High Grade Astrocytoma of the CNS: Antiangiogenic Inhibitors After Temozolomide Failure: Change in Treatment Paradigm?

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UT MD Anderson Cancer Center
Houston, Texas, USA
Disclosures

• Consulting
  – Advisory Board: Genentech, Novartis, Celldex
  – DSMB: VBL Therapeutics
  – Consulting: Celldex, Deciphera Pharmaceuticals

• Research Support
  – Sanofi-Aventis
  – AstraZeneca
  – EMD-Serono
  – Eli Lilly
  – Novartis
  – Deciphera Pharmaceuticals
Outline

• Background and rationale for targeting angiogenesis
• Mechanism of action of antiangiogenic therapy
• Update on efficacy for recurrent glioblastoma
• Fundamental unknowns for optimal treatment
• Potential biomarkers of outcome
• Conclusions and future directions
Glioblastoma Are Highly Angiogenic

- Vascular endothelial proliferation is a defining pathologic hallmark of glioblastoma
  - GB highly express VEGF and other pro-angiogenic growth factors
  - Hypoxia promotes invasion and treatment resistance
  - Newly formed blood vessels are often tortuous with blind loops and endothelial gaps

Rong et al., JNEN, 2006
Rationale for Targeting Angiogenesis in Glioblastoma

VEGF is highly expressed in glioblastoma

VEGF expression correlates with tumor grade and outcome

Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo

K. Jin Kim, Bing Li, Jane Winer, Mark Armanini, Nancy Gillett, Heidi S. Phillips & Napoleone Ferrara

Nature, 1993

Korkolopoulou et al., Neuropathol Appl Neurobiol, 2004
Potential Mechanisms of Action: Antiangiogenic Therapy

- Disrupt the angiogenic cascade
  - Small vessel pruning
  - Endothelial cell apoptosis
- Target the perivascular glioma stem cell niche
- Reduce influx of M2-skewed VEGFR1+ macrophages
- Block VEGF-mediated immune suppression
- Vascular Normalization
  - Reduce edema and ISF pressure
  - Improve blood flow efficiency and drug and oxygen delivery

R. Jain, Science 2005
Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma

Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T

University of California Los Angeles, Los Angeles, CA, University of California San Francisco, San Francisco, CA, Dana Farber Cancer Institute, Boston MA, Henry Ford Health System, Detroit MI, Memorial Sloan-Kettering Cancer Center, New York, NY, University of Virginia, Charlottesville, VA, MD Anderson Cancer Center, Houston, TX, Genentech, Inc., South San Francisco, CA, and Duke University, Durham, NC

JCO 2009
Patients with GBM
Randomized by
1st or 2nd Relapse
(N=167)

1:1

Bevacizumab*
(n=85)

1st Progressive Disease (PD)

Optional Post-PD Phase
Bevacizumab + CPT-11

Bevacizumab/CPT11**
(n=82)

Stratification by:
KPS: 70-80, 90-100
1st, 2nd relapse

Primary Objectives:
6 month PFS
ORR

Secondary Objectives:
OS
PFS
Duration of response
Safety

* Bevacizumab: 10 mg/kg every 2 weeks

** CPT-11: EIAED: 340 mg/m² IV over 90 minutes
Non-EIAED: 125 mg/m² IV over 90 minutes

(EIAEDs)=enzyme-inducing anti-epileptic drugs

A treatment cycle = 6 week period of therapy

Friedman et al JCO 2009; Kreisl et al JCO 2009
## Bevacizumab is Safe and Tolerable

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BRAIN Trial</th>
<th>NCI Trial</th>
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<tbody>
<tr>
<td></td>
<td>Bev alone</td>
<td>Bev+CPT11</td>
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<tr>
<td></td>
<td>(n=84)</td>
<td>(n=79)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10.7%</td>
<td>3.8%</td>
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<tr>
<td>Cerebral hemorrhage</td>
<td>0</td>
<td>1.3</td>
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<tr>
<td>Venous thromboembolism</td>
<td>3.6</td>
<td>10.1</td>
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<tr>
<td>Proteinuria</td>
<td>1.2</td>
<td>3.8</td>
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<tr>
<td>Wound healing complications</td>
<td>2.4</td>
<td>1.3</td>
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<tr>
<td>Arterial thromboembolism</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>GI perforation</td>
<td>0</td>
<td>2.5</td>
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Friedman et al JCO 2009; Kreisl et al JCO 2009
## BRAIN: Efficacy

