ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221208

RANDOMIZED PHASE II STUDY: CORTICOSTEROIDS + BEVACIZUMAB VS. CORTICOSTEROIDS + PLACEBO (BEST) FOR RADIONECROSIS AFTER RADIOSURGERY FOR BRAIN METASTASES

Industry-supplied agent: bevacizumab (IND EXEMPT), Commercial agent: corticosteroids.
ClinicalTrials.gov Identifier: NCT02490878

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Participating NCTN Groups:
Alliance/Alliance for Clinical Trials in Oncology (lead); ECOG-ACRIN/ECOG-ACRIN Cancer Research Group; NRG/NRG Oncology; SWOG/SWOG; CCTG/Canadian Cancer Trials Group

Protocol Resources

Adverse Event Reporting

[redacted]

Medidata Rave® iMedidata portal

[redacted]

OPEN (Oncology Patient Enrollment Network)

[redacted]

Biospecimen Management System

[redacted]

Protocol Contacts:

A221208 Nursing Contacts

[redacted]

A221208 Pharmacy Contact

[redacted]

Alliance Biorepository at Mayo Clinic BAP Freezer

[redacted]

IROC

[redacted]

Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox [redacted]
Questions regarding specimens/specimen submissions:	Roxann Neumann

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN), which can be accessed at [redacted]. Contact the CTSU Help Desk with any OPEN-related questions at [redacted].	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [redacted]. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted], or [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at [redacted]		

RANDOMIZED PHASE II STUDY: CORTICOSTEROIDS + BEVACIZUMAB VS. CORTICOSTEROIDS + PLACEBO (BEST) FOR RADIONECROSIS AFTER RADIOSURGERY FOR BRAIN METASTASES

Pre-registration Eligibility Criteria

Symptomatic brain radionecrosis after receiving radiosurgery for brain metastases (see §3.2.1)

Registration/Randomization Eligibility Criteria

Diagnosis of radionecrosis based on clinical onset of symptoms and radiological findings of radionecrosis at 3-24 months following radiosurgery, with or without pathological confirmation (see §3.3.1)
On a stable dose of corticosteroids ≥ 1 week before baseline MRI.
No systemic therapy within 2 weeks prior to, or within 8 weeks following registration (see §3.3.2)
No bevacizumab within 3 months prior to registration
Central imaging review to confirm eligibility, for institutions that opt to use real-time central imaging review to confirm eligibility
Not pregnant and not nursing (see §3.3.3)
Age ≥ 18 years
Karnofsky Performance Status ≥ 60%

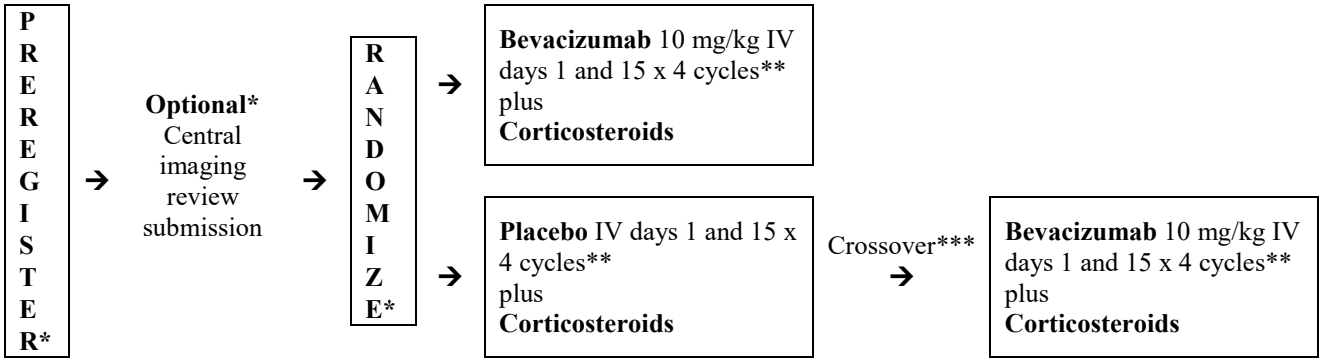
Required Initial Laboratory Values
≤ 14 days of registration

Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin	≥ 10 g/d *
BUN	< 30 mg/dL
Creatinine	< 1.7 mg/dL
Bilirubin	≤ 2.0 mg/dL
AST and ALT	≤ 3.0 x upper limits of normal (ULN)
INR	<1.5 x ULN *
UPC Ratio	<0.5 *

* See Section 3.3.6

Able to participate in patient-report outcomes (MDASI-BT, DSQ-C, LASA) questionnaires (see § 3.3.7)
No evidence of recent hemorrhage on baseline MRI of the brain (see § 3.3.8)
No excess risk of bleeding (see § 3.3.9)
No clinically significant cardiovascular disease (see § 3.3.10)
No bowel obstruction, abdominal fistula, GI perforation, or intra-abdominal abscess within past 12 months.
No central lung metastases with excessive active bleeding.
No uncontrolled intercurrent illness including, but not limited to any of the following: ongoing or active infection requiring IV antibiotics, cardiac arrhythmia, or psychiatric illness and/or social situations that would limit compliance with study requirements.
No history of serious non-healing wound, ulcer, or bone fractures

SCHEMA



* Central imaging review is not required for this study
** 1 cycle = 28 days
*** Patients who experience progression of radionecrosis while on blinded treatment may elect to cross over to open label bevacizumab.

Treatment is to continue for a total of 4 cycles or until progression or unacceptable adverse event (see Section 12.0). Patients will be followed every 2 months for 6 months with clinical visits and patient reported outcomes (MDASI-BT, DSQ-C, LASA); then will be followed for progression and survival follow-up only up to one year after end of treatment or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

1.1 Introduction

While brain tumor control is improving, the incidence of brain radionecrosis is rising as the cumulative doses of radiation used and the utilization of stereotactic radiosurgery for the treatment of both primary and secondary brain tumors is increasing. Approximately 10% of patients receiving radiosurgery for their brain tumor develop radionecrosis.[1] Gamma Knife usage statistics indicate that 50,000 patients per year receive Gamma Knife radiosurgery worldwide, therefore the number of patients treated with radiosurgery using all devices (Gamma Knife, Linac, Cyberknife) is much higher.

1.2 Corticosteroids

In current clinical practice, an initial trial of corticosteroids is started based on clinical presentation (neurological deterioration within the typical 3-18 month time-frame following radiosurgery) accompanied by radiological findings consistent with radionecrosis. Following the initiation of high-dose corticosteroids, if symptoms do not resolve, surgical resection may assist some patients. However, in rapidly progressive cases or for lesions that are not surgically amenable, there are no alternative effective therapies and patients can suffer significant morbidity and may ultimately die from progressive radionecrosis.[2-5] For patients who respond and notice neurological improvement with high-dose steroids, the toxicities of treatment can be quite troublesome – insomnia, acne, weight-gain, peripheral edema, severe mood instability, acid reflux, fatigue. [6] Although less common, high-dose and/or prolonged corticosteroid use can also result in significant morbidity and increased hospital admissions due to toxicities such as severe steroid-induced myopathy, avascular necrosis of the femoral head, bone fractures, high blood pressure, hyperglycemia complicated by metabolic disturbances and renal impairment, and increased infections.[7, 8] Therefore, it is imperative that novel and effective treatments for radionecrosis be developed.

1.3 Bevacizumab

The pathophysiology of radionecrosis in the brain is not well understood, but the development of brain edema, reflecting a disruption of the blood-brain barrier, is a consistent finding after high-dose radiation.[9-11] Once this barrier is disrupted, vasogenic edema and vascular compromise can result in tissue hypoxia, which induces the release of vasoactive proteins including vascular endothelial growth factor (VEGF).[10, 11] Studies have shown that hypoxia can increase microvessel permeability and that there is co-expression of EF5 (a marker of hypoxia), HIF1α (a marker of cellular response to hypoxia) and VEGF in areas of disruption of this barrier.[12, 13] VEGF has been shown to induce fenestrations in capillary endothelial cells and interfere with tight junction assembly thereby impairing the blood-brain barrier.[14, 15] This appears to be independent of VEGF binding to VEGF receptor.[16] Models of radiation necrosis have proposed that elevated levels of VEGF may perpetuate an avalanche effect of increased vascular permeability leading to further edema, hypoxia and eventually white matter necrosis.[17] Therefore, interruption of this cycle of damage by VEGF blockade is a rational target in the treatment of radionecrosis.

Bevacizumab (Avastin®) is a humanized murine monoclonal antibody that selectively binds and neutralizes the biological activity of human VEGF-A.[18] It has demonstrated therapeutic effect in the treatment of several solid tumors and more recently has shown some promise in the treatment of gliomas. Recent case reports and case series of patients with radionecrosis have demonstrated radiological and symptomatic improvement after bevacizumab treatment.[19, 20] Subsequently, a small prospective study of radionecrosis following high-dose radiotherapy for primary brain and head and neck cancers has suggested that bevacizumab results in radiological

and symptomatic improvement in patients with symptomatic radionecrosis.[21] In this study, 6 of 11 patients receiving bevacizumab for radionecrosis experienced adverse events including thrombotic, ischemic and infectious events. Therefore, the toxicities associated with bevacizumab administration in patients with radionecrosis following radiosurgery for brain metastases requires further evaluation in order to consider the true therapeutic benefit of this agent in this context.

1.4 Diagnosis of radionecrosis

It is recognized that a radiological diagnosis of brain radionecrosis can be challenging using conventional methods for acquisition and evaluation of CT and MR images, as the appearance of brain tumors and brain radionecrosis can be very similar. However, stereotactic biopsy has been faced with its own limitations and challenges such that it also fails to have 100% sensitivity or specificity. This is often due to spatial heterogeneity within these lesions, which can often contain both tumor cells (which may or may not be viable) and necrosis. As stereotactic biopsy is an invasive procedure with imperfect diagnostic capabilities that can be associated with additional risks to the patient, many practices do not utilize biopsy especially in the setting of possible radionecrosis after radiosurgery for brain metastases; therefore efforts have been made to improve the imaging techniques used to assist in the diagnosis of radionecrosis.

Further analysis of conventional MR imaging data have suggested that specific quantitative measures in the patterns of enhancement such as the lesion quotient (the proportional value of maximal cross-sectional area of the post-gadolinium T1-weighted contrast enhancement to the T2-weighted hyperintensity) may help identify cases suspicious for radionecrosis.[22] A lesion quotient of less than 0.3 was found in 80% of cases of pure radionecrosis whereas a lesion quotient of greater than 0.6 was found in tumor.[22] The incorporation of new physiological and metabolic imaging techniques including proton MR spectroscopy, perfusion MRI and diffusion-weighted MRI have been investigated as tools to further improve the radiological diagnosis of radionecrosis following radiotherapy. [7, 19-23] Following radiosurgery for brain metastases, relative cerebral blood volume (rCBV) measured on dynamic susceptibility-weighted contrast-enhanced (DSC) MRI has shown the greatest promise in differentiating radionecrosis from progressive or recurrent tumor.[23-25] Although both radionecrosis and progressive tumor show increased contrast enhancement, areas of radionecrosis have not shown the same increase in intravascular blood volume as seen in progressive tumor.[26-28] Specifically, several studies have suggested that a cut-off of rCBV value of 1.5-2.0 relative to white matter may be used to diagnose tumor progression rather than radionecrosis.[23, 25] Changes in rCBV have also been used to measure response to treatment with radiotherapy as well as anti-VEGF therapy.[29] Using a combination of these imaging parameters can improve the overall sensitivity and specificity of MRI in the radiological diagnosis of brain radionecrosis.

1.5 Study design

This randomized phase II study aims to investigate whether the addition of bevacizumab to standard corticosteroid therapy results in greater improvement in symptoms and less treatment-induced symptoms compared with standard corticosteroid therapy for patients with symptomatic brain radionecrosis following radiosurgery. We hypothesize that the addition of bevacizumab to standard care corticosteroids will reduce treatment-induced toxicities and improve neurologic impairments in patients with brain radionecrosis following radiosurgery for brain metastases. In part, we hypothesize that the use of bevacizumab will allow for rapid de-escalation of corticosteroid requirements and thereby decrease the corticosteroid-related toxicities. Recognizing that stereotactic biopsy is an invasive procedure with additional risks to the patient with imperfect diagnostic capabilities and acknowledging that many practices do not utilize biopsy-confirmation in the setting of suspected radionecrosis after radiosurgery for brain

metastases, we will be using a combination of imaging parameters to maximize the specificity for radionecrosis in conjunction with the clinical presentation.

As traditional endpoints, such as time to tumor progression and overall survival, are less clinically meaningful in patients requiring treatment for brain radionecrosis following radiosurgery for brain metastases, we have aimed to evaluate the impact of both the disease and therapy by using patient-reported symptoms as the primary endpoint.[30] Symptom assessment measures such as the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) have been specifically developed in patients with brain tumors to capture patient self-reports of symptom severity and interference with daily activities.[31-34] The MDASI-BT has demonstrated reliability and validity in the metastatic brain tumor patient population.[32] This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors. In RTOG 0525, a randomized study of standard vs. dose-intense adjuvant temozolomide in patients with glioblastoma, MDASI-BT demonstrated adequate sensitivity to detect differences in treatment-related toxicity between the two arms and early changes in MDASI-BT global scores were associated with progression free and overall survival [35]. In the small prospective study of bevacizumab versus placebo in patients with brain radionecrosis, the MDASI-BT was able to detect self-reported symptomatic improvement.[21] In RTOG 0825, the MDASI-BT was used to assess symptomatic differences in brain tumor patients treated with bevacizumab versus placebo and the results of these findings, which were presented at the American Society of Clinical Oncology (ASCO) annual meeting in June 2013, provided additional information about MDASI-BT changes over time with bevacizumab. As this study aims to evaluate the toxicities of bevacizumab and corticosteroids, we identified a Dexamethasone Symptom Questionnaire (DSQ) to gather more detailed information about symptoms associated with dexamethasone use. The DSQ was developed and the content validity evaluated in patients receiving prophylactic dexamethasone with their systemic therapy.[36] Subsequently, modifications have been added to create a DSQ-Chronic for patients with brain tumors, which is currently being evaluated in a validation study in patients with brain metastases at MD Anderson.

Finally, this study aims to additionally evaluate serial imaging and biofluid biomarker measures that may predict for treatment response and may ultimately assist in patient selection or adapted bevacizumab treatment regimens in patients with radionecrosis. This preliminary data would guide the utility of these biomarkers in a subsequent larger study. Although this study specifically evaluates radionecrosis following radiosurgery for brain metastases, the pathophysiology for brain radionecrosis is the same for fractionated radiotherapy and therefore results of this trial may be applicable to a broader patient population experiencing brain radionecrosis following radiation treatment.

