NVL 520-ROS TKI

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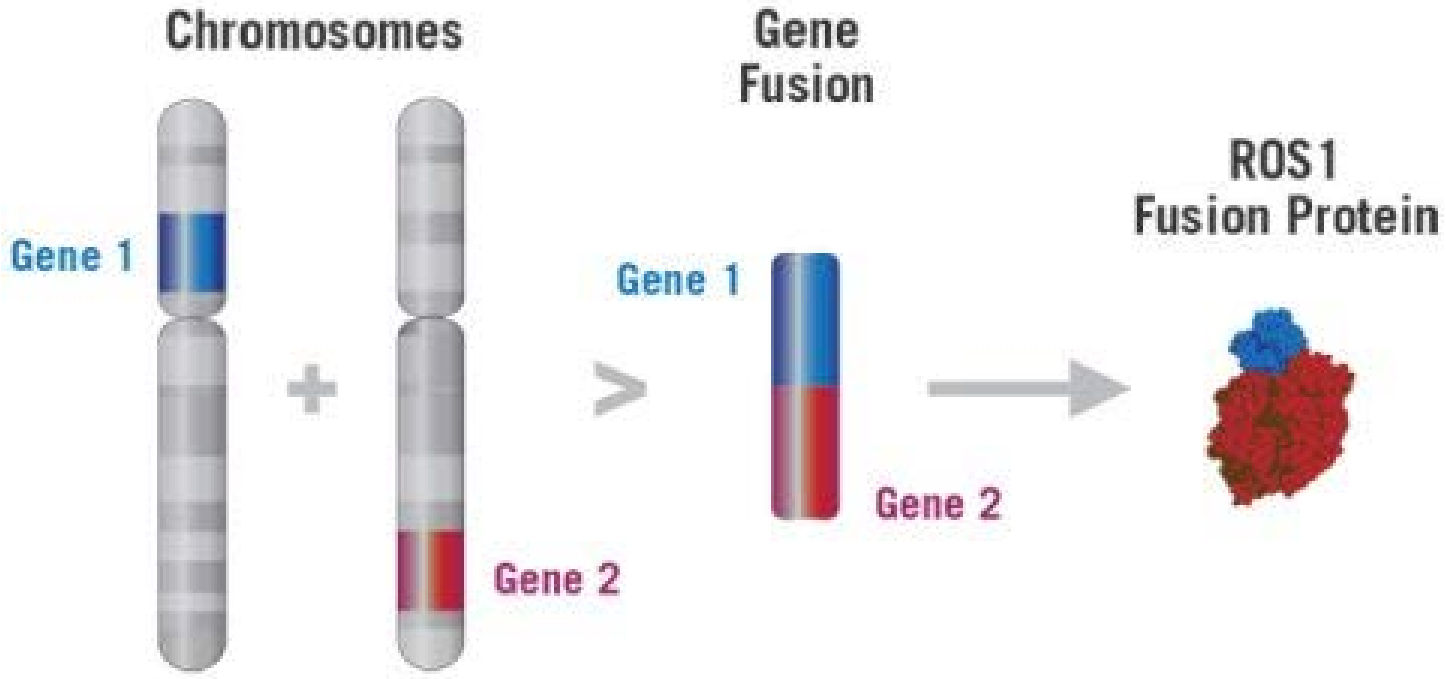
