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2026 World Conference on Lung Cancer



SEPTEMBER 12 – 15, 2026 | SEOUL, REPUBLIC OF KOREA

EP03.08 - Comprehensive genomic profiling of lung cancer across early and advanced stages: evidence of molecular signature and co mutational patterns from the LANTERN project cohort

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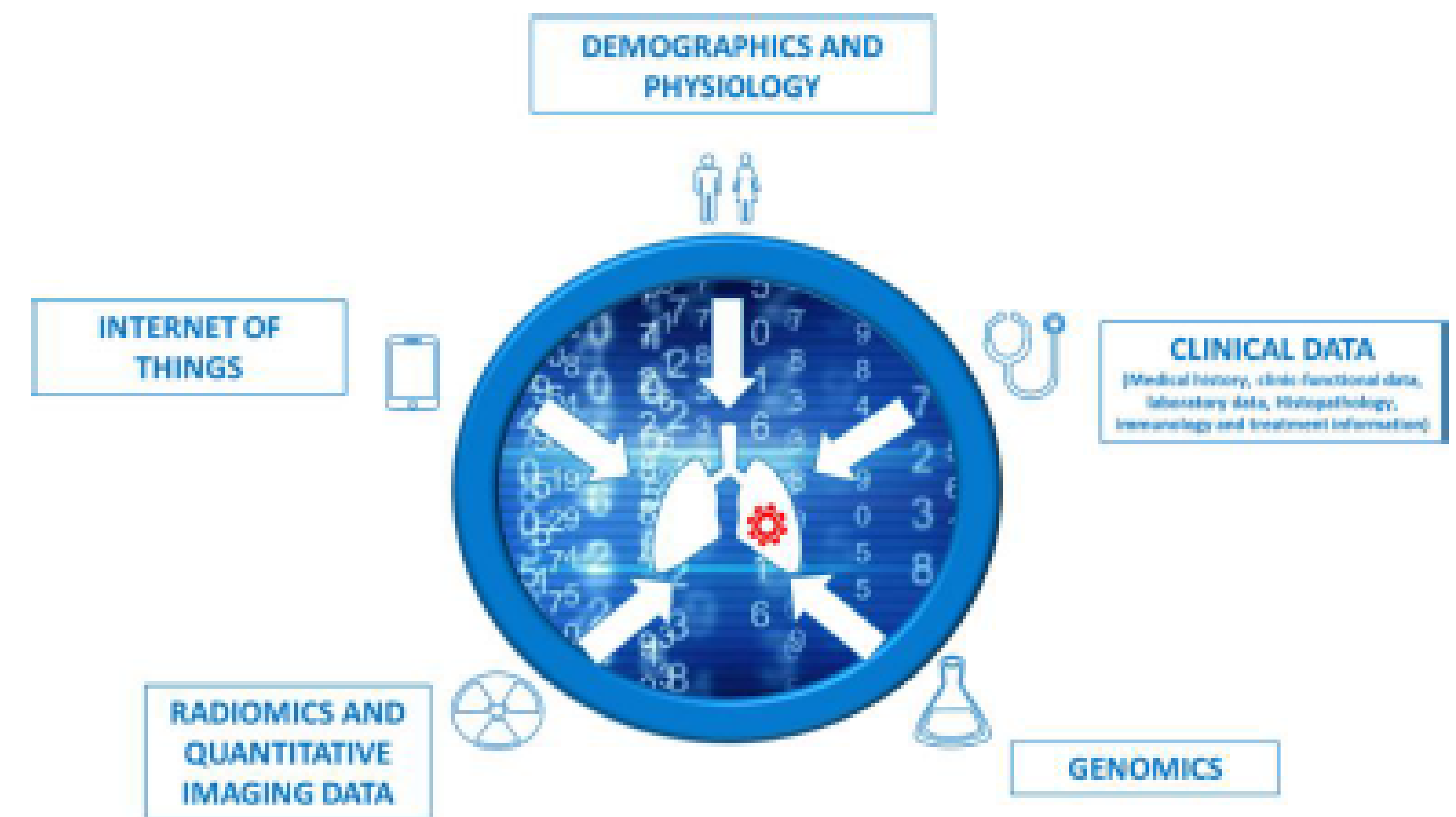
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Background & Aims

