Treatment and Outcomes of Metastatic Non-Small-Cell Lung Cancer Harboring Uncommon EGFR Mutations: Are They Different from Those with Common EGFR Mutations?

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Simple Summary: The present study showed the comprehensive analysis of disease characteristics and treatment patterns in uncommon EGFR mutation-positive NSCLC at a major cancer center. This study showed the efficacy of 1G or 2G EGFR-TKIs as the 1L treatment, and subsequent therapy including 3G EGFR-TKIs in the real-world setting.

Abstract: Approximately 10% of the epidermal growth factor receptor (EGFR) mutations in non-small-cell lung cancer (NSCLC) are uncommon EGFR mutations. Although the efficacy of second (2G) or third generation (3G) EGFR tyrosine kinase inhibitors (EGFR-TKIs) in the patients with uncommon EGFR mutation has been proven, further studies are warranted to define the optimal treatment approach for uncommon EGFR mutation-positive NSCLC. This study retrospectively investigated the treatment patterns and outcomes of patients with uncommon EGFR mutation-positive NSCLC from January 2011 to December 2019 at the Samsung Medical Center, Seoul, Korea. During the study, 2121 patients with EGFR mutation-positive NSCLC received first-generation (1G, gefitinib or erlotinib) or 2G EGFR-TKI (afatinib) as the first-line (1L) systemic therapy. Of this, 135 (6.4%) patients harbored uncommon EGFR mutations. Of 135, 54 (40%, 54/135) patients had overlapping mutations with major EGFR mutations. The objective response rate (ORR) for the 1L EGFR-TKI was 63.3%. The median progression-free survivals (PFSs) were 8.6 months (95% CI: 3.8–13.5), 11.7 months (95% CI: 6.6–16.7), 7.7 months (95% CI: 4.9–17.4), and 5.0 months (95% CI: 3.7–6.1) for major uncommon EGFR mutation (G719X, L861Q), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), other compound mutation, and other uncommon mutations, respectively. The median overall survivals (OSs) were 25.6 months (16.9–34.2), 28.8 (95% CI: 24.4–33.4), 13.5 months (95% CI: 7.4–27.8), and 9.4 months (95% CI: 3.4–10.5) for major uncommon EGFR mutation (G719X, L861Q), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), other compound mutation, and other uncommon mutations, respectively. The response rate, median PFS, and OS were 63.3%, 16.3 months (95% CI: 15.6–16.9), and 37.5 months (95% CI: 35.4–39.6) for common EGFR mutation-positive NSCLC. After failing 1L EGFR-TKI, repeated tissue or liquid biopsy were carried out on 44.9% (54/121) patients with major EGFR mutations. Of these, 35 (68%) patients harbored uncommon EGFR mutations. Of 35, 28.6% (10/35) patients had overlapping mutations with major EGFR mutations. The objective response rate (ORR) for the 3G EGFR-TKI was 100%. The median progression-free survivals (PFSs) were 8.9 months (95% CI: 8.0–9.8). These patients showed a median OS of 34.6 months (95% CI: 29.8–39.4). The ORR, PFS and OS were poorer in patients with uncommon (especially other compound and other uncommon mutation) than those with common EGFR mutations. T790M was detected in 28.6% of the uncommon EGFR mutation-positive patients for whom prior 1G/2G EGFR-TKIs failed and underwent repeat biopsy at the time of progression.
Keywords: uncommon EGFR mutation; EGFR-TKIs; T790M; overall survival; progression-free survival

1. Introduction

Exon 19 deletions (Del19) and epidermal growth factor receptor (EGFR) exon 21 p.L858R mutations account for approximately 45% and 40% of the cases of epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC). Uncommon EGFR mutations account for 7–23% of EGFR mutation-positive NSCLCs. Uncommon EGFR mutations can be categorized as follows: (i) de novo T790M; (ii) exon 20 insertions; (iii) “major” uncommon mutations Gly719Xaa (G719X), Leu861Gln (L861Q), and Ser768Ile (S768I); (iv) compound mutations; (v) other uncommon mutations [1].

