European Review for Medical and Pharmacological Sciences 2022; 26: 7632-7640

First-line treatment and overall survival in EGFR mutation-positive advanced non-small cell lung cancer: a national cohort study

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Abstract. – OBJECTIVE: Non-squamous non-small cell lung cancer (NSCLC) is the first leading cause of cancer-related deaths in Taiwan. This study aimed at evaluating the effectiveness of first-line targeted therapy for advanced epidermal growth factor receptor (EGFR) mutation-positive non-squamous NSCLC in Taiwan.

PATIENTS AND METHODS: This was a real-world, retrospective, observational study of patients diagnosed with advanced non-squamous NSCLC (N=63,248). Between 2011 and 2019, 19,458 patients received targeted therapy and 22,994 patients received chemotherapy alone; between 2002 and 2010, 20,796 patients received chemotherapy alone. Overall survival (OS) was determined.

RESULTS: The median OS for patients treated with first-line targeted therapy (22.9 months) was longer than that of patients receiving chemotherapy alone (11.7 months). HR: 0.521, log-rank test, $p<0.001$.

CONCLUSIONS: These data represent the potential survival outcomes of Taiwanese patients with advanced EGFR mutation-positive non-squamous NSCLC in clinical practice.

Key Words:
Non-Squamous non-small cell lung cancer, Adenocarcinoma, Tyrosine kinase inhibitor, Epidermal growth factor receptor, Overall survival.

Introduction

According to the 2018 Annual Cancer Registry Report, the crude incidence rate of lung cancer is approximately 65.1 per 100,000 people[1]. The mortality rate of tracheal, bronchial, and lung cancer is the highest among the top ten causes of cancer death, with a mortality rate of about 40.8 per 100,000 people[2].

There are two main types of lung cancer: small cell lung cancer and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 85% of all lung cancers. NSCLC can be classified into squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, depending on its histology[3]. Lung cancer is divided into stages I to IV depending on the size of the tumor, the degree of lymph node invasion, and whether the tumor has metastasized. Stage III disease can be divided into IIIA, IIIB, and IIIC. Most cases of lung cancer are inoperable once they have progressed to stage IIIB, and a diagnosis of stage IV indicates that the tumor has metastasized to organs other than the lungs[4].

It is recommended that patients diagnosed with advanced NSCLC should be tested for driver mutations[4]. The lung cancer driver mutation types include epidermal growth factor receptor (EGFR), ALK, ROS-1, MET, and BRAF. The proportion of EGFR mutations in this group is relatively high in Asians, at approximately 50%[4]. EGFR mutations are now known to occur more frequently in adenocarcinomas and are seen more often in Asian women with no smoking history[5,6]. The prevalence of EGFR mutations in NSCLC is higher in Asians than in other races, ranging from approximately 19-61% in the Asian region to only 5-10% in others[6]. Several studies have investigated NSCLC in Taiwan in particular[7-10]. One study[7] at Chang Gung Memorial Hospital analyzed 101 patients with NSCLC (69 cases of adenocarcinoma and 24 cases of squamous cell carcinoma) and found that the 39 cases with EGFR mutations were all adenocarcinoma cases. EGFR mutations accounted for 38.6% of all NSCLC[7]. In the second study[8], Taipei Veterans General Hospital obtained 54 patient samples (43 cases of adenocarcinoma and 10 cases of squamous cell carcinoma) from advanced NSCLC patients treated with gefitinib and found that 33 cases (61.1%) had a mutation in the EGFR gene. The third study[9] was conducted at Chi Mei Medical Center, which

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analyzed 77 patients with lung adenocarcinoma and found that 42 patients (54.4%) had a mutation in the EGFR gene. In another retrospective study[10], mutations in the EGFR gene were found in approximately 55.7% of lung adenocarcinoma patients in Taiwan. The rate of NSCLC with mutations in the EGFR gene in Taiwan was found to be between approximately 38.6% and 61.1%[7,8].

