



EP06.06: KRAS-mutant NSCLC in North India: A 74-Case Series Highlighting Clinicopathologic and Molecular Profiles

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INTRODUCTION

- KRAS** is among the most frequent oncogenic drivers in NSCLC, with increasing therapeutic relevance, particularly for **KRAS G12C**
- However, real-world data on the clinicopathological and molecular spectrum of **KRAS-mutant NSCLC** in Indian patients remain limited, including its occurrence in the post-treatment setting

METHODS

Design: Single-centre retrospective study of NSCLC cases undergoing predictive biomarker testing at AIIMS, New Delhi (Jan - Dec 2025)

- Treatment-naïve cohort:** EGFR/ALK/ROS1-negative tumours undergoing targeted NGS were evaluated for KRAS alterations
- Samples underwent pathologist-led assessment of tumour content and adequacy before molecular testing
- 40-gene targeted DNA/RNA NGS was performed using the AmoyDx HANDLE Classic panel
- Pathogenic/likely pathogenic KRAS variants were identified and classified by codon/subtype
- KRAS-mutant tumours** were correlated with age, sex, smoking status, histology, and specimen characteristics
- The co-mutational landscape, including TP53, STK11, KEAP1, PIK3CA and other alterations, was analyzed
- Post-progression samples** undergoing NGS were separately screened for KRAS mutations and concurrent oncogenic drivers

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- KRAS-mutant NSCLC is molecularly heterogeneous**, with non-G12C variants and clinically relevant co-mutations forming a substantial proportion of cases.
- Broad molecular profiling at diagnosis, with repeat testing at progression when feasible, can identify targetable alterations and potential resistance mechanisms.
- KRAS mutations were identified in 28.9% of treatment-naïve NSCLCs undergoing targeted NGS, higher than the ~10–14% reported in unselected Indian NSCLC cohorts, reflecting enrichment of the present NGS cohort for EGFR/ALK/ROS1-negative tumours.

Future Direction for Research

- Building directly on this cohort, the next step is to integrate STK11/KEAP1 co-mutation status, PD-L1 expression and tumour immune microenvironment features with KRAS subtype and treatment outcomes. This would allow identification of biologically and clinically distinct KRAS-mutant subgroups in Indian NSCLC and clarify whether these co-alterations modify response to immunotherapy or targeted treatment.

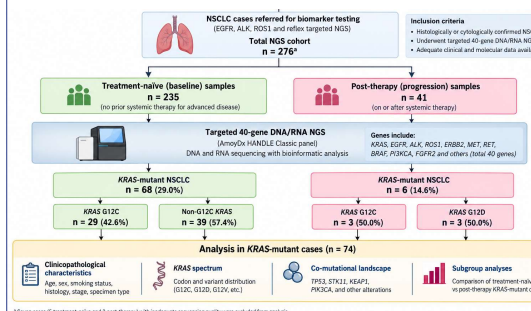
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ChatGPT was used for language refinement and creation of infographics. All scientific content, primary data, analyses and interpretations were reviewed and verified by the authors

RESULTS



*Seven cases (5 treatment-naïve and 2 post-therapy) with inadequate sequencing quality were excluded from analysis.

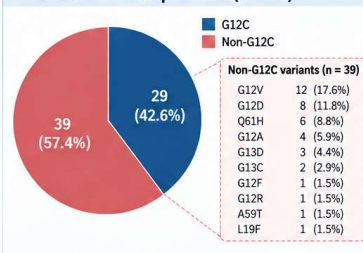
- KRAS mutations** were identified in 68/235 (28.9%) treatment-naïve NSCLCs and 6/41 (14.6%) post-therapy NSCLCs including in the evaluable targeted NGS cohort

In treatment naïve cohort:

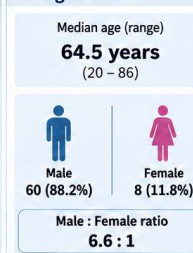
- KRAS-mutant tumours occurred predominantly in **male smokers** and **adenocarcinomas**; 83.7% of patients with available smoking data were smokers and 84% had adenocarcinoma histology
- Although **G12C** was the most frequent individual variant (29/68, 42.6%), non-G12C variants collectively predominated (39/68, 57.4%), demonstrating substantial KRAS subtype heterogeneity
- The molecular landscape was dominated by **TP53 co-mutation (48.5%)**, with less frequent **STK11 (11.8%)**, **PIK3CA (7.4%)** and **KEAP1 (4.4%)** alterations, highlighting molecular heterogeneity beyond the KRAS variant itself

Clinicopathological and Molecular Profile of Treatment-Naïve KRAS-Mutant NSCLC (n = 68)

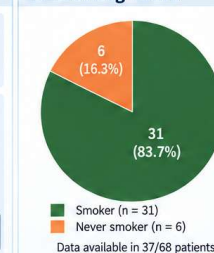
A. KRAS variant spectrum (n = 68)



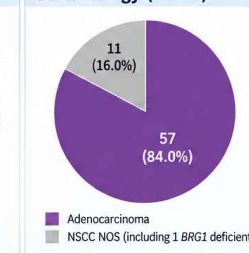
B. Age and sex



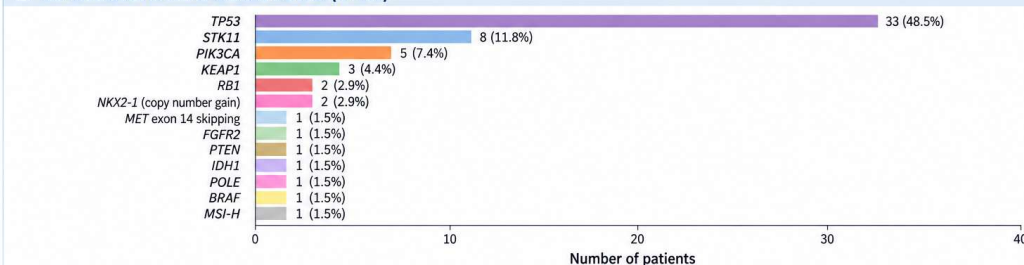
C. Smoking status



D. Histology (n = 68)



E. Co-mutations in KRAS-mutant NSCLC (n = 68)



NSCC NOS: non-small cell carcinoma, not otherwise specified; MSI-H: microsatellite instability-high.

Note: Percentages are calculated out of the total KRAS-mutant treatment-naïve cohort (n = 68). Smoking data were available for 37 patients.

Post-therapy (progression cohort)

- The 41 post-treatment/progression samples represented a clinically heterogeneous cohort: baseline testing had identified EGFR mutations in 16 cases (exon 19 deletion n=12, L858R n=3, G719X n=1), ALK positivity in 1, and ROS1 fusion in 2; 9 were EGFR/ALK/ROS1-negative, while 13 had incomplete/no baseline molecular data
- The cohort included both post-targeted-therapy and conventionally treated driver-negative tumours
- Repeat molecular testing was performed predominantly on small biopsies (38/41, including 2 cytology specimens), with 3 post-neoadjuvant lung resections also represented.

- KRAS mutations were identified in 6/41 (14.6%) cases, all adenocarcinomas, sampled equally from primary and metastatic sites
- Five occurred following non-TKI systemic therapy, while one arose in a ROS1-rearranged tumour progressing on crizotinib, raising the possibility of a bypass-resistance mechanism