Combinatorial Therapeutic Approaches with PD-1 Inhibition in Prostate Cancer

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Background: Checkpoint blockade targeting PD-1 or CTLA-4 works by fundamentally different mechanisms (with CTLA-4 inhibition acting at secondary lymphoid organs for activation of naïve T cells, and PD-1 interactions being regulated at the tissue / tumor level to effect T cells already exposed to antigen. The efficacy and toxicity profile of anti-PD-1/PD-L1 and anti-CTLA-4 therapies also differ greatly, with PD-1/PD-L1 therapy having very little toxicity. In both humans and animal models, PD-1 directed therapy for prostate cancer had not been shown to be efficacious in most cases. Here we investigate combinatorial strategies to augment the effect of PD-1 therapy in a mouse model.

Methods: Immuno−competent FVB mice were bilaterally implanted with Myc−CAP cells to form isogenic grafts. Four weeks after tumor introduction tumors were treated with either 10mg/kg of anti-PD-1 therapy alone or in combination with cryotherapy to one tumor. In a separate experiment, the same paradigm was followed but mice were pre-treated with 25mg/kg of Degarelix after palpable tumors were seen (followed by cryotherapy and anti-PD1). Finally, we performed a similar set of experiments but in the presence or absence of pretreatment with epigenetic modifiers (5-azaccytidine and Entinostat).

Results: Therapy with anti-PD1 or anti-PD1 combined with cryotherapy marginally and insignificantly increased mouse survival and time to logarithmic tumor growth. Addition of neoadjuvant androgen deprivation significantly increased median survival (from 40 days to 60 days, $p<0.001$). Pre-treatment with epigenetic modifiers did not significantly further increased mouse survival nor time to logarithmic tumor growth. Mice in this experimental arm showed clinical signs of distress with one death noted shortly after treatment.

Conclusions: Combinatorial strategies including anti-PD-1, androgen deprivation and tumor ablation at one metastatic site appear promising in a mouse model of prostate cancer. These results have formed the basis of a recently opened trial in men with low volume metastatic disease (NCT02489357).

Conflict of Interest: None

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