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# Outcome of Patients With Resected Early-Stage Non-small Cell Lung Cancer and EGFR Mutations: Results From the IFCT Biomarkers France Study

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## Abstract

**Molecular profile of localized non-small cell lung cancer has not been reported in Western Europe. In the nationwide Biomarker France study, EGFR mutations were found in 12.9% of resected stage I-II NSCLC, associated with 5-year DFS of 65% and 5-year OS of 75%. No difference was found between EGFR-mutant and EGFR-wt tumors regarding recurrence site, disease-free survival, and overall survival.**

**Introduction:** Molecular profile of resected stage I-II non-small cell lung cancer (NSCLC) would help refine prognosis and personalize induction or adjuvant strategies. We sought to report the molecular profile of resected stage I-II NSCLC and analyzed the impact of epidermal growth factor receptor (*EGFR*) mutations on outcomes in a Western population.

**Patients and Methods:** Surgical cases were identified from Biomarkers France study, a nationwide prospective study including NSCLC patients screened for *EGFR*, *HER2*, *KRAS*, *BRAF*, *PIK3CA*, *ALK* alterations from 2012 to 2013. Among surgical patients, clinical charts of the largest centers were reviewed in order to analyze the prognostic impact of *EGFR* mutations. **Results:** In the BMF database (n = 17,636), surgical patients (n = 854) were characterized by a higher proportion of *EGFR* mutations than nonsurgical patients (12.9% vs. 10.2%, *P* = .025), while the other molecular alterations did not differ. The proportion of *EGFR* mutations was 27% in women undergoing surgery. In the study group (n = 293; *EGFR* wild type, n = 235; usual mutation, n = 50; rare mutation, n = 8), after a median follow-up of 67 months, 215 patients (74.4%) had not relapsed. No difference was found between *EGFR*-mutant and *EGFR*-wt tumors regarding recurrence site, disease-free survival, and overall survival. The 5-year disease-free survival and overall survival after surgical resection of stage I-II *EGFR*-mutated tumors were 65% and 75%, respectively. **Conclusion:** In resected stage I to II NSCLC, *EGFR* mutations were found in 12.9% of cases, associated with a 5-year overall survival of 75%, with no impact on recurrence site, disease-free survival, and overall survival.

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**Keywords:** NSCLC, Surgery, Molecular profile, Prognosis, Stage I-II disease

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## Introduction

The last decade has seen several advances in the management of advanced non-small cell lung cancer (NSCLC), due to the increased use of targeted therapies and immunotherapy, which has led to dramatic outcome improvement for some patients.<sup>1</sup> In localized disease, surgery alone or with perioperative chemotherapy can cure more than half of patients.<sup>2</sup> The contribution of targeted therapies as induction or adjuvant treatment has long remained exploratory.<sup>3</sup> As a consequence, the molecular examination of early stage tumors was usually not recommended in Europe, but the field is now evolving rapidly.

Recently, the ADAURA trial reported a significant benefit of the third-generation EGFR-TKI osimertinib on Disease-Free Survival (DFS) following complete surgical resection of stage IB–III EGFR-mutant NSCLC.<sup>4</sup> In this trial, adjuvant EGFR-TKI was associated with an impressive improvement in DFS with a hazard ratio of 0.20, but the DFS of the control group was also disappointing for stage I-II disease, and mature overall survival (OS) data are not available yet. In this setting, additional data on the incidence and long term prognostic impact of EGFR mutation in unselected patients undergoing surgery for localized NSCLC are still needed.

The French National Cancer Institute (INCa) funded a nationwide program for the routine analysis of EGFR, HER2, KRAS, BRAF, PIK3CA, and ALK alterations in advanced nonsquamous NSCLC patients. The Biomarkers France (BMF) study sought to assess the characteristics, molecular profiles, and clinical outcomes of patients screened by this program, leading to the prospective collection of clinical and molecular data of 17,664 patients in 1 year.<sup>5</sup> Although this study intended to include only patients with advanced NSCLC, some patients had localized NSCLC. We conducted a retrospective study to analyze the prognostic impact of EGFR mutations in patients with resected localized NSCLC included in the BMF study.

## Patients and Methods

### BMF Study

The design of the BMF study has already been reported.<sup>5</sup> Briefly, this study prospectively included advanced NSCLC patients who were routinely screened for EGFR, HER2 (*ERBB2*), KRAS, BRAF, PIK3CA, and ALK alterations, by 28 certified regional genetics centers in France. Patients were consecutively assessed over a 1-year period from April 2012 to April 2013. Although the study focused on patients with advanced (stage III-IV) and relapsed disease, it also included patients with localized (stage I-II) disease. This latter group

is the subject of the current manuscript. The TNM classification reported in the BMF study and in this analysis is the 7th Edition published in 2007.<sup>6</sup>

### Ethics

The BMF study was approved by a national ethics committee for observational studies (Comité d'Évaluation des Protocoles de Recherche Observationnelle [CEPRO]) on September 28, 2011, 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 [CCTIRS]) on September 22, 2011, and by the National Commission of Informatics and Liberty (Commission Nationale Informatique et Libertés [CNIL]) on December 18, 2011, according to French laws.

