Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination for Glioblastoma

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Frontiers in Cancer Immunotherapy
New York Academy of Science

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Presentation Overview

Innovative Trial Design of DCVax®-L Phase 3 Trial

Results of DCVax®-L Phase 3 Trial
GBM Is a Particularly Difficult Cancer

Most common and lethal primary brain cancer

- Aggressive
- Immunologically “cold”
- Extremely heterogeneous
- Invasive phenotype; difficult to resect
- Nearly 100% recurrence rate

Standard of Care (SOC)
Surgery + 6 weeks daily chemo/radiation + monthly chemo

Survival

Newly diagnosed GBM patients: mOS ~15-17 months from surgery
Time to tumor recurrence: ~7-8 months from surgery
Recurrent GBM patients: mOS ~8 months from recurrence
5-year survival: <5%
GBM Clinical Trials – Years of Failures; Wide Range of Treatments Tested

2005-2016

- 417 clinical trials for Glioblastoma;
- 31,952 patients
- only 16 Phase 3 trials; only 1 positive (TFF device)

2016-2021

More failures of large Glioblastoma trials

- Checkpoint inhibitors
- CAR-Ts
- Peptide vaccines
- Gene therapy
- Chemo
- DCs + standardized peptides
GBM Survival Remains Dismal

- Temodar approved for newly diagnosed GBM in 2005 based on adding 2.5 months’ survival

- No systemic treatment has extended newly diagnosed GBM survival in 17 years since then

- Gliadel wafer approved for recurrent GBM in 1995 based on adding 2 months’ survival

- No treatment of any type has extended recurrent GBM survival in 27 years since then
DCVax®-L Phase 3 Trial: Innovative Trial Design
Trial Overview

Treatment: Autologous dendritic cells (DCs) pulsed with autologous tumor lysate (DCVax®-L). Intra-dermal injections in arm.

Trial design: Double-blind randomized trial with crossover

331 patients, 94 trial sites in 4 countries
(one of the largest trials of a personalized cell therapy)

Timeline:
- Began 2007
- Enrollment suspended 2008-2011 for financial reasons
- 92% of patients enrolled 2012-2015
- Last patient enrolled November 2015
- Long-term survival follow-up to determine survival tail
Screening and Enrollment

Surgery (<1 week after start of screening)
Leukapheresis (~3 weeks after surgery)

Day 0: Enrollment and Randomization (~10 days after eligibility scan)

Chemo/radiation (6 weeks)

Treatment with DCVax-L or Placebo + SOC adjuvant temozolomide

Manufacturing of DCVax-L for all prospective patients

Average time: 3.1 months

Start of Screening

End of Screening

Treatment Schedule

3 treatments in Month 1: Days 0, 10, 20
3 booster treatments: Months 2, 4, 8
Treatments 2X per year for maintenance
Crossover Design

All patients could cross over to receive DCVax-L following tumor recurrence

All parties (patients, physicians, sponsor, CRO) remained blinded as to what treatment received before crossover

Crossover was necessary for feasibility and ethical reasons:

- **Necessary for enrollment and retention of patients** in era when immune therapies not yet generally viewed as promising for cancer

- Important to justify all patients undergoing **invasive leukapheresis procedure**. No benefit to placebo patients unless they could receive their autologous product made from the leukapheresis.
Progression Free Survival & Pseudo-Progression

Original primary endpoint, when trial designed in 2007: Progression-Free Survival (PFS)

While the trial was underway, Pseudo-progression (PsPD) became recognized as major issue -- difficulty distinguishing real vs. PsPD

PsPD is an even bigger issue with immune cell therapies: vaccine-induced infiltration of immune cells

PFS endpoint not feasible due to PsPD. So, SAP focused on OS, and specified OS as the primary endpoint before unblinding.
• PFS was not significantly different between the DCVax-L arm and placebo arm: p=0.47

• mPFS was 6.2 months (95% CI: 5.7-7.4 months) for DCVax-L patients; mPFS was 7.6 months (95% CI: 5.6-10.9 months) for placebo patients

• The results in DCVax-L patients may reflect vaccine-induced PsPD.
Overall Survival Endpoints & External Controls

Since PFS was not feasible as the primary endpoint, due to PsPD, the SAP focused OS endpoints.

OS endpoints **could not be within-study comparisons** of DCVax-L patients vs. placebo patients, because placebo patients received DCVax-L following crossover.

