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Review Article

Anaplastic large cell lymphoma: pathology, genetics, and clinical aspects

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Anaplastic large cell lymphoma (ALCL) was first described in 1985 as a large-cell neoplasm with anaplastic morphology immunostained by the Ki-1 antibody, which recognizes CD30. In 1994, the nucleophosmin (NPM)-anaplastic lymphoma kinase (ALK) fusion receptor tyrosine kinase was identified in a subset of patients, leading to subdivision of this disease into ALK-positive and -negative ALCL in the present World Health Organization classification. Due to variations in morphology and immunophenotype, which may sometimes be atypical for lymphoma, many differential diagnoses should be considered, including solid cancers, lymphomas, and reactive processes. CD30 and ALK are key molecules involved in the pathogenesis, diagnosis, and treatment of ALCL. In addition, signal transducer and activator of transcription 3 (STAT3)-mediated mechanisms are relevant in both types of ALCL, and fusion/mutated receptor tyrosine kinases other than ALK have been reported in ALK-negative ALCL. ALK-positive ALCL has a better prognosis than ALK-negative ALCL or other peripheral T-cell lymphomas. Patients with ALK-positive ALCL are usually treated with anthracycline-based regimens, such as combination cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) or CHOEP (CHOP plus etoposide), which provide a favorable prognosis, except in patients with multiple International Prognostic Index factors. For targeted therapies, an anti-CD30 monoclonal antibody linked to a synthetic antimitotic agent (brentuximab vedotin) and ALK inhibitors (crizotinib, alectinib, and ceritinib) are being used in clinical settings.

Keywords: pathology, immunohistochemistry, mutation, therapy, history

HISTORY

In 1985, Stein *et al*. first described anaplastic large cell lymphoma (ALCL) as a large-cell neoplasm with an anaplastic morphology labeled by the Ki-1 antibody, a monoclonal antibody raised against Hodgkin and Reed-Sternberg (H/RS) cells of classical Hodgkin lymphoma (CHL).[1] The majority of these tumors harbor bizarre cells presenting abundant cytoplasm and prominent invasion of lymph node sinuses. They often resemble carcinoma and were sometimes diagnosed as anaplastic carcinoma, malignant histiocytosis, or non-lymphoid sarcoma. From immunohistological data, Stein considered that these neoplasms could be categorized as lymphoid neoplasms with T- or B-cell lineage (mostly T-cell phenotype) and therefore called them "anaplastic large-cell lymphomas" or other synonyms like "anaplastic large-cell Ki-1-positive lymphomas" in the original report. Subsequently, in 1988, the disease was defined in the updated Kiel classification as "large cell anaplastic (LCA) lymphoma, Ki-1 positive", a type of high-grade lymphoma in the B- or T-cell category.[2] The terminology "anaplastic large cell (ALC) lymphoma" was, however, preferred because the abbreviation LCA could be mistaken for leucocyte common antigen, which is also abbreviated as LCA.[3] In 1994, the Revised European-American Lymphoma (REAL) classification regarded ALCL of a T/null-cell phenotype as a distinct entity, whereas ALCL of B-cell type was included in diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma.[4] The third edition of the World Health Organization (WHO) classification adopted the idea that ALK-positive and -negative ALCLs were the same disease entity. This concept shifted in the fourth edition, where only ALK-positive ALCL was listed as a distinct entity, whereas ALK-negative ALCL was considered a provisional entity.[5] In the revised fourth edition of the WHO classification (2017), both lymphomas are listed as a distinct entity.

EPIDEMIOLOGY AND ETIOLOGY

ALCL, including ALK-positive and -negative ALCL, is a relatively rare subtype of non-Hodgkin lymphoma, accounting for 2% of total cases.[6] Among the adult nodal T-cell lymphomas, ALCL is the third most common subtype of lymphoma, following peripheral T-cell lymphoma, not

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otherwise specified (PTCL-NOS), and angioimmunoblastic T-cell lymphoma.[7] In children, ALK-positive ALCL is the most common subtype of T-cell lymphoma and represents 10–30% of all lymphomas.

Virtually all cases of ALK-positive ALCL are caused by genetic translocations involving *ALK*. Although no potential risk factors have been clearly demonstrated, a study reported five cases of systemic ALK-positive ALCL involving the skin as having a possible relationship with insect bites.[8]

