ORIGINAL ARTICLE

Updated Efficacy and Safety Data and Impact of the *EML4-ALK* Fusion Variant on the Efficacy of Alectinib in Untreated *ALK*-Positive Advanced Non–Small Cell Lung Cancer in the Global Phase III ALEX Study

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ABSTRACT

Introduction: At the prior data cutoff (February 9, 2017) the ALEX trial showed superior investigator-assessed progression-free survival (PFS) for alectinib versus crizotinib in untreated, anaplastic lymphoma kinase (*ALK*)-positive, advanced NSCLC (hazard ratio = 0.47, 95% confidence interval: 0.34–0.65, $p < 0.001$). The median PFS in the alectinib arm was not reached versus 11.1 months with crizotinib. Retrospective analyses suggest that the echinoderm microtubule-associated protein-like 4 gene-ALK variant (*EML4-ALK*) may influence ALK-inhibitor treatment benefit. We present updated analyses, including exploratory subgroup analysis by *EML4-ALK* variant, after an additional 10 months' follow-up (cutoff December 1, 2017).

Methods: Patients were randomized to receive twice-daily alectinib, 600 mg, or crizotinib, 250 mg, until disease progression, toxicity, death, or withdrawal. PFS was determined by the investigators. Baseline plasma and tissue biomarker samples were analyzed by using hybrid-capture, next-generation sequencing to determine *EML4-ALK* variant.

Results: Baseline characteristics were balanced. Investigator-assessed PFS was prolonged with alectinib (stratified hazard ratio = 0.43, 95% confidence interval: 0.32–0.58). The median PFS times were 34.8 months with alectinib and 10.9 months with crizotinib. *EML4-ALK* fusions were detectable in 129 patient plasma samples and 124 tissue samples; variants 1, 2, and 3/ab did not affect PFS, objective response rate, or duration of response. Investigator-assessed PFS was longer for alectinib than for crizotinib across *EML4-ALK* variants 1, 2, and 3a/b in plasma and tissue. Despite longer treatment duration (27.0 months in the case of alectinib versus 10.8 months in the case of crizotinib), the safety of alectinib compared favorably with that of crizotinib.

Conclusion: Alectinib continues to demonstrate superior investigator-assessed PFS versus crizotinib in untreated *ALK*-positive NSCLC, irrespective of *EML4-ALK* variant.

Keywords: Alectinib; Non–small cell lung cancer; ALEX; *EML4-ALK*; NGS

Introduction

Alectinib is a highly selective and potent inhibitor of anaplastic lymphoma kinase (ALK) that has demonstrated good activity in patients with anaplastic lymphoma kinase gene (*ALK*)-positive NSCLC who have progressed while taking crizotinib or are intolerant to it.[1,2] The phase III, global, randomized ALEX trial (BO28984; NCT02075840) demonstrated superior efficacy and safety of alectinib compared with crizotinib in patients with treatment-naive *ALK*-positive NSCLC.[3] The trial met its primary end point: at the primary analysis (data cutoff February 9, 2017), investigator-assessed progression-free survival (PFS) was improved with alectinib versus with crizotinib in patients with treatment-naive *ALK*-positive NSCLC.[3] In the intent-to-treat (ITT) population, the hazard ratio (HR) for disease progression or death was 0.47 (95% confidence interval [CI]: 0.34–0.65, $p < 0.001$), with the median PFS for alectinib not reached after a median follow-up of 18.6 months.[3]

ALK-positive disease is characterized by the presence of an oncogene rearrangement leading to a structural alteration of the chromosome and expression of constitutively active ALK fusion proteins.[4–6] The most common *ALK* fusion partner is the echinoderm microtubule-associated protein-like 4 gene (*EML4*); both are located on the short arm of chromosome 2.[5] The breakpoint of the *ALK* gene occurs at exon 20, whereas the *EML4* breakpoint differs to generate fusion protein variants.[5–7] More than 15 *EML4-ALK* fusion variants have been identified; the most common variants are 1 (*EML4* breakpoint exon 13 [in 43% of cases]), 2 (*EML4* breakpoint exon 20 [in 6% of cases]) and 3a/b (*EML4* breakpoint exon 6a/b [in 40% of cases]).[5,8]

Retrospective analyses have suggested that the expression of particular *EML4-ALK* variants may influence the degree of benefit experienced by patients with *ALK*-positive NSCLC in response to ALK inhibitors, potentially by influencing the propensity to develop specific secondary *ALK* resistance mutations. In one study, first-line crizotinib-treated patients with variant 1 were reported to have longer PFS than those with other *EML4-ALK* variants,[9] whereas patients with *EML4-ALK* variant 3 treated with lorlatinib in a second- or later-line setting were reported to have significantly longer PFS than those with variant 1.[8] However, the available evidence is limited; there is a lack of randomized clinical trial data on the impact of *EML4-ALK* variants on treatment efficacy with ALK inhibitors, including alectinib.[3,8]

Here we report updated efficacy and safety data from the ALEX study, with a further follow-up of approximately 10 months (data cutoff December 1, 2017) and an exploratory analysis of efficacy by *EML4-ALK* fusion variant. We discuss the impact of fusion variant type on benefit from the ALK inhibitors alectinib and crizotinib.

