TPS8666 **Poster Session**

Neladalkib (NVL-655), a highly selective anaplastic lymphoma kinase (ALK) inhibitor, compared to alectinib in first-line treatment of patients with ALK-positive advanced non-small cell lung cancer: The phase 3 ALKAZAR study.

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Background: Oncogenic *ALK* gene fusions are detected in ~5% of advanced non-small cell lung cancer (NSCLC) cases. Among these patients, the incidence of brain metastases at diagnosis is ~40%. Prior generations of ALK tyrosine kinase inhibitors (TKIs) present limitations that may influence efficacy and tolerability, such as inadequate control of brain metastases, treatment-emergent drug-resistant *ALK* mutations, or off-target adverse events, particularly neurological events associated with inhibition of the structurally related TRK kinases. Neladalkib is a potent, brain-penetrant, ALK-selective TKI with preclinical activity against diverse *ALK* fusions and resistance mutations (Lin et al., Cancer Discovery 2024). In the Phase 1/2 ALKOVE-1 study, neladalkib showed encouraging preliminary efficacy in patients with heavily pretreated *ALK+* NSCLC, including in those with *ALK* single or compound resistance mutations and brain metastases (Drilon et al., ESMO 2024). It also exhibited a favorable safety profile consistent with its ALK-selective, TRK-sparing design. The Phase 3 ALKAZAR study aims to demonstrate the superiority of neladalkib over a current standard of care, alectinib, in TKI-naïve patients with advanced *ALK+* NSCLC. **Methods:** ALKAZAR (NCT06765109) is a global, Phase 3, randomized, controlled, open-label study in adult patients with locally advanced or metastatic NSCLC harboring an *ALK* rearrangement per local testing of tissue or blood. Prior systemic anticancer treatment for metastatic disease is not allowed. Patients who received prior alectinib in the adjuvant setting are not eligible. Patients are required to have measurable disease by RECIST. Patients with untreated central nervous system (CNS) disease without progressive neurological symptoms or increasing corticosteroid doses are eligible. Patients with non-ALK oncogenic driver alterations are excluded. Approximately 450 patients will be randomized in a 1:1 ratio to receive either oral neladalkib (150 mg once daily) or oral alectinib (600 mg twice daily), stratified by brain metastases, ethnic origin (Asian vs. non-Asian), and Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 vs.1 vs. 2). The primary endpoint is progression-free survival by blinded independent central review. Secondary endpoints include intracranial activity, objective response rate, duration of response, overall survival, safety and tolerability, and patient-reported outcomes. Additional analyses will be conducted to investigate candidate biomarkers and molecular mechanisms of response and resistance to neladalkib and alectinib. The study is open to accrual. Clinical trial information: NCT06765109. Research Sponsor: Nuvalent.