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Original Research

EGFR Mutation-positive Lung Cancer in Real-world Treatment Outcomes: A Multicenter Study from Thailand

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Background: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) have been the standard of care as first-line (1L) therapy for patients with advanced EGFR mutated lung cancer since 2009. In Thailand, however, it was not fully introduced to all health care funds until 2020. The purpose of this study was to determine the overall survival (OS) and treatment pattern in the period before EGFR-TKI became universally available to all patients.

Methods: This was a retrospective study conducted at 10 medical centers in Thailand. Patients harboring the common mutation (exon 19 deletion or exon 21 L858R) diagnosed during January 2013 and December 2019 were enrolled.

Results: This study included 284 patients with a median follow-up time of 19.8 months and a death rate of 80.3% (228/284). Clinical characteristics included median age 62.5 years, female 65.5%, never-smoking 74.3%, stage 3B/4/recurrence 2.1/93.3/4.6%, exon 19/exon 21-60.9/38.7%. Treatment patterns to EGFR-TKI included not receiving (NR) (9.5%), first-line (1L) (56.0%), switch maintenance (MN) (3.5%), second-line (2L) (21.8%) and third-line (3L) or more (9.2%). Median OS of patient receiving EGFR-TKI as NR, 1L+MN, 2L and 3L or more was 11.10 (95%CI: 8.21 to14.00), 19.08 (95%CI: 15.76 to 22.41), 23.06 (95%CI: 15.91 to 30.21) and 32.46 (95%CI: 21.61 to 43.30) months (p=0.006), respectively. Factors contributing to poor prognosis in the multivariate model included poor ECOG-PS (HR 3.17, 95%CI: 1.96-5.13), not receiving EGFR-TKI (HR 3.83, 95%CI, 1.94-7.56) and receiving EGFR-TKI 1L (HR 2.30, 95%CI: 1.40-3.79)

Conclusion: OS of patients with EGFR mutation positive lung cancer treated with EGFR-TKIs in Thailand was comparable to clinical studies. EGFR-TKI treatment should be provided to patients as early as possible, but TKI remained beneficial at later points in the treatment timeline.

Introduction

Lung cancer is the leading cause of cancer-related mortality affecting more than 1.79-million deaths worldwide in 2020 [1]. Typically, a patient with lung cancer is not diagnosed until advanced stage. Non-small cell lung cancer (NSCLC) is the predominate type found in 80-90 % of all lung

cancer patients with adenocarcinoma being the most common subtype [2-3].

Epidermal growth factor receptor (EGFR) mutated tumor accounts for 10-20% of advanced lung adenocarcinomas in Caucasians and 50-60% in East/ Southeast Asian (including Thailand).They are typically found in non-smoking females. [4-5].

EGFR is a trans-membrane signaling receptor responsible for cell growth and survival. Normally, it works only when it binds to ligands or external stimuli such as epidermal growth factor. It then forms a dimerization and activates intracellular pathways. In contrast, EGFR mutated tumor constantly activates tumor growth and metastasizes independently of stimuli [6-7].

The two most common types of EGFR mutation occur at exon 19 (deletion) and exon 21 (L858R point mutation), which account for 45% and 40% of all mutated EGFR lung cancers, respectively These two types respond well to EGFR-tyrosine kinase inhibitor (EGFR-TKI) [2-3].

Available since 2009, EGFR-TKI is considered one of the most revolutionary targeted therapies approved for treatment of EGFR mutated advanced NSCLC patients. There are now three generations of EGFR-TKI approved for first-line (1L) treatment [2-3]. The first-generation including erlotinib and gefitinib is a reversible EGFR-TKI which has been shown to provide progression free survival (PFS) to 9.2-13.1 months and overall survival (OS) to 19.3-34.8 months [8-11]. The second-generation including afatinib and dacomitinib is an irreversible EGFR-TKI and provides PFS to 11.0-14.7 months and OS to 23.1- 34.1 months [12-14]. Most recently, the third-generation including osimertinib is an irreversible EGFR-TKI and is developed to overcome resistance mechanism (exon 20 T790M) to first- and second-generation therapies and provides PFS to 18.9 months and OS to 38.6 months [15]. Based on several landmark trials, first- and second- generation EGFR-TKIs as 1L therapy were proven clinical superiority over chemotherapy in terms of response rate (60-70% versus 20-30%) and PFS (9-13 months versus 4-5 months) [8-13]. However, the OS was comparable because of high crossover rate (59-93%) from chemotherapy to EGFR-TKIs.

