Vaccines Insights from Ongoing Trials

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Dallas, Texas
# Results of Non-Gene-Based Vaccines in IIIB/IV NSCLC

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Stage</th>
<th># Pts</th>
<th>Median Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL172</td>
<td>IIIB/IV</td>
<td>210</td>
<td>7.3 months</td>
<td>O’Brien et al; 2004</td>
</tr>
<tr>
<td>CIMAvax EGF</td>
<td>III, IV</td>
<td>80</td>
<td>11.7 months (GAR*) vs. 3.6 months (PAR*)</td>
<td>Neninger, V. et al; 2008</td>
</tr>
<tr>
<td>CIMAvax EGF</td>
<td>IIIB, IV</td>
<td>43</td>
<td>Low dose: 6.43 months; High does: 8.4 months</td>
<td>Ramos, T.C. et al; 2006</td>
</tr>
<tr>
<td>Telomerase peptide</td>
<td>IIIB, IV, (I,III A)</td>
<td>26</td>
<td>8.5 months (36% 1yr)</td>
<td>Brunsvig, P.F. et al; 2006</td>
</tr>
<tr>
<td>BLP25</td>
<td>IIIB</td>
<td>88</td>
<td>17 months</td>
<td>Butts, C. et al; 2005</td>
</tr>
<tr>
<td>BLP25</td>
<td>IIIB/IV</td>
<td>171</td>
<td>3 year OS 31% for BLP25 / 17% for BSC (p=0.035)</td>
<td>Butts, C. et al; 2011</td>
</tr>
<tr>
<td>EP2101</td>
<td>IIIB/IV</td>
<td>135</td>
<td>17 months</td>
<td>Barve, M.; 2008</td>
</tr>
<tr>
<td>1E10</td>
<td>IIIB/IV</td>
<td>71</td>
<td>9.9 months</td>
<td>Alfonso et al.; 2007</td>
</tr>
<tr>
<td>1E10</td>
<td>IIIB/IV</td>
<td>20</td>
<td>10.6 months</td>
<td>Hernandez et al.; 2008</td>
</tr>
<tr>
<td>CEA pulsed DC’s</td>
<td>IIIB/IV</td>
<td>14</td>
<td>22 months (64% 1 yr)</td>
<td>Zhang et al; 2011</td>
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<tr>
<td>Talactoferrin</td>
<td>IIIB/IV</td>
<td>110</td>
<td>RR° 47% (+Cb/Tx) vs. 29% (+Cb/Tx); p=0.05</td>
<td>Digumarti, R. et al. 2011</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>IIIB/IV</td>
<td>204</td>
<td>PFS 5.7 months (+Cb/Tx) vs. 4.6 (+Cb/Tx); p=0.05</td>
<td>Lynch, T. et al; 2012</td>
</tr>
</tbody>
</table>

* GAR = Good Antibody Response  
* PAR = Poor Antibody Response  
°RR=Response Rate  
x Phase III trial involving 1,500 patients negative overall
# Results of Gene-Based Vaccines in IIIB/IV NSCLC

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<tbody>
<tr>
<td>Allogenic Ad B 7.1</td>
<td>IIIB/IV</td>
<td>19</td>
<td>18 months (52% 1yr)</td>
<td>Raez, L.E. et al; 2004</td>
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<tr>
<td>GMCSF gene vaccine</td>
<td>IV</td>
<td>35</td>
<td>Not done</td>
<td>Salgia, R. et al; 2003</td>
</tr>
<tr>
<td>GMCSF gene vaccine</td>
<td>IIIB/IV</td>
<td>33</td>
<td>12 months (44% 1yr)</td>
<td>Nemunaitis, J. et al; 2004</td>
</tr>
<tr>
<td>GMCSF gene vaccine - bystander</td>
<td>IIIB/IV</td>
<td>49</td>
<td>7 months (31% 1 yr)</td>
<td>Nemunaitis, J. et al; 2006</td>
</tr>
<tr>
<td>Galactosyltransferase</td>
<td>IV</td>
<td>7</td>
<td>Not done</td>
<td>Morris, J.C. et al; 2005</td>
</tr>
<tr>
<td>Lucanix</td>
<td>IIIB/IV</td>
<td>61</td>
<td>14.4 months (56% 1 yr)</td>
<td>Nemunaitis, J. et al; 2007</td>
</tr>
<tr>
<td>Lucanix</td>
<td>IIIB/IV</td>
<td>21</td>
<td>15.5 months (72% 1 yr)</td>
<td>Nemunaitis, J. et al; 2008</td>
</tr>
<tr>
<td>TG4010</td>
<td>IIIB/IV</td>
<td>65</td>
<td>14.9 months (60% 1 yr)</td>
<td>Ramlau, R. et al.; 2008</td>
</tr>
<tr>
<td>TG4010</td>
<td>IIIB/IV</td>
<td>48</td>
<td>17.1 months</td>
<td>Quoix E et al; 2011</td>
</tr>
</tbody>
</table>
Adaptive Cancer Immune Mechanism
Concept: “Triad” Immunotherapy

