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Original Research

Efficacy and safety of crizotinib in *ALK*-positive systemic anaplastic large-cell lymphoma in children, adolescents, and adult patients: results of the French AcSé-crizotinib trial



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Anaplastic large-cell lymphoma ALK^+ ; Crizotinib; ALK inhibitors

Abstract Background: The French phase II AcSé-crizotinib trial aimed to evaluate the safety and efficacy of crizotinib in patients with ALK , $ROS1$, and MET -driven malignancies, including ALK -positive anaplastic large-cell lymphoma (ALK^+ ALCL).

Methods: ALK^+ ALCL patients 12 months or older with measurable disease and no standard care options available received crizotinib twice daily at 165 mg/m² in children and adolescents and 250 mg in adults. The primary end-point was the response rate at 8 weeks.

Results: Twenty-eight patients were enrolled between February 2014 and March 2018. Three patients who were not treated were excluded from the analysis. The median age was 19 years. The median previous line of chemotherapy was two. In the 24 patients with an evaluable response, the response rate at 8 weeks was 67% (95% CI: 47–82%). All patients discontinued crizotinib after a median treatment duration of 3.7 months: eight for progression, two for adverse events (AEs) related to prior treatments, and 15 by choice, including six for allogeneic stem-cell transplantation. The median follow-up was 45 months. Nine patients experienced an event: eight relapses (seven after crizotinib discontinuation and one after dose reduction), and one died in complete remission. The median duration of response was 43.3 months (95% CI: 8.3–not reached). The 3-year progression-free and overall survival rates were 40% (95% CI: 23–59%) and 63% (95% CI: 43–79%). Grade 3 or 4 treatment-related AEs occurred in 32% of patients.

Conclusion: Crizotinib shows efficacy and an acceptable safety profile in ALK^+ ALCL relapsed/refractory patients. However, a large proportion of patients experience a relapse after crizotinib discontinuation. Future studies will assess if prolonged ALK inhibitor exposure has curative potential without consolidation.

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1. Introduction

ALK -positive systemic anaplastic large-cell lymphoma (ALK^+ ALCL) is typically responsive to chemotherapy. Studies conducted on both paediatric and adult cohorts have reported progression-free survival (PFS) rates at 5 years of 70–80% in response to various chemotherapy regimens, including ALCL99 [1] in children and CHO(E) P in adults [2,3]. Recent studies have also shown promising results when these regimens are combined with the antibody–drug conjugate brentuximab vedotin [4,5]. After relapse or progression, children and adolescents have a 50–60% chance of survival [6–8], whereas survival rates in adults were under 40% before the availability of brentuximab vedotin but have since improved [9–11]. Nonetheless, poor outcomes remain a major concern for a subset of ALK^+ ALCL patients characterised by either

primary refractory disease or acquired chemoresistance after several sequential relapses.

The use of crizotinib, an inhibitor of ALK , $ROS1$, and MET receptor tyrosine kinases, has shown therapeutic activity in both children [12,13] and adults [14–16] with ALK^+ ALCL. However, data concerning the optimal dose and the outcome after crizotinib discontinuation are still limited.

The French National Cancer Institute (INCa) initiated the AcSé programme in 2013, which granted patients with molecular alterations and malignancies access to targeted therapies outside of market approval [17]. The programme aimed to identify potentially active targeted therapies and evaluate their efficacy and safety for oncological indications where no targeted therapy was approved. In this report, we present the efficacy and safety of crizotinib in ALK^+ ALCL patients enrolled in the AcSé trial.

2. Patients and methods

2.1. Study design

The AcSé-crizotinib trial (NCT02034981) is a non-controlled, open-label phase II study conducted at 17 French oncology centres. The original protocol was approved by the French Independent Ethics Committee (CPP IDF VII-Kremlin Bicêtre) on 5th May 2013, along with subsequent amendments, in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their parents before any study-related procedures.

2.2. Patients

All patients >12 months or older with a confirmed *ALK*⁺ ALCL that had relapsed, progressed, or inadequately responded to the available therapies were eligible for inclusion. The positivity of *ALK* immunostaining was considered a surrogate for the presence of an *ALK* fusion. Main inclusion criteria included the presence of a measurable lesion and ECOG performance status <2 or a Lansky score >50 in patients under 12 years of age. The full list of inclusion and non-inclusion criteria is presented in the protocol provided in the appendix.

2.3. Treatment

Crizotinib was prescribed at 165 mg/m² twice daily (BID) for patients aged 1–17 years and at 250 mg BID in adults. A liquid oral solution was available for children unable to swallow pills. Patients were to receive crizotinib until disease progression, unacceptable toxicity, or decision made by the investigator, the sponsor, or the patient/parents. Inpatient dose reductions were allowed in cases of toxicity. The mean daily dose (i.e., dose intensity) was calculated by dividing the total cumulative dose by the total treatment duration.

2.4. Response evaluation

During the study treatment, the patients had clinical evaluations every 4 weeks until disease progression. Computed tomography (CT) scans and/or magnetic resonance imaging were performed at baseline and then every 8 weeks.

