European Journal of Cancer 166 (2022) 51–59

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Lorlatinib for advanced anaplastic lymphoma kinase–positive non–small cell lung cancer: Results of the IFCT-1803 LORLATU cohort

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https://doi.org/10.1016/j.ejca.2022.01.018

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Received 31 October 2021; received in revised form 3 January 2022; accepted 9 January 2022
Available online 9 March 2022

KEYWORDS
Non–small cell lung cancer;
ALK;
Tyrosine kinase inhibitor;
Lorlatinib;
Resistance

Abstract ***Background:*** Anaplastic lymphoma kinase (*ALK*)-*rearranged* (*ALK*+) non–small cell lung cancer (NSCLC) represents a rare subset of lung cancer, with specific presentation, and multiple treatment options, including selective tyrosine kinase inhibitors (TKIs). Real-world evidence is insufficient regarding the actual real-life treatment sequences in the late line setting, and available clinical trials may not reflect real-world situation. Here, we took advantage of the French Expanded Access Program (EAP) of lorlatinib, a third-generation TKI targeting ALK and ROS1, to assess treatment sequencing, and lorlatinib efficacy and safety, in patients with *ALK*+ NSCLC.
Methods: All consecutive patients with advanced *ALK*+ NSCLC treated between October 2015 and June 2019 with lorlatinib as part of EAP were included. Data were collected and reviewed from medical records by independent research staff of the French Thoracic Cancer Intergroup. The primary endpoint was progression-free survival (PFS).
Results: Of the 208 patients included, 117 (56%) were female, 142 (69%) were never smokers, and 180 (87%) had stage IV NSCLC at diagnosis. The most frequent histology was adenocarcinoma (94%), and the median age was 60.9 years. At the time of lorlatinib initiation, 160 (77%) patients had brain metastases, and 125 (72%) were performance status 0/1. Lorlatinib was delivered as 2nd/3rd/4th/5th+ line in 4%/17%/30%/49% of patients. A total of 162 (78%) patients had previously been treated with chemotherapy, 194 (93%) with a first-generation ALK-TKI, 195 (94%) with a second-generation ALK-TKI. The median follow-up from lorlatinib initiation was 23.3 months. The median PFS, median overall survival (OS) from lorlatinib initiation and median OS from advanced NSCLC diagnosis were 9.9 months (95% confidence interval [CI] 6–12.3 months), 32.9 months (95% CI 18.7 months to not reached) and 97.3 months (95% CI 75.7–152.8 months), respectively. The median duration of treatment with lorlatinib was 11.8 months (95% CI 8.5–18.8 months). Overall response and disease control rate were 49% and 86%, respectively. Central nervous system objective response rate was 56%. Treatment was stopped due to toxicity in 28 patients (14%). The safety profile of lorlatinib was consistent with previously published data.
Conclusions: Real-world evidence indicates that lorlatinib offers a significant clinical benefit and high intracerebral antitumour activity in heavily pretreated patients with *ALK*+ NSCLC.
ClinicalTrials.gov identifier: NCT03727477.

1. Introduction

Three to five percent of non–small cell lung cancers (NSCLCs) display a rearrangement of the anaplastic lymphoma kinase (*ALK*) gene [1,2]. This alteration leads to the synthesis of a chimeric protein encompassing the ALK tyrosine kinase domain and driving the oncogenic process. *ALK*-positive (*ALK*+) NSCLCs represent a distinct subset of patients with aggressive disease that has a propensity towards central nervous system (CNS) involvement [3,4]. Based on current European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, the treatment strategy for metastatic ALK+ NSCLC mainly relies on ALK tyrosine kinase inhibitors (TKIs) [5,6]. Crizotinib has been the first ALK-TKI to demonstrate superiority over platinum-based chemotherapy as first-line treatment [7]. Subsequently, the so-called second-generation ALK-TKI, such as ceritinib, alectinib or brigatinib, showed superior efficacy in front line setting

compared with chemotherapy or crizotinib [8–10]. However, all patients eventually develop tumour progression because of resistance mechanisms, such as alternative signalling pathway activation or emergence of mutations within the ALK kinase domain, or pharmacodynamic patterns [11,12].

