Efficacy of Combination Immunotherapies in a Murine Squamous Cell Carcinoma Model

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Introduction and Objective

Head and neck squamous cell carcinomas (HNSCCs) are a type of neoplasm found in the epithelium of the oral cavity, oropharynx, larynx, or hypopharynx. Recent evidence has demonstrated that 70-90% of HNSCC are associated with Human Papillomavirus (HPV) infection, particularly strain 16 producing the oncogenic proteins E6/E7. The E6 and E7 HPV proteins exert oncogenic function by driving cell cycle progression and abet cell survival.¹

Currently, HNSCCs are primarily treated with surgery, chemotherapy, and radiation therapy. Recently, nivolumab (anti-PD1) was shown to improve survival rates in HNSCC when compared to standard chemotherapies.² Durvalumab, an antibody blocking PD-L1 interaction with PD1 on T cells, has also shown effectiveness in HNSCC clinical trials.³ Therefore, immunotherapy with immune checkpoint (PD-1) blocking agents promises to markedly improve outcomes in HNSCC.⁴

Methods

• Mice were injected subcutaneously with tumor cells that express HPV 16 E7 (TC-1). When tumors were established, mice were vaccinated with AXAL (3 injections)

• Mice were divided into eight groups. Each group contained 5 mice. One group of mice received no treatment. Another group of mice only received the vaccination alone. Another group mice received anti-PD1. A fourth group received radiation. A fifth group of mice received radiation with anti-PD1. A sixth group of mice received AXAL with anti-PD1. Another group of mice received the vaccination with radiation. Finally, the last group received the vaccination, anti-PD1 and a single dose of radiation.

• The efficacy of the AXAL vaccine was also compared a control vaccine with the tLLO vector (LmddA274) to determine its efficacy.

• Tumor volume was measured twice weekly to note the progression and regression of tumor size. Growth curves were generated.

This study examined the therapeutic effects of single, dual, and triple combination immunotherapies in a mouse model of HPV-associated HNSCC and tested the hypothesis that addition of immune checkpoint inhibitors further improves efficacy of the dual radiation/vaccine treatment. These treatment modalities include a tumor vaccine (attenuated Listeria monocytogenes based vaccine encoding HPV16 E7 (AXAL)), an immune checkpoint inhibitor targeting PD1 (RMP1-14) and topical subtherapeutic radiation (10Gy). These experiments will determine the baseline for assessment of immunophenotypes associated with therapeutic response and efficacy.

Results

• Response to the AXAL vaccine can be observed in TC-1 HNSCC models. The AXAL vaccine produced a greater reduction in tumor growth than the control vaccine.

• Partial responses were observed in some mice receiving dual combination therapies. However, most mice treated with triple immunotherapy revealed complete tumor regression.

• Combination immunotherapy of radiation therapy, AXAL vaccine, and anti-PD1 are effective in the TC-1 HNSCC model system and cooperatively reduce tumor burden compared to single modality treatments.

• Radiation therapy appears to demonstrate decreased survival in mice, along with the control LmddA274 vaccine. AXAL, anti-PD1, and dual combination therapy demonstrate similar survival rates. Triple combination therapy appears to have the best survival rate but does not increase overall survival when compared to the no treatment group.

• The data demonstrates that AXAL administration and anti-PD1 can be effective in a mouse tumor model and optimizes tumor rejection.

• The results obtained set the stage for investigating immune mechanism underpinning treatment-associated tumor regressions.

Conclusions

Acknowledgements

This work was supported by Advaxis Immunotherapies.

References


2. Gillison M, et al. Nivolumab vs investigator’s choice for recurrent or metastatic HNSCC. Phase 3 CheckMate-141 trial. Oral presentation at: AACR Annual Meeting 2016; April 16-20, 2016; New Orleans, LA
