Advances in the Treatment for the Patients with Glioblastoma (GBM)

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Disclosure

• No disclosure over past 12 months
• Consulting for advisory board committee of NovoCure in 2016
In Memory of John McCain
8-25-2018

National Brain Tumor Society
News Alert

Senator John McCain Remembered as a No-Nonsense Leader

Today, Senator John McCain passed away 13 months after being diagnosed with glioblastoma. He demonstrated, again and again, his toughness and strength in the face of overwhelming odds - as he’s done his entire life. With great sadness, we remember and honor The Maverick, who touched many lives during his career in the public eye.

Senator McCain was diagnosed with a glioblastoma brain tumor in July 2017. Glioblastoma, or GBM, is the most common and most aggressive type of brain cancer. The five-year relative survival rate of individuals with glioblastoma is only 5.5%. An estimated 16,616 people will die from malignant brain tumors in 2018.

We will always remember the Senator’s fighting spirit - whether in the fields of battle or in the halls of Washington. Everyone in the brain tumor community - regardless of political affiliation or views - can all recognize and empathize with his experience facing such a devastating diagnosis. Our condolences and thoughts go out to his family in this difficult time.

Please READ OUR STATEMENT concerning the Senator and his contributions to our country.
Objective of learning

• Understand the background of most malignant brain cancer – glioblastoma (GBM)
• Know the clinical symptoms of GBM
• Know how to diagnose GBM
• Understand standard therapy of GBM
• Understand advanced treatment for GBM
Outline

• Epidemiology
• Clinical presentation
• Diagnosis
• Current therapy for GBM
  – Standard therapy
  – **New therapy**
  – Clinical trials
  – Supportive care: Rehabilitation, seizure, DVT, PE, infection, headache, falls, PT/OT/ST
  – Palliative care
Background: GBM

- Glioblastoma multiforme (GBM)
  - The most common and aggressive primary malignant brain tumor in adults (47.1%)
  - Median overall survival of 14.6-20.5 months and 2-year survival rate only 26.5-43%
  - Five-year survival only 5.5%

Epidemiology: Primary Brain Tumor

**Fig. 4** Distribution of Primary Brain and Other CNS Tumors by Behavior (N=379,848), CBTRUS Statistical Report: NPCR and SEER, 2010-2014

Ostrom Q T et al. Neuro Oncol 2017;19 (s5): v1–v88
Epidemiology: Primary brain tumor

- 79,270 new cases of **primary CNS tumors** in the United States in 2017
- 26,070 primary **malignant** CNS tumors in 2017
- 12,500 **GBM** cases projected in 2017
- 16,947 deaths due to **primary malignant** CNS tumors in 2017

Ostrom Q T et al. Neuro Oncol 2014;16:iv1-iv63

More common in older adults
Incidence increased with age
1.58 times more common in males > females

† All or some of this histology are included in the CBTRUS definition of gliomas, including ICD-O-3 histology codes 9380-9384, 9391-9460, 9480 (Table 2a).
   a. Rates per 100,000 and age-adjusted to the 2000 United States standard population. b. ICD-O-3 Histology Codes: 9381, 9384, 9424, 9400, 9401, 9410, 9411, 9420.
   c. ICD-O-3 Histology Codes: 9450, 9451, 9460. d. ICD-O-3 Code: 9560. e. ICD-O-3 Histology Codes: 9530/0, 9530/1, 9531/0, 9532/0, 9533/0, 9534/0, 9537/0, 9538/1, 9539/1.