2.0 OBJECTIVES

2.1 Primary objective

To investigate whether the addition of bevacizumab to standard corticosteroid therapy results in greater improvement in symptoms (clinical and patient-reported symptom improvement associated with radionecrosis and less radionecrosis treatment-induced symptoms) compared with standard corticosteroid therapy.

2.2 Secondary objectives

2.2.1 To evaluate the toxicity profile associated with bevacizumab and corticosteroid therapy.

2.2.2 To compare self-reported health related quality of life (HRQOL) using LASA, Dexamethasone Symptoms Questionnaire-Chronic (DSQ-C), and MDASI-BT symptom and interference score between treatment arms.

2.2.3 To compare intracranial progression-free survival and time to maximum radiographic response between treatment arms.

2.2.4 To compare the dose and duration of corticosteroids required between treatment arms and correlate steroid requirement with DSQ-C and MDASI-BT scores.

2.3 Correlative objectives

2.3.1 To explore serum/urine biomarkers that predict for treatment response.

2.3.2 To explore early imaging biomarkers that predict for treatment response.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-Registration Eligibility Criteria

Following Update 2 to this protocol, central imaging review to confirm eligibility is not required. However, this central review will continue to be made available for institutions who wish to take advantage of this service.

___ **3.2.1 Documentation of Disease:** Patients who present with symptomatic brain radionecrosis after they have received radiosurgery for brain metastases from primary solid tumor including but not limited to lung, breast, colorectal cancer but excluding melanoma, choriocarcinoma, renal cell carcinoma or gliomas (due to high risk of intratumoral hemorrhage).

- **Patients at institutions that elect to utilize central imaging review to confirm eligibility** must be pre-registered prior to submission of these images. Images should be submitted as soon as possible after the pre-registration MRI is obtained. Turnaround time for this review will be ≤ 72 business hours after receipt of images by the IROC (see Section 6.3 and Appendix III).
- **Patients at institutions that elect to confirm eligibility locally** may be pre-registered at the same time as they are randomized (see Section 4.6).

3.3 Registration/Randomization Eligibility Criteria

3.3.1 A diagnosis of radionecrosis will be based on a clinical onset of symptoms and radiological findings of radionecrosis at 3-24 months following radiosurgery, with or without pathological confirmation.

___ • 'Symptomatic' brain radionecrosis to at least one lesion following radiosurgery treatment for brain metastases where 'symptomatic' is defined as:

  - New or increasing headache associated with mass effect, sensory or motor abnormality, cognitive changes, speech difficulty, balance or coordination difficulty, cranial nerve deficits
  - Symptoms are persistent or worsening despite administration of at least dexamethasone 4 mg (or equivalent corticosteroid) daily for 1 week

___ • Clinical eligibility supported by central imaging real-time review.

The presence of at least the following conventional MR image characteristic:

- **Conventional MR**
  Lesion quotient of < 0.3, where lesion quotient is defined as the proportional value of the maximum axial cross-sectional area of the T2-weighted defined lesion over the maximum axial cross-sectional area of the contrast-enhancing lesion on the T1-weighted post-gadolinium sequence on a comparable axial slice.

If the conventional MR findings are not seen, the following dynamic susceptibility-contrast (DSC) MR characteristics may be used to meet eligibility for this study:

- **DSC MR**
  The cut-offs below will be based on GRE EPI DSC perfusion images, acquired without using a gadolinium pre-load:
  1. Relative cerebral blood volume (rCBV) <1.5 in the enhancing-lesion relative to normal-appearing white matter (NAWM) [25]

2. Percentage of signal recovery (PSR) ≥ 76%, where PSR is determined by comparing the lower signal intensity during passage of the contrast bolus with the post-contrast signal intensity on the signal intensity-time curve.[25]

- Centers that standardly use PET or MRS to determine a diagnosis of radionecrosis are permitted to use these modalities to assist in their patient selection; however the criteria described for conventional MR and/or DSC should also be met for study eligibility. Both PET and MRS are not mandatory for study eligibility.

3.3.2 Prior to start of treatment

___ • Must have been taking a stable dose of corticosteroids for symptom management for at least 1 week before baseline MRI.

___ • No systemic therapy within 2 weeks prior to registration or plan for systemic therapy within the first 8 weeks after study registration. Exceptions: Appendix II provides a list of 'approved systemic' therapies that are allowed for concurrent use with bevacizumab.

___ • No bevacizumab ≤ 3 months of study registration.

___ • Central imaging real-time review (72 hour turn around) to confirm eligibility (for institutions that opt to utilize central imaging review to confirm eligibility).

___ **3.3.3 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown. **Therefore, for women of childbearing potential only, a negative urine or serum pregnancy test done ≤ 14 days prior to registration and confirmation they are not nursing is required.**

___ **3.3.4 Age ≥ 18 years**

___ **3.3.5 Karnofsky Performance Status ≥ 60%**

___ **3.3.6 Required Initial Laboratory Values ≤14 days of registration:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Hemoglobin	≥ 10 g/dL (allowing transfusion or other intervention to achieve this minimum hemoglobin)
BUN	< 30 mg/dL
Creatinine	< 1.7 mg/dL
Bilirubin	≤ 2.0 mg/dL
ALT	≤ 3.0 x upper limits of normal (ULN)
AST	≤ 3.0 x ULN
INR	<1.5 x ULN unless patients are receiving anti-coagulation therapy. Patients receiving anti-coagulation therapy with an agent such as warfarin or heparin are allowed to participate if INR ≤3.0.
UPC Ratio	<0.5 or if ≥ 0.5, 24-hour urine protein must be <1000 mg

___ **3.3.7 Able to participate in patient-report outcomes (MDASI-BT, DSQ-C, LASA) questionnaires.** Assistance by research personnel is acceptable if participant has disabilities that make reading or writing difficult.

___ **3.3.8** No evidence of recent hemorrhage at pre-registration MRI of the brain, **however the following are permitted**: presence of hemosiderin, resolving hemorrhagic changes related

to surgery, **and** presence of punctate hemorrhage in the tumor. If there are questions, the treating physician should contact the overall Study Chair, Dr. Caroline Chung.

___ **3.3.9 No excess risk of bleeding (any of the following):**

- Bleeding diathesis or coagulopathy
- Thrombocytopenia
- Major surgical procedure, open biopsy, or significant traumatic injury within the past 28 days or anticipation of need for major surgical procedure during the course of the study.
- Minor surgical procedures, stereotactic biopsy, fine needle aspiration, or core biopsy within the past 7 days.

___ **3.3.10 No clinically significant cardiovascular disease.**

- No uncontrolled hypertension (systolic blood pressure ≤ 160 mm Hg or diastolic ≤ 100 mm Hg). Patients with hypertension must be adequately controlled with appropriate anti-hypertensive therapy or diet.
- No history of arterial thrombotic events within the past 6 months, including:
  - transient ischemic attack (TIA)
  - cerebrovascular accident (CVA)
  - peripheral arterial thrombus
  - unstable angina or angina requiring surgical or medial intervention
  - myocardial infarction (MI)
  - significant peripheral artery disease (i.e., claudication on less than one block)
  - significant vascular disease (i.e., aortic aneurysm, history of aortic dissection)
- Patients who have had a deep vein thrombosis or pulmonary embolus within the past 6 months are eligible if they are on stable therapeutic anticoagulation.
- No current New York Heart Association classification II, III, or IV congestive heart failure.

___ **3.3.11 No history of bowel obstruction, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within past 12 months.**

___ **3.3.12 No central lung metastases with excessive active bleeding.**

___ **3.3.13 No uncontrolled intercurrent illness** including, but not limited to any of the following: ongoing or active infection requiring IV antibiotics, cardiac arrhythmia, or psychiatric illness and/or social situations that would limit compliance with study requirements.

___ **3.3.14 No history of serious non-healing wound, ulcer, or bone fractures.**

4.0 PATIENT REGISTRATION/RANDOMIZATION

4.1 CTEP / DCP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

Registration requires the submission of:

- Human Subject Protection (HSP) training certificate

4.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients.

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to:

- an active Federal Wide Assurance (FWA) number,
- an active roster affiliation with the Lead Network or a participating organization,
- a valid IRB approval, and
- compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study.

4.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A221208 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or,
- Click on the By Lead Organization folder to expand.
- Click on the Alliance link to expand, then select trial protocol # A221208.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.2.2 Requirements for A221208 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission Portal
When applicable, original documents should be mailed to:
[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website. Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password.
- Click on the Regulatory tab
- Click on the Site Registration tab.
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Pre-Registration/Registration Requirements

- **Informed consent:** the patient must be aware of the nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.
- **Patient completed booklets:** Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221208 website) and faxing the form to the CTSU data operations center at [redacted] Samples of the booklet questionnaires are found in Appendices V-VII.

4.4 Patient pre-registration (Step 0) procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at [redacted] and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted]. A user manual is available for OPEN users on the CTSU site.

Prior to accessing OPEN, site staff should verify the following:

- All pre-registration eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of pre-registration. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] or at [redacted] For any additional questions contact the CTSU Help Desk at [redacted]

4.5 Review of baseline MR imaging

Baseline MR images must be analyzed for eligibility based on imaging criteria. Images and the quantitative results for all patients must be submitted to IROC at the Ohio State University per Section 6.3 Images may be analyzed locally or may be submitted to IROC for real-time central review.

4.5.1 Local imaging review for determination of eligibility

Participating sites may use institutional resources to perform imaging review for the determination of eligibility. After the patient is determined to be eligible for this study, s/he may be pre-registered and registered/randomized at the same time.

4.5.2 Real time central review of baseline MR images

For institutions that are unable (or opt not) to complete the required imaging analysis, images may be submitted to IROC per Section 6.3 for determination of eligibility. These images must be submitted after pre-registration and prior to registration/randomization,. Within 72 hours after receipt of the images, baseline MR imaging data sets will be reviewed by the A221208 central review panel per Appendix III to determine patient eligibility.

The Alliance registration office will be notified by IROC of the central review result within 24 hours after receiving it from the central review panel. The enrolling institution will then be notified by email of the central review result.

Patients should be randomized within 3 days after receiving confirmation of patient eligibility following central imaging review.

4.6 Patient Registration/Randomization (Step 1) procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at [redacted]) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- Confirmation of patient eligibility must be received from IROC.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] or at [redacted]. For any additional questions contact the CTSU Help Desk at [redacted]

4.7 Registration to Correlative and Companion Studies

4.7.1 Registration to Sub-studies described in Section 14.0

There are two correlative sub-studies within Alliance A221208. Registration to these correlative sub-studies will be done at the same time as registration to the main cancer control study, A221208. These sub-studies do not require separate IRB approval. Registration to the main study and the sub-studies will not be completed if eligibility requirements are not met.

The following correlative science study **must be offered to all patients** enrolled on Alliance A221208 (although patients may opt to not participate):

- Alliance A221208-ST1: Evaluation of Biofluid Biomarkers of Radiation Necrosis Alliance A221208 (Section 14.1)

If a patient answers "yes" to the model consent question "My coded samples and related coded information may be used in the research described above to learn about, prevent, find or treat cancer", they have consented to participate in the sub-study described in Section 14.1. The patient should be registered to Alliance A221208-ST1 at the same time they are registered to the main cancer control trial (A221208). Blood and urine samples should be submitted per Section 6.2.

While all sites are encouraged to participate, institutional participation in the following correlative science study **is optional.** If an institution opts to participate in the following correlative study, the study **must be offered to all patients** enrolled on Alliance A221208 at that institution (although patients may opt to not participate):

- Alliance A221208-IM1: Evaluation of Imaging Biomarkers of Radionecrosis Response to Corticosteroid and Bevacizumab Therapy in Alliance A221208 (Section 14.2)

If a patient answers "yes" to the model consent question "I choose to take part in the imaging study and will have the extra MRIs", they have consented to participate in the sub-study described in Section 14.2. The patient should be registered to Alliance A221208-IM1 at the same time they are registered to the main cancer control trial (A221208). Images should be submitted per Section 6.3.

4.8 Stratification Factors and Treatment Assignments

4.8.1 Stratification Factors

4.8.1.1 Age: $\leq$ 65 years vs. > 65 years

4.8.1.2 Pathological Confirmation of Necrosis: yes vs. no

4.8.1.3 MDASI-BT mean global score (symptom + interference scores) [37, 38]:

$\leq$ 4.0 vs. > 4.0

(Site staff must calculate the average score on the MDASI questionnaire completed prior to randomization.)

4.8.1.4 Prior whole brain radiotherapy: yes vs. no

4.8.2 Treatment Assignments

The factors defined in 4.9.1 will be used as stratification factors for dynamic randomization.

After the patient has been registered into the study, the values of the stratification factors will be recorded, and the patient will be assigned to one of the following treatment groups using the Pocock and Simon dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups [39].

- Placebo + corticosteroids
- Bevacizumab + corticosteroids

To ensure both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the Registration Specialist will follow the double-blinding procedures outlined in Section 4.9.3 and unblinding procedures in Section 8.3.

4.8.3 Procedures for Double-Blinding the Treatment Assignment

After the treatment assignment has been ascertained by randomization, the Registration Specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be indicated on the eligibility checklist at the time of registration. This contact person may not be involved in assessing adverse events or any other outcome measure and should not be the same person listed on page one of the Eligibility Checklist Form as the person completing the form. The Eligibility Checklist Form should provide the source of communication, either fax or e-mail, and the appropriate contact information. The Registration Specialist will then communicate the treatment assignment "active or placebo" to designated contact at the patient's institution.

If the patient has been assigned to "active" treatment, the designated contact should order patient-specific bevacizumab per the instructions included in Section 10.2. If the patient assignment is "placebo," the designated contact should prepare placebo for delivery to the patient 1-3 days after registration/randomization. In order to maintain the blind, it is recommended that placebo not be delivered to the patient immediately after registration/randomization.

The dose will be prepared and labeled as "bevacizumab 10 mg/kg or placebo" so that the contents are not discernible to the person administering the treatment.

The pharmacist or designated contact person will maintain records that indicate the identity of the patient and their corresponding treatment assignment.

4.9 Crossover Re-registration (step 2) Procedures

Patients who meet the criteria for clinical progression will complete the MDASI-BT, DSQ-C, and LASA prior to unblinding. If the patient is on placebo, he/she will be allowed to receive bevacizumab 10 mg/kg IV or stop placebo. If on bevacizumab, the patient will be treated as per treating MD.

Patients receiving placebo who choose to crossover and receive bevacizumab must be registered to the bevacizumab arm of the study, as follows:

1. Site logs into OPEN registration system and selects the appropriate patient.
2. Select the next registration step.
3. Complete OPEN Enrollment Form for the patient to change arms.

