Primary Brain Tumors: Focus on Glioblastoma

Timothy Cloughesy MD
Professor and Director,
Neuro-oncology Program
UCLA
Objectives

- Primary brain tumor overview
- First-line Tx
  - Standard of care
  - Investigational approaches
- Recurrent
  - Standard of care
  - Investigational approaches
- Support and Management of AE
Glioma Overview

- Background, incidence, risk factors
- Molecular/genetic lifecycle of GBM
  - Origins › maintenance › treatment › progression
    - Attempts at therapeutic exploitation of molecular markers
- Prognostic and predictive biomarkers
  - Molecular
Primary Brain Tumor Background

- 18,500 new patients diagnosed with primary brain tumors in the United States in 2005\(^1,2\)
  - \(~50\%\) gliomas
  - \(~50\%\) of all gliomas are glioblastoma multiforme (GBM)
- Among patients with GBM\(^2,3\)
  - Median overall survival: 9 to 12 months
  - 2-year overall survival rates: 8\% to 12\%

Primary Brain Tumor Incidence

Distribution of All Primary Brain and CNS Tumors by Histology

- Glioblastoma: 20.3%
- Astrocytomas: 9.8%
- Ependymomas: 2.3%
- Oligodendrogliomas: 3.7%
- Embryonal, including medulloblastoma: 1.7%
- Meningioma: 30.1%
- Pituitary: 6.3%
- Nerve Sheath: 8.0%
- Craniopharyngioma: 0.7%
- Lymphoma: 3.1%
- All Other: 13.9%

Glioma Incidence

Distribution of All Gliomas by Histology Subtypes

- Glioblastoma: 50.7%
- All Other Astrocytomas: 9.1%
- Anaplastic Astrocytoma: 7.9%
- Diffuse Astrocytoma: 1.7%
- Pilocytic Astrocytoma: 5.7%
- Ependymomas: 5.6%
- Oligodendrogliomas: 9.2%
- All Other Gliomas: 10.1%

Malignant Gliomas

- Annual incidence of malignant brain tumors
  - 7.3 cases per 100,000 people

- Glioblastoma multiforme (GBM)
  - 54% of all gliomas
  - 17% of all brain tumors
  - ~ 9500 cases per year in 2004-2007

- GBM incidence
  - 1.6-fold higher in men than women
  - 4-fold higher when age ≥ 65 years compared to those < 55 years

  - 2-year: 12.6%, 5-year: 4.75%

Malignant Gliomas: Incidence by Age

Figure 1. Age-specific incidence of CNS tumors by histologies, from CBTRUS Report 2004-2005. (CBTRUS)

Risk Factors for Malignant Glioma

- Family history of cancer in 19% of patients\(^1\)
- Genetically inherited syndromes in 5% of patients with primary brain tumors\(^1\)
  - Neurofibromatosis types 1 and 2
  - Li-Fraumeni syndrome
  - von Hippel-Lindau syndrome
  - Turcot syndrome
  - Tuberous sclerosis
- Brain irradiation in childhood\(^2\)
- Viral, CMV?
- Cell phones?

No early detection
Symptoms
Incidence of Symptoms in Patients With Glioma

Symptom Etiology

• Direct infiltration and destruction of neurons
• Local pressure from
  – Edema
  – Hemorrhage
  – Tumor mass
• Intracranial hypertension
  – Mass effect
  – Ventricular obstruction
Glia progenitor cells

- Astrocyte
- Oligodendrocytes
- Ependyma

- Astrocytoma
- Oligoastrocytoma
- Oligodendroglioma
- Ependymoma
Model of Glioma Origins

