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Phase II Study of Axitinib in Patients with Neurofibromatosis Type 2 and Progressive Vestibular Schwannomas

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PRINCIPAL INVESTIGATOR

THEODORE NICOLAIDES, MD

CO-INVESTIGATORS

JEFFREY ALLEN, MD
SHARON GARDNER, MD
JUDITH GOLDBERG, ScD
MATTHIAS KARAJANNIS, MD, MS (MSKCC)
ANDREW LIN (MSKCC)
SRIVANDANA AKSHINTALA, MBBS, MPH

Primary/Coordinating Study Site: NYU Langone Medical Center

Study Sub-Site: Memorial Sloan Kettering Cancer Center (MSKCC)

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1 Introduction

1.1 Axitinib

Axitinib is an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. As of 27 August 2012, axitinib was approved in 6 countries (United States [US; January 2012], Switzerland [April 2012], Japan [June 2012], Canada [July 2012], Australia [July 2012] and Korea [August 2012]) for previously-treated patients with advanced renal cell carcinoma (RCC); the actual indication varies from country to country. The safety and efficacy of axitinib is being evaluated in patients with a variety of solid tumors, including in treatment-naïve patients with advanced RCC [Information from Investigator's Brochure, September 2012].

VEGF receptors are critical components of the processes leading to the branching, extension, and survival of endothelial cells which form new blood vessels during angiogenesis, an absolute necessity for tumor growth beyond microscopic size. In nonclinical tumor mouse models, twice-daily (BID) oral administration of axitinib demonstrated consistent and significant anti-tumor efficacy (marked inhibitory effect on local and distant tumor metastasis and prolonged animal survival). In multiple animal models, the combination of axitinib with various standard chemotherapies (e.g., docetaxel or carboplatin) and other antiangiogenic agents (e.g., bevacizumab) demonstrated improved benefit compared with single-agent chemotherapeutic/antiangiogenic agents.

The nonclinical safety profile of axitinib has been well characterized through the conduct of single-dose and repeat-dose toxicity studies of up to 39 weeks in duration, and safety pharmacology, genetic toxicity, reproductive and developmental toxicity, and phototoxicity studies. The primary target organ toxicities were observed in the gastrointestinal, hematopoietic, musculoskeletal, and reproductive systems. Additionally, hemodynamic effects (elevated blood pressure, reduced heart rate) were identified from repeat-dosing in conscious, telemetered animals. Axitinib was not identified as a mutagen or clastogen, but considered an aneugen at area under the plasma concentration-time curve (AUC) exposure that exceeds that at the recommended human dose (RHD) of 5 mg BID. While axitinib has relevant ultraviolet (UV) absorbance with the potential to distribute to sun-exposed tissues, no phototoxicity potential was identified from in vitro testing in 3T3 fibroblasts. Many of the findings identified from non-clinical safety testing are consistent with the anticipated pharmacological response to a VEGF receptor inhibitor, including the blood pressure changes, and effects on ovarian follicles and the growth plate of actively growing animals, which are reliant on angiogenesis for development. Fertility and developmental effects were also observed, consistent with the effects identified from toxicity studies on reproductive organs and role of angiogenesis in the development of a fetus.

Axitinib and its metabolites were widely distributed into tissues in mice, but did not accumulate and were not retained for long periods of time in most tissues. The plasma protein binding was 97%, 98%, and 99% in the mouse, dog, and human, respectively.

In humans, the median recovery of [14C] axitinib radioactivity in feces was 37.0% and in urine was 22.7% (total recovery = 59.7%) of the total orally administered dose (5 mg). In plasma, the glucuronide was the predominant metabolite and accounted for approximately 50% of the circulating radioactivity. The sulfoxide and unchanged parent drug accounted for approximately 20% of the circulating radioactivity. In feces, the parent drug represented the single most predominant radioactive component (12% of the dose).

As of 1 June 2012, 43 studies evaluating the safety, efficacy, and PK of axitinib have been completed or are ongoing. These studies include 15 Phase 1 studies in healthy subjects and 28 studies in subjects with cancer including 1 continued access and 1 compassionate-use study.

A study in healthy volunteers (A4061007) indicated that the mean absolute oral bioavailability of the drug was 58%. Interaction studies in healthy volunteers with the CYP3A4/5 inhibitor ketoconazole (A4061004) and CYP3A4/5 inducer rifampin (A4061026) produced a 2-fold increase and 79% reduction in axitinib plasma exposures, respectively. Axitinib has two major (non-pharmacologically active) circulating plasma metabolites, a glucuronide product and a sulfoxide product (A4061003). In subjects with moderate hepatic impairment (Child Pugh B), there was a ~2-fold increase in axitinib area under curve from zero to infinity (AUC (0-∞)) and a 1.3-fold increase in axitinib maximum plasma concentration (C_{max}) compared to subjects with normal hepatic function (A4061036). No difference in axitinib plasma pharmacokinetics was observed between Caucasian and first-generation Japanese volunteers (n=20 each) (A4061026). Phase 1 studies in combination with chemotherapeutic/anticancer agents in cancer patients have indicated plasma pharmacokinetics of docetaxel, paclitaxel, carboplatin, capecitabine, gemcitabine, cisplatin, pemetrexed, oxaliplatin, 5-fluorouracil (5-FU), bevacizumab, and irinotecan (including its SN-38 activated metabolite) were similar in the absence and presence of axitinib. Likewise, axitinib plasma profiles and pharmacokinetic parameters were similar in the presence and absence of these co-administered chemotherapeutic/anticancer agents (A4061019 and A4061020).

In ongoing clinical studies, the axitinib starting dose is 5 mg BID. Subjects who can tolerate axitinib with no adverse events related to axitinib above Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 for consecutive 2 week periods are permitted to increase their dose step-wise to 7 mg BID and then to a maximum of 10 mg BID, unless their blood pressure (BP) is >150/90 mm Hg. The dose of axitinib can be reduced to as low as 2 mg BID if > Grade 2 treatment-related adverse events occur.

Overall, the adverse events reported for axitinib in clinical studies are considered manageable, generally reversible and expected for this class of agents. For single-agent axitinib, the most common adverse events (>20%) reported from 699 cancer subjects regardless of causality included diarrhea (397 subjects, 56.8%), fatigue (368 subjects, 52.6%), hypertension (318 subjects, 45.5%), decrease appetite (286 subjects, 40.9%), nausea (264 subjects, 37.8%), dysphonia (242 subjects, 34.6%), palmar-plantar erythrodysaesthesia syndrome (202 subjects, 28.9%), weight decreased (197 subjects, 28.2%), vomiting (166 subjects, 23.7%), constipation (165 subjects, 23.6%), headache (151 subjects, 21.6%), cough (149 subjects, 21.3%), arthralgia and dyspnea (140 subjects, 20%). Grade 3+ events occurred most frequently for hypertension (134 subjects, 19.2%), fatigue (90 subjects, 12.9%), and diarrhea (65 subjects, 9.3%).

