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Original Article

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Crizotinib versus Chemotherapy in Asian Patients with *ALK*-Positive Advanced Non-small Cell Lung Cancer

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Purpose

Crizotinib has demonstrated superior progression-free survival (PFS) and objective response rates (ORRs) versus chemotherapy in previously treated and untreated patients with anaplastic lymphoma kinase (*ALK*)-positive advanced non-small cell lung cancer (NSCLC). We report the safety and efficacy of crizotinib in Asian subpopulations of two global phase III trials.

Materials and Methods

This analysis evaluated previously treated and untreated patients in two randomized, open-label phase III trials of crizotinib versus chemotherapy in *ALK*-positive advanced NSCLC in second-line (PROFILE 1007) and first-line settings (PROFILE 1014). Efficacy and safety were analyzed by race in the intention-to-treat and "as-treated" populations for efficacy and safety endpoints, respectively.

Results

In previously treated (n=157) and untreated (n=157) Asian patients, PFS was statistically significantly longer with crizotinib versus chemotherapy (hazard ratio for PFS, 0.526; 95% confidence interval, 0.363 to 0.762; $p < 0.001$ and hazard ratio, 0.442; 95% confidence interval, 0.302 to 0.648; $p < 0.001$, respectively). Similar antitumor activity was seen in the non-Asian and overall populations. ORRs were statistically significantly higher with crizotinib versus chemotherapy in both Asian and non-Asian previously treated and untreated patients ($p < 0.05$). The most common treatment-emergent adverse events (any grade) with crizotinib were vision disorder, diarrhea, and nausea, which were observed at a comparable incidence across Asian and non-Asian populations, irrespective of previous treatment status. Most adverse events were mild to moderate in severity.

Conclusion

These data, currently the only analysis showing Asian and non-Asian populations in the same study, support the efficacy and safety of crizotinib in Asian patients with previously treated or untreated *ALK*-positive advanced NSCLC.

Key words
Asia, Carboplatin, Cisplatin, Crizotinib, Non-small cell lung carcinoma, Pemetrexed

Introduction

Approximately 3% to 5% of all patients with non-small cell lung cancer (NSCLC) harbor a rearrangement of the anaplastic lymphoma kinase (*ALK*) gene, resulting in an oncogene that codes for ALK fusion proteins such as echinoderm microtubule-associated protein-like 4–*ALK*, which promotes tumor cell growth. The incidence of *ALK*-positive NSCLC is similar among Caucasian and Asian populations [1-3]. Although this subset represents only a small proportion of the overall NSCLC population, the number still translates into approximately 40,000 patients worldwide per year [4]. Crizotinib is a first-in-class, oral, small-molecule tyrosine kinase inhibitor of ALK, ROS1, and cMET kinases that was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the treatment of patients with locally advanced or metastatic NSCLC who test positive for the *ALK* fusion gene, as detected by an FDA-approved test. In 2016, the FDA further approved crizotinib for patients with metastatic NSCLC whose tumors are *ROS1* positive. Crizotinib also received approval in the European Union for the first-line treatment of adults with *ALK*-positive advanced NSCLC or in previously treated patients, as well as for the treatment of adults with *ROS1*-positive advanced NSCLC.

A series of clinical trials have shown and confirmed the efficacy and safety of crizotinib in patients with *ALK*-positive advanced NSCLC. Named the PROFILE series, these trials consist of a phase I dose-escalation study in an array of cancer indications, including *ALK*-positive advanced NSCLC (PROFILE 1001 [5,6]), a phase II study evaluating patients with *ALK*-positive advanced NSCLC (PROFILE 1005 [7]), and three phase III trials assessing crizotinib use in *ALK*-positive advanced NSCLC, in both second-line (PROFILE 1007 [8]) and first-line settings (PROFILE 1014 [9] and PROFILE 1029 [10]). In these studies, crizotinib has established a consistent safety profile, with the most common adverse events (AEs) of visual disturbances, gastrointestinal effects, and elevated liver aminotransferases [7-9].

