Original Study

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Activity of EGFR TKIs in Caucasian Patients With NSCLC Harboring Potentially Sensitive Uncommon EGFR Mutations

Antonio Passaro,[1] Arsela Prelaj,[2] Laura Bonanno,[3] Marcello Tiseo,[4] Alessandro Tuzi,[5] Claudia Proto,[2] Rita Chiari,[6] Danilo Rocco,[7] Carlo Genova,[8] Claudio Sini,[9] Diego Cortinovis,[10] Sara Pilotto,[11] Lorenza Landi,[12] Chiara Bennati,[12] Andrea Camerini,[13] Luca Toschi,[14] Carlo Putzu,[15] Giulio Cerea,[16] Gianluca Spitaleri,[1] Federico Cappuzzo,[12] Filippo de Marinis[1]

Abstract

Uncommon epidermal growth factor receptor (EGFR) mutations reported in non–small-cell lung cancer, accounting approximately 10%-15% of all EGFR mutations, are a heterogeneous group characterized by different clusters: exon 20 insertion and mutations, exon 18 mutations, and complex mutations. Although available data confirming the intrinsic resistance of exon 20 insertions to EGFR tyrosine kinase inhibitors (TKIs) of first- and second-line generation, data about exon 18 and complex mutations are suggesting the activity of EGFR TKIs. In this clinical study, we showed exon 18 and EGFR complex mutations might be considered sensitive uncommon mutations, showing interesting survival results.

Background: Molecular characterization of non–small-cell lung cancer (NSCLC), defined predictive and druggable mutations that greatly modified patient prognoses. The most frequent driver mutations detected in NSCLC are epidermal growth factor receptor (EGFR) mutations, accounting for approximately 90% of exon 19 deletions and exon 21 point mutations. The other EGFR mutations are classified as uncommon or nonclassical and include exon 18 point mutations, exon 20 insertions, and combined mutations, which present different sensitivity to tyrosine kinase inhibitor (TKI) targeting. **Patients and Methods:** We collected data from EGFR TKI-naive patients with metastatic NSCLC, harboring EGFR exon 18 mutations and EGFR combined mutations treated with first- or second-generation EGFR TKIs. Efficacy end points were evaluated considering the activity of EGFR TKIs in exon 18 versus double-mutation EGFR groups. **Results:** Eighty-eight patients harboring uncommon EGFR mutations were evaluated in our analysis, and subdivided into 2 group: complex mutations (cohort A = 46 patients) and double mutations in exon 18 (cohort B = 42 patients). The results showed a median progression-free survival of 8.3 versus 12.3 months (hazard ratio [HR], 0.65; $P = .06$) and a median overall survival of 17.0 versus 31.0 months (HR, 0.62, $P = .04$) favoring the EGFR combination group. Within the combination group, no detrimental effect was associated with exon 20 mutations. **Conclusion:** Our study confirmed that EGFR exon 18 and combination mutations might be considered potentially sensitive uncommon mutations, with a similar survival compared with the well known common EGFR mutations. Comparative analysis showed that patients with complex mutations achieved longer survival compared with the exon 18 group, without correlation with the presence of exon 20 mutations.

[1]Division of Thoracic Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy
[2]Division of Thoracic Oncology, IRCCS, Istituto Nazionale Tumori, Milan, Italy
[3]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy
[4]Medical Oncology Unit, University Hospital of Parma, Parma, Italy
[5]Medical Oncology, ASST-Settelaghi, Varese, Varese, Italy
[6]Medical Oncology, Santa Maria della Misericordia Hospital, AOU di Perugia, Perugia, Italy
[7]Department of Oncology, AORN Vincenzo Monaldi, Naples, Italy
[8]Lung Cancer Unit, IRCCS AOU San Martino-IST, Genova, Italy
[9]Medical Oncology, Olbia Hospital, Olbia, Italy
[10]Medical Oncology Unit, San Gerardo Hospital, Monza, Italy
[11]Medical Oncology, University of Verona, AOUI Verona, Verona, Italy
[12]Onco-Hematology Department, AUSL Romagna, Ravenna, Italy
[13]Medical Oncology, Versilia Hospital and Istituto Toscano Tumori, Lido di Camaiore, Italy
[14]Medical Oncology, Humanitas Research Hospital, Rozzano, Italy
[15]Oncology Unit, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy
[16]Department of Oncology and Hemato-Oncology, Niguarda Cancer Center, Milan, Italy

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Address for correspondence: Antonio Passaro, MD, PhD, Division of Thoracic Oncology, European Institute of Oncology - IEO, Via G. Ripamonti, 435 - 20141 Milan, Italy
Fax: 0294379235; e-mail contact: antonio.passaro@ieo.it

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Introduction

Metastatic non–small-cell lung cancer (NSCLC) is still associated with high morbidity and mortality, with 5-year survival for stage IV disease <5%.

