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Commentary

# Co-mutations in EGFR driven non-small cell lung cancer

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Epidermal growth factor receptor (EGFR) mutant non-small cell lung cancers (NSCLC) are commonly adenocarcinomas in never smokers, predominantly in females, and prevalent in certain geographical areas, such as East Asia and Latin America and, less frequently, in Europe and the United States. EGFR mutant NSCLC obtains dramatic response to oral EGFR tyrosine kinase inhibitors (TKIs). However, the median progression free survival (PFS) still ranges from only 10–18 months, depending on therapy with first- or third-generation EGFR TKI [1]. Single polymerase chain reaction assays serve to screen EGFR mutations, either in the tumor biopsy, or in the circulating free DNA (cfDNA) [2]. Multi-region next generation sequencing (NGS) using panels of more than 300 genes (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; MSK-IMPACT) has uncovered that, in addition to EGFR sensitizing mutations, mostly EGFR exon 19 deletions or missense L858R concur multiple genetic alterations, above all, TP53 mutations, as well as, copy number gains (CNGs). In 200 EGFR pre-treatment samples, frequent co-mutations in TP53, PIK3CA, catenin beta-1 (CTNB1) and retinoblastoma (RB1) were observed. Shorter PFS was related to ERBB2 and MET amplification or TP53 mutations [3]. In the current issue of EBioMedicine, Chen and colleagues have selected 71 of 423 patients with EGFR mutations treated with first-generation EGFR TKIs [4]. The 71 patients were selected based on the differences in PFS. Chen and colleagues interrogated these 71 patients using an NGS-based 416-gene panel. Among the 71 patients, 30 had a PFS of less than 6 months, and 41 had a PFS of more than 2 years [4]. The findings show that in the unfavorable group, pre-existing T790M mutations were more frequently seen, as well as other co-occurring driver mutations and PIK3CA mutations, but not TP53 mutations. Also, RB1, FAT tumor suppressor homolog 1 (FAT1), or ATP-binding cassette sub-family B member 1 (ABCB1) mutations were frequently identified in the unfavorable group. In the favorable group, small subgroups of patients had MAP2K2 mutations. One of the conundrums is the interpretation of the information that can be retrieved from the analysis of hundreds of genes. For example, MAP2K2 is a paralog of a canonical RAS effector pathway and MEK. This observation should be further elucidated in future studies. RB1 mutations can confer more aggressiveness and are involved in cell cycle dysregulation and transformation to small-cell lung cancer. Less known, but still intriguing, is the finding of FAT1 mutations in 17% of the unfavorable group of patients [4]. FAT1 mutations have been reported by The Cancer Genome Atlas (TCGA) research network in 19% of lung squamous cell carcinomas (LSCC) [5]. FAT1 deletions and missense mutations affect the response to cyclin dependent kinase 4/6 (CDK4/CDK6) inhibitors by amplification of CDK6 [6]. This finding is particularly worthy and could have implications in future studies. Mutations in ABCB1 are rather intriguing since they are related to cholesterol homeostasis and TP53 status and could be of relevance for targeting the cholesterol pathway in patients with TP53 and ABCB1 mutations. Currently, all studies applying NGS primarily focus on the capture of driver mutations and the interpretation of the abundant co-mutations, while CNGs and other alterations are not considered. It could be of great interest for the authors to provide further information on some genes, like the histone methyltransferase SET domain containing 2 (SETD2), that is mutated in 22% of lung adenocarcinomas in the TCGA research network [7]. ARID1A, in our experience, frequently coexists with EGFR mutations [8] or amplifications of protein kinase C iota (PRKCI), that is a common denominator in targetable lung adenocarcinomas and LSCC. TP53 and RB1 co-mutations have also been associated with short PFS in EGFR mutant patients resistant to first-generation EGFR TKIs. Recently it has been reported in cfDNA that EGFR mutations co-exist frequently with TP53 and other alterations. Among the 186 patients treated with gefitinib, they found that the PFS was shorter for patients with TP53, PTEN or RB1 mutations. Still, the PFS was shorter in a third subgroup of patients where other mutations were identified [9]. The study illustrates that NGS in tumor tissue or liquid biopsy can subcategorize EGFR mutations with other multiple co-occurring genetic alterations that could be faithfully druggable and pave the way for customizing combinatory therapy. In fact, at the time of progression to first- or third-generation EGFR TKIs, several studies have highlighted the new challenges and therapeutic opportunities [10].

## Disclosure

The author reports no conflicts of interest in this work.

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