ORIGINAL ARTICLE

Afatinib for the Treatment of NSCLC Harboring Uncommon *EGFR* Mutations: A Database of 693 Cases

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ABSTRACT

Introduction: Limited clinical data are available regarding the efficacy of EGFR tyrosine kinase inhibitors (EGFR TKIs) in patients with NSCLC harboring uncommon *EGFR* mutations. This pooled analysis assessed the activity of afatinib in 693 patients with tumors harboring uncommon *EGFR* mutations treated in randomized clinical trials, compassionate-use and expanded-access programs, phase IIIb trials, noninterventional trials, and case series or studies.

Methods: Patients had uncommon *EGFR* mutations, which were categorized as follows: (1) T790M; (2) exon 20 insertions; (3) "major" uncommon mutations (G719X, L861Q, and S768I, with or without any other mutation except T790M or an exon 20 insertion); (4) compound mutations; and (5) other uncommon mutations. Key end points were overall response rate (ORR), duration of response, and time to treatment failure (TTF).

Results: In EGFR TKI–naive patients (n = 315), afatinib demonstrated activity against major uncommon mutations (median TTF = 10.8 mo; 95% confidence interval [CI]: 8.1–16.6; ORR = 60.0%), compound mutations (median TTF = 14.7 mo; 95% CI: 6.8–18.5; ORR = 77.1%), other uncommon mutations (median TTF = 4.5 mo; 95% CI: 2.9–

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9.7; ORR = 65.2%), and some exon 20 insertions (median TTF = 4.2 mo; 95% CI: 2.8–5.3; ORR = 24.3%). The median duration of response for major uncommon mutations, compound mutations, other uncommon mutations, and some exon 20 insertions was 17.1, 16.6, 9.0, and 11.9 months, respectively. Activity of afatinib was also observed in EGFR TKI–pretreated patients (n = 378). A searchable database of these outcomes by individual genotype was generated.

Conclusions: Afatinib has clinical activity in NSCLC against major uncommon and compound *EGFR* mutations. It also has broad activity against other uncommon *EGFR* mutations and some exon 20 insertions. The data support the use of afatinib in these settings.

Keywords: Afatinib; Uncommon *EGFR* mutations; NSCLC; Compound EGFR mutation

Introduction

The first-line standard of care for patients with *EGFR* mutation–positive NSCLC are the EGFR tyrosine kinase inhibitors (TKIs), of which five are now clinically approved: the first-generation reversible EGFR TKIs, gefitinib and erlotinib[1-6]; the second-generation irreversible ErbB family blockers, afatinib and dacomitinib,[7-10] and the third-generation irreversible EGFR TKI, osimertinib.[11] Even though robust clinical trial data have demonstrated the efficacy and tolerability benefits of EGFR TKIs versus standard of care, the bulk of these trials were limited to patients whose tumors harbored the common *EGFR* mutations, exon 19 deletions (Del19) and L858R, which account for approximately 45% and 40% of cases of *EGFR* mutation–positive NSCLC, respectively.[12,13]

Despite being excluded from most clinical trials, 7% to 23% of NSCLC tumors harbor uncommon *EGFR* mutations.[14-21] These mutations represent a highly heterogeneous group with almost 600 variants identified.[22] The most prevalent categories include exon 20 insertions (~6% of all *EGFR* mutations), G719X (~3%), L861Q (~1%), S768I (~1%), and exon 19 insertions (0.6%).[22] Up to 25% of all uncommon *EGFR* mutation–positive tumors, coexist with other *EGFR* mutations within the same tumor (termed "compound" mutations).[13,23] The increasing use of modern, highly sensitive, next-generation sequencing (NGS) techniques are likely to expand the detection of targetable somatic mutations throughout *EGFR*, as they are not restricted to a few mutations or certain exons (as is the case with commercial genotyping assays, such as COBAS and Therascreen).[24] Moreover, the development and implementation of plasma-based mutation detection assays will facilitate increased uptake of baseline *EGFR* mutation testing in the clinic.[25] Therefore, the identification of uncommon mutations should increase in the future.

Preclinical and computational analysis of uncommon mutations has demonstrated a high degree of heterogeneity in terms of sensitivity to different EGFR TKIs.[22,23,26] The variable sensitivity of different uncommon mutations to different EGFR TKIs indicates that a personalized treatment strategy should be undertaken in patients depending on the underlying uncommon *EGFR* mutation. However, effective treatment decisions are compromised by the paucity of prospective clinical data. Of the EGFR TKI prospective randomized trials undertaken to date, only Iressa Pan-Asia Study (gefitinib),[4] North-East Japan Study Group (NEJ002; gefitinib),[5] and LUX-Lung 3 and 6 (afatinib)[7,8] included patients with uncommon *EGFR* mutations, albeit in small numbers.

In a post hoc analysis of the LUX-Lung trials, afatinib demonstrated clinical activity against the most prevalent uncommon mutations, G719X, L861Q, and S768I.[21] Accordingly, afatinib has been approved in more than 80 countries for the treatment of NSCLC harboring these mutations. As expected, based on preclinical data, afatinib was largely ineffective against tumors with de novo T790M mutations alone or in combination with other mutations, and also with exon 20 insertions, although the sample numbers were small. Less prospective clinical data are available for other EGFR TKIs against NSCLC tumors with uncommon mutations. Although both dacomitinib and osimertinib have shown strong efficacy in a first-line setting in patients with NSCLC and common mutations (Del19, L858R),[10,11] their clinical activity against uncommon mutations is largely unknown, although a recent ongoing phase II trial indicates that osimertinib has activity against some uncommon mutations.[27]

Given the lack of prospective data, and complexities of the *EGFR* mutational spectra, numerous real-world studies have assessed the activity of EGFR TKIs in patients with uncommon mutations. Such studies, although not a substitute for prospective data, can play an important complementary role to randomized trials for informing clinical decision making, especially in special populations.[28] The aim of this study was to analyze the available data for afatinib and provide a searchable database. The outcomes of close to 700 patients have been included.