Since 2004, the identification of different somatic mutations of epidermal growth factor receptor (EGFR) led to improved prognosis and survival outcomes in this molecularly classified subgroup of NSCLC.

Mutations occurring within EGFR exons 18 to 21 are present in approximately 10% to 15% of Caucasian and up to 50% of Asian patients with advanced or metastatic NSCLC and are strongly associated with adenocarcinoma histology, female sex, and no-smoking status.[1-6] Most patients present with either EGFR exon 19 deletions (50%-55%) or exon 21 (L858R) substitution (30%-35%), considered as common mutations,[2-6] showing significant improvements of efficacy outcomes when treated with first- or second-generation tyrosine kinase inhibitors (TKIs).[7-14]

Beyond classical mutations, the remaining 10% to 15% of patients present uncommon EGFR mutations, being part of a very heterogeneous group including exon 18 point mutations (3%-4%) and exon 20 insertions and point mutations, that account for approximately 8% to 10% of all EGFR-positive NSCLCs. Uncommon mutations can appear in a single form or in combination with another classical or nonclassical EGFR mutation.[15-18]

The efficacy of first- or second-generation EGFR-TKIs in NSCLC harboring uncommon mutations is not yet well established.[4,16,17]

Only a few small retrospective studies and a post hoc analysis from 3 trials of the LL (LUX-lung) program (LL2, LL3, and LL6) evaluated the activity of EGFR TKIs in exon 20 insertions and point mutations.[16-19] Point mutations, such as S768I, showed partial sensitivity to EGFR TKIs (overall response rate [ORR], 20%-100%) and median progression-free survival (mPFS) (1.6-14.7 months), with inferior outcomes for a single mutation, compared with combinations comprising exon 20 point mutations. Instead, the exon 20 insertion group, including V769_D770insASV, D770_N771insSVD, D770_N771insNPG, A763_Y764insFQEA, and H773_V774insH, appear heterogeneous with primary resistance to first- and second-generation EGFR TKIs; third-generation TKIs showed some promising activity and are now under investigation.[16-19]

Exon 18 point mutations account for 3% to 4% of all EGFR mutations and include G719X mutation with a substitution of glycine at position 719 to alanine (G719A), cysteine (G719C), or serine (G719S), and E709A/E790K mutations. In the exon 18 mutations, the G719X presents the highest frequency among all rare mutations and seems to have an outcome comparable with common mutations (deletion 19 and L858R), although data are not homogeneous despite being evaluated in a retrospective experience, and an individual patient data meta-analysis comprising data from ATLAS, BeTa, FASTACT-2, SATURN, TITANT, and TRUST clinical trials.[16-18]

Despite these limited data, the results from post hoc analysis from LL trials previously mentioned more recently led to broadening the afatinib indication by the US Food and Drug Administration in the naive population with tumors harboring uncommon *EGFR* alterations in L861Q, G719X, and/or S768I.

Among the uncommon single mutations, the EGFR baseline complex mutations (CMs), excluding exon 20 T790M, present a high incidence, up to 14%.[17] CMs showed different patterns of presentations including co-occurring classical mutations (del19 and L858R), classical with uncommon (del19/L858R and exon 18/20) and double nonclassical (exon 18 and exon 20). Data about the clinical activity of EGFR TKIs in CMs are difficult to compare because of the heterogeneity of the different groups; however, they present sensitivity to EGFR TKIs with an ORR of approximately 50% to 70%. In this group, there is persistent interest on exon 20 mutations and their role on sensitivity or resistance where they co-occur with other EGFR mutations.[17]

Despite the increasing amount of data about uncommon EGFR mutations, the efficacy and activity of EGFR TKIs in this setting have not yet been fully elucidated considering that patients with these biological characteristics are usually excluded from pivotal clinical trials, and available data are from Asian patient populations, usually evaluated in retrospective analyses.

We report a multi-institutional retrospective analysis evaluating and comparing the activity of EGFR TKIs in selected EGFR uncommon mutations classified into 2 groups: CMs (cohort A) and exon 18 mutations (cohort B).

Patients and Methods

Study Design

This was a retrospective observational multicenter study, including patients with stage IIIB/IV lung cancer harboring uncommon EGFR mutations treated from July 2004 to November 2017 with first- or second-generation EGFR TKIs in 18 Italian institutions. In this study we aimed to investigate the activity of EGFR TKIs in patients with NSCLC carrying 2 different clusters of EGFR mutations: CMs and exon 18 mutations. Overall survival (OS), progression-free survival (PFS), and ORR were evaluated as efficacy end points.

Patients with histologically or cytologically confirmed NSCLC diagnosis, stage IIIB/IV with EGFR CMs (combination of 2 or more EGFR mutations) or EGFR exon 18 single mutations, detected on tumor specimens obtained using either surgical or needle biopsy/aspiration procedures and locally sequenced for mutational analysis, were included. Patients with single common mutations (exon 19 deletions and exon 21 L858R) or exon 20 insertions, were excluded.

