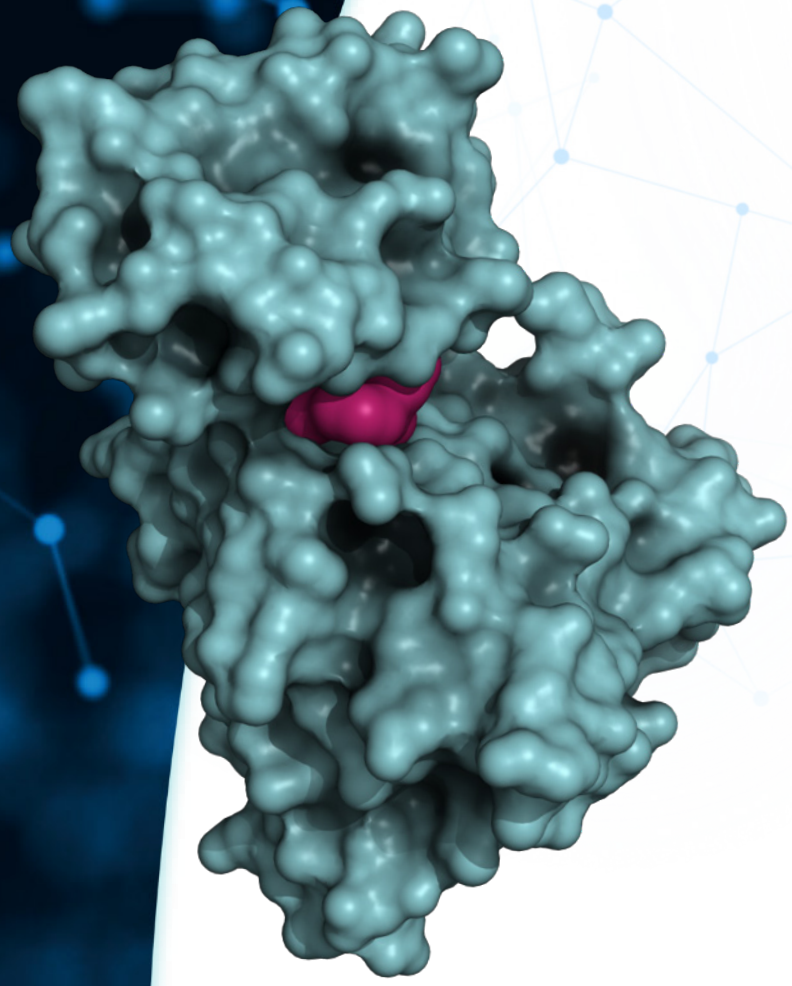
Nuvalent

Nuvalent Overview

January 8, 2024



PRECISELY

Targeted Therapies
for patients with cancer

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This presentation 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 period over which Nuvalent estimates its cash, cash equivalents and marketable securities will be sufficient to fund its future operating expenses and capital expenditure requirements; Nuvalent's estimate of its cash, cash equivalents and marketable securities as of December 31, 2023; the expected timing of data announcements and FDA approvals; 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 trials, including their intended pivotal registration-directed design; the potential of Nuvalent's pipeline programs, including NVL-520, NVL-655 and NVL-330; the implications of data readouts and presentations; timing and content of potential discussions with regulators and investigators; the design and timing of the planned Phase 2 portions of the ARROS-1 and ALKOVE-1 trials; 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 presentation 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 presentation, 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; the occurrence of adverse safety events; risks that the FDA may not approve our potential products on the timelines we expect, if 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; risks related to obtaining, maintaining, and protecting Nuvalent's intellectual property; and the risk that Nuvalent's estimate of its cash, cash equivalents and marketable securities as of December 31, 2023 may differ from the final amount determined upon completion of its year-end closing procedures. 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 September 30, 2023, 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 the date made 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.

Nuvalent | AT·A·GLANCE

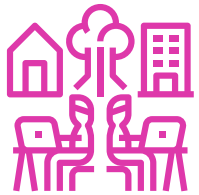
PRECISELY

Targeted Therapies *for patients with cancer*

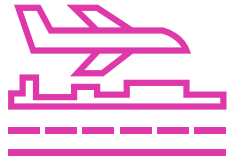
- **Parallel lead programs for ROS1+ and ALK+ NSCLC in global clinical development**
- **Proven discovery capabilities:** Third program for HER2+ NSCLC in IND enabling studies & active research pipeline

#NuCrew

Growing team (90+ FTEs)



Hybrid operations with offices in Cambridge, MA



Cash runway expected into 2027

NUVL

Nasdaq listed

PRECISELY

Targeted Therapies *for patients with cancer*

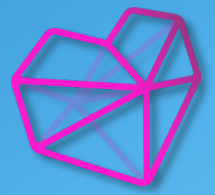
THE ▪ NUVALENT ▪ APPROACH

Deep Expertise in Chemistry and Structure-based Drug Design

Aim to “thread the needle” between kinase resistance and selectivity

Design of Target Product Profiles in Collaboration with Physician-Scientists

Aim to Compete in 1st Line with Best-in-Class Profiles



GOAL: Maximize Patient Impact

Nuvalent

Track Record of Success

Resource-efficient execution and value creation across an expanding portfolio of wholly-owned programs

2021

EMERGENCE FROM STEALTH

- Disclosed parallel lead programs (ROS1+ and ALK+ NSCLC)
- Presented preclinical profiles supporting desired Target Product Profiles
- Nasdaq listed: NUVL

2022

FIRST CLINICAL PROOF-OF-CONCEPT

- Initiated two global Phase 1/2 studies (ARROS-1, ALKOVE-1)
- Demonstrated clinical proof-of-concept for ROS1 program
- Disclosed third novel program (HER2 NSCLC)

2023

SECOND PROOF-OF-CONCEPT & FIRST PIVOTAL STUDY

- Demonstrated clinical proof-of-concept for ALK program
- Initiated ARROS-1 Phase 2 with registrational intent
- Advanced HER2 program towards IND

Ended 2023 with approximately $719.9M* in cash, cash equivalents and marketable securities (unaudited), with potential to deliver multiple transformative catalysts within cash runway window into 2027

* Preliminary, unaudited estimate only as of the date of this presentation; subject to change following completion of year-end closing procedures; does not present all information necessary for an understanding of financial position as of December 31, 2023.

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OnTarget 2026

The Path to Patient Impact

	2024	2025	2026
GOAL:	EXECUTE ON GLOBAL REGISTRATIONAL STRATEGIES	FIRST PIVOTAL DATA	FIRST APPROVED PRODUCT

MISSION: Bringing new, potential best-in-class medicines to patients with cancer

Anticipated 2024 Milestones:

- Progress ARROS-1 Phase 2 with registrational intent
- Initiate ALKOVE-1 Phase 2 with registrational intent
- Launch 1L ALK strategy
- Interim Ph 1/2 data for both ROS1 and ALK programs
- Initiate Phase 1 trial for HER2 program

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Meet the #NuCrew

Significant experience in drug discovery, development and company building

BOARD OF DIRECTORS

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Independent

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CEO, Nuvalent

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Harvard Professor of Chemistry & Chemical Biology

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Memorial Sloan Kettering Cancer Center

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Mass General Cancer Center

Pasi Jänne, MD, PhD
Clinical Advisor
Dana Farber Cancer Institute

Nancy Kohl, PhD
Translational Research Advisor
Independent Consultant

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Jessie Lin
VP, Corporate Strategy & Portfolio Management

Matthew Metivier
VP, Human Resources

Henry Pelish, PhD
SVP, Drug Discovery

John Soglia, PhD
SVP, Translational Development

Perrin Wilson, PhD
SVP, Business Development & Strategy

12 Prior FDA Approvals

mozobil (plerixafor) injection · Cloiar · pyrukynd (mitapivat) tablets · TIBSOVO (ivosidenib) tablets · Fabrazyme (agalsidase beta) · Brukinsa (zanubrutinib) · ALUNBRIG (brigatinib) · ICLUSIG (ponatinib) tablets · BAVENCIO (avelumab) · GAVRETO (pralsetinib) · Copiktra (duvelisib) · Tivicay (dolutegravir)

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Nuvalent PIPELINE

Advancing a portfolio of potentially best-in-class products, with complementary initial indications in NSCLC

ALK+ and ROS1+ NSCLC Landscape

Emerging resistance mutations, increasing CNS involvement, and treatment-related adverse events limit utility of approved therapies

Advanced/Metastatic ALK+ NSCLC

	NOTABLE POPULATIONS	CNS DISEASE	STANDARD OF CARE (2023)
1L	**Wild-type ALK kinase domain**	**~30 – 40%**	**Alectinib** *Alternatives: brigatinib, ceritinib, crizotinib, lorlatinib*
2L	**~50% ALK single resistance mutations (ex. G1202R, I1171N/S/T)**	**> 60%**	**Lorlatinib**
3L+	**~25 – 50% ALK compound resistance mutations**	**> 60%**	**No clear standard of care**

Advanced/Metastatic ROS1+ NSCLC

NOTABLE POPULATIONS	CNS DISEASE	STANDARD OF CARE (2023)
Wild-type ROS1 kinase domain	**~20 – 40%**	**Crizotinib** *Alternatives: entrectinib, repotrectinib*, ceritinib***
~40% ROS1 G2032R resistance mutation	**~30 – 55%**	**No clear standard of care** *Additional alternative: lorlatinib***

* Repotrectinib was approved November 2023; ** Not FDA approved, but in NCCN guidelines.

1L, 1st line; **2L**, 2nd line; **3L**, 3rd line; **CNS**, central nervous system.

Sources (ALK): Ou and Zhu Lung Cancer 2019; Kris et. al. JAMA 2014; Shaw and Engelman J Clin Onc 2013; Noé et. al. J Thor Onc 2019; Peters et. al. NEJM 2017; Shaw et. al. Lancet Onc 2017; Dagogo-Jack et. al. Clin Cancer Res 2019.

Sources (ROS1): Lin et al., J Thorac Oncol 2017; Gainor et al, JCO Precision Oncol 2017; Ou and Zhu Lung Cancer 2019; Patil et al, JTO 2018.

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Nuvalent ALK+ and ROS1+ NSCLC Strategy

Potential best-in-class ALK & ROS1 TKIs to overcome the combined medical needs of:

Selective inhibition of the oncogenic driver + **Overcoming treatment-emergent resistance mutations** + **Treating & preventing brain metastases** + **Avoiding treatment-limiting adverse events**

Comparable resistance mutation rates after 1L TKI: ~50% ALK single mutation [1,2] & ~40% ROS1 G2032R [3] vs. ~50% EGFR T790M [4]

CASE STUDY

Osimertinib *for* EGFR+ NSCLC [5]

Activity against resistance mutations

2L+ patients with T790M:

ORR: **65%**

mDOR: **11 months**

+

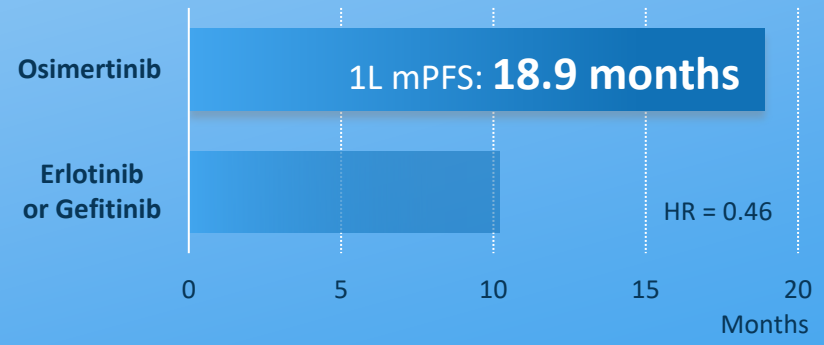
Improved CNS activity

1L intracranial ORR:

Osimertinib: **77%** with **18% CR**

Erlotinib or Gefitinib: **63%** with **0% CR**

Significant 1L mPFS improvement & Movement up the treatment paradigm



Sources: [1] Dagogo-Jack I. et al., Clin Cancer Res 2019; [2] Gainor J. et al. Cancer Discov. 2016; [4] Gainor J.F. et al., JCO Precision Oncol. 2017; [4] Ohashi K. et al., JCO 2013; [5] Osimertinib FDA package insert.