Immunotherapy that addresses the key elements necessary for an optimal immune attack against cancer

1) Patient Tumor Antigen (matrix)
2) Immune Activation
3) Inhibition of Afferent Immune Suppressors

Identify biorelevant surrogate of activity (correlating with survival)
BLP25

MUC1 antigen specific cancer immunotherapy advanced unresectable stage III NSCLC s/p so with concurrent or sequential XRT/chemo

START:

• 1,239 patient Phase III trial (2:1 randomization)
• Median OS 25.6 mo. BLP25
• AE’s >10% include cough, dyspnea, fatigue, nausea, headache, arthralgia
• No treatment unique grade 3, 4 toxicity
Subset Analysis START Trial

- Concurrent XRT/chemo group (n=806)
- Median OS 30.8 mo. BLP25 vs. 20.6 mo. BLP25 p=0.016
What Did We Learn From BLP25

• Single antigen immunotherapy can be well-tolerated
• Suggestion of relevant activity survival advantage in a large sub population
• Unclear why concurrent vs. sequential XRT/chemo different
• No surrogate measure of activity
Targeted Immune Activation Tumor Responses to GMCSF Gene Vaccine

3/10/00 baseline

8/2/00 post*

9/20/00 baseline

2/28/01 post

5/19/00 baseline

1/22/01 post*

* Still alive/no recurrence

So What Did We Learn With GVAX

- Clinically relevant immune mediated activity can be observed (limited degree)
  - Multi-antigen autologous cells despite “tolerance” can also provide immunogenic stimulus
  - No significant toxic effect was observed
  - Beneficial results can be prolonged (>10 year)
- No surrogate measure of activity
Vector/Effector – T-VEC

Modes of Action
1. Oncolytic (tumor specific)
   a. ICP34.5 (decreased normal tissue virulence)
   b. L→IE US11 (enhanced oncolytic cytotoxicity)
2. Immunogenic
   a. ICP47 (enhanced antigen presentation; increased levels class I MHC confirmed by FACS analysis)
- RECIST response was 26% (8CR, 5PR) and regression of local injected and distal (non injected) lesions were observed.

Patient 1502
Axillary injection of T-VEC (red↓) metastatic (yellow↓) disease regression shown by PET 16 months later

Patient 603: Baseline (red↑) and at 4 months.

(Senzer et al. JCO 2009; 27(34):5763-5771)
Belagenpumatucel: Inhibition of Intrinsic Tumor Immunosuppressors (4 allogeneic NSCLC lines / TGFβ2 AS transfection)

Overall survival for cohorts 1 vs. 2 and 3 for advanced stage patients (n=61, p=0.0186)

Radiographic evidence of response (3 of 6) comparing week 16 assessment (post therapy) to baseline

Patient #11

Patient #20

Patient #38

Nemunaitis et al. JCO 2006 10; 24(29):4721-4730.
Belagenpumatucel: Phase III (STOP Trial) Results

• Phase III testing in front line NSCLC were negative.
  – Subset analysis by NovaRx suggestive of benefit
IIIB/IV Subjects

\[
p = 0.224 \quad HR = 0.85
\]

