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ORIGINAL ARTICLE

Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (*ALK*+) non-small-cell lung cancer: CNS efficacy results from the ALEX study

S. Gadgeel[1*], S. Peters[2], T. Mok[3], A. T. Shaw[4], D. W. Kim[5], S. I. Ou[6], M. Pérol[7], A. Wrona[8], S. Novello[9], R. Rosell[10], A. Zeaiter[11†], T. Liu[11], E. Nüesch[11], B. Balas[11] & D. R. Camidge[12]

[1]Division of Hematology & Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, USA; [2]Department of Oncology, Lausanne University Hospital, Lausanne, Switzerland; [3]Department of Clinical Oncology, State Key Laboratory of South China, Chinese University of Hong Kong, Shatin, Hong Kong; [4]Department of Medicine, Massachusetts General Hospital, Boston, USA; [5]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea; [6]Irvine School of Medicine, Chao Family Comprehensive Cancer Center, University of California, Orange, USA; [7]Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; [8]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; [9]Department of Oncology, University of Turin, Turin, Italy; [10]Catalan Institute of Oncology, Barcelona, Spain; [11]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [12]Division of Medical Oncology, University of Colorado, Aurora, USA

*Correspondence to: Prof. Shirish Gadgeel, Department of Internal Medicine, Division of Hematology & Oncology, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA. Tel: +1 7346476883; E-mail: sgadgeel@med.umich.edu
†Affiliation correct at time of study conduct.

Background: The phase III ALEX study in patients with treatment-naive advanced anaplastic lymphoma kinase mutation-positive (*ALK*+) non-small-cell lung cancer (NSCLC) met its primary end point of improved progression-free survival (PFS) with alectinib versus crizotinib. Here, we present detailed central nervous system (CNS) efficacy data from ALEX.

Patients and methods: Overall, 303 patients aged ≥18 years underwent 1:1 randomization to receive twice-daily doses of alectinib 600 mg or crizotinib 250 mg. Brain imaging was conducted in all patients at baseline and every subsequent 8 weeks. End points (analyzed by subgroup: patients with/without baseline CNS metastases; patients with/without prior radiotherapy) included PFS, CNS objective response rate (ORR), and time to CNS progression.

Results: In total, 122 patients had Independent Review Committee-assessed baseline CNS metastases (alectinib, $n = 64$; crizotinib, $n = 58$), 43 had measurable lesions (alectinib, $n = 21$; crizotinib, $n = 22$), and 46 had received prior radiotherapy (alectinib, $n = 25$; crizotinib, $n = 21$). Investigator-assessed PFS with alectinib was consistent between patients with baseline CNS metastases [hazard ratio (HR) 0.40, 95% confidence interval (CI): 0.25–0.64] and those without (HR 0.51, 95% CI: 0.33–0.80, P interaction = 0.36). Similar results were seen in patients regardless of prior radiotherapy. Time to CNS progression was significantly longer with alectinib versus crizotinib and comparable between patients with and without baseline CNS metastases ($P < 0.0001$). CNS ORR was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy and 78.6% versus 40.0%, respectively, in those who had not.

Conclusion: Alectinib demonstrated superior CNS activity and significantly delayed CNS progression versus crizotinib in patients with previously untreated, advanced *ALK*+ NSCLC, irrespective of prior CNS disease or radiotherapy.

Clinical trial registration: ClinicalTrials.gov NCT02075840

Key words: alectinib, ALK-positive, CNS, NSCLC

Introduction

Anaplastic lymphoma kinase-positive (*ALK*+) non-small-cell lung cancer (NSCLC) is characterized by a high prevalence of central nervous system (CNS) involvement [1] and brain metastases [2, 3]. Previously, crizotinib was the standard of care (SOC) first-line treatment of *ALK*+ NSCLC [4]. Most crizotinib-treated patients relapse within 1 year because of poor CNS

penetration [5] or development of resistance mutations [6]. In the phase III PROFILE 1014 study, although intracranial disease control rate was significantly higher with crizotinib than with chemotherapy, there was no significant difference in intracranial time to tumor progression between the treatments [7].

Alectinib is a highly selective ALK inhibitor with proven CNS efficacy [8–13]. Unlike crizotinib, alectinib demonstrates effective CNS penetration and is not a substrate for P-glycoprotein, which promotes efflux at the blood–brain barrier [11]. The phase III ALEX trial (BO28984, NCT02075840) compared alectinib with crizotinib as the first-line treatment for *ALK*+ advanced NSCLC. Patients with/without asymptomatic CNS metastases, including treated/untreated CNS disease, were permitted. In the primary analysis, the primary end point [investigator-assessed progression-free survival (PFS)] was significantly improved with alectinib versus crizotinib: hazard ratio (HR) 0.47 [95% confidence interval (CI): 0.34–0.65; $P < 0.001$], median PFS for alectinib not reached (NR) [13]. With 10 months' longer follow-up, median PFS was 34.8 months (95% CI: 17.7–not estimable) with alectinib and 10.9 months (95% CI: 9.1–12.9) with crizotinib (HR 0.43, 95% CI: 0.32–0.58) [14]. Based on ALEX, alectinib was approved for the first-line treatment of *ALK*+ NSCLC.

