Original Study

Impact of Exon 19 Deletion Subtypes in *EGFR*-Mutant Metastatic Non–Small-Cell Lung Cancer Treated With First-Line Tyrosine Kinase Inhibitors

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Abstract

Patients affected by oncogene-addicted metastatic non–small-cell lung cancer harboring the uncommon epidermal growth factor receptor (*EGFR*) mutation seem to have similar survival outcomes compared to those with common *EGFR* mutations and have disease that responds either to gefitinib or afatinib.

Background: Common epidermal growth factor receptor (EGFR) mutations in non–small-cell lung cancer (NSCLC) predict sensitivity to EGFR tyrosine kinase inhibitors (TKIs), with exon 19 deletions being associated with better outcome compared to *L858R* mutations. We aimed to investigate the impact of different exon 19 deletions on patient outcome in *EGFR*-mutant NSCLC treated with first-line TKIs. **Patients and Methods:** In this retrospective analysis, 106 patients with metastatic NSCLC harboring EGFR exon 19 deletions and treated with first-line TKIs were included. The primary end point was overall survival (OS), the secondary end point progression-free survival (PFS). Analyses were performed by grouping exon 19 deletions according to 2 models: we compared different type of deletion (*delE746_A750* vs. deletions other than *delE746-A750*, defined as "uncommon") or different starting codon of deletion (*E746* vs. *L747*). **Results:** The frequency of uncommon deletions of exon 19 was 36%. When *delE746_A750* (n = 68) was compared to the other deletions in exon 19 (n = 38), no differences were found, either in terms of OS ($P = .65$) or PFS ($P = .65$). Similarly, no difference in OS ($P = .74$) or PFS ($P = .99$) emerged when comparing the *E746* group (n = 81) to the *L747* group (n = 25). On multivariate analysis including clinical characteristics and type of deletions (*delE746_A750* vs. uncommon deletions or *E746* vs. *L747*), only the presence of brain metastases at diagnosis or during TKI treatment was associated with shorter PFS but not with worse OS. **Conclusion:** Different exon 19 deletions are equally sensitive to first-line EGFR-TKIs in *EGFR*-mutant NSCLC.

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Introduction

Activating mutations in the epidermal growth factor receptor (*EGFR*) gene can be detected in approximately 10% to 15% of white patients and up to 50% of Asian patients with non–small-cell lung cancer (NSCLC) and are often associated with female gender, a nonsmoking history, and adenocarcinoma histology.[1,2] To date, sensitivity to tyrosine kinase inhibitors (TKIs) in oncogene-addicted NSCLC has been demonstrated only for few specific mutations of the *EGFR* gene, which may also be considered the most common. In particular, the in-frame deletions of exon 19 *delE746_A750*, specifically *2235_2249delELREA*, and the exon 21 *L858R* point

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mutation account for 85% of *EGFR* mutations.[3,4] Previous clinical studies also suggested that exon 19 deletions might be associated with better outcomes than other *EGFR* mutations, although no difference in OS has been proven.[5,6] Nevertheless, exon 19 deletions contain a large number of variants, and the most common—after *delE746_A750* (66.1%)—are *delL747_P753insS* (56.8%), *delL747_A750insP* (4.0%), and *delL747_T751* (3.7%).[7] The predictive value of the different exon 19 deletions to TKIs and their prognostic impact has not yet been determined because of the discordant results of previous studies and the small numbers patients with uncommon mutations; in addition, many clinical trials investigating the efficacy of first- and second-generation EGFR-TKIs included only patients with classical mutations.

In our retrospective analysis, we aimed to evaluate the survival outcome of patients with uncommon exon 19 deletions treated with TKIs as first-line therapy.

Patients and Methods

Patient Selection

This retrospective analysis included 106 patients with histologically proven stage IV NSCLC and deletions in exon 19 of the *EGFR* gene who were treated with first-line TKIs in 3 Italian centers between 2011 and 2016. All patients were aged $\geq$ 18 years and were treated with gefitinib or afatinib as first-line treatment, relying on clinical judgment; imaging assessment by computed tomography or positron emission tomography/computed tomography was performed at regular intervals, no longer than 4 months. Patients were excluded if they had a concomitant mutation in 2 or more exons or if they harbored resistance mutations. In addition, patients whose diagnosis was made after August 2016 were excluded to assure a minimum follow-up period of at least 1 year. All demographic and clinical data were extracted from medical records. Analyses were performed by grouping exon 19 deletions according to 2 different models: type of deletion (*delE746_A750* vs. uncommon deletions) and starting codon of deletion (*E746* vs. *L747*).

