



CASE REPORT

Central nervous system relapse in a child with anaplastic large cell lymphoma: potential for new therapeutic strategies

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Abstract

Background: Central nervous system (CNS) relapse is rare in childhood anaplastic large cell lymphoma (ALCL) and is associated with a poor prognosis.

Case: We describe an 8-year-old boy with ALCL who developed an early CNS relapse without initial CNS disease. Despite aggressive medical management, the patient's neurological status deteriorated rapidly and he died shortly after.

Conclusion: Optimal treatment for children with relapsed ALCL involving the CNS remains unclear. Novel agents, including ALK inhibitors, that have CNS-penetration might be helpful and pediatric studies are warranted.

KEYWORDS

ALK, anaplastic, case report, central nervous system, lymphoma, relapse

1 | INTRODUCTION

Anaplastic large cell lymphoma (ALCL) accounts for 20-30% of childhood non-Hodgkin lymphoma (NHL)^{1,2} and often presents with advanced-stage disease. Disease recurrence develops in 20%-40% of patients. CNS involvement at the time of diagnosis and relapse remains rare.^{3,4}

There is currently no consensus on the optimal treatment for children with ALCL with CNS involvement at presentation and even less clarity on therapy for those with relapsed disease involving the CNS. In this report, we describe a child with ALK+ ALCL with a CNS relapse during first-line therapy and review the literature on evolving therapeutic options.

2 | CASE

An 8-year-old young boy presented unwell with prolonged fevers, abdominal pain, and progressive respiratory distress. His physical exam was significant for adenopathy and splenomegaly.

Excisional cervical node biopsy revealed a dense proliferation of atypical lymphoid cells and multiple scattered "hallmark cells." Immunohistochemistry showed diffuse ALK1 expression (nuclear and cytoplasmic), CD30, CD4, focal staining with CD2, and negative CD3 confirming ALK+ ALCL. The pathology met the criteria for the lymphohistiocytic variant.

Diagnostic lumbar puncture (LP) and bone marrow (BM) exam were deferred as the patient could not be sedated due to significant

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respiratory distress. He was urgently started on therapy according to ALCL99 which includes a 5 day pre-phase and six alternating courses of intensive chemotherapy derived from the NHL-BFM protocol.^{5,6} Secondary to his compromised clinical state, intrathecal (IT) chemotherapy due on day 1 of pre-phase could not be administered. Positive emission tomography (PET/CT), completed 1 week post-initiation of therapy showed multiple sites of disease including nodal involvement above and below the diaphragm, lung parenchyma, stomach, small bowel, and bilateral kidneys as well as hypermetabolic lytic bone lesions.

Due to his degree of illness including anasarca, high dose methotrexate (HD MTX) was omitted from cycle 1. He clinically improved and was discharged home briefly before the second cycle. LP with triple IT chemotherapy (15 mg MTX and hydrocortisone and 30 mg cytarabine) was given during his second cycle and his cerebrospinal fluid (CSF) analysis was negative at the time.

On the 19th day of his second cycle of chemotherapy, 54 days from diagnosis, he complained of new-onset headaches, blurry vision, and photophobia. A diagnostics LP showed 135 WBC with blasts. CSF flow cytometry confirmed the presence of ALCL cells that were positive for CD4 and CD30. Magnetic resonance imaging (MRI) showed extensive leptomeningeal enhancement over the cerebral convexities and parenchymal abnormalities within the cerebellar hemispheres consistent with early CNS involvement of ALCL. (Figure 1A,B).