Fluorodeoxyglucose positron-emission tomography CT scans (FDG-PET/CT) were not mandatory. All imaging data were centrally reviewed. Clinical progressions were reported and classified as failures when

radiological or FDG-PET/CT evaluation was not available.

2.5. Objectives and outcomes

The primary objective was to investigate the antitumour activity of crizotinib as quantified by the objective response rate (ORR) at 8 weeks posttreatment initiation and confirmed at the following evaluation. The objective response was defined as a complete response (CR) or partial response (PR) based on RECIST 1.1 criteria for conventional imaging or according to the Lugano criteria [18] in patients evaluated by FDG-PET/CT.

The secondary efficacy objectives included the best overall response (BOR) rate during treatment, duration of response among responders, PFS and overall survival (OS), evaluation of safety.

All adverse events (AEs) recorded during the full duration of the investigated treatment were classified according to CTCAE v. 4.0 and counted as the maximum grade observed per category, patient, and cycle. AEs were assessed by clinical and paraclinical examinations at every scheduled visit during the whole treatment period and reported by 28-d period using a list of 27 predefined AEs. Laboratory tests, including blood count and liver tests, were performed monthly. Ophthalmological examinations were not mandatory during treatment and follow-up except in cases of visual side-effects.

2.6. Sample size calculation and statistical design

A Simon's two-stage design tested the null hypothesis and allowed the trial to stop for futility. Crizotinib was evaluated in the ALCL cohort with an ORR $\geq 40\%$ (P1) and $\leq 20\%$ (P0) for ineffective (alpha = 10%, beta = 10%). The final sample size was 37 patients with at least seven responses to conclude efficacy. The Steering Committee made the decision to halt inclusions in the AcSé trial in March 2018. At that time, the ALCL cohort had progressed to the second stage. A total of 28 patients had already been enrolled, and the number of responses was sufficient to conclude on the efficacy of crizotinib in this indication.

SAS v9.3 (SAS Institute Inc. NC, USA) was used to perform all statistical analyses based on data frozen on 30th October 2020.

2.7. Post-hoc analysis

Quantitative and qualitative characteristics of the patients with response at 8 weeks versus those without

Table 1
ALCL *ALK*⁺ treated in the AcSé-crizotinib trial: patients and treatment characteristics.

| Patients characteristics (N = 25) | |
|--|-------------------------------------|
| Age, median, and repartition in age group, n (%) | |
| Median (years)(range) | 19 (1–60) |
| ≤18 years | 11 (44%) |
| 18–40 years | 12 (48%) |
| > 40 years | 2 (8%) |
| Sex, n (%) | |
| Male | 16 (64) |
| Number of prior therapies, n (%) | |
| 0 | 1 (4) |
| 1 | 8 (33) |
| 2 | 10 (41) |
| 3 | 5 (20) |
| 4 | 1 (4) |
| Patients with at least one prior therapy, n | N = 24 |
| Details of prior therapies (some patients had several) | |
| Front-line chemotherapy | |
| ALCL99 prephase ₁ | 3 |
| ALCL99 ₂ | 7 |
| CHO(E)P ₃ | 9 |
| ACVBP ₄ | 4 |
| Brentuximab Vedotin | 1 |
| Autologous SCT | 4 |
| Allogeneic HSCT | 1 |
| Brentuximab Vedotin | 13 |
| Median time from initial diagnosis to inclusion, (months) (range) | 8 (0–45) |
| CNS involvement, n | N = 4 |
| Former | 3 |
| At inclusion | 1 |
| Treatment characteristics | |
| Crizotinib median dose intensity per age (mg/m ² BID) (range) | |
| Patients ≤18 years (n = 11) | 167 mg/m ² BID (124–208) |
| Patients > 18 years (n = 14) | 130 mg/m ² BID (111–158) |
| Median treatment duration, months (range) | 3.7 (0.37–47.2) |

Note: ₁ALCL99 prephase: dexamethasone, cyclophosphamide, triple intrathecal injection. ₂ALCL99: prephase followed by 6 courses combining dexamethasone, high-dose methotrexate and ifosfamide-aracytine-etoposide alternating with cyclophosphamide-doxorubicin. ₃CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone. ₄ACVBP: doxorubicin, cyclophosphamide, vindésine, bleomycin, prednisone.

response at 8 weeks were compared using Wilcoxon's and Exact Fisher's tests, respectively.

3. Results

3.1. Patients

Between February 2014 and March 2018, 28 *ALK*⁺ ALCL patients were enrolled. Three of them did not receive crizotinib, one due to consent withdrawal and two due to deaths during screening. All 25 patients who had received at least one dose of crizotinib were

included in the analysis. Twenty-one deviations from the inclusion criteria were reported in eight patients, including two major deviations. One concerned the inclusion at the initial diagnosis of a patient not fit enough for chemotherapy. The other one concerned a patient included with an evaluable but not measurable disease. The other deviations were minor and mostly related to abnormal laboratory values (haematological counts, calcium, magnesium titration) or poor performance status. None of these deviations led to the exclusion of the corresponding patient from any analysis presented in this report.

