Personalized Approaches to Immunotherapy

Phacilitate Immunotherapy Conference

January 26, 2015
Disclaimer

Certain statements made in this presentation are “forward-looking statements” of NW Bio as defined by the Securities and Exchange Commission (“SEC”). All statements, other than statements of historical fact, included in this presentation that address activities, events or developments that NW Bio believes or anticipates will or may occur in the future are forward-looking statements. These statements are based on certain assumptions made based on experience, expected future developments and other factors NW Bio believes are appropriate in the circumstances. Such statements are subject to a number of assumptions, risks and uncertainties, many of which are beyond the control of NW Bio. Investors and others are cautioned that any such statements are not guarantees of future performance. These forward-looking statements could cause actual results and developments to differ materially from those expressed or implied in such statements, including our ability to raise funds for general corporate purposes and operations, including our clinical trials, the commercial feasibility and success of our technology, our ability to recruit qualified management and technical personnel, our ability to scale up the manufacturing of our product candidates for commercialization, the success of our clinical trials and our ability to obtain and maintain required regulatory approvals for our products. Furthermore, NW Bio does not intend (and is not obligated) to update publicly any forward-looking statements. The contents of this presentation should be considered in conjunction with the risk factors contained in NW Bio’s recent filings with the SEC, including its most recent Form 10K. This communication is neither an offer to sell nor a solicitation of an offer to buy any securities mentioned herein. This publication is confidential for the information of the addressee only and may not be reproduced in whole or in part; copies circulated, or disclosed to another party, without the prior written consent of Northwest Biotherapeutics (NW Bio) are strictly prohibited.
Overview

• Cancers are highly variable. Correspondingly tailored (personalized) treatments are needed.

• “Personalized treatments” include a wide range of approaches and degrees of personalization. Most tend to involve “rifle shots.”

• A fully personalized approach such as DCVax® can...
  ✓ Address the extensive variation among patients, avoid “Russian Roulette”
  ✓ Complement and enhance other immunotherapies and targeted therapies
  ✓ Provide broad spectrum anti-tumor action, both local and systemic
  ✓ Offer an excellent safety profile

• A fully personalized approach such as DCVax® can also be cost-effective and operationally practical.
Cancer Is A Highly Variable Disease

Cancer Is A Highly Variable Disease

Cancer Is A Highly Variable Disease

- Extensive variation among cancers

- Extensive variation among patients, even with “same” cancer

- Significant variations within a single patient as disease progresses

- Extensive heterogeneity even within a single tumor
Personalized Approaches Vary Across A Spectrum

- Standardized Product
- Standardized Targets
- Personalized Profiling

- Personalized Product
- Standardized Targets
- Personalized Targets

- Peptide vaccines
- DNA vaccines
- Checkpoint inhibitors

- CAR-Ts
- DC vaccines with pre-selected peptide antigens

DCVax®
Issues With Standardized Products, Limited Targets

• **“Russian Roulette”**

  The patient’s tumor may or may not express the targets.

  Example: EGFRvIII mutation in GBM – only expressed on 30% of GBM

• **Tumor escape**

  Tumors can and do stop expressing 1 or a couple of antigens.

  Example: after treatment of GBM with EGFRvIII peptide, when tumor recurs, 82% have no EGFRvIII expression

• **Toxicity**
DCVax®: A Fully Personalized Immune Therapy

Personalized Product: autologous (personalized) dendritic cells
- Allows repeat doses, ongoing treatment

Personalized Targets: tumor antigens from patient’s own tumor
- Avoids “Russian Roulette”

Broad Scope of Targets: full set of tumor antigens
- Not just 1 or several pre-selected, standardized antigens
- Maximize obstacles to tumor escape

Excellent safety profile
- Some flu-like symptoms; no additional drugs, no hospital stays
## DCVax Applicable to All Types of Solid Tumors  
(Both Operable & Inoperable)

<table>
<thead>
<tr>
<th>Market</th>
<th>Product</th>
<th>Composition</th>
<th>Lead Program</th>
</tr>
</thead>
</table>
| All **Operable** Solid Tumors | **DCVax®-L** | Dendritic cells + biomarkers from tumor tissue sample surgically removed | Brain cancer  
*348-patient Phase III trial underway*  
Small ovarian cancer  
Phase I/II trial completed |
| All **Inoperable** Solid Tumors | **DCVax®-Direct** | Dendritic cells injected directly into tumor(s) + biomarkers picked up onsite in tumor | All solid tumor cancers  
*60-patient Phase I/II trial underway* |