Methods

Study Design

Full details of the ALEX study design have been previously published.[3] Briefly, 303 patients aged 18 years or older with stage III or IV *ALK*-positive NSCLC were randomized 1:1 to receive twice-daily alectinib, 600 mg, or crizotinib, 250 mg, until progressive disease (PD), toxicity, withdrawal, or death. Patients with asymptomatic brain metastases were permitted. Eligible patients had histologically or cytologically diagnosed advanced *ALK*-positive NSCLC, centrally tested by the VENTANA ALK (D5F3) immunohistochemistry assay (Ventana Medical Systems). Patients had no prior systemic treatment for advanced NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 2. Plasma and tumor tissue samples were collected at baseline, and biomarker-evaluable population (BEP) subgroups were assessed. BEP subgroups consisted of those patients with evaluable plasma or tissue samples (sufficient tumor tissue and/or circulating tumor DNA yield) that passed next-generation sequencing (NGS) quality control.

The study protocol was approved by the institutional review board or ethics committee at each participating center, and the study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws. Written and informed consent was obtained from all patients before enrollment.

Study End Points

The primary end point of ALEX was investigator-assessed PFS. Secondary end points included independent review committee (IRC)-assessed PFS, objective response rate (ORR), time to central nervous system (CNS) progression, duration of response (DOR), overall survival (OS), and safety. IRC-assessed end points were evaluated only for the primary analysis and were not planned for further analysis at later time points, including this data cutoff (December 1, 2017).

Study Assessment

As reported by Peters et al. in 2017,[3] brain imaging was performed in all patients at baseline and every 8 weeks until PD. Response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and were classified according to the Medical Dictionary for Regulatory Activities. PFS and ORR, assessed by the investigator, were determined in each of the BEP subgroups and for each of the *EML4-ALK* fusion variant populations (updated data cutoff December 1, 2017). PFS was defined as the time from randomization to the date of confirmed PD or death, whichever occurred first. ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR) according to RECIST version 1.1, and DOR was defined as the time from when the criteria for CR or PR were first met to the occurrence of a PFS event.

Identification of ALK Fusion Variant

ALK fusion variants were detected by a hybrid-capture NGS test method using proprietary computational algorithms that enabled variant cells to be accurately detected by discriminating sequencing artifacts from real mutations.[10] Plasma samples were analyzed by using the FoundationACT® platform and tissue samples were analyzed using FoundationOne® (Foundation Medicine, Cambridge, MA) (for details see Supplementary Materials).[10–12]

Statistical Analysis

Comparison between treatment groups with respect to PFS was based on a stratified log-rank test at a 5% level of significance (two-sided). The Kaplan-Meier method was used to estimate the median PFS for each treatment group with 95% CIs. The stratified Cox proportional hazards regression model was used to estimate the treatment effect, expressed as an HR with a 95% CI, and ORR was calculated by using the Clopper-Pearson method, with treatment groups compared by using a stratified Mantel-Haenszel test. Median DOR with 95% CIs was estimated with the Kaplan-Meier method. PFS between the *EML4-ALK* variant groups within each of the treatment arms was compared by using a two-sided log-rank test at a 5% significance level. ORR between *EML4-ALK* variants was compared by using the Pearson chi-square test.

Results

Patients

The overall patient population has been described previously.[3] Patients (the ITT population [N = 303]) were randomized to receive treatment with alectinib (n = 152) or crizotinib (n = 151). Of these, 122 patients had IRC-assessed baseline CNS metastases (64 treated with alectinib and 58 treated with crizotinib).[3] In the ITT population, baseline characteristics were generally

balanced between the treatment arms. In patients with CNS metastases at baseline, the number who received whole-brain radiotherapy (17 treated with alectinib and 16 treated with crizotinib) or stereotactic radiosurgery (six treated with alectinib and four treated with crizotinib) was balanced, as was the number of baseline lesions (a median of two per arm).[13]

Of the 303 patients in the ITT population, 222 (73%) were included in the plasma BEP subgroup (107 treated with alectinib and 115 treated with crizotinib) and 203 (67%) were included in the tissue BEP subgroup (107 treated with alectinib and 96 treated with crizotinib). Samples were not available for some patients because of a lack of tumor tissue and/or circulating tumor DNA yield or failure to pass NGS quality control. No *ALK* fusions were detected in the plasma samples of 77 patients or in the tissue samples of 67 patients. Non-*EML4-ALK* fusions were detected in both plasma samples (n = 10 [three from patients treated with alectinib and seven from patients treated with crizotinib]) and tissue samples (n = 12 [seven from patients treated with alectinib and five from patients treated with crizotinib]), whereas eight and 12 *EML4-ALK* variants other than variants 1, 2, and 3a/b were found in plasma and tissue samples, respectively. Baseline characteristics were generally comparable for *EML4-ALK* variants 1, 2, and 3a/b; this was also the case between treatment arms in both the plasma and tissue subgroups (Supplementary Table 1).

The median durations of follow-up were 27.8 months (range 0.5–38.7) with alectinib and 22.8 months (range 0.3–36.7) with crizotinib versus 18.6 months (range 0.5–29.0) and 17.6 months (range 0.3–27.0), respectively, in the primary analysis.[3] In all, 80 patients (52.6%) had discontinued alectinib and 123 (81.5%) had discontinued crizotinib (Supplementary Fig. 1).

Efficacy (ITT Population)

PD or death occurred in 188 patients in the ITT population (in 72 [47.4%] treated with alectinib and 116 [76.8%] treated with crizotinib). Investigator-assessed PFS was prolonged with alectinib versus with crizotinib in the ITT population (stratified HR = 0.43, 95% CI: 0.32–0.58) (Fig. 1*A*); the median PFS times were 34.8 months (95% CI: 17.7–not estimable [NE]) and 10.9 months (95% CI: 9.1–12.9), respectively. The HR for investigator-assessed PFS was less than 1.0 for all subgroups by baseline risk factor, with the exception of active smokers (n = 12) (Fig. 1*B*).

