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Original Research

Clinical outcomes of non–small-cell lung cancer patients with *BRAF* mutations: results from the French Cooperative Thoracic Intergroup biomarkers France study

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Abstract ***Introduction:*** Patients with stage IV non–small-cell lung cancer (NSCLC) and *BRAF* V600 mutations may benefit from targeted therapies. Chemotherapy outcomes are little known in this population.
Methods: The French Cooperative Thoracic Intergroup (IFCT) Biomarkers France study was a national prospective cohort study aiming to describe the molecular characteristics and clinical outcome of all consecutive NSCLC patients (N = 17,664) screened for molecular alterations. We used this data set to set up a case–control analysis. Cases had stage IV *BRAF*-mutated (*BRAF*-MT) NSCLC, whereas controls had NSCLC that was wild-type for *EGFR*, *KRAS*, *HER2*, *BRAF*, *PIK3CA* and *ALK*. Each case was matched for sex, age at diagnosis and smoking status to two controls randomly selected.
Results: Overall, 83 cases with *BRAF* mutant disease (66.3% V600E) were matched to 166 controls. Five cases received tyrosine kinase inhibition in the first-line and 16 in the second-line. All others were treated with standard chemotherapy. There was no significant difference in first-line and second-line progression-free survival (PFS) between the groups, as well as in the disease control rate, *BRAF* mutation was not found to be prognostic of overall survival. We found no significant difference in outcome between the treatment types used in first-line or second-line in patients with *BRAF*-MT disease compared with controls nor between *BRAF* V600E or non-V600E compared with controls.
Conclusions: *BRAF* mutation is not a strong prognostic factor in NSCLC. Although taxan-based therapy shows poorest PFS in first-line, no chemotherapy regimen was associated with prognosis.

1. Introduction

Mutation in *BRAF* exon 15 occurs in 2% of non–small-cell lung cancers (NSCLC) in France [1]. *BRAF* mutations are usually categorised into V600E (53–59%, depending on the series) and non-V600E substitutions [2,3], all of which almost exclusively detected in adenocarcinoma. V600E substitutions are more frequent among women and never-smokers. In addition, V600E appears to have a slightly better prognosis than non-V600E.

In 2011–2012, the French National Cancer Institute sponsored a large trial conducted by the French Cooperative Thoracic Intergroup (IFCT) aiming to describe molecular characteristics and associated outcomes in all NSCLC patients routinely screened for molecular alterations [1].

Planchard *et al.* showed that *BRAF* V600E mutations were targetable, and recently, a combination therapy with dabrafenib and trametinib was approved in the first-line for *BRAF* V600E NSCLC [4,5].

However, little is known about the optimal chemotherapy treatment for patient with *BRAF*-mutated (MT) disease and outcomes of *BRAF* mutation types. Of note, patients with *BRAF* non-V600E are not eligible for the abovementioned combination therapy, and there are currently no other targeted therapies for *BRAF* NSCLC. Thus, we availed of the large IFCT Biomarkers France (BMF) database to investigate the prognostic impact of *BRAF* mutations (and subtypes) overall and of different chemotherapy regimens. To that end, we designed a case-control analysis with *BRAF*-MT cases matched to wild-type (WT) controls within the IFCT BMF data set.

2. Materials and methods

2.1. The IFCT biomarkers France study

The IFCT BMF study was a national prospective cohort study conducted between April 2012 and April 2013. The main results and overall methodology have been previously reported [1]. Briefly, it aimed to describe the molecular characteristics and clinical outcome of all consecutive NSCLC patients routinely screened for molecular alterations. This molecular screening, which is

mandatory for advanced non-squamous NSCLC, was solely at the discretion of the treating physician [6]. In the end, 18,679 results from 17,664 NSCLC patients were included in the final database.

The analyses of *ALK* rearrangements and *EGFR* (exons 18–21), *HER2* (exon 20), *KRAS* (exon 2), *BRAF* (exon 15) and *PIK3CA* (exons 10 and 21) mutations were performed at 28 certified molecular genetics centres. The methodology for these analyses and the results of the prospective cross-validation quality assessment studies have been previously reported [7,8]. Full WT patients were defined as those without alterations in any of the genes screened, *i.e. EGFR*, *KRAS*, *HER2*, *BRAF*, *PIK3CA* and *ALK*.

The molecular test and histological results were sent directly to the IFCT by the certified molecular genetics centres. Each patient's treating physician (n = 3831) was simultaneously provided with secure access to their patient's data. Data were collected on sex; ethnicity (Asian versus non-Asian); smoking status (never, former or current smoker); past family history of cancer; Eastern Cooperative Oncology Group performance status (0–1 versus 2 or more); tumour-node-metastasis stage (7th, edition [9]) and pathological diagnosis (according to the 2011 IASLC/ATS/ERS classification [10]). The treatment type (first-line and second-line) and outcomes (overall response rate assessed by the treating physician, date(s) of progression and survival status)

