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Original Research

Long-term outcomes of adults with first-relapsed/refractory systemic anaplastic large-cell lymphoma in the pre-brentuximab vedotin era: A LYSA/SFGM-TC study☆

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Abstract ***Background:*** Long-term outcomes of adults with first-relapsed/refractory (R/R) systemic anaplastic large-cell lymphoma (ALCL) are not definitively established and should be evaluated.

☆ Results of this study were partially presented in an oral session at the 13th International Conference on Malignant Lymphoma, 17–20 June 2015, Lugano, Switzerland.

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ALK protein;
Relapse;
Survival

Patients and methods: We previously published the long-term outcomes of adults with ALCL initially treated with polychemotherapy in LYmphoma Study Association (LYSA) prospective clinical trials conducted during the pre-brentuximab vedotin era. Herein, we report the long-term outcomes of those patients after the first-relapsed/refractory (R/R) events.
Results: Among the 138 (64 (anaplastic lymphoma kinase (ALK(+)) and 74 ALK(−) ALCL) adults initially treated in clinical trials, 40 (14 ALK(+) and 26 ALK(−)) first-R/R ALCL patients and their long-term outcomes were analysed. Median follow-up from the first-R/R events was 12.5 years. For ALK(+) and ALK(−) patients, respectively, median [range] findings were as follows: age at first-R/R event: 35 [19–76] and 61 [34–81] years; time between inclusion in first-line clinical trials and first-R/R events was 6 [1.5–34] and 11.1 [1–67] months (P = 0.36); with median (95% confidence interval) progression-free survival after the first-R/R events: 3.8 (0.7–14.8) and 5.3 (2.4–8.4) months (P = 0.39); and overall survival: 13.6 (0.7–89) and 8.1 (3.3–25) months (P = 0.96). ALCL was the main cause of death.
Conclusion: Most adults with first-R/R ALCL have poor outcomes, with no significant differences between patients with ALK(+) or ALK(−) disease. These results could be used as reference for the evaluation of new drugs to treat R/R ALCL.

1. Introduction

Based on anaplastic lymphoma-kinase (ALK)− protein expression, the 2016 revised World Health Organization (WHO) classification recognises two types of systemic anaplastic large-cell lymphoma (ALCL) that share common morphological features and CD30 expression on virtually all tumour cells: ALK(+) and ALK(−) ALCL [1]. Notably, ALK(+) ALCL carries a better prognosis than ALK(−) ALCL, with 5-year overall survival (OS) rates of roughly 80% and 50%, respectively [2–6]; however, the favourable prognosis of ALK(+) ALCL mainly reflects the younger age at its diagnosis [2].

According to the British Columbia Cancer Agency (BCCA) registry study on first-relapsed/refractory (R/R), peripheral T-cell lymphoma (PTCL) in the absence of stem cell transplantation, the median second progression-free survival (PFS) and OS rates of 17 patients with first-R/R ALCL were 1.8 and 3 months, respectively [7]; in that study, ALK(+), ALK(−) and ALK-unknown ALCL were considered one group.

In their phase-II study, Pro *et al.* treated 58 R/R ALCL (16 ALK(+) and 42 ALK(−)) patients with the anti-CD30-antibody–drug conjugate, brentuximab vedotin [8]. Fifty (86%) patients achieved objective responses, and 33 patients (57%) achieved complete remissions. With short median follow-up, the median PFS was 13.3 months and the 1-year OS was 70%. Although response rates and median PFS were comparable for ALK(+) and ALK(−) ALCL patients, it is not known whether or not this absence of difference was attributable to a specific brentuximab-vedotin effect.

This retrospective study was undertaken to analyse long-term outcomes of adults with first-R/R ALCL enrolled in Lymphoma Study Association (LYSA, formerly the Groupe d'Étude des Lymphomes de l'Adulte, GELA) prospective clinical trials on first-line treatments.

