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BRIEF RESEARCH ARTICLE

Efficacy of tyrosine kinase inhibitors in *EGFR*-mutant lung cancer women in a real-world setting: the WORLD07 database

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Abstract
Background The WORLD07 project is a female specific database to assess the characteristics of women with lung cancer.
Methods WORLD07 database sets up in 2007, and prospectively stores clinical characteristics, treatment, outcome, and follow-up of lung cancer women. All women with epidermal growth factor receptor (*EGFR*) mutation non-small cell lung cancer (NSCLC) were selected for this analysis.
Results From October 2007 to December 2012, a total of 1775 NSCLC women were recruited. *EGFR* mutation was identified in 34.4% of patients. Upfront EGFR tyrosine kinase inhibitor (TKI) reported a response rate of 60%, a median progression-free survival of 11.7 months, and median overall survival of 23.0 months. EGFR TKI, EGFR-mutation type, and smoking status did not impact in the outcome of treated women.
Conclusion Prevalence of *EGFR* mutation in women with NSCLC is higher than overall population with NSCLC. Efficacy of EGFR TKI in this real-world setting is similar to that previously reported.

Keywords *EGFR* mutant · NSCLC · Women · TKI · Advanced

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Introduction

Deaths from lung cancer continue to rise in most European countries, as well as worldwide [1]. In 2017, lung cancer mortality rates will overcome those predicted in breast cancer among middle-aged European women [2]. Of note, between 2002 and 2012, overall lung cancer mortality in women increased by 17.5% in the EU in women, reaching 56% among Spanish women [3]. Varying patterns of smoking prevalence across different countries could explain such differences [3].

Personalised treatment, by the introduction of orally available small molecule tyrosine kinase inhibitors (TKIs) according to oncogenic driver mutations, has changed the treatment landscape of advanced non-small cell lung cancer (NSCLC) patients [4]. In Caucasian patients, the most frequent genetic alterations in advanced adenocarcinoma lung cancer are *KRAS* mutation ~29%, *EGFR* mutations ~11%, and *ALK* rearrangements ~5% [5]. Other less frequent mutations include: *MET* mutations (exon 14) in 4% [6], *BRAF* mutations in ~2%, and the *HER2* mutation [5] and *ROS1* rearrangements [7] in 1% of NSCLC patients, respectively.

Despite geographical differences in *EGFR* mutation among NSCLC patients, this mutation rate is higher in women compared to men, and in never-compared with ever-smokers [5, 8]. These mutations predict sensitivity to first- and second-generation EGFR TKIs such as erlotinib, gefitinib, afatinib, or icotinib (only available in China). Both, response rate and progression-free survival with EGFR TKIs are superior to standard first-line platinum doublet chemotherapy, making them the standard of care [9]. Moreover, this benefit with EGFR TKIs is significantly higher in women than in men [10].

All these observations prompted the Association for Research Lung Cancer in Women (ICAPEM) to create a female-specific database to prospectively analyse the characteristics of Spanish women with lung cancer and launched the WORLD07 project. One of the aims of this study was to characterize the clinical aspects and outcomes in a real-world setting of Spanish women diagnosed with NSCLC and *EGFR*-mutation included in the WORLD07 database.

Materials and methods

Design and study population

The WORLD07 project was a prospective, multicenter, female-specific epidemiological study conducted across 38 cancer centers through Spain, in accordance with the Declaration of Helsinki including all amendments. The Institutional Review Board at each participating hospital in the project approved the study, and all patients provided their written informed consent for the use of their data prior to inclusion. Clinical parameters included in the database have already been published [11]. Molecular analysis for *EGFR* mutation status was not centralized and different methods were used (not collected in the database).

From October 2007 to December 2012, a total of 2072 women with lung cancer were recruited and followed up until December 2013. Of these, 12 women were non-eligible, and hence, the study population comprised of 2060 patients. Women with small cell lung cancer were excluded for the present analysis and a total of 1775 NSCLC women were included.

Assessment of endpoints

Disease control rate (DCR) was defined as the percentage of patients on treatment with partial response, complete response, and stable disease at first imaging assessment according to the RECIST v1.1 criteria, which was not centrally review [12].

Progression-free survival (PFS) was calculated from the initiation of treatment until the date of progression or death (whichever came first), with censoring at the date of last follow-up if the patient had not progressed. Overall survival (OS) was calculated from the initiation of therapy until the date of death.

Statistical analysis

All patients were included in the statistical calculations. Follow-up was obtained in all cases, and was censored on December 31st 2013 when database was locked. The Kaplan–Meier method and log-rank tests were used to analyse and compare OS and PFS between different clinical parameters. p values were considered significant at <0.05 value.

