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The comparative effectiveness of first-line treatment EGFR TKIs in Asian lung cancer population: A systematic review and meta-analysis

Maria Wisnu Donowati[1,6*], Erna Kristin[2], Susanna Hilda Hutajulu[3], Dwi Endarti[4], Ricvan Dana Nindrea[5]

[1]Doctoral Program of Faculty Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[2]Department of Pharmacology and Therapy, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[3]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr Sardjito General Hospital, Yogyakarta, Indonesia.
[4]Department of Pharmaceutic, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[5]Department of Biostatistic and Epidemiology, Faculty of Medicine, Universitas Negeri Padang, Bukittinggi, Indonesia.
[6]Faculty of Pharmacy, Sanata Dharma University, Yogyakarta, Indonesia.

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ABSTRACT

Nonsmall cell lung cancer is the most common carcinoma in Asia with more than half identified as epidermal growth factor receptor mutation-positive (EGFRm+). First- and second-generation EGFR tyrosine kinase inhibitors (TKIs), a targeted therapy type, improved overall survival compared to platinum-based chemotherapy. We conducted an updated review comparing the clinical effectiveness of EGFR TKIs as a first-line treatment in Asian populations with EGFRm+. This systematic search was conducted in six databases, resulting in 30 eligible articles, which represented Asian ethnicity and were appraised quantitatively using the GRACE checklist. Thirteen eligible studies and 3,465 patients were included in the meta-analysis. Two models of effectiveness comparison were used to measure the pooled size effect: afatinib and dacomitinib. Afatinib in patients with brain metastases had a higher risk of progression and death, but lower time to treatment failure (TTF). Never-smoking patients had lower risk of TTF and death, but equivalent risk for progression. Dacomitinib had a lower risk of progression and death. Exon 19 deletion (e19del) or exon 21 substitution (L858R) benefited more from the second generation. L858R had a higher risk of survival, progression-free, and overall survival than e19del with second-generation agents. Coexisting e19del or L858R in uncommon mutation is associated with longer progression than without it.

INTRODUCTION

Lung cancer (LC) is the second most prevalent cancer but is the leading cause of cancer death worldwide [1]. It is mostly diagnosed in an advanced stage and metastatic [2,3]. Adenocarcinoma (ADC) is the most prevalent histology type of LC, with about 85% being caused by nonsmall cell lung cancer (NSCLC). Around 50%–80% of NSCLCs have epidermal growth factor receptor (EGFR) overexpression [4–7]. A higher proportion of Asians are positive for EGFR mutations (EGFRm+), around 40%–60%, compared with 10%–20% of Caucasians [8,9]. In general, the activity of EGFR tyrosine kinase inhibitors (TKIs) does not differ significantly between Asian and non-Asian populations [10]. However, there are likely to be differences in the mutation frequencies of NSCLC between Asian sub-groups, particularly South and Southeast Asian sub-groups [11].

Based on the improved overall survival (OS) for the human epidermal growth factor receptor 2 (HER2/ERBB2) mutations and mesenchymal-epithelial transition (MET) amplification with targeted therapies compared to conventional chemotherapy, the National Comprehensive Cancer Network (NCCN panel)

*Corresponding Author
Maria Wisnu Donowati, Doctoral Program of Faculty Medicine, Public Health, and Nursing, Universitas Gadjah Mada Gd Pascasarjana Tahir, Yogyakarta, Indonesia.
E-mail: mariawisnu@usd.ac.id

recommends molecular testing to target driver mutations in LC diagnosis [12]. A pertinent achievement in NSCLC research, EGFR gene mutation identification is considered to be the most robust predictive biomarker of response to EGFR TKIs [13]. In clinical practice, they increased the OS approach by 22–34 months [14]. First- and second-generation EGFR TKIs are the first-line treatments for patients with metastatic NSCLC who have EGFR mutation in e19del or L858R, while third-generation is a second-line setting [10,15]. The distribution rates of common (e19del and L858R) and rare common (exon 18 G179X, exon 20 S768I, and exon 21 L861Q) activating EGFR mutations vary across the region [16,17]. In general, e19del represents 45% and L858R 40% of patients and confers a prognostic advantage, significantly improving progression-free survival (PFS) in advanced EGFR + NSCLC compared to L858R mutation [18]. For EGFR single mutations, L858R was found more frequently than e19del in South and North Asia [17], while e19del is higher than L858R in Southeast Asia [19,20]. Gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib are the five EGFR TKIs available globally, and icotinib is exclusive to China. The type of EGFR mutation is one of many considerations when deciding on first-line treatment for an EGFRm+ patient. With numerous drugs available for EGFR-mutated NSCLC, a long-term treatment plan is needed to maximize survival [21]. Comparative effectiveness research (CER) seeks effectiveness by comparing outcomes through a direct comparison of interventions or studies in everyday clinical care which will lead to a health care improvement, better health outcomes, and lower costs [22]. Recently, published network meta-analysis (NMA) on the efficacy of first-line EGFR TKIs are limited by single osimertinib randomised control trial (RCT) investigation [23,24]. In Asian patients, Farris *et al.* concluded that dacomitinib showed a numerical improvement in OS compared to all other EGFR TKIs, while osimertinib showed no significant improvement in OS compared to the first generation [10]. In general, Qi *et al.* updated that osimertinib and second-generation EGFR TKIs were more effective than first-generation monotherapy in improving OS and PFS.

Therefore, data concerning the effectiveness of the choices of LC treatment based on EGFR mutation are presently of paramount importance in the Asian population. It is important to note that CER on EGFR TKIs is an alternative strategy to support decisive decision-making toward increasing the effectiveness of treatment while reducing health expenditures. Based on these findings, we focus on comparing effectiveness between Asian populations.

This study aimed to compare the clinical effectiveness of EGFR TKIs as a first-line therapy based on identified EGFR gene mutations in Asian populations. A systematic synthesis was conducted by accessing quantitative and qualitative data and a meta-analysis was done as a deeper investigation.

METHODS

Search strategy

Six comprehensive electronic databases were systematically searched: ScienceDirect, ProQuest, EBSCOhost, Scopus, Cochrane Library, and PubMed. PICO (Population Intervention Comparison Outcome) table and search terms were provided in Appendix A. All direct EGFR TKIs comparison articles before August 2022 which conformed with eligibility criteria were included, i.e., (i) patients with NSCLC harboring EGFR aberrant, (ii) treated with EGFR TKIs in the first-line setting, (iii) has primary either secondary efficacy outcomes, i.e., PFS or OS or time to treatment failure (TTF), and (iv) conducted in Asian population. Studies were excluded when it is a review, post hoc analysis of trial data, and without available full text. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline was used to report this systematic review [25].

Study selection and screening

After the removal of any duplication, selected articles were skimmed by title and abstract. Subsequently, full-text articles were retained for further appraisal. One author (MW) performed the study search and reference tracking was conducted to obtain comparative effectiveness results. Two authors (MW and EK) independently reviewed data extraction. An agreement was sought through discussion in any case of differences between reviewers.

Quality assessment and data extraction

All 30 selected articles were quantitatively assessed using the Good Research for Comparative Effectiveness (GRACE) checklist. The GRACE checklist has been tested for validity. It was designed as a tool to access the quality of observational CER [26]. We used the GRACE checklist tailored to lung oncology, and a final score was based on a range of 0 to 11 [22]. In addition, JADAD's scale is used to estimate the robustness of clinical trial comparative effectiveness studies [27]. The data extraction approach with thorough management of overlapping information and data at the synthesis stage addressed the potential scenario of sample overlap across multiple studies used in meta-analysis [28].

We extracted the following information: name of the first author, year of publication, the number of patients studied, ethnicity, treatments compared, study design, characteristic aberrant, statistical method, results of effectiveness, and conclusions.

Statistical analysis

The GRACE scores were analyzed using a t-test to compare the mean values of single-center to multicenter studies. This review investigated the association between EGFR aberrant and effectiveness through pooled hazard ratio (HR) of clinical outcome and 95% confidence interval (CI) in all. The significance effect of pooled HR was determined using the Z test ($p < 0.05$ considered statistically significant). The heterogenicity test was measured using I^2 and showed significant heterogeneous results ($p < 0.05$ or $I^2 > 50\%$). We used a fixed-effect model if $I^2 < 50\%$, whereas I^2 50%–90% used a random-effects model. This meta-analysis was conducted using Review Manager Software version 5.3 (RevMan v5.3, The Cochrane Collaboration, Oxford, UK).

