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ORIGINAL RESEARCH ARTICLE

# Clinical Characteristics of Patients with Advanced *ALK*-Translocated Non-small Cell Lung Cancers and Long-Term Responses to Crizotinib (CRIZOLONG GFPC 05-19 Study)

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## Abstract

**Background** Although *ALK*-translocated (*ALK*+) advanced non-small cell lung cancers (aNSCLCs) are currently treated with second- or third-generation *ALK* inhibitors (ALK-TKIs), some patients respond durably to the first-generation ALK-TKI crizotinib.

**Objective** This study aimed to describe the clinical characteristics of these long-term responders.

**Patients and Methods** This national, multicenter, retrospective, non-interventional study included patients with *ALK*+ aNSCLCs and long-term responses to first (L1)- or subsequent (≥L2)-line crizotinib, defined, respectively, as treatments lasting > 18 and > 10 months. Median treatment duration (mDOT) was the primary endpoint.

**Results** A total of 85 patients (32 L1 and 53 ≥L2 responders) from 23 centers were included (receiving crizotinib between 10/24/2011–10/02/2018): median age of 59 years, 83.6% non-smokers or ex-smokers, 85.9% performance status (PS) 0/1, 94.1% with adenocarcinomas, median of one metastatic site, and 22.4% with brain metastases (BMs). After median follow-up of 73.4 [95% confidence interval, 67.5–79.9] months, respective L1 and ≥L2 mDOTs were 43.3 [26.7–56.8] and 29.6 [22.6–35.8] months, with overall survival (OS) not reached (NR) and 116.2 [83.4–NR] months. BM presence or absence did not affect mDOT (31.4 versus 32.9 months) but significantly impacted median OS (70.6 versus 158.6 months; $p = 0.0008$). Progression on crizotinib was paucisymptomatic (74.1%) and oligometastatic (34.8%), especially BMs (42.4%). After crizotinib discontinuation, 65 (76.5%) patients received subsequent systemic therapy: 57 (67.1%) with second-generation ALK-TKIs. Respective mDOTs of first- and second-line post-crizotinib ALK-TKIs lasted 19.4 [14.9–25.6] and 11.1 [4.8–17.9] months, respectively.

**Conclusions** Most *ALK*+ aNSCLC patients with prolonged crizotinib efficacy had paucisymptomatic and oligometastatic disease without BMs. They subsequently benefited from a sequential strategy with other ALK-TKIs.

## 1 Introduction

Anaplastic lymphoma kinase (*ALK*)-gene translocation (*ALK*+) is observed in approximately 3–5% of patients with advanced non-small cell lung cancers (aNSCLCs) [1, 2]. This oncogenic driver, first described in bronchopulmonary adenocarcinomas in 2007, results from an intrachromosomal translocation on the short arm of chromosome 2, which, by an inversion-fusion mechanism, brings together two gene fragments: most often echinoderm microtubule-associated protein-like-4 (*EML4*), which has several variants depending on the breakpoint, and *ALK*, which represents the constant part that carries tyrosine kinase activity [3]. This rearrangement leads to the constitutive activation of a cytoplasmic chimeric protein, responsible for permanent tyrosine kinase activity at the origin of oncogenesis phenomena, including cell proliferation and survival [4, 5].

Crizotinib was the first oral *ALK*-targeting tyrosine kinase inhibitor (TKI) to receive first line (L1)-use approval for the management of *ALK*+ aNSCLCs based on the results of the randomized phase III PROFILE-1014 trial that compared

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**Key Points**

The place of crizotinib in the management of anaplastic lymphoma kinase-translocation (*ALK*+) advanced non-small cell lung cancer is still poorly established.

Prolonged efficacy has been observed in patients in good general condition with oligometastatic disease.

After median follow-up of 73.4 months, median first-line crizotinib administration lasted 43.3 months, and median second- or later-line crizotinib administration lasted 29.6 (95% CI 22.6–35.8) months.

Upon progression, these patients benefit from a sequential strategy with other anti-ALK tyrosine kinase inhibitor(s).

treatment-naïve patients given crizotinib to controls receiving platin-based chemotherapy and pemetrexed. Crizotinib significantly prolonged progression-free survival (PFS), the study's primary endpoint [10.9 versus 7 months; hazard ratio (HR) 0.45 [95% confidence interval (CI) 0.35–0.60]; $p < 0.001$] and improved the objective response rate (ORR) [6, 7]. However, that PFS benefit did not translate into longer overall survival (OS): with median follow-up at 46 months, median OS was not reached (NR) but the 4-year survival probability was 56.6% [95% CI 48.3–64.1] with crizotinib versus 49.1% [95% CI 40.5–57.1] for the chemotherapy arm (HR 0.76 [95% CI 0.548–1.053]; $p = 0.0978$) [8]. The absence of an OS benefit was attributed to expected high cross-over rate (84.2%) and potential subsequent access to other *ALK* inhibitors (ALK-TKIs).