Surviving patients were censored at the last follow-up date. All statistical analyses were carried out with the Statistical Package for the Social Sciences (version 13.0; SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

An *EGFR*-mutation test was performed for 922 women (52%) of the whole population and *EGFR*-mutation positivity was reported in 318 out of 922 (34.4%) women. According to *EGFR* mutation subtype, 174 (54.7%)

patients had *exon 19* deletions, 82 (25.7%) had exon 21 *L858R* substitution, and 14 (4.4%) patients had *exon 20* mutations, respectively. *EGFR* mutation subtype was unknown in 37 patients (11%), and 7 patients (2.2%) had double *EGFR* mutations. Clinicopathologic characteristics of *EGFR*-mutant vs. EGFR wild-type NSCLC women are summarized in Table 1. Women whose tumours harboured an *EGFR* mutation were older than those with wild-type tumours ($p < 0.001$) were usually never-smokers ($p < 0.001$) and adenocarcinoma ($p = 0.001$) was the most common histologic subtype.

A total of 227 patients had an advanced *EGFR*-mutant NSCLC, and 51 patients received upfront platinum-based chemotherapy followed by EGFR TKI as second-line treatment, whereas the others were treated with the first-generation EGFR TKI as the first-line treatment (gefitinib 57.1% and erlotinib 42.4%, Table 1).

Response rate to EGFR TKIs

Among advanced EGFR-mutant NSCLC women treated with upfront EGFR TKI and evaluable disease ($n = 155$), there were no differences in the proportion of patients who achieved an objective tumour response rate with gefitinib compared to erlotinib [50 (56.1%) vs. 41 (62.1%); $p = 0.70$]. Disease control rate was achieved in 80.8 and 83.3% of patients, respectively (Table 2).

Progression-free survival

Median PFS was 5.4 months (95% CI 4.0–6.8) for those patients treated with the first-line platinum-based chemotherapy compared to 11.7 months (95% CI 9.7–13.7) for those patients treated with upfront EGFR TKI.

Among women treated with EGFR TKI, there were no statistically significant differences in PFS according to EGFR TKI prescribed (10.8 months with gefitinib and 13.6 months with erlotinib, $p = 0.31$, respectively, Fig. 1), or common *EGFR*-mutation type (13.1 months in *EGFR Del19* vs. 9.9 in *EGFR L858R* substitution, $p = 0.59$, Fig. 2). No significant differences in PFS according to smoking status (never-smoker vs. others, 12.4 vs. 10.7; $p = 0.20$), age (<65 vs. ≥65 years, 10.0 vs. 13.2; $p = 0.23$), and treatment line with EGFR TKI (first line vs. second line; 11.7 vs. 12.4; $p = 0.93$), were reported.

Overall survival

The median survival time of patients with advanced disease receiving upfront platinum-based chemotherapy was 19.2 months (95% CI 9.3–29.1). In contrast, patients treated with upfront EGFR TKI achieved an OS of 23.0 months (95% CI 19.8–26.2) without differences according to the EGFR TKIs prescribed (median OS gefitinib vs. erlotinib: 22.7 vs. 24.0 months, $p = 0.29$, respectively, Fig. 1) or

Table 1 Clinicopathologic characteristics of patients according to *EGFR* mutation status

	EGFR wild type $N = 604$	*EGFR*-mutant $N = 318$	p**
Median age (range)-years	60 (22–90)	65 (31–99)	<0.001
Histology, *N* (%)			0.001
Adenocarcinoma	516 (85.4)	295 (92.7)	
Squamous	30 (5)	5 (1.6)	
Smoking status, *N* (%)			0.001
Never smoker	259 (42.8)	229 (72.0)	
Current	241 (39.9)	37 (11.6)	
Former smoker	98 (16.2)	45 (14.2)	
EGFR mutation subtype, *N* (%)[a]	NA		NA
Exon *19 deletion*		174 (54.7)	
Exon *21 L858R*		82 (25.7)	
Exon *20 mutations*		14 (4.4)	
Unknown		37 (11)	
EGFR TKI treatment line ($N = 227$)[b]	NA		NA
First-line treatment		176 (77.5)	
Second-line treatment		51 (22.5)	

NA nor applicable

** Chi-square test

[a] 7 patients double *EGFR* mutation and *4 EGFR* mutation exon 18 (not included in the table)