Hypothyroidism and proteinuria were reported as adverse events in 122/699 subjects (17.5%) and 117/699 subjects (16.7 %), respectively. Hemorrhagic events (including epistaxis, hematuria, hemoptysis, rectal hemorrhage, cerebral hemorrhage, gastric hemorrhage, and lower gastrointestinal hemorrhage) were reported in 182/699 subjects (26.0%); Grade 3+ hemorrhagic events occurred in 13/699 subjects (1.9%), including 1 death (gastric hemorrhage).

Arterial thromboembolic events (including cerebral infarction, cerebrovascular accident, embolism arterial, lacunar infarction, myocardial infarction, retinal artery occlusion, and transient ischemic attack) were reported in 16/699 subjects (2.3%) including 2 deaths (secondary to cerebrovascular accident). Venous thromboembolic events (including pulmonary embolism, deep vein thrombosis, retinal vein occlusion and jugular vein thrombosis) were reported in 21/699 subjects (3.0%) including 2 deaths (pulmonary embolism). Gastrointestinal perforation (including gastrointestinal perforation, large intestine perforation, and intestinal perforation) were reported in 5/699 subjects (0.7%) including 1 death (intestinal perforation). In addition to cases of gastrointestinal perforation, fistulas (including anal fistula and fistula) were reported in 4/699 subjects (0.6%). Reversible posterior leukoencephalopathy syndrome (RPLS) was reported in 3/699 subjects (0.4%).

Axitinib has been investigated in combination with various chemotherapy regimens (e.g., docetaxel, carboplatin/paclitaxel, gemcitabine, capecitabine/cisplatin, gemcitabine/cisplatin, weekly paclitaxel, capecitabine, FOLFIRI, FOLFOX, FOLFOX + bevacizumab, and pemetrexed/cisplatin). In general, axitinib at a starting dose of 5 mg BID administered continuously has been combined with the full dose of chemotherapy. Non-hematological safety events have been similar to those for the single-agent axitinib and those for the chemotherapy regimens. Preliminary evidence of antitumor activity has been observed with axitinib as a single agent and in combination with chemotherapy across multiple tumor types. Plasma concentrations as well as pharmacokinetic parameters of the co-administered chemotherapeutic/anti-cancer drug were similar in the presence and absence of axitinib. However, a clinical study conducted with axitinib in combination with docetaxel indicated that the docetaxel mean plasma exposure was increased in the presence of axitinib. The plasma pharmacokinetics of axitinib was similar in the presence of all chemotherapeutic agents evaluated.

A Phase 3 study comparing axitinib versus sorafenib in previously-treated (second-line) patients with advanced renal cell carcinoma (RCC) met the primary endpoint (progression- free survival [PFS] per blinded independent review).[1] The most common (≥20%) adverse reactions observed following treatment with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, palmar-plantar erythrodysesthesia (hand-foot) syndrome, weight decreased, vomiting, asthenia, and constipation. Based on the findings from this registrational study, as of 27 August 2012, axitinib was approved in 6 countries (United States [US; January 2012], Switzerland [April 2012], Japan [June 2012], Canada [July 2012], Australia [July 2012] and Korea [August 2012]) for previously-treated patients with advanced renal cell carcinoma (RCC); the actual indication varies from country to country. A Phase 3 study comparing axitinib vs sorafenib in treatment-naïve (first-line) patients with advanced RCC is ongoing. A double-

blind randomized Phase 2 study comparing dose titration with axitinib vs placebo in treatment-naïve (first-line) patients with advanced RCC is also ongoing.

In addition, a double-blind randomized study comparing axitinib vs placebo in previously-treated (second-line) patients with advanced hepatocellular carcinoma (HCC) is ongoing. Phase 1 and 2 studies are ongoing in other advanced solid tumors. Combination studies of axitinib with chemotherapy are being conducted in non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and gastric cancer.

Pediatric Studies

The Children's Oncology Group phase 1 study ADVL1315 (NCT02164838) for pediatric patients with recurrent/refractory solid tumors recently determined a recommended phase 2 dose (RP2D) of 2.4 mg/m^2 PO BID, corresponding to approximately 4mg PO BID in an average sized adult, or 80% of the adult standard starting dose [J Clin Oncol 34, 2016 (suppl; abstr 10558)]. In this study, oral axitinib tablets were administered twice daily, continuously in 28-day cycles. Dose levels 2.4 and 3.2 mg/m^2/dose were evaluated using a rolling 6 design. As of December 11, 2015, 17 patients were enrolled with 1 ineligible (inadequate time from prior therapy). The median age was 14 yrs (range 5–17 yrs); 9 were male. Patients received a median 3 prior chemotherapy regimens (range 1-8). Cancer diagnoses included soft tissue sarcomas (7), Ewing (2) and osteosarcoma (1), neuroblastoma (2), Wilms tumor (1), hepatoblastoma (1), hepatocellular carcinoma (1), medullary carcinoma (1), and epithelial-myoepithelial carcinoma (1). Toxicity data were available for 15 patients (6 at dose level 1, 5 at dose level 2, and 4 on an expanded PK cohort). One patient was inevaluable for toxicity due to inadequate drug exposure. DLTs occurred in 0/6 and 2/5 patients treated at dose level 1 and 2 respectively (palmar-plantar erythrodysesthesia syndrome (1); intratumoral hemorrhage (1)). Cycle 1 hematologic toxicities included grade 3 lymphopenia (1) and grade 1 or 2 anemia (4), lymphopenia (3), elevated hemoglobin (3), leukopenia (2), neutropenia (1), thrombocytopenia (1), and lymphocytosis (1). Non-hematologic toxicities included grade 1 or 2 nausea (5), hypertension (4), anorexia (3), creatinine elevation (2), diarrhea (2), fatigue (2), headache (2), lipase elevation (2), proteinuria (2), and acneiform rash (2). The most common subsequent cycle grade 3 or 4 toxicities included neutropenia (grade 3 (3), grade 4 (1)) and lymphopenia (grade 3 (1), grade 4 (1)).

1.2 Neurofibromatosis Type 2 (NF2) and Study Rationale

Neurofibromatosis type 2 (NF2) is an autosomal-dominant genetic disease with an incidence of approximately 1/40,000. The NF-2 gene is located on chromosome 22 and its gene product is named Merlin. Merlin's function is not well understood, but it appears to act as a tumor suppressor. The majority of NF2 patients develop progressive hearing loss in adolescence or young adulthood due to unilateral or bilateral vestibular schwannomas (VS).[2] Spinal tumors, including meningiomas, schwannomas and ependymomas, as well as intracranial tumors, mostly meningiomas, are also highly prevalent. NF2-related tumors, although mostly slow growing, cause considerable morbidity and mortality, particularly when first diagnosed at a young age. The available treatment options for these neoplasms, which often occur at multiple sites simultaneously, are non-curative and mostly limited to surgery and radiation therapy. As

a result, all NF2 patients suffer from major morbidity, mortality and significantly reduced life expectancy.