Notably, second- (ceritinib, alectinib, brigatinib) and third-generation (lorlatinib) ALK-TKIs are characterized by more specific anti-*ALK* activity and better intracerebral diffusion. Their efficacies at treating progression on crizotinib initially gave them a place in the post-crizotinib therapeutic strategy [9–13]. Alectinib, brigatinib and, more recently, lorlatinib have now been compared with L1 crizotinib for *ALK*+ aNSCLCs [14–16]; they achieved clear PFS, ORR, and brain activity superiority over crizotinib. These later-generation TKIs are now considered the standard-of-care for L1 therapy of patients with *ALK*+ aNSCLCs [17].

Some patients have been reported to benefit from prolonged responses to crizotinib, superior to those described in the principal trials [18–20], with "long responders" whose PFS exceeded 4 years. Such differences in crizotinib-efficacy durations might be explained by clinical and/or specific molecular characteristics, e.g., the presence of comutations, fusion partners, and *ALK*-gene fusion variants. Thus, as suggested by the authors of different studies, crizotinib would be more effective against *ALK*+ aNSCLCs with *EML4* variant-2 and less effective if a *TP53* mutation is associated [21–23].

The objective of this study was to analyze the clinical characteristics of a series of *ALK*+ aNSCLC patients considered to be long-responders to crizotinib to identify factors associated with this prolonged sensitivity profile to this first-generation ALK-TKI.

## 2 Methods

CRIZOLONG is a national multicenter retrospective non-interventional real-world study conducted in the centers associated or affiliated with the French Group of Pneumo-Cancerology (GFPC). In the absence of a consensus definition, long-term responders were defined as patients receiving crizotinib for a duration exceeding 150% of the median PFS obtained in the pivotal trials, i.e., in the first line lasting > 18 months, and in the second line or more (≥ L2) lasting > 10 months. The other inclusion criteria were age of > 18 years, histologically confirmed aNSCLC, and locally confirmed *ALK* translocation. Patients refusing to participate were excluded.

Patients satisfying the above criteria were identified by the participating center investigators and offered inclusion in the study during a follow-up consultation. The study was conducted in accordance with the Declaration of Helsinki, good clinical practices guidelines, and relevant French ethical and data protection regulations. It was submitted to CEPRO (Comité d'Evaluation des Protocoles de Recherche Observationnelle; reference no. 2021-027) and was validated by that Committee on 20 August 2021.

The following information were obtained from medical records: patient and disease characteristics, and management.

The primary endpoint, assessed locally, was median crizotinib duration of treatment (mDOT), defined as the time from starting crizotinib to its discontinuation. Secondary endpoints were mDOT according to treatment line, median OS (mOS) from the dates of aNSCLC diagnosis and crizotinib initiation, and mDOT and mOS according to brain metastasis presence (BM+) or absence (BM−) at diagnosis.

The probabilities of mDOT and mOS were estimated with the Kaplan–Meier method, compared with log-rank tests according to treatment line. Responses to crizotinib were assessed locally by the investigators applying RECIST 1.1 criteria. Clinical pathological characteristics are expressed as number (%) and [95% CI] for qualitative variables and medians (range) for quantitative variables. Statistical analyses were computed with SAS v9.4 software (SAS Institute, Cary, NC, USA).

## 3 Results

A total of 85 patients from 23 centers with *ALK*+ aNSCLCs who received crizotinib as L1 or ≥ L2 therapy between 10/24/2011 and 10/02/2018 were included (Fig. 1). Crizotinib was L1 for 32 (37.6%) patients and ≥ L2 for 53 (62.4%). Among the latter, 44 (83.0%) had received one treatment line (chemotherapy for 98.1%) before starting crizotinib; that initial mDOT lasted 6.8 [95% CI 3.8–9] months.

The main characteristics of the 85 patients are summarized in Table 1: median age of 59 (range 23–81) years, slight male predominance (52.9%), most patients were nonsmokers or ex-smokers (83.6%) and their general condition was good with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 for 85.9%. The aNSCLCs were almost exclusively adenocarcinomas (94.1%), with a median of one metastatic site at diagnosis and 63.6% had one to two metastatic sites. A total of 19 (22.4%) patients were BM+, with 7 (21.8%) patients in L1 and 12 (22.6%) in ≥ L2. Only one patient had carcinomatous meningitis. The most common metastatic sites were bone (30.6%), pleura (27.1%), brain (22.4%), lung (16.5%), liver (12.9%), and lymph nodes (10.6%). About half (51.8%) of the patients were paucisymptomatic. No patients received consolidative local treatment at diagnosis or prior to progression.

