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ORIGINAL RESEARCH

Final efficacy and safety data, and exploratory molecular profiling from the phase III ALUR study of alectinib versus chemotherapy in crizotinib-pretreated *ALK*-positive non-small-cell lung cancer

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Background: At the primary data cut-off, the ALUR study demonstrated significantly improved progression-free survival (PFS) and central nervous system (CNS) objective response rate (ORR) with alectinib versus chemotherapy in pretreated, advanced anaplastic lymphoma kinase (*ALK*)-positive non-small-cell lung cancer. We report final efficacy and safety data, and exploratory molecular profiling.

Patients and methods: Patients who received prior platinum-doublet chemotherapy and crizotinib were randomized 2 : 1 to receive alectinib 600 mg twice daily ($n = 79$) or chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2, every 3 weeks; $n = 40$) until progressive disease, death or withdrawal. The primary endpoint was investigator-assessed PFS. Secondary endpoints included ORR, CNS ORR and safety. Plasma samples were collected at baseline, then every 6 weeks until progressive disease; molecular factors detected by next-generation sequencing were correlated with outcomes.

Results: Investigator-assessed PFS was significantly longer with alectinib than chemotherapy (median 10.9 versus 1.4 months; hazard ratio 0.20, 95% confidence interval 0.12-0.33; $P < 0.001$). ORR was 50.6% with alectinib versus 2.5% with chemotherapy ($P < 0.001$). In patients with measurable CNS metastases at baseline, CNS ORR was 66.7% with alectinib versus 0% with chemotherapy ($P < 0.001$). No new safety signals were seen. *ALK* rearrangement was identified in 69.5% ($n = 41/59$) of baseline plasma samples. Confirmed partial responses were observed with alectinib in 6/11 patients with a secondary *ALK* mutation and 4/6 patients with a non-*EML4-ALK* (where *EML4* is echinoderm microtubule-associated protein-like 4) fusion. Detection of mutant *TP53* in baseline plasma resulted in numerically shorter PFS with alectinib (hazard ratio 1.88, 95% confidence interval 0.9-3.93).

Conclusions: Final efficacy data from ALUR confirmed the superior PFS, ORR and CNS ORR of alectinib versus chemotherapy in pretreated, advanced *ALK*-positive non-small-cell lung cancer. Alectinib prolonged PFS versus chemotherapy in patients with wild-type or mutant *TP53*; however, alectinib activity was considerably decreased in patients with mutant *TP53*.

Key words: *ALK*-positive NSCLC, ALUR, alectinib, chemotherapy, *TP53*

INTRODUCTION

Anaplastic lymphoma kinase-positive (*ALK*-positive) non-small-cell lung cancer (NSCLC) is a distinct subset of lung cancer, occurring in approximately 5% of patients with advanced NSCLC.[1,2] Alectinib is a highly selective and potent inhibitor of ALK that is approved for the treatment of patients with advanced *ALK*-positive NSCLC who have previously not received an ALK tyrosine kinase inhibitor

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(TKI), and for those who have progressed on or who are intolerant to crizotinib.[3,4] Alectinib is a preferred first-line treatment of advanced *ALK*-positive NSCLC,[5,6] having demonstrated superior progression-free survival (PFS) versus crizotinib in the global phase III ALEX trial, with a favorable safety profile,[7,8] and a clinically meaningful improvement in overall survival (OS) at the 5-year time point.[8] Approval of alectinib in the post-crizotinib setting was based on data from two phase II single-arm studies (NP28673 and NP28761).[9,10]

In the primary analysis of the phase III ALUR study (NCT02604342) of alectinib versus chemotherapy in crizotinib-pretreated *ALK*-positive NSCLC (data cut-off: 26 January 2017), investigator-assessed PFS and central nervous system (CNS) objective response rates (ORRs) were significantly improved with alectinib relative to chemotherapy.[11]

Crizotinib resistance mechanisms have been identified in patients with *ALK*-positive NSCLC, including secondary *ALK* mutations in 20%-30% of patients[12-15] and activation of bypass signaling pathways, such as HER2, KIT, MET and IGF1R.[12-14] Alectinib has demonstrated activity against several secondary *ALK* mutations that can arise following crizotinib treatment[16]; however, the mutational profile of *ALK* can become increasingly complex in patients who have progressed on multiple lines of ALK inhibitor therapies.[12] Concomitant *TP53* mutations may also have the potential to affect alectinib treatment efficacy, having been previously associated with unfavorable outcomes in patients with advanced *ALK*-positive NSCLC receiving ALK inhibitors.[17-19] The potential utility of blood-based next-generation sequencing (NGS) to detect these molecular factors is unclear.

