NECTAR Trial

NEOADJUVANT PHASE II STUDY OF EVEROLIMUS PLUS CISPLATIN IN TRIPLE NEGATIVE BREAST CANCER PATIENTS WITH RESIDUAL DISEASE AFTER STANDARD CHEMOTHERAPY.

Authors	Jenny Chang, M.D.
	Jaime A. Mejia, M.D.
Document type	Everolimus (RAD0001) Use Protocol
EUDRACT number	N/A
Version number	V1
Development phase	II
Document status	Final
Release date	(28/04/2013)
Referenced Investigator Brochure Edition	10, release date 07-Nov-2011

Table of contents

List of figures

List of tables

List of abbreviations

4E-BP1	4E-binding protein
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BAL	Bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CDS	Core data sheet
CoA	Coenzyme A
CPK	Creatine phosphokinase
CRF	Case Report Form
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
DNA	Deoxyribonucleic acid
DS&E	Drug Safety and Epidimology
EOT	End of treatment
EU	European Union
FDA	Food and drug administration
GERD	Gastroesophageal reflux disease
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HMG	3-hydroxy-3-methyl-glutaryl
IB	Investigator brochure
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
$\log_{10}$	Decadic logarithm (common logarithm)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
PCR	Polymerase chain reaction
PgP	P-glycoprotein
PFT	Pulmonary function tests
PI3K	Phosphoinositide 3-kinase
PNET	Pancreatic neuroendocrine tumor
RCC	Renal cell carcinoma
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SEGA	Subependymal giant cell astrocytoma
TS	Tuberous sclerosis
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WOCBP	Women of child-bearing potential

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	For efficacy evaluations, the baseline assessment will be the last available assessment before or on the date of randomization. For safety evaluations (i.e. laboratory assessments and vital signs), the baseline assessment will be the last available assessment before or on the start date of study treatment. The value obtained at baseline assessments, referred to as "baseline value" will be used as reference for the patient.
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Adjuvant chemotherapy is currently a component of standard treatment for most women with newly diagnosed invasive breast cancer. The development of adjuvant chemotherapy began with the demonstration of a survival benefit in node-positive patients treated with cyclophosphamide, methotrexate, and fluorouracil (CMF)[1]. Since then, survival benefits have been demonstrated in additional patient subsets, and the incorporation of innovative chemotherapy combinations, novel agents, and new administration schedules has further improved the efficacy of adjuvant therapy. Recently, multiple large trials have demonstrated improved efficacy when a taxane (paclitaxel or docetaxel) is added to the adjuvant chemotherapy regimen[2]. In the United States, one of the most commonly used taxane-containing adjuvant regimens consists of 4 cycles of doxorubicin/cyclophosphamide, followed by 4 cycles of paclitaxel[2]. This sequential regimen was one of the first taxane-containing adjuvant programs to be investigated, and was proven superior when compared with doxorubicin/cyclophosphamide (AC) alone (5-year disease-free survival [DFS] 75% vs. 65%, respectively). In the PACS01 trial, the sequential addition of 3 cycles of docetaxel following 3 cycles of FEC100 proved superior to 6 cycles of FEC100 (5-year DFS 78.3% vs. 73.2%, hazard ratio:0.83)[3]. Subsequent studies have compared the efficacy of various taxane schedules. Paclitaxel or docetaxel, given either weekly or every 3 weeks, were compared following 4 cycles of AC[4]. In this trial, weekly paclitaxel was more effective than paclitaxel administered every 3 weeks, and showed equal efficacy but less toxicity when compared with docetaxel. The use of a taxane with standard anthracycline regimen is now regarded as the standard of care.

In spite of the improvements resulting from the addition of the taxanes, a large number of women continue to relapse with breast cancer. Certain patient subsets have been shown to benefit disproportionately from taxane-containing regimens. Specifically, the benefit produced in estrogen receptor (ER)-negative patients is consistently larger than the benefit of ER-positive patients receiving identical regimens[5]. Patients with "triple negative" breast cancer (ER, progesterone receptor [PR], and HER2 negative) benefit from taxane-containing chemotherapy, but remain a poor prognosis group, with higher relapse rates and shorter survival than other subgroups[6]. Novel therapies, especially those targeting resistance pathway in patients who do not respond to standard chemotherapy, may be of benefit to TNBC patients who traditionally have poor prognosis.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Everolimus was developed in oncology as Afinitor® and was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TS. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Approximately 18,730 cancer patients have been treated with everolimus as of 30-Sep-2011:

- 9,528 patients in Novartis-sponsored clinical trials

- 2,559 patients in the individual patient supply program
- 6,638 in investigator-sponsored studies.
- In addition, healthy volunteer subjects and non-oncology hepatically impaired subjects have participated in the clinical pharmacology studies as described in Section 7.2.

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

1.2.1 Overview of Everolimus

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers [7].

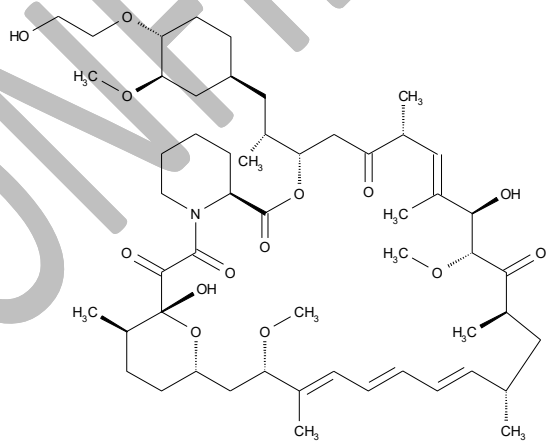
Everolimus is being investigated as an anticancer agent based on its potential to act

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

Table 1-1 Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1 Chemical structure of Everolimus



1.2.1.1 mTOR pathway and cancer

At the cellular and molecular level, Everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development [8].

The main known functions of mTOR include the following [9]:

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels;
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers [10];
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers [11]
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

1.2.1.2 Non-clinical experience

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

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

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relatively resistant" *in vitro*. In general, Everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

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

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

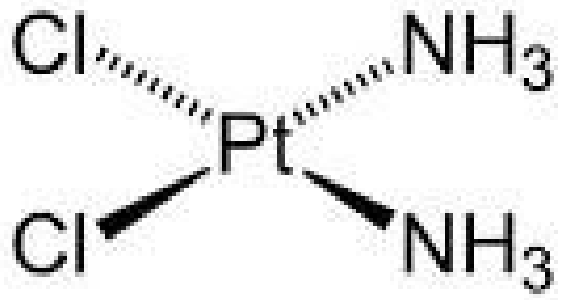
In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

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

1.2.2 Overview of Cisplatin

Cisplatin is similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function. After cisplatin enters the cells, the chloride ligands are replaced by water molecules. This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA. These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts thus preventing DNA, RNA and protein synthesis. This action is cell cycle phase-nonspecific. Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties.[12]

Figure 1-2 Chemical Structure of Cisplatin



Cisplatin was the first chemotherapeutic agent of its subclass to be discovered. It is an inorganic, water soluble complex containing a central platinum atom surrounded by 2 chlorine atoms and ammonia moieties in the cis position in the horizontal plane. Cisplatin forms irreversible covalent links with DNA, causing cross linking of DNA chains as well as breaks in the DNA chain and missense mutations. The DNA injury triggers programmed cell death (apoptosis) and inhibits RNA and protein synthesis, particularly in rapidly dividing cells. Cisplatin has activity against multiple tumor types and was approved for use by the United States in 1978. Current indications include testicular, ovarian, bladder, head and neck, breast, lung and colon cancer.

