DCVax®
Clinical Development of Dendritic Cell-Based Immunotherapy for Cancer

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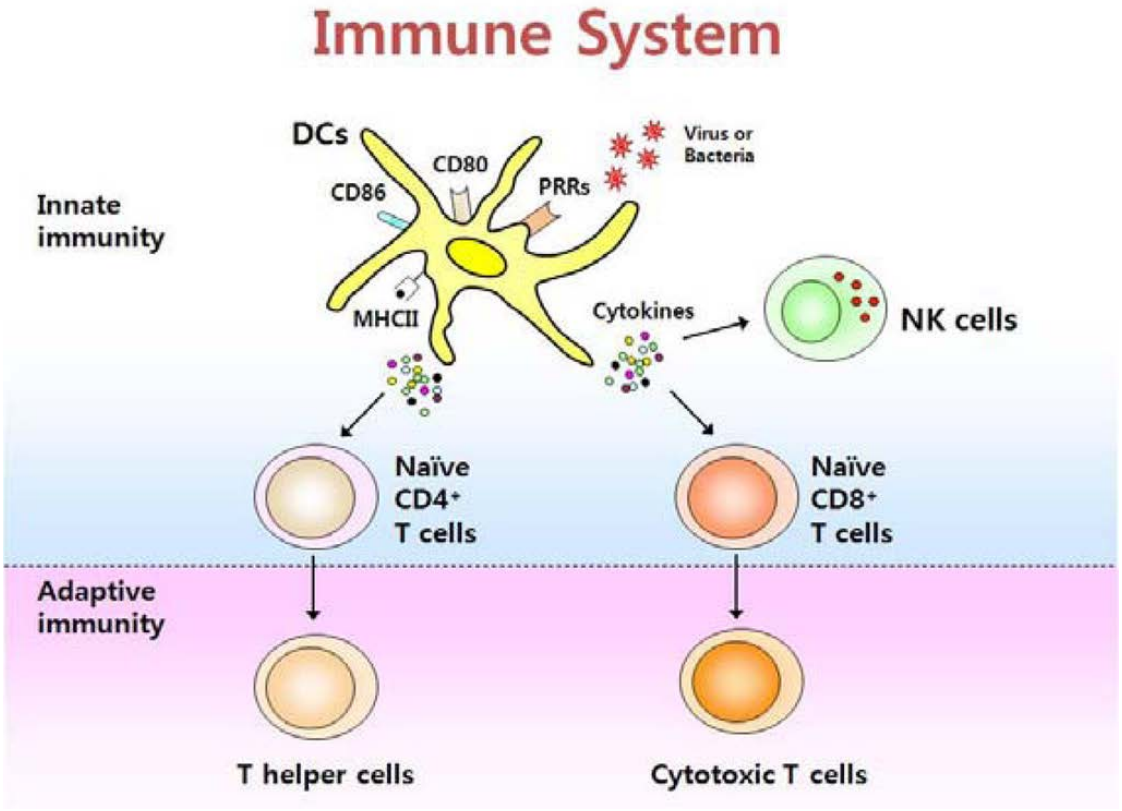
What are Dendritic Cells (DCs)

Dendritic cells (DCs) are antigen-presenting cells, that are required for the induction of an antigen-specific (adaptive) immune response, through cell-to-cell contact (CD80, CD86) and through soluble factors (**cytokines**).



How to obtain DCs?

1. Directly from the blood: 1- 5% of blood white cells are DCs
   - The presence of specific markers allow one to isolate these cells
   - The condition of these cells is dependent on patient pre-treatment

2. From the bone marrow
   - CD34+ stem cells in the bone marrow can be converted to DCs
   - Bone marrow punctures are unpleasant for the patient
   - Requires *in vitro* culture in the presence of cytokines

3. From blood monocytes (e.g., DCVax®-L and DCVax®-Direct)
   - Monocytes are easily obtained in large quantities through apheresis
   - Requires *in vitro* culture in the presence of cytokines