Here, we present final efficacy and safety data from the ALUR study. An exploratory analysis of cancer-related genes, isolated from pre-crizotinib tumor tissue and repeated in plasma biopsies, was carried out using NGS to improve understanding of alectinib efficacy and resistance mechanisms in patients who were pretreated with chemotherapy and crizotinib.

MATERIAL AND METHODS

Study design

The ALUR study design has been published previously.[11] Briefly, patients with advanced *ALK*-positive NSCLC previously treated with platinum-doublet chemotherapy and crizotinib were randomized 2 : 1 to receive alectinib 600 mg twice daily or chemotherapy (pemetrexed 500 mg/m^2 or docetaxel 75 mg/m^2, every 3 weeks, at the investigators' discretion) until progressive disease (PD), death or withdrawal. Randomization was stratified according to: Eastern Cooperative Oncology Group performance status (ECOG PS) (0/1 versus 2); baseline CNS metastases (yes/no); and, for patients with baseline CNS metastases, history of prior brain radiotherapy (yes/no). Crossover from chemotherapy to alectinib was permitted following RECIST v1.1-based PD. The final efficacy and safety data cut-off date was 28 September 2018.

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 informed consent was obtained from all patients before enrolment.

Study endpoints

The primary endpoint was investigator-assessed PFS in the intent-to-treat (ITT) population. A key secondary endpoint was CNS ORR in patients with measurable baseline CNS metastases, as assessed by an independent review committee (IRC). Other secondary endpoints included investigator-assessed ORR, OS and safety. As part of exploratory molecular profiling, we sought to identify secondary *ALK* mutations arising in crizotinib- and chemotherapy-pretreated patients treated with alectinib, and to investigate the impact of molecular factors detected in baseline plasma on clinical outcomes with alectinib.

Study assessments

Response (RECIST v1.1) was assessed at screening and every 6 weeks until PD using physical examinations, computed tomography scans and magnetic resonance imaging. Brain imaging was carried out in all patients at each study visit. Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, v4.0, and classified according to the Medical Dictionary for Regulatory Activities.

For exploratory molecular profiling, formalin-fixed paraffin-embedded (FFPE) tissue samples were collected before crizotinib treatment (archival) and/or at baseline (after crizotinib therapy but before alectinib treatment). Baseline and 'on-treatment'/PD plasma samples were collected, the latter during tumor assessments (every 6 weeks) until PD. DNA from tissue and plasma was tested for genetic aberrations (including single nucleotide variants, copy number variation and selected gene rearrangements) by NGS using FoundationOne® and FoundationACT™ (Foundation Medicine Inc.) assays, respectively.

Statistical analyses

The ITT population comprised all randomized patients. The safety population comprised all patients who received one or more doses of assigned study medication. Analysis of investigator-assessed PFS (ITT population) was carried out using a stratified Cox model including treatment arm variable and stratification factors. Estimates for median PFS and OS were obtained using a Kaplan—Meier approach, the *P*-value of log-rank test was calculated with estimated hazard ratio (HR) (stratified Cox model) and corresponding 95% confidence interval (CI) (Brookmeyer and Crowley method). The Align-GVGD program was used to classify *TP53* status [wild-type (WT) versus mutant] based on the

