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ORIGINAL ARTICLE

Clinical and molecular characteristics of non-small-cell lung cancer (NSCLC) harboring *EGFR* mutation: results of the nationwide French Cooperative Thoracic Intergroup (IFCT) program

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Background: *EGFR* mutations cause inconsistent response to EGFR tyrosine-kinase inhibitors (TKI). To better understand these features, we reviewed all cases of *EGFR*-mutated non-small-cell lung cancer collected in the Biomarkers France database.

Patients and methods: Of 17 664 patients, 1837 (11%) with *EGFR*-mutated non-small-cell lung cancer were retrospectively analyzed for clinical and molecular characteristics. Results were correlated with survival and treatment response for the 848 stage IV patients.

Results: *EGFR* exon 18, 19, 20 and 21 mutations were found in 102 (5.5%), 931 (51%), 102 (5.5%) and 702 (38%) patients, respectively. Over 50% of exon 18 and 20 mutated patients were smokers. The median follow-up was 51.7 months. *EGFR* mutation type was prognostic of overall survival (OS) versus wild-type {exon 19: hazard ratio (HR)=0.51 [95% confidence interval (CI): 0.41–0.64], $P < 0.0001$; exon 21: HR = 0.76 (95% CI: 0.61–0.95), $P = 0.002$; exon 20: HR = 1.56 (95% CI: 1.02–2.38), $P = 0.004$}. *EGFR* mutation type was prognostic of progression-free survival versus wild-type [exon 19: HR = 0.62 (95% CI: 0.49–0.78), $P < 0.0001$; exon 20: HR = 1.46 (95% CI: 0.96–2.21), $P = 0.07$]. First-line treatment choice did not influence OS in multivariate analysis. First-line TKI predicted improved progression-free survival versus chemotherapy [HR = 0.67 (95% CI: 0.53–0.85), $P = 0.001$]. OS was longer for del19 versus L858R, which was associated with better OS compared with other exon 21 mutations, including L861Q. TKI improved survival in patients with exon 18 mutations, while chemotherapy was more beneficial for exon 20-mutated patients.

Conclusion: *EGFR* mutation type can inform the most appropriate treatment. Therapeutic schedule had no impact on OS in our study, although TKI should be prescribed in first-line considering the risk of missing the opportunity to use this treatment.

Key words: non-small-cell lung cancer (NSCLC), epidermal growth factor receptor gene (*EGFR*) mutations, tyrosine-kinase inhibitors (TKI), epidemiology

Introduction

Epidermal growth factor receptor gene (*EGFR*) mutations are found in around 10% of Caucasian non-small-cell lung cancer (NSCLC) patients [1].

EGFR mutations are classified as either 'common' or 'rare', associated with different clinical patterns and outcomes. The most common mutations (85%–90%) are in-frame deletions of exon 19 (del19; 45%–50%) and the Leu858Arg (L858R) substitution in exon 21 (40%–45%) [2]. Common mutations sensitize the tumor to first- and second-generation EGFR tyrosine-kinase inhibitors (EGFR-TKI), whose superior efficacy compared with first-line chemotherapy has been demonstrated in several Phase III trials [3–10]. Exon 18 and 20 *EGFR* mutations are more heterogeneous, with exon 20 associated with EGFR-TKI resistance, while exon 18 mutations seem drug-sensitive, although less so than common mutations [11].

The Biomarkers France study is the largest worldwide study to have prospectively collected molecular and clinical data of 17 664 patients in 1 year [1]. We conducted a retrospective analysis in order to describe the clinical characteristics and outcomes of patients with *EGFR*-mutated NSCLC.

Materials and methods

Population and molecular analysis

All *EGFR*-mutated cases of the Biomarkers France cohort were reviewed. The methods used to asses *EGFR* mutations were previously described [1, 12]. Mutations were reclassified as common (del19 and L858R) or rare. Multiple mutations (*EGFR* with another genetic alteration) and exon 20 T790M mutations were excluded from the analysis, because they were the subject of separate studies (supplementary Figure S1, available at *Annals of Oncology* online). Clinical data were collected as previously described [1]. The effects of first- and second-line treatments (i.e. platinum-based doublet chemotherapy or EGFR-TKI) on objective response, disease control, progression-free survival (PFS), and overall survival (OS) were analyzed in stage IV patients. Evaluation of response and survival was done by each clinician according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, at the frequency of their current practice.