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ALK+ & ROS1+ NSCLC Market Opportunity

Meaningful Commercial Markets with ~$3B Combined WW Sales in 2022

~$2.5B

Potential best-in-class profiles designed with the goal to **supplant the current 1L standard of care**

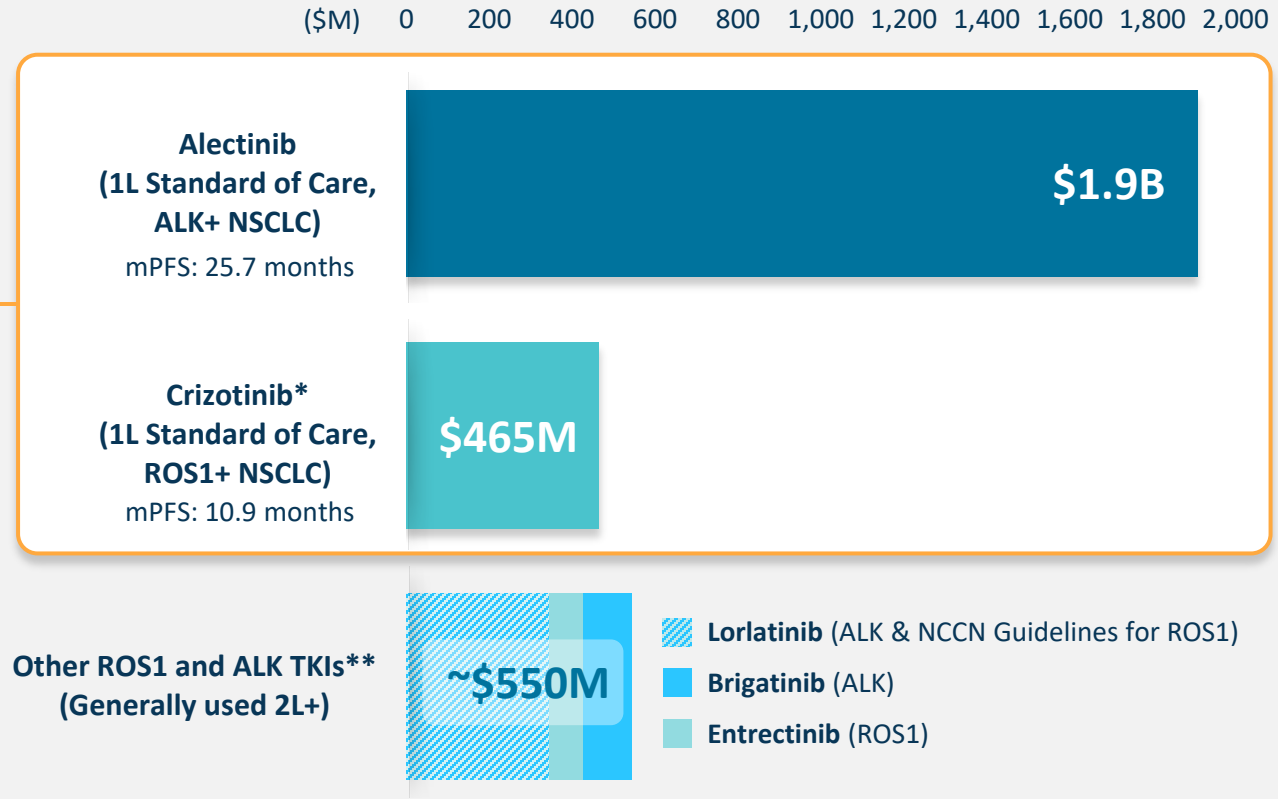
~$0.5B

Potential **near-term registrational opportunity for TKI-pretreated patients**

- Clinical **proof-of-concept** demonstrated in heavily pre-treated patient populations

Potential to **grow the market** through deeper, more durable responses

2022 GLOBAL SALES FOR ALK & ROS1 TKIs



1L, 1st line; **2L**, 2nd line; **3L**, 3rd line; **B,** billion; **F**, forecasted; **M**, million; **NCCN**, National Comprehensive Cancer Network; **NSCLC**, non-small cell lung cancer; **PFS**, progression-free survival; **TKI**, tyrosine kinase inhibitor.

* Crizotinib is FDA approved for ROS1+ NSCLC, ALK+ NSCLC, ALK+ ALCL and ALK+ IMT. Sales are not reported by indication.

** Ceritinib is FDA approved for ALK+ NSCLC and in NCCN guidelines for ROS1+ NSCLC, but sales are not reported. Repotrectinib received FDA approval for ROS1+ NSCLC in November 2023.

Sources: Cortellis Sales and Forecasts, accessed November 2023; FDA Package Inserts; NCCN Guidelines for NSCLC (version 5.2023).

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NVL-655 *for* ALK+ NSCLC

A brain-penetrant, selective inhibitor of ALK and ALK resistance mutations with the potential to minimize TRK-related CNS adverse events while providing CNS antitumor activity

AT · A · GLANCE

Mechanism of Action:
ALK-selective tyrosine kinase inhibitor

Stage of Development:
Global Phase 1

Initial Development Indication:
ALK-positive NSCLC

FDA Designations:
Orphan Drug Designation

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ALK+ NSCLC Patient Journey

~3 – 5% of NSCLC [1] | Majority are advanced/metastatic at diagnosis [2]

	1L	2L	3L+
STANDARD OF CARE	**Alectinib** ($1.9B WW sales, 2022) [3] • Brigatinib, ceritinib, crizotinib, and lorlatinib are FDA approved (line-agnostic) [4]	**Lorlatinib** ($343M WW sales, 2022) [3] • Lorlatinib was designed to address single ALK mutations that confer resistance to 1G (crizotinib) and 2G (alectinib, brigatinib, ceritinib) TKIs [5]	**No clear standard of care** • Patients may consider clinical trials or chemotherapy/I-O [4]
KEY LIMITATIONS	**Single ALK resistance mutations** *Observed in ~50% of patients progressing on 1G or 2G TKIs* [6, 7] **Brain penetrance** ○ *30 – 40% present with brain metastases at diagnosis* [8] ○ *>60% will develop brain metastases overall* [9]	**Compound ALK resistance mutations** *Observed in ~25 – 50% of patients progressing on sequential 2G to 3G TKIs* [6, 13] **Treatment-limiting off-target adverse events** *CNS adverse events associated with TRK inhibition observed in >50% of patients receiving lorlatinib* [10, 11, 12]	**Activity** *No approved therapies have demonstrated activity after sequential 2G to 3G TKIs* [10]

Sources: [1] Kwak E. et al., NEJM 2010. [2] Chia P.L. et al., Clin Epidemiol. 2014. [3] Cortellis Sales and Forecasts, accessed November 2023. [4] NCCN Guidelines for NSCLC (version 5.2023). [5] Basit S. et al., Eur. J. Med. Chem. 2017. [6] Dagogo-Jack I. et al., Clin Cancer Res 2019. [7] Gainor J. et al. Cancer Discov. 2016. [8] Gainor J et al. JCO Precis Oncol. 2017. [9] Shaw A. et al., Lancet Onc 2017. [10] FDA Package Inserts. [11] Cocco E et al., Nat Rev Clin Oncol. 2018. [12] Shaw A. et al., NEJM 2020. [13] Shiba-Ishii et al., Nature Cancer 2022.

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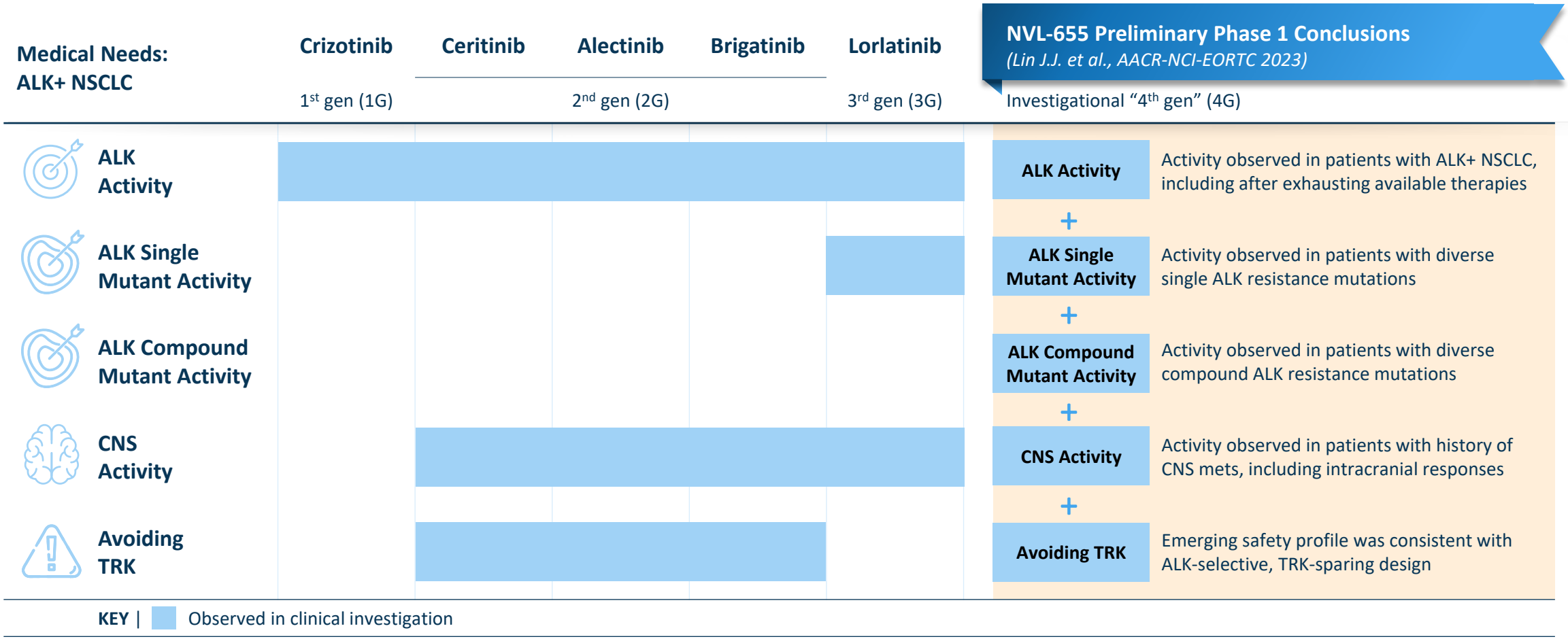
NVL-655: A Rationally Designed ALK-selective, TRK-sparing Inhibitor



Source: Lin J.J. et al., AACR-NCI-EORTC 2023. ***Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted.***

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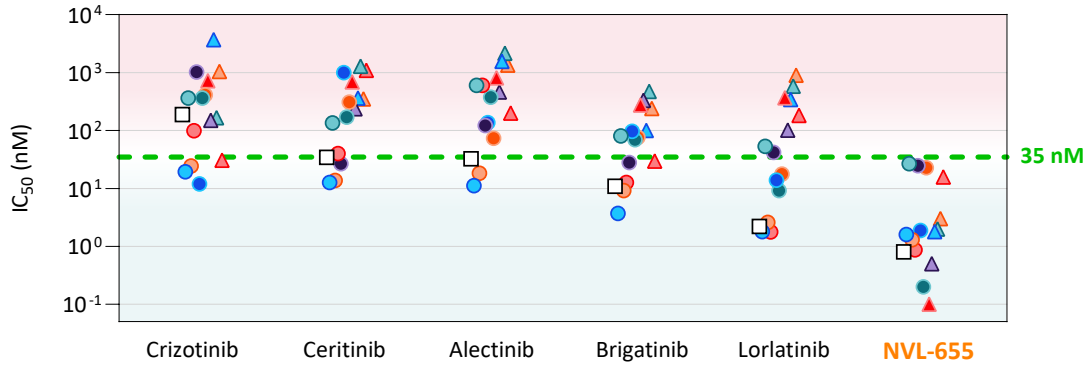
Preclinical Characterization Demonstrates Desired Target Product Profile

Inhibited Diverse ALK Fusions and Resistance Mutations

In Vitro Activity

Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants[1-6]



