Combining Radiotherapy with Immunotherapy
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Based on pre-clinical and anecdotal clinical data, there is a rationale for combining immunotherapy with radiation. We have conducted several trials at Penn combining immune checkpoint blockade with radiation therapy (RT). The first of these used the anti-CTLA-4 antibody ipilimumab with hypofractionated radiation therapy (HFRT). In this trial 22 patients with metastatic melanoma who had at least 2 sites of radiologically evident disease received HFRT to a single lesion followed by 4 cycles of ipilimumab. We found that this treatment was safe with no dose limiting toxicities (DLTs). We examined the radiologic response rate in unirradiated lesion using Response Evaluation Criteria in Solid Tumors (RECIST) and found that 5 of the 22 patients (23%). However, having a radiologic response did not ensure lack of progression. The median progression-free survival was only 3.1 months, but because many patients have been switched to the anti-PD1 antibody pembrolizumab and remain alive, the estimated 3-year survival is 30%.

Subsequently we initiated a trial at Penn using pembrolizumab in combination with HFRT. Patients with either metastatic melanoma or lung cancer who had progressed on prior anti-PD-1 therapy were eligible for Stratum 1 of the Safety phase (n=12). Stratum 2 (n = 12) includes those with metastatic breast, pancreatic or “other” cancers who had not previously been treated with anti-PD-1 therapy. We have completed enrollment on the Safety phase with no DLTs noted. In Stratum 1 we found that 2 of the 12 patients had a partial response (PR) by RECIST criteria. Specifically 1 out of 7 patients with non-small cell lung cancer and 1 out of 5 patients with metastatic melanoma responded to RT. The responder with NSCLC had received nivolumab for 8 month and had progressed before being enrolled on the trial whereas the responder with melanoma had received 4 cycles of ipilimumab and 13 cycles of pembrolizumab.

Currently we are investigating the use of resiquimod, an agonist of the toll-like receptors 7 and 8 (TLR 7/8), in combination with radiation. For our model we implant B16-F10-ova melanoma tumors bilaterally into the flanks of immune-intact mice. One of the tumors is irradiated, and growth of this tumor as well as the contralateral (unirradiated) tumor is tracked. Our studies indicate that intratumoral injection of resiquimod into subcutaneous B16-F10-ova melanoma tumors combined with RT to those tumors results in a retardation of tumor regrowth compared with either resiquimod alone or RT alone. Furthermore, there was some effect on the growth of tumors that were implanted in the contralateral flank that were neither irradiated nor injected with resiquimod.