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DIVISION OF MEDICINE

**Randomized Double-Blind Phase II Trial of Everolimus versus Placebo as  
Adjuvant Therapy in Patients with Locally Advanced Squamous Cell Cancer of  
the Head and Neck (SCCHN)**

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**List of abbreviations**

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

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HUVECS	human umbilical endothelial cells
IC50	Inhibitory concentration at 50%
IEC	Independent Ethics Committee
IGF1-R	Insulin-like Growth Factor 1 Receptor
IHC	immunohistochemistry
INN	International Non-proprietary Name
INR	International Normal Ratio
IRB	Institutional Review Board
LC-MS	liquid chromatography method with mass spectrometry
LDL	Low-density lipoproteins
<b>LFTs</b>	<b>liver function tests</b>
LLOQ	Lower limit of quantification
MAPK	Mitogen Activated Protein Kinase
mRNA	messenger Ribonucleic acid
mTOR	mammalian Target of Rapamycin
NIH/NCI	National Institutes of Health/National Cancer Institute
nM	nano-molar
NSCLC	Non-small cell lung cancer
OS	overall survival
P-AKT	phospho-AKT
<b>PCR</b>	<b>Polymerase Chain Reaction</b>
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PK/PD model	Pharmacokinetic/pharmacodynamic model
PT/PTT	prothrombin time
PTEN	Phosphatase and Tensin homolog deleted on chromosome 10
RBC	red blood cell count
REB	Research Ethics Board
<b>RNA</b>	<b>Ribonucleic acid</b>
RR	response rate
S6K1	S6 kinase 1
SAE	serious adverse event
SCLC	Small cell lung cancer
STAT3	Signal Transducer and Activator of Transcription 3

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TK	Tyrosine kinase
TSC2	Tuberous Sclerosis Complex 2
TUNNEL	Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin Nick End Labeling
ULN	upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	total white blood cell count
WHO	World Health Organization

## 1 Introduction

### 1.1 Everolimus (RAD001)

Everolimus is a novel oral derivative of rapamycin. Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. Everolimus has been in development for patients with various malignancies since 2002. Everolimus 5mg and 10mg tablets were recently approved under the trade name Afinitor® for patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide.

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

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

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

#### 1.1.1 mTOR pathway and mechanism of action

At cellular and molecular level Everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), a key and a highly conservative serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of Everolimus [Reviewed in <sup>1</sup>].

mTOR is downstream of PI3K/AKT pathway, a pathway known to be dysregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness, resistance to treatment and progression.

The main known functions of mTOR include the following <sup>1,2</sup>:

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

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

mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive)<sup>3</sup>.

mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2)<sup>2</sup>. Activated AKT phosphorylates TSC2, which lead to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1<sup>4,5</sup>.

mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signaling<sup>4</sup>. It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT, that is not upstream of mTORC1. PHLPP phosphatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton<sup>3</sup>.

mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as Everolimus. Once these agents bind to the 12 kDa cytosolic FK506-binding protein immunophilin FKBP12, the resulting rapamycin-FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity<sup>6</sup>. As many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis<sup>2</sup>. Studies using leukemic cells have also demonstrated that temsirolimus and everolimus block the mTORC2 complex which could be cell type or dose dependent<sup>7</sup>.

### 1.1.2 Preclinical studies

Pre-clinical investigations have demonstrated that Everolimus is a potent inhibitor of the proliferation of a range of human tumor cell lines *in-vitro* with IC50s ranging from sub/low nM to  $\mu$ M concentrations, concentrations capable of being reached in patients at the doses used in clinical trials.

Everolimus was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported<sup>8</sup>, as well as in acute myeloid leukemia cells<sup>7</sup>, adult T-cell leukemia cells<sup>9</sup>, diffuse large B cell lymphoma cells [DLBCL;<sup>10</sup>], pancreatic tumor cells<sup>11</sup>, ovarian cancer cells<sup>12, 13</sup> and hepatocellular carcinoma cells<sup>14</sup>.

As a single agent, Everolimus inhibited proliferation in three mantle cell lymphoma cell lines (Jeko1, SP49 and NCEB1) approximately 40–65% compared to control cells. This was associated with G1 cell-cycle arrest and reduced phosphorylation of the mTOR downstream target, 4E-BP1<sup>15</sup>.

In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma), Everolimus inhibited colony formation in a concentration-dependent manner. In addition, normal hematopoietic stem cells were insensitive to Everolimus, with an IC50 about 15 fold higher than the tumor lines.

Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF-induced proliferation. The inhibition of endothelial proliferation and antiangiogenic activity of Everolimus was confirmed *in vivo*, as Everolimus selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls at well tolerated doses. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus -treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

Everolimus also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of Everolimus monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease.

Everolimus administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- s.c. mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170 overexpressing multi-drug resistant tumor line
- in a series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3 lines), lung (22

lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines)

- in two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma)

Taken together, these data indicate the broad antiproliferative potential of Everolimus.

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. PTEN status alone may not be predictive of Everolimus relative *in vitro* sensitivity, however in some cases (i.e., GBM) there is also a correlation with PTEN status.

In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

### Pre-clinical safety

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

Everolimus is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with Everolimus in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative 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. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

More pre-clinical information is provided in the [Investigator's Brochure](#).

### 1.1.3 Clinical experience

#### 1.1.3.1 Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median  $t_{max}$  of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The  $AUC_{0-\tau}$  is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen.  $C_{max}$  is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in  $C_{max}$  is less than dose-proportional. The coefficient of variation between patients is approximately 50%.

Trough levels (24 hour post-dose) correlate well with  $AUC_{0-\tau}$  at steady-state during daily administration.

In whole blood, at a daily dose of 10 mg, about 20% of Everolimus is confined in plasma with 26% being unbound. The remaining 80% is sequestered in blood cells.

Everolimus is extensively metabolized in the liver and eliminated in the bile. Major metabolites are inactive. Elimination half-life is approximately 30 hours. The clearance of Everolimus is approximately halved in patients with mild-moderate hepatic impairment (Child-Pugh Class A or B), while renal impairment has little or no impact on the pharmacokinetics of Everolimus.

Age, weight and gender in the adult population do not affect the pharmacokinetics of Everolimus to a clinically relevant extent. The clearance of Everolimus is reduced in children.

Pharmacokinetic characteristics are not notably different between Caucasian and Japanese subjects, whereas in Black patients' population pharmacokinetic studies have shown an average 20% higher clearance.

A high-fat meal altered the absorption of Everolimus with 1.3 hour delay in  $t_{max}$ , a 60% reduction in  $C_{max}$  and a 16% reduction in AUC.

Everolimus is a substrate of CYP3A4 and a substrate and a moderate inhibitor of the multi-drug efflux pump P-glycoprotein (P-gP, MDR1, ABCB1). Hence, its metabolism is sensitive to drugs which modify these enzymes (substrates, inducers, or inhibitors of these enzymes). Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 or P-glycoprotein substrates

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

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

More information on Everolimus pharmacokinetics is provided in the [Investigator's Brochure](#).

### 1.1.3.2 Everolimus Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC] suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition {[[Study C2101](#)] / [[Study 2102](#)],<sup>16</sup>}. Furthermore, molecular pharmacodynamic (MPD) studies, using immunocytochemistry (IHC) in biopsied tumor tissue, assessed the degree of inhibition and its duration for pS6, p4E-BP1 and pAKT expression with the daily and weekly dosing. There was high inhibition of the downstream markers S6K1 and 4E-BP1 at 5mg/day, which was complete at 10 mg/day, while preliminary results suggest increase in pAKT expression with maximal effect at 10 mg daily {[[Study C2107](#)],<sup>17</sup>}.

More information is provided in the [Investigator's Brochure](#).

### 1.1.3.3 Clinical experience with Everolimus

Everolimus has been investigated as a component of multi-drug immunosuppression in solid organ transplantation since 1996 and was approved for the indication of prophylaxis of organ rejection in adult patients receiving an allogeneic renal or cardiac transplant on 8 Jul 2003 by the European Union under the trade name of Certican®. The most frequent adverse drug

reactions in this context are highly specific to the transplant context. However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels.

Everolimus has been in development for patients with cancer since 2002. Approximately 2586 patients with various malignancies have been treated in either Novartis sponsored or non-Novartis sponsored clinical studies as of 31 Aug 2007. Overall, Novartis sponsored a total of 22 studies of Everolimus administered either as single-agent (n=848), or in combination with other anti-tumor agents (n=663). Ongoing or completed Investigator sponsored studies also enrolled over 1000 patients globally.