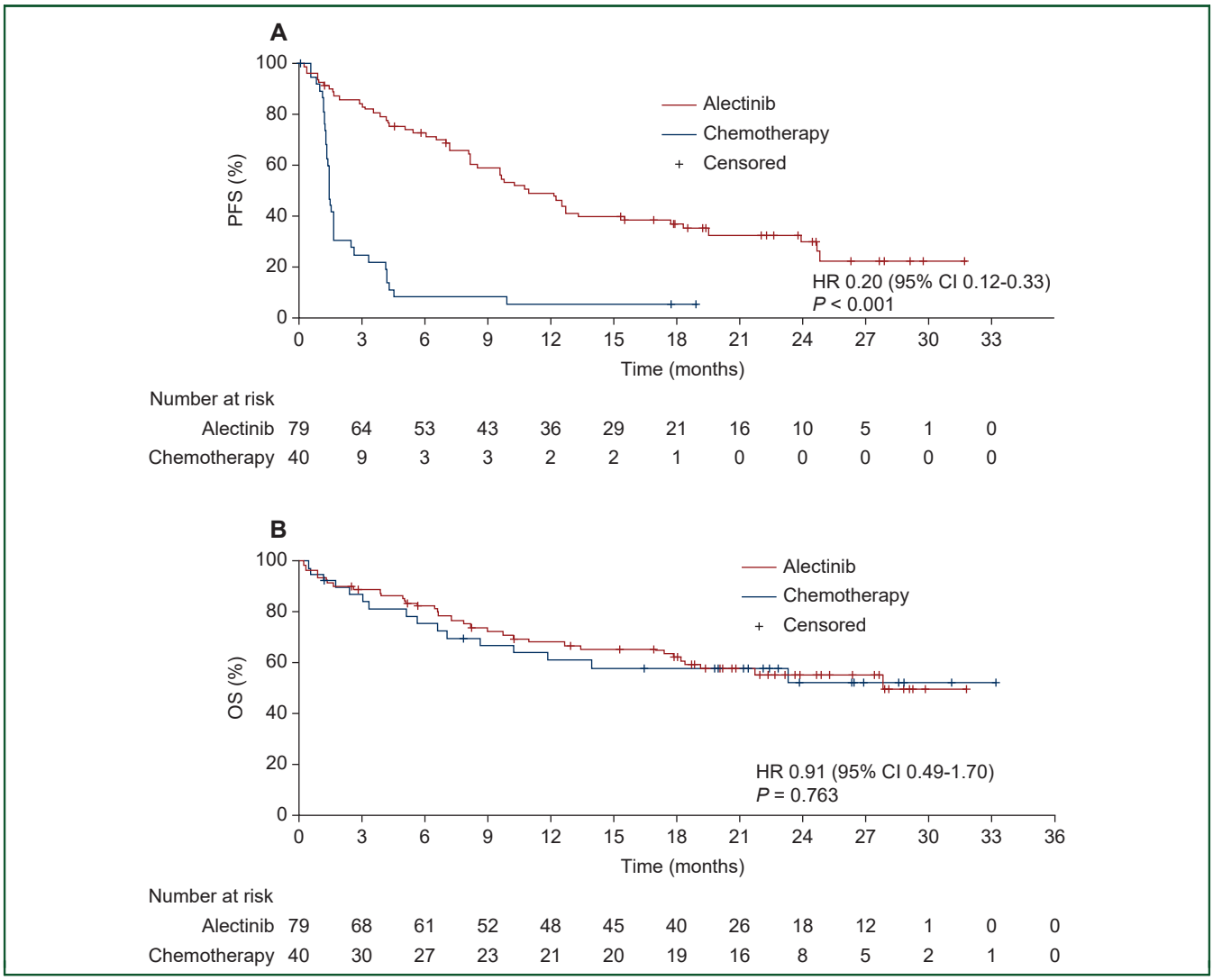


Figure 1. Kaplan—Meier curves of (A) final investigator-assessed PFS and (B) OS in the ITT population.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival.

damaging potential of *TP53* variants detected in baseline plasma samples, and Kaplan—Meier methodology was used to assess the effect of *TP53* mutations on PFS, along with an unstratified Cox model.

RESULTS

Patients

As of 28 September 2018, 119 patients had been randomized to receive alectinib ($n = 79$) or chemotherapy ($n = 40$; ITT population). Baseline characteristics were generally balanced between treatment arms. Compared with the chemotherapy arm, a slightly higher proportion of patients in the alectinib arm had an ECOG PS 0/1 (92.4% versus 87.5%, respectively) and no CNS metastases at baseline (38.0% versus 30.0%, respectively; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100333). The median duration of survival follow-up was similar between the alectinib (22.7 months) and chemotherapy (22.4 months) arms.

Efficacy

Final investigator-assessed median PFS was 10.9 months (95% CI 8.1-15.5 months) with alectinib versus 1.4 months (95% CI 1.2-1.6 months) with chemotherapy; HR 0.20 (95% CI 0.12-0.33) (Figure 1A). Investigator-assessed ORR was significantly higher in the alectinib arm [50.6%; 2 complete responses (CRs) and 38 partial responses (PRs)] compared with the chemotherapy arm (2.5%; 0 CRs and 1 PR; $P < 0.001$; Table 1). In patients with measurable CNS metastases at baseline, IRC-assessed CNS ORR was also significantly higher in the alectinib arm (66.7%; 2 CRs and 14 PRs) than in the chemotherapy arm (0%; $P < 0.001$; Table 1). Median OS was 27.8 months [95% CI 18.2 months-not estimable (NE)] with alectinib and NE (95% CI 8.6-NE) with chemotherapy (Figure 1B). Thirty-two patients (86.5%) in the chemotherapy arm crossed over to receive alectinib at PD.