[b] Treatment in 227 advanced *EGFR*-mutant patients

Table 2 Response rate to first-line EGFR TKIs

	Gefitinib $N = 89$	Erlotinib $N = 66$	p
Objective response	50 (56.1%)	41 (62.1%)	0.7
Complete response	2 (2.2%)	2 (3.0%)	
Partial response	48 (53.9%)	39 (59.1%)	
Stable disease	22 (24.7%)	14 (21.2%)	
Progressive disease	6 (6.7%)	8 (12.1%)	
Disease control	72 (80.8%)	55 (83.3)	

common *EGFR*-mutation type (23.9 months in *EGFR Del19* vs. 22.7 months in *EGFR L858R* substitution, $p = 0.50$, Fig. 2). No statistically significant differences in OS were reported according to smoking status (never-smoker vs. others: 22.9 vs. 16.8, $p = 0.37$), age (<65 vs. ≥65 years: 24.0 vs. 21.3; $p = 0.09$), and treatment line (first line vs. second line, 23.0 vs. 14.7; $p = 0.19$) were reported in *EGFR*-mutant NSCLC women treated with EGFR TKI.

Discussion

In this analysis conducted in a real-world setting among *EGFR*-mutant NSCLC women, upfront first-generation EGFR TKIs achieved a response rate of 60%, median PFS and OS of 11.7 and 23.0 months, respectively. These results are comparable to the efficacy reported with gefitinib and erlotinib in randomized phase III clinical trials [13, 14]. However, more than 20% of women with *EGFR*-mutant tumours treated between 2007 and 2012 did not receive personalised treatment upfront in our analysis, similar to previously reported data [5], and this lack of personalised treatment could have a negative impact in the outcome of these patients [5, 15]. It is important implementation of molecular tumour boards for avoiding inequalities in the access to targeted therapies. Tumour genotyping is an essential routine diagnostic tool in clinical practice, notably in cases of adenocarcinoma histology [4]. Both lack of Spanish molecular profiling program and WORLD07 data set initiated in 2007 may justify why only

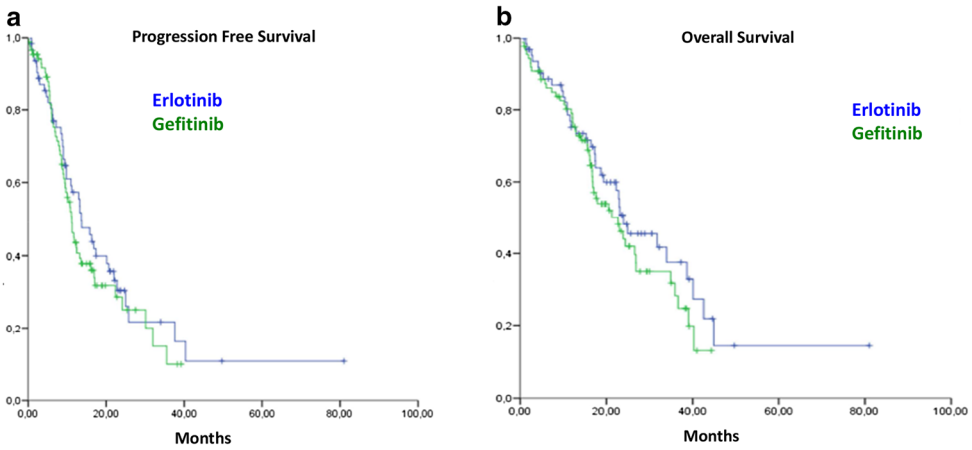

Fig. 1 **a** Progression-free survival and **b** overall survival in advanced *EGFR*-mutant NSCLC women treated with upfront EGFR TKI according to EGFR TKI prescribed (gefitinib vs. erlotinib)

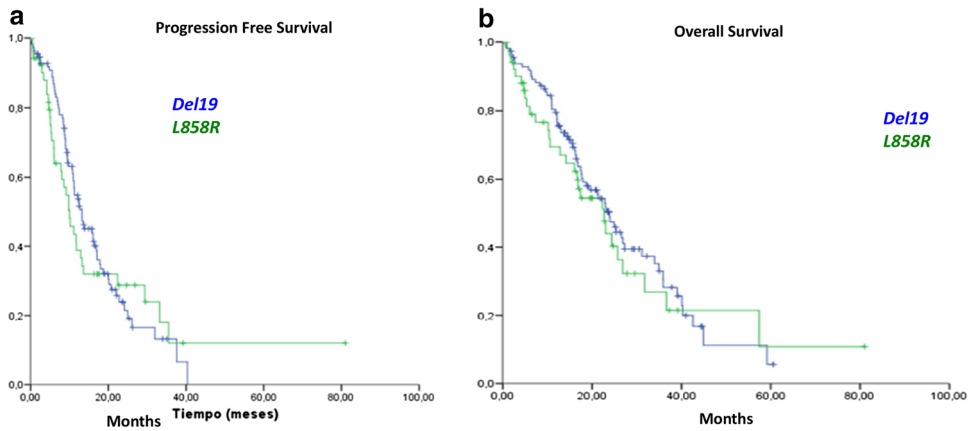

Fig. 2 **a** Progression-free survival and **b** overall survival in advanced *EGFR*-mutant NSCLC women treated with upfront EGFR TKI according to EGFR mutation subtype (*Del19* vs. *L858R*)