Treatment

Eligible patients received treatment with afatinib 40 mg/d, erlotinib 150 mg/d or gefitinib 250 mg/d. Treatment was administered until disease progression or unacceptable toxicity.

Data Collection

Data on patient characteristics were collected, including type of EGFR mutation, age, sex, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), histology, tumor stage, type of EGFR TKI used, response rate, and survival data (PFS and OS).

Light and heavy smokers were defined as patients who had smoked less or more than 100 cigarettes in their lifetime, respectively. Theses data were divided into 2 different cohorts as explained previously.

Response Evaluation

Baseline and subsequent disease assessments were at physicians' discretion and on the basis of personal clinical and routine experience.

Generally, evaluations were performed with full body computed tomography scan or whole-body positron emission tomography scan at baseline, and following routine clinical practice, to monitor the response, its duration, and disease progression.

Response evaluation was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria as complete response (CR), and partial response (PR), stable disease (SD), and progressive disease (PD).

Overall response rate was defined as the sum of CR and PR, and disease control rate (DCR) as the sum of CR, PR, and SD.

Progression-free survival and OS were calculated from the date of initiation of TKI treatment and, respectively, until PD (or death, if it occurred before PD) for PFS and until death/last follow-up for OS. Patients who did not progress at data cutoff (November 30, 2017) were censored at the last date of follow-up for the PFS analysis.

Statistical Analysis

The χ^2 test or Fisher exact tests were used to analyze categorical variables. Survival analysis and curves were performed using the Kaplan–Meier method, and the differences in PFS and OS were evaluated using the log rank test (Mantel–Cox) for statistical significance, which was defined at the $P < .05$ level.

Median PFS and OS were estimated with their 95% confidence interval (CI). A multivariate analysis with Cox proportional hazards models was performed to adjust imbalances in baseline characteristics and to evaluate independent predictive factors associated with PFS and OS. All of the analyses were performed using SPSS Statistics version 23 (IBM Corp, Armonk, NY).

Results

Patient Characteristics

From July 2004 to November 2017, 88 patients with advanced or metastatic lung adenocarcinoma were included in the analysis.

Patients were divided for the analysis into 2 main groups: 46 in cohort A (CMs) and 42 in cohort B (exon 18).

Patient characteristics are summarized in Table 1.

Most patients were female (cohort A = 27 patients [58.7%] and B = 23 patients [54.8%]); median age was older in cohort A at 72.0 years (range, 49-93 years) compared with cohort B at 63.5 (range, 41-87 years). Eighty-four patients had stage IV, and only 4 had stage IIIB (2 in the CM and 2 in the exon 18 group). Most patients were never or light smokers in both groups. ECOG PS 0 to 1 was reported in 87% of patients in the CM cohort and in 93% in the exon 18 cohort; 6 patients had ECOG PS 2 in the CM group and only 1 in the exon 18 Group.

Epidermal growth factor receptor TKIs were used mostly as first-line treatment (78.3% and 69.0% in cohort A and B, respectively), with a selection in favor of gefitinib (approximately 55%-64% in both groups), whereas afatinib was the least prescribed, because of the later approval in Italy by the Italian Medicines Agency compared with the other EGFR TKIs.

The choice of first-generation TKIs was well balanced between the 2 cohorts, whereas the use of afatinib was greater in the CM cohort (23.9%) compared with in the exon 18 cohort (9.5%).

Treatment Response Evaluation

All patients included in the study were assessable for response analysis.

The CM group showed 3 versus 0 CRs (6.5% vs. 0.0%), 21 versus 13 PRs (45.7% vs. 31.0%), and 16 versus 16 SD (34.8% vs. 38.0%) compared with the exon 18 group.

Overall response rate results were better for the CM compared with the exon 18 group: 52% (95% CI, 37%-67%) versus 31% (95% CI, 17.6%-47.0%; $P = .044$. DCR was 87% versus 69%, respectively, in the CM and exon 18 cohort.

Survival Outcomes in Cohort A (CM) and Cohort B (Exon 18)

Median PFS was 12.3 months (95% CI, 8.5-15.4) and 8.3 months (95% CI, 4.8*11.7) for cohort A and cohort B, respectively. Median OS was 31 months (95% CI, 18.2*43.7) for cohort A and 17 months (95% CI, 8.2-25.7) for cohort B.

The CM group reported better survival outcomes in terms of mPFS ($P = .06$; hazard ratio [HR], 0.65l 95% CI, 0.42-1.20) and median overall survival (mOS) ($P = .04$; HR, 0.62; 95% CI, 0.39-1.00) compared with exon 18 (Figures 1 and 2). Adjusted survival curves for age, sex, smoking history, ECOG PS, upfront TKIs, and different TKIs performed with Cox regression confirmed the survival benefit (OS) for the CM group compared with the exon 18 group ($P = .047$; HR, 0.57; 95% CI, 0.33-0.99).

