 8.4) and/or "serious" (See Section 8.2) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the OHRS at (732) 235-7577. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

In addition to reporting to the local IRB, the Novartis Clinical Safety and Epidemiology Department must also be notified.

CINJOG affiliates will report all SAEs to the OHRS who will be responsible for forwarding SAE reports to the IRB, FDA and Novartis Pharmaceuticals.

Reporting SAEs using commercially available drugs:
In addition, any unexpected (*not listed in the package insert*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of Abraxane, must be reported to the FDA within 7 working days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178). CINJOG affiliates will report all unexpected, related SAEs to the OHRS who will be responsible for submitting the MedWatch forms to the FDA.

Expedited reporting requirement for adverse events experienced by patients with commercial agents only					
Attribution	Grade 4		Grade 5[a]		**Protocol Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely					See footnote (b) for special requirements.
Possible, Probable, Definite	REPORT		REPORT		
FDA MedWatch form 3500: Indicates that an expedited report is to be submitted to the FDA within 7 working days					
a: This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above. b **Protocol-specific expedited reporting requirements:** All SAEs must be reported to Novartis as outlined below. All CINJOG affiliates continue to report all SAEs to the OHRS.					

Reporting SAEs to Novartis:
Each serious adverse event (but not pregnancies) must be reported by the Investigator to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Clinical Safety & Epidemiology (CS&E) Department may contact the Investigator to obtain further information. If warranted, an Investigator alert may be issued, to inform all Investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

The Investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax to:

- 1.888.299.4565 within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department.

The Investigator must then ensure that the form and coversheet are accurately and **fully** completed with follow-up information and fax those to Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form and Novartis SAE coversheet must be kept with the case report forms at the study site.

Novartis CS&E department a must be copied on any study related safety information sent to the IRB.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form and Novartis SAE coversheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be approved by Novartis and the IRB of each participating institution before implementation. A copy of the written approval of the IRB must be sent to Novartis. These requirements for approval should in no way prevent any immediate action from being taken by the Investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the Investigator and is implemented for safety reasons, Novartis must be notified and the IRB at the center must be informed immediately.

8.2 Definition of Serious Adverse Events (SAEs)

A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

8.3 Definition of Related

There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

8.4 Definition of Unexpected

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

8.5 Death

Any death while a patient is receiving treatment on this study or up to 30 days after the last protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended, but which is felt to be treatment related must be reported within 24 hours (i.e., one working day from the date of discovery) to the OHRS.

9. Treatment Evaluation/Criteria for Response

For the purposes of this study, patients should be reevaluated for response following every second cycle of therapy. In addition to baseline scan(s), confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval, not less than 6 weeks.

The main goal of confirmation of objective response is to avoid overestimating responses. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome that the response(s) is/are not confirmed.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (36). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

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

9.2 Non-Measurable Disease

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

9.3 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response. There may be occasions when progressive disease is suspected but cannot be fully characterized. In these cases, the treating physician may decide to continue treatment for one or two cycles before reassessment, if he/she feels it is in the patients' best interest and the patient agrees to continue treatment.

9.4 Non-Target Lesions

All other lesions (or sites of disease) will be identified as non-target lesions and will be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

9.5 Guidelines for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will 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 will be used whenever possible to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

9.5.1 Clinical lesions- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion.

9.5.2 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.

9.5.3 Conventional CT and MRI- These techniques will be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT will be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.

9.5.4 Ultrasound (US)- Because one of the endpoints of the study is objective response evaluation, US will not be used to measure tumor lesions. US might be used, at the discretion of the investigator, to confirm the complete disappearance of superficial lesions assessed by clinical examination.

9.5.6 Tumor markers- Tumor markers alone will not be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.5.7 Cytology, histology- These techniques may be used to differentiate between partial responses (PR) and complete responses (CR) if necessary and determined by the investigator. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.6 Response Criteria

9.6.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

9.6.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and *normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	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.
Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the investigator will prevail.	
*Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.	

9.6.3 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort will be made to document the objective progression.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination. The residual lesion will be investigated (fine needle aspirate/biopsy if possible) before confirming the complete response status.

9.7 Confirmatory Measurement/Duration of Response

9.7.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks.

9.7.2 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).

9.7.3 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.

9.8 Reporting of Results

All patients initially considered evaluable will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 8) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria and are evaluable, will be included in the main analysis of responses. Patients in response categories 4-8 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of a response. All conclusions will be based on all eligible patients.

