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REVIEW ARTICLE

Unveiling the Landscape of Uncommon EGFR Mutations in NSCLC-A Systematic Review

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ABSTRACT

Uncommon EGFR mutations represent a rare subgroup of NSCLC. Data on the efficacy of different generations of tyrosine kinase inhibitors (TKIs) in these rare mutations are scattered and limited to mostly retrospective small cohorts because these patients were usually excluded from clinical trials. This was a systematic review on the efficacy of TKIs in patients harboring uncommon EGFR mutations, defined as mutations other than exon 20 insertions mutations or T790M. Response rates (RRs) for different generations of TKIs were determined for individual uncommon mutations, compound mutations, and according to classical-like and P-loop alpha helix compressing mutations classes. This study was conducted in accordance with the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 1836 patients from 38 studies were included in the final analysis. Most available data (92.6%) were from patients treated with first- or second-generation TKIs. G719X, S768I, E709X, L747X, and E709-T710delinsD showed RRs ranging from 47.8% to 72.3% to second-generation TKIs, generally higher than for first- or third-generation TKIs. L861Q mutation exhibited 75% (95% confidence interval [CI]: 56.6%–88.5%) RRs to third-generation TKIs. Compound mutations with G719X, E709X, or S768I consistently showed RRs above 50% to second- and third-generation TKIs, although fewer data were available for third generations. For classical-like mutations, RRs were 35.4% (95% CI: 27.2%–44.2%), 51.9% (95% CI: 44.4%–59.3%), and 67.9% (95% CI: 47.6%–84.1%) to first-, second-, and third-generation TKIs, whereas for P-loop alpha helix compressing mutations classes mutations, RRs were 37.2% (95% CI: 32.4%–42.1%), 59.6% (95% CI: 54.8%–64.3%), and 46.3% (95% CI: 32.6%–60.4%), respectively. This systematic review supports the use of second-generation TKI afatinib for G719X, S768I, E709X, and L747X mutations and for compound uncommon mutations. For other uncommon mutations such as L861Q, third-generation TKI, such as osimertinib, could also be considered, given its activity and toxicity profile.

Keywords: Non–small cell lung cancer; Uncommon EGFR mutations; Tyrosine kinase inhibitors; EGFR PACC mutations; Systematic review

Introduction

Lung cancer remains the most common cause of cancer death globally,[1] with NSCLC representing 80% to 85% of cases.[2] Activating mutations in the kinase domain of the EGFR represent the most common targetable alterations in NSCLC, accounting for up to 45% to 50% of newly diagnosed lung adenocarcinoma in Asian patients, and 15% to 20% in Western countries.[3,4]

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EGFR tyrosine kinase inhibitors (TKIs) have consistently shown higher efficacy than chemotherapy in advanced or metastatic NSCLC with sensitizing EGFR mutations.[5–8] Although second- and third-generation TKIs have both proven to be superior to first-generation TKIs,[9,10] osimertinib, a third-generation TKI, showed a better safety profile and central nervous system activity and represents the standard of care in first line.[5]

Driver mutations in EGFR are essentially located in the kinase domain from exons 18 to 21, and lead to the constitutive downstream EGFR signaling, resulting in cellular proliferation and tumorigenesis. It has been shown that different mutations have different structural impacts, and therefore different functional consequences in terms of activation of the kinase domain and drug binding.[11] EGFR exon 19 deletion (ex19del) in amino acid residues 747 to 750 (Leu Arg Glu Ala residues) and L858R point mutation in exon 21 represent the most common EGFR activating mutations, accounting for up to 70% to 85% of newly diagnosed EGFR-positive NSCLC.[3] These are together referred to as "common" or "classical" EGFR mutations. Among other EGFR mutations, T790M point mutation in exon 20 generally develops as an acquired resistance mutation to first- or second-generation TKIs and remains sensitive to third-generation TKIs. De novo T790M mutation has also been described, although rarely.[12] Exon 20 insertions mutations (ex20ins) represent another subset of frequent EGFR mutations, accounting for approximately 10% of lung adenocarcinoma, and are resistant to classical EGFR TKIs.[13] Other mutations in the kinase domain (exon 18–21) have also been shown to activate EGFR and to be oncogenic.[14] These so-called uncommon mutations account for 10% to 15% of all EGFR mutations.[15,16] Moreover, some patients present with more than one mutation on the EGFR gene, a situation referred to as "compound mutations." Such compound mutations can comprise either two uncommon mutations or a common and an uncommon mutation.

More recently, a different EGFR classification system, also known as MD Anderson Cancer Center (MDACC) system, has been established using structural analysis.[12] Instead of using the frequency of occurrence as the primary classifier, structural similarities were used to group EGFR kinase domain mutations into four subclasses: classical-like, T790M-like, P-loop and alpha helix compressing mutations (PACC), and exon20. Many of the uncommon mutations fall into the PACC mutation subclass.

