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A Phase II Trial of Bevacizumab in Patients with Recurrent Solid Tumor Brain Metastases Who Have Failed Whole Brain Radiation Therapy

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STUDY SUMMARY

Title	A Phase II Trial of Bevacizumab in Patients with Recurrent Solid Tumor Brain Metastases Who Have Failed Whole Brain Radiation Therapy
Short Title	Bevacizumab in Recurrent Solid Tumor Brain Metastases
Protocol Date	February 6, 2019
Study Duration	12-18 months
Study Centers	Northwestern University (PI: P. Kumthekar); Columbia University (PI: A. Lassman); Northwestern Medicine Cancer Center (Cadence Health Cancer Center) (PI: Sean Grimm)
Objectives	Primary Determine the radiographic response in patient's brain metastases treated with bevacizumab. Secondary 1) Estimate progression free survival rate at 6 months. 2) Determine the time to progression based on MRI or CT scans. 3) Determine the time to response based on radiographic imaging. 4) Determine the duration of response based on radiographic imaging. 5) Determine the overall survival. 6) Collect safety data. 7) Assess changes in quality of life using the FACT-Br while on treatment.
Accrual Goal	27
Diagnosis and Main Inclusion Criteria	• Patients must have recurrent, measurable brain metastases from a solid tumor after whole brain radiation therapy (WBRT). • Patients must have failed prior WBRT. • Patients must have completed WBRT >12 weeks prior to enrollment to limit cases of pseudoprogression; however if new lesions are noted < 12 weeks but > 4 weeks prior to enrollment, those patients are eligible. • Patients may be on other systemic chemotherapies if progressive CNS disease occurs while on these treatments. New systemic chemotherapies should not be started unless required to treat systemic disease but should not start until at least 1 follow up imaging study has been performed. • Patients with leptomeningeal metastases are not eligible for therapy. • No limitations on prior CNS directed therapies • Patients must be age $\geq$ 18 years with a KPS of $\geq$ 60 • Patients must be > 4 weeks from any surgery. • Patients may not have known hypersensitivity to any component of bevacizumab.
Treatment Summary	Patients will receive bevacizumab at a dose of 10 mg/kg intravenously every two weeks until CNS disease progression or death from systemic disease.

Analysis Summary	The primary endpoint will be objective radiographic tumor response. Secondary endpoints will include PFS at 6 months, time to progression, time to response, duration of response, OS, and safety. *Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.* A Simon two-stage optimal phase II clinical trial design will be used. If 0 responses are observed in the first 9 patients, it will be concluded that the true response rate was 5% or less and no further patients will be enrolled. If 1 or more responses are observed in the first 9 patients, 15 additional patients will be enrolled to a total of 24 *evaluable* patients. If 3 or more responses are observed, there would be evidence that the regimen used was active (true response rate is at least 25%). This design will declare the regimen as active when the true response rate is 25% with 90% probability (power = 0.90) at the 1-sided 0.10 alpha level. To account for dropouts, we will plan for 27 patients total to be able to have 24 evaluable patients.

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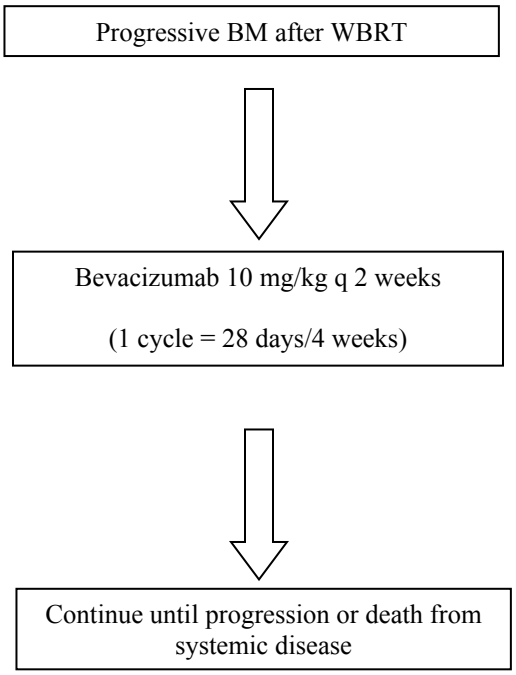
SCHEMA

This is a phase II trial for patients with brain metastases (BM) who progress after whole brain radiation therapy (WBRT). Patients will receive bevacizumab at a dose of 10 mg/kg IV every 2 weeks until CNS disease progression or death from systemic disease.



1 INTRODUCTION - BACKGROUND & RATIONALE

1.1 Metastatic Disease - Overview & Current Treatment Options

Metastatic brain tumors are by far the most common intracranial malignancy totaling about 170,000 per year and developing in about 40% of all cancer patients[1-4]. Metastases out number primary brain tumors by about 4:1. The most common primary malignancies of brain metastases include lung cancer (compromises about 50%), breast cancer (15%), melanoma (9%), and unknown primary (about 11%)[5]. Metastatic disease can cause neurologic issues ranging from headache to seizures, motor and sensory impairment, and other focal neurologic deficits. In general , prognosis is poor with a median survival time of 1 month for untreated patients, and approximately 4 months for treated patients[2], with only 10% being alive at one year after diagnosis[6].

When determining treatment for patients with brain metastases, histology, number of lesions, and resectability of lesions are taken into account. Because over 70% of patients present with multiple metastases at diagnosis[5], focal treatments such as surgical resection and radiosurgery are ineffective. For these patients, whole brain radiation therapy (WBRT) should be performed, although some practitioners use radiosurgery for patients with ≤ 3 lesions and withhold WBRT. Typically WBRT is given in 10 fractions of 3 Gy over 2 weeks for a total dose of 30 Gy, but other schedules have been used, such as 15 fractions of 2.5 Gy over 3 weeks for a total dose of 37.5 Gy. The Radiation Therapy Oncology Group (RTOG) has evaluated these and various other radiation fractionation schedules, however median survival seems independent of the dose schedule[3].

For patients with brain metastases from systemic cancers who fail WBRT, median survival is 4-6 months. Patients with the limited or no extracranial disease, KPS > 70, and age < 65 have survivals over 10 months. Using the updated GPA, survival is 2.8 to 11.1 months depending on score and histology[7]. This group of patients is increasing with improvements in systemic therapy; leading to a group of patients whose demise is from CNS involvement.

Systemic chemotherapy has been shown to have activity in the treatment of brain and leptomeningeal metastases[8, 9], but no one drug has proven to be overly effective. Lassman et al. treated 31 patients with CNS metastasis with HD MTX and found a median overall survival (OS) of approximately 5 months with a 28% response and stable disease rate[10]. Temozolomide has been shown to have median survivals of approximately 5 months in patients who have failed WBRT[11-13]. In a trial of HER2 positive breast cancer patients with BM, 22 patients treated lapatinib and capecitabine or topotecan, had a partial response (PR) rate of 22% and a stable disease (SD) rate of 40%; median time on trial was approximately 4 months[14]. Topotecan has been used in both breast and lung cancer patients with BM with survivals of 6.25 and 7.25 months[15, 16]. Finally patients with solid tumors who had BM entered in to various phase I trials had a survival of 7.5 months[17].

1.2 Bevacizumab

Bevacizumab is recombinant humanized monoclonal IgG_1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralization of the biologic activity of VEGF can result in the reduction of tumor vascularization and subsequent reduction in tumor growth. It is currently FDA approved for recurrent glioblastoma multiforme (GBM), lung cancer and

renal cell cancer[18]. Bevacizumab has shown activity in recurrent malignant GBM [19] leading to accelerated FDA approval.

1.2.1 Clinical Data

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 market 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 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 CRC, the addition of bevacizumab, 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 PFS (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 (bevacizumab Investigator Brochure, October 2005).

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 OS 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 OS 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).

1.2.2 Safety Profile

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.

1.2.2.1 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) [20, 21]. 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.

1.2.2.2 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. 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.

1.2.2.3 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.

1.2.2.3.1 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 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.

1.2.2.3.2 Arterial thromboembotic events

An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving 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 ATE events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the 5 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 ATE 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[22]. Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

1.2.2.4 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.

1.2.2.5 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 timepoints 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 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.

1.2.2.6 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[23]. 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).

1.2.2.7 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 (bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

1.2.2.7.1 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.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.
In Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥ 3 hemorrhage was 1.0% in the control arm (carboplatin and paclitaxel) versus 4.1% in the carboplatin and paclitaxel + bevacizumab arm (Sandler et al. 2006).
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.

1.2.2.7.2 Mucocutaneus Hemorrage

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly 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.

1.2.2.8 Reversible Posterior Leukoencephalopathy Syndrome

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[20, 21]. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with PRES.

1.2.2.9 Congestive heart failure

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[24]. In a randomized, phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as 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[25].

