New Biological and Immunological Therapies for Cancer

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# Promising Developments: Immunotherapy and Gene Therapy

## US FDA Approved Therapies
- Dendritic Cell Therapy
- Cancer Vaccines
- Oncolytic Viruses
- Immune Checkpoint Inhibitors (mAbs)

## In Clinical Development
- Targeted Retrovectors: Targeting the tumor microenvironment
  - **Rexin-G** (Cytocidal Gene)
  - **Reximmune-C** (GM-CSF)
- Targeted Lentivectors: Dendritic Cell Targeting
  - **LV305** (NY-ESO1 Gene)
Rexin-G Retroviral Vector: First Targeted, Injectable Gene Delivery

Molecular Components of Tumor-Targeted Rexin-G

**Therapeutic Payload (Bioactive Construct)**
- Killer gene provides broad-spectrum activity

**Vector Design Engineering**
- Stealth vector enables repeated i.v. infusions

**Active (XC-) Tumor-Targeting**
- Tumor-targeting seeks out cancerous lesions
Active Vector Targeting: Targeting the Tumor Microenvironment

Exposure of Collagenous (XC-)
Proteins is a HistoPathological
Feature of all Invasive Cancers

Abnormal Tumor Microenvironment:

The Collagenous XC-Proteins in a
Human Tumor Biopsy are Stained
Bright Blue by the Trichrome-stain

Tumor cells (t) immersed in a sea of
exposed collagenous (XC-) proteins:

XC-Proteins exposed by tumor invasion, stroma formation, & angiogenesis.
Advanced, Adaptive Phase I/II Trials
FDA-Approved Trials

**Advanced:**
Each clinical study included a Phase II efficacy component.

**Adaptive:**
Used comprehensive analysis of clinical response criteria for this targeted biologic.

**Across-the-board Dose Escalation:**
FDA allowance upon aggregate analysis.

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**Chemotherapy-resistant Cancers**

- **Phase I/II Study** – all types of sarcoma*
- **Phase I/II Study** – pancreatic cancer*
- **Phase II Study** – osteosarcoma*

**RESULTS:** Rexin-G® exhibits an outstanding safety record (with no DLT); dose-dependent single-agent efficacy; gains in tumor control, progression-free survival (PFS), and overall survival (OS).

- **FDA grants Orphan Drug**:
  Osteosarcoma, STS, and Pancreatic Cancer
Advanced Phase I/II Evaluation of Tumor-Targeted Gene Delivery: Intravenous Infusions of Rexin-G as Stand-alone Therapy for Chemotherapy-Resistant Bone and Soft tissue Sarcoma

- **Primary Endpoint:** Evaluation of clinical toxicity / safety
- **Secondary Endpoint # 1:** Evaluation of vector-related safety
- **Secondary Endpoint # 2:** Identify potential tumor responses

**Patients:**
Bone and Soft Tissue Sarcoma, chemotherapy-resistant (n = 36)

**Dosing Schedule:**
Dose Escalation, Doses I-V  [1-4 x 10^11 cfu i.v. BIW or TIW x 4 wks]
Note: Intra-patient dose-escalation was allowed up to Dose Level II; Additional treatment cycles were given if patient had < Grade 1 toxicity

**Enrollment:**
 n = 33 evaluable patients (completed one cycle with follow-up PET-CT)
Rexin-G Safety & Efficacy is Affirmed
US FDA Grants Orphan Drug: Osteosarcoma & STS

Wide Range of Sarcomas Treated
# Previous Chemotherapy Regimens
- Median ...................................... 4
- Range ....................................... (1-10)

Many Types of Sarcomas Treated
- Leiomyosarcoma ...................... 10 (27%)
- Liposarcoma ......................... 6 (16%)
- Synovial cell sarcoma ............ 4 (11%)
- Osteosarcoma ....................... 3 ( 8%)
- MMTT ovary ............................. 2 ( 6%)
- Ewing’s sarcoma ..................... 2 ( 6%)
- Angiosarcoma .......................... 2 ( 6%)
- Malignant fibrous histiocytoma ... 2 ( 6%)
- Chondrosarcoma ...................... 1 ( 3%)
- Malignant spindle cell sarcoma...1 ( 3%)
- Fibrosarcoma .......................... 1 ( 3%)
- Amelanotic schwannoma .......... 1 ( 3%)
- Alveolar Soft Parts Sarcoma ...... 1 ( 3%)

Results to Date: (33 evaluable patients)

✓ Primary Endpoint:
- No dose limiting toxicity (DLT) was observed;
- Grade 1 chills (n = 1), Grade 1 fatigue (n = 2);
- Grade 2 tumor pain (n = 2)

