A Trial of maintenance Rituximab with mTor inhibition after High-dose Consolidative Therapy in CD20+, B-cell Lymphomas, Gray Zone Lymphoma, and Hodgkin's Lymphoma

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List of abbreviations

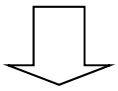
4E-BP1	4E-binding protein
Ab	Antibodies
ADR	Adverse Drug Reaction
AE	adverse event
ALT/SGPT	1 alanine aminotransferase/glutamic pyruvic transaminase/Serum glutamic-pyruvic transaminase
AST/SGOT	aspartate aminotransferase/glutamic oxaloacetic transaminase/Serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma-concentration time curve
BAC	Bronchoalveolar carcinoma
Cmax	Maximum plasma concentration
CR	Clinical research
CRF	Case report/Record form
CRO	Contract Research Organization
CT	Computer tomography
CTC	Common toxicity criteria
CV	Coefficient of Variation
CYP3A4	CytochromeP450 3A4 isoenzyme
DNA	Deoxyribonucleic Acid
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
eIF-4E	Eucariotic Initiation Factor 4E
EPR	Early progression rate
FDG-PET	Fluorine-18-2-fluoro-Deoxy-D-Glucose Positron Emission Tomography
FKBP-12	FK506-binding protein 12
GF	Growth factor
HBV	hepatitis B virus
HBcAb	hepatitis B core antibodies
HBs Ab	hepatitis B surface antibodies
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
INR	International Normalized Ratio

LDL	Low-density lypoproteins
LFTs	liver function tests
LLOQ	Lower limit of quantification
MAPK	Mitogen Activated Protein Kinase
mRNA	messenger Ribonucleic acid
mTOR	mammalian Target of Rapamycin
NIH/NCI	National Institutes of Health/National Cancer Institute
nM	nano-molar
NSCLC	Non-small cell lung cancer
OS	overall survival
P-AKT	phosphor-AKT
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PET	Proton emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/pharmacodynamic
PT/PTT	prothrombin time
PTEN	Phosphatase and Tensin homolog deleted on chromosome 10
QOD	Every other day
RBC	red blood cell count
REB	Research Ethics Board
RNA	Ribonucleic acid
RR	response rate
S6K1	S6 kinase 1
SAE	serious adverse event
SCLC	Small cell lung cancer
STAT3	Signal Transducer and Activator of Transcription 3
TK	Tyrosine kinase
TSC2	Tuberous Sclerosis Complex 2
TUNNEL	Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin Nick End Labeling
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	total white blood cell count

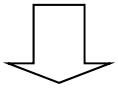
WHO World Health Organization

SCHEMA

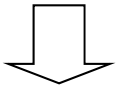
Diagnosis of CD20+, B cell Lymphoma, Gray Zone Lymphoma, or Hodgkin's Lymphoma



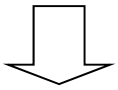
Standard Therapy



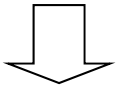
High-dose Consolidation Therapy



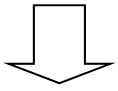
Registration for This Protocol



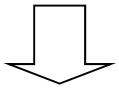
Evaluation of Eligibility for Protocol Participation



6 to 10 weeks after Initiation of High-dose Consolidation
Therapy for Maintenance Rituximab and Everolimus for 1 year



Treatment Evaluations with Radiographs, standard laboratories and examination for 3 years/correlative peripheral blood studies for 3 years



Follow-Up for 2 additional years to assess survival/disease status only

1.0 Introduction

1.1 Everolimus (RAD001)

Everolimus (RAD001) is a novel oral derivative of rapamycin. Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. Everolimus has been in development for patients with various malignancies since 2002. Everolimus 2.5mg, 5mg and 10mg tablets were approved under the trade name Afinitor® for patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide. Afinitor® was also approved in 2010 for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection. Affinitor ® received approval for the treatment of postmenopausal women with advance hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrolzole or ansastrozole.

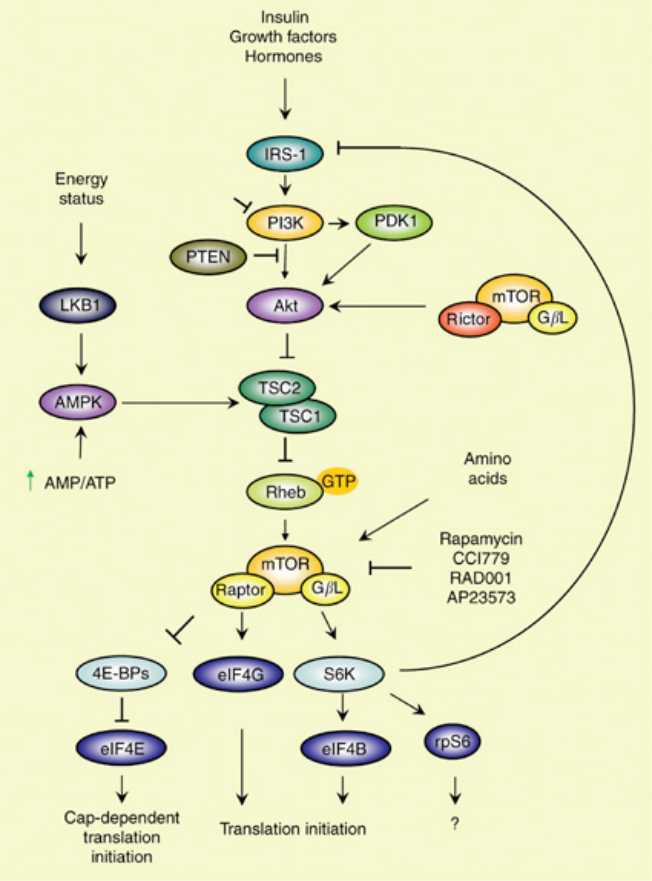
Everolimus is being investigated as an anticancer agent based on its potential to act:

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

At weekly and daily schedules and at various doses explored, RAD0001 is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

1.1.1 mTOR pathway and mechanism of action

The mammalian target of rapamycin (mTor): The mammalian target of rapamycin (mTOR) has emerged as a critical regulator of the malignant phenotype in human cancers.[1] "The mTOR protein is a serine-threonine kinase…central to a complex intracellular signaling pathway and is involved in a number of important processes such as cell growth and proliferation, cellular metabolism, autophagy, and angiogenesis. It responds to signals from the extracellular environment such as nutrient and growth factor supply, energy, and stress. Signaling through the pathway is promoted when there is an abundance of nutrients or energy and is down regulated in states of depletion and stress."[2] "mTOR exists within the cell complexed to the proteins involved in either raptor [TORC1 pathway] or rictor [TORC2 pathway]. The mTOR/rictor protein complex is [less] responsive to inhibition by rapalogs and will not be discussed in detail except to mention its interaction with mTOR/raptor."[2] The TORC1 pathway "can be activated by various stimuli through different upstream molecules. After stimulation, PI3K initiates a cascade that ultimately results in the phosphorylation and activation of Akt [T308]. Akt then acts via the tuberous sclerosis complex (TSC), consisting of the proteins TSC1 and TSC2, to exert its effect on mTOR. Phosphorylation of TSC2 by Akt inhibits TSC2, thereby releasing the inhibition that TSC2 otherwise exerts on mTOR via inhibition of Rheb, an activator of mTOR."[2] Downstream of [TORC1 pathway] are two main effectors, S6K1 and 4E-BP1, both of which control the translation of specific mRNAs and the synthesis of particular proteins.[2] Phosphorylation of 4E-BP1 by mTOR ultimately results in the initiation of translation of certain mRNAs that have regulatory subunits in the 5'-untranslated terminal regions, including those that are needed for cell cycle progression and are involved in cell cycle regulation. Phosphorylation and activation of S6K1 are also involved in cell growth and proliferation, possibly via translation of mRNAs that have a terminal 5'-oligopyrimidine tract such as those that encode ribosomal proteins and elongation factors. Importantly, S6K1 also has an inhibitory feedback function on the pathway by phosphorylating and inhibiting insulin receptor substrate-1, thus reducing growth factor–stimulated signaling through PI3K/Akt/mTOR. It also phosphorylates and inactivates BCL2 antagonist of cell death (BAD), a proapoptotic molecule. The numerous proteins whose translation is regulated through mTOR and its downstream targets include cyclin D1, MYC avian myelocytomatosis viral oncogene homolog (c-MYC), and hypoxia-inducible factor-lα (HIF-1α)."[2]



