BTN1A1-TARGETED IMMUNOTHERAPY COMBINED WITH STANDARD THERAPY IN SMALL CELL LUNG CANCER (SCLC) AND COLORECTAL CANCER

1STCube Pharmaceuticals, Inc, Gaithersburg, MD, USA; 2Korea University Anam Hospital, Seoul, Republic of Korea

Background Butyrophilin 1A1 (BTN1A1) has been identified as a novel immune checkpoint protein that could potentially be targeted to create new immunotherapeutic treatment options. We observed that BTN1A1 and PD-L1 expression are mutually exclusive in various human solid tumors. BTN1A1 and PD-L1 expression levels were found to be negatively correlated across cell lines and tumor samples from patients. This suggests that targeting BTN1A1 could benefit patients whose tumors do not respond to anti-PD-1/PD-L1 therapy. Recently, a phase 1 clinical trial of hSTC810, an antibody against BTN1A1, was successfully completed. We characterized patient tumor biopsy slides based on BTN1A1/PD-L1 expression. Additionally, we used zebrafish, organoid, and mouse models as multiple evaluation platforms to understand the heterogeneity of interaction mechanisms between immune cells and cancer cells.

Methods NCI-H345 cell lines were labeled and injected into the pericardium of zebrafish larvae (2 dpf) along with hPBMC, hSTC810, and 5-FU. Patient-derived lung cancer organoids were grown in Matrigel. The organoids were examined for morphologic disruption following hPBMC, hSTC810, and Paclitaxel treatment by assessing the organoid size and formation rate. MC38 cells were allografted by subcutaneously implanting into the right flank of a mouse. After 10 days, mice were injected with STC109 (an antibody against mouse BTN1A1), anti-PD-L1, and 5-FU. Patients’ FFPE specimens were stained to identify cancer and immune cells using Opal multiplex immunofluorescence. In every experiment, synergistic effects of anti-BTN1A1 and other therapies were analyzed in relation to the immune context of the tumor.

Results Inhibition of BTN1A1 by hSTC810 in cancer cell lines leads to a prominent upregulation of genes associated with the innate immune response, including the JAK-STAT pathway, as well as T-cell activation and tumor clearance. In the zebrafish, organoid, and mouse models, anti-BTN1A1 therapy enhanced the anti-tumor activity of hPBMC and synergized with chemotherapy and anti-PD-L1 therapy. Opal multiplex immunofluorescence analysis revealed that anti-BTN1A1 therapy increased the infiltration and activation of CD8+ T cells and NK cells in the tumor microenvironment. Additionally, we found the expression of BTN1A1 in Ki67-negative tumors from SCLC patients, which is opposite to PD-L1-expressing cancer cells.

Conclusions In vitro, in vivo, and clinical data show that hSTC810 treatment results in the activation of innate immune response pathways and enhances anti-tumor activity when combined with anti-PD-L1 therapy. Our results suggest that BTN1A1 is a novel immune checkpoint that can be targeted to overcome resistance to conventional therapies in SCLC patients.

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