2 Rationale

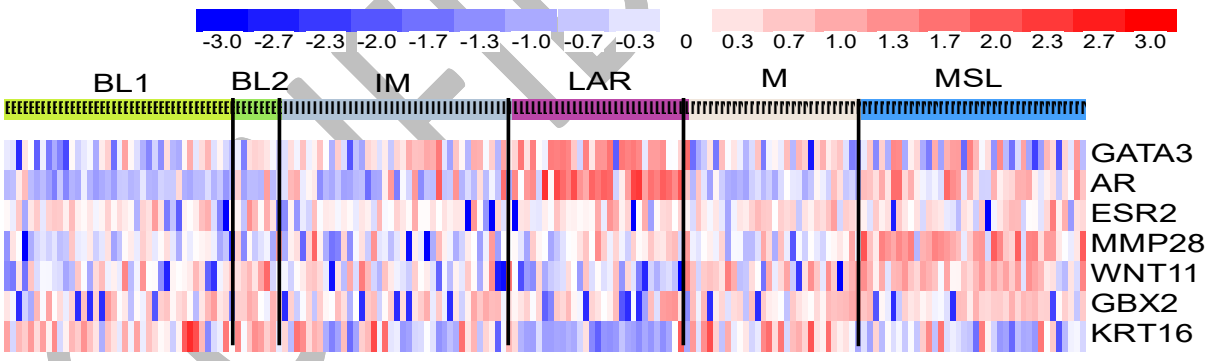
Recent DNA microarray profiling studies on breast tumors have identified distinct subtypes of breast carcinomas that are associated with different clinical outcomes[13]. Breast cancer can now be categorized into 5 groups: luminal A (ER+), luminal B (ER+), HER2 overexpressing, normal breast-like and basal-like[13]. The basal-like breast cancers tend to be clinically aggressive and usually have a poor outcome.

The phenotype of breast cancer can be reliably identified by a panel of 4 immunohistochemical antibodies: ER (negative), HER2 (negative), EGFR (positive), and cytokeratin 5/6 (positive)[13]. Tumors arising in BRCA1 carriers have many similarities to basal-like sporadic breast tumors, including a characteristic phenotype: they tend to be high-grade, ER/PR-negative, HER2-negative, and harbor mutant p53[14]. Basal keratins are expressed by both sporadic basal-like tumors and tumors with BRCA1 mutations, and both groups cluster together by gene expression profile[14]. Other studies support these data, in which familial-*BRCA1* breast cancers have shared features with a subset of sporadic tumors, indicating a common or similar etiology. Hallmarks of this "BRCAness" include basal-like phenotype (associated with the *BRCA1* phenotype but not with the *BRCA2* phenotype), ER-negativity, EGFR expression, *c-MYC* amplification, *TP53* mutations, loss of RAD51-focus formation, extreme genomic instability and sensitivity to DNA-crosslinking agents[15, 16]. The

clinical implications of the definition of a group of tumors with a "BRCAness" hallmark lies in its potential to influence the clinical management of these tumors, allowing for rational trials exploring the role of chemotherapy and biologic agents targeted towards DNA repair defects. In support of this hypothesis, Garber et al.[17] showed in a small phase II study remarkable activity of cisplatin single agent in the neoadjuvant setting treatment of patients with locally advanced triple-negative breast cancers, where the observed pCR was 23%. In another small study, 9/10 patients with stage I-III breast cancer harboring BRCA1 mutations achieved a pathological complete remission after neoadjuvant therapy with cisplatin[18]. Thus, these results support the use of cisplatin in TNBC patients who are refractory to standard taxane and anthracyclines chemotherapy, as in this proposal.

There are just a few studies that focus in the management of those TNBC with residual disease once they complete the systemic therapy and local therapy. TNBC patients with residual disease after neoadjuvant chemotherapy have a very poor prognosis with a recurrence rate up to 65% within the first two years[19].

Our recent data in profiling of ~450 TNBC patients with residual disease after neoadjuvant chemotherapy showed two distinct subpopulations with chemoresistant disease. We established a 7-gene prognostic signature using dChip and gene set enrichment analyses. In the independent validation cohort, the classifier predicted correctly with positive predictive value of 75.0% and negative predictive value (i.e., relapse-free survival [RFS]) of 76.9% at 3 years. Those predicted to relapse had a hazard ratio (HR) of 4.67 (95% CI, 1.27-17.15) for relapse in 3 years. In extended validation cohort, patients predicted not to relapse exhibited 3-year RFS of 78.9%, while in comparison, the 3-year RFS was 48.5% for patients predicted to relapse (log rank P<0.0001), with HR of 2.61 (95% CI, 1.52-4.49). The subgroup of TNBC patients predicted to have relatively favorable prognosis was characterized by high expression of "luminal-like" genes (androgen-receptor [AR] and GATA3); while the subgroup with worse prognosis was characterized by expression of cancer stem cell markers (WNT11 and MMP28). This group of TNBC with stem cell markers cluster with mesenchymal stem like (MSL) and mesenchymal subgroups of TNBC.



M and MSL subtypes are enriched in gene expression for epithelial-mesenchymal transition, and growth factor pathways and cell models responded to a PI3K/mTOR inhibitor (NVP-BEZ235).

Our collaborators at Vanderbilt University have generated a p73 gene expression signatures in H1299 cells (which lack expression of all p53 family members) transfected with TAp73β, an isoform of p73 capable of strong transactivation[20]. A combination of microarray profiling and chromatin immunoprecipitation followed by sequencing (ChIPSeq) was used to develop a p73 expression signature. Because microarray analyses do not allow discrimination between direct or indirect regulation by a transcription factor of interest, they also performed whole genome ChIP to identify sequences to which p73 is bound (ChIPSeq). Over 4,000 p73-bound DNA sequences were isolated, sequenced, and mapped to the mammalian genome. Tags that mapped inside or within 10 kb of genes were considered for further analysis. Several known p73 target genes, such as p2127 and MDM228, were identified by both microarray and ChIPSeq, thus validating their datasets. In addition, known genes ontologies were enriched in their datasets, including genes involved in

apoptosis and cell-cycle arrest. By using multiple genomic technologies, they generated a signature annotated with multiple levels of gene expression and p73 genomic location information. Overlay of their microarray dataset with the whole genome ChIP dataset gave a more refined list of potential candidate targets. Additional information was obtained from fold-change expression levels that were used to create rank-ordered lists of candidate target genes from this analysis, they also generated an initial set (1000 probes) of p73-regulated genes that could be used to query the Connectivity Map. The Connectivity Map is a collection of genome-wide transcriptional expression data from human cells treated with bioactive small molecules and simple pattern-matching algorithms that together enable the discovery of decisive functional connections between drugs, genes, and diseases through the transitory feature of common gene expression changes[21]. Genes whose transcript levels increased or decreased two-fold after ectopic p73 expression were analyzed using the Connectivity Map. Because they were interested in identifying pathways upstream of p73 rather than just drugs *per se*, they focused on the well-annotated "pharmaceutical" subset of perturbagens. Several of the top perturbagens in their list were either direct or indirect inhibitors of mammalian Target of Rapamycin (mTOR). More importantly, profiling by targeted next generation sequencing (NGS) for 182 oncogenes and tumor suppressors (Foundation Medicine, Cambridge, MA) and gene expression profiling (NanoString) of the residual cancer after neoadjuvant chemotherapy was conducted in 102 patients with TNBC. Of the tumors evaluated by NGS, 72/81 (89%) demonstrated mutations in *TP53,* 22 were *MCL1*-amplified (27%), and 17 were *MYC*-amplified (21%). Alterations in the PI3K/mTOR pathway (*AKT1-3*, *PIK3CA*, *PIK3R1*, *RAPTOR*, *PTEN,* and *TSC1*) were identified in 27 (33%) of TNBC tumors with residual disease after neoadjuvant chemotherapy.

In summary, these data strongly support the use of mTOR inhibitors with cisplatin in patients with residual disease following standard neo-adjuvant chemotherapy, in whom the majority will have a very high chance of relapse within two years.

Thus, we propose here to evaluate the benefit of mTOR inhibition with everolimus in combination with cisplatin in triple negative breast cancer patients with residual. We have demonstrated that the driving pathway in resistance in TNBC patients with chemotherapy-resistant disease is the mTOR/PI3K pathway. Thus, the effect of mTOR inhibition will be accentuated in patients with residual disease, rather than in patients treated with upfront neo-adjuvant everolismus, as the proportion of tumors will be enriched for MSL and M subtypes dependent on mTOR/PI3K pathway.

We hypothesize that using everolimus with cisplatin will increase pCR rates in TNBC patients who are refractory to standard chemotherapy.

3 Objectives and endpoints

Primary

- To evaluate the pathological response rate (pCR) after treatment with everolimus plus cisplatin in women with triple-negative breast cancer with documented residual disease after standard neo-adjuvant treatment.