Lorlatinib is a third-generation, reversible adenosine tri phosphate (ATP) competitive TKI of ALK and ROS1 covering most ALK-TKI resistance mutations, including the G1202R frequently found after second-generation TKI resistance [11,13]. In addition, lorlatinib has a significant penetration in the CNS, a frequent site of recurrence under ALK-TKI. Its efficacy in TKI-pretreated *ALK*+ NSCLC was evaluated in an uncontrolled, multicohort phase I/II clinical trial [14]. This trial led to its approval in Europe in metastatic *ALK*+ NSCLC after the failure of ceritinib or alectinib or after receiving crizotinib and at least one other ALK-TKI.

Few real-world evidence is available regarding treatment sequences and outcomes [15]. Here, we took advantage of the French Expanded Access Program (EAP) of lorlatinib to assess treatment sequencing, and lorlatinib efficacy and safety, in patients with *ALK*+ NSCLC.

2. Materials and methods

2.1. Study population and data collection

Consecutive adult patients, from 74 centres, with an advanced or metastatic *ALK*+ NSCLC, treated from October 2015 to June 2019 as part of the EAP with lorlatinib, 100 mg once daily for at least 7 d, were included in the present study. Patients were eligible for lorlatinib EAP if they had failed at least one line of ALK-TKI. The EAP database allowing patient identification was provided by Pfizer.

Data and survival follow-up were extracted from medical records by investigators in each centre and documented in a standard case report form. Database is hosted by the French Collaborative Thoracic Intergroup (IFCT) that ensured the quality of the data collected by monitoring the centres with periodic visits of IFCT clinical research associates.

2.2. Study oversight

This non-interventional study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, approved by a national ethics committee, French Advisory Committee on Information Processing in Material Research in the Field of Health, and France's national data protection authority (CNIL) in accordance with General Data Protection Regulation. All participating departments approved the study protocol, and all included patients still alive received information from their referring physician, with an opportunity not to participate.

2.3. Study endpoints

The primary endpoint was progression-free survival (PFS) measured from the date of first lorlatinib dose to the date of disease progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or death from any cause. Secondary endpoints included objective response rate (ORR) defined as the percentage of patients with partial or complete response to lorlatinib according to RECIST 1.1 evaluated by investigators; disease control rate (DCR) defined as the percentage of patients with partial or complete response or stable disease to lorlatinib according to RECIST 1.1 evaluated by investigators; overall survival (OS) calculated from the date of the lorlatinib first dose to the date of death from any cause; OS calculated from the date of advanced or metastatic NSCLC diagnosis; duration of treatment (DOT) measured from the date of lorlatinib first dose to the date of treatment discontinuation or death from any cause during the study; DOT response measured from the date of first lorlatinib RECIST 1.1 tumour response to the date of disease progression or death from any cause; CNS response rate defined as the rate of intracranial tumour response to lorlatinib according to RECIST 1.1 evaluated by investigators among patients with brain metastasis; and duration of CNS response, defined as the time from the first documentation of objective cerebral response to the first documentation of cerebral progression or to death from any cause. ORR, PFS and DOT were also collected for subsequent treatments after lorlatinib failure. Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0. Only grade 3 to 5 adverse events were recorded.

2.4. Statistical analysis

Categorical variables are expressed as frequencies and percentages. Quantitative variables are expressed as medians (range). The Kaplan–Meier method was used to estimate PFS and OS endpoints. The cut-off date for survival analysis was 2nd February 2020. All analyses were performed using SAS software, Version 9.4 (SAS Institute).

3. Results

3.1. Clinicopathological characteristics

Among the 343 patients identified in the lorlatinib EAP database, 208 met the predefined inclusion criteria (Supplementary Fig. 1). Patient characteristics are summarised in Table 1. Most patients were women

Table 1
Demographics of the cohort.

