

KEYNOTE SPEAKER PRESENTATION

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Mechanisms of synergy of radiotherapy and immunotherapy

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The success of immune checkpoint inhibitors in inducing tumor regression has demonstrated that specific inhibitory pathways are dominant rate-limiting steps in a significant number of patients with melanoma and other advanced cancers. However, in the majority of patients tumor rejection is hindered by multiple immunosuppressive mechanisms present in the tumor micro-environment. Obstacles to immune-mediated tumor control can be present at both the priming and effector phase of the anti-tumor response, and include defective function and activation of antigen-presenting cells, defective T cell recruitment and infiltration of tumors, and defective recognition and killing of cancer cells by T cells. Ionizing radiation therapy (RT) applied locally to a tumor at therapeutic doses has multiple effects that can potentially overcome each of these obstacles, and we have shown that RT is synergistic with immunotherapy. In pre-clinical models RT converted tumors unresponsive to anti-CTLA-4 mAb into responsive ones, achieving rejection of the irradiated tumor and non-irradiated metastases (abscopal effect) and improved survival [1,2]. At the effector phase, RT enhanced recruitment of activated T cells to the tumor by induction of chemokines [3], and enhanced immune synapse formation between CD8 T and tumor cells by induction of NKG2D ligands [4].

To test the hypothesis that successful tumor rejection induced by RT+anti-CTLA-4 requires a significant change in the quantity and quality of tumor-infiltrating lymphocytes (TILs) we performed a comprehensive evaluation of the breadth and depth of the T cell repertoire modulated by treatment using high-throughput sequencing technology. To gain insights into the changes in TILs induced by anti-CTLA-4 treatment in tumor hosts that respond or do not respond to therapy we used our well-characterized

4T1 mouse model in which anti-CTLA-4 treatment is effective only when combined with RT. Results show distinct contributions of RT and anti-CTLA-4 to increasing the number and clonality of TILs, and changes in clonal representation that are unique to the combination. These data suggest that RT effectively releases endogenous tumor antigens that prime anti-tumor T cells, supporting the concept that it can be used as a mean to generate an in situ individualized vaccine. We are currently exploring this hypothesis in clinical trials testing the combination of RT and checkpoint inhibitors.

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