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# Clinical evaluation of NVL-520, a highly selective ROS1 inhibitor in patients with advanced ROS1-positive solid tumors: The phase I/II ARROS-1 study

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## 78TiP Clinical evaluation of NVL-520, a highly selective ROS1 inhibitor in patients with advanced ROS1-positive solid tumors: The phase I/II ARROS-1 study

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**Background:** Oncogenic ROS1 gene rearrangements are implicated in the pathogenesis of various adult and pediatric cancers, including up to 3% of non-small cell lung cancers (NSCLC), where up to 40% of patients present with central nervous system (CNS) metastases. Tyrosine kinase inhibitors (TKIs) approved by the FDA and EMA for ROS1-positive NSCLC (crizotinib and entrectinib) are limited by acquired resistance, frequently mediated by secondary ROS1 kinase domain mutations. In addition, dual TRK/ROS1 kinase inhibitors, including entrectinib, are associated with neurologic adverse events. NVL-520 is a novel, brain-penetrant ROS1-selective kinase inhibitor that exhibits preclinical activity against a diverse array of ROS1 rearrangements and mutations, including G2032R, while sparing inhibition of TRKB. The ARROS-1 study evaluates the safety and activity of NVL-520 in patients with solid tumors

harboring ROS1 fusions, including those with resistance mutations and CNS metastases.

**Trial design:** ARROS-1 (NCT05118789) consists of a phase 1 dose escalation followed by phase 2 expansion in cohorts defined by tumor type and prior therapies that are designed to support potential registration. Phase 1 includes adult patients with any solid tumor type harboring a ROS1 gene fusion (by local testing), with evaluable disease, who have received $\geq$ 1 ROS1 TKI. Prior platinum-based chemotherapies and/or immunotherapies, as well as stable CNS disease, are allowed. Patients will receive NVL-520 by daily oral administration. Primary phase 1 objectives are to determine the NVL-520 recommended phase 2 dose, and, if applicable, maximum tolerated dose. Additional objectives include evaluation of safety/tolerability, preliminary activity, and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-520. Longitudinal analysis of circulating tumor DNA will be performed, including ROS1 mutation profiling and other relevant biomarkers. The phase 1 portion of the study is ongoing.

**Clinical trial identification:** NCT05118789 (November 12, 2021).

**Legal entity responsible for the study:** Nuvalent, Inc.

**Funding:** Nuvalent, Inc.

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## 79TiP A phase I, open-label, dose escalation, confirmation, and expansion trial of BI 1810631 as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations

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**Background:** HER2 mutations are present in 2–4% of NSCLC tumors; of these ~50% are exon 20 insertion (ex20ins) mutations. There is an unmet need for effective targeted therapy against HER2 mutations in solid tumors, particularly in NSCLC. BI 1810631 is a HER2 selective TKI that covalently binds to both wild-type/mutated HER2 receptors, including ex20ins, whilst sparing EGFR signaling; preclinical data suggest good tolerability and efficacy. This phase Ia/Ib, open-label, non-randomized study aims to determine safety, MTD, PK, pharmacodynamics, and preliminary efficacy of BI 1810631 in pts with HER2+ solid tumors (NCT04886804).

**Trial design:** ~96 pts from 3 sites in the US, Netherlands, and Japan will be recruited. Phase Ia: consecutive cohorts of pts will receive BI 1810631 QD or BID at escalating doses. Starting dose level: 15 mg BID; QD schedule will begin after one dose level above estimated therapeutic dose of BI 1810631 is determined safe by the Dose