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Disease progression/relapse during active treatment,
b) Intercurrent illness that prevents further administration of treatment,
c) Unacceptable adverse event(s).
d) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment,
e) Patient decides to withdraw from the study,
f) Noncompliance with treatment plan,
g) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator, or
h) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.
i) In the event of any drug-related life-threatening toxicity or laboratory abnormality the patient will be withdrawn from further treatment. When a patient is taken off study, this information should be communicated to the OHRS.

11. Laboratory Evaluations and Procedures/Correlative and Pharmacokinetic Studies

11.1 Immunohistochemistry analysis

Our Tissue Analytical Service will perform immunohistochemical staining on formalin-fixed and paraffin-embedded tissues. If substantial normal tissue is felt to be present within the biopsied tissue and quantification is attempted, a board-certified pathologist, Dr. Nicola Barnard or qualified designee, will assist in identifying malignant and non-malignant tissue.

11.2 Shipping Instructions for Archival Tumor Tissue

All samples are to be identified with the patient's assigned registration number and shipped with reference to Breast study CINJ # 040803. Slides and Tissue blocks are to be sent by overnight express to the Cancer Institute of New Jersey Tissue Analytical Service (TAS).

Paraffin Blocks

Please wrap paraffin blocks in bubble wrap or some material that will cushion them. During spring and summer months, paraffin blocks must be shipped with a cooler pack inside the shipping container or the wax will melt and the specimen will be compromised.

Glass Slides

Glass slides must be mailed/shipped in appropriate protective slide containers. These can be made of cardboard (flat slide holder) or plastic (slide box or slide shipper).

Documentation

Please have the name, address and the appropriate laboratory or office phone number of the institution that the patient specimens were shipped from. For any questions relating to shipment of samples please call (732) 235-8065.

Cancer Institute of New Jersey **mailing address:**
Rutgers Cancer Institute of New Jersey
Attention: Dr. Deborah L. Toppmeyer c/o Julie Friedman RM 2034
Protocol: Breast Study CINJ# 040803
195 Little Albany Street
New Brunswick, N.J. 08903

12. Pharmaceutical Information

12.1 Abraxane

Source: Abraxane is commercially available by the pharmaceutical company, Abraxis Oncology.

How Supplied: Abraxane is available, in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products.

Storage and Stability: Unreconstituted Abraxane should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its carton. Reconstituted Abraxane should be used immediately. If not used immediately, the vial of reconstituted ABRAXANE must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Study Medication Administration

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of Abraxane. In any event, filters of pore-size less than 15 micrometers must not be used.

Abraxane will be reconstituted by appropriate study personnel and administered to the patient in the study site. The investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of Abraxane to be administered.

Reconstitution and use of Abraxane:

1. Calculate the patient's body surface area at the beginning of the study. A variance of 5% of the calculated dose will be allowed.
2. Calculate the total dose (in mg) to be administered by:

   Total Dose (mg) = BSA x (study dose mg/m^2)
3. Calculate the total number of vials required by:

$$\text{Total Number of Vials} = \frac{\text{Total Dose (mg)}}{\text{100 (mg/vial)}}$$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (eg, if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Reconstitute each Abraxane vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.

- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Rapid agitation or shaking will result in foaming.
- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
- Each ml of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:

   Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)

8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.
9. Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Abraxane suspension will be drawn into a syringe and placed on a syringe pump for administration.
11. Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary. If used, in-line filters with pore sizes of < 15μ should not be used.
12. Use within 8 hours of reconstitution. If not used immediately, store reconstituted Abraxane in a refrigerator for no longer than 8 hours.

Toxicities
Most Frequent: Alopecia, Anemia, Arthralgia, Cough, Diarrhea, Dysgeusia, Dyspnea, Edema, General Weakness, Infection, Myalgia, Nausea, Neutropenic Disorder, Optic Neuropathy, Oral Candidiasis, Pneumonia, Stomatitis, Upper Respiratory Infection, Vomiting

Less Frequent: Bradycardia, Cardiac Arrest, Chest Pain, Hemorrhage, Hypersensitivity Drug Reactions, Hypertension, Hypotension, Injection Site Sequelae, Nail Disorders, Neuropathy, Neutropenia from Cancer Chemotherapy, Paroxysmal Supraventricular Tachycardia, Pulmonary Thromboembolism, Thrombocytopenic Disorder, Thrombotic Disorder, Visual Changes

Rare: Cerebrovascular Accident, Interstitial Pneumonitis, Pneumothorax, Pulmonary Fibrosis, Transient Cerebral Ischemia

Drug interactions: Based on two pharmacokinetic drug interaction studies (warfarin, cimetidine), review of data from large Phase III trials, and the in vitro results on cytochrome P450 enzymes, the potential of Abraxane to interact with other drugs is low. No dose adjustments are recommended nor required for patients with renal or liver impairment.