Glioma Maintenance: Tumor and Microenvironment Interface


Molecular analysis
Histopathology of Glioma Helps Predict Survival

- Pleomorphism
- Mitosis
- Endothelial Proliferation
- Necrosis

<table>
<thead>
<tr>
<th># Features</th>
<th>Grade</th>
<th>Prognosis (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>I</td>
<td>normal life</td>
</tr>
<tr>
<td>1</td>
<td>II</td>
<td>3-5 years</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>28 months</td>
</tr>
<tr>
<td>3-4</td>
<td>IV</td>
<td>12-18 months</td>
</tr>
</tbody>
</table>
IDH/1p19q co-delete vs IDH mt vs IDH wt

Glioma histologic subtype vs glioma molecular subtype

IDH/1p19q co-delete vs IDH mt vs IDH wt
Prognostic Classification: EORTC Recursive Partitioning Classification System

- Modified from RTOG
- Patients with glioblastoma from EORTC/NCIC XRT/TMZ study
- Stratification into groups (Class III-V) based on
  - Age
  - WHO performance status
  - Mini-mental status evaluation
  - Extent of resection
- Prognostic variables may be used for stratification of trial subjects

<table>
<thead>
<tr>
<th>Class</th>
<th>Median Survival, mo</th>
<th>2-Year Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>18.7</td>
<td>40.5</td>
</tr>
<tr>
<td>IV</td>
<td>16.3</td>
<td>29.1</td>
</tr>
<tr>
<td>V</td>
<td>10.7</td>
<td>18.2</td>
</tr>
</tbody>
</table>

J Clin Oncol 24:2563-2569
### Impact of MGMT methylation status in IDHwt Glioblastoma

<table>
<thead>
<tr>
<th>MGMT</th>
<th>Median Survival, mo</th>
<th>2-Year Survival, %</th>
<th>4-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meth</td>
<td>23.4</td>
<td>48.9</td>
<td>22.1</td>
</tr>
<tr>
<td>UnMeth</td>
<td>15.3</td>
<td>23.9</td>
<td>7.8</td>
</tr>
</tbody>
</table>
Milestones in Neuro-Oncology

Approvals

Radiotherapy

1970
- Lomustine

1980
- Carmustine

1990
- BCNU wafer

2000
- TMZ for relapsed AA accelerated approval
- TMZ up front for GBM

2010
- Bevacizumab for recurrent GBM

Technology Advances

1970
- First US commercial CT
- Levin criteria: CT scans

1980
- First US commercial MRI

1990
- Macdonald criteria: MRI + steroids; WHO Pathology Criteria

2000
- Brain Tumor Clinical Trial Endpoints Workshop

2010
- RANO Criteria
- ASCO Workshop
Current Treatment Challenges

• Biologically aggressive tumors
• Brain localization
• Pharmacologic delivery
  – Blood–brain barrier
• Limited therapeutic response
  – Intrinsic resistance to conventional therapies
• Microenvironment (hypoxia, interstitial pressure, angiogenesis)
• Neurotoxicity of glioma-directed treatments
  – Susceptibility of normal brain to therapy-related injury
• Spread of malignant cells into brain parenchyma

Current Treatment: Surgery

- Rationale for extensive resection
  - Provides adequate tissue for diagnosis
  - Palliates mass effect
  - Allows for improvements in tumor-related signs and symptoms
  - May increase survival
    - Helps halt disease progression by eliminating resistance clones

Current Treatment: Surgery

• Challenges
  – Biopsy vs resection
    • Tumor location
    • Patient factors
  – Co-administration of local therapy
    • Treatment toxicity
    • Clinical trial exclusion
Current Treatment: Surgery
Maximal Safe Resection

2. Courtesy of Michael A. Vogelbaum, MD; with permission.
Current Treatment: Surgery
Extent of Tumor Resection Is Associated With Improved Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
Current Treatment: Surgery Plus Local Therapy

- Carmustine (BCNU) wafers
  - Polyanhydride wafers, 7.7 mg carmustine (BCNU)\(^1\)
    - Carmustine released over 2 to 3 weeks
    - >70% degradation by Week 3
  - Approval
    - 1996 for recurrent GBM as adjunct to surgery\(^2\)
    - 2003 expanded for all high-grade gliomas, including newly diagnosed\(^3\)
  - Local delivery obviates the blood–brain barrier
  - Lower toxicity than systemic chemotherapy