Regarding EGFR uncommon mutations, limited information about the efficacy of TKIs is available because these patients were usually excluded from trials.[5] Classifications such as the MDACC system could help guide treatment choices for uncommon EGFR mutations. Further clinical prospective data are warranted to validate the clinical activity of TKIs for different uncommon EGFR mutations.

The goal of this review was to systematically collect the current available evidence regarding response rates (RRs) to different generations of TKIs for distinct uncommon EGFR mutations.

Materials and Methods

Systemic Literature Review

A systematic search of all relevant data was performed in March 2023 on Ovid MEDLINE in the time frame from 2001 to March 2023. This study was designed and conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The search was limited to studies in English language. Information on response to EGFR TKIs for uncommon EGFR mutations, other than T790M and exon 20 insertion, was searched. The research was conducted with the following terms and their synonyms: lung cancer, non–small cell lung cancer, EGFR, uncommon or rare mutations, tyrosine kinase inhibitors, response rates (RRs), or progression-free survival (PFS). Further relevant studies were searched in the citations of reviews on the subject. Titles, abstracts, and full-text articles were read, and relevant studies were then selected, by two authors (MB and FK). The risk of bias for the studies included were assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Case Series interpretation.[17]

Exclusion Criteria

Duplicates and case reports were excluded, to exclude potential multiple inclusion of the same cases. Case reports and case series with less than five cases were excluded, as they were considered at risk of positive publication bias and at risk of being included multiple times in the systematic review (e.g., case report also included in a case series). Potential double reporting in different case series was ruled out by scrutiny. Studies that did not report outcomes for each rare mutation separately (e.g., studies reporting the results for all uncommon mutations as a whole) were also excluded. Studies that reported outcomes for a particular mutation for several TKIs without distinction between different generations of TKIs were also excluded. The goal was to gather clinical information regarding different TKIs generations for individual uncommon EGFR mutations.

Definition of Common Uncommon and Rare Uncommon Mutations

Uncommon EGFR mutations were defined as nonsynonymous mutations that do not classify as common (e.g., L858R mutations and ex19del involving the 746 to

755 amino acid residues), nor ex20ins nor T790M. Common uncommon point mutations were defined as point mutations previously reported at a frequency of greater than 1%, among uncommon EGFR mutations.[12] Rare uncommon mutations were defined as all other uncommon point mutations. Compound mutations were defined as two mutations in the EGFR gene in the same patient, involving two uncommon mutations or an uncommon alongside a common mutation. Uncommon ex19del or ex19delins mutations refer to deletions in exon 19 occurring outside the 746 to 755 amino acid residues, or deletions in exon 19 also including an insertion.

Study End Points and Statistics

The primary end point was RRs and all data on response rate for a specific uncommon mutation on particular TKIs were extracted by two authors (MB and FK). RRs is the percentage of patients presenting a response (which is a measure of tumor shrinkage referring to Response Evaluation Criteria in Solid Tumors) when undergoing a specific treatment. TKIs were grouped by generation, as first, second or third generation, and RRs were reported for different uncommon mutations for different generations of TKIs in a descriptive manner. For further analysis, EGFR mutations were clustered according to the structured-based classification of Robichaux et al.[12] (MDACC system), in classical-like mutations or PACC mutations, and RRs for different generations of TKIs was reported for these clusters. Mutations that were not formally classified/attributed to a cluster by the MDACC system, were excluded from this particular analysis. The 95% confidence interval (CI) is reported for RRs, when the number of available cases exceeds five. R-statistics version 4.2.2 (P square) was used for statistical analysis. Figures were computed using the ggplot package with R-statistics. Detailed information on the conduction of the systematic review can be accessed in Supplementary Table 1.

Results

Patient Population

The systematic search retrieved 188 articles, and five articles were also retrieved through references review. Of these 193 articles, 157 were excluded and 38 were included in the final analysis.[18–55] One prospective study published after the time frame of the systematic review was also added, regarding its pertinence.[56] Figure 1 shows the flowchart diagram of the systematic research, with the reasons for studies exclusion. Studies' characteristics are described in Supplementary Table 2. A final total of 1838 patients with uncommon mutations and treated with TKI were included in the analysis. Most of the included studies were retrospective, and only four reported prospective data[18,19,21,56] (one study was a post hoc analysis of three prospective trials,[18] another was a post hoc analysis of two phase II trials[19]). G719X, L861Q, S768I, E709X, E709-T710delinsD, and L747X accounted for the most frequent uncommon mutations, representing 1095 patients in total. All mutations included in this literature review are shown in Table 1 and were classified into