Although classic chemotherapy is effective treatment for low-grade brain tumors, no such therapy has been validated for NF2 patients with multiple tumors for a variety of reasons. Most chemotherapeutic agents are mutagenic and there is reluctance to use them in patients with loss of tumor-suppressor function, such as NF2. Many chemotherapeutic drugs are neuro– and/or ototoxic, making them unsuitable for NF2 patients. No chemotherapy regimens have been identified to date for the most common tumors arising in NF-2 patients such as meningiomas, ependymomas and schwannomas. Surgery remains the mainstay of therapy for VS, but carries major risks including complete deafness, facial palsy, stroke and CSF leak. Medical treatment options for VS are therefore urgently needed.[3]
Although VS and meningiomas are the hallmark of NF2, the vast majority of VS and meningiomas arise sporadically in non-NF2 patients. The prevalence of idiopathic VS in the US is roughly 3,000 new cases per year and the incidence appears to be increasing in recent years.[4] These tumors cause unilateral hearing loss, tinnitus, imbalance and vertigo. The primary treatment modality for these tumors is surgical resection or radiosurgery. Surgery can be associated with the same complications listed above for NF2-related VS. Hence, RT is often offered in place of surgery. Although considered safer in idiopathic VS, long term efficacy has not been established and RT may complicate future procedures. Therefore, this large population of patients with sporadic VS may also benefit from a medical option either at initial diagnosis or at progression.

Axitinib is an oral multi-receptor tyrosine kinase (RTK) inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), and c-KIT. Axitinib inhibits VEGFR1/2/3, PDGFRα/β and c-KIT phosphorylation in the sub– to low nanomolar range.[5] Axitinib is currently FDA-approved for the second-line treatment of renal cell carcinoma. All of the molecular targets of axitinib represent clinically and/or preclinically validated molecular targets for VS:

VEGFR: Angiogenesis occurs in VS, and VEGFRs are expressed in these tumors.[6-8] Anti-VEGF(R)-directed therapy with bevacizumab and vandetanib normalized the vasculature of $NF2^{-/-}$ schwannoma xenografts in nude mice and decreased tumor growth.[9] Clinically, VEGF-targeted therapy with bevacizumab has been reported to lead to dramatic tumor shrinkage and hearing improvement in NF2 patients with VS.[8,10,11] Sporadic responses of meningiomas to bevacizumab have been reported,[12] and trials with angiogenesis inhibitors for sporadic meningiomas are ongoing.

PDGFRβ: Schwann cells express PDGFRα and PDGFRβ.[13] Signaling through these receptors activates the RAS-RAF-MEK-ERK and PI3K-AKT signaling pathways, and is important for Schwann cell proliferation *in vivo* and *in vitro.*[14-16] Overexpression of PDGFRβ has been observed in VS,[17-19] and PDGFR inhibitors including AG1296, imatinib and nilotinib are effective in preventing PDGFR-driven proliferation when tested in VS *in vitro* models.[17,20]

c-KIT: VS express activated c-KIT and are growth-inhibited by imatinib[19] and nilotinib.[20]

In summary, the molecular target profile of axitinib makes it a promising drug candidate for clinical study in NF2 patients with progressive VS. Although the potency of axitinib in inhibiting PDGFR and c-KIT is significantly lower than VEGFR1/2/3,[5] preclinical data indicates accumulation of axitinib in brain tissue,[5] and similarly, we have observed tumor tissue to plasma ratio of 4.3 +/-1.9 in human VS tissue treated with the EGFR/ErbB2 receptor tyrosine kinase inhibitor lapatinib (Karajannis, et. al, *Neuro-Oncology* 14:i19, 2012 [abstract]).

The favorable toxicity profile and tolerability of axitinib compared to other multi-kinase inhibitors is advantageous for potential long-term administration in NF2. Over the past 4 years, we have shown that we can successfully conduct and complete single-institution Phase 2 clinical trials in the NF2 population using molecular targeted agents including lapatinib and everolimus (ClinicalTrials.gov NCT00973739 and NCT01419639).[21]

2 Key Eligibility Criteria

1) Age ≥5 years
2) Clinically (NIH or Manchester criteria) or genetically confirmed diagnosis of NF2
3) Karnofsky (for >16 years) or Lansky (≤16 years) performance status of ≥60
4) Disease criteria:
   - At least one volumetrically measurable NF2-related VS (histological confirmation not required)
   - MRI evidence of progression over the past 18 months, OR progressive hearing loss
5) Adequate organ system function (bone marrow, renal, hepatic)

3 Research Strategy

Primary Objective: To estimate the objective volumetric response rates to axitinib in pediatric and adult NF2 patients with VS.

Secondary Objectives: To assess the toxicity of axitinib given daily in patients with NF2 and to examine the association of objective measures of response on MRI, i.e. volumetric tumor analysis with clinical measures of response, i.e. (audiogram), as well as quality of life assessments (NFTI-QOL). In addition, response in non-VS tumors, such as other schwannomas and meningiomas, may be explored.

Drug Dosage and Administration (adult patients, age ≥18 years): 5 mg axitinib PO BID, with increase to 7 mg PO BID and 10 mg BID after 2 and 4 weeks, respectively, provided no adverse reactions (i.e., not exceeding grade 2 toxicities) and normotensive and not receiving antihypertension medications. Axitinib will be given continuously in 28-day cycles.

Drug Dosage and Administration (pediatric patients, age <18 years): 2.4 mg/m^2 axitinib PO BID, with increase to 3.2 mg/m^2 PO BID after 2 weeks, provided no adverse reactions (i.e., not exceeding grade 2 toxicities) and normotensive and not receiving antihypertensive medications. Axitinib will be given continuously in 28-day cycles using a dosing nomogram shown in Section 7.3.1. The maximal dose of 3.2 mg/m^2 PO BID exceeds the recommended phase 2 dose from the pediatric phase 1 trial, with the rationale that young NF2 patients, who

are generally not pre-treated with myelotoxic chemotherapy are likely to tolerate a higher dose of axitinib compared to the heavily pre-treated, refractory cancer patients enrolled on the pediatric phase 1 study [J Clin Oncol 34, 2016 (suppl; abstr 10558)]. Similar to adult patients on this study, the option to escalate the dose is intended to optimize secondary target inhibition and therefore increase the likelihood of responses.

Study Assessments: MRIs including volumetrics and audiograms at baseline and after every 3rd cycle (i.e. 12 weeks). Monthly study visits including H&P, neurological examination and standard laboratory evaluations. Quality of life assessments (NFTI-QOL) at baseline and cycle 6.

Treatment Duration: Until radiographic progression or unacceptable toxicity.

4 Endpoints/Statistical Considerations

Volumetric tumor response by the end of cycle 12 is the *primary endpoint.* Response and progression are defined as ≥20% decrease or increase in tumor volume, respectively.[22]

To evaluate the volumetric tumor response, a 2-stage Simon design will be used.[23] Axitinib will be considered not of sufficient interest for further evaluation if the true response rate is 5% (p0) or less and considered active if the true response rate is 25% or greater (p1). With beta (probability of rejecting axitinib with true response rate 5%) set at 0.2 and alpha (probability of failing to reject a treatment with response probability of 25%) set at 0.05, the required sample size is 9 patients for stage 1 and an additional 8 patients for stage 2, (optimal and minimax design) . If there are no responses after the first stage is completed, axitinib will be deemed ineffective and the trial terminated. Recruitment will be halted after the 9th evaluable patient is enrolled (stage 1) until at least one response is observed during the first 12 cycles. Axitinib will be considered effective and of interest for further study if after successful completion of both stages, the cumulative number of responses is ≥3. Using this 2-stage design, the probability of early termination is 0.63 if the true response rate to axitinib is 5%.

