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Review Article

Optimizing the Treatment for Advanced Non–Small-Cell Lung Cancer with Mutated Epidermal Growth Factor Receptor in Low-Income Countries: A Review

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ABSTRACT

Introduction: Osimertinib is the treatment of choice for epidermal growth factor receptor (*EGFR*)-mutated advanced non–small-cell lung cancer (NSCLC). Because of its high price, many low-income countries, such as Syria, cannot provide osimertinib, which makes it difficult to choose the appropriate treatment for these patients. This study aimed to review articles that assessed tyrosine kinase inhibitors (TKIs) for advanced NSCLC and developed an appropriate treatment plan for Syrian patients. **Methods:** An electronic literature search was conducted of published phase II and III studies that assessed the efficacy of EGFR-TKIs for advanced NSCLC between January 2003 and May 2022. **Results:** Seventeen articles were reviewed. The results were similar when erlotinib or icotinib was compared with gefitinib. Progression-free survival and overall survival for afatinib and dacomitinib were longer than for gefitinib, with small significant differences. Osimertinib was the only TKI that showed efficacy against the T790M mutation, which showed an improvement over the first- and second-generation TKIs. Osimertinib as a first-line therapy is not cost-effective compared with first- and second-generation TKIs. **Conclusion:** Osimertinib is the preferred first-line treatment in patients with advanced *EGFR*-mutated NSCLC. First- and second-generation TKIs are still considered good options, especially in low-income countries that cannot cover the costs of osimertinib.

Keywords: non–small-cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, cost-effectiveness, low-income countries, Syria

INTRODUCTION

Lung cancer is the second most common cancer worldwide, with 2.2 million new cancer cases estimated in 2020 (11.4% of all new cancer cases), and is the leading cause of cancer-related deaths (18% of total cancer-related deaths).[1] Lung cancer is classified into two main types: non–small-cell lung cancer (NSCLC) (~80%) and small cell lung cancer (SCLC) (~15%).[2]

Before 2003, the treatment of NSCLC was chemotherapy based, with an improvement in overall survival (OS) of approximately 1.5 months compared with best supportive care,[3] which was the case until the discovery of epidermal growth factor receptor (*EGFR*) mutation involvement in the development of NSCLC. *EGFR* is one of the most common oncogenic mutations in NSCLC (particularly adenocarcinomas). Mutations in the *EGFR* gene lead to spontaneous activation and phosphorylation of cellular signal transduction pathways, such as mitogen-activated protein kinases (MAPKs), leading to uncontrolled cell proliferation.[4]

The frequency of *EGFR* mutations varies among different ethnicities. It is 10% in the United States and Europe and as high as 40% in Asian individuals. The frequency was higher in women and nonsmokers.[5] Multiple EGFR tyrosine kinase inhibitors (TKIs) have been developed, the most important of which are first-generation TKIs (gefitinib and erlotinib), second-generation TKIs (afatinib and dacomitinib), and third-generation TKIs, such as osimertinib. EGFR-TKIs improve

progression-free survival (PFS), quality of life, and OS. Currently, osimertinib is the preferred first-line therapy in patients with advanced *EGFR*-positive NSCLC.[6–9]

Because of the high cost of osimertinib, several studies have been conducted to investigate its cost-effectiveness as a first-line treatment in several countries, including high-, middle-, and low-income countries. Most of these studies have shown that osimertinib was not cost-effective compared with first- and second-generation TKIs.[10,11] In Syria, osimertinib has not yet been approved by the Syrian Ministry of Health, is not available in Syrian public health services (SPHS), and is not covered by health insurance, which causes confusion about first-line treatment and subsequent lines after progression.

This study aimed to present articles that assessed the treatment of *EGFR*-mutated advanced NSCLC, reviewed the prices and availability of TKIs in Syria, and discussed an approach for selecting the appropriate treatment protocol for patients with *EGFR*-mutated advanced NSCLC in Syria.

METHODS

We conducted a literature search of published articles on the treatment of *EGFR*-mutated NSCLC using PubMed and Google Scholar with the following keywords: non–small-cell lung cancer, NSCLC, *EGFR* mutation, tyrosine kinase inhibitors, randomized controlled trials, osimertinib, gefitinib, erlotinib, afatinib, dacomitinib, and icotinib.