Characteristics	N = 208 (%)
Gender	
Male	91 (44)
Female	117 (56)
Median age (years, range)	60.9 (20.7–83.8)
Smoking status	
Current or former smokers	64 (31)
Never smokers	142 (69)
Unknown	2
TNM staging at diagnosis	
I–II	4 (2)
III	24 (12)
IV	180 (86)
Brain metastasis at diagnosis	
Present	59 (28)
Absent	149 (72)
Histology	
Adenocarcinoma	195 (94)
Squamous carcinoma	5 (2)
Other	8 (4)
PS at lorlatinib initiation	
0–1	125 (72)
≥2	48 (28)
Unknown	35
Previous lines of systemic therapy	
1	8 (4)
2	36 (17)
3	62 (30)
≥4	102 (49)
Previous systemic therapy	
Chemotherapy	162 (78)
First-generation ALK-TKI	194 (93)
Second-generation ALK-TKI	195 (94)
Immune checkpoint inhibitors	10 (5)
Previous lines of ALK-TKI	
1	20 (9)
2	120 (58)
≥3	68 (33)
Previous brain radiotherapy	95 (46)
Brain metastasis at lorlatinib initiation	
Present	160 (77)
Absent	48 (23)

ALK, anaplastic lymphoma kinase; PS, performance status; TKI, tyrosine kinase inhibitor.

(56%), never smokers (69%) and displayed a stage IV disease at diagnosis (87%). The median age was 60.9 years (range 20.7–83.8). The most frequent histology was adenocarcinoma (94%). At lorlatinib initiation, most of the patients had a good performance status (PS 0–1: 72% of patients) and had brain metastases (77%). Patients were heavily pretreated because 79% of them had previously received at least three lines of systemic treatment, and 46% also had been treated with brain radiation therapy. Moreover, all patients had been previously treated with at least one ALK-TKI, 93% had received a first-generation ALK-TKI – crizotinib, and 94% had received a second-generation ALK-TKI – ceritinib, alectinib or brigatinib. At lorlatinib initiation, the number of patients who had previously received 1/2/3 or more lines of ALK-TKI were, respectively, 20 (9%)/120 (58%)/68 (33%).

3.2. Clinical outcomes

The median follow-up from lorlatinib initiation was 23.3 months (interquartile range: 16.5–29.5; Table 2). The median PFS and median OS from lorlatinib initiation were, respectively, 9.9 months (95% confidence interval [CI] 6.0–12.3 months) and 32.9 months (95% CI 18.7 months to not reached [NR]; Figs. 1 and 2). The median OS from advanced or metastatic NSCLC diagnosis was 97.3 months (95% CI 75.7–152.8 months). Of the 208 patients, 191 were assessable for response. Among these patients, ORR and DCR to lorlatinib treatment were, respectively, 49% and 86%. The median duration of response was 14.9 months (95% CI 10.1 months to NR). The CNS response rate was 56%, and the median duration of CNS response was 16.7 months (95% CI

Table 2
Lorlatinib therapy clinical outcome.

Characteristics	n = 208 (%)
Median follow-up (IQR, months)	23.3 (16.5–29.5)
Median PFS (95% CI, months)	9.9 (6.0–12.3)
Median OS (95% CI, months)	32.9 (18.7 to NR)
Median OS from advanced or metastatic NSCLC diagnosis (95% CI)	97.3 (75.7–152.8)
Best response to lorlatinib (n, %)	
Number of patients with available data	191 (92)
Complete response	8 (4)
Partial response	85 (45)
Objective response	93 (49)
Stable disease	71 (37)
Progression	25 (13)
Not evaluable	2 (1)
Median duration of response (95% CI, months)	14.9 (10.1 to NR)
CNS objective response[a] (available data; %)	84 (/149; 56)
CNS objective response in patients with prior brain radiotherapy[a] (available data; %)	38 (/82; 46)
CNS objective response in patients without prior brain radiotherapy[a] (available data; %)	46 (/67; 69)
Median duration of CNS response (95% CI, months)	16.7 (10.1 to NR)
Median duration of CNS response in patients with prior brain radiotherapy (95% CI, months)	17.9 (10.1 to NR)
Median duration of CNS response in patients without prior brain radiotherapy (95% CI, months)	13.4 (6.4 to NR)
Median lorlatinib duration (95% CI, months)	11.8 (8.5–18.8)
Median lorlatinib duration beyond progression (95% CI, months)	1.61 (0.76–4.01)
Treatment discontinuation	112 (54)
Cause of treatment discontinuation	
Disease progression	60 (29)
Toxicity	28 (14)
Death	15 (7)
Investigator's decision	7 (3)
Patient's decision	1 (1)
Intercurrent disease	1 (1)

PFS, progression-free survival; OS, overall survival; CNS, central nervous system; NSCLC, non–small cell lung cancer.
[a] Defined as the rate of intracranial tumour response according RECIST v1.1.