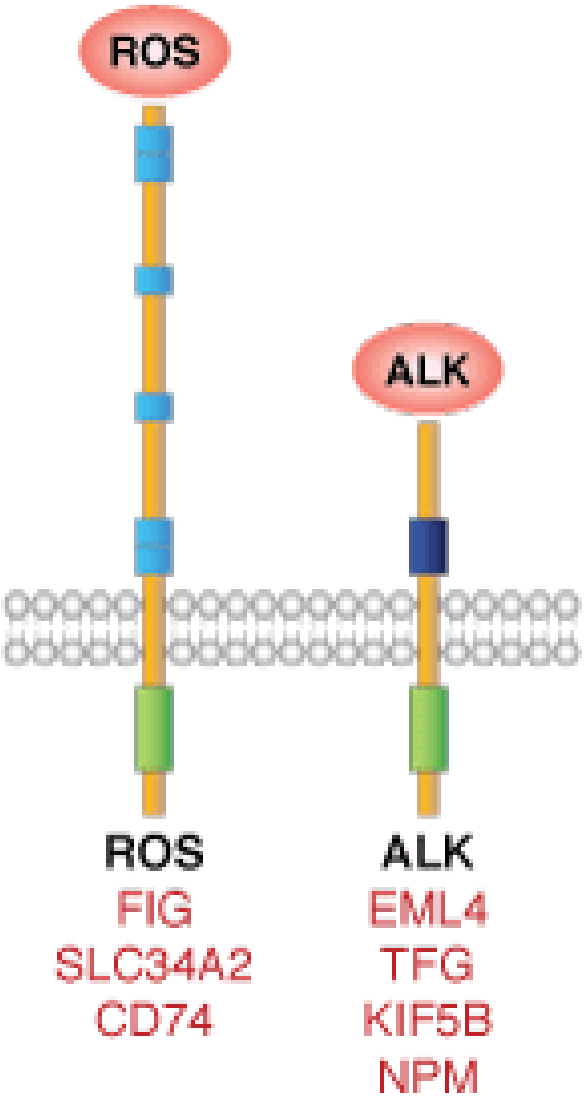
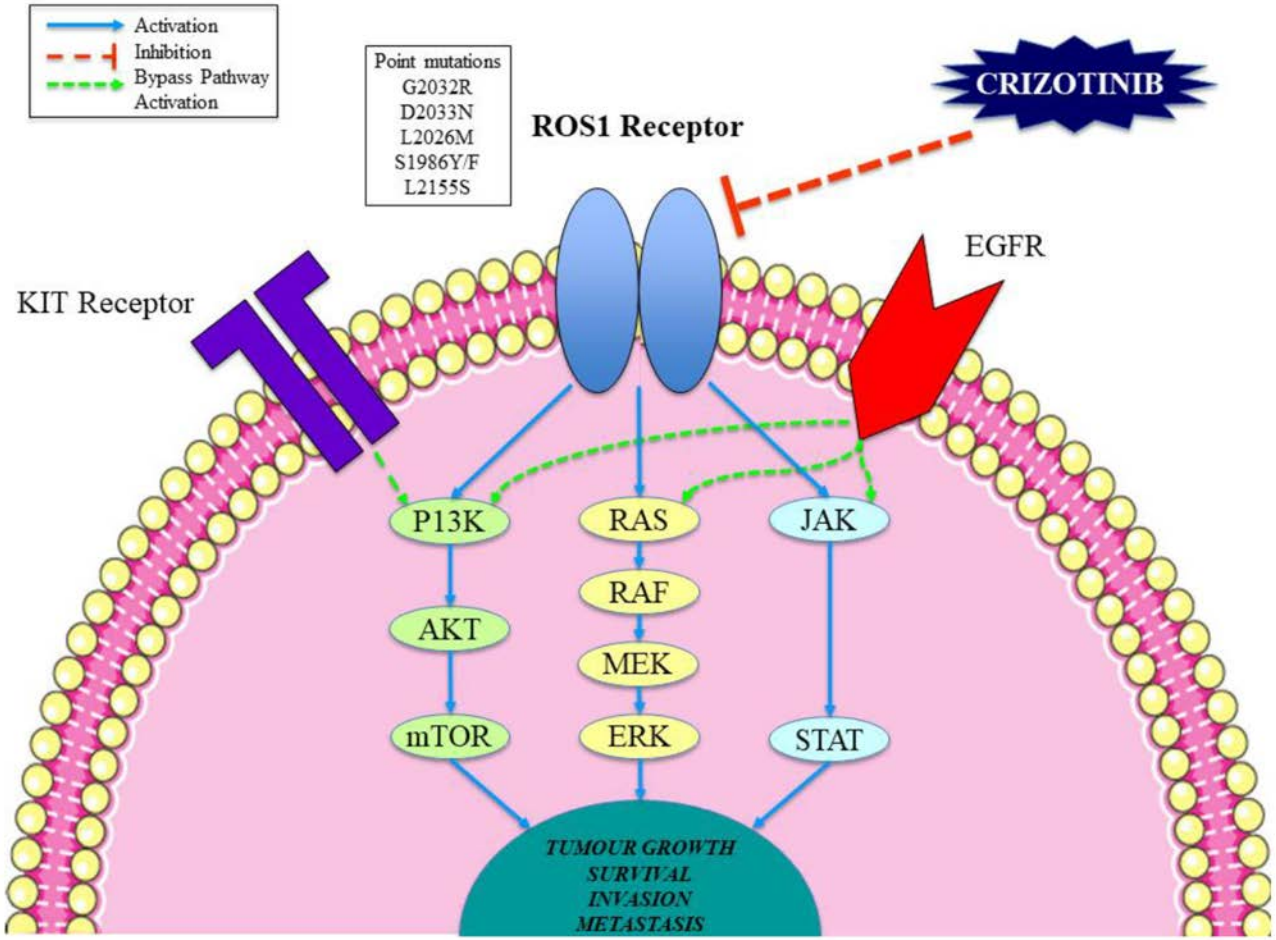

