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Adjunctive Traditional Chinese Medicine Improves Survival in Patients With Advanced Lung Adenocarcinoma Treated With First-Line Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKIs): A Nationwide, Population-Based Cohort Study

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Abstract

Objectives: The clinical effect of traditional Chinese medicine (TCM) on survival in patients with advanced lung adenocarcinoma treated with first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is a major concern and requires more evidence from large-scale clinical studies. **Materials and Methods:** This population-based cohort study used the Taiwan National Health Insurance Research Database to enroll patients between 2006 and 2012 who had newly diagnosed locally advanced and metastatic lung adenocarcinoma treated with first-line gefitinib or erlotinib. Survival was tracked until 2013. The patients were separated into TCM users and nonusers, and Cox regression models were applied to determine the association between the use of TCM and the survival of patients. **Results:** A total of 1988 patients receiving first-line gefitinib or erlotinib for the treatment of EGFR-mutated advanced lung adenocarcinoma, with the exclusion of TCM users after tumor progression, were included in this cohort study. Compared with TCM nonuse, TCM use for ≥180 days was associated with a significantly decreased risk of mortality by 68% (adjusted hazard ratio [HR], 0.32 [95% CI, 0.21-0.50], $P < .0001$). Compared with TCM nonuse, TCM use for ≥180 days was associated with a significantly decreased risk of disease progression by 59% (adjusted HR, 0.41 [95% CI, 0.29-0.58], $P < .0001$). **Conclusion:** This cohort study suggests that adjunctive TCM therapy could improve overall survival and progression-free survival in patients with advanced lung adenocarcinoma treated with first-line TKIs. Future randomized, controlled trials are required to validate these findings.

Keywords

advanced lung adenocarcinoma, EGFR-TKI, traditional Chinese medicine, National Health Insurance Research Database, overall survival, progression-free survival

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Introduction

The leading cause of cancer deaths worldwide is lung cancer, which is categorized as small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC). The subtypes of NSCLC include adenocarcinoma, squamous cell (epidermoid) carcinoma, large cell (undifferentiated) carcinoma, and other subtypes. Nowadays, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have become first-line therapy for advanced NSCLC with EGFR mutations because of dramatic tumor shrinkage and improved progression-free survival (PFS) compared with standard chemotherapy.[1-7]

The EGFR TKIs gefitinib and erlotinib were approved by the Food and Drug Administration (FDA) in May 2003 and November 2004, respectively. According to Taiwan National Health Insurance (NHI) payment regulations

since 2006, first-line TKIs, including gefitinib and erlotinib, are covered for patients with locally advanced lung adenocarcinoma (stage IIIB) and metastatic lung adenocarcinoma (stage IV) with EGFR mutations. Usually, patients receiving EGFR-TKIs do not receive other cancer treatments at the same time except for radiation therapy for brain or bone metastases. If patients with brain metastases agree to radiation therapy, they will receive brain radiation therapy. Patients with bone metastases may receive radiotherapy to relieve bone pain. If resistance occurs after first-line TKIs, they will undergo surgery, radiotherapy, or chemotherapy as second-line treatment. If second-line treatment fails, they may return to receiving TKIs as third-line treatment.

Three surveys found that the prevalence of EGFR mutations in NSCLC patients was approximately 10% in Europe, 17% in the United States, and 78.8% in East Asia.[8-10] The PIONEER study in 2014 was the first to confirm a high frequency of EGFR mutations (51.4%) in Asian patients with lung adenocarcinoma, with a rate of 62.1% in Taiwan.[11] An epidemiological study in 2015 reported that the EGFR mutation rate among patients with treatment-naïve lung adenocarcinoma in Taiwan was 55.4%, with the main mutations being del 19 (44.8%) and L858R point mutations (47.9%).[12]

Traditional Chinese medicine (TCM) is one of the most common complementary and alternative medicine therapies for lung cancer in Taiwan. According to the conceptual framework of TCM, cancer arises when the body constitution becomes imbalanced, which leads to accumulation of toxins and heat and blood stasis and eventually produces carcinogenic factors.[13] A recent investigation of Taiwan National Health Insurance Research Database (NHIRD) from 2001 to 2009 on the utilization among adult cancer patients revealed that most of the lung cancer patients were TCM nonusers (n = 58 168), and a small portion of them were TCM users (n = 6870).[14]

Although several studies indicate that TCM facilitates the treatment of lung cancer,[15-17] there are few large-scale clinical analyses of the effect of TCM on disease prognosis in advanced lung adenocarcinoma treated with EGFR-TKIs. Because of the high rate of EGFR mutations in lung adenocarcinoma in Taiwan, it is important to investigate whether a combination of TCM and EGFR-TKIs is beneficial to patients with advanced lung adenocarcinoma with EGFR mutations.

Materials and Methods

Research Database

The cohort data came from the population-based Taiwan NHIRD, which includes the Registry of Catastrophic Illnesses Patient Database (RCIPD). In Taiwan, the NHI is an obligatory program for all residents, and therefore the NHIRD is a detailed health care database that covers almost the whole population of 23.7 million.

We used the databases to gather information about admissions and outpatient visits from the RCIPD, both of which contained information on patient characteristics such as sex, age, admission date, discharge date, dates of visits, and discharge diagnoses or outpatient visit diagnoses (made according to the International Classification of Diseases, Ninth Revision [ICD-9] classification). The data also included information on patient prescriptions, including the names of the prescribed medications, dosage, duration, initiation date, and total expenditure.

Following rigorous secrecy guidelines according to personal electronic data protection rules, the National Health Research Institutes of Taiwan maintain an anonymous database of NHI reimbursement data that is adequate for research. This study was approved by the Ethics Review Board of Chang Gung Memorial Hospital, Chia-Yi Branch, Taiwan. The data were analyzed anonymously, and the

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requirement for informed consent was waived by the institution's review board.

