Original Article

Prevalence of *EGFR* gene mutations in patients with early-stage resectable non-small cell lung cancer in Spain: the ORIGEN study

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Background: Geographic variability in epidermal growth factor receptor (*EGFR*) mutation rates in early-stage non-small cell lung cancer (NSCLC) has been reported. However, the frequency of *EGFR* mutations in patients with early-stage resected NSCLC in Spain has not been previously investigated. We aimed to determine the prevalence of *EGFR* mutations in patients with early-stage resected NSCLC in Spain.

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Methods: This was an observational, multicenter, cross-sectional study. Sensitizing *EGFR* mutations were assessed via real-time polymerase chain reaction (PCR)-based molecular analysis with the Idylla™ EGFR Mutation Test, and next-generation sequencing (NGS) analysis with the Oncomine™ Precision Assay.

Results: A total of 172 patients with surgically resected non-squamous NSCLC were analysed. Median age was 67.5 years and 57.6% were male, 96.5% had adenocarcinoma histology and 65% had stage IA/IB. *EGFR* mutations were found using Idylla™ EGFR Mutation Test in 25 patients out of 172 patients (14.5%), which consisted of exon 19 deletion in 13 patients (7.6%), exon 21 L858R point mutation in 11 (6.4%), and exon 20 mutation (T790M) in 1 (0.6%) patient. The Oncomine™ test was conducted in 128 patients, which detected exon 19 deletions in 10 patients (7.8%), exon 21 mutations in 10 patients (7.8%), and exon 20 insertions in 5 (3.9%) patients. The Oncomine™ test was able to detect concurrent mutations in tumor suppressor genes (*TP53*, *PI3KCA*, *CDKN2A*, *PTEN*) and another actionable alteration beyond *EGFR*, such as mutations in *KRAS G12C* (22%), *ERBB2* (6%), *METex14* (2%), *BRAF V600E* (2%) and *ALK* and *ROS1* fusions (2%, each).

Conclusions: The prevalence of *EGFR* mutations in early stage (IA–IIIB), resectable, non-squamous NSCLC observed in our study is consistent with that reported in advanced NSCLC in Spain. Molecular testing is crucial in early-stage NSCLC and can be performed either with single-gene testing or NGS.

Keywords: Non-small cell lung cancer (NSCLC); early stage; epidermal growth factor receptor mutations (*EGFR* mutations); molecular testing

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Introduction

Epidermal growth factor receptor (*EGFR*) mutations are the second most common oncogenic driver in non-small cell lung cancer (NSCLC), following *KRAS* mutations (1,2). Exon 19 deletions and the exon 21 L858R point mutations are the most frequent *EGFR* actionable alterations, accounting for 85–90% of all *EGFR* mutations. Less frequent sensitizing *EGFR* alterations include exon 20 insertions (4–12%) and the following single nucleotide variants (SNVs): G719X, S768I, and L861Q (3%) (2-6).

The standard of care for patients with advanced NSCLC harboring actionable common *EGFR* mutations is first-line osimertinib (7). In surgically resected tumors harboring common *EGFR* mutations, the ADAURA study demonstrated that adjuvant osimertinib provided a significant benefit in terms of disease-free survival (DFS) (8) and overall survival (OS) (9). This study established adjuvant osimertinib therapy as a new standard of care for these patients. Therefore, the detection of *EGFR* mutations in surgically resected NSCLC is crucial for selecting patients who are candidates to adjuvant osimertinib (3). Molecular testing to identify *EGFR* mutations is recommended by guidelines not only for advanced NSCLC, but also for early-stage NSCLC (10-16).

