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ORIGINAL ARTICLE

Intracranial and extracranial efficacy of lorlatinib in patients with *ALK*-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs

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Background: Lorlatinib, a potent, brain-penetrant, third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI), has substantial activity against *ALK*-positive non-small-cell lung cancer (NSCLC). This study assessed the overall, intracranial, and extracranial efficacy of lorlatinib in *ALK*-positive NSCLC that progressed on second-generation ALK TKIs.

Patients and methods: In the ongoing phase II study (NCT01970865), patients with *ALK*-positive advanced NSCLC treated with $\geq$1 prior second-generation ALK TKI $\pm$ chemotherapy were enrolled in expansion cohorts (EXP) based on treatment history. Overall, intracranial and extracranial antitumor activity were assessed independently per modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Results: Of the 139 patients with $\geq$1 prior second-generation ALK TKI (EXP3B-5), 28 received one prior second-generation ALK TKI (EXP3B), 65 two prior ALK TKIs (EXP4), and 46 three prior ALK TKIs (EXP5). In EXP3B-5, the objective response rate (ORR) [95% confidence intervals] was 39.6% (31.4-48.2), intracranial ORR (IC-ORR) was 56.1% (42.4-69.3), extracranial ORR (EC-ORR) was 36.7% (28.7-45.3), median duration of response (DOR) was 9.6 months [5.6-16.7; IC-DOR, 12.4 (6.0-37.1); EC-DOR, 9.7 (6.1-33.3)], median progression-free survival was 6.6 (5.4-7.4) months, and median overall survival was 20.7 months (16.1-30.3). In EXP3B, the ORR was 42.9% (24.5-62.8), the IC-ORR was 66.7% (29.9-92.5), and the EC-ORR was 32.1% (15.9-52.4). In EXP4 and EXP5, the ORR was 38.7% (29.6-48.5), the IC-ORR was 54.2% (39.2-68.6), and the EC-ORR was 37.8% (28.8-47.5).

Conclusions: Lorlatinib had clinically meaningful intracranial and extracranial antitumor activity in the post-second-generation ALK TKI setting, with elevated intracranial versus extracranial ORR, particularly in patients with fewer lines of therapy.

Key words: Lorlatinib, ALK, non-small-cell lung cancer, second-generation ALK TKIs, third-generation ALK TKIs

INTRODUCTION

Development of resistance and progression of central nervous system (CNS) metastases remain ongoing issues despite the clinical benefit derived from second-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) for front-line treatment of patients with *ALK*-positive advanced non-small-cell lung cancer (NSCLC).[1-5]

Lorlatinib is a selective, brain-penetrant, third-generation macrocyclic TKI of ALK and ROS1 that was specifically developed to have broad activity against *ALK*-resistance mutations.[6] In the ongoing, open-label, phase I/II study (NCT01970865), treatment with lorlatinib resulted in clinically meaningful and durable responses in patients with *ALK*-positive NSCLC, many of whom had CNS metastases and experienced treatment failure with prior ALK TKI therapy.[7,8] In the initial results from the phase II trial with 7 months' median follow-up, the objective response rate (ORR) was 32% in patients refractory to first-line,

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second-generation ALK TKI therapy and 39% in patients with ≥2 prior ALK TKIs consisting predominantly of crizotinib and second-generation ALK TKIs.[8] Responses were durable, with median response durations not reached at the time of that analysis in both patient populations. Based on these findings, lorlatinib received approval for the treatment of patients with *ALK*-positive metastatic NSCLC whose disease has progressed after alectinib or ceritinib as the first ALK TKI, or after crizotinib and at least one other ALK TKI.[9]

We report updated efficacy data as of cutoff date 14 May 2019, including assessment of intracranial and extracranial efficacy of lorlatinib in the phase II portion of the study in patients with *ALK*-positive NSCLC previously treated with at least one second-generation ALK TKI. We also present updated safety data based on all phase I/II patients who received the recommended dose of lorlatinib.

PATIENTS AND METHODS

Patients

This analysis assessed the overall, intracranial, and extracranial efficacy of lorlatinib in the phase II portion of an ongoing study in patients with *ALK*-positive NSCLC previously treated with at least one second-generation ALK TKI (ClinicalTrials.gov, NCT01970865). The full methodology was previously described.[8] Eligible patients were aged ≥18 years and had Eastern Cooperative Oncology Group performance status 0-2, had histologically or cytologically confirmed metastatic NSCLC with an *ALK* or *ROS1* rearrangement, and had at least one measurable extracranial lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ALK positivity was determined locally by FDA-approved fluorescence *in situ* hybridization assay (Abbott Molecular Inc., Des Plaines, IL) or immunohistochemistry (Ventana Medical Systems, Inc., Tucson, AZ). Asymptomatic treated or untreated CNS metastases were permitted and could be newly diagnosed or present as progressive disease following surgery, whole-brain radiotherapy, or stereotactic radiosurgery. Prior radiotherapy must have been completed within 2 weeks of study entry; stereotactic or small field brain irradiation must have been completed at least 2 weeks before study entry; and whole-brain radiotherapy at least 4 weeks before study entry. Patients or their legal representative provided written, informed consent before participation. The institutional review board or independent ethics committee at each participating site approved the protocol, which complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws.

Study design and treatment

Patients were enrolled into expansion cohorts (EXP) according to their *ALK* (EXP1-5) or *ROS1* (EXP6) status and treatment history. This analysis included patients who were *ALK*-positive and previously treated with at least one second-generation ALK TKI (EXP3B-5; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.02.012). Enrollment criteria were progression following one prior second-generation ALK TKI, with or without chemotherapy, (EXP3B) and disease progression following two (EXP4) or three (EXP5) prior ALK TKIs with or without chemotherapy.