The median age was 19 years (range: 1–60) (Tables 1 and A1). Twenty-one patients were included for a relapse/progression. Among them, 10 never achieved complete remission before inclusion in the trial and were classified as being primarily refractory. Additionally, four patients with a clinical condition incompatible with intensive chemotherapy were included a few days after the initial diagnosis: one had not received previous chemotherapy, whereas three had experienced an inadequate response to the prephase combining cyclophosphamide and dexamethasone, resulting in a deterioration of their clinical condition that rendered intensive chemotherapy incompatible.

The median dose intensity of crizotinib was 492 mg/day (range 376–500) in adults, resulting in a median dose of 130 mg/m² BID (range: 111–158) and 167 mg/m² (range: 124–208) BID in patients under 18.

Table 2
Main end-point results among treated patients (n = 25).

| Criteria | Values |
|---|------------------------|
| Response evaluation criteria per patient | |
| RECIST | 16 |
| Lugano | 8 |
| ORR at 8 weeks (primary end-point) [95% CI] (evaluable patients N = 24) | 67% [47–82%] |
| BOR rate during treatment [95% CI] (evaluable patients N = 24) | 67% [47–82%] |
| Events for PFS | N = 17 |
| Progressions | |
| – under crizotinib medication | 9 |
| – after crizotinib discontinuation | 7 |
| – Death without previous progression | 1 |
| Deaths | N = 10 |
| – Due to progressive disease | 8 |
| – Due to complication after progression and/or alloSCT | 2 |
| Median follow-up (months) [95% CI] | 45 [28–50.9] |
| Median PFS (months) [95% CI] | 11.0 [1.7–47.6] |
| Median duration of response (months) [95% CI] | 43.3 [8.3–not reached] |
| Median OS (months) [95% CI] | Not reached |
| PFS rate at 3 years [95% CI] | 40% [23–59%] |
| OS rate at 3 years [95% CI] | 63% [43–79%] |

ORR, objective response rate; CI, confidence interval; BOR, Best overall response; PFS, progression-free survival; OS, overall survival.

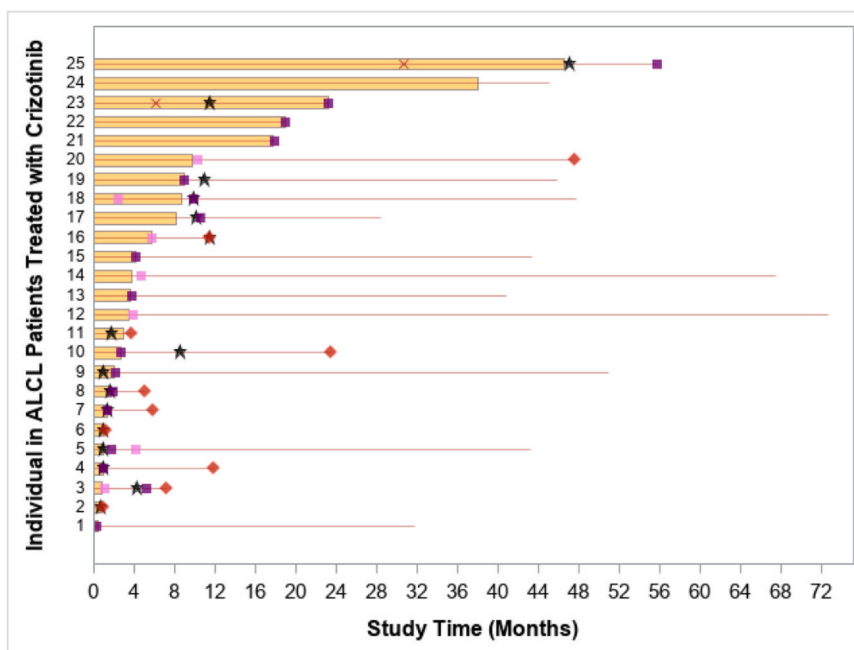


Fig. 1. Patients history. ■ Treatment duration; — Follow-up; ◆ Death; ★ Disease progression; ■ Allogeneic hematopoietic stem-cell transplantation (HSCT); ■ Treatment after crizotinib. Patient #25: Pseudoprogression limited to a minor radiological tumour size increase without clinical symptoms or further progression despite continued crizotinib use for 16 months. This pseudoprogression was not taken into account in the PFS analysis. Relapse a few days after crizotinib discontinuation. Patient #23: Pseudoprogression limited to a minor radiological tumour size increase without clinical symptoms (not taken into account in PFS analysis). Diagnosis of relapse based on a slight increase in the size of a hepatic hilum lymph node with metabolic activity (Deauville 4), which was not amenable to a biopsy. It occurred after a 20% reduction in the dose of crizotinib due to increased transaminase levels. The treatment was then resumed for 12 more months, with the dose increased to its initial level, leading to complete remission. PFS, progression-free survival.

