Management of Glioblastomas and Anaplastic Gliomas

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Co-Director, Northwestern Brain Tumor Institute
Objectives

• Describe risk factors for glioblastoma
• Describe treatment at diagnosis
• Identify pitfalls in tumor assessment
• Outline treatment options for recurrent glioblastoma
• Describe treatment of anaplastic astrocytoma and anaplastic oligodendroglioma
Background

• Approximately 4000 patients in the US are diagnosed with glioblastoma each year
• Represents 20% of all intracranial tumors
• 2\textsuperscript{nd} most common intracranial tumor
• Most common malignant primary brain tumor
• Affects all ages. Median age at diagnosis is 65 years.
• Not usually curable. Median survival is 9-14 months
Incidence
Distribution of All Intracranial Tumors by Histology

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

Risk Factors for Glioblastoma

• Genetically inherited syndromes
  – Li-Fraumeni syndrome
  – Turcot’s syndrome
  – NF

• Exposure to ionizing radiation
  – History of childhood cancer treated with whole brain radiotherapy
Gliomagenesis

 Astrocytic cell precursor or neural stem cell

- p53 mutation (>65%)
  - PDGF-A, PDGFR-α (~60%)

  Low-grade astrocytoma

  - LOH 19q (~50%)
  - RB alteration (~25%)

  Anaplastic astrocytoma

  - LOH 10q
  - PTEN mutation
    - DCC loss of expression (~50%)
    - PDGFR-α amplification

  Secondary glioblastoma
  - Glioblastoma in younger adults
  - Giant cell glioblastoma
  - Brainstem glioblastoma in children

- EGFR amplification (~40%)
  - EGFR overexpression (~60%)

  Primary glioblastoma
  - Glioblastoma in older adults
    - Rapidly progressive

- MDM2
  - Amplification (<10%)
  - Overexpression (~50%)

  p16 deletion (30–40%)

  LOH 10p and 10q

  PTEN mutation (~30%)

  RB alteration
Prognostic Classification

• World Health Organization (WHO) Classification System
  – Released in 1993; updated in 2007
  – Tumors classified by cell origin and level of aggression (Grades I–IV)\(^1,2\)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Histology</th>
<th>Proportion of All Gliomas</th>
<th>Median Survival (y)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pilocytic astrocytoma</td>
<td>&lt;5%</td>
<td>&gt;10</td>
</tr>
<tr>
<td>II</td>
<td>Well-differentiated astrocytoma</td>
<td>25%–30%</td>
<td>&gt;5</td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>25%–30%</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma multiforme</td>
<td>40%–50%</td>
<td>1</td>
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</tbody>
</table>
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
  - Ex: radiotherapy
- Spread of malignant cells into brain parenchyma
Presenting symptoms

- Symptoms of increased intracranial pressure
- Focal neurologic findings
- Seizures in 20% (less common than in low grade gliomas)
Symptoms
Incidence of Symptoms in Patients With Glioma

- Low-grade glioma
- Malignant glioma
Symptom Etiology

• Direct infiltration and destruction of neurons
• Local pressure from
  – Edema
  – Hemorrhage
  – Tumor mass
Treatment

• What is the role of surgery?
• What is the best treatment following surgery?
1936 – Loyal Davis: **Neurological Surgery**

73 GBMs - mean survival 12 mos

1 pt - 18 mos following 3 operations

operative mortality 26.7%

Cushing - 183 Astrocytomas – 6 yrs

operative mortality 24.2%
Important Advances

• Operative Microscope - 1966
• CT Scan - 1972
• MRI - 1985
• Computer Assisted Navigational Systems - 1993
Benefits of Surgical resection of malignant gliomas

Descriptive / Observational studies

- No class I or II evidence
- Existing literature methodologically flawed from evidence based medicine viewpoint
Benefits of Surgical Resection

High Grade Gliomas

• 1920’s - Walter Dandy: Hemispherectomy
  no impact on survival

• Recent reviews: Nazaro ’90, Quigley ’91, Hess ’99, Metcalf/Grant ’01 - no
  improvement in median survival with radical resection vs. biopsy for high grade
  gliomas.
Benefits of Surgical Resection

• High Grade Gliomas

Lacroix / Sawaya, ‘01: 416 patients – multivariate analysis yield identification of 5 radiographic and clinical independent predictors of survival:

- Age
- KPS
- Presence of necrosis and enhancement on MRI
- Extent of resection (>98% or more of enhancing vol) 13.4m vs. 8.8m
Surgery for Gliomas

- Techniques

Stereotactic biopsy - Frame based systems - CRW, BRW, Leksell
Surgery for Gliomas

• Techniques

Stereotactic biopsy - Frameless - Stealth, Brain lab
Surgery for Gliomas

**Techniques**
- Subtotal / Gross total resection
  - “Inside out”
  - “Circumferential” en bloc – lobectomy if safe distances from eloquent brain

**Histological anatomy of a GBM**

Kelly et al.
57-year-old male with 2 week history of headaches and mild confusion
Post-Operative Day #2
Surgical Tools

- Preoperatively/
  Intraoperatively

Frameless navigation
- increased accuracy
- smaller craniotomies
- improved resection

- Functional MRI

- MR spectroscopy
Diffusion Tensor Imaging

Coronal View of Track
Diffusion-tensor imaging
Surgery for Gliomas

Intraoperative Technical Advances

• Awake cortical mapping – speech, motor cortex
  - Ojemann: bipolar - square waves, 60-75 Hz.
    1-2 MS, 2-15 MA
Surgery for Gliomas

Intraoperative Technical Advances

• Navigational systems limited

• 2 D, 3 D ultrasound

Intraoperative ultrasound - GBM
Surgery for Gliomas

Intraoperative Technical Advances

- Intraoperative MRI

- Bohenski, et al., residual detected in 53% cases following presumed GTR

Surgery

• Convention is maximal SAFE surgical resection
• Establishes the diagnosis, histology, and tumor grade
• Most studies suggest that extensive surgery increases both duration and quality of survival
• Follow-up MRI should be performed within 48 hours after surgery to help differentiate post-surgical enhancement from residual tumor
Radiotherapy (RT)

- Radiotherapy is delivered to a limited field encompassing the tumor and a 2.5-3 cm margin to a dose of 60 Gy in 2 Gy fractions. Typically, treatment occurs five days per week over a six week period.
Radiation Therapy

- 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>
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</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

**RT +/- SRS**

![Survival Rate vs. Months](chart1.png)

- **RT**: Green line with markers, 70 patients, Median Survival Time: 13.5 mo
- **SRS+RT**: Red line with markers, 69 patients, Median Survival Time: 13.6 mo

Survival Rate (%) vs. Months

**P = 0.64**

**RT +/- SRS**

![Survival Probability](chart2.png)

- **RT**: Green line, 69 patients, Median Survival Time: 13.2 mo
- **SRS+RT**: Red line, 71 patients, Median Survival Time: 13.8 mo

Survival Probability vs. Months to Death Since Surgery

**P = 0.49**

SRS = stereotactic radiosurgery.


Radiotherapy

• Despite radiotherapy, almost all glioblastomas progress
• Is there a way to improve the efficacy of radiotherapy?
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

Chemotherapy

• Challenges
  – Issues of efficacy
  – Intrinsic resistance
  – Pharmacologic (tumor delivery)
  – Concurrent medications
    • Anticonvulsants
    • Steroids
  – Systemic toxicity
  – Response measurements
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

ABSTRACT

BACKGROUND
Glioblastoma, the most common primary brain tumor in adults, is usually rapidly fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by adjuvant radiotherapy. In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety.

METHODS
Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival.

RESULTS
A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio for death in the temozolomide group as compared with the radiotherapy-alone group was 0.70 (95% CI, 0.52 to 0.93; P = .02). The median duration of progression-free survival was 22.1 months with temozolomide as compared with 10.2 months without temozolomide (hazard ratio, 0.56; 95% CI, 0.44 to 0.72; P < .001). Toxicity was increased with the addition of temozolomide.
Temozolomide (TMZ)

• Methylating agent
  – Cytotoxic product is O\(^6\)-methylguanine DNA adducts
  – Initiates mismatch repair pathway recycling, resulting in apoptotic cell death

• Efficacy
  – Activity in newly diagnosed anaplastic glioma\(^1\)
  – Activity in recurrent anaplastic astrocytoma\(^2\)
  – Activity in recurrent GBM\(^3\)
  – Activity in adjuvant treatment of GBM\(^4,5\)

