JX-594, a Tumour-selective, GMCSF-Armed Oncolytic Poxvirus

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Medical Affairs
Transgene S.A., Illkirch-Graffenstaden, France

CGE
November 2\textsuperscript{nd}, 2011
### Transgene’s Clinical Products as of September 2011: immunotherapeutics against cancer and infectious diseases

<table>
<thead>
<tr>
<th>PRODUCT</th>
<th>INDICATION</th>
<th>PRE-CLINICAL</th>
<th>PHASE I</th>
<th>PHASE II</th>
<th>LATE STAGE CLINICAL TRIALS</th>
<th>PARTNERSHIP STRATEGY</th>
<th>CURRENT STATUS &amp; NEXT MILESTONES</th>
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<tbody>
<tr>
<td>TG4010 (MVA-MUC1-IL2)</td>
<td>Non Small Cell Lung Cancer (&quot;NSCLC&quot;)</td>
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<td>Phase IIb/III in NSCLC to start</td>
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<td>JX594/TG6006</td>
<td>Hepatocarcinoma (&quot;HCC&quot;) and Other Solid Tumors</td>
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<td>Phase IIb in HCC started</td>
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<td>and Phase I/II to start in CRC</td>
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<td>TG4001 (MVA-HPV-IL2)</td>
<td>Pre-cancerous Lesions of the Cervix Caused by HPV</td>
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<td>Phase IIb Interim Data Q1 2012</td>
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<td>TG4040 (MVA-HCV)</td>
<td>Chronic Hepatitis C (&quot;HCV&quot;)</td>
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<td>New co-development partnership</td>
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<td>Phase II Interim Data Q4 2011</td>
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## Oncolytic viruses in advanced stage of clinical development

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Virus/Payload</th>
<th>Mode of administration</th>
<th>Lead indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioVex</td>
<td>OncoVex&lt;sup&gt;GMCSF&lt;/sup&gt;</td>
<td>Herpes simplex virus/human GMCSF</td>
<td>IT only</td>
<td>Melanoma and head &amp; neck cancer</td>
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<tr>
<td>Oncolytics Biotech Inc</td>
<td>Reolysin®</td>
<td>Respiratory Enteric Orphan virus</td>
<td>IT/IV</td>
<td>Head &amp; neck cancer</td>
</tr>
<tr>
<td>Jennerex</td>
<td>JX-594</td>
<td>Vaccinia virus/human GMCSF</td>
<td>IT/IV</td>
<td>HCC, colorectal cancer</td>
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</tbody>
</table>
**JX-594 design: tumour–selective & GMCSF-armed vaccinia**

**TK inactivated**
- Tumour-selectivity

**lac-Z**
- Monitoring

**GM-CSF**
- Immune MOA

Wyeth vaccinia strain

Selective activation: cancer cells

Transgene expression: therapeutic relevance

- IV stability & systemic delivery
- Large transgene-hosting capacity
JX-594 oncolytic virus: tumour cell–selective replication and destruction driven by high TK content
JX-594 activity: Amplification, spread, cell killing within human tumours

3D human tumour spheroid in red, JX594 in green

Stanford Bio-Imaging Center by Thorne S
1. **Oncolyis**
   Cancer cell infection & lysis

2. **Immune response stimulation**
   - Invasion of cancer-targeted cytotoxic T-cells
   - Production of antibodies
   - Production of immune-stimulatory GMCSF

3. **Tumour vascular shutdown**
   Within as little as five days after treatment

Pharmacokinetics: unique replication-dependent PK

Input

Clearance
Replication waves

Genomes/mL blood

0.25 3 5 8 15 22

days post-treatment

Cohort 3
Cohort 1

Lancet Oncol 2008; 9: 533-42
Systemic JX-594 delivery to tumours after IV and IT injection

IV injection

IV spread post-IT injection
Phase 2/HCC: tumour destruction with JX-594: Acute vascular disruption & shutdown