Original articles written in English that studied the treatment of *EGFR*-mutated NSCLC between January 2003 and May 2022 were included. Head-to-head clinical trial studies comparing two EGFR-directed therapies (Phase II and Phase III) were selected. Moreover, a manual search of article references was performed. If there was a study complementary to previous studies, we included the most comprehensive. Reviews, case reports, and reports were excluded from the study.

The following information was extracted from each study: author, year of publication, place of study, study aim, study design, sample size, patient performance status, treatment line, *EGFR* gene status, histological subtype, *EGFR* gene mutation type, and patient outcomes, especially PFS, OS, response rate (RR), and disease control rate (DCR).

RESULTS

A total of 17 studies were conducted between 2003 and 2022. There were 11 studies on first-line treatment and six studies on second-line and subsequent treatments. These included 12 phase III studies, four phase II studies, and one study of pooled subset analyses from two randomized trials. Eight studies involved Asian patients and nine involved Asian and non-Asian patients. In 10 studies, the patients' performance status was (0–2) and in seven studies it was (0, 1). In five studies, *EGFR* was mutated or nonmutated, and was mutated in 12 studies. The results are presented in Table 1.[8,9,12–26]

DISCUSSION

Despite all the available treatments, lung cancer is a global problem because of its high incidence, aggressiveness, and fatality rate. Metastatic lung cancer is an incurable disease that can result in death. The 5-year survival rate did not exceed 5%.[2] In recent years, many studies have focused on the importance of discovering the pathogenic mechanisms and molecular biology, and thus, the possibility of developing drugs that target these mechanisms.

The treatment of metastatic NSCLC until the early 2000s relied on cytotoxic chemotherapy (until the discovery that *EGFR* gene mutations were involved in the pathogenesis of NSCLC). EGFR-TKIs have been developed, and three generations of them have been developed to date.

Gefitinib

The use of gefitinib in patients with metastatic NSCLC after tumor progression provided better results than conventional chemotherapy in terms of PFS and RR. Therefore, it was approved as a third-line treatment in 2003. In 2005, the ISEL randomized controlled trial[27] (ClinicalTrials.gov Identifier: NCT00242801) compared gefitinib with placebo and found no differences in the results. Consequently, the approval was withdrawn.

During the subsequent data analysis, a significant difference was found when *EGFR* mutations were present. In 2009, the IPASS study (ClinicalTrials.gov Identifier: NCT00322452) (by Mok et al.[28] and the OS study by Fukuoka et al.[6]) showed a benefit of gefitinib over chemotherapy in *EGFR*-positive patients, where PFS was 9.5 versus 6.3 months ($p < 0.001$), with better quality of life, but no difference in OS between the two groups; gefitinib was approved as a second-line treatment in this group. In 2015, it was approved as first-line treatment.

Erlotinib

Erlotinib is a first-generation TKI that provides clinical improvement as a second-line therapy, and several studies have shown improvement when compared with first-line chemotherapy (overall response rate [ORR] 83% vs 36%, $p < 0.0001$; PFS 13.1 vs 4.6 months, $p < 0.0001$) and fewer adverse event rates (AEs) (G 3/4 17% vs 65%),[29] without a significant difference in the OS.[30–32] When comparing erlotinib with gefitinib, the results were similar.[22] Erlotinib was approved as second-line therapy in patients with *EGFR*-mutant NSCLC in 2004. In 2013, it was approved as a first-line treatment and is still considered category 1

