

Patients with non-small-cell lung cancer harbouring a *BRAF* mutation: a multicentre study exploring clinical characteristics, management, and outcomes in a real-life setting: EXPLORE GFPC 02-14

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ABSTRACT

Background Mutations in *BRAF* are rare oncogene mutations, found in 2% of non-small-cell lung cancers (NSCLCs). Little information is available about the management of patients with *BRAF*-mutated NSCLC, except for those included in clinical trials. We undertook the present study to assess the clinical characteristics, management, and outcomes of those patients in a real-life setting.

Methods This retrospective multicentre observational study included all patients with *BRAF*-mutated NSCLC diagnosed between January 2012 and December 2014.

Results Patients ($n = 59$) from 24 centres were included: 57.6% men; mean age: 64.5 ± 14.5 years; 82% with a performance status of 0–1 at diagnosis; smoking status: 40.3% current, 32.6% former; 93% with adenocarcinoma histology; 75% stage IV; 78% with V600E mutations; 2 with *EGFR* and 2 with *ALK* co-mutations. Of the stage IV patients, 79% received first-line therapy (14.2% anti-*BRAF*), and 48% received second-line treatment (23.8% anti-*BRAF*). Response rate and progression-free survival were, respectively, 51.7% and 8.7 months [95% confidence interval (CI): 6.4 months to 15.2 months] for first-line therapy and 35.3% and 4.1 months (95% CI: 2 months to 10.9 months) for second-line treatments. The 2-year overall survival was 58.5% (95% CI: 45.8% to 74.8%). Outcomes in patients with stage IV NSCLC harbouring *BRAF* V600E mutations ($n = 32$) did not differ significantly from those of patients with other *BRAF* mutations.

Conclusions In this real-world analysis, most NSCLC patients with a *BRAF* mutation were men and current or former smokers. Survival appears to be better in these *BRAF*-mutated patients than in NSCLC patients without an oncogenic driver.

Key Words Lung adenocarcinoma, V600E, *BRAF* mutation, prognosis, management

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INTRODUCTION

Most lung cancers (85%–90%) are non-small-cell lung cancer (NSCLC)⁰. The discovery of common oncogenic drivers such as *EGFR* mutations, *EML-ALK* fusions, and *ROS1* rearrangements have led to the development of

new accurate and effective targeted therapies, which have radically improved the clinical outcomes of patients harbouring those driver mutations¹. In addition, genomic analyses have identified other potential targets for lung cancer treatment, including *MET* mutations and activating mutations in *KRAS*, *HER2*, and *BRAF*, among others^{2,3}.

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Mutations in *BRAF* constitutively activate the MAPK (mitogen-activated protein kinase) pathway, generating constant stimuli leading to cell growth and proliferation, and resistance to negative modulatory feedback signals⁴⁻⁷. In fact, *BRAF* activating mutations are responsible for structural modifications of its protein, keeping it in a permanently activated state that results in continuous activation of MEK and ERK⁷. Not all *BRAF* mutations induce MAPK pathway activation; some of them render the *BRAF* kinase inactive or dysfunctional^{7,8}.

The most frequent activating *BRAF* mutation, V600E, results in basal kinase activity that, compared with the activity of wild-type *BRAF*, is increased by a factor of 12.5. Other *BRAF* mutations have been described in NSCLC, but whether all of them are oncogenic drivers is not known⁹. Notably, 2% of NSCLC patients harbour a *BRAF* mutation^{3,10}. Specific inhibitors for mutated *BRAF* (dabrafenib, vemurafenib) were developed and initially used to treat patients with melanoma; more recently, they have been used for patients with NSCLC^{11,12}.

The prognostic significance of *BRAF* mutations is uncertain¹³⁻¹⁷. At least two series of patients harbouring *BRAF* mutations reported overall survival (OS) and other outcomes similar to those in the general population of patients with NSCLC. Cardarella *et al.*² observed no difference in the prognoses of patients with mutated and wild-type *BRAF* who received platinum-based chemotherapy. Considering the small number of patients included in those studies, the prognostic value of *BRAF* mutation remains unclear. Indeed, clinical findings for patients with *BRAF*-mutated disease are limited and often derived from patients included in clinical trials^{11,12}.

