Recurrent Glioblastoma: Current Obstacles & Future Directions in Care

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Disclosures
Patrick Y. Wen, MD

• Research Support
  – Boehringer Ingelheim
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  – Exelixis
  – Genentech
  – Merck
  – Novartis
• Advisory Board
  – Ark Therapeutics
  – Agios
  – Genzyme
  – Novartis
  – Imclone/Lilly
• I will be discussing drugs that are unlabeled or used for investigational purposes

Primary Brain Tumors

• 62,930 new cases each year in the US
• 22,000 malignant
• 17,000 are malignant glioma
• 13,000 deaths/year

Central Brain Tumor Registry of the United States, 2010
Incidence
Distribution of All Gliomas by Histology Subtypes

- Ependymomas: 5.6%
- All Other Gliomas: 10.1%
- Glioblastoma: 50.7%
- Diffuse Astrocytoma: 5.7%
- Pilocytic Astrocytoma: 5.7%
- Anaplastic Astrocytoma: 7.9%
- Oligodendrogliomas: 9.2%
- All Other Astrocytomas: 9.1%

Central Brain Tumor Registry of the United States 2004-2005.

Prognosis

<table>
<thead>
<tr>
<th>WHO Grade</th>
<th>Designation</th>
<th>Frequency (%) of gliomas</th>
<th>5-year Survival (%)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pilocytic Astrocytomas</td>
<td>5.7</td>
<td>&gt;90%</td>
<td>Potentially curable if tumor can be resected</td>
</tr>
<tr>
<td>II</td>
<td>Diffuse astrocytoma</td>
<td>1.7</td>
<td>46.9</td>
<td>3-8 yrs</td>
</tr>
<tr>
<td></td>
<td>Oligodendroglioma</td>
<td>9.2</td>
<td>70.5</td>
<td>10 yrs</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>7.9</td>
<td>29.4</td>
<td>2-3 yrs</td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligodendroglioma</td>
<td>5.1</td>
<td>40.1</td>
<td>3-6 yrs</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma</td>
<td>50.7</td>
<td>3.3</td>
<td>9-15 mos</td>
</tr>
</tbody>
</table>
Glioblastoma (IV)

T1 + gad

High cellularity/pleomorphism
Endothelial proliferation,
pseudopalisading necrosis

Outline

• Standard Therapies
• Novel Therapies
  – Overcoming temozolomide resistance
  – Overcoming Blood Brain Barrier
  – Targeted Molecular Therapies
  – Inhibitors of Angiogenesis
  – Miscellaneous Therapies
Standard Therapy

Surgery

- Removes mass effect and improves symptoms
- Provides tissue for diagnosis and molecular studies
- Modest prolongation in survival
AMIGO: Advanced multi-modality Image-guided OR

- Intra-operative imaging
- Anatomic and molecular imaging
- Cross modality validation
- Development of new techniques

Radiation Therapy

- Prolongs survival to 9-12 months
- T2 area of abnormality + 1-2 cm margin
- 6000 cGy in 180-200 cGy fractions
- 80-90% patient recur within primary site
Stereotactic Radiosurgery

Radiosurgery Boost: RTOG 9305

Chemotherapy

Temozolomide: Second-generation Alkylating Agent

TMZ spontaneously converts to MTIC at physiologic pH

MTIC, 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide.

Concomitant TMZ + RT* Adjuvant TMZ

RT Alone

R

TMZ 75 mg/m² PO QD for 6 weeks, then 150-200 mg/m² PO QD on Days 1-5 every 28 days for 6 cycles
Focal RT daily—30 x 200 cGy; total dose: 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.


Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT+TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo:</td>
<td>12.1</td>
<td>14.6</td>
</tr>
<tr>
<td>2-yr survival:</td>
<td>10%</td>
<td>26%</td>
</tr>
<tr>
<td>HR [95% C.I.]:</td>
<td>0.63 [0.52-0.75]</td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RT n = 286</th>
<th>RT+TMZ n = 287</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year OS (%)</td>
<td>10.9</td>
<td>27.2</td>
</tr>
<tr>
<td>3-year OS (%)</td>
<td>4.4</td>
<td>16.4</td>
</tr>
<tr>
<td>4-year OS (%)</td>
<td>3.0</td>
<td>12.1</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.63 [0.53 - 0.75]</td>
<td>( P &lt; 0.0001 )</td>
</tr>
</tbody>
</table>


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**Glioma with unmethylated MGMT**

- MGMT promoter
- Gene activation
- Alkyl group removed by MGMT from the DNA base guanine
- DNA cross-links cut, tumor cells unharmed

**Glioma with methylated MGMT**

- Methyl group
- MGMT promoter
- Gene inactivation
- Carmustine cross-links DNA strands, and there is no active MGMT to repair it
- DNA remains cross-linked, and tumor cells die

Phase III RTOG 0525: Conventional TMZ vs Dose-Intensive TMZ in New GBM

- \( N = 1154 \)

**Standard arm**
- Radiation (60 Gy in 2-Gy fractions) + Concurrent daily TMZ (x 49 days max)
- TMZ on Days 1-5 of 28-day cycle for 6 cycles*

**Experimental arm**
- TMZ on Days 1-21 of 28-day cycle for 6 cycles*
- *Up to 12 cycles may be given if continued improvement shown by MRI scan, decreasing corticosteroid requirement, improvement in performance status, or improvement in neurological function.

RTOG Summaries. Available at:

Recurrent Glioblastoma

Even with optimal treatment, nearly all malignant gliomas recur.

Median TTP from initiation of first-line therapy for GBM:
- 6.9 months

PFS6:
- 9-16%


Recurrent Malignant Gliomas
## Response Rate and 6-Month PFS 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>1-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 MD Anderson trials 1986–1995(^1)</td>
<td>225</td>
<td>6%</td>
<td>15%</td>
<td>5.7 months</td>
<td>21%</td>
</tr>
<tr>
<td>16 NCCTG trials 1980–2004</td>
<td>345</td>
<td>NA</td>
<td>9%</td>
<td>5.1 months</td>
<td>14%</td>
</tr>
<tr>
<td>12 NABTC trials 1998–2002(^3)</td>
<td>437</td>
<td>7%</td>
<td>16%</td>
<td>6.9 months</td>
<td>25%</td>
</tr>
<tr>
<td>Lomustine control arm, phase III study of enzastaurin(^4)</td>
<td>92</td>
<td>4.3%</td>
<td>19%</td>
<td>7.1 months</td>
<td>24%</td>
</tr>
</tbody>
</table>

PFS=progression-free survival.


## Pseudoprogression
Pseudoprogression

Before RT

8 wks after RT

4 wks after RT

6 months later

CLINICAL INVESTIGATION

POTENTIAL FOR DIFFERENTIATION OF PSEUDOPROGRESSION FROM TRUE TUMOR PROGRESSION WITH DYNAMIC SUSCEPTIBILITY-WEIGHTED CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING USING FERUMOXITOL VS. GADOTERIDOL: A PILOT STUDY

Seymur Gahramanov, M.D., Ahmed M. Raslan, M.D., Leslie L. Muldoon, Ph.D., Bronwyn E. Hamilton, M.D., William D. Rooney, Ph.D., Csarno G. Varolliyat, M.D., Jeffrey M. Neis, Ph.D., Marianne Haluska, A.N.P., and Edward A. Neuwelt, M.D.

From the Departments of Neurology, Neurosurgery, Radiology, and Advanced Imaging Research Center, Oregon Health and Science University, Portland, OR; Dept. of Neurosurgery, Universitätsklinikum Weinburg, Germany; and Portland Veterans Affairs Medical Center, Portland, OR.

