836 A NOVEL PD-L1 ANTIBODY-IL10 FUSION PROTEIN, PTL011, EXHIBITS SYNERGIZED THERAPEUTIC EFFECT IN HEPATOCELLULAR CARCINOMA MOUSE MODEL

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Background Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths. The liver's immune function is known for its tolerance and immunosuppression, making it difficult for immunotherapy such as immune checkpoint inhibitors (ICIs) to be effective. Consequently, immunotherapy has limited success in treating HCC. The T-cell response is a crucial factor in this process, and therapies that counteract these immunosuppressive mechanisms and enhance tumor-specific immunity can significantly improve clinical outcomes for HCC patients. A study found that interleukin-10-Fc fusion protein can rejuvenate terminally exhausted CD8+ tumor-infiltrating lymphocytes by promoting oxidative phosphorylation. In addition, overexpression of IL-10 or treatment with pegylated IL-10 (PEG-IL-10) has led to tumor rejection and long-lasting tumor immunity in mouse models of cancer.

Methods This study focuses on a newly developed humanized PD-L1 antibody merged with IL-10 protein, which we have named PLT011. Our goal is to enhance ICI treatment and more effectively deliver IL-10 into the tumor to induce superior anti-tumor responses and prevent potential complications. To evaluate the efficacy of PLT011, we conducted tests on a murine model of hepatocellular carcinoma caused by expression of b-catenin and Myc through hydrodynamic injection. To confirm tumor suppression, we compared the effectiveness of PLT011 with that of the anti-PD-L1 antibody, IL-10-Fc, and a combination of both IL-10-Fc and anti-PD-L1 antibody. Additionally, we utilized FACS to verify the immune cell profile in the HCC murine model.

Results The use of PLT011 treatment is more effective in suppressing tumor growth than using either monotherapy or combined treatment. Additionally, this treatment does not cause significant toxicity in mice. It is important to note that PLT011 treatment also increases the population of both $TCF1^{+}/PD1^{-}$ Progenitor exhausted T cells and $TCF1^{-}/PDL1^{+}$ Terminal exhausted T cells.

Conclusions PLT011 treatment triggers the activation of tumor-specific CD8 T cells and potentially restores the function of exhausted T cells in the tumor by reprogramming the metabolism. In this preclinical model, PTL011 has shown promising results in treating HCC with lower toxicity, indicating that this new approach could benefit more patients receiving immunotherapy.

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