IRB#: 09-131 A(15)

A Phase I/II Study of Temsirolimus + Weekly Paclitaxel + Carboplatin for Recurrent or Metastatic Head and Neck Squamous Cell Cancer (HNSCC)

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Summary

This is a single institution, single arm study that will be open at MSKCC and regional network affiliates.

Patients will not have received more than 2 prior chemotherapy regimens in the recurrent/metastatic disease setting.

In Part 1 (Phase I) of the study, the primary endpoint is to establish the phase II recommended dose for the combination of temsirolimus + weekly paclitaxel + carboplatin. Part 1 (Phase I) features a standard 3 + 3 phase I dose escalation design. Up to 3 dose levels are planned in the Phase I portion of the study. Rules for dose escalation are provided in Section 4.1.1. The dose of temsirolimus (the experimental drug) is escalated at each dose level, and the doses of paclitaxel and carboplatin (the standard chemotherapeutic agents) are fixed. The phase II recommended dose will be the maximum dose level at which <2/6 patients experience DLT.

In view of the available PK evidence regarding everolimus + paclitaxel [1], everolimus + cisplatin [2], and the planned phase I study temsirolimus + q 3 week paclitaxel + carboplatin [3], PK studies are not planned in Part 1 of this study.

Note: The dose escalation plan was revised in August 2010, and patients were enrolled on dose level 2 of the revised protocol.

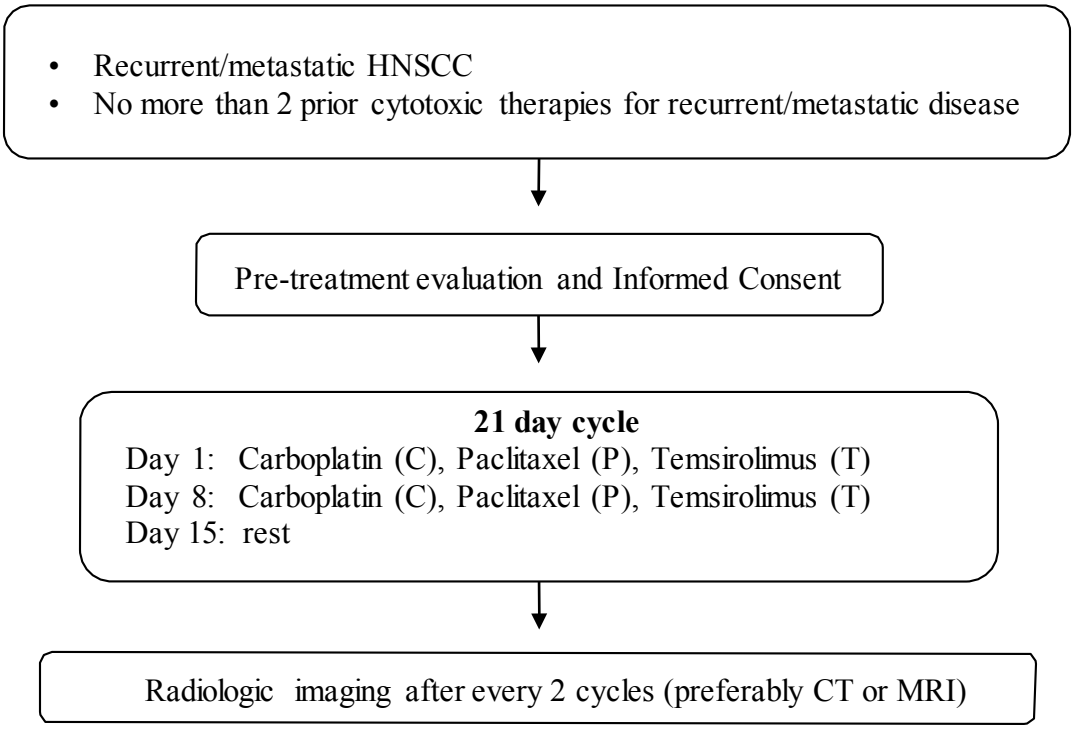
Table 1: Phase I Dose Levels (21 day cycle)

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1	N/A	N/A	N/A
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

In Part 2 (Phase II) of the study, the primary endpoint is to determine the objective response rate (CR or PR) after two cycles (approximately 6 weeks) of treatment with the combination of temsirolimus + weekly paclitaxel + carboplatin as palliative therapy for recurrent or metastatic HNSCC. A two-stage design will be employed.

Radiologic imaging of evaluable disease will take place after every 2 cycles. Patients may remain on study until progression of disease or unacceptable toxicity.

1.2 Schema


• Recurrent/metastatic HNSCC
• No more than 2 prior cytotoxic therapies for recurrent/metastatic disease
Pre-treatment evaluation and Informed Consent
21 day cycle
Day 1: Carboplatin (C), Paclitaxel (P), Temsirolimus (T)
Day 8: Carboplatin (C), Paclitaxel (P), Temsirolimus (T)
Day 15: rest
Radiologic imaging after every 2 cycles (preferably CT or MRI)

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objectives

2.1.1 Part 1: To establish the phase II recommended dose for the combination of temsirolimus + weekly paclitaxel + carboplatin

2.1.2 Part 2: To determine the objective response rate (CR or PR) after two cycles (approximately 6 weeks) of treatment with the combination of temsirolimus + weekly paclitaxel + carboplatin as palliative therapy for recurrent or metastatic HNSCC

2.2 Secondary Objectives

2.2.1 To establish the safety of temsirolimus + weekly paclitaxel + carboplatin

2.2.2 To estimate median overall survival

2.2.3 To identify potential molecular markers of resistance to mTOR inhibition in tumor specimens obtained as part of routine clinical care

3.0 BACKGROUND AND RATIONALE

3.1 Palliative chemotherapy for recurrent/metastatic HNSCC

Single agent chemotherapy as palliative treatment typically achieves objective responses in 10-30% of patients. Combination chemotherapy regimens appear to be associated with increased response rates and often with increased toxicities, but generally not with increased survival [4].

No combination chemotherapy regimen appears to be superior to another in terms of survival for patients with advanced head and neck cancer. A Southwest Oncology Group study reported by Forastiere randomized 277 patients with advanced head and neck cancer to treatment with cisplatin plus 5-fluorouracil, carboplatin plus 5-fluorouracil, or methotrextate monotherapy. In the comparision of the doublet regimens, cisplatin plus 5-fluorouracil yielded a higher response rate than carboplatin plus 5-fluorouracil (32% versus 21 %, p = 0.05). However, median survival times were similar in all three treatment groups in the study [5]. Gibson reported a randomized comparison of cisplatin plus 5-fluorouracil (CF) versus cisplatin plus paclitaxel (CP) for 218 patients with advanced head and neck cancer. Response rate (27% in CF group, 26% in CP group) and median survival (8.7 months in CF group, 8.1 months in CP group) did not differ signicantly [6].

These studies indicate the limitations of cytotoxic chemotherapy in the recurrent or metastatic disease setting, and highlight the need for new agents. Cetuximab, a mononoclonal antibibody directed against the epidermal growth factor receptor (EGFR), demonstrated an objective responsre rate of 13% in a phase II study of 103 patients with platinum-refractory recurrent and/or metastatic HNSCC [7]. Treatment was generally well tolerated and the most common adverse event was rash. In a phase III study by Burtness for patients with recurrent or metasatic disease who had not received any prior palliative chemotherapy, 117 subjects were randomized to cisplatin plus cetuximab versus cisplatin plus placebo. Objective response rate was higher for cisplatin plus cetuximab (26% versus 10%, $p = 0.03$), but there was no significant difference in survival between the two groups [8].

The addition of cetuximab to platinum-based chemotherapy was investigated further in a randomized clinical trial for 442 patients with untreated recurrent or metastatic head and neck cancer [9]. Patients were randomized to cisplatin (or carboplatin, at the disretion of the investigator) plus 5-fluorouracil in the control group versus the cisplatin (or carboplatin)/5-fluorouracil doublet plus weekly cetuximab in the experimental group. Objective response rate (20% v. 36%, $p < 0.001$), progression-free survival (3.3 v. 5.6 months, $p<0.001$), and overall survival (7.4 versus 10.1 months, $p = 0.04$) all favored the experimental group. Despite the addition of cetuximab as a therapeutic option, outcomes for patients with recurrent or metasatic head and neck cancer remain poor. The median survival in this group of patients is typically 10 months or less.

3.2 Rationale for mTOR inhibition in HNSCC

EGFR and other transmembrane receptors converge to control a variety of intracellular signaling pathways, such as the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. The importance of the PI3K/Akt/mTOR pathway in HNSCC was demonstrated in a study by the Head and Neck Cancer Tissue Array Initiative, which evaluated the this pathway in a study of 547 pathology cores, including controls, in a tissue microarray (TMA) [10]. The TMA was interrogated with antibodies directed against key signaling molecules in head and neck cancer, including p53, the epidermal growth factor receptor (EGFR), and components of the Akt-mTOR pathway. Alterations of the PI3K/Akt/mTOR pathway were found in most cases. As shown in Figure 1, $pAKT^{Ser473}$, $pAKT^{Thr308}$, and pS6 were significantly higher in HNSCC tumors, compared with normal mucosa, across all degrees of differentiation.