Complex Mutation Subgroup Analysis (Cohort A)

A subgroup analysis was performed considering patients with CM including an exon 18 mutation (CM Ex18+) and those without an exon18 mutation (CM Ex18-).

Median PFS was 12 months (95% CI, 7.2-16.7) versus 10.7 months (95% CI, 6.1-15.3; $P = .57$, and HR 1.18; 95% CI, 0.63-2.34), respectively, in CM Ex18+ and CM Ex18- groups. Median OS was 24.4 months (95% CI, 2.8-45.9) versus 30 months (95% CI, 20.5-45.7; $P = .50$; and HR 1.26; 95% CI, 0.63-2.55), respectively, in CM Ex18+ and CM Ex18- groups. No significant differences were seen among these groups, probably because of a positive effect of the common sensitizing mutations (Tables 2 and 3).

Another analysis was performed in the CM exon 20-positive (CM Ex20+) and -negative (CM Ex20-) patients. Again, in terms of activity and efficacy no differences were seen between these groups, with a mPFS of 10 versus 12 months, respectively ($P = .9$;

Table 1 Patient Characteristics (n = 88)

Characteristic	Cohort A (n = 46) Complex Mutations		Cohort B (n = 42) Exon 18	
	n[a]	%[a]	n[a]	%[a]
Sex				
Female	27	58.7	23	54.8
Male	19	41.3	19	45.2
Median Age, Years (Range)	72	49-93	63.5	41-87
Age				
<65 Years	9	19.6	22	52.4
>65 Years	37	80.4	20	47.6
Smoking Habit				
Never	23	50	21	50
Light	20	43.5	18	42.9
Heavy	3	6.5	3	7.1
ECOG PS				
0	18	39.1	15	35.7
1	22	47.8	26	61.9
2	6	13	1	2.4
Stage				
IIIB	2	4.3	2	4.7
IV	44	95.7	40	95.3
Best Response TKI				
CR	3	6.5	0	0
PR	21	45,7	13	31
SD	16	34.8	16	38
PD	6	21.6	13	31
ORR	24	52	13	31
DCR	40	87	29	69
MTS Sites				
< 3	31	67.4	23	54.8
≥ 3	15	32.6	19	45.2
TKI Upfront				
Yes	36	78.3	29	69
No	10	21.7	13	31
EGFR TKI				
Gefitinib	25	54.3	27	64.3
Erlotinib	10	21.7	11	26.2
Afatinib	11	23.9	4	9.5

Abbreviations: DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; MTS = metastases; TKI = tyrosine kinase inhibitor.
[a]Data are presented as n (%) except where otherwise noted.

HR 1.04; 95% CI, 0.55-1.94) for CM Ex20+ and CM Ex20-, and a mOS of 27 versus 31 months, respectively ($P = .97$; HR 1.01; 95% CI, 0.52-1.96) in the CM Ex20+ and CM Ex20- groups (Tables 2 and 3).

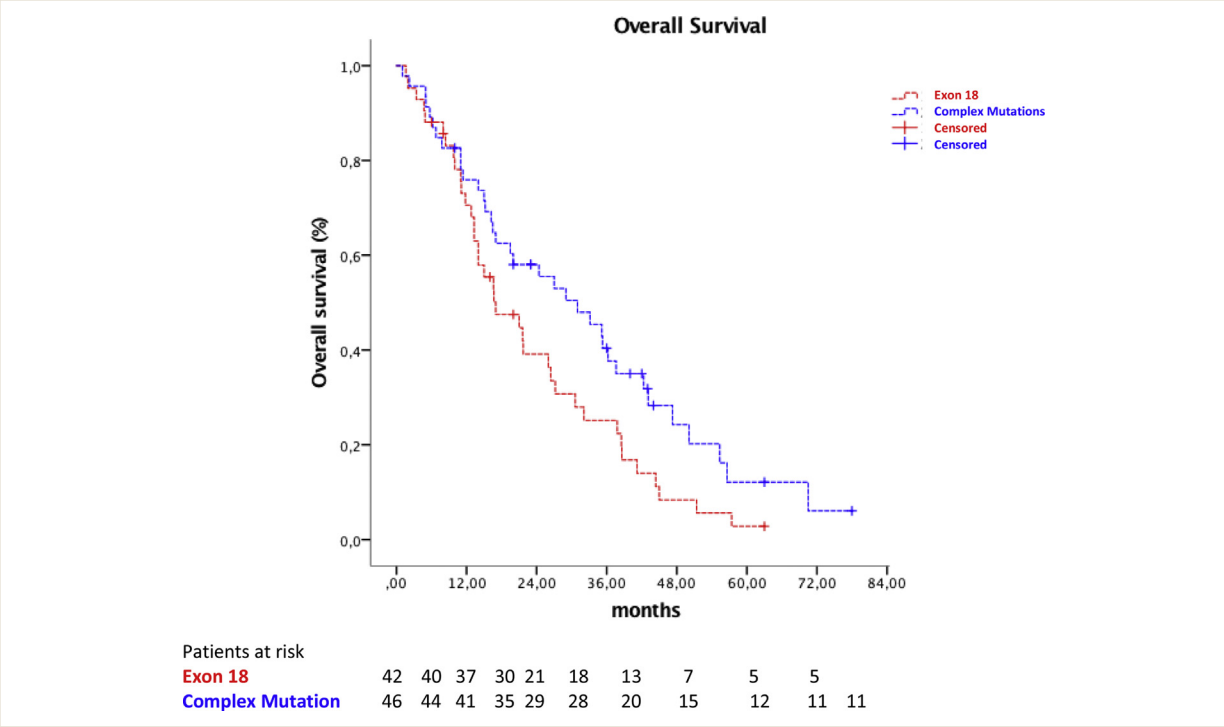
Specific Effects of the CMs and Exon 18 Mutations

