Nurix Therapeutics Announces Publication in the Journal Science Identifying a New Class of BTK Mutations That Are Susceptible to NX-2127, a Novel BTK and IKZF1/3 Degrader

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Data reveal oncogenic scaffold function of BTK mutations that lack kinase activity and show these mutations remain susceptible to degradation by NX-2127

NX-2127 degrades BTK in patients regardless of mutational status and shows proof-of-concept therapeutic benefit in chronic lymphocytic leukemia

Nurix recently presented positive clinical data from ongoing Phase 1 clinical trial of NX-2127 in patients with relapsed/refractory B-cell malignancies at the 65th American Society of Hematology (ASH) Annual Meeting

SAN FRANCISCO, Feb. 01, 2024 (GLOBE NEWSWIRE) -- Nurix Therapeutics, Inc. (Nasdaq: NRIX), a clinical stage biopharmaceutical company developing targeted protein modulation drugs designed to treat patients with cancer and inflammatory diseases, today announced the publication of a manuscript in the journal *Science* titled: “Kinase Impaired BTK Mutations Are Susceptible to Clinical Stage BTK and IKZF1/3 Degrader NX-2127” that elucidates a previously unappreciated oncogenic scaffold function of BTK responsible for clinical resistance to enzymatic inhibitors and shows that NX-2127, a potent targeted protein degrader with differentiated activity against BTK and IKZF1/3, can overcome this resistance across a broad range of acquired mutations.

“While BTK inhibitors have positively changed clinical outcomes for patients with B-cell malignancies, the emergence of acquired resistance to these medicines is a growing clinical problem,” said Alexey Danilov, M.D., Ph.D. Professor and Co-Director, Toni Stephenson Lymphoma Center, City of Hope National Medical Center. “Identification of the different types of mutations has important implications for the therapeutic sequencing of currently used targeted BTK inhibitors and reinforces the need for the development of novel agents, such as Nurix’s NX-2127 and NX-5948, that have the potential to provide improved mutation-agnostic treatment options for patients.”

The article describes studies designed to investigate and characterize acquired BTK mutations that confer resistance to BTK inhibitors commonly used in the treatment of B-cell malignancies. The research identified a new class of kinase impaired mutants that render BTK enzymatically inactive and revealed that these mutations create novel protein-protein interactions that can propagate biochemical signaling through a process known as scaffolding, a nonenzymatic function of the BTK protein that sustains B-cell receptor (BCR) signaling and promotes the growth of malignant B-cells. Importantly, the authors report data demonstrating efficient proteasomal degradation of BTK in the blood of all NX-2127-treated patients with chronic lymphocytic leukemia (CLL), resulting in reduction of BTK enzymatic activity and suppression of BCR signaling regardless of mutational status. The work was carried out by Nurix in collaboration with scientists and clinicians at several prominent cancer research centers, including Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine and the Sloan Kettering Institute at Memorial Sloan Kettering Cancer Center.

A Drug Annotation manuscript published contemporaneously in *The Journal of Medicinal Chemistry* entitled “Discovery and Preclinical Pharmacology of NX-2127, an Orally Bioavailable Degrader of Bruton’s Tyrosine Kinase with Immunomodulatory Activity for the Treatment of Patients with B Cell Malignancies” reports data detailing the discovery and optimization of NX-2127, including characterization of NX-2127’s activity in preclinical tumor models, cross-species pharmacokinetics and *in vitro* safety which supported the advancement of this molecule into clinical testing.

“These publications represent the first compendium of biochemical, cellular, and clinical evidence that NX-2127 degrades both previously described and newly discovered BTK inhibitor resistance mutations, a novel mechanism of action in the treatment of B-cell malignancies that is associated with meaningful clinical responses,” said Gwenn M. Hansen, Ph.D., chief scientific officer of Nurix. “The data described in this publication in *Science* reinforce the broad utility of the targeted protein degradation mechanism compared to inhibition approaches to more completely block BTK function and potentially other important enzymatic disease targets where development of acquired resistance is an issue.”