For alectinib versus for crizotinib, respectively, the median PFS times in patients with baseline CNS metastases were 27.7 months (95% CI: 9.2–NE) and 7.4 months (95% CI: 6.6–9.6) (HR = 0.35, 95% CI: 0.22–0.56), respectively, and for patients without baseline CNS metastases, the median PFS times were 34.8 months (95% CI: 22.4–NE) and 14.7 months (95% CI: 10.8–20.3) (HR = 0.47, 95% CI: 0.32–0.71), respectively.

ORR was consistent with that reported in the primary analysis; 82.9% for those treated with alectinib (95% CI: 75.95–88.51) versus 75.5% for those treated with crizotinib (95% CI: 67.84–82.12) (Supplementary Table 2). Overall, 119 of 152 alectinib-treated patients (78.3%) had a PR compared with 111 of 151 crizotinib-treated patients (73.5%) (Fig. 2). The median DOR was 33.1 months (95% CI: 31.3–NE) with alectinib versus 11.1 months (95% CI: 7.5–13.0) with crizotinib (Supplementary Fig. 2).

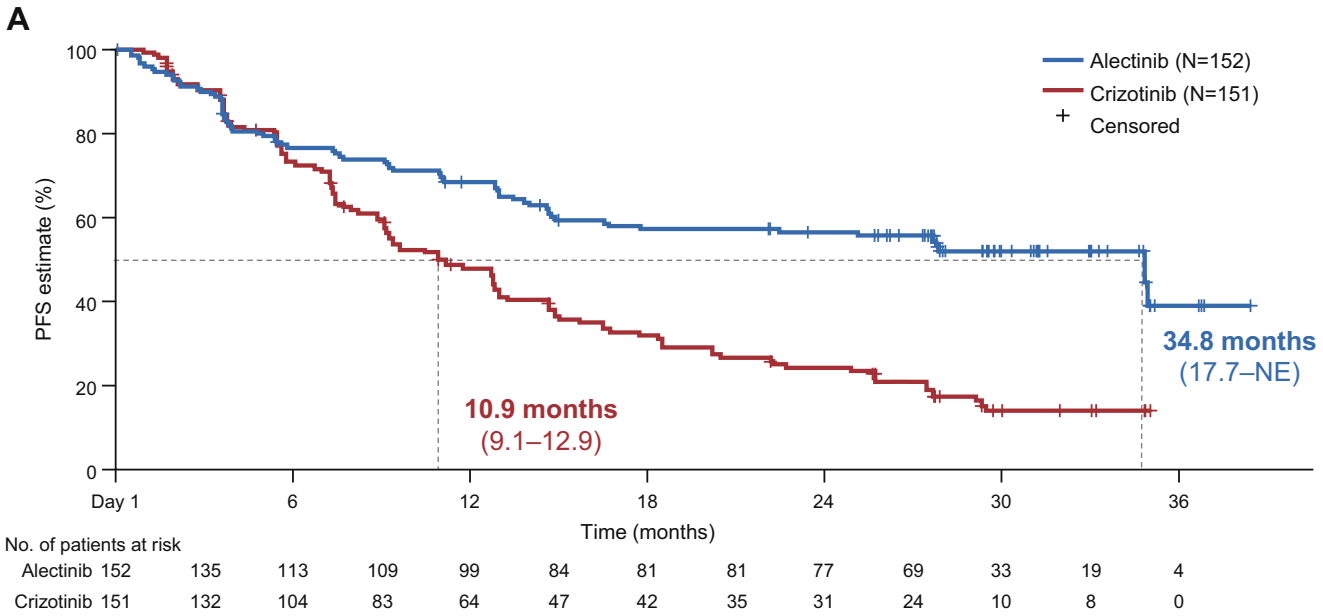
In patients with CNS metastases at baseline, 49 of 64 alectinib-treated patients (76.6%) had a PR compared with 38 of 58 crizotinib-treated patients (65.5%) (Supplementary Fig. 3). In patients without baseline CNS metastases, 70 of 88 alectinib-treated patients (79.5%) and 73 of 93 crizotinib-treated patients (78.5%) achieved a PR.

In the patients who responded, depth of response was more pronounced in those treated with alectinib: tumor reductions greater than 75.0%, greater than 50%, and greater than 25% occurred in 36.2%, 75.0%, and 82.9% of the alectinib-treated patients, respectively, compared with 19.9%, 50.3%, and 82.8% of the crizotinib-treated patients, respectively (Supplementary Table 3).

As of December 1, 2017, a total of 91 patients had died (43 of the 152 treated with alectinib [28.3%] and 48 of the 151 treated with crizotinib [31.8%]). The OS data are immature (stratified HR = 0.76, 95% CI: 0.50–1.15) (Supplementary Fig. 4).

Prevalence of Rearrangements and Variants (BEP)

The percentages of *ALK* rearrangements, *EML4-ALK* rearrangements, circulating nucleic acids, and *ALK* single-nucleotide variants (SNVs) are shown in Supplementary Figure 5. In total, three *ALK* SNVs of unknown clinical significance were detected in separate patients in the plasma BEP subgroup, two of which were found in *EML4-ALK* variant 1 (G1494R, R1084C); no information on the *ALK* fusion was available for the third. Overall, 13 *ALK* SNVs were detected in the tissue BEP subgroup: three in *EML4-ALK* variant 1 (G1018S, S737L, I248M), one in variant 2 (V1039M), and two in variant 3a/b (R137G, C1097Y) in the same patient, as well as seven *ALK* SNVs that were detected in patients without detectable *ALK* fusions (two of which mapped to the ALK kinase domain [T1151M and N1353K]). There was no evidence indicating the presence of any ALK inhibitor resistance mutations that might influence the *EML4-ALK* variant analysis.