Secondary

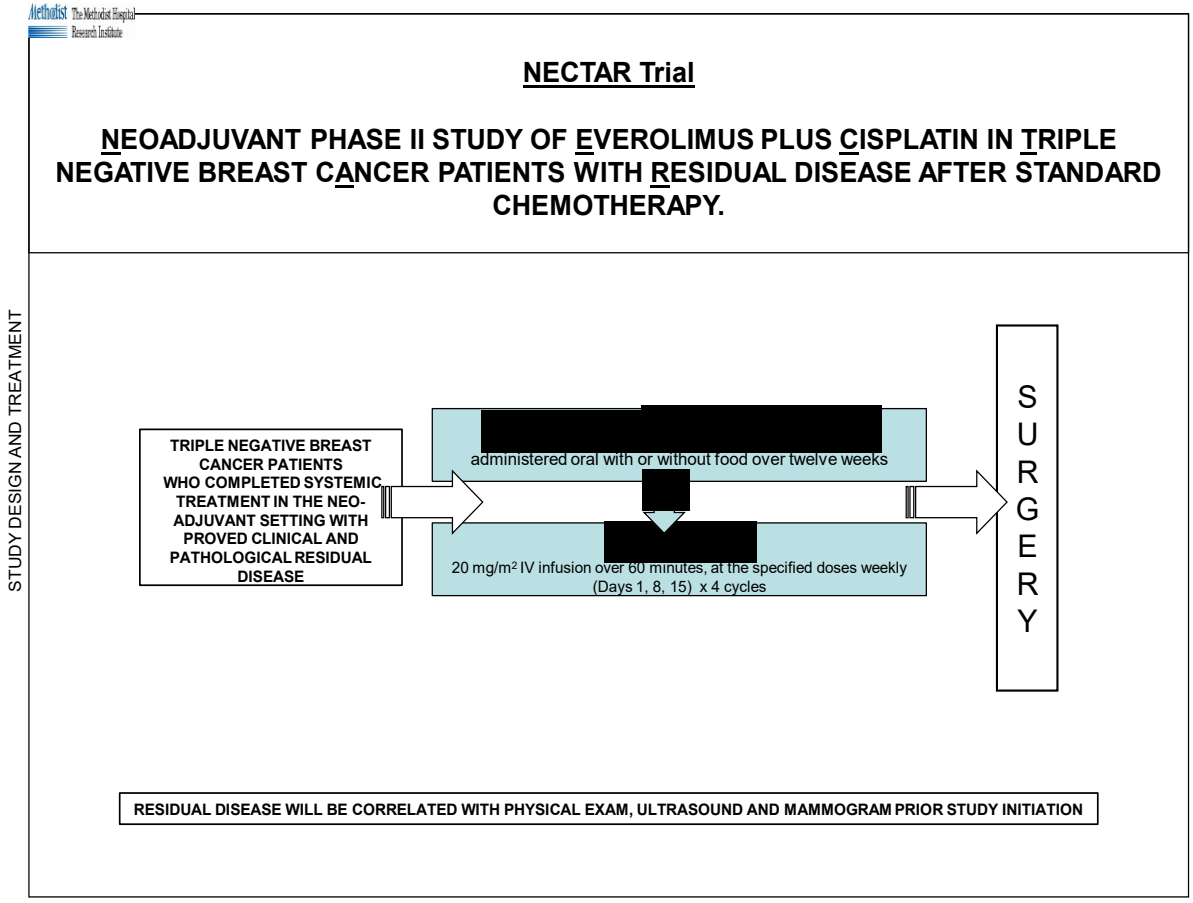
- To assess correlative markers in biopsies.

Exploratory objectives (if necessary)

- To assess effect of everolimus on cancer stem cells, DNA damage markers, and other markers. (We will correlate pCR with studies exploring changes in the p63/p73 and PI3K/Akt/mTOR pathways).

4 Study design

4.1 Description of study design



We propose to perform a phase II clinical trial in triple negative breast cancer (TNBC) patients who have completed systemic neoadjuvant chemotherapy and have documented clinical/pathological residual disease. Biopsies will be obtained from accessible sites at baseline only (Research procedure); biopsied tumor must measure at least 1cm at any direction; if main tumor is not detected, an abnormal (clinically or radiologically) axillary lymph node can be biopsied.

The correlation of specific molecular markers such as Ki67, mitotic index, apoptosis, levels of S6K and phospho S6K, p53, p63, and p73 levels as well as p73 and p63 gene signatures with clinical parameters such as tumor response and pathological complete response will help define a biomarker signature associated with p63/p73 and/or PI3K/Akt dependence in triple negative breast cancers as well as identification of new therapeutic options for this group of patients. We plan to store all the tissue collected during the study for future analysis including genomic studies.

As with all drugs, there is always the possibility that there may be unknown or impossible to predict risks/side effects. The use of everolimus plus cisplatin as part of the treatment may or may not increase the severity of side effects, and all risks associated with this research will be explained in the protocol and consent form. Nevertheless, this study may help provide better insight into new therapeutic options for breast cancer. The patients involved in this study will have a diagnosis of locally advanced triple negative breast cancer and are at high risk for developing metastatic recurrence of their disease. The doses proposed for this phase II study is the one that is already approved for renal cell carcinoma (RCC) which is 10 mg once daily administer oral with or without food over six months.

There are no other treatment options for triple negative breast cancer (TNBC) patients who have residual disease after systemic treatment in the neo-adjuvant setting. Historically, these patients have chemotherapy resistant disease, and the anticipated pCR rate is 0%, and we hypothesize that the addition of everolimus plus cisplatin will increase the pCR to least 5%.

5 Population

Female patients ≥18 years of age

Study Duration:

The duration of patient participation in the study treatment will be a total of 3 to 4 months, which is counted from the start of treatment. Study Follow-up for all patients will include medical history update (30 days after the last dose of the study drug)

Safety Criteria:

All participants will be assessed by a physician for pre-existing medical conditions and baseline physical abnormalities prior to the initiation of investigational therapy. Patients presenting with any medical history, physical exam, or laboratory abnormality that, in the in the opinion of the treating physician, would put the subject's safety at risk will be excluded. Baseline signs and symptoms are to be recorded and followed throughout the trial. These will be monitored throughout the study and recorded if they increase in severity or frequency during treatment or within the follow up period. Participants will be assessed for adverse events by a physician or designated midlevel provider prior to each chemotherapy infusion while the patient is on study. Vital signs including blood pressure, heart rate and temperature should be performed at each physical exam. Assessments may be performed more frequently if clinically indicated. In addition, hematology and serum chemistry profiles will be drawn prior to the initiation of treatment and prior to every infusion to determine whether the study drug combination affects hematologic values, electrolytes or liver function tests. Laboratory assessments will be performed more frequently if clinically indicated. This clinical and laboratory data will be used to determine whether these women in the study with everolimus plus cisplatin therapy have any symptoms or side effects associated with the study medications. Subjects will be followed for adverse events for a period of 30 days after the completion of investigational therapy (Six (6) months). Patients with abnormal laboratory or clinical findings that are believed to be treatment related will be followed every four weeks until the condition resolves or stabilizes, or until the laboratory values are no longer considered clinically significant. CTC Version 4.0 will be used to grade toxicities. Laboratory tests may be done more frequently if medically indicated. If CTC Grade 4 hematologic toxicity is seen; CBC + differential + platelets should be repeated every 3 - 4 days until recovery.

At suspected recurrence: CT scans of the chest, abdomen, pelvis, and additional directed evaluation as appropriate. Recurrence should be documented by biopsy and/or evidence of metastatic disease on radiologic studies. Abnormal blood studies alone (e.g., elevated liver function tests, CA 15-3, CEA, etc.) are not sufficient evidence of relapse.

5.1 Inclusion and Exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet 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 aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria:

1. Female patients ≥18 years of age.
2. Clinical/pathological documentation of residual disease after neo-adjuvant therapy.
3. Patients with synchronous bilateral cancers are eligible **only if**:
    - Index cancer is triple-negative, defined as ER-, PR-, and HER2-.
4. HER2 negative tumors. HER2 negativity must be confirmed by one of the following:
    - FISH-negative (FISH ratio <2.2), ***or***
    - IHC 0-1+, ***or***
    - IHC 2-3+ **AND** FISH-negative (FISH ratio <2.2).
5. Estrogen receptor negative and progesterone receptor negative (<10% staining by IHC for estrogen receptor and progesterone receptor).
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Adequate hematologic function, defined by:
    - Absolute neutrophil count [2] >1000/mm3
    - Platelet count ≥100,000/mm3
    - Hemoglobin >9 g/dL
8. Adequate liver function, defined by:
    - AST and ALT ≤2.5 x the upper limit of normal (ULN)
    - Total bilirubin ≤1.5 x ULN (unless the patient has grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin).
9. Adequate renal function, defined by:
    - Serum creatinine ≤1.5 x ULN
10. Complete staging work-up ≤24 weeks prior to initiation of study treatment with computed tomography (CT) scans of the chest and abdomen/pelvis (abdomen/pelvis preferred; abdomen accepted), a CT scan of the head or MRI of the brain (if symptomatic), and either a positron emission tomography (PET) scan or a bone scan.
11. Adequate cardiac function, defined by a left ventricular ejection fraction (LVEF) value of >50% (or normal per institutional guidelines) by MUGA scan or echocardiogram (ECHO).
12. Patients with previous history of invasive cancers (including breast cancer) are eligible if definitive treatment was completed more than 5 years prior to initiating current study treatment, and there is no evidence of recurrent disease.
13. Women of childbearing potential must have a negative serum or urine pregnancy test performed within 7 days prior to start of treatment. If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must agree to inform her treating physician immediately.
14. Patient must be accessible for treatment and follow-up.
15. Women of childbearing potential must agree to use an acceptable method of birth control to avoid pregnancy for the duration of study treatment, and for 3 months thereafter..
16. Able to swallow and retain oral medication.
17. Patient must be willing to undergo breast biopsies as required by the study protocol.
18. All patients must be able to understand the investigational nature of the study and give written informed consent prior to study entry.

