Therapeutic Cancer Vaccines: Successes and Failures in the Clinic

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Tumor Vaccines

- >100 years ago, W. B. Coley reported regression of tumors with injected bacterial extracts.
- Attempts to harness the immune system to mediate the rejection of tumors *in vivo*.
- Important discoveries in immunology and tumor cell biology: opportunities to explore the therapeutic potentials of cancer vaccines.
Tumor Vaccines

“To increase host’s immunity to own tumor”
Tumor Vaccines: The Successes
Tumor Vaccines Currently Being Used

- Peptide Vaccines
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines
Tumor Vaccines Currently Being Used

- Peptide Vaccines
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines
Peptide Vaccines

CD4 or CD8 T-Cell

TCR

Cell Surface Proteins

Class I TAA

MHC Class I

Tumor

Class II TAA

MHC Class II
Peptide Vaccines

- Overexpressed proteins (HER-2/neu)
- Oncogenes (ras)
- Embryonic proteins (MAGE)
- Viruses (HPV, HBV)
- Tissue specific proteins (MART-1/Melan-A, gp100, tyrosinase, PSA, PSMA)
- Mutated tumor suppressors (p53)
- Modified proteins (MUC-1)
- Idiotypic epitopes (B cell lymphoma)
Clinical Trial Results of the HER-2/neu (E75) Vaccine to Prevent Breast Cancer Recurrence in High-Risk Patients:
From US Military Cancer Institute Clinical Trials Group Study I-01 and I-02

Elizabeth A. Mittendorf, MD\textsuperscript{1}, Guy T. Clifton, MD\textsuperscript{2}, Jarrod P. Holmes, MD\textsuperscript{3}, Kevin S. Clive, MD\textsuperscript{2}, Ritesh Patil, MD\textsuperscript{4}, Linda C. Benavides, MD\textsuperscript{2}, Jeremy D. Gates, MD\textsuperscript{2}, Alan K. Sears, MD\textsuperscript{2}, Alexander Stojadinovic, MD\textsuperscript{5}, Sathibalan Ponniah, PhD\textsuperscript{6}, and George E. Peoples, MD\textsuperscript{2,6}
Timeline

Figure 1.
E75 vaccine trial schema. IND = Investigational New Drug.

Cancer 2012 May 15; 118(10): 2594-2602
Clinicopathologic Characteristics of Evaluable Patients in the E75 Vaccine Trials by Treatment Group at 24-Month Landmark Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vaccinated, n = 106, No. (%)</th>
<th>Controls, n = 76, No. (%)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, y</td>
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<td></td>
<td>.38</td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
<td>53</td>
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</tr>
<tr>
<td>Range (28–78)</td>
<td>(32–83)</td>
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<tr>
<td>Race</td>
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<tr>
<td>White (89.6%)</td>
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<tr>
<td>Black (4.7%)</td>
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<td>10</td>
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<tr>
<td>Other (5.7%)</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Time to enrollment in trial in days</td>
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<td></td>
<td>.25</td>
</tr>
<tr>
<td>Median</td>
<td>472</td>
<td>435</td>
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<tr>
<td>Tumor size</td>
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<td></td>
<td>.45</td>
</tr>
<tr>
<td>T1 (67.0%)</td>
<td>71</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>T2 (24.5%)</td>
<td>26</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>T3 (6.6%)</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>T4 (1.9%)</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
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<td></td>
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<tr>
<td>N0 (51.9%)</td>
<td>55</td>
<td>33</td>
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</tr>
<tr>
<td>N1 (36.8%)</td>
<td>39</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>N2 (8.5%)</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>N3 (2.8%)</td>
<td>5</td>
<td>7</td>
<td></td>
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<tr>
<td>Other tumor characteristics</td>
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<td>.45</td>
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<tr>
<td>Histologic grade 3</td>
<td>40 (38.8%)</td>
<td>30 (41.1%)</td>
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<tr>
<td>ER and PR negative</td>
<td>33 (31.7%)</td>
<td>14 (18.4%)</td>
<td>.06</td>
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<tr>
<td>HER2 overexpression</td>
<td>30 (30.3%)</td>
<td>18 (26.5%)</td>
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<tr>
<td>Trastuzumab</td>
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<tr>
<td>Treatment</td>
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<td></td>
<td>.13</td>
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<tr>
<td>Hormonal therapy</td>
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<td>57 (76.0%)</td>
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<td>Chemotherapy</td>
<td>79 (74.5%)</td>
<td>54 (71.1%)</td>
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<td>Radiation therapy</td>
<td>77 (72.8%)</td>
<td>62 (81.8%)</td>
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<tr>
<td>Received optimal dose of vaccine</td>
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<tr>
<td>Yes</td>
<td>37 (34.9%)</td>
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<tr>
<td>No</td>
<td>69 (65.1%)</td>
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</table>
E75 Dosing Regimens for Breast Cancer Node-Positive and Node-Negative Patient Groups by Trial Design

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Patients, No.</th>
<th>Peptide Dose, μg</th>
<th>GM-CSF Dose, μg</th>
<th>Months Vaccinated</th>
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<td>Node positive</td>
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<td>250</td>
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<td>500</td>
<td>250</td>
<td>0, 1, 2, 5</td>
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<td>500</td>
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<td>0, 1, 2, 3, 4, 5</td>
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<tr>
<td>1000.250.4</td>
<td>11</td>
<td>1000</td>
<td>250</td>
<td>0, 1, 2, 3, 4, 5</td>
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<tr>
<td>1000.250.6</td>
<td>27</td>
<td>1000</td>
<td>250</td>
<td>0, 1, 2, 3, 4, 5</td>
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<tr>
<td>Node negative</td>
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<td></td>
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<tr>
<td>500.125.3</td>
<td>10</td>
<td>500</td>
<td>125</td>
<td>0, 1, 5</td>
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<td>500.125.4</td>
<td>9</td>
<td>500</td>
<td>125</td>
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<tr>
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<td>1000</td>
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<tr>
<td>Total</td>
<td>106</td>
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</table>

Cancer 2012 May 15; 118(10): 2594-2602
Disease-Free Survival

Figure 2.
24-month disease-free survival for all vaccinated patients compared with unvaccinated control patients.