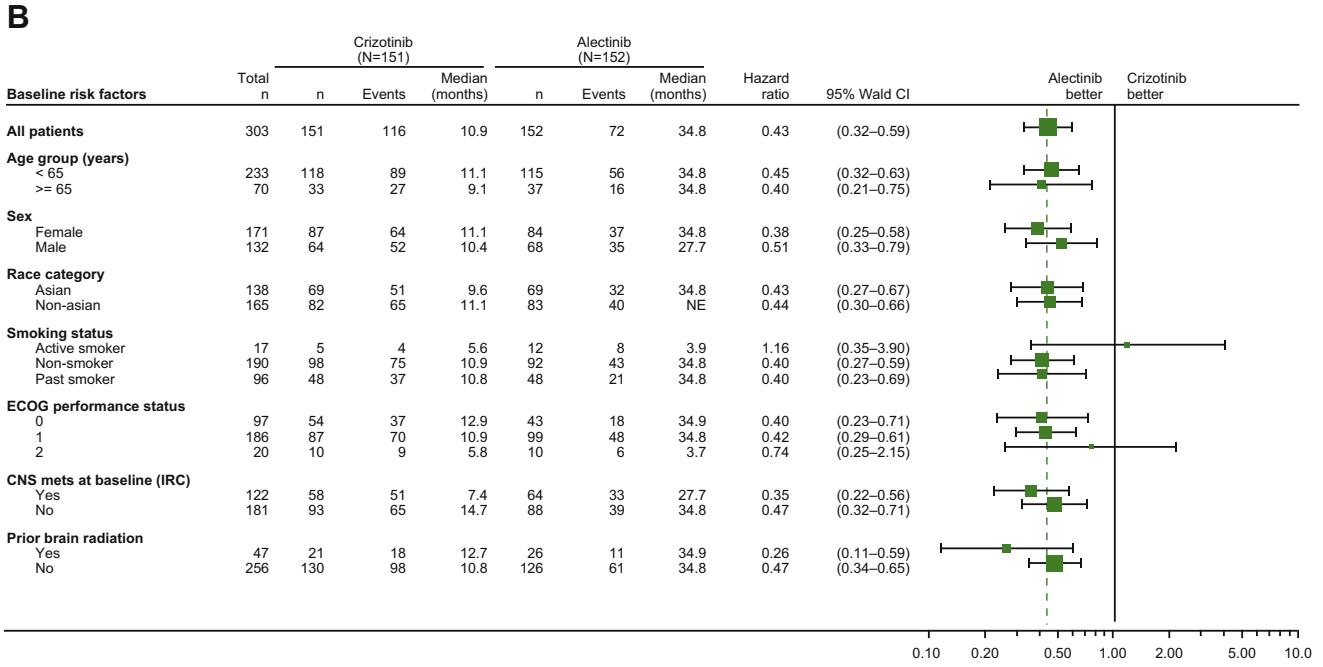


Figure 1. Efficacy outcomes (intent-to-treat population): progression-free survival (PFS) (*A*) and PFS subgroup analysis (*B*). Medians of PFS are Kaplan-Meier estimates. Hazard ratios were estimated by Cox regression. CI, confidence interval; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; NE, not estimable.

The prevalence of the three common *EML4-ALK* fusion variant populations (variants 1, 2, and 3a/b) was assessed for the plasma and tissue subgroups (Table 1). *EML4-ALK* fusion variants 1 and 3a/b were the most common, with similar prevalence across both the plasma and tissue samples (*EML4-ALK* fusion variant 1, 37.0% and 42.7% in the plasma and tissue samples, respectively; *EML4-ALK* fusion variant 3a/b, 36.3% and 37.1% in the plasma and tissue samples, respectively). *EML4-ALK* fusion variant 2 was less prevalent than fusion variants 1 and 3a/b in both plasma and tissue samples, but it was relatively more prevalent in plasma samples than in tissue samples (16.3% versus 10.5%, respectively). In the matched tumor (plasma and tissue) samples (n = 53) in which *EML4-ALK* fusions variants 1, 2, and 3a/b were detected, the same *EML4-ALK* variant was detected in 79.2% of matched samples (n = 42), possibly owing to tumor heterogeneity.

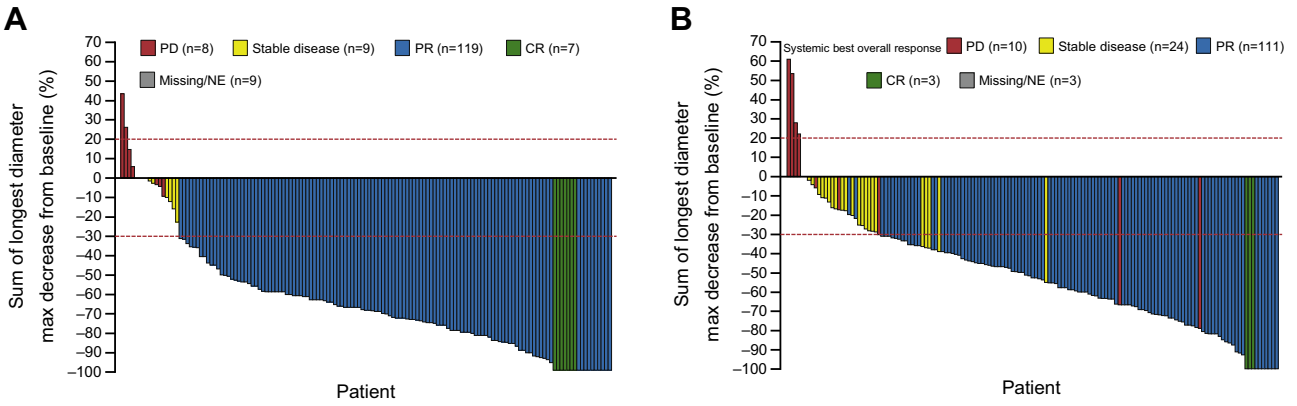


Figure 2. Investigator-assessed best overall response (intent-to-treat population): patients treated with alectinib (*A*) and patients treated with crizotinib (*B*). CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response.

