NUVALENT (NVL-655) (ALKOVE-1 Trial)

Several members of the ALK Positive UK charity have been recruited and are currently taking part in this trial. Using the search function on the charity's Facebook page for Nuvalent you can read about some of their experiences so far.

NVL-655 is a 4th generation ALK Tyrosine Kinase Inhibitor, (TKI), with good brain penetration. It is designed to remain active in tumours that have developed resistance to first, second, and third-generation ALK inhibitors. NVL-655 has been optimized for CNS (central nervous system) penetration to improve treatment options for patients with brain metastases. Side effects of other ALK TKIs including cognitive impairment, mood disorders, sleep disorders, dizziness, ataxia (poor muscle control), and weight gain, among others, are hoped to be minimized.

Following treatment with 1st and/or 2nd generation ALK therapies, approximately 40% of patients develop a mutation which confers resistance to crizotinib, ceritinib, alectinib, and brigatinib. Third generation ALK TKI lorlatinib has been approved for treating patients who have previously received 1st and/or 2nd generation ALK therapies. However compound mutations have been observed in patients who have progressive disease following lorlatinib. While 30-40% of ALK+ NSCLC patients have brain metastases at diagnosis, advanced patients with a history of progression on ALK TKI treatments show a higher incidence of brain metastases of about 60%.

Trial Design

This is a USA and Worldwide Phase 1/2, dose escalation and expansion study:

- Phase 1 will evaluate the safety and tolerability of NVL-655 and determine the recommended phase 2 dose (RP2D)
- Phase 2 will determine the objective response rate (ORR). Secondary objectives will include the duration of response (DOR), time to response (TTR), progression-free survival (PFS), overall survival (OS), and clinical benefit rate (CBR) of NVL-655 in patients with advanced ALK-positive NSCLC and other solid tumors

Treatment consists of a pill (or pills) taken orally.

Trial Sites UK and Dates

The Royal Marsden Hospital, London. The Christie, Manchester

It began in the USA in May, 2022 and the UK in 2023, and is expected to be completed by March, 2026.

214 patients will be enrolled. Patient cohorts:

- Cohort 2a: Patients with locally advanced or metastatic NSCLC harbouring an ALK rearrangement who have received 1 prior 2nd-generation ALK TKI (ceritinib, alectinib, brigatinib)

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- Cohort 2b: Patients with locally advanced or metastatic NSCLC harboring an ALK rearrangement, who have received 2-3 prior 1st or 2nd-generation ALK TKIs (crizotinib, ceritinib, alectinib, brigatinib)
- Cohort 2c: Patients with locally advanced or metastatic NSCLC harbouring an ALK rearrangement, who have received 2-3 prior ALK TKIs, with lorlatinib in the 2nd or 3rd line
- Cohort 2d: Patients with other solid tumours harbouring an ALK rearrangement or activating ALK mutation, including patients with NSCLC not eligible for cohorts 2a-c, who have received ≥1 prior systemic anticancer therapy, or for whom no satisfactory standard therapy exists

Headline news release Oct 2023: *Encouraging preliminary signs of activity observed in heavily pre-treated patients with ALK-positive NSCLC, including in subgroups of patients who have previously received a 2nd generation ALK TKI and lorlatinib, have brain metastases, or have single or compound ALK resistance mutations*
Favorable preliminary safety profile is consistent with an ALK-selective, TRK sparing design

References

https://clinicaltrials.gov/study/NCT05384626

Nuvalent reports preliminary phase 1 clinical data from ALKOVE-1 trial that support best-in-class potential of NVL-655 for patients with ALK-positive NSCLC. News Release. Nuvalent. October 13, 2023. https://investors.nuvalent.com/2023-10-13-Nuvalent-Reports-Preliminary-Phase-1-Clinical-Data-from-ALKOVE-1-Trial-that-Support-Best-In-Class-Potential-of-NVL-655-for-Patients-with-ALK-Positive-NSCLC