Exclusion criteria:

1. Women who are pregnant or breastfeeding.
2. History of previously treated ductal carcinoma *in situ* (DCIS) is acceptable.
3. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel.

4. Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus);
5. Previous cancer (with the exception of non-melanoma skin cancer or cervical carcinoma in situ) in the past 5 years.
6. Patients who have any severe and/or uncontrolled medical conditions such as:
    a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to start of Everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
    b. Symptomatic congestive heart failure of New York heart Association Class III or IV
    c. active (acute or chronic) or uncontrolled severe infection, liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HbsAg, quantifiable HCV-RNA),
    d. known severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air),
    e. active, bleeding diathesis;
7. Patients may not receive any other investigational or anti-cancer treatments while participating in this study.
8. Concurrent severe, uncontrolled infection or intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.
9. Mental condition that would prevent patient comprehension of the nature of, and risk associated with, the study.
10. Inability to comply with study and/or follow-up procedures.
11. 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;
12. Known history of HIV seropositivity;
13. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment. Highly effective contraception methods include combination of any two of the following (a+b or a+c or b+c):
    a. Use of oral, injected or implanted hormonal methods of contraception or;
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
    d. Total abstinence or;
    e. Male/female sterilization.

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

Screening for patients with hepatitis B

Prior to start Everolimus, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

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

The management guidelines, in Section 6.2.2.7, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for patients with hepatitis C

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

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

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

The management guidelines, in Section 6.2.2.7, are provided according to the results of the baseline assessment of hepatitis C viral load.

6 Treatment

6.1 Study treatment

Everolimus will be administered at 10 mg p.o daily.

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

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

Everolimus is supplied by Novartis. Everolimus is formulated as tablets for oral administration of 1mg, 2.5mg, 5mg, 10mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

Phase I data suggest a Recommended Phase 2 Dose (RP2D) of **Cisplatin at 20 mg/m2** with Everolimus at 10 mg/day in combination.

The proposed regimen will be: Everolimus 10 mg/day, Plus Cisplatin 20 mg/m2 (days 1, 8, and 15) on a 28-day cycle , for 4 cycles.

6.1.1 Dosing regimen

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

Everolimus should be administered orally once daily at the same time every day, either consistently with or consistently without food

Tablets

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed.

If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

6.2.1.1 Hepatic impairment dose modifications

Hormone receptor-positive advanced breast cancer, advanced neuroendocrine tumors of gastrointestinal, lung, or pancreatic origin, advanced renal cell carcinoma, and TSC with renal angiomyolipoma:

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.
- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 2.5 mg daily.
- Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.
- Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Afinitor is not recommended for patients with hepatic impairment who require doses below 2 mg every other day or 2.5 every other day.

6.2.1.2 Dosing modifications

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

Table 6-1 Study treatment schedule adjustments and dose levels

Dose level	Dose and schedule
0 (starting dose)	10 mg p.o daily
-1	7.5 mg p.o daily
-2	5.0 mg p.o daily

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients who need an additional dose reduction will be required to discontinue Everolimus/placebo or comparator drug.

Table 6-2 and Table 6-3 list the dosing guidelines for Everolimus-related non-hematologic and hematologic toxicities.

Table 6-2 Dosing guidelines for Everolimus-related non-hematologic toxicities

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

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

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

6.2.2 Management of specific toxicities

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

Adverse events most frequently observed with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2). Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in Table 3-2, Table 3-3 and Table 3-4, 3-5, and 3-6

6.2.2.1 Management of infections

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

6.2.2.2 Management of skin toxicity

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

6.2.2.3 Management of stomatitis / oral mucositis / mouth ulcers

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.
Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

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

6.2.2.4 Management of diarrhea

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

6.2.2.5 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.
Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of Everolimus and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on Everolimus.

6.2.2.6 Management of non-infectious pneumonitis

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

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.
- Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Everolimus therapy without dose alteration.

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Moreover, potential lung radiological changes can be detected by the chest CT/MRI scans that are performed on all patients every 4 weeks for tumor assessment according to the schedule of events (Table 7-1). In addition, pulmonary function tests (PFTs) will be conducted, if clinically indicated, to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in Table 6-4 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 6-4 Management of non-infectious pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus until symptoms improve to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 3	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. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue Everolimus.

6.2.2.7 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy [22]. 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 [22]. A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Monitoring and prophylactic treatment for hepatitis B reactivation

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

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

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

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

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

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA **OR** positive HBsAg ---------- **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	**Treat**: Start a second antiviral medication AND Interrupt Everolimus administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days**, Everolimus should be re-started at one dose lower, if available. (see Table 6-1 for dose levels available) If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of Everolimus. **If resolution occurs > 28 days** Patients should discontinue Everolimus but continue both antiviral therapies at least 4 weeks after last dose of Everolimus.
For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** **[**Positive HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb**]** ---------- **Reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat :** Start first antiviral medication AND **Interrupt** Everolimus administration until resolution: • ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days**, Everolimus should be re-started at one dose lower, if available (see Table 6-1 for dose levels available). If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of Everolimus. **If resolution occurs > 28 days** Patients should discontinue Everolimus but continue antiviral therapy at least 4 weeks after last dose of Everolimus.

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Monitoring for hepatitis C flare

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

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 6-7.

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

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA **AND** ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).		

6.3 Cisplatin General Information

Table 6.7.1 **PHARMACOKINETICS:**[12]

Interpatient variability	systemic clearance resulting in variable blood platinum concentrations or AUCs	
Oral Absorption	not absorbed	
Distribution	rapidly diffuses into tissues highest concentrations found in the liver, prostate and kidney; rapidly distributed into pleural effusions and ascitic fluid	
	cross blood brain barrier?	not readily
	volume of distribution	ultrafilterable platinum*: 41 L/m²
	plasma protein binding	>90%
Metabolism	undergoes non-enzymatic conversion to several inactive metabolites which are highly bound to plasma proteins	
	active metabolite	yes
	inactive metabolite	yes
Excretion	primarily in the urine urinary excretion of ultrafilterable platinum* was substantially greater after a 6-hour infusion than after a 15-minute injection	
	urine	> 90%8; 25% excreted during the first 24 h
	feces	insignificant
	terminal half life of ultrafilterable platinum*	20-45 min
	terminal half life of total platinum*	5 days or longer
	clearance	6.3 mL/min/kg
Gender	no clinically important differences found	
Elderly	no clinically important differences found	
Children	terminal half life of ultrafilterable platinum* < 1 h terminal half life of total platinum* 24-72 h	
Ethnicity	no clinically important differences found	

SPECIAL PRECAUTIONS:

Administer with caution to individuals with pre-existing renal impairment, myelosuppression or hearing impairment. [12]

Breastfeeding is not recommended as cisplatin is excreted in human milk.

Carcinogenicity: found to have a carcinogenic effect in laboratory animals.

Contraindicated: in patients who have a history of a hypersensitivity reaction to cisplatin or other platinum-containing compounds.

Fertility: Cisplatin therapy is associated with at least temporary infertility in the majority of patients. Among males receiving cisplatin for testicular cancer, almost all became azospermic within the first two cycles of therapy, but recovery of normal sperm morphology, motility, and sperm count occurred in 40% within 1.5-2 years.