“The first-in-human trial of NX-2127 is ongoing in patients with relapsed and refractory B-cell malignancies, including CLL. Based on our clinic data, which were recently presented at the 2023 ASH Annual Meeting, we have also initiated expansion cohorts in patients with diffuse large B cell lymphoma (DLBCL) and mantle cell lymphoma (MCL),” said Paula O’Connor, M.D., senior vice president of clinical development at Nurix. “With the ability to target BTK inhibitor resistance mutations and achieve clinical responses, we believe that BTK degraders have the potential to become the next dominant class of agents in the significant BTK-targeted therapy field. We look forward to presenting additional clinical data from this program, and from our NX-5948 BTK degrader program, which is also being evaluated in patients with CLL, at future medical meetings.”

About NX-2127
NX-2127 is a novel bifunctional, orally bioavailable, investigational new drug that degrades BTK and cereblon neosubstrates Ikaros (IKZF1) and Aiolos (IKZF3). NX-2127 is currently being evaluated in a Phase 1 clinical trial in patients with relapsed or refractory B cell malignancies. Additional information on the ongoing clinical trial can be accessed at www.clinicaltrials.gov (NCT04830137).

About NX-5948
NX-5948 is an investigational, orally bioavailable, small molecule degrader of BTK that, unlike NX-2127, has been designed to lack cereblon immunomodulatory activity. NX-5948 is currently being evaluated in a Phase 1 clinical trial in patients with relapsed or refractory B cell malignancies. Additional information on the ongoing clinical trial can be accessed at clinicaltrials.gov (NCT05131022).

About Nurix Therapeutics, Inc.
Nurix Therapeutics is a clinical stage biopharmaceutical company focused on the discovery, development and commercialization of innovative medicines based on the modulation of cellular protein levels as a novel treatment approach for cancer, inflammatory conditions and other challenging diseases. Leveraging extensive expertise in E3 ligases together with proprietary DNA-encoded libraries, Nurix has built DELigase, an integrated discovery platform, to identify and advance novel drug candidates targeting E3 ligases, a broad class of enzymes that can modulate proteins within the cell. Nurix's drug discovery approach is to either harness or inhibit the natural function of E3 ligases within the ubiquitin-proteasome system to selectively decrease or increase cellular protein levels. Nurix's wholly owned, clinical stage pipeline includes targeted protein degraders of Bruton's tyrosine kinase, a B-cell signaling protein, and inhibitors of Casitas B-lineage lymphoma proto-oncogene B, an E3 ligase that regulates activation of multiple immune cell types including T cell and NK cells. Nurix is headquartered in San Francisco, California. For additional information visit http://www.nurixtx.com.

Forward-Looking Statements

This press release contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this press release, the words "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "outlook," "plan," "predict," "should," "will," and similar expressions and their variants, as they relate to Nurix, may identify forward-looking statements. All statements that reflect Nurix's expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking statements, including, without limitation, statements regarding: Nurix's plans and strategies for NX-2127 and NX-5948; the therapeutic potential and other advantages of Nurix's BTK degraders, including the potential of NX-2127 and NX-5948 to address a range of acquired mutations; the planned timing for the provision of updates and findings from the NX-2127 and NX-5948 clinical trials; and the extent to which targeted protein degradation may potentially address a broad range of diseases. Forward-looking statements reflect Nurix's current beliefs, expectations, and assumptions regarding the future. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix's actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) whether Nurix will be able to successfully conduct clinical trials for its drug candidates and receive results on its expected timelines, or, at all; (ii) the unexpected emergence of adverse events or other undesirable side effects during clinical development; (iii) whether Nurix will be able to successfully complete clinical development for its drug candidates (iv) whether regulatory authorities will be satisfied with the results from Nurix's clinical studies; (v) whether Nurix will be able to obtain regulatory approval of and ultimately commercialize its drug candidates; (vi) whether Nurix will be able to fund development activities and achieve development goals; (vii) the impact of macroeconomic conditions and global events on Nurix's clinical trials and operations; and (vii) other risks and uncertainties described under the heading "Risk Factors" in Nurix's Quarterly Report on Form 10-Q for the fiscal quarter ended August 31, 2023, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this press release speak only as of the date of this press release, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

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