3.2. Tumour response

The study efficacy results are based on 24 patients (Tables 2 and A1, Fig. 1). A patient receiving frontline crizotinib showed significant clinical improvement and could be switched to standard chemotherapy just 11 days after starting crizotinib. Because there was no RECIST evaluation prior to the treatment change, the patient was deemed unevaluable for response. Among the 24 patients evaluated at 8 weeks using RECIST ($n = 16$) or Lugano criteria ($n = 8$), 16 showed responses, including nine with CR (seven radiological CR and two complete metabolic responses) and seven with PR (six radiological PR and one partial metabolic response). The overall response rate at 8 weeks was 67% (95% CI: 47–82%), with 80% (95% CI: 44–97%) in children/adolescents and 57% (95% CI: 29–82%) in patients over 18 (Table 3).

Over the total duration of treatment, 16 patients were responders with 12 CR and 4 PR. The best response rate was 67% (95% CI: 47–82). All responses were observed within the first 2 months of treatment.

Among the 16 responders, the median response duration was 43.3 months (95% CI: 8.3–not reached).

The median duration of crizotinib treatment was 3.7 months (range: 0.7–47.2); one month (0.7–2) in non-

Table 3
ALK⁺ ALCL included in AcSé-crizotinib trial: characteristics, treatment, and outcome of adult patients versus children.

| | Patients ≤ 18 years (N = 11) | Patients > 18 years (N = 14) |
|---|--------------------------------------|-----------------------------------|
| Median age (years) (range) | 11 (1–17) | 25.5 (19–60) |
| Status of the disease at inclusion | | |
| Front-line treatment | 4 | 0 |
| Refractory | 3 | 7 |
| Relapse | 4 | 7 |
| Nb of previous chemotherapy lines | | |
| 0 | 1 | 0 |
| 1 | 7 | 1 |
| 2 | 3 | 7 |
| 3 | 0 | 5 |
| 4 | 0 | 1 |
| Median dose intensity of crizotinib in mg/m^2 BID (range) | 172 (124–208) | 130 (111–158) |
| Response at 8 weeks | | |
| Number of responders | 8/11 | 8/14 |
| Response rate [95% CI] | 80% [44–97%] | 57% [29–82%] |
| Median duration of crizotinib treatment in responders (range) (months) [95% CI] | 18 [0.3–46] | 8 [3.5–10] |
| Median PFS (months) [95% CI] | 47.1 [1.4–NA] | 7.1 [0.9–11.5] |
| Median OS (months) [95% CI] | Not reached | 29.8 [3.8–NA] |
| 3 years-PFS [95% CI] | 64% [35–85%] | 21% [8–48%] |
| 3 years-OS [95% CI] | 78% [45–94%] | 50% [27–73%] |

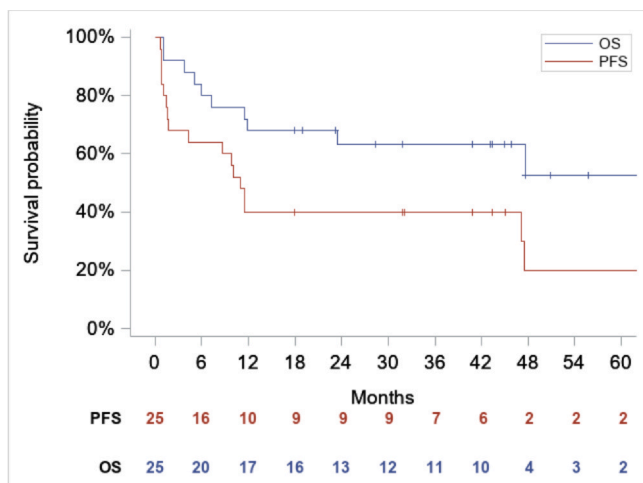


Fig. 2. PFS and OS (without taking into account the two unconfirmed pseudoprogressions). PFS, progression-free survival; OS, overall survival.

responders and nine months in responders (0.3–46). At the time of this report, the treatment has been discontinued in all the patients (Fig. 1 and Table A1): eight for disease progression, two for toxicity related to former allogeneic hematopoietic stem-cell transplantation (allo-SCT), and 15 based on the investigator's decision and/or patients' choice. Among those latter patients, the status before crizotinib discontinuation was CR [10], PR [4], or clinical improvement [1]. Two patients stopped crizotinib after 38 and 46 months of treatment without any further

treatment, and 13 patients were switched to another treatment. Treatment given in responders after discontinuation of crizotinib was allo-SCT in six patients after a median duration of crizotinib of 4.8 months (range: 0.8–10), conventional chemotherapy in three, nivolumab as a consolidation according to the NivoALCL trial (#NCT03703050) in four. Of note, in one patient, crizotinib was resumed for 7 months after allo-SCT.

The median follow-up was 45 months (95% CI: 28–50.9). Nine patients experienced an event after response: eight relapses and one death in remission.

