Nuvalent Announces Publication in Cancer Discovery Detailing Design and Characterization of ALK-selective inhibitor NVL-655

Publication provides comprehensive assessment of NVL-655's preclinical activity and includes preliminary clinical case studies

CAMBRIDGE, Mass., Sept. 13, 2024 /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-655 and details Nuvalent's approach to rationally targeting ALK. NVL-655 is currently being studied in the ongoing ALKOVE-1 Phase 1/2 clinical trial for patients with advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors.

The manuscript, entitled "NVL-655 is a selective and brain-penetrant inhibitor of diverse ALK mutant oncoproteins, including lorlatinib-resistant compound mutations," is published online and can be accessed here: https://aacrjournals.org/cancerdiscovery/article/doi/10.1158/2159-8290.CD-24-0231/748436/NVL-655-Is-a-Selective-and-Brain-Penetrant

"Currently available ALK tyrosine kinase inhibitors (TKIs) are important treatment options for patients with ALK-driven lung cancer. However, limitations including treatment-emergent drug resistance, off-target neurological adverse events, and inadequate control of brain metastases, support the need for continued development in this disease," said senior author Alexander Drilon, MD, Chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center, and investigator in the ALKOVE-1 trial. "As detailed in this publication, preclinical characterization and preliminary clinical data provide a compelling rationale for the ongoing clinical investigation of NVL-655 and evaluation of its potential to address the limitations of available ALK TKIs for patients with ALK-positive NSCLC."

The manuscript details the design principles underlying the activity of NVL-655 against ALK single and compound resistance mutations, including the most commonly occurring resistance mutation, ALK G1202R. Additionally, it outlines a molecular rationale for the selectivity of NVL-655 for ALK over the structurally related tropomyosin receptor kinase (TRK) family, whose inhibition has been associated with neurological adverse events that can be dose limiting. Preclinical characterization of the activity and selectivity of NVL-655 is presented, including *in vivo* xenograft studies, preclinical assessments of brain penetrance and intracranial activity, and a comparison of eight ALK TKIs across multiple biochemical and cellular assays.

The manuscript further documents three case studies from the ALKOVE-1 trial of patients with ALK fusion-positive lung cancers who had received a range of ALK TKIs, including lorlatinib, and presented with brain metastases or with tumors that harbored ALK G1202R. NVL-655 elicited tumor responses in these patients without accompanying CNS effects attributed to off-target TRK inhibition. These findings support the potential for NVL-655 as a future treatment for these patient populations that may also enhance tolerability through improved selectivity for ALK.

"With this publication in *Cancer Discovery*, we are pleased to have now also elucidated our focused approach for ALK-positive NSCLC. Along with our parallel lead program for ROS1-positive NSCLC, these selective inhibitors form the foundation for our pipeline of *precisely* targeted therapies which aim to deliver potential best-in-class activity against recalcitrant targets through solving for multiple, and at times competing, challenges in structure-based drug design," said Joshua Horan, Ph.D., Vice President, Chemistry at Nuvalent. "We are grateful to our collaborators for their contributions to this manuscript and to the continued advancement of NVL-655."

Enrollment is ongoing in the global Phase 2 portion of the ALKOVE-1 Phase 1/2 clinical trial, designed with registrational intent. Updated data from the Phase 1 portion of the trial will be presented at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona, Spain during a Proffered paper session on Saturday September 14, 2024 from 9:30 – 9:40 a.m. CEST.

About NVL-655

NVL-655 is a novel brain-penetrant ALK-selective inhibitor created with the aim 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 single or compound treatment-emergent ALK mutations such as G1202R. In addition, NVL-655 is designed for central nervous system (CNS) penetrance to improve treatment options for patients with brain metastases, and to avoid inhibition of the structurally related tropomyosin receptor kinase (TRK) family. Together, these characteristics have the potential to avoid TRK-related CNS adverse events seen with dual TRK/ALK inhibitors and to drive deep, durable responses for patients across all lines of therapy. NVL-655 has received breakthrough therapy designation for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have been previously treated with two or more ALK tyrosine kinase inhibitors and orphan drug designation for ALK-positive NSCLC. NVL-655 is currently being evaluated in the Phase 2 portion of the ALKOVE-1 Phase 1/2 clinical trial, a first-in-human study of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors (NCT05384626).

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 investigational candidates for ROS1-positive, ALK-positive, and HER2-altered non-

small cell lung cancer, and multiple discovery-stage research programs.

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 expected timing of data announcements; the clinical development program for NVL-655; the potential clinical effect of NVL-655; the design and enrollment of the ALKOVE-1 trial, including its intended pivotal registration-directed design; 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," "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 trial 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 risk that results of earlier clinical trials may not be predictive of the results of later-stage clinical trials; the risk that data from our clinical trials may not be sufficient to support registration and that Nuvalent may be required to conduct one or more additional studies or trials prior to seeking registration of our product candidates; the occurrence of adverse safety events; risks that the FDA may not approve our potential products on the timelines we expect, or at all; risks of unexpected costs, delays, or other unexpected hurdles; the direct or indirect impact of public health emergencies or global geopolitical circumstances on the timing and anticipated timing and results of Nuvalent's clinical trials, strategy, and future operations, including the ALKOVE-1 trial; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; risks related to obtaining, maintaining, and protecting Nuvalent's intellectual property. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Nuvalent's Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2024, 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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