Developing new vaccines to fight cancer and infectious diseases

Vaccins thérapeutiques en développement pour le traitement des néoplasies liées à HPV

Dr Jean-Marc Limacher, Transgene SA
8èmes Journées de Vaccinologie Clinique Jean-Gérard Guillet
Paris, Ecole du Val de Grace, 2 Avril 2015
Tumor Associated Non-self Antigens

- Proteins with altered glycosylation (MUC1)
- Mutated proteins or « mutanome » (p53, ras, ...)
- Proteins encoded by viral genes (HPV E6, E7...)

- Two main ways to mount an immune response against these antigens
  - With expression vectors
    - Plasmids + electroporation
    - Bacterias
    - Viruses
  - With peptides or proteins plus an adjuvant
Clinical Positioning of Therapeutic Vaccines in HPV Related Neoplasias

- HPV
  - Silent infection
  - PIN and cancer
  - CIN II/III
  - VIN and cancer
  - Cervical cancer
  - HNSCC
  - AIN
  - Anal cancer
  - Anal
  - Oral
  - Genital
The TG4001 product is a viral vector (Modified Vaccinia of Ankara) expressing E6/E7 genes of HPV 16 and IL-2. Non oncogenic and membrane anchored forms of E6 and E7.
MVA Virus Platform

MVA virus (Modified attenuated Vaccinia virus, strain Ankara)

- Highly attenuated strain of vaccinia virus
- Non-integrative and non-propagative virus in most mammalian cells
- Extensive history of safety
- Used for smallpox eradication campaign in more than 150,000 immuno-compromised individuals
## Clinical Experience with TG4001

<table>
<thead>
<tr>
<th>Study #</th>
<th>Phase</th>
<th>Country</th>
<th>Indication</th>
<th>Number of patients</th>
<th>Key Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG4001.01</td>
<td>1</td>
<td>USA</td>
<td>CIN3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>TG4001.02</td>
<td>1</td>
<td>Switzerland</td>
<td>Stage IB CxCa</td>
<td>3</td>
<td>Safety and feasibility</td>
</tr>
<tr>
<td>TG4001.03</td>
<td>1</td>
<td>USA &amp; Switzerland</td>
<td>Late stage CxCa (Stage IVB or non curable)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>TG4001.04</td>
<td>2</td>
<td>Mexico</td>
<td>Cervix Cancer relapse after radiotherapy</td>
<td>30</td>
<td>5.10⁶, Stabilizations&gt;6m 2/30, under consecutive chemotherapy in 5 pts 2PR&gt;6m and 2 SD&gt;6m</td>
</tr>
<tr>
<td>TG4001.05</td>
<td>2</td>
<td>France</td>
<td>CIN2/3 HPV16+</td>
<td>31</td>
<td>Dose dependant activity at 6 weeks 5.10⁷&gt;5.10⁵ 6/17 improvement in histology or viral clearance vs 0/14</td>
</tr>
<tr>
<td>TG4001.06</td>
<td>2</td>
<td>France</td>
<td>High-grade vulvar intraepithelial neoplasia (VIN3)</td>
<td>20</td>
<td>No significant activity at 5.10⁶ pfu</td>
</tr>
<tr>
<td>TG4001.07</td>
<td>2</td>
<td>France</td>
<td>CIN2/3 HPV16+</td>
<td>21</td>
<td>TG4001 5.10⁷ pfu avoided 6M LEEP in 50% patients</td>
</tr>
</tbody>
</table>
NV25025: Phase 2 Proof of Concept Study

A randomized, double blind, placebo controlled, parallel group, multicenter study of the safety and response rate of 3 subcutaneously administered doses of 5 x 10^7 pfu TG4001 in patients with high grade cervical intraepithelial neoplasia grade 2 or 3 associated with high risk HPV infection.

