Chemotherapy & targeted therapy in brain tumors

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DISTRIBUTION OF PRIMARY CNS TUMORS BY HISTOLOGY

- Meningioma 30.1%
- Glioblastoma 20.3%
- Embryonal, including medulloblastoma 1.7%
- Astrocitomas 9.8%
- Ependymomas 2.3%
- Oligodendrogliomas 3.7%
- Pituitary 6.3%
- Craniopharyngioma 0.7%
- Nerve sheath 8.0%
- Lymphoma 3.1%
- All others 13.9%

A BIT OF HISTORY..

- Surgery and radiation mainstays of treatment (and still are)

- Chemotherapy options
  - PCV standard of care for many years
    - Procarbazine 60 mg/sq. m PO D8-21
    - Carmustine (BCNU) 130 mg/sq. m PO D1
    - Vincristine 1.4 mg/sq. m IV D8 and D29
      - Significant side effects
  - Single agent nitrosurea (lomustine/carmustine) equivalent

Repeat every 8 weeks for 6 cycles
MECHANISM OF ACTION OF CHEMOTHERAPY AGENTS

- Monoclonal antibodies
- Hormone inhibitors
- Antibiotics
  - Anthracyclines
- Cell protein
- Transcription
- Centrioles
- Microtubule inhibitors
  - Vinca alkaloids
  - Taxanes
- Hormone receptor
- Antimetabolites
  - Folate
  - Purine
  - Pyrimidine analogs
- Alkylating agents
  - Mustards
  - Nitrosoureas
  - Platinum compounds
CHALLENGES TO TREATMENT

- Biologically aggressive
  - Most brain cancer are unresponsive to chemotherapy
- Drug delivery
  - Blood brain barrier
- Toxicity to normal brain
- Infiltration of malignant cells into brain parenchyma
  Blood Tumor Barrier
Characteristics of the BBB are indicated: (1) tight junctions that seal the pathway between the capillary (endothelial) cells; (2) the lipid nature of the cell membranes of the capillary wall which makes it a barrier to water-soluble molecules; (3), (4), and (5) represent some of the carriers and ion channels; (6) the 'enzymatic barrier' that removes molecules from the blood; (7) the efflux pumps which extrude fat-soluble molecules that have crossed into the cells.
The factors affecting particular substance to cross BBB

Drug related factors at the BBB

• Concentration at the BBB and the size,
• Flexibility,
• Conformation,
• Ionization (nonionized form penetrates BBB)
• Lipophilicity of the drug molecule,
• Cellular enzyme stability and cellular sequestration,
• Affinity for efflux mechanisms (i.e. P-glycoprotein),
• Hydrogen bonding potential (i.e. charge),
• Affinity for carrier mechanisms, and
• Effect on all of the above by the existing pathological conditions
How to overcome BBB ??

Newer delivery methods include:

*Interstitial chemotherapy* uses disc-shaped polymer wafers (known as Gliadel wafers) soaked with carmustine, the standard chemotherapeutic drug for brain cancer.

*Intrathecal chemotherapy* delivers chemotherapeutic drugs directly into the spinal fluid.

*Intra-arterial chemotherapy* delivers high-dose chemotherapy into arteries in the brain using tiny catheters.

*Convection-enhanced delivery (CED)* involves placing catheters into the brain tumor or nearby brain tissue to deliver slowly and continuously a cancer drug over several days.

http://www.umm.edu/patiented/articles/how_radiotherapy_used_treating_brain_tumors_000089_10.htm#ixzz256vtIvTr
GLIADEL WAFERS

- Gliadel wafers at time of surgery (carmustine soaked) in completely resected high grade glioma (3 or 4)
- The surgeon implants the wafer directly into the surgical cavity after a tumor is removed.
  Tumor < 4 cm in recurrent gliomas; cavity filled with I-125 liquid.
Standard ones include:

*Temozolomide (Temodar)*

-Taken oral

-First approved in 1999 for adult patients with anaplastic astrocytoma that did not respond to other treatments.

-In 2005, it was approved for use during and after radiation therapy for patients newly diagnosed with glioblastoma multiforme.

-Adverse effects: Relatively minor, but may include constipation, nausea and vomiting, fatigue, and headache.
GBM: Background

- Grade 4 astrocytoma \(^{(1)}\)
- Represents 2/3 of primary brain tumor diagnoses \(^{(2)}\)
  - Highly invasive, virtually incurable, rapidly fatal
  - Highly anaplastic, poorly differentiated, malignant neoplasms
  - Challenging to treat due to unpredictable chemosensitivity

High unmet need

- mOS of 10-12 months
- Recurrence occurs in 80% of patients \(^{(2)}\)
- Causes substantial morbidity with poor prognosis \(^{(3)}\)
  - 2-year OS: 26%
  - 4-year OS: 12%

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*
**STUPP TREATMENT SCHEMA**

- **Concomitant TMZ/RT**:
  - 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

- **Adjuvant TMZ**

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*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.*
SIGNIFICANT IMPROVEMENT IN SURVIVAL

Stupp et al. Lancet Oncology 2009
Methylation of MGMT promoter improves survival following adjuvant radiotherapy plus temozolomide

- MGMT methylation occurs in approximately 1/3 of patients\(^1\)
- Median survival\(^2\)
  - Methylation: 22 mo
  - No methylation: 15 mo
- 2-year survival\(^2\)
  - Methylation: 46%
  - No methylation: 25%

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Adjuvant RT in GBM

- Fractionated external beam RT an important component in postsurgical standard of care for GBM

- Median survival in phase III studies of adjuvant RT
  - 118 patients with grade 3/4 supratentorial astrocytoma: 10.8 vs 5.2 months with best supportive care only\(^1\)
  - 303 patients with anaplastic gliomas: 35 vs 14 weeks with best supportive care only\(^2\)

