Lung Cancer: Targets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Alectinib Efficacy Post-Brigatinib Against Advanced *ALK*+ Non-Small Cell Lung Cancer (BrigALK2-GFPC 02-2019 Study)

Renaud Descourt[1], Florian Guisier[2], Maurice Pérol[3], Jacques Cadranel[4], Helene Doubre[5], Michael Duruisseaux[6–8], Stéphane Culine[9], Bertrand Mennecier[10], Olivier Bylicki[11], Christos Chouaid[12], Laurent Greillier[13]

[1]Hopital La Cavale Blanche, CHU Brest, Brest, France; [2]CHU Rouen, Rouen, France; [3]CLCC Léon-Bérard, Lyon, France; [4]Hôpital Tenon, Assistance Publique des Hôpitaux de Paris, Paris, France; [5]Hôpital Foch, Suresnes, France; [6]Department of Respiratory Medicine and Early Phase (EPSILYON), Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, Lyon, France; [7]Oncopharmacology Laboratory, Cancer Research Centre of Lyon, UMR INSERM 1052 CNRS 5286, Lyon, France; [8]Claude Bernard University Lyon 1, University of Lyon, Lyon, France; [9]Hôpital Saint-Louis, Assistance Publique des Hôpitaux de Paris, Paris, France; [10]CHU Nancy, Nancy, France; [11]HIA Sainte-Anne, Toulon, France; [12]CHI Créteil, Créteil, France; [13]Assistance Publique-Hôpitaux de Marseille, Hôpital Nord, Aix–Marseille Université, Marseille, France

Correspondence: Renaud Descourt, Oncology department, Cavale Blanche Hospital, Brest University Hospital, Boulevard Tanguy-Prigent, Brest, 29200, France, Email renaud.descourt@chu-brest.fr

Background: Brigatinib and alectinib are next-generation anaplastic lymphoma kinase inhibitors (ALKis) showing efficacy against naïve and post-crizotinib-treated advanced *ALK*+ non-small-cell lung cancers (NSCLCs). Real-world data on alectinib efficacy after brigatinib failure are lacking.

Methods: Alectinib efficacy was retrospectively assessed in patients previously treated with brigatinib during an early-access program (EAP) from 1 August 2016 to 21 January 2019. The primary endpoint was alectinib median progression-free survival (mPFS) according to local investigators.

Results: Among the 183 patients included in the brigatinib EAP, 92 (50.3%) received ≥1 agent(s) post-brigatinib; 30 (16.4%) received alectinib, 19 (10.4%) immediately post-brigatinib; 11 (6%) after ≥1 other treatment line(s). With median follow-up at 25.5 (95% CI: 10.6–30.5) months, mPFS on brigatinib for the study population (n = 30) was 13.6 (95% CI: 6.3–17.7) months. For patients given alectinib immediately post-brigatinib, mPFS and median overall survival (mOS) were 4.8 (95% CI: 2.0–12.5) and 27 (95% CI: 12.5–not reached (NR)) months, respectively. In this subgroup, brigatinib was discontinued for toxicity or progression for 5/19 (26%) or 14/19 (74%) patients, with mPFS lasting 12.5 (95% CI: 3.3–17.9 and 3.4 (95% CI: 0.9–9.2) months, respectively. For patients receiving ≥1 agent(s) between brigatinib and alectinib, with median follow-up at 13.3 (95% CI: 2.3–31.5) months, mPFS and mOS were 5.0 (95% CI: 0.5–18.8) and 19 (95% CI: 2.3–NR) months, respectively.

Conclusion: According to the results of this retrospective real-world study, alectinib post-brigatinib showed limited overall activity but remains an option for patients with advanced *ALK*+ NSCLCs, especially when brigatinib was discontinued because of toxicity.