Chromosomes
Gene 1
Gene 2
Gene Fusion
Gene 1
Gene 2
ROS1
Fusion Protein


ROS
ALK
ROS
FIG
SLC34A2
CD74
ALK
EML4
TFG
KIF5B
NPM

ROS-1 :3% NSCLC


Activation
Inhibition
Bypass Pathway Activation
Point mutations
G2032R
D2033N
L2026M
S1986Y/F
L2155S
ROS1 Receptor
CRIZOTINIB
EGFR
KIT Receptor
P13K
RAS
JAK
RAF
AKT
MEK
mTOR
ERK
STAT
TUMOUR GROWTH
SURVIVAL
INVASION
METASTASIS

Crizotinib and Entrectinib

- ORR- 70%
- PFS-1.5yrs
- OS- 4yrs

Reason for acquired resistance

- KD mutations
- G2032R (40%)

Limitation with present TKIs

- PFS 1.5yrs -->resistance-->G2032R-->doesnot work
- Less CNS activity
- Off target NTRK activity -->CNS side effects

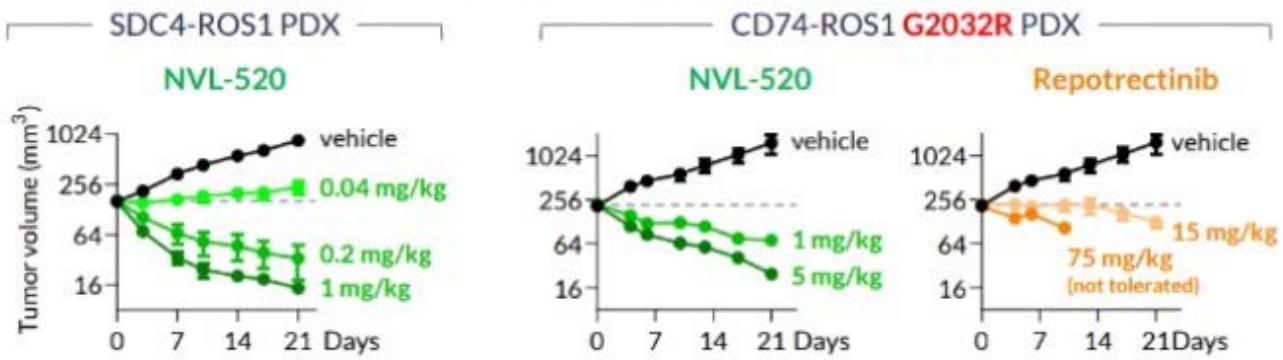
NVL 520

- Rationally designed TKI
- Highly selective for ROS1
- Negligeble NTRK activity -- less CNS side effects
- Highly active in brain

