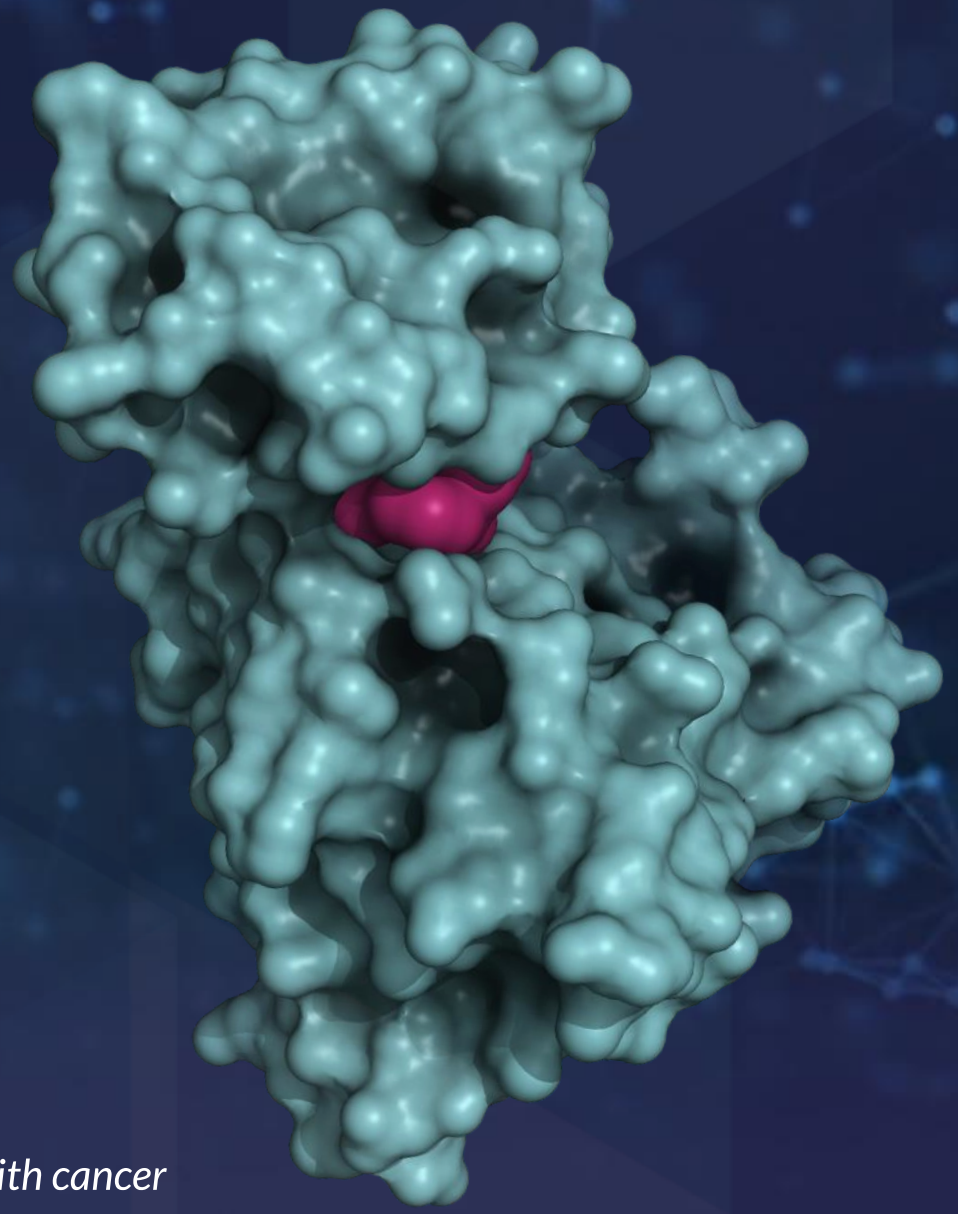
Nuvalent

Corporate Overview

May 11, 2023



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; the expected timing of data announcements; the preclinical and clinical development programs for NVL-520, NVL-655 and NVL-330; the potential clinical effect of NVL-520 and NVL-655; the design and enrollment of the ARROS-1 and ALKOVE-1 studies; the potential of Nuvalent's pipeline programs, including NVL-520, NVL-655 and NVL-330; 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.

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PRECISELY

Targeted Therapies *for patients with cancer*

Chemistry at the core

Expertise in chemistry and structure-based drug design drives wholly-owned pipeline of novel **targeted therapies**

Built for Patients

Our mission is to bring new *medicines* to **patients with cancer**

Driven by Purpose

Precisely designed solutions aiming to overcome limitations of existing therapies identified through close collaboration with physician-scientists

Nuvalent

2022 IN REVIEW

ARROS-1
NVL-520

Preliminary Phase 1 data presented at EORTC-NCI-AACR:
ARROS-1 Phase 1/2 study of NVL-520 for patients with advanced ROS1-positive NSCLC and other solid tumors

ALKove-1
NVL-655

Trial initiated for parallel lead program:
ALKOVE-1 Phase 1/2 study of NVL-655 for patients with advanced ALK-positive NSCLC and other solid tumors, with update on preliminary dose-escalation data expected in 2H'23

Nominated 3rd development candidate: NVL-330, a HER2ex20-selective inhibitor

Continued advancement of internal research & discovery pipeline

Continued team growth (60+ FTEs)

$264.5M upsized financing expected to extend cash runway into 2nd half of 2025

Vision

Discover, Develop & Deliver

Fully integrated pharmaceutical company with the goal of translating deep expertise in chemistry & structure-based drug design into best-in-class small molecule medicines for patients with cancer

Nuvalent

The Nuvalent Team

Significant Experience in Drug Discovery, Development and Company Building

LEADERSHIP TEAM

James Porter, PhD
Chief Executive Officer

Alex Balcom, MBA, CPA
Chief Financial Officer

Christopher Turner, MD
Chief Medical Officer

Deborah Miller, PhD, JD
Chief Legal Officer

Darlene Noci, ALM
Chief Development Officer

Ruth Adams
VP, Clinical Operations

Josh Horan, PhD
VP, Chemistry

Benjamin Lane, PhD
SVP, Technical Operations

Jessie Lin
VP, Corporate Strategy & Portfolio Management

Matthew Metivier
VP, Human Resources

Henry Pelish, PhD
SVP, Drug Discovery

John Soglia, PhD
SVP, Translational Development

PRIOR FDA APPROVAL EXPERIENCE

ALUNBRIG, MOZOBIL, ICLUSIG, Clolar, BAVENCIO, pyrukynd, GAVRETO, TIBSOVO, Copiktra, Fabrazyme, Brukinsa, Tivicay

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Translational Research Advisor
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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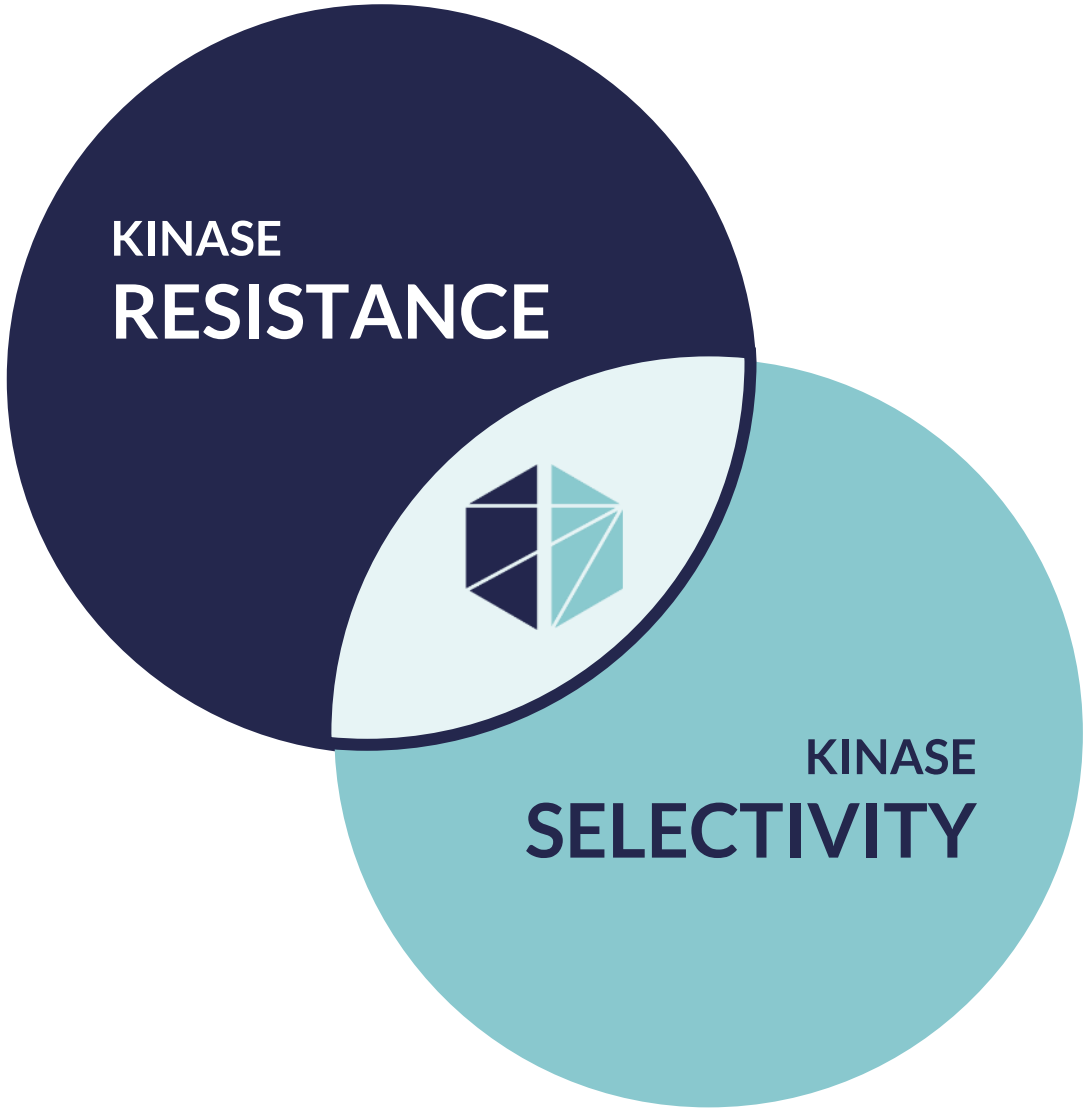
PRECISELY Targeted Therapies *for patients with cancer*

Nuvalent is focused on creating ***precisely*** **targeted therapies** to overcome key limitations of existing therapies for clinically proven kinases and renew hope for patients in need