The objective of the present retrospective multicentre observational study was to describe, in a real-life setting, the characteristics of patients with *BRAF*-mutated NSCLC, and the effects on OS and progression-free survival (PFS) of therapeutic strategies for patients with identified *BRAF* mutations.

METHODS

For the period from January 2012 to December 2014, physicians at French medical centres were asked to provide anonymized data from the medical records of patients at least 18 years of age diagnosed with a new *BRAF*-mutated NSCLC. In France, a network of regional molecular genetics centres performs molecular analyses of *BRAF* on a routine basis. This reflex testing was funded by the public health ministry for all patients with nonsquamous advanced NSCLC and also for non-smoking patients with squamous NSCLC. 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 for mutations in *EGFR* (exons 18–21), *HER2* (exon 20), *BRAF* (exon 15), *KRAS* (exon 2), and *PIK3CA* (exons 9 and 20). A certified break-apart fluorescence *in situ* hybridization assay was used to assess for *ALK* rearrangements.

Patient demographics and clinical characteristics at NSCLC diagnosis—including age, sex, smoking history [never smoked, current smoker, former smoker (that is, had smoked for at least 1 year and quit at any time before the

diagnosis)], cancer histology, the specific *BRAF* mutation, and presence of metastatic disease—were collected from patient charts. The location of metastases was assessed at the last follow-up. Patient treatment information was collected starting at diagnosis, including treatment sequence, type of therapy, and dates of treatment initiation and discontinuation. Clinical outcomes were also noted, including date of death (if applicable), and dates of any clinician-defined progression based on an increase of lesion size or appearance of new lesions. Overall survival was measured from diagnosis to death. Clinician-defined PFS was measured from the start of first-line and second-line treatment. A secondary analysis compared the OS and PFS of patients with and without the V600E mutation.

Patient characteristics and treatment information were analyzed descriptively. The Kaplan–Meier method was used to estimate median treatment duration, OS, and clinician-defined PFS. To assess OS, patients were censored at last follow-up. For the PFS analysis, patients who died were considered to have progressed. All analyses were conducted using the SAS software application (version 9.3; SAS Institute, Cary, NC, U.S.A.).

The study was approved by the internal review board of Saint Etienne (IRBN I02016/Chuste) and received Centre for Innovative Technologies in Rehabilitation Settings authorization 914146. In accordance with French legislation, verbal consent was obtained from each patient included in the study. The study complied with the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, the Good Clinical Practice Guidelines, the Declaration of Helsinki, and local laws.

RESULTS

Physicians from 24 medical centres extracted information for 59 patients (57.6% men; mean age: 64.5 years; 72.9% current or former smokers; Table 1). Almost all patients (93.1%) had adenocarcinoma histology, and 74% had the *BRAF* V600E mutation. Co-mutations were present in 4 patients: 2 *EGFR* mutations (exons 18 and 21) and 2 *ALK* translocations. A personal history of cancer was present in 20.3% of the patients, and a family history, in 31%. At diagnosis, 82.4% of the patients had a good performance status (0–1), and 77% had metastatic disease, with few metastatic sites (1 or 2, 85%). The most common metastatic sites were lung, brain, and liver. Presenting symptoms, demographics, and tumour characteristics did not differ between patients with and without the *BRAF* V600E mutation (Table 1).

First-line therapy after the diagnosis of locally advanced or metastatic NSCLC was chemotherapy for 62% of the patients. The remaining patients received *BRAF*-targeted therapy (14.2%) or best supportive cares (23.8%). The overall response rates to first-line therapy and disease control were, respectively, 51.7% and 81.7%, with no significant difference between the patients with and without the *BRAF* V600E mutation: 45% and 60% for first-line response and 81.8% and 80% for disease control respectively. The overall response and disease control rates were, respectively, 75% and 87% for patients treated with *BRAF*-targeted therapy (vemurafenib in all cases) and 45.9% and 78% for patients treated with first-line chemotherapy.