**Other**  
*Hormone independent prostate cancer*

| *DCVax®-Prostate* | Dendritic cells + recombinant prostate cancer biomarker (PSMA) | Prostate cancer  
*600-patient Phase III trial previously cleared by FDA* |

* The Company will seek to out-license this program
Dendritic Cells Mobilize Overall Immune System

**DENDRITIC CELLS**
the master immune cells

**INNATE IMMUNE SYSTEM**
“First-responders” (within hours/days)
Response is automatic
Response is non-specific
(not tailored to each particular threat)
Natural Killer Cells, Neutrophils, Granulocytes, Macrophages

**ADAPTIVE IMMUNE SYSTEM**
Follow-on defense (within week or weeks)
Response is triggered by exposure to particular threat (activation + "education")
Response is specific & creates memory
(tailored to each particular threat)

**CELLULAR IMMUNITY**
Helper T Cells
Killer T Cells

**HUMORAL IMMUNITY**
B Cells → Antibodies

Signals activate & biomarkers “educate” Dendritic Cells

Tumor Cell Death
Large Multiplier: Each Dendritic Cell Activates Hundreds of T Cells

- Resting anti-cancer T cell attaches to DC
- Anti-cancer T cell activates
- Activated anti-cancer T cells divide rapidly
- Activated anti-cancer T cells travel to tumor site
Potentially Complementary With Checkpoint Inhibitors

- Large number of “checkpoints” built into the immune system
- Response rates (%) to single checkpoint inhibitors limited to date
- T cells must be activated, to express checkpoints
- DCVax activates T cells
- DCVax mobilizes diverse T cell populations against diverse tumor antigens (targets)

Potentially Complementary With T Cell & Targeted Therapies

**T cell therapies (CAR-Ts, TCR, etc.)**
- Focus on a particular tumor antigen (CD-19, EGFR, etc.)
- Designed to boost T cell numbers, affinity, etc. for that antigen
- Durability not yet clear
- Addressing diverse antigens may be more important in solid tumors

**Targeted therapies**
- Focus on a particular cellular pathway
- Alternate/redundant pathways, tumor escape are an issue

DCVax offers broad spectrum anti-tumor action which can complement key “rifle shots”
DCVax Is Expanding the Reach of Immunotherapy

Front line treatment for newly diagnosed disease

- DCVax-L for newly diagnosed GBM, with SOC (Phase III)

Front line treatment for lower grade cancers

- DCVax-L for all grades of gliomas, with SOC (Hosp. Exemp., Germany)

Treatment for patients with very heavy tumor burdens

- DCVax-L for late stage, metastatic ovarian cancer
- DCVax-L for “rapid progressor” GBM
- DCVax-Direct for 4-5+ inoperable metastatic tumors
- DCVax-Direct for very large tumors (10 cm. lung; 15x19x17 cm. sarcoma)

Long tail of Overall Survival
DCVax-L for Newly Diagnosed GBM

PHASE I/II TRIALS

• 20 newly diagnosed GBM; 14 recurrent GBM; 5 lower grade gliomas

• Standard of care (surgery & 6 weeks radiation & chemo) + DCVax-L

• Primary endpoint: safety; Secondary endpoint: progression free survival

<table>
<thead>
<tr>
<th></th>
<th>Standard of Care*</th>
<th>Matched Concurrent Controls**</th>
<th>DCVax-L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression (Tumor Recurrence)</td>
<td>6.9 mos</td>
<td>8.1 mos</td>
<td>2 years</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>14.6 mos</td>
<td>17 mos</td>
<td>3 years</td>
</tr>
<tr>
<td>Long Tail of Survival</td>
<td>2 – 3% alive at 5 years</td>
<td></td>
<td>To date: 33% alive &gt;4 yrs 27% alive &gt;6 yrs 2 pts alive &gt;10 yrs</td>
</tr>
</tbody>
</table>


**matched for age, gender, Karnofsky score, extent of surgical resection, and same std of care treatment, at same hospital, in same time period
**DCVax-L for “Info Arm” Compassionate Use Patients**

- 55 patients who were not eligible for the Phase III clinical trial
  - 51 of the 55 patients were actual or potential Rapid Progressors
  - 4 patients were ineligible for other reasons (e.g., less than the minimum 5 doses)