- RT benefits older (> 70 years) patients with good PS\(^3\)
  - Median OS: 29.1 vs 16.9 weeks with best supportive care only
  - QOL and cognition not affected by RT

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Meta-analysis of 12 randomized clinical trials of patients with high-grade gliomas (N = 3004)

Adding chemotherapy to RT conferred a 15% reduction in risk of death
  - Year 1: 6% improvement
  - Year 2: 5% improvement
  - Benefit becomes apparent around Month 6
  - Effect independent of age, histology, PS, extent of resection

HR: 0.85 (P < .001)
Great Variation in MGMT methylation status: technique dependent

Pyrrosequencing: RT-PCR  TMH: routine

Representative gel showing MSP result:

Arti S, Sarkar C. et al Child Nerv Sys 2010
Carmustine (BCNU, BiCNU)

-Carmustine is used to treat many types of brain tumors, including glioblastoma, medulloblastoma, and astrocytoma.

-Administered IV or delivered through a wafer implant (Gliadel), which is surgically placed into the brain cavity after tumor removal.

-Adverse effects
  -Intravenously: Nausea and vomiting, fatigue, respiratory problems and pulmonary fibrosis, bone marrow impairment.

  -Delivered through a wafer: Seizures and cerebral infection
PCV Drug Regimen

-PCV is an abbreviation for a chemotherapy regimen that combines procarbazine (Matulane), lomustine (CCNU), and vincristine (Oncovin).

-PCV is commonly used to treat oligodendrogliomas and mixed oligoastrocytomas.

-Procarbazine and lomustine are taken by mouth. Vincristine is given by either injection or IV.

-Adverse effects:
  Drop in blood cell counts, nausea and vomiting, constipation, fatigue, and mouth sores.
  Procarbazine can cause high blood pressure when taken with foods high in tyramine. Patients should avoid foods such as beer, red wine, cheese, chocolate, processed meat, yogurt, and certain fruits and vegetables.
INVESTIGATIONAL DRUGS (TARGETED THERAPY)
Targeted therapies work on a molecular level by blocking specific mechanisms associated with cancer cell growth and division.

- less severe side effects.

Promising targeted therapies for brain tumors include:

1. Tyrosine kinase inhibitors

- It block proteins involved in tumor cell growth and production.

- Drugs that specifically target epidermal growth factor receptors (EGFR) are a type of tyrosine kinase inhibitor of special interest in brain tumor research.

- These drugs include erlotinib (Tarceva), imatinib (Gleevec), and gefitinib (Iressa).
Role of EGFR in GBM

- EGFR (Epidermal growth factor receptor)
  - is commonly over-expressed in malignant disease
  - regulates many vital cellular processes
  - seems to be a negative prognostic indicator

- EGFR frequently activated in GBM via overexpression or amplification
  - Amplification seen in > 40% and overexpression in > 60%
  - Focal amplifications with or without EGFR point mutations
  - EGFRvIII missing exons 2-7 most common EGFR mutant
  - Implicated in RT resistance

- EGFR inhibitors being studied for GBM treatment
  - Nimotuzumab
  - Cetuximab
  - Gefitinib
  - Lapatinib
  - Vandetanib
  - CDX-110 anti-EGFRvIII vaccine

EGFR
over expressed/amplified in 50-90% of GBM

Anti-EGFR therapies:
Erlonitib, Nimotuzumab, Cetuximab, Geftinib, Lapatanib

Anti EGFR therapies work especially in tumours with EGFR vIII mutations and intact p10 (NEJM 2005)
BIOMAb EGFR® (Nimotuzumab)

- Humanized IgG1 anti-EGFR monoclonal antibody with 95% human sequences
- Proven to be anti-proliferative, anti-angiogenic and pro-apoptotic
- Unique molecular profile leading to efficacy without associated toxicities in combination with chemo-radiotherapy/radiotherapy
- Approved in India for the treatment of locally advanced squamous cell carcinoma in head and neck (SCCHN)
- Approved globally for indications that include SCCHN, Glioma, Nasopharyngeal cancer & Esophageal cancer. It has received orphan drug designation for glioma in US and Europe
Mechanism of action

1. Proliferation
2. Invasion
3. Inhibition of apoptosis
4. Angiogenesis
5. Metastasis

**Cancer**

**Ligand**
EGF, TGF Alpha

**Tyrosine Phosphorylation**

**DIMERISATION**

**SIGNALING**

1. Proliferation
2. Invasion
3. Inhibition of apoptosis
4. Angiogenesis
5. Metastasis

**BiMAb EGFR®**
Comparative affinity & binding patterns

<table>
<thead>
<tr>
<th></th>
<th>Nimotuzumab</th>
<th>Cetuximab</th>
<th>Panitumumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affinity</td>
<td>$1 \times 10^{-9}$</td>
<td>$1 \times 10^{-10}$</td>
<td>$5 \times 10^{-11}$</td>
</tr>
<tr>
<td>Toxicity (Rash)</td>
<td>&lt; 10%</td>
<td>~90%</td>
<td>~100%</td>
</tr>
</tbody>
</table>

**Decoupling rash & Efficacy**

Optimal affinity & reliance on bivalent binding to form a strong stable bond lead to a better safety profile without compromising on efficacy.