Statistical analysis

The descriptive statistics used included medians and ranges for continuous variables and percentages for categorical variables, the latter compared using chi-squared or Fisher's exact tests, when necessary. Significance level was set at $P < 0.05$. OS, first-line PFS (PFS1) and second-line PFS (PFS2) were previously defined [1]. Survival curves were estimated using the Kaplan–Meier method. Disease control rate (DCR) was defined as the percentage of patients presenting stable disease, partial response or complete response to treatment, and overall response rate (ORR) as the percentage of patients with partial and complete response. A Cox model was applied to estimate hazard ratios (HR) and 95% confidence intervals (CI). The analyses were carried out using SAS software, Version 9.3 (SAS Institute, Cary, NC).

This study was approved by the national committee for the protection of persons (*Comité de protection des personnes*, CPP), according to French law.

Our funding source had no influence on study design, data collection, data analysis, data interpretation, or the preparation of this report.

Results

Molecular epidemiology of *EGFR* mutations in the overall population

EGFR mutations were found in 1,837 tumor specimens classed as follows: 102 (5.5%), 931 (51%), 102 (5.5%), and 702 (38%) in exons 18, 19, 20, and 21, respectively. Based on the COSMIC database (May 2017), we identified 42 previously unpublished *EGFR* mutations (supplementary Table S1, available at *Annals of Oncology* online). In exon 18, we identified only one deletion/insertion in four patients (E709_T710delinsD); the remaining mutations were substitutions, the most frequent concerning G719X (75%). Most of the exon 19 mutations were deletions (61%), the most frequently identified being the E746_A750del (51%). In exon 20, insertions (65%) were more common than substitutions. We identified one proximal insertion in one patient (E762_A763insVAS). In exon 21, L858R substitution was found in 89% of cases, whereas L861Q represented 6% of cases (Figures 1 and 2).

Stage IV patient characteristics

Most patients were not Asian ($n = 693$, 95%) and non-smokers ($n = 486$, 60%), which is consistent with previous Caucasian cohorts [7, 13]. The proportion of current or former smokers was significantly higher in those presenting with exon 18 (59%) and exon 20 (56%) mutations, compared with those with exon 19 (36%) and 21 (42%) mutations ($P = 0.02$). Family history of cancer was noted in 11/20 patients with exon 20 mutations (55%). First-line treatment was known for 818 of the 848 (96%) metastatic patients, consisting of EGFR-TKI for 481 (59%), platinum-based doublet chemotherapy for 222 (27%), other treatments for 50 (6%) (mono-chemotherapy or unspecified), and best supportive care only for 65 (8%). First-line treatment was adapted based on knowledge of *EGFR* mutation in 71% of cases ($n = 582$). At this time, 98 had received platinum-based doublet in first-line (46 with exon 19 mutations, 31 exon 20, 17 exon 20, and 7 exon 18). Patients with exon 19 and 21 mutations were more likely to receive first-line EGFR-TKI compared with those with exon 18 and 20 mutations (60.5% and 64% versus 38% and 15%, respectively, $P < 0.0001$). Of the 222 patients treated with first-line platinum-based chemotherapy, 79 (36%) did not receive second-line