4. Enter Cycle # of the last treatment received on the placebo arm, as well as Stratification/Grouping factors, on the OPEN Enrollment Form.
5. OPEN will determine eligibility for the patient to crossover to the new arm. If patient is not eligible, OPEN will indicate this.
6. Once the new arm assignment has been successfully completed a confirmation email will be sent to the CRA.
7. If assistance is needed with this process, contact the Alliance Registration Office at [redacted]

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Tests & Observations	**Pre-registration**	**≤ 14 days prior to randomization**	**Day 1 Cycles 1-4 prior to treatment**	**Day 15 Cycles 1-4 prior to treatment**	**At the end of Cycle 4**	**For patients who crossover to open label bevacizumab**	**Clinical Follow-up: Every 2 months for 6 months***
MRI (standard of care)	X(1)		A(1,2)		X(1,2)	Repeat tests and observations as listed in the previous three columns.**	X(1,2)
History and physical, weight, Karnofsky PS, blood pressure		X (8)	X (8)	X	X (8)		X (8)
Height		X					
Concomitant Medications		X	X(3)				
Recording corticosteroid dose		X	X	X	X		X
Adverse Event Assessment			X	X	X		X
Patient Assessments							
MDASI-BT (see Appendix VI)		X	X(*3,7*)	X(4)	X(7)	Repeat Assessments	X(*7*)
DSQ-C (see Appendix VII)		X	X(*3,7*)	X(*4*)	X(7)		X(7)
HRQOL/LASA (see Appdx VIII)		X	X(*3,7*)	X(4)	X(*7*)		X(7)
Laboratory Studies							
Hematology: CBC with diff. (ANC, PLTs, HgB, WBC and lymphocytes)		X	X(*3,5*)		X	Repeat Lab studies	
Chemistry: creatinine, glucose, BUN, bilirubin, ALT, AST		X	X(*3,5*)		X		
Coagulation PT/INR		X					
Urinalysis for urine protein creatinine (UPC) Ratio		X	X(*3,5*)		X		
Urine or serum pregnancy test		X(6)					
Correlative studies: For patients who consent to participate							
Biomarker MRI	*See Sections 6.3 and 7.4 for image collection requirements, time points, and submission instructions.*						
Blood and urine samples	*See Section 6.2 for sample collection time points and processing and submission instructions.*						

* After 6 months of clinical follow up, follow patients for progression and survival until 1 year following the end of treatment.

** The scan used to determine progression prior to crossover will be considered the Prior to Day 1 scan for crossover patients.

A Prior to Cycle 1 and Cycle 3 only. If the pre-registration scan includes all the imaging requirements of the study and is performed within 4 weeks prior to registration, MRI need not be repeated prior to Cycle 1.

1. See Sections 6.3 and 7.4.
2. For institutions and patients who are participating in the optional biomarker MRI substudy, the DCE + DSC protocol is to be used for <u>all</u> scans (including those done after crossover), starting with the scan performed prior to Cycle 2.
3. Tests/assessments/labs to be collected only on Day 1 of cycles 2-4 prior to treatment. These tests/assessments/labs do NOT need to be collected for Day 1 of cycle 1.
4. Patient assessments to be collected only on Day 15 of cycles 1 and 2 prior to treatment. These assessments do NOT need to be collected for Day 15 of cycles 3 and 4.
5. Lab tests obtained ≤ 2 days prior to day 1 start of the treatment cycle are acceptable.
6. For women of childbearing potential (see Section 3.3.3).
7. These assessments should be done before MRI results are given to the patient.
8. Neurological exam will be included in the history and physical at this visit.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at [redacted]) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login[redacted] using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted]

A **Schedule of Forms** is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). Samples of questionnaires are available in Appendices IV-VII for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail and site staff will enter patient responses into Rave.

CCTG institutions are to provide patient completed booklets translated into French to French speakers. The site is responsible for transcribing the patient responses from the French version into the English version, within Medidata Rave to submit to the Alliance Statistics and Data Center. The institution should retain the completed French version as source documentation.

6.2 Specimen collection and submission

All participating institutions must ask patients for their consent to participate in the correlative sub-studies planned for Alliance A221208-ST1 and A221208-IM1, although patient participation is optional. Biomarker and imaging studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, blood, urine and MRI imaging will be collected at the following time points for these studies:

For patients registered to A221208-ST1, submit the following:					
	After randomization prior to treatment	**Day 1 cycles 2 and 3 prior to treatment**	**After 4 cycles of treatment**	**Storage/ Shipping conditions**	**Submit to:**
Serum[1] No additive (red top)	2 x 10 mL	2 x 10 mL	2 x 10 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic
Plasma/buffy coat[1] EDTA (purple top)	1 x 10 mL	1 x 10 mL	1 x 10 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic
Urine[1] vacutainer cup	~1 x 50 mL	~1 x 50 mL	~1 x 50 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic

For patients registered to A221208-ST1 and who cross over to bevacizumab treatment, submit the following:					
	After crossover re-registration and prior to treatment	**Day 1 cycles 2 and 3 prior to treatment**	**After 4 cycles of treatment**	**Storage/ Shipping conditions**	**Submit to:**
Serum[1] No additive (red top)	2 x 10 mL	2 x 10 mL	2 x 10 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic
Plasma/buffy coat[1] EDTA (purple top)	1 x 10 mL	1 x 10 mL	1 x 10 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic
Urine[1] vacutainer cup	~1 x 50 mL	~1 x 50 mL	~1 x 50 mL	Dry ice, ship over night	Alliance BAP Mayo Clinic

1 Research blood products and urine to be used for biomarker analyses described in Section 14.1.

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A221208), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood, urine).

Note for CRA – The following PHI must be removed or blacked out for all specimens or reports: signature, name, date of birth, other identifying information, except initials and study identification number.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

The institution is expected to pay the cost of mailing specimens and will be reimbursed through capitation fees set for each individual study.

6.2.2 Blood and urine sample processing

For patients who consent to participate in A221208-ST1, serum, EDTA whole blood, and urine samples will be collected after randomization prior to cycle 1 treatment, after 1 cycle, after 2 cycles, and after 4 cycles of treatment and used for the biomarker analyses described in Section 14.1.

Draw blood sequentially into 2 x 10 mL red top (no additive) tubes and 1 x 10 mL EDTA purple top tube. Gently invert each tube 8-10 times.

Serum: Collect 20 mL peripheral venous blood into (2) 10 mL plain red top no additive vacutainer tubes. Gently invert approximately 8-10 times to mix clot activator with blood. Let blood clot for 15-30 minutes at room temperature. Observe a dense clot. Centrifuge at approximately 3000 rpm (or in accordance with centrifuge manufacturer's instructions) for 10 minutes at room temperature.

After centrifugation, aspirate the top clear serum layer from both red top vacutainer tubes (being careful to avoid the transfer of red cells or clot from the bottom layer) and transfer sera to clean 50 mL conical tube. Gently mix serum in conical tube. Aliquot approximately 1 mL aliquots into (6) 2.0 mL cryogenic vials*. Label and freeze cryovials at −70°C or

colder. If –70°C is not available, temporary storage on dry ice or at –20°C prior to shipment is acceptable for up to approximately 48 hours. Ship on dry ice to the BAP at Mayo Clinic per Section 6.2.1.

Plasma/Buffy Coat: Collect 10 mL peripheral venous blood into (1) 10 mL EDTA (purple-top) vacutainer tubes. Gently invert approximately 8-10 times to mix anti-coagulant with blood. Centrifuge at approximately 3000 rpm (or in accordance with centrifuge manufacturer's instructions) for 10 minutes at room temperature.

After centrifugation, three different fractions are distinguishable: the upper clear plasma layer, the intermediate buffy coat layer containing concentrated leukocytes, and the bottom layer of red cells. Aspirate the top plasma layer from the purple-top vacutainer tube, minimizing removal of the intermediate buffy coat layer and transfer to a clean 15 mL or 50 mL conical tube. Gently mix plasma in conical tube. Aliquot approximately 1 mL aliquots into (3) 2.0 mL cryogenic vials*. Also transfer off the intermediate buffer coat layer into a 2.0 mL cryogenic vial. Label and freeze cryovials at –70°C or colder. (If –70°C is not available, temporary storage on dry ice or at –20°C prior to shipment is acceptable for up to approximately 48 hours.) Ship on dry ice to the BAP at Mayo Clinic per Section 6.2.1).

*2 mL Cryovial Choices: Some examples of acceptable 2.0 mL cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat#16001-102).

Urine: Antiseptically collect urine (mid-stream collection), voided directly into a sterile container. Pour urine into a 50 mL conical tube and centrifuge at approximately 3000 rpm (or in accordance with centrifuge manufacturer's instructions) for 10 minutes at room temperature until sediment and debris settles to the bottom of the conical tube. Remove the clear urine from the 50 mL conical tube, minimizing removal of the sediment and debris at the bottom of the tube, and transfer to another clean 50 mL conical tube. Gently mix urine in conical tube. Aliquot approximately 4 mL aliquots into (6) 5 mL cryogenic vials.** Specimens must be stored at ≤ –20° as soon as possible after collection. Ship on dry ice to the BAP at Mayo Clinic per Section 6.2.1.

**5 mL Cryovial Choices: Some examples of acceptable 5.0 mL cryovials are: Nalgene (Cat #5000-5050), Fisher (Cat #03-391-168), Corning (Cat #8084-5).

6.2.3 Blood and urine sample labeling

Label all samples using a moisture-proof cryomarker (e.g., BioHit brand) with the following identification:

1. Alliance study number (A221208-ST1)
2. Alliance patient ID number
3. Patient's initials (L, F M)
4. Date and time of specimen procurement
5. Sample type (i.e. serum, plasma, buffy coat, urine, etc.)

6.2.4 Sample submission

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery" and an email should be sent with the tracking number to Mayo Clinic BAP contact (see 'Protocol Resources' page). **The bank cannot receive specimens on Sundays or holidays. Do not send specimens the day before a holiday.**

All blood and urine specimens should be sent to the following address:

6.3 Imaging submission

Imaging submission requirements for this study are provided in the table below. Submit all MR imaging data to IROC per instructions below. Additional details are provided in Sections 7.4 and 14.2.

		1	2	3	4	Crossover	After Protocol Treatment
	Pre-registration	**Prior to Cycle 1 (Baseline)**	**Prior to Cycle 2 (4 weeks)†**	**Prior to Cycle 3 (8 weeks)†**	**At the end of Cycle 4 (16 weeks)†**	**Repeat Columns 2-4*** **	**Every 2 months for 6 months**
MRI*	X	X (1)		X (2)	X (2)	X (2)	X (2)
Biomarker MRI**			X (2)			X (2)‡	

* Standard of care MRI, to be collected and submitted for all patients enrolled to A221208.

** Research MRI, to be collected and submitted for all patients participating in companion study A221208-IM1. Images will be used for the imaging biomarker analyses described in Section 14.2.

*** The scan used to determine progression prior to crossover will be considered the Prior to Day 1 scan for crossover patients.

† +/- 4 days

‡ Biomarker MRI is required only prior to Cycle 2 of crossover treatment.

1 If the pre-registration scan includes all the imaging requirements of the study and is performed within 4 weeks prior to registration, it need not be repeated prior to cycle 1.

2 For institutions and patients who are participating in the optional biomarker MRI substudy, the DCE + DSC protocol is to be used for all scans (including those done after crossover), starting with the scan performed prior to Cycle 2.

MRI Data Archiving, Storage, and Submission for Alliance A221208 (all images)

The complete MR imaging data sets must be submitted to IROC in digital DICOM format, within no more than **3 business days** following pre-registration and all other subsequent post MR image acquisition. **BMP files, JPEG files, or hard copies (films) are not acceptable.**

The Supplemental Information Form must be submitted to IROC by fax or email together with the entire MRI DICOM data sets.

De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the **patient ID number and protocol number** of the Alliance A221208 trial. The de-identified digital images may be burned to a CD or transferred to a PC based system for further electronic data transfer purposes.

Data should be **electronically** transferred to IROC by 1) Web Transfer or 2) FTP transfer:

1) **Web Transfer:** Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to transfer DICOM images and other required files to IROC through the website: upload.imagingcorelab.com. The standard Web Transfer information will be provided separately through the specific trial e-mail [redacted] per the request by participating sites before their first data submission.
2) **FTP Transfer:** Any FTP software can be used to initiate access to the secure FTP Server of the IROC. The standard FTP access information will be provided separately through the specific trial e-mail [redacted], per the request by participating sites before their first data submission.

   Send an e-mail notification to inform IROC at the specific trial email of the data submission **once the data transfer is completed**.
3) **Shipment/Mail (not recommended):** If the above electronic data transfers cannot be achieved, the de-identified images in DICOM format can be burned to a CD, labeled with info of patient ID, study ID, MRI date, MRI timepoint (e.g., baseline, after 1 cycle of treatment, after 2 cycles of treatment, etc.) listed on the CD cover, and mailed to the IROC via over-night shipment at:

   [redacted]

For questions about the data transfer, please contact IROC via either the trial email at [redacted]

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of randomization.

Bevacizumab/placebo may be administered within 1 business day before or after the protocol defined date. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Protocol therapy will consist of 4 cycles administered every 28 days or until clinical progression or unacceptable adverse event.

7.1 Bevacizumab and Placebo

Both arms: continue corticosteroid dose prior to study enrollment, taper as tolerated.

7.1.1 Bevacizumab

The patient will receive bevacizumab 10 mg/kg IV (prepared as described in Section 10.3) over 90 minutes* given on days 1 and 15 of a 28 day cycle for 4 cycles.

* Subsequent bevacizumab infusions may be administered over 60 minutes if tolerated. If tolerated over 60 minutes, may administer over 30 minutes.

7.1.2 Placebo

The patient will receive placebo 0.9% NaCl volume equal to bevacizumab volume added to 100 mL bag of 0.9% NaCl delivered IV over 90 minutes* given on days 1 and 15 of a 28 day cycle for 4 cycles.

* Subsequent placebo infusions may be administered over 60 minutes if tolerated. If tolerated over 60 minutes, may administer over 30 minutes.

7.1.3 Corticosteroid taper

Once the patient has started the study treatment (bevacizumab or placebo), the dose of corticosteroids will be tapered every 5 days (e.g., dexamethasone 2mg or prednisone 15 mg per taper), as tolerated, under the management of the treating MD

If patients deteriorate while tapering, dexamethasone will be increased up to a maximum of 16 mg per day, as per treating MD, to manage symptoms.

Example of a common dexamethasone tapering schedule is as follows:

- Dexamethasone 4 mg po BID x 2 weeks
- Then dexamethasone 4 mg po in AM and 2mg po in PM x 5 days
- Then dexamethasone 4 mg po in AM x 5 days
- Then dexamethasone 2 mg po in AM x 5 days
- Then dexamethasone 1 mg po in AM x 5 days then stop.

7.2 Clinical progression allowing cross-over to bevacizumab

Clinical progression is defined as neurological progression despite increases in dexamethasone (or equivalent corticosteroid) up to 16 mg a day or highest dose the patient tolerates for greater than 48 hours.

Patients who meet the criteria for clinical progression will complete the MDASI-BT, DSQ-C, and LASA prior to unblinding. If the patient is on placebo, he/she will be allowed to receive bevacizumab per the table below. If on bevacizumab, the patient will be treated as per treating MD.