The treatment of EGFR mutation-positive NSCLC has been revolutionized with the development of next-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs). Currently, five EGFR-TKIs are available as the first-line (1L) therapy for advanced EGFR mutation-positive NSCLC—first-generation (1G) reversible EGFR-TKIs, gefitinib, and erlotinib; second-generation (2G) irreversible ErbB family blockers, afatinib, and dacomitinib; third-generation (3G) irreversible EGFR-TKIs, osimertinib. Of the EGFR-TKI prospective randomized trials undertaken to date, only Iressa Pan-Asia Study (IPASS) [2], NEJ002 [3], and LUX-Lung 2, 3, and 6 [4,5] included patients with uncommon EGFR mutations. However, these studies included a small number of cases with uncommon EGFR mutations. Thus, it is unclear whether it is the best practice to use 2G or 3G EGFR-TKIs as the treatment of choice.

As to which treatment strategy is the best for the patients with major EGFR-mutation positive NSCLC, recently, the highly anticipated findings of the phase III FLAURA trial showed 38.6 months of overall survival (OS) with frontline osimertinib, a 3G EGFR-TKI, versus 31.8 months with erlotinib or gefitinib [6]. The results of sequential treatment in the GioTag study showed OS and updated time to treatment failure (TTF) analysis of patients with EGFR mutation-positive NSCLC who received sequential afatinib/osimertinib. The median OS was 41.3 months (90% confidence interval (CI): 36.8–46.3) in the total population and 45.7 months (90% CI: 45.3–51.5) in patients with Del 19 [7].

While robust data from clinical trials have demonstrated the efficacy, tolerability, and benefits of EGFR-TKIs and best sequential treatment, the bulk of these trials were limited to patients whose tumors harbored common EGFR mutations.

To the best of our knowledge, there have been no prospective studies on the use of 1G or 2G EGFR-TKIs, followed by sequential treatment including 3G EGFR-TKI and cytotoxic chemotherapy in patients with uncommon EGFR mutation-positive NSCLC. In this study, we describe the real-world data of practice pattern and treatment outcomes in patients with uncommon EGFR mutation-positive NSCLC, including objective response rate (ORR), progression-free survival (PFS), and OS.

2. Results

2.1. Patient Characteristics

From January 2011 to December 2019, 2121 patients with EGFR mutation-positive NSCLC received gefitinib, erlotinib, or afatinib as 1L chemotherapy at the Samsung Medical Center. A total of 135 (6.4%) patients harbored uncommon EGFR mutations such as G719A/G719C/G719X, L861Q, S781I, H351I, E709K, and de novo T790M. The types of uncommon EGFR mutations are described in Table 1. Major uncommon mutations, such as G719X, L861Q, and S791I were 118 (87.4%). Compound mutations were 54 (40%). De novo T790M cases were 15 (11.1%). Other uncommon mutations included L747S and H351I. In this study, there were no patients with EGFR insertion 20 who received EGFR-TKIs as a 1L treatment. We classified patients with uncommon EGFR mutation into the major uncommon EGFR mutation (G719X alone (n = 61), L861Q alone (n = 18), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R, n = 26), other compound mutations (n = 13), other uncommon
mutations ($n = 2$) and T790M ($n = 15$). There were 47.4% (64/135) male, and ex- or current smokers were 44.4% (60/135). About 25.9% of patients had symptomatic or asymptomatic brain metastasis at initial diagnosis.

