Translational development of Therapeutic Lymphoma Vaccines

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CME Disclosures

- Biovest International (consultant)
- Antigenics (consultant)
- Xeme Biopharma, Inc. (stockholder)
- Celgene (research support)
Types of vaccines

• Prevention

• Secondary prevention

• Therapeutic (e.g. Provenge)
Idiotype (Id): A clonal marker and model tumor antigen

Mature B cells

Plasma cells

* = malignant transformation
Personalized Human Vaccine Production

myeloma cell + tumor cell

fusion

heterohybridoma

LN biopsy

Id scale-up

KLH conjugation

affinity purification

Automated
Vaccine components

- **Idiotype** of the Ig antigen of a B-cell lymphoma can be used as a tumor-specific immunogen.

- **Keyhole lympet hemocyanin (KLH) carrier** serves as an immune stimulant.

- **GM-CSF administered concurrently at site of injection** as an adjuvant.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Vaccine</th>
<th>No. Patients</th>
<th>Histology</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Kwak, NEJM 1992 Hsu, Blood 1997</td>
<td>Id-KLH + Adjuvant</td>
<td>41</td>
<td>FL</td>
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<td>Bendandi, Nat Med 1999</td>
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<td>20</td>
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<td>Timmerman, Blood 2002</td>
<td>Id - DC</td>
<td>35</td>
<td>FL</td>
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<td>Timmerman, Clin Can Res 2002</td>
<td>Plasmid DNA</td>
<td>12</td>
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<td>Barrios, Hematologica 2002</td>
<td>Id-KLH + adjuvant</td>
<td>9</td>
<td>FL</td>
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<tr>
<td>Neelapu, Nat Med 2005</td>
<td>Id – KLH + GMCSF</td>
<td>26</td>
<td>MCL</td>
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<td>Inoges, JNCI 2006</td>
<td>Id – KLH + GMCSF</td>
<td>25</td>
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<td>Bertinetti, Can Res 2006</td>
<td>Fab + MF59 + GMCSF</td>
<td>18</td>
<td>various</td>
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<td>Redfern, JCO 2006</td>
<td>Id – KLH + GMCSF</td>
<td>31</td>
<td>indolent</td>
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</table>
First IND-supported Phase II Trial of Id Vaccine During Clinical Remission (NCI)

- Single-arm prospective study in 20 patients with follicular lymphoma
- Homogeneous group of patients in first remission after uniform induction chemotherapy *
- Vaccine treatment in setting of minimal residual disease
- Regimen
  - Started 6 months after completion of chemotherapy
  - Vaccine (Id-KLH 0.5 mg SC day 0 + GM-CSF 100 µg/m² SC days 0–3) injected monthly for 5 cycles

* PACE= prednisone, Adriamycin (doxorubicin), cyclophosphamide, and etoposide.
First IND-supported Phase II Vaccine Trial During 1\textsuperscript{st} Complete Remission (CR): Results

- **Anti-Id antibody response**: n=15, 75%
- **Tumor-specific CD4+ or CD8+ T-cell response**: n=19, 95%*
- **Conversion from t(14;18) positive to t(14;18) negative**: n=8, 73%†
- **CR after 9.2 yr of follow-up**: n=9, 45%

- **DFS after 9.2 yr of follow-up**

NCI/Biovest Phase III Vaccine Study Objectives

• **Primary Objective:**
  – To determine whether Id vaccine prolongs disease free survival (DFS) compared to control in patients with follicular lymphoma in complete remission (CR) after uniform standard chemotherapy

• **Secondary Objectives:**
  – Evaluate safety of Id vaccine
  – Immune response and biomarker assessment
NCI/Biovest Phase III Vaccine Study Design

8-Year Controlled Prospective Double-Blinded Multi-Center Clinical Trial

Id-KLH + GM-CSF (Id Vaccine)

KLH + GM-CSF (Control)

Stratify for IPI\(^1\), cycles of PACE\(^2\) 2:1 Randomization

Timeline

- 6 - 8 months
- 6 - 12 months
- 6 months

Chemo

LN Bx

Assign CR

- Primary endpoint: disease-free survival
- 14 sites enrolled patients from 2000-2007

\(^1\)low, low-intermediate or high-intermediate, high groups

\(^2\) < 8 or \(\geq\) 8 cycles
Statistical Design

Two Prospective Efficacy Analyses
• Intent-to-Treat Analysis (ITT) compared DFS in treatment arms for all randomized pts

• Modified Intent-to-Treat Analysis (mITT) compared DFS in treatment arms for randomized pts who remained in CR/CRu and received either Id- or control vaccine

Vaccine Isotype Subset Analysis (unplanned)
• DFS by vaccine isotype (IgM or IgG) for patients receiving Id vaccine

Schuster, Neelapu et al. (Kwak) J Clin Oncol 29:2787, 2011
Patient Flow

Enrollment

Stratify / Randomize (n=177)

Post-Induction Recovery Period (6-12m)
Relapse Not Vaccinated with Id or Control (n=60)

Randomized/Vaccinated (n=117)

Enrolled (n=234)

Excluded (n=57)

Randomized (n=177)

Id-vaccine arm (n=118)

