Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)

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Summary

Background The molecular profiling of patients with advanced non-small-cell lung cancer (NSCLC) for known oncogenic drivers is recommended during routine care. Nationally, however, the feasibility and effects on outcomes of this policy are unknown. We aimed to assess the characteristics, molecular profiles, and clinical outcomes of patients who were screened during a 1-year period by a nationwide programme funded by the French National Cancer Institute.

Methods This study included patients with advanced NSCLC, who were routinely screened for *EGFR* mutations, *ALK* rearrangements, as well as *HER2* (*ERBB2*), *KRAS*, *BRAF*, and *PIK3CA* mutations by 28 certified regional genetics centres in France. Patients were assessed consecutively during a 1-year period from April, 2012, to April, 2013. We measured the frequency of molecular alterations in the six routinely screened genes, the turnaround time in obtaining molecular results, and patients' clinical outcomes. This study is registered with ClinicalTrials.gov, number NCT01700582.

Findings 18 679 molecular analyses of 17 664 patients with NSCLC were done (of patients with known data, median age was 64·5 years [range 18–98], 65% were men, 81% were smokers or former smokers, and 76% had adenocarcinoma). The median interval between the initiation of analysis and provision of the written report was 11 days (IQR 7–16). A genetic alteration was recorded in about 50% of the analyses; *EGFR* mutations were reported in 1947 (11%) of 17 706 analyses for which data were available, *HER2* mutations in 98 (1%) of 11 723, *KRAS* mutations in 4894 (29%) of 17 001, *BRAF* mutations in 262 (2%) of 13 906, and *PIK3CA* mutations in 252 (2%) of 10 678; *ALK* rearrangements were reported in 388 (5%) of 8134 analyses. The median duration of follow-up at the time of analysis was 24·9 months (95% CI 24·8–25·0). The presence of a genetic alteration affected first-line treatment for 4176 (51%) of 8147 patients and was associated with a significant improvement in the proportion of patients achieving an overall response in first-line treatment (37% [95% CI 34·7–38·2] for presence of a genetic alteration *vs* 33% [29·5–35·6] for absence of a genetic alteration; p=0·03) and in second-line treatment (17% [15·0–18·8] *vs* 9% [6·7–11·9]; p<0·0001). Presence of a genetic alteration was also associated with improved first-line progression-free survival (10·0 months [95% CI 9·2–10·7] *vs* 7·1 months [6·1–7·9]; p<0·0001) and overall survival (16·5 months [15·0–18·3] *vs* 11·8 months [10·1–13·5]; p<0·0001) compared with absence of a genetic alteration.

Interpretation Routine nationwide molecular profiling of patients with advanced NSCLC is feasible. The frequency of genetic alterations, acceptable turnaround times in obtaining analysis results, and the clinical advantage provided by detection of a genetic alteration suggest that this policy provides a clinical benefit.

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Introduction

Lung cancer is one of the most frequent types of cancer in developed countries and is the leading cause of cancer deaths, with more than 1 million deaths expected per year.[1] However, understanding of the molecular hallmarks of this cancer has developed only recently.[2] The treatment of lung cancer has entered a new era because of the discovery of epidermal growth factor receptor (*EGFR*)-activating mutations and anaplastic lymphoma kinase (*ALK*) gene rearrangements, which lead to changes in outcomes in some patients with lung cancer.[3,4] Moreover, compared with other cancers, lung cancer has one of the highest rates of genetic alterations,[5] some of which are actionable via the administration of drugs that have already been approved, are available off-label for other indications

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Research in context

Evidence before this study

We did a systematic review of the scientific literature to identify studies assessing nationwide routine molecular profiling of patients with advanced non-small-cell lung cancer (NSCLC) for one or more genetic alterations known (or supposed) to be oncogenic drivers. We searched PubMed for English language reports published up to Dec 3, 2010, with the terms "non small cell lung cancer", "advanced" or "metastatic", and "EGFR" or "ALK" or "BRAF" or "HER2" or "PIK3CA" or "KRAS" or "multiplex" or "sequencing" and "nationwide", or names of various countries around the world. We also searched abstracts from ASCO and ESMO meetings (2007–10). We did not identify any published data.

Added value of this study

Our study shows that routine nationwide molecular profiling of patients with advanced NSCLC is feasible with an acceptable turnaround time in obtaining the results. Even with assessment of a limited number of genetic alterations (ie, currently six genes), the frequency of these genetic alterations might allow the consideration of targeted therapy for treating these patients (either commercially available for *EGFR* and *ALK*, or within a clinical trial for the other alterations). Finally, when a genetic alteration was detected, the outcome was a longer median overall survival, suggesting a possible prognostic advantage or a major change in the management of these patients with advanced NSCLC, or both.

Implications of all the available evidence

The Lung Cancer Mutation Consortium (LCMC) initiative (the largest multi-institutional study in developed countries) suggested that molecular profiling helps to orient patients towards targeted therapies and dedicated trials, and individuals with drivers receiving a matched targeted agent lived longer than patients who did not receive genotype-directed therapy. Our study extends the LCMC study to a nationwide scale, and suggests that routine nationwide molecular profiling provides a clinical benefit to patients with advanced NSCLC.

(eg, dabrafenib or vemurafenib for *BRAF* mutations,[6] trastuzumab or afatinib for *HER2* [also known as *ERBB2*] mutations,[7] and crizotinib for *ROS1* rearrangements[8]), or are under investigation in clinical trials. Therefore, high expectations are placed on personalised (also referred to as stratified or precision) medicine in this setting.

In this context, many medical centres have been organised to provide patients with lung cancer with routine assessments of *EGFR* mutations and *ALK* rearrangements. In some of these centres, additional molecular alterations are tested, typically by research programmes.[9–12] The preliminary data obtained from such programmes suggest that molecular profiling helps to orient patients towards targeted therapies and dedicated trials. However, the actual effects of broad molecular screening and subsequent personalised medicine have yet to be addressed in a prospective randomised trial.[10] Additionally, the characteristics and efficacy results reported by these programmes are based on a limited series of selected patients. Therefore, a wide overview is needed in an unselected, all-comer population to increase understanding of the epidemiology of lung cancer biomarkers and their potential effect on therapeutic strategies.

The French National Cancer Institute (INCa) funded a nationwide programme for the systematic routine analysis of *EGFR* mutations and *ALK* rearrangements as well as *HER2*, *KRAS*, *BRAF*, and *PIK3CA* mutations in patients with advanced stage, non-squamous, non-small-cell lung cancer (NSCLC) in 28 certified molecular genetics centres covering the whole of France, including overseas entities.[13–15] The Biomarkers France study assessed the characteristics, molecular profiles, and clinical outcomes of patients who were screened by this programme during a 1-year period.