Keywords: alectinib, brigatinib, management, ALK+ non-small cell lung cancer

Introduction

Brigatinib and alectinib are second-generation anaplastic lymphoma kinase inhibitors (ALKis) and both are used as first-line standard-of-care for advanced *ALK*-rearranged (*ALK*+) non-small-cell lung cancer (NSCLC) based on the results of two randomized Phase 3 trials.[1] The ALTA-1L trial compared brigatinib vs crizotinib as first-line therapy for *ALK*+ NSCLC; brigatinib significantly prolonged median progression-free survival (mPFS), the primary endpoint, from 11.1 to 24 months, according to the Blinded Independent Review Committee (BIRC) (HR: 0.48 [95% CI: 0.35–0.66]; $p < 0.0001$), with respective 3- and 4-year mPFS rates of 43% and 36%.[2] The ALEX trial that compared alectinib vs crizotinib as first-line therapy for *ALK*+ NSCLC, also found mPFS to be significantly prolonged with alectinib (25 vs

Received: 22 April 2025
Accepted: 5 July 2025
Published: 12 August 2025

11.1 months according to BIRC; HR: 0.50 [95% CI: 0.36–0.70]; p < 0.0001), with respective 3- and 4-year mPFS rates of 46.4% and 43.7%.[3]

In the management of ALK-rearranged NSCLC, several studies, especially in real-world conditions, have demonstrated the positive prognostic impact of the therapeutic sequence.[4,5] With this in mind, we have already made a focus on post-brigatinib lorlatinib efficacy in the real-world BrigALK2 study.[6] Another interesting sequence is post-brigatinib alectinib efficacy for which data are scarce.

BrigALK2 is a French, multicenter, retrospective, real-world study that evaluated brigatinib efficacy prescribed in an early-access program (EAP) in France, from 1 August 2016 to 21 January 2019. It enrolled 183 patients with pre-treated advanced *ALK*+ NSCLCs. For those heavily treated patients (median of two ALKis before brigatinib), mPFS and median overall survival (mOS) from brigatinib initiation were, respectively, 7.4 and 20.3 months.[6]

The aim of this ancillary analysis was to assess alectinib efficacy when administered after brigatinib to patients with advanced *ALK*+ NSCLCs in a real-world setting.

Patients and Methods

Study Design and Patients

As previously described, patients included in the BrigALK2 trial had advanced, ALK-rearranged NSCLC pre-treated with at least one ALKi, and had received brigatinib as part of its early access in France between August 1, 2016, and January 21, 2019. This analysis focused on alectinib efficacy post-brigatinib failure (toxicity or progressive disease). Patients were identified and included by each local investigator in participating centers. Alectinib could have been prescribed immediately post-brigatinib or after at least one other line of therapy.

Data Collection

Patient information, retrospectively collected from medical records and entered into a case-report form, included demographics and NSCLC characteristics, numbers and localizations of metastatic sites, numbers of previous treatments, reason for brigatinib discontinuation (progression or toxicity), therapeutic sequences, if any, between brigatinib and alectinib, and treatments after alectinib. All identified eligible patients were enrolled, without selection, in each participating center.

Endpoints

The primary endpoint was mPFS on alectinib, according to local investigators, defined as the time between alectinib onset and progression or death. Secondary endpoints were median duration of treatment (mDOT), mOS from alectinib onset, disease-control rate (DCR) and objective response rate (ORR). Each endpoint was evaluated according to therapeutic sequence, either alectinib initiation immediately post-brigatinib (brigatinib-alectinib) or after at least one intermediate line (chemotherapy or ALKi; brigatinib-X-alectinib).

Statistical Analyses

Patient characteristics were compared with a chi-square test or Fisher's exact test for discrete variables. The Kaplan–Meier method was used to estimate PFS, DOT and OS for the entire population, subgroups defined by their therapeutic sequences and reason for brigatinib discontinuation. The Log rank test compared survival according to treatment sequence. Responses to treatment were assessed by local investigators applying RECIST 1.1 criteria. Statistical analyses were computed with SAS v9.4 software (SAS Institute, Cary, NC, USA).

The study was conducted in accordance with French laws and regulations in force (law 78–17 of 6 January 1978 modified by laws 94–548 of 1 July 1994, 2002–303 of 4 March 2002, 2004–801 of 6 August 2004). The GFPC has committed to the French National Commission for Data Protection and Liberties (CNIL) to respect MR-004 reference methodology.