In randomized trials involving patients with *ALK*-positive advanced NSCLC (PROFILE 1007, PROFILE 1014, and PROFILE 1029), crizotinib has demonstrated efficacy superior to that of single-agent chemotherapy with pemetrexed or docetaxel in previously treated patients [8], and to pemetrexed plus platinum chemotherapy in previously untreated multinational [9] and Asian patients [10].

Across the PROFILE series, Asian patients have been well represented, accounting for 45% and 46% of the overall population in PROFILE 1007 and PROFILE 1014, respectively, and 100% in PROFILE 1029 [8-10]. Higher objective response rates (ORRs) have been frequently reported in Asian patients than in non-Asian patients [5,11].

Data from the phase III trial in the first-line setting with only Asian patients (PROFILE 1029) have been previously presented [10]. This report focuses on the results of multinational phase III trials that included Asian and non-Asian patients, in both the second-line (PROFILE 1007) [8] and the first-line (PROFILE 1014) [9] settings, to further evaluate the efficacy and safety profile of crizotinib in the Asian population.

Materials and Methods

Data from two randomized, open-label, phase III trials comparing crizotinib with chemotherapy and ongoing at the time of the analysis (PROFILE 1007 [8] [NCT00932893] and PROFILE 1014 [9] [NCT01154140]) were analyzed. The detailed methodologies and primary results for both studies have been previously published [8,9]. Each participating center's institutional review board or independent ethics committee approved these protocols. The studies complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent before enrollment.

1. Study design and treatment

In PROFILE 1007, patients with *ALK*-positive advanced NSCLC who had progressive disease following one prior platinum-based chemotherapy regimen were randomly assigned, in a 1:1 ratio, to receive continuous oral crizotinib at a dose of 250 mg twice daily in a 3-week cycle or intravenous chemotherapy, comprising either pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2, every 3 weeks. Previously untreated patients with *ALK*-positive advanced NSCLC were selected for the PROFILE 1014 study and were randomized (1:1) to receive continuous oral crizotinib at a dose of 250 mg twice daily or intravenous chemotherapy of pemetrexed 500 mg/m^2 plus a platinum agent (either cisplatin 75 mg/m^2 or carboplatin, target area under the curve 5-6 mg/mL/min) administered every 3 weeks. Randomization was stratified in both studies according to Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2) and presence or absence of brain metastases. Additional stratification factors included prior or no prior therapy with epidermal growth factor receptor tyrosine kinase inhibitors for PROFILE 1007 and Asian or non-Asian race for PROFILE 1014.

In both PROFILE studies:

- Treatment was continued (up to a maximum of six cycles of chemotherapy in PROFILE 1014) until disease progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 per independent radiology review (IRR) was observed, development of unacceptable toxicity, death, or withdrawal of consent.
- Crizotinib treatment could be continued beyond disease progression per IRR at the discretion of the investigator.
- Patients in the chemotherapy groups who had RECIST-defined disease progression, confirmed by IRR, were allowed to cross over to receive crizotinib. In PROFILE 1007, patients who crossed over were enrolled in a separate study (PROFILE 1005). In PROFILE 1014, patients were allowed to cross over and remain in the study if they met the safety eligibility criteria for crossover.
- The primary endpoint was progression-free survival (PFS), as assessed by IRR, and secondary endpoints included the objective response, as assessed by IRR, and safety.

2. Assessments

Tumor assessments were to be carried out every 6 weeks during treatment until RECIST-defined disease progression was documented by IRR. In PROFILE 1007, the brain was to be included in subsequent tumor assessments if a patient had brain metastases at baseline; otherwise, the brain was only to be evaluated when clinically indicated. Repeat bone scans were required every 12 weeks only if bone metastases were present at baseline; otherwise, a repeat bone scan was required only if new bone metastases were suspected. In PROFILE 1014, brain and bone scans were performed at baseline and were repeated every 6 weeks for patients reporting brain or bone lesions at baseline or every 12 weeks to monitor for new lesions in the other patients. Patients with brain metastases were eligible if treated and neurologically stable; untreated and asymptomatic patients with brain metastases were also eligible in PROFILE 1007. In both studies, all scans were submitted for central IRR, who were unaware of the group assignments, and the data from IRR were used to determine PFS and ORR. AEs were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events ver. 4.0.