Previous studies reported that the frequency of *EGFR* mutations in advanced NSCLC ranges from 12.8% to 14.1% in Europe (3,4). Consistently, in Spain, several observational studies conducted between 2005 and 2015 identified sensitizing *EGFR* mutations in 11.6% to 16.6% of

Highlight box

Key findings

- Epidermal growth factor receptor (*EGFR*) mutations were detected by Idylla™ EGFR Mutation Test, a polymerase chain reaction-based molecular test, in 14.5% of patients.
- Next-generation sequencing (NGS) provided consistent results but detected a higher percentage of *EGFR* mutations and additional actionable drivers and concurrent genomic alterations.

What is known and what is new?

- Studies of early-stage non-small cell lung cancer (NSCLC) in Western populations have shown *EGFR* mutation rates similar to those in advanced-stage NSCLC patients.
- The prevalence of *EGFR* mutations in patients with early-stage resected NSCLC has not been previously reported in Spain.

What is the implication, and what should change now?

- Molecular testing is crucial in early-stage NSCLC and can be performed either with single-gene testing or NGS.

patients with advanced NSCLC (17-19). Studies on early-stage NSCLC in Western populations have reported *EGFR* mutation rates comparable to those observed in advanced NSCLC patients (20-22).

To our knowledge, the frequency of *EGFR* mutations in patients with early stage resected NSCLC in Spain has not been previously investigated. This study provides information about the prevalence of this genomic alteration in Spain, but also contributes to understanding the variability in *EGFR* mutation rates in early-stage NSCLC across European countries.

We conducted a multicenter, observational study to determine the prevalence of *EGFR* mutations in patients with surgically resected early stage (IA to IIIB) non-squamous NSCLC in Spain using real-time polymerase chain reaction (PCR)-based molecular *EGFR* mutation tests. We used this PCR-based technique because in access to NGS in Spain is not universal, especially in the context of early-stage disease. To complement this information, we also evaluated the utility of next-generation sequencing (NGS) in the same cohort, as some centers had already adopted this approach and to compare the results obtained using both methods. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1146/rc).

Methods

Study design

This observational, non-interventional, multicenter, cross-sectional study was conducted at 19 centers in Spain (Table S1). Preliminary results from this study were presented at the ESMO Congress 2023 (23). The study was performed in accordance with the applicable local regulations for non-interventional and/or observational studies and following the ethical principles of the Declaration of Helsinki (as revised in 2013) and Good Clinical Practice guidelines (24). The study protocol and informed consent forms were reviewed and approved by the Ethical Committee of the University Hospital 12 de Octubre (Madrid, Spain; No. CEIm 21/230, 25 May 2021). All the study participants provided informed consent before undergoing any study procedure.

Study population

Patients were eligible for the study if they were male or female, were older than 18 years of age, had been histologically or cytologically diagnosed with early-stage [i.e., IA to IIIB, American Joint Committee on Cancer (AJCC) 8th Edition] (25) non-squamous NSCLC, and had their tumor surgically removed within 6 weeks before enrollment, or had undergone planned surgery within 8 weeks after inclusion in the study. Patients who presented with metastatic or unresectable tumors were excluded.

Study objectives

The primary endpoint of the study was to determine the prevalence of sensitizing *EGFR* mutations using real-time PCR-based molecular analysis in patients with early-stage nonsquamous NSCLC with stage IA–IIIB disease (according to the AJCC 8th), who underwent surgical resection in Spain. The secondary endpoints were to describe the baseline characteristics of the study population, to compare the results obtained using the Idylla™ EGFR Mutation Test (Biocartis, Mechelen, Belgium) with those obtained using the Oncomine™ Precision Assay GX (Thermo Fisher Scientific Inc., Waltham, MA, USA) and to determine the prevalence of uncommon *EGFR* mutations.