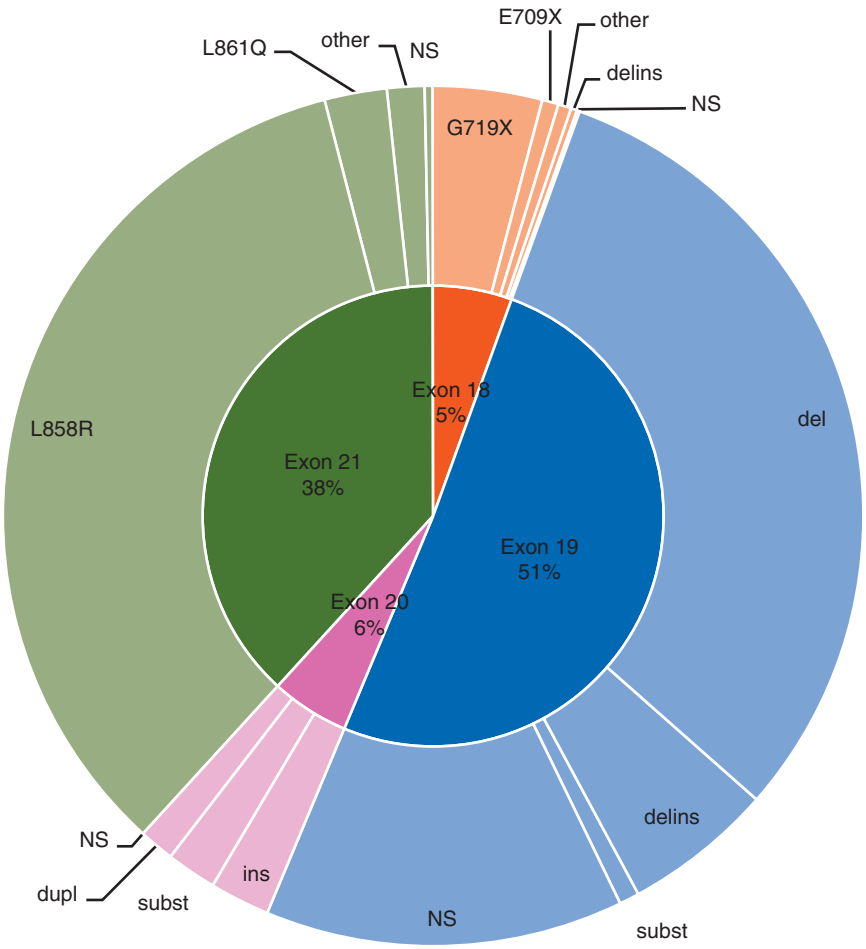

Figure 1. *EGFR* mutations in overall population ($n = 1837$). NS: not specified.

EGFR-TKI (supplementary Table S2, available at *Annals of Oncology* online).

Multivariate analysis of stage IV survival and treatment response

The median follow-up was 51.7 months (m) (95% CI: 51.2–52.3). The median OS was 19.0 m (95% CI: 17.8–20.8). On multivariate analysis, Eastern Cooperative Oncology Group performance status (PS) >1 [HR = 2.08, (95% CI: 1.89–2.30), $P < 0.0001$] and large cell histology [HR = 1.58, (95% CI: 1.14–2.19), $P = 0.006$] were associated with worse prognosis. Never-smokers had better prognosis than current-smokers [HR = 0.78 (95% CI: 0.64–0.94), $P = 0.009$]. *EGFR* mutation type was highly prognostic of OS, longer for patients with exon 19 [HR = 0.51 (95% CI: 0.41–0.64), $P < 0.0001$] and exon 21 [HR = 0.76 (95% CI: 0.61–0.95), $P = 0.002$] mutations compared with wild-type (WT). In contrast, patients with exon 20 mutations had worse OS compared with WT [HR = 1.56 (95% CI: 1.02–2.38), $P = 0.004$]. Interestingly, first-line treatment type did not influence OS on multivariate analysis (supplementary Tables S3–S5, available at *Annals of Oncology* online).

The median PFS was 9.8 m (95% CI: 9.0–10.7). Median PFS1-TKI was 11.0 m (95% CI: 10.2–12.9) and median PFS1-CT was 6.4 m (95% CI: 5.0–7.2). On multivariate analysis, elderly patients [HR = 0.69 (95% CI: 0.55–0.85), $P = 0.0008$] had better PFS compared with others, whereas patients with PS >1 [HR = 1.85 (95% CI: 1.68–2.03), $P < 0.0001$] and large cell carcinomas [HR = 1.56 (95% CI: 1.11–2.17), $P = 0.009$] exhibited worse PFS. PFS was longer for patients with exon 19 mutations [HR = 0.62 (95% CI: 0.49–0.78), $P < 0.0001$] and shorter for patients with exon 20 mutations, although not significantly so [HR = 1.46 (95% CI: 0.96–2.21), $P = 0.07$]. First-line TKI was associated with improved PFS compared with platinum-based chemotherapy [HR = 0.67 (95% CI: 0.53–0.85), $P = 0.001$].