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

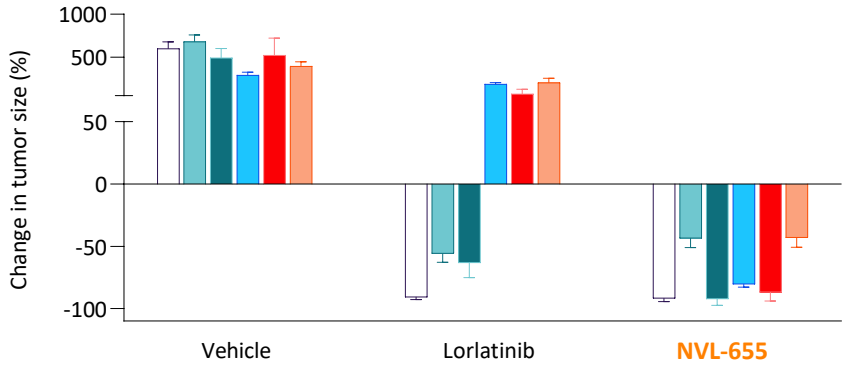
Compound mutant
- G1202R/T1151M | MR448re (v3)
- G1202R/F1174L | Ba/F3 (v3)
- G1202R/L1196M | MGH953-7 (v3)
- G1202R/L1198F | Ba/F3 (v1)
- G1202R/G1269A | Ba/F3 (v1)
- I1171N/L1198F | Ba/F3 (v1)

No resistance mutations | MGH048-1 (v1)

Single mutant
- T1151M | Ba/F3 (v3)
- I1171N | Ba/F3 (v1)
- F1174L | Ba/F3 (v3)
- V1180L | Ba/F3 (v1)
- L1196M | MGH045-1 (v1)
- L1198F | Ba/F3 (v1)
- G1202R | YU-1077 (v3)
- D1203N | Ba/F3 (v1)

In Vivo Activity

Tumor regression at well-tolerated doses in ALK models, including ALK single and compound mutants[1-6]



Xenograft models harboring ALK fusion

Single mutant
- I1171N | Ba/F3 (EML4-ALK v1)
- G1202R | MR619 (STRN-ALK)

No resistance mutations | Lu-01-0015 (HIP1-ALK)

Compound mutant
- G1202R/L1196M | MGH953-7 (EML4-ALK v3)
- G1202R/T1151M | MR448re (EML4-ALK v3)
- G1202R/G1269A | Ba/F3 (EML4-ALK v1)

NVL-655: 0.5 - 7.5 mg/kg, PO, BID; Lorlatinib: 5 mg/kg, PO, BID or 10 mg/kg, PO, QD
In some cases, dosing was not performed on weekends

BID, twice daily; **IC_{50}**, half-maximal inhibitory concentration; **PO**, orally; **QD**, once daily; **v**, EML4 breakpoint variant.

Sources: Lin J.J. et al., AACR-NCI-EORTC 2023. [1]Lee, J. *et al.* AACR 2023; [2]Fujino, T. *et al.* EORTC-NCI-AACR 2022; [3]Mizuta, H. *et al.* WCLC-IASLC 2022; [4]Tangpeerachaikul, A. *et al.* AACR 2022; [5]Tangpeerachaikul, A. *et al.* AACR-NCI-EORTC 2021; [6]Pelish, H. *et al.* AACR 2021. Data also reflect additional repeat testing and models.

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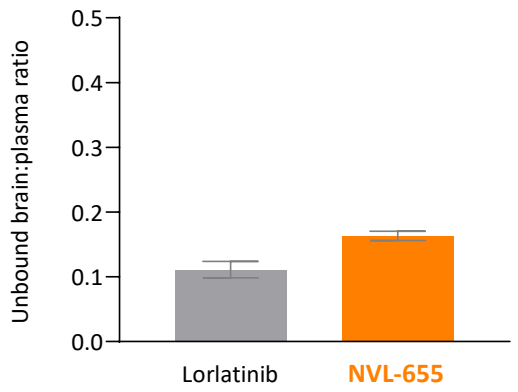
Preclinical Characterization Demonstrates Desired Target Product Profile

Brain-Penetrant with the Potential to Avoid TRK-Related CNS Adverse Events

Brain Penetrance

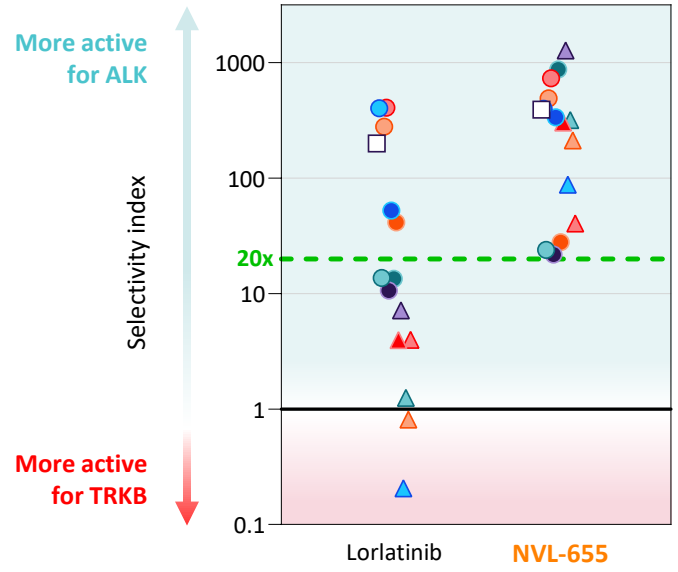
Pharmacokinetic data similar to preclinical observations for lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1 hour timepoint

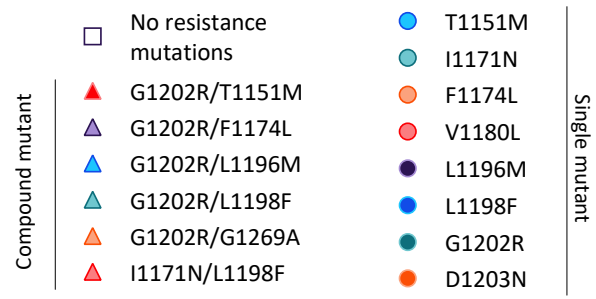
Avoiding TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (\text{pTRKB})}{IC_{50}\ (\text{Ba/F3 EML4-ALK})}$$

Selectivity for ALK over TRKB



Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted.

CNS, central nervous system; **IC50**, half-maximal inhibitory concentration; **PO**, orally; pTRKB, BDNF-stimulated TRKB phosphorylation.

Source: Lin J.J. et al., AACR-NCI-EORTC 2023. Mizuta, H. et al. WCLC-IASLC 2022; Tangpeerachaikul, A. et al. AACR-NCI-EORTC 2021; Pelish, H. et al. AACR 2021. Data presented here reflect updated values following additional repeat testing.

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A Global First-in-Human Phase 1/2 Clinical Trial of NVL-655 in Advanced ALK-Positive NSCLC and Other Solid Tumors (NCT05384626)

PHASE 1 DOSE-ESCALATION

Ongoing at global sites across sites in North America, Europe, Asia and Australia

PATIENT POPULATION

- Advanced solid tumors harboring ALK fusion or activating mutation (by local testing)
- Patients with NSCLC: ≥ 1 prior 2G or 3G ALK TKI
- ≤ 2 prior chemotherapies/immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., EGFR, ROS1, MET, RET, or BRAF) [a]
- Evaluable but non-measurable disease allowed [a]

PHASE 1 OBJECTIVES

- Selection of RP2D and, if applicable, MTD (primary)
- Overall safety and tolerability
- PK characterization
- Preliminary antitumor activity
- Intracranial activity

Preliminary Phase 1 data presented October 2023: All-Treated Population (N = 93)

Enrollment initiated June 2022 (Data cut-off: 8 Aug 2023)

NVL-655 Dose Cohorts	All Doses	15 mg QD	25 mg QD	50 mg QD	100 mg QD	150 mg QD	200 mg QD
BOIN Dose-Escalation	N = 18	3	3	3	3	3	3
Expansion (For Dose Optimization)	N = 75	0	9	9	27	22	8
All-Treated Population	**N = 93**	**3**	**12**	**12**	**30**	**25**	**11**
NSCLC Response-Evaluable Population [b]	**N = 51**	**3**	**7**	**10**	**20**	**7**	**4**

1G, 1st generation ALK TKI (i.e., crizotinib); **2G**, 2nd generation ALK TKI (i.e., ceritinib, alectinib, or brigatinib); **3G**, 3rd generation ALK TKI (i.e., lorlatinib); **ALK+,** ALK-positive; **CBR**, clinical benefit rate; **Chemo/I-O**, platinum-based chemotherapy ± immunotherapy; **DOR**, duration of response; **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate (RECIST 1.1); **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor; **TTR**, time to response.

[a] Patients with baseline concurrent oncogenic drivers identified on subsequent testing and patients without measurable disease are excluded from efficacy evaluation per prespecified protocol analysis plan.

[b] First response evaluation is pending for 27 patients. Response evaluable population prospectively defined as all NSCLC patients with measurable disease, without concurrent oncogenic driver, and who undergo ≥1 post-baseline response assessment (or discontinue treatment due to clinical progression/death prior to the first response assessment). Additional patients unevaluable for response: no measurable disease at baseline (n = 7); tumor with alternate oncogenic driver (MET amplification [n = 2] and BRAF G469A [n = 2]); no post-baseline scan and discontinued treatment for reasons other than PD (n = 2); other solid tumor (pancreatic and atypical carcinoid lung) (n = 2).

Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

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Patient Population: Heavily Pretreated ALK+ Solid Tumors

Patient Characteristic	All Treated (N = 93)
Age, median (range)	59 (24, 82)
Female	60 (65%)
ECOG PS	
0	38 (41%)
1	55 (59%)
Non-smoker	68 (73%)
Tumor Type	
NSCLC	91 (98%)
Pancreatic adenocarcinoma	1 (1%)
Atypical carcinoid, lung	1 (1%)
History of CNS metastases [a]	**54 (58%)**
ALK Fusion	**93 (100%)**
Secondary ALK mutation	**43 (46%)**
Single ALK mutation	19 (20%)
Compound (i.e., ≥2) ALK mutations [b]	**24 (26%)**
G1202R (single or compound)	22 (24%)

Treatment History	All Treated (N = 93)
Prior lines of anticancer treatment	
1	12 (13%)
2	16 (17%)
≥3	65 (70%)
Median (range)	**3 (1, 8)**
Prior treatments	
1 ALK TKI	14 (15%)
2 ALK TKIs	36 (39%)
≥3 ALK TKIs	43 (46%)
Chemotherapy	53 (57%)
ALK TKIs received [c]	
1G (crizotinib)	41 (44%)
2G	88 (95%)
alectinib	85 (91%)
brigatinib	21 (23%)
ceritinib	11 (12%)
3G (lorlatinib)	**77 (83%)**
Any 2G or lorlatinib	**93 (100%)**
≥2 ALK TKIs, including 2G and lorlatinib	**72 (77%)**
≥3 ALK TKIs, including 2G and lorlatinib	**41 (44%)**

Data cut-off: 8 Aug 2023. All data shown as n (%) unless otherwise specified.

1G, 1st generation ALK TKI; **2G**, 2nd generation ALK TKI; **3G**, 3rd generation ALK TKI; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **NSCLC**, non-small cell lung cancer; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **TKI**, tyrosine kinase inhibitor.

[a] Includes patients with untreated CNS lesions.

[b] Cis-allelic configuration not confirmed in all cases.

[c] Categories are not mutually exclusive.

Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

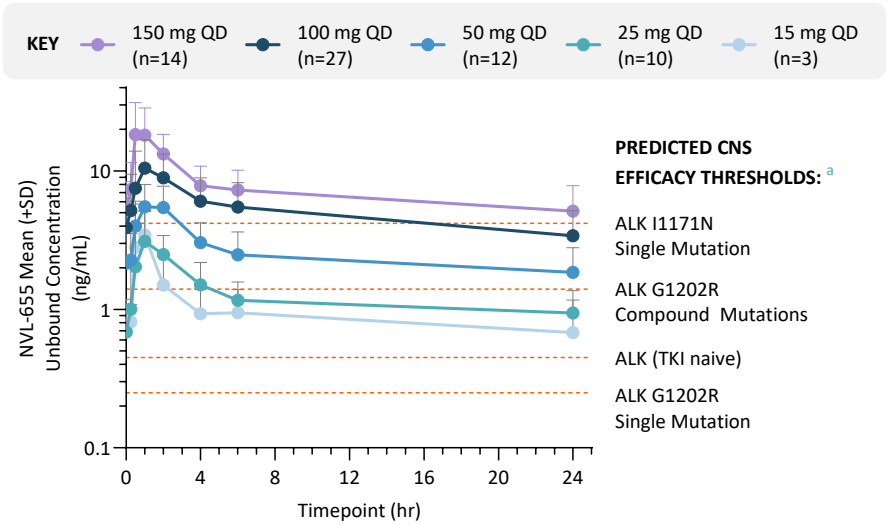
Nuvalent | ALKove-1

Ongoing RP2D Selection Supported by Favorable PK/PD Profiles

Dose levels ≥ 50 mg QD may provide increased coverage of single and compound mutations in the CNS

NVL-655 Exposure Achieved Predicted Efficacy Thresholds

NVL-655 Pharmacokinetics at Steady State (Day 15)



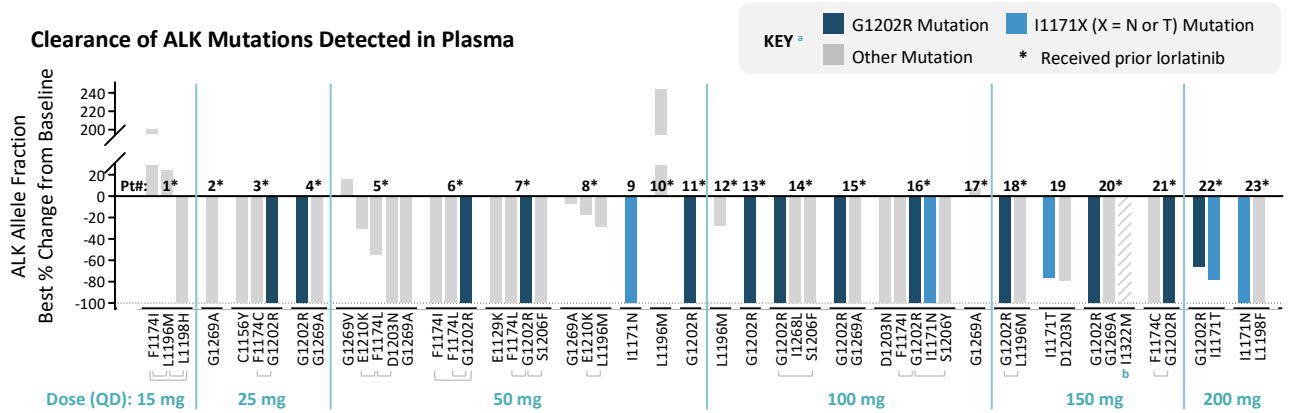
Pharmacokinetic data for 200 mg QD cohort are not shown due to immaturity.

[a] Based on ≥ 100% tumor growth inhibition (best response) in in vivo models bearing HIP1-ALK, Ba/F3 EML4-ALK v1 G1202R, EML4-ALK v3 G1202R/L1196M, and Ba/F3 EML4-ALK v1 I1171N, respectively, divided by predicted human CNS Kp (brain to plasma ratio).

Targets for CNS exceed corresponding periphery values.

NVL-655 Induced Clearance of Diverse ALK Resistance Mutation Alleles

- 100% clearance observed in 14/16 patients with centrally confirmed ALK G1202R or I1171X mutations, of whom 13 had received prior lorlatinib



Data are shown for all treated patients with ALK mutations detected on Cycle 1 Day 1 and with at least one follow-up assessment. One patient with only R1084C, an ALK mutant of unknown significance, is not included on the graph. Brackets indicate pairs with evidence of cis-allelic configuration by central ctDNA analysis.

[a] Refers to single or compound mutations. [b] ALK mutant variant of unknown significance.

Available data for patients enrolled as of 08 Aug 23. **CNS**, central nervous system; **h**, hours; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **Pt**, patient; **QD**, once daily; **SD**, standard deviation.

Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

Nuvalent | ALKove-1

Preliminary Activity: Tumor Response Across Heavily Pretreated Patient Populations

Patients with ALK+ NSCLC	All NSCLC Response-Evaluable	History of CNS Metastases	With ALK resistance mutation [a]				≥3 prior ALK TKI including 2G & lorlatinib		2G ± 1G, no lorlatinib
			Any	Single	Compound	G1202R [b]	All	+ Chemo	
ORR across all dose levels	**39%** (20/51)	**52%** (15/29)	**54%** (15/28)	**50%** (6/12)	**56%** (9/16)	**71%** (12/17)	**40%** (10/25)	**42%** (8/19)	**71%** (5/7)
Best Response									
PR [c]	20	15	15	6	9	12	10	8	5
SD	17	8	5	2	3	3	7	4	2
PD	11	4	7	3	4	2	6	5	0
NE [d]	3	2	1	1	0	0	2	2	0
ORR at doses ≥ 50 mg QD	**44%** (18/41)	**50%** (13/26)	**61%** (14/23)	**55%** (6/11)	**67%** (8/12)	**79%** (11/14)	**43%** (9/21)	**44%** (7/16)	**67%** (4/6)

Data cut-off: 8 Aug 2023. Response-evaluable patients with ALK+ NSCLC. **1G**, 1st generation ALK TKI (crizotinib); **2G**, 2nd generation ALK TKI (alectinib, brigatinib, or ceritinib); **CNS**, central nervous system; **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease, **PR**, partial response, **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **SD**, stable disease, **TKI**, tyrosine kinase inhibitor.

[a] Out of 16 patients harboring presumed compound ALK mutations, 8 have evidence of cis-allelic configuration by central ctDNA analysis.

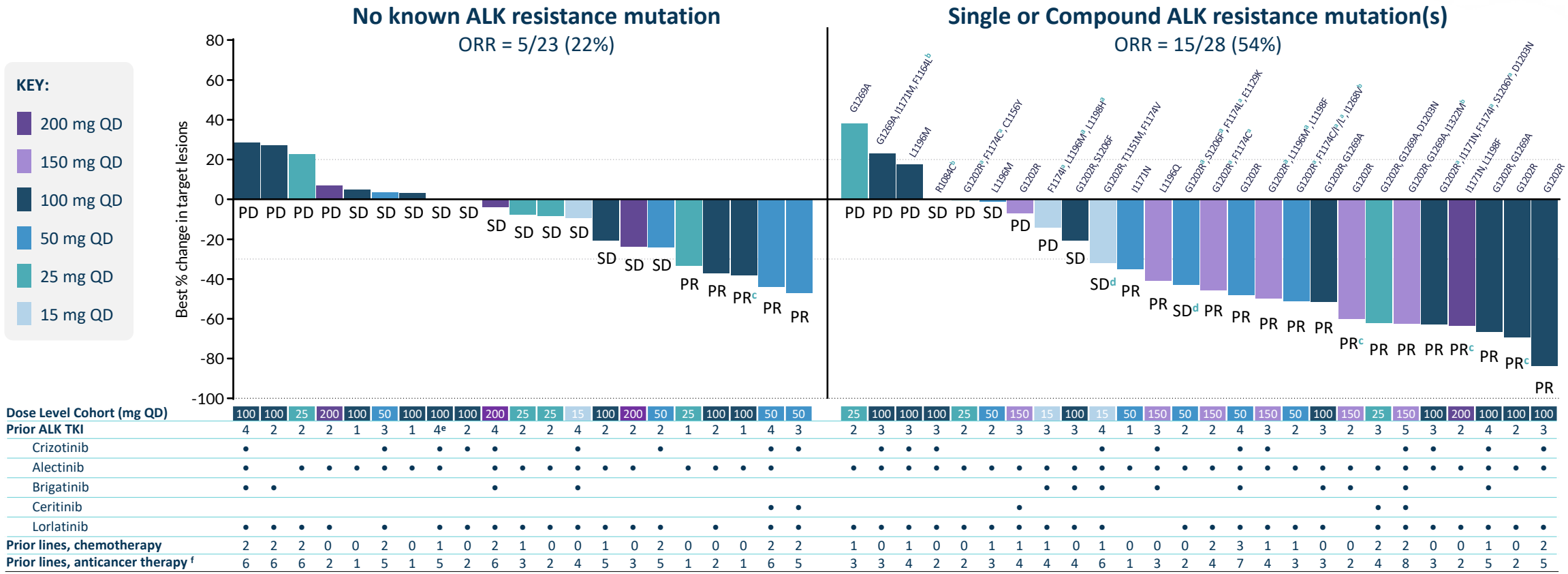
[b] Includes patients with single G1202R mutation (n=5) and G1202R with compound mutations (n=12; 6 with evidence of cis-allelic configuration).

[c] Includes 4 patients with ongoing partial responses pending confirmation.

[d] Three patients discontinued treatment due to clinical progression without post-baseline radiographic assessment.

Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

Preliminary Activity: Radiographic Tumor Response in Patients With and Without Known ALK Resistance Mutations



Dose Level Cohort (mg QD)	100	100	25	200	100	50	100	100	100	200	25	25	15	100	200	50	25	100	100	50	50	25	100	100	100	25	50	150	15	100	15	50	150	50	150	50	150	50	100	150	25	150	100	200	100	100	100
Prior ALK TKI	4	2	2	2	1	3	1	4e	2	4	2	2	4	2	2	2	1	2	1	4	3	2	3	3	3	2	2	3	3	3	4	1	3	2	2	4	3	2	3	2	3	5	3	2	4	2	3
Crizotinib	•					•		•	•	•			•			•				•	•		•	•				•				•				•	•				•	•		•			•
Alectinib	•		•	•	•	•	•	•		•	•	•	•	•	•		•	•	•	•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Brigatinib	•	•								•			•															•	•	•		•			•			•			•	•		•			•	
Ceritinib																				•	•									•													•	•					
Lorlatinib	•	•	•	•		•		•	•	•	•	•	•	•	•	•		•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Prior lines, chemotherapy	2	2	2	0	0	2	0	1	0	2	1	0	0	1	0	2	0	0	0	2	2	1	0	1	0	0	1	1	1	0	1	0	0	0	2	3	1	1	0	0	2	2	0	0	1	0	2
Prior lines, anticancer therapy f	6	6	6	2	1	5	1	5	2	6	3	2	4	5	3	5	1	2	1	6	5	3	3	4	2	2	3	4	4	4	6	1	3	2	4	7	4	3	3	2	4	8	3	2	5	2	5

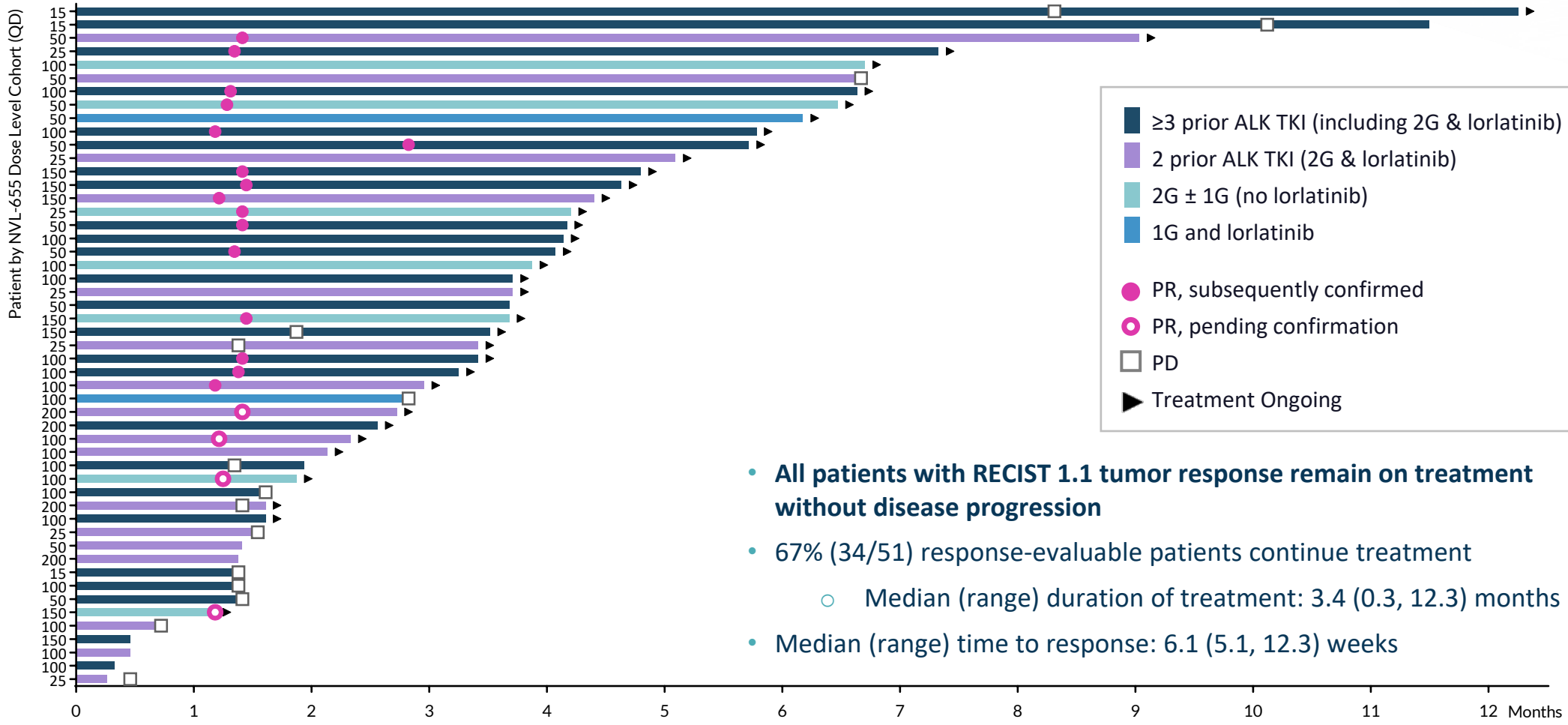
Data cut-off: 8 August 2023. Response-evaluable patients with NSCLC. Four response-evaluable patients (2 with no known ALK mutations and 2 with single or compound ALK mutations) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration. ALK mutation as per any prior local testing or central baseline ctDNA analyses. **PD**, progressive disease, **PR**, partial response, **QD**, once daily; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

[a] ALK mutations with evidence of cis-allelic configuration. [b] ALK mutation variant of unknown significance. [c] Ongoing partial responses pending confirmation. [d] Single-timepoint PR not confirmed. [e] Additional ALK TKI was TPX-0131.

