

# Efficacy of pemetrexed-based regimens in advanced non–small cell lung cancer patients with activating epidermal growth factor receptor mutations after tyrosine kinase inhibitor failure: a systematic review

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**Abstract:** Pemetrexed-based chemotherapy regimens (pem regimens) are the standard first-line treatment option in patients with non-squamous non–small cell lung cancer (NSCLC). The objective of this systematic review was to assess the efficacy of pemetrexed in the context of epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC following the failure of *EGFR*–tyrosine kinase inhibitor (TKI) treatment. We searched biomedical literature databases (PubMed, EMBASE, and the Cochrane library) and conference proceedings for studies evaluating the efficacy of pemetrexed monotherapy or pemetrexed combined with platinum or any other chemotherapeutic agent in *EGFR*–mutation-positive NSCLC after *EGFR*–TKI failure. We extracted data of primary outcomes of interest (progression-free survival [PFS], overall survival [OS], and overall response rate [ORR]). The weighted median PFS, OS, and ORR were then calculated. Of 83 potentially relevant studies, eight (three randomized studies and five retrospective studies) were identified (involving 1,193 patients) and included in this systematic review, with 640 patients receiving pem regimens. The weighted median PFS, median OS, and ORR for patients treated with pem regimens were 5.09 months, 15.91 months, and 30.19%, respectively. Our systematic review results showed a favorable efficacy profile of pem regimens in NSCLC patients with *EGFR* mutation after *EGFR*–TKI failure.

**Keywords:** pemetrexed, advanced non–small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor

## Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide for both men and women.<sup>1,2</sup> Non–small cell lung cancer (NSCLC) is the most common subtype, accounting for approximately 80%–85% of all lung cancers.<sup>1,2</sup> Most patients with NSCLC are diagnosed at advanced stages (IIIB and IV) of the disease, with only 16%–30% diagnosed at early stages.<sup>1–3</sup> Patients diagnosed with advanced NSCLC generally have a poor prognosis, with a median survival of 8–10 months as well as 2- and 5-year survival rates of approximately 20% and 15%, respectively.<sup>1,3,4</sup>

The standard treatment for NSCLC includes platinum-based doublet chemotherapy, which increases the survival time and quality of life of patients with advanced-stage disease.<sup>5</sup> However, the discovery of activating mutations in the kinase domain of the epidermal growth factor receptor (*EGFR*) gene in a subset of NSCLC cases has led

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to the development of new targeted therapeutic approaches. *EGFR*-tyrosine kinase inhibitors (TKIs) are now the preferred first-line therapy for patients with advanced non-squamous NSCLC with activating *EGFR* mutations, with randomized clinical studies confirming the superiority of *EGFR*-TKIs to traditional chemotherapy regimens in terms of the overall response rate (ORR), progression-free survival (PFS), and quality of life score.<sup>1,5,6</sup> Several clinical studies have indicated that *EGFR*-TKIs are not recommended for patients with *EGFR*-mutation-negative NSCLC.<sup>7</sup> In addition, although *EGFR*-TKIs are associated with an initially high tumor response rate in *EGFR*-mutation-positive NSCLC, the development of resistance to TKIs is inevitable and the majority of patients receiving *EGFR*-TKIs experience disease progression after 9–13 months of treatment.<sup>8,9</sup>

The most common cause of acquired resistance to *EGFR*-TKIs is the development of a secondary mutation in *EGFR*, threonine 790 to methionine (T790M), which accounts for approximately 50% of cases that progress after *EGFR*-TKI treatment.<sup>10</sup> The presence of the T790M variant prevents the binding of *EGFR*-TKIs to *EGFR*, which results in impairment of *EGFR*-TKI-mediated inhibition.<sup>8–10</sup> A third-generation *EGFR*-TKI, osimertinib, has been shown to be an effective treatment for patients with the *EGFR* T790M mutation.<sup>8</sup> Chemotherapy is the primary treatment option for patients who do not have the T790M mutation and experience progression after first-line *EGFR*-TKI.<sup>2</sup> However, the optimal chemotherapeutic regimens for *EGFR*-mutation-positive cases after *EGFR*-TKI failure are not well understood.