He received triple IT, dexamethasone (10 mg/m²/day), and a session of craniospinal irradiation. The following day he was unresponsive and had a generalized tonic-clonic seizure. Urgent CT showed obstructive tri ventricular hydrocephalus and diffuse extensive leptomeningeal enhancement, particularly in the cerebellum. He received mannitol, hypertonic saline, and an urgent extra ventricular drain (EVD) was inserted. Peripheral blood at that time became positive for circulating blasts, positive for CD30, CD3, and CD4. Ceritinib was started at 20 mg/kg daily through a feeding tube because of its demonstrated CNS efficacy in adult studies.⁷

Subsequent MRI 2 days later showed new cerebellar herniation, compression of the brainstem, and progression of the leptomeningeal enhancement (Figure 2A,B). Despite aggressive medical management, he died 10 days after the date of diagnosis of relapsed disease.

3 | DISCUSSION

CNS relapses, although rare, contribute to mortality in patients with ALK+ ALCL. Survival chance is 50% with intensive B-NHL-type CNS-directed therapy with or without cranial irradiation.^{8,9}

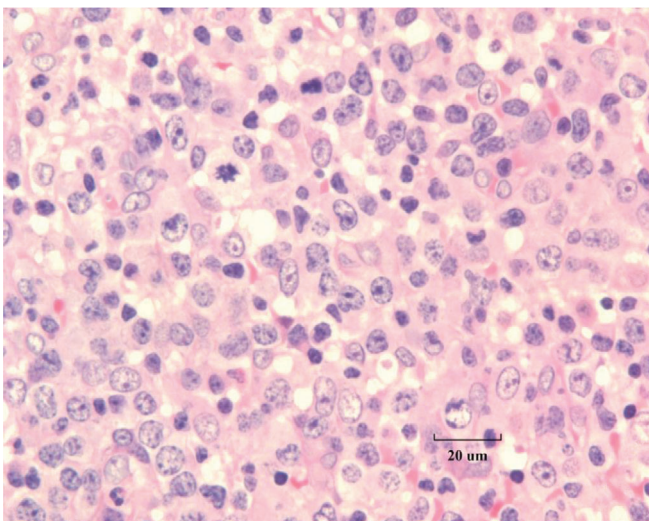
In the patient described, the involvement of the CNS or bone marrow at diagnosis cannot be excluded as these evaluations were not completed. He did have a negative CSF on day 1 of cycle 2 of therapy. He subsequently had clinical, CSF, and radiographic findings of disseminated CNS disease by day 48 of therapy.

Del Baldo et al. described the largest series of patients with CNS relapses in ALK+ ALCL registered on ALCL99 database with an estimated incidence of 4.2% and a 3 year overall survival of 48.7%.¹⁰ Risk factors specifically associated with CNS relapse include circulating peripheral blasts and bone marrow involvement at diagnosis.¹⁰

As most clinical trials of de novo ALCL exclude patients with CNS disease, evidence for the efficacy of treatment is lacking both at the time of initial presentation and at relapse. The role of novel agents in the relapsed setting is currently an area of active research. The main limitation in considering these agents for patients with CNS involvement at the time of relapse is whether the agent crosses the blood-brain barrier (BBB).

Data pertaining to CNS penetrance of these agents are now emerging from a number of clinical trials in adults with ALK+ non-small cell lung cancer (NSCLC) where 7.5% of patients will have brain metastasis at the time of presentation and 25% to 30% will develop brain metastasis during the course of their illness.^{11,12}

(A)



(B)

