Intratumoral ONCOS-102 Shapes the Tumor Microenvironment in Last-Line Refractory Solid Tumor Patients

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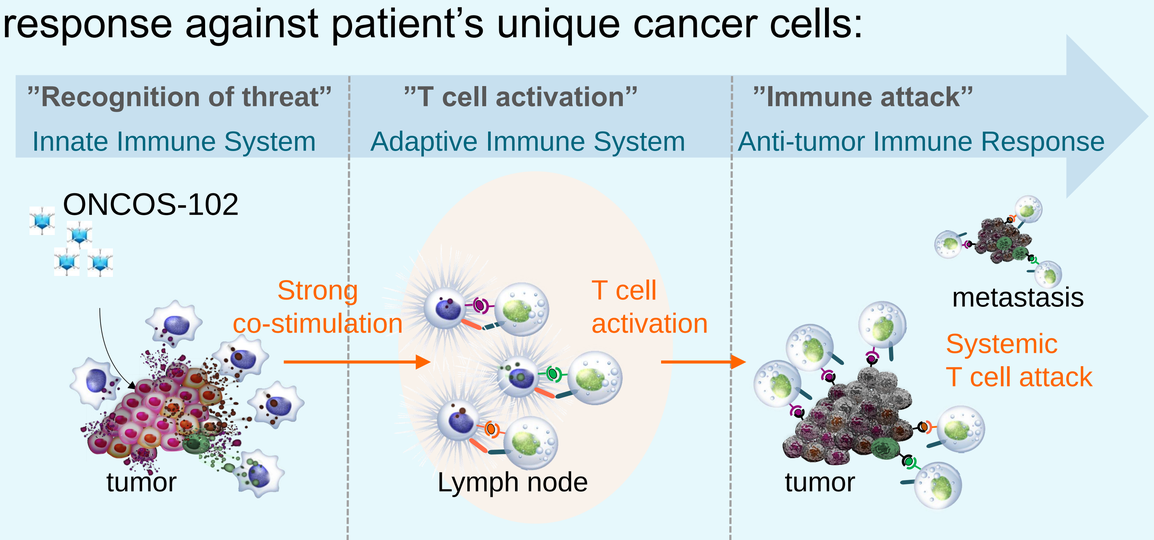
INTRODUCTION

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

Intratumoral ONCOS-102 induces a systemic CD8+ T cell response against patient's unique cancer cells:

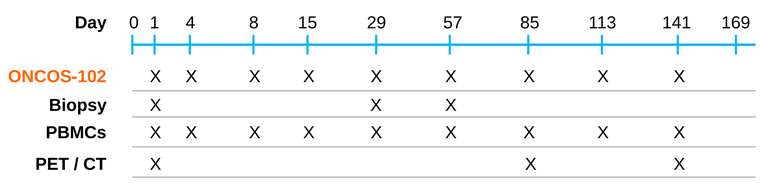


Multiple activatory mechanisms:
- TLR stimulation (TLR9)
- Pro-inflammatory cytokines
- Release of tumor antigens
- Local GMCSF expression

Targeted anti-tumor immune response:
- ONCOS-102 teaches immune system to recognize unique cancer cells of each patient

Systemic anti-tumor immune response
- *In situ* vaccination
- Immunological memory provides long term protection

Phase I study - design



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

- 12 last-line 100% chemo refractory solid tumor 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

