Diverse clinical outcomes for the EGFR-mutated and ALK-rearranged advanced non-squamous non-small cell lung cancer

CHUN-WEI LIN[1-3], KUO-YANG HUANG[1,2], CHING-HSIUNG LIN[1,2], MING-HON HOU[2-4] and SHENG-HAO LIN[1-3,5]

[1]Division of Chest Medicine, Department of Internal Medicine, Changhua Christian Hospital, Changhua 50006, Taiwan, R.O.C.;
[2]Institute of Genomics and Bioinformatics, National Chung Hsing University, Taichung 40227, Taiwan, R.O.C.;
[3]Department of Doctoral Program in Medical Biotechnology, National Chung Hsing University, Taichung 40227, Taiwan, R.O.C.;
[4]Department of Life Sciences, National Chung Hsing University, Taichung 40227, Taiwan, R.O.C.;
[5]Department of Post-baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung 40227, Taiwan, R.O.C.

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Abstract. EGFR and ALK are key driver mutations in non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitors are recommended as the first-line treatment for advanced NSCLC with driving oncogenes because they have fewer side effects and provide better disease control than chemotherapy. The present retrospective analysis aimed to investigate how altered driver genes impact cancer outcomes and clinical presentation. A total of 628 patients with advanced-stage NSCLC and documented EGFR and ALK mutations were enrolled at Changhua Christian Hospital in Taiwan between August 2011 and January 2021. EGFR mutations were identified by PCR. ALK rearrangements were identified by immunostaining. Patients without EGFR or ALK mutations were labeled as wild-type (WT). EGFR mutation was detected in 446 (71.02%) patients, ALK rearrangement in 36 (5.73%) patients and WT in 146 (23.25%) patients. EGFR mutations resulted in higher frequency of lung, brain and multiple extrapulmonary metastases than ALK rearrangement. The ALK group exhibited the longest median overall survival (OS), followed by EGFR and WT groups (ALK: 51.60±13.32, EGFR: 24.03±1.22 and WT: 19.63±2.43 months, respectively; P=0.011). In patients with brain metastases, ALK group had a longer median OS than the EGFR group. Because there were few recruited patients with ALK rearrangement, the results were not significant. According to the results of Cox regression model analysis, driver mutations with EGFR and ALK, lower smoking pack-years, younger age, better performance status, no pleural metastasis and fewer extrapulmonary metastases were key prognostic factors. In conclusion, diverse clinical outcomes are driven by different driver mutations. EGFR mutation leads to more extrapulmonary metastases. Median OS was superior in ALK-rearranged NSCLC than EGFR-mutated NSCLC regardless of brain metastases.

Correspondence to: Dr Sheng-Hao Lin, Division of Chest Medicine, Department of Internal Medicine, Changhua Christian Hospital, 135, Nanxiao Street, Changhua 50006, Taiwan, R.O.C.
E-mail: cmdr.linsh@gmail.com

Professor Ming-Hon Hou, Institute of Genomics and Bioinformatics, National Chung Hsing University, 145 Xingda Road, South, Taichung 40227, Taiwan, R.O.C.
E-mail: mhho@nchu.edu.tw

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HR, hazard ratio; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; WT, wild-type

Key words: EGFR mutation, ALK rearrangement, non-small cell lung cancer, metastasis, overall survival

Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). In Taiwan, ~16,000 patients were diagnosed with lung cancer and 10,000 patients died in 2020. Advanced-stage cancer accounts for more than half of lung cancer cases (2). Late diagnosis leads to low 5-year survival rate (26.5% for lung cancer in Taiwan in 2018) (3).

Driver mutations in non-small cell lung cancer (NSCLC) have been found, revolutionizing cancer treatment. Epidermal growth factor receptor gene (EGFR) mutation and anaplastic lymphoma kinase gene (ALK) rearrangement are key driving mutations in NSCLC (4,5). The distribution of activating EGFR mutations in lung cancer varies by area and ethnicity (6). EGFR and ALK mutations are commonly found in non- or light smokers, patients with adenocarcinoma and Asian patients (7).

Tyrosine kinase inhibitors (TKIs) to block the EGFR or ALK pathway yield lower toxicity, higher tumor response rate and a longer progression-free survival (PFS) than chemotherapy (8). Previous investigations have found greater prevalence of brain metastasis in cases of lung cancer with

EGFR and ALK mutations than those without driver mutation (9,10). As a result, substantial drug penetration across the blood-brain barrier is required for the new generation of TKI designs. In the FLAURA trial, PFS and overall survival (OS) were significantly superior in patients receiving the third-generation TKI osimertinib, than those receiving the first-generation TKIs gefitinib and erlotinib (PFS, 18.9 vs. 10.2 months; OS, 38.6 vs. 31.8 months) (11,12). In the ALEX trial, the alectinib group had greater PFS than the crizotinib group (34.8 vs. 10.9 months) (13). For these reasons, the newer generations of TKIs used in patients with EGFR mutation, such as osimertinib, and those used in patients with ALK rearrangement (alectinib, brigatinib and lorlatinib) have been recommended as first-line therapy for advanced lung cancer by European Society for Medical Oncology and National Comprehensive Cancer Network guidelines (14,15).

