



Taking action on actionable mutations: a French initiative on universality in precision cancer care

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The reality of precision or personalized cancer care is here. The discovery of oncogenic drivers (such as *BCR-ABL* translocations in chronic myelogenous leukemia, kinase domain mutations of the *epidermal growth factor receptor (EGFR)* gene or *EML4-ALK* fusion genes in lung adenocarcinoma, and *BRAF V600E* mutation in melanoma) has revolutionized the field of cancer biology. These drivers have led to new paradigms in cancer treatment (Table 1). Tumours that harbor these genomic aberrations, now commonly referred to as “actionable mutations”, are highly dependent for their growth and survival on the function of the protein products of these mutated driver genes (1). Patients with driver-addicted tumours can benefit from drugs that specifically inhibit the function of these driver genes, and a high percentage experiences significant treatment response and prolongation of survival.

However, the success of this precision cancer treatment strategy hinges on the availability of routine clinical testing programs to identify these actionable mutations. At present, routine testing for driver mutations is the standard in the prescription of targeted therapies with *bona fide* predictive biomarkers (2). Nevertheless, the number of approved targeted therapies in specific cancer type remains few (3).

During the last five years, we have witnessed rapid advances. Several cancer genomic profiling projects have identified increasing numbers of potentially actionable mutations across various tumour types, including lung cancer (4-7). Most of these actionable mutations occur at low frequency in each tumour type, and they are mostly mutually exclusive in each patient tumour. These discoveries have led to the acceleration of novel targeted

therapy development with associated clinical trials to evaluate their efficacy. There is thus greater incentive for increasing the throughput of driver mutation profiling in patient tumour samples, and tissue availability has become more of a limiting factor. In parallel, there have been rapid advances in DNA/RNA sequencing technologies not only increase the throughput but also lead to rapid reduction in the cost of molecular profiling (8,9). Against this background, many single or multi-institutional studies have been initiated to demonstrate the efficiency and value of broad and higher throughput molecular testing programs. The BATTLE trial (10) demonstrated the feasibility of prospective biomarker dependent clinical trials. In the United States, the Lung Cancer Mutation Consortium (LCMC), a coalition of 14 cancer centers, assessed the feasibility of conducting multiplex genotyping of 10 driver oncogenes in tumour samples of ~1,000 lung adenocarcinoma patients, in six academic but Clinical Laboratory Improvement Amendment (CLIA)-certified molecular testing laboratories (11). While this pioneering pilot project was successful in demonstrating the clinical benefit of obtaining multiplex genotyping information from patients with lung adenocarcinoma, the scale was limited. In contrast, the French Cooperative Thoracic Intergroup (IFCT), supported by the French National Cancer Institute (INCa) and in collaboration with the French Ministry of Health, launched a bold initiative that aimed to make molecular profiling available to all cancer patients in all regions of France, free of charge to patients, with tests being conducted in 28 regional molecular genetic centres (12,13). In a recent paper by Barlesi *et al.* (14), published in

Table 1 Actionable mutations in various cancer types and targeted drugs

Actionable mutation	Cancer type	FDA/EMA* approved drug
<i>BCR-ABL</i> translocation	Chronic myeloid or acute lymphoblastic leukaemia	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
<i>KIT & PDGFRA</i> mutations	Gastrointestinal stromal tumours	Imatinib
<i>HER2</i> amplification	Breast cancer	Trastuzumab, lapatinib, pertuzumab
<i>HER2</i> amplification	Gastric cancer	Trastuzumab
<i>EGFR</i> mutations	Non-small-cell lung cancer	Gefitinib, erlotinib, afatinib
<i>ALK</i> rearrangement	Non-small-cell lung cancer	Crizotinib, ceritinib, alectinib
<i>ROS1</i> rearrangement	Non-small cell lung cancer	Crizotinib
<i>BRAF</i> V600 mutation	Melanoma	Vemurafenib, dabrafenib, trametinib

*, FDA, Federal Drug Agency; EMA, European Medicines Agency.