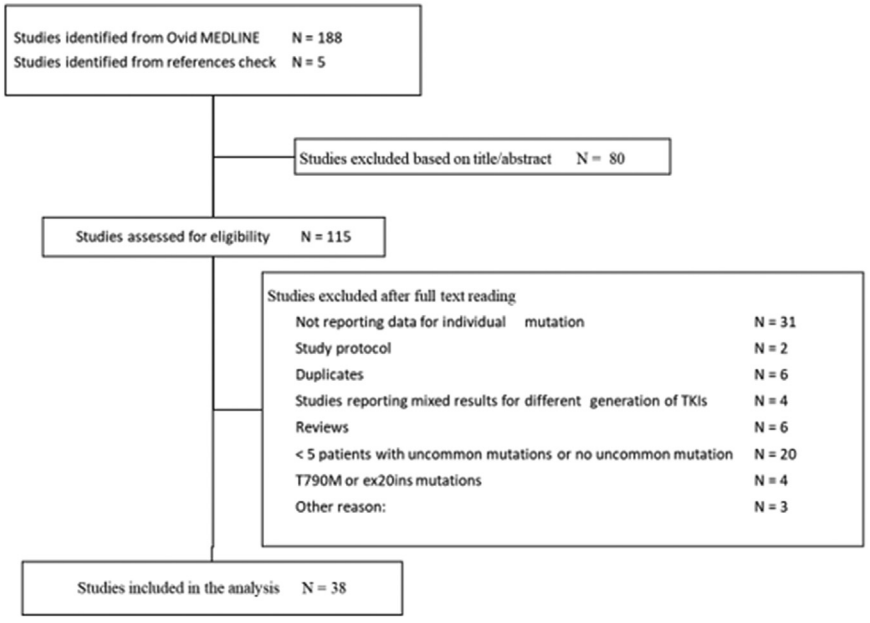

Figure 1. PRISMA flow diagram of study selection for inclusion in this review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Uncommon Mutations Included

Common Uncommon Point Mutations	Rare Uncommon Point Mutations	Compound Mutations Uncommon With Uncommon	Compound Mutations Uncommon With Common	Uncommon ex19del, ex19delins, ex18del
G719X	V689M	G709S - S768I	T854A - L858R	E709-T710delinsD
L861Q	P699S	G719X - S768I	L828V - L858R	K745_E746insNSRRYQ
S768I	L704F	G719X - L861Q	H870R - L858R	I745_E746insKIPVAI
E709X	I715L	G719X - R776H	L861Q - C797S - L858R	E746_S752delinsV
L747X	V717G	G719X - D761Y	L861Q - 19Del	E746_S752delinsV
	S720F	G719X - E709X	V689L - L858R	L747_P753delinsS
	S720A	G719X - S720F	S720P - L858R	L747_K754delinsSR
	F723I	G719X - L747X	K757R - L858R	L747_P753delinsQ
	F723S	G719X - R776C	I744 M - L858R	L747_T751delinsP
	G779F	G719X - L833V	S768I - L858R	L747_K754del
	F829G	G719X - P744M - S768I	R776H - L858R	L747_S752insP
	R831H	G719S - S768I - N1107D	L833V - L858R	L747-A750delinsS
	L833V	G719X - L747_P753delins	L858Q - L858R	T751_I759delinsS
	V843L	G719S - E709K - K744N		S752_I759del
	S768R	G719X - E709A - T710S		P753_I759delinsA
	V774M	delL747-P753insS - D671N L861Q - L858M		
		L861Q - S768I		
		L861Q - R776C		
		L861Q - R776H		
		L861Q - L833F		
		L861Q - G779F		
		L861Q - L62R		
		L861Q - G796S		
		S768I - V769L		
		S768I - V769I		
		S768I - G724S		

common uncommon point mutations, rare uncommon point mutations, compound mutation: uncommon-uncommon versus uncommon common, and uncommon exon 19 deletion or insertion.

Response in Common Uncommon EGFR Point Mutations

There were 1024 common uncommon EGFR mutation cases, which had response rate data for analysis (Fig. 2), including G719X (n = 594), L861Q (n = 298), S768I (n = 84), L747X (n = 33), and E709X (n = 15). The response rate to first-, second-, and third-generation TKIs, respectively, were G719X: 38.7% (95% CI: 33.2%–44.4%), 56.4% (95% CI: 50.0%–62.7%), and 33.3% (95% CI: 18.6%–50.9%); L861Q: 31.0% (95% CI: 22.8%–40.3%), 52.0% (95% CI: 43.7%–60.2%), and 75.0% (95% CI: 56.6%–88.5%); S768I: 31.0% (95% CI: 15.3%–50.8%), 47.8% (95% CI: 32.9%–63.1%), and 33.3% (95% CI: 7.5%–70.1%); L747X: 0% (95% CI: 0.0%–30.8%), 72.3% (95% CI: 49.7%–89.3%), and 100% (95% CI: not available [NA], n = 1); E709X: 0% (95% CI: 0.0%–52.1%), 50% (95% CI: 11.8%–88.2%), and 50% (95% CI: NA, n = 4).

