Collection of Recorded Radiotherapy Seminars

http://humanhealth.iaea.org
High Grade Gliomas: Review of Therapeutic Aspects

Dr. Luis Souhami
Professor
Department of Radiation Oncology
McGill University - Montreal, Canada

McGill
Gliomas: Median Survival (mos)
Precursor Cell

1p&19q loss

1p&19q loss

Low-Grade Oligo

Low-Grade Astro

1p4/19q loss

Rb mutation
p14/p16 loss/9p loss
CDK4 ampl
19p loss
11p loss

10 Chr loss

Anaplastic Oligo

Anaplastic Astro

1o GBM

P53 mut/17p loss
PDGF/R overexp
22p loss

1o GBM

p14/p16 loss/9p loss

p14/p16 loss/9p loss

2o GBM

Chr 10 loss
PTEN mutation
EGFR ampl,
p19/p14ARF deln.

2o GBM

Chr 10 loss

GBM

MDM2 ampl
CDK4 ampl
PDGFR ampl

Chr 10 loss

Stem Cell
Results of Chromosomal Deletion Analysis

Brat et al J Neurooncol 2004
Cairncross et al JNCI 1998
Anaplastic Oligodendrogliomas

AO is different from GBM
- Genetically different
- Better outcome
- Loss of 1p, 19q

Loss of 1p, 19q associated with chemotherapy response
### Genetic “Predictors” of Chemoresponse

<table>
<thead>
<tr>
<th>Genetic Alteration</th>
<th>Response Rate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chromosome 1p</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allelic loss</td>
<td>24/24 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intact</td>
<td>3/12 (25%)</td>
<td></td>
</tr>
<tr>
<td><strong>Chromosome 19q</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allelic loss</td>
<td>23/28 (82%)</td>
<td>0.126</td>
</tr>
<tr>
<td>Intact</td>
<td>3/6 (50%)</td>
<td></td>
</tr>
<tr>
<td><strong>Combined 1p/19q</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allelic loss</td>
<td>22/22 (100%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intact</td>
<td>4/13 (31%)</td>
<td></td>
</tr>
<tr>
<td><strong>Chromosome 10q</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allelic loss</td>
<td>5/8 (63%)</td>
<td>0.126</td>
</tr>
<tr>
<td>Intact</td>
<td>23/26 (88%)</td>
<td></td>
</tr>
<tr>
<td><strong>CDKN2A gene</strong></td>
<td></td>
<td></td>
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<tr>
<td>Deleted</td>
<td>5/8 (63%)</td>
<td>0.363</td>
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<tr>
<td>Intact</td>
<td>24/30 (25%)</td>
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<tr>
<td><strong>TP53 gene</strong></td>
<td></td>
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<tr>
<td>Mutant</td>
<td>3/6 (50%)</td>
<td>0.123</td>
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<tr>
<td>Wild-type</td>
<td>28/34 (82%)</td>
<td></td>
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</table>
Randomized Trials

Two Randomized Studies
RT vs. RT plus PCV

Overall Survival

Cairncross et al JCO 2006

van den Bent et al JCO 2006
RT vs. RT plus PCV

Overall Survival by Treatment and Genotype

Cairncross et al JCO 2006  van den Bent et al JCO 2006
Update RTOG 9402 - ASTRO 2008

Median follow-up: 6.9 years

Overall Survival

Progression-free Survival

 Courtesy Dr. G. Cairncross
# Survival by Genotype: Co-deleted

**Median (5-year rates)**

<table>
<thead>
<tr>
<th></th>
<th>PCV+RT</th>
<th>RT Alone</th>
<th>HR</th>
<th>95% CI</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>9.5 yr</td>
<td>7.3 yr</td>
<td>0.74</td>
<td>0.41 – 1.35</td>
<td>0.17</td>
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<tr>
<td></td>
<td>(69%)</td>
<td>(65%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>6.9 yr</td>
<td>2.6 yr</td>
<td>0.43</td>
<td>0.26 – 0.74</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(55%)</td>
<td>(29%)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* one-sided
Phase III Intergroup Trial of RT vs. RT+TMZ vs. TMZ in Anaplastic Oligodendroglioma and Anaplastic Mixed Glioma with 1p and 19q co-deletion