The study was conducted in accordance with rules of the local ethics committee and the Declaration of Helsinki. All patients provided written informed consent permitting the use of their clinical and biological data.

Treatment

All patients received gefitinib 250 mg daily or afatinib 40 mg daily according to clinician preference until systemic progression, unacceptable toxicity, or patient withdrawal. Treatment was suspended when grade 3 toxicities occurred (according to National Cancer Institute Common Terminology Criteria version 4.0) and restarted if they reduced to grade 1 or baseline. Permanent dose reductions of afatinib to 30 mg or 20 mg daily were adopted according to protocol recommendations. Treatment was permanently discontinued in case of grade 4 adverse events, grade 2 to 3 adverse events lasting more than 14 days despite adequate intervention, or interstitial pneumonitis or ulcerative keratitis. In case of oligoprogressive disease, TKIs were continued beyond progression with or without locoregional palliative radiotherapeutic treatments.

EGFR *Mutation Evaluation*

Hematoxylin and eosin–stained slides prepared from formalin-fixed, paraffin-embedded tissues were reviewed to ensure adequate tumor content (> 50% tumor cells) and manually microdissected if required. Genomic DNA was automatically extracted from tumor tissue, and *EGFR* point mutations in exons 18, 19, 20, and 21 and its classical rearrangements were analyzed according to institutional protocols. The method sensitivity for the common mutations are *EGFR E746_A750del* 2.5%, *EGFR L858R* 5%, and *EGFR T790M* 5%.

Statistical Analysis

The primary end point was overall survival (OS); progression-free survival (PFS) was considered a secondary end point. OS was calculated from the diagnosis of metastatic disease until death for any cause or last follow-up contact, PFS from the beginning of first-line therapy until the first radiologically assessed disease progression according to Response Evaluation Criteria in Solid Tumors 1.1,[8] or death by any cause. The outcome was censored if a patient had not reached survival end points (disease progression or death) at the time of analysis. The Kaplan-Meier method and log-rank test were used to estimate PFS and OS. The multivariate Cox regression model was used to identify the predictive effect on PFS and OS of different variables (type of deletion, starting codon of deletion, age, sex, smoking history, and presence of brain metastases at diagnosis or during TKI treatment). Chi-square test and Fisher exact test were used to compare proportions. Two-sided $P < .05$ was considered significant.

Results

Clinical Characteristics

According to selection criteria, 106 white patients were eligible. The most common deletion in exon 19 was *delE746_A750* (64.0%), followed by *delL747_P753* (10.4%), *delL747_T751* (6.6%), *delE746_T751* (5.7%) (Table 1). Patients were divided according to type of deletion into a *delE746_A750* group (n = 68) versus other deletions, which we defined as uncommon (n = 38) or according to starting codon of deletion in *E746* group (n = 81) versus *L747* group (n = 25). Most patients were female (63.2%) and never-smokers (56.6%). The median age of the entire population was 64 years (range, 38-86 years); 39.6% of patients had brain metastases since diagnosis or developed during TKI treatment,

Table 1 Exon 19 Deletion Subtypes

Deletion	N (%)
E746_A750	68 (64.0)
E746_E749	1 (0.9)
E746_P753	1 (0.9)
E746_S750	1 (0.9)
E746_S752	3 (2.8)
E746_T750	1 (0.9)
E746_T751	6 (5.7)
L747_A750	2 (1.9)
L747_E746	1 (0.9)
L747_E749	1 (0.9)
L747_I751	1 (0.9)
L747_P753	11 (10.4)
L747_S752	2 (1.9)
L747_T751	7 (6.6)