Study assessments and data collection

Data on the following variables were collected during the study visit from the available medical records: demographics, characteristics of the tumor [e.g., histological type, clinical and pathological staging according to the AJCC 8th Edition, type of diagnostic biopsy, adjuvant therapy, and time from first visit to any medical consultation (primary care or specialist care) until surgery], presence of residual tumor (R0 or R1), and *EGFR* mutation results based on the Idylla™ EGFR Mutation Test and Oncomine™ Precision Assay. Both tests are described in Table S2, and the *EGFR* mutations that were detected by the Idylla™ EGFR Mutation Test are shown in Table S3. The presence of concurrent pathogenic genomic alterations was assessed using the Oncomine™ Precision Assay. Compared to the Idylla™ EGFR Mutation Test, NGS performed with the Oncomine™ Precision Assay can identify distinct EGFR mutations in exons 18–21. Furthermore, the Oncomine™ Precision Assay is capable of simultaneously detecting hotspot mutations, copy number variations, and gene fusions involving 50 key genes, such as *EGFR*, *ALK*, *ROS1*, *RET*, *NTRK* and *KRAS*.

Surgical samples were analyzed at the local laboratory of each participating center using the Idylla™ EGFR Mutation Test, which is able to detect 51 EGFR mutations

including exon 18 (G719A/S/C), 36 deletions in exon 19, 2 exon 20 mutations (T790M, S768I), 5 insertions in exon 20 (c.2310_2311insGGT; p.D770_N771insG and c.2319_2320insCAC; p.H773_V774insH) and 2 exon 21 mutations (L858R, L861Q). However, it does not detect all EGFR exon 20 insertion mutations, as some variants fall outside its coverage (26,27). The Oncomine™ Precision Assay was performed on all surgical samples from the study subjects who provided their informed consent for NGS testing. The analysis was conducted in two central laboratories (*Molecular Biology Core Facility* from the Hospital Clínic of Barcelona and the *Laboratori Core d'Anàlisi Molecular* from the Hospital Universitari of Bellvitge and Institut Català d'Oncologia, Barcelona; Spain).

Statistical analysis

Based on the number of newly diagnosed NSCLC patients (n=22,000) in Spain in 2020 (28) and assuming that the percentage of patients with early stage and surgically resected NSCLC is approximately 25%, it was estimated that a total sample of 173 patients with early stage and surgically resected NSCLC would be required to detect a prevalence of *EGFR* mutations of 11.7%, with a precision of ±5%, and assuming a dropout rate of 10%.

The statistical analyses were primarily descriptive. Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented using descriptive statistics (mean and standard deviation or median and interquartile range). Missing data were not imputed.

The prevalence of sensitizing *EGFR* mutations in the study population was based on the percentage of evaluable patients with common sensitizing *EGFR* mutations (deletion of exon 19 and point mutation in exon 21), as detected by the Idylla™ EGFR Mutation Test and the Oncomine™ Precision Assay; these results are presented with the corresponding 95% confidence intervals (CIs). The concordance between the Idylla™ EGFR Mutation Test and the Oncomine Precision Assay in surgical samples was assessed using Cohen's kappa index. Additionally, the sensitivity, specificity, and positive and negative predictive values of the Idylla™ EGFR Mutation Test for comparing the mutation status between diagnostic samples (bronchoscopy/thoracic puncture) and surgical samples were calculated for the evaluable study population.

Finally, a multivariate logistic regression model was used to estimate the associations between *EGFR* mutation status and demographic and clinical characteristics of the evaluable study population. The following variables were included in the model: *EGFR* mutation status (*EGFR* mutated versus *EGFR* wild-type) of tumor samples as the dependent variable and key demographic and clinical characteristics, such as age (continuous), sex (female *vs.* male), histology (adenocarcinoma *vs.* non-adenocarcinoma), programmed death-ligand 1 (PD-L1) status (positive *vs.* negative) and Eastern Cooperative Oncology Group (ECOG) performance status (0 *vs.* ≥1), as independent variables. A stepwise backward approach was used for fitting the regression model.

All the analyses were performed using IBM SPSS version 26 software.