Eight single-agent Novartis sponsored trials have or are being conducted in various advanced malignancies. Five Phase I studies evaluated several escalating doses with either weekly or daily administration ([Studies C2101/02, C2106, C2107, C1101](#)) of Everolimus with the objective to identify an optimal regimen and dosage, based on safety, pharmacokinetics and knowledge of the drug's molecular effects on various tumors. The 10 mg/day and 50-70 mg/week dosages were proposed for further studies, when using Everolimus as a single agent, and as a target maximum dose in combination studies. In addition the Phase I studies, conducted in prostate cancer ([Study C2106](#)) and in Japanese patients with advanced cancers ([Study C1101](#)), evaluated the safety and the molecular changes in tumor, associated with the administration of Everolimus.

Two Phase II monotherapy studies were designed to evaluate the safety and efficacy of a single dose of 10 mg administered daily including [Study C2235](#) in advanced NSCLC (n=81) and [Study C2239](#) in advanced pancreatic neuroendocrine tumors (n=160).

Everolimus has shown activity in patients whose metastatic renal cell cancer has progressed despite treatment with VEGF-R inhibitors in a phase 2 study <sup>18</sup>. A Phase III, randomized, double blind, placebo controlled study in patients with mRCC who progressed on a VEGFR TKI demonstrated that everolimus, administered daily at an oral dose of 10 mg provides positive clinical benefit <sup>19</sup>. Median progression free survival (PFS) was prolonged from 1.87 months for patients receiving placebo to 4.01 months for everolimus treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.30, 95% CI 0.22-0.40, p<0.0001).

Overall, the most frequent mild-moderate Grade 1/2 adverse effects have been rash, stomatitis, fatigue, neutropenia and to a lesser extent gastrointestinal disorders (nausea, anorexia, diarrhea, vomiting), and headache. The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia. Reduced blood counts, hyperlipidemia (mainly hypercholesterolemia) and hyperglycemia are relatively frequent laboratory findings. Infections have not been notably frequent or severe. Non-infectious low-Grade (Grade 1/2) pneumonitis has led to development of treatment guidelines for the disorder (Table 3-2). Preliminary indications of anti-tumor activity are encouraging.

For more information on known undesirable effects of Everolimus refer to Section 3.2.5.

Further detailed information regarding Everolimus clinical development, safety and efficacy is provided in the [Investigator's Brochure](#).

### 1.1.4 Study Rationale

#### 1.1.4.1 Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Approximately 40,000 new cases of head and neck cancer are diagnosed annually in the United States. Of these patients, two-thirds present with locoregionally advanced disease (American Joint Committee on Cancer [AJCC] stage III or IV) and one-third with early stage disease (AJCC stage I or II). At presentation, 10% of patients may be found to have involvement of distant organs, most commonly the lung. In addition, 20% of patients will develop clinically detected distant metastases over the course of their disease. In autopsy series up to 50% of patients with head and neck cancer are found to have metastases. It is likely that with improvements in the rate of locoregional control, the risk of distant failure will become predominant, and that systemic therapy, if efficacious, will have a major impact on outcome. Approximately 95% of all head and neck malignancies are squamous cell carcinomas and this histological type is the focus of this review and study protocol. Also, it should be noted that even though head and neck malignancies are usually examined in one group, they represent a heterogeneous group of diseases, with variability in biologic behavior and natural history, prognosis, and considerations in management. Disease sites such as the hypopharynx and the base of tongue have a worse prognosis compared to the larynx or nasopharynx, and may require more aggressive treatment strategies. The vast majority of head and neck malignancies can be attributed to the use of tobacco and alcohol. These carcinogens are synergistic, and may damage the entire aerodigestive epithelium. Due to their frequent history of exposure to tobacco and alcohol patients with head and neck cancer are at high risk for the development of second primary tumors, synchronous or metachronous, that may involve the head and neck region as well as other organs, predominantly the lung.

For patients with resectable locally advanced head and neck cancer (AJCC stage III or IV), surgery and postoperative radiation have been traditionally considered the mainstay of treatment, whereas radiation therapy alone has been offered to patients with unresectable tumors. It is important to recognize that the distinction between resectable and unresectable disease lacks clear definition. With the exception of a few widely accepted signs of unresectability, such as involvement of the carotid artery, in most cases the assessment is subjective and relates to the experience of the surgeon and the availability of reconstructive strategies. Despite aggressive locoregional treatment with surgical resection and postoperative radiotherapy, locoregionally advanced disease has a poor prognosis with 5-year survival of less than 30%. The most common site of failure remains locoregional, whereas distant failure occurs in 20-30% of patients.

Localized treatment modalities have been considered as standard care. For patients with Stage I or II disease either surgery or radiation, are used as single treatment modalities with curative intent. Cure is achieved in the majority of cases (60-80%, depending on the exact stage and anatomic location) and, in this group of patients, the development of a second malignancy is a greater long-term risk than a recurrence of their primary disease.

For patients with locoregionally advanced disease (Stage III or IV) surgery and radiation have been used in sequence (unless the patient is medically inoperable or has unresectable disease). Despite this aggressive bimodality treatment approach, cure is achieved in only a minority of patients. Most patients die of locoregional persistence or recurrence of disease; some specific patient subgroups (e.g., laryngeal, nasopharyngeal disease) may have a better prognosis. In patients with stage III and IV disease, the addition of chemotherapy to the overall treatment plan has been studied intensively over the last 3 decades. Research strategies, generally, have included the use of induction (neoadjuvant) or adjuvant chemotherapy, as well as concomitant chemoradiotherapy. The primary goal of such research is to improve local control and survival.

After completion of curative intent local therapy there are no standard approaches to reduce the risk of SCCHN recurrence. Secondary prevention efforts have been attempted in the past but have either proven ineffective, too toxic, or both<sup>20</sup>. Surveillance for local or distant failure is standard practice but the frequency of examinations and radiographic assessments is not well defined in an asymptomatic patient. Therefore, routine management of patients at risk of recurrence of SCCHN currently does not include any active therapeutic intervention.

#### **1.1.4.2 Adjuvant Therapy with an mTOR Inhibitor**

The Akt/mTOR pathway is activated in the great majority of SCCHN. Expression of eIF4E is functionally active in SCCHN through activation of the Akt/mTOR signaling pathway<sup>21, 22</sup>. Moreover, activation of eIF4E in histologically tumor-free surgical margins appears to be an independent predictor of recurrence<sup>21, 22</sup>. Patients with advanced stage SCCHN have a high rate of recurrence after curative intent therapy. In a preclinical model of minimal residual SCCHN, mTOR inhibitors have been shown to inhibit tumor formation and increase survival<sup>23</sup>. An exploratory biomarker trial with temsirolimus in newly diagnosed advanced stage SCCHN patients showed inhibition of the Akt/mTOR pathway in tumors and PBMCs (surrogate markers) and proapoptotic activity of temsirolimus in patients with head and neck tumors.

There are data regarding long term toxicities of mTOR inhibitors. Analysis of special populations such as renal transplant patients and patients with tuberous sclerosis suggests that sirolimus and its analogues are well tolerated<sup>24</sup>. Studies in renal-transplant patients have always administered sirolimus in combination with cyclosporine and/or corticosteroids making interpretation of these data regarding single agent sirolimus difficult. Nonetheless, the studies suggest that adding sirolimus to allograft rejection prophylaxis regimens is safe and does not increase immunosuppression or rate of second malignancies<sup>25</sup>. Moreover, no increased incidence of immunosuppression has been observed in multiple trials of single-agent rapamycin or rapamycin analogues in cancer patients<sup>26, 27</sup>. However, the most relevant experience to this study is a trial in patients with tuberous sclerosis or sporadic lymphangioleiomyomatosis who received single-agent sirolimus for one year and had serum drug levels equal to or exceeding those in transplant patients<sup>24</sup>. The most common adverse events attributable to sirolimus included aphthous ulcers and diarrhea. Twenty-five subjects entered the study and 20 were able to complete 1 year of therapy. Of the 5 subjects that

withdrew prior to completing planned therapy, only 1 did so secondary to adverse effects of sirolimus.

Therefore, the Akt/mTOR pathway is active in SCCHN, mTOR inhibitors display biologic activity in preclinical and clinical SCCHN models, and currently available oral mTOR inhibitors appear to be well tolerated even for prolonged periods of time. Taken together and given the ability to identify patients who have no evidence of disease after therapy but a high risk of recurrence, we propose studying everolimus as adjuvant therapy in this setting.