half of all NSCLC patients included in the WORLD 07 database underwent an *EGFR* mutation test. The prevalence of *EGFR*-mutation in WORLD07 is higher than in unselected samples of newly diagnosed Spanish NSCLC patients [16] or than published data in Caucasian patients [5]. However, the WORLD 07 database only included women, mainly adenocarcinoma and mainly never-smokers, of all clinicopathologic characteristics correlated with an increased prevalence of *EGFR*-mutation, ranging from 20 to 40% among these subgroups [5, 16].

Globally, it has been demonstrated that never-smoker patients obtain greater benefit from EGFR TKI treatment than current or former smoker patients [10, 17] probably as a consequence of increased EGFR TKIs metabolism versus non-smoking patients [18]. However, in the WORLD07 database, efficacy of EGFR TKIs among women was independent of smoking status, consistent with results reported in the previous meta-analysis which suggests that the predictive effect of sex is largely independent of smoking status and *EGFR*-mutation subtype [10].

The WORLD07 analysis did not demonstrate any difference in outcome based on the EGFR TKI subtype. There is currently no consensus as to which inhibitor maximizes therapeutic efficacy in *EGFR*-mutant NSCLC patients. The phase III study CTONG 0901 (NCT01024413) did not report differences in outcome or toxicity between erlotinib and gefitinib [19] and the phase IIb LUX-Lung 7 trial (NCT01466660) showed increased responses and a modest yet significant PFS prolongation with afatinib (an irreversible EGFR TKI) compared to gefitinib [20], without survival improvement independently of *EGFR* mutation subtype [21].

For tumours with *EGFR Del19*, the PFS benefit was 50% greater than for tumours with *EGFR L858R* [10]. Predictive effect of sex could justify why in the WORLD07 database, *EGFR*-mutation subtype was not a predictive marker of EGFR TKIs efficacy. However, a trend toward greater benefit was observed between *EGFR Del19* tumours compared to *EGFR L858R* tumours in PFS but not in OS. Contrarily, in a recent analysis of the Biomarker France Database, significantly longer survival for *EGFR Del19* compared to *EGFR L858R* mutation was reported, but test interaction with sex was not performed [22]. These results suggest different population of *EGFR*-mutant lung cancer patients according to *EGFR*-mutation subtype. However, it remains unknown, as to which is the most powerful predictive factor, *EGFR*-mutation subtype, or sex.

As previously reported, in our analysis, EGFR TKI treatment line does not impact on the outcome of *EGFR*-mutant NSCLC patients [23]. In the NEJ002 trial, comparing gefitinib with carboplatin plus paclitaxel, sequence of treatment in *EGFR*-mutant patients did not influence in the OS [24]. Furthermore, irrespective of *EGFR*-mutation type, in the Biomarker France Database, no differences in OS were reported according to EGFR TKI treatment line (first- vs. second-line) [22]. These results suggest that EGFR TKIs must be a part of the treatment plan, but not necessarily as the first-line treatment.

In this setting, the outcome assessed by investigators, lack of a centralized *EGFR* mutational test (*EGFR*-mutation subtype was unknown in 11% of our population) even the different test for assessing *EGFR* mutation status not collected in our database, and the unknown of post-progression treatment, could be considered as limitations. Indeed, despite the fact that it was a prospective study, there was some missing or unknown data, which could have affected the results for some of the outcomes. The strength of our results regarding response and outcome rates is that they are similar to those reported in a clinical trial setting. In addition, based on our analysis, sex could be one of the most important predictive factors independently of smoking status or *EGFR*-mutation subtype among this lung cancer population. However, we do not have matched cohort of men with the same clinical characteristics. Overall, efficacy of EGFR TKIs in *EGFR*-mutant women in this real-world setting is similar to that previously reported and our results might suggest that sex is one of the most important predictive factors for this population.

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Compliance with ethical standards

Conflict of interests The authors declare that they do not have any conflict of interest.

Research involving Human participants This is an observational study, so not applicable.

Informed consent All patients signed an informed form before enrolling in this database.

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