<table>
<thead>
<tr>
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<th>BV Alone (n=85)</th>
<th>BV+CPT-11 (n=82)</th>
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<tbody>
<tr>
<td><em><em>Median Overall Survival</em>, months</em>*</td>
<td>9.2 (8.2 – 10.7)</td>
<td>8.7 (7.8 – 10.9)</td>
</tr>
<tr>
<td><strong>PFS6, %</strong></td>
<td>42.6 (29.6 – 55.5)</td>
<td>50.3 (36.8 – 63.9)</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>28.2 (18.5 – 40.3)</td>
<td>37.8 (26.5 – 50.8)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>27.1</td>
<td>35.4</td>
</tr>
<tr>
<td><strong>Median Duration of Response (months)</strong></td>
<td>5.6 (3.0 – 5.75)</td>
<td>4.3 (4.17, - )</td>
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</tbody>
</table>

*OS is based on data cutoff as of November 15, 2007.
All other efficacy results are based on September 15, 2007.
### Outcomes with Bevacizumab and Other Antiangiogenic Therapies

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Radiographic Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR (%)</strong></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>PR (%)</strong></td>
<td>27</td>
<td>35</td>
<td>16</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
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<td></td>
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<tr>
<td><strong>Median (wks)</strong></td>
<td>17</td>
<td>22</td>
<td>16</td>
<td>9</td>
<td>17</td>
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<tr>
<td><strong>6 month (%)</strong></td>
<td>43</td>
<td>50</td>
<td>29</td>
<td>15</td>
<td>25.8</td>
</tr>
</tbody>
</table>

- Bev: Bevacizumab
- Bev+CPT11
- Bev alone
- Multi
- Cediranib
- VEGF Trap

(n=84) (n=79) (n=48) (n=243) (n=32) (n=42)
## Outcomes with Bevacizumab and Other Antiangiogenic Therapies

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Bev alone (n=84)</td>
<td>Bev+CPT1 (n=79)</td>
<td>Bev alone (n=48)</td>
<td>Multi (n=243)</td>
<td>Cediranib (n=32)</td>
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<tr>
<td><strong>Radiographic Response</strong></td>
<td></td>
<td></td>
<td></td>
<td>VEGF Trap (n=42)</td>
</tr>
<tr>
<td>CR (%)</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PR (%)</td>
<td>27</td>
<td>35</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median (wks)</td>
<td>17</td>
<td>22</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>6 month (%)</td>
<td>43</td>
<td>50</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median OS (wks)</td>
<td>37</td>
<td>35</td>
<td>31</td>
<td>25</td>
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</tbody>
</table>

- Bev: Bevacizumab
- CPT11: CPT-11
- Multi: Multikin
- Cediranib: Cediranib
- VEGF Trap: VEGF Trap
“Success” of Antiangiogenic Therapy

Proof that VEGF-A mediates vessel permeability and contrast enhancement

*Percent Change in Smallest Post-Baseline SPD (Sum of the Product Diameter)

Friedman et al., J Clin Oncol, 2009
Fundamental Unknowns

- Is there an anti-tumor effect?

- What is the optimal way to treat?
  - Optimal dose
  - Combination
  - Schedule
  - When to treat: early versus late

- Why doesn’t antiangiogenic therapy prolong survival?
  - Does bevacizumab increase tumor aggressiveness?
Should Bevacizumab Be Given As Monotherapy?

