# DCVax
# Update on Clinical Programs

***Cancer Vaccines and Neoantigens***
***August 31, 2017***

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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

# DCVax Potentially Applicable to All Types of Solid Tumors

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

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# DCVax®-L for Newly Diagnosed Glioblastoma Multiforme (GBM)

## Phase III Trial Update

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# DCVax-L® Phase III Trial Design

Newly diagnosed Glioblastoma multiforme (GBM).

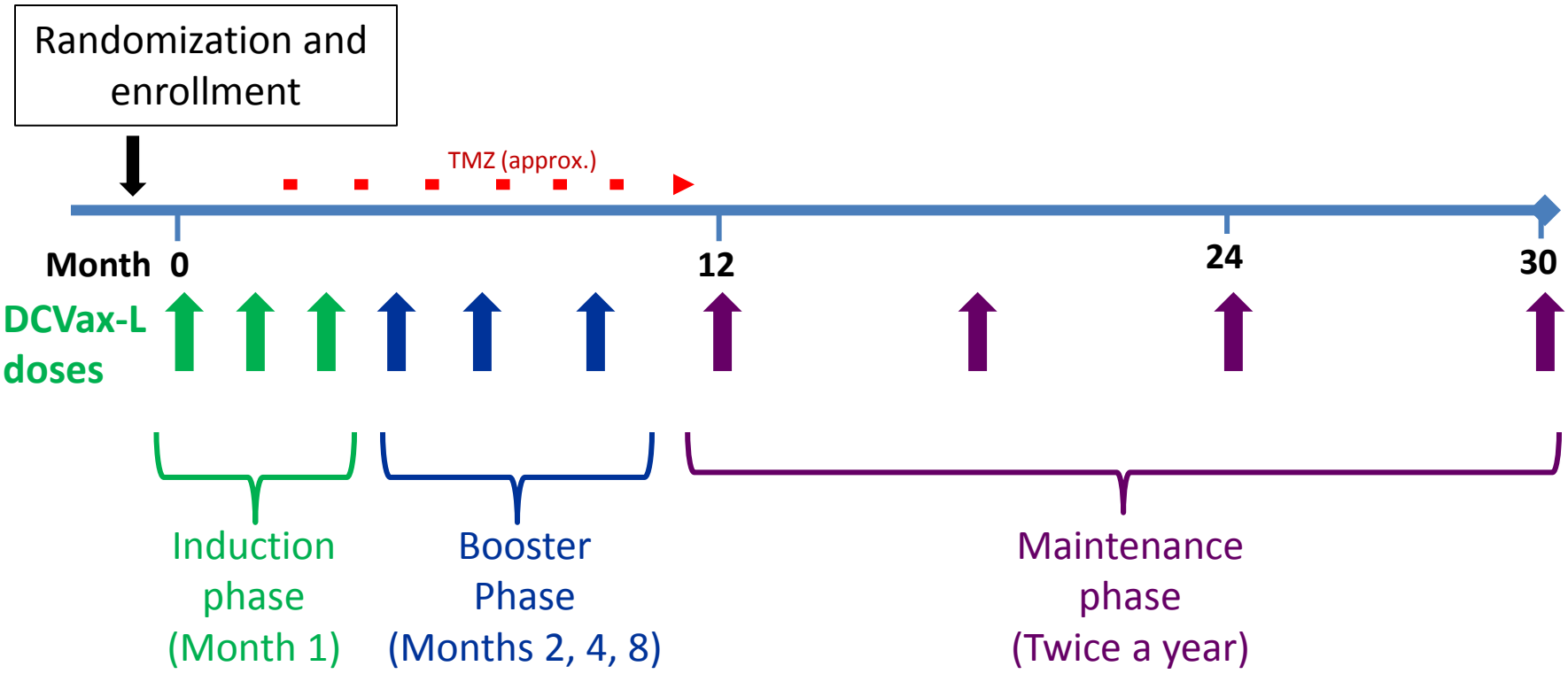
Double-blind, randomized, placebo-controlled, multi-center, International trial.

