Updated Data for Nuvalent's ALK-Selective Inhibitor, NVL-655, and ROS1-Selective Inhibitor, Zidesamtinib, Continue to Support Potential Best-in-Class Profiles

Updated Phase 1 data from ALKOVE-1 and ARROS-1 clinical trials to be presented at the ESMO Congress 2024

Durable activity of NVL-655 and

zidesamtinib in heavily pre-treated patient populations supports ongoing Phase 2 investigation in earlier lines of treatment

Company plans to host a conference call on September 14, 2024 at 8:30 a.m. ET/2:30 p.m. CEST following oral presentations at ESMO

CAMBRIDGE, Mass., Sept. 9, 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 data from abstracts to be presented at the European Society for Medical Oncology (ESMO) Congress 2024 in Barcelona, Spain, including updates from the Phase 1 portions of the ongoing ALKOVE-1 Phase 1/2 clinical trial of ALK-selective inhibitor NVL-655 and ARROS-1 Phase 1/2 clinical trial of ROS1-selective inhibitor zidesamtinib, and new preclinical data further characterizing the intracranial activity of zidesamtinib accepted for a poster session.

The Phase 1 data described in the abstracts will be updated in two oral presentations at ESMO and discussed during a live webcast and conference call with management on Saturday, September 14, 2024, at 8:30 a.m. ET/2:30 p.m. CEST, along with updates on the status of the global Phase 2 portions of both studies which are designed with registrational intent.

"Our development strategy has been anchored around our guiding hypothesis: that we could drive deep and durable responses for patients by creating *precisely* targeted therapies that address the limitations of currently available options. We believe the data from the fully enrolled Phase 1 portions of our ALKOVE-1 and ARROS-1 clinical trials continue to support the potential for our parallel lead programs to achieve this goal through addressing the combined challenges of treatment-emergent resistance, brain metastases, and off-target central nervous system (CNS) adverse events," said Christopher Turner, M.D., Chief Medical Officer of Nuvalent. "We are particularly encouraged by the durability of responses seen with both NVL-655 and zidesamtinib in these heavily pre-treated patient populations, which we believe has the potential to be differentiated and to translate into meaningful improvements in earlier lines of treatment."

"Complementary to our clinical updates at ESMO, we are pleased to also share new preclinical data that characterize the intracranial activity of our ROS1-selective inhibitor zidesamtinib in comparison to FDA-approved or investigational dual TRK/ROS1 inhibitors, which we believe supports the potential for zidesamtinib to deliver more durable intracranial responses while avoiding TRK inhibition," said Henry Pelish, Ph.D., Chief Scientific Officer at Nuvalent. "These data further add to the body of evidence that we believe supports the differentiated profile of zidesamtinib for patients with ROS1-positive NSCLC."

"At the outset of these programs, we set out to design best-in-class molecules that could deliver clinically meaningful outcomes for patients with ALK- or ROS1-positive NSCLC and eventually become the front-line standard of care. Our Phase 1 updates at ESMO are a critical milestone towards achieving our goal, with longer follow-up demonstrating that NVL-655 and zidesamtinib can drive deep and durable responses even in heavily pre-treated patients that have exhausted all other treatment options," said James Porter, Ph.D., Chief Executive Officer at Nuvalent. "These data support the ongoing Phase 2 investigation of NVL-655 and zidesamtinib in both TKI pre-treated and TKI naïve patients, and we look forward to providing further program updates during our conference call later this week."

Updated ALKOVE-1 Phase 1 Data

Title: Phase 1/2 ALKOVE-1 study of NVL-655 in ALK-positive solid tumors
Presentation Number: 1253O
Session Category: Proffered paper session
Session Title: NSCLC metastatic
Updated Presentation Date and Time: Saturday September 14, 2024, 9:30 – 9:40 a.m. CEST
Location: Barcelona Auditorium – Hall 2
Presenter: Alexander Drilon, M.D. (Memorial Sloan Kettering Cancer Center, New York,USA)

Background: NVL-655 is a potent, brain-penetrant, ALK-selective tyrosine kinase inhibitor (TKI) designed to address key limitations of prior generation ALK TKIs (first generation (1G), second generation (2G) and third generation (3G)); it demonstrates preclinical activity against diverse ALK fusions and resistance mutations, including lorlatinib-refractory compound mutations, while avoiding tropomyosin receptor kinase (TRK) inhibition, which is associated with neurologic toxicities.

