Presenter Disclosure:
John Nemunaitis, MD

The following relationships exist with this disclosure.
Gradalis, Inc. - shareholder
Clinical Update of bi-shRNA furin/GMCSF DNA Transfected Tumor Vaccine: FANG™ in Cancer Patients
Adaptive Cancer Immune Mechanism
Concept: “Triad” Immunotherapy

Construct a DNA based immunotherapy that addresses the key elements necessary for an effective 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
### Key Gene-Based Vaccines in IIIB/IV NSCLC ("not melanoma/renal cell")

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Stage</th>
<th># Pts</th>
<th>Median Survival</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<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>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; 2009</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>
Targeted Immune Activation Tumor Responses to GMCSF Gene Vaccine

* Still alive/no recurrence

So what did we learn with GVAX

• Clinically relevant immune mediated activity can be observed (limited degree)
  – Antigen (autologous cells despite “tolerance” can provide immunogenic stimulus)
  – Benefit of GMCSF DNA activation
• No surrogate measure of activity
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  
Pre-Therapy  |  Post-Therapy

Patient #20  
Pre-Therapy  |  Post-Therapy

Patient #38  
Pre-Therapy  |  Post-Therapy

Nemunaitis et al. JCO 2006 10; 24(29):4721-4730.

Friday, May 17, 2013
Mary Crowley Cancer Research Center
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Allogeneic TGFβ₂ AS transfection: Belagenpumatucel-L

- Preliminary results of Belagenpumatucel-L Phase III testing in front line NSCLC were negative.
  - Subset analysis underway by NovaRx
So What Did We Learn With Belagenpumatucel-L?

- Phase II trials suggested evidence of clinical benefit in subsets of patients with $\geq 2^{nd}$ 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%)?
- No Surrogate measure of activity
TG4010 (Recombinant Vaccinia Virus/MUC1 Antigen IL2 Transgene) Overall Survival in Patients with Normal Level of Activated NK Cells in Advanced NSCLC

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]

Early safety signal: correlation with aNK cells level

All patients

25%

Healthy volunteers
Patient PBMC
PBMC

aNK = CD16+CD56+ CD69+

25%

3.5%

75%
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

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

TGFB

bi-shRNA<sup>FURIN</sup>

= sense strand
= antisense strand

5140 bp
Programmed RISC loading Ago

Complementary guide strands

miR30a

DROSHA
DGCR8

RAN-GTP
EXPORTIN 5

bi-shRNA

pri-miRNA

pre-miRNA
(nuclear export)

RLC

RISC

Target mRNA

ORF, 3’UTR
AAA

Translational repression or p-body sequestration

(mRNA degradation)
mRNA cleavage

Passenger strand
Guide strand

+ Ago2

+ Ago1, [2], 3, 4

+ Ago, 2, 3, 4

TRBP
Triad Vaccine Mechanism

- GM-CSF
- TGFβ1,2
- Ag
- TGFβ1,2
- INFγ
- Tumor
- CTL
- TNr
- Ag
FANG™ Phase I Trial
6/8/09

• Vaccine constructed following autologous tissue harvest and electroporated transfer of bi-shRNA\textsuperscript{furin} GMCSF vector
• 2 dose levels (1x10\textsuperscript{7} / 2.5x10\textsuperscript{7} cells/inj)
• Monthly ID injection (maximum of 12 months)
• Two groups of patients: other options prior to FANG™ vs. no options → 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 predicated survival 8.4-6.2 months.
Survival of Treated Patients Since Procurement on FANG™ Phase I Protocol

Data as of 04/26/13

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
IFNγ Expression (ELISPOT) of FANG™ 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

- Negative ELISPOT (n=12)
- Positive ELISPOT (n=12)
- Negative ELISPOT censored
- Positive ELISPOT censored

Cumulative Survival

Days Since Treatment Start

Data as of 05/01/13

p = 0.036
# Moved into Phase II Trial Program*

<table>
<thead>
<tr>
<th>Trial Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL-PTL-105*</td>
<td>Randomized Phase II Trial of Adjuvant bi-shRNA&lt;sub&gt;furin&lt;/sub&gt; and GMCSF Augmented Autologous Tumor Cell Vaccine (FANG™) for High Risk Stage IIIc Ovarian Cancer <em>(Adjuvant)</em></td>
</tr>
<tr>
<td>CL-PTL-107</td>
<td>Randomized Phase II Trial of Post-operative Adjuvant Chemotherapy ± FANG™ Autologous Tumor Cell Vaccine in Colorectal Carcinoma with Liver Metastases <em>(Concurrent chemotherapy)</em></td>
</tr>
<tr>
<td>CL-PTL-114*</td>
<td>Phase II Trial of FANG™ Autologous Tumor Cell Vaccine in Advanced Melanoma <em>(Correlate Intratumoral/serologic immune markers)</em></td>
</tr>
</tbody>
</table>

* Secured orphan product designation in Stage III/IV melanoma and ovarian cancer
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

- **Disease-free Survival Since Procurement (Days)**
  - No FANG: n = 5, Mean = 384, Median = 330
  - FANG: n = 12, Mean = 601, Median = not reached

- **Disease-free Survival Since Study Start (Days)**
  - No FANG: n = 5, Mean = 193, Median = 91
  - FANG: n = 12, Mean = 470, Median = not reached
# 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

21%
Conclusion

• Overall clinical benefit is demonstrated using DNA based technology as Immunotherapy

• More specifically,
  – FANG vaccine is well tolerated and evidence of benefit is demonstrated in advanced cancer.

• Considering Breakthrough Application process of FANG vaccine in ovarian cancer with FDA