2. Methods

2.1. Patients

We previously reported the long-term outcomes of 138 patients with confirmed ALCL diagnoses after histopathological and immunohistochemical review, and known ALK-expression status [2]. Those patients had been enrolled between 1987 and 2003 in consecutive LYSA prospective trials on aggressive lymphomas and received polychemotherapy as first-line therapy [2]. Herein, we report the long-term outcomes of 40 of those 138 patients after first-R/R ALCL.

During enrolment in the LYSA clinical trials, tumour biopsies were centrally reviewed at the LYSA Pathology Institute and initially regrouped according to the Revised European-American Lymphoma (REAL) classification, based on histological examination of haematoxylin–eosin- and Giemsa-stained slides, and immunohistochemistry determinations of at least CD20, CD3 and CD30 when an ALCL diagnosis was suspected. To study ALCL patients given first-line therapy, four expert haematopathologists (J.B., L.L., G.D. and P.G.) reviewed all ALCL biopsies and extended the phenotypic analyses to reclassify them according to the 2008 WHO classification [2]. A panel of antibodies directed against CD20, CD30, ALK, T-cell antigens (CD2, CD3, CD5), epithelial membrane antigen (EMA; also known as mucin-1) and T-cell intracellular antigen-1 (TIA1) was used. ALCL was diagnosed based on the following WHO-classification criteria: characteristic morphological features (large malignant cells with abundant cytoplasm and pleomorphic, often

horseshoe-shaped, nuclei); CD30 labelling on the membrane and in the Golgi region of virtually all tumour cells; a cohesive growth pattern, often with lymph-node–sinus involvement [2].

After the first-R/R, surveillance imaging (predominantly computed-tomography scans) was obtained, and therapeutic responses were determined by the treating physician.

To ensure exhaustivity of information regarding high-dose therapy–autologous stem-cell transplantation (HDT–ASCT) or allogeneic stem-cell transplantation (alloSCT), the LYSA and French Society of Bone Marrow Transplantation and Cellular Therapy (SFGM-TC) databases were merged. This French registry goes back to the early 1970s and contains patients' clinical data, including diagnosis, first-line treatments, haematopoietic stem-cell transplantation (HSCT)-associated procedures, complications and outcomes. The study population consisted of patients who had undergone HSCT and are followed indefinitely. Data are reported by investigators at each participating centre performing any HSCT.

2.2. Statistical analyses

Patient characteristics and response rates were compared using Fisher's exact or χ^2 tests for discrete variables and Mann–Whitney test or Student's *t*-test for continuous variables. Treatment outcomes are defined by OS, i.e. the interval between first-R/R event and last follow-up visit or death from any cause, and PFS, i.e. the time from first-R/R event to the first sign of second events, relapse after response, progression or death from any cause. Probability of survival was estimated with the Kaplan–Meier method and curves were compared with log-rank tests. Two-sided $P < 0.05$ defined significance. Statistical analyses were computed with Statistical Application System (SAS) software (version 9.2; SAS Institute, Cary, NC).

3. Results

3.1. Patients' clinical and biological characteristics at first-R/R ALCL event

Among the 138 patients (64 ALK(+), 74 ALK(−)) who received first-line polychemotherapy, 40 (14 ALK(+) and 26 ALK(−)) suffered first-R/R events, with respective 5-year cumulative incidence for ALK(+) and ALK(−) ALCL of 22% and 38% (P = 0.038). In first-line, 29/40 (11 ALK(+) and 18 ALK(−)) had received doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone [ACVBP]-like regimen and 11 (3 ALK(+) and 8 ALK(−)) cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-like regimen; 6/40 (4 ALK(+) and 2 ALK(−)) had undergone first-line HDT–ASCT.

Table 1 summarises their main characteristics. Median follow-up from first-R/R events was 12.5 years (11.8–13.6).

