Biophysical and Genomic Drivers of Targeted Therapy Resistance: Analysis of Growth Dynamics in Non-Small Cell Lung Cancer

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Resistance to targeted therapies in non-small cell lung cancer (NSCLC) limits treatment efficacy. Mathematical models have shown promise in predicting resistance development by capturing biophysical parameters, such as treatment efficacy, or the conversation rate from sensitivity to resistance. Whether genomic profiles predict response patterns consistent with these contributions has also not been established. This year, we examined the genomic and treatment data of 824 NSCLC patients treated with osimertinib, gathered from MSK-IMPACT and MSK-CHORD; 172 initial responders were analyzed. Mann-Whitney U-tests with Benjamini-Hochberg correction were employed to examine differential response between clusters. Kaplan-Meier survival analysis and Cox regression were used to evaluate differences in progression-free survival (PFS). Compared to EGFR-only patients, EGFR+TP53 patients had 61% higher risk for progression events (HR=1.61, p=0.033), EGFR+RB1+TP53 patients had 159% higher risk (HR=2.59, p=0.025), and EGFR+SMAD4+TP53 patients had 182% higher risk (HR=2.82, p=0.033). Notably, EGFR+RB1+TP53 patients showed the strongest initial response ($p<0.01$ vs. four other clusters) despite extremely poor progression-free survival, linking genomics to the parameter contributions identified in previous research. The findings of this study may inform the development of genome-conscious treatment strategies, and call more broadly for treatment regimens that intentionally balance tumor reduction with resistance management, so as to avoid accelerating resistance development.

Awards Won:

Second Award of $2,400