[f] Including immunotherapy, bevacizumab, and investigational therapy. **Source**: Lin J.J. et al., AACR-NCI-EORTC 2023.

Nuvalent | ALKove-1

Time on Treatment: Sustained Duration with Follow-up Ongoing



- **All patients with RECIST 1.1 tumor response remain on treatment without disease progression**
- 67% (34/51) response-evaluable patients continue treatment
  - Median (range) duration of treatment: 3.4 (0.3, 12.3) months
- Median (range) time to response: 6.1 (5.1, 12.3) weeks

Data as of 8 August 2023, for response-evaluable patients with NSCLC. **PD**, progressive disease; **PR**, partial response; **QD**, once daily; **TKI**, tyrosine kinase inhibitor.

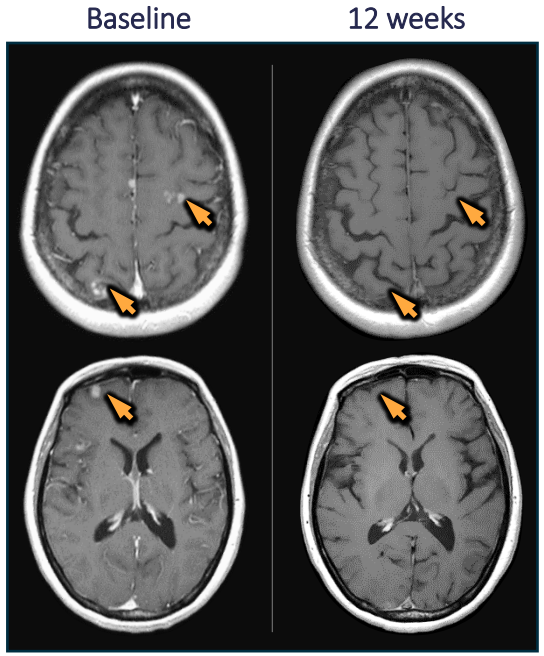
Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

Nuvalent | ALKove-1

CNS Activity: NVL-655 Induced Intracranial Responses in Patients with TKI-Refractory ALK+ NSCLC

Intracranial Complete Response in EML4-ALK fusion NSCLC:

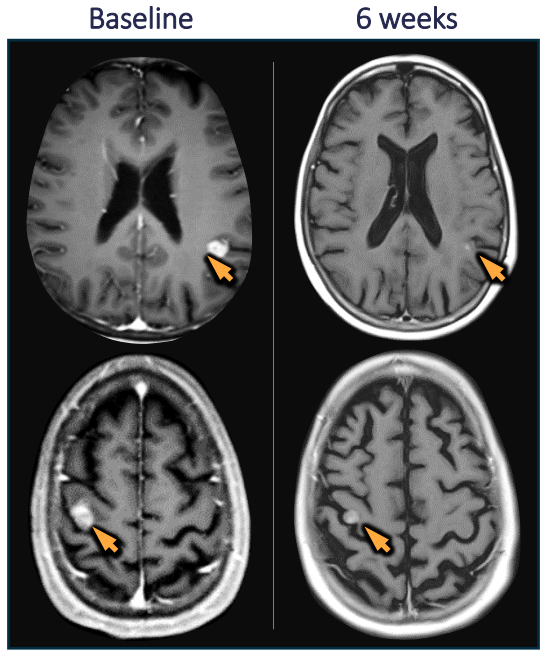
- EML4-ALK fusion NSCLC with no known ALK resistance mutations
- 5 lines of therapy, including crizotinib, ceritinib, lorlatinib and chemotherapy
- **NVL-655 (50 mg QD)**
  - ✓ **Complete resolution of parietal & parenchymal brain metastases after ~5 weeks**
  - ✓ **Treatment continues at 4.2 months with ongoing confirmed CNS CR**



Courtesy of Drs. Augusto Valdivia and Enriqueta Felip, Hospital Universitari Vall d'Hebron, Barcelona, Spain

Intracranial Partial Response in ALK L1196Q NSCLC:

- EML4-ALK fusion NSCLC with ALK L1196Q resistance mutation
- 3 lines of therapy consisting of crizotinib, alectinib, and brigatinib
- **NVL-655 (150 mg QD)**
  - ✓ **CNS PR after ~6 weeks**
  - ✓ **Treatment continues at 3.7 months with ongoing confirmed CNS PR (-59%)**



Courtesy of Dr. Joshua Reuss, Georgetown University, Washington DC, United States

Data as of 8 August 2023. **CNS**, central nervous system; **CR**, complete response; **NSCLC**, Non-small cell lung cancer; **PR**, partial response; **QD**, once daily; **TKI**, tyrosine kinase inhibitor.
Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

Nuvalent | ALKove-1

Preliminary Safety Profile: Favorable and Consistent with ALK-Selective, TRK-Sparing Design of NVL-655

- MTD has not been identified
  - 1 DLT: transient asymptomatic Grade 4 CPK increase (200 mg QD)
- Infrequent TRAEs requiring dose modification:
  - 2 (2%) discontinued due to TRAE [a]
  - 5 (5%) dose-reduced due to TRAE [b]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 5% of patients

All Treated Patients (N = 93)

	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)	Any Grade N (%)
Any TRAE	25 (27%)	14 (15%)	10 (11%)	49 (53%)
ALT increased	8 (9%)	4 (4%)	6 (6%)	18 (19%)
AST increased	11 (12%)	2 (2%)	4 (4%)	17 (18%)
Nausea	8 (9%)	1 (1%)	-	9 (10%)
Dysgeusia	7 (8%)	-	-	7 (8%)
Constipation	3 (3%)	3 (3%)	-	6 (6%)
Fatigue	5 (5%)	-	-	5 (5%)
Peripheral edema	4 (4%)	-	1 (1%)	5 (5%)

Data cut-off: 8 Aug 2023. **ALT**, Alanine aminotransferase; **AST**, Aspartate aminotransferase; **CPK**, creatinine phosphokinase; **DLT**, dose-limiting toxicity; **TRAE**, treatment-related adverse event.

[a] TRAEs resulting in treatment discontinuation were Grade 4 ALT/Grade 3 AST elevations (50 mg QD) and intolerable Grade 2 constipation (occurred at 100 mg QD following dose increase from 50 mg QD).

[b] TRAEs resulting in dose-reduction were Grade 2 ALT/AST elevation (50 mg), Grade 3 ALT/AST elevation (100 mg), Grade 2 nausea/cognitive disturbance (150 mg), Grade 4 CPK elevation (200 mg), and Grade 3 neutropenia (200 mg). Treatment continues at the reduced dose for 4 of these 5 patients.

Source: Lin J.J. et al., AACR-NCI-EORTC 2023.

NVL-655

Potential Best-in-class Profile for ALK+ NSCLC

Opportunity to both move up the treatment paradigm & grow the market with deep, durable responses

3L+

No clear standard of care (SOC)

~25 – 50% compound mutations

> 60% CNS disease

Demonstrated activity where current available therapies have failed

- ✓ Clinical activity observed in heavily-pretreated patients:
  - Who likely exhausted all available therapies
  - With single AND compound ALK mutations
  - With history of CNS metastasis, including intracranial responses

2L

Current SOC: Lorlatinib

~50% single mutations

> 60% CNS disease

Opportunity to differentiate with deep, durable responses and TRK-sparing profile

- ✓ Clinical activity observed in patients with single AND compound resistance mutations
- ✓ Clinical activity observed in patients who are lorlatinib naïve (ORR: 71%, 5/7)
- ✓ Favorable overall preliminary safety profile consistent with avoiding TRK-related neurotoxicities

1L

Current SOC: Alectinib

ALK: ~3 – 5% of NSCLC

~30 – 40% CNS disease

Opportunity to supplant standard of care with a differentiated profile

- ✓ Potential to address combined medical needs: ALK mutation coverage **+** CNS activity **+** avoiding off-target adverse events
- ✓ Opportunity to drive deep, durable responses
  - Comparative results for lorlatinib (CROWN) and alectinib (ALEX) suggest that PFS prolongment is possible in the 1L
  - TRK-related adverse events may continue to limit adoption of lorlatinib in 1L

Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted.

Sources: Cortellis Sales and Forecasts, accessed November 2023; Ou and Zhu Lung Cancer 2019; Kris et. al. JAMA 2014; Shaw and Engelman J Clin Onc 2013; Noé et. al. J Thor Onc 2019; Peters et. al. NEJM 2017; Shaw et. al. Lancet Onc 2017; Dagogo-Jack et. al. Clin Cancer Res 2019; Lin J.J. et al., AACR-NCI-EORTC 2023; FDA Package Inserts for alectinib and lorlatinib; Camidge D.R., J Thorac Oncol. 2021.

Nuvalent

Planned Clinical Development for ALK+ NSCLC

Multi-pronged development strategy supports goal of moving up the treatment paradigm

ALKOVE-1

for **previously-treated ALK+ NSCLC (lorlatinib-naïve and lorlatinib-treated)**

Planned global open-label multi-cohort Phase 2 with registrational intent for 2L+

+

1L ALK+ NSCLC Strategy (TKI-naïve)

Planned head-to-head phase 3 study with registrational intent

ALKOVE-1 Phase 2: Opportunity for accelerated approval in 2L+

ALKOVE-1 COHORT	TUMOR TYPE	PRIOR ALK TKI	PRIOR CHEMO/I-O	DETAIL
2a	ALK+ NSCLC	**1 prior 2G** *(ceritinib, alectinib, or brigatinib)*	0-2 lines	**Registrational Intent**
2b	ALK+ NSCLC	**2-3 prior 1G or 2G** *(crizotinib, ceritinib, alectinib, or brigatinib)*	0-2 lines	
2c	ALK+ NSCLC	**2-3 prior with lorlatinib in 2nd or 3rd line of therapy**	0-2 lines	
2d	Any ALK+ Solid Tumor	**≥ 1 prior ALK TKI or systemic therapy** (or for whom no satisfactory standard therapy exists)	Any	**Exploratory Cohort**

ALKOVE-1 PHASE 2 OBJECTIVES

- **Primary:** ORR by blinded, independent central review
- **Secondary:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile

1L, 1st line; **2L**, 2nd line; **3L**, 3rd Line; **CBR**, clinical benefit rate; **DOR**, duration of response; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression free survival; **PK**, pharmacokinetics; **TKI**, tyrosine kinase inhibitor; **TTR**, time to response.