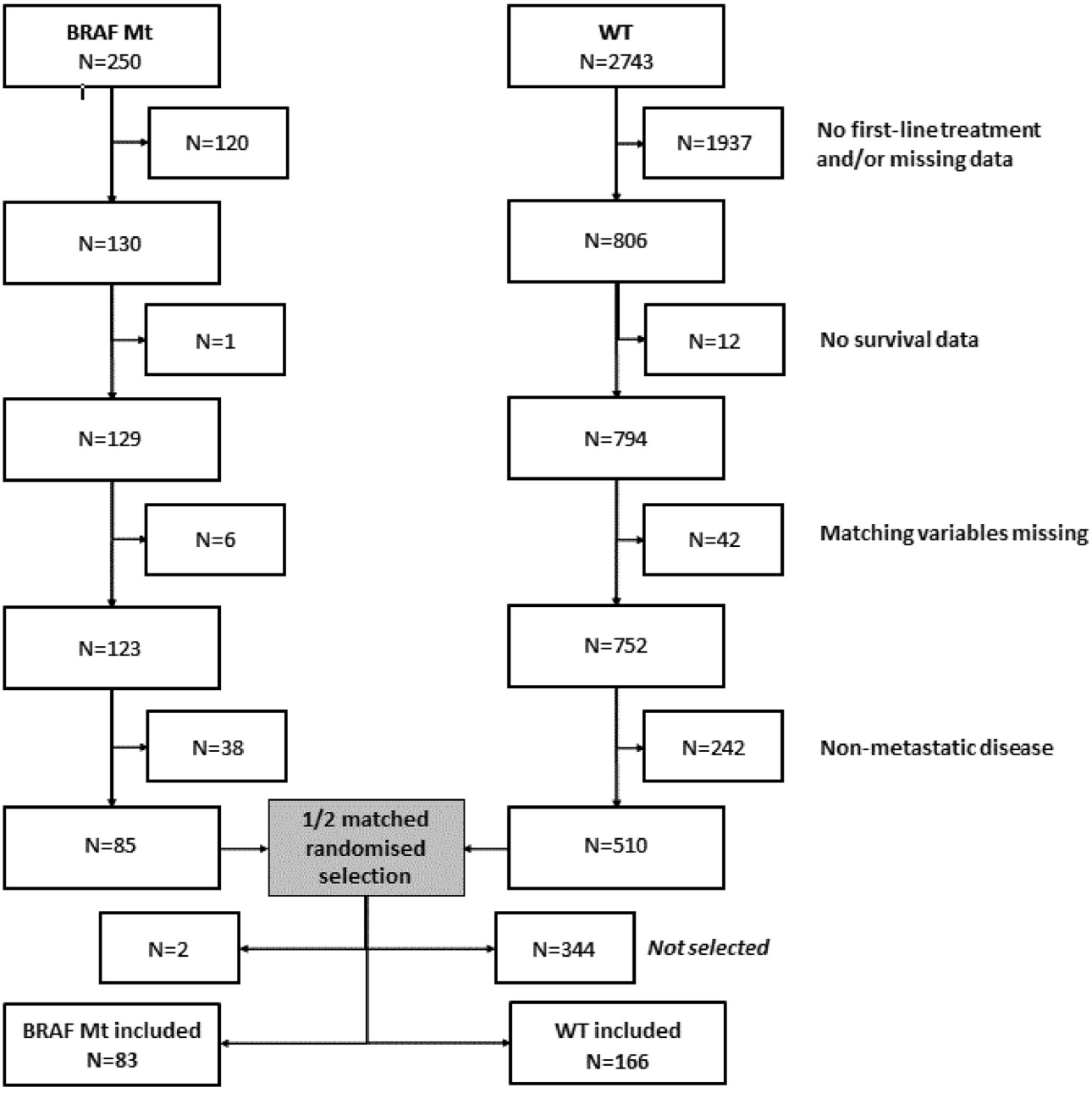

Fig. 1. Flowchart of the study. WT, wild-type.

Table 1
Main characteristics of cases and controls.

Variable	Category	BRAF-MT		WT		p value
		N = 83	%	N = 166	%	
Sex	Male	51	61.4%	102	61.4%	1.00
	Female	32	38.6%	64	38.6%	
Age	Mean (SD)	62.99	11.09	62.93	11.02	0.92
	≥65 years	33	39.8%	68	41.0%	0.85
Asian ethnicity	Yes	0	0.0%	2	1.3%	1.00
	Missing	10	11.8%	13	7.8%	
Smoking status	Current/former	67	80.7%	134	80.7%	1.00
	Never	16	19.3%	32	19.3%	
WHO PS	0	16	21.3%	36	22.4%	0.32
	1	34	45.3%	81	50.3%	
	2	22	29.3%	31	19.3%	
	3	3	4.0%	8	5.0%	
	4	0	0.0%	5	3.1%	
	Missing	8	9.4%	5	3.0%	
Personal history of cancer	Yes	10	12.0%	25	15.1%	0.52
Family history of cancer	Yes	15	19.0%	18	11.8%	0.34
	No	40	50.6%	84	55.3%	
	Unknown	24	30.4%	50	32.9%	
	Missing	4	4.7%	14	8.4%	
Histology	Squamous	1	1.2%	8	4.8%	0.10
	Adenocarcinoma	72	86.7%	122	73.5%	
	Large cell	2	2.4%	12	7.2%	
	Other	8	9.6%	24	14.5%	
Sample origin	Fibroscopy	29	34.9%	57	34.3%	0.79
	Surgery	17	20.5%	27	16.3%	
	TTNB	18	21.7%	36	21.7%	
	Other	19	22.9%	46	27.7%	
Concomitant mutations	EGFR	3	3.6%	–	–	–
	KRAS	6	7.2%	–	–	
	ALK	1	1.2%	–	–	
	EGFR + KRAS	1	1.2%	–	–	
First-line treatment	Pemetrexed	49	59.0%	90	54.2%	0.52
	Taxane	20	24.1%	44	26.5%	
	Vinorelbine	3	3.6%	13	7.8%	
	TKI	5	6.0%	3	1.8%	
	Gemcitabine	4	4.8%	9	5.4%	
	VePesid	1	1.2%	4	2.4%	
	Other	1	1.2%	3	1.8%	
Second-line treatment	Pemetrexed	7	9.5%	14	10.9%	0.35
	Taxane	12	16.2%	22	17.2%	
	Vinorelbine	1	1.4%	2	1.6%	
	TKI	16	21.6%	35	27.3%	
	Gemcitabine	7	9.5%	6	4.7%	
	VePesid	0	0%	0	0%	
	Other	2	2.7%	0	0%	
	No 2nd line treatment	29	39.2%	49	38.3%	
	Missing	9		38		

BRAF-MT, BRAF-mutated; WT, wild-type; WHO PS, World Health Organization's performance status; TTNB, transthoracic needle biopsy; TKI, tyrosine kinase inhibitor; SD, standard deviation; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog.

were collected and reported per investigator review. All data for the current analysis were obtained from the final BMF database.

