Nuvalent Announces New Preclinical Data for Selective Kinase Inhibitors NVL-330 and NVL-655

Preclinical data demonstrated that NVL-330 inhibits HER2 exon 20 insertion mutations, is selective for HER2 versus wild-type EGFR, and is brain-penetrant

NVL-655 preclinical data further support its best-in-class potential for patients with advanced ALK-

positive NSCLC and other solid tumors

Data Presented at the 34th EORTC-NCI-AACR (ENA) Symposium

CAMBRIDGE, Mass., Oct. 26, 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 presentation of new preclinical data for NVL-330, its recently nominated HER2-selective inhibitor, and NVL-655, its ALK-selective inhibitor currently under investigation in the ALKOVE-1 Phase 1/2 study for advanced ALK-positive non-small cell lung cancer (NSCLC) and other solid tumors.

The two posters will be presented at the EORTC-NCI-AACR (ENA) 2022 symposium taking place October 26-28, 2022 in Barcelona, Spain. The posters will also be available on the Nuvalent website.

"We believe the new preclinical data for NVL-330 and NVL-655 continue to support Nuvalent's foundational approach to the discovery of therapeutics which aim to solve for multiple, and sometimes competing, challenges in structure-based drug design," said Henry Pelish, Ph.D., Vice President of Drug Discovery at Nuvalent. "This first presentation of NVL-330's preclinical profile demonstrates the target characteristics set out for this program to address medical needs identified in collaboration with leading physician-scientists, including activity against tumors driven by HER2 exon 20 insertion mutations, selectivity for HER2 versus wild-type EGFR, and brain penetrance."

Preliminary data from the Phase 1 portion of the ARROS-1 study of Nuvalent's parallel lead program, NVL-520, will also be presented at the "New Drugs on the Horizon" oral plenary session on October 28, 2022.

"In our view, these NVL-330 and NVL-655 presentations, along with our NVL-520 clinical data presentation later this week, embody the rapid progress and growth we continue to achieve across our pipeline," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "NVL-330, our third novel drug candidate since company creation four years ago, is not only an exciting addition to our portfolio of selective kinase inhibitors but also a testament to our team's continued ability to advance novel discovery programs while executing in parallel against our development goals."

NVL-330 and NVL-655 Presentation Overviews
Title: NVL-330 is a selective, brain-penetrant inhibitor of oncogenic HER2 exon 20 insertion mutations in preclinical models
Poster Number: 212
Session Title: Poster Session, Molecular Targeted Agents 2
Session Date and Time: October 27, 2022, 10:00 a.m. - 5:00 p.m. CEST
Presenter: Kristin L. Andrews, Ph.D. (Nuvalent, Cambridge, USA)

NVL-330 is a novel, brain-penetrant HER2-selective tyrosine kinase inhibitor targeting HER2 exon 20 insertion mutations (HER2ex20). It was specifically designed with the aim to address the combined medical need of treating tumors driven by HER2ex20, avoiding treatment-limiting adverse events due to off-target inhibition of wild-type EGFR, and treating brain metastases. HER2ex20 are oncogenic driver mutations in an estimated 1-3% of all NSCLC, yet there are limited therapeutic options targeting these mutations.

The data presented at ENA represent the first characterization of this new development candidate. Preclinical data

demonstrated that NVL-330 potently inhibited HER2ex20 in cell-based assays and was highly selective for HER2ex20 over the structurally related wild-type EGFR. This selectivity is a critical aspect of NVL-330's design given that inhibition of wild-type EGFR is associated with dose-limiting side effects including skin rash and gastrointestinal toxicity.

In addition, the demonstrated preclinical brain penetrance and intracranial activity of NVL-330 suggests the potential for treating or preventing brain metastases. Brain metastases are present at diagnosis in an estimated 19% of *HER2* mutant-positive NSCLC patients, and more patients will develop them during treatment.

Title: Preclinical activity of NVL-655 in patient-derived models of ALK cancers, including those with lorlatinib-resistant G1202R/L1196M compound mutation
Poster Number: 218
Session Title: Poster Session, Molecular Targeted Agents 2
Session Date and Time: October 27, 2022, 10:00 a.m. - 5:00 p.m. CEST
Presenter: Anupong Tangpeerachaikul, Ph.D. (Nuvalent, Cambridge, USA)

NVL-655 is a brain penetrant, ALK-selective inhibitor with potent activity observed in preclinical studies across diverse tumor types, ALK alterations, and single and compound resistance mutation variants - some of which confer resistance to all other approved ALK kinase inhibitors.

This poster presentation adds to the growing body of data demonstrating NVL-655's well characterized preclinical profile. It includes new preclinical data in additional patient-derived models harboring single and compound ALK resistance mutations. Notably, NVL-655 induced regression in an in vivo model derived from a patient with ALK fusion-positive NSCLC harboring G1202R/L1196M compound mutation after disease progression on sequential crizotinib, alectinib and lorlatinib treatment. Among all inhibitors tested, we observed that NVL-655 showed the broadest preclinical activity across ALK fusion partners and resistance mutations while maintaining a wide selectivity window over TRKB.

Clinical investigation of NVL-655 is currently ongoing in the Phase 1 portion of the ALKOVE-1 Phase 1/2 study of NVL-655 for patients with advanced ALK-positive NSCLC and other solid tumors.

About NVL-330
NVL-330 is a novel, brain-penetrant HER2-selective tyrosine kinase inhibitor targeting HER2 exon 20 insertion mutations (HER2ex20). It was specifically designed to address the combined medical need of treating tumors driven by HER2ex20 mutations, avoiding treatment-limiting adverse events due to off-target inhibition of wild-type EGFR, and treating brain metastases.

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 designed 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 ½ clinical trial for patients with advanced ALK-positive 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, NVL-655 and NVL-330; the potential clinical effect of NVL-520 and NVL-655; the potential benefits of NVL-330; the design and enrollment of the ARROS-1 and ALKOVE-1 studies; the potential of Nuvalent's pipeline programs, including NVL-520, NVL-655 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: risks that Nuvalent may not fully enroll the ARROS-1 or ALKOVE-1 studies 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 ALK IXDN and other 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 ARROS-1 and ALKOVE-1 studies; 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 June 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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