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 intravenously administered oncolytic adenovirus armed with 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 subcutaneous model LLC1 and orthotopic metastasis-prone histopathology-specific NSCLC adenocarcinoma model (ASC) as well as clinical samples obtained from the patients undergoing surgical resection for NSCLC. We evaluated tumor responses, 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 ESAVU12559/2021). 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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