NVL-520 Exhibits *In Vitro* Potency Against ROS1 Fusions & Drug-resistant Mutations

ROS1	NVL-520	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib
Wild-type	1.2 nM	40 nM	23 nM	1.3 nM	4.4 nM
G2032R	3.5 nM	960 nM	1500 nM	300 nM	25 nM
S1986F	< 0.58 nM	39 nM	26 nM	< 0.27 nM	0.84 nM
L2026M	1.5 nM	110 nM	41 nM	0.77 nM	3.3 nM
D2033N	1.0 nM	77 nM	79 nM	0.44 nM	2.5 nM

NVL-520 Induces Tumor Regression and is Well-tolerated in PDX Models with ROS1 Fusions & Mutations

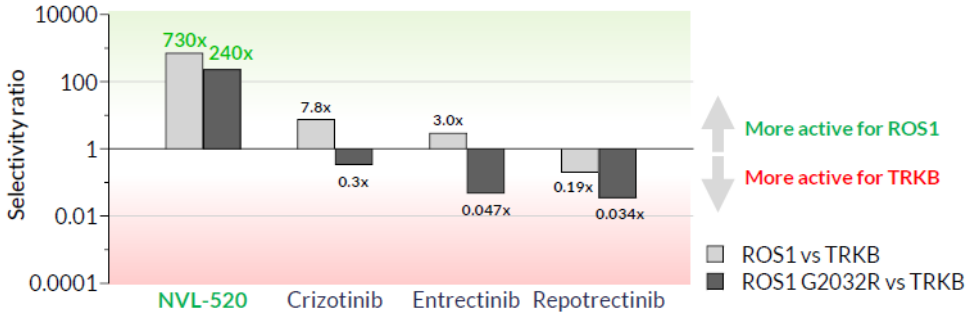


▲ Figure 1. (Top) Cell viability 3-day IC_{50} in Ba/F3 cells expressing CD74-ROS1 fusions. (Bottom) Subcutaneous PDXs in Balb/c nude mice (SDC4-ROS1) and Nude-*Foxn1*^{nu} mice (CD74-ROS1 G2032R), dosed orally twice daily, n=5 per group. "Days" denotes days on treatment.[5]

High Selectivity for ROS1 over TRKB

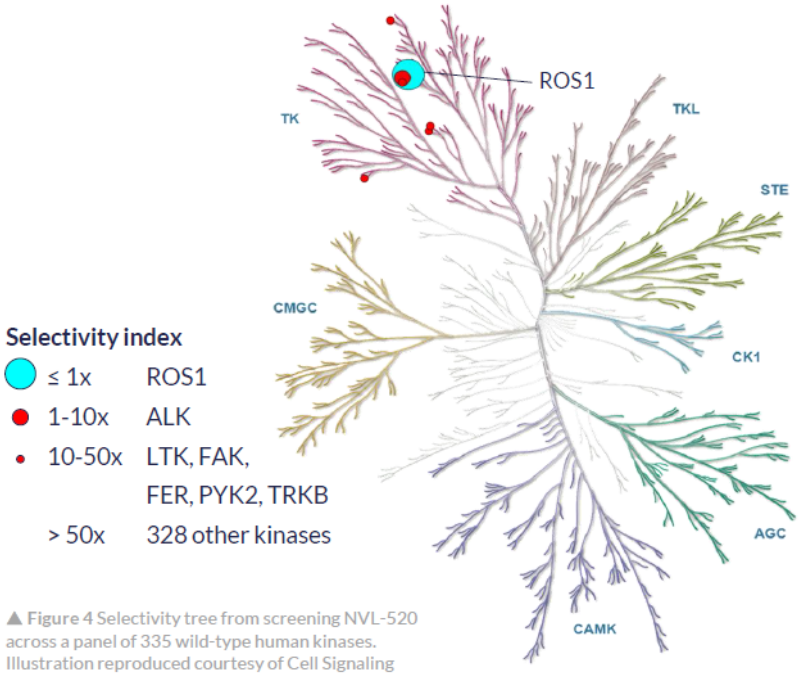
- TRK-family kinases (TRKA/B/C) play crucial neurological functions.
- Inhibition of TRKB is implicated in the neurologic adverse events associated with dual TRK/ROS1 inhibitors, including entrectinib.[9,10]
- NVL-520 is designed to selectively inhibit ROS1 while sparing TRKB.