The aforementioned clinical trials in cancer treatment have primarily focused on therapeutic efficacy in the case of individual gene alterations. However, less information has been reported about the impact of different driver genes on cancer survival (11-13). Few studies have addressed this issue and they did not include newer TKIs, such as osimertinib or lorlatinib (16,17). Therefore, the present retrospective study aimed to investigate the clinical outcome and characteristics of patients with advanced-stage NSCLC with different EGFR and ALK mutation status.

Materials and methods

Study participants. In the present retrospective observational study, the 628 patients (325 female and 303 male; age, >20 years old) were diagnosed with advanced NSCLC at Changhua Christian Hospital, a tertiary medical center of Changhua in Taiwan between August 2011 and January 2021. Clinical characteristics, treatment plans, laboratory analyses, imaging reports, cancer driver mutation, and survival status were compiled from electronic medical records. The inclusion criteria were as follows: i) Histologically diagnosed non-squamous NSCLC; ii) documented mutation status of EGFR and ALK; iii) cancer stage IIIB to IVB according to the 8th edition American Joint Committee on Cancer definition (18) and iv) receiving systemic therapy for >30 days. The exclusion criteria were as follows: i) Patients under the age of 20 years and ii) concomitant EGFR and ALK mutation in the initial diagnosis. A total of 1,346 patients with non-squamous NSCLC were included in the screening. Finally, 628 patients meeting the study criteria were divided into three groups (EGFR, ALK and WT) according to status of EGFR mutation and ALK rearrangement (Fig. 1). Patients who did not have an EGFR mutation in the PCR or an ALK rearrangement in the tissue immunohistochemistry (IHC) staining were labeled as WT for the analysis.

EGFR and ALK analysis. Tissue specimens from tumor biopsy, surgical resection or cell block of pleural effusion were routinely fixed with 10% neutral buffered formalin for 24-48 h at room temperature and then embedded in paraffin. Formalin-fixed paraffin-embedded tissue (FFPET) was cut at 5 μm thickness for the quantitative PCR of EGFR and at 4 μm thickness for the IHC stain of ALK.

For PCR analysis, genomic DNA was extracted from FFPET by using a Cobas® DNA Sample Preparation kit for DNA extraction (cat. no. 05985536190, Roche Diagnostics Operations Inc.) (19). PCR amplification and detection of TaqMan probe were performed in the region of EGFR exons 18-21 by using an automated Cobas® EGFR Mutation Test v2 (cat. no. 07248563190, Roche Diagnostics Operations Inc.) and *in vitro* diagnostic software. Table SI lists the genes that could be identified in the Cobas® platform. Positive EGFR mutation was defined as the presence of sensitive mutations for EGFR TKIs.

For ALK IHC, slides were stained immediately after FFPET was cut, as antigenicity of cut tissue sections may diminish over time. Solutions and kits of ALK IHC stain were all supplied by Roche. For antigen retrieval, Cell Conditioning 1 (cat. no. 950-124; Roche Diagnostics Operations Inc.) at 100˚C for 92 min was applied (20). Reaction Buffer Concentrate (10X; cat. no. 950-300; Roche Diagnostics Operations Inc.) was used for washing and rehydration and blocking at 37˚C for 5 min. Quenching step was performed using OV PEROX IHBTR (3% hydrogen peroxide solution) for 4 min. Anti-ALK D5F3 rabbit monoclonal primary antibody (cat. no. 1011879; Roche Diagnostics Operations Inc.) was incubated at 37˚C for 16 min. OV HQ UNIV LINKR secondary antibody was incubated for 12 min. OV DAB (cat. no. 760-700; Roche Molecular Systems, Inc.) was used for chromogen detection and hematoxylin II (cat. no. 790-2208; Roche Diagnostics Operations Inc.) was used as counterstain for 4 min. The whole stain procedure was automated by the Roche Ventana BenchMark ULTRA platform with Ventana system software 12.3 (Roche Diagnostics Operations Inc.) according to the manufacturer's instructions. Finally, light microscope was used to visualize ALK IHC stain. Staining elements on normal pulmonary tissue and inflammatory cells were excluded from analysis. Positive detection of ALK was defined as strong granular cytoplasmic staining in tumor cells.