Many real-world studies in Asian and Western populations showed that the median OS of a patient with EGFR mutated advanced NSCLC receiving an EGFR-TKI varied from 19.4 to 38.5 months [16-21].

In Thailand, EGFR-TK1 was not approved for the list of national essential drugs until October 2020 mainly due to the cost of the medication. Previously, only patients with government servant and state enterprise officer coverage (GSEO) could receive reimbursement for the medication as late-line treatment, regardless of EGFR mutation status, while patients with universal coverage (UC) or the social security scheme coverage (SSS) needed to pay out of pocket [22-23]. There were scant data regarding survival of patients with EGFR mutated lung cancer prior to the introduction of EGFR-TK1 in Thailand [23-24].

The purpose of this study is to find the survival rate and treatment pattern of patients with EGFR mutated lung cancer in Thailand during 2013-2019, which was the period before EGFR-TKI was approved for all health fund groups.

Materials and Methods

Eligibility Criteria

Patients with EGFR mutation positive (exon 19 deletion or exon 21, L858R), stage III-B or IV NSCLC treated at 10 medical centers in Thailand during January 2013 until December 2019 were enrolled in the study. The diagnosis was confirmed by pathology/cytology and staging was classified according to TNM 7th edition [25]. EGFR mutation testing was performed using real-time polymerase chain reaction.

Study Design

Baseline characteristics including gender, age, race, health fund, smoking status, Eastern Cooperative Oncology group performance status (ECOG-PS), tumor stage, and site of metastasis were recorded. Pathological data including date of report, tumor histology, EGFR mutation data were also collected. Tumor response, date of starting and stopping 1L to 3L systemic treatment, reasons for not received EGFR-TKI and for stopping treatments, and adverse events to EGFR-TKI were extracted from medical records.

The status of the patient at the study cut-off time of June 30, 2021, was taken from the medical record and registration information from the Thailand Ministry of Interior. The OS was calculated from the date of 1L therapy initiation to the date of death from any causes in patients receiving systemic therapy and from the date of diagnosis to the date of death from any causes in patients receiving only supportive care. PFS was calculated from the date of starting systemic therapy to the date of disease progression or death from any causes.

Tumor responses were assessed using Response Evaluation Criteria in Solid Tumors based on radiologic reports [26]. Adverse events were assessed using Common Terminology Criteria for Adverse Events Version 4.0 [27].

Statistical Analysis

OS was calculated using the Kaplan-Meier survival method. Comparisons of cumulative survival were obtained by univariate analyses using the log-rank test. Multivariate analyses were performed using Cox proportional hazard model. A p-value <0.05 in univariate analysis and multivariate analysis was chosen as the threshold for statistical significance. The Statistical Package for the Social Sciences (SPSS) version 16.0 was used in this study.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The ethics committee of each medical center approved the study protocol.

Results

Between January 2013 to December 2019, 284 NSCLC patients with common EGFR-mutation (exon 19 deletion and exon 21 L858R mutation) from 10 medical centers in Thailand were enrolled in this study (Supplementary Figure 1 and Table 1).

Figure 1. Survival of Patient Treated with First-line Chemotherapy Versus First-line EGFR-TKIs.

Characteristics	Total N=284
Median age (range), years	62.5 (33-90)
Gender, n (%)	
Female	186 (65.5)
Male	98 (34.5)
Race, n (%)	
Thai	282 (99.3)
Non-Thai	2 (0.7)
Smoking status, n (%)	
Never	211 (74.3)

Smoking	60 (21.1)
Unknown	13 (4.6)
Health fund, n (%)	
UC	144 (50.8)
SSS	35 (12.3)
GSEO	94 (33.1)
Self-pay	11 (3.9)
ECOG PS, n (%)	
0-1	156 (54.9)
2	79 (27.8)
3-4	39 (13.7)
Unknown	10 (3.8)
Stage, n (%)	
III-B	6 (2.1)
IV	265 (93.3)
Recurrence	13 (4.6)
Tumor pathology, n (%)	
ADC	268 (94.4)
SqCC	8 (2.8)
others	8 (2.8)
EGFR testing, n (%)	
Tissue	225 (79.2)
Plasma	59 (20.8)
EGFR mutation, n (%)	
Exon 19 deletion	173 (60.9)
L858R mutation	110 (38.7)
Exon 19 del+L858R	1 (0.4)

Table 1. Baseline and Clinical Characteristics.