Lung cancer (LC) remains a primary driver of oncology-related deaths globally. While precision medicine has revolutionized clinical outcomes through molecular-targeted interventions, its application in early-stage LC is not yet fully realized. The LANTERN project (NCT05802771) seeks to bridge this gap by developing AI-driven predictive frameworks based on Digital Human Avatars (DHA)—computational models of individual patients that simulate biological functions (1). By prospectively enrolling 600 participants, the study integrates multiomics data, specifically radiomics and genomics. This report presents preliminary genomic findings, providing a comprehensive mapping of the mutational landscape and emphasizing the critical role of stage-specific molecular profiling in early-stage disease management.





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Methods

This prospective, multicenter observational study reports on a cohort of 271 patients (135 females, 136 males) enrolled between March 2023 and December 2024. The cohort included: 137 LC stage I–III; 134 LC stage IV (2). Histological distribution was as follows: adk, 234/261 (89.6%); atypical carcinoid, 2/261 (0,7%); NEC, 3/261 (1,1%); squamous cell carcinoma, 12/261 (8,28%) (n=10 metastases). PD-L1 expression was assessed via immunohistochemistry (IHC) using the SP263 clone on the Ventana BenchMark platform. Comprehensive genomic profiling (CGP) was conducted using the TruSight Oncology 500 High Throughput (TSO500HT) assay to detect SNVs, indels, and CNVs across 523 genes, alongside fusion events in 55 genes, TMB and MSI evaluation. Data interpretation was facilitated by the VELsera Clinical Genomics Workspace, aligning variants with FDA-approved therapies and clinical guidelines using a tier-based classification system (3). Study data were managed through REDCap at the Fondazione Policlinico Universitario A. Gemelli IRCCS. Statistical analyses, including Fisher's exact tests for stage-specific enrichment and PD-L1 correlations, were performed using the maftools R package, with a significance threshold of $p < 0.05$.

References: (1) Loooco F, et al. Lung cancer multi-omics digital human avatars for integrating precision medicine into clinical practice: the LANTERN study. *BMC Cancer*. 2023 Jun 13;23(1):540. doi: 10.1186/s12885-023-10997-x. Erratum in: *BMC Cancer*. 2023 Nov 9;23(1):1082. doi: 10.1186/s12885-023-11606-7. PMID: 37312079; PMCID: PMC10262371. (2) Rami-Porta R, et al. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017 Mar;67(2):138-155. doi: 10.3322/caac.21390. Epub 2017 Jan 31. PMID: 28140453. (3) Li MM, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*. 2017 Jan;19(1):4-23. doi: 10.1016/j.jmoldx.2016.10.002. PMID: 27993330; PMCID: PMC5707196