Secondary endpoints include hearing response (rise of the word recognition score above the 95% critical difference interval from baseline) and quality of life assessments (NFTI-QOL).[24]

5 Proposed Sample Size and Timeline for Recruitment

A maximum of 17 evaluable subjects will be accrued to this study. According to our initial estimates, and based on our prior experience with lapatinib and everolimus phase 2 trials for adults and children with an average accrual rate of >2 patients per month, the expected accrual period was approximately 12 months. However, the widespread use of bevacizumab on clinical trials and off-label, has rendered a large number of NF2 patients ineligible for this study, resulting in slower than expected accrual. The protocol was amended to include pediatric patients after pediatric phase 1 data became available, to increase enrollment.

6 Study Objectives

Primary

- To estimate the volumetric response rates to axitinib in patients with NF2-related vestibular schwannomas (VS).

Secondary

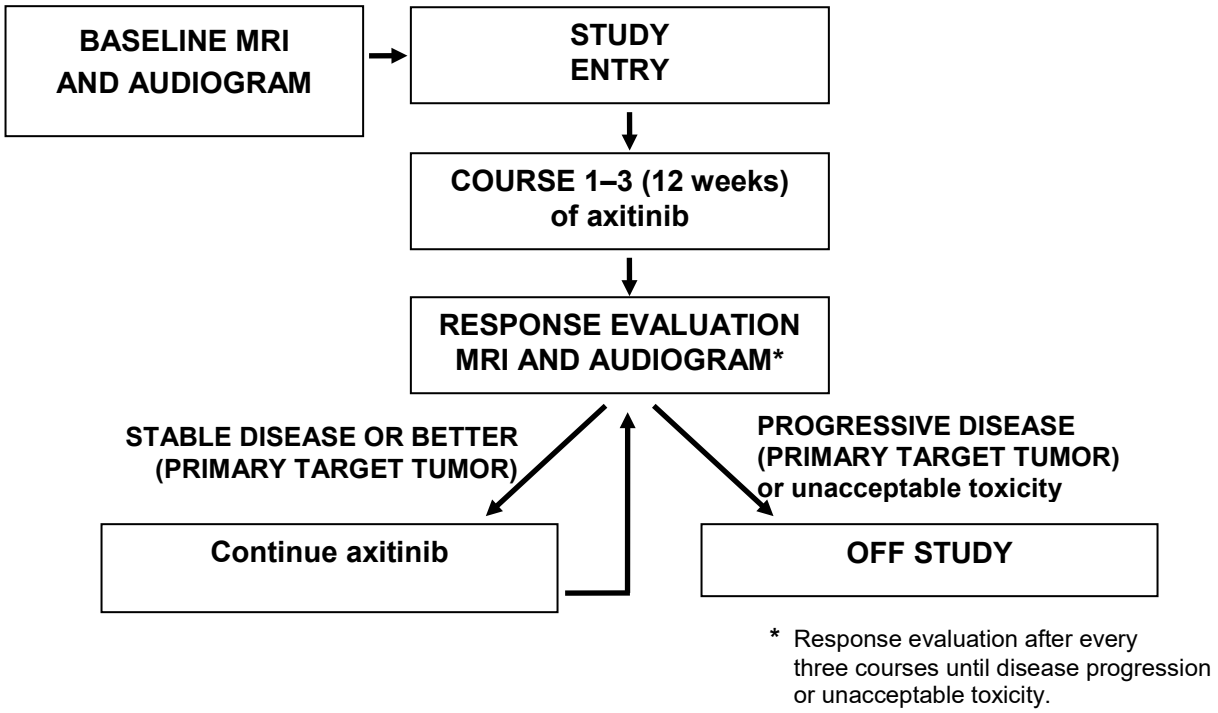
- To assess the toxicity of axitinib given daily in patients with NF2 and to examine the association of objective measures of response on MRI, i.e. volumetric tumor analysis with clinical measures of response, i.e. (audiogram), as well as quality of life assessments (NFTI-QOL). In addition, response in non-VS tumors, such as other schwannomas and meningiomas, may be explored.

7 Investigational Plan

7.1 Study Design and Treatment

- Multi Center, 2-stage, phase II open-label study
- *Planned treatment:* Axitinib PO taken continuously until disease progression or unacceptable toxicity:
    - **Staring dose (dose level 0):** 5 mg PO twice daily (approx. 12 hours apart) for adult patients (≥18 years of age) and 2.4 mg/m^2 axitinib PO BID for pediatric patients (<18 years of age).
    - **Dose titration:** Axitinib dose should be individually titrated up or down from the starting dose based on patient tolerance, as outlined in Section 7.3.
- *Response Evaluations:* MRI brain and spine (with 3D volumetrics) and audiograms (if applicable) at baseline and after every 3rd course (cycle), i.e. every 12 weeks. Spine MRI will be performed only in patients with known spinal tumors with medically relevant or symptomatic lesions.

The overall study design is shown in the following schema:



7.2 Study Population

7.2.1 Patient population

Minimum of 9, maximum of 17 evaluable patients (based on observed volumetric responses, 2-stage study design, see Section 11)

7.2.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient (or legal guardian for minors, as applicable) prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria

- Age ≥5 years
- Meets clinical diagnostic criteria for NF2 or genetically conformed NF2
- At least one volumetrically measurable and ≥1 cc NF2-related VS (histological confirmation not required)
- MRI evidence of progression (either as >2 mm increase in maximum linear diameter on conventional MRI, or a >20%volume increase by 3D volumetrics)[22] over the past ≤18 months, OR progressive hearing loss, defined as a decline in word recognition score below the 95% critical difference interval from baseline score related to VS (i.e., not due to prior interventions such as surgery or radiation)
- Karnofsky (>16 years of age) or Lansky (≤16 years of age) performance status (PS) 60–100%. Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
- Adequate bone marrow function as shown by: ANC ≥1.5 x 10^9/L, Platelets ≥100 x 10^9/L, Hb >9 g/dL
- Adequate liver function as shown by:
  - serum bilirubin ≤1.5 x ULN
  - ALT and AST ≤2.5x ULN
- INR ≤1.5. (anticoagulation with low molecular weight heparin is allowed if on a stable dose for >2 weeks at time of enrollment.)
- Adequate renal function: serum creatinine ≤1.5 x ULN
- Fully recovered from acute toxic effects of any prior chemotherapy, biological modifiers or radiotherapy
- Any neurologic deficits must be stable for ≥1 week
- Able to swallow tablets
- Able to provide signed informed consent (or consent provided by legal guardian for pediatric patients, as applicable)