Methods

Participants

All consecutive patients with NSCLC who were routinely screened for molecular alterations during a 1-year period at one of the 28 certified molecular genetics centres in France were eligible for inclusion in this study. The prescription of this routine molecular screening, mandatory for advanced non-squamous NSCLC, was solely the responsibility of the treating physician. Notably, national recommendations for screening for *EGFR* mutations (both activating and Thr790Met), *ALK* rearrangements, and four emerging biomarkers (*KRAS*, *BRAF*, *HER2*, and *PIK3CA* mutations) have been available since 2010.[16] Additionally, patients with a less advanced stage of NSCLC or patients carrying other tumour types (eg, mixed histology, never smokers) could have been screened upon approval by their local multidisciplinary tumour board.

This study was approved by a national ethics committee for observational studies (Comité d'Evaluation des Protocoles de Recherche Observationnelle), by the French Advisory Committee on Information Processing in Material Research in the Field of Health (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé), and by the National Commission of Informatics and Liberty (CNIL), according to French laws.

Each clinician identified as the prescriber of a molecular analysis between April, 2012, and April, 2013, received written information describing the study protocol and the process for accessing the database as well as a confidential password to connect to the Biomarkers France secured online case report form.

All patients with NSCLC included in this programme received information from their institution or referring clinician, as recommended by competent authorities,

which specified, according to French laws, that they were allowed to ask for complete access to and removal of their own collected data. Patients were not required to provide written informed consent to be included in the study.

The feasibility and potential technical issues of this project were initially investigated by analysing patients screened at three certified molecular genetics centres during a 3-month period (November, 2011, to January, 2012); this analysis served as a test for the subsequent nationwide study. Because no major difficulties were noted in this initial analysis of 346 patients, the steering committee decided to open the 1-year national recruitment period in April, 2012. The 28 molecular genetics centres had to send their results to the French Cooperative Thoracic Intergroup (IFCT) using a specific data sheet for each patient. Then, the data were recorded and monitored by the IFCT. The investigators had full access to the de-identified data and analyses for the current report.

Molecular analyses

The molecular analyses of *EGFR* (NG_007726.3), *HER2* (NG_007503.1), *KRAS* (NG_007524.1), *BRAF* (NG_007873.3), and *PIK3CA* (NG_012113.2) mutations and *ALK* (NG_009445.1) rearrangements were done on a routine basis at the molecular genetics centres (appendix p 13). The methods used in these analyses[16] and the results of the prospective cross-validation quality assessment studies have been reported elsewhere.[17–19] Briefly, each molecular genetics centre used either the Sanger sequencing method or a more sensitive validated allele-specific technique (generally to be confirmed by Sanger sequencing) to assess *EGFR* (exons 18–21),[17,18] *HER2* (exon 20), *BRAF* (exon 15), *KRAS* (exon 2),[17–19] and *PIK3CA* (exons 9 and 20) mutations (appendix pp 1–2). A certified break-apart fluorescence in-situ hybridisation assay was used to assess *ALK* rearrangements.[20] Additionally, each regional genetics centre either did a concurrent analysis of all recommended

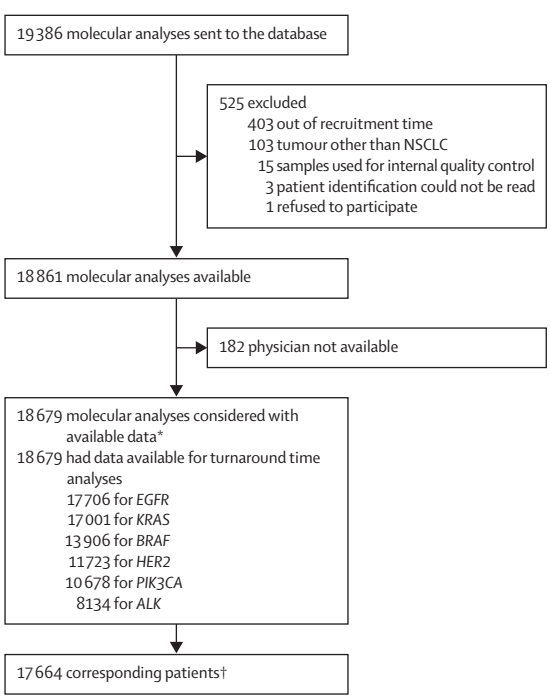

Figure 1: **Study flow chart**
NSCLC=non-small-cell lung cancer. *Data availability subject to sequential strategies at regional genetics centres. †Data availability (see table 1) subject to the completion of the database by treating physicians.

	Patients (N=17 664)
Age, years (n=17 664)	64·5 (18–98)*
Sex (n=17 555)	
Male	11 346 (65%)
Female	6209 (35%)
Ethnic origin (n=7350)	
Asian	96 (1%)
White or other	7254 (99%)
Smoking history (n=8619)	
Never	1619 (19%)
Former smoker	3597 (42%)
Current smoker	3403 (39%)
ECOG performance status (n=7817)	
0 or 1	5607 (72%)
2	1423 (18%)
3–4	787 (10%)
Previous cancer (n=7848)	
None	6887 (88%)
Within family	961 (12%)
Stage, TNM 2007 (n=8637)	
1 or 2	1392 (16%)
3, 4, or relapse	7245 (84%)
Histology (n=17 664)	
Adenocarcinoma	13 425 (76%)
Squamous	877 (5%)
Large-cell carcinoma	589 (3%)
NOS or other histology	2773 (16%)
Method of sample collection (n=17 664)	
Bronchoscopy	5038 (29%)
CT-guided transthoracic biopsy	4229 (24%)
Surgery	4712 (27%)
Other	3685 (21%)
Samples analysed per patient (n=17 664)	
1	16 696 (95%)
>1	968 (5%)
Turnaround time, days (n=18 679)†	
From sample collection to initiation of analysis	8·0 (4·0–16·0)‡
From initiation of analysis to report of results	11·0 (7·0–16·0)‡

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. NOS=not otherwise specified. *Median (IQR). †The turnaround times were reported by analysts and not by patients (18 679 analyses). ‡Median (range).

