An evaluation of local and systemic immune markers following intratumoral administration of a chimeric adenovirus Ad5/3-D24-GMCSF in refractory cancer patients with solid tumors

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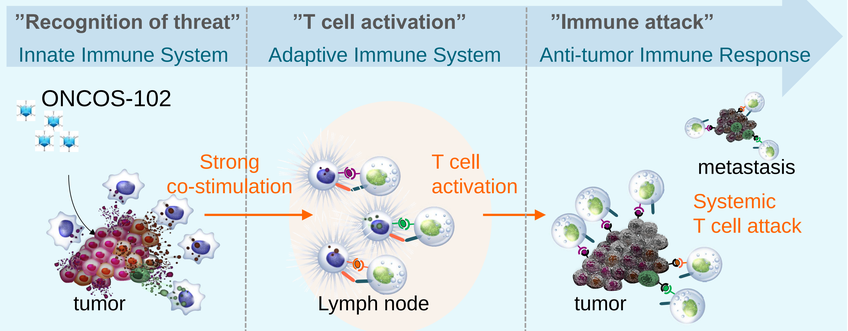
INTRODUCTION

ONCOS-102 (Ad5/3-D24-GMCSF) is a tumor-targeted immune activating adenovirus coding for human GM-CSF

Intratumoral ONCOS-102 has been shown to induce a systemic CD8+ T cell response against patient's unique cancer cells:



Multiple activatory mechanisms:
- TLR stimulation (TLR9)
- Pro-inflammatory cytokines
- Immunogenic cell death
- Release of tumor antigens
- Local GM-CSF expression

Targeted anti-tumor immune response:
- ONCOS-102 teaches immune system to recognize the unique repertoire of tumor (neo)antigens of each patient

Systemic anti-tumor immune response:
- *ONCOS-102 = in situ* vaccination
- Immunological memory provides long term protection

Phase I study - design

Day	0	1	4	8	15	29	57	85	113	141	169
ONCOS-102	X	X	X	X	X	X	X	X	X	X	
Biopsy	X					X	X				
PBMCs	X	X	X	X	X	X	X	X	X	X	
PET / CT	X							X		X	

Dose cohorts: 3x10^{10} VP, 1x10^{11} VP, 3x10^{11} VP
VP= viral particles

- 12 solid tumor cancer patients were treated with 3 dose levels (3+3+6 pts)
- Samples were collected at baseline and during the study to assess the immunological MoA

Activation of innate immune system following ONCOS-102

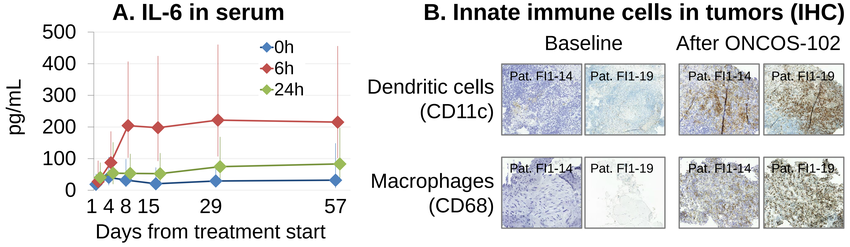
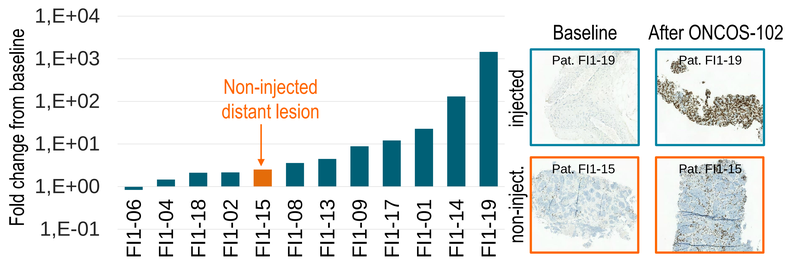


Figure 1. All patients showed an immediate short-term increase in systemic IL-6 (A) and IL-8 (not shown) following each intratumoral ONCOS-102 administration. Infiltration of dendritic cells and macrophages into tumors was seen after treatment initiation (B).