[2]

Inhibitors of the mTor Pathway: "Inhibitors of the [mTORC1] pathway include sirolimus, temsirolimus, everolimus, and deferolimus. Sirolimus and the rapalogs exert their effects by the same mechanism. Each drug binds to the intracellular binding protein FK506-binding protein (FKBP12) to form a complex, which then binds to mTOR at the FKBP12–rapamycin binding domain, interfering with its ability to signal adequately to its downstream effectors. Exactly how the sirolimus–FKBP12 complex interrupts mTOR signaling is not known, but it may involve a destabilization of the interaction between mTOR and raptor."[2]

Rituximab can act synergistically with mTOR inhibition: The SP49 cell line (a cell line established from MCL) which is sensitive to rituximab showed the combination of rituximab with Everolimus to produce a very strong synergistic effect on proliferation inhibition.[3] In NHL mTORCH1 inhibitors *have in-vitro* synergy with rituximab.[4]

Cancer Stem Cells: "Increasing data from several human cancers suggest that neoplastic cells within individual tumors are functionally heterogeneous cells despite their clonal

origins. In particular, the potential for long-term proliferation appears to be restricted to subpopulations of "cancer stem cells" functionally defined by their capacity to undergo self-renewal and give rise to differentiated cells that phenotypically recapitulate the original tumor."[5] Although most low grade B cell and MCL patients respond to initial treatment, disease relapse is virtually universal even after autologous stem cell transplantation.[6-11] The precise factors involved in tumor re-growth are unknown, but we have recently found that tumorogenic potential is restricted to distinct populations of MCL cells or MCL cancer stem cells.[12] We contest that novel agents should be introduced that focus on the cancer stem cell.

mTor and Mantle Cell Lymphoma (MCL): MCL cells have a distinct cytogenetic translocation t(11;14) which juxtaposes the cyclin D1 gene under the control of the immunoglobulin enhancer. The cyclins in general promote proliferation by interacting with the cyclin-dependent kinases and cyclin D1 appears to play a role in enhancing the proliferative capacity of MCL cells. Dysregulation of the cell cycle inhibitor p27 has also been implicated in MCL. In addition, MCL cells demonstrate defects in apoptosis further contributing to the growth advantage of this cancer. From a cell signaling perspective, the PI3-kinase/AKT/mTOR pathway has been implicated in driving gene expression in MCL.

Furthermore, our preliminary data suggest that this pathway is important for growth and survival of Aldehyde ^{high} MCL stem cells. Not surprisingly, these pathways play a role in promoting the expression of the cyclins, degrading p27 and promoting survival over apoptosis. In this regard there have been several clinical trials demonstrating activity of mTOR inhibitors in MCL. Data on the efficacy and safety of temsirolimus an intravenous mTOR inhibitor, as a single agent in patients with relapsed or refractory MCL have been published.[13]

Thirty-five patients were treated with temsirolimus 250mg intravenously every week as a single agent. Patients had previously received a median of 3 prior therapies and 54% had been refractory to the last therapy. The overall response rate was 38% (95% CI: 22% to 56%), with one complete response and 12 partial responses. Median time to progression was 6.5 months (95% CI: 2.9 to 8.3 months). Hematologic toxicities were the most common: Grade 3 for 71% of the patients (25/35) and Grade 4 for 11% of the patients (4/35). Thrombocytopenia was the most frequent reason for dose reductions but typically resolved within 1 week. Non-hematologic toxicities of all grades included hyperglycemia (91%), increased triglycerides (77%), mucositis (71%), fatigue (66%), infections without concomitant neutropenia (63%), rash (51%), nausea (49%), AST elevations (43%), hypercholesterolemia (40%) and sensory neuropathy (37%). The authors concluded that "single-agent temsirolimus has substantial antitumor activity in relapsed MCL."

mTor and follicular cell lymphoma and CLL: Preclinical models demonstrate that the mTOR pathway is aberrant in many lymphoma subtypes, including follicular lymphoma. In follicular lymphoma, activated mTOR was necessary for malignant cell survival in contrast to normal cells derived from activated tonsillar tissue.[14] In murine models, Akt overexpression confers an aggressive and drug-resistant phenotype that is reversed by

mTOR inhibition.[15] 54 patients with relapsed aggressive follicular and CLL received temsirolimus 25mg weekly for 2 months. Three (5%) had grade III/IV pulmonary toxicity with temsirolimus pneumonitis. Follicular cell patients had a complete response rate of 25.6% and CLL patients had a partial response rate of 11%.[16]

Possible Class effect of mTOR inhibition during ablative BMT: Sirolimus during ablative allogeneic bone marrow transplant increases the risk of veno-occlusive disease of the liver from 7.4% to 15.8%.[17]

1.1.2 Pre-clinical studies: Everolimus acts as an inhibitor of interleukin and growth-factor-dependent proliferation of cells. The only currently known target of everolimus is mTOR, a key regulatory protein affecting cell growth.[18] Everolimus exerts its activity through high affinity interaction with an intracellular receptor protein, the immunophilin FKBP12. The FKBP12/everolimus complex subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1 to S-phase transition.

The main known functions of mTOR include:

• Function as a sensor of mitogens, growth factors, energy and nutrient levels, facilitating cell-cycle progression from G1 - S phase in appropriate growth conditions.

• Regulation of protein synthesis important for tumor cell proliferation and angiogenesis through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (e.g. p70S6K1). For example, activation of the mTOR pathway leads to a) increased production of pro-angiogenic factors (e.g. VEGF) in tumors b) tumor, endothelial and smooth muscle cell growth and proliferation.

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

The mTOR inhibitory activities presumably contribute to the antiproliferative activity of everolimus against tumor cell lines. However, everolimus may also exert an antitumor effect through the inhibition of angiogenesis. Indeed, both rapamycin and everolimus potently inhibit proliferation of endothelial cells[19] and have antiangiogenic activity in vivo.[19,20] Exactly which molecular determinants predict responsiveness of tumor cells to everolimus is still unclear. Currently, the activation status of the PI3K/AKT/mTOR/p70 S6K pathway may be indicative of responsiveness to rapamycins. For example, pre-clinically, loss of PTEN or constitutive/hyper-activation of AKT has been suggested to sensitize tumors to the effects of inhibition of mTOR[20]. Also, clinically, it has been suggested that high p70S6K activation in baseline GBM tumor samples may predict a patient population more likely to derive benefit from mTOR inhibition.[21]

The antiproliferative effects of everolimus were investigated in a mixed panel of 48 different tumor cell lines (including breast, colon, epidermoid, glioblastoma, lung, melanoma, prostate and renal). The majority of tumor cell lines were highly sensitive to the anti-proliferative effects of everolimus while a few others appeared intrinsically insensitive, or 'resistant' (IC50 range 0.2 to 4125 nM).[22] The median IC50 value of the 48 cell lines was 0.5 nM. Similar findings have been observed for rapamycin.[23] Everolimus was also shown to have activity in in acute myeloid leukemia cells,[24] mantle cell lymphoma cells,[3] adult T-cell leukemia cells,[25] diffuse large B cell lymphoma cells.[4]

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

Everolimus is a highly specific inhibitor of mTOR, which is afforded by high-affinity binding to the protein FKBP-12 (IC_{50} of 5.3 nM) similar to that of rapamycin. Similar potency of rapamycin and everolimus was also demonstrated at forming the mTOR / FKBP-12 tertiary complex in vitro. Specificity was demonstrated by a lack of inhibitory activity against 10 other protein kinases at concentrations up to 10 μM. The antiproliferative effects of everolimus were investigated in a mixed panel of 48 different tumor cell lines (including breast, colon, epidermoid, glioblastoma, lung, melanoma, prostate and renal).

Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported,[26] as well as in acute myeloid leukemia cells,[24] mantle cell lymphoma cells,[3] adult T-cell leukemia cells,[25] diffuse large B cell lymphoma cells,[4] pancreatic tumor cells,[27] ovarian cancer cells[20,28] and hepatocellular carcinoma cells.[29] Everolimus was also evaluated in a clonogenic assay using cells derived from 81 patient derived tumor xenografts never cultured in vitro (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC, SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma). Everolimus inhibited colony formation in a concentration-dependent manner (mean IC_{50}: 175 nM). In addition, normal hematopoietic stem cells were found to be relatively insensitive to everolimus, with an IC_{50} about 15 fold higher than the tumor lines.

Everolimus was effective and well tolerated against subcutaneous (s.c.) tumors established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a PgP170-overexpressing, multi-drug resistant tumor line. Typically, the antitumor activity of everolimus was that of reduction of tumor growth rates rather than producing regressions or stable disease although, in the case of A549 and NCI-H596 lung and ARJ42 pancreatic tumors, regressions could be obtained. These effects occurred within the dose range of 2.5 to 10 mg/kg, p.o., once per day. The change in tumor volume of the treated mice divided by the change in tumor volume of control mice (T/C)

typically ranged from approximately 15 to 50% at optimal doses. A marked loss of antitumor activity occurred when tumor-bearing mice were treated with everolimus once per week, but improved moderately with twice per week dosing. Antitumor activity of everolimus has also been demonstrated in mouse models of ovarian,[20] breast[30] and gastrointestinal stromal tumors.[31]

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

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys, and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 4.2 and 0.2 times the estimated clinical exposure. In reproduction studies, everolimus was toxic to the conceptus in rats and rabbits, and was considered potentially teratogenic in rats. It is therefore recommended that women of childbearing potential should use highly effective contraceptive measures during the entire treatment period and for 8 weeks thereafter. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore women who are taking everolimus should not breastfeed.

Everolimus Pharmacokinetics: Everolimus is rapidly absorbed with a median tmax of 1-2 hours. The steady-state AUC0-τ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Steady-state was achieved within two weeks with the daily dosing regimen. Cmax is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in Cmax is less than dose proportional. In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

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

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of PgP. Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity. No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces. There was a significant correlation between AUC0-τ and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

1.1.3 Clinical Experience with Everolimus: Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and was approved in Europe in 2003 under the trade name Certican®, for the prevention of organ rejection in patients with renal and cardiac transplantation. Additional non-oncologic indications currently being explored are wet age-related macular degeneration (AMD) and autosomal dominant polycystic kidney disease (ADPKD).

In oncology, everolimus has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with antitumor agents. Malignancies that are currently being evaluated in Novartis sponsored studies include the following: metastatic renal cell carcinoma (mRCC), breast cancer, gastroenteropancreatic neuroendocrine tumors (GEP-NET), mantle cell lymphoma and diffuse large B cell lymphoma (DLBCL), hepatocellular cancer (HCC), gastric cancer, and lung cancer. In addition, treatment of patients with Tuberous Sclerosis Complex (TSC) associated subependymal giant cell astrocytoma (SEGA) and Angiomyolypoma is also being evaluated.

Everolimus 2.5 mg, 5mg and 10mg tablets were approved under the trade name Afinitor® for patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide. Afinitor®® was also recently approved in the US for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection. Affinitor ® received approval for the treatment of postmenopausal women with advance hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrolzole or ansastrozole.

Phase I dose escalating studies, exploratory Phase I/II studies with everolimus as single agent or in combination with other anti-cancer agents, Phase II/III studies of everolimus in indications, and Phase III double-blind studies are contributing to the extensive database.

Approximately 35,982 cancer patients have been treated with everolimus as of 31-March-2014:

- 19,668 patients in Novartis-sponsored clinical trials
- 2,394 patients in the individual patient supply program
- More than 13,930 patients in investigator-sponsored studies
- In addition, healthy volunteers have participated in the clinical pharmacology studies as described in Section 7.2 of the Investigator's Brochure

Clinical Experience of Everolimus in lymphoma: everolimus, an oral mTOR inhibitor, was tested at 10 mg qd in a Phase II study for patients with a number of different types of relapsed or refractory lymphomas – including aggressive, indolent and uncommon lymphomas[32,33] . Thirty-seven (37) patients were treated in the aggressive lymphoma group - 20 (54%) with diffuse large B-cell (DLBC), 14 (38%) with MCL, 2 high grade, and 1 follicular grade III. Patients were eligible to enter if they had measurable disease and had met the following hematologic parameters: ANC ≥ 1.0 x 109/L, platelets ≥ 75.0 x 109/L and hemoglobin ≥ 8 g/L. The median age was 72 years (range, 45-92). Patients had previously received a median of 4 prior therapies (range, 1-15). Prior stem cell transplant was allowed. The median treatment duration with Everolimus was 2 cycles (range 1-16+). The overall response rate was 32% (12/37; 95% CI: 20-49%) with 1 complete response and 11 partial responses. The overall response rate in the MCL patients was 29% (4/14); including one who received Everolimus for more than 14 cycles, while maintaining PR. The median time to progression for all 37 patients was 3.7 months (95% CI: 2.1 - 8.7). The median duration of response for the 12 responders was 5.5 months (95% CI: 2.3 - 9.2). Three patients are currently maintaining a response with a median of 10.5 months (2.9-15.6+ months). Everolimus was well tolerated. The incidence of grade 3 anemia, neutropenia, and thrombocytopenia in this heavily pretreated patient population was 11%, 16%, and 30%, respectively. Two patients developed grade 4 neutropenia. Grade 2 hypercholesterolemia occurred in 11%; grade 2 hyperglycemia in 16%; grade 3 hyperglycemia in 11% of the patients. One patient had grade 4 hypertriglyceridemia.

In the treatment of relapsed Hodgkin's disease, everolimus dosed at 10mg daily on a monthly cycle, the ORR was 47%. Ten of 19 patients had dose reductions or treatment delays. The median number of cycles at 10mg daily was five (range 1-20).

Everolimus serum levels are commercially available

- Quest Diagnostics (18883X) CPT code 80299, Mon-Fri
- Target trough concentrations 3-15 ng/mL

1.2 Hopkins experience of high-dose consolidative therapy with low grade B cell and Hodgkin's lymphoma.

The Sidney Kimmel Comprehensive Cancer center has pioneered the concept of high-dose cyclophosphamide without stem cell rescue for over a decade. This high-dose consolidative treatment was developed for two main reasons.