Table 2 Patient Characteristics

Characteristic	*delE746-A750*	Other *del19*	*P*	*delE746-XXX*	*delL747-XXX*	*P*
Total	68 (100)	38 (100)		81 (100)	28 (100)	
Female	45 (69.2)	22 (57.9)	.52	53 (65.4)	14 (56)	.54
Age at diagnosis (years), median (range)	62 (38-86)	66 (42-81)	.11	63 (38-86)	68 (44-81)	.07
Smoking History						
Current	3 (4.4)	5 (13.2)		5 (6.2)	3 (12)	
Former	26 (38.2)	12 (31.6)		32 (39.5)	8 (32)	
Never	39 (57.4)	21 (55.3)	.25	44 (54.3)	14 (56)	.56
TKI						
Afatinib	10 (14.7)	11 (28.9)		12 (14.8)	9 (36)	
Gefitinib	58 (85.3)	27 (71.1)	.13	69 (85.2)	16 (64)	.04
No. of Metastatic Sites						
1	28 (41.2)	12 (31.6)		31 (38.3)	9 (36)	
2	22 (32.4)	12 (31.6)		28 (34.6)	6 (24)	
$\geq$ 3	18 (26.4)	14 (36.8)	.48	22 (27.2)	10 (40)	.42
Brain Involvement						
At diagnosis	26 (38.2)	11 (28.9)	.45	28 (34.6)	9 (36)	.91
During TKI	3 (4.4)	2 (5.3)	.78	5 (6.2)	0 (0)	.46
Best Response						
CR	1 (1.5)	1 (2.6)		1 (1.2)	1 (4)	
PR	43 (63.2)	26 (68.4)		54 (66.7)	17 (68)	
SD	17 (25)	6 (15.8)		17 (21)	4 (16)	
PD	7 (10.3)	5 (13.2)	.70	9 (11.1)	3 (12)	.79
Second line	26 (48)	13 (39.4)	.57	31 (47)	8 (38.1)	.65

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.

and about one third of patients (30.2%) had 3 or more metastatic sites at diagnosis.

There was an imbalance in patients receiving first-line gefitinib (80.2%) compared to those treated with afatinib; 44.8% of patients received second-line therapy. All groups were well balanced in terms of patient characteristics, but the percentage of patients treated with gefitinib was significantly greater in the *E746* group compared to the *L747* group (P = .04). Patient characteristics are summarized in Table 2. Median follow-up period was 41 months, median OS of the study population was 25.4 months (95% confidence interval [CI], 22.4-34), and median PFS was 13.7 months (95% CI, 11.6-15.9).

Survival Analysis

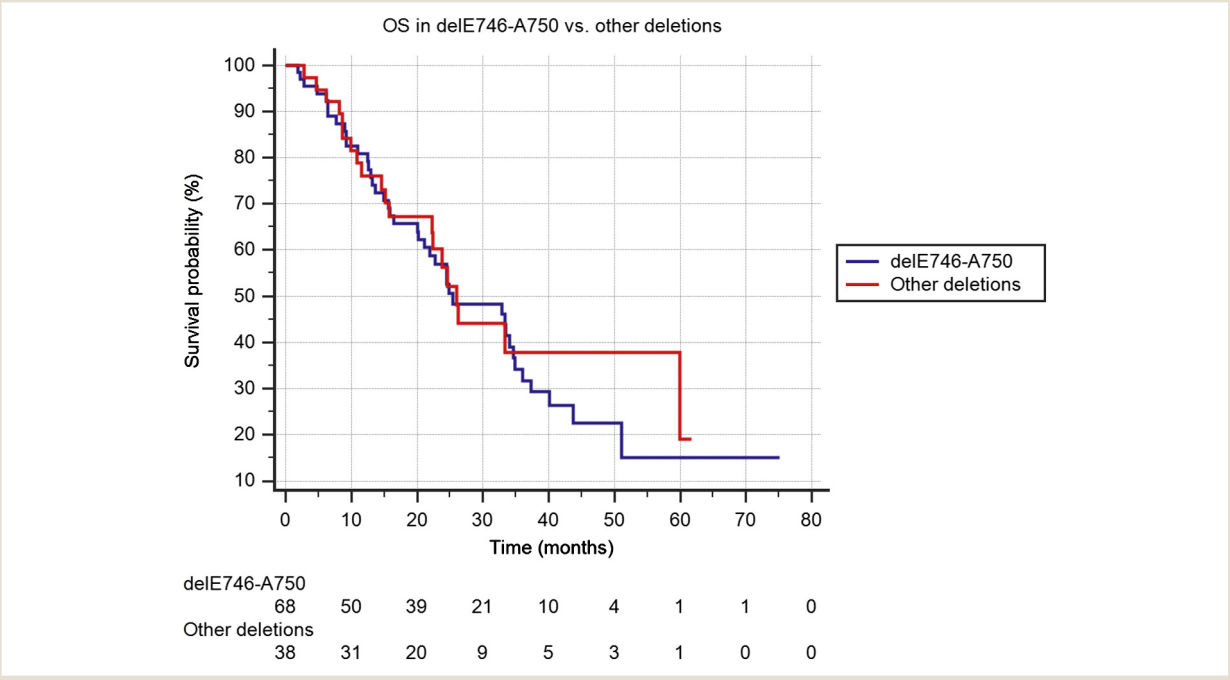
At the time of analysis, 19 (18%) of 106 patients were free of disease progression, 21% versus 13% in delE*746_A750* and other deletion groups, respectively, and 19% versus 16% in *E746* and *L747* groups, respectively; 45 (42%) of 106 were still alive, 40% versus 47% in the *delE746_A750* and uncommon deletions groups, respectively, and 42% versus 44% in the *E746* and *L747* groups, respectively. No difference in OS was found in patients harboring *delE746_A750* compared to other in-frame deletions (25.4 vs. 26.0 months; hazard ratio [HR] = 0.88; 95% CI, 0.52-1.49; P = .65; Figure 1) as well as in the *E746* group compared to the *L747* group (25.4 vs. 26.0 months; HR = 0.91; 95% CI, 0.51-1.62; P = .74; Figure 2). PFS was comparable in *delE746_A750* and other deletions (14.4 vs. 11.9 months; HR = 0.91; 95% CI, 0.58 to 1.41; P = .65) as well as in the *E746* and *L747* groups (14.4 vs. 11.9 months; HR = 1.00; 95% CI, 0.61-1.63; P = .99). When only patients treated with first-line gefitinib (n = 85) were considered, similar results were obtained for both OS and PFS comparing *delE746_A750* and uncommon deletions (OS: P = .76; PFS: P = .87) as well as the *E746* and *L747* groups (OS: P = .99; PFS: P = .74).