Unblinded (Cross-Over) Therapy

Agent*	Dose	Route	Day	ReRx
Bevacizumab	10 mg/kg	IV over 90 minutes*	Days 1 and 15	Every 28 days x 4 cycles

Continue corticosteroid, taper as tolerated.

* Subsequent bevacizumab infusions may be administered over 60 minutes if tolerated. If tolerated over 60 minutes, may administer over 30 minutes.

7.3 Clinical Assessments

Patients will be assessed every 2 weeks for the first 16 weeks of the study. The clinic visit will take place prior to each dose of placebo or bevacizumab. History and physical exam, including neurological examination will be completed within 14 days prior to randomization, day 1 of each cycle of treatment, and at each scheduled follow-up assessment. Further details are summarized in the Study Calendar, Section 5.0.

7.4 Neuro-imaging

7.4.1 Overview

Detailed study MR imaging will be acquired at the time points listed in Section 6.3.

Standard MRI imaging: For institutions and patients who <u>are not</u> participating in the optional biomarker MRI substudy, standard anatomic T2 weighted imaging, T2-weighted FLAIR imaging, diffusion-weighted imaging and pre- and post-contrast T1 weighted imaging will be performed.

DCE + DSC imaging protocol: For institutions and patients who <u>are</u> participating in the optional biomarker MRI substudy, the DCE + DSC protocol is to be used for <u>all</u> imaging excepting those collected after 6 months following the end of treatment (see Section 6.3). Images will include the following image sequences: (1) Anatomic T1, T2 weighted imaging (2) Variable flip angle (VFA) T1 weighted imaging (T1 mapping) – required for dynamic contrast enhanced (DCE) MR analysis (3) Diffusion weighted imaging (4) Dynamic susceptibility weighted (DSC) perfusion imaging (5) Dynamic contrast enhanced (DCE) perfusion imaging (6) Anatomic, post-contrast T1 weighted imaging.

7.4.2 MR Imaging Guidelines and Recommendations

General: The following general MR imaging equipment and procedures are recommended:

1) Accredited MR scanners are strongly preferred, e.g. by the American College of Radiology.
2) 3.0 Tesla field strength is preferred, but 1.5 Tesla is acceptable.
3) It is preferred for individual subjects to be scanned on the same scanner for their baseline and all follow-up MR exams, but at the least, the same field strength and scanner vendor are strongly suggested.

Brain Imaging should be performed per Appendix IV.

Gadolinium Contrast Injection

High T2 relaxivity gadolinium agents are also preferred over lower T2 relaxivity agents.

Single dose

Gadolinium Pre-load: IV gadolinium 0.05 mmol/kg at 5-10 minutes prior to the DSC series (DCE can be acquired with this preload injection OR series including the FSE/TSE T2-weighted images could be interposed between the 2 gad administrations)

Gadolinium bolus: IV gadolinium 0.05 mmol/kg administered with a power injector through an 18-20 gauge right antecubital IV at 3-5 mL/s (5 mL/s preferred), followed by a saline bolus at the same injection rate.

Double dose

Gadolinium Pre-load: IV gadolinium 0.1 mmol/kg at 5-10 minutes prior to the DSC series (DCE can be acquired with this preload injection OR series including the FSE/TSE T2-weighted images could be interposed between the 2 gad administrations)

Gadolinium bolus: IV gadolinium 0.1 mmol/kg administered with a power injector through an 18-20 gauge right antecubital IV at 3-5 mL/s (5 mL/s preferred), followed by a saline bolus at the same injection rate.

The Supplemental Information Form will be submitted with the images at each time point to capture the following details: Gadolinium agent, dose, and injection rate.

Dynamic Contrast Enhanced MRI (for optional A221208-IM1 sub-study):

If sites are capable of performing dynamic contrast enhanced (DCE) perfusion imaging in addition to DSC perfusion, the gadolinium administered for a DCE series will serve as the preload for a later DSC series.

Recommended parameters:

- fast T1-weighted spoiled gradient-recalled echo acquisition
- matrix 128 x 128 mm
- 5 mm slice thickness
- 3-6 second temporal resolution
- 3-6 minutes acquisition time
- IV gadolinium injection of 0.05 mmol/kg, at 2-4 mL/s, should occur 20 seconds or more after the start of the imaging series and should be followed by a saline bolus at the same injection rate.

7.5 Patient-Reported Symptoms

MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT) and Dexamethasone Symptom Questionnaire-Chronic (DSQ-C) will be administered prior to randomization, and prior to treatment on day 1 of cycles 2-4, and on day 15 of cycles 1 and 2, and every 2 months after 4 cycles of treatment for up to 6 months. These assessments should be completed before MRI results are given to the patient.

MDASI-BT [Appendix VI]

The MDASI-BT was developed and validated for use in the brain tumor patient population, including those with brain metastases and typically requires less than 4 minutes to complete. It consists of 23 symptoms rated on a 0 to 10 numerical rating scale (NRS) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." MDASI-BT Symptom Scoring: A global symptom score for the MDASI symptom severity scale is obtained by taking the average of the 23 items together. [33] MDASI-BT Interference Scoring: The MDASI-BT also includes ratings (from 0-10) of how symptoms have interfered with different aspects of the patient's life. These interference items include: general activity, mood, work (outside the home and housework), and relations with other people, walking, and enjoyment of life. The mean of the 6 interference items can be used as a measure of the overall symptom distress.

Dexamethasone Symptom Questionnaire-Chronic (DSQ-C) [Appendix VII]

The DSQ-C was developed for use in the brain tumor patient population. It consists of 18 questions rated on a 4-point scale (1 to 4) to indicate the presence and severity of symptoms. This is followed by 3 questions that address the patient's risk of diabetes and hyperglycemia and finally an open 'comment' section and rank of most bothersome symptoms.

7.6 Quality of Life

HRQOL will be measured using the single-item linear-analogue scale (LASA) [40] [Appendix VIII]. This instrument has demonstrated reliability and validity for measuring overall QOL in the brain tumor patient population while allowing for reduced patient burden. Quality of life measures will be acquired within 14 days prior to randomization, day 1 of cycles (cycles 2-4) prior to treatment, day 15 cycle 1 and cycle 2 prior to treatment, and every 2 months after 4 cycles of treatment for up to 6 months. These assessments should be completed before MRI results are given to the patient.

7.7 Definitions of Deviations in Protocol Performance

7.7.1 Major Deviations

The following will be considered major protocol deviations:

- MDASI-BT assessment completed beyond +/- 7 days during active treatment phase and beyond +/- 10 days during post-treatment follow-up, from the scheduled date.

7.7.2 Minor Deviations

The following will be considered minor protocol deviations:

- MDASI-BT assessments completed between 4-7 days beyond the scheduled date during the active treatment phase, and +/- 8 days beyond the scheduled treatment date during post-treatment follow-up.

8.0 TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint, except agents listed on the "approved systemic therapies" list in Appendix II.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones for non-disease-related conditions (e.g., insulin for diabetes) is permitted while on this study.

8.1.4 Antiemetics may be used at the discretion of the attending physician.

8.1.5 Hypertension: Blood pressure should be assessed before each administration of bevacizumab. High blood pressure may require initiation or increase in antihypertensive medication according to routine clinical practice.

8.1.6 Patients should not receive any live vaccines while receiving corticosteroids.

8.1.7 Patients who require radiation therapy during protocol treatment will be removed from protocol therapy and study treatment will be stopped prior to radiotherapy. These patients will continue to be followed on study for the brain specific endpoints.

8.2 Discontinuation of bevacizumab

There are no dose reductions for bevacizumab. Bevacizumab may be delayed or discontinued for toxicity as described below.

Bevacizumab will be temporarily suspended for at least 4 weeks prior to elective surgery

8.2.1 Hypersensitivity and/or Infusion Reactions

Allergic or Infusion-Related Reactions

- The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no hypersensitivity or infusion reactions occur, the second dose should be administered over a minimum of 60 minutes. If no hypersensitivity or infusion reactions occur with the second dose, the third and subsequent doses should be administered over a minimum of 30 minutes.
- For grade 1 or 2 hypersensitivity reactions during bevacizumab infusion, interrupt bevacizumab until symptoms resolve to < grade 1, then resume bevacizumab at the shortest infusion rate tolerated. Manage symptoms according to institutional procedures. Subsequent infusion rates should be titrated as stated above. Consider premedication with antihistamines for subsequent doses.
- Subjects who experience clinically evident bronchospasm (regardless of grade) should discontinue bevacizumab. Manage symptoms according to institutional procedures.

For grade 3 or 4 allergic reactions considered related to bevacizumab, discontinue bevacizumab. Manage symptoms according to institutional procedures.

For grade 1 or 2 infusion-related reaction or cytokine release syndrome as characterized by back pain, headache, rigors, erythema, vasodilation, considered related to bevacizumab,

decrease infusion rate to 50% of the previous rate. Manage symptoms according to institutional procedures. When symptoms improve to < grade 1, the infusion rate may be increased in 50% increments every 30 minutes. Subsequent infusions can be started at the planned rate.

For grade 3 or 4 infusion-related reaction or cytokine release syndrome considered related to bevacizumab, discontinue bevacizumab. Manage symptoms according to institutional procedures.

For anaphylaxis considered related to bevacizumab, discontinue bevacizumab. Manage anaphylaxis according to institutional procedures.

8.2.2 Injection Site Reactions

For grade 1 or 2 injection site reactions, continue on study; make sure to rotate injection sites as instructed in Administration section. Manage symptoms according to institutional procedures.

8.2.3 Hypertension

For grade 1 to 3 hypertension controlled with medication to <150/90 mmHg, continue bevacizumab.

For persistent or symptomatic hypertension despite antihypertensive therapy, delay bevacizumab for up to 6 weeks until BP <150/90 mmHg. If bevacizumab is held 6 weeks, patient is to discontinue bevacizumab.

For grade 4 hypertension, discontinue bevacizumab.

8.2.4 Hemorrhage

For grade 1 or 2 bleeding, restart bevacizumab once resolved to < grade 1. If bevacizumab is held 6 weeks, patient is to discontinue bevacizumab.

For grade 3 or 4 bleeding: Discontinue bevacizumab.

8.2.5 Venous thromboembolic events

Grade 1, 2, 3 or asymptomatic grade 4: Delay bevacizumab. If the planned duration of full-dose anticoagulation is <2 weeks, protocol treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, protocol treatment may be resumed during the period of full-dose anticoagulation if all the following criteria are met:

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) prior to restarting therapy;
- The patient must not have had a grade 3 or 4 hemorrhagic event while on study; and

For recurrent/worsening venous thromboembolic events after resumption of treatment: Discontinue bevacizumab.

For symptomatic grade 4: Discontinue bevacizumab.

If bevacizumab is held 6 weeks, patient is to discontinue bevacizumab.

8.2.6 Arterial thromboembolic events

Arterial thrombosis may include angina, myocardial infarction, stroke (CNS cerebrovascular ischemia), or other arterial thrombotic event. In the event of new or worsening grade 2 or any grade 3, or 4 arterial thrombotic event, treatment with bevacizumab should be discontinued.

8.2.7 Renal and urinary disorders: Proteinuria

For proteinuria of ≥ 2+: Confirm total urine protein with a 24-hour urine collection or urine protein to creatinine (UPC) ratio. For 2+ proteinuria, give scheduled bevacizumab while awaiting the results of the 24-hour collection or UPC ratio. For > 2+ proteinuria, delay bevacizumab while awaiting results of the 24-hour urine collection or UPC ratio.

If monitoring urine protein with UPC, no confirmation is necessary.

For urine protein 2-3.4 g/24 hours or UPC ratio 2-3.4: Delay bevacizumab until urine protein improves to < 2g/24 hours or UPC < 2. If bevacizumab is held 6 weeks, patient is to discontinue bevacizumab.

For urine protein ≥ 3.5 g/24 hours or UPC ratio ≥ 3.5: Discontinue bevacizumab.

8.2.8 Fistula, perforation involving any organ, bowel obstruction, and wound dehiscence

- **For any grade perforation of any organ, GI leak, or any fistula**: Discontinue bevacizumab.
- **For any grade bowel obstruction requiring medical intervention:** Hold bevacizumab therapy until complete resolution. Continue HSPCC-96. If surgery is required, the patient may restart bevacizumab after full recovery from surgery and after consultation with the study chair.
- **For wound dehiscence requiring medical or surgical intervention**: Discontinue bevacizumab.

If bevacizumab is held 6 weeks, patient is to discontinue bevacizumab.

8.2.9 Posterior leukoencephalopathy syndrome

For signs and symptoms suggestive of reversible posterior leukoencephalopathy syndrome (RPLS) such as confusion, headache, seizures, and cortical blindness, hold bevacizumab for up to 6 weeks. Suspected RPLS should be investigated with MRI as described in Section 11.5. If diagnosis of RPLS is confirmed, bevacizumab should be permanently discontinued. If RPLS is ruled out via MRI, and signs and symptoms attributed to another cause, may resume bevacizumab.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency or at the time protocol-specified unblinding is allowed. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

1. Emergency Unblinding Procedures:

   Emergency unblinding requests for A221208 should be made directly to the Alliance Executive Officer on call. This memorandum describes changes to the emergency unblinding procedure. Institution staff should contact the Alliance Executive Officer on call by calling [redacted] pressing 1 to speak with an operator and then asking for pager ID [redacted] to return their call.

   The institution must provide the following information to the Alliance Executive Officer:

   - Alliance study ID (A221208)
   - Alliance patient ID number
   - Patient initials (e.g., "L,FM")
   - Name and telephone number of treating physician
   - Name and contact information of person requesting unblinding procedure
   - Name and contact information of person to inform of treatment assignment
   - Reason for unblinding request

   Please remember that emergency unblinding requests may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

2. Protocol-specified Unblinding:

   Trial participants may be unblinded upon failure of the assigned treatment arm, defined as clinical deterioration despite increasing doses beyond their baseline dexamethasone (or equivalent corticosteroid) dose for greater than 48 hours. Patients who meet the criteria for clinical progression will complete the MDASI-BT, DSQ-C, and LASA **prior to unblinding**.

   Contact the Alliance Registration Office at [redacted] during regular business hours. Upon confirmation by the Primary Statistician (or designee) that the criteria for treatment failure have been met, the treatment assignment may be unblinded. If the patient is on placebo, he/she will be allowed to receive bevacizumab. Refer to Section 4.9 for details about crossover procedures. If on bevacizumab, the patient will be treated as per treating MD.