*NWBio technologies in **blue***

Source of Antigen/Specificity

a) Recombinant protein
b) Tumor lysate
c) Tumor tissue *in vivo*
d) (short) peptides
e) Tumor mRNA

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DCVax Potentially Applicable to All Types of Solid Tumors

Indication	Product / Administration	Composition	Lead Program
All Operable Solid Tumors	DCVax®-L Intra-dermal shot in arm	Monocyte-derived DCs + full set of tumor antigens from tumor tissue sample surgically removed	Brain cancer *331-patient Phase III trial underway*[1] Small ovarian cancer Phase I/II trial completed
All Inoperable Solid Tumors	DCVax®-Direct Direct injection into tumor	Monocyte-derived DCs directly injected into tumor(s) + full set of tumor antigens picked up *in situ* in tumor	All solid tumors (13 cancers treated to date) *40-patient Phase I trial completed*[2]
Non-operable, non-injectable Tumors	DCVax®-Prostate Intra-dermal, e.g. in leg	Monocyte-derived DCs loaded with recombinant Prostate Specific Membrane Antigen (PSMA)	Hormone-refractory prostate cancer *35-patient Phase II trial completed*

[1]Interim data analysis published in *Liau et al., Journal of Translational Medicine (2018), 16:142*

[2] First publication at *Subbiah et al., Clin Cancer Res, July 17 2018, DOI: 10.1158/1078-0432.CCR-17-2707*

DCVax®-Direct for Inoperable Solid Tumors

Program Update

Northwest Biotherapeutics

Key Points

- **DCVax-Direct uses a unique and proprietary manufacturing approach that dramatically increases cytokine levels**

- **The amounts of cytokines produced (e.g. IL-8, Il-12, TNFα) unexpectedly correlate with survival in a Phase I trial**
  - IL-8: broad acting cytokine
  - IL-12: essential in mediating the proper type of immune response
  - TNFα: induces tumor necrosis and supports proper type of immune response

- **DCVax-Direct may have multiple modes of action, and the produced cytokines may be directly or indirectly involved in some or all of these mechanisms**
  - Direct killing of tumor cells
  - Making the tumor more susceptible to immune attack
  - Induction of a systemic anti-tumor immune response

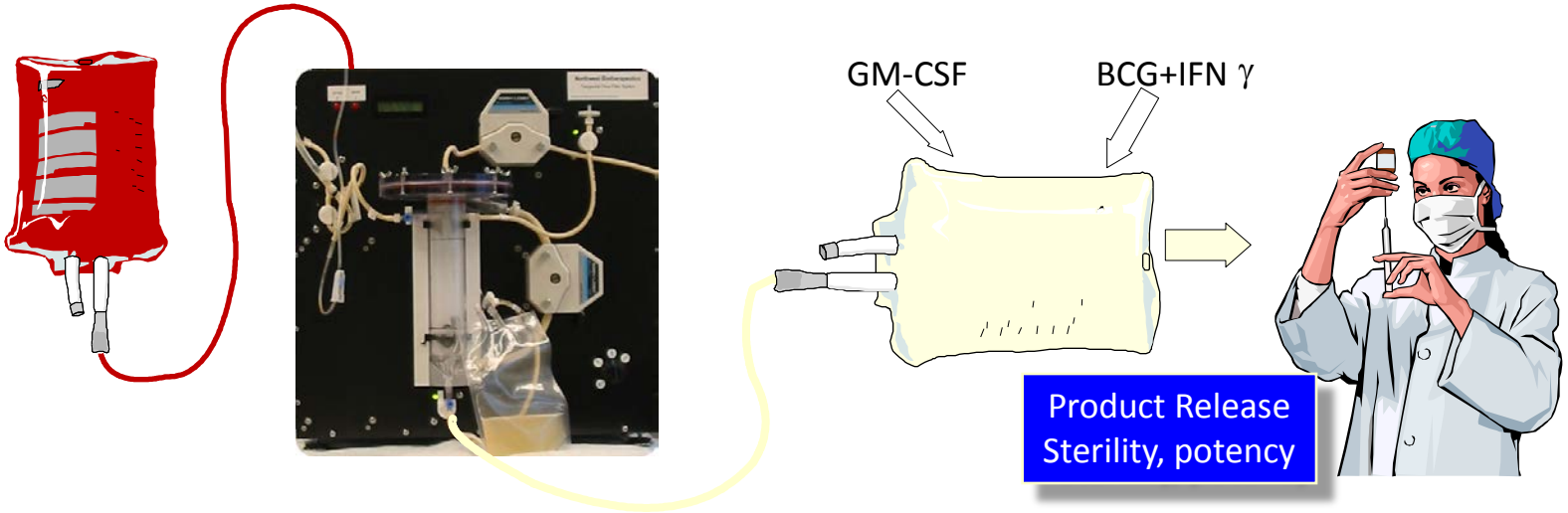
- **DCVax-Direct induces mild fevers as the main adverse advent, thus at least preliminarily safer than other cell therapies**