**Low EGFR density**

**High EGFR density**
BIOMAb EGFR as a therapy option for GBM

STUDY TITLE

An Open Label, Prospective, Multicentric Study to Evaluate the Safety and Efficacy of BIOMAb EGFR (Nimotuzumab) as Induction and Maintenance Therapy in Combination with Radiotherapy Plus Temozolomide (Concomitant & Adjuvant) in Indian Patients with Glioblastoma Multiforme
Objectives

To evaluate the safety and efficacy of BIOMAb EGFR (Nimotuzumab) in combination with Temozolomide and radiotherapy in the treatment of Glioblastoma multiforme

<table>
<thead>
<tr>
<th>Primary objective</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Objectives</td>
<td>Progression free-survival</td>
</tr>
<tr>
<td></td>
<td>Tumor Response</td>
</tr>
<tr>
<td></td>
<td>Safety &amp; Tolerability</td>
</tr>
</tbody>
</table>
## Centre wise Subject Disposition

<table>
<thead>
<tr>
<th>Centre no.</th>
<th>Centre Name</th>
<th>(N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>All Indian Institute Of Medical Sciences, New Delhi</td>
<td>7 (12.5%)</td>
</tr>
<tr>
<td>2</td>
<td>Dharamshila Cancer Hospital &amp; Research Centre, New Delhi</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>3</td>
<td>Rajiv Gandhi Cancer Institute And Research Centre, New Delhi</td>
<td>12 (21.4%)</td>
</tr>
<tr>
<td>4</td>
<td>Gujarat Cancer Research Institute, Ahmedabad</td>
<td>8 (14.3%)</td>
</tr>
<tr>
<td>5</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td>5 (8.9%)</td>
</tr>
<tr>
<td>6</td>
<td>Curie Centre of Oncology, St. Johns Medical College &amp; Hospital, Bangalore</td>
<td>7 (12.5%)</td>
</tr>
<tr>
<td>7</td>
<td>Christian Medical College, Vellore</td>
<td>6 (10.7%)</td>
</tr>
<tr>
<td>8</td>
<td>Regional Cancer Centre, Trivandrum</td>
<td>5 (8.9%)</td>
</tr>
</tbody>
</table>
## Study Details

<table>
<thead>
<tr>
<th>Phase</th>
<th>Phase II</th>
</tr>
</thead>
</table>
| **Design**          | ▪ Open Label  
▪ Prospective  
▪ Multicentric Study  
▪ Single Arm  |
| **Number of subjects** | 56 patients  |
| **Total duration of study** | Five years from enrollment (which includes maximum two years of treatment stage and three years of follow-up stage) |
## Study Details

### Inclusion Criteria

- Willingness to sign the informed consent.
- Newly diagnosed patients with GBM (Grade 4 Astrocytoma) confirmed by histopathology.
- Patients suitable for planned radiotherapy and chemotherapy with TMZ
- Patients who are chemotherapy naive
- Patients aged between 18-70 years (both inclusive).
- Karnofsky’s Performance Status ≥ 60%.
- Adequate hematological, renal & hepatic function
- Patients who have undergone debulking surgery or tumor biopsy in the last 4 weeks are eligible for enrollment
- Patients should be willing to use effective methods of contraception during the study

### Exclusion Criteria

- Female patients who are pregnant or breast feeding.
- Patients with severe underlying disease/ not controlled by treatment in the opinion of the principal investigator.
- HIV, Chronic Hepatitis B or C if found to be positive
- Hypersensitivity to TMZ & BIOMAb-EGFR™ (Nimotuzumab) or to any of its components.
- Previous or concurrent malignancies in other sites except surgically cured carcinoma-in-situ of cervix & non melanoma skin cancer
Study treatment plan

Concomitant Stage
Induction: Nimotuzumab 200mg weekly X 6 Weeks
+ RT once daily at 1.8-2Gy per fraction 5d/wk for a total of 54 - 60 Gy
+ TMZ 75mg/m^2 daily X 6 weeks
After the Induction: Nimotuzumab 200mg administration once every 3 weeks to continue

Adjuvant Stage
Administration of TMZ begins 4 weeks after end of radiation therapy.
Maintenance BIOMAb-EGFR® (Nimotuzumab) 200mg once every 3 weeks + adjuvant TMZ
150mg/m^2 for Cycle 1 and 200mg/m^2 for Cycle 2 to 6 (d1-d5 of 28-Day Cycle)

Maintenance Stage
Maintenance BIOMab EGFR® (Nimotuzumab) 200mg once every 3 weeks till disease progression
or end of the study (2 years)

Follow-up Stage
No study drug will be given in follow-up stage. Tumor response will be evaluated every three
months using MRI till disease progression or the completion of five years from enrollment,
whichever is earlier
Patients with newly diagnosed GBM (Grade 4 astrocytoma) confirmed with HPE

**Concomitant Phase**
- BIOMAb EGFR (Nimotuzumab) × 6 weeks (200 mg/dose wkly)
- + RT × 6 weeks (1.8-2 Gy/day × 5d/wk)
- + TMZ × 6 weeks (75mg/m²/day)

**Evaluation MRI**
- Objective Response

**Adjuvant Phase**
- BIOMAb EGFR (Nimotuzumab) every 3 wks (200 mg/dose wkly)
- + TMZ 6 (cycles) cycle 1= 150mg/m² Cycle 2-6 = 200 mg/m² (28 day cycle)

**Evaluation MRI**
- Objective Response

**Maintenance Phase**
- 1. BIOMAb EGFR (Nimotuzumab) every 3 wks (200 mg/dose wkly) till end of study (2 years)
- 2. MRI every 6 months till end of study

- Further treatment as per investigator discretion

**Progressive disease**
- Followed for survival till end of study
## Tumor Response Evaluation

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>Disappearance of all enhancing tumor on consecutive CT or MRI scans at least 1 month apart, off steroids, and neurologically stable or improved</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>&gt; 50% reduction in size of enhancing tumor on consecutive CT or MRI scans at least 1 month apart, steroids stable or reduced, and neurologically stable or improved</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>&gt; 25% increase in size of enhancing tumor or any new tumor on CT or MRI scans, or neurologically worse and steroids stable or increased.</td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>All other situations</td>
</tr>
</tbody>
</table>
**Number of Subjects in Each Population Set**

