Losartan in combination immunotherapy with PD-1/PD-L1 blockade to target oligometastatic head and neck cancer

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 7th most common cancer globally, and treatment options remain limited for recurrent / metastatic (R/M) HNSCC. Immune checkpoint inhibitor (ICI) **pembrolizumab** (anti-PD-1) is the frontline treatment for R/M HNSCC but only results in median survival time of 10.9 months and achieves durable response in 15-20% of patients.

Angiotensin II type I receptor (AT1R) is upregulated in squamous cell carcinoma (SCC) cells with known roles in tumor cell proliferation, angiogenesis, migration, and invasion. **Losartan** is an AT1R blocker (ARB) explored in combination immunotherapy, with ongoing phase 2 clinical trials in pancreatic and breast cancer.

This project seeks to evaluate the role of Losartan in enhancing the antitumor effects of radiation therapy combined with PD-L1 blockade via remodeling of the tumor microenvironment (TME).

METHODS

Figure 1. Phase 1b clinical trial (NCT06211335) of Losartan, pembrolizumab, and stereotactic body radiation therapy (SBRT) for locally recurrent, refractory, or oligometastatic HNSCC. PET, tumor biopsy, and blood collection throughout clinical trial. Plasma from pre- and post-treatment evaluated by cytokine array and TGF-β1 ELISA.

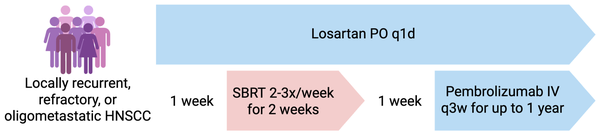
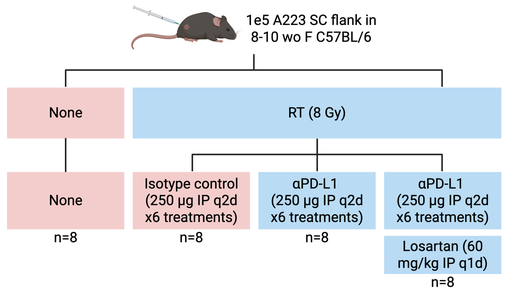


Figure 2. Murine model of SCC treated with or without radiation therapy (RT), αPD-L1, and Losartan. A223 SCC cell line derived from keratin 15+ stem cells harboring $Kras^{G12D}$ mutation and Smad4 deletion. Formalin-fixed paraffin-embedded primary tumors assessed by IHC, plasma evaluated by cytokine array and TGF-β1 ELISA.



RESULTS

Figure 3. Losartan results in increased intratumoral F4/80+ (A-B) and decreased intratumoral Ly6G+ cells (C-D). IHC staining of murine primary tumor for F4/80 and Ly6G, tumor edge vs. core boundary set at 500 µm.

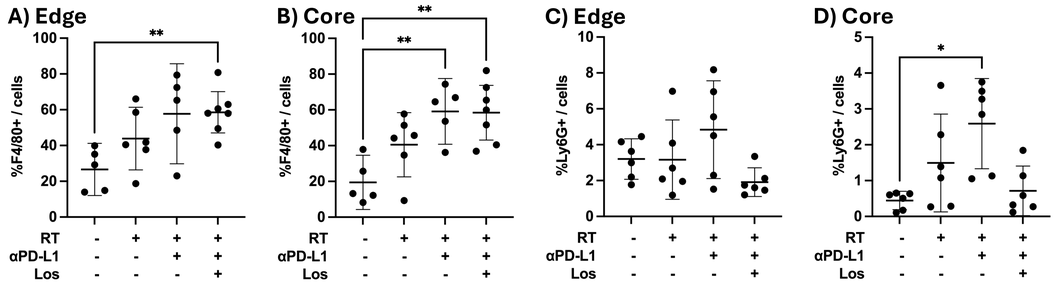
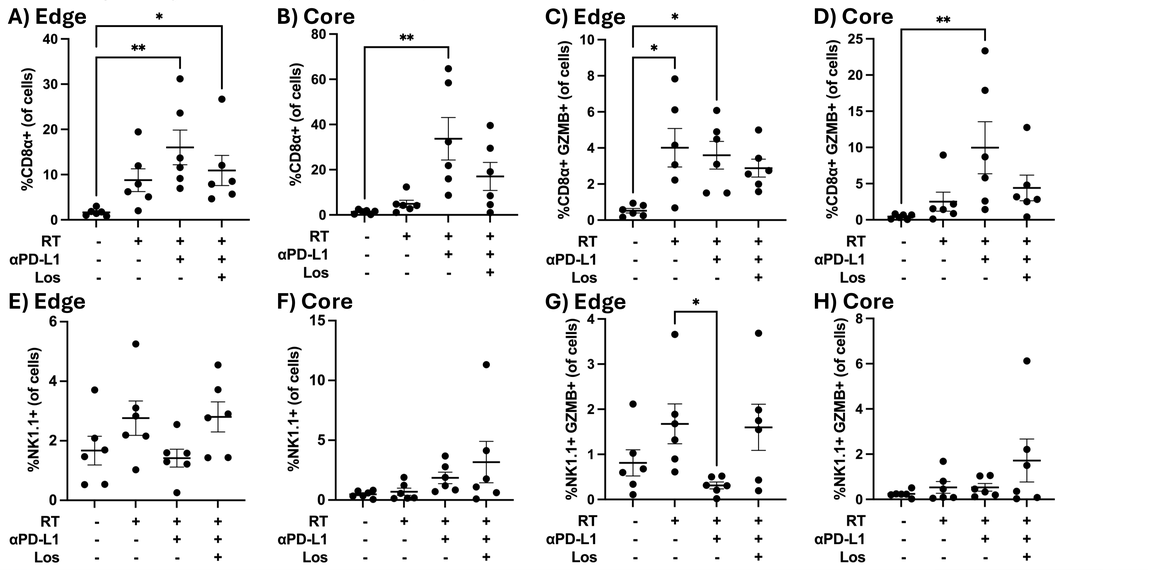