- **First publication at *Subbiah et al., Clin Cancer Res, July 17 2018, DOI: 10.1158/1078-0432.CCR-17-2707***

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

DCVax-Direct – Automated Manufacturing



Leukapheresis | TFF purification | DC culture | Treatment

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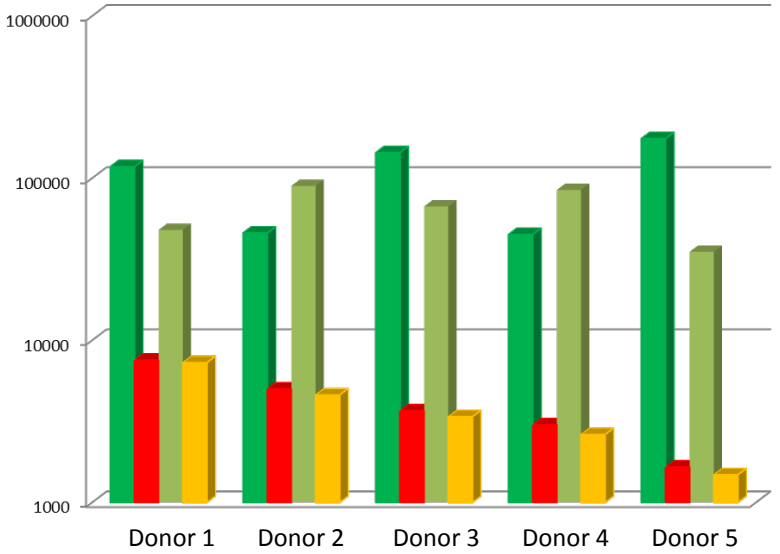
Advantages of the DCVax-Direct system

- **The system initially produces fully immature DC**
  - **Consequentially, one has full control over the DC activation process**
- **The potency of the produced DC, e.g. measured through cytokine production, is enhanced**
- **Will this translate into enhanced efficacy?**

