Treatment of CNS Radiation Necrosis with Bevacizumab, an Anti-VEGF Antibody

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Radiation Injury - Classification

- **Acute**
  - During RT
  - Frequently requires glucocorticoid therapy

- **Early delayed or sometimes called subacute**
  - Usually 2 to 12 weeks after RT
  - Some call it pseudoprogression today
  - Responds to glucocorticoid therapy

- **Late**
  - Months to years after RT and as late as 13 yrs
  - Necrosis with increased capillary leakage and destruction of surrounding CNS parenchyma
Radiation CNS Neurotoxicity

- RT “necrosis” 0.5 to 3 yrs after RT and as late as 13 yrs later
- Incomplete association with RT dose, field size, and frequency
  - White matter radiation necrosis: 2% (<54 Gy) to 18% (>77 Gy)\(^1\)
  - Some chemoradiation studies show necrosis rates of 24% to 55%\(^2\)

\(^1\) Corn et al. Cancer. 10:2828, 1994
\(^2\) Levin et al. IJROBP. 53:58, 2002

Radiation Necrosis in Oligodendroglioma
Patient 8 Months After Irradiation

[Images of brain scans showing progression]
Radiation Injury – MRI Imaging

- **Early Injury**
  - Depending on RT dose and fraction size
  - White matter confluent changes: 27% (<54 Gy) to 39% (>77 Gy)

- **Later Injury - RT Necrosis**
  - Gd-contrast enhancement on T1 images (short TR relaxation and TE excitation times enhance signals from fat-containing tissues)
    - Areas seen on previously nonenhancing tumor
    - Abnormal enhancement at a distance from the primary tumor
    - Periventricular areas of enhancement
    - Pattern of enhancement “soap bubble or Swiss cheese like”
  - T2 FLAIR (Fluid-Attenuated Inversion Recovery MRI sequence shows edema well)
    - Large size
    - Rapidly occurred
Radiation Injury - Mechanisms

- Continuous Process – poorly understood
  - Genes and molecular events
    - Apoptosis
    - Adhesion molecules
  - Cytokine-mediated vascular changes
    - Increased permeability
    - Angiogenesis?
    - Expression of VEGF
- Hypoxia
Radiation Injury – Clinical Signs/Symptoms

- Clinical symptoms and signs – can mimic tumor
  - Brain – depending on irradiated site
    - Neurocognitive slowing: Fatigue and dementia
    - Focal weakness: tumor-like behavior
    - Hormonal dysfunction
    - Death
  - Spinal cord
    - Growth arrest in children
    - Cardiac problems in children
    - Myelitis causing weakness, paresis, and sometimes pain
Radiation Injury - Treatment

- Historical treatments – ineffective and poorly studied
  - Glucocorticoids
  - Anticoagulation
  - Hyperbaric oxygen
  - High-dose vitamins
  - Anti-inflammatory agents

- Bevacizumab Case Study
Demographics – Bevacizumab Case Report (IJROBP 67:323, 2007)