Except for a patient who was diagnosed with a relapse after a dose reduction, all other progressions were observed following the discontinuation of crizotinib, with a median interval of 2 months (range: 0.2–36) after the completion of crizotinib treatment (Fig. 1 and Table A1). Overall, 5/8 patients with a relapse were rescued and alive at the last follow-up. Among the 16 responders, the median duration of crizotinib treatment was 8.5 months (range: 0.8–46) for the eight patients who underwent a relapse and 6.5 months (3–46) for those in whom no relapse was reported during the follow-up period.

Overall, 16 patients progressed (eight non-responders and eight relapses after response) and one died in remission. The median PFS was 11.0 months (95% CI: 1.7–47.6).

Ten patients died, eight from progressive disease, two from an intercurrent complication (viral infection several years after allo-SCT in one patient and unexplained multivisceral failure during treatment for a relapse in the

Table 4

Adverse events (AEs) reported in 10% or more of the patients: number of patients with at least an episode of each AE regardless of the inputability of the event.

| | All patients (N = 25) | | < 18 y (N = 11) | | > 18 y (N = 14) | |
|--------------------------------|-----------------------|------------|-----------------|----------------|-----------------|----------------|
| | All grades | Grades 3–4 | All grades | Grades 3–4 | All grades | Grades 3–4 |
| ALAT increase | 18 (72%) | 4 (1%) | 9 (82%) | 3 (27%) | 9 (64%) | 1 (7%) |
| Anaemia | 17 (68%) | 5 (20%) | 8 (73%) | 3 (27%) | 9 (64%) | 2 (14%) |
| Lymphopenia | 16 (64%) | 3 (12%) | 8 (73%) | 2 (9%) | 8 (57%) | 1 (7%) |
| Neutropenia | 14 (56%) | 8 (32%) | 8 (73%) | 6 (54%) | 6 (43%) | 2 (14%) |
| Leucopenia | 14 (30%) | 2 (8%) | 8 (73%) | 1 (9%) | 6 (43%) | 1 (7%) |
| Nausea | 12 (48%) | 0 | 6 (54%) | 0 | 6 (43%) | 0 |
| ASAT increase | 12 (30%) | 2 (8%) | 6 (54%) | 1 (9%) | 6 (43%) | 1 (7%) |
| Fatigue | 11 (44%) | 2 (8%) | 3 (27%) | 1 (9%) | 8 (57%) | 1 (7%) |
| Diarrhoea | 11 (44%) | 1 (4%) | 5 (45%) | 0 | 6 (43%) | 1 (7%) |
| Alkaline phosphatases increase | 10 (40%) | 0 | 2 (18%) | 0 | 8 (57%) | 0 |
| Vomiting | 9 (36%) | 0 | 5 (45%) | 0 | 4 (28%) | 0 |
| Rash | 8 (32%) | 0 | 3 (27%) | 0 | 5 (36%) | 0 |
| Hypophosphatemia | 7 (28%) | 1 | 5 (45%) | 0 | 2 (14%) | 1 (7%) |
| Visual disorders | 6 (24%) | 0 | 2 (18%) | 0 | 4 (28%) | 0 |
| Gastro-oesophageal disorders | 4 (16%) | 0 | 2 (18%) | 0 | 2 (14%) | 0 |
| Oedema | 4 (16%) | 0 | 1 (9%) | 0 | 3 (21%) | 0 |
| Constipation | 4 (16%) | 0 | 3 (27%) | 0 | 1 (7%) | 0 |
| Loss of appetite | 4 (16%) | 0 | 1 (9%) | 0 | 3 (21%) | 0 |
| Bilirubine increase | 3 (12%) | 0 | 1 (9%) | 0 | 2 (14%) | 0 |

other). The median OS was not reached at the time of analysis. The PFS and OS rates at 3 years were 40% (95% CI: 23–59%) and 63% (95% CI: 43–79%), respectively (Fig. 2).

3.3. Safety

AE reported during treatment duration is shown in Table 4. At least one grade 3 or 4 treatment-related AE was experienced by eight (32%) patients. The most common AE were haematological toxicities (mostly neutropenia, anaemia, fatigue, vomiting, and transaminases increase). The tolerance profile was similar between children and adults both in terms of frequency and severity except for a non-significant excess of grade 3–4 haematological toxicity and transaminases elevation in children as compared to adults. Only two patients discontinued crizotinib for toxicity reasons including a case of graft versus host disease and a systemic candidiasis, clearly related to a previous HSCT. A dose reduction or an interruption for more than 5 d was reported in five patients, in four cases for grade 4 neutropenia, and in one patient for prolonged QTc interval. Six patients (four adults and two children) experienced mild visual disorders (grade 1 or 2) that resolved without long-term sequelae.

3.4. Post-hoc exploratory analyses between responders and non-responders

No statistical difference was observed between responders (N = 16) and non-responders (N = 8) at 8 weeks regarding any of the criteria analysed: age at diagnosis (adults versus children, $p = 0.39$), disease status at inclusion (refractory versus relapse < 2 months from end of treatment versus relapse > 2 months, $p = 0.27$), number of previous chemotherapy lines ($p = 0.58$), dose intensity ($p = 0.98$), BSA ($p = 0.42$), or interval between the initial diagnosis and inclusion ($p = 0.67$).