Results

Patients' disposition and characteristics

Between August 2021 and February 2022, 183 patients were consecutively enrolled in the study by the Departments of Oncology of 19 Spanish centers. Of these, 172 met all the selection criteria and were ultimately included in the analyses (Figure S1). The patients had a median age of 67.5 years, 57.6% of the patients were male, and 83.1% were current or former smokers. The most common histological type was adenocarcinoma (96.5%), and most patients included in the study had stage IA/IB disease (65.1%). The baseline clinical characteristics of the patients are shown in *Table 1*. Additionally, only 38 (22.9%) of 166 patients with available information planned to receive adjuvant chemotherapy. The adjuvant chemotherapy regimens according to disease stage are shown in Table S4.

Frequency of EGFR mutations as determined by the Idylla™ EGFR Mutation Test

EGFR mutations were detected in 25 patients (14.5%; 95% CI: 0.7–28.3%) using the Idylla™ EGFR Mutation Test. Subjects harboring sensitizing *EGFR* mutations were more likely to be females (76% *vs.* 36.7%) and nonsmokers (40% *vs.* 9.5%) (*Table 1*). The following *EGFR* mutations were detected in this study using the Idylla™ EGFR Mutation Test: exon 19 deletion in 13 patients (7.6%), exon 21 L858R point mutation in 11 patients (6.4%), and exon 20 mutation (T790M) in 1 patient (0.6%) (*Figure 1*). The list of EGFR mutations detected using the Idylla™ test and clinical staging are shown in *Table 2*.

Table 1 Baseline clinical characteristics

Characteristics	Total (n=172)	EGFR wild type (n=147)	EGFR mutated (n=25)
Age (years)	67.5 (61.0–72.5)	68.0 (61.0–72.0)	66.0 (61.0–73.0)
Sex			
Male	99 (57.6)	93 (63.3)	6 (24.0)
Female	73 (42.4)	54 (36.7)	19 (76.0)
Smoking history			
Smoker	54 (31.4)	50 (34.0)	4 (16.0)
Former smoker	89 (51.7)	80 (54.4)	9 (36.0)
Non-smoker	24 (14.0)	14 (9.5)	10 (40.0)
Passive smoker	1 (0.6)	0 (0.0)	1 (4.0)
Unknown	4 (2.3)	3 (2.0)	1 (4.0)
Histology			
Adenocarcinoma	166 (96.5)	141 (95.9)	25 (100.0)
Large cell carcinoma	3 (1.7)	3 (2.0)	0 (0.0)
Sarcomatoid carcinoma	1 (0.6)	1 (0.7)	0 (0.0)
Carcinoid tumor	1 (0.6)	1 (0.7)	0 (0.0)
Adenosquamous carcinoma	1 (0.6)	1 (0.7)	0 (0.0)
Pathological stage			
IA	81 (47.1)	71 (48.3)	10 (40.0)
IB	31 (18.0)	24 (16.3)	7 (28.0)
IIA	7 (4.1)	7 (4.8)	0 (0.0)
IIB	25 (14.5)	19 (12.9)	6 (24.0)
IIIA	19 (11.0)	17 (11.6)	2 (8.0)
IIIB	4 (2.3)	4 (2.7)	0 (0.0)
Unknown	5 (2.9)	5 (3.4)	0 (0.0)
Diagnostic sample			
Biopsy	16 (9.3)	15 (10.2)	1 (4.0)
Bronchoscopy	30 (17.4)	23 (15.6)	7 (28.0)
Intraoperative diagnosis	1 (0.6)	1 (0.7)	0 (0.0)
Surgery	91 (52.9)	74 (50.3)	17 (68.0)
Trans-thoracic needle biopsy	34 (19.8)	34 (23.1)	0 (0.0)
Surgery			
Lobectomy	135 (78.9)	115 (78.8)	20 (80.0)
Segmentectomy	25 (14.6)	22 (15.1)	3 (12.0)
Pneumonectomy	5 (2.9)	4 (2.7)	1 (4.0)
Wedge resection	6 (3.5)	5 (3.4)	1 (4.0)
Adjuvant chemotherapy			
No	128 (77.1)	110 (78.0)	18 (72.0)
Yes	38 (22.9)	31 (22.0)	7 (28.0)

Data are presented as median (IQR) or n (%). There are missing data in the following characteristics: ECOG PS, surgery, resection margin and adjuvant chemotherapy. ECOG, European Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; IQR, interquartile range; PS, performance status; R0, complete tumor resection; R1, microscopic residual tumor.