Table 1. Baseline characteristics.

| Patient Characteristics | Number of Patient (%) | Total $n = 135$ |
|-------------------------|-----------------------|-----------------|
| Age                     | <60 years             | 47 (34.8%)      |
|                         | ≥60 years             | 88 (65.2%)      |
| Sex                     | Male                  | 64 (47.4%)      |
|                         | Female                | 71 (52.6%)      |
| ECOG PS                 | 0                     | 28 (20.7%)      |
|                         | 1                     | 96 (71.1%)      |
|                         | 2                     | 11 (8.1%)       |
| Smoking status          | Never smoker          | 75 (55.6%)      |
|                         | Ex-smoker             | 45 (33.3%)      |
|                         | Current smoker        | 15 (11.1%)      |
| History of curative thoracic surgery | Yes | 26 (19.2%) |
|                         | No                    | 109 (80.7%)     |
| EGFR mutation type      | G719X                 | 79 (58.5%)      |
|                         | +Del 19               | 2               |
|                         | +L858R                | 3               |
|                         | +S791I                | 11              |
|                         | +E709K                | 1               |
|                         | +L861Q                | 1               |
|                         | L861Q                 | 35 (25.9%)      |
|                         | +L858R                | 16              |
|                         | +G719X                | 1               |
|                         | S791I                 | 16 (11.9%)      |
|                         | +L858R                | 5               |
|                         | +G719X                | 11              |
|                         | T790M                 | 15 (11.1%)      |
|                         | +Del 19               | 4               |
|                         | +L858R                | 11              |
|                         | L747S                 | 1 (0.7%)        |
|                         | H835Y                 | 1 (0.7%)        |
| EGFR-TKI as the first-line treatment | Gefitinib | 53 (39.3%) |
|                         | Erlotinib             | 21 (15.6%)      |
|                         | Afatinib              | 61 (45.2%)      |

PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

2.2. Clinical Outcomes of the 1L-Treatment

The ORR (complete response or partial response) for the 1L 1G or 2G EGFR-TKIs was 63.3% (76/120). The median PFS was 11.1 months (95% CI: 7.2–15.0) for uncommon EGFR mutation-positive NSCLC (Table 2). The median PFSs were 8.6 months (95% CI: 3.8–13.5), 11.7 months (95% CI: 6.6–16.7), 7.7 months (95% CI: 4.9–17.4), and 5.0 months (95% CI: 3.7–6.1) for major uncommon EGFR mutation (G719X, L861Q), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), compound mutation (G719X and S791I, G719X and L861Q), and other uncommon mutations (L747S, H835Y), respectively. The median OS were 25.6 months (16.9–34.2), 28.8 (95% CI: 24.4–33.4), 13.5 months (95% CI: 7.4–27.8), and 9.4 months (95% CI: 3.4–10.5) for major uncommon EGFR mutation (G719X), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), compound mutation, and other uncommon mutations, respectively. From October 2014 to December 2019, in the uncommon EGFR mutation-positive NSCLC group, the median PFS was 15.1 months (95% CI: 12.5–17.7)
Among the 78 patients who experienced disease progression, 10 patients received osimertinib as a 3G (35/78) patients (Table 3). T790M was detected in 10/35 (28.6%) patients who were successfully biopsied. Among the 78 patients who experienced disease progression, 10 patients received osimertinib as a 3G EGFR-TKIs and cytotoxic chemotherapy, respectively (Table 3 and Figure 1B) (p = 0.03). There was no significant difference in sequential treatment after failing 1L treatment among the three EGFR-TKIs.

**Table 2.** Clinical outcomes of the first-line treatment.

| Uncommon EGFR Mutation | PFS | OS |
|-------------------------|-----|----|
| EGFR-TKI *              |     |    |
| Gefitinib or Erlotinib  | 7.7 (1.3–14.1) | 15.5 (9.0–22.0) |
| Afatinib                | 15.1 (12.5–17.7) | 34.6 (16.0–35.2) |

* From October 2014 to December 2019. PFS, progression-free survival; OS, overall survival; EGFR-TKI, EGFR tyrosine kinase inhibitor.

**Figure 1.** Clinical outcomes of the first-line treatment. (A) Median progression-free survival (PFS) according to the type of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) in uncommon EGFR mutation-positive non-small-cell lung cancer (NSCLC) patients (from October 2014 to December 2019). (B) Median overall survival (OS) according to the type of EGFR-TKIs in patients with uncommon EGFR mutation-positive NSCLC (from October 2014 to December 2019).

