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


#Abbreviations: (filed/pending); associated research paid to institution from Pfizer,

**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
- >90% of ROS1 fusions result from ROS1-3 or ROS1-4, which are created by chromosomal translocations and oncogenic drivers, respectively.
- ROS1 G2032R mutation, which confers resistance to crizotinib, entrectinib, and lorlatinib, develops in 40% of patients progressing on crizotinib.3
- Other clinically observed ROS1 fusions in ROS1+ tumors include S318F, L2036A, and G2032N.3,4

ANTITUMOR ACTIVITY IN THE CNS

- NVL-520 exhibits in vitro potency against ROS1 fusions and -drug-resistant mutations.
- NVL-520 exhibits in vivo tumor regression and is well-tolerated in PDx models with ROS1 Fusions & Mutations.

HIGH SELECTIVITY FOR ROS1 OVER TRKB

- TRK family kinases (TRK/A/B/C) play crucial neuronal functions.
- Inhibition of TRKB is implicated in the neurotoxic adverse events associated with dual TRK/Ros1 inhibitors, including entrectinib.5
- NVL-520 is designed to selectively inhibit ROS1 while sparing TRKB.

PHASE 1/2 EXPANSION DESIGN

**PHASE 1-DOSAGE ESCALATION**

- **PATIENT POPULATION**
- **BOIN DOSE ESCALATION**
- **PLANNED DOSE LEVELS**

**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 systems anticancer therapy or for whom no satisfactory standard therapy exists.
- Any number of prior platinum-based chemotherapy regimens and/or immunotherapies evaluated dose levels for the 0.75 mg/kg dose.

**EXCLUSION CRITERIA**
- Tumor harboring other oncogenic driver alterations.
- CNS disease is allowed, if stable (i.e., without progression).

**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

**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 alleviation at the discretion of the investigator in consultation with the Sponsor.

**STUDY TREATMENT 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.

**SUMMARY**
- NVL-520 has demonstrated CNS activity and potent and selective inhibition of ROS1 & ROS1 G2032R 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 in 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 ongoing and actively recruiting 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

**REFERENCES**
- A. Drilon et al., Cancer Discovery. 2017
- Jordan et al., Cancer Discovery. 2017
- Ou and Zhu, Lung Cancer. 2019

**ANALYTICAL METHODS**
- Plasma free concentrations of NVL were measured via high-performance liquid chromatography to identify any drug-related CNS adverse events.