PFS (BEP)

At the updated analysis cutoff (December 1, 2017), the investigator-assessed PFS values for alectinib versus for crizotinib resulted in comparable HRs between the plasma (HR = 0.32, 95% CI: 0.20–0.52, $p < 0.0001$) and tissue BEP subgroups (HR = 0.42, 95% CI: 0.25–0.70, $p = 0.001$); these were also comparable with the values found for the ITT population (see the section *Efficacy (ITT)* and Supplementary Fig. 6).

The investigator-assessed median PFS time for each of the *EML4-ALK* fusion variant populations was longer for alectinib than for crizotinib based on both plasma and tissue samples (Fig. 3*A* and *B*). In the plasma BEP subgroup, the median PFS times in patients treated with alectinib versus with crizotinib were 34.8 months versus 7.4 for variant 1; 24.8 months versus 8.8 months for variant 2; and 17.7 months versus 9.1 months for variant 3a/b. In the tissue BEP subgroup, the median PFS times in patients treated with alectinib versus those treated with crizotinib were NE versus 12.9 months for variant 1; 11.5 months versus 8.8 months for variant 2; and 34.9 months versus 14.6 months for variant 3a/b. The differences in PFS between variants 1, 2, and 3a/b were not significant in any treatment arm or sample type (for plasma from those treated with alectinib, $p = 0.4226$; for tissue from those treated with alectinib, $p = 0.1114$; for plasma from those treated with crizotinib, $p = 0.8504$; and for tissue from those treated with crizotinib, $p = 0.9623$).

ORR (BEP)

There was no significant difference in the investigator-assessed ORR between the *EML4-ALK* fusion variant populations based on either plasma or tissue samples from patients treated with alectinib or crizotinib (Fig. 4*A* and *B*). When plasma samples were used, the investigator-assessed ORR for patients with *EML4-ALK* fusion variants 1, 2, and 3a/b was higher for those

Table 1. *EML4-ALK* Fusion Variant and *ALK* SNV Prevalence in Both the Tissue Sample and Plasma BEP Subgroups

	Plasma BEP			Tissue BEP		
Variant	Combined (n = 222)	Crizotinib (n = 115)	Alectinib (n = 107)	Combined (n = 203)	Crizotinib (n = 96)	Alectinib (n = 107)
EML4-ALK variant 1, n (%)	50 (37.0)	28 (41.2)	22 (32.8)	53 (42.7)	28 (43.7)	25 (41.7)
No SNV, n	48			50		
SNV, n	2			3		
EML4-ALK variant 2, n (%)	22 (16.3)	12 (17.6)	10 (14.9)	13 (10.5)	5 (7.8)	8 (13.3)
No SNV, n	22			12		
SNV, n	0			1		
EML4-ALK variant 3, n (%)	49 (36.3)	24 (35.3)	25 (37.3)	46 (37.1)	25 (39.1)	21 (35.0)
No SNV, n	49			45		
SNV, n	0			1		
EML4-ALK other, n (%)	8 (5.9)	2 (2.9)	6 (9.0)	12 (9.7)	6 (9.4)	6 (10.0)
Missing, n (%)	6 (4.4)	2 (2.9)	4 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total, n (%)	135 (100)	68 (100)	67 (100)	124 (100)	64 (100)	60 (100)

ALK, anaplastic lymphoma kinase gene; BEP, biomarker-evaluable population; *EML4*, echinoderm microtubule-associated protein-like 4 gene; SNV, single-nucleotide variant.