It does not require stem cell rescue: it eliminates the potential of cancer re-introduction at time of stem cell rescue. Moreover, as this high-dose therapy does not require stem cell rescue all the components of autologous stem cell transplant: collection, preservation and re-infusion are eliminated making this therapy a more widely available treatment modality.

Tolerability: not only are the majority of the patients treated with this modality served in the outpatient setting, many have had a performance status or advanced age not otherwise well suited for an autologous stem cell transplant.

We put forward that the cytoreduction achieved by high-dose consolidative cyclophosphamide represents the ideal foundation for the integration of novel molecularly targeted compounds for these lymphomas.

81 adults received, as outpatients, rituximab [375mg/m^2 days 1, 4, 8, 11, 45, 52] and cyclophosphamide [50mg/kg days 15-18 with concurrent mesna] and pegfilgrastim (day +20). Forty-two participants had low grade B cell lymphoma [grade I/II follicular (69%), transformed lymphoma (17%), other (15%)]: 45% were treated without measurable disease. Thirty-nine had mantle cell lymphoma: 82% were treated without measurable disease. All achieved hematopoietic recovery; 46% required brief hospitalizations. The EFS for low grade B cell patients at 3 and 5 years was 49% and 40% with an overall survival (OS) at 3 and 5 years of 86% and 72%. The 3 and 5 year EFS for MCL patients was 57% and 39% with a 3 and 5 year OS 92% and 62%.

Hodgkin's data: Rituximab, high dose cy, and GM-CSF based immunotherapy for relapsed Hodgkin's lymphoma: This phase I/II, single-institution trial for relapsed classical Hodgkin lymphoma has just completed accrual of its planned 30 patients. Clinical outcomes of this platform, which was developed as a potentially less toxic alternative to autologous BMT, are encouraging. In the first 25 patients, whose median time between first-line therapy completion and relapse was 12 months, actuarial event-free survival is 79% at 1 year and 63% at 2 and 3 years following high-dose cyclophosphamide; overall survival is 100% at 2 years and 92% at 3 years. These early results are comparable to what is seen with autologous BMT. The toxicity profile has been manageable, and there has been no treatment-related mortality. Median time to neutrophil recovery after high dose cyclophosphamide was 17 days, and 21 days for platelet recovery with 5 patients not

requiring platelet transfusion. The trial was presented in a poster session at the 52nd American Society of Hematology annual meeting (Kasamon Y et al, *Blood* 2010, abstract 3954).

2.0 Primary Study Objective:

To determine the safety of maintenance rituximab and prolonged mTOR inhibition with everolimus in CD20+, B cell lymphomas, Gray Zone Lymphoma, and Hodgkin's Lymphoma after high-dose consolidative therapy.

- Safety will be determined by the extent of avoidance of ≥ grade III common toxicities (CTCAE version 4.0)

2.1 Secondary Objectives:

1) The secondary endpoint of this study is to evaluate event free survival (EFS) at three years based on histology.
    - EFS will be histology grade specific: Mantle cell lymphoma group, low-grade lymphoma group, high-grade lymphoma group
2) To determine whether maintenance rituximab with everolimus treatment reduces the frequency of circulating cancer cells.
3) To determine if relapsed disease is sensitive, in-vivo, to mTor kinase inhibition.

3 Investigational plan

3.1 Overall study design: After high dose consolidative therapy, patient will receive one year of adjuvant rituximab and everolimus. Treatment evaluation with radiographs, standard laboratories and examination will follow for the next three years. Survival/disease status will also be assessed for an additional two years, for up to 5 years total of follow-up.

3.2 Study population

Lymphoma histologies:

Mantle cell lymphoma

- Biopsy-proven diagnosis of Mantle Cell Lymphoma per the World Health Organization classification criteria
- The diagnosis is to be based on histologic and immunophenotypic criteria and include either immunohistochemical analysis for cyclin D1, cytogenetic analysis be either conventional karyotyping of fluorescence in situ hybridization (FISH) for 9(11;14)(q13;32), or both.
- Patient had met institutional standards for having high-dose consolidative therapy

Non-Mantle cell low grade B cell lymphomas (including SLL/CLL)

- Biopsy-proven diagnosis of lymphoma per the World Health Organization classification criteria
- Patient had met institutional standards for having high-dose consolidative therapy and relapsed disease despite the use of at least on chemotherapeutic agent (single agent Rituximab does not qualify for these histologies)
- Exception for mantle cell lymphoma and high risk SLL/CLL [defined as: del(17p), del (11q), or del(13q) concurrent with an unmutated IGVH status] who received high-dose consolidative therapy in first response are eligible for this protocol.

Transformed lymphoma/DLBCL/High risk DLBCL in first response/PMBCL

- Biopsy-proven diagnosis of lymphoma per the World Health Organization classification criteria
- Patient had met institutional standards for having high-dose consolidative therapy.

Gray Zone Lymphoma in first CR

- Biopsy-proven diagnosis of lymphoma per the World Health Organization classification criteria
- Patient had met institutional standards for having high-dose consolidative therapy.

Hodgkin's Disease

- Biopsy-proven diagnosis of lymphoma per the World Health Organization classification criteria
- Patient had met institutional standards for having high-dose consolidative therapy.

3.2.1 Patient population Patients must have had chemotherapy responsive disease (Partial response or better) before high-dose consolidative therapy. The accrual rate for this study is expected to be 20 patients per year. Assuming a three year recruitment period with a minimum follow-up of one year, 60 patients will give us 85% power to detect a 20% increase in EFS: 49% to 69%.Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meets all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment.

3.2.2. Inclusion Criteria

- Age ≥18 years of age
- ECOG performance status ≤ 2
- INR ≤ 2
- Adequate renal and hepatic function defined as a serum creatinine ≤2.0mg/dL, total bilirubin ≤5mg/dL, and AST and ALT < 2.5 ULN.• Platelet count ≥75 x 10^9/L
- Hemoglobin ≥10mg/dL
- ANC ≥3.0x10^9/L
- Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L and fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
- A willingness to use an accepted and effective method of birth control for sexually active women of childbearing potential during the study and for 8 weeks after the end of study drug treatment.
- Ability to sign informed consent.

Exclusion Criteria

- Patient who have previously received an mTor inhibitor
- Patients who are pre-terminal or moribund
- Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of Everolimus (including chemotherapy, radiation therapy, antibody based therapy, etc.)
- Uncontrolled diabetes mellitus as defined by HbA1c>8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
- Chronic treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled cortosteroids are allowed
- Patients who have received live attenuated vaccines within 1 week of start of Everolimus and during the study. Patient should also avoid close contact with others who have

received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;

- Patients who have a history of another primary solild malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥3 years;
- Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study;
- Patients with active bacterial or fungal infections requiring oral or intravenous antimicrobials are not eligible until resolution of the infection
- Female patients who are pregnant or breast feeding, or of reproductive potential whoe are not using effective birth control methods. Adequate contraception must be used throughout the trial and for 8 weeks after the last dose of study drug.

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- Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment
- Patients with known intolerance to rituximab
- Known history of HIV or Hepatitis C
- Active Hepatitis B as defined by seropositivity for hepatitis B surface antigen. Subjects with positive hepatitis B core antibody titers and normal liver transaminases are allowed provided that prophylaxis is administered per institutional guidelines. Please see Addendum 8 for the action to be taken for patients with positive baseline hepatitis B results.

3.2.3 Study Interruption or Study Withdrawal

A patient may be taken off this study early or may discontinue participation in this clinical study due to the following factors:

- Serious or intolerable adverse reaction to treatment
- Progression of disease
- Protocol violation
- Withdrawal of consent
- Withdrawal of sponsor support

There is no limit to how long a patient can have their treatment on hold. Prolonged holds are not considered “serious or intolerable adverse reactions to treatment.”