According to guidelines published by the National Comprehensive Cancer Network (NCCN) in February 2020[9], the first-line treatments recommended for metastatic or advanced NSCLC with EGFR mutations are as follows: patients with mutations in the gene for EGFR who have already started first-line systemic therapy may complete the course of treatment first. Alternatively, they may switch directly to osimertinib (preferred), erlotinib, afatinib, gefitinib, or dacomitinib, or be treated with erlotinib and ramucirumab in combination. Alternatively, patients with non-squamous cell carcinoma without hemoptysis symptoms may be treated with erlotinib and bevacizumab in combination until disease progression. According to the guidelines published by the European Society of Medical Oncology (ESMO) in 2018 and updated in September 2019, the recommendation for first-line treatment for metastatic or advanced NSCLC with mutations in the EGFR gene is as follows[10]: after a diagnosis of stage IV NSCLC with mutations in the EGFR gene, first-line treatment includes osimertinib, gefitinib, erlotinib (in combination with bevacizumab or ramucirumab), afatinib, dacomitinib, or a combination of gefitinib, carboplatin, and pemetrexed until disease progression. According to the top ten National Health Insurance (NHI) medical expenditures for various types of cancer in 2021, lung cancer accounts for the highest medical expenses, amounting to 22.896 billion NTD (around 763.2 million USD). In 2021, drug expenditures for lung cancer patients were analyzed to be 12.648 billion NTD (around 421.6 million USD), of which cancer drugs accounted for 55%, with targeted drugs being the majority[11].

The objective of this retrospective longitudinal cohort study was to compare the benefits of first-line targeted drugs covered by the NHI with those of chemotherapy in patients with stage IIIB-IV EGFR-positive lung cancer at the population level and the associated stage-specific survival.

Patients and Methods

According to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), patients with NSCLC were included if the primary site was the lung (diagnosis codes: C34.0-C34.9) and were excluded when diagnosed with a tissue type of small cell carcinoma (morphology codes: M-80413, M80423, M-80433, M-80443, and M-80453). The cancer stages IIIB-IV, as classified by the American Joint Committee on Cancer (AJCC) classification system, were included.

Study Design

In Taiwan, EGFR tyrosine kinase inhibitor (TKI) therapy for NSCLC has been reimbursed for NHI coverage since 2011. In this study, patients were divided into three cohorts for comparison: Group 1 consisted of patients who received targeted EGFR-TKI therapy from January 1, 2011, to December 31, 2019, while Group 2 consisted of patients who received chemotherapy as the first-line treatment over the same period. Group 3, the reference group, included patients who received chemotherapy as the first-line treatment from January 1, 2002, to December 31, 2010. All patients were followed up to the end of the following year to ensure at least 1 year of follow-up for all patients (the last follow-up date for Group 3 was December 31, 2011; the last follow-up date for Group 1 and Group 2 was December 31, 2020).

The treatment (targeted EGFR-TKI therapy or chemotherapy) used from the date when patients with advanced NSCLC were diagnosed for the first time to the following 3 months was considered the first-line drug therapy. Patients who used targeted therapy and chemotherapy in combination, and those who swapped, making it impossible to clearly categorize them during the observation period, were excluded. According to NCCN guidelines for the treatment of NSCLC, chemotherapy drugs included cisplatin, carboplatin, docetaxel, etoposide, gemcitabine, paclitaxel, pemetrexed, and vinorelbine. The drugs included in EGFR-TKI-targeted therapies included gefitinib, erlotinib, afatinib, osimertinib, and dacomitinib. The indications for targeted EGFR-TKI therapies for advanced NSCLC reimbursed in NHI coverage in Taiwan are summarized in Table I.

Data Sources

This study used the Taiwan National Health Insurance Research Database (NHIRD) and Cancer Registration Database to conduct retrospective analyses. Cancer registration data included the collection of diagnostic data for newly diagnosed cancer cases, including the date of diagno-

Table I. The indications of the targeted EGFR-TKI therapies for advanced NSCLC that were reimbursed in NHI coverage.