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

# DCVax-L Phase III Trial Design -- Treatment Schedule

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# 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)

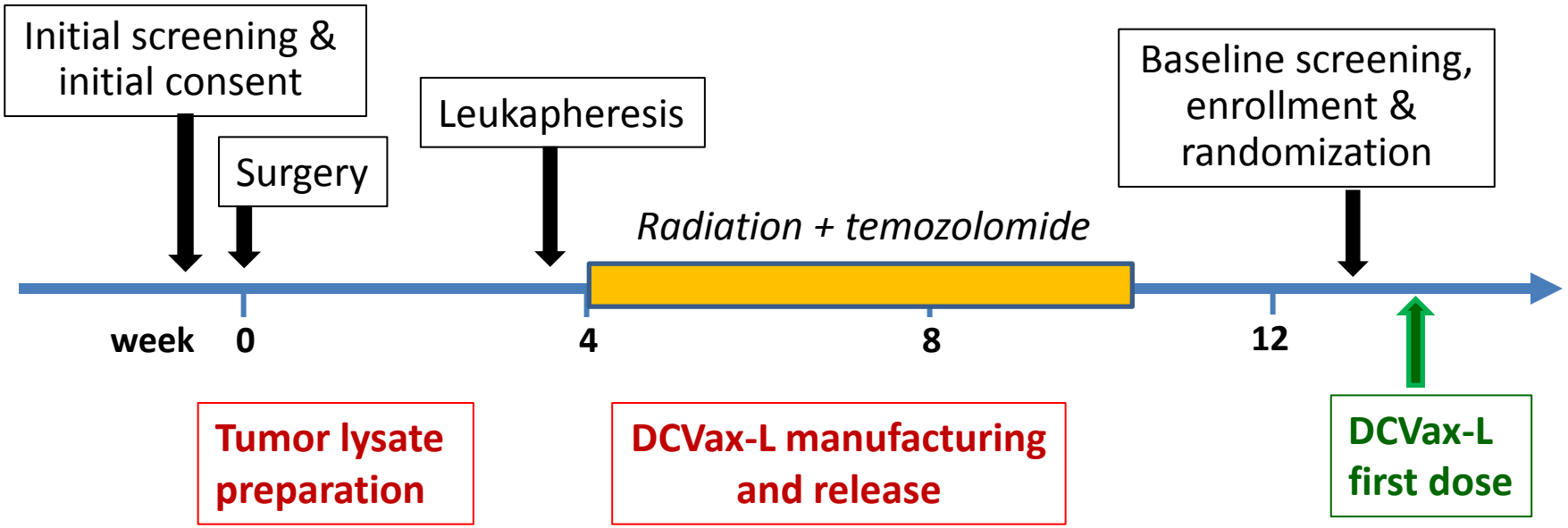
1 secondary endpoint: overall survival (OS)