<table>
<thead>
<tr>
<th>Population Set</th>
<th>Number of subjects in the set, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Population</td>
<td>56 (100.0 %)</td>
</tr>
<tr>
<td>ITT Population</td>
<td>56 (100.0 %)</td>
</tr>
<tr>
<td>Efficacy Evaluable Population</td>
<td>51 (91.1%)</td>
</tr>
</tbody>
</table>

- **Intention to treat** - All subjects who were administered at least one dose of BIOMAb EGFR
- **Efficacy evaluable Patients** - Patients who received at least 6 or more doses of BIOMAb EGFR
- **Safety analysis** was performed for all subjects who were administered at least some amount of study drug
### Demography at Enrolment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics /Category</th>
<th>Value (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>41 (73.2%)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>15 (26.8%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>Asian</td>
<td>56 (100.0%)</td>
</tr>
<tr>
<td><strong>Age (In Years)</strong></td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>51.0 ± 10.76</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>52.0</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(22.0, 70.00)</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td>Age &lt; 50</td>
<td>22 (39.3%)</td>
</tr>
<tr>
<td></td>
<td>Age &gt;= 50</td>
<td>34 (60.7%)</td>
</tr>
<tr>
<td><strong>Height(cm)</strong></td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>163.4 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>165.0</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(147.0, 177.0)</td>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
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<tr>
<td><strong>BSA</strong></td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(1.3, 2.1)</td>
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<table>
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<tr>
<th>Variable</th>
<th>Statistics /Category</th>
<th>Value(N=56)</th>
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</thead>
<tbody>
<tr>
<td><strong>Karnofsky's Performance Status</strong></td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>81.1 ± 8.9</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>80.0</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(60.0, 90.0)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics /Category</th>
<th>Value(N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KPS Category</strong></td>
<td>&lt; 70</td>
<td>3 (5.3%)</td>
</tr>
<tr>
<td></td>
<td>70-89</td>
<td>31 (55.4%)</td>
</tr>
<tr>
<td></td>
<td>90-100</td>
<td>22 (39.3%)</td>
</tr>
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</table>

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<tr>
<th>Variable</th>
<th>Statistics /Category</th>
<th>Value(N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time From Diagnosis (In Days)</strong></td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>14.6 ± 9.2</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(1.0, 63.0)</td>
</tr>
</tbody>
</table>

Note: SD - Standard Deviation ; (Min, Max) - (Minimum, Maximum)
Surgical History and Residual Tumour Status at Enrolment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of Residual Tumor *</td>
<td>Yes</td>
<td>29 (78.4%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>1 (2.7%)</td>
</tr>
</tbody>
</table>

* Denominator will be the subjects who have undergone prior surgery
Safety and Efficacy of BIOMAb EGFR® in Indian Patients with Glioblastoma Multiforme

RESULTS
**Overall Survival [ITT population]**

![Graph: Overall survival (in months) - ITT Population]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td>Mean (S.E)</td>
<td>14.5 (1.1)</td>
</tr>
<tr>
<td>Median (in months)</td>
<td>14.1</td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(10.9, 17.3)</td>
</tr>
</tbody>
</table>
Overall Survival [EE population]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>51</td>
</tr>
<tr>
<td>Mean (S.E)</td>
<td>15.0 (1.1)</td>
</tr>
<tr>
<td>Median (in months)</td>
<td>14.5</td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(11.2, 18.8)</td>
</tr>
</tbody>
</table>
Progression Free Survival [ITT population]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td>Mean (S.E)</td>
<td>10.5 (1.0)</td>
</tr>
<tr>
<td>Median (in months)</td>
<td>9.3</td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(6.7, 11.2)</td>
</tr>
</tbody>
</table>
Progression Free Survival [EE population]

<table>
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<tr>
<th>Statistics</th>
<th>Values</th>
</tr>
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<tbody>
<tr>
<td>N</td>
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</tr>
<tr>
<td>Mean (S.E)</td>
<td>10.8 (1.1)</td>
</tr>
<tr>
<td>Median (in months)</td>
<td>9.3</td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(6.9, 11.3)</td>
</tr>
</tbody>
</table>
RPA Analysis

A recursive partition analysis (RPA) model was defined post-hoc and the data was analyzed.

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>Definition Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPA III</td>
<td>Age&lt;50 ;KPS 90-100 (both inclusive)</td>
</tr>
<tr>
<td>RPA IV</td>
<td>Age&lt;50;KPS &lt; 90</td>
</tr>
<tr>
<td>RPA V</td>
<td>Age≥50;KPS &lt; 70 OR Age≥50;KPS 70-100</td>
</tr>
</tbody>
</table>

*KPS :Kamofsky’s Performance Status*
Overall Survival Results
RPA Classification [ITT Population Set]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>RPA Class III</th>
<th>RPA Class IV</th>
<th>RPA Class V</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>9</td>
<td>13</td>
<td>34</td>
<td>0.0310</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>21.6 (0.8)</td>
<td>11.8 (1.7)</td>
<td>12.9 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>10.9</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(20.8, NA)</td>
<td>(8.8, 18.8)</td>
<td>(8.9, 15.0)</td>
<td></td>
</tr>
</tbody>
</table>

mOS not yet reached at 2-year follow-up in RPA Class III patient subset

Median follow-up period of 27.1 months
### Progression Free Survival
**RPA Classification [ITT Population Set]**

<table>
<thead>
<tr>
<th>Statistics</th>
<th>RPA Class III</th>
<th>RPA Class IV</th>
<th>RPA Class V</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>12</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>18.9 (1.9)</td>
<td>9.7 (2.0)</td>
<td>8.8 (1.2)</td>
<td>0.0236</td>
</tr>
<tr>
<td>Median</td>
<td>20.8</td>
<td>8.8</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>95% CI for Median</td>
<td>(13.6, NA)</td>
<td>(5.0, 12.8)</td>
<td>(4.3, 10.3)</td>
<td></td>
</tr>
</tbody>
</table>