Drugs	Scope of NHI Benefits	Indications
Gefitinib	The first-line treatment is limited to: (1) Patients with locally invasive or metastatic (i.e., stage IIIB, IIIC, or IV) lung adenocarcinoma with the EGFR-TK gene mutation. (2) Lung adenocarcinoma that has been treated with first-line platinum-containing chemotherapy or has been treated with first-line chemotherapy at age 70 or older but has still progressed locally or metastasized.	(1) First-line treatment for patients with EGFR-TK mutations in locally invasive or metastatic NSCLC. (2) Second-line drugs for patients with lung adenocarcinoma who have been treated with chemotherapy but whose cancer has still progressed locally or metastasized.
Erlotinib	Limited to: (1) First-line treatment of patients with EGFR-TK mutations in locally invasive or metastatic (i.e., stage IIIB, IIIC or IV) lung adenocarcinoma. (2) Maintenance therapy for patients with locally advanced or metastatic lung adenocarcinoma with stable disease (without partial response or complete response) after 4 cycles of platinum-based first-line chemotherapy. (3) Second-line drugs for patients with adenocarcinoma of NSCLC who have been treated with platinum-based first line chemotherapy or have been treated with first-line chemotherapy at age 70 or older, but whose conditions are still locally progressive or metastatic. (4) Third-line drugs for patients with NSCLC, who have previously been treated with platinum-based chemotherapy and docetaxel or paclitaxel chemotherapy but are still locally progressive or metastatic.	(1) First-line and maintenance therapy for patients with EGFR-TK mutations in locally invasive or metastatic NSCLC. (2) Second-line drugs for patients with lung adenocarcinoma who have been treated with chemotherapy but whose cancer has still progressed locally or metastasized.
Afatinib	Limited to: (1) First-line treatment for patients with locally advanced or metastatic (i.e., stages IIIB, IIIC, or IV) lung adenocarcinoma with EGFR-TK gene mutations. (2) Second-line treatment for patients with locally advanced or metastatic squamous NSCLC that has previously been treated with first-line platinum-based chemotherapy and still deteriorated.	(1) First-line therapy for patients with EGFR-TK mutations in locally advanced or metastatic NSCLC. (2) Patients with locally advanced or metastatic squamous NSCLC that has progressed during or after platinum-based chemotherapy.
Osimertinib	Limited to: (1) First-line treatment for patients with metastatic (stage IV) lung adenocarcinoma with the EGFR exon 19 deletion gene mutation and brain metastasis. (2) Second-line treatment for patients with locally invasive or metastatic NSCLC with the EGFR T790M mutation that has been previously unsuccessfully treated with the following EGFR targeted drugs: gefitinib, erlotinib, afatinib, or dacomitinib.	(1) Adjuvant therapy for EGFR mutation-positive NSCLC: For patients with the (EGFR exon 19 deletion or exon 21 L858R mutation as adjuvant therapy after tumor resection. (2) First-line treatment for EGFR mutation positive metastatic NSCLC: Suitable as first-line treatment for patients with locally invasive or metastatic NSCLC with an EGFR mutation. (3) EGFR T790M mutation-positive metastatic NSCLC that was treated previously: Suitable for treating patients with locally invasive or metastatic NSCLC with the EGFR T790M mutation whose disease has progressed during or after EGFR TKI therapy.
Dacomitinib	A first-line treatment that is limited to patients with EGFR-TK exon 19 del or exon 21 L858R point mutations in locally invasive or metastatic (i.e., stage IIIB, IIIC, or IV) lung adenocarcinoma without brain metastasis (non-CNS).	A single therapy suitable as a first-line treatment for adult patients with EGFR mutations in locally advanced or metastatic NSCLC.

NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor, TK, tyrosine kinase, CNS, central nervous system

sis, age at diagnosis, primary site, histopathology, and stage. In this study, cancer registration data from 2002 to 2019 for patients with advanced NSCLC were obtained. The NHIRD covers 99% of Taiwan's medical insurance claims, including drug use records. From 2002 to 2020, the NHIRD was used to observe first-line drug use in patients with advanced NSCLC.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics and treatment outcomes. Data processing and analysis were performed using SAS software (version 9.4; SAS Institute, Cary, North Carolina, USA). Differences in continuous and categorical variables were compared separately using *t*-tests and χ^2 tests. The OS of the targeted EGFR-TKI therapy and chemotherapy groups was compared using Kaplan-Meier survival analysis. Subsequently, survival curves were plotted and the differences between the two groups were compared using the log-rank test.