Translational correlates
- 1p/19q translocation
- MGMT promotor methylation
- QOL / neurocognitive analyses

Primary Endpoint: OS
Phase III Trial: Anaplastic Gliomas
EORTC/RTOG/NCIC/MRC/HUB

No 1p/19q loss
Gliomas: Median Survival (mos)

- GBM
- AA
- AO
- LG astro
- LG oligo

Median Survival
Curran W et al. J Natl Inst Cancer 1993
## RTOG RPA Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Med Survival (mos)</th>
<th>2-yr Survival %</th>
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</thead>
<tbody>
<tr>
<td>1 AA</td>
<td>58.6</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>37.4</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>17.9</td>
<td>35</td>
</tr>
<tr>
<td>4 GBM</td>
<td>11.1</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>8.9</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>4.6</td>
<td>4</td>
</tr>
</tbody>
</table>
New RPA Classification

New RPA Classification

Early Trials for Malignant Gliomas

- RT improves survival

BTSG Trials
  RT vs SX: 8.3 vs 3.2 mos
  RT vs BCNU: 8.3 vs 5.5 mos

Walker et al J Neurosurg 1978
GBM - FACTS

- Poor prognostic
- Recurrences near the surgical margin
  Hochberg, Pruitt Neurology 1980
- Unifocal > 90%
- Rarely metastasizes
- Dose-response effect
  - Walker et al Int J Radiat Oncol Biol Phys 1979
  - Bleehen, Stenning Br J Cancer 1991
Brachytherapy

- 2 randomized trials

Toronto and BTCG
No difference in survival
Similar local control

Laperriere IJROBP 1998
Selker Neurosurgery 2002
RTOG 9305 Radiosurgery Trial

Souhami et al. IJROBP 2004

Overall Survival

Percent Alive

RT + BCNU
RS + RT + BCNU

p = 0.5328
How About Chemotherapy?

Stewart: Lancet 359:1011, 2002
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*

N Engl J Med 2005
Treatment Schema

(Glioblastoma Multiform – GBM)

Concurrent TMZ/RT

Adjuvant TMZ

RT Alone

Temozolomide 75 mg/m² po qd for 6 weeks, then 150-200 mg/m² po qd d1-5 every 28 days for 6 cycles

Focal RT daily – 30 x 200 cGy
Total dose 60 Gy

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>TMZ/RT</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>$p &lt;0.0001$</td>
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</table>

Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial


Summary
Background In 2004, a randomised phase III trial by the European Organisation for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC) reported improved median and 2-year survival for patients with glioblastoma treated with concomitant and adjuvant temozolomide and radiotherapy. We report the final results with a median follow-up of more than 5 years.