Cancer 2012 May 15; 118(10): 2594-2602
DFS by Subgroups

Figure 3.
24-month disease-free survival (DFS) determined for clinicopathologic subgroups. DFS was compared between vaccinated patients and unvaccinated controls in patients with (A) node-positive breast cancer, (B) HER2 low-expressing (IHC 1+ or 2+ or FISH < 2.0) breast cancer, and (C) low-grade (grade 1 or 2) breast cancer.
Conclusion

• E75 + GM-CSF vaccine effective in certain subsets of patients (HER2 low, positive LN, low grade)
• Boosting is beneficial
• Ongoing phase 3 trial comparing E75 + GM-CSF to GM-CSF alone in HLA-A2+/A3+ patients
Tumor Vaccines Currently Being Used

- Peptide Vaccines
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines
Gene-Modified Cell Therapy
Gene Therapy

- Cytokines (GM-CSF, IL-12)
- Tumor Antigens
- Viral Genes
- MHC Genes
- Co-Stimulatory Molecules
A Lethally Irradiated Allogeneic Granulocyte-Macrophage Colony Stimulating Factor-Secreting Tumor Vaccine for Pancreatic Adenocarcinoma: A Phase II Trial of Safety, Efficacy, and Immune Activation

Eric Lutz, PhD*,§§, Charles J. Yeo, MD**, Keith D. Lillemoe, MD††, Barbara Biedrzycki, NP*, Barry Kobrin, PhD*, Joseph Herman, MD, MSc†, Elizabeth Sugar, PhD††, Steven Piantadosi, MD, PhD***, John L. Cameron, MD‡, Sara Solt, BS*, Beth Onners, RN*, Irena Tartakovsky, MS*, Miri Choi, BS*, Rajni Sharma, PhD§, Peter B. Illei, MD§, Ralph H. Hruban, MD*,§, Ross A. Abrams, MD††, Dung Le, MD*, Elizabeth Jaffee, MD***,§§,†††, and Dan Laheru, MD*
Methods

Surgical resection

First vaccine

Adjuvant radiation and chemotherapy

2nd, 3rd, 4th, 5th Vaccinations

0 4 8 10 16 20 24 28 32 36 40 44 48 72

Weeks

Amylase, CBC with differential and platelets, and complete chemistry profile for toxicity; CA19-9 and CT scans for recurrence; PBL and serum for immune analyses.

Amylase, CBC with differential and platelets, and complete chemistry profile for toxicity; CA19-9 and CT scans for recurrence; PBL and serum for immune analyses.

DFS and OS

17.3 months (14.6-22.8)

24.8 months (21.2-31.6)

Ann Surg. 2011 February; 253(2): 328–335
OS compared to SOC

V=24.8 months (21.2-31.6)
C=20.3 months (18.0-23.9)
Postimmunotherapy enhancement of mesothelin-specific CD8+ T cell responses in HLA-A0101+ and HLA-A201+ patients correlates with disease-free survival.
Tumor Vaccines Currently Being Used

- Peptide Vaccines
- Gene-Modified Cellular Vaccines
- Dendritic Cell Vaccines
DC Vaccines

- **Tumor**
- **DC**
  - MHC Class I
  - MHC Class II
  - TAA
  - TCR
- **CD8+ CTL**
  - TAA
  - TCR
- **CD4+ T-Helper**
  - TAA
  - TCR
Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory PC.

Small EJ, Schellhammer PF, Higano CS et al

J Clin Oncol 2006; 24: 3089-3094
Methods

A Stages in sipuleucel-T treatment

- Patient’s white blood cells harvested by leukapheresis
- Short-term culture with protein ‘cassette’
- GM-CSF
- PAP
- Shipping
- Cells infused BACK into patient (IV)

B Proposed mechanism of action of sipuleucel-T in prostate cancer

- Recombinant PAP antigen combines with resting APC
- APC takes up antigen
- Antigen is processed and presented on surface of APC
- Fully activated APC = sipuleucel-T

- Sipuleucel-T activates T cells
- Activated T-cells proliferate and attack tumour cells
Results

**Fig 2.** Primary end point, time to disease progression (intent-to-treat population). HR, hazard ratio.

**Fig 3.** Final overall survival (intent-to-treat population). HR, hazard ratio.
Kaplan-Meier Estimates of Overall Survival

N= 512
2:1 randomization
1° endpoint: OS

HR: 0.78 (0.61-0.98)  P=0.03

HR: 0.65 (0.47-0.90)  P=0.009

Vaccines: The Challenges

- Cytokines (IL-10, TGF-β)
- Tumor
- CTL
- Fas  FasL
- VEGF
- TAA
- Tregs/MDSC
- DC
Summary

• Significant advances in the basic science of tumor immunology
• Some clinical trials report sustained responses and survival advantage in patients with advanced cancer
Future Directions

• Patients who have failed conventional cancer treatment → Patients who have completed conventional treatment
• HLA-restricted → HLA-unrestricted
• Preventive vaccines
• CMT: Sx + CT + RT + BT