12.2 RAD001

Source: RAD001 will be supplied to patients by Novartis.

How supplied: Formulated as tables for oral administration of 5 mg and 10 mg strength, blister-packed under aluminum foil in units of 10 tablets. Blister packs should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

Storage and stability: The commercial product bears an expiration date. Store below 30^{o}C an in the original blister packs. Shelf-life will be described on the investigational medication label.

Route of administration: Oral. RAD001 may be taken with or without food. Patients will be advised to take their tablets at the same time of the day and at the same time in relation to meals. Tablets must be swallowed whole with a glass of water.

Toxicities

Most frequent: fatigue, mouth sores, nausea, vomiting, headache, rash and diarrhea.

Less Frequent: hypercholesterolemia (increased cholesterol blood levels), hypertriglyceridemia (increased triglyceride blood level), increased liver function blood levels, neutropenia and thrombocytopenia.

Rare: hemorrhagic gastritis and epistaxis. Lenticular alteration ocular disorders have been observed in rats in preclinical toxiclogy studies and have not been reported in human subjects. However, patients treated with RAD001 who complain of a sudden reduction in visual acuity should have an ophthalmic exam to rule out lenticular alteration.

The Investigator Drug Brochure for RAD001 should be referenced for any additional information regarding RAD001.

13. Data Collection and Records to be Kept

13.1 Case Report Forms

The Principal Investigator (PI) at each institution will be responsible for assuring that all data specified in the study-specific data capture plan is collected and entered onto the electronic case report forms (eCRFs). In accordance with FDA instructions any abnormal test results including laboratory tests, radiologic examinations, and findings on physical examinations will be collected, graded and causality assigned and resolution reported.

Data submission guidelines are in concordance with those expected by the National Cancer Institute, i.e.: Baseline data is to be entered onto eCRFs within 2 weeks of initiation of treatment. Subsequent eCRFs are to be completed within 2 weeks of the date in which the previous cycle was completed. All e-CRFs will be submitted to the OHRS at the Cancer Institute of New Jersey via its secure web-based data management system.

The e-CRFs are found in the study specific calendar that has been created in the data management system. The system will prompt the user to the forms that are required based upon the patient's enrollment and treatment dates.

Periodically, monitoring and /or auditing visits will be conducted by staff from the Cancer Institute of New Jersey monitoring/auditing staff for the purpose of verifying data entered onto eCRFs with source documentation. The participating institution will provide access to his/her original records to permit verification data entry.

13.2 Research Charts

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Completed paper CRFs and copies of the most significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS. It is recommended that CINJOG centers maintain research charts as indicated above.

13.3 Reports

Publications and annual reports for submission to the IRB will be written by the Cancer Institute of New Jersey PI using the data captured on the CRFs. Study progress reports will be provided to CINJOG participants for submission to local IRBs.

14. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the Cancer Institute of New Jersey's NCI approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted at the Cancer Institute of New Jersey in accordance with the DSMP following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur on an annual basis prior to annual IRB continuing review, if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. All CINJOG centers will be monitored at least quarterly and audited annually. Prior audit findings and/or situations that may arise during the course of the study will determine the need for more frequent auditing. All audit findings will be reported to Cancer Institute of New Jersey's Human Research Oversight Committee and the PI.

15. Multi-Institutional Guidelines

15.1 IRB Approvals

As the Coordinating Center for a trial, it is the Cancer Institute of New Jerse's responsibility to ensure that no patients are entered on the trial at a participating institution without full IRB approval. Thus, OHRS will approve the addition of each participating institution to the study. A copy of the IRB approval document from each participating institution will be obtained prior to activation of the study at the participating institution.

15.2 Other Pre-Study Documents

Each participating center is required to have the following documents on file at the Cancer Institute of New Jersey OHRS:

- Curricula Vitae of all physician Investigators
- Signed FDA form 1572 of all physician Investigators
- Medical license from each Investigator

15.3 Initiation Site Visits

Initiation site visits will be conducted at each participating CINJOG institution prior to enrollment of patients from the institution. OHRS staff will conduct the initiation visit in close proximity to IRB approval of the study at the participating center.

15.4 IRB Continuing Approvals

The CINJOG investigators must provide, through the OHRS, a copy of the institution's approved continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the Cancer Institute of New Jersey.