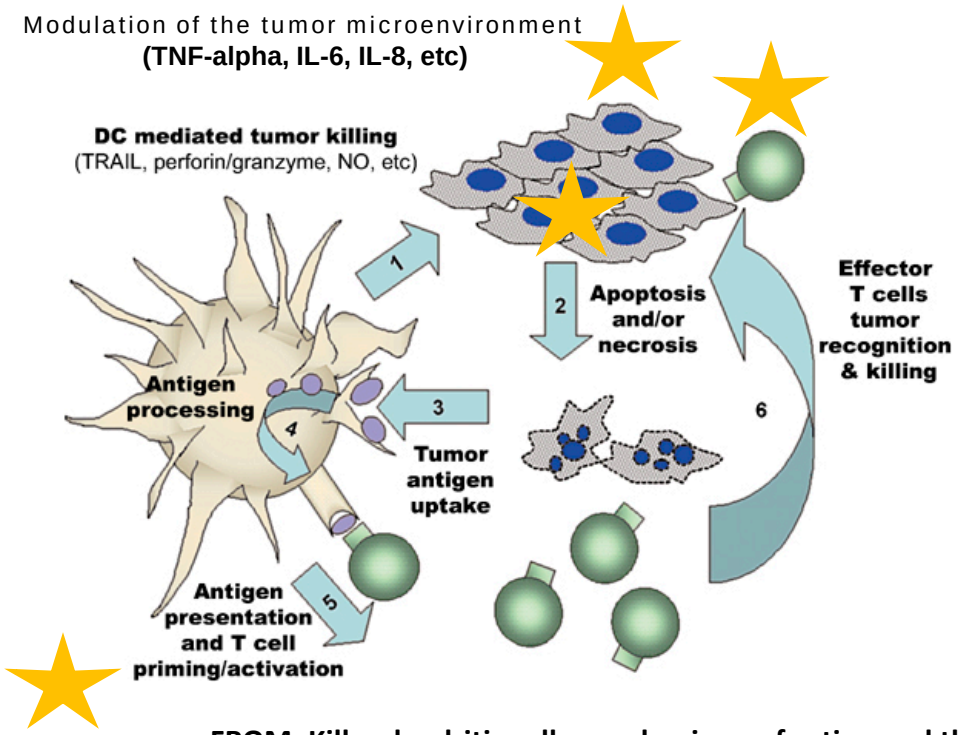


Cytokine production by DCVax-Direct DCs (green bars) vs. 'traditional DCs' (red/orange bars)

DCVax-Direct Mechanism of Action

DCVax-Direct DCs may attack the tumor in three ways:

- Direct killing of tumor cells
- Induction of a systemic anti-tumor immune response
- Rendering the tumor microenvironment more conducive to immune attack
  - ➢ **DC-produced cytokines may play a role in all three postulated mechanisms**



FROM: Killer dendritic cells: mechanisms of action and therapeutic implications for cancer A K Wesa and W J Storkus

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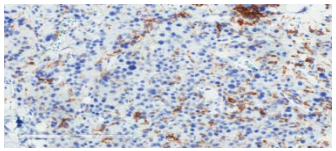
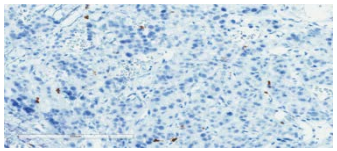
DCVax-Direct -- Mechanism of Action

Change of the Tumor Microenvironment ("cold" to "hot" conversion)

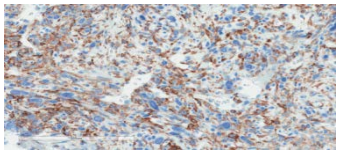


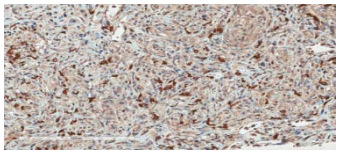


Day 0

CD4

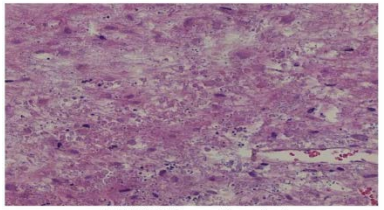
CD8



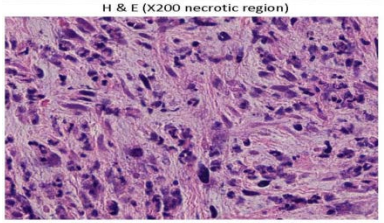


Day 7

Induction of Necrosis

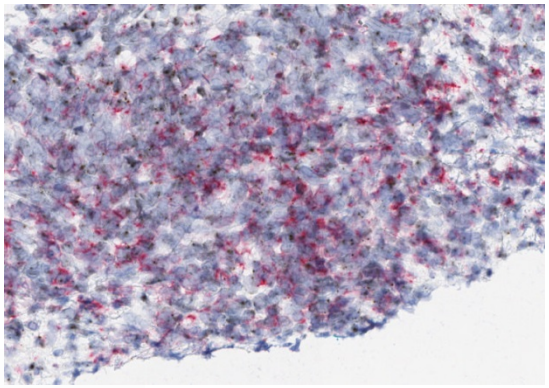


H & E (X200 necrotic region)