Table 1: **Patient characteristics**

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See Online for appendix

	EGFR				*KRAS*			*BRAF*		
	Mutation*	Resistant mutation (Thr790Met)	Wild-type	Unknown	Mutation*	Wild-type	Unknown	Mutation*	Wild-type	Unknown
Number (%)	1786 (10%)	161 (1%)	15759 (84%)	973 (5%)	4894 (26%)	12107 (65%)	1678 (9%)	262 (1%)	13644 (73%)	4773 (26%)
Age (median)	68·4†	65·7†	64·5†	65·8†	63·3†	65·4†	66·6†	65·9	64·7	65·7
Sex‡										
Male	568 (32%)†	49 (30%)†	10699 (68%)†	631 (65%)†	3245 (66%)†	7698 (64%)†	1004 (60%)†	160 (61%)	8881 (65%)	2906 (61%)
Female	1208 (68%)†	111 (69%)†	4963 (31%)†	339 (35%)†	1621 (33%)†	4331 (36%)†	669 (40%)†	101 (39%)	4686 (34%)	1834 (38%)
Ethnic origin										
Asian	49 (5%)†	6 (7%)†	46 (1%)†	7 (2%)†	15 (1%)†	79 (2%)†	14 (2%)†	0	72 (1%)	36 (2%)
Other	938 (95%)†	79 (93%)†	6365 (99%)†	421 (98%)†	1954 (99%)†	5101 (98%)†	748 (98%)†	150 (100%)	5800 (99%)	1853 (98%)
Smoking history										
Never	683 (60%)†	53 (57%)†	939 (12%)†	98 (20%)†	138 (6%)†	1397 (23%)†	238 (28%)†	41 (25%)	1229 (18%)	503 (22%)
Former	316 (28%)†	31 (33%)†	3305 (44%)†	213 (44%)†	1104 (47%)†	2410 (40%)†	351 (41%)†	63 (38%)	2887 (42%)	915 (40%)
Current	142 (12%)†	9 (10%)†	3312 (44%)†	170 (35%)†	1113 (47%)†	2260 (37%)†	260 (31%)†	60 (37%)	2709 (40%)	864 (38%)
ECOG PS										
0 or 1	784 (76%)†	71 (78%)†	4916 (72%)†	314 (70%)†	1526 (71%)	4028 (73%)	531 (68%)	109 (74%)	4538 (73%)	1438 (71%)
≥2	247 (24%)†	20 (22%)†	1932 (28%)†	132 (30%)†	609 (29%)	1472 (27%)	250 (32%)	38 (26%)	1700 (27%)	593 (29%)
Previous cancer within family	148 (14%)†	23 (25%)†	834 (12%)†	45 (10%)†	267 (13%)	703 (13%)	80 (10%)	19 (12%)	775 (12%)	256 (13%)
Stage (TNM 2007)										
1 or 2	177 (15%)	13 (13%)	1248 (17%)	61 (12%)	391 (17%)	1015 (17%)	93 (11%)	23 (14%)	1143 (17%)	333 (15%)
3, 4, or relapse	971 (85%)	84 (87%)	6293 (83%)	428 (88%)	1955 (83%)	5063 (83%)	758 (89%)	143 (86%)	5692 (83%)	1941 (85%)
Histology										
Adenocarcinoma	1502 (84%)†	145 (90%)†	11854 (75%)†	742 (76%)†	4069 (83%)†	8845 (73%)†	1329 (79%)†	228 (87%)†	10610 (78%)†	3405 (71%)†
Squamous	23 (1%)†	1 (1%)†	838 (5%)†	47 (5%)†	47 (1%)†	792 (7%)†	70 (4%)†	1 (<1%)†	708 (5%)†	200 (4%)†
Large-cell carcinoma	25 (1%)†	1 (1%)†	557 (6%)†	31 (3%)†	131 (3%)†	432 (4%)†	51 (3%)†	6 (2%)†	471 (3%)†	137 (3%)†
NOS or other	236 (13%)†	14 (9%)†	2510 (16%)†	153 (16%)†	647 (13%)†	2038 (17%)†	228 (14%)†	27 (10%)†	1855 (14%)†	1031 (22%)†
Turnaround time (days)										
Coll–lab	7 (3–15)†	9 (3–16)†	8 (4–16)†	9 (5–27)†	8 (4–15)	8 (4–16)	10 (5–25)	9 (6–15)	8 (4–16)	7 (0–15)
Lab–result	12 (8–17)†	13·5 (8–20)†	11 (7–16)†	12 (7–17)†	13 (9–18)	13 (8–18)	14 (10–20)	14 (9–21)	13 (9–19)	15 (10–23)

Data are n (%), median, or median (IQR). See appendix (pp 3–4) for data presented as per row percentages. ECOG PS=Eastern Cooperative Oncology Group performance status. NOS=not otherwise specified. Coll–lab=from sample collection to initiation of analysis. Lab–result=from initiation of analysis to report of results. *Activating mutation. †Comparison between the population with the molecular alteration under consideration and the population with unknown or full wild-type is significantly different (p<0·05). ‡In 109 (0·6%) cases, sex was not specified in the report.

***Table 2*: Results of the 18 679 molecular analyses for *EGFR*, *KRAS*, and *BRAF* genes stratified by clinical characteristics**

molecular alterations in the six genes or used a sequential approach in which the *EGFR* and *ALK* assessments were done first, and then each of the other molecular alterations were assessed until a mutation was found.

Data collection

The molecular genetics centres provided IFCT with the results of molecular assessments of the six genes under investigation, histological typing and the percentage of

