Grey Matters: Together with Courage

New and Emerging Medical Therapies

Nicole Shonka, MD
Associate Professor
Division of Oncology & Hematology
Disclosures

I have no financial disclosures

Member of the National Comprehensive Cancer Network (NCCN) CNS tumors working group

Track leader, Cancer Education Committee, CNS tumors group for ASCO 2017

Planning team member, Clinical Science Symposium CNS tumors group for ASCO 2017
Optune delivers TTFIELDS to selectively disrupt mitosis\textsuperscript{1,2}

- **Metaphase (A)\textsuperscript{1}**
  - Impair microtubule assembly

- **Anaphase (B)\textsuperscript{3}**
  - Impede midline localization of cytokinetic band
  - Induce cytoplasmic blebbing and mitotic failure
  - Cause asymmetric chromosome segregation

- **Telophase (C)\textsuperscript{1}**
  - Induce intracellular dielectrophoresis of macromolecules and organelles
Optune added to first line therapy in GBM

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population

A) Progression-free survival

- TTFields plus temozolomide
- Temozolomide alone

HR, 0.62 (98.7% CI, 0.43-0.89); log-rank P = .001

B) Overall survival

- TTFields plus temozolomide
- Temozolomide alone

HR, 0.74 (95% CI, 0.56-0.98); log-rank P = .03

Survival analyses on time from date of randomization until tumor progression, death, or last follow-up (censored patients) according to the Kaplan-Meier method. The small vertical ticks on the curves indicate censored patients. HR indicates hazard ratio; TTFields, tumor-treating fields.

JAMA. 2015 Dec 15;314(23):2535
Intratumoral and Vaccine therapy
By nature’s design, RRVs selectively infect cancer due to immune deficiency.

RRVs infect tumors due to immune deficiency.

RRVs infect tumors due to immune deficiency.

RRV budding from infected cell

Normal brain cells (uninfected)

Brain tumor (infected with RRV)

TOCA-511 (on fast track with FDA)
Platform Selectively Infects Cancer Cells and Persists
Technology Built on Unique Retroviral Replicating Vector (RRV)

Creates a factory for RRV production

Toca 511, first RRV, Delivers Prodrug Activator Gene, CD

Regulatory genes → Structural RRV genes → CD gene → Regulatory genes

Optimized CD (cytosine deaminase)

5-FU has a very short half-life with direct cell killing localized to cancer microenvironment

5-FC (Toca FC) Antifungal Prodrug

5-FU Anticancer Drug

Copyright
**Study Ongoing – Overall and Subgroup Survival Compared to Historical Benchmarks**

<table>
<thead>
<tr>
<th>Population (Efficacy Evaluable)*</th>
<th>N</th>
<th>Median Survival Months (95% CI)</th>
<th>Historical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent high grade glioma (HGG)</td>
<td>43</td>
<td>13.6 (10.8, 20.0)</td>
<td>7.2 (n=110)²</td>
</tr>
<tr>
<td>Recurrent HGG, 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; recurrence</td>
<td>32</td>
<td>14.4 (11.3, 32.3)</td>
<td></td>
</tr>
<tr>
<td>Recurrent GBM</td>
<td>35</td>
<td>11.6 (9.2, 14.6)</td>
<td></td>
</tr>
<tr>
<td>Recurrent GBM, 1&lt;sup&gt;st&lt;/sup&gt; and 2&lt;sup&gt;nd&lt;/sup&gt; recurrence</td>
<td>27</td>
<td>13.6 (11.1, 20.0)</td>
<td>7.2-8.2²</td>
</tr>
</tbody>
</table>

Recurrent HGG
- OS6: 87.9%
- OS9: 72.4%
- OS12: 52.5%
- OS 24: 31.6%

---

*Efficacy evaluable population included all subjects who received at least one dose of Toca 511 and one full course of Toca FC
1) Brem et. al., Lancet 345: 1008-1012, 1995
Dendritic cell vaccine (DC Vax)

Dendritic cells orchestrate the immune response
activate hundreds of anti-cancer cells
Typically require patient’s own tumor tissue

Phase III for newly dx GBM
Randomization 2:1 DCVaxL vs placebo
Crossover allowed at progression
Dec 8, 2016: CTA (331 pts enrolled)

Problems: GTR and enough tissue to make vaccine
Stimulating dendritic cells

- Cytomegalovirus (CMV) RNA found in >90% Glioblastoma
- 13 patients with GBM that had been entirely removed had radiation + Temodar
- Each was given a shot on one thigh of either mature DC cells OR Tetanus/diphtheria toxoid
- Each patient then was vaccinated in both legs with DCs that were conditioned against CMV
- Those who had Td toxoid injected had greater numbers of DCs accumulate in the lymph nodes draining that leg
Tetanus toxoid improves DC vaccine