Materials and Methods

Details of patients with tumors harboring uncommon mutations treated with afatinib in randomized clinical trials, compassionate-use and expanded-access programs, phase IIIb trials, and noninterventional trials have been collected prospectively since the start of development of afatinib by Boehringer Ingelheim medical information. In addition, a systematic literature review was undertaken on September 19, 2019 (Supplementary Methods). All identified cases with outcome data provided (either time to treatment failure [TTF] or objective response rate [ORR]) were included. Double reporting was ruled out by scrutiny.

Central testing was only performed in patients enrolled in the LUX-Lung trials. In all other patients, mutation detection was undertaken locally using different methodologies (Table 1[29-58]). Patients were categorized into four key groups: (1) T790M-positive, (2) exon 20 insertion–positive (but T790M-negative), (3) major uncommon mutations (G719X, L861Q, and S768I, with or without any other uncommon mutation except T790M or an exon 20 insertion), and (4) other uncommon mutations (T790M, exon 20 insertion, and major uncommon mutation negative). Furthermore, compound mutations defined as cases in which at least two uncommon mutations were present with or without a common mutation were analyzed. Fifteen unusual cases with four or more different mutations, and both Del19 and L858R, were excluded from the analysis.

The key end points were ORR, duration of response (DoR) and TTF, defined as time from the start of therapy to treatment discontinuation for any reason, or death. This was chosen as a pragmatic end point suited to real-world studies (Supplementary Methods). Apart from the LUX-Lung studies, tumor response was assessed by the treating investigator by local assessment. TTF and DoR were calculated using Kaplan-Meier estimates. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs). All statistical analyses were exploratory; there was no formal statistical analysis plan.

Results

Patients

A total of 693 patients were included in this study, and 98 different uncommon mutations were identified (Fig. 1; Table 1). Three hundred fifteen patients had not been previously treated with an EGFR TKI before afatinib; 378 patients had received previous EGFR TKI treatment. Details of the main studies included in this analysis are shown in Table 1.

Mutation categories and available baseline characteristics are shown in Table 2. Overall, 29% of patients included in the analysis had a tumor harboring a major uncommon mutation (G719X, L861Q, S768I), 25% harbored a T790M mutation (predominantly in the EGFR TKI–pretreated patients), 21% had an exon 20 insertion, 13% had other uncommon *EGFR* mutations, and 12% had a compound mutation.

Outcomes in Patients Who Were EGFR TKI Naive Before Afatinib

TTF data were available for 272 of the 315 EGFR TKI–naive patients, and TTF was longest in patients with tumors harboring compound mutations (median 14.7 mo; 95% CI: 6.8–18.5; Fig. 2*A*), particularly in cases in which one of the mutations was a major uncommon mutation (median 16.6 mo; 95% CI: 6.8–18.7; Fig. 2*B*). Median TTF of almost 1 year was observed in patients with major uncommon mutations (median 10.8 mo; 95% CI: 8.1–16.6; Fig. 2*B*). Of those, median TTF was 14.7, 10.0, and 15.6 months in patients with G719X, L861Q, and S768I mutations, respectively. As expected, TTF was shorter in patients harboring exon 20 insertions (median 4.2 mo; 95% CI: 2.8–5.3; Fig. 2*A*), T790M (median 4.7 mo; 95% CI: 1.8–6.5; Fig. 2*A*), or other uncommon mutations (median 4.5 mo; 95% CI: 2.9–9.7; Fig. 2*A*). Of note, 11 patients with uncommon mutations (seven with a major uncommon mutation and four harboring an exon 20 insertion) remained on treatment for more than 3 years.

Best tumor response was reported in 265 EGFR TKI–naive patients (Table 3). High activity was observed in patients harboring compound mutations (ORR = 77.1%) and patients with major uncommon mutations (overall: 60.0%; G719X: 63.4%; L861Q: 59.6%; S768I: 62.5%). Activity was also notable in patients harboring other uncommon mutations (65.2%). Response rate was lower in patients harboring T790M mutations and exon 20 insertions, but it still approached 25%. Durable responses were observed in several patients harboring compound mutations (median DoR = 16.6 mo; 95% CI: 13.8–18.7; Table 3; Supplementary Fig. 1*A*) and major uncommon mutations (median DoR = 17.1 mo; 95% CI: 11.0–20.8; Table 3, Supplementary Fig. 1*B*). Although only a minority of patients harboring *EGFR* exon 20 insertions responded to treatment, the median DoR was 11.9 months (95% CI: 5.4–26.7). Median DoR was 9.0 months (95% CI: 3.5–11.9) and 4.7 months (95% CI: 3.8–11.0) in patients with tumors harboring other uncommon mutations or T790M, respectively.

