Advancing Research to Treatments:
Unmet Needs In Glioblastoma

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Unmet Need

Senator Kennedy’s tragic death brought greater visibility to the tremendous need for improved brain tumor treatment options.

- 76 years old at diagnosis
- May 17, 2008: Seizure at his home in Hyannis, MA
- Medflight from Cape Cod Hospital to Mass General Hospital in Boston
- Diagnosed with Glioblastoma Multiforme
- August 25, 2009: Died 15 months after diagnosis

By annual incidence, glioblastomas are the most common type of malignant brain tumor.

Source: CBTRUS, American Brain Tumor Association website.
Unmet Need

Glioblastomas progress rapidly without therapy.

Clinical history is less than three months in majority of patients; Prognosis worse for elderly patients

Relative Survival Rates for Primary Malignant Gliomas

Note: Relative survival rates for primary malignant gliomas are from SEER, 1973-2004.
Source: DataMonitor, CBTRUS, SG Cowen, Medscape.
The best current standard of care extends overall survival to about 14 to 16 months.

### Median Overall Survival Time of Glioblastoma Patients by Therapy

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery Only</td>
<td>0</td>
</tr>
<tr>
<td>+ Radiotherapy (RT)</td>
<td>6</td>
</tr>
<tr>
<td>+ RT + Carmustine</td>
<td>12</td>
</tr>
<tr>
<td>+ RT + Carmustine Implant</td>
<td>18</td>
</tr>
<tr>
<td>+ RT + Temozolomide</td>
<td>24</td>
</tr>
<tr>
<td>+ RT + Temozolomide + Bevacizumab*</td>
<td>24</td>
</tr>
</tbody>
</table>

* Data for bevacizumab represents newly-diagnosed glioblastoma and is from a phase II clinical trial with no placebo control.

Temozolomide with radiation is the first line treatment of choice.

- MRI and/or CT Suggestive of Glioblastoma
- Biopsy
- Confirmation of Glioblastoma
- Surgical Resection
- First-Line Therapies
  - Radiotherapy
  - Temozolomide
  - GLIADEL WAFER
    - Polileprosan 20 with carmustine implant
  - Nitrosoureas
    - AVASTIN (bevacizumab)
- Second-Line Therapies
- Clinical Trials
The basic patent on Temodar will expire in 2014.

**GLIADEL WAFER**
(polifeprosan 20 with carmustine implant)
- Implant
- Approved 1996

**AVASTIN**
(bevacizumab)
- IV
- Approved for 2nd line glioblastoma in 2009
- Evaluation as addition to 1rst line

Total Market: ~ $1.4B

- Oral and IV
- Approved 2005
- Generic launch in August 2013

Source: Company 10ks, websites, Datamonitor, UpToDate, Analyst Reports.
Drug Development Challenges

Anticipating the path to market involves a series of connected questions.
Dramatic unmet needs will drive interest in any new therapy.

**Challenges**

- **Blood-Brain Barrier**
  - Formulation and delivery?

- **Tumor Heterogeneity**
  - Breadth of use?

- **Lack of Screening Tools**
  - Risk factors?
  - DX prior to malignancy?

- **Paucity of Biomarkers**
  - Assessing prognosis?
  - Patient segmentation?
  - Differential treatment?

- **Low Incidence/Rapid Progression**
  - Market potential?
  - Trial recruitment?

**Opportunities**

- **High Unmet Need**
  - Incremental improvement
  - Risk tolerant
  - Rapid market uptake

- **Small Population, Orphan Drug Potential**

- **Survival Drives Prevalence**
  - Increased population
  - Extended duration of therapy

- **Pricing Flexibility**
  - Extreme mortality
  - Low generic impact

- **Combination Therapy**
  - Multiple mechanisms

- **Centers of Excellence**
  - Focused call points
  - Specialty market strategy
Development Challenges

Better understanding of specific patients sub-segments can be valuable for clinical development and precision in selecting treatment options.

<table>
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<tr>
<th>EGFRvIII</th>
<th>MGMT Gene</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for EGFRvIII</td>
<td>Methylated MGMT</td>
<td>Under 65</td>
</tr>
<tr>
<td>Negative for EGFRvIII</td>
<td>Unmethylated MGMT</td>
<td>Over 65</td>
</tr>
</tbody>
</table>

**Frequency**

- 25% (Positive for EGFRvIII)
- 75% (Negative for EGFRvIII)
- 45% (Methylated MGMT)
- 55% (Unmethylated MGMT)
- 50% (Under 65)
- 50% (Over 65)

**Overall Survival**

- 23 months\(^1\) (Positive for EGFRvIII)
- 15 months (Negative for EGFRvIII)
- 22 months\(^2\) (Methylated MGMT)
- 13 months\(^2\) (Unmethylated MGMT)
- 15 months\(^2\) (Under 65)
- 9 months\(^2\) (Over 65)

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1 Data based on general patient populations treated with rindopepimut immunotherapy and temozolomide and lacking a placebo control.
2 Data based on patient populations receiving radiotherapy and temozolomide.

Pipeline Activity

An active early stage pipeline with multiple different approaches.

Number of Glioblastoma Therapies in Development

By Category

- Clinical Trial Phase* refers to the highest regulatory phase reached worldwide and excludes therapies already launched in another indication.

Source: Pipeline databases, company websites, clinicaltrial.gov.
Presentations today reflect the diversity of therapeutic approaches being investigated.

Today’s Presentations

- Small molecule glycolysis inhibitor
- Drug-resistant cellular therapy
- Therapeutic vaccine
- Bi-specific antibody

Other Approaches
- Gene therapy
- Lytic viruses
- Nucleic acid therapies
- Nanoparticles
- Stem cell therapy

Immunotherapies
- Active immunization
- Adoptive therapies

Monoclonal Antibodies
- Small Molecule Chemotherapy

New Options for Glioblastoma Patients
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