ALEX was designed to capture CNS progression by prospectively monitoring patients with uniform brain imaging. At the primary data analysis, 18 patients (12%) receiving alectinib had CNS progression as the first progression event versus 68 patients (45%) receiving crizotinib [cause-specific HR (csHR) 0.16; 95% CI: 0.10–0.28; $P < 0.001$] [13]. Here, we report further CNS efficacy results from ALEX.

Methods

Study design

Full methodology has been published [13]. Patients with stage III/IV *ALK*+ NSCLC (by central immunohistochemistry testing) were randomized 1:1 to receive alectinib 600 or crizotinib 250 mg twice-daily until disease progression, toxicity, withdrawal, or death. Randomization was stratified by performance status, race, and CNS metastases status. Patients with treated/untreated asymptomatic brain metastases were eligible; previous CNS radiotherapy was allowed if completed ≥14 days before enrolment. Crossover was not permitted.

ALEX was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients.

End points

CNS efficacy end points [PFS, time to CNS progression, CNS objective response rate (ORR), and CNS duration of response (DoR)] were analyzed by subgroup: patients with/without baseline CNS disease and patients with baseline CNS disease with/without prior radiotherapy.

Assessments

Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and brain were carried out at screening. Subsequent tumor assessment, including systematic brain imaging, was carried out every 8 weeks until progression, and at the post-treatment visit (4 weeks after treatment discontinuation). Scans were repeated for suspected progression.

CNS end points were assessed by an Independent Review Committee (IRC). Baseline CNS metastases with a minimum size of 10 mm (CT/MRI scan), 10 mm caliper measurement (clinical examination), or 20 mm (chest X-ray) were considered measurable. Response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Exploratory CNS end points (ORR, DoR, and time to CNS progression) were assessed by Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria in patients with baseline CNS metastases.

Statistical analysis

Comparisons of PFS between treatment groups were based on a two-sided log-rank test. Kaplan–Meier methods were used to estimate median PFS with 95% CIs. HRs with 95% CIs were estimated using Cox proportional-hazards regression. CNS end points assessed by RANO-BM were analyzed using the same methods as those assessed by RECIST [13].

Time to CNS progression was analyzed using competing risk methodology with minor statistical differences for the cumulative incidence rates (CIR) of CNS progression and time to CNS progression analysis. These analyses consider the possibility that at the time of analysis, a patient may have CNS progression (with/without systemic progression), non-CNS progression, or death, and include only the first event (see supplementary Appendix, available at *Annals of Oncology* online).

Results

Patients

At data cutoff (9 February 2017), 303 patients (alectinib, $n = 152$; crizotinib, $n = 151$) were randomized; baseline characteristics of the intent-to-treat (ITT) population have been reported [13]. Forty percent of patients had IRC-assessed baseline CNS metastases ($n = 122$, measurable and/or non-measurable; $n = 43$, measurable [Figure 1]). Baseline characteristics were generally balanced between arms (Table 1). A higher proportion of past and current smokers received alectinib versus crizotinib (36% and 11% versus 24% and 2%, respectively). Among patients with measurable and/or non-measurable baseline CNS metastases, 46 had received prior radiotherapy. Patients who received treatment for CNS progression after study start are described in supplementary Table S1, available at *Annals of Oncology* online). The median number of measurable/non-measurable baseline CNS lesions per patient was two in both treatment arms (alectinib, range: 1–10; crizotinib, range: 1–6).

PFS

Investigator-assessed PFS was significantly prolonged with alectinib versus crizotinib in patients with (HR 0.40, 95% CI: 0.25–0.64) and without baseline CNS metastases (HR 0.51, 95% CI: 0.33–0.80; Figure 2). There was no discernable difference in the effect of alectinib between patients with/without baseline CNS metastases (interaction $P = 0.36$). PFS was significantly longer with alectinib versus crizotinib in patients with (HR 0.34, 95% CI: 0.15–0.78) and without prior radiotherapy (HR 0.44, 95% CI: 0.25–0.78; Figure 2).