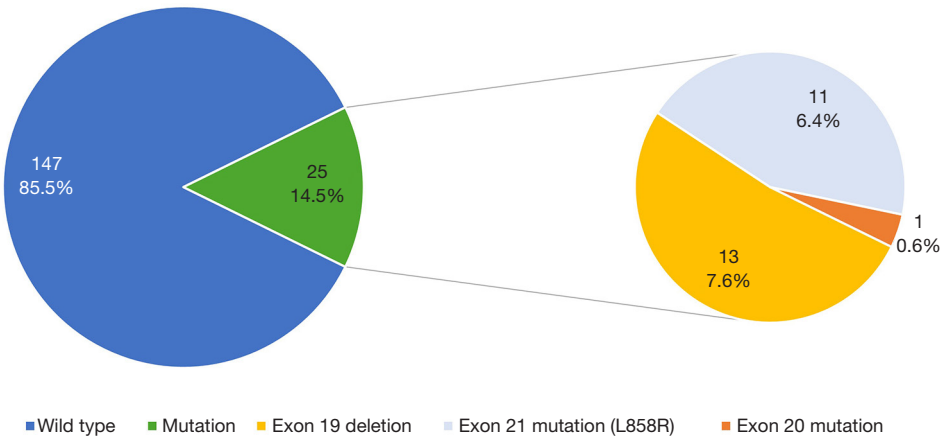

Figure 1 *EGFR* mutations based on Idylla™ test. *EGFR*, epidermal growth factor receptor.

Table 2 *EGFR* mutation detected using the Idylla™ EGFR Mutation Test, categorized according to TNM pathological staging

Stage	Mutated	Exon 19 deletion	L858R mutation	Exon 20 mutation
IA (n=81)	10 (12.3)	4 (4.9)	6 (7.4)	0 (0.0)
IB (n=31)	7 (22.6)	4 (12.9)	3 (9.7)	0 (0.0)
IIA (n=7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IIB (n=25)	6 (24.0)	3 (12.0)	2 (8.0)	1 (4.0)
IIIA (n=19)	2 (10.5)	2 (10.5)	0 (0.0)	0 (0.0)
IIIB (n=4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown (n=5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total (n=172)	25 (14.5)	13 (7.6)	11 (6.4)	1 (0.6)

Data are presented as n (%). *EGFR*, epidermal growth factor receptor; TNM, tumor, node, metastasis.

Table 3 *EGFR* testing results according to the diagnostic method used

Variable	Idylla™	Oncomine™ Precision Assay
Samples tested	172	128*
EGFR mutation	25 (14.5)	25 (19.5)
Other *EGFR* alteration	–	1 amplification
Exon 19 deletion	13 (52.0)	10 (40.0)
Exon 20 mutation	1 (4.0)	5 (20.0)
L858R mutation	11 (44.0)	10 (40.0)

Data are presented as n (%). *, the Oncomine™ Precision Assay was not performed in four patients with *EGFR* mutations detected by Idylla™. Among these patients, three patients had exon 19 deletions, and one had an exon 21 L858R mutation. *EGFR*, epidermal growth factor receptor.

