의학석사 학위논문

ALK 양성 폐선암 환자에서 ALK 억제제의 효과에 대한 현실 데이터 연구

Real world outcome of crizotinib for non-small cell lung cancer patients with positive anaplastic lymphoma kinase (ALK) mutation: A single center retrospective cohort study in South Korea

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이 논문을 의학석사 학위 논문으로 제출함

2018년 12월

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김연주의 의학석사학위 논문을 인준함

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Abstract

Background: Crizotinib has shown its superiority in clinical trials compared to conventional chemotherapy in patients with anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC) patient, but its use and outcomes in real-world settings are yet to be investigated. This study aimed to assess treatment patterns and outcomes of crizotinib therapy in ALK-positive NSCLC patients, as well as to seek factors associated with progression-free survival and overall survival of ALK-positive NSCLC patients.

Methods: A retrospective medical record review of 176 patients who are diagnosed as metastatic or recurred NSCLC from January 1st, 2006 to June 30th, 2018 and treated with crizotinib was performed. Descriptive analyses were conducted to assess treatment patterns and objective response rate (ORR). Survival analysis to estimate progression-free survival (PFS) and overall survival (OS) was performed. Comparison of the treatment outcomes by the setting of crizotinib initiation was done. Cox regression analysis was used to find predictive factors associated with PFS and OS from initiation of crizotinib.

Results: Median age was 55.7 (ranged 20 to 84) years and 85 patients (48.3%) were male. Seventy-two (40.9%) patients died at the time of analysis. Seventy-eight patients initiated crizotinib as first-line therapy. Overall response rate was 54.5% (50.0% for first-line recipients, 58.2% for second-/later-line). Median (95% CI) PFS from crizotinib initiation and OS from first dose of chemotherapeutic agent were 14.3 (11.6-17.0) and 41.7 (25.4-58.1) months, respectively. No significant difference of ORR, OS, and PFS, according to the setting of crizotinib initiation was observed. Post-progression survival was significantly longer in patients who received subsequent ALK inhibitors. Multivariate Cox analysis showed poor performance status (HR 3.472, p-value < 0.001) and number of metastatic organs (≥3, HR 1.648, p-value 0.017) were independently associated to shorter PFS and OS, while history of getting pemetrexed before use of crizotinib (HR 0.638, p-value 0.039) was independently related to longer OS.

Conclusions: Outcomes for crizotinib recipients were in line with previous trials, with PFS and OS appearing more favorable. Subsequent treatment of ALK inhibitors after progression under crizotinib showed better survival outcome. Poor performance status and number of

metastatic organs correlated to worse PFS and OS, while history of previous use of pemetrexed before crizotinib correlated to better OS.

Keywords: Anaplastic lymphoma kinase, Lung cancer, Crizotinib

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Introduction

Lung cancer is the leading cause of cancer-related deaths in South Korea, with a projected 19,317 deaths (consisting 23.5% of cancer-related death) in 2018 [1]. Majority of cases are classified as non-small cell lung cancer (NSCLC) and metastatic NSCLC patients were traditionally treated with platinum-based chemotherapy, which showed grave prognosis [2]. However, with an increased understanding of the molecular heterogeneity that drives carcinogenesis, NSCLC is subclassified by the presence of specific oncogenic mutations and new targeted therapies are already commercialized, proving their superiority to conventional chemotherapy [2, 3].

Anaplastic lymphoma kinase (ALK) is constitutively activated due to the gene rearrangement of echinoderm microtubule-associated protein like-4-ALK (EML-4-ALK), which is detected in 3-5% of NSCLC patients [4]. Crizotinib is an inhibitor of ALK kinase activiy that achieved higher response rates and a significantly longer median progression-free survival in recent randomized phase III trials, and is approved in the various international markets for the standard treatment of patients with metastatic ALK positive NSCLC [5-7].

Despite the effectiveness of crizotinib, patients ultimately develop resistance to therapy. Various molecular mechanisms of resistance to crizotinib are being elucidated [8], and second-generation ALK inhibitors (ALKis) such as ceritinib and alectinib are granted for the treatment of ALK positive NSCLC patients who experience crizotinib failure [9-11]. In this regard, predicting the risk of disease progression during crizotinib treatment and providing sequential ALK inhibitor therapy is important to clinicians. However, clinical factors significantly affect crizotinib are yet to be elucidated.

Although data from the clinical studies using ALK inhibitors have been evolving, there are limited data describing the use of ALKis and their outcomes in real-world practice settings, outside the highly controlled environments of clinical trials [12, 13].

The objective of current study was therefore to assess real world efficacy of crizotinib in patients with ALK positive NSCLC and to identify factors associated with progression-free survival (PFS) and overall survival (OS) after crizotinib initiation in regular clinical practice,

especially in South Korea.

Methods

Study design and patient selection

This was a single center retrospective chart review study included only patients with diagnosis of ALK-rearranged NSCLC determined by fluorescent in situ hybridization (FISH) [14], with recurrent/metastatic NSCLC, aged ≥18 years, having received crizotinib as first- or later-line therapy from 1 January 2006 to 30 June 2018, in Asan Medical Center. Patients who had pre-existing or coexisting malignancies in other parts except for effectively treated non-melanoma skin cancer, carcinoma-in-situ cervical cancer, ductal carcinoma in-situ breast cancer or malignancies that were effectively treated, have maintained at least 3 years of remission state can be regarded as completely cured, and patients who are not confirmed to have ALK positive NSCLC by histology or cytology were excluded. Patients who received second-generation ALKis before crizotinib therapy were also excluded.

Molecular testing

ALK status was determined using the Vysis ALK Break Apart FISH probe kit (Abbott Molecular, Inc, Abbott Park, IL).

Study variables and endpoints

Baseline dermographic characteristics and clinical characteristics such as age, sex, smoking history, initial performance status (PS) by Eastern Cooperative Oncology Group (ECOG), metastatic organs (brain, lung-to-lung, bone, liver, lymph node, and pleura, etc.) before crizotinib treatment were extracted from each patient's medical record. Treatment patterns of crizotinib including time from diagnosis to crizotinib initiation, last adjusted crizotinib dose, reason of crizotinib dose change or final discontinuation, and other treatments received after discontinuation of crizotinib were assessed and compared by line of crizotinib treatment.

Several clinical endpoints were also estimated. Objective response rate (ORR) was defined as the proportion of patients achieving a best clinical response to crizotinib of either complete response or partial response, as recorded in the patient's medical record, based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 [15]. PFS was calculated from

the starting date of crizotinib treatment to the date of disease progression confirmed by imaging, death before the initiation of new therapy, or the last available medical record if censored. OS was measured from the initiation of crizotinib treatment or first chemotherapeutic dose until any cause of death and patients still alive at the time of data collection were censored at the date of data collection.

