823 IMM20059, A NOVEL ANTI-EPN1 ANTIBODY, IN COMBINATION WITH ATEZOLIZUMAB SIGNIFICANTLY ENHANCES TUMOR REGRESSION IN THE B16.F10 SYNGENEIC MELANOMA MODEL COMPARED TO ANTI-PD-L1 MONOTHERAPY

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Background Immune checkpoint inhibitors (ICI), such as anti-PD-L1 and anti-PD-1 antibodies, have exhibited remarkable efficacy in the clinic. However only a small subset of patients will ultimately respond to therapy and there is a dire need for expanding the patient population who will benefit from ICI treatments. Immunome's proprietary platform allows the interrogation of the memory B cell population for potential therapeutic antibodies, including those that may enhance ICI responses.

Methods In this study, IMM20059, an antibody discovered using Immunome's proprietary platform, is assessed for target specificity using immunoprecipitation/mass spectrometry (IP/MS), surface plasmon resonance (SPR), and epitope mapping. Tumor cell binding is evaluated via flow cytometry. Anti-tumor efficacy of IMM20059 in combination with anti-PD-L1 is evaluated in the syngeneic B16.F10 melanoma model in C57BL/6 mice and intra-tumoral chemokines are assessed by Luminex.

Results IMM20059 selectively binds to the N-terminal domain of epsin 1 (EPN1), an adapter protein involved in clathrin-mediated endocytosis, as compared to other epsin family members. Although expressed in multiple tissues, EPN1 is specifically upregulated in multiple cancer types, including lung, breast, and prostate cancers. Strikingly, while this expression is largely restricted to the intracellular compartment in normal cells, EPN1 appears to be ectopically expressed on the cell surface in multiple cancer cell lines, allowing for tumor specific targeting. The selectivity of IMM20059 and surface expression of EPN1 was confirmed by knockout of EPN1 and competition with recombinant protein. IMM20059 cross reacts with murine EPN1, exhibits a favorable pharmacokinetic profile *in vivo*, and exhibits a good tolerability profile in C57BL/6 mice. In the B16.F10 melanoma syngeneic model, combination treatment of IMM20059 and anti-PD-L1 (Atezolizumab) induced significant tumor regression compared to IMM20059 or Atezolizumab treatment alone, suggesting a combinatorial effect between the two pathways. Furthermore, this combination treatment significantly enhanced production of intratumoral chemokines, including MIP-1α, MIP-1β, and RANTES.

Conclusions This study suggests that EPN1 is a promising tumor target. Combination treatment of IMM20059 and anti-PD-L1 could enhance the efficacy of anti-PD-L1 therapy by boosting intratumoral chemokines and attracting immune cells to the immunologically cold tumor microenvironment.

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