In patients treated with afatinib (n = 21), no differences in terms of survival outcomes were found when comparing either *delE746_A750* and other deletions (OS: P = .66; PFS: P = .50) or the *E746* and *L747* groups (OS: P = .48; PFS: P = .63). On multivariate analysis including type of deletion, starting codon of deletion, age, sex, smoking history, and presence of brain metastases, only the presence of brain metastases at diagnosis or during TKI treatment was associated with shorter PFS but not with worse OS.

Disease Control Rate, Response Rate, and Subsequent Lines of Therapy

The disease control rate in the entire cohort was 88.7% and the response rate 68%, with 2 patients experiencing complete response. No differences in terms of disease control rate and response rate were found between the *delE746_A750* group and other deletions (89.7% vs. 86.8%, P = .90; and 66% vs. 71%, P = .95, respectively) and between the *E746* and *L747* groups (88.9% vs. 88%, P = .81, and 67% vs. 72%, P = .97, respectively). Best response to EGFR-TKIs

Figure 1 Overall Survival in *delE746_A750* Versus Other Deletions



in patients with uncommon exon 19 deletions is summarized in Table 3. Among those whose disease progressed while receiving TKIs, 48% and 39.4% received a second-line treatment in the *delE746_A750* and uncommon deletions groups, respectively ($P = .57$), and 47% and 38.1% in *E746* and *L747* groups, respectively ($P = .65$). Among second-line therapies, patients who underwent repeat biopsy that showed the resistance mutation *T790M* received osimertinib within a clinical trial (n = 14), while