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin, and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40%[26]. In a small phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m^2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m^2, one Grade 4 event after a cumulative doxorubicin

dose of 420 mg/m^2); an additional 4 patients had asymptomatic decreases in LVEF (D'Adamo et al. 2004).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.

1.2.2.10 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[27].

1.3 Rationale for the Current Study

Many patients who have controlled systemic disease often have progressive or recurrent BM. For these patients no standard option for treatment exists. Repeat WBRT may be an option but is best suited for those who had a durable initial response. For some patients, radiosurgery might be used for 1-3 lesions and then chemotherapy can be considered. Limited data exist for patients who have repeat WBRT. In this clinical setting, survival is estimated at about 4 months[28, 29]. For patients who receive chemotherapy survival is about 6 months[30, 31] with variable responses to treatment and time to tumor progression. Data is limited in patients who fail WBRT.

Bevacizumab administration has proven to be safe without an increased incidence of CNS bleeding in malignant glioma[32]. A more recent review has shown that specifically in patients with BM treated with bevacizumab, the bleed rate is comparable to those not receiving bevacizumab[33]. One additional report of 6 patients noted safety and activity of bevacizumab in patients with BM from NSCLC[34]. It is rational and appears safe to consider treating patients with progressive or recurrent BM post-WBRT with bevacizumab as options are limited with no standard agent used for salvage therapy.

We propose to conduct a phase II trial of patients with brain metastases who have failed WBRT. Patients will receive bevacizumab at a dose of 10 mg/kg IV every 2 weeks until CNS disease progression or death from systemic disease. This will be a dual-center, open-label trial following a Simon two-stage optimum design. If 0 responses are observed in the first 9 patients, it will be concluded that the true response rate was less that 5% and no further patients will be enrolled. If 1 or more responses are observed in the first 9 patients, a total of 24 *evaluable* patients will be required. We will plan for 27 patients total to be able to have 24 evaluable patients.

2 OBJECTIVES & ENDPOINTS

2.1 Primary Objective

The primary objective of this study will be to determine the radiographic response rate in patients with solid tumor brain metastases treated with bevacizumab after failing WBRT.

2.2 Secondary Objectives

Secondary objectives will include the following:

2.2.1 Estimate the PFS rate at 6 months
2.2.2 Determine the time to progression based on MRI or CT scans.
2.2.3 Determine the time to response based on radiographic imaging.
2.2.4 Determine the duration of response based on radiographic imaging.
2.2.5 Determine overall survival.
2.2.6 Collect additional safety data.
2.2.7 Assess changes in quality of life using the FACT-Br while on treatment.

2.3 Primary Endpoint

The primary endpoint will be objective radiographic tumor response. Response will be assessed prior to every odd-numbered cycle.

2.4 Secondary Endpoints

Secondary endpoints will include:
2.4.1 PFS assessed at 6 months.
2.4.2 Time to progression of disease based on MRI or CT scans performed prior to every odd-numbered cycle.
2.4.3 Time to response based on radiographic imaging performed prior to every odd-numbered cycle.
2.4.4 Duration of the response based on radiographic imaging performed prior to every odd-numbered cycle.
2.4.5 OS rate.
2.4.6 Safety as measured by adverse events assessed prior to every cycle.
2.4.7 Quality of life will be assessed at baseline and prior to every odd-numbered cycle during treatment using the FACT-Br tool.

3 SELECTION OF SUBJECTS

The target population for this phase II trial is patients with BM from solid tumor malignancies who have failed WBRT. Males and females ≥ 18 years of age will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate. The eligibility criteria listed below are interpreted literally and will not be waived.

Patients will be recruited in the Neuro-Oncology clinics of Northwestern University, Northwestern Medicine Cancer Center/Cadence Health Cancer Center and Columbia University. This will be a multi-center trial with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University serving as the lead site. Patients may be referred to the Principal Investigator (PI), Dr. Priya Kumthekar, MD, at 312-503-1818, or to the local PIs at Columbia University or Northwestern Medicine Cancer Center/Cadence Health Cancer Center. Enrollment will be on a first-come-first-serve basis. A total accrual of 27 patients is planned for this study. It is estimated that approximately 1-2 patients may be enrolled per month. It is anticipated that this trial will take place over approximately 12-18 months in which time we expect to undergo accrual, evaluation and follow-up.

3.1 Inclusion Criteria

3.1.1 Patients must have a histologically or cytologically confirmed non-CNS primary solid malignancy at the time of initial diagnosis. *NOTE: Brain lesions are not required to have pathologic confirmation. In addition, a copy of the pathology report for the primary tumor is sufficient for registration purposes.*
3.1.2 Patients must have radiographically-confirmed recurrent brain metastases from a solid tumor after WBRT.

3.1.3 Patients must have measurable disease in the brain, defined as at least 1 lesion measuring ≥ 5 mm unidimensionally on imaging.

3.1.4 Patients must have been on a stable dose of corticosteroids ≥ 5 days prior to obtaining their baseline Gd-MRI of brain.

3.1.5 Patients must have completed WBRT >12 weeks prior to enrollment to limit cases of pseudoprogression; however if *new lesions* are noted < 12 weeks but > 4 weeks prior to enrollment, those patients are eligible.

3.1.6 Patients who underwent radiosurgery to treat a progressive lesion must have confirmation of tumor by tissue, MRS, MR perfusion or PET and the lesion must be measurable. *NOTE: Radiosurgery may be done to a lesion that will not be used for response evaluation and should be done > 2 weeks prior to enrollment*.

3.1.7 Patients may be on other systemic chemotherapies if progressive CNS disease occurs while on these treatments. *NOTE: New systemic chemotherapies should not be started unless required to treat systemic disease and should not start until at least 1 follow up imaging study has been performed.*

3.1.8 Patients may have received any number of prior CNS directed therapies – there are no limitations.

3.1.9 Patients must be age ≥ 18 years.

3.1.10 Patients must have a life expectancy of ≥ 12 weeks.

3.1.11 Patients must have a Karnofsky Performance Score (KPS) of ≥ 60.

3.1.12 Patients must exhibit adequate bone marrow, liver, and renal function, within 14 days prior to registration, defined as:

WBC	≥ 3,000/μl
ANC	≥ 1,500/mm^3
Platelets	≥ 100,000/mm^3
Hemoglobin	≥ 10 gm/dl (may be reached by transfusion)
SGOT and bilirubin	< 2 x ULN (or < 5 x ULN if liver is involved)
Creatinine	< 1.5 x ULN

3.1.13 Patients of both sexes must agree to the use of barrier contraceptives throughout the duration of treatment on this trial and for 3 months after discontinuing treatment. *NOTE: Hormonal contraceptives are not acceptable as a sole method of contraception.*

3.1.14 Patients must be > 4 weeks from any major surgery.

3.1.15 Patients NOT on warfarin must have a PT/INR < 1.4 within 14 days prior to registration.

Patients on full-dose anticoagulants (e.g., warfarin or LMW heparin) must meet BOTH of the following criteria within 14 days prior to registration:

- No active bleeding or pathological condition that carries a high risk of bleeding (e.g., tumor involving major vessels or known varices).
- In-range INR (between 2 and 3) on a stable dose of oral anticoagulant or on a stable dose of LMW heparin.

3.1.16 Female patients of child-bearing potential must have a negative pregnancy test within 14 days prior to registration.

3.1.17 Patients must be willing and able to comply with study and/or follow-up procedures.

3.1.18 Patients must sign an informed consent prior to registration and before undergoing any study-specific procedures indicating that they are aware of the investigational nature of this study.

3.2 Exclusion Criteria

3.2.1 Patients with a diagnosis of intrathoracic lung carcinoma of squamous cell histology are not eligible for participation.

3.2.2 Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using barrier birth control methods, are not eligible for participation.

3.2.3 Patients must not have baseline proteinuria within 14 days prior to registration as demonstrated by either:

- Urine protein: creatinine (UPC) ratio < 1.0 at screening,
  OR
- Urine dipstick for proteinuria ≤ 2+.

NOTE: Patients discovered to have ≥ 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible.

3.2.4 Patients must not have experienced any major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to registration, or be anticipated to need a major surgical procedure during the course of the study. *NOTE: The exception is craniotomy. Patients with brain tumors who have undergone craniotomy or intracranial biopsy must be cleared by their neuro-surgeon to participate at the time of registration.*

3.2.5 Patients must not have experienced a core biopsy or other minor surgical procedure within 7 days prior to registration. *NOTE: This excludes placement of a vascular access device up to 2 days prior to registration.*

3.2.6 Patients with a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within the previous 6 months are not eligible for participation.

3.2.7 Patients with a serious, non-healing wound, ulcer, or bone fracture are not eligible for participation due to the effects on vasculature by bevacizumab which may impair healing.