Pemetrexed – an anti-folate cytotoxic agent – is effective in the treatment of patients with advanced non-squamous NSCLC and has a favorable safety profile.<sup>11,12</sup> Pemetrexed is indicated for use in the first-line, maintenance, and second-line settings for patients with non-squamous NSCLC,<sup>11–13</sup> in addition, it was found to be effective and well tolerated in patients with NSCLC after *EGFR*-TKI failure.<sup>14</sup> Among many chemotherapeutic drugs that are widely used for lung cancer, pemetrexed is the preferred candidate in patients with non-squamous NSCLC who have *EGFR* mutations because of its low toxicity and relatively good efficacy.<sup>15</sup> To better understand the efficacy of pemetrexed in this latter setting, we conducted a systematic review, searching the relevant literature and assessing the evidence supporting pemetrexed-based regimens (pem regimens) in NSCLC patients after *EGFR*-TKI failure. The objective of this systematic review was to assess the efficacy of pemetrexed in the context of *EGFR*-mutation-positive NSCLC following the failure of *EGFR*-TKI treatment.

## Materials and methods

### Search strategy

A comprehensive literature search was undertaken to identify published studies that evaluated pemetrexed monotherapy or combination therapy with pemetrexed and platinum or another chemotherapeutic agent in *EGFR*-mutation-positive NSCLC after *EGFR*-TKI failure. The PubMed, EMBASE, and Cochrane databases were searched for relevant trials. The search strategy included the following term combination, without restrictions on language and sex: “pemetrexed,” “NSCLC,” “non–small cell lung cancer,” “TKI failure,” “gefitinib failure,” “afatinib failure,” “erlotinib failure,” and “icotinib failure.” Additional searches through Google Scholar were conducted. Moreover, bibliographies and citation sections of retrieved articles were reviewed for additional pertinent studies. An initial review of the title and abstract of these studies was conducted to exclude irrelevant studies. The full texts of the remaining articles were read to extract information on the topic of interest. Abstracts of research presented at related conferences (American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO], and American Association for Cancer Research [AACR]) were also searched.

Two of the authors conducted the search independently, with no language or date restrictions set. These two authors – who were not blinded to the names of original researchers, journals, or institutions – independently checked the titles, abstracts, and keywords from the searches to identify potentially eligible studies. Upon obtaining the full texts of potentially eligible studies, the same two authors conducted an independent study selection; disagreements were resolved by consensus and, if necessary, by consultation with a third reviewer.

### Selection criteria

To be eligible for inclusion, studies had to meet all of the following criteria: 1) the study population included patients with advanced non-squamous NSCLC who have activating *EGFR* mutations; 2) the study population included NSCLC patients with acquired resistance or progression after *EGFR*-TKIs; 3) studies evaluated the efficacy of pemetrexed monotherapy or pemetrexed combined with platinum/other chemotherapeutic agent(s); and 4) studies reported outcomes of interest (PFS, overall survival [OS], and ORR).

### Data extraction

Data were extracted using a standardized collection process. The following information was extracted from each selected

study: 1) first author's last name, year of publication, and nationality of the population studied; 2) study design; 3) intervention type/treatment arms; 4) number of patients per treatment arm/group; and 5) outcomes of interest (PFS, OS, and ORR).