*ALK* status, mostly based on primary lesion biopsies (64.7%), was determined conventionally with immunohistochemistry (67.1%) and/or florescent in situ hybridization (71.8%), or more rarely with reverse transcription polymerase chain reaction for two (2.4%) and next-generation sequencing of RNA for one patient.

At data censoring (06/20/2022), 16 patients were still on crizotinib, 10 were on L1, and 6 were on ≥ L2 treatment. A total of 28 patients died (5 and 23 in the L1 and ≥ L2 subgroups, respectively).

After a median [95% CI] follow-up of 73.4 [67.5–79.9] months, overall crizotinib mDOT was 31.9 [26.5–41.7] months, with 43.3 [26.7–56.8] and 29.6 [22.6–35.8] months follow-up for L1 (Fig. 2A) and ≥ L2 recipients, respectively (Fig. 2B). mOS lasted 120 [90.3–NR] months post-diagnosis and 118 [78.6–NR] months from crizotinib onset. mOS for

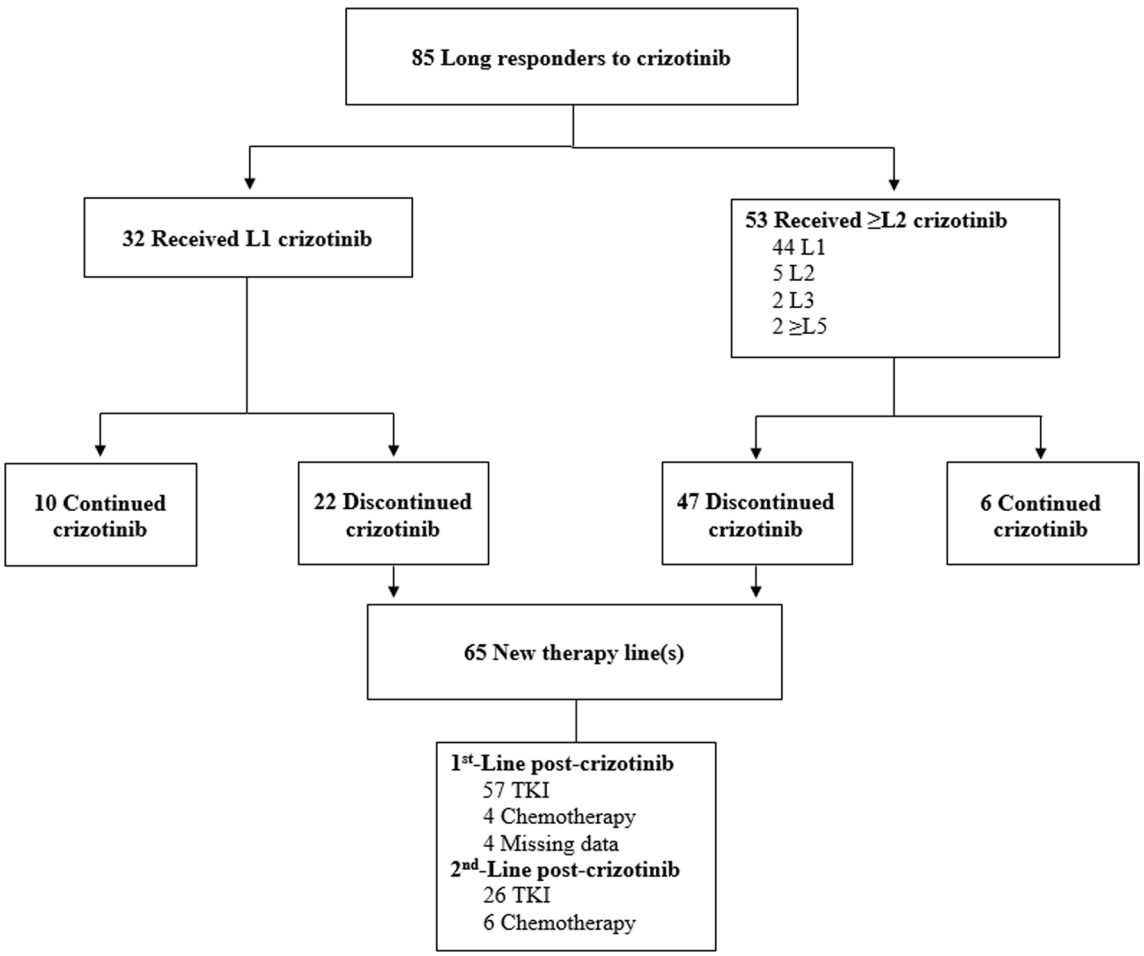


**Fig. 1** Study flow chart. L1/≥2, crizotinib line 1 or ≥ L2; TKI, tyrosine kinase inhibitor

**Table 1** Characteristics of the 85 aNSCLC patients at crizotinib onset

| Characteristic | *n* (%) |
|---|---|
| Crizotinib | |
| Line 1 | 32 (37.6) |
| Line 2 or more | 53 (62.4) |
| Age, median (range), years | 59 (23–81) |
| Male sex | 45 (52.9) |
| ECOG PS | |
| 0 | 46 (54.1) |
| 1 | 27 (31.8) |
| ≥ 2 | 5 (5.9) |
| Missing data | 7 (8.2) |
| Smoking status | |
| Never-smoker | 53 (62.4) |
| Ex-smoker | 18 (21.2) |
| Current-smoker | 10 (11.8) |
| Missing data | 4 (4.7) |
| Histology | |
| Adenocarcinoma | 80 (94.1) |
| Large-cell carcinoma | 2 (2.4) |
| Missing data | 3 (3.5) |
| *ALK*-rearrangement detection technique | |
| Immunohistochemistry | 57 (67.1) |
| Fluorescent in situ hybridization | 61 (71.8) |
| Reverse transcriptase polymerase chain reaction | 2 (2.4) |
| Next-generation sequencing | 1 (1.2) |
| Missing data | 8 (9.4) |
| Number of metastatic sites at diagnosis | |
| 1 | 36 (42.4) |
| 2 | 18 (21.2) |
| 3 | 6 (7.1) |
| > 3 | 9 (10.6) |
| Missing data | 16 (18.8) |
| Metastatic sites | |
| Central nervous system | 19 (22.4) |
| Carcinomatous meningitis | 1 (1.2) |
| Bone | 26 (30.6) |
| Lung | 14 (16.5) |
| Pleura | 23 (27.1) |
| Liver | 11 (12.9) |
| Lymph nodes | 9 (10.6) |
| Adrenal glands | 4 (4.7) |