Study Population

This study recruited patients who were diagnosed with lung cancer according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code 162.x), between January 1, 2006, and December 31, 2012, and survival was tracked until December 31, 2013. The date of initiation of first-line therapy with EGFR-TKIs (including erlotinib and gefitinib) was defined as the index date. The endpoint of observation was death or withdrawal from the NHIRD.

Patients with other cancers that were diagnosed before lung cancer or that coexisted with lung cancer were excluded. To confirm TKIs as first-line therapy, we excluded patients who underwent surgery, chemotherapy, or radiation therapy before TKI treatment. To determine the effects of TCM on TKIs, we also excluded patients who used TCM after tumor progression. Although cytologic findings cannot be obtained from the NHIRD, we could identify patients with advanced lung adenocarcinoma with EGFR mutations as those who had received EGFR-TKI treatment according to Taiwan NHI payment regulations.

TCM Exposure

In Taiwan, TCM is covered by the NHI and is a generally established form of medical treatment. TCM treatment under the NHI is prescribed by board-certified Chinese medical physicians according to TCM syndrome differentiations. The NHIRD is the only computerized reimbursement database in the world that stores longitudinal prescription data for both TCM and Western medicine. This makes the NHIRD an optimal platform to determine the efficacy of TCM in reducing the risks of death and disease progression for patients with advanced lung adenocarcinoma treated with first-line EGFR-TKIs.

Patients who received combined TCM therapy for ≥30 days were classified as TCM users, and those treated for <30 days were classified as TCM nonusers.[18] Furthermore, to observe a dose-response relationship, we separated TCM users into 2 groups: users of TCM for 30 to 179 days and users of TCM for ≥180 days.

Potential Confounders

We identified some comorbidities as potential confounding risk factors for lung cancer, which included the following diagnoses recorded during the study period: tuberculosis (ICD-9 codes 010-012), hypertension (ICD-9 codes 401-405), diabetes mellitus (ICD-9 codes 249-250), hyperlipidemia (ICD-9 code 272), coronary artery disease (CAD; ICD-9 codes 410-419), heart failure (ICD-9 code 428), stroke (ICD-9 codes 430-438), chronic obstructive pulmonary disease (COPD; ICD-9 codes 491, 492, 496), and liver cirrhosis (ICD-9 codes 571.2, 571.5, 571.6).[19] We also considered sociodemographic characteristics, namely age, sex, monthly insurance income, and level of urbanization[20] in the model. Treatments consisting of surgery, chemotherapy, or radiation after tumor progression were also included in our study.

Overall Survival and Progression-Free Survival

Overall survival (OS) was defined as the time from the initiation of first-line EGFR-TKIs to death from any cause or withdrawal from the NHIRD. Progression-free survival (PFS) was defined as the time from the initiation of first-line EGFR-TKIs to the time that we withdraw the EGFR-TKIs or other kind of cancer therapy.

Each patient with advanced lung adenocarcinoma treated with first-line EGFR-TKIs was requested to undergo imaging studies. Once the disease progressed, EGFR-TKIs were declined by the NHI, and other cancer treatments were censored in the NHIRD.

First-line EGFR-TKI responders were defined as patients who received first-line EGFR-TKI therapy for ≥90 days and the remaining patients were defined as non-responders. EGFR-TKI responders were also used as a surrogate for PFS.

Matched Cohort

To further examine the effect of TCM integration, we used propensity scores to estimate the probabilities of assigning a patient to use TCM, given background variables including age, sex, monthly insurance income, level of urbanization, and all comorbidities mentioned above. TCM users and nonusers were matched by using propensity scores at a ratio of 1:4. Overall, 985 insured adults (197 matched sets) were included in the matched cohort. The results of the analysis for both the study cohort and the matched cohort are presented in Tables 1 to 4 and Figures 1 and 2.

Statistical Analysis

The distribution of baseline characteristics, the proportions of comorbidities, treatments after tumor progression, the proportions of first-line EGFR-TKI responses, the proportions of first-line EGFR-TKI, and the proportions of third-line EGFR-TKI were compared between the TCM nonusers and users in the study cohort and in the matched cohort.

We used the Kaplan-Meier method to estimate the cumulative probability of OS and PFS for TCM nonusers and users. The log-rank test was performed to compare the curves of OS and PFS between the groups. Finally, Cox proportional hazards models were used to calculate the hazard ratios (HRs) coexisting with 95% confidence intervals after adjustment for

Table 1. Baseline Patient Characteristics of the Study Cohort and the Matched Cohort.

	Study Cohort					Matched Cohort				
	TCM (N = 217)		Non-TCM (N = 1771)			TCM (N = 197)		Non-TCM (N = 788)		
	n	%	n	%	*P*	n	%	n	%	*P*
Age (years)					<.0001					.6777
<65	124	57.14	654	36.93		104	52.79	429	54.44	
≥65	93	42.86	1117	63.07		93	47.21	359	45.56	
Sex					.0177					.7843
Male	64	29.49	668	37.72		61	30.96	252	31.98	
Female	153	70.51	1103	62.28		136	69.04	536	68.02	
Monthly insurance income (NT$)					.216					.9791
0	36	16.59	378	21.34		33	16.75	142	18.02	
1-15 840	28	12.90	236	13.33		26	13.20	101	12.82	
15 841-25 000	102	47.00	826	46.64		92	46.70	366	46.45	
>25 000	51	23.50	331	18.69		46	23.35	179	22.72	
Urbanization level[a]					.8588					.9959
1 (city)	60	27.65	516	29.14		56	28.43	229	29.06	
2	102	47.00	778	43.93		93	47.21	368	46.70	
3	35	16.13	299	16.88		30	15.23	122	15.48	
4 (village)	20	9.22	178	10.05		18	9.14	69	8.79	
Comorbidities										
Tuberculosis					.2559					.7438
Yes	7	3.23	88	4.97		7	3.55	32	4.06	
No	210	96.77	1683	95.03		190	96.45	756	95.94	
Hypertension					.0004					.8734
Yes	98	45.16	1025	57.88		96	48.73	389	49.37	
No	119	54.84	746	42.12		101	51.27	399	50.63	
Diabetes mellitus					.0051					.8090
Yes	37	17.05	456	25.75		37	18.78	154	19.54	
No	180	82.95	1,315	74.25		160	81.22	634	80.46	
Hyperlipidemia					.0775					.9724
Yes	63	29.03	621	35.06		60	30.46	241	30.58	
No	154	70.97	1150	64.94		137	69.54	547	69.42	
CAD					.061					.7675
Yes	49	22.58	507	28.63		47	23.86	196	24.87	
No	168	77.42	1264	71.37		150	76.14	592	75.13	
Heart failure					.0051					.8686
Yes	8	3.69	166	9.37		8	4.06	30	3.81	
No	209	96.31	1605	90.63		189	95.94	758	96.19	
Stroke					.0003					.6892
Yes	21	9.68	349	19.71		21	10.66	92	11.68	
No	196	90.32	1422	80.29		176	89.34	696	88.32	
COPD					.0036					.6865
Yes	9	4.15	183	10.33		9	4.57	31	3.93	
No	208	95.85	1588	89.67		188	95.43	757	96.07	
Liver cirrhosis					.5130					.8067
Yes	4	1.84	23	1.30		3	1.52	14	1.78	
No	213	98.16	1748	98.70		194	98.48	774	98.22	
Surgery					.9573					1.0000
Yes	19	8.76	157	8.87		18	9.14	72	9.14	
No	198	91.24	1614	91.13		179	90.86	716	90.86	