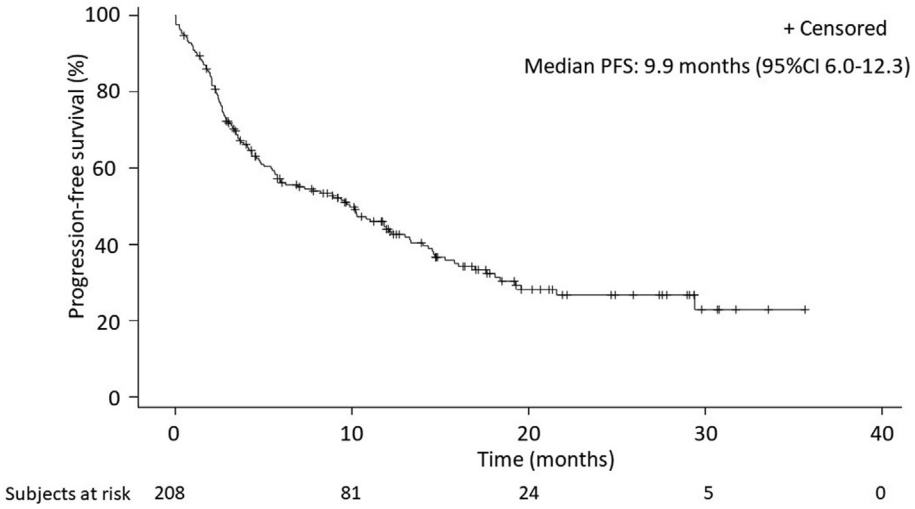

Fig. 1. Progression-free survival. Kaplan–Meier estimate of progression-free survival (PFS). Tick marks on the survival curves indicate censoring of data. CI, confidence interval.

10.12 months to NR). The CNS response rate and the median duration of CNS response were, respectively, 46% and 17.9 months among patients who received brain radiotherapy prior lorlatinib and 69% and 13.4 months among patients who did not receive this treatment. Overall, 107 patients experienced tumour progression, and the two main sites of relapse were the thorax and the brain (Supplementary Fig. 2). The median duration of lorlatinib treatment was 11.8 months (95% CI 8.5–18.8 months). When lorlatinib was continued beyond progression (n = 89), the median DOT was 1.6 months (95% CI 0.8–4.0 months). Among the patients who had received before lorlatinib initiation only one previous ALK-TKI, two previous ALK-TKIs, and three or more ALK-TKIs, the median PFS and OS were 10.3 months (95% CI 2.3 months to NR) and NR, 11.8 months (95% CI 7.3–14.6 months) and 32.9 months (95% CI 17.6 months to NR), and 5.8 months (95% CI 3.7–10.2 months) and 18.7 months (95% CI 11.6 months to NR), respectively. The ORR depending on whether patients had received one previous ALK-TKI, two previous ALK-TKI and three or more previous ALK-TKI before lorlatinib initiation were 63%, 47% and 47%, respectively.

3.3. Safety

Grade 3 to 5 adverse events occurred in 30% of the patients (Table 3). The most common grade 3 or more adverse events were elevated cholesterol levels (12%), cognitive effects (5%), elevated triglyceride levels (4%), peripheral neuropathies (2%), oedema (2%), left