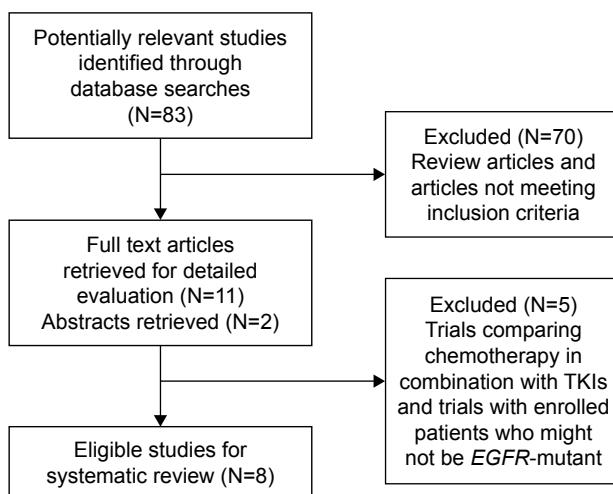
## Statistical analysis

The median PFS, median OS, and ORR for each regimen were extracted and classified for the pem regimen group and the non-pemetrexed-based chemotherapy (non-pem) regimen group. Pooled median PFS, median OS, and ORR were calculated with sample size as weight for each group. However, no formal statistical comparison was conducted to compare regimen groups due to lack of sufficient data.

## Results

### Search results

Figure 1 represents the selection process for clinical studies included in this systematic review. A total of 83 potentially relevant studies were identified through database searches, of which 75 were considered ineligible because they did not meet the specified inclusion criteria. Eight studies<sup>1,5,6,9,16–19</sup> (published between 2014 and 2017) met the eligibility criteria for this systematic review and were subjected to data evaluation. Of the eight eligible studies, one was published in abstract form at the ASCO and the remaining seven were published as full-text articles. Three were randomized controlled trials (two Phase III studies and one Phase II study), and five were retrospective observational studies. All studies included in the systematic review are summarized in



**Figure 1** Flowchart representing the selection process of clinical studies in the systematic review.

**Abbreviations:** EGFR, epidermal growth factor receptor; N, number of studies; TKI, tyrosine kinase inhibitor.

Table 1. In all of the eight studies, the majority of patients with *EGFR*-mutation-positive NSCLC had been previously treated with gefitinib and erlotinib and had subsequently developed resistance. Of the eight studies, two were conducted globally, three were in Taiwan, and three in Korea. A total of 1,193 patients participated in the eight studies. Of the patients with *EGFR*-mutation-positive NSCLC who experienced resistance or disease progression after *EGFR*-TKI treatment, 640 received pem regimens and 97 received non-pem regimens. For the pem regimen group, data from 640 patients (eight studies), 343 patients (five studies), and 606 patients (seven studies) were available to evaluate PFS (Table 2), OS (Table 3), and ORR (Table 4), respectively. For the non-pem regimen group, data for 97 patients (three studies) are included to evaluate PFS (Table 2) and OS (Table 3), and data for 71 patients (two studies) are included to evaluate ORR (Table 4).

### Progression-free survival analysis

All eight studies reported PFS in patients treated with pemetrexed monotherapy or a combination of pemetrexed with platinum-based regimens. Only three studies<sup>1,5,19</sup> evaluated pemetrexed monotherapy (n=114), with PFS ranging from 2.7 to 6.4 months. Seven studies<sup>5,6,9,16–19</sup> evaluated the combination of pemetrexed with platinum-based regimens (n=526), with PFS ranging from 4.4 to 6.4 months. Weighted median PFS for patients treated with pemetrexed monotherapy and those treated with a combination of pemetrexed with platinum-based regimens was between 4.75 and 5.16 months, respectively. Pemetrexed – either alone or in combination with other chemotherapy regimens – was effective among NSCLC patients with *EGFR* mutations who experienced resistance or disease progression after failure of *EGFR*-TKI treatment, with PFS ranging from 2.7 to 6.4 months and a weighted median PFS of 5.09 months (Table 2). Three studies<sup>1,16,17</sup> directly compared the PFS data of pem regimens (n=148) versus non-pem regimens (n=97) in NSCLC patients with *EGFR* mutations who experienced resistance or disease progression after failure of *EGFR*-TKI treatment (Table 2). In all three studies, median PFS was longer for the pem regimens as compared to the non-pem regimens (Table 2). In two studies,<sup>1,16</sup> pemetrexed-based chemotherapy significantly extended PFS in *EGFR*-mutant NSCLC patients who failed first-line treatment with *EGFR*-TKIs (Park et al<sup>1</sup>: hazard ratio [HR] [95% CI] = 0.54 [0.34, 0.86], *p*=0.009; Yang et al<sup>16</sup>: 0.47 [0.26, 0.84], *p*=0.0101). Furthermore, Tseng et al<sup>17</sup> showed numerically longer PFS in NSCLC patients treated with pem regimens (median 4.7 months) compared to non-pem