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<td>Age</td>
<td>39</td>
<td>70</td>
<td>32</td>
<td>56</td>
<td>50</td>
<td>60</td>
<td>24</td>
<td>54</td>
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<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
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<td>Histology</td>
<td>AOA</td>
<td>HEPC</td>
<td>AO</td>
<td>AA</td>
<td>GBM</td>
<td>GBM</td>
<td>GBM</td>
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<tr>
<td>RT dose, Gy</td>
<td>61</td>
<td>54</td>
<td>57</td>
<td>50</td>
<td>60</td>
<td>60</td>
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<tr>
<td>RS 80-85% isodose, Gy</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>17</td>
<td>15</td>
<td>15</td>
<td>17</td>
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<tr>
<td>Drug with Avastin</td>
<td>TMZ</td>
<td>TMZ</td>
<td>Carbo</td>
<td>Carbo</td>
<td>CPT11</td>
<td>CPT11</td>
<td>TMZ</td>
<td>TMZ</td>
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<tr>
<td>Pre-BVZ T1(cm²)</td>
<td>4.47</td>
<td>4.42</td>
<td>10.9</td>
<td>6.5</td>
<td>8.07</td>
<td>7.8</td>
<td>7.3</td>
<td>7.33</td>
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<tr>
<td>Pre-BVZ FLAIR(cm²)</td>
<td>22.83</td>
<td>16.21</td>
<td>35.34</td>
<td>18.6</td>
<td>37.3</td>
<td>34.6</td>
<td>27.5</td>
<td>34.4</td>
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<tr>
<td>Post-BVZ T1(cm²)</td>
<td>3.01</td>
<td>3.71</td>
<td>5.6</td>
<td>3.07</td>
<td>4.91</td>
<td>2.06</td>
<td>2.04</td>
<td>6.15</td>
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<tr>
<td>Post-BVZ FLAIR(cm²)</td>
<td>7.2</td>
<td>10.41</td>
<td>14.26</td>
<td>4.2</td>
<td>11.26</td>
<td>25.18</td>
<td>6.9</td>
<td>12</td>
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<tr>
<td>Change in daily dexamethasone</td>
<td>-10</td>
<td>-16</td>
<td>-6</td>
<td>-6</td>
<td>-8</td>
<td>-8</td>
<td>0</td>
<td>-6</td>
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<tr>
<td>Diagnosis of RTN</td>
<td>MRI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Biopsy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Location of RTN</td>
<td>RP</td>
<td>LT</td>
<td>LF</td>
<td>LT</td>
<td>LP</td>
<td>LP</td>
<td>RT</td>
<td>RT</td>
</tr>
<tr>
<td>Weeks between MRI</td>
<td>8.0</td>
<td>7.9</td>
<td>7.7</td>
<td>8.7</td>
<td>7.1</td>
<td>8.6</td>
<td>10.7</td>
<td>6.0</td>
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<tr>
<td>% Reduction in T1</td>
<td>33%</td>
<td>16%</td>
<td>49%</td>
<td>53%</td>
<td>39%</td>
<td>74%</td>
<td>72%</td>
<td>16%</td>
</tr>
<tr>
<td>% Reduction in FLAIR</td>
<td>68%</td>
<td>36%</td>
<td>60%</td>
<td>77%</td>
<td>70%</td>
<td>27%</td>
<td>75%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Patient 3 – Anaplastic Oligodendroglioma
Patient 40 Months Post-RT

Pre-Bevacizumab

Post-Bevacizumab
Patient 5 – Glioblastoma Patient 9
Months Post-RT

Pre-Bevacizumab

Post-Bevacizumab
# MRI and MR Spectroscopy Differentiate RT Necrosis From High-Grade Gliomas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WHO grade 2/3 gliomas</th>
<th>Glioblastoma</th>
<th>RT treatment effect/necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gad T1</td>
<td>homogeneous</td>
<td>heterogeneous</td>
<td>heterogeneous</td>
</tr>
<tr>
<td>rCBV/DCE</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>ADC</td>
<td>medium/high</td>
<td>lower</td>
<td>very high</td>
</tr>
<tr>
<td>MRS lipid alone</td>
<td>low</td>
<td>high in necrosis/cystic part</td>
<td>high</td>
</tr>
<tr>
<td>MRS lipid +choline</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>MRS lactate alone</td>
<td>low</td>
<td>high in necrosis/cystic part</td>
<td>high</td>
</tr>
<tr>
<td>MRS lactate+choline</td>
<td>low</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>MRS choline alone</td>
<td>can be high in oligos</td>
<td>high except in necrotic region</td>
<td>low</td>
</tr>
</tbody>
</table>

Prepared by Sarah Nelson, Ph.D., 2009
Bevacizumab Treatment for RT Necrosis

- Changes observed in 8 patients with RT necrosis
  - Average 8 week later
  - 60% reduction T2 FLAIR
  - 48% reduction Gd-contrast T1 images
  - 8 mg reduction in dexamethasone dose
- Patients 1, 2, 3, and 5 right

A Randomized Phase 2 Trial of Bevacizumab to Control Brain Radiation Damage

NCI #7955
MDACC #2006-0890
Group A – IV
Bevacizumab, 7.5 mg/kg at 3 week intervals

6 wk MRI
better

6 wk MRI
Group A – IV
Bevacizumab, 7.5 mg/kg at 3 week intervals
worse
Stop

Group B – IV
Placebo at 3 week intervals

6 wk MRI
better

6 wk MRI
Follow
worse
Stop

Cross-over – IV
Bevacizumab, 7.5 mg/kg; 3 wk intervals

6 wk MRI
better

6 wk MRI
Follow
Stable or better
worse
Stop

Non-GBM patients with radiation necrosis and progressive neurological signs or symptoms

Randomize

6 wk MRI
better

6 wk MRI
Follow
Stable or better
worse
Stop
Eligibility Criteria - partial list

- Patients must have received cranial irradiation for histologically confirmed WHO grade 2-3 primary brain neoplasm, meningioma, or head and neck cancer
- Prior irradiation $\geq$ 6 months prior to study entry
- Radiographic evidence to support the diagnosis of radiation necrosis and/or surgical biopsy evidence of necrosis without tumor $\leq$ 2 months of study entry
- Karnofsky performance status $\geq$ 60
- Evidence of progressive neurologic signs or symptoms appropriate to the location of the radiation necrosis.
- No prior bevacizumab therapy
Eligibility Criteria - partial list

