Predictive molecular pathology in non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the principal cause of cancer mortality worldwide. In the last decade, the approval of different targeted drugs, including tyrosine kinase inhibitors (TKIs) and monoclonal antibodies, has led to a significant improvement in patients' outcome and quality of life (1,2). Thus, as established by the different international guidelines it is pivotal to assess the molecular status of clinical relevant predictive biomarkers for each advanced NSCLC patient. However, beyond these so-called "must test genes" a plethora of different genomic alterations and several novel molecules are being currently under investigation (3,4). In this complex molecular scenario, tissue still represents an issue. In fact, as it is well known a vast majority (about 70%) of NSCLC patients are diagnosed in advanced stage of disease. For these patients, surgical excision of neoplastic lesions is not feasible, and the only available tissue material for morph-molecular purposes is represented by small tissue samples (histological biopsies or cytological samples) (5). It has been widely established the suitability of cytological samples for molecular analysis. However, cytological specimens, in particular smears, suffer from the limited amount of available material. In fact, these samples, often unique and unrepeatable, are not sufficient enough to undergo a "sequential approach", in which through single gene testing (SGT) approaches each single clinical relevant biomarker is analyzed hierarchically (6-8). To overcome this limitation and to optimize the limited amount of available tissue material, next generation sequencing (NGS) represents a fascinating and robust tool. NGS approach enables the molecular assessment of several biomarkers for different patients, simultaneously, starting from DNA and/or RNA input. In addition, and different from targeted based approaches, such as polymerase chain reaction (PCR) based ones, NGS allows the analysis of either known and well characterized or unknown genomic alterations within the gene panel adopted (9,10). In our experience, at the Predictive Molecular Pathology Laboratory at the Department of Public Health of the University of Naples Federico II, we have designed, validated and implemented in the diagnostic routine practice a narrow NGS panel able to analyze DNA-based clinical relevant alterations within seven genes (*EGFR*, *KRAS*, *NRAS*, *BRAF*, *KIT*, *PDGFRA* and *PIK3CA*) (11). We have adopted this panel in a series of n=322 advanced stage NSCLC patients and we have highlighted a high performance in both histological (surgical resection and biopsies) and cytological (smears and cell block) specimens, with a limited percentage of inadequate (8.6%) molecular results (12). In addition to DNA-based biomarkers, in our experience we have also designed, validate and implemented an RNA-based panel, namely SiRe fusion panel, able to cover clinical relevant gene fusions in *ALK*, *ROS1*, *RET*, *NTRK* as well as *MET* exon 14 skipping alterations (13). In the validation study, we retrospectively analyzed a series of n=48 advanced stage NSCLC tissue samples previously tested with immunohistochemistry or immunocytochemistry (IHC or ICC), fluorescent *in situ* hybridization (FISH) and other NGS approaches, with our panel. Overall, only two cases failed the analysis and a high concordance rate has been reported (13). Beyond the analysis of clinical relevant biomarkers for TKI administration, it is crucial the evaluation of the expression of programmed death ligand 1 (PD-L1) in order to administrated immune checkpoint inhibitors (ICIs) (3). Despite PD-L1 role as a predictive biomarker for immunotherapy is widely established, several efforts have been spent to identify novel biomarkers of response for ICIs (3,14). Among these, tumor mutational burden (TMB) may be promising. In a recent meta-analysis, it has been reported a benefit in overall survival for ICIs respect to chemotherapy in the TMB-high population. In addition, it has been demonstrated the possibility to analyze TMB in cytological preparations adopting broad NGS panels (15,16).

Despite the technological improvements, a not negligible percentage (about 30%) of advanced stage NSCLC patients do not have tissue availability for molecular analysis. In this setting, liquid biopsy, and in particular the analysis of circulating tumor DNA (ctDNA) extracted from plasma, is a valid solution to avoid leaving any patients behind (17). In our experience, by using our ultra-deep NGS approach with the SiRe® panel, we analyzed patients at diagnosis before starting any treatment (basal setting) without tissue availability and we were able to identify *EGFR*, *KRAS* and *BRAF* mutated NSCLC patients who may potentially benefit from a TKI administration (18). Beyond the predictive role, ctDNA analysis may be a useful tool to monitor cancer evolution and the development of resistance under treatment pressure before radiological evidence (19).

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Footnote

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