3.2.8 Patients *known* to be HIV or Hepatitis B and/or C positive are not eligible for participation. *NOTE: HIV and hepatitis testing is not required for study participation*.

3.2.9 Patients with a history of any other cancer (except for non-melanoma skin cancer or carcinoma in-situ of the cervix), are not eligible for participation unless they are in complete remission and have been off of all therapy for that disease for a minimum of 3 years.

3.2.10 Patients receiving or participating on any other experimental agents/clinical trials are not eligible for participation.

3.2.11 Patients with a known hypersensitivity to any component of bevacizumab are not eligible for participation.

3.2.12 Patients with any significant medical illnesses or infection that, in the investigator's opinion, cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy are not eligible for participation.

3.2.13 Patients with leptomeningeal disease are not eligible for participation.

3.2.14 Patients who have received previous treatment with bevacizumab for CNS disease are not eligible for participation.

3.2.15 Patients with inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure > 100 mmHg) are not eligible for participation.

4 PATIENT REGISTRATION

Patients *may not* begin protocol treatment prior to registration. All patient registrations will be centralized through the Clinical Research Office (CRO) at the lead site, Northwestern University. Patients from both sites will be registered on a first-come-first serve basis. Please contact the Quality Assurance Monitor (QAM) at croqualityassurance@northwestern.edu with questions. Study-specific training will be provided prior to site activation.

4.1 Access to the Registration Program

Eligible patients will be registered to the study via the Northwestern Oncology Trial Information System (NOTIS) using the web-based application, which can be found through the CRO's website at: https://www.cancertrials.northwestern.edu. Please note that a password is required to use this program. If needed, one will be provided during the study activation period, prior to training on the NOTIS system.

4.2 Registering a Patient

4.2.1 For potential patients, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

4.2.2 BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive a subject identification number:

- Patient's signed and dated informed consent form.
- Copy of the pathology report (to confirm diagnosis).
- Eligibility eCRF (complete in NOTIS)
- Eligibility checklist (signed and dated by the treating physician – upload in NOTIS)

4.2.3 Go to NOTIS to register the patient and complete the Eligibility electronic case report form (eCRF). Please refer to the CRO's website for instructional videos on registering a patient. Study-specific training will also be provided prior to study activation.

4.2.4 The QAM will review the registration, register the patient, assign an identification number, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

4.3 Beginning Study Treatment

Once eligibility is confirmed, the patient will be registered to the study and a subject I.D. number will be assigned by the QAM. An email will be sent to confirm approval of the Eligibility eCRF. Registration will then be complete and patient may begin study treatment.

5 TREATMENT PLAN

5.1 Treatment Administration

Patients will receive bevacizumab at a dose of 10 mg/kg IV every 2 weeks per local institutional guidelines. One cycle of treatment will be defined as 28 days (or approximately 4 weeks). Treatment will continue until CNS disease progression or death from systemic disease. The dose will remain stable unless there is a > 10% increase in weight from baseline. The initial dose will be delivered over a period of 90 +/-15 minutes.

If the first infusion is tolerated without infusion-associated adverse events (fevers or chills), the second infusion may be delivered over a period of 60 +/-10 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be delivered over a period of 30 +/-10 minutes. The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms. 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.

If a subject experiences an infusion-associated adverse event, he or she may be pre-medicated for the next study drug infusion per treating investigator's discretion; however, the infusion time may not be decreased for the subsequent infusion. If done, pre-medication should be according to local institutional practice for infusions. 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 pre-medicated. 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.

Prior to administration of bevacizumab, all patients with have their urine dipped for protein. If a result of 2+ is seen, urine will be sent for random urine and protein for a UPC ratio. If the UPC is >1.0, a 24 hour urine protein will be required to confirm the result is < 1 g protein. Patients must also have a blood pressure of ≤ 160/90 in order to receive treatment.

5.2 Dose Modifications & Toxicity Management

5.2.1 Dose Delays/Interruptions

There will be no reductions to the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1 below. Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 4 weeks; the only exception to this is for a surgical procedure in a patient who is benefiting from treatment.

5.2.2 Toxicity Management Guidelines

Any toxicity associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice and should be based on the NCI's Common Toxicity Criteria for Adverse Events version 4.0 (CTCAE v. 4.0). 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.

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, treatment with bevacizumab should be discontinued.

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

All AEs – including all out of range laboratory values – should be recorded as on the appropriate eCRF as outlined in Section 10. Abnormal laboratory tests and other objective measures that meet the criteria for an SAE or result in discontinuation of the trial drug should be reported as outlined in Section 10. All patients who have grade 3 or 4 laboratory values at the time of withdrawal must be followed up until the lab values have returned to grade 1 or 2 or until 30 days after the date of withdrawal (whichever comes first), unless these values are not likely to improve because of the underlying disease.

Table1: Bevacizumab Dose Management Due to Adverse Events	
Hypertension	
Grade/Event	**Action to be Taken**
Grade 1 or 2	None
Grade 3	If not controlled to ≤ 150/100 mmHg with medication, discontinue bevacizumab.
Grade 4 (including hypertensive encephalopathy)	Discontinue bevacizumab.
Hemorrhage	
Grade/Event	**Action to be Taken**
Grade 1 or 2 non-pulmonary & non-CNS events	None
Grade 3 non-pulmonary & non-CNS events	Subjects who are also receiving full-dose anticoagulation will be discontinued from 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 events	Discontinue bevacuzimab.
Grade 1 pulmonary event	Subjects who are also receiving full-dose anticoagulation will be discontinued from 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 pulmonary event	Discontinue bevacizumab.
Any Grade CNS bleeding	Discontinue bevacizumab.
Venous Thrombosis	
Grade/Event	**Action to be Taken**
Grade 1 or 2	None
Grade 3 (1st occurrence)	Hold bevacizumab. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin. • LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment. • The subject must not have had a grade 3 or 4 hemorrhagic event while on anticoagulation.
Grade 3 (recurrent) or Grade 4 (any occurrence)	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	
Grade/Event	**Action to be Taken**
Grade 1 or 2	None
Grade ≥ 3	Discontinue bevacizumab.
Proteinuria	
Grade/Event	**Action to be Taken**
Grade 1	None
Grade 2	Hold bevacizumab for ≥ 2 g/24hrs, and resume when proteinuria is < 2 g/24hrs. For 2+ dipstick: may administer bevacizumab and obtain 24 hr urine prior to next dose. For 3+ dipstick: obtain 24 hr urine prior to bevacizumab administration.
Grade 3	Hold bevacizumab treatment until proteinuria is < 2 g/24hrs, as measured by 24 hr urine collection.
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab.

GI Perforation	
Any grade	Discontinue bevacizumab.
Fistula	
Grade/Event	**Action to be Taken**
TE fistula – any grade	Discontinue bevacizumab.
Grade 4 fistula	Discontinue bevacizumab.
Bowel Obstruction	
Grade/Event	**Action to be Taken**
Grade 1	Continue patient on bevacizumab for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade ≥ 3	Hold bevacizumab for complete obstruction. If surgery is necessary, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Wound Dehiscence	
Any grade (requiring medical or surgical therapy)	Discontinue bevacizumab.
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab.
Hematologic	
Grade 4 febrile neutropenia and/or Grade 4 thrombocytopenia (regardless of attribution)	Hold bevacizumab until recovery to ≤ grade 1 or baseline.
Hypersensitivity/Allergic Reactions	
Any grade (related to bevacizumab)	Discontinue bevacizumab.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade/Event	**Action to be Taken**
Grade 1 or 2	None
Grade 3	Hold bevacizumab until recovery to ≤ grade 1.
Grade 4	Discontinue bevacizumab.

5.3 Supportive Care Guidelines

Supportive care includes any prescription medications, transfusions, or over-the-counter preparations used by a patient. All supportive care therapies must be recorded on the appropriate eCRF. Throughout the study, investigators may prescribe any concomitant medication or treatment deemed necessary to provide adequate supportive care, except for those listed below in 5.3.2.

5.3.1 Permitted Supportive Care & Concomitant Therapies

- Preventative measures such as prophylactic cytokine are permitted.
- Transfusion of blood products and hematopoietic growth factors are allowed per local institutional guidelines.
- Febrile neutropenia may be managed according to local institutional Infectious Disease guidelines. Measures may include appropriate laboratory testing (such as blood and urine cultures) and the institution of broad-spectrum antibiotics. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.
- The use of antiemetics will be left to the treating investigators' discretion.
- Therapies considered necessary for the well-being of the patient may be given at the discretion of the investigator, such as analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems.
- Non-protocol systemic anti-cancer therapies may be started if needed due to progressive systemic disease as long as patients have stable or improved metastatic brain metastases.