This study was sponsored by the IFCT and funded by an unrestricted grant from the French National Cancer Institute. The 28 molecular genetics centres sent their results to the IFCT using a specific datasheet for each patient. The data were then recorded and monitored by the IFCT. The authors had full access to the anonymised data and analyses for this report.

2.2. Case and control selection

We performed a case-control analysis within the entire BMF database. Cases and controls were selected among patients with metastatic disease only. Demographic characteristics were recorded, as was available treatment and survival data.

Cases were defined as those with a detected *BRAF* mutation in exon 15. Each case was matched to two controls defined as WT for *KRAS*, *EGFR*, *BRAF*,

Table 2
Main outcomes regarding treatment used in cases and controls.

Outcome	BRAF-MT		Control WT		P
	N	Median [95% CI]	N	Median [95% CI]	
PFS 1	83	5.8 [5.1–7.5]	166	5.4 [4.8–7.2]	0.32
Pemetrexed	49	6.2 [5.3–7.8]	90	5.7 [5.0–8.4]	0.69
Taxane	20	4.2 [2.6–8.7]	44	4.8 [3.2–7.6]	0.67
Other	14	6.4 [1.5-NR]	32	5.3 [2.7–8.4]	0.06
TKI	5	NR	3	2.4 [0.3-4.8]	0.02
Vinorelbine	3	10.3 [1.2-10.3]	13	8.4 [1.5-12.4]	0.94
Gemcitabine	4	6.4 [5.8-15.2]	9	5.3 [2.1-10.1]	0.41
VePesid	1	1.5	4	4.2 [1.8-5.3]	0.045
Other	1	0.39	3	8.5 [1.2-8.5]	0.08
PFS 2	45	6.1 [4.1–14.0]	79	3.7 [2.5–5.5]	0.06
Pemetrexed	7	10.9 [1.7–14.2]	14	5.5 [1.8–7.3]	0.27
Taxane	12	4.6 [1.6–6.0]	22	3.7 [2.1–4.7]	0.74
TKI	16	NR	35	3.6 [2.2–7.7]	0.04
No 2nd line treatment	28	0.7 [0.3–1.5]	45	1.5 [0.8–3.0]	0.56
Other	10	6.1 [2.1-NR]	8	9.0 [4.8–13.2]	0.54
Vinorelbine	1	NR	2	13.2	NA
Gemcitabine	7	6.1 [2.1-NR]	6	4.8 [NR]	0.68
VePesid	0	-	0	-	-
Other	2	2.20	0	-	NA
PFS 1 + 2	45	12.7 [11.1–19.1]	79	10.0 [8.5–11.6]	0.06
Pemetrexed	51	11.9 [9.6–16.9]	78	9.1 [7.5–12.3]	0.17
Taxane	27	11.1 [6.9–16.9]	59	8.6 [7.1–10.6]	0.48
Vinorelbine	4	24.3 [1.2–24.3]	10	12.4 [1.2–14.6]	0.46
Gemcitabine	11	11.4 [6.4–15.2]	13	10.6 [8.7-NR]	0.90
OS	83	13.4 [8.3–17.2]	166	10.2 [8.3–12.7]	0.39
Pemetrexed	49	13.50 [10.1–25.1]	90	10.2 [7.7–17.7]	0.75
Taxane	20	8.5 [3.5–17.9]	44	9.5 [5.2–17.3]	0.89
Other	14	15.2 [1.5-NR]	32	11.8 [4.0–14.4]	0.14
Vinorelbine	3	NR	13	12.4 [1.7-22.8]	0.44
TKI	5	NR	3	2.4 [0.3-11.9]	0.02
Gemcitabine	4	10.8 [6.4-15.2]	9	11.8 [4.0-14.5]	0.89
VePesid	1	1.5	4	4.5 [3.1-NR]	0.045
Other	1	0.39	3	11.8 [1.2-15.9]	0.08

BRAF-MT, BRAF-mutated; WT, wild-type; PFS 1, first-line progression-free survival; PFS 2, second-line progression-free survival; PFS 1 + 2, first- and second-line progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; CI, confidence interval.

HER2, *PIK3CA* and *ALK*. Cases and controls were matched for sex, age at diagnosis (5-year categories) and smoking status (never versus former or current) and randomly selected within the data set.

2.3. Statistics

Proportion comparisons were performed using the chi-square test. Mean comparisons were performed with Student t-test. Survival estimates were computed using the Kaplan–Meier method and compared with the log-rank test. Univariate Cox regression analysis was used to compute hazard ratios for survival. All tests were two-sided, and the significance threshold was set at 5%. Missing values were reported as such.

2.4. Ethics

This analysis was part of the BMF study, with no additional data collected. The BMF study was approved in accordance with French law by a French ethics committee for observational studies (*Comité d'évaluation des protocoles de recherche observationnelle*) on September 28, 2011, by the French advisory committee on information processing in health research (*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé*) on September 22, 2011 and by the French data protection agency (*Commission Nationale Informatique et Liberté*) on December 18, 2011. The study was registered on ClinicalTrials.gov under the ID number NCT01700582. Each clinician identified as a molecular analysis prescriber between April 2012 and April 2013 received written information describing the study protocol and the process for accessing the database. As recommended by the competent authorities, all NSCLC patients included received information from their care centre or referring clinician, which specified that they were legally entitled to apply for complete access to, or the removal of, the data collected about them.

