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Real-life Effectiveness of Afatinib *Versus* Gefitinib in Patients With Non-small-cell Lung Cancer: A Czech Multicentre Study

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Abstract. *Background/Aim: We investigated efficacy differences for afatinib versus gefitinib in non-small-cell lung cancer (NSCLC) according to epidermal growth factor receptor (EGFR) mutations. Patients and Methods: We retrospectively analysed data for 343 patients with NSCLC with performance status 1 having EGFR mutations treated with gefitinib or afatinib. Overall response rate (ORR) was tested by Fisher's exact test. Overall (OS) and progression-free (PFS) survival were estimated by Kaplan–Meier method. Results: ORR did not differ in any group or subgroup. Among all patients, we observed significantly longer PFS for those treated with afatinib vs. gefitinib (median 13.4 vs. 9.5 months, p=0.026), but only a nonsignificant trend was observed for OS. We showed nonsignificant trends of better PFS and OS using afatinib for exon 19 deletion and L858R subgroups. We observed no significant PFS differences for other EGFR mutations but a nonsignificant trend towards better OS for those treated with afatinib. Conclusion: Afatinib led to longer PFS for patients with common EGFR mutations but not for those with rare mutations.*

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) constitute standard treatments for non-small-cell lung cancer (NSCLC), especially lung adenocarcinomas, with sensitive *EGFR* mutations (1). First- (gefitinib, erlotinib), second- (afatinib, dacomitinib), and third-generation (osimertinib) TKIs are used (1). Osimertinib has been shown not only to confer significantly longer progression-free survival (PFS) but also longer overall survival (OS) in comparison with first-generation TKIs in cases with common *EGFR* mutations (*i.e.* *EGFR* exon 19 deletions and *EGFR* exon 21 L858R mutations) (2, 3). This trial did not, however, include other ('rare') *EGFR* mutations, and second-generation TKIs were also not evaluated. Moreover, in many countries, including the Czech Republic, osimertinib is not reimbursed by public health insurance. Therefore, it is appropriate to assess whether it is

Table I. *Baseline patient characteristics (whole group).*

		Total	Afatinib	Gefitinib
Patients	N (%)	343 (100%)	145 (42.3%)	198 (57.7%)
Age at diagnosis, years	Median (range)	68.1 (23.6-89.7)	66.4 (23.6-84.2)	70.1 (34.6- 89.7)
Gender, n (%)	Male	114 (33.2%)	52 (35.9%)	62 (31.3%)
	Female	229 (66.8%)	93 (64.1%)	136 (68.7%)
Smoking status, n (%)	Non-smoker	185 (53.9%)	68 (46.9%)	117 (59.1%)
	Former smoker	86 (25.1%)	39 (26.9%)	47 (23.7%)
	Smoker	72 (21.0%)	38 (26.2%)	34 (17.2%)
T Classification*, n (%)	T1	42 (12.2%)	19 (13.1.%)	23 (11.6%)
	T2	102 (29.8%)	39 (26.9%)	63 (31.8%)
	T3	56 (16.3%)	19 (13.1%)	37 (18.7%)
	T4	115 (33.5%)	55 (37.9%)	60 (30.3%)
	TX	28 (8.2%)	13 (9.0%)	15 (7.6%)
N Classification*, n (%)	N0	55 (16.0%)	20 (13.8%)	35 (17.7%)
	N1	38 (11.1%)	16 (11.0%)	22 (11.1%)
	N2	95 (27.7%)	39 (26.9%)	56 (28.3%)
	N3	119 (34.7%)	57 (39.3%)	62 (31.3%)
	NX	36 (10.5%)	13 (9.0%)	23 (11.6%)
M Classification*, n (%)	M0	38 (11.1%)	13 (9.0%)	25 (12.6%)
	M1 (until 1 Jan 2011)	20 (5.8%)	5 (3.4%)	15 (7.6%)
	M1a	98 (28.6%)	44 (30.3%)	54 (27.3%)
	M1b	160 (46.6%)	62 (42.8%)	98 (49.5%)
	M1c	27 (7.9%)	21 (14.5%)	6 (3.0%)
EGFR mutation#, n (%)	Exon 19 deletion	192 (55.3%)	83 (57.2%)	109 (54.0%)
	L858R	104 (30.0%)	40 (27.6%)	64 (31.7%)
	Other	51 (14.7%)	22 (15.2%)	29 (14.4%)

