The combinatory treatment of the oncolytic adenovirus ONCOS-102 with anti PD-1 (KEYTRUDA®) show synergistic anti-tumor effect in humanized A2058 melanoma huNOG mouse model

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INTRODUCTION

With clinical introductions of checkpoint inhibitors (CPIs), both response rates (RR) and overall survival (OS) have been improved in advanced melanoma. However, despite significant clinical advancements, at least 40% of patients do not respond to CPIs.

Adenoviruses are excellent immunotherapeutic agents with a unique ability to both prime and boost immune responses. ONCOS-102 is a serotype 5, human, double-targeted oncolytic adenovirus with a chimeric 5/3 capsid for enhanced cancer cell transduction. It has a 24 bp deletion in the Rb binding site of the E1A gene for cancer-cell restricted replication. The virus codes for human granulocyte macrophage colony-stimulating factor (GM-CSF) to enhance anti-tumor immunity (Figure 1)[1,2]. ONCOS-102 induced both innate and adaptive immune activation (Figure 2) correlated with overall survival (OS) in a phase I study of different types of treatment refractory solid tumors. In the same study PD-L1 was upregulated in tumor lesions[3-5]. There may be further enhanced clinical benefits by combining with CPIs as inhibition of immune checkpoints is crucial for efficient immunotherapy and immune responses stimulated by oncolytic viruses exhibit antitumor effects. Therefore, we have performed a series of pre-clinical studies to investigate any potential enhanced anticancer properties when combining ONCOS-102 and Keytruda®.

MATERIAL AND METHODS

To study the efficacy of combinatory therapy of ONCOS-102 and Keytruda® in melanoma, we have developed a humanized A2058 melanoma huNOG mouse model. The NOG mouse strain was engrafted with cord blood-derived CD34+ hematopoietic stem cells after chemical myeloablative treatment. Fourteen weeks after cell injection, engraftment level was monitored with the analysis of human CD45+ cells among total blood leukocytes. Humanization rate was defined as the ratio of circulating hCD45+/total CD45+ (mCD45+hCD45). 60 humanized NOG mice were engrafted with A2058 tumor cells and randomized in 8 groups. Different treatment regimens of the ONCOS-102, Keytruda® and their combinations were investigated. Throughout the study, tumor volume and body weight was monitored and sacrifice was scheduled on day 40. Immune cell infiltration and PD-L1 expression in a tumor was analyzed by flow cytometry.

RESULTS

ONCOS-102 significantly reduced tumor volume by 52% while the treatment with Keytruda® did not show therapeutic effect compared to vehicle. The combinatory therapy with the virus and Keytruda® showed a reduction of 69% compared to vehicle (p=0.004) (Figure 3 and 4). The treatment with ONCOS-102 increased hCD3+ and hCD8+ T cells infiltration whereas Keytruda® alone did not have an effect on T cell recruitment within the tumor. The highest increase of CD8+ infiltrating T cells was observed in the combinatory group of ONCOS-102 and Keytruda® (p<0.05) (Figure 7). The treatment was well tolerated. The highest overall survival was reported for animals treated with ONCOS-102 and Keytruda® (Figure 5 and 6).

Figure 1. The structure of ONCOS-102

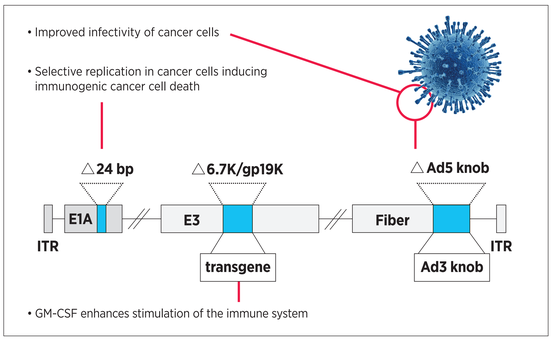


Figure 2. ONCOS-102 mechanism of action

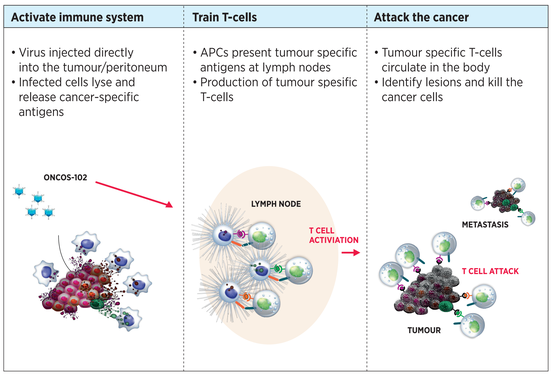


Figure 3. Effects of ONCOS-102 and Keytruda® on tumor volume on day 40 pooled for left and right tumors. Data represent mean ± SD, P* < 0.05, P < 0.01 vs vehicle.**