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




**Main Reasons for Screen Failure:**

- Not GBM
- Tumor too small
- Leukapheresis failure
- Progressive disease

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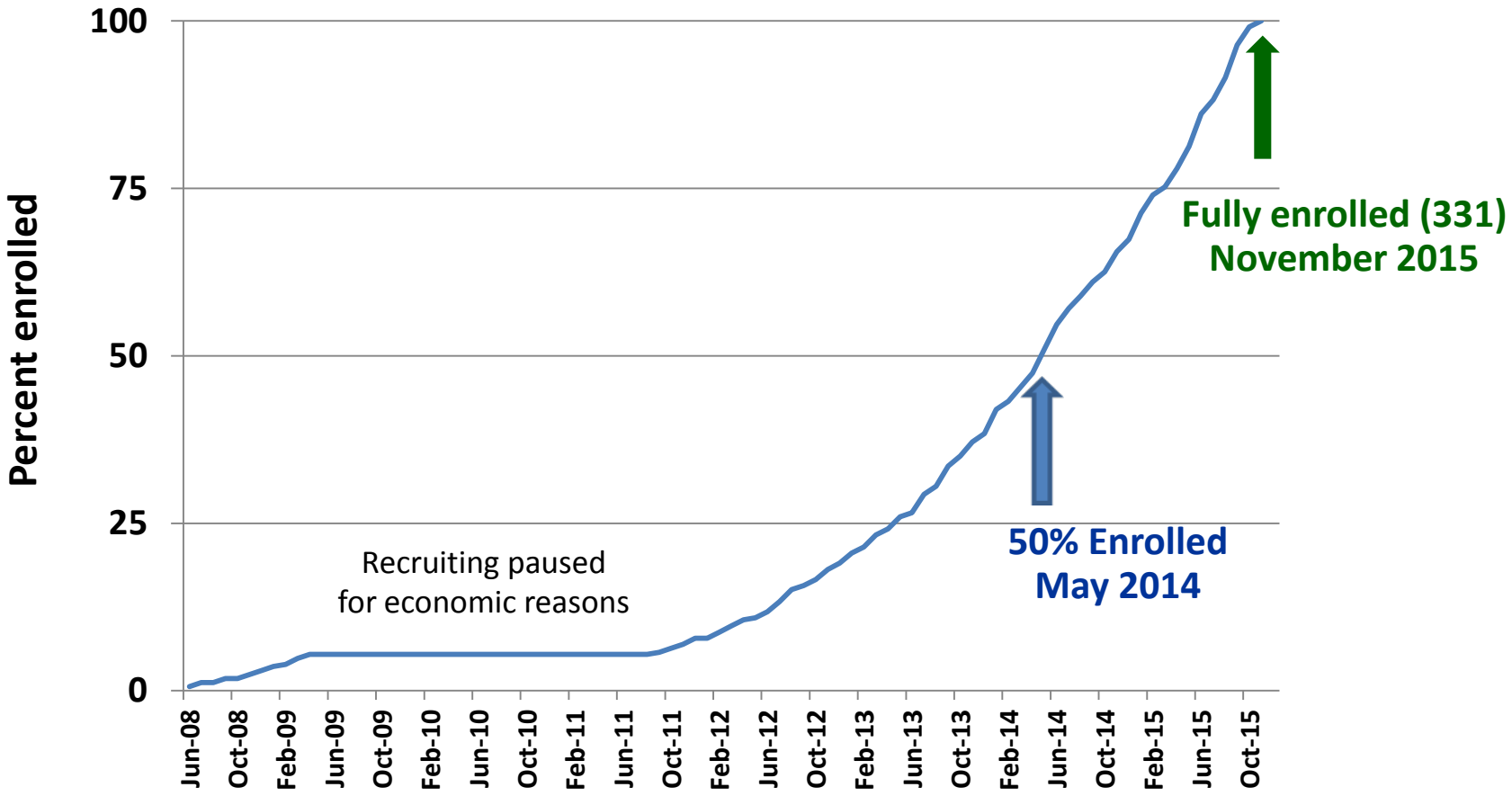
# DCVax-L Phase III Trial -- Enrollment Timeline

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# 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 drafted over summer with input from investigators now being finalized.

# Third Party Observations
## (not specifically endorsed by the company)

- *"The new **blinded** data released at ASCO further strengthens the hypothesis that we are seeing longer patient survival in the trial due to DCVax—L."* (Larry Smith, independent analyst)
- *"We know that the lower end of the range is 22 months of survival but what is a good estimate of the upper end?"* (Larry Smith, independent analyst)
- *"Statistical analysis on available [**blinded**] DCVax-L Phase 3 Trial Data showing the potential for significant efficacy with progression free survival (PFS)."* (Bohsie, Seeking Alpha)

# 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.

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# DCVax®-Direct for Inoperable Solid Tumors