RESULTS

Literature search

There were 1,373 finding articles and 799 articles were excluded by title. A total of 541 abstracts were screened

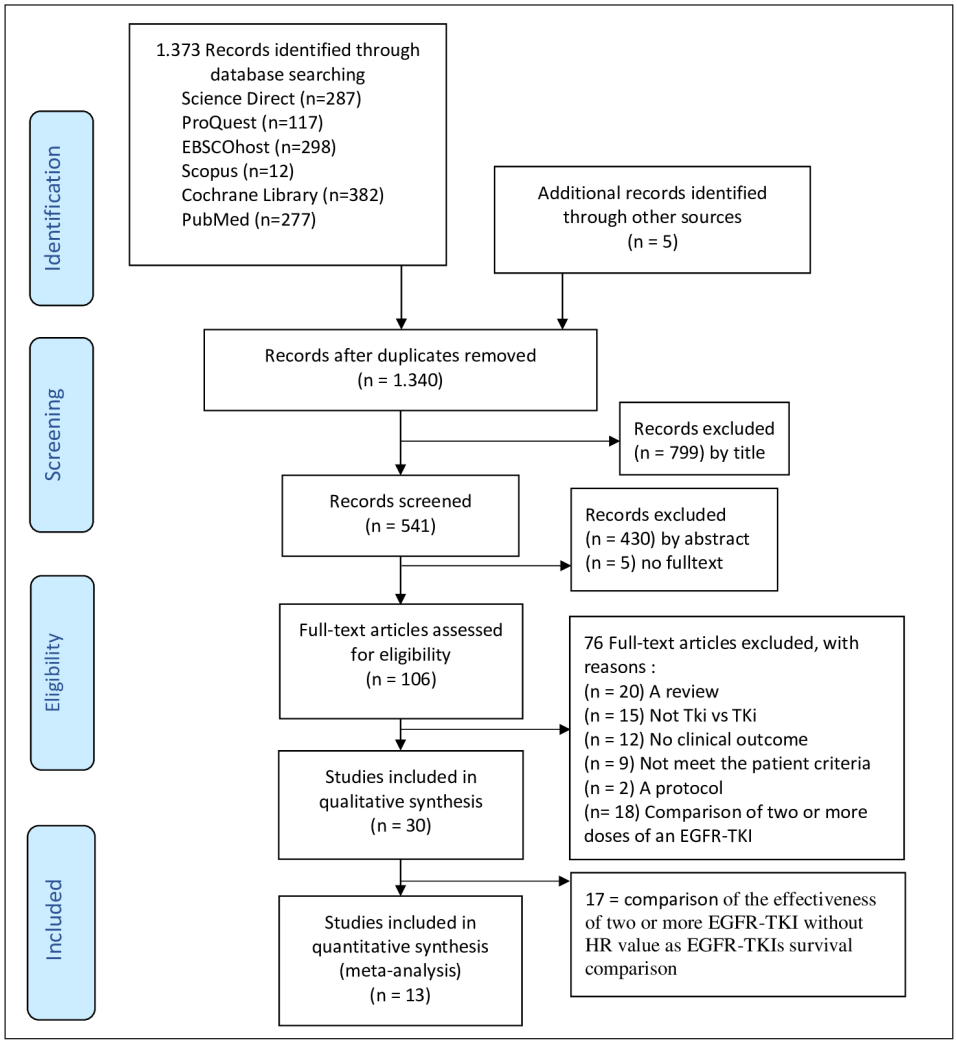

Figure 1. Flowchart of the literature search process.

and 106 full-text articles were assessed. In addition, 30 eligible articles were critically appraised using the GRACE instrument. The literature search process is described in Figure 1.

Characteristics of included studies

Fifteen of 30 eligible articles were conducted by multicenter and eight of 30 eligible articles were from five trials which were conducted as prospective randomized phase II and phase III clinical trials, i.e., FLAURA [29], ARCHER 1009 [30], ARCHER 1050 [31–33], LUX lung 7 [34,35], and ICOGEN [36]. Moreover, most of these articles had a cohort retrospective study design.

Furthermore, these findings were tabulated in two categories: first, there were 17 articles (Table 1) without HR of EGFR TKIs as survival effectiveness comparison and the second was 13 articles (Table 2) with the effectiveness comparison. There were seven ethicists revealed based on geographical locations, i.e., Chinese, Japanese, Indian, Indonesian, Korean, Singaporean, and Taiwanese. We found the most frequently used comparator therapy was gefitinib.

From these eligible articles, we compared the efficacy of the first generation of EGFR-TKIs (gefitinib or erlotinib or icotinib) with the second (afatinib or dacomitinib) and third generation (osimertinib). Meta-analyses were performed on 13 articles (Table 3), 8 clinical trial comparative effectiveness articles [29–36], and 5 retrospective cohorts [37–41]. We found potential patient overlap when comparing the efficacy outcome of dacomitinib and gefitinib/erlotinib, i.e., PFS [31,32] and OS [32,33] from ARCHER 1050 studies [31–33]. Based on geographical location, we found data on the effectiveness comparison of Chinese [29,36], Japanese [37], Korean [40], and Taiwanese [38,39,42]. In addition, there were two Taiwanese [39,42] and one Korean [40] articles comparing PFS and OS of afatinib and first-generation TKIs. A meta-analysis of efficacy in these two ethnicities is, therefore, possible.

Quality assessment

Articles tabulated in Table 1 and statistically analyzed in Appendix B (a). The average GRACE score was 6.15 with minimum–maximum (min–max) 3.5–9.5 and a standard deviation (SD) of 1.59. It did not differ significantly ($p = 0.14$)

Table 1. The comparative effectiveness result of EGFR TKI without HR as survival effectiveness comparison.

No.	ID (Author, year, study)	Number of patients studied	Comparison (*n*)	Study design	Ethnicity	PFS (95% CI)		OS (95% CI)		TTF (95% CI)		GRACE score
						Median (months)	HR	Median (months)	HR	Median (months)	HR	
1	Sun *et al.*, 2011 [41]	77 TKIs/164	(i) 35 erlotinib versus 42 gefitinib (ii) 58 exon 19del versus 19 L858R	Cohort retrospective	Korean	(i) 8.0 versus 11.9, $p = 0.30$ (ii) 9.5 versus 7.7, $p = 0.029$	(i) - (ii) 2.72 (1.38–5.38)	(i) 15.8 versus 30.7, $p = 0.59$ (ii) 21.4 versus 30.7, $p = 0.70$	N/A	N/A	N/A	6
2	Keam *et al.*, 2014 [43]	306	269 common versus 16 uncommon versus 16 complex common-uncommon versus 16 common T790M	Cohort retrospective	Korean	11.9 (10.4–13.5) versus 1.4 (0.3–2.5) versus 8.1 (3.2–13.1) versus 8.0 (0.8–1.52) $p < 0.001$	N/A	N/A	N/A	N/A	N/A	5.5
3	Nakao *et al.*, 2015 [44]	17 elderly (80–96 yearsold)	One erlotinib 16 gefitinib	Cohort retrospective	Japanese	2.8 versus 7.4	N/A	3.6 versus 15.1	N/A	N/A		6.5
4	Yang *et al.*, 2015 [45]	24 uncommon mutation	9/13 EGFR TKI first-line Seven gefitinib Four erlotinib One icotinib One afatinib	Cohort retrospective	Chinese	7.4 (1.1–21.7)	N/A	N/A	N/A	N/A	N/A	5.5
5	Hirano *et al.*, 2016 [46]	26	(i) 16 erlotinib versus 10 gefitinib (ii) Low BSA versus high BSA	Cohort retrospective	Japanese	(i) 14.1 versus 22.4 (ii) 25.6 versus 9.7 $p = 0.0131$	N/A	(i) 32.4 versus 30.5 (ii) 38.2 versus 27.2, $p = 0.189$	N/A	N/A	N/A	3.5
6	Lu and Fan, 2016 [47]	39	Concurrent EGFR TKI and WBRT versus EGFR TKI or WBRT alone Nine icotinib 23 erlotinib	Cohort retrospective	Chinese	N/A	N/A	26.0 (18.09–33.90) versus 25.0 (22.30–27.69) versus 27.0, $p = 0.65$	N/A	N/A	N/A	8
7	Aiko *et al.*, 2018 [48]	77	Seven gefitinib 22 erlotinib versus 55 gefitinib (i) All patients (ii) BM (iii) Without BM	Cohort retrospective	Japanese	(i) 11.1 versus 9.6 $p = 0.860$ (ii) 11.5 versus 9.7 $p = 0.257$ (iii) 8.5 versus 9.6 $p = 0.466$	(i) - (ii) 0.25 (0.08–0.81) (iii) 0.57 (0.13–3.01)	N/A	N/A	N/A	N/A	9.5