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Median Survival</th>
<th>N</th>
<th>Percent Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucanix</td>
<td>20.9</td>
<td>229</td>
<td>55%</td>
</tr>
<tr>
<td>Control</td>
<td>16.7</td>
<td>226</td>
<td>50%</td>
</tr>
<tr>
<td>Difference</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
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</table>

IIIB/IV Subjects Enrolled Within 12 Weeks of Chemotherapy*

\[
p = 0.036 \quad HR = 0.71
\]

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<tr>
<td>Lucanix</td>
<td>20.9</td>
<td>157</td>
<td>56%</td>
</tr>
<tr>
<td>Control</td>
<td>12.9</td>
<td>136</td>
<td>45%</td>
</tr>
<tr>
<td>Difference</td>
<td>8.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data from all clinical sites except one with significant compliance issues
So What Did We Learn With Belagenpumatumcel?

- Phase II trials suggested evidence of clinical benefit in subsets of patients with \( \geq 2^{\text{nd}} \) line NSCLC
- Phase III trial suggests insufficient clinical response in front line NSCLC

- But Why?
  - Allogeneic tumor antigens less efficient than autologous tumor antigen?
  - TGF\( \beta_2 \) knockdown insufficient (TGF\( \beta_1 \) is dominant TGF\( \beta \) cancer immunosuppressor)
  - Level of Knockdown insufficient (35-50%)?
  - Physiologic effects related to subset sensitivity/resistance

- No Surrogate measure of activity
TG4010 (Recombinant Vaccinia Virus/MUC1 Antigen IL2 Transgene) Early Safety Signal: Correlation with aNK Cells Level

All patients

Healthy volunteers Patient PBMC

PBMC

% of activated NK cells

aNK = CD16+CD56+ CD69+

25%

3.5%

75%

0% 25% 50% 75% 100%

0 5 10 15 20 25 30 35 40

Survival(months)

Fraction of Patient Population Surviving

ARM 1: TG4010 + CT

ARM 2: CT ALONE

n=148

HR=0.88 [95% CI: 0.60-1.30]

p=0.438

med = 10.7 m n=74

med = 10.3 m n=74

Complete

Censored

Confidential
TG4010 Overall Survival in Patients with Normal Level of Activated NK Cells in Advanced NSCL


Median 17.1 mos [9.8 - 24.9] n=48

Median 11.3 mos [8.3 - 12.5] n=53

Log-Rank (strat PS, Stage) : p=0.062
HR: 0.62 [95% CI : 0.40 - 0.96]
What Did We Learn From TG4010?

• Subsets of patients may benefit from relevant tumor antigen education
• Immune function enhancement may contribute to clinical benefit
• Identification of predictor biorelevant measures of activity may be feasible
  – Level of Activated NK cell activity affects outcome: possible predictive marker
Could “Triad” Approach Provide a Greater Activity

- Patient/tumor-specific antigen education
- Enhanced afferent immune activation
- Blockade of intrinsic immune suppressors

☐ Identify surrogate measure of biorelevant activity

Triad Vaccine Mechanism
Furin pro-protein convertase – immunomodulatory TGFβ₁, β₂ (Gradalis, Inc., Dallas, TX)

- Inhibits GMCSF stimulation
- Blocks macrophage activation
- Blocks Ag presentation
- Blocks expression of MHC class II
- Blocks dendritic cell response

bi-shRNA<sub>FURIN</sub>

FANG

5140 bp

TGFβ₁

TGFβ₂
FANG™ Phase I Trial
6/8/09

- Vaccine constructed following autologous tissue harvest and electroporated transfer of bi-shRNA$_{furin}$ GMCSF vector
- 2 dose levels (1x$10^7$ / 2.5x$10^7$ cells/inj)
- Monthly ID injection (maximum of 12 months)
- Two groups of patients: other options prior to FANG™ vs. no options $\rightarrow$ FANG™
- ELISPOT for T cell activation at baseline and follow up timepoints
Survival of Treated Patients Since Treatment Start on FANG™ Phase I Protocol

Mean survival 18.7 months (Wheler et al. 2012) Phase I risk score 2.2 predicted survival 8.4-6.2 months.
Survival of Treated Patients Since Procurement on FANG™ Phase I Protocol