5.3.2 Concomitant Therapies Not Permitted

Patients should not schedule any elective surgeries (excluding placement of vascular access device) during the study treatment period or until 28 days after their last administration of study treatment. If a patient undergoes any unexpected surgery during the course of the study, the patient must discontinue all study treatment immediately, and the PI should be notified as soon as possible. A patient may be allowed to resume study treatment after the surgical case is reviewed by the PI and study team to determine the appropriateness of resuming study treatment.

5.4 Duration of Therapy

Patients will remain on treatment as long as there is no evidence of disease progression or development of unacceptable toxicity. In addition, the patient and/or treating investigator may choose to discontinue treatment if it is felt to be in the best interest of the patient or if the patient is no longer able to comply with study requirements.

5.5 Duration of Follow Up

Follow-up for survival and documentation of subsequent anti-cancer treatments will occur at the time of routine clinic visits which occur approximately every 8-12 weeks. Survival follow-up will continue until disease progression or death.

Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.

6 ENDPOINT ASSESSMENT

Response will be assessed based on RANO Criteria[35]: For patients with residual tumor post-operatively or measurable tumor after failing a prior therapy.

6.1 Response Criteria

Criterion	CR	PR	SD	PD#
T1 gadolinium enhancing disease	None	≥ 50% 2 ↓	< 50% ↓ but < 25% ↑	≥25%↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	NA**
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for Response	All	All	All	Any*

* Progression occurs when this criterion is present.

**Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

NB: Note up to 5 largest lesions will be measured, the remaining will be evaluable.

6.2 Definitions

6.2.1 Measurable disease
At least 1 unidimensionally measurable lesion ≥ 5 mm with clearly defined margins by CT or MRI scan.

6.2.2 Evaluable disease
Unidimensionally measurable lesions, masses with margins not clearly defined.

6.2.3 Non-evaluable disease
Not applicable for response evaluation.

6.2.4 Objective status (to be recorded at each evaluation)
If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

6.2.5 Complete response (CR)
Requires ALL of the following:

6.2.5.1 Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks

6.2.5.2 No new lesions

6.2.5.3 Stable or improved nonenhancing (T2/FLAIR) lesions

6.2.5.4 Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically.

Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.

6.2.6 Partial response (PR)
Requires ALL of the following:

- A 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
- No progression of nonmeasurable disease and no new lesions.
- Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan and stable or improved clinically.

Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.

6.2.7 Stable disease (SD)
Requires ALL of the following:

- Does not qualify for CR, PR, or PD.
- Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.

  In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

6.2.8 Progressive disease (PD)
Defined by ANY of the following:

- A 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with baseline, on stable or increasing doses of corticosteroids
- Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).
- Any new lesion(s).
- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc) or changes in corticosteroid dose.
- Failure to return for evaluation as a result of death or deteriorating condition.
- Clear progression of nonmeasurable disease.

6.2.9 Unknown
Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

6.2.10 Best response

This will be calculated from the sequence of objective statuses. For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to the definitions above. If the response does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained (is still present on the subsequent MRI), it will be recorded as a sustained response, lasting until the time of tumor progression. Best response is unknown if the patient does not qualify for a best response or increasing disease and if all objective status determinations before progression are unknown.

6.3 Assessment of Secondary Endpoints

6.3.1 Progression-free survival (PFS)

PFS will be defined as the time from the first study treatment to the first occurrence of progression or death up to 6 months.

6.3.2 Time to progression

Time to progression will be defined as the time from the date of first treatment to the date of first observation of progressive disease, non-reversible neurologic progression or increasing steroid requirements (applies to SD only), death due to any cause, or early discontinuation of treatment. This will be assessed based on MRI or CT scans.

6.3.3 Duration of response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.3.4 Overall survival (OS)

Overall survival will be calculated from date of first dose of bevacizumab to the date of death.

Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.

6.3.5 Evaluation of toxicity/safety data

All patients will be evaluable for toxicity from the time of their first treatment with bevacizumab. Adverse events will be assessed prior to the start of every cycle.

7 STUDY PARAMETERS

Assessment or Procedure	Screening	Treatment [10]					Treatment Discontinuation
	Baseline [8]	Cycle 1		Subsequent cycles		Prior to every odd cycle	
		D1 [12]	D15 [12]	D1 [12]	D15 [12]		
Informed consent	X						
Review of eligibility	X						
Medical history	X			X			
Physical examination [1]	X			X			X
Vital signs [2]	X	X	X	X	X		X
12-lead ECG [3]	X						
Karnofsky performance score	X			X			X
Intra-cranial tumor assessment (Gd-MRI or CT) [4]	X					X	X
CT C/A/P [9]	X					X	
FACT-Br [11]	X					X	
CBC and platelets	X			X			
Complete chemistry panel	X			X			
Urinalysis or dipstick [13]	X	X	X	X	X		
Pregnancy test [5]	X						
PT, INR and aPTT [14]	X						
Review of concomitant medications		X	X	X	X		X
Adverse events		X	X	X	X		X
Study treatment				Bevacizumab administration [6, 12]			
Follow-up [7]							X

1. Physical exam including neurologic exam. Baseline exam should include height and weight; height does not need to be re-recorded at subsequent exams.
2. Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Blood pressure should be ≤ 160/90 on the day of treatment in order to receive the next bevacizumab dose.
3. ECG is *required* only at screening and then as clinically indicated thereafter.
4. Ideally Gd-MRI of brain or CT if MRI contra-indicated.
5. Urine or serum pregnancy test for female patients of child-bearing potential.
6. Patients will receive bevacizumab at a dose of 10 mg/kg IV every 2 weeks per local institutional guidelines (1 cycle = 28 days). Treatment will continue until CNS disease progression or death from systemic disease.
7. Follow-up for survival and documentation of subsequent anti-cancer treatments. Patients will be seen at the time of routine clinic visits which occur approximately every 8-12 weeks. Survival follow-up will continue until disease progression or death. **Note: As of December 31, 2018, patients will no longer be followed and follow up information will not be collected.**
8. Baseline assessments should be completed within 14 days prior to registration unless otherwise noted.
9. Baseline CT of chest/abdomen/pelvis should be within 28 days prior to registration.
10. One cycle of treatment = 28 days (or approximately 4 weeks).
11. The FACT-Br will be administered to patients prior to every odd-numbered cycles ***before*** the scheduled MRI/CT is performed
12. A window of ±3 days is allowed for completion of tests, assessments, and treatment.
13. If urine dipstick shows > 2+ protein, results of UPC and CBC must be obtained prior to receiving the next bevacizumab dose.
14. PT/INR and aPTT should be repeated as clinical indicated thereafter.

8 DRUG FORMULATION AND PROCUREMENT

8.1 Bevacizumab

8.1.1 Other names

Avastin®, rhuMAb VEGF, RO4876646

8.1.2 Classification/type of agent

Bevacizumab is a vascular endothelial growth factor-specific angiogenesis inhibitor. The structure consists of human IgG1 framework regions and antigen-binding complementary-determining regions from a murine monoclonal antibody

8.1.3 Mode of action

Bevacizumab is a recombinant humanized immunoglobulin G (IgG1) monoclonal antibody that binds VEGF, a secreted factor that regulates angiogenesis. Bevacizumab prevents the interaction of VEGF with its receptors and neutralizes the biological activity of VEGF. Many human tumors have been shown to have increased VEGF gene expression, when compared to normal surrounding tissues. Bevacizumab has been shown to inhibit *in vivo* growth of a variety of human tumors, providing proof of preclinical efficacy and the role of VEGF in oncogenesis. For further details and molecule characterization, please refer to the bevacizumab Investigator Brochure.

8.1.4 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.

8.1.5 Dose specifics

Patients will receive bevacizumab at a dose of 10 mg/kg every 2 weeks (1 cycle = 28 days/4 weeks). It is not necessary to correct dosing based on ideal weight.

8.1.6 Preparation

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 and 16 mL of 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. Bevacizumab should be diluted in a total volume of 100 mL of 0.9 Sodium Chloride Injection, USP.

8.1.7 Protocol administration

Administration will be as continuous IV infusion per local institutional practice. Anaphylaxis precautions should be observed during study drug administration. Please refer to Section 5.1 for further details.

8.1.8 Incompatibilities

Bevacizumab is incompatible with dextrose and should not be administered or mixed with dextrose solutions.

8.1.9 Availability

Bevacizumab will be provided to patients by the study sponsor, Northwestern University, with support from Genentech. The contact information for bevacizumab supply is as follows:
Avastin IST Clinical Trials Associate
650-225-5250 (fax)
avastinistdrug-d@gene.com

Drug will be shipped from Genentech directly to each study site.

8.1.10 Side effects

Major side effects reported include: hypertension, proteinuria (ranging from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome), thromboembolic events-venous and arterial thromboembolic (TE) events (ranging in severity from catheter-associated phlebitis to fatal), gastrointestinal perforation, wound-healing complications, hemorrhage, and congestive heart failure. For additional information regarding adverse events and the safety experience with bevacizumab, please refer to the bevacizumab Investigator Brochure. The frequency of bevacizumab-related side effects is summarized below.