Continued

No.	ID (Author, year, study)	Number of patients studied	Comparison (*n*)	Study design	Ethnicity	PFS (95% CI)		OS (95% CI)		TTF (95% CI)		GRACE score
						Median (months)	HR	Median (months)	HR	Median (months)	HR	
8	Zhu *et al.*, 2018 [49]	208	(i) 76 icotinib versus 31 erlotinib versus 101 gefitinib (ii) With elevated versus without elevated ALT (iii) Normal versus with elevated AST	Cohort retrospective	Chinese	(i) 15.0 (11.0–18.9) versus 8.4 (5.6–11.1) versus 10.0 (7.9–12.0) $p = 0.001$ (ii) 10.0 (8.8–11.1) vesus 11.5 (10.1–12.8) (iii) 12.6 (10.6–14.5) versus 9.5 (7.9–11.0)	(i) - (ii) 0.75 (0.46–1.21) (iii) 0.68 (0.49–0.95)	N/A	N/A	N/A	N/A	7
9	Laitupa and Wulanari, 2019 [50]	94	75 gefitinib versus 17 erlotinib	Cohort retrospective	Indonesian	7 (2–14) versus 6 (2–18) $p = 0.82$	N/A	10 (3–15) versus 8 (3–24) $p = 0.559$	N/A	N/A	N/A	7.5
10	Matsumoto *et al.*, 2019 [51]	52	PD-L1/CD8 + TILs high/high versus low/low versus high/low versus low/high 20 gefitinib 12 erlotinib	Cohort retrospective	Japanese	2.4 (1.3–5.3) versus 11.3 (6.5–15.2) versus 8.4 (1.2–18.8) versus 17.5 (11.3–40.9) $p = 0.00000077$	N/A	N/A	N/A	N/A	N/A	8
11	Ni *et al.*, 2019 [52]	71	Two afatinib Progression before thermal ablations (PFS1) versus after thermal ablation (PFS2) correlation to OS 36 gefitinib 25 erlotinib Four afatinib (Six icotinib)	Cohort retrospective	Chinese	N/A	N/A	26.4 (6–86)	N/A	N/A	N/A	6
12	Sutandyo *et al.*, 2019 [53]	88	Seven afatinib versus 22 erlotinib versus 59 gefitinib	Cohort retrospective	Indonesian	Not reach versus 13 versus 9, $p = 0.28$	N/A	N/A	N/A	N/A	N/A	6.5
13	Chang *et al.*, 2021 [54]	205	(i) 72 afatinib versus 38 erlotinib versus 95 gefitinib (ii) BM versus without BM	Cohort retrospective	Taiwanese	(i) 21.4 versus 13.2 versus 13.7, $p < 0.001$ (ii) 12.2 versus 16.2 $p = 0.033$	N/A	(i) 29.0 versus 20.0 versus 20.2 $p = 0.086$ (ii) 17.7 versus 26.7, $p = 0.0023$	N/A	N/A	N/A	6.5
14	Fitri *et al.*, 2021 [55]	129	17 afatinib versus 50 erlotinib versus 62 gefitinib	Cohort retrospective	Indonesian	5 (2–19) versus 8 (2–25) versus 12 (2–28)	N/A	N/A	N/A	N/A	N/A	3.5

Continued

No.	ID (Author, year, study)	Number of patients studied	Comparison (*n*)	Study design	Ethnicity	PFS (95% CI)		OS (95% CI)		TTF (95% CI)		GRACE score
						Median (months)	HR	Median (months)	HR	Median (months)	HR	
15	Liu *et al.*, 2021 [56]	99	85 PD-L1 TPS low/ negative (<50%) versus 14 PD-L1 TPS high (≥50%) All patients: 9 afatinib 116 versus 14 erlotinib 38 versus 9 gefiinib	Cohort retrospective	Asian	13.0 versus 6.6[a]	2.6 (1.6–4.2)[a]	32.9 versus 11.5	3.3 (1.9–5.7)[a]	24.3 versus 8.7[a]	2.9 (1.1–7.7)[a]	5
16	Popat *et al.*, 2022 [57]	156 Asian/179 major uncommon	69 afatinib versus 71 first-gen TKIs	Cohort retrospective UpSwinG study	Taiwanese Korean Japanese	N/A	N/A	24.5 (18.4–34.0) versus 30.2 (19.4–35.7)	N/A	15.7 (10.5–18.7) versus 10.4 (7.8–15.5)	N/A	5.5
17	Sari *et al.*, 2022 [58]	113	27 afatinib versus 86 gefitinib	Cohort retrospective	Indonesian	14.7 (12–17.4) versus 11.3 (8.4–14.3) $p = 0.002$	N/A	15.5 (13.8–17.2) versus 21.4 (18–24.8) $p = 0.302$	N/A	N/A	N/A	4.5

[a]All patients data.
PFS: progression free survival, OS: overall survival, TTF: time to treatment failure.

between studies from multicenter and single center. Similarly, the assessment results of Table 2 revealed a scoring average of 9.35 (min–max: 6.0–11.5; SD 3.68) and were not statistically significant (p = 0.25) under the statistical analysis shown in Appendix B (b). In addition, assessing the JADAD score for RCT articles according to the Cochrane Assessment Criteria resulted in a mean score of 3.5 (min–max: 3–4; SD 0.55).

First-generation EGFR TKIs

Gefitinib and erlotinib have shown acceptable efficacy in NSCLC patients aged ≥ 80 years, but a dose reduction was required due to adverse events [44]. A study in Japan revealed that low-dose EGFR TKIs may provide sufficient disease control without side effects in lung cancer patients with a body surface area (BSA) <1.45 m^2. PFS was significantly prolonged in the low BSA group, but no significant correlation was found between OS and BSA in those who received a reduced dose of gefitinib or erlotinib [46].

Gefitinib was associated with more cases of alanine aminotransferase (ALT) and aspartate transaminase (AST) elevation compared to erlotinib and icotinib. The increased ALT was more pronounced than the increased AST. Those with normal ALT levels had a significantly longer PFS than those with increased ALT levels [46]. A Korean study found that older people with EGFR-mutant NSCLCs had significantly shorter survival compared with younger people treated with gefitinib/ erlotinib. In addition, the patients receiving erlotinib were more likely to have moderate to severe rash than those receiving gefitinib [41].

A multivariate analysis showed that erlotinib was associated with longer PFS than gefitinib (p = 0.025). Although with a 0.33 times higher rate, the uncommon EGFR aberrations had no significant association (p = 0.309) [37]. Icotinib was noninferior to gefitinib for PFS or OS with HR 0.84 95% CI: 0.67–1.05 and HR 1.02 95% CI: 0.82–1.27, respectively [36].

Microenvironment tumor

The tumor microenvironment based on programmed death-ligand 1 (PD-L1) tumor expression and $CD8^+$ tumor-infiltrating lymphocytes (TIL) had a potential impact on the efficacy of EGFR TKI. There was no difference in outcome in high PD-L1 (≥ 50%) or low tumors stratified by type of TKI received. Tumors with high expression of PD-L1 were more likely to have de novo resistance and numerically less likely to receive subsequent treatment after progression [56]. Patients with high PD-L1 had a significantly shorter median PFS than those with low PD-L1, with 5.9 months and 13.2 months (p = 0.0059), respectively. A PD-L1 high/CD8+ TIL high phenotype may be the subset that would not benefit or poorly progress from EGFR TKI treatment [51].