Preclinical Ability of NVL-520 to Avoid Off-target TRK Inhibition



▲ Figure 3. Selectivity was calculated as ratio of IC_{50} for cellular BDNF-stimulated TRKB phosphorylation in Ba/F3 TRKB cells to IC_{50} for Ba/F3 CD74-ROS1 3-day viability.[11]

NVL-520 is Highly Selective for ROS1 Over Other Kinases



▲ Figure 4 Selectivity tree from screening NVL-520 across a panel of 335 wild-type human kinases. Illustration reproduced courtesy of Cell Signaling Technologies, Inc. (www.cellsignal.com).[6,12]

Phase I/II ARROS – 1 Study

PHASE 1 DOSE-ESCALATION DESIGN

PATIENT POPULATION

KEY INCLUSION CRITERIA

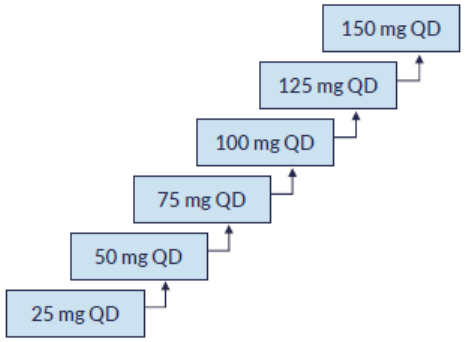
- Adults with a solid tumor harboring a ROS1 gene fusion (by local testing)
- Prior treatments
  - NSCLC: ≥ 1 ROS1 TKI
  - Other solid tumors: ≥ 1 systemic anticancer therapy (or for whom no satisfactory standard therapy exists)
  - Any number of prior platinum-based chemotherapies and/or immunotherapies
- Evaluable disease (RECIST 1.1 target or nontarget disease)
- CNS disease is allowed, if stable (i.e., without progressive neurologic symptoms or increasing corticosteroid doses)

KEY EXCLUSION CRITERIA

- Tumor harboring other oncogenic driver alterations

BOIN DOSE ESCALATION

PLANNED DOSE LEVELS



Up to ~54 patients may be enrolled, including additional patients allowed at previously-evaluated dose levels for the purpose of dose-optimization.

OBJECTIVES

PRIMARY

- Selection of the RP2D
- Identification of the MTD (if applicable, based on DLT)

SECONDARY

- Overall safety and tolerability
- Characterization of PK
- Preliminary antitumor activity (including ORR and DOR)
- Intracranial activity

▲ **Table 1.** Abbreviations: **BOIN**, Bayesian optimal interval design; **DLT**, dose-limiting toxicity; **DOR**, duration of response; **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **ORR**, overall response rate (RECIST 1.1); PK, pharmacokinetics; **QD**, once daily; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **RP2D**, Recommended Phase 2 Dose; **TKI**, Tyrosine Kinase Inhibitor

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%)

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 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.

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.