Outcomes in Patients Who Were EGFR TKI Pretreated Before Afatinib

All 378 EGFR TKI–pretreated patients were included in the analysis of TTF. As with the EGFR TKI–naive

Table 1. Data Derivation

Study	Study Type	Patients With Uncommon Mutations, n	Mutation Detection Methodology	References
LUX-Lung 2	Phase II trial in patients with EGFR TKI-naive *EGFR*m+ NSCLC	23	Central testing; direct sequencing of exon 18–21	Yang et al., 2012[29]
LUX-Lung 3	Phase III trial in patients with previously untreated *EGFR*m+ NSCLC	26	Central testing; Therascreen EGFR 29, Qiagen, Manchester, United Kingdom	Sequist et al., 2013[8]
LUX-Lung 6	Phase III trial in patients with previously untreated *EGFR*m+ NSCLC	26	Central testing; rtPCR	Wu et al., 2014[7]
1200.55	Phase IIIb open-label trial in patients with EGFR TKI-naive *EGFR*m+ NSCLC	69	Local testing; individual institutions' methodology	Unpublished (NCT01853826)
1200.66	Phase IIIb open-label trial in patients with EGFR TKI-naive *EGFR*m+ NSCLC	31	Local testing; individual institutions' methodology	Unpublished (NCT01953913)
1200.193	Phase IIIb open-label trial in patients with EGFR TKI-naive *EGFR*m+ NSCLC	15	Local testing; individual institutions' methodology	Unpublished (NCT01931306)
1200.51	Compassionate-use program in EGFR TKI-pretreated patients: German subgroup	57	Local testing; methodology not documented	Heigener et al., 2015[20]
1200.45	United States expanded access program	46	Local testing; methodology not documented	Kim et al., 2017[30]
Global compassionate use program	Compassionate use program in EGFR TKI-pretreated patients	294	Local testing; methodology not documented	Heigener et al., 2015[20]; Cappuzzo et al., 2018[31]
1200.205	Multicenter German cohort study in patients with EGFR TKI-naive *EGFR*m+ NSCLC	20	Local testing; methodology not documented	Brueckl et al., 2018[32]
Italian cohort study	Multicenter Italian cohort study in patients with NSCLC harboring uncommon mutations	5	Local testing; direct sequencing	Passaro et al., 2019[33]
Korean cohort study	Single-center Korean cohort study in patients with previously untreated *EGFR*m+ NSCLC	12	In-house PNA clamp kit and rtPCR assay	Kim et al., 2019[34]
Taiwanese cohort study	Single-center Taiwanese cohort study in patients with previously untreated *EGFR*m+ NSCLC	35	Local testing; Therascreen, MassARRAY genotyping or direct sequencing	Liang et al., 2019[35]; Liang et al., 2017[36]
Chinese cohort study	Single-center Chinese cohort study in patients with NSCLC harboring uncommon mutations	2	Direct sequencing of exon 18–21	Shen et al., 2017[16]
Japanese cohort study	Single-center Japanese cohort study in patients with NSCLC harboring uncommon mutations	8	Not reported	Tanaka et al., 2019[37]
Indian cohort study	Single-center Indian cohort study in patients with NSCLC harboring uncommon mutations	1	Nested PCR method with in-house TaqMan primers and probes	Kate et al., 2019[38]
Case reports or case series	Various	23	Various	Cai et al., 2019[39]; Chan, 2018[40]; Kobayashi et al., 2015[41]; Chen et al., 2019[42]; Duan et al., 2018[43]; Frega et al., 2016[44]; Galli et al., 2018[45]; Ibrahim et al., 2017[46]; Ikeuchi et al., 2019[47]; Iwamoto et al., 2019[48]; Kimura et al., 2018[49]; Martin et al., 2019[50]; Nakamura et al., 2018[51]; Niogret et al., 2018[52]; Coupkova et al., 2018[53]; Zeng et al., 2018[54]; Peled et al., 2017[55], Chikamori et al., 2016[56]; Zhou et al., 2018[57]; Raez et al., 2018[58]

*EGFR*m+, *EGFR* mutation positive; TKI, tyrosine kinase inhibitor; rtPCR, real-time polymerase chain reaction.

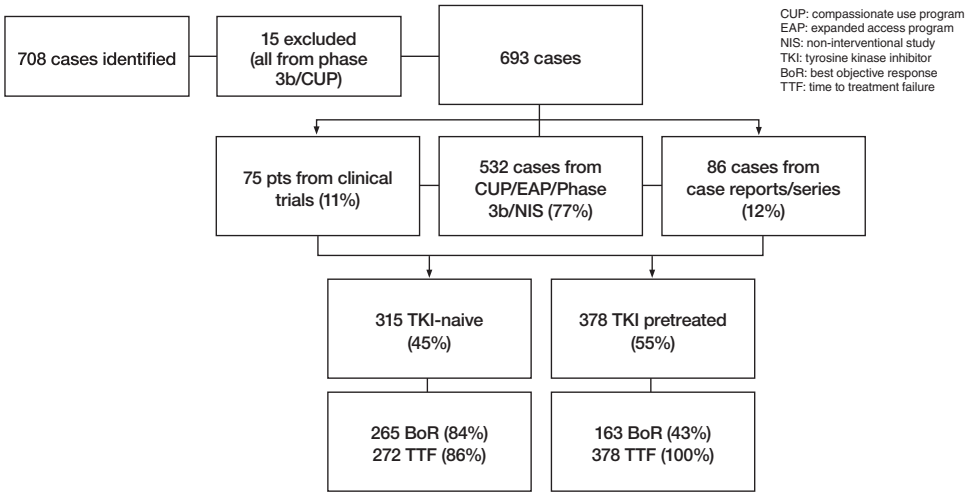


Figure 1. Overview of selection process.