- Expertise in structure-based drug design to create innovative small molecules
- "**Threading the needle**": Aim to achieve high affinity for drug-resistant kinases while avoiding off-target kinases in the central nervous system (CNS) and in the periphery
    - Potential to minimize adverse events **AND** drive more durable responses



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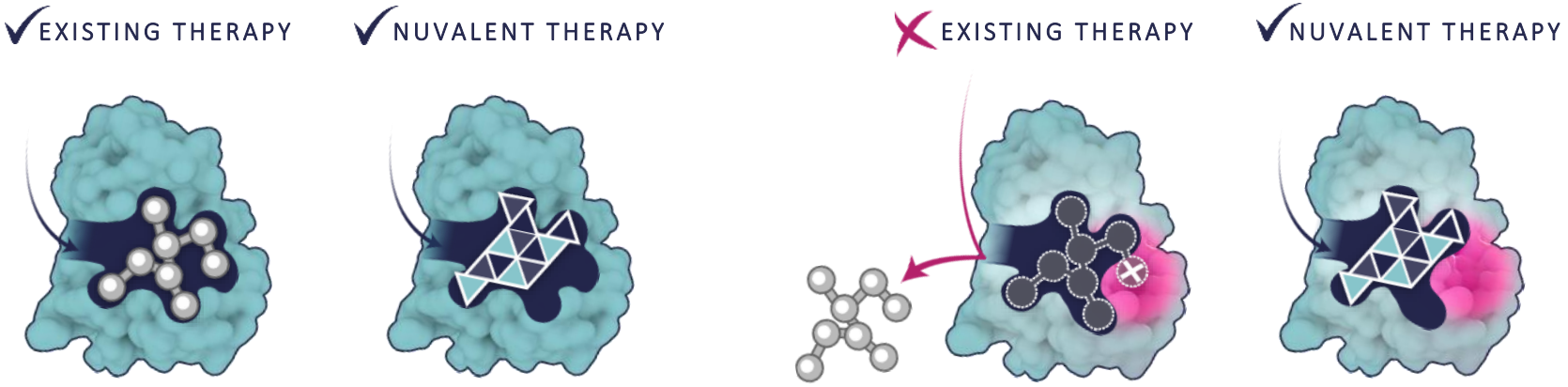
Kinase Resistance

Structural innovations designed to overcome drug-resistance due to kinase mutations



Successful inhibition of target kinase

Mutation confers resistance

Designed to overcome drug-resistance mutation

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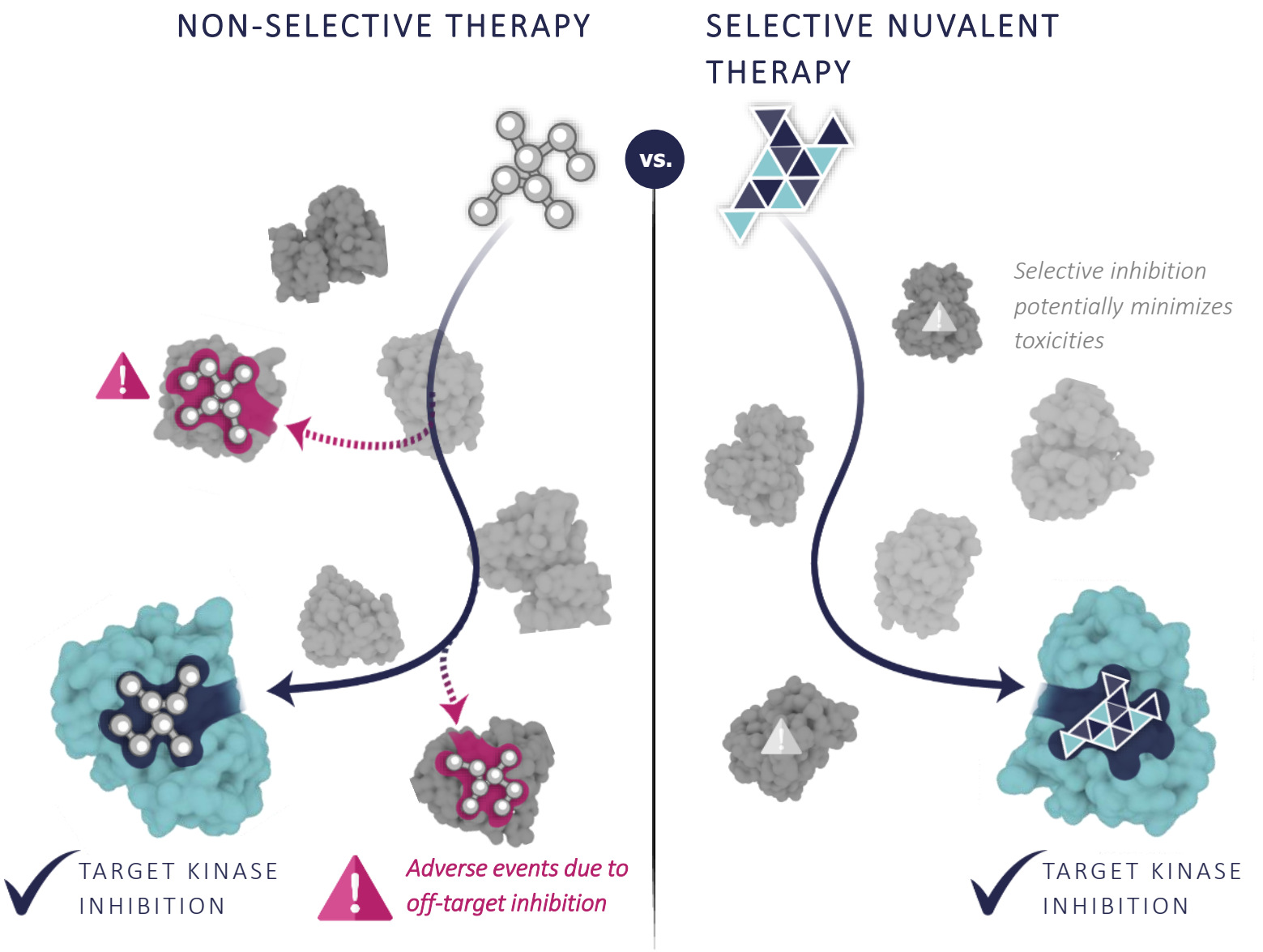
Kinase Selectivity

Structural innovations designed to increase selectivity to potentially minimize therapy-limiting adverse events related to off-target inhibition **AND** drive more durable responses



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NVL-520 *for* ROS1-Positive Advanced NSCLC and other Solid Tumors

TARGET PRODUCT PROFILE:

- Active against wild-type ROS1 fusions
- Active against treatment-emergent ROS1 resistance mutations: G2032R, D2033N, L2026M, S1986Y/F
- Brain penetrant
- TRK sparing to minimize CNS adverse events

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ROS1-positive NSCLC Market Overview

Emerging resistance mutations and increasing CNS involvement limit utility of approved therapies

LINE OF THERAPY	SUB-POPULATION	INCIDENCE (US)	CNS DISEASE	STANDARD OF CARE (2022)
Kinase inhibitor naïve ROS1+ NSCLC	Wild-type kinase domain	~3,000 – 4,500 newly diagnosed patients / year	~20 – 40%	Crizotinib Entrectinib
1 prior kinase inhibitor ROS1+ NSCLC	Non-G2032R mutation		~30 – 55%	
	G2032R mutation	~41%		

Sources: 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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NVL-520

Differentiated Product Candidate for ROS1-positive NSCLC Patients

	NUVALENT IN VITRO PRECLINICAL CHARACTERIZATION			
	WILD TYPE ROS1 FUSION ACTIVITY	G2032R ROS1 ACTIVITY	TRKB SPARING	CNS ACTIVITY
NVL-520 Investigational ROS1-selective inhibitor	Yes	Yes	Yes	Yes Predicted based on preclinical experiments
FDA APPROVED				
CRIZOTINIB Dual ALK/ROS1	Yes	No	No	No Not in FDA approved label
ENTRECTINIB Dual TRK/ROS1	Yes	No	No	Yes In FDA label
INVESTIGATIONAL				
LORLATINIB Dual ALK/ROS1	Yes	No	No Limited selectivity at dose developed for ALK GR	Yes In FDA label for ALK NSCLC
REPOTRECTINIB Dual TRK/ROS1	Yes	Yes	No	Yes Investigational: CNS activity reported in preliminary Phase 1 data

No head-to-head clinical studies have been conducted for currently approved or investigational therapies versus NVL-520. Clinical investigation of NVL-520 is ongoing.
Other than as indicated in the CNS Activity column, data in table above is based on preclinical experiments conducted by Nuvalent. Characterization of CNS activity for each ROS1 inhibitor is based on FDA labels and/or available clinical and preclinical data independently generated by each sponsor and not based on any preclinical experiments conducted by Nuvalent.

Overcoming Kinase Selectivity in NSCLC

ROS1 and ALK both share strong structural similarities to TRK

Brain penetration is needed to address associated CNS disease in ROS1 and ALK driven cancers

Inhibitors must be highly selective to avoid CNS toxicities from off-target inhibition of TRK