	HER2			*PIK3CA*			*ALK*			Full WT
	Mutation*	Wild-type	Unknown	Mutation*	Wild-type	Unknown	Rearranged	Wild-type	Unknown	
Number (%)	98 (1%)	11 625 (62%)	6956 (37%)	252 (1%)	10 426 (56%)	8001 (43%)	388 (2%)	7746 (41%)	10 545 (56%)	2833 (15%)
Age (median)	66·2	64·7	65·3	67·9†	64·6†	65·3†	61·2†	65·0†	65·1†	64·8
Sex‡										
Male	40 (41%)†	7577 (65%)†	4330 (62%)†	154 (61%)	6812 (65%)	4981 (62%)	206 (53%)†	5016 (65%)†	6725 (64%)†	2033 (72%)
Female	58 (59%)†	3971 (34%)†	2592 (37%)†	98 (39%)	3549 (34%)	2974 (37%)	180 (46%)†	2675 (35%)†	3766 (36%)†	775 (27%)
Ethnic origin										
Asian	0	64 (1%)	44 (2%)	1 (1%)	63 (1%)	44 (1%)	5 (2%)	38 (1%)	65 (2%)	8 (1%)
Other	63 (100%)	5054 (99%)	2686 (98%)	101 (99%)	4634 (99%)	3068 (99%)	238 (98%)	3304 (99%)	4261 (98%)	1141 (99%)
Smoking history										
Never	42 (64%)†	1065 (18%)†	666 (21%)†	38 (31%)†	987 (18%)†	748 (20%)†	116 (43%)†	697 (19%)†	960 (18%)†	167 (13%)
Former	16 (24%)†	2553 (42%)†	1296 (41%)†	49 (40%)†	2292 (42%)†	1524 (41%)†	92 (34%)†	1638 (44%)†	2135 (41%)†	574 (45%)
Current	8 (12%)†	2419 (40%)†	1206 (38%)†	36 (29%)†	2178 (40%)†	1419 (38%)†	60 (22%)†	1422 (38%)†	2151 (41%)†	532 (42%)
ECOG PS										
0 or 1	51 (81%)	3921 (72%)	2113 (72%)	80 (70%)	3610 (73%)	2395 (71%)	205 (81%)†	2476 (71%)†	3404 (73%)†	817 (69%)
≥2	12 (19%)	1506 (28%)	813 (28%)	34 (30%)	1334 (27%)	963 (29%)	49 (19%)†	1003 (29%)†	1279 (27%)†	364 (31%)
Previous cancer within family	8 (12%)	731 (13%)	311 (11%)	14 (13%)	633 (13%)	403 (12%)	28 (11%)	457 (13%)	565 (12%)	156 (13%)
Stage (TNM 2007)										
1 or 2	5 (7%)†	1086 (18%)†	408 (13%)†	25 (20%)	980 (18%)	494 (13%)	34 (13%)	527 (14%)	938 (18%)	215 (17%)
3, 4, or relapse	64 (93%)†	4931 (82%)†	2781 (87%)†	101 (80%)	4480 (82%)	3195 (87%)	238 (88%)	3228 (86%)	4310 (82%)	1061 (83%)
Histology										
Adenocarcinoma	90 (92%)†	8959 (77%)†	5194 (75%)†	161 (64%)†	8079 (77%)†	6003 (75%)†	331 (85%)†	6218 (80%)†	7694 (73%)†	2084 (74%)
Squamous	0†	656 (6%)†	253 (4%)†	45 (18%)†	577 (6%)†	287 (4%)†	4 (1%)†	346 (4%)†	559 (5%)†	232 (8%)
Large-cell carcinoma	0†	436 (4%)†	178 (3%)†	8 (3%)†	405 (4%)†	201 (3%)†	12 (3%)†	262 (3%)†	340 (3%)†	140 (5%)
NOS or other	8 (8%)†	1574 (14%)†	1331 (19%)†	38 (15%)†	1365 (13%)†	1510 (19%)†	41 (11%)†	920 (12%)†	1952 (19%)†	377 (13%)
Turnaround time (days)										
Coll–lab	9 (5–23)	8 (5–16)	7 (1–15)	9 (5–17)	8 (5–16)	7 (1–16)	7 (3–13)†	7 (3–15)†	9 (5–17)†	7 (3–14)
Lab–result	17 (10·5–29)†	14 (9–20)†	16 (10–23)†	15 (10–21)	14 (9–22)	16 (11–23)	21 (12–35·5)†	16 (8–28)†	26 (13–48)†	24 (14–40)

Data are n (%), median, or median (IQR). See appendix (pp 3–4) for data presented as per row percentages. Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2*, or *PIK3CA* mutation or *ALK* rearrangement. ECOG PS=Eastern Cooperative Oncology Group performance status. NOS=not otherwise specified. Coll–lab=from sample collection to initiation of analysis. Lab–result=from initiation of analysis to report of results. *Activating mutation. †Comparison between the population with the molecular alteration under consideration and the population with unknown or full WT is significantly different (p<0·05). ‡In 109 (0·6%) cases, sex was not specified in the report.

***Table 3*: Results of the 18 679 molecular analyses for *HER2* (*ERBB2*), *PIK3CA*, and *ALK* genes stratified by clinical characteristics**

tumour cells measured by the referring pathologist, and the turnaround time before obtaining the analysis results (from the date of tumour receipt to the date of submission of the written molecular report to the clinician). Simultaneously, the treating physician (n=3831) of each patient was provided with secure access to his or her own patient's data.

The following data were obtained: sex; ethnic origin (Asian *vs* non-Asian); smoking history (never, former, or current smoker); past familial medical history of cancer;

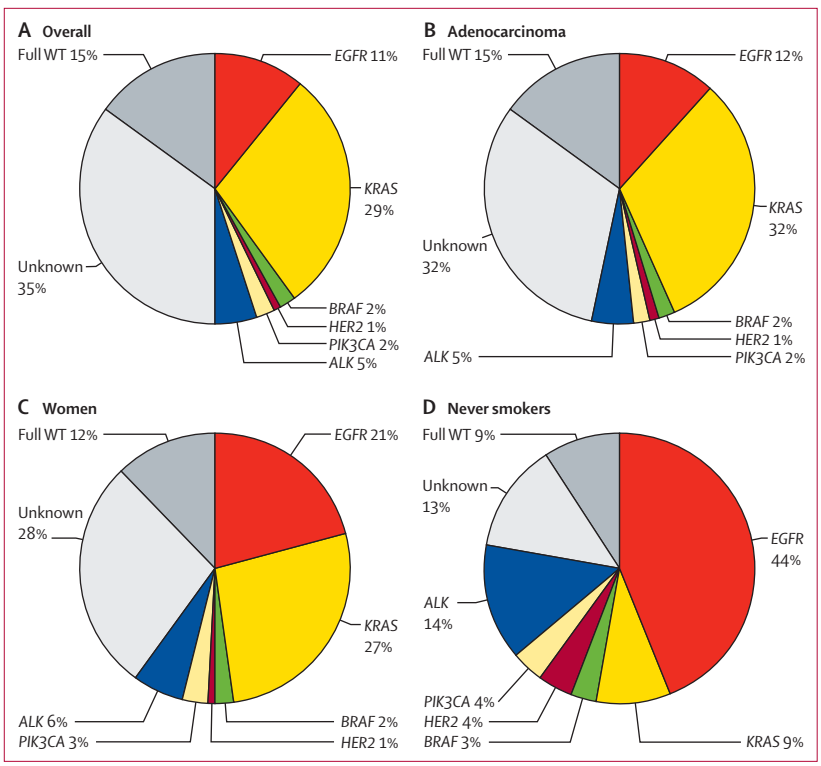

Figure 2: **Frequency of genetic alterations**
Frequency of molecular alterations in six genes from 18 679 analysed samples (expressed as the percentage of positive samples for each molecular alteration relative to the number of available analyses, with unknown representing the cases with at least one unknown result after assessment of the six genes). Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2* (*ERBB2*), or *PIK3CA* mutation or *ALK* rearrangement. (A) Overall population, (B) adenocarcinoma only, (C) women only, and (D) never smokers only.

