ONCOS-102: AN ADENOVIRUS BASED IMMUNE THERAPY IN SOLID TUMORS

Magnus Jaderberg MD, FFPM
Chief Medical Officer

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THERE IS A HIGH MEDICAL NEED FOR IMMUNE ACTIVATING AGENTS

**Checkpoint inhibitors** are revolutionizing cancer therapy...  
...but minority of patients respond...  
...leading to a high need for immune activators to boost checkpoint response rates

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22 bn USD  
Global CPI market\(^1\)

44 %  
Patients eligible for CPI\(^2\):

10 - 40 %  
Responders

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\(^1\) Immune Checkpoint Inhibitors Markets Report, 2020 January, ResearchAndMarkets.com  
\(^2\) Estimation of the Percentage of US Patients With Cancer Who Are Eligible for and Respond to Checkpoint Inhibitor Immunotherapy Drugs, JAMA Netw Open. 2019 May; 2(5), Haslam A., Prasad V.
TARGOVAX’S FOCUS IS TO DEVELOP IMMUNE ACTIVATORS TO ENHANCE THE EFFECT OF CHECKPOINT INHIBITORS
FOUR CRITICAL COMPONENTS OF IMMUNE ACTIVATION

1. Access to tumor antigens, cross-presentation by APCs and priming of T-cells

2. T-cell migration and infiltration into the tumor

3. Expansion and survival of T-cells in the tumor

4. Tumor cell recognition and elimination

Adapted from Chen & Mellman, Immunity 2013
RESISTANCE TO CHECKPOINT INHIBITION

1. Access to tumor antigens, cross-presentation by APCs and priming of T-cells
   
   **Problem:** Low tumor immunogenicity and ineffective T-cell priming

2. T-cell migration and infiltration into the tumor
   
   **Problem:** T-cells do not reach the tumor

3. Expansion and survival of T-cells in the tumor
   
   **Problem:** Exhaustion of T-cells in the tumor

4. Tumor cell recognition and elimination
   
   **Problem:** Immunosuppression in the tumor
THE ONCOS ONCOLYTIC VIRUS HAS BEEN ENGINEERED TO PROVIDE SOLUTIONS TO PROBLEMS OF RESISTANCE

Selective replication in cancer cells

Boosting the immune activation

Enhanced infection of cancer cells

**Lead candidate ONCOS-102**

Δ24 bp

Δ6.7K/gp19K

ΔAd5 knob

E1A

E3

Fiber knob

GM-CSF Transgene

Ad3 knob

ITR

DNA insertion site – opportunity to deliver genetic payload of choice
SOLUTION 1: ONCOS-102 DRIVES DANGER SIGNALLING AND INDUCES T-CELL PRIMING

Underlying causes
- Lack of neoantigens and/or poor neoantigen fitness
- Failure to activate danger signals

Impact of ONCOS
- Upregulation of TLR9 expression
- Induction of tumour antigen specific T-cells

TLR9 signaling in tumor RNAseq -fold change D36 vs. baseline\(^1\), mesothelioma

Tumor-specific T-cells IFN\(_\gamma\) Elispot assay, patient case examples\(^2\)

- Example - anti-Mesothelin; MAGE-A1, MAGE-A3 and NY-ESO-1 also detected
- NY-ESO-1 present at 17 mo. follow-up
- Example - anti-MAGE-A3
- Present also at 6 mo. follow-up

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\(^1\) Unpublished company data
\(^2\) Ranki et al. JITC 2016
SOLUTION 2: ROBUST INCREASE IN T-CELL TUMOR INFILTRATION FOLLOWING ONCOS-102 TREATMENT

Underlying causes
- Production of CXCL12 by stromal fibroblasts
- Trapping of T-cells in stroma

Impact of ONCOS
- Upregulation of several chemokines
- T-cell infiltration in response to virus injection

ONCOS-102 induced tumor T-cell infiltration
Ovarian cancer patient case example, monotherapy

Tumor biopsy mIHC – CD8+ T-cells

- >1000-fold increase of CD8+ T-cells in tumor
- Ovarian cancer patient – stable disease for three years

Pre-treatment
Baseline

Post-treatment
Week 8

Ranki et al. JITC 2016
ONCOS-102 PROMOTES PD-L1 UPREGULATION IN THE TUMOR

PD-L1 upregulation in mesothelioma tumors at day 36
Fold change, ONCOS-102 treated vs. untreated