At the time of first-R/R events, ALK(+) ALCL patients were significantly younger than those with ALK(−) ALCL (median age 35 versus 61 years, P = 0.005) with significantly more patients <40 years old being ALK(+): 8/14 (57%) versus 3/26 (12%) (P = 0.007). ALK(+) and ALK(−) ALCL patients did not differ for distribution in first-line–therapy clinical trials, gender ratio, immunohistochemistry at diagnosis (CD3 and EMA), first-line chemotherapy regimen or first-line planned HDT–ASCT.

All 40 ALCLs were in first-R/R after polychemotherapy. Only one ALK(−) patient did not receive a first-line anthracycline-based regimen. Six

Table 1
Characteristics of the 40 patients with first-relapsed/refractory ALK+ or ALK− systemic ALCL.

Characteristic	ALK(+)	ALK(−)	P
No. of patients	14 (35%)	26 (65%)	
Gender			0.720
Male	9/14 (64%)	19/26 (73%)	
Female	5/14 (36%)	7/26 (27%)	
IPI at diagnosis			0.728
0–2	8/14 (57%)	9/20 (45%)	
3–5	6/14 (43%)	11/20 (55%)	
PIT at diagnosis			0.147
0–1	10/13 (77%)	9/19 (47%)	
2–4	3/13 (23%)	10/19 (53%)	
β_2-Microglobulin at diagnosis			0.395
<3 mg/l	6/8 (75%)	9/18 (50%)	
≥3 mg/l	2/8 (25%)	9/18 (50%)	
Immunohistochemistry at diagnosis			
CD3+	3/11 (27%)	10/23 (43%)	0.465
EMA+	7/8 (88%)	12/17 (71%)	0.624
First-line clinical trial			0.822
LNH87	2/14 (14%)	5/26 (19%)	
LNH93	7/14 (50%)	14/26 (54%)	
LNH98	5/14 (36%)	7/26 (27%)	
First-line chemotherapy regimen			0.715
Conventional (CHOP-like)	3/14 (21%)	8/26 (31%)	
Intensive (ACVBP-like)	11/14 (79%)	18/26 (69%)	
First-line HDT–ASCT			0.159
Yes	4/14 (29%)	2/26 (8%)	
No	10/14 (71%)	24/26 (92%)	
Age at first-relapsed/refractory event			
Median (years)	35	61	0.005
Range (years)	19–76	34–81	
<60 years	11/14 (79%)	12/26 (46%)	0.092
<40 years	8/14 (57%)	3/26 (12%)	0.007
5-year second PFS, %	21% (5–45)	4% (0–16)	0.393
5-year second OS, %	36% (13–59)	19% (7–36)	0.963
10-year second PFS, %	14% (2–37)	0%	0.393
10-year second OS, %	14% (2–37)	15% (5–32)	0.963

Abbreviations: ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; EMA, epithelial membrane antigen; HDT–ASCT, high-dose therapy–autologous stem-cell transplantation; NS, non-significant; OS, overall survival; PFS, progression-free survival.

patients (4 ALK(+), 2 ALK(−)) had undergone planned HDT−ASCT as first-line treatment consolidation. The median [range] times between inclusion in first-line clinical trials and first-R/R events were 6 [1.5−34] months and 11.1 [1−67] months for ALK(+) and ALK(−) patients, respectively (P = 0.36).

3.2. Treatment and survival after the first-R/R ALCL events

Unfortunately, details of the treatment(s) administered after first-R/R events were not systematically recorded; they were retrieved for 26 patients (7 ALK(+), 19 ALK(−)): 24 received standard salvage chemotherapy (mainly dexamethasone, cytarabine and cisplatin [DHAP] or etoposide, methylprednisolone, cytarabine and cisplatin [ESHAP]) and two ALK(−) patients were given only supportive care. The overall response rate to salvage chemotherapy for the 24 patients was 54% (ALK(+), 71%; ALK(−), 47%; complete response 46%, partial response 8%). Among the 13 responding patients, 6 (2 ALK(+), 4 ALK(−)) underwent HDT−ASCT and 2 (1 ALK(+), 1 ALK(−)) underwent alloSCT (both patients had received first-line HDT-ASCT), with a transplant rate for responding patients of 62%. The other five responders were elderly (1 ALK(+), 3 ALK(−)) or had already undergone first-line HDT−ASCT (1 ALK(+)). No HDT−ASCT or alloSCT was performed for the 11 non-responding patients. Median PFS and OS were 12 and 51 months for responding patients, and 1.6 and 2.9 months for non-responding patients, respectively. Neither PFS (median 5.6 versus 4.5 months, P = 0.31) nor OS (median 12.7 versus 4.5 months, P = 0.13) differed significantly between patients with therapy details after the first-R/R event and those without, respectively.