Statistical analysis

Analysis variables were summarized using univariate statistics and were stratified by the setting (first-line *versus* second-/later-line) in which crizotinib was initiated for the treatment of metastatic NSCLC. Significant differences in descriptive variables between these groups were assessed with the chi-squared or Fisher's exact tests for qualitative variables and Student's t-test for quantitative variables. The Kaplan-Meier method was used to estimate PFS and OS and survival differences by line of crizotinib were assessed using a non-parametric log-rank test. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) using a Cox model. Univariate Cox models were applied to select the most promising prognostic variables (threshold p=0.10). A multivariate Cox model was then applied using a backwards procedure to adjust for potential confounders. All analyses were conducted using the IBM SPSS Version 22.0 (IBM Corp. Released 2013. IBM SPSS Statics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Ethics

The study protocol was approved by the Institutional Review Board of Asan Medical Center (approval number: 2018-1399) and was conducted in an accordance with the Principles of the Declaration of Helsinki. Informed consent was waived by the IRB, since it was retrospective analysis and did not affect the clinical outcome of the subject.

Results

Patient characteristics by line of crizotinib therapy

A total of 176 patients were identified for study inclusion. 78 patients received crizotinib as first-line palliative chemotherapy, while 98 patients had crizotinib therapy as second- or later-line (Table 1). In the overall cohort, median (range) age at diagnosis of recurred or metastatic ALK+ NSCLC was 55.7 (20-84) years, which did not vary significantly by line of crizotinib initiation. The majority of the cohort was female, with the percentage of male being 48.4%. More than half of patients (61.5%) were recorded as having never smoked at the time of diagnosis of metastatic ALK+ NSCLC, with former smoker being 33.5% and 4.9% being current smokers at the time of diagnosis. Fifty-five (30.2%) patients had brain metastasis at or prior to initiation of crizotinib. Patients who received crizotinib as first-line therapy had more proportion of recurrent NSCLC compared to second-/later-line crizotinib recipient group. First-line recipient group therefore had 32.1% of patients who underwent surgery, which was significantly larger number than the other group. Among patients receiving prior therapy, chemotherapy, and radiotherapy were most common anti-cancer treatment modalities observed before crizotinib initiation. 78 (47.8%) patients had more than 2 metastatic organs at the time of diagnosis, and lymph node was the most common metastatic organ. Ninety-seven (53.3%) patients were alive at the time of record abstraction, with the proportion of living patients being higher in the first line group. Median total observational duration, from crizotinib initiation until last available medical record, was 26.7 months.

Table 1. Dermographic and Clinical characteristics

	All patients	Setting of Crizotinib Initiation		
	(n = 176)	First-Line (n = 78)	Second- or Later-Line (n = 98)	P value
Age (years) at diagnosis, median (range) [a]	55.7 (20-84)	57.0 (20-84)	54.7 (26-78)	0.227
Male	85 (48.3)	37 (47.4)	41 (52.6)	0.880
Smoking status at diagnosis [a]				0.932
Current smoker	9 (5.1)	4 (5.1)	5 (5.1)	
Former smoker	59 (33.5)	25 (32.1)	34 (34.7)	
Never smoked	108 (61.4)	49 (62.8)	59 (60.2)	
Palliative reason				0.001
Recurred	39 (22.2)	26 (33.3)	13 (13.3)	
Initially metastatic	137 (77.8)	52 (66.7)	85 (86.7)	
ECOG performance status at diagnosis [a]				0.474
0-1	144 (81.8)	62 (79.5)	82 (83.7)	
2-4	32 (18.2)	16 (20.5)	16 (16.3)	
Brain metastasis present at/prior to crizotinib initiation	52 (29.5)	26 (33.3)	26 (26.5)	0.326
Number of metastatic organs				0.581
1-2	102 (58.0)	47 (60.3)	55 (56.1)	
≥3	74 (42.0)	31 (39.7)	43 (43.9)	
Metastatic organ				
CNS	41 (23.3)	23 (29.5)	18 (18.4)	
Lung-to-lung	83 (47.2)	39 (50.0)	44 (44.9)	
Bone	67 (38.1)	31 (39.7)	36 (36.7)	
Liver	21 (11.9)	8 (10.3)	13 (13.3)	
LN	130 (73.9)	52 (66.7)	78 (79.6)	
Pleura	79 (44.9)	34 (43.6)	45 (45.9)	
Adrenal	25 (14.2)	12 (15.4)	13 (13.3)	
Pancreas	4 (2.3)	2 (2.6)	2 (2.0)	
Other soft tissue (ex. muscle, omentum, pericardium, …)	17 (9.7)	7 (9.0)	10 (10.2)	
Vital status at medical record abstraction				0.050
Alive	94 (53.4)	49 (62.8)	45 (45.9)	
Deceased	72 (40.9)	24 (30.8)	48 (49.0)	
Unknown	10 (5.7)	5 (6.4)	5 (5.1)	
Other cancer-directed therapies administered prior to crizotinib initiation				
None (supportive care only)	37 (21.0)	37 (47.4)	-	N/A
Surgery	42 (23.9)	25 (32.1)	17 (17.3)	0.230
Radiotherapy	59 (33.5)	24 (30.8)	35 (35.7)	0.490
Chemotherapy	91 (51.7)	-	91 (92.9)	N/A

Table 1. Continued

Targeted therapy [b]	13 (7.4)	-	13 (13.3)	N/A
Gamma-knife radiosurgery	21 (11.9)	10 (12.8)	11 (11.2)	0.746
Duration (months) of observation, from chemotherapy initiation until last available medical record, median (95% CI)	26.7 (19.2-34.3)	26.2 (15.2-37.2)	21.2 (10.2-32.1)	0.112
Crizotinib response				0.346
PR	96 (54.5)	39 (50.0)	57 (58.2)	
SD	57 (32.4)	28 (35.9)	29 (29.6)	
PD	12 (6.8)	4 (5.1)	8 (8.2)	
Not evaluable	11 (6.3)	7 (9.0)	4 (4.1)	
ORR, %	54.5	50.0	58.2	0.280

Values are presented as mean (SD) or number (%) unless otherwise indicated. SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor; ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; N/A = not applicable; CI = confidence interval.

[a] "At diagnosis" refers, more specifically, to at diagnosis of metastatic ALK+ NSCLC.

[b] Anti-EGFR (afatinib, erlotinib, or gefitinib) or anti-VEGF (bevacizumab).