Eastern Cooperative Oncology Group performance status (0–1 *vs* ≥2); TNM stage, as defined by the seventh edition of the American Joint Committee on Cancer;[21] pathological diagnosis, as defined by the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification;[22] and the method of sample collection (bronchoscopy, transthoracic biopsy, thoracic surgery, or other). The following information was obtained and reported per investigator review: the type of treatment (standard chemotherapy, type of chemotherapy or targeted therapy, or, if applicable, the clinical trial along with the type of treatment); the effect of the molecular results on the treatment decision; and outcomes (overall response assessed by treating physician, usually according to Response Evaluation Criteria in Solid Tumors [RECIST], which define a response by a decrease in target lesions by at least 30% and disease progression by an increase of target lesions by at least 20%; first-line treatment and, when applicable, second-line treatment and date[s] of disease progression; and survival status).

Patients were treated on a routine basis after review by a local multidisciplinary tumour board and in accordance with national and international guidelines.[23–25] At the time the study was done, erlotinib and gefitinib were approved for the treatment of patients with *EGFR* mutations (including first-line treatment), whereas crizotinib was available only for the second-line treatment of patients with *ALK* rearrangements. *KRAS*, *BRAF*, *HER2*, and *PIK3CA* mutations were targetable by drugs available through clinical trials. Connection to and completion of the database was done voluntarily by the treating physicians.

Outcomes

The primary objective of this study was to describe the frequency of the molecular alterations in six genes that were routinely screened via a nationwide approach in consecutive patients with NSCLC. The secondary objectives were to combine the clinical and biological databases, document the turnaround time in obtaining molecular results, assess the ability of the treating physician to use these data to select an ad-hoc therapy (on a standard basis or via inclusion in a clinical trial), and measure patients' outcomes (progression-free survival and overall survival).

Statistical analysis

Descriptive statistics, including median and range or quartiles for continuous variables or frequencies, and percentages for categorical variables, were used. Median duration of follow-up was defined as the time from date of molecular analysis assessment to the closing date of the analysis. Median time until results were obtained was expressed to first and third quartiles (IQR) to avoid excessive data dispersion. First-line progression-free survival was defined as the time from the date of molecular analysis assessment to the date of the first progression or death from any cause. Second-line progression-free survival was defined as the time from initiation of second-line treatment to the date of the second progression or death from any cause. Overall survival was defined as the date of the molecular analysis assessment to the date of death or final follow-up. Survival curves were estimated for the total population and for groups of interest by the Kaplan-Meier method. We compared the groups of interest by use of the two-sided log-rank test. Patient characteristics (with or without gene alteration of each biomarker) were compared with the χ^2 test for qualitative variables or with a non-parametric test for quantitative variables. Univariate Cox models were applied to select the most promising prognostic variables (threshold p=0·20). A multivariate Cox model was then applied to adjust for potential confounders (clinical or molecular characteristics associated with progression-free survival or overall survival). Adjusted hazard ratios (HRs) with 95% CIs were calculated. All statistical tests were two-sided, and a p value of less than 0·05 was deemed statistically significant. All analyses were done with SAS software, version 9.3 (SAS Institute).

	Overall population (n=17 664)	*EGFR* mutation (n=1787)		*KRAS* mutation (n=4588)		*BRAF* mutation (n=230)		*HER2 (ERBB2)* mutation (n=92)		*PIK3CA* mutation (n=157)		*ALK* rearrangement (n=340)		Full WT (n=2769)
		All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All	Adapted*	All
First-line treatment														
Number with data (%)	8448 (48%)	1128 (63%)	662 (37%)	2085 (45%)	979 (21%)	146 (63%)	64 (28%)	62 (67%)	28 (30%)	73 (46%)	29 (18%)	236 (69%)	120 (35%)	1214 (44%)
Pemetrexed-based regimen	2747 (33%)	188 (17%)	57 (9%)	792 (38%)	525 (54%)	51 (35%)	34 (53%)	31 (50%)	18 (64%)	17 (23%)	11 (38%)	111 (47%)	55 (46%)	401 (33%)
Vinorelbine-based regimen	504 (6%)	39 (3%)	9 (1%)	128 (6%)	68 (7%)	5 (3%)	2 (3%)	0	0	7 (10%)	3 (10%)	13 (6%)	9 (8%)	80 (7%)
Taxane-based regimen	1064 (13%)	60 (5%)	18 (3%)	261 (13%)	166 (17%)	20 (14%)	12 (19%)	8 (13%)	4 (14%)	11 (15%)	7 (24%)	17 (7%)	11 (9%)	188 (15%)
EGFR-TKI	684 (8%)	543 (48%)	520 (79%)	26 (1%)†	9 (1%)†	3 (2%)†	2 (3%)†	0	0	1 (1%)†	1 (3%)†	4 (2%)†	2 (2%)†	17 (1%)
Crizotinib	18 (<1%)	0	0	0	0	0	0	0	0	0	0	18 (8%)	18 (15%)	0
Trial‡	253 (3%)	36 (3%)	31 (5%)	63 (3%)	48 (5%)	8 (5%)	5 (8%)	3 (5%)	1 (4%)	0	0	16 (7%)	12 (10%)	36 (3%)
Other§	709 (8%)	27 (2%)	9 (1%)	171 (8%)	77 (8%)	11 (8%)	3 (5%)	5 (8%)	3 (11%)	10 (14%)	5 (17%)	6 (3%)	3 (3%)	131 (11%)
BSC only	2469 (29%)	235 (21%)	18 (3%)	644 (31%)	86 (9%)	48 (33%)	6 (9%)	15 (24%)	2 (7%)	27 (37%)	2 (7%)	51 (22%)	10 (8%)	361 (30%)
Second-line treatment														
Number with data (%)	5518 (31%)	698 (39%)	381 (21%)	1358 (30%)	566 (12%)	106 (46%)	37 (16%)	43 (47%)	22 (24%)	48 (31%)	12 (8%)	157 (46%)	102 (30%)	797 (29%)
Taxane	782 (14%)	46 (7%)	34 (9%)	236 (17%)	203 (36%)	16 (15%)	8 (22%)	6 (14%)	4 (18%)	5 (10%)	2 (17%)	5 (3%)	4 (4%)	119 (15%)
Pemetrexed	612 (11%)	125 (18%)	97 (25%)	136 (10%)	105 (19%)	8 (8%)	6 (16%)	5 (12%)	4 (18%)	4 (8%)	2 (17%)	13 (8%)	10 (10%)	81 (10%)
Erlotinib	776 (14%)	231 (33%)	218 (57%)	125 (9%)	94 (17%)	9 (8%)	4 (11%)	5 (12%)	4 (18%)	2 (4%)	2 (17%)	10 (6%)	6 (6%)	96 (12%)
Crizotinib	73 (1%)	0	0	0	0	0	0	0	0	0	0	73 (46%)	73 (72%)	0
Trial‡	116 (2%)	8 (1%)	7 (2%)	33 (2%)	27 (5%)	5 (5%)	5 (14%)	3 (7%)	2 (9%)	2 (4%)	1 (8%)	4 (3%)	4 (4%)	25 (3%)
Other§	442 (8%)	10 (1%)	6 (2%)	90 (7%)	60 (11%)	8 (8%)	7 (19%)	8 (19%)	8 (36%)	2 (4%)	2 (17%)	5 (3%)	3 (3%)	79 (10%)
BSC only	2711 (49%)	272 (39%)	15 (4%)	738 (54%)	77 (14%)	60 (57%)	7 (19%)	16 (37%)	0	33 (69%)	3 (25%)	47 (30%)	2 (2%)	397 (50%)

Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2*, or *PIK3CA* mutation or *ALK* rearrangement. EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor. BSC=best supportive care. *The treatment was selected on the basis of the results of the molecular analyses (eg, targeted therapy if an actionable alteration had been identified, chemotherapy for wild-type patients). †Patients with tumour displaying two molecular alterations including *EGFR* mutation. ‡Usually based on targeted agents. §Including, but not limited to, another type of chemotherapy, crizotinib via an expanded access programme before its registration, off-label targeted therapy, or a non-registered combination of therapies.

Table 4: **Patient treatment stratified by line of therapy and the results of routine molecular analyses**

This study is registered with ClinicalTrials.gov, number NCT01700582.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or preparation of the report. The study's steering committee included representatives of the certified molecular genetics centres, INCa, and the IFCT. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study recruitment period was from April, 2012, to April, 2013, and the database was locked for the current analysis on July 23, 2014. Overall, 19 386 results of routine molecular analyses were recorded in the database. After review, 707 (4%) analyses were excluded (figure 1). The final analysis consisted of 18 679 results, representing 17 664 patients with NSCLC.

Table 1 shows the primary characteristics of the 17 664 patients. The number of samples analysed per patient was typically one (16 696 [95%] patients), but two or

	Overall population	*EGFR* mutation	*KRAS* mutation	*BRAF* mutation	*HER2* (*ERBB2*) mutation	*PIK3CA* mutation	*ALK* rearrangement	Unknown*	Full WT
First-line treatment									
Overall response (available data)	6319	896	1499	109	50	54	191	2546	896
Overall response (%)	34%	48%	30%	23%	32%	46%	41%	32%	33%
95% CI	32·9–35·3	44·3–50·8	27·6–32·3	15·0–30·8	19·1–44·9	33·0–59·6	34·4–48·3	30·2–33·8	29·5–35·7
PFS (available data)	7821	1017	1966	132	56	72	214	3131	1137
PFS (months), median	8·3	15·4	7·3	7·5	7·3	13·7	14·5	7·5	7·1
95% CI	8·0–8·7	13·7–17·6	6·5–8·0	5·6–12·3	4·9–21·2	8·3–NR	11·0–16·7	7·0–8·0	6·1–7·9
6-month PFS (%)	59%	76%	55%	57%	58%	71%	67%	57%	54%
95% CI	57·8–60·2	73·0–78·6	52·7–57·4	47·8–65·7	44·3–71·3	59·4–82·3	60·7–73·8	55·0–58·8	50·8–57·2
12-month PFS (%)	42%	56%	39%	42%	45%	54%	54%	38%	38%
95% CI	40·3–42·8	52·6–59·5	36·4–41·5	32·3–50·9	30·5–58·5	40·2–68·4	46·8–61·3	36·2–40·2	34·6–41·3
Second-line treatment									
Overall response (available data)	3325	441	762	59	34	26	115	1361	482
Overall response (%)	13%	31%	8%	9%	12%	4%	35%	9%	9%
95% CI	11·6–13·8	26·5–35·1	5·8–9·6	1·4–15·6	0·9–22·6	0–11·2	26·1–43·5	7·8–10·9	6·7–11·9
PFS (available data)	4029	518	1017	71	35	30	125	1585	598
PFS (months), median	3·1	5·6	2·5	3·1	4·5	4·6	9·3	2·9	3·0
95% CI	3·0–3·3	4·3–6·6	2·3–2·9	1·4–6·1	2·4–6·6	1·5–9·0	6·7–12·0	2·7–3·2	2·8–3·6
6-month PFS (%)	36%	48%	33%	41%	43%	36%	60%	34%	34%
95% CI	34·7–38·0	43·5–53·1	29·5–36·0	28·7–53·9	24·6–60·4	15·6–56·4	50·4–69·0	30·9–36·1	29·4–37·9
12-month PFS (%)	24%	33%	25%	18%	23%	23%	41%	20%	23%
95% CI	22·1–25·5	27·4–37·8	21·3–27·9	6·2–30·1	5·3–40·0	3·3–42·9	30·2–51·9	17·2–22·4	19·1–27·8
Overall survival (available data)	7821	1017	1966	132	56	72	214	3131	1137
Overall survival (months), median	13·8	NR	11·7	13·8	NR	13·7	20·7	12·2	11·8
95% CI	13·3–14·4	NR	10·6–13·1	8·5–21·9	NR	8·7–NR	17·0–NR	11·5–13·0	10·1–13·5
6-month OS (%)	70%	84%	65%	68%	81%	74%	80%	68%	68%
95% CI	68·9–71·0	81·9–86·6	62·2–66·7	59·5–76·2	69·7–91·5	62·9–85·0	74·7–85·7	66·6–70·2	64·7–70·6
12-month OS (%)	54%	73%	49%	52%	61%	57%	70%	50%	49%
95% CI	52·7–55·3	69·8–75·9	46·6–51·9	42·4–61·6	47·0–75·7	43·4–71·4	63·6–76·8	48·2–52·4	45·7–52·7

Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2*, or *PIK3CA* mutation or *ALK* rearrangement. PFS=progression-free survival. NR=not reached. *Cases with at least one unknown result after the assessment of the six genes.

