DCVax
Update on Clinical Programs

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DCVax® Personalized Immune Therapy

Personalized Product: personalized dendritic cells
(master cells of the immune system)

- Allows repeat doses, ongoing treatment

Personalized Targets: tumor antigens from patient’s own tumor

- Ensures proper targeting of the immune response

Broad Scope of Targets: full array of tumor antigens

- Not just 1 or several pre-selected, standardized antigens
- Maximizes obstacles to tumor “escape”

Excellent safety profile

- Some flu-like symptoms; no additional drugs, no hospital stays
Large Multiplier: Each Dendritic Cell Activates Hundreds of Anti-Cancer T Cells

- A resting anti-cancer T cell attaches to a Dendritic Cell (DC).
- The DC activates the anti-cancer T cell.
- Activated anti-cancer T cells divide rapidly.
- Activated anti-cancer T cells travel to the tumor site to target proteins.
### DCVax Potentially Applicable to All Types of Solid Tumors

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<thead>
<tr>
<th>Market</th>
<th>Product / Administration</th>
<th>Composition</th>
<th>Lead Program</th>
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<tbody>
<tr>
<td><strong>All Operable Solid Tumors</strong></td>
<td>DCVax®-L</td>
<td>Dendritic cells and full array of tumor antigens from tumor tissue sample surgically removed</td>
<td>Brain cancer&lt;br&gt;<strong>331-patient Phase III trial underway</strong>&lt;br&gt;Small ovarian cancer&lt;br&gt;Phase I/II trial completed</td>
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<td>Intra-dermal injection in arm</td>
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<tr>
<td><strong>All Inoperable Solid Tumors</strong></td>
<td>DCVax®-Direct</td>
<td>Dendritic cells directly injected into tumor(s); full set of tumor antigens picked up <em>in situ</em> in tumor</td>
<td>All solid tumors&lt;br&gt;(13 cancers treated to date)&lt;br&gt;<strong>40 patient Phase I completed</strong>&lt;br&gt;<em>Phase II trials pending</em></td>
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<tr>
<td>Direct injection into tumor</td>
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DCVax®-L for Newly Diagnosed Glioblastoma Multiforme (GBM)

Phase III Trial Update
DCVax-L® Phase III Trial Design

Newly diagnosed Glioblastoma multiforme (GBM).

Double-blind, randomized, placebo-controlled, multi-center, International trial.

331 patients enrolled, randomized 2:1 (DCVax-L: placebo).

Key eligibility and efficacy determinations through central review by independent experts:

- Diagnosis of GBM
- Extent of surgical resection
- Apparent rapid progression before enrollment (exclusion)
- Disease progression during the trial
Randomization and enrollment

Month 0

DCVax-L doses

Induction phase (Month 1)

Booster Phase (Months 2, 4, 8)

TMZ (approx.)

Maintenance phase (Twice a year)

DCVax-L Phase III Trial Design -- Treatment Schedule
DCVax-L Phase II Trial Design -- Crossover

• DCVax-L made for all patients during their 6 weeks of chemo/RT

• Patients initially randomized to SOC + DCVax-L may continue DCVax-L after progression

• Patients initially randomized to SOC + placebo may also receive DCVax-L after progression ("cross over")

• Approx. 90% of all patients in ITT received DCVax-L treatment

• All patients (from either arm) who receive DCVax-L after progression do so on same basis -- patients and investigators remain blinded, do not find out which arm they were in initially
DCVax-L Phase III Trial Design -- Endpoints

1 primary endpoint: progression free survival (PFS)

1 secondary endpoint: overall survival (OS)

Trial is powered both for PFS and for OS, independently

Multiple tertiary endpoints:

- Immune responses
- Decline in Karnofsky Performance Status (KPS)
- Landmark survival analyses
- Time to Progression (TTP)
DCVax-L Phase III Trial -- Enrollment Process

Initial screening & initial consent

Surgery

Leukapheresis

Baseline screening, enrollment & randomization

Radiation + temozolomide

Tumor lysate preparation

DCVax-L manufacturing and release

Main Reasons for Screen Failure:
- Not GBM
- Tumor too small
- Leukapheresis failure
- Progressive disease
DCVax-L Phase III Trial -- Enrollment Timeline