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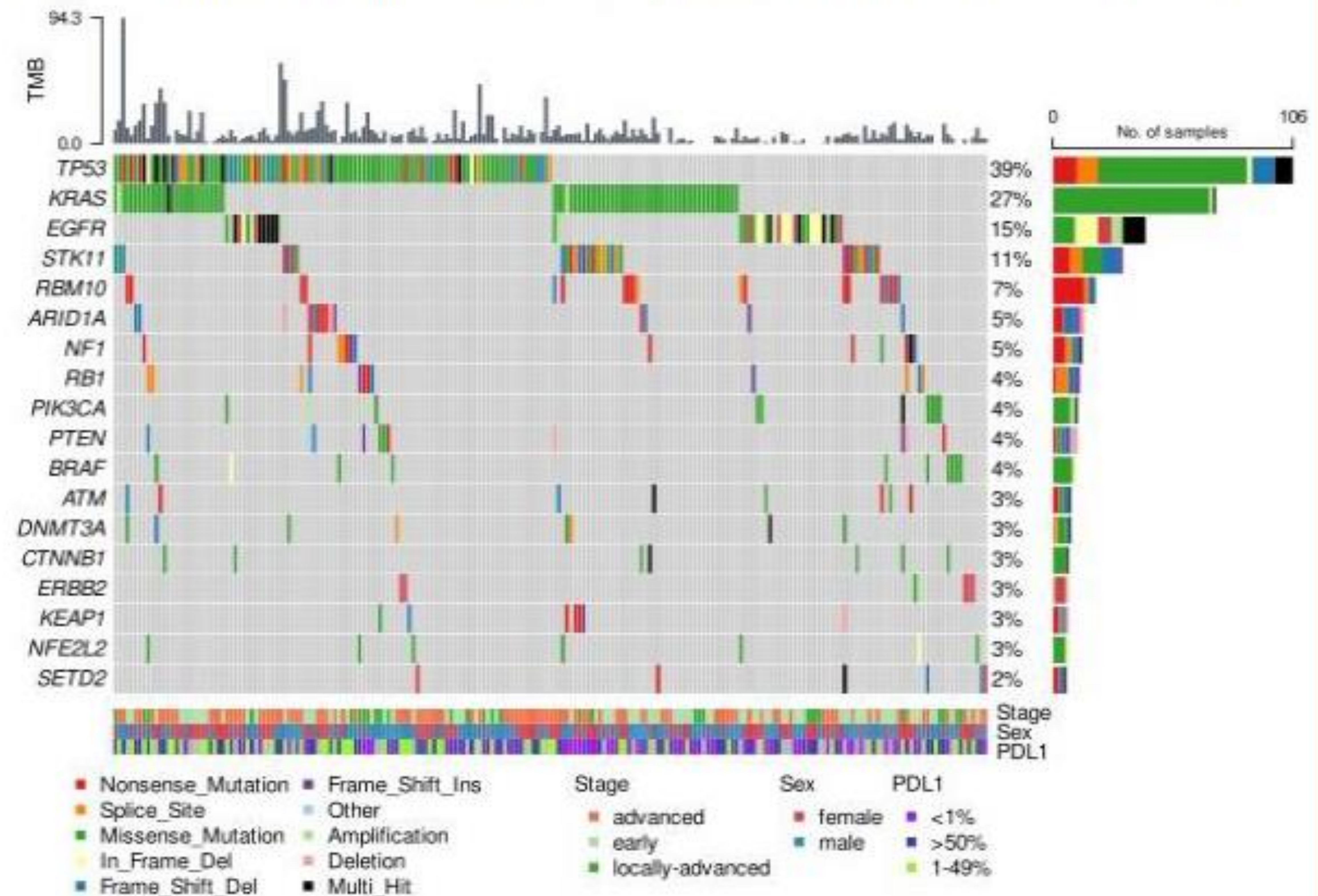
Results

CGP of the study cohort yielded a high-resolution genomic map of lung cancer across diverse clinical stages. These findings underscore the significant diagnostic utility of expanded genomic profiling in identifying actionable alterations.

1 - Overall Mutational Landscape of the LANTERN Cohort

CGP of the 271-patient cohort identified at least one Tier I–II molecular alteration in 228 cases (84%). Key findings include:

- *TP53* was the most prevalent genomic alteration (39%), followed by *KRAS* (27%) and *EGFR* (15%). Other clinically significant mutations were detected in *STK11* (11%), *RBM10* (7%), and *ARID1A* (5%).
- The cohort displayed a heterogeneous TMB distribution. Several "outliers" with high TMB values were identified, frequently co-occurring with *TP53* and *STK11* alterations.