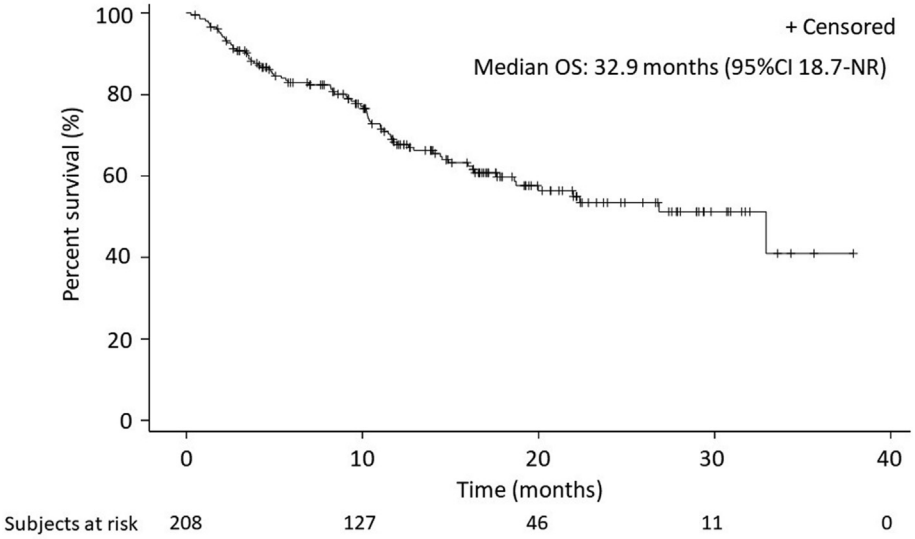

Fig. 2. Overall survival. Kaplan–Meier estimate of overall survival (OS) measured from lorlatinib initiation. Tick marks on the survival curves indicate censoring of data. CI, confidence interval. NR, not reached.

Table 3
Serious adverse events in patients treated with lorlatinib (reported in more than 1% of patients).

Total	n = 208 (%)			
	Grade 3–5	Grade 3	Grade 4	Grade 5
Any adverse event	62 (30)	48 (23)	13 (6)	1 (1)
Hypercholesterolaemia	24 (12)	17 (8)	7 (3)	0 (0)
Cognitive effect	11 (5)	10 (5)	1 (0.5)	0 (0)
Hypertriglyceridemia	8 (4)	6 (3)	2 (1)	0 (0)
Peripheral neuropathy	5 (2)	5 (2)	0 (0)	0 (0)
Oedema	5 (2)	5 (2)	0 (0)	0 (0)
Ejection fraction decrease	4 (2)	4 (2)	0 (0)	0 (0)
Mood effect	3 (1)	2 (1)	1 (0.5)	0 (0)
Fatigue	3 (1)	2 (1)	1 (0.5)	0 (0)
Arthralgia	2 (1)	2 (1)	0 (0)	0 (0)
Pulmonary hypertension	2 (1)	1 (0.5)	1 (0.5)	0 (0)

ventricular ejection fraction decreases (2%) and mood effects (1%). Fatal adverse events occurred in one patient who died from hypercapnic acute respiratory failure. Adverse events leading to treatment discontinuation occurred in 14% of the patients included in the study. They were mainly represented by cognitive effects, arthralgia, left ventricular ejection fraction decreased, mood effects, oedema and pulmonary hypertension (Supplementary Table S1).

3.4. Subsequent therapy

After lorlatinib treatment, 66 patients received at least one subsequent systemic therapy mainly represented by chemotherapy and second-generation ALK-TKI (Supplementary Table S2 and Supplementary Fig. 3). Apart from a higher proportion of women, the characteristics of patients who received subsequent systemic therapy were broadly similar to those who did not receive any systemic therapy after lorlatinib (Supplementary Table S3). Among the subsequent treatments given as first or second line after discontinuation of lorlatinib, ALK-TKI had the longest median DOT followed by platinum-doublet chemotherapy, immunotherapy and non-platinum-based chemotherapy (Supplementary Table S2). For the 33 patients who received an ALK-TKI as the first subsequent line after the lorlatinib, the ORR and the median PFS were 24% and 4 months (95% CI 2.8–8.7 months; Supplementary Table S4). The OS from the initiation of ALK-TKI as the first subsequent line after the lorlatinib was 21.9 months (95% CI 16–21.9 months).