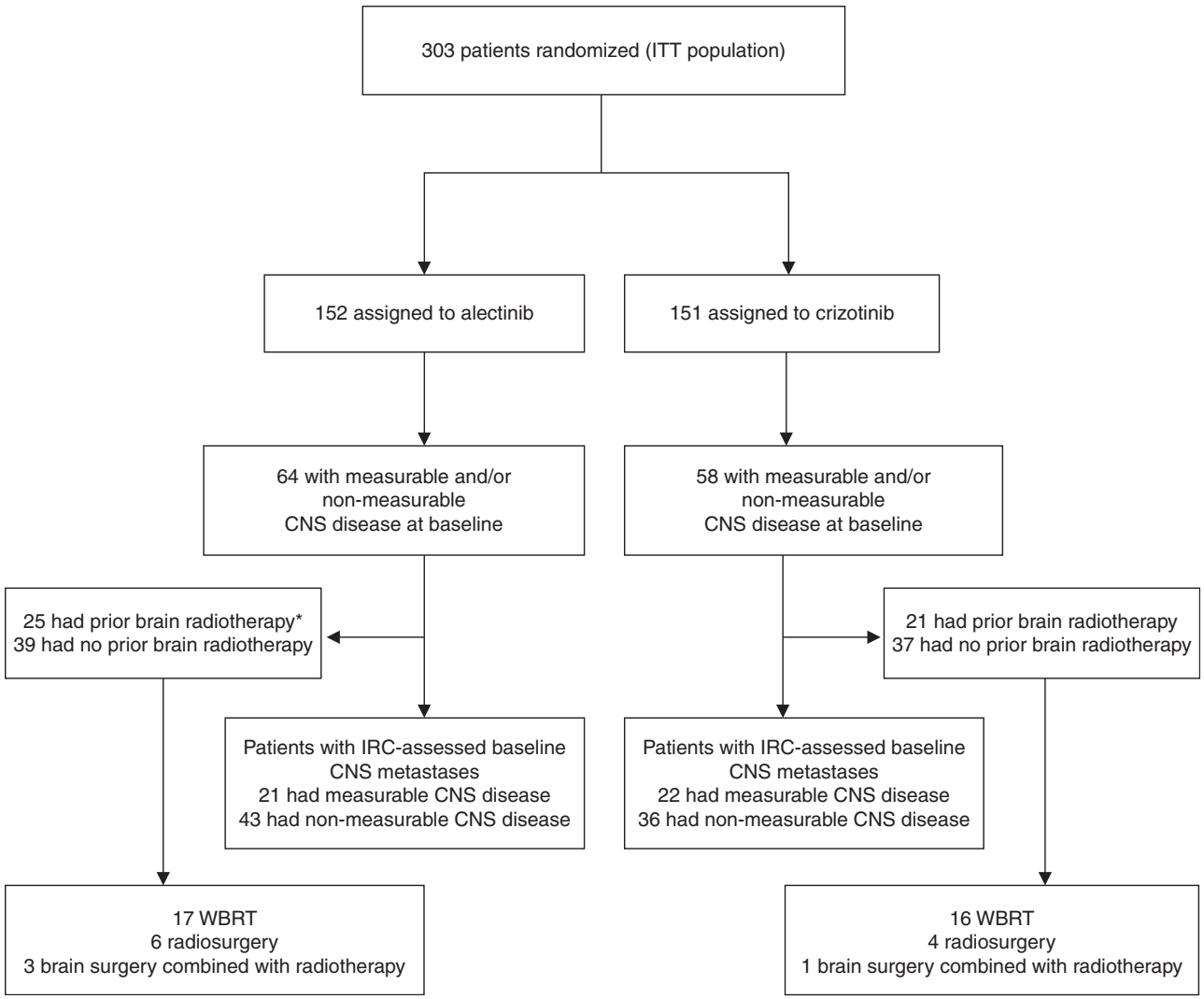

Figure 1. Study population overview. *One patient in the alectinib arm received both radiosurgery and whole-brain radiotherapy (WBRT). CNS, central nervous system; IRC, independent review committee; ITT, intent-to-treat.

Time to CNS progression

Time to CNS progression, without prior non-CNS progression, was significantly longer with alectinib versus crizotinib, and comparable between patients with [csHR 0.18 (95% CI: 0.09–0.36)] and without baseline CNS metastases [csHR 0.14 (95% CI: 0.06–0.33); Table 2] or with [csHR 0.11 (95% CI: 0.03–0.42)] or without prior radiotherapy [csHR 0.22 (95% CI: 0.10–0.50); supplementary Table S2, available at *Annals of Oncology* online].

The CIR of CNS progression, without prior non-CNS progression, was lower over time with alectinib versus crizotinib regardless of baseline CNS metastases or prior radiotherapy (Figure 3). Twelve-month CIR for CNS progression (without prior non-CNS progression) were: 58.3% (95% CI: 43.4–70.5) crizotinib and 16.0% (95% CI: 8.2–26.2) alectinib in patients with baseline CNS metastases; and 31.5% (95% CI: 22.1–41.3) crizotinib and 4.6% (95% CI: 1.5–10.6) alectinib in patients without (Figure 3 and supplementary Table S3, available at *Annals of Oncology* online). Twelve-month CIR for non-CNS progression (without prior CNS progression) were: 24.2% (95% CI: 13.6–36.5) crizotinib and 12.9% (95% CI: 6.0–22.5) alectinib in patients with baseline CNS metastases; and 25.3% (95% CI: 16.7–34.9) crizotinib and 16.7% (95% CI: 9.8–25.2) alectinib in patients without (supplementary Figure S1 and Table S3, available at *Annals of Oncology* online). At primary analysis, 18 alectinib and 68 crizotinib patients had CNS progression without prior non-CNS progression; of these, 6 and 8, respectively, had systemic progression at the time of CNS progression. CIR for death (without prior progression) for the subgroups are shown in supplementary Figure S1 and Table S3, available at *Annals of Oncology* online. Similar differences between 12-month CIRs for CNS or non-CNS progression as the first site of progression between alectinib and crizotinib were seen in patients with/without prior radiotherapy.