### Study Design

We conducted a retrospective study of the prospective BMF database. Clinical, biological, and outcome data were provided by clinicians that had included the patients. DFS and overall survival (OS) were assessed by each clinician. To analyze the prognostic impact of EGFR mutations within surgical patients, we reviewed the clinical charts and outcomes of centers with at least one case of EGFR-mutant early stages NSCLC, in order to favor patients with usual EGFR mutations (ie, del19 and L858R). Thus, the study group was composed of patients whose data have been verified and completed on site. Two subgroups were then formed based on EGFR status: patients with usual EGFR mutations and patients with wild-type (wt) EGFR. Analysis was performed on data that had been exported on September 9, 2019.

### Molecular Analyses

The molecular analyses of EGFR (exons 18-21), HER2 (exon 20), KRAS (exon 2), BRAF (exon 15), and PIK3CA (exons 9 and 20) mutations, as well as of ALK rearrangements, were performed on a routine basis at 28 certified molecular genetics centers as previously reported.<sup>5,7-9</sup>

### Objectives

The primary objective of this study was to study the prognostic impact of EGFR mutations in localized NSCLC patients, with a special focus on the impact of EGFR mutations on OS, DFS, type of recurrence, and second cancer. Secondary objective was to report the molecular profile of localized NSCLC patients undergoing surgical resection with a curative intent included in a nationwide database.

### Statistical Analysis

Descriptive statistics were used, including the median and range or quartiles for continuous variables or frequencies and percentages for categorical variables. The median follow-up duration was defined as the time from the date of the molecular analysis assessment to the closing date of the analysis. DFS was defined as the time from the date of molecular analysis assessment to the date of the first recurrence or death from any cause. OS was defined as the time from the date of the molecular analysis assessment to the date of death or

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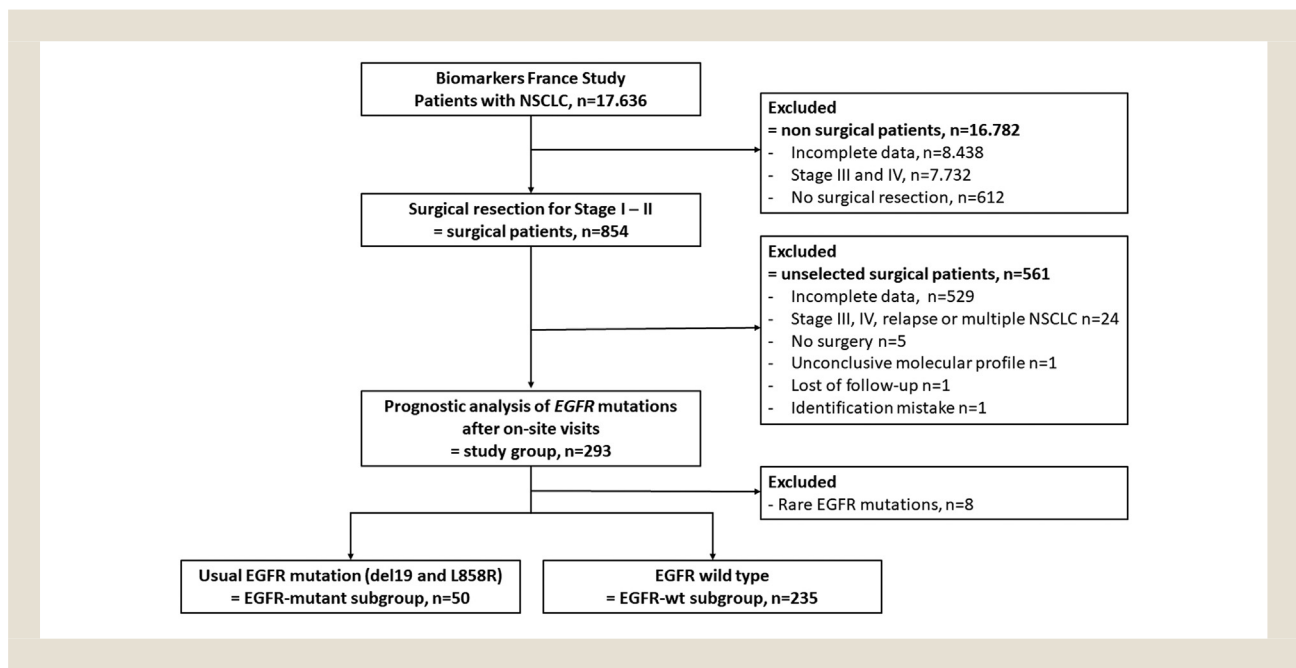
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Figure 1 Study flowchart.



final follow-up. Survival curves were estimated using the Kaplan-Meier method and compared using the 2-sided log-rank test. The characteristics (with or without mutation) of each biomarker were compared using the  $\chi^2$  test for qualitative variables or the nonparametric test for quantitative variables. Univariate Cox models were applied to select the most-promising prognostic variables (threshold  $P = .20$ ). A multivariate Cox model was then applied to adjust for potential confounders (clinical or molecular characteristics associated with DFS or OS). Adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were also calculated. We then matched patients from EGFR-mutant and EGFR-wt groups according to sex, tobacco use, and stage, and compared the characteristics and prognosis of the matched groups. All statistical tests were 2-sided, and a  $P$ -value below .05 was considered statistically significant. All analyses were performed using SAS software (version 9.3, SAS Institute).