Temozolomide

EORTC/NCIC Trial

- EORTC/NCIC trial¹
  - RT alone vs. RT plus TMZ
  - Primary endpoint: overall survival
  - Secondary endpoints: progression-free survival, quality of life (QOL), safety
  - No negative impact on QOL

<table>
<thead>
<tr>
<th>Survival</th>
<th>RT</th>
<th>RT + TMZ</th>
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</thead>
<tbody>
<tr>
<td>2-year</td>
<td>10.4%</td>
<td>26.5%</td>
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</table>

Figure 2: Kaplan-Meier estimates of overall survival by treatment group

<table>
<thead>
<tr>
<th>Survival</th>
<th>RT</th>
<th>RT + TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year</td>
<td>10.9%</td>
<td>27.3%</td>
</tr>
<tr>
<td>3-year</td>
<td>4.4%</td>
<td>16.0%</td>
</tr>
<tr>
<td>4-year</td>
<td>3.0%</td>
<td>12.1%</td>
</tr>
<tr>
<td>5-year</td>
<td>1.9%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>
Temozolomide

• DNA repair
  – O$^6$-methylguanine-DNA-methyltransferase (MGMT)$^1$
    • Also known as hepatic O$^6$-alkylguanine-DNA alkyltransferase (AGT, AGAT)
    • Reverses alkylation at O$^6$ position of guanine, prevents cell death
    • High tumor levels cause resistance to alkylating agents
    • Low tumor levels cause susceptibility to alkylating drugs

  – MGMT and TMZ$^2$
    • Retrospective analysis of MGMT tumor content and TMZ sensitivity in EORTC/NCIC trial data
    • Low levels of MGMT in glioblastoma tumors correspond with improved response to TMZ

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>2-yr</th>
<th>3-yr</th>
<th>4-yr</th>
<th>5-yr</th>
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<tbody>
<tr>
<td><strong>MGMT unmethylated</strong></td>
<td><strong>TMZ</strong></td>
<td>12.6 mns</td>
<td>14.8%</td>
<td>11/1%</td>
<td>11.1%</td>
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<tr>
<td></td>
<td><strong>RT only</strong></td>
<td>11.8 mns</td>
<td>1.8%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td><strong>MGMT methylated</strong></td>
<td><strong>TMZ</strong></td>
<td>23.4 mns</td>
<td>48.9%</td>
<td>23.1%</td>
<td>23.1%</td>
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<tr>
<td></td>
<td><strong>RT only</strong></td>
<td>15.3 mns</td>
<td>23.9%</td>
<td>7.8%</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

**A**

- **Number at risk**
  - Combined: 37, 35, 22, 11, 6, 2
  - Radiotherapy: 43, 30, 11, 3, 1, 0

- **Survival (%)**
  - Combined: p=0.004

**B**

- **Number at risk**
  - Combined: 54, 34, 8, 6, 4, 3, 1
  - Radiotherapy: 54, 25, 1, 0, 0, 0, 0

- **Survival (%)**
  - Combined: p=0.035
Survival by period and age group, amongst patients treated with surgery and radiation

<table>
<thead>
<tr>
<th>Age range</th>
<th>2000–2003 BCNU era, overall median survival 8.1m/12.1 surg,xrt,che</th>
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<tbody>
<tr>
<td></td>
<td>Age range</td>
</tr>
<tr>
<td>20–29 years</td>
<td>20–29 years</td>
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<tr>
<td>30–39 years</td>
<td>30–39 years</td>
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<tr>
<td>40–49 years</td>
<td>40–49 years</td>
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<tr>
<td>50–59 years</td>
<td>50–59 years</td>
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<tr>
<td>60–69 years</td>
<td>60–69 years</td>
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<tr>
<td>70–79 years</td>
<td>70–79 years</td>
</tr>
<tr>
<td>80+ years</td>
<td>80+ years</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percent surviving (corresponding standard error)