Hydration is required to minimize nephrotoxicity. The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose. Hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis is used to effectively decrease cisplatin-induced nephrotoxicity.8 Lower doses of cisplatin are given with less intensive hydration. For example, patients receiving doses of 35 mg/m2 have been pre-treated with 500 mL NS over 1 hour, with no post-hydration. Patients receiving doses of 25 mg/m2 have been pre-treated with vigorous oral hydration (e.g., 600-900 mL) the morning of treatment and 8 glasses (e.g., 2000 mL/day) daily for a few days following treatment. **Please refer to the "Nephrotoxicity" paragraph, found below the Side Effects table for a suggested hydration guideline.**

Inadvertent substitution of cisplatin for carboplatin can result in a potentially fatal overdosage. Precautions should be taken to avoid overdosing such as writing the cisplatin dose as a daily dose, not as a total cisplatin dose used in one course of therapy. The manufacturer recommends that an alerting mechanism be instituted to verify any order for cisplatin >100 mg/m2 per course every 3-4 weeks. [12]

Mutagenicity: shown to be a mild to moderate mutagen in the Ames test.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. [12]

Table 6.7.2

ORGAN SITE	SIDE EFFECT	ONSET
Clinically important side effects are in ***bold, italics*** I = immediate [onset in hours to days]; E = early[days to weeks]; D = delayed [weeks to months] L = late [months to years]		
allergy/immunology	hypersensitivity (rare)	I
auditory/hearing	***ototoxicity (31%)***	E
audiogram abnormalities (24%)		E
tinnitus (9%)		E
vestibular toxicity (rare)		E
blood/bone marrow/ febrile neutropenia	***myelosuppression (25-30%) WBC nadir 18-23 days (range 7.5-45), platelet nadir 18-23 days (range 7.5-45), recovery 39 days (range 13-62)***	I
anemia (25-30)%		I
cardiovascular (arrhythmia)	arrhythmias1	E
cardiovascular (general)	bradycardia (rare)	E
vascular toxicities may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy or cerebral arteritis		E
constitutional symptoms	hiccoughs	I
dermatology/skin	*extravasation hazard: irritant*	
	alopecia (uncommon)	E
rash (uncommon)		E
local soft tissue toxicity (rare)		E
endocrine glucose intolerance		
gastrointestinal	*emetogenic potential: high*	
	nausea and vomiting (> 90%)	I
delayed nausea and vomiting		I
diarrhea		E
loss of taste		E
pancreatitis		E
stomatitis		E
hepatic	transient elevation of hepatic enzymes and bilirubin	I
metabolic/laboratory	elevated serum amylase	I
electrolyte disturbances2		I
hyperuricemia		E
musculoskeletal	muscle cramps	E
neurology	autonomic neuropathy	E
dorsal column myelopathy		E
Lhermitte's sign		E
neurotoxicity, usually peripheral neuropathies		E
seizures (rare)		E
ocular/visual	visual impairment (rare)	E
altered colour perception		E
blurred vision		E
cerebral blindness (infrequent)		E
optic neuritis		E
papilledema		E
renal/genitourinary	***nephrotoxicity (28-36%)***	E
secondary malignancy	acute leukemia (rare)	L
syndromes	inappropriate antidiuretic hormone syndrome	E

Anemia observed with cisplatin use may be caused by a decrease in erythropoietin or erythroid stem cells. Cisplatin has been shown to sensitize red blood cells, sometimes resulting in a direct Coombs' positive hemolytic anemia.

Electrolyte disturbances can be serious and mainly includes hypomagnesemia, hypocalcemia and hypokalemia. Hypophosphatemia and hyponatremia have occurred in some patients receiving cisplatin combination regimens. These effects are due to renal tubular damage. Cisplatin greatly increases the urinary excretion of magnesium and calcium; increased excretion of potassium, zinc, copper and amino acids also occurs. Hypomagnesemia and or hypocalcemia may become symptomatic, with muscle irritability or cramps, clonus, tremor, carpopedal spasm and/or tetany. Children may be at greater risk for developing hypomagnesemia. [12]

Emetogenic effects are common with cisplatin therapy and may be serotonin-mediated. **Acute** nausea and vomiting may occur within 1-6 (usually 2-3) hours after administration of cisplatin. This early period is the most severe and usually lasts 8 hours, but can last up to 24 hours. Various levels of nausea, vomiting and anorexia may persist for up to 5-10 days. **Delayed** nausea and vomiting can occur 24 hours or longer following chemotherapy when complete emetic control had been attained on the day of cisplatin therapy. The incidence and severity of cisplatin-induced nausea and vomiting appear to be increased in: females, the young, high doses, rapid infusion and combinations with other emetogenic drugs. Incidence and severity may be decreased in patients with a history of chronic alcohol use. **Acute** nausea and vomiting can be prevented by pre-treatment with a 5-HT3 antagonist (e.g., granisetron, ondansetron) plus a corticosteroid; this can be continued for the first 24 hours following chemotherapy. **Delayed** nausea and vomiting should not routinely be treated with 5-HT3 antagonists; although there is anecdotal evidence that some patients can benefit from 5-HT3 antagonists, generally these agents are ineffective more than 24 hours after chemotherapy. Corticosteroids are the cornerstone of the treatment for delayed nausea, although other combinations are widely used.

Nephrotoxicity is a major concern when prescribing cisplatin. Renal dysfunction due to cisplatin may manifest as renal insufficiency, hypokalemia and hypomagnesemia. The risk for these adverse effects is related to the dose and interval of cisplatin and may be minimized by adequate hydration. Geriatric patients may also be at increased risk.

The manufacturer recommends pre-treatment hydration with 1 or 2 L of fluid infused 8-12 hours prior to a cisplatin dose. Others suggest hydration with NS, hypertonic saline infusion, and mannitol, or furosemide-induced diuresis to effectively decrease cisplatin-induced nephrotoxicity.

Numerous hydration regimens exist. Hydration regimens should take into account the following conditions for the patient ; adequate renal function, clinically euvolemic prior to administration of cisplatin, no contraindication to saline loading (e.g., uncompensated cardiac conditions, anasarca), and ability to comply with recommended oral hydration protocol, or expectation that volume status can be maintained (e.g., with fluids via enteral feeding tube or IV). Below is one suggested hydration regimen for adults. [12]

Table 6.7.3

Cisplatin (mg/m2)	Hydration	Electrolyte Additives*	Comments
> 80	4000 mL* NS over 4 h	KCl 20 mEq MgSO4 1 g Mannitol 30 g	inpatient or medical daycare unit admission to monitor urine output
60-80	2000 mL* NS over 2 h	KCl 20 mEq MgSO4 1 g Mannitol 30 g	
40-60	1000 mL* NS over 1 h	KCl 10 mEq MgSO4 0.5 g	includes regimens with cisplatin administered over multiple days
<40	500 mL* NS over 30 min	none	includes regimens with cisplatin administered over multiple days

*Volume may include hydration associated with the administration of other drugs (e.g., other chemotherapy agents, supportive IV medications). The volumes and durations are minimum administration standards to accommodate the wide variation in clinical practice in delivery of cisplatin. They should be individualized based on the clinical situation, which may affect the hydration regimen and addition of electrolytes.

Nervous system effects are usually peripheral neuropathies and sensory in nature (e.g., parethesias of the upper and lower extremities). They can also include motor difficulties (especially gait); reduced or absent deep-tendon reflexes and leg weakness may also occur. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow. Geriatric patients may be at greater risk for these cisplatin-induced neuropathies. Muscle cramps have been reported, and usually occurred in patients with symptomatic peripheral neuropathy who received relatively high cumulative doses of cisplatin. Lhermitte's sign (a sensation during neck flexion resembling electric shock) often is present with cisplatin-induced neuropathy. The occurrence of Lhermitte's sign may coincide with the onset of peripheral neuropathies, and can last for 2-8 months. When signs of neuropathy occur, cisplatin should be discontinued. [12]

Otic effects include tinnitus, with or without clinical hearing loss, and occasional deafness. Ototoxicity is cumulative and irreversible and results from damage to the inner ear. These effects may be more severe in children than in adults. The manufacturer recommends that audiograms be performed prior to initiating therapy and prior to each subsequent dose of drug. Initially, there is loss of high frequency acuity (4000 to 8000 Hz). When acuity is affected in the range of speech, cisplatin should be discontinued under most circumstances and carboplatin substituted where appropriate. Ototoxicity appears to be dose related. Higher cumulative doses, higher individual doses and administration by IV bolus resulted in more severe ototoxicity, corresponding with higher plasma levels of ultrafilterable platinum. Ototoxicity may be enhanced in patients with prior or simultaneous cranial irradiation. Vestibular ototoxicity may increase with increasing cumulative dosage and may be more likely to occur in patients with pre-existing vestibular dysfunction. [12]

