Afatinib for the Treatment of Non-Small Cell Lung Cancer Harboring Uncommon EGFR Mutations: An Updated Database of 1023 Cases Brief Report

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Introduction: Previously, we developed a database of 693 patients with NSCLC and uncommon EGFR mutations treated with afatinib. Here, we provide an update of >1000 patients, with more data on specific mutations.

Methods: Patients were identified from a prospective database developed by Boehringer Ingelheim and via literature review. Mutations were categorized as T790M-positive, exon 20 insertions, major uncommon (G719X, L861Q, S768I) and ‘others’. Patients with compound mutations (≥2 EGFR mutations) were analyzed separately. Key endpoints were time to treatment failure (TTF) and objective response rate (ORR).

Results: Of 1023 patients included, 587 patients were EGFR TKI-naïve and 425 were EGFR TKI-pretreated. The distribution of mutation categories was: major uncommon (41.4%); exon 20 insertions (22.3%); T790M (20.3%); and ‘others’ (15.9%). Overall, median TTF (TKI naïve/pretreated) was 10.7 and 4.5 months. ORR was 49.8% and 26.8%, respectively. In TKI-naïve patients, afatinib demonstrated activity against major uncommon mutations (median TTF: 12.6 months; ORR: 59.0%), ‘other’ mutations (median TTF: 11.4 months; ORR: 80.0%), and compound mutations (11.5 months; 63.9%). Although sample sizes were small, notable activity was observed against specific exon 20 insertions at residues A763, M766, N771, and V769, and against osimertinib resistance mutations (G724S, L718X, C797S).
INTRODUCTION

In head-to-head clinical trials, afatinib, dacomitinib and osimertinib have all demonstrated superiority to first-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with EGFR mutation-positive non-small cell lung cancer (NSCLC) (1–3). However, these studies were exclusively undertaken in patients with tumors harboring common EGFR mutations (exon 19 deletions [Del19] and the L858R mutation in exon 21). Therefore, few prospective data are available to help inform treatment decisions for patients with tumors harboring uncommon EGFR mutations. In general, preclinical studies (4–6) and retrospective clinical data (7) indicate that second- and third-generation TKIs have broader activity across uncommon mutations than first-generation agents. However, as uncommon EGFR mutations are highly heterogeneous it is difficult to know which EGFR TKI is the best option for specific uncommon mutations. There is a largely unmet need for robust clinical data.

We recently constructed a searchable database of 693 NSCLC patients with tumors harboring uncommon EGFR mutations treated with afatinib (www.uncommonEGFRmutations.com) (8). Here, we describe an updated analysis of the database that now includes over 1,000 patients, including data on specific uncommon mutations.

METHODS

Methodology has been previously described (8). In brief, patients were identified from a prospective database developed by Boehringer Ingelheim and via literature review.

Central mutation testing was only performed in patients enrolled in the LUX-Lung trials (9). In all other patients, mutation detection was undertaken locally using different methodologies. Mutations were categorized into four groups: i) T790M; ii) exon 20 insertions; iii) ‘major’ uncommon mutations; iv) ‘other’ uncommon mutations. Compound mutations, defined as cases where at least two EGFR mutations were present (at least one of which was an uncommon mutation), were analyzed separately.

The key endpoints were objective response rate (ORR) and time to treatment failure (TTF), defined as time from start of therapy to treatment discontinuation for any reason, or death. Apart from the LUX-Lung studies, tumor response was assessed by the treating investigator by local assessment. TTF was calculated using Kaplan–Meier estimates. A Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs). There was no formal statistical analysis plan.

RESULTS

Patients

A total of 1,023 patients (EGFR TKI-naïve: n = 587; EGFR TKI-pretreated: n = 425) were included (Supplementary Figure 1). Patient demographics are shown in Supplementary Table 1. The source of 693 patients has been previously reported (8). The source references for the additional 330 patients are listed in the Supplementary Appendix.

Overall, 41.4% of patients had a tumor harboring a major uncommon mutation, 22.3% had an exon 20 insertion (of which only 18.4% were fully informative), 20.3% had a T790M mutation (predominantly in the EGFR TKI-pretreated patients), and 15.9% had other uncommon EGFR mutations (Supplementary Table 2). Overall, 38.6% of patients had a compound mutation. In both TKI-naïve and EGFR TKI-pretreated patients, compound mutations were more common in the T790M category and less common in the exon 20 insertion category (Figure 1).