**Stratification**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
<th>Stratum 1</th>
<th>Stratum 2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG4001</td>
<td>5x10^7 pfu</td>
<td>(N=56)</td>
<td>HPV16 single infection only</td>
<td>(N=80)</td>
</tr>
<tr>
<td></td>
<td>W x 3 inj</td>
<td></td>
<td>All Other HR-HPV single/multiple infections*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=136</td>
<td></td>
<td>LTFU</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>qW x 3 inj</td>
<td>(N=29)</td>
<td>HPV16 single infection only</td>
<td>(N=41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All Other HR-HPV single/multiple infections*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LTFU</td>
<td></td>
</tr>
</tbody>
</table>

**Primary Endpoint**

- LTFU

*The following sub-populations were defined for analysis in stratum 2: (a) HPV16 + HPV16-related, (b) HPV16 related only, (c) Non-HPV16/16-related (e.g., HPV18), (d) HPV16 + Non-HPV16/16-related and (e) HPV16 related + Non-HPV16/16-related*
<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TG4001</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>CIN Grade*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CIN2</td>
<td>54 (40)</td>
<td>30 (43)</td>
</tr>
<tr>
<td>- CIN3</td>
<td>75 (55)</td>
<td>33 (47)</td>
</tr>
<tr>
<td>- &lt;CIN2</td>
<td>5 (4)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>- &gt;CIN3</td>
<td>1 (&lt;1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>- Indeterminate</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Hx of Small Pox Vaccine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No</td>
<td>92 (68)</td>
<td>41 (59)</td>
</tr>
<tr>
<td>- Unknown</td>
<td>35 (26)</td>
<td>23 (33)</td>
</tr>
<tr>
<td>- Yes</td>
<td>9 (7)</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>

* CPR diagnosis
Baseline HPV Genotype Frequency (mITT Population)
## Categories of HPV Single and Multiple Infection Genotypes (mITT)

<table>
<thead>
<tr>
<th>Genotype Categories</th>
<th>TG4001 N (%)</th>
<th>PLACEBO N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>129</td>
<td>63</td>
</tr>
<tr>
<td>Single Genotype</td>
<td>81 (63)</td>
<td>39 (62)</td>
</tr>
<tr>
<td>Multiple Genotypes</td>
<td>48 (37)</td>
<td>24 (38)</td>
</tr>
<tr>
<td>- 2 Genotypes</td>
<td>23 (18)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>- 3 Genotypes</td>
<td>19 (15)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>- 4 Genotypes</td>
<td>6 (5)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>- 5 Genotypes</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
TG4001: Curative Activity at 6 Months

- TG4001 was 5 fold superior in HPV16 patients compared to placebo to induce complete disease regression.
- TG4001 showed an efficacy 4 fold superior compared to placebo regarding the viral clearance.
# TG4001 Phase IIb Results

<table>
<thead>
<tr>
<th></th>
<th>HPV16 mono-infected</th>
<th>All genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TG4001</td>
<td>Placebo</td>
</tr>
<tr>
<td>Resolution</td>
<td>11/55 (20%)</td>
<td>1/27 (4%)</td>
</tr>
<tr>
<td>Response</td>
<td>17/55 (31%)</td>
<td>6/27 (22%)</td>
</tr>
<tr>
<td>Viral clearance</td>
<td>20/52 (38%)</td>
<td>2/23 (9%)</td>
</tr>
</tbody>
</table>
TG4001 Future Development

- Combination with immune checkpoint inhibitors
  - PD1 or PDL1 blockers
- In patients with refractory or relapsing HPV tumors
  - Cervix carcinoma
  - HPV+ head and neck cancer
  - others
ADXS-HPV / ADXS11-001 (Advaxis)

- Listeria monocytogenes
- Transfected with plasmids coding for a fusion protein between a fragment of Lysteriolysin-O and E7 of HPV16 (Lm-LLO-E7)
ADXS-HPV in Recurrent or Persistent Cervix Carcinoma

