NOVEL ONCOLYTIC VIRAL IMMUNOTHERAPY VET3-TGI
DISPLAYS ENHANCED SYSTEMIC DELIVERY AND
INHIBITS TGFβ-SIGNALING WHILE AUGMENTING TYPE-1
IMMUNE RESPONSE IN THE TUMOR

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Background The clinical success of oncolytic viral immunotherapies will likely require development of technologies to achieve targeted intravenous delivery to the tumor bed, and the expression of novel therapeutic transgene combinations to simultaneously destroy the tumor through multiple mechanisms.

Methods VET3-TGI has been designed using the VET™ viral backbone to achieve systemic delivery, even in the face of pre-existing anti-viral immunity. This was achieved through insertion of the chemokine receptor CXCR3 into the viral backbone. CXCR3 is then expressed in hematopoietic cells that become infected soon after intravenous delivery of the viral therapy, resulting in directed trafficking of these cells towards tumors expressing matching chemokines. This was demonstrated in vitro and in vivo in both naïve and immunized or pre-treated mouse tumor models.

Further, VET3-TGI contains a novel therapeutic transgene combination, combining a TGFβ1 inhibitor (TGFβ mini-monomer, TGFβMM) with IL12 expression. Counteracting the immunosuppressive activity of TGFβ1 and enhancing Type-1 immune responses in the tumor microenvironment led to greatly increased anti-tumor immunity and durable complete responses.

Results The therapeutic efficacy of VET3-TGI over control viruses was tested in multiple pre-clinical in vivo mouse tumor models (including B16, MC38, RENCA, EMT6), and potent therapeutic activity was demonstrated, including 100% CRs in multiple models, even at doses several logs below expected equivalent clinical doses.

Post-mortem analysis showed that VET3-TGI reduced systemic toxicity and improved systemic delivery. Analysis of the tumor microenvironment revealed profound changes with VET3-TGI treatment, including greatly enhanced infiltration of CD3+CD8+ T cell, polarization to a type-1 immune response and concomitant decreases in TGFβ1-associated genes.

Conclusions Altogether, VET3-TGI demonstrated good ability to counter TGFβ1 mediated immunosuppression and dramatically enhanced anti-tumor immune responses leading to safe and potent therapeutic activity in multiple mouse tumor models. Based on the above, VET3-TGI was selected as a lead clinical candidate and clinical manufacture and toxicity testing is undergoing with a human version of this virus.

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