Sensitivity reactions can include anaphylactoid reactions consisting of facial edema, flushing, wheezing or respiratory difficulties, tachycardia, and hypotension. These reactions can occur within a few minutes after IV administration of cisplatin; diaphoresis, nasal stuffiness, rhinorrhea, conjunctivitis, generalized erythema, apprehension, and sensation of chest constriction may also occur. Cisplatin-induced anaphylactoid reactions usually have occurred after multiple cycles of cisplatin (e.g., at least 5 doses), but also can occur after the first dose. There is a case report of a patient who experienced an anaphylaxis to cisplatin following nine previous uncomplicated cycles. Some reactions may also be due to the mannitol that is given with cisplatin to prevent nephrotoxicity. Occasionally, patients who experienced anaphylactoid reactions have been safely retreated with cisplatin following pre-treatment with corticosteroids and/or antihistamines; however, such prophylaxis is not uniformly effective in preventing recurrence. [12]

Table 6.7.4 **INTERACTIONS:**

AGENT	EFFECT	MECHANISM	MANAGEMENT
etoposide	synergistic antineoplastic activity against testicular, small cell lung and, non-small cell lung cancers	possible impaired elimination of etoposide in patients previously treated with cisplatin	some protocols are designed to take advantage of this effect; monitor toxicity closely
nephrotoxic drugs such as aminoglycoside antibiotics and amphotericin	increased risk of nephrotoxicity	cumulative nephrotoxoixity	use with extreme caution during or shortly after cisplatin
ototoxic drugs such as aminoglycoside antibiotics or loop diuretics (e.g., ethacrynic acid, furosemide)	increased risk of ototoxicity	cumulative ototoxicity	carefully monitor for signs of ototoxicity

phenytoin	decreased phenytoin serum levels	decreased absorption and/or increased metabolism of phenytoin	monitor serum levels of phenytoin
pyridoxine	decrease in cisplatin activity	further investigation required	avoid concomitant use of pyridoxine with cisplatin
renally excreted drugs	increase the serum levels of renally excreted drugs	reduced renal function caused by cisplatin	monitor toxicity

SUPPLY AND STORAGE: [12]

Injection: Cisplatin is available as sterile, unpreserved; single-dose vials (10 mg/10 mL, 50 mg/50 mL and 100 mg/100 mL) at a concentration of 1 mg/mL.17 Unopened vials are stored at room temperature. Do not refrigerate or freeze cisplatin solutions as a precipitate will form. Protect from light.

Do not use IV needles, syringes or sets that have aluminum components in the preparation or administration of cisplatin. An interaction between aluminum and platinum will occur resulting in the formation of a black precipitate, accompanied with a loss of potency.

Diluted solution for infusion: Dilute the prepared cisplatin injection in 2 L of D51/2S or 0.3%NS, containing 37.5 g of mannitol. The solution is not preserved and should be used within 24 hours. Any unused portion should be discarded. In children, the administration volume of cisplatin should be maintained at >125 mL/m²/hr, and contain mannitol 15 g/m2 and MgSo4 20 mEq/L.23 Urine output should be maintained at > 90 mL/m²/hr during administration.

Compatibility: The following are compatible with cisplatin via Y-site injection: allopurinol, aztreonam, bleomycin, chlorpromazine, cimetidine, cladribine, cyclophosphamide, dexamethasone, diphenhydramine, doxorubicin, doxorubicin liposome, droperidol, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, gatifloxacin, gemcitabine, granisetron, heparin, hydromorphone, leucovorin, linezolid, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, promethazine, propofol, ranitidine, sargramostim, teniposide, topotecan, vinblastine, vincristine, vinorelbine.

The following are compatible with cisplatin in the same syringe in certain concentrations: bleomycin, cyclophosphamide, doxapram, doxorubicin, droperidol, fluorouracil, furosemide, heparin, leucovorin, methotrexate, metoclopramide, mitomycin, vinblastine, and vincristine.

The following are compatible with cisplatin in the same infusion bag in certain concentrations and diluents: carboplatin, cyclophosphamide with etoposide, etoposide, etoposide with floxuridine, etoposide with mannitol and KCL, floxuridine, floxuridine with leucovorin, hydroxyzine, ifosfamide, and ifosfamide with etoposide, leucovorin, magnesium, mannitol, ondansetron and paclitaxel.

The following solutions are compatible with cisplatin at the stated concentrations: cisplatin 50 mg, 500 mg, 300 mg in D51/2NS 1L; cisplatin 50 mg, 300 mg, 500 mg in D5NS 1L; cisplatin 50 mg, 100 mg, 200 mg in D51/2NS with mannitol 1.875%; cisplatin 300 mg in D5W 1L; cisplatin 50 mg, 100 mg, 167 mg, 200 mg, 300 mg, 500 mg, 600 mg, 900 mg in NS 1L; cisplatin 50 mg, 100 mg, 200 mg in 1/2NS.

Incompatibility 28***:*** The following are incompatible with cisplatin via Y-site injection: amifostine, amphotericin, cefepime, piperacillin-tazobactam and thiotepa.

The following are incompatible with cisplatin in the same infusion solution at the stated concentrations: cisplatin 200 mg with etoposide 400 mg, mannitol 1.875%, KCl 20 mEq in NS 1L; cisplatin 200 mg with fluorouracil 1 g in NS 1L; cisplatin 500 mg with fluorouracil 10 g in 1L NS; cisplatin 67 mg with mesna 3.33 g in NS 1L; cisplatin 67 mg with mesna 110 mg in NS 1L; cisplatin 200 mg with paclitaxel 1.2 g in NS 1L; cisplatin 200 mg with thiotepa 1 g in NS 1L.

The following solutions are incompatible with cisplatin at the stated concentrations: cisplatin 100 mg/L in D5W 5%; cisplatin 75 mg/L in D5W; cisplatin 50 mg/L in Sodium bicarbonate 5%; cisplatin 500 mg/L in Sodium bicarbonate 5%.

6.4 Concomitant medications

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

6.4.1 Permitted concomitant therapy

Standard Cisplatin premedications only

Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

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

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus . Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.
- Grapefruit or citrus juices affect P450 and PgP activity. Concomitant use should be avoided.
- Co-administration with strong inducers of CYP3A4 should be avoided. If a patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of Everolimus up to twice the currently used daily dose should be considered, 5mg increments. Enzyme induction usually occurs within 7-10 days; therefore Everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of Everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

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

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

Inducers
carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate, avasimibe, bosentan, etravirine, nafcillin, ritonavir, talviraline (not available in US market), tipranavir, amprenavir, aprepitant, armodafinil (R-modafinil), dexamethasone, nevirapine, prednisone, pleconaril (not available in US market), rufinamide
Inhibitors
Strong inhibitors: clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, tipranavir, elvitegravir, Posaconazole [24] **Moderate inhibitors:** aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice (citrus parasidi fruit juice), imatinib, tofisopam, verapamil, amprenavir, fosamprenavir, dronedarone

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

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

Vaccinations

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

6.4.2 Prohibited concomitant therapy

Anti-neoplastic therapies

Prior neo-adjuvant treatment for triple negative breast cancer disease is allowed. A clinical an pathological residual desiase must be documented.

