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Phase 2 Study of Bevacizumab in Children and Young Adults With NF 2 and Progressive Vestibular

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ABBREVIATIONS:

AAO-HNS: American Academy of Otolaryngology, Head and Neck Surgery
ASCO: American Society of Clinical Oncology
ABI: auditory brainstem implant
AST/ALT: alanine transaminase/alanine transaminase
ATE: arterial thromboembolic events
BAER: brainstem auditory evoked responses
BMD: bone mineral density
CHF: congestive heart failure
CNS: central nervous system
COV: coefficient of variation
CRC: colorectal cancer
CRF: case report form
CTC: Common Terminology Criteria for Adverse Events
CTCAE: Common Terminology Criteria for Adverse Events
DBP: diastolic blood pressure
DF/HCC: Dana Farber/Harvard Cancer Center
DPOAE: distortion product otoacoustic emissions
DMAC: Data Management and Analysis Center
DSMB: Data and safety monitoring board
EGFR: epidermal growth factor receptor
FU/LV: fluorouracil/leucovorin
HIV: human immunodeficiency virus
HTN: hypertension
LMWH: low molecular weight heparins
IAC: internal auditory canal
I.B.: investigator brochure
IgG: immunoglobulin G
IMP: investigational medicinal product
IV: intravenous
LVEF: left ventricular ejection fraction
MAb: monoclonal antibody
MLV: monitored live voice
MTD: maximum tolerated dose
NF2: neurofibromatosis 2
NSCLC: non-small cell lung cancer
OAE: otoacoustic emissions
PDGFR: platelet derived growth factor receptor
PI: Principal Investigator
P.I.: package insert
PK: pharmacokinetics
PTA: pure-tone average
RECIST: Response Evaluation Criteria in Solid Tumors
RPLS: Reversible Posterior Leukoencephalopathy Syndrome
SAE: serious adverse event

SRT: speech reception threshold
TE: thromboembolic
TIA: transient ischemic attack
ULN: upper limit of normal
UPC: urine protein: creatinine
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor
VS(s): vestibular schwannoma(s)
VTE: venous thromboembolism

PRECIS

Background

- Bilateral vestibular schwannomas are the hallmark of neurofibromatosis 2 (NF2). As these tumors enlarge, they cause sensorineural hearing loss and, ultimately, complete hearing loss.
- Sporadic and NF2-related vestibular schwannomas express vascular endothelial growth factor (VEGF).
- Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF with high affinity.
- The initial experience treating ten NF2 patients at risk for complete hearing loss with bevacizumab outside of a clinical trial showed promising results with 6/10 patients experiencing ≥ 20% reduction in tumor volume and 4/7 evaluable patients having significantly improved word recognition scores.

Primary Objective

- To determine the hearing response rate at 24 weeks after treatment with bevacizumab for symptomatic vestibular schwannomas (VS) in children and young adults with NF2.

Eligibility

- Patients ≥ 6 years old with NF2
- Subjects must have a target VS with the following qualities:
    - Not amenable to surgery due to patient preference or high risk for surgical complications
    - Associated with a word recognition score of < 85% and > 5%
    - Documented clinical progression defined as EITHER:
        - Progressive hearing loss (defined as a decline in word recognition score below the 95% critical difference interval from baseline score, Appendix A) related to VS.

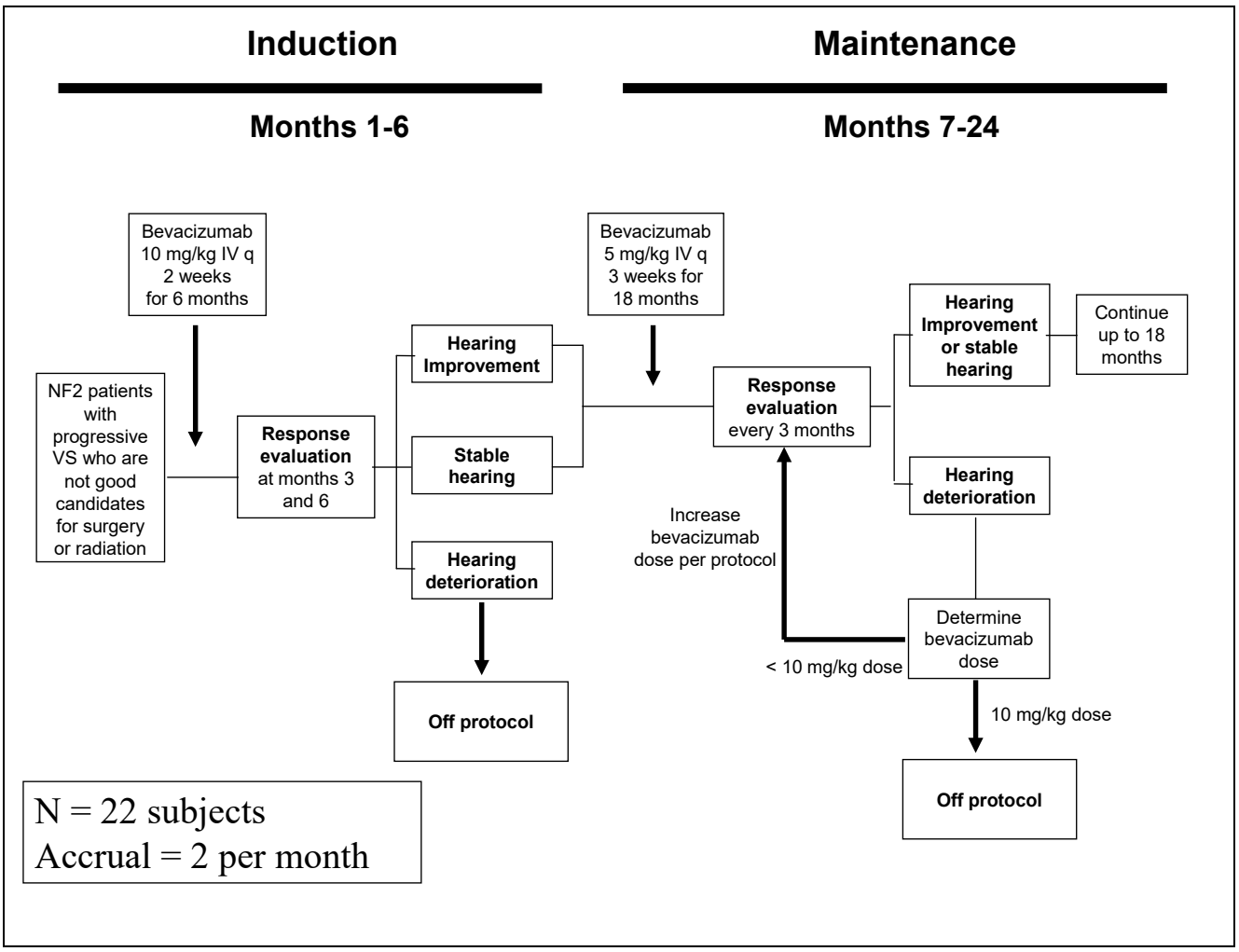
          OR
        - Progressive tumor growth in the preceding 18 months, defined as ≥ 20% increase in volume.

Design

- Bevacizumab will be administered by IV infusion at a dose of 10 mg/kg every 2 weeks for 24 weeks (induction therapy).
- Clinical response will be assessed by audiology and MRI at weeks 12 and 24. Subjects with hearing decline during induction therapy (defined as a decline in word recognition score below the 95% critical difference interval from baseline score, Appendix A) will be taken off of protocol (section 5.5).
- At week 25, patients with a clinical response or stable disease (together comprising "clinical benefit") will transition to maintenance therapy with bevacizumab.
- During the maintenance phase, subjects will be treated with open-label bevacizumab 5 mg/kg every 3 weeks for up to 72 weeks.

- During maintenance therapy, subjects will be allowed to increase their bevacizumab dose to 10 mg/kg every 2 weeks if they experience hearing decline compared to their highest word recognition score during treatment. Subjects will be taken off of study if their word recognition drops below the 95% critical difference (new hearing baseline defined as the word recognition score leading subject to receive 10 mg/kg dose every 2 weeks) after receiving bevacizumab 10 mg/kg every 2 weeks for at least 12 weeks (section 5.5).

SCHEMA



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1. OBJECTIVES

1.1 Study Design

Subjects will be treated with open-label bevacizumab 10 mg/kg every 2 weeks for 24 weeks (induction therapy). Clinical response will be assessed by audiology and MRI at weeks 12 and 24. Subjects with hearing decline at weeks 12 or 24 will be taken off of protocol. At week 24, patients with a clinical response or stable disease (together comprising "clinical benefit") will transition to maintenance therapy with bevacizumab. During the maintenance phase, subjects will be treated with open-label bevacizumab 5 mg/kg every 3 weeks for up to 72 weeks. Subjects will be followed with audiology and MRI scans every 12 weeks. The total time of the study will be 96 weeks (24 weeks induction + 72 weeks maintenance).

Subjects will be allowed to increase their bevacizumab dose to 10 mg/kg every 2 weeks during maintenance therapy if they experience hearing decline during maintenance therapy (defined as decrease in word recognition score below the 95% critical difference compared with the word recognition score at baseline, Appendix A). Subjects will be taken off of study if their word recognition score does not remain within the 95% critical difference after receiving bevacizumab 10 mg/kg every 2 weeks.

1.2 Primary Objectives

The primary objective of this study is to determine the hearing response rate at 24 weeks in children and young adults with neurofibromatosis 2 (NF2) treated with bevacizumab for symptomatic vestibular schwannomas.

1.3 Secondary Objectives

The secondary objectives are: (1) to determine the safety and tolerability of bevacizumab in this patient population; (2) to determine the radiographic response rate (defined as an decrease in VS volume by ≥ 20% compared to baseline) during bevacizumab treatment; (3) to determine the durability of hearing response, as measured by freedom from hearing loss from the time of hearing response (defined as a decrease in word recognition score below the upper limit of the 95% critical difference of the baseline word recognition score, Appendix A); (4) to determine the durability of radiographic response, as measured from the time of first response to tumor progression (defined as an increase in volume of > 20% compared to lowest tumor volume during treatment) (5) to determine changes in function of the auditory system during bevacizumab treatment; (6) to explore changes in tinnitus during treatment.

2. BACKGROUND

2.1 Neurofibromatosis 2

An estimated 43,800 primary brain tumors were diagnosed in 2005 and 16,600 (38%) of these tumors were meningiomas or nerve sheath tumors. Surprisingly, meningiomas and vestibular schwannomas (VSs) are as common as all types of gliomas combined.[1]

Neurofibromatosis 2 (NF2) is a tumor suppressor syndrome characterized by multiple schwannomas, meningiomas, and ependymomas. The birth prevalence is estimated to be 1 in 25,000 births and NF2 affects more than 10,000 individuals in the United States. The average age at onset of symptoms is 17 to 21 years.

Despite the benign histology of schwannomas, meningiomas, and ependymomas, NF2 patients experience significant morbidity and mortality related to their disease. Actuarial survival after diagnosis of NF2 is 85% at 5 years, 67% at 10 years, and 38% at 20 years.[2] Bilateral VSs are the hallmark of NF2. As these tumors enlarge, they cause sensorineural hearing loss and, ultimately, complete hearing loss. In addition, half of all patients have intracranial meningiomas and 75% have spinal tumors (*i.e.*, schwannomas, meningiomas, ependymomas). Most patients require surgery during their lifetime and most patients have multiple procedures. Morbidity related to NF2 is severe and includes early deafness, facial weakness, blindness, seizures, and hemiparesis.

There are two forms of hearing loss in patients with NF2. Gradual hearing loss is the rule, and it most commonly occurs with progression of tumor size over time. Although there is a rough correlation with tumor size, gradual hearing loss can occur with tumors of any size. Although surgical implantation of cochlear and auditory brainstem implants provides benefit for a small minority of patients, there is no widely effective treatment for this type of hearing loss. In addition, some patients can experience episodes of sudden hearing loss superimposed on baseline hearing dysfunction. Treatment with a short course of corticosteroids can often correct this acute hearing loss. The mechanism of acute hearing loss is not clearly understood but probably involves compression of the auditory nerve from tumor mass and associated edema. Previous studies of pressure within the internal auditory canal (IAC) of patients with VSs suggest that intracannalicular pressure is directly correlated with the amount of tumor in the IAC and may be inversely associated with preoperative hearing.[3] Thus, therapies that reduce edema, a common cause of increased pressure in brain tumors, are a rational approach to treating hearing loss in NF2 patients.

In patients with NF2, standard therapy involves surgery for progressive, symptomatic tumors. Due to the large number of tumors encountered in the brain and spinal cord, surgical removal of all tumors is not possible or advisable. Iatrogenic morbidity after surgery for NF2-related lesions is, unfortunately, relatively common due to the intimate association between tumors and vital neurologic structures. For example, complete surgical resection of VSs typically results in ipsilateral anacusis except in a minority of tumors that are smaller than 1.5 cm and smooth in outline. As well, facial palsy, spinal fluid leaks and infection are all common complications of VS resection.

Radiation has been used in a subset of tumors that progress despite surgical treatment or in individuals who are considered high risk for surgical complications. However, this modality should be used with caution since secondary malignancies after treatment have been reported.[4] In addition, many patients lose functional hearing after provision of radiation with hearing preservation rates of 73% at 1 year, 59% at 2 years, and 48% at 5 years after radiosurgery.[5]

There are no known effective medical treatments for NF2-related tumors. Given the limitations of surgery or radiation and the devastating impact of these tumors, medical treatments are desperately needed. We have recently identified VEGF inhibition as a possible therapy. The initial experience treating ten NF2 patients at risk for complete hearing loss with bevacizumab outside of a clinical trial showed promising results with 6/10 patients experiencing ≥ 20% reduction in tumor volume and 4/7 evaluable patients having significantly improved word recognition scores .[6] Trials of other targeted agents for treatment of NF2-related tumors are currently underway. A phase 2 study of the VEGF inhibitor PTC299 for NF2-related vestibular schwannoma (NCT00911248) has completed stage 1 of accrual, and a phase 2 study of the HER1/HER2 inhibitor lapatinib for NF2-related tumors has completed enrollment (NCT00973739). Other planned studies include trials of everolimus (NCT01490476, NCT01419639, NCT01345136).

Hearing loss and NF2

Hearing loss is a critical problem for patients with NF2. Unlike patients with sporadic VSs who can function with unilateral hearing loss, patients with NF2 are at risk for complete deafness. This hearing loss typically occurs during late adolescence or early adulthood and leads to social isolation and underemployment. Although hearing loss is related to VSs, the degree of hearing sensitivity (threshold) is only loosely correlated with tumor size. This dissociation may be due to direct compression of the auditory nerve, presence of intratumoral edema, disruption of blood flow to the cochlea, degeneration of certain cochlear structures, and distortion of auditory centers in the brainstem. There is evidence that the cochlea, as well as the 8th cranial nerve, is a site of both cell degeneration and the accumulation of precipitate in cases of VS.[7] This means that sites anywhere along the auditory pathways—from the periphery to the brainstem—may contribute to the observed loss of hearing function. Thus, we will use the full range of audiologic diagnostic tools available to assess function of the pathway.

Hearing is monitored in clinical practice by measuring pure tone thresholds, word recognition scores, brainstem auditory evoked responses (BAERs), and otoacoustic emissions (OAEs).

Pure tone thresholds measure the minimum sound level that an ear can perceive. Thresholds are typically measured at octaves and half-octaves from 250 Hz to 8000 Hz. An average of thresholds at 500, 1000, 2000 and 4000 Hz (PTA) is recommended as a standard outcome measure by the American Academy of Otolaryngology, Head and Neck Surgery (AAO-HNS) for reporting in cases of VS.

Word recognition scores measure the ability to recognize (as opposed to detect) auditory information. Patients are presented a list of 50 words at a fully audible level and the percentage identified correctly is the score. This study will use full 50-item monosyllable lists and standardized recordings.

Brainstem auditory evoked responses are small electrical voltage potentials recorded from the scalp in response to auditory stimuli (such as clicks). These signals originate from auditory structures (*e.g.*, the cochlea, 8th cranial nerve, and auditory brainstem) and provide information about the synchronous conduction of auditory information to the brain. The latency (ms) and

amplitude of the peaks of waves I and V will be differentially evaluated to show the status of peripheral versus brainstem effects.

Otoacoustic emissions (OAEs) are sounds that are generated from within the cochlea as it acts to amplify incoming sounds. OAEs are a sensitive measure of cochlear health and often disappear after the cochlea has been damaged. The presence (significantly above noise-floor) of measurable emissions, called distortion product otoacoustic emissions (DPOAEs) across frequencies from 1000 to 8000 Hz will be used as an indicator of functioning cochlear regions.

Because tumors associated with NF2 have benign histology, overall survival is not an appropriate endpoint for clinical trials in this condition. Instead, the goal of treatment is to minimize neurologic morbidity (including hearing loss) and to defer surgical treatments that may cause iatrogenic dysfunction. For this reason, hearing function is the most important way to monitor the activity of new agents designed to treat VSs.

Word recognition is the measure most closely associated with daily hearing function since it measures the ability to comprehend speech (rather than "detect" it). If word recognition quality improves, the patient can converse successfully, even if a hearing aid is needed to make sounds sufficiently loud. Statistical methods have been developed to determine significant changes in this measure. Word recognition scores represent summary scores from a collection of binary endpoints (correct/incorrect responses) and thus follow a binomial distribution (*e.g.*, non-Gaussian distribution). Although it is tempting to use a set change in word recognition score (*e.g.*, fifteen percentage points) as a clinical response, this approach is inappropriate given the binomial model of variance. A more rigorous approach involves the use of the 95% ($p=0.05$) critical difference table [8] (Appendix A). The 95% critical differences for 50-word lists as proposed here have been used in previous studies[9] and in clinical trials evaluating the effect of drug treatment on hearing.

Quality of life and NF2

NF2 is associated with decreased quality of life. Recently, there have been efforts to develop a reliable and validated score to measure disease-specific quality of life (QOL) in NF2 patients. This effort has resulted in an 8-item scale that is called NFTI-QOL (Appendix B).[10] The eight questions include items about balance, hearing, facial weakness, sight, mobility, functional role, pain, and mood. In a sample of 50 subjects with NF2, NFTI-QOL score correlated with two established quality of life measures: the EuroQOL and the SF-36 (Pearson correlation, $p \leq 0.001$). In addition, there was a strong significant correlation with physician-ranked disease severity (Pearson correlation, $p<0.001$).

Imaging vestibular schwannomas

Although many clinicians believe that hearing loss related to VSs is irreversible, there are cases with transient hearing restoration after a course of corticosteroids or decompression of the auditory canal without removal of the tumor. Our preliminary observations indicate that neutralizing VEGF can reverse profound hearing loss and subsequently maintain hearing. Based on these experiences, we hypothesize that the restoration of hearing function with bevacizumab is

in part due to reduction in intraneural edema that compresses the auditory nerve. In this proposal, we will investigate the mechanism(s) by which bevacizumab inhibits tumor growth and/or induces hearing recovery using advanced MRI techniques specifically designed to assess the vascular profile of tumors and the tumor environment.

Internal auditory canal (IAC) imaging. The vestibular and auditory nerves together comprise the 8th cranial nerve. The nerve exits the lateral brainstem, travels through the subarachnoid space in the IAC to terminate in the cochlea (auditory nerve) and semicircular canals (vestibular nerve). Detailed imaging of the IAC is essential to identify and follow VSs in patients with NF2. MRIs must therefore include thin cuts through the IAC (3mm, no skip) in addition to the traditional pre- and post-contrast images (5 mm, 1 mm skip) that are performed for malignant brain tumors.

Volumetric analysis. Traditionally, VSs have been measured using either 1-dimensional measurements (in the long axis) or 2-dimensional measurements (calculated by taking the square root of the product of the short axis * long axis measured to the plane perpendicular to the face of the temporal bone).[11] However, the irregular shape of VSs, as determined by the unique anatomy of the IAC and cerebellopontine angle, makes it difficult for linear measurements to accurately and fully represent growth for the entire tumor. As a result, VS growth may be underestimated by linear measurement criteria. Semi-automated volumetric analysis overcomes these limitations since it uses data from 3 dimensions. The coefficient of variation (COV) ranges from 0.6% to 6.8% and is generally below 5% for lesions greater than 1 cc.[12] Volumetric analysis not only better reflects tumor size, but also allows accurate detection of smaller changes in tumor size compared to standard solid tumor response criteria (*e.g.*, RECIST criteria). This ability to detect small changes in size is critical for tumors with slow growth rates such as VS, and, when used in clinical trials, helps limit exposure to potentially toxic and/or inactive agents. Trials for NF-related tumors, such as plexiform neurofibromas, are now routinely using volumetric changes as the primary endpoint, typically choosing a 20% increase for progression and 20% decrease for radiographic response.[13-15]

2.2 Study Agent(s)

2.2.1 Bevacizumab (NSC #704865)

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity (k_d = 1.1 nM) (40). The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.[16-18]

Mechanism of Action
Of known proangiogenic factors, VEGF is one of the most potent and specific, and has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial

cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by A.4.6.1 or bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells *in vitro*, and decrease microvessel density and interstitial pressure in tumor xenografts *in vivo*. In patients, preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab.[19]

Nonclinical Studies
The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition *in vivo* in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdomyosarcoma, Calu-6, and MCF-7 cell lines.[16, 18, 20, 21] The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Combined blockage of the VEGF and other growth factor pathways (*e.g.*, EGFR or PDGFR) has also demonstrated additive effects *in vivo*.[22, 23] Associated with the anti-tumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts as well as reduced vascular permeability and interstitial pressure

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced endometrial proliferation and uterine weight as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption, as well as specific gross and skeletal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia, which was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits. This effect appeared to be dose-dependent and characterized by a reduction of wound tensile strength.