Td group had enhanced DC migration and OS
Oncolytic polio/rhinovirus recombinant (PVS-RIPO)

• Type of poliovirus mixed with rhinovirus to keep it from causing polio

  Recognizes CD155, an antigen expressed on most cancer cells

  Ability of PVS-RIPO to kill depends on chemical abnormalities only present in cancer cells

  Injected directly into the tumor

  Patients must have an anti-polio titer

• In recurrent GBM, at 24 months, 23.3% vs 13.7% historical controls living

  (80% PVSRIPO patients had GTR vs 58.9% controls)
EGFR variant III-rindopepimut

March 2016 negative study
• Control 21.1 mos OS vs
• RINTEGA 20.4 mos OS

Progressive EGFRvIII mutant GBM randomized to RINTEGA plus bevacizumab vs KLH injection plus bevacizumab
Group 1 (bev-naïve) updated at SNO November 2015: 2 year OS 25% in study group vs 0% in controls
Immune and Targeted therapy
Nivolumab Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function\(^\text{10}\)

- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function\(^\text{11-13}\)
CHECKmate-143  
nivolumab +/- ipilimumab in recurrent GBM  
• Anti PD-1 Ab Nivolumab with/without Anti-CTLA-4 Ab Ipilimumab  
  First progression after CRT  
  N=nivolumab, I=ipilimumab

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Number of patients</th>
<th>Regimen</th>
<th>12 mo OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>N3-I1</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N1-I3</td>
<td>30%</td>
</tr>
<tr>
<td>1B</td>
<td>20</td>
<td>N alone</td>
<td>40% **</td>
</tr>
</tbody>
</table>

J Clin Oncol 34, 2016 (suppl; abstr 2014)
Genetic alterations in GBM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary glioblastoma, % (95%)</th>
<th>Secondary glioblastoma, % (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promoter methylation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGMT</td>
<td>36</td>
<td>75</td>
</tr>
<tr>
<td>TIMP-3</td>
<td>28</td>
<td>71</td>
</tr>
<tr>
<td>RB</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>CDKN2A-p14^ARF</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>CDKN2A-p16^INK4a</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Genetic alterations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1 mutation</td>
<td>5</td>
<td>67–85</td>
</tr>
<tr>
<td>IDH2 mutation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EGFR amplification</td>
<td>36–60</td>
<td>8</td>
</tr>
<tr>
<td>TERT mutation</td>
<td>58</td>
<td>28</td>
</tr>
<tr>
<td>CDKN2A-p16^INK4a deletion</td>
<td>31–78</td>
<td>19</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>LOH 10p</td>
<td>47</td>
<td>8</td>
</tr>
<tr>
<td>LOH 10q</td>
<td>47; 70</td>
<td>54; 63</td>
</tr>
<tr>
<td>LOH 12q</td>
<td>41</td>
<td>82</td>
</tr>
<tr>
<td>LOH 1p</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>LOH 13q</td>
<td>12</td>
<td>38</td>
</tr>
<tr>
<td>LOH 19q</td>
<td>6</td>
<td>54</td>
</tr>
</tbody>
</table>

IDH mutations are the most common genetic alteration in secondary GBM, whereas EGFR amplification is highly likely in primary GBM.
Afatinib in GBM

- Afatinib +/- Temozolomide in unselected recurrent GBM. PFS and OS no different in entire group.
  PFS 2.73 mos combination therapy vs 1.87 mos if IHC++ EGFRvIII or FISH+ EGFR amplification with PTEN loss.

- Case report 58 y/o F with GBM. PFS after 2^{nd} recurrence >5 years.
  63 cycles Afa+TMZ
  EGFR amp + EGFRvIII mut.

Neuro-Oncology 17(3), 430–439, 2015
Oncotarget 2015 Oct 20;6(32):34030-7
ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 152,806 studies with locations in all 50 states and in 184 countries.

Search for Studies
Example: “Heart attack” AND “Los Angeles”

Search Help
- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies
- Non-U.S. Only (50%)
- U.S. Only (44%)
- Both U.S. & Non-U.S. (6%)

Total N = 31,003 studies
Data as of September 30, 2013
- See more trends, charts, and maps

For Patients & Families
- How to find studies
- See studies by topic
- Learn about clinical studies
- Learn more…

For Researchers
- How to submit studies
- Download content for analysis
- About the results database
- Learn more…

For Study Record Managers
- Why register?
- How to register study records
- FDCAA 801 Requirements
- Learn more…

Learn More
- ClinicalTrials.gov Online Training
- Glossary of common site terms
- For the Press
- Using our RSS Feeds
Thank You!

nshonka@unmc.edu