Lorlatinib 100 mg once daily (QD) was administered orally in 21-day cycles until progression, unacceptable toxicity, death, or withdrawal of consent. Treatment beyond progression was permitted if the patient was still experiencing clinical benefit per the investigator's discretion.

Assessments

Tumor imaging [computed tomography (chest, abdomen, and pelvis) and magnetic resonance imaging (brain)] was carried out every 6 weeks for the first 30 months and then every 12 weeks thereafter. All adverse events (AEs) during the study were recorded and graded using National Cancer Institute Common Terminology Criteria for Adverse Events, v4.03.

Endpoints

The primary endpoint was objective tumor response [defined as a confirmed complete response (CR) or partial response (PR)] and intracranial tumor response according to modified RECIST v1.1, which allowed for up to five CNS target lesions, as assessed by independent central radiology review (ICR); responses were confirmed at least 4 weeks later. Additional endpoints included overall and intracranial duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety.

Statistical analysis

Analyses of activity and safety reported here were based on the safety analysis set (i.e. all patients who received at least one dose of lorlatinib). Patients with measurable CNS metastases at baseline by ICR were included in the analyses of intracranial activity. Patients who had extracranial lesions at baseline by ICR were included in the analyses of extracranial activity. Efficacy was assessed for patients in cohorts EXP3B-5 who received lorlatinib. EXP4 and EXP5 were pooled, because they represented the more advanced lines of treatment where no treatment options with other ALK TKIs are currently available. The proportions of patients with objective response (overall, intracranial, or extracranial) were defined as those who achieved a confirmed CR or confirmed PR according to RECIST v1.1 as their best response. The corresponding 95% confidence intervals (CIs) were calculated using the exact method based on the binomial distribution. Median time for time-to-event endpoints (DOR, PFS, and OS) were estimated using the Kaplan—Meier method with two-sided 95% CIs. DOR was defined as the time from first objective tumor response that was subsequently confirmed to disease progression or death. PFS was defined as time from the first dose of lorlatinib to first objective disease progression or death. The probability of a first event being a CNS progression, non-CNS progression, or death was estimated by cumulative

incidences using a competing risks approach in patients with or without baseline CNS metastases. Safety was summarized descriptively for the safety analysis set of the phase I/II study. Other statistical parameters have been previously described.[8]

RESULTS

Patients

Overall, 139 patients received at least one prior second-generation ALK TKI (EXP3B-5), including 28 patients with one prior second-generation ALK TKI only (EXP3B) and 111 patients with at least two prior ALK TKIs (EXP4-5). Demographics and baseline disease characteristics are summarized in Table 1 and Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2021.02.012. In the overall population of patients who had received at least one prior second-generation ALK TKI (EXP3B-5), brain metastases were present at baseline in 95 (68.3%) patients; 67 (48.2%) patients had received prior brain-directed radiotherapy. The median time from prior brain-directed radiotherapy was 13.0 months (range, 0.5-68.5). Most patients received alectinib (44.6%) or ceritinib (33.8%) as their last prior ALK TKI before receiving lorlatinib. At the data cutoff, 26 (18.7%) patients were on treatment. Median treatment duration was EXP3B-5, 10.1 months (range, 0.2-43.2); EXP3B, 8.7 months (range, 0.3-39.9); and EXP4-5, 10.1 months (range, 0.2-43.2).

Overall efficacy

Among 139 patients with at least one prior second-generation ALK TKI (EXP3B-5), the ORR was 39.6% [95% confidence intervals (CI), 31.4-48.2], with three CRs and 52 PRs (Table 2, Figure 1A). At the data cutoff, 16 of 55 (29.1%) responses were ongoing, and the median DOR was 9.6 months (95% CI, 5.6-16.7). Median PFS was 6.6 months (95% CI, 5.4-7.4), with a median follow-up time for PFS of 30.6 months (95% CI, 26.2-33.8). Median OS was 20.7 months (95% CI, 16.1-30.3), with a median follow-up time for OS of 35.4 months (95% CI, 34.2-36.3); 82 (59.0%) patients had died by the data cutoff.

In patients with one prior second-generation ALK TKI (EXP3B), the ORR was 42.9% (95% CI, 24.5-62.8), with one CR and 11 PRs. Four (33.3%) responses were ongoing at the data cutoff, and the median DOR was 6.2 months (95% CI, 4.2-35.3). Median PFS was 5.5 months (95% CI, 2.9-8.2). Median OS was 38.5 months [95% CI, 12.3-not evaluable (NE)]; 13 (46.4%) patients had died.

Among patients with at least two prior TKIs (EXP4-5), the ORR was 38.7% (95% CI, 29.6-48.5), with two CRs and 41 PRs. Twelve (27.9%) responses were ongoing at the data cutoff, and median DOR was 9.9 months (95% CI, 5.7-16.7). Median PFS was 6.9 months (95% CI, 4.2-8.3). Median OS was 19.2 months (95% CI, 15.4-30.2); 69 (62.2%) patients had died. Efficacy data for patients who had received two (EXP4) or three prior ALK TKIs (EXP5) are reported in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2021.02.012.