Glioblastoma is the only disease where bevacizumab is approved as monotherapy for recurrent disease

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year</th>
<th>Combination</th>
<th>Improvement in RR (%)</th>
<th>Improvement in PFS (months)</th>
<th>Improvement in OS (months)</th>
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<td>2004</td>
<td>Yes</td>
<td>10</td>
<td>4.4</td>
<td>4.7</td>
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<tr>
<td>mNSCLC</td>
<td>2006</td>
<td>Yes</td>
<td>20</td>
<td>1.7</td>
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<tr>
<td>mBreast Ca</td>
<td>2010</td>
<td>Yes</td>
<td>16</td>
<td>5.9</td>
<td>NS</td>
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<tr>
<td>mRCC</td>
<td>2009</td>
<td>Yes</td>
<td>18</td>
<td>4.8</td>
<td>NS</td>
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<tr>
<td>rGlioblastoma</td>
<td>2009</td>
<td>No</td>
<td>18</td>
<td>Only phase II data</td>
<td>NS</td>
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</tbody>
</table>

Upfront studies do not show a benefit in overall survival when bevacizumab is combined with the standard of care
Efficacy of Targeting Angiogenesis in Glioblastoma in Preclinical Models

Improvement in OS without reduction in tumor size
Despite prolonged survival, no decrease in tumor volume

Kamoun W S et al. JCO 2009
Bevacizumab Dose: Does it Matter?

All schedules dose at 2.5 mg/kg/week or higher

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>5</th>
<th>10</th>
<th>10</th>
<th>15</th>
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<td>Frequency</td>
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<td>2 weeks</td>
<td>3 weeks</td>
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<td>Prospective</td>
<td>Prospective</td>
<td>Prospective</td>
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<tr>
<td>n</td>
<td>44</td>
<td>48</td>
<td>85</td>
<td>61</td>
</tr>
<tr>
<td>PFS-6 (%)</td>
<td>41</td>
<td>29</td>
<td>43</td>
<td>25</td>
</tr>
<tr>
<td>OS (months)</td>
<td>9.0</td>
<td>7.8</td>
<td>9.2</td>
<td>6.4</td>
</tr>
</tbody>
</table>
Determining the Optimal Biologic Dose

Jain R, Science, 2005
Anti-VEGF therapy: Exacerbating hypoxia?

- Excessive vascular pruning
- Inadequate perfusion
- Increase tumor hypoxia

Jain R, Science, 2005

de Groot J, Neuro-Oncology 2010
Modulating Resistance to Anti-VEGF Therapy

**Excessive** Anti-VEGF Therapy

- ↑ Hypoxia
- BMDC infiltration
- Proangiogenic factors
- EMT
- Invasion

Mediates Resistance

**Current Approach**

**Therapeutic Goal**

- Maintain “normalization”
- Limit hypoxia
- Improve oxygenation
- Increase drug delivery
- Limit/block invasion
- Modulate BMDC infiltration

How do we get from our current approach to our goal?

Is it too late to figure it out?
Discard the Maximum Tolerated Dose Approach

- High-dose therapy
  - Hypoxia
  - Necrosis
  - Phenotype Delta

- Low-dose therapy
  - Drug delivery

Duration of anti-VEGF therapy (time)

© 2011 American Association for Cancer Research

**CCR Translations**

**High-Dose Antiangiogenic Therapy for Glioblastoma: Less May Be More?**

John F de Groot

*Clin Cancer Res* Published OnlineFirst August 18, 2011.
Focus on Optimal Biologic Dose

What we think we were doing

Winkler F et al, Cancer Cell 2004
Can alternate doses and/or schedules improve the efficacy of bevacizumab?

*Optimal (dosing every 3-4 wks?)*

Lorgis et al. Journal of Neuro-Oncology, 2012
Randomized phase II trial: Bev vs low dose Bev + CCNU

Reduced bevacizumab dose
CCNU given during ‘normalization window’ – day 3

Recurrent Glioblastoma (n=102)

BEV 10 mg/kg (every 2 weeks)

BEV 5 mg/kg (every 3 weeks)
CCNU 90 mg/m² (every 6 weeks)

MD Anderson Cancer Center
Houston, TX USA
Fall 2009
PI: J de Groot
Optimal Biologic Dose

• STOP focus on Maximum Tolerated Dose (MTD)
• Aim to re-establish homeostasis
  – Not flip the balance in the complete opposite direction (e.g. hypoxia)
• Explore dose and frequency
  – Continuous, low-dose
  – Pulsed, low-dose
  – Alternate antiangiogenic target (VEGF-A → bFGF → VEGF-C →…)
• Use advanced imaging to determine time between doses when vascular normalization is optimized
  – ‘Biomarker’ of effect on tumor microenvironment
  – Evaluate multiple doses
  – Evaluate multiple intervals of drug administration
Optimal Drug Combinations: Inherent Challenges in Glioblastoma