Table 5: **Outcomes stratified by line of therapy and molecular alteration**

more samples were analysed in 927 (5%) patients and 41 (<1%) patients, respectively. The median interval between tissue specimen collection and the initiation of molecular analysis was 8 days (IQR 4–16), and the median interval from the initiation of molecular analysis to the final written report of the analysis (the results for *EGFR* mutation if the analyses were done sequentially) was 11 days (7–16).

A genetic alteration was recorded in about 50% of the analyses: *EGFR* mutations were reported in 1947 (11%) of 17706 analyses for which data were available, *HER2* mutations in 98 (1%) of 11723, *KRAS* mutations in 4894 (29%) of 17001, *BRAF* mutations in 262 (2%) of 13906, and *PIK3CA* mutations in 252 (2%) of 10678; *ALK* rearrangements were reported in 388 (5%) of 8134 analyses (table 2, table 3, and appendix pp 3–5). Figure 2 shows the frequencies of the molecular alterations in these six genes, overall and for three specific subgroups (ie, adenocarcinoma, women, and never smokers). The screen failure rates varied from 1% to 4%. 170 (1%) of 18679 samples had two molecular alterations; three (<1%) samples had three or more molecular alterations (appendix p 6).

Of the 8448 patients with known data about their treatment and, specifically, the 8147 patients with known data about whether their molecular profile results were considered when deciding the treatment (yes *vs* no), results of the routine molecular profiling were considered when planning the first-line therapeutic strategy for 4176 (51%) of 8147 patients. Conversely, for 836 (23%) of 3707 patients who had known data for the reason to plan the treatment strategy without consideration of these results, the too-long turnaround time motivated the local multidisciplinary tumour board's decision to start before getting these results. The frequencies of genetic alterations in the patients who were managed without considering the results of the molecular analyses (data not shown) were similar to those in the total population of patients with known data about their treatment, apart from *EGFR* mutations (443 [11%] patients had *EGFR* mutations out of 3971 patients managed without considering the results of

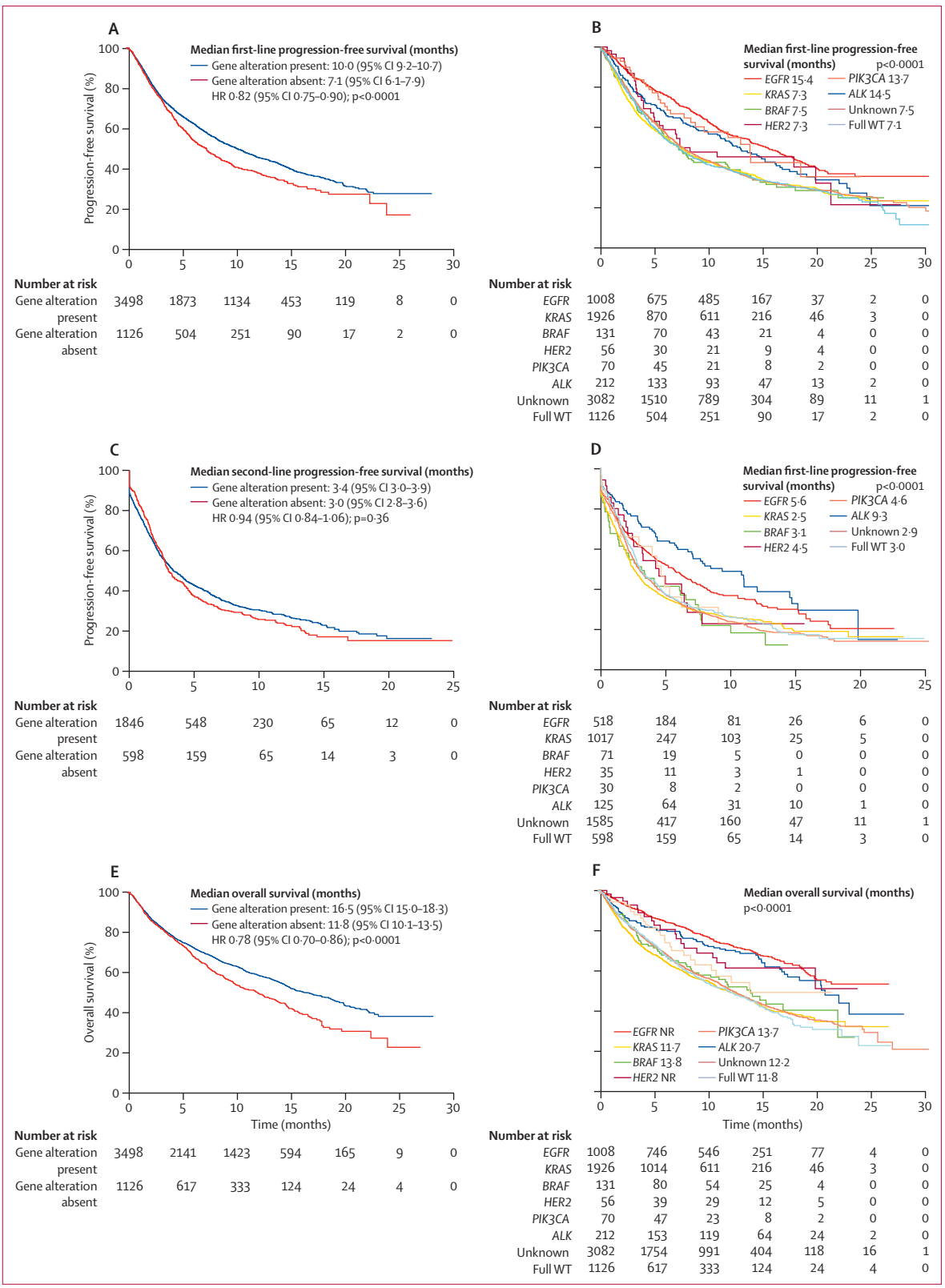

***Figure 3*: Outcomes of the 17 664 patients undergoing molecular analyses**

(A) First-line progression-free survival for patients with and without genetic alteration; (B) first-line progression-free survival stratified by molecular profile; (C) second-line progression-free survival for patients with and without a genetic alteration; (D) second-line progression-free survival stratified by molecular profile; (E) overall survival of patients with and without a genetic molecular alteration; and (F) overall survival stratified by molecular profile. Unknown in panels B, D, and F represents the cases with at least one unknown result after assessment of the six genes. Full WT=patients with an established molecular profile without an *EGFR*, *KRAS*, *BRAF*, *HER2*, or *PIK3CA* mutation or *ALK* rearrangement. HR=hazard ratio.

the molecular analyses *vs* 1128 [13%] with *EGFR* mutations out of 8448 patients in the total population, respectively; p=0·003). The types of first-line and second-line treatments are shown in table 4. Because treatment-resistant *EGFR* Thr790Met mutations were systematically found concomitantly with an activating *EGFR* mutation, the frequencies of these two mutations are reported jointly. Radiotherapy was given to 796 (10%) of 7909 patients to improve local thoracic control and to 2030 (26%) of 7909 patients as a palliative treatment.