Table 1. Articles that studied EGFR-TKIs in the treatment of NSCLC

Study	Population or Country	Treatment	No. of Pts	Study Design	Histological Subtype	ECOG PS	*EGFR* Mutation Status	Outcomes
Ramalingam SS, 2012[19]	Asian and non-Asian, White >70%	≥ Second line: dacomitinib vs erlotinib	94 vs 94	Phase II	NSCLC (ADK 66% vs 64.9%)	0–2	+/−	ORR 17.0% vs 5.3%, $p = 0.011$ PFS 2.86 vs 1.91 mo, $p = 0.012$ OS 9.53 vs 7.44 mo, $p = 0.205$
Kim ST, 2012[20]	Korea	Second line: gefitinib vs erlotinib	48 vs 48	Phase II	NSCLC (ADK > 90%)	1, 2	+/−	RR 47.9% vs 39.6%, $p = 0.26$ PFS 4.9 vs. 3.1 mo, $p = 0.33$
Shi Y, 2013 (ICOGEN)[21]	China	≥ Second line: icotinib vs gefitinib	200 vs 199	RCT phase III	NSCLC	0–2	+/−	PFS 4.6 vs 3.4 mo, $p = 0.13$ AEs 61% vs 70%, $p = 0.04$ OS 13.3 vs 13.9 mo, $p = 0.57$
Yang JJ, 2017[22]	China	≥ First line: erlotinib vs gefitinib	128 vs 128	RCT phase III	NSCLC (ADK > 96%)	0–2	+ (Exon 19 deletion or exon 21 L858R mutation)	RR 56.3% vs 52.3%, $p = 0.530$ PFS 13 vs 10.4 mo, $p = 0.1$ OS 22.9 vs 20.1 mo, $p = 0.2$ AEs 3/4 5.4% vs 1.6%, $p = 0.17$
Soria JC, 2015 (LUX-Lung 8)[23]	Asian and non-Asian	Second line: afatinib vs erlotinib	398 vs 397	RCT phase III	SCC	0–2	+/−	DCR 51% vs 40%, $p = 0.0020$ PFS 2.6 vs 1.9 mo, $p = 0.0103$ OS 7.9 vs 6.8 mo, $p = 0.0077$
Urata Y, 2016 (WJOG 5108L)[24]	Japan	≥ Second line: gefitinib vs erlotinib	279 vs 280	RCT phase III	ADK	0–2	+/− (+, 66.4%)	*EGFR* +/− PFS 6.5 vs 7.5 mo, $p = 0.25$ OS 22.8 vs 24.5 mo, $p = 0.768$ *EGFR* + PFS 8.3 vs 10.0 mo, $p = 0.42$
Park K, 2016 (LUX-Lung 7)[25]	Asian and non-Asian, Asian >55%	First line: afatinib vs gefitinib	160 vs 159	RCT phase 2B	ADK (99%)	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 70% vs 59%, $p = 0.008$ TTF 13.7 vs 11.5 mo, $p = 0.0073$ PFS 11.0 vs 10.9 mo, $p = 0.01$ Serious AEs 11% vs 4% Fatal AEs 9% vs 6%

Table 1 continues on next page

Table 1. Continued

Study	Population or Country	Treatment	No. of Pts	Study Design	Histological Subtype	ECOG PS	*EGFR* Mutation Status	Outcomes
Ramalingam SS, 2016[26]	Asian and non-Asian	Second or third line: dacomitinib vs erlotinib	53 vs 48	pooled subset analyses from two randomized trials	NSCLC	0–2	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 67.9% vs 64.6% PFS 14.6 vs 9.6 mo, $p = 0.146$ OS 26.6 vs 23.2 mo, $p = 0.265$
Paz-Ares L, 2017 (LUX-Lung 7, OS)[12]	Asian and non-Asian, Asian >55%	First line: afatinib vs gefitinib	160 vs 159	RCT phase 2b	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 72.5% vs 56.0%, $p = 0.0018$ DCR 91.3% vs. 87.4%, $p = 0.2372$ PFS 11 vs 10.9 mo, $p = 0.01$ OS 27.9 vs 24.5 mo, $p = 0.25$ AEs 3/4 56.9% vs 53.5%
Mok TS, 2018 (ARCHER 1050)[8]	Asian and non-Asian, Asian >75%	First line: dacomitinib vs gefitinib	227 vs 225	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	PFS 14.7 vs. 9.2 mo, $p < 0.0001$ OS 34.1 vs 26.8 mo, $p = 0.04$
Mok TS, 2021 (ARCHER 1050, updated OS)[13]	Asian and non-Asian, Asian >75%	First line: dacomitinib vs gefitinib	227 vs 225	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	OS 34.1 vs 27.0 mo, $p = 0.0155$
Nishio M, 2020 (ARCHER 1050)[14]	Japan	First line: dacomitinib vs gefitinib	40 vs 41	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 75.0% vs 75.6%, $p = 0.9493$ PFS 18.2 vs 9.3 mo, $p = 0.0327$ OS data: pending
Cheng Y, 2021 (ARCHER 1050)[15]	Asian	First line: dacomitinib vs gefitinib	170 vs 176	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 77.1% vs 72.7%, $p = 0.1766$ PFS 16.5 vs 9.3 mo, $p < 0.0001$ OS 37.7 vs 29.1 mo
Soria JC, 2018 (FLAURA)[9]	Asian and non-Asian	First line: osimertinib vs other TKIs (gefitinib and erlotinib)	279 vs 277	RCT phase III	NSCLC (ADK > 98%)	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 80% vs 76%, $p = 0.24$ PFS 18.9 vs 10.2 mo, $p < 0.001$ OS: pending AEs grade 3/4 34% vs 45%
Ohe Y, 2019 (FLAURA Japanese subset)[16]	Japan	First line: osimertinib vs TKIs	65 vs 55	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	ORR 75.4% vs 76.4% DCR 96.9% vs 96.4% PFS 19.1 vs 13.8 mo, $p = 0.04$ OS data: pending