Statistical analysis. Categorical data are presented as a number and percentage; continuous variables are presented as the mean ± standard deviation. Continuous variables within groups were compared using one-way ANOVA followed by post hoc test of Scheffé. Categorical data were compared using Pearson's χ^2 test. Prognostic factors for lung cancer survival were identified using Cox proportional regression model with backward elimination. The Kaplan-Meier curve was used to estimate the survival rate over time and differences were compared by log-rank test. Data were analyzed using IBM SPSS Statistics for Windows (Version 26; IBM Corp.). Survival curves were plotted with RStudio (2022.12.0+353, posit.co/products/open-source/rstudio/). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The study population consisted of 628 patients, with a mean age of 66.55±12.56 years and 52% female. EGFR mutation was found in 446 (71.02%) patients, ALK rearrangement in 36 (5.73%) and WT in the remaining

Table I. Clinical characteristics of patients.

Characteristic	EGFR (n=446)	ALK (n=36)	Wild-type (n=146)	P-value
Age, years	67.64±12.45	61.97±13.84	64.36±12.10	0.020
Sex (%)				<0.001
Female	251 (56.28)	23 (63.89)	51 (34.93)	
Male	195 (43.72)	13 (36.11)	95 (65.07)	
BMI, kg/m	23.24±3.58	22.88±3.07	23.17±3.97	0.845
Smoking status (%)				0.004
Never	370 (83.33)	31 (88.57)	104 (71.23)	
Former	11 (2.48)	0 (0.00)	2 (1.37)	
Current	63 (14.19)	4 (11.43)	40 (27.4)	
Smoking pack-years	11.06±25.76	5.34±18.38	27±38.01	<0.001
ECOG (%)				0.440
0-1	353 (84.86)	32 (88.89)	127 (88.81)	
≥2	63 (15.14)	4 (11.11)	16 (11.19)	
Hypertension (%)	31 (6.95)	1 (2.78)	9 (6.16)	0.609
Arrythmia (%)	53 (11.88)	4 (11.11)	9 (6.16)	0.147
DM (%)	124 (27.80)	12 (33.33)	38 (26.03)	0.678
Hyperlipidemia (%)	93 (20.85)	9 (25.00)	34 (23.29)	0.727
COPD (%)	121 (27.13)	5 (13.89)	56 (38.36)	0.004
CKD (%)	78 (17.49)	7 (19.44)	31 (21.23)	0.592
Pathology (%)				0.370
Adenocarcinoma	434 (97.31)	33 (91.67)	140 (95.89)	
Adenosquamous carcinoma	6 (1.35)	1 (2.78)	3 (2.05)	
Carcinoma, NOS	6 (1.35)	2 (5.56)	3 (2.05)	
Tumor diameter, cm	4.57±2.07	4.24±2.01	4.54±2.25	0.693
Stage (%)				<0.001
IIIB	17 (3.81)	3 (8.33)	15 (10.27)	
IIC	8 (1.79)	4 (11.11)	9 (6.16)	
IVA	170 (38.12)	11 (30.56)	53 (36.3)	
IVB	251 (56.28)	18 (50.00)	69 (47.26)	

Data are presented as the mean ± standard deviation. ECOG, Eastern Cooperative Oncology Group; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NOS, not otherwise specified.

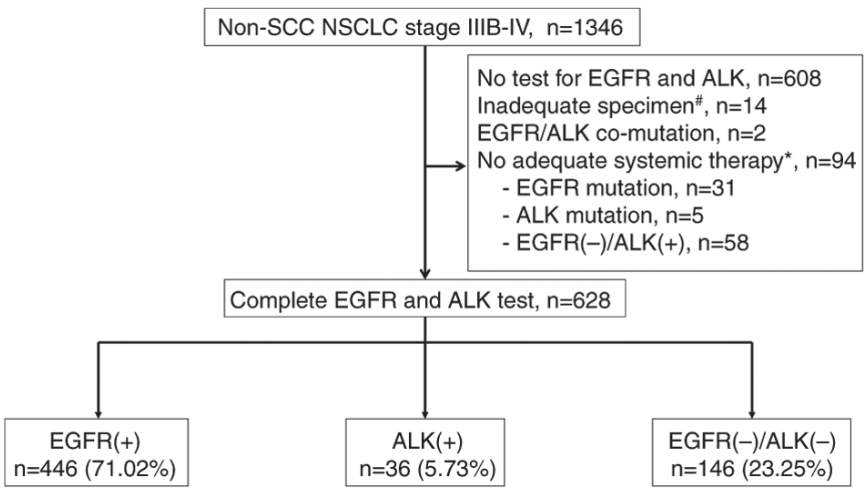

Figure 1. Patient recruitment. Of 1,346 patients screened, 628 patients with documented EGFR and ALK results were included. Patients were separated into three groups based on their oncogene mutation. # indicates majority of the specimen is necrosis or the absence of cancer cells. *, systemic therapy ≤30 days. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SCC, squamous cell carcinoma; NSCLC, non-small cell lung cancer.