Median PFS of 20.8 months observed in RPA class III. mPFS between RPA classes was statistically significant.
Prognostic Significance of Recursive Partitioning Analysis in GBM

• RPA classification developed to compare survival categories and determine homogenous patient subsets
  • Useful for refining stratification and phase III study design
  • Can determine which patient subsets will benefit from specific treatments (and which may be spared unnecessary treatment)

<table>
<thead>
<tr>
<th>RPA Class</th>
<th>Median Survival Months</th>
<th>95% CI</th>
<th>2-Yr Survival %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>III*</td>
<td>17</td>
<td>15-21</td>
<td>32</td>
<td>21-42</td>
</tr>
<tr>
<td>IV</td>
<td>15</td>
<td>13-16</td>
<td>19</td>
<td>15-24</td>
</tr>
<tr>
<td>V</td>
<td>10</td>
<td>9-12</td>
<td>11</td>
<td>7-16</td>
</tr>
</tbody>
</table>

## BIOMAb Study vs. Stupp’s Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BIOMAb Study</th>
<th>Stupp’s study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival (median)</td>
<td>14.1 Mo</td>
<td>14.6 Mo</td>
</tr>
<tr>
<td>Progression Free Survival (median)</td>
<td>9.3 Mo</td>
<td>6.9 Mo</td>
</tr>
<tr>
<td>RPA Class III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>Not Reached (&gt;24mo)</td>
<td>17 Mo</td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td>20.8 Mo</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>
## Objective Response Rate [ITT Population set]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>At 6 months (N=51)</th>
<th>At 12 months (N=51)</th>
<th>At 18 months (N=50)</th>
<th>At 24 months (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>9 (17.6%)</td>
<td>9 (17.6%)</td>
<td>9 (18.0%)</td>
<td>6 (12.0%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.2, 28.1)</td>
<td>(7.2, 28.1)</td>
<td>(7.4, 28.6)</td>
<td>3.0% to 21.0%</td>
</tr>
</tbody>
</table>

**ORR of 17.6% observed after 1 year of treatment with BIOMAb EGFR in combination with chemotherapy (ITT population)**
Objective Response Rate [EE Population set]

<table>
<thead>
<tr>
<th>Statistics</th>
<th>At 6 months (N=49)</th>
<th>At 12 months (N=49)</th>
<th>At 18 months (N=48)</th>
<th>At 24 months (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PR</td>
<td>9</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>9 (18.4%)</td>
<td>9 (18.4%)</td>
<td>9 (18.8%)</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.2, 29.2)</td>
<td>(7.5, 29.2)</td>
<td>(7.7, 29.8)</td>
<td>(3.1, 21.9)</td>
</tr>
</tbody>
</table>

**ORR of 18.4% observed after 1 year of treatment with BIOMAb EGFR in combination with chemotherapy (EE population)**
## Duration of BIOMAb EGFR® (Nimotuzumab) Exposure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics</th>
<th>N = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of Exposure (Days)</td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>272.3 ± 230.3</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>199</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(1, 715)</td>
</tr>
</tbody>
</table>

## Cumulative Dose of BIOMAb EGFR® (Nimotuzumab)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics</th>
<th>N = 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Dose (mg)</td>
<td>N</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>3389.3 ± 2214.5</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>2800</td>
</tr>
<tr>
<td></td>
<td>(Min, Max)</td>
<td>(200, 7600)</td>
</tr>
</tbody>
</table>
Conclusion

At median follow-up period of 27.1 months, Nimotuzumab in combination with TMZ and radiotherapy reported:

- **mOS** of 14.1 months
  - mOS observed in RPA class III and Class V were better than median OS observed in Stupp et al., (2009) study showing a possible median survival benefit in these two RPA sub-classes III and V by the addition of Nimotuzumab

- **mPFS** of 9.3 months, whereas it was 6.2 months in the Stupp et al., (2009) study on TMZ with radiotherapy

- Nimotuzumab in combination with standard of care was well tolerated with a good safety profile

Addition of BIOMAb EGFR (Nimotuzumab) to the temozolomide based chemoradiotherapy has an apparent progression free survival benefit and a possible overall survival benefit in RPA class III and V without major safety concerns
2. Farnesyl protein transferase inhibitors

Tipifarnib (Zarnestra) and Lonafarnib (Sarasar)

-These drugs target a protein involved in the functioning of the cancer-causing Ras protein.

-Lonafarnib is being studied in combination with temozolomide, and tipifarnib in combination with radiation therapy.

3. MTOR inhibitors

-Everolimus (RAD-001) is being studied for glioblastoma multiforme and astrocytoma.

-Everolimus is related to rapamycin (Sirolimus) and tacrolimus (Prograf), which are also being investigated for brain tumor treatment.

-These drugs are commonly used to suppress the immune system to prevent rejection after organ transplantation.

www.umm.edu/patiented/articles/how_radiotherapy_used_treating_brain_tumors_000089_10.htm#ixzz256wfm64B
4. Anti-angiogenesis drugs:

Bevacizumab (Avastin)

- It is being studied in combination with irinotecan for treatment of recurrent malignant gliomas.