4. Discussion

LORLATU cohort represents the largest real-life study describing the efficacy and safety of lorlatinib after the failure of at least one ALK-TKI in *ALK*+ NSCLC. This study confirms the efficacy of lorlatinib in this setting. Indeed, we observed an ORR of 49% and a median PFS of 9.9 months with lorlatinib, close to the ORR of 47% and a median PFS of 7.3 months reported among the 198 patients pretreated with at least one ALK-TKI in the pivotal phase II study [14]. In our cohort, The CNS response rate of 56.4% and the median duration of the CNS response of 16.7 months were also close to the 63% of intracranial objective response and the 14.5 months of median duration of intracranial response described in a study by Solomon *et al.* In addition, the CNS response rate was 69% in patients who were naive of cerebral radiation with a median duration of intracranial response of 13.4 months. These results were indicative of significant intracerebral antitumour activity. As expected, we found a decrease in the lorlatinib efficacy with the number of lines of previous ALK-TKIs received; this was also observed in the phase II clinical trial and in a real-life study [14,16]. In our study, for instance, the PFS decreased from 11.7 months to 5.8 months depending on whether patients had received two or more previous ALK-TKIs. These results suggest a benefit of using lorlatinib early in the patient's management and highlight the need for further analysis of treatment sequences. However, the question of where to place lorlatinib in the treatment sequence has recently become more complex, with the results of the phase 3 CROWN trial showing the superiority first-line setting of lorlatinib over crizotinib in terms of PFS [17]. In the absence of a direct comparison of first-line lorlatinib with second-generation ALK-TKIs, it is difficult to provide a definitive answer.

The safety profile of lorlatinib was consistent with previously published data [14,16–18]. The most common serious adverse events were metabolic disorders such as hypercholesterolaemia or hypertriglyceridemia, neurological disorders such as cognitive impairment, peripheral neuropathy or mood disorders, and oedema. Although the median DOT between our study and the pivotal phase 2 trial was comparable (7.6 months versus 8.3 months), the frequency of grade 3 or higher hypercholesterolaemia and hypertriglyceridemia was lower in our study compared with the pivotal phase 2 trial (12% versus 15% and 4% versus 16%, respectively). However, these frequencies were comparable to those obtained in other real-life studies [16,18]. These discrepancies could be related to the fact that patient follow-up is probably less protocolised and less rigorous in real-life situations. Interestingly, the frequency of discontinuation of treatment due to toxicity was higher in our study than in the Salomon *et al.* trial (14% versus 3%). In both cases, the main cause of discontinuation was cognitive effects, highlighting the difficulty of managing this kind of adverse event.

Most patients in our study received at least one additional line of systemic therapy after stopping lorlatinib, mainly chemotherapy or ALK-TKIs. There are very few data on the use of ALK-TKIs after progression on lorlatinib. A real-life study reported a PFS of 7.5 months with brigatinib in 37 patients pretreated with

lorlatinib [19]. Here we observed a median PFS of 4.0 months and an ORR of 24% among 33 patients treated with an ALK-TKI as the first subsequent therapy after lorlatinib. Moreover, ALK-TKI had the longest median DOT among subsequent therapies after discontinuation of lorlatinib. Further investigation, including an exhaustive description of the mechanisms of resistance to lorlatinib, is needed to address this question of the ALK-TKI therapy after lorlatinib failure.

Our study has several limitations mainly related to its retrospective nature. This type of design prevents standardisation of the tumour follow-up and evaluation of adverse events. Moreover, because of this retrospective design, centralisation of RECIST evaluations and molecular analyses was not feasible. Because of the lack of systematic molecular analysis at tumour progression with ALK-TKIs, these real-life data do not allow us to evaluate the efficacy of lorlatinib according to the mechanisms of resistance to the ALK-TKI previously received. Indeed, while preclinical data show that lorlatinib is effective against most resistance mutations to first- or second-generation ALK-TKIs, its efficacy may be reduced in the presence of an off-target resistance mechanism, such as *MET* or *HER2* amplification or *KRAS* mutation [11,20–22]. The value of lorlatinib compared with other systemic treatments such as chemotherapy could be questioned in the presence of such alterations. For similar reasons, we were also not able to evaluate the impact of the EML4-ALK fusion variants on lorlatinib efficacy. Finally, because of the absence of systematic molecular analysis at tumour progression, we cannot describe the mechanisms of resistance to lorlatinib. The ongoing IFCT-1902 ORAKLE trial evaluating the efficacy of lorlatinib after a first-line with alectinib or brigatinib has planned to centralise molecular testing and will provide important data on these issues.