patients, median TTF was highest in patients with tumors harboring compound mutations (median TTF = 5.8 mo; 95% CI: 3.4–8.9; Fig. 2*C*), especially those with a major uncommon mutation (median TTF = 9.3 mo; 95% CI: 2.2–not reached; Fig. 2*D*). Median TTF was similar in patients with tumors harboring a major uncommon mutation (median TTF = 4.4 mo; 95% CI: 3.0–6.8; Fig. 2*D*), an exon 20 insertion (median TTF = 4.4 mo; 95% CI: 2.4–8.4; Fig. 2*C*), or other mutations (median TTF = 4.9 mo; 95% CI: 2.2–8.5; Fig. 2*C*). Median TTF in patients harboring T790M was 3.8 months (95%: 3.0–5.6; Fig. 2*C*). Of note, 66 of 378 EGFR TKI–pretreated patients (17.5%) remained on afatinib for more than 1.5 years (major uncommon mutations: 13 of 77 [16.9%]; compound mutations: 10 of 46 [21.7%] of whom eight had a major uncommon mutation; exon 20 insertions: 15 of 66 [22.1%]; other mutations: 10 of 53 [18.9%]; T790M: 18 of 136 [12.2%]).

Best tumor response was reported in 163 EGFR TKI–pretreated patients (Table 3). ORR was highest in patients with tumors harboring other uncommon mutations (36.0%), compound mutations (28.6%), or major uncommon mutations (25.0%). Some activity was noted in patients with exon 20 insertions (14.3%) or a T790M mutation (18.8%). The longest median DoR was observed in the compound mutation group (16.7 mo; 95% CI: 9.9–21.8; Table 3, Supplementary Fig. 1*C*). Median DoR was 4.9 months (95% CI: 2.0–18.0; Table 3; Supplementary Fig. 1*D*), 3.7 months (95% CI: 2.7–10.1), 6.1 months (95% CI: 2.6–7.9), and 6.3 months (95% CI: 0.8–11.3; Table 3; Supplementary Fig. 1*C*) in the major uncommon mutation, exon 20 insertion, T790M, and other mutation groups, respectively.

Details of Other Uncommon Mutations

In total, 87 patients with tumors harboring other uncommon *EGFR* mutations received afatinib. This category was highly heterogeneous and encompassed rare *EGFR* mutations across exon 18 (n = 19), exon 19 (n = 25), exon 20 (n = 25), exon 21 (n = 14), and noncanonical mutations (n = 4). Afatinib demonstrated clinical activity across a broad range of uncommon mutations including E709_T710>D, E709X, T725M, V717A, K739_I744dup6, L747_P753>Q, L747P, Q787Q, R776H, V765M, L861P, L858M, H870R, and Exon21Del (Supplementary Table 1). A searchable database of these outcomes for afatinib reported by *EGFR* genotype was created for individual genotype-efficacy critique (www.uncommonEGFRmutations.com).

Discussion

To the best of our knowledge, this study represents the most comprehensive analysis of clinical outcomes of EGFR TKI treatment in patients with NSCLC tumors harboring uncommon *EGFR* mutations. Results in both TKI-naive and TKI-pretreated patients are consistent with previously published data for afatinib.[21,59] Strong activity was observed against tumors harboring major uncommon mutations and compound mutations (both TKI-naive and pretreated patients). In addition, afatinib demonstrated durable responses in some patients with exon 20 insertions. Generally, afatinib demonstrated broad activity across very rare (other) mutations, consistent with preclinical findings.[22,23]

The widespread implementation of NGS in routine clinical practice,[24] together with improvements in the sensitivity of NGS assays and their transfer into the liquid biopsy setting[25] are likely to improve the detection of *EGFR* mutations in the future, including uncommon mutations. Accordingly, the data herein will provide important information when considering optimal treatment for patients with NSCLC tumors harboring specific uncommon *EGFR* mutations, including compound

Table 2. Mutation Frequency and Available Baseline Characteristics

	TKI Naive				TKI Pretreated			
Mutation Category	Total, n (%)	Median Age, y (range)	Sex, M/F/NA, n	Ethnicity, Asian/Non-Asian/NA, n	Total, n (%)	Median Age, y (range)	Sex, M/F/NA, n	Ethnicity, Asian/Non-Asian/NA, n
Major uncommon mutation	127 (40.3)	64 (32-81)	44/50/33	58/34/35	77 (20.4)	64 (34-89)	32/45/0	3/15/59
G719X	62 (48.9)	64 (32-81)	22/23/17	23/20/19	43 (55.8)	62.5 (34-89)	19/24/0	2/11/30
L861Q	55 (43.3)	62 (39-79)	14/25/16	30/9/16	22 (28.6)	66.5 (44-84)	7/15/0	0/4/18
S768I	10 (7.9)	65.5 (42-78)	8/2/0	5/5/0	12 (15.6)	59 (37-72)	6/6/0	1/0/11
Compound[a]	40 (12.7)	60.5 (35-79)	12/21/7	21/10/9	46 (12.2)	61 (36-88)	12/29/5	1/16/29
With major uncommon mutation	26 (65.0)	56 (35-79)	8/14/5	17/4/6	23 (50.0)	62 (37-88)	5/17/1	0/7/16
Exon 20 insertion	77 (24.4)	62 (30-86)	27/45/5	24/44/9	66 (17.5)	60 (33-89)	26/39/1	2/10/54
T790M	37 (11.7)	62 (45-82)	17/11/9	8/13/16	136 (36.0)	61 (24-88)	51/80/5	5/37/94
Others	34 (10.8)	66 (44-79)	8/16/10	7/11/16	53 (14.0)	63 (34-80)	15/33/5	2/14/37