TABLE I Baseline characteristics of patients with non-small-cell lung cancer according to *BRAF*V600E mutation status

Characteristic	<i>BRAF</i> V600E mutation status		
	All	Yes	No
Patients (n)	59 ^a	46	11
Mean age (years)	64.5±14.5	65.3±10.6	61.1±11
Sex (% men)	56.6	63	45.4
Nonsmokers (%)	28	27.3	18.2
PS 0–1 (%)	82.4	82.5	77.8
Weight loss <5% (%)	83.9	86.0	81.8
Adenocarcinoma (%)	93.1	95	90
Previous cancer (%)	20.3	26	0
Family history of cancer (%)	31	28	36
Stage IV (%)	75	75	81.8
Symptomatic	84.5	80.0	100
Main symptoms (%)			
Respiratory	75	80.6	63.6
Pain	27	31.4	18.2
Neurologic	13.7	8.3	27.3
Others	24.5	25.0	18.2

^a Data missing for 2 patients.

Median time to clinician-defined PFS after first-line therapy start was 8.7 months [95% confidence interval (CI): 6.4 months to 15.2 months]; 8.2 months (95% CI: 5.9 months to 19.0 months) for carriers of the *BRAF*V600E-mutation, and 8.7 months (95% CI: 6 months to 18.7 months) for the non-carriers. Patients treated with *BRAF*-targeted therapy had a PFS of 9.2 months (95% CI: 6.4 months to 22.2 months).

The type of progression after first-line therapy had no specific characteristics, being mainly increased size of existing lesions (78.6%) and the appearance of new lesions, but with no particular metastatic sites. Of new biopsies obtained in 8 patients at first progression, 5 resulted in analyzable material, and only 2 had a therapeutic impact (1 patient underwent histologic modification to small-cell lung cancer, and in 1 patient, a *KRAS* mutation not present at NSCLC diagnosis appeared).

Among patients with locally advanced or metastatic NSCLC who discontinued first-line chemotherapy, 48% received second-line treatment: 66.7% chemotherapy, 23.8% anti-*BRAF* therapy, and 9.5% best supportive care. The response rate was 35.3%. Median time to clinician-defined PFS for second-line therapy was 4.1 months (95% CI: 2 months to 10.9 months). For the patients overall, 2-year OS was 58.5% (95% CI: 45.8% to 74.8%), with no significant difference observed between patients with and without the *BRAF*V600E mutation: 58.4% (95% CI: 44.5% to 76.7%) and 70.7% (95% CI: 47.6% to 100%) respectively.

DISCUSSION

The results of the present study reveal that PFS after first- and second-line treatment for patients with *BRAF*-mutated

NSCLC, managed in a real-life setting, was 8.7 months and 4.8 months respectively, with a 58.5% 2-year OS overall, and no significant outcome differences for stage IV patients with *BRAF* V600E mutations compared with other *BRAF* mutations. Unlike their counterparts with other oncogene mutations (*EGFR* or *ALK*), patients with NSCLC harbouring *BRAF* mutations appear to have a clinical profile similar to that of patients without such mutations: no sex predominance, a high percentage of smokers, and comparable age at diagnosis. Histology was almost always adenocarcinoma, but in France, testing for squamous cell NSCLC is not recommended. Patients with non-V600E-mutated *BRAF* were smokers (82%), which accords with previously reported results^{14,15}. Our observations also confirmed that non-V600E *BRAF* mutations are more common in patients with lung cancer than in those with melanoma. The rate we observed is consistent with the 38%–47% range for non-V600E *BRAF* mutations in patients with NSCLC reported previously^{2,7,10}.

In contrast to initial reports^{15,16}, *BRAF* mutation in our cohort was not strictly exclusive of other oncogene mutations. Co-mutations were found in 4 patients. That finding is now well described in the literature. A recent Asian publication reported 5 patients with non-V600E *BRAF* mutations who had concomitant *EGFR* mutations. Brustugun *et al.*¹⁷ described *BRAF*V600E and *KRAS* mutations in a heavy smoker. And as occurred in one of our patients, a *KRAS* mutation at the time of progression has been reported in a patient with a *BRAF*-mutated tumour¹⁸. Inhibition of *BRAF* V600E-mutated kinase can activate feedback, leading to increased activity of, and dependence on, *RAS*^{19,20}.