## Program Update

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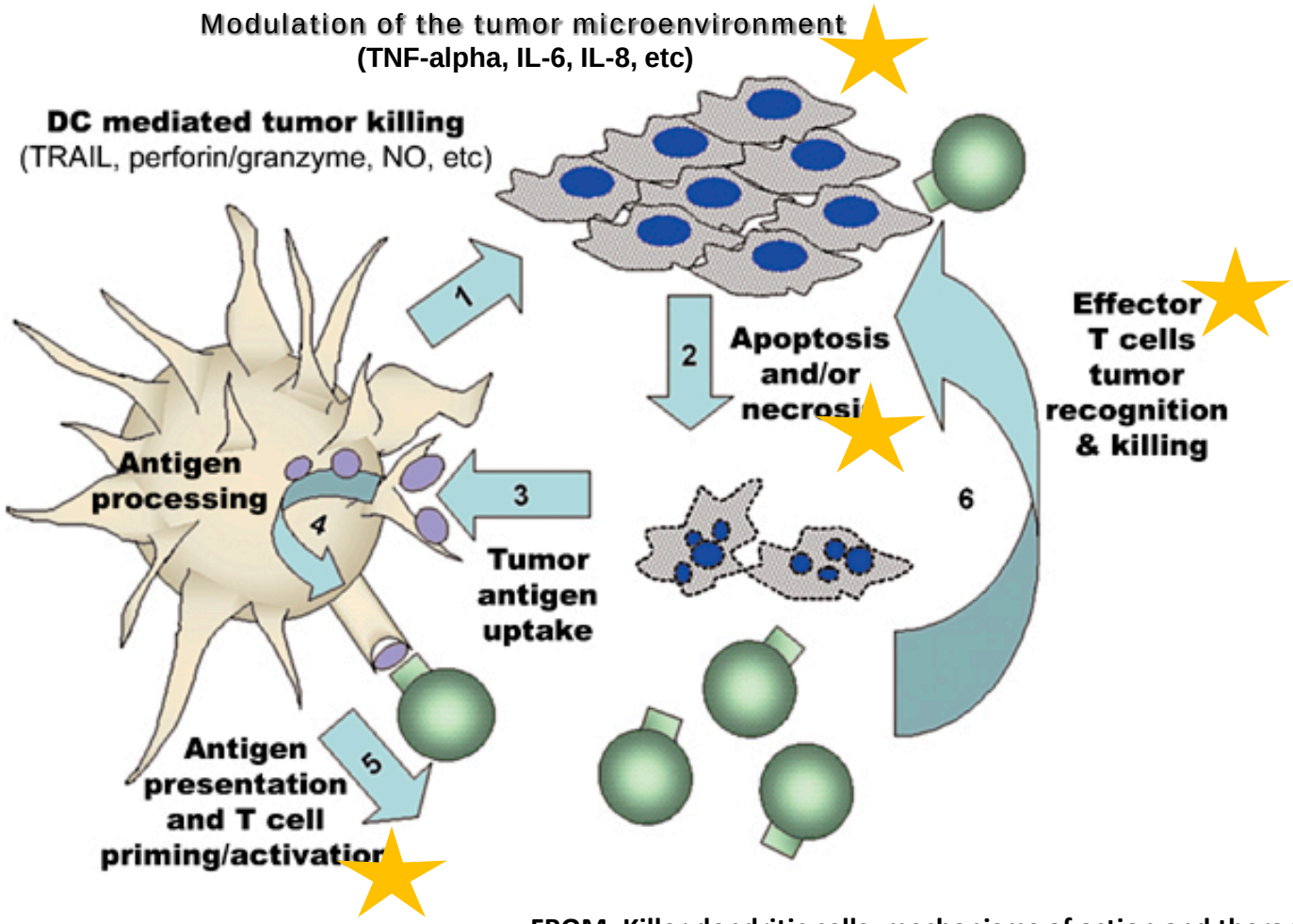
# DCVax-Direct

- 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 Mechanism of Action




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

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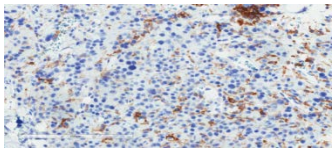
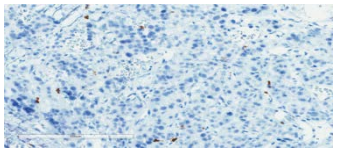
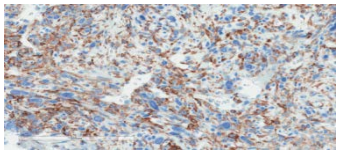
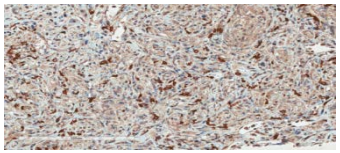
# DCVax-Direct -- Mechanism of Action

## Modulation of the Tumor Microenvironment ("cold" to "hot" conversion)

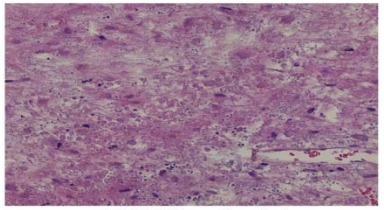
**Day 0**

CD4 CD8

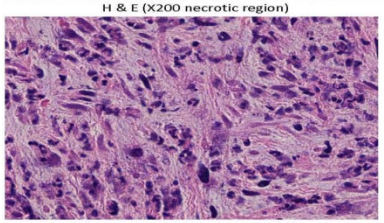



**Day 7**

## Induction of Necrosis

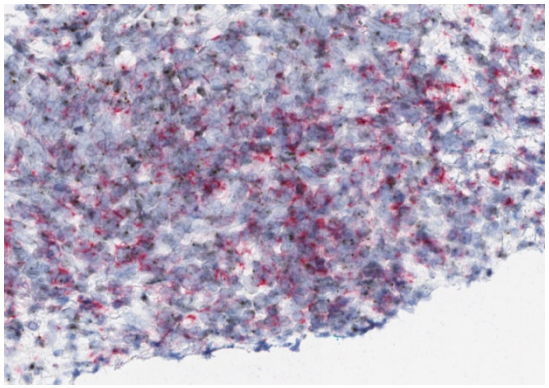


H & E (X200 necrotic region)