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Table 1. Continued

Study	Population or Country	Treatment	No. of Pts	Study Design	Histological Subtype	ECOG PS	*EGFR* Mutation Status	Outcomes
Ramalingam SS, 2020 (FLAURA)[17]	Asian and non-Asian	First line: osimertinib vs TKIs (gefitinib and erlotinib)	279 vs 277	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	OS 38.6 vs 31.8 mo, $p = 0.04$ AEs G 3/4 42% vs 47%
Cheng Y, 2021 (FLAURA)[18]	China	First line: osimertinib vs TKI (gefitinib)	71 vs 65	RCT phase III	NSCLC	0, 1	+ (Exon 19 deletion or exon 21 L858R mutation)	PFS 17.8 vs 9.8 mo, $p = 0.007$ OS 33.1 vs 25.7 mo, $p = 0.44$ AEs Grade 3/4 54% vs 28%

+: positive; –: negative.
AEs: adverse events; ADK: adenocarcinoma; DCR: disease control rate; ECOG: Eastern Cooperative Oncology Group; *EGFR*: epidermal growth factor receptor; NSCLC: non–small-cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PS: performance status; Pts: patients; RCT: randomized clinical trial; RR: response rate; SCC: squamous cell carcinoma; TKIs: tyrosine kinase inhibitors; TTF: time-to-treatment failure.

according to the National Comprehensive Cancer Network guidelines.

Afatinib

Afatinib is a second-generation EGFR-TKI. The LUX-Lung-3 study (ClinicalTrials.gov Identifier: NCT00949650) showed that the PFS was longer with afatinib than with cisplatin plus pemetrexed (11.1 vs 6.9 months), with a similar rate of AEs (G 3/4 49% vs 48%).[7] When compared with gefitinib, PFS was longer with afatinib but without OS difference.[12,25]

Dacomitinib

Dacomitinib is a second-generation EGFR-TKI. In a phase II study by Jänne et al.,[33] the PFS for dacomitinib as first-line treatment when *EGFR*-mutated was 18.2 months and the OS for *EGFR*-mutated patients was 40 months. The ARCHER 1050 (ClinicalTrials.gov Identifier: NCT01774721) study showed that OS was longer when dacomitinib was administered than gefitinib; it is worth mentioning that this study excluded patients with brain metastases.[8] Also, most studies conducted on dacomitinib and afatinib were open-label; therefore, there may be a bias in the patients' preference to continue with the new drug.[8,13,14,26]

Osimertinib

Osimertinib is a third-generation EGFR-TKI. In addition to sensitizing mutations, it is also effective against the T790M mutation. The T790M mutation is the most common mutation causing resistance to first- and second-generation TKIs.

The AURA study (ClinicalTrials.gov Identifier: NCT01802632) was conducted on second-line osimertinib after failed TKI treatment with T790M positivity and resulted in ORR of 62% and PFS of 12.3 months, with tolerable AEs; the most common AEs were diarrhea (43%) and rash (40%).[34]

The AURA3 (ClinicalTrials.gov Identifier: NCT02151981) study demonstrated that osimertinib significantly improved RR and PFS with lower toxicity than cisplatin/pemetrexed with maintenance pemetrexed after first-line TKI treatment in patients with sensitizing mutations.[35]

The FLAURA study (ClinicalTrials.gov Identifier: NCT02296125) also demonstrated better results for osimertinib than for gefitinib in terms of PFS and RR, with a significant difference in OS and similar rate of AEs.[9,17]

Icotinib

The China Food and Drug Administration approved icotinib, but the US Food and Drug Administration and European Medicines Agency did not. The CONVINCE study (ClinicalTrials.gov Identifier: NCT01719536) conducted in China showed that icotinib had a longer PFS than cisplatin/pemetrexed with pemetrexed maintenance, with fewer AEs; however, there was no difference in the OS.[36]