3. Statistical analysis

Efficacy endpoints were analyzed in the intention-to-treat population (all randomized patients) in both studies. The Kaplan-Meier method was used to estimate time-to-event endpoints. One-sided log-rank tests (stratified for baseline factors in the overall populations of both studies and unstratified in the Asian and non-Asian subgroups) were used to compare PFS between the crizotinib and chemotherapy groups; Cox regression models were used to estimate hazard ratios (HRs; stratified in the overall populations and unstratified in the Asian and non-Asian subgroups). The ORR between crizotinib and chemotherapy groups was compared using a two-sided Pearson chi-square test. For the analyses presented here, no adjustment of the type I error was made for multiplicity. AEs were summarized in the "as-treated" population in both studies that included all patients who received at least one dose of study drug. The statistical analysis plans for both studies have been previously described [8,9].

Results

1. Patients

Baseline patient and disease characteristics were well balanced across randomized study groups and are summarized in S1 Table. In addition, the baseline characteristics in both studies were similar between Asian and non-Asian patients. A total of 314 Asian patients were randomized across the two studies (PROFILE 1007, 157/347 [45%]; PROFILE 1014, 157/343 [46%]). The majority of Asian patients were either Korean (34%) or Japanese (32%), and the majority of non-Asian patients were white (95%) (S1 Table).

2. Efficacy

Overall, PFS, as determined by IRR, was significantly longer with crizotinib than with chemotherapy in both studies (Fig. 1A and D). In previously treated Asian patients, the HR for PFS with crizotinib was 0.526 (95% confidence interval [CI], 0.363 to 0.762; $p < 0.001$); median PFS was 8.1 and 2.8 months in the crizotinib and chemotherapy groups, respectively (Fig. 1B). A comparable benefit was observed for PFS with crizotinib in previously treated non-Asian patients (HR, 0.447; 95% CI, 0.304 to 0.655; $p < 0.001$); median PFS was 7.1 months with crizotinib and 3.2 months with chemotherapy (Fig. 1C). PFS was also significantly longer with crizotinib than with chemotherapy in treatment-naïve patients, both Asian (HR, 0.442; 95% CI, 0.302 to 0.648; $p < 0.001$; median PFS, 13.6 and 7.0 months, respectively) and non-Asian (HR, 0.525; 95% CI, 0.363 to 0.760; $p < 0.001$; median PFS, 9.6 and 7.2 months, respectively) (Fig. 1E and F).

In both previously treated and untreated patients with *ALK*-positive advanced NSCLC, comparable efficacy of crizotinib versus chemotherapy was observed in both Asian