- Patients can be on dexamethasone but must be on a stable dose for $\geq 1$ week prior to study and the on study MRI.
- Patients on full-dose anticoagulants (e.g., warfarin) with PT INR $>1.5$ are eligible provided that:
  - The patient has an in-range INR (usually between 2 and 3) on a stable dose of oral anticoagulant for 1 week or on a stable dose of low molecular weight heparin.
  - The patient has no active bleeding or pathological condition that carries a high risk of bleeding.
  - There is no evidence of serious or non-healing wound, ulcer or bone fracture.
Exclusion Criteria - partial list

- H&N cancer with metastatic disease, invasion to major vessels, or history of bleeding related to tumor or radiotherapy during or after completion of radiation.
- Active CNS hemorrhage, bleeding diathesis, coagulopathy
- Abdominal fistula, abscess, or GI perforation within 28 days
- Invasive procedures defined as follows:
  - Major surgery or significant traumatic injury within 28 days
- Clinically significant cardiovascular disease
  - HTN (SBP > 140 and/or DBP > 90 mmHg despite meds
  - CVA, MI, arrhythmias, unstable angina, CHF in past 6 mos
  - Aortic aneurysm, aortic dissection, PVD
MRI Evaluation of Radiation Necrosis

- Pre-contrast MRI
  - Axial T1, T2, FLAIR
  - Coronal FLAIR
  - Axial diffusion weighted (b=1000 s/mm2)
  - Axial T2* (susceptibility-weighted for blood)
  - Axial diffusion tensor imaging (b=1200 s/mm2, 27 diffusion encoding directions)

- Post-contrast MRI
  - Axial 3D T1 post-Gd
  - Coronal T1 post-Gd
  - Sagittal T1 post-Gd
  - DCE (dynamic contrast enhancement) with Ktrans, ve, vp
MRI Endpoints

- Reduction in bidirectional measurements of T2 FLAIR – augmented with volumetric measure
- Reduction in intensity of Gd-enhanced of T1-weighted images as measured by DCE (dynamic contrast enhancement)-MRI (Ktrans, ve, vp) – augmented with volumetric measure
- Response Criteria
  - At least 25% reduction in bidirectional T2 FLAIR
  - Duration of response
Other Response Parameters

- Neurological symptoms and signs obtained at minimum of 6- and 12-weeks and scored improved (+2), no change (0), or worse (-2) from the baseline.

- QOL MDASI results may not provide information since number of patients studied in each arm is small and changes of a scale of >2 are unexpected.

- Neurocognitive Testing (NP ~ 1 hr)
  - Scoring of The Trail Making Test, Hopkin's Verbal Learning Test-Revised, and the Controlled Oral Word Association subtest of the Multilingual Aphasia Examination tests.
  - Scoring of tests and comparisons between the two different testing periods evaluated using the Reliable Change Index.
Statistical Considerations

- Set alpha 0.10, beta 0.95, ratio 0.1 (placebo group) compared to 0.8 (bevacizumab group) and calculated sample size between 6 and 8 patients per arm using a 2-tailed test.

- Following 4 cycles (12 weeks) patients will not be treated further but followed by MRI at 3-month intervals for evidence of renewed radiation necrosis activity.

- Dexamethasone dosing at 12-weeks evaluated by t-test.
## Patient Demographics To Date

