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Comparing genomic landscape of early stage, treatment naïve and late stage, drug resistant *EGFR*-mutant lung adenocarcinomas

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Abstract

While, the genomic landscape of early stage, treatment naïve lung adenocarcinomas (LUADs) has been described quite elaborately in recent literature, the genomic profile of late stage, drug resistant tumors remains largely unknown. Further, most of the published studies are based on smoker dominated Caucasian cohorts and *EGFR*-mutant LUAD remains under-represented in them. Despite response rates of upto 70% to *EGFR* tyrosine kinase inhibitors (TKIs), resistance ensues in most of these *EGFR*-mutant patients, limiting responses to a median of 10-12 months. Thus, to better understand the evolution of these tumors in context of drug resistance, we perform a comparative analysis of the mutational and copy number landscape of early stage, treatment naïve vs late stage, resistant tumors. Whole exome sequencing was performed on: (i) 100 tumor sectors from 24 early stage, treatment naïve *EGFR*-mutant LUAD cases. (ii) 81 biopsies from 58 late stage, TKI and chemotherapy resistant cases. Copy number analysis using SNP arrays was performed for a subset of these patients. The significantly higher mutation burden in the late stage, drug resistant tumors elucidated a driver mutation landscape beyond just recurrent *TP53* mutations, which was dominated by *PIK3CA* (14%), *RB1* (10%), *NF1* (7%) and other rare mutations in *EGFR* (in 5/58 cases), many of which co-occurred with the T790M mutation. Functional studies validated the oncogenicity of some of these rare mutations in the PI3K/AKT1 pathway. The copy number landscape revealed pervasive, truncal genome doubling events in both cohorts (~80% cases). While comparable fraction of genome was affected by overall copy number gains or losses (copy change >=1) across the two cohorts (49.2% vs 46.3%, P=0.51), significantly higher fraction of genome was affected by amplifications (copy change >=2; 8.7% vs 5%, P=0.02) and loss of heterozygosity (LOH; 33.1% vs 20.6%, P=0.003) in the drug resistant tumors compared to the treatment naive tumors. In summary, our study reveals (i) increased mutation and driver burden with co-occurring resistance

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mutations and (ii) higher fraction of genome with amplifications and LOH in the drug resistant cohort, suggesting ways in which genomic landscape of EGFR-mutant LUAD evolves, potentially making them more tolerant to drug treatment.

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