Nuvalent Presents Preclinical Data Demonstrating That ROS1 Inhibitor NUV-520 and ALK Inhibitor NUV-655 are Selective, Brain-Penetrant, and Active Against Drug-Resistance Mutations

Preclinical data presented at the 2021 AACR Annual Virtual Meeting supports

advancement of parallel lead programs in ROS1-positive and ALK-positive NSCLC

Leading medical oncologist Alexander Drilon, M.D. appointed to Scientific Advisory Board

Cambridge, Mass., April 10, 2021 – Nuvalent, Inc., a biotechnology company creating precisely targeted therapies for clinically proven kinase targets in cancer, today announced preclinical data supporting advancement of its parallel lead programs in non-small cell lung cancer (NSCLC), including NUV-520 – a potential best-in-class ROS1-selective inhibitor – and NUV-655 – an ALK-selective inhibitor. Data are being presented at the 2021 American Association for Cancer Research (AACR) Virtual Annual Meeting from April 10-15 in two separate poster presentations. Posters will be archived on the Nuvalent website at www.nuvalent.com.

In addition, Nuvalent announces the appointment of leading medical oncologist Alexander Drilon, M.D., to its Scientific Advisory Board (SAB). Dr. Drilon currently serves as Chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center (MSK) and brings deep expertise in early-phase clinical trials for cancer. At MSK, his research focuses on the development of novel therapeutics for cancer patients who have developed drug-resistance mutations.

“Our parallel lead compounds NUV-520 and NUV-655 were designed to meet a precise set of patient needs identified through close partnership with leading physician-scientists and advisors. We are pleased to share the data leading to the selection of these drug candidates for advancement towards clinical studies based on their demonstrated preclinical ability to meet the identified needs of selectivity, brain penetrance, and activity against drug-resistance mutations in ROS1-and ALK-driven tumors,” said James Porter, Ph.D., Chief Executive Officer at Nuvalent. “We are also excited to welcome Dr. Alexander Drilon to our Scientific Advisory Board as part of this ongoing partnership with leading physician-scientists to understand the limitations of existing cancer therapies, with the goal of developing precisely targeted therapies to treat cancer.”

NUV-520 and NUV-655 are designed to specifically solve for the dual challenges of kinase resistance and selectivity commonly seen with other kinase inhibitors approved for the treatment of advanced NSCLC. NUV-520 selectively inhibits ROS1 compared to the structurally related tropomyosin receptor kinase (TRK) with the potential to minimize TRK-related central nervous system (CNS) adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1-mutant variants. NUV-655 is designed to inhibit ALK fusions and remain active in tumors that have developed resistance to first-, second-, and third-generation ALK inhibitors.

In addition to selective ROS1 and ALK inhibition, Nuvalent is exploring a robust pipeline of programs with a focus

on addressing the limitations of existing therapies for other clinically proven kinase targets in oncology.

“I am both encouraged by the treatment opportunities that targeted kinase inhibitors have enabled for patients and inspired to continue pursuing the development of additional therapy options that can overcome remaining clinical challenges,” said Dr. Drilon. “Drug-resistant mutations and off-target adverse events can limit the therapeutic impact of kinase inhibitors across various targets in NSCLC as well as other tumor types. I look forward to working with Nuvalent to inform clinical development and advance its novel discovery pipeline of precisely targeted therapies designed specifically to meet these challenges.”

AACR 2021 Presentation Overview:

Title: NUV-520 is a brain-penetrant and highly selective ROS1 inhibitor with antitumor activity against the G2032R solvent front mutation

Authors: Henry E. Pelish*, Anupong Tangpeerachaikul, Nancy E. Kohl, James R. Porter, Matthew D. Shair, Joshua C. Horan

Poster Number: 1465

Session Title: PO.ET06.07 Tyrosine Kinase and Phosphatase Inhibitors

Date: April 10, 2021, 8:30 a.m. – 11:59 p.m.

Summary:

- NUV-520 is a potent, highly selective, and brain-penetrant ROS1 inhibitor as demonstrated by *in vitro* and *in vivo* studies.
- NUV-520 has broad activity against ROS1 resistance mutations, including G2032R, and multiple ROS1 fusions.
- NUV-520 is highly selective for ROS1 and ROS1 G2032R over TRKB, indicating the potential to minimize TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1 mutations.

Title: NUV-655 is a selective, brain-penetrant ALK inhibitor with antitumor activity against the lorlatinib-resistant G1202R/L1196M compound mutation

Authors: Henry E. Pelish*, Anupong Tangpeerachaikul, Nancy E. Kohl, James R. Porter, Matthew D. Shair, Joshua C. Horan

Poster Number: 1468

Session Title: PO.ET06.07 Tyrosine Kinase and Phosphatase Inhibitors

Date: April 10, 2021, 8:30 a.m. – 11:59 p.m.

Summary:

- NUV-655 is a potent, selective, and brain-penetrant ALK inhibitor as demonstrated by *in vitro* and *in vivo* studies.
- NUV-655 is active against G1202R+ mutations including compound mutations G1202R/L1196M, G1202R/G1269A, and G1202R/L1198F, which confer resistance to all approved ALK therapies.
- NUV-655 is selective for ALK and ALK G1202R+ mutations over TRKB, indicating the potential to minimize TRK-related CNS adverse events and drive more durable responses for patients.

About Nuvalent

Nuvalent, Inc. is 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 structure-based design, Nuvalent develops innovative small molecules with exquisite target selectivity to overcome resistance, minimize adverse events, 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. To learn more, visit www.nuvalent.com and follow us on Twitter and LinkedIn.