3. Results

3.1. Population

The flow chart of this analysis is presented in Fig. 1. From the entire data set, we analysed 83 out of 250 cases with *BRAF*-MT disease matched to 166 WT controls. The main demographics are displayed in Table 1. As age, sex and smoking status were matching criteria, they were identical in the three groups. Most patients were non-Asian and had a performance status of 0–2. The vast majority had no personal or family history of cancer and had adenocarcinoma. The rate of patients with no second-line treatment was similar in both groups (around 39%).

3.2. Outcome depending on BRAF or WT status

We found no significant difference in first-line progression-free survival (PFS) and overall survival (OS) between cases and controls (Table 2 and Supplementary Fig. 1). Disease control rate (DCR) in the first-line was similar in both groups (62.9% in *BRAF*-MT versus 60.0% in controls; p = 0.61). DCR in the second-line was found to be significantly higher in cases than in controls (48.8% versus 30.0%; p = 0.03 respectively). Median PFS in the second-line (PFS 2) and median PFS in the first plus second lines (PFS 1 + 2) were numerically higher in patients with *BRAF*-MT disease than in controls, although not significantly. On univariate Cox regression, *BRAF*-MT was not found to be a prognostic factor for first-line PFS (hazard ratio [HR] = 0.85 [0.61–1.18]; p = 0.32) or OS (HR = 0.86 [0.61–1.22]; p = 0.39).

Regarding histologic subtypes, we found that PFS 2 and PFS 1 + 2 were significantly increased in patients with adenocarcinoma and *BRAF*-MT as compared with WT-controls (Supplemental Table 1). Outcomes in patients harbouring other alterations than *BRAF* are shown in Supplemental Table 2.

3.3. Comparison of chemotherapy regimens

We found no significant difference in outcome between patients with *BRAF* mutation and controls depending on the type of treatment used in the first or second lines (Table 2).

In the *BRAF*-MT group, the use of taxans in the first-line was associated with decreased first-line PFS (Supplementary Fig. 2). We found no significant prognostic outcomes for other treatments in the *BRAF*-MT group (Table 3).

3.4. BRAF V600E versus non-V600E

Overall, 55 of the 83 (66.3%) cases were found to be harbouring a *BRAF* V600E mutation, and 28 a non-V600E mutation. The main characteristics are shown in Table 4. We found a higher rate of male patients in non-V600E mutations (78.6% versus 52.7% in V600E patients; p = 0.02) and a higher rate of never-smokers in V600E patients (27.3% versus 3.6% in non-V600E; p = 0.01). We observed no significant difference in first-line PFS or OS between these two groups (Supplementary Fig. 3) or compared with controls (Supplementary Fig. 4). We also found no significant or relevant difference in the main outcomes between the chemotherapy drugs used (Table 5 and Supplementary Figs. 5 and 6).

Table 3
Outcomes in BRAF-MT patients regarding the type of chemotherapy used in first-line or second-line.

Outcome in BRAF-MT patients	N	HR	[95% CI]	p value
		All other treatments compiled used as reference		
PFS 1				
Pemetrexed	49	0.80	[0.5–1.4]	0.40
Taxane	20	1.84	[1.02–3.3]	0.04
Other	14	1.41	[0.7–2.9]	0.35
TKI	5	0.29	[0.07-1.2]	0.09
Vinorelbine	3	0.88	[0.2-3.6]	0.85
Gemcitabine	4	0.90	[0.3-2.9]	0.85
VePesid	1	15.52	[1.8-132.9]	0.01
Other	1	-		-
PFS 2				
Pemetrexed	7	0.71	[0.3–1.8]	0.47
Taxane	12	1.21	[0.6–2.4]	0.58
TKI	16	0.20	[0.07–0.6]	0.002
No 2nd line treatment	28	3.30	[1.9–5.8]	<0.001
Other	10	0.58	[0.3–1.2]	0.16
Vinorelbine	1	NA		NA
Gemcitabine	7	0.57	[0.2-1.8]	0.35
VePesid	0	-		-
Other	2	0.77	[0.1-5.6]	0.80
PFS 1 + 2				
Pemetrexed	51	0.60	[0.33–1.11]	0.11
Taxane	27	1.28	[0.71–2.30]	0.42
Vinorelbine	4	0.77	[0.18–3.19]	0.72
Gemcitabine	11	0.93	[0.39–2.20]	0.86
OS				
Pemetrexed	49	0.80	[0.5–1.4]	0.44
Taxane	20	1.70	[0.9–3.1]	0.09
Other	14	1.38	[0.6–3.1]	0.43
Vinorelbine	3	0.48	[0.06-3.5]	0.47
TKI	5	0.18	[0.02-1.3]	0.09
Gemcitabine	4	1.43	[0.4-4.6]	0.55
VePesid	1	26.7	[2.8-257.1]	0.004
Other	1	NA		NA

BRAF-MT, BRAF-mutated; PFS 1, first-line progression-free survival; PFS 2, second-line progression-free survival; PFS 1 + 2, first- and second-line progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; HR, hazard ratio; 95% CI, 95% confidence interval.

4. Discussion

The advent of targeted therapies has dramatically altered the landscape of therapeutic care for lung cancer

Table 4
Characteristics of BRAF V600E and non-V600E Patients.