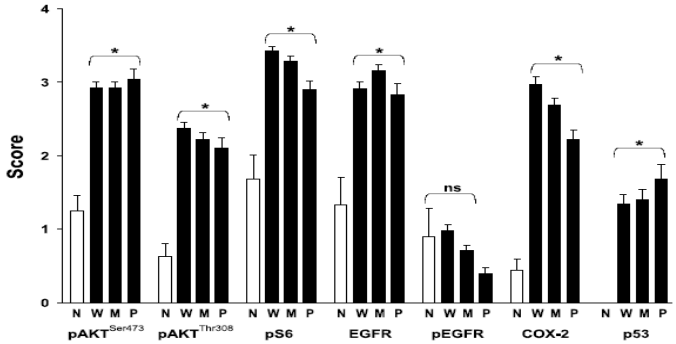


Figure 1: Distribution of immunoreactivity segregated by differentiation groups. Differences in normal (N) tissue versus well differentiated (W), moderately differentiated (M), and poorly differentiated (P) tumors were significant (*) for all proteins except pEGFR (NS) [10].

A key finding in this work was that the majority of head and neck cancers appear to have EGFR-independent activation of the PI3K/Akt/mTOR pathway. Within the collection of HNSCC samples, an unsupervised clustering approach provided a clear separation of certain clusters, and demonstrated that the pathway often appeared to be activated in the setting of negative staining for pEGFR [10]. This suggests that activation of the PI3K/Akt/mTOR pathway may occur independently of EGFR activation in many head and neck cancer patients. These findings may provide insight into the relatively low-to-modest clinical efficacy of EGFR inhibition strategies in this disease [11], and suggest that downstream inhibition of mTOR merits further study as a potential therapeutic strategy in HNSCC.

3.3 mTOR inhibitors + platinum/taxane agents in HNSCC

Rapamycin, the prototypic mTOR inhibitor, demonstrates modest antiproliferative effects against HNSCC cell lines, with IC50s in the range of 5 – 20 μM [12]. In HNSCC xenografts, dramatic tumor growth inhibition was achieved with temsirolimus [13] or rapamycin [14]. Because it is probable that mTOR inhibitors will have no better than modest clinical activity against HNSCC when given as single agents, the true utility of these agents may derive from their ability to potentiate the antitumor effects of other cytotoxic chemotherapeutic agents.

In 1995, Mills and coworkers reported that rapamycin enhances the cytotoxic effects of cisplatin against a human leukemia cell line (HL-60) and an ovarian cancer cell line (SKOV3) [15]. Subsequent pre-clinical studies demonstrated additive or synergistic effects when mTOR inhibitors are combined with platinum or taxane chemotherapy agents in studies of non-small cell lung cancer [16], breast cancer [17], and more recently HNSCC cell lines [12]. In the study of HNSCC cell lines, mTOR inhibition yielded synergistic effects when combined with carboplatin and paclitaxel [12]. The authors proposed that mTOR inhibition may be a strategy to decrease resistance to paclitaxel and carboplatin. Consistent with this, mTOR inhibition appears to reverse resistance to paclitaxel in a cervical cancer cell line (CaSki) [18], and also appears to reverse resistance to cisplatin in lung cancer cell line (SCLCSR2) [19].

We have recently completed the dose escalation phase of IRB 06-129, "A Phase I study of Weekly Low-Dose Cisplatin Plus Escalating Doses of Oral RAD001 (Everolimus) for Patients with Advanced Solid Tumors." Partial response has been seen in pulmonary carcinoid (n=1) and HNSCC (n=1). Another HNSCC patient achieved a minor radiographic response, but was removed from study after experiencing a pulmonary embolus during cycle 2 of RAD001 + cisplatin. Off study, the patient subsequently received an additional 2 cycles of cisplatin alone with progression of disease [2]. This phase I experience suggests that mTOR inhibitors + platinum based chemotherapy may achieve greater activity than would be seen with cisplatin alone, although no firm conclusions can be drawn from this small study. The favorable safety profile of the IRB 06-129 regimen suggests that it should be feasible to add paclitaxel to the mTOR inhibitor + platinum backbone, which is an obvious research direction to pursue because paclitaxel has significant palliative activity in HNSCC [20].

3.4 Temsirolimus (Torisel®, CCI-779)

Temsirolimus (Torisel®, CCI-779) and other rapamycin analogues ("rapalogues"), such as everolimus and deforolimus, share the same mechanism of action: binding to the intracellular protein FKBP-12 to form a complex that inhibits mTOR signaling [21]. In phase I studies, temsirolimus demonstrated encouraging activity against renal cell carcinoma [22]. A phase II study randomized 111 patients with cytokine-refractory metastatic renal carcinoma to receive one of three doses of temsirolimus, either 25, 75 or 250 mg intravenously (IV) once weekly. Median time to progression was 5.8 months, which compared favorably to the typical 2.5 to 3.0 months time to progression seen with other investigational agents following cytokine therapy [23]. Given the similar outcomes with the three doses of temsirolimus, the lowest dose of 25 mgIV once weekly was chosen for the subsequent pivotal phase III trial [24].

The pivotal phase III trial included 626 previously untreated patients with advanced renal cancer randomized to one of three arms; a control group receiving escalating doses of alpha interferon alone, one treatment arm of 25 mg IV once weekly temsirolimus and another treatment arm consisting of a lower dose of temsirolimus (15 mg) IV once weekly combined with interferon alpha 6 MU subcutaneously three times per week [24]. The overall survival was significantly greater in the temsirolimus group (median value 10.9 months) compared with the interferon monotherapy group (median value 7.3 months). The overall survival of patients receiving the combination of temsirolimus and interferon was not greater than that of patients receiving interferon alone. Among the grade 3 and 4 toxicities, asthenia was the most common. Temsirolimus was also associated with a variety of laboratory anomalies, including anemia, hyperglycemia, hyperlipidemia and hypercholesterolemia. In 2007, temsirolimus received FDA approval for use in patients with advanced kidney carcinoma.

3.5 Rationale for Dose and Schedule

We feel that the appropriate follow-up clinical trial is a phase I/II study of temsirolimus + weekly paclitaxel + carboplatin. Studies in other tumor types suggest that paclitaxel on a weekly schedule has a more favorable toxicity profile than q 3 week paclitaxel [25] [26]. The weekly paclitaxel schedule pairs well with weekly temsirolimus administration. Weekly everolimus was well tolerated when combined with weekly paclitaxel in a phase I study, and no significant pharmacokinetic interaction between the mTOR inhibitor and paclitaxel was identified [1]. The regimen of carboplatin (day 1) and paclitaxel (days 1, 8, and 15) on a 28-day schedule has excellent activity as induction chemotherapy for patients with local-regionally advanced HNSCC [27]. In the current study, we propose somewhat lower doses of carboplatin and paclitaxel in the palliative-intent setting for pre-treated patients. The regimen in this proposal, if it shows significant activity in this study, would be attractive for further study as an induction chemotherapy regimen in HNSCC because the carboplatin-based regimen may be better tolerated than the widely-used cisplatin-based induction chemotherapy regimens [28-30].

The dose escalation scheme selected for this study builds upon the phase I experience reported by Oza et al [31], in which temsirolimus (25 mg intravenously, day 1 and day 8) was well tolerated when combined with paclitaxel (175 mg/m^2, day 1) + carboplatin (AUC 5, day 1) on a 21 day cycle. However, when temsirolimus was given on Days 8 and 15 (combined with paclitaxel 175 mg/m^2 and carboplatin AUC 5 on day 1 of a 21 day cycle), treatment was not feasible due to myelosuppression.

The current study features a 21-day cycle with a break week. In view of the potential for myelosuppression with the addition of temsirolimus to standard chemotherapy, 3 dose levels of temsirolimus (15 mg, 20 mg, and 25 mg) are planned. The doses of the standard chemotherapeutic agents (carboplatin, paclitaxel) are fixed. Dose escalation beyond temsirolimus 25 mg weekly is not planned because this is the FDA-approved dose for this agent in advanced renal cell cancer [24].

3.6 Rationale for Tissue Correlates

Basic and preclinical studies from the laboratories of Dr. Wendel and others have established the striking synergy of drugs like temsirolimus with conventional chemotherapeutic drugs, and revealed a strong dependence of this anti-tumor effect on the genetics of the tumor [32-33]. Accordingly, Secondary Aim 2.2.4 of the protocol is "To identify potential molecular markers of resistance to mTOR inhibition in tumor specimens obtained as part of routine clinical care." The intent of this secondary aim is to collect pilot data that may guide the development of a new HNSCC research program in Dr. Wendel's lab.

Our working hypothesis is that HNSCC tumors with constitutive activation of the Akt/mTOR pathway (i.e. due PI3K mutation or PTEN loss) will be associated with responsiveness to temsirolimus-based treatment, and HNSCC tumors with lesions that act downstream of mTOR (ie, eIF4E) or disable apoptosis (bcl-2 or loss of p53) will be associated with resistance to temsirolimus-based treatment.