3.2.4 Monitoring of everolimus suspected toxicities: Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to everolimus must be followed at least weekly until the adverse event or abnormal laboratory completely resolves or returns to baseline as clinically appropriate. For patients whose treatment is on hold, labs will be monitored every two weeks while on hold.

3.2.5 Known Undesirable Side Effects of everolimus

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

Adverse events most frequently observed with everolimus are stomatitis, rash, diarrhea, fatigue, infections, asthenia, nausea, peripheral edema, decreased appetite, headache,dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting,pruritus, cough, dyspnea, dry skin, nail disorder, and pyrexia. Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia); increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

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

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

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer

therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus. Addendum 8 details the action to be taken for a patient with a positive baseline hepatitis B result. For hepatitis B reactivation, definition, and management guidelines, please see Addendum 9. For patients who have already received study drug prior to the approval of Protocol Version date February 18, 2014, HBV-DNA testing will be performed at the patient's next visit, and the result will be regarded as baseline.

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

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on everolimus. Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with everolimus. In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function. Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

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

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

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

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

Addendums 4-7 provide recommendations for the management of patients, with suspected drug toxicities while on treatment with everolimus.

More detailed information regarding everolimus reported suspected toxicities and individual cases is provided in the Investigator's Brochure. Management of non-infectious pneumonitis is described in Addendum 7.

3.3 Treatment

Pre-treatment evaluation (to be completed ≤30 days before treatment initiation)

History and Physical Examination

History should try to document the pre high dose consolidative therapy MIPI score (age at diagnosis, ECOG performance status, LDH and WBC) and FLIPI score (age of diagnosis, LDH, ECOG performance status, number of extranodal sites, Ann Arbor stage) for Mantle and follicular lymphoma patients, respectively.

A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus. Please see Addendum 8 for action to be taken for patients with a positive baseline hepatitis B result.

CBC with platelet and reticulocyte count

Complete metabolic panel, immunoglobulin panel (IGG, IGA, IGM), fasting triglycerides, glucose and total cholesterol (cholesterol and triglycerides can be measured on either the screening visit or the day 1 visit)

PET/CT scans. If PET/CT is not possible a CT of the chest/abdomen/pelvis is required.

Bone marrow aspirate and biopsy: if bone marrow was previously involved

HCG urine pregnancy test for women of child bearing potential

Treatment initiation: treatment is to begin between six (6) weeks and ten (10) weeks after high dose consolidative therapy

3.3.1 Everolimus administration

The initial dose of everolimus will be 2.5mg orally daily for a total of one year to maintain a target trough concentration between 3-15 ng/mL

Everolimus should be administered orally once daily, preferably in the morning, at the same time every day with or without food.

Everolimus tablets should be swallowed whole with a glass of water.

The tablets must not be chewed or crushed.

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

Everolimus will be provided by Novartis. Everolimus is formulated as tablets for oral administration of 2.5mg, 5mg, and 10mg strength.

Dose modification will occur as per Addendum 4.

Everolimus can still be administered per protocol even if Rituximab treatment is on hold.

3.3.2 Concomitant therapy

Rituximab will be administered concomitantly with everolimus as per the dose and schedule below. Instructions for administration of Bactrim and Valtrex for PCP prophylaxis and herpes prophylaxis treatment, respectively, are also listed.

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the patient will be asked about any new medications he/she is or has taken after the start of the study drug. Additional information about clinically relevant drug interactions can be found in Addendums 1-3.

All Concomitant medications/significant non-drug therapies taken ≤30 days prior to the start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

Rituximab administration

Dose and schedule: 375mg/m^2 day +1and then every 90 days for 1 year (a total of 4 infusions)

Rituximab will not be given unless the patient's ANC is greater than 1.5.

Administration as per institutional standard, with infusions 90 days apart, regardless of the study date that it was given. For example, if Rituximab is given on day 95 instead of 90, the next infusion will be given on day 185, not 180.

Rituximab can still be administered per protocol even if Everolimus treatment is on hold.

It is not considered a protocol deviation if Rituximab is withheld due to Rituximab-induced cytopenias. There is no limit to the number of Rituximab doses that can be held. For example, some patients may not get any doses of Rituximab, or possibly only one dose, if their counts have a history of extreme sensitivity to Rituximab.

Primary antimicrobial prophylaxis

Bactrim SS PO qd or equivalent/suitable antimicrobial regimen for PCP prophylaxis during everolimus administration

Valtrex 500mg PO bid or acyclovir 400 mg PO tid for herpes prophylaxis in HSV/CMV positive individuals during everolimus administration

3.3.3 Treatment compliance:

Everolimus compliance will be monitored by serum blood analysis. Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication. Rituximab will be infused at the cancer center.

3.4 Visit schedule and assessments

3.4.1 Visit schedule: Examination and Laboratory evaluations

Physical examination: Complete lymphomatous physical examination every ninety (90) days for the first two (years), then every six (6) months for the third year.

CBC with platelet count every two (2) weeks for the first sixty (60) days then monthly for a total of one (1) year, then every 90 days for the next two (2) years.

Metabolic panel every two (2) weeks for the first sixty (60) days then monthly for a total of one (1) year

Imunoglobulin panel (IgG, IgA, IgM), fasting triglycerides and fasting cholesterol levels monthly for a total of one (1) year.

Patients will be scheduled for an IVIG infusion if their IgG level falls below 500 mg/dL.

Patients with an IgG serum level of <500mg/dL will either have supplemental Ig administration or changes in primary oral antimicrobial prophylaxis per PI discretion.

HCG urine pregnancy testing every 4 weeks during everolimus administration and for 8 weeks post everolimus administration for women of child bearing potential

Everolimus serum trough levels every two (2) weeks for the first sixty (60) days then monthly for a total of one (1) year. Everolimus levels will not be drawn during a hold once the level is less than 1.0.

Research peripheral blood labs (2 green top tubes) every ninety (90) days for a total of three (3) years.

Bone marrow evaluation at ninety (90) days and at the end of cycle 13 (or the 365 day appointment when patients move into the follow-up stage) at PI's discretion. If a bone marrow evaluation is performed, an additional 10 ml green top tube of aspirate will be drawn for research purposes.

Adverse events and concomitant medications will be monitored throughout the duration of the study.

Survival/disease status will be assessed at year 4 and year 5.

Radiographic evaluation

Computerized Tomography (CT) of chest/abdomen/pelvis and whole body Positron emission tomography (PET) scanning every ninety (90) days for two (2) years, then every six (6) months for the third year.

CT scans of the neck and other structures as determined by physical examination

3.4.2 Study Calendar

Study procedures are detailed in the study calendar, which is located on the following pages.