The Lancet, the IFCT investigators reported the results of this program during its first year of operation, on routine molecular profiling of 18,679 patients with advanced non-small cell lung carcinoma (NSCLC).

The network of 28 certified regional genetic centres was established by INCa in 2006, nationwide across France, approximately one centre per administrative region (12). Each centre was a partnership between several university hospitals and cancer centre laboratories that provided free molecular testing across many tumour types to the surrounding population, regardless of where they were treated (13). With the involvement of 3,831 treating physicians, the study collected routine molecular profiling and clinical data on 17,664 patients with NSCLC during a 1-year period from April, 2012 to April, 2013 (Figure 1). The IFCT reported results for the molecular profiling of six routinely screened genes selected in 2009 for NSCLC, including *EGFR* mutations and *ALK* rearrangements, as well as mutations in *HER2 (ERBB2)*, *KRAS*, *BRAF*, *PIK3CA*, using Sanger sequencing and/or more sensitive validated sequence-specific techniques. The authors demonstrated that a genetic alteration was present in about half of the tumours analyzed, with a median turnaround time of 11 days

between the initiation of analysis and reporting. Importantly, the presence of a genetic alteration affected first-line treatment decisions in 51% (4,176/8,147) of the patients with alterations. The investigators demonstrated that routine molecular profiling of patients with advanced NSCLC is not only feasible, but also provided a significant clinical benefit: the presence of a genetic alteration was associated with a significant improvement in the proportions of patients achieving an overall response to both first-line (37% vs. 33%, $P=0.03$) and second-line treatments (17% vs. 9%, $P<0.0001$), compared with the absence of a genetic alteration; the presence of a genetic alteration was significantly associated with improved first-line progression free survival (10 vs. 7.1 months, $P<0.0001$) and overall survival (16.5 vs. 11.8 months, $P<0.0001$) compared with the absence of a genetic alteration. However, similar to the LCMC study, whether the survival benefit was due to the presence of the alteration (prognostic effect) or the effectiveness of the targeted agent (predictive effect), or both, remained in question and could not be teased apart in this study.

In this large population-based molecular profiling study, the reported prevalence of the six genetic alterations can be compared with the results reported in other studies of more limited scope. *EGFR* mutations were detected in 11% of analyzed tumours, which is significantly lower than the 22% reported in the LCMC (11) or 20.6% in the Canadian province of Ontario (15). The prevalence of *ALK* gene rearrangements was found to be 5% in the IFCT analyses, compared to 7.9% in the LCMC. LCMC detected *HER2 (ERBB2)* mutations at a 2.7% frequency, while the IFCT screening reported 0.8%; these are in contrast to the single-institution analyses at Memorial Sloan Kettering Cancer Center (MSKCC) with a 6% mutation rate (16). *BRAF* was detected at 1.9% frequency in the IFCT, comparable to 2.6% in LCMC. The *PIK3CA* mutation rate was 2.3% in the IFCT study, 2% at MSKCC (17), and 0.8% in the LCMC. Institutional referral bias or differences in population characteristics (such as ethnicity) could potentially account for these differences. Given the high incidence of lung cancer, these findings warrant routine testing of the rarer mutations (*HER2*, *PIK3CA*, *BRAF*) as they represent a substantial number of patients in the population that might benefit from targeted therapy.

The network structure of the 28 molecular laboratories spread across France benefited from rapid, uniform, high quality molecular testing and unhindered flow of information across testing centers. As a push for standardization, France mandated all medical laboratories to obtain an accreditation to ISO 15189 standard by 2016.