Forty crizotinib-treated patients experienced an isolated asymptomatic CNS progression per investigator, regardless of baseline CNS metastases, versus 5 alectinib-treated patients. Of those, 30/40 patients (75%, crizotinib), and 5/5 patients (100%, alectinib) received allocated to study treatment after

Table 1. Baseline characteristics in patients with central nervous system (CNS) disease [Independent Review Committee (IRC)] at baseline

	Measurable and/or non-measurable CNS disease (IRC) at baseline ($n = 122$)	
	Crizotinib ($n = 58$)	Alectinib ($n = 64$)
Median age, years (range)	54 (18–81)	58 (25–81)
Gender, *n* (%)		
Male	22 (38)	34 (53)
Female	36 (62)	30 (47)
Ethnicity, *n* (%)		
Asian	28 (48)	27 (42)
Non-Asian	30 (52)	37 (58)
ECOG performance status, *n* (%)		
0–1	53 (91)	59 (92)
2	5 (9)	5 (8)
Smoking history, *n* (%)		
Current smoker	1 (2)	7 (11)
Past smoker	14 (24)	23 (36)
Never smoked	43 (74)	34 (53)
Stage, *n* (%)[a]		
IIIB	1 (2)	0
IV	57 (98)	64 (100)
Histology, *n* (%)		
Adenocarcinoma	56 (97)	57 (89)
Squamous cell carcinoma	0	2 (3)
Other	2 (3)	3 (5)
Undifferentiated	0	2 (3)
Prior brain radiation, *n* (%)[b]		
Yes	21 (36)	25 (39)
Whole-brain radiotherapy	16	17
Radiosurgery	4	6
Brain surgery plus radiotherapy	1	3
No	37 (64)	39 (61)
Patients with measurable CNS disease (IRC), *n* (%)		
Yes	22 (38)	21 (33)
No	36 (62)	43 (67)

[a]Disease stage was assessed by investigators following commonly used staging systems in local practice.
[b]One patient in the alectinib arm received both radiosurgery and whole-brain radiotherapy.
ECOG, Eastern Cooperative Oncology Group.

asymptomatic CNS progression. Continuation of study treatment after symptomatic CNS progression was not permitted.

CNS response (RECIST)

CNS ORR in patients with measurable baseline CNS metastases was 85.7% ($n = 6/7$) alectinib versus 71.4% ($n = 5/7$) crizotinib in patients with prior radiotherapy, and 78.6% ($n = 11/14$) alectinib versus 40.0% ($n = 6/15$) crizotinib in patients without (Figure 4). In patients with measurable/non-measurable baseline CNS metastases, CNS ORR was 36.0% ($n = 9/25$) alectinib versus 28.6% ($n = 6/21$) crizotinib in patients with prior radiotherapy and 74.4% ($n = 29/39$) alectinib versus 24.3% ($n = 9/37$) crizotinib without prior radiotherapy (Figure 4). Complete response (CR) rates were higher for alectinib versus crizotinib in patients with measurable/non-measurable baseline CNS metastases with prior radiotherapy (61.5% versus 10.8%) and without (20.0% versus 4.8%; Figure 4).

CNS DoR in patients with measurable/non-measurable baseline CNS metastases was longer for alectinib versus crizotinib in patients with prior radiotherapy [median NR (95% CI: 14.8–NR) versus 11.1 months (95% CI: 13.7–18.1); Figure 4C] and without [median NR (95% CI: 13.4–NR) versus 3.7 months (95% CI: 2.3–5.5); Figure 4D]. Data were similar for patients with measurable baseline CNS metastases.

Efficacy by RANO-BM criteria

Data assessed by RANO-BM criteria were consistent with RECIST-assessed findings (supplementary Table S4, available at *Annals of Oncology* online). In 32 patients with measurable baseline CNS metastases (alectinib, $n = 15$; crizotinib, $n = 17$), 33% ($n = 5$) achieved a CNS CR with alectinib versus 0% with crizotinib; 20% ($n = 3$) achieved a partial response with alectinib versus 29.4% ($n = 5$) with crizotinib although the sample size was small (supplementary Table S5, available at *Annals of Oncology* online). Median CNS DoR in patients with baseline measurable CNS metastases was 17.3 months with crizotinib and NR with alectinib. CNS ORR according to prior radiotherapy treatment is shown in supplementary Table S5, available at *Annals of Oncology* online.