Likely (occurring in more than 20% of patients)

hypertension	anorexia	dysgeusia
generalized pain	constipation	weakness
headache	diarrhea	proteinuria (possible kidney damage
dizziness	stomatitis	respiratory infection
alopecia	GI bleeding	epistaxis
abdominal pain	dyspepsia	dyspnea
vomiting		neutropenia & subsequent infection (including pneumonia)

Common (occurring in 3-20% of patients)

hypotension	hypokalemia	dehydration
fatigue (possible weakness)	hyponatremia	urinary urgency/frequency
nerve damage (possible numbness, tingling, and/or burning)	flatus	vaginal bleeding
confusion (possible headache, confusion, seizures, and/or coma)	weight loss	fever/infection/neutropenia
abnormal gait	nausea	hemorrhage
dry skin	dry mouth	hyperbilirubinemia
desquamation	gastritis	muscle and/or bone pain
skin discoloration	decreased intestinal function (possible vomiting, swelling,	hyperlacrimation

	and/or pain)	
nail disorder	tumor hemorrhage	dysphonia
syncope	tumor pain	pleuritis
chills	shivering	build-up in the lung tissues
palpitations	bradycardia	infusion reactions
leukemia	hematuria	anemia

Bevacizumab may commonly cause thrombosis to the brain, heart, lungs, or other organs, which may cause stroke and/or myocardial infarction.

Bevacizumab may commonly cause perforation to the stomach, small intestine or large intestine, which can cause leakage of the contents of these organs and lead to infection.

Rare but serious (occurring in fewer than 3% of patients)

heart failure	peritoneal abscess	pulmonary hemorrhage
myocardial infarction	intestinal necrosis	pulmonary hypertension
angina	intestinal obstruction	wound dehiscence
severe hypertension	portal vein obstruction	sudden, rapid loss of a skin graft or other grafted tissue
cerebral hemorrhage, causing stroke	eye infection	wound healing problems
subarachnoid hemorrhage	blurry vision	allergic reaction
bleeding gums	kidney damage	homonymous hemianopsia
liver damage	nasal fistula	confusion
alexia	hymoptysis	sudden decrease in blood supply to the brain resulting in decreased brain function
spinal compression fracture	pericardial and pleural effusion worsening	

Bevacizumab may rarely cause brain damage (encephalopathy), including reversible posterior leukoencephalopathy syndrome (RPLS), a medical condition related to leakiness of blood vessels in the brain, which can cause confusion, blindness or vision changes, seizure, changes in brain scans, and/or other symptoms. Leukoencephalopathy may occur up to 18 months after the last dose of study drug.

Bevacizumab may rarely cause fistulas between areas of the body which may result in death.

8.1.11 Other side effects

- Rarely (in about 1-2% of patients), bevacizumab may cause bleeding in the brain in patients who have received bevacizumab for the treatment of primary brain tumors.
- In most patients, blood pressure can be controlled with routine medications taken by mouth while bevacizumab is continued. However,

uncontrolled high blood pressure and high blood pressure resulting in disturbance of organ function may occur.

- Bevacizumab may also block VEGF. VEGF is important for the formation of new blood vessels at sites of low blood flow. Low blood flow exists in conditions such as coronary artery disease and cerebrovascular disease (abnormality of the brain resulting from blood vessel problems). Prolonged blockage of VEGF with bevacizumab could worsen any pre-existing heart or cerebrovascular disease.
- The impact of bevacizumab on future fertility is currently unknown. However, it is possible that treatment with bevacizumab may affect fertility and decrease the likelihood of becoming pregnant in the future.

9 STATISTICAL CONSIDERATIONS

9.1 Study Design

A Simon two-stage optimum phase II clinical trial design will be used in this study. If zero responses are observed in the first 9 patients, it could be concluded that the true response rate was 5% or less and no further patients would be enrolled. If one or more responses are observed in the first stage, a total of 24 evaluable patients would be required. If three or more responses are observed, there would be evidence that the regimen used was active (true response rate is at least 25%). The primary endpoint will be objective radiographic tumor response. Secondary endpoints include progression-free survival at 6 months, time to progression, time to response, duration of response, overall survival, and safety.

9.2 Sample Size & Power Calculations

A Simon two-stage optimal phase II clinical trial design will be used. If 0 responses are observed in the first 9 patients, it will be concluded that the true response rate was 5% or less and no further patients will be enrolled. If 1 or more responses are observed in the first 9 patients, 15 additional patients will be enrolled to a total of 24. If 3 or more responses are observed, there would be evidence that the regimen used was active (true response rate is at least 25%). This design will declare the regimen as active when the true response rate is 25% with 90% probability (power=.90) at the 1-sided 0.10 alpha level. To account for dropouts, we will plan for 27 patients total to have 24 evaluable patients.

9.3 Planned Analyses

The primary outcome, radiographic response rate, will be estimated using the Atkinson and Brown confidence limits (new reference). To estimate time to progression, progression-free survival and overall survival, Kaplan-Meier curves will be calculated. PFS6 will be determined from the progression-free survival curve. Time to response in responders will be estimated using a Kaplan-Meier curve. Duration of response in responders will be estimated as the time from response to progression, and will be summarized using descriptive statistics such as median and range. Safety data will be summarized using frequencies and percentages, and adverse events will be characterized by type, frequency, timing of occurrence and attribution. Changes in FACT-BR while on treatment will be analyzed using a longitudinal linear model that estimates the mean level at specific times, or a population averaged mean FACT-BR as a function of time.

10 ADVERSE EVENTS

This trial will be conducted in accordance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center (Lurie Cancer Center) of Northwestern University (see Appendices for link). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

10.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 7 and the study calendar for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

The study period during which all AEs and serious adverse events (SAEs) must be reported begins after informed consent is obtained and initiation of study treatment 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.

10.2 Definitions & Descriptions

10.2.1 Adverse Event

An AE is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests

are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

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 solid tumor brain metastases that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions.
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated interventions.
- 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.

10.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 available at http://ctep.cancer.gov/reporting/ctc.html.

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

10.2.3 Causality of AEs

Expected AEs are those adverse events that are listed or characterized in the current Investigator Brochure (IB). *Unexpected* AEs are those not listed in the current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the IB. For example, under this definition, hepatic necrosis would be unexpected if the IB only referred to elevated hepatic enzymes or hepatitis.

The relationship of an AE to the study drug(s) should be defined as unrelated, unlikely, possibly, probably, or definitely related.

10.2.3.1 Related

A causal relationship is clinically/biologically highly plausibly, there is a plausible time sequence between onset of the AE and administration of the study drug, there is a reasonable response on withdrawal, the AE cannot be reasonably explained by any other known factor and the event re-appears upon rechallenge.

10.2.3.2 Probable

A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the study drug and there is a reasonable response on withdrawal.

10.2.3.3 Possible

A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the study drug.

10.2.3.4 Unlikely

A causal relationship is improbable and another documented cause of the AE is most plausible.

10.2.3.5 Unrelated

A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

10.2.4 Serious Adverse Event (SAE)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is any untoward medical occurrence that at any dose results in one of the following outcomes:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

10.2.5 Exceptions to AE & SAE Definitions

Generally speaking, any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, as described above. Likewise, any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. However, for the purposes of

this study, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

- Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization is required for study-directed therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.
- Hospitalization or prolonged hospitalization is due to social reasons (i.e. awaiting transport home).

10.2.6 Unanticipated Problems Involving Risk to Subject or Others (UPIRSO)

In order for an adverse event to be reported to the Northwestern University IRB, it must qualify as a UPIRSO. In order to qualify as a UPIRSO, the event must meet ALL three of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

10.3 Procedures for Eliciting & Recording AEs

10.3.1 Eliciting AEs

A consistent methodology for eliciting AEs at all subject evaluation timepoints 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?"

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 appropriately. 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 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 bevacizumab or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the AE has an etiology other than 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).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure (IB).

Unexpected adverse events are those not listed in the package insert or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the package insert or IB For example, under this definition, hepatic necrosis would be unexpected if the package insert or IB only referred to elevated hepatic enzymes or hepatitis.

10.3.2 Recording AEs
Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

10.3.2.1 Diagnosis vs. Signs & 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.

10.3.2.2Deaths
All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties (see 10.4). 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.”

10.3.2.3Preexisting 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”).

10.3.2.4Hospitalizations 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. Please refer to Section 10.2.5 for certain exceptions under which hospitalization or prolongation of hospitalization does not require reporting.

10.3.2.5Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the appropriate parties, including Genentech, Inc. 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 bevacizumab should be reported as an SAE.

10.3.2.6Post-Study AEs

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.