### 2.3. Clinical Outcomes of the Second-Line Treatment

Among 120 patients (except de novo T790M), 78 experienced disease progression until January 2020. Among them, EGFR mutations were evaluated by repeated tissue or liquid biopsy in 44.9% (35/78) patients (Table 3). T790M was detected in 10/35 (28.6%) patients who were successfully biopsied. Among the 78 patients who experienced disease progression, 10 patients received osimertinib as a 3G EGFR-TKIs (8/10 patients had overlapping EGFR mutations with Del 19 or EGFR exon 21 p.L858R), seven patients who did not have T790M received other EGFR-TKIs (e.g., olmutinib), 41 patients received cytotoxic chemotherapy, and 20 patients did not receive any sequential treatment.

In 58 patients who experienced disease progression and received sequential treatment, the median PFS2 was 8.9 months (95% CI: 8.0–9.8) and 4.2 months (95% CI: 2.3–6.2) for third-generation EGFR-TKIs and cytotoxic chemotherapy, respectively (Table 3 and Figure 2A) (p = 0.05). In 58 patients who experienced disease progression and received sequential treatment, the median OS2 was 15.1 months (95% CI: 9.0–21.2) and 11.0 months (95% CI: 5.1–16.9) for 3G EGFR-TKIs and cytotoxic chemotherapy, respectively (Table 3 and Figure 2B) (p = 0.214). The median OS was 34.6 months (95% CI: 29.8–39.4),
24.4 months (95% CI: 17.4–31.4), and 5.3 months (95% CI: 2.9–7.7) for 3G EGFR-TKIs, cytotoxic chemotherapy, and no sequential treatment, respectively (Figure 2C, \( p < 0.001 \)).

Table 3. Clinical outcomes of second-line treatment.

| Patient Characteristics | Uncommon Mutation (Except De Novo 790M) \((n = 120)\) |
|-------------------------|-------------------------------------------------|
| No. of patients who experienced disease progression | 78 |
| Rate of re-biopsy after failing first-line EGFR-TKIs | 35 (44.9%, 35/78) |
| Detection rate of T790M | 10 (28.6%, 10/35) |
| Sequential Treatment | Number of Patient (%) | Median PFS2 \((95% CI)\) | OS2 \((95% CI)\) | Median OS \((95% CI)\) |
|-------------------------|----------------------|----------------|----------------|----------------|
| 3G EGFR-TKIs | 17 (21.8%) | 8.9 (8.0–9.8) | 15.1 (9.0–21.2) | 34.6 (29.8–39.4) |
| Cytotoxic chemotherapy | 41 (52.6%) | 4.2 (2.3–6.2) | 11.0 (5.1–16.9) | 24.4 (17.4–31.4) |
| No sequential treatment | 20 (25.6%) | 5.3 | |

PFS, progression-free survival; OS, overall survival; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; CI, confidential interval. PFS2 was defined as the first date of sequential treatment after failing 1L EGFR-TKIs until progression or death resulting from any cause. OS was defined as the first date of EGFR-TKIs until death resulting from any cause. OS2 was defined as the first date of sequential treatment after failing 1L EGFR-TKIs until death resulting from any cause.

2.4. Clinical Outcomes of Patients with De Novo T790M Mutation in the Uncommon EGFR Mutation Group

Among the 15 patients with de novo T790M mutation, 11 patients had an EGFR exon 21 p.L858R mutation and four patients had a Deletion 19 as a coexisting mutation. As a 1L treatment, seven patients received gefitinib, one patient received erlotinib, and seven patients received afatinib. Among them, eight patients received 3G EGFR-TKIs after failing the 1L EGFR-TKI treatment. The median PFS was 4.9 months (95% CI: 3.8–6.0), and the median OS was 24.0 months (95% CI: 0.7–4.8). Patients who received 3G EGFR-TKIs showed a median OS of 38.0 months (95% CI: 10.5–65.4).