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

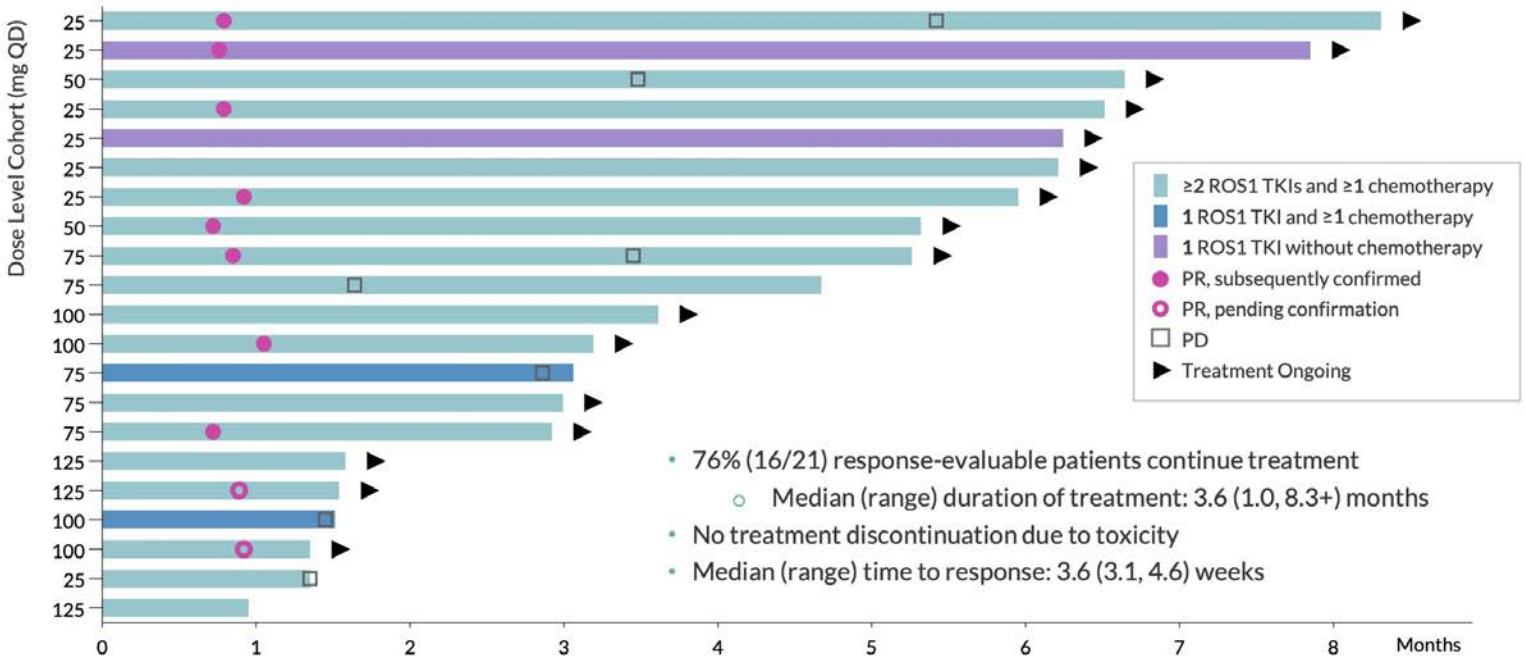
Treatment-Related Adverse Events (TRAEs) in >1 Patient

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%)

