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

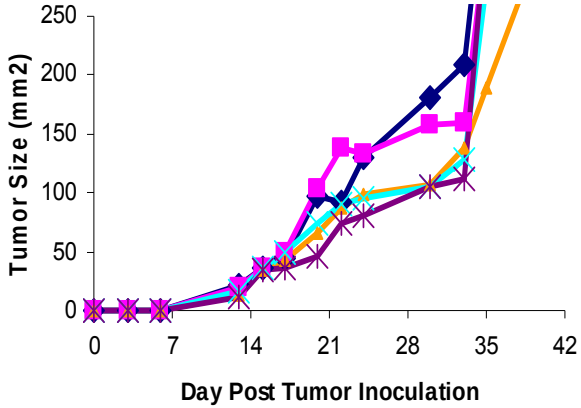
Scientific Background: Animal Data

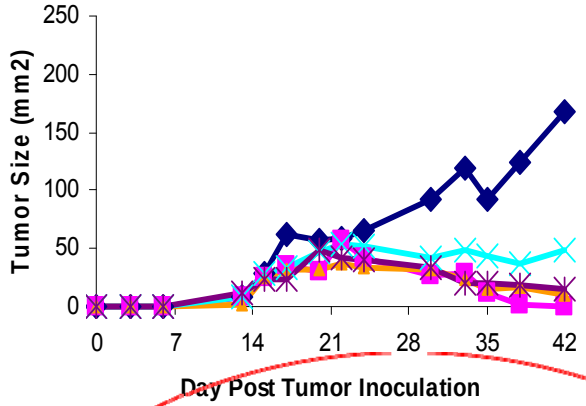
- Experiment: CT26 colon carcinoma cells are implanted in the right and (3 days later) the left flanks of BALB/c mice
- After 15 days, the animals are given a low dose of intraperitoneal cyclophosphamide
- Next, either immature or activated DC are injected into the right-flank tumor only
- Tumor growth 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 <u>same</u> side of body after direct injection in animal studies

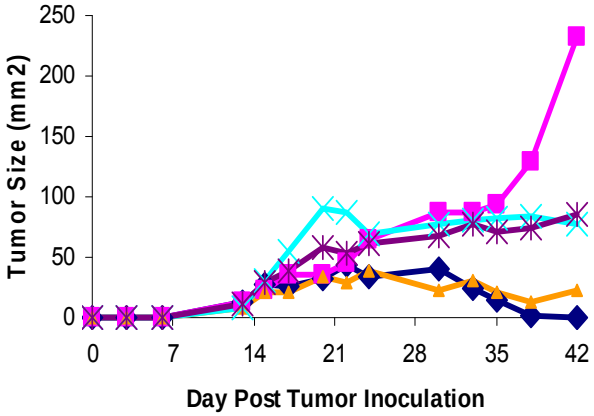
chemo only

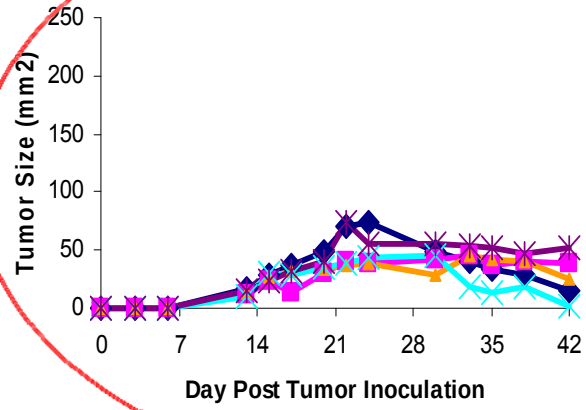




\+ partially activated DCs

\+ immature DCs





\+ optimally partially activated DCs

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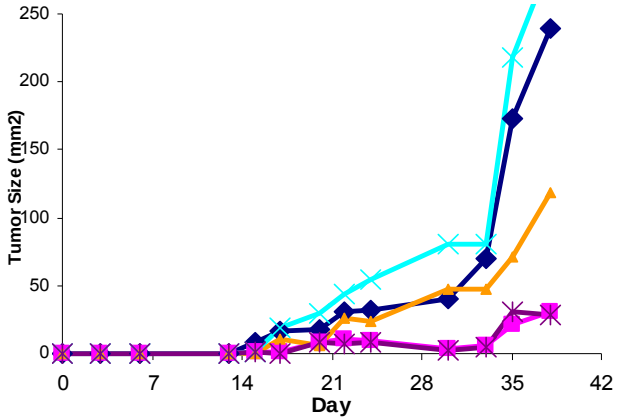
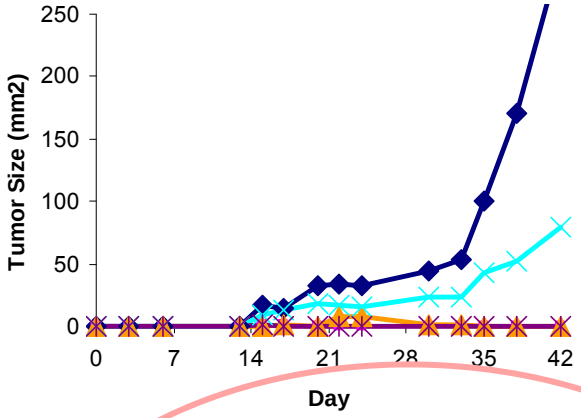
DCVax-Direct: **Pre-Clinical Results (2)**

Tumor clearance on <u>opposite</u> side of body after direct injection in animal studies