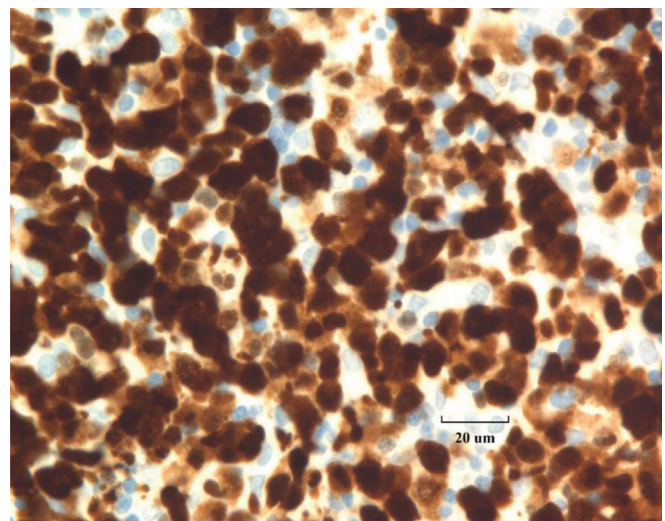
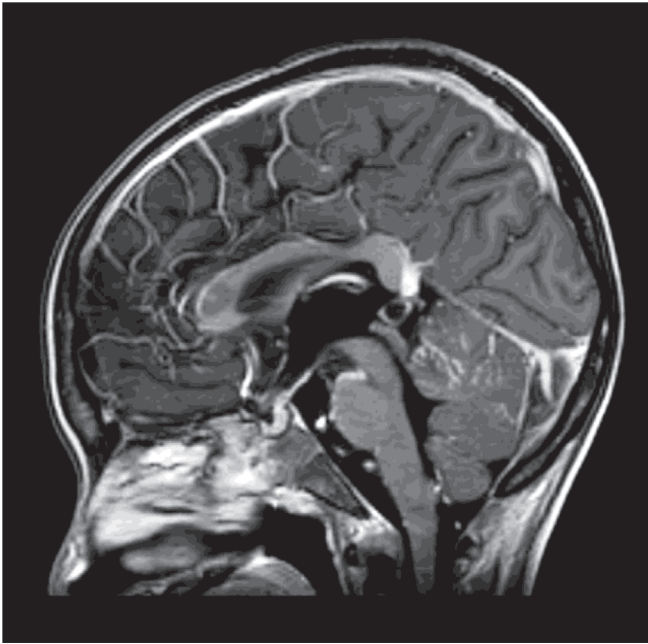


FIGURE 1 (A) H&E showing the subcapsular and paracortical area of the lymph node replaced by anaplastic large cell lymphoma (ALCL) infiltrate. (B) ALCL cells showed nuclear and cytoplasmic immunostaining for ALK-1

(A)



(B)

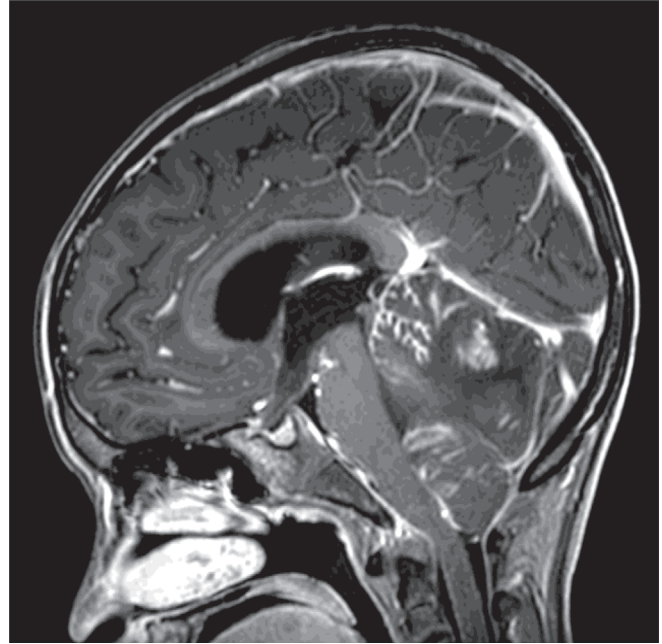


FIGURE 2 (A) Sagittal post-Gadolinium T1 image which demonstrates extensive leptomeningeal enhancement in the cerebellar vermis, along the pons and infundibular recess with signal hypointensity in the genu of the corpus callosum. (B) Sagittal post-Gadolinium T1 image which demonstrates more extensive leptomeningeal enhancement in the cerebellum and vermis which is severely swollen with now effacement of the basal cisterns, compression of the brainstem, and cerebellar tonsillar herniation with hydrocephalus

