Nuvalent Announces Publication in Cancer Discovery Detailing Design and Characterization of ROS1-selective inhibitor NVL-520

Publication provides comprehensive assessment of NVL-520's activity spanning preclinical characterization and preliminary clinical case studies

CAMBRIDGE, Mass., Dec. 13, 2022 /PRNewswire/ -- Nuvalent, Inc. (Nasdaq: NUVL), a clinical-stage biopharmaceutical

company focused on creating *precisely* targeted therapies for clinically proven kinase targets in cancer, today announced the publication of a manuscript in *Cancer Discovery,* a journal of the American Association for Cancer Research, which describes the design and characterization of NVL-520 and details Nuvalent's approach to rationally targeting ROS1. NVL-520 is currently being studied in the ongoing ARROS-1 Phase 1/2 clinical trial for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other solid tumors.

The paper, entitled "NVL-520 is a selective, TRK-sparing, and brain-penetrant inhibitor of ROS1 fusions and secondary resistance mutations," is published online and can be accessed here: https://aacrjournals.org/cancerdiscovery/article/doi/10.1158/2159-8290.CD-22-0968/

"The ROS1 kinase is a clinically validated target for the treatment of NSCLC, and ROS1 tyrosine kinase inhibitors (TKIs) are established as an important treatment option for ROS1-driven lung cancers. However, limitations do exist with available ROS1 TKIs, including treatment-emergent drug resistance, off-target neurological adverse events, and inadequate control or prevention of brain metastases," said senior author Jessica J. Lin, M.D., Thoracic Oncologist at Mass General Cancer Center, Assistant Professor of Medicine at Harvard Medical School, and investigator in the ARROS-1 trial. "As described in this paper and earlier this year at the EORTC-NCI-AACR Symposium, preclinical characterization and preliminary clinical data support the opportunity for NVL-520 to overcome these limitations as a potential best-in-class ROS1 kinase inhibitor and provide compelling rationale for its ongoing evaluation in patients with TKI-experienced ROS1 fusion-positive cancers and planned evaluation in treatment-naïve patients."

The paper details the design principles underlying the activity of NVL-520 against ROS1 and its most commonly occurring resistance mutation, ROS1 G2032R, and a molecular rationale for the selectivity of NVL-520 for ROS1 over the structurally-related TRK family. TRK inhibition in the CNS by approved or investigational ROS1 TKIs has been associated with neurological adverse events that can be dose limiting. Extensive preclinical characterization of the activity and selectivity of NVL-520 is presented, spanning biochemical and cellular assays, in vivo xenograft studies, and preclinical assessments of brain penetrance and intracranial activity.

In addition, the paper includes three case studies of patients with ROS1 fusion-positive lung cancers that had relapsed on or were refractory to a range of ROS1 TKIs, and includes patients with tumors that harbored ROS1 G2032R or had intracranial metastases. NVL-520 elicited tumor responses in the patients with no observed neurological toxicities. These findings support the potential for NVL-520 to treat these patient populations while also enhancing tolerability through improved selectivity for ROS1.

"At Nuvalent, we aim to solve for multiple, and at times competing, challenges in structure-based drug design with the goal to advance novel therapeutics with the potential for best-in-class activity against recalcitrant targets. This publication in *Cancer Discovery* provides insight into our focused approach to the discovery of NVL-520 and additional support for the potential achievement of our design goals through comprehensive biochemical and cellular profiling, evaluation across diverse ROS1-fusion driven preclinical models, and patient case studies, said Joshua Horan, Ph.D., Vice President, Chemistry at Nuvalent. "We are grateful to our collaborators for their contributions to this paper and to the continued advancement of NVL-520."

Initial data from the Phase 1 dose-escalation portion of the trial were presented during the "New Drugs on the Horizon" plenary session at the 2022 EORTC-NCI-AACR Symposium. The ARROS-1 trial is continuing to enroll patients in the Phase 1 portion of the study and is focused on further characterizing the safety profile of NVL-520, its pharmacokinetic profile, and determining the recommended Phase 2 dose.

About NVL-520
NVL-520 is a novel brain-penetrant ROS1-selective inhibitor designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with the prevalent G2032R resistance mutation and those with the S1986Y/F, L2026M, or D2033N resistance mutations. NVL-520 has been optimized for brain penetrance to potentially improve treatment options for patients with brain metastases. NVL-520 has been observed in preclinical studies to selectively inhibit wild-type ROS1 and its resistance variants over the structurally related tropomyosin receptor kinase (TRK) family to potentially avoid TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients. NVL-520 is currently being investigated in the ARROS-1 study (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced non-small cell lung cancer (NSCLC) and other solid tumors.

About Nuvalent
Nuvalent, Inc. (Nasdaq: NUVL) is a clinical-stage biopharmaceutical company focused on creating *precisely* targeted therapies for patients with cancer, designed to overcome the limitations of existing therapies for clinically proven kinase targets. Leveraging deep expertise in chemistry and structure-based drug design, we develop innovative small molecules that have the potential to overcome resistance, minimize adverse events, address brain metastases, and drive more durable responses. Nuvalent is advancing a robust pipeline with parallel lead programs in ROS1-positive and ALK-positive non-small cell lung cancer (NSCLC), a program in HER2 Exon 20 insertion-positive cancers, and multiple discovery-stage research programs. We routinely post information that may be important to investors on our website at www.nuvalent.com. Follow us on Twitter (@nuvalent) and LinkedIn.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements regarding Nuvalent's strategy, business plans, and focus; the preclinical and clinical development programs for NVL-520; the potential clinical effect of NVL-520; the design and enrollment of the ARROS-1 study; the potential of NVL-520; Nuvalent's research and development programs for the treatment of cancer; and risks and uncertainties associated with drug development. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "aim," "goal," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" or the negative of these terms and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Drug development and commercialization involve a high degree of risk, and only a small number of research and development programs result in commercialization of a product. You should not place undue reliance on these statements or the scientific data presented.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties, and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation: risks that Nuvalent may not fully enroll the ARROS-1 study or that enrollment will take longer than expected; unexpected concerns that may arise from additional data, analysis, or results obtained during preclinical studies or clinical trials; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; the direct or indirect impact of COVID-19 or other global geopolitical circumstances on the timing and anticipated timing and results of Nuvalent's clinical trials, strategy, and future operations, including the ARROS-1 study; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; and obtaining, maintaining, and protecting its intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's Quarterly Report on Form 10-Q for the quarterly period ended September 30, 2022, as well as any prior and subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Nuvalent's views only as of today and should not be relied upon as representing its views as of any subsequent date. Nuvalent explicitly disclaims any obligation to update any forward-looking statements.

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