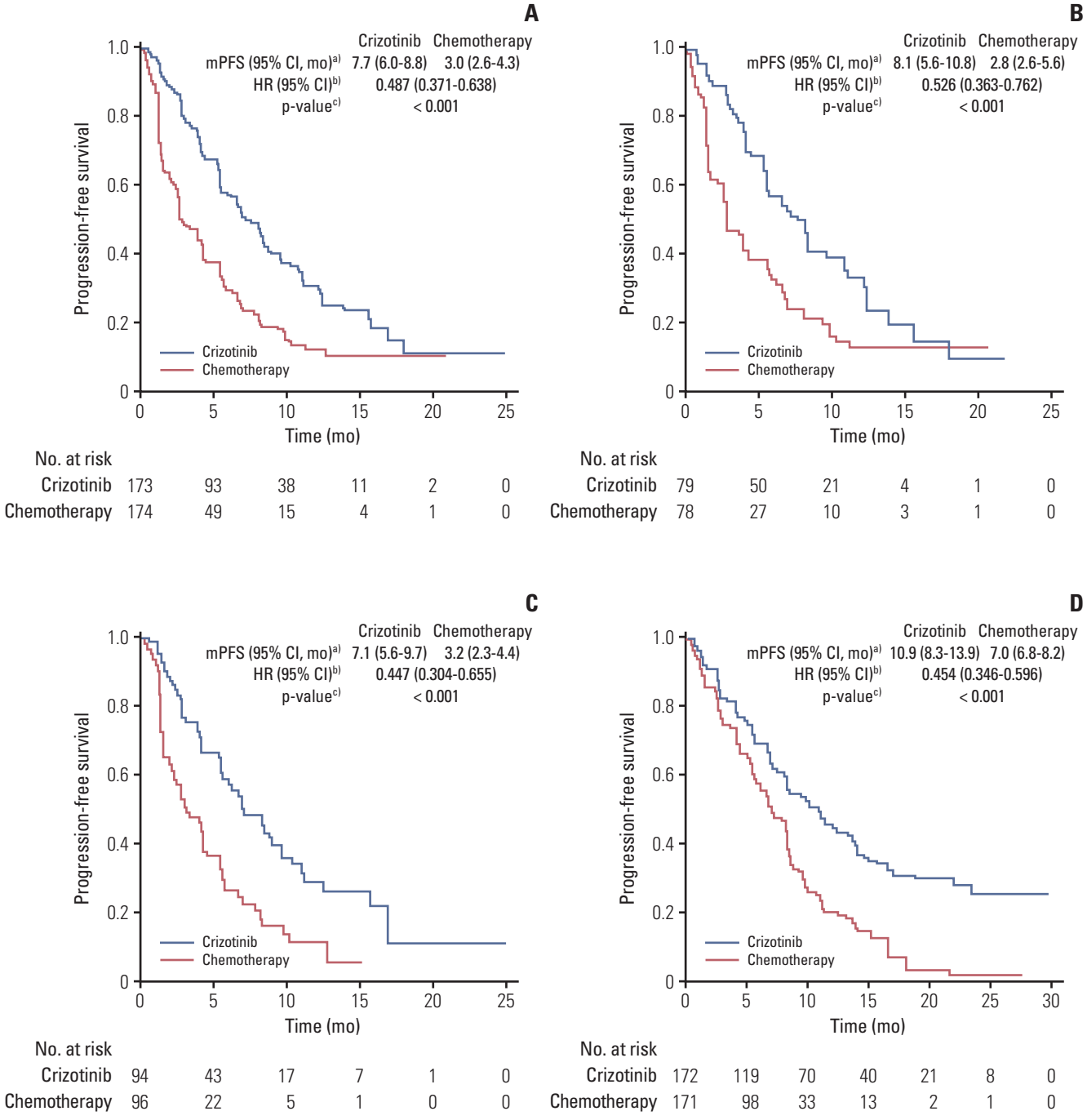

Fig. 1. Progression-free survival by independent radiology review for all previously treated patients (A); previously treated Asian patients (B); previously treated non-Asian patients (C); all previously untreated patients (D); previously untreated Asian patients (E); and previously untreated non-Asian patients (F). mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status. [a]Based on the Brookmeyer and Crowley method, [b]Based on the Cox proportional hazards model (assuming proportional hazards, an HR < 1 indicates a reduction in hazard rate in favor of crizotinib; an HR > 1 indicates a reduction in hazard rate in favor of chemotherapy), [c]One-sided p-value from the log-rank test stratified by ECOG PS, brain metastases, and prior epidermal growth factor receptor tyrosine kinase inhibitor treatment (PROFILE 1007) or by ECOG PS, race, and brain metastases (PROFILE 1014), [d]One-sided p-value from the unstratified log-rank test. *(Continued to the next page)*

