THE PTPN2/N1 SMALL MOLECULE INHIBITOR ABBV-CLS-484 PROMOTES NK CELL ACTIVITY DRIVING PRIMARY TUMOR REGRESSION AND PREVENTING METASTASIS

Chirag Patel1, Kathleen A. McGuire2, Hakimeh Ebrahim-Nik3, Meng Sun1, Yue Liu4, Kelly Klinge4, Jacqueline Aguado3, Audrey J. Muscato5, Payal Tiwari6, Omar Avila-Monge7, Kayla J. Covlin8, Kira Olander9, Kyle Halliwell9, Joseph Klain9, Alexander Schutte9, Marcia N. Paddock10, Jonathan Powell11, Keith M. Hamel12, Jennifer M. Frost12, Kathleen B. Yates12, Philip R. Kym13, Robert T. M Angus13, Christina K. Baumgartner13, Calico Life Sciences, South San Francisco, CA, USA1; AbbVie Inc., North Chicago, IL, USA2; Broad Institute of MIT and Harvard, Cambridge, MA, USA3; AbbVie Inc., South San Francisco, CA, USA4; AbbVie Inc., Elk Grove Village, IL, USA5; 2Philip R. Kym, 3Robert T M Angus, 4Christina K Baumgartner. Calico Life Sciences, South San Francisco, CA, USA; 2AbbVie Inc., North Chicago, IL, USA; 3Broad Institute of MIT and Harvard, Cambridge, MA, USA; 4AbbVie Inc., South San Francisco, CA, USA; 2AbbVie Inc., Elk Grove Village, IL, USA

Background The tyrosine phosphatases PTPN2 and PTPN1 negatively regulate several signaling pathways in immune and tumor cells. We previously demonstrated that oral administration of our recently discovered active site PTPN2/N1 small molecule inhibitor ABBV-CLS-484 (AC-484) promotes anti-tumor immunity in several syngeneic mouse tumor models. AC-484 improves T cell activation and function upon TCR stimulation and enhances dendritic cell and macrophage activation in vitro consistent with prior findings in PTPN2 or PTPN1 genetically deficient T cells and myeloid cells. However, a role for PTPN2 or PTPN1 in NK cells has not been previously described. NK cells are essential for eliminating tumors that typically evade the adaptive T cell response and are critically important to control metastasis formation. Given the role of inhibitory signaling pathways, we hypothesized that PTPN2 and PTPN1 may also negatively regulate NK activity and therefore AC-484 should enhance NK cell function and NK-mediated anti-tumor immunity.

Methods To understand the impact of AC-484 on NK cells, we employed cytotoxicity assays in vitro and utilized immunophenotyping and single cell RNA sequencing of tumor-infiltrating immune cells isolated from mouse syngeneic tumor models. We also assessed the contribution of NK cells to AC-484-mediated efficacy in subcutaneous primary tumor and spontaneous lung metastasis formation models.

Results AC-484 treatment enhanced NK cell function and NK-mediated tumor cell killing in vitro. Consistent with these findings, immunophenotyping and single cell RNAseq analyses demonstrated that in vivo AC-484 therapy increased NK cell abundance and activation in mouse tumor models with varying responsiveness to immune checkpoint blockade. Further, in tumor models that do not rely on T cells for tumor control such as those with MHC-I or Jak1 deficiency, AC-484 therapy improved NK-mediated efficacy. In addition to controlling primary tumors, AC-484 also potently prevented lung metastasis formation in the B16F10 intravenous and the 4T1 orthotopic breast cancer models in an NK cell-dependent manner.

Conclusions Here, we describe for the first time a role for PTPN2 and PTPN1 in NK cells. Our findings suggest that AC-484 can both control primary tumors and prevent tumor metastasis in an NK cell-dependent manner. We further show that AC-484 treatment overcomes various common immune evasion mechanisms developed by tumors, including those acquired via mutations in Beta-2-microglobulin, HLA, and JAK1/2. These findings, along with our previous reports, underscore how AC-484 significantly promotes anti-tumor efficacy through a multifaceted mechanism by sensitizing tumor cells to inflammation and enhancing the activity of a variety of immune subsets.

Ethics Approval

Human Human blood samples were acquired through the internal AbbVie Inc’s blood donation program in accordance with AbbVie’s Occupational Safety and Health Administration protocols or healthy donors from Stanford University.

Animals All in vivo experiments conducted at AbbVie were in compliance with the NIH Guide for Care and Use of Laboratory Animals guidelines in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC). All in vivo studies conducted at the Broad Institute or Calico Life Sciences were approved by the respective IACUC committees.


http://dx.doi.org/10.1136/jitc-2023-SITC2023.0999

Abstracts