Anti-VEGF plus TMZ: Decrease TMZ efficacy

Anti-VEGF plus Erlotinib: Decrease drug penetration

P= placebo  V= vandetanib  T= TMZ


Unpublished data from Drs. J. Sarkaria and W. Elmquist
# Bevacizumab: Single agent therapy

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Dose interval (weeks)</th>
<th>Study Design</th>
<th>Number Patients</th>
<th>CR/PR (%)</th>
<th>PFS, median (weeks)</th>
<th>PFS-6 (%)</th>
<th>OS, median (weeks)</th>
<th>Citation</th>
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<tbody>
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<td>Phase II</td>
<td>85</td>
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<td>10</td>
<td>2</td>
<td>Phase II</td>
<td>48</td>
<td>35</td>
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<td>15</td>
<td>3</td>
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<td>25</td>
<td>11</td>
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<td>Retrospective series</td>
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<td>58</td>
<td>40</td>
<td>42</td>
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# Bevacizumab plus chemotherapy

<table>
<thead>
<tr>
<th>BV dose (mg/kg)</th>
<th>Chemotherapy</th>
<th>Study Design</th>
<th>Number Patients</th>
<th>CR/PR (%)</th>
<th>PFS, median (weeks)</th>
<th>PFS-6 (%)</th>
<th>OS, median (weeks)</th>
<th>Citation</th>
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<td>10</td>
<td>Carboplatin + cetuximab</td>
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<td>18</td>
<td>45</td>
<td>46</td>
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<td>47</td>
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<td>25</td>
<td>28</td>
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<td>Retrospective series</td>
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<td>77</td>
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<td>NR</td>
<td>27</td>
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<td>5 or 10</td>
<td>Irinotecan + cetuximab</td>
<td>Phase II</td>
<td>43</td>
<td>26</td>
<td>16</td>
<td>30</td>
<td>29</td>
<td>Hasselbalch139</td>
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<td>5</td>
<td>Irinotecan or carboplatin or lomustine or etoposide</td>
<td>Retrospective series</td>
<td>44</td>
<td>NR</td>
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<td>41</td>
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<td>40</td>
<td>NR</td>
<td>NR</td>
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<td>Pope132</td>
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</table>

# Bevacizumab plus biologic agent

<table>
<thead>
<tr>
<th>Agent</th>
<th>Class</th>
<th>Study Design</th>
<th>Number patients</th>
<th>CR/PR (%)</th>
<th>PFS, median (weeks)</th>
<th>PFS-6 (%)</th>
<th>OS, median (weeks)</th>
<th>Citation</th>
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<td>EGFR tyrosine kinase inhibitor</td>
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<td>18</td>
<td>29</td>
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# Bevacizumab plus stereotactic radiosurgery

<table>
<thead>
<tr>
<th>Total irradiation dose (Gy)</th>
<th>Number fractions</th>
<th>Study Design</th>
<th>Number patients</th>
<th>CR/PR (%)</th>
<th>PFS, median (weeks)</th>
<th>PFS-6 (%)</th>
<th>OS, median (weeks)</th>
<th>Citation</th>
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</thead>
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<td>30</td>
<td>5</td>
<td>Phase II</td>
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<td>50</td>
<td>29</td>
<td>65</td>
<td>50</td>
<td>Guse133</td>
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</tbody>
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Are we surprised that combination approaches aren’t better?  
- Ineffective agents?  
- Lack of synergy?
Randomized phase II study in patients with recurrent glioblastoma

Bevacizumab vs Bevacizumab plus Lomustine vs Lomustine

Taal W. et al., Abstract 2001 ASCO 2013
# Bev + Lomustine May Improve mOS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lomustine</th>
<th>Bevacizumab</th>
<th>Bev/Lom 90</th>
<th>Bev/Lom all</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 mo OS</td>
<td>43% (29-57%)</td>
<td>38% (25-51%)</td>
<td>59% (43-72%)</td>
<td>63% (49-75%)</td>
</tr>
<tr>
<td>Median OS</td>
<td>8 mo</td>
<td>8 mo</td>
<td>11 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>6 mo PFS</td>
<td>13% (5-24%)</td>
<td>16% (7-27%)</td>
<td>41% (26-55%)</td>
<td>42% (29-55%)</td>
</tr>
</tbody>
</table>