   No Alliance Executive Officer (or designee) approval is required.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients 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 according to the study calendar in Section 5.0. For this trial, the Adverse Event Form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Allergic reaction	Immune system disorders; not at baseline
Infusion related reaction	General disorders and administration site conditions; not at baseline
Injection site reaction	General disorders and administration site conditions; not at baseline
Hypertension	Vascular disorders
Thromboembolic event, venous or arterial	Vascular disorders
Proteinuria	Renal and urinary disorders
Wound dehiscence	Injury, poisoning and procedural complications

9.2 CTCAE Routine Study Reporting Requirements

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting System (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at:

[redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND ≤ 30 Days of the Last Administration of the Investigational Agent/Placebo. [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Additional Instructions or Exclusions to CTEP-AERS Reporting Requirements for Phase 2 and 3 Trials:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors.

  Secondary Malignancy:

  A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy

  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

  Second Malignancy:

  A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

  Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available. New primary malignancies should also be reported via routine reporting in Medidata Rave.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- Treatment expected adverse events include those listed in Section 10.0 and in the CAEPR for bevacizumab. NOTE: the SPEER (specific protocol exceptions to expedited reporting) list in the bevacizumab CAEPR includes "expected" severity grades in addition to event terms.
- Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero."
- Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

- Pregnancies and suspected pregnancies occurring in female patients during or within 120 days after completion of treatment on A221208 must be reported via CTEP-AERS..

  CTEP-AERS reports and pregnancy information forms should be amended upon completion of the pregnancy to report pregnancy outcome (e.g., normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).

10.0 DRUG INFORMATION

10.1 General Considerations:

- The total administered dose of bevacizumab may be rounded up or down within a range of 5% of the actual calculated dose.
- It is not necessary to change the doses of bevacizumab or placebo due to changes in weight unless the calculated dose changes by ≥10%.

10.2 Bevacizumab (Avastin®)

Genentech will supply bevacizumab. The Mayo Clinic Cancer Treatment Center Pharmacy in Rochester, MN will store and ship bevacizumab to the non-Canadian Alliance institutions. Roche Canada will distribute bevacizumab to participating Canadian sites. Because bevacizumab must be stored at 2°C-8°C, it will be shipped via FedEx Overnight in a cooler with an ice pack. Bevacizumab will only be shipped out Monday-Thursday with delivery to occur on Tuesday-Friday. No shipments will be made the day before a Holiday.

Participating institutions will order patient-specific supplies of bevacizumab from the Alliance Research Base Pharmacy each time a patient is enrolled to the study and randomized to the bevacizumab arm. Complete the Clinical Drug/Order/Return Form, which is available on the A221208 page of the Alliance [redacted] web site and fax the completed form to:

[redacted]

Patient-specific supplies of bevacizumab for participants who cross over from placebo to bevacizumab treatment must also be ordered as above at the time of registration to bevacizumab per Section 4.9.

Drug accountability

Agent disposition (receipt, dispensing, transfer, return or authorized local destruction of un-dispensed agent) shall be documented on the NCI Investigational Agent (Drug) Accountability

Record (DARF) or the NCI Investigational Agent Accountability Record (DARF) as appropriate. Electronic accountability systems may be used. Paper printouts of electronic DARFs must be identical to the NCI DARF.

IND Status

Bevacizumab is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for bevacizumab. This investigation will use an approved route of administration and dosage of bevacizumab and has no factors that increase the risk of the product. This investigation will be in compliance with 21CFR parts 56, 50, and 312.7 and neither the investigator nor sponsor will promote or represent that bevacizumab is safe or effective for the context that is under investigation in this study. This investigation will not commercially distribute or test market the study agent, and will not unnecessarily prolong an investigation.

Formulation

Bevacizumab is manufactured by recombinant DNA technology, using a genetically engineered Chinese hamster ovary (CHO) cell line. The protein is purified from the cell culture medium by routine methods of column chromatography and filtration. The final product is tested for quality, identity, safety, purity, potency, strength, and excipient/chemical composition according to International Conference on Harmonisation (ICH) guidelines. The purity of bevacizumab is > 95%.

Bevacizumab is supplied as 400 mg (25 mg/mL x 16 mL) glass vials. These will come as a box with 2 x 16mL vials. 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.

Storage and Stability:

Bevacizumab vials should be stored in a refrigerator at 2°C-8°C. Keep vial in the outer carton due to light sensitivity. **DO NOT FREEZE. DO NOT SHAKE.**

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. **Do not administer or mix with dextrose solution.** From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Preparation

Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The dose will be prepared and labeled as “bevacizumab 10 mg/kg or placebo” so that the contents are not discernible to the person administering the treatment.

Administration

Do not administer as an intravenous push or bolus. Administer only as an intravenous (IV) infusion. Do not initiate bevacizumab for 28 days following major surgery and until surgical wound is fully healed. Refer to Section 7 for protocol-specific administration instructions.

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

Drug Interactions

Increased Effect/Toxicity: Bevacizumab may increase the levels/effects of anthracyclines, inotecan, sorafenib, and sunitinib. Serum concentrations of irinotecan's active metabolite may be increased by bevacizumab; an approximate 33% increase has been observed.

Pharmacokinetics

Distribution: $V_{d:}$ 46 mL/kg (limited extravascular distribution)

Half-life elimination: ~20 days (range: 11-50 days)

Clearance: 2.75-5 mL/kg/day. A low serum albumin and high tumor burden increase clearance by 30% and 7% respectively. Clearance increases with increasing body weight, and is 15% slower in women than men.

Time to steady state: 100 days

Adverse Events

Consult the investigator's brochure and package insert for the most current and complete information. U.S. Boxed Warnings include severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous system hemorrhage, epistaxis, and vaginal bleeding. Avoid use in patients with serious hemorrhage or recent hemoptysis.

Revised Bevacizumab CAEPR – Version 2.5, May 2, 2018

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [redacted] for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for Bevacizumab (rhuMAb VEGF).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***
		Chest pain - cardiac[3]	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes

GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.3 Placebo

The placebo will be 0.9% Sodium Chloride Injection (0.9% NaCl). Sites will provide their own 0.9% NaCl.

Each institution will use 100 ml bags or bottles of 0.9% NaCl as the placebo agent. A volume of 0.9% NaCl equal to the volume of bevacizumab will be added to the 100 mL bag of 0.9%

NaCl. The placebo will be given intravenously over 90 minutes at specified infusion time points (see Section 7.1). Each institution will use 0.9% NaCl from their commercial inventory. The Alliance will not provide placebo (0.9% NaCl) to study sites.

The dose will be prepared and labeled as "bevacizumab 10 mg/kg or placebo" so that the contents are not discernible to the person administering the treatment.

Refer to Section 7.0 for protocol-specific administration instructions.

First infusion: Administer infusion over 90 minutes. Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

10.4 Nursing Guidelines

10.4.1 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact treating physician. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by treating physician.

10.4.2 Monitor urine dipstick or UPC as required by the test schedule.

10.4.3 Evaluate IV site regularly for signs of infiltration.

10.4.4 Bleeding in the absence of thrombocytopenia is a serious toxicity that necessitates patient monitoring. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.

10.4.5 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.

10.4.6 Patient may experience Grade 1-2 nausea, however, vomiting is uncommon. Medicate as ordered and monitor for effectiveness.

10.4.7 Monitor for skin rash, instruct patient to report to treating physician.

10.4.8 Monitor blood pressure. Administer antihypertensives as ordered by treating physician.

10.4.9 Monitor for signs and symptoms of deep vein thrombosis (DVT) or pulmonary embolism (PE), or myocardial infarction (MI) including new or worsening angina. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or shortness of breath to treating physician immediately.

10.4.10 Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.

10.4.11 Monitor CBC, including platelets. Instruct patient to report signs and symptoms of **i**nfection, unusual bruising or bleeding to the treating physician.

10.4.12 Patients receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained. For patients on warfarin for venous

access prophylaxis, routine monthly monitoring is satisfactory; however, more frequent monitoring can be done according to local standard practices.

10.4.13 A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.

10.4.14 Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated with constipation and vomiting. Instruct patient to report abdominal pain to the treating physician.

10.4.15 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but **s**erious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the treating physician immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

10.4.16 Warn female patients of the possibility of ovarian failure and subsequent infertility. Vaginal hemorrhage is also possible. Instruct patients to report any heavy or unusual vaginal bleeding to health care team.

11.0 MEASUREMENT OF EFFECT

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated on Days 1 and 15 of each cycle of bevacizumab or placebo.

11.2 Guidelines for Evaluation of Measurable Disease

11.2.1 Response and Progression Criteria

11.2.1.1 Clinical Response is defined as neurological and MDASI-BT global score stability or improvement. Progression is defined as neurological progression despite increases in dexamethasone (or equivalent corticosteroid) back to or beyond the patient's baseline corticosteroid dose for greater than 48 hours.

11.2.1.2 Radiographic response: Measurable disease will be defined as a contrast-enhancing lesion with clearly defined margins on MRI and perpendicular diameters of at least 10 mm (i.e. with two transaxial perpendicular diameters of at least 10 mm and also visualized on two or more contiguous axial slices summing up to at least 10 mm). Thin enhancement around a cyst or surgical cavity should be considered non-measurable unless there is a nodular component measuring at least 10 mm in diameter.

11.2.1.3 Radiographic response and progression will follow RANO criteria for the target lesion(s).

11.2.2 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.3 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 Responding: Patients who are symptomatically stable or improving on treatment will continue on the assigned therapy for a total of 4 cycles. After treatment is discontinued, patients will be followed per the study calendar in section 5.0.

12.1.2 Progression of radionecrosis

Patients who experience progression of radionecrosis while on blinded treatment may be unblinded. See Section 8.3 for unblinding instructions.

- Patients who were receiving placebo may elect to crossover to open label bevacizumab treatment. See Section 4.9 for cross-over instructions.
- Patients who experience progression of radionecrosis while receiving bevacizumab treatment (either blinded or open-label) will discontinue bevacizumab and will be followed for survival.

12.1.3 Progression of metastatic disease

Patients on blinded drug who experience metastatic progression requiring systemic therapy that is <u>not</u> listed in the Appendix II as safe to give with bevacizumab will discontinue protocol treatment and be treated per the treating physician. These patients will be followed for survival.

Patients on blinded drug who experience metastatic progression requiring systemic therapy that is listed in the Appendix II as safe to give with bevacizumab will continue protocol treatment and may start systemic therapy per the treating physician.

Patients who have progression of metastatic disease <u>after</u> completion of bevacizumab should continue to be followed for progression of radionecrosis and survival per the study calendar in Section 5.0. Document details, including measurements of the target lesion(s), on data forms.

12.1.4 Discontinuation of study agent: Patients who discontinue treatment for reasons other than progression should be followed per the study calendar (Section 5.0).

12.2 Managing ineligible patients and major protocol violations

Data must be submitted per Section 5.0 for patients deemed ineligible. See also the Forms Packet for full details of data submission requirements.

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete baseline, on-study and off-treatment notice data submission.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Overview

This is a randomized double-blinded phase II study of corticosteroids with bevacizumab vs. corticosteroids with placebo for brain radionecrosis following radiosurgery for brain metastases.

13.2 Sample Size, Accrual Time and Study Duration

13.2.1 Sample Size

Applying guidelines used in the evaluation of the minimal clinically important difference (MCID) [57] in health-related quality of life instruments to estimate the sample size for this study, that is, the MCID is expressed in standard deviation (σ).

Assuming a compound symmetry structure, we have calculated the number of patients required to achieve 80% power to detect the specified effect sizes in slope at the 5% or 10% significance level in the following table. This is a direct application of equation (2.4.1) on page 20 of Diggle et al. [41]

Effect size in slope (t=8)	Compound symmetry ρ	Type I error α	Power (%)	Sample size per arm
$0.25\sigma/t$	0.8	0.10	80	64
$0.30\sigma/t$	0.8	0.10	80	44
$0.30\sigma/t$	0.8	0.05	80	56
$0.50\sigma/t$	0.8	0.05	80	21

Although 0.50σ is generally considered for a moderate effect size, we believe a smaller effect size (0.30σ) is still clinically meaningful and thus warranted for a comparison of bevacizumab plus corticosteroid vs. placebo plus corticosteroid for this patient population. Therefore, we will need a sample size of 112 patients, which will be further inflated by approximately 15% to 130 patients (65 patients per arm) to account for patient ineligibility and major violation.

13.2.2 Accrual Rate and Accrual Duration

The accrual rate for Alliance is estimated as 30 patients per year, which lead to approximately 4.5 years for patient accrual.

13.2.3 Primary Endpoint Completion Date for ClinicalTrials.gov Reporting

For purpose of ClinicalTrial.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least four months.

13.3 Statistical Design and Analysis for the Primary Endpoint

13.3.1 Primary Endpoint

Patient-reported outcome (symptoms) of radionecrosis as repeatedly measured by MDASI-BT symptom score during the first two cycles of treatment (prior to first treatment, 2, 4, 6 and 8 weeks).

13.3.2 Statistical Design

This is a two-arm randomized phase II clinical trial with parallel group design for longitudinal quality of life endpoint. There is no formal interim analysis specified due to the sample size.

13.3.3 Analysis Plan

13.3.3.1 A modified intent-to-treat principle will be applied for statistical analysis of efficacy in all evaluable patients, where 'evaluable patients' are defined as all patients meeting the eligibility criteria who received their assigned study treatment with no major violations and completed MDASI-BT at baseline and at least once in follow-up.

13.3.3.2 For patients who cross-over from placebo to bevacizumab or discontinue bevacizumab, primary analysis will only be applied to their assessments prior to cross-over. Further sensitivity analyses will explore additional per-treatment approaches for analyzing the primary endpoint data, such as incorporating a time-dependent treatment covariate.

13.3.3.3 Generalized linear models with repeated measures will be used to compare the rates of change in MDASI-BT symptom score ($\boldsymbol{y_{ij}}$) between treatment arms ($\boldsymbol{x_i}$) during the first two cycles of treatment.

$$y_{ij} = \beta_1 x_i + \beta_2 x_i t_{ij} + \beta_3 z_i + \varepsilon_{ij}$$

Where time index $j = 0, 2, 4, 6, 8$ week, subject index $i = 1, 2, \ldots, m$ patient and possibly other covariate such as stratification factors (z_i). In this notation, β_2 represents the difference in rates of change in MDASI-BT symptom score when $x_i = 1$ for bevacizumab plus corticosteroid arm and $x_i = 0$ for placebo plus corticosteroid arm. Generalized estimating equation (GEE) approach with an independence working correlation matrix will be utilized and parameter estimation will account for the covariance between repeated measures [41]. Since the identity link function is used for the MDASI-BT symptom score, we will also explore the random effects model approach with a random intercept. Supplementary graphical procedures associated with repeated measures of MDASI-BT will include a stream plot of individual scores over time and a line plot of average symptom scores over time for each arm.

13.3.3.4 For the primary analysis described above, all patients deemed to be eligible at enrollment will be included; however, after central review of imaging data, some of these patients may be reclassified as ineligible. Thus, we will re-run the above primary analyses using only patients who are determined to be eligible based on central review of imaging data. These can be considered additional sensitivity analyses.