(continued)

Table 1. (continued)

	Study Cohort					Matched Cohort				
	TCM (N = 217)		Non-TCM (N = 1771)			TCM (N = 197)		Non-TCM (N = 788)		
	n	%	n	%	*P*	n	%	n	%	*P*
CT/RT					.0569					.9719
CT + RT	58	26.73	389	21.96		50	25.38	206	26.14	
CT	64	29.49	436	24.62		55	27.92	229	29.06	
RT	21	9.68	236	13.33		21	10.66	80	10.15	
No CT or RT	74	34.10	710	40.09		71	36.04	273	34.64	
EGFR-TKI response					<.0001					.6708
Responder	193	88.94	1219	68.83		173	87.82	683	86.68	
Nonresponder	24	11.06	552	31.17		24	12.18	105	13.32	
TKI					.2423					.4322
Gefitinib	212	97.70	1702	96.10		192	97.46	759	96.32	
Erlotinib	5	2.30	69	3.84		5	2.54	29	3.68	
Third-line EGFR-TKI										
Gefitinib-CT-erlotinib	55	25.35	273	15.42	.0002	47	23.86	143	18.15	.0692
Erlotinib-CT-gefitinib	0	0.00	2	0.11	1.0000	0	0.00	0	0.00	0
RT					.7459					.9472
Yes	79	36.41	625	35.29		71	36.04	286	36.29	
No	138	63.59	1146	64.71		126	63.96	502	63.71	

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; EGFR, epidermal growth factor receptor; RT, radiotherapy; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.
[a]Urbanization levels in Taiwan are divided into 4 strata according to previous research, with level 1 referring to the most urbanized communities and level 4 to the least urbanized communities.[20]

TCM usage, age, sex, monthly insurance income, level of urbanization, comorbidities, treatments after tumor progression, and first-line EGFR-TKI response. A 2-tailed $P < .05$ was considered to indicate a significant difference.

The study endpoint was all-cause mortality. Data from patients who were alive at the time of the last follow-up were censored at the date of withdrawal from the NHI or the end of the study period, whichever came first. To verify the dose-response relationship of TCM use with mortality and disease progression, we treated the TCM use category as a continuous variable to calculate the *p* value of the linear trend. All analyses were conducted with SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Results

A total of 64 021 patients were newly diagnosed with lung cancer in the RCIPD of the NHIRD from 2006 to 2012. Of these, 6562 patients were excluded because of other cancers existing before or coexisting with lung cancer. Another 40 271 patients were excluded because they did not receive gefitinib or erlotinib. Patients who had undergone surgery (n = 4359), radiotherapy (n = 4925), or chemotherapy (n = 5737) before TKI treatment were also excluded. Another 179 patients were excluded who had used TCM after tumor progression. The remaining 1988 patients received gefitinib or erlotinib for locally advanced and metastatic lung adenocarcinoma with EGFR mutations. The number of patients who were TCM users was 217 (10.9%), whereas 1771 patients (89.1%) were TCM nonusers. After using propensity scores with a ratio of 1:4, the numbers of TCM users and TCM nonusers were 197 and 788, respectively (Figure 1).

The mean age of both TCM users and nonusers was 63.7 years. In the matched cohort, patient baseline characteristics did not differ significantly between TCM users and nonusers (Table 1).

Overall Survival

For evaluation of OS, the mean follow-up time was 18.7 months for TCM users and 13.9 months for TCM nonusers. A total of 1134 deaths occurred during the 7-year period.

Multivariate analysis showed that men had a significantly higher risk of mortality than women (adjusted HR, 1.54 [95% CI, 1.26-1.89] for men, $P < .0001$). Compared with TCM nonuse, TCM use for ≥180 days was associated with a significantly decreased risk of mortality by 68% (adjusted HR, 0.32 [95% CI, 0.21-0.50], $P < .0001$). Although TCM use between 30 and 179 days was associated with a nonsignificantly lower risk of mortality (adjusted

Table 2. Adjusted Cox Proportional Hazards Model Analysis of Mortality in Patients With Advanced Lung Adenocarcinoma Treated With First-Line EGFR-TKIs According to TCM Usage During the Follow-up Period in the Study Cohort and the Matched Cohort.