Beyond progression

Continued TKI treatment beyond disease progression has been used to delay the need for chemotherapy and to avoid the risk of relapse. Thermal ablation of isolated oligoprogressive lesions in combination with continuous EGFR TKI may extend the use of TKI therapy in acquired TKI resistance [52]. Osimertinib was the clear treatment of choice for T790M [57].

Table 2. The comparative effectiveness result of EGFR TKI with HR as survival effectiveness comparison.

No	ID (Author, year, study)	Number of patients studied	Comparison (*n*)	Study design	Ethnicity	Median (months)			GRACE score	JADAD score
						PFS	OS	TTF		
1	Shi *et al.*, 2013 ICOGEN study [36]	308	151 Icotinib versus 157 gefitinib	RCT	Chinese	4.6 versus 3.4	13.3 versus 13.9	N/A	10.0	4
2	Ramalingam *et al.*, 2014 ARCHER 1009 study [30]	174	89 Asian/439 dacomitinib versus 85 Asian/439 erlotinib	RCT	Chinese Indian Japanese Korean	3.7 versus 4.8	17.0 versus 13.4	N/A	11.5	4
3	Otsuka *et al.*, 2015 HANSHIN Oncology Group 0212 study [37]	44	Nine erlotinib versus 35 gefitinib	Cohort retrospective	Japanese	7.50 versus 5.83	N/A	N/A	7.5	N/A
4	Park *et al.*, 2016 LUX-Lung 7 study [34]	182	94 Asian/160 afatinib versus 88 Asian/159 gefitinib	RCT	Singaporean Korean Chinese Taiwanese	11.0 versus 11.0	N/A	13.2 versus 11.4	10	4
5	Paz-Ares *et al.*, 2017 LUX-Lung 7 study [35]	319	160 afatinib versus 159 gefitinib Asian: 133 event/182 patients	RCT	Chinese Korean Singaporean Taiwanese	11.0 versus 10.9[a]	27.9 versus 24.5[a]	13.7 versus 11.5[a]	10.5	4
6	Wu *et al.*, 2017 ARCHER 1050 study [31]	346	69 events/131px /170 Asian/227 dacomitinib (66 ongoing treatment) versus 107 events/128 px/176 Asian/225 gefitinib (38 on going treatment)	RCT	Chinese Japanese Korean	18.2 versus 10.9	N/A	N/A	11.5	3
7	Chang *et al.*, 2019 [38]	72 analyzed/ 177 uncommon EGFR mutation	(i) 33 afatinib versus 39 fist-gen TKIs (26 gefitinib 13 erlotinib) (ii) 19 BM afatinib versus gefitinib (iii) Coexisting common mutation	Cohort retrospective	Taiwanese	(i) 12.0 (9.5–14.5) versus 8.8 (4.8–12.8) $p = 0.163$ (ii) 10.4 (5.7–15.0) versus 6.2 (4.2–8.2) $p = 0.042$ (iii) 11.2 (5.3–17.1) versus 9.9 (8.7–11.1) $p = 0.841$	(i) 27.6 (2.1–53.1) versus 29.0 (22.8–35.2) $p = 0.334$ (ii) 11.6 (11.3–11.9) versus 31.3 (4.3–58.3) $p = 0.665$ (iii) -	N/A	8.5	N/A
8	Su *et al.*, 2020 [39]	853	(i) 99 afatinib versus 534 gefitinib (ii) 99 afatinib versus 220 erlotinib (iii) 220 erlotinib versus 534 gefitinib	Cohort retrospective	Taiwanese	N/A	Afatinib 16.1 Erlotinib 11.7 Gefitinib 11.5	N/A	7	N/A

Continued

No	ID (Author, year, study)	Number of patients studied	Comparison (*n*)	Study design	Ethnicity	Median (months)			GRACE score	JADAD score
						PFS	OS	TTF		
9	Ng *et al*., 2021 [42]	107	47 afatinib versus fiirst-gen (27 gefitinib/33 erlotinib)	Cohort retrospective	Taiwanese	12.0 versus 13.0 (p = 0.360)	35.6 versus 21.4 (p = 0.016)	N/A	7	N/A
10	Park *et al*., 2021 [40]	363	102 afatinib versus first-gen (139 erlotinib/122 gefitinib)	Cohort retrospective	Korean	17.0 versus 11.2 versus 10.9	N/A	N/A	6	N/A
11	Cheng *et al*., 2021 ARCHER 1050 study [32]	346	Dacomitinib versus gefitinib	RCT	Chinese Japanese Korean	16.5 versus 9.3	37.7 versus 29.1	12.9 versus 9.2	11.5	3
12	Mok *et al*., 2021 ARCHER 1050 study [33]	285	170 Asian/133 events/227 dacomitinib 176 Asian/152 events/ 225 gefitinib	RCT	Chinese Korean Japanese	N/A	37.7 versus 29.1	N/A	10.5	3
13	Cheng *et al*., 2021 FLAURA study [29]	136	71 osimertinib versus 65 gefitinib	RCT	Chinese	17.8 versus 9.8	33.1 versus 25.7	N/A	10.0	4

[a]All patients data.

PFS: progression free survival, OS: overall survival, TTF: time to treatment failure.

Uncommon EGFR mutation

There were 10.3% uncommon mutation frequencies among EGFR mutation-positive patients [43]. These uncommon mutations are exon 18 G179X, exon 20 S768I, and exon 21 L861Q. The use of erlotinib for L858R and gefitinib for uncommon EGFR mutations should be approached with caution [40]. Compared with first-generation EGFR TKIs, afatinib may be more appropriate [45]. A multicenter at three hospitals in Taiwan showed that afatinib may provide a better treatment response but no survival benefit compared with its alternatives. Afatinib had a longer median PFS and median OS than first-generation EGFR TKIs, but it was not statistically significant, p = 0.163 and p = 0.334, respectively. In contrast, uncommon patients with brain metastases (BMs) treated with afatinib had significantly longer median PFS and not significantly shorter OS [38]. An update revealed that both afatinib and first-generation EGFR TKIs have robust activity, with an overall response rate of 51% and longer median TTF with afatinib, with 14.3 months versus 9.8 months, respectively. It was slightly higher in Asian populations with 15.7 months and 10.4 months, respectively [57].

BM EGFR mutation

EGFR TKIs plus concurrent whole-brain radiotherapy (WBRT) could effectively control intracranial lesions and significantly improve OS in patients with BM. In combination, gefitinib had the longest OS compared to icotinib and erlotinib, but the benefit comparison is not statistically significant [47]. Instead, a multivariable analysis from a Japanese study showed that in the absence of BM before EGFR TKI therapy, erlotinib had a significant favorable PFS effect on central nervous system (CNS) progression compared to gefitinib (HR 0.321; 95% CI: 0.114–0.903; p = 0.031) (BM *vs.* no BM HR 2.54; 95% CI: 1.131–5.702; p = 0.024). In common mutation patients with BM, erlotinib more prolonged PFS compared with gefitinib, while the median PFS was longer in the gefitinib group in patients without BM [48]. Another study in Taiwan revealed that afatinib prolonged PFS and OS in relatively younger patients without BM [54].

First-generation versus second-generation EGFR TKIs

Pooling of first-generation TKI data in two studies in Taiwanese [38,42] showed no significant difference in PFS compared to afatinib (p = 0.163 and p = 0.360), but a significant difference in OS (p = 0.334 *vs*. p = 0.016). The results showed that the treatment with afatinib was 0.7 times more likely to improve PFS with 0.72 and 0.54 times higher likelihood of improving OS, respectively [38,42].