## 2 Study objectives

### Primary

Two-year progression-free survival (PFS) probability in subjects treated with everolimus versus placebo after definitive local therapy

### Secondary

- Toxicity of everolimus versus placebo as adjuvant therapy
- Site of disease progression (locoregional vs. distant) in subjects treated with everolimus versus placebo
- Incidence of second primary tumors in subjects treated with everolimus versus placebo
- Prevalence of Akt/mTOR pathway activation in locally advanced SCCHN
- Determine correlation between progression free survival (PFS) and the degree of activation of the Akt/mTOR pathway biomarkers in tumors and adjacent mucosa treated with everolimus versus placebo
- Determine if PTEN status is predictive marker of Everolimus sensitivity

## 3 Investigational plan

### 3.1 Overall study design

This is a randomized, double-blind, phase 2 study of everolimus versus placebo. Randomization will be stratified for disease stage and type of local therapy (IVa surgical vs. IVa non-surgical vs. IVb) as well as treating institution. Eight to 16 weeks after completion of definitive, curative-intent therapy for locally advanced SCCHN, potentially eligible subjects will be consented and randomized to receive either everolimus or placebo for a maximum of 1 year. Subjects will be evaluated prior to starting therapy; 4, 16, 32 and 52 weeks after starting therapy; and then at least every 4 months for a minimum of 2 years (those enrolled early will be followed for 3 years).

Radiographic assessments (CT, PET-CT, PET and/or MRI) will be conducted prior to initiating therapy and every 4-6 months for 2 years then every 6 months in year 3. Not all patients will be followed for 3 years at end of study. Minimum radiographic follow-up will be 2 years for all patients. For those subjects enrolled early, longer follow-up will determine secondary endpoints such as PFS and OS.

### 3.2 Study population

#### 3.2.1 Patient population

160 subjects (80 per arm, everolimus vs. placebo)

### 3.2.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion 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

- Squamous cell carcinoma of the head and neck that is pathologically confirmed
- Patients must have no evidence of disease (NED) within 16 weeks after receiving curative intent therapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN).
  - NED is defined as ANY of the following:
    - Biopsy demonstrating no cancer cells
    - Radiographic studies (CT, MRI, or PET) demonstrating complete response or absence of cancer as judged by the investigator
    - Clinical assessment including direct visualization by nasopharyngolaryngoscopy demonstrating complete response
  - Initial TNM stage IVa or IVb (AJCC 6<sup>th</sup> edition)
  - Tumor tissue available for correlative analyses (see Section 3.4.7). Patient can be registered, randomized, and start therapy prior to specimen shipment.
  - Primary tumor site is oral cavity, oropharynx, hypopharynx, or larynx (including supraglottis and subglottis)
  - For oropharynx cancer patients only:
    - Human papilloma virus negative by in-situ hybridization, polymerase chain reaction, or negative p16 immunohistochemistry
    - Human papilloma virus positive with a history of tobacco use. Minimal tobacco exposure must be 10 pack years (pack years = average number of packs smoked per day multiplied by number of years smoked)
  - Age  $\geq$  18 years
  - Karnofsky performance status  $> 70\%$
  - Adequate bone marrow function as shown by: ANC  $\geq 1.5 \times 10^9/L$ , Platelets  $\geq 100 \times 10^9/L$ , Hb  $> 9 \text{ g/dL}$
  - Adequate liver function as shown by:
    - serum bilirubin  $\leq 1.5 \times \text{ULN}$
    - ALT and AST  $\leq 2.5 \times \text{ULN}$
  - INR and PTT  $\leq 1.5$ . (Anticoagulation is allowed if target INR  $\leq 1.5$  on a stable dose of warfarin or on a stable dose of LMW heparin for  $> 2$  weeks at time of randomization.)
  - Adequate renal function: serum creatinine  $\leq 1.5 \times \text{ULN}$

- Fasting serum cholesterol  $\leq 300$  mg/dL OR  $\leq 7.75$  mmol/L AND fasting triglycerides  $\leq 2.5 \times$  ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication and confirmation of lipid levels within acceptable criteria.
- Signed informed consent

### **Exclusion criteria**

- Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of study drug (including chemotherapy, radiation therapy, antibody based therapy, etc.)
- Patients, who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia)
- Patients with acute radiotherapy related mucositis and dermatitis  $>$  grade 1 (all other acute radiotherapy related toxicities  $>$  grade 1 may be eligible per sponsor discretion)
- Prior treatment with any investigational drug within the preceding 4 weeks
- Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period.
- Lip, nasopharynx, nasal cavity, paranasal sinus, salivary gland, skin, or thyroid primary tumors
- Evidence of metastatic disease
- Other malignancies within the past 3 years except for adequately treated CIS of the cervix or basal or squamous cell carcinomas of the skin
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
  - Symptomatic congestive heart failure of New York heart Association Class III or IV
  - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
  - severely impaired lung function – if suspected, pulmonary function tests should be performed with severely impaired function defined as spirometry and DLCO that is 50% of the normal predicted value and/or  $O_2$  saturation that is 88% or less at rest on room air
  - uncontrolled diabetes as defined by fasting serum glucose  $> 1.5 \times$  ULN
  - active (acute or chronic) or uncontrolled severe infections (Note: Optimal glycemic control should be achieved before starting trial therapy.)
  - liver disease such as cirrhosis, or severe hepatic impairment (Child-Pugh class C).

- Chronic or active hepatitis B or C. Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection (see Section 4.6.1.2).
- A known history of HIV seropositivity
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of Everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
  - N.B.: patients are allowed to administer everolimus through a feeding tube (see Appendix A)
- Patients with an active, bleeding diathesis
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Adequate contraception must be used throughout the trial by both sexes and for at least 8 weeks after the last dose of study drug, by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of Everolimus)
- Male patient whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment
- Patients who have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus).
- Patients with a known hypersensitivity to Everolimus or other rapamycin analogues (sirolimus, temsirolimus) or to its excipients
- History of noncompliance to medical regimens
- Patients unwilling to or unable to comply with the protocol

### 3.2.3 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of Everolimus must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in [Table 3-1](#). Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0, ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf))).

**Table 3.0 Everolimus dose level modification guidelines**

<b>Dose level</b>	<b>Dose and schedule</b>
0 (starting dose)	10 mg daily
-1	5 mg daily
-2	5 mg every other day

**Table 3-1 Criteria for dose-modification in case of suspected Everolimus  
Everolimus toxicity and re-initiation of Everolimus treatment**

Toxicity	Actions
Non-hematological toxicity	
<b>Grade 2</b> (except pneumonitis – refer to Table 3-2)	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt Everolimus until recovery to grade $\leq 1$ . Then reintroduce Everolimus at same dose. If event returns to grade 2, then interrupt Everolimus until recovery to grade $\leq 1$ . Then reintroduce Everolimus at the lower dose level.
<b>Grade 3</b> (except hyperlipidemia*) (except pneumonitis – refer to Table 3-2)	Interrupt Everolimus until recovery to grade $\leq 1$ . Then reintroduce Everolimus at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
<b>Grade 4</b>	Discontinue Everolimus.
Hematological toxicity	
<b>Grade 2 Thrombocytopenia (platelets <math>&lt;75, \geq 50 \times 10^9/L</math>)</b>	Interrupt Everolimus until recovery to grade $\leq 1$ ( $>75 \times 10^9/L$ ). Then reintroduce Everolimus at initial dose. If thrombocytopenia again returns to grade 2, interrupt Everolimus until recovery to grade $\leq 1$ . Then reintroduce Everolimus at the lower dose level.
<b>Grade 3 Thrombocytopenia (platelets <math>&lt;50, \geq 25 \times 10^9/L</math>)</b>	Interrupt Everolimus until recovery to grade $\leq 1$ (platelets $\geq 75 \times 10^9/L$ ). Then resume Everolimus at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue Everolimus.
<b>Grade 4 Thrombocytopenia (platelets <math>&lt;25 \times 10^9/L</math>)</b>	Discontinue Everolimus.
<b>Grade 3 Neutropenia (neutrophils <math>&lt;1, \geq 0.5 \times 10^9/L</math>)</b>	Interrupt Everolimus until recovery to grade $\leq 1$ (neutrophils $\geq 1.5 \times 10^9/L$ ). Then resume Everolimus at the initial dose. If ANC again returns to Grade 3, hold Everolimus until the ANC $\geq 1.5 \times 10^9/L$ . Then resume Everolimus dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
<b>Grade 4 Neutropenia (neutrophils <math>&lt;0.5 \times 10^9/L</math>)</b>	Interrupt Everolimus until recovery to grade $\leq 1$ (neutrophils $\geq 1.5 \times 10^9/L$ ). Then resume Everolimus at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue Everolimus.
<b>Grade 3 febrile neutropenia (not life-threatening)</b>	Interrupt Everolimus until resolution of fever and neutropenia to grade $\leq 1$ . Hold further Everolimus until the ANC $\geq 1,500/\text{mm}^3$ and fever has resolved. Then resume Everolimus at the lower dose level. If febrile neutropenia recurs, discontinue Everolimus.
<b>Grade 4 febrile neutropenia (life-threatening)</b>	Discontinue Everolimus.
Any hematological or non-hematological toxicity requiring interruption for $\geq 3$ weeks	Discontinue Everolimus.