10.3.2.7Reconciliation

The study Sponsor (Northwestern University) 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. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

10.3.2.8AEs of Special Interest (AESIs)

AE*SI*s are defined as a potential safety problem, identified as a result of safety monitoring of the product. The *bevacizumab (*Avastin*)* AESIs are:

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Haemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 haemoptysis
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (any grade)
- CHF ≥ grade 3

- Non-GI fistula or abscess ≥ grade 2

10.3.2.9 Other Non-serious AESIs

Required to be reported no more than 24 hours after learning of the event:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice
- Suspected transmission of an infectious agent by the study drug

10.4 Adverse Event Reporting

All SAEs and AESIs, regardless of attribution, occurring during the study or within 30 days of the last administration of bevacizumab must be reported upon discovery or occurrence. Additional expedited or routine reporting to other entities may be required, depending on the nature of the SAE.

The NU CRO SAE Form is the preferred format for reporting.

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 form:

- Protocol description (and number)
- The patient's identification number
- Description of the 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
- The hospital discharge summary (if available/applicable)

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

- Adding to the original NU CRO SAE Form and submitting it as follow-up.
- Adding supplemental summary information and submitting it as follow-up with the original NU CRO SAE Form.
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. DOB, initial, patient number), protocol description and number, brief AE description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report).

10.4.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

10.4.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
    - Definite: AE is clearly related to the study treatment.
    - Probable: AE is likely related to the study treatment.
    - Possible: AE may be related to the study treatment.
    - Unlikely: AE not likely to be related to the study treatment.
    - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
    - the current protocol
    - the drug package insert
    - the current Investigator's Brochure

10.4.3 Expedited Reporting of SAEs/Other Events

10.4.3.1 Reporting to the Northwestern University QAM/DMC
All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

10.4.3.2 Reporting to the Northwestern University IRB
The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any <u>death of an NU subject</u> that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB <u>within 24 hours of notification</u>.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)

- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

10.4.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening. Such reports should also be faxed to Genentech within 7 calendar days of first learning of the event.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be faxed to Genentech Drug Safety:

Fax: (650) 238-6067

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).

10.4.3.4 Reporting to Genentech

Investigators must report all SAEs to Genentech within the timelines described below. The completed NU CRO SAE Form should be faxed or emailed immediately upon completion to Genentech Drug Safety at:

Fax: (650) 238-6067
Email: us_drug.safety@gene.com

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

SAEs, pregnancy reports and AEs of special interest (AESIs), where the patient has been exposed to bevacizumab, will be sent on a the NU CRO SAE Form to the fax/email listed above. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- Serious AE reports that are related to bevacizumab shall be transmitted to Roche within fifteen (15) calendar days of the awareness date.
- Serious AE reports that are unrelated to the Product shall be transmitted to Roche within thirty (30) calendar days of the awareness date.
- Pregnancy reports: While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy, where the fetus may have been exposed to the Product, shall be transmitted to Roche within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.
- AESIs requiring expedited reporting shall be forwarded to Roche within fifteen (15) calendar days of the awareness date. Others shall be sent within thirty (30) calendar days.

All non-serious AEs originating from the study will be forwarded in a quarterly report to Roche.

Special situation reports
In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected and transmitted to Roche even in the absence of an Adverse Event within 30 calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Data related to a suspected transmission of an infectious agent via a medicinal product (STIAMP)
- Lack of therapeutic efficacy

In addition, reasonable attempts should made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

10.4.3.4 Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies

of such reports should be mailed to the assigned Clinical Operations contact for the study:

Avastin (bevacizumab) Protocols
avastin-gsur@gene.com
650-745-0978 (fax)

11 DATA COLLECTION & SUBMISSION

Study-specific instructions regarding the entry and submission of data using eCRFs through NOTIS will be provided at the time of training prior to study activation. In addition, instructional videos on data entry using NOTIS and eCRFs are available on the CRO's website at: https://www.cancertrials.northwestern.edu/working-with-the-cro. The Internal and Affiliate Data Compliance Policies of the Lurie Cancer Center's DMC regarding will be strictly enforced.

11.1 Study Chart

In addition to the regular hospital chart, a separate patient folder will be kept which includes:

- The patient's signed, dated informed consent document.
- A pathology report confirming study disease.

11.2 Patient Registration (please refer to Section 4.0)

Please refer to Section 4.0 for more extensive instructions. BEFORE a patient can be treated on study, please complete and submit the following items through NOTIS to confirm patient eligibility and receive a subject registration number:

- Eligibility eCRF.
- Signed and dated informed consent document.
- Pathology Report or other documentation of disease as required by the protocol.

11.3 Data Submission Guidelines

Once a subject is confirmed and enrolled to the study, eCRFs should be submitted to the QAM through NOTIS according to the detailed data submission guidelines (provided in a separate document in NOTIS). Specific timeframes will be defined according to the study parameters table (Section 7.0), but in general, on-study data should be submitted no later than 5 business days after the date of subject registration. Generally, for all phase II patients, data are due at the end of each cycle. Accrual on a trial may be suspended if data is not submitted within 90 days after the data's due date (as it is defined by the protocol).

12 PATHOLOGY REQUIREMENTS

All patients who were not operated on at Northwestern Memorial Hospital or Columbia University or Northwestern Medicine Cancer Center/Cadence Health Cancer Center will be asked to submit their pathology for review at whichever site they intend to enroll. One to two representative H&E stained slides from a pre-registration biopsy-demonstrating lesion along with a copy of the pathology report will be requested for this review. *NOTE: A copy of the pathology report is sufficient for registration purposes.*

13 ADMINISTRATIVE, ETHICAL & REGULATORY CONSIDERATIONS

13.1 Conduct

This study will be conducted in accordance with the Declaration of Helsinki, Good Clinical Practices (GCP) guidelines. and all applicable government regulations and Institutional research policies and procedures. The Principal Investigator or qualified designees are responsible for reporting all amendments, safety updates, and protocol violations. This study will be monitored in accordance with the Data Safety Monitoring Plan of the Lurie Cancer Center of Northwestern University and will abide by its policies and practices.

13.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendment s will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

13.3 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

The investigator is responsible for ensuring that no patient participates in any study-related examination or activity before that patient has given informed consent. The informed consent will be provided both through the written informed consent document and through verbal review of all information contained therein. Information provided in this way is to include potential benefits, aims of the study, potential harms or side effects and methods of the study. The patient will be given opportunity to ask questions about any aspect of the information and will be given time to review the information on their own. The patient may, after having been provided with this detailed written and verbal information, provide written consent. The patient will then be provided a copy of the executed informed consent for their reference. The patient is free to withdraw consent at any time and for any reason. The only consequence of consent withdrawal is that the patient is no longer able to participate in the study.

13.4 Protected Health Information (PHI)

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study. This authorization may be combined with the informed consent form in accordance with local institutional practice.

13.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.

- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

13.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. The level of risk attributed to this study requires High Risk Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to NOTIS for additional data submission instructions.

13.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

13.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.

- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

13.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

13.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

REFERENCES

1. Alexandru DBD, Linskey ME. Epidemiology of Central Nervous System metastases. Prog Neurol Surg 2012;25 13-29.
2. Antonadou D PG, Coliarokis I, et al. Phase II radomized trial of temozolamide and concurrent radiotherapy in patients with brain metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2002;20:3644-3650.
3. Biswas G BR, Khurana R et al. Brain Metastases-Evidence Based Management. J Can Res Ther 2006;2:5-13.
4. Ferrarase V BP, Zorat L, Fiore D. Treatment and Prophylaxis for Brain Metastases from small cell lung cancer: whole brain treatment versus stereotactic radiosurgery. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2006;17:ii71-ii72.
5. Glantz MJ CB, Recht L, Akerley W, Mills P, Saris S, Hochberg F, Calabresi P, Egorin MJ. High dose Intravenous Methotrexate for patients with nonleukemic leptomeningeal cancer:is intrathecal chemotherapy necessary? JClin Oncol 1998;16:1561-1567.
6. Khuntia D BP, Li J, Mehta M Whole Brain Radiotherapy in the Management of Brain Metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24 1295-1304.
7. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2012;30:419-425.
8. Lassman A AL, Begemann M, Picconi K, Vuksanaj K, Malkin M, Raizer J. Systemic High Dose Methotrexate (HD MTX) for central nervous system (CNS) metastases Proceedings ASCO 2002 2002;Abstract 2083.
9. Patchell R. The Management of Brain Metastases. Cancer Treatment Reviews 2003;29:533-540.
10. Lassman AB, Abrey LE, Shah GD, et al. Systemic high-dose intravenous methotrexate for central nervous system metastases. Journal of neuro-oncology 2006;78:255-260.
11. Abrey LE, Christodoulou C. Temozolomide for treating brain metastases. Seminars in oncology 2001;28:34-42.
12. Christodoulou C, Bafaloukos D, Kosmidis P, et al. Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2001;12:249-254.
13. Abrey LE, Olson JD, Raizer JJ, et al. A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. Journal of neuro-oncology 2001;53:259-265.
14. Lin NU, Eierman W, Greil R, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. Journal of neuro-oncology 2011;105:613-620.
15. Oberhoff C, Kieback DG, Wurstlein R, et al. Topotecan chemotherapy in patients with breast cancer and brain metastases: results of a pilot study. Onkologie 2001;24:256-260.
16. Lorusso V, Galetta D, Giotta F, et al. Topotecan in the treatment of brain metastases. A phase II study of GOIM (Gruppo Oncologico dell'Italia Meridionale). Anticancer research 2006;26:2259-2263.
17. Tsimberidou AM, Letourneau K, Wen S, et al. Phase I clinical trial outcomes in 93 patients with brain metastases: the MD anderson cancer center experience. Clinical cancer