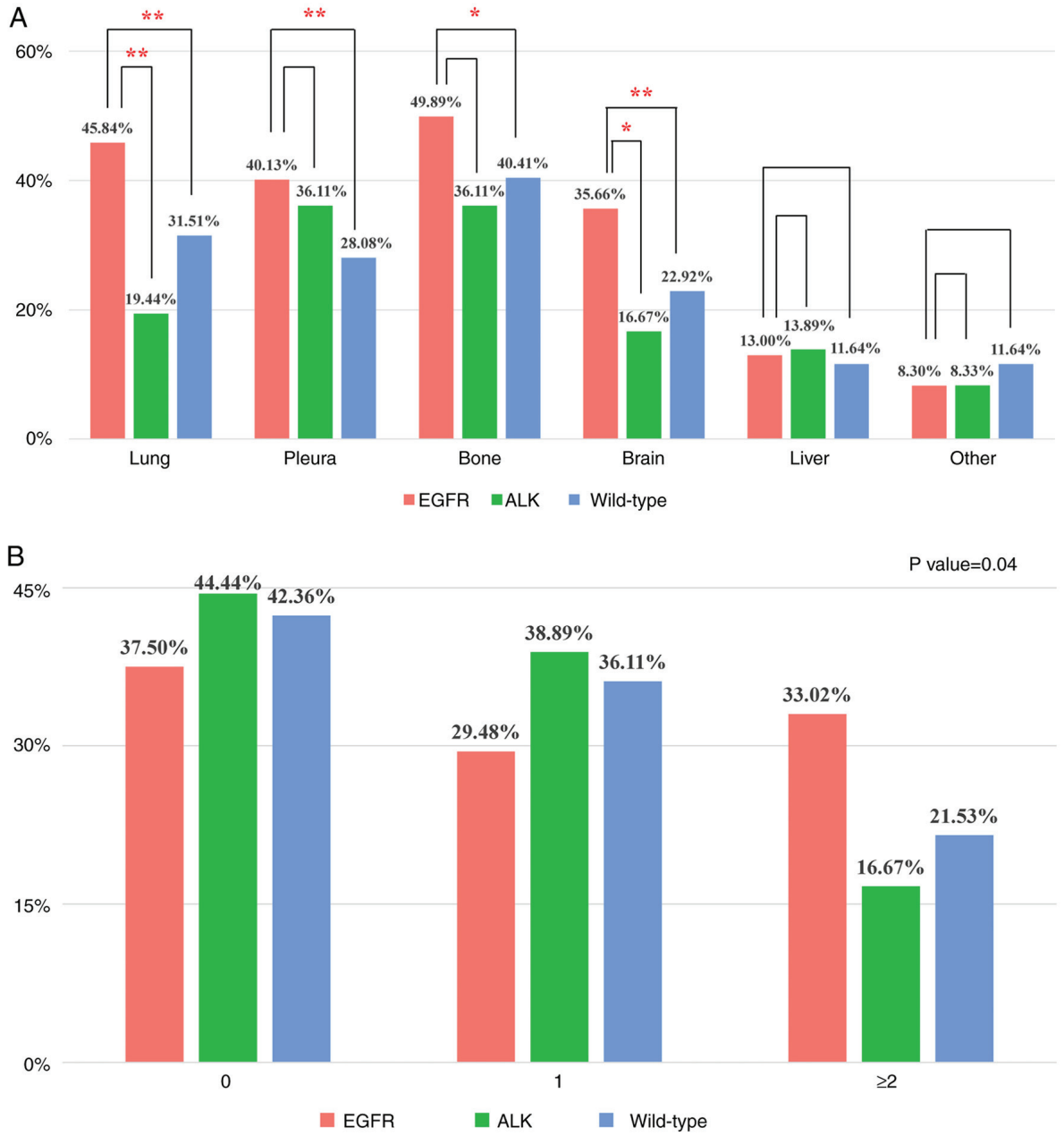

Figure 2. Common metastases of NSCLCs with different mutated genes. (A) Distinct metastatic sites based on oncogenes. (B) Extrapulmonary metastatic sites for different oncogenes. *P<0.05. **P<0.01. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

146 (23.25%) patients. A total of 548 (87.3%) patients had died. The mean follow-up time was 26.50±22.24 months.