Single-agent vinblastine (VBL) has shown efficacy when given in relapsed ALCL for prolonged durations.^{9,13,14} There has been inadequate evidence of VBL CNS/CSF penetration in high-risk ALCL relapses. Ruf et al. reported four cases of CNS relapses occurring in patients treated with VBL for a first systemic progression/relapse. They highlight the risk of CNS progression during re-induction in relapses receiving treatment with limited CNS penetration.¹⁵

Some patients with CD30+ ALCL treated with Brentuximab vedotin (BV), an anti CD30 chimeric antibody, have subsequently relapsed with CD30-disease, suggesting a potential mechanism of failure.^{16,17} Its high molecular weight makes it less likely to cross the BBB. Although BV has been shown to induce an objective response in recurrent ALCL,^{18,19} there are reports of CNS progression during re-induction in relapsed ALCL treated with BV. An adult case report also described isolated CNS relapse despite excellent systemic response to BV.^{15,20}

In children, more than 95% of ALCL is ALK+, predominantly due to a translocation NPM-ALK fusion t(2;5)(p23;q35) making it one of the ideal targets.²¹⁻²³ Crizotinib (CRZ), a first-generation ALK inhibitor, studied in ALK+ pediatric ALCL and in adults with NSCLC showed good responses and prolonged survival.²⁴⁻²⁷ However, studies have demonstrated low CSF concentrations of CRZ during systemic chemotherapy.^{28,29} CNS relapse or progression while on CRZ treatment have been described,³⁰⁻³² even in patients who were initially CNS negative.³³

Several second- and third-generation TKI (Table 1) have since been developed to overcome the resistance to CRZ as well as manage

CNS localizations which has been challenging in adults with NSCLC. Ceritinib, a potent oral second-generation ALK inhibitor, has been shown to have 20-fold greater potency than CRZ and highly effective against common CRZ associated mutations.³⁴ In phase II ASCEND 2 trial, ceritinib achieved intracranial responses in patients with baseline brain metastasis. Subsequent data from ASCEND 8 showed similar efficacy and tolerable gastrointestinal toxicity with reduced dosing.³⁵⁻³⁷ Data is still lacking in the pediatric population. Final analysis from a pediatric phase I study (NCT01742286) in pediatric patients with advanced, mostly pre-treated, ALK-aberrant malignancies showed the toxicity profile is similar to that in adults. Of note, out of the 55 patients treated with ceritinib, eight had a diagnosis of ALCL. The overall response rate (ORR) (95% CI) was 75% for the patients with ALCL.³⁸

Alectinib, another second-generation highly selective inhibitor, has been shown to have activity against L1196M, a common mutation causing CRZ resistance.³⁹ Based on the ALEX study of ALK+ NSCLC with brain metastasis, alectinib showed a higher ALK inhibitory potency,⁴⁰ BBB transport, superior CNS activity, and significantly delayed CNS progression, irrespective of prior CNS disease or radiotherapy when compared to CRZ.⁴¹⁻⁴⁴ The excellent intracranial control translated into survival benefit.⁴⁵ Results from a phase II trial evaluating alectinib in refractory/relapsed ALCL in 10 patients, four of which were pediatric patients, showed favorable clinical activity where eight out of 10 patients achieved complete response.^{46,47}

Brigatinib, another second generation, dual inhibitor of ALK and EGFR, showed activity in NSCLC with CNS lesions in an early phase