Examination	Screening ≤30 days before treatment initiation	First 60 days	Year 1 (after first 60 days) ± 3 days					Year 2 ± 3 days	Year 3 ± 1 month	Year 4 and Year 5
		Every 2 weeks	Monthly	At Day 90	Every 60 days	Every 90 days	End of cycle 13	Every 90 days	Every 6 months	At patient's routine visits
Informed consent	**X**									
Inclusion/exclusion criteria	**X**									
Vital signs	**X**									
Physical examination[1]	**X**					**X**		**X**	**X**	
Medical History[2]	**X**									
Concomitant medication review	**X**	Continuous								
ECOG performance status	**X**									
Urine HCG test for applicable women only	**X[3]**	**X[3]**	**X[3]**					**X[3]**		
PET/CT[14]	**X**					**X**		**X**	**X**	
Hematology[4]	**X**	**X**	**X**					**X**		
Reticulocyte Count	**X**									
Chemistry[5]	**X**	**X**	**X**							
INR	**X**									
Fasting Cholesterol and Triglycerides	**X**		**X**							

Examination	Screening ≤30 days before treatment initiation	First 60 days	Year 1 (after first 60 days) ± 3 days					Year 2 ± 3 days	Year 3 ± 1 month	Year 4 and Year 5
Immunoglobulin panel (IGG, IGA, IGM)	**X**		**X**							
Hepatitis B and C screening[6]	**X**[6]									
HIV screening	**X**									
Bone marrow aspirate and biopsy[7]	**X**			**X**[7]			**X**			
Non-drug therapies and Blood transfusion record[8]	**X**									
Research peripheral blood[9]	**X**					**X**		**X**	**X**	
Study Drug Administration[10]			Daily for 1 year							
Everolimus Serum trough levels[11]		**X**	**X**							
Rituximab[12]						**X**				
Appropriate birth control measures			**X**[13]							
Adverse events			Continuous							
Survival/Disease Status			Continuous							

[1] Should include a complete lymphomatous physical examination.

[2] History should try to document the pre high dose consolidative therapy MIPI score (age at diagnosis, ECOG performance status, LDH and WBC) and FLIPI score (age of diagnosis, LDH, ECOG performance status, number of extranodal sites, Ann Arbor stage) for Mantle and follicular lymphoma patients, respectively.

[3] Urine HCG testing for applicable women conducted pre-study, every 4 weeks during everolimus administration until 8 weeks post everolimus administration.

[4] Should include a heme 8 with differential

[5] Chemistry should include a complete metabolic panel and glucose.

[6] A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus. Please see section Addendums 8 and 9 for action to be taken for patients with positive baseline hepatitis B results and management of hepatitis reactivation.

[7] Done at PI's discretion. When bone marrow biopsies are being performed, an additional 10 ml green top tube of aspirate will be collected for research samples.

[8] All Concomitant medications/significant non-drug therapies taken ≤30 days prior to the start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

[9] Collect 2-10ml green tops.

[10] Bactrim SS PO qd or equivalent/suitable antimicrobial regimen for PCP prophylaxis during everolimus administration. Valtrex 500mg PO bid or acyclovir 400 mg PO tid for herpes prophylaxis in HSV/CMV positive individuals during everolimus administration. The initial dose of everolimus will be 10mg orally daily for a total of one year to maintain a target trough concentration between 3-15 ng/mL. Dose modification will occur as per Addendum 4. Treatment is to begin between six (6) weeks and ten (10) weeks after high dose consolidative therapy.

[11] Everolimus compliance will be monitored by serum blood analysis. Everolimus serum levels are commercially available through Quest Diagnostics (18883X) CPT code 80299, Mon-Fri. The target trough concentrations 3-15 ng/mL.

[12] Dose and schedule of Rituximab: 375mg/m^2 day +1 and then every 90 days for 1 year (a total of 4 infusions). Administration as per institutional standard. Rituxumab should only be given if patient's ANC > 1.5.

[13] Patient must agree to use TWO acceptable versions of birth control monthly during everolimus administration and for 8 weeks after everolimus has been stopped.

[14] PET/CT scans are recommended. If a PET/CT is not possible a CT of the chest, abdomen, and pelvis can suffice.

[15] Years 4 and 5 of follow-up are for survival and disease status only and will occur at the patient's routine visits

3.4.3 Efficacy assessments

Response Evaluation: Conventional response criteria are modeled after the 1999 International Working Group criteria for non-Hodgkin's lymphoma.[34] Disease sites that are considered non-measurable, such as malignant effusions, ascites, or bony lesions, will be considered in the overall response.

Complete Response: Complete disappearance of all detectable clinical and radiographic evidence of disease.

Nonspecific laboratory measures such as LDH or ESR are not included in the response assessment.

All lymph nodes and nodal masses must have regressed to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in greatest transverse diameter must have decreased to < 1 cm, or by > 75% in the sum of the products of the greatest diameters (SPD).

The spleen, if previously enlarged due to lymphoma, must have regressed in size and must not be palpable. Macroscopic nodules in any organs should no longer be present. Other organs considered to be enlarged before therapy due to lymphoma, such as liver and kidneys, must have decreased in size.

Negative bone marrow biopsy and aspirate, if bone marrow previously involved

Partial response (PR):

> 50% decrease in the sum of the products of greatest diameter (SPD) of the six largest (or fewer) dominant nodes or nodal masses. These nodes or masses should be a) clearly measurable in at least two perpendicular dimensions; b) be from as disparate regions of the body as possible; and c) include mediastinal and retroperitoneal areas of disease when involved.

Regression of splenic and hepatic nodules by > 50% in SPD

Bone marrow assessment is not relevant for determination of a PR

No sites of new or progressive disease

Stable disease (SD): less than a PR but is not progressive disease (see below), and must be maintained for a minimum of 4 weeks

Relapsed disease (after CR) / Progressive disease (after PR or SD)

Appearance of any new lesion or increase by > 50% in size of previously involved sites.

50% increase in greatest diameter of any previously identified node >1 cm in short axis, or in the SPD of more than one node

Standard Definitions of Disease and Survival Endpoints

Overall survival (OS) will be measured from registration to the time of death from any cause or last patient contact.

Event-free survival (EFS) is defined as the interval from registration to the date of first objective disease progression, death from any cause, or last patient evaluation. Patients who have not progressed or died will be censored at the last date they were assessed and deemed relapse-free.

Failure-free survival (FFS) is defined as the interval from registration to the date of first objective disease progression or last patient evaluation. Patients who have not progressed, or patients who have died without evidence of lymphoma progression, will be censored at the last date they were assessed and deemed progression- or relapse-free.

Time to tumor progression (TTP) is defined as the interval from the date the patient was last found to be progression-free, to the date of first objective disease progression.

3.4.4 Safety assessments

Safety assessments will consist of monitoring and recording adverse events that are grade 3 and above and all serious adverse events, the regular monitoring of hematology and blood chemistry values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ± 2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

3.4.4.1 Adverse Events

Information about adverse events that are grade 3 or above, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal

laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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

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

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

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

3.4.4.2 Serious Adverse Events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Reporting of Serious Adverse Events:

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

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

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

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

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

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

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

3.4.5 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

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

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

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

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

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

3.4.6 Pregnancy and assessments of fertility for Everolimus

There are no adequate data from the use of everolimus in pregnant women. Studies inanimals have shown reproductive toxicity effects including embryo-toxicity and feto-toxicity. The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

It is not known whether everolimus is excreted in breast milk. However, in animal studies, everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking everolimus should therefore not breast-feed.

Women of childbearing potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

Male Contraception

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomised men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

Pregnancy Reporting

Preclinical data regarding reproductive toxicity is described in the most recent Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimu and up to 8 weeks after treatment has been stopped.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

4 Protocol amendments, or changes in study conduct

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

5 Data Management

5.1 Data Collection

Investigators must record the information required by the protocol.

5.2 Data Safety and Monitoring Plan

The CRO website link describing the CRO monitoring plans can be found here:

http://cro.onc.jhmi.edu/news/SKCCC_DSMP.doc

Internal Monitoring Plan

The PI will review data to assure the validity of data, as well as, the safety of the subjects. The PI will monitor the progress of the trial, review safety reports and clinical trial efficacy endpoints –on an ongoing basis to confirm that the safety outcomes favor continuation of the study.

The PI will be responsible for maintaining the clinical protocol, timely reporting of adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the annual report submitted to the IRB and to the Safety Monitoring Committee per the SKCCC Data and Safety Monitoring Plan.