Cediranib (Recentin, AZD2171)

- It is another VEGF inhibitor being investigated for glioblastoma treatment.
Bevacizumab (Avastin)

- To date mainly investigated in Phase II trials
- Usually in combination with irinotecan chemotherapy
- No trials have demonstrated a survival benefit

Side effects include
- Hypertension (9%)
- Delayed wound healing (2%)
- Bowel perforation (2%)
- Intracranial haemorrhage (2%)
- Venous and arterial clots (4%)
**Bevacizumab**  **Irinotecan in Recurrent GBM**

- Phase II study in 167 patients

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab (n = 85)</th>
<th>Bevacizumab + Irinotecan (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response %</td>
<td>28.2</td>
<td>37.8</td>
</tr>
<tr>
<td>6-mo PFS %</td>
<td>42.6</td>
<td>50.3</td>
</tr>
<tr>
<td>Survival (months)</td>
<td>9.2</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Friedman HS, et al. JCO 2009
Bevacizumab (Anti-VEGF mAB)

Before 6 cycles Bevacizumab After
### Experience with anti-angiogenic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Number patients</th>
<th>CR/PR (%)</th>
<th>PFS-6 (%)</th>
<th>OS, median (months)</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>85</td>
<td>28.2</td>
<td>42.6</td>
<td>9.2</td>
<td>Friedman 2009</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>48</td>
<td>35</td>
<td>29</td>
<td>7.8</td>
<td>Kreisl 2009</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>50</td>
<td>NR</td>
<td>25</td>
<td>6.4</td>
<td>Raizer 2010</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>82</td>
<td>37.8</td>
<td>50</td>
<td>8.7</td>
<td>Friedman 2009</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>35</td>
<td>57</td>
<td>46</td>
<td>10.5</td>
<td>Vredenburgh, 2007</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>23</td>
<td>61</td>
<td>30</td>
<td>10.0</td>
<td>Vredenburgh, 2007</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>20</td>
<td>50</td>
<td>65</td>
<td>12.5</td>
<td>Gutin 2009</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>25</td>
<td>48</td>
<td>29.2</td>
<td>11.1</td>
<td>Sathornsumetee 2010</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>27</td>
<td>23</td>
<td>44.4</td>
<td>11.6</td>
<td>Reardon 2009</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>43</td>
<td>34</td>
<td>33</td>
<td>7.3</td>
<td>Hasselbalch 2010</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>35</td>
<td>5.7</td>
<td>3</td>
<td>8.8</td>
<td>Iwamoto 2010</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>21²</td>
<td>0</td>
<td>NR</td>
<td>3.8</td>
<td>Neyns 2010</td>
</tr>
</tbody>
</table>

---

Reardon Perry Brandes Jalali Wick *Expt Opin Drug Discovery* 2011
Phase III Trials of Bevacizumab in newly diagnosed GBM

**AVAGLIO**[1]

- Newly diagnosed GBM (planned N = 920)
- **Placebo** q2w + standard RT (60 Gy D1-5) x 6 wks + TMZ 75 mg/m² PO/day for 6 wks then 150-200 mg/m² Days 1-5 of each 6 x 4-wk cycle until progression
- **Bevacizumab** 10 mg/kg q2w + standard RT (60 Gy D1-5) x 6 wks + TMZ 75 mg/m² PO/day for 6 wks then 150-200 mg/m² Days 1-5 of each 6 x 4-wk cycle until progression

**RTOG 0825**[2]

- Newly Diagnosed GBM ≥ 18 years; KPS 70% to 100%
- Standard RT + concurrent TMZ (Planned N = 942)
- Wk 4 of chemoRT: Bevacizumab q2w, continuing until completion of adjuvant TMZ
- 4 wks after chemoRT: Adjuvant TMZ 200 mg/m² D1-5 Q28D for up to 12 courses + placebo
- 4 wks after chemoRT: Adjuvant TMZ 200 mg/m² Days 1-5 Q28D for up to 12 courses + placebo

Results

• The results of the phase III AVAglio trial were presented at the 49th (ASCO) in the Central Nervous System Tumours Session by Professor Wolfgang Wick, M.D., Professor of Neurology, Chairman of the Division of Neuro-oncology at the Neurology Centre.

• People who received Avastin plus radiotherapy and temozolomide chemotherapy did not have a statistically significant improvement in OS (the other co-primary endpoint), compared to those who received radiotherapy and temozolomide chemotherapy plus placebo (HR=0.88; [95% CI 0.76, 1.02], p=0.0987). Median survival was similar in both arms (16.8 months versus 16.7 months, respectively). No new safety findings were observed in the AVAglio study and adverse events were consistent with those seen in previous trials of Avastin across tumour types for approved indications.
# Angiogenesis-Targeting Agents for Glioblastoma

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Disease Setting</th>
<th>Study Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrins</td>
<td>Cilengitide</td>
<td>nGBM, rGBM</td>
<td>Phase III, Phase I/II</td>
</tr>
<tr>
<td>Angiopoietin/Tie 2</td>
<td>CVX-060</td>
<td>rGBM</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>VEGF</td>
<td>VEGF-trap (afibercept)</td>
<td>rGBM</td>
<td>Phase II, Phase I</td>
</tr>
<tr>
<td></td>
<td>VEGFR TKIs (cabozantinib, cediranib, axitinib, pazopanib)</td>
<td>rGBM, nGBM</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab + strategies</td>
<td>nGBM, rGBM</td>
<td>Phase I, II, III</td>
</tr>
<tr>
<td>Endothelial cell proliferation</td>
<td>Metronomic temozolomide</td>
<td>nGBM, rGBM</td>
<td>Phase II, III</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov
Cilengetide
Anti-integrin

Phase III Randomised Clinical trial of S+RT+TMZ Vs S+RT+TMZ+Cilengitide (EORTC); Global accrual completed including in India

‘CENTRIC and CORE trials’

2 year OS: 35%
Stupp et al JCO 2010
GENETIC TARGETS IN GLIOBLASTOMA

- EGFR, mutated/amplified in 45%
- HER2, mutated in 8%
- PDGFRα, amplified in 13%
- MET, amplified in 4%

RAS, mutated in 2%
NF1, mutated/deleted in 18%
Proliferation, survival, translation

PI3K, mutated in 15%
AKT, amplified in 2%
FOXO, mutated in 1%
PTEN, mutated/deleted in 36%

Anti EGFR vIII vaccine in recurrent GBM

Impressive results  SNO 2011

Ongoing clinical ‘vaccine’ trials against EGFR vIII (CDX-110 Indian centres participating)
GBM in relation to stem cell niches – a novel approach
Irradiation of the potential cancer stem cell niches in the adult brain improves progression-free survival of patients with malignant glioma

Evers et al BMC Cancer 2010;10:384

Possible Clinical Trial: Std Volume RT Vs RT Volumes encompassing stem cell niches
• In 2011, the FDA approved a portable medical device that generates low intensity electric fields termed Tumor Treating Fields (TTF) for recurrent glioblastoma.