Updated Time to Treatment Failure and Tumor Response

Overall, median TTF was 10.7 months (95% CI: 9.7–11.5) in EGFR TKI-naïve patients and 4.5 months (95% CI: 3.9–5.6; Table 1 and Supplementary Figure 2A) in EGFR TKI-pretreated patients. Median TTF was similar regardless of ethnicity (Supplementary Figure 2B). Median TTF in patients with confirmed brain metastases (56% major uncommon, 25% exon 20 insertions, 9% T790M and 10% others) was 8.2 months (Supplementary Figure 2C). In EGFR TKI-naïve patients, median TTF was 12.6 months (95% CI: 11.5–15.9) in patients with major uncommon mutations, 10.7 months (95% CI: 7.0–12.0; Table 1 and Supplementary Figure 2D) in patients with ‘other’ uncommon mutations and 11.5 months (95% CI: 9.5–13.8; Table 1) in patients with compound mutations. The large sample size in this study facilitated meaningful analysis of TTF with afatinib against specific uncommon mutations, including the major uncommon mutations, G719X (median 14.2 months), L861Q (median 11.5 months), S768I (median 15.9 months) and the ‘other’ uncommon mutations, E709X (median 11.4 months) and L747X (median 14.7 months; Table 1).

Conclusion: Afatinib should be considered as a first-line treatment option for NSCLC patients with major uncommon, compound, ‘other’ (including E709X and L747X) and some specific exon 20 insertion mutations. Moderate activity was seen against osimertinib resistance EGFR mutations.

Keywords: afatinib, non-small-cell lung cancer, uncommon EGFR mutations, compound mutations, EGFR exon 20 insertions
FIGURE 1 | Distribution of uncommon mutations. (A) EGFR TKI naïve. (B) EGFR TKI pretreated. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
Overall, 252 EGFR TKI-naive patients (49.8%) responded to treatment (Table 1). The ORR was 53.8% in Asians, 43.4% in non-Asians and 43.9% in patients with confirmed brain metastases. ORR was higher in patients with ‘other’ uncommon mutations (63.9%) and major uncommon mutations (59.0%). Moderate activity was observed in patients with exon 20 insertions (27.2%) and those with T790M (26.2%). High response rates were observed in patients with the specific uncommon mutations, G719X (61.3%), L861Q (84.6%) and L747X (80.0%). In patients with compound mutations, ORR was 63.9%.

Outcomes in Patients With Specific Fully-Defined Exon 20 Insertions

In the 42 patients with informative exon 20 insertions, median TTF was 9.1 months (95% CI: 7.4–14.2). Median TTF was 9.1 months in EGFR TKI-naive patients and 10.8 months in EGFR TKI-pre treated patients. ORR was 48% and 17%, respectively (Table 2). In terms of individual mutation types, insertions at amino acid A763, M766, N771 and V769 showed evidence of sensitivity to afatinib, with TTF ranging from 8.0 to 39.0 months and ORRs ranging from 50 to 100% (Table 2).

### TABLE 1 | TTF and ORR with afatinib in patients with NSCLC harboring uncommon mutations.

| Mutation Type | TTF, months (95% CI) | ORR, % |
|---------------|----------------------|--------|
| Overall       | 587                  | 10.7 (9.7–11.5) | 506 |
| EGFR TKI Naive| 23 (54.8)            | 9.1 (7.4–14.2) | 33 |
| EGFR TKI Pretreated | 42 (100) | 9.9 (6.2–14.2) | 76 |

