Immunologic correlates of ONCOS-102 therapy in patients with advanced solid tumors

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Memorial Sloan Kettering Cancer Center
on behalf of ONCOS-102 investigators
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Presenter Disclosure Information

Dmitriy Zamarin MD PhD

The following relationships exist related to this presentation:

No relationships to disclose
ONCOS-102: genetically modified oncolytic adenovirus encoding GM-CSF

Selective replication in Rb/p16 defective cancer cells

Improved infectivity of cancer cells

Transgene expression coupled to virus replication
-> expression only in tumor cells
ONCOS-102 replicates in cancer cells and induces immunogenic cell death

Intratumoral administration

- ONCOS-102 replicates in cancer cells and induces immunogenic cell death
- CRT
- GM-CSF
- Cytokines
- ATP
- HMGB1
- Calreticulin A

Cell viability

- Low passage melanoma
- Lung cancer

H226 Mesothelioma

- Untreated cells
- ONCOS-102 treated cells

Cell viability graphs for low passage melanoma and lung cancer, showing the effect of ONCOS-102 and Ad5wt on cell viability.
Phase I study of intratumoral ONCOS-102 with low dose cyclophosphamide in patients with advanced solid tumors

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patient number</th>
<th>WHO score</th>
<th>Age/Sex</th>
<th>Cancer type</th>
<th>Number of previous lines of therapy</th>
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<tbody>
<tr>
<td>$3 \times 10^{10}$ VP</td>
<td>FI1-01</td>
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<td>64 / F</td>
<td>Ovarian</td>
<td>16</td>
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<td>61 / M</td>
<td>Colon</td>
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<tr>
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<td>FI1-04</td>
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<td>$1 \times 10^{11}$ VP</td>
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<td>63 / M</td>
<td>Liver</td>
<td>2</td>
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<tr>
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<td>FI1-08</td>
<td>1</td>
<td>63 / F</td>
<td>Lung</td>
<td>3</td>
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<td>FI1-09</td>
<td>1</td>
<td>63 / M</td>
<td>Mesothelioma</td>
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</tr>
<tr>
<td>$3 \times 10^{11}$ VP</td>
<td>FI1-13</td>
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<td>53 / M</td>
<td>Rectum</td>
<td>4</td>
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<tr>
<td></td>
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<td>64 / F</td>
<td>STS</td>
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<td>Breast</td>
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<td>FI1-18</td>
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<td>38 / F</td>
<td>Ovarian</td>
<td>7</td>
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</table>

- 115 cancer patients with solid refractory tumors were treated with ONCOS-102 in Advanced Therapy Access Program (ATAP) before the current Phase 1 study.
ONCOS C1: a Phase I study of intratumoral ONCOS-102 with low dose cyclophosphamide in patients with advanced solid tumors

- No DLT’s were seen in any treatment groups
- Most AEs were grade 1-2, primarily pyrexia and flu-like symptoms.
## Efficacy assessment

### Patients
- 100% chemo refractory (up to 16 lines)
- 66% had prior surgery
- 50% had prior radiotherapy
- 2 pts died before 3 months

### Table: RECIST1.1 (3 months)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Type</th>
<th>RECIST1.1 (3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI1-01</td>
<td>Ovarian</td>
<td>SD</td>
</tr>
<tr>
<td>FI1-02</td>
<td>Colon</td>
<td>SD</td>
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<td>FI1-04</td>
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<td>Liver</td>
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<td>FI1-08</td>
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<td>FI1-09</td>
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<td>PD</td>
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<tr>
<td>FI1-13</td>
<td>Rectum</td>
<td>PD</td>
</tr>
<tr>
<td>FI1-14</td>
<td>Mesothelioma</td>
<td>SD</td>
</tr>
<tr>
<td>FI1-17</td>
<td>STS</td>
<td>PD</td>
</tr>
<tr>
<td>FI1-19</td>
<td>Ovarian</td>
<td>SD</td>
</tr>
</tbody>
</table>

