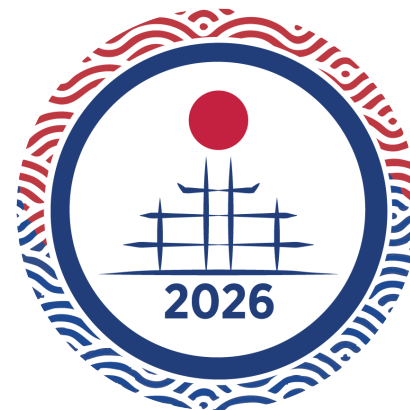


Challenges in interpretation of pathological response in patients with *ALK*-rearranged NSCLC receiving alectinib in NAUTIKA1

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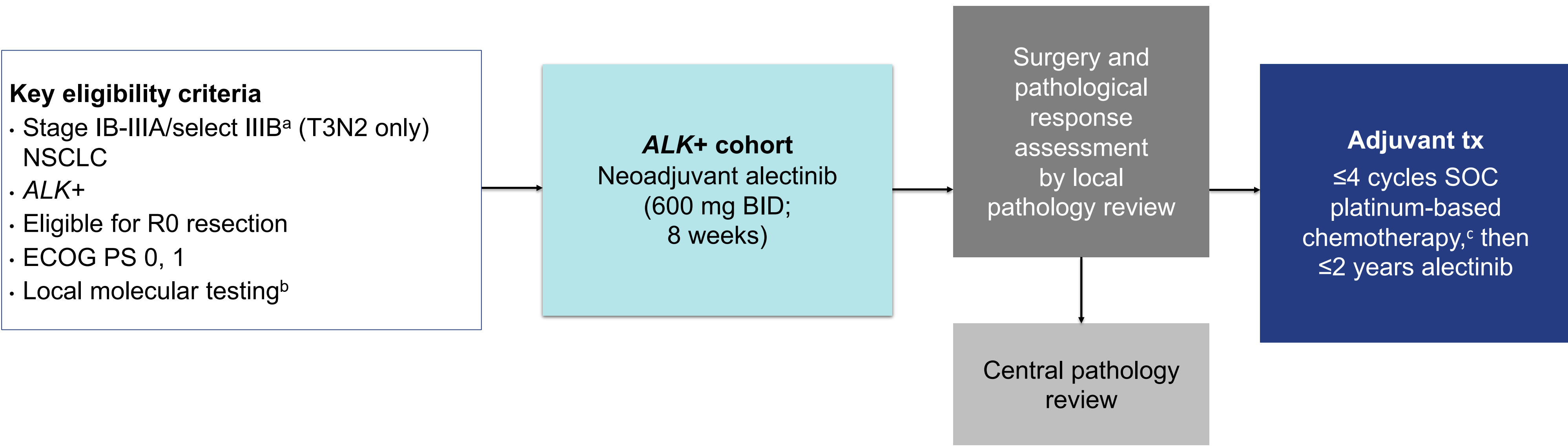
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BACKGROUND

- Anaplastic lymphoma kinase (*ALK*) rearrangements are reported in approximately 5% of patients with non-small cell lung cancer (NSCLC), and they predict response to *ALK*-targeted tyrosine kinase inhibitors (TKIs), including alectinib¹
 - NAUTIKA1 (NCT04302025) is a Phase II umbrella study of neoadjuvant targeted treatment in patients with early-stage NSCLC harboring study-eligible oncogenic drivers²
 - Neoadjuvant alectinib was evaluated in the cohort of patients with resectable stage IB-IIIB *ALK*+ NSCLC as previously described (Figure 1)²

Figure 1. Study design for *ALK*+ cohort in the NAUTIKA1 umbrella study



AJCC, American Joint Committee on Cancer; BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; R0, complete resection; SOC, standard of care; tx, treatment. ^aAJCC 8th edition. ^bLocal biomarker testing in CLIA-certified lab via FISH, IHC or NGS. ^cUnless contraindicated/patient declined.