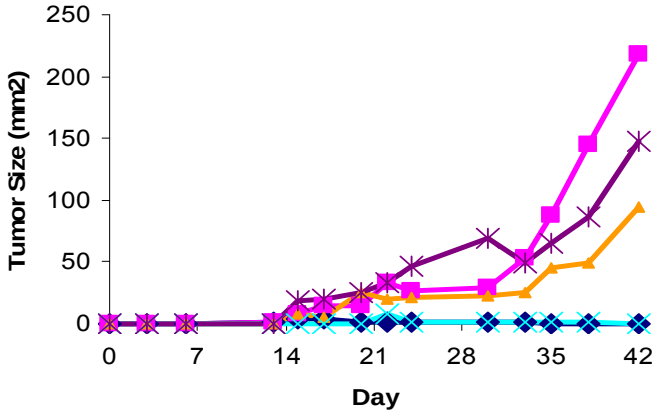
chemo only

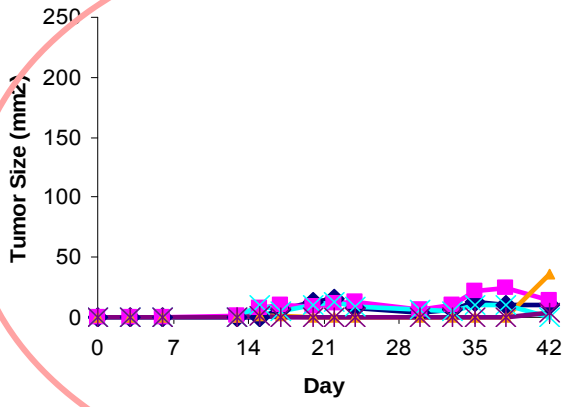




\+ partially activated DCs

\+ immature DCs





\+ optimally partially activated DCs

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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

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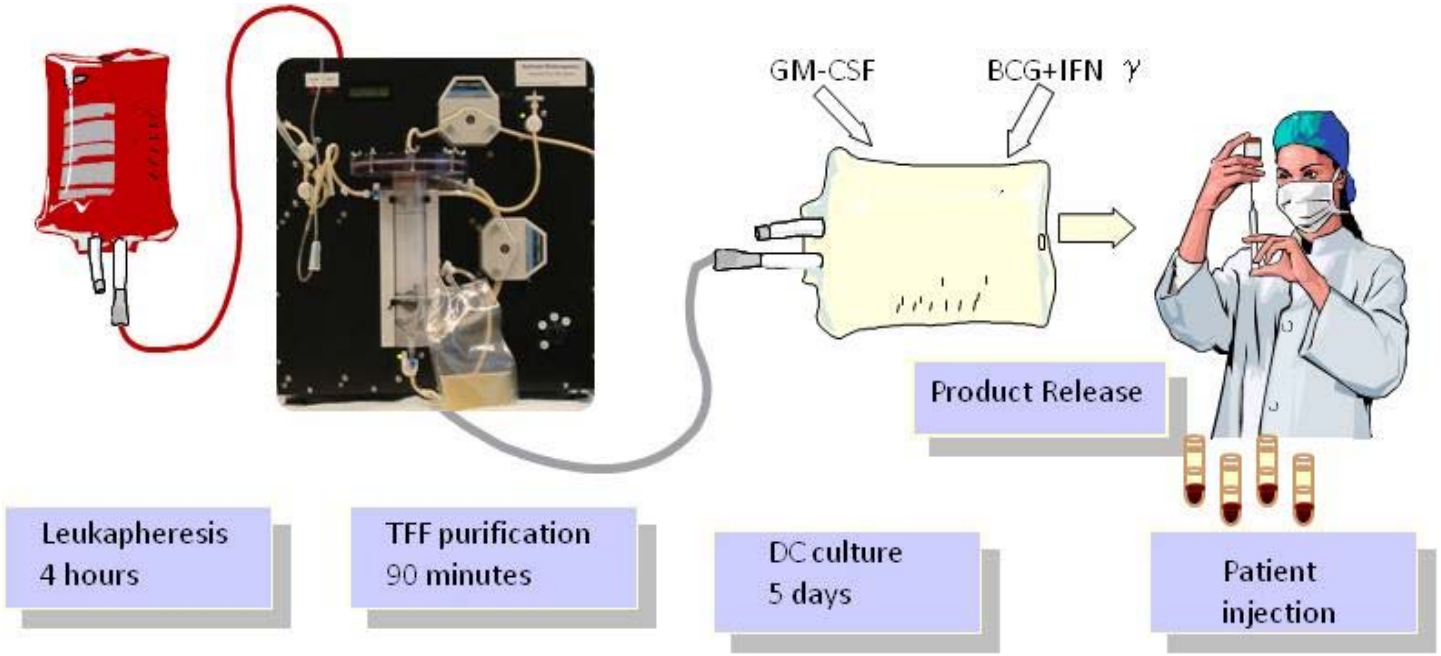
Manufacturing system for DCVax-Direct



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DCVax Direct: Potential Clinical Effects

	Possible Clinical Effects	Causes	Seen in Pre-Clinical Studies?
Local effects in tumors injected with DCVax-Direct	Tumor necrosis (tumor cell death)	Secretion of cytokines (e.g., TNFα, IL-6, IL-8) by activated DCs	✓
Systemic effects in tumors not injected	Tumor shrinkage or elimination	Immune system activation	✓
Immune memory	Lack of recurrence even when re-challenged	Immune system activation	✓

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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