Ostrom Q T et al. Neuro Oncol 2017;19 (s5): v1–v88
Clinical presentation

Symptoms

Incidence of Symptoms in Patients With Glioma

- Headache
- Seizure
- Hemiparesis
- Mental Abnormalities

Glioblastoma Multiforme

- **Imaging:** infiltrating, enhance, necrosis
  - Viable tumor extends beyond signal abnormalities
  - Relentless progression, spreads along white matter tracts

- **Tumor size can double every two weeks**
Diagnosis

- **Initial Presentation:**
  - Headache
  - Mental Status Changes
  - “Acute tumor attack” 5-10% of the patients: seizures, stroke-like symptoms

- **Imaging:**
  - MRI is superior to the CT
  - More accurate detection of multiple lesions
  - Better diagnosis of smaller lesions (under 2 cm)
  - No bone artifacts
Diagnosis

• Symptoms
• Imaging
• Pathology

• Microscopically, it shows high cellularity, nuclear anaplasia, which is the basis of the designation "multiforme", mitoses, microvascular proliferation, and necrosis.

• Densely cellular arrays of tumor cells are arranged in a perpendicular (pseudopalisading) fashion around necrotic areas.

• MGMT methylated, IDH1 wide type, negative 1p19q do-deletion,

• Loss of ATRX; Ki 67-45%

• Glioblastoma Multiforme (GBM), IDH wild type
Differential Diagnosis

• Symptoms
• Imaging
• Pathology
Current therapy for GBM

- **Conventional GBM treatment**
  - Surgery
  - Radiation
  - Chemotherapy

- **Advance in GBM treatment**
  - Device- Optune/NOVO TTF (Tumor Treating Field)
  - Angiogenesis (VEGF) inhibitors

- **Ongoing clinical trials**
  - Immunotherapy-trials in primary brain tumor
  - Target therapy- trials in primary brain tumor
  - Proteosome inhibitors
Surgery

Gross total resection is better than subtotal resection

* GTR 95% CI: 11.4-14.6 months (13 mo)
** STR 95% CI: 7.4-10.2 months (8.8 mo)
P<0.05

Lacroix M, Abi-Said D, Fourney DR, et al.
Radiotherapy (RT)

Increased overall survival (OS) of GBM

6 weeks of radiotherapy, 1.8 Gy
5 days per week, total 50 Gy

Chemotherapy

RT plus TMZ are standard of care for newly diagnosed GBM

The NEW ENGLAND JOURNAL of MEDICINE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D.,

Stupp R, et al. NEJM, 2005
Progression-Free Survival

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>XRT + TMZ</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>14.6</td>
<td>12.1</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>6.9</td>
<td>5.0</td>
</tr>
<tr>
<td>OS 1 yr (%)</td>
<td>61.1</td>
<td>50.6</td>
</tr>
<tr>
<td>OS 2 yr (%)</td>
<td>26.5</td>
<td>10.4</td>
</tr>
</tbody>
</table>

XRT + TMZ for Newly Diagnosed GBM: Stupp NEJM 352 987,2005
Current therapy for GBM

• Conventional tumor treatment
  – Surgery
  – Radiation
  – Chemotherapy

• Advance in tumor treatment
  – Device- Optune/NOVO TTF (Tumor Treating Field)
  – Angiogenesis (VEGF) inhibitors

• Ongoing clinical trials
  – Immunotherapy-trials in primary brain tumor
  – Target therapy- trials in primary brain tumor
  – Proteosome inhibitors
Device-Optune

- Alternating electrical fields disrupt the rapid cell division exhibited by malignant glioma cells through transducer arrays placed on the scalp.
https://www.optune.com/resources/videos?videoid=how-ttfieldswork
December 15, 2015¹

**Preclinical Communication**

**Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial**


**Objective**: To determine whether the addition of TTFs significantly improves overall survival in patients with glioblastoma.

**Conclusion**: The addition of TTFs to standard therapy significantly improved overall survival in patients with glioblastoma.

**References**


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December 17, 2017²

**Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial**


**Objective**: To determine whether the addition of TTFs to maintenance therapy significantly improves overall survival in patients with glioblastoma.

**Conclusion**: The addition of TTFs to maintenance therapy significantly improved overall survival in patients with glioblastoma.

