Oncos Therapeutics

Oncolytic adenovirus CGTG-102: Preclinical testing

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Oncos Therapeutics - background

2002
- Oncos Co-founder professor Hemminki starts CGTG
- In 2011, largest research unit in Europe in oncolytic viruses

2007
- Advanced Therapy Access Program (ATAP) started with Docrates
- 300 patients treated with oncolytic adenoviruses

2008
- Oncos founded to sponsor clinical studies on oncolytic viruses

2010
- Series A: 9 MEUR raised from HealthCap and public sources
- CGTG-102 as the Lead Compound for clinical development

2012: CGTG-102 enters Clinical trials
Title of protocol:

Exploratory open label study of GMCSF coding oncolytic adenovirus CGTG-102, with low dose cyclophosphamide in patients with refractory injectable solid tumours

Background: Advanced Therapy Access Program: 115 patients treated, safety has been good
## ONCOS-C1

**Desicion points (arrows):** Part I: Safety and tolerability at D29, Part II: Disease control at D85 and/or D169

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Screening visit Lab, blood effusion Biopsy</td>
</tr>
<tr>
<td>D4</td>
<td>CGTG-102 (i.t.) Lab, blood</td>
</tr>
<tr>
<td>D8</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion</td>
</tr>
<tr>
<td>D15</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, Biopsy</td>
</tr>
<tr>
<td>D29</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, Biopsy</td>
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<tr>
<td>D57</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, Biopsy</td>
</tr>
<tr>
<td>D85</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, PET and CT</td>
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<tr>
<td>D113</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, PET and CT</td>
</tr>
<tr>
<td>D141</td>
<td>CGTG-102 (i.t.) Lab, blood, effusion, PET and CT</td>
</tr>
<tr>
<td>D169</td>
<td>End of treatment Lab, blood, PET and CT</td>
</tr>
<tr>
<td>D190</td>
<td>End of trial visit</td>
</tr>
</tbody>
</table>

**Cyclophosphamide (CPO) daily p.o. 50 mg starting on D2**

- **Dose escalation recruiting 12-18 patients**
  - Doses $3 \times 10^{10}$, $1 \times 10^{11}$ and $3 \times 10^{11}$ VP
- **Combination therapy, CGTG-102 + low-dose oral CPO**
- **Front loaded regimen with 4 injections during first two weeks, continuing with monthly injections for five months**
  - Total of nine administrations

**i.t.=intratumoral**
**i.v.=intravenous**
**p.o.=oral**
CGTG-102 a.k.a. Ad5/3-Δ24-GMCSF

Partial deletion in the gene coding for E1A-protein

- Cancer specific replication

Chimeric fiber
- Enhanced transduction of cancer cells

GM-CSF transgene
- Enhanced anti-tumor immune response
Planning preclinical trials

• EMEA regulations for
  • Virus and vector shedding
  • Repeated toxicity, committee for proprietary medicinal products (applied)
  • Non-clinicals required before first clinical use of GTMPs
  • (Non-clinical testing for inadvertent germline transmission)
  • Quality, preclinical and clinical aspectsof GTMPs
  • Oncolytic viruses (very short)

F.i. NOT for

• requirements for first-in man clinical trials for potential high-risk medicinal products
• Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals

NOT ICH (Intl conference on harmonisation) Preclinical safety evaluation of biotechnology-derived pharmaceuticals
Planning preclinical trials

- EU-direktiivi ATMP’s:
  - ”Lääkkeiden farmakologiset ja toksikologiset testausvaatimukset eivät aina sovellu ATMP-tuotteisiin niiden ainutlaatuisten ja monimuotoisten rakenteellisten ja biologisten ominaisuuksien vuoksi.”
- FIMEA scientific advice
- FDA: Planning & executing the experiments according to EMEA, FIMEA requirements has been a good foundation to fulfill FDA requirements also
  - Pre-IND Scientific advice
- Scientific advice works two ways, setting and fulfilling requirements is a learning process for both sides.
Preclinical requirements: what to study