### TABLE 2 | TTF, ORR and DCR in patients with NSCLC harboring fully-defined exon 20 insertion mutations.

| Exon 20 Insertion Type | n (%) | Median TTF, months (95% CI) | ORR, % | DCR, % |
|------------------------|-------|-----------------------------|--------|--------|
| All informative exon 20 insertions | 42 (100) | 9.1 (7.4–14.2) | 33 | 76 |
| EGFR TKI naive | 23 (54.8) | 9.9 (6.2–14.2) | 47 | 79 |
| EGFR TKI Pretreated | 42 (100) | 9.9 (6.2–14.2) | 47 | 79 |
| A763, Y764insFQEA; A763, V765dup | 4 (9.5) | 39.0 (8.2–39.0) | 50 | 100 |
| A767, S768insSVA; V769dup/ASV; insASVD | 4 (9.5) | 39.0 (8.2–39.0) | 50 | 100 |
| D770, N771insGL/SVD | 4 (9.5) | 39.0 (8.2–39.0) | 50 | 100 |
| H773, R776insYNPY; V774dup/insH; dup | 4 (9.5) | 39.0 (8.2–39.0) | 50 | 100 |
| M766delinsMATL; insASV | 2 (4.8) | 129.0 (11.6–14.2) | 100 | 100 |
| N771, H773dup; R774PhG; delinsKG; P772insGY | 7 (16.7) | 10.0 (5.2–NE) | 71 | 100 |
| S768, D770dup | 4 (9.5) | 8.5 (NE–NE) | 0 | 25 |
| V769, D770insSVA; D770insASV/GVW | 6 (14.3) | 7.0 (6.0–NE) | 71 | 100 |

CI, confidence interval; DCR, disease control rate; EGFR, epidermal growth factor receptor; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitors; TTF, time to treatment failure. *A767: n = 2; H773: n = 3; N771: n = 1; S768: n = 2; V769: n = 3.
of partial response (PR); SD and not reported, respectively. TTF ranged from 9.0 to 12.3 months.

DISCUSSION

This updated analysis demonstrated that NSCLC tumors with certain uncommon mutations respond well to first-line afatinib, with an ORR approaching 50% and median TTF of nearly a year in the overall dataset. In line with previous reports (7–9), activity was higher in patients with major uncommon mutations (with similar response rates against G719X, L861Q and S768I) and 'other' uncommon mutations. Activity was observed against specific exon 20 insertion mutations. Compound mutations were relatively common in the database (nearly 40% of cases) and responded well to afatinib; approximately two-thirds of patients responded. Overall, the data demonstrate that afatinib should be considered for the treatment of NSCLC harboring uncommon mutations, depending on the precise nature of the mutation.

The large sample size in this study facilitated the analysis of specific uncommon mutations for which clinical evidence was previously lacking. For example, 26 patients were identified with the exon 18 mutation, E709X, and 22 were identified with the exon 19 mutation, L747X. These mutations responded well to treatment with ORRs of >80%. Interestingly, both E709X and L747X have been identified as pocket volume reducing (PVR) mutations that appear to be sensitive to afatinib. Notably, treatment ranged from 3 to 10 months in patients pretreated with osimertinib. Interestingly, one TKI-naïve patient remained on treatment with afatinib for 17 months. Patients with L718X demonstrated an ORR of 60%. Given the current paucity of targeted treatment options following failure of osimertinib, further clinical assessment of afatinib in this setting is warranted in patients with tertiary EGFR mutations.

Although exon 20 insertions are widely considered to be insensitive to EGFR TKIs they are highly heterogeneous; both the position of the insertion and the specific residues that are inserted can have distinct effects on the tertiary structure of EGFR, thus influencing the sensitivity of TKIs. For example, insertions between residues 764 and 770 are thought to have a minimal impact on the EGFR TKI binding domain of the receptor (11). Also, the insertion of FQEA at A763 is thought to elicit structural changes to EGFR that are similar to Del19 mutations and thus remains sensitive to EGFR TKIs (12). Therefore, it is important that the exon 20 insertion mutation category is not considered as a single clinical entity. In this analysis, we identified several specific mutations, particularly at the A763, M766, N771 and V769 residues, that appeared to be sensitive to afatinib. Notably, treatment options have recently become available for patients with exon 20 insertions. The TKI, mobocertinib, and the EGFR MET bispecific antibody, amivantamab, have both been approved by the FDA post-platinum doublet chemotherapy (13, 14). These options have conferred response rates of 28% and 40% respectively (15, 16). It remains to be determined whether afatinib may have a role in this setting in certain patients depending on the precise nature of the mutation.