Current Treatment: Surgery Plus Local Therapy

BCNU Wafer Improves Survival vs Placebo


Salvage

Hazard Ratio: 0.67

P = 0.02

Adjuvant

Hazard Ratio: 0.73

95% CI: 0.56–0.95

Risk Reduction: 29%

P = 0.018

Current Treatment: Surgery Plus Local Therapy

- Convection-Enhanced Delivery (CED)
  - Positive persistent drug infusion using intracranial catheters developed by National Institutes of Health in 1990s\(^1\)
    - Allows for direct delivery of high-concentration therapeutics
    - Circumvents blood–brain barrier, limits systemic toxicity
    - Creates challenges in determining efficacy\(^2\)
  - Two glioblastoma Phase III trials: treatment delivered by CED
    - **PRECISE**: IL-13 (Cintredekin besudotox) linked to *Pseudomonas* exotoxin
      - Efficacy comparable to BCNU wafer\(^3\)
    - **TransMID**: transferrin-CRM107 (linked to diphtheria toxin)
      - Study terminated (unlikely to meet trial criteria for efficacy)\(^4\)

Current Treatment: Radiation Therapy (RT)

- Challenges
  - Recurrence is the major source of therapeutic failure
  - Surgery and radiation therapy often fail to prevent recurrence
  - Most recurrent gliomas occur at close proximity to initial tumor

<table>
<thead>
<tr>
<th>Distance from Edge of Initial Tumor (cm)</th>
<th>Incidence (% of All Recurrent Gliomas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>60</td>
</tr>
<tr>
<td>1−2</td>
<td>19</td>
</tr>
<tr>
<td>2−3</td>
<td>18</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3</td>
</tr>
</tbody>
</table>

Current Treatment: Radiation Therapy

- RTOG Trial Analyses
  - Improved outcomes with involved-field vs. whole-brain RT
  - Dose-response relationship: best response with 60 to 65 Gy conventional external beam RT (cEBRT)
  - No apparent survival benefit with:
    - >65 Gy cEBRT
    - Conformal RT
    - Accelerated or hyperfractionated schedules
    - Boost gamma knife RT
    - Brachytherapy boost

Current Treatment: Radiation Therapy

SRS +/- RT

<table>
<thead>
<tr>
<th>Survival Rate (%)</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>90</td>
<td>6</td>
</tr>
<tr>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>70</td>
<td>18</td>
</tr>
<tr>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

SRS +/− RT

<table>
<thead>
<tr>
<th>Median Survival Time</th>
<th>n</th>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.5 mo</td>
<td>70</td>
<td>RT</td>
</tr>
<tr>
<td>13.6 mo</td>
<td>69</td>
<td>SRS+RT</td>
</tr>
</tbody>
</table>

P=0.64


SRS=stereotactic radiosurgery.

SRS +/- RT

<table>
<thead>
<tr>
<th>Median Survival Time</th>
<th>n</th>
<th>Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.2 mo</td>
<td>69</td>
<td>RT</td>
</tr>
<tr>
<td>13.8 mo</td>
<td>71</td>
<td>SRS+RT</td>
</tr>
</tbody>
</table>

P=0.49

Current Treatment: Radiation Therapy

- Radiosensitizers
  - Motexafin gadolinium (MGd)\(^1\)
    - Putative radiation enhancer
    - Phase I trial (safety, tolerability) 2- to 6-week course of MGd\(^1\)
    - Phase II trial currently underway (RTOG 0513)
  - Temozolomide (TMZ)\(^2,3\)
    - Pre-clinical activity

