

ONCOLYTIC ADENOVIRUS ENCODING HUMAN INTERLEUKIN-7 IN COMBINATION WITH ICIS AS A TREATMENT STRATEGY AGAINST RENAL CELL CARCINOMA (RCC)

¹Victor Arias*, ¹Tatiana Kudling, ^{1,2}James Clubb, ^{1,2}Lyna Haybout, ¹Elise Jirovec, ^{1,3}Santeri A Pakola, ⁴Saru Basnet, ^{1,2}Dafne CA Quixabeira, ^{1,5}Otto Hemminki, ^{1,3}Susanna AM Grönberg-Vähä-Koskela, ^{1,2}Joao Manuel Santos, ^{1,2}Victor Cervera-Carrascon, ^{1,2,3}Akseli Hemminki. ¹Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki, Finland; ²TILT Biotherapeutics, Helsinki, Finland; ³Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; ⁴University of Helsinki, Helsinki, Finland; ⁵Department of Urology, Helsinki University Hospital, Helsinki, Finland

Background Renal cell carcinoma (RCC) remains the most common type of kidney cancer. Despite being characterized by a rich and heterogenous immunogenic profile, a higher presence of immune content has been associated with poor prognosis, most likely due to an immunosuppressive tumor environment and following T cell exhaustion. Thus, there is an unmet need for current immunotherapies against RCC to increase activation, but also a reduction of this exhausted and immunosuppressive state. In this case, we suggest that the use of oncolytic viruses (OVs) would contribute to reinforce the previously mentioned objectives, as they are well-known to induce a powerful immune response. In this study, we focus on Ad5/3-E2F-d24-hIL7 (also known as TILT-517), an oncolytic adenovirus expressing interleukin-7 (IL-7) which has been previously described to be effective in preclinical studies involving other tumor types.¹ We believe that combining this virus with other immunotherapies such as Immune Checkpoint inhibitors (ICIs), which have previously shown synergies with other OVs and that are also part of RCC first-treatment line, might be beneficial to improve the therapeutic outcome. Hence, the aim is to evaluate the efficacy and explore the properties of Ad5/3-E2F-d24-hIL7 in RCC in combination with ICIs.

Methods Patient derived *ex-vivo* tumors were obtained from RCC patients, processed, and treated with either human anti-PD-1 or anti-PD-L1 mAb, with or without Ad5/3-E2F-d24-hIL7. Cell viability was assessed through MTS assays to determine antitumor efficacy, and flow cytometry and other immunoprotein detection methods were used to evaluate changes in the immune landscape compared to non-treated RCC samples. Infection of the samples was also verified through qPCR against viral genes.

Results The use of Ad5/3-E2F-d24-hIL7 in combination with ICIs offered better antitumor efficacy than ICIs monotherapies. Virus replication (oncolysis) was not compromised by their presence. In addition, changes in the tumor immune microenvironment were evaluated in all groups. Significant differences in the percentage of immune cell populations such as CD4+, CD8+ T cells as well as NK cells were detected after treatment exposure, in both activated and exhausted T cell subsets. Similar and corresponding effects were observed when analyzing the presence of cytokines from supernatants from treated samples.

Conclusions We demonstrate that combining Ad5/3-E2F-d24-hIL7 with either aPD-1 or aPD-L1 increases antitumor efficacy and changes in the tumor immune microenvironment in *ex-vivo* RCC tumor histocultures. This combination therapy holds promise as a novel immunotherapeutic strategy for RCC, and the data obtained warrant translation into a clinical setting.

REFERENCE

1. Kudling TV, Clubb JHA, Quixabeira DCA, Santos JM, Havunen R, Kononov A, Heiniö C, Cervera-Carrascon V, Pakola S, Basnet S, Grönberg-Vähä-Koskela S, Arias V, Gladwyn-Ng I, Aro K, Bäck L, Räsänen J, Ilonen I, Borenus K, Räsänen M, ... Hemminki A. Local delivery of interleukin 7 with an oncolytic adenovirus activates tumor-infiltrating lymphocytes and causes tumor regression. *Oncoimmunology*, 2022;**11**(1).

Ethics Approval Cancer samples were collected from the patients undergoing surgical resection at the Helsinki University Central Hospital (HUS, Helsinki, Finland). Sample collection was approved by HUS Operatives Ethics Committee (permit numbers HUS/850/2017, HUS/3360/2019 and HUS/259/2021) and the patients gave their written consent.

<http://dx.doi.org/10.1136/jitc-2023-SITC2023.0805>