Results

During the brigatinib EAP, 183 patients managed in 66 centers were enrolled. At data cut-off date (7 July 2022), 92 (50.3%) patients had received at least one agent(s) post-brigatinib (ALKi or chemotherapy); 30 (16.4%) who received alectinib post-brigatinib—regardless of treatment line—constituted the study population (Figure 1). Median age was 53 years, and all NSCLCs had adenocarcinoma histology. Patients were heavily pre-treated with a median of four therapeutic lines before alectinib, receiving a median of three ALKis (Table 1). Under brigatinib, mPFS and mDOT were 13.6 (95% CI: 6,3–17,7) and 10.9 (95% CI: 6,2–20,2) months, respectively. Brigatinib was discontinued because of progression for 22 (73.3%) patients and toxicity for 8 (26.7%). Under brigatinib, the main progression site was the brain (71%), including 20% of patients with carcinomatous meningitis as progression.

Among the 30 patients, 19 (63%) received alectinib immediately post-brigatinib and 11 (37%) after at least one other chemotherapy or ALKi line (Figure 1).

After median follow-up of 25.5 (95% CI: 10.6–30.5) months, brigatinib-alectinib–sequence patients' mPFS and mOS were 4.8 (95% CI: 2.0–12.5) and 27.0 (95% CI: 12.5–not reached (NR)) months, respectively (Figure 2); alectinib ORR was 26.3% (5/19) with no complete responses, DCR was 63% and mDOT, 7.1 (95% CI: 2.1–18.2) months. For patients who discontinued brigatinib because of treatment-related adverse event(s)/toxicity, mPFS and mDOT lasted 12.5 (95% CI: 3.3–17.9) and 18.2 (95% CI: 3.4–21.6) months, respectively, vs 3.4 (95% CI: 0.9–9.2) and 5.7 (95% CI: 0.9–10.6) months for those who stopped brigatinib because of progression (Table 2).

For patients treated with alectinib after at least one other treatment line post-brigatinib, mPFS and mDOT were 5.0 (95% CI: 0.5–18.8) and 11.7 (95% CI: 0.7–21.5) months, respectively, mOS was 19.0 (95% CI: 2.3–NR) months (Figure 3) with ORR of 10% and DCR of 30% (Table 2).

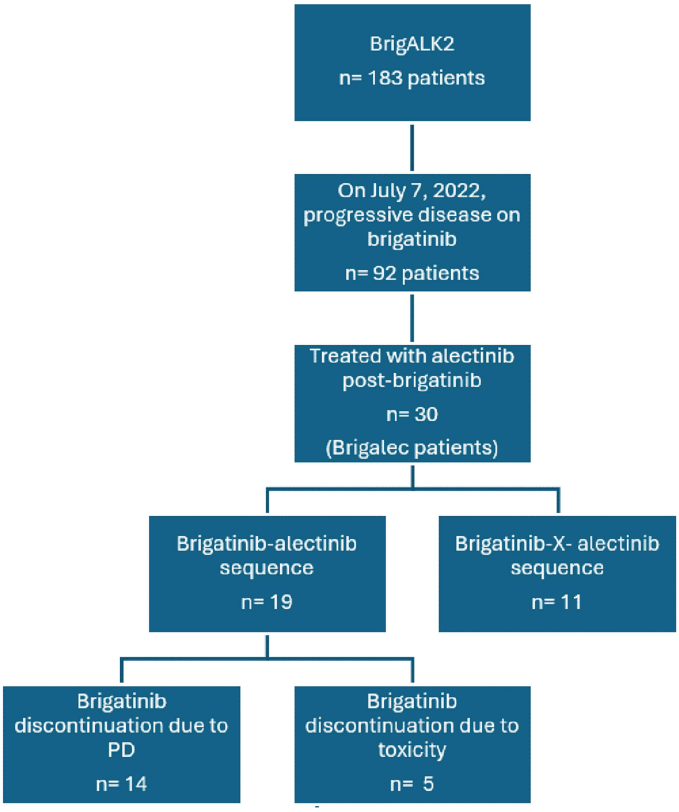

Figure 1 Flowchart.