13.3.3.5 As study sites are not required to have imaging credentials at the time of activation, there may be some between-patient variability in the quality of the imaging data. If a noticeable proportion of patients are determined to have poor quality imaging data, we may also re-run the above primary analyses using only those patients whose images meet (or have minor deviations from) the recommended imaging protocol (Appendix IV).

13.4 Supplementary Analysis Plans

13.4.1 Secondary Endpoints

13.4.1.1 Toxicities associated with bevacizumab and corticosteroids in patients with radionecrosis using CTCAE Version 4.0 and DSQ-C.

13.4.1.2 Quality of life measured using the Single Item Linear Analogue Scale (LASA), Dexamethasone Symptoms Questionnaire – Chronic (DSQ-C), MDASI-BT symptom score (12 and 16 weeks) and the MDASI-BT interference score.

13.4.1.3 Progression free survival and time from start of treatment to maximum radiographic response.

13.4.1.4 Corticosteroid dose over time and time to stopping corticosteroids.

13.4.2 Correlative Endpoints

13.4.2.1 Biofluid Biomarkers: angiogenic factors (VEGF-A, B, C, D, angiopoietin-1 and 2, PDGF), inflammatory cytokines (TNF-α, TGF-β, IL1, and IL6) and genetic markers (Apo E).

13.4.2.2 Imaging Biomarker Measures: Diffusion weighted imaging (apparent diffusion coefficient = ADC), Dynamic susceptibility weighted contrast enhanced (DSC), Dynamic contrast enhanced (DCE measures - Ktrans, iAUGC).

13.4.3 Secondary Analyses

Statistically significant findings from secondary analyses are exploratory in nature and therefore shall be interpreted as such because multiplicity from multiple secondary analyses will not be adjusted. Descriptive statistics and graphical approaches will form the basis for most secondary analyses, though statistical comparisons may be conducted in some appropriate circumstances.

13.4.3.1 Toxicities associated with bevacizumab and corticosteroids in patients with radionecrosis using CTCAE Version 4.0 and DSQ-C will be summarized in descriptive statistics. Chi-square tests may be conducted to investigate differences in incidence rates of toxicities between arms.

13.4.3.2 Quality of life measured using the Linear Analog Self-Assessment (LASA), Dexamethasone Symptoms Questionnaire – Chronic (DSQ-C), MDASI-BT symptom score (baseline, 2, 4, 8 and 12 and 16 weeks and during follow-up) and the MDASI-BT interference score will be analyzed with the same approach as the primary analysis, i.e., generalized linear models.

13.4.3.3 Progression free survival and time (from start of treatment) to maximum radiographic response will be summarized by Kaplan-Meier curve. Date of progression for progression free survival will be the date the patient stops placebo or bevacizumab for either alternative therapy or crossover to bevacizumab, if initially on placebo. Log-rank statistics may be conducted to investigate differences in time to event (progression and maximum radiographic response) between treatment arms.

13.4.3.4 Corticosteroid dose over time will be summarized by descriptive statistics and may be incorporated a**s a time-dependent covariate in the following joint models:**

- Time to stopping corticosteroid will be summarized by Kaplan-Meier curve with log-rank tests conducted to investigate differences between treatment arms.
- In order to study the correlation and trend between corticosteroid dose and MDASI-BT symptom score, we will extend the generalized linear model to allow the covariate to be time-dependent (z_{ij}).
- In order to study the correlation and trend between corticosteroid dose and PFS and time to maximum radiographic response, we will use the joint models [42] for survival and longitudinal data.

13.4.4 Correlative Studies Analyses

The serial changes in biofluid and imaging biomarkers for radionecrosis will be summarized using descriptive statistics. The correlation between these biomarkers will be explored by generalized linear models allowing for time-dependent covariate (for longitudinal primary endpoint) and/or joint models (for time to event secondary endpoints).

13.5 Study Monitoring

13.5.1 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite) that satisfy the following criteria:

- If 7 or more of the first 20 treated patients (or 35% of all patients after 20 patients have been accrued) experience a grade 3 or higher non-hematologic adverse event and the adverse event rate is higher in the active treatment arm.
- If 3 or more of the first 20 treated patients (or 15% of all patients after 20 patients have been accrued) experience a grade 4 or higher non-hematologic adverse event and the adverse event rate is higher in the active treatment arm.

13.5.2 Accrual Monitoring Stopping Rule

Patient accrual will be closely monitored by the investigators and secondary statistician on a monthly basis. If the accrual rate falls below 50% of expected accrual rate, investigators will carefully review feedback from sites and consider taking measures to encourage patient enrollment.

13.6 Study Reporting

13.6.1 This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.6.2 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Descriptive Factors

None

13.8 Missing Data

We will examine the mechanisms of missing data if the proportion of missing assessments is not small (≥ 5%). Graphical presentation, correlation analysis (Kendall's) and logistic regression will be performed to examine whether the missing data mechanism depends on the covariates (patient characteristics and other baseline risk factors), observed patient-reported outcome (PRO) scores, and missing PRO scores.

13.8.1 If the missing data mechanism solely depends on the covariates (missing completely at random, MCAR) or depends on the covariates and observed PRO scores only (missing at random, MAR) [43], we will enhance the primary analysis to incorporate these covariates in the repeated measures model. The generalized linear model with repeated measures model is a quasi-likelihood based approach that uses all observed data and the covariates that explain the missing data mechanism, therefore results in unbiased estimates under MCAR and MAR [44].

13.8.2 If the missing data mechanism depends not only on the covariates and observed PRO scores, but also on the missing PRO score (missing not at random, MNAR), we will explore advanced models that consider both longitudinal PRO assessments and missing data mechanism, such as pattern mixture model and selection model [44].

13.9 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 13.5% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 11.6% of patients will be classified as minorities by race and about 60% of patients will be women. Expected sizes of racial by gender subsets for patients randomized to this study are shown in the following table.

Racial Categories	**Ethnic Categories**				
	Not Hispanic or Latino		**Hispanic or Latino**		**Total**
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	**1**
Asian	2	1	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	8	7	0	0	**15**
White	62	45	3	1	**111**
More Than One Race	0	0	0	0	**0**
Total	**73**	**53**	**3**	**1**	**130**

14.0 CORRELATIVE AND COMPANION STUDIES

There will be two sub-studies and all patients are encouraged to participate.

14.1 Alliance A221208-ST1

Evaluation of Biofluid Biomarkers of Radiation Necrosis in Alliance A221208

14.1.1 Background

Radiation necrosis in the brain and clinical response to treatments of radiation necrosis in the brain is associated with alterations in inflammatory cytokines, including TNFα, TGFβ, IL1, and IL6: Biomarkers of tissue damage associated with radiation late toxicities are poorly studied in the brain. However, in other tumor systems, alterations in the serum level of a number of inflammatory cytokines have been associated with radiation effects. In breast cancer patients, baseline levels of transforming growth factor β1 (TGFβ1) have been associated with subsequent radiation fibrosis [45]. Similarly, in non-small cell lung cancer, normalization of TGFβ1 levels has been associated with decreased occurrence of radiation pneumonitis [46]. In addition, both interleukin-1α and 6 (IL1α and IL6, respectively) have been associated with radiation pneumonitis e. We will therefore investigate an association between these cytokines and alternations in radiation necrosis.

Alternations in serum markers of angiogenesis, specifically VEGF subtypes, Ang-1, Ang-2, PDGF, Tie-2, and Hif1α, correlate with improvement of radiation response using the anti-angiogenic agent bevacizumab: .Bevacizumab targets VEGF-A, a member of the platelet-derived growth factor (PDGF) family, which modulates microvascular permeability. Other family members include VEGF-B, C, D as well as PDGF. Other angiogenesis factors, including angiopoieten-1 (Ang-1) and angiopoieten-2 (Ang-2) are known to be differentially expressed, along with VEGF-A, following cranial irradiation in animal models and may play important roles in microvascular alterations in response to radiotherapy. We will profile changes in such factors, as well as known inflammatory cytokines (TNF-α, TGF-β, etc. which may play unknown roles) as a function of time following bevacizumab or dexamethasone therapy.

Therapy-induced changes in serum inflammatory markers (those indicated in 1.2.3) predict for cognitive alterations (as measured by MDASI-BT): Markers of inflammation are elevated with aging and their increase has been associated with cognitive decline ([47, 48]. Epidemiological and retrospective data reveals an improvement in neurocognitive function with the use of NSAIDs in patients with Alzheimer's dementia, hence, supporting an inflammatory process involved in neurocognitive decline [49]. Chronic inflammation as a result of mass effect from tumor or treatment related inflammation may be associated with neurocognitive deficits and can be measured in plasma. Interleukin 1 (IL-1), Interleukin 6 (IL-6), and Tumor Necrosis Factor alpha are pro-inflammatory cytokines that are a measure of inflammation and have been shown to be elevated in patients with Alzheimer's dementia [50-54]. In this study, inflammatory biomarkers will be measured at baseline (after registration, but prior to treatment) and at each follow-up visit when MDASI-BT questionnaires are completed.

Germline alterations in Apo E (Apo E2, Apo E3, and Apo E4) are associated with cognitive alterations (as measured by MDASI-BT): Apolipoprotein E (ApoE) is an important factor in remodelling and repairing neurons in response to injury or stress through its lipid transport function. In fact, recent data suggests that patients having the Apo E4 isoform realize Alzheimer's dementia far earlier than those without it [55]. This allele is present in 16% of the general population and 50% of patients with late onset Alzheimer's dementia [49]. Given the similar mechanisms of dementia between Alzheimer's dementia

and radiation induced dementia (e.g. vascular or metabolic), Apo E4 genotyping may prove to be a predictor of radiation induced neuronal damage. The Apo E4 protein binds rapidly and tightly to beta amyloid. Normally beta amyloid exists in a soluble form. However, when bound by Apo E4 protein, beta amyloid becomes insoluble and is more likely to be deposited in plaques, which may lead to changes in microvasculature, ultimately leading to neurocognitive decline. Further, patients with just one copy of the Apo E4 allele have demonstrated accelerated hippocampal volume loss which can also compromise neurocognitive function [56]. Recent preclinical mouse data from Crawford and Villasana have shown neurogenesis in the hippocampus and hippocampal dysfunction depending on Apo E status [57, 58]. Patients with Apo E2 and Apo E3 alleles, on the contrary, tend to have ¼ the risk of developing Alzheimer's disease. It is felt that the E2 and E3 alleles are able to facilitate repair and protection from neuronal damage. Apo E genotyping will be performed to assess whether a subgroup of patients exists that is genetically predisposed to developing cognitive decline.

14.1.2 Objectives

See Section 2.3 for correlative objectives.

14.1.3 Methods

Research blood products and urine will be collected at baseline (after randomization and prior to treatment), prior to cycles 2 and 3, and after cycle 4. For patients who crossover, collection will be performed at the same time points following cross-over. At each interval, (2) 10 mL red top no additive tubes and (1) 10 mL EDTA purple top of blood and (1) (50 mL) random urine will be collected. In addition, urine will be collected in a urine collection container and transferred to aliquot tubes for transport. Analysis of all cytokine alterations, pre and post therapy, will be performed in urine and serum specimens using the xMAP microsphere system (Luminex Corp.), which allows for the simultaneous quantification numerous sera factors within a single 50µl sample. Ambiguous results will be validated using commercially available ELISAs (R&D Systems). To minimize variability, pre and post therapy serum samples from each patient will be analyzed on individual plates in triplicate. DNA will be extracted from whole blood samples by Mayo BAP, and Apo E genotype determination will be performed by evaluation of single nucleotide polymorphisms (SNPs) using real-time PCR methods. Serum profile changes and SNPs will in turn be correlated with alterations in neurocognitive function and objective imaging response. All assays will be performed in the laboratories study translational co-investigators (EPS and DRG) at the University of Texas M.D. Anderson Cancer Center. Results of cytokine analysis and genetic testing will not be released to the patient or their treating physician. Correlative studies will be performed blinded to the overall trial outcome with analysis performed under central statistical review. According to patient consent information, the remaining body fluid biospecimens will be stored in the Alliance tissue bank.

14.2 Alliance A221208-IM1

Evaluation of Imaging Biomarkers of Radionecrosis Response to Corticosteroid and Bevacizumab Therapy in Alliance A221208

14.2.1 Background

Early reduction in DCE-MRI measures (k_{trans}, iAUGC) at 1 month will predict for clinical and radiological response: Radiological response to bevacizumab in the setting of radionecrosis has predominantly been reported in terms of change in volume of T2-FLAIR hyperintensity and change in volume of the post-gadolinium T1-weighted contrast-enhancement. In the study by Levin et al., DCE-MRI was acquired serially and a dramatic reduction in Ktrans was reported at their earliest time point, 6 weeks following initiation of bevacizumab. [21] All patients in this small study demonstrated a Ktrans (a constant that reflects the rate at which contrast extrudes from the intravascular to extravascular space) and clinical response to bevacizumab. Given the dramatic and rapid decrease in Ktrans in these patients, we will be evaluating changes in DCE-MRI measures (Ktrans and iAUGC) at an earlier time point of 4 weeks following the start of study treatment to determine whether these early measures can be used to predict for ultimate clinical response and thereby facilitate treatment optimization.

14.2.2 Objectives

See Section 2.3 for correlative objectives.

14.2.3 Methods

Patients enrolled to A221208-IM1 will have serial multiparametric MRI including DCE-MRI, DWI to acquire ADC and gadolinium enhanced T1-weighted at the time points listed in Section 6.3.

Detailed imaging analysis will be centrally and retrospectively performed to evaluate the correlation of the following measures with clinical outcome:

- Change in volume of the enhancement on post-contrast T1-weighted images over time
- Change in volume of T2 or FLAIR hyperintensity over time
- Change in apparent diffusion coefficient (ADC) on diffusion weighted imaging over time
- Change in rCBV on DSC over time
- Change in ktrans on DCE over time

For ADC and rCBV measurement, image datasets for post-gadolinium T1-weighted images, T2/FLAIR images, ADC and DSC will be spatially co-registered. Regions of interest (ROIs) will be delineated as (1) contrast-enhancing abnormalities on the post-gadolinium T1-weighted images and (2) T2 signal abnormality. ADC and rCBV measures will be sampled in all ROIs at each time point. Delineation of ROIs on both the post-gadolinium T1-weighted images and T2/FLAIR images will enable consistent comparison of changes in ADC and DSC over time, particularly in cases where the enhancing lesions significantly decrease at early time points following bevacizumab.

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APPENDIX I: INFORMED CONSENT

Consent Form

Study Title for Study Participants:

Testing the addition of the antibody, bevacizumab, to the usual treatment for radionecrosis that results from brain radiation.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

A221208 Randomized Phase II Study: Corticosteroids + Bevacizumab vs. Corticosteroids + Placebo (BeSt) for Radionecrosis after Radiosurgery for Brain Metastases

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What is the usual approach to my diagnosis?