ADC, adenocarcinoma; GSEO, government servant and state enterprise officer coverage, SqCC, squamous cell carcinoma; SSS, social security scheme coverage; UC, universal coverage

At the cut-point date of June 30, 2021, with a median follow-up time of 19.8-month, 228 patients had (80.3%) died.

Patient characteristics

Baseline and clinical characteristics of patients are shown in Table 1. Females represented nearly two-thirds (65.5%) of patients. Median age was 62.5 years (33 to 90). Non-smokers represented 74.3% of patients. One-third (33.1%) of patients were covered by the GSEO fund which had authorized EGFR-TK1 treatment since the start of the study period. Metastatic sites at initial diagnosis included: lung 63.8%, pleura 52.6 %, bone 33.5 %, liver 14.7%, brain 14.2 %, distant lymph node 7.6%, adrenal gland 4.0%, and pericardium 4.0%. The median number of metastatic organs was 2 (Q1-Q3, 1.0-2.0). Year of diagnosis distribution was: 2013 4.6% (n=13), 2014 5.3% (n=15), 2015 5.3% (n=15), 2016 10.2% (n=29) 2017 17.2% (n=49), 2018 30.3% (n=86) and 2019 27.1% (n=77).

Treatment and efficacy

A total of 282 out of 284 enrolled patients received at least one regiment of systemic therapy with two patients receiving only best supportive care. EGFR-TK1 treatment was given to 257 patients (90.5%) at some point during systemic treatment. The initial TKI drugs selected were gefitinib 65.8% (n=187), erlotinib 20.8% (n=59), afatinib 3.2% (n=9) and osimertinib 0.7% (n=2). Treatment regimen and response are shown in Table 2.

	First-line		Second-line		Third-line	
	N=282		N= 177		N=99	
Regimens	n (%)	ORR	n (%)	ORR	n (%)	ORR
EGFR-TKI						
Gefitinib	116 (41.1)	80.1	47 (36.1)	68	23 (23.2)	65.2
Erlotinib	35 (12.4)	85.7	17 (9.6)	52.9	5 (5.0)	80
Afatinib	9 (3.2)	66.7	3 (1.7)	0	3 (3.0)	0
Osimertinib	2 (0.7)	100	22 (12.4)*	50	14 (14.1)*	64.2
Chemotherapy						
Platinum-doublets #	107 (37.9)	37.4	40 (22.6)	25	9 (9.1)	33.3
Docetaxel	-	-	36 (20.3)	36.1	32 (32.3)	28.1
Pemetrexed	-	-	6 (3.4)	16.7	12 (12.1)	8.3
Single agent chemotherapy $	13 (4.6)	0	6 (3.4)	0	1 (1.0)	0

Table 2. Treatment and Response Rate Based on Regimens and Line of Treatments.

ORR, overall response rate; # Including 9 patients who received switched MN EGFR TKI therapy; * Patients with acquired T790M mutation received osimertinib as a subsequent line treatment; $ Single agent chemotherapy: first-line, n=13 (gemcitabine, n=10, carboplatin, n=2, paclitaxel, n=1); second-line, n=6 (gemcitabine, n=3, carboplatin, n=3); third-line, n= 1 (etoposide, n=1))

Patients treated with 1L chemotherapy versus EGFR-TKI

Clinical characteristics of patients receiving 1L chemotherapy and EGFR-TK1 were comparable, except for age and EGFR mutation type (Supplementary Table 2). Median age of patients receiving EGFR-TKI 1L was higher than those receiving chemotherapy 1L, and there was imbalance in the type of EGFR mutation between both groups.

Median months of PFS of patients receiving 1L chemotherapy with 6.60 (95%CI: 5.75 to 7.45) was significantly lower than those of EGFR-TKI patients with11.53 (95%CI: 10.20 to 12.85; p<0.001). (data not shown).

Median months of OS of patients receiving 1L chemotherapy with 23.26 (95%CI: 19.64 to 26.88 was not significantly different (p=0.274) than those of EGFR-TKI with 19.78 (95%CI: 16.21 to 23.34) (Figure 1).

Subsequent treatment

The number of patients treated with chemotherapy 1L received significantly more second-line (2L) and third-line (3L) treatments than those who received EGFR-TKI 1L with 84.2 % versus 46.9 % (p<0.001) and 54.2% versus 21.0% (p<0.001) for 2L and 3L treatments, respectively. The number of patients receiving 2L and 3L treatments and regimens are showed in Table 3.