Methods: The global ALKOVE-1 Phase 1 (NCT05384626) enrolled patients with pretreated advanced ALK-positive solid tumors. Key objectives were selection of a recommended Phase 2 dose (RP2D), safety, and efficacy (RECIST 1.1, investigator assessment).

Results: As of the data cut-off date ofMarch 23, 2024, 133 patients (131 NSCLC, 2 other) received NVL-655 (15-200 mg orally once daily (QD)) in Phase 1. Patients were heavily pre-treated with a median of 3 (range: 1-8) prior anticancer therapies and included:

- patients treated with a 2G ALK TKI (alectinib, brigatinib, ceritinib)or the 3G ALK TKI lorlatinib (100%);
- patients who had received ≥1 2G ALK TKIand the 3G ALK TKI lorlatinib (79%);
- patients who had received ≥3 prior ALK TKIs (46%);
- patients who had also received prior chemotherapy (56%); and,
- patients with a history of treated/untreated CNS metastases (56%).

A maximum tolerated dose was not reached. 150 mg QD was selected as the RP2D, providing favorable safety, activity and exposure exceeding targeted efficacy thresholds for ALK resistance mutations. The most common treatment-related adverse events (TRAEs) were ALT increase (33%), AST increase (29%), constipation (15%), nausea (12%) and dysgeusia (11%); 2% discontinued due to TRAEs.

ALK+ NSCLC response-evaluable (± chemo)	ORR at all doses, % (n/n)	Median DOR, months (m), (95% CI)	% DOR > 6 m (95% CI)	ORR at 150 mg, % (n/n)
All	38% (39/103)	9.2 (6.9, NE)	79% (56, 91)	39% (15/38) *
≥3 prior ALK TKI inc. 2G and lorlatinib	37% (16/43)	7.7 (5.6, NE)	79% (37, 95)	38% (6/16)
lorlatinib-naïve (≥1 2G ± 1G)	53% (9/17)	NR (3.5, NE)	83% (27, 97)	57% (4/7)

***ALK* mutation**	55% (30/55)	14.4 (6.9, NE)	86% (63, 95)	57% (12/21)
G1202R	76% (22/29)	14.4 (6.9, NE)	88% (60, 97)	83% (10/12)
prior lorlatinib	49% (23/47)	14.4 (6.9, NE)	83% (56, 94)	50% (8/16)
compound (≥2) mut.	58% (15/26)	14.4 (5.1, NE)	80% (50, 93)	78% (7/9)
lorlatinib-naïve (≥1 2G ± 1G)	88% (7/8)	NR (NE, NE)	100% (100, 100)	80% (4/5)
NE, not estimable; NR, not reached *13/15 responses ongoing (DOR range 1.1 – 9.0 m)				

CNS activity, including complete resolution of CNS metastases in lorlatinib-experienced patients, was observed.

Conclusions: NVL-655 demonstrated encouraging efficacy and durability in heavily pretreated ALK-positive NSCLC patients, including patients who exhausted available therapies (including lorlatinib), with ALK single and compound resistance mutations, and with CNS metastases. Safety was favorable, consistent with the ALK-selective, TRK-sparing design. Phase 2 enrollment is ongoing with registrational intent for previously treated patients.

Updated ARROS-1 Phase 1 Data

Title: Phase 1/2 ARROS-1 study of zidesamtinib (NVL-520) in ROS1 fusion-positive solid tumors
Presentation Number: 1256MO
Session Category: Mini oral session
Session Title: NSCLC metastatic
Updated Presentation Date and Time: Saturday September 14, 2024, 10:25 – 10:30 a.m. CEST
Location: Santander Auditorium – Hall 5
Presenter: Benjamin Besse, M.D., Ph.D. (Institut Gustav Roussy, Villejuif, France)

Background: Zidesamtinib is a brain-penetrant, TRK-sparing, highly selective ROS1 TKI with activity against diverse ROS1 fusions and resistance mutations including G2032R.

Methods: The global ARROS-1 Phase 1 (NCT05118789) enrolled patients with heavily pretreated advanced/metastatic ROS1-positive solid tumors. Key objectives were selection of the RP2D and evaluation of safety and efficacy (RECIST 1.1, investigator assessment).

