



Concurrent TP53 Severe Loss-of-Function Identifies an Immunologically Suppressed Subtype of EGFR-TKI–Resistant NSCLC with Inferior Benefit from Immunochemotherapy

Yunhuan Liu¹, Caicun Zhou¹

¹Department of Clinical Oncology, Shanghai East Hospital

Correspondence: Caicun Zhou: caicunzhoudr@163.com



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INTRODUCTION

In Asian patients with non-small-cell lung cancer (NSCLC), EGFR mutations represent the most prevalent and clinically important actionable driver alteration. Although EGFR/TP53 co-mutant NSCLC has been extensively investigated in the first-line treatment setting, the clinical significance of concurrent TP53 alterations after inevitable progression on first-line EGFR-TKIs, particularly in the context of second-line immunotherapy-based treatment, remains insufficiently explored.

METHODS

Tumor–normal whole-exome sequencing (WES) was performed on all samples to systematically profile SNVs/indels, copy number variations (CNVs), structural variants (SVs), and fusion-related events. RNA sequencing was available for 18 samples. Immune-regulatory transcriptional programs were quantified by single-sample gene set enrichment analysis (ssGSEA), and immune cell infiltration was estimated using CIBERSORT. All these genomic alterations, immune-related program scores, and inferred immune cell fractions were statistically compared between TP53 severe loss-of-function (LOF) and non-severe LOF groups using Fisher's exact test or the Wilcoxon rank-sum test, as appropriate.

DISCUSSION AND CONCLUSION

Concurrent TP53 severe LOR may define a biologically distinct and clinically unfavorable subgroup of EGFR-TKI-resistant NSCLC. This subgroup was characterized by structural genomic remodeling, chromosome 6/MHC-region loss, coordinated suppression of the IFN–MHC-I axis, and downstream attenuation of CD8⁺ T-cell recruitment, collectively suggesting a mechanistic basis for the limited efficacy of immunotherapy-based approaches.

REFERENCES & ACKNOWLEDGEMENTS

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RESULTS

Among 34 EGFR-TKI-resistant NSCLC patients treated with immno-chemotherapy, TP53 severe LOF was associated with significantly shorter progression-free survival (PFS) (5.65 vs 10.25 months; $p = 0.01$). At the SNV level, TP53 severe LOF group did not show a significantly increased nonsynonymous mutation burden. In contrast, integrative genomic analyses revealed more prominent structural abnormalities in the severe LOF group, including broader copy-number remodeling, enrichment of chromosome 6 loss involving the MHC-associated region ($p=0.048$), and a subset-driven, inversion-dominant pattern of structural variation (SV). RNA-seq analysis of 18 available samples further showed coordinated suppression of the IFN-MHC-I axis ($p=0.01$; $p=0.03$), characterized by reduced expression of representative interferon-responsive (STAT1, $p=0.03$; IFIT3, $p=0.02$; OAS1, $p=0.04$) and antigen-processing genes (HLA-A, $p=0.01$; TAP2, $p=0.01$; NLRC5, $p=0.03$), with a concomitant downstream attenuation of CD8⁺ T-cell recruitment ($p=0.02$).