So, the OS endpoints compared DCVax-L patients with **external controls**.

This approach fits well with growing commentary in support of streamlined trial designs and use of external controls where classic within-study comparisons are not feasible.

**This approach also enabled two OS endpoints: nGBM and rGBM.**
Primary Endpoint: OS in newly diagnosed GBM
DCVax-L arm (n=232) vs. External controls (n=1,366) (control arms of external studies)

Secondary Endpoint: OS in recurrent GBM
Placebo arm crossovers* (n=64) vs. External controls (n=640) *(Placebo arm patients received only SOC + placebo until recurrence, then DCVax-L) (control arms of external studies)

This SAP and its Endpoints were pre-specified and submitted to regulators before unblinding.
External Controls: Sources and Validation
External Controls: Process & Selection Criteria

Independent expert firm (not sponsor) evaluated other GBM trials, and selected the most closely matched using 14 criteria:

- Contemporaneous, same patient population, same SOC, RCT design, etc.

The independent expert selected 5 nGBM trials & 10 rGBM trials

The control arm patients from these comparator trials served as the external controls for the DCVax-L trial

- Controls from nGBM trials => controls for nGBM DCVax-L patients
- Controls from rGBM trials => controls for rGBM DCVax-L patients

These external controls were pre-specified in the Statistical Analysis Plan (SAP) for the DCVax-L trial
External Controls: Validation

4 sets of analyses were conducted to obtain controls rigorously matched to the DCVax-L study population, minimize potential biases and confirm the robustness of the survival results.

1. Matching of the DCVax-L trial and the comparator trials
   Matching of the trials whose control arm patients served as external controls for DCVax-L trial, using 14 criteria as described above.

2. Validation of the external controls approach
   For each comparator study, the treatment arm was compared against the external controls determined for DCVax-L trial. For each of the 15 comparator studies, results were same as originally reported.
3. Sensitivity analyses to check for comparator differences

5 sensitivity analyses conducted, removing each of the 5 comparator studies for nGBM, one at a time. No change in comparison with DCVax-L trial seen.

6th sensitivity analysis removed 2 of the 5 comparator trials, in which it was unclear whether they excluded patients with early progression as did other 3 comparators and the DCVax-L trial. No change in comparison seen.

4. Adjustments for individual patient characteristics

Matching Adjusted Indirect Comparison (MAIC) methodology used to adjust for even small differences in individual patient characteristics. Comparison of DCVax-L vs. external controls OS remained statistically significant. (Propensity score matching was not feasible with the available data.)
# External Controls for nGBM – 5 Comparator RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median OS (months)</th>
<th>95 CI (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilbert et al 2013</td>
<td>411</td>
<td>16.6</td>
<td>14.9 – 18.0</td>
</tr>
<tr>
<td>Gilbert et al. 2014</td>
<td>309</td>
<td>16.1</td>
<td>14.8 – 18.7</td>
</tr>
<tr>
<td>Weller et al. 2017</td>
<td>374</td>
<td>17.4</td>
<td>16.2 – 18.8</td>
</tr>
<tr>
<td>Stupp et al. 2017</td>
<td>229</td>
<td>16.0</td>
<td>14.0 – 18.4</td>
</tr>
<tr>
<td>Wen et al. 2019</td>
<td>43</td>
<td>15.0</td>
<td>12.3 – 23.1</td>
</tr>
<tr>
<td><strong>Aggregate Newly Diagnosed(^1)</strong></td>
<td><strong>1,366</strong></td>
<td><strong>16.5</strong></td>
<td><strong>16.0 – 17.5</strong></td>
</tr>
</tbody>
</table>

1) Based on reconstructed individual patient data (IPD)