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Patient Characteristics

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

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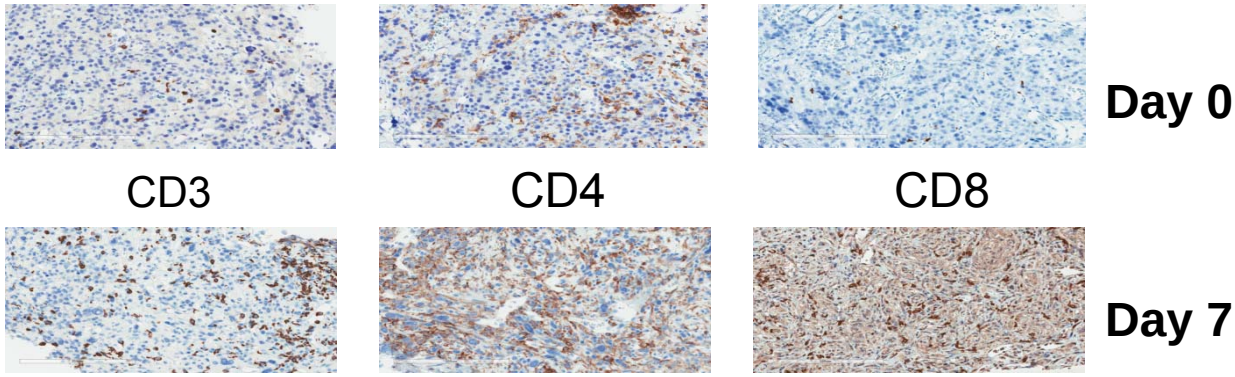
Safety Findings

- 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

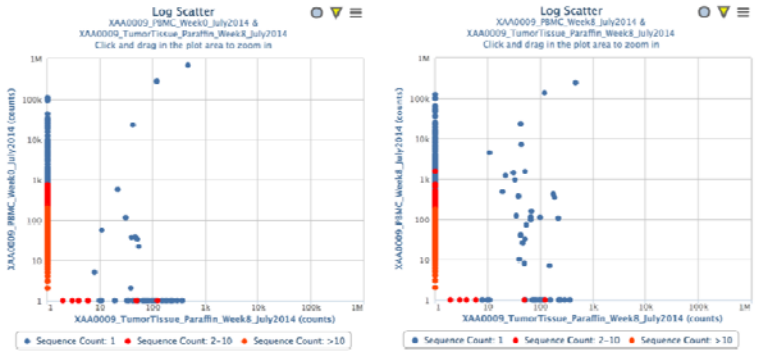
Example: clear cell sarcoma



Day 0

Day 7

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



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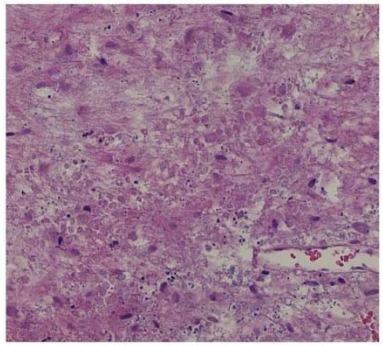
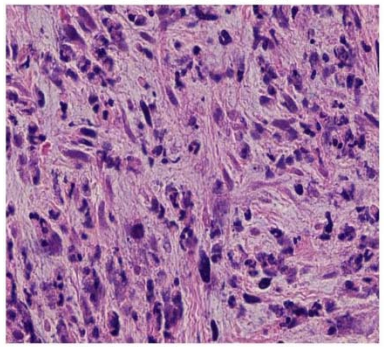
Imaging challenges

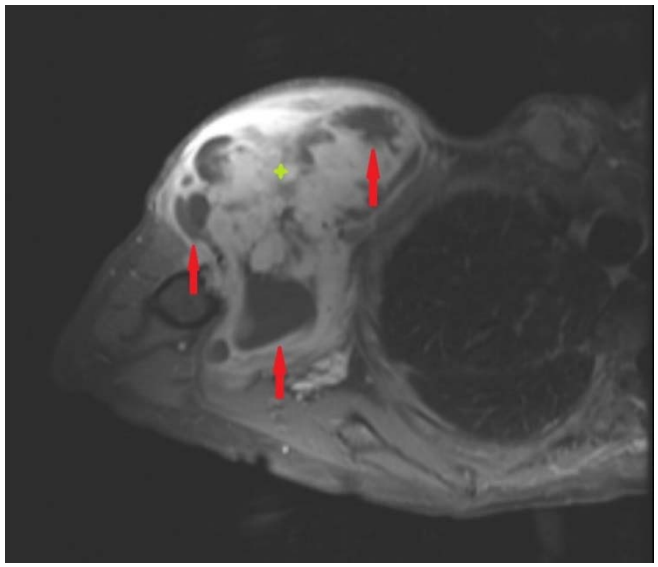
- Tumors can appear larger due to infiltration of inflammatory cells and/or immune cells
- Tumors can appear larger due to accumulation of fluids
- Tumors can appear to maintain size, despite extensive necrosis



H & E (X200 necrotic region)



H & E (undergoing tumor necrosis)



Dedifferentiated Liposarcoma

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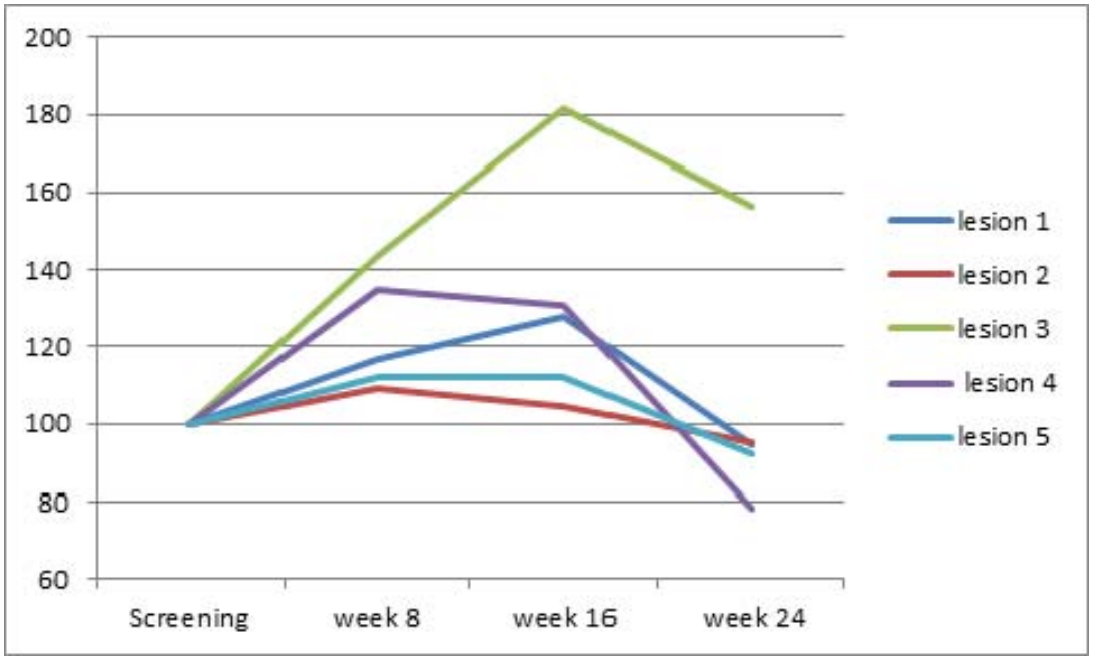
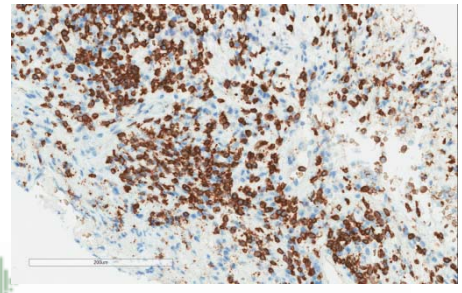
T cell Infiltration can be Associated with Apparent PD