**References**


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February 1, 2018³

**Influence of Treatment With Tumor-Treating Fields on Health-Related Quality of Life of Patients With Newly Diagnosed Glioblastoma: A Secondary Analysis of a Randomized Clinical Trial**


**Objective**: To determine the impact of TTFs on health-related quality of life in patients with newly diagnosed glioblastoma.

**Conclusion**: The addition of TTFs to standard therapy had a minimal impact on health-related quality of life.

**References**

EF-14: Phase 3 Pivotal Trial Design\textsuperscript{1-3}

- Newly diagnosed GBM N=700
- Biopsy/debulking
- Radiation + TMZ

\textbf{Enrollment window (4-7 weeks after RT + TMZ)}

\textbf{Randomized 2:1}

- Optune $\geq$18 h/day + TMZ $\times$ 6 cycles
- Optune + 2L chemotherapy, surgery, SRS, or combination*

1st progression

2L chemotherapy, surgery, SRS, or combination

2nd progression or 24 months

- Primary endpoint (ITT population): PFS
- Secondary endpoint (PP population): OS
- Additional secondary endpoints: PFS6, 1-y/2-y survival, ORR, safety, QoL

\textbf{Stratification by}

1. Resection (biopsy vs partial vs gross total)
2. MGMT promoter methylation status

*Treatment with Optune was continued for 24 months or until second progression, whichever occurred first unless prohibited by the patient's clinical condition.\textsuperscript{1,2}

GBM, glioblastoma multiforme; TMZ, temozolomide; RT, radiation therapy; 2L, second-line; SRS, stereotactic radiosurgery; ITT, intent-to-treat; PFS, progression-free survival; PP, per protocol; OS, overall survival; PFS6, the percentage of patients alive and progression-free at 6 months; ORR, objective response rate; QoL, quality of life; MGMT, O6-methylguanine-DNA methyltransferase.
EF-14: Overall Survival (5-year survival analysis)\(^1\)

This 5-year survival analysis (n=695) confirms the results from the interim analysis in the per protocol population (n=280) where Optune + TMZ extended OS by 4.9 months\(^1,3\)

\(^1\) Stupp et al, 2017
EF-14: Long-term Survival Rates (5-year survival analysis)\textsuperscript{1,2}

- Optune + TMZ provides unprecedented 5-year survival rates in newly diagnosed GBM

![Graph showing survival rates over time with statistical significance levels.](image-url)
EF-14: Overall Survival by Compliance (5-year survival analysis)

**ITT Population**

<table>
<thead>
<tr>
<th>Metric</th>
<th>≥75% Compliance</th>
<th>&lt;75% Compliance</th>
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</thead>
<tbody>
<tr>
<td>Median survival, mo</td>
<td>22.6</td>
<td>19.1</td>
</tr>
<tr>
<td>95% CI, mo</td>
<td>19.7-25.1</td>
<td>16.5-21.9</td>
</tr>
<tr>
<td>Stratified log-rank</td>
<td></td>
<td>P=0.009</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.79 (0.64-0.99)</td>
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</table>
Optune for recurrent GBM

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td><img src="Baseline.png" alt="Image" /></td>
<td><img src="6_months.png" alt="Image" /></td>
<td><img src="12_months.png" alt="Image" /></td>
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<tr>
<td>B</td>
<td><img src="Baseline.png" alt="Image" /></td>
<td><img src="6_months.png" alt="Image" /></td>
<td><img src="12_months.png" alt="Image" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Optune (n=120)</th>
<th>Chemotherapy (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>P-value</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>1-year survival</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>2-year survival</td>
<td>8%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Stupp R et al. EJC 2012
# EF-14 Safety Summary: Incidence of Grade 3/4 Adverse Events in ≥5% of Patients (5-year survival analysis)\(^1\)