Results: As of the data cut-off date ofMarch 12, 2024, 104 patients (99 NSCLC, 5 other) received zidesamtinib (25-150 mg orally QD) in Phase 1. Patients were heavily pre-treated with a median of 3 (range: 1-11) prior anticancer therapies including any ROS1 TKI (99%), and included:

- the most heavily pre-treated of patients, receiving two or more prior ROS1 TKIs (69%) and one or more prior lines of chemotherapy (66%);
- patients previously treated with lorlatinib (55%), repotrectinib (repo; 21%), or either (67%); and,
- patients with a history of treated/untreated CNS metastases (53%).

100 mg QD was selected as the RP2D with no observed dose relationships for safety or efficacy. No dose-limiting toxicity or discontinuation due to TRAE occurred. TRAE led to dose reduction in 5.8%. Most common TRAEs were peripheral edema (18%) and transaminase increase (12%); TRAEs were grade ≥3 in 7.7%.

73 patients with ROS1-positive NSCLC were response-evaluable:

# Prior ROS1 TKIs ± Chemo	**ORR**	**Median DOR, months (m) (95% CI)**	**% DOR > 6m (95% CI)**	**% DOR > 12m (95% CI)**

Any prior ROS1 TKI (range: 1-4)	38% (28/73*)	NR (10.2, NE)	85% (64, 94)	69% (45, 84)
Repo-naïve	45% (25/55*)	NR (10.2, NE)	91% (69, 98)	74% (48, 89)
≥2	36% (19/53*)	15.8 (6, NE)	79% (53, 92)	62% (35, 80)
Repo-naïve	42% (16/38*)	NR (6.4, NE)	88% (59, 97)	68% (38, 85)
1 (crizotinib)	64% (7/11)	NR (NE, NE)	All ongoing (range, 1.8+ - 22.8+m)	
NE, not estimable; NR, not reached. *2 complete responses (CRs), ongoing with DOR 16.6+ and 23.5+m Median follow-up for response evaluable patients 9.4m (range, 0.8 – 25.8m)				

In patients with known ROS1 G2032R, ORR was 65% (11/17) with a median duration of response (mDOR) of 15.8m (6, NE) among repo-naïve patients and ORR was 38% (3/8) among repo-pretreated patients. In patients with measurable intracranial (IC) metastases and ≥2 prior ROS1 TKIs (all with prior lorlatinib and/or repo), IC-ORR was 57% (4/7), and IC-DOR range was 1.9+ - 17.3+m with no IC progression.

Conclusions: Zidesamtinib demonstrated encouraging efficacy and durability in patients with pretreated ROS1-positive NSCLC, including those who had exhausted available therapies, with ROS1 resistance mutations including G2032R, and/or with CNS metastases. Safety was favorable and consistent with the highly ROS1-selective and TRK-sparing design. Phase 2 enrollment is ongoing with registrational intent in patients with TKI-naïve and pre-treated ROS1-positive NSCLC.

Preclinical Intracranial Activity of Zidesamtinib

Title: Profiling of Zidesamtinib and Other ROS1 Inhibitors in an Intracranial CD74-ROS1 G2032R Preclinical Model
Presentation Number: 8P
Abstract Number: 4811
Onsite Poster Display Date: Sunday September 15, 2024
Presenter: Anupong Tangpeerachaikul (Nuvalent, Inc., Cambridge, Massachusetts, United States)

Introduction. TKIs crizotinib, entrectinib, and repotrectinib (US only) are approved for the treatment of *ROS1*-positive non-small cell lung cancer. Depth and durability of responses can be limited by the ROS1 G2032R resistance mutation and brain metastases, identified in ~40% and ~50% of patients, respectively, after disease progression on crizotinib. ROS1-selective TKI zidesamtinib and dual-TRK/ROS1 TKIs repotrectinib and taletrectinib have reported clinical activity against ROS1 G2032R and intracranial activity, with different adverse event profiles. In this study, we compared these three TKIs in a preclinical ROS1 G2032R brain tumor model.

Methods. Ba/F3 CD74-ROS1 G2032R luciferase cells were implanted in the brain of Balb/c nude mice. Mice were orally treated with TKIs for 25 days QD or twice daily (BID). Brain tumors were monitored 1 – 2 times per week by bioluminescence imaging (BLI). At the endpoint, plasma and brain samples were collected for pharmacokinetics analyses.