**Table 1** Characteristics of studies included in the systematic review

Study	Study design	Previous EGFR TKIs	Intervention type		Sample size (EA, CA)
			EA	CA	
Yang et al <sup>16</sup>	Retrospective	Gefitinib, erlotinib	Pemetrexed + platinum	Non-pem platinum doublet	60 (34, 26)
Park et al <sup>1</sup>	Retrospective	Gefitinib, erlotinib	Pemetrexed	Non-pem platinum doublet	83 (37, 46)
Soria et al <sup>6</sup>	Randomized Phase III trial	Gefitinib	Gefitinib + pemetrexed + cisplatin (maximum of six cycles)	Pemetrexed + cisplatin (maximum of six cycles)	265 (133, 132)
Yoo et al <sup>19</sup>	Randomized Phase II trial	EGFR TKI (not specified)	Pemetrexed + cisplatin (four cycles) – pemetrexed maintenance	Pemetrexed (until progressive disease)	96 (48, 48)
Tseng et al <sup>18</sup>	Retrospective	Gefitinib, erlotinib, and afatinib	Pemetrexed + platinum	Pemetrexed + platinum as first-line therapy	105 (61, 44)
Tseng et al <sup>17</sup>	Retrospective	Gefitinib, erlotinib, and afatinib	Pem chemotherapy – pemetrexed + platinum	Non-pem platinum doublet or single agent	102 (77, 25)
Mok et al <sup>9</sup>	Randomized Phase III trial	Gefitinib, erlotinib, and afatinib	Osimertinib	Platinum – pemetrexed + pemetrexed maintenance	419 (279, 140)
Lee et al <sup>5</sup>	Retrospective	Gefitinib, erlotinib, and afatinib	Pemetrexed + platinum (maintenance pemetrexed after four cycles of pemetrexed + platinum)	Pemetrexed maintenance	63 (34, 29)

**Abbreviations:** CA, control arm; EA, experimental arm; EGFR, epidermal growth factor receptor; Pem, pemetrexed-based; TKI, tyrosine kinase inhibitor.

regimens (median 3.3 months). Overall, the weighted median PFS was numerically longer in patients treated with pemetrexed (5.09 months) than in patients receiving non-pem regimens (3.23 months; Table 2).

## Overall survival analysis

Similar results to those of PFS were reported for OS. Five studies<sup>1,5,6,16,17</sup> reported OS in patients treated with pemetrexed monotherapy or a combination of pemetrexed with

**Table 2** Median PFS of pemetrexed-based regimens and non-pemetrexed-based regimens in published studies

Study	Pem regimens (number of patients) N=640	Non-pem regimens (number of patients) N=97	Median PFS (months)		HR (95% CI), p-value (pem vs non-pem regimens)
			Pem regimens	Non-pem regimens	
Soria et al <sup>6</sup>	Pemetrexed + cisplatin (132)	–	5.4	–	–
Yoo et al <sup>19</sup>	Pemetrexed + cisplatin (48)	–	5.4	–	–
Yoo et al <sup>19</sup>	Pemetrexed (48)	–	6.4	–	–
Tseng et al <sup>18</sup>	Pemetrexed + platinum (61)	–	6.1	–	–
Park et al <sup>1</sup>	Pemetrexed (37)	Non-pem platinum doublet (46)	4.2	2.7	0.54 (0.34–0.86), p=0.009
Yang et al <sup>16</sup>	Pemetrexed + platinum (34)	Non-pem platinum doublet (26)	6.4	4.1	0.47 (0.26–0.84), p=0.0101
Tseng et al <sup>17</sup>	Pemetrexed + platinum (77)	Non-pem platinum doublet (25)	4.7	3.3	p=0.62 <sup>a</sup>
Lee et al <sup>5</sup>	Pemetrexed + platinum (34)	–	5.2	–	–
Lee et al <sup>5</sup>	Pemetrexed (29)	–	2.7	–	–
Mok et al <sup>9</sup>	Platinum + pemetrexed (140)	–	4.4	–	–
Weighted median PFS (months)			5.09	3.23	

**Notes:** p-value was calculated based on log-rank test. “–” indicates data not available in included studies. <sup>a</sup>HR and CI are not available in the full-text article.

