COMBINATION IMMUNE CHECKPOINT THERAPY AND RADIOTHERAPY FOR CASTRATION-RESISTANT PROSTATE CANCER

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We were interested in the effect of immune checkpoint inhibitors and radiotherapy combination on castration resistant prostate cancer in mice models. Five treatment groups were created (anti-CTLA-4 + anti-PD-1 + RT, anti-CTLA-4 + anti-PD-1, anti-PD-1 + radiotherapy, anti-CTLA-4 alone, and radiotherapy alone). The group treated with anti-CTLA-4 + anti-PD-1 + 20 Gy in 2 treatments of radiotherapy showed the most promising results outlasting all other groups with a statistically significant superior median survival of 32 days.

Immune checkpoint inhibitors are not currently widely used in the treatment of metastatic prostate cancer. A large randomized trial for patients with metastatic castration-resistant prostate cancer showed ipilimumab (anti-CTLA4) combined with 8Gy radiotherapy increased the median survival by 7 months in a subgroup of 288 patients with low tumor burden compared to radiotherapy alone (Kwon et al). Long-term survivors had a significant 6-8% increase in 2, 3, 4-year overall survival for the whole cohort XRT+ipiliumumab arm vs XRT alone (Fizazi et al). Therefore, we sought to model this approach in a mouse model for castration-resistant prostate cancer in order to test various combination therapy approaches, including anti-PD1, anti-CTLA4, and radiotherapy doses to provide the best survival outcome.

We followed a previously used method by Kirschner et al. MycCaP prostate tumors were engrafted in wild-type castrated FVB mice. Five treatment groups of 6-9 mice each were compared for survival and tumor graft volume after one-time injections of ICI and/or radiotherapy 20 Gy in 2 treatments given on consecutive days. Treatment groups: anti-CTLA-4 + anti-PD-1 + RT, anti-CTLA-4 + anti-PD-1, anti-PD-1 + radiotherapy, anti-CTLA-4 alone, and radiotherapy alone. Tumor sizes were measured by digital calipers at least 2 times per week and tumor volume was calculated as 0.5 x long-dimension x short-dimension^2. A Kaplan-Meier analysis was used to assess survival.

For mice with castration-resistant prostate cancer, the triple combination therapy of anti-CTLA-4 + anti-PD-1 + RT resulted in the longest median survival of 32 days compared to anti-CTLA-4 alone (11 days, p=0.0002), radiotherapy alone (22 days, p=0.0058), and combination anti-CTLA-4 + anti-PD-1 (19.5 days, p=0.0036). Triple combination therapy had a trend for improved survival compared to combination anti-PD-1 + RT (24 days, p=0.0529). While monitoring tumor volume measurements, the tumor growth was the slowest for triple combination therapy compared those treated with dual and

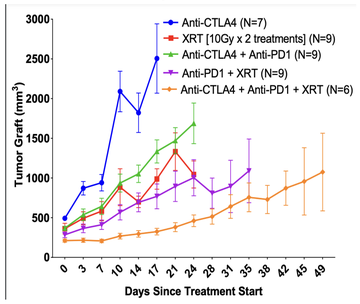

Figure 1. Illustration of tumor sizes and post treatment survival days.

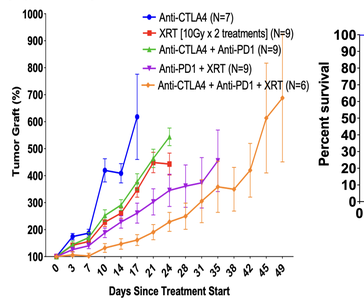

Figure 2. Illustration of the normalized tumor sizes and post treatment survival days.

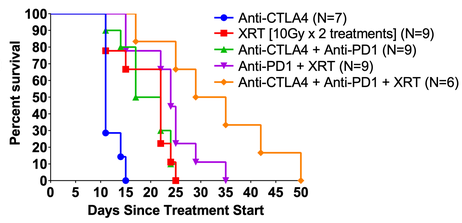

Figure 3. Illustration of percent survival and length among the different treatment groups

The triple combination therapy of anti-CTLA-4 + anti-PD-1 + 20 Gy in 2 treatments of radiotherapy proved statistically superior in survival and tumor growth delay compared to dual and monotherapies. Adding RT to anti-CTLA-4 + anti-PD-1 improves survival among FBV mice and delays tumor growth. This work elucidates the simultaneous use of two immune checkpoint inhibitors in combination with RT has the greatest anti-tumor activity and should be considered in design of clinical trials.

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