TRK INHIBITION SAFETY IMPLICATIONS

TRKB

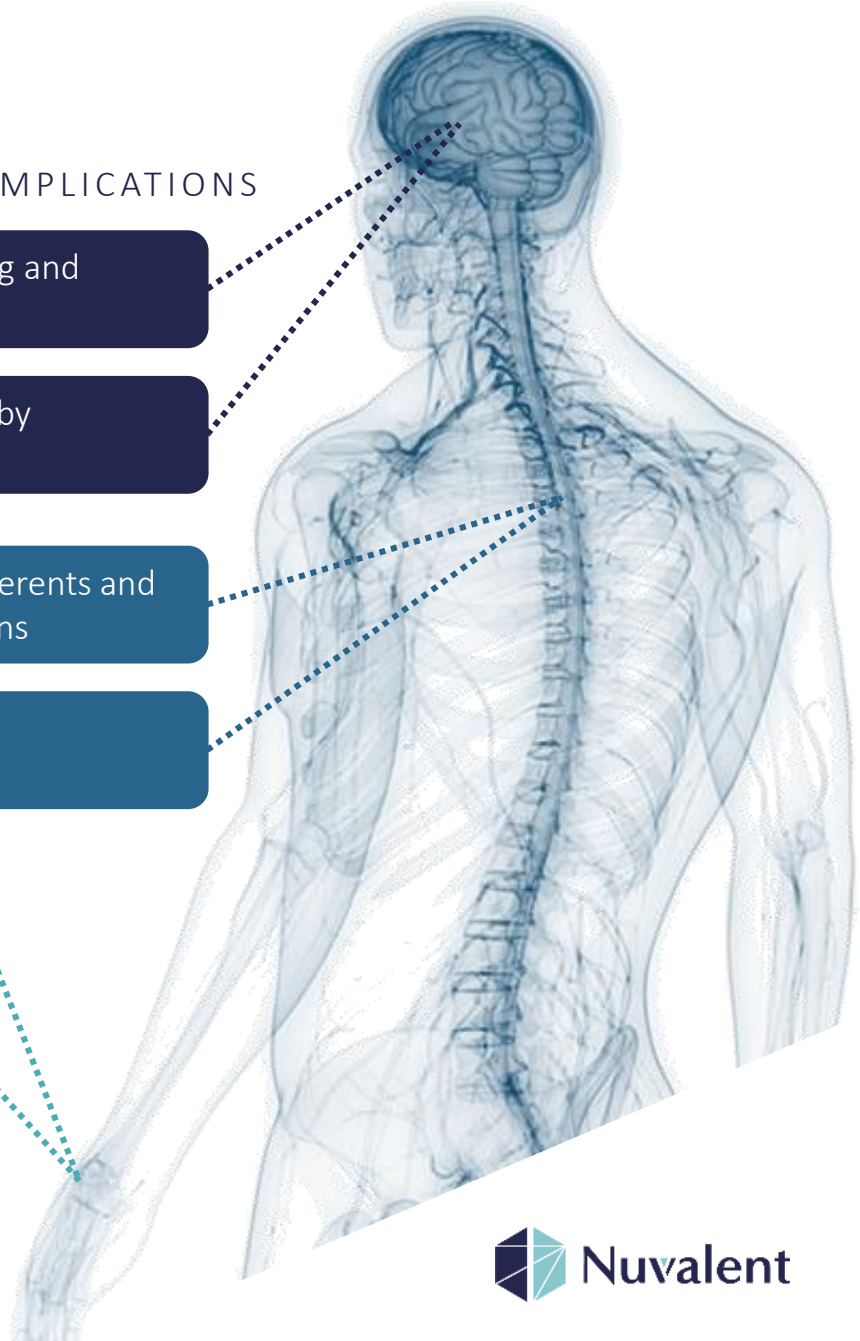
- Impairments in memory, learning and nociception
- Development of obesity caused by hyperphagia and hyperdipsia

TRKC

- Impairment of motor neuron afferents and loss of dorsal root ganglia neurons
- Defect in proprioception

TRKA

- Congenital insensitivity to pain with anhidrosis (CIPA)
- Severe sensory and sympathetic neuropathies



Sources: Adapted from Cocco, Scaltriti and Drilon Nat Rev Clin Oncol 2018

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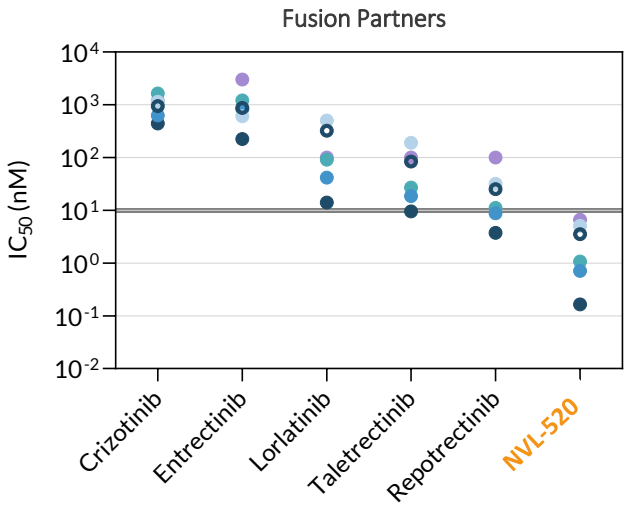
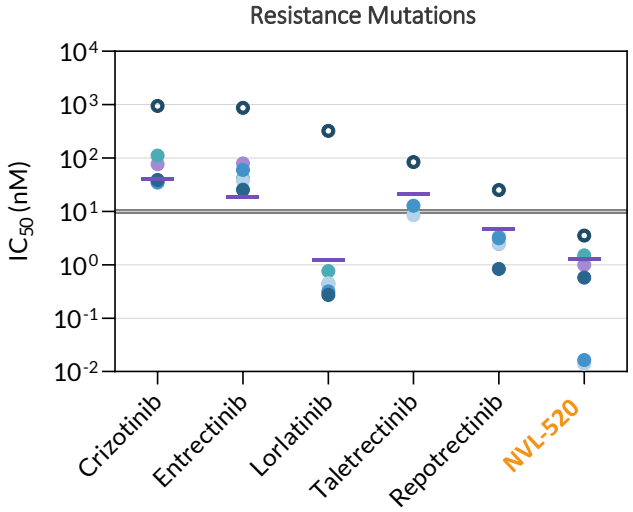
Preclinical | NVL-520 Exhibits Potent Activity Across Diverse ROS1 Fusion Partners and Resistance Mutations

IN VITRO ACTIVITY, ROS1 WILD-TYPE & MUTANT

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





ROS1 fusion G2032R mutant cell lines:

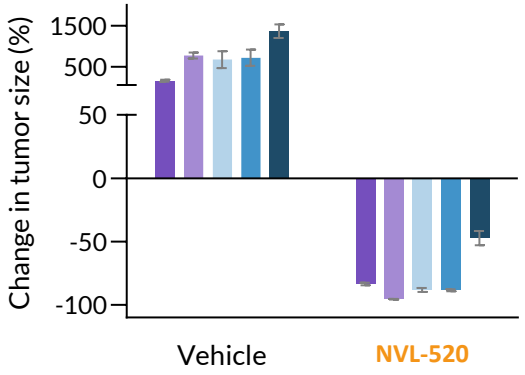
- **CD74** (MGH9018-1 PDC)
- **CD74** (Ba/F3)
- **EZR** (Ba/F3)
- **GOPC(L)** (Ba/F3)
- **GOPC(S)** (Ba/F3)
- **SLC34A2** (Ba/F3)

Ba/F3 expressing WT or mutant CD74-ROS1 fusion:

- Wild-type
- G2032R
- S1986F
- F2004C
- F2004V
- L2026M
- D2033N

IN VIVO EFFICACY, ROS1 WILD-TYPE & MUTANT

Tumor regression at well-tolerated doses in engineered and patient-derived murine models



- CTG-0848 | CD74-ROS1
- Lu01-0414 | SDC4-ROS1
- MGH9018-1 | CD74-ROS1 G2032R
- CTG-2532 | CD74-ROS1 G2032R
- Ba/F3 | CD74-ROS1 G2032R

Dose range 0.2 - 5 mg/kg BID

BID, twice daily; IC50, half-maximal inhibitory concentration; PDC, patient-derived cell line

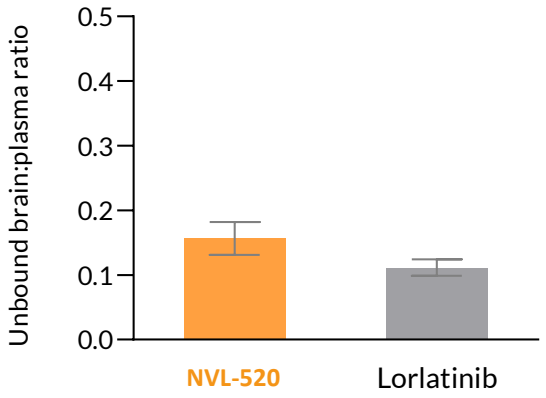
Sources: Drilon A. et al., Cancer Discov (2023) 13 (3): 598–615.; Tangpeerachaikul, A. et al., AACR 2022; Deshpande, A. et al., EORTC-NCI-AACR 2021; Pelish, H.E. et al., AACR 2021.

Nuvalent

Preclinical | NVL-520 is a Brain Penetrant, ROS1-Selective Inhibitor with the Potential to Avoid TRK-Related CNS Adverse Events

BRAIN PENETRANCE

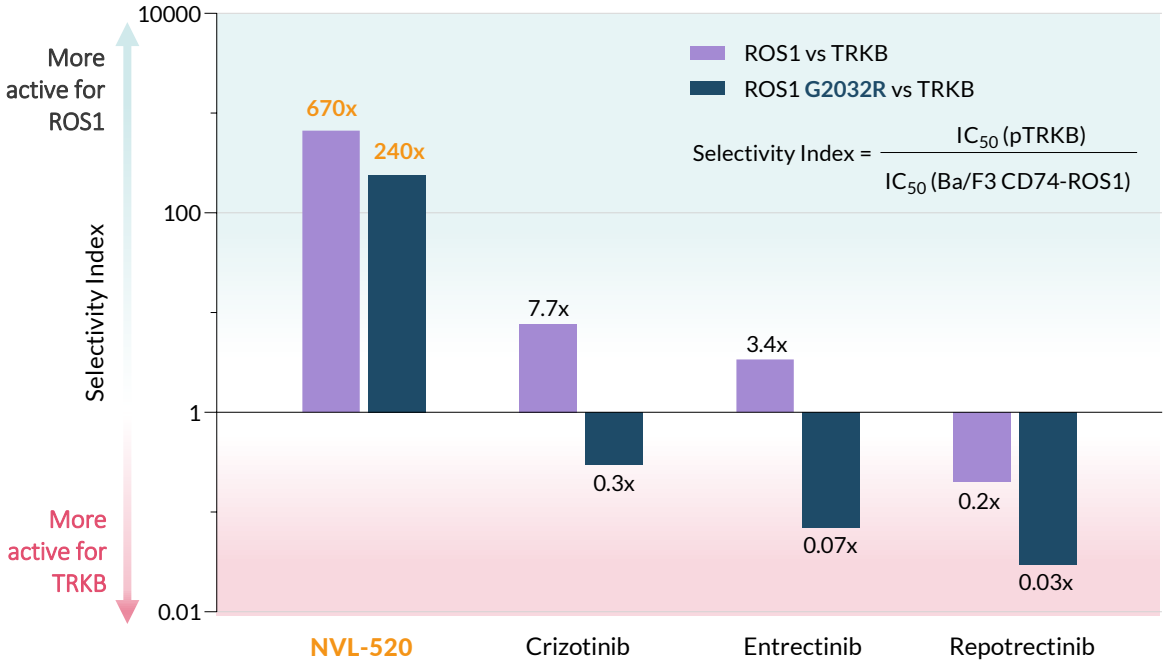
Pharmacokinetic data similar to preclinical observations for lorlatinib



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

AVOIDING TRK INHIBITION

Selectivity for ROS1 and ROS1 G2032R over TRK



IC50, half-maximal inhibitory concentration; PO, orally; pTRK, BDNF-stimulated TRKB phosphorylation.
Head-to-head clinical studies comparing NVL-520 with currently approved or investigational therapies have not been conducted. Above data from preclinical studies.
Sources: Drilon A. et al., Cancer Discov (2023) 13 (3): 598–615.; Tangpeerachaikul, A. et al., EORTC-NCI-AACR 2021; Data on file.