<table>
<thead>
<tr>
<th>Safety Population</th>
<th>Optune + TMZ (n=456) %</th>
<th>TMZ Alone (n=216) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 Adverse event</td>
<td>48</td>
<td>44</td>
</tr>
<tr>
<td>Blood and lymphatic system disorder*</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Asthenia, fatigue, and gait disturbance</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Infections</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications (falls and medical device site reaction)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Seizures</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- The most common (≥10%) adverse events involving Optune in combination with TMZ were thrombocytopenia, nausea, constipation, vomiting, fatigue, medical device site reaction, headache, convulsions, and depression\(^2\)
Bevacizumab (Avastin)-Angiogenesis inhibitor
Standard treatment for recurrent GBM

Bevacizumab
Antibody to vascular endothelial growth factor (VEGF), improve survival and disease-related morbidity
Recombinant humanized monoclonal IgG1 antibody

Folkman at Rev Drug Discov. 2007;6:273-286; Dr. L Nghiemphu with permission
Bevacizumab (Avastin) - Angiogenesis inhibition
Standard treatment for recurrent GBM

Brain Trial, Phase II study, 167 cases, FDA approval for recurrent GBM in 2009

AE: ICH, HTN, proteinuria, fatigue

Vredenburgh, J et al. JCO, 2007
Bevacizumab (Avastin)-Angiogenesis inhibition
NOT standard treatment for newly diagnosed GBM

Gilbert et al. NEJM 2014
Current therapy for GBM

• Conventional tumor treatment
  – Surgery
  – Radiation
  – Chemotherapy

• Advance in tumor treatment
  – Device- Optune/NOVO TTF (Tumor Treating Field)
  – Angiogenesis (VEGF) inhibitors

• Ongoing clinical trials
  – Immunotherapy-trials in primary brain tumor
  – Target therapy- trials in primary brain tumor
  – Proteosome inhibitors
Immune therapy

• To effectively treat existing tumors and to prevent future relapse by generating tumor-specific immune memory responses
  – Tumor vaccine-to sensitize the immune system against brain tumors
  – Immune checkpoint inhibitor therapies
  – Adoptive T cell therapy- to engineer T cells to specifically attack tumor but not self. The transgenic T cells only target tumor specific antigens.
Immune therapy

- Vaccines - to sensitize the immune system against glioma, to evoke meaningful antitumor responses
  - Whole tumor cell lysate vaccines (DCVax-L, ERC 1671) - sensitize against any and multiple antigens expressed by tumor cells
  - Tumor associated antigen vaccines (ICT 107, Rindopepimut)
    - Peptide or protein share expression with normal tissue and hence may be subject to immune tolerance and therefore generate less robust immune responses than tumor-specific antigens
  - Tumor specific antigen vaccines
    - Exclusively expressed by tumor cells
    - Focused on single antigen target
    - To generate robust and tumor specific immune responses
Immune checkpoint inhibitor therapies

PD-L1 binds to PD-1 and inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Immune checkpoint inhibitor therapies

- **PD-1 inhibitors**
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
- **PD-L1 inhibitors**
  - Atezolizumab
  - Durvalumab
  - Avelumab
- **CTLA-4 Inhibitors**
  - Tremelimumab
  - Lpilimumab
Efficacy of immune checkpoint inhibitor therapies are expected in the future.