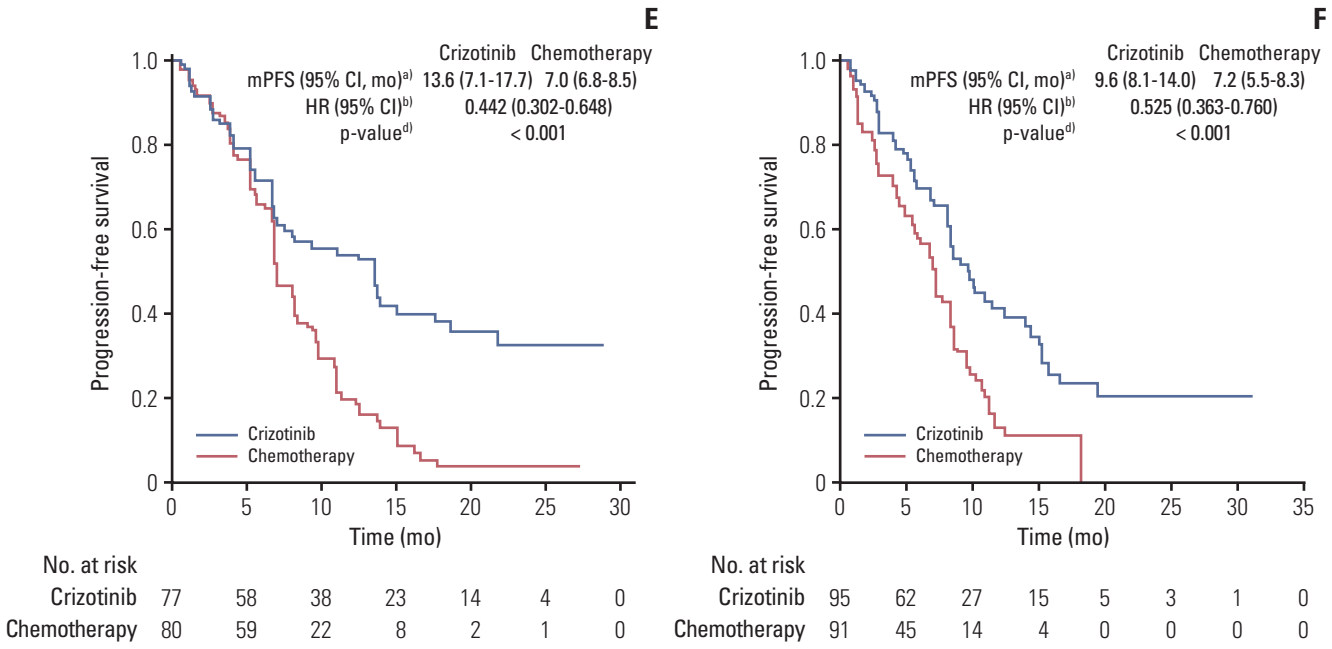

Fig. 1. *(Continued from the previous page)*

and non-Asian patients, as well as in the overall population (Table 1). As assessed by IRR, the ORRs in the intention-to-treat populations were statistically significantly higher with crizotinib than with chemotherapy, respectively, in both previously treated (75% vs. 22%) and untreated (70% vs. 54%) Asian patients ($p < 0.05$). A similar effect was observed in previously treated (57% vs. 18%, respectively) and untreated (78% vs. 37%, respectively) non-Asian patients ($p < 0.001$) (S2 Fig.). Objective responses among crizotinib-treated patients were both rapid in onset (median time to response, up to 6 weeks; coinciding with the first tumor assessment per protocol) and durable (median duration of response, 31 and 32 weeks in previously treated patients, respectively, and 42 and 54 weeks in previously untreated patients, respectively) among Asian and non-Asian patients (Table 1).

3. Safety

In the crizotinib group, the most common treatment-emergent AEs of any cause (any grade) in previously treated or untreated Asian and non-Asian patients, respectively, were vision disorders (44%-79%), diarrhea (52%-70%), nausea (45%-66%), vomiting (33%-62%), constipation (37%-51%), elevated transaminases (25%-49%), and edema (23%-55%). In both studies, reported incidence rates of grades 1-2 AEs across all populations and treatment groups were between 37% (lowest incidence rate [previously untreated non-Asian patients in the crizotinib group]) and 53% (highest incidence rate [previously treated Asian patients in the chemotherapy group]).

Overall, the AE profiles of crizotinib among Asian pretreated and treatment-naïve patients were generally comparable with those observed in the corresponding non-Asian patients. However, AEs of elevated transaminases and decreased appetite were reported more frequently in Asian patients than in non-Asian patients treated with crizotinib or chemotherapy in both studies (Table 2). Among previously treated patients, diarrhea, vomiting, and neutropenia were more common in Asian patients treated with either crizotinib or chemotherapy than in the non-Asian population.