Table 1. Demographics and baseline characteristics of patients with ≥1 prior second-generation ALK TKI

	≥1 prior second-generation ALK TKI ± CT (EXP3B-5) (*n* = 139)	1 prior second-generation ALK TKI ± CT (EXP3B) (*n* = 28)	≥2 prior ALK TKIs[a] ± CT (EXP4-5) (*n* = 111)
Age, years			
Median	52	54	51
Range	29-83	33-77	29-83
Sex, *n* (%)			
Female	78 (56.1)	16 (57.1)	62 (55.9)
Male	61 (43.9)	12 (42.9)	49 (44.1)
Race, *n* (%)			
White	66 (47.5)	7 (25.0)	59 (53.2)
Black	1 (0.7)	1 (3.6)	0
Asian	53 (38.1)	16 (57.1)	37 (33.3)
Other	6 (4.3)	1 (3.6)	5 (4.5)
Unspecified[b]	13 (9.4)	3 (10.7)	10 (9.0)
ECOG performance status, *n* (%)			
0	61 (43.9)	15 (53.6)	46 (41.4)
1	72 (51.8)	13 (46.4)	59 (53.2)
2	6 (4.3)	0 (0.0)	6 (5.4)
Brain metastases present at baseline,[c] *n* (%)	95 (68.3)	13 (46.4)	82 (73.9)
Patients with prior brain-directed radiation therapy, *n* (%)	67 (48.2)	8 (28.6)	59 (53.2)
Last prior ALK TKI before lorlatinib, *n* (%)			
Alectinib	62 (44.6)	13 (46.4)	49 (44.1)
Brigatinib	8 (5.8)	1 (3.6)	7 (6.3)
Ceritinib	47 (33.8)	13 (46.4)	34 (30.6)
Crizotinib	18 (12.9)	0	18 (16.2)
Other[d]	4 (2.9)	1 (3.6)	3 (2.7)

ALK, anaplastic lymphoma kinase; CNS, central nervous system; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EXP, expansion cohort; TKI, tyrosine kinase inhibitor.

[a] Lines of therapy; if the same TKI was given twice, it was counted as two previous lines of treatment.

[b] In France, information about race was not allowed to be collected per local regulations.

[c] By independent central review; includes measurable and non-measurable CNS lesions at baseline.

[d] Other TKIs included entrectinib and ensartinib.

Table 2. Efficacy overall and based on prior chemotherapy

	≥1 prior second-generation ALK TKI (EXP3B-5)	1 prior second-generation ALK TKI (EXP3B)	≥2 prior ALK TKIs (EXP4-5)
Overall			
N	139	28	111
ORR, *n* (%)	55 (39.6)	12 (42.9)	43 (38.7)
95% CI	31.4-48.2	24.5-62.8	29.6-48.5
Best overall response, *n* (%)			
Complete response	3 (2.2)	1 (3.6)	2 (1.8)
Partial response	52 (37.4)	11 (39.3)	41 (36.9)
Stable disease/no response	44 (31.7)	8 (28.6)	36 (32.4)
Progressive disease	28 (20.1)	6 (21.4)	22 (19.8)
Indeterminate	12 (8.6)	2 (7.1)	10 (9.0)
Duration of objective response,[a] months	*n* = 55	*n* = 12	*n* = 43
Median	9.6	6.2	9.9
95% CI	5.6-16.7	4.2-35.3	5.7-16.7
Progression-free survival,[a] months			
Median	6.6	5.5	6.9
95% CI	5.4-7.4	2.9-8.2	4.2-8.3
Overall survival,[a] months			
Median	20.7	38.5	19.2
95% CI	16.1-30.3	12.3-NE	15.4-30.2
Chemotherapy-pretreated			
N	93	12	81
ORR, *n* (%)	40 (43.0)	5 (41.7)	35 (43.2)
95% CI	32.8-53.7	15.2-72.3	32.2-54.7
Best overall response, *n* (%)			
Complete response	3 (3.2)	1 (8.3)	2 (2.5)
Partial response	37 (39.8)	4 (33.3)	33 (40.7)
Stable disease/no response	29 (31.2)	5 (41.7)	24 (29.6)
Progressive disease	18 (19.4)	2 (16.7)	16 (19.8)
Indeterminate	6 (6.5)	0	6 (7.4)
Chemotherapy-naive			
N	46	16	30
ORR, *n* (%)	15 (32.6)	7 (43.8)	8 (26.7)
95% CI	19.5-48.0	19.8-70.1	12.3-45.9
Best overall response, *n* (%)			
Complete response	0	0	0
Partial response	15 (32.6)	7 (43.8)	8 (26.7)
Stable disease/no response	15 (32.6)	3 (18.8)	12 (40.0)
Progressive disease	10 (21.7)	4 (25.0)	6 (20.0)
Indeterminate	6 (13.0)	2 (12.5)	4 (13.3)

ALK, anaplastic lymphoma kinase; CI, confidence interval; EXP, expansion cohort; NE, not evaluable; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
[a] Kaplan—Meier estimates; CIs were derived using the Brookmeyer Crowley method.

In patients who had previously received chemotherapy for advanced or metastatic disease, the ORR was 43.0% (95% CI, 32.8-53.7) for those who had received at least one prior ALK TKI (EXP3B-5), 41.7% (15.2-72.3) for those who had received one prior ALK TKI (EXP3B), and 43.2% (95% CI, 32.2-54.7) for those who had received at least two prior ALK TKIs (EXP4-5) (Table 2). Among patients who were chemotherapy-naive, the ORR was 32.6% (95% CI, 19.5-48.0) for those who had received at least one prior ALK TKI (EXP3B-5), 43.8% (19.8-70.1) for those who had received one prior ALK TKI (EXP3B), and 26.7% (95% CI, 12.3-45.9) for those who had received at least two prior ALK TKIs (EXP4-5).

