REVIEW ARTICLE

Liquid Biopsy for Advanced Non-Small Cell Lung Cancer (NSCLC): A Statement Paper from the IASLC

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ABSTRACT

The isolation and analysis of circulating cell-free tumor DNA in plasma is a powerful tool with considerable potential to improve clinical outcomes across multiple cancer types, including NSCLC. Assays of this nature that use blood as opposed to tumor samples are frequently referred to as liquid biopsies. An increasing number of innovative platforms have been recently developed that improve not only the fidelity of the molecular analysis but also the number of tests performed on a single specimen. Circulating tumor DNA assays for detection of both EGFR sensitizing and resistance mutations have already entered clinical practice and many other molecular tests — such as detection of resistance mutations for Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase rearrangements — are likely to do so in the near future. Due to an abundance of new evidence, an appraisal was warranted to review strengths and weaknesses, to describe what is already in clinical practice and what has yet to be implemented, and to highlight areas in need of further investigation. A multidisciplinary panel of experts in the field of thoracic oncology with interest and expertise in liquid biopsy and molecular pathology was convened by the International Association for the Study of Lung Cancer to evaluate current available evidence with the aim of producing a set of recommendations for the use of liquid biopsy for molecular analysis in guiding the clinical management of advanced NSCLC patients as well as identifying unmet needs. In summary, the panel concluded that liquid biopsy approaches have significant potential to improve patient care, and immediate implementation in the clinic is justified in a number of therapeutic settings relevant to NSCLC.

Keywords: Liquid biopsy; NSCLC; cfDNA; ctDNA; Biomarkers; Resistance; Molecular analysis; Targeted therapies

Introduction

One of the hallmarks of NSCLC is represented by the expanding array of effective targeted therapies with activity in specific molecular subsets of this disease. Because acquired resistance to targeted inhibitors is nearly universal, development of next-generation agents able to overcome common resistance mechanisms has been a vital key of experimental and therapeutic research. As a primary example, the approval of first-generation *EGFR* tyrosine kinase inhibitors (*EGFR* TKIs) in 2009 was rapidly followed by the development of second- and third-generation TKIs, with a fourth-generation inhibitor currently being studied.[1-7] In particular, third-generation inhibitors, such osimertinib, were designed to selectively target specific mutant forms of *EGFR*. This new class of agents provide several advantages: high potency against common *EGFR* activating mutations, the ability to inhibit the EGFR protein harboring the T790M mutation that confers resistance to first- and second-generation EGFR TKIs, and its relatively lower affinity for wild-type (WT) *EGFR,* which substantially reduces class toxicities. Similarly, an expanding repertoire of agents that target anaplastic lymphoma kinase (*ALK*) fusion kinase provides significant therapeutic options for patients with acquired resistance to the first-generation ALK TKI crizotinib.[8] Approximately one-third of patients acquire resistance to crizotinib through emergence of any one of the growing list of *ALK*-specific point mutations that interfere with drug binding. Next-generation ALK TKIs such as alectinib, ceritinib, brigatinib, ensartinib, and lorlatinib are capable of binding to and inhibiting mutant forms of *ALK*. However, these drugs have different binding affinities in the context of different resistance mutations and optimal patient treatment may benefit from identification of the specific resistance mutation to deliver to the patients the most appropriate agent to restore activity.[8]