First-line treatment	EGFR-TKI	Chemotherapy	EGFR-TKI	Chemotherapy

n/N (%) of first-line	76/162 (46.9)	101/120 (84.2)	34/162 (21.0)	65/120 (54.2)
n/N (%) of second-line	-	-	34/76 (44.7)	65/101 (64.3)
Subsequent treatment	Second-line, n (%)		Third-line, n (%)	
Regimen	N=76	N=101	N=34	N=65
Erlotinib/gefitinib	2 (2.6)	62 (61.4)	7 (20.6)	21 (32.3)
Afatinib	3 (3.9)	0	3 (8.8)	0
Osimertinib	21 (27.6)	1 (1.0)	5 (14.7)	9 (13.8)
Platinum doublets	39 (51.3)	1 (1.0)	5 (14.7)	4 (6.2)
Docetaxel	4 (5.3)	32 (31.7)	11 (32.4)	21 (32.3)
Pemetrexed	2 (2.6)	4 (4.0)	3 (8.8)	9 (13.8)
Single agent chemotherapy	5 (6.6)	1 (1.0)	0	1 (1.5)

Table 3. Subsequent Treatments Based on First-line Systemic Therapy.

The number of patients treated with chemotherapy 1L who received EGFR-TKI (first- or second generations) as one of the subsequent treatments was 78.5 %, while the number of patients receiving EGFR-TKI 1L who were given chemotherapy as one of subsequent treatments was 41.8 %. The number of patients receiving chemotherapy 1L and EGFR-TKI 1L who received osimertinib as 2L or more was 13.3% and 17.3 % (p= 0.366), respectively.

Efficacy of first- and second-generation EGFR-TKI

The number of patients receiving EGFR-TKI as 1L, 2L and 3L or more was 56.3% (160/284), 21.8% (62/284) and 9.2% (26/284), respectively. Switch maintenance (MN) EGFR-TKI was found in 3.2% (9/284) cases with 5 patients switching once after EGFR mutation reported and 4 switching after completed course of chemotherapy 1L. In addition, 27 (9.5%) patients did not receive (NR) any EGFR-TKI. The reasons for not receiving EGFR-TK1 were financial problems (53.9%), poor ECOG-PS (15.4%), slow progression of disease (7.7%), loss to follow up (7.7%), death before EGFR mutation status known (7.7%), and unknown reason (7.7%).

Median number of systemic treatment regimens in patients receiving EGFR-TKI as NR, 1L+MN, 2L and 3 L or more was 1.0 (Q1-Q3, 1.0-1.5), 2.0 (Q1-Q3, 1.0-2.0), 3.0 (Q1-Q3, 2.0-3.5) and 3.0 (Q1-Q3, 3.0-5.0) (p<0.001), respectively.

Median PFS of patients receiving EGFR-TKI line as 1L+MN, 2L and 3L or more was 12.39 (95%CI: 10.84 to13.94), 10.55 (95%CI: 8.78 to 12.31), and 9.89 (95%CI: 6.34 to13.38) months (p=0.472), respectively.

Median OS of patients receiving EGFR-TKI as NR, 1L+MN, 2L and 3L or more was 11.10 (95%CI: 8.21 to 14.00), 19.08 (95%CI: 15.76 to 22.41), 23.06 (95%CI: 15.91 to 30.21) and 32.46 (95%CI: 21.61 to 43.30) months (p=0.006), respectively (Figure 2).

Figure 2. Survival of Patients Based on Line of EGFR-TKI Received.

Looking at the MN group only, the median OS (n=9) was 16.85 months (95%CI: 3.35 to 40.67).

Reasons for stopping EGFR-TKI treatment were progression of disease (75.1%), death (8.0 %), lost to follow-up (6.2%), financial problems (4.9%), adverse events (0.9%), completion of treatment course as an induction systemic therapy before concurrent chemo- radiation (0.4%) and unknown reason (4.4 %).

Waiting time before receiving EGFR-TKI treatment

Waiting time of patients with stage 4 NSCLC who received EGFR-TKI 1L was analyzed by the EGFR mutation report and TKI treatment. The percentage of patients who had their EGFR mutation status identified when first visiting the oncology clinic was 10.4 %, while 89.6 % had unknown EGFR status.