✓ Secondary Endpoint # 1:
- No vector-neutralizing antibodies; No vector integration and no RCR detected in peripheral blood lymphocytes (No Long-term Concerns)

✓ Secondary Endpoint # 2:
- Dose-dependent improvements in tumor control rates, progression-free survival (PFS) and overall survival (OS) times were improved
RESULTS of the Phase I / II Study  
Chemo-Resistant Bone and Soft Tissue Sarcomas

Evaluation of Anti-tumor Activity of  
Intravenous Infusions of Rexin-G as Stand-alone Therapy

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Tumor Response By RECIST Criteria</th>
<th>Tumor Response By PET Criteria</th>
<th>Tumor Response By CHOI Criteria</th>
<th>Median PFS By RECIST, Months</th>
<th>Median OS, Months</th>
<th>One-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=6)</td>
<td>3SD, 3PD</td>
<td>1PR, 4SD, 1PD</td>
<td>2PR, 4SD</td>
<td>1.2</td>
<td>3.2</td>
<td>0%</td>
</tr>
<tr>
<td>II, III (n=14)</td>
<td>10SD, 4PD</td>
<td>4PR, 9SD, 1PD</td>
<td>7PR, 7SD</td>
<td>3.8</td>
<td>7.8</td>
<td>28.6% 2 yr = 0%</td>
</tr>
<tr>
<td>IV, V (n=13)</td>
<td>9SD, 4PD</td>
<td>3PR, 8SD, 2PD</td>
<td>1PR, 10SD, 2PD</td>
<td>4.1</td>
<td>11.5</td>
<td>38.5% 2 yr = 31.0%</td>
</tr>
</tbody>
</table>

Dose-dependent survival benefits, p = 0.002
A Case Study: Single-Agent Efficacy in Osteosarcoma

Osteosarcoma

Note: life-threatening metastatic lesions in lungs and ~heart (A)

• Evidence of Rexin-G efficacy as seen in a 17-year old male

• Tumor responses by PET and CHOI are noteworthy (B vs C,D)

• Rapid progression of disease is halted (inset)

• Gains in expected survival (PFS, OS)
A Case of Surgical Remission in Chemo-Resistant Osteosarcoma

**Rexin-G plus Surgery: A Lasting Remission**

- Rexin-G Treatment Halts Progression of the Metastatic Disease
- Surgical excision of two remaining lesions shows:
  - A,C: Ossification
  - C,D: Cystic Conversion
- Neoadjuvant / Adjuvant Treatment produces a **Sustained Remission with no evidence of residual disease (>7 Yrs)**
Long-Term Follow Up  
Dose-Dependent Survival Benefits

Advanced Phase I/II Study using Rexin-G, an XC-Targeted Gene Therapy Vector for Chemotherapy Resistant Sarcoma (Chawla et al., 2016)

✓ SAFETY:
  • No dose-limiting toxicity
  • No vector related toxicity

✓ EFFICACY:
  • Controls tumor growth
  • Improves Progression-Free Survival (PFS);
  • Improves Overall Survival (dose-dependent OS)

Bone & ST Sarcoma  
Overall Survival, p = 0.002

Dose Escalation Study  
Dose-Dependent Survival Benefits: the Gold Standard for Objective Response Criteria

Note: 2 Long-term (>7 Yr) Cancer-free Survivors
Primary Endpoint: Evaluation of efficacy
Secondary Endpoint # 1: Evaluation of safety

Patients:
Osteosarcoma, chemotherapy-resistant (n = 22)

Dosing Schedule:
Dose Escalation, Doses I-II [1-3 x 10^11 cfu i.v. BIW or TIW x 4 wks]
Note: Intra-patient dose-escalation was allowed up to Dose Level II;
Additional treatment cycles were given if patient had ≤ Grade 1 toxicity

Enrollment:
n = 17 evaluable patients (completed one cycle with follow-up PET-CT)
Confirmatory Phase II Study
Efficacy in Chemo-resistant Osteosarcoma

A. Phase I/II Sarcoma
Initial results
N = 20

- Dose Level 0 (n = 6)
- Dose Levels I,II (n = 14)  

p = 0.005

B. Phase II Osteosarcoma
Simultaneous Study
N = 22

- Dose Levels I,II (n = 22)

Note: 27% One-Year Survival (ITT)  23% Two-Year Survival
mITT: 35% 1Yr; 29% 2Yr
Advanced Phase I/II Evaluation of Tumor-Targeted Gene Delivery: Intravenous Infusions of Rexin-G as Stand-alone Therapy for Chemotherapy-Resistant Pancreatic Cancer