**TABLE 1** CNS efficacy and toxicity reported with different generation ALK inhibitors

ALK inhibitors	Target kinase	CNS penetrance	Clinical Trial	CNS efficacy in adults with ALK+ NSCLC	Toxicity	Pediatric trials/cases	References
Crizotinib	ALK c-MET ROS1	Poor	PROFILE 1005 and 1007 PROFILE 1014 ALEX NCT02075840	CNS progression on crizotinib in 72% of patients with ALK+ NSCLC Intracranial time to tumor progression not significantly different between crizotinib vs chemotherapy arm CNS progression in 45% of patients in treatment naïve ALK+NSCLC	Neutropenia, lymphopenia, elevated ALT, and hypophosphatemia	Phase I/II trial NCT00939770: CNS metastasis/tumors excluded after two patients had intratumoral hemorrhage (Mosse 2013) Ruf et al. (2018): Case series: 2 patients with CNS progression on crizotinib Mosse et al 2017:26 patients with R/R ALCL. CNS status not given	15,25,26,28,29,61-64
Ceritinib	ALK IGR-1R INSR STK22D	Yes	ASCEND-1 to 5 ASCEND- 4 ASCEND-7	Reported intracranial responses in pts with measurable baseline brain lesions in ALK+ NSCLC Overall IC-RR was 57% with ceritinib vs 22% with chemotherapy Median PFS: 5.2 months and the median OS: 7.2 months.	Vision disorder, bradycardia, interstitial lung disease/pneumonitis, hepatotoxicity, and renal failure	Phase I study NCT01742286: no CNS data	7,35,65
Alectinib	ALK LTK GAK	Yes	ALEX trial	CNS progression under crizotinib in 45% of cases vs 12% with alectinib, OS benefit in pts with CNS metastasis	Elevated ALT, elevated AST, elevated creatinine, anemia, pneumonia	Phase II UMIN000016991: 10 pts with R/R ALCL. 1 year PFS 58.3%, EFS 70% and OS 70%. Pts with CNS disease excluded	47,63,66
Brigatinib	ALK ROS1	Yes	ALTA 1 L	CNS progression 9% brigatinib vs 19% with crizotinib IC-ORR observed in 53% of pts, median IC-PFS was 14.6 months.	Fatigue, diarrhea, visual disturbance, pneumonia, interstitial lung disease/pneumonitis	None	49,67
Lorlatinib	ALK ROS1	Yes (CSF drug concentrations 75% of plasma levels)	Phase II NCT01970865	IC-ORR 66.7% in treatment-naïve patients and 63% in pre-treated	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy and central nervous system effects	NANT 2015-02 NCT03107988: Recruiting	37,51

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; IC-ORR, intracranial objective response rate; IC-PFS, intracranial progression-free survival; OS, overall survival; PFS, progressionfree survival; R/R, relapsed, refractory.

I/II trials.⁴⁸ In the phase III ALTA-1L trial, brigatinib also demonstrated superior intracranial efficacy as compared to CRZ.⁴⁹

Lorlatinib is a third-generation ALK inhibitor designed to have a pan-inhibitory activity against ALK. In phase I, NSCLC study response rates with lorlatinib in patients with measurable and non-

measurable brain metastases reached 39% and 31%, respectively.⁵⁰ In the phase II study, lorlatinib yielded intracranial overall response rates of 66.7% in treatment-naïve patients with measurable brain metastases and 63% in those treated with at least one ALK inhibitor.⁵¹

Other alternatives include the use of immune checkpoint inhibitors. Programmed death ligand 1 (PD-L1), whose expression is induced by NPM-ALK to promote immune evasion by STAT3 pathway activation, is being targeted. Nivolumab, a PD1 inhibitor, showed a prolonged response in patients with refractory ALK+ ALCL.^{52,53} It was also reported to have a good response activity in adults with primary CNS lymphoma.⁵⁴

CD30 is a promising target universally expressed in all ALCL among other lymphomas. Two recent clinical trials of CD30-directed Chimeric Antigen Receptor T (CAR-T) cells in relapsed/refractory (r/r) CD30+ lymphomas have shown preliminary efficacy in patients with heavily treated r/r disease.⁵⁵⁻⁵⁸ Frigault et al. described eight patients with secondary CNS lymphoma treated with tisagenlecleucel where the activity of CAR T cells within the CNS space was demonstrated.⁵⁹ Barriers still to overcome for CNS efficacy include an immunosuppressive microenvironment, unique properties to the CNS that limit T cell entry, and risks of immune-based toxicities in this highly sensitive organ.⁶⁰

In summary, we describe a child with an early CNS relapse of ALK + ALCL who died despite aggressive management. Optimizing CNS-directed therapy for children with ALCL both in initial therapy and at the time of relapse deserves further research. Multiple agents in development may have an important role in this setting.