Median period from pathological report to EGFR mutation report tested by tissue pathology and plasma was 21.5 days (95%CI: 0.00 to 93.45) and 21.0 days (95%CI: 0.00 to 57.00), respectively. Median time from EGFR mutation report to received EGFR-TKI treatment was 7.0 days (95%CI: -7.65 to 39.10). In addition, 7.5% of patients received the medication before EGFR mutation status was known.

Adverse events of first-generation EGFR-TKI

Adverse events were assessed in 195 of 246 patients (79.2%) who received erlotinib and gefitinib (Supplementary Table 3). Diarrhea and paronychiae were the two most common adverse events reported. Other adverse events reported included fatigue (n=1) and an eye rash (n=3) with erlotinib and eye rash (n=1) with gefitinib.

Drug modification occurred due to adverse events with both drugs. Gefitinib dose reduction occurred in 16.4% of patients, and 1.4% of those changing to receive erlotinib. The recommended initial dose of gefitinib was 1750 mg per week (250 mg per day). After drug modification, the median dose was reduced to 875 mg per week (Q1-Q3, 750-1250 mg per week). Erlotinib dose reduction occurred in 25.6% of patients. While the recommended dose of erlotinib was 1,050 mg per week (150 mg per day), the median dose after reduction was 725 mg per week (Q1-Q3, 625-862 mg per week).

Median survival of patients receiving and not receiving dose reductions due to adverse events was 33.05 months (95%CI: 15.70 to 50.39) compared to 20.14 months (95%CI: 17.69 to 22.58) (p=0.207), respectively.

Prognostic factors

Unfavorable prognostic factors in the multivariate analysis for overall survival included poor ECOG-PS (OR=3.17; 95%CI: 1.96-5.13; p<.001), not received EGFR-TKI (OR=3.83; 95%CI=1.94-7.56; p<.001) and received EGFR-TKI as 1L or MN (OR=2.30; 95%CI=1.40-3.79; p=.001). (Table 4).

		Univariate analysis				Multivariate analysis	
Factors	Median survival		95 % CI	P	HR	95% CI	P
Sex	Male	18.49	13.86-23.13	0.153	-		-
	Female	22.63	19.38-25.89				
Age	<65	23.06	20.03-27.67	0.273	-		-
	≥65	19.05	13.89-24.22				
ECOG-PS	0-2	22.7	19.19-26.93	0.002	1		
	04-Mar	11.92	4.89-18.96		3.17	1.96-5.13	<0.001
	unknown	24.47	13.42-35.52		1.06	0.49-2.30	0.868
Smoking	never	22.34	18.83-25.84	0.135	-		-
	smoking	15.86	10.99-20.75				
	unknown	23.29	13.26-33.32				
Health fund	UC	21.32	18.03-24.60	0.962	-		-

	SSS	20.17	13.33-27.00				
	GSEO	20.99	16.64-25.33				
	self-pay	26.21	17.03-35.39				
Tumor type	ADC	21.32	18.47-24.17	0.334	-		-
	SqCC	12.4	0.00-28.51				
	Others	18.23	0.00-36.59				
Stage	III-B	23.29	21.30-25.28	0.068	-		-
	IV	20	17.97-22.04				
	recurrence	42.41	34.18-50.64				
EGFR mutation	exon 19	23.26	19.67-26.84	0.212	-		-
	exon 21	18.03	13.62-22.44				
EGFR-TKI	gefitinib	21.75	18.47-25.02	0.087	-		-
	erlotinib	28.68	14.18-43.18				
	others	13.21	0.00-29.16				
First-line	chemotherapy	23.26	19.64-26.88	0.274	-		-
treatment	EGFR-TKI	19.78	16.21-23.34				
EGFR-TKI treatment	not received	11.1	8.21-14.00	0.006	3.83	1.94-7.56	<0.001
	1L + MN	19.08	15.76-22.30		2.3	1.40-3.79	0.001
	2L	23.06	15.91-30.21		1.4	0.80-2.43	0.227
	3L or more	32.46	21.61-43.30		1		

Table 4. Prognostic Factors for Survival by Univariate and Multivariate Analysis.