Exclusion criteria

- Patients currently receiving medical anticancer therapies or who have received medical anticancer therapies within 4 weeks of the start of study drug (including chemotherapy, antibody based therapy, etc.)
- Radiation therapy to a study target tumor within 1 year prior to enrollment, or any radiation therapy within 4 weeks prior to enrollment.
- Patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study
- Prior treatment with bevacizumab or other agents targeting VEGF or VEGFR

- Prior treatment with any investigational drug within the preceding 4 weeks
- Unstable or rapidly progressive disease, including patients who require glucocorticoids for symptomatic control of brain or spinal tumors
- Treatment with strong CYP3A4 enzyme inhibitors or inducers, including but not limited to ketoconazole, itraconazole, ritonavir, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital and St. John's wort. Please refer to the list in Appendix I.
- Requirement of therapeutic anticoagulant therapy with oral vitamin K antagonists; low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed; therapeutic use of low molecular weight heparin (or similar parenteral drug) for venous-thromboembolic disease is allowed.
- Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Symptomatic congestive heart failure of New York heart Association Class III or IV
    - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
    - severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O_2 saturation that is 90% or less at rest on room air
    - active (acute or chronic) or uncontrolled severe infections
    - liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of axitinib (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
- Patients with an active bleeding diathesis
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. Adequate contraception must be used throughout the trial and for 8 weeks after the last dose of study drug, by both sexes. (Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to administration of axitinib)
- Male patient whose sexual partner(s) are women of child bearing potential, who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment
- History of noncompliance to medical regimens
- Patients unwilling to or unable to comply with the protocol

7.2.3 Description of the Recruitment Process

Patients who are evaluated for NF-2 related vestibular schwannomas at the approved study sites may be considered potential study candidates and will be advised about the study by their physicians. Physicians not included as approved study investigators may refer their patients for enrollment on this study, and if the patient provides their permission, can provide the patients' contact information to study team members so that they can contact the potential participant to discuss the study. If patients are interested in participating, they will be asked to provide informed consent as described in Section 8.

7.2.4 Monitoring of axitinib suspected toxicities

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

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

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

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

7.3 Treatment

7.3.1 Axitinib administration

The study drug axitinib will be self-administered. The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Axitinib should be administered orally twice daily, approximately 12 hours apart, preferably in the morning and evening, at approximately the same time every day with or without food. Axitinib should be swallowed whole with a glass of water. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.

Axitinib will be provided by Pfizer, Inc. Two strengths of tablets (1 mg and 5 mg) are being used in the clinical program and approved for use in those countries in which axitinib (Inlyta®) is marketed. All tablets contain common compendial excipients and film-coating materials. The tablets will be packaged in appropriate packaging material and stored at room temperature.

Axitinib PO will be taken continuously until disease progression or unacceptable toxicity, in continuous treatment cycles of 28 days each (maximum of 12 cycles):

Adult patients (≥18 years of age)

- **Starting dose (dose level 0):** 5 mg PO twice daily (approx. 12 hours apart)
- **Dose titration:** Adult patients who tolerate axitinib with no adverse events related to axitinib above CTCAE Grade 2 for consecutive 2 week periods, are normotensive, and are not receiving anti-hypertension medication, should have their dose increased by one dose level until dose level +2 is reached. Axitinib dose should be individually titrated up or down from the starting dose based on patient tolerance:

Dose Level	Total dose [mg] BID	5 mg tabs BID	1 mg tabs BID
+2	10	2	
+1	7	1	2
0	**5**	**1**	
-1	3		3
-2	2		2

Pediatric Patients (<18 years of age)

- **Starting dose (dose level 0):** 2.4 mg/m^2 PO twice daily (approx. 12 hours apart)
- **Dose titration:** Pediatric patients who tolerate axitinib with no adverse events related to axitinib above CTCAE Grade 2 for2 weeks , are normotensive, and are not receiving anti-hypertension medication, should have their dose increased by one dose level (Dose level + 1, 3.2 mg/m^2/dose). Hypertension in the pediatric patients is defined as systolic or diastolic BP >95th percentile for age, height, and sex. Axitinib dose should be individually titrated up or down from the starting dose based on patient tolerance. Dosing will be based using a nomogram as shown below:

Axitinib 1.8 mg/m^2 BID (Dose Level -1

BSA (m^2)	Total Daily Dose (mg/day)	mg q am	mg q pm
0.53-0.72	2	1	1
0.73-0.97	3	2	1
0.98-1.25	4	2	2
1.26-1.52	5	3	2
1.53-1.80	6	3	3
1.81-2.08	7	4	3
≥2.09	8	4	4

Axitinib 2.4 mg/m^2 BID (Dose Level 0)

BSA (m^2)	Total Daily Dose (mg/day)	mg q am	mg q pm
0.53-0.72	3	2	1
0.73-0.93	4	2	2
0.94-1.14	5	3	2
1.15-1.35	6	3	3
1.36-1.56	7	4	3
1.57-1.77	8	4	4
1.78-1.97	9	5	4
>1.98	10	5	5

Axitinib 3.2 mg/m^2 BID (Dose Level +1)

BSA (m^2)	Total Daily Dose (mg/day)	mg q am	mg q pm
0.53-0.70	4	2	2
0.71-0.85	5	3	2
0.86-1.01	6	3	3
1.02-1.17	7	4	3
1.18-1.32	8	4	4
1.33-1.48	9	5	4
1.49-1.64	10	5	5
1.65-1.79	11	6	5
≥1.80	12	6	6

7.3.2 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of axitinib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Section 7.3.3. Dose Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0,http://evs.nci.nih.gov/ftp1/CTCAE/).

7.3.3 General criteria for dose-modification of axitinib

General criteria for dose-modification in case of suspected axitinib toxicity and re-initiation of axitinib treatment

Toxicity	Actions
Non-hematological toxicity	
Grade 2	**If the toxicity is tolerable to the patient, maintain the same dose.If the toxicity is intolerable to patient, interrupt axitinib until recovery to grade ≤1. Then reintroduce axitinib at same dose. If event returns to grade 2, then interrupt axitinib until recovery to grade ≤1. Then reintroduce axitinib at the lower dose level.**
Grade 3	**Interrupt axitinib until recovery to grade ≤1. Then reintroduce axitinib at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.**
Grade 4	**Discontinue axitinib.**
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥50x10^9/L)	**Interrupt axitinib until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce axitinib at initial dose. If thrombocytopenia again returns to grade 2, interrupt axitinib until recovery to grade ≤1. Then reintroduce axitinib at the lower dose level.**
Grade 3 Thrombocytopenia (platelets <50, ≥25 x10^9/L)	**Interrupt axitinib until recovery to grade ≤1 (platelets ≥75 x10^9/L). Then resume axitinib at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue axitinib.**
Grade 4 Thrombocytopenia (platelets <25 x10^9/L)	**Discontinue axitinib.**
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	**Interrupt axitinib until recovery to grade ≤1 (neutrophils ≥1.5 x 10^9/L). Then resume axitinib at the initial dose. If ANC again returns to Grade 3, hold axitinib until the ANC ≥1.5 x 10^9/L. Then resume axitinib dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.**
Grade 4 Neutropenia (neutrophils <0.5 x10^9/L)	**Interrupt axitinib until recovery to grade ≤1 (neutrophils ≥1.5 x 10^9/L). Then resume axitinib at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue axitinib.**
Grade 3 febrile neutropenia (not life-threatening)	**Interrupt axitinib until resolution of fever and neutropenia to grade ≤1. Hold further axitinib until the ANC ≥1,500/mm^3 and fever has resolved. Then resume axitinib at the lower dose level. If febrile neutropenia recurs, discontinue axitinib.**
Grade 4 febrile neutropenia (life-threatening)	**Discontinue axitinib.**
Any hematological or non-hematological toxicity requiring interruption for ≥3 weeks	**Discontinue axitinib**