Treatment patterns of crizotinib

Median number of months to crizotinib initiation after initial metastatic NSCLC diagnosis was 3.3 months (Table 2). In the overall cohort, 250 mg b.i.d. was the most common adjusted dosage of crizotinib (81.9% of patients). Dose changes were infrequent once crizotinib was initiated: 79.5% of patients had no dose reduction or escalation during the course of treatment. Nausea, vomiting, neutropenia, hepatotoxicity, and epigastric soreness was commonly cited reason of crizotinib dose changes. Disease progression after initial response to crizotinib was the most common reported reason (33.0% of patients) of final discontinuation of crizotinib; 14 patients died during the crizotinib treatment. Treatment-related toxicities or side effects were cited as a reason for final crizotinib discontinuation in 4.4% of patients. More than one-third of all patients (36.9%) received subsequent ALK inhibitor therapy after discontinuation of crizotinib.

Table 2. Treatment patterns of crizotinib

	All patients	Setting of Crizotinib Initiation		
	(n = 176)	First-Line (n = 78)	Second- or Later-Line (n = 98)	P value
Times (months) from initial diagnosis to crizotinib initiation				
Mean (SD)	10.6 (1.3)	2.0 (0.5)	17.4 (2.0)	
Median (95% CI)	3.3 (1.7-4.9)	0.93 (0.9-1.0)	11.0 (8.1-13.9)	<0.001
Range (minimum, maximum)	(0.1-101.1)	(0.1-34.7)	(0.5-101.1)	
Last adjusted daily dose of crizotinib prescribed				
200 mg b.i.d.	16 (9.1)	5 (6.4)	11 (11.2)	0.270
250 mg b.i.d.	145 (82.4)	68 (81.2)	77 (78.6)	0.136
200 mg q.d.	2 (1.1)	0 (0.0)	2 (2.0)	0.504
250 mg q.d.	13 (7.4)	5 (6.4)	8 (8.2)	0.659
Crizotinib dose changes				
Had ≥ 1 dose reduction	31 (17.6)	10 (12.8)	21 (21.4)	0.136
Had ≥ 1 dose escalation	1 (0.6)	0 (0.0)	1 (1.0)	1.000
Had no dose changes	140 (79.5)	64 (82.1)	76 (77.6)	0.462
Hold for more than 2 weeks and retrial without dose change	2 (1.1)	2 (2.6)	0 (0.0)	0.195
Stop of crizotinib without further retrial	2 (1.1)	2 (2.6)	0 (0.0)	0.195
Reason of crizotinib dose changes				
Epigastric soreness	3 (1.7)	0 (0.0)	3 (3.1)	0.255
Nausea, vomiting	8 (4.5)	1 (1.3)	7 (7.1)	0.078
Neutropenia	7 (4.0)	2 (2.6)	5 (5.1)	0.465
Hepatotoxicity	6 (3.4)	3 (3.8)	3 (3.1)	1.000
Pneumonitis	1 (0.6)	0 (0.0)	1 (1.0)	1.000
Complicated kidney cyst	2 (1.1)	1 (1.3)	1 (1.0)	1.000
Leg edema	2 (1.1)	2 (2.6)	0 (0.0)	0.195
Anorexia	2 (1.1)	1 (1.3)	1 (1.0)	1.000
General malaise	3 (1.7)	2 (2.6)	1 (1.0)	0.585
Other intolerability reported by patient	4 (2.3)	2 (2.6)	2 (2.0)	1.000
Duration (months) of crizotinib treatment, from initiation to last observed dose, median (95% CI)	12.1 (8.8-15.4)	12.1 (5.7-18.5)	12.6 (8.8-16.4)	0.623
Reason(s) for final discontinuation of crizotinib				0.261
Death	13 (7.4)	3 (3.8)	10 (10.2)	0.109
Disease progression following initial response	59 (33.5)	23 (29.5)	36 (36.7)	0.312
Disease progression following no initial response	25 (14.2)	11 (14.1)	14 (14.3)	0.972
Treatment-related toxicity or side effects	7 (4.0)	4 (5.1)	3 (3.1)	0.701

Table 2. Continued

Patient request	1 (0.6)	1 (1.3)	0 (0.0)	0.443
Other reason(s)	8 (4.5)	2 (2.6)	6 (6.1)	0.304
Unknown	7 (4.0)	3 (3.8)	4 (4.1)	1.000
Other treatments received after crizotinib discontinuation/completion				
Best supportive care	14 (8.0)	4 (5.1)	10 (10.2)	0.216
Chemotherapy	11 (6.3)	4 (5.1)	7 (7.1)	0.757
Other ALK inhibitor in a clinical trial	62 (35.2)	25 (32.1)	37 (37.8)	0.570
Targeted therapy	5 (2.8)	2 (2.6)	3 (3.1)	1.000
Unknown	15 (8.5)	7 (9.0)	8 (8.2)	0.848

Values are presented as mean (SD) or number (%) unless otherwise indicated. SD = standard deviation; ECOG = Eastern Cooperative Oncology Group; CNS = central nervous system; EGFR = epidermal growth factor receptor; VEGF = vascular endothelial growth factor; ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; CI = confidence interval.

