Nuvalent Presents New Preclinical Data Supporting Intracranial Activity of NVL-655 at AACR Annual Meeting 2023

CAMBRIDGE, Mass., April 18, 2023 /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 presentation of new preclinical data supporting the intracranial activity NVL-655. NVL-655 is a brain-penetrant, ALK-selective tyrosine kinase inhibitor (TKI) designed to maintain activity against ALK and ALK mutations that confer resistance to currently approved therapies, and to avoid neurological adverse events and dose-limiting toxicities associated with TRK inhibition.

The data result from a collaboration with Yonsei University College of Medicine and will be presented at the American Association for Cancer Research (AACR) Annual Meeting 2023, taking place April 14-19 in Orlando, Florida. The poster will also be available on the Nuvalent website at www.nuvalent.com following the presentation.

"Brain penetrance is a critical medical need for ALK TKIs due to the high incidence of brain metastases in ALK-positive non-small cell lung cancer (NSCLC), both at initial diagnosis and upon progression with currently available therapies. Treatment-emergent ALK resistance mutations as well as the structural similarity between the ALK and TRK kinases pose additional challenges for development of brain penetrant TKIs," said Professor Byoung Chul Cho, M.D., Ph.D., Yonsei University College of Medicine. "Careful design of highly potent ALK-selective compounds is needed to inhibit treatment-resistant ALK-driven disease while avoiding neurological effects associated with inhibition of TRK in the brain."

Professor Cho continued, "The potent preclinical efficacy of NVL-655 in a challenging patient-derived model of treatment-resistant intracranial ALK NSCLC was consistent with its design as a brain-penetrant ALK-selective TKI with activity against the G1202R mutation, and supportive of a differentiated preclinical profile for NVL-655 compared with approved and other investigational ALK TKIs."

The YU-1077 patient-derived cell line was developed from a patient with alectinib-resistant NSCLC harboring an EML4-ALK fusion with the G1202R resistance mutation. Cell viability and ALK signaling assays confirmed potent in vitro activity of NVL-655 and limited sensitivity to first- and second-generation ALK TKIs, consistent with prior relapse on alectinib and the G1202R resistance mutation. A mouse model of drug-resistant lung cancer that had metastasized to the brain was established through intracranial injection of YU-1077 cells. Upon treatment with

NVL-655, intracranial efficacy was confirmed via MRI.

"This study marks the first utilization of a patient-derived model to assess the preclinical intracranial activity of NVL-655 and represents an enhancement in physiological relevance over our previous preclinical experiments," said Henry Pelish, Ph.D., Senior Vice President of Drug Discovery at Nuvalent. "The resulting data are an important addition to the growing body of preclinical evidence demonstrating NVL-655's differentiated ability to target ALK and display intracranial activity against brain tumors bearing resistance mutations."

NVL-655 has previously demonstrated preclinical efficacy in a cell line model of intracranial disease, as well as broad preclinical activity across diverse ALK resistance mutations and tumor types while maintaining strong selectivity for ALK over TRKB. NVL-655 is currently being investigated in the ALKOVE-1 study (NCT05384626), a first-in-human Phase 1/2 clinical trial for patients with advanced ALK-positive NSCLC and other solid tumors.

AACR Presentation Overview:

Title: Preclinical intracranial activity of NVL-655 in an alectinib-resistant patient-derived model harboring EML4-ALK fusion with G1202R mutation
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Permanent Abstract: 4022
Session Category: Experimental and Molecular Therapeutics
Session Title: Tyrosine Kinase and Phosphatase Inhibitors 1
Session Date and Time: Tuesday April 18, 2023 from 9:00 a.m. – 12:30 p.m. ET
Location: Orange County Convention Center, Poster Section 20
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**Equal contributions*
+Presenter

Summary of Presentation:

- In the YU-1077 intracranial tumor model derived from a patient with alectinib-resistant lung cancer, NVL-655 showed potent preclinical efficacy, consistent with its design as a brain-penetrant ALK TKI with activity against the G1202R mutation.
- These results—together with broad ALK mutational coverage, brain penetrance, and sparing TRK—further support NVL-655's preclinical profile that is differentiated from that of FDA/EMA-approved and other investigational ALK TKIs.

About NVL-655

NVL-655 is a novel brain-penetrant ALK-selective inhibitor created to overcome limitations observed with currently available ALK inhibitors. NVL-655 is designed to remain active in tumors that have developed resistance to first-, second-, and third-generation ALK inhibitors, including tumors with the solvent front G1202R mutation or compound mutations G1202R / L1196M ("GRLM"), G1202R / G1269A ("GRGA"), or G1202R/L1198F ("GRLF"). NVL-655 has been optimized for CNS penetrance to improve treatment options for patients with brain metastases. NVL-655 has been observed in preclinical studies to selectively inhibit wild-type ALK 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/ALK inhibitors and drive more durable responses for patients. NVL-655 is currently being investigated in the ALKOVE-1 study (NCT05384626), a first-in-human Phase 1/2 clinical trial for patients with advanced ALK-positive 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-655; the potential clinical effect of NVL-655; the design and enrollment of the ALKOVE-1 study; the potential of Nuvalent's pipeline programs, including NVL-655; 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 ALKOVE-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; risks that Nuvalent may not be able to nominate drug candidates from its discovery programs; 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 ALKOVE-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 Annual Report on Form 10-K for the fiscal year ended December 31, 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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