The SFGM-TC registry enabled us to identify all HDT-ASCT and alloSCT performed after the first-R/R event for the 40 patients. As previously mentioned, 6 (2 ALK(+), 4 ALK(−)) underwent salvage HDT−ASCT after the first event; all of them relapsed or progressed thereafter, with a median of 3.9 months between HDT−ASCT and the second-R/R event, and median PFS and OS from first-R/R events of 8.1 and 12.7 months, respectively. Three patients (1 ALK(+), 2 ALK(−)) underwent alloSCT, all after failure of a previous HDT−ASCT (two patients had received first-line HDT-ASCT as previously mentioned and one ALK(−) patient after first relapse). The first ALK(−) ALCL patient died of alloSCT-related complications on day+160. The second ALK(−) ALCL patient relapsed 3 months after alloSCT and died of ALCL 3 months later. The ALK(+) patient is still alive and relapse-free more than 13 years after alloSCT.

From the first-R/R event, median PFS and OS for the entire cohort were 5.2 and 9.1 months, respectively (Fig. 1). For ALK(+) and ALK(−) ALCL patients, respectively, median (95% CI) PFS rates were 3.8 (0.7−14.8) and 5.3 (2.4−8.4) months, and 10-year (95% CI) PFS rates were 14% (2−37%) and 0% (P = 0.39) (Fig. 2A). Their respective median (95% CI) OS rates were 13.6 (0.7−89) and 8.1 (3.3−25) months, and 10-year OS (95% CI) rates were 14% (2−37) and 15% (5−32%) (P = 0.96) (Fig. 2B).

3.3. Deaths

Among the 40 patients, 37 (13 ALK(+), 24 ALK(−)) died. ALCL caused 31 deaths, solid tumours two, post-alloSCT complications one and unknown for three. The distributions of those causes according to ALK status are shown in Table 2. Concerning the three long-term survivors, one ALK(+) ALCL patient has remained relapse-free more than 13 years after alloSCT and the two ALK(−) ALCL patients, both of whom experienced second R/R events (one after salvage HDT−ASCT), were successfully treated with chemotherapy alone.

3.4. Prognostic factors

Clinical characteristics of the 40 patients were subjected to univariate analyses to evaluate their impact on PFS and OS (Table 3). Notably, ALK and age had no prognostic impact on PFS and OS. There was also no impact of first-line treatment (chemotherapy regimen or HDT−ASCT); however, there was probably not enough power to formally rule out a difference. The small number of cases prevented multivariate analyses.

4. Discussion

This study's long median follow-up of 12.5 years from first-R/R event gave us a unique opportunity to analyse long-term outcomes of a series of adults with first-R/R systemic ALCL.

According to our analysis, 93% of the patients with first-R/R ALCL had poor short-term survival, with only 3/40 (one ALK(+), two ALK(−)) long-term survivors. Although our findings confirmed those of the BCCA registry study [7], ALK(+), ALK(−) and ALK-unknown ALCL were considered one group in that study, making it impossible to compare the outcomes of ALK(+) and ALK(−) ALCL subsets. It should be noted that the BCCA study excluded patients that received transplantation after relapse or progression. In our study, from the first-R/R event onward, no significant PFS or OS differences were found between ALK(+) and ALK(−) ALCL patients. This absence of significant differences was also observed in the phase-II study by Pro *et al.* on 58 R/R ALCL (16 ALK(+) and 42 ALK(−)) patients treated with brentuximab vedotin [8]. Our results suggest that this absence of survival differences between ALK(+) and ALK(−) R/R ALCL patients is not related to a specific brentuximab vedotin effect but rather to disease characteristics.