- To date, the patterns of pathological response to neoadjuvant *ALK*-targeted TKIs have not been described
- Here, we present the final results of the central pathological review of tumor samples for the 40 patients who had R0 resection after neoadjuvant alectinib treatment
- Dr. Jay M. Lee will be presenting the clinical results and biomarker analysis in mini oral #MO06.01³

METHODS

- All tumor bed slides were reviewed for percentage residual viable tumor, necrosis, and stroma for major pathological response (MPR),^{4,5} defined as ≤10% residual viable tumor in the tumor bed, and pathological complete response (pCR), defined as 0% residual viable tumor in the tumor bed and lymph nodes
- Lymph nodes were evaluated for metastatic tumor and treatment effect
- Local *ALK* IHC results were recorded when available
- Primary endpoint:** MPR by local pathology review of the resected tumor bed
- Secondary endpoints:**
 - pCR by local pathology review (including all sampled regional lymph nodes)
 - pCR and MPR by assessment of hematoxylin and eosin (H&E)-stained digital whole-slide images scanned at up to 40× magnification, with independent central pathology review performed by 2 expert thoracic pathologists
- Tumor beds that had MPR or pCR results that were discordant between the central reviewers were discussed and re-reviewed to achieve consensus
- When consensus between central reviewers could not be achieved for discordant cases based on H&E alone, central *ALK* IHC was conducted at CellCarta using the *ALK* D5F3 clone with the Ventana Benchmark ULTRA system

RESULTS

- Data presented in the previously submitted abstract for this analysis were the initial results based on a March 2026 data cut; the final data presented here are from the 40 patients with *ALK*+ NSCLC who received neoadjuvant alectinib and then underwent R0 resection by the primary analysis snapshot on June 30, 2026

Concordance between local and central reviewers

- Concordance between local and central pathology reviewers was observed in 35/40 cases (87.5%) for both tumor bed and lymph node assessments (Table 1)
- By central review, 25/40 patients (62.5%) had MPR, which included 4/40 (10.0%) with pCR

Table 1. Results of local and central review of patients with *ALK*+ NSCLC who had R0 primary tumor resection

Local assessment	Final central assessment (N=40)			Total
	pCR	MPR (excluding pCR)	Non-MPR/pCR	
pCR	4	4	0	8
MPR (excluding pCR)	0	16	0	16
Non-MPR/pCR	0	1	15	16
Total	4	21	15	40

Blue shading indicates concordance between local and central reviewers. Pink shading indicates discordance between local and central reviewers.