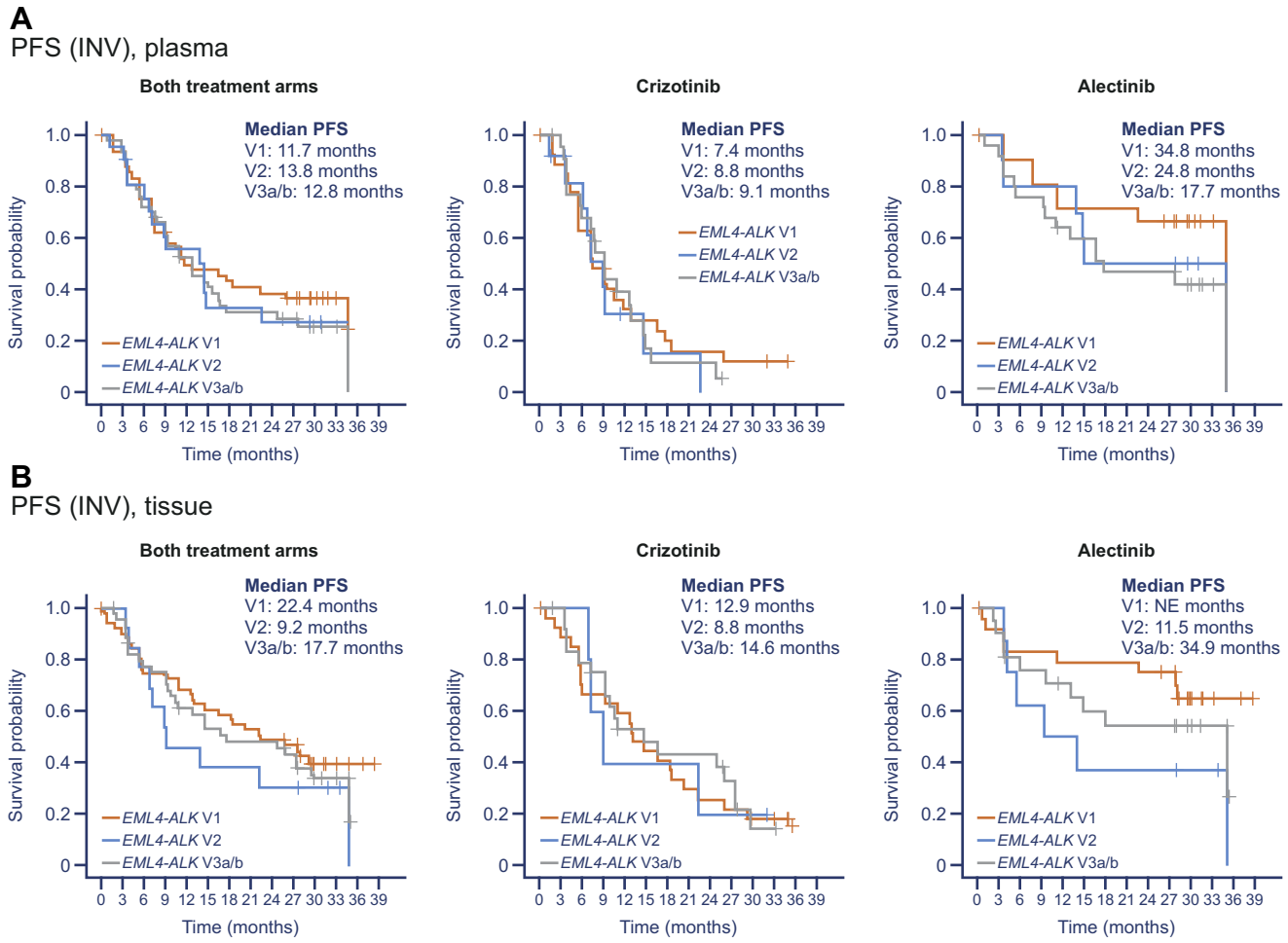


Figure 3. Progression-free survival (PFS) (investigator [INV]) by echinoderm microtubule-associated protein-like 4 gene (*EML4*)-anaplastic lymphoma kinase gene (*ALK*) fusion variant in both the tissue and plasma biomarker-evaluable population subgroups.

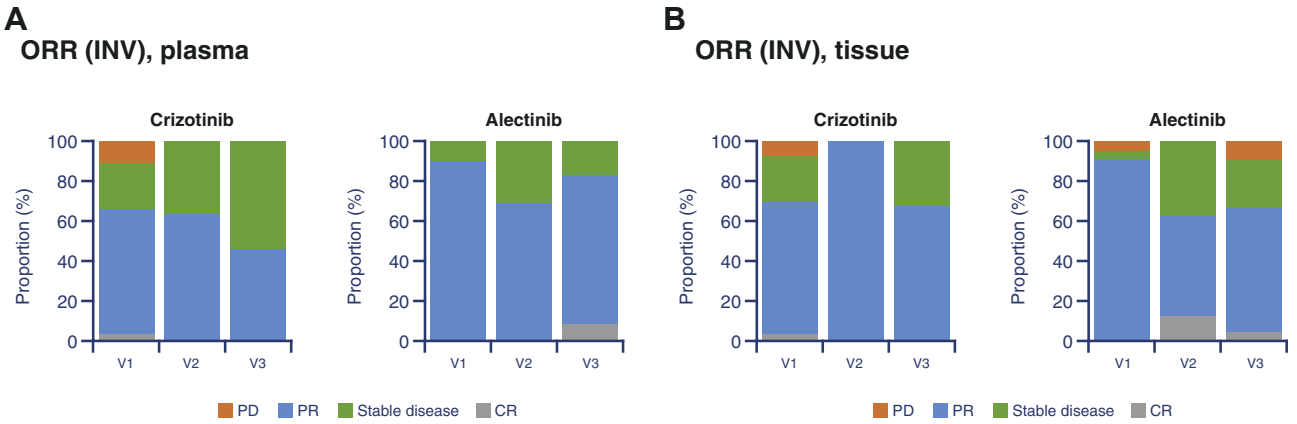
treated with alectinib than that for those treated with crizotinib. When tissue samples were used, the investigator-assessed ORR was higher with alectinib than with crizotinib for patients with variant 1, similar for patients with variant 3a/b, and lower for patients with variant 2 (62.5% for those treated with alectinib versus 100% for those treated with crizotinib [see Fig. 4*B*]). However, the numbers of patients with variant 2 were too low to draw meaningful conclusions (n = 8 and n = 5, respectively).

DOR (BEP)

The median investigator-assessed objective DOR in patients treated with alectinib was comparable for all three *EML4-ALK* fusion variant populations according to both plasma and tissue samples (Supplementary Fig. 7). When plasma samples were used, the median investigator-assessed objective DOR for patients treated with crizotinib was comparable for *EML4-ALK* fusion variant populations 1 and 2, but longer for variant population 3a/b (see Supplementary Fig. 7). When tissue samples were used, the median investigator-assessed objective DOR for patients treated with crizotinib was comparable for *EML4-ALK* fusion variant populations 1 and 3a/b. Patients with *EML4-ALK* fusion variant 2 had a shorter median DOR; however, the patient numbers were low (n = 5 [see Supplementary Fig. 7]). The median investigator-assessed DOR was longer with alectinib than with crizotinib in all three *EML4-ALK* fusion variant populations using both plasma and tissue samples.