Median follow-up: 61 months
EORTC/NCIC Update

<table>
<thead>
<tr>
<th></th>
<th>Deaths/patients</th>
<th>Hazard ratio (95% CI)</th>
<th>Median (months; 95% CI)</th>
<th>2 years (%)</th>
<th>3 years (%)</th>
<th>4 years (%)</th>
<th>5 years (%)</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Radiotherapy</td>
<td>278/286</td>
<td>1.0</td>
<td>12.1 (11.2-13.0)</td>
<td>10.9 (7.6-14.8)</td>
<td>4.4 (2.4-7.2)</td>
<td>3.0 (1.4-5.7)</td>
<td>1.9 (0.6-4.4)</td>
</tr>
<tr>
<td>Combined</td>
<td>254/287</td>
<td>0.6 (0.5-0.7)</td>
<td>14.6 (13.2-16.8)</td>
<td>27.2 (22.2-32.5)</td>
<td>16.0 (12.0-20.6)</td>
<td>12.1 (8.5-16.4)</td>
<td>9.8 (6.4-14.0)</td>
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<td><strong>RPA class III</strong></td>
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<td></td>
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<tr>
<td>Radiotherapy</td>
<td>36/39</td>
<td>1.0</td>
<td>14.8 (11.1-17.0)</td>
<td>20.5 (9.6-34.2)</td>
<td>10.3 (3.3-22.0)</td>
<td>6.8 (1.5-18.3)</td>
<td>6.8 (1.4-18.3)</td>
</tr>
<tr>
<td>Combined</td>
<td>31/42</td>
<td>0.5 (0.3-0.9)</td>
<td>18.7 (16.4-36.0)</td>
<td>40.5 (25.7-54.7)</td>
<td>31.5 (17.8-46.2)</td>
<td>28.0 (14.8-42.9)</td>
<td>28.0 (14.8-43.0)</td>
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<tr>
<td><strong>RPA class IV</strong></td>
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<tr>
<td>Radiotherapy</td>
<td>146/150</td>
<td>1.0</td>
<td>13.3 (12.2-15.0)</td>
<td>11.3 (6.9-17.0)</td>
<td>4.1 (1.6-8.4)</td>
<td>3.3 (1.2-7.4)</td>
<td>1.6 (0.2-6.5)</td>
</tr>
<tr>
<td>Combined</td>
<td>136/152</td>
<td>0.6 (0.5-0.8)</td>
<td>16.3 (14.1-18.4)</td>
<td>29.1 (22.1-36.5)</td>
<td>15.8 (10.5-22.0)</td>
<td>11.3 (6.8-17.1)</td>
<td>8.9 (4.7-14.7)</td>
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<tr>
<td><strong>RPA class V</strong></td>
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<tr>
<td>Radiotherapy</td>
<td>96/97</td>
<td>1.0</td>
<td>9.1 (7.9-11.8)</td>
<td>6.3 (2.6-12.3)</td>
<td>2.1 (0.4-6.6)</td>
<td>1.0 (0.1-5.1)</td>
<td>0</td>
</tr>
<tr>
<td>Combined</td>
<td>87/93</td>
<td>0.7 (0.5-0.9)</td>
<td>10.7 (9.0-12.6)</td>
<td>18.2 (11.1-26.6)</td>
<td>9.9 (4.8-17.3)</td>
<td>6.8 (2.6-13.9)</td>
<td>3.4 (0.7-9.9)</td>
</tr>
<tr>
<td><strong>MGMT unmethylated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>54/54</td>
<td>1.0</td>
<td>11.8 (10.0-14.4)</td>
<td>1.8 (0.1-8.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combined</td>
<td>54/60</td>
<td>0.6 (0.4-0.8)</td>
<td>12.6 (11.6-14.4)</td>
<td>14.8 (7.2-25.0)</td>
<td>11.1 (4.7-20.7)</td>
<td>11.1 (4.7-20.7)</td>
<td>8.3 (2.7-18.0)</td>
</tr>
<tr>
<td><strong>MGMT methylated</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>43/46</td>
<td>0.5 (0.3-0.7)</td>
<td>15.3 (13.0-20.9)</td>
<td>23.9 (12.9-36.9)</td>
<td>7.8 (2.2-18.3)</td>
<td>7.8 (2.2-18.3)</td>
<td>5.2 (1.0-15.0)</td>
</tr>
<tr>
<td>Combined</td>
<td>37/46</td>
<td>0.3 (0.2-0.4)</td>
<td>23.4 (18.6-32.8)</td>
<td>48.9 (33.7-62.4)</td>
<td>27.6 (15.4-41.4)</td>
<td>22.1 (11.0-35.7)</td>
<td>13.8 (4.5-28.2)</td>
</tr>
</tbody>
</table>

Stupp et al. Lancet Oncol 2009
EORTC/NCIC: Complete Resection and Treatment

Overall log-rank test: $P < .0001$

- **RT + TMZ**
- **RT**

Patients, %

Months
### Outcome in Figures

<table>
<thead>
<tr>
<th>Survival</th>
<th>Biopsy only</th>
<th>Partial resection</th>
<th>Complete resection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT</td>
<td>RT + TMZ</td>
<td>RT</td>
</tr>
<tr>
<td>Median</td>
<td>7.6 [5.4-10.6]</td>
<td>9.4 [7.5-13.2]</td>
<td>11.7 [9.7-13.1]</td>
</tr>
<tr>
<td>2 years</td>
<td>4.6 [0-10.8]</td>
<td>10.0 [1.3-18.7]</td>
<td>8.9 [3.9-14.0]</td>
</tr>
<tr>
<td></td>
<td>23.2 [15.5-30.9]</td>
<td>14.5 [7.8-21.2]</td>
<td>37.1 [28.0-46.3]</td>
</tr>
</tbody>
</table>
Is more surgery better?