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

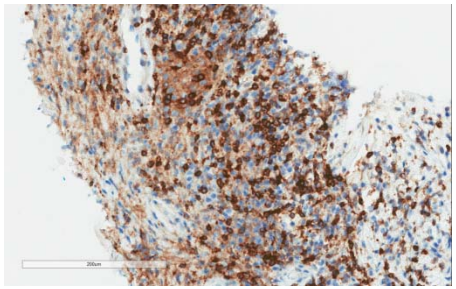


Substantial T-cell infiltration (week 8):

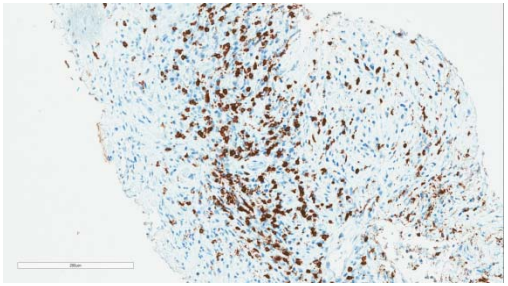
CD3 cells



CD4 cells



CD8 cells



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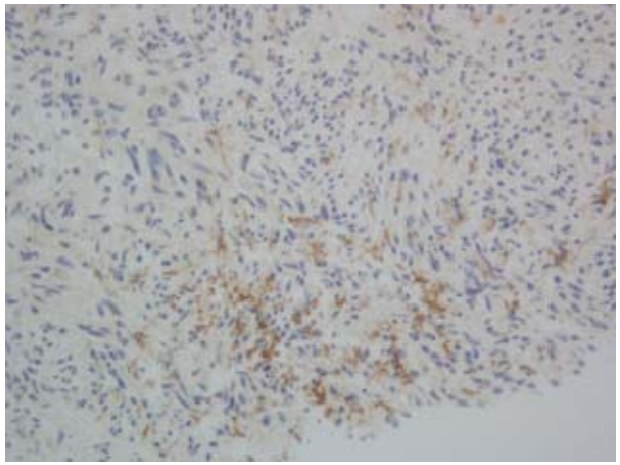
Induction of Immune Checkpoint expression

- 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

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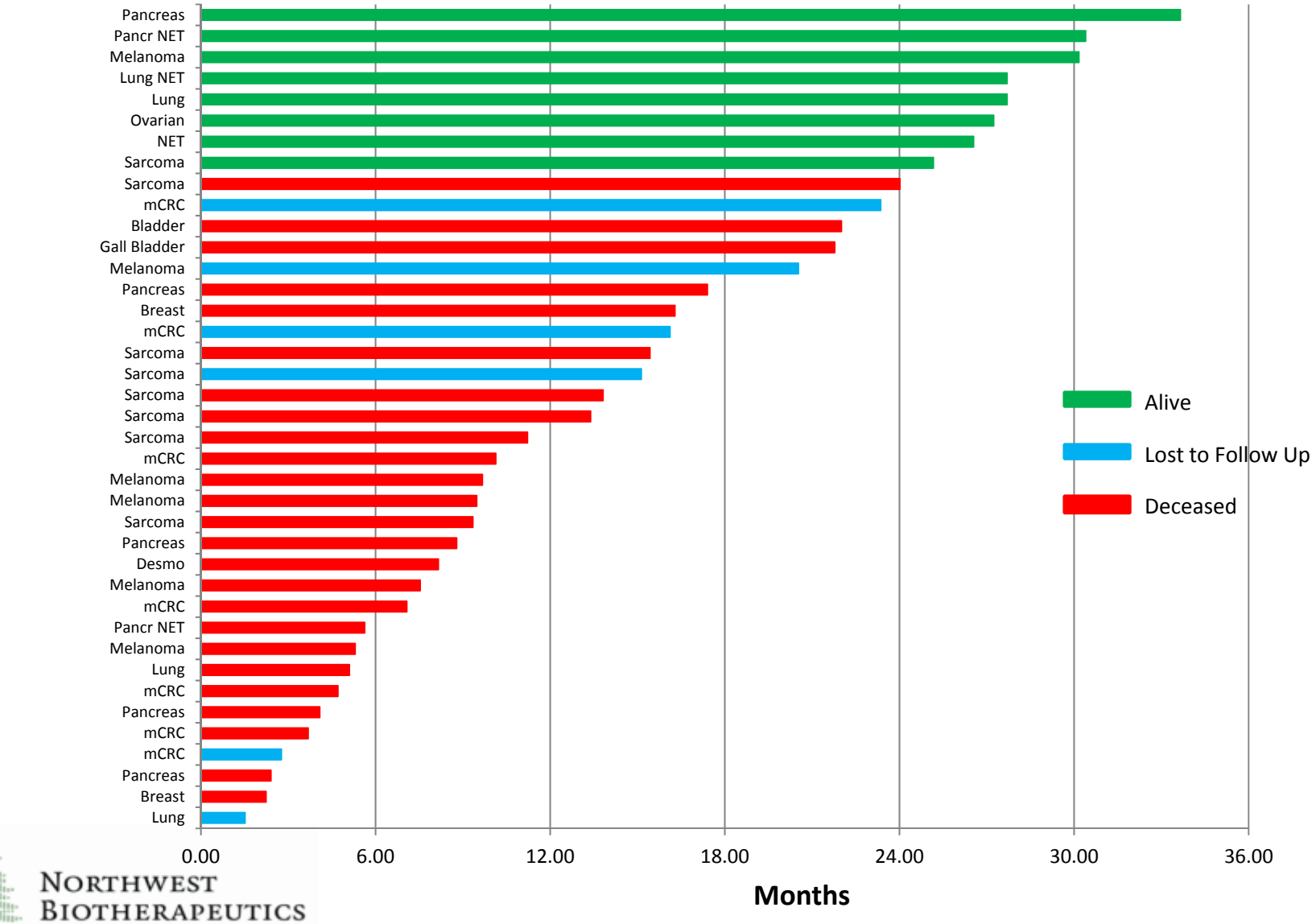
Survival