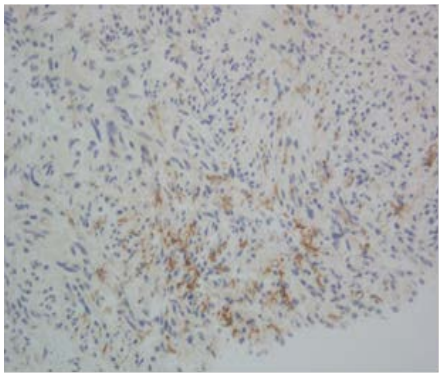


H & E (undergoing tumor necrosis)

## Induction of cytotoxic T cells



## Induction of PD-1



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# DCVax-Direct Phase I Trial

## Trial was very information-rich, helping guide further development

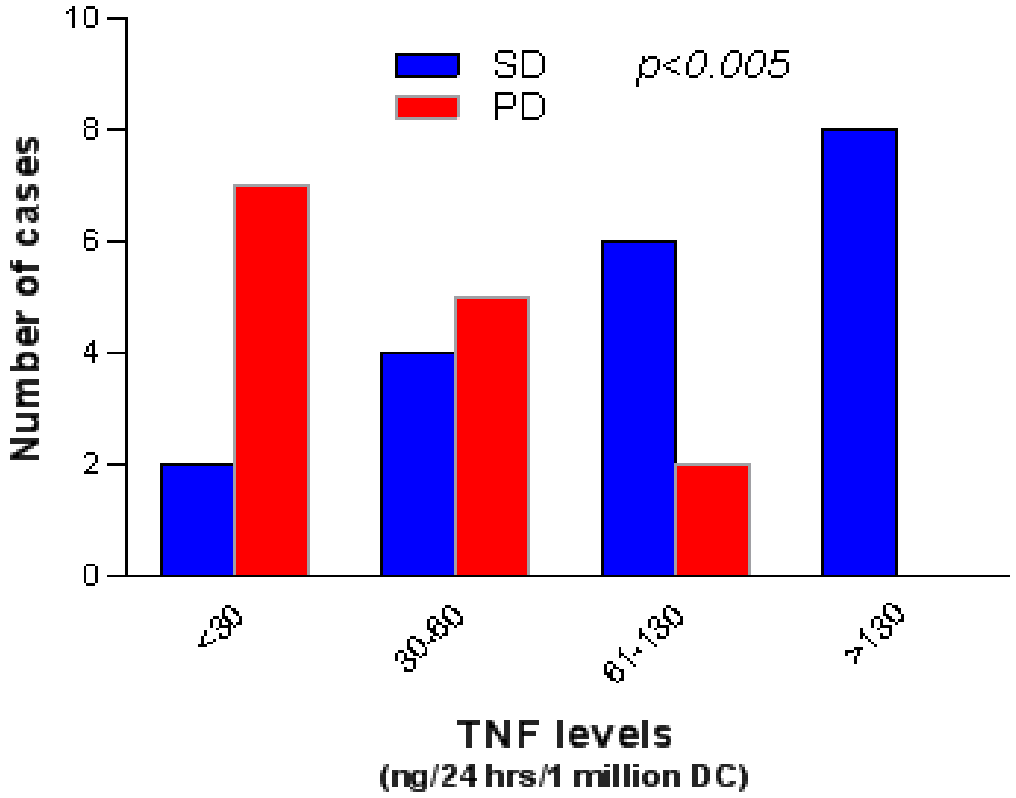
- 13 different cancers treated, including very aggressive cancers
- 3 dose levels tested: 2M, 6M and 16M cells
- 2 different product formulations tested
- Feasibility of image-guided injections tested (multiple methods)
- Both imaging and biopsies used to monitor responses, correlate with clinical outcomes 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)