In PROFILE 1007, the median duration of treatment was 31 weeks with crizotinib and 12 weeks with chemotherapy. Median duration of treatment in PROFILE 1014 was 47 weeks with crizotinib and 18 weeks with chemotherapy. Overall, permanent discontinuation of crizotinib associated with treatment-related AEs occurred at a similar rate in both studies (6.4% and 4.7% for PROFILE 1007 and PROFILE 1014, respectively). Rates of permanent treatment discontinuation of crizotinib were higher among Asian than non-Asian patients in both studies (PROFILE 1007: 11.4% vs. 2.2%, respectively; PROFILE 1014: 6.5% vs. 3.2%, respectively). The AE most frequently associated with permanent treatment discontinuation of crizotinib was interstitial lung disease in

Table 1. Response to treatment in Asian and non-Asian patients

	Asian patients		Non-Asian patients		All patients	
	Crizotinib	Chemotherapy[a]	Crizotinib	Chemotherapy[a]	Crizotinib	Chemotherapy[a]
PROFILE 1007	**n=79**	**n=78**	**n=94**	**n=96**	**n=173**	**n=174**
Type of response						
Complete response	1 (1)	0	0	0	1 (1)	0
Partial response	58 (73)	17 (22)	54 (57)	17 (18)	112 (65)	34 (20)
Stable disease	10 (13)	28 (36)	22 (23)	35 (37)	32 (19)	63 (36)
Progressive disease	6 (8)	29 (37)	5 (5)	31 (32)	11 (6)	60 (35)
Not evaluable[b]	4 (5)	4 (5)	13 (14)	13 (14)	17 (10)	17 (10)
Objective response rate (%)	75	22	57	18	65	20
95% CI[c]	64-84	13-33	47-68	11-27	58-72	14-26
p-value[d]	< 0.001		< 0.001		< 0.001	
Duration of response (wk)[e]						
Median	31.0	24.4	32.1	19.9	32.1	24.4
95% CI[f]	23.1-42.3	15.0-NR	24.4-51.3	12.1-43.6	26.4-42.3	15.0-36.0
Time to response (wk)						
Median	6.3	19	6.4	11.9	6.3	12.6
Range	5.3-18.1	5.0-37.0	4.4-48.4	5.1-37.1	4.4-48.4	5.0-37.1
PROFILE 1014	**n=77**	**n=80**	**n=95**	**n=91**	**n=172**	**n=171**
Type of response						
Complete response	1 (1)	1 (1)	2 (2)	1 (1)	3 (2)	2 (1)
Partial response	53 (69)	42 (53)	72 (76)	33 (36)	125 (73)	75 (44)
Stable disease	16 (21)	27 (34)	13 (14)	36 (40)	29 (17)	63 (37)
Progressive disease	5 (7)	8 (10)	3 (3)	13 (14)	8 (5)	21 (12)
Not evaluable[b]	2 (3)	2 (3)	5 (5)	8 (9)	7 (4)	10 (6)
Objective response rate (%)	70	54	78	37	74	45
95% CI[c]	59-80	42-65	68-86	27-48	67-81	37-53
p-value[d]	0.048		< 0.001		< 0.001	
Duration of response (wk)[e]						
Median	54.3	18.6	42.0	24.3	49.0	22.9
95% CI[f]	42.1-NR	12.3-24.1	30.6-58.9	19.3-25.9	35.1-60.0	18.0-25.1
Time to response (wk)						
Median	6.1	12.1	6.3	12.1	6.1	12.1
Range	5.1-29.6	5.3-36.7	2.7-41.4	5.1-25.0	2.7-41.4	5.1-36.7

Values are presented as number (%) unless otherwise indicated. CI, confidence interval; NR, not reported. [a]PROFILE 1007: pemetrexed or docetaxel; PROFILE 1014: pemetrexed plus cisplatin or carboplatin, [b]Could not be evaluated, including early death and indeterminate, [c]Using exact method based on F-distribution, [d]p-value is from a two-sided Pearson chi-square test, [e]Kaplan-Meier estimate of duration of response, [f]Based on the Brookmeyer and Crowley method.

2.3% (5.1% Asian vs. 0.0% non-Asian) and 1.2% (1.3% Asian vs. 1.1% non-Asian) of patients in PROFILE 1007 and PROFILE 1014, respectively. Other AEs associated with permanent discontinuation in both studies included elevated transaminases, hepatotoxicity, and nausea (S3 and S4 Tables).