Response in Compound Mutations

We evaluated the RRs in compound mutations. RR information was obtained for G719X with another uncommon mutation (n = 156), G719X with a common mutation (n = 3), S768I with an uncommon mutation (n = 79), S768I with a common mutation (n = 17), E709X with another uncommon mutation (n = 25), E709X with a common mutation (n = 22), and L861Q with another uncommon mutation (n = 15) and L861Q with a common mutation (n = 10) (Fig. 3). For G719X with common and L861Q with common compound mutations, only data on RRs to second-generation TKIs were found. Data were also retrieved for other rarer compound mutations that are listed in Table 1, however with a limited number of patients (n = 18).

RRs for the most frequent compound mutations for first-, second-, and third-generation TKIs, respectively, were G719X with uncommon: 42.3% (95% CI: 28.7%–56.7%), 76.6% (95% CI: 65.6%–85.5%), and 59.3% (95% CI: 38.8%–77.6%); S768I with uncommon: 54.5% (95% CI: 23.4%–83.2%), 63.5% (95% CI: 48.9%–76.3%), and 56.2% (95% CI: 29.9%–80.2%); S768I with common: 14.2% (95% CI: 0.4%–57.0%), 77.8% (95% CI:

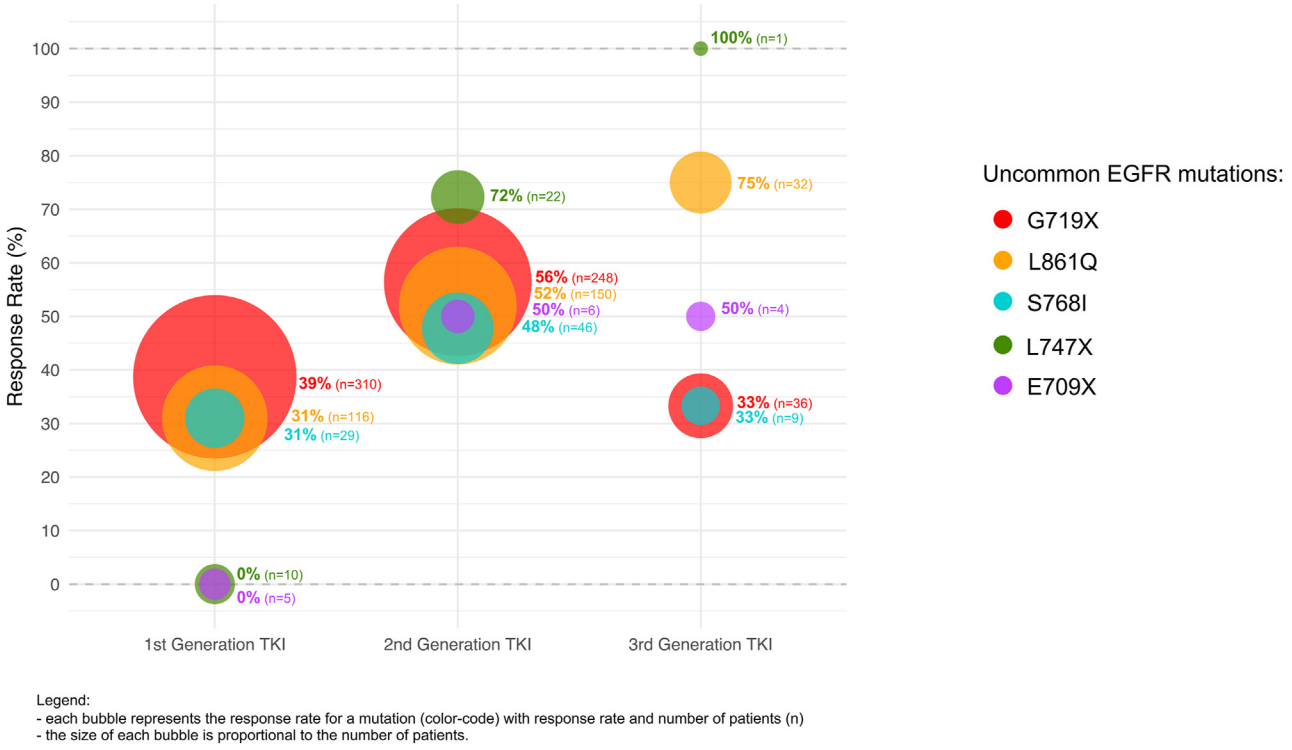

Figure 2. Response rates for common uncommon EGFR point mutations, for different generations of TKIs. TKI, tyrosine kinase inhibitor.

