Targeting Angiogenesis in GBM

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• Clinical Research funding
  Lilly, Inc
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  Exelixis, Inc

I will discuss “off-label” use of chemotherapy

Recurrent Glioblastoma Multiforme (GBM)

• Invasive
• Hypoxic
• Angiogenic
• Genotypically heterogeneous
• Resistant to therapy
• Disease changes over time
Targeting Angiogenesis in GBM Seems to Make Sense

- Endothelial proliferation and neovascularization are defining features of GBM
  - GBM tumors express VEGF and other pro-angiogenic growth factors
  - Hypoxic areas possible cause of treatment resistance (increase in HIF-1alpha)
- Antiangiogenic agents normalize tumor vasculature
  - Facilitates delivery of drugs and oxygen to tumor
  - Enhances efficacy of certain cytotoxic agents
  - Evaluation in GBM as monotherapies and with chemotherapy

Highly unmet need! Most patients die of disease quickly

Clinical Trials of Anti-angiogenic Agents in Gliomas

- Thalidomide
- COX-2 inhibitors
- Erlotinib, imatinib, RAD001
- PTK 787 (VEGF/PDGF inhibitor)
- EMD 121974 (avb3 inhibitor)
- Lenalidomide (Revlimid)
- AEE788 (VEGF + EGFR inhibitor)
- Endostatin
- Enzastaurin (LY317615)
- Low dose (metronomic) chemotherapy
- Bevacizumab (Avastin)
- Sorafenib (Bay43-9006)[Raf kinase, VEGFR, PDGFR inhibitor]
- AZD2171 (Cidiranib)
- ZD6474(VEGFR + EGFR inhibitor)
- Sunitinib (Sutent) (Raf, VEGFR, PDGFR, cKIT inhibitor)
- GW786034
- VEGF Trap
Rationale for targeting VEGF in GBM

**VEGF** is highly expressed in Human GBM

**Anti-VEGF** inhibits growth of GBM xenograft

**VEGF** expression correlates with tumour grade and outcome

| Survival (weeks) r = -0.42 |

**VEGF mRNA signal**

*Nature* • Vol 362 • 29 April 1993

Mode of Action of Bevacizumab

**Bevacizumab**

Ligand Sequestration

**Angiogenesis**

**Lymphangiogenesis**

Bevacizumab & Irinotecan

- Early report suggested activity in 9 patients
- Recent Phase II study
  - Bevacizumab 10 mg/kg q 2 weeks
  - Irinotecan 125 mg/m² (no EIACDs) or Irinotecan 340 mg/m² (on EIACDs) q 2 weeks
- 35 patients accrued
  - GBM: 26
  - AG: 9

Bevacizumab with Irinotecan

- 2 cohorts evaluated (N = 35)
  - Cohort 1 (n = 23): bev 10 mg/kg + irinotecan every 2 weeks for 6 weeks
  - Cohort 2 (n = 12): bev 15 mg/kg every 21 days + irinotecan on Days 1, 8, 22, and 29 for 6 weeks

- 20/35 patients (57%) had radiologic response


6-month OS for all patients: 77% 6-month PFS for all patients: 46%

Radiographic Responses

A Phase II, Randomized, Non-comparative Clinical Trial of Bevacizumab Alone or in Combination with CPT-11 in Recurrent, Treatment-Refractory Glioblastoma

T Cloughesy, M Prados, PY Wen, TM Mikkelsen, L Abrey, D Schiff, WK Yung, M Zheng, I Dimery, H Friedman

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 Arizona, Tucson, AZ. MD Anderson Cancer Center, Houston, TX. Genentech, Inc., South San Francisco, CA. and Duke University, Durham, NC.
Bevacizumab: 10mg/kg every 2 weeks

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

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

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

* Bevacizumab: 10mg/kg every 2 weeks
** CPT-11: EIAED: 340mg/m² IV over 90 min
Non-EIAED: 125 mg/m² IV over 90 min

A treatment cycle = 6 week period of therapy

Study Design

Objectives

• Primary endpoints
  - Efficacy of bevacizumab alone or in combination with CPT-11 (irinotecan) in the treatment of patients with recurrent GBM by:
    • Progression-free survival-6 (PFS at 24 weeks)
    • Objective response rate (ORR)

• Secondary endpoints
  - Overall Survival (OS)
  - PFS
  - Duration of response
  - Safety

Tumor and Efficacy Assessments

• Tumor assessments every 6 weeks
• Response and PFS determined by Independent Radiology Facility review (IRF)
  - Contrast-enhancing (CE) tumor (target lesions) evaluated by 2 radiologists
    • Non-contrast enhancing (nCE) lesions considered "non-target"
• Progression assessment includes CE and nCE tumors
  - Discrepancy between readers resolved by an Adjudicator, blinded to the identity of the primary readers
  - For patients with CR and PR, oncology review evaluated the corticosteroid dosing while on therapy
Efficacy