Nuvalent

Study Design | ARROS-1: A Global Phase 1/2 Study of NVL-520 in Patients with Advanced ROS1-Positive NSCLC and Other Solid Tumors (NCT05118789)

ONGOING

PHASE 1 DOSE-ESCALATION

PATIENT POPULATION

- Advanced solid tumors harboring ROS1 fusions (by local testing)
- ≥ 1 prior ROS1 TKI for NSCLC
- No limit to number of prior chemotherapies/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

OPEN-LABEL PHASE 2 COHORTS *(PLANNED)*

COHORT	TUMOR TYPE	PRIOR ROS1 TKI	PRIOR CHEMO/I-O
2a	ROS1+ NSCLC	Naive	≤ 1
2b	ROS1+ NSCLC	1	Naive
2c	ROS1+ NSCLC	1	1
2d	ROS1+ NSCLC	≥ 2	≤ 1
2e	Any ROS1+ solid tumor	Any	Any

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

Cohorts 2a – 2d are designed to support potential registration in TKI-naïve and/or previously treated ROS1+ NSCLC

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, overall response rate (RECIST 1.1); OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RP2D, recommended phase 2 dose; ROS1+, ROS1-positive; 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.

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

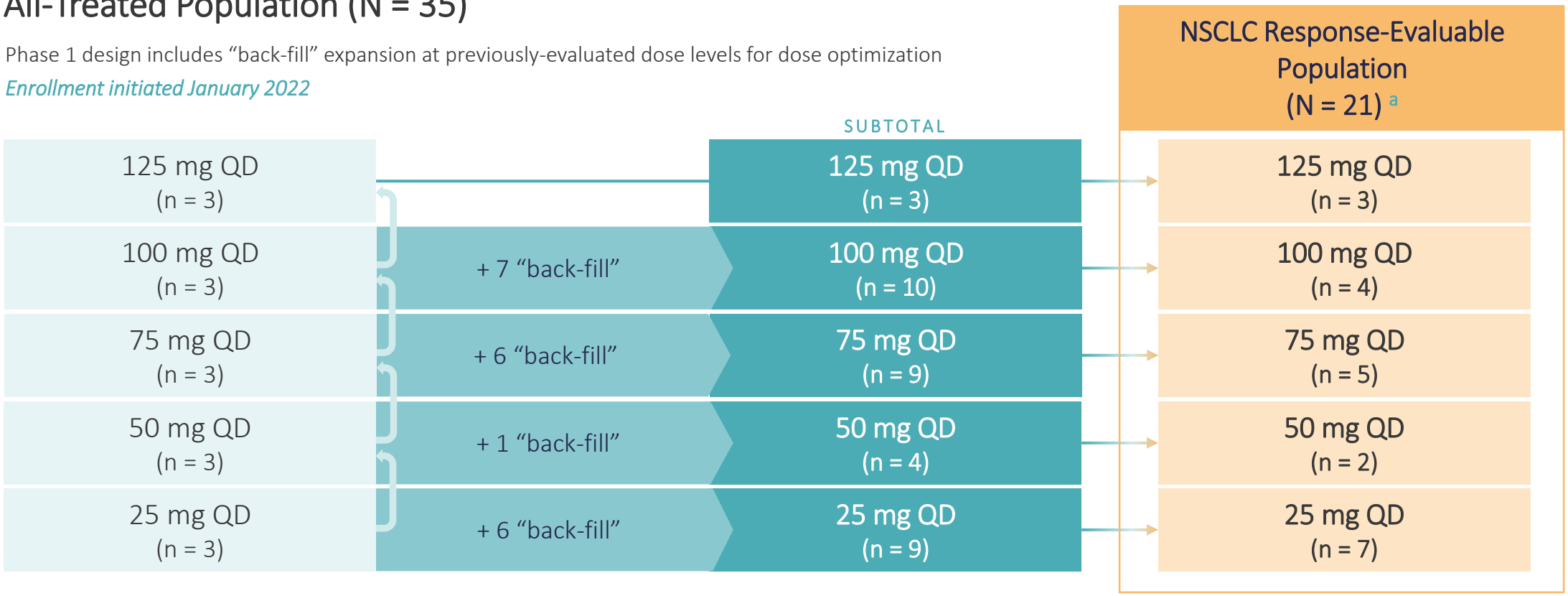
Nuvalent | ARROS-1

Cohort Accrual | ARROS-1 Phase 1 Dose-Escalation

All-Treated Population (N = 35)

Phase 1 design includes "back-fill" expansion at previously-evaluated dose levels for dose optimization

Enrollment initiated January 2022



Data as of 13 Sep 22, for patients treated by 01 Sep 2022. mg, milligram; NSCLC, non-small cell lung cancer; QD, once daily.

[a] 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.

ARROS-1 Phase 1 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%)

Data as of 13 Sep 22, 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.

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%)

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

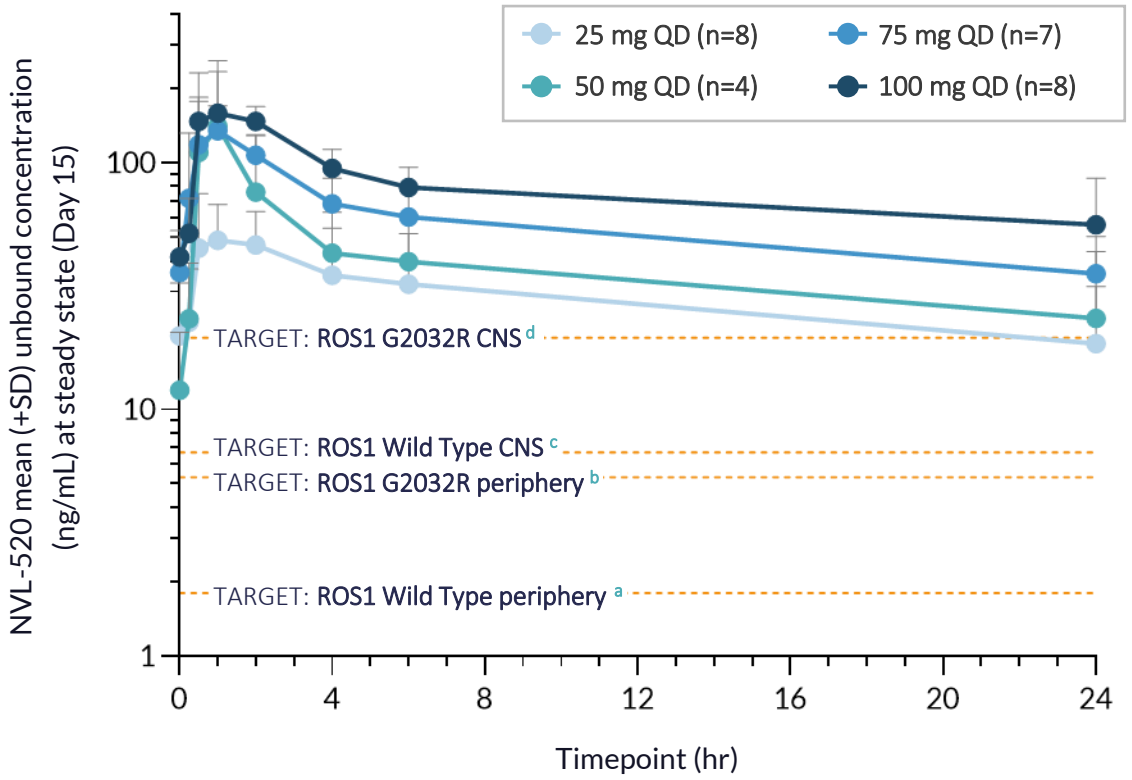
Treatment-Related Adverse Events (TRAEs) in >1 Patient

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 22, 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.

Pharmacokinetics | NVL-520 Exposure Exceeded Predicted Efficacy Thresholds



- NVL-520 exposure exceeded target levels that provide regression in preclinical models
- Favorable pharmacokinetics
  - Low intra-cohort patient PK variability
  - Exposure increasing with increasing dose level
  - Half-life of approximately 20h supports QD dosing

Data as of 13 Sep 22, 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: Drilon A. et al., EORTC-NCI-AACR 2022.

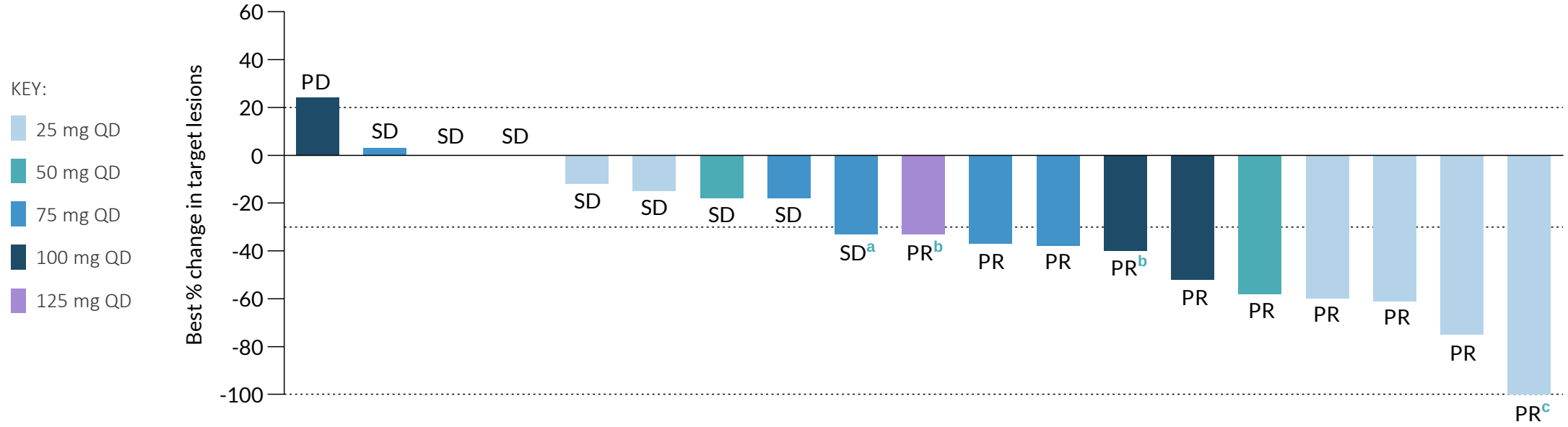
Nuvalent | ARROS-1

Preliminary Efficacy | NVL-520 Induced Tumor Response Across Heavily Pretreated Patient Populations