**Abbreviations:** CI, confidence interval; HR, hazard ratio; N, total number of patients; Pem, pemetrexed-based; PFS, progression-free survival.

**Table 3** Median OS of pemetrexed-based regimens and non-pemetrexed-based regimens in published studies

Study	Pem regimens (number of patients) N=343	Non-pem regimens (number of patients) N=97	Median OS (months)		HR (95% CI), p-value (pem vs non-pem regimens)
			Pem regimens	Non-pem regimens	
Soria et al <sup>6</sup>	Pemetrexed + cisplatin (132)	–	17.2	–	–
Park et al <sup>1</sup>	Pemetrexed (37)	Non-pem platinum doublet (46)	15.1	11.0	0.92 (0.50–1.68) p=0.785
Yang et al <sup>16</sup>	Pemetrexed + platinum (34)	Non-pem platinum doublet (26)	19.2	14.1	0.50 (0.22–1.13), p=0.0972
Tseng et al <sup>17</sup>	Pemetrexed + platinum (77)	Non-pem platinum doublet (25)	15.1	8.1	p=0.168 <sup>a</sup>
Lee et al <sup>5</sup>	Pemetrexed + platinum (34)	–	15.1	–	–
Lee et al <sup>5</sup>	Pemetrexed (29)	–	10.3	–	–
Weighted median OS (months)			15.91	11.08	

**Notes:** p-value was calculated based on log-rank test. “–” indicates data not available in included studies. <sup>a</sup>HR and CI are not available in full-text article.

**Abbreviations:** CI, confidence interval; HR, hazard ratio; N, total number of patients; OS, overall survival; Pem, pemetrexed-based.

platinum-based regimens. Only two studies<sup>1,5</sup> evaluated pemetrexed monotherapy (n=66), with OS ranging from 10.3 to 15.1 months. Four studies<sup>5,6,16,17</sup> evaluated the combination of pemetrexed with platinum-based regimens (n=277), with OS ranging from 15.1 to 19.2 months. Weighted median OS for patients treated with pemetrexed monotherapy and those treated with a combination of pemetrexed with platinum-based regimens was between 12.99 and 16.60 months, respectively. Pemetrexed – either alone or in combination

with other chemotherapy regimens – was effective among NSCLC patients with *EGFR* mutations who experienced resistance or disease progression after failure of *EGFR*-TKI treatment, with median OS ranging from 10.3 to 19.2 months and a weighted median OS of 15.91 months (Table 3).

Three studies<sup>1,16,17</sup> compared the OS data of pem regimens (n=148) versus non-pem regimens (n=97) in *EGFR*-mutation-positive NSCLC patients who experienced disease progression after *EGFR*-TKI treatment. In all three studies,

**Table 4** Overall response rates of pemetrexed-based regimens and non-pemetrexed-based regimens in published studies

Study	Pem regimens (number of patients) N=606	Non-pem regimens (number of patients) N=71	Overall response rate (%)		p-value (pem vs non-pem regimens)
			Pem regimens	Non-pem regimens	
Soria et al <sup>6</sup>	Pemetrexed + cisplatin (132)	–	34.00	–	–
Yoo et al <sup>19</sup>	Pemetrexed + cisplatin (48)	–	34.80	–	–
Yoo et al <sup>19</sup>	Pemetrexed (48)	–	17.80	–	–
Tseng et al <sup>18</sup>	Pemetrexed + platinum (61)	–	24.60	–	–
Park et al <sup>1</sup>	Pemetrexed (37)	Non-pem platinum doublet (46)	32.40	17.40	0.111
Tseng et al <sup>17</sup>	Pemetrexed + platinum (77)	Non-pem platinum doublet (25)	26.00	20.00	0.799
Lee et al <sup>5</sup>	Pemetrexed + platinum (34)	–	43.80	–	–
Lee et al <sup>5</sup>	Pemetrexed (29)	–	25.90	–	–
Mok et al <sup>9</sup>	Platinum + pemetrexed (140)	–	31.00	–	–
Weighted ORR (%)			30.19	18.32	