Frequency of EGFR mutations as determined by the Oncomine™ Precision Assay

The Oncomine™ Precision Assay was performed on surgical samples from 128 patients. Compared to the Idylla™ test results shown above, *EGFR* mutations were detected in 25 (19.5%) of the 128 patients (*Table 3*). More specifically, the Oncomine™ test detected exon 19 deletions in 10 patients (7.8%), exon 21 mutations in 10 patients (7.8%), and exon 20 insertions in 5 patients (3.9%). The following exon 20 mutations were identified using the Oncomine™ test: c.2319_2320insTGTCCACAC, c.2314_2319dup, c.2308G>A, c.2408G>T, and c.2308_2309insCCAGCGTGG. Interestingly, the Idylla™ and Oncomine™ tests detected different mutations in exon

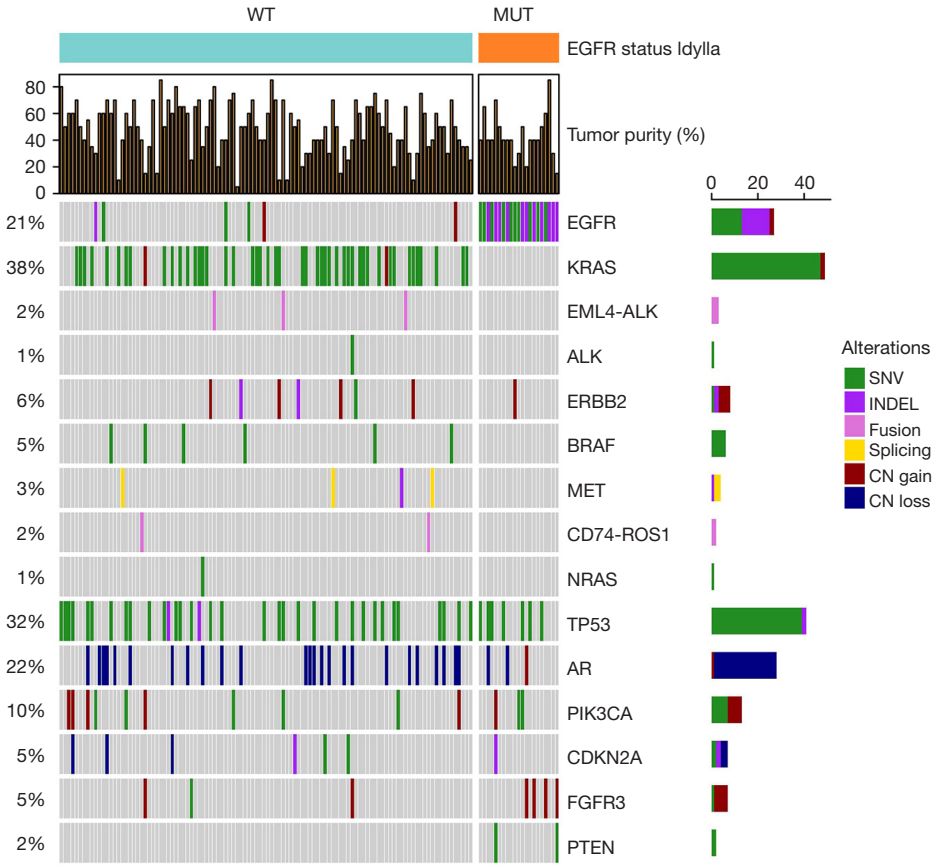

Figure 2 Oncoplot showing the most relevant genomic alterations detected by the Oncomine™ Precision Assay test in patients with *EGFR* WT or *EGFR* mutated tumors as detected by the Idylla test. *ALK*, anaplastic lymphoma kinase; *BRAF*, B-rapidly accelerated fibrosarcoma; *CD74*, cluster of differentiation 74; *CDKN2A*, cyclin-dependent kinase inhibitor 2A; CN, copy number; *EGFR*, epidermal growth factor receptor; *EML4*, Echinoderm microtubule-associated protein-like 4; *ERBB2*, erythroblastic oncogene B2; *FGFR3*, fibroblast growth factor receptor 3; *KRAS*, Kirsten rat sarcoma virus; *MET*, mesenchymal-epithelial transition; MUT, mutated; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *ROS1*, proto-oncogene tyrosine-protein kinase-1; SNV, single nucleotide variation; WT, wild type.