These are leading contemporaneous studies in the field; well known.
# External Controls for nGBM – Patient Demographics and Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>KPS</th>
<th>MGMT</th>
<th>IDH-1</th>
<th>Resection</th>
<th>Res. Disease</th>
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<td>73</td>
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<td>42</td>
<td>34</td>
<td>66</td>
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<td><strong>Gilbert 2013</strong></td>
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<td><strong>Weller 2017</strong></td>
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<td><strong>Wen 2019</strong></td>
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<tr>
<td><strong>All nGBM ECP</strong></td>
<td>1366</td>
<td>25</td>
<td>75</td>
<td>77</td>
<td>23</td>
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<td>38</td>
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<tr>
<td><strong>nGBM DCVax</strong></td>
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<td>75</td>
<td>78</td>
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<th>Newly Diagnosed GBM (nGBM)</th>
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<th>Part</th>
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<tr>
<td>74</td>
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</table>
## External Controls for rGBM – 10 Comparator RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median OS (months)</th>
<th>95 CI (months)</th>
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</thead>
<tbody>
<tr>
<td>Wick et al. 2010</td>
<td>92</td>
<td>7.1</td>
<td>6.0 – 8.8</td>
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<tr>
<td>Taal et al. 2014</td>
<td>46</td>
<td>8.0</td>
<td>6.0 – 11.0</td>
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<tr>
<td>Brandes et al. 2016</td>
<td>40</td>
<td>7.5</td>
<td>5.6 – 10.3</td>
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<tr>
<td>Cloughesy et al. 2017</td>
<td>65</td>
<td>12.6</td>
<td>n.a.</td>
</tr>
<tr>
<td>Wick et al. 2017</td>
<td>149</td>
<td>8.6</td>
<td>7.6 – 10.4</td>
</tr>
<tr>
<td>Brandes et al. 2018</td>
<td>62</td>
<td>5.5</td>
<td>3.9 – 7.2</td>
</tr>
<tr>
<td>Galanis et al. 2019</td>
<td>38</td>
<td>7.7</td>
<td>n.a.</td>
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<tr>
<td>Lombardi et al. 2019</td>
<td>60</td>
<td>5.6</td>
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<tr>
<td>Narita et al. 2019</td>
<td>30</td>
<td>8.0</td>
<td>4.8 – 12.9</td>
</tr>
<tr>
<td>Lee et al. 2020</td>
<td>58</td>
<td>11.5</td>
<td>8.4 – 14.2</td>
</tr>
</tbody>
</table>

| Aggregate Recurrent GBM | 640 | 7.8          | 7.2 – 8.2      |

1) Based on reconstructed individual patient data (IPD);
2) not available from referenced publication
# External Controls for rGBM – Patient Demographics and Prognostic Factors

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Race</th>
<th>MGMT</th>
<th>IDH-1</th>
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<tr>
<td></td>
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<tr>
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<td><strong>All rGBM ECP</strong></td>
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<td><strong>75</strong></td>
<td><strong>63</strong></td>
<td><strong>38</strong></td>
</tr>
<tr>
<td><strong>rGBM DCVax</strong></td>
<td><strong>64</strong></td>
<td><strong>56</strong></td>
<td><strong>27</strong></td>
<td><strong>73</strong></td>
<td><strong>66</strong></td>
</tr>
</tbody>
</table>
020221 Study Results
Overall Results

- **Primary endpoint met (mOS in nGBM),** with statistical significance

- **Secondary endpoint met (mOS in rGBM),** with statistical significance

- **Excellent safety profile:**
  - 2,193 doses of DCVax®-L administered
  - only 5 SAEs at least possibly related
  - No autoimmune reactions
  - No cytokine storms
Overall Results – 5 Key Data Points

NEWLY DIAGNOSED GBM:

- mOS: 19.3 mos from randomization (22.4 mos from surgery) vs. 16.5 mos from randomization in controls

- mMGMT mOS: 30.2 mos from randomization (33 mos from surgery) vs 21.3 mos from randomization in controls

- Survival Tail: 13% vs 5.7% at 5 years

RECURRENT GBM:

- mOS: 13.2 mos vs. 7.8 mos from recurrence

- Survival Tail: 20.7% vs. 9.6% at 24 mos after recurrence
  11.1% vs. 5.1% at 30 mos after recurrence
Innovation

- First Phase 3 trial of a systemic treatment in 17 years to show a significant extension of mOS in nGBM.

- First Phase 3 trial of any type of treatment in 27 years to show a significant extension of mOS in rGBM.

- One of the first, if not the first, Phase 3 trial to show meaningful increases in the long-term tails of the survival curves in both nGBM and rGBM.
Broader Perspective

• DCVax-L suitable for combinations with wide range of other treatments
  (checkpoint inhibitors, oncolytic viruses, cytokines, chemo, etc.)