<table>
<thead>
<tr>
<th>Immune checkpoint agent</th>
<th>Target</th>
<th>Additional treatment</th>
<th>Phase</th>
<th>Population</th>
<th>Clinicaltrials.gov</th>
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<tbody>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>None</td>
<td>3</td>
<td>Recurrent</td>
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<td>Pembrolizumab</td>
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<td>Varulimumab</td>
<td>2</td>
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<td>Nivolumab</td>
<td>PD-1</td>
<td>Galunisertib</td>
<td>1 &amp; 2</td>
<td>Recurrent</td>
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<td>PD-1</td>
<td>CMV pp65 LAMP mRNA vaccine</td>
<td>1</td>
<td>Recurrent</td>
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<td>Pembrolizumab</td>
<td>PD-1</td>
<td>Laser ablation</td>
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<td>Stereotactic radiosurgery</td>
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<td>Tremelimumab</td>
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<td>Epacadostat</td>
<td>1 &amp; 2</td>
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<td>Durvalumab</td>
<td>PD-L1</td>
<td>Stereotactic radiosurgery</td>
<td>1 &amp; 2</td>
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<td>PD-1</td>
<td>Ipilimumab</td>
<td>1</td>
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<td>Durvalumab</td>
<td>PD-L1</td>
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<td>Radiation</td>
<td>3</td>
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<td>Pembrolizumab</td>
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<td>Radiation and temozolomide</td>
<td>1 &amp; 2</td>
<td>Newly diagnosed</td>
<td>NCT02530502</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; DNX2401, proprietary name of vaccine product; LAG, lymphocyte activation gene 3; PD, programmed death.
Targeted cancer therapy

- Targeting specific genes or proteins expressed on the tumor surface
Targeting EGFR and EGFR v III for the treatment of tumor

Padfield E et al, Front Oncol 2015

EGFR: Epidermal Growth Factor Receptor
Targeting therapy is successful in many systemic cancers but not GBM.

Table 1 | A summary of therapies targeting EGFR and EGFRvIII.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Target</th>
<th>Current clinical applications</th>
<th>Problems reported in glioma trials</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cetuximab (L01XC06)</td>
<td>EGFR/HER1</td>
<td>Colorectal cancer</td>
<td>Head and neck cancer</td>
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<tr>
<td>Panitumumab (L01XC08)</td>
<td>EGFR/HER1</td>
<td>Metastatic colorectal cancer</td>
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<tr>
<td>Nimotuzumab (L01XC)</td>
<td>EGFR/HER1</td>
<td>Squamous cell carcinoma of head and neck</td>
<td>Orphan status for glioma and pancreatic cancer</td>
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<tr>
<td>125 I-Mab 425</td>
<td>EGFR</td>
<td>N/A</td>
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<tr>
<td>mAb806</td>
<td>EGFRvIII</td>
<td>N/A</td>
<td></td>
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<tr>
<td>DAB389EGF</td>
<td>EGFR</td>
<td>N/A</td>
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<tr>
<td><strong>Small molecule inhibitors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Gefitinib (L01XE02)</td>
<td>EGFR/HER1</td>
<td>NSCLC</td>
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<tr>
<td>Erlotinib (L01XE03)</td>
<td>EGFR/HER1</td>
<td>NSCLC and pancreatic cancer</td>
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<tr>
<td>Lapatinib (L01XE07)</td>
<td>EGFR/HER1/HER2</td>
<td>HER2+ breast cancer</td>
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<tr>
<td>Afatinib (L01XE13)</td>
<td>EGFR/HER1/HER2/HER4</td>
<td>Metastatic NSCLC</td>
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<td>Dacomitinib</td>
<td>EGFR/HER1/HER2/HER4</td>
<td>N/A</td>
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<td><strong>Vaccines</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rindopepimut (CDX-110)</td>
<td>EGFRvIII</td>
<td>N/A</td>
<td>Tumor heterogeneity</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Patient selection</td>
<td></td>
</tr>
</tbody>
</table>
Proteosome inhibitors

- **Bortezomib**
  - A slowly reversible proteasome inhibitor
  - Enhancing apoptosis
    - Modulating p53 and Bax
    - Inducing TRAIL activation-triggered cell death
    - Inhibiting survival protein NFkB
  - Blocking caspase 8&3 degradation
  - Increasing cell cycle arrest
    - Modulation of p21 and p27