On the other hand, the ICOGEN study (ClinicalTrials.gov Identifier: NCT01040780) showed comparable PFS and OS to gefitinib, but gefitinib was less toxic. The standard dosage of icotinib is 125 mg three times per day (because of its short half-life).[21]

TKIs in Combination with Angiogenesis Inhibitors (Bevacizumab or Ramucirumab) or Chemotherapy

As seen, treatment with TKIs increases PFS and OS; however, all *EGFR*-positive NCSLCs eventually develop resistance to the treatment. Preclinical studies have shown improved antitumor efficacy when angiogenesis inhibitors are added to TKIs.[37]

The RELAY study (ClinicalTrials.gov Identifier: NCT02411448) revealed that the combination of ramucirumab and erlotinib improved PFS compared with erlotinib alone (PFS 19.4 vs 12.4 months, $p < 0.0001$).[38]

Another angiogenesis inhibitor is bevacizumab. The combination of bevacizumab and erlotinib also improved PFS by several months compared with erlotinib alone,[39,40] but without improvement in OS (47 vs 47.4 months, $p = 0.3$).[41] Based on these studies, the combination of bevacizumab or ramucirumab with erlotinib has been approved as first-line therapy.

The combination of chemotherapy and TKIs has shown promising results. The study by Hosomi et al.[42] demonstrated that the combination of gefitinib plus pemetrexed/carboplatin improved PFS and OS compared with gefitinib alone (PFS 20.9 vs 11.9 months, $p < 0.001$; OS 50.9 vs 38.8 mos., $p = 0.02$). Although combination therapy demonstrated better results than TKIs alone, it was associated with higher toxicities; however, most of these toxicities were manageable.[40,42]

The combination studies have several limitations: most of them started before the adoption of osimertinib as first-line treatment; therefore, there are no comparative studies with it, and the OS data of most of them are not yet complete. Therefore, these results should be cautiously interpreted.

Results of Treatment with EGFR-TKIs by Type of Mutation

The *EGFR* gene is located on chromosome 7p11.2, has approximately 200,000 base pairs, and consists of 28 exons and 27 introns. The most common mutations were the exon 19 deletion and point mutation (L858R) in exon 21. There are a few uncommon mutations, such as G719X, that are sensitive to first-, second-, and third-generation TKIs.[9,12] Most mutations in exon 20 are refractory to first- and second-generation TKIs, most commonly the T790M mutation. The presence of T790M mutations at the beginning of diagnosis is rare, and, when present, it is necessary to search for hereditary lung cancers.[43]

The response of patients with NSCLC to TKI treatment varies according to the type of *EGFR* mutation. Some studies have reported that the outcomes of TKIs at exon 19 deletion were better than those of mutation in exon 21 (L898R).[44] On the other hand, many studies have demonstrated no difference between the two mutations.[8,24,25,31,32]

The T790M mutation in exon 20 is resistant to first-generation TKIs. Preclinical studies have demonstrated the efficacy of afatinib against this mutation; however, clinically, afatinib was ineffective. Osimertinib was effective against the T790M mutation. In the BELIEF study (ClinicalTrials.gov Identifier: NCT01562028), the administration of bevacizumab plus erlotinib resulted in better outcomes in T790M-positive patients than in mutation-negative patients; however, the sample size was small. Therefore, these results should be cautiously interpreted.[45] The T790M mutation is responsible for approximately 50% of the cases of resistance to first- and second-generation TKIs.[46,47]

Choosing the Best Treatment for NSCLCs That Harbor the *EGFR* Mutation

Osimertinib is the only TKI that has shown an OS improvement compared with chemotherapy and first- and second-generation TKIs. Osimertinib is currently preferred for the treatment of NSCLC harboring sensitizing *EGFR* mutations and it is the only TKI that has been approved for the treatment of T790M-positive NSCLC.