Fluorescence-guided surgery using ALA

Stummer et al. Lancet 2006/ J Neurosurg 2010

CR: 65% VS. 36% (p=<0.0001)

Normal illumination

Violet-blue illumination

Courtesy Dr. W. Stummer
Temodal Adds Methyl Groups to DNA

DNA is made up of molecules of guanine, cystine, adenine, and thymidine. Temodal adds methyl groups to guanine.
MGMT Removes Methyl Groups from DNA

Guanine methylated by Temodal

Normal Guanine

repair by MGMT

Irreversibly inactivated
MGMT Promoter Methylation

- MGMT gene can be silenced by hypermethylation of its promoter
- MGMT promoter methylation is present in GBM
- MGMT promoter methylation is associated with prolonged survival
Overall Survival: Predictive Factor?

Overall Wald test: $p < 0.0001$ (df=3)

MGMT Depletion by Temozolomide

7 days on/7 days off (75 - 175 mg/m$^2$/day)

21 days every 28 days (85 - 125 mg/m$^2$/day)

72% reduction from baseline on day 8

67% reduction (day 15)

73% reduction (day 22)

Completed GBM Trial
RTOG-0525

RT/TMZ → ADJUVANT TMZ

1 6 10 30 weeks

150-200 mg/m² d1-5 every 28 d x 6-12 cycles

100 mg/m² d1-21 every 28 d x 6-12 cycles
Precursor Cell

Low-Grade Astro
- Rb mutation
- p14/p16 loss/9p loss
- CDK4 ampl
- 19p loss
- 11p loss

Low-Grade Oligo
- Chr 10 loss
- PTEN mutation
- EGFR ampl, p19/p14<sup>ARF</sup> deln.

Anaplastic Astro
- Chr 10 loss
- MDM2 ampl
- CDK4 ampl
- PDGFR ampl

1<sup>o</sup> GBM

Anaplastic Oligo
- p14/p16 loss/9p loss

2<sup>o</sup> GBM

GBM
- Chr 10 loss
- PTEN mutation

Stem Cell

1p&19q loss
- 1p&19q loss

p53 mut/17p loss
- PDGF/R overexp
- 22p loss
<table>
<thead>
<tr>
<th>Agents</th>
<th>Phase</th>
<th>Diagnosis</th>
<th>Sponsor</th>
<th>Primary endpoint</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept, TMZ, and RT</td>
<td>I</td>
<td>New GBM; recurrent or stable MG</td>
<td>NCI</td>
<td>MTD</td>
<td>NABTC</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>PFS6</td>
<td>NABTC</td>
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<tr>
<td>Bev and bortezomib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Genentech, Millenium</td>
<td>PFS6</td>
<td>Duke</td>
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<tr>
<td>Bev and enzastaurin</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>PFS6</td>
<td>NCI</td>
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<td>Bev and erlotinib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>Genentech</td>
<td>PFS6</td>
<td>Duke</td>
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<tr>
<td>Bev and etoposide</td>
<td>II</td>
<td>Recurrent MG</td>
<td>Genentech</td>
<td>PFS6</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev and irinotecan</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>RR</td>
<td>NCI</td>
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<tr>
<td>Bev and sorafenib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>PFS6</td>
<td>NCCTG</td>
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<tr>
<td>Bev and tandutinib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>PFS6</td>
<td>NCI</td>
</tr>
<tr>
<td>Bev and TMZ</td>
<td>II</td>
<td>New GBM, unresectable or multifocal</td>
<td>Genentech</td>
<td>RR</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev and TMZ</td>
<td>II</td>
<td>New GBM</td>
<td>Genentech</td>
<td>PFS, RR</td>
<td>University of Chicago</td>
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<tr>
<td>Bev and metronomic TMZ</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Genentech, Schering-Plough</td>
<td>PFS</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev, TMZ, and erlotinib</td>
<td>II</td>
<td>Stable GBM following RT</td>
<td>NCI</td>
<td>OS, PFS</td>
<td>UCSF</td>
</tr>
<tr>
<td>Bev and TMZ or etoposide</td>
<td>II</td>
<td>Recurrent GBM following bev and irinotecan</td>
<td>Genentech</td>
<td>PFS6</td>
<td>Duke</td>
</tr>
<tr>
<td>Bev, TMZ, irinotecan, and RT</td>
<td>II</td>
<td>New GBM</td>
<td>Genentech, Schering-Plough</td>
<td>OS</td>
<td>Duke</td>
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</table>
### Table 2 Selected ongoing clinical trials of vascular endothelial growth factor inhibitors