Data as of 04/26/13

Cumulative Survival

Days Since Procurement

p<0.000001
FANG Vaccine: Toxicity

Patient #018
Colon Adenocarcinoma

- No treatment related Grade 3, 4 toxic events
- Minor low grade events such as injection site irritation, fatigue observed
FANG Phase I Trial

IFN\(\gamma\) Expression (ELISPOT) of FANG\textsuperscript{TM} Vaccine Treated Patient PBMC’s in Response to Non-transfected Autologous Tumor Cells (n=24)
FANG Phase I Survival Relationship to Immune Response

Survival Based on Month 4 ELISPOT Response

- Red line: Negative ELISPOT (n=12)
- Blue line: Positive ELISPOT (n=12)
- Red dashed line: Negative ELISPOT-censored
- Blue dashed line: Positive ELISPOT-censored

Cumulative Survival vs Days Since Treatment Start

Data as of 05/01/13

p = 0.036
Moved into Phase I Expansion Phase II Trial Program*

<table>
<thead>
<tr>
<th>Trial Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL-PTL-101</td>
<td>Phase I Trial of FANG Expansion of NSCLC, Hepatocellular, Renal, Ewings, Thyroid</td>
</tr>
<tr>
<td>CL-PTL-105*</td>
<td>Randomized Phase II Trial of Adjuvant bi-shRNA\textsuperscript{furin} and GMCSF Augmented Autologous Tumor Cell Vaccine (FANG\textsuperscript{TM}) for High Risk Stage IIIc Ovarian Cancer (Adjuvant)</td>
</tr>
<tr>
<td>CL-PTL-107</td>
<td>Randomized Phase II Trial of Post-operative Adjuvant Chemotherapy ± FANG\textsuperscript{TM} Autologous Tumor Cell Vaccine in Colorectal Carcinoma with Liver Metastases (Concurrent chemotherapy)</td>
</tr>
<tr>
<td>CL-PTL-114*</td>
<td>Phase II Trial of FANG\textsuperscript{TM} Autologous Tumor Cell Vaccine in Advanced Melanoma (Correlate Intratumoral/serologic immune markers)</td>
</tr>
</tbody>
</table>

* Secured orphan product designation in Stage III/IV melanoma and ovarian cancer
# Successful Vaccine Construction Rate

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Successful Vials Manufactured</th>
<th>Successful Patient Samples Manufactured</th>
<th>Insufficient Patient Samples</th>
<th>Failed Patient Samples</th>
<th>Vaccines Administered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I CL-PTL 101</td>
<td>559</td>
<td>60*</td>
<td>7</td>
<td>5</td>
<td>174</td>
</tr>
<tr>
<td>Phase II OV CL-PTL 105</td>
<td>501</td>
<td>52</td>
<td>4</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>Phase II CLM CL-PTL 107</td>
<td>21</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Phase II Mel CL-PTL 114</td>
<td>66</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1147</strong></td>
<td><strong>121</strong></td>
<td><strong>14</strong></td>
<td><strong>20</strong></td>
<td><strong>347</strong></td>
</tr>
</tbody>
</table>

*including 2 pre-clinical and 1 benign*
Phase II Ovarian (III/IV) Trial Design

• 2:1 randomized trial
  – FANG vs. No FANG (n=60 treated/evaluable)

• 1x10^7 cells/inj 2 month (max 12/minimum 4)

• Standard of care (debulking surgery → 6 cycles carboplatin/taxol±IP) prior to FANG

• Crossover if PD (FANG/Avastin)
Disease-Free Survival Interval: Preliminary Analysis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>No FANG</td>
<td>5</td>
<td>384</td>
<td>330</td>
</tr>
<tr>
<td>FANG</td>
<td>12</td>
<td>601</td>
<td>not reached</td>
</tr>
</tbody>
</table>

Data as of 04/08/13
Conclusion

- Evidence of increasing beneficial and safe immune modulatory activity is observed in advanced NSCLC to novel targeted immunotherapies
- Employment of “Triad” functions to vaccine effect should be considered (multi vaccines/single “triad” therapeutics)
- Surrogate biomarkers correlating response/survival to mechanism facilitate immunotherapy development