Time to CNS progression was significantly longer with alectinib versus crizotinib in patients with baseline measurable/non-measurable CNS metastases (csHR 0.23; 95% CI: 0.12–0.48; supplementary Table S6, available at *Annals of Oncology* online). CIR of CNS progression in patients with measurable/non-measurable baseline CNS metastases (supplementary Figure S2, available at *Annals of Oncology* online) were consistently lower over time with alectinib versus crizotinib. Twelve-month CIRs of CNS progression (without prior non-CNS progression) were 59.4% (95% CI: 43.6–72.1) crizotinib and 19.0% (95% CI: 9.7–30.7) alectinib in patients with measurable/non-measurable baseline CNS metastases (supplementary Table S7, available at *Annals of Oncology* online). The CIR of non-CNS progression and death in these patients are shown in supplementary Figure S2, available at *Annals of Oncology* online.

Discussion

Based on the ALEX data, the National Comprehensive Cancer Network guidelines were updated to include alectinib as a category 1 recommendation for first-line treatment of *ALK*+ NSCLC [15]. Our data confirm that alectinib demonstrates superior efficacy versus crizotinib in treatment-naive advanced *ALK*+ NSCLC, regardless of baseline CNS disease or prior radiotherapy.

Baseline CNS metastases are an adverse prognostic factor in *ALK*+ advanced NSCLC [16]. Although PROFILE 1014 established crizotinib as the SOC first-line therapy for *ALK*+ NSCLC [2], only patients with treated and stable CNS disease were enrolled, and, in contrast to ALEX, regular CNS imaging was only conducted in patients with known baseline CNS disease [4, 7]. In ASCEND-4 (phase III; first-line ceritinib versus chemotherapy), 32% of patients had asymptomatic or neurologically stable