	Study Cohort					Matched Cohort				
		Adjusted					Adjusted			
Variables	Death Events	HR	95% CI		*P*	Death Events	HR	95% CI		*P*
TCM (days)										
<30	1049	1.00	Reference			396	1.00	Reference		
30-179	61	0.82	0.63	1.07	.1470	57	0.80	0.60	1.06	.1182
≥180	24	0.37	0.24	0.55	<.0001	22	0.32	0.21	0.50	<.0001
Age (years)										
<65	402	1.00	Reference			263	1.00	Reference		
≥65	732	1.26	1.09	1.46	.0015	212	1.04	0.83	1.29	.7494
Sex										
Male	472	1.53	1.34	1.73	<.0001	170	1.54	1.26	1.89	<.0001
Female	662	1.00	Reference			305	1.00	Reference		
Monthly insurance income (NT$)										
0	263	1.00	Reference			99	1.00	Reference		
1-15 840	162	0.99	0.81	1.21	.9350	62	0.66	0.47	0.91	.0121
15 841-25 000	519	0.87	0.75	1.02	.0843	211	0.66	0.51	0.84	.0009
>25 000	190	0.69	0.57	0.84	.0003	103	0.54	0.40	0.73	<.0001
Urbanization level[a]										
1 (city)	331	0.85	0.68	1.05	.1372	136	0.83	0.58	1.19	.3028
2	492	0.87	0.70	1.07	.1727	225	0.91	0.65	1.27	.5748
3	198	0.97	0.77	1.23	.8255	73	0.97	0.66	1.42	.8606
4 (village)	113	1.00	Reference			41	1.00	Reference		
Comorbidities (yes/no)										
Tuberculosis	60	1.07	0.82	1.40	.6115	22	1.22	0.79	1.90	.3719
Hypertension	651	1.05	0.91	1.21	.4943	218	0.92	0.74	1.14	.4192
Diabetes mellitus	307	1.23	1.06	1.43	.0055	99	1.36	1.06	1.74	.0164
Hyperlipidemia	390	0.90	0.78	1.03	.1310	134	0.82	0.65	1.03	.0864
CAD	331	0.92	0.79	1.07	.2784	118	1.05	0.83	1.34	.6775
Heart failure	111	1.07	0.87	1.33	.5196	15	0.89	0.52	1.52	.6565
Stroke	238	1.14	0.98	1.34	.0898	58	1.28	0.95	1.72	.1103
COPD	125	0.94	0.77	1.15	.5441	18	0.92	0.56	1.52	.7532
Liver cirrhosis	17	1.20	0.74	1.95	.4618	8	0.94	0.46	1.92	.8554
Surgery										
Yes	119	0.98	0.81	1.19	0.8363	54	0.95	0.70	1.28	0.7183
No	1015	1.00	Reference			421	1.00	Reference		
CT/RT										
CT + RT	289	0.73	0.62	0.87	.0003	150	1.06	0.82	1.36	.6549
CT	235	0.66	0.56	0.78	<.0001	116	0.82	0.63	1.06	.1287
RT	199	1.17	0.98	1.41	.0874	71	2.17	1.60	2.93	<.0001
No CT or RT	411	1.00	Reference			138	1.00	Reference		
1st-line EGFR-TKI response										
Responder	658	0.26	0.23	0.30	<.0001	380	0.33	0.26	0.42	<.0001
Nonresponder	476	1.00	Reference			95	1.00	Reference		

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; RT, radiotherapy; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.

[a]Urbanization levels in Taiwan are divided into 4 strata according to previous research, with level 1 referring to the most urbanized communities and level 4 to the least urbanized communities.[20]

Table 3. Adjusted Cox Proportional Hazards Model Analysis of PFS in Patients With Advanced Lung Adenocarcinoma Treated With First-Line EGFR-TKIs According to TCM Usage During the Follow-up Period in the Study Cohort and the Matched Cohort.

	Study Cohort					Matched Cohort				
		Adjusted					Adjusted			
Variables	PD Events	HR	95% CI		*P*	PD Events	HR	95% CI		*P*
TCM (days)										
<30	1599	1.00	Reference			568	1.00	Reference		
30-179	101	0.88	0.72	1.09	.2393	101	0.91	0.74	1.14	.4150
≥180	37	0.42	0.30	0.58	<.0001	37	0.41	0.29	0.58	<.0001
Age (years)										
<65	701	1.00	Reference			417	1.00	Reference		
≥65	1036	0.93	0.83	1.04	.1921	289	0.88	0.73	1.06	.1709
Sex										
Male	658	1.17	1.05	1.30	.004	228	1.29	1.09	1.52	.0035
Female	1079	1.00	Reference			478	1.00	Reference		
Monthly insurance income (NT$)										
0	357	1.00	Reference			104	1.00	Reference		
1-15 840	241	1.06	0.89	1.25	.5163	92	0.99	0.74	1.32	.9364
15 841-25 000	815	0.91	0.80	1.04	.1731	347	0.86	0.68	1.08	.1830
>25 000	324	0.66	0.56	0.78	<.0001	163	0.69	0.53	0.89	.0048
Urbanization level[a]										
1 (city)	493	0.87	0.73	1.05	.1418	176	0.68	0.51	0.91	.0092
2	783	0.86	0.72	1.01	.0707	328	0.67	0.51	0.87	.0024
3	292	0.94	0.78	1.13	.5064	127	0.79	0.59	1.07	.1246
4 (village)	169	1.00	Reference			75	1.00	Reference		
Comorbidities (yes/no)										
Tuberculosis	81	1.10	0.88	1.38	.4055	17	0.73	0.45	1.21	.2204
Hypertension	971	1.12	0.99	1.25	.0642	325	1.02	0.85	1.22	.8571
Diabetes mellitus	425	1.04	0.92	1.17	.5745	108	1.06	0.84	1.34	.6104
Hyperlipidemia	591	0.87	0.78	0.98	.0175	211	0.85	0.71	1.03	.0978
CAD	475	0.98	0.86	1.10	.7079	156	1.10	0.89	1.36	.3828
Heart failure	154	1.25	1.05	1.50	.0142	30	1.28	0.87	1.90	.2143
Stroke	319	1.02	0.90	1.17	.7258	68	0.92	0.70	1.22	.5775
COPD	165	1.01	0.85	1.20	.9471	31	0.83	0.56	1.23	.3606
Liver cirrhosis	26	1.37	0.93	2.03	.1141	15	1.81	1.07	3.06	.0266
Surgery										
Yes	106	1.50	1.22	1.84	<.0001	24	1.68	1.10	2.57	.0173
No	1631	1.00	Reference			682	1.00	Reference		
CT/RT										
CT + RT	447	2.62	2.28	3.02	<.0001	207	4.87	3.90	6.07	<.0001
CT	494	1.91	1.68	2.17	<.0001	233	3.07	2.50	3.76	<.0001
RT	257	3.00	2.56	3.52	<.0001	81	4.58	3.46	6.07	<.0001
No CT or RT	539	1.00	Reference			185	1.00	Reference		
1st-line EGFR-TKI response										
Responder	1,165	0.04	0.04	0.05	<.0001	654	0.04	0.03	0.06	<.0001
Nonresponder	572	1.00	Reference			52	1.00	Reference		