	All Response-Evaluable	ROS1 G2032R Resistance Mutation	History of CNS Metastases	≥2 Prior ROS1 TKI and ≥1 Chemotherapy	Prior Lorlatinib or Repotrectinib [d]
NSCLC Response-Evaluable Patients	n = 21	n = 9	n = 11	n = 17	n = 18
ORR (RECIST 1.1)	10 (48%)	7 (78%)	8 (73%)	9 (53%)	9 (50%)
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]

Data as of 13 Sep 22, 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, RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease, TKI, tyrosine kinase inhibitor.
[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.
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Preliminary Efficacy | Radiographic Tumor Regression Observed Across All NVL-520 Dose Levels



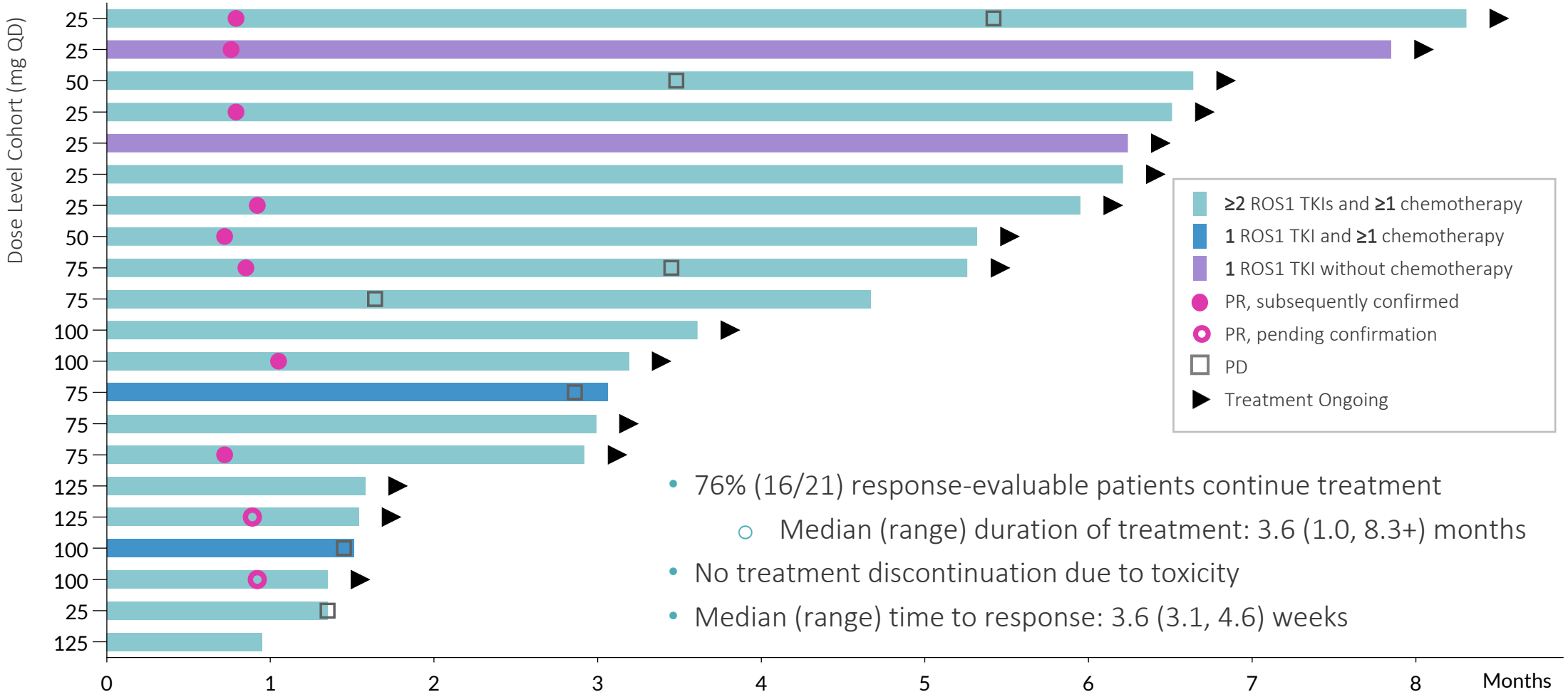
Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3 [d]	2	1	2	2	2	2	3 [d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
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 22, for response-evaluable patients with NSCLC treated by 01 Sep 2022. 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. PD, progressive disease, PR, partial response, QD, once daily; SD, stable disease; TKI, tyrosine kinase inhibitor. [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

Time on Treatment | Sustained Duration with Follow-up Ongoing



- 76% (16/21) response-evaluable patients continue treatment
  - Median (range) duration of treatment: 3.6 (1.0, 8.3+) months
- No treatment discontinuation due to toxicity
- Median (range) time to response: 3.6 (3.1, 4.6) weeks

Data as of 13 Sep 22, for response-evaluable patients with NSCLC treated by 01 Sep 2022. PD, progressive disease; PR, partial response; QD, once daily; TKI, tyrosine kinase inhibitor.
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent | ARROS-1

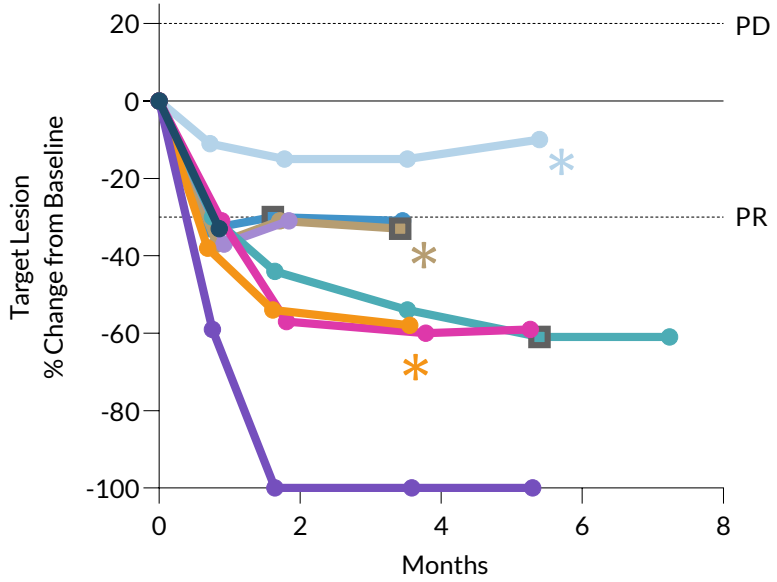
ROS1 Resistance Mutations | NVL-520 Induced Rapid Responses in TKI-Resistant Patients

Subgroup with known ROS1 G2032R resistance mutation

- ORR: 78% (7/9) [a]
- 100% (9/9) with tumor shrinkage

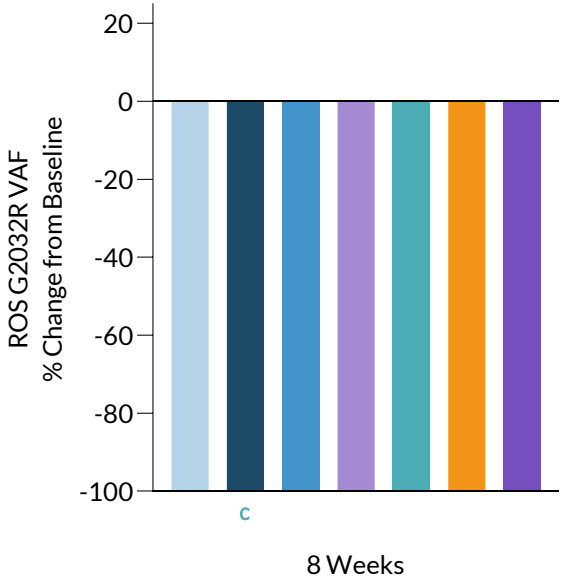
One patient with **ROS1 D2033N** with ongoing PR (-40%) pending confirmation

Reduction in Tumor Burden in Cancers with ROS1 G2032R



Reduction in ROS1 G2032R Allele

Complete clearance in 7/7 patients [b]



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)

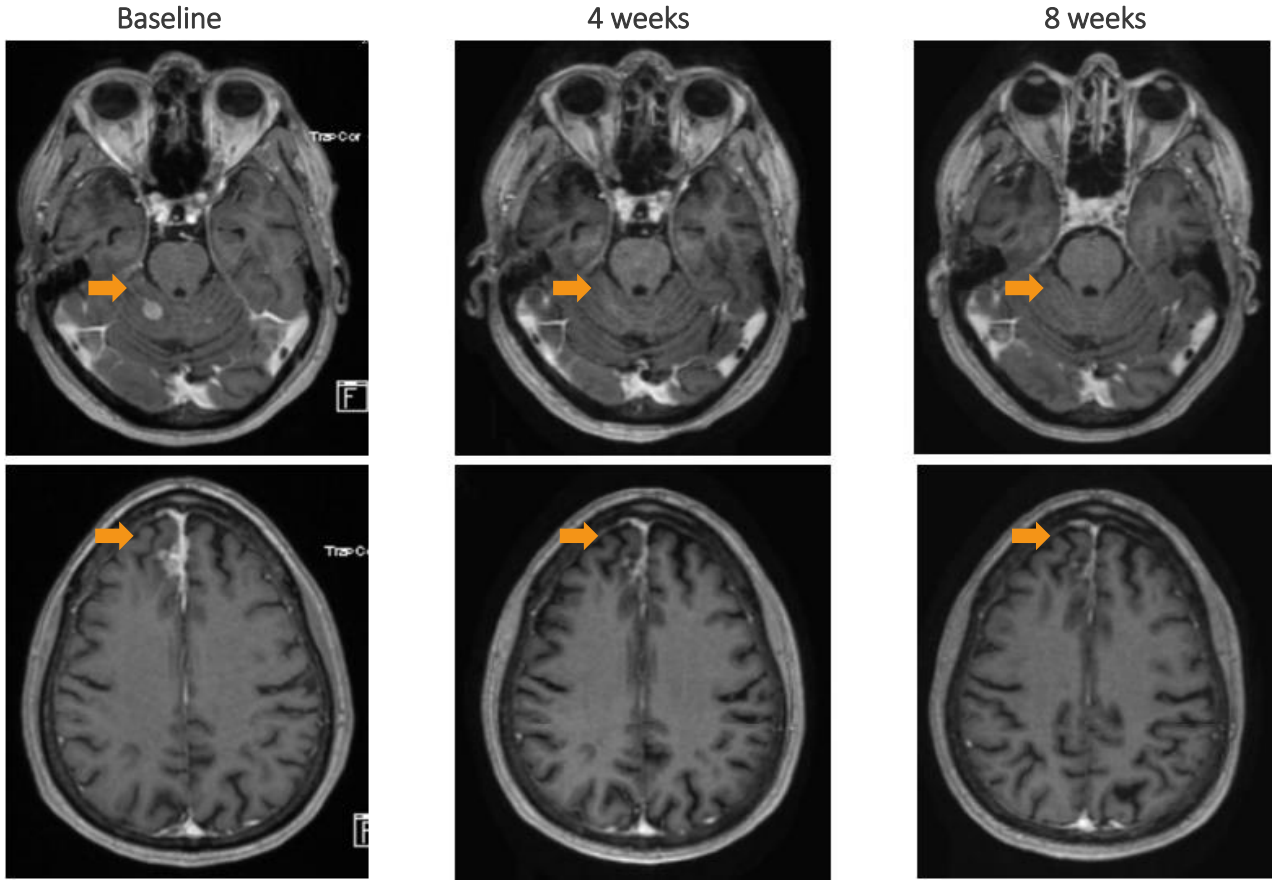
Data as of 13 Sep 22, for response-evaluable patients with NSCLC treated by 01 Sep 2022. ctDNA, circulating tumor deoxyribonucleic acid; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor. [a] Includes 1 ongoing partial response 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.