Intracranial and extracranial efficacy

Of the 139 patients in EXP3B-5, 57 (41.0%) patients had measurable baseline CNS metastases. Among these, the intracranial ORR (IC-ORR) was 56.1% (95% CI, 42.4-69.3), with 12 CRs and 20 PRs. The extracranial ORR (EC-ORR) among all patients in EXP3B-5 was 36.7% (95% CI, 28.7-45.3), with five CRs and 46 PRs (Table 3, Figures 1B and C). For EXP3B-5, the median intracranial DOR (IC-DOR) was 12.4 months (95% CI, 6.0-37.1), and the median extracranial DOR (EC-DOR) was 9.7 months (95% CI, 6.1-33.3).

Among 9 of 28 (32.1%) patients in EXP3B with measurable baseline CNS metastases, the IC-ORR was 66.7% (95% CI, 29.9-92.5), with two CRs and four PRs. The EC-ORR among all patients in EXP3B was 32.1% (95% CI, 15.9-52.4), with one CR and eight PRs (Table 3). For EXP3B, the median IC-DOR was 20.7 months (95% CI, 4.1-37.1); the median EC-DOR was not evaluable (95% CI, 6.8-NE).

Among 48 of 111 (43.2%) patients in EXP4-5 with measurable baseline CNS metastases, the IC-ORR was 54.2% (95% CI, 39.2-68.6), with ten CRs and 16 PRs. The EC-ORR among all patients in EXP4-5 was 37.8% (95% CI, 28.8-47.5), with four CRs and 38 PRs. For EXP4-5, the median IC-DOR was 12.4 months (95% CI, 6.0-16.7), and the median EC-DOR was 7.1 months (95% CI, 5.6-32.2).

We have investigated the possibility that some of the observed responses attributed to lorlatinib were delayed response to radiotherapy. Efficacy analyses on intracranial

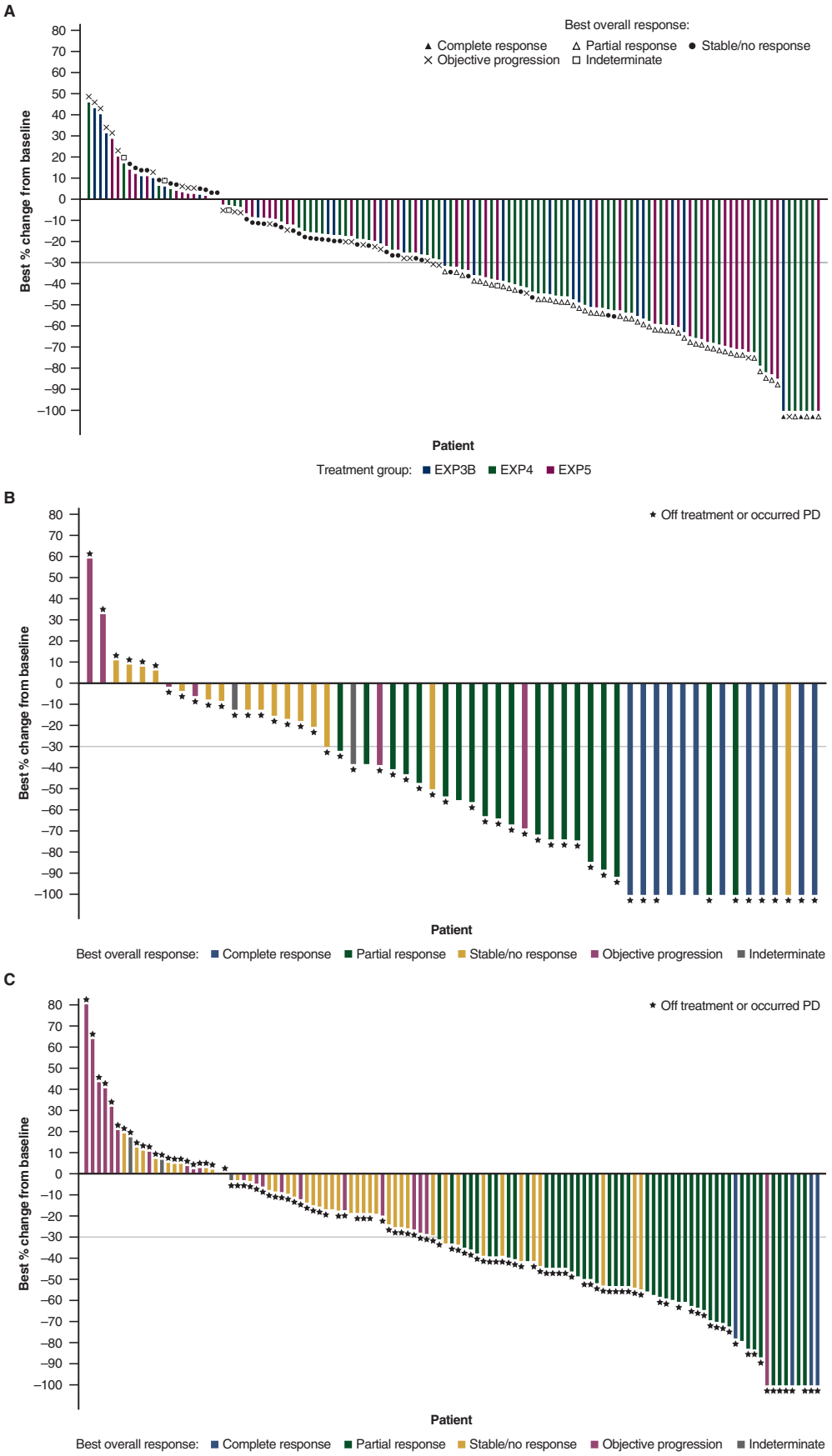

Figure 1. Best percent change in (A) all tumor size, (B) CNS metastases, and (C) extracranial tumor size from baseline in patients with at least one prior second-generation ALK TKI (EXP3B-5). Footnote to follow on the next page.