Among single EGFR exon18 mutations, the most frequent was G719A (21 patients) followed by G719C (5 patients), G719S (6 patients), and G71X (2 patients). All of these mutations had a heterogeneous pattern of response.

In a group of 3 patients with rare exon 18 mutations (E709K, E790S, and pE790K), the response rate to gefitinib was poor, with 2 patients with PD and 1 with SD. In another 4 with nonspecified exon 18 type mutations, the response was limited (2 PD and 2 SD). Afatinib was used in 4 patients (2 G719A, 1 G719C, and 1 G719X) and all of them showed a PR to the treatment.

The overall frequency of the combination of double mutations are reported in Table 4, and the most frequent combinations were among exon 20 and exon 21 (usually a resistance and sensitizing mutation) and between exon 20 and exon 18; both were 19.6%. The detected rarer CMs were the combinations of 2 mutations from the same exon, such as exon 19-exon 19 (1 patient) and exon 20-exon 20 (1 patient).

Figure 1 Kaplan–Meier Curve of Adjusted Overall Survival. Multivariate Cox Regression for Overall Survival Analysis of 88 Patients With Sensitive Uncommon EGFR Mutations (Group A = Exon 18; Group B = Complex Mutations). Analysis Was Adjusted for Age, Sex, Smoking History, ECOG PS, Upfront TKI Use, and Different TKIs



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

Data showed that when a rare mutation is coupled with a common sensitizing mutation (n = 27), such as deletion of exon 19 and L858R-exon 21 mutation, patients had a good response to TKIs (ORR 60% and 61% and a DCR of 100% and 96%, respectively) and better survival compared with CMs without exon 19 or 21 mutations: PFS 12.9 versus 7.9 ($P = .140$) and OS 35.1 versus 15.0 ($P = .038$).

In our study, 5 of 28 patients showed a nonclassical exon 21 mutation, different from the usual L858R. Of these, only 1 with 3 concomitant EGFR mutations (exon 18 [E790K] and exon 21 [L833V] and exon 21 [H835L]) responded to afatinib, and 3 of them had PD. This can probably be explained because of the number of mutations (triple mutation; Table 5).

Among patients with CMs including exon 19 mutations (deletion and not), no patient had PD and 100% had a DCR. Patients showing CM Ex18+/Ex20+ (2 rare mutations together) had a lower ORR and DCR compared with those with 1 sensitizing mutation (ORR and a DCR of 44% and 77%, respectively; Table 2).

Post-Progression Resistance Biological Assessment

At the time of disease progression, respectively 58.7% (27 of 46) and 42.9% (18 of 42) of patients with CMs and CM Ex18+, were evaluated to investigate the presence of T790M resistance mutation.

Twelve patients with CMs (12 of 27; 44.4%) and 6 patients with CM Ex18+ (6 of 18; 33.3%) showed acquired T790M.