Outcomes according to different *EGFR* mutations

The median OS values according to mutation in decreasing order were: 22.6 m for exon 19, 16.2 m for exon 21, 12.2 m for exon 18, 8.3 m for exon 20, and 7.9 m for WT ($P < 0.001$). Median PFS1-TKI values were: 14.6 m for exon 18, 12.9 m for exon 19, 10.1 m for exon 21, 2.7 m for exon 20, and 1.6 m for WT ($P < 0.0001$). Median PFS1-CT values were comparable between *EGFR*-mutated and WT patients (Table 1 and Figure 3A).

Focusing on common *EGFR* mutations only, OS was longer for del19 patients compared with those with L858R (22.6 m versus 16.9 m, $P = 0.002$). Of the exon 21 mutations, L858R was associated with better prognosis compared with others, including L861Q (median OS: 16.9 m versus 12.2 m, $P = 0.04$; median

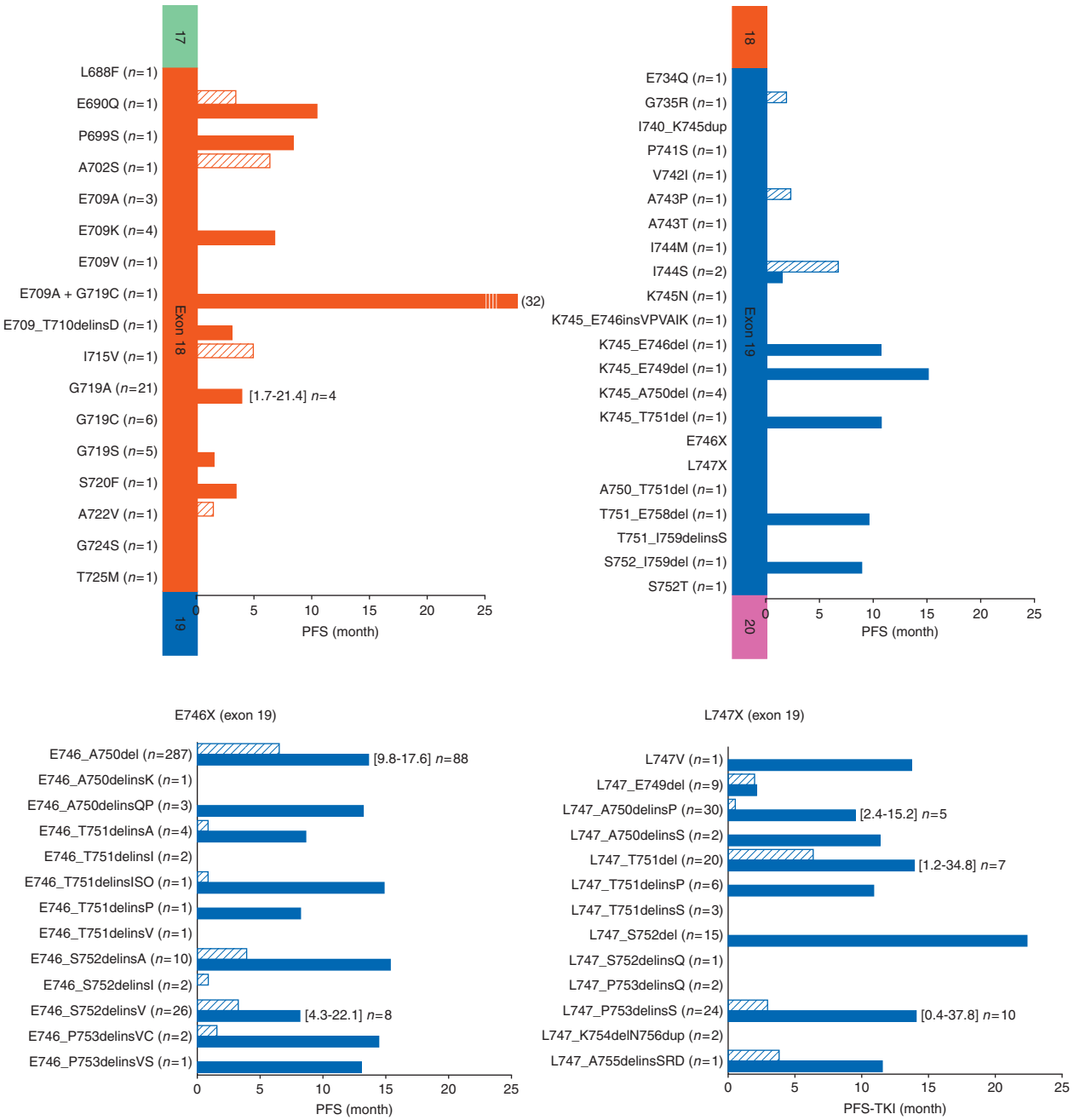

Figure 2. Progression-free survival (PFS) for each *EGFR* mutations, exon by exon. Left section of each exon: overall population (*n*=1837); right section of each exon: stage IV population (*n*=848). Solid line: first-line tyrosine kinase inhibitors (TKI); dashed line: first-line platinum-based chemotherapy.

PFS1-TKI: 10.4 m versus 4.5 m, $P = 0.003$) (Figure 3B). Of the exon 20 mutations, median OS was longer for insertions ($n = 28$) than substitutions ($n = 9$), although not significantly so (10.1 m versus 8.1 m, $P = 0.80$).

Detailed PFS findings according to mutation type are presented in Figure 2.

Discussion

Of the 17 664 Biomarkers France patients [1], 1837 (11%) with *EGFR* mutations were analyzed in this real-life study, corresponding to 158 different *EGFR* mutations, 67 of which had never previously been reported. This cohort represents the largest Caucasian *EGFR*-mutated cohort ever analyzed.

Over 40% of *EGFR*-mutated patients and almost 60% of patients with exon 18 and 20 mutations, were current or former smokers, in line with previous publications [11, 14]. In contrast, in Asian cohorts, never-smoker patients are the majority [15]. Family history of cancer has been reported in a high proportion of patients with exon 20 mutations ($n = 11$, 55%). To our knowledge, this has never been described, suggesting that germ-line mutations should be detected in these patients [16] in these patients.