Median TTF in Taiwanese with the exon 19 deletion was significantly longer in the afatinib group compared to gefitinib and erlotinib, with 18.2 months versus 11.1 months versus 11.9 months (log-rank test, p = 0.003). Conversely, in patients with the L858R mutation, no differences were observed: afatinib 16.1 months versus gefitinib 12.0 months versus erlotinib 11.4 months (log-rank test, p = 0.187) [39]. On the other hand, the risk factor analysis of L858R versus e19del in Taiwanese NSCLC treated with EGFR TKIs which was not

Table 3. The comparative effectiveness of EGFR TKI included in the meta-analysis.

No	ID (Author, year)	Patient (*n*)	PFS (95% CI)	Patient (*n*)	OS (95% CI)	Patient (*n*)	TTF (95% CI)
Afatinib versus gefitinib/erlotinib							
1	Park *et al.*, 2016 [34]	94/88	0.76 (0.54–1.06)	Null	Null	168/182	0.82 (0.6–1.11)
	Exon 19 Del[a]	93/93	0.76 (0.55–1.06)	Null	Null	165/186	0.73 (0.54–0.99)
	Exon 21 L858R[a]	67/66	0.71 (0.48–1.06)	Null	Null	124/133	0.75 (0.53–1.07)
	Never smoke[a]	161/212	0.80 (0.58–1.10)	Null	Null	195/212	0.75 (0.57–1.00)
	BM	42/51	0.76 (0.41–1.44)	Null	Null	46/51	1.14 (0.64–2.03)
2	Paz-Ares *et al.*, 2017 [35]	Null	Null	133/182	0.95 (0.67–1.33)	Null	Null
	Exon 19 Del[a]	Null	Null	127/186	0.83 (0.58–1.17)	Null	Null
	Exon 21 L858R[a]	Null	Null	99/133	0.91 (0.62–1.36)	Null	Null
	Never smoke[a]	Null	Null	146	0.92 (0.67–1.28)	Null	Null
	BM[a]	Null	Null	37	1.16 (0.61–2.21)	Null	Null
3	Chang *et al.*, 2019 [38]	33/39	0.70 (0.42–1.19)	33/39	0.72 (0.35–1.46)	Null	Null
	Uncommon mutation co	7/11	0.35 (0.15–0.79)	7/11	0.69 (0.29–1.64)	Null	Null
	Existing del 19 or L858R[a]	26/28	0.89 (0.37–2.13)	26/28	0.41 (0.11–1.54)	Null	Null
	Never smoke[a]	8/11	2.49 (1.29–4.83)	8/11	3.22 (1.41–7.35)	Null	Null
	BM						
4	Su *et al.*, 2020 [39]	Null	Null	99/534	0.67 (0.45–1.00)	99/534	0.54 (0.41–0.71)
	Exon 19 Del	Null	Null	Null	Null	53/238	0.51 (0.35–0.74)
	Exon 21 L858R	Null	Null	Null	Null	31/272	0.61 (0.37–1.20)
	Ex 21 L858R versus Ex 19 Del[a]	Null	Null	Null	Null	303/291	0.94 (0.80–1.10)
	Never smoke	Null	Null	Null	Null	64/443	0.43 (0.30–0.62)
	BM	Null	Null	Null	Null	36/174	0.45 (0.29–0.70)
5	Ng *et al.*, 2021 [42]	47/60	0.79 (0.48–1.30)	47/60	0.54 (0.33–0.89)	Null	Null
	Ex 21 L858R versus Ex 19 Del	21/16	0.79 (0.47–1.34)	21/16	1.02 (0.61–1.69)	Null	Null
	Other mutation versus Ex 19 Del	10/16	1.03 (0.46–2.31)	10/16	0.78 (0.32–1.91)	Null	Null
	Never smoke[b]	16/17	1.01 (0.59–1.71)	16/17	1.10 (0.66–1.83)	Null	Null
6	Park *et al.*, 2021 [40]	102/261	0.72 (0.55–0.94)	Null	Null	Null	Null
	Uncommon versus classical mutation	34/229	2.553 (1.715–3.802)	Null	Null	Null Null	Null Null
	Never smoke[b]	258/363	1.171 (0.976-1.405)	Null	Null		
Dacomitinib versus gefitinib/erlotinib							
1	Ramalingam *et al.*, 2014 [30]	52/58	0.88 (0.56–1.39)	89/85	0.83 (0.54–1.27)	Null	Null
	Never smoke[a]	45/59	0.93 (0.57–1.50)	79/82	0.85 (0.54–1.34)	Null	Null
2	Wu *et al.*, 2017 [31]	97/170	0.51 (0.39–0.66)	Null	Null	Null	Null
	Exon 19 Del[a]	75/134	0.55 (0.41–0.75)	Null	Null	Null	Null
	Exon 21 L858R[a]	61/93	0.63 (0.44–1.06)	Null	Null	Null	Null
	Never smoke[a]	87/147	0.51 (0.39–0.68)	Null	Null	Null	Null
3	Cheng *et al.*, 2021 [32]	97/140	0.509 (0.391–0.662)	95/115	0.759 (0.578–0.996)	121/155	0.586 (0.46–0.746)
	Exon 19 Del	56/79	0.514 (0.364–0.727)	52/61	0.857 (0.592–1.241)	Null	Null
	Exon 21 L858R	41/61	0.505 (0.337–0.758)	43/54	0.622 (0.415–0.931)	Null	Null
	Never smoke	62/95	0.436 (0.314–0.605)	61/76	0.739 (0.528–1.036)	Null	Null
4	Mok *et al.*, 2021 [33]	Null	Null	95/115	0.759 (0.578–0.996)	Null	Null
	Exon 19 Del[a]	Null	Null	73/82	0.847 (0.618–1.161)	Null	Null
	Exon 21 L858R[a]	Null	Null	60/70	0.665 (0.470–0.941)	Null	Null
	Never smoke[a]	Null	Null	86/97	0.747 (0.559–0.999)	Null	Null
Osimertinib versus gefitinib							
Cheng	*et al.*, 2021 [29]	71/65	0.56 (0.37–0.85)	71/65	0.85 (0.56–1.29)	Null	Null
	Exon 19 Del	36/33	0.41 (0.22–0.77)	36/33	0.61 (0.32–1.18)	Null	Null
	Exon 21 L858R	35/32	0.69 (0.39–1.21)	35/32	1.02 (0.59–1.78)	Null	Null
	Never smoke	53/50	0.53 (0.32–0.86)	53/50	0.94 (0.57–1.55)	Null	Null
Erlotinib versus gefitinib							
1	Otsuka *et al.*, 2015 [37]	35/9	0.3 (0.11–0.87)	Null	Null	Null	Null
2	Su *et al.*, 2020 [39]	Null	Null	534/220	0.66 (0.52–0.85)	534/220	0.88 (0.73–1.05)
	Exon 19 Del	Null	Null	Null	Null	238/86	0.81 (0.61–1.09)
	Exon 21 L858R	Null	Null	Null	Null	272/129	0.93 (0.73–1.20)
	Never smoke	Null	Null	Null	Null	443/153	0.75 (0.60–0.93)
	BM	Null	Null	Null	Null	174/123	0.66 (0.51–0.85)

[a]All patients data.

[b]Smoking status/smoking history.

PFS = progression free survival, OS = overall survival, TTF = time to treatment failure, BM = brain metastasis.

statistically significant revealed that L858R had a 6% lower risk of treatment failure and a 21% lower risk of progression than e19del, with HR 0.94 (0.80–1.10; $p = 0.413$) and 0.79 (0.47–1.34; $p = 0.381$), respectively. And those had the same risk of survival, HR 1.02 (0.61–1.69; $p = 0.951$) [39,42].

The LUX lung 7 trial was the only RCT comparing afatinib with first-generation TKI. It showed that the median PFS of afatinib and gefitinib was 11.0 months with an HR of 0.76. The median TTF of afatinib and gefitinib were 13.2 and 11.4 months with HR 0.82. The OS comparing afatinib and gefitinib was 0.95 [34,35]. Afatinib was significantly associated with longer PFS and showed consistent efficacy across all EGFR mutation types, although a recent multivariate analysis showed that a specific TKI regimen was not associated with better PFS in a specific EGFR mutation type [40].