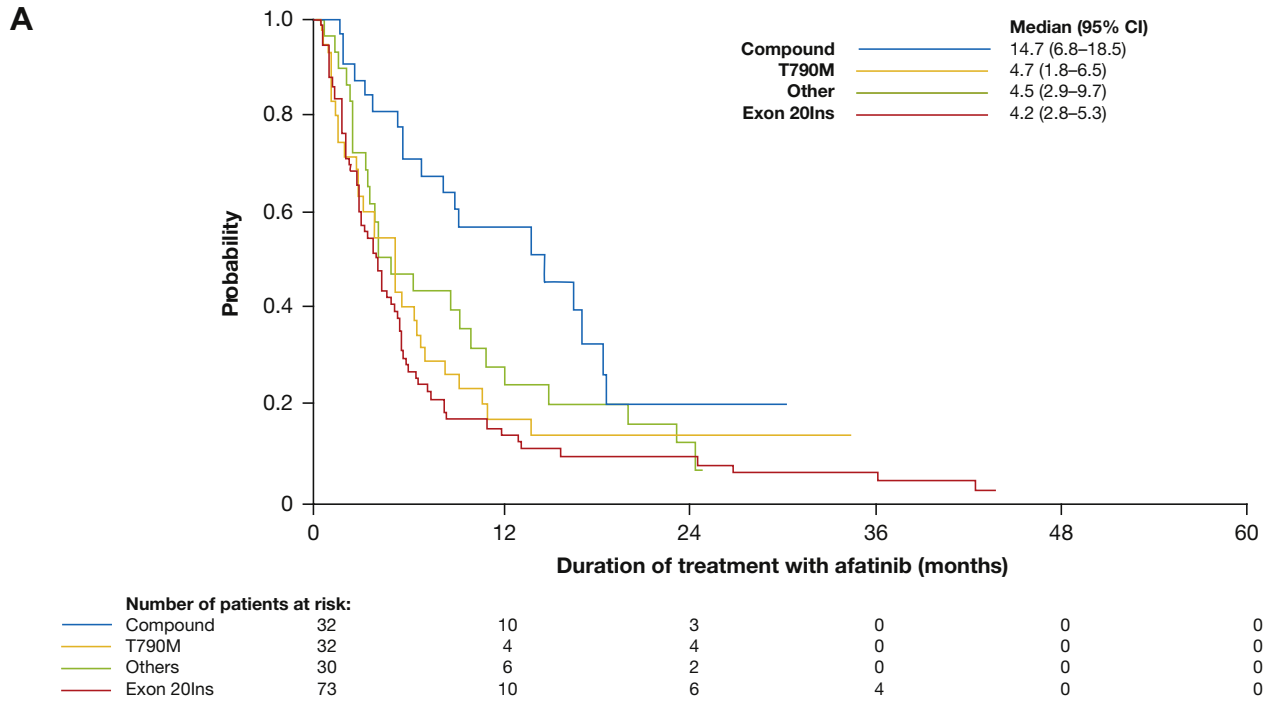
[a]Two patients in the TKI-naive group, and three in the TKI-pretreated group had tumors harboring a common *EGFR* mutation and a compound uncommon mutation.
TKI, tyrosine kinase inhibitor; M, male; F, female; NA, not available.

mutations. At present, optimal treatment for tumors with uncommon mutations remains uncertain, with several studies suggesting that chemotherapy[60,61] or immunotherapy[62,63] may be preferable to EGFR TKIs in some patients. However, these data support the use of afatinib as a treatment option in patients with major uncommon *EGFR* mutations and compound mutations. Moreover, even though median TTF was short in the overall "other mutations" and "exon 20 insertions" categories, evidence suggests that certain mutations in these categories are sensitive to afatinib.

The activity of afatinib observed in patients with NSCLC tumors harboring a major uncommon mutation (alone or as part of a compound mutation) is consistent with findings from the LUX-Lung trials. In LUX-Lung 2, 3, and 6, the response rate in this category (n = 38) was 71.1% and median DoR was 11.1 months.[21] The response rate in patients with NSCLC tumors harboring G719X (n = 18), L861Q (n = 16), and S768I (n = 8) was 77.8%, 56.3%, and 100.0%, respectively. In the current, much larger, real-world data set of major uncommon mutations (n = 142), the response rate was 60.0% in EGFR TKI–naive patients (L861Q: 59.6%; G719X: 63.4%; S768I: 62.5%) and 25.0% in EGFR TKI–pretreated patients. Of the EGFR TKI–naive patients, seven patients (6.8%) remained on treatment for more than 3 years. This is slightly lower than observed in clinical trials (10%–12%).[64] Overall, these extensive and robust data support the use of afatinib as a first-line treatment option against major uncommon *EGFR* mutations.

Currently, osimertinib has demonstrated preclinical activity against major uncommon mutations.[65] In a recent phase II trial of 35 patients with uncommon mutations, osimertinib conferred an ORR of 50.0%[27] (L861Q: 77.8%; G719X: 52.6%; S768I: 37.5%), indicating that osimertinib may be a treatment option, though more data are required. However, the response rate and median DoR (9.8 mo) were lower than those observed with osimertinib in patients with common mutations (Del19, L858R).[11] Available clinical data indicate that first-generation EGFR TKIs have limited activity against major uncommon mutations.[66,67]

Compound *EGFR* mutations are present in up to a quarter of NSCLC tumors and are associated with poor prognosis.[13,23] Consistent with preclinical data, the current analysis demonstrates that afatinib is active across most compound mutations, with the exception of those including T790M.[23] The ORR with afatinib against compound mutations (77%) and median DoR (16.6 mo) is comparable with that observed against common *EGFR* mutations (Del19/L858R).[9] Limited data are available assessing the clinical activity of other EGFR TKIs, including osimertinib, against compound mutations.