\*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 3.2.5.2).

Subjects who require anticoagulation after randomization should be treated according to their physician's discretion and can continue on study. Since everolimus can interact with warfarin, the use of low-molecular weight heparins or non-coumarin containing anticoagulants is encouraged. If warfain is administered, close monitoring of INR is warranted.

### **3.2.4 Monitoring of Everolimus suspected toxicities**

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

### **3.2.5 Known Undesirable Side Effects of Everolimus**

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

The median duration of blinded study treatment was 141 days (range 19 to 451) for patients receiving everolimus and 60 days (range 21 to 295) for those receiving placebo. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most treatment-emergent adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 39% versus 7% of patients receiving everolimus and placebo, respectively. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm.

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

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

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

be done for all patients at screening, with testing performed prior to the first dose of everolimus.

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

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on everolimus. Mouth ulcers, stomatitis and oral mucositis have been seen in patients treated with everolimus. In such cases topical treatments are recommended, but alcohol- or peroxide-containing

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

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

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

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

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

**Table 3-1** provides general recommendations for the management of patients, with suspected drug toxicities while on treatment with Everolimus as single-agent therapy.

More detailed information regarding Everolimus reported suspected toxicities and individual cases is provided in the [Investigator's Brochure](#).

### **3.2.5.1 Management of stomatitis/oral mucositis/mouth ulcers**

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

1. For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain

adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids**, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives (e.g. Thymol) may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of Everolimus metabolism, thereby leading to higher Everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 3.0.

### **3.2.5.2 Management of hyperlipidemia and hyperglycemia**

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state.. Hyperlipidemia and hypertriglyceridemia should be treated according to local best clinical practice. Patients should be monitored clinically and through serum chemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting trial therapy.

### **3.2.5.3 Management of non-infectious pneumonitis**

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus (see [Section 5](#) Adverse drug reactions). Some of these have been severe and on rare occasions, a fatal outcome was observed.

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

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration. If symptoms are moderate (Grade 2), consideration should be given to interruption of therapy until

symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a reduced dose until recovery to Grade 1 or better.

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

**Table 3-5 Management of non-infectious pneumonitis**

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
<b>Grade 1</b>	<b>CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O<sub>2</sub> saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.</b>	<b>No specific therapy is required</b>	<b>Administer 100% of Everolimus dose.</b>
<b>Grade 2</b>	<b>CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O<sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *</b>	<b>Symptomatic only. Prescribe corticosteroids if cough is troublesome.</b>	<b>Reduce Everolimus dose until recovery to ≤ Grade 1. Everolimus may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.</b>
<b>Grade 3</b>	<b>CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O<sub>2</sub> saturation at rest; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *</b>	<b>Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.</b>	<b>Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.</b>
<b>Grade 4</b>	<b>CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O<sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *</b>	<b>Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.</b>	<b>Discontinue treatment.</b>

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

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

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

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent

7. lost to follow-up
8. administrative problems
9. death

### **3.3 Treatments**

#### **3.3.1 Everolimus Administration**

The study drug Everolimus or placebo will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Everolimus /placebo will be administered orally as once daily dose of 10 mg (two 5 mg tablets) continuously from study day 1 until progression of disease, unacceptable toxicity, or 1 year from start of therapy. Patients will be instructed to take Everolimus /placebo in the morning, at the same time each day. Everolimus /placebo can be taken with or without food (a low-fat meal is recommended). Dietary habits around the time of Everolimus /placebo intake should be as consistent as possible throughout the study. If vomiting occurs, no attempt should be made to replace the vomited dose. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

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

For this trial, Everolimus and placebo are supplied, by Novartis, 10 tablets per card. Tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Drug request forms will be provided to use when ordering Everolimus and placebo. Everolimus will only be shipped once all required regulatory documents are received.

#### **3.3.2 Treatment assignment**

- 8-16 weeks after completion of curative intent therapy for locally advanced squamous cell carcinoma of the head and neck patients will be randomized to receive everolimus 10 mg or placebo
- Treatment assignment will be double-blinded. Unblinding will occur at the conclusion of the study (approximately 2 years after completion of accrual) or if required for patient safety
- Expected treatment duration is 1 year from day 1 of everolimus or placebo administration
- Randomization will be stratified for disease stage and type of local therapy (IVa surgical vs. IVa non-surgical vs. IVb) as well as treating institution.
- A secure online registration interface has been developed to register patients, and is integrated with the randomization component, as well as data collection and storage system. This type of an interface has been used successfully in other Head and Neck cancer clinical trials at the University of Chicago (e.g. DeCIDE).

- Stratified randomization sequences will be generated using the method of permuted blocks. At the time of patient registration an electronic notification will be sent to the study pharmacist. To randomize this patient, the pharmacist will login into the registration system, which will provide the randomized treatment assignment. Only the pharmacist will have access to the treatment assignment to maintain the blinding.

### 3.3.3 Concomitant therapy

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

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

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

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Oral contraceptives in preclinical and clinical data have shown everolimus to have CYP3A4 inhibitory activity rather than induction activity, induction of metabolism of contraceptive hormones by everolimus is unlikely. Consequently, administration of everolimus should not reduce the efficacy of oral contraceptives.
- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events, if this is thought to be appropriate.
- Concurrent administration of Everolimus and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of Everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.

- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with systemic steroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with Everolimus.

### **Inhibitors of CYP3A4 and/or PgP**

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

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

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

### **Inducers of CYP3A4 and/or PgP**

Avoid the use of strong CYP3A4 inducers. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of everolimus up to twice the currently used daily dose should be considered, using 2.5mg - 5mg increments. Enzyme induction usually occurs within 7-10 days, therefore everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.

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

**Table 3-6 Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.**

Substrates (competitive inhibition)	
Antibiotics <sup>1</sup> : clarithromycin* erythromycin telithromycin*	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil
Anti-arrhythmics: quinidine	HMG CoA Reductase Inhibitors <sup>2</sup> : atorvastatin cerivastatin lovastatin simvastatin
Benzodiazepines: alprazolam diazepam midazolam triazolam	Miscellaneous: aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
Immune Modulators: cyclosporine tacrolimus (FK506)	
HIV Protease Inhibitors: indinavir* ritonavir* saquinavir*	
Prokinetic: cisapride	
Antihistamines: astemizole chlorpheniramine30	
Inducers	
Carbamazepine Phenobarbital Phenytoin* Rifabutin*	Rifampin* St John's wort Troglitazone
Inhibitors	
Amiodarone Cimetidine Clarithromycin Delavirdine Diltiazem Erythromycin Fluvoxamine* Grapefruit juice Sevilla orange	Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole* Mibepridil Nefazodone* Nelfinavir* Troleandomycin Verapamil

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

\* asterisk denotes strong inhibition/ induction

Please note:

- strong inhibitor implies that it can cause  $\geq 5$ -fold increase in AUC or  $\geq 80\%$  decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

(Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotic therapy with a macrolide is desirable in a patient being treated with **Everolimus**
2. Statins: Atorvastatin and pravastatin may be administered with **Everolimus**, since a PK interaction study has shown that there is no relevant PK interaction.

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

- No chronic treatment with systemic steroids (at a dose equivalent of greater than 20 mg prednisone per day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

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

Examples are provided in Table 3-5 (CYP3A4 inhibitors/inducers) and Table 3-6 (Drug interactions mediated by P-glycoprotein). A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at <http://medicine.iupui.edu/flockhart>. This website is continually revised and should be checked frequently for updates.