Osimertinib is the treatment of choice in the presence of brain metastases. Studies have shown a higher crossing rate of the cerebral vascular barrier with a higher response rate than first-generation TKIs.[17,48]

There are no adequate studies on second-line TKIs if osimertinib is used as first-line treatment. Interestingly, the T790M mutation did not occur during the osimertinib treatment. Therefore, the expectation of targeted treatment after progression to osimertinib depends on knowledge of the mechanisms of resistance, some of which have been known so far: *MET* amplification, *EGFR* amplification, *KRAS* amplification, *MEK1* mutation, *PIK3CA* mutations, *EGFR* C797S mutation, *JAK2* mutation, and *HER2* exon 20 insertion.[49]

However, if first- or second-generation TKIs are administered as first-line treatment and when relapse occurs, a new biopsy or liquid biopsy must be performed to negate the neoplastic transformation of SCLC and determine the status of the T790M mutation. Osimertinib is the preferred treatment if the T790M mutation is present. The GioTag study (ClinicalTrials.gov Identifier: NCT03370770) showed that administration of afatinib as first-line therapy followed by osimertinib as second-line therapy when a positive T790M mutation occurred gave promising results, especially in Asian patients (OS 46.7 months); however, this study is retrospective, and therefore, its results should be approached with caution.[50]

Table 2. Articles that studied TKI cost-effectiveness in the treatment of *EGFR*-positive NSCLC

Study	Country	Treatment	Cost	QALYs Gained	ICER per QALY Gained
Ezeife DA, 2018[10]	Canada	First line: osimertinib vs standard EGFR-TKI, (gefitinib or afatinib)	*Per 1 week* 2063 vs (653 vs 541) CAD	0.79 vs NA	223,133 CAD
Aguiar PN, 2018[55]	US and Brazil	First line: osimertinib vs first- and second-generation EGFR-TKIs (erlotinib, gefitinib, and afatinib)	*Per month* *US:* 17,028.90 vs (9390.44 vs 9117.36, vs 9785.72) USD	*US and Brazil:* 2.122 vs 1.514	*US:* approximately 225,000 USD
			Brazil: 8789.96 vs (2127.60 vs 1029.94 vs 1349.14) USD		*Brazil:* approximately 172,000 USD
Khoo T, 2021[56]	Australia	First line: osimertinib vs. standard EGFR-TKI (gefitinib or erlotinib)	*Per month* 7962.12 vs (1211.45 vs 1151.77) AUD	2.062 vs 1.788	432,197 AUD
Wu B, 2019[57]	US and China	First line: osimertinib versus standard EGFR-TKI (gefitinib or erlotinib)	*Per month* *US:* 17,040 vs (9120 vs 9390) USD	*US:* 2.316 vs 1.465	*US:* 312,903 USD
			China: 7770 vs (1050 vs 870) USD	*China:* 2.244 vs 1.487	*China:* 41,512 USD
Aguilar-Serra J, 2019[54]	Spain	First line: osimertinib vs. standard EGFR-TKI (gefitinib or erlotinib)	*Per 28-day cycle* €5447.36 vs €1,836,48	0.61 vs 0.42	€273,895.36
Aziz MIA, 2020[58]	Singapore	First line: osimertinib vs with standard EGFR-TKIs (erlotinib or gefitinib)	*Per 1 week* 2042 vs (507 vs 637) SGD	2.251 vs 1.932*	304,277 USD*
Li WQ, 2021[11]	China	First line: osimertinib vs. standard EGFR-TKI (gefitinib or erlotinib)	*Per month* 2171.48 vs (679.5 vs 302.4) USD	1.56 vs 1.48*,**	416,560.02 USD
		First line: dacomitinib vs gefitinib	*Per month* 803.30 vs 679.5 USD	1.83 vs 1.80**	1,897,750.74 USD

*For osimertinib versus Standard EGFR TKI.
**QALYs for 5 years.
AUD: Australian dollar; CAD: Canadian dollar; EGFR: epidermal growth factor receptor; ICER: incremental cost-effectiveness ratio; NA: not available; NSCLC: non–small-cell lung cancer; QALYs: quality-adjusted life-years; SGD: Singapore dollar; TKI: tyrosine kinase inhibitor; US: United States; USD: US dollar.

Cost-effectiveness

A study of the cost-effectiveness of TKIs is valuable. This will contribute to the development of plans that achieve clinical benefits at the lowest cost. Gefitinib and erlotinib are cost-effective compared with chemotherapy, given the cost of performing *EGFR* genetic analysis owing to improved quality of life, reduced hospitalization, and fewer AEs. No differences were observed between gefitinib and erlotinib treatments.[51]

Second-generation TKIs (afatinib and dacomitinib) are more expensive than gefitinib; however, the study by Chouaid et al.[52] in France based on the LUX-Lung 7 study (ClinicalTrials.gov Identifier: NCT01466660) protocol showed that afatinib was more cost-effective than gefitinib because it led to an improvement in PFS. On the contrary, a study by Kimura et al.[53] in Japan showed that gefitinib was more cost-effective than afatinib. A study by Li et al.[11] showed that first-line therapy with first-generation TKIs is more cost-effective than dacomitinib and osimertinib.