Results. Zidesamtinib (3 mg/kg BID) suppressed CD74-ROS1 G2032R brain tumors to <5% of initial BLI signal through day 25. Brain tumors were suppressed by repotrectinib (15 or 75 mg/kg BID) and taletrectinib (100 mg/kg QD) up to day 8 but regrew and eventually exceeded the initial BLI signal by 300 – 3,000%. Switching from repotrectinib (15 mg/kg BID) to zidesamtinib (3 mg/kg BID) on day 8 kept brain tumors to <15% of initial BLI signal. In this study, all TKIs achieved plasma exposures near or above their reported clinical plasma exposures. Zidesamtinib brain exposure exceeded its in vitro ROS1 G2032R IC_{50} but not TRKB IC_{50}; by contrast, repotrectinib brain exposure exceeded its TRKB IC_{50} but not ROS1 G2032R IC_{50}.

Conclusion. In this preclinical model, zidesamtinib demonstrated more durable intracranial activity than repotrectinib and taletrectinib at clinically relevant plasma concentrations. Switching treatment from repotrectinib to zidesamtinib resulted in improved preclinical intracranial activity. Preclinical activity against ROS1 G2032R, including in the brain, together with a TRK-sparing design supports zidesamtinib as a potential best-in-class ROS1-selective therapy.

Conference Call Information

Following oral presentations at the ESMO Congress 2024 inBarcelona, Spain, management will host a live webcast and conference call on Saturday, September 14, 2024 at 8:30 a.m. ET/2:30 p.m. CEST.

To access the call, register online here for the live webcast or dial +1 (800) 836-8184 (domestic) or +1 (646) 357-8785 (international) at least 10 minutes prior to the start time and ask to be joined to the Nuvalent call. Accompanying slides and a live video webcast will be available in the Investors section of the Nuvalent website at https://investors.nuvalent.com/events. A replay and accompanying slides will be archived on the Nuvalent website for 30 days.

About NVL-655 and the ALKOVE-1 Phase 1/2 Clinical Trial

NVL-655 is a novel brain-penetrant ALK-selective inhibitor created with the aim 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 single or compound treatment-emergent ALK mutations such as G1202R. In addition, NVL-655 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/ALK inhibitors and to drive deep, durable responses for patients across all lines of therapy. NVL-655 has received breakthrough therapy designation for the treatment of patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who have been previously treated with 2 or more ALK tyrosine kinase inhibitors and orphan drug designation for ALK-positive NSCLC.

NVL-655 is currently being evaluated in the Phase 2 portion of the ALKOVE-1 Phase 1/2 clinical trial, a first-in-human study of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors (NCT05384626). The completed Phase 1 portion enrolled ALK-positive NSCLC patients who previously received at least one ALK TKI and patients with other ALK-positive solid tumors who had been previously treated with at least one prior systemic anticancer therapy. The primary objectives were to determine the recommended Phase 2 dose (RP2D) and if applicable, the maximum tolerated dose (MTD) of NVL-655 in patients with ALK-positive solid tumors. Additional objectives included characterization of the overall safety, tolerability, and pharmacokinetic profile, and evaluation of the preliminary antitumor activity of NVL-655. The ongoing global, single arm, open label Phase 2 portion is designed with registrational intent for TKI pre-treated patients with ALK-positive NSCLC and to enable preliminary investigation for patients with ALK-positive NSCLC who are TKI naïve.

About Zidesamtinib and the ARROS-1 Phase 1/2 Clinical Trial

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. The completed Phase 1 portion enrolled ROS1-positive NSCLC patients who previously received at least one ROS1 TKI, or patients with other ROS1-positive solid tumors who had been previously treated. The Phase 1 portion of the trial was designed to evaluate the overall safety and tolerability of NVL-520, with additional objectives including determination of the recommended Phase 2 dose (RP2D), characterization of the pharmacokinetic profile, and evaluation of preliminary anti-tumor activity. The ongoing global, single arm, open label Phase 2 portion is designed with registrational intent for TKI naïve and TKI pre-treated patients with ROS1-positive NSCLC.

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-altered 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 clinical development programs for zidesamtinib and NVL-655; the potential clinical effects of zidesamtinib and NVL-655; the potential of Nuvalent's pipeline programs, including zidesamtinib and NVL-655; the implications of 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 trials 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 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; risks that Nuvalent may not achieve the goals and milestones set forth in its OnTarget 2026 operating plan; the occurrence of adverse safety events; risks that the U.S. Food and Drug Administration, European Medicines Agency or other foreign regulators 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, including the ARROS-1 and ALKOVE-1 trials; 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 Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2024, 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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