Evaluating the Impact of Complex Genomic Alterations in Deciding the Fate of Advanced Non Small Cell Lung Cancers (NSCLC)

Karishma Todi
PhD Scholar, Department of Microbiology Swarnim University of Science, Gandhinagar, Gujarat, India
Department of Molecular Oncology Mumbai Oncocare Center, Mumbai, Maharashtra, India

Archana Pandey
Department of Microbiology Swarnim University of Science, Gandhinagar, Gujarat, India

Chirantan Bose
Department of Molecular Oncology Mumbai Oncocare Center, Mumbai, Maharashtra, India

Abstract:

In India, environmental changes and lifestyle factors have led to a significant rise in cancer cases, particularly lung cancer with traditional treatments like chemotherapy have long been the mainstay, but advancements in molecular diagnostics have identified targetable biomarkers—such as EGFR, ALK, and ROS1—that respond to tyrosine kinase inhibitors (TKIs). These therapies have extended overall survival (OS) from 11 months to up to 5 years in 17.8% of patients. However, a substantial proportion of patients still face early progression or recurrence. A retrospective genomic analysis was conducted on 242 therapy-naïve NSCLC patients from Mumbai Oncocare Centre to determine the impact of secondary molecular alterations, which may lead to reduced TKI efficacy. Out of 242 patients, 31% (n=74) had TKI-sensitive mutations co-occurring with secondary mutations potentially affecting TKI efficacy. The major contribution of complex mutation was observed with EGFR mutation (66%). EGFR mutations that are accompanied by resistance mutations, activate downstream pathways such as RAS/RAF/ERK or PI3K/AKT/mTOR. These intrinsic pathway alterations can drive oncogenic proliferation independently of EGFR signaling, thereby bypassing the inhibitory effects of TKIs that act on the extracellular domain of EGFR. In such cases, combination therapies—targeting primary driver and the downstream resistance pathways—may be essential.