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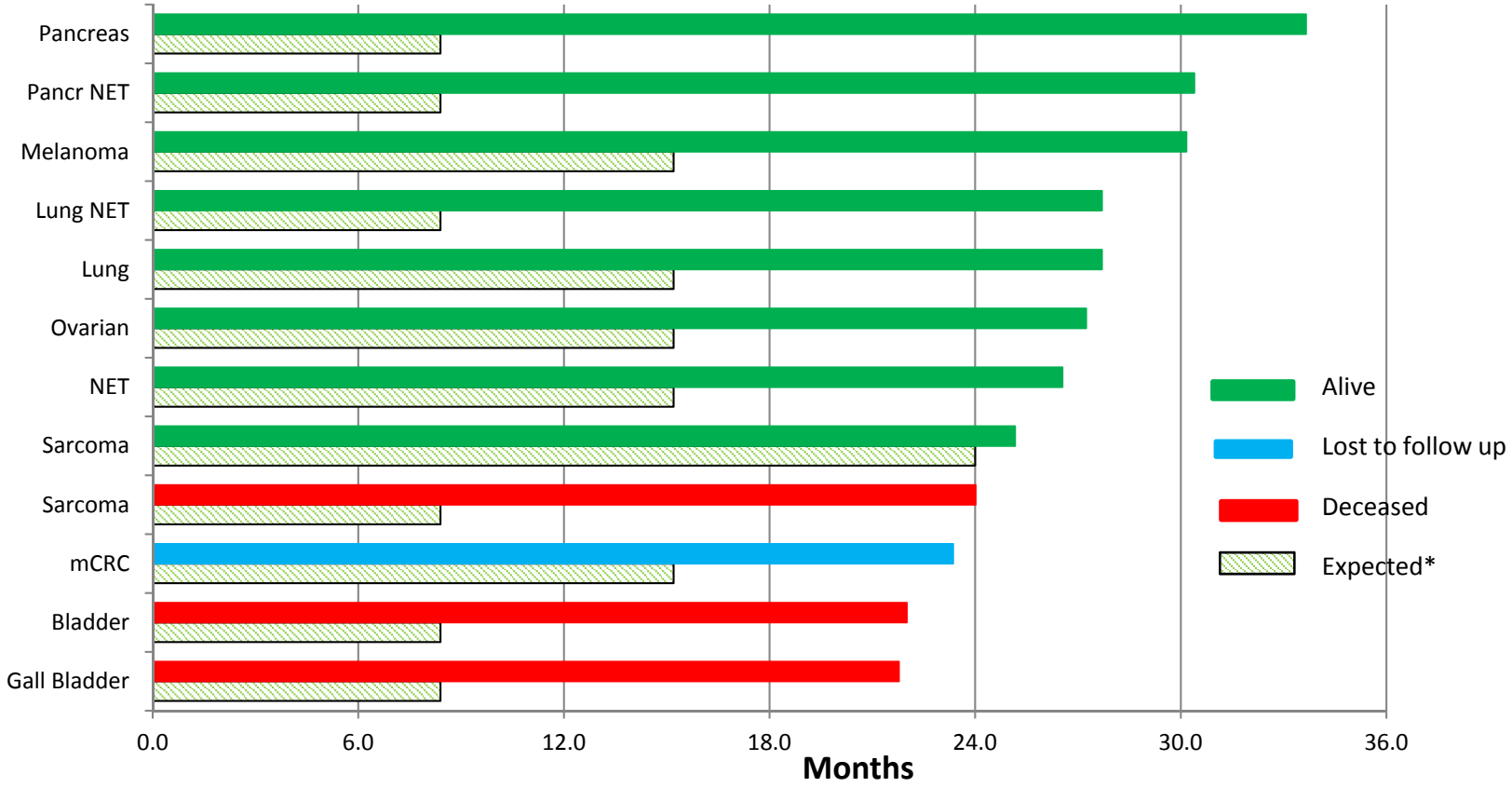
Survival: Actual vs. Expected*



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

*Scores for life expectancy obtained from scales developed based on 1,181 patients in Phase I trials: *Wheler et al. 2012: Survival of 1,181 Patients in a Phase I Clinic: The MD Anderson Clinical Center for Targeted Therapy Experience. Clin. Cancer Res. 2012 May 15; 18(10): 2922–2929.*