Current Treatment: Chemotherapy

• Challenges
  – Issues of efficacy
  – Intrinsic resistance
  – Pharmacologic (tumor delivery)
  – Concurrent medications
    • Anticonvulsants
    • Steroids
  – Systemic toxicity
  – Response measurements
## Current Treatment: Chemotherapy
### Three Major Meta-Analyses

<table>
<thead>
<tr>
<th></th>
<th>Fine et al.(^1)</th>
<th>Stewart (^2)</th>
<th>Spiegel et al.(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Date of meta-analysis</strong></td>
<td>1993</td>
<td>2002</td>
<td>2007</td>
</tr>
<tr>
<td><strong>Trials analyzed, (n)</strong></td>
<td>16</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td><strong>Patients analyzed, (n)</strong></td>
<td>(&gt;3,000)</td>
<td>3,004</td>
<td>(&gt;3,000)</td>
</tr>
<tr>
<td><strong>Agent(s) used</strong></td>
<td>Various</td>
<td>Various</td>
<td>Various</td>
</tr>
<tr>
<td><strong>Absolute increase in survival, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1 year</strong></td>
<td>10.1</td>
<td>6.0</td>
<td>15.0(^*)</td>
</tr>
<tr>
<td><strong>2 year</strong></td>
<td>8.6</td>
<td>4.0</td>
<td>17.0(^*)</td>
</tr>
</tbody>
</table>

\(^*\) TMZ treatment group only.

First Line GBM < 70 years

- Standard of Care
  - Surgery, XRT, TMZ
  - Gliadel

- Impact of MGMT methylation status

- Results of dose dense TMZ (RTOG 0525)
  - More is not better
  - How many adjuvant cycles should we give?

- Pending reports from Phase III studies
  - Bevacizumab (AVAglio, RTOG 0825)
    - Sequencing, PFS
    - Celingitide Centric

- Vaccines
Prognostic Classification: EORTC Recursive Partitioning Classification System

- Modified from RTOG
- Patients with glioblastoma from EORTC/NCIC XRT/TMZ study
- Stratification into groups (Class III-V) based on
  - Age
  - WHO performance status
  - Mini-mental status evaluation
  - Extent of resection
- Prognostic variables may be used for stratification of trial subjects

<table>
<thead>
<tr>
<th>Class</th>
<th>Median Survival, mo</th>
<th>2-Year Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>18.7</td>
<td>40.5</td>
</tr>
<tr>
<td>IV</td>
<td>16.3</td>
<td>29.1</td>
</tr>
<tr>
<td>V</td>
<td>10.7</td>
<td>18.2</td>
</tr>
</tbody>
</table>

J Clin Oncol 24:2563-2569
**EORTC-NCIC GBM trial: Overall Survival (update Oct 2007)**

<table>
<thead>
<tr>
<th>Survival, %</th>
<th>RT</th>
<th>TMZ/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>10.9</td>
<td>27.2</td>
</tr>
<tr>
<td>3-year</td>
<td>4.4</td>
<td>16.4</td>
</tr>
<tr>
<td>4-year</td>
<td>3.0</td>
<td>12.1</td>
</tr>
</tbody>
</table>

**Hazard ratio** 0.63 [0.53 - 0.75]  

*p < 0.0001*

Number of patients at risk:

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>278</td>
<td>286</td>
<td>RT</td>
</tr>
<tr>
<td>144</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| 254 | 287 | TMZ/RT |
| 175 | 76  | 14     |
| 39  | 23  | 14     |
| 23  | 14  | 14     |
| 6   | 6   | 6      |

*Mirimanoff et al. ASTRO 2007*
Effect of *MGMT* Promoter Methylation Status on Survival in Glioblastoma

EORTC / NCIC Trial

Predictive Markers: *MGMT* Methylation Status

First Line GBM > 65

- RT alone short course
- TMZ
- TMZ/BEV
- RT/TMZ
  - CAN-NCIC-CE6, EORTC-26062-22061 RT vs TMZ/RT