<table>
<thead>
<tr>
<th>Agents</th>
<th>Phase</th>
<th>Diagnosis</th>
<th>Sponsor</th>
<th>Primary endpoint</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cediranib and lomustine</td>
<td>I</td>
<td>Recurrent GBM</td>
<td>AZ</td>
<td>MTD</td>
<td>MGH</td>
</tr>
<tr>
<td>Cediranib, TMZ, and RT</td>
<td>I/II</td>
<td>New GBM</td>
<td>NCI</td>
<td>MTD (phase I), PFS (phase II)</td>
<td>MGH, DFCI</td>
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<tr>
<td>Pazopanib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>PFS6</td>
<td>NABTC</td>
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<tr>
<td>Pazopanib and lapatinib</td>
<td>I/II</td>
<td>Recurrent MG</td>
<td>GSK</td>
<td>MTD (phase I), PFS (phase II)</td>
<td>Multiple</td>
</tr>
<tr>
<td>Sorafenib and bevacizumab</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>PFS6</td>
<td>NCCTG</td>
</tr>
<tr>
<td>Sorafenib and erlotinib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>OS</td>
<td>Multiple</td>
</tr>
<tr>
<td>Sorafenib and erlotinib, tipifarnib, or temsirolimus</td>
<td>II/II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>MTD (phase I), PFS (phase II)</td>
<td>NCCTG</td>
</tr>
<tr>
<td>Sorafenib and temsirolimus</td>
<td>II/II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>MTD (phase I), PFS (phase II)</td>
<td>NCCTG</td>
</tr>
<tr>
<td>Sorafenib and TMZ</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Bayer, S-P</td>
<td>PFS6</td>
<td>Duke</td>
</tr>
<tr>
<td>Sorafenib and TMZ</td>
<td>II</td>
<td>New GBM</td>
<td>Bayer</td>
<td>PFS</td>
<td>SCRI</td>
</tr>
<tr>
<td>Sorafenib, TMZ, and RT</td>
<td>I</td>
<td>CNS tumor</td>
<td>Bayer</td>
<td>MTD</td>
<td>Thomas Jefferson University</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>PFS6</td>
<td>Multiple</td>
</tr>
<tr>
<td>Sunitinib and irinotecan</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Pfizer</td>
<td>MTD</td>
<td>Duke</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>I/II</td>
<td>Recurrent glioma</td>
<td>NCI</td>
<td>MTD (phase I), PFS (phase II)</td>
<td>NCI</td>
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<tr>
<td>Vandetanib, imatinib, and hydroxyurea</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Novartis, AZ</td>
<td>MTD</td>
<td>Duke</td>
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<tr>
<td>Vandetanib, TMZ, and RT</td>
<td>I/II</td>
<td>New GBM</td>
<td>AZ</td>
<td>MTD (phase I), OS (phase II)</td>
<td>Multiple</td>
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<tr>
<td>XL184</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>Exelixis</td>
<td>PFS6</td>
<td>DFCI, UCSF, MDACC</td>
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</tbody>
</table>