Nuvalent

NVL-520 *for* ROS1+ NSCLC

A brain-penetrant, selective inhibitor of ROS1 and ROS1 resistance mutations with the potential to minimize TRK-related CNS adverse events while providing CNS antitumor activity

AT · A · GLANCE

Mechanism of Action:
ROS1-selective tyrosine kinase inhibitor

Stage of Development:
Global Phase 2 with registrational intent

Initial Development Indication:
ROS1-positive NSCLC

FDA Designations:
Orphan Drug Designation

Nuvalent

ROS1+ NSCLC Patient Journey

~1 – 3% of NSCLC [1,2] | Majority are advanced/metastatic at diagnosis [3]

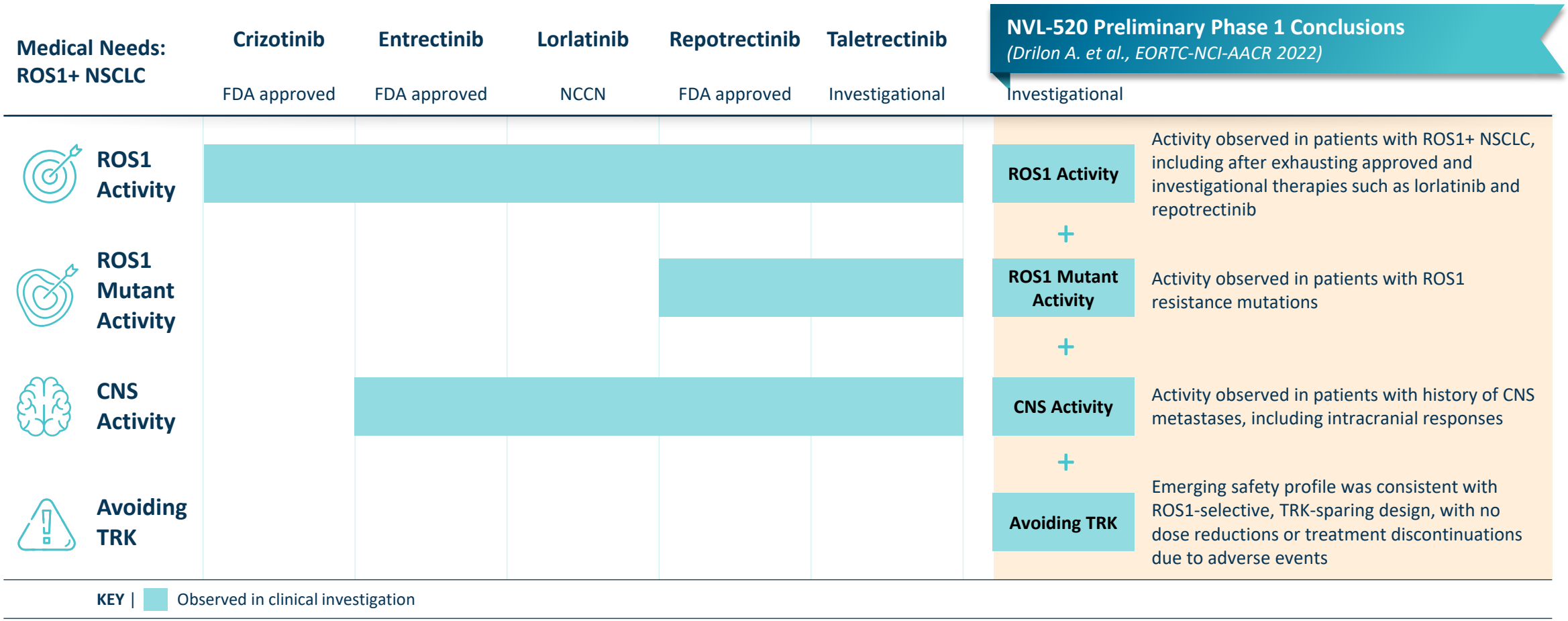
Illustrative patient image

	1L	2L+
STANDARD OF CARE	**Crizotinib** ($465M WW sales, 2022) [4] • Crizotinib, entrectinib, and repotrectinib are FDA approved (line-agnostic) [5] • Ceritinib included in NCCN guidelines as an alternative option [5]	**No clear standard of care** • In addition to 1L options, lorlatinib is included in NCCN guidelines as an option following 1L TKI [5] • Patients may consider clinical trials or chemotherapy/I-O [5]
KEY LIMITATIONS	**Brain penetrance** ○ *~20 – 40% present with brain metastases at diagnosis [6,7]* ○ *~50% of patients progressing on crizotinib have brain metastases [7]* **Coverage of ROS1 resistance mutations** ○ *~40% of patients progressing on crizotinib have G2023R ROS1 resistance mutation [8]*	**Activity in TKI-experienced patients** ○ *Repotrectinib has been studied in patients with 1 prior ROS1 TKI and no prior chemo/I-O, with ORR of 38% (N = 56) [9]* **Treatment-limiting off-target adverse events** ○ *CNS adverse events associated with TRK-inhibition observed in 75% of patients receiving repotrectinib [9, 10, 11]*

Sources: [1] Drilon A. et al., Nat Rev Clin Oncol. 2021. [2] Jordan E.J. et al., Cancer Discovery 2017. [3] Parikh D.A. et al., JCO Oncol Pract. 2020. [4] Cortellis Sales and Forecasts, accessed November 2023. [5] NCCN Guidelines for NSCLC (version 5.2023). [6] Ou S.I. and Zhu V.W., Lung Cancer 2019. [7] Patil T. et al., J Thorac Oncol. 2018. [8] Gainor J.F. et al., JCO Precision Oncol. 2017. [9] FDA Prescribing Information. [10] Cocco, E. et al. Nat Rev Clin Oncol. 2018; [11] Shaw, A. et al. NEJM 2020.

Nuvalent

NVL-520: A Rationally Designed ROS1-selective, TRK-sparing Inhibitor



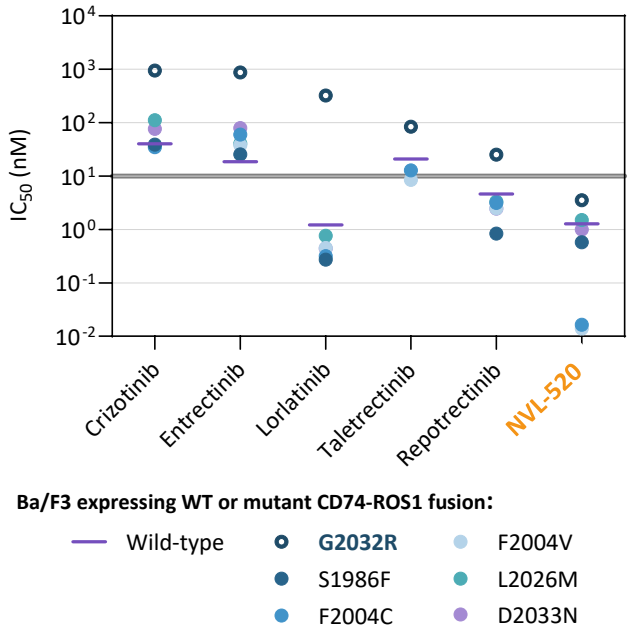
Source: Drilon A. et al., EORTC-NCI-AACR 2022. ***Head-to-head clinical studies comparing NVL-520 with currently approved or investigational therapies have not been conducted.***

Nuvalent

Preclinical Characterization Demonstrates Desired Target Product Profile

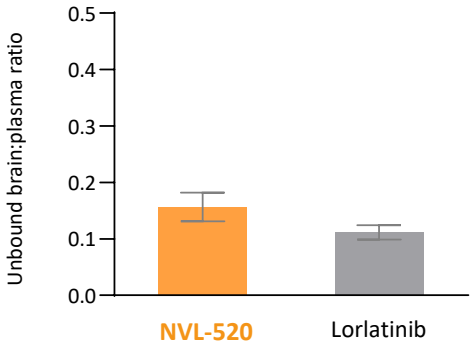
In Vitro Activity, ROS1 Wild-type & Mutant

Sub-10nM activity in 3-day cell viability assays



Brain Penetrance

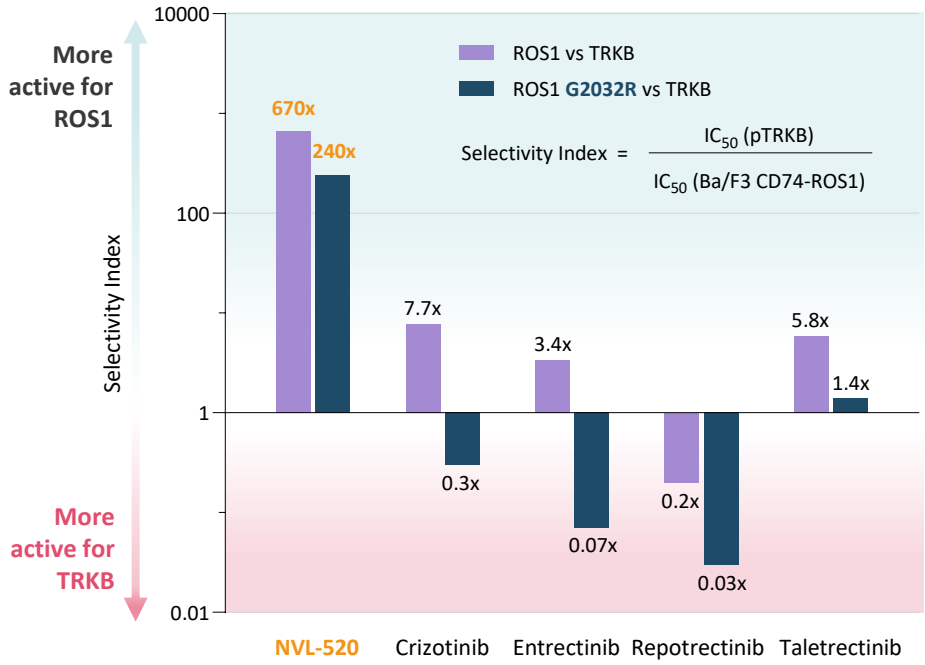
Pharmacokinetic data similar to preclinical observations for lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1 hour timepoint

Avoiding TRK Inhibition

Selectivity for ROS1 and ROS1 G2032R over TRK



Head-to-head clinical studies comparing NVL-520 with currently approved or investigational therapies have not been conducted. Above data from preclinical studies.

BID, twice daily; **IC50**, half-maximal inhibitory concentration; **PDC**, patient-derived cell line; **PO**, orally; **pTRK**, BDNF-stimulated TRKB phosphorylation.

Sources: Drilon A. et al., Cancer Discov 2023; Tangpeerachaikul, A. et al., AACR 2022; Deshpande, A. et al., EORTC-NCI-AACR 2021; Pelish, H.E. et al., AACR 2021.

Nuvalent

A Global First-in-Human Phase 1/2 Clinical Trial of NVL-520 in Advanced ROS1-Positive NSCLC and Other Solid Tumors (NCT05118789)

PHASE 1 DOSE-ESCALATION

Phase 1 enrollment completed August 2023: Updated data to be presented at a medical meeting in 2024

PATIENT POPULATION

- Advanced solid tumors harboring ROS1 fusions (by local testing)
- ≥ 1 prior ROS1 TKI for NSCLC
- No limit to number of prior chemotherapies or immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., EGFR, ALK, MET, RET, or BRAF) [a]
- Evaluable but non-measurable disease allowed [a]

OBJECTIVES

- Selection of RP2D and, if applicable, MTD (primary)
- Overall safety and tolerability
- PK characterization
- Preliminary antitumor activity
- Intracranial activity

Preliminary Phase 1 data presented October 2022: All-Treated Population (N = 35)

Enrollment initiated January 2022 (Data as of 13 Sep 2022, for patients treated by 01 Sep 2022)

NVL-520 Dose Cohorts	All Doses	25 mg QD	50 mg QD	75 mg QD	100 mg QD	125 mg QD
BOIN Dose-Escalation	N = 15	3	3	3	3	3
Expansion (For Dose Optimization)	N = 20	6	1	6	7	0
All-Treated Population	**N = 35**	**9**	**4**	**9**	**10**	**3**
NSCLC Response-Evaluable Population [b]	**N = 21**	**7**	**2**	**5**	**4**	**3**

CNS, central nervous system; DLTs, dose-limiting toxicities; mg, milligram; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase 2 dose; ROS1+, ROS1-positive; TKI, tyrosine kinase inhibitor.

[a] Patients with baseline concurrent oncogenic drivers identified on subsequent testing and patients without measurable disease are excluded from efficacy evaluation per prespecified protocol analysis plan.