• Approval was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy.

• Similar survival was observed in both arms with TTF having lower toxicity and improved QOL.

• Due to lack of efficacy, not all panelists recommend treatment.
<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTOR inhibitors</td>
<td>Everolimus, sirolimus, temsirolimus, deforolimus</td>
</tr>
<tr>
<td>PI3K inhibitors</td>
<td>BEZ235, XL765</td>
</tr>
<tr>
<td>PKCβ</td>
<td>Enzastaurin</td>
</tr>
<tr>
<td>PDGFR inhibitors</td>
<td>Dasatinib, imatinib, tandutinib</td>
</tr>
<tr>
<td>Proteasome</td>
<td>Bortezomib</td>
</tr>
<tr>
<td>Raf</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>Src</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>TGF-β</td>
<td>AP12009</td>
</tr>
<tr>
<td>Combination therapies</td>
<td>Erlotinib plus temsirolimus, gefitinib plus everolimus, gefitinib plus sirolimus, sorafenib plus temsirolimus erlotinib, or tipifarnib, pazopanib plus lapatinib</td>
</tr>
<tr>
<td>Immunotherapies</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell and EGFRvIII peptide vaccines</td>
<td>DCVax, CDX-110</td>
</tr>
</tbody>
</table>
Molecular targeting agents in pediatric patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>Tumor type</th>
<th>Study group</th>
<th>Study number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipifarnib</td>
<td>II</td>
<td>Recurrent or progressive HGG, MBL/PNET, BSG</td>
<td>COG</td>
<td>COG-ACNS0226</td>
</tr>
<tr>
<td>Erlotinib + TMZ</td>
<td>I</td>
<td>Recurrent/refractory solid tumors</td>
<td>COG</td>
<td>COG-ADVL0214</td>
</tr>
<tr>
<td>Imatinib</td>
<td>I/II</td>
<td>Newly diagnosed BSG, recurrent intracranial malignant gliomas</td>
<td>PBTC</td>
<td>PBTC-006</td>
</tr>
<tr>
<td>Iressa + XRT</td>
<td>I/II</td>
<td>Newly diagnosed BSG, incompletely resected supratentorial gliomas</td>
<td>PBTC</td>
<td>PBTC-007</td>
</tr>
<tr>
<td>Tipifarnib + XRT</td>
<td>I/II</td>
<td>Newly diagnosed BSG</td>
<td>PBTC</td>
<td>PBTC-014</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>I</td>
<td>Recurrent/refractory MBL, malignant gliomas, EP</td>
<td>PBTC</td>
<td>PBTC-016</td>
</tr>
</tbody>
</table>
Ongoing trials of targeted therapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase of trial</th>
<th>Target</th>
<th>Patient population</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus + trastuzumab + vinorelbine</td>
<td>II</td>
<td>mTOR</td>
<td>HER2+ breast cancer</td>
<td>NCT01305941</td>
</tr>
<tr>
<td>BKM120 + trastuzumab</td>
<td>I</td>
<td>PI3K</td>
<td>HER2+ breast cancer</td>
<td>NCT01132664</td>
</tr>
<tr>
<td>Lapatinib + WBRT</td>
<td>II</td>
<td>HER2</td>
<td>HER2+ breast cancer</td>
<td>NCT01622868</td>
</tr>
<tr>
<td>Neratinib</td>
<td>II</td>
<td>HER2</td>
<td>HER2+ breast cancer</td>
<td>NCT01494662</td>
</tr>
<tr>
<td>Afatinib</td>
<td>II</td>
<td>HER2</td>
<td>HER2+ breast cancer</td>
<td>NCT01441596</td>
</tr>
<tr>
<td>ARRY-380 + trastuzumab</td>
<td>I</td>
<td>HER2</td>
<td>HER2+ breast cancer</td>
<td>NCT01921335</td>
</tr>
<tr>
<td>WBRT +/- erlotinib</td>
<td>II</td>
<td>EGFR</td>
<td>NSCLC</td>
<td>NCT01518621</td>
</tr>
<tr>
<td>WBRT + bevacizumab</td>
<td>I</td>
<td>VEGF</td>
<td>Solid tumors</td>
<td>NCT01332929</td>
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<tr>
<td>Bevacizumab</td>
<td>II</td>
<td>VEGF</td>
<td>Solid tumors</td>
<td>NCT01898130</td>
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<td>Sunitinib + SRS</td>
<td>I</td>
<td>VEGFR</td>
<td>Solid tumors</td>
<td>NCT00981890</td>
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<tr>
<td>Sorafenib + SRS</td>
<td>I</td>
<td>VEGFR</td>
<td>Solid tumors</td>
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<tr>
<td>Dabrafenib + SRS</td>
<td>II</td>
<td>BRAF</td>
<td>Melanoma</td>
<td>NCT01721603</td>
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<td>Vemurafenib</td>
<td>II</td>
<td>BRAF</td>
<td>Melanoma</td>
<td>NCT01781026</td>
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<td>Ipilimumab + WBRT or SRS</td>
<td>I</td>
<td>CLTA-4</td>
<td>Melanoma</td>
<td>NCT01703507</td>
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<td>Veliparib + WBRT</td>
<td>II</td>
<td>PARP</td>
<td>NSCLC</td>
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## NCCN Guidelines Version 2.2014
Central Nervous System Cancers

### PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

#### Adult Low-Grade Infiltrative Supratentorial Astrocytoma/Oligodendroglioma (excluding pilocytic astrocytoma)
- **Adjuvant Treatment:**
  - Temozolomide
  - Recurrence or Progressive, Low grade disease:
    - Temozolomide
    - Lomustine or carmustine
    - Combination PCV (lomustine + procarbazine + vincristine)
    - Platinum based regimens

#### Glioblastoma
- **Adjuvant Treatment:**
  - Concurrent (with RT) temozolomide daily
  - Post RT temozolomide 150-200 mg/m² 5/28 schedule
- **Recurrence/Salvage therapy**
  - Bevacizumab
  - Bevacizumab + chemotherapy
  - Irinotecan, carmustine/omustine, temozolomide, carboplatin [category 2B for carboplatin]
  - Temozolomide
  - Lomustine or carmustine
  - Combination PCV
  - Cyclophosphamide (category 2B)
  - Platinum-based regimens

#### Anaplastic Gliomas
- **Adjuvant Treatment:**
  - Temozolomide or PCV with deferred RT
  - Concurrent (with RT) temozolomide 75 mg/m² daily
  - Recurrence/Salvage therapy
  - Temozolomide
  - Lomustine or carmustine
  - Combination PCV
  - Bevacizumab
  - Bevacizumab + chemotherapy
  - Irinotecan, carmustine/omustine, temozolomide, carboplatin [category 2B for carboplatin]
  - Irinotecan
  - Cyclophosphamide (category 2B)
  - Platinum-based regimens

#### Adult Intracranial and Spinal Ependymoma (excluding subependymoma)
- **Recurrence**
  - Platinum-based regimens
  - Single agent or combination
  - Etoposide
  - Lomustine or carmustine
  - Bevacizumab
  - Temozolomide

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*Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.*
PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Adult Medulloblastoma and Supratentorial PNET
- Adjuvant Treatment
  ≣ Weekly vincristine\(^6\) during craniospinal radiation therapy followed by either of the following regimens:
    ≣ Cisplatin, cyclophosphamide, and vincristine\(^37,\)\(^39\)
    ≣ Cisplatin, lomustine, and vincristine\(^37,\)\(^9\)
- Recurrence/Salvage therapy
  ≣ No prior chemotherapy
    ≣ High-dose cyclophosphamide ± etoposide
    ≣ Carboplatin, etoposide, and cyclophosphamide
    ≣ Cisplatin, etoposide, and cyclophosphamide
    ≣ Consider high-dose chemotherapy with autologous stem cell reinfusion\(^38\) in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection
  ≣ Prior chemotherapy
    ≣ High dose cyclophosphamide ± etoposide
    ≣ Oral etoposide\(^38,\)\(^40\)
    ≣ Temozolomide\(^3\)
    ≣ Consider high-dose chemotherapy with autologous stem cell reinfusion\(^38\) in patients who achieve a complete response with conventional doses of salvage chemotherapy or have no residual disease after re-resection

Primary CNS Lymphoma
- Primary Treatment
  ≣ High dose methotrexate 3.5 g/m\(^2\) combined with the following plus RT\(^6\):
    ≣ Vincristine, procarbazine, cytarabine ± rituximab\(^41-43\)
    ≣ Cytarabine\(^44\)
    ≣ Ifosfamide ± RT\(^45\)
  ≣ High dose methotrexate 8 g/m\(^2\) combined with the following plus deferred RT\(^46\):
    ≣ Rituximab\(^47,\)\(^48\)
    ≣ Rituximab and temozolomide\(^49\)
  ≣ Consider urgent glucarpidase (carboxypeptidase G2) for prolonged methotrexate clearance due to methotrexate induced renal toxicity\(^50\)
- Recurrence or Progressive Disease
  ≣ Retreat with high-dose methotrexate\(^46\)
  ≣ Temozolomide
  ≣ Rituximab ± temozolomide\(^51\)
  ≣ Topotecan
  ≣ Consider high-dose chemotherapy with autologous stem cell reinfusion in patients who achieve a complete response with conventional doses of salvage chemotherapy
  ≣ High-dose cytarabine\(^52\)
  ≣ Dexamethasone, high-dose cytarabine, cisplatin\(^53\)
  ≣ Pemetrexed\(^54\)

Meningiomas
- Interferon alfa (category 2B)\(^55\)
- Somatostatin analogue\(^56\)

\(^6\)Omission of vincristine during radiotherapy phase of therapy or dose modification may be required for adults because they do not tolerate this regimen as well. Data supporting vincristine’s use have been found in pediatric trials only. Patients should be closely monitored for neurologic toxicity with periodic exams.
\(^*\)Other combinations with methotrexate may be used.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Progress Against Brain Cancer

2000–Present

2003: Chemotherapy "wafer" active against malignant gliomas
Progress Against Brain Cancer

2000–Present

2005: MGMT gene alteration predicts response to chemotherapy

2005-2008: Researchers begin mapping the genome of glioblastoma
Progress Against Brain Cancer

2000–Present

2006: Genetic mutations affect survival for oligodendroglioma
2006: Chemically "illuminating" glioma tumors during surgery postpones recurrence
2006: Molecular sub-classification of high-grade gliomas predicts prognosis
Progress Against Brain Cancer

2000–Present

2008: Bevacizumab (Avastin) receives FDA approval for glioblastoma
Progress Against Brain Cancer

2000–Present

2009: Gene mutations linked to tumor aggressiveness
2010: Nine-gene test can predict glioblastoma outcome
Progress Against Brain Cancer

Five-Year Survival

% of Patients Surviving Five Years

Year of Diagnosis

Source: National Cancer Institute
THANK YOU