External Monitoring Plan

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (9/22/2011). The Clinical Research Office QA Group will perform an audit after the first subject has been treated and then periodically depending on the rate of accrual and prior audit results. All trial monitoring and reporting will be reviewed by the SKCCC Safety Monitoring Committee in accordance with the Data and Safety Monitoring Plan and IRB policies.

6.0 Statistical Considerations

This is a study of maintenance rituximab with mTor inhibition (everolimus) after high-dose consolidative therapy in CD20+, B-cell Lymphomas and Hodgkin's Lymphoma. It is hypothesized that the addition of new agents in patients with minimal residual disease will improve event free survival and that everolimus may act synergistically with rituximab.

Primary Objective:

To determine the safety of maintenance rituximab and prolonged mTOR inhibition with everolimus in CD20+, B cell lymphoma and Hodgkin's Lymphoma after high-dose consolidative therapy.

Secondary Objectives:

1. The secondary endpoint of this study is to evaluate event-free survival (EFS) at three years. EFS is defined as the interval from registration to the date of first objective disease progression, death from any cause, or last patient evaluation. Patients who have not progressed or died will be censored at the last date they were assessed and deemed relapse-free.
2. To determine whether maintenance rituximab with everolimus treatment reduces the frequency circulating cancer cells.
3. To determine if relapsed disease is sensitive, in-vivo, to mTor kinase inhibition.

Study Design:

Treatment will consist of rituximab 375mg/m^2 q 90 days (4 infusions) with everolimus 2.5 mg orally daily for one year. There will be no drug escalation in this study however serum drug levels will be monitored and the level of everolimus will be maintained in the therapeutic window. For patients outside the range of 3 – 15ng/mL and not experiencing grade 3 or higher toxicity, the dose will either be increased or decreased by 2.5mg per day to bring patients within range, down to 2.5 mg every 4 days. Addendum 4 provides details on dose adjustments and treatment holds. For patients experiencing grade 3 or higher toxicities adjustments will be made as detailed in addendum 4. The study will be monitored continuously for safety.

Sample size/Accrual Rate:

The accrual rate for this study is expected to be 20 patients per year. The safety objective of this trial is based on the precision of estimating grade 3 or higher toxicities. Sixty patients will allow us to estimate the proportion of patients experiencing grade 3 or higher toxicities with a precision of ± 13%.

Early Stopping Guideline for Safety:

Because dose will be managed to target a therapeutic window, toxicity evaluation in this study will be based on events that would indicate either the therapeutic dose was too toxic to maintain or that this method increased the probability of unexpected complications. These events include any patient for which the minimum 2.5 mg everolimus every other day was not tolerable or any unexpected hospitalizations during protocol participation. We will monitor the study continuously. If it becomes evident that the proportion of failures convincingly exceeds 15%, the study will be halted for a safety consultation. The stopping rule will hold enrollment if the posterior probability of failure being larger than 0.15 is 75% or higher. The prior for this monitoring rule is beta(1, 6). This means that our prior guess at the proportion of failures is 14.3%, and there is 90% probability that this proportion is between 0.85% and 39%.

Stop if	2AEs	3AEs	4AEs	5AEs	6AEs	7AEs	8AEs	9AEs	10AEs	11AEs	12AEs
in N	2-5	6-11	12-16	17-22	23-28	29-34	35-40	41-46	47-52	53-58	59-60

The next table shows the percent of the time that the stopping rule will terminate the study under different hypothetical risks of AEs, along with the average sample size (based on 5000 simulations).

Risk of AE	0.05	0.10	0.15	0.20	0.25	0.30	0.35
% of Time Study Stops	3.2%	18.5%	49.7%	79.4%	95.2%	99.2%	99.9%
Expected Sample Size	58.3	51.2	38.6	25.4	16.1	10.9	8.0

Early Stopping Guideline for Futility and Simulation Sample Size:
This study will be monitored for efficacy as well as toxicity. If the study meets the accrual goal of 20 patients per year, accrual would be completed by the time the first patients enrolled on study reach the three year efficacy endpoint. We will therefore monitor the study based on one-year EFS, knowing that if the one-year EFS is convincingly less than our targeted EFS at three years, the study would not meet its efficacy objective and the trial should be halted. Patients that have not progressed or died will be censored at the last date they were assessed and deemed relapse-free. The non-parametric Kaplan-Meier estimate will be used to estimate the EFS function at one year. After 20 patients have been enrolled, the design will include interim analyses for futility that could halt the trial if it seems likely that the drug combination does not have sufficient clinical activity.

The sample size of 60 and the study design operating characteristics assume a three-year recruitment period with an additional follow-up of one year. Based on a study of high dose cyclophosphamide and rituximab without stem cell transplantation at our institution [2], the one and three-year EFS for low grade B cell lympohmas was 67 and 49% respectively. The simulation below demonstrates how the operating characteristics of the design varies when the uncertainty of the one-year EFS is characterized with the prior: beta(3,2). This implies that our prior guess at one-year EFS for these patients is 60%, and there is 90% probability that the EFS at 12 months is between 25% and 90%.

We have designed this study to stop early only if it appears that this treatment is associated with a lower one-year EFS than 50%. Specifically, the stopping rule will hold enrollment if the posterior probability of one-year EFS being less than 50% is 70% or higher. Simulations were carried out with exponential survival and staggered patient entry. We assumed, on average, 2 patients would enter the study per month. Interim analyses began once 20 patients entered the study and occurred after groups of 10 patients thereafter, up to a maximum of 60 patients. The interim analysis estimates of one-year EFS are based on analyses with an underlying Dirichlet process prior. We approximated the posterior distribution, which is actually a mixture of Beta distributions, the mixture depending on the amount of censoring, with a single Beta distribution. The parameters of this posterior Beta distribution are based on the number of failures and the effective sample size at 12 months, combined with the parameters of the prior. The following tables summarize the operating characteristics under various scenarios for the underlying exponential EFS, based on 1000 simulations. The 95% posterior intervals are the quantiles of

the simulated one-year EFS corresponding to probabilities of .025 and .957. The interpretation is that the posterior probability that the estimate of one-year PFS lies in this interval is 95%.

Prior is beta(3,2) : Mean is 0.60

1-yr EFS	Prob Stop for Futility	Avg N	Est 1-yr PFS	Lo 95% Post Int'l	Hi 95% Post Int'l	Prob H0 Rejected
0.45	0.60	40.3	0.42	0.25	0.58	0.03
0.5	0.37	47.7	0.47	0.25	0.62	0.12
0.55	0.17	54.1	0.53	0.35	0.67	0.28
0.60	0.07	57.5	0.59	0.40	0.72	0.57
0.65	0.02	59.1	0.64	0.50	0.77	0.83
0.7.0	0.01	59.8	0.70	0.58	0.82	0.96

Analysis of primary objective:

The proportion of patients positive for the toxicity evaluation as define for this study: patients for which the minimum 2.5 mg everolimus every other day was not tolerable or any unexpected hospitalizations during protocol participation will be reported with an exact binomial calculation and 95% confidence interval. The proportion of patients requiring dose adjustments down as well as the proportion requiring dose adjustments up will be reported separately with confidence intervals. All other grade 1 and 2 toxicities will be reported by type and grade, overall and within intervals throughout the study (0, 60], (60, 90], (90,120], (120, 180], (180, 365] and (365, 1460].

Analysis of secondary objectives:

Standard life table methods will be used to analyze EFS. We will report the one and three-year EFS with 95% confidence intervals. The three-year EFS will be compared to the null EFS of 49% with a Z-score and a one-sided alpha level of 0.05.