HNSCC is a genetically heterogeneous disease and we have assembled a panel of cell lines that represents this heterogeneity. Specifically, we will study cell lines with known mutational activation of the Akt-mTOR signaling pathway, such as Detroit 562 cells, which harbor a PIK3CA mutation [34], RPMI 2650 cells that activate mTOR via a LKB1 exon 5 missense mutation [35], the FaDu line lacks PTEN [36]. We will also include cell lines harboring mutations in apoptotic regulators, such as SCC-15, which is p53 mutant and expresses high levels of Bcl2 [37]. Lines like CAL27 [38], SCC-25 [39] are less well characterized and will be examined here. Finally, while A549 cells are not primarily HNSCC, but a pathologically similar lung cancer line, this line is especially interesting as it maintains an intact mTOR-mediated feedback signal that has been reported to counter the cellular effects of mTOR inhibition [40]. Thus, these cell lines represent the major types of genetic lesions seen in HNSCC.

We will analyze these HNSCC lines for markers that have been implicated in rapamycin (temsirolimus) responses. Briefly, we will use established assays (immunoblot, expression and sequence analyses) to probe mTOR activation, parallel and downstream signaling pathways, and regulators of cell death. These cell lines will also provide us with an opportunity to evaluate response patterns to temsirolimus in a panel of HNSCC lines, and to identify associations with marker expression as determined above. Ultimately, these in vitro studies will inform our interpretation of data obtained from clinical specimens.

The proposed tissue correlative studies, which are described in Section 9.2 of this protocol, build largely on previous investigations of PI3K/Akt/mTOR signaling in other tumor types by Dr. Wendel. Key observations from this body of work include the following:

1) There is dramatic synergy of mTOR inhibition with chemotherapeutics in vivo [33, 41].
2) This effect was strictly dependent on the tumor genotype, e.g. PTEN, Akt, Rheb and TSC2 were positive and Bcl2 negative predictors [42].
3) The eIF4E translation factor is an oncogene in vivo and can block responses to rapamycin [33]. Of note: eIF4E is an independent predictor of outcome in HNSCC [43].
4) eIF4E functions in cancer require the eIF4E kinase MNK [44-45].
5) Direct mTOR activation by the Rheb GTPase is sufficient for oncogenesis [46].
6) Tumors that express Rheb are particularly sensitive to rapamycin (temsirolimus) and that inhibitors of farnesyltransferase direct block Rheb activity [47].
7) Apoptotic regulators including p53 or Bim, and also parallel kinase pathways (e.g. Pim kinases) can affect rapamycin (temsirolimus) activity in vivo [42, 48].
8) Levels of the anti-apoptotic Mcl1 protein are regulated by mTOR and eIF4E. Moreover, Mcl1 can block the therapeutic effect of mTOR inhibition [46, 49].

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be an open-label non-randomized phase I/II study open at MSKCC and regional network affiliates.

4.1.1 Part I (Phase I)

Part 1 (phase I) features three planned dose levels.

Note: The dose escalation plan was revised in August 2010, and patients were enrolled on dose level 2 of the revised protocol.

Table 1: Phase I Dose Levels (21 day cycle)

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1 (starting dose)	N/A	N/A	N/A
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Cycle length is 21 days. If 0/3 patients experience DLT during Cycle 1 at a given dose level, 3 patients will entered at the next higher dose level. If 1/3 patients experienced DLT during Cycle 1, 3 additional patients will be entered at this dose level (for a total of 6).

If none of these additional 3 patients experience DLT during Cycle 1, escalation to the next higher dose level will take place. If at least one of the additional patients experience DLT during Cycle 1, the MTD is exceeded.

If the MTD is exceeded at a dose level, patients may be enrolled at the next lower dose level. This lower dose at which patients tolerate the combination would then become the phase II recommended dose if no more than 1/6 patients experience a DLT during Cycle 1.

There will be no escalation beyond Level 3. If 0/3 or 1/3 patients experience dose-limiting toxicity at Level 3, this dose level will be expanded to 6 patients. If no more than 1/6 patients experience DLT at Level 3, this will be the phase II recommended dose.

Adverse events (AEs) will be assessed according to NCI common toxicity criteria (CTC) version 3.0. Dose Limiting Toxicity (DLT) include all **toxicities of grade 3 or higher, with the exception of those listed below:**

The following will **not** be considered to be DLT:

- Grade 3 dysphagia and/or grade 3 odynophagia (pain) (even if PEG tube is required), if the investigator's impression is that dysphagia/odynophagia is due to head and neck cancer
- Grade 3 or 4 lymphopenia
- Grade 3 fatigue
- Grade 3 acneiform rash
- Grade 3 hypomagnesemia
- Grade 3 diarrhea lasting $\leq$ 48 hours
- Grade 3 nausea and/or grade 3 vomiting lasting $\leq$ 72 hours
- Uncomplicated Grade 3 or 4 neutropenia lasting $\leq$ 7 days
- Grade 3 thrombocytopenia
- Grade 3 low hemoglobin, even if treatment is given with stimulators of erythropoiesis or pack red blood cell transfusions
- Non-infectious pneumonitis, because this is an uncommon temsirolimus-related toxicity that is not strictly related to the dose levels in this study
- Deep vein thrombosis or pulmonary embolus, because such events are common in patients with cancer and are not strictly related to chemotherapy dose
- Hypersensitivity reaction to any of the study drugs regardless of grade, because such events are not strictly dose-related.
- Grade 3 hyperglycemia
- Uncomplicated Grade 4 hyperglycemia for $\leq$ 24 hours
- Grade 3 hypercholesterolemia
- Uncomplicated Grade 4 hypercholesterolemia for $\leq$ 7 days
- Grade 3 hypertriglyceridemia
- Uncomplicated Grade 4 hypercholesterolemia for $\leq$ 7 days
- Grade 3 hypokalemia
- Grade 3 hypocalcemia
- Grade 3 hypophosphatemia
- Grade 3 leukopenia

4.1.2 Part 2 (Phase II)

Part 2 (Phase II) of the study will open after the phase II recommended dose is established in Part 1. In Part II, all patients will be treated at the phase II recommended dose.

In the first stage of this design, 11 patients will be accrued. If 2 or less patients among the first 11 patients have a response after 2 cycles of treatment, then the study will be terminated and declared negative. If 3 or more patients have a response, than an additional 25 patients will be accrued to the second stage. At the end of the study, if 12 or more patients have a response after 2 cycles of treatment out of a total of 36 patients enrolled, the regimen will be considered worthy of further investigation.

4.2 Intervention

In Part 1, on Cycle 1/Day 1 patients receive paclitaxel (P), carboplatin (C), and temsirolimus (T) intravenously on Days 1 and 8 of each cycle, according the dose level plan. The sequence of administration will be P→C→T, in view of preclinical data that administration of mTOR inhibitor prior to paclitaxel is suboptimal in HN cell lines [12]. Cycle 1/Day 15 marks the beginning of the rest week in the 21 day cycle. During Cycle 1, patients are evaluated for each weekly treatment in clinic. For Cycle 2 and beyond, clinic evaluation will occur on Day 1 of the cycle, and additional clinic evaluations may be scheduled as needed on other dates. During the rest week at the end of Cycle 2, patients undergo response assessment imaging (CT and/or MRI) of sites of measurable disease. Patients may remain on study until time of progression of disease and/or unacceptable toxicity.

In view of the available PK evidence regarding everolimus + paclitaxel [1], everolimus + cisplatin [2], and the planned phase I study temsirolimus + q 3 week paclitaxel + carboplatin [3], PK studies are not planned in Part 1 of this study.

In Part 2, of the study, patients are treated according to schedule used in Part 1, at the phase II recommended dose established in Part 1. Adverse event management guidelines, including dose reductions for toxicity, will be provided in Section 11 of this protocol document.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Temsirolimus

Availability

Temsirolimus is provided by Pfizer in kits containing 25 mg/mL temsirolimus plus a 1.8 mL diluent vial.

Storage and Stability

Temsirolimus should be stored at refrigerated temperature (2 – 8 C). Do not freeze. Protect vials from light. Reconstituted vials are stable for 24 hours at room temperature in the original vial. Infusions prepared in Normal Saline are stable for 6 hours.

Preparation and Administration

Temsirolimus must be diluted prior to infusion. Inject 1.8 mL of the diluent into the vial of temsirolimus injection. The temsirolimus vial contains an overfill of 0.2 mL (30 mg/1.2 mL). Therefore, addition of the diluent yields a concentration of 10 mg/mL, with a total volume of 3 mL. Mix well by inversion of the vial. Allow sufficient time for air bubbles to subside.

Do not use PVC infusion bags or infusion sets. Add the calculated dose to 250 mL NS. Dispense infusions in amber bag. Premedication with diphenhydramine 25 – 50 mg IV should be given to prevent/reduce the severity of reactions, at the discretion of the investigator. Administer temsirolimus as an IV infusion over approximately 30 minutes.

Toxicities

Metabolic: hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypophosphatemia, hypokalemia

Hematologic: anemia, thrombocytopenia, leukopenia, lymphopenia

Gastrointestinal: mucositis, anorexia, nausea, vomiting, diarrhea

Renal: elevated serum creatinine, renal failure

Hepatic: elevated liver function tests

Pulmonary: dyspnea, cough, interstitial lung disease (ILD)

Reproductive: possible infertility; may be teratogen

Miscellaneous: fatigue, asthenia, moderate-severe hypersensitivity reactions, abnormal wound healing, rash, edema, headache, temporary muscle and joint aches/pains

5.2 Paclitaxel

Availability

Paclitaxel is commercially supplied as a non-aqueous solution intended for dilution with suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available as 30 mg (5ml), 100 mg (16.7 ml) and 300 mg (50 ml) multiuse vials.

