Editorial

Screening for mutations in lung cancer in France: purpose of precision medicine

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In non-small cell lung cancer (NSCLC), the purpose of precision medicine is to use the latest genomic knowledge to adapt treatments to patients. It is essential that drugs are designed to hit a molecular abnormality, mutation or translocation, inducing NSCLC. Compared with other cancers, genetic alterations in NSCLC are notably high (1). In NSCLC, FDA and EMEA have already approved epidermal growth factor receptor (*EGFR*) inhibitors, gefitinib, erlotinib or afatinib, in the front line setting of *EGFR* mutated NSCLC and anaplastic lymphoma kinase (*ALK*) inhibitor, crizotinib, in *ALK* or *ROS1* translocated NSCLC (2,3). Several novel cancer therapies targeting oncogenic mutations as *BRAF* or *MET* mutations may be approved in NSCLC in the next years.

The two major issues of precision medicine are the complex biology and the economic costs (4). Thus, targeted drugs need to be accompanied by valid diagnostic tests to identify patients who will benefit of these therapies. EGFR or ALK testing are cost saving as expensive drugs will be exclusively prescribed to patients who will gain benefit (5). However many health-care systems have no funding to pay for these tests.

Proceeding efforts are necessary in molecular dismantling of NSCLC to provide a tailored therapy to a maximum of patients. In France, prescription of *EGFR* or *ALK* targeting therapies are conditioned by molecular alterations and these testings are done routinely. In 2006, the French National Cancer Institute (INCa) has set up a national program to support molecular testing with the establishment of 28 regional molecular genetics centres. Screened molecular alterations were selected in 2009, including *EGFR* mutations, *ALK* gene rearrangements, but also emerging biomarkers such as *KRAS*, *BRAF*, *HER2* or *PI3KCA* mutations. Furthermore, INCa developed a quality assurance program for molecular testing (ISO 15189).

The BIOMARKER France study assessed the characteristics, molecular profiles and clinical outcomes of patients who were screened by this programme from 04/2012 to 04/2013. Data reported in Lancet on more than 17,000 patients show the presence of at least one genetic alteration in about 50% of analysed samples (6). Thus, *EGFR* mutations were detected in 11% of samples, *HER2* mutations un 1%, *KRAS* mutations in 29%, *BRAF* mutations in 2% and *PI3K* mutations in 2% of patients; *ALK* rearrangements were detected in 5% of the analysed samples (*Figure 1*). The presence of a genetic alteration affected first line treatment for 51% of patients with a significant improvement in the proportion of patients achieving an overall response in the first line or second line treatment and an improved overall survival [16.5 months (15.0–18.3 months) *versus* without a genetic alteration 11.8 months (10.1–13.5 months); P<0.0001]. However improved prognosis in NSCLC harbouring *EGFR* mutations or *ALK* rearrangements compared to wild-type NSCLC is reported. Thus whether this effect on overall survival is related to specific medications such as *EGFR* and *ALK* inhibitors (predictive) or to the prognosis of NSCLC is hypothetical. This systematic biomarker analysis was greeted as a major innovation by ASCO in 2013 (7).

This French project, as well as other initiatives as the German Network Genomic Medecine (NGM), the national wide Japanese Lung Cancer Screening Network (LC-SCRUM) and the American Lung Cancer Mutational Consortium (LCMC), participate to a better understanding

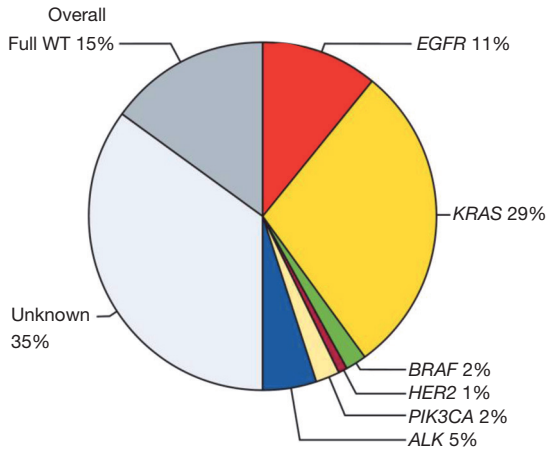

Figure 1 Frequency of molecular alterations in six genes from 18,679 analyzed samples. Full WT, patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2*, or *PIK3CA* mutation or *ALK* rearrangement.

of NSCLC.

In the BIOMARKER France study, no improvement in the inclusion rate of clinical trials was noticed; thus only 3% of patients with a molecular alteration were included in a clinical trial. Molecular alterations were selected in 2009 and emerging biomarkers such as *KRAS*, *HER2*, *BRAF* and *PI3KCA* mutations were routinely analyzed, also for these molecular abnormalities, no targeted therapies were available. Data on targeting *HER2* or *BRAF* mutations are now robust (8,9). It is not certain that *KRAS* or *PI3KCA* are effective targets for tailored therapy and whether these mutations should be routinely detected is speculative. *ROS1* testing and *MET* amplification/mutations are now part of the routine molecular testing on the molecular platforms. Since 2014, INCa supports ACSé program to assess the effectiveness of crizotinib in *MET* amplified/mutated or *ROS* rearranged and vemurafenib in *BRAF* mutated NSCLC (9-11). Further large scale molecular screening studies should collaborate with pharmaceutical companies to target emerging biomarkers. Thus, the Japanese LC-SCRUM study includes a genomic analysis by next generation sequencing multiplexing diagnostics and a collaboration with 13 pharmaceutical companies to deliver drugs on the basis of the patients genomic alteration (12).

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Footnote

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