| Others | 10 (11.8) |
| Brain metastasis(es) | |
| Yes | 19 (22.4) |
| Patients receiving line 1 crizotinib, *n* | 32 |
| Yes | 7 (21.9) |
| Patients receiving line 2 or more crizotinib, *n* | 53 |
| Yes | 12 (22.6) |
| Treatment lines before crizotinib, *n* | 53 |
| 1 | 44 (83.0) |
| 2 | 5 (9.4) |
| ≥ 3 | 4 (7.6) |

patients receiving L1 crizotinib was NR and lasted 116.2 [83.4–NR] months for patients receiving ≥ L2 crizotinib (Fig. 3).

Having BMs at diagnosis did not impact the mDOT: for BM+ or BM− patients, respectively, mDOT lasted 42.9 [20.2–64.3] and 43.7 [26.7–56.8] months for L1 and 21.6 [11.9–51.3] and 29.9 [23.7–39.4] months for ≥ L2. However, mOS differed significantly between patients BM+ and BM− at diagnosis, respectively: 70.6 [44.6–120] versus 158.6 [92.3–NR] months ($p = 0.0008$) (Fig. 4). That difference reflects patients who received crizotinib as ≥ L2, with respective mOS rates for BM+ and BM− patients of 63.1 [40.7–120] versus 158.6 [90.3–NR] ($p < 0.0027$). For the two subgroups of patients given L1 crizotinib, mOS was NR.

The complete response rate was 21.2% ($n = 18$) and 60 (70.6%) patients had partial responses. Four (4.7%) patients stopped treatment because of toxicity.

At the censoring date, 22 (25.9%) L1 and 47 (55.3%) ≥ L2 recipients had experienced progression that was most often asymptomatic (74.1%) and oligometastatic (38.4%) defined as progression limited to one to three metastatic sites. The main metastatic sites were brain (42.4%), pleuropulmonary (24.7%) and bone (14.1%). Crizotinib was continued at progression for 38 (44.7%) patients, in combination with local treatment for 27.1%, mainly radiotherapy (25.9%), particularly cerebral radiotherapy (16.5%); their mOS was significantly longer than for patients who discontinued crizotinib at progression (29.6 versus 10.8 months, respectively; HR 0.30; $p < 0.0001$).

At progression, 12 (14.1%) patients had a new biopsy, mostly of metastases (7.1%) and 2.4% had liquid biopsies. Three resistance mutations were identified: two *G1202R* mutations and one *D1160G*. A v-*RAF* murine sarcoma viral oncogene homolog B (*BRAF*) or phosphoinositide 3-kinase (*PI3K*) comutation was also identified.

