

POSTER PRESENTATION

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# Improved efficacy of radiation in combination with TGF $\beta$ inhibition in a colorectal cancer mouse model

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Colorectal cancer patients with high levels of tumor-infiltrating T cells have better survival than patients with low levels. It is not clear whether the T cells are directly responsible for improved prognosis or are a sign of a tumor that is more responsive to conventional cancer therapies. If tumor infiltrating T cell numbers are associated with improved outcome, then we hypothesize that increasing T cell infiltrates using immunotherapy will improve the efficacy of chemoradiation. To test this hypothesis, we established CT26 colorectal carcinomas subcutaneously in immunocompetent BALB/c mice. Tumors were treated with 20Gy of radiation in a single fraction delivered using a clinical linear accelerator. To increase T cell infiltration into the tumor, an oral anti-TGF $\beta$  type I receptor small molecule inhibitor was given for one week prior to radiation. Outcomes included tumor kinetics, survival, and immune infiltrate measured by flow cytometry. TGF $\beta$  inhibition increased total T cells, activated CD8 T cells, and reduced inhibitory T regulatory cell tumor infiltrate in the tumor prior to radiation therapy. Radiation in mice pretreated with TGF $\beta$  inhibitor exhibited improved survival compared to either modality alone. In vitro clonogenic assay demonstrated equivalent radiosensitivity in control and TGF $\beta$ -inhibited cells at doses >6Gy. Small molecule penetrance measured using quantitative fluorimetry for FITC-dextran was equivalent in both treated and untreated groups. In vivo depletion of CD8 cells abrogated the efficacy of both radiation and TGF $\beta$  inhibition plus radiation. Therapy aimed at optimizing the immune environment holds promise for those colorectal cancer patients with poor immune infiltrates. Our preliminary data suggests TGF $\beta$  inhibition is a therapeutic strategy to alter tumor immune infiltrates and improve the

efficacy of conventional therapies. Further studies are needed to determine the mechanism by which increased immune infiltrates improves outcome.

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