- Recruiting paused for economic reasons
- 50% Enrolled May 2014
- Fully enrolled (331) November 2015
DCVax Phase III Trial – Update

mOS with SOC is 15 - 17 months

Last enrollment in DCVax-L Phase III trial was 19 months ago
  ➢ Last screening/recruitment was 22 months ago

Median point of the overall trial enrollment was 37 months ago

Approx. 90% of all 331 patients in Phase III trial treated with DCVax-L

Approx. 100 patients still alive (231 OS events; a few lost to follow-up)

Minimum of 233 OS events expected before analyses

Minimum OS threshold anticipated to be reached in first half of July/mid-summer (approx. 2 OS events per month)

Publication about data in preparation with our investigators.
DCVax-L -- Excellent Safety Profile

DCVax-L administered more than 2,000 times to the 331 patients in the Phase III trial

Only 7 patients had an SAE “related” or “possibly related” to the DCVax-L treatments or placebo

• 5 nervous system disorders (e.g., seizure, edema); 1 gastrointestinal (nausea); 1 lymph node infection

Generally, AEs were related to underlying GBM or SOC/other treatments: 132 patients had SAEs considered unrelated to DCVax-L

Rate of adverse events with SOC + DCVax-L approximately same as rate of adverse events with SOC alone.
Patients not eligible to enroll in trial due to radiographic evidence of rapid disease progression prior to Baseline screening visit were accepted into an Information Arm.

Classifications (to Info Arm & within it) determined through Central Review by independent experts.

**Information Arm**

51 patients had evidence *(25% increase or new lesion >1 cm)* of disease progression in imaging at Baseline Visit following 6 weeks’ chemo-radiation

↓

Patients re-imaged at Month 2 after Baseline Visit to confirm actual disease progression *(another 25% increase or another new lesion >1 cm)*

(patients categorized by independent medical imaging company)

- 20 patients had further progression *(another 25% increase or new lesion >1 cm)* at Month 2: Rapid-Progressors
- 25 patients had stable disease, or modest (<25%) progression or regression at Month 2: Indeterminate
- 1 patient had all original 25% increase gone at Month 2: Confirmed Pseudo-progressor
- 5 patients Unclassified due to lack of images
Informational Arm: Indeterminate patients (N=25)

Overall Survival Update

mOS = 21.5 months
24% of patients have exceeded 48 mos. OS
40% of patients have exceeded 35 mos. OS

Comparison from literature:
surgery, RT+TMZ
mOS = 15 – 17 mos.
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DCVax®-Direct for
Inoperable Solid Tumors

Program Update
DCVax-Direct

- DCVax-Direct is comprised of partially activated, autologous dendritic cells for intra-tumoral injection
  - Partially activated DC retain the capability to take up antigen, and are irrevocably committed to full maturation

- In preclinical work, optimally activated DC were meaningfully more effective in clearing established tumors than immature DC

- DCVax-Direct is manufactured using a proprietary, automated manufacturing system
FROM: Killer dendritic cells: mechanisms of action and therapeutic implications for cancer  A K Wesa and W J Storkus
Modulation of the Tumor Microenvironment ("cold" to "hot" conversion)

Day 0

CD4

CD8

Day 7

Induction of Necrosis

Induction of cytotoxic T cells

Induction of PD-1
DCVax-Direct Phase I Trial

Trial was very information-rich, helping guide further development

• 13 different cancers treated, including very aggressive cancers
• 3 dose levels tested: 2M, 6M and 16M cells
• 2 different product formulations tested
• Feasibility of image-guided injections tested (multiple methods)
• Both imaging and biopsies used to monitor responses, correlate with clinical outcomes and evaluate treatment schedule
• Both local and systemic responses evaluated
• Potential endpoints evaluated, including tumor responses and disease control

Trial was also very conservative

• Only 1 tumor injected, although patients had multiple inoperable tumors
• Most patients received only 3 treatments (day 0, week 1, week 2); some received additional treatments (week 8 and beyond)
Cytokine production, especially TNFα, was correlated with tumor control.
DCVax-Direct Phase I Trial: Tumor Control, Stable Disease

- Stable Disease (SD) at week 8 was used as a measure of tumor control
- 23 of 37 (62%) of evaluable patients achieved SD at week 8
- SD at week 8 is predictive of longer survival

DCVax-Direct: All Phase I patients

![Graph showing survival rates with SD and PD, p<0.01]
Induction of Checkpoint Expression (PD-L1)

- 20 of 25 evaluable patients (80%) in DCVax-Direct Phase I trial showed either de novo or significantly increased expression of PD-L1 following DCVax-Direct treatment.

