TGFβRI Inhibition Prior to Radiation Enhances Efficacy in a CD8 Dependent Fashion

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Purpose/Objective(s): The immune infiltrate in colorectal cancer has been correlated with outcome, such that individuals with higher infiltrations of T cells have increased survival independent of disease stage. For those patients with poor immune infiltrates, overall survival is severely limited. Since the colorectal cancer patients studied received conventional cancer therapies, these data could be interpreted to mean that the pre-treatment tumor environment increases the efficacy of treatments such as chemotherapy, surgical resection and radiation therapy. This study was designed to test the hypothesis that an improved immune environment in the tumor at the time of treatment will increase the efficacy of radiation therapy.

Materials/Methods: Balb/c mice were challenged with either CT26 colorectal or Panc02 pancreatic tumor cells and seven days later treated with mouse chow containing control or a TGFβ type I inhibitor, SM16, for one week followed by tumor-only high-dose radiation. Survival, tumor growth, and tumor cell immune infiltrate were analyzed.

Results: We demonstrate that inhibition of TGFβ using the orally available small molecule inhibitor SM16 improved the immune environment of tumors in mice by increasing T cell infiltrate and decreasing inhibitory immune cell infiltrate including T regulatory cells and myeloid derived suppressor cells (p<0.05); and significantly improved the efficacy of subsequent radiation therapy in colorectal (median survival 74 days versus 49.5 days, p<0.01) and pancreatic tumor models (median survival 70 days versus 56 days, p<0.05). This effect was not due to changes in radiosensitivity, epithelial to mesenchymal transition or changes in vascular function in the tumor; rather, this effect was entirely dependent on adaptive immunity and resulted in distant tumor responses (p<0.05) and long-term protective immunity in cured mice.

Conclusions: These data demonstrate that immunotherapy is an option to improve the immune status of patients with poor tumor infiltrates and that pre-treatment improves the efficacy of radiation therapy.

Future Directions: 1) Further characterize the mechanism of improved radiation efficacy. 2) Translate into the clinic for locally advanced rectal adenocarcinoma patients receiving neoadjuvant chemoradiation.