## Results

### BMF Database

At the last monitoring data-lock in March 2018, the BMF database gathered 17,636 patients with NSCLC and available molecular profile. The study flowchart is shown in **Figure 1**, and patients characteristics are summarized in Supplemental Table 1. As compared to nonsurgical patients, surgical patients were characterized by a more frequent past-medical history of cancer (30% vs. 20.4%, respectively,  $P < .001$ ) and more frequent *EGFR* mutations (12.9% vs. 10.2%, respectively,  $P = .025$ ). *EGFR* mutation rates were also higher in women than in men, and in women undergoing surgery than in all women (27% vs. 20%,  $P < .01$ ).

### Study Group

After on-site visits, 293 surgical patients were included in the study group. Their characteristics are described in Supplemental Table 2. Compared with unselected surgical patients, patients included in the study group were more frequently recruited in university hospitals (62.8% vs. 35.8%, respectively,  $P < .001$ ) and more frequently women (44.9% vs. 35%, respectively,  $P = .005$ ).

### EGFR Mutation

The study group included 235 patients with *EGFR*-wt tumors (80.3%), 50 patients with usual *EGFR* mutations (17%) and 8 patients with rare *EGFR* mutations (2.7%). The clinical and histological characteristics of patients with *EGFR*-mutant and *EGFR*-wt tumors are described in **Table 1**. Interestingly, *EGFR* mutations were more frequent in stage I than in stage II disease (21.9% vs. 7%, respectively,  $P = .003$ ), leading to a tumor stage imbalance between groups with a majority of T1 tumors ( $n = 28$ , 57.1%) in patients with *EGFR* mutations and a majority of T2-T3 tumors ( $n = 139$ , 60.9%) in patients without *EGFR* mutations ( $P = .006$ ).

### Relapse

The median follow-up of the study group was 67 months (63.6-69.7). At the time of analysis, 215 patients (74.4%) had not relapsed, 67 (23.5%) had relapsed, and 3 (1%) were lost to follow-up. No difference was found between patients with *EGFR*-mutant and *EGFR*-wt tumors regarding the recurrence rate, site of recurrence, and occurrence of metachronous cancer, as shown in **Table 2**. Among the 58 patients with *EGFR* mutant tumor, 13 patients received adjuvant treatment based on chemotherapy while no patient received adjuvant TKI. Among the 16 patients with *EGFR* mutant tumors who experienced tumor relapse, 8 patients

**Table 1** Characteristics of Patients With *EGFR*-Mutant and *EGFR*-Wild Type Tumors (n = 285 after Exclusion of 8 Patients With Rare *EGFR* Mutations)