Safety

Median duration of treatment was 10.2 months (95% CI 8.0-13.2 months) with alectinib and 1.4 months (95%

Table 1. Investigator-assessed systemic ORR in the ITT population and IRC-assessed CNS ORR in patients with measurable CNS metastases at baseline

	Alectinib ($n = 79$)	Chemotherapy ($n = 40$)
Systemic ORR, % (95% CI, %)	50.6 (39-62)	2.5 (0-13)
Difference between arms, %	48.1 ($P < 0.001$)	
BOR, *n* (%)		
CR	2 (2.5)	0
PR	38 (48.1)	1 (2.5)
	Alectinib ($n = 24$)	**Chemotherapy ($n = 17$)**
CNS ORR, % (95% CI, %)	66.7 (45-84)	0
Difference between arms, %	66.7 ($P < 0.001$)	
CNS BOR, *n* (%)		
CR	2 (8.3)	0
PR	14 (58.3)	0

BOR, best overall response; CI, confidence interval; CNS, central nervous system; CR, complete response; IRC, independent review committee; ITT, intent-to-treat; ORR, objective response rate; PR, partial response.

CI 1.3-1.4 months) with chemotherapy. Fewer patients in the alectinib arm versus the chemotherapy arm experienced grade 3-5 AEs (37.7% alectinib, 43.2% chemotherapy), treatment-related AEs (59.7% alectinib, 67.6% chemotherapy), AEs leading to treatment discontinuation (5.2% alectinib, 10.8% chemotherapy) or dose reduction (7.8% alectinib, 10.8% chemotherapy) (Table 2). Two patients had a fatal AE, one with alectinib due to unknown reason and one with chemotherapy due to bacterial pneumonia.

More patients in the alectinib arm experienced serious AEs (26.0% alectinib, 18.9% chemotherapy) and AEs leading to dose interruptions (23.4% alectinib, 13.5% chemotherapy); however, fewer serious AEs were considered related to alectinib (6.5%) than chemotherapy (13.5%). The most common treatment-emergent AEs in patients receiving alectinib were constipation (20.8%), anemia (15.6%), myalgia (14.3%) and peripheral edema (14.3%), compared with fatigue (24.3%), alopecia (21.6%) and nausea (18.9%) with chemotherapy (Table 2).

Exploratory molecular profiling

In total, 61 FFPE tissue samples collected before crizotinib treatment and/or at baseline were analyzed, in addition to 109 baseline plasma samples and 184 on-treatment/PD samples from alectinib-treated patients who had three or more on-treatment samples available for testing (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100333).

Evaluable NGS results were received from 34 tissue samples (31 archival and 3 baseline samples from 33 patients), 74 baseline plasma samples and 171 on-treatment/PD plasma samples (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100333). Somatic aberrations, fusions or copy number variations were detected in 34/34 (100%) tissue samples, 59/74 (80%) baseline plasma samples and 100/171 (58%) on-treatment/PD plasma samples.

