UMCC 2016.040: Phase II Expansion Trial Evaluating Axitinib in Patients with Unresectable Recurrent, or Metastatic Head and Neck Cancer utilizing Choi Response Criteria

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Principal Investigators: **PI: Paul Swiecicki, M.D.**

Co-Investigators & Consultants

Medical Oncology: **Co-PI: Francis P. Worden, M.D.**
Susan Urba, M.D.

Otolaryngology: **Thomas Carey, Ph.D.**

Research Staff
Nurse Coordinators: **Heidi Mason, N.P-C, M.S.N., O.C.N.**
Mary Beth DeRubeis, NP-C, M.S.N., O.C.N.
Leah Shults, RN, B.S.N., O.C.N.
Terri Jobkar, RN, B.S.N., O.C.N
Shantel Musser, RN, B.S.N

Statistician: **Emily Bellile, M.S.**

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1. INTRODUCTION

1.1. Background

Head and neck cancer comprises approximately 2-3% of all malignancies and account for about 2-3% of all cancer-related deaths (1). Ninety-five percent of all head and neck cancers are squamous cell carcinomas. Head and neck cancers (except for nasopharyngeal carcinoma) have traditionally been grouped together, based on common etiology, predisposing factors, histology, approaches to treatment (2). Only 10% of patients present with distant metastases (3). However, in the course of their illness, about half of head and neck patients present with or develop recurrent or metastatic disease (5). Prognosis in such patients is poor (7). The role of chemotherapy in this setting is palliative. Survival in patients with recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M SCCHN) is 6-9 months, even with aggressive therapy (8). Cisplatin and 5-fluorouracil have traditionally been the combination of choice in the treatment of incurable disease (2). Single agents, such as methotrexate, can be used as well. Response rates to chemotherapy are low, between 10-30% for single-agent regimens and 20-40% for multi-drug regimens (9, 10). However, the more efficacious regimens and combinations are fraught with toxicities and side effects that impair quality of life of the patients (9). Currently, targeted therapies are being developed for a variety of cancers, with good clinical activity. They have been administered in patients with R/M SCCHN with promising results (4, 9, 11). Since vascular endothelial growth factor (VEGF) plays a crucial role in tumorigenesis and metastasis of R/M SCCHN, this protocol aims to investigate clinical activity of Axitinib in this cancer type.

1.1.1. Molecular Formula and Molecular Activity

Axitinib is a substituted indazole derivative that was discovered using structure-based drug design. The molecular formula is C22H18N4OS with molecular weight of 386.47. The chemical name is N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide:

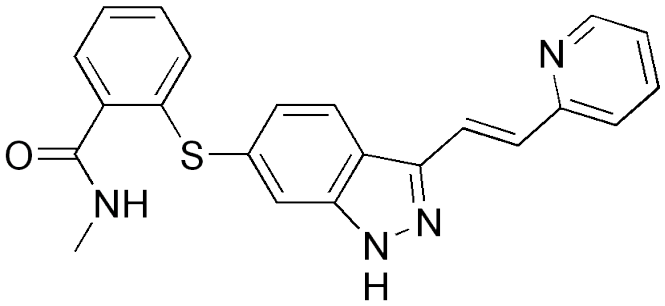


Figure 1. Molecular structure of Axitinib (AG-013736)
From: en.wikipedia.org/wiki/File:Axitinib.png

Table 1. Receptor tyrosine kinase affinities and selectivity of Axitinib (4)

Table 1. Receptor tyrosine kinase affinities and selectivity of Axitinib (4)

Target	Cell potency (IC50, nM)
VEGFR-2	0.2
VEGFR-1	0.1
VEGFR-3	0.1-0.3
PDGFR-β	1.6
KIT	1.7
PDGFR-α	5.0
CSF-1R	73
FGFR-1	231
Flt3	>1000

Wilmes et al. (12) showed by dynamic contrast-enhanced magnetic resonance imaging (MRI) that tumors formed in immune-deficient mice from breast cancer cells had decreased blood flow/permeability in Axitinib-treated animals. Animal xenogaft models also demonstrated that Axitinib inhibits angiogenesis and tumor growth of colon cancer culture cells in host animals (13).

1.1.2. Clinical activity of Axitinib

Axitinib is a substituted indazole derivative that acts as a potent inhibitor of angiogenesis. It is a receptor tyrosine kinase inhibitor of VEGF receptors 1, 2, and 3, platelet-derived growth factor (PDGF) receptor beta and c-kit (13, 14). It has been evaluated in metastatic settings in a variety of cancers.

Axitinib is FDA approved for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy.

Axitinib has been most extensively studied in renal cell carcinoma. Rixe et al. reported on efficacy of axitinib in patients with renal cell carcinoma (RCC) who failed prior cytokine treatment (15). In this study, single-agent axitinib yielded objective response rate (ORR) of 44.2%, with median duration of response of 23 months. Axitinib was also active in patients with RCC who previously progressed on sorafenib (16). In this population, Axitinib gave ORR of 22.6%, with median duration of response of 17.5 months. Median PFS was 7.4 months. A recently reported phase III trial compared Axitinib with sorafenib in patients with metastatic RCC is second-line setting (17). Median PFS was significantly longer with the former (6.7 months vs. 4.7 months, HR of 0.665, $P<0.0001$). ORR was 19.4% for axitinib and 9.4% for sorafenib ($P=0.0001$).

Axitinib has shown clinical activity in various histologic subtypes of advanced thyroid cancer, with objective response rate of 30% and stable disease in an additional 38% (18), with resultant disease control rate of 68%. Median progression-free survival (PFS) was 18.1 months.

Schiller et al. (19) reported on efficacy of axitinib in patients with advanced non-small cell lung cancer (NSCLC), mostly adenocarcinoma (75%), most were pretreated (72%). Partial response (PR) was observed in 9% of patients, disease control rate was 41%. Median PFS was 4.9 months.

Axitinib was also studied in patients with advanced pancreatic cancer in combination with gemcitabine (20, 21). An initial, phase II trial offered a promising result of improved overall survival (OS) with axitinib plus gemcitabine vs. gemcitabine alone (6.9 months vs. 5.6 months, which was not statistically significant, however). However, a subsequent phase III trial did not show any survival advantage to the combination (21).

In all of these studies, the starting dose of Axitinib was 5 mg twice a day (BID). In most studies, Axitinib dose was titrated up from a starting dose of 5 mg BID in 1 – 3 mg increments in patients tolerating Axitinib. Those subjects who could tolerate Axitinib with no adverse events related to Axitinib above Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 for consecutive 2 week periods were permitted to increase their dose step-wise to 7 mg BID and then to 10 mg BID, unless their BP was >150/90 mm Hg or the subject was receiving antihypertensive medication. All ongoing studies allow Axitinib dose reductions to as low as 2 mg BID for treatment-related adverse events. Except for an increase in hand-foot syndrome and slight increase in the incidence of hypertension, it appears that the patients dose titrated to between 6-10 mg BID doses do not experience increased toxicities if they have previously tolerated 5 mg BID starting dose.

Growth factors such as VEGF and epidermal growth factor (EGF) have been implicated in the growth of cancer cells in head and neck cancer (reviewed in ref 22, 23, 24). Therefore, a phase 2 trial of Axitinib in metastatic head and neck cancer is warranted. Furthermore, despite numerous lines of evidence suggesting that growth factors and cytokines play a role in SCCHN, these molecules and their dynamics have not been studied systematically in such patients, nor have predictive markers of response to targeted therapies been elucidated in patients with SCCHN.

1.1.3. Overall clinical safety.

Overall, the adverse events reported in Axitinib clinical studies are considered manageable, generally reversible and expected for this class of agents. A Pfizer, Inc. summary of observed Axitinib toxicity gathered on 515 subjects treated with single-agent Axitinib is listed below (Tables 2 and 3).

Table 2 Treatment-Emergent, All-Causality Adverse Events Summarized by Descending Frequency Occurring in at Least 10% of Subjects with Solid Tumors Receiving Single-Agent Axitinib (N =515, ref 6)

MedDRA Preferred Term	All Grades n (%)		Grade 3+ n (%)	
Fatigue	284	(55.1)	56	(10.9)
Diarrhoea	254	(49.3)	29	(5.6)
Hypertension	246	(47.8)	92	(17.9)
Anorexia	197	(38.3)	12	(2.3)
Nausea	177	(34.4)	6	(1.2)
Dysphonia	175	(34.0)	0	(0.0)
Palmar-plantar erythrodysaesthesia syndrome	134	(26.0)	33	(6.4)
Weight decreased	132	(25.6)	19	(3.7)
Headache	122	(23.7)	8	(1.6)
Cough	113	(21.9)	5	(1.0)
Constipation	109	(21.2)	2	(0.4)
Dyspnoea	102	(19.8)	32	(6.2)
Arthralgia	100	(19.4)	11	(2.1)
Proteinuria	95	(18.4)	15	(2.9)
Vomiting	93	(18.1)	6	(1.2)
Pain in extremity	91	(17.7)	11	(2.1)
Stomatitis	81	(15.7)	7	(1.4)
Rash	79	(15.3)	2	(0.4)
Mucosal inflammation	78	(15.1)	3	(0.6)
Back pain	75	(14.6)	9	(1.7)
Dyspepsia	75	(14.6)	1	(0.2)
Abdominal pain	71	(13.8)	16	(3.1)
Hypothyroidism	71	(13.8)	0	(0.0)
Dizziness	62	(12.0)	2	(0.4)
Dysgeusia	61	(11.8)	0	(0.0)
Dry skin	57	(11.1)	1	(0.2)
Epistaxis	55	(10.7)	0	(0.0)
Insomnia	53	(10.3)	0	(0.0)
Musculoskeletal pain	53	(10.3)	5	(1.0)
Oedema peripheral	53	(10.3)	0	(0.0)
Pyrexia	53	(10.3)	0	(0.0)

Laboratory test abnormalities are summarized in Table 3 and are excerpted from NCCN Request for Proposals (6).

