DCVax-Direct
Dendritic Cell Therapy for Solid Tumors

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Scientific Background: DC and cancer

- Dendritic Cells (DC) are professional antigen-presenting cells which are required for inducing any adaptive immune response.
- In cancer subjects, factors produced by the tumor block functional maturation of DC.
- The tumor microenvironment is highly immuno-suppressive, and hampers induction of de novo immune responses as well as the function of effector cells.
- Thus, to generate an effective immune response in cancer subjects, DC must be generated ex vivo and the tumor microenvironment must be modified.
Scientific Background: DC Maturation

- Immature DC take up and process antigen
- Mature DC present antigen and activate the immune system, mainly through interaction with T cells
- DC maturation, i.e. the transition from immature to mature DC, is a time-dependent process that takes 48 – 72 hours
- Activated, or partially matured, DC have been exposed to maturation agents, and have been arrested in the maturation process by cryopreservation
- If done correctly, the DC will continue the maturation process after thawing
Scientific Background: Activated DC

- Activated DC:
  - Still pick up and process antigen (especially dead and dying tumor cells)
  - Continue the maturation process upon thawing as the required signal transduction pathways have been activated
  - Are less susceptible to the suppressive effects of the tumor microenvironment
  - Produce high amounts of cytokines to modulate tumor-based immunosuppression

Hypothesis: Activated DC will be more efficacious than immature DC or than fully mature DC
Scientific Background: Animal Data

• Experiment: CT26 colon carcinoma cells are implanted in the right and (3 days later) the left flanks of BALB/c mice
• After 15 days, the animals are given a low dose of intraperitoneal cyclophosphamide
• Next, either immature or activated DC are injected into the right-flank tumor only
• Tumor growth on both sides is followed over time
• Animals that clear their tumors are re-challenged 60 days later with 10-fold higher tumor cell dose
DCVax-Direct: Pre-Clinical Results

Tumor clearance on same side of body after direct injection in animal studies
Tumor clearance on opposite side of body after direct injection in animal studies

- Chemo only
- + partially activated DCs
- + immature DCs
- + optimally partially activated DCs
Preclinical Data: Conclusions

• Optimally activated DC are meaningfully more effective in clearing established tumors than immature DC
• The activation conditions are essential for maximum efficacy
• Clearance of non-injected tumors demonstrates effective systemic anti-tumor immunity
• Animals that have cleared their tumors demonstrate long-term protection from re-challenge
DCVax-Direct Phase I Trial

• DCVax-Direct: autologous, activated dendritic cells (DC) for intratumoral injection

• Indication: potentially applicable for any non-resectable (or partially resected) solid tumor, including
  – Lung cancer
  – Pancreatic cancer
  – Soft tissue sarcoma
  – Melanoma
  – Ovarian cancer
  – Etc., etc., etc.

• Manufactured at low cost in our proprietary system

• System designed to deliver maximum efficacy
Manufacturing system for DCVax-Direct
## DCVax Direct: Potential Clinical Effects

<table>
<thead>
<tr>
<th>Possible Clinical Effects</th>
<th>Causes</th>
<th>Seen in Pre-Clinical Studies?</th>
</tr>
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<tbody>
<tr>
<td><strong>Local effects</strong> in tumors injected with DCVax-Direct</td>
<td>Tumor necrosis (tumor cell death)</td>
<td>Secretion of cytokines (e.g., TNFα, IL-6, IL-8) by activated DCs</td>
</tr>
<tr>
<td><strong>Systemic effects</strong> in tumors not injected</td>
<td>Tumor shrinkage or elimination</td>
<td>Immune system activation</td>
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<tr>
<td>Immune memory</td>
<td>Lack of recurrence even when re-challenged</td>
<td>Immune system activation</td>
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DCVax-Direct Phase I Trial: Factors Evaluated

Trial is very information-rich, helping to accelerate development

• More than 10 different cancers were treated
  • DCVax-Direct can in theory be applied to any solid tumor
• 3 dose levels: 2M, 6M and 15M cells
• Feasibility assessments of dose and product administration
  • Including choice of optimal image guidance, e.g. CT vs. US
• Both imaging and biopsies used to monitor responses, correlate with clinical outcomes and evaluate treatment schedule
• Both local and systemic immune responses evaluated
• Potential endpoints evaluated, including tumor response and clinical benefit rate
• Safety
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics, n=39</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>53 (30-73)</td>
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<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (46.2)</td>
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<tr>
<td>Female</td>
<td>21 (53.8)</td>
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<tr>
<td><strong>Disease type, n (%)</strong></td>
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<tr>
<td>Pancreatic adenocancer + NET</td>
<td>7 (17.9)</td>
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<tr>
<td>Sarcoma</td>
<td>8 (20.5)</td>
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<tr>
<td>Desmoplastic tumor</td>
<td>1 (2.6)</td>
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<tr>
<td>Colorectal</td>
<td>7 (17.9)</td>
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<tr>
<td>Neuroendocrine</td>
<td>1 (2.6)</td>
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<tr>
<td>Melanoma</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (10.2)</td>
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<tr>
<td>Breast</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1 (2.6)</td>
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<tr>
<td>Bladder</td>
<td>1 (2.6)</td>
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<tr>
<td>Cholangiocarcinoma</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td><strong>No. of prior therapies in metastatic setting</strong></td>
<td></td>
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<tr>
<td>≤2</td>
<td>20 (51.3)</td>
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<tr>
<td>3–5</td>
<td>12 (30.8)</td>
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<tr>
<td>≥6</td>
<td>7 (17.9)</td>
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Safety Findings