7.3.4 Precautions and management of specific toxicities

Hypertension

In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, hypertension was reported in 145/359 patients (40%) receiving axitinib. Grade 3 hypertension was observed in 55/359 patients (15%) and Grade 4 hypertension was observed in 1/359 patients (<1%) receiving axitinib. Hypertensive crisis was reported in 2/359 patients (<1%). The median onset time for hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >100 mmHg) was within the first month of the start of axitinib and blood pressure increases have been observed as early as 4 days after starting axitinib. Hypertension was managed with standard antihypertensive therapy. Discontinuation of axitinib treatment due to hypertension occurred in 1/359 patients (<1%)[Information from Investigator's Brochure, September 2012].

Blood pressure should be well-controlled prior to initiating axitinib. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, the axitinib dose should be reduced. For patients who develop severe hypertension, temporarily interrupt axitinib treatment and restart at a lower dose once the patient is normotensive (see Section 7.3.3). If axitinib is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

Thyroid dysfunction

In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, hypothyroidism was reported in 69/359 patients (19%) receiving axitinib. Hyperthyroidism was reported in 4/359 patients (1%). In patients who had thyroid stimulating hormone (TSH) <5 μU/mL before treatment, elevations of TSH to ≥10 μU/mL occurred in 79/245 patients (32%) receiving axitinib.

Thyroid function will be monitored before initiation of, and periodically throughout, treatment with axitinib. Hypothyroidism and hyperthyroidism should be treated according to standard medical practice to maintain euthyroid state.

Arterial thromboembolic events

In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, Grade 3/4 arterial thromboembolic events were reported in 4/359 patients (1%) receiving axitinib. The most frequent arterial thromboembolic event was transient ischemic attack (1%). Fatal cerebrovascular accident was reported in 1/359 patients (<1%).

In monotherapy studies with axitinib, arterial thromboembolic events (including transient ischemic attack, cerebrovascular accident, myocardial infarction, cerebral infarction, arterial embolism, lucunar infarction, and retinal artery occlusion) were reported in 16/699 subjects (2%).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had an arterial thromboembolic event within the previous 12 months.

Venous thromboembolic events
In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, venous thromboembolic events were reported in 11/359 patients (3%) receiving axitinib. Grade 3/4 venous thromboembolic events (including pulmonary embolism, deep vein thrombosis, and retinal-vein occlusion/thrombosis) were reported in 9/359 patients (3%). Fatal pulmonary embolism was reported in 1/359 patients (<1%).

Axitinib should be used with caution in patients who are at risk for, or who have a history of, these events. Axitinib has not been studied in patients who had a venous thromboembolic event within the previous 6 months.

Elevation of hemoglobin or hematocrit
Increases in hemoglobin or hematocrit, reflective of increases in red blood cell mass, may occur during treatment with axitinib. An increase in red blood cell mass may increase the risk of thromboembolic events.

In Phase 3 study A4061032 with axitinib for treatment of patients with RCC, elevated hemoglobin above the upper limit of normal (ULN) was observed in 31/320 patients (10%) receiving axitinib.

Monitoring of hemoglobin/hematocrit will be performed before initiation of, and periodically throughout, treatment with axitinib. If hemoglobin or hematocrit becomes elevated above the normal level, patients should be treated according to standard medical practice to decrease hemoglobin or hematocrit to an acceptable level.

Hemorrhage
In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, hemorrhagic events were reported in 58/359 patients (16%) receiving axitinib. The most common hemorrhagic events in patients treated with axitinib were epistaxis (6%), hematuria (3%), hemoptysis (2%), and rectal hemorrhage (2%). Grade 3/4 hemorrhagic events (including cerebral hemorrhage, haematuria, hemoptysis, lower gastrointestinal hemorrhage, and melaena) were reported in 5/359 (1%) patients. Fatal hemorrhage (gastric hemorrhage) was reported in 1/359 patients (<1%) receiving axitinib.

Axitinib has not been studied in patients who have evidence of untreated brain metastasis or recent active gastrointestinal bleeding and should not be used in those patients. If any bleeding requires medical intervention, temporarily interrupt the axitinib dose.

Gastrointestinal perforation and fistula formation
In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, gastrointestinal perforation was reported in 1/359 patients (<1%) receiving axitinib. In addition to cases of gastrointestinal perforation, fistulas were reported in 2/359 patients (1%). In monotherapy studies with axitinib (N=699), fatal gastrointestinal perforation was reported in 1/699 patient (<1%).

Monitoring for symptoms of gastrointestinal perforation should be performed throughout treatment with axitinib.

Wound healing complications
No formal studies of the effect of axitinib on wound healing have been conducted. In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, all-causality adverse events suggestive of wound healing complications were reported in 4/359 patients (1%).

Treatment with axitinib should be stopped at least 24 hours prior to scheduled surgery. The decision to resume axitinib therapy after surgery should be based on clinical judgment of adequate wound healing.

Reversible posterior leukoencephalopathy syndrome/posterior reversible encephalopathy syndrome
In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, reversible posterior leukoencephalopathy syndrome (RPLS)/posterior reversible encephalopathy syndrome (PRES) was reported in 1/359 patients (<1%).

RPLS/PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS/PRES. In patients with signs/symptoms of RPLS/PRES, temporarily interrupt or permanently discontinue axitinib. The safety of reinitiating axitinib therapy in patients previously experiencing RPLS/PRES is not known.

Proteinuria
In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, proteinuria was reported in 39/359 patients (11%). Grade 3 or 4 proteinuria was reported in 11/359 patients (3%).

Monitoring for proteinuria will be performed before initiation of, and periodically throughout, treatment with axitinib.

Elevation of liver enzymes
In the first-in-human dose-finding study A4060010, concurrent elevations of alanine aminotransferase [ALT] (12 times the ULN) and bilirubin (2.3 times the ULN), considered to be drug-related hepatotoxicity, were observed in 1 patient who received axitinib at a starting dose of 20 mg twice daily (4 times the recommended starting dose). In Phase 3 study A4061032 with axitinib for the treatment of patients with RCC, no concurrent elevations of ALT (>3 times the ULN) and bilirubin (>2 times the ULN) were observed for axitinib (N=359).

ALT, aspartate aminotransferase (AST) and bilirubin will be monitored before initiation of and periodically throughout treatment with axitinib.

Cardiac failure events

In clinical studies with axitinib for the treatment of patients with renal cell carcinoma, cardiac failure events (including cardiac failure, cardiac failure congestive, cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 12/672 patients (1.8%) receiving axitinib. Grade 3/4 cardiac failure events were reported in 7/672 patients (1.0%) and fatal cardiac failure events were reported in 2/672 patients (0.3%) receiving axitinib.