Most patients in EGFR and ALK groups were female (EGFR, 56.28; ALK, 63.89; WT, 34.93%), never smoked (EGFR, 83.33; ALK, 88.57; WT, 71.23%) or had lower smoking pack-years (EGFR, 11.06±25.76; ALK, 5.34±18.38; WT, 27±38.01) and had less chronic obstructive pulmonary disease comorbidity (EGFR, 27.13; ALK, 13.89; WT, 38.36%; Table I). Compared with ALK and WT groups, patients in EGFR group were older and possessed a higher proportion of stage IVB (EGFR, 56.28; ALK, 50.00; WT, 47.26%).

Distant metastasis of NSCLC with different genetic mutations. EGFR group more commonly developed metastases in the lung (EGFR, 45.84; WT, 31.51%), pleura (EGFR, 40.13; WT, 28.08%), bone (EGFR, 49.89; WT, 40.41%) and brain (EGFR, 35.66; WT, 22.92%) than WT group (Fig. 2A). Compared with the ALK group, EGFR group more commonly exhibited lung (EGFR, 45.84; ALK, 19.44%) and brain (EGFR, 35.66; ALK, 16.67%) metastases. Patients with EGFR mutation were more likely to have multiple extrapulmonary organ metastases than those with ALK rearrangement and WT group (EGFR, 33.02; ALK, 16.67; WT, 21.53%; Fig. 2B).

Treatment of patients with advanced lung cancer. TKIs were the predominant treatments for the EGFR and ALK groups, whereas chemotherapy was used for patients in the WT group (Table II). EGFR group had the highest proportion of patients receiving geftinib as first-line therapy and the ALK group had the highest proportion receiving treatment with crizotinib.

Table II. Systemic treatment of patients with advanced non-small cell lung cancer.

Treatment (%)	EGFR (n=446)	ALK (n=36)	Wild-type (n=146)	P-value
Chemotherapy	244 (54.71)	24 (66.67)	141 (96.58)	<0.001[a]
Line of chemotherapy				<0.001[a]
1	119 (26.68)	12 (33.33)	61 (41.78)	
2	66 (14.80)	5 (13.89)	41 (28.08)	
≥3	59 (13.23)	7 (19.44)	39 (26.71)	
EGFR TKI	444 (99.55)	9 (25.00)	60 (41.10)	<0.001[a]
Geftinib	270 (60.54)	5 (13.89)	23 (15.75)	<0.001[a]
Erlotnib	179 (40.13)	4 (11.11)	44 (30.14)	0.001[b]
Afatinib	97 (21.75)	0 (0.00)	2 (1.37)	<0.001[a]
Osimertinib	39 (8.74)	0 (0.00)	3 (2.05)	0.005[b]
ALK TKI	0 (0.00)	33 (91.67)	6 (4.11)	<0.001[a]
Crizotinib	0 (0.00)	25 (69.44)	6 (4.11)	<0.001[a]
Ceritinib	0 (0.00)	10 (27.78)	0 (0.00)	<0.001[a]
Alectinib	0 (0.00)	14 (38.89)	1 (0.68)	<0.001[a]
Brigatinib	0 (0.00)	3 (8.33)	0 (0.00)	<0.001[a]
Lorlatinib	0 (0.00)	4 (11.11)	1 (0.68)	<0.001[a]

[a]P<0.001, [b]P<0.05. TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Some patients with driver mutations did not receive chemotherapy (EGFR, 45.29%; ALK, 33.33%; Table II). In the WT group, 41.78% of patients did not receive second-line chemotherapy when disease progressed, due to potential side effects or deteriorating health.

Survival analysis. In the Cox-regression analysis with backward elimination, driver mutations of EGFR and ALK, lower smoking pack-years, younger age, better performance status (Eastern Cooperative Oncology Group score, 0-1) (21), no pleural metastasis and fewer extrapulmonary metastases led to significantly better OS (Table III). The hazard ratio (HR) for ALK rearrangement (0.545, 95% CI 0.325-0.913) was lower than for EGFR mutation (0.764, 95% CI 0.593-0.985) compared with WT. ALK group had a significantly longer OS time than the WT group (HR, 0.487, 95% CI 0.301-0.787). No significant difference was observed between the EGFR and WT groups (HR, 0.91, 95% CI 0.728-1.138). This was consistent with Kaplan-Meier survival analysis (Fig. 3A). Patients with ALK rearrangement had the longest median OS, followed by those with EGFR mutation, then WT group (ALK, 51.6±13.32; EGFR, 24.03±1.22; WT, 19.63±2.43 months). 19 deletion (19-Del) and L858R were key mutations in the EGFR driver gene (Fig. S1A). The 19-Del and L858R EGFR mutations were included in the survival analysis (Fig. S1B). ALK group still had the longest median survival time, followed by 19-Del and L858R EGFR mutations. The prognosis was worst for the WT group. The order of median survival time in the ALK, EGFR and WT groups was not changed in the subgroup analysis for stage IV NSCLC (ALK, 34.43±4.60; EGFR, 23.80±1.17; WT, 19.63±3.54 months; Fig. 3B) and brain metastasis (ALK, 27.80±13.29; EGFR, 21.57±1.83; WT, 16.50±3.42 months; Fig. 3C) but the difference didn't reach the statistical significance.