2.5. Comparison between Common and Uncommon EGFR Mutation

In the uncommon EGFR mutation group, there were relatively more male patients and current/ex-smokers than in the common EGFR mutation group (Table S1A). During treatment, the re-biopsy rate in the common EGFR mutation group was 66.6% (75% between October 2014 and December 2019), and in the uncommon EGFR mutation group it was relatively low at 44.9%. Although there was a difference between the two groups in the re-biopsy rate, the T790M detection rate in the patients who underwent re-biopsy was 63.5% in the common EGFR mutation group but was 28.6% in the uncommon EGFR mutation group. The response rate was 63.3% and 86.6% for the uncommon and common EGFR mutation groups, respectively. The median PFS was 16.3 months (95% CI: 15.6–16.9) and 11.1 months (95% CI: 7.2–15.0) for common EGFR mutation-positive NSCLC and uncommon EGFR mutation-positive NSCLC, respectively (Figure S1A) \(( p < 0.001) \).

In the overall population, the median OS was 37.5 months (95% CI: 35.4–39.6) and 25.6 months (95% CI: 18.2–33.0) for common EGFR mutation-positive NSCLC and uncommon EGFR mutation-positive NSCLC, respectively (Figure S1B) \(( p < 0.001) \). In the patients who received 3G EGFR-TKIs after failing 1L EGFR-TKIs, the median OS was 44.4 months (95% CI: 38.9–49.9) and
34.6 months (95% CI: 29.8–39.4) for common EGFR mutation-positive NSCLC and uncommon EGFR mutation-positive NSCLC, respectively.

The median ORR, PFS and OS of patients with uncommon EGFR mutation-positive NSCLC were lower than those of patients with common EGFR mutation-positive NSCLC (Figure S1A,B). The PFS was not significantly different among the 1G or 2G EGFR-TKIs but showed a trend favoring the afatinib group in patients with uncommon EGFR mutation-positive NSCLC. There was no significant difference in sequential treatment after failing 1L treatment among the three 1G or 2G EGFR-TKIs. However, in comparison to gefitinib or erlotinib, the afatinib group showed statistically superior OS results. Especially in patients with major uncommon EGFR mutation (G719X, L861Q), compound mutation with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), afatinib showed superior OS results. In our study, less than one-third of the patients with uncommon EGFR mutation-positive NSCLC had a T790M mutation in the re-biopsy after failing 1L EGFR-TKIs. Most T790M mutation positive cases had overlapping mutations with major (Del 19 or EGFR exon 21 p.L858R) and uncommon EGFR

3. Discussion

The present study showed the comprehensive analysis of disease characteristics and treatment patterns in uncommon EGFR mutation-positive NSCLC at a major cancer center. This study showed the efficacy of 1G or 2G EGFR-TKIs as the 1L treatment, and subsequent therapy including 3G EGFR-TKIs in the real-world setting.

In our study, less than one-third of the patients with uncommon EGFR mutation-positive NSCLC had a T790M mutation in the re-biopsy after failing 1L EGFR-TKIs. Most T790M mutation positive cases had overlapping mutations with major (Del 19 or EGFR exon 21 p.L858R) and uncommon EGFR
mutations. The rate of T790M mutations after failing 1L EGFR TKI treatment in our study was only 28.6%, relatively lower than that of common EGFR mutation [8–11]. In a previous study by Yang et al., a lower incidence of acquired T790M mutations was reported in uncommon EGFR mutation-positive NSCLCs than in common EGFR mutation-positive NSCLCs (27.1 % vs. 45.2%) [12]. It needs to be further prospectively investigated whether the rate of T790M-associated acquired resistance in patients with uncommon EGFR mutations after failing EGFR-TKI is lower than in patients with common EGFR mutations.

