TPS8665 **Poster Session**

NVL-330, a selective HER2 tyrosine kinase inhibitor, in patients with advanced or metastatic HER2-altered non-small cell lung cancer: The phase 1 HEROEX-1 study.

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Background: Oncogenic mutations and gene amplifications in the HER2 receptor tyrosine kinase are detected in approximately 2-4% and 1-5% of non-small cell lung cancers (NSCLC) in the US, respectively. Exon 20 insertion mutations (exon20ins) are the predominant *HER2* mutations in NSCLC, and ~50% of patients with *HER2*-mutant metastatic NSCLC develop brain metastases. The antibody drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) has received FDA accelerated approval for *HER2*-mutant NSCLC, but no tyrosine kinase inhibitors (TKIs) are currently approved for this indication. NVL-330 is a novel, brain-penetrant, HER2-selective investigational TKI, designed to address the medical need of targeting *HER2*-mutant tumors, and treating brain metastases, while minimizing treatment related adverse events due to off-target inhibition of wild-type EGFR. **Methods:** HEROEX-1 (NCT06521554) is a first-in-human, Phase 1a/1b trial. The Phase 1a dose escalation portion employs a Bayesian optimal interval design with a 3+3 run-in, followed by a Phase 1b dose expansion. The study population includes adult patients with advanced or metastatic NSCLC with a *HER2* oncogenic mutation (Phase 1a/1b) or amplification (Phase 1a only) determined by local testing. Eligible patients must have received at least one prior systemic therapy including platinum-based chemotherapy with or without immunotherapy, or are unsuitable candidates for available therapies. Prior HER2-directed antibodies and HER2-directed ADCs are allowed. Prior HER2 TKIs are allowed in Phase 1a only. Patients will receive NVL-330 by oral administration once or twice daily. The primary objectives are to evaluate safety and tolerability, determine the recommended Phase 2 dose, and, if applicable, the maximum tolerated dose of NVL-330. Additional objectives include assessment of preliminary activity and characterization of the pharmacokinetic and pharmacodynamic profiles of NVL-330. Analyses will be performed to evaluate tumor and blood-based biomarkers of response and other relevant biomarkers. The study is open to accrual. Clinical trial information: NCT06521554. Research Sponsor: Nuvalent.