			EGFR-Mutant (N = 50)	EGFR-Wild Type (N = 235)	P-Value
<b>Sex</b>		<b>N</b>	50	234	<.001
	<b>Male</b>	<b>N (%)</b>	10 (20.0)	149 (63.7)	
	<b>Female</b>	<b>N (%)</b>	40 (80.0)	85 (36.3)	
<b>Age (years)</b>		<b>N</b>	50	235	.16
		<b>Mean ± SD</b>	66.04 ± 9.56	63.87 ± 9.85	
		<b>Median</b>	67.87	64.29	
		<b>Range</b>	[48.7-83.4]	[38.2-91.5]	
<b>Asian origin</b>		<b>N</b>	38	171	.61
	<b>Yes</b>	<b>N (%)</b>	2 (5.3)	5 (2.9)	
	<b>No</b>	<b>N (%)</b>	36 (94.7)	166 (97.1)	
<b>Smoking</b>		<b>N</b>	47	229	<.001
	<b>Smoker</b>	<b>N (%)</b>	2 (4.3)	111 (48.5)	
	<b>Former smoker</b>	<b>N (%)</b>	17 (36.2)	98 (42.8)	
	<b>Non-smoker</b>	<b>N (%)</b>	28 (59.6)	20 (8.7)	
<b>Personal history of cancer</b>		<b>N</b>	47	226	.79
	<b>Yes</b>	<b>N (%)</b>	12 (25.5)	62 (27.4)	
	<b>No</b>	<b>N (%)</b>	35 (74.5)	164 (72.6)	
<b>Type of surgery</b>		<b>N</b>	49	235	.52
	<b>Wedge resection</b>	<b>N (%)</b>	3 (6.1)	30 (12.8)	
	<b>Lobectomy</b>	<b>N (%)</b>	45 (91.8)	197 (83.8)	
	<b>Pneumonectomy</b>	<b>N (%)</b>	0	3 (1.3)	
	<b>Other</b>	<b>N (%)</b>	1 (2.0)	5 (2.1)	
<b>TNM - Tumor</b>		<b>N</b>	49	228	.006
	<b>T1a</b>	<b>N (%)</b>	15 (30.6)	60 (26.3)	
	<b>T1b</b>	<b>N (%)</b>	13 (26.5)	29 (12.7)	
	<b>T2a</b>	<b>N (%)</b>	18 (36.7)	80 (35.1)	
	<b>T2b</b>	<b>N (%)</b>	2 (4.1)	19 (8.3)	
	<b>T3</b>	<b>N (%)</b>	1 (2.0)	40 (17.5)	
<b>TNM - Node</b>		<b>N</b>	49	231	.16
	<b>0</b>	<b>N (%)</b>	45 (90.0)	206 (88.0)	
	<b>1</b>	<b>N (%)</b>	3 (6.0)	25 (10.7)	
	<b>2</b>	<b>N (%)</b>	1 (2.0)	0	
<b>Stage</b>		<b>N</b>	48	228	.003
	<b>I</b>	<b>N (%)</b>	42 (87.5)	149 (65.4)	
	<b>II</b>	<b>N (%)</b>	6 (12.5)	79 (34.6)	
<b>Perioperative treatments</b>		<b>N</b>	50	232	.57
	<b>No</b>	<b>N (%)</b>	38 (76.0)	168 (72.1)	
	<b>Yes</b>	<b>N (%)</b>	12 (24.0)	65 (27.9)	
<b>Induction treatment</b>		<b>N</b>	50	232	.69
	<b>No</b>	<b>N (%)</b>	49 (98.0)	223 (95.7)	
	<b>Yes</b>	<b>N (%)</b>	1 (2.0)	10 (4.3)	
<b>Adjuvant treatment</b>		<b>N</b>	50	232	.61
	<b>No</b>	<b>N (%)</b>	39 (78.0)	173 (74.6)	
	<b>Yes</b>	<b>N (%)</b>	11 (22.0)	59 (25.4)	

Abbreviations: PS = performance status; SD = standard deviation.

were treated with TKI and 2 patients were treated with chemotherapy.

### Survival

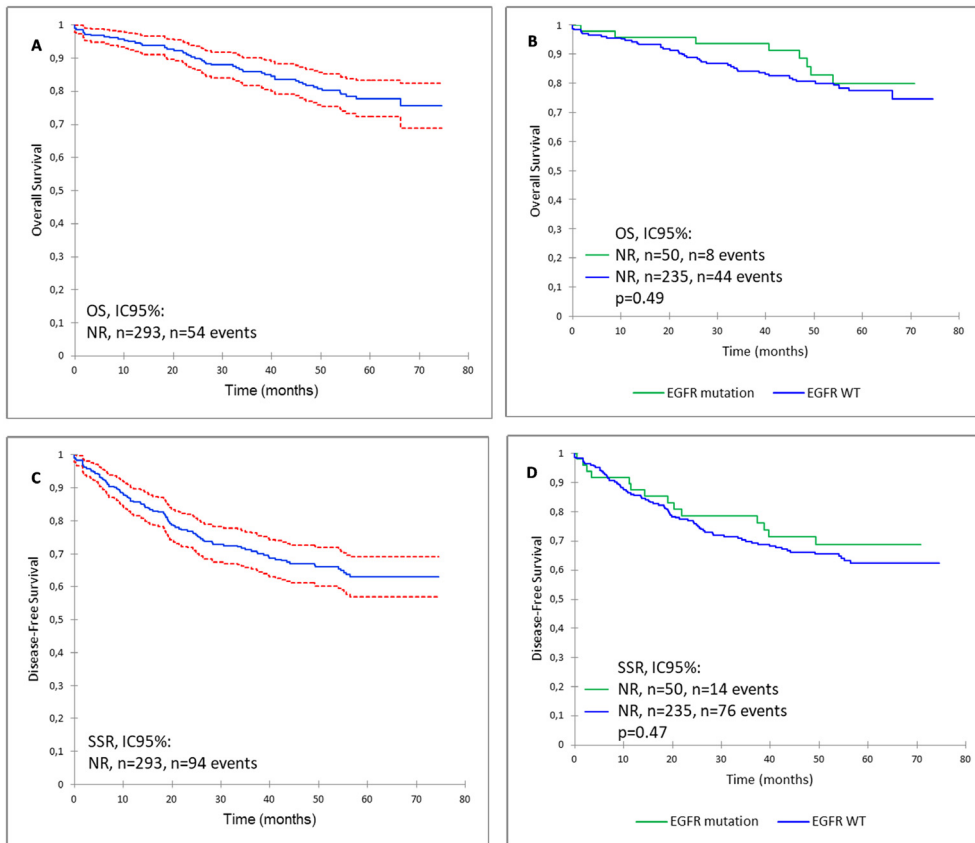
DFS and OS are reported in **Figure 2**. In the study group, the 5-year DFS and OS were 65% and 75%, respectively. No significant difference was found in OS and DFS between *EGFR*-mutant