Tumor infiltrating CD8+ T cells detected in 11 out of 12 pts

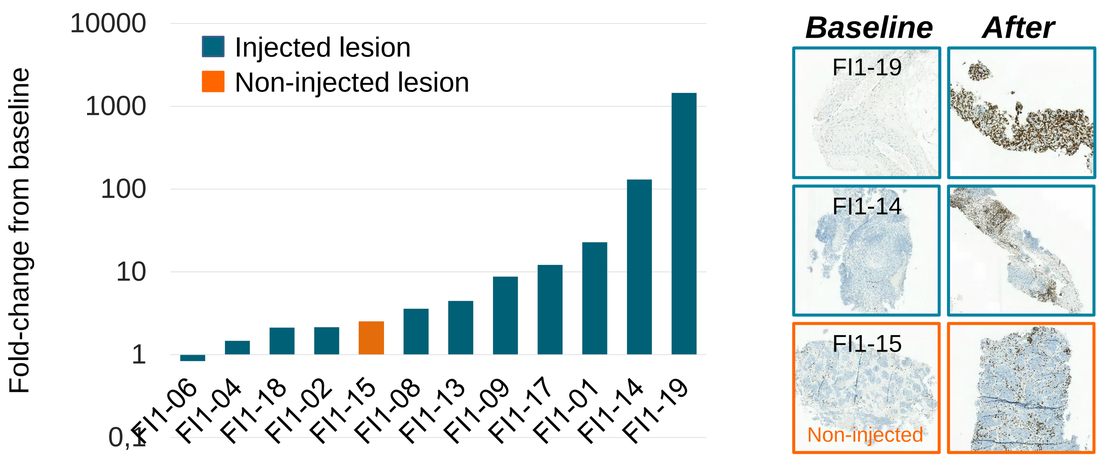


Figure 1. Three sequential biopsies (baseline, 1 month, 2 months) were collected either from injected lesion (11 pts), or non-injected distant metastasis (1 pt). 11 patients showed post-treatment increase in tumor infiltrating CD8+ T cells. Also non-injected distant lesion showed 2.5 fold increase in CD8+ cells post-treatment.

Correlation between post-treatment increase in TILs and OS

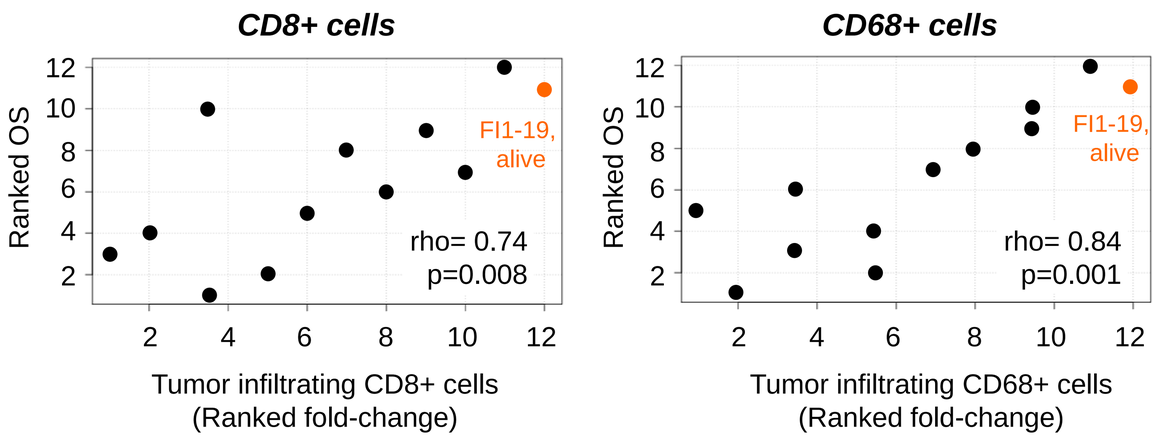
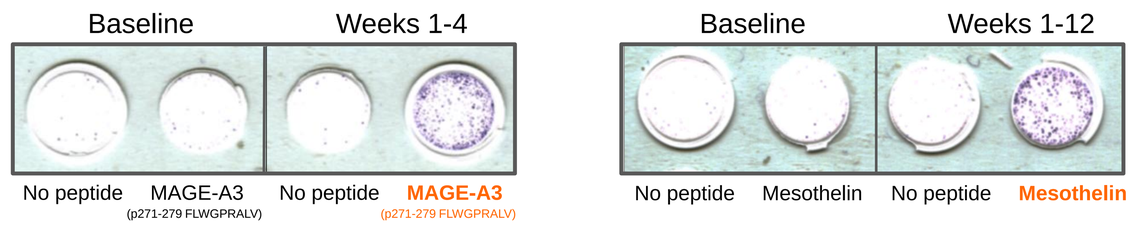


Figure 2. Tumor infiltrating CD8+ T cells and CD68+ macrophages were stained with IHC and whole tissue sections were quantified by computer assisted method. Positive correlation (by Spearman Rank Correlation) was seen between post-treatment increase in tumor infiltrating immune cells and OS.