4. Discussion

The *ALK* inhibitor crizotinib was approved for relapsed/refractory *ALK*⁺ ALCL in children, adolescents, and young adults in January 2021 by the FDA [19] and in children and adolescents only in November 2022 in Europe, more than 8 years after the first demonstration of its efficacy in *ALK*⁺ ALCL. Initiated in 2013, the AcSé-crizotinib trial aimed to further assess the efficacy and safety profile of crizotinib in *ALK*⁺ ALCL patients

and to make this drug available to patients with relapsed/resistant ALCL before its approval. In this trial, 67% of patients responded within 2 months of starting treatment, with a median response duration of 43 months. However, a significant proportion of responders (43%) experienced a relapse after discontinuing crizotinib. Toxicity was acceptable in these patients who had undergone extensive prior treatment.

The response rate in the AcSé trial was slightly lower than that reported in a previous phase 1/2 crizotinib trial conducted by the Children Oncology Group (COG) on 26 children and young adults with relapsed/refractory *ALK*⁺ ALCL [13]. In that trial, Mossé reported response rates of 83% in patients treated with crizotinib at 165 mg/m² (n = 6) and 90% in patients treated at 280 mg/m² (n = 20).

As the COG intended to evaluate crizotinib efficacy not only in *ALK*⁺ ALCL but also in paediatric tumours with *ALK* mutations, which are generally less responsive to *ALK* inhibitors than tumours with *ALK* fusion, Mossé and colleagues [12,13] determined the recommended phase 2 dose of crizotinib to be 280 mg/m² BID, the maximum tolerated dose, a dose, which is almost double the standard adult dose. Whether such a high dose is required for *ALK*⁺ ALCL is questionable. Pharmacokinetics studies associated with this trial indicated that, for doses ranging from 100 to 280 mg/m² BID, the crizotinib plasmatic level exceeded the required inhibitory concentrations observed in ALCL cell lines (IC50: 10 ng/mL) [20].

In the AcSé-crizotinib trial, our aim was to further investigate the efficacy and safety of crizotinib at a dose of 250 mg BID in adults and 165 mg/m² BID in children, which is deemed suitable for combination studies [21]. The ADVL1212 trial (NCT01606878) revealed that crizotinib at 280 mg/m² BID, when administered alongside cytotoxic chemotherapy, exceeded the maximum tolerated dose [21]. Conversely, the combination of crizotinib at 165 mg/m² BID with multiagent chemotherapy as a front-line treatment for patients with ALCL (ANHL12P1, COG trial, [NCT01979536]) was tolerable, albeit with an excess of thromboembolic events necessitating preventive anticoagulation [22].

The dose of 250 mg BID used in the AcSé trial for adults is the approved standard dose for *ALK*-positive non-small-cell lung cancer (NSCLC). However, in the present trial, the median crizotinib dose intensity was only 130 mg/m² BID in adults compared to 167 mg/m² BID in children. This dose demonstrated efficacy in adults with relapsed/resistant ALCL even though the

Table 5
Main results reported in previous trials testing *ALK* inhibitors in *ALK*⁺ ALCL.

| Authors trial identification | Nb of patients | Median age years (range) | Drug | Drug/dose BID | Response rate [95% CI] | Median duration of treatment (months) (range) | Discontinuation for progression after response time to progression in months (m) |
|--------------------------------------|----------------|-----------------------------|------------|-----------------------|------------------------|---|--|
| Mosse (13) NCT00939770 | 26 | 6 (3–13) | Crizotinib | 165 mg/m ² | 83%[36–99] | 94 m | N = 0 |
| | 6 | 12 (–20) | | 280 mg/m ² | 90%[68–99] | 3 m(1- > 24) | N = 2 |
| | 20 | | | | | | 3 m, 18 m |
| Gambacorti-Passerini (15) NCT0121588 | 17 * | 25(15–37) | Crizotinib | 250 mg | 53%[28–77] | 35 m | NA all within 3 months |
| Bossi (16,23) NCT 02419287 | 12 | 31 (18–83) | Crizotinib | 250 mg | 83%[55–95] | 16.5 m (0.6–66) | N = 2 (both with a CNS relapse) 2 m,3 m |
| Fukano (30) UMIN0016991 | 10 | 19 (6–70) | Alectinib | 300 mg | 80%[56–96] | 11.3 m | N = 0 |
| Fischer (31) NCT01742286 | 8 | | Ceritinib | | 75%[56–96] | 2.8 m (0.1–63) | NA |
| Present trial NCT02034981 | 25 | 19 (1–60) < 18y:11 > 18y:14 | Crizotinib | 165 mg/m ² | 67%[47–82] | 3.7 m (0.3–47.2) | N = 0 |
| | | | | 250 mg | 80%[44–97] | | |
| | | | | | 57%[29–82] | | |