7.0 References

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Addendum 1: Inhibitors of CYP3A4 and/or PgP

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

Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus to half the currently used dose. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.

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

Addendum 2: Inducers of CYP3A4 and/or PgP

If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of Afinitor (based on pharmacokinetic data), using increments of 5 mg or less. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the Afinitor dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.

This dose adjustment of everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Addendum 3: Clinically relevant drug interactions: substrates, inducers, and inhibitors of isoenzyme CYP3A

<table>
<tr><td colspan="2">SUBSTRATES</td></tr>
<tr><td>Antibiotics:
Clarithromycin, erythromycin, telithromycin</td><td>Calcium channel blockers:
Amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil</td></tr>
<tr><td>Anti-arrhythmics:
Quinidine</td><td>HMG CoA reductase inhibitors:
Cerivastatin, lovastatin, simvastatin</td></tr>
<tr><td>Benzodiazepines:
Alprazolam, diazepam, midazolam, triazolam</td><td>Steroid 6beta-OH:
estradiol, hydrocortisone, progesterone, testosterone</td></tr>
<tr><td>Immune modulators:
Cyclosporine, tacrolimus (FK506)</td><td rowspan="4">Miscellaneous:
Alfentanil, aprepitant, aripirazole, buspirone, cafergot, caffeine, cilostazol, cocaine, codeine-N-demethylation, dapsone, dexamethasone, dextromethorphan, docetaxel domperidone, eplerenone, fentanyl, finasteride, Gleevec/imatinib, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, risperidone, salmeterol, sildenafil, sirolimus, sorafenib, sunitinib, tamoxifen, taxol, terfenadine, torisel, trazodone, vincristine, zaleplon, ziprasidone, zolpidem</td></tr>
<tr><td>HIV Antivirals:
Indinavir, nelfinavir, ritonavir, saquinavir</td></tr>
<tr><td>Prokinetic:
Cisapride</td></tr>
<tr><td>Antihistamines:
Astemizole, chlorpheniramine, terfenadine</td></tr>
<tr><td colspan="2">INDUCERS</td></tr>
<tr><td colspan="2">Strong inducers:
avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)</td></tr>
</table>

Moderate inducers:
bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir

Weak inducers:
amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine

INHIBITORS

Clinically relevant drug interactions mediated by PgP

PgP Substrates	PgP Inhibitors and PgP/CYP3A Dual Inhibitors	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel, talinolol, everolimus	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, (GF120918), fexofenadine, fluvoxamine, ginko (ginko biloba), indinavir, itraconazole, lopinavir, (LY335979), mibefradil, milk thistle (silybum marianum), nelfinavir,	rifampin, St John's wort

PgP Substrates	PgP Inhibitors and PgP/CYP3A Dual Inhibitors	PgP Inducers
	nifedipine, nitrendipine, (PSC833), paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinesis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan valspodar, verapamil	

Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Addendum 4: Dose Modifications for abnormal serum drug concentrations without grade III/IV toxicities, grade ≥III toxicities (CTCAE version 4.0) except for stomatitis and lipid/hyperglycemia toxicities

- Patient will have regularly scheduled everolimus levels drawn throughout the study
- Everolimus is available in 2.5mg, 5mg and 10mg strengths
- The reference range for patients experiencing a <II common toxicity (CTCAE version 4.0) is 3-15ng/mL
- Anytime a dose is adjusted, repeat everolimus serum trough levels will be re-drawn 14 days (± 3 days) later. As clinically possible, all patients' other labs will be reset to match this new everolimus serum trough level schedule.
- Once everolimus is held due to high serum trough levels, everolimus should be held for 7 days before restarting at a lower dose level.
- During a treatment hold, everolimus levels will not be drawn once the serum trough level is less than 1.0.
- There is no limit on how long a patient can be on everolimus treatment hold. Labs will be monitored every two weeks while the patient is on hold.
- For patients >15ng/mL or <3.0ng/mL and not experiencing >II grade common toxicity, their dose will be adjusted by +/-2.5mg/day; lowest dose allowed is 2.5mg every 4 days. The study nurse will provide a calendar to patients when the dose level is 2.5 mg taken every 3 or 4 days
- If a patient on a schedule of 2.5 mg (QOD) or lower misses a dose, that dose should be made up.
- Non-hematologic grade ≥ III CTCAE toxicities: hold drug until CTCAE toxicity is (I) but can be continued at grade 2 if the baseline values were within the range of grade 2 and restart at a dose level -2.5mg/day. Lowest dose allowed is 2.5mg every 4 days
- Grade 4 or 4 clinical failure – discontinue RAD001
- Recurrence of grade 4 toxicity after dose reduction – discontinue RAD001
- Hematologic grade ≥III CTCAE toxicity
    - Anemia
        - Hgb <8.0g/dL: transfuse RBC; hold drug for 7 days or until Hgb >10mg/dL (untransfused): whichever is longer. Restart at a dose -2.5mg/day. Lowest dose allowed is 2.5mg every 4 days
    - Thrombocytopenia
        - Platelets < 50,000: hold drug until platelet count is >75,000 and restart at a dose level -2.5mg/day. Lowest dose allowed is 2.5mg every 4 days

        - Platelets <10,000: transfuse PLT: when platelet count is >75,000 (transfusion independent: at least 7 days). Restart at a dose level -2.5mg/day; lowest dose allowed is 2.5mg every 4 days
    - Neutropenia:
        - ANC <1,000/mm3 hold drug (and rituximab) until ANC >1,500 and restart at a dose level -2.5mg/day.Lowest dose allowed is 2.5mg every 4 days
        - No adjustments will be made for lymphopenia
- Lowest dose allowed on protocol is 2.5mg every 4 days. If serum concentrations on this dosing schedule are >15ng/mL or if on this dosing schedule greater than grade II toxicities are experienced the patient will be taken off study. However, patients will be followed until toxicities return to grade 1 or baseline as appropriate.

Addendum 5: Management of stomatitis/oral mucositis/mouth ulcers

Management of stomatitis / oral mucositis / mouth ulcers

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

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

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be

instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

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

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

Addendum 6: 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. Hyperlipidemia and hypertriglyceridemia should be treated according to local best clinical practice. Patients should be monitored clinically and through serum chemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Management of hyperlipidemia and hyperglycemia

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

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

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

Addendum 7: Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

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

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

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

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

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

Management of non-infectious pneumonitis

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

Addendum 8: Action to be taken for positive baseline hepatitis B results

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

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

For patients who have already received study drug prior to the approval of Protocol Version date February 18, 2014, HBV-DNA testing will be performed at the patient's next visit, and the result will be regarded as baseline. Any action for positive hepatitis results will then proceed as detailed in the table above.

Addendum 9: Guidelines for management of hepatitis B

<table>
<tr><td colspan="2">HBV reactivation (with or without clinical signs and symptoms)*</td></tr>
<tr><td>For patients with baseline results:
Positive HBV-DNA
OR
positive HBsAg
----
reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]
AND
ALT elevation x 5 ULN</td><td>Treat: Start a second antiviral
AND
Interrupt study drug administration until resolution:
≤ grade 1 ALT (or baseline ALT, if > grade 1) and
≤ baseline HBV-DNA levels
If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug.
If resolution occurs > 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.</td></tr>
<tr><td>For patients with baseline results:
Negative HBV-DNA and HBsAg
AND
Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab
----
reactivation is defined as:
New appearance of measurable HBV-DNA</td><td>Treat : Start first antiviral medication
AND
Interrupt study drug administration until resolution:
≤ baseline HBV-DNA levels
If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug.</td></tr>
</table>

	If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which **both** DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).