Storage and Stability

Unopened vials of paclitaxel are stable until the date indicated on the package when stored between 20 – 25 C, in the original package. Neither freezing nor refrigeration adversely affects the stability of the product. Upon refrigeration, components of the paclitaxel vial may precipitate, but will re-dissolve upon reaching room temperature with little or no agitation.

Preparation and Administration

Prior to infusion paclitaxel should be diluted in 0.9% Sodium Chloride injection or 5% Dextrose injection or 5% Dextrose and 0.9% Sodium Chloride or 5% Dextrose in Ringers Lactate to a final concentration of 0.3 to 1.2 mg/mL. Paclitaxel must be prepared in glass, polypropylene or polyolefin containers and non-PVC containing infusion sets. Prepared solutions are stable at room temperature (20-25 C) and protected from light, up to 72 hours. In-line filtration with micropore no greater than 0.22 micron filter is required. Chemo dispensing pin devices or similar devices should not be used with paclitaxel vials since they can cause the stopper to collapse resulting in loss of sterile integrity

Safety Precautions – Paclitaxel

Paclitaxel does not contain antimicrobials; therefore, extreme care must be taken to ensure sterility of the prepared solution.

Subjects should be pre-medicated to reduce risk of severe hypersensitivity reaction. Decadron pre-medication prior to paclitaxel will follow institutional guidelines, and may be tapered at the discretion of the investigator.

Toxicities

Hematologic: neutropenia, leukopenia, thrombocytopenia, anemia

Gastrointestinal: nausea/vomiting, diarrhea, mucositis

Hepatic: elevated liver function tests

Cardiac: heart block, bradycardia

Neurologic: peripheral neuropathy, arthralgia/myalgia

Dermatologic: alopecia, onycholysis

Reproductive: Infertility; may be teratogen

Miscellaneous: moderate – severe hypersensitivity reactions, flushing, rash, dyspnea, fatigue

5.3 Carboplatin

Availability

Carboplatin is commercially supplied as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 250 mg of the drug, in equal parts by weight with mannitol.

Storage and Stability

Carboplatin in unopened vials is stable for as long as three years when stored at temperatures of 15-30 C and when protected from light.

Preparation

Immediately prior to use, each vial of carboplatin should be reconstituted with either sterile water for injection, D5W, or sodium chloride injection, in sufficient volume to produce a carboplatin concentration of 10 mg/ml.

Administration

IV infusion over 30 minutes. Do not use aluminum products in the mixing or administration of carboplatin because aluminum may react with it and cause potential loss of potency. Anti-emetics generally will follow institutional guidelines, but may be altered at the discretion of the investigator.

Toxicities

Hematologic: leukopenia, anemia, thrombocytopenia

Gastrointestinal: anorexia, nausea, vomiting, hyperbilirubinemia, elevated liver enzymes.

Renal: rarely, alterations in renal function are seen.

Neurosensory: sensory neuropathy, tinnitus, high frequency hearing loss

Reproductive: Infertility; may be teratogen

Miscellaneous: rarely, severe allergic reaction; hair thinning and hair loss

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

6.1.1 Patients must have microscopically confirmed head and neck squamous cell carcinoma (HNSCC), recurrent and/or metastatic.

Note: Confirmation of HNSCC may be obtained from the primary site or metastatic disease.

6.1.2 Patients must be at least 18 years of age.

6.1.3 Karnofsky Performance status must be ≥ 70%.

6.1.4 Disease must be measurable by RECIST criteria.

6.1.5 At least 6 weeks must have elapsed from previous radiation therapy. Patient must have recovered from the acute toxic effects of treatment prior to study enrollment.

6.1.6 Adequate organ function, as follows:

Adequate bone marrow reserve: absolute neutrophil count (ANC) ≥ 1.5 X 10^9/L, platelets ≥ 100 X 10^9/L, and hemoglobin ≥ 9 g/dL.

Hepatic: total bilirubin within normal limits (≤ 1.0 mg/dL); alkaline phosphatase (AP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 X ULN (upper limit of normal)

Renal: Serum creatinine ≤ 1.3 mg/dL. Patients with serum creatinine > 1.3 mg/dL may be eligible if creatinine clearance (CrCl) ≥ 45 mL/min based on the standard Cockroft and Gault formula.

6.1.7 Patients of childbearing potential must have a negative serum pregnancy test within 14 days of treatment. Patients must agree to use a reliable method of birth control during and for 3 months following the last dose of study drug.

6.1.8 Patients must sign an informed consent document.

6.2 Subject Exclusion Criteria

6.2.1 Previous exposure to temsirolimus or other mTOR inhibitors

6.2.2 More than 2 prior cytotoxic regimens in the recurrent/metastatic disease setting

6.2.3 History of any brain metastases

6.2.4 Patients who require concomitant medications that are metabolized by hepatic CYP3A4, due to potential drug-drug interaction with temsirolimus (prohibited medication list provided in Appendix A.)

6.2.5 Patients with known active interstitial pneumonitis

6.2.6 Active infection or serious underlying medical condition that would impair the patient's ability to receive protocol treatment.

6.2.7 Women who are pregnant or lactating

6.2.8 Other active malignancy, other than indolent malignancies which the investigator determines are unlikely to interfere with treatment and safety analysis

6.2.9 Diagnosis of Nasopharyngeal cancer is excluded.

6.2.9 Patients with multifocal peripheral sensory alterations or paresthesias (including tingling) interfering with function, per patient report (example: activities of daily living)

6.2.10 Therapeutic anticoagulation with Coumadin (warfarin)

6.2.11 Hypertriglyceridemia $\geq$ grade 2 (CTCAE version 3.0).

6.2.12 Impaired lung function: O2 saturation 88% or less at rest on room air by Pulse Oximetry. If O2 saturation is $\leq$ 88% at rest, further pulmonary function tests (PFTs) should be ordered to confirm normal pulmonary function and eligibility.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). Patient recruitment will occur in medical oncology clinics of the Head and Neck Disease management team at main campus and in medical oncology clinics of MSKCC regional network sites. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

8.0 PRETREATMENT EVALUATION

8.1 Required Data

8.1.2 Complete medical history including current medications, physical examination including evaluation of Karnofsky performance status.

8.1.3 Pathology review at MSKCC must confirm diagnosis of HNSCC prior to treatment. Confirmation of HNSCC may be obtained from the primary site or metastatic disease.

8.1.4 The following laboratory studies will be obtained within 21 days prior to therapy: Complete blood count with white blood cell differential and platelet counts; Comprehensive profile (including electrolytes, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, and glucose); lipid panel; prothrombin time and activated partial thromboplastin time.

8.1.5 Serum pregnancy test for women of childbearing potential within 14 days prior to therapy.

8.1.6 Electrocardiogram within 8 weeks prior to therapy

8.1.7 Radiologic imaging of neck (preferably, CT scan or MRI), chest (preferably, CT scan), and any other sites of measureable disease will be obtained within 4 weeks prior to therapy. Dermal lesions may be evaluated by physical exam, supplemented by photographs.

8.1.8 CT scan of the chest (with or without contrast).

9.0 TREATMENT/INTERVENTION PLAN

9.1 Schedule of Events

9.1.1 Every attempt will be made to administer chemotherapy on schedule. Treatment may be given 2 working days before or after the scheduled date, if necessary. Treatment delay of up to 21 days may be allowed for medical or personal reasons. Reasons for treatment delay will be outlined in the medical record.

9.1.2 To faciliate the timely administration of chemotherapy on treatment days, CBC and BMP with magnesium level may be obtained 1 calendar day prior the chemotherapy treatment date, if need be. For Day 1 of each cycle, liver Function Tests and Lipid Panel may be obtained within 7 calendar days prior to the chemotherapy treatment date, if need be. For Cycle 1 only, Liver Function Tests and Lipid Panel are optional if previously obtained within 14 days prior.

9.1.3 On (or before, See Section 9.1.2) Day 1 of each cycle, complete blood count and basic metabolic panel with magnesium level, liver function tests, and lipid panel will be checked.

Note in clarification: Lipid panel results are not necessary to clear a patient for treatment.

9.1.4 Patients will be examined on Day 1 of each cycle. During Cycle 1 of the Phase I portion of the study patients will be evaluated for each weekly treatment in clinic by physician and/or nurse. After Cycle 1 in Phase 1, the requirement will be one MD clinic visit per cycle, with additional clinic visits scheduled as needed. In Phase II of the study, again the requirement will be one MD clinic visit per cycle, with additional clinic visits scheduled as needed.

9.1.5 On Day 1 and Day 8 of each Cycle, patients receive paclitaxel (P), carboplatin (C), and temsirolimus (T) intravenously according the dose level plan. The sequence of administration will be P→C→T.