https://doi.org/10.2147/LCTT.S522038

Table 1 Patients Characteristics

	Total Population n= 30 n (%)	**B-A seq. n= 19 n (%)**	**B-X-A seq. n= 11 n (%)**
Age (median)	53	52	53
Sex (female)	19 (63.3)	14 (73.7)	5 (45.5)
Smocking status			
Current smoker	3 (10)	1 (5.3)	2 (18.2)
Former smoker	10 (33.3)	6 (31.6)	4 (36.4)
Never smoker	17 (56.7)	12 (63.2)	5 (45.5)
Histology			
Adenocarcinoma	30 (100)	19 (100)	11 (100)
ECOG PS	n= 19	n= 11	n= 8
0	10	7	3
1	7	2	5
≥ 2	2	2	0
Metastatic sites, n	n= 27	n= 18	n= 9
1	8 (29.6)	7 (38.9)	1 (11.1)
2	9 (33.3)	6 (33.3)	3 (33.3)
>2	10 (37)	5 (27.7)	5 (55.6)
Metastatic sites (main locations),			
Central nervous system	11 (36.7)	8 (42.1)	3 (27.3)
Leptomningeal carcinomatosis	1 (3.3)	0	1 (9.1)
Bone	12 (40)	6 (31.6)	6 (54.5)
Lung	8 (26.7)	6 (31.6)	2 (18.2)
Liver	5 (16.7)	3 (15.8)	2 (18.2)
Pleura	5 (16.7)	2 (10.2)	3 (27.3)
Treatment lines before alectinib, med	4 ± 2	4 ± 2	4 ± 2
TKI number before alectinib, med	3 ± 1	3 ± 1	3 ± 1

Abbreviations: B-A seq, brigatinib-Alectinib sequence; B-X-A, Brigatinib-Other-Alectinib.

Table 2 Alectinib Efficacy Post-Brigatinib Failure According to Sequence

	Patients Treated with Alectinib Post-Brigatinib in BrigALK 2 Study: n = 30			
	Overall n = 30	**Brigatinib-Alectinib Sequence n = 19**		**Brigatinib-X-Alectinib Sequence n = 11**
		Bdisc. Due to Toxicity n = 5	**Bdisc. Due to Progression n = 14**	
mDOT, months (95% CIs)	7.1 (2.1–18.2)	18.2 (3.4–21.6)	5.7 (0.9–10.6)	11.7 (0.7–21.5)
mPFS, months (95% Cis)	4.8 (2–12.5)	12.5 (3.3–17.9)	3.4 (0.9–9.2)	5 (0.5–18.8)
mOS, months (95% Cis)	27 (12.5–NR)			19 (2.3–NR)
RR, %	25			10
DCR, %	60			30

Abbreviations: Bdisc, Brigatinib discontinuation; X, any agent(s) between brigatinib and alectinib (iALK or chemo); NR, not reached.