ADC, adenocarcinoma; GSEO, government servant and state enterprise officer coverage; SqCC, squamous cell carcinoma; SSS, social security scheme coverage; UC, universal coverage

Discussion

This retrospective study was conducted to determine survival and treatment patterns of patients with advanced NSCLC in the period before EGFR-TKI was listed in the national essential drug in Thailand and could be reimbursed by all health fund groups. Prior to 2020, only patients with GSEO could receive reimbursement for the medication as 2L or more, while those with UC and SSS needed to pay out of pocket for access to the drug [22-23]. Our study found that patients who received EGFR- TKI or chemotherapy as 1L treatment had comparable survival times. This was likely the result of high crossover rate in subsequent treatments with 61.4% of patients receiving erlotinib or gefitinib as 2L. This phenomenon was also found in clinical trials [8-9, 11-13]. Real world data from Japan by Okamoto et al [16] found that the number of patients who received chemotherapy 1L crossed to receive subsequent EGFR-TKI more frequently than those receiving EGFR-TKI 1L who crossed to receive chemotherapy in 2L or 3L. This study also showed that the number of patients who received chemotherapy 1L had received 2L and 3L systemic therapy in a higher proportion than those of who received EGFR-TKI 1L. It should be pointed out that patient groups had statistical differences in both age and EGFR mutation type.

This study showed that the OS of EGFR-mutation positive advanced NSCLC patients receiving EGFR-TKI 1L fell in the lower range (19.78 months) of the phase 3 landmark studies (range 19.5-37.3 months) [8-13]. This could be the result of our study including a higher proportion of poor ECOG-PS patients. An analysis of the less severe ECOG-PS 0-2 patients who received 1L EGFR-TKI found a median OS of 22.70 months.

Patients who received EGFR-TKIs as 3L or more had longer survival compared to those received it as 1L. This might be the consequence of a higher number of systemic treatments in patients

receiving TKI as 3L or more compared to those who received TKI as 1L or MN. In addition, the course of the disease among groups might be different, especially at initiation. The survival plot in Figure 2 illustrates that the graph of each group separated since the beginning and the graph of patients who received TKI as 3L or more had no death events until after 12 months.

Clinical practice guidelines recommend EGFR-TKI as 1L treatment because it provides longer PFS, higher ORR and better quality of life when compared to chemotherapy [2-3]. These conclusions are based on clinical phase 3 trials which were conducted under optimum condition [8-11]. Our real-world study revealed that 40% of advanced NSCLC patients visiting oncology clinics had fair to poor ECOG-PS (ECOG 2-4), and 90% had unknown EGFR mutation status. In addition, the waiting time from the diagnosis of lung cancer to EGFR mutation status report, either from tissue or plasma testing, was approximately 3 weeks long, which lead to delays in TKI treatment. Based on a previous study waiting time for the EGFR report in Thailand is influenced by processing time including referral time and/or tissue paraffin-block request time rather than turn-around time of EGFR mutation testing [23].

In Thailand, EGFR-TKI was approved for treatment to all health fund groups with advanced NSCLC harboring EGFR mutation since 2020. However, it was reimbursed only for patients previously not receiving chemotherapy with documented EGFR mutation-positive. The result of this study indicated that EGFR-TKI treatment remained beneficial regardless of the EGFR-TKI treatment line.

No differences in outcomes among health fund groups were also found. Switching maintenance to EGFR-TKI treatment in EGFR-mutated lung cancer patients previously receiving 1L chemotherapy has already been supported by robust clinical evidence [3, 19, 28-29]. Additionally, real world data also showed that EGFR-TKI was a rational option in patients without many treatment choices such as patients in intensive care units or those on mechanical ventilators before EGFR mutation status was confirmed, especially in areas with a high incidence of EGFR mutation such as Thailand [30-31]. Based on these data, the indication for reimbursing EGFR-TKI should be extended to treatment points including when switching therapies during/after chemotherapy and when critically ill or poor performance status patients become unsuitable for receiving chemotherapy while waiting for the EGFR mutation report. This recommendation is keeping with defending patients' rights to access novel treatments like EGFR-TKI.

The incidence of common adverse events including diarrhea, rash, hepatitis, and stomatitis in this study did not differ from the phase 3 studies. However, the incidence of paronychiae in this study among patients treated with erlotinib (46%) and gefitinib (38%) was higher than previous studies: erlotinib (4-18%) and gefitinib (12-28%) [8-11, 32-33]. This study also showed that EGFR-TKI dose reduction due to adverse events did not contribute to a negative impact on survival.