**Table 2** Outcome of Patients With *EGFR*-Mutant and *EGFR*-Wild Type Tumors (Study Group, n = 285 After Exclusion of 8 Patients With Rare *EGFR* Mutations)

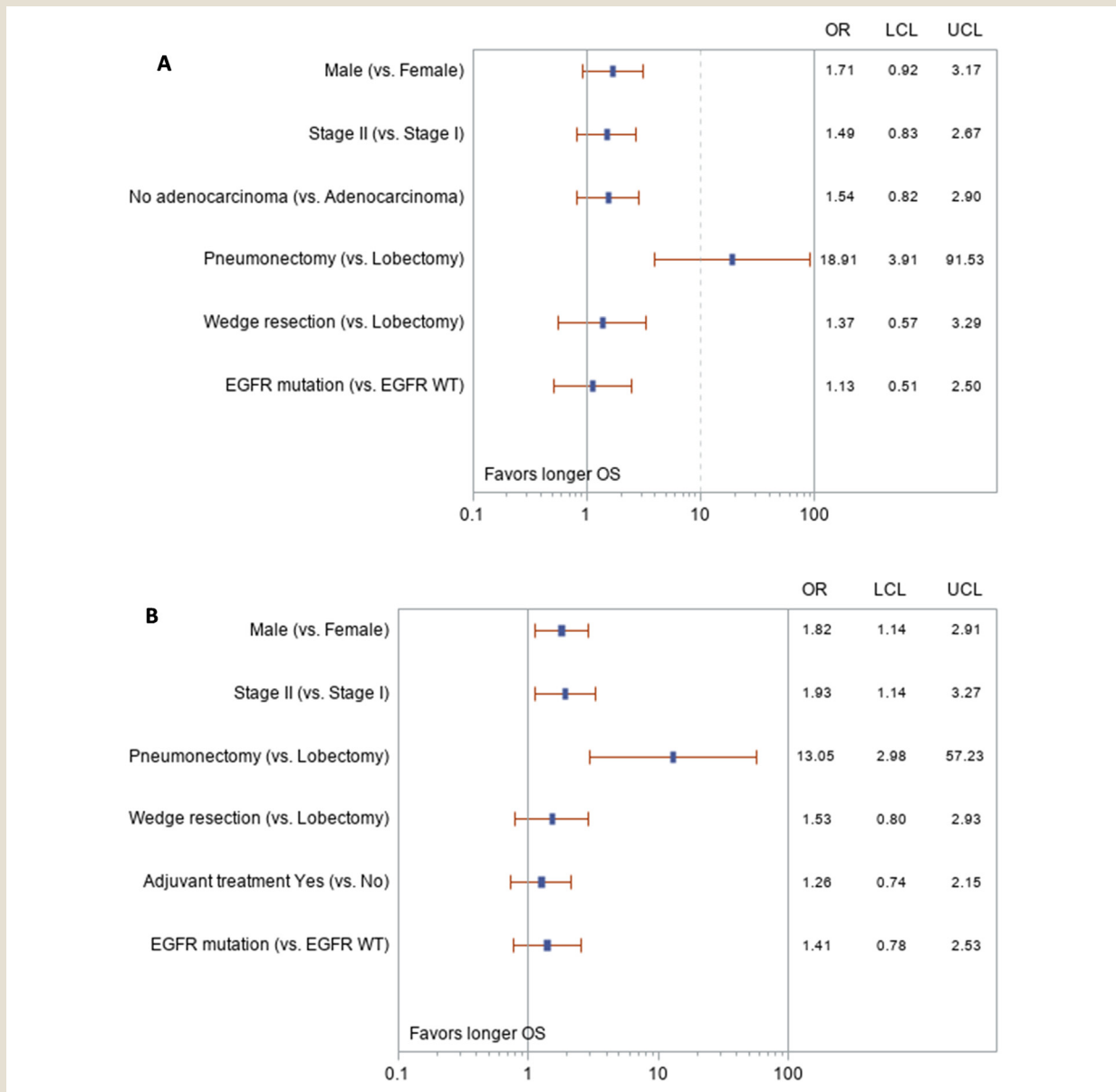
			<i>EGFR</i> -Mutant (N = 50)	<i>EGFR</i> -Wild Type (N = 235)	Total (N = 285)	P-Value
<b>Disease recurrence</b>		<b>N</b>	50	229	282	.96
	<b>No</b>	<b>N (%)</b>	38 (76.0)	177 (76.3)	215 (75.4)	
	<b>Yes</b>	<b>N (%)</b>	12 (24.0)	55 (23.7)	67 (23.5)	
<b>Local recurrence</b>		<b>N</b>	12	55	67	1.0
	<b>No</b>	<b>N (%)</b>	4 (33.3)	18 (32.7)	22 (7.7)	
	<b>Yes</b>	<b>N (%)</b>	8 (66.7)	37 (67.3)	45 (15.8)	
<b>Brain metastasis</b>		<b>N</b>	8	28	36	1.00
	<b>No</b>	<b>N (%)</b>	4 (50.0)	16 (57.1)	20 (7.0)	
	<b>Yes</b>	<b>N (%)</b>	4 (50.0)	12 (42.9)	16 (5.6)	
<b>Extra cerebral metastasis</b>		<b>N</b>	50	235	285	.56
	<b>No</b>	<b>N (%)</b>	45 (90.0)	218 (92.8)	263 (92.3)	
	<b>Yes</b>	<b>N (%)</b>	5 (10.0)	17 (7.2)	22 (7.7)	
<b>Metachronous NSCLC</b>		<b>N</b>	50	232	283	.21
	<b>No</b>	<b>N (%)</b>	49 (98.0)	216 (92.7)	265 (93.0)	
	<b>Yes</b>	<b>N (%)</b>	1 (2.0)	17 (7.3)	18 (6.3)	

