

Nuvalent Presents New Preclinical Data Supporting Potential Best-in-Class Profile for ALK-Selective Inhibitor NVL-655 at IASLC 2022 World Conference on Lung Cancer Annual Meeting

Trial in progress poster also to be presented for Phase 1/2 ARROS-1 study of ROS1-selective inhibitor NVL-520

company focused on creating *precisely* targeted therapies for clinically proven kinase targets in cancer, today announced new preclinical data supporting the potential best-in-class profile of NVL-655 – an ALK-selective inhibitor, and a "Trial in Progress" poster for the Phase 1/2 ARROS-1 study of NVL-520 – a ROS1-selective inhibitor. NVL-520 and NVL-655 are central nervous system (CNS)-penetrant kinase inhibitors designed to specifically solve for the dual challenges of kinase resistance and selectivity commonly observed with currently available inhibitors.

The two posters will be presented at the IASLC 2022 World Conference on Lung Cancer (WCLC) Annual Meeting taking place August 6-9, 2022 in Vienna, Austria. The posters will also be available on the [Nuvalent website](#).

"Our presentations at WCLC showcase the value that our collaborations with leading physician-scientists and translational investigators bring towards characterizing and developing our parallel lead programs for patients with non-small cell lung cancer (NSCLC)," said James Porter, Ph.D., Chief Executive Officer of Nuvalent. "We are grateful for our continued collaborations focused on advancing the understanding of resistance to kinase inhibitors, as well as the dedication and support of the Phase 1 clinical investigators participating in our ongoing studies for patients with advanced NSCLC and other solid tumors."

"We selected NVL-520 and NVL-655 based on the demonstrated strength of their preclinical profiles and their potential to drive deep, durable responses for patients with ROS1-positive and ALK-positive cancers, respectively. With both programs now under clinical investigation, we remain committed to continued, rigorous preclinical characterization to both deepen our understanding of our programs as well as to support the advancement of tools and models that may help accelerate the development of new therapies for genomically-driven cancers," said Henry Pelish, Ph.D., Vice President of Biology at Nuvalent. "We are pleased to share data further characterizing NVL-655 in a new patient-derived model of lorlatinib-resistant ALK-positive NSCLC with the treatment-emergent G1202R/T1151M compound resistance mutation, developed by our clinical and translational collaborators at Gustave Roussy."

The MR448re patient-derived model was established from cancer cells retrieved from a NSCLC patient previously treated with four prior ALK kinase inhibitors and most recently progressing following treatment with lorlatinib. Presence of an EML4-ALK fusion and the G1202R/T1151M compound mutation was confirmed by sequencing.

"The rapid development of the MR448re patient-derived model and subsequent evaluation of NVL-655 is a testament to the efficient cooperation between our clinical and translational investigators, and our collaborators at Nuvalent," said Luc Friboulet, Ph.D., investigator at Gustave Roussy. "NVL-655 showed strong antitumor activity in this heavily refractory model, while lorlatinib showed limited inhibitory activity consistent with treatment history. This further supports the differentiating and potentially best-in-class preclinical profile of NVL-655, which has previously demonstrated the ability to retain activity in the presence of a broad spectrum of single and compound ALK resistance mutations while maintaining a wide selectivity window over TRKB."

A "Trial in Progress" poster summarizing the preclinical profile of NVL-520 and clinical trial design of the Phase 1/2 ARROS-1 study ([NCT05118789](#)) for NVL-520 will also be presented. This multicenter, open-label, dose-escalation and expansion trial is designed to evaluate NVL-520 as an oral monotherapy for patients with advanced ROS1-positive NSCLC and other solid tumors. The ongoing Phase 1 dose-escalation portion of the study is currently enrolling ROS1-positive NSCLC patients who have previously received at least one ROS1 TKI, or patients with other ROS1-positive solid tumors previously treated with any prior therapy. Nuvalent plans to share preliminary dose-escalation data from ARROS-1 in the second half of 2022.

WCLC Presentation Overview:

Title: Preclinical Activity of NVL-655 in a Patient-Derived NSCLC Model with Lorlatinib-Resistant ALK G1202R/T1151M Mutation

Authors: H. Mizuta¹, L. Bigot¹, A. Tangpeerachaiku², H.E. Pelish², L. Friboulet¹

Abstract Number: EP08.02-020

Session Category: Metastatic Non-small Cell Lung Cancer

Session Title: Molecular Targeted Treatments

Session Date and Time: August 7, 2022, 9:45am – 6:00pm CEST

¹Gustave-Roussy, Villejuif, France; ²Nuvalent, Inc., Cambridge, MA, USA

Summary of Presentation:

- ALK G1202R single and compound mutations are recurrent mechanisms of resistance to previous-generation therapies, including alectinib and lorlatinib.
- NVL-655 showed strong antitumor activity in preclinical models derived from ALK positive patients who have progressed on treatment with earlier-generation ALK inhibitors, including a G1202R/T1151M compound mutation model derived from a patient previously treated with crizotinib, alectinib, brigatinib, and lorlatinib.
- Among all inhibitors tested, NVL-655 continues to show the broadest activity across ALK fusion partners and resistance mutations while maintaining a wide selectivity window over TRKB.
- NVL-655 is currently being evaluated in the Phase 1/2 ALKOVE-1 study for patients with advanced ALK+ NSCLC and

other solid tumors, including those with ALK resistance mutations and CNS metastases ([NCT05384626](#)).

Title: NVL-520, a Highly Selective ROS1 Inhibitor, in Patients with Advanced ROS1-Positive Solid Tumors: The Phase 1/2 ARROS-1 Study

Authors: A. Drilon¹, S.-H.I. Ou², S. Gadgee³, M. Johnson⁴, A. Spira⁵, G. Lopes⁶, B. Besse⁷, E. Felip⁸, A.J. van der Wekken⁹, A. Calles¹⁰, M.J. de Miguel¹¹, D.R. Camidge¹², Y. Elamin¹³, S. Liu¹⁴, J. Bauman¹⁵, D. Haggstrom¹⁶, G. Riley¹⁷, H.E. Pelish¹⁷, V.W. Zhu¹⁷, J.J. Lin¹⁸

Abstract Number: EP08.02-041

Session Category: Metastatic Non-small Cell Lung Cancer

Session Title: Molecular Targeted Treatments

Session Date and Time: August 7, 2022, 9:45am – 6:00pm CEST

¹Memorial Sloan Kettering Cancer Center, New York/NY/USA, ²University Of California Irvine Medical Center, Orange/CA/USA, ³Henry Ford Cancer Institute, Detroit/MI/USA, ⁴Sarah Cannon Research Institute, Nashville/TN/USA, ⁵NEXT Oncology - Virginia Cancer Specialists, Fairfax/VA/USA, ⁶Sylvester Comprehensive Cancer Center at the University of Miami and the Miller School of Medicine, Miami/FL/USA, ⁷Institut Gustave Roussy, Villejuif Cedex/FR, ⁸Hospital Vall d'Hebron, Barcelona/ES, ⁹University of Groningen, University Medical Centre Groningen, Groningen/NL, ¹⁰Hospital Universitario Gregorio Marañón, Madrid/ES, ¹¹START Madrid-HM CIOCC, Madrid/ES, ¹²University of Colorado Cancer Center, Anschutz Medical Campus, Aurora/CO/USA, ¹³MD Anderson Cancer Center, Houston/TX/USA, ¹⁴Georgetown University, Washington/DC/USA, ¹⁵Fox Chase Cancer Center, Philadelphia/PA/USA, ¹⁶Levine Cancer Institute, Atrium Health, Charlotte/NC/USA, ¹⁷Nuvalent, Inc., Cambridge/MA/USA, ¹⁸Massachusetts General Hospital, Boston/MA/USA

Summary of Presentation:

- NVL-520 has demonstrated CNS activity and potent and selective inhibition of ROS1 & ROS1 G2032R over TRKB in preclinical models. These data indicate the potential to minimize TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1+ tumors, including those with ROS1 resistance mutations and CNS metastases.
- ARROS-1 is a Phase 1/2 study evaluating the safety and activity of NVL-520 in patients with advanced ROS1+ NSCLC and other solid tumors, including those with ROS1 resistance mutations and CNS metastases.
- The Phase 1 portion of the study is open and actively enrolling in the USA, Spain, the Netherlands, and France, with further global expansion planned.
- Phase 2 cohorts are designed to support potential registration in TKI-naïve or previously treated ROS1+ NSCLC.

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-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 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](https://twitter.com/nuvalent)) and [LinkedIn](https://www.linkedin.com/company/nuvalent).

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 clinical development programs for NVL-520 and NVL-655 and the timing thereof; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 and ALKOVE-1 studies and the timing thereof; the potential of Nuvalent's pipeline programs, including NVL-520 and NVL-655; Nuvalent's research and development programs for the treatment of cancer; risks and uncertainties associated with drug development; and capital allocation. 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 HER2 Exon 20 and ALK IXDN 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 Annual Report on Form 10-K for the year ended December 31, 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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<https://investors.nuvalent.com/2022-08-05-Nuvalent-Presents-New-Preclinical-Data-Supporting-Potential-Best-in-Class-Profile-for-ALK-Selective-Inhibitor-NVL-655-at-IASLC-2022-World-Conference-on-Lung-Cancer-Annual-Meeting>