Discussion

The present study retrospectively analyzed patients with non-squamous NSCLC in the advanced stage. Patients with ALK rearrangement had a better clinical outcome than those with EGFR mutation and WT. Those with ALK rearrangement exhibited significantly longer OS than those with EGFR mutation (51.6±13.32 vs. 24.03±1.22 months). Among the patients with brain metastasis, a longer median OS was observed in ALK than in EGFR group. Driver mutations in EGFR and ALK, lower smoking pack-years, younger age, better performance status (ECOG 0-1), no pleural metastasis and fewer extrapulmonary metastasis were key prognostic factors. To the best of our knowledge, the present study is the largest to assess real-world outcomes in patients with advanced NSCLC according to driver mutation status.

High prevalence of EGFR and ALK mutations (71.02 and 5.73%, respectively) were observed. In previous studies, both mutations were frequently detected in never or light smokers, patients with adenocarcinoma and Asian patients (6,7). Graham *et al* (6) found incidence of EGFR mutations in NSCLC varies by area. In Asia, India and South Korea have the lowest EGFR mutation rates (both 29.1%). The highest EGFR mutation rate (54.9%) is in Taiwan (Fig. S2). Here, all of the enrolled patients were Taiwanese. In the initial screening, patients with squamous cell carcinoma were excluded. More WT patients who did not receive appropriate treatment were excluded compared with the EGFR and ALK groups. These reasons could explain the high EGFR mutation rate.

Table III. Survival analysis by multivariate Cox-regression model with backward elimination.

	Multivariate analysis		Multivariate analysis with backward elimination	
Characteristic	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Group				
Wild-type	1.000		1.000	
EGFR	0.910 (0.728-1.138)	0.409	0.764 (0.593-0.985)	0.038[a]
ALK	0.487 (0.301-0.787)	0.003[a]	0.545 (0.325-0.913)	0.021[a]
Smoking	1.022 (0.989-1.056)	0.198	1.004 (1-1.007)	0.044[a]
Age	1.019 (1.011-1.027)	<0.001[b]	1.016 (1.007-1.026)	0.001[a]
BMI	0.973 (0.946-0.100)	0.046[a]		
ECOG				
0-1	1.000		1.000	
2-4	2.032 (1.571-2.629)	<0.001[b]	1.795 (1.328-2.427)	<0.001[b]
Arrythmia	1.598 (1.200-2.126)	0.001[a]		
CKD	1.400 (1.154-1.699)	0.001[a]		
Tumor size	1.060 (1.015-1.108)	0.009[a]		
Lung metastasis	1.121 (0.927-1.357)	0.239		
Pleural metastasis	1.146 (0.943-1.391)	0.17	1.260 (1.006-1.578)	0.045[a]
EPMS				
0	1.000		1.000	
1	1.397 (1.107-1.765)	0.005[a]	1.358 (1.045-1.763)	0.022[a]
≥2	1.880 (1.481-2.386)	<0.001[b]	1.840 (1.4-2.42)	<0.001[b]

Data are presented as the mean (95% confidence interval). [a]P<0.05, [b]P<0.001. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; CKD, chronic kidney disease; EPMS, extrapulmonary metastatic site; aHR, adjusted hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

More lung and pleural metastases were observed in the EGFR than in the WT group. No significant difference was observed between the ALK and WT groups. Patients with EGFR mutation more commonly presented with lung metastasis than those with the ALK rearrangement. Previous studies reported the same metastatic distribution according to mutation status (22,23). EGFR-mutated NSCLC was associated with an increase in lung metastases. Mendoza *et al* (23) found that there was a lower frequency of lung metastasis for ALK-rearranged NSCLC than EGFR mutation and WT. Besides, our study found that EGFR group more commonly had brain metastasis than ALK rearrangement and WT in the initial diagnosis. It deserved our attention before planning cancer therapy.

Bone, brain, liver and adrenal gland are well-known as common extrapulmonary metastatic sites (EPMSs) (23,24). A total of 40% of patients with NSCLC with EPMS have ≥2 extrapulmonary metastases in the initial diagnosis (24). Here, bone and brain metastases were the most common. Up to 48% of patients with EPMS had ≥2 distant metastatic sites. EGFR group exhibited more extrapulmonary metastases than the ALK and WT groups. These observations indicated metastatic sites in lung cancer are affected by the type of driver mutation.

