Novel Single-Agent Immunotheerapies

PTPN2/N1 INHIBITOR ABBV-CLS-484 UNLEASHERS POTENT ANTI-TUMOR IMMUNITY

Background Immune checkpoint blockade is effective for a subset of patients across many cancers, but most patients are refractory to current immunotherapies and new approaches are needed to overcome resistance. The protein tyrosine phosphatase PTPN2 and the closely related PTPN1 are central regulators of inflammation, and their genetic deletion in either tumor cells or host immune cells promotes anti-tumor immunity. However, phosphatases are challenging drug targets and in particular, the active site has been considered undruggable. Here, we present the discovery and characterization of ABBV-CLS-484 (AC484), a first-in-class, orally bioavailable, potent PTPN2/N1 active site inhibitor.

Methods In this study, we characterize AC484 and evaluate its effects in vitro and in vivo. We conduct in vitro experiments to investigate the interferon response and the activation and function of various immune cell subsets in response to AC484. We employ murine cancer models resistant to PD-1 blockade and assess the anti-tumor efficacy of AC484 monotherapy in these models. Additionally, through single-cell transcriptional profiling of tumor-infiltrating immune cells, we examine the transcriptional and functional effects of AC484 treatment, with a focus on CD8+ T cells.

Results AC484 treatment demonstrates the ability to amplify the response to interferon and enhance the activation and function of multiple immune cell subsets in vitro. In murine cancer models resistant to PD-1 blockade, monotherapy AC484 treatment generates robust anti-tumor immunity. Transcriptomic and functional analyses of tumor-infiltrating immune cells reveal that AC484 treatment elicits broad effects on myeloid and lymphoid compartments, particularly influencing CD8+ T cells. Surprisingly, we find that AC484 treatment induces a unique transcriptional state in CD8+ T cells mediated by enhanced JAK-STAT signaling, whereby T cells display a highly cytotoxic effector profile, increased memory signatures, and reduced exhaustion and dysfunction.

Conclusions Our results demonstrate that oral administration of small molecule inhibitors of key intracellular immune regulators can achieve efficacy comparable to or exceeding antibody-based immune checkpoint blockade in preclinical models. Finally, to our knowledge AC484 represents the first active site phosphatase inhibitor to enter clinical evaluation for cancer immunotherapy and may pave the way for additional therapeutics targeting this important class of enzymes.

REFERENCES


Ethics Approval The protocol, under which human blood samples were acquired, was approved by and is reviewed on an annual basis by WCG IRB (Paywalup, Washington), WCG IRB is in full compliance with the Good Clinical Practices as defined under the U.S. Food and Drug Administration (FDA) Regulations, U.S. Department of Health and Human Services (HHS) regulations and the International Conference on Harmonisation (ICH) Guidelines. All human research participants signed informed consent forms. All animal studies at AbbVie, were reviewed and approved by AbbVie’s Institutional Animal Care and Use Committee and in compliance with the NIH Guide for Care and Use of Laboratory Animals guidelines. Animal studies were conducted in an AAALAC accredited program where veterinary care and oversight was provided to ensure appropriate animal care. All in vivo studies conducted at the Broad Institute were approved by the Broad Institute IACUC committee and mice were housed in a specific-pathogen free facility. All in vivo studies at Calico were conducted according to protocols approved by the Calico Institutional Animal Care and Use Committee.

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