**Survival by period and age group, amongst patients treated with surgery and radiation**

<table>
<thead>
<tr>
<th>Age range</th>
<th>N</th>
<th>Median (mo)</th>
<th>24-month(a)</th>
<th>36-month(a)</th>
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</thead>
<tbody>
<tr>
<td>20–29 years</td>
<td>82</td>
<td>31.9</td>
<td>59.6 (6.3)</td>
<td>46.0 (7.2)</td>
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<tr>
<td>30–39 years</td>
<td>161</td>
<td>25.8</td>
<td>52.2 (4.8)</td>
<td>32.5 (5.3)</td>
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<tr>
<td>40–49 years</td>
<td>653</td>
<td>18.1</td>
<td>33.7 (2.4)</td>
<td>22.8 (2.4)</td>
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<tr>
<td>50–59 years</td>
<td>1324</td>
<td>16.7</td>
<td>31.9 (1.6)</td>
<td>18.0 (1.6)</td>
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<tr>
<td>60–69 years</td>
<td>1238</td>
<td>13.0</td>
<td>21.0 (1.5)</td>
<td>11.8 (1.5)</td>
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<tr>
<td>70–79 years</td>
<td>778</td>
<td>9.3</td>
<td>12.1 (1.5)</td>
<td>3.3 (1.1)</td>
</tr>
<tr>
<td>80+ years</td>
<td>176</td>
<td>5.6</td>
<td>2.9 (1.9)</td>
<td>1.5 (1.4)</td>
</tr>
</tbody>
</table>

7,259 pts   \(a\)  Percent surviving (corresponding standard error)

Initial Treatment Summary

- Maximum safe resection
- Conventional fractionated EBRT (as defined by RTOG and EORTC studies)
- RT and concomitant TMZ (EORTC/NCIC study)
- Post-RT TMZ chemotherapy for 6 months (EORTC/NCIC study)

Genetic prognostic factors

- MGMT methylation
- 1p19q co-deletion
- Isocitrate dehydrogenase mutation (IDH)
Options for Salvage Therapy

- Re-operation (if possible and clinically appropriate)
- Re-irradiation (if no other options or small-volume recurrence)
- Chemotherapy
- Targeted therapy (i.e., bevacizumab)
- Investigational therapy
Vascular endothelial growth factor (VEGF) pathway inhibitors

- Malignant gliomas are highly vascular tumors that depend on angiogenesis for growth and proliferation
- VEGF pathway inhibitors were developed to inhibit tumor angiogenesis
VEGF inhibitors

- Bevacizumab (Avastin)
- Cediranib (Recentin)
- Vatalanib (PTK 787)
- Vandetinib
- Other tyrosine kinase inhibitors
Bevacizumab Plus Irinotecan in Recurrent Glioblastoma Multiforme

James J. Vredenburgh, Annick Desjardins, James E. Herndon II, Jennifer Marcello, David A. Reardon, Jennifer A. Quinn, Jeremy N. Rich, Sith Sathornsumetee, Sridharan Gururangan, John Sampson, Melissa Wagner, Leighann Bailey, Darell D. Bigner, Allan H. Friedman, and Henry S. Friedman

Abstract

Purpose
The prognosis for patients with recurrent glioblastoma multiforme is poor, with a median survival of 3 to 6 months. We performed a phase II trial of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, in combination with irinotecan.

Patients and Methods
This phase II trial included two cohorts of patients. The initial cohort, comprising 23 patients, received bevacizumab at 10 mg/kg plus irinotecan every 2 weeks. The dose of irinotecan was based on the patient’s anticonvulsant: Patients taking enzyme-inducing antiepileptic drugs (EIAEDs) received 340 mg/m², and patients not taking EIAEDs received 125 mg/m². After this regimen was deemed safe and effective, the irinotecan schedule was changed to an accepted brain tumor regimen of four doses in 6 weeks, in anticipation of a phase III randomized trial of irinotecan versus irinotecan and bevacizumab. The second cohort, comprising 12 patients, received bevacizumab 15 mg/kg every 21 days and irinotecan on days 1, 8, 22, and 29. Each cycle was 6 weeks long and concluded with patient evaluations, including magnetic resonance imaging.

Results
The 6-month progression-free survival among all 35 patients was 46% (95% CI, 32% to 66%). The 6-month overall survival was 77% (95% CI, 64% to 92%). Twenty of the 35 patients (57%; 95% CI, 39% to 74%) had at least a partial response. One patient developed a CNS hemorrhage, which occurred in his 10th cycle. Four patients developed thromboembolic complications (deep venous thrombosis and/or pulmonary emboli).