<table>
<thead>
<tr>
<th>“Information Arm”</th>
<th>Median OS w/Std of Care</th>
<th>Median OS w/DCVax-L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid progressors, pseudo progressors &amp; patients w/insufficient doses</td>
<td>Approx 7-10 months</td>
<td>Approx 18 months**</td>
</tr>
</tbody>
</table>

**12 of the 51 patients (~24%) are still alive at up to 42 months; All 12 are well past 2 years, and more than half are past 30 months.**

- These patients received DCVax-L on same treatment regimen used in the Phase III trial, at medical centers participating as sites in the Phase III trial
- Data were collected and maintained by independent CRO (same CRO as in Ph III trial)
DCVax-L for Advanced Metastatic Ovarian Cancer

- Advanced metastatic ovarian cancer
  - Patients who had failed standard therapy, including Avastin

- Two-stage trial: 6 patients
  - Stage 1: DCVax-L treatments
  - Stage 2: autologous T cell infusions

- Efficacy endpoints: tumor response (shrinkage), PFS and OS

- Site: U Penn Center of Excellence in Ovarian Cancer

- Results after DCVax treatment:
  - Partial tumor clearance in 2 patients with strong immune response
  - Disease stabilization in 2 patients with moderate immune response

4 of 6 patients still alive at 25, 26, 37 and 46 months

Northwest Biotherapeutics


DCVax-Direct for Multiple Inoperable Tumors: Pancreatic

- Pancreatic patient with 5 tumors
  (including liver metastases and abdominal tumors)

- Substantial prior chemotherapy – patient failed
  (6 cycles FOLFOX, then Xeloda)

- Stable disease (and some tumor shrinkage in liver)
  through Week 16 on DCVax-Direct

- Recently, abdominal tumor had shrunk enough to enable
  surgical removal

- Patient is now >22 months from diagnosis and doing well:
  working and continuing normal life

Patient’s video for National Geographic:
http://files.natgeonetworks.com/_sqDLtIshExehkR
DCVax-Direct for Multiple Inoperable Tumors: Sarcoma

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

Substantial T-cell infiltration:

CD3 cells  CD4 cells  CD8 cells
DCVax-Direct for Large Inoperable Tumors: Sarcoma

- Lipo-sarcoma. Prior surgery, radiation and 3 lines of chemotherapy.
  Primary tumor 15 x 19 x 17 cm. Multiple lung metastases.

- DCVax-Direct treatment...

  **Effects on primary tumor:**
  - At 8 wks, increase in interval size [holes], increased bleeding and necrosis
  - At 16 wks, extensive necrosis, decrease in size
  - At 20 wks, further necrosis, small increase

  **Effects on lung metastases:**
  - At 20 wks, 1 shrinking, others stable

Biopsy confirms infiltration and accumulation of immune cells.
DCVax-Direct for Large Inoperable Tumors: Lung Cancer

• Non-small cell lung cancer.
  Stage IV at initial diagnosis: 10 cm. tumor.

• No prior treatment except radiation.

• Tumor enlarged before shrinking after 5 DCVax-Direct injections.

• Difficulty breathing before DCVax treatment;
  now back to full life, and swimming.

email from patient’s physician:

.... was the pt with radiation as the only therapy! no chemotherapy.
She presented w Stage 4 lung cancer - DC vax is the only systemic therapy.
Interesting pt - she has recovered and has great QOL.
DCVax®-L: Cost-Effective, Rapid Batch Manufacturing

• DAY 1: Tumor tissue & blood at manufacturing facility.

• DAY 2: Precursors of dendritic cells isolated.

• DAY 2-7: Precursors differentiated into dendritic cells.

• DAY 7: Dendritic cells “educated” by exposure to biomarkers from tumor tissue.

• DAY 8: “Educated” dendritic cells harvested & frozen. Manufacturing finished. (Release tests follow)

**Single manufacturing run yields 3-5 years of doses of DCVax-L product.**

**Only 2 grams of tumor tissue needed for full batch.**

**With <2 grams of tumor tissue, a partial batch can be produced.**
DCVax®: Operationally Practical for Commercialization

- Only 1 manufacturing run per patient
- Frozen product (“off the shelf”); frozen shelf life validated
- Simple administration to patient: intra-dermal or image guided intra-tumoral injection
- Compatible with Standard of Care and other experimental treatments
- Pricing in line with other new cancer drugs