89P-Novel Resistance Mechanisms to Second-Generation EGFR Tyrosine Kinase Inhibitor Afatinib in NSCLC

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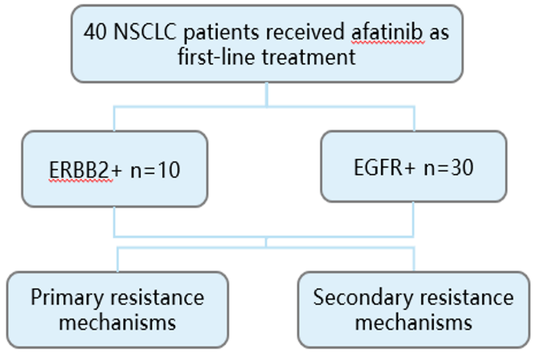
Background

Afatinib, an irreversible pan-ErbB family inhibitor, has demonstrated promising efficacy in non-small cell lung cancer (NSCLC) patients with uncommon *EGFR* activating mutations. However, besides the acquisition of secondary T790M mutation, other resistance mechanisms to afatinib remained to be explored.

Methods

This study retrospectively included 40 NSCLC patients harboring either *EGFR* or *ERBB2* mutations, who had received afatinib as first-line treatment. Targeted next-generation sequencing(NGS) data on the baseline and post-treatment samples were subjected to analysis. Comparative analyses of genetic features and clinical parameters were performed.

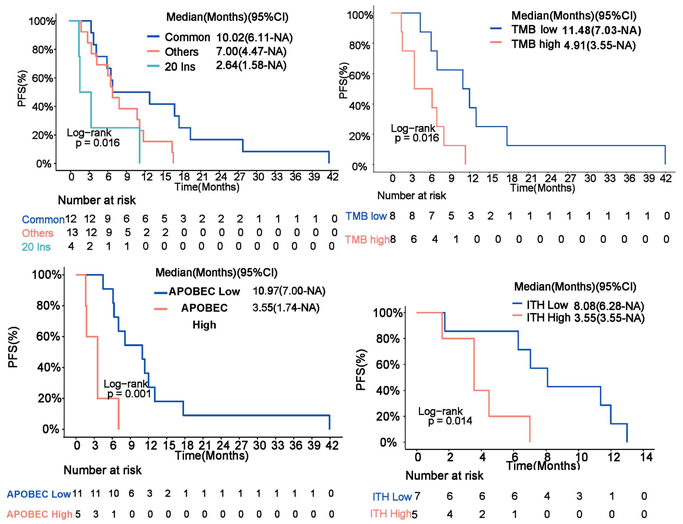


Conflict of Interest

The presenter has no conflict of interest to declare.

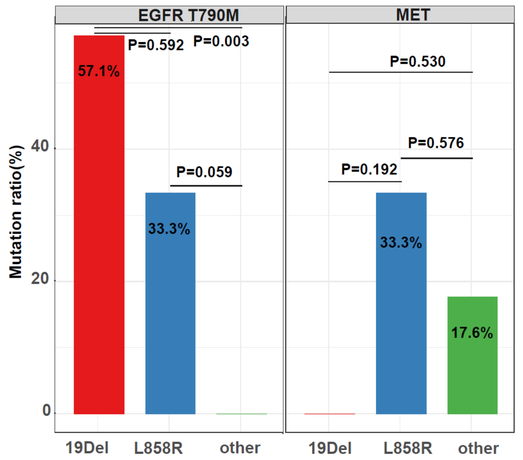
Results

Figure 1. Primary resistance in the EGFR-positive subgroup



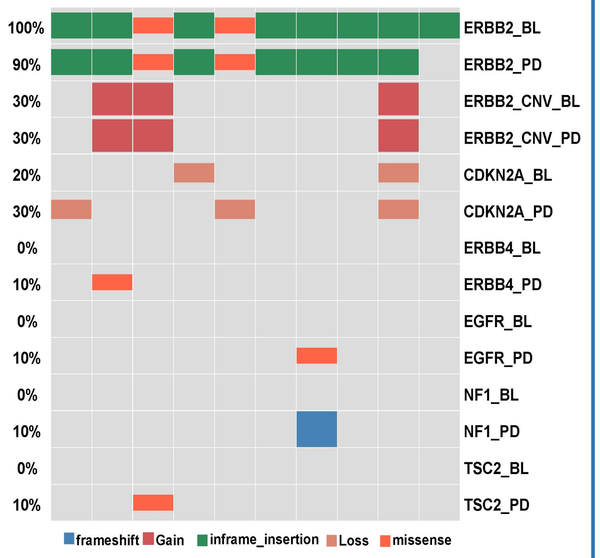
- Primary resistance was associated with the presence of *EGFR* exon 20 insertion mutation, higher tumor mutational burden, higher proportion of APOBEC signature and higher tumor heterogeneity.

Figure 2. Secondary resistance in the EGFR-positive subgroup



- Secondary resistance mainly involved *EGFR* T790M and *MET* amplification.
- Patients with 19del were more likely to acquire T790M mutation compared with those harboring L858R or other *EGFR* mutations.

Figure 3. Secondary resistance in the ERBB2-positive subgroup



- Secondary resistance mechanisms in the ERBB2-positive subgroup included alterations in *ERBB4*, *EGFR*, *TSC2*, *NF1* and *CDKN2A* that participate in the bypass or downstream pathway of *ERBB2* and the cell cycle pathway.

Table 1. Primary resistance in the ERBB2-positive subgroup

Characteristics	HR (95%CI)	P value	mPFS (Months)
ERBB2 p.Y772_A775dup vs. other mutations	0.19 (0.02~1.56)	0.088	8.10 vs. 4.37
PIK3CA Variant vs Wild	2.27e+09 (0~Inf)	0.001	1.30 vs. 5.47
Cell Cycle pathway Variant vs Wildtype	3.79 (0.75~19.10)	0.084	1.94 vs. 5.98

- Patients with the p.Y772_A775dup mutation tended to have a longer PFS than those harboring *ERBB2* mutations.
- Alterations in *PIK3CA* or genes in the cell cycle pathway were associated with primary resistance to afatinib in the *ERBB2*-positive patients.

Conclusions

The study identified multiple genomic characteristics associated with primary and secondary resistance to afatinib in EGFR- and ERBB2-positive subpopulations.