### **3.3.4 Treatment compliance**

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication. A drug diary should be given to each patient to complete (see Appendix B)

### **3.3.5 Definition of Curative Intent Therapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck**

Specific curative intent therapy is left to the discretion of investigators but the following criteria should be met for patients to be considered to have received curative intent therapy for locally advanced SCCHN and to be eligible for study:

- Acceptable chemoradiotherapy regimens:
  - Cisplatin or carboplatin based regimens
  - 5FU/hydroxyurea based regimens
  - Cetuximab based regimens
- Radiotherapy dose to gross disease must be > 58 Gy if treated post-operatively and > 64Gy if treated with primary chemoradiotherapy or radiotherapy alone
- Neoadjuvant or induction chemotherapy is permitted

- Any questions regarding the acceptability of curative intent therapy should be directed to Cherie-Ann Nathan (318 675 6262) or Ezra Cohen (773 702 4137)

### 3.4 Visit schedule and assessments

#### 3.4.1 Pre-study Procedures

- All patients must have completed curative intent therapy for locally advanced SCCHN 8-16 weeks prior to randomization (as defined in 3.3.5 AND be NED as defined in 3.2.2).
- Tissue must have been collected **PRIOR** to starting curative intent therapy on all patients (see Section 3.4.7)
- A detailed assessment of hepatitis B/C medical history and risk factors must be done for all patients at screening.

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

- All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece.  
[<http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx#849> ]
- Patients with any of the following risk factors:
  - known or suspected past hepatitis B infection,
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - household contact with hepatitis B infected patient(s),
  - current or prior high-risk sexual activity,
  - body piercing or tattoos,
  - mother known to have hepatitis B
  - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper abdomen pain.
- Additional patients at the discretion of the investigator

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

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

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

### 3.4.2 Visit schedule

**Table 3-4 Evaluation and visit schedule**

Examination	Screening/ Baseline	Week									
		4	16	32	52	64	80	96	112	128	144
<b>Informed consent</b>	X										
<b>No Evidence of Disease<sup>1</sup></b>	X										
<b>Inclusion/exclusion criteria</b>	X										
<b>Tissue Biopsy<sup>2</sup></b>	X										
<b>Radiographic assessment<sup>3</sup></b>	X										
<b>Physical examination</b>	X										
<b>ECG</b>	X										
<b>Laboratory test<sup>4</sup></b>	X	X	X	X	X	X	X	X	X	X	X
<b>Research Blood Draw<sup>5</sup></b>	X	X	X		X						
<b>HBV-DNA, HbsAg, HBs Ab, HBs Ab, HCV-RNA-PCR<sup>6</sup></b>	X										
<b>Patient Questionnaire<sup>7</sup></b>	X										
<b>Follow Up Form<sup>8</sup></b>		X	X	X	X	X	X	X	X	X	X

<sup>1</sup>See Section 3.2.2

<sup>2</sup>See Section 3.4.7; Tissue biopsy must have been obtained PRIOR to curative intent therapy

<sup>3</sup>Baseline radiographic assessment (CT, PET-CT, PET and/or MRI as appropriate) must be preformed within 12 weeks of starting everolimus. CT, PET-CT, PET and/or MRI as appropriate should be performed at least every 4-6 months in years 1 and 2 then every 6 months in year 3.

<sup>4</sup>Baseline assessments must be performed within 7 days of starting everolimus. Hemoglobin, platelets, total white blood cell count (WBC), and differential; sodium, potassium, chloride, bicarbonate, calcium, glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, phosphorus, serum lipid profile (triglycerides, total cholesterol, HDL and LDL); PT (INR) evaluation only at baseline unless otherwise indicated. Patients should be fasting at the time of the blood sampling.

<sup>5</sup>Blood draw for serum, whole blood and optional PBMC isolation (see Section 3.4.7). Serum will be drawn at screening, weeks 4, 16 and 52. Whole blood will be drawn at weeks 4, 16 and 52. Optional PBMC will be drawn at screening and week 4.

<sup>6</sup>All patients should be **screened** for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. If the patient has any of the risk factors outlined in section 3.4.1 then serologic testing must be done.

<sup>7</sup>All patients should fill out the Patient Questionnaire prior to first dose. See the Study Procedures manual.

<sup>8</sup>See the Study Procedures Manual

### **3.4.3 Efficacy assessments**

The primary study endpoint is progression-free survival. Disease progression will be evaluated by clinical and radiographic methods and date of progression will be recorded. If in question, disease progression should be confirmed pathologically. Site of disease progression will be classified as local (progression at primary tumor site), regional (progression in cervical lymph nodes), and/or distant (metastatic disease).

A diagnosis of second primary tumor must be confirmed pathologically. Deaths on study should be classified as disease (SCCHN), non-disease, or study treatment related.

### **3.4.4 Safety assessments**

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

These assessments should be performed within  $\pm 2$  days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTC [http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_5x7.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

#### **3.4.4.1 Adverse events**

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

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

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

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)

4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

Grading for all adverse events will utilize NCI CTCAE v4.0.

CTCAE version 4.0 is available at: <http://ctep.cancer.gov/reporting/ctc.html>

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

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

#### 3.4.4.2 Serious adverse events

A serious adverse event is 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
- Pregnancy

To ensure patient safety, the principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis, **regardless of suspected causality**, occurring:

- after the patient has provided informed consent and until 30 days after the patient has stopped study treatment/participation

- after the patient is randomized and until 30 days after the patient has stopped study treatment/participation
- after the patient begins taking study drug and until 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 until 30 days after the patient has stopped study treatment/participation
- 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/participation

SAEs must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the Novartis study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax as specified in Section 4.6. The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

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

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

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form). Reporting guidelines are provided in the following table:

UNEXPECTED EVENT		EXPECTED EVENT	
GRADES 2 – 3 <b>Attribution of Possible, Probable or Definite</b>	GRADES 4 and 5 <b>Regardless of Attribution</b>	GRADES 1 - 3	GRADES 4 and 5 <b>Regardless of Attribution</b>
<p>Written report within 10 working days. (Grade 1 SAE Reporting NOT required.) Any pregnancy should be reported as specified under Unexpected Grade 4 and 5 events.</p>	<p>Report by phone to University of Chicago Study Coordinator and University of Chicago Cancer Clinical Trials Office within 24 hours. Information will be distributed to Principal Investigators, University of Chicago IRB, and Novartis within 24 hrs. Written report to follow <b>within 5 calendar days</b>.</p> <p>This includes all deaths within 30 days of the last dose of treatment regardless of attribution.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 calendar days.</p>	<p>Adverse Event Expedited Reporting NOT required.</p>	<p>Written report, within 10 working days except for deaths within 30 days of the last dose of treatment regardless of attribution, which must be reported within <b>5 calendar days</b>.</p> <p>Any late death attributed to the agent (possible, probable, or definite) should be reported within 5 calendar days.</p>

### 3.4.5 Laboratory Evaluations

#### Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential. PT (INR) evaluation will be included for baseline evaluations.

#### Blood chemistry

Blood chemistry must include sodium, potassium, chloride, bicarbonate, calcium, glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, phosphorus, serum lipid profile (triglycerides, total cholesterol, HDL and LDL).

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

### 3.4.6 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight.

### **3.4.6.1 Physical examination**

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

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

### **3.4.6.2 ECG**

A standard 12 lead ECG is to be performed (during screening only to confirm I/E criteria) and significant findings must be recorded.

### **3.4.6.3 Performance status**

Performance status will be assessed using the Karnofsky scale

### **3.4.7 Research tests**

Tissue obtained (PRIOR to curative intent therapy) from the diagnostic biopsy/panendoscopy and/or during surgical resection, PBMC, serum and whole blood samples will be used for the correlative studies. The studies will be performed in Dr. Cherie-Ann Nathan's research laboratory (LSUHSC, Shreveport, LA) and at the University of Chicago.

The tumor suppressor gene PTEN is an important regulator of the Akt/mTOR pathway and often found to be mutated in HNSCC patients<sup>29</sup>. Hence we will evaluate PTEN status by FISH and mutation analysis in all patients. Correlation between PTEN status and the sensitivity to Everolimus will be determined.

We will determine the correlation of the Akt/mTOR pathway activation [pAkt(S473), pmTOR(S2448), pS6(S235/236), p4EBP1(T37/46) and eIF4E] by IHC and/or western blot (when available) analysis in tumors and adjacent normal mucosa. The Kaplan-Meier method with logrank test and/or Cox Regression model will be used to compare PFS between HNSCC patients with different degree of biomarker upregulation in tumors but more importantly in the normal surrounding mucosa as previous studies have shown that patients with mTOR activation in the margins are at a higher risk for recurrence.