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted until disease progression is documented per RECIST.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 Visit evaluation schedule

Assessment	Screening/Baseline Visit	Study Treatment (4 cycles) Day 1	Day 8	Day 15	End-of- Treatment Visit [a]	End of Study [q] / Follow-up [s]
Eligibility Assessments						
Obtain Informed Consent	X					
Confirm Inclusion/Exclusion Criteria Met [b]	X					
Obtain Medical History	X					
Safety Assessments						
Physical Exam	X	X			X	X
ECOG performance scale [a b]	X	X			X	X
Record Weight and Height	X	X			X	X
Document Vital Signs [c]	X	X			X	X
Perform Pregnancy Test in WOCBP [d]	X					
Perform mammogram [e *]	X				X	
Perform ultrasound of breast and nodal region [e *]	X				X	
Perform Laboratory Tests [f g]	X	X	X	X	X	
Biopsies [n]	X				*	
Perform Electrocardiogram [i]	X					
LVEF assessment [j]	X					
Efficacy Assessments						
Evaluate Tumor Response RECIST Criteria [k]	X				X	
Clinical Drug Supplies						
Everolimus administration [l]		X				
Patient Pill Diary [m]		X				
Cisplatin Infusion [n o, p]		X	X	X		
Concomitant medications	X	X			X	
Assess Signs and Symptoms and Adverse Events [c]	X	X			X	X
Clinical Evaluation [r]	X					X
Survival Status [s]						X

a. Evaluate subjects who discontinue the protocol for reasons other than disease progression (AEs) every 4 weeks until progression or until they receive additional anti-cancer therapy.
b. ECOG Performance Status of 0-1 is required for study entry. ECOG performance status will be recorded at baseline, prior to each cycle, at the end of treatment and at the end of the study assessment.
c. Document signs and symptoms and adverse events at least every 4 weeks until all study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible.
d. Pregnancy tests (serum or urine) should be performed within 72 hours of study start, or whenever pregnancy is suspected.
e. Unilateral and/or bilateral mammogram and ultrasound should have been performed any time within 4 weeks prior to beginning of the study treatment. *MRI (magnetic resonance imaging) should be performed only if requested by the physician.
f. Comprehensive Metabolic Panel must include sodium, potassium, magnesium, chloride, calcium, glucose, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, and albumin. Complete blood count must include Hemoglobin, Hematocrit, RBC, WBC, Platelets with differential Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils. CrCL "CrCl = [(140 - age) x IBW] / (Scr x 72) (x 0.85 for females)" before every cycle for patients with an abnormal creatinine.
g. Perform laboratory tests within 72 hours of beginning each cycle. Perform baseline laboratory tests within four (4) weeks before administration of study drug.
h. Biopsies will be obtained from accessible sites at baseline only (Research procedure); biopsied tumor must measure at least 1cm at any direction; if main tumor is not detected, an abnormal (clinically or radiologically) axillary lymph node can be biopsied. Exploratory analyses may include, but are not limited to p63/p73 and PI3K/Akt/mTOR pathways.
* Surgical specimen will be used to correlate mTOR related biomarkers.
i. A 12-lead EKG at baseline; QRS measurement is required. Electrocardiogram (EKG) with QRS measurement will be repeated whenever clinically indicated.
i. LVEF may be assessed by MUGA scan or ECHO. Follow-up LVEF assessments are required **ONLY** for symptomatic patients.
k. Evaluate tumor response using RECIST criteria before chemotherapy and every 6 weeks from the beginning of the treatment till disease progression.
l. Everolimus will be given at 10mg p.o. daily. Everolimus will be self-administered daily with water with or without meal. The site must perform all appropriate drug accountability.
m. Pill Diary dispensed with study drug and retrieved the day after the treatment is completed. The Research Coordinator will revise it at every visit.
n. Cisplatin infusion 20 mg/m^2 IV infusion over 60 minutes, at the specified doses weekly (Days 1, 8, 15) x 4 cycles.
o. Subjects will be pre-medicated approximately 1 hour before Cisplatin therapy. Standard anti-emetics for moderately emetogenic regimen, together with standard premedication will be prescribed with chemotherapy. Recommended prophylaxis for fluid retention/hypersensitivity reactions will be provided per institution standards.
p. Monitor the subject for hypersensitivity reactions during and after all infusions.
q. End of study visit will occur due to disease progression, as determined by the investigator until intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor. Vital signs including blood pressure, heart rate and temperature will be performed during this visit. Toxicity assessment will be continuous throughout the study. CTC Version 4.0 will be used to grade toxicities.
r. Clinical evaluation will include a record of the date and site(s) of recurrence, subsequent breast cancer treatment administered, and late treatment-related toxicity.
s. The duration of patient participation in the study will be a total of three (3) to four (4) months from the start of treatment. Every patient has to have a two (2) weeks washout period before starting the trial. Follow-up for all patients will include: ·Medical history update (30 days after the last dose of the study drug)

* All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral (i.e. Lamivudine) for 1-2 weeks prior to receiving study drug (see Section 3.2). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR.

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

7.2 Assessment types

ECOG Performance Status of 0-1 is required for study entry. ECOG performance status will be recorded at baseline, prior to each cycle, at the end of treatment and at the end of the study assessment.

Document signs and symptoms and adverse events at least every 4 weeks until all study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible.

Pregnancy tests (serum or urine) should be performed within 72 hours of study start, or whenever pregnancy is suspected.

Unilateral and/or bilateral mammogram and ultrasound should have been performed any time within 4 weeks prior to beginning of the study treatment. *MRI (magnetic resonance imaging) should be performed only if requested by the physician.

Biopsies will be obtained from accessible sites at baseline only (Research procedure); biopsied tumor must measure at least 1cm at any direction; if main tumor is not detected, an abnormal (clinically or radiologically) axillary lymph node can be biopsied. Exploratory analyses may include, but are not limited to p63/p73 and PI3K/Akt/mTOR pathways.

* Surgical specimen will be used to correlate mTOR related biomarkers.

A 12-lead EKG at baseline; QRS measurement is required. Electrocardiogram (EKG) with QRS measurement will be repeated whenever clinically indicated.

LVEF may be assessed by MUGA scan or ECHO. Follow-up LVEF assessments are required **ONLY** for symptomatic patients.

Evaluate tumor response using RECIST criteria before chemotherapy and every 6 weeks from the beginig of the treatment till disease progression.

Everolimus will be given at 10mg p.o. daily. Everolimus will be self-administered daily with water with or without meal. The site must perform all appropriate drug accountability.

Pill Diary dispensed with study drug and retrieved the day after the treatment is completed. The Research Coordinator will revise it at every visit.

Cisplatin infusion 20 mg/m^2 IV infusion over 60 minutes, at the specified doses weekly (Days 1, 8, 15) x 4 cycles.

Subjects will be pre-medicated approximately 1 hour before Cisplatin therapy. Standard anti-emetics for moderately emetogenic regimen, together with standard premedication will be prescribed with chemotherapy. Recommended prophylaxis for fluid retention/hypersensitivity reactions will be provided per institution standards.

Monitor the subject for hypersensitivity reactions during and after all infusions.

End of study visit will occur due to disease progression, as determined by the investigator until intolerable AEs, death, voluntary withdrawal from the study by the patient, or discontinuation of the study by the sponsor. Vital signs including blood pressure, heart rate and temperature will be performed during this visit.

Toxicity assessment will be continuous throughout the study. CTC Version 4.0 will be used to grade toxicities.

Clinical evaluation will include a record of the date and site(s) of recurrence, subsequent breast cancer treatment administered, and late treatment-related toxicity.

The duration of patient participation in the study will be a total of three (3) to four (4) months from the start of treatment. Every patient has to have a two (2) weeks washout period before starting the trial. Follow-up for all patients will include: ·Medical history update (30 days after the last dose of the study drug) Evaluate subjects who discontinue the protocol for reasons other than disease progression (AEs) every 4 weeks until progression or until they receive additional anti-cancer therapy.

7.2.1 Pregnancy and assessments of fertility

Pregnancy testing is required at screening or whenever pregnancy is suspected. Serum pregnancy testing should be performed at screening and at the end of the study. Urine pregnancy testing will be performed at each visit (every 4 weeks).

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.

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.

7.2.2 Laboratory evaluations

Comprehensive Metabolic Panel must include sodium, potassium, magnesium, chloride, calcium, glucose, BUN, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, and albumin. Complete blood count must include Hemoglobin, Hematocrit, RBC, WBC, Platelets with differential Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils. CrCL "CrCl = [(140 - age) x IBW] / (Scr x 72) (x 0.85 for females)" before every cycle for patients with an abnormal creatinine.

Perform laboratory tests within 72 hours of beginning each cycle. Perform baseline laboratory tests within four (4) weeks before administration of study drug.

7.2.2.1 HBV testing for patients with hepatitis B

Prior to start the treatment, the categories of patients listed in Section 4.1 should be tested for hepatitis B serologic markers and viral load (local results are acceptable for screening only):

- HBV-DNA, HBsAg, HBc Ab, and HBs Ab.
- During the treatment period, HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 6-5.

7.2.2.2 HCV testing for patients with hepatitis C

Patients with hepatitis C risk factors and at the discretion of the investigator should be tested for HCV RNA prior to treatment (local results are acceptable for screening only). For a list of hepatitis C risk factors, refer to Section

7.2.3 Drug levels and pharmacokinetic assessments N/A

8 Safety monitoring and reporting

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

8.1 Adverse events

8.1.1 Definitions and reporting

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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 (CTCAE Grade 1-4)
2. Its duration (Start and end dates or if continuing at the Safety Follow-up Visit)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

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.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

8.1.3 Adverse events of special interest *(optional)*

In clinical trials, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression.