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CT, chemotherapy; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival; RT, radiotherapy; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.

[a]Urbanization levels in Taiwan are divided into 4 strata according to previous research, with level 1 referring to the most urbanized communities and level 4 to the least urbanized communities.[20]

Table 4. Adjusted Cox Proportional Hazards Model Analysis of Mortality for the Commonly Used TCMs in Patients With Advanced Lung Adenocarcinoma Treated With First-Line EGFR-TKIs in the Study Cohort and the Matched Cohort.

	Study Cohort				Matched Cohort			
	Adjusted[a]				Adjusted[a]			
TCM Name	HR	95% CI		*P*	HR	95% CI		*P*
Fritillaria thunbergii	0.44	0.26	0.74	.0023	0.37	0.21	0.66	.0007
Oldenlandia diffusa	0.60	0.39	0.92	.0192	0.60	0.38	0.96	.0312
Platycodon grandiflorum	0.24	0.10	0.57	.0014	0.20	0.08	0.50	.0005
Prunus armeniaca	0.52	0.27	1.01	.0542	0.57	0.29	1.13	.1059
Astragalus membranaceus	0.52	0.27	1.01	.0522	0.50	0.25	1.01	.0546
Xiang Sha Liu Jun Zi Tang	0.58	0.31	1.09	.0883	0.61	0.32	1.15	.1244
Xiao Chai Hu Tang	0.47	0.21	1.07	.0707	0.57	0.25	1.29	.1764
Mai Men Dong Tang	0.54	0.27	1.08	.0830	0.62	0.31	1.26	.1852
Sheng Mai San	0.64	0.30	1.35	.2427	0.59	0.26	1.34	.2095
Bai He Gu Jin Tang	0.43	0.22	0.84	.0128	0.29	0.13	0.62	.0015

Abbreviations: EGFR, epidermal growth factor receptor; HR, hazard ratio; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.
[a]Adjusted for age, sex, insurance income, urbanization, comorbidities, surgery, chemotherapy/radiotherapy, and EGFR-TKI response.

HR, 0.80 [95% CI, 0.60-1.06], $P = .1182$), we can still conclude that the longer the duration of TCM usage, the lower the mortality rate. A dose-response relationship was observed between TCM use and survival (Table 2).

Patients with a higher monthly insurance income had a significantly lower risk of mortality, and patients with a lower monthly insurance income had a significantly higher risk of mortality (adjusted HR, 0.66 [95% CI, 0.47-0.91] for NT$ 1-15 840, $P = .0121$; adjusted HR, 0.66 [95% CI, 0.51-0.84] for NT$ 15 841-25 000, $P = .0009$; adjusted HR, 0.54 [95% CI, 0.40-0.73] for NT$ >25 000, $P < .0001$).

Diabetes mellitus, one of the comorbidities, was found to increase mortality significantly (adjusted HR, 1.36 [95% CI, 1.06-1.74], $P = .0164$). Radiation therapy after disease progression or simultaneously for brain metastases or bone metastases increased mortality significantly in comparison with patients who did not undergo chemotherapy or radiation therapy (adjusted HR, 2.17 [95% CI, 1.60-2.93], $P < .0001$). Compared with nonresponders to first-line EGFR-TKI, TKI responders had a significantly decreased risk of mortality by 67% (adjusted HR, 0.33 [95% CI, 0.26-0.42], $P < .0001$) (Table 2).

Progression-Free Survival

For evaluation of PFS, the mean follow-up time was 12.5 months for TCM users and 8.3 months for TCM nonusers.

Multivariate analysis showed that men had a significantly higher risk of disease progression than women (adjusted HR, 1.29 [95% CI, 1.09-1.52] for men, $P = .0035$). Compared with TCM nonuse, TCM use for ≥180 days was associated with a significantly decreased risk of disease progression by 59% (adjusted HR, 0.41 [95% CI, 0.29-0.58], $P < .0001$). Although TCM use between 30 and 179 days was associated with a nonsignificantly lower risk of disease progression (adjusted HR, 0.91 [95% CI, 0.74-1.14], $P = .4150$), we can still conclude that the longer the duration of TCM usage, the lower the rate of disease progression. A dose-response relationship was observed between TCM use and PFS (Table 3).

Monthly insurance income >NT$ 25 000 was associated with a significantly decreased risk of disease progression (adjusted HR, 0.69 [95% CI, 0.53-0.89], $P = .0048$). Urbanization levels of 1 (city) and 2 were associated with lower risks of disease progression (adjusted HR, 0.68 [95% CI, 0.51-0.91] for level 1, $P = .0092$; adjusted HR, 0.67 [95% CI, 0.51-0.87] for level 2, $P = .0024$). Liver cirrhosis, one of the comorbidities, was found to increase the rate of disease progression significantly (adjusted HR, 1.81 [95% CI, 1.07-3.06], $P = .0266$).

