Background Myeloid antigen presenting cells (APCs) are critical to PD-1 inhibition (PD1i) and radiotherapy responses in Head and Neck Squamous Cell Carcinoma (HNSCC), but are inhibited by the ‘don’t eat me’ immune checkpoint molecule CD47 overexpressed on tumor cells that interacts with SIRPα receptor found on myeloid cells, impeding their immune function. Evorpacept is a high affinity CD47 blocking fusion protein with a SIRPα binding domain coupled to an inactive Fc domain that avoids anemia and hematologic toxicities. We hypothesize that Evorpacept maximizes PD1i and tumor-targeted stereotactic body radiation therapy (SBRT) responses in HNSCC by expansion of tumor-antigen specific cytotoxic T cells and enhancing antigen presentation by APCs.

Methods To explore this, we employed our tobacco-signature, orthotopic murine oral squamous cell carcinoma (OSCC) models, one of which matches the immune infiltrate and PD1i response of human OSCC and the other of which is immune-cold with no response to PD1i. We also used Selective CRISPR Antigen Removal (SCAR) lentiviral vector system to knock out CD47 from the model and eliminate the remaining immunogenic cas9 editing machinery. Using these models, we investigated the synergistic effects and immune mechanism of Evorpacept on PD1i and tumor-targeted SBRT responses.

Results First, we find that CD47 knock out from our OSCC preclinical model leads to complete tumor regression, emphasizing CD47 as an immune oncology target in HNSCC (figure 1). Then, we show that Evorpacept potentiates both PD1i and tumor-targeted SBRT responses and leads to durable immunity in our immune-responsive and immune-cold OSCC preclinical model (figure 2). Using IRDye-tagged Tilmanocept to map the tumor draining lymph nodes (tdLNs), we find that Evorpacept increases cytotoxic tumor-antigen specific T cells populations in the tdLNs and the tumor microenvironment (TME) with PD1i or tumor-targeted SBRT administration (figure 3). Lastly, within the tdLNs, we find increased tumor-specific antigen presentation by professional APCs, including macrophages, dendritic cells, and B-cells (figure 4).

Conclusions We demonstrate that Evorpacept synergizes with PD1i and tumor-targeted SBRT and enhances anti-tumor immunity by promoting APC tumor-specific antigen presentation from the TME to the tdENS to prime and expand tumor-specific cytotoxic T cell populations. This work highlights CD47 as a bridge between innate and adaptive antitumor immunity in HNSCC (figure 5).