Table 3. Intracranial and extracranial efficacy

	≥1 prior second-generation ALK TKI (EXP3B-5)	1 prior second-generation ALK TKI (EXP3B)	≥2 prior ALK TKIs (EXP4-5)
Intracranial with ≥1 measurable CNS lesion			
N	57	9	48
IC-ORR, *n* (%)	32 (56.1)	6 (66.7)	26 (54.2)
95% CI	42.4-69.3	29.9-92.5	39.2-68.6
Best overall response, *n* (%)			
Complete response	12 (21.1)	2 (22.2)	10 (20.8)
Partial response	20 (35.1)	4 (44.4)	16 (33.3)
Stable disease/no response	16 (28.1)	0	16 (33.3)
Progressive disease	6 (10.5)	2 (22.2)	4 (8.3)
Indeterminate	3 (5.3)	1 (11.1)	2 (4.2)
Duration of IC objective response,[a] months			
Median	12.4	20.7	12.4
95% CI	6.0-37.1	4.1-37.1	6.0-16.7
Extracranial			
N	139	28	111
EC-ORR, *n* (%)	51 (36.7)	9 (32.1)	42 (37.8)
95% CI	28.7-45.3	15.9-52.4	28.8-47.5
Best overall response, *n* (%)			
Complete response	5 (3.6)	1 (3.6)	4 (3.6)
Partial response	46 (33.1)	8 (28.6)	38 (34.2)
Stable disease/no response	55 (39.6)	13 (46.4)	42 (37.8)
Progressive disease	21 (15.1)	4 (14.3)	17 (15.3)
Indeterminate	12 (8.6)	2 (7.1)	10 (9.0)
Duration of EC objective response,[a] months			
Median	9.7	NE	7.1
95% CI	6.1-33.3	6.8-NE	5.6-32.2

ALK, anaplastic lymphoma kinase; CI, confidence interval; CNS, central nervous system; EC, extracranial; EXP, expansion cohort; IC, intracranial; NE, not estimable; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
[a] Kaplan—Meier estimates; CIs were derived using the Brookmeyer Crowley method.

activity were also carried out by excluding patients who underwent prior radiotherapy <8 weeks and <12 weeks before start of lorlatinib (Supplementary Tables S4 and S5, available at https://doi.org/10.1016/j.annonc.2021.02.012). When excluding patients who had prior brain radiation either <8 or <12 weeks before start of lorlatinib therapy, the intracranial clinical efficacy (i.e. ORR and DOR) remained consistent with those reported for all patients with measurable brain metastases at baseline, suggesting that prior radiotherapy that was finished 8 or 12 weeks before lorlatinib treatment had no impact on intracranial efficacy.

Competing risk analysis showed that the probability of the first event being CNS progression was consistently lower than the first event being non-CNS progression, and in particular, in patients without baseline CNS metastases, the probability of an initial CNS progression remained consistently low across a 2-year period (Figures 2A and B).

Efficacy by last prior second-generation ALK TKI

Efficacy by last second-generation ALK TKI received before lorlatinib is summarized in Table 4. The ORRs (95% CI) among patients in EXP3B-5 who received alectinib, brigatinib, and ceritinib as the last prior ALK TKI before lorlatinib were 40.3% (28.1-53.6), 37.5% (8.5-75.5), and 40.4% (26.4-55.7), respectively. IC-ORRs were 40.5% (24.8-57.9), 40.0% (5.3-85.3), and 55.6% (38.1-72.1), respectively.

Safety

The safety profile of lorlatinib has been previously reported and was established based on all *ALK*/*ROS1*-positive patients who received the recommended dose of lorlatinib (100 mg QD) in the phase I/II study ($N = 295$).[10] With additional follow-up [median treatment duration, 16.33 months (range, 0.03-55.03)], no new safety signals were reported (Table 5). The most frequently reported treatment-related AEs (all grades) were hypercholesterolemia (84.4%), hypertriglyceridemia (67.1%), edema (45.8%), peripheral neuropathy (34.2%), cognitive effects (23.7%), weight increase (23.7%), and mood effects (15.6%). Fatigue was experienced by 10.2% of patients. Dose reductions occurred in 25.4% of patients, temporary dose interruptions occurred in 81.7% of patients, and 3.4% of patients discontinued treatment due to a treatment-related AE.

DISCUSSION

Despite the availability of effective second-generation ALK TKIs, CNS metastases and the development of resistance due to *ALK* mutations remain substantial obstacles in the treatment of advanced *ALK*-positive NSCLC.[1-5] In the

The best percent change from baseline was calculated from start of study treatment up to first visit with disease progression or to the last visit available before the start of new anticancer therapy in all patients (A), patients with intracranial disease (B), or patients with extracranial disease (C).
ALK, anaplastic lymphoma kinase; CNS, central nervous system; EXP, expansion cohort; PD, progressive disease; TKI, tyrosine kinase inhibitor.