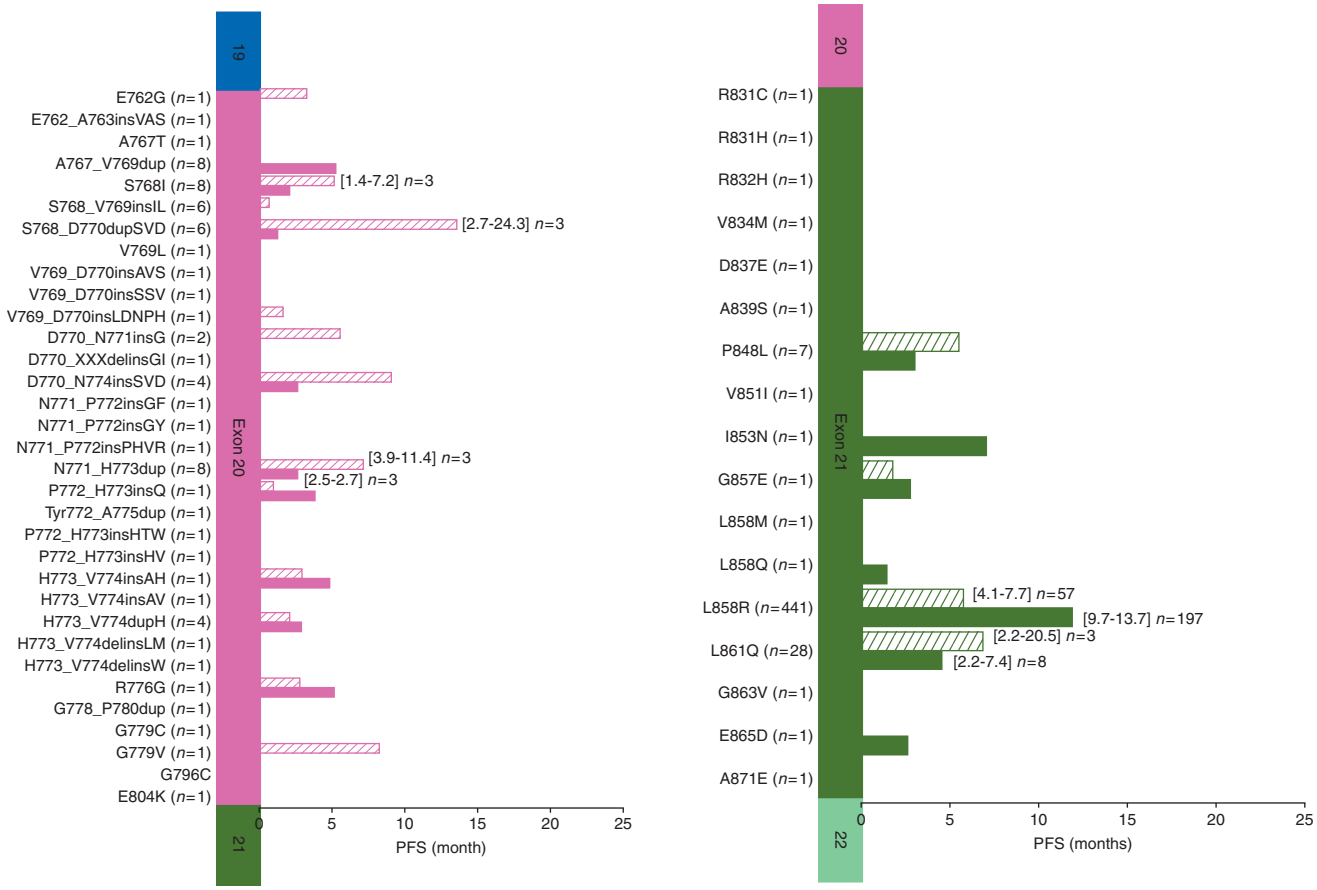

Figure 2. Continued

Table 1. Outcomes according to exon-mutation type compared with wild-type population for stage IV patients exposed to *EGFR* tyrosine-kinase inhibitors (TKI) and platinum-based chemotherapy regimen (CT)

	Wild-type	Exon 18	Exon 19	Exon 20	Exon 21	*P*
OS, months	7.9 [7.1–8.9] (*n* =880)	12.2 [4.7-NR] (*n* =28)	22.6 [19.8–27.0] (*n* =413)	8.3 [5.9–18.1] (*n* =40)	16.2 [13.3–19.0] (*n* =322)	<0.001
PFS1-all, months	4.4 [4.0–5.0] (*n* =856)	6.4 [4.8–14.6] (*n* =28)	11.1 [10.0–13.1] (*n* =407)	3.9 [2.7–7.1] (*n* =39)	9.1 [7.6–10.1] (*n* =317)	<0.0001
PFS1-TKI, months	1.6 [1.2–3.4] (*n* =19)	14.6 [5.7–19.5] (*n* =10)	12.9 [10.9–15.2] (*n* =250)	2.7 [2.5–6.4] (*n* =6)	10.1 [9.1–11.9] (*n* =201)	<0.0001
DCR (TKI), %	21 (*n* =14)	89 (*n* =9)	82 (*n* =220)	40 (*n* =5)	76 (*n* =187)	<0.0001
ORR (TKI), %	21 (*n* =14)	11 (*n* =9)	66 (*n* =220)	0 (*n* =5)	57 (*n* =187)	<0.0001
PFS1-CT, months	5.3 [4.6–5.8] (*n* =507)	5.8 [3.4–9.6] (*n* =12)	6.5 [4.9–8.0] (*n* =96)	5.5 [3.6–8.1] (*n* =22)	6.8 [4.2–7.7] (*n* =64)	0.73
DCR (CT), %	68 (*n* =600)	69 (*n* =13)	69 (*n* =91)	56 (*n* =23)	74 (*n* =57)	0.68
ORR (CT), %	39 (*n* =600)	31 (*n* =13)	40 (*n* =91)	35 (*n* =23)	40 (*n* =57)	0.96

OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; CT, chemotherapy; DCR, disease control rate; ORR, overall response rate.

Data on first-line treatment were available for 96% of the advanced NSCLC patients. In 30% of cases, clinicians did not consider *EGFR* status when initiating first-line treatment. This may be explained by (i) their having no molecular information at the beginning of the treatment, (ii) the rationale of exposing all patients to a platinum-based doublet, (iii) the fact that, at this time (2012), optimal therapeutic sequences were not extensively discussed, and (iv) the fact that the therapeutic sequence has no impact on OS.