EGFR: Epidermal growth factor receptor. *According to 7th and 8th TNM edition. #Patient may have had more than one mutation.

better to use treatment with afatinib or a first-generation *EGFR* TKI (in the Czech Republic, particularly gefitinib). The Lux-Lung 7 (LL7) trial sought an answer to this question (4). It was not a phase III trial, however, only a IIB trial. In addition, clinical practice shows that results from clinical trials and real-life data may differ somewhat (5, 6). In addition, apart from the excellent efficacy of afatinib in particular on the EGFR mutation at exon 19, its use also appears to be effective for rare EGFR mutations (7, 8). These rare mutations were not included in the LL7 study (4). Therefore, we decided to examine real-life data from the Czech Republic.

Our aim was to assess the effectiveness of afatinib compared with gefitinib, both in general and in relation to specific mutations (common as well as rare EGFR mutations).

Patients and Methods

Study design and treatment. This study retrospectively analysed clinical data of patients with cytologically or histologically confirmed advanced NSCLC that were treated with afatinib or gefitinib during 2010-2020 at 12 oncology and pneumo-oncology centres in the Czech Republic. Inclusion criteria were stage III or IV lung adenocarcinoma with Eastern Cooperative Oncology Group performance status (ECOG PS) 1 at treatment initialization, first-line treatment, and with record of EGFR mutation. Afatinib was administered orally at the approved doses of 40 mg (reduction to 30 or 20 mg due to adverse events was permitted). Gefitinib was administered orally at the approved doses of 250 mg daily. The treatments were administered until progression or unacceptable toxicity. Clinical follow-up included physical examination, chest X-ray, and routine laboratory tests performed at least every 4 weeks. Computed tomography was performed at regular intervals according to the local standards or when progression was suspected based on clinical or chest X-ray examination. The data source was the Czech Republic's national TULUNG register, a non-interventional post-registration database of epidemiological and clinical data from patients with advanced-stage NSCLC receiving expensive oncology treatments in the Czech Republic. The patients had given their informed consent to be included in this database and for use of these data for scientific purposes.

Statistical methods. Patients' demographic and disease characteristics were summarized. Continuous parameters are described using the mean with 95% confidence interval (CI) and the median with minimum and maximum, together with the total number of non-missing observations. Categorical parameters were summarized using absolute and relative frequencies.

For comparison of treatment groups, the representation of baseline parameters was evaluated and statistically significant differences were noted. Continuous parameters were tested using Mann–Whitney *U*-test, and categorical parameters by Fisher's exact test. In cases of incomparability in observed baseline characteristics, matching technique was used. Comparable patients were matched by nearest neighbour of propensity score method with calliper of

0.2 and max ratio 1:2. Patients were matched based on: Exon 19 subgroup: age, smoking, and M classification; L858R subgroup: age, M, and T classification; all mutations: age, smoking, M, and T classification (7th or 8th edition of TNM classification - according to the date of diagnosis) (9, 10). Subgroups of patients were chosen from treatment groups with propensity score so that differences in baseline parameters between treatment groups were no longer significant.

The overall response rate [ORR, *i.e.* complete response plus partial response defined by RECIST 1.1. (11)] was tested by Fisher's exact test. OS was defined as the time from treatment initiation to the date of death due to any cause. PFS was defined as the time from treatment initiation to the date of first documented progression or death due to any cause. OS and PFS were estimated by Kaplan–Meier method and all point estimates include 95% CIs. Differences in OS and PFS were tested by log-rank test, or Tarone–Ware test when crossing survival curves appeared.

Statistical analyses were performed using IBM SPSS, Statistics (version 25.0; IBM, Armonk, NY, USA) and R software (version 3.5.1). For decisions on statistical significance, α=0.05 was used.