Monitoring for cardiac events will include a physical examination and measuring of vital signs at each study visit, in addition to a baseline ECG. Any additional cardiac assessments will be performed when clinically indicated.

7.3.5 Concomitant therapy

CYP3A4/5 inhibitors/inducers
In vitro data indicate that axitinib is metabolized primarily by CYP3A4/5. Ketoconazole, a strong inhibitor of CYP3A4/5, administered at a dose of 400 mg once daily for 7 days, increased the mean area under the curve (AUC) 2-fold and Cmax 1.5-fold of a single 5-mg oral dose of axitinib in healthy volunteers[Information from Investigator's Brochure, September 2012]. Co-administration of axitinib with strong CYP3A4/5 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) may increase axitinib plasma concentrations. Grapefruit may also increase axitinib plasma concentrations. Rifampin, a strong inducer of CYP3A4/5, administered at a dose of 600 mg once daily for 9 days, reduced the mean AUC by 79% and Cmax by 71% of a single 5-mg dose of axitinib in healthy volunteers. Co-administration of axitinib with strong CYP3A4/5 inducers (e.g., rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and Hypericum perforatum [also known as St. John's wort]) may decrease axitinib plasma concentrations. Concomitant medication with strong CYP3A4/5 inhibition potential is therefore not allowed on study.

Anticoagulants
Patients who require therapeutic anticoagulant therapy with oral vitamin K antagonists are ineligible for enrollment; low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed; therapeutic use of low molecular weight heparin (or similar parenteral drug) for venous-thromboembolic disease is allowed.

Steroids
If clinically indicated, short (≤7 days) courses of steroids, such as dexamethasone, are allowed for patients with vestibular schwannomas and sudden-onset, transient hearing loss on protocol therapy. All such treatments must be documented in the clinical chart and study records.

7.4 Visit Schedule and Assessments

Visit schedule and required on-study evaluations are outlined below:

7.4.1 Visit schedule

Table 3-4 Evaluation and visit schedule

Examination	Baseline	Day†	Week		Cycle (each cycle is 28 days)										
		1	2	3	2	3	4	5	6	7	8	9	10	11	12
Informed consent	X														
Inclusion/ exclusion criteria	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NFTI-QOL[#]	X								X						
ECG	X														
MRI[‡]	X					X			X			X			X
Audiogram*	X					X			X			X			X
INR	X														
Free T4/TSH	X	X			X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test**	X	X			X	X	X	X	X	X	X	X	X	X	X
CBC, diff., comprehensive metabolic panel, Mg, Phos	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

† Includes drug dispensing and repeat baseline evaluations if time between first screening and dispensing exceeds 4 weeks. Otherwise, Day 1 not performed.

[#] Only in adult patients ≥18 years of age

[‡] Should be performed at the end of cycle

[*]Should be performed at the end of cycle. Not required for patients with no measurable hearing

[**]Required for women of childbearing potential within 7 days of starting axitinib

Additional treatment cycles beyond 12, if applicable, will continue according to the same schedule.

7.4.2 Efficacy assessments

Primary efficacy endpoint is best radiographic tumor response (i.e. maximum tumor shrinkage) during the first 12 cycles of treatment; secondary efficacy endpoint is audiologic response, as defined by the following **Response Criteria**, which were chosen based on recently published recommendations for NF2 clinical trials:[22]

Primary: *Radiographic response:* for study purposes, a ≥20% reduction in tumor volume in any of the target tumors will constitute a partial response (PR). Complete disappearance of any of the target tumors will constitute a complete response (CR).

Secondary: *Audiologic response:* improvement in speech discrimination score (SDS), defined as an improvement in the score above the 95% critical difference threshold, compared to baseline audiogram at initiation of treatment. *Audiologic worsening:* decrease in SDS score below the 95% critical difference threshold, compared to baseline audiogram at initiation of treatment.

MRI of the brain and spine (in patients with spinal tumors with medically relevant or symptomatic lesions) with 3D tumor volumetrics will be performed every 3 months. Patients with vestibular schwannomas will receive baseline audiograms within 28 days before enrollment and subsequent audiograms at the time of each MRI. If an objective response, defined as a 20% reduction in tumor volume compared to baseline is observed in any target tumor or stable disease in all target tumors (i.e. less than 20% increase in size), Axitinib will be continued. Therapy will be discontinued if the **primary** target tumor enlarges by 20%. **All additional target tumors will be monitored for growth or response, but any progression in those tumors will not trigger discontinuation of therapy.** Audiologic responses will be determined, but will not be used as primary response criteria.

7.4.3 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

7.4.4 Safety assessments

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

These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI Common Toxicity Criteria (CTC)(http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Patients who will discontinue study treatment for any reasons are to be followed until one of the following occurs:

• Thirty days after the last dose of axitinib or until any significant drug-related toxicity resolves, whichever is longer;

• Death;

• Lost to follow-up after at least two reasonable attempts to contact the patient have been made;

• Withdrawal of consent for any further data collection or submission;

• Initiation of any other disease-directed treatment for NF2-related tumors

7.4.4.1 Adverse events

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

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

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

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

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

7.4.4.2 Serious adverse events

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition

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

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment must be reported to Pfizer immediately upon learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Pfizer if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

7.4.5 Instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Pfizer.

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

From the time that the subject receives the first dose of axitinib and including 28 calendar days after the last administration, **all events must be reported to Pfizer within 24 hours of learning of its occurrence. Furthermore, serious adverse events must be reported immediately upon awareness if the SAE is fatal or life-threatening** —regardless of the extent of available information.

Like an SAE, all other reportable events must be reported to Pfizer within 24 hours of awareness on an *IIR SAE Form* (or other agreed reporting method) and followed up to determine outcome, including the later occurrence of an associated SAE..

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported to the Institutional Review Board.

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

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

7.4.5.1 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Pfizer within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

7.4.6 Laboratory evaluations

Schedule and timing of all laboratory evaluations are listed in Table 3-4.

Pregnancy Test
A serum pregnancy test is required for all females of child-bearing potential within 7 days prior to the first dose of axitinib and during treatment.

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

Blood chemistry
Blood chemistry must include a comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase), as well as magnesium and phosphorus.

Urinalysis
Standard urinalysis dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes) will be performed. This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

Sample Storage and Genetic Testing
Samples will not be stored for future use and will not be used for genetic testing.

7.4.6.1 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

7.4.6.2 Physical examination

Physical examination will be performed which must comprise a neurological examination.

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

7.4.6.3 ECG

A standard 12 lead ECG is to be performed during screening and significant findings must be recorded.

7.4.6.4 Performance status

Performance status (PS) will be assessed using the Karnofsky scale for patients >16 years and Lansky scale for patients ≤16 years of age. Note: Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

7.4.6.5 Drug levels and pharmacokinetic assessments

None.

