KRAS has a role in acquired resistance to EGFR-TKIs in NSCLC: an analysis on circulating tumor DNA

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Introduction: Activating mutations of *KRAS* oncogene drive resistance to EGFR inhibition by providing an alternative signal transduction pathway. In non-small cell lung cancer (NSCLC), the efficacy of treatment with EGFR tyrosine kinase inhibitors (EGFR-TKIs) depends on activating *EGFR* mutations that are mutually exclusive with *KRAS* mutations. However, pharmacological inhibition of *EGFR* signaling may select cell resistance based on alternative proliferation pathways, including KRAS, or continued EGFR signaling due to the c.2369C>T (p.T790M) gatekeeper mutation. The aim of this study was to investigate if *KRAS* mutations appear during EGFR-TKi treatment and are associated or contribute to drug resistance.
Methods: This study used cell-free circulating tumor DNA (cftDNA) to evaluate the appearance of codon 12 *KRAS* and p.T790M *EGFR* mutations in 33 advanced NSCLC patients that progressed after an EGFR-TKI. **Results:** *KRAS* mutation at codon 12 alone or in combination with p.T790M was demonstrated in 3 (9.1%) and 13 patients (39.4%), respectively. p.T790M was detected in 11 subjects (33.3%) alone and in 13 patients (39.4%) with mutant *KRAS*. Six patients (18.2%) were negative for both *KRAS* and p.T790M. In 8 subjects paired tumor re-biopsy/plasma samples were available; the percent concordance of tissue/plasma was 62,5% for p.T790M and 37,5% for *KRAS*. **Conclusions**: Mutation of *KRAS* could be an additional mechanism of escape from EGFR-TKI inhibition and cftDNA is a feasible approach to monitor the molecular development of drug resistance.