Table 3 Laboratory Test Results Reported for Subjects with Solid Tumors Receiving Single-Agent Axitinib n (%) at Maximum Grade (6)

Group/Parameter	N	Grade 1	Grade 2	Grade 3	Grade 4	Total
Chemistry						
Amylase	88	16 (18.2)	3 (3.4)	2 (2.3)	0 (0.0)	21 (23.9)
Aspartate Aminotransferase (AST)	456	131 (28.7)	28 (6.1)	13 (2.9)	0 (0.0)	172 (37.7)
Alanine Aminotransferase (ALT)	456	109 (23.9)	36 (7.9)	10 (2.2)	0 (0.0)	155 (34.0)
Bilirubin (Total)	456	58 (12.7)	23 (5.0)	1 (0.2)	1 (0.2)	83 (18.2)
Alkaline Phosphatase	456	141 (30.9)	30 (6.6)	7 (1.5)	0 (0.0)	178 (39.0)
Bicarbonate	342	101 (29.5)	9 (2.6)	1 (0.3)	0 (0.0)	111 (32.5)
Creatinine	456	141 (30.9)	31 (6.8)	1 (0.2)	3 (0.7)	176 (38.6)
Creatine Kinase	7	2 (28.6)	0 (0.0)	0 0.0)	0 (0.0)	2 (28.6)
Hypoalbuminemia	456	132 (28.9)	43 (9.4)	13 (2.9)	0 (0.0)	188 (41.2)
Hypernatremia	456	22 (4.8)	1 (0.2)	0 (0.0)	0 (0.0)	23 (5.0)
Hyponatremia	456	119 (26.1)	0 (0.0)	22 (4.8)	0 (0.0)	141 (30.9)
Hyperkalemia	456	90 (19.7)	29 (6.4)	9 (2.0)	0 (0.0)	128 (28.1)
Hypokalemia	456	58 (12.7)	0 (0.0)	7 (1.5)	0 (0.0)	65 (14.3)
Hypercalcemia	240	31 (12.9)	2 (0.8)	1 (0.4)	1 (0.4)	35 (14.6)
Hypocalcemia	240	40 (16.7)	12 (5.0)	2 (0.8)	2 (0.8)	56 (23.3)
Hyperglycemia	456	200 (43.9)	63 (13.8)	16 (3.5)	6 (1.3)	285 (62.5)
Hypoglycemia	456	55 (12.1)	13 (2.9)	2 (0.4)	1 (0.2)	71 (15.6)
Hypophosphatemia	69	0 (0.0)	6 (8.7)	2 (2.9)	0 (0.0)	8 (11.6)-
Lipase	88	10 (11.4)	3 (3.4)	3 (3.4)	1 (1.1)	17 (19.3)
Hematology						
Hemoglobin	456	170 (37.3)	36 (7.9)	1 (0.2)	11 (2.4)	218 (47.8)
Platelets	454	100 (22.0)	4 (0.9)	1 (0.2)	1 (0.2)	106 (23.3)
White Blood Cells	456	74 (16.2)	15 (3.3)	0 (0.0)	2 (0.4)	91 (20.0)
Neutrophils (Abs)	454	40 (8.8)	9 (2.0)	4 (0.9)	1 (0.2)	54 (11.9)
Lymphocytes (Abs)	423	85 (20.1)	75 (17.7)	33 (7.8)	3 (0.7)	196 (46.3)
Urinalysis						
Urine Protein	476	73 (15.3)	88 (18.5)	14 (2.9)	0 (0.0)	175 (36.8)

1.2. Rationale for Trial

Based off the known translational data and targeted mechanism of Axitinib, UMCC 2011.53 'A Phase II Trial Evaluating Axitinib in Patients with Unresectable, Recurrent, or Metastatic Head and Neck Cancer' accrued patients between 2012-2014. This study included patients with unresectable recurrent or distant metastatic (R/M HNSCC) at any line of therapy as long as their ECOG performance status was 0-2. It was powered with the primary objective of detecting an improvement in 6-month progression free survival. Of particular note, tumor response was judged by RECIST v1.0 with planned treatment cessation if radiologic progression was noted.

Forty-two patients were enrolled and available for safety analysis of which only 30 were available for efficacy. We noted that many patients in this cohort had significant clinical improvement as witnessed by symptomatic improvement, improved energy, and increased performance status. However, interval imaging of patients demonstrated evidence of mild/moderate tumor swelling with cystic attenuation and edema suggestive of drug effect. In some of the patients, this likely treatment response was interpreted as progression per RECIST v1.0. Planned interim analyses were conducted as to investigate efficacy as based on 6 month progression free survival (PFS). The first a priori interim analysis was performed after enrollment of 20 patients and marginal benefit was seen hence a second interim analysis was performed after enrollment of 30 patients evaluable for efficacy. Using the endpoint of 6 month PFS, the study was stopped due to futility as the observed rate for patients on axitinib was 27%.

Final results of this trial were recently published (55). Although the trial was considered negative on grounds of lack in improvement of PFS compared to historical controls (3.7 months (95% CI 3.5-5.7), observed responses and survival data suggested significant efficacy in a heavily pre-treated population (disease control rate (DCR) of 76.7%, median OS of 10.9 months (95% CI 6.4-17.8)) (Table 8, Figure 3, Figure 4). In addition, Axitinib was extremely well tolerated with no bleeding episodes or reductions due to home blood pressure readings.

Table 4: UMCC 2011.53 Response Rates

Response	**RECIST v1.0**	**Choi Criteria**
Complete Response	0 (0%)	0 (0%)
Partial Response	2 (6.7%)	19 (65%)
Stable Disease	21 (70%)	2 (6.9%)
Progressive Disease	7 (23%)	8 (27.6%)
Disease Control Rate	76.6%	80.8%
Overall Response	6.7%	65%

Figure 2: Waterfall Plot of Tumor Response to Therapy in UMCC 2011.53

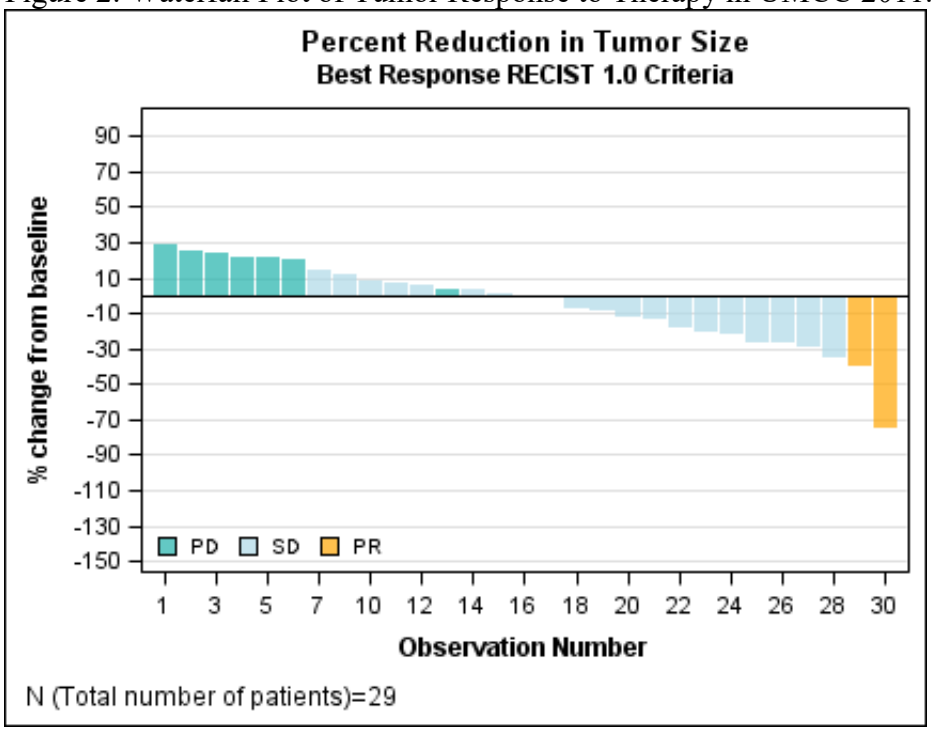
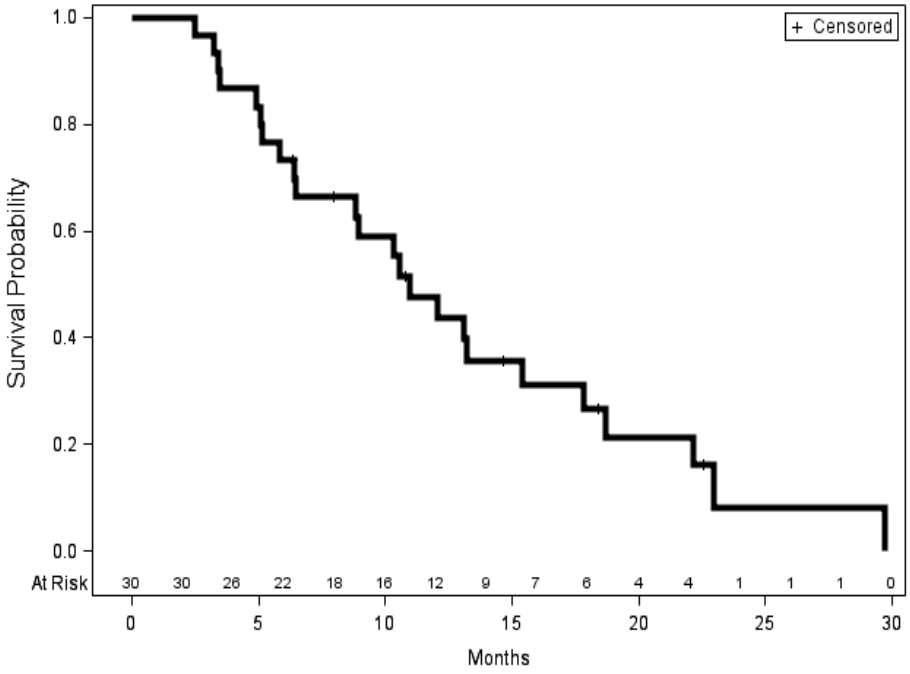