Results

From 2002 to 2019, the number of patients with lung cancer in Taiwan increased from 1,463 to 15,539 and the number of patients with stage IV disease increased from 682 to 7,804. The percentage of patients with stage I lung cancer in Taiwan ranged from 12% to 30% and that of patients with stage IV lung cancer ranged from 47% to 50% over this time period. The 5-year survival rate of patients with lung cancer in Taiwan ranged from 11.3% to 33.5%. The 5-year survival rate of stage IV patients ranged from 3.3% to 10.2%. There was a significant increase in the number of patients with stage I lung cancer, and their 5-year survival rate increased the most, resulting in a significant increase in the overall 5-year survival rate of lung cancer regardless of stage. As stage IV lung cancer was more severe, it seemed inappropriate to assess the 5-year survival rate. The 3-year survival rate of patients with stage IV lung cancer improved from 8% to 19%.

Cohorts and Baseline Characteristics

Based on the relevant ICD-O-3 diagnostic codes, 177,612 individuals were diagnosed with lung cancer between January 1, 2002, and December 31, 2019. The source population for this study included 63,248 patients with advanced cell lung cancer (see patients' flow chart in Figure 1). In that group, 106,192 individuals (59.8%) were diagnosed with advanced NSCLC, with 59.56% (n=63,248) included to observe first-line drug use in patients with advanced NSCLC. This analysis was based on patients who received first-line targeted treatment or chemotherapy. The patients' use of drugs within 3 months of diagnosis was used as the basis for judgment and to divide the sample into three groups. Group 1 included 19,458 patients who received targeted therapy as the first-line treatment between January 1, 2011, and December 31, 2019. Group 2 included 22,994 patients who received chemotherapy as the first-line treatment between January 1, 2011, and December 31, 2019. Group 3 included 20,796 patients who received chemotherapy as the first-line treatment between January 1, 2002, and December 31, 2010.

Baseline patient characteristics are summarized in Table II for the full study population by group; the mean (SD) age was 65.6 (12.3) years, 58.4% were male, and 71.2% were diagnosed with adenocarcinoma. Group 1 (which received first-line targeted treatment, 2011-2019) also included advanced lung adenocarcinoma with EGFR mutation-positive patients, and approximately 62.5% were female.

Overall Survival

The median OS (mOS) for all patients with stage IV cancer was 4.8 months [95% confidence interval (CI): 4.7-5.0]. The survival rates from year 1 to year 5 were 74% to 15% for Group 1 and 49% to 6% for Group 3.

For advanced non-squamous NSCLC patients, the mOS was more than 22.9 months in Group 1 and 11.7 months in Group 3.

In the survival analysis of patients with advanced NSCLC, it was found that the survival rate of Group 1 was significantly higher than that of Group 3 (HR: 0.521, log-rank test, $p<0.001$) (Table III, Figure 2), indicating that the first-line treatment of advanced lung adenocarcinoma with EGFR-TKI gene mutations with targeted drugs covered by NHI was beneficial to patient survival compared to chemotherapy alone. In the comparison of survival rates between the two groups, that of Group 1 was higher than both Groups 2 and 3 from year 1 to year 5, especially in year 1.