Variable	Category	BRAF V600E		BRAF non-V600E		p value
		N = 55	%	N = 28	%	
Sex	Male	29	52.7%	22	78.6%	0.02
	Female	26	47.3%	6	21.4%	
Age	Mean (SD)	63.51	11.06%	61.97	11.29%	0.49
	≥65 years	23	41.8%	10	35.7%	0.59
Asian ethnicity	Yes	0	0.0%	0	0.0%	NC
	Missing	6	10.9%	4	14.3%	
Smoking status	Current/former	40	72.7%	27	96.4%	0.01
	Never	15	27.3%	1	3.6%	
WHO PS	0	13	25.5%	3	12.5%	0.07
	1	18	35.3%	16	66.7%	
	2	18	35.3%	4	16.7%	
	3	2	3.9%	1	4.2%	
	4	0	0.0%	0	0.0%	
	Missing	4	7.3%	4	14.3%	
Personal history of cancer	Yes	4	7.3%	6	21.4%	0.08
Family history of cancer	Yes	9	17.3%	6	22.2%	0.52
	No	25	48.1%	15	55.6%	
	Unknown	18	34.6%	6	22.2%	
	Missing	3	5.5%	1	0.6%	
Histology	Squamous	1	1.8%	0	0.0%	1.00
	Adenocarcinoma	48	87.3%	24	85.7%	
	Large cell	1	1.8%	1	3.6%	
	Other	5	9.1%	3	10.7%	
Sample origin	Fibroscopy	21	38.2%	8	28.6%	0.30
	Surgery	8	14.5%	9	32.1%	
	TTNB	13	23.6%	5	17.9%	
	Other	13	23.6%	6	21.4%	
Concomitant mutation	EGFR	1	1.8%	2	7.1%	1.0
	KRAS	0	0%	6	21.4%	
	ALK	1	1.8%	0	0%	
	EGFR + KRAS	1	1.8%	0	0%	
First-line treatment	Pemetrexed	31	56.4%	18	64.3%	0.4
	Taxane	12	21.8%	8	28.6%	
	Vinorelbine	3	5.5%	0	0%	
	TKI	4	7.3%	1	3.6%	
	Gemcitabine	4	7.3%	0	0%	
	VePesid	1	1.8%	0	0%	
	Other	0	0%	1	3.6%	
Second-line treatment	Pemetrexed	5	10.2%	2	8.0%	0.35
	Taxane	6	12.2%	6	24.0%	
	Vinorelbine	1	2.0%	0	0%	
	TKI	14	28.6%	2	8.0%	
	Gemcitabine	4	8.2%	3	12.0%	
	VePesid	0	0%	0	0%	
	Other	1	2.0%	1	4.0%	
	No 2nd line treatment	18	36.7%	11	44.0%	
	Missing	6		3		

WHO PS, World Health Organization's performance status; TTNB, transthoracic needle biopsy; TKI, tyrosine kinase inhibitor; SD, standard deviation.

patients with tumours harbouring oncogenic driver alterations such as *EGFR*, *ALK* and *ROS1*, while patients with *BRAF* V600E MT tumours now also fall under the category of targeted therapy care. Although major clinical benefits have been reported with targeted therapy using BRAF inhibitors alone or in combination with a MEK inhibitor [4,5,11,12], data on this population when treated with standard chemotherapy are limited.

The objective of this French retrospective study was to use the largest national prospective cohort with molecular profiling available to determine prognosis in 83 patients with *BRAF*-MT lung cancer treated with chemotherapy compared with a control group of 166 patients (matched for smoking status, sex and age) WT for a panel of six genes (*EGFR*, *ALK*, *BRAF*, *KRAS*, *HER2* and PIK3CA) [1]. In addition, we compared patients with *BRAF* V600E MT against those with a

Table 5
Main outcomes regarding treatment used in BRAF V600E and non-V600E Cases.

Outcome	BRAF V600E				BRAF non-V600E				P (median survival comparison)
	N	Median survival [95% CI]	HR [95% CI][a]	P (for HR)	N	Median survival [95% CI]	HR [95% CI][a]	P (for HR)	
PFS 1									
Pemetrexed	31	7.5 [4.3–17.2]	0.66 [0.34–1.29]	0.23	18	5.5 [4.3–6.3]	1.04 [0.38–2.80]	0.94	0.06
Taxane	12	4.2 [1.4–9.0]	2.23 [1.04–4.78]	0.04	8	3.2 [1.2–17.9]	1.31 [0.47–3.70]	0.60	0.79
Other	12	6.4 [1.5-NR]	1.17 [0.53–2.58]	0.70	2	NR	0.44 [0.06–3.39]	0.43	0.98
Vinorelbine	3	10.3 [1.2-10.3]	1.05 [0.25-4.45]	0.94	0	–	–	–	NA
TKI	4	21.0 [2.7-NR]	0.45 [0.11-1.90]	0.28	1	NR	NA	NA	0.44
Gemcitabine	4	6.4 [5.8-15.2]	1.03 [0.31-3.39]	0.96	0	–	–	–	NA
VePesid	1	1.5	16.74 [1.74-160.95]	0.01	0	–	–	–	NA
Other	0	–	–	–	1	0.39	NA	NA	NA
PFS 2									
Pemetrexed	5	10.9 [2.4–14.0]	0.71 [0.21–2.34]	0.57	2	8.0 [1.7–14.3]	0.84 [0.19–3.72]	0.82	0.75
Taxane	6	6.0 [0.3–7.5]	1.29 [0.44–3.77]	0.64	6	3.4 [1.6–16.4]	0.90 [0.36–2.49]	0.92	0.75
No 2nd line treatment	18	0.4 [0.1–1.5]	5.02 [2.33–10.84]	<0.0001	10	1.4 [0.0–2.8]	1.83 [0.74–4.49]	0.19	0.39
Other	20	NR	4.76 [1.78–12.73]	0.002	6	6.1 [2.20-NR]	0.49 [0.14–1.70]	0.26	0.37
Vinorelbine	1	NR	NA	NA	0	–	–	–	NA
TKI	14	NR	0.16 [0.05-0.54]	0.003	2	2.8	1.02 [0.13-7.82]	0.99	0.07
Gemcitabine	4	4.4 [2.1-NR]	1.03 [0.24-4.42]	0.97	3	7.2 [6.1-NR]	0.23 [0.03-1.75]	0.16	0.16
VePesid	0	–	–	–	0	–	–	–	NA
Other	1	NR	NA	NA	1	2.20	0.60 [0.08-4.72]	0.63	NA
OS									
Pemetrexed	31	17.2 [6.7-NR]	0.69 [0.35–1.37]	0.29	18	13.2 [5.4–14.5]	0.88 [0.33–2.39]	0.81	0.26
Taxane	12	8.7 [3.4–19.5]	1.91 [0.90–4.08]	0.09	8	6.8 [2.7-NR]	1.28 [0.45–3.63]	0.64	0.82
Other	12	15.2 [1.5-NR]	0.85 [0.35–2.06]	0.71	2	NR	0.71 [0.09-5.40]	0.74	0.82
Vinorelbine	3	NR	0.61 [0.08-4.49]	0.63	0	–	–	–	NA
TKI	4	NR	0.28 [0.04-2.06]	0.21	1	NR	NA	NA	0.62
Gemcitabine	4	10.8 [6.4-15.2]	1.65 [0.49-5.53]	0.41	0	–	–	–	NA
VePesid	1	1.5	26.3 [2.39-290.35]	0.008	0	–	–	–	NA
Other	0	–	–	–	1	0.39	NA	NA	NA