Clinical Studies in Adults
To date, over 7000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens.[17]

Pharmacokinetics
The pharmacokinetics (PK) of bevacizumab have been characterized in several phase 1 and phase 2 clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

Maximum Tolerated Dose
The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated severe headaches.[24] The dose schedule of

either 10 mg/kg q2w or 15 mg/kg q3w is used in most phase 2 or 3 trials with only a few exceptions (*e.g.*, the pivotal phase 3 trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg q2w).[25]
Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two post-marketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$). Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm.[17]

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic CRC (E3200), non–small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy. In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, HR = 0.75; $p < 0.01$) in a population of previously treated CRC patients.

There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; HR = 0.80; $p = 0.003$). The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (13.3 vs. 6.7 months, respectively; HR = 0.48; $p < 0.0001$) (see the Bevacizumab Investigator Brochure for additional details).

Clinical Studies in Children

Compassionate-use and phase 1 trials of bevacizumab as single agent have been completed for children with refractory solid tumors.[26, 27] In these studies, doses from 5 mg/kg to 15 mg/kg every 2 weeks were well tolerated. In the phase 1 study, eighteen of 21 children completed ≥ 1 treatment cycle (median number of cycles 3, range 1-16 cycles). No dose limiting toxicity was seen nor was hemorrhage/thrombosis noted. Interestingly, the typical adverse events seen in adults—hypertension, proteinuria, arterial thromboembolic events, hemorrhage, congestive heart failure (CHF), gastrointestinal perforations, wound healing complications, reversible posterior leukoencephalopathy syndrome and fistula formation—were not seen in children.[28] Bony toxicity was not observed, but cumulative toxicity could not be evaluated given the fairly short treatment duration with bevacizumab. Based on these results, phase 2 studies at doses similar to adults were recommended.

Additional studies of bevacizumab in combination with chemotherapy have been performed.[29-32] In one study of 10 patients with recurrent low grade gliomas, durable objective responses (up to 22 months) to combination chemotherapy with improvement in clinical function. No dose-limiting toxicity was reported.[29] In a separate phase 2 study of 31 patients with recurrent malignant glioma and diffuse brainstem glioma, bevacizumab plus irinotecan was not effective; toxicity associated with chemotherapy included fatigue, hypertension, CNS hemorrhage (grade 1), and CNS ischemia (grade 4 in 2 patients).[30] In a retrospective study of 30 patients with a range of primary CNS tumors, bevacizumab was given with chemotherapy at a median dose of 9.5 mg/kg every 2 weeks. No hemorrhage or thrombosis was noted in this cohort. The toxicity profile was consistent with other studies including hypertension, proteinuria, lymphopenia, and delayed wound healing.[31]

Safety Profile

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae

of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS).[33, 34]

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved.
If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio at least every 6 weeks. If the UPC ratio is not available, a dipstick urinalysis may be used to allow treatment to proceed.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus

chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure). In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

***Arterial Thromboembotic Events*:** An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving a control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients treated with chemotherapy alone. (See the Bevacizumab Investigator Brochure for additional details.)

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to

325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005.[35] Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation: Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (*e.g.*, ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%–1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (*e.g.*, tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various time points during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae, new gastrointestinal fistula (any grade), or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

***Wound healing complications*:** Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone.[36] Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab

until 4 weeks after that procedure. In the case of high-risk procedures (such as liver resection, thoracotomy, or neurosurgery), it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types.[17] The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

***Tumor-Associated Hemorrhage*:** Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

***Mucocutaneus Hemorrage*:** Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

***Reversible Posterior Leukoencephalopathy Syndrome (RPLS)*:** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in

patients previously experiencing RPLS is not known.[33, 34]

***Congestive heart failure (CHF)*:** In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.[37]

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well.[38]

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

***Neutropenia*:** Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.[39]

Fertility and Pregnancy. Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in

human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, ranging from 11 to 50 days).

Immunogenicity. As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

***Additional Adverse Events*:** See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

2.3 Rationale

Patients with NF2 develop multiple tumors, including bilateral vestibular schwannomas, meningiomas, and ependymomas. As bilateral VS enlarge, they cause sensorineural hearing loss and, ultimately, complete deafness. Disease-specific mortality is extremely high for NF2 with greater than 90% of NF2 patients dying from their disease or from complications in the immediate post-operative period.[40] Standard treatment options for VS include surgery or radiation, which often cause hearing loss or cranial nerve dysfunction. Sporadic and NF2-related vestibular schwannomas express vascular endothelial growth factor (VEGF). Bevacizumab is an antibody that binds VEGF with high affinity and is approved for treatment of multiple cancers including glioblastoma. Our initial experience treating ten NF2 patients at risk for complete hearing loss or brainstem compression with bevacizumab on compassionate-care basis showed promising results with 6/10 patients experiencing ≥ 20% tumor volume reduction and 4/7 experiencing significantly improved hearing.[6] The proposed trial is designed to confirm the clinical response rate of bevacizumab in a larger cohort of pediatric patients with NF2 treated at multiple centers. Because patients with NF2 have long life expectancy, the optimum duration of treatment with bevacizumab is an important question to address. An exploratory aim of this study is to determine the durability of clinical response to bevacizumab in subjects with progressive vestibular schwannomas who either respond to therapy or experience stable disease after initial treatment.

2.4 Correlative Studies Background

Our study and others suggest that there are dose- and time-dependent increases in soluble VEGF and PlGF and decreases in soluble VEGFR following treatment with anti-angiogenic agents [19, 41, 42]. Our studies have also shown that circulating biomarkers can help predict tumor progression. For example, progression of glioblastoma during treatment with AZD2171 is associated with significant increases in basic fibroblast growth factor (b-FGF) and stromal cell-derived factor 1 alpha (SDF-1α), whereas progression in hepatocellular carcinoma after sunitinib is correlated with increases in IL-6 and SDF-1α. Finally, we found that baseline sVEGFR1 concentration in plasma may predict response to bevacizumab therapy in rectal cancer patients [41].

There is no published data on molecular biomarkers for anti-VEGF agents in patients with NF2 and this study proposes to analyze baseline biomarkers with respect to outcomes (response) as well as the possible effect of bevacizumab on biomarker levels over time (see section 8.3.1).

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Patients must have a confirmed diagnosis of neurofibromatosis 2 by fulfilling National Institute of Health (NIH) criteria or Manchester criteria, or by detection of a causative mutation in the *NF2* gene.

The NIH criteria[43] includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass **OR** two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity.

The Manchester criteria[44] includes presence of:

- Bilateral vestibular schwannomas, **OR**
- First-degree relative with NF2 and **EITHER** unilateral eighth nerve mass **OR** two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, OR
- Unilateral vestibular schwannoma AND any two of: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity, **OR**
- Multiple meningiomas (two or more) **AND** unilateral vestibular schwannoma **OR** any two of: schwannoma, glioma, neurofibroma, cataract.

3.1.2 Patients must have measurable disease, defined as at least one VS $\geq$0.4 ml (on volumetric analysis) that can be accurately measured by contrast-enhanced cranial MRI scan with fine cuts through the internal auditory canal (3 mm slices, no skip).

3.1.3 Age $\geq$ 6 years on day 1 of treatment.

3.1.4 Life expectancy of greater than 1 year.

3.1.5 Karnofsky performance status $\geq$ 70 (see Appendix C).

3.1.6 Participants must have normal organ and marrow function as defined below:

- Leukocytes $\geq$ 3,000/mcL

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Total bilirubin within normal institutional limits
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Patients must have a creatinine clearance or radioisotope GFR ≥60ml/min/1.73 m2 or a normal serum creatinine based on age/gender described in the table below:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.1.7 Subjects must have a target VS with the following qualities:

- Not amenable to surgery due to patient refusal, high risk for surgical complications (*e.g.*, damage to lower cranial nerve function, tumor size > 3 cm in longest diameter, or multilobulated tumor appearance on MRI scan).
- Associated with a word recognition score of < 85% and > 5%
- Documented clinical progression defined as **EITHER**:
  - Progressive hearing loss (defined as a decline in word recognition score below the 95% critical difference interval from baseline score (Appendix A) related to VS (*i.e.*, not due to prior interventions such as surgery or radiation)

    OR

  - Progressive tumor growth in the preceding 18 months, defined as ≥ 20% increase in volume

3.1.8 The effects of bevacizumab on the developing human fetus are unknown. For this reason and because bevacizumab agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence; surgical sterilization) prior to study entry and for the duration of study participation. Should a woman become

pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.9 Ability to understand and the willingness to sign written informed consent and assent documents.

3.1.10 Must have established relationship with primary care physician and provide contact information

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Patients who have had chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Prior radiation treatment to the target vestibular schwannoma is allowed if provided 3 years prior to participation in the clinical trial. Prior radiation treatment to non-target tumors is allowed.

3.2.2 Participants may not be receiving any other study agents.

3.2.3 Patients with nervous system tumors associated with NF2 (*e.g.*, schwannomas, meningiomas, ependymomas, or gliomas) will **not** be excluded from this clinical trial unless (in the opinion of the investigator) these tumors are growing and are likely to require treatment during the clinical trial.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bevacizumab.

3.2.5 Patients with known hypersensitivity of Chinese hamster ovary cell products, other recombinant human antibodies, or compounds of similar chemical or biologic composition to bevacizumab.

3.2.6 Inability to tolerate periodic MRI scans or gadolinium contrast.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 History of arterial/myocardial disease.

3.2.9 Clinically significant cardiovascular disease, such as:

- Inadequately controlled HTN (for adults: SBP > 160 mmHg and/or DBP > 90 mmHg despite antihypertensive medication; for children: please refer to Appendix D for age-appropriate values indicating ≥ Grade 2)
- History of CVA within 12 months
- Myocardial infarction or unstable angina within 12 months
- New York heart association grade II or greater congestive heart failure
- Serious and inadequately controlled cardiac arrhythmia
- Significant vascular disease (*e.g.*, aortic aneurysm, history of aortic dissection)
- Clinically significant peripheral vascular disease

3.2.10 Pregnant women are excluded from this study because bevacizumab is an anti-angiogenic agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with bevacizumab, breastfeeding should be discontinued if the mother is treated with bevacizumab. These potential risks may also apply to other agents used in this study.

3.2.11 HIV-positive patients or cancer survivors are eligible for this study if they fulfill all other eligibility criteria.

3.2.12 Concurrent use of anti-coagulant drugs (not including prophylactic doses), history of coagulopathy, or evidence of bleeding diathesis or coagulopathy.

3.2.13 Imaging (CT or MRI) evidence of hemorrhage deemed significant by the treating physician (> grade 1). Subjects with history of CNS hemorrhage are not eligible.

3.2.14 Urine protein should be screened by urine analysis for Urine Protein Creatinine (UPC) ratio. For UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be <1000 mg for patient enrollment. **NOTE:** UPC ratio of spot urine is an estimation of the 24-urine protein excretion. A UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.2.15 Serious or non-healing wound, ulcer or bone fracture.

3.2.16 History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to Day 1.

3.2.17 Invasive procedures defined as follows:

- Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to Day 1 therapy

- Brain biopsy within 28 days prior to day 1 of therapy (wounds must be fully healed from brain biopsies performed more than 28 days prior to Day 1 of therapy)
- Anticipation of need for major surgical procedures during the course of the study
- Core biopsy within 7 days prior to Day 1 of therapy

3.2.18 Prior treatment with bevacizumab.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Both men and women, and members of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for NF Consortium Institutions

Institutions will register eligible participants through a web-based data entry system created for that purpose by the NF Consortium Data Management and Analysis Center (DMAC). Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A physician on the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the protocol Principal Investigator (PI).

4.2 Registration Process for NF Consortium Institutions

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

3. Enrollment and exclusion criteria will be entered through the NF Consortium's web-based data entry system after receiving email confirmation from the Protocol PI (or his designee) that consented subject is eligible for study entry.

4. NF Consortium's web-based data entry system will send enrollment confirmation via automated email alerts to study protocol team, Operations Center, site PI and site study coordinator.

4.3 General Guidelines for all Participating Institutions

The required forms for subject registration can be found on the UAB online entry system.

Following registration, participants should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. The Research Nurse Manager (Operations Center) should be notified of participant status changes as soon as possible by email.

Each participating institution will order the study agent from the UAB Research Pharmacy. A participating site may order the agent only after the initial IRB approval for the site has been forwarded by the Operations Center.

4.4 Registration Process for All Participating Institutions

To register a participant, the following documents should be completed and information entered online by the study coordinator or designee:

- CBC, Chemistry-12, urinalysis, urine protein:creatinine ratio
- Confirmation of signed study consent form
- Confirmation of HIPAA authorization form
- Confirmation of acceptability of baseline audiology by clinical research team in Principal Investigator's office (Dr. Scott Plotkin) or Dr. Chris Halpin (Massachusetts Eye and Ear Infirmary)
- Confirmation of baseline MRI scan including internal auditory canal protocol (3 mm slices, 0 mm gap)
- Completion of Inclusion/Exclusion, Eligibility Checklist, and Registration forms located on the UAB web-based data entry system.

NOTE: Registration with NF Consortium's web-based data entry system can be conducted anytime, but the DMAC support can only be provided during the business hours of 8am – 5pm CST Monday through Friday. Study sites are responsible for arranging initial and follow-up study treatments.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for bevacizumab are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). Reported adverse events and potential risks are described in Section 2.1. No investigational or commercial agents or therapies

other than those described below may be administered with the intent to treat the participant's malignancy.

Bevacizumab is administered by IV infusion at a dose of 10 mg/kg every 2 weeks for 24 weeks (induction therapy, see Schema). One cycle lasts 28 days and includes two infusions of bevacizumab. Clinical response will be assessed by audiology and MRI at weeks 13 and 25. Subjects with hearing decline at weeks 13 and 25 will be taken off of protocol. After week 25, patients with a clinical response or stable disease (together comprising "clinical benefit") will transition to maintenance therapy with bevacizumab. During the maintenance phase, subjects will be treated with open-label bevacizumab 5 mg/kg every 3 weeks for up to 72 weeks. Subjects will be followed with audiology and MRI scans every 12 weeks. The total time of the study will be 96 weeks (24 week induction + 72 weeks maintenance).

During maintenance therapy, subjects will be allowed to increase their bevacizumab dose to 10 mg/kg every 2 weeks if they experience hearing decline (defined as decrease in word recognition score below the 95% critical difference compared with the word recognition score at baseline, Appendix A) compared with the highest word recognition score during treatment. Subjects will be taken off of study if their word recognition drops below the 95% critical difference (new hearing baseline defined as the word recognition score leading subject to receive 10 mg/kg dose every 2 weeks) after receiving bevacizumab 10 mg/kg every 2 weeks for at least 12 weeks.

The planned treatment duration will be 96 weeks, but continued therapy on study will be allowed at the study chair's discretion based on individual risk-benefit assessment. The consequence of treatment interruption/discontinuation in subjects who respond to treatment is not known. For example, discontinuation of VEGF receptor inhibitors has been associated with rebound edema in some patients with recurrent glioblastoma.[45]

5.1 Pre-treatment Criteria

5.1.1 Cycle 1, Day 1

Patients must have organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- creatinine < 1.5 ULN for age
- total bilirubin ≤2 X institutional ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional ULN
- urine protein:creatinine ratio ≤ 1

5.1.2 Subsequent Cycles, Day 1

Patients must have organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- creatinine < 1.5 ULN for age
- total bilirubin ≤2 X institutional ULN
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional ULN
- urinary dipstick/urinalysis ≤ 2+ protein
- urine protein:creatinine ratio < 3.5 (if urine dipstick > 2+)

Special Precautions/Safety Issues
Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events, as well as symptoms or signs of bowel perforation and RPLS. Decisions for retreatment or dose modification/interruption should follow the dose modification guidelines in Section 6.3.

Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

Infusional reactions. Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and for premedication as needed. Anaphylactic precautions should be observed during bevacizumab administration.

Hypertension. Patients should have BP monitored prior to each infusion of bevacizumab. Hypertensive medication should be initiated or increased for optimal BP control according to Appendix D. Specific guidelines for the management of hypertension are provided for children 6 through 17 years old enrolled on this trial (Sections 6.3 and Appendix D).

Proteinuria. Proteinuria should be monitored by urine protein: creatinine (UPC) ratio and dipstick as indicated in study calendar. If urine dipstick ≤ 2+ protein, bevacizumab can be infused. If urine dipstick > 2+, infusion can be provided once the UPC ratio is reported to be < 3.5.

Surgery and wound complication issues. The appropriate interval from discontinuation of bevacizumab to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab should be discontinued at least 4-8 weeks prior to major elective surgery. In addition, bevacizumab should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed; in cases of high-risk procedures such as

liver resection, thoracotomy or neurosurgery, it is recommended that bevacizumab be resumed no earlier than 8 weeks after surgery. **NOTE**: If bevacizumab is interrupted for ANY reasons for > 12 weeks, the patient should discontinue bevacizumab therapy on protocol.

Bony toxicity. Children 6 through 17 years old will be carefully monitored for the development of bony toxicity (Sections 6.3 and Appendix E).

For patients with open growth plates on tibial radiographs at baseline, measurements of stature (height) will be measured at visits on weeks 13, 25, 49, 73, and 91. Bevacizumab will be discontinued if:

- <1 cm growth is noted prior to week 25
- <2.5 cm growth is noted prior to week 49
- Subsequently, <2cm/year annualized growth velocity noted every 24 weeks (for patients with open growth plates only)

5.2 Bevacizumab Administration

Bevacizumab is administered by IV infusion at a dose of 10 mg/kg every 2 weeks (dose level +1) for 24 weeks (induction therapy) followed by a dose of 5 mg/kg every 3 weeks (dose level 0) for 72 weeks (maintenance therapy). During induction therapy, one cycle lasts 28 days and includes two infusions of bevacizumab; during maintenance therapy, one cycle lasts 42 days and includes two infusions. The dose should be based on the patient's actual body weight. The first dose of bevacizumab should be given over 90 minutes. If well-tolerated, the second dose can be given over 60 minutes. If this dose is well tolerated, then all subsequent infusions can be administered over 30 minutes. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well tolerated.

5.3 Definition of Dose-Limiting Toxicity

N/A

5.4 General Concomitant Medication and Supportive Care Guidelines

There is no known interaction of bevacizumab with other concomitantly administered drugs. Prophylactic low-dose (81 mg or 325 mg/day) acetylsalicylic acid and systemic anticoagulation is allowed (LMWH preferred relative to warfarin). Other medication considered necessary for the subject's safety and well being may be given at the discretion of the investigator.

Prolonged systemic corticosteroid treatment should not be given during the study, except for topical applications (*e.g.*, rash), inhaled sprays (*e.g.*, obstructive airways diseases), eye drops or local injections (*e.g.*, intra-articular). A short duration (≤ 15

days) of systemic corticosteroids is allowed (*e.g.*, for sudden hearing loss, chronic obstructive pulmonary disease, or as an anti-emetic).

Cases of sudden hearing loss during treatment (defined as hearing loss with onset over a period of less than 72 hours) may be treated with a short course of high dose glucocorticoids (*e.g.*, prednisone 60 mg daily for 10 days followed by a taper of 10 mg every day). These patients should have repeat audiology performed during the episode at the discretion of the treating physician to document hearing function (see section 5.5 for guidance on continuing therapy).

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 2 years (96 weeks) or until one of the following criteria applies (whichever occurs first):

- Hearing decline at the 10 mg/kg every 2 week dose during induction therapy. **NOTE:** Patients with episodes of sudden hearing loss (Section 5.4) or hearing loss related to other causes (e.g., otitis media, allergic symptoms, or other infectious causes) should remain on treatment provided their word recognition score returns to the 95% critical difference compared with baseline [Appendix A] within 14 days of the start of the event.)
- Hearing decline at the 10 mg/kg every 2 week dose during maintenance therapy (hearing decline is defined as a decline in word recognition score below the 95% critical difference interval from word recognition score leading subject to receive 10 mg/kg dose [Appendix A]) after receiving bevacizumab 10 mg/kg every 2 weeks for at least 12 weeks. **NOTE:** Patients with episodes of sudden hearing loss (Section 5.4) or hearing loss related to other causes (e.g., otitis media, allergic symptoms, or other infectious causes) should remain on treatment provided their word recognition score returns to the 95% critical difference compared with baseline [Appendix A] within 14 days of the start of the event.)
- Radiographic progression of NF2-associated tumors (target VS, contralateral VS, meningiomas, or ependymomas) that require additional or alternate therapies (Section 10.1.4); (**NOTE:** Growth of NF2-associated tumors that is consistent with the natural history of the disease is not a criterion for discontinuing protocol therapy.)
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s), including, but not limited to:
    - Grade 4 hypertension or Grade 3 hypertension not controlled with medication
    - Nephrotic syndrome
    - Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
    - ≥ Grade 2 venous thromboembolic event
    - Any grade arterial thromboembolic event
    - ≥ Grade 2 congestive heart failure
    - Gastrointestinal perforation or new gastrointestinal fistula (any Grade)
    - Tracheoesophageal fistula (any grade) or Grade 4 fistula

- Grade ≥ 2 bowel obstruction
- Wound dehiscence requiring medical or surgical intervention
- Pregnancy during the study period (for female participants)
- All Grade 4 events thought to be related to bevacizumab by the investigator (**NOTE:** Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible [See Section 7.1.3].)

- Participant decides to withdraw from the study; or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation; subject data up to withdrawal of consent will be included in the subject's study data. Any subject may withdraw full consent to participate in the study at any time during the study. The investigator will discuss with the subject appropriate procedures for withdrawal from the study.

Withdrawal of partial consent means that the subject does not wish to take protocol-specified product any longer but is still willing to collaborate in providing further data by continuing on study (eg, participate in any or all subsequent study visits or procedures). Subjects may decline to continue receiving protocol-specified product at any time during the study. If this occurs, the investigator will discuss with the subject appropriate procedures for withdrawal from protocol-specified therapy. These subjects, as well as those who have stopped receiving protocol-specified product(s) for other reasons (eg, investigator or sponsor concern) should continue the schedule of study observations at the discretion of the principal investigator.

NOTE: A course of high dose glucocorticoids (typically prednisone 60 mg daily for 10 days followed by a taper of 10 mg every day) is permitted at the discretion of the treating physician in cases of sudden hearing loss during treatment (defined as hearing loss with onset over a period of less than 72 hours).