# DCVax-Direct Phase I Trial: Cytokines and Tumor Control

Cytokine production, especially TNFα, was correlated with tumor control

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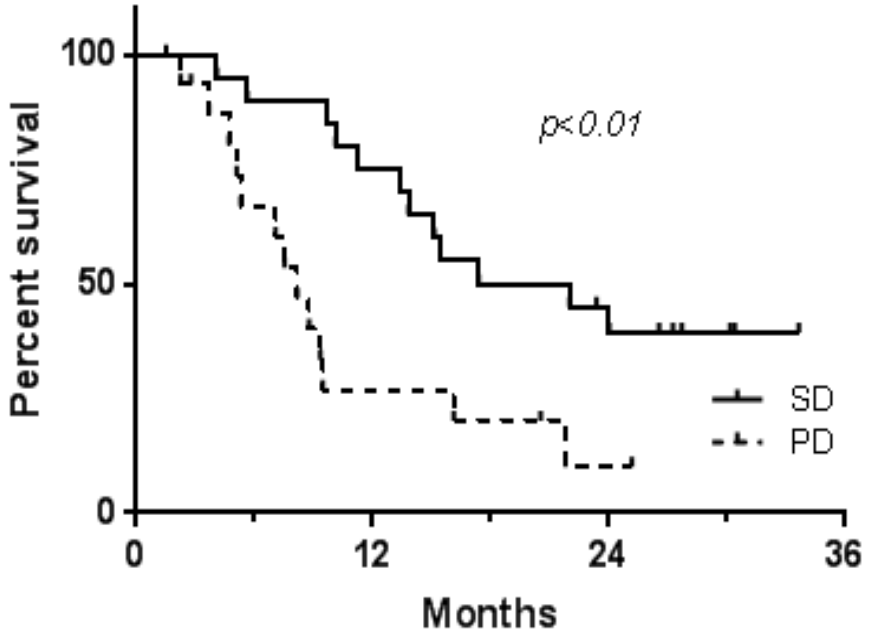
# DCVax-Direct Phase I Trial: Tumor Control, Stable Disease

- 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

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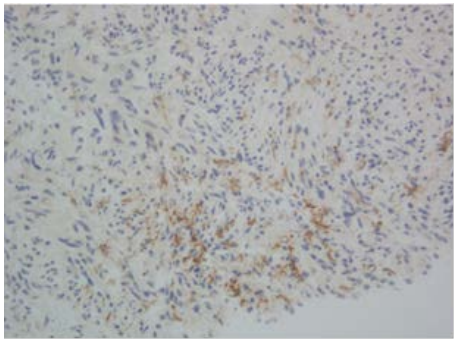
# Induction of Checkpoint Expression (PD-L1)