Crizotinib efficacy and analysis of survival with crizotinib

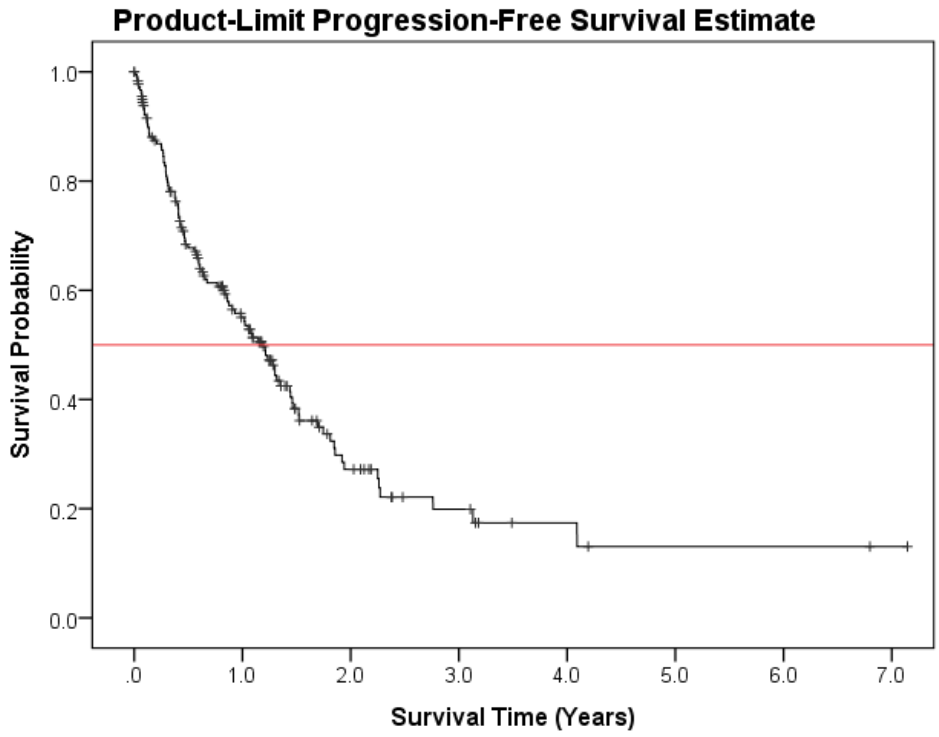
In the overall patients, the ORR for crizotinib treatment was 54.5%. Patients initiating crizotinib as first-line treatment had no significant superiority in response to the drug than second/later-line group of patients. Partial response (PR) during crizotinib treatment was the most common best clinical response recorded (Table 1). Stable disease (SD) was recorded as best response for 32.4% of the patients and 6.8% experienced disease progression (PD) as their best clinical response during crizotinib treatment. Median PFS (95% confidence interval, CI) from crizotinib initiation was 14.3 (11.6-17.0) months (Table 3, figure 1); by setting of crizotinib initiation, median PFS estimates were 15.8 (10.0-21.6) for first-line and 13.1 (9.1-17.0) for second-/later-line initiators, respectively (p = 0.699). From crizotinib initiation or first dose of chemotherapeutic agent, median (95% CI) OS was 41.7 (25.4-58.1) months for the overall cohort. For patients initiating crizotinib as first-line treatment, median (95% CI) OS was 26.3 (14.7-37.9) months, while median OS for second-/later-line crizotinib initiator was 43.9 (25.7-62.1) months (p = 0.137). Kaplan-Meier estimates of 1-year and 2-year survival (95% CI) from crizotinib initiation were 87.1% (86.7-87.5%) and 65.7% (65.0-66.4%), respectively. One-year and two-year survival was not significantly different between two groups.

Table 3. Kaplan-Meier point estimates of progression-free and overall survival

	All patients	Setting of Crizotinib Initiation		
	(n = 176)	First-Line (n = 78)	Second- or Later-Line (n = 98)	P value
Progression-free survival				0.699
Mean (SE)	25.0 (3.1)	28.0 (6.4)	16.6 (1.5)	
Median (95% CI)	14.3 (11.6-17.0)	15.8 (10.0-21.6)	13.1 (9.1-17.0)	
Q1, Q3	5, 27	5, 22	5, 27	
Overall survival				0.137
Mean (SE)	54.1 (4.2)	40.6 (6.1)	57.8 (4.9)	
Median (95% CI)	41.7 (25.4-58.1)	26.3 (14.7-37.9)	43.9 (25.7-62.1)	
Q1, Q3	18, 109	17, 77	19, 109	
1- and 2-year survival rates				
Percent still alive at 1 year after diagnosis (95% CI)	87.1 (86.7-87.5)	85.4 (84.3-86.5)	88.5 (87.8-89.2)	0.483
Percent still alive at 2 years after diagnosis (95% CI)	65.7 (65.0-66.4)	55.4 (51.9-58.9)	69.0 (68.0-70.0)	0.213

Figure 1. Kaplan-Meier curves for progression-free survival from crizotinib initiation.