After stopping crizotinib, 65 (76.5%) patients received subsequent systemic therapy, with a median of 1 (range 1–5) line, and 57 (67.1%) received a second-generation ALK-TKI. The mDOT for this ALK-TKI line was 19.4 [14.9–25.6] months for patients given L1 crizotinib and 11.1 [4.8–17.9] months for patients receiving ≥ L2 crizotinib.

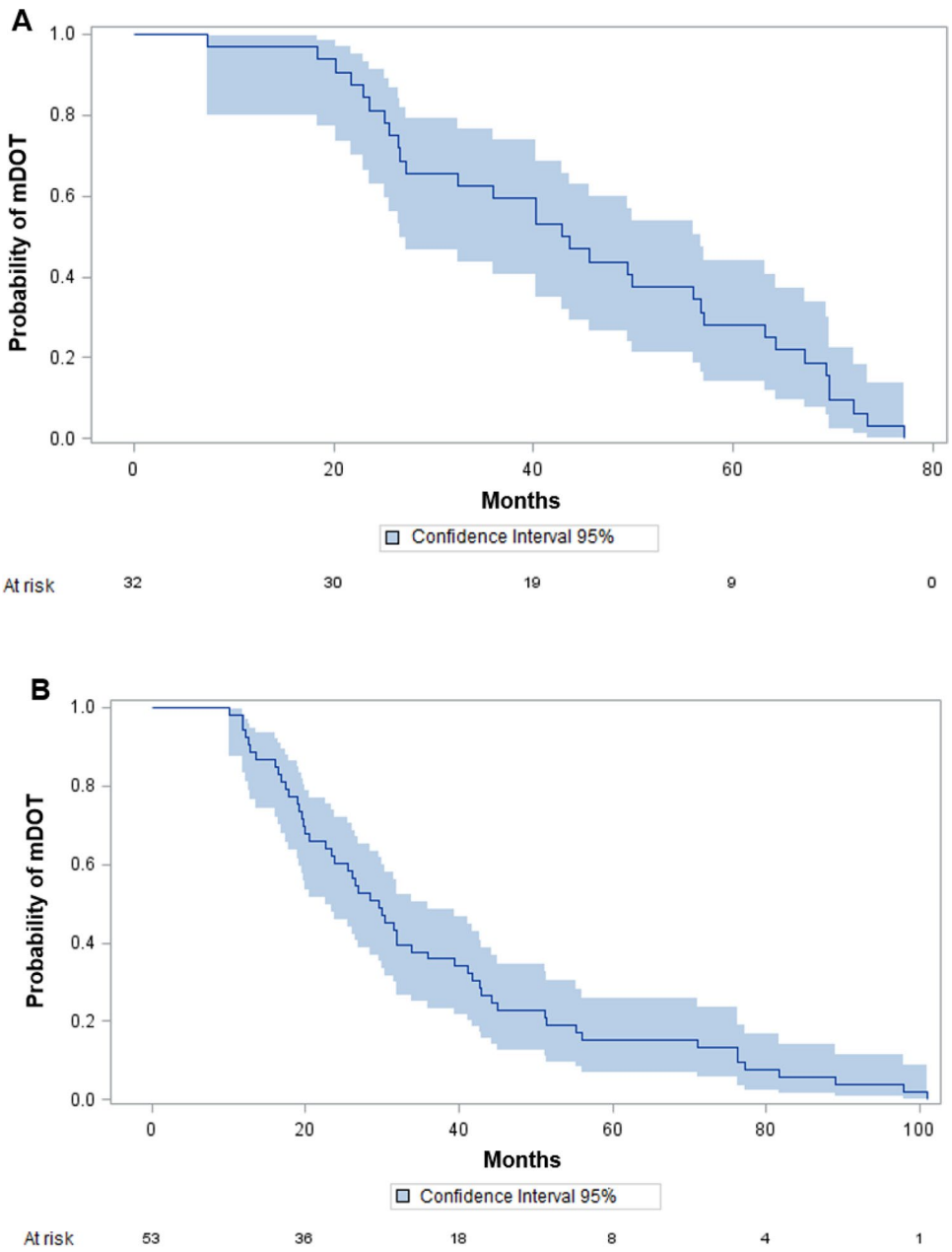


**Fig. 2** Kaplan–Meier estimated probability of median [95% CI in blue] durations of line 1 (**A**) or line 2 or more (**B**) crizotinib administration (mDOT) for aNSCLC patients