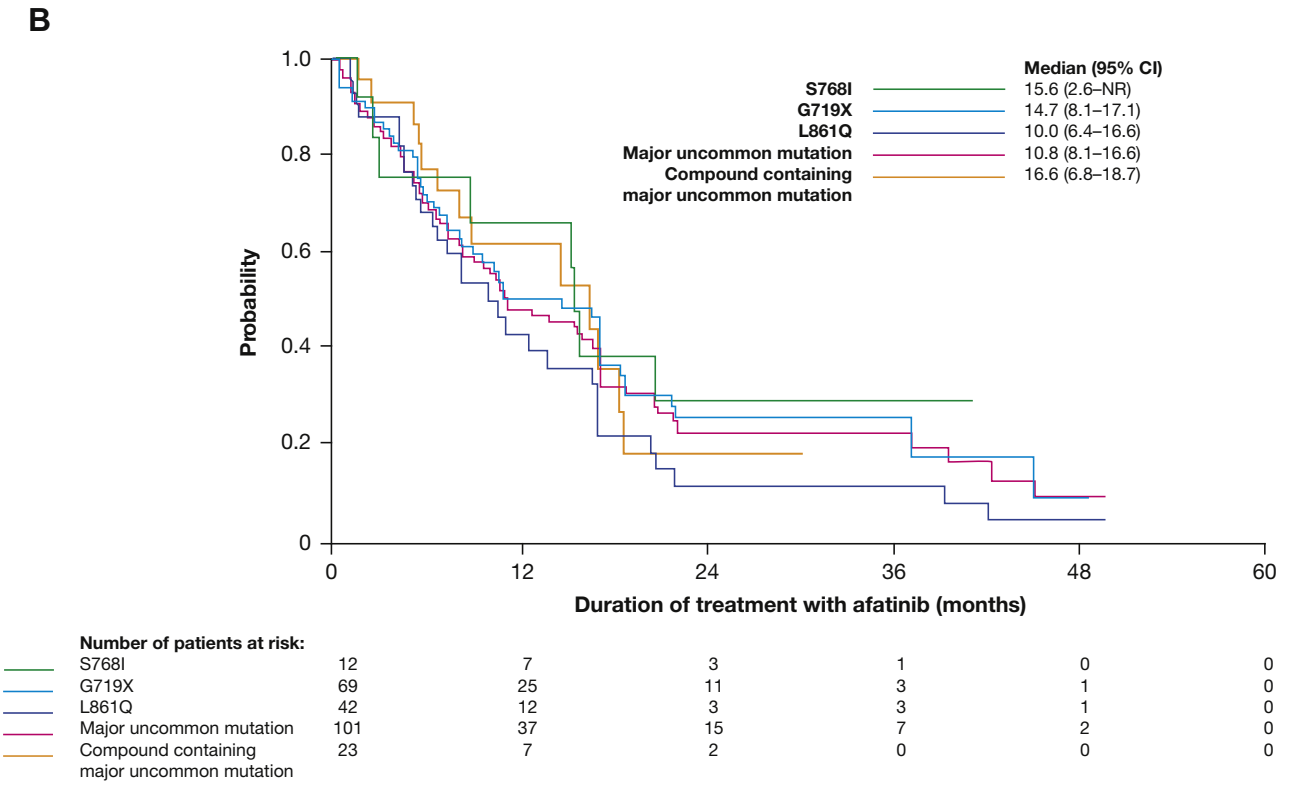


Figure 2. Time to treatment failure in patients with NSCLC tumors harboring uncommon *EGFR* mutations. (*A*) Tyrosine kinase inhibitor (TKI)–naive patients with compound mutations, T790M, exon 20 insertions, and other uncommon mutations; (*B*) TKI-naive patients with major uncommon mutations (S768I, G719X, L861Q) and compound mutations containing a major uncommon mutation; (*C*) TKI-pretreated patients with compound mutations, T790M, exon 20 insertions, and other uncommon mutations; (*D*) TKI-pretreated patients with major uncommon mutations (S768I, G719X, L861Q) and compound mutations containing a major uncommon mutation.

