Nuvalent Presents New Preclinical Data Supporting Profiles of HER2-Selective Inhibitor, NVL-330, and ROS1-Selective Inhibitor, Zidesamtinib, at AACR Annual Meeting 2024

Preclinical data continue to support NVL-330's broad activity against HER2 oncogenic alterations, selectivity over wild-type EGFR, and differentiated

brain-penetrant profile

Zidesamtinib shown to be effective at suppressing on-target ROS1 resistance mutations in preclinical mutagenesis screens

CAMBRIDGE, Mass., April 8, 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 presentation of new preclinical data for its novel HER2-selective inhibitor, NVL-330, and novel ROS1-selective inhibitor, zidesamtinib (NVL-520). The two posters will be presented at the American Association for Cancer Research (AACR) Annual Meeting taking place from April 5 – 10 in San Diego. The posters will also be available on the Nuvalent website at www.nuvalent.com following the presentations.

"Today's presentations continue to reinforce the differentiated profiles of our drug candidates," said Henry Pelish, Ph.D., Senior Vice President of Drug Discovery at Nuvalent. "In comparative *in vitro* and *in vivo* analyses of NVL-330 with currently approved and investigational HER2-targeting agents, NVL-330 demonstrated a differentiated preclinical profile by achieving higher CNS penetration and deeper intracranial response. Importantly, in these preclinical studies, NVL-330 also demonstrated potency against a broad range of HER2 oncogenic alterations and selectivity over wild-type EGFR, in line with our goal of designing molecules that can thread the needle between multiple competing challenges."

Dr. Pelish continued, "In our ongoing ARROS-1 clinical trial of zidesamtinib, preliminary Phase 1 data has demonstrated a differentiated profile combining activity against ROS1 resistance mutations, CNS penetrance, and TRK avoidance which we believe has the potential to translate to deep, durable responses for patients with ROS1-driven cancers. A new preclinical mutagenesis screen reinforces this potential, showing that on-target resistance is unlikely following treatment with zidesamtinib at its average observed clinical concentration."

In 2024, the company expects to initiate a Phase 1 trial for its HER2 program and to share updated data from the ARROS-1 trial at a medical meeting.

AACR Presentation Overviews:

Title: Preclinical characterization of NVL-330, a selective and brain penetrant HER2 tyrosine kinase inhibitor with broad activity on HER2 oncogenic alterations
Authors: Yuting Sun*[1], Kristin L. Andrews[1], Anupong Tangpeerachaikul[1], Tuan M. Nguyen[1], Baudouin Gerard[1], Nancy E. Kohl[2], Joshua C. Horan[1], Henry E. Pelish[1]
Abstract Number: 1979
Session Category: Experimental and Molecular Therapeutics
Session Title: Kinase and Phosphatase Inhibitors 2
Session Date and Time: Monday April 8, 2024, from 9:00 –12:30 p.m. PT
Location: Poster Section 25

Presentation summary:

- NVL-330 had broad preclinical activity on HER2 oncogenic alterations, including HER2 exon20ins, HER2 activating point mutations, and amplified wild-type HER2.

- In a preclinical comparison with the selective tyrosine kinase inhibitor, zongertinib, NVL-330 demonstrated:
    - Similar potency and selectivity over wild-type EGFR; and,
    - Higher CNS penetrance.
- In a preclinical comparison with antibody drug conjugate, T-DXd (Enhertu), NVL-330 demonstrated:
    - Deeper response and higher CNS penetrance in an intracranial tumor model; and,
    - Activity in cells with acquired resistance to T-DXd.

Title: Mutagenesis screens support potential best-in-class profile for selective, brain-penetrant, and TRK-sparing ROS1 inhibitor zidesamtinib (NVL-520)
Authors: Anupong Tangpeerachaikul*[1], Franklin Gu[1], Henry E. Pelish[1]
Abstract Number: LB182
Session Title: Late-Breaking Research: Experimental and Molecular Therapies 2
Session Date and Time: Monday April 8, 2024, from 1:30 –5:00 p.m. PT
Location: Poster Section 52

Presentation summary:

- Comparison of the clinical concentration of zidesamtinib to its efficacious in vitro concentration suggests a potential for a deep and sustained inhibition of ROS1 and ROS1 G2032R fusions in humans, including in the CNS.
- Zidesamtinib effectively suppressed on-target resistance in ENU mutagenesis screens with both ROS1 and ROS1 G2032R fusions, predicting that on-target resistance is unlikely when used as either a first-line or a later-line therapy.
- On-target resistance is predicted to be more likely for earlier-generation ROS1 inhibitors crizotinib, entrectinib, and potentially repotrectinib as a first-line therapy.
- These mutagenesis screens provide additional preclinical support for zidesamtinib's potential to drive deep and durable responses for patients with ROS1-driven cancers.

**Presenter, corresponding author; [1]Nuvalent, Inc., Cambridge, MA, USA; [2]Kohl Consulting, Wellesley, MA, USA*

About NVL-330
NVL-330 is a novel brain-penetrant HER2-selective tyrosine kinase inhibitor designed to address the combined medical need of treating HER2-mutant tumors, including those with HER2 exon 20 insertion mutations, avoiding treatment related adverse events due to off-target inhibition of wild-type EGFR, and treating brain metastases.

About zidesamtinib (NVL-520)
Zidesamtinib is a novel brain-penetrant ROS1-selective inhibitor created with the aim to overcome limitations observed with currently available ROS1 inhibitors. Zidesamtinib is designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with treatment-emergent ROS1 mutations such as G2032R. In addition, zidesamtinib 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/ROS1 inhibitors and to drive deep, durable responses for patients across all lines of therapy. Zidesamtinib has received breakthrough therapy designation for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have been previously treated with 2 or more ROS1 tyrosine kinase inhibitors and orphan drug designation for ROS1-positive NSCLC. Zidesamtinib is currently being investigated in the ARROS-1 trial (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced ROS1-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 investigational candidates for ROS1-positive, ALK-positive, and HER2-positive 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 development programs for zidesamtinib (NVL-520) and NVL-330; the potential benefits of zidesamtinib and NVL-330; the potential of Nuvalent's pipeline programs, including zidesamtinib and NVL-330; 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: 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; risks that Nuvalent may not be able to nominate drug candidates from its discovery programs; 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; the timing and outcome of Nuvalent's planned interactions with regulatory authorities; and 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 Annual Report on Form 10-K for the fiscal year ended December 31, 2023, 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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