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None.

AUTHOR CONTRIBUTIONS

Helen Branson: Resources. **Bo-Yee Ngan:** Resources. **Sarah Alexander:** Supervision; writing-review & editing. **Oussama Abila:** Supervision; writing-review & editing.

CONFLICT OF INTEREST

No potential sources of conflict of interest.

ETHICAL STATEMENT

Institutional approval was not required for a case report. All the patient information was de-identified for the purpose of this case report. Patient consent was therefore not obtained for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

- Sandlund JT, Downing JR, Crist WM. Non-Hodgkin's lymphoma in childhood. *N Engl J Med.* 1996;334(19):1238-1248.

- Lowe EJ, Gross TG. Anaplastic large cell lymphoma in children and adolescents. *Pediatr Hematol Oncol.* 2013;30(6):509-519.
- Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: a Berlin-Frankfurt-Munster Group Report. *J Clin Oncol.* 2007;25(25):3915-3922.
- Laver JH, Kravaka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. *J Clin Oncol.* 2005;23(3):541-547.
- Seidemann K, Tiemann M, Schrappe M, et al. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: a report of the Berlin-Frankfurt-Munster Group Trial NHL-BFM 90. *Blood.* 2001;97(12):3699-3706.
- Brugieres L, Le Deley M-C, Rosolen A, et al. Impact of the methotrexate administration dose on the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of a randomized trial of the EICNHL Group. *J Clin Oncol.* 2009;27(6):897-903.
- Chow L, Barlesi F, Bertino E, et al. Results of the ASCEND-7 phase II study evaluating ALK inhibitor (ALKi) ceritinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) metastatic to the brain. *Ann Oncol.* 2019;30:v602-v603.
- Pillon M, Gregucci F, Lombardi A, et al. Results of AIEOP LNH-97 protocol for the treatment of anaplastic large cell lymphoma of childhood. *Pediatr Blood Cancer.* 2012;59(5):828-833.
- Le Deley M-C, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *J Clin Oncol.* 2010;28(25):3987-3993.
- Del Baldo G, Abbas R, Woessmann W, et al. Neuro-meningeal relapse in anaplastic large-cell lymphoma: incidence, risk factors and prognosis—a report from the European intergroup for childhood non-Hodgkin lymphoma. *Br J Haematol.* 2020. <https://doi.org/10.1111/bjh.16755>.
- Schuetz W. Treatment of brain metastases from lung cancer: chemotherapy. *Lung Cancer.* 2004;45:S253-S257.
- Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol.* 2005;23(25):6207-6219.
- Brugieres L, Quartier P, Le Deley M, et al. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children—a report from the French Society of Pediatric Oncology. *Ann Oncol.* 2000;11(1):53-58.
- Brugieres L, Pacquement H, Le Deley M-C, et al. Single-drug vinblastine as salvage treatment for refractory or relapsed anaplastic large-cell lymphoma: a report from the French Society of Pediatric Oncology. *J Clin Oncol.* 2009;27(30):5056-5061.
- Ruf S, Hebart H, Hjalgrim LL, et al. CNS progression during vinblastine or targeted therapies for high-risk relapsed ALK-positive anaplastic large cell lymphoma: a case series. *Pediatr Blood Cancer.* 2018;65(6):e27003.
- Al-Rohil RN, Torres-Cabala CA, Patel A, et al. Loss of CD30 expression after treatment with brentuximab vedotin in a patient with anaplastic large cell lymphoma: a novel finding. *J Cutan Pathol.* 2016;43(12):1161-1166.
- Colton Nielson B, Ryan Fischer M, Garth FM. Loss of CD30 expression in anaplastic large cell lymphoma following brentuximab therapy. *J Drugs Dermatol.* 2016;15(7):894-895.
- Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol.* 2012;30(18):2190-2196.