15.5 Amendments and Consents

The OHRS will maintain a copy of all amendments, consent forms and approvals from each participating institution. Consent forms will be reviewed and approved by OHRS to ensure consistency with the Rutgers Biomedical Health Sciences Institutional Review Board approved consent form. Should changes to the protocol become necessary, protocol amendments will be submitted in writing to the Cancer Institute of New Jersey PI and local IRB for approval prior to implementation; unless the patient's best interest is endangered. In that case, notification to PI and local IRB will be made as soon as possible.

15.6 Patient Registration

All patients from participating institutions must register patients with the OHRS central registration desk, as described in Section 5.6 of this protocol.

15.7 Data Collection and Toxicity Reporting

The PI at each institution will be responsible for assuring that all the required data is collected and entered onto the CRFs accurately and completed CRFs submitted at the time points specified in Section 13.2 and the study data collection plan.

15.8 Data Monitoring and Source Document Verification

Each site participating in the accrual of patients to this protocol will be audited for protocol and regulatory compliance, data verification and source documentation.

The Cancer Institute of New Jersey staff will conduct monitoring visits to participating institutions of CINJOG no less frequently than every 3 months. The monitoring visits will focus on verifying CRF data with source documents. Adherence to the protocol(s), including the prompt reporting of serious adverse events, will be assessed. Findings of all monitoring

visits are recorded in a CINJOG Monitors Report, which is sent to the Cancer Institute of New Jersey PI and the CINJOG PI. All CINJOG Monitor's Reports are reviewed at regular meetings of the Human Research Oversight Committee.

15.9 Data and Center Audits

Cancer Institute of New Jersey staff will conduct annual audits to each participating center in accordance with OHRS Standard Operating Procedures (SOPs). The audit guidelines are in accordance with the Cancer Institute of New Jersey Data and Safety Monitoring Plan.

16. Statistical Considerations

16.1 Trial Design

This is a one-arm Phase I/II trial combining Abraxane and RAD001 in the treatment of women who have receive no prior chemotherapy regimens for the treatment of locally advanced or metastatic breast cancer. The primary end point for efficacy is response as defined by the Response Evaluation Criteria in Solid Tumor (RECIST). Data with regard to secondary endpoints (see Section 1.2) will be descriptive and considered exploratory and hypothesis generating.

16.2 Sample Size Justification

The combination treatment will be considered effective if the response probability is 40% or higher. We will thus test the null hypothesis $p_0 \leq .40$ against the alternative hypothesis $p > .40$. We also require that the power of the test be at least 80% if the true response probability of the combination treatment is $p \geq .55$. For $\alpha = .05$, Simon's two-stage Phase II design (with admissible solution) will be used to monitor the study as follows: The study will first accrue 39 patients in the first stage. If there are 17 or fewer responses among these 39 patients, the study will be terminated and the combination therapy will be rejected. Otherwise, the study will continue until another 33 patients are accrued (i.e. for a total of 72 patients). If stage two is conducted, the null hypothesis will be accepted if 35 or fewer responses are observed in the two stages combined. Otherwise, the null will be rejected. Therefore, the proposed sample size is a minimum of 39 patients and a maximum of 72 patients.

16.3 Study Duration

This study will require approximately 15 to 24 months to complete accrual of 39 to 72 total patients onto this trial. It is estimated that three to six patients per month may be accrued onto this trial between the Cancer Institute of New Jersey and its partners and affiliate institutions (i.e., CINJOG).

16.4 Data Analysis

The time to progression will be summarized using the standard Kaplan-Meier method. The frequency of serious adverse events as outlined in Section 6 will be described by summary statistics. Biological end points obtained from biopsy specimens are likely to be assessed semi-quantitatively, and compared using nonparametric methods to determine correlations with tumor response and disease progression.

17. Human Subjects

17.1 Patient Population

Women with locally advanced or metastatic breast cancer who have received no prior chemotherapy regimens for metastatic disease may participate in this trial if they meet the eligibility criteria. The inclusion and exclusion criteria detailed in this protocol are designed to exclude patients solely for medical reasons. Study participants will be patients who are receiving care for their disease at the Cancer Institute of New Jersey or at CINJOG affiliated medical oncology practices and community hospitals. The Principal Investigator and Cancer Institute of New Jersey research personnel will closely monitor the status of the study (and individual patient data) at all centers. Males will not be eligible for this study. Breast cancer in men is rare and the efficacy of Abraxane in males is limited.

17.2 Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Reported side effects of Abraxane and RAD001 are presented Section 12.