Carboplatin dose iscalculated according to the Cockcroft and Gault Method. For Cycle 1/Day 1 dose, the investigator (at his/her discretion) may use either (a) the serum creatinine and body weight measurements obtained on Cycle 1/Day 1, or (b) the most recent serum creatinine and body weight measurements prior to Cycle 1/Day 1, if this was obtained within 21 days prior to therapy.

For overweight patients (body mass index ≥ 27), adjusted body weight is allowed for the calculation of carboplatin and paclitaxel dosing in this protocol [50], but is not mandatory, at the discretion of the investigator.

The study will adhere to recent FDA guidelines regarding capping of carboplatin dosage (http://www.hematology.org/News/?filter_Id=335). Specifically, the FDA recommends capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses were calculated as follows in the recent FDA memorandum regarding carboplatin dosing:

Total Carboplatin Dose (mg) = (target AUC) x (GFR +25) [Calvert formula]

Maximum Carboplatin Dose (mg) = target AUC (mg•min/mL) x (150 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 1.5, the maximum dose is 1.5 x 150 = 225 mg
For a target AUC = 1, the maximum dose is 1 x 150 = 150 mg

9.1.6 On Day 15 of each cycle, patients begin the rest week.

9.1.7 Guidelines for dose reductions are provided in Section 11.

If carboplatin dose reduction is not required at the completion of a cycle, the investigator may use the same "flat dose" of carboplatin for the next cycle. Alternatively, at his/her discretion, the investigator may re-calculate the dose of carboplatin for Day 1 of the new cycle, according the Cockcroft and Gault Method, as discussed in Section 9.1.5.

9.1.8 Radiologic imaging of indicator lesions will be performed after every 2 cycles of therapy. Either CT scans and/or MRI scans will be performed to evaluate a particular lesion. Additional imaging may be obtained as clinically indicated. Dermal lesions may be evaluated by physical exam, supplemented by photographs.

Radiologic response assessment typically will take place during the "break week" of each even-numbered cycle. For patients who develop intercurrent medical problems or logistical issues, response assessment and study treatment may be delayed at the discretion of the treating physician.

9.1.9 Treatment may be discontinued at any time for progression of disease, unacceptable side effects, life-threatening toxicity, patient request, or investigator judgment.

9.1.10 At any time after 6 cycles of study treatment, patients who maintain stable disease (or better) have the *option* of remaining on treatment with temsirolimus alone. The temsirolimus dose and schedule would be unchanged (2 weeks on, 1 week off). However, a clinic visit with laboratory studies would only be required on week 1 of each cycle for patients who opt to receive temsirolimus alone. Response assessment interval typically would remain q 2 cycles. (For patients who remain on study beyond the imaging assessment at the end of cycle 6, the interval of subsequent response assessment imaging studies may be increased to q3 cycles, at investigator discretion.) For any patient who opts to receive temsirolimus alone after 6 cycles, the reasons for the treatment change will be documented in a clinic note.

Alternatively, patients may continue to receive temsirolimus + carboplatin + paclitaxel, per protocol, after completion of 6 cycles of treatment. If a patient opts to receive temsirolimus alone, he/she will not be allowed to receive additional carboplatin + paclitaxel on the study.

9.2 Correlative Studies

Secondary Aim 2.2.4 of the protocol is "To identify potential molecular markers of resistance to mTOR inhibition in tumor specimens obtained as part of routine clinical care." We expect to collect approximately 30 HNSCC tissue paraffin-embedded specimens from patients enrolled in the clinical study. No research biopsies are planned in the course of the study.

Tissue correlates will be performed on biopsy or surgical pathology material that was obtained as part of routine care at time of diagnosis or at any point in the management of the patients HNSCC. Tumor tissue from the primary site or from a metastatic deposit would be considered to be acceptable for purposes of the study.

To characterize the expression patterns of biomarkers, conventional immunohistochemistry (IHC) or tissue microarray (TMA) analysis will be performed. Dr. Wendel's group has used the same TMA analyses in hematopoietic cancers before and is experienced with the techniques and the antibody and staining parameters [51-52]. In the Core Facility of the Department of Pathology, Dr. M. Drobnjak will supervise tissue TMA construction from all patient samples (typically, paraffin sections approximately 5 μm thick) as previously described [51-55]. Normal squamous epithelium will be included as negative controls with each array. For biopsies where material is inadequate for TMA construction, immunohistochemistry will be performed on whole mount tissue sections instead.

We have established positive and negative controls for each antibody to ensure correct interpretation of stains [51-52]. Antibodies to be used in TMA interrogation include: total and phosphorylated eIF4E (Cell Signaling, #9742 and #2215); total and phosphorylated 4E-BP1 (Cell Signaling, #9644 and #2855), total and phosphorylated (Ser 473) Akt (1:1000; Cell Signaling #9272, #9271); total and phosphorylated (Ser240/244) ribosomal S6 (1:1000; Cell Signaling, #2317, #2215); p53 (1:500; Novocastra, NCL-p530505); p21 (1:1000, Santa Cruz Biotechnologies, c-19); Rheb (1:1000; Cell Signaling, #4935); MCL1 (1:1000, Santa Cruz Biotechnologies, S-19); Actin (1:5000; Sigma, AC-15); and anti-HA (1:5000, Roche, #12013819).

If sufficient tissue is available, we will also perform genomic analysis. DNA will be extracted from FFPE surgical pathology samples. We will perform the MSK-IMPACT assay (Integrated Mutation Profiling of Actionable Cancer Targets), as follows. Barcoded sequence libraries will be prepared (Kapa Biosystems, New England Biolabs) according to a modified protocol. We will perform exon capture on barcoded pools of libraries by hybridization (Nimblegen EZ SeqCap) using custom oligonucleotides to capture all exons and select introns of approximately 279 cancer genes. These oligonucleotides have been optimized to achieve uniform sequence coverage across all targets. The resulting selected libraries will be sequenced on an Illumina HiSeq 2000 and analyzed for somatic point mutations, small indels, copy number amplifications and deletions, and structural rearrangements.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Pre-Rx[a]	Day 1 (of 21)[g]	Day 8 (of 21)[g]	Day 15 (of 21)[g]
Dx HNSCC	X			
Carboplatin		X	X	
Paclitaxel		X	X	Break Week
Temsirolimus		X	X	
H and P[b]	X	X		
Complete blood cell counts (CBC)[c]	X	X	X	
Basic Metabolic Panel (BMP), with magnesium[c]	X	X		
Liver Function Tests (LFTS), Lipid Panel[c,d]	X	X		
PT, aPTT	X			
EKG	X			
Pregnancy Test[e]	X			
Imaging Studies[f]	X			
Adverse Event Monitoring		Continuous Monitoring for Adverse Events		

[a] See Section 8 for required time frames for pre-treatment studies

[b] During Cycle 1 of the Phase I portion of the study, patients will be evaluated for each weekly treatment in clinic by physician and/or nurse. After Cycle 1 in Phase 1, the requirement will be one MD clinic visit per cycle, with additional clinic visits scheduled as needed. In Phase II of the study, the requirement will be one MD clinic visit per cycle, with additional clinic visits scheduled as needed.

[c] To faciliate the timely administration of chemotherapy on treatment days, CBC and BMP with magnesium level may be obtained 1 calendar day prior the chemotherapy treatment date, if need be. For Day 1 of each cycle, Liver Function Tests and Lipid Panel may be obtained within 7 calendar days prior to the chemotherapy treatment date, if need be.

Note in clarification: On Day 8, the only required lab test is CBC.

[d] For Cycle 1 only, Liver Function Tests and Lipid Panel are optional if previously obtained within 14 days prior.

[e] Serum pregnancy test for women of childbearing potential within 14 days prior to therapy.

[f]Radiologic imaging (CT scan and/or MRI of neck, CT chest [with our without contrast], and appropriate imaging of other sites of measureable disease) will be obtained at baseline and after every 2 cycles to assess for response to treatment (Please see Section 9.1.10 regarding option to perform subsequent imaging q3 cycles for patients who remain on study after the imaging studies at end of cycle 6). For patients who do not follow up at MSKCC after completion of study treatments, the investigator and/or the study team may attempt to contact the patient by telephone for intermittent follow up.[g] Treatment may be given 2 working days before or after the scheduled date, if necessary. Treatment delay of up to 21 days may be allowed for medical or personal reasons. Reasons for treatment delay will be outlined in the medical record.

11.0 TOXICITIES/SIDE EFFECTS

11.1 Toxicity management: general considerations

Potential toxicities of Temsirolimus, Paclitaxel, and Carboplatin are discussed in Section 5 of this protocol. The following sections provide guidelines for mandatory dose delays and/or dose reductions for treatment-related toxicities.

For patients who experience more than one toxicity, it is possible that subsections 11.2-11.12 may provide conflicting recommendations for dose reductions. If a patient experiences more than one toxicity requiring dose delay and/or dose reduction and there are conflicting recommendations for each, the investigator will select the reduction to the lower dose and/or the longer treatment delay.

Even when the patient meets criteria for continued treatment at full dose per the protocol, the investigator retains the discretion to delay the next treatment and/or reduce dose if there are safety concerns and/or logistical issues. Any dose reductions not specified in the protocol should be discussed with the principal investigator.

Any patient who requires dose reduction in temsirolimus below 15 mg weekly will be removed from study. Any patient who requires reduction in paclitaxel below 60 mg/m^2 weekly will be removed from study. Any patient who required reduction in carboplatin below AUC 1 will be removed from study.

