INITIAL CLINICAL CHARACTERIZATION OF NOVEL PROXIMAL BIOMARKERS FOR NX-1607, A FIRST-IN-CLASS ORAL CBL-B INHIBITOR, IN PATIENTS WITH ADVANCED MALIGNANCIES


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Background Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is an E3 ubiquitin ligase expressed in multiple immune cell lineages and is a master regulator of the immune response. NX-1607 is a first-in-class oral small molecule inhibitor of CBL-B that has demonstrated potent anti-tumor activity in animal models by reversing T cell dysfunction and overcoming suppressive signaling in the tumor microenvironment. Nurix has identified and characterized novel proximal biomarkers of CBL-B inhibition that correlate with anti-tumor activity in syngeneic tumor models. Assays for these biomarkers characterize the activity of NX-1607 in a first-in-human clinical trial (NCT05107674).

Methods Agnostic screening campaigns utilizing flow cytometry protein phosphorylation signals and mass spectrometry-based methods to measure direct ubiquitination substrates identified multiple proprietary proximal biomarkers of CBL-B inhibition in activated T cells. Validation of these biomarkers in mouse and non-human primate (NHP) in vivo models, coupled with allometric scaling of pharmacokinetic (PK) profiles, were used to inform clinical dose selection. PK and pharmacodynamic (PD) data are currently being monitored in a Phase I trial with daily oral dosing in 21-day cycles.

Results Phosphorylated hematopoietic lineage cell-specific protein 1 (pHS1), a regulator of T cell-receptor signaling, was identified as a robust and reproducible biologically relevant proximal biomarker for monitoring pharmacologic inhibition of CBL-B in whole blood. Validation of proximal biomarkers in vivo demonstrated target engagement with dose-dependent increases of pHS1 in CD8+ T cells in both mice and NHP dosed orally with NX-1607. As of June 16, 2022, 10 patients have enrolled on study at 4 ascending oral dose levels (5, 15, 25 and 50 mg once daily). Dose-proportional increases of pHS1-expressing T cells were observed in cycle 1. Preliminary PK data suggest a half-life of 4 to 9 hours and dose-proportional exposures with no apparent accumulation. Together these data are consistent with preclinical human dose projections and compare to pHS1 levels associated with anti-tumor activity in mouse models.

Conclusions NX-1607 is a first-in-class oral CBL-B inhibitor displaying linear PK, dose-dependent target engagement as measured by the validated proximal biomarker, pHS1, and downstream signals of T cell engagement. PK and PD data derived from non-clinical and clinical studies have shown remarkable concordance with biomarker levels observed in the clinic corresponding to those levels associated with potent anti-tumor activity observed in mouse models. The study continues to enroll, and updated PK and PD data will be presented.

Trial Registration NCT05107674

REFERENCE

Ethics Approval The study obtained ethics committee(s) approval, and participants gave informed consent before taking part.