Patients enrolled in Pro *et al.*'s study had good performance status (0 or 1), they had received a median of two (range, 1–6) chemotherapy regimens prior to brentuximab vedotin and, in an updated analysis with median follow-up at roughly 6 years, the 5-year PFS and OS were 39% and 60%, respectively [9]. Notably, 16 patients received consolidation transplants (eight HDT–ASCT and eight alloSCT) and, at last follow-up, 16 patients remained in complete remission (eight after a consolidative SCT, and the other eight after single-agent, brentuximab vedotin). Our study patients had received one prior chemotherapy regimen and their 5-year PFS and OS rates were 10% and 25%, respectively. Although Pro *et al.*'s extended study and ours are not comparable, their results might suggest that brentuximab vedotin could be more useful than standard chemotherapy regimens to treat R/R ALCL. However, only prospective randomised studies would be able to

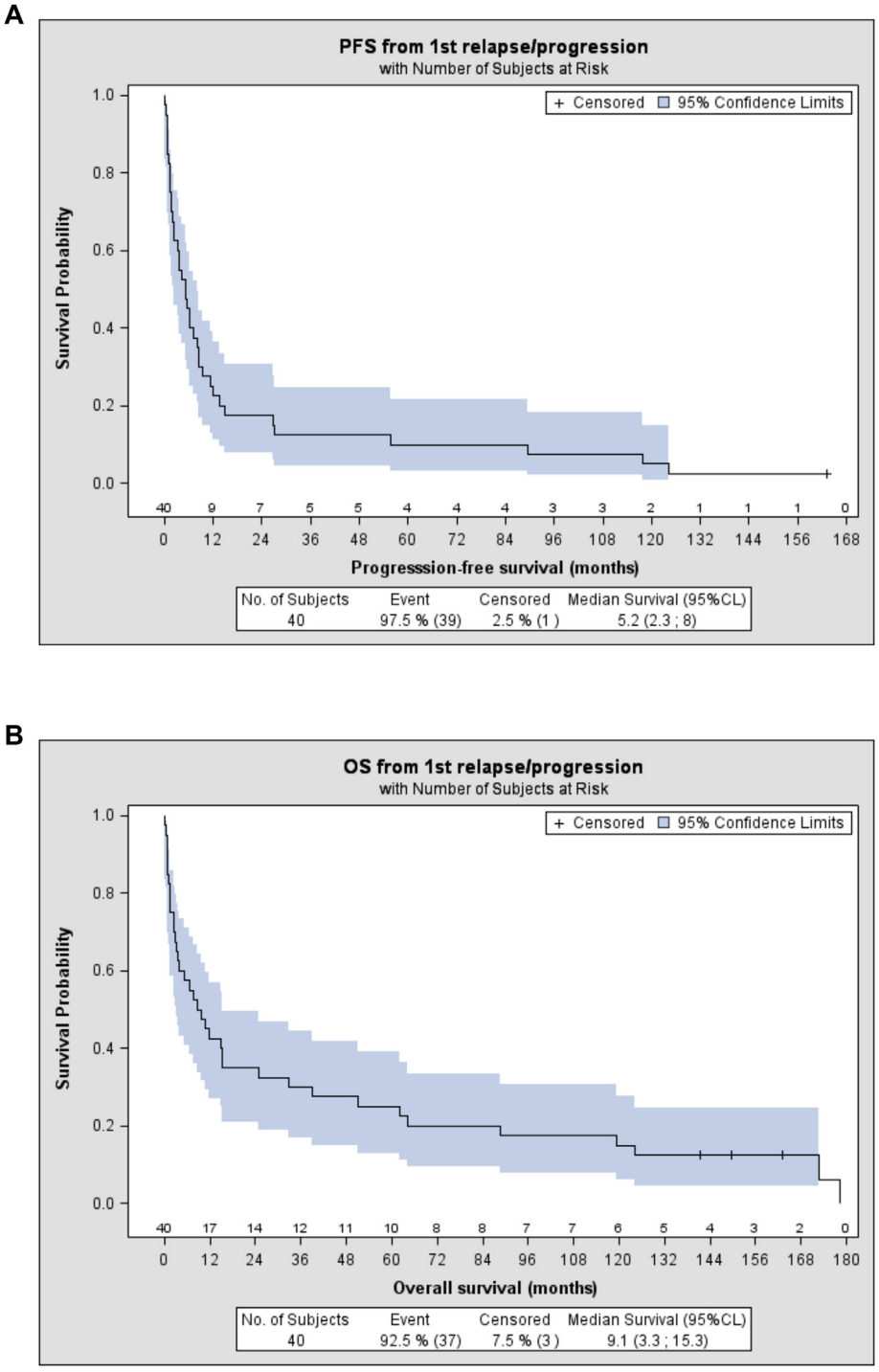
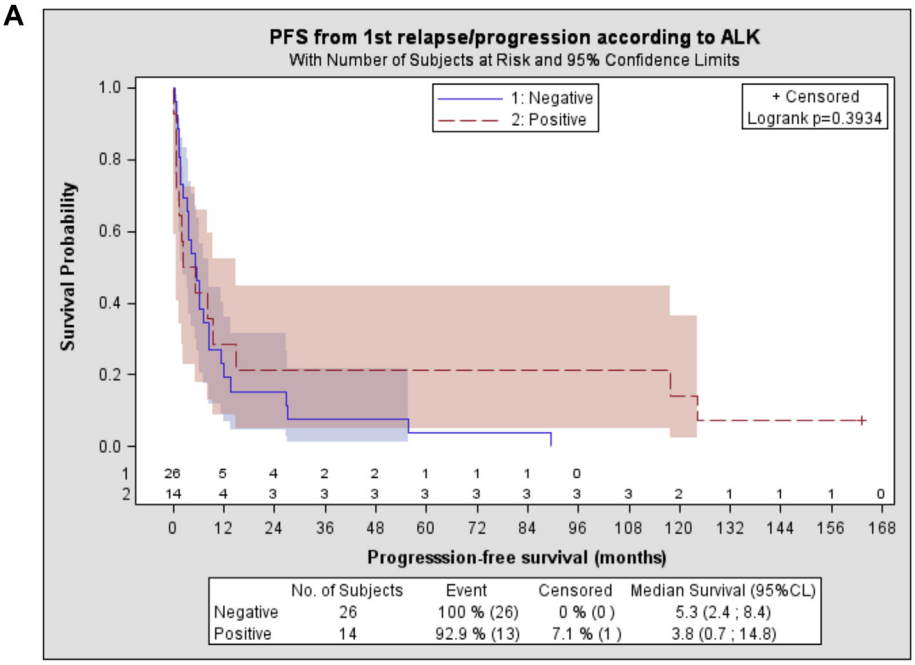


Fig. 1. (**A**) Progression-free survival and (**B**) overall survival of the 40 ALCL adults after the first-relapsed/refractory event. Median follow-up from the first event was 12.5 years.