Upregulation of the Akt/mTOR pathway is associated with an increased survival of cancer cells and their decreased sensitivity to chemo- and radiotherapy<sup>30, 31</sup>. Also it was shown for some types of cancer that tumors with heightened Akt activation are more sensitive to mTOR inhibition<sup>30, 31</sup>. Based on these evidences we hypothesize that the risk of disease recurrence correlates with the degree of activation of the Akt/mTOR pathway biomarkers and that the patients with heightened Akt activation will benefit the most from adjuvant therapy with everolimus. Thus we will test the hypothesis that either the adjacent normal mucosa or tumor tissue or both from SCCHN patients who recurred after treatment will have higher pAkt/pmTOR expression as compared to the tissue samples from the SCCHN patients who did not recur after treatment.

#### **Tissue Sample:**

Diagnostic tumor biopsy should be preferably obtained from advancing edge of the tumor. Normal mucosa should be biopsied at least 1 cm away from the tumor.

At the minimum, **10 slides** of the tumor/biopsy and **10 slides** of all the histologically tumor free surgical resection margins/adjacent normal mucosa from the paraffin embedded blocks should be mounted on positively charged slides. Slides should be labeled with institution, protocol number, patient initials, patient registration number, and the date of biopsy. If tissue blocks are available these are preferable to the slides.

If frozen tissue obtained (PRIOR to curative intent therapy) from the diagnostic biopsy/panendoscopy and/or during surgical resection is available, resected tumor tissue and adjacent normal mucosa measuring minimum 1 cm x 5 mm should be placed in cryovials and clearly labeled with appropriate study identifiers. These samples should be stored at -80°C until shipment and they will be used for western blot biomarker analysis.

All tumor tissue should be accompanied by a de-identified pathology report and be shipped to LSUHSC in Shreveport for correlative studies at the address indicated below with accompanying Notification of Correlative Study Samples Shipment form (Appendix C).

**Peripheral Blood Mononuclear Cells (PBMC) (optional procedure based on the sites ability to process sample):**

Venous blood sample will be collected prior to therapy and at week 4 in 1 blue and black tiger top tube (~8 cc). See Appendix D for PBMC isolation protocol. Sample should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. PBMC sample should be stored at -80°C till shipment. PBMC sample should be shipped with accompanying Sample Shipping Form and Notification of Correlative Study Samples Shipment form (Appendix C) to LSUHSC in Shreveport for correlative studies at the address indicated below. (As this is an adjuvant trial, patients will not have any post-treatment tumor tissue. Hence, biomarker changes in PBMC can be used as surrogate marker of tumor response.)

**Serum and whole blood:**

Serum samples will be collected prior to therapy on all patients and at weeks 4, 16 and 52 in three 7-10 cc gold top tubes. Blood in the serum collection tube should be allowed to clot for 60 minutes and then centrifuged to separate serum. Serum should be stored in 2 mL cryovial tubes (Nalgene Cat# 5000-0020) in 410uL aliquots. Samples should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. Serum samples should be stored at -80°C till shipment. Serum samples collected from two gold top tubes should be shipped with a copy of accompanying Sample Shipping Form and Notification of Correlative Study Samples Shipment form (Appendix C) to LSUHSC in Shreveport for correlative studies at the address indicated below. Serum samples collected from one gold top tube should be shipped with accompanying Sample Shipping Form (Appendix C) to the University of Chicago at the address indicated below.

Whole blood samples will be collected on all patients at weeks 4, 16 and 52 in 1 lavender top tube (10 cc). The tube will be inverted several times to mix contents of the tube immediately after collection of the blood sample. Samples should be labeled with institution, protocol number, patient initials, patient registration number, and the date and time of draw. Freeze at

-80°C within 60 minutes of draw until shipment. Whole blood samples collected from one lavender top tube should be shipped with accompanying Sample Shipping Form (Appendix C) to the University of Chicago at the address indicated below.

We may store all samples until publication of the study results to potentially address reviewers concerns. It is not expected that any study samples will remain at the conclusion of the study as we have proposed an extensive number of biomarkers to analyze.

**Sample Shipping:**

All the tissue, PBMC, whole blood and serum samples will be packaged and transported by carrier service in batched samples following the government regulation 42 CFR Part 72 – “Interstate Shipment of Etiologic Agents,” which describes the requirements for the proper packaging and shipping of infectious substances and other biomedical material. All the samples will be packaged and delivered in such a way that the contents will not leak and will arrive in good condition. The tissue, PBMC, whole blood and serum samples will be transported in the packages with the biohazard label on the front to Dr. Nathan’s laboratory or to Leslie Martin at the University of Chicago. Frozen tissue samples, PBMCs whole blood and serum samples should be shipped on dry ice. Paraffin-embedded tissue sections mounted on positively charged slides and paraffin-embedded tissue blocks should be shipped at ambient temperature. All institutional requirements for safety and confidentiality will be met during specimen transmittance. All samples must be accompanied by a Sample Shipping Form (Appendix C).

Correlative study investigator: (tissue, PBMC, 2 serum samples)	Research samples: (1 serum sample, whole blood)
Dr. Cherie-Ann O. Nathan, M.D., F.A.C.S.,	Leslie Martin
Department of Otolaryngology/HNS,	University of Chicago
Louisiana State University Health Sciences Center	5841 S. Maryland Ave.
Building: Medical School; Room #9-203	Room P-616A
1501 Kings Highway, Shreveport, LA 71130	Chicago, IL 60637-1470
Tel: (318)-675-6262; Fax: (318)-675-6260	Phone: 773-834-8392
See Appendix C for further shipping instructions.	

## 4 Regulatory Procedures

### 4.1 New Protocol Distribution and IRB Submission

Once final Novartis and University of Chicago (U of C) IRB approval is received, the protocol and consent form will be distributed to the participating affiliate institutions electronically. Upon receipt of the email, the affiliate institution is expected to do the following:

- The affiliate must reply to the email indicating that the protocol was received by the institution.
- The affiliate institution is expected to submit the protocol to their IRB as soon as possible after receipt.
- **The U of C version date must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form.
- When the protocol and consent receive IRB approval at the affiliate institution **a copy of the IRB approval letter, the IRB approved protocol and the IRB approved consent form** must be faxed or emailed to the Regulatory Coordinator, Kurombi Wade-Oliver at (773) 702-1561, [kwadeoli@medicine.bsd.uchicago.edu](mailto:kwadeoli@medicine.bsd.uchicago.edu).

#### **4.2 Amendment Distribution and IRB Submission**

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,
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.

All modifications to the protocol, or consent form will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the P.I. at the central institution can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the U of C IRB, the Regulatory Coordinator will send the amended protocol and consent form to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Affairs Administrator indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.
- **The U of C version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the U of C IRB amendment approval letter that is sent with the protocol/amendment mailing.
- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be faxed or emailed to the Regulatory Affairs Administrator.

#### **4.3 Annual IRB Renewals, Continuing Review and Final Reports**

A continuing review of the protocol will be completed by the University of Chicago IRB and the affiliates' IRBs at least once a year for the duration of the study. The annual IRB renewals for the affiliate institution should be faxed promptly to the Regulatory Affairs Administrator. If the institution's IRB requires a new version of the consent form with the annual renewal the consent form should be included with the renewal letter.

Continuing review reports will include the following: the number of subjects accrued; a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; a summary of research literature, findings obtained thus far, amendments or modifications since the last review, reports of multi-center trials and any other relevant information, especially information about the risks associated with the research; and a copy of the current informed consent document.

#### **4.4 Departure from the Protocol**

An investigator cannot modify the protocol without satisfying procedures in 4.2. Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the study subject, must be reviewed and approved by the local IRB. When a variation from the protocol is deemed necessary for an individual subject, the principal investigator must be contacted by phone or email (Ezra Cohen, 773 702 4137, [ecohen@medicine.bsd.uchicago.edu](mailto:ecohen@medicine.bsd.uchicago.edu)). Such contact must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study.

The principal investigator must be informed of all intentional or unintentional departures from the protocol and will decide whether or not the subject is to continue in the study (Ezra Cohen, 773 702 4137, [ecohen@medicine.bsd.uchicago.edu](mailto:ecohen@medicine.bsd.uchicago.edu)). All departures from the protocol, intentional and unintentional, along with the decision of the principal investigator will be submitted in a written report to the local and University of Chicago IRB.