Ethics. The study was approved by the Institutional Ethics Committees of all participating centres of the TULUNG registry [University Hospital Brno, University Hospital Pilsen, University Hospital Olomouc, University Hospital Hradec Kralove, University Hospital Motol (Prague), University Hospital Prague-Bulovka, Thomayer Hospital (Prague), and VFN (Prague)]. This study was approved by the Ethics Committee of University Hospital Hradec Kralove on 11 May 2018, reference number: 201805 I134R.

Results

Patient characteristics. In total, 343 patients (114 males and 229 females) with a median age of 68.1 years were included in this retrospective analysis. The baseline patient characteristics are summarized in Table I. For the whole analysis, 292 patients with matched data were used; 154 patients for the subgroup with *EGFR* deletion 19; 79 patients for the subgroup with *EGFR* L858R; and 51 patients for the subgroup with other mutations. Other mutation types (*i.e.* so-called rare *EGFR* mutations) are specified in Table II.

ORR, PFS, and OS for the whole group of patients. We observed no significant difference in ORR between afatinib- and gefitinib-treated groups (46.4% *vs*. 44.4%, p=0.809). We determined significantly longer PFS in afatinib group (median=13.4 months, 95% CI=3.6-45.7 months) compared to gefitinib group (median=9.5 months, 95% CI=3.9-11.2 months), p=0.026. There was only a nonsignificant trend, however, in differences in OS between those treated with afatinib (median=36.2 months, 95% CI=21.2- not achieved) and gefitinib (median=19.7 months, 95% CI=16.3-25.3), p=0.267. Kaplan–Meier curves for PFS and OS are shown in Figure 1.

ORR, PFS, and OS according to EGFR mutation subgroups. We observed no significant differences in ORR between afatinib-, and gefitinib-treated patients within subgroups divided by mutation types (*EGFR* exon 19 deletion, *EGFR* point mutation L858R, and patients with other *EGFR* mutations). We found only a trend for more favourable median PFS and OS for the subgroup with *EGFR* exon 19 deletion and that with *EGFR* L858R within the afatinib-treated group. We also observed a trend for better OS within the afatinib-treated patients of the other mutation subgroups. In the other mutation subgroups PFS did not significantly differ by afatinib and gefitinib treatment. Detailed results can be seen in Table III and Figure 2.

Table II. *Characterization of rare epidermal growth factor receptor mutations (whole cohort).*

Mutation type	n
Exon 18 G179X	28
Exon 18 E709G	1
Exon 18 unspecified	4
Exon 18 G719X + exon 20 S678I	4
Exon 20 S678I	1
Exon 20 T790M	2
Exon 20 insertion	7
Exon 20 unspecified	3
Exon 21 L861Q	1
Overall	51

Discussion

This multicentre trial presents a retrospective analysis from the Czech Republic comparing the efficacy of afatinib and gefitinib treatments. To the best of our knowledge, this is the first study comparing real-life data in a Caucasian population on such a large sample of patients. In addition, our analysis provides data not only on common *EGFR* mutations but also for rare *EGFR* mutations.

Similarly as in the LL7 trial (4), we showed significantly better PFS considering the whole group. Numerically, the median PFS for afatinib was even longer in our study than that reported for the LL7 trial. This has been typical for a number of modern NSCLC treatment modalities used in the Czech Republic (5). An influence of centralizing care within regional centres having sufficient experience as well as a close connection between oncological and pneumological care may be contributing factors here. As in the LL7 trial, we demonstrated only a nonsignificant trend for longer PFS in patients treated with afatinib for individual types of frequent EGFR mutation and also for OS. This may be related to the lower numbers of patients in the subgroups for PFS and an overall insufficient number of patients for OS evaluation (4, 12). According to the results of the LL7 trial, possible reductionsof afatinib dose to avoid side effects should not play a role in its efficacy. The network meta-