Conclusion
Bevacizumab and irinotecan is an effective treatment for recurrent glioblastoma multiforme and has moderate toxicity.
Bevacizumab and GBM

• Dose = 10 mg/kg q2 weeks
• FDA approved as single agent therapy
• Side effects of bevacizumab include hemorrhage, hypertension, fatigue, bowel rupture, thrombotic event, impaired wound healing
Figure 3  Diffuse recurrence in a patient with recurrent malignant glioma treated with bevacizumab and irinotecan

Post-gadolinium T1-weighted (A) and FLAIR (D) MRI scans before treatment with bevacizumab and irinotecan. After 6 weeks of treatment, there is reduction in the size and intensity of enhancement sufficient to achieve a partial response (B). Abnormal FLAIR hyperintensity is proportionately reduced (E). After 6 months of treatment with bevacizumab and irinotecan, there has been further reduction in enhancement (C), yet the extent of abnormal FLAIR hyperintensity has increased markedly, suggesting nonenhancing tumor infiltration (F).
Prospective Trials Bevacizumab for Recurrent GBM

<table>
<thead>
<tr>
<th>Author</th>
<th>Agent</th>
<th>N</th>
<th>Objective Response Rate, %</th>
<th>6-Month PFS, %</th>
<th>PFS, months</th>
<th>mOS, months</th>
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<tr>
<td>Kreisl, 2009</td>
<td>Bev</td>
<td>49</td>
<td>35</td>
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<td>Bev</td>
<td>85</td>
<td>28</td>
<td>43</td>
<td>4.2</td>
<td>9.2</td>
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<tr>
<td>Friedman, 2009</td>
<td>Bev + CPT11</td>
<td>82</td>
<td>38</td>
<td>50</td>
<td>5.6</td>
<td>8.7</td>
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<tr>
<td>Vredenburgh, 2007</td>
<td>Bev + CPT11</td>
<td>35</td>
<td>57</td>
<td>46</td>
<td>5.6</td>
<td>9.8</td>
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<tr>
<td>Gilbert, 2009</td>
<td>Bev + CPT11</td>
<td>57</td>
<td>NS</td>
<td>37</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Gutin, 2009</td>
<td>Bev + SRT</td>
<td>20</td>
<td>50</td>
<td>65</td>
<td>7.3</td>
<td>12.5</td>
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<tr>
<td>Reardon, 2008</td>
<td>Bev + VP16</td>
<td>27</td>
<td>NS</td>
<td>44</td>
<td>NS</td>
<td>10.7</td>
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<tr>
<td>Sathornsumetee, 2009</td>
<td>Bev + erlotinib</td>
<td>25</td>
<td>48</td>
<td>24</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Maron, 2008</td>
<td>Bev + TMZ</td>
<td>32</td>
<td>38</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Soffietti, 2009</td>
<td>Bev + fotemustine</td>
<td>22</td>
<td>35</td>
<td>NS</td>
<td>NS</td>
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</table>
Results

• 6 month progression free survival was 29-43% (most GBM trials, < 15%)
  – TMZ 21%

• 6 month overall survival was 77%
  – TMZ 60%

• Median overall survival was 7.2-9.2 months
Bevacizumab questions

- What is the best dose and schedule?
- Should bevacizumab be part of initial glioblastoma therapy?
- Should bevacizumab be combined with a cytotoxic chemotherapy agent?
- Should bevacizumab treatment be continued indefinitely?
Using Both Arms of Immune System

• IMMUNOTHERAPY – ICT-107

Cellular Vaccine With Survival Benefit (ICT-107)

- Dendritic cell vaccine to elicit persistent and targeted T cell immune response against tumor associated antigens/CSC antigens
- Phase I trial recently showed survival benefit for brain tumors
- Phase II initiated in Q1, 2011
ICT-107 targets Cancer Stem Cells & GBM, but has broad potential

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Tumor Expression</th>
<th>CSC Expression</th>
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</thead>
<tbody>
<tr>
<td>gp100</td>
<td>Melanoma, brain cancer</td>
<td></td>
</tr>
<tr>
<td>Trp-2</td>
<td>Melanoma, brain cancer</td>
<td>High</td>
</tr>
<tr>
<td>Her-2/neu</td>
<td>Breast, ovarian cancer</td>
<td>Medium</td>
</tr>
<tr>
<td>MAGE-1</td>
<td>Melanoma, brain cancer</td>
<td></td>
</tr>
<tr>
<td>AIM-2</td>
<td>Breast, ovarian, colon, brain</td>
<td>High</td>
</tr>
<tr>
<td>IL-13aR2</td>
<td>Brain cancer</td>
<td></td>
</tr>
</tbody>
</table>