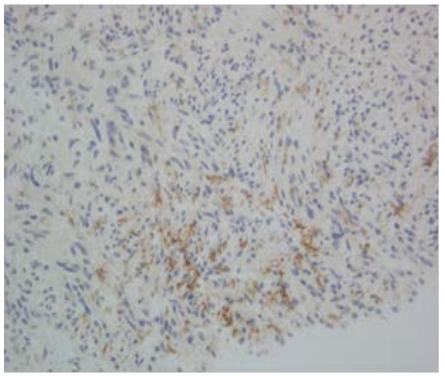


H & E (undergoing tumor necrosis)

Induction of cytotoxic T cells



Induction of PD-L1



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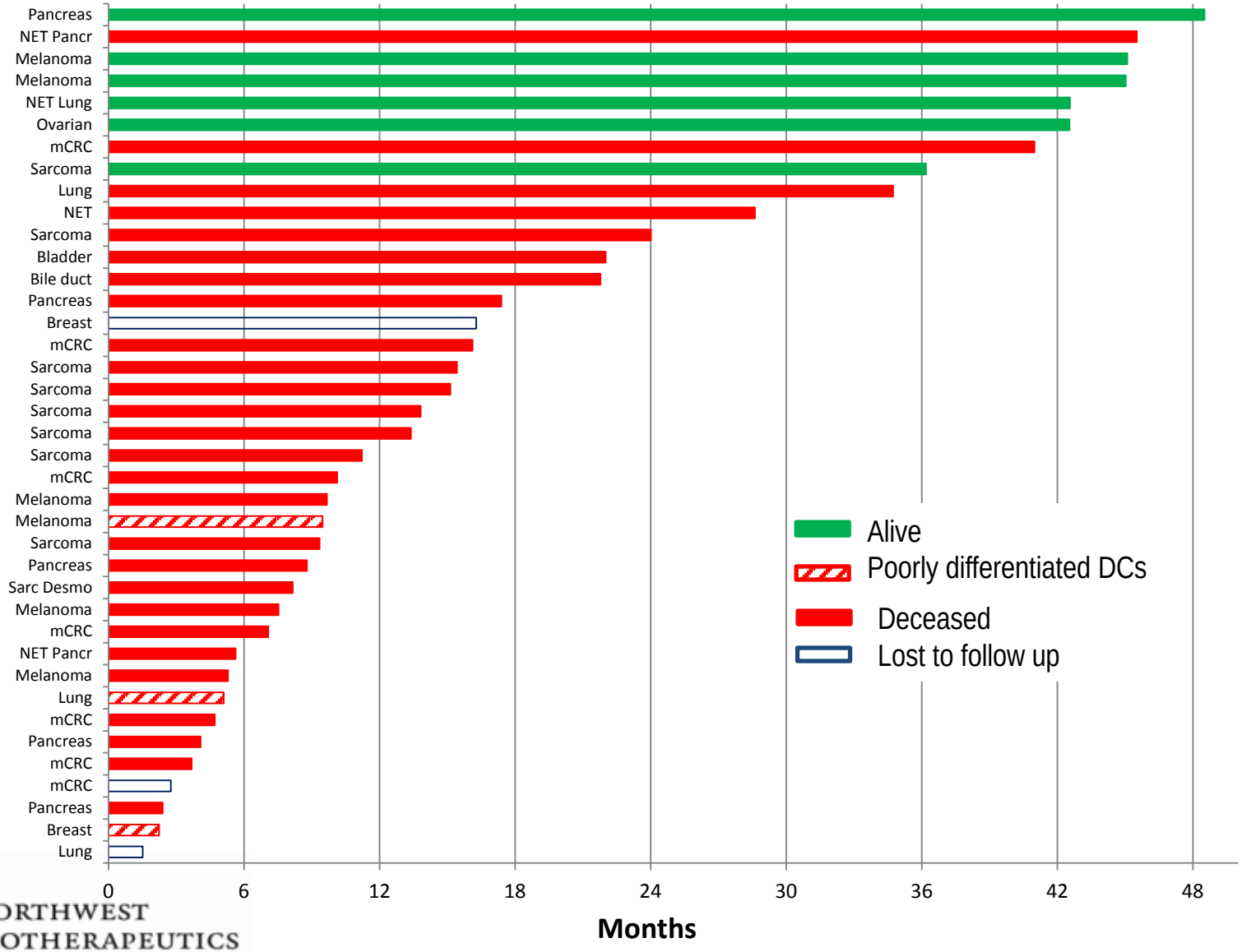
Long Tail of Durable Outcomes:
DCVax-Direct Phase I Trial; 13 Cancers