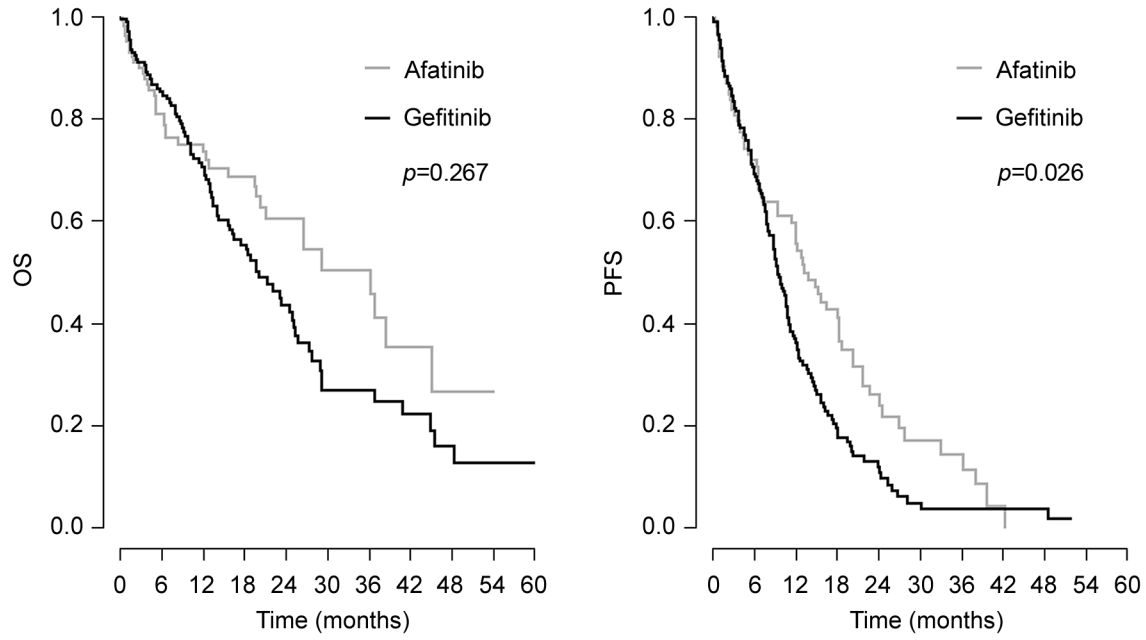

Figure 1. *Kaplan–Meier curves for overall (OS) and progression-free (PFS) survival for the whole cohort according to therapy.*

analysis from randomized phase III control trials showed no significant differences in efficacy between afatinib gefitinib, erlotinib, and icotinib (13). Although 2-year OS was better in patients treated by afatinib and 12-month PFS was also higher in the afatinib-treated group than in the gefitinib-treated group, these two regimens were not compared to one another due to the design of this study.

The use of afatinib in first-line treatment is also supported by studie by Tamiya *et al*., who showed a trend towards better PFS with osimertinib in patients with acquired EGFR T79M after pretreatment with afatinib versus gefitinib (14).

Results similar to those in our study were also presented for two Asian trials (15, 16). Kim *et al*. compared efficacy of afatinib versus first-generation TKIs for 467 patients (15). Afatinib also led to significantly longer PFS (median of 19.1 months for afatinib *vs*. 13.7 and 14.0 months for gefitinib and erlotinib, respectively). On the other hand, no difference was observed in OS. This was despite a significantly higher proportion of more patients with the favourable EGFR exon 19 deletion in the afatinib-treated group (15, 17). On the contrary, we consider an advantage of our work to be the relatively even distribution of EGFR mutation types between the afatinib and gefitinib arms. Moreover, our analyses differ in their results regarding rare EGFR mutations from those of Kim *et al*., who had reported a strong trend in favour of afatinib for better PFS (15). This might be due to the different proportions of EGFR mutation types between these analyses, and, in particular, the low number of patients with rare EGFR mutations in the data of Kim *et al*. compared to our study. The difference between the studies in terms of patient ethnic group should also not be forgotten. Tu *et al*. also compared efficacy of afatinib *vs*. gefitinib *vs*. erlotinib in a group of 422 Asian patients with EGFR-mutated NSCLC (16). Similarly to our study, they demonstrated significantly longer PFS in the afatinib-treated group compared with gefitinib-treated (median: 12.2 *vs*. 9.8 months, p=0.035). That study again differed in the efficacy of afatinib for those with rare mutations (the median PFS for those treated with gefitinib was similar to that in our study). Unfortunately, it is not possible to determine which specific types of EGFR rare mutations were treated in the study of Tu *et al*.