20 in the same patient, namely, T790M (c.2369C>T) and c.2308_2309insCCAGCGTGG, respectively.

The concordance analysis between the two tests showed a kappa coefficient of 0.89 (Table S5). Furthermore, using Oncomine™ as a reference test, the Idylla™ test showed high specificity (100%), sensitivity (84.0%; 95% CI: 77.6–90.4%), positive predictive value (100%), and negative predictive value (96.3%; 95% CI: 93.0–99.5%). A subsequent concordance analysis between the two tests excluding the *EGFR* exon 20 insertion mutations yielded a kappa coefficient of 1.00.

We performed a multivariate logistic regression analysis, and we observed that age [odds ratio (OR) 0.973, 95% CI: 0.964–0.983] and female sex (OR 2.435, 95% CI: 1.058–5.604) were significantly associated with *EGFR* mutation detected by the Oncomine™ Precision Assay (Table S6).

Additional alterations identified by OncomineTM Precision Assay

The Oncomine™ Precision Assay enabled the detection of concurrent genomic alterations in patients with *EGFR*-mutant NSCLC (*Figure 2*), being the most common concurrent alterations in these patients *TP53*, *FGFR3*, *PIK3CA*, *PTEN*, and *CDKN2A*. Furthermore, NGS allowed the identification of additional actionable alterations in

the remaining patients: *KRAS*^{G12C} (22%), *ERBB2* (6%), *METex14* (2%), *EML4-ALK* fusions (2%), *BRAF*^{V600E} (2%), and CD74-*ROS1* fusions (2%). We also detected *ALK* imbalance in 6 cases (4%) and 1 case with *RET* imbalance (1%). An *ALK* SNV (C1156*) was detected in 1 patient (variant allele frequency =0.038).

Discussion

In our study, we found that 14.5% of the patients harbored a sensitizing *EGFR* mutation. This frequency is consistent with the results of other studies conducted in Western countries that included patients with early-stage NSCLC. Similarly, as observed in other studies, patients with *EGFR*-mutated tumors in our study were more likely to be female, nonsmokers, and have adenocarcinoma histology (20,21,29,30). *EGFR* testing using the Idylla™ test showed that the most frequent variants consisted of exon 19 deletions, followed by exon 21 L858R point mutations, accounting for more than 90% of all the sensitizing mutations that were detected. Exon 20 mutations were found in only 4% of patients. Similar rates have been previously reported in similar studies assessing the frequency of *EGFR* mutations in surgical samples from early-stage NSCLC patients (20,21,29,30). To our knowledge, this is the first epidemiological study to assess the prevalence of sensitizing *EGFR* mutations in patients with surgically resected early-stage NSCLC in Spain.