## 4 Discussion

The results of this retrospective multicenter real-world study confirmed the possibility of prolonged L1 or ≥ L2 crizotinib efficacy for highly selected patients with *ALK*+ aNSCLCs. With median follow-up of 73.4 [95% CI 67.5–79.9] months, the mDOT on crizotinib for these 85 patients was 31.9 [95% CI 26.5–41.7] months, with L1 and ≥ L2 post-chemotherapy mDOTs, respectively, of 43.3 [95% CI 26.7–56.8] and 29.6 [95% CI 22.6–35.8] months. These substantial benefits are reflected in mOS (NR for L1 crizotinib recipients and 116.2 [95% CI 83.4–NR] months for patients on crizotinib ≥ L2). In addition to the common characteristics of patients with *ALK*+ NSCLCs, analysis of the clinical data from this series suggests long-term responders have a particular profile: the vast majority were in good general condition, with paucisymptomatic disease, monometastatic at diagnosis and an oligo-progressive evolution pattern. The main progression site was the brain, allowing for local treatments and crizotinib continuation.

The mDOT with crizotinib for these selected patients was significantly longer than those observed in various prospective and retrospective trials that evaluated this TKI [7, 12, 13, 24]. In real-life conditions, the median PFS (mPFS) was 15.8 months in a retrospective multicenter Spanish study that exhaustively included all *ALK*+ patients treated with

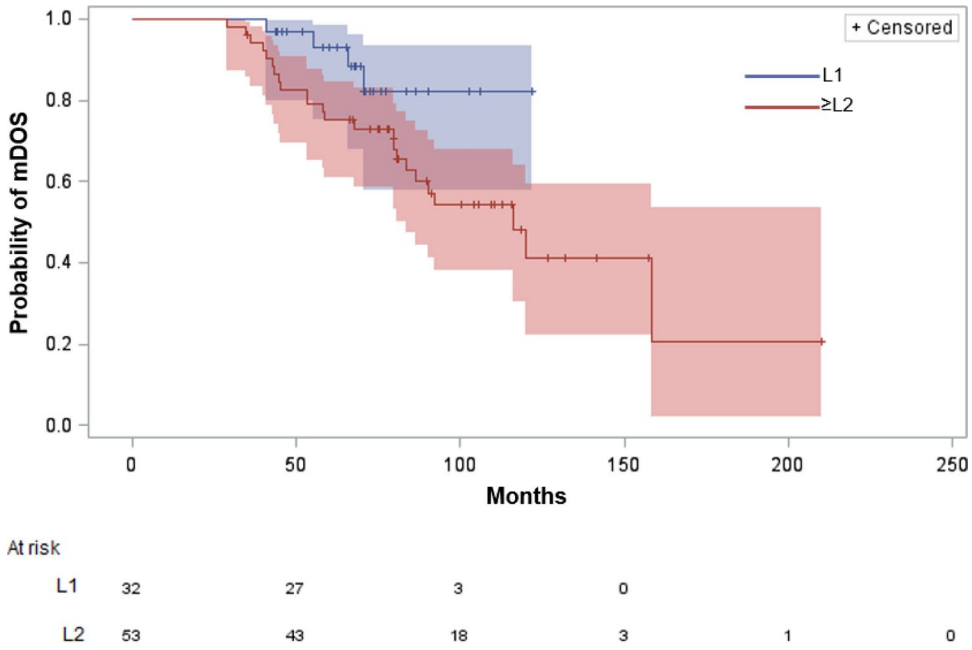


**Fig. 3** Kaplan–Meier estimated probability of median [95% CI] overall survival (mOS) from diagnosis of aNSCLC patients treated with line 1 (L1; blue) or line 2 or more (≥ L2; red) crizotinib