Abbreviations: NSCLC, non-small cell lung cancer.

**Figure 2** Kaplan-Meier Curves of the 293 Patients included in the study group according to *EGFR* mutation after a follow-up of 67.0 months (IQR: 63.6-69.7): (A) overall survival (study group, n = 293); (B) Overall Survival According to *EGFR* Status after exclusion of 8 patients with rare *EGFR* mutations (n = 285); (C) disease-free survival (study group, n = 293); (D) disease-free survival according to *EGFR* status after exclusion of 8 patients with rare *EGFR* mutations (n = 285).



**Figure 3** Prognostic Factors included in the Multivariate Analysis of Associated with Survival (A) overall survival (study group, n = 293); (B) disease-free survival (study group, n = 293).



and *EGFR*-wt patients. The prognostic factors associated with OS and DFS in the 2 groups are reported in **Figure 3**. In multivariate analyses including disease stage as a covariate, *EGFR* mutation was not associated with OS (HR 1.13, 95% CI 0.51-2.50,  $P = 0.76$ ) or with DFS (HR 1.41, 95% CI 0.78-2.53,  $P = .25$ ).

### Matching

We then matched 39 patients with *EGFR*-mutant tumors with 39 patients with *EGFR*-wild type tumors with the same sex, tobacco history, and disease stage. The characteristics and prognosis of the matched groups are shown in **Table 3**. The survival curves of the matched groups are presented in **Figure 4**. There was no significant

difference between groups regarding their characteristics, treatment, frequency of recurrence, and overall survival.

### Discussion

By studying the molecular profile and prognostic impact of *EGFR* mutations in patients with resected stage I-II NSCLC included in the BMF study, we found that the proportion of *KRAS*, *ALK*, *PIK3CA*, *BRAF*, and *HER2* alterations did not significantly differ between surgical and nonsurgical patients. The proportion of *EGFR* mutations was higher in surgical than in non-surgical patients, ranging from 4% of men to 27% of women undergoing surgery, with no significant impact on DFS and OS. After surgical resection

**Table 3** Characteristics and Outcomes of Patients With *EGFR*-Mutant and *EGFR*-Wild Type Tumors (Matched Groups According to Sex, Tobacco Use, and Stage, n = 78).