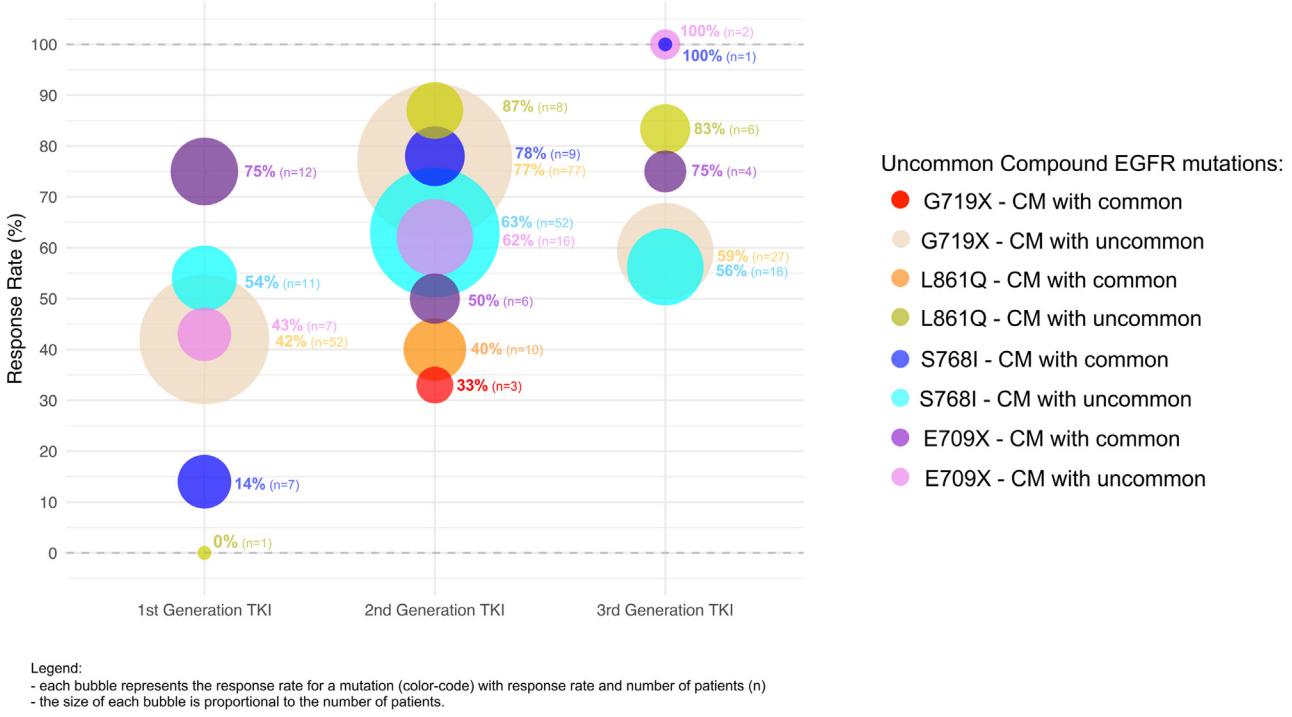

Figure 3. Response rates for uncommon EGFR CMs, for different generations of TKIs. CM, compound mutation; TKI, tyrosine kinase inhibitor.

40.0%–97.2%), and 100% (95% CI: NA, n = 1); E709X with common: 75% (95% CI: 42.8%–94.5%), 50% (95% CI: 11.8%–88.2%), and 75% (95% CI: NA, n = 4); E709X with uncommon: 42.8% (95% CI: 9.8%–81.5%), 62.5% (95% CI: 35.4%–84.8%), and 100% (95% CI: NA, n = 2); L861Q with uncommon: 0% (95% CI: NA, n = 1), 87.5% (95% CI: 47.3%–99.7%), and 83.3% (95% CI: 35.9%–99.6%).

Response in Uncommon exon 19 del/ins, ex18delins and Rare Uncommon Point EGFR Mutations

RRs for rarer uncommon EGFR mutations were then evaluated, for E709-T710delinsD in exon 18 (n = 38), uncommon ex19del (n = 18), ex19delins (n = 51), ex19ins (n = 5), (Fig. 4), and other rare uncommon single point mutations (n = 21) (Supplementary Fig. 1). Of note, most patients with ex19delins had either the L747_P753delinsS (n = 25) or the L747_A750delinsS (n = 23), and most patients with an atypical ex19del had the S752_I759del mutation (n = 17).