research : an official journal of the American Association for Cancer Research 2011;17:4110-4118.
18. Cohen MH SY, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastomamultiforme. Oncologist 2009;14:1131-1138.
19. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2009;27:4733-4740.
20. Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. The New England journal of medicine 2006;354:980-982; discussion 980-982.
21. Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. The New England journal of medicine 2006;354:980-982; discussion 980-982.
22. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:5180-5186.
23. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. Journal of surgical oncology 2005;91:173-180.
24. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:792-799.
25. Karp JE, Gojo I, Pili R, et al. Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. Clinical cancer research : an official journal of the American Association for Cancer Research 2004;10:3577-3585.
26. Wedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:769-777.
27. Sanborn RE, Sandler AB. The safety of bevacizumab. Expert opinion on drug safety 2006;5:289-301.
28. Sadikov E BA, Yi QL, Wells W, Dawson L, Millar BA, Laperriere N. Value of Whole Brain Re-irradiation for Brain Metastases-single center experience. Clin Oncol (R Coll Radiol) 2007;19:532-538.
29. Wong WW SS, Sawyer TE, Shaw EG. Analysis of Outcome in Patients reirradiated for Brain Metastases. Int J Radiat Oncol Biol Phys 1996;34:585-590.
30. Abrey LE OJ, Raizer JJ, Mack M, Rodavitch A, Boutros DY, Malkin MG. A phase II trial of temozolomide for patients with recurrent or progressive brain metastases. J Neurooncol 2001;53:259-265.
31. Iwamoto FM OA, Raizer JJ, Nolan CP, Hormigo A, Lassman AB, Gavrilovic IT, Abrey LE. A phase II trial of vinorelbine and intensive temozolomide for patients with recurrent or progressive brain metastases. J Neurooncol 2008;81:85-90.
32. Nghiemphu PL GR, Pope WB, Lai A, Cloughesy TF. Safety of anticoagulation use and bevacizumab in patients with glioma. Neuro Oncol 2008;10:355-360.
33. Besse B LS, Compton P, Huang J, Augustus S, Rohr U. Bevacizumab safety in patients with central nervous system metastases. Clin Caner Res 2010;16:269-278.

34. De Braganca KC JY, Azzoli CG, Kris MG, Pietanza MC, Nolan CP, Omuro AM, Holodny AI, Lassman AB. Efficacy and safety of bevacizumab in active brain metastases from non-small cell lung cancer. J Neurooncol 2010;100:443-447.
35. Quant EC WP. Response Assessment in Neuro-Oncology. Curr Oncol Rep 2011;13:50-56.Atkinson EN & Brown BW. Confidence limits for probability of response in multistage Phase II clinical trials. Biometrics 1985;41:741-744.

14 APPENDIX

14.1 Appendix I – Karnofsky Performance Status and Neurological Function

Patient's performance status and Neurologic Functions will be graded according to the following scales:

Karnofsky Performance Status

KPS 100	Normal; no complaints; no evidence of disease
KPS 90	Able to carry on normal activity; minor signs or symptoms of disease
KPS 80	Normal activity with effort; some sign or symptoms of disease
KPS 70	Cares for self; unable to carry on normal activity or do active work
KPS 60	Requires occasional assistance, but is able to care for most personal needs
KPS 50	Requires considerable assistance and frequent medical care
KPS 40	Disabled; requires special care and assistance
KPS 30	Severely disabled; hospitalization is indicated, although death no imminent
KPS 20	Very sick; hospitalization necessary; active support treatment is necessary
KPS 10	Moribund; fatal processes progressing rapidly
KPS 0	Dead

14.2 Appendix II – New York Heart Association (NYHA) Guidelines

The Stages of Heart Failure – NYHA Classification

In order to determine the best course of of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

14.3 Appendix III – Procedures for Obtaining a Urine Protein

1) Obtain at least 4 ml of a random urine sample (does not have to be a 24 hour urine)
2) Determine protein concentration (mg/dL)
3) Determine creatinine concentration (mg/dL)
4) Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / creatinine concentration (mg /dL)

The UPC directly correlates with the amount of protein excreted in the urine per 24 hrs (i.e. a UPC of 1 should be equivalent to 1g protein in a 24hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

14.4 Appendix IV – SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET
Genentech Supported Research

FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

14.5 Appendix V – Protocol History of Changes

Initial Version Approved by Scientific Review Committee – January 10, 2013			
Updated Version Prior to IRB Submission – April 30, 2013 *Approved by Scientific Review Committee: April 30, 2013*			
Section(s) Affected	***Prior Version***	***Updates***	***Rationale***
Title Page	n/a	Adds NU Sub-Investigators: Kristin Swanson, PhD Carly Bridge, ND	Administrative
Title Page	IND status listed as "TBD".	Updates IND status to "Exemption # 117883	Administrative updated based on receipt of FDA exemption notification.
Synopsis, 9.0 (Statistical Considerations).	n/a	Revises wording of the sample size and power calculation (does not change actual numbers).	Clarifications requested by Genetech.
Appendices	n/a	Adds Appendix V – Protocol History of Changes	Administrative
Updated Version During Initial IRB Review – May 23, 2013 *Approved by Scientific Review Committee – May 23, 2013*			
Section(s) Affected	***Prior Version***	***Updates***	***Rationale***
Synopsis, 9.0 (Statistical Considerations)	Accrual for the second stage of enrollment incorrectly listed as an additional **17** patients.	Corrects this to an additional **15** patients.	This corrects an error that was noted in the previous version. This change does not affect the overall (total) accrual for the study.
Updated Version #2 During Initial IRB Review – May 30, 2013 *Approved by Scientific Review Committee – June 5, 2013*			
Section(s) Affected	***Prior Version***	***Updates***	***Rationale***
Throughout	n/a	Correction of minor grammatical and/or typographical errors.	Administration
Section 1.2.2.8 (Reversible Posterior	n/a	Adds that adequate brain imaging with MRI should	Added for clarity.

Leukoencephalopathy Syndrome)		be performed for any patients developing RPLS.	
Section 3.2 (Exclusion Criteria)	n/a	Adds language clarifying the eligibility of patients with brain tumors who have had a recent craniotomy or cranial biopsy, as well as patients who have had placement of a vascular access device prior to registration.	Added for clarity.
Section 5.2.2 – Table 1 (Bevacizumab Dose Management Due to Adverse Events)	1. Allowed treatment to be held for Grade 1 CNS bleed & then restarted under certain conditions. 2. n/a 3. Allowed treatment to be held for Grade 4 thrombosis & then restarted under certain conditions. 4. Allowed treatment to be held for Grade 3 congestive heart failure & then restarted under certain conditions. 5. n/a	1. Changed to "Discontinue bevacizumab" for any grade CNS bleed. 2. Adds that for *recurrent* Grade 3 thrombosis, bevacizumab should be discontinued. 3. Changed to "Discontinue bevacizumab" for any Grade 4 thrombosis. 4. Changed to "Discontinue bevacizumab" for any ≥ Grade 3 CHF. 5. Adds instructions for grade 4 febrile neutropenia and/or grade 4 thrombocytopenia (regardless of relationship to bevacizumab); adds	All changes made at the request of the drug supplier (Genentech).