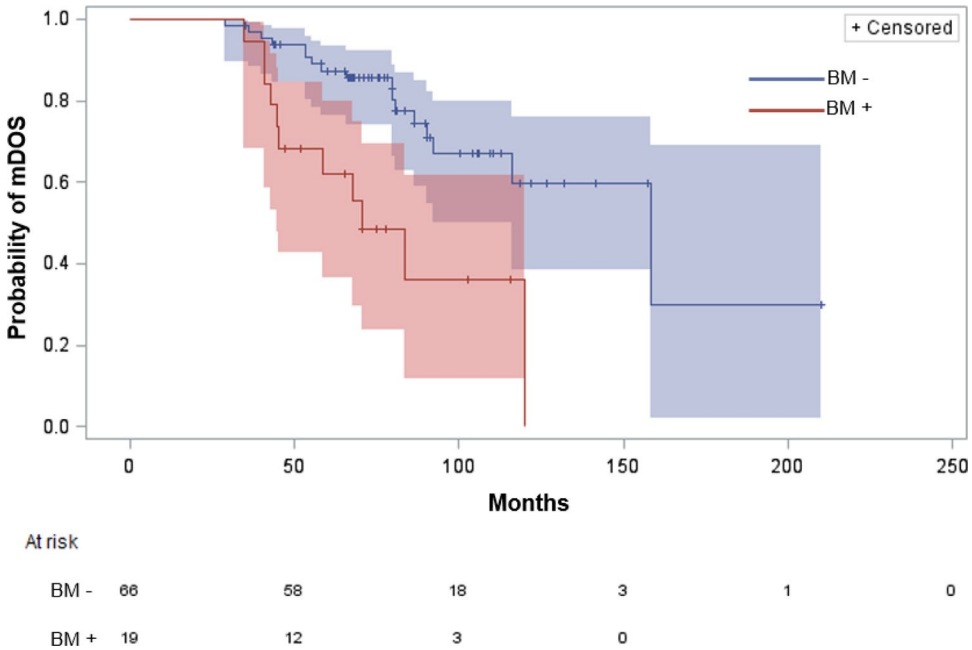


**Fig. 4** Kaplan–Meier estimated probability of median overall survival [95% CI] according to brain metastasis presence (BM+; red) or absence (BM−; blue) at aNSCLC diagnosis

crizotinib [25]. The French CLINALK study that assessed crizotinib efficacy when it had been accorded a temporary use authorization, reported mOS at nearly 90 months post-diagnosis of aNSCLCs [26]. However, because we enrolled only long responders for this analysis, those data are not comparable.

Here, the mOS was only numerically superior for L1 crizotinib recipients compared with those given crizotinib as ≥ L2 (NR versus 116.2 months, respectively; $p = 0.0717$). These results support the principle that ALK-TKIs should be prescribed early during the treatment sequence to these patients [27].

Some authors described prolonged responses to crizotinib [27–34], with 5-year PFS sometimes associated with complete responses [14–16]. Emirzeoglu and Olmez reported on a 49-year-old non-smoker woman with advanced *ALK*+ NSCLC who was in complete response on crizotinib for more than 6 years before isolated brain recurrence [28].

The general profiles of these long-term responders are consistent with the traditionally recognized characteristics

of patients with *ALK*+ NSCLCs, namely younger age, lung adenocarcinomas, and predominantly non-smokers. But an initial clinical picture seems to emerge for the long-term responders: mainly in good general condition (85.9% ECOG PS 0/1), with paucisymptomatic and relatively indolent monometastatic disease at diagnosis and progression. Few studies have analyzed the clinical profile and its impact on OS. The CLINALK study included unselected patients treated with crizotinib, across all lines; its multivariate analyses revealed that ex- or non-smoker status at diagnosis, adenocarcinoma histology, and ECOG PS 0/1 were significantly associated with a lower risk of death [26]. Pacheco et al. analyzed a retrospective single-center cohort of *ALK*+ aNSCLCs [35] and found mOS to be 81 months for the 105 L1 crizotinib recipients and the number of metastatic sites was associated with poor OS; in that population, the long-term responders were younger, with a median of two metastatic sites, fewer BMs (17%), and an oligoprogressive profile with 75% of them having been able to continue crizotinib beyond progression in combination with local treatment. Herein, oligoprogression was documented in nearly 40% of the patients, and crizotinib was continued, which partly explains the mDOT results [36, 37]. Moreover, it supports their significantly longer mOS than for patients who discontinued crizotinib at progression and suggests a continued benefit of crizotinib after oligoprogression accessible to local combination therapy.

In our study, the brain was the most frequent site of progression, representing 42.4% of the metastatic sites. That finding is explained, in part, by the poor blood–brain barrier penetration of crizotinib [9, 38–40]. It agrees with the results of the retrospective study by Weickhardt et al., who found 46% of patients on crizotinib had brain progression, and with the retrospective analysis of patients included in the PROFILE-1005 and -1007 studies: the brain activity of crizotinib controlled the disease in 55% of the patients after 12 weeks of treatment but was transient. Cerebral progression rates ranged from 20 to 72%, depending on whether the patients had BM(s) at diagnosis and whether those metastases were paucisymptomatic or not [41, 42]. In accordance with the literature, we also found that BM(s) at diagnosis had an unfavorable impact on OS.