In comparison with patients who did not undergo chemotherapy or radiation therapy, patients who received chemotherapy with radiotherapy, chemotherapy, and radiotherapy were found to increase the rate of disease progression significantly (adjusted HR, 4.87 [95% CI, 3.90-6.07] for chemotherapy with radiotherapy, $P < .0001$; adjusted HR, 3.07 [95% CI, 2.50-3.76] for chemotherapy, $P < .0001$ and adjusted HR, 4.58 [95% CI, 3.46-6.07] for radiotherapy, $P < .0001$). Compared with nonresponders to first-line EGFR-TKI, TKI responders had a significantly decreased risk of disease progression by 96% (adjusted HR, 0.04 [95% CI, 0.03-0.06], $P < .0001$) (Table 3).

Probabilities of OS and PFS

Figure 2A-D illustrate the results of the Kaplan-Meier analysis in the study cohort and the matched cohort for the probabilities of OS and PFS in patients with advanced lung

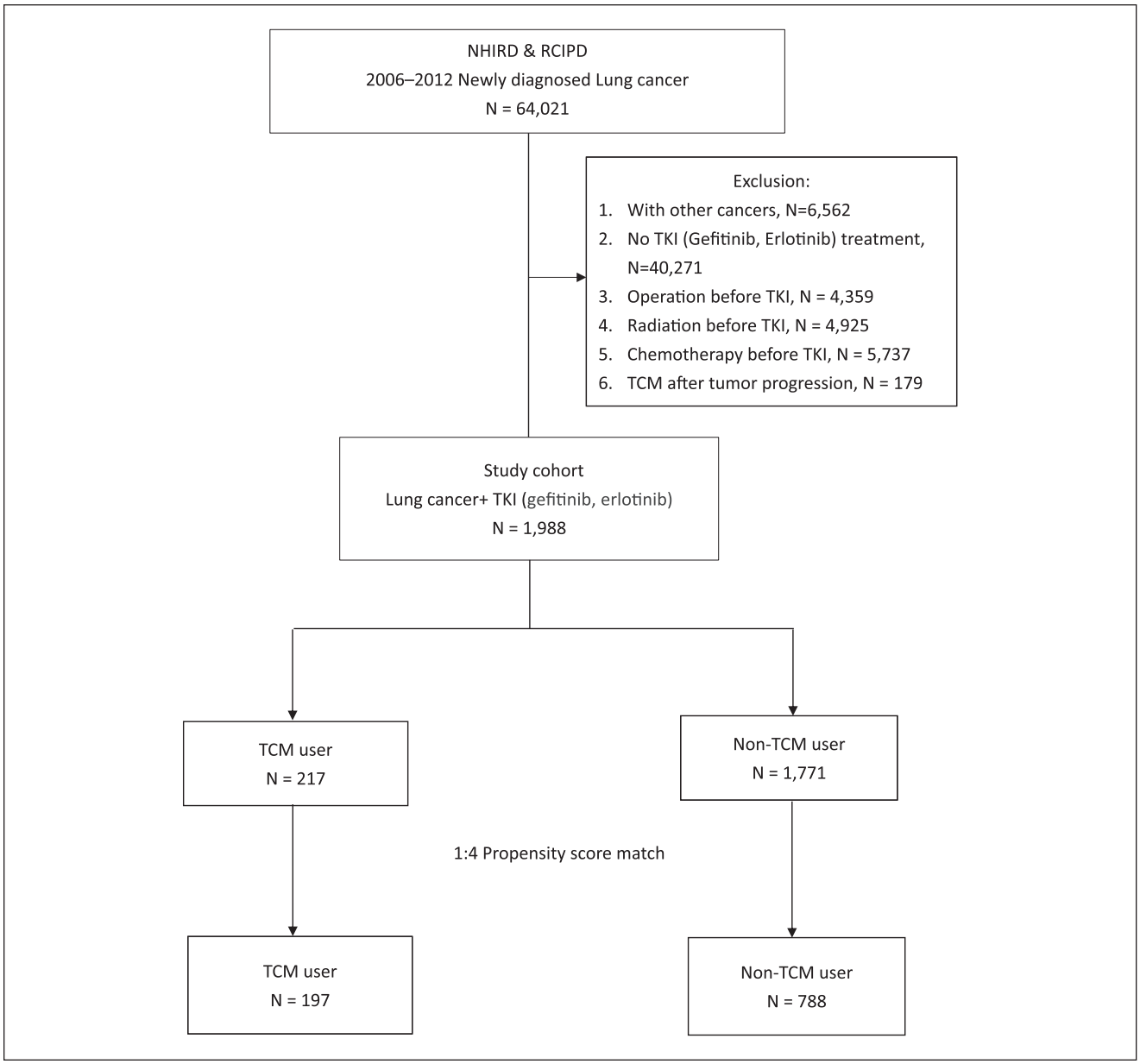

Figure 1. Flowchart of the patient enrollment process of the study cohort and the matched cohort. Abbreviations: NHIRD, Taiwan National Health Insurance Research Database; NSCLC, non–small cell lung cancer; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.

adenocarcinoma treated with first-line gefitinib or erlotinib according to TCM usage. Improvement in OS and PFS displayed a progressive dose-response relationship in the study cohort and the matched cohort. The log-rank test indicated a significant difference over the Kaplan-Meier curve of OS ($P < .001$) and PFS ($P = .019$) in the matched cohort.

In the cohort, the 5 most commonly used herbs were *Fritillaria thunbergii, Oldenlandia diffusa, Platycodon grandiflorum, Prunus armeniaca*, and *Astragalus membranaceus*. The 5 most commonly used formulas were Xiang Sha Liu Jun Zi Tang, Xiao Chai Hu Tang, Mai Men Dong Tang, Sheng Mai San, and Bai He Gu Jin Tang. Among them, 3 herbs could significantly reduce mortality, including *F thunbergii* (adjusted HR, 0.37 [95% CI, 0.21-0.66], $P = .0007$), *O diffusa* (adjusted HR, 0.60 [95% CI, 0.38-0.96], $P = .0312$), and *P grandiflorum* (adjusted HR, 0.20 [95% CI, 0.08-0.50], $P = .0005$). One formula, Bai He Gu Jin Tang, could significantly reduce mortality (adjusted HR, 0.29 [95% CI, 0.13-0.62], $P = .0015$) (Table 4).