5.6 Duration of Follow-Up

Participants will be followed in person or by telephone for 12 weeks after removal from study. Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the participant was

removed must be documented in the data entry system. Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Scott Plotkin, MD, PhD at 617-726-2000 (pager #34635) and Bruce Korf, MD, PhD, at 205-934-9411 (UAB Operations Center Office) or Liz Davis at 205-934-5376 (Research Nurse Manager) or email: nfconsortium@uab.edu.

6. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 3.2) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 5.5).

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure is recommended for patients on treatment with or without bevacizumab. Blood pressure monitoring during study drug administration should be performed according to institutional guidelines.
- Proteinuria will be monitored by urine protein:creatinine (UPC) ratio and urinalysis/dipstick at least every 6 weeks.
- If patients on treatment with bevacizumab require major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure. In the case of high risk procedures (such as liver resection, thoracotomy, or neurosurgery), it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Dose Level	Bevacizumab Dose
-2	3 mg/kg IV every 3 weeks
-1	4 mg/kg IV every 3 weeks
0	5 mg/kg IV every 3 weeks
+1	10 mg/kg IV every 2 weeks

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

Toxicities with a possible association to bevacizumab treatment include:

Frequent (Chance of 10-50% that this will happen)

- Fatigue
- Headaches
- High blood pressure, with increased risk of heart problems, headache and stroke.
- Pain
- Abdominal pain
- Shortness of breath
- Mouth sores
- Weakness
- Upper respiratory infection
- Chills
- Loss of appetite
- Bleeding (including in stomach or intestines)
- Runny nose or increase in tears in your eyes
- Kidney damage, found by testing your urine
- Irregular menstrual period or loss of menstrual period
- Loss of function of the ovaries (female sex glands), that can lead to menopause. Studies in humans have shown a decrease in the function of ovaries during treatment with bevacizumab with chemotherapy. This condition results in difficulty becoming pregnant. In some participants, the function of the ovaries returned to normal after treatment with bevacizumab and chemotherapy was stopped.

Occasional (Chance of 5-10% that this will happen)

- Hoarseness
- Nosebleeds
- Low levels of potassium in the blood (can cause an irregular heartbeat)
- Hair loss
- Dry Skin
- Hole in your intestine; requires hospitalization and/or surgery; could be fatal.
- Blood clots in your veins and arteries. These can cause chest pain, heart attack, or stroke. A blood clot in your eye might cause vision loss. Clots can be serious and life threatening.
- Allergic reaction when infusion is given. Serious allergic reaction may result in death.
- Slowed growth in height and development (for children and young adults who are still growing). Laboratory studies have shown a decreased in growth during treatment with bevacizumab .

Rare (Chance < 5% that this will happen)

- Congestive heart failure (fluid that builds up in your lungs because your heart isn't working properly).
- Bevacizumab might affect the ability of your wounds to heal. This can lead to infections, hospitalization, or could possibly be fatal.
- A very rare problem in your brain that may cause confusion, blindness, and coma has been seen in some patients that were given Bevacizumab. This is associated with very high blood pressure and is not thought to be a permanent condition.
- Confusion
- Abdominal abscess or infection in your abdomen
- Fistula or hole in your bowel. This is an abnormal connection between two different organs and may lead to life threatening complications including serious infections, bleeding, or dysfunction of the organs.
- Dehydration
- Abnormal bleeding in your body or from the tumor, which may be fatal.
- Laboratory studies of bevacizumab showed abnormal bone growth. These and other effects of bevacizumab could possibly cause problems with growth and development. Abnormal changes in the bones after treatment with bevacizumab have been seen in young children with growing bones. This side effect appeared to be reversible after the drug was stopped, but has not been studied with long-term use of the drug. All participants in this study who receive bevacizumab and are still growing will be monitored for changes to bones by the use of x-rays performed throughout the study treatment.
- Fistula or hole in your gallbladder (part of the intestines that helps with digestion). This may require surgery and be serious or life threatening.
- Osteonecrosis of the jaw. A severe bone disease in which the jaw bone becomes visible (exposed) inside the mouth. This can be associated with pain and infection.

6.2 Toxicity Management

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

6.3 Dose Modifications/Delays

A list of the adverse events and potential risks associated with the agents administered in this study appear below.
NOTE 1: Treatment should be interrupted or discontinued for certain adverse events, as described below. Doses missed while recovering from toxicity will not be made up. The AEs will be defined based on CTCAE term (AE description) and grade. The descriptions and grading scales found in the CTEP Version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 4.03 of the CTCAE is identified and located on the CTEP website at: http://ctep.cancer.gov/. All appropriate treatment areas will have access to a copy of the CTEP Version 4.03 of CTCAE. Details of actions to be taken based on a particular AE (using the most active CTCAE version) are provided below.

NOTE 2: If bevacizumab is interrupted for ANY reasons for > 12 weeks, the patient should discontinue bevacizumab therapy on protocol.

NOTE 3: Subjects will be allowed to increase their bevacizumab dose to 10 mg/kg every 2 weeks during maintenance therapy if they experience hearing decline during maintenance therapy (defined as decrease in word recognition score below the 95% critical difference compared with the word recognition score at baseline, Appendix A). Subjects will be taken off of study if their word recognition score does not remain within the 95% critical difference (determined from word recognition score leading subject to receive 10 mg/kg dose) after receiving bevacizumab 10 mg/kg every 2 weeks for at least 3 months.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study (Table 1), treatment with bevacizumab should be discontinued.

Infusion Reaction: Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a NCI CTCAE v. 4.3 Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's

symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Adverse events requiring delays, dose reductions, or permanent discontinuation of bevacizumab are listed in Table 1.

Table 1: Bevacizumab Dose Management Due to Adverse Events

Event	***Action to be Taken***
Hypertension (in adults only)	
No dose modifications for grade 1 or 2 events	
Grade 3	*If not controlled to 150/100 mmHg with medication, reduce one dose level. For second occurrence, reduce a second dose level. For third occurrence, discontinue bevacizumab.*
Grade 4 (including hypertensive encephalopathy)	*Discontinue bevacizumab.*
*Specific guidelines for the management of hypertension are provided for adults and children 6 through 17 years (Appendix D).	
Hemorrhage	
No dose modifications for grade 1or 2 non-pulmonary and non-CNS events	
Grade 3 Non-pulmonary and non-CNS hemorrhage	*Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab.* *All other subjects will have bevacizumab held until all of the following criteria are met:* • *The bleeding has resolved and hemoglobin is stable.* • *There is no bleeding diathesis that would increase the risk of therapy.* • *There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.* *Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.*
Grade 4 non-pulmonary or non-CNS hemorrhage	*Discontinue bevacizumab.*

Grade 1 pulmonary or CNS hemorrhage	*Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab.* *All other subjects will have bevacizumab held until all of the following criteria are met:* • *The bleeding has resolved and hemoglobin is stable.* • *There is no bleeding diathesis that would increase the risk of therapy.* • *There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.*
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	*Discontinue bevacizumab.*
Venous Thrombosis *No dose modifications for grade 1 events*	
Grade 2, 3, or 4	*Discontinue bevacizumab.*
Arterial Thromboembolic event *(New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)*	
Any grade	*Discontinue bevacizumab.*
Congestive Heart Failure (Left ventricular systolic dysfunction) *No dose modifications for grade 1 events*	
Grade 2, 3, and 4	*Discontinue bevacizumab.*
Proteinuria *No dose modifications for grade 1/2 events*	
Grade 3 (UPC> 3.5, urine collection > 3.5 g/24 hr)	*Hold bevacizumab treatment until ≤ Grade 2, as determined by either UPC ratio ≤ 3.5 or 24 hr collection ≤ 3.5 g, and reduce by one dose level. For second occurrence, reduce by a second dose level. For third occurrence, discontinue bevacizumab.*
Grade 4 (nephrotic syndrome)	*Discontinue bevacizumab.*
GI Perforation	*Discontinue bevacizumab.*
Fistula	
Any grade (TE or gastrointestinal fistula)	*Discontinue bevacizumab.*
Grade 4 fistula	*Discontinue bevacizumab.*
Bowel Obstruction	
Grade 1	*Continue patient on study for partial obstruction NOT requiring medical intervention.*

Grade 2, 3, or 4	*Discontinue bevacizumab.*
Wound dehiscence Any grade (requiring medical or surgical therapy)	***Discontinue bevacizumab.***
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	
Any grade (confirmed by MRI)	*Discontinue bevacizumab.*
Ovarian function	
Follicle stimulating hormone (FSH) > 20 Units/L	*Hold bevacizumab and refer patient to qualified practitioner (eg., reproductive endocrinology specialist) to assess ovarian function. Subject should have measurement of anti-Mullerian hormone (AMH) and ultrasound of ovaries for determination of antral follicle count by qualified practitioner. If assessment reveals evidence of premature ovarian failure, consider discontinuation of bevacizumab after discussion with subject, medical monitor, and study PI. No additional actions are required for subsequent occurrences.*
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	*Hold bevacizumab until recovery to ≤ Grade 1*
Grade 4	*Discontinue bevacizumab.*

Hypertension in children aged 6 - 17 years:
Any patient with a diastolic blood pressure greater than 25 mmHg above the 95th% for age and gender (Appendix D) confirmed by repeated measurements will result in reduction of one dose level. For a second occurrence, discontinue bevacizumab. (See Appendix D for assessment of blood pressure recordings and for management.)

In children on antihypertensive therapy, a diastolic blood pressure ≥25 mmHg above the 95th % for age and gender for >14 days will result in reduction of one dose level. For a second occurrence, discontinue bevacizumab (see Appendix D).

Dose limiting bony changes in children aged 6 - 17 years

Children 6 - 17 years old will be carefully monitored for the development of bony toxicity (Sections 6.3 and Appendix E).

For patients with open growth plates on tibial radiographs at baseline, measurements of stature (height) will be measured at weeks 13, 25, 49, 73, and 91. Bevacizumab will be discontinued if:

- <1 cm growth is noted prior to week 25
- <2.5 cm growth is noted prior to week 49
- Subsequently, <2cm/year annualized growth velocity noted every 24 weeks for patients with open growth plates only

7. DRUG FORMULATION AND ADMINISTRATION

7.1 Bevacizumab

7.1.1 Description

Other Names. rhuMAb VEGF, Avastin®

Classification. Recombinant humanized monoclonal antibody

Molecular Weight. Approximate molecular weight is 149,000 daltons

Mode of Action. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

Description. Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions

Route of Administration. Intravenous

Terminal half-life. 21 days

For further details and molecule characterization, see the bevacizumab Investigator Brochure.

7.1.2 Form

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab may be supplied in 5-cc (100-mg) and 20-cc (400-mg) glass vials containing 4 mL or 16 mL bevacizumab, respectively (all at 25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

7.1.3 Storage and Stability

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light. Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

7.1.4 Compatibility

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP.

7.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

7.1.6 Availability

Distribution: Bevacizumab will be supplied free of charge by Genentech, Inc. and will be distributed to investigators by a designated central pharmacy (UAB Pharmacy).

7.1.7 Preparation

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 patient may not be used for any other patient. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

7.1.8 Administration

Anaphylaxis precautions should be observed during study drug administration. The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (*e.g.*, fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated.

It is not necessary to correct dosing based on ideal weight.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

- When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

- Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing. **NOTE**: the flush is not included in the total recommended infusion times.

7.1.9 Ordering

(See Appendix B for Bevacizumab Supply Request Form)

Initial Shipments (new patients registered to study)
When a site has received Sponsor IRB approval and has identified potential patients to screen, the study site will complete a 'Drug Order Request Form' and submit this request to UAB Pharmacy.

After faxing to the request, study site will:
- Place a call UAB Pharmacy confirming the faxed order was received, and confirm estimated day and time of arrival for the study drug.
- UAB will pack and ship the required number of bevacizumab vials to the site for the patient to complete treatment for 24 weeks based on the patient's weight (kg). Initially, 20 vials will be sent.

Subsequent Shipments (active patients requiring additional bevacizumab supply)
When additional bevacizumab is required for a subject, the study site will complete a 'Bevacizumab Supply Request' and submit to UAB by calling 205-975-6647.

After faxing to UAB, site will:
- Place a call to UAB to confirm the order was received, and arrange day and time of arrival for the study drug.
- UAB will pack and ship the required number of bevacizumab vials to the site.
- UAB Pharmacy will pack and ship the additional vials of bevacizumab vials for 24 weeks based on the subject's weight (kg).

For all drug shipments from UAB:

- Bevacizumab will be shipped in original manufacturers packaging. Boxes are placed in a ZipLock bag. Subject-specific labeling will be added at the clinical study site.

- A complete accountability record (including date of dispense, site name, quantity dispensed, and balance forward) will be recorded. Study accountability records are documented in electronic 21 CFR format and are kept in a secured area for duration of the study.

- Require a Pharmacist review; a licensed pharmacist checks off package for accuracy of contents, authorizing order via 21 CFR compliant trial accountability log.

- Each shipment includes the following information:
    - Study number
    - IND caution statement and/or local regulatory statements
    - Drug identification
    - Lot number and expiration
    - Storage conditions
    - Dosing instructions (Take as Directed per Protocol)
      (Subject ID number, initials and date dispensed will be provided by the study site pharmacy.)

- Enclose a packing slip that includes the quantity of drug provided with a section to be completed once received by the site coordinator. This section includes confirmation of drug receipt, verification of package contents, and instruction to fax the completed packing slip to UAB.

- Process and ship authorized and completed orders "same day" of patient randomization if received Monday through Thursday. Authorized and completed orders received after 12N CST Thursday, will be sent on the following Monday or Tuesday if Monday is a Holiday. Orders will be processed and shipped the next business morning.

All drug orders are shipped via *FedEx for Priority Overnight* delivery. Bevacizumab is shipped with a gel pack to maintain temperature stability.

Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

Once study drug is received at the clinical trial site:

- The designated site coordinator or Investigational pharmacy representative validates that contents of package matches information provided on packing slip, signs off on the packing slip, and contacts UAB to validate shipment has been received and is accurate.

The order transaction is completed by entering the receipt confirmation and signed packing slip into the study file.

Drug Destruction and Transfer of Study Drug
Sites will be instructed to destroy unused/returned drug per institution policy and note in the accountability record after site Pharmacy Drug Destruction Policy is sent to Operations Center and policy is placed in the regulatory files. Drug destruction policy should also be maintained in Pharmacy.

Since study drug vials are sent to study sites, Bevacizumab may be used for all consented subjects. Use of all study drug vials will be documented on study drug accountability records.

Central Pharmacy – UAB
Rebecca Quinn, PharmD
Senior Pharmacist -Investigational Drug Service
UAB Hospital
North Pavilion, room 3470
1802 6th Avenue South
Birmingham, AL 35249
205-934-7191 (phone)
205-975-6647 (fax)
UAB paging: 205-934-3411, pager 4295

7.1.10 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

Sites will be required to send site drug accountability records to Operations Center on a quarterly basis. The site study drug accountability records will be checked against UAB Pharmacy study drug administration data accountability records.

Drug accountability records should be submitted quarterly to UAB:

Roy McDonald, MPH
Research Compliance Manager
Department of Genetics
University of Alabama at Birmingham
1720 20th Street South, MCML 262A
Birmingham, AL 35294-0024
205-975-4075 (phone)
205-975-3543 (fax)
Email: rmcdonald@uab.edu

7.1.11 Destruction and Return

At the end of the study, unused supplies of bevacizumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies

N/A

8.2 Pharmacodynamic Studies

N/A

8.3 Laboratory correlative markers

8.3.1 Markers of angiogenesis and tumor growth

Recent development in understanding the molecular basis of cancer has dramatically advanced the field in cancer drug discovery and development. Now it is clear that the translation of molecularly targeted cancer therapy into useful and practical therapeutic approaches is highly complex. The discovery of mechanism-based biomarkers can facilitate the efficient development of new anti-tumor medicines and potentially serve as true intermediate or surrogate end point biomarkers for future clinical trials. Biomarkers can also help guiding rational selection of therapeutic agents for patient likely to respond to therapy. Two recent studies show that collagen IV structure was modified after VEGFR2 blockade. These data together with other data on different biomarkers indicate that it is important to include measurement on the serum levels of biomarkers in future clinical practices.

To measure numerous biomarkers simultaneously with exceptional sensitivity but only small amount of plasma proteins, the MSD (Meso Scale Discovery, Maryland) platform will be used. MSD technology utilizes electrochemiluminescence detection to detect binding events on patterned arrays. By customizing the Multi-Array, multiple serum molecules can be tested. We will collect blood samples from the patients before and during the course of treatment (see study table). Analysis will be performed for VEGF-A, VEGF-C, sVEGFR1, sVEGFR2, sVEGFR3, Col IV, SDF1a, IL-1beta, IL-6, IL-8, TNFalpha, G-CSF, Ang1, Ang2, sTie2, s-cKIT, MMP-1, MMP-2, MMP-3, MMP-9, MMP-10, PlGF, and bFGF using the Meso-Scale Discovery multiplex array reader and custom multiplex plates and R&D Systems ELISA kits for collagen IV and SDF1α. This assay provides a sensitivity of 0.001 ng/mL and low variability. The level of these biomarkers during treatment with bevacizumab will be compared to the baseline level.

8.3.2 Collection of specimen(s)

Sample Collection Time Points

Blood samples will be obtained for protein analysis of potential biomarkers for anti-angiogenic therapy ~3 hours prior to bevacizumab infusion (i.e., when baseline labs are drawn) at the following time points:

- Prior to initiating therapy
- Weeks 3, 5, and 25

Blood collection (needed for each time point sample)

- Collect 16 ml of blood in 2 polypropylene tubes (8 mL in each tube) containing the anticoagulant EDTA. Tubes should be pre-cooled in an ice bath.
  - SARSTEDT Monovette® EDTA KE (9 ml), Part # 02.1333.001
    or
  - Becton-Dickinson Vacutainer™ K2E (10 ml), Part # 367525
    or
  - Greiner Bio-One Vacuette® K3E EDTA K3 (9 ml), Part 455036
- Blood tubes must be gently inverted several times after collection to ensure thorough mixing of EDTA with the sample to prevent clotting.
- Cool all tubes in an ice bath immediately after collection.
- **Glass tubes MUST NOT be used** as they may break during transport and freeze-thaw cycles.
  Heparin must not be used as an anticoagulant as it may interfere with downstream genotyping methodology.

8.3.3 Handling of specimens

Centrifuge tubes collected at 700 G for 20 minutes at 4C° with no breaks within 30 minutes of collection.

Prepare two labels each printed with Study-No., patient ID, initials and day/time of sample collection (24-hour clock format, *i.e.*, 6:30 pm = 18:30). A label example is provided below:

Study-No.: NFCTC104	Investigator:
Patient-ID:	Sample Type: *Plasma*
Date of sampling: *(mm/dd/yy)*	Time of Sampling: *(hh:mm) (24-hr format)*

- Plasma is pipetted in 1 ml aliquots into two red-labeled Nalgene cryovials.
- Clearly label tubes as "plasma" and store at -80°C.
- When samples from all time-points have been collected (after the patient goes off trial) the plasma samples should be shipped to the Steele Laboratory at Massachusetts General Hospital on DRY ICE in a Styrofoam box (Thermo Safe shippers, Fisher Scientific, cat# :11-676-14; 12/case; $122.30). If a deep freezer is not available on site, the plasma sample should be kept and shipped on dry ice on the same day.
- Specimens should be shipped Monday to Wednesday only by overnight FedEx to the Testing Core Facility.

8.3.4 Shipping and analysis of specimen(s)

Ship all specimens to the following Testing Core Facility address:

Attn : Julia Kahn or Anna Khachatryan or Ms. Sylvie Roberge
100 Blossom St.
MGH, Cox-734
Boston, MA 02114
Tel. (617) 724-1353
Fax (617) 724-5841
Pager 14082 (617-726-2000)

On the day of shipment, the study coordinator will notify the Testing Core Facility via email: jakahn@partners.org or AKHACHATRYAN@PARTNERS.ORG or Sylvie@steele.mgh.harvard.edu to expect the upcoming shipment and include the estimated date of arrival and FedEX tracking number.

All analysis will be performed within the Steele Laboratory under the direction of Dr. Dan Duda. The Steele Laboratory has 6 years experience in analyzing and understanding variation in circulating angiogenic markers in various clinical trials [19, 45, 46].

8.3.5 Future use of specimen(s)

Blood specimens will be stored for future use in NF studies approved by the IRB. Specimens will be labeled as noted above (see 8.3.3) and stored indefinitely in the Steele Laboratory at MGH. Neither cell lines nor commercial products will be developed from the blood specimens. Specimens will be banked under the current study protocol. Access to specimen samples will be limited to research personnel approved by the IRB. Subjects who wish to have their samples removed from storage (e.g., withdraw consent for biomarker storage) should contact the study PI who will work with the Steele Laboratory to have the sample destroyed.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans must be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Appropriate study assessments must be performed prior to administration of study medication. **All study assessments should be administered within $\pm$ 7 days of the protocol-specified date, unless otherwise noted. Audiology and MRI scans should be performed on day 1 of appropriate cycles (see table below).** Bevacizumab should be provided on days 1 and 15 of each induction cycle and on days 1 and 22 of each maintenance cycle (window: -1 to +3 days).