Doses that have been reduced for toxicity must not be re-escalated.

Treatment delays of up to 21 total days per cycle in temsirolimus (and/or carboplatin and/or paclitaxel) are allowed.

In the phase I portion of the study, dose reductions are not allowed during cycle 1. Patients who require dose reduction during cycle 1 will be removed from study. Sections 11.2 -11.12 provide toxicity management guidelines for patients in the phase II portion of the study, and for patients in the phase I portion of the study who have completed at least one cycle of treatment.

11.2 Hematologic Toxicity Management

The dose reduction plan reflects concern for the potential of temsirolimus to worsen the myelosuppression associated with carboplatin and paclitaxel. As such, the initial dose reductions are for the study drug, temsirolimus.

The following dose reduction table will be used for myelosuppression:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
Minus 1	15 mg	60 mg/m^2	AUC 1.0
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1.

Day 1 of Cycle

ANC (K/mcL) and Platelet Count (K/mcL)
ANC ≥ 1.5 and Plts ≥ 100: Treat without dose reduction
ANC < 1.5 and/or Platelets <100: Hold. If repeat ANC the next week ≥ 1.5 and repeat Plts next week ≥ 100, resume treatment. Dose reduction by one dose level is not mandatory, but is allowed at the discretion of the investigator.
*Febrile Neutropenia**: Hold until resolution. When ANC ≥ 1.5 and afebrile and Plts ≥ 100, may proceed but reduce by 1 dose level

Day 8 of Cycle (ie, treatment week 2 of Cycle)

ANC (K/mcL) and Platelet Count (K/mcL)
ANC ≥ 1.0 and Plts ≥ 75: Treat without dose reduction
ANC < 1.0 and/or Platelets <75: Hold. If repeat ANC the next week ≥ 1.0 and repeat Plts next week ≥ 75, resume treatment without dose reduction
*Febrile Neutropenia**: Hold until resolution. When ANC ≥ 1.5 and afebrile and Plts ≥ 100, may proceed but reduce by 1 dose level

For patients who require dose reductions on Day 8 (ie, treatment week 2 of the Cycle), the dose reduction will also apply to carboplatin on Day 1 of the next cycle.

**Febrile neutropenia*: The definition of febrile neutropenia is ANC < 1.0 and fever ≥ 38.5°C (CTCAE v. 3.0). Any patient with febrile neutropenia will undergo appropriate pre-antibiotic evaluation and will be admitted to hospital for empiric antibiotic therapy. At the discretion of the investigator, inpatient hospitalization for empiric antibiotics may be instituted for any patient with ANC ≤ 1.5 and fever ≥ 38.0°C.

Use of stimulators of erythropoiesis is allowed, according to established guidelines.

11.3 Hepatic Toxicity Management

This section provides guidelines for dose delays and reductions for the first incidence of hepatic toxicity. Temsirolimus, paclitaxel, and carboplatin can be associated with abnormalities in liver function tests (LFTs). Because of concern for the potential of the study drug (temsirolimus) to worsen LFT abnormalities associated with the standard drugs (carboplatin and paclitaxel), the initial dose reductions are for the study drug temsirolimus.

The following dose reduction table will be used for hepatic toxicity:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1and 8
Minus 1	15 mg	60 mg/m^2	AUC 1
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1.

11.3.1 Alkaline Phosphatase, ALT, AST

Both AST and ALT should be drawn. The more abnormal of the two values (AST or ALT) should be used in determining the dose.

	AST or ALT:			
ALK PHOS:	**≤ ULN**	**>1X but ≤1.5X ULN**	**>1.5X but ≤5X ULN**	**>5X ULN**
≤ 1.5 X ULN	Full Dose	Full Dose	Treat at Full Dose, Or Treat at Reduced Dose, Or Hold, at discretion of investigator*	Hold*,[2]
>1.5 X but ≤ 2.5X ULN	Full Dose	Full Dose	Hold or Treat at Reduced Dose, at discretion of investigator*	Hold*,[2]
>2.5X but ≤ 5X	Full Dose	Hold*	Hold*,[1]	Hold*,[2]
>5X ULN	Hold*	Hold*	Hold*,[2]	Hold*,[2]

*If treatment is held, treatment should not resume until liver function tests have "recovered", maximum 21 days. "Recovered" is defined as meeting requirements for treatment according to this table.

[1] Upon recovery, resume treatment at full dose or reduced by 1 dose level, at the discretion of the investigator.

[2] Upon recovery, resume treatment at next lower dose level

11.3.2 Bilirubin

Total bilirubin > ULN but ≤ 1.5 X ULN: May hold treatment, treat at full dose, or treat at reduced dose, at the discretion of the investigator

Total bilirubin > 1.5 X ULN: Hold treatment until serum total bilirubin is ≤ 1.5 X ULN (maximum 21 days), then re-treat at next lower dose level

11.4 Mucositis/Stomatitis

Mucositis/Stomatitis will be assessed according to clinical exam criteria. For management of musositis, supportive measures such as analgesics and oral rinses will be administered according to standard practice.

Systemic administration of **imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided** in all patients due to their potential to alter the metabolism of temsirolimus and paclitaxel. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

Temsirolimus and paclitaxel may be associated with mucositis. Because of concern for the potential of temsirolimus to cause mucositis and/or intensify mucositis associated with paclitaxel, the following table calls for initial dose reductions in temsirolimus.

The following dose reduction table will be used for mucositis:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1. If a patient at Dose Level 1 experiences mucositis that requires dose reduction, the patient will be removed from study.
Guidelines for dose reductions/dose delays are as follows:

Grade 1 or Grade 2 Mucositis: May hold, treat at full dose, or treat at next lower dose level, at the discretion of the investigator. Dose reduction is at the discretion of the investigator.

Grade 3 Mucositis: Hold until ≤ Grade 2, then resume treatment at next lower dose level
Grade 4 Mucositis: Off Study

11.5 Nausea/Vomiting

All patients will receive anti-emetics and hydration, per institutional guidelines.

The dose reduction plan reflects concern for the potential of temsirolimus to worsen nausea/vomiting associated with carboplatin + paclitaxel. As such, the initial dose reductions are for the study drug, temsirolimus.

The following dose reduction table will be used for nausea/vomiting:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
Minus 1	15 mg	60 mg/m^2	AUC 1
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1.For any patient experiencing nausea and/or vomiting, the chemotherapy treatment will be delayed until any vomiting has resolved to ≤ Grade 1 (1 episode in 24 hours) and any nausea has resolved to ≤ Grade 1 (loss of appetite without alteration in eating habits).

For any patient experiencing ≥ Grade 3 nausea and/or vomiting, treatment will be given at the next lower dose level when nausea and vomiting are ≤ Grade 1.

11.6 Diarrhea

Because of concern for the potential for temsirolimus-associated diarrhea, the initial dose reductions are for the study drug, temsirolimus.

The following dose reduction table will be used for diarrhea:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
Minus 1	15 mg	60 mg/m^2	AUC 1.5
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1.

Grade 1 or Grade 2 Diarrhea:

Chemotherapy treatment may be continued at full dose, continued at the next lower dose level, or held. Antidiarrheals may be used as needed. Dose reduction is at the discretion of the investigator.

Grade 3 Diarrhea:

In the event of diarrhea requiring hospitalization (ie, Grade 3), supportive measures may include hydration, octreotide, and antidiarrheals.

Chemotherapy treatment will be held until diarrhea has improved to ≤ Grade 1, with dose reductions as follows:

If Grade 3 diarrhea duration is ≤ 48 hours, the next treatment may be given at full dose or at the next lower dose level, at the discretion of the investigator.

If Grade 3 diarrhea duration is > 48 hours, the next cycle will be given at the next lower dose level

Grade 4 diarrhea: Off Study

11.7 Sensory Neuropathy

Paclitaxel and carboplatin can be associated with sensory neuropathy. Temsirolimus is unlikely to cause sensory neuropathy but we cannot exclude the possibility that temsirolimus could worsen to neuropathy associated with carboplatin and paclitaxel. Therefore, sensory neuropathy management features dose reductions for all three agents.

If the patient develops Grade 1 or Grade 2 sensory neuropathy, chemotherapy treatment may be given at full dose or may be held for ≤ 21 days, at the discretion of the investigator.

If a patient develops ≥ Grade 3 sensory neuropathy, treatment will be held. Upon resolution to grade 1, treatment may resume at the dose and schedule shown in the following table (regardless of the current dose level):

Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
15 mg	60 mg/m^2	AUC 1

An patient who requires reduction below this dose and schedule will be removed from the study.

11.8 Renal Toxicity Management

If serum creatinine is ≥ 1.5 on planned treatment date, estimate the creatinine clearance (CrCl) by the Cockcroft and Gault Equation.

Calculated Creatinine Clearance (CrCl)	Management
≥ 45 ml/min	Hydrate as clinically indicated. May treat at full dose, treat at next lower dose level, or hold treatment, at the discretion of the investigator.
< 45 ml/min	Hold treatment for the week and hydrate as clinically indicated. If repeat CrCl ≥ 45 ml/min, may resume treatment at the next lower dose level.