Standard Therapies

- Reoperation
- Prolifeprosan 20 With Carmustine Implant
- Reirradiation
- Chemotherapy
  - Dose dense temozolomide
  - Nitrosoureas (CCNU, BCNU)
  - Others (carboplatin, irinotecan, etoposide)
- Bevacizumab

Prolifeprosan 20 With Carmustine Implant (Gliadel Wafers)
Prolifeprosan 20 With Carmustine Implant (Gliadel Wafers)

Carmustine Wafer Improves Survival vs Placebo

Median survival
GLIADEL® Wafer 31 wk
Placebo 23 wk
P value = 0.006 *


Stereotactic Radiosurgery
Bevacizumab + Hypofractionated Radiotherapy

Fig. 1. Baseline (A) and posttreatment (B) gadolinium-enhanced brain MRI in a patient with glioblastoma showing a partial response.


25 patients
50% Response
PFS6 65%

Novel Therapies for Recurrent Gliomas

- Overcoming temozolomide resistance
- Bypassing the blood-brain barrier
- Targeted molecular therapies
- Anti-angiogenic therapies
- Stem cell directed therapy
- Miscellaneous
Overcoming Resistance to Temozolomide

Rationale for Re-Challenge

- MGMT expression levels play a role in TMZ resistance
- Dose intense or extended TMZ may target and overcome MGMT expression

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose mg/m²/day</th>
<th>Schedule</th>
<th>Dose Intensity (mg/m²/28 days)</th>
<th>Relative Dose Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/28</td>
<td>150-200</td>
<td>5 days in every 28 days</td>
<td>1000</td>
<td>1</td>
</tr>
<tr>
<td>7/14</td>
<td>150</td>
<td>7 days on, 7 days off</td>
<td>2100</td>
<td>2.1</td>
</tr>
<tr>
<td>21/28</td>
<td>85-100</td>
<td>3 weeks on, 1 week off</td>
<td>2100</td>
<td>2.1</td>
</tr>
<tr>
<td>Continuous</td>
<td>50</td>
<td>4 weeks on, no weeks off</td>
<td>1400</td>
<td>1.4</td>
</tr>
<tr>
<td>42-49/56</td>
<td>75</td>
<td>6-7 weeks on, 2 weeks off</td>
<td>1575</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Continuous TMZ Study Design

GBM at 1st recurrence (after standard chemoradiation)

TMZ 50 mg/m²/day Continuously (up to 12 months)

Early adjuvant failure (Failure during months 3-6)

Extended adjuvant failure (Extended treatment ≥ 6 mo)

Completed adjuvant failure (Completed TMZ therapy)

stratified by prior failure

6-Month PFS

N = 90

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Extended</th>
<th>Completed</th>
<th>Anaplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Month PFS (%)</td>
<td>28.6%</td>
<td>9.5%</td>
<td>30.4%</td>
<td>42.1%</td>
</tr>
</tbody>
</table>

Bypassing The Blood Brain Barrier

Endothelial cells forming the BBB:
- Express tight junctions
- Lack fenestra
- Lack transendothelial channels
- Lack pinocytic vesicles
- High levels of active efflux proteins, Pgp

Convection-Enhanced Delivery
Targeted Molecular Therapies
Pathways in the Development of Malignant Gliomas

Cell-of-Origin: Differentiated Glial or Stem or Progenitor Cells

- Low-Grade Astrocytoma (5–19 yr)*
  - WHO Grade II
  - LOH 10q (~50%)
  - RB mutated (~21%)
  - CDKN2A amplified (35%)
  - MGMT overexpressed (10%)
  - PI3K/Akt1/2/3, PTEN loss (4%)
  - LOH 17p (~35%)

- Anaplastic Astrocytoma (2–3 yr)*
  - WHO Grade III
  - LOH 10q (~70%)
  - DCC loss (~50%)
  - P53/MDM2 amplified (~10%)
  - PI3K/Akt1/2/3 mutated (~10%)
  - PIK3CA mutated/ amplified (~10%)
  - VEGF overexpressed

- Secondary Glioblastoma (12–15 mth)*
  - WHO Grade IV
  - LOH 17p (~100%)

- Primary Glioblastoma (12–15 mth)*
  - WHO Grade IV
  - EGFR amplified (~40%)
  - PI3K/Akt1/2/3, PTEN mutated (~35%)
  - RB mutated (~21%)
  - MGMT overexpressed (~30%)