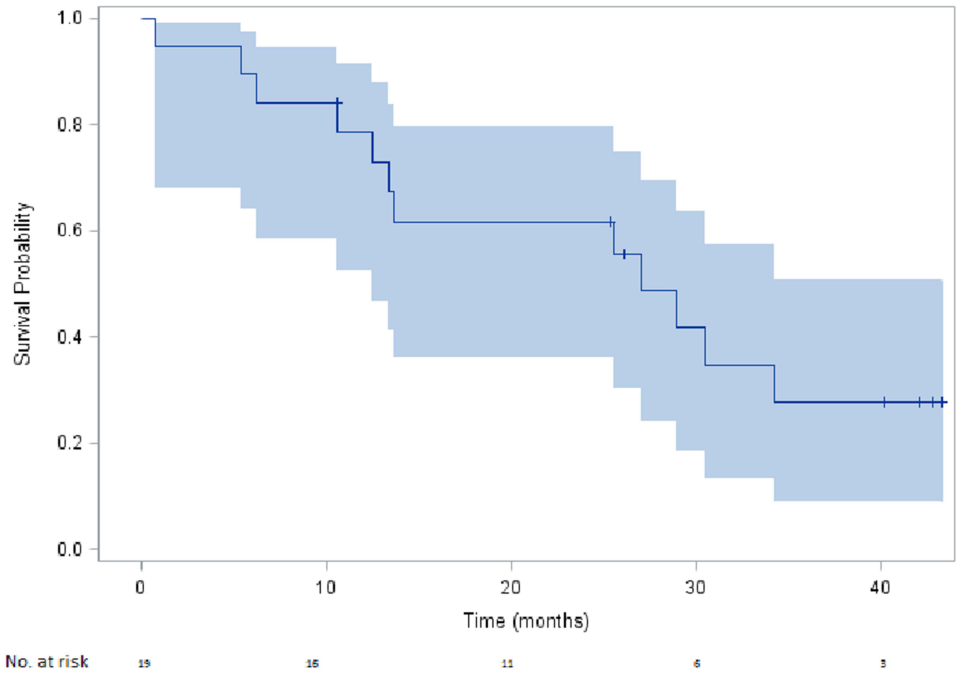

Figure 2 Median overall survival curve for patients treated with the brigatinib-alectinib sequence (n=19).

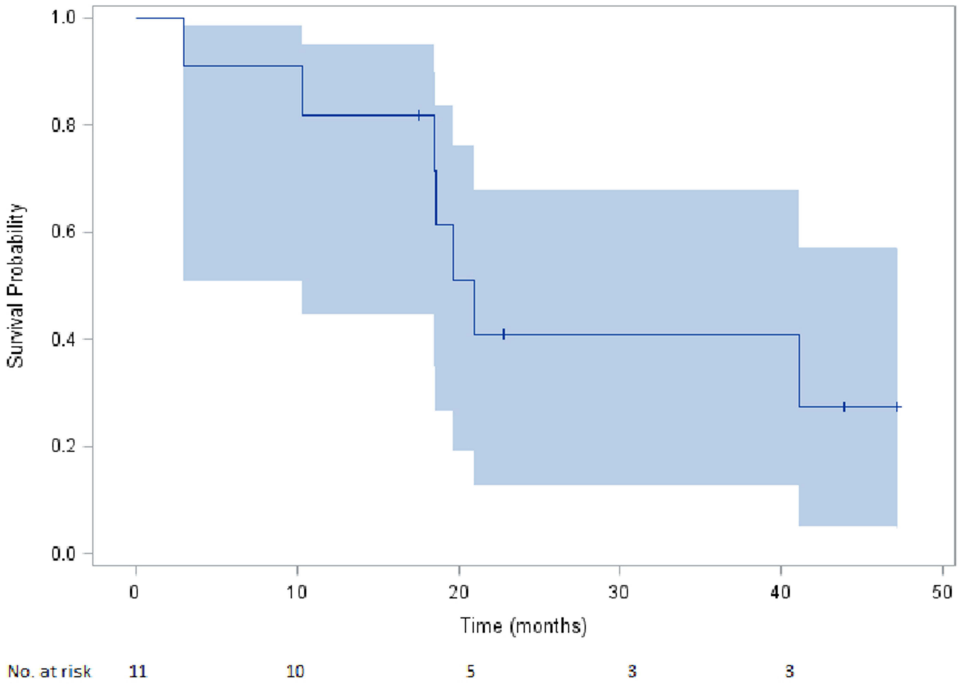

Figure 3 Median overall survival curve for patients treated with the brigatinib-X-alectinib sequence (n=11).

Discussion

In this multicenter population of EAP patients with heavily pre-treated advanced *ALK*+ NSCLCs, alectinib immediately post-brigatinib showed limited overall activity with respective mPFS and mDOT of 4.8 and 7.1 months. Those durations,

https://doi.org/10.2147/LCTT.S522038

respectively, were dependent on whether brigatinib was discontinued for toxicity (12.5 and 18.2 months) or progression (3.4 and 5.7 months).

