Arming the patient’s immune system to fight cancer

CMC outsourcing in small virtual biotech company

28.02.2018
Subjects

- Introduction to Targovax and technology platforms
- Outsourcing to CDMOs
- Selection of CDMO
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- Introduction to Targovax and technology platforms
- Outsourcing to CDMOs
- Selection of CDMO
- Small biotech company in antigen specific cancer immunotherapy
- Located in Oslo and Helsinki
- History
Targovax has two immuno-oncology programs in clinical development

**ONCOS**
**Oncolytic virus**
- Genetically **designed adenovirus**
- Makes **cancer antigens** visible to immune system
- **Induces T-cells** specific to patients’ tumor

**TG**
**RAS neoantigen vaccine**
- Cocktail of **synthetic peptides**
- Mimics cancer causing **RAS neoantigens**
- **Induces T-cells** specific to **RAS mutations**
Targovax strategy is to boost the effect of immunotherapy by targeting multiple aspects of the cancer immunity cycle.

1. **Release of cancer antigens**
   - **ONCOS-102**
   - Oncolytic virus

2. **Cancer antigen presentation**
   - **TG01**
   - Peptide vaccine

3. **T-cell activation**

4. **T-cell trafficking**

5. **T-cell tumor infiltration**

6. **Cancer cell identification**

7. ** Destruction of cancer cells**

**Checkpoint inhibitors**
- Yervoy, Keytruda, etc...

Adapted from Chen et al. Immunity 2013; 39:1
ONCOS-102 is a cancer targeting adenovirus armed with an immune stimulating transgene

Selective replication in cancer cells

- Δ24 bp

Immune system booster

- Δ6.7K/gp19K

Enhanced cancer cell infection

- ΔAd5 knob

Transgene

- GM-CSF transgene
- Triggers innate immune response and recruits APCs
Resected pancreatic cancer is the lead indication, but all RAS mutated cancers are potential TG targets

1. Pancreatic cancer (resected)
   - TG01 lead indication
   - Completing phase I/II
   - Planning phase II/III
   - > 90% RAS mutated
   - 40,000 patients
   - Up to 500,000 patients

2. Colorectal cancer
   - TG02 lead indication
   - Phase I trial recruiting
   - 50% RAS mutated
   - Up to 500,000 patients

3. Lung cancer (NSCLC)
   - TG02 potential future indication
   - 30% RAS mutated
   - Up to 500,000 patients

4. All mutRAS cancers
   - TG02 + TG03 ultimate long-term potential
   - 30% of all cancers
   - Up to 30% of all cancer patients

Source: Global data, Riva et al. Plos One 2017
Estimated total addressable patient number with RAS mutations in US, EU and China

www.targovax.com
# Overview of Targovax’ full clinical program

<table>
<thead>
<tr>
<th>Cancer Indication</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
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<tr>
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<td>H1</td>
<td>H2</td>
<td>H1</td>
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<td>Resected Pancreas</td>
<td>Ph I/II</td>
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<td>Planned Phase II</td>
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<tr>
<td>Colorectal</td>
<td>Phase Ib</td>
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<td><strong>TG</strong></td>
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<tr>
<td>Resected Pancreas</td>
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<td>Planned registration program</td>
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<tr>
<td>Melanoma</td>
<td>Phase I</td>
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<tr>
<td>Mesothelioma</td>
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<td>Phase Ib/II</td>
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<td>Dose escalating Ph I</td>
<td>Ph II</td>
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<td>Prostate</td>
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<td>Phase I</td>
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<td>Partnered w/Sotio</td>
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- **Interim data**:Diamond Icon
- **Clinical, immune and safety data**:Yellow Diamond Icon
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Targovax strategy for CMC outsourcing

- Targovax is a virtual company and will outsource:
  - All development work and validation for manufacture processes and analytical methods for our IMPs.
  - GMP manufacture and quality control, and supply to clinical trials towards commercialization.

- Key CDMO and contract laboratory selection criteria:
  - Need to have in place quality standards to supply IMPs and commercial products to relevant markets, including EU, US and others as appropriate.
  - Need to have with high competency, skills and regulatory knowledge for the relevant outsourced scopes and products.
Targovax uses three IMPs in the clinical programs

**ONCOS**
- Oncolytic virus
- Genetically designed *adenovirus* 5
- Produced from human cancer cell line

**TG**
- RAS neoantigen vaccine
- Mixture of 7-8 *synthetic peptides* of 17 amino acids
- Lyophilized drug product

**GM-CSF**
- Immunomodulating adjuvant
- *rHuGM-CSF* expressed from *E.coli*
- Lyophilized drug product
IMP supply and development for clinical trials

- Targovax is outsourcing all development, manufacture and analytical testing for 3 IMPs
- Currently
  - Supply of IMPs to clinical Phase I/II trials
  - Development of manufacture process and analytical methods for Phase III and commercial product
TG peptides

- Supply of TG to Phase I/II clinical trials:

- Development & manufacture of TG for Phase III clinical trials
TG peptides

The CDMO picture for TG peptides

- Well known middle size CDMO for DS manufacture
  - Long history with Targovax
  - Financial strong
  - Located in central Europe, but global company
  - Strong expertise in development and manufacture of peptides
  - Regulatory compliant to EU and FDA GMP
  - Strong project management

- Small CDMO for current DP manufacture
  - Strong and long time connection to DS CDMO
  - Communication mainly organized by DS CDMO
  - Limited capacity for large batch sizes
  - Limited methodologies for DP release testing
Recombinant GM-CSF