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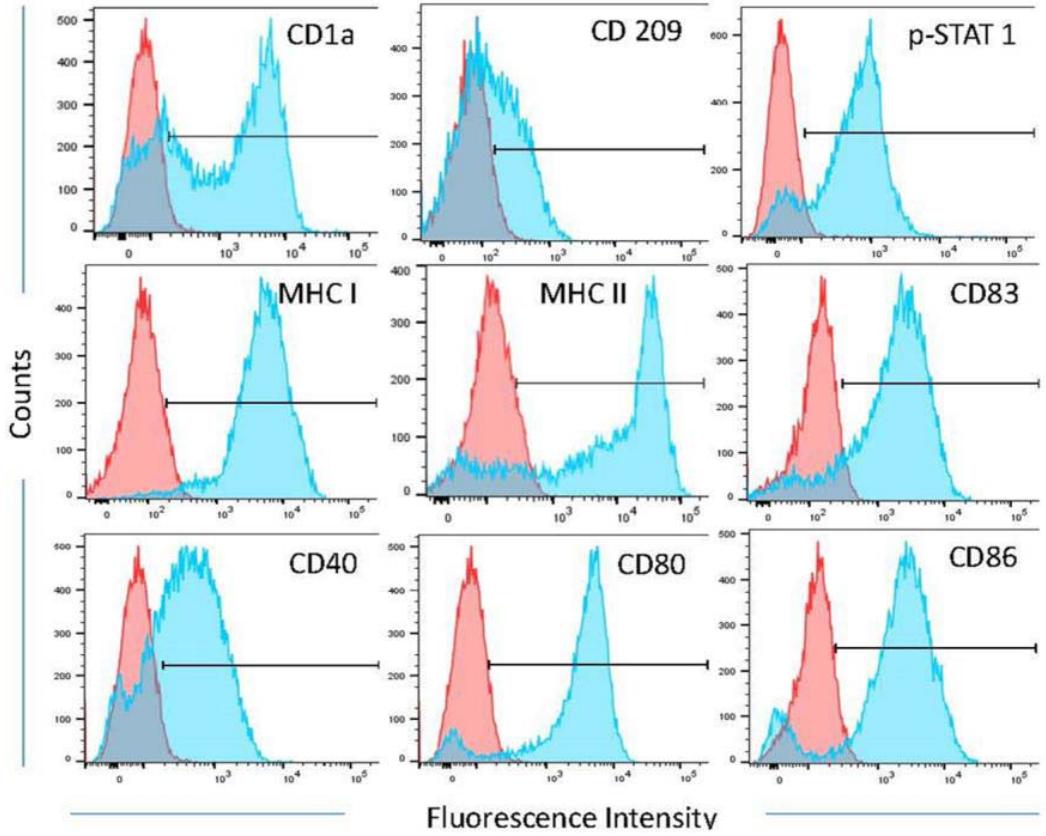
Dendritic Cell Characteristics

- Phenotypic/Cell Surface Characteristics



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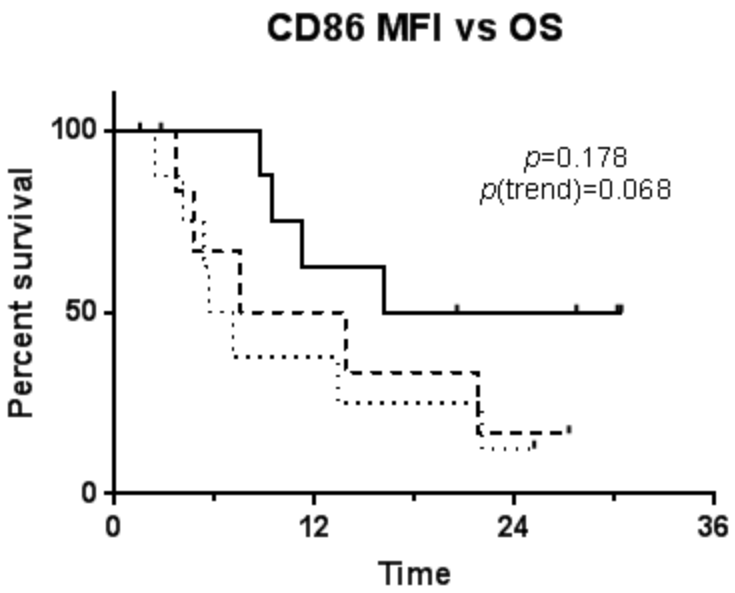
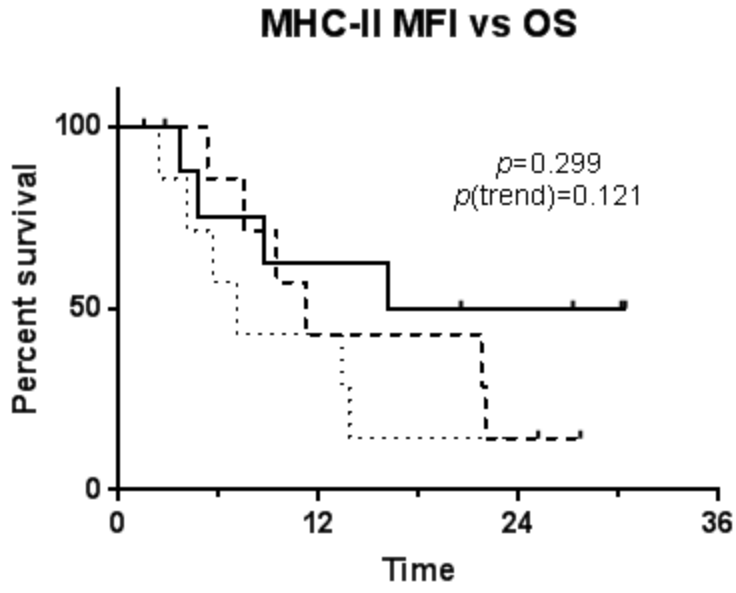
Correlations Between DC Phenotype and Survival