• When a DCVax-L patient has recurrence(s), new batch(es) of DCVax-L can be made
  (treatment targets not lost, as they are with targeted therapies)

• DCVax-L can potentially apply to any type of solid tumor
  (multiple other cancers treated in compassionate uses cases and a prior small pilot trial)

• DCVax-L can be administered in community settings as well as major cancer centers.
Future Opportunities for Combination Therapies

Datsi A, Sorg RV. *Frontiers in Immunology*, 2021
Newly Diagnosed GBM
Overall Survival in Newly Diagnosed GBM

Hazard Ratio 0.80 (-, 0.94)
DCVax-L vs External (98% CI)

p-value <0.002
1-sided log-rank

mOS of DCVax arm = 19.3 mos from randomization; 22.4 mos from surgery
mOS of controls = 16.5 mos from randomization
## Survival Tail In Newly Diagnosed GBM

### Landmark Survival Rate (%) in nGBM measured from date of randomization*
*(3 months after surgery)*

<table>
<thead>
<tr>
<th></th>
<th>External (n = 1366)</th>
<th>DCVax-L (n=232)</th>
<th>Comparative Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>15.5%</td>
<td>20.2%</td>
<td>130%</td>
</tr>
<tr>
<td>48 months</td>
<td>9.9%</td>
<td>15.7%</td>
<td>159%</td>
</tr>
<tr>
<td>60 months</td>
<td>5.7%</td>
<td>13.0%</td>
<td>&gt;228%</td>
</tr>
</tbody>
</table>
Pre-Defined Sub-Groups: Summary

Hazard Ratio (two-sided 95% CI)

- Age ≥ 65
  - 0.4
  - 0.63
  - 0.99

- Age < 65
  - 0.62
  - 0.78
  - 0.98

- Significant Residual Disease
  - 0.48
  - 0.65
  - 0.87

- Minimal Residual Disease
  - 0.73
  - 0.95
  - 1.22

- MGMT Methylated
  - 0.55
  - 0.74
  - 1.0

- MGMT Unmethylated
  - 0.75
  - 0.93
  - 1.14
Newly Diagnosed GBM: Age ≥ 65

Hazard Ratio 0.63 (--, 0.99)
DCVax-L vs External (97.591% CI)

p-value 0.021
1-sided log-rank

Probability of Overall Survival

Months from Randomization

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>50</th>
<th>30</th>
<th>17</th>
<th>11</th>
<th>6</th>
<th>5</th>
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<tr>
<td>45</td>
<td>24</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Newly Diagnosed GBM: Age < 65

Hazard Ratio 0.78 (0.7, 0.98)
DCVax-L vs External (97.59% CI)

p-value 0.016
1-sided log-rank
Newly Diagnosed GBM: Significant Residual Disease

Hazard Ratio 0.56 (-, 0.71)
DCVax-L vs External (97.591% CI)

p-value < 0.001
1-sided log-rank

Number of Patients at Risk:

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tr>
<td>External Controls</td>
<td>163</td>
<td>98</td>
<td>19</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>DCVax-L</td>
<td>86</td>
<td>63</td>
<td>25</td>
<td>14</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>
Newly Diagnosed GBM: Minimal Residual Disease

Hazard Ratio 1.01 (-, 1.43)
DCVax-L vs External (97.591% CI)

p-value 0.524
1-sided log-rank

Probability of Overall Survival

Months from Randomization

Number at Risk

146 115 56 31 22 16
210 169 53 7 0 0
Newly Diagnosed GBM: MGMT Methylated

Hazard Ratio 0.74 (-, 1.19)
DCVax-L vs External (99.9% CI)

p-value 0.027
1-sided log-rank

mMGMT DCVax-L patients mOS = 30.2 mos from randomization; 33 mos from surgery
mMGMT control patients mOS = 21.3 mos from randomization
Newly Diagnosed GBM: MGMT Unmethylated

Hazard Ratio 0.93 (-, 1.15)
DCVax-L vs External (97.591% CI)

p-value 0.238
1-sided log-rank

Probability of Overall Survival

Months from Randomization

Number at Risk

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<thead>
<tr>
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<tbody>
<tr>
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<td>207</td>
<td>73</td>
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<td>4</td>
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Recurrent GBM
Overall Survival in Recurrent GBM

Hazard Ratio 0.58 (-, 0.76)
Placebo Crossed Over vs. External (97.591% CI)

p-value <0.001
1-sided log-rank

mOS = 13.2 months from recurrence with DCVax-L vs. 7.8 months in controls
## Survival Tail in Recurrent GBM