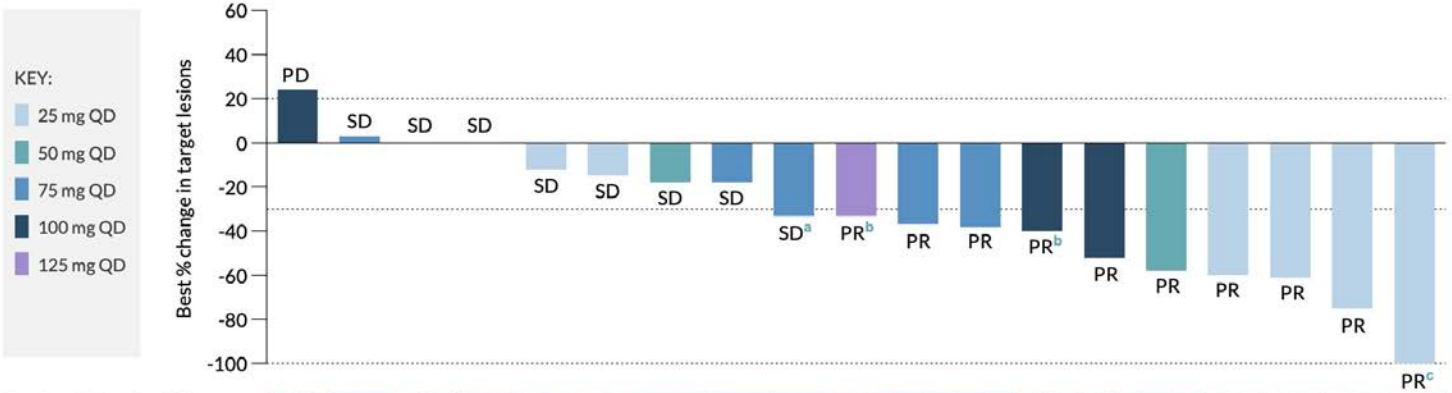
Data as of 13 Sep 22, for patients treated by 01 Sep 2022. AE, adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; DLT, dose-limiting toxicity; SAE, serious adverse event.
[a] Including oedema and oedema peripheral.

Time on Treatment | Sustained Duration with Follow-up Ongoing



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.

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

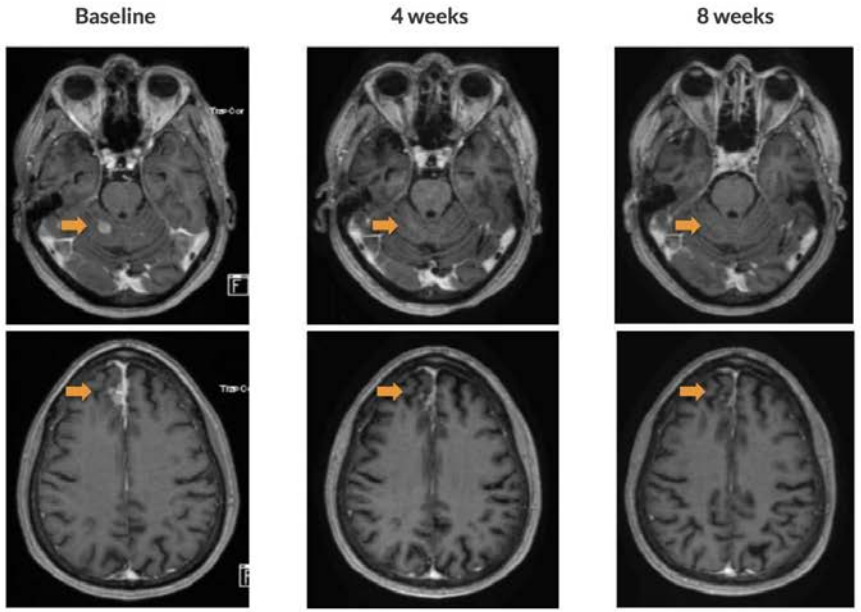


Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3[d]	2	1	2	2	2	2	3[d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
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.