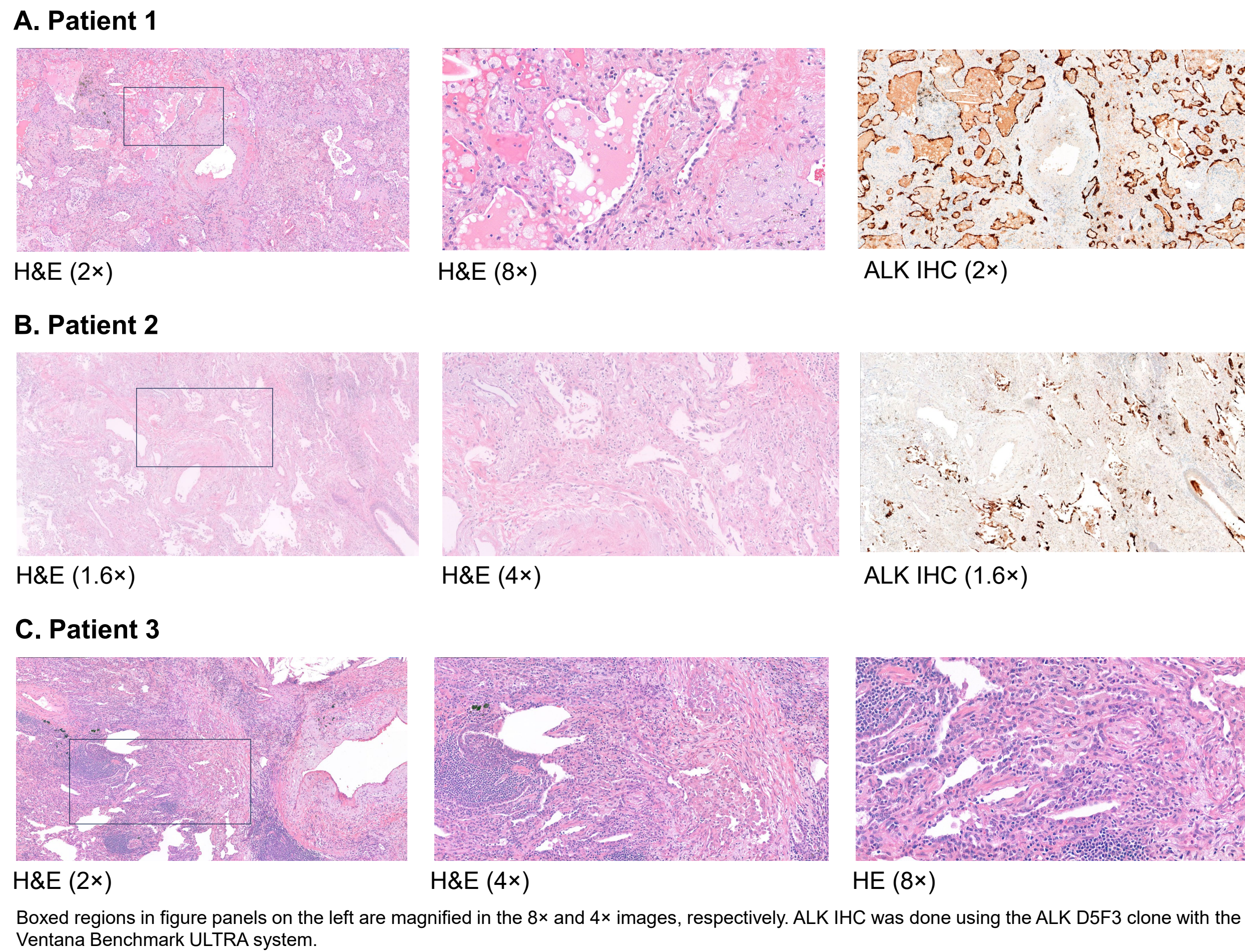
Discordance between local and central reviewers

- Discordance was present in 5 patients (12.5%)
 - Local pCR and central MPR
 - Of the 8 cases classified as pCR by local pathology review, 4 (50.0%) were re-classified by central review as non-pCR MPR
 - Local non-MPR/pCR and central MPR
 - One case classified by local assessment as non-MPR/pCR (17% viable tumor) was reclassified by central review as MPR

Resolving discrepancies between local/central and central-only reviews

- Among the 5 cases that were initially discordant between local and central assessment, 4 cases were resolved based on H&E slides alone
 - In Patients 1 and 2, the mild pneumocyte atypia corresponded to residual neoplastic cells; this was confirmed with *ALK* IHC (Figures 2A and 2B)
- For 1 patient, *ALK* IHC was required to achieve consensus regarding pCR between central reviewers (Figure 2C); the *ALK* IHC stain was negative, confirming pCR
 - Patient 3 had no residual carcinoma as confirmed with *ALK* IHC (not shown)
- Tumor cells showed unique histologic changes following TKI therapy, including small cell size and, in some cases, a residual population of lepidic growth with striking resemblance to reactive pneumocyte hyperplasia (Figure 2A–C)

Figure 2. (A) and (B) Resolving local vs. central assessment discordance in 2 patients; (C) Case confirmed as pCR by central review after *ALK* IHC



CONCLUSIONS

- Central pathological review demonstrated 100% concordance with local pathological assessment of MPR, whereas concordance for pCR was lower
- Discrepancies between local and central pathological review of tumor beds following neoadjuvant alectinib were likely caused by local pathologists misinterpreting the neoplastic cells as post-treatment reactive pneumocytes
- We demonstrate the need for increased awareness of the subtle cytological features of post-alectinib treatment, since this has potential implications for clinical trials and peri-operative management
- These findings highlight the specific morphological challenges of assessing response following neoadjuvant *ALK*-targeted therapy, and provide a foundation for developing pathology guidelines that integrate *ALK* IHC as an adjunct to morphologic assessment following *ALK* inhibition

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