		Induction Therapy Cycle = 4 weeks							**Maintenance Therapy Cycle = 6 weeks**												
Study week	Pre-Study	1	3	5	9	13	17	21	25	31	37	43	49	55	61	67	73	79	85	91	Off Study[f]
Cycle number	Pre-Study	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Off Study[f]
Bevacizumab	X	X----------X [a]							X ----------X [b]												
Informed consent	X																				
Demographics	X																				
Medical history	X																				
Concurrent meds Interval history	X	X ---------- X																			X
Physical exam	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																				X
Weight	X	X	X	X	X	X	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
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation studies (PT/PTT/INR)	X								X				X				X				X
Serum chemistry[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X																				

Adverse event evaluation	X	X ---------- X																		X
B-HCG [e]	X					X			X		X		X		X		X		X	X
FSH[i]	X					X			X		X		X		X		X		X	X
Radiologic evaluation [j]	X					X			X		X		X		X		X		X	X
Tumor volume measurements	X					X			X		X		X		X		X		X	X
Hearing assessment[g]	X					X			X		X		X		X		X		X	X
Tinnitus Assessments[h]	X					X			X				X				X			X
NFTI-QOL[k]	X								X				X				X			X
Plasma biomarkers		X	X	X					X											

a: Bevacizumab 10 mg/kg by vein (IV) every 2 weeks. Doses should be provided on days 1 and 15 of each cycle (window: -1 to +3 days).
b: Bevacizumab 5 mg/kg by vein (IV) every 3 weeks starting on week 25. Doses should be provided on days 1 and 22 of each cycle (window: -1 to +3 days). For subjects on dosing every 2 weeks (dose level +1), doses should be provided on days 1, 15, and 29 of each 6 week cycle (window: -1 to +3 days).
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
d: Proteinuria will be monitored by urine dipstick and by urine protein:creatinine (UPC) ratio at least every cycle. If urine dipstick $\leq$ 2+ protein, bevacizumab can be infused. If urine dipstick > 2+, infusion can be provided once the UPC ratio is reported to be < 3.5. If UPC ratio is $\geq$ 2, collection of 24 hour urine for measurement of urine protein level is recommended but not required.
UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:
- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

e: Serum pregnancy test (women of childbearing potential).
f: Off-study evaluation. Patients who have an on-going study agent-related serious adverse event upon study completion or at discontinuation from the study should be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be

irreversible. Patients who continue with off-label bevacizumab after completion of the study will be contacted by the investigator or his/her designee for 30 days after removal from the study. Adverse events during this time period will be assessed as part of the study. Patients who do not receive off-label bevacizumab after completion of the study will be be contacted by the investigator or his/her designee for 12 weeks after removal from study. Adverse events during this time period will be assessed as part of the study.

g: Audiology will include measurement of pure tone thresholds and determination of word recognition scores as described in Appendix F . Audiograms should be performed on day 1 of each designated cycle (window: -5 days to day of infusion). Audiograms must be reviewed prior to bevacizumab infusion.

h: Tinnitus reaction questionnaire is given in Appendix H. Children 11 and younger on day 1 of the protocol should not complete NFTI-QOL during trial participation.

i: Follicle stimulating hormone (FSH) should be measured in post-pubescent/pre-menopausal women only. The day of the menstrual cycle (the onset of menses is day 1) on which the labs are drawn should be recorded (if the subject is menstruating). Off-study levels should be drawn 30 days (+/-2 days) after discontinuing bevacizumab (can be drawn locally).

j: MRI scans should be performed on day 1 of each designated cycle (window: -5 days to day of infusion).

k: See Appendix B for NFTI-QOL questionnaire. Children 11 and younger on day 1 of the protocol should not complete NFTI-QOL during trial participation.

Additional Evaluations for Bony Toxicity <u>for Children only (ages 6 to 17)</u>

		Induction Therapy Cycle = 4 weeks							**Maintenance Therapy Cycle = 6 weeks**												
Study week	Pre-Study	1	3	5	9	13	17	21	25	31	37	43	49	55	61	67	73	79	85	91	Off Study[b]
Cycle number	Pre-Study	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Off Study[b]
Height	X					X			X				X				X			X	X
Radiograph of tibial growth plate	X					X[a]			X[a]				X[a]				X[a]			X[a]	X[a]

a: Radiographs of tibial growth plates will be repeated if growth plates are open at baseline.
b: Off-study evaluation. Patients who have an on-going study agent-related serious adverse event upon study completion or at discontinuation from the study should be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible. Patients who continue with off-label bevacizumab after completion of the study will be contacted by the investigator or his/her designee for 30 days after removal from the study. Adverse events during this time period will be assessed as part of the study. Patients who do not receive off-label bevacizumab after completion of the study will be be contacted by the investigator or his/her designee for 12 weeks after removal from study. Adverse events during this time period will be assessed as part of the study.

10. MEASUREMENT OF EFFECT

10.1 Antitumor Effect– Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. Response and progression will be evaluated in this study using the criteria proposed by Widemann and colleagues[15] for neurofibromatosis-associated lesions. Response and progression will not be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST)[47] or by MacDonald Criteria[48], since they may underestimate progression in these irregularly shaped tumors. However, linear measurements will be collected as part of the trial for comparison with volumetric measurements.

10.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with bevacizumab.

Evaluable for objective response. Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured using volumetric analysis of cranial MRI scans. All study MRI scans should include standard brain imaging sequences as well as fine cuts through the internal auditory canal (3 mm slice, no gaps) to image small tumors. In patients who have had surgery for tumors in the cerebellopontine angle, fat-saturation should be performed with the post-contrast sequences to compensate for the possible presence of post-operative fat packing.

NOTE: Tumor lesions that are situated in a previously irradiated area are considered measurable.

Non-measurable disease. Non-measurable lesions include skull-base lesions that are obscured by artifact from auditory brainstem implants (ABIs) or lesions whose margins are completely obscured by neighboring tumors (*i.e.*, "collision" tumors).

Target lesions. Investigators should identify a single target lesion in all subjects. The target lesion in this study is the progressive VS (*e.g.*, the lesion that is enlarging or is associated with hearing loss) that led to enrollment in the protocol. In cases where subjects have a single ear with hearing, the target lesion should be the enlarging VS ipsilateral to the hearing ear. In cases where subjects have hearing in both ears, the target lesion should be the tumor associated with word recognition score < 85% and is growing the fastest or is causing the most rapid hearing loss. In rare cases where both VSs are

associated with word recognition < 85% and progressing equally rapidly, the target lesion should be the larger of the two tumors on imaging. Target lesions should be identified at baseline and measured using volumetric analysis of the baseline MRI scan. The baseline volumetric MRI scan will be used as reference for comparison of all future MRI scans to characterize the objective tumor response.

Non-target lesions. Non-target lesions in this study include VSs contralateral to the target lesion (if present). The baseline contralateral VS will be used as reference by which to characterize the objective tumor response.

NOTE: Histologic confirmation of tumor type is not required. Designation of tumor type will be determined by the radiographic appearance by the study radiologist.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation [*i.e.*, cubic centimeters (cm3) and in millimeters (or decimal fractions of centimeters)] for linear measures. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 8 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Cranial MRI. Volumetric analysis of MRI scans should be performed on sequences with fine cuts through the internal auditory canal (3 mm slices, no gap; Appendix G).

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

For the purpose of this study, radiographic response will be defined by the change in tumor volume compared to baseline, as previously defined in previous studies in NF1.[15] Hearing will be measured in standardized fashion as described in Appendix F. Hearing response (Section 10.3) will be defined by the change in word recognition scores, taking as reference the baseline word recognition score (Appendix A and Section 10.3).

Radiographic Response (RR): At least a 20% decrease in the volume of the target lesions, taking as reference the baseline volume.

Progressive Disease (PD): At least a 20% increase in the volume of the target lesion, taking as reference the lower volume during treatment

Stable Disease (SD): Does not meet criteria for radiographic response or for progressive disease.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

10.1.4.2 Evaluation of Non-Target Lesions

Radiographic evaluations should be calculated separately for non-target lesions (contralateral VS).

Radiographic Response (RR): At least a 20% decrease in the non- target lesions, taking as reference the baseline volumes.

Stable Disease (SD): Does not meet criteria for radiographic response or progressive disease.

Progressive Disease (PD): At least a 20% increase in the volume of the non-target lesions, taking as reference the baseline volume

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response for the target vestibular schwannoma recorded from the start of the treatment until disease progression (taking as reference for progressive disease the hearing measurements recorded at baseline and the minimal tumor volume during treatment).

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.5 Duration of Response

Hearing evaluations should be performed for non-target (contralateral) VS if present and if hearing is present in the ipsilateral ear.

Duration of hearing response: The duration of hearing response (HR) is measured from the time that measurement criteria are met for HR until the first

date that the word recognition score decreases beneath the upper limit of the 95% critical difference of the baseline word recognition score..

Duration of stable hearing: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the word recognition score recorded at baseline.

Duration of radiographic response: The duration of radiographic response is measured from the time measurement criteria are met for RR until the first date that progressive disease is objectively documented (taking as reference for progressive disease the lowest tumor volume during treatment).

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the measurements recorded at baseline.

10.1.6 Progression-Free Survival: Freedom from hearing loss and freedom from tumor progression

The proportion of patients alive and free from progressive hearing loss at 24, 48, 72, and 96 weeks from the start of treatment will be determined. The proportion of patients alive and free from progressive tumor growth at 24, 48, 72, and 96 weeks from the start of treatment will be determined.

10.1.7 Response Review

Central review of audiologic and radiologic data will be performed at MGH/MEEI. Audiograms collected during the study period will be sent to the Operations Center and then forwarded to the team at MGH/MEEI for analysis. A study member (under the guidance of lead study audiologist Chris Halpin, PhD) will extract data for review by the Principal Investigator and lead audiologist. The expected time to review audiologic data is ≤ 2 business days once it is received at MGH/MEEI.

MRI images from enrolled subjects will transmitted by the "MedCommons On Demand" platform to the Dana-Farber/Harvard Cancer Center Tumor Imaging Metric Core (TIMC) for central analysis of tumor volume. The procedure for clinical sites to upload MRI scans are provided in Appendix G. MedCommons On Demand is a HIPAA-compliant and customizable web service that provides secure communications for document management and storage of medical images. The application allows users to conveniently upload DICOM CDs to cloud standards. The system requirements to launch MedCommons include 1) Windows, Mac, or Linux system with access to the internet 2) modern web browsers such as Internet Explorer, Firefox, Safari, or Chrome and 3) Java. All activities are monitored by MedCommons and full support team is available for problem resolution.

Enhancing lesions will be outlined using a volumetric approach that includes outlining each enhancing voxel on post-contrast scans and then summing the voxels to calculate an overall lesion volume. A report will be generated and

then sent to the Principal Investigator at each study site within 2 business days of receiving the files.

10.2 Antitumor Effect – Hematologic Tumors

N/A

10.3 Other Response Parameters: Hearing Response

Hearing Response (HR): Improvement in word recognition score above the 95% critical difference, taking as reference the baseline word recognition score (Appendix A).

Stable Hearing (SH): Persistence of word recognition score within the 95% critical difference, taking as reference the baseline word recognition score (Appendix A).

Progressive Hearing Loss (PHL): Decline in word recognition score below the 95% critical difference, taking as reference the baseline word recognition score (Appendix A).

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to bevacizumab, all events of death, and any study specific issue of concern.

11.1.2 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with neurofibromatosis 2 that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (*e.g.*, invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they are accompanied by clinical symptoms, result in a change in study treatment or require a medical intervention, or are considered to be clinically significant in the investigators judgment.

Abnormal vital signs constitute adverse events only if they are accompanied by clinical symptoms, results in a change in study treatment, or require a medical intervention, or are considered to be clinically significant in the investigators judgment.

In the event of an adverse event the first concern will be for the safety of the subject.

11.1.3 Serious Adverse Event (SAE)

Investigators are required to report to Operations Center ANY serious treatment emergent adverse event as soon as possible. Operations Center will report ANY serious treatment emergent adverse to Genentech Drug Safety and the Protocol Chair.

An AE should be classified as an SAE if the following criteria are met:

- It results in death (*i.e.*, the AE actually causes or leads to death).
- It is life threatening (*i.e.*, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (*i.e.*, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (*e.g.*, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures;
- elective or pre-planned treatment for a pre-existing condition that did not worsen;
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission; and/or
- respite care

11.1.4 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.4.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.4.2 Unexpected adverse event

For the purposes of this study, unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

11.2 Methods and Timing for Assessing and Recording Safety Variable

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports) and with the most recent approved protocol document.

11.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of any study procedures and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

11.2.2 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported in the participant's medical record and on the appropriate study-specific case report forms and entered into the NF Consortium's web-based data entry system. Each reported AE or SAE will be described by its duration (*i.e.*, start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the bevacizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes: There is a plausible temporal relationship between the onset of the AE and administration of bevacizumab; and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to bevacizumab; and/or the AE abates or resolves upon discontinuation of the bevacizumab or dose reduction and, if applicable, reappears upon re-challenge.

No : Evidence exists that the AE has an etiology other than the bevacizumab (*e.g.*, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to bevacizumab administration (*e.g.*, cancer diagnosed 2 days after first dose of study drug).

11.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

11.3.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

11.3.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations. The descriptions and grading scales found in the CTEP Version 4.03 of the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03) will be utilized for AE reporting. The CTEP Version 4.03 of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/

All appropriate treatment areas should have access to a copy of the CTEP Version 4 of CTCAE.

11.3.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (*e.g.*, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

11.3.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or

contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

11.3.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (*e.g.*, "more frequent headaches").

11.3.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions;
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

11.3.2.5 Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 30 days after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc as an SAE. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the bevacizumab should be reported as an SAE.

11.3.2.6 Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior bevacizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

11.3.2.7 Reconciliation/Genentech

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

11.3.2.8 AEs of Special Interest (AESIs)/Genentech

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the product. The Avastin AESIs are:

- Hypertension ≥ Gr 3
- Proteinuria ≥ Gr 3
- GI Perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ Gr 3
- Hemorrhage ≥ Grade 3 (any grade CNS bleeding; ≥ Gr 2 hemoptysis
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ Gr 3
- RPLS (any grade)
- CHF ≥ Gr 3
- Non-GI fistula or abscess ≥ Gr 2

11.3.2.9 SAE Reporting/Genentech

All SAEs should be recorded on a MedWatch 3500a Form and SAE CRF and sent to NF Consortium Operations Center (Attn: Research Nurse Manager) within 24 hours.

The NF Consortium Operations Center must report all SAEs reported by a clinical site and entered into the electronic data entry system to Genentech within the timelines described below. The completed MedWatch/case report should be faxed immediately upon completion to Genentech Drug Safety at: (650) 225-4682 or (650) 225-5288.

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available.
- Serious AE reports that are related to bevacizumab will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the bevacizumab will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.

- Serious AE reports that are related to the study drug and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.

The Operations Center will complete Genentech Drug Safety fax cover sheet with contact information for appropriate follow-up.

The NF Consortium is also responsible for notifying the NF Consortium IRB, DSMB and appropriate Regulatory agencies. Because this is an IND study, the IND holder, Dr. Bruce Korf, will submit the report to the FDA.

MedWatch 3500a Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up;
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form; or
- Summarizing new information and faxing it with a cover letter including subject identifiers (*i.e.*, D.O.B. initials, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted. (The subject identifiers are important so that the new information is added to the correct initial report.)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative

noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Additional reporting requirements

All pregnancies whether reported by the participant, discovered during questioning, directly observed, or detected by physician examination, laboratory test(s) or by other means, will be recorded in the participant's medical records and on the appropriate study-specific case report form and entered into the data-base subject record. The pregnancy will also be recorded on a MedWatch 3500a Form and SAE CRF and the NF Consortium Operations Center will be notified within 24 hours. The NF Consortium Operations Center is responsible for notifying Genentech of any reports of pregnancy following the start of administration with bevacizumb will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date. The NF Consortium Operations Center is also responsible for notifying the NF Consortium IRB (UAB and the DOD), DSMB, the FDA, and all other appropriate regulatory agencies.

11.4 Adverse Event Reporting to the US Army

This trial receives funding by a Grant of the U.S. Army. Per US Army request, adverse events will therefore also be reported by the NF Consortium Operations Center to the US Army as follows: All adverse events, which require prompt reporting (as defined in Section 10.5), will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality (301-619-2165) (non-duty hours call 301-619-2165, email or by facsimile to (301-619-7803). A written report will follow the initial contact within three working days to the NF Consortium Operations Center. The NF Operations Center will notify all appropriate study regulatory personnel and send a written report to the U.S. Army Medical Research and Materiel Command within seven working days of the initial contact to ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012 or email.

11.5 Reporting Requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the Principal Investigator.

Each investigative site will be responsible for reporting SAEs that occur at that institution to their respective IRB. It is the responsibility of the Operations Center to report serious adverse events (SAEs) to the study sponsor and/or others as previously described and according to the schedule below.

11.6 Reporting to the Study Sponsor

11.6.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the NF Consortium Research Nurse Manager using the appropriate SAE reporting forms, MedWatch Form 3500a. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the NF Consortium Operations Center Research Nurse Manager (Liz Davis) within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (*e.g.*, participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by email to:

NF Consortium Operations Center Research Nurse Manager
Attn: Liz Davis, RN, MPH, CCRC
Email: lvdavis@uab.edu

and

Scott R. Plotkin, MD, PhD
Telephone: 617-724-8770
Email: splotkin@partners.org
Fax: 617-724-8769

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.6.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the NF Consortium via the UAB web-based data entry system on the adverse event screen(s). All non-serious adverse events will be forwarded, at most, on a quarterly report to Genentech.

11.7 Reporting to the Institutional Review Board (IRB)

All participating study sites will report all serious adverse events directly to their institutional regulatory agencies according to their institutional policies and procedures.

A copy of the submitted institutional SAE documentation should be forwarded to:

NF Consortium Operations Center
Attn: Roy McDonald
Phone: (205) 975-4075
Email: rmcdonald@uab.edu

All SAE reports will be reported to Study PI by the Operations Center.

11.8 Reporting to the Food and Drug Administration (FDA)

For Investigator-Sponsored IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

All related adverse events that are both serious and unexpected will be sent to the FDA on Form FDA 3500A MedWatch Form (http://www.fda.gov/medwatch/getforms.htm) by Dr. Bruce Korf and the Operations Center. MedWatch Form will be sent by mail or fax to:

MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports by Dr. Bruce Korf according to the following guidance and timelines:

- 7 Calendar Day via Telephone or Fax Report
  The IND-holder is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of bevacizumab. An unexpected adverse event is one that is not already described in the bevacizumab Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event.
- 15 Calendar Day via Written Report
  The IND-holder with support of Protocol Chair is also required to notify the FDA and all participating investigators, in a written IND Safety

Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of bevacizumab. An unexpected adverse event is one that is not already described in the bevacizumab investigator brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (*e.g.*, summary letter).

FDA Fax number for IND Safety Reports:
1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech Drug Safety at:

(650) 225-4682 or (650) 225-5288

and to the Site IRBs: (see contact information about Consortium Participating Sites at the beginning of the document)

For questions related to safety reporting, please contact Genentech Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-5288

IND Annual Report

Copies to Genentech: All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should also be faxed to Genentech Drug Safety:

Fax: (650) 225-4682 or (650) 225-5288

11.9 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/A

11.10 Reporting to the Institutional Biosafety Committee (IBC)

N/A.

11.11 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.12 Monitoring of Adverse Events and Period of Observation

All adverse events attributable to study drug, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate written or electronic case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (*e.g.*, hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Study PI and Operations Center and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The NF Consortium Data Management and Analysis Center (DMAC) will collect, manage, and monitor data for this study.

DMAC Director: Gary Cutter, PhD
Phone: 205-975-5048
Email: cutterg@ms.soph.uab.edu

DMAC Deputy Director: Joan Hilner, MPH, MA
Phone: 205-934-4943
Email: jhilner@uab.edu

DMAC Program Manager: Steve Powell, PhD
Phone: 205-934-6741
powells@uab.edu

DMAC Fax: 205-975-2540

12.1.2 Data Submission

The schedule for completion and submission of electronic case report forms (paper or electronic) to the NF Consortium via a web-based data entry system as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration and enrollment with NF DMAC
On Study Form	Within 14 days of registration
Baseline Assessment Form	Complete prior to enrollment
Treatment Form	Within 10 days of the last day of the treatment
Adverse Event Report Form	Within 10 days of the last day of the evaluation
Serious Adverse Event Reporting	Initial reporting within 24 hours of awareness of occurrence
Response Assessment Form (*i.e.*, audiology and MRI assessment forms)	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

The NF Consortium DMAC is responsible for compiling and providing the data to the Principal Investigator for review.

12.2 Safety Meetings

The trial PI and clinical coordinator will review the study progress regularly. Patients entered on the trial and adverse events will be reviewed to ensure that the study is implemented as outlined in the protocol. Monthly reports will be generated by the NF Consortium to assess completeness and timeliness of data. There will be monthly phone conferences between the NF Consortium and the Principal Investigator to address QA issues. A Data Safety Monitoring Board has been established for the purpose of ensuring data compliance and regular monitoring of this trial.

A medical monitor has been selected for this study (Dr. Christopher Moertel, see roster at beginning of protocol). The medical monitor is a qualified physician and is not associated with this particular protocol. The monitor will work closely with the DSMB and Protocol Chair to monitor the participants' treatment while on this study.

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the USAMRMC ORP HRPO.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Protocol Chair or NF Consortium Operations Center. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements and to ensure subject safety.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements.

12.4 Privacy

Data provided must be treated in strictest confidence. No information provided from individual subject's records may be discussed with anyone other than those individuals mentioned in the collaborative research agreement. Data may not be released in any form except as provided in the agreement.

12.5 Confidentiality

Each subject enrolled will, from that point forward, be identified by a unique identifier (study number). This study number will also be used for any research specimens collected and shipped to analysts outside of the NF Consortium. 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**.** For standard of care procedure reimbursement, clinical information may be shared with insurers.

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (*e.g.*, advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the DSMB, Genentech, and the UAB IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The NF Consortium Operations Center will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The process of informed consent should also be documented in the subject research record. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki

    - Title 21 Part 11 – Electronic Records; Electronic Signatures
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html

    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html

    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

    - Title 21 Part 312 – Investigational New Drug Application
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

State laws

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant, including all protocol deviations. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the electronic data entry system include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. To standardize data collection and entry, study staff can complete a hard copy of the eCRFs prior to entry into the web-based data collection system.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of NF Consortium IRB and the Sponsor. The specific responsibilities of the Protocol Chair, NF Consortium Coordinating Center, and Participating Institutions are presented in the Multi-Center Data and Safety Monitoring Plan.

- The Protocol Chair and NF Consortium Coordinating Center are responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the agent from a licensed drug distribution vendor. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the drug distribution center at UAB.