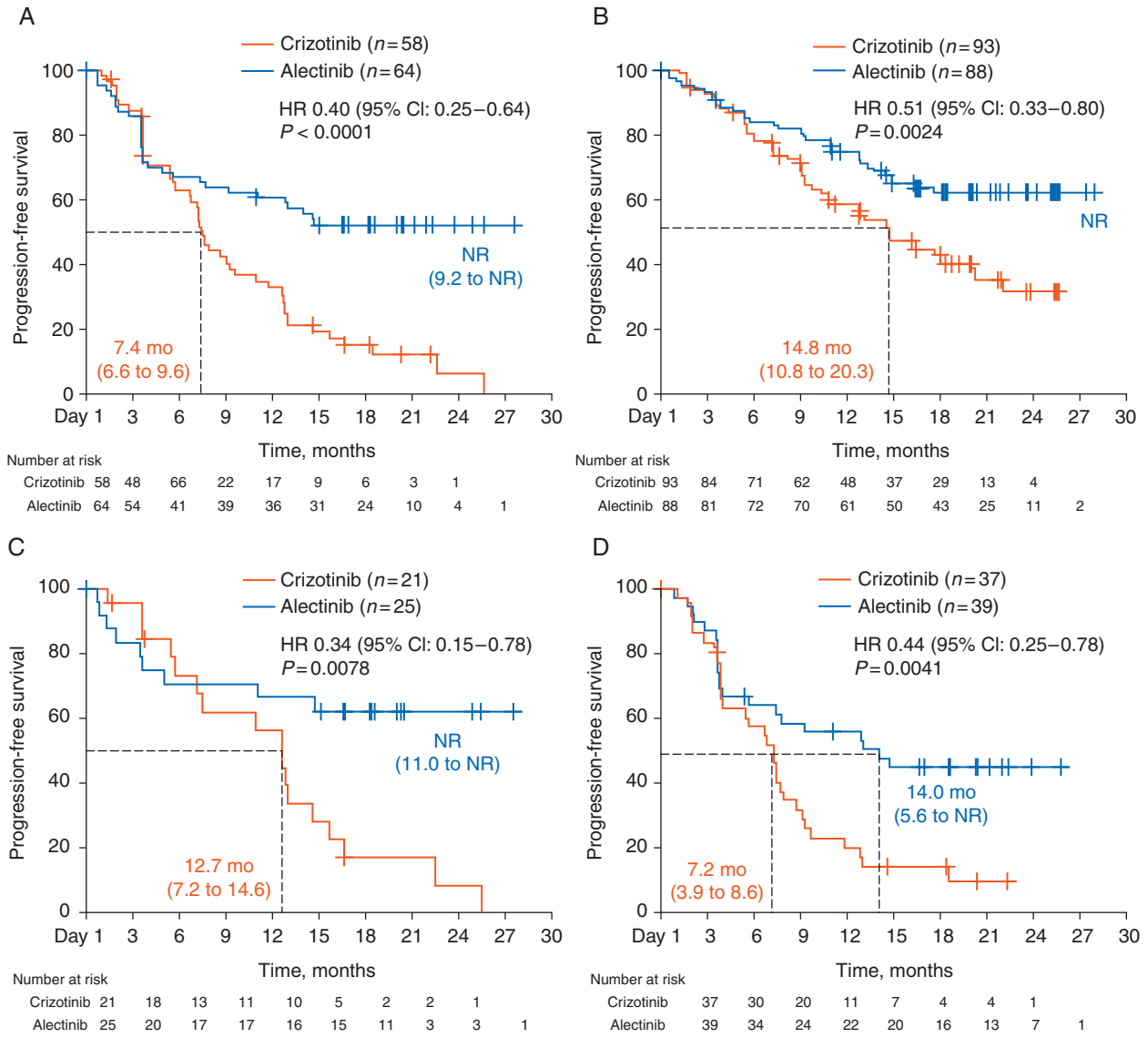

Figure 2. Progression-free survival according to central nervous system (CNS) metastatic status at baseline and history of radiotherapy: (A) patients with CNS metastases at baseline, (B) patients without CNS metastases at baseline, (C) patients with CNS metastases at baseline who had received prior radiotherapy, and (D) patients with CNS metastases at baseline who had not received prior radiotherapy. CI, confidence interval; HR, hazard ratio; NR, not reached.

baseline CNS disease [17]. PFS was longer with ceritinib versus chemotherapy in patients without baseline CNS metastases [HR 0.48 (95% CI: 0.33–0.69), median PFS 26.3 versus 8.3 months] [17]. Although CNS responses are well documented with ceritinib, these differences, together with the median PFS of ceritinib in those with baseline CNS metastases (10.7 months), raise concerns about the durability of the CNS efficacy of ceritinib. Indeed, the CNS is a common site of progression in patients treated with crizotinib or ceritinib [17, 18].

ALEX is the first ALK-inhibitor study to include prospective, standardized assessment of CNS lesions in the ITT population, regardless of baseline CNS disease, allowing the potential CNS protective effect of the drug to be assessed. Alectinib significantly prolonged PFS in patients with/without baseline CNS disease versus crizotinib, and significantly improved intracranial ORR versus crizotinib, irrespective of radiotherapy history.

Our data are in agreement with a pooled analysis of alectinib phase II trials, which demonstrated that CNS efficacy of alectinib is maintained regardless of radiotherapy history in crizotinib-pretreated patients [12]. ALEX CNS progression data are consistent with findings from the phase III J-ALEX trial, in which first-line alectinib reduced the risk of CNS progression versus crizotinib [19]. However, CNS metastases were not stratified in J-ALEX. CNS DoR was longer with alectinib versus crizotinib in all ALEX subgroups. As ALEX only permitted patients with asymptomatic CNS disease, we do not yet know the potential of alectinib in improving CNS outcomes in symptomatic patients versus local CNS therapies. The ALEX data strongly suggest that in asymptomatic patients, treating CNS metastases with alectinib alone may result in a reduced or delayed need for local CNS treatment.

Alectinib significantly reduced the risk of CNS progression versus crizotinib irrespective of the subgroup analyzed, suggesting

Table 2. Risk of central nervous system (CNS) progression, non-CNS progression, and death [Independent review committee (IRC) Response Evaluation Criteria in Solid Tumors (RECIST) v1.1] in patients with/without baseline CNS metastases

Patients with baseline CNS metastases	Crizotinib ($n = 58$) Patients with event, *n* (%)	Alectinib ($n = 64$) Patients with event, *n* (%)	Cause-specific HR (95% CI)	*P* value (log-rank)
CNS progression without prior non-CNS PD	33 (56.9)	12 (18.8)	0.18 (0.09–0.36)	<0.0001
Non-CNS progression without prior CNS PD	14 (24.1)	11 (17.2)	0.35 (0.15–0.84)	0.0154
Death without prior CNS or non-CNS PD	4 (6.9)	7 (10.9)	0.66 (0.17–2.55)	0.55
Patients without baseline CNS metastases	**Crizotinib ($n = 93$) Patients with event, *n* (%)**	**Alectinib ($n = 88$) Patients with event, *n* (%)**	**Cause-specific HR (95% CI)**	***P* value (log-rank)**
CNS progression without prior non-CNS PD	35 (37.6)	6 (6.8)	0.14 (0.06–0.33)	<0.0001
Non-CNS progression without prior CNS PD	19 (20.4)	25 (28.4)	1.16 (0.64–2.11)	0.63
Death without prior CNS or non-CNS PD	5 (5.4)	4 (4.5)	0.71 (0.19–2.65)	0.60

For each patient, the first event of CNS progression, systemic progression, or death was counted. Therefore, patients who had CNS progression first were no longer at risk for a systemic progression or death in this analysis. Patients with CNS progression who also had systemic progression were included in the CNS progression group. Hazard ratios (HRs) and 95% confidence interval (CI) were estimated by Cox regression where patients with competing events were censored at the time of these events. *P* values are from two-sided cause-specific log-rank tests. PD, disease progression.

