ALLIANCE A221208: Phase II Randomized Study of Bevacizumab vs. Steroids (BeSt) for Radionecrosis after Radiosurgery for Brain Mets

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Rad Onc Co-chairs: Paul Brown
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Med Onc Co-Chair: Glenn Lesser
Community Oncology Co-Chair: Christopher Goulet
Neurosurgery Co-Chair: Ian Parney
Neuroradiology Imaging Co-Chair: Tim Kaufmann
Health Outcomes Co-Chair: Terri Armstrong
Biomarkers Correlative Co-Chairs: Erik Sulman

Statistics: David Grosshans
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Background

~10–30% patients develop brain radionecrosis following SRS¹

- Incidence of brain radionecrosis ↑ (longer survival, more high-dose RT, SRS, repeat RT)

- Corticosteroids are effective, but not for all patients

- Prolonged corticosteroids can be associated with ++ toxicity

Proposed mechanism:

VEGF ↑ → vascular permeability ↑ → edema, hypoxia ↑ → white matter necrosis

Clinical evidence:

- Small studies of bevacizumab for radionecrosis show radiological and clinical response²–⁴

Hypothesis

- Hypothesis: Bevacizumab will provide greater clinical and radiological improvement resulting in greater improvement in the severity of symptoms, neurological and cognitive impairment compared to conservative management with corticosteroids.
Randomized phase II study of bevacizumab vs. steroid therapy in patients diagnosed with radionecrosis following radiosurgery. **N= 130, 65 per arm**

**Study Schema**

Randomized phase II study of bevacizumab vs. steroid therapy in patients diagnosed with radionecrosis following radiosurgery.

Bevacizumab 10 mg/kg IV days 1 and 15 for 1 cycle (30 days) x 4 cycles + corticosteroids

Placebo IV days 1 and 15 for 1 cycle (30 days) x 4 cycles + corticosteroids

Central Imaging review

Stratified for:
- Age
- Pathological confirmation
- Baseline MDASI
- Prior WBRT

Symptomatic brain radionecrosis requiring corticosteroids following SRS for brain metastases

Cross-over allowed at progression

FU every 2 months (up to 6 months): MR brain + clinical visit with PRO

After 6 months: event monitoring only

Drug is provided
Eligibility

Inclusion Criteria
- Symptomatic brain radionecrosis defined by onset of symptoms at 3–24 months post-SRS that requires steroid intervention and meets the following radiological criteria:
  - Lesion quotient < 0.3
  - DSC: At least 1:
    - rCBV <1.5
    - PSR ≥ 76%
- Life expectancy > 6 months
- KPS ≥ 60%
- Acceptable organ function (bone marrow, renal, liver)

Exclusion Criteria
- Acute intracranial/intratumoral hemorrhage
- Glioma or brain mets from melanoma, RCC
- Non-approved systemic therapies (2 wks prior to registration or planned < 1 mo after registration)
  - Except: Maintenance herceptin or hormonal therapies OR ‘Approved systemic’ therapies [Appendix]

Standard C/I to bevacizumab:
- Major surgical procedure within 28 days or core biopsy within 7 days
- Pregnant or nursing
- PT INR >1.5
- Bleeding diathesis, coagulopathy, non-healing wound/ulcer, bowel obstruction/fistula/GI perforation
- Significant cardiovascular disease
- Central lung met with xs active bleeding

1Kumar – Radiology 2000
2 Barajas – AJNR 2009
Radiological Diagnosis of Radionecrosis: Conventional Imaging

LESION QUOTIENT = maximal cross-sectional area of T2-w hyperintensity
maximal cross-sectional area of T1-gad enhancement

Stockham et al.
(n = 51 patients)

<table>
<thead>
<tr>
<th>Tumor (LQ &gt; 0.6)</th>
<th>Radionecrosis (LQ &lt; 0.3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>59%</td>
</tr>
<tr>
<td>Specificity</td>
<td>41%</td>
</tr>
<tr>
<td>PPV</td>
<td>62%</td>
</tr>
<tr>
<td>NPV</td>
<td>39%</td>
</tr>
</tbody>
</table>

Kumar – Radiology 2000
Radionecrosis & Conventional Imaging: Lesion Quotient

LQ > 0.6 in tumor

LQ < 0.3 in 80% of radionecrosis

LESION QUOTIENT = maximal cross-sectional area of T2-w hyperintensity
maximal cross-sectional area of T1-gad enhancement

Kumar – Radiology 2000
Radionecrosis & Perfusion Imaging

Eligibility Criteria:
- rCBV < 1.5
- PSR > 76%

Tumor

Radionecrosis

DSC Perfusion MR Imaging Measurements

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Mean ± SD</th>
<th>Maximum ± SD</th>
<th>Minimum ± SD</th>
<th>Mean ± SD</th>
<th>Maximum ± SD</th>
<th>Minimum ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent tumor</td>
<td>2.38 ± 0.87</td>
<td>8.16 ± 2.92</td>
<td>1.61 ± 0.65</td>
<td>80.2 ± 10.3</td>
<td>92.5 ± 18.8</td>
<td>68.8 ± 10.9</td>
</tr>
<tr>
<td>Recurrent tumor</td>
<td>(2.13, 2.63)</td>
<td>(7.31, 9.01)</td>
<td>(1.42, 1.80)</td>
<td>(77.2, 83.2)</td>
<td>(87.1, 97.9)</td>
<td>(65.6, 72.0)</td>
</tr>
<tr>
<td>Radiation necrosis</td>
<td>1.57 ± 0.67</td>
<td>4.63 ± 1.98</td>
<td>0.94 ± 0.34</td>
<td>89.3 ± 12.4</td>
<td>100 ± 12.0</td>
<td>77.2 ± 15.0</td>
</tr>
<tr>
<td>Radiation necrosis</td>
<td>(1.28, 1.86)</td>
<td>(3.76, 5.50)</td>
<td>(0.79, 1.09)</td>
<td>(83.9, 94.7)</td>
<td>(94.7, 105.3)</td>
<td>(70.6, 83.8)</td>
</tr>
</tbody>
</table>
Endpoints

- **Primary Endpoint**
  - Improvement in patient-reported symptoms measured by MDASI-BT global symptom score (baseline then weeks 2, 4, 6, and 8)

- **Secondary Endpoint(s)**
  - Toxicities: CTCAE version 4.0 & DSQ–C
  - QoL: LASA, MDASI–BT symptoms and interference scores
  - PFS (progression = restart higher dose steroids or alternative tx)
  - Time to maximum radiographic response
  - Corticosteroid requirements

- **Correlative Endpoints:**
  - Biofluid Biomarkers: angiogenic factors:
    - Angiogenic markers: VEGF–A, B, C, D, angiopoietin–1 and 2, PDGF
    - inflammatory cytokines (TNF–α, TGF–β, IL1, and IL6)
    - genetic markers (Apo E)
  - Imaging Biomarker Measures: DWI (ADC), DCE (Ktrans, iAUC)
Progress Update

Central study activation April 29, 2016

Note:
- Drug is provided for initial randomization & cross-over
- Correlative biomarker studies are optional

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