Lau *et al*. presented a Canadian study with mixed Asian and Caucasian population (ca 50:50) consisting of 484 patients treated with first-generation TKIs or afatinib (18). That trial examined only OS, and afatinib conferred significantly better OS compared to first-generation EGFR TKIs. In a subgroup analysis based on mutation type, results were significantly positive only for the group with EGFR exon 19 deletion but not for the EGFR L858R group, where there was a trend only very slightly favouring afatinib. This was seen also for PFS in the study of Tu *et al*. (16). That was in contrast to our results indicating a similar trend with better efficacy of afatinib as well in the group with EGFR exon 19 deletion.

A possible important influence of region of origin was shown by an Italian study from Del Re *et al*., who reported a longer time to progression in the group treated with

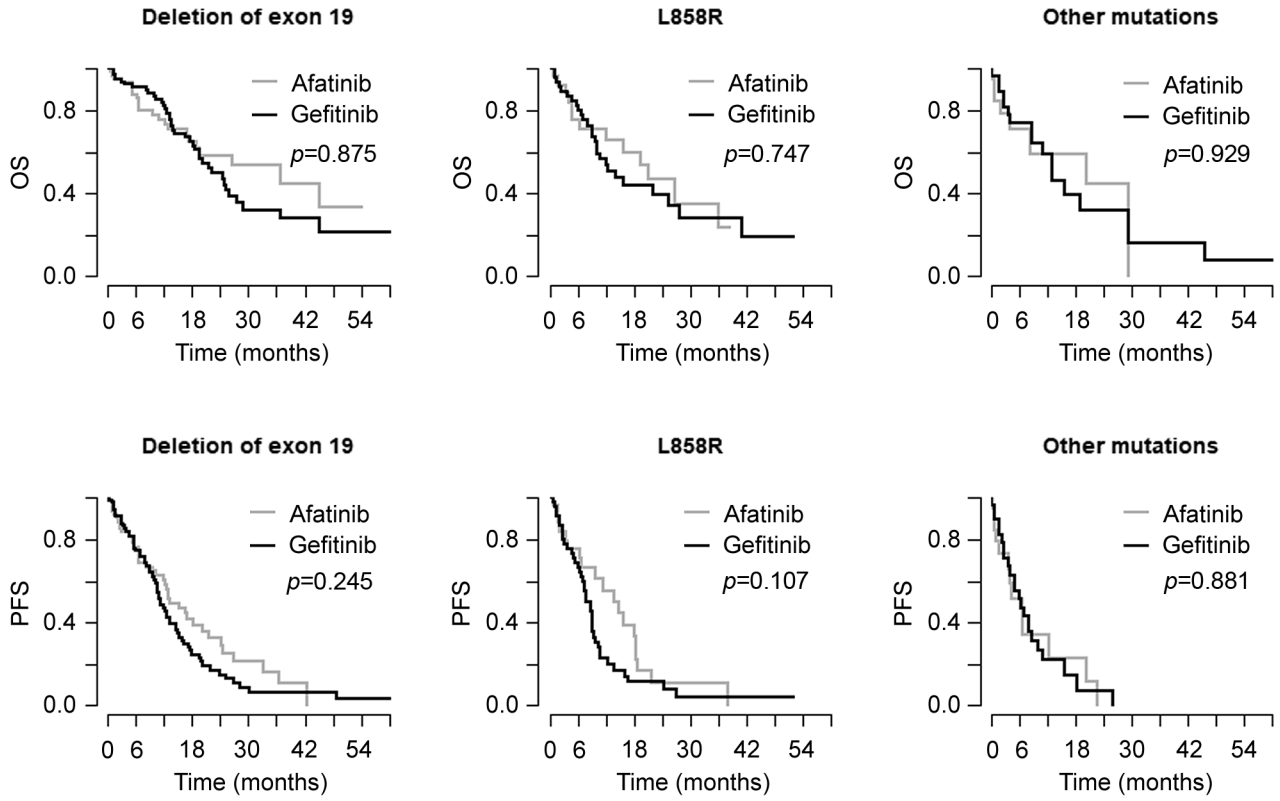

Figure 2. *Kaplan–Meier curves for overall (OS) and progression-free (PFS) survival by epidermal growth factor receptor mutation type according to therapy.*

Table III. *Comparison of overall response rate (ORR), and progression-free (PFS), and overall (OS) survival results between afatinib vs. gefitinib according to mutation type.*

EGFR			Afatinib	Gefitinib	*p*-Value
Exon 19 deletion	ORR, n (%)		30 (44.8%)	46 (52.9%)	0.334
	PFS, months	Median (95% CI)	13.4 (12.0-24.2)	11.3 (9.8-14.6)	0.245
	OS, months	Median (95% CI)	36.8 (18.9-NA)	22.1 (18.5-36.9)	0.875
Point mutation L858	ORR, n (%)		15 (50.0%)	26 (53.1%)	0.820
	PFS months	Median (95% CI)	13.9 (6.9-18.8)	8.8 (6.8-9.9)	0.107
	OS months	Median (95% CI)	21.2 (12.1-NA)	14.2 (10.2-NA)	0.747
Other mutations	ORR, n (%)		5 (22.7%)	4 (13.8%)	0.474
	PFS months	Median (95% CI)	6.6 (3.6-45.7)	6.3 (3.9-11.2)	0.881
	OS months	Median (95% CI)	20.3 (8.4-NA)	13.1 (8.8-45.7)	0.929

EGFR: Epidermal growth factor receptor; NA: not achieved.