Induction of systemic anti-tumor CD8+ T cell response



- 47% reduction in total tumor burden between 6-month and 7.5-month PET
- Currently responding to standard chemotherapy, alive >15 months after study

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.

FI1-14: The pattern of PD-L1 expression in tumor cells followed the expression levels of Th1 related genes

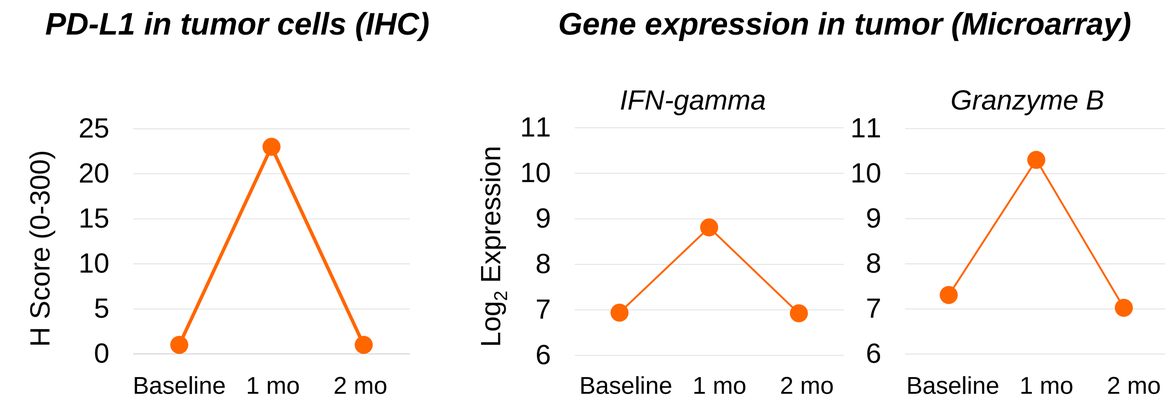


Figure 4. PD-L1 is expressed on tumor cells as a response to IFN-gamma. Increased PD-L1 expression in tumor cells was seen in several patients. In patient FI1-14 this was seen concomitantly with the systemic induction of tumor-specific CD8+ T cells.

FI1-19: Increase in TIM-3 levels in TILs concomitantly with the induction of tumor specific CD8+ T cells

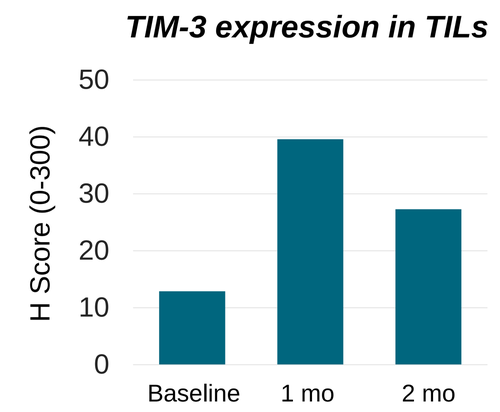


Figure 5. Membrane expression of TIM-3 in tumor infiltrating lymphocytes (TILs) was assessed with IHC and quantified by H score. Clear post-treatment increase in membrane TIM-3 expression was seen in several patients. Increase in membrane TIM-3 level was seen in patient FI1-19 who responded to treatment with an induction of systemic tumor-specific (mesothelin) CD8+ T cell response.

CONCLUSIONS

- ONCOS-102 treatment induced systemic tumor-specific CD8+ T cell response in the last-line refratory solid tumor patients who showed no evidence of anti-tumor immunity before treatment
- Infiltration of CD8+ T cells was seen in 92% (11/12) of patients following ONCOS-102 administration
- Post-treatment increase in TILs correlated with OS
- ONCOS-102 treatment induced PD-L1 expression in tumor cells concomitantly with the induction of systemic tumor-specific CD8+ T cell response
- Increased TIM-3 expression in TILs was seen in a patient who responded to treatment with induction of tumor-specific CD8+ T cells