In our study, first line treatments were chemotherapies, *BRAF*-targeted therapy, and best supportive care in 62%, 14.2%, and 21.8% of patients respectively, generating a response rate of 51.7%. Those treatment percentages are consistent with percentages reported in the lung cancer literature^{2,13}. Paik *et al.*¹³ observed a 40% response rate to chemotherapy in 10 patients with NSCLC harbouring mutated *BRAF*, which is similar to rates obtained in contemporary phase III trials evaluating chemotherapy. In a retrospective multicentre cohort study in Europe of 35 patients with advanced *BRAF*-mutated NSCLC, 86% of the patients received first-line chemotherapy, with the OS being 25.3 months for V600E carriers and 11.8 months for non-carriers of V600E. A *BRAF* inhibitor was given to 31 patients, and of those, 4 received a second inhibitor. The overall response rate with anti-*BRAF* therapy was 53%, and the disease control rate was 85%. Median PFS with anti-*BRAF* therapy was 5.0 months, and OS was 10.8 months²¹. Those durations accord well with the durations of response observed in our study. We found no response rate or disease control differences between patients with and without a *BRAF*V600E mutation, but the samples sizes in both studies were small, precluding definitive conclusions. In a recent nonrandomized multicentre open-label phase II study¹¹ of 84 patients with metastatic *BRAF*V600E-mutated NSCLC who received oral dabrafenib (150 mg twice daily), the investigator-assessed overall response rate was 33% (95% CI: 23% to 45%). In another multicentre nonrandomized phase II open-label study, a dabrafenib–trametinib combination tested in 59 previously treated patients with metastatic stage IV *BRAF* V600E-mutated NSCLC, with documented tumour progression

after at least 1 prior platinum-based chemotherapy, was even more promising¹²: the investigator-assessed overall response rate reached 63.2% (95% CI: 49.3% to 75.6%). Tolerance of that combination seemed acceptable.

In our series, the 2-year OS for all-stage patients with BRAF-mutated NSCLC was 58%. That rate is consistent with the findings of Brustugun *et al.*¹⁷, who reported a median OS of 23.2 months in a similar population. It is also consistent with the results of the BIOMARQUEURS-France studies³ and with Paik *et al.*¹³, who described 57% OS at 2 years.

The prognostic role of BRAF mutations—and particularly the significance of the non-V600E mutations—has not been clearly established. In our analysis, survival was not different whether patients had the V600E BRAF mutation or another BRAF mutation. Authors of a previous publication reporting a surgical series found that a poorer prognosis was associated with NSCLC having the BRAF V600E mutation than with NSCLC having wild-type BRAF¹⁴. Other authors^{15–17} found that 3-year OS rates were better in patients with V600E mutations than in patients with non-V600E mutations, but that difference was not found by Marchetti *et al.*¹⁴, whose multivariate analyses indicated that the V600E mutation was a negative prognostic factor, significantly associated with shorter OS.

The limitations of the present study are its retrospective design and the fact that management of this patient group has evolved rapidly, especially with respect to targeted therapies. It was, nonetheless, a multicentre study that included all consecutive patients managed at each participating centre, providing information about the real-life management of patients with BRAF-mutated NSCLC.

CONCLUSIONS

In this study, patients harbouring BRAF mutations did not have clinical characteristics that particularly differed from those for patients without oncogenic addiction. We did not observe notable differences between patients with V600E mutations and those with other BRAF mutations. Prognosis for these patients seems to be better than that for patients without oncogenic addiction. Targeted therapies, especially those targeting the V600E mutations, will probably markedly modify prognosis for these patients.

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CONFLICT OF INTEREST DISCLOSURES

In the past 5 years, JBA, AV, and CC received fees for attending scientific meetings, speaking, organizing research, or consulting from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline,

Roche, Sanofi Aventis, Bristol–Myers Squibb, Merck Sharp and Dohme, Lilly, Novartis, and Amgen. The other authors declare that they have no conflicts to disclose.

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