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

Nuvalent | ARROS-1

CNS Activity | NVL-520 Induced Responses in Intracranial Lesions

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



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.

Data as of 13 Sep 22, for patients treated by 01 Sep 2022. CNS, central nervous system; NSCLC, non-small cell lung cancer; ORR, objective response rate; PR, partial response; QD, once daily.
[a] One patient with an ongoing intracranial PR pending confirmation.
[b] Includes 2 ongoing partial responses pending confirmation.
Images courtesy of Jessica J Lin, Massachusetts General Hospital
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

Nuvalent | ARROS-1

Case Study | Intracranial and Extracranial Activity in TKI-Refractory ROS1 G2032R+ NSCLC

Diagnosis: EZR-ROS1 fusion NSCLC

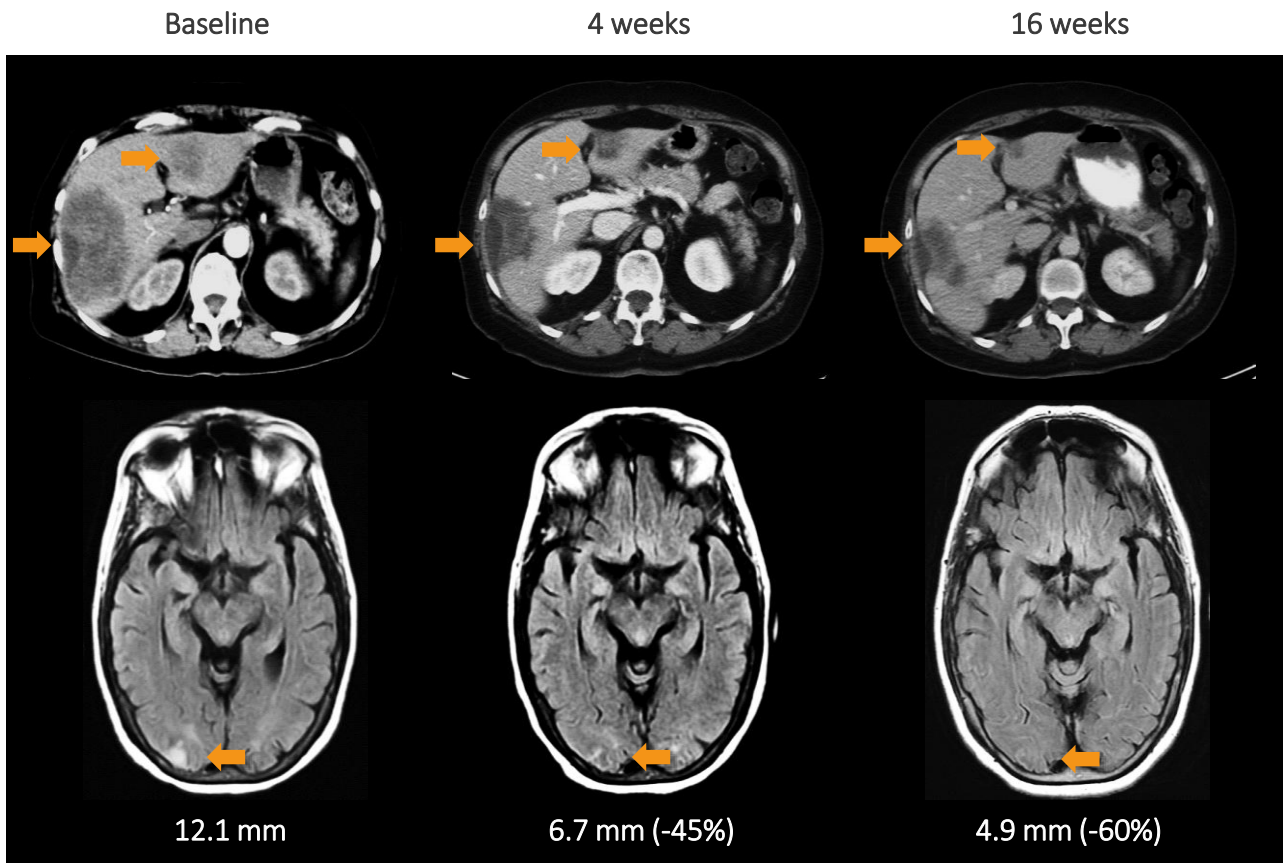
Entrectinib
~9 months, ROS1 G2032R found on PD

Repotrectinib
~8 weeks

Platinum-based chemo + bevacizumab + entrectinib
Administered for PD, ~8 weeks, primary PD, G2032R still present

NVL-520 (50 mg QD)

- PR (-38% by RECIST 1.1) at 4 weeks: right occipital lobe metastasis contraction, decrease in several liver/lung metastases
- Further disease regression (-58%) at 16 weeks, near-complete resolution of brain lesion
- Treatment well-tolerated without dizziness, orthostasis, or paresthesia
- Continues to receive NVL-520 with ongoing response at 5.3 months



Upper panel: CT indicating segment 5/6 and 3 liver metastases with continuous regression over the course of treatment. **Lower panel:** MRI demonstrating right occipital lobe metastasis that decreased in size at week 4 and became barely appreciable at week 16.

Data as of 13 Sep 22. CT, computed tomography; MRI, magnetic resonance imagine; NSCLC, non-small cell lung cancer; PD, Progressive Disease; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKI, tyrosine kinase inhibitor. Images courtesy of Alexander Drilon, Memorial Sloan Kettering Cancer Center.

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

Nuvalent | ARROS-1

CONCLUSIONS – PRELIMINARY DOSE ESCALATION DATA

NVL-520 is 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

- In the ongoing ARROS-1 Phase 1 dose-escalation, a wide dose range resulted in exposures exceeding predicted efficacy thresholds without indication of off-target toxicity
  - NVL-520 has been well tolerated with no DLTs
  - There have been no dose reductions or treatment discontinuations due to adverse events
  - Emerging safety profile is consistent with ROS1-selective, TRK-sparing design
- This preliminary dataset indicates encouraging clinical activity in a heavily pre-treated population, with responses observed in patients:
  - with and without ROS1 G2032R resistance
  - who progressed through lorlatinib or repotrectinib
  - with brain metastases
- Phase 1 ongoing to further understand the safety profile, PK, and preliminary efficacy, and determine the RP2D

CNS, central nervous system; DLTs, dose-limiting toxicities; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; RP2D, recommended phase 2 dose.
Source: Drilon A. et al., EORTC-NCI-AACR 2022.

NVL-655 *for* ALK-Positive Advanced NSCLC and Other Solid Tumors

TARGET PRODUCT PROFILE:

- Active against wild-type ALK fusions
- Active against treatment-emergent ALK G1202R single and compound resistance mutations
  e.g., G1202R/L1196M, G1202R/G1269A, G1202R/L1198F
- Brain penetrant
  ~30 – 40% of patients with ALK-positive NSCLC present with brain metastases
- TRK sparing to minimize CNS adverse events

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ALK-Positive NSCLC Market Overview

Emerging Resistance Mutations and Increasing CNS Involvement Limit Utility of Approved Therapies

LINE OF THERAPY	SUB-POPULATION	INCIDENCE (US)	CNS DISEASE	STANDARD OF CARE (2022)
Kinase inhibitor naïve ALK+ NSCLC	Wild-type kinase domain	~9,000 – 18,000 newly diagnosed patients / year	~30 – 40%	Alectinib *(preferred)*; Brigatinib; Ceritinib; Crizotinib; Lorlatinib
1 prior kinase inhibitor ALK+ NSCLC	G1202R	~35%	> 60%	Lorlatinib
	I1171N/S/T	~15 – 30%		
	Other			
2 prior kinase inhibitors ALK+ NSCLC	G1202R/L1196M		> 60%	
	G1202R/G1269A			
	G1202R/L1198F			
	I1171N / D1203N			
	Other			

Sources: 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

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NVL-655

Differentiated Product Candidate for ALK-positive NSCLC patients

	NUVALENT IN VITRO PRECLINICAL CHARACTERIZATION				
	WILD-TYPE ALK FUSION ACTIVITY	G1202R ALK ACTIVITY	GRLM, GRGA & GRLF ALK ACTIVITY	TRKB SPARING	CNS ACTIVITY
NVL-655 Investigational ALK-selective inhibitor (Nuvalent)	Yes	Yes	Yes	Yes	Yes Predicted based on preclinical experiments
FDA APPROVED					
CRIZOTINIB	Yes	No	No	No	No Not in FDA label
CERITINIB	Yes	No	No	Yes	Yes In FDA label
ALECTINIB	Yes	No	No	Yes	Yes In FDA label
BRIGATINIB	Yes	No	No	Yes	Yes In FDA label
LORLATINIB	Yes	Yes	No	No Limited selectivity at dose developed for ALK GR	Yes In FDA label