<table>
<thead>
<tr>
<th></th>
<th>BV Alone</th>
<th>BV+CPT-11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=85)</td>
<td>(n=82)</td>
</tr>
<tr>
<td>Median OS*, months (95% CI)</td>
<td>9.2 (8.2 – 10.7)</td>
<td>8.7 (7.8 – 10.9)</td>
</tr>
<tr>
<td>PFS6, % (97.5% CI)</td>
<td>42.6 (29.6-55.5)</td>
<td>50.3 (36.8-63.9)</td>
</tr>
<tr>
<td>ORR, % (97.5% CI)</td>
<td>28.2 (18.5-40.3)</td>
<td>37.8 (26.5-50.8)</td>
</tr>
<tr>
<td>CR</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>PR</td>
<td>27.1</td>
<td>35.4</td>
</tr>
<tr>
<td>Median Duration of Response (months) (95% CI)</td>
<td>5.6 (3.0 – 5.75)</td>
<td>4.3 (4.14, - )</td>
</tr>
</tbody>
</table>

Percent Change in Smallest Post-Baseline SPD From Baseline (determined by External Review)

Safety (All Treated Patients)

|                                | BV Alone  | BV+CPT-11 |
|                                | (n=84)    | (n=79)    |
| Grade > 3 Adverse Event (AE)   | 39 (46.4 ) | 52 (65.8 ) |
| Serious AE                     | 22 (26.2 ) | 34 (43.0 ) |
| AE leading to Treatment Discontinuation Bevacizumab | 4 (4.8 ) | 14 (17.7 ) |
| CPT-11                         | (0.0)     | (0.0)     |
| AE Leading to Death            | 2 (2.4)   | 1 (1.3)   |
Response Rate and Outcomes in Pooled Analyses of Trials for Relapsed Glioblastoma

<table>
<thead>
<tr>
<th>Publication</th>
<th>Sample Size</th>
<th>Response Rate</th>
<th>6 Month PFS</th>
<th>Overall Survival</th>
<th>12 month Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson Trials 1986-1995 (Wong 1999)</td>
<td>325</td>
<td>6%</td>
<td>13%</td>
<td>5.7 mo</td>
<td>27%</td>
</tr>
<tr>
<td>NCCTG Trials 1980-2004 (Ballman 2007)</td>
<td>345</td>
<td>n/a</td>
<td>9%</td>
<td>5.1 mo</td>
<td>14%</td>
</tr>
<tr>
<td>NABTC Trials 1998-2002 (Lamborn 2008)</td>
<td>437</td>
<td>7%</td>
<td>16%</td>
<td>6.9 mo</td>
<td>23%</td>
</tr>
<tr>
<td>Lomustine control arm from Phase III study of Enzastaurin (Fie et al 2008)</td>
<td>92</td>
<td>4.3%</td>
<td>19%</td>
<td>7.1 mo</td>
<td>24%</td>
</tr>
</tbody>
</table>

Frontline Bevacizumab for GBM
• XRT + TMZ + Bev
• XRT + TMZ + Erlotinib + Bev (UCSF)
• Adjuvant TMZ + Bev only
• Phase III trial (Roche, RTOG)
  – XRT + TMZ + Bev

AZD2171

Angiogenesis Lymphangiogenesis

VEGF-A VEGF-B VEGF-C VEGF-D

VEGFR-1 (Flt-1) VEGFR-2 (KDR) VEGFR-3 (Flt-4)

AZD2171

AZD2171

AZD2171

VEGFR TK inhibitor
Clinical Outcomes

Radiographic Responses: (N = 16)

APF6 [95% CI] (N = 30)

PFS [95% CI] (N = 30)

OS [95% CI] (N = 30)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>12-Month PFS</th>
<th>24-Month PFS</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZD2171</td>
<td></td>
<td>16/30 (53%)</td>
<td>117 days</td>
<td>221 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>22/30 (73%)</td>
<td>[14.7%, 46.9%]</td>
<td>[172, 285]</td>
<td></td>
</tr>
</tbody>
</table>

Wong, et al
J Clin Oncol 1999

N/A 63 days 175 days

What are some of the major problems?

• Variable time of progression
• Non-enhancing T1 tumor growth
• Flair extension
• Infiltrative/invasion phenotype
20 y.o. man, GBM, 1st relapse after XRT, TMZ, CRA

1-07

9-07

U87 Xenograft After Bevacizumab
U87 Xenograft After Bevacizumab

Eterovic, Piao and de Groot. CCR. In Press.

Prolonged Treatment of VEGF Trap Induces an Invasive Phenotype


Anti-Angiogenic Agents in Clinical Practice

- Early MRI response
- Marked decrease in edema
- Impressive RR and PFS-6mo
- Response still short lived
- ? Increase in survival
Are there salvage therapies?

- Second Bev containing regimens: MTP 38d, PFS6 2% (Wen)
- Other cytotoxics, rare response
- Other signal drugs, rare response

Many Questions

- What drives the invasion phenotype?
- How to salvage anti-VEGF failure?
- What are the best cytotoxics to use in combination?
- What are the best biomarkers to use for selection and to follow progression and response?