* Including also one patient with *ALK*⁺ DLBCL. CI, confidence interval; BID, twice daily; NA, non-available.

response rate reported so far in adults is lower in most trials than those reported by Mosse and colleagues [14–16,23] (Table 5). The difference in response rates observed between children (80%) and adults (53.8%) in this study was not statistically significant, but the small sample size limits the power of this comparison. No link between dose intensity and response was found, but we cannot exclude that some non-responders may have had low drug exposure. In NSCLC, crizotinib efficacy is correlated to drug exposure, which varies widely between individuals treated at the same dose level [21,24]. Lower response rates and shorter PFS have been reported with minimum plasma concentration below 235 ng/mL compared to those above this threshold [24,25]. These observations suggest that drug level monitoring should be an inherent part of the crizotinib standard of care [25], including for *ALK*⁺ ALCL patients, especially adult patients treated at 250 mg BID, where drug exposure is lower than in children and adolescents.

The FDA has approved crizotinib solely for the treatment of children and young adults with *ALK*⁺ ALCL due to the lack of data on adult patients with relapsed/refractory ALCL [19]. In Europe, crizotinib is only approved for patients under 18-years old. However, there is no evidence supporting the notion that *ALK*⁺ ALCL is a distinct disease in adults and children, and therefore, approval should not be restricted by age. Given the well-characterised safety profile of crizotinib in adults with NSCLC, expanding its indication to adults with relapsed/refractory *ALK*⁺ ALCL is expected to be safe. Future trials should evaluate the optimal dose of crizotinib in both adult and paediatric patients, with consideration for individual pharmacokinetic variations.

Our study revealed that, although a significant proportion of patients experienced haematological and/or hepatic AEs due to crizotinib treatment, none of them had to discontinue the treatment due to toxicity. Visual side-effects, which can be severe with *ALK* inhibitors [26], were reported in 25% of patients but were mild and short-lived in all cases.

Interestingly, all the events considered occurred after crizotinib discontinuation or dose reduction. This finding is consistent with previous data on *ALK* inhibitors in ALCL, suggesting that most progressions occur within the first three months of treatment (Table 4) and are potentially due to *de novo* rather than acquired resistance to crizotinib. After achieving a CR, patients are unlikely to experience further progression while being treated with crizotinib, except for a small risk of CNS progression due to poor CNS penetration of the drug rather than *ALK* inhibitor resistance [15,16,23,27,28–30].

The potential curative effect of *ALK* inhibitors for ALCL in the absence of additional consolidation

remains an open question. In the present trial, only one patient achieved sustained remission with prolonged crizotinib treatment, without additional consolidation therapy. Among the 16 patients who discontinued treatment after achieving response, eight subsequently experienced relapse, including three of the six patients who stopped Crizotinib to have allogeneic-SCT as consolidation. This risk of relapse after crizotinib discontinuation is consistent with our previous observations [31]. It is important to note that, among the eight relapsed, five were successfully rescued, leading to an overall 3-year survival rate exceeding 60%. Due to its design, our trial does not provide sufficient evidence to evaluate the optimal duration of crizotinib or the potential benefits of consolidation therapy following crizotinib-induced remission.

Our findings suggest that crizotinib is an effective and well-tolerated treatment option for both paediatric and adult patients with relapsed/refractory *ALK*⁺ ALCL. However, additional research is needed to address several important questions. First, optimal dosing of crizotinib needs to be determined for both children and adults. Second, it is important to investigate whether prolonged exposure to *ALK* inhibitors can lead to a cure without the need for consolidation therapy. Third, identifying factors associated with treatment failure is crucial for improving patient outcomes. Additionally, further investigations are necessary to evaluate the role of these inhibitors in frontline treatment for high-risk patients to reduce the need for genotoxic chemotherapy and improve overall outcomes.

Ethics approval and consent to participation

Trial registration: NCT02034981

Approval of the original protocol and subsequent amendments by the French Independent Ethics Committee (CPP IDF VII (Kremlin Bicêtre))

The study protocol complies with the principles expressed in the Declaration of Helsinki.

All patients and/or their parents provided written informed consent before initiation of any study-related procedure

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CRediT authorship contribution statement

GV, NHL, CM, and NC designed the trial. CM organised the trial and collected data. NC performed the statistical analysis and LB, NC, and RH analysed the data and wrote the first draught of the manuscript. LB, CR, JAR, PB, AD, SD, NG, AL, FM, FM, MN, AP, YR, LR, AS, DS, MS, and AV included patients, provided data, and contributed to the redaction of the manuscript. LL performed the histological review. SM and AC performed the radiological analyses. All authors read and approved the final draught of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

Table A1.