EORTC26101 transitioned into a randomized phase III trial for recurrent glioblastoma

Taal W. et al., Abstract 2001 ASCO 2013

(Between brackets: 95% confidence interval)
Optimal Drug Combinations

• Need to determine which therapies may benefit from co-administration of an antiangiogenic therapy

• Administer drug/therapy during the ‘normalization’ window
  – Requires knowledge of the optimal biologic dose
  – Not all therapies will be enhanced with vascular normalization

• Drug combinations should include therapies that are effective in the treatment of glioblastoma
  – Limited benefit from an additional *cytostatic* agent

• Efficacy of *cytotoxic* therapies are more likely to be enhanced

• Small molecules may required high-dose pulsed dosing
When to Treat: Newly Diagnosed versus Recurrent

- Newly diagnosed versus recurrence?
- At recurrence?
  - Early versus late
- As maintenance therapy?
**AVAGLIO**

**Overall Survival (Co-Primary Endpoint)**

<table>
<thead>
<tr>
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<th>RT/TMZ/BEV (n=458)</th>
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<td>333</td>
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<td>0.987</td>
</tr>
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<td>p-value (log-rank test)</td>
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<td>1-year survival rate, % (95% CI)</td>
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<td>p-value</td>
<td>0.235</td>
<td></td>
</tr>
</tbody>
</table>

Designed to achieve a HR of 0.80 (20% reduction in the risk of death) with 80% power (log-rank test, 2-sided 4% α level adjusted using O’Brien and Fleming): 683 events were required for analysis.

Slide courtesy of L. Abrey
## Do a Subset of Patients Benefit?
### Overall Survival Subset Analysis

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>Bevacizumab better</th>
<th>Placebo better</th>
<th>N</th>
<th>HR*</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td></td>
<td></td>
<td>921</td>
<td>0.90</td>
<td>0.78–1.05</td>
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<tr>
<td>Age category II (years)</td>
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<tr>
<td>&lt;50</td>
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<td></td>
<td>229</td>
<td>1.05</td>
<td>0.76–1.44</td>
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<td>50–59</td>
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<td>323</td>
<td>0.90</td>
<td>0.70–1.16</td>
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<td>60–69</td>
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<td>296</td>
<td>0.81</td>
<td>0.63–1.05</td>
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<tr>
<td>≥70</td>
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<td></td>
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<td>73</td>
<td>0.83</td>
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<td>465</td>
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<td>1–2</td>
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<td>455</td>
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<td>MGMT gene promoter status</td>
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<tr>
<td>Methylated</td>
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<td>237</td>
<td>0.93</td>
<td>0.65–1.32</td>
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<tr>
<td>Missing</td>
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<td></td>
<td></td>
<td>222</td>
<td>0.80</td>
<td>0.59–1.08</td>
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<tr>
<td>Non-methylated</td>
<td></td>
<td></td>
<td></td>
<td>462</td>
<td>0.91</td>
<td>0.74–1.11</td>
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<td>RPA class</td>
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<td>III</td>
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<td>151</td>
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<td>0.60–1.33</td>
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<td>IV</td>
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<td>0.73–1.07</td>
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<tr>
<td>V</td>
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<td>229</td>
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<td>Surgical status</td>
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<td>Biopsy only</td>
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<td>104</td>
<td>1.06</td>
<td>0.67–1.68</td>
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<tr>
<td>Completely resected</td>
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<td></td>
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<td>384</td>
<td>0.78</td>
<td>0.61–0.99</td>
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<tr>
<td>Partially resected</td>
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<td>433</td>
<td>0.97</td>
<td>0.79–1.21</td>
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<tr>
<td>MMSE score</td>
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<tr>
<td>&lt;27</td>
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<td></td>
<td></td>
<td>213</td>
<td>1.03</td>
<td>0.76–1.39</td>
</tr>
<tr>
<td>≥27</td>
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<td></td>
<td></td>
<td>696</td>
<td>0.87</td>
<td>0.73–1.04</td>
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<tr>
<td>Corticosteroid use at baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Missing</td>
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<td>4</td>
<td>0.39</td>
<td>0.03–4.44</td>
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<tr>
<td>Off</td>
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<td>522</td>
<td>0.88</td>
<td>0.72–1.08</td>
</tr>
<tr>
<td>On</td>
<td></td>
<td></td>
<td></td>
<td>395</td>
<td>0.98</td>
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Slide courtesy of L. Abrey
Recurrent Glioblastoma: Early Versus Late

