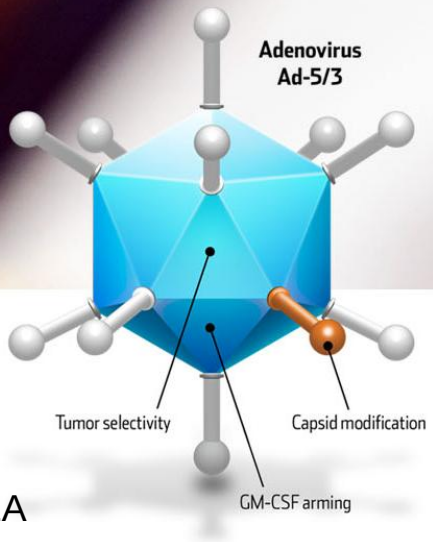
## Oncos Therapeutics

# 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

# Oncos-C1

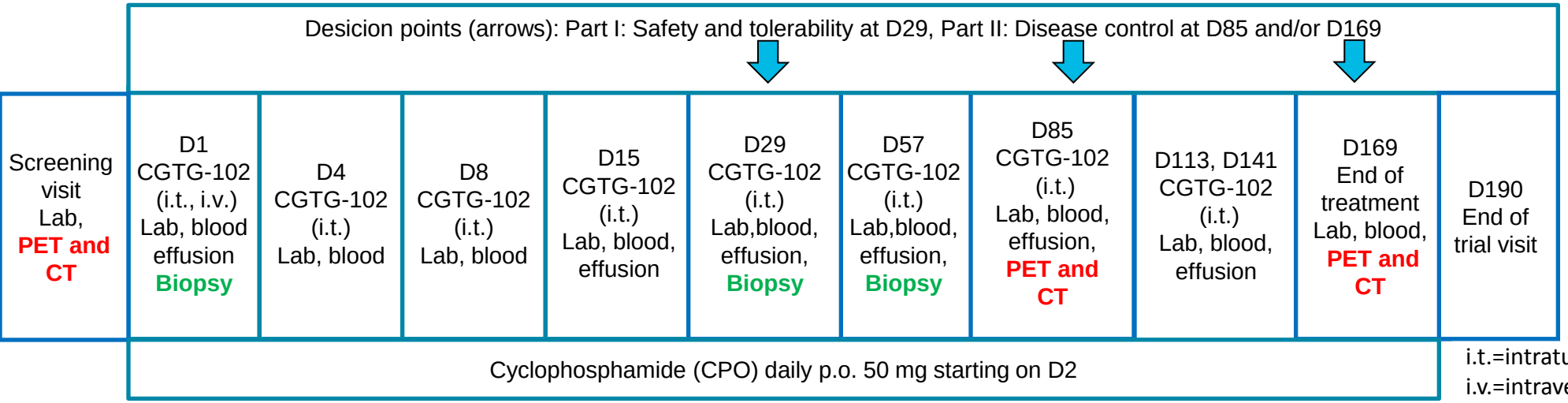
Title of protocol:

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

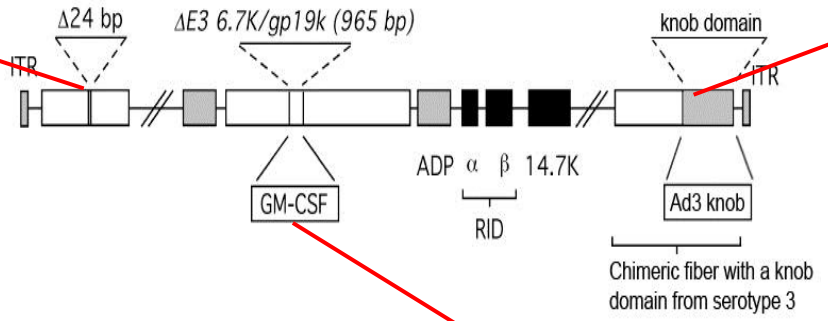



- Dose escalation recruiting 12-18 patients
  - Doses 3 x $10^{10}$, 1 x $10^{11}$ and 3 x $10^{11}$ VP
- Combination therapy, CGTG-102 + low-dose oral CPO
- Front loaded regimen with 4 injections during first two weeks, continuing with monthly injections for five months
  - Total of nine administrations

# 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) Preclinincal 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 fullfill 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 spesificity & activity (site, duration)
- Biological activity -> effects of the transgene product  (if possible)
  - TG needs to bring additional efficacy without compromizing safety
- Effects of additional drugs, in our case cyclophosphamide
  - needs to bring additional efficacy without compromizing 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:
  - Semipermissive 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

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

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→ Oncos C-1

# CGTG-102 preclinical trials; sarcoma and melanoma for future trials

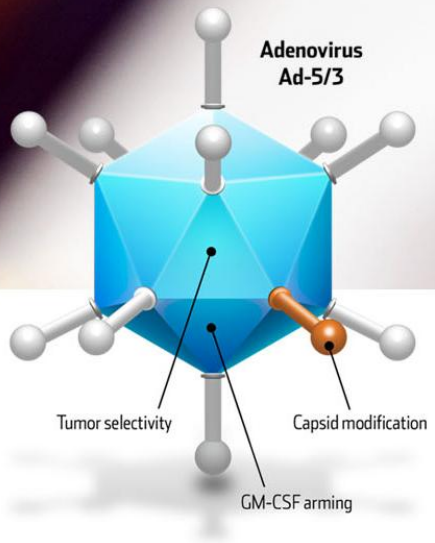
| Trial | Study description | Result |
|---|---|---|
| ONCOS 1-11 | Efficacy study in nude mice human sarcoma model. | **Efficacy, improves with:**<br>•Replication<br>•Capsid modification<br>•GMCSF-transgene improves efficacy (why?) |
| ONCOS 2-11 | Efficacy study in hamsters; sarcoma model. Dose escalation and multiple dosing included. | **Efficacy, better with :**<br>•Multiple dosing<br>•Higher dose |
| ONCOS 3-11 | Efficacy study ONCOS 3-11 in human melanoma tumour-bearing mice | **Efficacy** |

Oncos C-X

# 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 capasity
  - 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!

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