Table A1
Details on disease status at inclusion, dose, response and outcome in each patient.

| N° | pt | Age y) | Disease status at inclusion | BSA | Dose (mg/d) | Dose (mg/m ² BID) | Best response | Response Criteria | Duration of treatment (months) | Reason of end of treatment | Further relapse (Months after end of crizotinib) | Survival outcome (months since the beginning of crizotinib) |
|----|-------|--------------|-----------------------------|-----|-------------|------------------------------|---------------|-------------------|--------------------------------|--|--|---|
| 25 | 5-10 | Refractory | 0.96 | 400 | 208 | CR | RECIST | 46 | Stop with no further treatment | Pseudoprogression after 30 m of crizotinib | Relapse (0.2) | Alive (55) |
| 24 | 11-15 | Relapse | 1.94 | 500 | 128 | CR | RECIST | 38 | Stop with no further treatment | OT: Nivolumab | | Alive (45) |
| 23 | 11-15 | Refractory | 1.46 | 500 | 171 | PR | RECIST | 23 | OT: Nivolumab | Pseudoprogression after 6 m of crizotinib | Pseudoprogression after 6 m of crizotinib | Alive (23) |
| 22 | 5-10 | Relapse | 0.92 | 400 | 217 | CR | RECIST | 19 | OT: Nivolumab | | | Alive (19) |
| 21 | 11-15 | Relapse | 1.28 | 400 | 156 | CR | RECIST | 18 | OT: Nivolumab | | | Alive (18) |
| 20 | 21-25 | Refractory | 1.98 | 500 | 128 | CR | RECIST | 10 | OT: AlloSCT | | | Death (47) (viral infection) |
| 19 | 26-35 | Relapse | 1.57 | 500 | 159 | CR | RECIST | 9 | Complication | | Relapse (2) | Alive (46) |
| 18 | 21-25 | Refractory | 1.51 | 500 | 165 | CMR | Lugano | 9 | OT: AlloSCT +crizotinib (7 m) | | Relapse (1.1) | Alive (47) |
| 17 | 26-35 | Relapse | 1.56 | 500 | 160 | CR | RECIST | 8 | Complication | | Relapse (2) | Alive (28) |
| 16 | 36-60 | Relapse | 2.03 | 500 | 123 | CMR | Lugano | 6 | OT:AlloSCT | | Relapse (5.8) | DOD (11) |
| 15 | 10-15 | At diagnosis | 1.69 | 500 | 147 | CR | RECIST | 4 | OT:vinblastine | | | Alive (44) |
| 14 | 21-25 | Relapse | 2.02 | 500 | 123 | PR | RECIST | 4 | OT:AlloSCT | | | Alive (67) |
| 13 | < 5 | At diagnosis | 0.47 | 100 | 106 | CR | RECIST | 4 | OT: ALCL99 | | | Alive (41) |
| 12 | 21-25 | Refractory | 1.97 | 500 | 126 | CR | RECIST | 3.5 | OT: AlloSCT | | | Alive (72) |
| 11 | 26-35 | Relapse | 1.45 | 400 | 137 | MP | Lugano | 3 | Progression | | | DOD (3.8) |
| 10 | < 5 | At diagnosis | 0.64 | 220 | 171 | PR | RECIST | 3 | OT: ALCL99 | | Relapse (6) | Death (23) (multiorgan failure) |
| 9 | 16-20 | Refractory | 1.96 | 500 | 127 | MP | Lugano | 2 | Progression | | | Alive (51) |
| 8 | 21-25 | Relapse | 1.56 | 500 | 160 | MP | Lugano | 1.8 | Progression | | | DOD (5) |
| 7 | < 5 | Relapse | 0.61 | 206 | 168 | PD | RECIST | 1.4 | Progression | | | DOD (6) |
| 6 | 36-60 | Refractory | 1.62 | 500 | 154 | PD | RECIST | 1 | Progression | | | DOD (1) |
| 5 | 36-60 | Refractory | 2.09 | 500 | 119 | MP | Lugano | 1 | Progression | | | Alive (43) |
| 4 | 16-20 | Relapse | 1.85 | 500 | 135 | MP | Lugano | 0.9 | Progression | | | DOD (12) |
| 3 | 16-20 | Refractory | 1.79 | 500 | 139 | PMR | Lugano | 0.8 | OT: AlloSCT | | Relapse (3.5) | DOD (7.2) |
| 2 | 26-35 | Refractory | 2.2 | 500 | 113 | PD | RECIST | 0.7 | Progression | | | DOD (1) |
| 1 | 10-15 | At diagnosis | 1.22 | 400 | 163 | CI | clinical | 0.4 | OT: ALCL99 | | | Alive (32) |

Male, male; F, female; CR, complete response; PR, partial response; PD, progressive disease; CMR, complete metabolic response; PMR, partial metabolic response; MP, metabolic progression; CI, clinical improvement; alloSCT, allogeneic stem-cell transplantation; OT, other treatment; DOD, dead of disease; ALCL99: paediatric current front-line chemotherapy for ALCL; Pseudoprogression: unproven relapse limited to a minor radiological tumour size increase without clinical symptoms or further progression despite continued crizotinib use (not taken into account in PFS analysis).

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2023.112984](https://doi.org/10.1016/j.ejca.2023.112984).

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