<table>
<thead>
<tr>
<th>Study</th>
<th>ASCO 2013 Abst 2042</th>
<th>BRAIN Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bev Timing</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; PD</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; PD</td>
</tr>
<tr>
<td>Design</td>
<td>Retrospective</td>
<td>Prospective</td>
</tr>
<tr>
<td>n</td>
<td>149</td>
<td>134</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.7</td>
<td>4.3 (p=0.07)</td>
</tr>
<tr>
<td>Median OS (months)</td>
<td>19.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Citations</td>
<td>Hamza et al. ASCO 2013, abstract 2042</td>
<td>Friedman JCO 27:4733, 2009</td>
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</table>

![Graph showing survival curves for Early BEV and Delayed BEV with P=0.005](image)

Does Sequencing Matter?

MO22968/EORTC26101: Phase II Trial Exploring the Sequence of Bevacizumab and Lomustine in Patients with First Recurrence of a GBM

Patients with recurrent GBM (n=249)

2:2:2:1

CCNU + Avastin
Bevacizumab
n=71

CCNU
n=71

Bevacizumab
n=71

CCNU
n=36

PD

Investigator’s choice

PD

Bevacizumab

CCNU + Avastin
Bevacizumab

PD

Investigator’s choice

Decision rule for activity: 27 pts alive at 1 yr for the BEV-containing arms

Key Eligibility Criteria
GBM with progression after RT with concurrent/adjuvant chemotherapy and at least 3 months off concomitant part of the radiochemotherapy

Endpoints
Primary: 12 month OS
Secondary: PFS6, PFS, TTF, OS, neurological progression, toxicity, QoL

PI: W Wick
Is Maintenance Bevacizumab Effective?

MO28347: Phase 3 Study of Continuous Bevacizumab in Combination with Standard of Care Following Disease Progression in Glioblastoma

- Primary endpoint: OS (from randomization)
- Secondary endpoints: PFS, ORR, Safety, QOL, Biomarkers (from randomisation)
- Exploratory endpoints: 1L data
Why Doesn’t Bevacizumab Prolong OS In Recurrent Glioblastoma?

• Is glioblastoma vasculature intrinsically resistant to anti-VEGF targeted therapy?
  – Vessel insensitivity to VEGF blockade

• Think about the problem differently
  – Anti-VEGF therapy is not an anti-tumor therapy
  – Is angiogenesis involved in resistance to RT/TMZ→TMZ?
  – Inhibiting one growth factor isn’t going to make a dramatic difference
    • Multiple simultaneous events occur after VEGF-A inhibition
      – Survival of endothelial-supporting pericytes
      – Secretion of alternate pro-angiogenic factors
      – Infiltration of bone marrow derived cells and endothelial precursors
      – Continued non-enhancing tumor progression; mesenchymal shift
Resistance phenotype dominates

- Recurrent glioblastoma: Acquired resistance
  - Median response duration
    - Bevacizumab ~4 months\(^1\)
    - Cediranib ~ 3-4 months\(^2\)
  - Resistant tumors are not responsive to salvage therapies
    - Anti-VEGF $\rightarrow$ Chemotherapy: mPFS 38 days\(^3\)
    - VEGFR TKI $\rightarrow$ anti-VEGF: mTTP 8 wks\(^4\)

- Newly diagnosed glioblastoma: Intrinsic resistance
  - No improvement in OS in randomized phase III trials\(^5,6\)

\(^1\)Friedman et al., J Clin Oncol, 2009; \(^2\)Batchelor et al., J Clin Oncol, 2011;
\(^3\)Quant et al. Neuro-Oncol, 2009; \(^4\)Scott et al., Neuro-Oncol, 2010;
\(^5\)Chinot et al., AVAglio, NEJM, 2014; \(^6\)Gilbert et al., RTOG 0825, NEJM 2014
• **Sensitive:**
  – *Central location (central necrosis)*
  – Mother vessels (MV)
  – *Glomeruloid microvascular proliferations (GMP)*