**Notes:** p-value was calculated based on log-rank test. “–” indicates data not available in included studies.

**Abbreviations:** N, total number of patients; ORR, overall response rate; Pem, pemetrexed-based regimen.

OS was longer following pemetrexed chemotherapy; however, the difference was not statistically significant ( $p>0.05$ ) in any of the studies (Table 3). Overall, the weighted median OS was numerically longer in patients treated with pem regimens (15.91 months) than in patients receiving non-pem regimens (11.08 months; Table 3).

## Overall response rate analysis

Similar results to those of PFS and OS were also reported for ORR. Seven studies<sup>1,5,6,9,17–19</sup> reported ORR in patients treated with pemetrexed monotherapy or a combination of pemetrexed with platinum-based regimens. Three studies<sup>1,5,19</sup> evaluated pemetrexed monotherapy (n=114 patients), with ORR ranging from 17.8% to 32.4%. Six studies<sup>5,6,9,17–19</sup> evaluated the combination of pemetrexed with platinum-based regimens involving 492 patients, with ORR ranging from 24.6% to 43.8%. Weighted ORR for patients treated with pemetrexed monotherapy and the combination of pemetrexed with platinum-based regimens was 24.6% and 31.5%, respectively. Pemetrexed – either alone or in combination with other chemotherapy regimens – was effective among NSCLC patients with *EGFR* mutations who experienced resistance or disease progression after failure of *EGFR*-TKI treatment, with ORR ranging from 17.8% to 43.8% and a weighted ORR of 30.19% (Table 4).

Two studies<sup>1,17</sup> compared the ORR data of pem regimens (n=114) versus non-pem regimens (n=71) in *EGFR*-mutation-positive NSCLC patients who experienced disease progression after *EGFR*-TKI treatment. In both studies, the ORR was higher in patients receiving pemetrexed chemotherapy; however, the difference was not statistically significant ( $p>0.05$ ) in either study (Table 4). Overall, the weighted ORR was higher in patients treated with pem regimens (30.19%) than in patients receiving non-pem regimens (18.32%; Table 4).

## Discussion

Recently, *EGFR* mutation has emerged as an important target in the treatment of patients with advanced NSCLC. Several randomized controlled clinical trials established the superiority of first-generation *EGFR*-TKIs (gefitinib or erlotinib) over chemotherapy in terms of PFS and ORR in patients with *EGFR*-mutation-positive NSCLC, with PFS ranging from 9.2 to 13.1 months and ORR ranging from 58% to 83%.<sup>20–24</sup> Unfortunately, patients who initially respond to first-generation *EGFR*-TKIs inevitably experience acquired resistance within 1–2 years.<sup>25</sup> The possible mechanisms of resistance have been investigated in several

studies and include second-site mutation (such as *EGFR* T790M mutation),<sup>26</sup> *EGFR* amplification, activation of parallel pathways (eg, MET amplification), and downstream signaling pathways (eg, PI3K/AKT/mTOR).<sup>27–29</sup> The most common mechanism of acquired resistance to the first- and second-generation *EGFR*-TKIs involves the development of an *EGFR* T790M mutation,<sup>26,27</sup> accounting for approximately 50% of *EGFR*-mutant resistance cases.<sup>26</sup> Clinical trials have been conducted for several T790M-targeting third-generation *EGFR*-TKIs. AURA3 is the first randomized, Phase III study of third-generation, oral, irreversible *EGFR*-TKI (osimertinib) versus a platinum-based pemetrexed regimen in patients with the *EGFR* T790M mutation.<sup>9</sup> In the AURA3 study, median PFS was significantly longer in patients treated with osimertinib compared to those treated with a platinum-based pemetrexed regimen (10.1 vs 4.4 months, respectively; HR [95% CI] = 0.30 [0.23–0.41];  $p<0.001$ ); a significantly higher response was observed in patients treated with osimertinib compared to those treated with a platinum-based pemetrexed regimen (71% vs 31%, respectively; OR [95% CI] = 5.39 [3.47–8.48];  $p<0.001$ ).<sup>9</sup>