19. Pro B, Advani R, Brice P, et al. Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. *Blood*. 2017;130(25):2709-2717.
20. Abid MB, Wang S, Loi HY, Poon L. ALK-negative anaplastic large cell lymphoma with CNS involvement needs more than just brentuximab vedotin. *Ann Hematol*. 2016;95(10):1725-1726.
21. Tole S, Wheaton L, Alexander S. Pediatric anaplastic large cell lymphoma—a review. *Oncol Hematol Rev*. 2018;14:21-27.
22. Perkins SL, Pickering D, Lowe EJ, et al. Childhood anaplastic large cell lymphoma has a high incidence of ALK gene rearrangement as determined by immunohistochemical staining and fluorescent in situ hybridisation: a genetic and pathological correlation. *Br J Haematol*. 2005;131(5):624-627.
23. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. *Nat Rev Cancer*. 2008;8(1):11-23.
24. Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177.
25. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a Children's Oncology Group Study. *J Clin Oncol*. 2017;35(28):3215-3221.
26. Mossé YP, Lim MS, Voss SD, et al. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. *Lancet Oncol*. 2013;14(6):472-480.
27. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378.
28. Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. *J Clin Oncol*. 2011;29(15):e443-e445.
29. Metro G, Lunardi G, Floridi P, et al. CSF concentration of crizotinib in two ALK-positive non-small-cell lung cancer patients with CNS metastases deriving clinical benefit from treatment. *J Thorac Oncol*. 2015;10(5):e26-e27.
30. Chun SG, Choe KS, Iyengar P, Yordy JS, Timmerman RD. Isolated central nervous system progression on Crizotinib: an Achilles heel of non-small cell lung cancer with EML4-ALK translocation? *Cancer Biol Ther*. 2012;13(14):1376-1383.
31. Yoshida T, Oya Y, Tanaka K, et al. Clinical impact of crizotinib on central nervous system progression in ALK-positive non-small lung cancer. *Lung Cancer*. 2016;97:43-47.
32. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol*. 2013;8(5):654-657.
33. Costa DB, Shaw AT, Ou S-HI, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. *J Clin Oncol*. 2015;33(17):1881-1888.
34. Friboulet L, Li N, Katayama R, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. *Cancer Discov*. 2014;4(6):662-673.
35. Crinò L, Ahn M-J, De Marinis F, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. *J Clin Oncol*. 2016;34(24):2866-2873.
36. Richly H, Kim TM, Schuler M, et al. Ceritinib in patients with advanced anaplastic lymphoma kinase-rearranged anaplastic large-cell lymphoma. *Blood*. 2015;126(10):1257-1258.
37. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
38. Schulte JH, Moreno L, Ziegler DS, et al. Final analysis of phase I study of ceritinib in pediatric patients with malignancies harboring activated anaplastic lymphoma kinase (ALK). *Proc Am Soc Clin Oncol*. 2020;38:10505.
39. Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. *Cancer Cell*. 2011;19(5):679-690.
40. Kodama T, Hasegawa M, Takanashi K, Sakurai Y, Kondoh O, Sakamoto H. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. *Cancer Chemother Pharmacol*. 2014;74(5):1023-1028.
41. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol*. 2018;29(11):2214-2222.
42. Wrona A. Management of CNS disease in ALK-positive non-small cell lung cancer: is whole brain radiotherapy still needed? *Cancer/Radiothérapie*. 2019;23(5):432-438.
43. Tomlinson SB, Sandwell S, Chuang ST, Johnson MD, Vates GE, Reagan PM. Central nervous system relapse of systemic ALK-rearranged anaplastic large cell lymphoma treated with alectinib. *Leuk Res*. 2019;83:106164.
44. Reed DR, Hall RD, Gentzler RD, Volodin L, Douvas MG, Portell CA. Treatment of refractory ALK rearranged anaplastic large cell lymphoma with alectinib. *Clin Lymphoma Myeloma Leuk*. 2019;19(6):e247-e250.
45. Gourd E. Alectinib shows CNS efficacy in ALK-positive NSCLC. *Lancet Oncol*. 2018;19(10):e520.
46. Nagai H, Fukano R, Sekimizu M, et al. Phase II trial of CH5424802 (alectinib hydrochloride) for recurrent or refractory ALK-positive anaplastic large cell lymphoma: study protocol for a non-randomized non-controlled trial. *Nagoya J Med Sci*. 2017;79(3):407-413.
47. Fukano R, Mori T, Sekimizu M, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: an open-label phase II trial. *Cancer Sci*. 2020;111(12):4540-4547.
48. Camidge DR, Bazhenova L, Salgia R, et al. Safety and efficacy of brigatinib (AP26113) in advanced malignancies, including ALK+ non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol*. 2015;33:8062.
49. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2027-2039.
50. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol*. 2017;18(12):1590-1599.
51. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667.
52. Rigaud C, Abbou S, Minard-Colin V, et al. Efficacy of nivolumab in a patient with systemic refractory ALK+ anaplastic large cell lymphoma. *Pediatr Blood Cancer*. 2018;65(4). <https://doi.org/10.1002/psc.26902>.
53. Hebart H, Lang P, Woessmann W. Nivolumab for refractory anaplastic large cell lymphoma: a case report. *Ann Intern Med*. 2016;165(8):607-608.
54. Nayak L, Iwamoto FM, LaCasce A, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood*. 2017;129(23):3071-3073.
55. Wang C-M, Wu Z-Q, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin's lymphoma: an open-label phase 1 trial. *Lancet*. 2015;386:S12.



