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Clinical Evaluation of NVL-520, a Highly Selective ROS1 Inhibitor, in Patients with Advanced ROS1-Positive Solid Tumors: The Phase 1/2 ARROS-1 Study

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NVL-520: DESIGNED TO ADDRESS MEDICAL NEEDS IN ROS1+ CANCERS

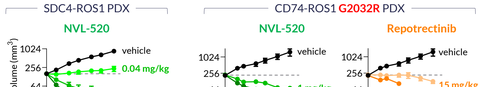
ACTIVITY AGAINST ROS1 FUSIONS & MUTATIONS, INCLUDING G2032R

- ROS1 fusions are oncogenic drivers in various adult and pediatric cancers, including up to 3% of NSCLC.[1,2]
- TKIs approved by the FDA and EMA for ROS1+ NSCLC (crizotinib and entrectinib) are partly limited by acquired resistance, frequently mediated by secondary ROS1 kinase-domain mutations.[3,4,5]
- ROS1 G2032R mutation, which confers resistance to crizotinib, entrectinib, and lorlatinib, develops in ~40% of patients progressing on crizotinib.[3,5]
- Other clinically observed ROS1 resistance mutations include S1986F, L2026M, and D2033N.[1,3]

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

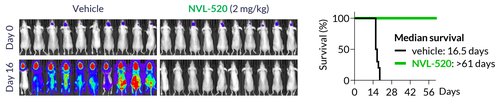
NVL-520 Induces Tumor Regression and is Well-tolerated in PDX Models with ROS1 Fusions & Mutations



▲ **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.[6]

ANTITUMOR ACTIVITY IN THE CNS

NVL-520 Shrinks Intracranial Tumors and Extends Median Survival in an Intracranial CD74-ROS1 G2032R Tumor Model



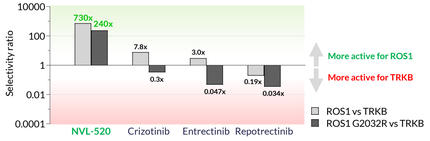
▲ **Figure 2.** Ba/F3 CD74-ROS1 G2032R luciferase cells intracranially injected into Balb/c nude mice and dosed orally twice daily. "Day(s)" denotes days on treatment.[6]

- Up to 40% of patients with ROS1+ NSCLC present with CNS metastases.[7,8]
- CNS metastases represent the sole site of progression in ~50% of patients receiving crizotinib.[8]
- In rats, NVL-520 shows brain-to-plasma free-drug ratio (Kpuu) = 0.16, similar to lorlatinib = 0.11. Both were determined at 1 hour after dosing at 10 mg/kg.

HIGH SELECTIVITY FOR ROS1 OVER TRKB

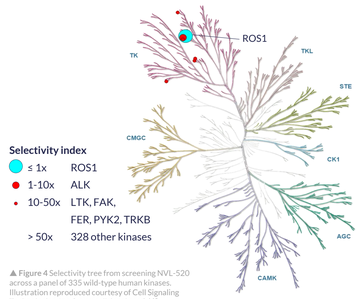
- TRK-family kinases (TRKA/B/C) play crucial neurological functions.
- Inhibition of TRKB is implicated in the neurologic adverse events associated with dual TRK/ROS1 inhibitors, including entrectinib.[9,10]
- NVL-520 is designed to selectively inhibit ROS1 while sparing TRKB.

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 1/2 ARROS-1 STUDY

PHASE 1 DOSE-ESCALATION DESIGN

PATIENT POPULATION

KEY INCLUSION CRITERIA

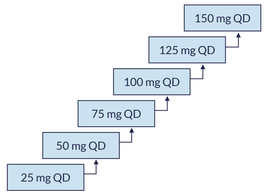
- Adults with a solid tumor harboring a ROS1 gene fusion (by local testing)
- Prior treatments
  - NSCLC: ≥ 1 ROS1 TKI
  - Other solid tumors: ≥ 1 systemic anticancer therapy (or for whom no satisfactory standard therapy exists)
  - Any number of prior platinum-based chemotherapies and/or immunotherapies
- 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

PHASE 2 EXPANSION DESIGN

COHORT[a]	N	TUMOR TYPE	PRIOR ROS1 TKI	PRIOR CHEMO/I-O
2a	~70	ROS1+ NSCLC	Naive	≤ 1
2b[b]	~45	ROS1+ NSCLC	1[c]	Naive
2c[b]	~37	ROS1+ NSCLC	1[c]	1
2d[b]	~21	ROS1+ NSCLC	≥ 2	≤ 1
2e	~20	Any ROS1+ solid tumor[d]	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

▲ **Table 2.** Abbreviations: **CBR**, clinical benefit rate; **Chemo/I-O**, platinum-based chemotherapy ± immunotherapy; **DOR**, duration of response; **NSCLC**, non-small cell lung cancer; **ORR**, overall response rate (RECIST 1.1); **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **ROS1+**, ROS1-positive; **TTR**, time to response
a. Open-label expansion cohorts. Cohorts 2a-2d are designed with registrational intent.
b. Additional efficacy analyses for subset of patients with ROS1 resistance mutations, including G2032R.
c. Either crizotinib or entrectinib.
d. Exploratory cohort. Includes patients age ≥ 12 years with weight > 40 kg, and those with NSCLC who do not qualify for any of the other cohorts.

STUDY TREATMENT

- NVL-520, oral, once-daily dosing.
- Treatment continues until intolerance or disease progression.
- Patients may continue to receive NVL-520 following progression suitable for local ablation at the discretion of the Investigator in consultation with the Sponsor.

PROCEDURES

- Safety assessments include adverse events, clinical laboratory tests, vital signs, physical exam, neurologic assessment, ocular exam and ECG.
- Tumor assessments as per RECIST 1.1 (including brain MRI for all patients at baseline).
- Longitudinal analysis of circulating tumor DNA includes ROS1 mutation profiling and other relevant biomarkers.

SUMMARY

- NVL-520 has demonstrated CNS activity and potent and selective inhibition of ROS1 & ROS1 G2032R over TRKB in preclinical models. These data indicate the potential to minimize TRK-related CNS adverse events seen with dual TRK/ROS1 inhibitors and drive more durable responses for patients with ROS1+ tumors, including those with ROS1 resistance mutations and CNS metastases.
- ARROS-1 is a phase 1/2 study evaluating the safety and activity of NVL-520 in patients with advanced ROS1+ NSCLC and other solid tumors, including those with ROS1 resistance mutations and CNS metastases.
- The Phase 1 portion of the study is open and actively enrolling in the USA, Spain, the Netherlands, and France, with further global expansion planned.
- Phase 2 cohorts are designed to support potential registration in TKI-naive or previously treated ROS1+ NSCLC.
- For additional information, please contact: medical@nuvalent.com

Study ID: **NCT05118789**

Additional abbreviations
CNS, central nervous system; **PDX**, patient-derived xenograft; **DNA**, deoxyribonucleic acid; **FDA**, US Food and Drug Administration; **EMA**, European Medicines Agency; **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **ROS1+**, ROS1-positive; **TKI**, tyrosine kinase inhibitor

Disclosures
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Disclaimer
Preclinical experiments not powered to determine the statistical significance of differences in measurements between any of the inhibitors tested. No head-to-head clinical studies have been conducted for currently approved or investigational therapies versus NVL-520. NVL-520 is an investigational new drug and clinical investigation is ongoing.

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