Four studies in Indonesia showed efficacy between first- and second-generation EGFR TKIs. Their different results prompted further investigation. There was no difference in efficacy between gefitinib and erlotinib [50] and both have similar efficacy [53]. Afatinib tends to be associated with longer PFS [53]. Compared to gefitinib, afatinib had a significantly longer median PFS but did not have a significantly longer OS [59]. In contrast, Fitri *et al.* [55], revealed that gefitinib had a longer median PFS than erlotinib and afatinib.

In the same way, a comparison of the irreversible second-generation TKIs, dacomitinib versus gefitinib, showed that dacomitinib's OS advantage persisted with longer follow-up and dose reduction (HR = 0.759, $p = 0.0457$). A significant improvement in OS was observed in patients with the L858R (HR = 0.622, $p = 0.0203$). In patients with e9del, no significance was reached ($p = 0.3021$), although longer OS was observed (HR = 0.857) [32,33]. Dacomitinib treatment significantly improved PFS over gefitinib, 0.43 times higher (95% CI: 0.32–0.59) [31]. Dacomitinib was not superior to erlotinib in unselected advanced NSCLC (HR 0.941, $p = 0.229$) or KRAS wild-type tumors (HR 1.022, $p = 0.587$) [30].

First-generation versus third-generation EGFR TKIs

As with the reversible second-generation TKI, osimertinib showed a clinically meaningful PFS benefit compared to gefitinib, HR 0.56 (95% CI: 0.37–0.85). Subgroup analyses revealed significant PFS in e19del (HR 0.41 95% CI: 0.22–0.77) and not significant in L858R (HR 0.69 95% CI: 0.39–1.21). However, OS was not significant in common aberrations, HR 0.61 95% CI: 0.32–1.18 and HR 1.02 95% CI: 0.59–1.78, respectively [29].

The HR data representing the comparative effectiveness of first-, second-, and third-generation EGFR TKIs are presented in Table 3.

Meta-analysis of first-generation versus second-generation EGFR TKIs

The forest plot and reference table of CER between afatinib and gefitinib/erlotinib are presented in Figure 2 which favors afatinib in PFS, OS, and TTF. Uncertainty was found due to the upper bound of the pooled HR 0.66 (0.44–1.00) for afatinib in TTF as data from two studies, while the evidence for PFS and OS were more robust when compared to TTF. Treatment with afatinib was associated with a 26% lower risk of progression and a 27% lower risk of death, with HR 0.74 (0.61–0.88) and 0.73 (0.57–0.94), respectively.

Moreover, the CER of dacomitinib, with no data in TTF is shown in Figure 3 which favors dacomitinib in PFS and OS. There was no variation in effect estimates beyond change found in OS due to significant association ($p = 0.004$) and nonsubstantial heterogeneity ($p = 0.93$; I^2 0%).

Meta-analysis results of clinical outcomes comparing afatinib and dacomitinib toward gefitinib/erlotinib are presented in Table 4. It showed that the pooled HR of the second generation of EGFR TKIs versus gefitinib/erlotinib in PFS and OS had a significant overall effect ($p < 0.05$). A substantial heterogeneity (I^2>50%) was observed for TTF in afatinib versus gefitinib/erlotinib and PFS in dacomitinib versus gefitinib/erlotinib. For all survival outcomes, the comparative effectiveness results favor the second generation.

We used a random effects model for subgroup analysis of EGFR mutation type to see if the comparative effect of comparison would vary and show similarity in characteristics, including smoking, BM, and ethnicity to explore the source of substantial heterogeneity. The results of the subgroup analysis are presented in Table 5.

Although there was no significant overall effect ($p = 0.42$) in the efficacy comparison results between afatinib and the first-generation EGFR TKIs in terms of OS. Interestingly, our results showed that patients with BM had significant heterogeneity ($p = 0.06$; I^2 73%). Therefore, there is a significant overall effect in terms of PFS ($p = 0.02$) and TTF ($p < 0.00001$) with also significant heterogeneity in patients with BM ($p = 0.010$; I^2 85%) and ($p = 0.01$; I^2 84%), respectively. Potential sample overlap in the ARCHER 1050 study [31–33] may have contributed to the nonsubstantial heterogeneity in the subgroup analysis of the overall comparison of dacomitinib versus gefitinib/erlotinib on PFS and OS, ($p = 0.97$; I^2 0%) and ($p = 0.51$; I^2 0%), respectively.

As detailed in Table 5, patients with BM had a 37% higher risk of progression and an 87% higher risk of death when treated with afatinib compared to gefitinib/erlotinib. However, remarkably, there was a 30% lower risk of TTF with afatinib compared to gefitinib/erlotinib.

As a result, as shown in Table 5, the meta-analysis revealed that in never-smoking NSCLC EGFRm+ patients, there was significant heterogeneity in the comparative efficacy results between afatinib and the first-generation EGFR TKIs only for TTF ($p = 0.02$; I^2 83%). In addition, there was heterogeneity only in PFS ($p = 0.04$; I^2 69%) in the comparative efficacy results between dacomitinib and the first-generation EGFR TKIs. These patients treated with afatinib had a 0.42-fold lower risk of TTF and a 0.08-fold longer OS, but an equal risk of PFS. When treated with dacomitinib, they had a 0.4-fold lower risk of progression and a 0.3-fold lower risk of death compared to gefitinib/erlotinib.

In addition, in Table 5, the meta-analysis showed that patients with exon 19 deletion or exon 21 substitution aberrations benefited more from the second generation of EGFR TKIs than gefitinib/erlotinib. There was significant heterogeneity (I^2 53%)

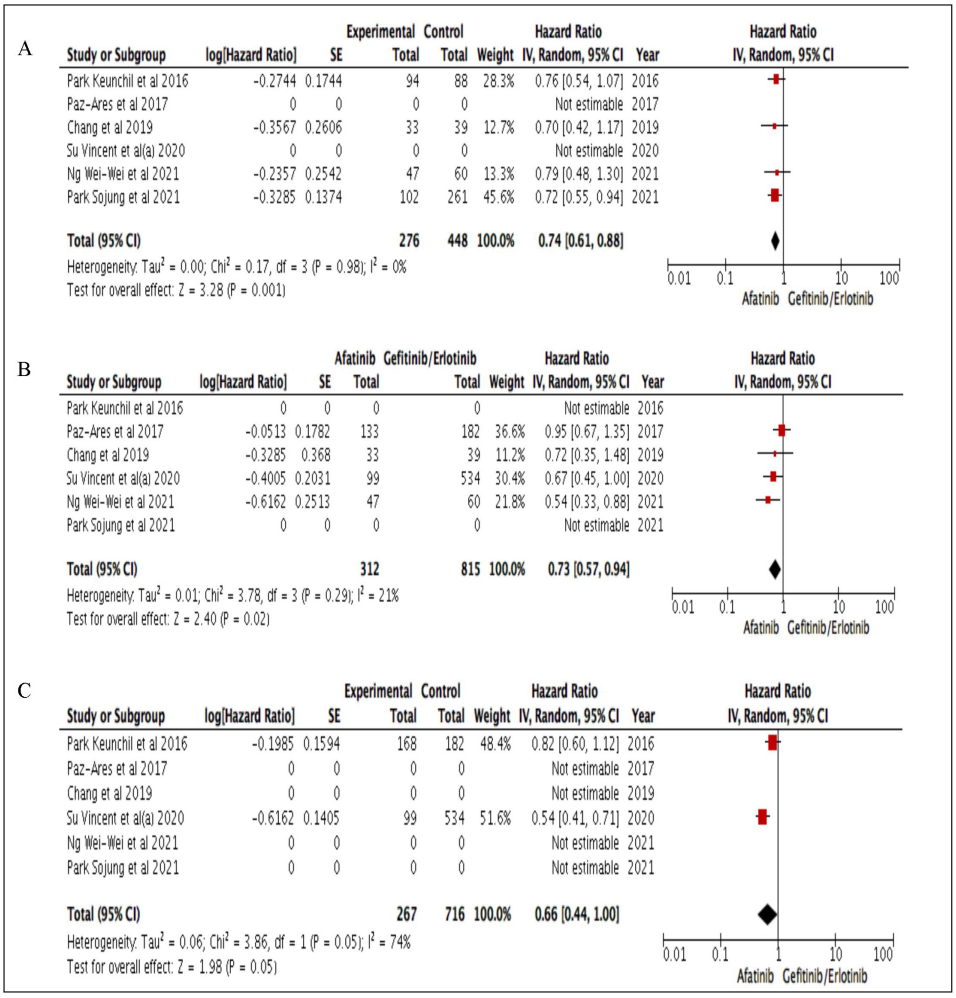

Figure 2. Table and Forest plot of comparative effectiveness results of afatinib and gefitinib/erlotinib survival outcome within studies conducted in Asia. A. PFS; B. OS; C. TTF.