High
Med
Low

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

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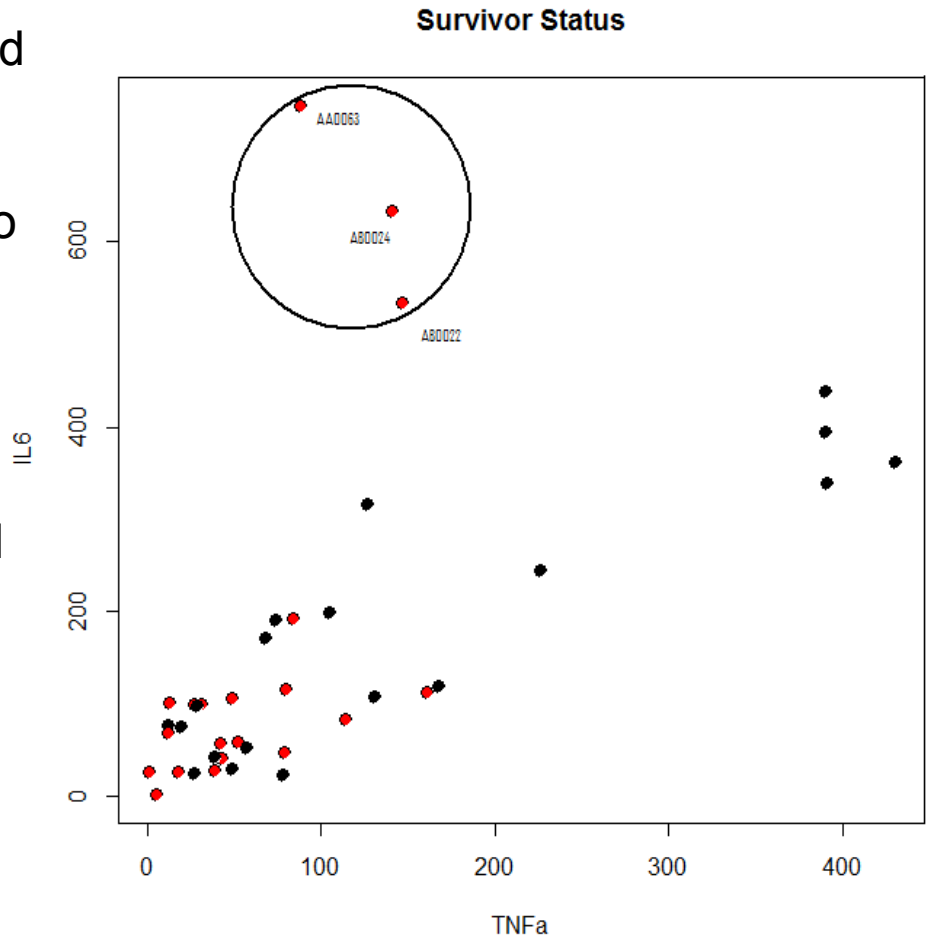
Dendritic Cell Characteristics
Soluble Factors Production

- 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 he 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



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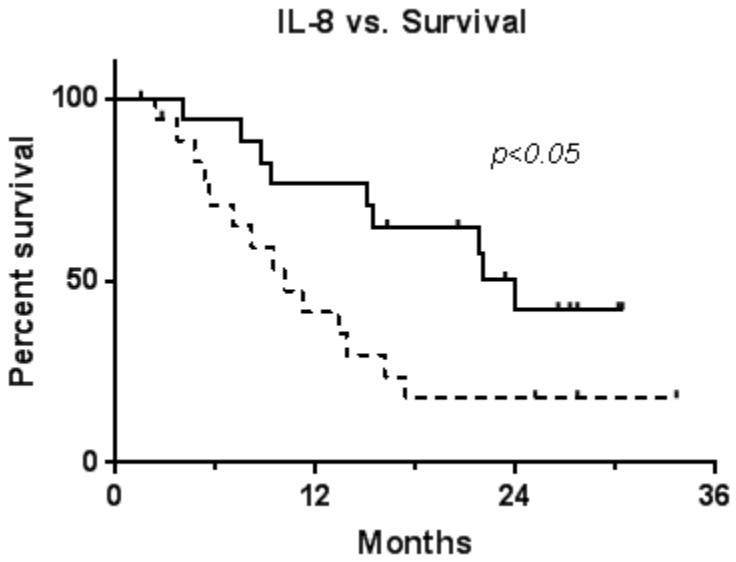
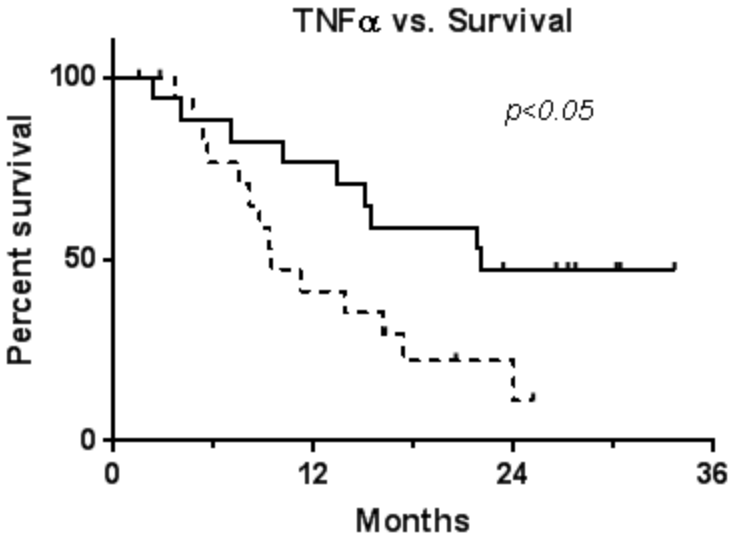
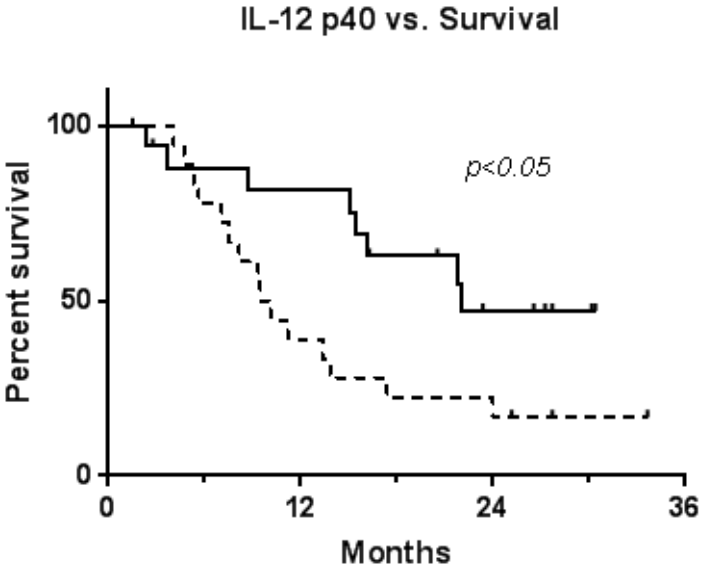
Correlations Between Cytokine Production and Survival