Osimertinib was approved by the US Food and Drug Administration in November 2015 for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC. However, the C797S mutation is the most commonly acquired mutation that confers resistance to third-generation *EGFR* TKIs.<sup>28–30</sup> EAI045 is a fourth-generation *EGFR* inhibitor that has recently been reported to be an allosteric *EGFR* inhibitor that overcomes T790M- and C797S-mediated resistance.<sup>28–30</sup> For patients without the T790M mutation, chemotherapy is still the primary treatment. A few studies have explored the efficacy of chemotherapy regimens in patients after TKI failure. Of these, pemetrexed is the most frequently reported regimen. Pemetrexed acts as an anti-folate, inhibiting three enzymes in the folate metabolic pathway that are essential for cell replication: thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase.<sup>18,31</sup> A series of randomized Phase II and III clinical trials have shown that pemetrexed is effective and safe for the treatment of advanced non-squamous NSCLC, confirming its role in the treatment of advanced NSCLC in both first- and second-line settings. Moreover, pemetrexed has a significant role in maintenance therapy for NSCLC.<sup>11</sup>

The JMDB study<sup>32</sup> investigated the efficacy of first-line pemetrexed plus cisplatin without maintenance therapy, whereas the PARAMOUNT study<sup>33</sup> investigated efficacy of first-line pemetrexed-cisplatin therapy followed by

pemetrexed maintenance therapy. In the current review, we found that the PFS and ORR results are similar to that of the JMDB study<sup>32</sup> for patients treated with a pem regimen (PFS: between 5.09 and 4.80 months, respectively; ORR: 30.19% and 30.6%, respectively). In addition, we found that in *EGFR*-mutation-positive NSCLC, the OS (15.9 months) with a pem regimen is numerically longer than that in the JMDB study<sup>32</sup> (11.8 months in non-squamous carcinoma) and is comparable with that in the PARAMOUNT study<sup>33</sup> (15.9 vs 16.9 months, respectively). In the current systematic review, only three studies specified that patients received pemetrexed maintenance therapy; other studies did not clarify whether patients received pemetrexed maintenance therapy. This may be one of the reasons why OS is numerically longer in the current review than that in the JMDB study, which indicates that pemetrexed is also efficacious in NSCLC patients after *EGFR*-TKI failure. When used as the first-line treatment, TKI may not impair the efficacy of pemetrexed. This result is consistent with a study that analyzed the efficacy of pemetrexed plus platinum as first- versus second-line treatment in chemotherapy-naïve patients with advanced *EGFR*-mutation-positive lung adenocarcinoma, which suggested that prior *EGFR*-TKI treatment would not influence the efficacy of subsequent pemetrexed plus platinum therapy in chemotherapy-naïve patients with advanced *EGFR*-mutation-positive lung adenocarcinoma.<sup>18</sup> However, Zeng et al<sup>34</sup> reported that front-line *EGFR*-TKI treatment significantly reduced the sensitivity of subsequent chemotherapy compared with that of TKI-naïve front-line chemotherapy in *EGFR*-mutation-positive patients; more prospective studies are needed to clarify this finding.