Safety (Safety Population)

The median treatment durations (as of December 1, 2017) were 27.0 months (range 0.0–39.0) with alectinib and 10.8 months (range 0.0–37.0) with crizotinib versus 17.9 months (range 0.0–29.0) and 10.7 months (range 0.0–27.0), respectively, in the primary analysis.[3]



	Crizotinib			Alectinib		
	V1 (n=27)	V2 (n=11)	V3a/b (n=24)	V1 (n=21)	V2 (n=10)	V3a/b (n=24)
ORR (%)	66.7	63.6	45.8	90.5	70.0	83.3
	p = 0.2959*			p = 0.3538*		

	Crizotinib			Alectinib		
	V1 (n=27)	V2 (n=5)	V3a/b (n=25)	V1 (n=22)	V2 (n=8)	V3a/b (n=21)
ORR (%)	70.4	100.0	68.0	90.9	62.5	66.7
	p = 0.3371*			p = 0.1034*		

Figure 4. Objective response rate (ORR) (investigator [INV]-confirmed) by echinoderm microtubule-associated protein-like 4 gene (*EML4*)-anaplastic lymphoma kinase gene (*ALK*) fusion variant in both the tissue and plasma biomarker-evaluable population subgroups. *Pearson's chi-square test comparing all three variants. CR, complete response; PD, progressive disease; PR, partial response; V, variant.

The median dose intensity was 100.0% for both treatments.

Despite the longer treatment duration, fewer patients had grade 3 to 5 AEs with alectinib (44.7%) than with crizotinib (51.0% [Table 2 and Supplementary Table 4]). Fewer alectinib-treated patients had fatal AEs (3.9%) than did the crizotinib-treated patients (4.6%) (Supplementary Table 5). Compared with the crizotinib-treated patients, fewer alectinib-treated patients had AEs leading to dose reduction (16.4% with alectinib versus 20.5% with crizotinib) or interruption (22.4% with alectinib versus 25.2% with crizotinib).

In the case of AEs for which the rate differed by ≥5% between treatment arms, most occurred at a higher frequency with crizotinib than with alectinib (Table 2). With regard to AEs that occurred with an incidence rate of ≥10% in either treatment arm, the most common was constipation (35.5% with alectinib versus 33.8% with crizotinib) (Supplementary Table 6).

The most frequently reported AEs considered to be related to study treatment (any grade, incidence of ≥30% in any arm) were nausea (7.9% with alectinib versus 43.0% with crizotinib), increased alanine transaminase level (14.5% with alectinib versus 30.5% with crizotinib), and diarrhea (6% with alectinib versus 38% with crizotinib). AEs related to study treatment occurring in ≥5% of patients in either treatment arm are listed in Supplementary Table 7.

The proportion of patients with AEs leading to treatment discontinuation was 13.2% with both alectinib and crizotinib; the most common of these AEs (incidence ≥3% in any arm) were increased alanine transaminase level (1.3% with alectinib versus 6.0% with crizotinib), increased aspartate transaminase level (1.3% with alectinib versus 4.0% with crizotinib), and pneumonitis (0.7% with alectinib versus 3.3% with crizotinib) (Supplementary Table 8).

Discussion

In this updated exploratory analysis, with approximately 10 more months of follow-up than in the primary analysis, the superior efficacy of alectinib versus that of crizotinib was confirmed. The median follow-up was longer with alectinib (27.8 months) than with crizotinib (22.8 months). In the ITT population, alectinib reduced the risk of PD or death by 57% (stratified HR = 0.43, 95% CI: 0.32–0.58 [previous data cutoff HR = 0.47]). The investigator-assessed median PFS was longer with alectinib (34.8 months [previous data cutoff NE]) than with crizotinib (10.9 months). The data for the crizotinib arm remain comparable with that of the primary analysis[3] and with that reported in the PROFILE 1014 trial of first-line crizotinib versus chemotherapy (median PFS for crizotinib 10.9 months), whereas the longer follow-up shows improved efficacy in terms of prolonged median PFS and DOR in the alectinib arm than in the prior analysis.[14]

Although caution must be used when comparing results across trials, the median PFS achieved with alectinib in the first-line setting in the current analysis is

Table 2. Safety Overview and AEs of Any Grade That Differed by ≥5% in Frequency between Treatment Arms (Safety Population)

AE, n (%)	Crizotinib (n = 151)	Alectinib (n = 152)
All-grade AEs	147 (97.4)	147 (96.7)
Serious AEs	46 (30.5)	46 (30.3)
Grade 3-5 AEs	77 (51.0)	68 (44.7)
Fatal AEs	7 (4.6)	6 (3.9)
AEs leading to treatment discontinuation	20 (13.2)	20 (13.2)
AEs leading to dose reduction	31 (20.5)	25 (16.4)
AEs leading to dose interruption	38 (25.2)	34 (22.4)
Total patients with any grade AEs with ≥5% difference in frequency between arms	135 (89.4)	115 (75.7)
Anemia	11 (7.3)	34 (22.4)
Blood bilirubin level increased	2 (1.3)	29 (19.1)
Peripheral edema	48 (31.8)	28 (18.4)
ALT level increased	50 (33.1)	26 (17.1)
AST level increased	40 (26.5)	24 (15.8)
Myalgia	3 (2.0)	25 (16.4)
Nausea	75 (49.7)	24 (15.8)
Diarrhea	70 (46.4)	20 (13.2)
Insomnia	9 (6.0)	18 (11.8)
Vomiting	62 (41.1)	14 (9.2)
Weight increased	0	14 (9.2)
Dizziness	23 (15.2)	13 (8.6)
Musculoskeletal pain	4 (2.6)	12 (7.9)
Photosensitivity reaction	0	9 (5.9)
Neutropenia	12 (7.9)	4 (2.6)
Dysgeusia	30 (19.9)	5 (3.3)
Dyspepsia	14 (9.3)	5 (3.3)
Visual impairment	18 (11.9)	3 (2.0)
Vision blurred	11 (7.3)	3 (2.0)
Alopecia	12 (7.9)	1 (0.7)
γ-Glutamyltransferase level increased	11 (7.3)	1 (0.7)
Photopsia	10 (6.6)	0
ECG QT prolonged	8 (5.3)	0