[b] First response evaluation is pending for 6 patients. Response evaluable population prospectively defined as all NSCLC patients with measurable disease, without concurrent oncogenic driver, and who undergo ≥1 post-baseline response assessment (or discontinue treatment due to clinical progression/death prior to the first response assessment). Additional patients unevaluable for response: no measurable disease at baseline (n = 3); tumor with alternate oncogenic driver (MET amplification, BRAF V600E) (n = 3); voluntarily discontinued study treatment prior to first response assessment (n = 1); other solid tumor (pancreatic cancer) (n = 1).

Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent

Patient Population: Heavily Pretreated ROS1+ Solid Tumors

Patient Characteristic	All Treated (N = 35)
Age, median (range)	57 (29, 80)
Female	24 (69%)
Tumor Type	
NSCLC	34 (97%)
Pancreatic adenocarcinoma	1 (3%)
ECOG PS	
0	9 (26%)
1	25 (71%)
2	1 (3%)
Non-smoker	25 (71%)
History of CNS metastases [a]	18 (51%)
Measurable (RECIST 1.1) CNS lesions	3 (9%)

Treatment History	All Treated (N = 35)
Prior lines of anticancer treatment	
1	2 (6%)
2	6 (17%)
≥3	**27 (77%)**
Median (range)	3 (1, 11)
Prior treatments	
1 ROS1 TKI without chemotherapy	3 (9%)
1 ROS1 TKI and ≥1 chemotherapy	4 (11%)
≥2 ROS1 TKIs without chemotherapy	3 (9%)
≥2 ROS1 TKIs and ≥1 chemotherapy	**25 (71%)**
ROS1 TKIs received [b]	
Crizotinib	24 (69%)
Entrectinib	11 (31%)
Other ROS1 TKI	**28 (80%)**
Lorlatinib	20 (57%)
Repotrectinib	12 (34%)
Ceritinib	2 (6%)
Cabozantinib	1 (3%)

Data as of 13 Sep 2022, for patients treated by 01 Sep 2022. All data shown as n (%) unless otherwise specified. **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **NSCLC**, non-small cell lung cancer; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **TKI**, tyrosine kinase inhibitor.

[a] Includes patients with untreated CNS lesions. [b] Categories are not mutually exclusive.

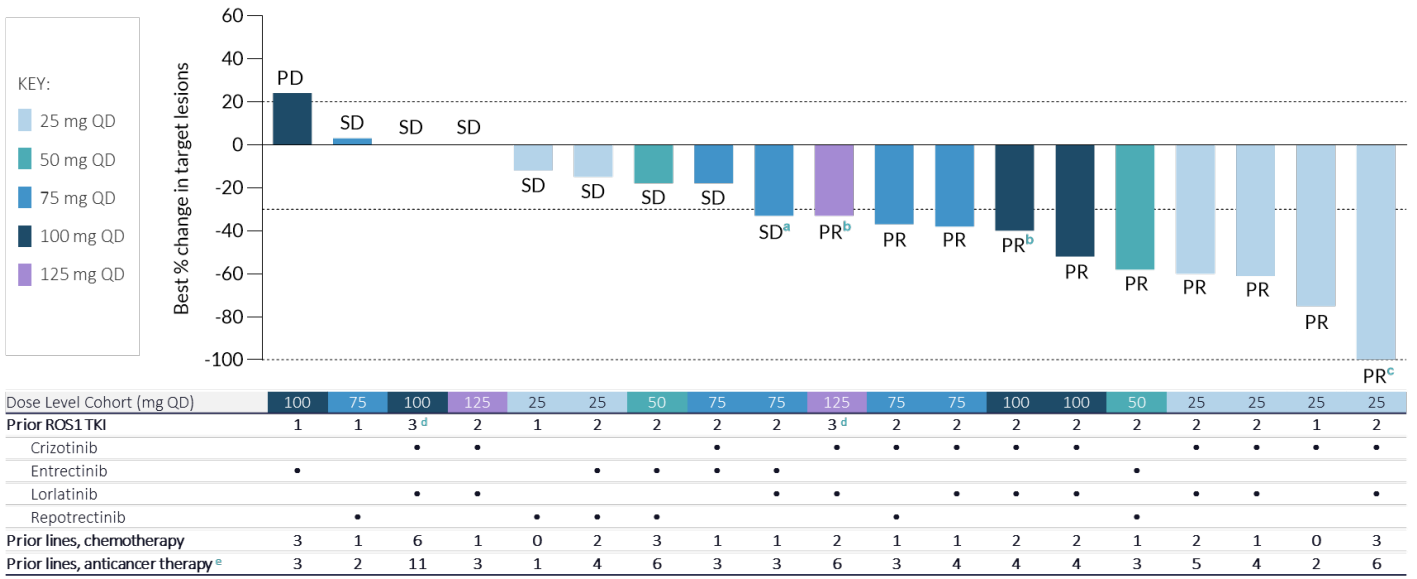
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Preliminary Activity

- NVL-520 induced tumor response across heavily pretreated patient populations
- Radiographic tumor regression observed across all NVL-520 dose levels

Patients with ROS1+ NSCLC	All NSCLC Response-Evaluable	ROS1 G2032R Resistance Mutation	History of CNS Metastases	≥2 Prior ROS1 TKI and ≥1 Chemotherapy	Prior Lorlatinib or Repotrectinib [d]
ORR across all dose levels (RECIST 1.1)	**48% (10/21)**	**78% (7/9)**	**73% (8/11)**	**53% (9/17)**	**50% (9/18)**
Best Response					
PR	**10** [a]	**7** [b]	**8** [a]	**9** [a]	**9** [a]
SD	**8**	**2**	**2**	**6**	**7**
PD	**2**	**0**	**1**	**1**	**1**
NE	**1** [c]	**0**	**0**	**1** [c]	**1** [c]

[a] Includes 2 ongoing partial responses pending confirmation. [b] Includes 1 ongoing partial response pending confirmation.
[c] Patient discontinued treatment due to clinical progression without post-baseline radiographic assessment.
[d] These prior ROS1 TKIs were discontinued due to progressive disease in 17/18 patients.



Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3 [d]	2	1	2	2	2	2	3 [d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
Prior lines, chemotherapy	3	1	6	1	0	2	3	1	1	2	1	1	2	2	1	2	1	0	3
Prior lines, anticancer therapy [e]	3	2	11	3	1	4	6	3	3	6	3	4	4	4	3	5	4	2	6

Data as of 13 Sep 2022, for response-evaluable patients with NSCLC treated by 01 Sep 2022.

CNS, central nervous system, **NE**, not evaluable; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **QD**, once daily; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

Footnotes for waterfall: Two patients (25 mg QD and 125 mg QD dose cohorts, both with prior therapies consisting of crizotinib, lorlatinib and chemotherapy) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD and symptomatic deterioration.
[a] Single-timepoint PR not confirmed.
[b] Ongoing partial responses pending confirmation.
[c] Best response PR due to residual nontarget disease.
[d] Additional prior ROS1 TKI was ceritinib.
[e] Including immunotherapy, bevacizumab, and investigational therapy.

Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent | ARROS-1

Key Subgroups

ROS1 Resistance Mutations:

- Subgroup with known ROS1 G2032R resistance mutation:
  - ORR: 78% (7/9) [a]
  - 100% (9/9) with tumor shrinkage
- One patient with **ROS1 D2033N** with ongoing PR (-40%) pending confirmation

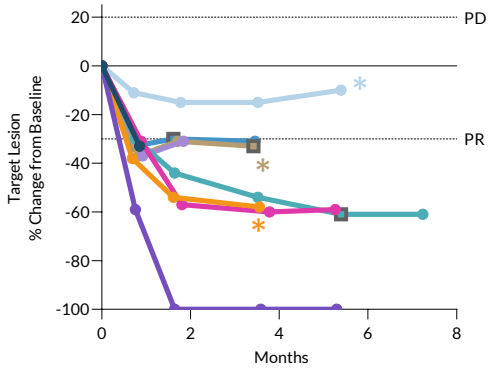
CNS Activity:

- Intracranial PR in 3/3 [d] patients with measurable (>10 mm) CNS metastases
- ORR of 73% (8/11) [e] in response-evaluable patients with history of CNS metastases
- No CNS progression observed in any of the 35 treated patients

Source: Drilon A. et al., EORTC-NCI-AACR 2022.

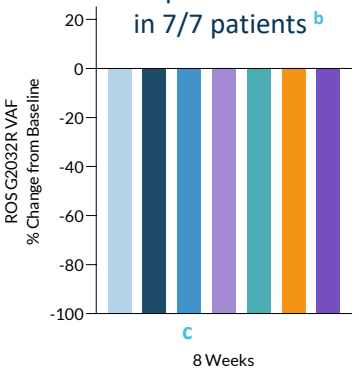
NVL-520 Induced Rapid Responses in TKI-Resistant Patients

Reduction in Tumor Burden in Cancers with ROS1 G2032R



Reduction in ROS1 G2032R Allele

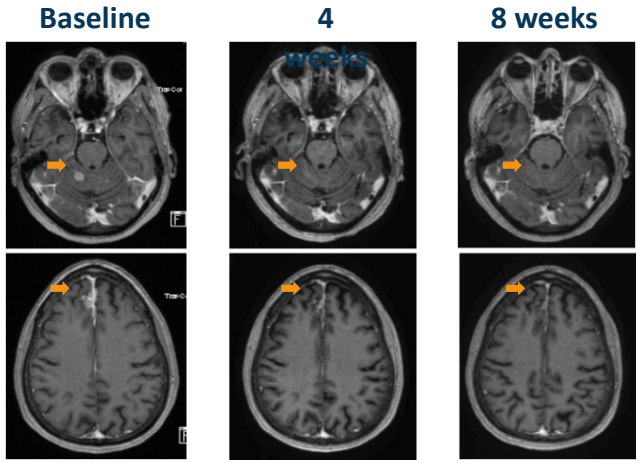
Complete clearance in 7/7 patients [b]



KEY

- Each unique color indicates data from the same patient across both figures
- PD (due to new lesions and/or progression of nontarget lesions)
- * Prior treatments include repotrectinib (Best response on NVL-520: 2 PR, 1 SD)

NVL-520 Induced Responses in Intracranial Lesions



Intracranial response in 65-year-old female with CD74-ROS1 fusion NSCLC, previously treated with chemotherapy, crizotinib, and lorlatinib with CNS progression and no known ROS1 resistance mutations. Patient continues NVL-520 (100 mg QD) at 3.2 months with ongoing response.

Images courtesy of Jessica J Lin Massachusetts General Hospital

Data as of 13 Sep 2022, for patients treated by 01 Sep 2022.

CNS, central nervous system; **ctDNA**, circulating tumor deoxyribonucleic acid; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **QD**, once daily; **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

[a] Includes 1 ongoing partial response pending confirmation.

[b] Central ctDNA analysis by Guardant 360; includes patients with detectable ROS1 G2032R at baseline and at least one on-treatment follow-up assessment.

[c] Bar represents week 2 result; week 8 results are pending.

[d] One patient with an ongoing intracranial PR pending confirmation.

[e] Includes 2 ongoing partial responses pending confirmation.

Nuvalent | ARROS-1

Preliminary Safety Profile: Favorable and Consistent with the Highly ROS1-Selective, TRK-Sparing Design of NVL-520

- No DLTs
- No treatment-related SAEs
- No AEs leading to dose reduction or discontinuation
- No treatment-related dizziness

Treatment-Related Adverse Events (TRAEs) in >1 Patient

All Treated Patients (N = 35)

	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)	Any Grade N (%)
Fatigue	4 (11%)	-	-	4 (11%)
Nausea	3 (9%)	-	-	3 (9%)
ALT increased	2 (6%)	-	-	2 (6%)
AST increased	2 (6%)	-	-	2 (6%)
Oedema [a]	1 (3%)	1 (3%)	-	2 (6%)
Myalgia	2 (6%)	-	-	2 (6%)

Data as of 13 Sep 2022, for patients treated by 01 Sep 2022. **AE**, adverse event; **ALT**, Alanine aminotransferase; **AST**, Aspartate aminotransferase; **DLT**, dose-limiting toxicity; **SAE**, serious adverse event.

[a] Including oedema and oedema peripheral.