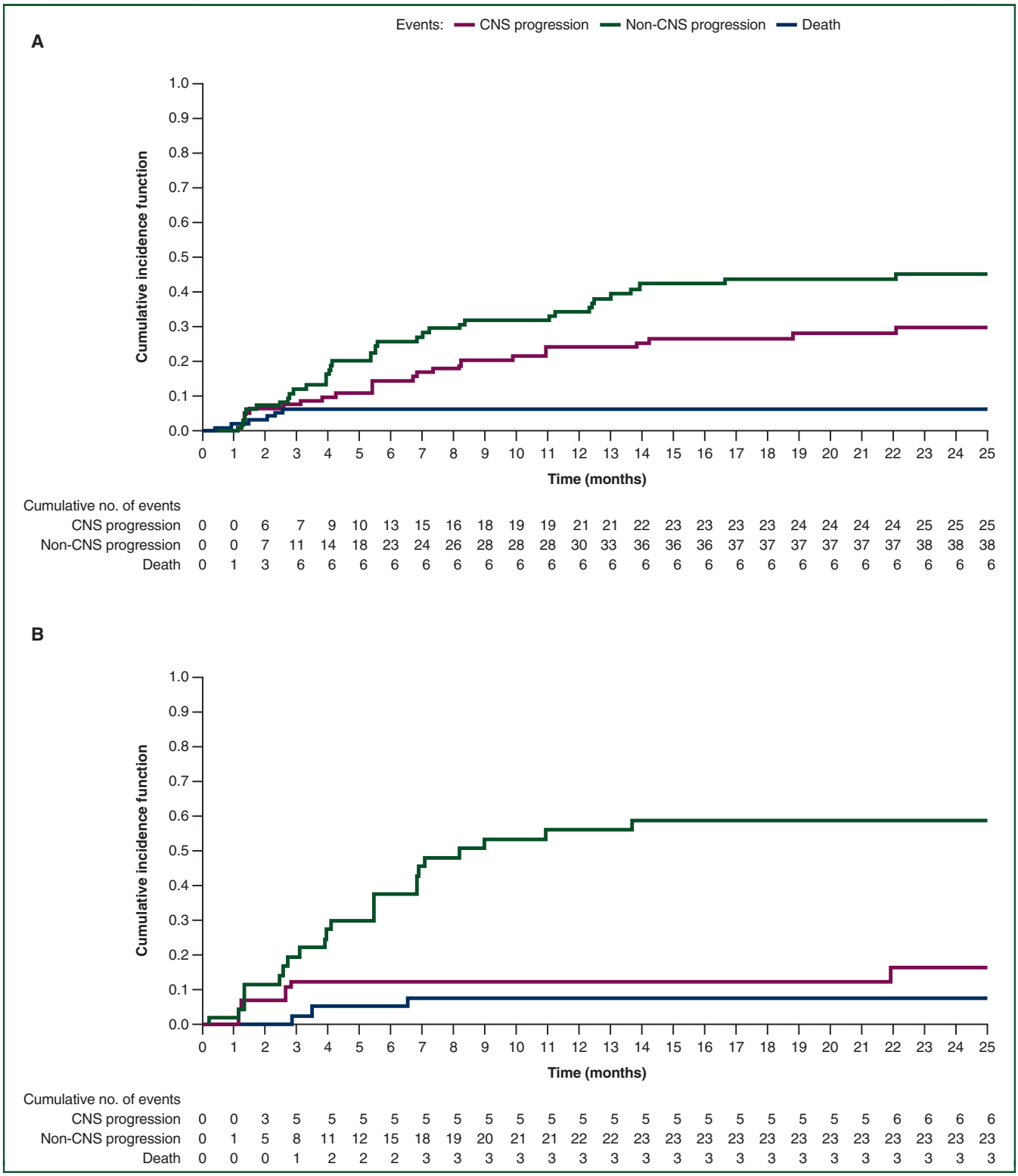

Figure 2. Cumulative incidence of CNS progression, non-CNS progression, or death in (A) patients with CNS metastases at baseline and (B) patients without CNS metastases at baseline.
CNS, central nervous system.

phase II portion of this open-label phase I/II study, lorlatinib, a third-generation inhibitor of ALK and ROS1, showed robust overall and intracranial antitumor activity in patients with *ALK*-positive advanced NSCLC who had previo usly received at least one second-generation ALK TKI. Among patients who had received at least one prior ALK TKI (EXP3B-5), the overall ORR was 39.6% (95% CI, 31.4-48.2), with median DOR of 9.6 months (95% CI, 5.6-16.7), whereas the IC-ORR was 56.1% (95% CI, 42.4-69.3), with median IC-DOR of 12.4 months (95% CI, 6.0-37.1). These updated