PFS 1, first-line progression-free survival; PFS 2, second-line progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; HR, hazard ratio; 95% CI, 95% confidence interval.
[a] HR reference is all other treatments combined in each group (Cases/WT).

non-V600E *BRAF* mutation. To our knowledge, this retrospective study is the largest multicentre cohort of patients with *BRAF*-MT advanced lung cancer.

The BMF study is a national program in which molecular and clinical data were collected from patients with advanced lung cancer who underwent molecular profiling in 1 of 28 certified molecular biology centres. The data collected over a 1-year period in 17,664 patients was reported in 2015 [1]. In total, 13,906 tumours were tested for *BRAF* mutations, of which 2% (262 patients) were identified as positive. In the equivalent North American lung cancer mutation consortium (LCMC) study of 1007 patients with confirmed adenocarcinoma, 951 were tested for *BRAF* mutations, yielding a comparable 2.2% positivity rate (21 patients) [13].

Patients harbouring *BRAF* mutations are associated with distinct clinicopathologic characteristics compared with other genomic subtypes. This point is not fully addressed in our study, because sex, age and smoking status were all matching criteria to avoid any bias in the prognosis assessment. *BRAF* mutations are found almost exclusively in patients with adenocarcinomas (87%) and predominantly in men (61%) and current or former smokers (81%). These characteristics differ notably from those reported in populations with *EGFR* or *ALK* mutations, which are predominantly found in never-smokers, and where *EGFR* mutations are concerned, more commonly in women. In the North American LCMC study, 81% of *BRAF*-MT patients were current or former smokers, and the proportions of men and women were equivalent [13]. In a study by Paik *et al.*, *BRAF* mutations were found in 18 of 697 adenocarcinoma patients tested (3%), and all *BRAF*-MT patients were current or former smokers [14]. Of note, in the study by Marchetti *et al.*, *BRAF* mutations were found in 36 of 739 adenocarcinoma patients tested (4.9%), and *BRAF* V600E mutations were significantly more common in never-smokers and in women, whereas all non-V600E *BRAF* mutations were found in smokers [3]. Similar results were found by Tissot *et al.* in 80 patients with *BRAF*-MT (53% V600E) [2]. In our cohort, the percentage of never-smokers was also higher among patients with *BRAF* V600E MT than among

non-V600E *BRAF*-MT (27% *BRAF* V600E versus 4% non-V600E; p = 0.001) as was the percentage of male patients (79% *BRAF* V600E versus 53% non-V600E; p = 0.02). No other significant epidemiological differences were identified between *BRAF* V600E and non-V600E patients. These findings are similar to those reported in a prospective phase II study in patients with *BRAF* V600E MT treated with dabrafenib alone or in combination with trametinib. That study included 179 patients in three cohorts in an almost exclusively adenocarcinoma population (89–98%, depending on the cohort) with a minority of never-smokers (28–37%, depending on the cohort). However, the proportion of male and female patients was approximately equivalent (39–51% males, depending on the cohort) [4,5,11].

The majority of *BRAF* mutations detected in our study were the V600E mutation in exon 15 (66%, 55/83 patients). This was also the case in the LCMC study, although the rate was slightly higher (81%) probably because of the particularly high proportion of never-smokers in their cohort (32% versus 19% in our cohort) [13]. In the other lung cancer cohorts, the rate of V600E mutations has been lower (accounting for 50–57% of *BRAF* mutations) [2,3,14–16], although these studies had small patient numbers and less advanced tumours (31–44% of patients were stage I to III in the studies by Paik *et al.* and Cardarella *et al.*, and almost all of the patients in the Marchetti *et al.* study had localised disease). It should be noted that in the BMF study, sequencing of *BRAF* exon 15 (to identify the V600 mutation) was performed in all cases, but not of the other exons, notably exon 11.