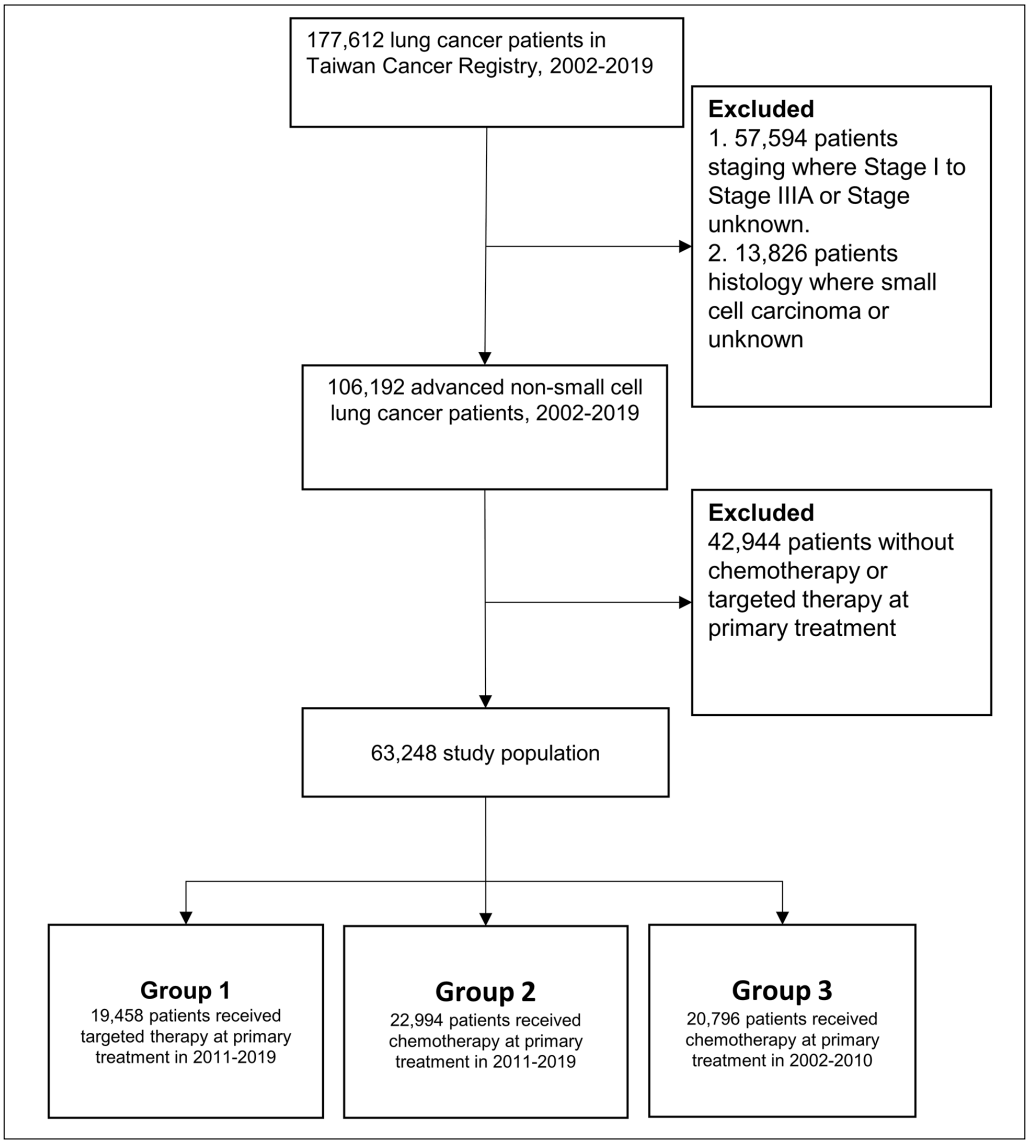

Figure 1. Flowchart of study population selection criteria.

Discussion

Cancer is the leading cause of death in Taiwan[12]. In 2020, approximately 797,000 patients with cancer required treatment in Taiwan[11]. The total cost of treatment, including examination and hospitalization, was 130.1 billion NTD[11]. Our retrospective study provides a population-based real-world perspective on the OS benefit of patients with advanced lung adenocarcinoma with an EGFR-TKI gene mutation who received first-line targeted drugs in Taiwan. The National Health Insurance Administration (NHIA), Taiwan's single-payer health insurance system, increasingly requires information about the clinical benefits, cost-effectiveness, and potential budget impacts of new cancer treatments. The study period of more than 18 years provided data concerning some of the more recent practice changes affecting lung cancer and sufficient time to assess the survival associated with these treatments. One of the key observations from our study is that the first-line treatment of EGFR-mutation-positive advanced lung adenocarcinoma with targeted drugs covered by NHI is beneficial to patient survival compared with chemotherapy alone.