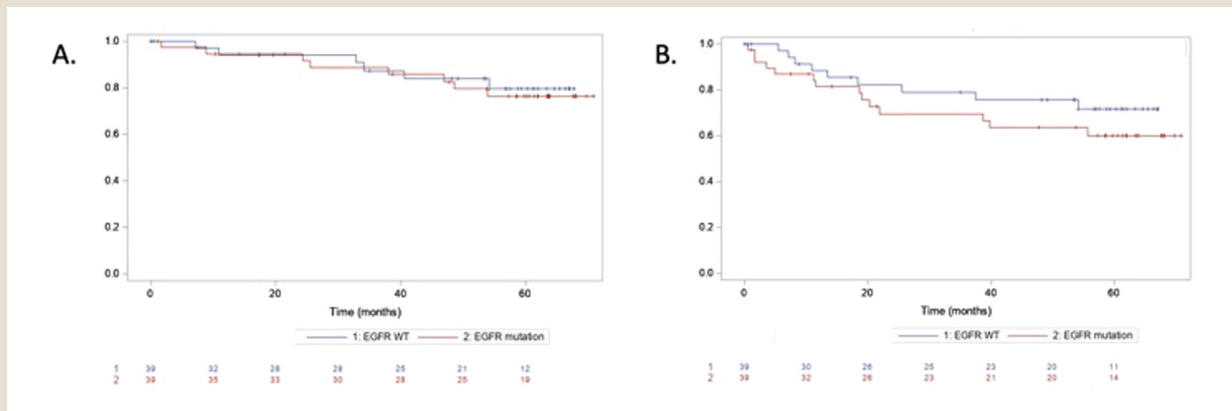
			EGFR-Mutant (N = 39)	EGFR-Wild Type (N = 39)	P-Value
Sex		N	39	39	
	Male	N (%)	9 (23.1)	9 (23.1)	1.00
	Female	N (%)	30 (76.9)	30 (76.9)	
Age (y)		N	39	39	
		Mean ± SD	64.54 ± 8.85	66.17 ± 10.70	.51
		Median	66.31	66.70	
		Range	[51.3-78.9]	[48.8-84.0]	
Asian origin		N	33	29	
	Yes	N (%)	1 (3.0)	0	1.00
	No	N (%)	32 (97.0)	29 (100.0)	
Smoking		N	39	39	
	Smoker + former smoker	N (%)	21 (53.8)	21 (53.8)	1.00
	Non smoker	N (%)	18 (46.2)	18 (46.2)	
PS		N	32	34	
	0	N (%)	14 (43.8)	19 (55.9)	.68
	1	N (%)	16 (50.0)	13 (38.2)	
	2	N (%)	2 (6.3)	2 (5.9)	
Personal history of cancer		N	39	39	
	Yes	N (%)	6 (15.4)	13 (33.3)	.06
	No	N (%)	33 (84.6)	26 (66.7)	
Type of surgery		N	38	39	
	Wedge	N (%)	1 (2.6)	7 (17.9)	.06
	Lobectomy	N (%)	36 (94.7)	31 (79.5)	
	Pneumonectomy	N (%)	0	0	
	Other	N (%)	1 (2.6)	1 (2.6)	
Stage		N	39	39	
	I	N (%)	30 (76.9)	30 (76.9)	1.0
	II	N (%)	9 (23.1)	9 (23.1)	
Adjuvant treatment		N	39	39	
	No	N (%)	26 (66.7)	32 (82.1)	.12
	Yes	N (%)	13 (33.3)	7 (17.9)	
Induction treatment		N	39	39	
	No	N (%)	39 (100.0)	39 (100.0)	-
	Yes	N (%)	0	0	
Recurrence		N	39	39	
	No	N (%)	26 (66.7)	33 (84.6)	.06
	Yes	N (%)	13 (33.3)	6 (15.4)	

of stage I to II *EGFR*-mutated tumors, the 5-year DFS and OS were 65% and 75%, respectively.

The frequency of *EGFR* mutations has been widely studied in advanced NSCLC. *Post hoc* analyses of the historical TRIBUTE and INTACT trials found *EGFR* mutations to be present in 12%<sup>10</sup> to 13%<sup>11</sup> of cases. Consecutive studies have proven that the

presence of *EGFR* mutations correlates with adenocarcinoma histology, female sex, Asian ethnicity, and non-smoking status.<sup>12,13</sup> In the United States, the Lung Cancer Mutation Consortium (LCMC) was formed to analyze 10 oncogenic driver mutations in lung adenocarcinoma patients. Among the 1007 cases with mutation analysis performed, *EGFR* mutations were detected in 22%.<sup>14</sup> Conversely,

**Figure 4** Kaplan-Meier Curves of the 78 Patients Included in the Matched groups (A) Overall survival (matched groups, n = 39 per group,  $P = .76$ ); (B) disease-free survival (matched groups, n = 39 per group,  $P = .30$ ).



**Table 4** Results of Phase 3 Randomized Clinical Trials Studying the Impact of Adjuvant TKI in Patients With Stage I to III Resectable EGFRm NSCLC

Trial	Country	Stage	N	TKI	Design	DFS (95%CI)	P	OS	P	Ref
ADJUVANT CTONG 1104	China	II-IIIa	222	G	G vs. ACT	0,60 (0,42-0,87)	,0054	0,92 (0,62-1,36)	,67	3, 22
EVIDENCE	China	II-IIIa	322	I	I vs ACT	0,37 (0,24-0,55)	,0001	Immature	-	23
IMPACT	Japan	II-IIIa	232	G	G vs. ACT	0,92 (0,67-1,28)	,63	1,03 (0,65-1,65)	,89	24
ADAURA	International	IB-II-IIIa	682	O	O+ACT vs ACT	0,20 (0,14-0,30)	<,001	Immature	-	4

Abbreviations: TKI = tyrosine kinase inhibitor; DFS = disease free survival; OS = overall survival; G, gefitinib; I, icotinib; O, osimertinib; ACT = Adjuvant Chemotherapy.

reports on the frequency of EGFR mutations in patients with localized NSCLC are scarce. In Japan, Suda et al. recently analyzed 5780 surgically resected lung cancer, detecting *EGFR* mutations in 41% of them.<sup>15</sup> In France, the BMF study included 18,679 molecular analyses of 17,664 NSCLC patients, with EGFR mutations detected in 10.2%.<sup>5</sup> We found a significantly higher frequency of *EGFR* mutations in the subgroup of patients resected for stage I to II NSCLC. Although this may be the result of selection bias, it still constitutes an interesting milestone for the future management of localized NSCLC in a Western population.