- Low-Grade Oligodendroglioma (5–10 yr)*
  - WHO Grade II
  - LOH 1p (~70%)
  - PI3K/Akt1/2/3, PTEN loss (~20%)
  - PTEN-mutated (~40%)
  - PIK3CA mutated/ amplified (~20%)
  - RB mutated
  - MGMT overexpressed

- Anaplastic Oligodendroglioma (1–3 yr)*
  - WHO Grade III
  - P53/MDM2, PI3K/Akt1/2/3 mutated (~65%)
  - p53 mutated (~35%)
  - P739 mutated
  - CDKN2A/2B/2C, MYC amplified
  - VEGF overexpressed

Frequent Genetic Alterations in Three Critical Signaling Pathways

- p53 signaling altered in 87%
  - Amplification in 16%
  - Homozygous deletion/mutation in 31%

- PI3K/Akt1/2/3, PTEN mutated in 45%
  - Mutation, homozygous deletion in 15%
  - Homozygous deletion/mutation in 31%

- EGFR
  - Amplification in 15%
  - Mutation, homozygous deletion in 36%

- Met
  - Amplification in 2%
  - Homozygous deletion in 1%

- RAS
  - Mutation in 2%
  - Proliferation

- Activated onco
genese

- APC, ATM
  - Mutation, homozygous deletion in 21%
  - Senescence

- MDM2
  - Amplification in 7%
  - Homozygous deletion/mutation in 31%

- BAX, BCl2
  - Apoptosis

- Retinoblastoma
  - G1/S progression

Pathways in the Development of Malignant Gliomas


An Integrated Genomic Analysis of Human Glioblastoma Multiforme


Table 2. Most frequently altered GBM CAN-genes. All CAN-genes are listed in Table S7.

<table>
<thead>
<tr>
<th>Gene</th>
<th>No. of tumors</th>
<th>Amplification (b)</th>
<th>Homogeneous deletion (b)</th>
<th>Fraction of tumors with any alteration (%)</th>
<th>P-value (b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN2A</td>
<td>0/22</td>
<td>0</td>
<td>0/22</td>
<td>1/22</td>
<td>0.50</td>
</tr>
<tr>
<td>TP53</td>
<td>3/245</td>
<td>2</td>
<td>3/245</td>
<td>6/245</td>
<td>0.40</td>
</tr>
<tr>
<td>EGFR</td>
<td>14/1685</td>
<td>14</td>
<td>14/1685</td>
<td>20/1685</td>
<td>0.01</td>
</tr>
<tr>
<td>PLEN</td>
<td>2/1285</td>
<td>2</td>
<td>2/1285</td>
<td>8/1285</td>
<td>0.01</td>
</tr>
<tr>
<td>NPM1</td>
<td>13/1685</td>
<td>13</td>
<td>13/1685</td>
<td>16/1685</td>
<td>0.01</td>
</tr>
<tr>
<td>CDK4</td>
<td>0/22</td>
<td>0</td>
<td>0/22</td>
<td>1/22</td>
<td>0.50</td>
</tr>
<tr>
<td>HBO1</td>
<td>8/1285</td>
<td>8</td>
<td>8/1285</td>
<td>16/1285</td>
<td>0.01</td>
</tr>
<tr>
<td>IDH1</td>
<td>11/13015</td>
<td>11</td>
<td>11/13015</td>
<td>22/13015</td>
<td>0.01</td>
</tr>
<tr>
<td>IDH2</td>
<td>12/13015</td>
<td>12</td>
<td>12/13015</td>
<td>24/13015</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IDH1 and IDH2 Mutations in Gliomas

Haiyan, M.D., Ph.D., D. Williams Parsons, M.D., Ph.D., Genglin Jin, Ph.D., Roger McLendon, M.D., B. Ahmed Rasheed, Ph.D., Weishi Yuan, Ph.D., Ivan Kos, Ph.D., Ines Batinić-Haberle, Ph.D., Slán Jones, Ph.D., Gregory J. Riggins, M.D., Ph.D., Henry Friedman, M.D., Allan Friedman, M.D., David Reardon, M.D., James Herndon, Ph.D., Kenneth W. Kinzler, Ph.D., Victor E. Velculescu, M.D., Ph.D., Bert Vogelstein, M.D., and Darell D. Bigner, M.D., Ph.D.