According to a systematic literature review and meta-analysis[13] published in the Cochrane Library

Table II. Demographic and clinical characteristics of patients with non-small cell lung cancer.

Characteristics	Overall n=63,248	Group 1 n=19,458	Group 2 n=22,994	Group 3 n=20,796
Age at diagnosis (years)				
Mean (SD†)	65.6 (12.3)	67.4 (12.2)	65.2 (12.1)	64.3 (12.3)
Median (IQR‡)	66 (18.0)	67 (18.0)	65 (17.0)	66 (19.0)
Sex, n (%)				
Female	26,284 (41.6)	12,168 (62.5)	6,655 (28.9)	7,461 (35.9)
Male	36,964 (58.4)	7,290 (37.5)	16,339 (71.1)	13,335 (64.1)
AJCC§ stage, n (%)				
IIIB	10,448 (16.5)	881 (4.5)	4,256 (18.5)	5,311 (25.5)
IV	52,800 (83.5)	18,577 (95.5)	18,738 (81.5)	15,485 (74.5)
Histology, n (%)				
Adenocarcinoma	45,038 (71.2)	18,574 (95.5)	13,462 (58.5)	13,002 (62.5)
Squamous cell carcinoma	10,397 (16.4)	61 (0.3)	6,200 (27.0)	4,136 (19.9)
Other malignancy	7,813 (12.4)	823 (4.2)	3,332 (14.5)	3,658 (17.6)
Subsequent therapy, n (%)				
Yes	45,969 (72.7)	12,184 (62.6)	17,380 (75.6)	16,405 (78.9)
No	17,279 (27.3)	7,274 (37.4)	5,614 (24.4)	4,391 (21.1)

†SD, standard deviation; ‡IQR, interquartile range; §AJCC, American Joint Committee on Cancer.

Table III. Hazard ratio for overall survival.

	Crude			Adjusted		
	HR†	95% CI‡	*p*-value	HR	95% CI	*p*-value
Group						
Group 1	0.576	0.564-0.589	<0.001	0.521	0.508-0.534	<.001
Group 2	1.011	0.991-1.031	0.29	0.914	0.895-0.933	<.001
Group 3	1	(reference)		1	(reference)	
Age at diagnosis (years)	1.017	1.016-1.017	<0.001	1.017	1.016-1.018	<.001
Sex						
Female	1	(reference)		1	(reference)	
Male	1.574	1.547-1.602	<0.001	1.357	1.332-1.383	<.001
AJCC§ stage						
IIIB	1	(reference)		1	(reference)	
IV	1.176	1.148-1.203	<0.001	1.641	1.602-1.682	<.001
Histology						
Adenocarcinoma	1	(reference)		1	(reference	
Squamous cell carcinoma	1.726	1.687-1.765	<0.001	1.336	1.302-1.370	<.001
Other malignancy	1.569	1.529-1.610	<0.001	1.307	1.273-1.343	<.001
Subsequent therapy						
Yes	1	(reference)		1	(reference)	
No	1.478	1.450-1.507	<0.001	1.579	1.548-1.611	<.001

†SD, standard deviation; ‡IQR, interquartile range; §AJCC, American Joint Committee on Cancer.

in 2021, which focused on the relative efficacy of EGFR-TKI first-line therapy in the treatment of EGFR mutation-positive NSCLC, 22 trials met the inclusion criteria. Among them, only EGFR mutation-positive NSCLC patients were recruited for 10 trials and mixed groups were recruit-