Unpublished company data
* Control patients treated with standard-of-care chemotherapy

Unpublished company data
* Control patients treated with standard-of-care chemotherapy
**Underlying causes**
- Low expression of co-stimulatory molecules and pro-inflammatory cytokines
- Co-expression of multiple co-inhibitory receptors by T-cells

**Impact of ONCOS**
- Up-regulation of several co-stimulators and pro-inflammatory cytokines, such as IFNγ
- Increased fraction of intra-tumoral cytotoxic T-cells

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**Relative level of cytotoxic GrB+ / CD8+ T-cells at day 36**
Alive vs. deceased at 12 months, mesothelioma

**ONCOS-102 treated**
- Alive: n=15
- Deceased

**Control**
- Alive: n=5
- Deceased

Unpublished company data
* Control patients treated with standard-of-care chemotherapy
SOLUTION 4: ONCOS-102 INDUCES POLARIZATION TOWARDS INFLAMMATORY M1 MACROPHAGES

**Underlying causes**
- Increased level of inhibitory myeloid cells, such as M2 macrophages
- Induction of inhibitory regulatory T-cells

**Impact of ONCOS**
- Shift towards inflammatory immune cell population
- Polarization of M2 to M1 macrophage phenotype

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**M1 vs. M2 macrophage ratio in tumors at day 36**
Alive vs. deceased at 12 months, mesothelioma

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<table>
<thead>
<tr>
<th></th>
<th>Alive</th>
<th>Deceased</th>
<th>Alive</th>
<th>Deceased</th>
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<tbody>
<tr>
<td><strong>ONCOS-102 treated</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n=14</td>
<td></td>
<td></td>
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<tr>
<td><strong>Control</strong></td>
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<tr>
<td>n=4</td>
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* Unpublished company data
  * Control patients treated with standard-of-care chemotherapy
INFLAMMATORY MODULATION LINKED TO SURVIVAL (MONOTHERAPY)

Fold-change CD68+ macrophages vs. survival
Intra-tumoral, ONCOS-102 monotherapy

$r = 0.74$  $p = 0.006$

Overall survival (months)

CD68+ fold-change from baseline

**Overall survival (months)**
BROAD IMMUNE ACTIVATION IS LINKED TO CLINICAL BENEFIT (WITH CHEMO)

- Powerful immune activation compared to control across all parameters analysed in mesothelioma
- Immune activation pattern suggests **ONCOS-102 induces sensitivity to checkpoint inhibitor treatment**

**Mesothelioma 12-month data**

<table>
<thead>
<tr>
<th>ONCOS+SoC vs. SoC</th>
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<tbody>
<tr>
<td>ONCOS-102 treated - Alive</td>
</tr>
<tr>
<td>ONCOS-102 treated - Deceased</td>
</tr>
<tr>
<td>Control - Alive</td>
</tr>
<tr>
<td>Control - Deceased</td>
</tr>
</tbody>
</table>

- CD8+ T-cells
- Cytotoxic CD8+ T-cells
- PD-L1 expression
- M1: M2 macrophage ratio
- Ratio of cytotoxic T-cells % relative to total CD8+
- M1 macrophages

\[ \text{fold change} \]
ONCOS-102 IMMUNE ACTIVATION - CONCLUSIONS

ONCOS-102 activates the immune system and counteracts multiple mechanisms of immuno-suppression operating at different steps of the cancer immunity cycle.

Modulation of the tumor micro-environment is linked to clinical benefit in patients with different tumor types.

Immune activation provides broad and powerful priming to sensitize patients to respond to subsequent treatment with checkpoint inhibitors.
# DEVELOPMENT PROGRAM

<table>
<thead>
<tr>
<th>Product candidate</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Collaborator</th>
<th>Next expected event</th>
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<tbody>
<tr>
<td><strong>ONCOS-102</strong></td>
<td>Mesothelioma Combination w/ pemetrexed/cisplatin</td>
<td></td>
<td>MERCK</td>
<td>2H 2020 Survival data</td>
<td></td>
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<tr>
<td></td>
<td>Melanoma Combination w/Keytruda</td>
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<td></td>
<td>Colorectal Combination w/Imfinzi</td>
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<td>AstraZeneca</td>
<td>2H 2020 Part 2 clinical data</td>
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<td>Prostate Combination w/DCvac</td>
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<td>Sotio</td>
<td>Update by collaborator</td>
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<td><strong>ONCOS-200 series</strong></td>
<td>Next Gen viruses</td>
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<td><strong>Novel mutRAS concepts</strong></td>
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<td>OBlique</td>
<td>Updates at conferences</td>
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ONCOS-102 + KEYTRUDA IN ANTI-PD1 REFRACTORY MELANOMA
PROMISING OUTCOME IN FIRST NINE PATIENTS