Figure 2 Overall Survival in *delE746* Starting Codon Versus *delL747*

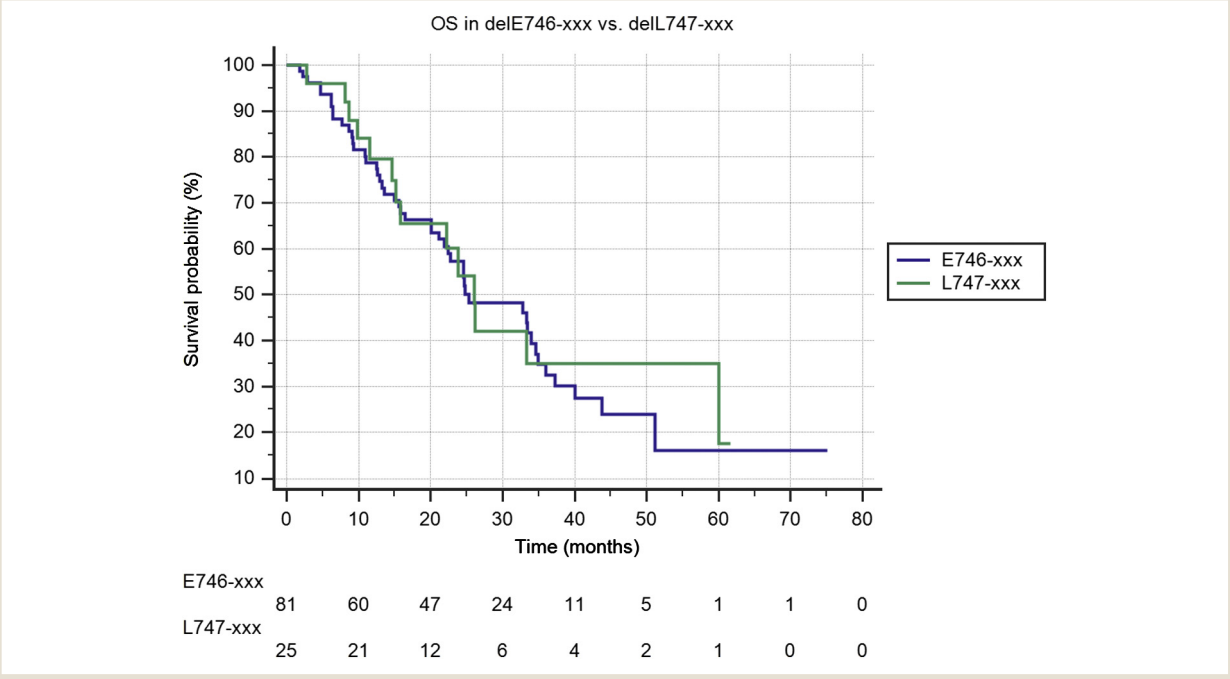


Table 3 Patient Characteristics and Response to EGFR-TKIs in Uncommon Deletions of Exon 19

Mutation	Age (Years)	Sex	Smoking	Treatment	Best Response
E746_E749	72	F	Never	Gefitinib	PR
E746_P753	56	F	Former	Gefitinib	SD
E746_S750	44	M	Current	Gefitinib	PR
E746_S752	72	M	Former	Gefitinib	PR
E746_S752	79	M	Former	Afatinib	PR
E746_S752	70	F	Never	Gefitinib	SD
E746_T750	66	F	Never	Gefitinib	PR
E746_T751	42	M	Former	Afatinib	PR
E746_T751	48	F	Current	Gefitinib	PR
E746_T751	72	M	Former	Gefitinib	PR
E746_T751	50	F	Never	Gefitinib	PD
E746_T751	73	F	Former	Gefitinib	PR
E746_T751	65	F	Former	Gefitinib	PD
L747_A750	49	F	Former	Gefitinib	PR
L747_A750	63	F	Never	Gefitinib	PR
L747_E746	76	F	Never	Afatinib	PR
L747_E749	66	F	Former	Gefitinib	PR
L747_I751	75	F	Former	Gefitinib	PR
L747_P753	68	F	Former	Gefitinib	SD
L747_P753	44	M	Never	Afatinib	RP
L747_P753	81	M	Former	Gefitinib	RP
L747_P753	71	M	Current	Gefitinib	RP
L747_P753	65	M	Current	Gefitinib	SD
L747_P753	80	M	Never	Gefitinib	RP
L747_P753	73	F	Never	Gefitinib	PD
L747_P753	66	F	Never	Gefitinib	PR
L747_P753	70	F	Never	Gefitinib	PR
L747_P753	62	M	Former	Gefitinib	PD
L747_P753	63	F	Never	Gefitinib	PR
L747_S752	65	F	Former	Afatinib	PR
L747_S752	55	F	Never	Gefitinib	CR
L747_T751	52	M	Current	Afatinib	PR
L747_T751	74	F	Never	Afatinib	PR
L747_T751	74	M	Never	Afatinib	PR
L747_T751	68	M	Never	Afatinib	SD
L747_T751	72	M	Former	Afatinib	SD
L747_T751	51	F	Never	Gefitinib	PD
L747_T751	81	M	Never	Afatinib	SD

Abbreviations: CR = complete response; EGFR = epidermal growth factor receptor; PD = progressive disease; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.

platinum doublets (n = 17) or single-agent chemotherapy (n = 8) were the preferred options in cases of *T790M*-negative (n = 9) or unknown disease at progression.