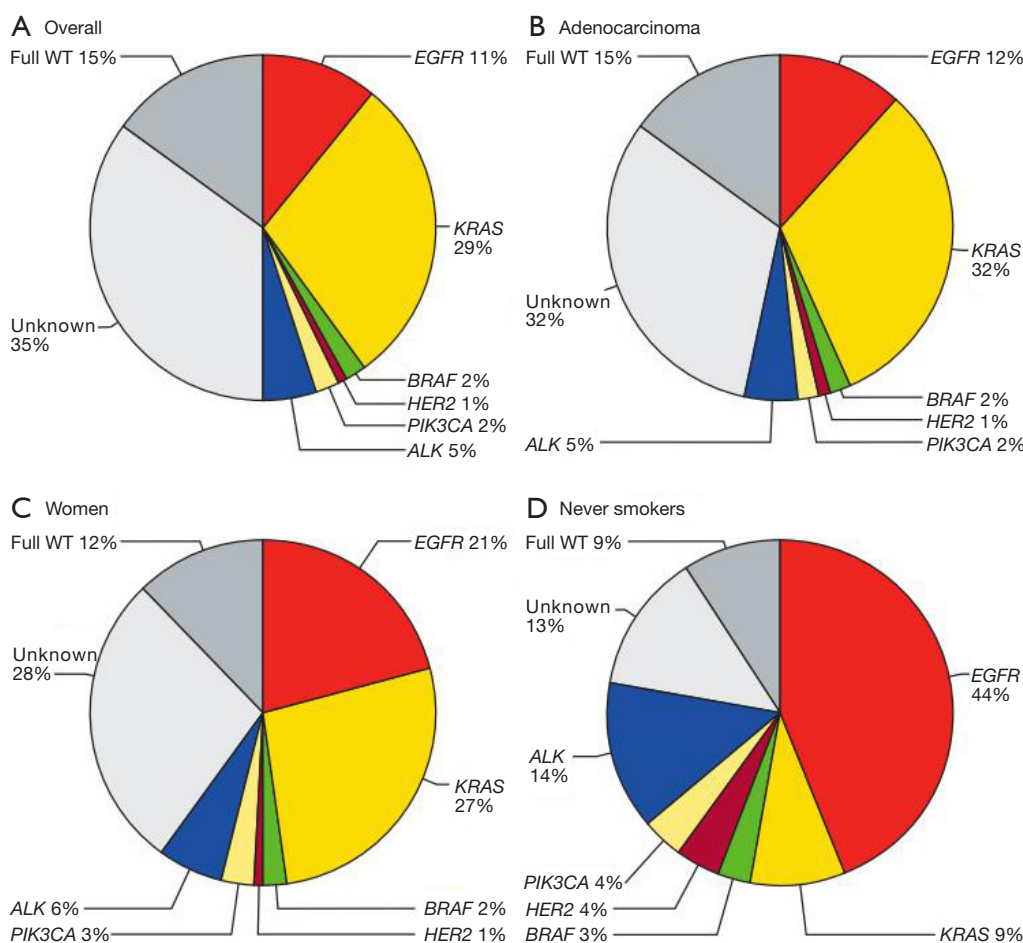


Figure 1 Frequency of genetic alterations in the French Cooperative Thoracic Intergroup (IFCT) study. (A) Overall population; (B) adenocarcinoma only; (C) women only; and (D) never smokers only. [Adapted and reproduced with permission from reference (14)].

Moreover, the network allowed for the creation of a large centralized national database that provides a major advantage to precision cancer treatment strategies, as it becomes a large resource for epidemiological analyses on the utility of approved targeted treatments, as well as a mechanism to direct patients harboring specific mutations without approved targeted agents into clinical trials. Prior to this, no program or initiative had been able to set up as extensively as this cancer molecular profiling program, which gathered epidemiological, clinical, histological, and therapeutic data, along with follow-up information. To facilitate rapid recruitment of patients to early-phase clinical trials, the French also utilized a network of 16 INCa-certified early phase centers (CLIP²) distributed across the country with the goal of helping clinicians match patients to early-phase clinical trials (18). With collaborative efforts between academia and pharmaceutical industry, CLIP² allowed selection of potential therapeutic targets to be rapidly

investigated in clinical trial. Disappointingly, the promise of increasing clinical trial recruitment by molecular profiling programs has yet to bear fruit. No clear improvement in clinical trial recruitment resulted during the IFCT 1-year period of molecular profiling for NSCLC; only 3% of patients with a molecular alteration were enrolled into clinical trials. This failure is a concern as similar molecular profiling studies performed in other centers across the world have also failed to show significant trial participation after testing. The MD Anderson genomic testing protocol matched 83/2,000 (4%) of patients to clinical trials (19). The *SAFIR-01* breast cancer trial matched 28/295 (9%) (20). The British Columbia Cancer Agency Personalized Oncogenomics trial only matched 1/78 (1%) patient (21).