Figure 4. Losartan preserves CD8 T cell (A-D) and improves NK cell (E-H) infiltration and cytotoxicity. Multiplex IHC staining of murine primary tumor for CD8α, NK1.1, and GZMB.



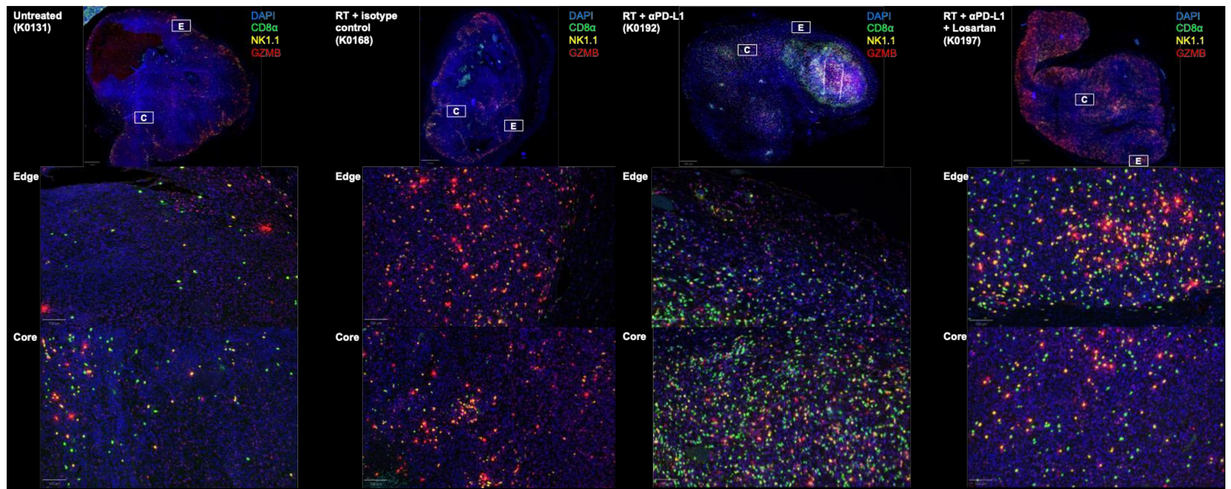
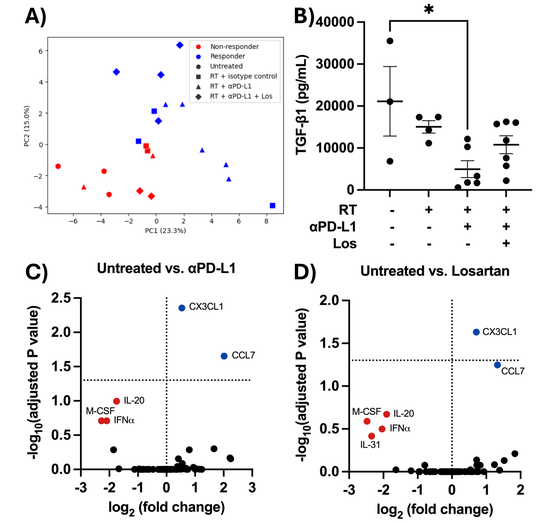


Figure 5. Plasma cytokine and TGF-β1 vary by response status and treatment group. PCA (A) and volcano plots (C-D) of plasma cytokine array. Plasma TGF-β1 ELISA (B).



CONCLUSIONS

Losartan in combination with RT and PD-L1 blockade may preserve CD8 T cell and improve NK cell infiltration and cytotoxicity, as well as decrease tumor-associated neutrophils. Plasma cytokine changes reflect responder vs. non-responder status, and PD-L1 blockade reduces plasma TGF- β1. Further investigation into the tumor microenvironment and immunomodulatory effects of ARBs is necessary to inform combination immunotherapies for improved targeting and treatment of R/M HNSCC.

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