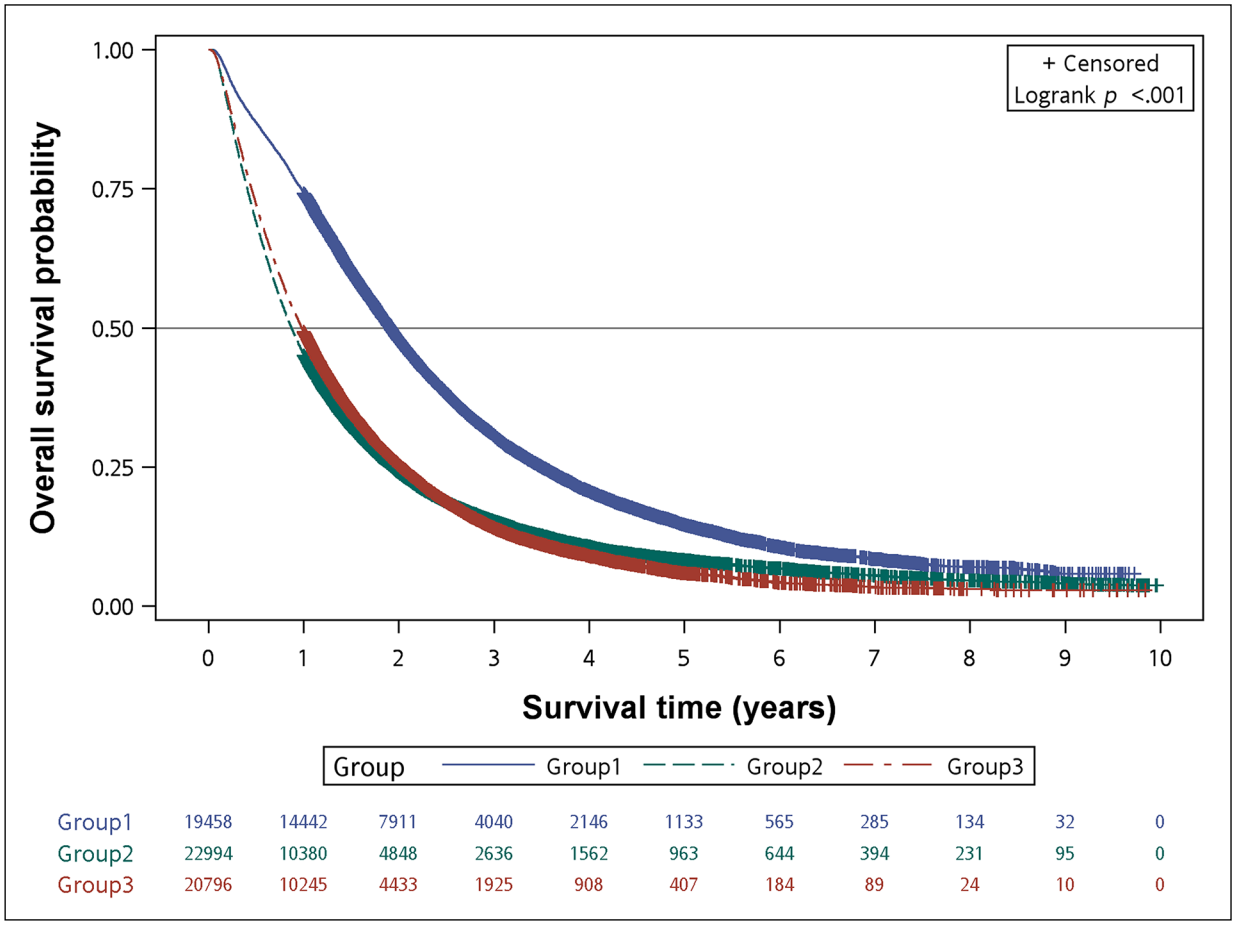

Figure 2. Kaplan-Meier survival curves of study groups for overall survival.

ed for the remaining trials. The results of EGFR mutation-positive NSCLC patients were reported for subgroup analysis. The number of participants with EGFR mutation-positive tumors was 3,023. Among them, 2,563 were Asians[13].

Meta-analysis results have pointed out that the OS results among the trials included and compared for EGFR target therapy and cytotoxic chemotherapy or placebo were inconsistent[13].

