Nuvalent Investors

New Preclinical Data Supports Nuvalent Lead Programs in ROS1-Positive, ALK-Positive NSCLC

Nuvalent to present at AACR-NCI-EORTC Molecular Targets Conference

Data provided further evidence that NVL-520 and NVL-655 selectively inhibited ROS1 and ALK compared to TRKB, were brain-penetrant, and were active against drug-resistance mutations in preclinical models

CAMBRIDGE, Mass., Oct. 7, 2021 /PRNewswire/ -- Nuvalent, Inc., (Nasdaq: NUVL), a biopharmaceutical company focused on creating *precisely* targeted therapies for clinically proven kinase targets in cancer, provided new preclinical data on Thursday supporting advancement of its parallel lead programs in non-small cell lung cancer (NSCLC). NVL-520, a ROS1-selective inhibitor, and NVL-655, an ALK-selective inhibitor, were specifically designed to solve for the dual challenges of kinase resistance and selectivity which limit the activity and durability of currently available cancer therapies.

The data are available via three on-demand "short-talk" posters at the 2021 AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics, which runs from Oct. 7 through Oct. 10. The presentations detail additional preclinical evidence that NVL-520 and NVL-655 1) were active against both wild-type and various known resistance variants of ROS1 or ALK, respectively; 2) were brain-penetrant with the potential to address brain metastases; and 3) selectively inhibited their targets compared to the structurally related tropomyosin receptor kinase B (TRKB), thereby minimizing the potential for off-target TRKB-related central nervous system (CNS) adverse events. The posters will also be available on the Nuvalent website.

"The Nuvalent discovery team operates under an ethos of thorough investigation, with the goal of ensuring that we nominate drug candidates that best embody the product profiles we have defined in close collaboration with physician-scientists," said Henry Pelish, Ph.D., Vice President of Biology at Nuvalent and a presenting poster author. "This is exemplified in our approach to comprehensive *in vitro* characterization of target selectivity compared to the structurally similar kinase TRKB during the discovery and early development of both NVL-520 and NVL-655, which we detail here.

"Our physician-scientist collaborators are instrumental not only in helping us to identify the desired product characteristics that we believe are most impactful to treatment paradigms today, but also in furthering the investigation of our compounds," continued Dr. Pelish. "It has been a privilege to work closely alongside Dr. Aaron Hata's group at Mass General Cancer Center to generate the new data presented here in support of the broad preclinical activity of NVL-520 against ROS1 wild type and resistance variants. We look forward to continued collaboration as we work to advance NVL-520 and NVL-655 into clinical studies, and further mature our discovery programs."

Aaron N. Hata, M.D., Ph.D., is a Nuvalent scientific advisor and co-author whose lab at Mass General Cancer Center in Boston focuses on advancing targeted therapies for patients with lung cancer.

"Resistance mutations, off-target adverse events, and brain metastases present significant challenges in the development of the next-generation of targeted therapies for kinases such as ROS1 and ALK," said Dr. Hata. "I am encouraged by the growing body of preclinical data showing that both NVL-520 and NVL-655 maintained selective inhibition of their targets even in the presence of a wide variety of resistance mutations and displayed the important combination of both TRKB selectivity and brain penetrance to open up the potential to treat brain metastases while avoiding off-target CNS adverse events. Together, this combination of characteristics may have the potential to drive more durable responses for patients."

The U.S. Food and Drug Administration has cleared the company's Investigational New Drug application for NVL-520. Nuvalent plans to initiate the Phase 1 portion of a First-in-Human (FIH) Phase 1/2 clinical trial for NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors in the second half of 2021. Nuvalent plans to initiate the Phase 1 portion of a FIH Phase 1/2 clinical trial investigating NVL-655 in advanced ALK-positive NSCLC and other cancers during the first half of 2022.