Discussion

Crizotinib has demonstrated superior efficacy over standard chemotherapy in phase III studies of previously treated and untreated patients with *ALK*-positive advanced NSCLC. In comparison with chemotherapy, crizotinib significantly prolonged PFS and increased ORRs. Responses in patients treated with crizotinib were generally seen within up to 6 weeks of treatment initiation, irrespective of prior treatment

Table 2. Treatment-emergent AEs of any cause occurring in ≥ 20%[a)] of patients in the overall crizotinib group

Adverse event	Asian patients				Non-Asian patients				All patients			
	Crizotinib		Chemotherapy		Crizotinib		Chemotherapy		Crizotinib		Chemotherapy	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
PROFILE 1007	**n=79**		**n=77**		**n=93**		**n=94**		**n=172**		**n=171**	
Any adverse event	100	47	99	39	100	42	98	45	100	44	98	42
Vision disorder[b)]	79	0	14	0	44	0	5	0	60	0	9	0
Diarrhea	70	0	29	1	52	0	12	0	60	0	19	1
Nausea	66	1	39	0	45	1	36	1	55	1	37	1
Vomiting	62	1	26	0	33	1	11	0	47	1	18	0
Constipation	48	4	26	0	38	1	20	0	42	2	23	0
Elevated transaminases[b)]	46	20	21	3	32	12	10	2	38	16	15	2
ALT increased[b)]	44	18	16	3	29	9	9	2	36	13	12	2
Edema[b)]	23	0	17	0	39	0	15	0	31	0	16	0
Decreased appetite	41	3	40	3	16	2	15	1	27	2	26	2
Fatigue	39	3	35	1	16	2	32	6	27	2	33	4
Neutropenia[b)]	38	19	27	22	18	9	19	17	27	13	23	19
Dysgeusia	41	0	14	0	13	0	5	0	26	0	9	0
AST increased[b)]	33	10	13	1	20	1	6	0	26	5	9	1
Upper respiratory tract infection[b)]	32	0	13	0	20	0	13	1	26	0	13	1
Dizziness[b)]	33	1	9	0	12	0	7	0	22	1	8	0

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Table 2. Continued

Adverse event	Asian patients				Non-Asian patients				All patients			
	Crizotinib		Chemotherapy		Crizotinib		Chemotherapy		Crizotinib		Chemotherapy	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
PROFILE 1014	**n=77**		**n=80**		**n=94**		**n=89**		**n=171**		**n=169**	
Any adverse event	100	44	99	49	99	48	100	54	99	46	99	52
Vision disorder[b]	66	0	9	0	76	1	10	0	71	1	10	0
Diarrhea	61	0	11	0	62	4	15	1	61	2	13	1
Nausea	52	0	60	1	59	2	57	2	56	1	59	2
Edema[b]	40	1	10	0	55	0	15	1	49	1	12	1
Vomiting	47	1	33	3	45	2	38	3	46	2	36	3
Constipation	51	0	28	0	37	3	33	0	43	2	30	0
Elevated transaminases[b]	49	20	19	3	25	10	8	2	36	14	13	2
Upper respiratory tract infection[b]	46	0	13	1	21	0	12	0	32	0	12	1
Decreased appetite	43	5	48	1	19	0	21	0	30	2	34	1
Fatigue	34	3	39	1	25	3	38	3	29	3	39	2
Dysgeusia	30	0	4	0	23	0	7	0	26	0	5	0
Abdominal pain[b]	26	0	15	0	27	0	9	0	26	0	12	0
Cough[b]	23	0	19	0	22	0	20	0	23	0	20	0
Headache	26	1	11	0	18	1	18	0	22	1	15	0
Neutropenia[b]	21	10	30	13	21	12	30	18	21	11	30	15
Neuropathy[b]	20	0	26	0	21	2	19	0	21	1	23	0

Values are presented as percentages. ALT, alanine aminotransferase; AST, aspartate aminotransferase. [a]In decreasing order of frequency in the overall crizotinib group, [b]This item comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes, listed in S4 Table.

status, and durable [8,9].