The response rate for first-, second-, and third-generation TKIs for E709-T710delinsD was 0% (95% CI: 0.0%–45.9%), 65.5% (95% CI: 45.6%–82.1%), and 0% (95% CI: NA, n = 3), respectively. For uncommon ex19del and ex19delins, most data were retrieved for first-generation TKIs, with RRs of 61.1% (95% CI: 35.7%–82.7%) and 66.2% (95% CI: 53.0%–77.7%), respectively. Two patients with ex19delins (L747_P753delinsS) received second-generation TKIs, and two patients received third-generation TKIs. All four patients had a response to TKIs. Regarding ex19ins, without a deletion, three patients received second-generation TKIs, and all had a response. Two patients received first-generation TKIs, and one responded.

Among the 21 patients with rare uncommon point mutations, treated with various TKIs (12 patients treated with first-generation TKIs, three with second-generation TKIs, and six with third-generation TKIs), 6 patients experienced a response to therapy.

Response by MDACC System

The MDACC system was developed to classify kinase domain EGFR mutations by their structural function.[12] We classified uncommon EGFR mutations (Table 1) per MDACC system and evaluated the clinical responses by different generations of TKIs. As expected, most of the uncommon mutations included in our analysis corresponded to PACC mutations or classical-like mutations according to the classification. For a significant number of patients, their mutations could not be classified according to the MDACC system (n = 621). For the classical-like mutations, RRs were 35.4% (95% CI: 27.2%–44.2%), 51.9% (95% CI: 44.4%–59.3%), and 67.9% (95% CI: 47.6%–84.1%) for first-, second-, and third generation TKIs, respectively (Table 2). For PACC

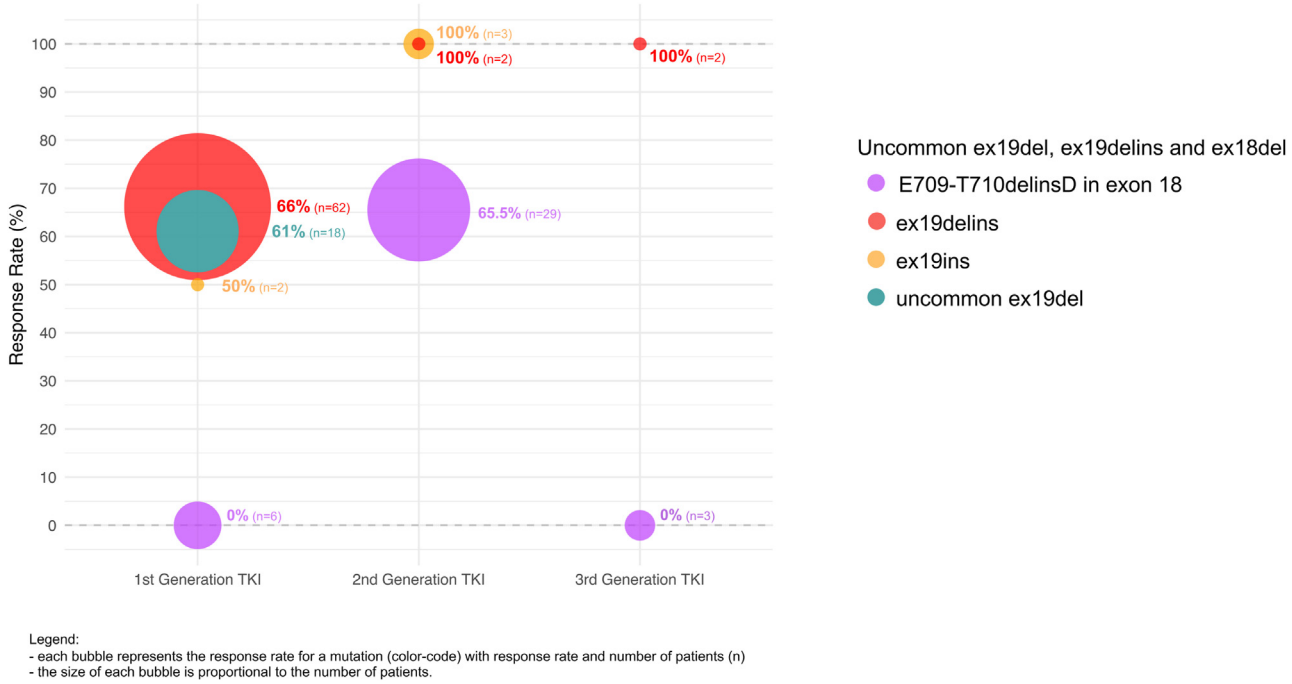

Figure 4. Response rates for deletion-insertions in exon 19 (ex29delins), uncommon deletions in exon 19 (uncommon ex19del), insertions in exon 19 (ex19ins), and E709-T710delinsD in exon 18, for different generations of TKIs. TKI, tyrosine kinase inhibitor.