AACR-NCI-EORTC Presentation Overview:

***Presenting author**

Title: Preclinical Antitumor Activity of NVL-520 in Patient-Derived Models Harboring ROS1 Fusions, Including G2032R Solvent Front Mutation
Authors: Amit Deshpande, Satoshi Yoda, Anupong Tangpeerachaikul, Nancy E. Kohl, Joshua C. Horan, Aaron N. Hata, Henry E. Pelish*
Poster Number: P249

Summary of Presentation:

- NVL-520 is a potent, highly selective, and brain-penetrant ROS1 inhibitor as previously demonstrated by *in vitro* and *in vivo* studies.
- NVL-520 demonstrated potent activity against multiple additional ROS1+ NSCLC patient-derived *in vitro* cell line (PDC) and *in vivo* xenograft (PDX) models.
- Activity was observed irrespective of fusion partner and against both the wild-type and TKI-resistant solvent front mutation (G2032R) ROS1 kinase domain.
- Pharmacodynamic analysis of tumors from mice treated with NVL-520 revealed a dose-dependent reduction in ROS1 levels, markers of downstream signaling, and cell proliferation across multiple models of ROS1-driven disease.

Title: NVL-655 Exhibits Antitumor Activity in Lorlatinib-Resistant Subcutaneous and Intracranial Models of ALK-Rearranged NSCLC
Authors: Anupong Tangpeerachaikul*, Amit Deshpande, Nancy E. Kohl, Joshua C. Horan, Henry E. Pelish
Poster Number: P244

Summary of Presentation:

- NVL-655 is a potent and brain-penetrant ALK inhibitor as demonstrated by activity in a mouse intracranial tumor model study.
- NVL-655 showed activity against a wide variety of ALK mutations, particularly G1202R+ mutations, whether as a single mutation (G1202R) or as compound mutations (G1202R/L1196M and G1202R/G1269A).
- Activity was observed both *in vitro* and *in vivo* across various contexts, including fusion partners, EML4 breakpoint variants, and tumor contexts.

Title: Evaluating TRKB Activity of Novel Preclinical Brain-Penetrant ROS1 and ALK Inhibitors
Authors: Anupong Tangpeerachaikul*, Joshua C. Horan, Henry E. Pelish
Poster Number: P247

Summary of Presentation:

- TRKB-related central nervous system adverse events present a key challenge for the development of brain-penetrant ROS1 and ALK therapies, as both on-target kinases exhibit ~70% kinase domain similarity to the off-target TRKB.
- Nuvalent devised a multi-assay approach to evaluate TRKB inhibition and guide the discovery of selective ROS1 and ALK inhibitors, with the goal of minimizing adverse events and driving durable responses for patients.
- Leveraging multiple biochemical and cell-based assays increases confidence that results are reproducible across various biological contexts.
- All examined assays indicated that NVL-520 and NVL-655 were highly selective for their wild-type and treatment-resistant oncogenic targets over TRKB.

About Nuvalent
Nuvalent, Inc. (Nasdaq: NUVL) is a preclinical 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 NSCLC, along with 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 progress and timing of the preclinical and clinical development of Nuvalent's programs, including NVL-520 and NVL-655; the potential clinical effect of NVL-520 and NVL-655; expectations regarding the planned clinical trial initiation of NVL-520 and NVL-655, including timing; 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," "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 associated with: the impact of COVID-19 on countries or regions in which Nuvalent has operations or does business, as well as on the timing and anticipated timing and results of its clinical trials, strategy, and future operations, including the planned initiation of the Phase 1 portion of a global Phase 1/2 clinical trial for NVL-520 and a Phase 1/2 clinical trial for NVL-655; Nuvalent's expectations regarding the preclinical data for NVL-520 and NVL-655 presented at the AACR-NCI-EORTC Molecular Targets Conference, including the potential therapeutic benefit of its lead product candidates; unexpected concerns that may arise from additional data, analysis, or results obtained during clinical trials; the occurrence of adverse safety events; risks of unexpected costs, delays, or other unexpected hurdles; 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 quarter ended June 30, 2021 as well as any 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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