These subgroup analyses have shown that the efficacy of crizotinib in previously treated and untreated Asian patients is consistent with that seen for non-Asian populations. Comparable PFS and ORRs for Asian and non-Asian patients have been observed in both studies, although a higher ORR was seen with crizotinib in the second-line setting among Asian patients (ORR, 75%; 95% CI, 64 to 84) than among non-Asian patients (ORR, 57%; 95% CI, 47 to 68), but the 95% CI overlapped.

The safety of crizotinib for Asian and non-Asian patients was consistent with previous publications, exhibiting a distinct AE profile compared with chemotherapy and a low incidence of permanent treatment discontinuations. The most common AEs observed with crizotinib included visual impairment, diarrhea, nausea, vomiting and constipation, elevated transaminases, and peripheral edema, which were commonly reported AEs across the Asian and non-Asian populations in both studies. However, some AEs were reported with higher frequency for Asian than non-Asian patients in both studies, as noted below.

In this subgroup analysis, AEs across both PROFILE 1007 and PROFILE 1014 were generally of low-grade severity (grades 1-2), with a similar incidence of grades 3-4 AEs for both Asian and non-Asian patients treated with crizotinib, and were associated with few permanent treatment discontinuations.

However, the incidence of selected AEs for patients treated with either crizotinib or chemotherapy was higher for the Asian population than for the non-Asian population in previously treated patients. For example, gastrointestinal events, such as diarrhea and vomiting, were observed at a higher frequency (≥ 10%) in the Asian subgroup than in the non-Asian subgroup of both treatment groups of PROFILE 1007. In contrast, the incidence of these AEs was similar in previously untreated Asian and non-Asian patients, although the incidence of constipation was higher among Asian patients in PROFILE 1014. The higher incidence of AEs among Asian patients than non-Asian patients noted in PROFILE 1007 is consistent with previous reports for crizotinib [11] and chemotherapy [12].

While patient and disease characteristics were well balanced between the Asian and non-Asian subgroups across both studies, neither PROFILE 1007 nor PROFILE 1014 was designed or powered to support inferential analyses of these subgroups.

Notwithstanding previously noted limitations, the efficacy and safety of crizotinib in Asian patients with *ALK*-positive advanced NSCLC were comparable to those observed in non-Asian patients, further supporting the use of crizotinib in the Asian population. These studies, currently the only trials that have included Asian and non-Asian populations in the same study, provide evidence supporting the efficacy and safety of crizotinib in Asian patients, both in the first-line setting and in previously treated patients.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (http://www.e-crt.org).

Conflicts of Interest

BJS has received honoraria from and participated in advisory boards for AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, Pfizer, and Roche. He has also received institutional research funding from AstraZeneca, Merck, Novartis, Pfizer, and Roche and has patent/intellectual property to disclose from Biodesix. ATS has received research funding from and participated in advisory boards for Genentech, Novartis, Pfizer, and Roche. She participated in advisory boards for ARIAD, Blueprint Medicines, Daiichi Sankyo, EMD Serono, Loxo Oncology, and Taiho. EO, TU, JP, AP, and KDW are all employees of Pfizer and have stock ownership in Pfizer. TM has a company leadership role and stock ownership in Sanomics Ltd. He has received honoraria and participated in advisory boards for ACEA Biosciences, Inc., AstraZeneca, AVEO, Biodesix, BioMarin, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Eli Lilly and Company, GlaxoSmithKline, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, OncoGenex Pharmaceuticals Inc., Pfizer, Roche/Genentech, SFJ Pharmaceuticals, and Vertex Pharmaceuticals. He has also received honoraria from Amgen and Prime Oncology and participated in advisory boards for geneDecode Co., Ltd. He has received research funding and speakers bureau fees in the last 2 years from AstraZeneca, Boeh-ringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Merck Sharp & Dohme, Novartis, Pfizer, and Roche. He has received speakers bureau fees from Amgen, Eli Lilly and Company, GlaxoSmithKline, Janssen, and Prime Oncology and received research funding from ARIAD Pharmaceuticals, Inc. and SFJ Pharmaceuticals. The remaining authors have no conflicts of interest to disclose.

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