Carboplatin and temsirolimus may be associated with renal toxicity. Paclitaxel is unlikely to cause renal toxicity. Therefore, dose reduction for renal toxicity involves carboplatin and paclitaxel.

For patients who require dose reduction for renal toxicity, upon resolution of renal toxicity (ie, creatinine clearance ≥ 45 ml/min) treatment will be at the reduced doses shown in the following table:

Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
15 mg	80 mg/m^2	AUC 1

If a patient requires dose reduction during the middle of a cycle (ie, the Day 8 or Day 15 dose), the dose reduction will continue for subsequent cycles as well.

Any patient who requires reduction below the temsirolimus dose (15 mg) or the carboplatin dose (AUC 1) will be removed from study.

11.9 Dermatologic Toxicity

Temsirolimus and has been associated with rash. Paclitaxel is less likely to be associated with rash. As such, the toxicity management plan calls for dose reductions in temsirolimus.

The following dose reduction table will be used for rash:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Dose reductions begin from the patient's current dose level. For example, if a patient is being treated at Dose Level 2 and requires dose reduction, his next treatment would be at Dose Level 1. If a patient at Dose Level 1 experiences rash that requires dose reduction, the patient will be removed from study.

Grade 1: No specific supportive care is usually needed or indicated.

Grade 2: May treat with supportive measures, at the discretion of the investigator. Options include: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, and oral prednisone (short course). Interruption of chemotherapy will be at the discretion of the investigator. Dose reductions are not necessary.

Grade 3: Hold chemotherapy treatment until resolution $\leq$ Grade 2. The need for oral or topical treatments will be at the discretion of the investigator and may be accompanied by a culture of the affected area and a dermatology consult. When toxicity resolves to Grade 2 or better, the patient may resume treatment at the next lower dose level.

Grade 4: Off Study

11.10 Hyperlipidemia

Lipid panel is checked according on the dates indicated in Section 10.

Temsirolimus and has been associated with hyperlipidemia. As such, the dose reduction scheme calls for dose reductions in temsirolimus.

The following dose reduction table will be used for hyperlipidemia:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Any patient who is being treated at the lowest dose level of temsirolimus (15 mg weekly) who meets criteria for further temsirolimus dose reduction will be removed from study.

Grade 1 hypercholesterolemia (> upper limit of normal to 300 mg/dL or 7.75 mmol/L) or grade 1 hypertriglyceridemia (> upper limit of normal to 2.5X upper limit of normal): Continue chemotherapy treatment without any dose reductions. A statin or appropriate lipid-lowering agent may be started at the discretion of the investigator.

Grade 2 hypercholesterolemia (> 300 - 400mg/dL, or >7.75 - 10.34 mmol/L) or grade 2 hypertriglyceridemia (> 2.5 -5.0 X upper limit of normal): Continue chemotherapy treatment without any dose reductions. A statin or appropriate lipid-lowering medication should be used in addition to diet, per investigator'rs discretion.

≥Grade 3 hypercholesterolemia (> 400 mg/dL or > 10.34 mmol/L) or ≥ grade 3 hypertriglyceridemia (> 5X upper limit of normal): Hold chemotherapy treatment. A statin or appropriate lipid-lowering medication should be used in addition to diet, per investigator'rs discretion. When toxicity resolves to Grade 2 or better, may resume treatment at full dose or at the next lower dose level, at the discretion of the investigator.

11.11 Interstitial Lung Disease (ILD)

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving temsirolimus therapy. Any patient who develops any new or worsening pulmonary symptoms (ie, dyspnea and/or cough) should undergo either chest X-ray and/or CT scan of the chest.

The dose reduction scheme calls for dose reductions in temsirolimus.

The following dose reduction table will be used for ILD:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Any patient who is being treated at the lowest dose level of temsirolimus (15 mg weekly) who meets criteria for further temsirolimus dose reduction will be removed from study.

Management on Interstitial Lung Disease (ILD)

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Chemotherapy Treatment
Grade 1	Chest X-ray and/or CT scans of chest. Consider pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat chest x-ray/CT scan every 2 months until return to baseline.	No specific therapy is required	May continue at Full Dose, Continue at next lower dose level, or hold treatment for up to 21 days, at the discretion of the investigator
Grade 2	CT scan of chest. Consider pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat imaging each month until return to baseline. Consider bronchoscopy	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	May continue at Full Dose, Continue at next lower dose level, or hold treatment for up to 21 days, at the discretion of the investigator
Grade 3	CT scan of chest and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Repeat imaging each month until return to baseline. Consider bronchoscopy.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to Grade 1within 21 days.
Grade 4	CT scan of chest and required pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Repeat imaging each month until return to baseline. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

11.12 Toxicities Not Otherwise Specified

For toxicities not specifically addressed in Section 11, this subsection provides general guidelines. Because a potential role for the study drug temsirolimus may be suspected in unanticipated toxicities, the dose reduction scheme will initially call for dose reductions in the study drug, as follows:

Dose Level	Temsirolimus, Days 1 and 8	Paclitaxel, Days 1 and 8	Carboplatin Days 1 and 8
Minus 1	15 mg	60 mg/m^2	AUC 1
1	15 mg	80 mg/m^2	AUC 1.5
2	20 mg	80 mg/m^2	AUC 1.5
3	25 mg	80 mg/m^2	AUC 1.5

Any patient who requires reduction below "Dose Level Minus 1" will be removed from the study.

The general approach to toxicity management will be:

Grade 1: Treat at full dose.

Grade 2: May hold, treat at full dose, or treat at next lower dose level, at the discretion of the investigator. Dose reduction is at the discretion of the investigator.

Grade 3: Hold until ≤ Grade 2, then resume treatment at next lower dose level

Grade 4: Hold treatment. When toxicity resolves to ≤ Grade 2, may resume treatment at the next lower dose level.

The investigator retains the authority to remove any patient from study for any toxicity if he/she believes that it is in the best interest of the patient to discontinue study treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Radiologic response criteria are based on previously published RECIST guidelines [56]. At baseline, tumor lesions will be categorized as follows: Measurable: lesions that can be accurately measured in at least one dimension (longest diameter to be recorded as ≥ 10 mm with spiral CT scan); Nonmeasurable: all other lesions, including small lesions (<10 mm with spiral CT scan). All measurements will be recorded in metric notation by use of a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions. Tumor lesions that are situated in a previously irradiated area are measurable only if unequivocal growth can be documented in the baseline scan compared to a scan obtained within one month of radiation treatment.

MRI or Spiral CT scanning, using a contiguous reconstruction algorithm, will be used to characterize each identified and reported lesion at baseline and during follow-up. Intravenous contrast agents will be given, unless contraindicated for medical reasons such as allergy or other reasons, at the discretion of the treating physician. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. In patients in whom the abdomen and pelvis are being imaged, oral contrast agents should be given to accentuate the bowel against other soft-tissue masses. During physical exam assessment, clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable. The same imaging modality will be used throughout the study to measure disease, without interjection of data from ultrasound or MRI examinations, unless contraindicated for medical reasons such as allergy or other reasons, at the discretion of the treating physician

Baseline Evaluation: Only patients with measurable disease at baseline will be included in this protocol. Only known sites of disease, or areas clinically suspected of disease involvement, need be imaged. All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterize the objective tumor response. All other lesions (or sites of disease) will be identified as nontarget lesions and will also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of target lesions: Complete Response (CR): the disappearance of all target lesions; Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; Progressive Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started, or the appearance of one or more new lesions; Stable Disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

Evaluation of nontarget lesions: Complete Response (CR): the disappearance of all nontarget lesions; Stable Disease (SD): the persistence of one or more nontarget lesion(s); Progressive Disease (PD): the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Data from observation of all target and non-target lesions will be combined in order to determine overall response, according to the following table:

Target	Non-Target	New Lesions	Overall Response
CR	CR	No	CR
CR	SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated by fine-needle aspiration/biopsy or PET scan before confirming the complete response status.

The minimal time interval required between two measurements for determination of overall response is 4 weeks. The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented. Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started).

Radiologic scans will be reviewed by a designated member of the MSKCC Department of Radiology. When nonmeasurable disease is being assessed, the radiologist and attending physician will confer to determine the presence or absence of unequivocal disease progression.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

Patients may be removed from the study for protocol non-compliance.

If at any time the patient develops unacceptable toxicity he/she will be removed from study. Participants can be removed from the study at any time if the study doctor feels that it is in their best interest to do so.

14.0 BIOSTATISTICS

This is a single arm Phase I/ Phase II trial open to patients with recurrent/metastatic HNSCC who did not receive more than 2 prior cytotoxic therapies for recurrent/metastatic disease.

14.1 Part 1 (Phase 1)

The primary objective of this part is to determine the phase II-recommended dose of temsirolimus, when given in combination to paclitaxel and carboplatin. This will be the recommended dose that will be used in the Part II (Phase II) of the trial.

Patients will be treated in cohorts of size three-six and the dosage will be escalated if the clinical toxicity is acceptable. A patient is considered toxicity-free for the purpose of the trial if he/she completes the first cycle of therapy (21 days) without experiencing dose limiting toxicity (DLT, as described in section 4.1.1). If therapy is discontinued during the first cycle for reasons other than toxicity (see Section 13.0), an additional patient may be enrolled at that dose level to ensure adequate evaluation of toxicity. However, patients will not be replaced unless they cannot be evaluated for DLT in cycle 1 of the Phase I portion of the study. Three dose levels will be considered for escalation, as described in Section 4.1.1. No within-patient escalation will be performed.