Published data on post-brigatinib alectinib efficacy against advanced *ALK*+ NSCLCs are scarce. ALTA-L1-trial results of second-line ALKi, after progression on first-line brigatinib were reported recently. In that post hoc analysis, 40 patients received treatment post-brigatinib, an ALKi for 30, including alectinib for 8 of them.[7] For the latter patients given the brigatinib-alectinib sequence, after a median follow-up of 17 months, mPFS and time to treatment discontinuation were 16.1 months and NR, respectively. The considerable difference between those results and ours can probably be explained by our patients having been heavily pre-treated, with a median of three ALKis before alectinib. Reasons for brigatinib discontinuation in the ALTA-L1 trial were not specified, whereas our results revealed very different efficacy profiles depending on whether patients stopped brigatinib because of toxicity or progression.

To our knowledge, very few studies have examined the therapeutic sequences and efficacy of ALKi according to the cause of discontinuation, progression or toxicity. This seems to be the most important point to emerge from our analyses, all things being equal, of course, as this is a retrospective study with few patients in the analyses carried out. Such data are addressed in the CROWN trial, in the analysis of post-first-line treatments.[8]

CROWN has recently revolutionized first-line management of ALK+ stage 4 NSCLC. Previously, lorlatinib was the standard second line TKI in cases of progression with first line alectinib or brigatinib, based on clinical trial[7,9] and real-world data.[10] More recently, CROWN trial demonstrated lorlatinib superiority over crizotinib as first-line therapy. A post-hoc analysis with 5 years of follow-up showed that the mPFS was NR on lorlatinib (NR [95% CI: 64.3–NR]) and 9.1 months [95% CI: 7.4–19] with crizotinib (HR: 0.19. [95% CI: 0.13–0.27], with respective 5-year mPFS rates of 60% vs 8%.[11] Those findings clearly established lorlatinib as a first-line therapy option, but no direct comparison was made with a second-generation ALKi and, thus, the optimal sequence choice is not yet evident. Management after progression on first-line lorlatinib was reported in a CROWN-trial update: 33/149 (22.1%) patients received second-line therapy: 21/33 (63.6%) patients another ALKi, usually alectinib (12/21, 57.1%). On a first ALKi as subsequent post-lorlatinib therapy, mDOT was 9.6 months. Swimmer plots of data tended to show that patients benefiting the most from another ALKi were those who discontinued lorlatinib because of toxicity. Those preliminary data must be confirmed with future CROWN trial updates. Although the brigatinib-alectinib sequence has been poorly studied specifically, switching from one second-generation ALKi to another has been evaluated with other molecules. A single-arm, prospective, Phase II trial on 103 patients who had received a maximum of three treatment lines examined brigatinib efficacy after progression on ceritinib or alectinib.[12] Those authors found disappointing clinical activity: ORR of 26.2%, and respective mPFS and mDOT of 3.8 and 6.3 months. Lin et al retrospectively analyzed 22 patients with alectinib-refractory advanced ALK+ NSCLCs in a multicenter population.[13] Most of those patients had received brigatinib immediately after alectinib. That strategy had limited efficacy, with PFS at 4.4 months and ORR of 17%. All those studies analyzed second-generation ALKi efficacy in the event of progression, whereas, notably, our study results showed greater efficacy in patients who had discontinued brigatinib because of toxicity.

The data available for our study population did not allow us to analyze the resistance mechanisms at progression on brigatinib. Such investigations were not routine practice when the brigatinib EAP was ongoing. However, identification of a resistance mutation at disease progression might help adapt subsequent treatments. Unfortunately, information on ALKi activity according to resistance mechanisms determined on rebiopsy specimens obtained at progression are limited and derived from retrospective series. For example, Lin et al had those data for only 9 patients, with tissue or liquid biopsies obtained at progression on alectinib.[13] A resistance mutation was found in 6/9 (66.7%) specimens and theoretical brigatinib-susceptibility mutations were found in 5/6 (83.3%) samples. On brigatinib, one patient had a partial response or progressed and three achieved stable disease.