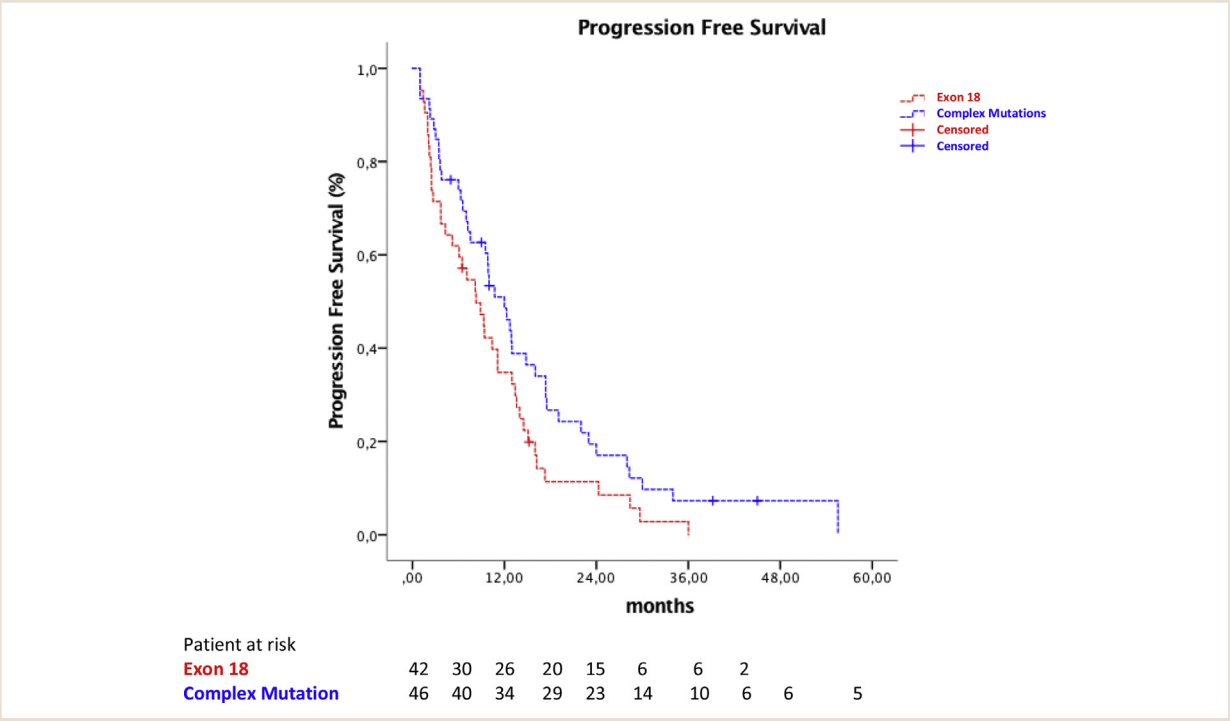
It was very interesting to note that in patients with CMs, the presence of T790M mutation appeared in addition to the other 2 mutations, without affecting the initial setup even in the presence of a baseline exon 20 mutation comutation.

Discussion

Nowadays, data of uncommon EGFR mutations are limited, considering that patients carrying these rare alterations are usually excluded from clinical trials.[20] Available survival data of activity of EGFR TKIs on this class of mutations, coming from a small number of usually retrospective studies, suggests that patients with these nonclassical mutations who received EGFR TKIs might present shorter PFS and OS compared with patients harboring common EGFR mutations (deletion in exon 19 and exon 21 L858R). However, these premises are not completely correct, considering that uncommon mutations are part of a heterogeneous group, in which we can potentially speculate the existence of 2 different cohorts: sensitive (exon 18 and CMs) and resistant (exon 20 insertions) uncommon EGFR mutations.

At first, our analysis confirmed the high heterogeneity of the nonclassical EGFR mutations, even considering only the sensitive variants. Indeed, 9 variants for the CM group and 7 variants for the

Figure 2 Kaplan–Meier Curve of Adjusted Progression-Free Survival. Multivariate Cox Regression Progression-Free Survival Analysis of 88 Patients With Sensitive Uncommon EGFR Mutations (Group A = Exon 18; Group B = Complex Mutations). Analysis Was Adjusted for Age, Sex, Smoking History, ECOG PS, Upfront TKI Use, and Different TKIs



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

exon 18 group were found, counting overall 30 different EGFR mutations.

To our knowledge, this is the largest study to systematically examine 46 patients with complex EGFR mutations. The analysis showed that this group of patients presented survival and responses similar to those of patients with common mutations when treated with EGFR TKIs, confirming a median PFS of 12.3 months and median OS of 31 months.

In the previous articles that reported clinical outcomes of CMs, excluding co-occurring T790M mutations, treated with EGFR TKIs,[17] median PFS was variable from 3.5 to 11.9 months.[21-30]

In 2015, Chiu et al reported a PFS of 11.9 months on the basis of 19 patients who presented only G719X, L861Q, and S768I EGFR mutations, and were split into 2 groups (G719X/L861Q and G719X/S768I). In this analysis, response rates differed according to the co-occurring pattern of mutations: 89% for G719X/L861Q and 50% for G719X/S768I.[21]

Table 2 Response According to Different EGFR Complex Mutations

	Patients		ORR		DCR	
Subgroup	n	%	n	%	n	%
Exon 18, Total	42/88	47.7	13/42	31	29/42	69
CMs, Total	46/88	52.3	24/46	52	40/46	87
CM 18+	19/46	41	11/19	58	17/19	89
CM 18–	27/46	59	13/27	48	23/27	85
CM 20+	24/46	52	13/24	54	20/24	83
CM 20–	22/46	48	11/22	50	20/22	91
CM 18+ 20+	9/46	20	4/9	44	7/9	77
CM 21+ (All)	28/46	61	15/28	53	24/28	85
CM 21+ (L858R)	23/28	82	14/23	61	22/23	96
CM 21+ (Other)	5/28	18	1/5	20	2/5	40

Abbreviations: CM = complex mutation; DCR = disease control rate; EGFR = epidermal growth factor receptor; + = positive or pos; – = negative or neg.