(A) Overall



(B) By line of crizotinib

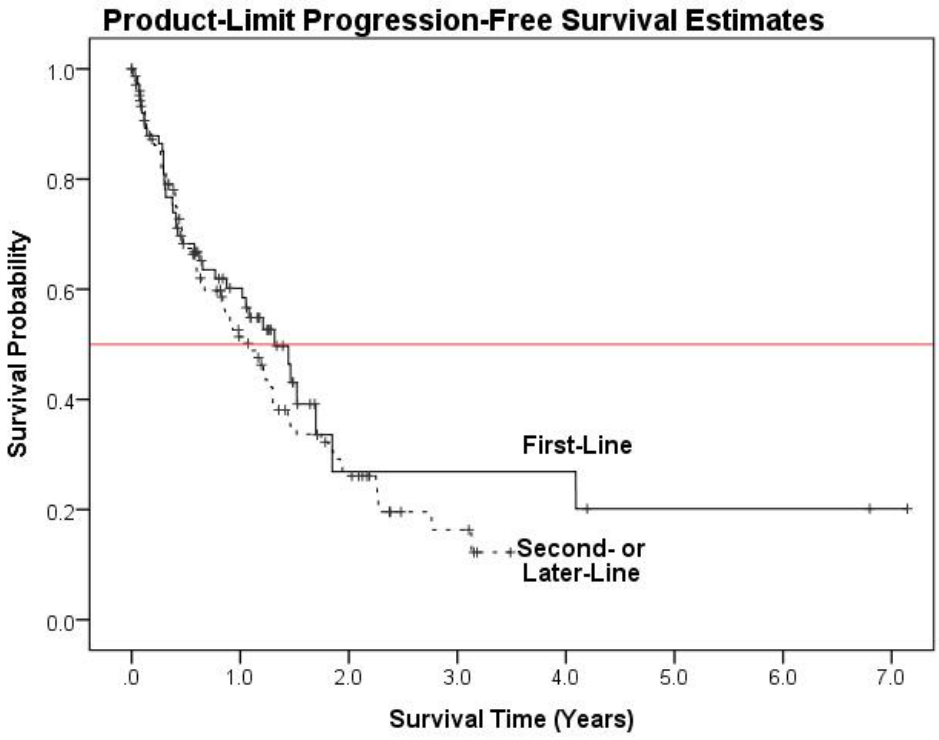
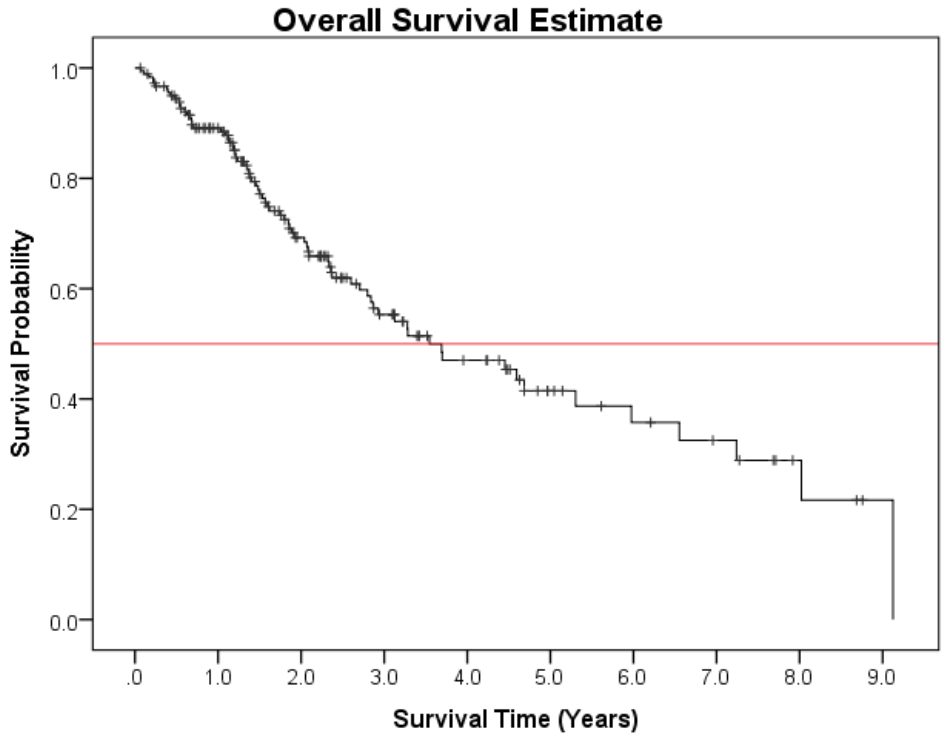
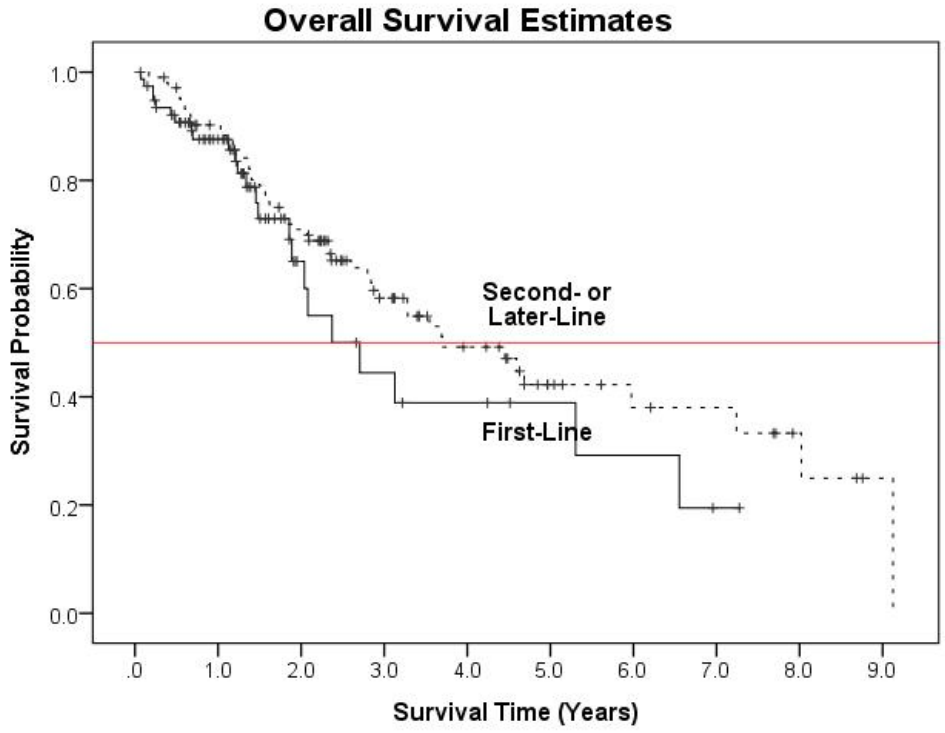


Figure 2. Kaplan-Meier curves for overall survival from chemotherapy initiation.

(A) Overall



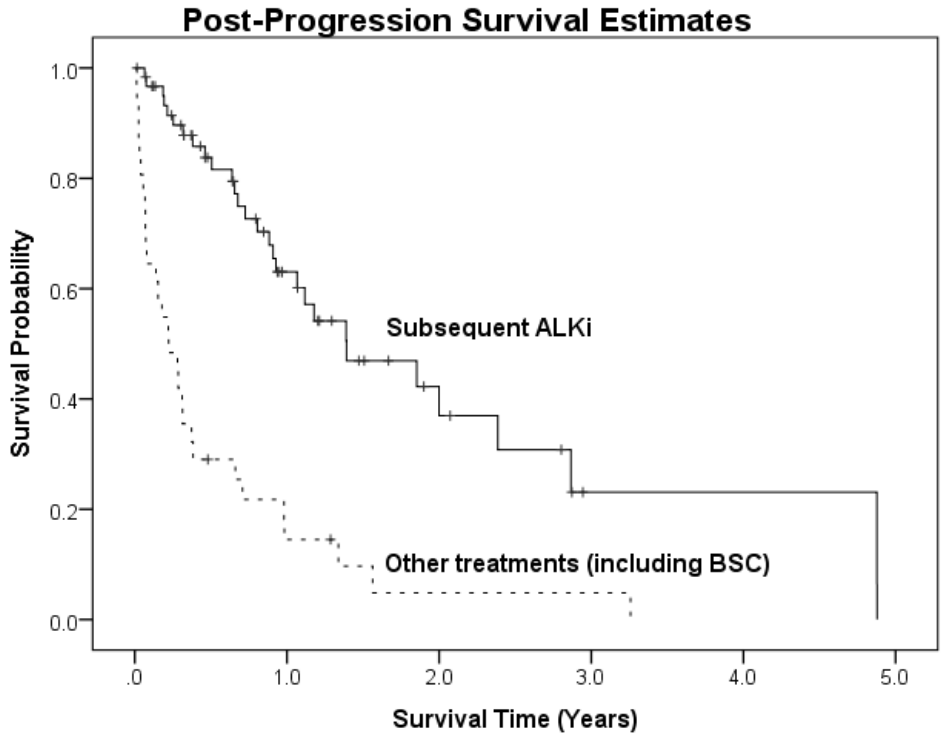
(B) By line of crizotinib



Effect on post-progressive survival of subsequent systemic treatments after progressive disease on crizotinib

Among a population of 93 with documented progressive disease, most of the patients (66.7%) received sequential ALK inhibitor therapy, followed by other chemotherapy and best supportive care (8.6% and 7.5%, respectively). 7 patients continued crizotinib beyond progression. Median post-PD survival (95% CI) was 11.1 (7.3-14.9) months. Patients who received next-generation ALK inhibitors including alectinib or ceritinib had longest post-PD survival (16.7 months, 95% CI 7.2-26.2), compared to other group of patients. (Figure 3).