Table 4. Efficacy by last prior second-generation ALK TKI received

	Alectinib			Brigatinib			Ceritinib		
	EXP3B-5	EXP3B	EXP4-5	EXP3B-5	EXP3B	EXP4-5	EXP3B-5	EXP3B	EXP4-5
Overall									
N	62	13	49	8	1	7	47	13	34
ORR, *n* (%)	25 (40.3)	5 (38.5)	20 (40.8)	3 (37.5)	0	3 (42.9)	19 (40.4)	7 (53.8)	12 (35.3)
95% CI	28.1-53.6	13.9-68.4	27.0-55.8	8.5-75.5	0-97.5	9.9-81.6	26.4-55.7	25.1-80.8	19.7-53.5
Best overall response, *n* (%)									
Complete response	2 (3.2)	1 (7.7)	1 (2.0)	0	0	0	1 (2.1)	0	1 (2.9)
Partial response	23 (37.1)	4 (30.8)	19 (38.8)	3 (37.5)	0	3 (42.9)	18 (38.3)	7 (53.8)	11 (32.4)
Stable disease/no response	21 (33.9)	4 (30.8)	17 (34.7)	1 (12.5)	0	1 (14.3)	18 (38.3)	4 (30.8)	14 (41.2)
Progressive disease	12 (19.4)	3 (23.1)	9 (18.4)	3 (37.5)	1 (100)	2 (28.6)	7 (14.9)	2 (15.4)	5 (14.7)
Indeterminate	4 (6.5)	1 (7.7)	3 (6.1)	1 (12.5)	0	1 (14.3)	3 (6.4)	0	3 (8.8)
Progression-free survival, months[a]									
Median	5.5	5.5	5.6	2.8	1.2	4.8	6.9	6.9	6.9
95% CI	4.1-7.1	1.4-NE	4.1-8.2	1.4-NE	NE-NE	1.4-NE	5.5-11.1	5.4-16.7	3.9-12.5
Intracranial[b]									
N	37	2	35	5	1	4	36	10	26
IC-ORR, *n* (%)	15 (40.5)	0	15 (42.9)	2 (40.0)	0	2 (50)	20 (55.6)	6 (60.0)	14 (53.8)
95% CI	24.8-57.9	0-84.2	26.3-60.6	5.3-85.3	0-97.5	6.8-93.2	38.1-72.1	26.2-87.8	33.4-73.4
Best overall response, *n* (%)									
Complete response	9 (24.3)	0	9 (25.7)	1 (20)	0	1 (25)	11 (30.6)	2 (20)	9 (34.6)
Partial response	6 (16.2)	0	6 (17.1)	1 (20)	0	1 (25)	9 (25)	4 (40)	5 (19.2)
Stable disease/no response	16 (43.2)	1 (50)	15 (42.9)	1 (20)	0	1 (25)	9 (25)	2 (20)	7 (26.9)
Progressive disease	2 (5.4)	0	2 (5.7)	1 (20)	1 (100)	0	5 (13.9)	2 (20)	3 (11.5)
Indeterminate	4 (10.8)	1 (50)	3 (8.6)	1 (20)	0	1 (25)	2 (5.6)	0	2 (7.7)

ALK, anaplastic lymphoma kinase; CI, confidence interval; EXP, expansion cohort; IC, intracranial; NE, not estimable; ORR, objective response rate; TKI, tyrosine kinase inhibitor.
[a] Kaplan—Meier estimates; CIs were derived using the Brookmeyer Crowley method.
[b] By independent central review; includes measurable and non-measurable CNS lesions at baseline.

data are well aligned with outcomes previously reported for these cohorts.[8] Notably, our observations indicate that overall ORRs were similar regardless of whether patients had previously received treatment with chemotherapy.

Data with other ALK TKIs in the post-second-generation ALK TKI setting are still limited. In a retrospective multicenter study ($N = 22$), treatment with brigatinib in patients with alectinib-refractory, *ALK*-positive advanced NSCLC led to an ORR of 17% and median duration of treatment of 5.7 months (95% CI, 1.8-6.2).[11] In a phase II study in patients with alectinib-refractory, *ALK*-positive, metastatic NSCLC ($N = 20$) treated with ceritinib, the ORR was 25% (95% CI, 8.7-49.1), with median DOR of 6.3 months (95% CI, 3.5-9.2).[12] Similarly, modest efficacy has been observed with platinum/pemetrexed-based chemotherapy in patients with *ALK*-positive NSCLC refractory to second-generation ALK TKIs.[13]

Conversely, lorlatinib elicited remarkable responses in both the intracranial and extracranial compartments. As previously reported,[8] lorlatinib showed substantial intracranial activity in patients with pretreated *ALK*-positive NSCLC, with or without baseline CNS metastases, whose disease progressed on crizotinib or second-generation ALK TKIs. In the current analysis, IC-ORRs in patients with one prior second-generation ALK TKI (EXP3B), at least one prior second-generation ALK TKI (EXP3B-5), and at least two prior second-generation ALK TKIs (EXP4-5) were 66.7%, 56.1%, and 54.2%, respectively, whereas EC-ORRs were similar across the three cohorts (32.1%, 36.7%, and 37.8%, respectively). Our findings suggest elevated IC-ORR compared with EC-ORR. The intracranial efficacy of lorlatinib is of particular importance, given that progression in the brain remains a significant clinical problem in patients with NSCLC,[1-5] as highlighted by the high proportion of patients with brain metastases at baseline (68.3% in EXP3B-5) in our study. Recent data from the phase III CROWN study showed an IC-ORR of 82% (14/17) in patients with *ALK*-positive NSCLC and measurable brain metastases who were treated with lorlatinib in the first-line setting (DOR not estimable at data cutoff), compared with 23% (3/13) in patients who received crizotinib (DOR 9.4-11.1 months) in this setting.[14] Competing risk analysis remained consistent with earlier results,[15] showing a generally lower probability of first extracranial progression, supporting that lorlatinib may also prevent the spread of *ALK*-positive NSCLC to the brain.

Exploratory analyses conducted in subgroups defined by the last prior second-generation ALK TKI before lorlatinib treatment showed that ORRs and IC-ORRs were similar, irrespective of the last treatment received. Differences in the IC-ORRs might derive from the small sample size of the subgroup of patients with brain metastases at baseline.