only in the efficacy comparison results between afatinib and the first-generation EGFR TKIs for TTF in patients with e19del. Afatinib had a 0.3-fold lower risk of treatment failure compared to gefitinib/erlotinib (HR 0.62; 95% CI: 0.44–0.88; $p = 0.008$) (HR 0.7; 95% CI: 0.53–0.93; $p = 0.01$) in patients with e19del and L858R, respectively. Dacomitinib had a half lower risk of progression compared to gefitinib/erlotinib in both patients with e19del and L858R. Dacomitinib had a lower risk of death in both e19del and L858R patients, with a 0.15-fold lower risk and a 0.35-fold lower risk, respectively, compared to gefitinib/erlotinib. As tabulated in Table 3, they had a 0.3-fold lower risk of progression when treated with afatinib compared with gefitinib/erlotinib, (HR 0.76; 95% CI: 0.55–1.06) (HR 0.71; 95% CI: 0.48–1.06) in e19del and L858R patients, respectively [34]. In addition, OS was 0.3-fold longer in patients with an uncommon mutation with coexisting e19del or L858R [38]. It should be noted that afatinib treatment in uncommon mutation versus common mutation patients had a 2.5-fold higher risk of progression [40].

Furthermore, there was no significant overall effect ($p = 0.25$) between the Korean and Taiwanese populations comparing afatinib and the first-generation EGFR TKIs, pooled HR 0.84 (95% CI: 0.62–1.13) as presented in Table 5. Interestingly, our results revealed significant statistical heterogeneity in overall effect ($p = 0.003$; I^2 72%) and subgroup differences ($p = 0.002$; I^2 83.5%). Although afatinib had significantly a 0.4-fold lower risk of death in Korean and Taiwanese (HR 0.62; 95% CI: 0.45–0.84; $p = 0.002$), there was no significant heterogeneity (I^2 0%, $p = 0.5$).

DISCUSSION

In this systematic review, we present all previously published EGFR TKI studies in lung oncology. We identified a large qualified number of published CER studies. However, one-third of these studies varied in their overall quality score measured with the GRACE checklist, but there was no statistically significant difference in mean GRACE score between multicenter and single-center studies. Therefore, the center design did not significantly affect the quality of this CER study.

Only one-sixth of the identified results could be further analyzed as an effectivity comparison of EGFR TKIs.

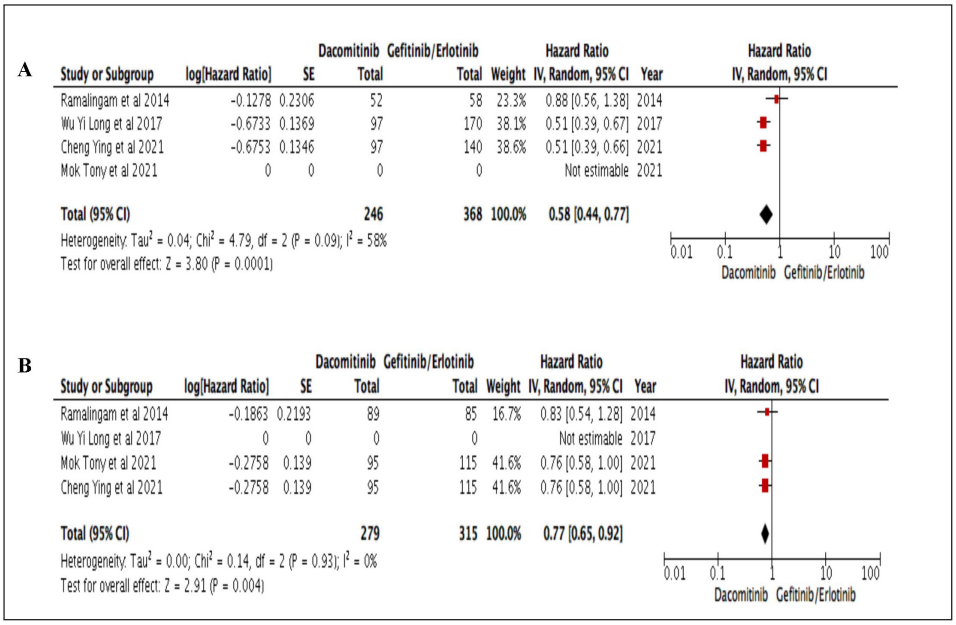

Figure 3. Table and Forest plot of comparative effectiveness results of dacomitinib and gefitinib/erlotinib survival outcome within studies conducted in Asia. A. PFS; B. OS.

Table 4. Meta-analysis result of effectiveness comparison of afatinib and dacomitinib for gefitinib/erlotinib.

CER	Sample size		Association test			Heterogeneity test		Model
	Case	Control	HR (95% CI)	*Z*	*p*-value	*p*-value	I^2 (%)	
Afatinib versus gefitinib/erlotinib								
PFS	276	448	0.74 (0.61–0.88)	3.27	0.001	0.98	0	R
OS	312	815	0.73 (0.57–0.94)	2.40	0.02	0.29	21	R
TTF	267	716	0.66 (0.44–1.00)	1.98	0.05	0.05	74	R
Dacomitinib versus gefitinib/erlotinib								
PFS	246	368	0.58 (0.44–0.77)	3.80	0.0001	0.09	58	R
OS	279	315	0.77 (0.65–0.92)	2.91	0.004	0.93	0	R

PFS: progression free survival, OS: overall survival, TTF: time to treatment failure, HR: hazard ratio, R: random model; a heterogeneity were used to determine whether fixed or random model would be applied.

Since there is a clear difference in EGFR mutation frequencies between Asian and non-Asian NSCLC patients [16–20], we compared the efficacy of EGFR TKI as a first-line therapy in Asian populations with common and uncommon mutations.

The Chinese and Korean ethnic groups were the most involved in this result, and gefitinib was the most compared to other EGFR TKIs.

A narrative review found that Japanese patients are strongly affected by second-generation EGFR-TKIs, and more Asian studies are needed to confirm whether osimertinib is best used in first- or second-line treatment [10]. The Chinese Thoracic Oncology Group (CTONG) 0901 study revealed that patients with e19del had better outcomes than those with L858R. Equally important in terms of safety, a meta-analysis revealed that the overall incidence of adverse events with afatinib was similar to erlotinib, but higher than with gefitinib. Afatinib caused more diarrhea than gefitinib or erlotinib. Afatinib compared to gefitinib caused more rash but less liver dysfunction, although afatinib compared to erlotinib caused more stomatitis but less rash [60].

The activity of EGFR TKIs varies by EGFR type of mutation. Uncommon EGFR mutations are heterogeneous and represent a distinct subset of classic mutations with variable responses to EGFR TKIs. Uncommon EGFR mutations such as G719X, L861Q, and S768I are highly heterogeneous in both composition and sensitivity. Mixed mutations are common in patients with EGFRm+ NSCLC. In a real-world setting, EGFR TKI was the preferred treatment option in patients with EGFR aberrations. The use of second- and first-generation TKIs in patients with EGFRm+ should be used with caution based on mutation identification results. An appropriate sequencing of EGFR TKI will maximize clinical outcome benefit [61]. The risk for progression was 2.55 times higher for patients with uncommon mutations on afatinib treatment compared with the first generation of TKIs [40]. Treatment with afatinib compared to pooled first-generation EGFR TKIs in uncommon mutation

Table 5. Subgroup analysis of effectiveness comparison (using random model effect).