7.4.6.6 NFTI-QOL (Neurofibromatosis 2 Impact on Quality of Life)

At Baseline, 6-months, and off-study, adult subjects (≥18 years of age) will be asked to complete the validated NFTI-QOL,[24] to assess the impact of their disease on their ability to perform activities of daily life. The questionnaire has not been validated in pediatric NF2 patients.

7.4.6.7 MRI and audiogram

MRI (including volumetrics) and audiogram, i.e. efficacy assessments, will be obtained at baseline and after every 3rd cycle, as previously described[21] and outlined in Section 7.4.1.

8 Protocol Amendments, or Changes in Study Conduct

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

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

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

Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

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

9 Description of the Informed Consent/Assent Process

Patients will be recruited by physicians at NYULMC and approved study sub-sites. Consenting will take place under the direct supervision of the PI or one of the approved study co-investigators. Prospective subjects will receive detailed information about this study and its investigational nature. They will also be informed about risks and potential benefits of the study. All questions will be answered by the PI or one of the approved study co-investigators. All patients (or their legal guardian for pediatric patients, as applicable) will sign an IRB-approved informed consent detailing the patient's protection of human subjects involved in clinical trials. In addition, assent will be sought from pediatric patients ≥7 years of age. All subjects will receive a copy of their signed consent/assent form. The IRB-approved informed consent document will also be signed by one of the approved study investigators. This process as well as patient eligibility will be documented in the medical record. This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the PI and study investigators that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The investigator is responsible for the retention of the patient log and patient records.

10 Withdrawal from the Protocol

Volunteers may discontinue participation in the study at any time without penalty or loss of benefits to which the volunteer is otherwise entitled.

If a patient decides to withdraw his/her consent, we will ask that he/she contact Dr. Theodore Nicolaides and let her know that he/she is withdrawing from the study. Her mailing address is 160 East 32nd Street, 2nd Floor, New York, NY 10016. If he/she wishes to withdraw his/her Authorization as well he/she must contact Dr. Theodore Nicolaides in writing.

Remember that withdrawing Authorization only affects uses and sharing of information after the subject's written request has been received, and he/she may not withdraw his/her Authorization for uses or disclosures that we have previously made or must continue to make to complete analyses or report data from the research

11 Data Management and Collection

The investigators will record all information required by the protocol.

11.1 Confidentiality

Each subject enrolled will, from that point forward, be identified by a unique identifier (subject number). This subject number will also be used for research specimens collected and shipped to analysts outside of the study sites. All records generated will be stored in a locked office area, only accessible to study personnel. Clinical information will be accessed, according to HIPAA requirements, by study personnel to complete study documents, as needed.

Only the PI and the study coordinator will have access to the log linking the subject number to the patient name, birth date and medical record number. The log will be kept in a locked drawer in the study coordinator's office. A secure password-protected computer file will be generated as well.

Medical records will be kept in accordance with state and federal laws concerning the privacy and confidentiality of medical information. Each participant in this research study may be asked to sign a separate informed consent document for specific procedures or treatment, and that informed consent form may be included in the medical record of that facility. The confidentiality of each volunteer's medical record is also protected by federal privacy regulations, as described below.

Study records include information that identifies the patient and that is kept in research files. All efforts will be made to keep this information confidential, but it cannot be guaranteed. If data from this study are to be published or presented, all information that identifies the patient will be first taken out. Volunteers will be informed of all protected health information used in this study. The consent form will seek written permission from the participant to use and disclose the following information for this research. The volunteer is required to sign this form. This Authorization will not expire unless the volunteer withdraws it in writing. The volunteer has the right to withdraw authorization at any time, except to the extent that NYULMC has already relied upon it or must continue to use the information to complete data analysis or to report data for this study.

12 Data Monitoring

12.1 Monitoring Plan

An internal Data and Safety Monitoring Committee (DSMC) of the NYUCI is the monitoring board for this study. The committee will review safety at scheduled intervals (not less than once/year) and at the time of planned interim analyses according to the NYUCI DSMC Charter. As described further in the "Statistical Methods" section of this protocol, an interim analysis will be done after stage 1 is completed (9 evaluable patients have been enrolled).

12.2 Stopping Rules

If safety concerns arise, the DSMC will identify these concerns and recommend modification or termination of the clinical trial. As described further in the "Statistical Methods" section of this protocol, if the number of responses is <1 after the first stage is completed, axitinib will be deemed ineffective and the trial terminated. Recruitment will be halted after the 9th evaluable patient is enrolled (stage 1) until at least one response is observed.

13 Statistical Methods

To evaluate efficacy, radiographic response is treated as a binary variable whereby patients who achieve either a CR or a PR in any of the target tumors at any point within 12 months from beginning of therapy are considered responders and all others nonresponders.. A 2-stage Simon design will be used [23]. Axitinib will be considered not of sufficient interest for further evaluation if the true response rate is 5% (p0) or less and considered active if the true response rate is 25% or greater (p1). With beta (probability of rejecting axitinib with true response rate 5%) set at 0.2 and alpha (probability of failing to reject a treatment with response probability of 25%) set at 0.05, the required sample size is 9 patients for stage 1 and an additional 8 patients for stage 2.If there are no responses after the first stage is completed, axitinib will be deemed ineffective and the trial terminated. Recruitment will be halted after the 9th evaluable patient is enrolled (stage 1) until at least one response is observed during the first 12 cycles. Axitinib will be considered effective and of interest for further study if after successful completion of both stages, the cumulative number of responses is ≥3. Using this 2-stage design, the probability of early termination is 0.63 if the true response rate to axitinib is 5%.

Stage	Cumulative number of patients with radiographic responses	Decision
Stage 1: enter 9 patients	0	Terminate the trial: agent **ineffective**
	1 or more	Inconclusive result: continue trial (proceed to Stage 2)
Stage 2: enter 8 additional patients	2 or less	Terminate the trial: agent **ineffective**
	3 or more	Terminate the trial: agent **effective**

Disease and patient characteristics at baseline will be summarized using descriptive statistics. For qualitative variables, frequency distributions and proportions will be provided; for quantitative variables, summary statistics (e.g., mean, median, quartiles, standard deviations, etc.) and graphical displays (e.g., boxplots). Overall response rates will be estimated upon completion of the study along with exact 95% confidence intervals.
Secondary endpoints: Audiologic responses will be summarized over time using descriptive statistics and graphical displays. Similarly, quality of life will be summarized over time in these patients.

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Appendix I

List of Strong CYP3A4/5 inhibitors and inducers

Inhibitors	Inducers
• Atazanavir • Clarithromycin • Conivaptan • Delavirdine • Grapefruit juice • Indinavir • Itraconazole • Ketoconazole • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Voriconazole • Seville oranges • Star fruit products	• Aprepitant • Armodafinil (unknown) • Carbamazepine • Dabrafenib (unknown) • Eslicarbazepine (unknown) • Felbamate (unknown) • Fosphenytoin • Modafinil (unknown) • Nevirapine (unknown) • Oxcarbazepine (unknown) • Pioglitazone (unknown) • Phenytoin • Phenobarbital • Primidone • Rifabutin • Rifampin • Topiramate (unknown) • Vemurafenib (unknown) • St. John's Wort