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2 - Comparative Molecular Profiling by Disease Stage

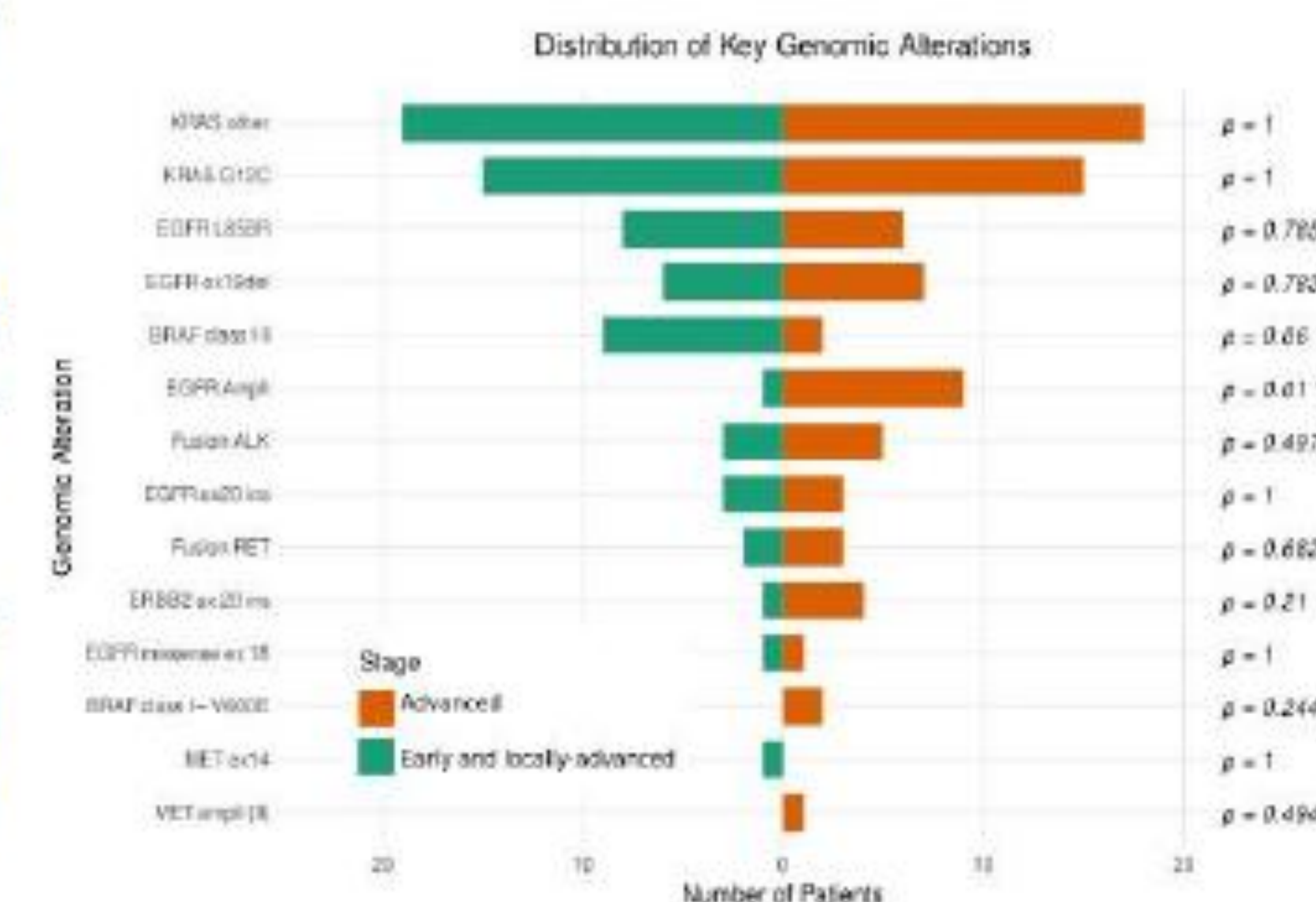
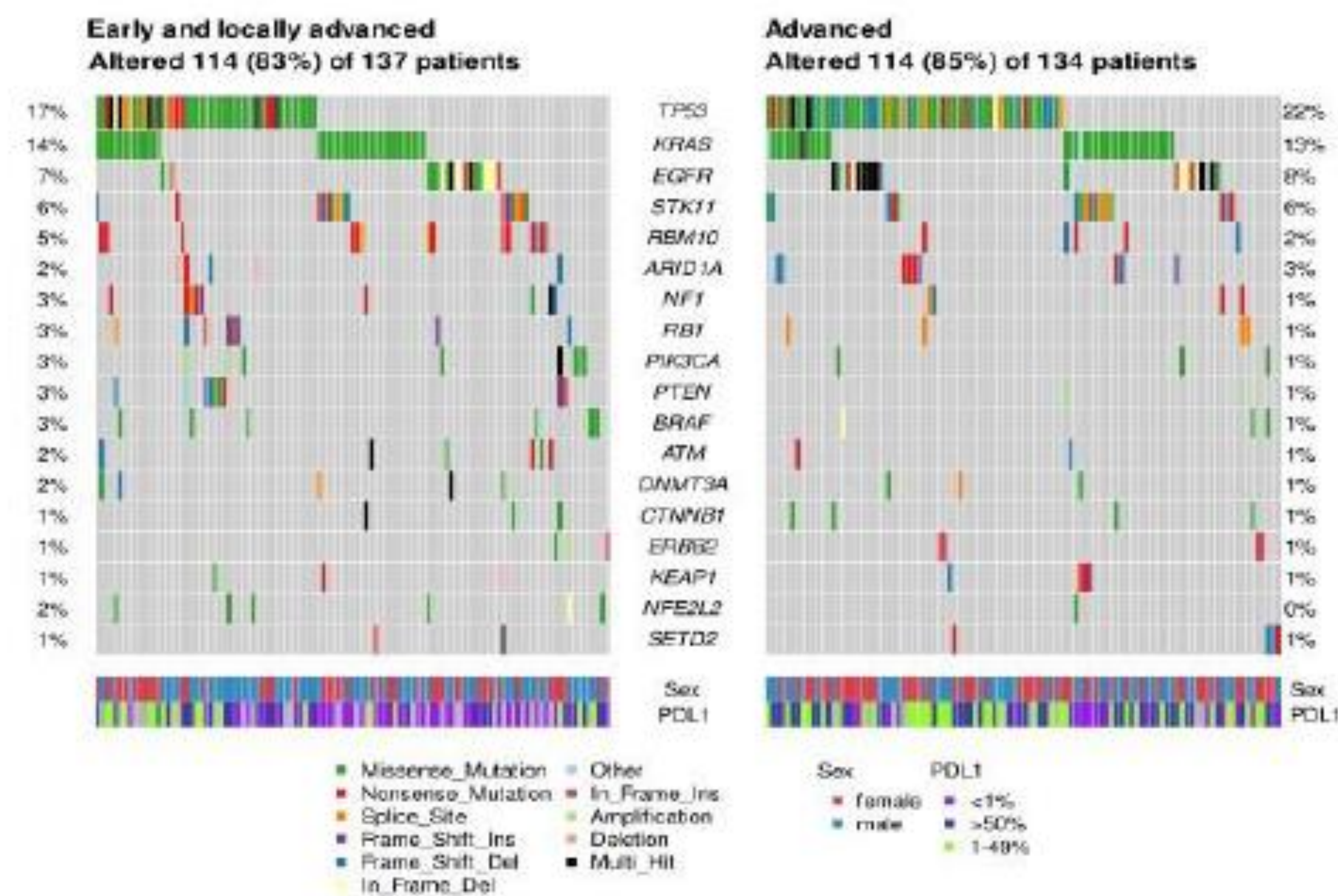
The cohort was stratified into Early/Locally Advanced (Stages I–III; n=137) and Advanced (Stage IV; n=134) subgroups. Both categories exhibited a high and comparable prevalence of genomic alterations (83% vs. 85%, respectively). Stage-specific comparative analysis identified a core set of conserved mutational drivers alongside distinct areas of genetic divergence and enrichment:

- *TP53* showed a higher prevalence in the advanced setting (22% vs. 17%) ($p>0.05$). *KRAS* and *EGFR* mutation frequencies remained stable across disease stages.

- The early/locally advanced group shows a slightly higher diversity in secondary mutations like *RBM10* (5% vs. 2%) and *NFE2L2* (2% vs. 0%).

- The advanced-stage landscape is characterized by a higher density of multi-hit events (black squares) was observed in *TP53* and *EGFR* within the advanced-stage cohort. This increased mutational burden and complexity likely reflect the heightened genomic instability associated with disease progression.

- Analysis of established and emerging biomarkers revealed that *KRAS* variants (including G12C) and *EGFR* mutations (ex19del, L858R) were distributed similarly across both cohorts. The lack of statistical significance between stages suggests these alterations are early events in lung carcinogenesis. A significant enrichment of *EGFR* amplifications was identified in the advanced group ($p < 0.05$). *BRAF* Class I-II mutations showed a trend toward higher prevalence in the early/locally advanced group ($p = 0.06$), further validation in larger cohorts is required. Targetable alterations such as *ALK* and *RET* fusions, as well as *ERBB2* exon 20 insertions, were present across all stages, reinforcing the clinical necessity of broad molecular profiling in early-stage settings.





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3 - Comparative co-mutational profiling by Disease Stage

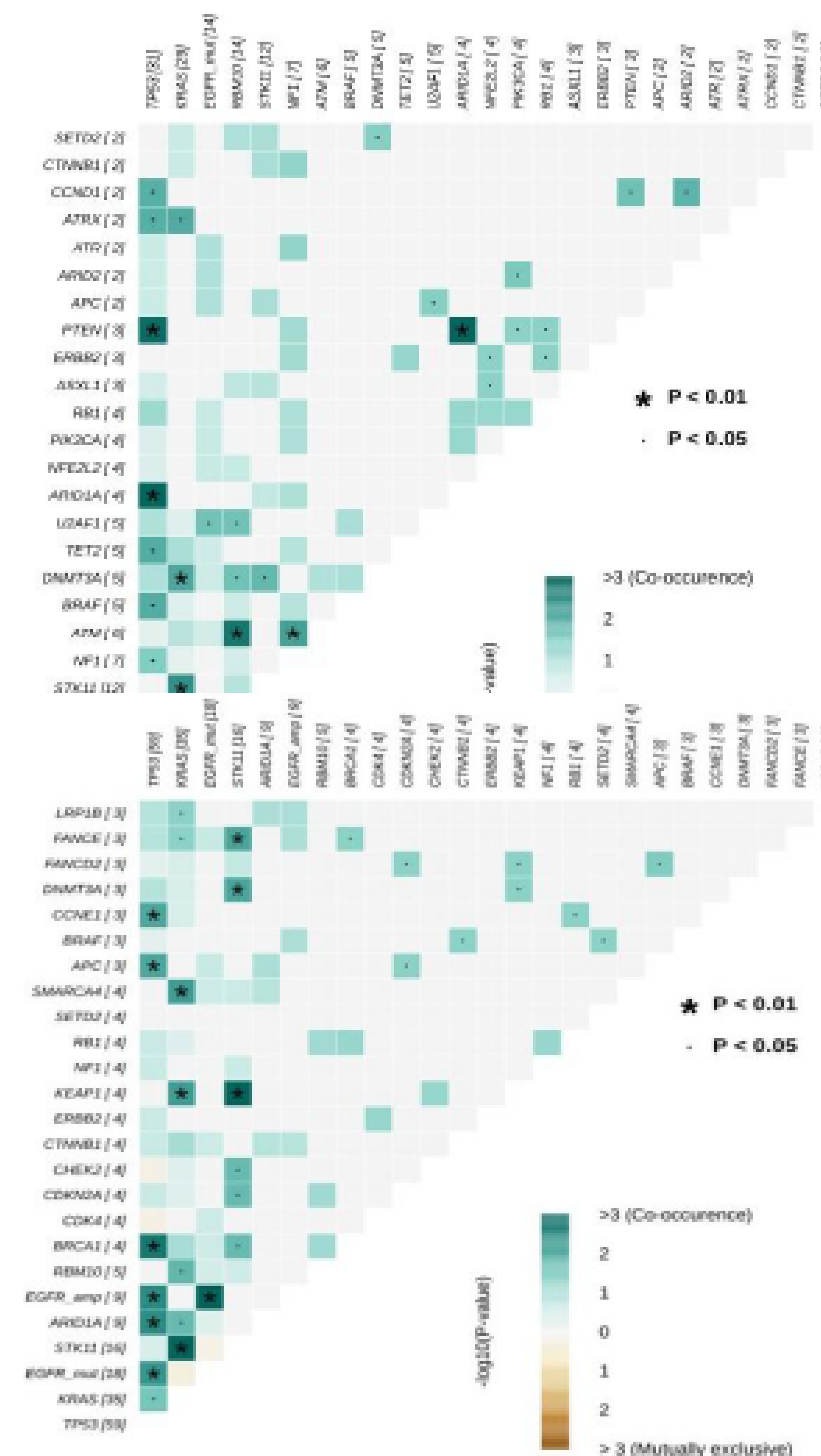
The comparative analysis across disease stages reveals a transition from key driver mutations to a more complex genomic landscape.