Figure 3: Kaplan-Meier Analysis of Overall Survival in UMCC 2011.53



We strongly believe that Axitinib is a promising therapeutic, merits further consideration as a novel therapeutic in R/M HNSCC, and that the results of the UMCC 2011.53 are misleading for several reasons. First, we note the impressive overall survival (median 10.9 months) observed in the heavily pretreated UMCC 2011.53 population with a low incidence of grade 3 or 4 toxicities. The current first line therapy in newly diagnosed R/M HNSCC is a triplet therapy (the 'EXTREME' regimen) consisting of Cetuximab, Cisplatin, and 5-flurouracil which has been shown to be associated with a median OS of 10.1 months with relatively high rate of grade 3 or 4 toxicities(82%) (9). In studies of patients failing first line therapy, median overall survival (OS) is typically on the order of 4-8 months. Ninety percent of the patients in our study had previous lines of therapy in the R/M setting suggestive of significant survival benefit with Axitinib therapy.

We believe that the reason UMCC 2011.53 demonstrated impressive OS but did not demonstrate improvement in PFS (and hence was stopped for futility) is that tumor response to therapy (swelling, cystic attenuation) was registered as progression by RECIST v1.0. Similar results regarding responses have been described with tyrosine kinase inhibitors, most notably in advanced gastrointestinal stromal tumors (GISTs). To account for these alternate radiologic changes, an alternate set of response criteria have been proposed for patients treated with tyrosine kinase inhibitors known as the Choi Criteria (Table 9). In one study, it was demonstrated that radiologic changes defined by Choi Criteria correlated with patient directed endpoints (PFS, DSS, OS) whereas RECIST did not capture these correlations.

Table 5: Definition of Choi Criteria

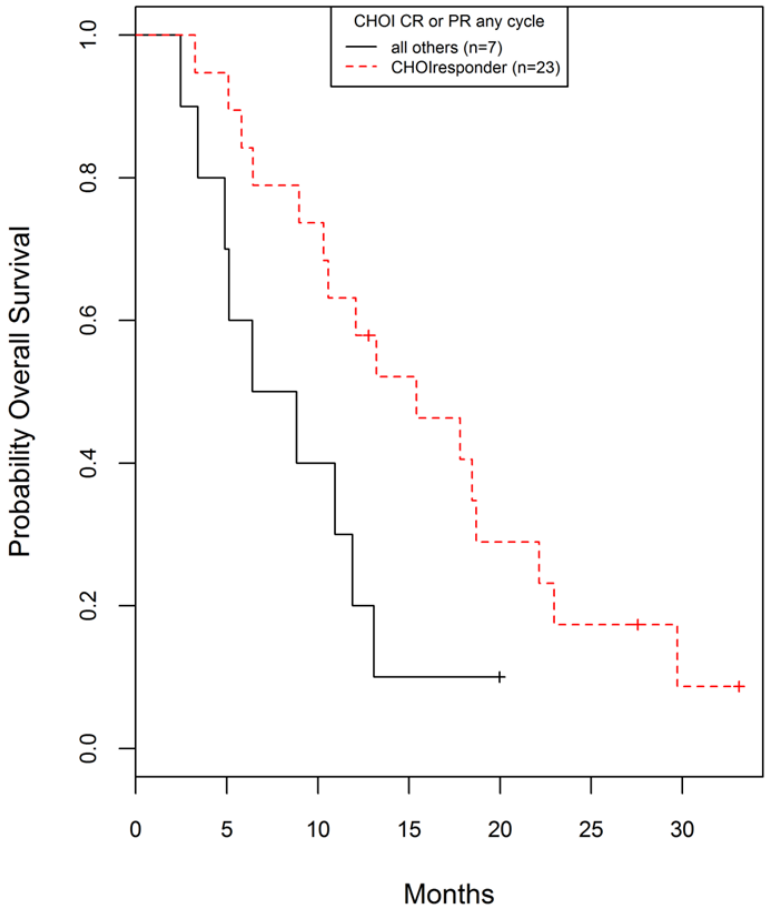
Response	Definition
CR	Disappearance of all lesions
	No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT
	No new lesions
	No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD
	No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT
	New lesions
	New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.[10]

We have reviewed all the radiographic images for all of the patients on UMCC 2011.53 by Choi Criteria as a hypothesis generating exploratory analysis. Of note, only 29/30 patients evaluable for response had imaging for which the Choi Criteria could be applied. In addition, imaging was not optimized for interpreting images with alternate radiologic criteria. Preliminary exploratory analyses demonstrate that (23/29) 65% of patients enrolled on UMCC 2011.53 had a response (PR) by Choi Criteria with an additional 2 patients achieving stable disease (6.9%) (Table 4).

Furthermore, overall survival was found to be significantly improved in patients with a response by Choi Criteria versus non-responders (KM estimate of OS (95% CI): 13.2(10.3,18.7) months versus 5.1 (2.5, 8.8) months) (Figure 5). Further analyses was limited as treatment decisions were made off of RECIST but predicted survival at 12 months was 63% (95% CI: 38-80%) in patients with a response versus 20% (95% CI: 3-47%) in non-responders.

Figure 4: Kaplan-Meier Analysis of Overall Survival by Choi Response in UMCC 2011.53



Given the existing literature in other malignancies treated with tyrosine kinase inhibitors, mechanism of action of Axitinib, and our exploratory analysis in evaluating response with alternate criteria we feel that use of Choi Criteria for assessment for tumor response and treatment decisions is more appropriate for ongoing R/M HNSCC trials. We believe that improvements in survival endpoints (ie PFS) may be underestimated in the existing UMCC 2011.53 cohort as Axitinib was stopped in the setting of a RECIST progression despite Choi response.

Therefore, we propose a trial examining the use of Axitinib in R/M HNSCC using the Choi Criteria for response assessment. We would power this cohort to detect a 20% improvement in 6 month overall survival compared to historical data (from 50% to 70% at 6 months). This cohort would consist of 37 patients and treatment plan would be identical to the previous UMCC 2011.53 protocol with the exception that Choi criteria would be used to evaluate response. In addition, treatment with Axitinib would be continued if patients were felt to be deriving clinical benefit.