The activating *BRAF*, *EGFR* and *KRAS* mutations are generally mutually exclusive [17]. In our series, the rate of mutations co-occurring with *BRAF* was 13% (six patients with a *KRAS* mutation, three with an *EGFR* mutation, one with an *ALK* rearrangement and one with both *EGFR* and *ALK* alterations). Interestingly, most (8/11) were found in non-V600E patients. A similar overall rate was reported in the LCMC study (16% co-mutation in *BRAF*-MT patients), and cases have also been reported in other studies, including 19% (5/26) in Kinno *et al.* (all in non-V600E *BRAF* and all involving *EGFR* mutations); 11% (4/36) in Cardarella *et al.* (one patient with *BRAF* V600E and *PIK3CA* mutations, two patients with *BRAF*-G464 and *KRAS* and one patient with *BRAF*-G466 and *KRAS*); 5% (2/37) in Marchetti *et al.* (*BRAF* V600E and *EGFR* mutations) and 6% (5/80) in Tissot *et al.* (all with *KRAS* mutations and all in non-V600E cases) [2,3,13,15,16]. Of course, this rate was strongly associated with the panel of alterations tested in each study. But overall, in the BMF study, the rate of *BRAF* co-mutation (9%; 22/262) was high compared with 3% (67/1947) for *EGFR*, 2% (108/4894) for *KRAS* and 2% (2/98) for *HER2,* whereas it was similar to *ALK* (37/388; 10%) and lower than PIK3CA (88/252; 35%) [1,17]. In addition, *BRAF* co-mutations appears more frequent in non-V600E mutations in our cohort, while non-V600E appears to be associated with the ever-smoker phenotype. However, multiple mutations in biomarkers such as *KRAS*, *PI3K* or *EGFR* are generally associated with the never-smoker phenotype [17]. Little is known about the impact of co-mutations on the prognosis of these patients and their response to therapy. These patients had poorer OS compared with patients with *BRAF* mutation alone in a study from the Lung Cancer Mutation Consortium (HR 4.9; 95% confidence interval = 1.5–16.1; p = 0.006), whereas we found that patients with *BRAF* co-mutations had similar PFS but numerically higher OS [13].

Survival outcomes in patients with *BRAF*-MT disease under standard chemotherapy has been poorly studied, and to our knowledge, this is the largest cohort reported to date of advanced lung cancer patients receiving chemotherapy as first-line or second-line treatment. The PFS in these *BRAF*-MT patients was equivalent to that of the non-MT control cohort in both the first and second lines, although there was a non-significant trend towards better PFS in the second-line setting in patients with *BRAF*-MT cancer. The results do not appear to be because of any imbalance between the subgroups in terms of the chemotherapy regimen received. It is likely that the *BRAF*-MT patients received more targeted anti-BRAF therapies in the second-line than in the first (22% versus 6%), a fact that may have influenced the trend towards better PFS compared with the control group. Unfortunately, the type of tyrosine kinase inhibitor prescribed was not recorded in our database. OS was similar in the two patient groups (median OS of 13.4 months in *BRAF*-MT versus 10.2 months in controls; p = 0.39), which was low but similar to that reported in patients treated with chemotherapy, notably pemetrexed or taxans. Nonetheless, it was a good deal lower than that observed in patients with molecular abnormalities such as *EGFR* or *ALK* who received targeted therapy.[12,13] The proportion of patients who did not receive second-line treatment was similar in the two groups (39 versus 38%). A trend towards a better prognosis was apparent in patients with *BRAF*-MT disease who received pemetrexed as either first-line or second-line therapy (HR = 0.80 and 0.71 as first-line or second-line therapy, respectively) compared with a taxan-based therapy, although it was not statistically significant (median OS of 13.5 months with pemetrexed versus 8.5 months with a taxan-based therapy). Pemetrexed confers a clear benefit in patients with altered *ALK*, *ROS1* and *RET* as previously reported [18,19]. Analyses of most of the other *BRAF*-MT cohorts (with advanced or localised disease) did not demonstrate any significant differences in survival in *BRAF*-MT patients compared with patients with other molecular abnormalities or without any identified molecular abnormality [2,13–16]. The study by Marchetti *et al.* showed lower disease-free survival in patients with *BRAF*-MT cancer (HR 2.67,

$p < 0.001$ for PFS; HR 2.97, $p < 0.001$ for OS), yet that was a retrospective series and was primarily based on surgery [3]. Only the study by Cardarella *et al.* evaluated response to chemotherapy in patients with *BRAF*-MT advanced lung cancer specifically in the first-line, assessing 14 patients eligible for tumour response evaluation [15]. Median PFS in patients with *BRAF*-MT cancer treated with chemotherapy combined with a platinum salt was 5.2 months versus 6.7 months for WT patients ($p = 0.622$). In the same setting, median PFS in patients with *BRAF* V600E was shorter, although not significantly, compared with patients with non-V600E mutations (4.1 versus 8.9 months; $p = 0.297$). Survival outcomes were similar for the two groups (median OS of 15.2 months in patients with *BRAF*-MT versus 15.9 months in WT patients; $p = 0.707$). Median OS in *BRAF* V600E patients was 10.8 months compared with 15.2 months in patients with non-V600E mutations ($p = 0.726$) [15].

Based on our own experience with advanced-stage patients and other reported cohorts, there is no clear evidence that *BRAF* status influences PFS or OS in patients treated with chemotherapy, while the overall benefit of chemotherapy is limited, with OS largely equivalent to that of non-*BRAF*-MT patients. It is difficult to draw any clear conclusions in terms of subgroups, in particular patients harbouring or not harbouring the V600E mutation, with the small patient numbers limiting the power of any analyses. In addition, the results of our study should be interpreted with caution given the limitations of retrospective observational studies and the potential selection biases that this can lead to. Finally, we performed multiple comparisons without using any correction or adjustments and some of our results may be positive by random. Of note, this cohort was constituted before immunotherapy era in NSCLC, and we do not assess outcomes with this strategy. That said, our study has the advantage of availing of a large national multicentre study with prospective molecular profiling which did not specifically focus on *BRAF*-MT patients. In addition, the case-control design of our analysis also strengthened our results. Finally, the small number of patients and the diversity of treatments received may also limit the analysis of the results in terms of type of treatment, as well as prohibit multivariate analysis.

