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


OBJECTIVES

- **Phase 1/2 Study:**
  - **Patient population:** Adults with a solid tumor harboring a ROS1 gene fusion. (Available at the time of writing)
  - **Primary endpoint:** Identification of recommended phase 2 dose (RP2D).
  - **Secondary endpoints:**
    - Overall safety and tolerability
    - Development of resistance
    - Preliminary antitumor activity
  - **Cohorts:**
    - **Cohort A:** Patients with any prior platinum chemotherapy (or for whom no satisfactory standard therapies exist or are available); patients with CNS disease and/or resistance mutations; patients with lung adenocarcinoma; patients with stage IV disease.
    - **Cohort B:** Patients with any prior platinum chemotherapy (or for whom no satisfactory standard therapies exist or are available); patients with CNS disease; patients with resistance mutations; patients with lung adenocarcinoma; patients with stage IV disease.
  - **Study duration:** 21 months

STUDY TREATMENT

- **Dose level 1 (DL1):**
  - **Dose level 2 (DL2):**
  - **Dose level 3 (DL3):**

ANTITUMOR ACTIVITY IN THE CNS

- NVT-520 Shrinks Intracranial Tumors and Extends Median Survival in a Rat Model of Intracranial C70-ROS1 G2032R Mutation

HIGH SELECTIVITY FOR ROS1 OVER TRKB

- **Trk family:** Trk family proteins play crucial neurological functions.
- **Inhibition of TrkA/B/C:** Inhibits the TrkA/B/C family kinases (TRKA/B/C) play a crucial role in various neurological processes. NVT-520 shows brain penetrance and therapeutic selectivity vs. TrkA/B/C.
- **NVT-520 is Highly Selective for ROS1 Over Other Kinases:**
  - **Selectivity:** Selectivity was calculated as ratio of IC50 of NVT-520 for cellular BDNF-stimulated TRKB phosphorylation in Ba/F3 cells (IC50) divided by the plasma concentration of NVT-520 after oral dosing.
- **NVT-520 Induces Tumor Regression and is Well Tolerated in NSCLC Models with ROS1 fusions and Mutations:**

ACTIVITY AGAINST ROS1 FUSIONS & MUTATIONS, INCLUDING G2032R

- **NVT-520 Exhibits In Vitro Potency against ROS1 Fusions and Mutations:**
  - **Table 1:** IC50 values for NVT-520 in various ROS1 fusion cell lines and patient samples.

PHASE 1 DOSE ESCALATION DESIGN

- **Patient population:** Adults with a solid tumor harboring a ROS1 gene fusion.
- **Key inclusion criteria:**
  - Adults with a solid tumor harboring a ROS1 gene fusion.
  - Prior treatments:
    - NSCLC: ≥ 1 ROS1 TKI
    - Any number of prior platinum-based chemotherapies and/or immunotherapies.
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  - CNS disease is allowed, if stable (i.e., without signs and symptoms of disease progression).
  - Patients may continue to receive NVT-520 following progression for selected patients. (Available at the time of writing)

PHASE 2 EXPANSION DESIGN

- **Table 2:** Baseline characteristics of patients in the expansion study.

STUDY TREATMENT

- **Study treatment:** NVT-520, oral, once daily.

PRINCIPAL INVESTIGATOR

- **Principal investigator:** Daniel R. Haber, MD, FACP, FRCPC, Associate Professor of Medicine, Dana-Farber Cancer Institute, Boston, MA, USA; Director of Clinical Research, Dana-Farber Cancer Institute, Boston, MA, USA.

DISCLOSURES

- **Affiliations:** For all authors, please see the online version of this article for details.

SUMMARY

- **NVT-520** has demonstrated CNS activity and potent and selective inhibition of ROS1 & G2032R TRKB in preclinical models. This data indicate the potential of NVT-520 to inhibit TRK-related CNS adverse events seen with dual TRK inhibitors.

- **NVT-520** has demonstrated safety and tolerability in patients with advanced ROS1+ NSCLC and other solid tumors, including those with ROS1 resistance mutations and CNS metastases.

- **NVT-520** is a potential oncology drug for patients with advanced ROS1+ NSCLC, other solid tumors, and CNS metastases.

- **Additional information:** For more information, please contact: medinfo@nusantent.com