Discussion

Until now, there have been few clinical studies on the efficacy of adjunctive TCM for patients with advanced lung

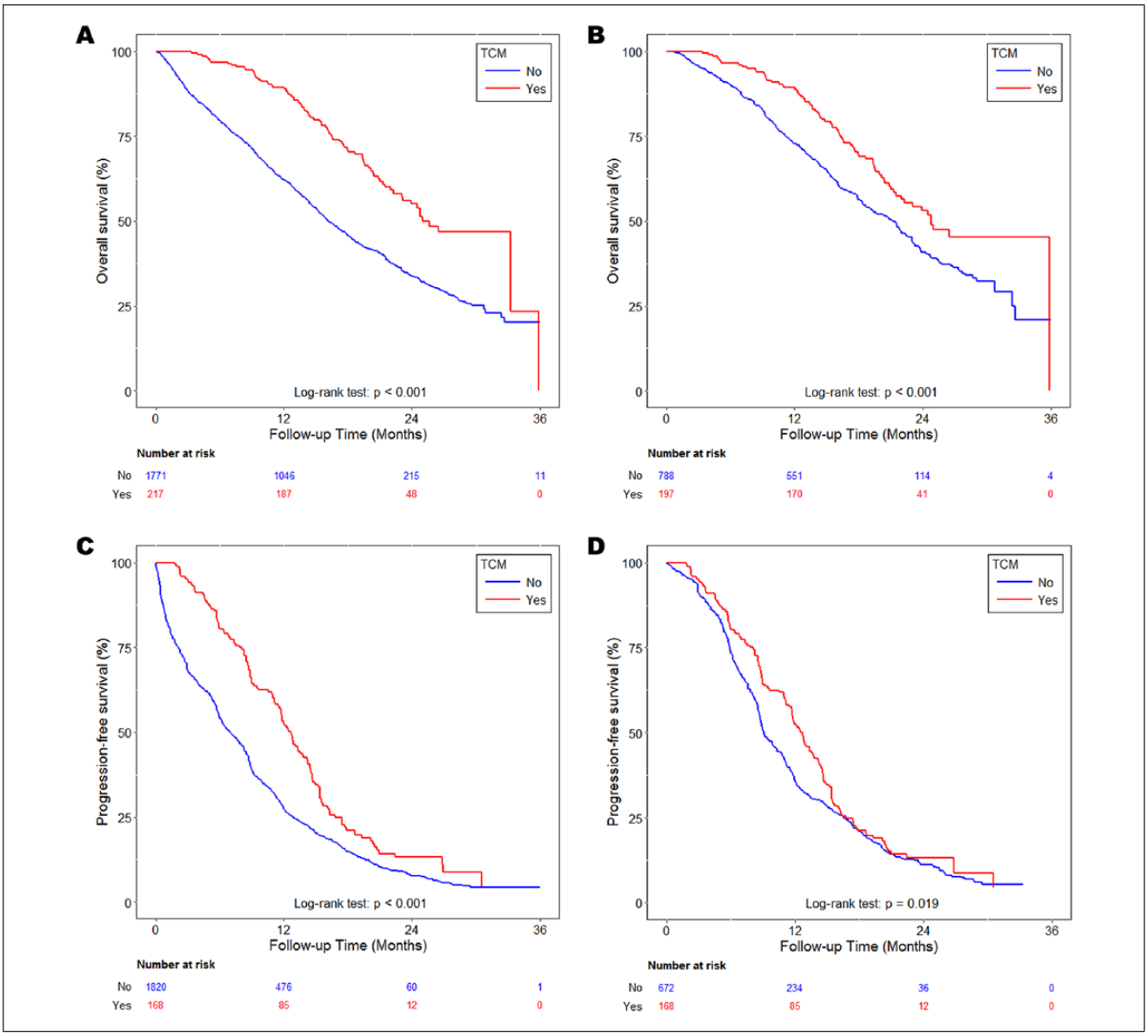

Figure 2. Kaplan-Meier curves of OS in patients with advanced lung adenocarcinoma treated with first-line EGFR-TKIs according to TCM usage during the follow-up period from the study cohort (A) and matched cohort (B) and PFS in patients with advanced lung adenocarcinoma treated with first-line EGFR-TKIs according to TCM usage during the follow-up period from the study cohort (C) and the matched cohort (D). Abbreviations: EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; TCM, traditional Chinese medicine; TKI, tyrosine kinase inhibitor.

adenocarcinoma treated with first-line EGFR-TKIs. To our knowledge, our study is the first large-scale, nationwide cohort study to investigate the influence of adjunctive TCM therapy on OS and PFS in this patient population.

Our study concludes that integrative TCM can improve OS and PFS significantly in patients with advanced lung adenocarcinoma treated with first-line gefitinib or erlotinib. However, this finding seems inconsistent with that of another retrospective study from one hospital in Taiwan, which observed that among patients treated with EGFR-TKIs, PFS and OS were nonsignificantly better in TCM users than in TCM nonusers.[21]

There are some possible explanations for the different outcomes. First, the earlier study had a smaller sample size (34 patients receiving TCM and EGFR-TKIs at the same time) than our study (217 patients). Second, the earlier study did not exclude patients receiving Chinese herbal medicine treatment after their disease progressed to EGFR-TKI treatment. Third, their patients came from only one hospital in Taiwan, whereas our patients came

from the NHIRD, which covers all of Taiwan. Fourth, their patients might have received TCM treatment in other hospitals or clinics, whereas we collected all patients from the NHIRD.