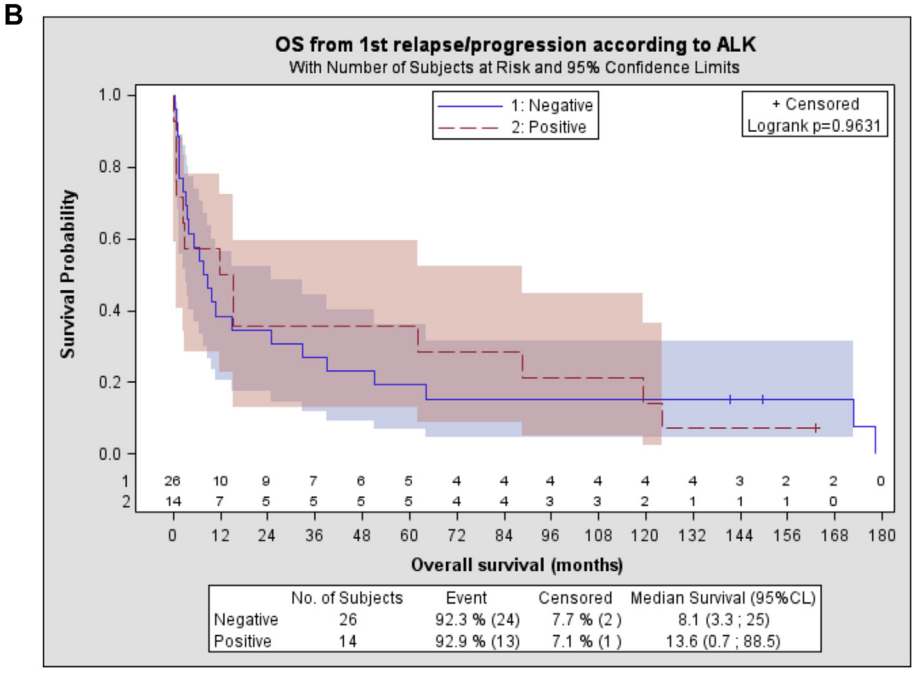


Fig. 2. (**A**) Progression-free survival and (**B**) overall survival of the 40 ALCL adults after the first-relapsed/refractory event according to ALK expression. Median follow-up from the first event was 12.5 years.

demonstrate the potential superiority of brentuximab vedotin over standard chemotherapy regimens.

Survival of adults with relapsed ALK(+) ALCL is much shorter when compared to children, who still have a 50–60% chance of survival after relapse [10]. Because chemotherapy strategies for children and adults differ, questions arise concerning whether age-related differences of tumour biology, host characteristics and/or treatment contribute to the better outcomes of paediatric than adult ALK(+) ALCL patients.

Other agents could be of interest to treat R/R ALCL (Table 4). Crizotinib has been shown to have therapeutic activity against R/R ALK(+) lymphomas, mostly ALCL, in children and adults [11–13]. However, crizotinib discontinuation—even after several years of complete molecular remission—may be followed by

Table 2
Distribution of causes of death according to ALK status.

Cause of death	ALK(+)	ALK(−)
ALCL	10	21
Solid tumour		
Cholangiocarcinoma	1	
Rectal adenocarcinoma	1	
Post-alloSCT complication		1
Unknown	1	2

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; alloSCT, allogeneic stem-cell transplantation.

early ALK(+) ALCL relapse, suggesting the persistence of lymphoma stem cells [14]. Prospective studies are ongoing to assess crizotinib efficacy in larger cohorts of children and adults with ALK(+) ALCL.

Other studies that assessed new drugs for R/R PTCL included some, mainly ALK(−) ALCL patients. Pralatrexate, romidepsin, belinostat or lenalidomide seem to have limited activity in this setting, with overall response rates of 10–35% [15–18].

Vinblastine was highly effective against paediatric R/R ALK(+) ALCL [19]: after median follow-up of 9.2 years from vinblastine initiation for a series of 36 children (35 ALK(+), one ALK unknown; median age at diagnosis, 6 years) in France, 5-year event-free survival (EFS) was 30% and 5-year OS was 65%. Interestingly, vinblastine was still effective against subsequent relapses.

Finally, the respective roles of HDT–ASCT and alloSCT in treating R/R ALCL remain a matter of debate, for both adults and children [6,10,20]. The recent European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL) ALCL-relapse trial on children assessed a risk-adapted strategy. The final trial results confirmed the good alloSCT efficacy after high-risk relapse, achieving 64% 3-year EFS after

Table 3
Univariate analyses of parameters influencing second PFS and OS for all ALCL patients.