		instructions for hypersensitivity/allergic reactions.	
Section 7.0 (Study Parameters)	1. Medical history to be performed at treatment discontinuation. 2. Chemistry panel only performed at baseline. 3. Adverse events assessment & review concomitant medications only done on day 1 of each cycle. 4. n/a	1. Removes this test (not necessary). 2. Adds a chemistry panel to every cycle (day 1). 3. Adds AE assessment and conmeds review to day 15 of every cycle. 4. Adds a footnote stating that PT/PTT should be repeated after baseline only as clinically indicated.	Safety – all changes made at the request of the drug supplier (Genentech).
Section 10.3.2 (Recording AEs)	n/a	Adds a section on non-serious adverse events of special interest (AESIs) that should be reported to Genentech within stated timeframes.	Change made at the request of the drug supplier (Genentech).
Amendment 1 – April 3, 2014 *Approved by Scientific Review Committee – May 7, 2014*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover-page	Carly Bridge, ND listed as a sub-investigator.	Removes Dr. Bridge as a sub-investigator.	Administrative – she is no longer at NU.
3.1 (Inclusion Criteria), 6.2 (Definitions)	Defined measureable disease as being ≥ 1 cm (10 mm).	Changes the definition of measurable disease to ≥ 5 mm.	The previous requirement was too restrictive for the population being studied.
5.2.2 (Toxicity Management Guidelines)	Previously stated that only certain out-of-range lab	Clarifies that ALL out-of-range lab values must be reported (along with any	Updated to be consistent with what was

	values needed to be reported as AEs.	other AE) on the appropriate eCRF as outlined in Section 10 of the protocol.	required in Section 10.
Amendment 2 – April 15, 2015 *Approved by Scientific Review Committee – April 15, 2015*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
7.0 (Study Parameters)	Footnote 12: A window of +/- 3 days is allowed for completion of tests and assessments.	A window of +/- 3 days is allowed for completion of tests, assessments**, and treatment.**	Allows for a window of +/- 3 days for treatment
Amendment 3 – January 8, 2016			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Cover-page	NA	Added Northwestern Medicine Cancer Center, Warrenville, IL as a new participating site.	New participating has been added.
Synopsis	NA	Added Northwestern Medicine Cancer Center under study centers	To update the external site that has been added.
Section 3.0 Selection of Subjects	NA	Added Northwestern Medicine Cancer Center (Cadence Health Cancer Center) to the list of sites where patients will be recruited from.	To complete the list of participating sites.
Section 12.0 Pathology Requirements	NA	Added Northwestern Medicine Cancer Center (Cadence Health Cancer Center) to the list of sites.	To complete the list of participating sites.
Amendment 4 – March 17, 2017 Approved by Scientific Review Committee - 3/22/2017			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Title page	Statistician	Biostatistician	Aligns with new NU IIT template
	n/a	Study Intervention: Bevacizumab	Aligns with new NU IIT template
	n/a	Added Version Date	Aligns with new NU IIT template
Study Summary	Title “Synopsis”	Title: “Study Summary”	Aligns with new NU IIT template
Section 3.1.3 (Inclusion Criteria)	n/a	Clarified that lesion measurement must be	Per PI. For clarification,

		≥5mm **unidimensionally**	definition of measurable disease stated "bidimensional" lesion measurement ≥ 5mm, however this study is using modified RANO criteria that requires only unidimensional lesion measurement ≥5mm.
Section 3.1.12 Inclusion Criteria	List of organ and bone marrow function requirements for eligibility	Converted list of organ and bone marrow function requirements into a table	To adhere to NU protocol template
Section 4.0 (Patient Registration)	Listed QAM phone number (312-69-1355) and business hours	• Removes phone number and business hours Adds QAM email address	The QAM email provides faster access to QA as it is a group email. Business hours are not listed because QA email inbox is monitored outside of regular business hours.
Section 4.2 (Registering a Patient)	n/a	Adds additional instructions for registration procedures including using NOTIS to provide an eligibility checklist and eCRF	Aligns with new NU IIT Template
Section 5.5 Duration of Follow Up	n/a	Addition of description of duration of follow up	Clarification of length of time patients will be followed for survival.
Section 6.2.1 (Measurable Disease Definition)	"At least 1 **bidimensionally** measurable lesion ≥ 5 mm with clearly defined margins by CT	"At least 1 **unidimensionally** measurable lesion ≥ 5 mm with clearly defined margins by CT or MRI	Per PI. For clarification, definition of measurable disease stated

	or MRI scan."	scan."	"bidimensional" measurable lesion ≥ 5mm, however this study is using modified RANO criteria that requires only unidimensional measurable lesion ≥5mm.
Section 7.0 Study Parameters	• Footnote #5 – n/a Footnote #6: Follow up will occur approximately every 8 weeks.	• Footnote #5: length of cycle (1 cycle = 28 days) • Footnote #6: follow up will occur approximately every 8-12 weeks. Duration of follow up added	• Clarification of length of cycle • To extend the window of when patients schedule their follow up visits. Allow for fewer deviations. Clarification of duration of follow up
Section 10.0 (Adverse Event Monitoring and Reporting) Section 10.1 Adverse Event Monitoring	n/a	Adds a reference to safety reporting abiding by the Code of Federal Regulations	Administrative
	Description of AE monitoring	Clarifies monitoring of AEs with standard NU IIT template language	To adhere to NU IIT template
	n/a	Included AE language from the NU IIT template	To adhere to NU IIT template
Section 10.2.1 Adverse Event	n/a	Further define adverse event	To adhere to NU IIT template
Section 10.2.2 (Severity of AEs)	Stated that AE's should follow CTCAE v4.0	• Changes CTCAE version to 4.03 Adds language for general severity grading if no CTCAE grading is available	• Administrative Added for reference
Section 10.2.4 Serious Adverse Event	Description of SAEs	Further clarifies SAEs using language from the NU IIT Template	To adhere to NU IIT template

Section 10.2.6 Unanticipated Problems Involving Risk to Subject or Others (UPIRSO)	Description of UPIRSO	Further clarifies UPIRSOs using language from the NU IIT Template	To adhere to NU IIT template
10.3.1 Eliciting AEs	n/a	Addition of language from Genentech AE template regarding eliciting AEs from patients	Per Genentech, further explanation on eliciting AEs was necessary.
Section 10.4 (Reporting of SAEs),	• Referred to the MedWatch 3500A form for reporting SAE's • n/a • UPIRSO's had to be reported within 10 calendar days to the IRB Listed Reporting requirements to the FDA	• Deletes MedWatch 3500A and adds reference to the NU CRO SAE form. Also adds the patient identification number and discharge summary as required reporting information • Adds 10.4.2.2 - death of an NU patient on study treatment must be reported to the IRB • Changes UPIRSO reporting requirement to 5 days Removes language for FDA reporting requirements	• Administrative - the NU CRO SAE Form and added requirements align with CRO policies • Added to align with CRO policies • Changed to align with CRO policies • The study is IND-exempt and does not require FDA reporting
Section 10.4.3 Expedited Reporting of SAEs/Other Events Section 10.4.3.4 Reporting to Genentech	n/a	Addition of reporting instruction from NU IIT Template	To adhere to the NU IIT template
	Included inaccurate fax number for reporting SAE's to Genentech 650-225-5288 and no email	Updates contact information to include email address and new fax number: us_drug.safety@gene.com 650-238-6067	Administrative update from sponsor
	n/a	Addition of AE/SAE reporting instructions for Genentech	Per Genentech, added from the Genentech template
	n/a	Addition of "Special Situation Reports" instructions	Per Genentech, added from the Genentech template

Section 10.4.3.5 Study Close-Out	Directions for contacting Genentech for study close out	Updated language explaining study close-out communications with Genentech	Per Genentech, added from the Genentech template
Section 11.3 (Data Submission Guidelines)	Included Data Submission Guidelines in the protocol	Removes Data Submission Guidelines from the protocol. Refers to a separate document in NOTIS for data submission guidelines	Administrative – guidelines will no longer be included in NU protocols. In effect, changes to the guidelines will not require a protocol amendment
Section 13.3 (IRB Approval and Consent)	Listed requirements for patients to give consent prior to study participation	Adds the requirement for the consent to be IRB-approved and to follow GCP	Administrative – language added to align with CRO policies
Sections 13.5 (Instructions for Participating Sites), 13.6 (Data Management and Monitoring/Auditing) , 13.7 (Adherence to the Protocol), 13.8 (Investigator Obligations), 13.9 (Publication Policy)	n/a	Adds listed sections from the NU IIT template	Additional administrative language added to align with CRO policies
Amendment 5 – February 6, 2019 *Approved by Scientific Review Committee:*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
Study Summary; Section 5.5 (Duration of Follow-Up); Section 6.3.4 (Overall Survival); Section 7 (Study Parameters)	Patients followed until death	As of December 31, 2018, patients will no longer be followed and follow up information will not be collected	Study PIs are already working on publication and not going to collect any more data.
Section 6.2.8 (Progressive Disease)	• A 25% increase in sum of the products of perpendicular diameters of enhancing lesions **compared with the smallest tumor**	• A 25% increase in sum of the products of perpendicular diameters of enhancing lesions **compared with baseline**, on stable or	Update the definitions of response to match the data that has been obtained

	measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids **compared with baseline scan or best response** after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).	increasing doses of corticosteroids • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids **compared with baseline scan** after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).	