• Virus replication (specificity, kinetics)
• Efficacy
• Transgene expression specificity & activity (site, duration)
• Biological activity -> effects of the transgene product (if possible)
  – TG needs to bring additional efficacy without compromising safety
• Effects of additional drugs, in our case cyclophosphamide
  – needs to bring additional efficacy without compromising safety
Preclinical requirements: what to study

- Biodistribution (kinetics: virus, transgene product)
- Toxicity (dose escalation). Preferably aim at some degree of toxicity with the higher doses
- Biodistribution vs. toxicity
- Tumor bearing/non-tumor bearing?
- Shedding, genotox (applied)

- Follow the clinical protocol as closely as possible (if you have preferences)
  - Route of administration
  - Treatment schedule
  - Dosing
CGTG-102 preclinical models

- **Nude mice:**
  - basic efficacy experiments in human tumor bearing animals
  - Lacks many immunological components, MOA may be different

- **Syrian hamster:**
  - Semipermisssive to adenoviral replication
  - Human GMCSF is active

- **Planned: Immunocompetent mice**
  - Allowes many MOA (immunological) studies that can’t be done in hamsters (no reagents available)
  - Tumor-specific immune response, T-cell trafficking & activation etc.

  - MOA-studies are the most demanding ones in this type of drug, since the effects are numerous (many unknown) and causalities often unclear
## CGTG-102 preclinical trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study description</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONCOS 1-10</td>
<td>Tumour selectivity of CGTG-102 replication and GMCSF expression in immune-competent Syrian hamsters.</td>
<td>Replication is tumour selective. GMCSF expression is restricted to tumours</td>
</tr>
<tr>
<td>ONCOS 2-10</td>
<td>Tumour selectivity of CGTG-102 replication and GMCSF expression in immune-competent Syrian hamsters.</td>
<td>Efficacy Additional benefit of cyclophosphamide</td>
</tr>
<tr>
<td>ONCOS 6-10</td>
<td>Potency of CGTG-102 in i.p disseminated tumour-bearing immune competent Syrian hamsters.</td>
<td>Efficacy in intraperitoneal tumor Feasibility of intraperitoneal administration</td>
</tr>
<tr>
<td>ONCOS-A0</td>
<td>Acute toxicity of very high doses of CGTG-102 in Syrian hamsters with low dose cyclophosphamide (Biotest)</td>
<td>Toxicity with the highest (1000x) dose (hydrocephalus, necrotising hepatitis)</td>
</tr>
<tr>
<td>ONCOS-A1</td>
<td>Toxicity and biodistribution in Syrian hamsters. Dose excursion in TOX part (GLP-study at Biotest)</td>
<td>No marked toxicity (dosing up to 100x) Minimal shedding</td>
</tr>
</tbody>
</table>
CGTG-102 preclinical trials; sarcoma and melanoma for future trials

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<tr>
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<tr>
<td>ONCOS 1-11</td>
<td>Efficacy study in nude mice human sarcoma model.</td>
<td>Efficacy, improves with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Replication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Capsid modification</td>
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<tr>
<td></td>
<td></td>
<td>• GMCSF-transgene improves efficacy (why?)</td>
</tr>
<tr>
<td>ONCOS 2-11</td>
<td>Efficacy study in hamsters; sarcoma model. Dose escalation and multiple dosing included.</td>
<td>Efficacy, better with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multiple dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Higher dose</td>
</tr>
<tr>
<td>ONCOS 3-11</td>
<td>Efficacy study ONCOS 3-11 in human melanoma tumour-bearing mice</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>
Outsourcing of BD and tox GLP study

- Challenge: preclinical model Syrian hamster with i.v. Injection
- Initial discussions with >5 preclinical CRO’s
  - No one had experience with the administration route
  - Surprisingly big variation in the cost of proposals
  - US considered to be too far
- BioTest in the Czech was chosen to do the big BD& tox
  - Attractive pricing, big performance capacity
  - A small prestudy to demonstrate their ability with the GLP setup
  - GLP audit during the prestudy to ensure GLP compliance
  - At audit, the further outsourcing sites (II, III etc.) are equally important with the main test site
Thank you!