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal ones) and proteinuria. Renal function will be monitored throughout the study. In clinical trials Everolimus has been associated with certain adverse events.

Clinically Notable AE grouping	**Risk Definition in RMP**	**Comment**
Amenorrhea	Amenorrhea	Included under potential risk in RMP
Cytopenia	N/A	Included under clinically notable AEs
Hemorrhages	Hemorrhages	Included as important identified risk in the RMP
Hyperglycemia/ new onset of diabetes mellitus	N/A	Included under clinically notable AEs
Hypersensitivity reactions (anaphylactic reaction)	N/A	Included under clinically notable AEs
Infections and infestations	N/A	Included under clinically notable AEs
Intestinal obstruction/ileus	Intestinal obstruction/ileus	Included under potential risk
N/A	Cardiac Failure	Not reported in the MAP. (important identified risk- RMP specific
N/A	Increased creatinine	Please note that this RMP specific identified risk is based on lab data and is defined as newly occurring or worsening increase to CTC grade 3 or 4
Non infectious pneumonitis	Non infectious pneumonitis	Name changed from pulmonary events to non infectious pneumonitis in the MAP. Included under important identified risk in RMP
Rash and similar events	N/A	Not included in the RMP
Renal events	Renal failure/proteinuria	The names in RMP and MAP are different but the search terms are the same. It is included important identified risk in RMP
Stomatitis/oral mucositis/ulcers	N/A	Included under clinically notable AEs
Thromboembolism	Thromboembolism	Included as important identified risk in the RMP

8.2 Serious Adverse Events

8.2.1 Definitions

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

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

8.2.2 Reporting

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).

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

- after the patient has provided informed consent and until atleast 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence **(fax: 877-778-9739)**. 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 SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

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

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, 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 Everolimus Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E 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.
For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the comapartor drug company by the investigator.

8.3 Emergency unblinding of treatment assignment

N/A

8.4 Pregnancy

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 everolimus 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.

9 Statistical methods

9.1 Sample Size.

Demographics and pre-treatment characteristics will be summarized for all patients using descriptive statistics. TNBC patients will be eligible if they are at high risk of recurrence (residual disease after neo-adjuvant treatment).

An overall sample size of 32 subjects achieves 81% power, using a one-sided binomial test (alpha=0.05), will give us a 5% increase in the pCR rate.
The study lasts for 30 days after the last dose of the study drug.
The primary endpoint of this trial is pCR.
Patients who do not exhibit recurrence or death will be censored at their last tumor assessment.
The safety profiles of the study will be assessed through summaries of adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, and treatment-related death. All patients who receive at least 1 dose of treatment will be included in the analysis for safety. The safety analysis will report the frequency of all AEs and laboratory abnormalities, as well as the frequency of dose interruptions, dose reductions, and treatment discontinuation for toxicity. Toxicity rates will be presented using the worst NCI CTCAE grade per patient.

10 Protocol amendments, or changes in study conduct

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

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

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

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

11 References:

1. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. New England J Med, 294:405-10, 1976.

2. Henderson C, Berry DA, Demetri GD, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J of Clinical Oncology. 21:976-83, 2003.

3. Roche H, Fumoleau P, Spielman M, et al. Five years analysis of the PAC01 trial: 6 cycles of FEC 100 vs. 3 cycles of FEC 100 followed by 3 cycles of docetaxel for the adjuvant treatment of node positive breast cancer. J Clinical Oncology, 24:564-71, 2006.

4. Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. New England J Med, 358:1663-71, 2008.

5. Berry DA, Cirrincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. JAMA, 295:1658-67, 2006.

6. Rakha EA, Reis-Filho JS, Ellis IO. Basal-like breast cancer: A critical review. J Clinical Oncology, 26:2568-81, 2008.

7. Boulay A, Lane HA (2007) The mammalian target of rapamycin kinase and tumor growth inhibition. Recent Results Cancer Res. 2007;172:99-124.

8. Cohen HT, McGovern FJ (2005) Renal Cell Carcinoma. N Engl J Med; 353(23):2477-90.

9. Bjornsti MA, Houghton PJ (2004) The TOR Pathway: A target for Cancer therapy. Nat Rev Cancer; 4(5):335-48.

10. Frattini M, Signoroni S, Pilotti S (2005) Phosphatase protein homologue to tensin expression and phosphatidylinositol-3 phosphate kinase mutations in colorectal cancer. Cancer Res; 65(23):11227.

11. 11 Goel A, Arnold CN, Niedzwiecki D, et al (2004) Frequent inactivation of PTEN by promoter hypermethylation in microsatellite instability-high sporadic colorectal cancers. Cancer Res; 64(9):3014-21.

12. Cisplatin Package Insert

13. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A, 100:8418-23, 2003.

14. Matros E, Wang ZC, Lodeiro G, Miron A, Iglehart JD, Richardson AL. BRCA1 promoter methylation in sporadic breast tumors: relationship to gene expression profiles. Breast Cancer Research and Treatment, 91:179-86, 2005.

15. Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer, 4:814-9, 2004.

16. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A, 98:10869-74, 2001.

17. Garber JE, Richardson AL, Harris LN, et al. Neo-adjuvant cisplatin (CDDP) in "triple-negative" breast cancer (BC). 29th Annual San Antonio Breast Cancer Symposium 2006; abstract 3074.

18. Byrski T, Gronwald J, Huzarski T, et al. Response to neo-adjuvant chemotherapy in women with BRCA1-positive breast cancers. Breast Cancer Research and Treatment, 108:289- 96, 2008.

19. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. Journal of Clinical Oncology, 26:1275-81, 2008.

20. De Laurenzi V, Costanzo A, Barcaroli D, et al. Two new p73 splice variants, gamma and delta, with different transcriptional activity. J Exp Med, 188:1763-8, 1998.

21. Lamb J, Crawford ED, Peck D, et al. The Connectivity Map: Using gene-expression signatures to connect small molecules, genes, and disease. Science, 313:1929-35, 2006.

22. Yeo W, Lam KC, Zee B, et al. (2004) Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. Annals of Oncology 15: 1661-1666

23. Loomba R, Rowley A, Wesley R, et al (2008). Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 148(7): 519-28.

24. Krishna G, Moton A, Lei Ma L, Savant I, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: A phase I, randomized, open-label, crossover study in healthy volunteers. Clinical Therapeutics, 2009; 31: 286-98

12 Appendices

Appendix A: ECOG/ Karnofsky Performance Status Criteria

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

Appendix B: New York Heart Association (NYHA) Classifications

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

This table is an excerpt from the Oxford Textbook of Medicine, 2nd ed. Oxford; New York: Oxford University Press, 1987, p. 2228.

Appendix C: Version 4.0 (dated June-14-2010)

13 CTCAE Files

NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files and related documents are published here. The most current release files appear in this directory:

Files: Booklet	Content
CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf	Most recent release of core terminology: PDF document, traditional small booklet format.

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix D: WOCBP & Determination of Menopausal Status

WOCBP

Women of childbearing potential and men must agree to use adequate contraception (one of the following listed below) prior to study entry, for the duration of study participation and up to 90 days following completion of therapy. Additionally, male subjects (including those who are vasectomized) whose partners are pregnant or might be pregnant must agree to use condoms for the duration of the study and for 90 days following completion of therapy.

- Total abstinence from sexual intercourse (minimum one complete menstrual cycle).
- Vasectomized male subjects or vasectomized partner of female subjects.
- Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration.
- Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream).
- Intrauterine device (IUD).

The following criteria will be used in the NECTAR trial to define postmenopausal:

- Age 56 or older with no spontaneous menses for at least 12 months prior to study entry;

Or

- Age 55 or younger with no spontaneous menses for at least 12 months prior to study entry (e.g., spontaneous or secondary to hysterectomy) and with a documented estradiol level in the postmenopausal range according to local institutional/laboratory standard;

Or

- Documented bilateral oophorectomy.

Women failing to meet one of these criteria will be classified as pre-menopausal.

Appendix D: Trial Logistics

No. of Centers:

Key Milestones:

FPFV / First Dose: With documented Residual Disease after Ne0-Adj standard treatment

LPLV / Last Subject completed: Sep/2014

Database Lock: Nov/2014

Final Report: Jan/2015

Sponsoring Department: TMHCC _____TMHRI _____TMHS_____

Prepared by: _____ Date _____