Abstracts

814  ENHANCING ANTI-TUMOR RESPONSE IN ICI-
REFRACTORY NON-SMALL CELL LUNG CANCER
THROUGH INTRAVENOUS ADMINISTRATION OF
ONCOLYTIC ADENOVIRUS ARMED WITH hTNFα AND
hIL-2 IN COMBINATION WITH aPD-1 BLOCKADE

Tatiana V Kuding1, James Clubb2, Santeri A Palola1, Dafne Alves Quixabeira3, Iris Lähteenkari4, Camilla Heinö1, Victor Arias5, Susanna AM Grönberg-Vähälä-Koskiela6, Ritikka Havunen7, Victor Cevera-Carrascon8, Iñigo Manuel Santos9, Eva Sutinen10, Jari Räsänen10, Kristian Borenius4, Mikko Mylärnpää10, Zero Altonen10, Suvi Sorsa1, Otto Hemminki10, Anna Kanerva3,4, Emmy W Verschuren4,8, Ilkka Ilonen1,2,5, Akseli Hemminki1, Cancer Gene Therapy Group, Translational Immunology Research Program, University of Helsinki, Helsinki, Finland; 2TILT Biotherapeutics Ltd., Helsinki, Finland; 3Translational Lung Cancer Research Group, Institute for Molecular Medicine Finland (FIMM), HIUF, University of Helsinki, Helsinki, Finland; 4ICAN Digital Precision Cancer Medicine Flagship, Helsinki, Finland; 5Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; 6Individualized Drug Therapy Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland; 7Department of Pulmonary Medicine, Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland; 8General Thoracic and Esophageal Surgery, Heart and Lung Center, Helsinki University Hospital and Faculty of Medicine, University of Helsinki, Helsinki, Finland; 9Pathology, University of Helsinki and Helsinki University Hospital (HUSLAB), Helsinki, Finland; 10Institute for Molecular Medicine Finland (FIMM), HIUF, University of Helsinki, Helsinki, Finland

Background  Despite significant achievements in targeted and immunotherapies, including immune checkpoint inhibitors (ICI), treatment outcomes for advanced non-small cell lung cancer (NSCLC) remain challenging, particularly in patients who develop therapy resistance. This study explores the efficacy of a combination therapy involving aPD-1 checkpoint blockade and Ad5/3-E2F-d24-hTNFα-RES-hIL-2 (a.k.a. hTILT-123), a serotype chimeric oncolytic adenovirus armed with tumor necrosis factor alpha (hTNFα) and interleukin 2 (hIL-2), administered intravenously. The aim of this study is to investigate the potential of this approach for overcoming checkpoint resistance and improving anti-tumor response.

Methods  We utilized immunocompetent murine pre-clinical models, including ICI-refractory spontaneous model LLC1 and orthotopic metastasis-prone histopathology-specific NSCLC adenosquamous carcinoma model (ASC) as well as clinical samples obtained from the patients undergoing surgical resection for NSCLC. We evaluated tumor growth, cells activation, cytokine profiles, and immune cell populations within the tumor microenvironment. Additionally, a depletion study was conducted to assess the role of key immune cells in therapeutic efficacy.

Results  The combination treatment of aPD-1 checkpoint blockade with intravenous administration of armed oncolytic adenovirus demonstrated a significant reduction in tumor growth, even in the presence of neutralizing antibodies against the viral treatment. This therapy led to an increased activation of cytotoxic tumor-infiltrating lymphocytes, including tumor-specific CD8+ T cells. Furthermore, the treatment resulted in a decrease in immunosuppressive tumor-associated macrophages, enhanced dendritic cell maturation, and expansion of the tumor-specific memory T cell compartment.

Conclusions  Our findings highlight the potential of intravenously delivered oncolytic adenovirus armed with hTNFα and hIL-2 in combination with aPD-1 checkpoint blockade to overcome checkpoint resistance and improve treatment outcomes in advanced NSCLC. This approach is promising for addressing the major unmet clinical need in patients with checkpoint refractory/resistant NSCLC and supports further investigation in clinical trials.

Ethics Approval  All animal experiments were approved by the Provincial Government of Southern Finland and the Experimental Animal Committee of the University of Helsinki (license number E555/12559/2021). Cancer samples were collected from patients undergoing surgical resection at Helsinki University Central Hospital (HUS, Helsinki, Finland). Sample collection was approved by the HUS Ethics Committee (47§/17.3.2021; HUS/552/2021), and study permits were obtained (17.05.2021; reference number HUS/259/2021). Written informed consent was obtained from all participants.

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