Tumor reduction in target lesions

Best % change in tumor burden from baseline

33% Overall response rate

Stage IIIb, Prior therapies
- Surgery x 3
- Yervoy
- Dabrafenib + Trametinib
- Keytruda

Case example: Early and durable complete response (CR)

Baseline: Progression on Keytruda
Week 3: 3x ONCOS-102 only
Week 9: 3x ONCOS-102 & 2x Keytruda

* Non-target progression / new lesion (PD)
Letters and numbers indicating disease stage
Preliminary data presented at SITC 2019
ONCOS-102 has produced efficacy data competitive to leading drug candidates in PD1 refractory melanoma.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-PD1 Retreatment</th>
<th>CR</th>
<th>PR</th>
<th>ORR (Patients)</th>
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</thead>
<tbody>
<tr>
<td>ONCOS-102</td>
<td></td>
<td>11%</td>
<td>22%</td>
<td>33% (3/9 pats.)</td>
</tr>
<tr>
<td>RP1</td>
<td></td>
<td>0%</td>
<td>31%</td>
<td>31% (5/16 pats.)</td>
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<tr>
<td>CMP-001</td>
<td></td>
<td>3%</td>
<td>22%</td>
<td>25% (21/83 pats.)</td>
</tr>
<tr>
<td>Entinostat</td>
<td></td>
<td>2%</td>
<td>17%</td>
<td>19% (10/53 pats.)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-CTLA-4 Combination</th>
<th>CR</th>
<th>PR</th>
<th>ORR (Patients)</th>
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<tbody>
<tr>
<td>Cavatak</td>
<td></td>
<td>0%</td>
<td>36%</td>
<td>36% (4/11 pats.)</td>
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<tr>
<td>Tilsotomolid</td>
<td></td>
<td>6%</td>
<td>18%</td>
<td>24% (12/49 pats.)</td>
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</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adoptive T-cell Therapy</th>
<th>CR</th>
<th>PR</th>
<th>ORR (Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifileucel</td>
<td></td>
<td>3%</td>
<td>32%</td>
<td>35% (23/66 pats.)</td>
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</tbody>
</table>

**Comment**
- Adenovirus expressing GM-CSF
- Herpesvirus expressing GM-CSF and GALV
- TLR-9 agonist
- Data from high dose cohort
- HDAC inhibitor
- CTLA4 naïve, 10-20% ORR expected
  - Coxsackievirus, no transgene
  - TLR-9 agonist
- Autologous TIL therapy with IL-2
  - Complex and expensive manufacturing

**SOURCE:** Targovax market analysis, May 2020
CLINICAL BENEFIT IS ALSO DEMONSTRATED IN MESOTHELIOMA
ONCOS-102 COMBINED WITH CHEMO VS CHEMO ALONE IN FIRST LINE

ORR / BORR

1. Tsao 2019 (JCO) compared cediranib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
2. Vogelzang 2003 was the basis for FDA approval of pemetrexed. FDA review disputed originally reported data, reducing confirmed BORR to 21% (Hazarika 2005)
3. Pemetrexed plus carboplatin, BORR
4. Scagliotti 2019 (Lancet) compared nintedanib + pem/cis vs pem/cis; data from pem/cis arm presented on plot
5. Baas 2020 CheckMate 743. Nivolumab + ipilimumab for two years vs pem/cis (or carboplatin) for 6 months
6. Zalcman 2016 (Lancet) compared bevacizumab + pem/cis vs pem/cis; data from pem/cis arm presented on plot. Not specified if ORR or BORR.
7. mPFS may change: Experimental group 11 patients (3 censored)
ACTIVATING THE PATIENT’S IMMUNE SYSTEM 
TO FIGHT CANCER

BEST-IN-CLASS IMMUNE ACTIVATION

ONCOS-102 has clinically demonstrated the broadest and most powerful immune activation of any oncolytic virus, both as monotherapy and in combinations

ENCOURAGING CLINICAL EFFICACY

This powerful immune activation translates into clinical benefit for patients, in combination with both checkpoint inhibitors and chemotherapy