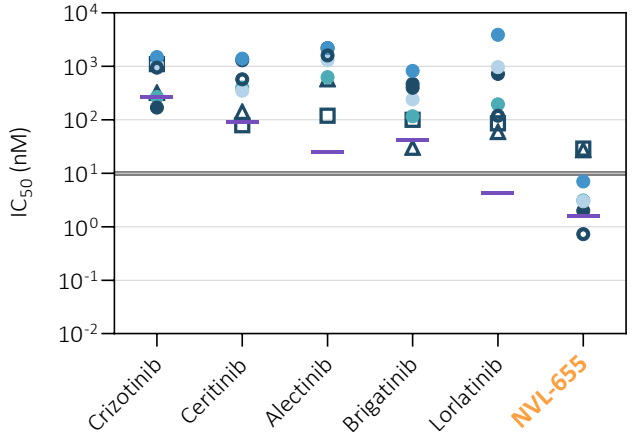
No head-to-head clinical studies have been conducted for currently approved or investigational therapies versus NVL-655. Clinical investigation of NVL-655 is ongoing.
Other than as indicated in the CNS Activity column, data in table above is based on preclinical experiments conducted by Nuvalent. Characterization of CNS activity for each ALK inhibitor is based on FDA labels and/or available clinical and preclinical data independently generated by each sponsor and not based on any preclinical experiments conducted by Nuvalent.
GR: G1202R; LM: L1196M; GA: G1269A; LF: L1198F

Nuvalent

Preclinical | NVL-655 is a Brain Penetrant, ALK-Selective Inhibitor with the Potential to Avoid TRK-Related CNS Adverse Events

ACTIVITY AGAINST ALK WILD-TYPE AND MUTANTS

Sub-10 nM activity for ALK G1202R single and compound mutations in 3-day cell viability assays

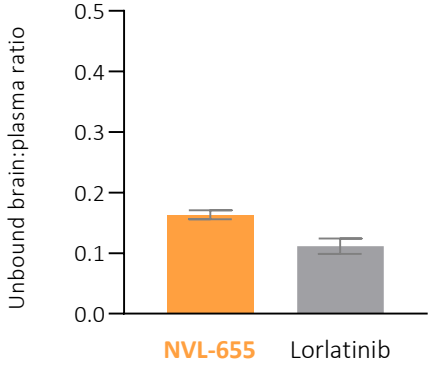


Ba/F3 expressing WT or mutant EML4-ALK (v1 or v3) fusion:

- wild-type
- G1202R
- G1202R/L1196M
- G1202R/G1269A
- G1202R/L1198F
- G1202R/T1151M
- L1196M
- I1171N

BRAIN PENETRANCE

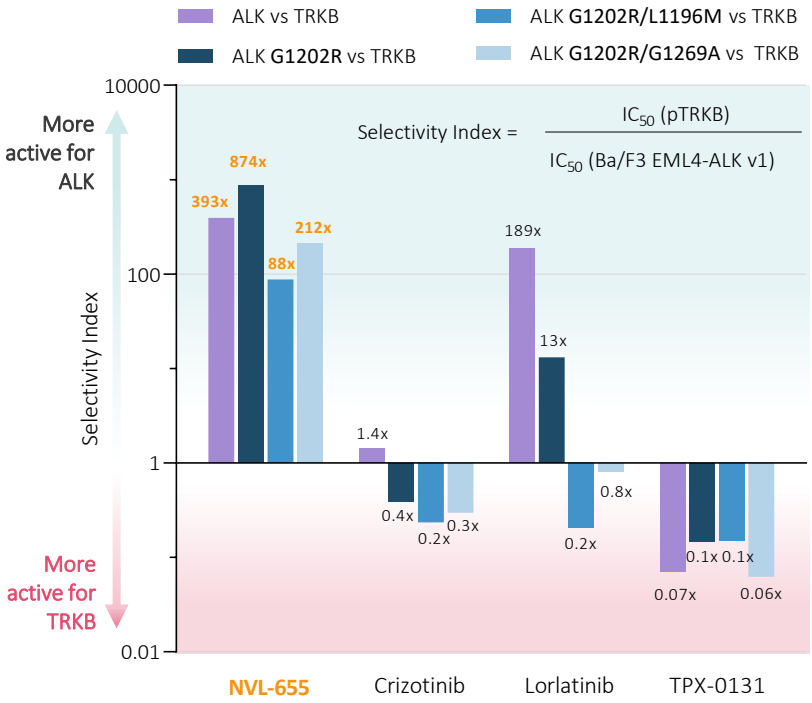
Pharmacokinetic data similar to preclinical observations for lorlatinib



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

AVOIDING TRK INHIBITION

Selective inhibition of ALK, including ALK G1202R single and compound mutations, over TRK



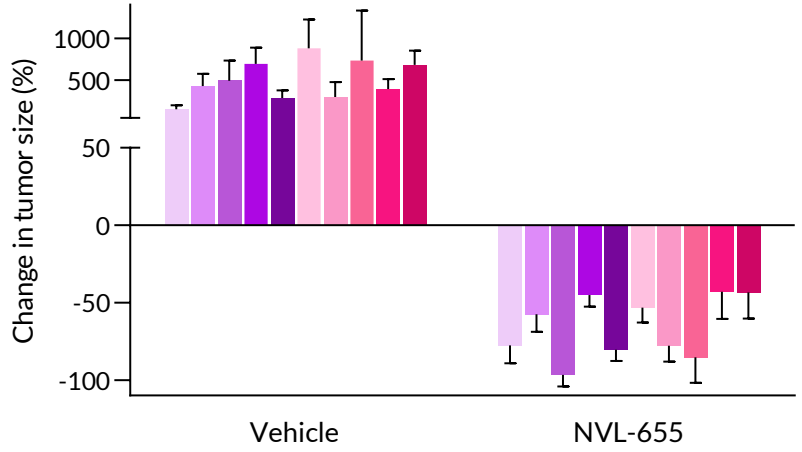
IC50, half-maximal inhibitory concentration; PO, orally; pTRK, BDNF-stimulated TRKB phosphorylation.
Head-to-head clinical studies comparing NVL-655 with currently approved or investigational therapies have not been conducted. Above data from preclinical studies.
Sources: Mizuta, H. et al., WCLC 2022; Pelish, H.E. et al., AACR 2021; Data on file.

Nuvalent

Preclinical | NVL-655 Induced Tumor Regression Across Models of Diverse ALK Single and Compound Resistance Mutations

IN VIVO ACTIVITY, ALK WILD-TYPE & MUTANTS (SINGLE AND COMPOUND)

Tumor regression at well-tolerated doses in engineered, cell line-, and patient-derived murine models

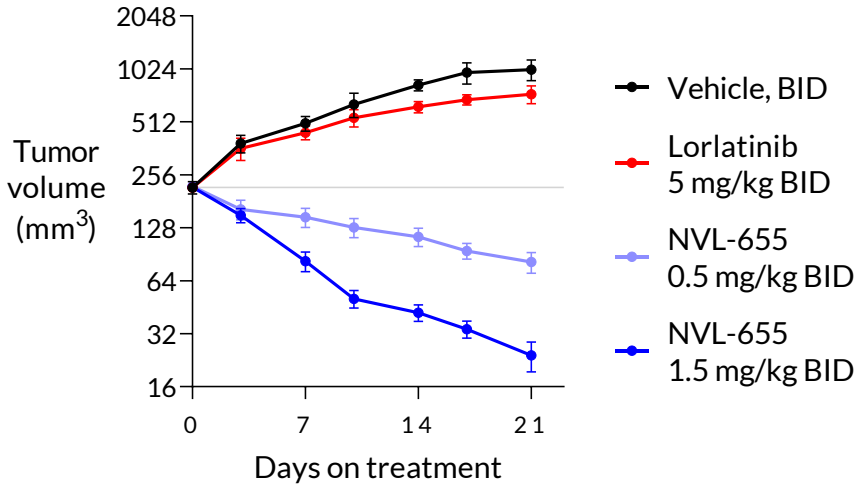


Dose range 0.5 - 7.5 mg/kg
BID or BID 5 on/2 off

- LU01-0015 | HIP1-ALK
- NCI-H3122 | EML4-ALK v1
- MR619 | STRN-ALK **G1202R**
- Ba/F3 | EML4-ALK v1 **G1202R**
- MGH953-7 | EML4-ALK v3 **G1202R/L1196M**
- Ba/F3 | EML4-ALK v1 **G1202R/L1196M**
- NCI-H3122 | EML4-ALK v1 **G1202R/L1196M**
- MR448re | EML4-ALK v3 **G1202R/T1151M**
- Ba/F3 | EML4-ALK v1 **G1202R/G1269A**
- Ba/F3 | EML4-ALK v1 **I1171N**

IN VIVO ACTIVITY, PATIENT-DERIVED XENOGRAFT (PDX) ALK+ NSCLC WITH G1202R/L1196M COMPOUND MUTATION

Tumor regression at well-tolerated doses



- MGH953-7 model derived from a patient with ALK fusion-positive NSCLC
- Progressed on sequential treatments with crizotinib, alectinib, and lorlatinib
- Harbors EML4-ALK v3 G1202R/L1196M

BID, twice daily; Sources: Pelish H.E. et al., AACR 2021; Tangpeerachaikul A. et al., EORTC-NCI-AACR 2021; Tangpeerachaikul A. et al., AACR 2022; Mizuta H. et al., WCLC 2022; Fujino T. et al., EORTC-NCI-AACR 2022.

Nuvalent

ALKove-1

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

Phase 1 Portion Open & Enrolling

Phase 1 ALK-positive Solid Tumors with ≥1 ALK TKI*	Phase 2			
	COHORT	TUMOR TYPE	PRIOR ALK TKI**	PRIOR CHEMO and/or I-O
200 mg QD	2a	ALK fusion-positive NSCLC	1 prior 2nd generation (ceritinib, alectinib, or brigatinib)	0 – 2 lines
150 mg QD	2b	ALK fusion-positive NSCLC	2 – 3 prior 1st or 2nd generation (crizotinib, ceritinib, alectinib, or brigatinib)	0 – 2 lines
100 mg QD	2c	ALK fusion-positive NSCLC	2 – 3 prior, with lorlatinib in 2nd or 3rd line of therapy	0 – 2 lines
50 mg QD	2d***	Other ALK-positive solid tumors & ALK-positive NSCLC not eligible for 2a-c	≥ 1 prior systemic therapy (or for whom no satisfactory standard therapy exists)	Any
25 mg QD				
15 mg QD				
PURPOSE ✓ Safety / Tolerability ✓ Determine/Confirm RP2D	Cohorts 2a, 2b, and 2c may be expanded to support potential registration			

* Patients with ALK fusion-positive NSCLC must have previously received ≥1 ALK TKI, one of which must be a 2nd or 3rd generation TKI (ceritinib, alectinib, brigatinib, or lorlatinib), while those with other solid tumors must have previously received ≥1 prior systemic anticancer therapy or be those for whom no satisfactory standard therapy exists.