13.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

N/A

14. STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

The primary endpoint for the study is hearing response at 24 weeks, defined as an improvement in word recognition score above the 95% critical difference, taking as reference the baseline word recognition score (Appendix A). We will use a Simon two stage MinMax design with a one sided significance level of .05 and 90% power for a null response rate of .03 vs. an alternative of .23. This design calls for accruing 14 patients in the first stage. If none respond, the study will be terminated with the conclusion that bevacizumab is not effective. Otherwise we will accrue 8 additional patients for a total of 22. Bevacizumab will be considered effective if and only if 3 or more of the 22 respond.

14.2 Sample Size/Accrual Rate

A maximum of 22 evaluable subjects will be accrued into the trial. Allowing for 10% inevaluable, we may need to accrue a total of 24. We believe this 10% rate is reasonable since no patients discontinued treatment due to toxicity in the previous study using bevacizumab. Similarly, no patients have discontinued treatment in an ongoing study of PTC299 in adult patients with NF2. The estimated accrual rate is 2 subjects per month with an expected accrual period will be about 12 months.

If the true response rate for bevacizumab is .03 then the probability of stopping after only 14 patients is .65 and the expected sample size is 16.78.

14.3 Stratification Factors

None

14.4 Analysis of Secondary Endpoints

The secondary endpoints include:

- Frequency of adverse events (possibly, probably, or definitely) related to bevacizumab use in this patient population;
- Proportion of patients with a radiographic response at 24, 48, 72, and 96 weeks;
- Proportion of patients with a hearing response at weeks 48, 72, and 96 (response defined as a statistically significant improvement in word recognition score compared with baseline score—Appendix A);
- Proportion of patients free from progressive hearing loss at 24, 48, 72, and 96 weeks (response defined as a statistically significant decline in word recognition score compared with baseline score);

- Proportion of patients free from tumor progression at weeks 24, 48, 72, and 96 (progression defined as an increase in VS volume by ≥ 20%);
- Durability of hearing response in patients with a hearing response at 24 weeks, as measured freedom from hearing loss at weeks 48, 72, and 96 (progression defined as a decrease in word recognition score below the 95% critical difference compared with values at 24 weeks, Appendix A);
- Durability of radiographic response in patients with a radiographic response at 24 weeks, as measured by freedom from tumor progression at weeks 48, 72, and 96 (progression defined as an increase in VS volume by ≥ 20% compared with volume at 24 weeks, Appendix A);
- Change in 4-tone pure tone average compared to baseline. The proportions above will be estimated from our data and exact 95% confidence intervals will be constructed. Changes in 4-tone pure tone average will be described descriptively by means, medians, and standard deviations.
- Change in tinnitus as measured by the Tinnitus Questionnaire (Appendix H). The proportions above will be estimated from our data and exact 95% confidence intervals will be constructed. Changes in tinnitus will be described descriptively by means, medians, and standard deviations.

Radiographic response rate

The secondary endpoint of change in target tumor size will be assessed by volumetric analysis of MRI scans. In a longitudinal study of plexiform neurofibromas in 49 patients, no patients experienced spontaneous tumor regression, as assessed by volumetric MRI scanning.[49] Similarly, the proportion of patients with spontaneous tumor regression of vestibular schwannoma in the international Natural History of NF2 Study was < 5%.[50] The radiologic response rate will be reported for all patients in the study and for all patients who complete at least 12 weeks of treatment. Radiologic response rates will be reported with exact 95% confidence limits. The durability of radiographic response over time will estimated using the Kaplan-Meier method. The median of the duration of response time with 95% confidence limits will be reported. The proportion of patients free from tumor progression at weeks 24, 48, 72, and 96 will be reported with 95% confidence limits.

Audiometric outcomes

Secondary endpoints will include changes in word recognition scores, pure-tone averages (PTAs), and tinnitus questionnaire scores. These tests will be performed at baseline and every 24 weeks.

- Word recognition score: A hearing response will be defined as improvement in word recognition score above the 95% critical difference (Appendix A) in the affected ear. The hearing response rate will be reported for all patients in the study and for all patients who complete at least 12 weeks of treatment. Hearing response rates at weeks 24, 72, and 96 will be reported with exact 95% confidence limits. The durability of hearing response over time will be estimated using the Kaplan-Meier method. The median time with 95% confidence limits will be reported. The proportion of patients free from hearing decline at weeks 24, 48 72, and 96 will be reported with 95% confidence limits.

- Pure tone average: A 12 dB change in 4-frequency Pure Tone Average will be considered clinically significant. The proportion with this change will be estimated and an exact 95% confidence interval computed.
- Tinnitus: In the analysis of the Tinnitus Questionnaire data, compliance with questionnaire administration (defined as the proportion of questionnaires actually received out of the expected number) will be calculated. Questionnaires will be scored as recommended in the user manual for the instrument.

14.5 Reporting and Exclusions

14.5.1 Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with bevacizumab.

14.5.2 Evaluation of response. Only those patients who have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. Each participant should be assigned one of the following categories: 1) hearing response, 2) stable hearing, 3) progressive hearing loss, 4) early death from NF2-related condition, 5) early death from toxicity, 6) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

All of the participants who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Participants in response categories 5-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

15. PUBLICATION PLAN

The results of this study will be made public within 24 months of the end of data collection. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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17. APPENDICES

Appendix A: Hearing Response Guidelines

Clinical criteria for definition of hearing response based on a 50-word hearing test. Upper and lower limits for the 95% critical differences for percentage scores are adapted from Thornton.[8]

Baseline word recognition score (%)	95% critical difference (%)	Hearing Response (%)	Progressive hearing loss (%)
0	0–4	≥ 6	n/a
2	0–10	≥ 12	n/a
4	0–14	≥ 16	n/a
6	2–18	≥ 20	0
8	2–22	≥ 24	0
10	2–24	≥ 26	0
12	4–26	≥ 28	≤ 2
14	4–30	≥ 32	≤ 2
16	6–32	≥ 34	≤ 4
18	6–34	≥ 36	≤ 4
20	8–36	≥ 38	≤ 6
22	8–40	≥ 42	≤ 6
24	10–42	≥ 44	≤ 8
26	12–44	≥ 46	≤ 10
28	14–46	≥ 48	≤ 12
30	14–48	≥ 50	≤ 12
32	16–50	≥ 52	≤ 14
34	18–52	≥ 54	≤ 16
36	20–54	≥ 56	≤ 18
38	22–56	≥ 58	≤ 20
40	22–58	≥ 60	≤ 20
42	24–60	≥ 62	≤ 22
44	26–62	≥ 64	≤ 24
46	28–64	≥ 66	≤ 26
48	30–66	≥ 68	≤ 28
50	32–68	≥ 70	≤ 30
52	34–70	≥ 72	≤ 32
54	36–72	≥ 74	≤ 34
56	38–74	≥ 76	≤ 36
58	40–76	≥78	≤ 38
60	42–78	≥ 80	≤ 40
62	44–78	≥ 80	≤ 42
64	46–80	≥ 82	≤ 44
66	48–82	≥ 84	≤ 46
68	50–84	≥ 86	≤ 48
70	52–86	≥ 88	≤ 50
72	54–86	≥ 88	≤ 52

74	56–88	≥ 90	≤ 54
76	58–90	≥ 92	≤ 56
78	60–92	≥ 94	≤ 58
80	64–92	≥ 94	≤ 62
82	66–94	≥ 96	≤ 64
84	68–94	≥ 96	≤ 66
86	70–96	≥ 98	≤ 68
88	74–96	≥ 98	≤ 72
90	76–98	100	≤ 74
92	78–98	100	≤ 76
94	82–98	100	≤ 80
96	86–100	n/a	≤ 84
98	90–100	n/a	≤ 88
100	96–100	n/a	≤ 94

Appendix B: NFTI-QOL (Neurofibromatosis 2 impact on quality of life)

SUBJECT IDENTIFIER: _____

INSTRUCTIONS FOR COMPLETING THE NFTI-QOL

Please complete the following information:

Age: _____ years

Gender: Male 1 Female 2 (please tick)

For each of the questions on the next page, please tick the one box that describes how you feel today

Usual activities include: work; housework; study; sport; social; family or leisure activities

Guy's NFTI-QOL

Q1. Do balance or dizziness problems stop you performing your usual activities?

No balance problems or dizziness ☐0
Balance or dizziness problems but no difficulties ☐1
Balance or dizziness problems cause me some difficulties ☐2
Balance or dizziness problems stop my usual activities ☐3

Q2. Do hearing problems stop you performing your usual activities?

No hearing problems ☐0
Hearing problems but no difficulty ☐1
Hearing problems cause me some difficulty ☐2
Hearing problems stop my usual activities ☐3

Q3. Does facial weakness stop you performing your usual activities?

No facial weakness ☐0
Facial weakness, but no difficulty ☐1
Facial weakness causes some difficulty ☐2
Facial weakness stops my usual activities ☐3

Q4. Do problems with your sight stop you performing your usual activities?

No problems with sight	☐0
Sight problems, but no difficulty	☐1
Sight problems cause me some difficulty	☐2
Sight problems stop my usual activities	☐3

Q5. Do you have any problems in mobility and walking?

No problems in mobility and walking	☐0
Some difficulty but can manage on my own	☐1
Unable to walk around without some help	☐2
Unable to walk at all	☐3

Q6. Has your medical condition affected your role and outlook on life? (*e.g.*, confidence, vulnerability, relationships, caring for family, career, having children)

No effect or positive effect	☐0
Small negative effect	☐1
Moderately negative effect	☐2
Large negative effect	☐3

Q7. Pain; throughout our lives, most of us have had pain from time to time such as mild headaches, sprains and toothaches. Have you had pain *other than this* in the last week?

None	☐0
Mild pain	☐1
Moderate pain	☐2
Severe pain	☐3

Q8. Do you currently suffer from anxiety or depression?

No	☐0
Mild anxiety or depression	☐1
Moderate anxiety or depression	☐2
Extreme anxiety or depression	☐3

If you have any further comments regarding the impact of NF2 on your quality of life, please write them here:

You have now completed the NFTI-QOL. Thank you for your input.

Appendix C: Performance Status Criteria

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

Appendix D: Grading and management of hypertension for adults and for children 6 through 17 years old.

Suggested management of hypertension for adults

Hypertension*	Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice, including confirming that BP is elevated across three separate measurements on three separate days and all other contributing factors have been addressed (*i.e.,* pain, anxiety).	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication, if appropriate.
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue bevacizumab.
	Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	If not controlled to 150/100 mmHg with medication, reduce one dose level. For second occurrence, discontinue bevacizumab.
	Grade 4	Discontinue bevacizumab.

Grading of hypertension for children 6 through 17 years old

Diastolic blood pressure levels for BOYS aged 6-17 years

	1	2	3	4
Age (years)	**ULN* DBP mmHg**	**DBP ≤10 mmHg above ULN**	**DBP >10 or ≤25 mmHg above ULN**	**DBP>25 mmHg above ULN**
6	73	74-83	84-98	99
7	75	76-85	86-100	101
8	77	78-87	88-102	103
9	78	79-88	89-103	104
10	79	80-89	90-104	105
11	79	80-89	90-104	105
12	80	81-90	91-105	106
13	80	81-90	91-105	106
14	81	82-91	92-106	107
15	82	83-92	93-107	108
16	83	84-93	94-108	109
17	86	85-94	95-111	112

*** ≤95th percentile for age and 50% height percentile**

Diastolic blood pressure levels for GIRLS aged 6-17 years

	1	2	3	4
Age (years)	**ULN* DBP mmHg**	**DBP ≤10 mmHg above ULN**	**DBP>10 or ≤25 mmHg above ULN**	**DBP>25 mmHg above ULN**
6	73	74-83	84-98	99
7	74	75-84	85-99	100
8	75	76-85	86-100	101
9	76	77-86	87-101	102
10	77	78-87	88-102	103
11	78	79-88	89-103	104
12	79	80-89	90-104	105
13	80	81-90	91-105	106
14	81	82-91	92-106	107
15	82	83-92	93-107	108
16	83	84-93	94-108	109
17	83	84-93	94-108	109

*** ≤95th percentile for age and 50% height percentile**

These charts list DBP levels within the ULN (1), within 10 mmHg above the ULN (2), within 11-25 mmHg above the ULN (3), and >25 mmHg above the ULN (taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576).

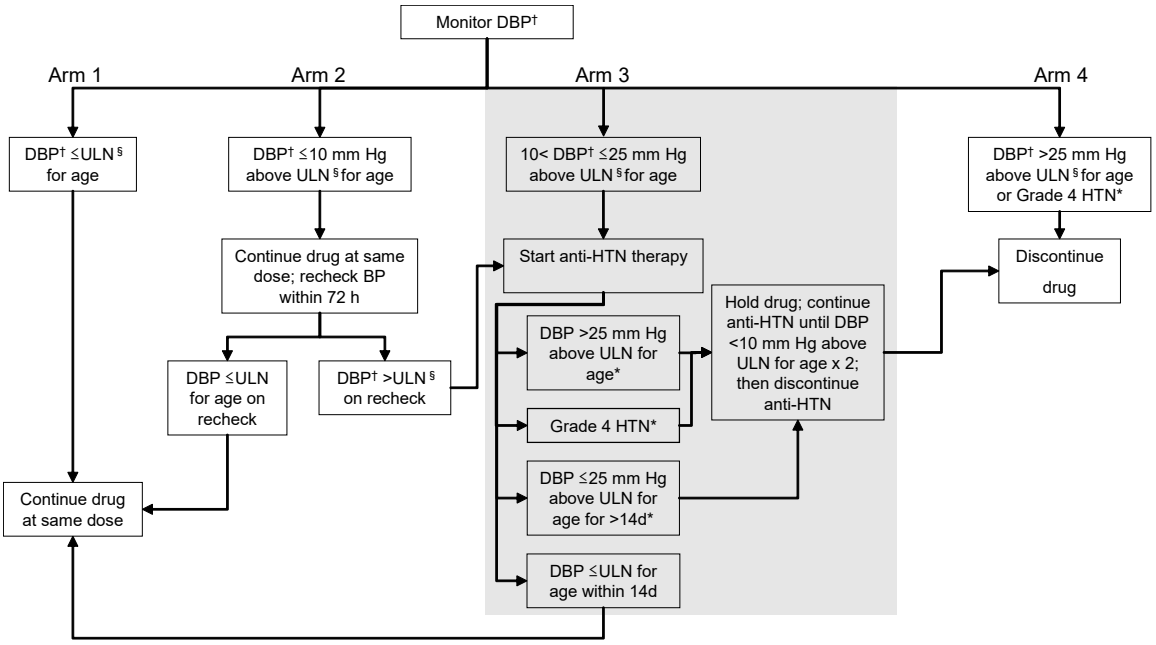
Instructions for using this BP chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient. Age should be rounded to the nearest year.
3. Using the "age" row determine if the DBP is within the ULN (1) or elevated (2, 3, 4).
4. See Section 6 for definition of dose limiting hypertension.

Management of Bevacizumab-related Hypertension in Children

The algorithm outline below will be used to grade and manage bevacizumab-related hypertension. A diastolic blood pressure (DBP) equal to the 95th % for age and gender will be defined as the upper limit of normal (ULN).

Patients with elevated DBP at any time should have blood pressure measurements performed twice weekly until DBP is within the ULN.



† Elevated diastolic blood pressure (DBP) measurements should be repeated on the same day to confirm the elevation
§ ULN (Upper Limit of Normal) is a DBP ≤ the 95th percentile from age and gender-appropriate normal values (Appendix G)
* If DBP >25 mm Hg above ULN for age (verified) or grade 4 HTN at any time, discontinue drug. Antihypertensive agents can be used to control hypertension as clinically indicated after study drug is discontinued.

Arm 1 of algorithm:

- If DBP ≤95% for age and gender, continue bevacizumab at the same dose.

Arm 2 of algorithm:

- If DBP ≤10 mm Hg above the ULN for age and gender, continue bevacizumab at same dose.
- If the DBP ≤ 95% for age and gender on recheck, continue bevacizumab at same dose.
- If the DBP remains above the ULN for age and gender on recheck, then start single agent antihypertensive therapy (consider a calcium channel blocker such as amlodipine or nifedipine) and follow arm 3 of the algorithm from the point that anti-hypertensive therapy is started.

Arm 3 of algorithm:

- If DBP is 11 to 25 mm Hg above the 95% for age and gender on ≥2 of 3 measurements, start single agent anti-hypertension therapy (consider a calcium channel blocker such as amlodipine or nifedipine), continue bevacizumab at the same dose and monitor blood pressure at least every 3 days.
    - If the DBP remains elevated ≤25 mm Hg above 95% for age and gender for more than 14 days after the institution of single agent anti-hypertensive therapy, reduce bevacizumab one dose level and continue the antihypertensive agent until the DBP is ≤10 mm Hg above the 95% for age and gender on 2 measurements at least 3 days apart. If the DBP remains elevated ≤25 mm Hg above 95% for age and gender for more than 56 days after the institution of single agent anti-hypertensive therapy, discontinue bevacizumab.
    - If the DBP increases to ≥25 mm Hg above the 95% for age and gender despite antihypertensive therapy or the participant develops grade 4 hypertension (CTCAE), discontinue bevacizumab permanently, but continue the antihypertensive agent until the DBP is ≤10 mm Hg above the 95% for age and gender on 2 measurements at least 3 days apart.

Arm 4 of algorithm:

- If DBP is >25 mm Hg above the 95% for age and gender or the participant develops a grade 4 hypertension (CTCAE), discontinue bevacizumab permanently and monitor blood pressure at least every 3 days. Antihypertensive agents can be used until the DBP is <10 mm Hg above the 95% for age and gender on 2 measurements at least 3 days apart.
- The cycle remains 28 consecutive days in patients who have dose interruptions.

Appendix E: Management of Bone Related Toxicity.

Potential bone related toxicity is of great concern for this study based on pre-clinical data and because bevacizumab will be used in a pediatric population. Therefore, we will carefully monitor for it, utilizing multiple serial measurements of height (in patients with open growth plates at baseline).

For patients with open growth plates on tibial radiographs at baseline, measurements of stature (height) will be measured at weeks 13, 25, 49, 73, and 91. Bevacizumab will be discontinued if:

- <1 cm growth is noted prior to week 25
- <2.5 cm growth is noted prior to week 49
- Subsequently, <2cm/year annualized growth velocity noted every 24 weeks for patients with open growth plates only

Appendix F: Audiology Procedures

1.0 INTRODUCTION

The purpose of this appendix is twofold: In the first section, procedures for local audiologists will be outlined. In the second section, procedures for transfer of the audiometric data from the local audiogram to the data form will be specified.

2.0 AUDIOLOGY PERSONNEL

The primary source of reliability and validity will be the qualifications of the clinical audiologists performing the tests, and their adherence to standard practices. These practices will be specified in this section. A secondary source of reliability and validity will be the oversight of the local Lead Audiologist appointed for each clinical site. The Lead Audiologist will compile information assuring standard calibration, installation of reference-calibrated equipment, etc. [1] The local Lead Audiologist will also act as a stable contact on behalf of their center. Finally, the Senior Study Audiologist (MEEI) will provide a final layer of assurance by developing and updating the procedures in this manual in response to any problems and by maintaining regular contact with each site's Lead Audiologist.

2.1 Lead Audiologist

Each Clinical Site will designate a Lead Audiologist who will be the contact for study-related issues with the Senior Study Audiologist. This audiologist will oversee local audiology operations and also communicate with the site PI. The lead audiologist may train other audiologists at the site for testing.

2.2 Qualifications

Each evaluation will be performed by a fully qualified audiologist. The precise definition of qualification can vary from state to state depending on licensure laws, etc. For the purposes of this study, full qualification is defined as the highest local level of qualification, certification or licensure. Basic requirements for Lead Audiologist will be no different, but only one audiologist per center will be designated for this duty.

2.3 Training

Each site's Lead Audiologist will be responsible for local training of any audiologist performing assessments for this protocol. This training will be based on this appendix, and the appendix will remain available to all trained audiologists as a resource. All Lead Audiologists will be contacted in advance of the initiation of participant enrollment at the site, and the Senior Study Audiologist will discuss and demonstrate the procedures contained in this Appendix. These will include personnel, test protocols, data cross checking, procedures for correcting or completing evaluations, and reporting results.

2.4 Contacts

A system of regular contact between the Senior Study Audiologist and each Lead Audiologist will be initiated before any participant's enrollment. This will take place

primarily by e-mail, with documents faxed as necessary. As audiologic issues arise, the local audiologists will be asked to contact the Lead Audiologist, who will act as liaison with the Senior Study Audiologist. Other local issues are expected to be addressed by contact among the clinical site PIs, their Lead Audiologists, and the CRCs.

3.0 AUDIOLOGY FILES

Each clinical site's Lead Audiologist will, at the commencement of the study, create a filing system for audiology facility records and correspondence. System features will be at the discretion of the Lead Audiologist, incorporating the local filing protocols. However, at minimum this system will contain three recognizable sections: general information, correspondence, and worksheets.

3.1 General Information Section

This section will include site-specific information as to the identification of the PI, the Lead Audiologist, Senior Study Audiologist, and others associated with the study, along with extensive contact and coverage information. This section will also include the local location of this appendix, and the data reporting protocol along with copies of calibrations and other equipment records sufficient to document validity. Finally, the general section will include a comment log, in which dated and initialed entries by any audiologist may make note of any events or concerns.

3.2 Correspondence Section

This section will include records of conference calls and other correspondence regarding procedural issues, changes in equipment or personnel, and any adverse events.

3.3 Audiogram Section

This section will include audiograms generated for each audiologic evaluation related to this study.

4.0 AUDIOLOGY TESTING PROTOCOL OVERVIEW

Participants will be referred for each evaluation by the local site PI or CRC, who will determine the timing of return visits. At minimum, the referral will include designation of the target ear. When the participant arrives for each test, the audiologist will greet the participant and accompanying persons and briefly and privately discuss progress if the participant wishes. Study questions may be referred to the local PI or CRC. Audiologists will not be formally blinded to any aspect of the study.

