Next generation ONCOS oncolytic adenovirus with novel anti-cancer double-transgenes shows synergistic anti-cancer effect in a melanoma mouse model

Lukasz Kuryk[1], Anne-Sophie W Møller[2]
[1]Targovax Oy, Clinical Science, Helsinki, Finland
[2]Targovax ASA, Clinical Science, Oslo, Norway

Poster Session Title: Vaccines
Poster Number: 4562

INTRODUCTION

Oncolytic virotherapy is a promising and fast emerging anti-cancer strategy. Oncolytic adenoviruses with the E1A Δ24 deletion provide an anti-cancer platform that specifically replicates in tumor cells with impaired retinoblastoma pathways.

Genetically engineered OVs can be armed with different co-stimulatory molecules in order to boost the anti-tumour immune responses. Building on the **ONCOS-102 backbone**, we have engineered two different next generation ONCOS viruses (**Fig. 1**), ONCOS-210 and ONCOS-212, both expressing the same novel double transgenes designed to inhibit tumor growth and metabolism. ONCOS-210 and ONCOS-212 differ in the way the transgenes are inserted into the backbone. Here, we describe the characterization and pre-clinical *in vitro* and *in vivo* testing of **ONCOS-210 and ONCOS-212** vectors **(ONCOS-200 series)**, (**Fig. 2**).

Fig. 1. ONCOS-102 backbone – matrix for the development of ONCOS-200 series.

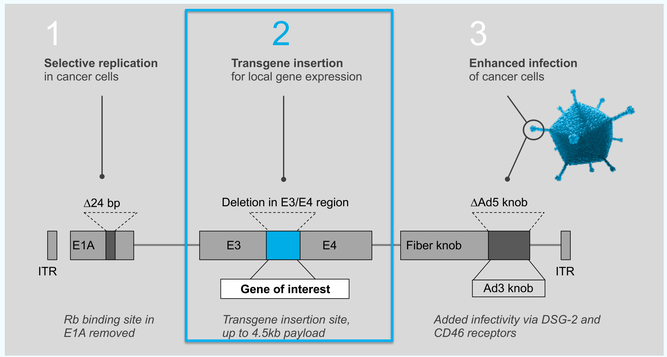
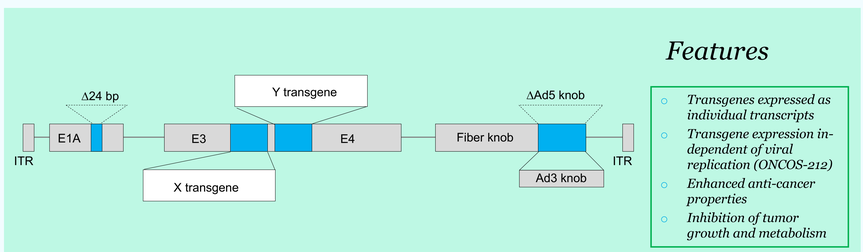


Fig. 2. ONCOS-210 & 212 structure (transgenes undisclosed).



PURPOSE OF THE STUDY

The purpose of this study was to engineer next generation ONCOS-based virus with enhanced anti-cancer properties and assess its efficacy in pre-clinical studies.

METHODS

Next generation double transgene ONCOS-200 series were engineered using standard cloning tools. Two single transgene vectors containing either transgene X or Y were also cloned. The oncolytic properties of ONCOS-210 & 212 were confirmed in 4 melanoma cell lines *in vitro*. Anti-cancer effects of the virus were also assessed *in vivo* in i) immunodeficient xenograft and ii) humanized xenograft melanoma mouse models to further understand the anti-cancer and immune stimulatory potency of the constructs.

CONCLUSIONS

- These pre-clinical findings demonstrated that both ONCOS-210 & ONCOS-212 have anti-cancer properties.
- The encouraging preclinical finding should be further investigated to elucidate the mode of action in detail before a decision on bringing ONCOS-210 or ONCOS-212 towards toxicology and clinical testing can be made.