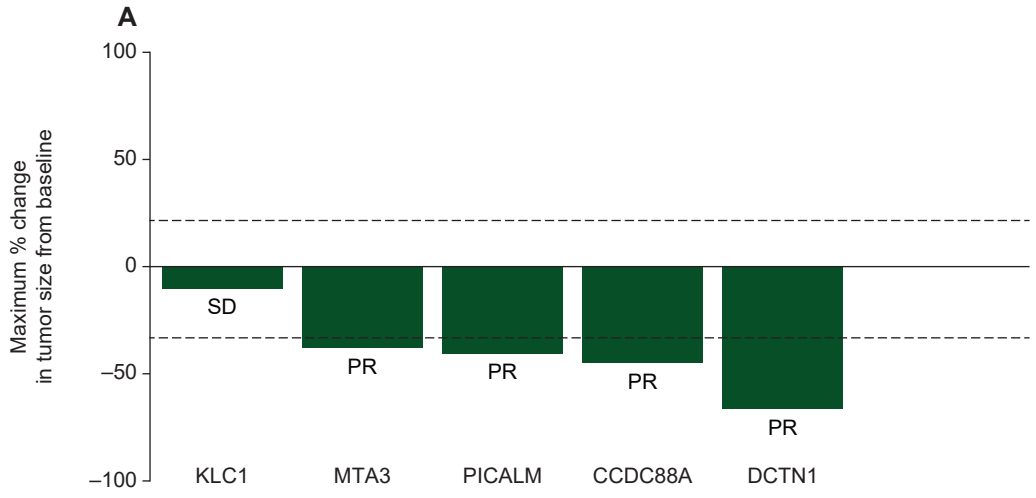
Table 2. Safety summary

	Alectinib ($n = 77$)	Chemotherapy ($n = 37$)
Median treatment duration, months (95% CI, months)	10.2 (8.0-13.2)	1.4 (1.3-1.4)
Patients with at least one event, *n* (%)		
Any-grade AE	69 (89.6)	33 (89.2)
AE related to study treatment	46 (59.7)	25 (67.6)
Serious AE	20 (26.0)	7 (18.9)
Serious AE related to study treatment	5 (6.5)	5 (13.5)
Grade 3-5 AE	29 (37.7)	16 (43.2)
Treatment-related AE	46 (59.7)	25 (67.6)
Fatal AE	1 (1.3)	1 (2.7)
AE leading to treatment discontinuation	4 (5.2)	4 (10.8)
AE leading to dose reduction	6 (7.8)	4 (10.8)
AE leading to dose interruption	18 (23.4)	5 (13.5)
Patients with at least one TEAE occurring in ≥10% of patients in either arm, *n* (%)		
Constipation	16 (20.8)	4 (10.8)
Anemia	12 (15.6)	6 (16.2)
Myalgia	11 (14.3)	4 (10.8)
Peripheral edema	11 (14.3)	2 (5.4)
Back pain	10 (13.0)	2 (5.4)
Asthenia	9 (11.7)	6 (16.2)
Dyspnea	9 (11.7)	0
Pneumonia	9 (11.7)	0
Cough	8 (10.4)	4 (10.8)
Decreased appetite	7 (9.1)	4 (10.8)
Fatigue	5 (6.5)	9 (24.3)
Nausea	3 (3.9)	7 (18.9)
Alopecia	1 (1.3)	8 (21.6)
Neutropenia	0	5 (13.5)

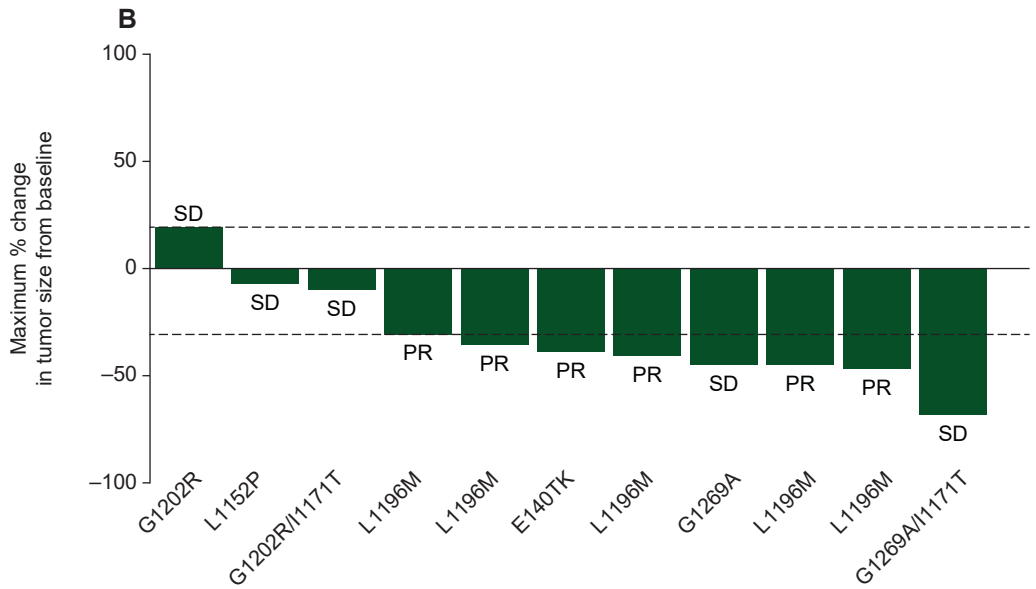
AE, adverse event; CI, confidence interval; TEAE, treatment-emergent adverse event.