gefitinib (median=14.4 months) compared to afatinib (median=10.2 months) (19). This result was not statistically significant (p=0.09), however, and might have been due to the relatively low number of patients and imbalance between the two groups. Krawczyk *et al*. published an analysis comparing efficacy in patients treated with afatinib, gefitinib, and erlotinib (20). They observed no significant differences in PFS or OS. Only 16 patients were treated with afatinib in that study, however, and, similarly to our study, the median PFS and OS showed trends favouring afatinib over gefitinib. If we also take into account the predominance of the Asian population in the LL7 trial, our work is the first study within

a predominantly Caucasian population demonstrating better efficacy of afatinib over gefitinib in PFS and a trend in this direction for OS.

The present study has several limitations. Firstly, this was a retrospective study with a possible bias in the choice of treatment for specific patients. In general, until 2020, gefitinib was used in patients with ECOG PS 0-2 in the Czech Republic and afatinib only in patients with ECOG PS 0-1. This may have led to the treatment of frail patients with gefitinib. We tried to prevent this bias by selecting only patients with ECOG PS1 for both groups and then by matching of patients. Secondly, the PFS was not reviewed by an independent commission. Finally, subgroups of patients according to EGFR mutations contained relatively few patients, and this probably led to suboptimal strength of statistical tests. This might similarly be the case for OS for the overall group, where we showed a clear numerical trend but one that did not reach statistical significance.

In conclusion, our data point to a longer PFS and trend for OS in patients treated with afatinib compared to gefitinib. However, these results concerned only common EGFR mutations, in the group of rare EGFR mutations we did not notice any differences.

Conflicts of Interest

In connection with this article, the Authors declare that they have in the past provided consulting services to both Boehringer Ingelheim and AstraZeneca.

Authors' Contributions

MS and JS conceived the presented idea. MS, MB, OF, JK, LK, MC, MH, MZ, HC, BP, DD, and TT conceived and planned the study and collected the data. KH and MB analysed the data. MS wrote the article with support from JS. JS helped supervise the project.

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