Brain Tumor Immunotherapy: Against All Odds

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Disclosures

• Research support from:
  • Northwest Biotherapeutics, Inc.

• Consultant for:
  • Arbor Pharmaceuticals
  • Actuate Therapeutics
Western Neurosurgical Society (1997)

WNS Lanai, HI; 1996

WNS Ojai, CA; 1997

**Treataement of Intracranial Gliomas with Bone Marrow-Derived Dendritic Cells Pulsed with Tumor Antigens**
“Treatment of intracranial gliomas with bone marrow-derived dendritic cells pulsed with tumor antigens”

CD8+ T cells

Control DC treated

Liau LM et al, J Neurosurg, 1999
NIH K08-CA82666
First-in-human treatment of a patient by vaccination with autologous dendritic cells pulsed with glioma peptides

WNS Mauna Lani, 2000
DC-based vaccine: Each “Educated” Dendritic Cell Activates Hundreds of Anti-Cancer T Cells

- Resting anti-cancer T cell attaches to DC
- Dendritic Cell
- Tumor target proteins
- Activated anti-cancer T cell activated
- Activated anti-cancer T cells divide rapidly
- Activated anti-cancer T cells travel to tumor site
FDA IND #8434: Phase I Clinical Trial of DC Immunotherapy for Malignant Gliomas

Leukapheresis (Day −7) → Monocyte (DC precursor) enrichment → DCs develop in cell culture

Antigens (acid-eluted peptides, autologous tumor lysates) from surgical resection → Cultured dendritic cells

3 bi-weekly Injections (Days 0, 14, 28) + GM-CSF + IL-4

NIH R21-CA91545 (2001)
First in human clinical trial of brain cancer vaccine
DC vaccination in glioblastoma patients induces systemic and intracranial T-cell responses modulated by the local CNS brain tumor microenvironment.

Increased CD8+ T-cell infiltration correlated with increased survival.

Increased TGF-β expression correlated with decreased survival.

Patient #1: OS = 30.2 mos
Patient #2: OS = 11.4 mos
Patient #12: OS = 9.3 mos.
Patient #5: OS > 120 mos.

Phase I/II clinical trial of DC-tumor lysate vaccine: Survival of glioblastoma patients from time of diagnosis

<table>
<thead>
<tr>
<th>Patient population</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
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<tbody>
<tr>
<td>DC vaccine treated (n=23)</td>
<td>91</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>Institutional controls (n=119)</td>
<td>69</td>
<td>34</td>
<td>21</td>
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<tr>
<td>Stupp et al. 2005 (n=287)</td>
<td>61</td>
<td>26</td>
<td>20</td>
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<tr>
<td>Mirimanoff et al. RPA III</td>
<td>32</td>
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<tr>
<td>Mirimanoff et al. RPA IV</td>
<td>19</td>
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</tbody>
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Median survival = 31.4 mos.

Liau LM et al, Cancer Res, 2000
Liau LM et al, Cancer Res, 2002
Liau LM et al., Clin Cancer Res, 2005
Prins RM & Liau LM, NEJM, 2008
NIH funding

• R01-CA112358
• R01-CA121131
• R01-CA123396
• K01-CA111402 (mentor)

WNS, Hawaii 2007
Collaboration with Industry: Clinical Development of DCVax-L®

Linda Powers, CEO

First Phase I trial in GBM at UCLA 2000-2002

Second Phase I/II trial in GBM at UCLA 2003-06¹

Non-blinded, randomized

FDA grants first IND

Collaboration with Northwest Biotherapeutics, Inc.

UCLA Health
Gene expression profile correlates with increased survival in glioblastoma patients vaccinated with DC immunotherapy

“Mesenchymal” gene expression signature associated with increased tumor-infiltrating lymphocytes

Prins RM et al., *Clin Cancer Res*, 2011
Tumor-infiltrating lymphocyte content is predictive biomarker of survival after DC vaccination

Hsu MS et al., *Cancer Immunol Res*, 2016
Increases in TCR overlap in tumor vs. peripheral blood leads to increased survival

**OS = 71.3 mos**

**OS = 6.3 mos**

Hsu MS et al., *Cancer Immunol Res*, 2016
PD-1 blockade enhances vaccination-induced immune response in glioma

Collaboration with Industry: Clinical Development of DCVax-L®

- First Phase I trial in GBM at UCLA 2000-2002
- Second Phase I/II trial in GBM at UCLA 2003-06
  - Multi-center Phase II Trial 2007
- Phase II trial in GBM 2010-12
- Phase III trial in GBM 2012—

- 1999
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- 2012

- FDA grants first IND
- Collaboration with Northwest Biotherapeutics, Inc.
- FDA approves Phase III status
Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=331)
Phase III multi-center, randomized clinical trial of DCVax-Brain™ for newly diagnosed GBM (n=331)

Northwest Biotherapeutics Protocol 020221 Site Map

$50 million
50 sites in US, Canada, UK, Germany
Phase III DCVax-L® Trial Design

• Multi-center, double-blind, randomized, placebo controlled trial

• 348 newly diagnosed GBM patients, randomized 2:1 (treatment:placebo) with cross-over

• DCVax-L adjuvant to standard of care (surgery, radiation, Temodar); injections interspersed with adjuvant Temodar

• Centralized imaging review with reassessment of pseudo-progression

• Primary endpoint: Progression-Free Survival
• Secondary endpoints: Overall Survival, TTP, Immune Responses, Safety, Landmark analyses for survival
DCVax-L Phase III Trial for GBM – Projections

• Recruitment completed in U.S. (n = 331)

• Final analysis by early 2017 (depending on events)

• Regardless of efficacy of DCVax-L® for GBM, there will be a wealth of clinical information, centralized imaging, and tumor/blood samples for genomic subgroup analysis, development of immunological biomarkers, and new avenues of clinical research.
THANK YOU!

UCLA Department of Neurosurgery