The audiologist will seat the participant in a sound-treated room. [2] No more than one person will be allowed to accompany the participant to this area and this person will not be allowed to sit in the booth or to be in the line of sight of the participant. As much as possible, light levels in the participant and the tester sides will be adjusted to provide a good view of the participant and a poorer view of the audiologist (*i.e.*, participant side bright, tester side dark). The participant should be seated perpendicular to the audiologist to minimize cues. The room door will be fully closed. The participant will be asked to respond by hand raise or by button push, whichever is customary at the clinical site.

The Lead Audiologist at each site will ensure that threshold tests are performed in the standard manner. This includes the Hughson-Westlake bracketing procedure [3, 4]. A 200 ms. ON versus 200 ms. OFF duty cycle for tone presentation is recommended with an opportunity to appreciate 4 tones per trial. Narrow band noises or FM modulated tones will not be substituted for standard pure tones. Thresholds will be transcribed on the Clinical Site's standard audiogram, using standard symbols.[5] At the conclusion of the evaluation, the audiologist may briefly discuss the result with the participant and accompanying persons, again referring most study questions to the PI or CRC where possible. Discussion of helpful strategies and devices as indicated by the case is expected.

4.1 The Sound Pathway

The testing audiologist will perform a visual inspection of both ears using an otoscope. If there is sufficient access to the tympanic membrane to allow testing, the audiologist will proceed. If there are concerns as to cerumen or other factors, the audiologist may elect to perform tympanometry. When complete, the outcome of tympanometry will be noted on the audiogram in the customary manner for that site. If occluding cerumen or similar factors cannot be resolved, testing will not proceed. The local PI has overall responsibility to ensure unoccluded ears if referrals are required.

4.2 Pure Tone Thresholds

Pure tone thresholds will be found in the standard manner by bone conduction at 250, 500, 1000, 2000 and 4000 Hz. Air conduction thresholds will be found at 250,500, 1000, 2000, 3000, 4000 and 8000 Hz. Masking will be used in any case where it is considered necessary to establish which ear is responding.[6] Air-bone gaps larger than 10 dB will be masked. For air conduction, masking will be applied for each threshold where the possibility of crossover exists. The possibility of overmasking will be evaluated by the audiologist and may be addressed, for example, by using insert phones. A masking plateau procedure will be performed at the discretion of the audiologist.[7] The local audiologists have discretion to test other frequencies or to repeat testing to ensure validity. In addition, further testing (Stenger's test; SRT; OAE) is at the discretion of the local audiologist to ensure validity. Auditory brainstem response testing is not indicated in these patients because their retrocochlear diagnosis is established prior to entry.

4.2.1 Transducer

Air conduction thresholds may be evaluated using both standard headphones (TDH-39, 49, 50) or calibrated insert phones (Etymotic ER-3A), as long as specific correction factors are in place.[8] The transducer type (*i.e.*, TDH-49, ER 3-A) should be entered on the local clinical audiogram form reflecting the method by which the final recorded threshold was obtained.

4.3 Vibrotactile and Responses at Limits

Vibrotactile responses will never be reported as thresholds. On discussing the nature of the percept with the participant and determining that they are vibrotactile, the audiologist will mark the response as "out at limits" at the vibrotactile response level. Other "out at limits" responses will be noted at the highest actual stimulus level with the standard "down arrow" notation. None of the study frequencies should ever be left blank.

4.4 Word Recognition

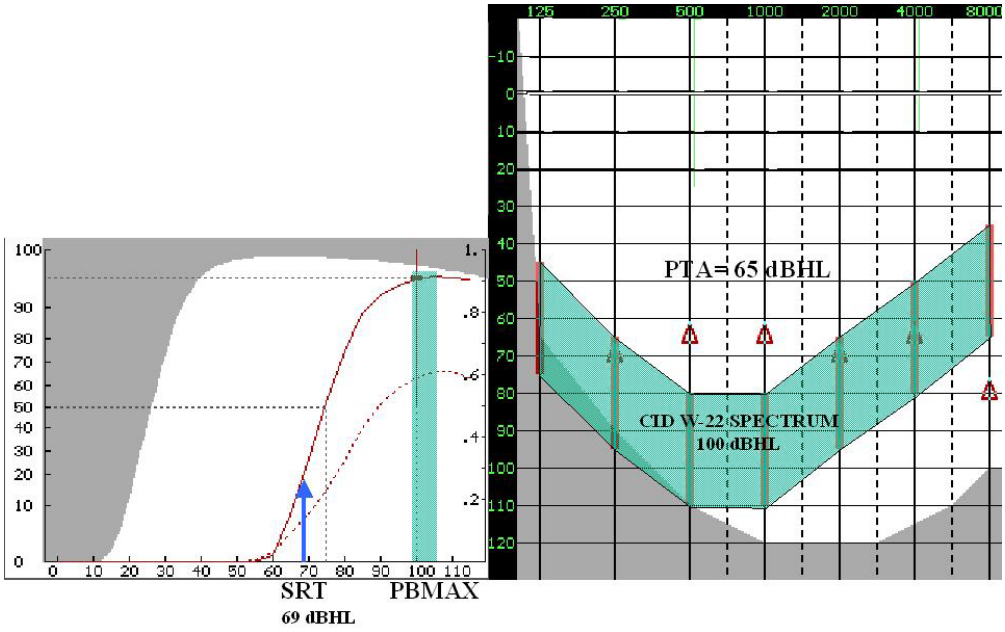
Speech intelligibility will be evaluated for each ear using standard word recognition of monosyllables.[9] All tests will use recorded lists (CID-W22, Ira Hirsh recording, Q/MASS v 2) from a compact disk supplied by the Senior Study Audiologist, [10] including standardized score sheets. Each disk contains a calibration reference 1 KHz tone (track 1) which will be used to set the input sensitivity (V.U. meter) to "0" before each set of tests. The recording and list must be noted on the clinical audiogram. This is necessary to verify the list used in all cases when the report of this study is made. Since the results are analyzed as repeated measures, a participant may be evaluated using English materials if the local audiologist decides that the results reasonably reflect comparative (test to test) performance. In such a case, the participant may be instructed to produce the sounds of the words, even if they do not necessarily recognize the meaning. All lists will be recorded (no live voice tests) and 50 items always given.

4.4.1 Setting the "High" and "Low" speech test levels

The principal guiding the initial level setting for speech tests is: The level should be set where maximum performance is expected for each ear. Performance has been shown to exhibit "rollover" in some NF2 cases,[11,51] so an empirical search using at least two levels will also be used. These will be designated the "High" and the "Low " levels. The "High " level will be the level calculated for maximum audibility, as in the standard method for level setting in non-tumor cases. The "Low" level will be the maximum level minus 10-15 dB as chosen by the audiologist to reflect a level with less chance of rollover.

Fletcher's Articulation Index[12] will be used to assist in calculation of the initial ("High") presentation level. This formula can be used to draw a cumulative (ogive) optimum performance/intensity (P/I) function for any audiogram (Figure 1, below). If rollover was not a factor, the maximum performance would be expected at levels

Figure 1. Cumulative optimum performance/intensity (P/I) function.



on the asymptote of the curve. [13] Using software developed for this purpose[14], Table 1 was created for setting "High" speech levels:

Table 1. High Speech Level Settings:

PTA2	Monosyllable level
30	-
35	-
40	70
45	75
50	80
55	85
60	90
65	95

The PTA2 parameter designates Fletcher's 2-frequency average. [15] PTA2 is the average of the two best (lowest) thresholds of the set 500 Hz, 1 KHz and 2 KHz. This value is easy to calculate and delivers better performance predicting speech reception threshold (SRT) and other speech level values than the more inclusive PTAs.[16] The levels were developed Monte Carlo fashion by submitting a representative sample of audiograms to the P/I function generator and relating the PTA2 to the lower levels of the asymptotic portion of the curve. The step size is 5 dB. Smaller gradations are available on some audiometers and may be used at the discretion of the audiologist. No "High" level list will ever be given lower than 70 dB HL. The advantage of this minimum level is that normal, mild, and moderate loss cases can all be tested at the same physical level.[17]

Table 1 is designed to replace rule-based level setting schemes since they may not be optimal, especially given severe losses (PTA ≥ 50 dB HL). For example, a common rule requires a further test (SRT) to allow levels set at SRT + 40 dB. While this provides reasonable maximum performance for milder cases, with severe losses the dynamic range is reduced below the 40 dB constant. On the other hand, no rule or table can replace good clinical sense when very high levels are required. In abandoning the table values, the audiologist will be asked to decrease levels minimally below the participant's Uncomfortable Level (UCL) rather than set the level at a determined Most Comfortable Level (MCL). No levels should exceed 95 dB HL.

As described above, after performing a word list at the "High" level, the Audiologist will reduce the intensity by 10-15 dB and present a 50-item list at the "Low " level. If the speech stimulus exceeds most frequencies at a level 15 dB below the "High" level then that level should be used. If, on the other hand, many important frequencies are no longer audible, then the level 10 dB below should be used. This procedure will be used for the target and the contralateral ear, with the exception that the "High" level may be used alone for the contralateral ear if there is no vestibular schwannoma on that side.

4.4.2 Participant responses

Participants with poor speech intelligibility are expected to initially report no intelligibility (*i.e.*, "I can't get it"). The audiologist is required to explain that guessing is very helpful and that, in order for the test to proceed, the participant must guess a monosyllable each time the carrier phase is heard. Instead of reporting no recognition, a "wild guess" should be substituted. This strategy will optimize responses in cases of low speech intelligibility and is surprisingly effective with participants who are really only uncertain. Dropped plurals are to be scored wrong. If the participant responds with several options, the first one said will be scored. Items will not be repeated. Small variations in regional dialect (*i.e.*, vowel boundaries) are scored at the discretion of the audiologist. Fifty items will be given unless the audiologist is convinced that the participant has no speech-like percept at all. Fifty wrong guesses will be scored as 0% and this represents an optimal test by both the participant and the audiologist. If there is no speech-like percept at all, the test can be scored CNT (could not test). Skipping the word recognition test and entering the notation "DNT" (did not test) is never acceptable. The audiology evaluation will be considered incomplete if the notation DNT appears. Under no circumstances will half-lists or screening lists be accepted.

4.4.3 Masking for word recognition

Masking will be applied to the contralateral ear during speech tests if there exists a possibility of significant contribution due to crossover. [18] To facilitate this application for this study, the Articulation Index was again used to calculate the maximum score possible by crossover given the difference in PTA2 and the effective masking required to reduce this contribution to zero[19] (Table 2).

Table 2. Calculation/Crossover Scores

Speech Level minus Non-test PTA2	Speech Noise TDH	Speech Noise Inserts
50	15	-
55	20	-
60	25	-
65	30	-
70	35	10
75	40	15
80	45	20
85	50	25
90	55	30
95	60	35
100	65	40

Table 2 includes values based on published interaural attenuation values for both TDH phones[20] and insert phones.[21] Standard speech-shaped noise is assumed in this calculation and will be the masker used at the study centers.

4.5 Validity

If the audiologist determines that the test is valid she/he will indicate this in the space used for this purpose on the local audiogram form and need not enter any further information regarding validity. If the audiologist decides to perform other tests (for example SRT, to rule out functional loss) this will be noted along with the outcome in the text section. In most cases, the principles and procedures outlined above will allow reliable and valid data. One example of an exception requiring different tests would be when functional hearing loss (pseudohypoacusis) is suspected. Hesitant threshold responses or a history of litigation for loss are some of the many warning signs audiologists use to initiate tests to rule out functional loss. In this study, audiologists, supported by their local Lead Audiologist will rule out functional loss on a case-by-case basis. For example, SRTs may be done to evaluate the match with the pure tones. [22] Stenger's test [23] may be performed. The text section of the local audiogram will also be used to convey any testing issues such as participant cooperation, noise, equipment issues, etc., which might adversely affect validity.

4.6 The Target Ear

All referrals to the local audiologist from the local investigator site must include a designation of the target ear. Designation of the target ear is noted to occur redundantly on many forms of documentation in this study. The local audiologist will ensure that the special "High" and "Low" level word recognition testing is performed on the target ear at minimum during the evaluation. This strategy should also be applied to the contralateral ear if that ear is known to have a vestibular schwannoma or its status is unknown. The audiologist will specify the target ear on their audiogram at every evaluation.

4.7 Example Audiogram

Figure 2 shows an example audiogram which satisfies the needs of this study protocol. It is for example only and local variation is expected.

AUDIOLOGIC EVALUATION

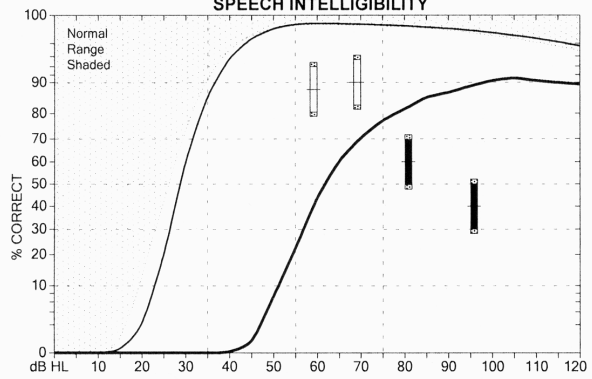
Massachusetts Eye and Ear Infirmary
Audiology Department

NAME: BEVA CIZUMAB **UNIT:** 9999999
DOB: 1/21/1990
REFERRED BY: PLOTKIN **AGE:** 20 **SEX:** M

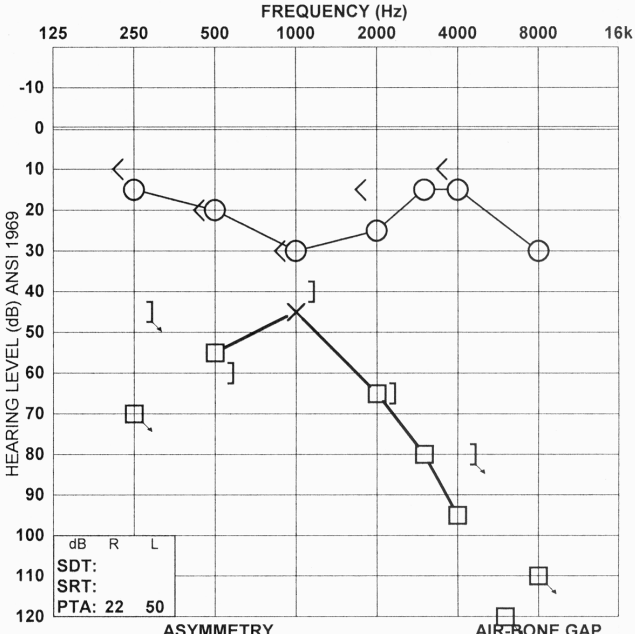
AUDIOLOGIST: Chris Halpin, Ph.D., CCC-A

ID: 111 **DATE:** 09/16/2010 **TIME:** 14:51 **ROOM:** CFH

SPEECH INTELLIGIBILITY



FREQUENCY (Hz)

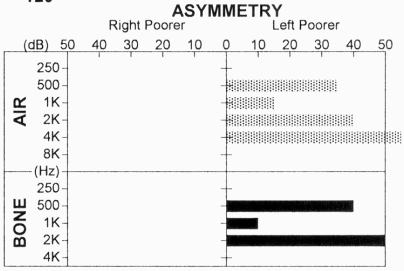


WORD RECOGNITION

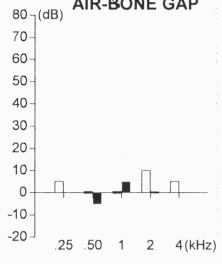
RIGHT			LEFT		
LIST	dB	(%)	LIST	dB	(%)
W22 3B	70	90	W22 1A	95	40
W22 4B	60	88	W22 2A	80	60

SYMBOLS	RIGHT	LEFT
Speech Intelligibility Index Prediction		
Speech Score		
84%CI 95%CD		
90%CI 98%CD		
Air Conduction		
AC Masked		
Bone Conduction		
BC Masked		
Response at Limit		
No Response		
Acoustic Reflex Ipsilateral Probe		
Acoustic Reflex Contralateral Probe		

ASYMMETRY



AIR-BONE GAP



TYMPANOMETRY

FEATURE	RIGHT	LEFT
VOLUME	Normal	Normal
PRESSURE	Normal	Normal
MOBILITY	Normal	Normal
SHAPE	Normal	Normal
RESONANCE		

REFLEX DECAY

FREQUENCY	RIGHT	LEFT
500 Hz		
1000 Hz		
2000 Hz		
4000 Hz		

REASON FOR TEST (from physician requisition):
vestibular schwannoma

HISTORY
Patient reports a diagnosis of NF2 with bilateral vestibular schwannomas. The patient is in the bevacizumab NF2 study with a target ear: Left.

HEARING MEASUREMENT
Some cerumen noted on the left, but test was completed following normal tympanometry. Word recognition was done using study CD, lists 3B and 4B right; and 1A and 2A left. Results considered valid.

IMPRESSIONS
There is a large sensory loss on the left.

CONSULTATION
Result discussed with patient and his family.

FORM ID AU 4 '92

AUDIOLOGY

5.0 DATA CROSS CHECKS

This section will describe data cross check activities performed by the testing audiologist and the Lead Audiologist, as well as the mechanism for reporting unforeseen problems or concerns.

5.1 Testing Audiologist

The primary data cross checks will be the responsibility of the testing audiologist. Specifically, equipment and training will be maintained which will allow such procedures as masking plateau verification, tympanometry, SRT, Stenger's test, etc. These tests will be applied at the discretion of the testing audiologist to verify results and to rule out functional or retrocochlear hearing loss. None of these tests will be used as data, but will be noted on the local audiogram form along with the overall judgment of the audiologist as to validity.

5.2 Lead Audiologist

The audiogram will then be given to the Lead Audiologist or placed in the study "Audiograms" file section for data awaiting review. The Lead Audiologist will verify the audiologic aspects of the data. The Lead Audiologist will verify validity and completeness, or will contact the CRC for rescheduling for other testing if necessary. The completed form will be faxed or emailed (scanned) to the NF Consortium Operations Center.

5.3 Problems and Concerns

The Senior Study Audiologist will be responsible for resolution of problems in audiology data interpretation. If these arise at the office of the PI, they will be communicated to the Senior Study Audiologist (*i.e.*, not the local Lead Audiologist directly), who will have discretion as to resolution study-wide or site-specific. If problems arise at an individual site, they will be communicated by the local Lead Audiologist to the Senior Study Audiologist, who will again be responsible for resolution either study-wide or site-specific. The anticipated mechanism for resolution of study-wide issues will be communication with all local Lead Audiologists and changes or additions to this Appendix. The Senior Study Audiologist will be responsible for informing and receiving advice and approval from the Study Chair as appropriate.

6.0 AUDIOGRAM ACCEPTANCE

After the audiogram is faxed (or emailed) to the NF Consortium Operations Center, it will be forwarded to the Senior Audiologist in the office of the overall study PI for review and approval for use in the study. This is particularly critical in the case of the initial audiometric evaluation. All subsequent evaluations and outcomes will be compared to this initial audiometric evaluation and, following intent-to-treat principles, patients will not be removed from the study after the fact if the audiogram is found to be invalid. If the audiogram is not accepted, it must be re-scheduled by the study local PI's office, re-done and re-submitted for acceptance. The Senior Study Audiologist will be responsible for providing any required materials and advice in order to ensure audiogram acceptance before the fact. It is necessary that each site make contact with the Senior Study Audiologist (C. Halpin, chris_halpin@meei.harvard.edu, 617-573-3266) when they are

contacted by referral sites in order to initiate this support. The following sections will describe some factors which will cause the audiogram not to be accepted.

6.1 Improper Referral

If a patient arrives at the audiologist's office without that office being previously contacted about the study, or provided full materials and adequate time to have questions addressed, this evaluation is not expected to be possible and the result will be a request by the Senior Audiologist and the Study PI to the referring center for adequate referral procedures.

6.2 Ear Occluded With Cerumen

If the audiologist finds the ear occluded with cerumen (it is recommended that this be confirmed using tympanometry), the patient's audiologic evaluation cannot be performed and the patient should be returned to the referral source for remediation if the cerumen cannot be managed in the audiologists' office. If a notation is found that either ear was occluded with cerumen, the audiogram will not be accepted.

6.3 Word Recognition

If word recognition is recorded as "DNT" (Did Not Test) on either side, the patient's audiologic evaluation cannot be accepted. This is also true if a half (25-item) or screening list was given, or if the word recognition test was delivered using monitored live voice (MLV). Word recognition must be positively noted as having been done using the provided CD, 50 items and done at high and low levels as described in section 5.6.1 in order to be accepted. The software used to create Table 2 may be used to evaluate the potential for influence of the contralateral ear, though significant crossover is unlikely.

6.4 Pure Tone Thresholds

If pure tone thresholds do not include all frequencies specified in section 5.4, for example if bone conduction was not done, the audiogram cannot be accepted. With regard to masking, thresholds may be input to the Harvard Audiometry software for evaluation of crossover. If significant chance that the non-test ear was responding is found, the audiogram cannot be accepted.

7.0 EQUIPMENT

The following section contains specifications for equipment used in this study.

7.1 Sound-treated Enclosure

A single- or double-walled sound-treated enclosure that meets American National Standard Criteria for Maximum Permissible Ambient Noise Levels for Audiometric Test Rooms shall be used to conduct pure tone air and bone conduction thresholds and word recognition testing.

An illuminated otoscope is used to examine a participant's ear canals. If any possible contraindications to audiometric testing (such as excess cerumen, eardrum abnormalities, etc.) are detected, the participant must be referred for medical evaluation before audiometric testing can proceed.

7.2 Audiometer

Audiometers that meet the American National Standard Specifications for Audiometers[1] and have two channels are used to conduct pure tone air and bone conduction threshold, SRT and word recognition testing. One channel of the audiometer generates and delivers the test signals, either pure-tones or prerecorded speech. The second channel delivers narrow-band or speech-band masking noise simultaneously with the test signal, but to the non-test ear whenever necessary. The audiometer must have an input jack for external equipment such as a compact disc player or tape player, which will be used to present speech stimuli for word recognition testing.