Randomized studies TMZ vs XRT:
- NOA-08 no difference between XRT and TMZ
- Nordic trial: over 70 vs under 70
- Both show mMGMT predicts TMZ for PFS…..not survival (trend)
- NOA-08 show uMGMT predicts XRT for PFS…not survival (trend)
2nd line GBM

- Defining tumor progression after first line therapy
- Chemotherapies
- Antiangiogenic therapies
- Alternating electrical fields device
Time Course of PseudoProgression (PsP)

XRT/TMZ Effect

Steroid Taper

Tumor Growth pre-XRT

PSI

Postop MRI

Front-line Therapy

Surgery 2-6 wks

XRT/Chemo 2-4 wks

Post-XRT MRI 4-8 wks

MRI

25% PD

Worse

Stable or better

25% PseudoPD

Worse

Stable or better

50% Stable Disease
Time Course of PseudoProgression (PsP)

- Surgery
- XRT/Chemo
- MRI

- 50% Stable Disease
- 25% PD
- 25% PseudoPD Worse

- Stable or better

2-6 wks
2-4 wks
4-8 wks

Postop MRI
XRT/Chemo
Post-XRT MRI

MRI

Front-line Therapy

Surgery

PSI

XRT/TMZ Effect

Steroid Taper

Tumor Growth pre-XRT

Worse

25% PseudoPD

50% Stable Disease
Time Course of PseudoProgresion (PsP)

- **Surgery**: 2-6 wks
- **XRT/Chemo**: 2-4 wks

**Front-line Therapy**

**MRI**
- Stability or better: 50%
- Stable Disease: 25%
- PD: 25%
- PseudoPD Worse: 25%

**Steroid Taper**
- Day 0/0 mg Dex
- Day 5/12 mg Dex
- Day 21/0 mg Dex

**XRT/TMZ Effect**
- Front-line Therapy
- Surgery
- Steroid Taper

**25% PseudoPD**

**Stable or better**
- 50%
Surgery

XRT/Chemo

MRI

Stable or better

50% Stable Disease

25% PD

25% PseudoPD Worse

Worse

2-6 wks

2-4 wks

4-8 wks

Time Course of PseudoProgression (PsP)

Front-line Therapy

PSI

XRT/TMZ Effect

Tumor Growth

Steroid Taper

Postop MRI

Post-XRT MRI

MRI

25% PD

Worse

Stable or better

25% PseudoPD

Worse

Stable or better

50% Stable Disease

Smith JS et al. J Neurosurg 2005 Sep; 103:428-38
Postop MRI

Surgery

2-6 wks

Front-line Therapy

XRT/Chemo

2-4 wks

Tumor Growth pre-XRT

Post-XRT MRI

MRI

4-8 wks

Worse

25% PseudoPD

25% PD

Worse

Stable or better

50% Stable Disease

Pirzkall et al.: Neuro-Oncology 11, 842–852, 2009
Time Course of PseudoProgression (PsP)

- XRT/TMZ Effect
  - Steroid Taper
  - Tumor Growth pre-XRT
  - PSI

Front-line Therapy

- Surgery 2-6 wks
- XRT/Chemo 2-4 wks
- Postop MRI
- Post-XRT MRI

MRI

- 25% PD
- Stable or better
- Worse
- 25% PseudoPD
- Stable or better
- 50% Stable Disease
Postop MRI
Surgery
Postop MRI
XRT/Chemo
Front-line Therapy

Surgery
2-6 wks

XRT/Chemo
2-4 wks

Post-XRT MRI

MRI

25% PD
Stable or better
Worse

25% PseudoPD
Worse

50% Stable Disease

Modified example courtesy of M Van den Bent
PsP: Polynomial Regression Trend Lines

3 months

Tran AN et al. Neuro Oncol. 2013 Dec 4. [Epub ahead of print]
Other situations that might interfere with interpreting tumor progression