2. HYPOTHESIS:

2.1 Administration of Axitinib to patients with R/M SCCHN will result in an improvement in 6 month overall survival compared to historical control

2. 2 Use of the Choi Criteria to assess response to Axitinib will yield more accurate assessment regarding tumor response in R/M SCCHN

3. OBJECTIVES:

3.1 Primary objective

To determine the 6 month overall survival in patients with unresectable recurrent and metastatic head and neck cancer treated with Axitinib

3.2 Secondary objectives

1. To determine the overall survival of patients treated with Axitinib
2. To determine the progression free survival of patients treated with Axitinib
3. To determine the disease control rate at 16 weeks and response rate as defined by Choi Criteria
4. To determine the duration of response (as defined by Choi Criteria) of patients treated with Axitinib
5. To assess the toxicities associated with the treatment of Axitinib of patients treated with Axitinib

4. STUDY DESIGN:

This study will be a prospective, single-institution, single-arm phase II study of Axitinib in patients with unresectable recurrent and metastatic head and neck squamous cell carcinoma with ECOG performance status 0-2, for recurrent or metastatic head and neck cancer. The subjects will be started on treatment with 5 mg of Axitinib twice a day continuously, with subsequent dose escalation to 7 mg and then 10 mg twice a day in the absence of grade 2 or worse toxicities. This will be followed by clinical and/or radiologic response assessment after 8 weeks and subsequently every 2 months until disease progression (defined per Choi criteria, or obvious progression on clinical or laryngoscopic/endoscopic exam) or intolerable toxicity (defined as below). Patients with confirmed progressive disease who, in the investigator's opinion, continue to receive benefit from Axitinib treatment and who meet the criteria for treatment may continue to receive treatment as described in Section 8.3. Axitinib should be discontinued if there is further evidence of progression defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

During treatment on this protocol, all patients will be evaluated for safety as detailed below.

5. STUDY POPULATION:

5.1. Stage:

Unresectable, recurrent or metastatic squamous cell carcinoma of head and neck.

5.2. Inclusion Criteria:

1. Histologically documented squamous cell head and neck cancer with or without metastases, not amenable to curative treatment; or the patient has documented refusal of curative treatment.

2. Presence of measurable disease by CT scan or

a. for cutaneous squamous cell carcinoma not present on CT imaging but present on physical exam with lesion(s) greater than >/= 10mm

b. patients with non-target lesions are permissible per PI discretion

3. Adequate bone marrow, hepatic, and renal function (including absence of proteinuria, PT<1.5, WBC≥ $3x10^9$ cells/ml, ANC ≥ $1.5x10^9$ cell/ml, platelets ≥75,000 cells/mm^3, hemoglobin ≥ 9.0 g/dL, concentrations of total serum bilirubin within 1.5 x upper limit of normal (ULN), AST, ALT within 2.5x institutional upper limits of normal unless there are liver metastases in which case AST and ALT within 5.0 x ULN, serum creatinine clearance ≥ 30 ml/min), urinary protein <2+ by urine dipstick (if dipstick is ≥2+ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours).

4. Age ≥18 years.

5. ECOG performance status of 0-2.

6. Life expectancy of ≥12 weeks.

7. No evidence of preexisting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 30 minutes apart. The baseline systolic blood pressure readings must be ≤140 mm Hg, and the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

8. Women of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to treatment.

9. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

10. Willingness and ability to comply with scheduled visits, treatment plans, including willingness to take Axitinib, laboratory tests, and other study procedures.

11. If a curative treatment option in the form of chemoradiation exists in a patient with unresectable disease, this has to be attempted first and must have failed, unless the patient has documented refusal of curative treatment.

5.3. Exclusion Criteria:

1. Central lung lesions involving major blood vessels (arteries or veins) or a tumor encasing major blood vessels (i.e. carotid artery).

2. Active hemoptysis (defined as >1/2 tsp of bright red blood per day).

3. Gastrointestinal abnormalities causing impaired absorption requiring intravenous alimentation, prior surgical procedures affecting absorption including gastric resection, treatment for active peptic ulcer disease in the past 6 months, active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy, malabsorption syndromes.

4. Previous treatment with anti-angiogenesis agents including thalidomide, or inhibitors of epidermal growth factor (EGF), platelet derived growth factor (PDGF), or fibroblast growth factors (FGF) receptors within 30 days preceding study entrance.

5. Current use or anticipated inability to avoid use of drugs that are known strong CYP3A4/5 inhibitors (atazanavir, boceprevir, conivaptan, clarithromycin, grapefruit or grapefruit juice, indinavir, itraconazole, ketoconazole, nelfinavir, nefazodone, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole).

6. Current use or anticipated inability to avoid use of drugs that are known strong CYP3A4/5 inducers (carbamazepine, dexamethasone, fosphenytoin, phenytoin, phenobarbital, rifabutin, rifampin, rifapentin, St. John's wort).

7. Active seizure disorder or evidence of untreated or progressive brain metastases, spinal cord compression, or carcinomatous meningitis.

   a. Subjects with brain metastases are eligible if they have been treated and there is no CT or MRI evidence for at least 4 weeks after CNS metastasis treatment is complete.

8. A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.

9. History of a malignancy (other than head and neck cancer) except those treated with curative intent for skin cancer (other than melanoma), in situ breast or in situ cervical cancer, or those treated with curative intent for any other cancer with no evidence of disease for 2 years.

10. Major surgery <4 weeks or radiation therapy <2 weeks of starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.

   a. Radiotherapy is defined as whole brain radiation, external beam radiation therapy (EBRT), or stereotactic brain radiation (SBRT).

11. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.

12. Patients (male and female) having procreative potential who are not willing or not able to use adequate contraception or practicing abstinence.

13. Women who are pregnant or breast-feeding.

14. Patients with history of bleeding diathesis, arterial thromboembolism, current use of therapeutic anticoagulation with oral vitamin K antagonists, factor Xa inhibitors, heparin products, oral direct thrombin inhibitors, or presence of non-healing wounds. Low-dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis is allowed.

15. Patients residing in prison.

16. Prior experimental therapy within 30 days of planned start of this trial.

17. HIV virus infection irrespective of viral load, treatment status, or CD4 count, or acquired immunodeficiency syndrome (AIDS)-related illness. HIV testing is not required by this protocol.

18. Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.

19. History of deep vein thrombosis or pulmonary embolism within 6 month of anticipated starting of Axitinib.

20. Availability of curative treatment option for the patient's cancer, whether surgery, chemotherapy, radiation, or combination thereof, unless the patient has documented refusal of curative treatment.

21. Increased risk of wound dehiscence or presence of non-healing wounds.

5.4. Patient Registration.

All patients will be registered with the University of Michigan Rogel Cancer Center Oncology Clinical Trials Support Unit (O-CTSU) prior to initiating treatment. The patient or their representative will sign and date the informed consent for the trial.

5.5. Life Style Guidelines

During the study female patients of childbearing potential must take precautions to prevent pregnancy since the effects on the fetus are unknown. Male patients with partners of childbearing potential must take precautions to prevent pregnancy of the partner since the effects of these drugs on sperm are unknown. These restrictions should remain in force for 6 months from the last dose of Axitinib. Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. Adequate contraception should be discussed with the physician before the treatment start.

6. TRIAL PROCEDURES

6.1. Subject Enrollment

Once eligibility is verified the clinical representative will confirm by facsimile that the patient has been accepted into the trial. If the patient fails to start treatment within 14 days of registration the clinical representative should be contacted before the start of treatment.

6.2. Trial procedures

During treatment on this protocol, all patients will be followed and monitored as follows:

Table 6. Trial Procedures.

Required studies	Pre-therapy[12]	Cycle 1, Day 1	1 week	2 weeks	3 weeks	4 weeks	8 weeks	Following each cycle thru 12 cycles[1]	Following completion of even numbered cycles	Survival[11]
Clinic visit	X	X		X		X	X	X	X	
H&P	X	X[10]		X		X	X	X	X	
Vital signs and PS	X	X		X		X	X	X	X	
PTT, PT, INR	X									
CBC, Diff, platelets	X	X[9]		X		X	X	X	X	
Comprehensive Panel, Mg[2]	X[3]	X[9]		X		X	X	X	X	
Urine dip[3]	X					X	X	X	X	
TSH, free T4[4]	X	X[9,]		X		X			X	
Clinical toxicity assessment				X		X	X	X	X	
Radiologic imaging for tumor measurement[5]	X						X		X	
Pregnancy Test[6]		X[9]								
Informed Consent	X									
Planned dose escalation[7]				X	X					
Telephone assessment of toxicities[8]			X		X					
Survival Monitoring										X

1- Following completion of 12 cycles, assessments will be obtained every 8 weeks.
2- Comprehensive Panel includes Basic Panel (Na, K, Cl, CO2, BUN, Cr, Gluc), AST/SGOT, ALT/SGPT, Alk Phos, T.bili, Alb, Ca, Total Protein. Also will obtain magnesium.
3- Urine dipstick may be done in clinic or lab.
4- Serum or plasma Thyroid Function Tests (Free T4 and TSH) should be performed within 14 days of starting treatment. Subsequently, TSH should be done every 2 weeks X 2, then following completion of even numbered cycles of chemotherapy.