<table>
<thead>
<tr>
<th>Landmark Survival Rate (%) in rGBM Measured from Date of Recurrence</th>
<th>External* (N = 640)</th>
<th>DCVax-L (N = 64)</th>
<th>Comparative Increase</th>
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</thead>
<tbody>
<tr>
<td>6 months</td>
<td>64.0%</td>
<td>90.6%</td>
<td>142%</td>
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<tr>
<td>12 months</td>
<td>30.8%</td>
<td>54.1%</td>
<td>175%</td>
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<td>18 months</td>
<td>15.9%</td>
<td>31.8%</td>
<td>200%</td>
</tr>
<tr>
<td>24 months</td>
<td>9.6%</td>
<td>20.7%</td>
<td>215%</td>
</tr>
<tr>
<td>30 months</td>
<td>5.1%</td>
<td>11.1%</td>
<td>217%</td>
</tr>
</tbody>
</table>
Why/How Does DCVax-L Work?
Key Characteristics of DCVax-L

1. Uses master cells of immune system: dendritic cells
   - Mobilizes multiple elements of the immune system

2. Fully personalized
   - Inherently targets antigens actually on the patient’s tumor -- fits the patient’s version of the cancer.

3. Uses **ALL** tumor antigens, not just 1 or a few
   - Makes it difficult for tumors to mutate around the antigens targeted. Minimizes tumor escape after (or during) treatment.

Addresses extensive complexity and variability of solid tumors.
Large Multiplier: Dendritic Cell Activates

**Hundreds of T Cells, Diverse T Cells & Other Immune Cells**

- Dendritic Cell
- **tumor target proteins**
- anti-cancer T cell activated
- resting anti-cancer T cell attaches to DC
- activated anti-cancer T cells divide rapidly
- activated anti-cancer T cells travel to tumor site
T Cells Can Cross the Blood Brain Barrier; T Cells Infiltrate Glioblastoma Tumors After DCVax-L

Infiltration of T cells into Glioblastoma tumors is observed in patients treated with DCVax®-L

Both CD4 and CD8 T cells are seen

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Conclusions (1)

• The completion of a large, phase 3 trial including 331 patients, 94 sites, over 70 clinical investigators, in 4 countries using an autologous, dendritic cell, tumor lysate (DCVax-L) shows efficacy to meet the primary and secondary end-points of an increase in O.S. for nGBM and rGBM

• The vaccine is easily administered and has a favorable safety profile.

• The use of external, contemporaneous clinical trials (n = 5 for nGBM and n =10 for rGBM) is innovative, and going forward, could be transformative given the poor track record and numerous failed trails in neuro-oncology.

• There is a significant percentage of long-term survivors, consistent with an immune memory effect by the T-cells, potentially changing the natural history of GBM from a uniformly fatal to a chronic, manageable disease.
Conclusions (2)

• Specific subpopulations show an unanticipated benefit including; a) older patients, and b) patients with residual disease after surgery. As expected, patients with methylated MGMT promoter fare better than unmethylated group.

• The feasibility of the vaccination process enables widespread application in the community setting, as well as in major academic centers of excellence.

• The use of dendritic cells as the master, professional antigen presenting cells allows for combination therapy using other approaches such as blockade of immunosuppressive cytokines, CAR T cells, viral oncolytic therapy, electric field therapy, DNA vaccines, etc.

• Preliminary data shows evidence of T cell infiltration into the target tissue (Glioblastoma).
Summary

Patients treated with DCVax-L showed a clinically meaningful and statistically significant extension of survival...

...in both newly diagnosed and recurrent GBM,

...with an excellent safety profile, and

...noteworthy long tails of survival.
Acknowledgments

• **UCLA** (US lead): Prof. Linda Liau and Dr. Robert Prins

• **Kings College Hospital** (Europe lead): Prof. Keyoumars Ashkan

• **Trial Steering Committee:**
  - Prof. Steven Brem (UPenn)
  - Dr. Jian Campian (Wash. U., now Mayo Clinic)
  - Dr. Fabio Iwamoto (Columbia University)
  - Dr. John Trusheim (Allina Health)

• **Investigators and sub-investigators** of the 020221 trial

• **Patients and their families**