Model	Subgroup	HR (95% CI)	Overall effect		Heterogeneity		Subgroup differences	
			Z	*p*-value	*p*-value	I^2 (%)	*p*-value	I^2 (%)
Afatinib versus gefitinib/erlotinib								
PFS	Overall	0.90 (0.74–1.11)	0.97	0.02	0.007	60	0.07	63.1
	Never smoke	1.01 (0.81–1.21)	0.10	0.92	0.23	30		
	Brain metastasis	1.37 (0.43–4.38)	0.53	0.60	0.010	85		
OS	Overall	0.90 (0.69–1.17)	0.80	0.42	0.02	56	0.12	52.3
	Never smoke	0.93 (0.72–1.22)	0.51	0.61	0.39	0		
	Brain metastasis	1.87 (0.69–1.17)	1.23	0.22	0.06	73		
TTF	Overall	0.64 (0.54–0.75)	5.33	<0.00001	0.02	53	0.97	0
	Never smoke	0.58 (0.33–0.99)	1.99	0.05	0.02	83		
	Brain metastasis	0.7 (0.28–1.74)	0.76	0.45	0.01	84		
	Exon 19 Del	0.62 (0.44–0.88)	2.67	0.008	0.15	53		
	Exon 21 L858R	0.7 (0.53–0.93)	2.44	0.01	0.51	0		
Korean versus Taiwanese								
	Overall	0.84 (0.62–1.13)	1.15	0.25	0.003	72	0.002	83.5
	PFS never smoke	1.15 (0.97–1.37)	1.62	0.1	0.61	0		
	PFS	0.90 (0.42–1.92)	0.28	0.78	0.18	43		
	OS	0.62 (0.45–0.84)	3.07	0.002	0.5	0		
Dacomitinib versus gefitinib								
PFS	Overall	0.55 (0.49–0.62)	9.64	<0.00001	0.20	27	0.97	0
	Never smoke	0.56 (0.39–0.81)	3.06	0.002	0.04	69		
	Exon 19 Del	0.53 (0.43–0.67)	5.47	<0.00001	0.77	0		
	Exon 21 L858R	0.57 (0.44–0.75)	4.08	<0.0001	0.42	0		
OS	Overall	0.76 (0.69–0.85)	5.06	<0.00001	0.97	0	0.51	0
	Never smoke	0.76 (0.63–0.93)	2.69	0.007	0.87	0		
	Exon 19 Del	0.85 (0.67–1.08)	1.32	0.19	0.96	0		
	Exon 21 L858R	0.65 (0.50–0.84)	3.25	0.001	0.81	0		

PFS: progression free survival, OS: overall survival, TTF: time to treatment failure, HR: hazard ratio.

with co-existing e19del or L858R had a 0.65-fold lower risk of progression than without co-existing mutations and the survival had a 0.3-fold lower risk [38]. Again, the survival of the e19del mutation group was 0.2-fold lower than the other EGFR mutations [42]. A narrative review revealed a similar result, showing a favorable outcome of afatinib compared to first-generation TKIs. While afatinib was active against L861Q, S768I, or G719X, there were no significant differences between gefitinib and erlotinib in OS, but patients had a much longer median PFS. These patients had a median PFS similar to those with L858R, but shorter than those with e19del [62]. A recent systematic review identified a need for improvement in the detection and reporting of EGFR mutations due to the heterogeneity of uncommon mutations and differential sensitivity to afatinib [63].

Furthermore, this meta-analysis showed that L858R has a higher risk of short survival, PFS, and OS than e19del when treated with second generation compared with gefitinib/erlotinib. A recent systematic review found that e19del patients have a better OS than L858R patients due to the higher incidence of EGFR T790M in NSCLC after progression on first- or second-generation EGFR TKIs [64]. In addition, afatinib had a 0.04–0.08-fold higher risk of treatment failure, and dacomitinib had a 0.05–0.2-fold lower risk of survival (progression and death) than first generation. This is similar to the Taiwanese finding that L858R patients had a 0.2-fold longer time to progression (HR 0.79; 95% CI: 0.47–1.34) but similar OS (HR 1.02; 95% CI: 0.61–1.69) compared to e19del when treated with afatinib than with gefitinib or erlotinib [42]. However, erlotinib had a 0.1-fold difference lower risk of TTF compared with gefitinib in patients with e19del or L858R, (HR 0.51; 95% CI: 0.35–0.74) (HR 0.61; 95% CI: 0.37–1.20), respectively [39]. A review of Chinese patients with EGFRm+ NSCLC revealed that afatinib was effective and well-tolerated as a first-line treatment, suggesting osimertinib as a second-line option [61]. Narrative reviews in the Asian population suggested that efficient molecular diagnostic services were paramount to

consider sequential therapy of osimertinib because it found that e19del mutation had positive testing for the T790M [40,62].

In never-smoking EGFRm+ NSCLC patients, second-generation EGFR TKIs conferred longer survival compared with first-generation EGFR TKIs. Conversely, in patients with BM, our results showed that first-generation EGFR TKIs conferred a lower risk of disease progression and death but a higher risk of TTF, regardless of EGFR mutation type. Concurrent EGFR TKI therapy and WBRT effectively controlled intracranial lesions.

In comparison to other published Asian reviews [10,61,62], this review conducted a meta-analysis that assessed the comparative efficacy outcome of EGFR TKI generation as a first-line therapy with EGFR aberrant among the Asian population. The two narrative reviews published in 2021 [10,62] collated data and did not provide qualitative or quantitative analysis. Notably, the clinical outcomes of PFS, OS, and as well as TTF were reported. A review published in 2020 was limited to the Chinese population [61]. This current systematic review has several strengths. First, it summarized the direct evidence concerning the comparative effectiveness results of EGFR TKIs from the majority of studies conducted with an RCT method design, that had appraised the data quantitatively. Second, it is a systematic search result of several databases and a comprehensive dataset, thus allowing us to obtain precise estimates and conduct meta-analysis. Third, it showed statistically there was heterogeneity between studies in comparing afatinib and first generation of EGFR TKIs, with *p*-values of 0.007, 0.02, and 0.02 on overall PFS, OS, and TTF, respectively.

The main limitation of this study is the unavailability of complete clinical outcomes according to the study criteria to compare efficacy between second- and first-generation agents. This prevents us from drawing a firm survival conclusion on the comparative efficacy of osimertinib, among first-generation, and common-uncommon comparison. Another limitation of the present work is the lack of data on adverse events, mainly because most of the included studies did not report them separately. Our findings due to the limited number of included studies comparing the efficacy of EGFR TKIs in Asian ethnicities should be clarified by other studies that include the number of studies and more diverse ethnic results.

CONCLUSION

In summary, we conclude that patients with common mutations survive longer on EGFR TKIs than those with uncommon. From the forest plot and survival risk meta-analysis, second-generation TKIs offer more favorable survival outcomes than first-generation agents, particularly in patients with e19del or L858R mutations.

L858R has a higher risk of survival, progression-free survival, and overall survival than e19del on second-generation agents. Afatinib treatment in uncommon mutations with coexisting e19del or L858R was associated with longer progression than without coexistence. There should be a comparison between ethnic groups in the Asian population with regard to EGFR TKIs CER.

AUTHOR CONTRIBUTIONS

EK conceived CER as a systematic review. MW performed the study search and got data extraction with reference tracking then approved by EK. MW calculated the data for the meta-analysis, furthermore, the results were checked by RD and confirmed by DE. MW prepared this manuscript. EK, SH, and DE revised the manuscript critically for important intellectual content and gave final approval for the version to be published. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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LIST OF ABBREVIATIONS

BM, brain metastases; CI, confidence interval; EGFR TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; EGFRm+, epidermal growth factor receptor mutation-positive; GRACE, good research for comparative effectiveness; HR, hazard ratio; LC, lung cancer; NCCN, national comprehensive cancer network; NSCLC, nonsmall cell lung cancer; OS, overall survival; PICO, population intervention comparison outcome; PFS, progression-free survival; SD, standard deviation; TTF, time to treatment failure.

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APPENDIX

Appendix can be downloaded from the link [https://japsonline.com/admin/php/uploadss/4240_pdf.pdf]