The median duration of follow-up at the time of analysis was 24·9 months (95% CI 24·8–25·0). Table 5 shows the outcomes of patients for whom data were available (see appendix pp 7–8 for patients with advanced stage cancer only). The presence of a genetic alteration was associated with a significantly higher proportion of patients achieving an overall response in first-line treatment (37% [95% CI 34·7–38·2] for presence of a genetic alteration *vs* 33% [29·5–35·6] for absence of a genetic alteration; p=0·03) and in second-line treatment (17% [15·0–18·8] *vs* 9% [6·7–11·9]; p<0·0001) compared with absence of a genetic alteration. The presence of a genetic alteration was also associated with significantly longer first-line progression-free survival and overall survival compared with the absence of a genetic alteration (figure 3 and appendix p 14).

When patients carrying an *EGFR* mutation were excluded from the analysis, the presence of a genetic alteration resulted in a non-significant difference in the proportion of patients achieving an overall response in first-line treatment (31% [95% CI 29·4–33·5] *vs* 33% [29·5–35·7]; p=0·54) or second-line treatment (11% [9·1–12·8] *vs* 9% [6·7–11·9]; p=0·34), and a non-significant difference in overall survival (13·3 months [95% CI 12·1–14·3] *vs* 11·8 months [10·1–13·4]; p=0·37) compared with absence of a genetic alteration. Cox multivariate analysis confirmed that *ALK* rearrangements (HR 0·70, 95% CI 0·5–0·9), *EGFR* mutations (HR 0·53, 0·4–0·6), and *HER2* mutations (HR 0·60, 95% CI 0·4–1·0) had a favourable effect on prognosis (appendix pp 9–10).

Discussion

One challenge of personalised medicine for patients with cancer is the provision of an assessment of molecular alterations that are related to the management of their disease. The results of our study show the success of a nationwide programme in this setting. The molecular screening done in the programme, which involved nearly 20 000 patients with advanced NSCLC per year, enabled the detection (with an acceptable turnaround time) of at least one potentially actionable molecular alteration in almost 50% of the analyses and affected the treatment decisions for 51% of patients. When a genetic alteration was detected, median overall survival was 4·7 months longer than when a genetic alteration was absent, suggesting a possible prognostic advantage or a major change in management for these patients, or both.

The successful implementation of molecular profiling of patients with lung cancer at a single institution or in a consortium of institutions has been reported previously.[8–11] However, the number of examined patients was frequently small, with the largest multi-institutional study in developed countries—the Lung Cancer Mutation Consortium (LCMC) initiative—including 1007 patients. Our study follows LCMC but aims to broaden the number of centres able to provide molecular profiling, with a clear ambition of a nationwide approach. Because about 39 000 new cases of lung cancer (of any stage and histology) are reported every year in France,[26] 18 000 patients with advanced non-squamous NSCLC are expected to be screened for *EGFR* mutations and *ALK* rearrangements according to current guidelines.[23–25] Our results not only involved the largest sample (17 664 patients), but were also unlikely to have been affected by patient selection at a specific institution or participation in a given clinical trial or research programme.[27]

The frequency of some molecular alterations might seem to be lower than previously reported (eg, 11% of *EGFR* mutations compared with 17% for LCMC in the USA),[9] but our results most likely reflect the characteristics of an unselected population, particularly in developed countries. To the best of our knowledge, no other study at a nationwide level has been published. Therefore, our results provide solid evidence for clinical trials or routine programmes of molecular screening in patients with lung cancer, especially the *HER2, BRAF*, and *PIK3CA* data, because very rare genetic alterations at these three loci (0·8%, 1·9%, and 2·3%, respectively) could represent a large population in view of the high incidence of lung cancer worldwide.

Our study attempted to collect data from a common cancer population from daily practice during a 1-year period. On the basis of this objective, a fairly simple case report form was selected and more than 3800 treating physicians were approached for the study. This design implied the acceptance of some degree of missing data, which was a drawback of the study. Another limitation of the study was related to the molecular alterations that were screened. Several potential actionable targets for lung cancer have been described in recent years, and some of these targets were not included in the programme (including some of the known genetic alterations occurring at the time of disease progression). The molecular alterations screened in this programme were selected in 2009 and this strategy was largely a success, because the data for *BRAF* and *HER2* targeting are now robust.[6,7] However, other emerging biomarkers, such as *KRAS* mutations, remained uncertain.[28] *PIK3CA* mutations are no longer routinely assessed, whereas *ROS1* assessment is now part of routine molecular testing at certified molecular genetics centres in France.[29] More importantly, our results do not suggest an improvement in the inclusion rate of clinical trials. Only

3% of the patients in the national database were enrolled in clinical trials while being assessed for molecular alterations that were actionable only with experimental compounds in clinical development; therefore, this objective of the national programme remains to be met.[30]

In conclusion, this national programme broadly (and exhaustively) screened patients with lung cancer for genetic alterations in six genes, including four emerging genetic alterations, to identify actionable targets that improved the survival of about 50% of patients, although at a non-negligible financial cost.[16] Therefore, our results should encourage all continuing worldwide initiatives to provide patients with cancer with access to personalised treatment, and provide robust information to inform these initiatives.

Contributors

FB, JMa, DD, FM, BM, QT, JC, J-CSo, and GZ designed the study; all authors participated in data acquisition; FB, JMa, FM, QT, PM, ALa, JC, J-CSo, and GZ analysed and interpreted the data; FB, JMa, FM, QT, PM, ALa, JC, J-CSo, and GZ wrote the manuscript; all authors approved the final version.

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