56. Wang C-M, Wu Z-Q, Wang Y, et al. Autologous T cells expressing CD30 chimeric antigen receptors for relapsed or refractory Hodgkin lymphoma: an open-label phase I trial. *Clin Cancer Res*. 2017;23(5): 1156-1166.
57. Grover NS, Savoldo B. Challenges of driving CD30-directed CAR-T cells to the clinic. *BMC Cancer*. 2019;19(1):203.
58. Ramos CA, Bilgi M, Gerken CP, et al. CD30-chimeric antigen receptor (CAR) T cells for therapy of Hodgkin lymphoma (HL). *Blood*. 2018;132 (Supplement 1):680-680.
59. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. *Blood*. 2019;134(11): 860-866.
60. Akhavan D, Alizadeh D, Wang D, Weist MR, Shepphird JK, Brown CE. CAR T cells for brain tumors: lessons learned and road ahead. *Immunol Rev*. 2019;290(1):60-84.
61. Gridelli C, Peters S, Sgambato A, Casaluca F, Adjei AA, Ciardiello F. ALK inhibitors in the treatment of advanced NSCLC. *Cancer Treat Rev*. 2014;40(2):300-306.
62. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. *J Clin Oncol*. 2016;34(24):2858-2865.
63. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838.
64. Kwak EL, Bang Y-J, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*. 2010;363(18): 1693-1703.
65. Soria J-C, Tan DS, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet*. 2017;389(10072):917-929.
66. Mok T, Camidge D, Gadgeel S, 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.
67. Huber RM, Hansen KH, Rodríguez LP-A, et al. Brigatinib in crizotinib-refractory ALK+ NSCLC: 2-year follow-up on systemic and intracranial outcomes in the phase 2 ALTA trial. *J Thorac Oncol*. 2020;15(3): 404-415.

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