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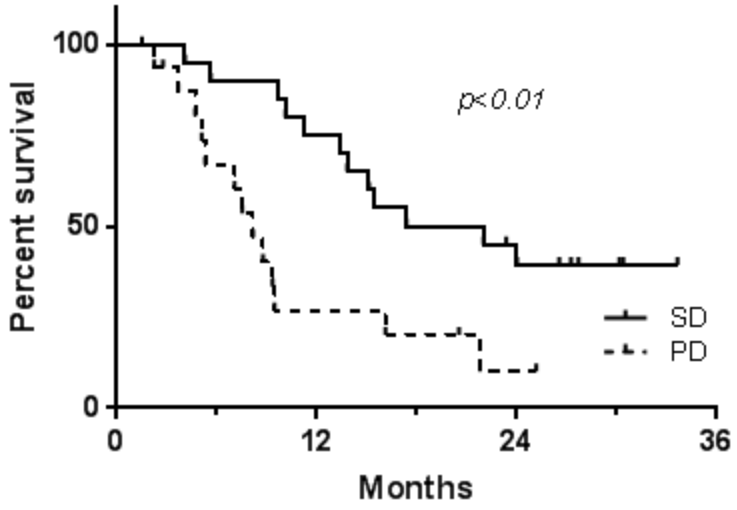
Associations Between Cytokines and Survival

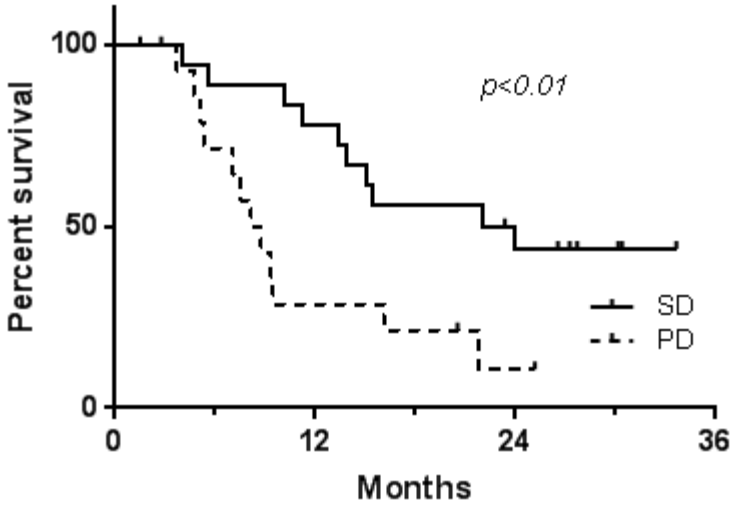
- The noted associations between cytokine production and survival may be either direct, or they can be a reflection of overall DC quality or potency, or both
- Interleukin 8 is a pleiotropic chemokine, which can act as a chemotactive factor for leukocytes, and this function may aid in enhancing anti-tumor 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



All patients



Outliers removed

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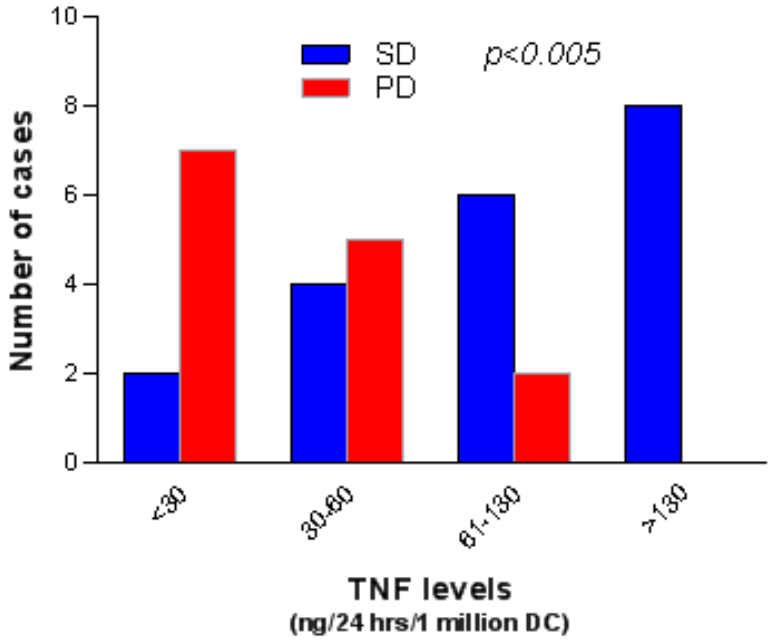
Tumor Control vs. Cytokines

- 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



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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 eficacy:

- 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

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