You are being asked to take part in this study because you have symptoms and test results showing you have brain radionecrosis. Brain radionecrosis is a non-cancerous condition that makes up an area of dead tissue in the brain that is surrounded by inflamed (swollen) tissue. Brain radionecrosis can cause headaches, nausea, vomiting, weakness and other neurological symptoms. This condition can happen after you receive intense radiation therapy for brain cancer, such as if you have radiosurgery. Radiosurgery is an intense radiation therapy that targets brain cancers and is usually given as a one-day treatment.

The most common initial treatment for brain radionecrosis is corticosteroid therapy (drugs given to reduce inflammation, or swelling). However, not all patients respond to corticosteroid therapy alone. If the symptoms of brain radionecrosis become worse while receiving corticosteroid therapy, you may need to have surgery to remove the tissue where the radionecrosis in the brain has occurred. This is only done if your doctors think it is safe and appropriate procedure for you.

Why is this study being done?

Usually the first treatment for brain radionecrosis only works for some patients and can cause significant side effects in many patients. The purpose of this study is test whether adding a drug called bevacizumab to your standard corticosteroid therapy will improve your symptoms over corticosteroid therapy alone by improving the radionecrosis and minimizing treatment-related

side effects. The effects of bevacizumab with standard corticosteroid therapy will be compared to a placebo with standard corticosteroid therapy

Bevacizumab has been approved for the treatment of many types of cancer, including brain cancers. In cancers, bevacizumab is thought to prevent the growth of new blood vessels (that feed tumor growth) and stop the leakage of other blood vessels to improve oxygen and chemotherapy delivery. In the case of radionecrosis, it is thought that bevacizumab can reduce inflammation (by reducing leaking of the blood vessels) and lessen the symptoms of the radionecrosis.

In this study, we will compare the effects of receiving bevacizumab with standard corticosteroid therapy to the effects of receiving a placebo with standard corticosteroid therapy. A placebo is a liquid that looks like the study drug but contains no medication.

How many people will take part in the study?

About 130 people will take part in this study.

What will happen if I take part in this research study?

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

This study has two study groups:

Group 1 will receive the study drug bevacizumab with corticosteroids
Group 2 will receive a placebo, a liquid that looks like the study drug but contains no medication, with corticosteroids.

Whether you are in Group 1 or 2, the corticosteroid dose will be adjusted by your doctor in order to manage your symptoms.

Each treatment group will receive treatment over 4 weeks. This 4-week period is called “a cycle.” Regardless of which treatment group you are in, you will receive treatment on the following schedule:

Study Schedule

Each cycle is made up of 4 weeks

	Week 1	Week 2	Week 3	Week 4
Bevacizumab/placebo	X	Rest	X	Rest
Corticosteroids	Daily	Daily	Daily	Daily

At any time after you begin study treatment, if you have worsening symptoms despite increasing corticosteroids, you will be informed about whether you have been receiving bevacizumab or placebo. If you have been receiving placebo, you may decide to "cross-over" and receive bevacizumab. If you decide to receive bevacizumab, you will receive treatment for an additional 4 cycles as shown above.

This will require ongoing on-study assessments including clinical assessments, laboratory testing, MRI and patient-reported outcome questionnaires.

How long will I be in this study?

You will receive either bevacizumab or a placebo, as well as corticosteroids, as recommended by your treating doctor to manage your symptoms, for up to four 4-week cycles, as tolerated. As mentioned above, if you have worsening symptoms and you have been receiving placebo, you may crossover and receive bevacizumab for four additional 4-week cycles.

After you finish the study treatment of about 16 weeks (or 32 weeks if you have "crossed over"), your doctor will continue to watch you for side effects and follow your condition for up to 1 year after you stopped study treatment.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and assessments that you will need to have if you take part in this study.

Before you begin the study:
You will need to have the following extra tests to find out if you can be in the study:

- MRI images of your brain will be sent to a central radiology lab for review ("central review"). Any identifying information will be removed from the images sent to the radiology lab. Even though images are sent to the lab, your doctor may decide to review your MRI images at your hospital to see if you can be in the study.
- Blood tests and urine tests to determine blood counts and urine proteins
- Pregnancy test (if you are able to have children)

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests during the study. They are not part of the

usual approach for your condition but they are part of usual monitoring while taking bevacizumab.

During the study:
- Blood tests every 4 weeks while on study treatment
- Urine tests every 4 weeks while on study treatment,

You will also be asked to complete questionnaires before you start treatment and 2, 4, 6, 8 and 12 weeks after you start treatment. If you "cross-over" to bevacizumab treatment, you will need to repeat these questionnaires at the same time points. After treatment, you will be asked to complete the questionnaires every 2 months for 6 months.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:
- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your condition.

The drugs used in this study may affect how different parts of your body work such as your kidneys, heart, and blood. The study doctor will be testing your blood and urine will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug.

Here are important points about side effects:
- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:
- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Bevacizumab:

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), from 4 to 20 may have:
• Anemia which may require blood transfusion • Low white cell count that may increase the risk of infection • Infection, including collection of pus in the belly or rectum • Abnormal heartbeat which may cause palpitations or fainting • Pain in the belly, rectum, chest, joints, muscles, or tumor • Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration • Bleeding from multiple sites including the vagina or nose • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Blockage of internal organs which may cause vomiting or inability to pass stool • Sores in the mouth • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Delay in healing of wounds or spontaneous opening of wounds • Weight loss, tiredness, or dizziness • Muscle weakness • Damage to the jawbone which may cause loss of teeth • Headache • Numbness, tingling or pain in the fingers or toes • Hoarseness, stuffy nose, or cough • Dry skin • Swelling and redness of the skin • Blood clot in limbs or lungs which may cause swelling, pain, shortness of breath • Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Sores in the throat • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Damage to organs (bone, lungs, others) which may cause loss of motion • Bleeding in the tumor, brain, belly or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Redness, pain or peeling of palms and soles

Additional Notes on Possible Side Effects for Bevacizumab:

- Risk in children or adolescents: abnormal bone changes which may interfere with growth.
- Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Possible Side Effects of Corticosteroids:

COMMON, SOME MAY BE SERIOUS In 100 people receiving corticosteroids, more than 20 and up to 100 may have:
• Trouble sleeping • Weight gain around the stomach • Puffiness (especially in the face) • Buildup of fluids and a rise in blood pressure • Possible rise in your blood sugar • Muscle weakness • Mood swings

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving corticosteroids, from 4 to 20 may have:
• Changes in the blood levels of potassium. • Infection • Menstrual changes • Changes in personality • Dizziness • Stomach and throat ulcers or worsening of any ulcers you had before treatment

RARE, AND SERIOUS In 100 people receiving corticosteroids, 3 or fewer may have:
• Depression • Seizures • Patients who are more likely to get heart disease may have heart failure • Brittle bones • Swelling and pain of the pancreas • Itching, and other allergic reactions, some severe.

R**eproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study and for at least 90 days after you stop taking the study drugs. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. If you suspect you may be pregnant, immediately inform your study doctor or health care team. It is not known whether bevacizumab will affect your ability to have children in the future. You should talk to your doctor about your choices.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

It is not possible to know at this time if the study drug/study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

What other choices do I have if I do not take part in this study?

If you decide not to take part in this study, you have other choices. Your other choices may include:

- Getting treatment or care for your radionecrosis without being in a study
- Taking part in another study
- Getting no treatment

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ (insert name of center) Institutional Review Board at _____ (insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)

What are the costs of taking part in this study?

The bevacizumab or placebo will be supplied at no charge while you take part in this study. The cost of getting the bevacizumab/placebo ready and giving it to you is not paid by the study so you or insurance company may have to pay for this. It is possible that the bevacizumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your condition while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before

you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may or may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Will my medical information be kept private?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance for Clinical Trials in Oncology (Alliance)
- The Alliance Data and Safety Monitoring Board, a group of experts who regularly review the progress of the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP), and the National Cancer Institute (NCI) in the U.S., and similar ones if other countries are involved in the study.
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the NCI to provide greater access to cancer trials.
- Genentech Inc. and the Roche Group, makers of bevacizumab

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ (insert name of study doctor[s]) at _____ (insert telephone number).

ADDITIONAL STUDIES SECTION:

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You will not get health benefits from any of these additional studies. The researchers leading these optional studies hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Optional imaging study – extra research MRIs

NOTE TO INSTITUTIONS: The Optional Imaging study section is not to be removed from the consent. Please select one of the following based on whether or not your institution elected to participate in the advanced imaging sub-study.*
*This note for investigators is instructional and should not be included in the consent form sent to IRBs.

☐ Your health care facility has extra MRI testing available, known as "DCE" MRI. DCE MRI is a specialized kind of MRI that allows analysis of blood vessels related to a brain tumor or brain lesions like radionecrosis. If your facility has this available, researchers would like to use these scans for a related research study to see whether they can predict how well a patient will do following treatment. If you choose to take part in this study, you will have extra research MRIs. These scans are already used in medical care but extra scans would be taken at a time point in your treatment that is not usual. Your scans will be submitted to a central image library. Researchers would use these scans to see if there are early imaging markers that may predict how you will respond to treatment, so that in future studies, these markers may be used to guide treatment in patients with the same condition. These scans will be saved so that researchers can look back at these scans after the study is over.

If you agree to have extra scans, it would involve extra time to have an extra MRI done after 1 cycle of bevacizumab/placebo treatment, and again after 1 cycle of bevacizumab if you "cross-over." The most common risks related to the MRI are anxiety/stress, claustrophobia, and discomfort. The most common risks related to the drug used for MRI (called gadolinium) are headache, nausea, vomiting, hives, temporary low blood pressure, and allergic-like reaction. The scan would only be used for research and not to guide your medical care. There are educational materials available about this type of scan. Ask your study doctor about them, if you would like more information.

The costs of these optional extra scans will not be paid by the study or your insurance company, but your hospital will cover these costs.

☐ Your health care facility does NOT have extra DCE MRI testing which will be necessary for the optional imaging study. DCE MRI is a specialized kind of MRI that allows analysis of blood vessels related to a brain tumor or brain lesions like radionecrosis. You should circle the answer "no" below.

Please circle your answer to show whether or not you would like to take part:

1. I choose to take part in the imaging study and will have the extra MRIs.

YES NO

Initial: _____ Date: _____

Optional Sample Collections for Laboratory Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect blood and urine for research to study possible markers that may predict how you will respond to treatment so that in future studies, these markers may be used to guide treatment in patients with the same condition.

What is involved?

If you agree to take part, here is what will happen next:

1) About 2 tablespoons of blood will be collected from a vein in your arm and you will be asked to provide a random urine sample. These samples will be collected before you start treatment and after 1, 2, and 4 months of treatment.
2) Your sample and some related health information will be sent to a researcher for use in the study described above. Remaining samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

Biobanking for Possible Future Studies

The researchers will also ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by the Alliance and supported by the National Cancer Institute.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part of this additional study. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

How will information related to my samples be protected?

We have many ways to protect the information related to your samples:
Your samples and information receive a unique code. Researchers only receive coded samples and information, and will not be able to link the code to you. Only approved people in the Alliance can match you to the code on your samples and related information.

Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information. Steps we take include, but are not limited to, restricted access to buildings, rooms and freezers housing patient samples, numeric coding of both patient data and samples, and password protected access to databases housing patient data.

Before samples are given to researchers, studies are reviewed for the quality of the science and for patient protection. Records from research studies can be reviewed by the Cooperative Group,

by the sponsor, and by government agencies. This is to make sure the research follows the rules of the Cooperative Group and state or federal laws.

In most cases, research results will not be returned to you or your doctor. If research results are required to make a decision regarding your treatment on this study then research results may be shared with you or your doctor. If research results are published, your name and other personal information will not be given.

The Alliance also has a Certificate of Confidentiality from the U.S. Department of Health and Human Services. The Certificate protects against the forced release of personal information from the Cooperative Group bank or database.

What this means is that Alliance cannot be forced to disclose your identity to any third party. It is possible that for some legal proceedings, the Certificate of Confidentiality could be over-ridden by a court of law.

Making your choice

The choice to take part is up to you. You may choose not to let us use and store your samples. If you decide not to let us store and use your samples, you will still receive the same medical care. You may also take part in other research studies.
To learn more, ask the study staff for the booklet called “Giving Samples for Research" or visit http://www.cancer.gov. You may want to read the section “What types of research use samples?”
If you decide that your samples can be kept, you may change your mind at any time. Contact the study staff at your hospital and let them know that you do not want your samples used for research. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers cannot be returned or destroyed.
Thank you for considering whether to allow your samples to be used for the research described above and/or banked for future research.
Please circle your answer to show whether or not you would like to take part in each option:

2. My coded samples and related coded information **may be used** in the research described above to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families).

   Yes____ No____

3. My coded samples and related coded information **may be kept for use** in future research to learn about, prevent, find or treat **cancer**. This may also include research on inherited traits (genes passed on in families).

   Yes____ No____

4. My coded samples and related coded information may be **kept for use** in future research to learn about, prevent, find or treat **other health problems** (for example: diabetes,

Alzheimer's disease, or heart disease). This may also include research on inherited traits (genes passed on in families).

Yes____ No____

5. Someone from my hospital or Alliance may contact me in the future to ask me to take part in more research.

Yes____ No____

Are there any costs or payments?

There are no costs to you or your insurance. **You will not be paid for taking part.** If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, (insert name of study doctor for main trial) at _____ (insert telephone number of study doctor for main trial) who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, (insert name of study doctor for main trial), at _____ (insert telephone number of study doctor for main trial).

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

APPENDIX II: SYSTEMIC THERAPIES ALLOWED CONCURRENTLY WITH BEVACIZUMAB

- Irinotecan
- Fluorouracil / leucovorin
- Doxorubicin (with close cardiac assessment)
- Carboplatin
- Paclitaxel
- Cyclophosphamide
- Vincristine
- Endocrine therapy for breast or prostate cancer
- Trastuzumab
- Xeloda
- Abraxane
- Pemetrexed
- Erlotinib
- Gemcitabine
- Lapatinib
- Hormonal therapy for breast or prostate cancer

APPENDIX III: MR Imaging Remote Central Review

The following procedures will be followed in cases where institutions opt to utilize real time central review of baseline imaging for the determination of patient eligibility (see Section 4.6):

MR imaging data sets of baseline will be reviewed by the A221208 central review panel **within no more than 72 hours after data receipt to determine patient eligibility.**

IROC will contact the A221208 central review panel, **within 24 hours (except weekends and holidays) after images being received**, for scheduling a real-time remote review. Reviewers' availabilities (at least monthly) need to be sent to the IROC in advance for this purpose.

IROC notifies both the participating site and Alliance of the central review result **within 24 hours after receiving the result from the central review panel**. If there are any uncertainties or the participating site disagrees with the first central review result, a second review by either another central reviewer or an adjudicator [redacted] will be performed. This process may take additional 24-48 hours turn-around time, and such review result will be used as the final decision for the response determinations. The Alliance A221208 trial committee makes decisions of A221208 patient inclusion or exclusion, if a participating site eventually disagrees with the central review result.