Manton et al
Preclinical studies: Bortezomib against GBM

- GBM cell lines has good sensitivity to bortezomib induced cell death
- Cause growth arrest of GBM cell lines via NFkB inhibition
- Sensitize GBM cells to TMZ and cause down regulation of MGMT expression
- A radiosensitizer
- Chemosensitizing effect when administered together with other antitumoral drugs

Styczynski, et al. Anticancer research 2006;26:4499-504
Phase II Study of Bortezomib in Combination with Temozolomide and Regional Radiation Therapy for Upfront Treatment of Patients with Newly-Diagnosed GBM: Safety and Efficacy Assessment

- Xiao-Tang Kong, M.D., Ph.D., Nhung T. Nguyen, Yoon J. Choi, M.D., Guicheng Zhang, M.D., Ph.D, HuyTram N. Nguyen, Emese Filka, M.D., Stacey Green MSN, William H. Yong, M.D., Linda M. Liau, M.D., Ph.D., Richard M. Green, M.D., Tania Kaprealian, M.D., Whitney B. Pope, M.D., Ph.D., P. Leia Nghiemphu, M.D., Tim Cloughesy, M.D., Andrew Lassman, M.D., and Albert Lai, M.D., Ph.D.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years: median (range)</td>
<td>57 (27-75)</td>
</tr>
<tr>
<td>Gender - no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Female</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Karnofsky performance score - no. (%)</td>
<td></td>
</tr>
<tr>
<td>60-80</td>
<td>8 (33)</td>
</tr>
<tr>
<td>90-100</td>
<td>16 (67)</td>
</tr>
<tr>
<td>Pre-surgery lesion location - no. (%)</td>
<td></td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>9 (38)</td>
</tr>
<tr>
<td>Parietal lobe</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Extent of resection - no. (%)</td>
<td></td>
</tr>
<tr>
<td>Sub-total resection</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Gross total resection</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Use of glucocorticoids at baseline - no. (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (42)</td>
</tr>
<tr>
<td>No</td>
<td>14 (58)</td>
</tr>
<tr>
<td>MGMT methylation status - no. (%)</td>
<td></td>
</tr>
<tr>
<td>Total # of patients tested</td>
<td>23</td>
</tr>
<tr>
<td>Methylated</td>
<td>10 (43)</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>13 (57)</td>
</tr>
<tr>
<td>IDH mutation status - no. (%)</td>
<td></td>
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<tr>
<td>Total # of patients tested (IDH1/IDH2)</td>
<td>24/21</td>
</tr>
<tr>
<td>Mutant type (IDH1/IDH2)</td>
<td>3/0 (13/0)</td>
</tr>
<tr>
<td>Wild type (IDH1/IDH2)</td>
<td>21/21 (88/100)</td>
</tr>
<tr>
<td>Month (95% CI)</td>
<td>Median Progression Free Survival (PFS) N=24</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>6.2 (3.7-8.8)</td>
<td>19.1 (6.7-31.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Survival Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months</td>
</tr>
<tr>
<td>54.2 (32.7-71.4)</td>
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<tr>
<td>95.8 (73.9-99.4)</td>
</tr>
<tr>
<td>At 12 months</td>
</tr>
<tr>
<td>29.2 (13.0-47.6)</td>
</tr>
<tr>
<td>87.5 (66.1-95.8)</td>
</tr>
<tr>
<td>At 18 months</td>
</tr>
<tr>
<td>25.0 (10.2-43.1)</td>
</tr>
<tr>
<td>54.2 (32.7-71.4)</td>
</tr>
<tr>
<td>At 24 months</td>
</tr>
<tr>
<td>25.0 (10.2-43.1)</td>
</tr>
<tr>
<td>50.0 (29.1-67.8)</td>
</tr>
<tr>
<td>At 30 months</td>
</tr>
<tr>
<td>16.7 (5.2-33.7)</td>
</tr>
<tr>
<td>45.5 (25.2-63.7)</td>
</tr>
<tr>
<td>At 36 months</td>
</tr>
<tr>
<td>12.5 (3.1-28.7)</td>
</tr>
<tr>
<td>34.1 (15.4-53.9)</td>
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<tr>
<td>At 48 months</td>
</tr>
<tr>
<td>NA</td>
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<tr>
<td>34.1 (15.4-53.9)</td>
</tr>
<tr>
<td>At 60 months</td>
</tr>
<tr>
<td>NA</td>
</tr>
<tr>
<td>34.1 (15.4-53.9)</td>
</tr>
</tbody>
</table>
Results: MGMT methylated patients with longer PFS and OS