This meta-analysis included 8 erlotinib clinical trials, 9 gefitinib trials, 2 afatinib trials, 2 cetuximab trials, and 1 icotinib-related clinical trial[13]. The FASTACT 2 trial results showed that compared to the sole use of cytotoxic chemotherapy, the patients who received erlotinib combined with cytotoxic chemotherapy had a prolonged OS[13]. The Han trial in 2017 showed that gefitinib combined with cytotoxic chemotherapy produced the same benefits. However, the results of both trials were conducted with only a small number of participants (n=97 and 122, respectively)[13].

In 7 trials[13], different methods were used to report health-related quality of life and symptom improvement. Each of the drugs erlotinib, gefitinib, and afatinib had two trials, which showed that compared to chemotherapy, TKI improved one or more indicators.

The comparison of erlotinib, gefitinib, and cytotoxic chemotherapy and the comparison of afatinib and cytotoxic chemotherapy showed considerable quality of evidence[13].

The meta-analysis findings provide limited evidence that TKIs can prolong OS compared to standard therapy[13]. However, the included trials mostly allowed participants to replace treatment following disease progression, which interfered with OS analysis. Single-drug TKIs remain the standard care therapy, while the benefits of combined TKIs and chemotherapy remain uncertain because the evidence was obtained from a small number of patients. Compared with erlotinib, gefitinib, afatinib, or icotinib, cytotoxic chemotherapy produced inferior results in EGFR muta-

tion-positive NSCLC, with stronger accompanying toxicity.

Currently, data supporting the use of monoclonal antibody therapy are unavailable[13]. Another systematic review with meta-analysis published in 2021 by Lee et al[14], found that EGFR-TKI therapy had improved progression-free survival (PFS), and reduced severe adverse events (SAEs), but had not improved OS compared to standard chemotherapy in advanced EGFR-mutated NSCLC.

Our study analyzed big data from the NHI database over the last 20 years. We found that the survival rate in Group 1 (received first-line targeted drugs from 2011 to 2019) was significantly higher than that of the control group (2002-2010 chemotherapy, Group 3) (log-rank test, $p<0.001$). Compared with chemotherapy, first-line targeted drug therapy in the treatment of late-stage EGFR mutation-positive NSCLC was found to be beneficial to patient survival. These results can compensate for the uncertainty in existing evidence-based clinical trials.

Limitations

This study has a few limitations. Firstly, some clinically important patient characteristics (such as performance status, tumor size and location, detailed smoking history, and comorbidities), additional treatment modalities (e.g., surgery and radiation therapy), and clinical outcomes (e.g., disease progression) were not available in the database. Secondly, in this study, patients who received targeted therapy within 3 months of diagnosis were defined as targeted treatment. Patients who started targeted treatment after the fourth month were categorized as non-targeted treatment. Consequently, the number of non-targeted treatment patients could have been overestimated. Finally, another limitation is the possibility that the use of subsequent therapies may also influence the outcome measures.

Conclusions

In our study, undertaken in a real-world setting, the mOS of advanced non-squamous NSCLC patients was more than 22.9 months and 15% survived for 5 years. This study explored the OS of patients with advanced NSCLC receiving first-line systemic therapies in a large national healthcare system. In a cohort of patients with advanced EGFR mutation-positive NSCLC, patients who received TKIs had a survival advantage.

Conflicts of Interest

The authors have nothing to disclose.

Acknowledgments

The authors thank the National Health Insurance Administration (NHIA), and Health Promotion Administration (HPA), Ministry of Health and Welfare (MOHW) for their database support.

Ethics Approval

The protocol was approved by the institutional review board (No.: N202005012).

Informed Consent

Informed consent was not required because of the retrospective nature of the study.

Authors' Contributions

Li-Ying Huang, Hui-Ping Chang, Ruei-Yi Chang, Hsueh-Yung Tai, Yu-Wen Huang, and Po-Chang Lee contributed to the design and implementation of research, to the analysis of results and to the writing of manuscript.

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