- Patient-to-patient variation in timing of when PD-L1 expression appears.

- At least in some types of cancers, PD-L1 expression is correlated with (and may predict) patient responsiveness to checkpoint inhibitors (e.g., gastric cancers).

De novo PD-L1 staining on sarcoma tissue, 8 weeks after initiation of DCVax-Direct treatment.
DCVax-Direct Phase I Trial: Survival Update

7 patients (18%) have exceeded 30 mos.
9 patients (23%) have exceeded 24 mos.
As of April 2017
Patients in the DCVax-Direct Phase I trial had exhausted other treatment options.

For such patients, several methods can be used to predict survival (e.g., RMH Score, MDACC Score, neutrophil – lymphocyte ratio).

Using the MDACC Score (Wheler et al. 2012), predicted survival was determined for all DCVax-Direct Phase I patients and compared to actual survival. Results were similar with other methods.

- 23 of 39 evaluable patients (59%) exceeded their expected survival time, by an average of 11 months.
- 7 of 8 sarcoma patients exceeded their expected survival times, by an average of 7 months.

Publication in preparation with our investigators, with more detailed information.
DCVax-Direct Phase I Trial: Excellent Safety Profile

- >140 treatments administered to 40 patients in Phase I trial
- 4 SAEs “related” or “possibly related” to DCVax-L treatment
  - Fevers (n=2), fever and chills (n=1), systemic inflammatory response syndrome (n=1)
- Most patients developed mild to moderate fevers following DCVax-Direct injections
  - Typically ≤ 2º C, and typically ≤ 2 days
- No dose limiting toxicities were observed at any of the dose levels (2 million, 6 million or 15 million DCs per injection)
DCVax-Direct Phase I Trial: Key Observations

- Activated DC can be safely administered intra-tumorally in patients with unresectable solid tumors

- Early T cell infiltration demonstrates modulation of the tumor microenvironment by the injected DC to allow influx of pre-existing anti-tumor T cells

- Later emerging T cell infiltration, coupled with the emergence of shared TCR sequences between tumor and blood, demonstrates induction of a systemic anti-tumor immune response

- Functional staining of infiltrating T cells for interferon gamma reveals cytokine production by these cells, which is indicative of cytotoxic T cell activity

- Induction of PD-L1 in tumor tissue in response to DCVax-Direct indicates the potential for combination therapy with immune checkpoint inhibitors
DCVax-Direct Phase I Trial: Key Observations (cont.)

- 23% of patients show long term survival (>24 months)

- DC quality, defined either phenotypically or by the production of soluble factors, is predictive for survival

- The noted correlations between cytokine/chemokine production and survival supports the hypothesized mechanisms of action of DCVax-Direct:
  - Direct killing of tumor cells
  - Making tumor micro-environment more permissive
  - Inducing anti-tumor T cells to initiate tumor cell killing

- DC-produced cytokines such as TNFα may be directly responsible for mediating tumor control in patients treated with DCVax-Direct

- Both local and systemic T cell responses observed
DCVax-Direct Phase II Trials: Plans

Enhanced trial design:
• More frequent immunizations, spaced closer together
• Multiple injections, into multiple tumors, at each visit
• Pre-conditioning of patient’s immune system with low dose cyclophosphamide
• More biopsies and other analytics

Multiple indications, building on Phase I trial experience
• All under same IND, but will be conducted separately
• Simply deliver an Indication Memo to sites to start each one

DCVax-Direct both alone and in combos with checkpoint inhibitors
• Where there is an approved CI, the trial will be combo
• Where there is no approved CI, trial will be DCVax-Direct alone
First DCVax-Direct Phase II Trial: Sarcoma

Approvals and agreements completed with a leading sarcoma center: Sarcoma Oncology Center (Dr. Sant Chawla)
- Anticipate beginning this summer

Both soft tissue sarcoma and osteosarcoma

Targeting adult patients who have relapsed following frontline treatments
- Significant unmet medical need in these patients
- Short survival times and lack of good treatment options, SOC
- Can later expand focus to include patients with profile at time of frontline treatment for high risk of later relapse
- Can later expand focus to include pediatric
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