A pooled safety analysis of EGFR-TKI treatment for EGFR mutation-positive NSCLC demonstrated that the most common withdrawal adverse effects were skin toxicity, interstitial lung disease, hepatotoxicity, and diarrhea.[22] Some patients with advanced lung adenocarcinoma treated with first-line EGFR-TKIs would choose TCM because of the adverse effects of TKIs, which may lead to TKI dose reduction, TKI discontinuation, TKI withdrawal, or worsening quality of life. Some of these patients may continue to take TKIs, since TCMs improve TKI toxicities. The number of TCM users excluded from out study after progression was 179. Some patients still chose TCM treatment after progression, and the survival of these patients needs to be analyzed.

Our study showed there were "dose-responsive" effects of TCM treatments. We had used time-dependent Cox proportional hazard model to adjust immortal time bias before, and the results showed that the adjusted hazard ratio for study cohort was 0.30 (95% CI 0.16-0.56) for TCM users with more than 14 days per 12 weeks. The results of time-dependent Cox proportional hazard model and Cox proportional hazard model were compatible so that there was no immortal time bias in our analysis.

Our study showed that 3 herbs, *F thunbergii, O diffusa*, and *P grandiflorum*, could significantly reduce mortality in patients with advanced lung adenocarcinoma treated with first-line EGFR-TKIs (gefitinib and erlotinib). These herbs may have the characteristics of relieving TKI adverse effects or improving OS and PFS. The bulb of *F thunbergii* is used as a mucoregulator and expectorant for treating airway inflammatory diseases in TCM. Extracts from the bulb of *F thunbergii* (verticine, ebeiedine, and suchengbeisine) can inhibit the gene expression and production of MUC5AC mucin from human airway epithelial cells.[23] Another extract from the bulb of *F thunbergii* (peiminine) was found to inhibit colorectal cancer cell proliferation by inducing apoptosis and autophagy.[24] *O diffusa* is a common anticancer herb in TCM. Its anticancer mechanisms include augmenting the macrophage oxidative burst, inhibiting tumor growth, inducing a significant increase in apoptosis, and significantly inhibiting lung metastases in an animal model without adverse effects.[25,26] *P grandiflorum* is known for its immune modulation and antitumor effects in TCM. The aqueous extract from the root of *P grandiflorum* can decrease telomerase activity and downregulate Bcl-2 expression, thus inducing apoptosis and growth inhibition in human lung carcinoma cells.[27] The aqueous extract from the root of *P grandiflorum* can also inhibit the adhesion of tumor cells to the basement membrane and activate natural killer cells, thus reducing the range of lung metastases.[28] Another study showed that platycodin D can induce autophagy via PI3K/Akt/mTOR and MAPK signaling pathways in NSCLC cells.[29]

Most of the Chinese herbal formulas had no significant reduction of hazard ratio. It may because some of the formulas were used for decreasing the side effect of EGFR TKIs, relieving original symptoms of cancer patients or improving fatigue of the patients, not just for cancer therapies. For example, Xiang Sha Liu Jun Zi Tang may relieve diarrhea caused by EGFR TKIs, Xiao Chai Hu Tang may reduce gastrointestinal discomforts, Mai Men Dong Tang may subside cough, and Sheng Mai San may improve fatigue.

Our study showed that the longer the duration of TCM usage, the lower the rate of disease progression. Thus, integrated use of TKI and TCM resulted in better PFS than TKI alone. The combination of TKI and TCM may delay acquired resistance to TKI. Some studies also found that EGFR-TKI plus TCM compared with EGFR-TKI alone in patients with NSCLC could prolong PFS and median survival time, increase efficacy, and reduce toxicity.[15,16] However, one case report mentioned that inappropriate use of TCM, including ginseng, *Fomes fomentarius, Inonotus obliquus, Phellinus linteus*, and selenium, could decrease sensitivity to gefitinib, while withdrawing these herbs restored sensitivity to gefitinib.[30] Therefore, which TCM formulas and herbs are used would be the key to determining their efficacy.

There are several limitations to this study. First, the NHI program only pays for TCM treatment prescribed by Chinese medicine physicians, and not for over-the-counter TCM treatment. Thus, the use of TCM may be underestimated. A recent investigation of Taiwan NHIRD from 2001 to 2009 on the application among adult cancer patients demonstrated that TCM treatments could be separated into only Chinese herbal medicines (N = 69 086), only acupuncture or traumatology (N = 459), or together (N = 5057).[14] This research reflects the current situation of Taiwan NHIRD that we are unable to know whether the patients receive moxibustion, manipulation, other TCM treatment, and over-the-counter TCM treatment or not from NHIRD. Second, there may not have been full compliance with prescriptions among TCM users, but we could still demonstrate improvement in OS and PFS from TCM application. Third, we did not compare dose reductions, delays, discontinuations, or decreasing starting doses of EGFR-TKIs. Fourth, we could not determine the subtype of EGFR mutation from the NHIRD, but we could confirm that patients with advanced lung adenocarcinoma had EGFR mutations from their EGFR-TKI treatment according to Taiwan NHI payment regulations. Fifth, it was unclear whether the patients had ever participated in other clinical trials before and after the EGFR-TKIs treatment. But patients participating in other clinical trials would not receive TCM at the same time except in TCM clinical trials. Finally, because the Registry of Catastrophic Illness Database of the NHIRD only records the date of death and not the cause of death, the effects of TCM on patients with advanced lung adenocarcinoma

treated with first-line EGFR-TKIs dying of specific causes could not be analyzed.

The outcome of our study suggests that adjunctive TCM can improve OS and PFS in patients with advanced lung adenocarcinoma treated with EGFR-TKIs. TCM may play an important, integrative role in cancer treatment. Further randomized controlled trials are needed to validate these observational discoveries.

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Author Contributions

Chia-Ling Li: conception of study design, interpretation of the data, literature review, and writing the manuscript. Te-Chun Hsia: conception of study design, interpretation of the data, and critical revision. Chia-Hsiang Li: conception of study design, interpretation of the data, and critical revision. Ko-Jung Chen: statistical analysis and interpretation of the data. Yao-Hsu Yang: statistical analysis, interpretation of the data, critical revision, and study supervision. Su-Tso Yang: conception of study design, interpretation of the data, critical revision, and study supervision.

Declaration of Conflicting Interests

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