• In general, the treatment was well tolerated

• No dose limiting toxicities were observed at either 2 million, 6 million or 15 million DCs per injection

• Most patients reported only mild adverse events, consisting mostly of flu-like symptoms
  – Low grade fevers (80%)
  – Chills (41%)
  – Fatigue (30%)
  – Injection site pain or discomfort (28%)
  – Night sweats (26%)
  – Decreased appetite (23%)
  – Myalgia (18%)

• There were four grade 3 and one grade 4 adverse events
  – Grade 3: Fatigue, Anemia, Hypokalemia (all resolved)
  – Grade 4: Systemic inflammatory response syndrome (resolved)
Tumor infiltrating T cells (TILs)

TILs, including both CD4+ helper cells and CD8+ killer cells increased from baseline in 15 of 27 (55%) of assessed patients.

TILs sharing sequences with peripheral T cells also increased, indicating a systemic response.

Example:
clear cell sarcoma

Day 0

Day 7

CD3

CD4

CD8
Imaging challenges

- Tumors can appear larger due to infiltration of inflammatory cells and/or immune cells
- Tumors can appear larger due to accumulation of fluids
- Tumors can appear to maintain size, despite extensive necrosis
T cell Infiltration can be Associated with Apparent PD

- Clear cell sarcoma
- Patient failed multiple other treatments
- 5 measurable tumors

Substantial T-cell infiltration (week 8):

CD3 cells

CD4 cells

CD8 cells
Induction of Immune Checkpoint expression

• Expression of immune checkpoint molecules in tumor tissue modulates anti-tumor immune responses
• Checkpoint inhibitors (CIs) incur their effects through ‘unblocking’ of an existing anti-tumor immune response, but are likely to be ineffective absent an effective pre-existing response
• In the DCVax-Direct Phase I trial cohort, 14 of 22 evaluable patients (64%) showed either de novo or significantly increased expression of the PDL-1 checkpoint molecule following DCVax-Direct treatment – these patients may become subsequent candidates for CI treatment

De novo PDL-1 staining on sarcoma tissue, 8 weeks after initiation of DCVax-Direct treatment
**Survival: Actual vs. Expected***

Average life expectancy of top 30% combined: 12.3 months*
Average survival to date of top 30% combined: 26.7 months

Dendritic Cell Characteristics

- Phenotypic/Cell Surface Characteristics
Correlations Between DC Phenotype and Survival

These relationships between phenotypic markers on the DC and survival, albeit largely non-significant, suggest that DC quality may play a role in determining clinical outcome.
Dendritic Cell Characteristics
Soluble Factors Production

- The supernatant from the DC activation stage is harvested and evaluated for the presence of cytokines and chemokines.
- The observed chemokine/cytokine profile is commensurate with the DC1 phenotype.
- Cytokine/chemokine production is re-triggered by interactions with tumor cells and T cells.
Cytokine Production: Identification of Outliers

• Analyzing cytokine production and survival shows that the vast majority of patients show a tight cluster despite the large patient to patient variation in this trial (e.g. with respect to cancer type, age, prior treatments etc)

• We identified 3 outliers, suggesting that the DC of a small minority of patients may respond differently

• These outliers are excluded from subsequent correlative analyses between cytokine production and survival or other disease characteristics
Correlations Between Cytokine Production and Survival

**IL-8 vs. Survival**

- Percent survival
- Months
- $p < 0.05$

**TNFα vs. Survival**

- Percent survival
- Months
- $p < 0.05$

**IL-12 p40 vs. Survival**

- Percent survival
- Months
- $p < 0.05$

* >median

* <median
Associations Between Cytokines and Survival

- The noted associations between cytokine production and survival may be either direct, or they can be a reflection of overall DC quality or potency, or both.

- Interleukin 8 is a pleiotropic chemokine, which can act as a chemotactic factor for leukocytes, and this function may aid in enhancing anti-tumor immune responses.

- Tumor necrosis factor alpha (TNFα) has both direct tumor cell killing effects, and also acts as a Th1 cytokine, promoting anti-tumor immune responses.

- IL-12 p40 is one of the 2 components of IL-12 p70, which is a potent Th1 cytokine.
  - At the time of harvest, the DC do not yet produce large amounts of p70 and correlations with p70 production are therefore difficult to assess.
Stable Disease/Tumor Control

- 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 wk8 is predictive of longer survival

![Survival curves for all patients and outliers removed](image)

- *p < 0.01*
Tumor Control vs. Cytokines

• Cytokine production, esp. TNFα, is correlated with tumor control

This correlation, if indicative of a causal relationship, could represent a direct effect of the DC on the tumor following injection, could reflect TNFα’s function as a TH1 cytokine, or both
Conclusions

• Activated DC can be safely administered into the tumor, in patients with unresectable cancers

• 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
Conclusions (cont.)

• A meaningful proportion of patients show long term survival, e.g. >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
  – Changing the tumor micro-environment to become more conducive to immune activities
  – 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
Future Plans

Phase II trial design optimized for efficacy:
• Selected indications, as well as basket trial for ‘all comers’
  – e.g. NSCLC, Sarcoma
• More frequent immunizations, spaced closer together
• Multiple injections, into multiple tumors, at each visit
• Pre-condition patient’s immune system with low dose cyclophosphamide
• Allow approved immune checkpoint inhibitors
## Acknowledgments

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<tr>
<th>MD Anderson Cancer Center</th>
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<tr>
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<td>Dr. Robert Brown</td>
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