Parameter	Progression-free survival			Overall survival		
	P	HR	95% CI	P	HR	95% CI
Age ≥40 years at first relapse	0.22	0.644	0.318–1.303	0.89	0.946	0.441–2.032
ALK(+)	0.39	0.732	0.357–1.504	0.96	1.016	0.510–2.028
Male gender	0.03	2.304	1.057–5.019	0.04	2.207	1.012–4.815
IPI 3–5 at diagnosis	0.51	0.784	0.381–1.617	0.41	1.355	0.659–2.788
PIT 2–4 at diagnosis	0.41	0.730	0.344–1.549	0.7	1.161	0.540–2.499
β_2-Microglobulin ≥3 mg/l at diagnosis	0.23	1.625	0.727–3.634	0.01	2.845	1.191–6.793
First-line clinical trial[a]						
LNH93	0.84	0.912	0.383–2.169	0.51	0.744	0.310–1.787
LNH98	0.45	0.69	0.261–1.821	0.20	0.52	0.188–1.411
First-line chemotherapy regimen[b]	0.1	0.549	0.266–1.135	0.05	0.491	0.237–1.017
First-line HDT–ASCT	0.15	0.495	0.187–1.309	0.70	0.831	0.321–2.148
Relapse/refractory event ≥1 year[c]	0.11	0.58	0.296–1.134	0.43	0.757	0.380–1.508
Relapse/refractory event ≥2 years[c]	0.56	0.783	0.341–1.801	0.91	1.051	0.454–2.434
CD3+	0.86	1.069	0.522–2.188	0.20	1.639	0.77–3.488
EMA+	0.95	1.033	0.403–2.647	0.89	1.073	0.411–2.799

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; CI, confidence interval; EMA, epithelial membrane antigen; HDT–ASCT, high-dose therapy–autologous stem-cell transplantation; HR, hazard ratio; IPI, International Prognostic Index; PIT, Prognostic Index for T-cell lymphoma.
[a] Compared to LNH87.
[b] Conventional (cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]-like) versus intensive (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone [ACVBP]-like).
[c] Time between initial inclusion and first-relapsed/refractory event.

Table 4
Studies evaluating single-agent therapy to treat relapsed/refractory ALCL (including at least 9 patients).

Agent	No. of patients			Overall response rate			Reference
	ALK(+)	ALK(−)	ALK^{unknown}	All	ALK(+)	ALK(−)	
Brentuximab vedotin	16	42	0	86%	81%	88%	Pro *et al.* [8]
Pralatrexate	4	11	2	35%	–	–	O'Connor *et al.* [15]
Romidepsin	1	21	0	–	–	24%	Coiffier *et al.* [16]
Belinostat	2	13	0	13%	0%	15%	O'Connor *et al.* [17]
Lenalidomide	0	0	10	10%	–	–	Toumishey *et al.* [18]
Crizotinib	9	0	0	100%	100%	–	Gambacorti-Passerini *et al.* [13]
Crizotinib (paediatric)	9	0	0	89%	89%	–	Mossé *et al.* [12]
Vinblastine (paediatric)	35	0	1	83%[a]	–	–	Brugières *et al.* [19]

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase.
[a] 30 assessable patients.

relapse, whereas the results obtained with HDT-ASCT for intermediate-risk relapse were quite disappointing (only 41% 3-year EFS) [21].

In conclusion, this long-term analysis confirmed the poor outcomes of adults with first-R/R ALCL. We found no significant survival difference between ALK(+) and ALK(−) ALCL patients. Treatment of R/R adult ALCL remains an important unmet clinical need and the results of clinical trials evaluating new therapies, especially targeted approaches, are eagerly awaited. In this setting, this long-term study could serve as a reference when studying new drugs to treat adult R/R ALCL.

Conflict of interest statement

None declared.

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