Table 3 Survival of EGFR TKI Treatment in NSCLC With EGFR-Sensitive Uncommon Mutations

	n	Months	95% CI	HR	*P*
Median PFS					
Exon 18, total	42	8.3	4.8-11.7	0.65 (0.42-1,02)	.06
Double mutations, total	46	12.3	8.5-15.4		
Double Exon 20+	22	10	3.1-16.8	1.04 (0.55-1.94)	.9
Double Exon 20−	24	12	8.0-15.9		
Double Exon 18+	19	12	7.2-16.7	1.18 (0.63-2.34)	.57
Double Exon 18−	27	10.7	6.1-15.3		
Median OS					
Exon 18, total	42	17.0	8.2-25.7	0.62 (0.39-1.0)	.04
Double mutations, total	46	31.0	18.2-43.7		
Double Exon 20+	22	27.0	7.8-46.1	1.01 (0.52-1.96)	.97
Double Exon 20−	24	31.0	10-51.9		
Double Exon 18+	19	24.4	2.8-45.9	1.26 (0.63-2.55)	.50
Double Exon 18−	27	30.1	20.5-45.7		

Abbreviations: EGFR = epidermal growth factor receptor; HR = hazard ratio; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor; + = positive or pos; − = negative or neg.

In 2011, Wu and colleagues reported the results of a retrospective analysis of 1261 Asian patients diagnosed and treated at the National Taiwan University Hospital. In this analysis, 32 patients showed CMs excluding co-occurring T790M mutations, but more than 50% (20 of 32) of EGFR mutation data from evaluated patients lacked specification, and were reported as "other EGFR mutations," comprising sensitive and resistant alterations. In this analysis, ORR was 56% and survival was lower than for common mutations, with a median PFS of 3.5 and median OS of 8.5 months, because of the heterogeneity of EGFR-uncommon characteristics, comprising sensitive and resistant mutations to EGFR TKIs; in 7 patients harboring 1 classical mutation in the complex presentation, the PFS grew to 10 months.[27]

In our analysis, we evaluated the role of exon 20 mutations (non-T790M) when associated with other EGFR mutations, in a complex model. Patients were well balanced in both groups of CMs with or without exon 20 mutations (n = 22 and 24). The results support that the presence of exon 20 mutation, when associated with another co-occurring EGFR mutation, either common or uncommon (exon 18, exon 19, or exon 21) loses its resistance effect and silences itself (mPFS 10 vs. 12 months and mOS 27 vs. 31 months, respectively, for CM Ex20+ and CM Ex20-). As for the exon 20 CMs, the analysis showed no statistical difference for patients with or without exon 18 in combined mutations.

Although the data are retrospective and limited to a small number of patients, they confirm that CMs of the EGFR, with or without exon 20 or 18, might be considered similar to common mutations in terms of response and survival when treated with first- or second-generation EGFR TKIs.

Moreover, published data about exon 18 mutations showed a range of ORRs from 8.0% to 77.8%, and a median PFS from 2 to 13.8 months.[17] These differences in efficacy were also detected in our analysis, for which we report an ORR of 31% and mPFS and OS, respectively, of 8.3 and 17.0 months.

These data confirm that the exon 18 group might perform a bit worse than the common mutations during treatment with EGFR TKIs, in terms of response and survival. Analyzing the activity of the exon 18 group, it is very important to remember that this group is

Table 4 Different Patterns of EGFR-Sensitive Uncommon Mutations

Cohort A: Double Mutations (n = 46)				Cohort B: Exon 18 (n = 42)
Exon 18 (n = 19)	**Exon 19 (n = 15)**	**Exon 20 (n = 24)**	**Exon 21 (n = 31)**	
G719C (n = 4)	Del 19 (N = 10)	S7681 (n = 16)	L858R (n = 25)	G719A (n = 21)
G719A (n = 4)	G746S (n = 1)	V774M (n = 1)	N842S (n = 1)	Not specified (n = 4)
Not specified (n = 4)	E746S (n = 1)	R776H (n = 1)	L833F (n = 1)	G719S (n = 6)
E790K (n = 1)	L747_T751 (n = 2)	T790M (n = 3)	L833V (n = 1)	G719C (n = 6)
E709A (n = 1)	I744M (n = 1)	G2303A (n = 1)	V834L (n = 1)	G719X (n = 2)
G719S (n = 1)		V765M (n = 1)	H835L (n = 1)	E709K (n = 2)
G724S (n = 2)		p772_H773insQAA (n = 1)	L861Q (n = 1)	E790S (n = 1)
G719X (n = 1)				
V689M (n = 1)				

Abbreviations: Del = deletion; EGFR = epidermal growth factor receptor.

