

Supplemental Table 1. Details of CNS Hemorrhage Events Observed on Protocol

Patient	Summary of Event
Pt 025	Grade 1 asymptomatic punctate hemorrhage observed on restaging brain MRI prior to cycle 5 of therapy. Bevacizumab held; brain MRI repeated without progression of CNS bleeding, and bevacizumab resumed without incident.
Pt 034	Grade 1 petechial hemorrhage observed on early restaging brain MRI in setting of headaches. Was found to have evidence of tumor progression in liver, lungs, and brain. Transitioned to hospice shortly thereafter.
Pt 036	Grade 1 asymptomatic hemorrhage observed on restaging brain MRI prior to cycle 3 of therapy. Bevacizumab held; brain MRI repeated without progression of CNS bleeding, and bevacizumab resumed without incident.
Pt 027	Grade 2 hemorrhage presenting with altered mental status and paranoia. Bevacizumab permanently discontinued. Brain MRI ~2 months later demonstrated progressive CNS disease without worsening of CNS hemorrhage.

Supplemental Table 2. Relationship Between VEGF Single Nucleotide Polymorphisms and Clinical Outcomes. No significant association was found between genotypes with PFS or OS. The table shows the p values of the tests.

Clinical Outcome	-634 G/C (rs2010963)	-1498 C/T (rs833061)	-2578 C/A (rs699947)	-1154 G/A (rs1570360)
OS	0.54	0.56	0.76	0.54
PFS	0.75	0.39	0.34	0.75

Abbreviations: OS, overall survival; PFS, progression-free survival

Supplemental Figure 1. MRI/MRA Specifications

MRI:

MRI brain scans will be done at baseline, and at each follow-up. Brain MRI should have 5 mm or less slice thickness for axial post-contrast images using T1 or SPGR sequence.

MRI brain scans at baseline, following the first dose of bevacizumab, and prior to cycle 3 of treatment will be performed at MGH Charlestown Navy Yard. All other MRI brain scans may be performed at the patient's study site, according to the specifications in paragraph 1, above.

MRI brain scans at baseline, following bevacizumab, and prior to cycle 3 of treatment will include the following:

- T1- weighted images
- T2-weighted images
- FLAIR (fluid- attenuated inversion recovery)
- Arterial Spin Labeling (ASL) perfusion
- Contrast agent enhanced T1-weighted permeability
- DTI (diffusion tensor imaging)
- T2/T2*-weighted perfusion
- Modified MRA (See below)

Modified MRA:

- The entire brain should be covered. (The neck does not need to be covered.)
- The sequence should be obtained **PRIOR** to the administration of intravenous contrast.
- The following are suggested parameters

Seq	TR Msec	TE msec	Flip Angle	Matrix	FOV	Slice thick mm	Voxel Size mm ³
MRA	35	3.5	22	309*448	230*230	0.8	0.5*0.5*0.8

Supplemental Figure 2. Neurological Examination Worksheet

NEUROLOGICAL EXAMINATION WORKSHEET

(to be completed at baseline and at the end of each 3-week cycle)

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PLEASE NOTE IF SIGNS/SYMPTOMS ARE THOUGHT RELATED OR NOT RELATED TO PATIENT'S
BRAIN METASTASES

Patient _____ Examiner _____ Date _____

Level of consciousness (check one)

- Normal
- Somnolence or sedation not interfering with function
- Somnolence or sedation interfering with function, but not interfering with ADLs
- Obtundation or stupor; difficult to arouse; interfering with ADLs
- Coma

Neurological Symptoms (check if present, and specify CTCAE grade)

*if asymptomatic, check here _____

- Headache _____ present, specify grade _____
- Dizziness/lightheadedness _____ present, specify grade _____
- Vertigo _____ present, specify grade _____
- Nausea/vomiting _____ present, specify grade _____
- Visual problems _____ present, specify grade _____
- Seizure _____ present, specify grade _____
- Other _____ absent _____ present, specify _____ grade _____

Cranial nerves II-XII⁺

- Normal
 - present, not interfering w/ADLs
 - present, interfering w/ADLs
 - life-threatening, disabling
- +If abnormal, please specify which cranial nerve(s) affected _____

Language

- Dysphasia or aphasia _____ absent
- awareness of receptive or expressive aphasia, not impairing ability to communicate
- receptive or expressive dysphasia, impairing ability to communicate
- inability to communicate

Sensation**

- normal
- loss of deep tendon reflexes or paresthesia, but not interfering with function
- objective sensory loss or paresthesia interfering with function, but not with ADLs
- Sensory loss or paresthesia interfering with ADLs
- Permanent sensory loss that interferes with function

**If abnormal, please specify location/distribution _____

NEUROLOGICAL EXAMINATION WORKSHEET

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Patient _____ Examiner _____ Date _____

Strength*

R upper extremity	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal; please specify _____
L upper extremity	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal; please specify _____
R lower extremity	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal; please specify _____
L lower extremity	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal; please specify _____

*If abnormal, please specify muscle group and grade according to the scale below: (e.g. biceps, grade 2)

grade 1 = asymptomatic with weakness on physical exam

grade 2 = symptomatic and interfering w/function, but not interfering with ADLs

grade 3 = symptomatic and interfering with activities of daily living

grade 4 = bedridden or disabling

Ataxia***

R upper extremity (finger-to-nose testing)	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal, specify grade _____
L upper extremity (finger-to-nose testing)	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal, specify grade _____
Gait	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal, specify grade _____
Balance (Romberg)	<input type="checkbox"/> Normal	<input type="checkbox"/> Abnormal, specify grade _____

***If any of above abnormal, please assign grade using the following criteria

grade 1 = asymptomatic but abnormal on physical exam, and not interfering with function

grade 2 = mild symptoms interfering with function, but not interfering with ADLs

grade 3 = moderate symptoms interfering with ADLs

grade 4 = bedridden or disabling

In the opinion of the treating physician, overall, are the patient's *tumor-related* neurological signs and symptoms worsening, stable, or improved (please check one)?

Worsening

Stable

Improved

Is the patient currently taking corticosteroids?

Yes

No

If yes, please list name of medication and dose (e.g. decadron, 4 mg QD) _____

Please indicate the patients ECOG Performance Status: _____