• **Resistant:**
  – *Peripheral location*
  – Vascular malformations (VM)
  – Feeding arteries (FA)
  – Draining veins (DV)

Sitohy et al., Cancer Res, 2011
Multiple Simultaneous Events
Before/During VEGF Targeting

- Increased pericyte coverage
- Increase in VEGF-independent angiogenesis
  *Enhancing Progression*
- Infiltration of Bone Marrow Derived Cells
- Increase invasion/vessel co-option
  *Non-Enhancing Progression*

Bergers and Hanahan, 2008
Anti-VEGF therapy and hypoxia promotes a proneural to mesenchymal (‘PMT’) shift

p-STAT3 Expression

Anti-VEGF Therapy

de Groot J et al, Oncotarget 2012
Piao Y, et al. CCR 2013
Anti-VEGF Therapy and Invasion

Increased invasion or non-enhancing tumor growth?

Un-coupling of angiogenesis and continued invasion
Does Antiangiogenic Therapy Promote Aggressive Tumor Behavior?

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Increased Invasion: Not Observed
- Pope WB et al., Neurology 2011
- Wick W et al., Curr Neurol Neurosci Rep 2011

Brennan CW, et al. (TCGA) Cell 2013
Making antiangiogenic therapy effective in glioblastoma: The Future

- VEGF-A-mediated angiogenesis is un-coupled from tumor cell invasion, proliferation and tumor progression

- Too many concurrent events drive continued progression
  - Multiplicity and complexity of growth factor signals limits ability of single target inhibitor to individually provide anti-tumor activity

- How do we use anti-VEGF therapy to increase the efficacy of known effective treatments?
  - Determine the optimal biologic dose of antiangiogenic therapy
  - Identify the correct drug/therapy combination
  - Find a way to use uncoupling to therapeutic advantage?

- Identify predictive biomarkers
  - Select patients that will benefit most
The Elusive Biomarker

Candidate biomarkers of response and resistance to antiangiogenic therapy

No validated biomarkers

Jain R K et al., Nat Rev Clin Oncol 2009
The Elusive Biomarker

High VEGF-A levels associated with poor prognosis/decreased OS

Inconsistently predict benefit from drug

Lambrechts D. et al., J Clin Oncol, 2013
Recent Updates: Elusive Biomarker List

- RTOG 0825: Tissue mesenchymal signature may be associated with worse outcome with bevacizumab
  - Post-hoc analysis identified alternate gene signature predictive of OS (different mesenchymal signature?)

- AVAglio: Circulating VEGF-A and VEGFR2 levels not predictive of PFS

Sulman E., et al. Late Breaking Abstract 201, ASCO 2013
Nishikawa et al., Abstract 2023, ASCO 2013
Recent Updates:
Elusive Biomarker List

Response predicts OS

Challenges to Identifying Biomarkers

• Angiogenesis is *complex and adaptive*
  – Multiple pro-angiogenic factors are involved

• VEGF-A inhibition has variable effects on tumor, BMDCs, ECs, vessel type

• The tumor cell isn’t the drug’s target
  – Specific tumor (sub)types are unlikely to be more or less ‘sensitive’
  – Is there a tumor that is ONLY VEGF-A driven (e.g. radiation necrosis)?
  – Is there a tumor microenvironment signature?

• Clinical trial endpoints do not accurately identify patients that benefit
  – Radiologic response does not correlate with OS
  – Crossover ‘contamination’

• Validation requires additional clinical trials (time, $)
Conclusion and Future Directions

- Antiangiogenic therapy is safe
- Not all antiangiogenic agents have equal efficacy
- Changes in the tumor and TME following VEGF-A inhibition are complex and multifaceted
- Antiangiogenic therapy should be used to increase the efficacy of drugs known to be effective in glioblastoma
- The optimal biologic dose of bevacizumab is unknown
- The most efficacious combination requires identification and utilization of the optimal biologic dose
- Benefit is unlikely to be predicted based on known biomarkers
Thank you for your attention.

jdegroot@mdanderson.org