This analysis has several weaknesses. Seventy-three patients were included from published case studies and 209 from case series where selection criteria were not always fully reported. As positive cases are more likely to be published, response rates with

**TABLE 3 | Outcomes in patients with NSCLC harboring uncommon EGFR mutations which are known to be resistance mechanisms to osimertinib.**

| Ethnicity | Gender | Age | Smoking status | Brain metastases | EGFR mutations | Afatinib treatment setting | Best response | TTF, months |
|-----------|--------|-----|----------------|------------------|----------------|--------------------------|--------------|------------|
| Asian     | F      | 55  | No             | Yes              | G724S Del19    | –                        | Post osimertinib | PR 3.8+    |
| Non-Asian | F      | 49  | NS             | Yes              | G724S Del19    | –                        | Post osimertinib | 3.0*       |
| Asian     | F      | 64  | NS             | –                | G724S R776H    | –                        | TKI naive      | 17.6*      |
| Asian     | –      | –   | –              | –                | G724S E746_S752delinsV | –                        | Post osimertinib | SD 4.5    |
| Asian     | –      | –   | –              | –                | G724S E746_S752delinsV | –                        | Post osimertinib | SD 5.4    |
| Asian     | –      | –   | –              | –                | G724S S768I    | –                        | Osimertinib naive | SD 4.0    |
| Asian     | –      | –   | –              | –                | G724S S768I    | Del19                    | Osimertinib naive | SD 4.0    |
| Asian     | –      | –   | –              | –                | G724S Exon20ins | –                        | Osimertinib naive | SD 4.0    |
| Asian     | M      | 51  | NS             | Yes              | G724S Del19    | –                        | Post osimertinib | SD 10.0+   |
| Asian     | F      | 49  | –              | –                | G724S E746_S752delinsV | –                        | Post osimertinib | SD 4.0    |
| Non-Asian | M      | 51  | NS             | Yes              | G724S Del19    | –                        | Post osimertinib | PR 8.0+    |
| Asian     | F      | 65  | –              | Yes              | L718Q L868R    | (BRAF)                   | Post osimertinib | SD 4.0    |
| Asian     | F      | 62  | S              | –                | L718Q L868R    | –                        | Post osimertinib | PR 4.5+    |
| Asian     | F      | 69  | NS             | –                | L718Q L868R    | –                        | Post osimertinib | PR 4.0    |
| Asian     | F      | 65  | NS             | –                | L718V L868R    | –                        | Post osimertinib | PR 6.0+    |
| Asian     | –      | –   | –              | –                | L718V L868R    | –                        | Post osimertinib | SD 15.0    |
| Asian     | –      | –   | –              | –                | C797S L868R    | –                        | Post osimertinib | SD 4.0    |

EGFR, epidermal growth factor receptor; NS, never smoker; NSCLC, non-small-cell lung cancer; PR, partial response; S, smoker; SD, stable disease; TTF, time to treatment failure.

*Received afatinib combined with osimertinib.

†Received afatinib combined with bevacizumab.
afatinib against uncommon mutation categories may be overestimated. Secondly, central EGFR mutation testing was only undertaken in a minority of patients. A wide range of different testing methods would have been used at the local level which may have introduced some unrecognized biases. Also, in many of the EGFR TKI-pretested cases, it is not documented whether mutations were detected prior to the initial EGFR TKI or afatinib. The database only includes patients treated with afatinib and not other EGFR TKIs. Recent data suggest that osimertinib may also have activity against certain uncommon EGFR mutations, although it appears to have limited activity against exon 20 insertions (17, 18).

In conclusion, afatinib should be considered as first-line treatment for patients with major uncommon mutations, compound mutations (other than those containing T790M) and certain ‘other’ uncommon mutations, possibly including PVR mutations. Expanded analysis demonstrated strong activity with afatinib against E709X, L747X and certain exon 20 insertions. Moderate activity was observed against EGFR mutations implicated in acquired resistance to osimertinib. The heterogeneity of uncommon mutations and their differential sensitivity to afatinib, and other EGFR TKIs, necessitates an improvement in the detection and reporting of EGFR mutations in real-world clinical practice, with specific and precise details of mutations required (e.g., regarding exon 20 insertions).

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the study are available from author AM on reasonable request.

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AUTHOR CONTRIBUTIONS

Study concept and design: JC-HY, EK. Acquisition, analysis, or interpretation of data: All authors. Drafting and critical revision of the manuscript for important intellectual content: All authors. Study supervision: JC-HY, EK. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.834704/full#supplementary-material

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