152-B: TG6050, an oncolytic vaccinia virus encoding interleukin-12 and anti-CTLA-4 antibody, favors tumor regression via profound immune remodeling of the tumor microenvironment

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Background: TG6050 was designed as an improved oncolytic vector, combining the intrinsic properties of vaccinia virus to selectively replicate in tumor, and the tumor restricted expression of recombinant immune effectors to modify the tumor immune phenotype. These properties might be of particular interest for “cold” tumors, either poorly infiltered tumors, or tumors infiltered with anergic T cells.

Methods: TG6050, an oncolytic vaccinia virus encodes single-chain human interleukin-12 (hIL-12) and full length anti-cytotoxic T-lymphocyte-associated antigen-4 (@CTLA-4) monoclonal antibody. The relevant properties of TG6050 (replication, cytopathy, transgenes expression and functionality) were extensively characterized in vitro. The biodistribution and pharmacokinetics of both the viral vector, @CTLA-4 and IL-12, as well as antitumoral activities (alone or combined with immune checkpoint inhibitors) were investigated in several “hot” (highly infiltered) and “cold” (poorly infiltered) syngeneic murine tumor models. The mechanism of action was deciphered by monitoring both systemic and intratumoral immune responses, and by tumor transcriptome analysis. The safety of TG6050 after repeated intravenous administrations was evaluated in cynomolgus monkeys with a focus on the level of circulating IL-12.

Results: Multiplication and propagation of TG6050 in tumor cells in vitro and in vivo was associated with local expression of functional IL-12 and @CTLA-4. This dual mechanism translated into a strong antitumoral activity in both “cold” and “hot” tumor models (B16F10, LLC1 or EMT6, CT26, respectively) that was further amplified by combination with anti-PD-1. Analysis of changes in the tumor microenvironment (TME) upon treatment with TG6050 showed increases of interferon gamma, of CD8+ T cells, and of M1/M2 macrophages ratio, and a drastic decrease of regulatory T cells. These local modifications were observed alongside bolstering a systemic and specific antitumor adaptive immune response. In toxicology studies, TG6050 did not display any observable adverse effects in cynomolgus monkeys.

Conclusions: TG6050 effectively delivers functional IL-12 and @CTLA-4 into tumor, resulting in a strong antitumor activity. The shift towards an inflamed TME correlated with a boost of the systemic antitumor T cells. The solid preclinical data, and favorable risk/benefit ratio paved the way for clinical evaluation of TG6050 in metastatic non-small cell lung cancer (NCT05788926 trial in progress).