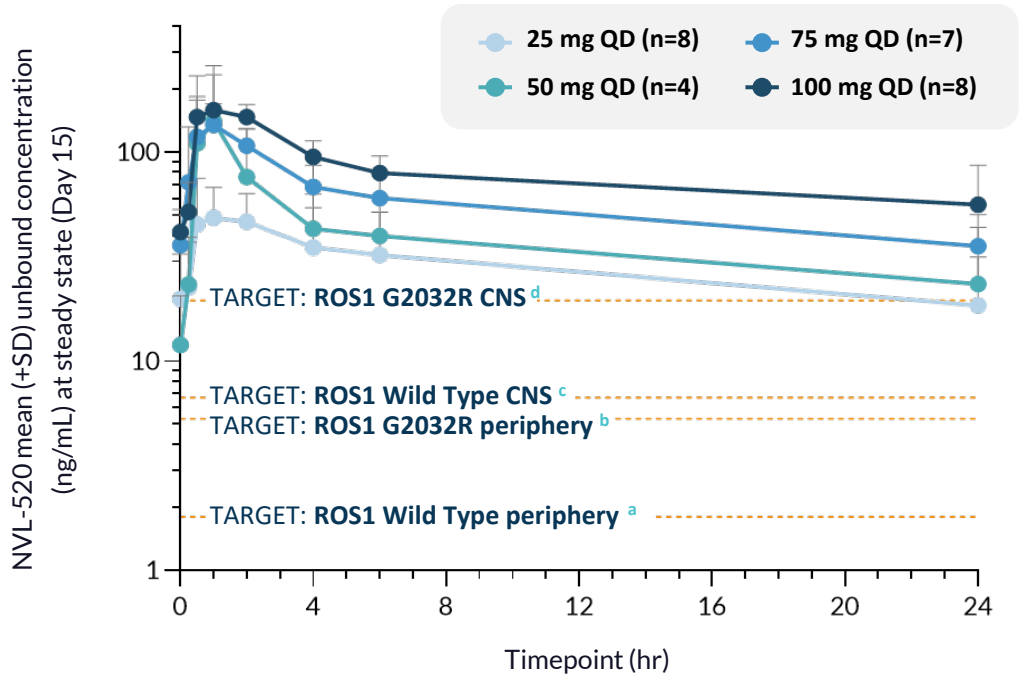
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

RP2D of 100mg QD Met All Desired Clinical Characteristics

Favorable tolerability of NVL-520 was observed in 87 ROS1+ patients enrolled across six dose levels (25 mg QD – 150 mg QD) as of May 2023:

- ✓ MTD was not reached
- ✓ No clinically significant exposure-response relationships for safety and efficacy were observed
- ✓ Wide therapeutic window was consistent with ROS1-selective, TRK-sparing design
- ✓ **The dose level of 100 mg daily maintained steady state plasma levels above all target efficacy thresholds**

Preliminary pharmacokinetic profile (Presented October 2022)



Data as of 13 Sep 2022, for patients treated by 01 Sep 2022. Pharmacokinetic data for 125 mg QD cohort are not shown due to immaturity.

CNS, central nervous system; **h**, hours; **PK**, pharmacokinetics; **QD**, once daily; **SD**, standard deviation.

[a, b] Based on tumor regression in in vivo models bearing SDC4-ROS1 and CD74-ROS1 G2032R, respectively. [c, d] Values for a and b divided by predicted human CNS Kp (brain to plasma ratio), respectively.

Source: Data on file; Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent | ARROS-1

Potential Best-in-class Profile for ROS1+ NSCLC

Opportunity to both move up the treatment paradigm & grow the market with deep, durable responses

2L+

No clear standard of care (SOC)

~40% ROS1 G2032R mutation

~30 – 55% CNS disease

Demonstrated activity where current available therapies have failed

- ✓ Clinical activity observed in heavily pretreated patients with ROS1+ NSCLC:
  - Who likely exhausted all available therapies, including after lorlatinib or repotrectinib (ORR: 50%)
  - With ROS1 resistance mutations (ORR: 78%)
  - With history of CNS metastasis (ORR: 73%) including intracranial responses (3/3 PRs)

1L

Current SOC: Crizotinib

ROS1: ~1 – 3% of NSCLC

~20 – 40% CNS disease

Opportunity to supplant standard of care with a differentiated profile

- ✓ Potential to address combined medical needs: ROS1 mutation coverage **+** CNS activity **+** avoiding off-target adverse events
- ✓ Opportunity to drive deep, durable responses
- ✓ Favorable preliminary safety profile consistent with ROS1-selective, TRK-sparing design

Sources: Cortellis Sales and Forecasts, accessed November 2023; Lin et al., J Thorac Oncol 2017; Gainor et al, JCO Precision Oncol 2017; Ou and Zhu Lung Cancer 2019; Patil et al, JTO 2018; Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent

Clinical Development Strategy for ROS1+ NSCLC

Ongoing ARROS-1 Phase 2 supports goal of moving up the treatment paradigm

ARROS-1

for **TKI-naïve and TKI pre-treated ROS1+ NSCLC (N ≈ 225)**

Ongoing global open-label, multi-cohort Phase 2 with registrational intent

- Enrollment planned across North America, Europe, Asia and Australia
- All patients receive NVL-520 at 100 mg QD
- **Primary Objective:** ORR by blinded, independent central review
- **Secondary Objectives:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile, PROs

ARROS-1 Phase 2: Opportunity for approval in both 2L+ and 1L

ARROS-1 COHORT	N[a]	TUMOR TYPE	TREATMENT STATUS	PRIOR ROS1 TKI	PRIOR CHEMO/I-O	DETAIL
2a	~78	ROS1-positive NSCLC	ROS1 TKI Naive	None	≤ 1	Registrational Intent
2b	~59	ROS1-positive NSCLC	ROS1 TKI Pre-treated	1[b]	None	
2c	~45			1[b]	1[c]	
2d	~23			≥ 2[d]	≤ 1	
2e	~20	Any ROS1-positive Solid Tumor[e]	Any Prior Therapy	Any	Any	Exploratory Cohort

1L, 1st line; **2L**, 2nd line; **CBR**, clinical benefit rate; **DOR**, duration of response; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression free survival; **PK**, pharmacokinetics; **PRO**, patient reported outcomes; **QD**, once daily; **TKI**, tyrosine kinase inhibitor; **TTR**, time to response.
[a] Approximate cohort size, subject to change; [b] Either crizotinib or entrectinib; [c] Platinum-based chemotherapy with or without immunotherapy; [d] With initial TKI of either crizotinib or entrectinib; [e] Includes NSCLC who do not qualify for any of the other cohorts.

Nuvalent

NVL-330 *for* HER2+ NSCLC

A brain-penetrant, HER2-selective inhibitor with activity against HER2 mutations and the potential to minimize EGFR-related adverse events

AT A GLANCE

Mechanism of Action:
HER2-selective tyrosine kinase inhibitor

Stage of Development:
IND-enabling studies; Phase 1 initiation planned in 2024

Initial Development Indication:
HER2-positive NSCLC

Target Product Profile:

Active against HER2 and HER2ex20

EGFR sparing
Related adverse events include skin rash and diarrhea

Brain penetrant
~19% of patients with HER2-positive NSCLC present with brain metastases

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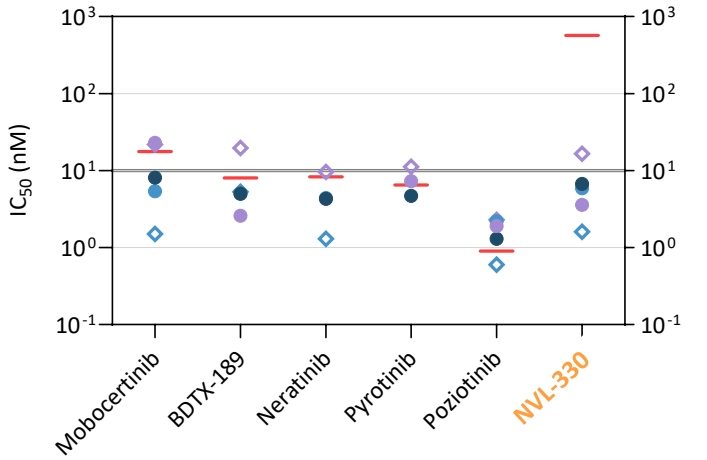
Preclinical Characterization Demonstrates Desired Target Product Profile

In Vitro Activity, HER2 AND HER2ex20

Potent inhibition of HER2 and HER2ex20 mutations in cell-based phosphorylation and viability assays



pHER2 Assays:
- Ba/F3 HER2^{YVMA}
- NCI-H1781 (HER2^{VC})
- NCI-N87 (HER2^{amp})

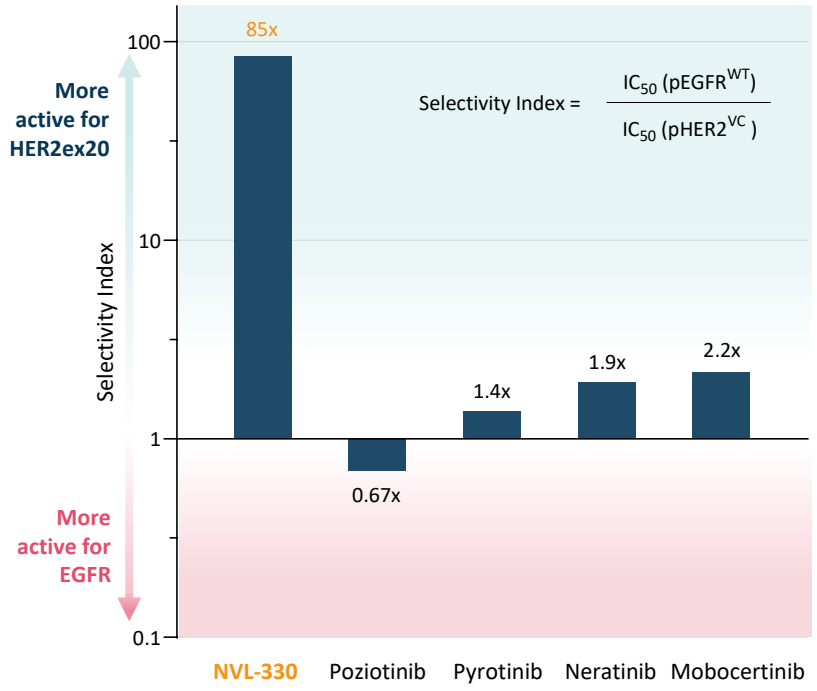
Viability Assays:
- Ba/F3 HER2^{YVMA}
- NCI-N87 (HER2^{amp})

pEGFR Assay:
- A431 (EGFR^{WT})

HER2 Exon 20 insertion mutations, such as Y772dupYVMA (HER2^{YVMA}) and G776del insVC (HER2^{VC}), induce constitutive kinase activation.

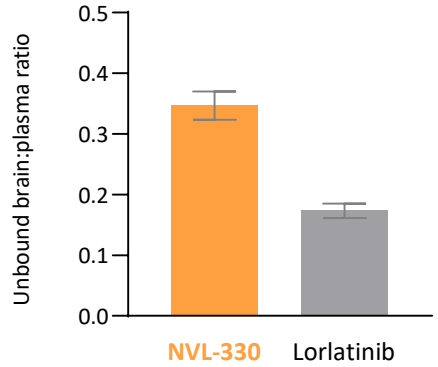
Avoiding EGFR Inhibition

Greater selectivity for HER2ex20 mutations over EGFR than pan-ERBB inhibitors



Brain Penetrance

Pharmacokinetic data similar to preclinical observations for lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1 hour timepoint

No head-to-head clinical studies have been conducted for currently approved or investigational therapies versus NVL-330. Above data from preclinical studies. **HER2ex20**, HER2 exon 20 insertion; **IC50**, half-maximal inhibitory concentration; **PO**, orally.
Source: Andrews K.L. et al., EORTC-NCI-AACR 2022.

Nuvalent

The Path to Patient Impact

Program Status:

- **NVL-520 (ARROS-1 study *for* ROS1+ NSCLC)**
  Phase 2 ongoing with registrational intent for patients with 1L and 2L+ ROS1+ NSCLC
- **NVL-655 (ALKOVE-1 study *for* ALK+ NSCLC)**
  Demonstrated clinical proof-of-concept in Phase 1 with planned development in both 1L and 2L+ ALK+ NSCLC
- **NVL-330 *for* HER2+ NSCLC**
  Planned Phase 1 initiation in 2024
- **Additional Discovery Research Programs Ongoing**

OnTarget 2026

MISSION: Bringing new, best-in-class medicines to patients with cancer

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