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An HPV-E6/E7 immunotherapy plus PD-1 checkpoint inhibition results in tumor regression and reduction in PD-L1 expression

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The prevalence of head and neck cancers in the USA is estimated to be about 370,000 and between 25% to 38% of these are human papilloma virus (HPV)-associated head and neck squamous cell carcinomas (HNSCC). We have developed a viral gene delivery platform to immunize against HPV 16 genes E6 and E7 (Ad5 [E1-, E2b-]-E6/E7) for the treatment of HPV-associated HNSCC. We tested the Ad5 [E1-, E2b-]-E6/E7 immunotherapy alone and in combination with programmed death-ligand 1 (PD-1) blockade in a murine HPV$^+$ tumor model. As a single agent, Ad5 [E1-, E2b-]-E6/E7 induced HPV-E6/E7 cell-mediated immunity and resulted in the clearance of small tumors and an overall survival benefit in mice with larger established tumors. When immunotherapy was combined with PD-1 immune checkpoint blockade, an increased level of anti-tumor activity against large tumors was observed in addition to an improvement in survival. Tumor microenvironment analysis in Ad5 [E1-, E2b-]-E6/E7 treated mice revealed an increase in CD8$^+$ tumor-infiltrating lymphocytes (TILs). In addition, we observed induction of suppressive mechanisms such as programmed death-ligand 1 (PD-L1) expression on tumor cells and an increase in PD-1$^+$ TILs. When Ad5 [E1-, E2b-]-E6/E7 immunotherapy was combined with anti-PD-1 antibody, we observed CD8$^+$ TILs at the same increased level but found that a smaller fraction of these were PD-1$^+$. Furthermore, we observed a reduction in PD-L1 expression on tumor cells, providing a mechanism by which combination therapy favors tumor clearance and a rationale for pairing antigen-specific vaccines with checkpoint inhibitors in future clinical trials.

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