CNS Activity | NVL-520 Induced Responses in Intracranial Lesions

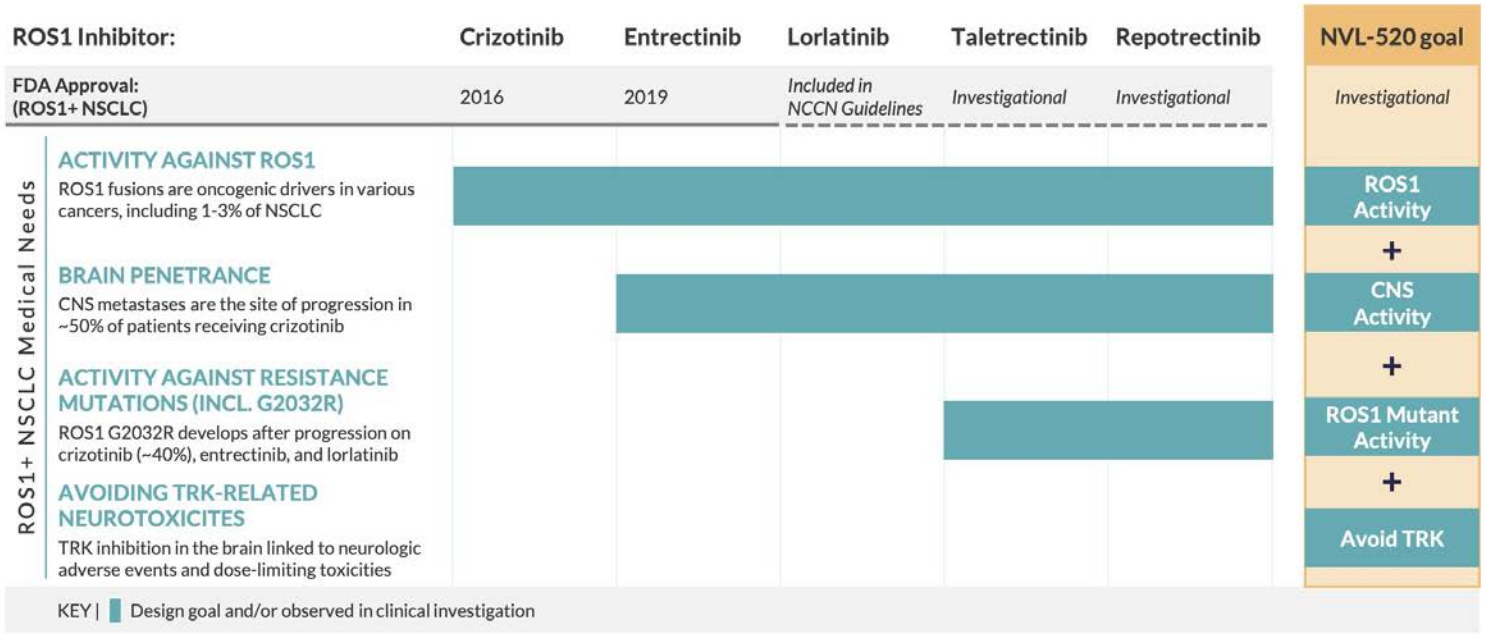
- Intracranial PR in 3/3 [a] patients with measurable (>10 mm) CNS metastases
- ORR of 73% (8/11) [b] in response-evaluable patients with history of CNS metastases
- No CNS progression observed in any of the 35 treated patients



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

NVL-520 | A Rationally Designed Kinase Inhibitor for ROS1



CNS, central nervous system; NCCN, National Comprehensive Cancer Network®; NSCLC, non-small cell lung cancer; ROS1+, ROS1-positive. Sources: Drilon et al., Nat. Rev. Clin. Oncol. 2021; Jordan et al., Cancer Discovery. 2017; Patil et al., J. Thorac. Oncol. 2018; Gainor et al., JCO Precision Oncol. 2017; Lin et al., CCR 2021; Cocco et al., Nat. Rev. Clin. Oncol. 2018; Drilon et al., Lancet Oncol. 2020; Doebele et al., Ann. Oncol. 2019; Shaw et al., NEJM 2020; Li et al., JCO 2022; Drilon et al., Ann. Oncol. 2019; Papadopoulos et al., Clin Cancer Res. 2020; crizotinib prescribing information; entrectinib prescribing information.