Table 5 Type of Uncommon Mutation and Singular Response to EGFR-TKIs

	n	Response
Cohort A: Double Combination Mutations (n = 46)		
Exon 20 to exon 21	9	
S7681/L858R	4	2 PR 1 SD 1 PD
R776H/L858R	1	1 PR
T790M/L858R	1	1 PR
T790M/T790M	1	1 PD
V765M/L858R	1	1 CR
P.P772_H773insQAA/N842S	1	1 SD
Exon 20 to exon 18	9	
S768I/G719C	3	2 CR 1 SD
S768I/NS	2	1 PR 1 SD
S768I/G719X	1	1 PD
S768I/G724S	2	1 PD 1 SD
S768I/G719S	1	1 PR
Exon 20 to exon 19	5	
S768I/del19	2	2 PR
S768I/L747_T751	1	1 PR
S768I/del c.2240_2254del15	1	1 SD
T790M/del19	1	1 PR
Exon 20 to exon 20	1	
S768I/V774M	1	
Exon 18 to exon 21	8	
G719A/L858R	3	3 PR
T725M/L858R	1	1 PR
G719C/L858R	1	1 PR
E709A/L858R	1	1 SD
E790K/L833V and H835L	1	1 PR
NS/L858R	1	1 SD
Exon 18 to exon 19	2	
G719A/del19	1	1 SD
V689M/del19	1	1 PR
Exon 21 to exon 19	7	
L858R/del19	6	3 PR 3 SD
L858R/I744M	1	1 PR
Exon 19 to exon 19	1	
G746S/E746S	1	1 SD
Exon 21 to exon 21	4	
V834L/L858R	1	1 SD
T854S/L858R	1	1 SD
L833F/V834L/L861Q	1	1 PD
pL833F/L861R	1	1 PD
Cohort B: exon 18 single mutations (n = 42)		
G719A	21	7 PR 7 SD 7 PD
G719C	6	3 PR 3 SD
G719S	6	2 PR 3 SD 1 PD
G719X	2	1 PR 1 PD
E709K	1	1 PD
E790S	1	1 PD
pE790K	1	1SD
Not specified	4	2 SD 2 PD

Abbreviations: EGFR = epidermal growth factor receptor; NS = not specified; TKI = tyrosine kinase inhibitor.

very heterogeneous, including many variants and mutations, such as G719A, G719C, G719S, G719X, E709K, E790S, or E790K, performing not all in the same way. Currently, overall data from 178 patients are reported in the literature on the basis of 9 retrospective studies; among these, Chiu et al reported the largest group of exon 18 mutations, in which 76 Asian patients presented a G719X mutation, achieving a median PFS of 6.3 months.[21,23,25,27,28,31-34]

To date, the only available data of uncommon EGFR patients in pivotal trials have been achieved with afatinib in the LL2, LL3, and LL6 studies.[19] Instead, most of the retrospective studies published on this topic evaluated the role of erlotinib and gefitinib in this setting.[17] As in the other retrospective analyses, in our research, most of the patients received treatment with first-generation EGFR TKIs: erlotinib (n = 21) and gefitinib (n = 52), because of the subsequent approval of afatinib (n = 15) in the same setting.

Although our results are positive, we report data of a retrospective analysis. Therefore, findings of borderline significance should be interpreted with caution.

Conclusion

This study confirms the importance of investigating an extended molecular profiling in NSCLC, to identify the less common alterations that can improve survival of patients, when receiving EGFR TKIs. In addition, our multivariate analysis suggests the equal role of first- and second-generation EGFR TKIs in patients with sensitive uncommon EGFR mutations including exon 18 mutations and CMs, including or not exon 20 mutations.

Clinical Practice Points

- Non–small-cell lung cancer harboring common EGFR mutations is associated with high efficacy to EGFR TKIs.
- Uncommon mutations (accounting overall 10%-15%) are represented by a heterogeneous group including different mutations, which mainly concern exon 20 insertions and point mutations and exon 18 point mutations.
- Patients with exon 20 insertions present poor response to first- and second-generation EGFR TKIs.
- Those with exon 18 mutations showed moderate activity in terms of PFS (8.3 months) and OS (17.0 months), confirming the use of EGFR TKIs as a valid therapeutic option.
- The complex mutations group, although extremely heterogeneous, showed a median PFS (12.3 months) and median OS (31.0 months), overlapping the results in patients with exon 19

deletion and exon 21 L858R mutations, previously reported in different clinical trials.

- In the CMs group, no detrimental effect was associated with the presence of exon 20 mutations.

Disclosure

A.Pa., M.T., F.d.M., D.C. served as advisor/consultant for AstraZeneca, Boehringer-Ingelheim, and Roche. L.T. served as advisor/consultant for AstraZeneca and Boehringer-Ingelheim. R.C. and C.G. received speaker's bureau fees from AstraZeneca, Roche, Boehringer-Ingelheim. F.C. has served as advisor/consultant for AstraZeneca and Roche. The remaining authors have stated that they have no conflicts of interest.

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