ALK rearrangements were identified by central NGS testing in tissue from 26/33 (79%) patients and in baseline plasma from 41/59 (69.5%) patients. ORR with alectinib was higher in patients with an *ALK* rearrangement detected in baseline plasma versus those without (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100333). Non-*EML4-ALK* fusions (where *EML4* is echinoderm microtubule-associated protein-like 4) were detected in eight patients, of whom six were treated with alectinib and had a post-baseline tumor assessment. A confirmed PR was observed with alectinib in 4/6 patients (Figure 2A).

Nineteen secondary *ALK* mutations were identified in baseline plasma from 16/59 (27%) patients; L1196M was the most frequently observed ($n = 7$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100333). In the alectinib arm, 6/11 patients with a secondary *ALK* mutation achieved a confirmed PR (Figure 2B); in the chemotherapy arm, all 5 patients with a secondary *ALK* mutation had stable disease, PD or were not evaluable. There was no numerical difference in PFS in the alectinib arm, irrespective of the presence or absence of *ALK* mutations (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100333). When analyzing both baseline and on-treatment/PD plasma samples, secondary *ALK* mutations were detected in 62 samples from 23 patients in the alectinib arm. Mutations detected at baseline or shortly after commencing alectinib therapy (week -1 to week 13) included G1202R, L1196M,



Confirmed response	Alectinib (*n* = 6)	Chemotherapy (*n* = 2)
CR, *n* (%)	0	0
PR, *n* (%)	4 (67)	0
SD/PD/NE, *n* (%)	2 (33)	2 (100)



Confirmed response	Alectinib (*n* = 11)	Chemotherapy (*n* = 5)
CR, *n* (%)	0	0
PR, *n* (%)	6 (55)	0
SD/PD/NE, *n* (%)	5 (45)	5 (100)

Figure 2. Maximum change in tumor size from baseline and confirmed response observed in alectinib-treated patients with (A) a non-*EML4-ALK* fusion detected and (B) a secondary *ALK* mutation detected in baseline plasma.

Figures show best change in tumor size from baseline and tables show confirmed response category at last tumor assessment (as assessed by RECIST v1.1). The response of one patient with a non-*EML4-ALK* fusion was NE and was therefore excluded from the waterfall plot.

ALK, anaplastic lymphoma kinase; CR, complete response; *EML4*, echinoderm microtubule-associated protein-like 4; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

G1269A, I1171T, E1407K and L1152P; other *ALK* mutations were detected after a longer duration of treatment (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2021.100333).

TP53 mutations were detected in 29/59 (49%) baseline plasma samples. Median investigator-assessed PFS with alectinib was 3.8 months in patients with a baseline *TP53* mutation and 9.6 months in patients without.