### Table 3  Selected ongoing clinical trials of non-vascular endothelial growth factor pathway antiangiogenic agents

<table>
<thead>
<tr>
<th>Agents</th>
<th>Phase</th>
<th>Diagnosis</th>
<th>Sponsor</th>
<th>Primary endpoint</th>
<th>Sites</th>
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<tbody>
<tr>
<td>AMG102</td>
<td>II</td>
<td>Recurrent MG</td>
<td>Amgen</td>
<td>RR</td>
<td>Multiple</td>
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<tr>
<td>Dasatinib and erlotinib</td>
<td>I</td>
<td>Recurrent MG</td>
<td>BMS, Genentech</td>
<td>MTD</td>
<td>Duke</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>II</td>
<td>Recurrent GBM</td>
<td>RTOG</td>
<td>RR or PFS6</td>
<td>RTOG</td>
</tr>
<tr>
<td>Imatinib, everolimus, and hydroxyurea</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Novartis</td>
<td>MTD</td>
<td>Duke</td>
</tr>
<tr>
<td>Imatinib and TMZ</td>
<td>I</td>
<td>Stable or recurrent MG in first relapse</td>
<td>NCI</td>
<td>MTD</td>
<td>Duke</td>
</tr>
<tr>
<td>Imatinib, vandetanib, and hydroxyurea</td>
<td>I</td>
<td>Recurrent MG</td>
<td>Novartis, AZ</td>
<td>MTD</td>
<td>Duke</td>
</tr>
<tr>
<td>Tandutinib</td>
<td>I/II</td>
<td>Recurrent GBM</td>
<td>NCI</td>
<td>MTD (phase I), RR (phase II)</td>
<td>NABTT</td>
</tr>
<tr>
<td>Tandutinib and bev</td>
<td>II</td>
<td>Recurrent MG</td>
<td>NCI</td>
<td>PFS6</td>
<td>NCI</td>
</tr>
<tr>
<td>TMZ or lomustine + 6-TG, capecitabine, or celecoxib</td>
<td>II</td>
<td>Recurrent MG</td>
<td>MDACC</td>
<td>PFS12</td>
<td>MDACC</td>
</tr>
<tr>
<td>TMZ ± thalidomide and/or cis-retinoic acid and/or celecoxib</td>
<td>II</td>
<td>Stable GBM following RT</td>
<td>NCI</td>
<td>PFS6</td>
<td>MDACC</td>
</tr>
</tbody>
</table>

Wen, Kesari NEJM 2008

Major Signalling Pathways in Malignant Gliomas

New RTOG Trial - 0825
- RT + TMZ → TMZ + Placebo
- RT + TMZ → TMZ + Avastin

New EORTC Trial
- RT + TMZ → TMZ
- RT + TMZ → TMZ + Cilengitide
Tumor Stem Cells in GBM

Fatoo A et al. J Neurooncol 2010
Careful IMRT Planning
On-Going McGill Trial

Surgery

Neoadjuvant TMZ
75 mg/m² x 2 weeks

Hypo-IMRT (60 Gy/20fxs)
TMZ (75 mg/m² x 2 weeks)

TMZ 150-200 mg/m²
12 cycles
Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial

Il Han Kim · Chul-Kee Park · Dae Seog Heo · Chae-Yong Kim · Chang Hun Rhee · Do-Hyun Nam · Seung Hoon Lee · Jung Ho Han · Se-Hoon Lee · Tae Min Kim · Dong-Wan Kim · Jeong Eun Kim · Sun Ha Paek · Dong Gyu Kim · In Ah Kim · Yu Jung Kim · Jee Hyun Kim · Byung-Joo Park · Hee-Won Jung

Control: RT + TMZ (adjuvant)
Treatment: neoadj nimustine+cisplatin followed by RT + TMZ (adjuv)

Median survival: control arm - 18.9 mos
                treatment      28.4 mos

Overall Survival
  1 yr  2 yr
Control    81.7%  27.8%
Treatment  72.4%  50.9%

J Neurooncol Nov 2010 (on line)
Early Progression vs. Pseudo Progression

McGill
52 F  MRI pre-op vs. Post-op
Path: GBM, unmethylated

5.1 x 5 x 3.8 cm enhancing mass in L frontal lobe
Plan 1:
46 Gy in 23 fractions using 7 fields IMRT technique

Plan 2:
14 Gy in 7 fractions using 7 fields IMRT technique

Treatment Plan:
Adjuvant RT 60 Gy + Concurrent Temodal Then maintenance Temodal
After treatment

- Finished RT Dec 11
- Brought to ER on Dec 29
  - R hemiparesis, aphasia
  - Responsive to pain, non-reactive L pupil
- CT scan Dec 29: Edema, herniation
  - Early progression?
  - No reoperation
  - Decadron 28mg QD + Mannitol 20% → Much improved
- MRS & MRI Jan 4: PsPD vs. early progression
- D/C home Jan 11
Follow-up MR – January 04
MRI Post-Op vs. Jan 04

