Clinical applications of a next-generation sequencing panel in non-small cell lung cancer

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Introduction: Molecular markers have become important predictors of response to targeted therapies in non-small cell lung cancer (NSCLC), and Next-Generation Sequencing (NGS) has recently emerged as a cost-effective method able to provide more comprehensive genomic information with potential repercussions in clinical practice. The aim of this study was to identify potential actionable mutations in advanced NSCLC. Here we report the findings obtained for an initial group of patients screened in our Lung Cancer Unit.

Patients and methods: Twenty patients with advanced lung adenocarcinoma were evaluated. DNA was extracted from 4 cytological samples and 16 FFPE biopsies from primary or metastatic lesions. The specimens were analyzed for 22 cancer-associated genes using the Ion AmpliSeq Colon and Lung Cancer Panel v.1 (Life Technologies) and sequenced through Ion Torrent PGM™ (Life Technologies). Data were analyzed with the Ion Torrent Software Suite v.4.4 (Life Technologies) using the plugin Variant Caller (VC) v.4.4.2.1.

Results: Patients’ characteristics: median age 65 (42-81); 30% males, 70% females; never smoker 60%, former smoker/smoker 40%. Data analysis reported an average of one genetic variant per patient annotated in the Catalogue of Somatic Mutation in Cancer (COSMIC database) (range 0-5). Twenty-one mutations were diagnosed in 12 patients (55%) in the following genes: EGFR (4), KRAS (1), MET (4), TP53 (8), NRAS (1), BRAF (1), and PI3KCA (2). In addition to the known mutations in EGFR, we found a BRAF mutation resulting in an amino-acid substitution (K601E) potentially sensitive to BRAF or MEK inhibitors on the basis of preclinical studies on BRAF downstream signaling. A potentially druggable mutation was found in NRAS gene (Q61R), which is sensitive to MEK inhibitors in in vitro models. Among EGFR mutated patients, one case showed a PI3KCA missense mutation (E545K) synchronous with the EGFR exon 19 deletion (del746-750); notably, the E545K mutation has been described to activate EGFR downstream signaling pathway, resulting in TKIs resistance. Finally, 7 patients (35%) had a mutation of the gene encoding for TP53, which is reported as a prognostic marker of poor outcome in advanced NSCLC.

Conclusion: Targeted NGS is a sensitive tool to screen multiple genes simultaneously and represents an attractive system to identify relevant mutations. The potential clinical significance of these variations needs to be elucidated in further studies.