The dose escalation scheme is as follows:

1. If none of the initial three patients at a given dose level experience DLT, the next dose level will be studied.
2. If one of the initial three patients at a given dose level experiences DLT, three additional patients will be treated at the same dose level. Escalation will continue only if there has been no additional DLT observed.
3. If two or more patients experience DLT at a given dose, the previous dose will be declared the maximum tolerated dose (MTD).
4. If only three patients were treated at a dose under consideration as MTD, an additional three patients will be treated at that level to confirm previous results.

The MTD will be the phase II recommended dose. However, if the MTD is not exceeded at dose level 3, then dose level 3 will be the phase II recommended dose.

The design is constructed to minimize the chances of escalating the dose when the probability of DLT is high, and maximize the chance of escalating the dose when the probability of DLT is low. The probabilities of escalating to the next dose level under this scheme for various true toxicity rates are given in the table below.

Toxicity rate	0.10	0.20	0.30	0.40	0.50
Probability of escalation	91%	71%	49%	31%	17%

A minimum of 2 and a maximum of 18 patients will be required to complete this phase of the trial. With a planned accrual of 2 patients/month, this part of the study should be completed within $\leq$ 9 months.

14.2 Part 2 (Phase II)

In Part 2, the primary endpoint will be objective radiographic response rate (CR+PR) after 2 cycles (6 weeks) of therapy. As a historical control, Gibson et al reported a response rate of 26% with cisplatin + paclitaxel as palliative therapy for patients who had not received prior chemotherapy for recurrent/metastatic HNSCC [6]. In the current study, we estimate that half of patients will receive study treatment as first line therapy for recurrent/metastatic disease. We estimate that half of the study patients will receive study treatment as second or third line therapy, for which the historical estimate for objective response rate with palliative chemotherapy is 15% [57-58]. As such, the estimated response rate for this patient population is p0= (.26 X 0.5) + (0.15 X 0.5) = 0.21.

A Simon optimal two-stage design will be employed to assess the primary endpoint of radiographic response rate (by RECIST criteria) at 6 weeks after therapy start (2 cycles). A 21% response-rate is considered not promising, a 41% response rate is considered promising, and the probabilities of a Type I error (falsely accepting a non-promising therapy) and Type II error (falsely rejecting a promising therapy) are set to 0.05 and 0.2, respectively. In the first stage of this design, 11 patients will be accrued. If 2 or less patients among the first 11 patients have a response, then the study will be terminated and declared negative. If 3 or more patients have a response, than an additional 25 patients will be accrued to the second stage. At the end of the study, if 12 or more patients have a response out of a total of 36 patients enrolled, the regimen will be considered worthy of further investigation.

We anticipate that the patient population in the study will be consistent with the historical control population as regards prior treatment. To ensure consistency between the study population and the historical control population:

- In the first part of the two stage design, no more than 6 of 11 patients will have 0 prior chemotherapy regimens for recurrent/metastatic disease, and no more than 6 of 11 patients will have had 1 or 2 prior chemotherapy regimens for recurrent metastatic disease. No more than 6 patients in each group (no previous therapy vs. 1-2 previous cycles) should be included in first part of the two stage design. Accrual in each group will stop when the maximum number of patients per group is reached.
- For the entire accrual to the phase II portion of the study, no more than 20 of 36 patients will have 0 prior chemotherapy regimens for recurrent/metastatic disease, and no more than 20 of 36 patients will have had 1 or 2 prior chemotherapy regimens for recurrent metastatic disease. No more than 20 patients in each group (no previous therapy vs. 1-2 previous cycles) should be included in the total phase II population. Accrual in each group will stop when the maximum number of patients per group is reached.

All the patients enrolled in the trial will be included in the main analysis of the objective response rate, even if there are major protocol deviations. Patients who do not complete the first two cycles of treatment (due to any of the criteria listed in Section 13.0 or to death) are considered non-responses.

The 6 patients from Part 1 who are treated at the phase II recommended dose will be included in the efficacy analysis for response rate. As such, a minimum of 5 and a maximum of 30 additional patients need to be enrolled in Part 2 to achieve the sample size of 11 to 36 evaluable patients. With an expected accrual rate of 1.5 patients/month, this phase of the study should be completed in $\leq$ 15 months.

Safety will be assessed in terms of AEs, laboratory data and vital sign data, which will be collected for all patients. Appropriate summaries of these data will be presented. AE will be listed individually per patient according to CTCAE version 3.0, and the number of patients experiencing each AE will be summarized. The safety population will comprise all patients who receive at least one dose of study treatment.

Overall survival will be estimated using Kaplan-Meier methodology, with time origin at the start of the treatment.

Data analysis for correlative studies will be descriptive. The antibodies whose expression patterns will be investigated by tissue microarray (TMA) interrogation are listed in section 9.2. For each antibody, each tumor sample will be scored as "positive" or "negative." For immunohistochemistry, positivity will be defined as at least 30% of tumor cells stained for the probed antigen [51].

We will explore if positive/negative status for each antibody may be associated with objective radiographic response to study treatment using non-parametric Wilcoxon statistics. Only patients who already have biopsy or surgical pathology material collected as part of routine care at time of diagnosis or at any point in the management of the patients HNSCC will contribute to this analysis. No research biopsies are planned in the course of the study. We anticipate that archived tissue for correlative studies will be available for approximately 30 subjects in the study.

14.3 Accrual rate

The projection of 2 accruals per month is based on prior accrual rates in the HN DMT, and also reflects the expansion of the HN research program. Our service recently completed a phase II study of gemcitabine + pemetrexed for patients with advanced HNSCC (MSK IRB 06-087). Accrual of 25 patients was completed between 10/2006 and 2/2008 (1.5 accruals per month). Our HN service included 2 medical oncologists during that time. Currently our HN group includes 3 full time medical oncologists, plus the addition of a 4th medical oncologist who will join our group in 8/2009. Of note, IRB 06-087 was open only at MSKCC main campus. For the proposed study, the four MSKCC regional network affiliates (Commack, NY; Phelps, NY; Rockville Center, NY; Basking Ridge, NJ) will be participating sites to further enhance accrual in the phase II portion of the study.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.
During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb5.mskcc.org/intranet/_assets/_tables/content/359709/DSMPlans07.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol is assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

17.2.1 SAE Reporting to Pfizer and NCCN

Adverse Event Reporting. Institution shall ensure that Investigator will report all Adverse Events to Regulatory Authorities, health authorities and the IRB as required by applicable law, within the required timeframes. Investigator also will conduct follow-up on Adverse Events as required by law.

The term "Serious Adverse Event" (or "SAE") shall mean any adverse drug experience occurring at any dose that results in any of the following outcomes: death, is Life-Threatening, as defined below, requires inpatient hospitalization or prolongation of an existing hospitalization, results in a persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, results in cancer, or results in an important medical event. Important medical events which are AEs that may not result in death, be Life-Threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the Study Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

In addition to complying with all applicable regulatory reporting laws and regulations, Institution will ensure that the Investigator report the following information to Grantor and NCCN in writing via fax within one business day of the occurrence, using the cover page provided as Appendix B hereto, and referencing the applicable Protocol number that is assigned by Grantor upon approval of the Study. Such report shall be directed to NCCN via fax at 215-358-7699 or e-mailed to ORPReports@nccn.org and to Pfizer U.S. Clinical Trial Department at 1-866-997-8322:

(a) All SAEs;

(b) Reports of pregnancy exposure (pregnancy encompasses the entire course of pregnancy and delivery, perinatal and neonatal outcomes, even if there were no abnormal findings; both maternal and paternal exposure is collected);

(c) Reports of lactation exposure;

(d) Overdose (with or without an SAE);

(e) Abuse (use for non-clinical reasons with or without an SAE);

(f) Inadvertent or accidental exposure; and

(g) Follow-up information regarding any of the above.

The Investigator should include his or her assessment of the causal relationship between each SAE and the Grantor product in the form faxed to Grantor and NCCN.

17.3 Risks, Benefits, Toxicities/side effects

Potential risks to human subjects include drug related toxicity, pain and discomfort associated with mucositis, temsirolimus side effects (Section 5.1), paclitaxel side effects (Section 5.2), carboplatin side effects (Section 5.3) , placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (eg, CT scan, PET scan). All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.

If an adverse medical event occurs, the patient will first contact the primary oncologist or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

17.4 Alternatives/options

Participation in this trial is voluntary. Depending on the specific details of the situation, patient options without being in a study might include:

- Other palliative chemotherapy off study. For example, carboplatin and paclitaxel, without temsirolimus.
- Participation in a different clinical trial
- Best supportive care

17.5 Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include the costs of carboplatin, paclitaxel, hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor's fees. Patients will not be charged for any research tests performed on research specimens.

Temsirolimus is provided by Pfizer and therefore is not billable to research participants.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.
Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A - PROHIBITED MEDICATION LIST
Appendix B - SAE FAX COVER SHEET