- NCT01266460 (recruiting)
- GOG trial
- Second line for advanced stage
- Monotherapy, 3 infusions \(10^9\) cfu iv every 28 days
- Objectives: safety and overall survival
- 2 stage design (18+29)
- Endpoint for first stage reached (January 2015)

- NCT02164461 (recruiting) - High Dose
- Not more than one systemic line for advanced stage
- Monotherapy, 3 infusions \(10^{10}\) cfu
ADXS-HPV combination with chemo-radiotherapy

- NCT01671488 (recruiting)
- Anal cancer, N+ or T\( \geq 2 \)
- 4 infusions \((10^9 \text{ cfu})\) every 28 days along with IMRT, 5FU and Mitomycin
- After 10 pts: all in complete response, no relapse (March 2015)

- Pivotal phase III (planned)
- Sponsor GOG
- High risk locally advanced cervix carcinoma
- Concurrent chemotherapy and radiation therapy (CCRT) with or without ADXS-HPV
ADXS-HPV + MEDI4736

- NCT02291055 Not yet recruiting
- HPV+ recurrent or metastatic head and neck or cervix carcinoma
- 3 arms Phase I/II, 66 patients
  - ADX-HPV
  - MEDI4736 (anti-PDL1)
  - ADXS-HPV + MEDI3746
- Primary objectives: safety and PFS
- Supportive preclinical evidence

*J Immunother Cancer. 2013 Aug 29;1:15*
VGX-3100 (Inovio)

- VGX-3100 includes plasmids targeting the E6 and E7 proteins of HPV types 16 and 18
- IM injection + electroporation
- Phase II in CIN2/3
- Per protocol analysis, CIN 2/3 regression to CIN 1 or no disease
  - 53 of 107 (49.5%) with VGX-3100
  - 11 of 36 (30.6%) with placebo. (statistically significant)
- Clearance of HPV in conjunction with regression of lesions
  - 43 of 107 (40.2%) with VGX-3100
  - 5 of 35 (14.3%) with placebo
Procervix® (Genticel)

- CyaA: Genetically modified adenylate cyclase (Bordetella pertussis) expressing E7
- Bivalent, HPV 16 and HPV18
Procervix®

- Ongoing randomized phase II (NCT01957878)
- 220 patients with silent infection
- Cervical HPV 16 and/or 18 infection confirmed by RT-PCR
- Cytological evaluation with a normal, ASCUS or LSIL
- Topical administration (powder) adjuvanted with imiquimod (Aldara®)
- Primary objective: viral clearance at M12
ISA101 (ISA Pharmaceuticals)

- 25-35 a.a. long overlapping peptides 9 for E6 4 for E7 of HPV16
- 13x0,3mg admixtured with Montanide ISA-51, SC, 2.8 ml
- CD4+ and CD8+ immunogenicity in almost all patients

- Phase II in grade 3 VIN
- 20 pts
- 4 injections 3 weeks apart
- At 12 month FU:
  - 15/19 (79%) patients with an objective response,
  - 9 (47%) complete response, viral clearance in four of them
ISA101 ongoing studies

- Ongoing phase I/II study in advanced recurrent or metastatic cervix carcinoma (NCT02128126)
  - 48 patients
  - Combination with Carboplatine and Paclitaxel and PEG-IFN
  - Objectives: immunogenicity, clinical activity

- Ongoing phase I/II in anal intra-epithelial neoplasia (AIN) recurrent or resistant to local treatment
  - 45 patients HIV+ men
  - Intra-dermal, different doses + PEG-IFN
  - Objectives: safety, activity, immunogenicity
Conclusion

- Several therapeutic vaccines in development in HPV induced neoplasias
- Different classes of products but all target E6 and/or E7 of HPV 16 and/or 18
- Various positionings from silent infection to advanced refractory disease
- Monotherapy for silent infections or low grade intra-epithelial neoplasia
- Combination with chemotherapy, chemo-radiation (locally advanced) or with checkpoint inhibitors
- Good safety
- Immunogenicity
- Clinical activity demonstrated in randomized controlled trials and encouraging single arm series