- Steroid taper or increase
- Seizure
- Stroke
- Anti-VEGF therapy
<table>
<thead>
<tr>
<th></th>
<th>PCV Brada&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Lomustine (CCNU)&lt;sup&gt;2&lt;/sup&gt;</th>
<th>CCNU&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CCNU + Cediranib&lt;sup&gt;3&lt;/sup&gt;</th>
<th>All NCCTG Trials&lt;sup&gt;4&lt;/sup&gt;</th>
<th>All Phase II NABTC Trials&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>224*</td>
<td>92</td>
<td>65</td>
<td>129</td>
<td>345</td>
<td>437</td>
</tr>
<tr>
<td>ORR</td>
<td>NR</td>
<td>4.3%</td>
<td>9%</td>
<td>17%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PFS-6</td>
<td>34.5%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>19%</td>
<td>24.5%</td>
<td>34.5%</td>
<td>9%</td>
<td>16%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>~30%</td>
<td>26%</td>
<td>NR</td>
<td>NR</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>24-month OS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median survival</td>
<td>6.7 months</td>
<td>7.1 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No prior tx on TMZ and some grade III.
NR, not reported

Inhibiting VEGF

Permeability/edema effect only?

Antiangiogenic

Antitumor effect

Microenvironment—stem cell population?
## Bevacizumab in rGBM

<table>
<thead>
<tr>
<th></th>
<th>BRAIN Study(^1)</th>
<th>NIH(^2)</th>
<th>RTOG 0625(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BV Alone (n = 85)</td>
<td>BV + CPT-11 (n = 82)</td>
<td>BV Alone (n = 48)</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>28.2</td>
<td>37.8</td>
<td>35</td>
</tr>
<tr>
<td><strong>PFS6, %</strong></td>
<td>42.6</td>
<td>50.3</td>
<td>29</td>
</tr>
<tr>
<td><strong>Median overall survival</strong>, months</td>
<td>9.2</td>
<td>8.7</td>
<td>7.2</td>
</tr>
</tbody>
</table>

## Comparison of BRAIN with Other Studies (Efficacy Outcomes)

<table>
<thead>
<tr>
<th></th>
<th>BEV(^1) (n = 85)</th>
<th>BEV+CPT-11(^1) (n = 82)</th>
<th>CCNU(^2,3) (n = 92)</th>
<th>TMZ/BCNU(^4) (n = 56)</th>
<th>TMZ(^5) (n = 112)</th>
<th>All NCCTG Trials(^6) (n = 345)</th>
<th>All Phase II NABTC Trials(^7) (n = 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR Rate, %</td>
<td>28.2</td>
<td>37.8</td>
<td>4.3</td>
<td>9.6</td>
<td>5.4</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>6-Month PFS, %</td>
<td>42.6</td>
<td>50.3</td>
<td>19</td>
<td>24.1</td>
<td>21</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>% Survival at</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>38</td>
<td>38</td>
<td>~26</td>
<td>26.7</td>
<td>~23</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>18 months</td>
<td>24</td>
<td>18</td>
<td>–</td>
<td>–</td>
<td>~11</td>
<td>–</td>
<td>13</td>
</tr>
<tr>
<td>24 months</td>
<td>16</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>30 months</td>
<td>11</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

BEV, bevacizumab; CPT-11, irinotecan; CCNU, lomustine; BCNU, carmustine; TMZ, temozolomide; NCCTG, North Central Cancer Treatment Group; NABTC, North American Brain Tumor Coalition; OR, objective response; PFS, progression-free survival

