



P3.081 Exploring functional consequences of phosphorylated ALK expression and co-mutations in patients with ALK positive Non-small cell lung carcinoma : An Indian cohort

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INTRODUCTION

- ALK rearrangements occur in approximately 7–10% of NSCLC cases in India and represent an important actionable molecular alteration.
- Conventional ALK IHC detects ALK protein expression, but may not fully reflect functional ALK pathway activation.
- Phosphorylated ALK (p-ALK) represents activated ALK signaling and may provide additional information on ALK pathway activity and treatment response.
- Comprehensive genomic profiling can further identify co-occurring alterations that may contribute to tumor biology and treatment response.
- This study evaluated the concordance between conventional ALK IHC and p-ALK expression, explored their association with clinical outcomes, and characterized the genomic landscape using targeted NGS.

METHODS

- Study design & population: Ambispective pilot study including 70 ALK-positive NSCLC patients with available tumor tissue at AIIMS, India.
- p-ALK assessment: ALK protein expression was evaluated by immunohistochemistry (IHC) and patients were categorized as p-ALK positive or p-ALK negative.
- Clinical assessment: Demographic characteristics, smoking history, treatment received, treatment response, disease progression, and survival outcomes were evaluated.
- Genomic profiling: Targeted NGS using a 1,212-gene panel was performed in a subset of patients to characterize somatic genomic alterations, gene fusions, and copy-number alterations.
- Biomarker assessment: Tumor mutational burden (TMB) and microsatellite stability (MSS/MSI) were evaluated from NGS data.

RESULTS

- p-ALK positivite: 62/70 (88.6%); p-ALK negative: 8/70 (11.4%).
- Clinical profile: Never-smokers predominated; females comprised 40.3% of p-ALK positive patients.
- Clinical outcomes: TKI-based therapy predominated in p-ALK positive patients; progression occurred in 10 p-ALK positive vs 3 p-ALK negative patients. PR (n=3) and SD (n=9) were observed in p-ALK positive patients.
- Genomic profiling: NGS (n=29) identified recurrent alterations in *TP53*, *KMT2C*, *SETD2*, *RASA1* and *MUTYH* with *EML4-ALK* fusions and copy-number amplifications involving *CEP72*, *TERT*, *SDHA*, *CCNE1* and *CCND1* were identified.
- TMB ranged 0.9–8 mut/Mb and all profiled tumors were microsatellite stable.

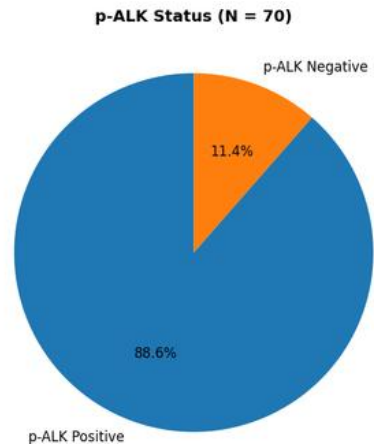
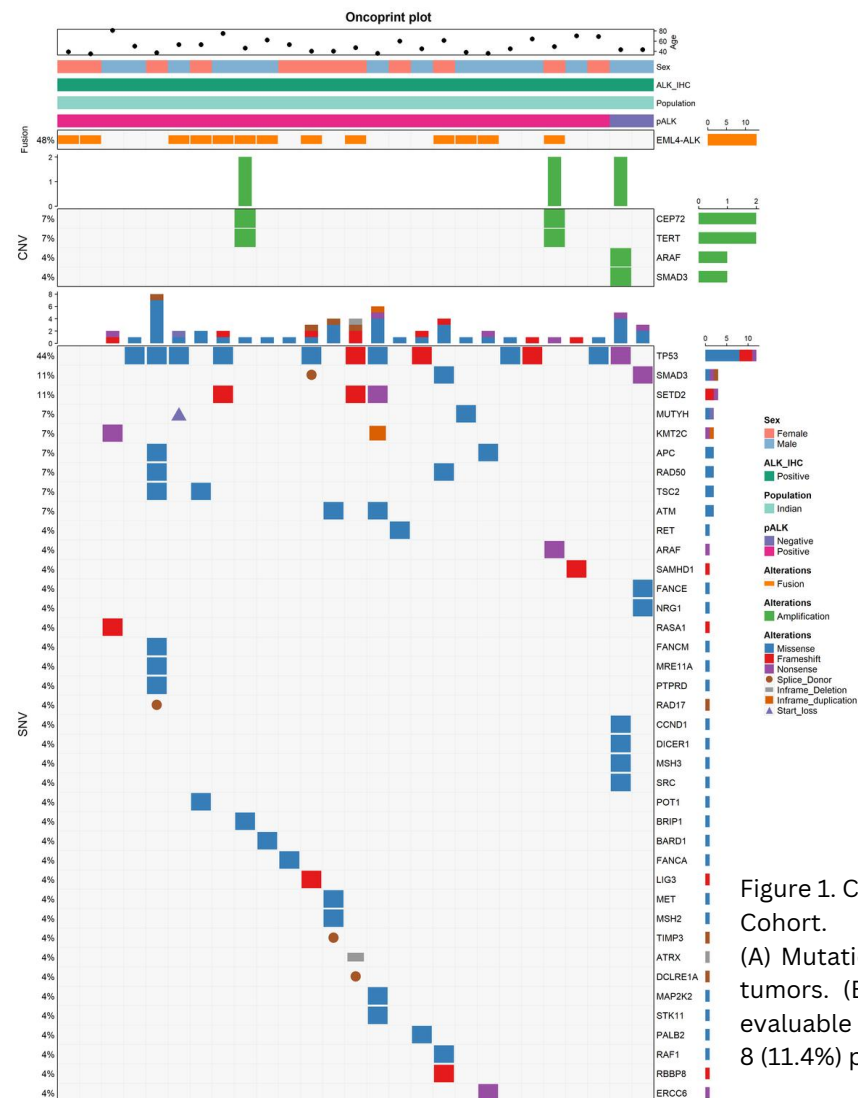


Figure 1. Clinical and Genomic Characteristics of the Study Cohort.
(A) Mutational landscape of profiled ALK-positive NSCLC tumors. (B) Distribution of p-ALK status among the 70 evaluable patients, showing 62 (88.6%) p-ALK-positive and 8 (11.4%) p-ALK-negative cases.

DISCUSSION AND CONCLUSION

- High p-ALK positivity was observed in this clinically selected ALK-positive NSCLC cohort.
- The predominance of never-smokers and female patients is consistent with the clinical characteristics commonly associated with ALK-driven NSCLC.
- Despite ALK-directed therapy, disease progression was observed in a subset, highlighting the potential contribution of additional genomic alterations.
- Recurrent alterations in TP53 and DNA-repair/signaling pathways suggest potential molecular heterogeneity beyond the primary ALK alteration. Detection of EML4-ALK fusions and recurrent CNV alterations provides additional genomic context for ALK-positive disease.
- Ongoing evaluation of additional p-ALK cases and NGS-based genomic analysis is underway to better define predictive biomarkers and clinical outcomes.

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