5- Radiologic imaging of the areas involved with recurrent/metastatic disease, such as the neck, chest, or other areas if needed because of the location of the metastatic disease; baseline within 28 days prior to treatment. On study assessments, may be within +/- 2 weeks. Imaging will be interpreted by Choi Criteria, interpretation to be performed by centralized UMCC Tumor Response and Assessment Core (TRAC).
6- Pregnancy test (urine or serum) will be performed for women of childbearing age within 3 days before first dose of Axitinib and if clinical concern for pregnancy arises.
7- Dose escalation is planned at 2 weeks (to 7 mg BID) and 3 weeks (to 10 mg BID), in the absence of toxicities grade 2 or greater. Dose escalation may be resumed after 1 week if all toxicities have diminished to grade 1 or less (see below), and measures have been taken to reasonably prevent recurrence of these toxicities with the higher dose.
8- Telephone call to the patient must be made by a study staff member (RN or MD with a current nursing/medical license) at 1 and 3 weeks. During these calls, toxicity assessment will be conducted, per patient report, and toxicity management advice given, including initiation or titration of anti-hypertensive treatment. During the Week 3 call, if toxicities are grade 1 or less dose escalation to 10 mg BID will be made.
9- All baseline labs are required within 14 days of starting treatment (Cycle 1, Day 1).
10- H&P not required on Cycle 1, Day 1 if performed for screening within 72 hours
11- Survival assessment can be done by phone and will be performed once every three months (+/- 1 month)
12- Labs are eligible for screening if obtained within the past 28 days

6.3 Initial Clinical Evaluation

1. Complete history and physical exam.
2. CBC with differential and platelet count (CBCDP) ; within 14 days prior to start of treatment
3. Serum chemistry profile to include: comprehensive panel (Na, K, Cl, CO2, BUN, Cr, Gluc, AST/SGOT, ALT/SGPT, Alk Phos, T.bili, Alb, Ca, Total Protein), serum magnesium; within 14 days prior to start of treatment.
4. Urine dip (in clinic or lab)
5. TSH, free T4; within 14 days prior to start of treatment
6. Pregnancy test (serum or urine Beta-HCG) in women of childbearing potential; within 3 days prior to start of treatment.
7. Radiologic imaging of the areas involved with recurrent/metastatic disease, such as the neck, chest, or other areas if needed because of the location of the metastatic disease; within 28 days prior to treatment.

7. STUDY PLAN

7.1. Study overview

The patients will receive 5 mg Axitinib twice a day. Dose escalation is planned at 2 weeks (to 7 mg BID) and at 3 weeks (to 10 mg BID), in the absence of toxicities grade 2 or greater. Dose escalation may be resumed at next visit if all toxicities have diminished to grade 1 or less (see

below) since last follow-up. Each patient will be seen in clinic at 2, 4, 8 weeks after initiation of treatment and at monthly intervals thereafter, unless more frequent follow-up is clinically indicated.

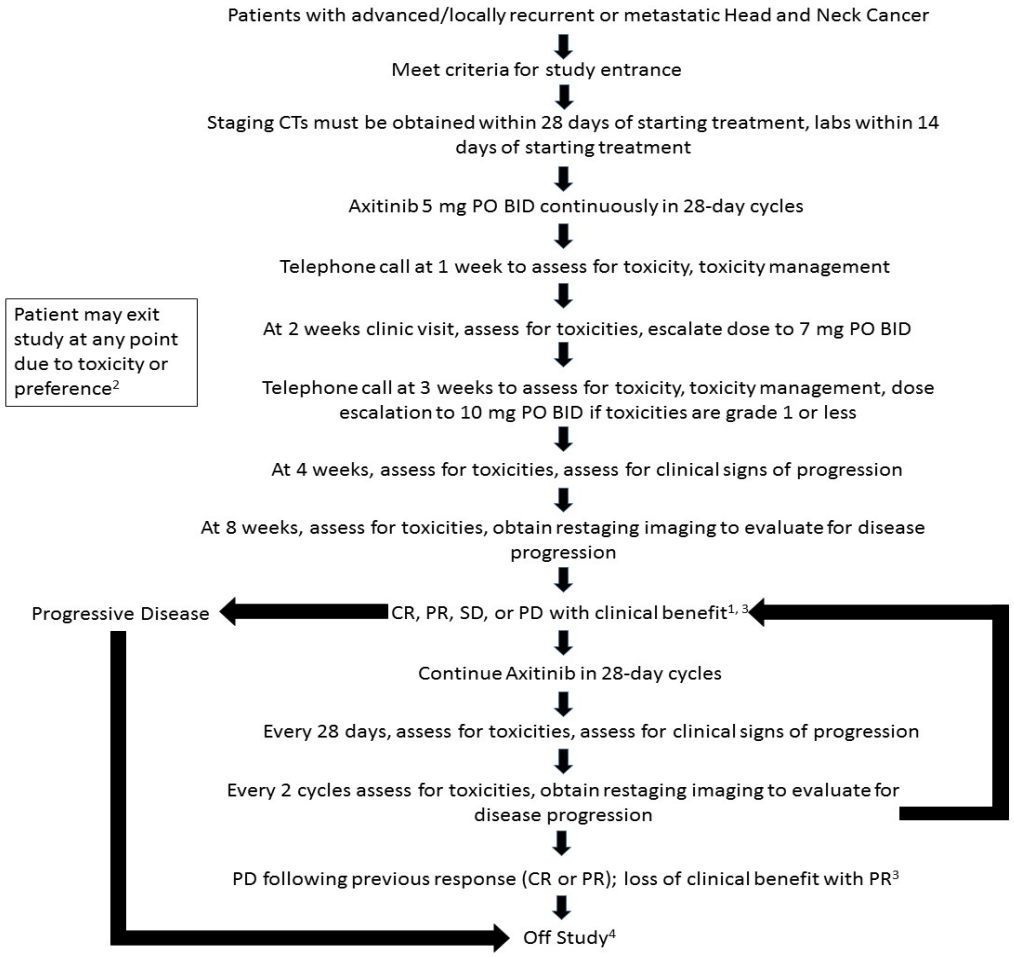
During follow-up visits, we will assess the toxicities, including checking vital signs, review of systems, physical exam and CBCDP, comprehensive metabolic panel, test for proteinuria. TSH should be checked within 14 days of cycle 1, day 1 then should be done every 2 weeks for two assessments. Following completion of these assessments, TSH should be checked following the completion of even numbered cycles of chemotherapy.

Telephone call to the patient must be made by a study staff member (licensed RN or MD) at 1 and 3 weeks. During these calls, toxicity assessment will be conducted, per patient report, and toxicity management advice given, including initiation or titration of anti-hypertensive treatment. During the Week 3 call, if toxicities are grade 1 or less since last follow-up, dose escalation to 10 mg BID will be made. Dose escalation may be resumed at least 1 week later if all toxicities have diminished to grade 1 or less (see below), and measures have been taken to reasonably prevent recurrence of these toxicities with the higher dose since last follow-up.

The response to treatment will be assessed clinically at each visit, as well as by appropriate radiologic imaging, starting at 8 weeks +/- 2 weeks and then at 8-week intervals, +/- 2 weeks. Tumor response to therapy will be interpreted by Choi Criteria with interpretation performed by UMCC Tumor Response and Assessment Core. Patients will be taken off trial for significant side effects, per patient preference, or for noncompliance with treatment plan. Beyond progression, survival will be assessed every 12 weeks. Patients will also be followed for 28 days after cessation of study participation for safety monitoring. Patients with confirmed progressive disease who, in the investigator's opinion, continue to receive benefit from Axitinib treatment and who meet the criteria for treatment may continue to receive treatment as described in Section 8.3. Axitinib should be discontinued if there is further evidence of progression defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

7.2 Study schema

Figure 5. Study schema



[1] Patients with confirmed progressive disease who, in the investigator's opinion, continue to receive benefit from Axitinib treatment and who meet the criteria for treatment may continue to receive treatment as per Section 8.3.

[2] Patients who do not complete at least one month of treatment nor undergo tumor-reimaging for reasons other than progression of disease will be considered non evaluable for the primary endpoint and will be replaced unless tumor progression is obvious by clinical exam. All patients who received at least 1 dose of Axitinib under this protocol will be included in the safety analysis

[3]Response will be assessed by Choi Criteria

[4]Survival assessment can be done by phone and will be performed once every three months (+/- 1 month)

8. TREATMENT PLAN:

8.1. Allocation to Treatment

This trial is open label. All subjects will receive Axitinib. The starting dose of Axitinib will be 5 mg orally twice daily. The dose will be escalated to 10 mg orally BID (see below) or modified as needed for toxicities (see below).

8.2. Drug Supplies

This trial will utilize the commercially available, marketed Axitinib. Pfizer, Inc. will provide the medication free of charge.

8.2.1. Formulation and Packaging

Axitinib will be supplied as 1-mg and 5-mg film coated tablets for oral administration (Table 7). The appropriate dose may be achieved by any combination of these tablets during the dose titration phase, and pills will be counted into prescription bottles accordingly. Every effort will be made to simplify dosage (decrease the number of tablets, and limit to a single kind of tablets, either 1-mg or 5-mg) once stable dose is achieved. The tablets may not be split in order to achieve the desired dose. At each visit, patient will be asked how many doses were missed and when. This information will be recorded in the patient study record. Please see "**Patient Follow-up Form".**

8.2.2. Administration

Axitinib will be administered orally at 5 mg twice a day (morning and evening), starting on Day 1 of the study. Tablets can be taken with or without food, at approximately the same time each day. Doses should be taken approximately 12 hours apart. Patients should be instructed that if they vomit any time after taking a dose, that they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. On day of visit patient may hold their morning dose until assessed by clinic. Missed doses may be taken late, up to 3 hours before the next scheduled dose, otherwise should be skipped.