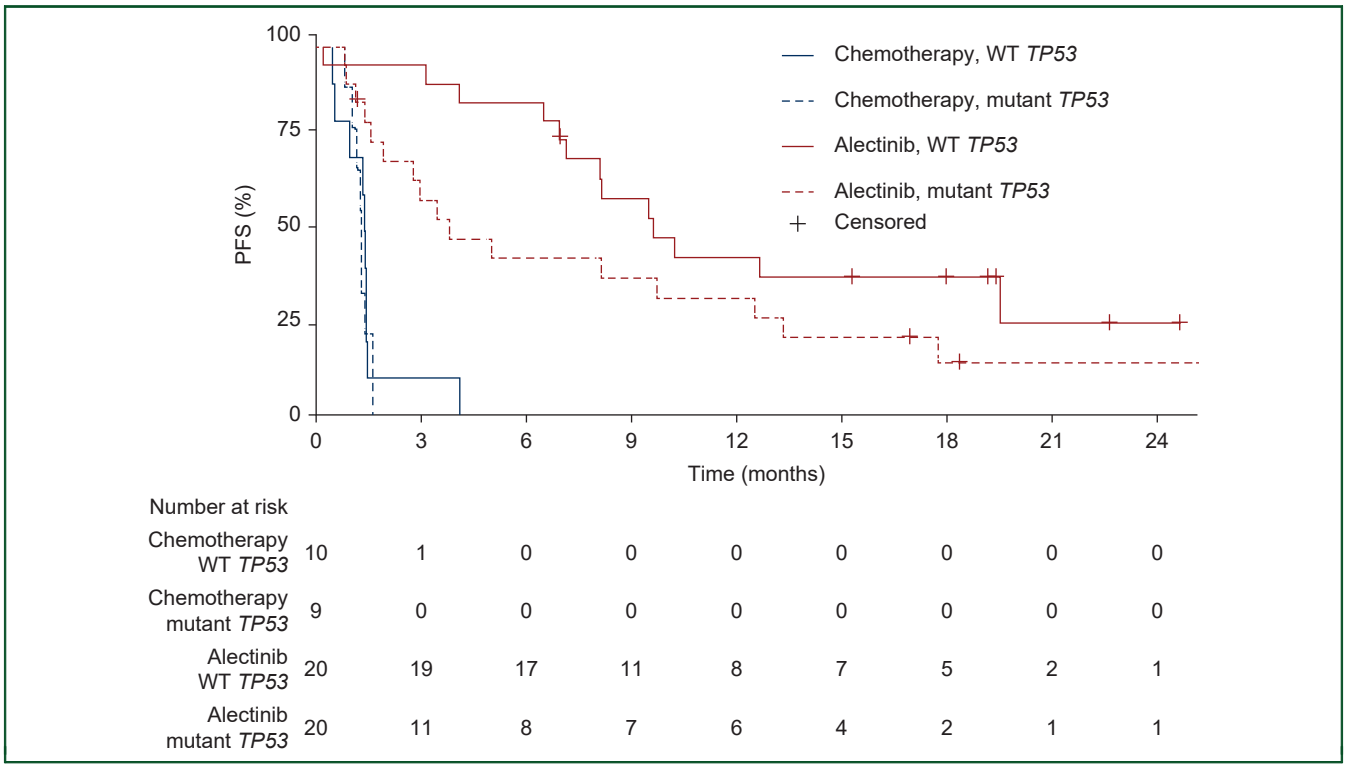


Figure 3. Kaplan–Meier curve of investigator-assessed PFS by baseline *TP53* status (WT or mutant) in each treatment arm.
PFS, progression-free survival; WT, wild-type.

Corresponding median PFS in the chemotherapy arm was 1.2 and 1.4 months, respectively (Figure 3). Patients with a *TP53* mutation had significantly longer PFS when treated with alectinib rather than chemotherapy (HR 0.14, 95% CI 0.04-0.43; $P < 0.001$). In the alectinib arm, patients with a *TP53* mutation had numerically shorter PFS compared with patients without (HR 1.88, 95% CI 0.9-3.93; $P = 0.09$). Alectinib-treated patients with a *TP53* mutation also demonstrated a lower ORR [35% (95% CI 15.4% to 59.2%)] than patients without [65% (95% CI 40.8% to 84.6%)] (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100333).

DISCUSSION

Final data from ALUR confirm the results of the primary analysis, demonstrating superior efficacy of alectinib versus chemotherapy in patients with advanced *ALK*-positive NSCLC who had previously received crizotinib and chemotherapy; median PFS was 10.9 months (95% CI 8.1-15.5 months) with alectinib versus 1.4 months (95% CI 1.2-1.6 months) with chemotherapy (HR 0.20, 95% CI 0.12-0.33). Investigator-assessed ORR with alectinib (50.6% versus 2.5% with chemotherapy) was similar to that reported in pivotal phase II trials that led to the approval of alectinib in the post-crizotinib setting (pooled analysis: 51%).[20] Additionally, the high CNS ORR with alectinib (66.7% versus 0% with chemotherapy) is consistent with the CNS activity of alectinib reported in previous clinical trials[9,10] and preclinical models.[21] The ALUR study was not powered to detect a statistically significant difference in OS between treatment arms, and any comparison of OS benefit is confounded by the high rate of crossover from chemotherapy to alectinib at the time of PD (86.5% of patients).

The safety profile of alectinib was consistent with the primary analysis, previous clinical trial data and post-marketing experience, and continued to compare favorably with that of chemotherapy.[11] Even with the longer treatment duration for alectinib, fewer patients experienced grade 3-5 AEs, treatment-related AEs and AEs leading to treatment discontinuation or dose reduction compared with chemotherapy. Many of the treatment-emergent AEs occurring with alectinib were consistent with those reported in other alectinib studies.[8,20,22,23]

Final data from ALUR support treatment guidelines for advanced *ALK*-positive NSCLC, which recommend treatment with a second ALK TKI after PD on an ALK TKI in the first-line setting.[5,6] A number of ALK TKIs have demonstrated efficacy in the post-crizotinib setting including ceritinib, brigatinib and lorlatinib.[24-26]