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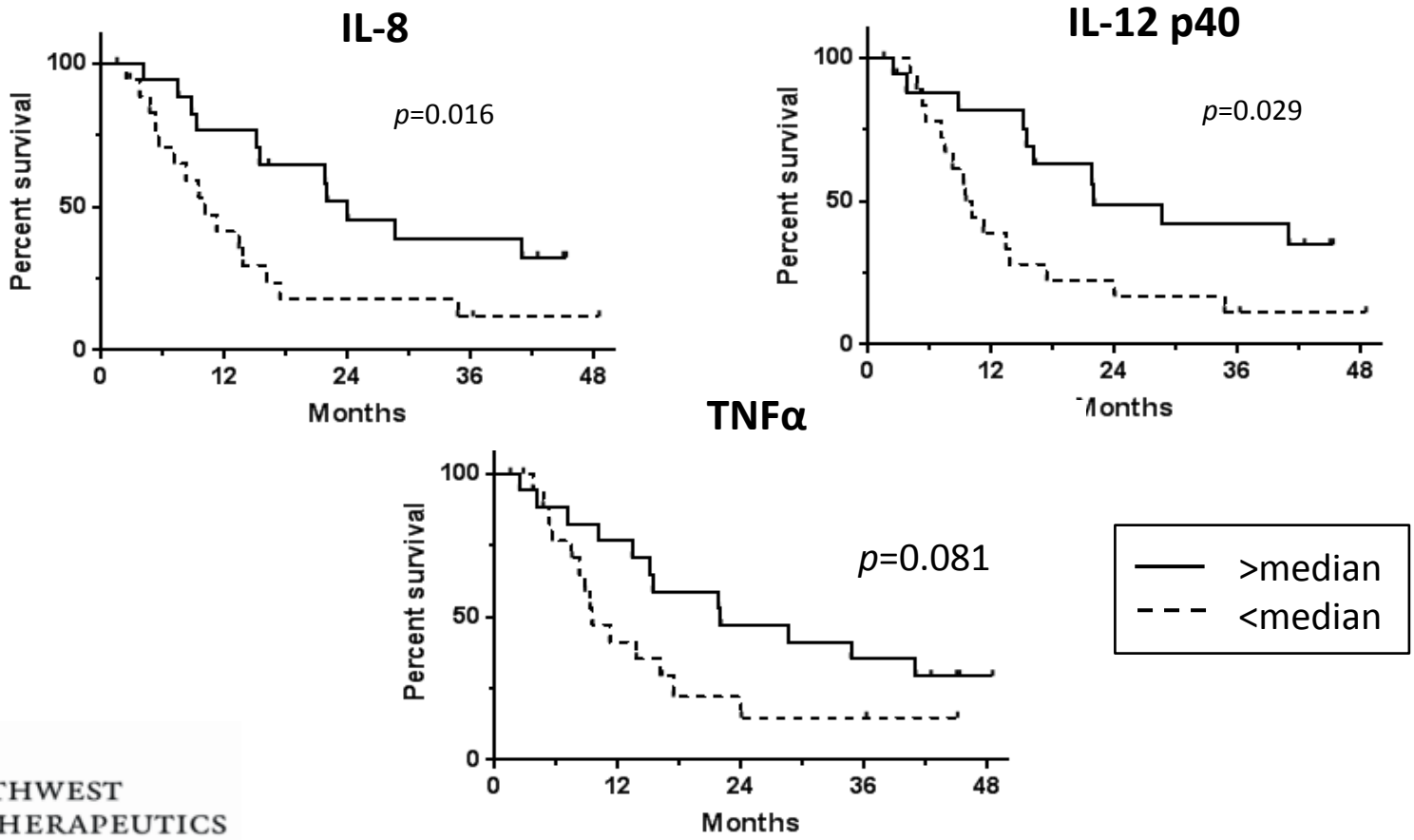
Cytokine Production and Survival