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>PFS (Month)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MGMT-methylated</td>
<td>24.7 (8.5-41.0) a)</td>
<td>10.3 (6.5-14.0)</td>
<td>14.1 (10.5-16.1)</td>
</tr>
<tr>
<td>MGMT-unmethylated</td>
<td>5.1 (3.9-6.2) a)</td>
<td>5.3 (5.0-7.6)</td>
<td>8.2 (7.5-9.2)</td>
</tr>
<tr>
<td>Log rank test</td>
<td>P=0.00004</td>
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<td></td>
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<tr>
<td><strong>OS (Month)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT-methylated</td>
<td>61 (NR) a)</td>
<td>21.7 (17.4-30.4)</td>
<td>23.2 (20.1-28.3)</td>
</tr>
<tr>
<td></td>
<td>49.4 (38.3-60.6) b)</td>
<td></td>
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</tr>
<tr>
<td>MGMT-unmethylated</td>
<td>16.4 (11.8-21.0) a)</td>
<td>12.7 (11.6-14.4)</td>
<td>14.3 (13.6-15.3)</td>
</tr>
<tr>
<td></td>
<td>15.6 (12.3-18.9) b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log rank test</td>
<td>P=0.0002</td>
<td></td>
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</tbody>
</table>

a) Median value (95% Confidence Interval bounds). NR: the upper bound of 95% confidence interval could not be researched because 7 out of 10 patients were still alive at the time of the data analysis.
b) Mean value (95% Confidence Interval bounds), which was used for statistical comparison because of the above reason in NR.)
Summary: Current treatment for GBM

Newly Diagnosed → Surgery

Temodar Plus Radiation

Recurrence

Clin Trials

Temodar Plus Optune

Clin Trials

Avastin or Other chemo (CCNU, PCV et al) or Optune

Clin Trials

Palliative care/Hospice

Supportive care for: seizure, DVT, PE, infection, headache, falls, PT/OT/ST
Current therapy for GBM

• Conventional tumor treatment
  – Surgery
  – Radiation
  – Chemotherapy

• Advance in tumor treatment
  – Device- Optune/NOVO TTF (Tumor Treating Field)
  – Angiogenesis (VEGF) inhibitors

• Ongoing clinical trials
  – Immunotherapy-trials in primary brain tumor
  – Target therapy- trials in primary brain tumor
  – Proteosome inhibitors
Acknowledgement for those who manage neuro-oncology patients

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  Dr. Daniela Bota
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  Beverly Fu, NP
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  Marilou Schoffstall
  Michelle Willet

- Other Services
  General Neurology Medicine
  Hem/Oncology
  Rehabilitation

- Surgical Neurological Oncology
  Dr. Frank Hsu
  Dr. Mark Linskey
  Dr. Jeff Chen
  Dr. Kiarash Golshani
  Dr. Gilbert Cadena

- Rad-Onc Brain Tumor Group
  Dr. Nilam Ramsinghani
  Dr. Jeffery Kuo
  Dr. Parima Darouei

- Neuropathology
  Dr. Ronald Kim

- Neuroradiology
  Dr. Anton Hasso
  Dr. Daniel Chow
  Dr. David Floriolli

- Tumor board
  Muth, Paula
References

- Styczynski et al. Activity of Bortezomib in glioblastoma. Anticancer research 2006;26:4499-504
THANK YOU

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