#### 4.5 Registration

All patients must be registered with the University of Chicago Study Coordinator at least 48 hours prior to the commencement of treatment. Confirm all selection criteria listed in Section 3.2.2, and then call the Study Coordinator at 773-702-1679 with the following information:

Provider of information  
Study # and Institution  
Treating Physician  
Patient name and hospital ID number  
Patient's zip code of residence  
Date of signed informed consent  
Race, gender, date of birth of patient  
Diagnosis and date of initial diagnosis

The Study Coordinator will issue a confirmation of registration. The Study Coordinator will ensure that all necessary supporting documents have been received and that the potential patient is eligible to start treatment on schedule. Photocopies of the appropriate pages of the protocol will be used to determine eligibility. If there are questions about eligibility, the Study Coordinator will question the principal investigator, who will be responsible for any final decisions on eligibility. The date the patient is registered will be considered the patient's "On-Study Date." Patients that sign consent and do not go "On-Study" will be recorded in the database with the date that they signed consent and the reason for not going "On-Study" (either Ineligible or Withdrawn Consent). The treatment start date will also be tracked.

At the time of registration, the registering institution will:

- Confirm that their institution has IRB approval of the correct version of protocol/consent and has an annual update on file.
- Fax or email all required forms (see data submission Section 5) and source documentation for the protocol required eligibility criteria and pre-study procedures, including labs, radiology, pathology reports, and signed consent form to the Study Coordinator's attention.
- Communicate with the Study Coordinator to ensure that all necessary supporting documents have been received and that the potential patient is eligible to start treatment on schedule.

#### 4.6 Reporting of Adverse Events

Serious Adverse Events that require phone reporting within 24 hrs per section 3.4.4.2 should be phoned and emailed to the University Of Chicago Cancer Clinical Trials Office (CCTO) at 773-702-5149 and faxed to Novartis Clinical Safety and Epidemiology Department. (888-299-4565) by the end of the business day during which the investigator becomes aware of the event or by 12 noon the following day if the event occurs after normal business hours.

The following information is required when calling in the event:

- Reporter's Name and Telephone Number

- Patient Initials
- Patient Medical Record Number
- IRB Protocol Number
- PI of Study
- Attending Physician
- Date of Event
- Description of Event (including grade of the event and if the event required hospitalization)

Upon receipt of the 24-hour notification, the CCTO will send an e-mail to the research nurse, attending physician, all PI's, and to Novartis Pharmaceuticals CS&E Department FAX (888-299-4565).

All serious adverse events, except those exempted from reporting per section 3.4.4.2, must be reported to the University of Chicago Cancer Center Clinical Trials Office in writing within **10 calendar days of event occurrence (5 calendar days for an unexpected grade 4 or 5 event, or death within 30 days of discontinuing investigational therapy)**. MedWatch form (FDA form 3500A) should be utilized. Report should also be submitted to the affiliate institution's local IRB according to institutional guidelines. Reports should be sent to the address or fax number below with any appropriate source documentation.

Quality Assurance Coordinator  
Cancer Clinical Trials Office  
University of Chicago, MC 1140  
5841 S. Maryland Ave.  
Chicago, IL 60637-1470  
Fax: 773-702-8855  
Email: [qaccto@bsd.uchicago.edu](mailto:qaccto@bsd.uchicago.edu)

Adverse Events will be recorded and followed until the adverse event has subsided and abnormal findings have returned to normal or stabilized. In addition, any events with a suspected causal relationship to Novartis study drug will be reported as AEs or SAEs (as applicable) throughout follow-up.

The sponsor will stop the study at any time if new knowledge is obtained indicating that:

- Safety for all participating patients can no longer be assumed; and/or
- The risk-benefit ratio is no longer acceptable for the participating patients.

New adverse events for patients who discontinue the study will not be recorded past their date of discontinuation but events that are ongoing will be followed, if feasible, until they resolve. All patients will be followed for survival.

A weekly report of delinquent or pending documents will be forwarded to Denise Friesema, RN (U of C Events Only). All delinquent reporting (greater than 10 days from event occurrence) must include documentation of reason for delinquency and may require implementation of an action plan.

SAEs that have not resolved at the time of reporting should have a follow up written report within 10 calendar days of resolution. This includes any pregnancies in which the outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications should be reported.

Once the appropriate SAE documents have been received, the University of Chicago Cancer Center Clinical Trials office forwards these to the Principal Investigator. The Principal Investigator should comment on the outcomes of the event or problem including likely relationship to study drug. The Principal Investigator should also indicate whether he/she concurs with the details of the report provided by the study investigator and provide any recommendations for actions to be taken in response to the SAE.

Once the University of Chicago Cancer Center Clinical Trials Office receives the Principal Investigator's report, they will forward all documents to the IRB, research nurse, all participating institutional PI's, the FDA, and Novartis FAX (888-299-4565).

#### **4.6.1 Novartis instructions for rapid notification of serious adverse events**

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

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

**All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

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

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

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

##### **4.6.1.1 Pregnancies**

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

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

#### 4.6.1.2 Testing for Hepatitis

##### **Hepatitis B Virus testing**

Prior to randomization the categories of patients listed in Section 3.2 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.

##### **Hepatitis C Virus testing**

Patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be tested for HCV RNA-PCR test at baseline. For a list of hepatitis C risk factors, refer to Section 3.2.5.

**Note – serologic testing is not mandatory for all subjects. Rather, each subject needs to be screened by history taking for risk factors and ONLY if they are at risk for HBV or HCV should serologic testing be performed.**

#### 4.7 Data and Safety Monitoring

Subject accrual and all reported serious adverse events will be monitored at the University of Chicago during the weekly Phase 2 Conference. This meeting will include study investigators, independent investigators, and study coordinators. Quarterly reports of completed and missing Case Report Forms will be generated and reviewed by the principal investigators.

A Data and Safety Monitoring Board (DSMB) will be convened to review toxicity and efficacy data. The DSMB will consist of a statistician and two experts in SCCHN. DSMB members cannot be investigators or co-investigators involved in the clinical trial. After the annual meeting of the DSMB a report to the principal investigators will be issued recommending study continuation/discontinuation or proposed changes to the protocol.

Toxicity will be reviewed annually, with the first review approximately coinciding with the first 30 patients being enrolled and on-treatment for at least 3 months. A single formal interim analysis will take place after 36 events have occurred, which corresponds to 50% of the expected number of on-study events. The DSMB may be convened more often should significant toxicities be observed. The guideline to stop early for futility will be if the conditional power at the interim look is less than 10% using the stochastic curtailment approach (as described in Jennison and Turnbull). Based on this approach, the effect of adding the interim look on overall power will be negligible (Jennison C, Turnbull BW. Group Sequential Methods: Applications to Clinical Trials. 1999. Chapman & Hall/ CRC).

## 5 Data management

### 5.1 Data collection

Investigators must record the information required by the protocol. Case Report Forms (CRF) will be made available for all data elements required by the study. CRFs should be faxed or emailed to the Study Coordinator at (773) 834-2058.

## 6 Statistical methods

### 6.1 Statistical methods

This is a multicenter, randomized, placebo-controlled, double-blind Phase II clinical trial of adjuvant Everolimus vs. placebo. Patients will be randomized 8-16 weeks after the completion of curative intent therapy. The primary endpoint is 2-year progression-free survival (PFS) rate. Progression-free survival will be estimated using the method of Kaplan-Meier, and compared between the two treatment arms using the stratified logrank test. Multivariate regression models will be used to compare treatment effect between treatment groups adjusting for other important prognostic factors. Adverse event rates will be summarized and compared between treatment groups using Chi-squared or Fisher's exact test. Continuous variables will be compared between groups using t-test or Wilcoxon rank sum test as appropriate, and categorical variables will be compared using Cox Regression Analysis. Regression models will be used as part of exploratory analysis to explore treatment effects adjusting for other important prognostic factors. The guideline to stop early for futility will be if the conditional power at the interim look (Section 4.7) is less than 10% using the stochastic curtailment approach (as described in Jennison and Turnbull).