Our study has several limitations. First is its retrospective design without data monitoring. Treatment assessment was not centralized, so local investigator-assessment bias cannot be excluded. In this real-world study, alectinib efficacy was evaluated in heavily pre-treated patients having received a median of four previous lines. Therefore, we cannot rule out a potential immortality time bias that limits interpretation of the results obtained. However, one of the strengths of this

study is the absence of stringent criteria for study inclusion, meaning that the population is representative of real-world, heavily treated patients with advanced *ALK*+ NSCLCs.[14]

Conclusion

According to the results of our retrospective real-world study, alectinib post-brigatinib showed limited overall activity but seems to remain an interesting option for patients with advanced *ALK*+ NSCLCs who discontinued brigatinib because of toxicity.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the ethics committee Ile de France II Protocol: GFPC 02-2019, date of approval: May 25, 2020. N°20.03.24.67745.

Informed Consent Statement

Patients received written and oral information on the study and gave their consent to participate in the study and for the use of their medical data for research purposes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study received an academic grant from Takeda.

Disclosure

Dr Renaud Descourt reports personal fees and non-financial support from AstraZeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Takeda, and Chugai, outside the submitted work. Prof. Dr Florian Guisier reports grants, personal fees from Roche, grants, personal fees from Takeda, grants, personal fees from Pfizer, during the conduct of the study; personal fees from Astra Zeneca, personal fees from BMS, personal fees from Johnson & Johnson, personal fees from MSD, grants, personal fees from Pfizer, grants, personal fees from Roche, personal fees from Sanofi, grants, personal fees from Takeda, personal fees from Viatris, personal fees from Amgen, personal fees from Regeneron, outside the submitted work; Dr Maurice Pérol reports personal fees, non-financial support from Takeda, personal fees, non-financial support from Roche, personal fees, non-financial support from Pfizer, personal fees, non-financial support from AstraZeneca, personal fees, non-financial support from MSD, personal fees from BMS, personal fees, non-financial support from Janssen, personal fees, non-financial support from Amgen, personal fees from Nuvation Bio, personal fees from AnHeart Therapeutics, personal fees from AbbVie, personal fees from Daiichi Sankyo, outside the submitted work; Dr Jacques Cadranel reports personal fees from AZ, personal fees from Takeda, personal fees from Pfizer, personal fees from Roche, personal fees from MSD, personal fees from Daiichi, outside the submitted work; Dr Helene Doubre reports non-financial support, travel expenses from Takeda, non-financial support, travel expenses from Pfizer, non-financial support, travel expenses from MSD, non-financial support, travel expenses from Novartis, non-financial support from Bristol Myers Squibb, non-financial support from Roche, personal fees, non-financial support, travel expenses from leo Pharma, outside the submitted work; Professor Michael Duruisseaux reports non-financial support from Roche, during the conduct of the study; personal fees, non-financial support from Roche, non-financial support from Takeda, personal fees from Pfizer, outside the submitted work; Dr Stéphane Culine reports personal fees from Astellas, personal fees from Bayer, personal fees from Bristol-Myers Squibb, personal fees from Ipsen,