- **Primary Endpoint:** Evaluation of clinical toxicity / safety
- **Secondary Endpoint # 1:** Evaluation of vector-related safety
- **Secondary Endpoint # 2:** Identify potential tumor responses

**Patients:**
Pancreatic cancer, chemotherapy-resistant (n = 20)

**Dosing Schedule:**
Dose Escalation, Doses I-IV  [1-3 x 10e11 cfu i.v. BIW or TIW x 4 wks]
- Note: Intra-patient dose-escalation was allowed up to Dose Level II;
- Additional treatment cycles were given if patient had < Grade 1 toxicity

**Enrollment:**
n = 15 evaluable patients (completed one cycle with follow-up PET-CT)
Kaplan Meier plot suggests a trend toward a dose-response relationship between progression-free survival and Rexin-G dosage (n = 15 evaluable).

A significant dose-response relationship between overall survival and Rexin-G dosage in the Intention to Treat Patient Population (n = 20; 5% statistical level).
The GeneVieve Protocol for Cancer Immunotherapy

A Dual Targeted Approach: 
**Rexin-G** (Tumor Control) followed by 
**Reximmune-C** (GM-CSF expression vector provides vaccination in situ).

- **Rexin-G** is a tumor-targeted retroviral vector bearing a cytocidal Cyclin G1 construct, utilized to bring the tumor burden under control.

- **Reximmune-C** is a tumor-targeted retroviral expression vector bearing a GM-CSF gene, utilized to provide localized expression within residual tumors, thereby recruiting TILs and stimulating anti-tumor immunity.
**First Study Results (Genevieve Protocol):**
A Phase I/II Study of Intravenous Rexin-G plus Reximmune-C for Chemotherapy-resistant Cancers

**Primary Endpoint:** No dose limiting toxicity (DLT); Grade 2 tumor pain (n = 2)

**Secondary Endpoint # 1:** No detectable GM-CSF in patients’ serum; No vector-neutralizing antibodies; No vector integration and no RCR detected in peripheral blood lymphocytes

**Secondary Endpoint # 2:** See Table below for positive indications of efficacy

<table>
<thead>
<tr>
<th>Reximmune-C Dose Level</th>
<th>Best Tumor Response RECIST, PET* or Bone Scan**</th>
<th>Median PFS RECIST, PET* or Bone Scan** Months</th>
<th>Median OS, (Months) From Start of Rexin-G Rx</th>
<th>Per Cent &gt; One Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 5)</td>
<td><strong>2PR</strong>, 1SD, 2PD</td>
<td>4.5</td>
<td>21</td>
<td>80</td>
</tr>
<tr>
<td>II (n = 4)</td>
<td>1PR, 3SD</td>
<td>9</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>III (n = 7)</td>
<td><strong>2PR</strong>, 5SD</td>
<td>13</td>
<td>&gt; 22</td>
<td>86</td>
</tr>
</tbody>
</table>

Note: One patient at Dose II, and one patient at Dose III had SD with extensive tumor necrosis.
The residual tumor was resected two days after infusion of Rexin-G and Reximmune C. (A) H&E: areas of tumor necrosis with tumor infiltrating lymphocytes (TILs); (B) CEA+ tumor cells, (C) immunoreactive GM-CSF transgene (reddish-brown staining material) in a necrotic tumor, (D) MPO staining granulocytes; (E-G) CD4+, CD8+ and CD20+ TILs, indicating effective recruitment of patient’s tumor infiltrating lymphocytes into the residual tumor.
The Genevieve Protocol: Rexin-G Treatment Followed by Tumor-Targeted Reximmune-C (i.v.)

Combined Effects of Rexin-G plus Reximmune-C

Progressive tumor regression was observed in serial bone scans obtained over 20 months following treatment initiation with Rexin-G to control tumor growth, followed by the Reximmune-C to stimulate a local immune response.

Regression of Skeletal Metastases in a Patient with Chemo-Resistant Ductal Carcinoma of Breast

A  
Anterior  Posterior  
Before Treatment  07.01.2008

B  
Anterior  Posterior  
After Rexin-G  01.26.2009

C  
Anterior  Posterior  
After GeneVieve  03.02.2010
Taken together these studies indicate that:

- **Tumor-Targeted vectors** (Rexin-G and Reximmune-C) are well-tolerated with no dose-limiting or organ-related toxicity.

- **Rexin-G** controls tumor growth and may improve progression-free survival (PFS) and overall survival (OS) in chemo-resistant cancers.

- **Reximmune-C** provides an opportunity for local stimulation of tumor immune responses.

Targeted, Injectable Retroviral Expression Vectors Deliver Therapeutic Genes for Tumor Control
Thank You

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