#### Sample Size

Assuming uniform 3-year accrual and 2-year follow-up, a two-sided logrank test with a sample size of 132 (66 patients per treatment arm) will achieve 80% power at  $\alpha=0.05$  to detect a difference between 50% and 70% progression free survival at 2 years. This difference corresponds to median survival times of 24 months and 46.6 months, respectively, and a hazard ratio HR=1.94, assuming exponential survival distribution (The HR is based on a 2-year PFS that would be clinically meaningful – 50% to 70%, the preclinical animal data, and the hazard ratio associated with activated mTOR in patient samples. As no historical data exists for this type of trial these assumptions are rational given what information is available). Assuming 20% loss to follow-up, **N=160 patients (80 per arm) will be enrolled.**

The stratified logrank test will also be used for the analysis of secondary endpoints, specifically comparing PFS in patients with evidence of Akt/mTOR pathway activation (mTOR+ vs. mTOR-) in the adjacent normal mucosa. Whereas progression-free survival is expected to be similar among mTOR+ and mTOR- patients in the everolimus arm, mTOR+ patients on placebo are expected to do worse than mTOR- patients. Assuming 50% mTOR+ prevalence in each arm (n=33/arm), a two-sided logrank test will have 80% power and  $\alpha=0.05$  to detect a difference in 2-year PFS of 70% vs. 40.7%, which corresponds to median time to progression or death of 46.6 and 18.5 months, and a hazard ratio HR=2.5. Similarly, assuming 40% prevalence of upregulated Akt/mTOR pathway (n=26/arm), a two-sided logrank test will achieve 80% power at  $\alpha=0.05$  to detect a difference between 70% vs. 36.4%

2-year PFS, which corresponds to median time to progression or death of 46.6 and 16.5 months, and HR=2.8. While the detectable differences are quite large, they are comparable to those observed in other studies – for example, patients with FOE+ and FOE- in the retrospective study (Nathan et al, 1999) had median PFS of 82 and 31.5, which corresponds to HR=2.6.

## 7

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## **8 Procedures and instructions**

### **8.1.1 Publication of results**

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

### **8.1.2 Disclosure and confidentiality**

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

### **8.1.3 Discontinuation of study**

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

## **8.2 Ethics and Good Clinical Practice**

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

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

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

### **8.2.1      Institutional Review Board/Independent Ethics Committee**

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

### **8.2.2      Informed consent**

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

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

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

### **8.2.3      Declaration of Helsinki**

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

## 9 Appendices

### 9.1 Appendix A - Procedure for Administration of Everolimus in Water via Gastrostomy Tube

In cases where tablets cannot be swallowed, the tablets should be dissolved in water just prior to administration. Approximately 30 ml of water should be put into a glass. The tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablets are disintegrated. The contents should then be swallowed by the patient. Afterwards, the glass should be rinsed with an additional 30 ml of liquid and drunk by the patient.

In cases where the patient cannot swallow, follow the same procedure as above and administer the water with dissolved tablets via gastrostomy tube. After administration flush gastrostomy tube with at least 30ml of liquid.

## 9.2

## Appendix B - Patient's Medication Diary



**Randomized Double-Blind Phase II Trial of Everolimus vs.  
Placebo as Adjuvant Therapy in Patients with  
Locally Advanced Squamous Cell Cancer of the Head and Neck**

Rev. 0

Name: Last \_\_\_\_\_ First \_\_\_\_\_ MI \_\_\_\_\_

Patient's Study ID: \_\_\_\_\_ - \_\_\_\_\_

**Instructions:**

1. For each dose of the study medication, please record the time and the number of tablets you took. Write "0" if you missed a dose. Please complete this diary **every day**.
2. If you experience any health/medical complaints, please record this information on the back of this form.
3. Please bring your diary and study medication blister packs (empty packs and packs containing any unused medication) to EACH appointment with the research nurse.

DATE	TIME OF DOSE	# OF TABLETS
01 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
02 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
03 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
04 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
05 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
06 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
07 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
08 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
09 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
10 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
11 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
12 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	

DATE	TIME OF DOSE	# OF TABLETS
17 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
18 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
19 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
20 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
21 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
22 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
23 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
24 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
25 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
26 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
27 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	
28 Mar 2010	____ : ____ <input type="checkbox"/> am <input type="checkbox"/> pm	

13 Mar 2010	— : — <input type="checkbox"/> am <input type="checkbox"/> pm
14 Mar 2010	— : — <input type="checkbox"/> am <input type="checkbox"/> pm
15 Mar 2010	— : — <input type="checkbox"/> am <input type="checkbox"/> pm
16 Mar 2010	— : — <input type="checkbox"/> am <input type="checkbox"/> pm

<b>29 Mar 2010</b>	— — : — — <input type="checkbox"/> am <input type="checkbox"/> pm	
<b>30 Mar 2010</b>	— — : — — <input type="checkbox"/> am <input type="checkbox"/> pm	
<b>31 Mar 2010</b>	— — : — — <input type="checkbox"/> am <input type="checkbox"/> pm	

## **Health or Medical Complaints**

Please record any medical or health complaints. Please use an extra sheet of paper if you need more space.

Please describe what you experienced	Date started	Dated stopped

## **Other Medication**

Please record only non-study medication (prescription and/or over-the counter, including herbal medications and vitamins). Please use an extra sheet of paper if you need more space.

Name of Medication	Why did you take the medication?	Date started	Date Stopped



### 9.3 Appendix C - Tissue and Blood Sample Collection Forms

See separate form.

### 9.4 Appendix D - PBMC isolation protocol

#### Specimen

Venous blood (~8ml) in one BD Vacutainer CPT® (8 mL blue & black tiger top) tube.

#### Required Materials and Equipment

- Vacutainer-CPT (Blue Tiger tops) (BD Scientific, Cat. #362761)
- Class II Biological Safety Cabinet
- A timer regulated centrifuge with swinging bucket style rotor capable of maintaining a spin rate of 1500 x g for 20 minutes
- Table-top centrifuge
- Vacuum pump with trap flask
- -80 °C freezer
- Dry Ice
- Dulbecco's Phosphate-Buffered Saline (PBS); Sterile; Store at room temperature
- Red Blood Cells Lysis Buffer (Pure Gene Gentra RBC Lysis Solution, Cat. #D-5001)
- Adjustable, automatic micropipette (P1000)
- P1000 aerosol tips
- Pipette aid
- 10 ml pipettes
- 15 ml polypropylene centrifuge tubes
- 1.5 ml eppendorf tubes to store PBMC pellets

For each tube / sample received:

Testing procedure must be performed in a class II Biological Safety Cabinet. Powder-free gloves must be worn at all steps. All disposables and reagents must be sterile. Any pipette or tip that comes in contact with a specimen must be disposed of after use and a new, sterile one used for the next specimen or reagent. All reagents must be at room temperature before use.

1. Invert the tube gently 8 times.
2. Centrifuge the tube at room temperature in a horizontal swinging bucket rotor at 1500 x g for 20 minutes, no brake.
  - Check that loaded buckets swing freely.
  - Check that bucket inserts are lined up, so that tubes are seated at the bottom.
  - Carefully remove tubes after spinning; avoid shaking
3. After centrifugation there are four different layers visible in the tube:

a top layer of approximately 4 mL of plasma  
a white buffy coat of PBMCs (just underneath the serum)  
a solid agar gel barrier  
and red blood cells (below the agar barrier)

4. Remove and discard plasma layer.
5. Add 5 ml sterile PBS (room temperature) to the cell layer in the CPT tube.
6. Cap and invert tube gently 8 times.
7. Transfer the cell suspension (all the liquid above the agar gel barrier) into a labeled 15mL polypropylene centrifuge tube.
8. Add another 3ml of sterile PBS back to the CPT vacutainer tube to wash remaining cells.
9. Cap the tube again and invert gently 8 times.
10. Transfer the cell suspension into the same labeled 15mL polypropylene centrifuge tube.
11. Centrifuge the tube at 450 x g for 5 minutes, with brake.
12. Aspirate the supernatant, being careful not to disturb the cell pellet.
13. Re-suspend PBMC pellet in 3 ml of PBS. Re-suspend thoroughly by aspirating up and down using a pipette aid with serological pipette.
14. Centrifuge in the 15 ml conical tube at room temperature at 450 x g 5 min, with brake.
15. After centrifugation, aspirate the supernatant. Do not disturb the cell pellet.
16. Add RBC Lysis Buffer 1:3 cell pellet:buffer ratio.
17. Incubate at room temperature 5 min.
18. Transfer the cell suspension into a 1.5 ml eppendorf tube.
19. Centrifuge at room temperature in a table-top centrifuge at 6,000 rpm for 3 min.
20. Aspirate supernatant.
21. Add 1 ml of PBS to the cell pellet. Re-suspend thoroughly.
22. Centrifuge at room temperature in a table-top centrifuge at 6,000 rpm for 5 minutes.
23. Aspirate the supernatant using an aspirating pipette and unfiltered micropipette tip attached to a vacuum pump. Do not disturb the cell pellet. Store eppendorf tubes with PBMC pellets at -80°C until shipment.