Figure 3. Kaplan-Meier curves for post-PD survival, according to subsequent treatments after progression on crizotinib



	Median	95% CI	P-value
Subsequent ALKi (n=62)	16.7	7.2-26.2	<0.001
Other treatments (n=31)	2.7	0.9-4.4	

Predicting factors associated to PFS and OS

Univariate and multivariate Cox regression analysis for PFS and OS after crizotinib initiation were performed (Table 4, 5). Univariate Cox analysis showed poor performance status (ECOG status 2 or 3), initially metastatic disease (not recurred disease), ≥3 metastatic organs, and presence of brain metastasis at the time of crizotinib initiation significantly affected shorter PFS, while poor PS and number of metastasis were the statistically significant factor associated with longer OS. Multivariate Cox analysis revealed that poor PS and ≥3 metastatic organs independently associated with shorter PFS and OS, as previous history of receiving pemetrexed therapy before crizotinib initiation independently affected longer OS. However, log rank analysis for overall survival according to previous pemetrexed use showed statistically insignificant benefit in pemetrexed user group (Figure 4A, 4B).

Table 4. Univariate and multivariate Cox regression analysis of progression-free survival with crizotinib

Variables	Progression-free survival			
	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age	0.998 (0.981-1.016)	0.829		
Male	1.318 (0.896-1.939)	0.161		
ECOG PS ≥ 2	3.299 (2.066-5.268)	<0.001	3.472 (2.162-5.576)	<0.001
Smoking history				
Non-smoker	1			
Current smoker	1.415 (0.510-3.926)	0.505		
Ex-smoker	1.332 (0.895-1.983)	0.157		
Palliative reason				
Recurred	1			
Initially metastatic	1.972 (1.121-3.466)	0.018	1.631 (0.899-2.961)	0.108
No. of metastatic organs ≥ 3	1.796 (1.220-2.643)	0.003	1.648 (1.093-2.484)	0.017
Baseline brain metastasis	1.509 (1.004-2.267)	0.048		
Line of crizotinib				
First-line	1			
Second- or later-line	1.082 (0.724-1.617)	0.699		
Response to crizotinib				
Responder (CR + PR)	1			
No responder (SD + PD)	1.218 (0.814-1.824)	0.338		
Pemetrexed before crizotinib	0.785 (0.709-1.576)	0.785		

Values are presented as hazards ratio (HR) or 95% confidence interval (CI) unless otherwise indicated. ECOG = Eastern Cooperative Oncology Group; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; N/A = not applicable; CI = confidence interval.

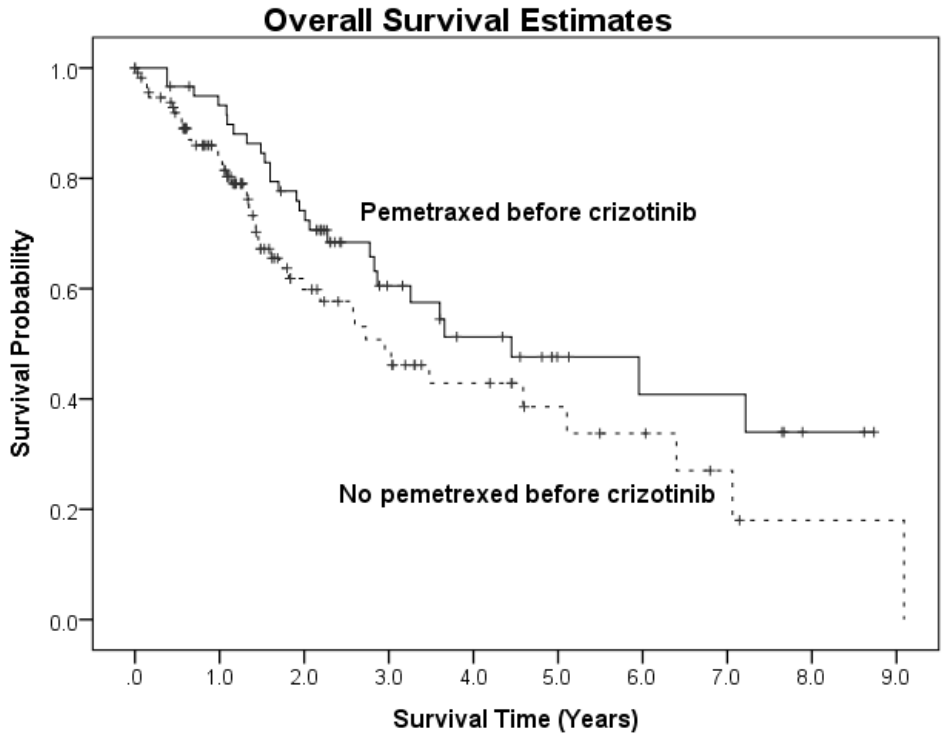
Table 5. Univariate and multivariate Cox regression analysis of overall survival with crizotinib

Variables	Overall survival			
	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.014 (0.992-1.036)	0.223		
Male	1.130 (0.707-1.806)	0.610		
ECOG PS ≥ 2	2.865 (1.619-5.070)	<0.001	2.849 (1.604-5.058)	<0.001
Smoking history				
Non-smoker	1			
Current smoker	0.495 (0.068-3.618)	0.489		
Ex-smoker	1.135 (0.703-1.832)	0.605		
Palliative reason				
Recurred	1			
Initially metastatic	1.507 (0.747-3.040)	0.252		
No. of metastatic organs ≥ 3	1.708 (1.059-2.754)	0.028	1.732 (1.072-2.799)	0.025
Baseline brain metastasis	1.176 (0.710-1.946)	0.529		
Line of crizotinib				
First-line	1			
Second- or later-line	0.680 (0.408-1.134)	0.139		
Response to crizotinib				
Responder (CR + PR)	1			
No responder (SD + PD)	1.336 (0.821-2.176)	0.244		
Pemetrexed before crizotinib	0.638 (0.392-1.040)	0.071	0.597 (0.366-0.974)	0.039

Values are presented as hazards ratio (HR) or 95% confidence interval (CI) unless otherwise indicated. ECOG = Eastern Cooperative Oncology Group; PR = partial response; SD = stable disease; PD = progressive disease; ORR = objective response rate; N/A = not applicable; CI = confidence interval.