7.3 Audiometer Transducers

Earphones mounted in supra-aural cushions and calibrated according to the American National Standard Specification for Audiometers[1] are used to deliver the test material from the audiometer to the participant. The earphones are designated as "right" and "left" and will be placed comfortably over the participant's right and left ears, respectively. Bone vibrators calibrated according to the same standards are used to obtain bone conduction thresholds. During the testing, the bone vibrator is positioned over the mastoid area of the participant's test ear, taking care that it is not in contact with the posterior part of the pinna.

7.4 Compact Disc Player

A compact disc player must be used to deliver pre-recorded speech material to the audiometer and subsequently to the transducers positioned over the participant's ears. A cable extends between the output jack of the compact disc player and the input jack of the audiometer.

7.5 Acoustic Immittance Equipment

Immitance is not required by this study protocol, but may be used at the audiologists' discretion. An immittance device that meets the American National Standard Specifications for Instruments to Measure Aural Acoustic Impedance and Admittance is used to conduct tympanometry and acoustic reflex threshold testing. Test results will be printed directly from the immittance device or recorded manually at the conclusion of testing on each ear. Probe tips must be appropriate in size to seal the participant's ear canal tightly during tympanometry and acoustic reflex testing. Clinical centers must have an adequate variety of sizes of probe tips to accommodate ear canals of varying dimensions.

7.6 Maintenance

Each clinical center is responsible for the proper operation and maintenance of its audiometric equipment. Responsibility for proper maintenance is assumed by the Lead Audiologist, and all staff are instructed to report promptly any real or suspected equipment problems to that person. All checks, inspections, and repairs are documented and recorded by date in a permanent log. The Study PI and Study Senior Audiologist may review this log at periodic site visits. All study test equipment including audiometers and acoustic immittance devices must be calibrated according to the American National Standards Institute. Listening checks may help to identify problems that could influence participants' test behavior and audiometric results in between scheduled physical calibrations. Study audiologists should perform a listening check on any day when a participant enrolled in the protocol will be tested.

8.0 Data Reporting

Audiograms done using the procedures described above will be faxed or emailed from the NF Consortium Operations Center to the office of the Senior Study Audiologist (C. Halpin, PhD) and the Principal Investigator. The Senior Study Audiologist and others at the PI's office, will have direct access to the eCRF software used for data collection in the study. The clinical audiograms will be checked and the data transferred to the study eCRF system. The PI's office (Senior Study Audiologist) will keep copies of each of the study audiograms and records of the transfer process.

Appendix G: MRI Protocols

Image Acquisition

Each patient will be scanned on the same MRI system. Each scanning session must include the following sequences (although additional sequences can be performed per institutional protocol):

1) Scout sequence
2) T2-weighted imaging
3) Fluid-attenuated inversion recovery (FLAIR) imaging
4) T1-weighted pre-contrast imaging
5) Diffusion weighted imaging (DWI)
6) Post-contrast T1-weighted imaging (including post-contrast T1 weighted imaging with fine cuts through the internal auditory canal)

NOTE: The post-contrast T1 weighted imaging with fine cuts through the internal auditory canal (3 mm slices, no skip) and volumetric analysis will be used to assess the endpoint of radiographic response (defined as ≥ 20% decrease in tumor volume by MRI scan). The total scan time for the required images for the primary endpoint is roughly 10 minutes.

Image Analysis

Enhancing lesions will be quantitatively analyzed by an experienced neuroradiologist blinded to the order of the scans, patient identity and treatment status of the patients. Bi-dimensional diameters will be created and outlined using electronic calipers in accordance with the Macdonald criteria [48]. The lesions will also be outlined using a volumetric approach described previously [52] that includes outlining each enhancing voxel on post-contrast scans and then summing the voxels to calculate an overall lesion volume.

Secure File Transfer

The procedure for uploading MRI scans to the Tumor Imaging Metrics Core are listed below.

MRI images from enrolled subjects should be de-identified and will be transmitted electronically to the Dana-Farber/Harvard Cancer Center Tumor Imaging Metric Core (TIMC) under the direction of Dr. Gordon Harris for central analysis of tumor volume. (see section 10.1.7).

Welcome to the TIMC

The TIMC provides standardized measurement of imaging scans for oncology clinical trials. TIMC's web-based system ensures easy ordering and access with exceptionally fast turnaround. Tumor response assessment criteria include RECIST, RECIST 1.1, Cheson, irRC, SUV, and 3D volume.

Getting Started

This document provides step-by-step instructions to help you use the TIMC website. Topics covered include:

- New User Registration
- Patient Registration
- Scan Assessment Requests
- Results Reporting
- Resources

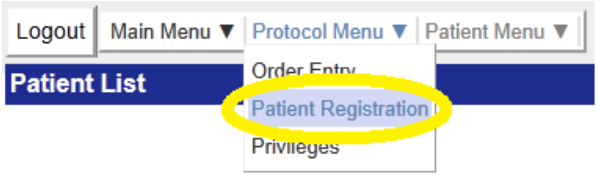
Please contact the TIMC help desk at timc@nmr.mgh.harvard.edu for any questions or concerns that are not addressed below.

New User Registration:

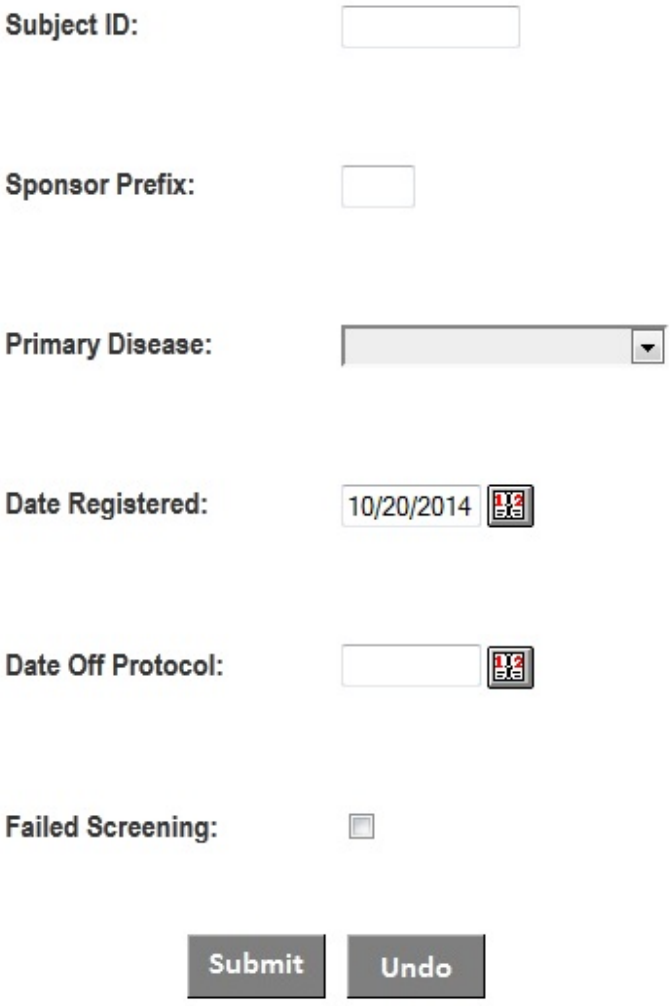
1. Please email the TIMC help desk at timc@nmr.mgh.harvard.edu and provide the following information:
   - User Full name
   - Home institution
   - Study role
   - Disease group affiliation
2. After account set-up, TIMC will notify you via email with your username and temporary password. Please go to www.tumormetrics.org and click **Client Login** or go to www.timclogin.org to directly access the login page.
3. Login with your TIMC username and password. The password can be changed by going to Main Menu → My Profile → Edit. You will be required to enter your current password and new password (alphanumeric, case sensitive, 6-10 characters). Click OK.

Patient Registration:

1. After login, click on the link for the appropriate protocol number (12-466).
2. Select **Patient Registration** from the **Protocol Menu** pull-down.



3. Click **Add New Record** to register a new research subject.



Subject ID

- Enter the PID1 upon initial registration. Once the PID2 is issued, edit this field to reflect the PID2.

Sponsor Prefix

- Enter your site's code according to the chart below:

CHLA, Children's Hospital Los Angeles	CLA
CHOP, Children's Hospital of Philadelphia	CHP
CHB, Children's Hospital Boston	CHB
UAB, University of Alabama at Birmingham	UAB
MGH	MGH
CNMC, Children's National Medical Center	CHN
UChicago, University of Chicago	UCH
LCH, Lurie Children's Hospital	LCH
WU, Washington University	WAU

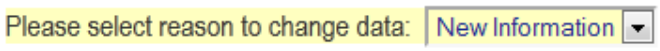
	NYUMC, New York University Medical Center | NYU JHU, Johns Hopkins University | JHU CCHMC, Cincinnati Children's Medical Center | CCH IU, Indiana University | INU
Primary Disease	• Select Patient's primary disease from pull-down. • Please email timc@nmr.mgh.harvard.edu if the patient's primary disease is not included in the list.
Date Registered	• This date will auto-populate with the date the patient is registered in the system.
Date Off Protocol	• Leave Date off Protocol field blank at this time. • Date off Protocol will auto-populate with the date of response assessment progression. • Please manually fill in Date Off Protocol if the patient comes off study for another reason (i.e., toxicity, *etc*).
Failed Screening	• Failed Screening should be checked if the patient does not meet enrollment criteria per imaging assessment.

4. Click **Submit**.

Making Changes:

TIMC website has an audit trail which requires users to enter a reason for the change before they can edit.

1. **Please select the reason to change the data** from the pull-down highlighted in yellow near the top right hand side of the browser window.

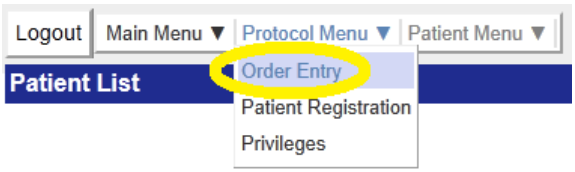


2. Click **Edit** to make changes to data entry.

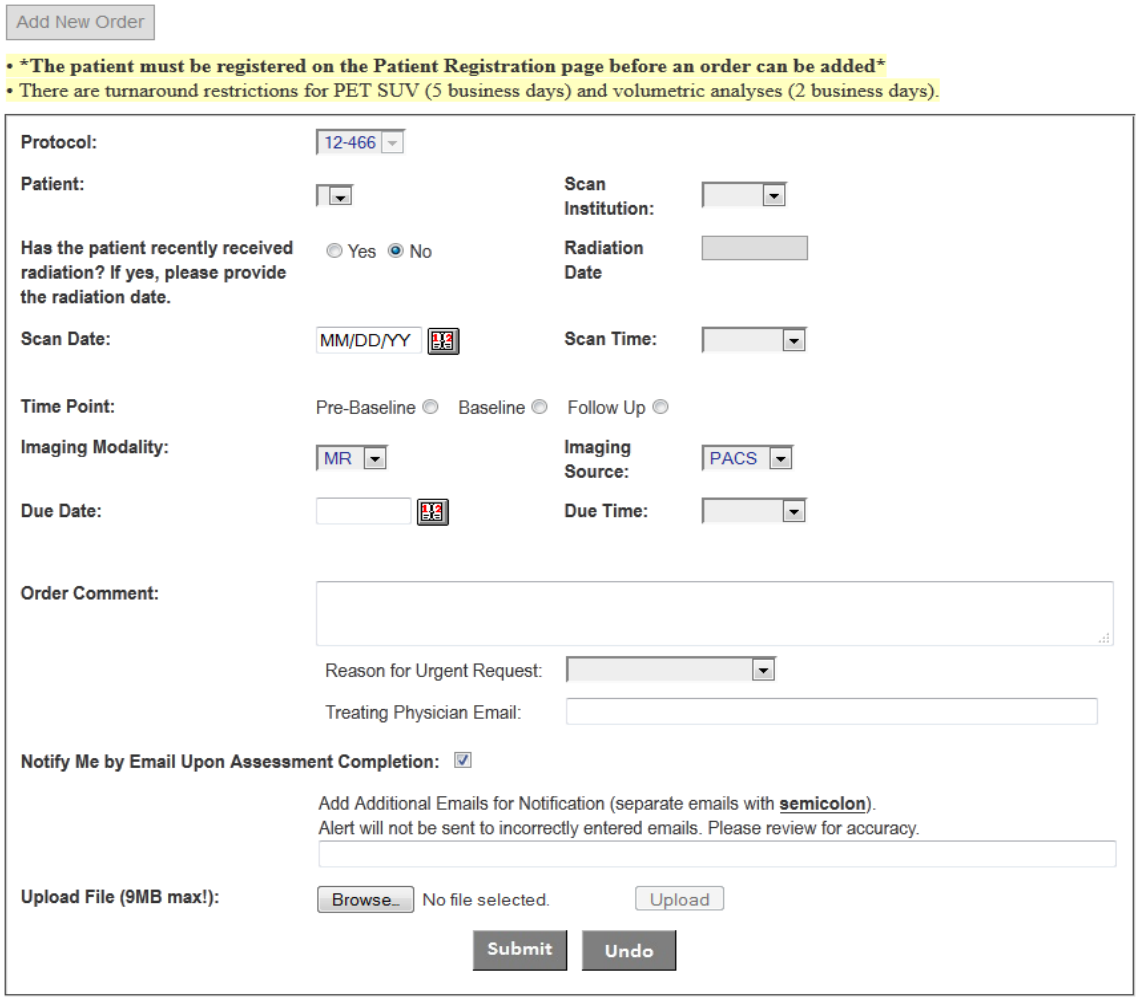
Scan Assessment Requests:

1. Click on the appropriate protocol number. (is automatically prepopulated)

2. Select **Order Entry** from the **Protocol Menu** pull-down.



3. Click **Add New Order**.



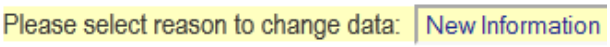
Protocol	• Automatically populates the protocol for which the patient is registered to (12-466).
Patient	• Select the patient from the **Patient** pull-down. • Only registered patients will appear in this list.

Scan Institution	• Select the institution where the scan was performed.
Radiation Date	• Select whether the patient has received radiation recently. If yes, enter the date of radiation.
Scan Date	• Enter date as MM/DD/YY or click the calendar button to select the scan date.
Scan Time	• Round time to the nearest 30 minutes.
Time Point	• Choose screening, baseline, or follow-up.
Imaging Modality	• Select the scan modality from the pull-down (i.e., CT, MR, PT).
Imaging Source	**PACS** • Select **PACS** if the scans were uploaded into the hospital's imaging archive (PACS). **CD** • Select CD if the scan is from an outside institution and needs to be uploaded manually.
Due Date	• Enter date as MM/DD/YY or click the calendar button to select the scan date.
Due Time	• Round time to the nearest 30 minutes.
Order Comment	• **Indicate if left and/or right schwannoma should be assessed.** • Enter information about the scan (i.e., scans to include in the assessment, lesion(s) of interest, *etc*).
Reason for Urgent Request	• Select a reason for urgent request from the **Reason** pull-down. • This field is required for urgent scans.

Treating Physician Email	• Enter the treating physician's email address • This field is required for urgent scans
Notify by Email Upon Assessment Completion	• Check the box if you would like to be notified by email when the scan assessment has been completed. • Add up to 3 additional email addresses to receive notifications
Status	This field is not editable and refers to the scan assessment status. • Ordered = Scan request has been made by trial staff • Inquiry = Inquiry initiated by TIMC; email response required by trial staff. • Processed = TIMC has started scan analysis. • Complete = Preliminary results are complete but scan has not been reviewed by a radiologist. • Final = Radiologist has reviewed and approved the scan assessment.

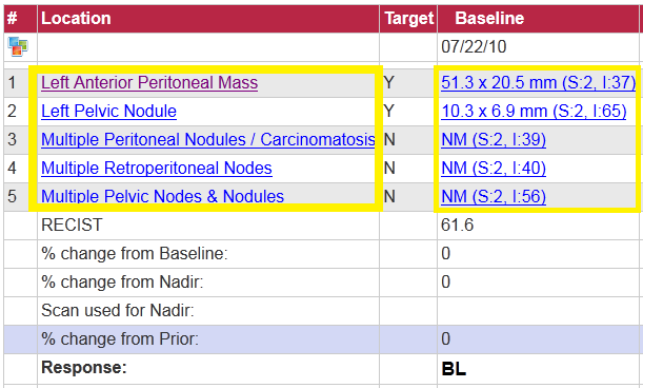
4. Click **Submit.**

   Note: The online system has an audit trail. To change data, please select the reason to change the data from the pull-down highlighted in yellow near the top right hand side of the browser window. Once a reason has been selected, click on 'Edit' to edit the patient information.



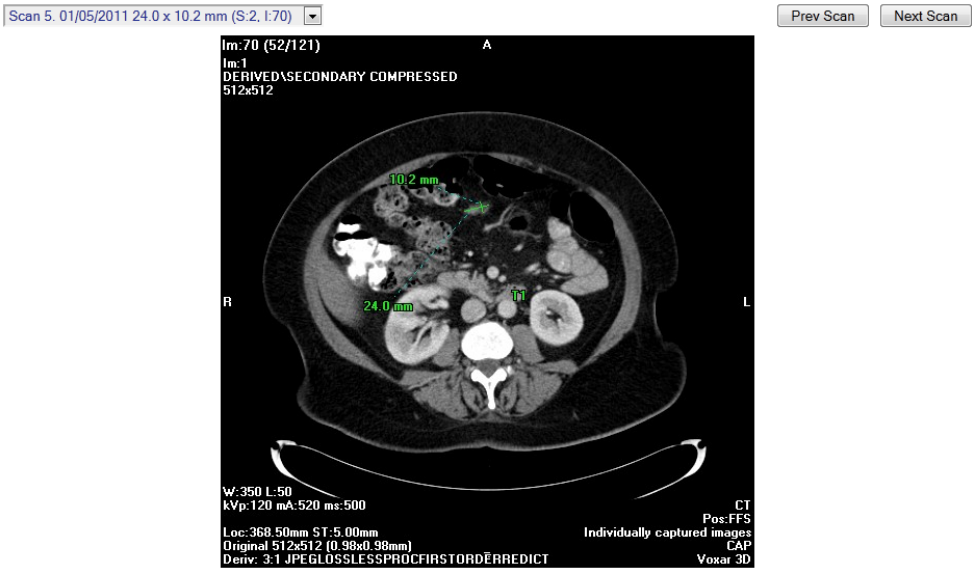
Results Reporting:

- Click on the appropriate protocol.
- From the **Patient List** page, click on the appropriate patient link.
- Compare image captures across time points by clicking the lesion location link (left box).
- View annotated images for a specific scan date by clicking on the measurement link (right box).



#	Location	Target	Baseline
			07/22/10
1	Left Anterior Peritoneal Mass	Y	51.3 x 20.5 mm (S:2, I:37)
2	Left Pelvic Nodule	Y	10.3 x 6.9 mm (S:2, I:65)
3	Multiple Peritoneal Nodules / Carcinomatosis	N	NM (S:2, I:39)
4	Multiple Retroperitoneal Nodes	N	NM (S:2, I:40)
5	Multiple Pelvic Nodes & Nodules	N	NM (S:2, I:56)
	RECIST		61.6
	% change from Baseline:		0
	% change from Nadir:		0
	Scan used for Nadir:		
	% change from Prior:		0
	Response:		**BL**

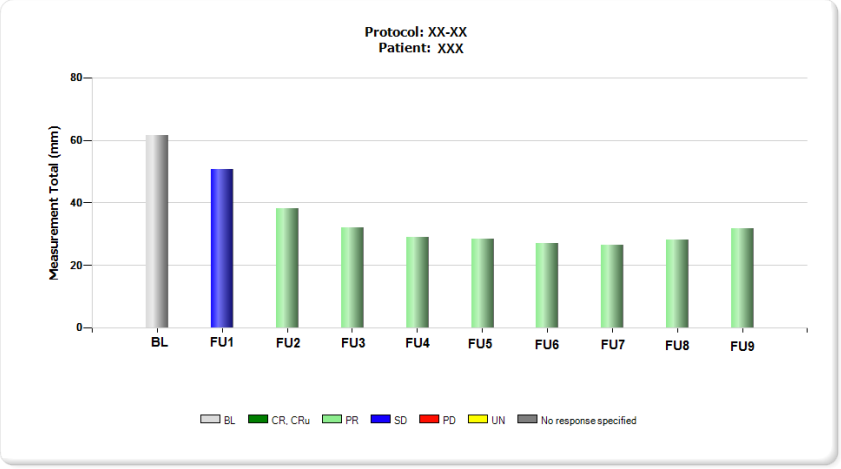
- Click the **Next Lesion** button located near the top right hand side of the screen to view the image capture for the next lesion or select the lesion of interest from the **Select Lesion** pull-down located under the patient information.
- Click the **Next Scan** button located to the right hand side of the image capture (on the right) to go to the next scan or select the desired scan date from the pull-downs located above the image captures.



- Select **Patient Summary** from the **Patient Menu** pull-down to go back to results

Longitudinal Graphs:

- Click the graph button  to view graphs. This button is located near the bottom left hand side of the screen on the **Patient Summary** page, or Select **Response Graph** from the **Patient Menu** pull-down
- Compare time point and individual lesion measurement data to baseline, nadir (scan with the lowest measurement total), and prior scans.



Request Re-Review:

If the central review is felt to be discordant with the clinical assessment, trial staff has the option to request a re-review of the scan.

- Click on the appropriate protocol.
- From the **Patient List** page, click on the appropriate patient link.
- Click the **Request Re-review** button.
- Populate all fields in the email template.

Resources:

Click on the Resources button at the top right hand side of the website to go to our Resources website. This website provides:

- Tutorials on imaging assessment criteria for clinical trials
- Documents to incorporate imaging metrics in study protocols
- Service and workflow requirement policies
- "How to" documents for navigating the TIMC website
- Imaging specific manuals and policies, only accessible to core staff

For additional information about our services, please visit www.tumormetrics.org.