** Excluding investigational agents targeting ALK (except for cohort 2d).

*** Exploratory cohort, includes patients age ≥ 12 years with weight > 40 kg.

ALK-positive: Positive for Anaplastic Lymphoma Kinase fusion or mutation; NSCLC: Non small cell lung cancer; RP2D: Recommended Phase 2 Dose; TKI: Tyrosine Kinase Inhibitor

Preliminary data update from dose-escalation planned in 2H 2023

Nuvalent

NVL-330 *for* Malignancies Driven by HER2 Exon 20 Insertion Mutations (HER2ex20)

TARGET PRODUCT PROFILE:

Active against HER2 and HER2ex20

EGFR sparing

Related adverse events include skin rash and diarrhea

Brain penetrant

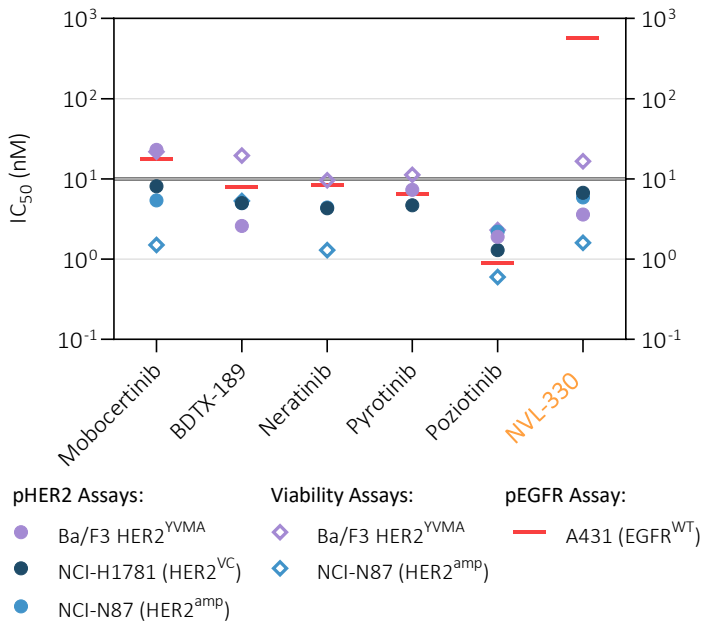
~20% of patients with HER2-positive NSCLC present with brain metastases

Nuvalent

Preclinical | NVL-330 is a Brain Penetrant, HER2ex20-Selective Kinase Inhibitor with Potential to Avoid Adverse Events Related to EGFR Inhibition

IN VITRO ACTIVITY, HER2 AND HER2ex20

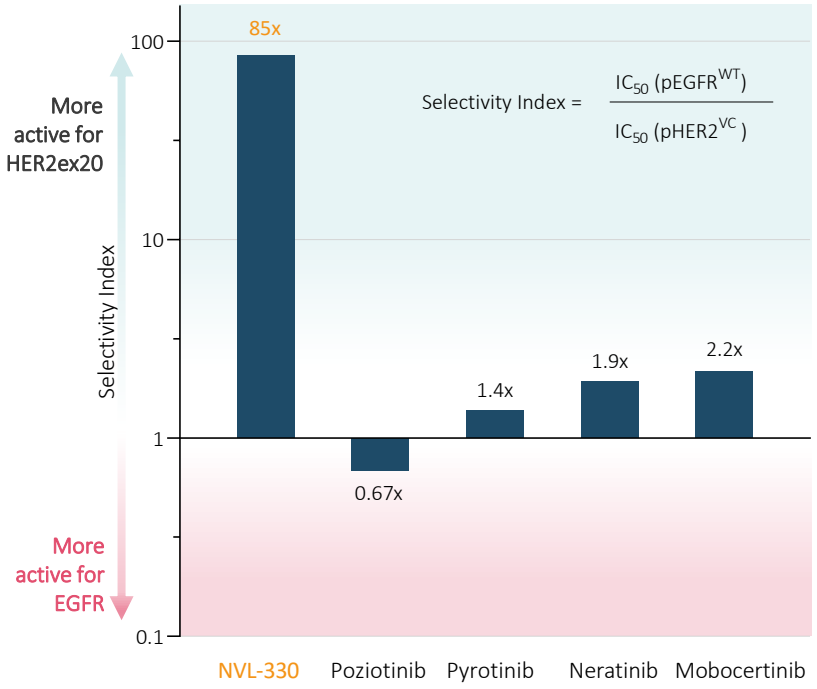
Potent inhibition of HER2 and HER2ex20 mutations in cell-based phosphorylation and viability assays



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

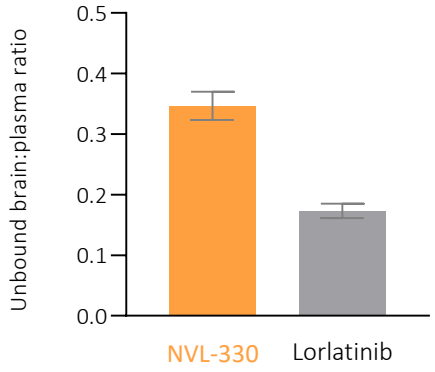
AVOIDING EGFR INHIBITION

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

IC50, half-maximal inhibitory concentration; PO, orally; Head-to-head clinical studies comparing NVL-330 with currently approved or investigational therapies have not been conducted. Above data from preclinical studies

Source: Andrews K.L. et al., EORTC-NCI-AACR 2022.

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Pipeline Expansion

Nuvalent

Pipeline Expansion

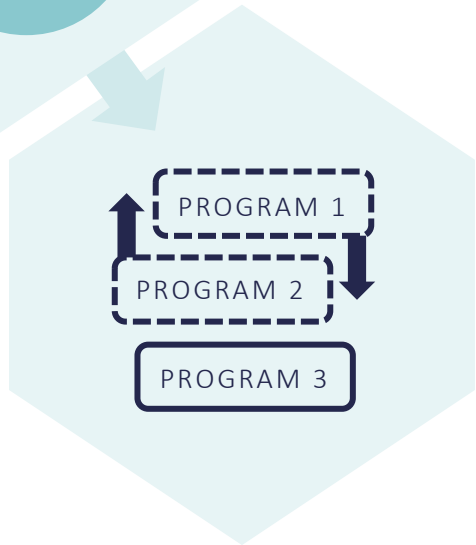
Rigorous Target Selection and Disciplined Advancement of Discovery Programs

Close Partnership with Physician-Scientists

- Characterize emerging medical needs for patients
- Refine understanding of safety events observed with currently available multi-kinase inhibitors

Rigorous Target Selection

- Combine clinical insights with internal expertise in chemistry and structure-based drug design and development
- Prioritize opportunities with an aim to maximize patient impact through more selective kinase inhibitor design



Disciplined Program Advancement

- Well defined selection criteria
- Focused resource deployment on opportunities with potential for immediate impact

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Nuvalent Pipeline – Ongoing Programs

Advancing parallel lead programs in ROS1-positive and ALK-positive NSCLC, and multiple early-stage discovery programs

LEAD INDICATION	PRODUCT CANDIDATE	SELECTED MUTATION(S)	DISCOVERY	IND ENABLING	PHASE 1	PHASE 2	PHASE 3	RECENT/ ANTICIPATED MILESTONES	WORLDWIDE RIGHTS
ROS1 NSCLC	NVL-520	G2032R, S1986Y/F, L2026M, D2033N	*Open & Enrolling:* Phase 1 portion of Phase 1/2 trial		ARROS-1			Preliminary dose-escalation data presented at EORTC-NCI-AACR 2022	Nuvalent
ALK NSCLC	NVL-655	G1202R G1202R/L1196M G1202R/G1269A G1202R/L1198F	*Open & Enrolling:* Phase 1 portion of Phase 1/2 trial		ALKOVE-1			Preliminary dose-escalation data update planned in 2H'23	Nuvalent
ALK NSCLC		I1171X / D1203N (X = N, S, or T)							Nuvalent
HER2 NSCLC	NVL-330	Exon 20 Insertions						Preclinical profile presented at EORTC-NCI-AACR 2022	Nuvalent

Additional Discovery Research Programs Ongoing

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PRECISELY

Targeted Therapies *for patients with cancer*

- Innovative molecular structures with the potential to overcome the dual challenges of kinase resistance and selectivity in the CNS and in the periphery
- Potential for differentiated inhibition of proven kinase targets with opportunities for clinical utility earlier in the treatment paradigm

Parallel lead clinical programs in ROS1-positive and ALK-positive NSCLC:

- 2023 operational focus on advancement of concurrent Phase 1/2 clinical trials
- Preliminary data from dose-escalation portion of Phase 1/2 AR**ROS-1** study presented at EORTC-NCI-AACR 2022
- Preliminary data update from **ALK**OVE-1 dose-escalation planned in 2H'23

Robust development pipeline leveraging established approach:

NVL-330 selected as new development candidate for HER2ex20-positive tumors

Expected cash runway into second half of 2025

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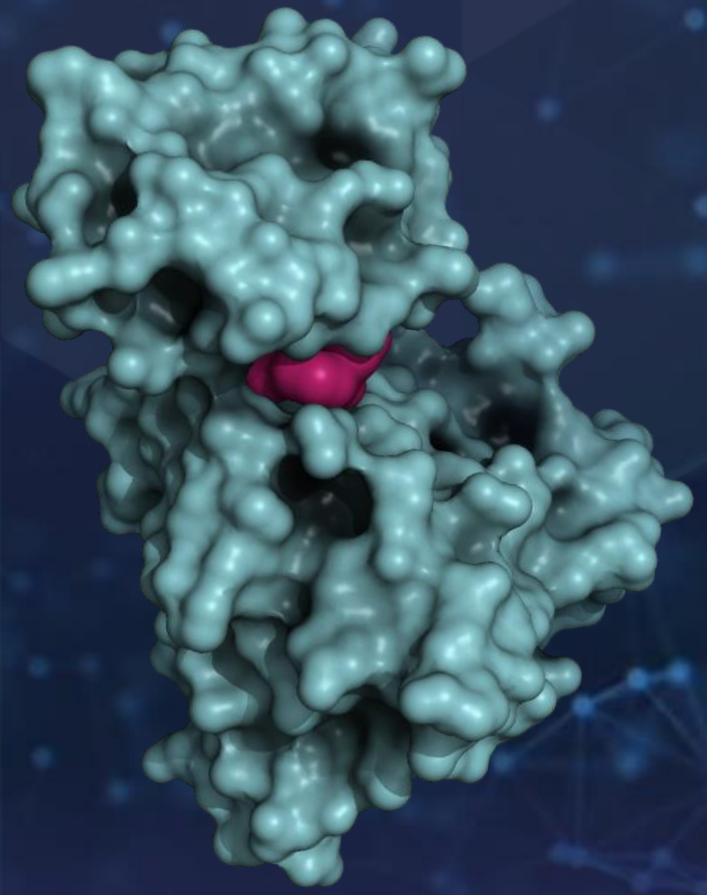
www.nuvalent.com



PRECISELY

Targeted Therapies *for patients with cancer*