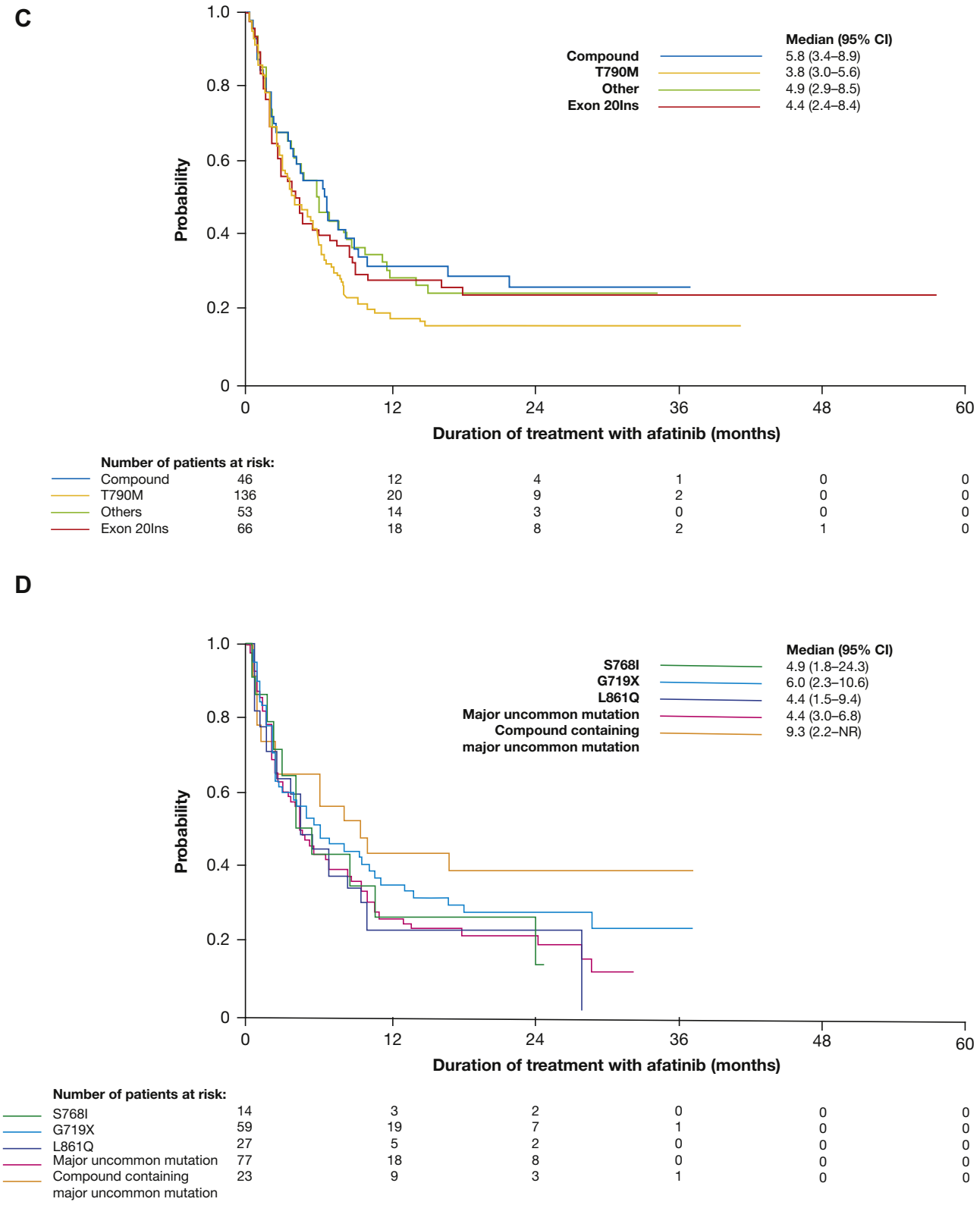


Figure 2. (*continued*).

Therefore, the data presented herein make the case for considering afatinib as a treatment option if a compound mutation is detected, especially if it includes a major uncommon *EGFR* mutation.

Apart from certain mutations (i.e., A763_Y764insFQEA; V769_D770ins ASV),[68] exon 20 insertions are generally considered unresponsive to EGFR TKIs.[21,23,69] In this analysis, afatinib demonstrated modest activity

Table 3. Response Rates With Afatinib in Patients With NSCLC Harboring Uncommon Mutations

Mutation Type	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DCR, n (%)	ORR,n (%)	DoR, Mo (95% CI)
EGFR TKI-naive patients							
Major uncommon mutation (n = 110)	5 (4.5)	61 (55.5)	35 (31.8)	9 (8.2)	101 (91.8)	66 (60.0)	17.1 (11.0-20.8)
G719X (n = 55)	4 (7.3)	31 (56.4)	16 (29.1)	4 (7.3)	51 (92.7)	35 (63.4)	17.1 (10.3-22.0)
L861Q (n = 47)	0 (0.0)	28 (59.6)	14 (29.8)	5 (10.6)	42 (89.4)	28 (59.6)	13.8 (7.4-20.6)
S768I (n = 8)	1 (12.5)	4 (50.0)	3 (37.5)	0 (0.0)	8 (100.0)	5 (62.5)	NR (15.9-NR)
Compound (n = 35)	0 (0.0)	27 (77.1)	5 (14.3)	3 (8.6)	32 (91.4)	27 (77.1)	16.6 (13.8-18.7)
With major uncommon mutation (n = 23)	0 (0.0)	18 (78.3)	4 (17.4)	1 (4.3)	22 (95.7)	18 (78.3)	17.1 (14.7-NR)
Exon 20 insertion (n = 70)	2 (2.9)	15 (21.4)	41 (58.6)	12 (17.1)	58 (82.9)	17 (24.3)	11.9 (5.4-26.7)
T790M (n = 25)	0 (0.0)	6 (24.0)	13 (52.0)	6 (24.0)	19 (76.0)	6 (24.0)	4.7 (3.8-11.0)
Others (n = 23)	0 (0.0)	15 (65.2)	5 (21.7)	3 (13.0)	20 (87.0)	15 (65.2)	9.0 (3.5-11.9)
EGFR TKI-pretreated patients							
Major uncommon mutation (n = 32)	0 (0.0)	8 (25.0)	14 (43.8)	10 (31.3)	22 (68.8)	8 (25.0)	4.9 (2.0-18.0)
G719X (n = 19)	0 (0.0)	2 (10.5)	10 (52.6)	7 (36.8)	12 (63.2)	2 (10.5)	10.0 (2.0-18.0)
L861Q (n = 11)	0 (0.0)	5 (45.5)	3 (27.3)	3 (27.3)	8 (72.7)	5 (45.5)	4.4 (4.3-8.4)
S768I (n = 2)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2 (100.0)	1 (50.0)	NR
Compound (n = 21)	0 (0.0)	6 (28.6)	10 (47.6)	5 (23.9)	16 (76.2)	6 (28.6)	16.7 (9.9-21.8)
With major uncommon mutation (n = 8)	0 (0.0)	3 (37.5)	3 (37.5)	2 (25.0)	6 (75.0)	3 (37.5)	16.7 (9.9-16.7)
Exon 20 insertion (n = 21)	0 (0.0)	3 (14.3)	9 (42.9)	9 (42.9)	12 (57.1)	3 (14.3)	3.7 (2.7-10.1)
T790M (n = 64)	0 (0.0)	12 (18.8)	31 (48.4)	21 (32.8)	43 (67.2)	12 (18.8)	6.1 (2.6-7.9)
Others (n = 25)	0 (0.0)	9 (36.0)	8 (32.0)	8 (32.0)	17 (68.0)	9 (36.0)	6.3 (0.8-11.3)