Patients whose DCs produced higher levels of cytokines during the manufacturing process had better survival outcomes

- **IL-8: mOS of 24 months vs 10 months**
- **IL-12: mOS of 22 months vs. 10 months**



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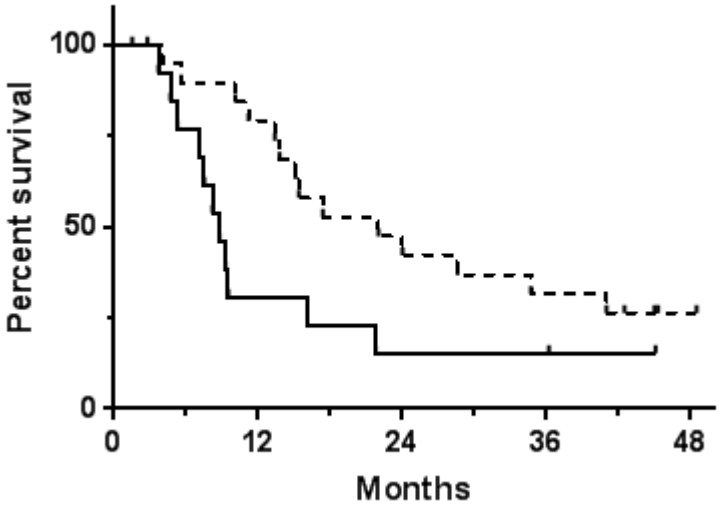
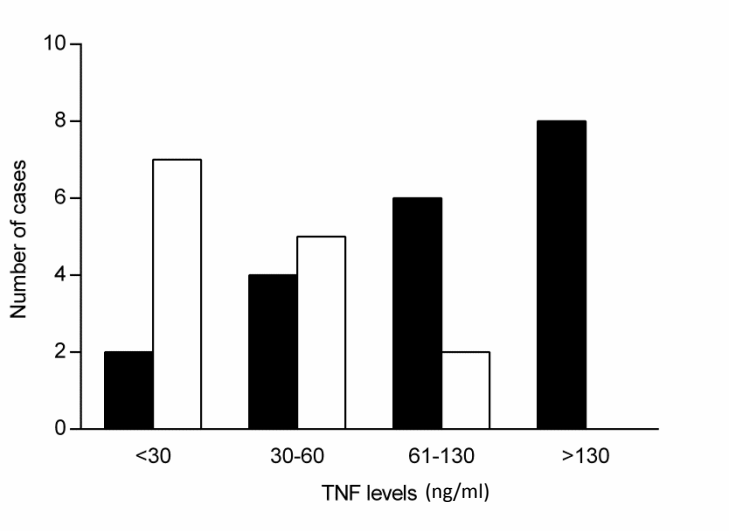
Stable Disease and Survival

Patients with stable disease (SD) at week 8 (left panel, dashed line) live longer than patients with progressive disease (solid line): **mOS of 22 months vs. 8.8 months**.