SD = Stable disease, PD = Progressive disease

**Alive with SD >24 months**

FI1-14  Mesothelioma

- 6 months
- 7.5 months

**Total PET activity (> 2.5 SUVmax)**

- 6 months: 4000
- 7.5 months: 1500
Several immune cell subsets were increased in tumors following ONCOS-102

**CD68**

- SD at 3 months
- PD at 3 months
- Tumor-specific CD8+ T cells in blood

**CD8**

**CD4**

Fold-change from baseline

SD at 3 months
PD at 3 months
Tumor-specific CD8+ T cells in blood
Increase in tumor-infiltrating immune cells following ONCOS-102 treatment is associated with increased survival.

**CD3**

- Fold change from baseline
- Absolute overall survival (months)
- $r=0.87$
- $p=0.0003$

**CD8**

- Pt FI1-19, (alive)
- $r=0.75$
- $p=0.005$

**CD68**

- $r=0.74$
- $p=0.006$

**CD11c**

- $r=0.71$
- $p=0.009$
High number of CD68+ TAMs in baseline tumors was associated with short survival

High number of intratumoral CD68+ cells after ONCOS-102 therapy was associated with increased survival

Spearman’s rank correlation  
$\rho = 0.04$  
$R = -0.59$

Spearman’s rank correlation  
$\rho = 0.01$  
$R = 0.71$
Macrophage plasticity

M1 macrophage
- Promote T\(_H\)1 response
- Efficient antigen presentation
- Tumor destruction

M2 macrophage
- Promote T\(_H\)2 response
- Anti-inflammatory
- Immunoregulation

Adapted from Biswas and Mantovani Nature Immunol 2010
Tumors with increased CD68+ cells exhibit M1 macrophage transcriptional signature

Gene expression analysis

CD68+ cells in tumor (Fold change from baseline)

M1 markers

M2 markers

CXCL9

CXCL10

CCL17

CCL22

CCL24
Local ONCOS-102 administration leads to induction of systemic tumor-specific CD8+ T cell response:

**Mesothelioma pt FI1-14:** induction of MAGE-A3 specific CD8+ T cells

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Weeks 1-4</th>
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<tbody>
<tr>
<td>No peptide</td>
<td><img src="image1.png" alt="Image 1" /></td>
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<tr>
<td>MAGE-A3 p271-279</td>
<td><img src="image3.png" alt="Image 3" /></td>
<td><img src="image4.png" alt="Image 4" /></td>
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</table>

**OvCa pt FI1-19:** multiple tumor-specific CD8+ T cell populations induced by ONCOS-102

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Weeks 1-12</th>
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<td>No peptide</td>
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<td>Mesothelin</td>
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<td><img src="image8.png" alt="Image 8" /></td>
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</table>

**Fold-change from baseline**

![Bar chart](chart.png)

NY-ESO-1 specific CD8+ T cells present 17 mo after previous ONCOS-102 treatment, alive and SD >24 mo
CD8+ T cell infiltration was associated with an increased PD-L1 expression in mesothelioma tumors

<table>
<thead>
<tr>
<th>CD8+ cells in tumors</th>
<th>IFN-gamma in tumors</th>
<th>PD-L1 in tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>After ONCOS-102</td>
<td>Baseline</td>
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<tr>
<td>Pat. FI1-09</td>
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<td>After ONCOS-102</td>
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<td>Log gene expression</td>
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Summary and Take Home Points

- Intratumoral administration of ONCOS-102 to patients with advanced solid tumors was safe and had evidence of clinical benefit.
- High density of CD68+ TAMs in baseline tumor biopsies was associated with short survival.
- Increase in CD68+ TAMs and other immune cells in post-treatment biopsies was associated with increased survival.
- Treatment with ONCOS-102 converts tumors to "inflamed" phenotype with evidence of systemic tumor-specific immune response.
- Data suggest that ONCOS-102 may reduce local immune suppression by recruiting beneficial immune cells into tumors.
- There is a rationale for evaluation of ONCOS-102 in combination with other immunotherapies (e.g. checkpoint inhibitors).
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The patients and their families!!!