Early/locally advanced stage (I–III):

- *TP53* exhibits the most diverse and significant interactions, showing significant co-occurrence with *KRAS*, *ARID1A*, *PTEN* ($p < 0.01$).
- *KRAS* and *STK11* co-occurrence ($p < 0.01$): this key prognostic co-mutation cluster is already prevalent and significantly established in early stages.
- *PTEN* and *ARID1A* co-occurrence ($p < 0.01$): this interaction may point toward cooperative roles in epigenetic regulation and signaling pathway modulation even in early tumorigenesis.
- A trend toward mutual exclusivity between *EGFR* and *KRAS* emerged, consistent with LC biology where these two drivers rarely co-occur.

Advanced stage LC (IV):

- *KRAS*, *STK11*, and *KEAP1* significant co-occurrence ($p < 0.01$): this molecular "trio" is a hallmark of advanced lung adenocarcinoma and defines a specific tumor subset often associated with poor prognosis.
- *TP53* maintains a robust network of co-occurrences. There is a remarkably association ($p < 0.01$) between *EGFR* mutations and amplifications, suggesting that in advanced stages, the *EGFR* driver often undergoes "double-hit" reinforcement through both sequence variants and copy number gains.
- *KRAS* shows a very strong co-occurrence ($p < 0.01$) with *SMARCA4*. This is clinically significant as *KRAS/SMARCA4*-deficient tumors represent a particularly aggressive clinical phenotype.
- A trend toward mutual exclusivity persists between *EGFR* and the *KRAS/STK11* cluster, confirming these remain largely distinct oncogenic pathways even during disease progression