Several studies have investigated the cost-effectiveness of osimertinib as a first-line treatment in high-, middle-, and low-income countries, all of which have shown that it is not cost-effective. Table 2 summarizes studies on the cost-effectiveness of osimertinib.[10,11,54–58]

Consequently, osimertinib is not cost-effective as a first-line treatment compared with first-generation TKIs, and its price must be reduced to make it economically viable.[54,55] Second-line osimertinib after first-generation TKIs when positive for the T790M mutation is cost-effective compared with chemotherapy.[59]

In Syria, osimertinib has not yet been approved by the Syrian Ministry of Health, is not available at public healthcare institution hospitals, and is not covered by health insurance. It can be provided to the patient privately, and any patient who can afford to pay for a drug has access as soon as it is made commercially available by the company. The osimertinib (Tagrisso, Astra Zeneca, Inc., London, UK) box price for 1 month was 10,264,000 Syrian pounds (SP) (equivalent to 4000 euros; SPs were converted into euros by using the

Table 3. Prices of generic drugs used to treat non–small-cell lung cancer available in Syrian public health services

Treatment	Generic Name (Country)	Price, USD*	Price, SP
Gefitinib	Gefitinib (Iran)	543.3	1,364,940
Erlotinib	Tarsoban (Iran)	1341.1	3,370,320
Carboplatin	Carboplatin (India)	42.1	105,850
Cisplatin	Platifirst (India)	25.3	63,695
Paclitaxel	Drifen (Argentina)	42.7	107,383
Docetaxel	Celtere (India)	18.2	45,862
Pemetrexed	Trexam (Argentina)	213.1	535,323
Gemcitabine	Gemcitabine (Iran)	19.9	50,187.4

*Prices for tyrosine kinase inhibitors are per month but chemotherapies are based on a 3-week cycle, as per person BSA 1.7.
USD: United States dollar; SP: Syrian pound; BSA: body surface area.

following exchange rate: 1 euro = 2566 SPs, the price to the Syrian Central Bank, on August 11, 2022).

For gefitinib (Iressa, Astra Zeneca, Inc., London, UK), the price of one pill was 33,358 SP or 1,000,740 SP per month (equivalent to 390 euros per month). In other words, the price of osimertinib (Tagrisso) is more than 10 times that of gefitinib (Iressa).

First-generation TKIs are available in the SPHS. The cost of gefitinib (Gefitinib, Noavaran Daroui Kimia Co., Tehran, Iran) for 1 month is 1,364,940 SP (543.3 U.S. dollars [USD], SPs were converted into USD using the following exchange rate: 1 USD = 2512 SP, the price to the Syrian Central Bank, on August 11, 2022) and erlotinib (Tarsoban, Sobhan Oncology Co., Tehran, Iran) 3,370,320 SP (USD 1341.1). The price of TKIs in the SPHS includes the fees for their registration with the Ministry of Health and taxes, along with the cost of *EGFR* analysis, which is charged by the company providing the drug. The prices of the targets and chemotherapeutic drugs used to treat NSCLC in the SPHS are listed in Table 3.[60] Owing to economic difficulties and the current crisis in Syria, some newly approved targeted or immunotherapy drugs are not available, and generic drugs are frequently used in cancer treatment.

To the best of our knowledge, second-generation EGFR-TKIs, ALK, ROS1, and TRK inhibitors are unavailable in Syria.

This study is a comprehensive review of EGFR-TKIs as first-line treatment for patients with advanced NSCLC. In addition to comparing osimertinib (standard of care) with first- and second-generation TKIs, this review also compares first- and second-generation TKIs with each other. Further, this review discusses the cost-effectiveness of osimertinib in comparison with first- and second-generation TKIs, as well as the availability and price of these treatments in Syria (as an example of a low-income country).

CONCLUSION

Treatment plans for *EGFR*-mutated NSCLC are constantly evolving, with improvements in the quality of life and survival. The treatment of choice is osimertinib; however, owing to its high cost, non–cost-effectiveness, and unavailability in public health services, it has not been used in several low-income countries, such as Syria. Therefore, first- and second-generation TKIs are still considered a good choice as first-line treatment for NSCLC that harbors sensitizing *EGFR* mutations.

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