In the current review, the results favor pem regimens (15.91 months) compared to non-pem regimens (11.08 months), with numerically longer median OS after *EGFR* TKI failure. This is also consistent with treatment outcome in the first-line setting in non-squamous NSCLC. A meta-analysis showed that pemetrexed alone or in combination with other chemotherapeutic agents was superior to other chemotherapy regimens in patients with non-squamous NSCLC (HR [95% CI] = 0.89 [0.80, 0.99]) and was associated with significantly longer OS and less toxicity.<sup>12</sup> However, until now, only one prospective randomized study reported the comparison of single-agent pemetrexed and pemetrexed/platinum doublets in *EGFR*-mutation-positive NSCLC after front-line *EGFR*-TKI failure.<sup>19</sup> This study concluded that the pemetrexed with platinum-based regimens showed a higher response rate than pemetrexed monotherapy; however, no significant difference was observed in PFS between

treatment groups.<sup>19</sup> Another prospective, multicenter, open-label, randomized, Phase II ongoing clinical study was designed to evaluate the efficacy of pemetrexed versus pemetrexed plus cisplatin in *EGFR*-mutant-positive NSCLC patients after failure of first-line *EGFR* TKIs, in the People's Republic of China (NCT02725918). More prospective studies are needed to determine the optimal chemotherapy regimens for *EGFR*-mutant NSCLC in the post-*EGFR*-TKI failure setting.

Checkpoint blockade antibodies targeting programmed cell-death protein 1 (PD-1) have shown promising clinical responses and offer survival benefits with acceptable safety profile in patients with advanced NSCLC.<sup>35–37</sup> Results of KEYNOTE-021<sup>38</sup> – a randomized, open-label, Phase II cohort of a multicohort study – showed that the addition of pembrolizumab to carboplatin and pemetrexed improved efficacy, with manageable safety profiles in patients with chemotherapy-naïve, advanced non-squamous NSCLC.<sup>38</sup> Recent findings from a retrospective study suggested that the efficacy of nivolumab, a PD-1 antibody, tended to be greater in patients with *EGFR*-mutation-positive NSCLC who develop resistance to TKIs due to mechanisms other than acquisition of the secondary T790M mutation of *EGFR* than in the patients who had T790M-positive mutation;<sup>39</sup> the difference in efficacy of nivolumab may be due to a higher level of expression of the PD-1 ligand in the patients with T790M-negative NSCLC. To confirm this, a randomized, Phase II trial (WJOG8515L) comparing nivolumab with a combination of carboplatin and pemetrexed in patients with *EGFR*-mutation-positive non-squamous NSCLC who acquire resistance to *EGFR*-TKIs due to mechanisms other than T790M was conducted and is currently ongoing.<sup>40</sup> Due to heterogeneity in resistance mechanisms,<sup>41</sup> a combination of *EGFR* TKIs with other agents, such as immune checkpoint inhibitors,<sup>42–44</sup> cMET inhibitors,<sup>45</sup> and chemotherapeutic agents (eg, pem regimens), should be considered as future therapeutic modalities to overcome the acquired mutation among NSCLC patients.

This is the first systematic review to assess the evidence supporting pem regimens in NSCLC patients after *EGFR*-TKI failure. However, this systematic review has some limitations: 1) due to the unavailability of sufficient data, no formal statistical inference was achieved; 2) we only searched the PubMed, EMBASE, Cochrane library, ASCO, ESMO, and AACR databases and, therefore, other potentially relevant articles that were published in other databases were not identified; 3) for the direct comparison of pem regimens to non-pem regimens, we only included studies

that compared pem regimens and non-pem regimens; and 4) a limited number of both randomized and retrospective studies with heterogeneity of treatment regimens (with and without maintenance therapy) were available.

## Conclusion

The results of our systematic review showed a favorable efficacy profile of pem regimens in NSCLC patients with EGFR mutation after EGFR TKI failure.

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## Author contributions

All authors were involved in design of the study, data analysis and interpretation, and critical revision of the manuscript. All authors reviewed and approved the final manuscript draft.

## Disclosure

LLY, XW, and LDY are employees of Eli Lilly and Company. HBH was involved in the design and conduct of the systematic literature review, funded by Eli Lilly and Company. The authors report no other conflicts of interest in this work.

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