This study may involve risks to patients that are currently unforeseeable. Patients enrolled in this trial will receive their treatment in an outpatient setting. In addition, monthly blood work will be taken to monitor side effects. Evaluations at each cycle to monitor the treatment of patients will be performed and recorded in the patient chart. For patients at the Cancer Institute of New Jersey or at the affiliated sites who do not customarily receive their care at the affiliated institution, a local oncologist should be identified to monitor for complications and to improve long term care. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

17.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the patient's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

The investigational nature and objectives of this trial, the procedures and treatments involved and their attendant risks, discomforts, and potential benefits will be carefully explained to the patient. This process will include a general description of the disease process, as well as a description of the patient's expected clinical course. Alternative therapies will be fully described, and outlined in the consent document. The patient will be asked to read the consent at his/her convenience and will be encouraged to ask questions. Enrollment on this

study will only occur if the patient meets all eligibility criteria, is judged by the Principal Investigator or participating investigator to potentially benefit from the therapy, is able and willing to provide full consent, and has signed the consent document. Moreover, any experimental invasive procedure will require a separate consent form (standard procedure consent form).

17.4 Potential Benefits

It is likely that a significant proportion of patients who participate in this clinical trial will receive direct clinical benefit because they will be receiving a drug that is commonly used for their disease. This benefit may be reduction in the size of their tumor, stability in the size of their tumor, and/or improvement in symptoms related to their disease.

17.5 Risk-Benefit Ratio

The potential benefit that may result from this study balances the potential risks to the patients. There is extensive data to support the efficacy of Abraxane in patients with metastatic breast cancer. However, it is not clear whether the combination of Abraxane and RAD001 are superior to Abraxane alone, however the mechanism of RAD001 provides substantial rationale to suggest that the combination will be more effective than Abraxane alone. This protocol may or may not be helpful to a specific patient, but the results may help the investigators learn about the administration and effectiveness of Abraxane and RAD001 in breast cancer and may aid in the treatment of other patients. This research treatment is not curative, but may offer temporary control of the disease. Benefit cannot be promised nor can the chance of benefit be accurately predicted.

17.6 Gender and Minorities

The National Institute of Health and NCI have stressed the importance of gender and minority inclusion in clinical services and research. Female patients accounted for 58% of cancer patients seen within The Cancer Institute of New Jersey's clinical programs within the last year. African-Americans comprised 7%, Hispanics 8%, and Asians 3% of female patients, respectively. For all patients entering clinical trials, the percentages were 52% women, 6% African-American, 5% Hispanic, and 3% Asian.

No person shall on the grounds of race, color or national origin, be excluded from participation in, be denied the benefits of, enrollment in this study. There is a restriction regarding the sex of the patient (see Section 5.3). Minorities are prevalent in the New Brunswick area.

18. Economic/Financial Considerations

Patients and/or their insurance carriers will be expected to pay for costs related to monitoring and follow-up. Patients will be expected to pay for any costs not paid by their insurance carrier. The cost of correlative studies will not be billed to the patient or insurer. The study drug, RAD001, will be provided for free and will not be charged to the patient or their insurance carrier. The study drug, Abraxane, is commercially available and will be charged to the patient or their insure carrier.

19. Publication of Research Findings

The policies and procedures of The Rutgers University legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The Cancer Institute of New Jersey PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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

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Appendix A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties an polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

Examples of Drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A

Inducers note: strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampicin
Nafcillin	Rofecoxib
Nevirapine	St John's wort
Oxcarbazepine	Sulfadimidine
Phenobarbital	Sulfinpyrazone
Phenylbutazone	Troglitazone
Inhibitors note: moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Aprenavir	Mibefradil
Azithromycin	Miconazole
Bromocriptine	Nefazodone
Cannabinoids	Nelfinavir
Cimetidine	Nevirapine
Cisapride	Norfloxacin
Clarithromycin	Norfluoxetine
Clotrimazole	Omeprazole
Cyclosporine	Oxiconazole
Danazol	Paroxetine
Delavirdine	Propoxyphene
Dexamethasone	Quinidine
Diethyldithiocarbamate	Quinine
Diltiazem	Quinupristin and dalfopristin
Dirithromycin	Ranitidine
Disulfiram	Ritonavir
Entacapone (high dose)	Saquinavir
Erythromycin	Sertindole
Ethinyl estradiol	Sertraline
Fluconazole	Telithromycin
Fluoxetine	Troglitazone
Fluvoxamine	Troleandomycin
Gestodene	Valproic acid
Grapefruit juice	Verapamil
lndinavir	Zafirlukast
lsoniazid, ltraconazole	Zileuton