IDH1 and IDH2 Mutations in Human Gliomas


Survival of Adult Patients with Malignant Gliomas with or without IDH Gene Mutations

Median Survival

31 mo vs 15 mo

65 mo vs 25 mo

Oncometabolite
Bypassing The Blood Brain Barrier

Endothelial cells forming the BBB:
- Express tight junctions
- Lack fenestra
- Lack transendothelial channels
- Lack pinocytic vesicles
- High levels of active efflux proteins, Pgp
Phase II design for recurrent malignant glioma with concurrent pilot tissue correlate study for targeted agents

Progression

Eligible for surgery

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard phase II study</td>
<td>Administer Drug</td>
</tr>
</tbody>
</table>

Administer Drug

Surgery

Tissue Correlates

Slide courtesy of Susan Chang (UCSF)

Method for phospho-RTK discovery


Multiple RTKs are activated in primary tumors
Targeted Molecular Therapies

- Single agents likely to have only modest activity
- Use drugs with multiple targets: “Dirty Drugs”
- Need to get to effective combinations more rapidly
  - Other targeted drugs
  - Chemotherapy
  - Radiation Therapy
  - Drugs targeting stem cells
- Need to use drugs that inhibit final common pathways

PI3 Kinase/Akt Inhibitors

Growth Factors, etc

Akt inhibitor
Perifosine
MK2206

PI3K inhibitor
XL765
XL147
BKM120

PI3K

PTEN

PTEN

PI3K inhibitor
XL765
XL147
BKM120

Proliferation

Translation ON

ATF-4

mTOR

PDK1

Akt

Raf

Mek

Erk

Ras

Raf

Mek

Erk

BKM120
Glioblastoma Pathogenesis: Major Signaling Pathways

Cellular membrane
- EGF
- EGFR
- PI3K/PIK3CA
- Grb2
- Shc
- NF1
- RAS
- PI(4,5)P2
- PI(3,4,5)P3
- PI(4,5)P2

Nuclear membrane
- p16
- INK4a
- PTEN
- NF1
- RAS
- RAF
- MEK
- ERK
- PI(4,5)P2
- PI(3,4,5)P3
- PI(4,5)P2
- AKT (PKB)
- TSC1/2
- mTOR

Genetic alterations typical for pGBM
- sGBM
- Both subtypes


CDK 4/6 inhibitors
PD-0332991
Michaud et al.
Cancer Res 70(8):3228-38

Sequencing
Epigenetic Analysis
Set of activated kinases and pathways
Combinations of appropriate drugs

Key: Foundation Early Phase Clinical Trials Consortium
- DF/HCC
- MSKCC
- UCLA
- UCSF
New Clinical Trial Designs

• Improve efficiency
  – Rapid elimination of ineffective regimens
  – Test multiple combinations simultaneously
  – Shorter path to definitive testing

• Designs
  – “Pick the Winner”
  – Seamless integration of phase II/III trials
  – Sequential Accrual Design for Phase I/II studies
  – Factorial Design
  – Adaptive Randomization
  – Randomized Discontinuation Design

Neural Stem Cells
Glioma Stem Cells

Gamma secretase inhibitors
- MRK0752
- R4929097


Sonic Hedgehog Pathway

Sonic Hedgehog Inhibitor
GDC-4409
Glioma Stem Cells

Inhibition of Angiogenesis
Perivascular Niche For Brain Tumor Stem Cells

Mode of Action of Bevacizumab

Bevacizumab

Ligand Sequestration

VEGF-A

VEGF-B

VEGF-C

VEGF-D

VEGFR-1 (Flt-1)

VEGFR-2 (KDR)

VEGFR-3 (Flt-4)