Table 2. Overall Response to Different Generation of TKIs for Structured-Based Clusters of EGFR Uncommon Mutations

Mutations Type	Response Rates to First-Generation TKIs	Response Rates to Second-Generation TKIs	Response Rates to Third-Generation TKIs
Classical-like mutations (N = 343), %	35.4 (95% CI: 27.2-44.2)	51.9 (95% CI: 44.4-59.3)	68.3 (95% CI: 50.6-86)
PACC mutations (N = 811), %	37.2 (95% CI: 32.4-42.1)	59.6 (95% CI: 54.8-64.3)	45.4 (95% CI: 32.5-58.3)

CI, confidence interval; TKI, tyrosine kinase inhibitor; PACC, P-loop and alpha helix compressing mutations.

mutations, the RRs were 37.2% (95% CI: 32.4%–42.1%), 59.6% (95% CI: 54.8%–64.3%), and 46.3% (95% CI: 32.6%–60.4%) for first-, second-, and third-generation TKIs, respectively.

Discussion

In this systematic review, a total of 1838 patients with lung cancer with uncommon EGFR mutations treated with an EGFR TKI were identified. We analyzed the RRs, which is a measure of the activity of a drug, by the type of uncommon mutation and generations of EGFR TKIs.

The uncommon EGFR mutations generally exhibited lower RRs to TKI than observed in common mutations in prospective trials. This is a finding that has already been described.[57,58] However, TKIs, especially the second generation, still showed moderate activity in uncommon EGFR mutations. G719X, S768I, L747X, E709X, and E709-T710delinsD showed a rather good RR of 47.8% to 72.3% to the second-generation TKI, afatinib. Even if comparison should be made with caution, second-generation TKIs seemed to exhibit better RRs for these mutations than first- or third-generation TKIs. On the other hand, RRs for L861Q mutation was rather good for second- and third-generation TKIs, ranging from 52% to 75%, bearing in mind that conclusions should be drawn with caution due to the retrospective nature of most of the data and possible confoundings.

Regarding EGFR compound mutations, second-generation TKIs, especially afatinib, consistently showed RRs above 50% for the most frequent compound uncommon mutations. Only few data on third-generation TKIs in uncommon compound mutations were retrieved. Uncommon compound mutations, however, such as G719X or S768I with another uncommon mutation, also showed interesting RRs with third-generation TKIs, of 56.2% to 59.3%. Of note, for most uncommon mutations, RRs was rather comparable between compound mutations and single mutations for all generations of TKIs, with a trend toward compound mutations having more response to TKI than single mutations. We postulate that this may be due to better activity of TKIs in the presence of a classical EGFR mutation.

Recently, results from the ACHILLES/TORG1834 were presented at the European Society of Medical Oncology Congress 2023.[59] This was the first randomized phase III trial in uncommon EGFR mutation-positive NSCLC, comparing afatinib against platinum-pemetrexed chemotherapy. A total of 107 patients were randomized in a 2:1 manner to receive afatinib (n = 73) or chemotherapy (n = 36). The study met its primary end point of PFS, with PFS being 10.6 months and 5.7 months for afatinib and chemotherapy, respectively (hazard ratio, 0.422; 95% CI: 0.256–0.694; $p = 0.0007$). RRs was 61.4% in the afatinib arm, whereas it was 47.1% for chemotherapy. This study was not included in our analysis as a final manuscript with individual mutation data has not yet published but further adds weight to the efficacy of afatinib in patients with NSCLC with uncommon EFGR mutations.

Our analysis also shows that uncommon ex19del, ex19delins, and ex19ins exhibited a high RR to TKIs. However, L747_P753delinsS and L747_A750delinsS, and S752_I759del represented the vast majority of patients with an ex19delins or an uncommon ex19del, respectively. Extrapolation of these results to other rare ex19delins and uncommon ex19del is therefore difficult.

When classified according to the structured-based MDACC system, EGFR mutations classified as PACC mutations exhibited a higher response rate to second-generation TKIs. As expected, classical-like uncommon EGFR mutations also showed lower RRs to the first-generation than to second- and third-generation TKIs. A higher RR was observed for third-generation TKIs, albeit the number of cases treated with third-generation TKIs was limited (n=28). The common L858R and ex19del mutations, on the other hand, tend to exhibit good RRs to every generation of TKIs in prospective phase III trials. This finding could underscore that classical-like mutations according to MDACC system may not be all equal, and perhaps not entirely similar to classical EGFR mutations in terms of drug sensitivity. Regarding PACC mutations, our findings are concordant with previous series and preclinical studies that reported a lower affinity for first- and third-generation

TKIs for EGFR PACC mutations.[12] However, although PACC mutations were predicted to be rather insensitive to first- and third-generation TKIs in preclinical models, the RRs in this systematic review were nonetheless 37.2% and 46.3% in PACC mutation for first- and third-generation TKIs, respectively.