In conclusion, this study confirms the position of lorlatinib as an effective rescue treatment after resistance to first- and second-generation ALK-TKIs. The overall safety profile was favourable, although neurological side-effects could lead to treatment discontinuation. The recent results from the phase 3 CROWN trial demonstrating the superiority of lorlatinib over crizotinib in the first-line setting will complexify treatment sequences for ALK+ NSCLC [17]. However, in *ALK*+ NSCLC, first-line treatment is now based on second-generation ALK-TKIs, and the optimal sequencing of ALK-TKIs remains to be further analysed.

Author contributions

N.G. and S.B. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. N.G. contributed to concept and design and supervision and obtained funding. All authors contributed to acquisition, analysis or interpretation of data and critical revision of the article of important intellectual content. N.G. and S.B. drafted the article. A.L. contributed to statistical analysis. F.M. and A.L. contributed to administrative, technical or material support.

Funding

The study was sponsored by the IFCT and funded by an unrestricted grant from Pfizer. The funding source had no role in the design, data collection, analysis or interpretation of the study or in the preparation of this article.

Conflict of interest statement

S.B., V.A., X.Q., M.D., C.C.-D., S.C., C.R., P.M., J.O., S.S., F.M., A.L. and N.G. report no conflict of interest. S.B. reports non-financial support from Lilly, GSK, Roche and Pfizer, personal fees from Roche and Boehringer ingelheim and grants from Intergroupe Francophone de Cancérologie Thoracique. B.B. reports grants from Abbvie, Amgen, Aptitude Health, AstraZeneca, BeiGene, Blueprint Medicines, BMS, Boehringer Ingelheim, Celgene, Cergentis, Cristal Therapeutics, Daiichi-Sankyo, Eli Lilly, GSK, Inivata, Janssen, Onxeo, OSE immunotherapeutics, Pfizer, Roche-Genentech, Sanofi, Takeda and Tolero Pharmaceuticals. B.M. reports consulting fees from Pfizer and served as a consultant (Data Safety Monitoring or Advisory Boards) for Pfizer. J.M. served as a consultant (Advisory Board) for Merck, Roche, AstraZeneca, MSD, BMS, Pfizer, Hengrui, Daiichi, Boehringer and Pierre Fabre and reports research grants from Roche, AstraZeneca, Pierre Fabre. P.D.-L. reports grants from MSD and AstraZeneca and non-financial support from Chugai. A.B.C. reports consulting fees from Novartis and Roche, honoraria from Novartis, Pfizer and Takeda and served as a consultant (Data Safety Monitoring or Advisory Boards) for Roche, Novartis, Pfizer, and Takeda. R.D. reports support for attending meetings and/or travel from Takeda, Roche and Pfizer and served as a consultant (Data Safety Monitoring or Advisory Boards) for Takeda, Roche, Pfizer and Novartis. Dr. Houbre reports support for attending meetings and/or travel from Leo Pharma, BMS, Roche and Pfizer and served as a consultant (Data Safety Monitoring or Advisory Boards) for BMS and Amgen. X.Q. reports support for attending meetings and/or travel from Pfizer. I.M. reports non-financial support from Pfizer and Roche. D.M.-S. reports grants from Pfizer, Roche, AstraZeneca, BMS and MSD, personal fees from Pfizer, Roche, Takeda, AstraZeneca, Lilly, BMS, MSDN,

Novartis, Amgen, Abbvie and Becton Dickinson and non-financial support from Pfizer, Roche, Takeda, AstraZeneca, BMS and MSD. J.C. reports personal fees from Pfizer, Roche, Takeda, Novartis, AstraZeneca, MSD, BMS and Boehringer Ilgenheim. V.W. reports honoraria from Roche, AstraZeneca, BMS and MSD and non-financial support from Roche and Pfizer. NG reports grants and personal fees from Bristol Myers Squibb, grants and personal fees from MSD, grants and personal fees from Roche, grants and personal fees from Novartis, grants and personal fees from Astra Zeneca, grants and personal fees from Janssen, grants and personal fees from Pfizer, grants and personal fees from Sanofi, grants and personal fees from Lilly, grants and personal fees from Amgen, grants from Boehringer Ingelheim, grants from Beigene, grants from Daiichi Sankyo, outside the submitted work.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.01.018.

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