Nuvalent Investors

Nuvalent to Present Preliminary Phase 1 Data from ARROS-1 Clinical Trial of NVL-520 at 34th EORTC-NCI-AACR Symposium and Announces Pipeline Updates

Preliminary Dose Escalation Data on ROS1-selective Inhibitor NVL-520 to be Presented in the "New Drugs on the Horizon" Oral Plenary Session

New Preclinical Data to be Presented on Parallel-lead, Clinical-stage Candidate NVL-655, an ALK-selective Inhibitor

Selection of Third Development Candidate NVL-330, a Potential Best-in-Class HER2-selective Inhibitor for Patients with HER2 Exon 20 Insertion-Positive Cancers, and Preclinical Characterization to be Presented

Company Plans to Host Conference Call in Conjunction with Data Presentation on October 28, 2022

CAMBRIDGE, Mass., Sept. 7, 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 it will present preliminary dose escalation data from its ongoing ARROS-1 Phase 1/2 clinical trial of NVL-520 for patients with advanced ROS1-positive non-small cell lung cancer (NSCLC) and other solid tumors during an oral plenary session at the 34th EORTC-NCI-AACR (ENA) Symposium taking place October 26-28, 2022 in Barcelona, Spain. In addition, new preclinical data will be presented in poster sessions for its ALK-selective inhibitor NVL-655 and its recently nominated HER2-selective inhibitor, NVL-330.

The NVL-520 oral presentation represents the first report of preliminary safety and clinical activity data from the dose-escalation portion of the company's ongoing Phase 1/2 ARROS-1 study, evaluating NVL-520 in patients with advanced ROS1-positive NSCLC and other solid tumors. NVL-520 has been designed to address the clinical challenges of emergent treatment resistance, off-target central nervous system (CNS) adverse events, and brain metastases that may limit the use of currently available ROS1 kinase inhibitors. The ARROS-1 clinical trial is continuing to enroll patients in the Phase 1 portion of the study.

The NVL-655 poster presentation will describe new preclinical data demonstrating activity of NVL-655 in additional models derived from patients who have progressed on treatment with earlier-generation ALK inhibitors. NVL-655 has previously demonstrated the potential for a best-in-class profile through broad preclinical activity across diverse ALK oncoproteins, single and compound resistance mutations, and tumor types while maintaining strong selectivity for ALK over TRKB and CNS penetrance.

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. Nuvalent also continues to advance a discovery program for ALK IXDN compound mutations and plans to leverage insights from the ALKOVE-1 clinical trial to guide development candidate selection, which is no longer planned for 2022.

Nuvalent recently selected NVL-330 as the development candidate from its HER2 exon 20 insertion discovery program. Preclinical characterization of NVL-330 as a HER2-selective, brain-penetrant, small molecule inhibitor with activity against HER2 exon 20 insertion mutations will be shared in a poster presentation.

Nuvalent plans to host a conference call and webcast in conjunction with the data presentation on October 28, 2022. Details for the conference call will be provided at a future date, and, once available, presentation and poster information will be archived on the Nuvalent website at www.nuvalent.com.

Details for the presentations are as follows:

Title: Safety and preliminary clinical activity of NVL-520, a highly selective ROS1 inhibitor, in patients with advanced ROS1 fusion-positive solid tumors
Abstract Number: ENA22-0275
Session Topic: Molecular Targeted Agents
Session Title: New Drugs on the Horizon, Plenary Session 6

Session Date and Time: October 28, 2022, 1:00 p.m. - 1:10 p.m. CEST
Presenter: Alexander Drilon, M.D. (Memorial Sloan Kettering Cancer Center, New York, USA)

Title: Preclinical activity of NVL-655 in patient-derived models of ALK cancers, including those with lorlatinib-resistant G1202R/L1196M compound mutation
Abstract Number: ENA22-0105
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)

Title: NVL-330 is a selective, brain-penetrant inhibitor of oncogenic HER2 exon 20 insertion mutations in preclinical models
Abstract Number: ENA22-0150
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)

About NVL-520
NVL-520 is a novel brain-penetrant ROS1-selective inhibitor designed to remain active in tumors that have developed resistance to currently available ROS1 inhibitors, including tumors with the prevalent G2032R resistance mutation and those with the S1986Y/F, L2026M, or D2033N resistance mutations. NVL-520 has been optimized for brain penetrance to potentially improve treatment options for patients with brain metastases. NVL-520 has been observed in preclinical studies to selectively inhibit wild-type ROS1 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/ROS1 inhibitors and drive more durable responses for patients. NVL-520 is currently being investigated in the ARROS-1 study (NCT05118789), a first-in-human Phase 1/2 clinical trial for patients with advanced non-small cell lung cancer (NSCLC) and other solid tumors.

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 non-small cell lung cancer (NSCLC) and other solid tumors.

About NVL-330
NVL-330 is a novel, selective, brain-penetrant HER2 inhibitor designed to treat patients with HER2 exon 20 insertion-positive tumors, including those with brain metastases, and to minimize adverse events and dose-limiting toxicities related to off-target inhibition of epidermal growth factor receptor ("EGFR" or "ErbB1"), a HER2 family member.

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), 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 preclinical and clinical development programs for NVL-520, NVL-655 and NVL-330 the potential clinical effect of NVL-520 and NVL-655; 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 plans for ALK IXDN; data readouts and presentations; 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 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 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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