The safety profile of lorlatinib was consistent with previous reports,[8,10] with no new safety signals identified in this updated analysis. Hypercholesterolemia and hypertriglyceridemia were the most frequently reported treatment-related AEs and were mostly grade 1 or 2 in severity. Phase I data showed that these events are typically easy to manage with appropriate lipid-lowering therapy and dose interruptions or modifications.[10]

This study was strengthened by its global, multicenter design; ability to compare intrapatient responses to

Table 5. Treatment-related adverse events in ≥5% of patients in the phase I/II study[a]

Adverse events, *n* (%)	Total (*N* = 295)				
	Total	Grade 1-2	Grade 3	Grade 4	Grade 5
Any treatment-related AE	281 (95.3)	139 (47.1)	119 (40.3)	23 (7.8)	0
Hypercholesterolemia[b]	249 (84.4)	197 (66.8)	47 (15.9)	5 (1.7)	0
Hypertriglyceridemia[b]	198 (67.1)	143 (48.5)	46 (15.6)	9 (3.1)	0
Edema[b]	135 (45.8)	129 (43.7)	6 (2.0)	0	0
Peripheral neuropathy[b]	101 (34.2)	95 (32.2)	6 (2.0)	0	0
Cognitive effects[b]	70 (23.7)	65 (22.0)	5 (1.7)	0	0
Weight increased	70 (23.7)	55 (18.6)	15 (5.1)	0	0
Mood effects[b]	46 (15.6)	43 (14.6)	3 (1.0)	0	0
Aspartate aminotransferase increased	38 (12.9)	37 (12.5)	1 (0.3)	0	0
Diarrhea	37 (12.5)	36 (12.2)	1 (0.3)	0	0
Arthralgia	35 (11.9)	34 (11.5)	1 (0.3)	0	0
Alanine aminotransferase increased	34 (11.5)	32 (10.8)	2 (0.7)	0	0
Lipase increased	31 (10.5)	15 (5.1)	12 (4.1)	4 (1.4)	0
Fatigue	30 (10.2)	29 (9.8)	1 (0.3)	0	0
Constipation	29 (9.8)	29 (9.8)	0	0	0
Vision disorder[b]	28 (9.5)	28 (9.5)	0	0	0
Dizziness	27 (9.2)	24 (8.1)	3 (1.0)	0	0
Nausea	27 (9.2)	27 (9.2)	0	0	0
Amylase increased	26 (8.8)	22 (7.5)	4 (1.4)	0	0
Speech effects[b]	25 (8.5)	24 (8.1)	1 (0.3)	0	0
Anemia	21 (7.1)	18 (6.1)	3 (1.0)	0	0
Asthenia	21 (7.1)	21 (7.1)	0	0	0
Headache	21 (7.1)	21 (7.1)	0	0	0
Myalgia	20 (6.8)	20 (6.8)	0	0	0
Psychotic effects[b]	19 (6.4)	17 (5.8)	1 (0.3)	1 (0.3)	0
Sleep effects[b]	19 (6.4)	19 (6.4)	0	0	0
Rash	17 (5.8)	16 (5.4)	1 (0.3)	0	0
Blood creatinine phosphokinase increased	16 (5.4)	15 (5.1)	1 (0.3)	0	0
Electrocardiogram QT prolonged	16 (5.4)	15 (5.1)	1 (0.3)	0	0
Tinnitus	16 (5.4)	16 (5.4)	0	0	0
Hypertension	15 (5.1)	8 (2.7)	7 (2.4)	0	0
Vomiting	15 (5.1)	14 (4.7)	1 (0.3)	0	0

AE, adverse event; ALK, anaplastic lymphoma kinase; QD, once daily; *ROS1*, *ROS* proto-oncogene 1.
[a] Based on all *ALK*-positive/*ROS1*-positive patients who received the recommended dose of lorlatinib (100 mg QD) in the phase I/II study.
[b] Refers to AE cluster terms of cognitive effects, edema, hypercholesterolemia, hypertriglyceridemia, mood effects, peripheral neuropathy, psychotic effects, sleep effects, speech effects, vision disorder.

lorlatinib and prior ALK TKI; increased precision of prospective intracranial assessments due to modified RECIST v1.1, which allowed assessment for up to five CNS target lesions; broad extracranial and intracranial activity, regardless of the multiple prior therapies received; and favorable duration of follow-up. As a single-arm trial that did not include a randomized comparison to standard treatment, this study was limited by the relatively small numbers of patients in subgroups, including those who progressed on a second-generation ALK TKI (EXP3B), and the heterogeneity of subgroups based on the number of prior ALK TKIs. Further limitations were that information regarding the technique used for any prior brain radiotherapy (e.g. whole-brain or stereotactic ablative radiotherapy) and the status of CNS metastases at baseline (stable or progressive) were not collected. Studies to further assess the efficacy of lorlatinib in the post-second-generation ALK TKI setting are ongoing (ClinicalTrials.gov, NCT04362072 and NCT04111705).

In conclusion, these updated efficacy data from the phase II portion of this study further support that lorlatinib has robust intracranial and extracranial antitumor activity in the post-second-generation ALK TKI setting in patients with advanced *ALK*-positive NSCLC. The safety profile of lorlatinib also remained favorable in this population of patients. Thus, lorlatinib provides an effective treatment option for patients with *ALK*-positive advanced NSCLC who have progressed on second-generation ALK TKIs.

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DATA SHARING

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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