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; ECG, electrocardiogram.

numerically greater than that reported with sequential first-line crizotinib (10.9 months)[14] followed by second-line ceritinib (7.2 months) or alectinib (8.3 months).[15] These data highlight the benefit of alectinib as a first-line treatment for *ALK*-positive NSCLC as reflected in National Comprehensive Cancer Network guidelines, which recommend alectinib as the preferred first-line treatment in this indication,[16] and the European Society for Medical Oncology guidelines, which recognize alectinib as a better first-line treatment option than crizotinib.[17]

In this updated analysis, the ORR in the ITT population remained the same as in the primary analysis (82.9% with alectinib versus 75.5% with crizotinib). To gain a better understanding of response quality, we assessed tumor reductions beyond the RECIST criteria. Compared with the crizotinib arm, the alectinib arm included more patients who had tumor reductions greater than 50% or greater than 75%. This improvement was seen in patients with and without baseline CNS metastases. In keeping with the greater depth of response in the alectinib arm, PFS curves began to show a clear separation between treatment arms at 6 months.

Although the numbers per *EML4-ALK* variant are relatively small (particularly for variant 2), this study represents the largest analysis of ALK inhibitor efficacy by *ALK* fusion variant type in the context of a prospective phase III randomized clinical trial. Data on the association between variant type and treatment outcomes are important but limited, as commonly used methods to detect *ALK*-positive NSCLC (e.g., immunohistochemistry or fluorescence in situ hybridization) do not provide information on the specific *ALK* variant. The prevalences of *EML4-ALK* variants in the ALEX study are consistent with those in previous reports.[5,8]

Efficacy analyzed by the presence of specific *EML4-ALK* fusion variants in tissue and plasma samples was similar to that in the ITT population and demonstrates that the efficacy benefit of alectinib versus crizotinib in the phase III ALEX trial is observed across all *EML4-ALK* fusion variants. A possible exception was in the efficacy assessments of patients with variant 2 in tissue samples, which were likely affected by the low sample numbers (eight from those treated with alectinib and five from those treated with crizotinib). It was also of note that the median PFS and DOR were generally shorter in the analysis of *EML4-ALK* variants than in the ITT population, which may also be related to the lower numbers of patients with valid samples.

A study led by Lin et al. in 2018 showed that tumors with the *EML4-ALK* variant 3a/b are more prone to development of resistance mutations (*ALK* G1202R in particular) and that there is a trend toward lower median PFS in patients with variant 3a/b versus those with variant 1, when treated with second-generation ALK inhibitors after crizotinib.[8] That study also reported a significantly longer PFS in patients with variant 3 than in patients with variant 1, who were treated with the third-generation ALK inhibitor lorlatinib after crizotinib and at least one second-generation inhibitor.[8] However, the current analysis using prospective phase III data suggests that there is a similar level of benefit (in terms of PFS, ORR, and DOR) from treatment with alectinib and crizotinib in patients with variants 1 and 3a/b in the first-line setting. Furthermore, there was no evidence for the presence of any baseline *ALK* resistance mutations in patients from the ALEX trial that may have biased efficacy outcomes in response to either alectinib or crizotinib treatment. Future retrospective analyses will likely provide further

information on the association of the efficacy of other ALK inhibitors and *ALK* fusion variant type.

There were no new or unexpected safety findings for alectinib. The safety profile of alectinib compared favorably with that of crizotinib, despite an increase in median treatment duration of approximately 9 months versus that in the primary analysis (27.0 months versus 17.9 months); the median treatment duration for crizotinib remained approximately the same (10.8 months versus 10.7 months in the primary analysis).

Limitations

Limitations of the updated analysis include the fact that it was exploratory and that IRC assessments were not collected after the cutoff date for the primary analysis. Further follow-up for OS is required, as the OS data are not yet mature (a future survival analysis is planned; patients are still receiving treatment). The *EML4-ALK* fusion variant analysis is limited by the relatively small patient numbers and by the fact that it was exploratory. In addition, only the three most common *EML4-ALK* fusion variants were compared; the impact of other variants (including non–*EML4-ALK*) is unknown. Although further assessment of postprogression samples may provide insight into how *ALK* fusion variants can affect mechanisms of resistance to ALK- inhibitor treatment, data are not yet available to assess this or the potential of *ALK* fusion variant type on OS.

Conclusion

With longer follow-up, the superior benefit of alectinib versus crizotinib in investigator-assessed PFS in untreated *ALK*-positive NSCLC is greater than in the initial analyses. PFS, ORR, and DOR were unaffected by baseline *EML4-ALK* variant, and alectinib remained superior to crizotinib across variant subtypes. Alectinib was better tolerated than crizotinib despite longer treatment duration.

Data Sharing

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available at https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see the discussion of Roche's commitment to data sharing at https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.03.007.

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