Lynch *et al* (25) found that NSCLC responsiveness to TKI is mainly related to specific mutations in the EGFR gene, rather than EGFR overexpression. Molecular therapy has been extensively used in patients with lung cancer and driver mutations (14,15). More potent next-generation TKIs have been successively developed (26,27). FLAURA trial demonstrated superior PFS and OS in patients with EGFR-mutated NSCLC receiving the third-generation TKI osimertinib compared with those receiving the first-generation TKIs gefitinib and erlotinib (PFS, 18.9 vs. 10.2; OS, 38.6 vs. 31.8 months, respectively) (11,12). For ALK-rearranged NSCLC, a longer PFS was observed in treatment with second- than first-generation TKI (brigatinib vs. crizotinib, 24 vs. 11.1 months in ALTA-1L trial; alectinib vs. crizotinib, 34.8 vs. 10.4 months in ALEX trial) (13,28). The ALEX trial also demonstrated superior OS following first-line treatment with alectinib than crizotinib (5-year OS, 62.5 with alectinib and 45.5% with crizotinib) (13). For the more potent third-generation ALK TKI lorlatinib, the PFS curve did not reach the 50% line after 36.7 month observation in the Crown study (29).

According to Kaplan-Meier survival analysis, ALK-rearranged advanced NSCLC exhibited a better OS outcome than EGFR and WT. Patients without EGFR or ALK driver mutation had poorer median OS. The superior survival outcome in the ALK group was observed in the subgroup analysis of patients with stage IV NSCLC or brain metastasis compared with the EGFR group. From the indirect comparison of previous clinical trials, we observed significantly longer PFS and OS in ALK-rearranged NSCLC with the second- or third generation ALK TKI therapy than in EGFR-mutated NSCLC