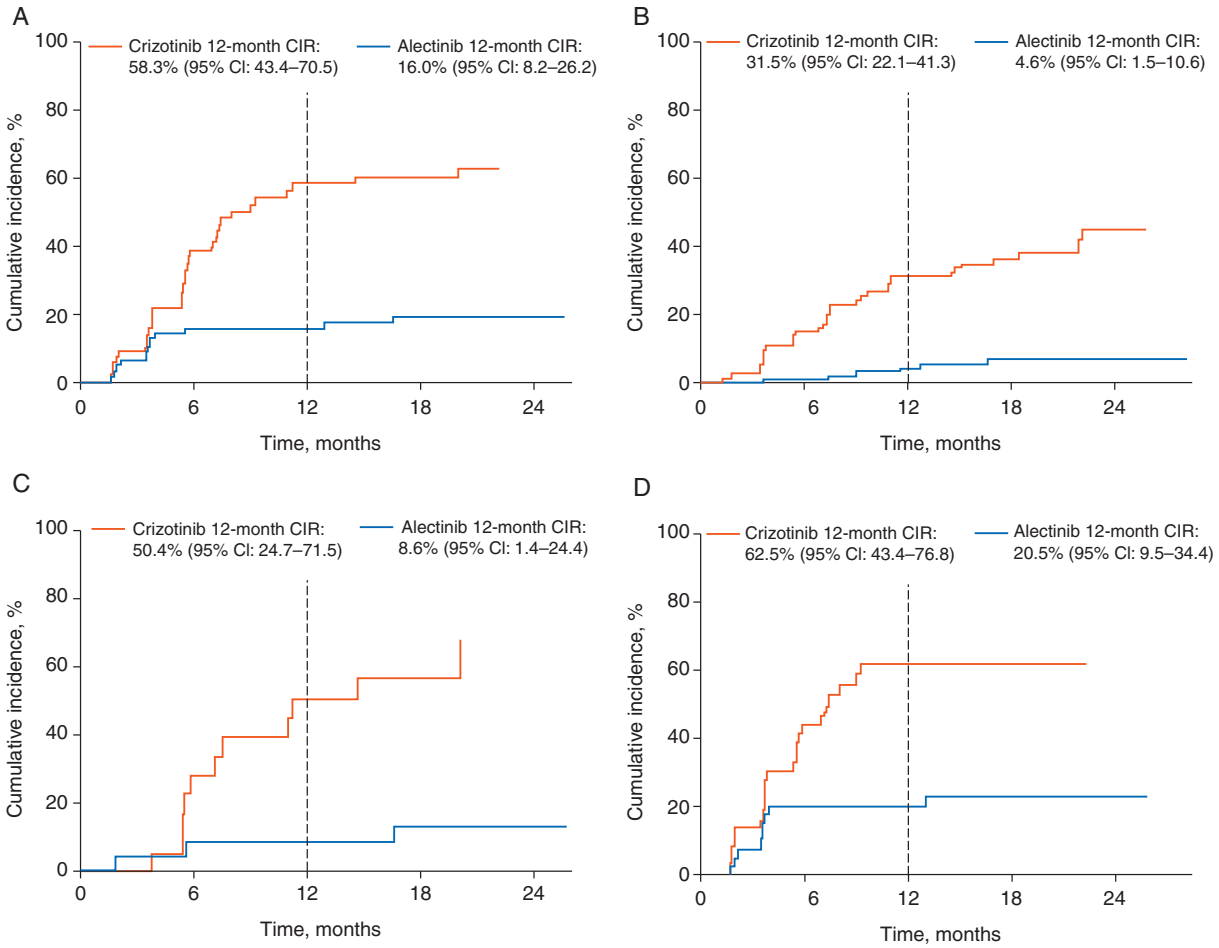

Figure 3. Cumulative incidence rate (CIR) of central nervous system (CNS) progression. For each patient, the first event of CNS or non-CNS progression or death was counted: (A) patients with CNS metastases at baseline, (B) patients without CNS metastases at baseline, (C) patients with CNS metastases at baseline who had received prior radiotherapy, and (D) patients with CNS metastases at baseline who had not received prior radiotherapy. CI, confidence interval.