In our cohort, only a small proportion of patients with *BRAF*-MT disease received targeted therapy because of the lack of sufficient data to show a benefit of such treatment at the time of care. This limited the possibility of any change in the natural history of these tumours beyond the trend towards improved PFS with second-line treatment. To date, it has been demonstrated that patients with *BRAF* V600 MT benefit from BRAF-specific inhibitors such as vemurafenib or dabrafenib alone (objective response rate [ORR] of 42% and 33% respectively; median PFS of 7.3 and 5.5 months, respectively) or combined with a MEK inhibitor such as trametinib (ORR 63%; median PFS of 9.7 months) [4,5,11,12]. In the phase II prospective multicohort study involving patients harbouring the *BRAF* V600E mutation, targeted therapy with combined dabrafenib and trametinib yielded a high response rate (64–67%) and prolonged PFS (10.2–10.9 months) irrespective of the line of therapy (first or later) [5,11]. This benefit translated into prolonged survival (median OS of 18.2–24.6 months), which an indirect comparison showed to be much longer than that observed in our cohort treated with chemotherapy. The benefit in patients with *BRAF* V600E MT cancer treated with combined dabrafenib and trametinib is similar to that in *EGFR* MT and *ALK* or *ROS1* rearranged patients treated with a tyrosine kinase inhibitor [20,21]. This resulted in approval by the European Medicines Agency and the Food and Drug Administration of the combination of dabrafenib and trametinib in lung cancer patients harbouring a *BRAF* V600 mutation.

Our results reinforce the importance of molecular screening strategy to personalised therapy as it has been done in various personalised medical programs including the MOSCATO study [22]. In this prospective phase I trial, high-throughput genomics testing led to a matched targeted treatment for 19% of successfully screened patients, and 33% of those matched-treated patients or 7% of those successfully screened obtained a PFS ratio above the predefined threshold. Next steps include better defining which patients could derive benefit from this type of approach and the further development of new methods to detect cancer drivers in individuals.

Today, immunotherapy also represents a major therapeutic option for lung cancer in the first-line and later settings. Nonetheless, more than half of these patients do not respond to immunotherapy in the first-line setting, and we currently have very little data on the benefit of these treatments in the *BRAF*-MT population [23]. Mazières *et al.* reported the results of the international IMMUNOTARGET study at the 2018 American Society of Clinical Oncology (ASCO) meeting (ASCO 2018, #9010). This cohort study aimed to assess clinical outcomes in patients harbouring a molecular abnormality (including *BRAF*, *MET*, *KRAS*, *EGFR*, *HER2*, *ROS1*, *ALK* and *RET*) and treated with immune checkpoint inhibitors (ICIs). Overall, 43 patients harboured a *BRAF* mutation (48% V600E). DCR on ICIs was 54% in patients with *BRAF*-MT cancer. This was the highest DCR observed compared with the other alterations treated with ICIs (*MET*, *KRAS*, *EGFR*, *HER2*, *ROS1*, *ALK* and *RET*). PFS and OS were slightly higher (although not significant) in patients with *BRAF* mutated disease compared with the other alterations except those with *KRAS* mutation who exhibited a similar pattern. Interestingly, PFS was slightly higher in the non-V600E subgroup (not

significant) as well as in the ever-smoker group ($p = 0.03$). Studies evaluating the combination of targeted therapies with PD-1/PD-L1 inhibitors in melanoma patients are ongoing. In lung cancer, whereas patients with *EGFR* mutations or *ALK* rearrangements have been excluded from immunotherapy studies, *BRAF*-MT patients remain eligible. Indeed, preliminary data with ICIs in *EGFR* MT or *ALK* rearranged patients suggests that the benefit of these treatments is disappointing [24–27]. The IMMUNOTARGET study found similar outcomes (Mazières *et al.* ASCO 2018, #9010). Overall, these results show that lung cancer patients harbouring a tumour with an oncogenic alteration such as *EGFR*, *ALK* or *ROS1* and now *BRAF* V600E, should be treated with targeted therapies. *BRAF* mutations are generally more frequent in smokers. This may result in a higher mutational load and a greater benefit with immunotherapy. Non-V600 BRAF mutations, which are excluded from the approved targeted therapies and associated with ever-smoking and multiple mutation, may be an interesting candidate for ICI. However, further studies are needed. Despite the limitations of the retrospective nature of our study, this large prospective French study of molecular profiling in lung cancer patients offers a rich source of insight within the current treatment landscape.

Conflict of interest statement

S.C. reports grants from Novartis, Pfizer, Roche, Boehringher Ingelheim, MSD, AstraZeneca and BMS, personal fees from Pfizer, Roche, Lilly, Boehringher Ingelheim, MSD, AstraZeneca and BMS and non-financial supports from Pfizer, Roche, Boehringher Ingelheim, AstraZeneca, BMS and Sysmex Inostics.

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V.W. served as speakers' bureau for AstraZeneca, MSD, Roche, Lilly Pharma, Bristol-Myers Squibb, Boehringer Ingelheim International GmbH, served as consultant for MSD, Roche, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim International GmbH, has been reimbursed for travel, accommodation, expenses from AstraZeneca, Novartis, Roche, Bristol-Myers Squibb, Boehringer Ingelheim International GmbH.

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D.P. reports consulting, advisory role or lectures for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, MedImmune, Novartis, Pfizer, prIME Oncology, Peer CME and Roche, received honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME and Roche, worked as Clinical trials research as principal or co-investigator (Institutional financial interests) for AstraZeneca, Bristol-Myers Squibb, Abbvie, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, MedImmune, Sanofi-Aventis, Taiho Pharma, Novocure and Daiichi Sankyo and received travel and accommodations and expenses from AstraZeneca, Roche, Novartis, prIME Oncology and Pfizer.

All remaining authors (D.D., J.P.M., L.M., M.B.F., J.M., F.A.F., L.H.O., A.M., P.M., A.L. and F.M.) have declared no conflicts of interest.

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Appendix A. Supplementary data

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