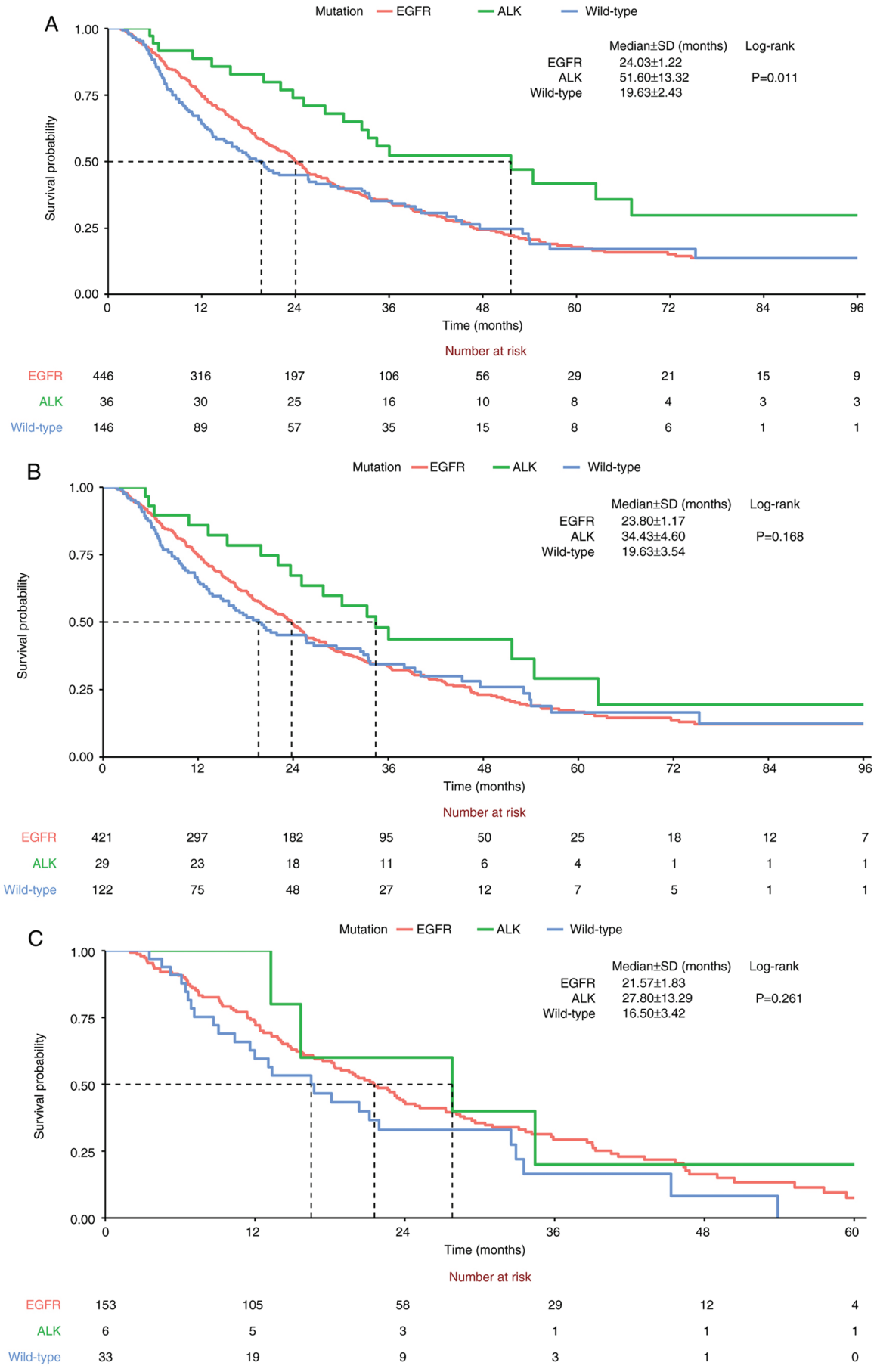

Figure 3. Kaplan-Meier survival curves of patients with advanced NSCLC and driver mutations. (A) All patients. (B) Patients with stage IV NSCLC. (C) Patients with brain metastasis. Longer median overall survival was observed in ALK than EGFR and wild-type. NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

with the most potent EGFR TKI of osimertinib (11-13,28,29). In addition, Camidge *et al* (30) found that ALK-positive patients have notably extended PFS following pemetrexed chemotherapy in comparison with patients without a driver mutation. However, patients with EGFR mutation do not exhibit the same therapeutic efficacy to chemotherapy as patients with ALK rearrangement. These results may explain why ALK-rearranged NSCLC has more diverse and favorable clinical outcomes than EGFR-mutated NSCLC.

For EGFR and WT groups, survival rates initially differed notably but converged after 24 months. This may be because patients with the EGFR mutation received TKI as the primary therapy, whereas patients without a driver mutation received chemotherapy. The initial difference in survival rates might be caused by a highly effective EGFR TKI. Secondly, the EGFR group had a larger number of EPMSs than the WT group. The larger EPMS burden, the worse the prognosis (24). Larger EPMS burden of EGFR group may explain why the survival curves of the EGFR and WT groups coincided.

Driver mutations with EGFR and ALK, lower smoking pack-years, younger age, better performance status, no pleural metastasis and fewer extrapulmonary metastases were key prognostic factors for survival. Alexander's lung cancer prognostic index assesses key prognostic factors, including stage, histology, mutation status, performance status, weight loss, smoking history, respiratory comorbidity, sex and age (31). In addition, Wu *et al* found that patients with malignant pleural effusions (MPEs) at the initial diagnosis have worse OS than those who develop MPEs after disease progression (32). The aforementioned studies corroborate the present findings.

The present retrospective study had limitations. Firstly, some data about smoking pack-year and performance status were missing. Secondly, the sample size for ALK rearrangement in a single medical center was relatively small. In addition, EGFR PCR and ALK IHC were used to analyze tumor driver genes rather than next generation sequencing (NGS). Owing to the high cost of testing, few patients underwent NGS analysis. Therefore, NGS results were not analyzed. Certain co-mutations, such TP-53, RB-1 and PIK3CA, might have an impact on patient survival (33). Finally, most of patients received lung cancer treatment with reimbursement of Taiwan National Health Insurance (NHI). Under Taiwan NHI regulations, patients with EGFR and ALK gene mutations are not eligible for immune checkpoint inhibitors as subsequent treatment (34). Osimertinib is only allowed as the first line therapy for patients with lung cancer with 19-del EGFR mutation and brain metastasis. To recruit more patients with ALK mutations, the trial enrollment period was 10 years. Therefore, most patients did not receive treatment with current standard of care TKIs.

In conclusion, clinical outcomes are driven by different driver mutations. EGFR mutation leads to more extrapulmonary metastases. Driver mutation, lower smoking burden, younger age, better performance status, no pleural metastasis and fewer extrapulmonary metastases are key prognostic factors for patient outcomes. Superior median OS was observed in patients with ALK rearrangement than with EGFR-mutated NSCLC regardless of brain metastasis.

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Availability of data and materials

The data generated in the study may be requested from the corresponding author.

Authors' contributions

CWL, MHH and SHL conceived the study and edited the manuscript. CWL analyzed data and wrote the manuscript. CWL and SHL confirm the authenticity of all the raw data. CWL, KYH, CHL and SHL performed experiments. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Changhua Christian Hospital, Changhua, Taiwan (approval no. 200323) and all procedures were carried out in accordance with the 1996 Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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