The patients will be asked to bring medication bottles to each follow-up visit, and remaining pills in bottle will be counted at each visit to document compliance. This information will be recorded in each patient's data file.

Table 7. Available Axitinib Dose Levels

Dose level	**Dose**	**Dispensed as**
+2	10 mg BID	2x5mg tablets BID
+1	7 mg BID	1x5mg tablets + 2x1mg tablets BID
0 (starting dose)	**5 mg BID**	**1x5mg tablets BID**
-1	3 mg BID	3x1mg tablets BID
-2	2 mg BID	2x1 mg tablets BID

Patients experiencing drug reaction greater than CTCAE Grade 2 should undergo dose modification as recommended in section 8.2.4.

8.2.3. Dose escalations

Dose escalation is planned at 2 weeks (to 7 mg BID) and at 3 weeks (to 10 mg BID), in the absence of toxicities grade 2 or greater since last follow-up. Dose escalation may be resumed after at least 1 week if all toxicities have diminished to grade 1 or less since last follow-up. Each patient will be seen in clinic at 2, 4, 8 weeks after initiation of treatment and at monthly intervals thereafter, unless more frequent follow-up is clinically indicated. Telephone call to the patient must be made by a study staff member (a doctor or a nurse) at 1 and 3 weeks, +/- 3 days. During these calls, toxicity assessment will be conducted, per patient report, and toxicity management advice given. During the Week 3 call, if toxicities are grade 1 or less since last follow-up, Axitinib dose escalation to 10 mg BID will be made. Dose escalation up to 10 mg po BID may be resumed after at least 1 week if all toxicities have diminished to grade 1 or less (see below), and measures have been taken to reasonably prevent recurrence of these toxicities with the higher dose. The contents of each planned and patient-initiated phone called will be recorded in patient's study record.

If a patient has a dose reduction for study drug related toxicity, the dose may be considered for re-escalation in patients who tolerate the lower dose without toxicities above Grade 1 for at least 1 week, and measures have been taken to reasonably prevent recurrence of these toxicities with the higher dose.

8.2.4. Dose Interruption and Reductions

Adverse events and other symptoms will be graded according to the current Common Terminology for Adverse Events version 4.03 (CTCAE v4.03). This section contains management of adverse events except hypertension, hemoptysis and proteinuria which are discussed in subsequent sections.

Patients developing a treatment-related CTCAE Grade 1 or 2 adverse event will have their dose continued at the same dose level. Patients developing a treatment-related CTCAE Grade 3 or above adverse event will have dose reductions as described below.

Treatment delays due to drug-related toxicity > 2 weeks will result in discontinuation of treatment. Patients removed from treatment for intolerable toxicity will still be followed for survival.
The criteria for dose modification for study drug related adverse events is summarized Table 8 below.

Table 8. Criteria for Dose Modification for Axitinib Related Adverse Events other than Hypertension, Hemoptysis, or Proteinuria

Related Adverse Events	**Intervention**
Grade 1	Continue at same dose level May escalate dose per protocol Manage toxicities as medically necessary
Grade 2	Continue at same dose level Manage toxicities as medically necessary
Grade 3 nonhematologic drug-related toxicity	Decrease dose to one lower dose level Manage toxicities as medically necessary Treatment may be interrupted up to 2 weeks per investigator discretion
Grade 4 nonhematologic drug-related toxicity or Grade 4 hematologic toxicity* *Patients who develop grade 4 lymphopenia may continue study treatment without interruption.	Interrupt dosing (up to 2 weeks); re-start at one lower dose level as soon as improvement to CTCAE Grade 2. If patient requires dose reduction below 2 mg BID, discontinue trial participation. Manage toxicities as medically necessary

Guidelines for dose reductions for specific adverse events are provided in the following sections.

8.2.4.1. Axitinib Dose Reduction for Hypertension

Patients treated with Axitinib will monitored for hypertension closely in the office. Blood pressure will be monitored closely at routine visits. If hypertension is noted at the time of the initial encounter, it will be checked 5 minutes after sitting quietly.

Guidance on dose interruption and reduction for hypertension is summarized in Table 9 below. If "white coat hypertension" is suspected by the clinician same anti-hypertensive regimen and dose of Axitinib can be continued.

Table 9. Hypertension Management Plan for Axitinib

Degree of Blood Pressure Elevation	**Management**
2 BP readings separated by at least 30 min show systolic pressure 141-160 mm Hg OR diastolic pressure 91-100 mm Hg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain dose of study drug. If on maximal antihypertensive treatment (3 agents including a diuretic, and no further safe and efficacious escalation of antihypertensive therapy is deemed possible by the investigators), reduce study drug to one lower dose level.
2 BP readings separated by at least 30 min show systolic Pressure 161 or above OR diastolic pressure 101 or above	Interrupt dosing; adjust antihypertensive medication; as soon as BP is 140/90 mm Hg or less, restart study drug at one lower dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 30 min show systolic pressure 141-160 mm Hg OR diastolic pressure 91-100 mm Hg	Repeat study drug dose reduction by one lower dose level. If a patient requires dose reduction below 2 mg BID, take off study.
Hypertensive urgency or emergency while on study drug, with any blood pressure level above 140/90	Take patient off study immediately. Manage as medically appropriate, in the appropriate hospital setting.

If study drug is held, patients receiving antihypertensive medications should monitor closely for hypotension. Plasma half-life of Axitinib is 2 – 4 hours and BP usually decreases within 1-2 days following dose interruption.

8.2.4.2. Axitinib Dose Reduction for Hemoptysis

Bleeding from the lungs as evidenced by hemoptysis will be graded according to the site specific hemorrhage category of CTCAE v4.03.

Treatment with Axitinib will be discontinued for hemoptysis of >½ tsp of bright red blood per day. In addition, a radiologic assessment (e.g., chest x-ray) should be considered for patients who have hemoptysis >½ tsp of bright red blood per day. If the hemoptysis resolves to baseline within 1 week and there is no evidence of disease cavitation, treatment with Axitinib may continue at the current dose level. Patients who experience hemoptysis without resolution to

baseline within 1 week, or with evidence of disease cavitation should discontinue from treatment with Axitinib.

8.2.4.3. Axitinib Dose Reduction for Proteinuria

At documentation of >1+ proteinuria by dipstick, patients should have a 24-hour urine collection for total protein. Axitinib dosing may continue while waiting for test results.

If ≤2 g proteinuria/24 hours is reported, treatment with Axitinib may continue without dose reduction.

If >2 g proteinuria/24 hours is reported, treatment with Axitinib should be interrupted. A twenty-four hour urine collection for total protein and creatinine clearance should be performed weekly until results show ≤2 g proteinuria/24 hours, at which time treatment with Axitinib may be restarted at one lower dose level. Patients, once restarted on Axitinib, will have every-2-weeks monitoring for proteinuria by semiquantitative testing (e.g., dipstick) as long as the proteinuria reading is higher than 1+. The 24-hour urine collection to monitor the degree of proteinuria should be repeated every 4 weeks until it has decreased to <500 mg/24 hours. If recurrent >2 g proteinuria/24 hours is reported, treatment with Axitinib should be interrupted again. Twenty-four hour urine collection for total protein and creatinine clearance should be performed every 2 weeks until results show ≤2 g proteinuria/24 hours, at which time treatment with Axitinib may be restarted at one lower dose level. If a patient requires dose reduction below 2 mg BID, stop trial participation.

8.2.4.4. Axitinib Dose Interruption for Surgery or Surgical Procedures

If surgery is required, treatment with Axitinib must be interrupted at least 24 hours before the procedure and the patient's blood pressure should be monitored closely for hypotension. Patients may resume Axitinib seven days after minor surgery and 2-3 weeks after major surgery, assuming wound has completely healed and no wound healing complications, at the discretion of the prescribing physician.

8.2.4.5. Thyroid Function Tests

Patients receiving Axitinib should be monitored for signs and symptoms of hypothyroidism, such as fatigue, deepening of voice, cold intolerance, constipation, anorexia, periorbital edema, myxedema, or changes in skin or hair. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state. Dose reduction or interruption should not be made for thyroid abnormalities alone.

8.3 Treatment Beyond Disease Progression

As described in Section 1.2, traditional imaging response criteria may not fully capture response to tyrosine-kinase inhibitors, particularly anti-angiogenic agents. Although the Choi Criteria have been proposed for evaluating response to tyrosine kinase inhibitors, these response criteria

likely still do not fully capture patients who may derive clinical benefit despite radiologic evidence of PD.

Subjects will be permitted to continue on Axitinib treatment beyond initial Choi defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (i.e. CNS metastases)
- Subject provides written informed consent prior to receiving any additional Axitinib treatment, using an informed consent describing any reasonably foreseeable risk or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be documented in the study records. Subjects will be re-consented with an informed consent describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analysis that include the investigator-assessed progression date, subjects who continue treatment beyond investigator-assessed, Choi Response defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

8.4. Drug Storage and Drug Accountability

A co-investigator or an approved representative (e.g., research pharmacists) will ensure that all trial drugs are stored in a secure area, under recommended storage conditions and in accordance with applicable regulatory requirements.