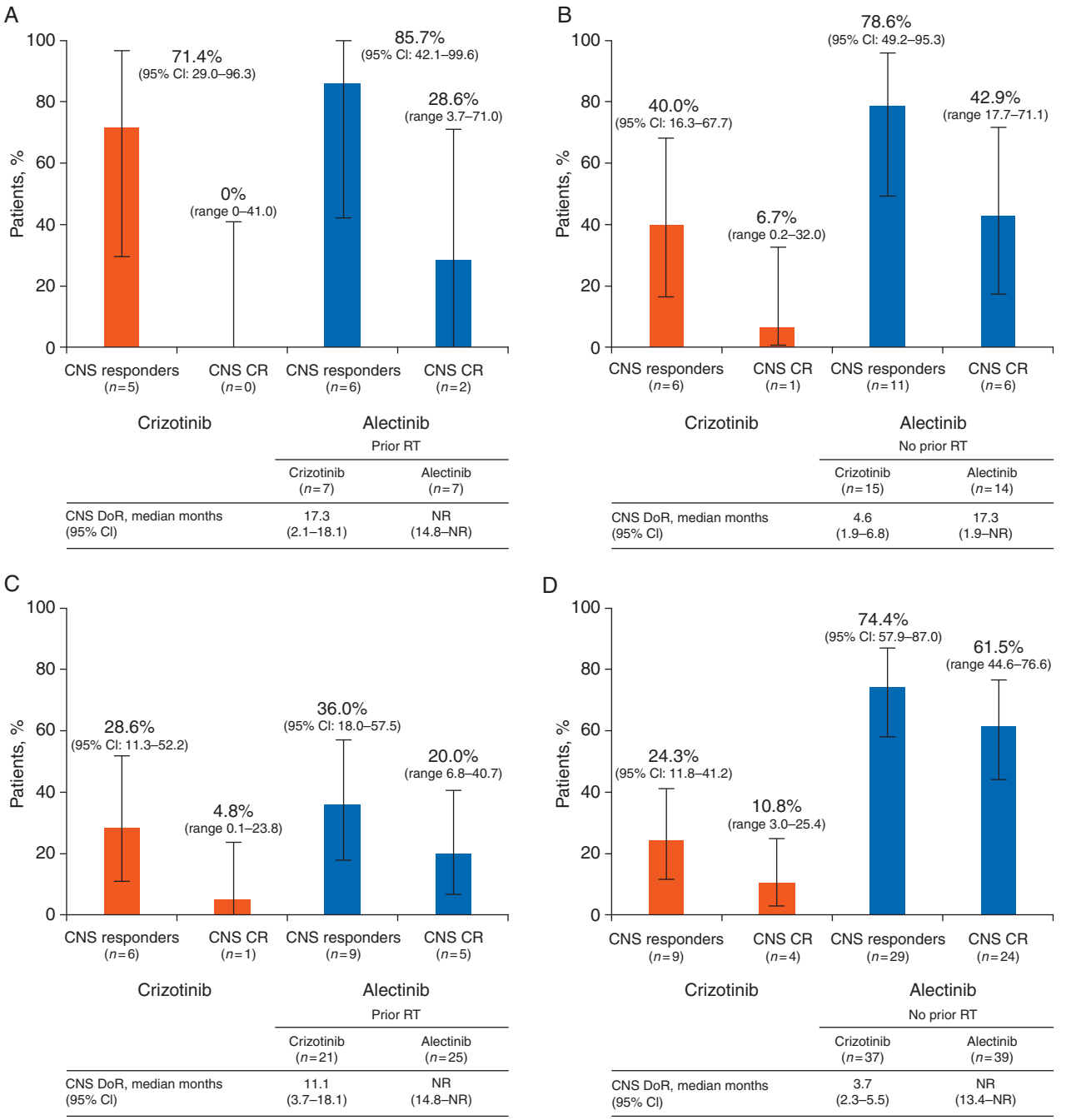

Figure 4. Central nervous system (CNS) response: (A) patients with measurable CNS disease at baseline who had received prior radiotherapy, (B) patients with measurable CNS disease at baseline who had not received prior radiotherapy, (C) patients with measurable or non-measurable CNS disease at baseline who had received prior radiotherapy, and (D) patients with measurable or non-measurable CNS disease at baseline who had not received prior radiotherapy. CI, confidence interval; CR, complete response; DoR, duration of response; NR, not reached; RT, radiotherapy.

that alectinib may have protective effect against development of CNS metastases. When interpreting the CIR of non-CNS progression and death, we must consider the methodology used. Once a patient develops CNS progression, CIR analysis does not analyze whether subsequent systemic progression occurred earlier with alectinib or crizotinib. As such, some patients were documented as having CNS progression but may also have experienced non-CNS progression.

Pooled analysis of phase II studies demonstrated that alectinib is active against treated/untreated CNS metastases in *ALK*+ NSCLC, regardless of assessment criteria (RECIST v1.1 versus RANO-BM, http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf) [20]. Trends we observed are consistent with the pooled phase II data, and the ALEX ITT data [13]. Although some subgroups contained small patient numbers, our findings are consistent with those reported previously [12, 19].

The key strength of our analysis comes from prospective assessment of CNS secondary lesions in the ITT population.

CNS results from ALEX consolidate alectinib as the SOC for untreated, advanced *ALK*+ NSCLC irrespective of presence/absence of baseline CNS metastases.

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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 here (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 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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