In our study, we used two *EGFR* testing methods: the Idylla™ EGFR Mutation Test, which is a fully automated, real-time (RT) quantitative polymerase chain reaction (qPCR)-based molecular test that covers 51 mutations in exons 18–21, and the Oncomine™ precision assay, which is an integrated NGS-based test. The Oncomine™ precision assay is considered to be a more sensitive method than qPCR because it covers the entire *EGFR* coding sequence and allows the assessment of additional concurrent genomic alterations, covering 50 cancer driver genes. Both tests provided consistent results regarding exon 19 and exon 21 mutations, but the Oncomine™ test detected a higher percentage of *EGFR* mutations, with five additional mutations located in exon 20 that were not covered by the Idylla™ test (31). Moreover, by using the Oncomine™ test, we detected additional concurrent genomic alterations in patients with *EGFR*-mutant NSCLC, such as *TP53*, *FGFR3*, *PIK3CA*, *PTEN*, and *CDKN2A*, as well as additional actionable alterations in patients with wild-type *EGFR*, such as *KRAS G12C*, *BRAF V600E* and *ERBB2* mutations, *METex14* and *ALK* and *ROS1* fusions. These findings are clinically relevant because the presence of concurrent mutations in *TP53* and *PIK3CA* has been associated with a worse prognosis and a greater risk of histological transformation upon osimertinib treatment (32-35). Furthermore, we believe that this information may be highly relevant for clinical practice, considering that new additional targeted therapies, such as alectinib, an *ALK* inhibitor, have demonstrated clinical benefit in the adjuvant setting for *ALK* rearranged tumors, as observed in the ALINA study (36). In addition, detecting other actionable alterations, such as *RET* rearrangements, could allow the enrollment of patients in ongoing clinical trials. On the other hand, the incorporation of immunotherapy in the adjuvant setting is also increasing the relevance of molecular testing in surgically resected NSCLC, as *EGFR*- and *ALK*-positive tumors are not deemed candidates for adjuvant atezolizumab or pembrolizumab. In fact, real-world evidence and guidelines endorse the use of NGS rather than RT-PCR as the preferred method for identifying a wider array of actionable *EGFR* mutations in NSCLC (12,16,26,37). However, by the time the present study was conducted, access to NGS testing for *EGFR* mutation screening and detection had not been universally implemented within the Spanish Health System. However, although the Oncomine™ test is a more sensitive technique for detecting *EGFR* mutations, allowing the detection of some false negatives that are missed by conventional testing methods, the Idylla™ test is simple, fast, widely implemented, and reliable for detecting common *EGFR* mutations. Furthermore, both techniques showed high concordance, and the Idylla™ test showed high sensitivity, specificity, and predictive value. A similar high concordance between RT-PCR and NGS testing technologies has been previously reported (27).

The emergence of *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) has changed the paradigm for the management of *EGFR*-mutated NSCLC. Several *EGFR* mutations are sensitive to TKIs, particularly osimertinib, a third-generation *EGFR*-TKI that prolongs progression-free survival and OS in advanced and early-stage *EGFR*-mutated NSCLC patients (8,9,38). However, none of the patients included in the study received adjuvant osimertinib because it was not reimbursed in Spain when the study was conducted. Currently, osimertinib is reimbursed by the Spanish National Health System for patients with completely resected stage IB-IIIA NSCLC with common *EGFR* mutations. In addition, although it is not yet a widely

adopted standard practice, reflex single gene or NGS testing has been recommended to optimize the molecular characterization of NSCLC (27). A process in which the pathologist is responsible for initiating and controlling testing for a set of preapproved biomarkers (including *EGFR*) at the time of initial diagnosis, without direct oncologist involvement, has contributed to enhancing the quality of biomarker testing, shortening turnaround time, and improving patient outcomes (11,37,39-41). Moreover, recently published international guidelines recommend reflex biomarker testing for all patients diagnosed with non-squamous NSCLC, regardless of disease stage (16).

Our study had several limitations. Despite consecutive and prospective sampling, some sources of selection bias cannot be ruled out. We included only patients with non-squamous NSCLC, as *EGFR* mutations are generally more clinically relevant and prevalent in this histological subtype (8). In addition, NGS was not conducted for all patients because not all patients provided the consent or have adequate material.

Conclusions

In conclusion, the prevalence of *EGFR* mutations in early stage, resectable, nonsquamous NSCLC in Spain is consistent with the observed frequency in advanced NSCLC and with previous reports in this clinical setting. Whenever feasible, NGS is the technology of choice because it provides a more complete genomic profile. However, single-gene testing could also be considered a valid method to screen for common EGFR mutations in early-stage NSCLC to identify patients who are candidates for adjuvant osimertinib, following the recommendations of the Spanish and European clinical guidelines (12,15).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed in accordance with the applicable local regulations for noninterventional and/or observational studies and following the ethical principles of the Declaration of Helsinki (as revised in 2013) and Good

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