- Supply of GM-CSF to Phase I/II clinical trials:
  - Commercial drug product Chinese supplier
  - Import & EU QP release

- Development & manufacture of GM-CSF for Phase III clinical trials:
  - DP Formulation Development
  - DS Process Development
  - GM-CSF Development
  - DS Release Methods
  - DS Other Release Methods
  - DS Characterisation Methods
  - DP Release Methods
  - GM-CSF Manufacture
  - DS Manufacture
  - DS Release Methods
  - DS Other Release Methods
  - DS Characterisation Methods
  - DP Manufacture
Recombinant GM-CSF

The CDMO picture for GM-CSF

- Well known small/middle size CDMO selected for DS manufacture
  - Financial strong
  - Located in central Europe
  - Strong expertise in development and manufacture of recombinant proteins
  - Regulatory compliant to EU and FDA GMP
  - Contracts with other CDMOs for additional testing methodologies
  - Strong project management

- Small size CRO for formulation development
  - Large flexibility (order of work packages, experimental design)
  - Strong expertise in formulation development
  - Request high involvement from customer (experimental design & decision making)

- CDMO for DP manufacture is not selected
ONCOS-102 Viral vector

- Supply of ONCOS-102 viral vector to Phase I/II clinical trials:

- Development & manufacture of ONCOS-102 viral vector for Phase III clinical trials:
ONCOS-102 viral vector

The CDMO picture for ONCOS-102

- Small CDMO for DS and DP manufacture
  - Long history with ONCOS
  - Located in Finland
  - Strong expertise on cell culture, viruses and quality control testing
  - Regulatory compliant to EU GMP
  - Strong project management
  - Strong involvement from Targovax
  - Limited capacity for large batch sizes of DP

- Several CDMOs for additional quality control testing on DS and DP stage
  - Well known testing labs
  - Contracted mainly by Targovax
  - Coordination responsibility and contracts to be moved to CDMO selected for DS and DP manufacture
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Selection of CDMO

- Assessment of DP CDMO for TG peptides, GM-CSF and ONCOS-102
- Define the strategy and goals
  - Strategic decision with long-term consequences
- Define your team: CMC, QA, Regulatory, BD
  - Identify stakeholders

Stage I: Search by Internet / Networks / Consultants / Other CMOs (50 CMOs)

Stage II: Emails / Company presentations / Calls / Meetings (5-10 CMOs)

Stage III: Request for proposals / Proposals / Audits (3-5 CMOs)
Selection of CDMO – Stage I

- Definition of Targovax specific requirements: Operations, Technical, Quality, Business
  - Location
  - DS and/or DP
  - Technology and equipment
  - Safety, containment, e.g. biosafety levels
  - Capacities
  - Regulatory compliance (EU, US)

- Availability of CDMOs, e.g. "Directory of Biopharmaceutical Contract Manufacturers" – 80 CDMOs

- Matrix: CDMO services vs. requirements

- CDMO, consultants & personal contacts
  - Recommendations

- Partnering conferences / Trade shows

- First screening
Selection of CDMO – Stage II

- Direct contact with CDMO
  - Emails / calls / presentations / meetings
  - Request for Information (RFI) based on criteria
    - Technical
      - Confirmation of data from Stage I
        - More detail info vs requirements
        - Premises, technology and equipment
        - Capacities (batch sizes, new customers)
        - Analytical capability
    - Quality
  - CDA – Confidential Disclosure Agreement
  - Ballpark figures
    - RFI & CDMO questionnaire
  - Site visits – Define the agenda
    - Facility tour
    - Financial strength
    - Project management, communication, transparency
    - Staff competency and trust
    - Track record

- Second screening

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CALL WITH XXXX, DATE XX.YY.ZZZZ

Fill & Finish
Viral vector, protein -GM-CSF, peptides

- Where is the facility located?
- Do you have commercial manufacturing?
- Fill & finish manufacturing
  - TTEC: 10,000 sq. ft
  - CDMO: 10,000 sq. ft
  - TTEC and CDMO about 100-200 employees each
data processing vs. development:
  - TTEC: 50,000 sq. ft
  - CDMO: 100,000 sq. ft
  - Fill & finish capability
    - Bovine serum albumin 10mg
    - Bovine serum albumin 50mg
    - Bovine serum albumin 100mg
    - Bovine serum albumin 200mg
- CDA – Confidential Disclosure Agreement
- Ballpark figures
  - RFI & CDMO questionnaire
- Site visits – Define the agenda
  - Facility tour
  - Financial strength
  - Project management, communication, transparency
  - Staff competency and trust
  - Track record

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Selection of CDMO – Stage III

- Request for proposals (RFP)
  - Scope of services, technical data and milestones
  - Proposal
    - Commercial proposal (breakdown in all project and manufacture costs)
      - Design for a competitive bidding process
    - Proprietary technology
    - Master program incl. Gantt chart
    - Sub-contractors
    - Contract conditions
    - GMP certificates & Site master file
    - Financial statements
    - References

- Proposal evaluation (and previous evaluation)

- Technical Due Diligence / Quality audits
  - 1-3 CDMO

- Selection of Targovax CDMO for DP manufacture
  - Term Sheet, Letter of Intent
  - Master Service Agreement, QA agreement
CDMO learnings

- Building trust and good working relationship
- Frequently communication & site visits – transparency
- Be present on CDMO site
- Stepwise approach to CDMO services - development
- CDMO full responsibility of sub-contractors
- Master Service Agreements & QA agreements
- Budget with additional costs