Angiogenesis

Lymphangiogenesis

Retrospective Trials With Bevacizumab

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Regimen</th>
<th>ORR</th>
<th>PFS6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stark Vance</td>
<td>29</td>
<td>Bev 5 mg/kg every 2 weeks; CPT-11 125 mg/m² for 4 weeks, 2 week break</td>
<td>66%</td>
<td>NR</td>
</tr>
<tr>
<td>Pope, et al</td>
<td>14</td>
<td>Bev + CPT-11 and others</td>
<td>50%</td>
<td>NR</td>
</tr>
<tr>
<td>Norden, et al</td>
<td>44</td>
<td>Bev + CPT-11 and others</td>
<td>34%</td>
<td>39% GBM, 33% AG</td>
</tr>
<tr>
<td>Guiu, et al</td>
<td>77</td>
<td>Bev + CPT-11</td>
<td>54% AG</td>
<td>NR</td>
</tr>
<tr>
<td>Nghiemphu, et al</td>
<td>44</td>
<td>Bev + CPT-11 and others</td>
<td>NR</td>
<td>44% GBM</td>
</tr>
</tbody>
</table>

Protocol AVF3708g Study Design

- GBM – 1st or 2nd PD
- Measurable disease
- KPS > 70%
- Adequate organ function
- No prior irinotecan, VEGF or VEGFR directed FX
- No CNS hemorrhage

Bevacizumab 1
Alone
(n = 80)
Repeat Cycles
Every 6 Weeks

Bevacizumab 1
Plus Irinotecan 2
(n = 80)
Repeat Cycles
Every 6 Weeks

Randomize

Repeat Cycles
Every 6 Weeks

Primary Endpoints:
- 6 – month PFS
- Radiographic Response

- 6-month PFS
- Radiographic Response

1 Bevacizumab – 10mg/kg IV every 2 weeks
2 Irinotecan – IV every 2 weeks
- 340 mg/m² if on EIAEDs
- 125 mg/m² if not on EIAEDs


Measurable Disease with BV

Percent Change in Smallest Post-Baseline SPD (Sum of the Product Diameter) from Baseline (determined by External Review)

Patients with measurable disease at baseline and at least one post-baseline tumor assessment
### Treatment With Bevacizumab

**AVF3708g Bevacizumab**

- **Response Rate**
  - Investigator: 41.2% (30.6, 52.3)
  - Independent Review: 28.2% (18.5, 40.3)
  - FDA Review: 25.9% (15.9, 37.8)

- **Median Duration of Response**
  - Investigator: 8.1 m (5.6, -)
  - Independent Review: 5.6 m (3.0, 5.8)
  - FDA: 4.2 m (3.0, 5.7)

**AVF3708g Bevacizumab + CPT-11**

- **Response Rate**
  - Investigator: 51.2%
  - Independent Review: 37.8%

**NCI 06-C-0064E Bevacizumab**

- **Response Rate**
  - Investigator: 35%
  - Independent Review: 19.6% (10.9, 31.3)

- **Median Duration of Response**
  - Investigator: 8.3 m
  - Independent Review: 4.4 m
  - FDA: 3.9 m (2.4, 17.4)
Comparison of Response Rates in Bevacizumab Only Arm and Historic Controls

6-Month Progression-Free Survival (PFS6)

<table>
<thead>
<tr>
<th></th>
<th>AVF3708g Bevacizumab</th>
<th>AVF3708g Bevacizumab + Irinotecan</th>
<th>NCI 06-C-0064E Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator</td>
<td>43.6% (33.0, 54.3)</td>
<td>57.9% (46.6, 69.2)</td>
<td>35%</td>
</tr>
<tr>
<td>Independent Review</td>
<td>42.6% (33.0, 54.3)</td>
<td>50.3% (36.8, 63.9)</td>
<td></td>
</tr>
<tr>
<td>FDA Review</td>
<td>36.0% (24.0, 48.0)</td>
<td></td>
<td>19.6%</td>
</tr>
</tbody>
</table>

INV—investigator; IRC—Independent Review Facility.
Note: Confidence intervals are 97.5% for Study AVF3708g by independent review, and 95% otherwise.
Comparison of PFS6 in Bevacizumab Only Arm and Historic Controls