The research pharmacy will assist with management of drug storage and accountability. Drug accountability forms will be used to maintain accurate records of receipt, dispensing and return

of trial medication. Any drug that is not dispensed at the end of the trial or any returned drug supplies should be returned to Pfizer Inc., or disposed of in accordance with instructions received in writing from Pfizer, Inc.

8.5. Concomitant Medication(s)

In vitro studies with human liver microenzymes and recombinant CYP450 enzymes indicated that Axitinib metabolism was primarily mediated by the drug-metabolizing enzyme CYP3A, and to a lesser extent by CYP1A2. Additionally, the drug also undergoes N-glucuronidation in liver microsomes of some species. Clinically, there is likelihood that Axitinib plasma concentrations may be increased in the presence of co-administered potent inhibitors of the CYP3A and glucuronosyl transferase enzymes. The potential exists for drug-drug interactions with strong CYP3A4/5 inhibitors and inducers.

Axitinib metabolism may be induced in patients taking strong CYP3A4/5 inducers and inhibitors as these may alter Axitinib plasma concentrations.

The following potent CYP3A4/5 strong inhibitors and CYP3A4/5 strong inducers are prohibited:

CYP3A4/5 INHIBITORS (Strong)	CYP3A4/5 INDUCERS (Strong)
Atazanavir	Carbamazepine
Boceprevir	Dexamethasone
Coniveptan	Fosphenytoin
Clarithromycin	Phenytoin
Grapefruit and grapefruit juice	Phenobarbital
Indinavir	Rifampin
Itraconazole	Rifapentin
Ketoconazole	Rifabutin
Nefazodone	St. John's Wort
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

Other CYP3A4/5 inhibitors and inducers are allowed per investigator's discretion.

Since CYP1A2 is also known to be induced in chronic smokers, there is likelihood that Axitinib plasma concentrations may be reduced in these individuals. Based on preclinical and extensive clinical experience, clinically significant drug interactions are unlikely.

8.6. Rescue Therapy

No mechanistically specific antagonists for Axitinib are available and standard supportive measures should be used in the case of excessive pharmacological effects or adverse reaction.

9. RESPONSE CRITERIA

The Choi Criteria will be used to assess tumor response to therapy. Interpretation will be performed by centralized UMCC Tumor Response and Assessment Core (TRAC). If density measurements are not available and cannot be accurately measured by photography or imaging, response can be dictated by measurement alone (i.e.for cutaneous squamous cell carcinomas that are not visualized on CT scan but are measurable on physical exam only). Non-target lesions are also permissible in which case overall assessment would be limited to complete response, stable disease, and progressive disease.

Complete Response:

- Disappearance of all lesions
- No new lesions

Partial Response:

- A decrease in size[1] of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT
- No new lesions
- No obvious progression of non-measurable disease

Stable Disease

- Does not meet the criteria for CR, PR, or PD
- No symptomatic deterioration attributed to tumor progression

Progressive Disease

- An increase in tumor size of ≥ 10% and dose not meet criteria of PR by tumor density (HU) on CT
- New lesions
- New intratumoral nodules or increase in the size of the existing intratumoral nodules

[1-] The sum of longest diameters of target lesions as defined in RECIST

10. CRITERIA FOR DISCONTINUATION OF TREATMENT

1. Unacceptable toxicity.
2. Intercurrent illness, which prevents further administration of treatment.
3. Patient preference.
4. Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with Axitinib (per section 8.3)
5. Treatment delays due to drug-related toxicity > 2 weeks.
6. Non-compliance with treatment.

7. If the disease becomes amenable to resection or (chemo) radiation with curative intent as a result of Axitinib treatment, Axitinib will be stopped, and the alternative treatment instituted that would offer the best chance of cure for the patient. Such patients will be included in safety and efficacy analysis.

11. SAFETY ASSESSMENTS

The safety of Axitinib should be evaluated using the standard clinical practice, with special attention paid to hypertension, proteinuria, thrombosis, hemoptysis, bleeding risk, and concomitant medications. Patients receiving Axitinib should be monitored for signs and symptoms of hypothyroidism, such as fatigue, deepening of voice, cold intolerance, constipation, anorexia, periorbital edema, myxedema, or changes in skin or hair. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state.

12. ADVERSE EVENT REPORTING

12.1. Adverse Events

All observed or volunteered adverse events regardless of suspected causal relationship to Axitinib will be reported as described in the following sections.

For all adverse events the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer, Inc. or its designated representative. For all adverse events sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to Axitinib, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer, Inc. concurs with that assessment.

12.2. Reporting Period

Adverse events reporting, including suspected, unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations. For serious adverse events, the reporting period to Pfizer, Inc. or its designated representative begins from the time that the subject has taken at least one dose of trial treatment through the last subject visit. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to Axitinib is suspected.

Adverse events should be recorded on the CRF from the time the subject has taken at least one dose of trial treatment through last subject visit.

If a patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs

during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

12.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:
- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity.

Additionally, they may include the signs or symptoms resulting from exposure in Utero.

Worsening of signs and symptoms of the malignancy under trial should be reported as adverse events in the appropriate section of the CRF . Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

12.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:
- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in trial dosing outside of protocol-stipulated dose adjustments or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

12.5. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:
- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as serious adverse events unless the outcome is fatal during the trial or within the safety reporting period. Hospitalizations due to signs and symptoms of disease

progression should not be reported as serious adverse events. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTC grade 5 (See Severity Assessment). Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject and may require intervention to prevent one of the other outcomes, the important medical event should be reported as serious.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.6. Hospitalization

Adverse events reported from clinical studies associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).
Hospitalization does not include the following:
- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:
- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g., for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported and it meets the definition of an adverse event. For example, an

acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

12.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	no change from normal or reference range
1	mild adverse event
2	moderate adverse event
3	severe adverse event
4	life-threatening or disabling adverse event
5	death related to adverse event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

12.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious), the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Axitinib caused or contributed to an adverse event. If the investigator does not know whether or not Axitinib caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by Pfizer, Inc. (See Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on trial records.

In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

12.9. Exposure In Utero

An Exposure In Utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) Axitinib, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to Axitinib (maternal exposure);

2. A male has been exposed, either due to treatment or environmental, to Axitinib prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with Axitinib, the investigator must submit this information to Pfizer, Inc. on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to Pfizer, Inc. product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-Up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer, Inc. of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:
- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to Axitinib should be reported.

Additional information regarding the Exposure in Utero may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator must obtain permission from the subject's partner in order to conduct any follow-up or collect any information.

12.10. Withdrawal Due to Adverse Events

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

12.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject. In addition, each trial subject will be questioned about adverse events.

12.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, it will be reported via submission of Pfizer, Inc. Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, according to guidelines provided in Pfizer, Inc. IIR Safety Reporting Reference Manual Version 3, and IIR SAE Form Completion Guide, or Form FDA 3500 A (Med Watch Form) . This will be faxed to Pfizer, Inc. U.S. Clinical Trial Department at 1-866-997-8322 using the Pfizer, Inc. Investigator Initiated Research Reportable Event Fax Cover Sheet. The Investigator-Initiated Research Serious Adverse Event (IIR SAE) form must be submitted to Pfizer, Inc. immediately for a death or life-threatening event, and within 24 hours for all other types of SAEs. Any SAEs reported to Pfizer, Inc. should also be faxed to NCCN at 215-358-7699 or emailed via ORPReports@nccn.org.

All Serious adverse Events (SAE's) will have written report sent to:

1. Principal Investigator of the study: Fax 647-8792

2. Data Manager

3. The Oncology Clinical Trials Support Unit (O-CTSU) staff will coordinate the reporting process between the Investigator and the IRBMED as well as other applicable reporting agencies (FDA, CTEP, NCCN, Pfizer, Inc.). Copies of all related correspondence and reporting documents will be maintained in the regulatory file.

Deaths or life-threatening adverse events will be reported to the University of Michigan Medical Institutional Review Board (IRBMED) in accordance with the reporting policy of the IRB.

12.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, NCCN and Pfizer, Inc. are to be notified within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer, Inc. must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero cases. Pfizer, Inc. and NCCN should be notified via the reporting requirements stipulated in Section 12.12 (Reporting Requirements). Such events will be reported via submission of Pfizer, Inc. Investigator-Initiated Research Serious Adverse Event (IIR SAE) form, according to guidelines provided in Pfizer, Inc. IIR Safety Reporting Reference Manual Version 3, and IIR SAE Form Completion Guide, or Form FDA 3500 A (Med Watch Form) . This will be faxed to Pfizer, Inc. U.S. Clinical Trial Department at 1-866-997-8322 using the Pfizer, Inc. Investigator Initiated Research Reportable Event Fax Cover Sheet. The Investigator-Initiated Research Serious Adverse Event (IIR SAE) form must be submitted to Pfizer, Inc. immediately for a death or life-threatening event, and within 24 hours for all other types of SAEs. Any SAEs reported to Pfizer, Inc. should also be faxed to NCCN at 215-358-7699 or emailed via ORPReports@nccn.org.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to NCCN and Pfizer, Inc. in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer, Inc. to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer, Inc. or its designated representative.