Discussion

Activating mutations in the *EGFR* gene were first identified in 2004, thus allowing a personalized therapeutic approach and leading to improved outcomes.[9] The general scientific consensus supports that mutations in exons 18 to 21 are usually sensitive to EGFR-TKIs, except for de novo *T790M* mutation and exon 20 insertions. Overall, deletions in exon 19 and the point mutation of *L858R* constitute about 90% of all *EGFR*-activating mutations and are known as classical activating mutations. Within exon 19 deletions, most encompass the amino acids from codons L747 to E749 (leucine–arginine–glutamate fragment),[10] among which *delE746_A750* accounts for 66.1% of all in-frame deletions.[11] To date, discordant results have been published regarding the responsiveness to EGFR-TKIs in patients with uncommon mutations, mainly because of their low frequency, but also because of the strict inclusion criteria of the main trials investigating the efficacy of TKIs.

To our knowledge, our cohort is one of the largest including only exon 19 deletions in a white population, and our data support the use of first-line TKIs regardless of the subtype of exon 19 deletion. A post hoc analysis of BE-POSITIVE trial data included 35 uncommon mutations of exons 18, 19, and 21, and only 6 uncommon mutations of exon 19 were found: unspecified mutation and concurrent *delE746_A750*, *delL747_S752*, and *delE746_A750* in homozygosis, one complex mutation in an untranslated location, and two *del747_751*.[12] The authors observed in patients with alternative exon 19 deletions a median PFS of 5.95 months and a median OS of 12.21 months; nevertheless, the small sample size makes these data controversial. In the post hoc analysis of LUX–Lung 2, LUX–Lung 3, and LUX–Lung 6, the efficacy of afatinib was evaluated in 100 patients with uncommon *EGFR* mutations, defined as any mutation other than deletions of exon 19 or *L858R* point mutation, thus excluding all uncommon *del19*.[13] The authors categorized rare mutations in point mutations or duplications in exons 18-21, de novo *T790M* mutation alone or in combination with other mutations, and exon 20 insertions, suggesting that afatinib is a valid treatment option for patients with some uncommon *EGFR* mutations.

In our retrospective series, the frequency of uncommon deletions of exon 19 (36%) and the percentage of each rare deletion reported are similar to those described in the literature.[7,14] Furthermore, rare exon 19 deletions—in contrast to *delE746_A750*—seemed associated with smoking, with current smokers more represented, albeit not significantly, in this subgroup of patients, as described in previous studies.[15] A higher percentage of male subjects has also been evidenced. In terms of efficacy, no differences in PFS, OS, and disease control rate were found when rare deletions were compared to *delE746_A750*, and no survival advantage was found when comparing different starting codon of deletion. Survival analysis did not show any difference even when patients were divided according to TKI received (85 patients for gefitinib and 21 for afatinib), indicating that uncommon deletions are equally sensitive to the different treatments.

Our study has several limitations; first, this is a retrospective series that may contain selection bias, and second, patients received predominantly gefitinib as first-line therapy while only a small number was treated with afatinib. In addition, because of the small sample size of patients receiving osimertinib at the time of analysis (n = 14), we did not investigate this subgroup.

In conclusion, different subtypes of exon 19 deletions showed similar outcomes and did not demonstrate any predictive impact in NSCLC patients treated with first-line TKIs. In addition, these findings suggest that uncommon exon 19 deletions are equally sensitive to different TKIs, with comparable activity of gefitinib and afatinib in this subset of patients.

Clinical Practice Points

- Uncommon exon 19 deletions are mostly excluded from clinical trials.
- No survival advantage was found comparing *delE746-A750* to uncommon exon 19 deletion or different starting codons of deletion.
- Uncommon mutations are equally sensitive to gefitinib or afatinib therapy.

Disclosure

The authors have stated that they have no conflict of interest.

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