As molecular profiling evolved from single gene assays into multiplex genotyping platforms such as next-generation sequencing, common actionable mutations shared across many tumour types are being recognized

and provide a strong rationale for using similar targeted agents as treatment. For example, while the *ALK*-inhibitor crizotinib is only approved for use in *EML4-ALK* and *ROS-1* rearranged NSCLC, the presence of *ALK* and/or *ROS-1* alterations in other tumour types, including breast, colorectal, melanoma, and thyroid cancer, as well as a variety of other blood and solid tumours have led investigators and clinicians to off-label use (22). The problem arises in that most approved targeted therapies have been rigorously tested in a clinical trial for only a specific subset of tumours. Without proper clinical trial investigation, off-label use in non-approved tumour types runs the risk of toxicity with only anecdotal evidence of a treatment benefit. To this end and as part of the French National Cancer plan, France has set up the AcSe (Secured Access to Innovative Therapies) program, to bridge the results of molecular testing with investigative clinical trials of targeted drugs for patients harboring actionable mutations outside a drug's market authorization. The AcSe program will help generate safety and efficacy data on these targeted agents outside their approved indications, and has already shown proof of concept with crizotinib and verumafinib trials in various tumours not currently approved for use (22). Even if the drug's market authorization holder does not submit for a new indication, the safety and efficacy data generated from these trials will be useful for future off-label prescriptions.

The French initiative's synergistic approach has given the world a great example of how to implement a precision or personalized cancer care strategy that benefits all citizens of a country. Moreover, the central database that was included in the establishment of this program provides an invaluable and real time resource for crucial molecular epidemiological studies in personalized cancer care. By offering free molecular testing nationwide, they have provided universal access to predictive biomarkers that may be implemented in clinical treatment decisions. Even if no clinically approved drug is currently available, these patients will not be left out because the AcSe programme allows for a quick way to investigate innovative targeted agents based on their molecular profile. This approach also seems to be cost-effective compared to prior strategies, with the overall cost of molecular testing balanced by the savings on prescription drugs for patients without the intended biomarker or actionable mutation. A similar initiative in the United Kingdom is now ongoing (23), which could be extended to other European countries.

In the United States, the plethora of private health insurance systems might require significant modifications when building such an infrastructure. However, a renewed commitment to precision medicine has been undertaken, and the NCI has launched multiple initiatives with the

goal of matching patients with an actionable mutation to an agent that targets that specific molecular alteration or pathway, ensuring clinical trial participation. The NCI Molecular Analysis for Therapy Choice (MATCH) serves as a prescreening histology-agnostic basket trial to designate patients with particular mutations to targeted treatment arms (24). The Lung-Master Protocol (LUNG-MAP) aims to overcome the difficulty in recruiting patients with lung squamous cell carcinoma into specific clinical trials by utilizing an umbrella model, where comprehensive molecular profiling is performed and the results of these tests will determine enrollment in four substudies (25). These substudies are based on targeted treatment of patients with mutations in *PIK3CA*, *CCND1/2/3* or *CDK4* amplifications, and *FGFR* alterations. Those without any defined alterations are placed into a randomized PD-L1 immunotherapy arm or chemotherapy. These new trial designs hope to overcome the many challenges of genotype-matched trials. Leading by example, France, along with other countries, has paved the way for precision cancer care by promoting the revolution of taking action against actionable mutations.

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Footnote

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