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age/ Sex</th>
<th>Reason for irradiation</th>
<th>Site of radiation necrosis</th>
<th>Months from RT to study entry</th>
<th>Major symptom or sign of RT necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/F</td>
<td>Anaplastic astrocytoma, right temporal</td>
<td>Right periventricular/trigone</td>
<td>17 mo from R</td>
<td>Headache and fatigue</td>
</tr>
<tr>
<td>2</td>
<td>43/F</td>
<td>Anaplastic astrocytoma, left frontal</td>
<td>Left frontal</td>
<td>25 mo from R</td>
<td>Worsened concentration</td>
</tr>
<tr>
<td>3</td>
<td>40/M</td>
<td>Malignant schwannoma, left inferior alveolar nerve</td>
<td>Left temporal</td>
<td>54 mo from R</td>
<td>Increased blurred vision</td>
</tr>
<tr>
<td>4</td>
<td>41/M</td>
<td>Astrocytoma, left frontal</td>
<td>Left anterior frontal</td>
<td>82 mo from R</td>
<td>Seizure</td>
</tr>
<tr>
<td>5</td>
<td>55/F</td>
<td>Ologodendriglioma, right temporal</td>
<td>Right temporal</td>
<td>8 mo from R</td>
<td>Left-side weakness</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>Ologodendriglioma, right frontal</td>
<td>Right frontal</td>
<td>11 mo from R</td>
<td>Seizure</td>
</tr>
<tr>
<td>7*</td>
<td>56/F</td>
<td>Left orbital squamous cell carcinoma</td>
<td>Left frontal</td>
<td>21 mo from R</td>
<td>Pain behind left eye</td>
</tr>
<tr>
<td>8</td>
<td>43/F</td>
<td>Nasopharyngeal carcinoma</td>
<td>Right temporal</td>
<td>40 mo from R</td>
<td>Headache</td>
</tr>
<tr>
<td>9</td>
<td>53/M</td>
<td>Nasopharyngeal carcinoma</td>
<td>Right temporal</td>
<td>44mo from R, 43 mo from Brachy</td>
<td>Memory loss</td>
</tr>
<tr>
<td>10</td>
<td>66/M</td>
<td>Squamous cell carcinoma, left cheek</td>
<td>Left temporal</td>
<td>39 mo from R</td>
<td>Word finding difficulty</td>
</tr>
<tr>
<td>11</td>
<td>49/M</td>
<td>Posterior fossa hemangiopericytoma</td>
<td>Bilateral occipital lobes</td>
<td>47 mo from R</td>
<td>Decreased peripheral vision</td>
</tr>
<tr>
<td>12</td>
<td>47/M</td>
<td>Pituitary adenoma</td>
<td>Bilateral anterior temporal lobes</td>
<td>21 yrs from R, 39 mo from SRS</td>
<td>Confusion</td>
</tr>
<tr>
<td>13</td>
<td>48/M</td>
<td>Left frontotemporal oligodendroglioma</td>
<td>Periventricular</td>
<td>88 mo from R, 8 mo from definite R</td>
<td>Right-sided weakness, dysphasia, change of mental status</td>
</tr>
</tbody>
</table>

* = NE  
R = conventional external beam RT; SRS = radiosurgery; Brachy = brachytherapy
Patient 1 at study entry on – 10/22/2007

T2-FLAIR
V=64.1 cm³
Patient 1 on 11/30/2007, 38 days after two IV placebo injections 3 weeks apart

T2-FLAIR $V=165.8 \text{ cm}^3$

T1-Gd contrast $V=48.68 \text{ cm}^3$
Patient 1 on 01/11/2008, 3 weeks after second Bevacizumab dose

T2-FLAIR $V=16.1 \text{ cm}^3$

T1-Gd contrast $V=19.3 \text{ cm}^3$ $\kappa_{\text{trans}}$
Patient 1 on 02/20/2008, 3 weeks after fourth Bevacizumab dose

T2-FLAIR \( V = 17.7 \text{ cm}^3 \)

\( K_{\text{trans}} \)

T1-Gd contrast \( V = 6.0 \text{ cm}^3 \)
## Placebo Arm Protocol 2006-0890 – All Progressive Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weeks on study</th>
<th>T2 FLAIR change from baseline</th>
<th>Gd-contrast change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.6</td>
<td>112%</td>
<td>421%</td>
</tr>
<tr>
<td>2</td>
<td>6.1</td>
<td>20%</td>
<td>2%</td>
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<td>6</td>
<td>6.7</td>
<td>-2%</td>
<td>17%</td>
</tr>
<tr>
<td>10</td>
<td>5.6</td>
<td>-12%</td>
<td>-27%</td>
</tr>
<tr>
<td>11</td>
<td>4.7</td>
<td>-31%</td>
<td>18%</td>
</tr>
<tr>
<td>13</td>
<td>7.4</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>6.0(±0.4)</td>
<td>+17%(±20)</td>
<td>+73%(±70)</td>
</tr>
<tr>
<td>Median</td>
<td>5.8</td>
<td>6%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Bevacizumab Arm Protocol 2006-0890 – All Responses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Weeks on study</th>
<th>T2 FLAIR change from baseline</th>
<th>Gd-contrast change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.7</td>
<td>-88%</td>
<td>-70%</td>
</tr>
<tr>
<td>2</td>
<td>28.3</td>
<td>-84%</td>
<td>-73%</td>
</tr>
<tr>
<td>3</td>
<td>36.3</td>
<td>-49%</td>
<td>-84%</td>
</tr>
<tr>
<td>5</td>
<td>16.7</td>
<td>-23%</td>
<td>-42%</td>
</tr>
<tr>
<td>6</td>
<td>23.8</td>
<td>-58%</td>
<td>-36%</td>
</tr>
<tr>
<td>7*</td>
<td>2.7</td>
<td>-59%</td>
<td>-32%</td>
</tr>
<tr>
<td>8</td>
<td>24.9</td>
<td>-70%</td>
<td>-64%</td>
</tr>
<tr>
<td>9</td>
<td>18.7</td>
<td>-96%</td>
<td>-67%</td>
</tr>
<tr>
<td>10</td>
<td>17.4</td>
<td>-54%</td>
<td>-49%</td>
</tr>
<tr>
<td>11</td>
<td>11.8</td>
<td>-28%</td>
<td>-76%</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>-59%</td>
<td>-70%</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>20.0 (±3)</td>
<td>-61% (±7)</td>
<td>-60% (±5)</td>
</tr>
<tr>
<td>Median</td>
<td>18.7</td>
<td>-59%</td>
<td>-67%</td>
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## Adverse Events