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; PD, progressive disease; ORR, overall response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; NR, not reported.

against exon 20 insertion mutations. In LUX-Lung 2, 3, and 6, the ORR in patients with exon 20 insertions (n = 23) was only 8.7%. In this report, the corresponding ORR was 24.3% and median DoR was 11.9 months (n = 70). Four of these patients (5.7%) remained on treatment for more than 3 years. These data demonstrate that some exon 20 insertions are clinically sensitive to afatinib. Sensitive variants may not have been highly represented in the LUX-Lung studies, owing to the relatively small sample size and the high heterogeneity of exon 20 insertions. More than 100 variants have been reported,[70] some of which (those proximal to codon 769) have been predicted to retain sensitivity to EGFR TKIs based on *in silico* modeling.[71] However, many of the more prevalent exon 20 insertions (e.g., D770_N771insSVD, D770_N771insNPG, H773_V774insH) are considered resistant to first-generation TKIs.[70] The heterogeneity of exon 20 insertions and their differing functional effects indicate that they should not be considered as a single entity in the clinic, and further research should be undertaken to assess the activity of EGFR TKIs against specific *EGFR* exon 20 insertion variants. Only limited details regarding insertion subtype were available in this analysis. However, certain rare exon 20 insertions were documented that were sensitive to afatinib, including A767delinsASVD[39] and A767_S768insSVA.[40] Therefore, afatinib could be a treatment option against some exon 20 insertions in the future, which remains an area of unmet medical need, despite recent progress in the development of specific agents. Osimertinib has demonstrated preclinical activity against a range of exon 20 insertions,[72] and several trials are ongoing (e.g., NCT03424759, NCT03434418). Poziotinib has shown promising clinical activity in an ongoing phase II trial.[73] Other TKIs specifically targeting exon 20 insertions, such as TAK-788 and JNJ-372, have demonstrated modest activity in clinical trials.[74,75] The activity of these agents against specific *EGFR* exon 20 insertion subtypes requires further elucidation.

Afatinib also demonstrated activity against several mutations in the "other" category. For example, responses were observed in patients with tumors harboring uncommon exon 18 mutations including E709_T710>D, E709X, T725M, and V717A. Preclinical evidence indicates that such mutations are more sensitive to afatinib and other second-generation TKIs than first- or third-generation TKIs.[23,41] Accordingly, available clinical evidence indicates that first-generation EGFR TKIs are generally ineffective in this setting,[18,76] whereas second-generation TKIs are active.[77] Of note, exon 18 mutations are often present in compound mutations,[70] which could potentially explain, in some cases, the strong activity of afatinib in the compound mutation category. Other types of uncommon mutation that demonstrated sensitivity to afatinib included missense exon 19 mutations (e.g., L747P, L747S), missense exon 20 mutations (e.g., Q787Q, R776H, V765M), missense

exon 21 mutations (e.g., H870R, L861P), and exon 21 deletions.

We acknowledge that this study has several limitations. First, 86 of the patients included in the analysis were published case studies, and this may introduce bias because it is more likely that positive cases are published. Second, *EGFR* mutation detection platforms vary widely, and different testing methods have been used across studies in our analysis; central testing was only performed in the LUX-Lung trials. This may have introduced some unrecognized biases. Third, the database currently only captures treatment of patients with afatinib (versus other EGFR TKIs). Finally, as is the case with most real-world studies, tumor response was based on investigators' report without monitor or audit. For this reason, TTF was chosen as a pragmatic end point suited to real-world studies because it is not dependent on Response Evaluation Criteria in Solid Tumors classification of tumors; it encompasses the common clinical practice of continuing treatment beyond radiologic progression and can be measured from electronic health records or claims databases. Recently, TTF has been found to correlate with progression-free survival in clinical trials.[78]

In conclusion, this study supports the use of afatinib for the treatment of tumors harboring several uncommon mutation categories: (1) major uncommon mutations; (2) compound mutations, especially those including a major uncommon mutation; and (3) perhaps certain uncommon mutations in the "other" category and certain exon 20 insertions. These categories require further clinical evaluation to identify specific mutation subtypes that may be sensitive. The data summarized herein are described in full in a searchable database (to be periodically updated) that includes information on a range of very uncommon *EGFR* mutations that will be potentially helpful for clinicians (www.uncommonEGFRmutations.com).

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.12.126.

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