Percent Change of Lowest Corticosteroid Dose from Baseline

Responders are colored in orange.
Study AVF3708g: Selected Adverse Events of Interest
(Safety-Evaluable Patients)

<table>
<thead>
<tr>
<th>Selected Adverse Events</th>
<th>Avastin (n=84)</th>
<th>Avastin + Irinotecan (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade</td>
<td>Grade ≥ 3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.7%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>27.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Seizure</td>
<td>17.5%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Wound-healing complications</td>
<td>6.0%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Arterial thromboembolic events</td>
<td>4.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>3.6%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>2.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>RPLS</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

RPLS = reversible posterior leukoencephalopathy syndrome.

Each of the selected adverse events of interest is a composite of MedDRA preferred terms reviewed by the Genentech Medical Monitor.

Cediranib (AZD2171)

- VEGF-A
- VEGF-B
- PIGF
- VEGF-C
- VEGF-D
- VEGF-1 (Flt-1)
- VEGF-2 (KDR)
- VEGF-3 (Flt-4)
- VEGFR TK Inhibitor

Inhibitor
Phase III Trial of Cediranib vs Cediranib and CCNU vs CCNU alone

N = 300

Recurrent GBM
1 prior treatment with TMZ

CCNU 110mg/m2 (60 pts)

Cediranib 30mg daily (120 pts)

Cediranib 20mg daily + CCNU 110mg/m2 (120 pts)

Primary endpoint PFS
Secondary endpoints: survival, response, PFS6
### Regal Trial (PFS)

<table>
<thead>
<tr>
<th></th>
<th>Cediranib</th>
<th>Cediranib + CCNU</th>
<th>CCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td>92 days</td>
<td>125 days</td>
<td>82 days</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Regal Trial (PFS6)

<table>
<thead>
<tr>
<th></th>
<th>Cediranib</th>
<th>Cediranib + CCNU</th>
<th>CCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.2%</td>
<td>34.5%</td>
<td>24.5%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Cediranib prolongs survival despite persistent tumor growth

![Graph showing survival data](image)


Alleviation of brain edema increases survival

![Graph showing water content and survival data](image)

What Next?

Trials of Anti-angiogenic Agents for Newly-Diagnosed Glioblastomas

- **VEGF**
  - Bevacizumab (RTOG, Roche)
  - Aflibercept (VEGF-Trap) (ABTC)

- **VEGFR**
  - Cediranib (VEGFR, PDGFR) (DF/HCC, RTOG)
  - Vandetanib (VEGFR, EGFR) (DF/HCC)
  - Sorafenib (VEGFR, PDGFR, Raf)
  - XL184 (VEGFR, Met) (Exelixis)

- **PKCβ**
  - Enzastaurin (UCSF, multiple)

- **Integrins**
  - Cilengitide (Merck KG)
Most patients eventually progress

- Retrospective review of 54 patients
- Malignant gliomas who developed progression

Bevacizumab + chemo 1 → Bevacizumab + chemo 2

**PD**

PR 25% → PR 0%

PFS6 33% → PFS 2%

Mechanisms of Resistance

Adaptive Evasion to VEGF inhibitors
Upregulation of additional proangiogenic growth factors

At Recurrence
Increase bFGF
Increase SDF1a
Increase Tie 2
Increase circulating endothelial cells

Selected Studies Targeting Alternate Angiogenic Pathways

- Targeting VEGFR+FGFR
  - BIBF1120 (also targets PDGFR)
  - E7080 (also targets PDGFR)
  - Brivanib
- Targeting Angiopoietins
  - CVX060
    - Selective angiopoietin 2 neutralizing peptibody
  - AMG 386
    - Selective angiopoietin 1/2 neutralizing peptibody

Adaptive Resistance to Anti-VEGF Agents

Treatment With Cediranib

Recurrence 7 months after treatment with cediranib
Vascular co-option / increased invasion during anti-VEGF treatment


Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis

Marta Plácido-Ribeiro,1,3 Elizabeth Allen,3,5 James Haddock,2 Takashi Takada,3 Hiroshi Otsuji,4 François Vivlhi,3,4 Masahiro Inoue,3 Gabriele Bengera,6 Douglas Hanahan,3,7 and Oriol Casalnovas1

Accelerated Metastasis after Short-Term Treatment with a Potent Inhibitor of Tumor Angiogenesis

John M. L. Elbow,1,5 Christine R. Lee,1 William Cruz-Munoz,1 Georg A. Bjarnason,2 James G. Christensen,3 and Robert S. Kerbel3,7
A new alternative mechanism in glioblastoma vascularization: tubular vasculogenic mimicry

Soufiane El Hallani,1* Blaudine Destaillet,1* Florian Pigillon,1 Audrey Routseau,2 Carole Coligny,3 Ahmed Ihsali,4,6 Yannick Marie,1 Karima Multari,7 Jean-Luc Thomas,1 Anne Estournet,5 Jean-Yves Delattre,1,4 Andrew J. Maniatis* and Marc Simon1,4

• Analysed human GBM tissues and found non-endothelial cell-lined blood vessels that were formed by tumor cells (vasculogenic mimicry of the tubular type)

• Hypothesized that CD133+ GBM cells express pro-vascular molecules allowing them to form blood vessels de novo

Glioma stem cells labeled with GFP in 3D culture in Matrigel

Glioma stem cells from GBM with tumor-lined vessels forms tubular structures in matrigel

Glioma stem cells from GBM with no tumor-lined vessels forms **did not** form tubular structures in matrigel

Selected Studies to Overcome Invasion

- Bevacizumab + Cilengitide
- Bevacizumab + CXCR4 inhibitor (plerixafor)
- Bevacizumab + Notch inhibitor
- Cediranib + Cilengitide
- CVX060 (Anti Ang 2 peptibody)
- XL184 (VEGFR+ Met)
- ? + FAK, HSP90 inhibitors
Best Time Point Response per IRF in All Patients with \( \geq 1 \) Post-Baseline Scan

97/148 (66%) patients experienced disease stabilization (-49% to +24% change in SPD)
44/148 (30%) patients experienced \( \geq 50\% \) reduction in SPD


Non-enhancing tumor progression
“Macdonald Criteria”

• Tumor size:
  – Maximum cross-sectional area of contrast enhancing tumor on CT or MRI
• Neurological function
• Steroid dose

Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group


## RANO Criteria Summary

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-Gd +</td>
<td>0</td>
<td>≥50%↓</td>
<td>&lt;50%↓</td>
<td>≥25%↑*</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>=,↓</td>
<td>=,↓</td>
<td>=,↓</td>
<td>=,↑*</td>
</tr>
<tr>
<td>New Lesion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Present*</td>
</tr>
<tr>
<td>Steroids</td>
<td>0</td>
<td>=,↓</td>
<td>=,↓</td>
<td>NA*</td>
</tr>
<tr>
<td>Clinical</td>
<td>=,↑</td>
<td>=,↑</td>
<td>=,↑</td>
<td>↓*</td>
</tr>
<tr>
<td></td>
<td>all</td>
<td>all</td>
<td>all</td>
<td>any*</td>
</tr>
</tbody>
</table>

* Progression occurs when this criterion is present


### Conventional therapies

- **Recurrence** → **Progression** → **Death**

### Antiangiogenic Therapies

- **Recurrence** → **Progression** → **Death**

Other Strategies

- Ultimately anti-angiogenic therapies alone will only have limited activity
- Need to combine with
  - Cytotoxic therapies (RT, chemotherapy)
  - Immunotherapy
  - Agents targeting tumor stem cells
  - Agents targeting metabolism
  - Others

Miscellaneous Therapies

- Viral Gene Therapy
- Immunotherapy
- \( ^{131}I \)-TM-601
- Novocure TTF
- \( ^{131}I \)-chTNT-1/R MAb (Cotara)
- Ritonavir/Lopinavir
- Bendamustine
- EM-1421