Uncommon EGFR mutations are heterogeneous and have various sensitivities to EGFR-TKIs. In addition, the mechanism of acquired resistance to 1L EGFR-TKIs has not yet been well defined. Several retrospective studies and case reports of 1G EGFR-TKIs showed inconsistent responses in patients with uncommon EGFR mutation-positive NSCLC. A post-hoc analysis of prospectively collected data from the participants of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 trials showed the clinical activity of afatinib in patients with advanced uncommon EGFR mutation-positive NSCLC, especially G719X, L861Q, and S768I. However, it reported a low activity against T790M and exon 20 insertion mutations. Afatinib showed an ORR of 71% and a median PFS of 10.7 months (95% CI: 5.6–14.7), except for those with T790M or exon 20 insertion mutations, for whom ORR was 9–14%, and PFS was less than 3 months. The median OS was 19.4 months (95% CI: 16.4–26.9) [13]. In a recent afatinib study (n = 315), it showed activity against major uncommon mutations (median TTF, 10.8 months; 95% CI: 8.1–16.6; ORR, 60.0%), compound mutations (median TTF, 14.7 months; 95% CI: 6.8–18.5; ORR, 77.1%), other uncommon mutations (median TTF, 4.5 months; 95% CI: 2.9–9.7; ORR, 65.2%), and some exon 20 insertions (median TTF, 4.2 months; 95% CI: 2.8–5.3; ORR, 24.3%) in EGFR-TKI naïve patients [1].

In the phase II study of osimertinib for EGFR-TKI naïve patients with uncommon EGFR mutation-positive NSCLC (KCSG-LU15-09), 22 of the 36 patients received osimertinib as the 1L treatment [14]. A total of 14 patients received osimertinib as a sequential treatment after failing the 1L treatment, except for EGFR-TKIs. Osimertinib conferred an ORR of 50%. The median PFS was 8.2 months (95% CI: 5.9–10.5), and the median OS was not reached. Furthermore, the response rate and median duration of response (11.2 months) were lower than those observed with osimertinib in patients with common mutations (Del19, EGFR exon 21 p.L858R). In our study, the median PFS of 1G or 2G generation EGFR-TKI was 11.1 months (95% CI: 7.2–15.0), and the median OS was 25.6 months (95% CI: 18.2–33.0) in patients with uncommon EGFR mutant-positive NSCLC.

This study has several limitations due to its retrospective nature and single center experience. We had a small number of patients with brain metastasis at initial diagnosis. This study could not evaluate for CNS-specific outcomes or subgroup analysis. Among other things, only 44.9% of the patients were evaluated by repeated tissue or liquid biopsy at the time of progression because there was no accessible site for biopsy (e.g., brain). Furthermore, the polymerase chain reaction-based or direct sequencing methods might have had limitations in detecting compound EGFR mutations because of low sensitivity compared to the NGS [15,16]. Success rates for obtaining adequate sample for institutional analysis has ranged from 30% to 80% and is influenced by the quality of the sample, the assay used and resources within institutional molecular laboratories. Initial testing utilized Sanger’s sequencing in isolated DNA from formalin-fixed paraffin embedded (FFPE) tissue but required at least 25% tumor cellularity. Commercial assays such as Therascreen (Qiagen Manchester, U.K.) and Cobas (Roche, Basel, Switzerland), which consider “hot spots” thought predictive of TKI response, are widely utilized. More recently, droplet digital PCR (ddPCR) and next generation sequencing (NGS) coupled with exon-capture strategies have been shown to have increased sensitivity down to 0.01% tumor cellularity. NGS gene panels have improved EGFR mutation detection accuracy [17]. It is also well known that the prognosis differs according to the co-existing mutations (P53) in common EGFR mutation-positive NSCLC. However, in our study, few patients had an NGS result; therefore, further studies are needed to determine the prognostic effect of co-mutations in uncommon EGFR mutation-positive NSCLC.
4. Materials and Methods