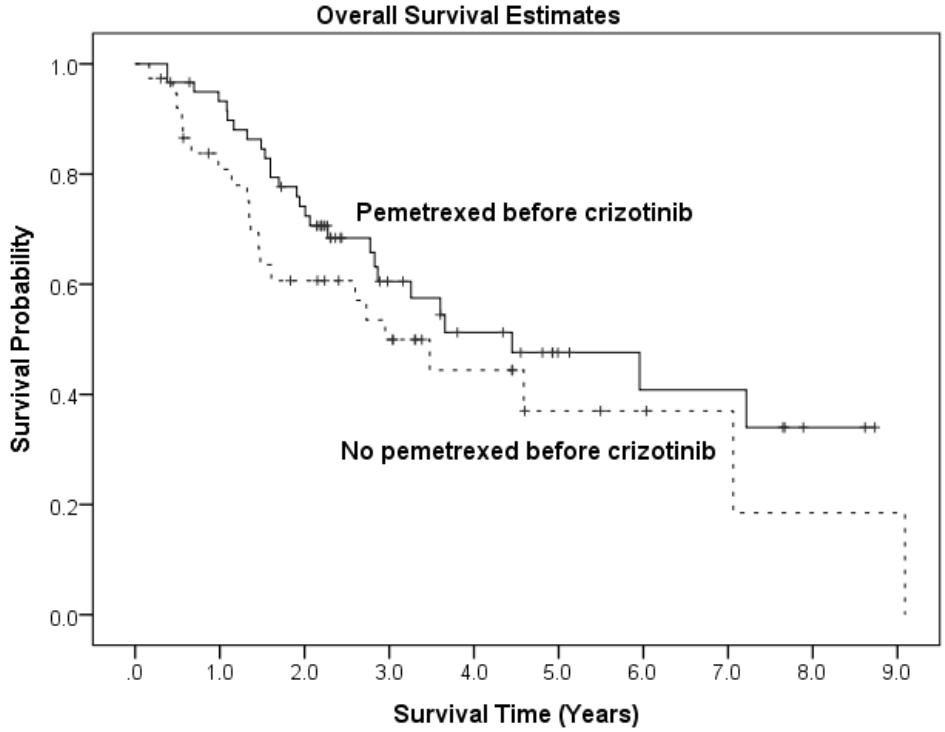
Figure 4. Kaplan-Meier curves for overall survival from chemotherapy initiation, according to previous pemetrexed-based chemotherapy

(A) Overall



	Median	95% CI	P-value
PP-Yes (n=60)	53.4	23.1-83.7	0.069
PP-No (n=38)	35.4	24.3-46.5	

(B) Only in a patients who received crizotinib as second-line therapy



	Median	95% CI	P-value
PP-Yes (n=60)	53.4	23.1-83.7	0.206
PP-No (n=38)	35.4	21.1-49.8	

Discussion

Data describing the use of crizotinib and its outcomes among ALK positive metastatic NSCLC patients in real-world practice settings are evolving, but the need for Asian data still exists. Current study bear some comparable points to previous reports of clinical trials of crizotinib [6, 7, 16-18] as well as real-world outcome assessment of crizotinib; US/Canada [12] and French nationwide [13] retrospective cohort study. First, overall response rates to crizotinib was 54.5% for overall study sample, 50.0% for first-line crizotinib initiators, and 58.2% for second-/later-line initiators in this study. These data goes similar with French (50.2% for overall sample) data[13] but lower than US-Canadian retrospective analysis (66% for the overall, 69% for first-line, and 60% for second-/later-line) [12] and phase 3 crizotinib trials (74% in treatment-naïve patients and 65% for previously treated patients) [6, 7]. ORRs observed in Asian subpopulation analysis of the two global phase III trials, PROFILE 1007 and PROFILE 1014, ORR was 70% for first-line, and 75% for second-/later-line, which showed higher ORR with crizotinib in the second-line setting similar to this study. This might be associated with the fact that our study population contained larger proportion of recurred NSCLC patients who have undergone surgery or concurrent chemo-radiotherapy, which could affect tumor response to crizotinib. And also, time to crizotinib initiation from the diagnosis being longer than other studies might be another reason of lower response.

Median PFS for crizotinib recipients (14.3 months for overall, 15.8 months for first-line, and 13.1 months for second-/later-line), however, was numerically longer than other studies, including 10.9 months for the treatment-naïve patients reported by Solomon *et al*. [7], 7.7 and 6.8 months for second-line recipients estimated by Shaw *et al*. and Duruisseaux *et al*. [6, 13], 9.6 months for first-line and 9.0 months for second-/later-line initiators reported by Davis *et al*. [12], and 13.6 months for first-line and 8.1 months for second-line showed in Asian population analysis of PROFILE 1014 and 1007 [18]. This superiority in PFS in current study might infer that Korean patients with ALK+ NSCLC may receive longer effect of crizotinib than western patients, due to different resistance-acquiring mechanism or other trait of ALK-positive NSCLC, although they show relatively low response rate to crizotinib.

Overall survival was also consistent and seemed to be a little better in the present study

compared to previous studies. Solomon *et al*. [7], for example, reported a 1-year survival probability of 84% for treatment-naïve (first-line) crizotinib recipients and Davis *et al*. [12] reported 84.9% for first-line crizotinib initiator and 47.2% of 2-year survival, which are consistent with 85.4% of 1-year and 55.4% of 2-year survival probability observed in our study for patients received crizotinib as first-line therapy. Median OS from crizotinib initiation in the setting of first-line did not reached in the final analysis of phase III PROFILE 1014 trial [16] and Davis *et al* [12]. reported 23.4 months of median OS for first-line recipients, which appears generally in line with our data of 26.3 months. As for second-/later-line therapy, we defined OS from the first dose of chemotherapy, which is not crizotinib initiation. This remained not many studies for us to directly compare with. Shaw *et al*. reported a median OS of 21.7 months for second-line crizotinib recipients from crizotinib initiation [6] and 49.5 months for the 145 patients who received at least one ALK inhibitor (crizotinib as first subsequent treatment for 144 patients and ceritinib for one patient) in any line of subsequent treamtment after conventional chemotherapy [16]. Davis *et al*. [12] reported near two years as median OS for second-line crizotinib initiators, while our data revealed median OS of 43.9 months for second-/later-line crizotinib recipients. Median OS of crizotinib in current study seem no inferior compared to previous studies. Retrospective study by Shaw *et al*. [19] assessed 1- and 2-year survival rates as 70% and 55%, respectively, while Davis et al. showed 1- and 2-year survival rates as 82% and 49%, respectively [12].This goes along with our data of 1- and 2-year survival rate of 88.5% and 69.0%, repectively. And there were no significant differences by lines of crizotinib treatment in the study of Davis *et al* [12], which was also the result of our study.