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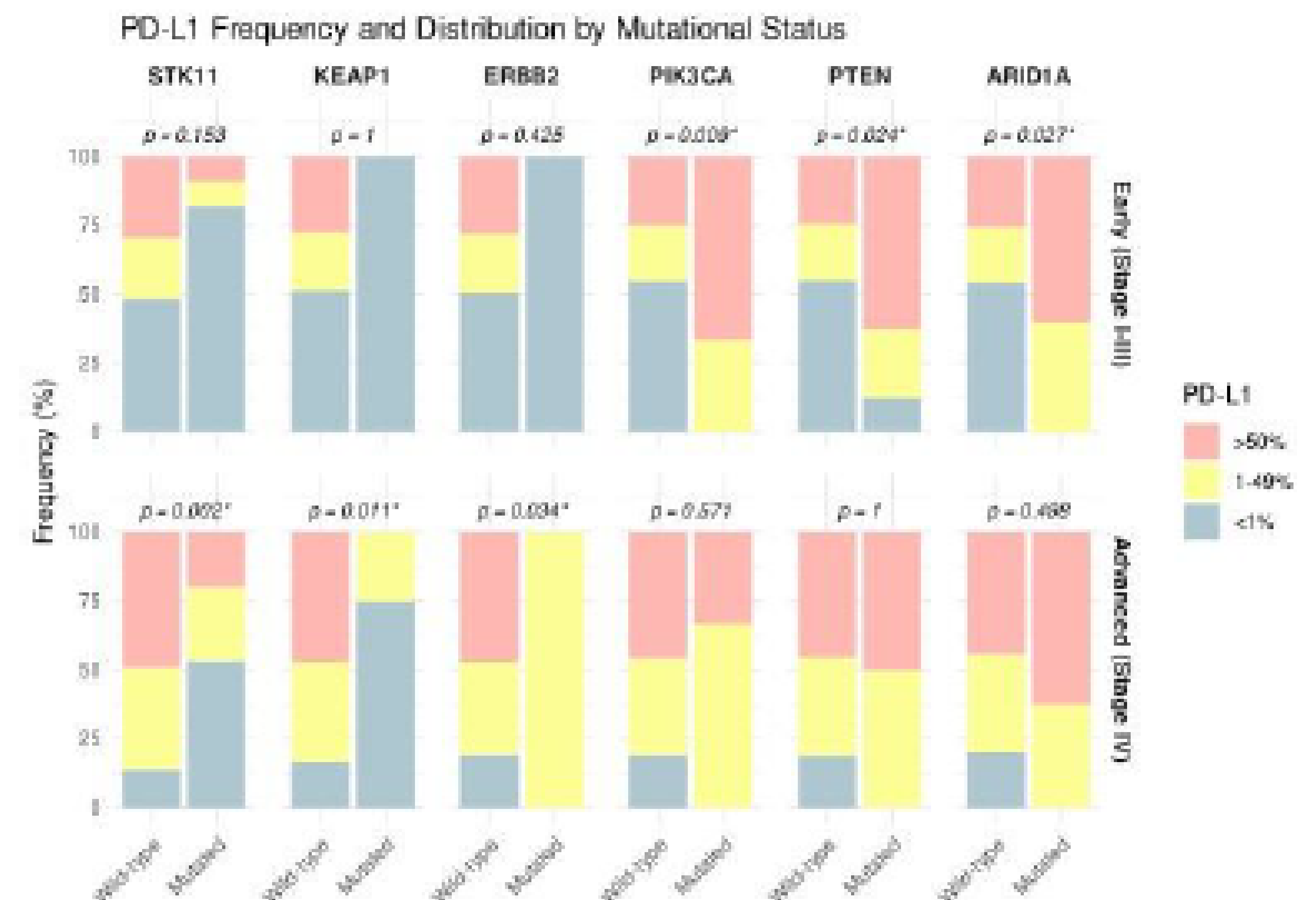
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4 - PD-L1 Expression and Mutational Correlations

The association between key genomic alterations and PD-L1 expression revealed distinct immunological profiles that varied by disease stage and mutational status. Our analysis identified the following:

- In advanced disease, mutations in STK11 ($p=0.002$) and KEAP1 ($p=0.011$) were strongly associated with low PD-L1 expression ($<1\%$). This correlation, which was non-significant in early-stage disease, suggests a progressive immune-escape mechanism associated with these alterations.
- In early-stage patients, mutations in PIK3CA ($p=0.009$), PTEN ($p=0.024$), and ARID1A ($p=0.027$) significantly correlated with higher PD-L1 expression levels (1–49% and $>50\%$).
- Within the advanced cohort, ERBB2 mutations ($p=0.034$) were associated with a shift toward intermediate (1–49%) PD-L1 expression levels compared to wild-type counterparts.





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Summary of Findings & Clinical Take-home Messages

The molecular blueprint of the LC is largely defined long before metastasis, providing a clinical mandate for extended genomic testing even at initial diagnosis. The core mutational landscape, led by *TP53*, *KRAS*, and *EGFR*, is established early in carcinogenesis and remains consistent across stages. Disease progression is marked by distinct evolutionary shifts consisting in *EGFR* gains and the emerging of aggressive *KRAS/STK11/KEAP1* co-mutation axis. Genetic evolution reshapes the tumor microenvironment in a stage-specific manner, suggesting a critical therapeutic window for enhanced immunotherapy efficacy in neoadjuvant or adjuvant settings. Finally, broad genomic testing should not be reserved for metastatic disease; identifying stage-specific biomarkers of both oncogenic drive and immune evasion is vital at the time of initial diagnosis to optimize and personalize the entire disease trajectory.