Pt. 1703

10 cm
massive tumour
highly vascular

Acute response
diffuse vascular disruption
tumour-specific

50% necrosis
on day 5
Phase 2/HCC IT-injected tumours: RECIST and Choi responses
Case report following IT JX-594 therapy:
Liver cancer metastasis complete response

- Failed 5 prior therapies
- Rapidly growing tumour
- Severe neck pain
- Lack of neck mobility
- Severe weight loss

- Cancer-free ~ 1 year later
- Pain gone
- Normal mobility regained
- 10 kg weight gain
Case report following IV JX-594 therapy
Mesothelioma partial response

Baseline  Day 29  Week 10
Phase2/HCC Tumour destruction: dense lymphocyte infiltration of non-injected tumour after ~ 1.5 years
Randomised Phase 2 Trial Design: Advanced HCC

JX-594 high dose vs low dose (active) control

- **Advanced HCC**
  - \( n = 30 \)
  - Heavily pre-treated; 80% sorafenib-naïve

- **Randomised, stratified enrolment: viral /non-viral etiology**
  - High dose JX-594 (1 x 10^9 pfu)
  - Low dose JX-594 (1 x 10^8 pfu)

- **Three total IT doses (day 1, 15, 29)**

- **Proof Of Concept for MOA: necrosis, vascular ablation, active immunotherapy**

- **Survival, tumour response, PFS, safety**

- **Multi-national: US, Canada, S. Korea**
# Phase 2/HCC safety profile: flu-like symptoms for 24 hrs

**Most common adverse events (regardless of relationship)**

<table>
<thead>
<tr>
<th></th>
<th>1 x 10^8 pfu (n=11)</th>
<th>1 x 10^9 pfu (n=15)</th>
<th>Total (n=26)</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1/2</td>
<td>Grade 3</td>
<td>Grade 4/5</td>
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<tr>
<td>Fever</td>
<td>10 (91%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>8 (73%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Injection site pain</td>
<td>6 (55%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Vomiting</td>
<td>7 (64%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Nausea</td>
<td>3 (27%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain (+upper)</td>
<td>3 (27%)</td>
<td>1 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (36%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Anorexia</td>
<td>1 (9%)</td>
<td>1 (9%)</td>
<td>0</td>
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<tr>
<td>Fatigue</td>
<td>2 (18%)</td>
<td>0</td>
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Phase 2/HCC: survival benefit for high dose patients

- Hazard Ratio = 0.41
- Median OS: 13.7 vs. 6.8 months
- p = 0.029 (1-side high dose; Gen Wilcoxon)
### JX-594 Clinical Development: Next Steps

#### HCC (1st & 2nd line) Randomised Ph 2b / 3 trials

<table>
<thead>
<tr>
<th>Advanced HCC 1st &amp; 2nd line</th>
<th>Metastatic CRC 3rd line</th>
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<tr>
<td><strong>Single Arm Phase 1-2</strong></td>
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<tr>
<td>Ph 1 melanoma single agent IT (n=10)</td>
<td>Ph 1-2 CRC 3rd line single agent multiple IV (n ~15)</td>
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<tr>
<td>Ph 1 liver tumours single agent IT (n=15)</td>
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<tr>
<td>Ph 1 solid tumour single agent, single dose IV (n=23)</td>
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<tr>
<td>Ph 1-2 HCC Nexavar combo IV-IT (n~20)</td>
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<tr>
<td><strong>Randomised Phase 1-2</strong></td>
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</tr>
<tr>
<td>Advanced HCC single agent IT JX-594 high vs low dose (n=30)</td>
<td>Ph 1-2 CRC 3rd line single agent &amp; irinotecan combo multiple IV (n ~ 30-50)</td>
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<tr>
<td><strong>Randomised Phase 3</strong></td>
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<tr>
<td>1st line HCC JX-594 IV-IT vs Nexavar</td>
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<tr>
<td>2nd line HCC (“TRAVERSE”): JX-594 IV-IT vs BSC (n=120)</td>
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Acknowledgements

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Clinical trial sites

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  Leyo Ruo

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Samsung
  Ho Yeong Lim

Yonei
  Hyun Choel Chung

The Patients and their Families