Response determinations will be based on the centralized review results and NOT on local assessment within this trial.

For any such related questions, participating sites may directly contact the IROC instead of the central reviewer(s), via either the trial email at [redacted]

APPENDIX IV: A221208 TUMOR IMAGING PROTOCOLS

Recommended 1.5T Protocol* - Option A – Double Dose of Contrast

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Contrast Preload, or DCE	Ax 2D T2w	3D T1w Post	DSC-MRI
Sequence	IR-GRE	TSE	EPI	Option A: 0.1 mmol/kg	TSE	IR-GRE	**GRE-EPI**: Option A: 0.1 mmol/kg
Plane	Axial	Axial	Axial		Axial	Axial	Axial
Mode	3D	2D	2D		2D	3D	2D
TR [ms]	2100	>6000	>5000		>3500	2100	1000-1500
TE [ms]	Min	100-140	Min		100-120	Min	25-35ms
TI [ms]	1100	2200				1100	N/A
Flip Angle	10°-15°	90°/≥ 160°	90°/180°		90°/≥ 160°	10°-15°	60°
Frequency	≥ 172	≥ 256	128		≥ 256	≥ 172	≥ 96
Phase	≥ 172	≥ 256	128		≥ 256	≥ 172	≥ 96
NEX	≥ 1	≥ 1	≥ 1		≥ 1	≥ 1	1
Pre-bolus Time Points							30-60
Total Time Points	N/A	N/A	N/A		N/A	N/A	≥120
FOV	256 mm	240 mm	240 mm		240 mm	256 mm	240 mm
Slice thickness	≤ 1.5 mm	≤ 4 mm	≤ 4 mm		≤ 4 mm	≤ 1.5 mm	As needed for optimal tumor coverage (Typically 3-5mm)
Gap/spacing	0	0	0		0	0	As needed for optimal tumor coverage (Typically 0-1)
Diffusion Options	N/A	N/A	B=0, 500, and 1000 s/mm^2 ≥3 directions		N/A	N/A	N/A
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x

* For contrast agent dosing the option chosen must be consistent between the preload and DSC dose (i.e. either option 1 or 2 for both injections).

Recommended 1.5T Protocol* - Option B – Single Dose of Contrast

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Contrast Preload, or DCE	Ax 2D T2w	DSC-MRI	3D T1w Post
Sequence	IR-GRE	TSE	EPI	Option B: 0.05 mmol/kg	TSE	**GRE-EPI**: Option B: 0.05 mmol/kg	IR-GRE
Plane	Axial	Axial	Axial		Axial	Axial	Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100	>6000	>5000		>3500	1000-1500	2100
TE [ms]	Min	100-140	Min		100-120	25-35ms	Min
TI [ms]	1100	2200				N/A	1100
Flip Angle	10°-15°	90°/≥ 160°	90°/180°		90°/≥ 160°	60°	10°-15°
Frequency	≥ 172	≥ 256	128		≥ 256	≥ 96	≥ 172
Phase	≥ 172	≥ 256	128		≥ 256	≥ 96	≥ 172
NEX	≥ 1	≥ 1	≥ 1		≥ 1	1	≥ 1
Pre-bolus Time Points						30-60	
Total Time Points	N/A	N/A	N/A		N/A	>120	N/A
FOV	256 mm	240 mm	240 mm		240 mm	240 mm	256 mm
Slice thickness	≤ 1.5 mm	≤ 4 mm	≤ 4 mm		≤ 4 mm	As needed for optimal tumor coverage (Typically 3-5mm)	≤ 1.5 mm
Gap/spacing	0	0	0		0	As needed for optimal tumor coverage (Typically 0-1)	0
Diffusion Options	N/A	N/A	B=0, 500, and 1000 s/mm^2 ≥3 directions		N/A	N/A	N/A
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x

* For contrast agent dosing the option chosen must be consistent between the preload and DSC dose (i.e. either option 1 or 2 for both injections).

Recommended 3T Protocol* - Option A – Double Dose of Contrast

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Contrast Preload, or DCE	Ax 2D T2w	3D T1w Post	DSC-MRI
Sequence	IR-GRE	TSE	EPI	Option A: 0.1 mmol/kg	TSE	IR-GRE	**GRE-EPI** Option A: 0.1 mmol/kg
Plane	Axial	Axial	Axial		Axial	Axial	Axial
Mode	3D	2D	2D		2D	3D	2D
TR [ms]	2100	>6000	>5000		>2500	2100	1000- 1500
TE [ms]	Min	100-140	Min		80-120	Min	25-35ms
TI [ms]	1100	2500				1100	N/A
Flip Angle	10°-15°	90°/≥ 160°	90°/180°		90°/≥ 160°	10°-15°	60°
Frequency	256	≥ 256	128		≥ 256	256	≥ 96
Phase	256	≥ 256	128		≥ 256	256	≥ 96
NEX	≥ 1	≥ 1	≥ 1		≥ 1	≥ 1	1
Pre-bolus Time Points							30-60
Total Time Points	N/A	N/A	N/A		N/A	N/A	120
FOV	256 mm	240 mm	240 mm		240 mm	256 mm	240mm
Slice thickness	1 mm	3 mm	3 mm		3 mm	1 mm	As needed for optimal tumor coverage (Typically 3-5mm)
Gap/spacing	0	0	0		0	0	As needed for optimal tumor coverage (Typically 0-1)
Diffusion Options	N/A	N/A	B=0, 500, and 1000 s/mm^2 ≥3 directions		N/A	N/A	N/A
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x

* For contrast agent dosing the option chosen must be consistent between the preload and DSC dose (i.e. either option 1 or 2 for both injections).

Recommended 3T Protocol* - Option B – Single Dose of Contrast

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Contrast Preload, or DCE	Ax 2D T2w	DSC-MRI	3D T1w Post
Sequence	IR-GRE	TSE	EPI	Option B: 0.05 mmol/kg	TSE	**GRE-EPI** Option B: 0.05 mmol/kg	IR-GRE
Plane	Axial	Axial	Axial		Axial	Axial	Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100	>6000	>5000		>2500	1000- 1500	2100
TE [ms]	Min	100-140	Min		80-120	25-35ms	Min
TI [ms]	1100	2500				N/A	1100
Flip Angle	10°-15°	90°/≥ 160°	90°/180°		90°/≥ 160°	60°	10°-15°
Frequency	256	≥ 256	128		≥ 256	≥ 96	256
Phase	256	≥ 256	128		≥ 256	≥ 96	256
NEX	≥ 1	≥ 1	≥ 1		≥ 1	1	≥ 1
Pre-bolus Time Points						30-60	
Total Time Points	N/A	N/A	N/A		N/A	120	N/A
FOV	256 mm	240 mm	240 mm		240 mm	240mm	256 mm
Slice thickness	1 mm	3 mm	3 mm		3 mm	As needed for optimal tumor coverage (Typically 3-5mm)	1 mm
Gap/spacing	0	0	0		0	As needed for optimal tumor coverage (Typically 0-1)	0
Diffusion Options	N/A	N/A	B=0, 500, and 1000 s/mm^2 ≥3 directions		N/A	N/A	N/A
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x

* For contrast agent dosing the option chosen must be consistent between the preload and DSC dose (i.e. either option 1 or 2 for both injections).

Footnote on GE vs. Siemens vs. Philips – T1 pre and post recommendations

DCE Recommended parameters:

- fast T1-weighted spoiled gradient-recalled echo acquisition
- matrix 128 x 128 mm
- 3-5 mm slice thickness
- 3-6 second temporal resolution
- minimum 5 minutes acquisition time
- IV gadolinium injection of 0.05 mmol/kg, at 2-4 mL/s, should occur 20 seconds or more after the start of the imaging series and should be followed by a saline bolus at the same injection rate.
- 25-35 deg flip angle

Abbreviations:

2DFL, 2-dimensional FLASH (fast low angle shot) gradient recalled echo;

3D, 2-dimensional;

A/P, anterior to posterior;

ADC, apparent diffusion coefficient;

Ax, Axial;

DSC, dynamic susceptibility contrast;

DWI, diffusion-weighted imaging;

EPI, echo-planar imaging;

FLAIR, fluid-attenuated inversion recovery;

FOV, field of view;

GE-EPI, gradient-echo echo-planar imaging;

IR-GRE, inversion-recovery gradient-recalled echo.

MPRAGE, magnetization prepared rapid gradient-echo;

NEX, number of excitations or averages;

PD, proton density;

R/L, right to left;

SS-EPI, single-shot echo-planar imaging;

TE, echo time;

TI, inversion time;

TR, repetition time;

TSE, turbo spin-echo.

APPENDIX V: PATIENT INFORMATION SHEET

PATIENT INFORMATION SHEET
TREATMENT
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet is to be completed at each study visit.

2. The booklet contains 3 sets of questions:
    a. M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) (28 questions)
    b. Dexamethasone Symptoms Questionnaire-Chronic (22 questions)
    c. Linear Analogue Self Assessment (LASA) (5 questions)

3. Directions on how to complete this set of questions are written on the top of the page.

4. You may call a member of the study team to answer any questions you might have. You will be given a name and telephone number. You can call anytime with any concerns or questions.

5. Bring booklet with you to your next clinical visit. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help

APPENDIX VI: MD ANDERSON SYMPTOM INVENTORY-BT

Date: ☐☐ / ☐☐ / ☐☐
(month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

PLEASE USE BLACK INK PEN

M. D. Anderson Symptom Inventory (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____

Protocol #: _____

PI: _____

Subject Initials: _____

MD Anderson # : ☐☐☐☐☐☐ PDMS # : ☐☐☐☐

PLEASE USE BLACK INK PEN

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your seizures at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your vision at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in appearance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in bowel pattern (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. General activity?	○	○	○	○	○	○	○	○	○	○	○
24. Mood?	○	○	○	○	○	○	○	○	○	○	○
25. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
26. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
27. Walking?	○	○	○	○	○	○	○	○	○	○	○
28. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

APPENDIX VII: DEXAMETHASONE SYMPTOMS QUESTIONNAIRE-CHRONIC

Dexamethasone Symptom Questionnaire –Chronic (DSQ-Chronic)

PDMS Number: Patient Initials:

Today's date (day, month, year):

We are interested in some things about you and your health. Please answer all the questions by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential. **IN THE LAST WEEK**:

Patient question	Not at all	A little	Quite a bit	Very much
1. Did you have indigestion/heartburn/reflux or discomfort in the upper abdomen?	1	2	3	4
2. Did you have trouble with sleep? *(getting or staying asleep)?*	1	2	3	4
3. Have you felt nauseated?	1	2	3	4
4. Have you vomited?	1	2	3	4
5. Have you lacked appetite?	1	2	3	4
6. Have you had increased appetite?	1	2	3	4
7. Have you had hiccups?	1	2	3	4
8. Have you lost weight?	1	2	3	4
9. Have you gained weight?	1	2	3	4
10. Have you felt agitated/nervous?	1	2	3	4
11. Have you had a rash/acne on your face?	1	2	3	4
12. Have you had thrush/yeast infection in your mouth?	1	2	3	4
13. Have you noticed increased roundness of your face?	1	2	3	4
14. Have you experienced low mood, sadness, depression and/or easy crying?	1	2	3	4
15. Have you experienced increased levels of anger or irritability?	1	2	3	4
16. Have you had difficulty standing from a seated position or walking up stairs?	1	2	3	4

Patient question	Not at all	A little	Quite a bit	Very much
17. Have you had problems with your skin being fragile, developed stretch marks or easily bruised?	1	2	3	4
18. Have you had headaches?	1	2	3	4
19. Are you Diabetic? **If no, go to Question 21**	Yes / No (please circle)			
20a. If yes, was the diabetes diagnosed since you started corticosteroids (e.g. dexamethasone, prednisone)	Yes / No (please circle)			
20b. If yes, have you had trouble controlling your blood sugars?	1	2	3	4

Patient question
21. What other problems have you noticed due to corticosteroids? _____ _____ _____ _____
22. Of all the symptoms you've experienced due to corticosteroids, please list the 3 you have found the most bothersome: 1. (Most bothersome):_____ 2. (2nd most bothersome):_____ 3. (3rd most bothersome):_____

Patient Signature

APPENDIX VIII: LINEAR ANALOGUE SELF ASSESSMENT (LASA)

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

2. your overall mental (intellectual) well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

3. your overall physical well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

4. your overall emotional well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

5. your overall spiritual well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

APPENDIX IX: CORTICOSTEROID MEDICATION LOG

Corticosteroid Medication Log

PLEASE FILL OUT AND BRING THIS SHEET TO ALL VISITS.

While participating in this study, you will be asked to gradually reduce your corticosteroid treatment and fill out the following pill diary to record your schedule of reduction.

SPECIAL INSTRUCTIONS

1. Take your corticosteroid tablets orally, as instructed by your doctor with or without food.
2. If a dose is missed, please take the dose as soon as possible, but only if there are 6 or more hours remaining before the next dose (if taking two doses per day), or 12 or more hours remaining before the next dose (if taking only one dose per day).
3. If vomiting occurs after taking your corticosteroid, do not take a replacement dose on that day. Resume at the next scheduled dose
4. Corticosteroid tablets should be stored at room temperature

CYCLE #: _____ # of WEEKS_____

DAY	Medication	Dose of medication	DATE	TIME		TIME		Number of tablets taken (AM/PM)	Comments
Example	*Dexamethasone*	*4 mg*	*07/01/2015*	*9:00*	*AM*	*9:00*	*PM*	*2/2*	
1					AM		PM		
2					AM		PM		
3					AM		PM		
4					AM		PM		
5					AM		PM		
6					AM		PM		
7					AM		PM		
8					AM		PM		
9					AM		PM		
10					AM		PM		
11					AM		PM		
12					AM		PM		
13					AM		PM		
14					AM		PM		
15					AM		PM		
16					AM		PM		
17					AM		PM		
18					AM		PM		
19					AM		PM		
20					AM		PM		
21					AM		PM		
22					AM		PM		
23					AM		PM		
24					AM		PM		
25					AM		PM		
26					AM		PM		
27					AM		PM		
28					AM		PM		
29					AM		PM		
30					AM		PM		
31					AM		PM		
32					AM		PM		
33					AM		PM		
34					AM		PM		

Patient Signature: _____Date:_____
Consenting Professional/Research RN Signature: _____ Date:_____
Comments:_____

APPENDIX X: INTELLECTUAL PROPERTY OPTION TO COLLABORATORS

The NCI's "Cancer Therapy Evaluation Program Intellectual Property Option to Collaborators" terms of award modifications (as revised April 1, 2011) apply to this study and to any institutions or investigators participating in this study or any future study that uses specimens treated with the bevacizumab being provided for this study. Under the terms of the Option, Genentech shall be considered a "Collaborator" and Study Drug bevacizumab shall be considered an "Agent" within the meaning of the Option.