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Oncolytic Seneca Valley Virus (SVV-001) Overcomes Checkpoint Inhibitor Resistance and Demonstrates a Systemic Anti-tumor Response in a Syngeneic Tumor Model

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BACKGROUND

Oncolytic viruses (OV) hold potential for not only delivering durable anti-tumor responses but also converting immunologically "cold" tumors to "hot" tumors. Seneca Valley Virus (SVV-001) is a naturally occurring oncolytic picornavirus found to have selectivity for tumor cells with neuroendocrine (NE) properties. Because of the paucity of syngeneic murine NE tumor models, we evaluated the efficacy of Seneca Valley Virus (SVV), in combination with checkpoint inhibitors (CPI) using the CPI-resistant Pan02 model that is permissive for SVV replication. SVV has been tested in three clinical trials of patients having neuroendocrine neoplasms as a single intravenous dose monotherapy. The results were encouraging with patients showing evidence of clinical benefit and only one reported DLT in the 76 patients treated.

METHODS

SVV was injected intra-tumorally in established Pan02 tumors along with systemic injection of anti-PD-1 and/or anti-CTLA4 (CPIs). Naïve Pan02 tumors were injected on the contralateral side of animals showing tumor growth control or regression and growth of primary treated and untreated contralateral tumors monitored. Tumors were resected to evaluate immune cell infiltration via FACS analysis.

RESULTS

SVV reversed resistance to CPIs and enhanced efficacy over CPI(s) alone resulting in complete cures in >83% of mice with primary and abscopal tumors. SVV plus aPD1+aCTLA4 resulted in 5 of 6 mice cured of their primary tumor. The animals were challenged on their contralateral flank with naïve Pan02 tumor cells to evaluate systemic and abscopal immune effects. All mice (5/5) that cleared the primary Pan02 tumor also eradicated the abscopal secondary tumors. Control treated Pan02 tumor-bearing mice were all sacrificed due to tumor burden by day 70 (median survival <50 days). Control animals treated with aPD1+aCTLA4 showed transient tumor regressions but these animals all grew large tumors, requiring sacrifice. In contrast, the SVV+aPD1+aCTLA4 primary tumors were eliminated within 44 days and these animals remain tumor-free for >160 days. Contralateral tumors were eradicated in all 5 animals that rejected the primary tumor, demonstrating potent systemic immunity. SVV treatment showed marked increases in CD3+ and CD8+ T-cell infiltration of tumors with the combination of SVV+CPIs showing the highest infiltration.

CONCLUSIONS

These data show that SVV+CPI converted immunologically “cold” tumors to “hot” tumors. These studies serve as a foundation for translating SVV oncolytic virotherapy combined with anti-PD-1 and anti-CTLA4 antibodies in patients with neuroendocrine neoplasms with a clinical trial anticipated to begin in H2, 2022.

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