personal fees from Johnson and Johnson, personal fees from Merck, personal fees from MSD, outside the submitted work; Dr Bertrand Mennecier reports personal fees from Takeda for lectures, invitation in congress from Takeda. Professor Olivier Bylicki reports personal fees, travel for congress from MSD, personal fees, travel for congress from ASTRA-ZENECA, outside the submitted work; Dr Christos Chouaid reports grants, personal fees, non-financial support from Boehringer Ingelheim, Hoffman-Roche, Takeda, BMS, MSD, Astra Zeneca, Amgen, Janssen and Pfizer, during the conduct of the study; Prof. Dr Laurent Greillier reports grants, personal fees, non-financial support from BMS, grants, personal fees, non-financial support from MSD, grants, personal fees, non-financial support from Takeda, grants, personal fees, non-financial support from Pfizer, grants, personal fees, non-financial support from Roche, grants, personal fees, non-financial support from Amgen, grants, personal fees, non-financial support from Sanofi, grants, personal fees, non-financial support from J&J, grants, personal fees, non-financial support from Lilly, grants, personal fees, non-financial support from Novartis, grants, personal fees, non-financial support from Regeneron, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):339–357. doi:10.1016/j.annonc.2022.12.009
2. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial. *J Thorac Oncol*. 2021;16(12):2091–2108. doi:10.1016/j.jtho.2021.07.035
3. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056–1064. doi:10.1016/j.annonc.2020.04.478
4. Chazan G, Franchini F, Shah R, et al. Real-world treatment and outcomes in ALK-rearranged NSCLC: results from a large U.S.-based database. *JTO Clin Res Rep*. 2024;5(8):100662. doi:10.1016/j.jtocrr.2024.100662
5. Duruisseaux M, Besse B, Cadranel J, et al. Overall survival with crizotinib and next-generation ALK inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study. *Oncotarget*. 2017;8(13):21903–21917. doi:10.18632/oncotarget.15746
6. Descourt R, Pérol M, Rousseau-Bussac G, et al. Brigatinib for pretreated, ALK-positive, advanced non-small-cell lung cancers: long-term follow-up and focus on post-brigatinib lorlatinib efficacy in the multicenter, real-world BrigALK2 study. *Cancers*. 2022;14(7):1751. doi:10.3390/cancers14071751
7. Ahn MJ. Real-world outcomes of 2L ALK TKIs following 1L brigatinib for patients with ALK+ NSCLC from the ALTA-1L Trial. *J Thorac Oncol*. 2010;5:S200. doi:10.1097/JTO.0b013e3181dd0a8d
8. Solomon BJ, Bauer TM, Mok TSK, et al. Efficacy and safety of first-line lorlatinib versus crizotinib in patients with advanced, ALK-positive non-small-cell lung cancer: updated analysis of data from the phase 3, randomised, open-label CROWN study. *Lancet Respir Med*. 2023;11(4):354–366. doi:10.1016/S2213-2600(22)00437-4
9. Felip E, Shaw AT, Bearz A, et al. Intracranial and extracranial efficacy of lorlatinib in patients with ALK-positive non-small-cell lung cancer previously treated with second-generation ALK TKIs. *Ann Oncol*. 2021;32(5):620–630. doi:10.1016/j.annonc.2021.02.012
10. Baldacci S, Besse B, Avrillon V, et al. Lorlatinib for advanced anaplastic lymphoma kinase-positive non-small cell lung cancer: results of the IFCT-1803 LORLATU cohort. *Eur J Cancer*. 2022;166:51–59. doi:10.1016/j.ejca.2022.01.018
11. Solomon BJ, Liu G, Felip E, et al. Lorlatinib versus crizotinib in patients with advanced ALK-positive non-small cell lung cancer: 5-year outcomes from the phase III CROWN study. *J Clin Oncol*. 2024;42(29):3400–3409. doi:10.1200/JCO.24.00581
12. Ou SHI, Nishio M, Ahn MJ, et al. Efficacy of brigatinib in patients with advanced ALK-positive NSCLC who progressed on alectinib or ceritinib: ALK in lung cancer trial of brigAtinib-2 (ALTA-2). *J Thorac Oncol*. 2022;17(12):1404–1414. doi:10.1016/j.jtho.2022.08.018
13. Lin JJ, Zhu VW, Schoenfeld AJ, et al. Brigatinib in patients with alectinib-refractory ALK-positive NSCLC. *J Thorac Oncol*. 2018;13(10):1530–1538. doi:10.1016/j.jtho.2018.06.005
14. Mudumba R, Nieva JJ, Padula WV. First-line alectinib, brigatinib, and lorlatinib for advanced anaplastic lymphoma kinase-positive non-small cell lung cancer: a cost-effectiveness analysis. *Value Health*. 2025;28:S1098–3015(25)02284–3. doi:10.1016/j.jval.2025.03.014