12.12.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to Pfizer, Inc..

12.13. Data and Safety Monitoring

12.13.1 This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan.

12.13.2. The study team will meet quarterly or more frequently depending on the activity of the protocol. During these regular meetings, the study team will discuss matters related to:
1. safety of study participants (SAE/UaP reporting)
2. validity and integrity of the data
3. enrollment rate relative to expectations, characteristics of participants
4. retention of participants, adherence to protocol (potential or real protocol deviations)
5. data completeness

12.13.3. Study team meetings will be documented by the Protocol Specific Data and Safety Monitoring Report (DSMR). The data manager or designee assigned to the trial will be responsible for completing the report. DSMRs will be signed by the Principal Investigator or by one of the co-investigators and will be kept on file in the Oncology Clinical Trials Support Unit (O-CTSU).

12.13.4. The University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) will provide independent oversight of the safety and data integrity for this trial. DSMRs and any other pertinent documents will be submitted to the DSMC for review on a quarterly basis unless specified more frequently by a DSMC ruling.

12.13.5. The Principal Investigator or designee will forward all correspondence and recommendations generated by the DSMC to the Institutional Review Board.

13. STATISTICAL METHODS

13.1. Primary Objectives:

The primary aim of this study is to compare 6-month overall survival after treatment with Axitinib in patients with unresectable, recurrent or metastatic head and neck cancer to historical rates. Based on results in the literature, we assume a 6-month mortality rate of **50%** under current standard care in this patient population (11, 52). We will test whether survival after treatment with Axitinib is improved to 70% at 6-months compared to 50%.

Overall survival will be determined from the date of treatment initiation to date of death from any cause. For the primary endpoint, patients that are alive at 6 months following the initiation of study treatment will be considered successful. All other patients will be considered unsuccessful. Patients will be considered evaluable for the primary endpoint if they receive any dose of Axitinib.

13.2. Sample size justification:

We will enroll 37 additional patients for comparison of overall survival. Based on historical data, 6 month OS in heavily pretreated patients such as those included in this study is 50%. Thirty-seven patients will provide 80% power to detect a meaningful difference in proportion alive at 6-months (70% vs 50% historically) with a type I error rate of 5%. For the primary endpoint of overall survival we anticipate no missing data and will test whether the proportion alive at 6 months is greater than the historical rate of 50% with an upper tailed test of binomial proportion.

Based on our prior experience at the University of Michigan, we anticipate accrual of approximately 4 patients every 5 months. With this rate of accrual, we can enroll 40 eligible patients in 50 months. With a minimum follow-up of 6 month for each patient, the study will complete in about 56 months.

13.3. Stopping rules for futility:

As we observed considerable evidence of activity in UMCC 2011.053, we plan no interim analysis for futility with data collected in the expansion cohort B. Formal analysis of efficacy will be performed at trial completion.

13.4. Analysis plan:

- To estimate survival rates.

Overall and progression-free survival rates at 2, 4 and 6 months will be reported along with 95% confidence intervals based on the binomial distribution. Kaplan-Meier methods will also be conducted to estimate these rates and the medians of PFS and overall survival (OS) of the 37 evaluable patients, with a corresponding standard error estimate based on Greenwood's formula (53).

Among this cohort of patients, progression will be determined based on Choi critieria.

- To determine the response.

The best overall response rate will be determined for each evaluable patient at 8 and 16 weeks following the start of Axitinib. The proportion of evaluable patients who have an objective response (complete or partial) and stable disease will be calculated, and a 95% exact binomial confidence interval will be determined.

- To determine the toxicity profile of this treatment regimen.

The proportion of treated patients experiencing any clinically significant (Grade 3 or worse) toxicity will be determined, with a 95% exact binomial confidence interval; specific toxicities of all grades will be tabulated.

14. DATA ANALYSIS

14.1. Analysis of Overall Survival

Overall survival will be determined from the date of treatment initiation to date of death from any cause. For the primary endpoint, patients that are alive at 6 months following the initiation of study treatment will be considered successful. All other patients will be considered unsuccessful. Patients will be considered evaluable for the primary endpoint if they receive any dose of Axitinib. For the primary endpoint we anticipate no missing data and will test whether the proportion alive at 6 months is greater than the historical rate of 50% with an upper tailed test of binomial proportion.

14.2. Safety Analysis

All patients receiving at least 1 dose of Axitinib under this protocol will be included in the safety analyses. Adverse events will be coded and grouped by body system. The incidence of each adverse event will be tabulated and displayed by starting dose level. Tabulations by maximum severity and relationship to Axitinib will also be included. Summary patient listings will be provided for SAEs, adverse events resulting in discontinuation of Axitinib, and deaths within 28 days of drug discontinuation and possibly or probably related to Axitinib.

14.3. Efficacy Analysis

Efficacy analysis will include Progression-free survival (PFS), Overall response rate (ORR), including complete (CR) and partial response (PR), stable disease, disease control rate (CR+PR+stable disease) at 16 weeks, along with overall survival (OS).

15. QUALITY CONTROL AND QUALITY ASSURANCE

During trial conduct, Pfizer, Inc. or its agent may conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer, Inc. monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, Inc., and/or to inspection by appropriate regulatory authorities.

It is important that the investigators and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

16. DATA HANDLING AND RECORD KEEPING

16.1. Case Report Forms / Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this trial.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer, Inc. and should not be made available in any form to third parties, except for authorized representatives of Pfizer, Inc. or appropriate regulatory authorities, without written permission from Pfizer, Inc..

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, Pfizer, Inc. and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

16.2. Record Retention

To enable evaluations and/or audits from regulatory authorities, NCCN or Pfizer, Inc., the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed

records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the NCCN Research Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, NCCN should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator or another institution. The investigator must obtain NCCN's written permission before disposing of any records, even if retention requirements have been met.

17. ETHICS

17.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to NCCN. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and NCCN in writing within 5 working days after the implementation.

17.2. Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

17.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any Pfizer, Inc. forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer, Inc. will maintain high standards of confidentiality and protection of subject personal data.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and NCCN before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's

signed consent form.

17.4. Reporting of safety issues and serious breaches of the protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of Axitinib, Pfizer, Inc. should be informed immediately.

In addition, the investigator will inform Pfizer, Inc. immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

18. COMPLETION OF TREATMENT AND FOLLOW-UP

After completion of treatment on study patients will be followed for survival. Survival assessment can be done by phone and will be performed once every three months (+/- 1 month)

19. NCCN DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of NCCN. In addition, Pfizer, Inc. retains the right to discontinue development of Axitinib at any time. NCCN reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. If a trial is prematurely terminated or discontinued, NCCN will promptly notify the investigator. After notification, the investigator must contact all participating patients within a 4-week time period. As directed by NCCN, all trial materials must be collected and all CRFs completed to the greatest extent possible.

20. PUBLICATION OF TRIAL RESULTS

20.1. Communication of Results by Pfizer, Inc.

Pfizer, Inc. fulfills its commitment to publicly disclose the results of studies through posting the results of this study on ClinicalStudyResults.org. Pfizer, Inc. posts the results of studies that fall into either of the following categories:
- Studies that Pfizer, Inc. registered on www.clinicaltrials.gov, (ClinicalTrials.gov) regardless of the reason for registration; OR
- All other studies for which the results have scientific or medical importance as determined by Pfizer, Inc.. For studies involving a Pfizer, Inc. product, the timing of the posting depends on whether the Pfizer, Inc. product is approved for marketing in any country at the time the study is completed:
- For studies involving products already approved in any country and for studies that do not involve a Pfizer, Inc. product, Pfizer, Inc. posts results within one year after study completion,

defined as Last Subject Last Visit (LSLV);
- For studies involving products that are not yet approved in any country, Pfizer, Inc. posts the results of already-completed studies within one year after the first regulatory approval of the product;
- For studies involving products whose drug development is discontinued before approval, Pfizer, Inc. posts the results within one year after such discontinuation.
Pfizer, Inc.'s posting on ClinicalStudyResults.org includes the following elements:
- Protocol title, study phase, and indication;
- A link to approved product labeling, if applicable;
- The synopsis of study results;
- Citations of known study publications;
- Legal disclaimer.

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis. If posting of study results to ClinicalStudyResults.org jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has issued or two years have elapsed, whichever occurs first. Pfizer, Inc. posts citations only for publications that are accessible in recognized (searchable) publication databases.

20.2. Publications by Investigators

Pfizer, Inc. has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide NCCN and Pfizer, Inc. an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to NCCN at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the study results themselves) before disclosure.

For all publications relating to the study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the NCCN Research Agreement between NCCN and the institution. In this section entitled Publications, the defined terms shall

have the meanings given to them in the NCCN Research Agreement.

21. REFERENCES:

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