ASD141, AN INNATE CHECKPOINT INHIBITOR, MODULATES TUMOR ASSOCIATED MYELOID CELLS THROUGH CD11B AND ENHANCES CURRENT IMMUNE CHECKPOINT BLOCKADE IN PRECLINICAL MODEL

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Background Tumor-associated myeloid cells (TAMCs) are a heterogeneous population of myeloid cells present in the tumor microenvironment (TME). They contribute to immunosuppression and growth of solid tumor. These myeloid cells are highly expressed with CD11b, the alpha-chain of integrin receptor alphaMbeta2 (also known as CD11b/CD18, Mac-1, CR3). It has been suggested that activation of CD11b could facilitate the development of peripheral tolerance by inhibiting T helper 17 differentiation. Antigen-presenting cells (dendritic cells and macrophages) have been shown to enhance T cell proliferation with the treatment of anti-CD11b antibody. Furthermore, CD11b plays a critical role in inflammation by modulating Toll-Like receptor (TLR) responses. High avidity activated form of CD11b leads to a rapid inhibition of TLR signaling by promoting degradation of MyD88 and TRIFs. Therefore, CD11b may serve as an innate checkpoint that function as a negative immune regulator.

Methods In order to investigate the impact of CD11b in modulating the TME and tumor growth, ASCENDO Biotechnology generated a surrogate chimeric mouse IgG1 antibody, mouse ASD141 (Xi2396), which targets mouse CD11b. These antibodies were then tested in murine MC38 colon cancer.

Results Mouse ASD141 as monotherapy results in statistically significant growth inhibition in murine colon cancer models. Xi2396 remodels the TME by decreasing infiltration of TAMCs, and increased infiltration of dendritic cells (cDCs, NKDCs, and pDCs). Furthermore, Xi2396 also enhanced the antigen presentation ability, which is accompanied by an increased expression of MHCII, CD80 and CD86. These results indicate that the anti-CD11b monoclonal antibody, ASD141, designed to modulate TAMCs of the TME represents a novel approach of cancer immunotherapy. Xi2396 treatment also induced high levels of PD-L1 expression in the TME. Since PD-L1 expression in the TME was associated with response to current immune checkpoint blockades, we sought to determine whether Xi2396 treatment is capable of enhancing anti-tumor response to anti-PD1 therapy. Our results showed that combination of Xi2396 and anti-PD1 synergistically suppressed tumor growth.

Conclusions Altogether, our results provide support for clinical efforts to evaluate ASD141 as an innate immune checkpoint drug, especially in combination with commercial immune checkpoint inhibitors.

Ethics Approval This study was approved by National Laboratory Animal Center's Institutional Animal Care and Use Committee; approval number NLAC-110-D-006-R2.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.263>