Other classifications than the MDACC have also been proposed.[18,60] Janning et al.[60] have suggested a pragmatic classification of uncommon EGFR mutations based on responses to TKIs observed in the German National Network of Genomic Medicine (nNGM). The first group of uncommon mutations in this classification ("nNGM UC1 TKI-sensitive EGFR mutations") includes all uncommon EGFR for which sensitivity to EGFR TKIs has been documented. Groups 2 and 3 correspond to T790M and ex20ins mutation, respectively. A fourth group (nNGM UC4 very rare EGFR mutations) includes very rare mutations, with insufficient functional and clinical data on TKIs efficacy. Of note, the majority of uncommon mutations included in our analysis would have fallen into the first subgroup according to nNGM classification. Unlike the MDACC classification though, the nNGM classification does not provide a comprehensive insight on how different uncommon mutations respond to different TKI generations and does not offer a mechanistic hypothesis.

Our systematic review has strengths and limitations. First, this is the most comprehensive and up-to-date review focusing on uncommon EGFR mutation, thus providing potentially clinically relevant insights. Second, we classified uncommon mutations encompassing current classifications, including the MDACC system. This study also has limitations. First, most of the data come from case series and retrospective studies. A second limitation comes from the heterogeneity in molecular testing, with a risk of missing compound EGFR mutations in some cases. Third, although most of the patients included in this systematic review received TKIs as a first-line therapy, it is likely that many had previous systemic treatment, that is, chemotherapy, and had received TKIs afterward, which may have affected the RRs reported here. Fourth, most data were available for first and especially second generation of TKIs, although fewer data were available for third-generation agents, probably due to the later approval and lesser availability of third-generation TKIs across the large period of time and the wide clinical settings of this systematic review. In our systematic review, data regarding duration of response, PFS, or time to treatment failure remained limited to a few patients\, and data were more heterogeneous. In that regard, a combined analysis of PFS from prospective clinical trials evaluating TKIs in uncommon EGFR, such as the UNICORN, Achilles-TORG-1834, KCSG and Lux-lung trials, in which the evaluation of PFS is more reliable, is warranted in the future if access to individual data is granted. Data for overall survival was unfortunately too scarce for reporting and might not reflect the true clinical efficacy of a specific drug in rare mutations. This is particularly important in the context of postprogression treatment, which may also vary considerably between different situations in real-world settings.

Conclusion

This systematic review provides a comprehensive analysis of activity of different drugs in patients with NSCLC harboring uncommon EGFR mutations. The results highlight that the clinical evidence guiding treatment choice in uncommon EGFR mutations continues to evolve, especially the data regarding the efficacy of third-generation TKIs in that setting. Our review supports the use of afatinib for G719X, S768I, E709X, and L747X mutations and for compound uncommon mutations, whereas for other uncommon mutations such as L861Q, the use of a third-generation TKI, such as osimertinib, can also be considered beside afatinib, based on its activity, high central nervous system penetration, and favorable toxicity profile. Our data also tend to confirm that PACC mutations generally display greater RRs than second-generation TKIs. As sensitivities of newer sequencing techniques improve and global adoption of next-generation sequencing increases, the detection of uncommon EGFR mutations will also correspondingly increase, reinforcing the need for more prospective trials for this population.

Disclosure

Dr Parikh reports advisory board fees from Guardant Health and Jazz Pharmaceuticals. Dr Banna reported personal fees from Astellas and AstraZeneca. Dr Le declares **Stock and Other Ownership Interests:** BlossomHill Therapeutics; **Consulting or Advisory Role:** AstraZeneca, Lilly, EMD Serono, Spectrum Pharmaceuticals, Daiichi Sankyo/Lilly, Novartis, Hengrui Therapeutics, Janssen Oncology, Blueprint Medicines, Sensei Biotherapeutics, AbbVie, ArriVent Biopharma, Regeneron, ABION, Boehringer Ingelheim, Bayer, Taiho Pharmaceutical, Systimmune; **Research Funding:** Lilly (Inst), Boehringer Ingelheim (Inst), ArriVent Biopharma (Inst), Teligene (Inst), Regeneron (Inst), Janssen (Inst), EMD Serono (Inst)**; Travel, Accommodations, Expenses:** Spectrum Pharmaceuticals, EMD Serono. Dr Addeo reports having consulting or advisory role for Bristol-Myers Squibb, AstraZeneca, Roche, Merck Sharp & Dohme, Pfizer, Eli Lilly, Astellas, Amgen,

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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.2024.03.016.

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