4.1. Study Subjects and Data Collection

This study included patients with EGFR mutation-positive NSCLC, who started 1L gefitinib, erlotinib, or afatinib treatment for recurrent or metastatic NSCLC at the Samsung Medical Center between January 2011 and December 2019. This non-interventional observational study through big data analysis retrospectively collected de-identified patient data from a clinical data warehouse (CDW) using a unique algorithm with Standard Query Language (SQL) called the ROOT project. Patient demographic characteristics, such as age, sex, smoking history, performance status, and EGFR mutation type, were reviewed. We classified the uncommon EGFR mutation-positive NSCLC into the group with major uncommon EGFR mutation (G719X, L861Q), compound mutations with major EGFR mutation (Del 19 or EGFR exon 21 p.L858R), other compound mutations, other uncommon mutations (L747S, H835Y) and T790M. Demographic information was obtained when the 1L EGFR-TKI treatment was initiated. EGFR mutations were identified using a peptide nucleic acid (PNA)-clamp kit and real-time polymerase chain reaction, COBAS (cobas® EGFR Mutation Test v2 [18], or next-generation sequencing (NGS) (sequencing using a cancer panel (CancerSCAN™)).

4.2. Ethics Statement

This study was reviewed and approved by the Institutional Review Board (IRB) at the Samsung Medical Center (IRB No. 2018-05-130). The trial was conducted following the Declaration of Helsinki (as revised in 2013).

4.3. Statistical Analysis

The all-data cut-off date for the analyses was February 2020. PFS and OS were calculated using a Kaplan–Meier estimator and compared using the log-rank test. PFS and OS were presented as median values, with two-sided 95% CIs. PFS was defined as the first date of EGFR-TKIs until progression or death resulting from any cause. PFS2 was defined as the first date of sequential treatment after failing 1L EGFR-TKIs until progression or death resulting from any cause. OS was defined as the first date of EGFR-TKIs until death resulting from any cause. OS2 was defined as the first date of sequential treatment after failing 1L EGFR-TKIs until death resulting from any cause. All p-values were two-sided, and p-value < 0.05 was considered statistically significant. The Korea Food and Drug Administration approved afatinib in October 2014. Among the three 1G or 2G EGFR-TKIs, PFS and OS were analyzed in patients who received EGFR-TKIs between October 2014 and December 2019.

5. Conclusions

The patients with uncommon EGFR-mutant NSCLC showed lower ORR, PFS, and OS than the patients with common EGFR-mutant NSCLC. In particular, among the uncommon EGFR mutation, compared to the group with compounding mutation with major EGFR mutation and the group with major uncommon EGFR mutation, the group with other compounding mutation or other uncommon EGFR mutation showed inferior outcomes. Compared to common EGFR mutation-positive NSCLC, a lower percentage of patients underwent repeated biopsy and showed a lower detection rate of T790M. Less than one-third of the patients received 3G EGFR-TKI after failing the 1L EGFR-TKIs. However, like the common EGFR group, patients with T790M mutation after failing the 1L EGFR-TKI who received 3G TKI showed a favorable OS compared to other sequential treatments in the uncommon EGFR group. With the availability of more EGFR TKIs and a better understanding of tumor biology, further prospective studies are warranted to define the optimal treatment approach for uncommon EGFR mutant-positive NSCLC.
Supplementary Materials: The following are available online at http://www.mdpi.com/2079-7737/9/10/326/s1,
Table S1: Comparison of the baseline characteristics between common and uncommon EGFR mutation NSCLC,
Figure S1: (A) Median progression-free survival (PFS) according to the type of epidermal growth factor receptor
(EGFR) mutation (common versus uncommon). (B) Median overall survival (OS) according to the type of EGFR
mutation (common versus uncommon).

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Abbreviations

CI confidence interval
EGFR epidermal growth factor receptor
TKI tyrosine kinase inhibitor
NGS next-generation sequencing
NSCLC non-small-cell lung cancer
OS overall survival
PFS progression-free survival

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