## Bevacizumab-Failure GBM

<table>
<thead>
<tr>
<th>Design</th>
<th>RX</th>
<th># Patients</th>
<th>Median PFS</th>
<th>PFS-6</th>
<th>Median OS</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, subset</td>
<td>BV + CPT-11</td>
<td>19</td>
<td>1.1 months</td>
<td>NR</td>
<td>NR</td>
<td>Kreisl et al. J Clin Oncol. 2009¹</td>
</tr>
<tr>
<td>Retrospective</td>
<td>BV + misc</td>
<td>54 (35 GBM)</td>
<td>1.3 months</td>
<td>2%</td>
<td>2.9 months</td>
<td>Quant et al. Neuro Oncol. 2009²</td>
</tr>
<tr>
<td>Retrospective</td>
<td>BV + misc</td>
<td>19</td>
<td>2 months</td>
<td>0%</td>
<td>5.2 months</td>
<td>Iwamoto et al. Neurology. 2009³</td>
</tr>
<tr>
<td>Retrospective</td>
<td>BV + misc</td>
<td>23</td>
<td>1.8 months</td>
<td>NR</td>
<td>NR</td>
<td>Norden et al. Neurology. 2008⁴</td>
</tr>
<tr>
<td>Retrospective</td>
<td>BV + SRS/chemo</td>
<td>23</td>
<td>2.6 months</td>
<td>NR</td>
<td>7.2 months</td>
<td>Torcuator et al. J Neurooncol. 2010⁵</td>
</tr>
<tr>
<td>Retrospective</td>
<td>BV + chemo</td>
<td>23</td>
<td>1.7 months</td>
<td>NR</td>
<td>3.3 months</td>
<td>Torcuator et al. J Neurooncol. 2010⁵</td>
</tr>
<tr>
<td>Prospective</td>
<td>BV + metro VP-16 or TMZ</td>
<td>23</td>
<td>1.8 months</td>
<td>4.4%</td>
<td>4.1 months</td>
<td>Reardon; In press⁶</td>
</tr>
<tr>
<td>Prospective</td>
<td>BV + carbo/CPT-11</td>
<td>25</td>
<td>2.3 months</td>
<td>16%</td>
<td>5.8 months</td>
<td>Reardon; In press⁶</td>
</tr>
</tbody>
</table>

---

**Courtesy of David Reardon**
Targeted Therapy in rGBM
Agents Used in Targeted Therapy

- RTK (imatinib, dasatinib, gefitinib, erlotinib, lapatinib, AEE788, XL184)
- RAS-FTI (tipifarnib)
- RAF- (sorafenib)
- HGF- (AMG102)
- Avb3 integrins (cilengitide)
- Multikinase (sorafenib, sunitinib, sorafenib)
- SRC (dasatinib)
- mTor rapalog (temsirolimus, sirolimus, everolimus)
- TORki (CC-223)
- PI3K (XL765, GDC 0084)
- PI3K/ mTORi (XL 147, BKM 120)
- AKT inhibitors (MK2206)
- PKC (enzastaurine, tamoxifen)
- VEGF/R (PTK, AEE788, pazopanib, bevacizumab, AZD2171, afiblercept, CT-322)
- HDAC inhibitors- SAHA
NEW GBM DIAGNOSIS
ACADEMIC CENTERS

STANDARD THERAPY

≥THREE MONTHS

RECURRANCE

CENTRALIZED TUMOR GENOTYPING

MET AMP
PDGFRA AMP
PI3K MUT
EGFR MUT/HER2 MUT
OTHER

MET TKI
PDGFR TKI
PI3Ki/Akti
ErbB TKI

CENTRAL REGISTRY

Mellinghoff 2009

GENOTYPE TARGETED CLINICAL TRIAL
Implications of the adaptive immune resistance mechanism for combinatorial immunotherapy of cancer

Pardol et.al. Natures Reviews Cancer vol. 12 2012
Conclusion

- Glioma is a difficult disease with a growing elderly population
  - No early detection and no prevention
  - Two broad categories base upon IDH mutation status
- Standards of care exist but are largely unsatisfactory except in IDH mutated, 1p19q co-deleted tumors
- Recurrence is inevitable
- Improved understanding of molecular characterization and anti-tumor immune related processes provide promise in this difficulty to treat tumor.