As in the retrospective study by Davis *et al*. [12], this study assessed reasons for final crizotinib discontinuation as well as dose changes of crizotinib during the treatment course. Although categories of reason for discontinuation and dose change of crizotinib is not fully comparable to the study by Davis *et al*., disease progression was the most commonly cited reason for crizotinib discontinuation in both studies, and more than 80% of patients experienced no change in crizotinib dose during the therapy, which combined about 4% discontinuation rate due to toxicities, implying that relatively favorable tolerability of the treatment in both study patients.

We also tried to identify factors that can affect PFS and OS from initiation of crizotinib and found that poor performance status (ECOG PS ≥2) and more than 3 metastatic organs at the time of diagnosis were independently associated with shorter PFS and OS, and previous usage of pemetrexed is related to longer OS. This result is comparable to recent study of Ock *et al*. [20], which identified performance status more than ECOG ≥2, ≥3 metastatic organs at the time of diagnosis, and no response to crizotinib as factors affecting shorter PFS and OS. The study of Ock *et al*. was a retrospective cohort study of reviewing the patients enrolled in PROFILE 1001, 1005, 1007, and 1014 [6, 7]. They developed a model consisted of 3 predicting factors and validated the model in two validation cohorts if it can make distinction in prognosis by score. Our data differs with data of Ock *et al*.in that the response to crizotinib were not significantly associated to PFS or OS of crizotinib. Rather, the previous treatment with pemetrexed independently affected OS after initiation of chemotherapy. These differences may come from the disparities between the controlled cohort and the unselected real-world setting population. Further study is needed to identify the validity of the prediction model proposed by Ock *et al*.

The finding that pemetrexed treatment before crizotinib associated to longer OS was interesting point of this study. The reason why pemetrexed benefits OS of the ALK-positive patients may be related to histologic type of adenocarcinoma of our population [21, 22], level of thymidylate synthase in patients with ALK+ NSCLC [23], potential intracranial activity of pemetrexed [24]. In a study by Berge *et al*. [25] it was reported that efficacy of crizotinib does not decrease before and after the pemetrexed therapy, and efficacy of pemetrexed significantly decreased after the crizotinib therapy. Jo *et al*. [26] reported that pemetrexed showed prolonged PFS from initiation of first dose of cytotoxic chemotherapy in a patients with ALK+ NSCLC, but no benefit from OS, while Shaw *et al*. [27] reported that PFS rates of pemetrexed were similar regardless of ALK status. Although controversies about effect of pemetrexed in ALK+ NSCLC patients still exist, there evidently are some portion of ALK-positive NSCLC patients who benefit from pemetrexed therapy [22].

Our study has some limitations. First, the current study was a single center retrospective study, which cannot represent the whole South Korea. Therefore, study findings may not be generalizable to all ALK+ NSCLC patiens treated with crizotinib. However, given the fact

that this hospital harbors the biggest population of lung cancer patients in Korea, and based on the overall rarity of ALK mutation in NSCLC, it is reasonable to expect that the population selected for the current study would not differ greatly from other ALK+ populations in previous trials and observational studies. Second, in retrospective studies, response criteria are not dictated by a protocol, and assessments (such as imaging studies) may not be done on a uniformed schedule. Therefore, results regarding this endpoint may not be directly comparable to those observed in clinical trials. Finally, some of data for this study were drawn from a timeframe prior to the approval of other ALK inhibitors. The impact of follow-up treatment with alternative ALK inhibitors after crizotinib discontinuation therefore could not be exactly assessed.

Despite these limitations, this study provides meaningful information on the use and outcomes of crizotinib in a real-world population of ALK+ metastatic NSCLC patients treated with crizotinib.

Conclusion

ALK+ metastatic NSCLC patients have favorable prognosis when treated with crizotinib, and the subsequent treatment with ALK inhibitors affect longer post-progressive survival after crizotinib failure. Patients with poor PS, high number of metastatic organs may have shorter PFS and OS, and pemetrexed-based regimen before crizotinib may benefit OS.

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국문요약

연구 배경: 크리조티닙 (crizotinib) 이 고식적 항암치료에 비해 anaplastic lymphoma kinase (ALK) 변이 양성 비소세포폐암 환자에서 우월한 효과를 보인다는 것은 여러 임상연구에서 확인되었으나, 실세계에서 crizotinib 의 효과에 대하여는 아직 연구가 필요하다. 본 연구에서는 ALK 변이 양성 비소세포폐암 환자에서 crizotinib 의 실제 효과를 분석하고, 무진행 생존 및 전체 생존기간에 영향을 미치는 인자를 찾고자 하였다.

연구 방법: 2006 년 1 월부터 2018 년 6 월까지 국내의 3 차 의료기관인 서울아산병원에서 전이성 또는 재발성 비소세포폐암으로 진단된 성인 환자들을 대상으로 후향적 연구를 진행하였다. 반응율 (Objective response rate, ORR) 과 치료 경향을 기술통계를 사용하여 분석하였다. 생존분석을 시행하여 무진행 생존 (progression-free survival, PFS) 및 전체 생존기간 (overall survival, OS) 을 확인하였고 crizotinib 의 차수에 따른 치료 효과를 비교하였다. PFS 와 OS 와 연관된 예후인자를 함께 분석하였다.

연구 결과: 중간 나이는 55.7 세 (범위 20-84 세) 이고 85 명(48.3%) 의 환자가 남성이었다. 72 명 (40.9%) 의 환자가 분석 당시 사망한 것으로 확인되었다. ORR 은 54.5% (1 차 크리조티닙 사용군에서 50.0%, 2 차 이상 사용군에서 58.2%) 로 확인되었고, PFS 와 OS 는 각각 14.3 개월 (11.6-17.0 개월), 41.7 개월 (25.4-58.1 개월) 로 확인되었다. Crizotinib 투약의 차수에 따른 ORR, OS, PFS 의 차이는 없었다. Crizotinib 이후 ALK 억제제를 투약한 군에서 진행후 생존이 더 긴 것을 확인하였다. 다변량 Cox 분석에서 낮은 performance status, (HR 3.472, p-value < 0.001) 및 전이 병변이 3 개 이상인 경우 (HR 1.648, p-value 0.017) PFS 와 OS 가 짧았고, crizotinib 이전 pemetrexed 투약력이 긴 OS 와 독립적으로 연관되었다.

연구 결론: Crizotinib 에 따른 PFS 와 OS 는 다른 연구에 비해 본 연구에서 조금 더 양호한 경향을 보였다. 진행 후 ALK 억제제를 추가 투약하는 경우 생존기간이 길어졌다. 낮은 performance status 와 전이병변의 개수는 낮은 PFS 와 OS 를 의미하고, pemetrexed 투약력이 긴 OS 와 연관되었다.

중심 단어: Anaplastic lymphoma kinase, 비소세포폐암, Crizotinib