<table>
<thead>
<tr>
<th>Patient</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 wks after 2nd cycle developed ischemic changes with worsening of visual field – off study but no SAE</td>
</tr>
<tr>
<td>5</td>
<td>3 wks after 2nd cycle had possible ischemic changes and worsening of hemiplegia but no SAE</td>
</tr>
<tr>
<td>6</td>
<td>Wk 24 visit had ischemic changes but no SAE</td>
</tr>
<tr>
<td>9</td>
<td>Pt admitted for pneumonia and aspiration pneumonia – 2 SAEs filed</td>
</tr>
<tr>
<td>11</td>
<td>3 wks after 2nd cycle showed dramatic improvement in RT necrosis but developed superior sagittal sinus thrombosis – SAE filed</td>
</tr>
<tr>
<td>13</td>
<td>Developed DVT and PE within 1 wk of BVZ – SAE filed but continues with Lovenox</td>
</tr>
</tbody>
</table>
Recap: MRI Endpoints - Proposed

- Reduction in bidirectional measurements of T2 FLAIR – augmented with volumetric measure
- Reduction in intensity of Gd-enhanced of T1-weighted images as measured by DCE (dynamic contrast enhancement)-MRI (Ktrans, ve, vp) – augmented with volumetric measure
- Response Criteria
  - At least 25% reduction in bidirectional T2 FLAIR
  - Duration of response
Recap: MRI Endpoints - Achieved

- 0% (0/6) placebo and 100% (11/11) of evaluable Bevacizumab-treated patients had improved neurological symptoms/signs
  - Bevacizumab reduced all T2 FLAIR volumes 23% to 96%
  - Bevacizumab reduced all Gd-contrast T1 volumes 32% to 84%
  - Chi squared test p = .002
- DCE (dynamic contrast enhancement)-MRI (Ktrans, ve, vp) did not appear to be as sensitive as T2 FLAIR and Gd-contrast volume
- Insufficient pre-treatment glucocorticoid dosing to evaluate
- Aside from patient symptoms and signs of small vessel stroke or thrombosis, no patient had RT necrosis return at median 6 months
Recap: Study Objectives

- **Primary Objectives**
  - Determine to what extent IV bevacizumab given every 3 weeks can reduce active radiation toxicity to the central nervous system

- **Secondary Objectives**
  - Determine to what extent bevacizumab can reduce dexamethasone dependence
  - Determine to what extent bevacizumab can improve neurocognitive and neurologic function
  - Determine to what extent bevacizumab can improve quality-of-life
Conclusions – Based On Objectives

- **Primary Objective**
  - IV bevacizumab at 7.5 mg/kg given every 3 weeks reduced active radiation toxicity to the CNS based on MRI and clinical improvement

- **Secondary Objectives**
  - All patients were not receiving dexamethasone prior to bevacizumab and those who did were on low doses.
  - Bevacizumab improved neurologic symptoms/signs in all cases
  - Quality of life paralleled improved symptoms
Randomized study found 0% Placebo and 100% Bevacizumab patients with radiation necrosis improved on therapy.

Small vessel strokes can occur in setting of RT necrosis, but whether they occur more frequently in setting with Bevacizumab remains problematic.

**Conclusion**: Bevacizumab is the best and only proven therapy for the treatment of CNS RT necrosis.

Inhibitors of VEGFR function may also work to reduce RT necrosis, but likely that only binding VEGF ligand will turn off what appears to be an aberrant cytokine loop that initiates RT necrosis.