483 PRECLINICAL EVALUATION OF JTX-1484, AN ANTI-LILRB4 ANTAGONIST ANTIBODY, FOR RE-PROGRAMMING OF IMMUNOSUPPRESSIVE MYELOID CELLS

Heather Condurso, Amy Mueller, Jessica Jimenez, Lauren Badalucco, Kelly Aldridge, Pauline Sarraf, Michelle Priess, Vikki Spaulding, Sarah Jaffe, Prashanna Balaji Venkatasubramanian, Alexa Diiorio, Geneva Young, Kameron Mori, Karl Wetterhorn, Jeffrey Smith, Morgan Thompson, Jean-Christophe Pignon, Changyun Hu, Brandon Chin, Briana Murphy, Matthew Southard, Katalin Kis-Toth, Monica Gostissa, Dmitri Wiederschain, Andre da Cunha*. *Jounce Therapeutics, Cambridge, MA, United States*

Background Immune checkpoint therapy has achieved durable clinical responses, but only in a subset of cancer patients. Immunosuppressive myeloid cells, a heterogenous group of innate immune cells, have emerged as key contributors to resistance to T cell based immune checkpoint therapy. Leukocyte immunoglobulin-like receptor B4 (LILRB4), also known as immunoglobulin-like transcript 3 (ILT3), is an inhibitory receptor selectively expressed on myeloid cells, enriched in the tumor microenvironment and contributes to myeloid-driven immunosuppression. Recently, fibronectin has been identified as a functional ligand for LILRB4, and the LILRB4-fibronectin interaction was proposed as a stromal checkpoint suppressing myeloid cell anti-tumor activity. Targeting LILRB4 could represent a strategy to reprogram immunosuppressive myeloid cells and promote anti-tumor response. We developed JTX-1484, a highly selective, high-affinity humanized monoclonal antibody that binds to and antagonizes LILRB4 and blocks its interaction with fibronectin.

Methods A diverse panel of high affinity monoclonal antibodies that bind specifically to LILRB4 was generated. JTX-1484 activity alone or in combination with an anti-PD1 antibody was evaluated in vitro in different functional assays. Human primary myeloid-derived suppressor cells (MDSCs) were used in a T cell suppression assay and treated with JTX-1484. Primary monocyte-derived tolerogenic dendritic cells (tDCs) were utilized in mixed lymphocyte reactions with T cells and treated with JTX-1484 in combination with anti-PD1. JTX-1484's ability to block fibronectin inhibitory activity on tDCs and THP-1 cells was also tested. Finally, the pharmacodynamic effect of anti-LILRB4 treatment in human tumor samples was evaluated by assessing gene expression changes in an ex vivo histoculture system.

Results JTX-1484 reprogramed tDCs to a stimulatory phenotype as evidenced by increased pro-inflammatory cytokine production and increased ability to induce T cell activation in combination with anti-PD1. LILRB4 antagonism by JTX-1484 also reversed fibronectin-mediated inhibition of tDC activation and reduced MDSC-mediated T cell immunosuppression. Moreover, LILRB4 blockade in ex vivo human tumor samples induced pharmacodynamic responses consistent with increased immune activation and reduced myeloid immunosuppression.

Conclusions Results from our preclinical studies demonstrate that JTX-1484 is a highly specific and potent antagonist of LILRB4 that leads to myeloid cell reprogramming and more efficient T cell activation that could result in enhanced anti-tumor responses. JTX-1484 immunostimulatory properties towards myeloid cells could be complementary to immune checkpoint blockade therapy. Our data therefore support clinical development of JTX-1484. Indication selection will be guided by multiple factors including predictive biomarkers such as target and ligand abundance, as well as complementarity and combination potential with other therapies.

Ethics Approval Human blood and tumor samples were acquired from commercial providers and from the CHTN and NDRI networks respectively. Specimens were collected under each provider's human subject research institutional review board approved protocols and were fully anonymized or otherwise permanently de-identified to recipient investigators.

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