Journal for ImmunoTherapy of Cancer

POSTER PRESENTATION Open Access

Combinatorial therapy with an IL-15 superagonist (ALT-803) and anti-PD-L1 mAb augment T cell mediated anti-tumor immunity in mice

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From Society for Immunotherapy of Cancer 29th Annual Meeting
National Harbor, MD, USA. 6-9 November 2014

The adoptive transfer of tumor-reactive T cells has shown great promise in treating patients with metastatic cancer. However, effective T cell responses are limited by the availability of T cell growth factors such as IL-2 and tumor-induced suppressive pathways. As tumor-induced suppression may hamper cytokine responsiveness, we hypothesized that combinatorial therapy providing exogenous cytokine with blockade of inhibitory pathways would lead to synergistic anti-tumor responses. We evaluated this hypothesis by treating mice with palpable B16 melanoma tumors with lymphodepletion and transfer of activated, tumor-reactive $CD8^+$ T cells (pmel-1 TCR transgenic). The persistence of the adoptively transferred tumor-reactive $CD8^+$ T cells was dramatically augmented in the recipient mice with injections of an IL-15 superagonist (ALT-803) which, compared with IL-2, has greater biological activity and does not expand T regulatory cells. The ALT-803-treated mice also survived significantly longer than the untreated mice. B16 melanoma tumor cells were found to express PD-L1 and activated $CD8^+$ T cells have PD-1 on their surface. Thus, we also gave mice anti-PD-L1 mAb treatment to block this PD-1/PD-L-1 inhibitory pathway. Our preliminary data suggest that combinatorial therapy with anti-PD-L1 mAb led to synergistic improvement in anti-tumor efficacy. We are now determining the optimal timing and dosing of ALT-803 and anti-PD-L1 mAb therapy to confirm these results. Currently, ALT-803 is in clinical trials for treating patients with various solid and hematologic tumors. Our findings suggest combinatorial therapy relieving T cell dysfunction using checkpoint inhibitors and providing ALT-803 cytokine therapy may lead to substantially improved outcomes over currently available therapies for patients with metastatic cancer.

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Published: 6 November 2014

doi:10.1186/2051-1426-2-S3-P234
Cite this article as: Johnson *et al.*: Combinatorial therapy with an IL-15 superagonist (ALT-803) and anti-PD-L1 mAb augment T cell mediated anti-tumor immunity in mice. *Journal for ImmunoTherapy of Cancer* 2014 **2**(Suppl 3):P234.

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