Regarding prognostic factors, this study showed that poor ECOG-PS was an unfavorable prognostic factor for OS similar to previous studies from Japan and Taiwan [18,34]. Patients who received EGFR-TKI as NR or 1L exhibited a poor prognosis compared to those who received it as 3L or later as discussed above.

In conclusion, although EGFR-TKI was not reimbursable under all health fund groups during the study period, the OS of patients with EGFR mutation positive lung cancer treated with EGFR-TKIs in Thailand was comparable to clinical studies. Patients who were able to receive EGFR-TKI gained benefit from the treatment regardless of line of TKI treatment or health fund group.

References

References

1. International Agency for Research on Lung Cancer. GLOBOCAN 2020. *Available at: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf [Accessed 16 May 2022].*
2. Planchard D., Popat S., Kerr K., Novello S., Smit E. F., Faivre-Finn C., Mok T. S., Reck M., Van Schil P. E., Hellmann M. D., Peters S.. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology: Official Journal of the European Society for Medical Oncology.* 2018; 29(Suppl 4)DOI
3. NCCN guideline, National Practice Guideline in Oncology. Non-Small Cell Lung Cancer Version 3-2022. National Comprehensive Cancer Network. 2022. *Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf [Accessed 16 May 2022].*
4. Mitsudomi T. Molecular epidemiology of lung cancer and geographic variations with special reference to EGFR mutations. *Translational Lung Cancer Research.* 2014; 3(4)DOI
5. Wiriyaukaradecha K, Bunyoo C, Udomchaiprasertkul W, Sricharunrat T, Petchjorm S, Lamlertthon W, Sritana N. Frequency of EGFR Mutations among Thai Non-Small Cell Lung Cancer [NSCLC] Patients. *JOURNAL OF THE MEDICAL ASSOCIATION OF THAILAND.* 2018; 101(6)
6. Ciardiello F, Tortora G. EGFR antagonists in cancer treatment. *The New England Journal of Medicine.* 2008; 358(11)DOI
7. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *The New England Journal of Medicine.* 2008; 359(13)DOI
8. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *The New England Journal of Medicine.* 2010; 362(25)DOI
9. Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *The Lancet. Oncology.* 2010; 11(2)DOI
10. Zhou C, Wu Y, Chen G, Feng J, Liu X, Wang C, Zhang S, Wang J, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *The Lancet. Oncology.* 2011; 12(8)DOI
11. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *The Lancet. Oncology.* 2012; 13(3)DOI
12. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, Geater SL, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2013; 31(27)DOI
13. Wu Y, Zhou C, Hu C, Feng J, Lu S, Huang Y, Li W, Hou M, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *The Lancet. Oncology.* 2014; 15(2)DOI
14. Mok T. S. K., Cheng Y., Zhou X., Lee K. H., Nakagawa K., Niho S., Linke R., Rosell R., Corral J., Migliorino M. R., Pluzanski A., Noonan K., Tang Y., Wilner K. D., Wu Y. -L.. LBA19 - Updated overall survival (OS) from extended follow up in ARCHER 1050: A randomized phase III study comparing dacomitinib with gefitinib as first-line therapy for patients (pts) with EGFR mutations. *Annals of Oncology.* 2019; 30DOI
15. Ramalingam SS, Vansteenkiste J, Planchard D, Cho BC, Gray JE, Ohe Y, Zhou C, Reungwetwattana T, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *The New England Journal of Medicine.* 2020; 382(1)DOI
16. Okamoto I, Morita S, Tashiro N, Imamura F, Inoue A, Seto T, Yamamoto N, Ohe Y, Nakagawa K, Fukuoka M. Real world treatment and outcomes in EGFR mutation-positive non-small cell lung cancer: Long-term follow-up of a large patient cohort. *Lung Cancer (Amsterdam, Netherlands).* 2018; 117DOI