In this setting of durable responses to first-generation ALK inhibitors (ALKi), after crizotinib failure and its discontinuation, subsequent administration of new-generation ALK-TKIs was feasible, achieving next-generation ALKi mDOTs of 19.4 [95% CI 14.9–25.6] and 11.1 [95% CI 4.8–17.9] months for patients who had received L1 and ≥ L2 crizotinib, respectively. Despite selection biases of several retrospective studies, which means their results must be interpreted with caution, those findings nonetheless suggested a treatment-sequence effect on OS and the possibility of several years' survival with sequential treatments: Gainor et al. described a series of 73 patients given crizotinib followed by ceritinib who had a cumulative mPFS of 17.4 months and mOS of 49.4 months post-diagnosis of metastatic disease [43]. The updated analysis of a larger cohort of patients by Watanabe et al. showed a significantly longer time to failure for crizotinib followed by alectinib than for alectinib (34.4 versus 27.2 months, respectively; HR 0.709 [95% CI 0.559–0.899]; $p = 0.0044$), with no OS benefit of sequential crizotinib–alectinib treatment [44]. Finally, our results are similar to those of the post hoc analysis of the impact of next-generation ALK-TKIs after crizotinib failure in PROFILE-1014 trial: the authors identified four groups of patients according to the anti-*ALK* therapies received or not; the mOS was NR for the crizotinib-arm patients who benefited from new TKIs at progression [8].

This work has several limitations inherent to its retrospective design, as selection bias is inevitable because it analyzed a selected population, composed of so-called long-term responders to crizotinib with a favorable clinical profile and probably treated, in part, within the framework of clinical trials, notably for resistance treatments, with the new ALK-TKIs. Similarly, the selection of patients for the study was based on an arbitrarily set threshold (DOT > 150% of the PFS of the principal trials) to define the "long-term responder" cohort. In addition, patients received crizotinib at different times during their therapeutic trajectories and access to subsequent treatments varied among centers, leading to therapeutic heterogeneity of the population. Another limitation of this study reflects the current anti-*ALK* therapeutic spectrum, which is largely dominated by the newer generation ALK-TKIs: it is legitimate to wonder whether "even longer responders" to the new ALK-TKIs—with much longer OS and treatment times than with crizotinib—exist, given their remarkable efficacy on PFS and intracranial disease control. Finally, the limited molecular data available on *ALK* fusion partners and variants, comutations, and resistance mutations should be highlighted. It can be attributed, among other things, to the absence of their systematic search in routine practice outside clinical trials. Unfortunately, we did not have access to the biopsies of these patients at the time of the analysis. The biological mechanisms underlying the heterogeneity of responses to TKIs are certainly numerous and remain to be elucidated. An increasing number of studies, mainly retrospective, are looking at the sensitivity and efficacy profiles of ALK-TKIs, according to the partner and/or the variant fusing with *ALK* [45]. In addition, advances in next generation sequencing (NGS) are helping to identify new fusion partner genes for the *ALK* rearrangement in patients with lung adenocarcinoma, which are of particular clinical and therapeutic interest [46–48]. Therefore, and in the era of precision medicine, merged data of

clinical and molecular features will be needed to fully characterize the group of *ALK*-rearranged NSCLC patients who may benefit from crizotinib in the first line.

## 5 Conclusion

The results of this real-world study confirmed that some patients with *ALK*+ aNSCLCs—mainly paucisymptomatic, oligometastatic, and without initial BM(s)—benefit from prolonged and remarkable survival on crizotinib, the first-ever validated ALK-TKI in the anti-*ALK* therapeutic arsenal. In addition to these clinical characteristics, it seems important to better understand the molecular profile of these aNSCLCs at diagnosis (fusion partner, comutations, and possible resistance mutation), which will enable us to identify these "crizotinib-addicted" patients.

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### Declarations

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**Conflict of interest** Estelle Dhamelincourt, Renaud Descourt, Gaelle Rousseau-Bussac, Hélène Doubre, Chantal Decroisette, Pierre Demontrond, Gwenaelle Le Garff, Lionel Falchero, Eric Huchot, Sabine Vieillot, Romain Corre, Laure Kazulinski, Acya Bizieux, Laurence Bigay-Gamé, Hugues Morel, Olivier Molinier, Christos Chouaïd, and Florian Guisier declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

**Availability of data and material** The data presented in this study are available on justified request from the corresponding author.

**Ethics approval** The study was conducted in accordance with the Declaration of Helsinki, good clinical practices guidelines, and relevant French ethical and data protection regulations. It was submitted to Comité d'Evaluation des Protocoles de Recherche Observationnelle (CEPRO; reference no. 2021-027) and was validated by that committee on 20 August 2021.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Code availability** Not applicable.

**Author contributions** Conception and design: FG, CC, and RD. Data curation: ED, CC, and RD. Formal analysis: ED, RD, and GRB. Funding acquisition: CC and FG. Investigation: HD, CD, PD, GL, LF, SV, RR, LK, AB, and LBG. Methodology: RD, CC, GRB, and FG. Project administration: CD, CC, and FG. Resources: CD, CC, and FG. Software: not applicable. Supervision: RD, CC, and FG. All authors have read and approved the final version of the manuscript.

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