NGS identified *ALK* rearrangements in 79% of patients with evaluable tumor tissue and 69.5% of patients with evaluable baseline plasma. *ALK* rearrangements may not have been identified in all patients due to the use of different testing methods before and after enrolment into ALUR (local immunohistochemistry or FISH and central NGS, respectively), with different assay sensitivities and specificities. Interestingly, patients were less likely to respond to alectinib if they tested negative for *ALK* rearrangement via central NGS. The 10% difference in *ALK* rearrangement detection between plasma and tumor tissue may have been caused by a higher false-negative rate

with plasma testing, indicated by the higher number of plasma samples from which a somatic aberration could not be detected (20%) compared with tissue (0%). One patient was *ALK* rearrangement-positive via local testing, but tested negative for *ALK* rearrangement via NGS of baseline tissue; at week 36 of alectinib treatment, a secondary *ALK* mutation was detected via NGS of plasma. These findings reiterate the need to elucidate the role of blood-based testing in everyday clinical practice.

Four of six patients with a non-*EML4-ALK* fusion detected in baseline plasma or tumor tissue achieved a PR with alectinib, suggesting that alectinib may be efficacious against *ALK* rearrangements other than *EML4-ALK*. Furthermore, alectinib demonstrated activity against secondary *ALK* mutations detected via NGS of baseline plasma, with 6/11 patients achieving a PR. This finding is consistent with the broad range of *ALK* mutations known to arise in patients treated with crizotinib, including the L1196M gatekeeper mutation,[12,27] which occurred in baseline plasma in 7/59 (12%) patients in this study.

Next-generation ALK TKIs have been previously shown to enrich different secondary *ALK* mutations, though the G1202R mutation appears to be a common mutation arising with each TKI.[12,27] We observed this mutation in 11/23 (43%) patients on treatment or at PD with alectinib. Interpretation of these data is complicated, however, by genetic heterogeneity introduced by prior treatment with crizotinib and chemotherapy. We are also unable to report on novel *ALK*-independent resistance mechanisms, as these were not identified in this study. As alectinib is a preferred first-line treatment option for advanced *ALK*-positive NSCLC,[5,6] it will be important for future studies to investigate the resistance mechanisms that can arise with first-line alectinib.

Mutant *TP53* was detected in 49% of plasma samples after prior chemotherapy and crizotinib treatment, greater than the 20% commonly observed upon diagnosis of metastatic disease.[28] In the alectinib arm, patients with a *TP53* mutation had numerically shorter PFS compared with patients without a *TP53* mutation. These data are consistent with another study which reported an association between concurrent *TP53* mutations and unfavorable PFS and OS in patients with advanced *ALK*-positive NSCLC treated with chemotherapy, crizotinib and chemotherapy (in any order) or crizotinib followed by ceritinib.[29] Interestingly, alectinib prolonged PFS versus chemotherapy irrespective of baseline *TP53* status, though the effect was much greater in patients without a *TP53* mutation, suggesting a potential prognostic difference between the treatment arms when a *TP53* mutation is detected. We also observed that patients were less likely to respond to alectinib if they had a *TP53* mutation. These findings suggest that mutant *TP53* limits the efficacy of alectinib as a third-line therapy when detected in baseline plasma.

Limitations of the ALUR study have been previously reported.[11] These include the small sample size in subpopulations of interest, many of which have been explored in this manuscript, as well as the small sample size of the chemotherapy arm and an imbalance between the number of patients receiving docetaxel or pemetrexed within that arm. Additionally, there was a considerable difference in median treatment duration between the alectinib and chemotherapy arms (10.2 and 1.4 months, respectively). It should be emphasized that the molecular profiling findings are exploratory and require further investigation in prospectively designed trials recruiting larger study populations.

Conclusions

Final results from the ALUR study confirm the significant improvements in PFS, ORR and CNS ORR with alectinib versus chemotherapy in crizotinib- and chemotherapy-pretreated patients with advanced *ALK*-positive NSCLC. The safety profile of alectinib continued to compare favorably with that of chemotherapy and no new safety signals were observed. Exploratory molecular profiling data demonstrated the effectiveness of alectinib against several secondary *ALK* mutations and the superior activity of alectinib versus chemotherapy in patients with WT or mutant *TP53*, detected in baseline plasma.

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AC, TR, KT and VS are employees of F. Hoffmann-La Roche Ltd. TR and KT also own Roche stocks. SN has received personal fees from AMG, AZ, BMS, Eli Lilly, MSD and Roche, and participated in speakers' bureaus for BeiGene, Pfizer, Sanofi and Takeda.

DATA SHARING

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). 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 here (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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