First Indication is Brain Cancer, but broad potential
Phase I Trial of ICT-107

Design

- Phase I glioblastoma trial initiated in May 2007
- To determine safety and immune response
- Patients received three vaccinations, two weeks apart
- 19 patients (16 newly diagnosed and 3 recurrent patients) treated at CSMC
- Patient specific cell manufacturing (3 doses)
## Summary

### PFS and OS - Newly Diagnosed Patients

<table>
<thead>
<tr>
<th></th>
<th>ICT-107 + SOC* (n=16)</th>
<th>SOC (Stupp, NEJM, 2005) (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td><strong>PFS (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>100</td>
<td>53.9</td>
</tr>
<tr>
<td>At 12 months</td>
<td>62.5</td>
<td>26.9</td>
</tr>
<tr>
<td>At 18 months</td>
<td>43.8</td>
<td>18.4</td>
</tr>
<tr>
<td>At 24 months</td>
<td>43.8</td>
<td>10.7</td>
</tr>
<tr>
<td><strong>Median (months)</strong></td>
<td>16.9</td>
<td>6.9</td>
</tr>
<tr>
<td><strong>OS (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>100</td>
<td>86.3</td>
</tr>
<tr>
<td>At 12 months</td>
<td>100</td>
<td>61.1</td>
</tr>
<tr>
<td>At 18 months</td>
<td>93.8</td>
<td>39.4</td>
</tr>
<tr>
<td>At 24 months</td>
<td>80.2</td>
<td>26.5</td>
</tr>
<tr>
<td><strong>Median (months)</strong></td>
<td>NR &gt; 30</td>
<td>14.6</td>
</tr>
</tbody>
</table>

* SOC = Standard of Care (XRT + TMZ)  
* NR = Not reached
Phase II Trial Design

- 102 patients at 15 centers in US/Canada
- 2:1 randomization, double blind
- Placebo: Unloaded dendritic cells
- Primary End Points: OS and PFS
- Secondary End Points:
  - OS/PFS at various time intervals
  - Immune Response
  - Safety
- Interim analysis after 17 months (based on 50% events)
Centralized GMP manufacturing process for Phase II clinical trials and commercialization

Outpatient apheresis → Ship → Apheresis product → GMP manufacturing facility

- Ship dose
- Monocyte enrichment
- Culture with cytokines
- Antigen pulse and maturation

~20 doses from one apheresis
Anaplastic Astrocytoma (WHO grade III astrocytoma)

- Initial treatment is variable
- Radiotherapy alone
- Most neuro-oncologists treat with combination radiotherapy and TMZ chemotherapy
- Phase III trial of Concurrent and Adjuvant TMZ Chemotherapy in Non-1p/19q Deleted Anaplastic Glioma. The CATNON Intergroup trial
  - Arm 1: RT and further treatment including chemotherapy if indicated at progression
  - Arm 2: RT & concurrent TMZ
  - Arm 3: RT + adjuvant TMZ for 12 cycles
  - Arm 4: RT & concurrent TMZ + adjuvant TMZ x 12 cycles
Anaplastic Oligodendroglioma

- Most chemosensitive glial tumor
- Allelic loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is an important prognostic marker of chemosensitivity and longer survival
- No defined standard for the management of anaplastic oligodendrogliomas or specific guidelines for integrating the results of molecular studies into a therapeutic plan.
- Anaplastic oligodendroglioma is a relatively rare tumor, so large prospective studies take many years to accrue and patterns of clinical practice have evolved independently of prospective data.
Anaplastic Oligodendroglioma

• The current recommended management of anaplastic oligodendrogliomas by the National Comprehensive Cancer Network (NCCN) is maximal resection followed by:
  – A. focal radiotherapy (RT) alone
  – B. Chemotherpay alone
  – C. Focal RT with concurrent chemotherapy followed by adjuvant chemotherapy
Anaplastic Oligodendroglioma (WHO grade III oligodendroglialoma)

- Phase III Intergroup Study of RT versus TMZ Alone versus Radiotherapy with Concomitant and Adjuvant TMZ for Patients with 1p/19q Codeleted Anaplastic Glioma
  - Arm A – RT alone
  - Arm B – RT + concomitant TMZ → TMZ x 6 cycles
  - Arm C – TMZ alone x 12 cycles
Thank You