Several studies have demonstrated that EGFR-TKI significantly delay progression compared with chemotherapy. Nevertheless, none of these studies reported any improvement on OS [17]. Recent subgroup and pooled analyses of the LUX-Lung 3 and 6 trials have indicated the importance of the therapeutic schedule, reporting OS improvement with first-line afatinib for patients with common *EGFR* mutations, especially del19 [18]. Most of studies recommend prescribing EGFR-TKI as the standard first-line treatment of *EGFR*-mutated patients, taking into account

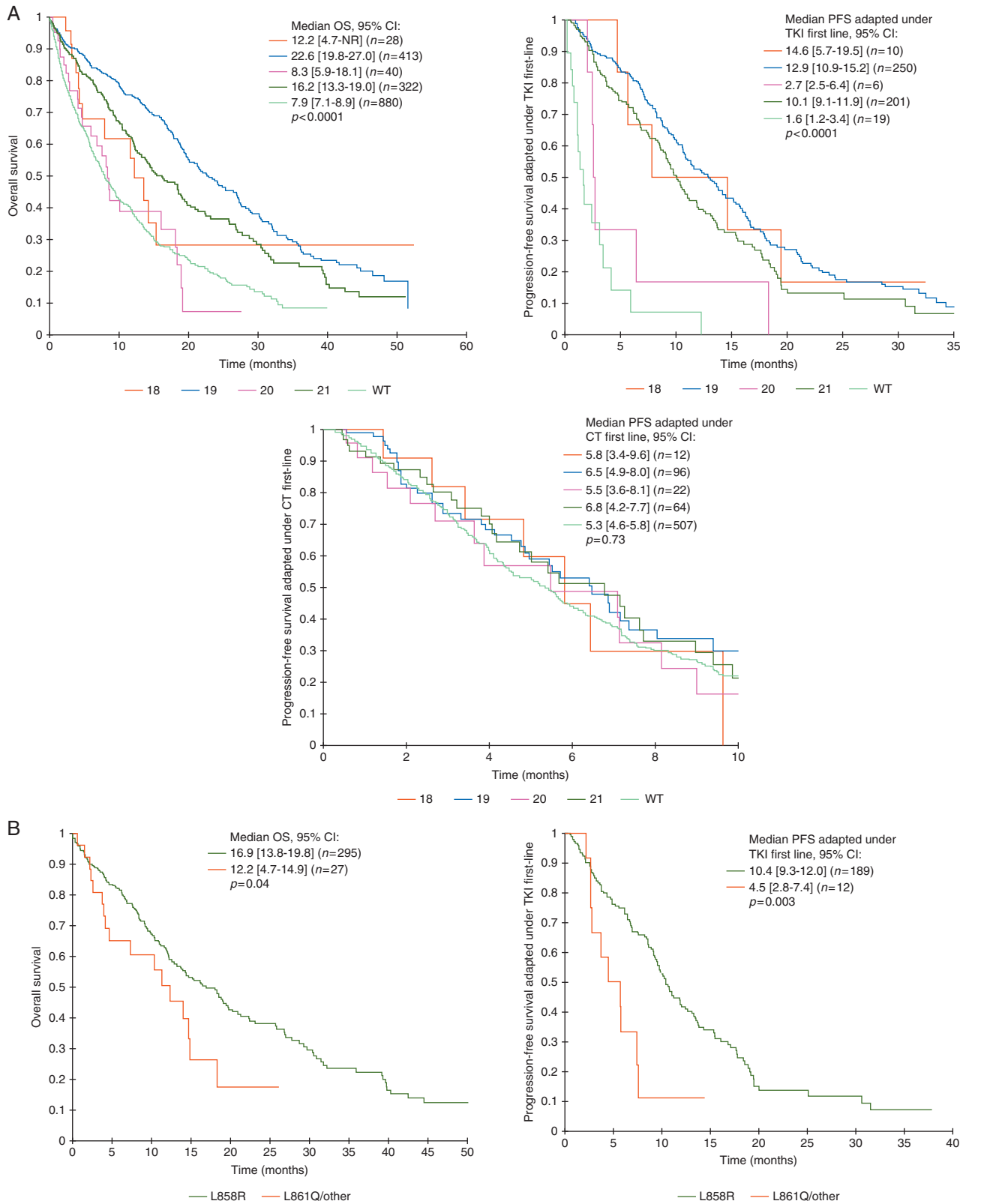

Figure 3. (A) Survival and curves according to different *EGFR*-mutated exons (18, 19, 20, 21, wild-type). upper left part: overall survival (OS); upper right part: progression-free survival (PFS) with first-line TKI; lower center part: PFS with first-line chemotherapy. (B) Survival curves according to exon 21 *EGFR* mutations: L858R mutations versus other exon 21 mutations (included L861Q). Left part: overall survival (OS); right part: Progression-free-survival (PFS). OS, overall survival; TKI, tyrosine kinase inhibitors; CI, confidence interval; PFS, progression-free survival; CT, chemotherapy; WT, wild-type.

clinical benefit, quality of life, safety, and the risk of missing the opportunity to use this treatment. In our study, multivariate analysis revealed no link between therapeutic schedule and OS. This confirms that what matters is not prescribing EGFR-TKI as first-line therapy, but rather the fact that all patients ultimately receive EGFR-TKI at some point in their treatment setting. However, 36% of patients treated with first-line chemotherapy never received second-line TKI in our cohort, which is consistent with previous publications [19]. Considering this risk, and the fact that chemotherapy is not more efficient than in the WT population (Figure 3A), first-line EGFR-TKI should be preferred for *EGFR*-mutated patients, except those with exon 20 mutations.

Patients with del19 have consistently shown improved outcomes versus those with L858R mutations when treated with EGFR-TKI [20], which is confirmed in our study. Patients with uncommon exon 21 mutations (including L861Q) exhibit worse prognosis than those with L858R, as previously suggested in a very small cohort [21]. Their prognosis is noneless better than that of the WT population, and they may slightly benefit from EGFR-TKI. The efficacy of first-line EGFR-TKI is greater for patients with exon 18 mutations (PFS1-TKI = 14.6 m versus PFS1-CT = 5.8 m). When analyzing exon 18 mutations in detail (Figure 2), we can see that response to TKI is highly variable, with greater benefit seemingly achieved for proximal exon 18 substitutions. G719X and E709X point mutations are usually associated with EGFR-TKI treatment efficacy [11, 14]. In light of our results, first-line TKI should be administrated in all exon 18-mutated patients in order to maximize the proportion of responders. Exon 20 insertions are usually associated with TKI resistance [22], and our study accordingly observed very short PFS1-TKI in these patients, whereas first-line PFS with chemotherapy is longer (2.7 versus 5.5 m, respectively). This subgroup of *EGFR*-mutated patients have to be considered separately, and treated with first-line chemotherapy. A recent *in vivo* model demonstrated that exon 20 insertions may be sensitive to dual *EGFR* blockade with osimertinib and an *EGFR*-monoclonal antibody [23]. In the BELIEF trial, combination of erlotinib plus bevacizumab increased PFS in patients with *EGFR*-mutant NSCLC and pretreatment T790M [13]. It should represent an interesting approach for patients with other exon 20 insertions.

This study also had some limitations. First, it was a prospective non-randomized study. Secondly, we have no information regarding the type of EGFR-TKI used in first-line. This cohort dates from 2012, at which point afatinib was only available in clinical trials, so we can assume that very few people were exposed to it here. Afatinib has since been proven active in certain types of uncommon *EGFR* mutations, especially G719X, L861Q, and S768I [24], as well as correlating with slight outcome improvements compared with gefinitib in first-line [25]. Similarly, we have no information concerning the use of bevacizumab or maintenance, and we know that these strategies improve patient outcomes [26].

To conclude, type of mutation should be precisely determined at diagnosis in order to select the most appropriate treatment. While PFS1-CT durations are the same regardless of *EGFR*-mutation status, PFS1-TKI can significantly differ, meaning it is crucial to carefully select patients who may benefit from TKI. Even the therapeutic schedule had no impact on OS in our study, yet TKI should still be prescribed in first-line due to the risk of missing the opportunity to use this treatment.

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Appendix

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