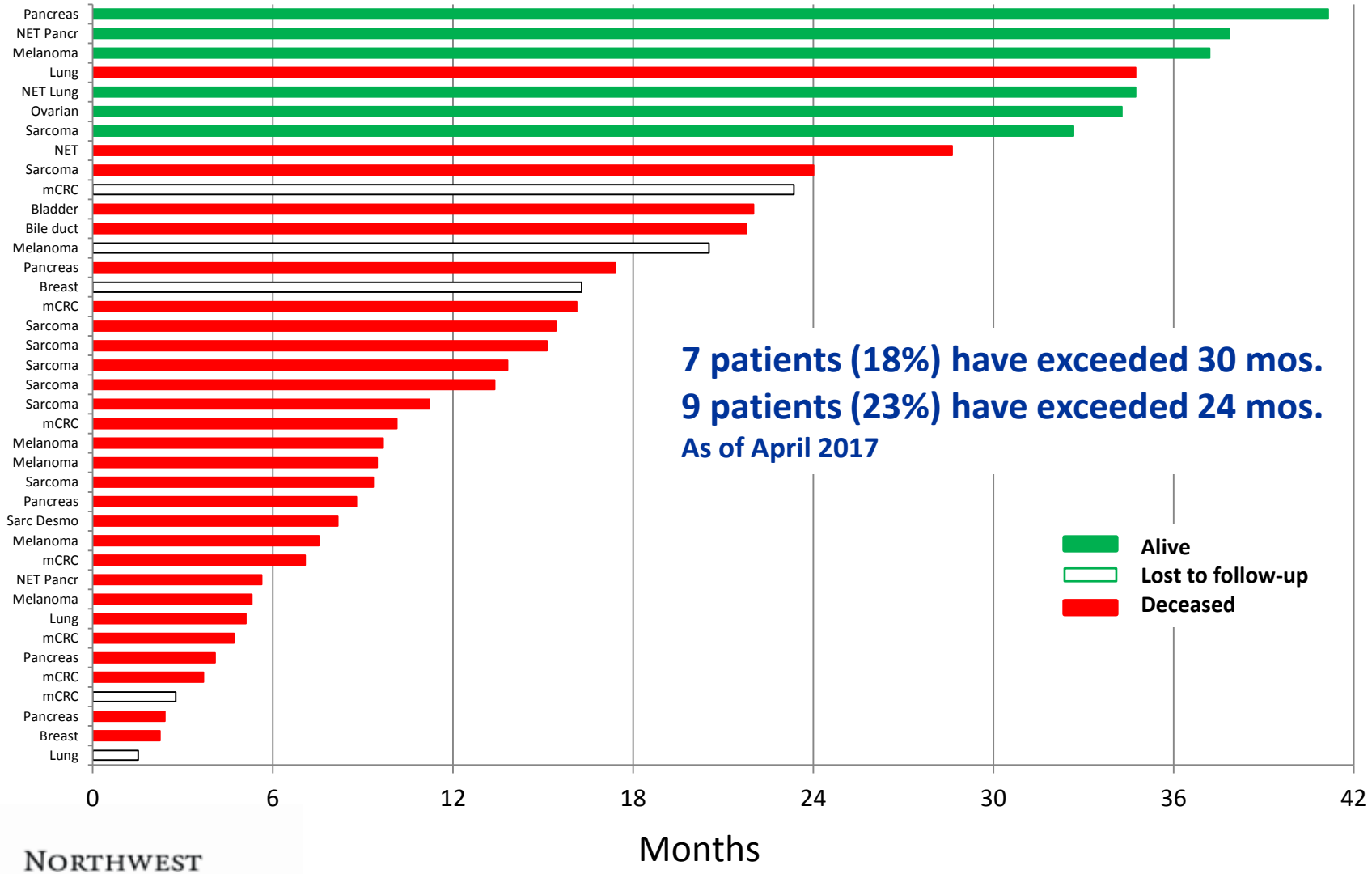
- 20 of 25 evaluable patients (80%) in DCVax-Direct Phase I trial showed either *de novo* or significantly increased expression of PD-L1 following DCVax-Direct treatment
- Patient-to-patient variation in timing of when PD-L1 expression appears



*De novo* PD-L1 staining on sarcoma tissue, 8 weeks after initiation of DCVax-Direct treatment

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

# DCVax-Direct Phase I Trial: Survival Update

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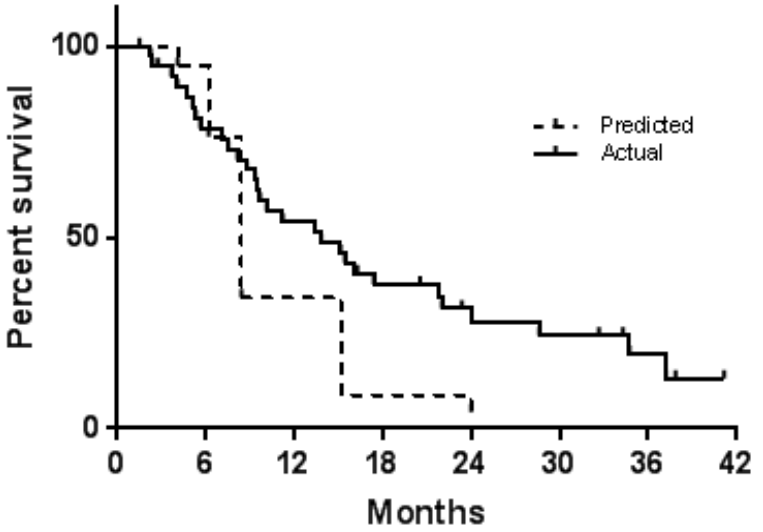
# DCVax-Direct Phase I Trial: Actual vs. Predicted Survival

- 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.

- 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

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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.)

- 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)

- Preparations are ongoing and trial expected to be initiated in the fall of 2017

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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