ONCOS-102 induced CD8+ T cell infiltration and Th1 polarization in tumors

A. ONCOS-102 attracted CD8+ T cells into injected and non-injected tumors



B. Th1 type signature was detected in tumors after ONCOS-102 administration

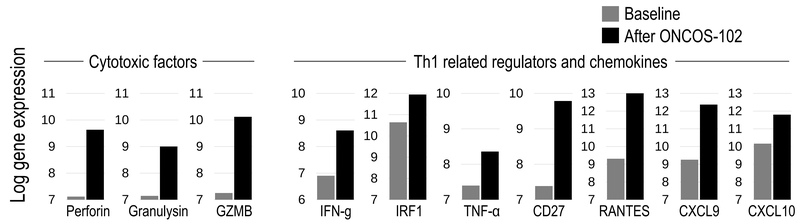
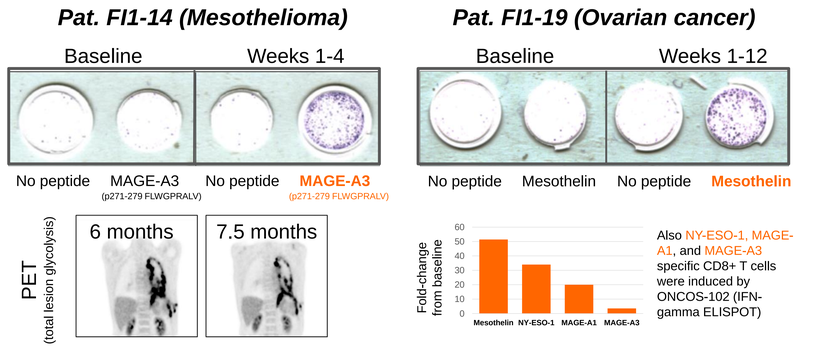


Figure 2. Gene expression profiling (FI1-14) showed markedly elevated expression levels of genes encoding cytotoxic factors and genes related to Th1 signature in post-treatment sample suggesting that CD8+ TILs had an effector phenotype.

ONCOS-102 targets multiple tumor-derived antigens and induces long-term tumor-specific CD8+ T cell responses



- 47% reduction in total tumor burden between 6-month and 7.5-month PET
- Long-term disease stabilization and maintenance of anti-tumor CD8+ T cells (NY-ESO-1) 17 months after previous ONCOS-102 (alive >24 months)

Figure 3. IFN-γ ELISPOT for tumor specific CD8+ T cells was performed. Purified CD8+ were pre-sensitized with peptide-pulsed, irradiated autologous PBMCs depleted of CD4+ and CD8+ T cells and tested on day 10 by IFN-γ ELISPOT assay for recognition of autologous antigen-presenting cells.

CD8+ T cell infiltration was associated with an increased PD-L1 expression in mesothelioma tumors

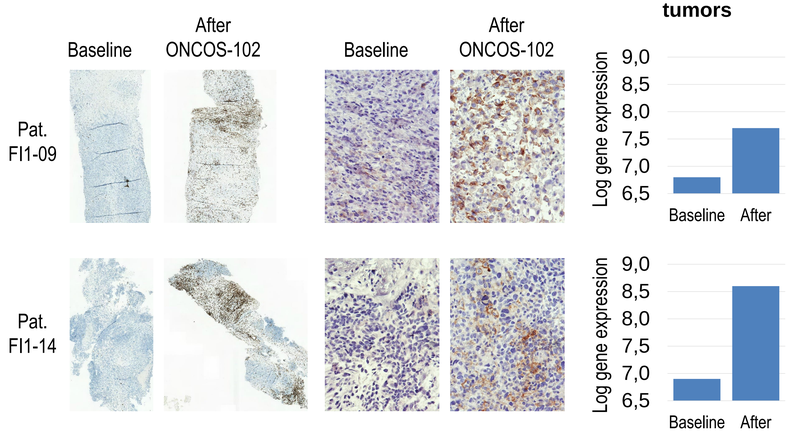


Figure 4. Infiltration of CD8+ T cells and increased PD-L1 expression in mesothelioma tumors was seen following ONCOS-102 administration. Gene expression analysis showed a concomitant increase in intratumoral IFN-gamma expression. Data suggest that ONCOS-102 mediated anti-tumor immune attack triggered an adaptive resistance in tumors as measured by upregulated PD-L1 expression post ONCOS-102.

CONCLUSIONS

- **Infiltration of CD8+ T cells was seen in 92% (11/12) of patients following ONCOS-102 administration both in injected and non-injected tumors**
- **Local ONCOS-102 treatment induced a systemic tumor-specific CD8+ T cell response in the last-line refratory solid tumor patients who showed no evidence of anti-tumor immunity at baseline**
- **Concomitant increase in CD8+ TILs and PD-L1 expression in tumor cells suggests that ONCOS-102 mediated anti-tumor immune attack triggered an adaptive resistance in tumors**
- **Data provide a strong rationale for combinatorial use of ONCOS-102 and PD-(L)1 blockade**

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