Relapse (n=38)
Other (n=4)

Control arm (n=59)

Received Id-vaccine (n=76)

Relapse (n=17)
Other (n=1)

Received Control (n=41)
Disease Free Survival from Randomization (mITT)

Median Follow-up
56.6 mo (range 12.6 – 89.3)

Median DFS
Id vaccine = 44.2 mo
Control vaccine = 30.6 mo

Events
Id vaccine = 44
Control vaccine = 29

Cox PH Model
HR = 0.62; [95% CI: 0.39,0.99] (p=0.047)
FL surface Ig can be either IgG or IgM Isotype

IgM Isotype Immunoglobulin

IgG Isotype Immunoglobulin

- Light Chain
- Heavy Chain
- Constant Region
- Variable Region
- Carbohydrate
Disease Free Survival for Patients with IgM-isotype lymphomas (n = 60)

Median Follow-up
56.6 mo (range 12.6 – 89.3)

N = 60
IgM-Id vaccine N = 35
Control N = 25

Median DFS
IgM-Id vaccine = 52.9 mo
[95% CI:40.2,NA]
Control = 28.7 mo
[95% CI:21.0,39.8]

Events
IgM-Id vaccine = 17
Control = 20
Positive Phase III trial: Potential challenges to “Delivery”

- Patient accrual stopped early/treatment effect apparent only in modified ITT

- requirement for biopsy and personalized manufacture

- optimal treatment requires sustained complete remission
Future directions

• Identify/stratify the subgroup of patients most likely to benefit from this vaccine (e.g. MRD?; predictive biomarkers) and determine the mechanism underlying the observed clinical effects

• Make further improvements in the vaccine product (e.g. 2nd generation DNA fusion vaccines)

• Additional clinical trials combining this vaccine with anti-CD20 mAb (rituximab)-containing chemotherapy regimens
Mantle cell lymphoma clinical trial schema

- LN Bx
- EPOCH-R Begins
- EPOCH-R Ends
- Id/KLH + GM-CSF s.c.

Weeks
-18 0 12 16 20 24 32

n = 26

EPOCH-R 6 cycles

• EPOCH-R – Rituximab on day 1
  -- Continuous iv infusion of Etoposide, Doxorubicin and Vincristine over 96 hrs (days 1-5)
  -- Cyclophosphamide iv on day 5
  -- Prednisone days 1-5.

• Id-KLH+GM-CSF – 0.5 mg autologous Id + 0.5 mg KLH + 100 μg/m² GM-CSF

KLH Ab and B-cell recovery

Representative patient

• 17/23 (74%) patients were positive for anti-KLH antibody.
Response to autologous tumor - IFNg

- 20/23 (87%) patients had a positive T cell response by cytokine induction assay.
Conclusions – MCL vaccine study

• Antibody responses to KLH carrier were delayed but present in 17/23 (74%) patients, and Id-specific antibody responses were detected in 8/23 (35%) patients.

• Tumor-specific T cell responses were detected in 20/23 (87%) patients following rituximab containing chemotherapy regimen.

• These results suggest that severe B-cell depletion does not impair induction of T-cell responses.
Conclusions

• Administration of vaccine following immunosuppressive chemotherapy is feasible (duration of recovery period required unknown)

• In a Phase III trial vaccination improved disease-free survival (DFS) following chemotherapy in patients already in complete remission at time of vaccination (secondary prevention)

• The clinical effect of the vaccine is validated by the subgroup analysis of patients expressing the IgM isotype

• Long-term clinical experience with idiotype protein vaccines demonstrates low toxicity profile, making it ideal for consolidation or maintenance therapy
Factors which may explain differences in outcomes between randomized Phase III studies

<table>
<thead>
<tr>
<th>Critical variable</th>
<th>NCI Phase 2</th>
<th>NCI/Biovest</th>
<th>Genitope</th>
<th>Favrille</th>
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</thead>
<tbody>
<tr>
<td>Pre-requisite to vaccine</td>
<td>CR only</td>
<td>CR only</td>
<td>CR or PR</td>
<td>CR or PR or SD</td>
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<tr>
<td>Induction therapy</td>
<td>PACE</td>
<td>PACE</td>
<td>CVP</td>
<td>rituximab</td>
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<td>Id protein</td>
<td>Native protein from hybridoma</td>
<td>Native protein</td>
<td>Recombinant protein</td>
<td>Recombinant protein</td>
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<tr>
<td>Isotype of Id-vaccine</td>
<td>IgM and IgG (tumor-matched)</td>
<td>IgM and IgG</td>
<td>IgG</td>
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<tr>
<td>Stratification</td>
<td>Prognostic index; # cycles chemotherapy</td>
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Phase III Clinical Trial Sites

- National Cancer Institute
- Duke University Medical Center
- Emory University Winship Cancer Institute
- H. Lee Moffitt Cancer Center
- New England Medical Center
- New York University Medical Center
- Virginia Oncology Associates
- North Mississippi Hem & Oncology Associates
- Northwestern University
- St. Mary's/Duluth Clinic (SMDC) Health System
- University of Pennsylvania
- The University Of Texas MD Anderson Cancer Center
- Westchester Oncology & Hematology Group
- Southern Oncology Research