*EGFR* mutation may generate a different natural history and therefore a different prognosis than that observed for wild-type tumors. In localized NSCLC, Suda et al. found that survival was significantly longer in *EGFR*-mutant than in *EGFR*-wt patients.<sup>15</sup> Conversely, our study suggests that *EGFR* mutations have no significant prognostic impact in localized resected NSCLC in a Western population. In advanced NSCLC, *EGFR* mutations have been reported to be associated with improved prognosis, compared to wt tumors.<sup>8,11,16</sup> Since these studies, EGFR mutations have been found to be associated with improved response to EGFR-TKI,<sup>17,18</sup> and the presence of an *EGFR* mutation has been associated with longer survival, due to successive improvements in the efficacy of EGFR-TKI.<sup>19</sup> Taken together, these data suggest that, in addition to a possible favorable natural history that has not been confirmed in our study, the subset of NSCLC harboring EGFR mutations mostly benefit from the efficacy of TKIs.

The development of adjuvant targeted therapy is thus highly desirable to optimize the outcome of resected localized *EGFR*-mutant NSCLC and reduce the toxicity of adjuvant treatments. The TASTE study demonstrated the feasibility of a biology-driven trial in the adjuvant setting, as 80% of patients with complete biomarker status were able to start adjuvant treatment within 2 months of surgery.<sup>20</sup> Further trials studying the impact of adjuvant TKI in *EGFR*-mutant NSCLC patients have been limited by the use of unreliable biomarkers,<sup>21</sup> a limited number of patients,<sup>22</sup> a focus on higher stages<sup>22</sup> or on an Asian population,<sup>3</sup> and the absence of data on OS.<sup>3,21,22</sup> The results of available phase 3 trials studying the impact of adjuvant TKI in *EGFR*-mutant NSCLC patients are summarized in **Table 4**.<sup>3,4,23,24,25</sup> Among them, the ADJUVANT CTONG trial of gefitinib in EGFR-mutated early stage NSCLC failed to demonstrate an OS benefit despite profound improvements in DFS.<sup>3,23</sup>

Wu et al. recently reported the results of the ADAURA trial randomizing 682 patients with *EGFR*-mutant stage IB to IIIa NSCLC to receive osimertinib or a placebo for 3 years after tumor resection and adjuvant chemotherapy, as indicated.<sup>4</sup> The trial was unblinded early due to efficacy, as an unplanned interim analysis showed a statistically significant improvement in DFS (HR = 0.20; 99.12% CI, 0.14-0.30;  $P < .001$ ). Interestingly, even if the direct comparison of prognosis is not possible between different studies, the DFS after surgical resection of EGFR-mutated tumors reported in our study appears higher than the DFS of the control arm of

the ADAURA trial. This difference might be due to the presence of stage III disease in the ADAURA trial. However, even in stages Ib and II, the prognosis of the control arm of the ADAURA trial is indeed disappointing, urging the need to clarify the quality of preoperative staging and surgical resection in this study. Brain imaging was mandatory but PET-CT was not, and the completeness of lymph node dissection has not been reported so far.<sup>26</sup> Whether the improvement in DFS reported in the ADAURA trial will correlate with an improvement in OS will be scrutinized in the near future.

Since the BMF study was designed to collect data on a common cancer population from daily practice, it was limited by the shortness of the case-report form, the amount of missing data, the use of the 7th TNM, and the limited number of molecular alterations screened. These limitations might have been counterbalanced by the large number of patients included in the BMF study, and by the specific design of the study reported here, including on-site visits and a focus on *EGFR* mutations.

In conclusion, using a large national registry to study the molecular alteration and outcome of resected early stages NSCLC, we found that 12.9% of operated patients harbored *EGFR*-mutant tumors, which had no significant impact on DFS and OS.

## Clinical Practice Points

- The molecular profile of non-small cell lung cancer has been reported in Asian populations and in the United States, but it has not been analyzed in large scale studies in Western Europe.
- The prognostic impact of *EGFR* mutations is still discussed.
- We sought to determine the frequency and the prognostic impact of *EGFR* mutations in patients with resected non-small cell lung cancer included in the nationwide Biomarker France study.
- *EGFR* mutations were found in 12.9% of resected stage I-II NSCLC
- *EGFR* mutations were associated with 5-year DFS of 65% and 5-year OS of 75%.
- No difference was found between *EGFR*-mutant and *EGFR*-wt tumors regarding recurrence site, disease-free survival, and overall survival.
- The molecular profile of resected NSCLC should be determined as adjuvant targeted therapies could be beneficial in those patients.

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*Concept and design:* Mordant, Brosseau, Milleron, Barlesi, Westeel  
Acquisition, analysis, or interpretation of data: All

*Drafting of the manuscript:* Mordant, Brosseau, Milleron

Critical revision of the manuscript of important intellectual content: All

Statistical analysis: Missy, Langlais

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## Disclosure

Dr Mordant, Dr Brosseau, Dr Milleron, Dr Santelmo, Dr Fraboulet, Mrs Langlais, Dr Gossot, Dr Thomas, Dr Pujol, Dr Madelaine, Dr Lamy, Dr Missy, Dr Blons report no conflict of interest.

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