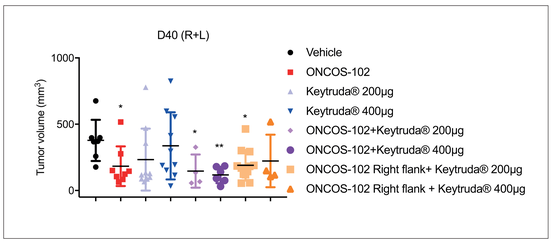


Figure 4. Effects of ONCOS-102 and Keytruda® on tumor volume, pooled for left and right tumors. Data represent mean ± SD.

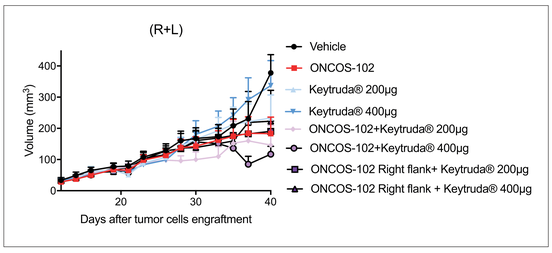


Figure 5. Effects of ONCOS-102 and Keytruda® on mouse survival.

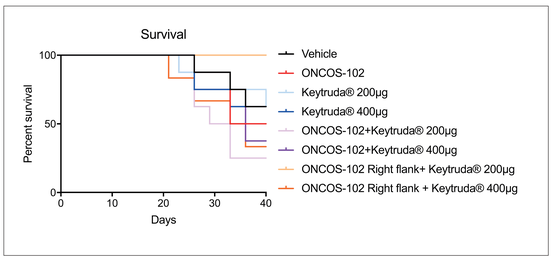


Figure 6. Effects of ONCOS-102 and Keytruda® on body weight loss. Body weight was monitored three times per week and calculated by taking the difference of the first measurement of the study to the measurement of the day. Data represent mean ± SD, n=6-8/group.

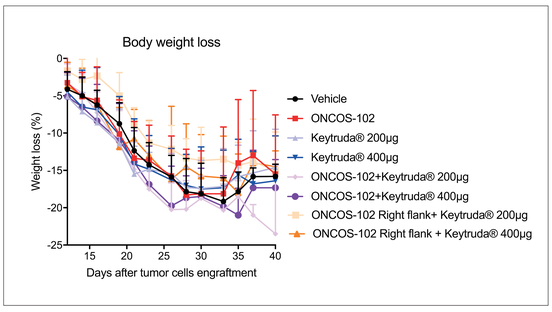
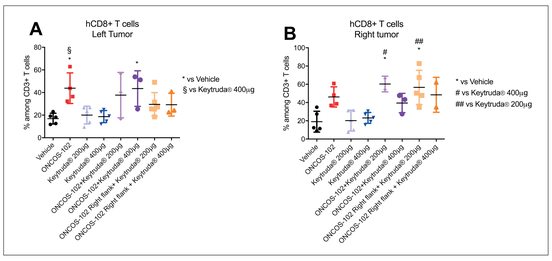


Figure 7. Effects of ONCOS-102 and Keytruda® on percentage of hCD8+ leukocytes among hCD3+ leukocytes in tumors on left flank (left panel) and right flank (right panel). Data represent mean ± SD. n = 2-6, P* < 0.05, P < 0.01 vs vehicle.**



CONCLUSIONS

This study demonstrate synergism between ONCOS-102 and Keytruda® and support the scientific rationale for the ongoing clinical study of ONCOS-102 and Keytruda® in CPI refractory advanced melanoma (NCT03003676).

SUMMARY (HOME MESSAGE)

- **Reduction of tumor volume vs vehicle:**
  - ✓ Keytruda® alone at both doses did not reduce tumor volume
  - ✓ ONCOS-102 reduced volume by 51%
  - ✓ ONCOS-102 + Keytruda® reduced volume by 61% (lower dose) and 69% (higher dose)
- **CD8+ T-cell infiltration:**
  - ✓ Vehicle vs Keytruda® alone (N.S.)
  - ✓ ONCOS-102 + Keytruda® vs Keytruda®, p<0.05
  - ✓ ONCOS-102 + Keytruda® vs vehicle, p<0.05
- **Synergistic anti-tumor effect of combinatory therapy of ONCOS-102 and Keytruda® (Day 26 and Day 37)**
- **Study data support the scientific rationale of the ongoing clinical melanoma study of ONCOS-102 and Keytruda® (NCT03003676)**

REFERENCES

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