Appendix H: Tinnitus Reaction Questionnaire (TRQ) [a]

SUBJECT IDENTIFIER : _____

Number	Item	Scores[b]				
1	My tinnitus has made me unhappy.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2	My tinnitus has made me feel tense.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3	My tinnitus has made me feel irritable.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4	My tinnitus has made me feel angry.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5	My tinnitus has led me to cry.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6	My tinnitus has led me to avoid quiet situations.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7	My tinnitus has made me feel less interested in going out.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8	My tinnitus has made me feel depressed.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9	My tinnitus has made me feel annoyed.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10	My tinnitus has made me feel confused.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11	My tinnitus “driven me crazy”.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12	My tinnitus interfered with my enjoyment of life.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13	My tinnitus made it hard for me to concentrate.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14	My tinnitus has made it hard for me to relax.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15	My tinnitus has made feel distressed.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16	My tinnitus has me feel helpless.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17	My tinnitus has made me feel frustrated with things.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18	My tinnitus has interfered with my ability to work.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

19	My tinnitus has led me to despair.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20	My tinnitus has led me to avoid noisy situations.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
21	My tinnitus has led me to avoid social situations.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
22	My tinnitus has made me feel hopeless about the future.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
23	My tinnitus has interfered with my sleep.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
24	My tinnitus led me to think about suicide.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
25	My tinnitus has made me feel panicky.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
26	My tinnitus has made me feel tormented.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

a From Wilson et al, 1991

b 0 = not at all, 1 = a little of the time, 2 = some of the time, 3 = a good deal of the time, and 4 = almost all of the time.

Protocol Title: Open-label, Phase 2 study of bevacizumab in children and adults with neurofibromatosis 2 and progressive vestibular schwannomas that are poor candidates for standard treatment with surgery or radiation

IND Number: 112096

SITE IRB Protocol Number:

Sponsor: US Army, Dept. of Defense and Genentech

Principal Research Doctor/Institution: SITE PI

If you are a parent or guardian of a child under 19 years old, the word "you" refers to your child. You, the parent, will be asked to read and sign this document to give permission for your child to participate.

INTRODUCTION

You are invited to take part in a clinical trial, a type of research study. You are invited to take part because you have neurofibromatosis type 2 (NF2) and a tumor on your hearing nerve (vestibular schwannoma) that is causing you to lose hearing. At this time, you may have been told that surgery to remove the tumor or radiation treatments are not favorable options. This research study is a way of gaining new knowledge about vestibular schwannomas. If you decide to take part, you will be known as a "participant" rather than a "patient". This research study is evaluating a drug called bevacizumab as a possible treatment for vestibular schwannoma.

It is expected that about 22 people will take part in this research study. At SITE, we will enroll 2 to 5 participants. Some research studies are supported in some way by an outside organization. Genentech, Inc. and the US Army, Department of Defense (DOD) are supporting this research study by providing bevacizumab (Genentech) and by providing funds (DOD and Genentech) to cover the costs of running this clinical trial.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of the research study, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your regular doctor.

We encourage you to take some time to think this over, to discuss it with other people and your doctor, and to ask questions now and at any time in the future.

WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the effectiveness of an investigational drug to learn whether it works in treating a specific tumor. "Investigational" means that bevacizumab is still being studied in NF2 and that research doctors are trying to find out more about it(such as the safest dose to use), the side-effects it may cause, and if it is effective for treating different types of tumors. Bevacizumab is an investigational agent that has been approved by the U.S. Food and Drug Administration (FDA) for use in cancers of the colon, breast, brain, pancreas, and kidneys. However, bevacizumab is not approved to treat vestibular schwannomas.

The purpose of this study is to find out what effects, good and/or bad, bevacizumab has on you and your vestibular schwannoma. Bevacizumab acts by preventing the growth of new blood vessels in tumors. Because tumors need new blood vessels to grow and spread, bevacizumab may stop blood vessel growth and slow or reverse the growth of the vestibular schwannoma or improve your hearing.

WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Radiation treatments to your vestibular schwannoma
- Surgery to remove your vestibular schwannoma
- Participate in another research study
- No therapy specific to your tumor
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the tumor. It does not treat the tumor directly, but instead tries to treat the symptoms

The study doctor will discuss with you alternate procedures or courses of treatment. Please talk to the research doctor about your options before you decide whether you want to take part in this research study.

WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study. The study doctor will discuss with you your responsibilities as a participant.

Before the research starts (screening): After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study.

If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **Physical exam**, including measurement of vital signs (temperature, heart rate and blood pressure)
- **Medical history**, including questions about your health, current medications, and any allergies
- **Blood tests**. Blood will be drawn (about 4 tablespoons) for tests to monitor your health, including blood counts and clotting studies, chemistry, and liver and kidney function
- **Urine test** to measure the amount of protein
- **Pregnancy test**. If you are a woman who can have children, you will have a blood pregnancy test. (If you are pregnant, you will not be able to participate in this research study)
- **Electrocardiogram (EKG)**. The function of your heart will be checked with an EKG, which traces the electrical activity of your heart
- **MRI scan of the brain** to measure the size of your tumor
- **Hearing assessment** to measure your ability to hear sounds and words
- **Questionnaires** to measure any effect your treatment may have on your tinnitus ("ringing" in the ears) and other symptoms that affect quality of life
- For participants less than 18 years of age: **X-rays** of the leg to determine whether you are still growing

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm that you are eligible to participate in the research study:

If you take part in this research study, you will come to the outpatient clinic for all of your evaluations and procedures over the course of 24 months. All participants will receive treatment for 6 months (the induction phase). Participants who benefit from treatment will continue receiving treatment for an additional 18 months (the maintenance phase). Participants who do not benefit from treatment by 6 months will not be allowed to continue receiving treatment.

Treatment will be divided into time periods called cycles. Each cycle is 4 weeks (28 days) during the first 6 months. You will come to clinic every 2 weeks to receive bevacizumab by vein. After the first 6 months, you will come to clinic every 3 weeks to receive bevacizumab by vein as long as your hearing is stable or improving. Each cycle after the first 6 months is 6 weeks as long as your hearing is stable or improves. If your hearing gets worse, then you will come to the clinic every 2 weeks to receive bevacizumab by vein.

The following tests and procedures are part of regular tumor care and will be done throughout the study:

- Physical exam, including measurement of vital signs (height, weight, temperature, heart rate and blood pressure)
- Questions about how you are able to perform activities of daily living (performance status assessment)
- Blood tests. Blood will be drawn (about 4 tablespoons) for tests to monitor your health, including blood counts, chemistry, and liver and kidney function
- MRI scan to measure the size of your tumor

You will need the following tests and procedures repeated throughout the study. These tests are part of regular tumor care, but are being done more often because you are in this study:

- Urine test to measure the amount of protein
- Hearing assessment to measure your ability to hear sounds and words
- Pregnancy test. If you are a female who can have children, you will have occasional blood pregnancy test
- Blood tests for hormone levels. If you are a woman who has reached puberty, blood will be drawn (about 1 tablespoon) for tests to monitor the function of your ovaries
- Questionnaires to measure any effect your treatment may have on your tinnitus ("ringing" in the ears) and other symptoms that affect quality of life

The following procedures will be done as part of the research trial to see how the study treatment is affecting your body:

- Questionnaires to measure any effect your treatment may have on your tinnitus and other symptoms that affect quality of life
- For participants less than 18 years of age that are still growing: X-rays of the leg to determine the effect of treatment on your growth
- Blood samples (about 5 teaspoons) will also be collected to test if you have any biomarkers or special measurements to see if bevacizumab is working to preventing the growth of blood vessels into your tumor. This collection is done prior to the first treatment, at week 3, week 5 and week 25.

The chart below shows what will happen to you during Cycle 1 and future treatment cycles, as previously explained. The left-hand column shows the day in the cycle and the right-hand column tells you what to expect on that day.

Cycle 1

Day	Tests/Procedures
Day 1	• Routine blood tests (about 2 tablespoons), urine test, and exams: • Medical History • Physical exam • Vital signs, height and weight • Performance status. • Receive first treatment of bevacizumab
Day 15	• Routine blood tests (about 2 tablespoons), urine test, and exams: • Physical exam • Vital signs and weight • Research blood samples (about 5 teaspoons) will also be collected to test for biomarkers during week 3 • Receive second treatment of bevacizumab
Day 28	• Cycle 1 ends. Return to clinic the following day (day 1 of cycle 2) for next infusion of bevacizumab

Cycles 2 to 6

Day	Tests/Procedures
Day 1	• Urine test and physical exams every cycle (more if your doctor tells you to). • Routine blood tests (about 2 tablespoons) • Brain MRI scan and hearing assessments during cycle 4 • Tinnitus Questionnaire and Quality of Life questionnaire during cycle 4 • For participants under the age of 18 who are still growing: x-ray of the leg during cycle 4 • Research blood samples (about 5 teaspoons) will also be collected to test for biomarkers during week 5 (cycle 2) • Receive treatment of bevacizumab
Day 15	• Receive treatment of bevacizumab
Day 28	• Cycle ends. Return to clinic the following day (day 1 of next cycle) for infusion of bevacizumab

Future cycles – after the first 6 months

Day	Tests/Procedures
Day 1	• Urine test and physical exams every cycle (more if your doctor tells you to) • Routine blood tests (about 2 tablespoons) • Brain MRI scan and hearing assessments during cycles 7, 9, 11, 13, 15, and 17. • Tinnitus Questionnaire and Quality of Life questionnaire during cycles 7, 11, and 15 • For participants under the age of 18 who are still growing: x-ray of the leg during cycles 7, 11, and 15 • Research blood samples (about 5 teaspoons) will also be collected to test for biomarkers at week 25 (cycle 6) • Receive treatment of bevacizumab
Day 22	• Receive treatment of bevacizumab
Day 42	• Cycle ends. Return to clinic (day 1 of next cycle) for infusion of bevacizumab

After the final dose of the study drug: After the final dose of bevacizumab, you will have tests and procedures including urine test, physical exam, routine blood tests (about 2 tablespoons), performance status, brain MRI, hearing assessment, tinnitus Questionnaire and Quality of Life questionnaire, research blood tests for biomarkers (about 5 teaspoons), and x-ray of the leg (for participants under the age of 18 who are still growing). Afterwards, you will resume standard care for your neurofibromatosis 2 and vestibular schwannomas. No research tests are scheduled after the final round of testing noted above. However, we would like to keep track of your medical condition 12 weeks after you finish taking bevacizumab. We would like to do this by calling you on the telephone once a year to see how you are doing.

HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be asked to take bevacizumab for 2 years or until your tumor grows or your hearing gets worse. After you are finished taking bevacizumab, the study doctor will ask you to visit the office or follow-up by telephone for at least 12 weeks.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed. In addition, you can stop participating in the research study at any time. If you decide to stop participating in this research study, e it is very important that you talk to the research doctor and your regular doctor first.

In addition, you can stop participating in the research study at any time; however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your regular doctor first.

WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side-effects.

All chemotherapy drugs have side-effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a wide range of side-effects between different drugs and between individuals. For investigational drugs, not all of the risks are known at this time. **You need to tell your doctor or a member of the study team immediately if you experience any side-effects.**

Since many drugs used to treat tumors are designed to cause the rapidly dividing tumor cells in your body to slow down or die, these drugs can also cause other rapidly dividing normal cells in your body to slow down or die. These include the blood cells that help to fight infection (white blood cells), the blood cells that help the blood clot (platelets), and the blood cells that carry oxygen in your body (red blood cells). When anticancer drugs cause a decrease in these blood cells, it is called bone marrow suppression. While you are participating in this research study, your blood cell levels will be monitored closely.

Please notify your doctor if any of the following occur:

- A fever of 100.5 or above.
  This could be a sign of an infection. If you have a low white blood cell count, this can be serious, life-threatening or fatal. You may have to take antibiotics or be admitted to the hospital.

- Low energy or shortness of breath.
  This could be a sign of anemia (not enough red blood cells). If this becomes severe, you may need to come into the clinic or hospital to have a transfusion of red blood cells.

- You bruise easily, or, when injured, you do not stop bleeding.
  This could be a sign that your platelets (blood cells that help with clotting) are low. This can be serious or life-threatening. You may need to come into the clinic or hospital for a transfusion of platelets.

Many cancers are associated with an increased risk of blood clots forming that could lead to swelling in the legs and arms. These clots may travel to the lungs causing shortness of breath or to the brain causing a stroke. This may become serious and life threatening. Some cancer drugs can increase this risk. It is important to let your doctor know if you have increased shortness of breath or difficulty breathing.

Everyone in the research study will be watched carefully for side-effects. You will be monitored during your chemotherapy to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side-effects, they may go away after you stop taking the study drug. Some side-effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side-effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Bevacizumab:

Frequent (Chance of 10-50% that this will happen)

- Fatigue
- Headaches
- High blood pressure, with increased risk of heart problems, headache and stroke.
- Pain
- Abdominal pain
- Shortness of breath
- Mouth sores
- Weakness
- Upper respiratory infection
- Chills
- Loss of appetite
- Bleeding (including in stomach or intestines)
- Runny nose or increase in tears in your eyes
- Kidney damage, found by testing your urine
- Loss of function of the ovaries (female sex glands), that can lead to menopause. Studies in humans have shown a decrease in the function of ovaries during treatment with bevacizumab with chemotherapy. This condition results in difficulty becoming pregnant. In some participants, the

function of the ovaries returned to normal after treatment with bevacizumab and chemotherapy was stopped.

- Changes in menstrual period, including abnormally heavy menstrual bleeding, decreased menstrual bleeding, absent menstrual bleeding, or irregularity in time between the menstrual periods

Occasional (Chance of 1-10% that this will happen)

- Hoarseness
- Nosebleeds
- Low levels of potassium in the blood (can cause an irregular heartbeat)
- Hair loss
- Dry Skin
- Hole in your intestine; requires hospitalization and/or surgery; could be fatal.
- Blood clots in your veins and arteries. These can cause chest pain, heart attack, or stroke. A blood clot in your eye might cause vision loss. Clots can be serious and life threatening.
- Allergic reaction when infusion is given. Serious allergic reaction may result in death.
- Slowed growth in height and development (for children and young adults who are still growing). Laboratory studies have shown a decreased in growth during treatment with bevacizumab.

Rare (Chance of less than 5% that this will happen)

- Congestive heart failure (fluid that builds up in your lungs because your heart isn't working properly).
- Bevacizumab might affect the ability of your wounds to heal. This can lead to infections, hospitalization, or could possibly be fatal.
- A very rare problem in your brain that may cause confusion, blindness, and coma has been seen in some patients that were given Bevacizumab. This is associated with very high blood pressure and is not thought to be a permanent condition.
- Confusion
- Abdominal abscess or infection in your abdomen
- Fistula or hole in your bowel. This is an abnormal connection between two different organs and may lead to life threatening complications including serious infections, bleeding, or dysfunction of the organs.
- Dehydration
- Abnormal bleeding in your body or from the tumor, which may be fatal.
- Laboratory studies of bevacizumab showed abnormal bone growth. These and other effects of bevacizumab could possibly cause problems with growth and development. Abnormal changes in the bones after treatment with bevacizumab have been seen in young children with growing bones. This side effect appeared to be reversible after the drug was stopped, but has not been studied with long-term use of the drug. All participants in this study who receive bevacizumab and are still growing will be monitored for changes to bones by the use of x-rays performed throughout the study treatment.

- Fistual or hole in your gallbladder (part of the intestines that helps with digestion). This may require surgery and be serious or life threatening.
- Osteonecrosis of the jaw. A severe bone disease in which the jaw bone becomes visible (exposed) inside the mouth. This can be associated with pain and infection.
- Pulmonary hypertension. Abnormally high blood pressure in the blood vessels in the lungs, which makes it harder to pump blood into the lungs. May cause fatigue, shortness of breath, chest pain, and ankle swelling. Can lead to loss of consciousness and could be serious and life threatening.

Cancer research often included biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures down only for the purposes or research.

Reproductive Risks:

Because the drug in this study can possibly affect an unborn baby and infants, you should not become pregnant or father a baby or breast feed while you are on this study. Also, because bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of bevacizumab, although the optimal or the maximal time required for drug clearance cannot be precisely predicted. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants. In addition, the effect of the study drug on the ability have children in the future is uncertain. The study drug may make it more difficult or impossible to have children in the future.

NON-PHYSICAL RISKS

Because of side-effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

Questionnaires

The questionnaires used in this study may be upsetting. If you find the questionnaires upsetting, you may speak with the research doctor or ask to be referred for additional emotional support.

WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

Taking part in this research study may or may not make your health better. We hope the information learned from this research study will help doctors learn more about bevacizumab as a treatment for vestibular schwannomas in the future.

CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you choose not to participate in this research study, do not sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study treatment with bevacizumab. In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

WHO IS CONDUCTING THE RESEARCH STUDY?

The study is being conducted here at SITE as part of the Neurofibromatosis Consortium. This group is dedicated to the treatment of NF-related tumors and other problems resulting from NF. It is made up of thirteen clinical centers within the United States and Australia and an Operations Center (University of Alabama at Birmingham, AL). The Neurofibromatosis Consortium is a clinical cooperative group (a network of hospitals working together) funded by the Department of Defense (DoD). Each clinical site has NF specialists, health care providers, nurses, and other scientists who are dedicated to the development of new treatments and cures for the tumors of infants, children, adolescents, and young adults with NF. We also conduct research on the causes, prevention and treatment of tumors, and the long-term effects of treatment on patients.

This research study is also being supported by an outside organization called Genentech, Inc. They are supporting this research study by providing the study drug and modest monetary support.

WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid as part of this research study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company. The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

You will not be charged for bevacizumab.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. Typical standard care for NF2 patients includes MRI scans and hearing tests. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- SITE: SITE PHONE NUMBER

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

http://www.cancer.gov/clinicaltrials/learning/insurance-coverage

WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

The SITE, Department of Defense and the Neurofibromatosis Consortium has made no provision for monetary compensation in the event of injury from the research, and in the event of such injury, treatment will be provided, but is not free of charge.

The Principal Investigator or his/her designee will assist you and your child in obtaining appropriate medical treatment if it is required. If you have any questions, please discuss this issue thoroughly with the Principal Investigator or his/her designee before you enroll in this study. This is not a waiver or release of your legal rights.

What about confidentiality?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a SITE research database. Representatives of the Department of Defense, the outside organization that is partly funding the study, are authorized to review research records.

The results of this research study may be shared with the sponsors and published. You will not be identified in publications without your permission.

Your information may also be shared with outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research. This may include, but not limited to, other research doctors and medical centers participating in this research, labs, insurance agencies, Federal and state regulatory agencies and safety monitoring boards.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor, SITE PI at SITE PHONE NUMBER . She will be glad to answer any of your questions. After hour number to call are: SITE PHONE NUMBER. You may also use these numbers if you have questions about any part of this study or consent form either now or at any time in the future or if you believe you have been injured as a result of being in this study

If you have any questions or concerns about your rights as a research participant, or concerns or complaints about the research, you may contact The SITE Office of the IRB (OIRB) at SITE PHONE NUMBER. Regular hours for the Office of the IRB are 8:00 a.m. to 5:00 p.m. Central Time Zone, Monday through Friday. You may also call this number in the event the research staff cannot be reached or you wish to talk to someone else.

Storage of Specimens for Future Use

We will try to collect the blood used for this research at the same time as blood is drawn to monitor your health during your study treatment and at follow-up visits, in order not to increase the number of times you will have blood drawn. If you agree, any blood sample that is left over after the research for this study is complete will be stored for future use. Please read each sentence below and think about your choice. After reading each sentence, circle "yes" or "no" for each type of specimen and write your initials. Then sign your name at the bottom of this section. If you have any questions, please talk to

your doctor or nurse, or call the Principal Investigator for this study (SITE PI at SITE PHONE NUMBER).

No matter what you decide to do, it will not affect your care.

You may request at any time that your research samples be removed from storage and not be used for future research. If you decide you want your samples removed, you may contact SITE PI at SITE PHONE NUMBER. Once your request is received, and if your samples have not already been used for other research, they will be destroyed. If you do not make such a request, your specimens will be stored indefinitely or until used.

1. My blood specimens may be kept for use in future research to learn about, prevent, or treat neurofibromatosis 2:

   ☐ Yes ☐ No _____ _____
   Signature Date

2. My blood specimens may be kept for use in future research to learn about, prevent, or treat other health problems (for example, diabetes, Alzheimer's disease, or heart disease):

   ☐ Yes ☐ No _____ _____
   Signature Date

3. Someone may contact me in the future to ask me to take part in more research:

   ☐ Yes ☐ No _____ _____
   Signature Date

Document of Assent

Signature of participant between age of 14 and 17: The person doing this research study has explained what will happen to me if I take part in this research study. My signature below means that I want to be in this research study. I can decide not to take part in this research study if I do not want to and nothing will happen to me if I decide I do not want to participate.

_____ _____
Signature of Participant Date

Document of Consent

My signature below indicates that I agree to participate in this study. I am aware that I will receive a copy of this signed agreement:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____
Signature of Participant Date
Or Legally Authorized Representative

_____
Relationship of Legally Authorized Representative to Participant

_____ _____
Signature of Witness Date

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:

Age _____ Maturity _____ Psychological state of the child _____

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ The participant is an adult and provided consent to participate.

☐ The participant is a non-English speaker and signed the translated Short Form in lieu of English consent document

☐ The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ gave permission for the adult participant to participate

☐ did not give permission for the adult participant to participate

or

For Minor Participants

☐ The parent or legally authorized representative gave permission for the minor to participate.

☐ parent or legally authorized representative is a non-English speaker and signed the translated Short Form in lieu of English consent document

☐ The parent or legally authorized representative did not give permission for the minor to participate

Signature of Individual obtaining consent: _____

Printed name of above: _____

Date: _____

Medical Release of Information

Permission is hereby given:

_____
Name

_____
Address

_____
City State Zip

To release to the SITE, any and all medical information contained in the record of:

_____
Name of Patient

_____
Address

_____
City State Zip

_____
Date

Signed: _____
Patient

Signed: _____
Witness

_____
Address

_____
City State Zip