Sept 26

Vol: 14.9 → 50.3 cm³

Jan 4
Brought back to ER on Jan 19th
- R hemiparesis, aphasia, decreased LOC
- CT: Worsening enhancement + edema
- Decadron 32mg QD + Mannitol +3%NS
- Jan 29: Avastin 10mg/kg q2wks

- Feb 3: Resolution of shift on CT
- Alert, improved speech + hemiparesis
MRI after 3 treatments

Jan 4

Vol: 50.3 → 15.91 cm³

April 9- Decadron 16mg QD
Decadron 6 mg QD
Temodal
Avastin

Last MRI - Sept 6 2010
53 M, RT temporo-parietal GBM

MRI
Feb 11, 2005

CT
Feb 16

5.8 x 5.5 x 3.8 cm
Summary and Plan

- 53M, R temporo-parietal GBM, RPA class IV
- Subtotal resection

Plan:
- Adjuvant RT 60 Gy 3D-CRT
- Concurrent Temodal
- Then maintenance Temodal
During treatment

- RT from March 21 to May 3

- Decadron increased 10mg QD on April 27
  - Increased L hand numbness, slurred speech
Post-treatment course

- Follow-up July 5: weakness + numbness L
  - MRI: slight progression in enhancing lesion with increase edema
  
  Progression?

  - Increase Decadron to 16 mg QD
  - Procarbazine 125mg/m2 QD x 28d q56 d
  - Continue Temodal maintenance
MRI May & July

May 12 - post RT

July 18

Vol: 29.2 → 33.7 cm³
Follow-up

- Continuous improvement on MRI
- Occasional L hand numbness

Jan 16 – 8 mo post-RT
Vol = 33.7 → 26.3 cm³
A long term GBM survivor

Sept 7, 2010
Temodal
<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Tx</th>
<th>Progression on 1st MRI</th>
<th>PsPD</th>
<th>PsPD Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Wit (2004)</td>
<td>32</td>
<td>RT only</td>
<td>9</td>
<td>3 (9%)</td>
<td>Improvement or stabilization x 6mo w/o treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI: -0.7-19.5%)</td>
<td></td>
</tr>
<tr>
<td>Chamberlain (2007)</td>
<td>51</td>
<td>RT + TMZ</td>
<td>15 clinical deterioration</td>
<td>7 (14%)</td>
<td>Pathologically confirmed necrosis, no tumor</td>
</tr>
<tr>
<td>Taal (2008)- R</td>
<td>85</td>
<td>RT + TMZ</td>
<td>36</td>
<td>18 (21%)</td>
<td>50% decrease in enhancing lesion + clinically stable next F/U OR Clinically + radiologically stable x 6mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI: 12.5-29.9%)</td>
<td></td>
</tr>
<tr>
<td>Bandes (2008)</td>
<td>103</td>
<td></td>
<td>50</td>
<td>32 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

**Progression on 1st MRI:**
- MGMT methyl: 90% probability of having PsPD.
- MGMT unmethyl: Equal chances of PsPD vs ePD.
Overall Survival (Bandes 2008)

Median OS
psPD = 38 mo
ePD = 10.2 mo
Non-PD = 20.1 mo
p < 0.0001

Brandes A A et al. JCO 2008;26:2192-2197
OS by presence of MGMT promoter methylation status \textit{(Bandes, 2008)}

\begin{itemize}
  \item Median OS
    \begin{itemize}
      \item MGMT methyl = 43.6 mo
      \item MGMT unmethyl = 16.8 mo
      \item \( p < 0.0001 \)
    \end{itemize}
\end{itemize}

Brandes A A et al. JCO 2008;26:2192-2197
Conclusions
Anaplastic Gliomas

- Chemotherapy trials failed to improve overall survival
- Progression free survival improved
- Loss of chromosomes 1p19q important prognostic factor

McGill
Conclusions

Glioblastoma

- Surgery + radiotherapy + temozolomide is current standard therapy
- Survival rates remain poor
- Important progress achieved recently
Conclusions

• Very important to differentiate pseudo progression from early progression
• Molecular and genetic roles being identified
• New upcoming studies may help selecting therapy by tumor genotype