17. Wang Q, Gao W, Gao F, Jin S, Qu T, Lin F, Zhang C, Zhang J, Zhang Z, Chen L, Guo R. Efficacy and acquired resistance of EGFR-TKI combined with chemotherapy as first-line treatment for Chinese patients with advanced non-small cell lung cancer in a real-world setting. *BMC cancer.* 2021; 21(1)DOI
18. Yao Z, Liao W, Ho C, Chen K, Shih J, Chen J, Lin Z, Lin C, Chih-Hsin Yang J, Yu C. Real-World Data on Prognostic Factors for Overall Survival in EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer Patients Treated with First-Line Gefitinib. *The Oncologist.* 2017; 22(9)DOI
19. Arriola E, García Gómez R, Diz P, Majem M, Martínez Aguillo M, Valdivia J, Paredes A, Sánchez-Torres JM, et al. Clinical management and outcome of patients with advanced NSCLC carrying EGFR mutations in Spain. *BMC cancer.* 2018; 18(1)DOI
20. Cuppens K, Lodewyckx L, Demedts I, Decoster L, Colinet B, Deschepper K, Janssens A, Galdermans D, Pieters T. Real-World Treatment Patterns, Epidermal Growth Factor Receptor (EGFR) Testing and Outcomes in EGFR-Mutated Advanced Non-small Cell Lung Cancer Patients in Belgium: Results from the REVEAL Study. *Drugs - Real World Outcomes.* 2021; 8(2)DOI
21. Pluzanski A, Krzakowski M, Kowalski D, Dziadziuszko R. Real-world clinical outcomes of first-generation and second-generation epidermal growth factor receptor tyrosine kinase inhibitors in a large cohort of European non-small-cell lung cancer patients. *ESMO open.* 2020; 5(6)DOI
22. Reungwetwattana T, Oranratnachai S, Puataweepong P, Tangsujaritvijit V, Cherntanomwong P. Lung Cancer in Thailand. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer.* 2020; 15(11)DOI
23. Sukauichai S, Tovanabutra C, Wanglikitkul S, Chomprasert K. Survival of patients with advanced NSCLC treated with first-generation EGFRTKIs at a cancer hospital in Thailand, 2011-2016. *Journal of Medical Oncology and Therapy.* 2018; 3(2):23-31. DOI
24. Supavavej A, Handsakul M, Sungkasubun P, Siripaibun J, Chaiwiriyawong W, Ungtrakul T, Lamlertthon W. The Survival of Advanced Non-small Cell Lung Cancer Patients Treated with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in Thailand: A Single Institution Review. *JOURNAL OF THE MEDICAL ASSOCIATION OF THAILAND.* 2021; 104(7)
25. Mirsadraee S, Oswal D, Alizadeh Y, Caulo A, Beek E. The 7th lung cancer TNM classification and staging system: Review of the changes and implications. *World Journal of Radiology.* 2012; 4(4)DOI
26. Eisenhauer E. A., Therasse P., Bogaerts J., Schwartz L. H., Sargent D., Ford R., Dancey J., Arbuck S., Gwyther S., Mooney M., Rubinstein L., Shankar L., Dodd L., Kaplan R., Lacombe D., Verweij J.. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer (Oxford, England: 1990).* 2009; 45(2)DOI
27. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. *Available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. [Accessed 12 Dec 2021].*
28. Cappuzzo F, Ciuleanu T, Stelmakh L, Cicenas S, Szczésna A, Juhász E, Esteban E, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. *The Lancet. Oncology.* 2010; 11(6)DOI
29. Zhao H, Fan Y, Ma S, Song X, Han B, Cheng Y, Huang C, et al. Final overall survival results from a phase III, randomized, placebo-controlled, parallel-group study of gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804). *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer.* 2015; 10(4)DOI
30. Chen Y, Lin J, Ho C, Yang C, Chang C, Huang T, Chen C, et al. Outcomes of cancer therapy administered to treatment-naïve lung cancer patients in the intensive care unit. *Journal of Cancer.* 2017; 8(11)DOI
31. Chien C, Chen H. Lazarus response to treatment of patients with lung cancer and oncogenic mutations in the intensive care unit. *Journal of Thoracic Disease.* 2016; 8(11)DOI
32. Mok TS, Wu Y, Thongprasert S, Yang C, Chu D, Saijo N, Sunpaweravong P, et al. Gefitinib

or carboplatin-paclitaxel in pulmonary adenocarcinoma. *The New England Journal of Medicine.* 2009; 361(10)DOI

33. Urata Y, Katakami N, Morita S, Kaji R, Yoshioka H, Seto T, Satouchi M, et al Y. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.* 2016; 34(27)DOI
34. Inoue A, Yoshida K, Morita S, Imamura F, Seto T, Okamoto I, Nakagawa K, et al. Characteristics and overall survival of EGFR mutation-positive non-small cell lung cancer treated with EGFR tyrosine kinase inhibitors: a retrospective analysis for 1660 Japanese patients. *Japanese Journal of Clinical Oncology.* 2016; 46(5)DOI