Patients with higher TNFα levels had a greater likelihood of having SD (solid bars) at week 8



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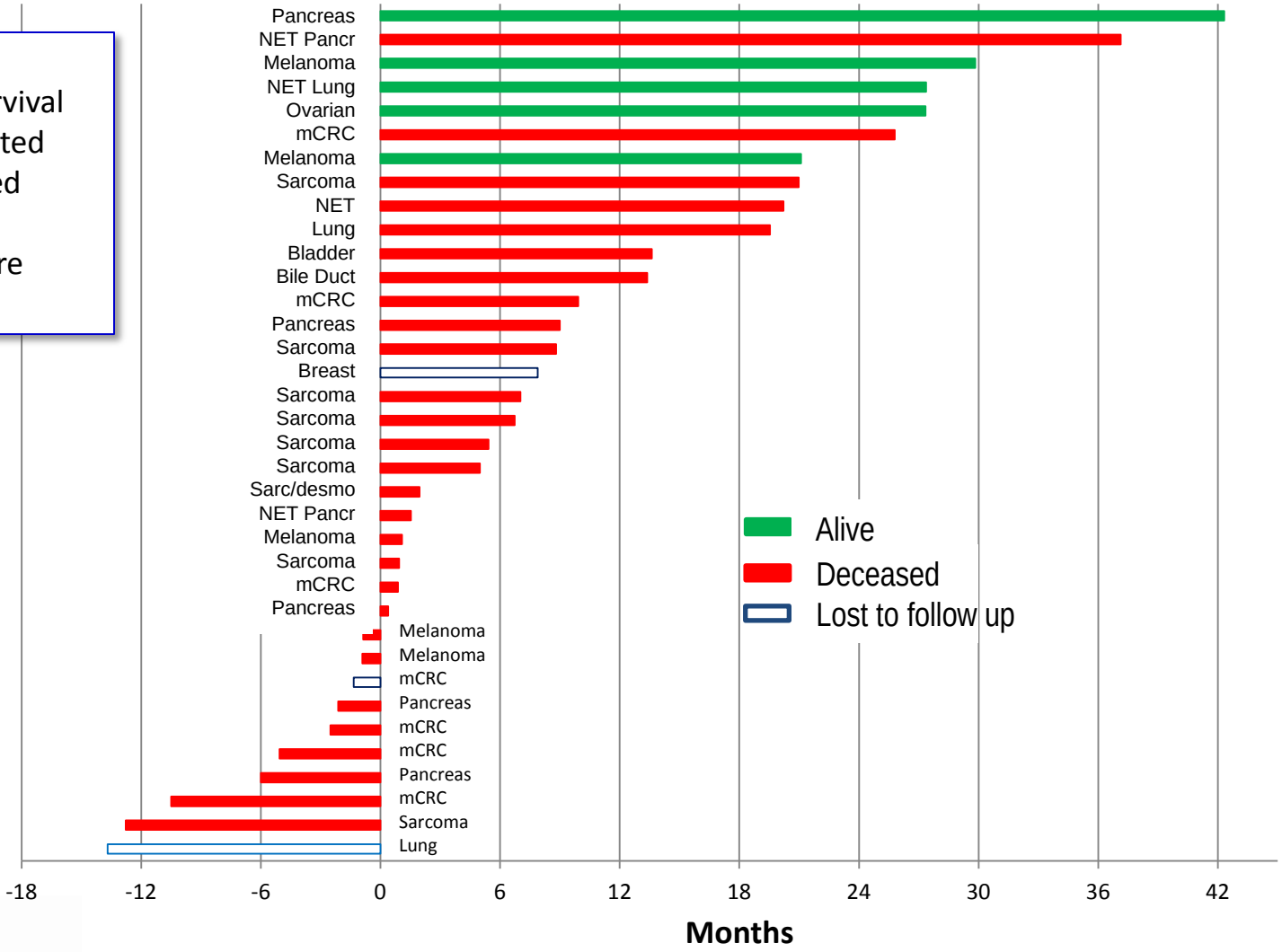
DCVax-Direct Phase I Trial: Actual vs. Predicted Survival

- 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.
- The MDACC Score assumes that patients have access to other experimental therapies

The encouraging findings will form the basis of a publication that is currently in preparation with our investigators, with more detailed information

Survival: Actual minus Predicted

For each patient,
the predicted survival time was subtracted from the observed survival time
and the results are plotted.



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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.)

- 28% 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 TNF**α** may be directly responsible for mediating tumor control in patients treated with DCVax-Direct
- Both local and systemic T cell responses observed

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