AN ACTIVE SITE PTPN2/N1 SMALL MOLECULE INHIBITOR PROMOTES ANTI-TUMOR EFFICACY BY SENSITIZING TUMOR CELLS TO INFLAMMATORY SIGNALS AND ENHANCING IMMUNE CELL ACTIVITY

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Background The tyrosine phosphatases PTPN2 and PTPN1 are important negative regulators of immune signaling pathways and genetic deletion of these proteins in tumor or immune cells has been shown to overcome unresponsiveness to checkpoint blockade and increase anti-tumor immunity in vivo. Thus, these proteins should be promising immunotherapy targets, but drugging phosphatases has proven difficult.

Methods Here, we demonstrate that our active site PTPN2 and PTPN1 small molecule inhibitor, ABBV-CLS-484 (AC-484), promotes anti-tumor immunity in several syngeneic mouse tumor models upon oral administration. This first-in-class PTPN2/N1 inhibitor sensitizes tumor cells to inflammation and augments the activity of a variety of immune cell subsets in vitro and in vivo.

Results Specifically, AC-484 sensitizes tumor cells to inflammation by augmenting interferon signaling, leading to enhanced growth arrest and antigen presentation. AC-484 also promotes T cell activation and function upon TCR stimulation and enhances activity of dendritic cells and macrophages in vitro. Consistent with our in vitro findings, immunophenotyping and single-cell RNA sequencing analyses demonstrate AC-484 treatment leads to a more inflamed tumor microenvironment characterized by increased abundance of inflammatory macrophages producing pro-inflammatory chemokines such as IP-10, which are important for immune cell recruitment. Further, AC-484 leads to an increased abundance and activation of intratumoral NK and CD8 T cells not only in inflamed but also in less inflamed tumors. Interestingly, PTPN2/N1i also decreased the frequency of dysfunctional/exhausted T cells and increased the frequency of polyfunctional CD8 T cells. To directly confirm these effects on exhausted T cells, we assessed how AC-484 affected T cell dysfunction under T cell exhaustion conditions in vitro. Consistent with our in vivo findings, AC-484 reduced the frequency of exhausted T cells and promoted polyfunctional T cells with improved cytotoxic activity under chronic antigen stimulation.

Conclusions Taken together, PTPN2/N1 inhibition appears to promote anti-tumor activity by acting on tumor cells directly and promoting the anti-tumor activity of several immune cell subsets including dysfunctional CD8 T cells, which are enriched in the tumor microenvironment. This two-pronged mechanism leads to efficacy in murine tumor models unresponsive to PD-1 pathway blockade. Based on our preclinical data on this novel and efficacious therapeutic approach, ABBV-CLS-484 is currently under Phase I clinical evaluation in cancer patients with solid tumors.

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