RESULTS

The oncolytic properties of ONCOS-210 and ONCOS-212 were confirmed in 4 melanoma cell lines *in vitro*, demonstrating robust cell lysis and induction of immunogenic cell death (**Fig. 3**). Anti-cancer effects of the viruses were also assessed in i) immunodeficient xenograft (**Fig. 4**) and ii) humanized xenograft mouse models (**Fig. 5**) to further understand the anti-cancer and immune stimulatory potency of the constructs. Intra-tumoral injected ONCOS-210 and ONCOS-212 resulted in robust anti-cancer activity in both immune-deficient and immune-competent mice. The double transgenes were shown to act synergistically *in vivo*, in line with the design hypotheses and proposed mode of action to induce cell lysis and prevent tumor growth (**Fig. 4**). Moreover, the vectors were able to increase tumor infiltration of various immune subsets including CD4+, CD8+, CD8+ expressing PD1+ or CD8+ expressing Granzyme B T cells and reduction of regulatory T-cells and MDSC in the tumour microenvironment, suggesting an ability to prime immune-suppressive tumors to better respond to immunotherapy (**Fig. 5**).

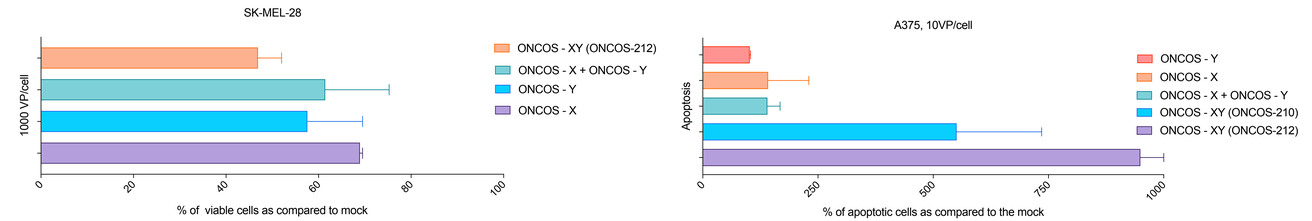


Fig. 3. A: Anti-cancer effect *in vitro* (cell viability assay). **B: Apoptotoc cells death analyses *in vitro***. Results are expressed as mean +/- SEM and % of untreated cells. * p<0.05, ** p<0.01, ***p<0.001.

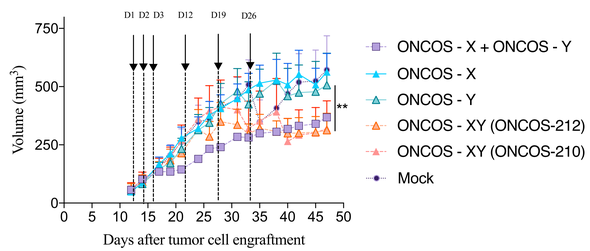


Fig. 4. A: Anti-cancer effect *in vivo* in immunodeficient BALB/c nude melanoma mouse model. Results are expressed as mean +/- SEM and % of untreated cells. * p<0.05, ** p<0.01, ***p<0.001.

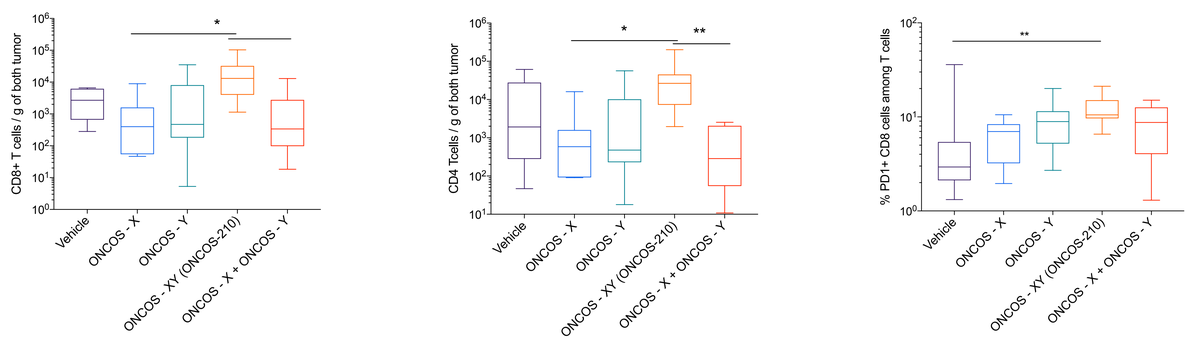


Fig. 5. Infiltration of human immune cells into the tumor mass post treatment (humanized xenograft melanoma mouse model). Results are expressed as mean +/- SEM and % of untreated cells. * p<0.05, ** p<0.01, ***p<0.001.

www.targovax.com
e-mail: lukasz.kuryk@targovax.com
e-mail: anne-sophie.moller@targovax.com