CLINICAL FEATURES

ALK-positive ALCL is most frequently observed in the first three decades of life, unlike ALK-negative ALCL (peak incidence, aged 40-65 years) and PTCL-NOS (very rare in children). A male predominance is observed, and the male-to-female ratio is approximately 1.2 to 3.0.[5,9-17] The majority (50–70%) of patients present with stage III–IV advanced disease with peripheral, including mediastinal, and/or abdominal lymphadenopathy.[5,10-14] Patients often have B symptoms (54–75%),[5,9,10,12,13,15] and extranodal involvement is frequently observed (approximately 60% of cases).[5,10,12,18] The most commonly found extranodal sites are the skin (8–21%), bone (12–17%), soft tissue (17–21%), lung (6–13%), liver (3–17%), and spleen (8–21%), as well as bone marrow (0–16%).[5,9,10,12-14,19] In a report analyzing bone marrow involvement in ALCL, the incidence was 17% with histology only, whereas 40% of cases were found to be positive when immunohistochemistry was combined.[20] Circulating tumor cells or involvement of the gastrointestinal tract or central nervous system (CNS) are rarely detected at diagnosis.[5,9,10] CNS relapse occurs in a small subset of patients.[21-24] Notably, patients with the small cell variant may exhibit a leukemic presentation.[5,25,26] In a report from the International Peripheral T cell Lymphoma (IPTL) project, a retrospective study in which the clinical features of 87 patients with ALK-positive ALCL were analyzed, the incidence of abnormal laboratory results were as follows: lactate dehydrogenase (LDH) elevation (37%), anemia (27%), and thrombocytopenia (10%).[9]

HISTOPATHOLOGY

Initially, ALCL was found to have distinct histopathological features of anaplastic large-cell proliferation. Subsequently, several studies demonstrated that ALCL showed morphological heterogeneity, exhibiting a large and pleomorphic, small-cell, Hodgkin-like, or sarcomatoid appearance. Currently, ALCL is thought to have a broad range of cytological features. Five morphological patterns are described in the fourth edition of the WHO classification based on the variability of cell size and morphology as well as histological architecture.

All morphological patterns shared the presence of large tumor cells, so-called "hallmark" cells, which were first termed by Benharroch *et al*. to be distinctive in ALCL.[15] The cells are large with a bizarre, horseshoe- or kidney-shaped nucleus, and have abundant cytoplasm. The background of the tumor cells differs with each histological variant. Although the different histological patterns do not seem to affect the prognosis, it is critical to differentiate ALK-positive ALCL from other T-cell lymphomas because the latter have a poorer prognosis.[7] In most cases, ALK-positive ALCL can be identified by strong expression of CD30 and ALK in virtually all neoplastic cells. Thus, typical ALK-positive ALCL cases do not seem to present a diagnostic challenge. However, it should be noted that neither CD30 nor ALK is absolutely specific for ALCL; accordingly, the diagnostic significance of the expression of these proteins must be carefully assessed in combination with other phenotypic, morphological, clinical, and even genetic information.

Common pattern

The common variant of ALCL (C-ALCL) is, as the name suggests, the most frequent morphological form of ALCL, accounting for 60% or more of cases.[15] Cytologically, the neoplastic cells represent the hallmark cells; these cells are typically large and contain round, oval, lobulated, horseshoe-shaped, and bizarre nuclei (Figure 1), corresponding to the morphology of the cells in cases initially reported by Stein *et al*. Additionally, multinucleated and wreath-like tumor cells may be observed, often resembling H/RS cells of CHL. The cytoplasm is abundant compared with that in other non-Hodgkin lymphomas and appears pale, amphophilic, basophilic, or eosinophilic. The characteristic pattern of invasion is lymph node sinus involvement and perivascular distribution, which can be found in approximately 75% of cases.[15] The clusters of large cells packing the sinuses may mimic metastatic carcinoma. Partial effacement and surrounding of the residual germinal center are also observed.

C-ALCL has been reported to have two cytological forms.[15,27,28] One is a typical pleomorphic large cell type, including multinucleated and H/RS-like cells, with pale cytoplasm, and the other is a relatively smaller and monomorphic cell type with basophilic cytoplasm. With regard to differential diagnosis, the former, a very large-cell type, should be distinguished from non-lymphoid malignancies, including poorly differentiated carcinoma, while the latter should be differentiated from non-ALCL PTCLs with monomorphic features. These two forms may not be clearly separated and instead are often mixed, exhibiting features of other morphological variants such as small cell and lymphohistiocytic patterns (described below). Additionally, several patterns may be observed in the same patient at different stages of the disease, suggesting that these morphological variants represent the different morphological appearances of a single disease.[15,29,30]

Small cell pattern

In the small cell variant of ALCL (S-ALCL), large hallmark cells are in the minority and the predominant population is small- to medium-sized tumor cells. This variant was first recognized by Kinney *et al*. in 1993 as primary Ki-1-positive T-cell lymphoma with histological features different

from typical ALCL, but with a t(2;5)(p23;q35) translocation.[26] They reviewed more than 100 cases of Ki-1-positive lymphoma and identified nine cases of the small-cell predominant variant.

Histologically, large hallmark cells can usually be identified in and around small vessels. These cells are highlighted by immunostaining for CD30 and ALK. S-ALCL was previously in the category of peripheral T-cell lymphomas other

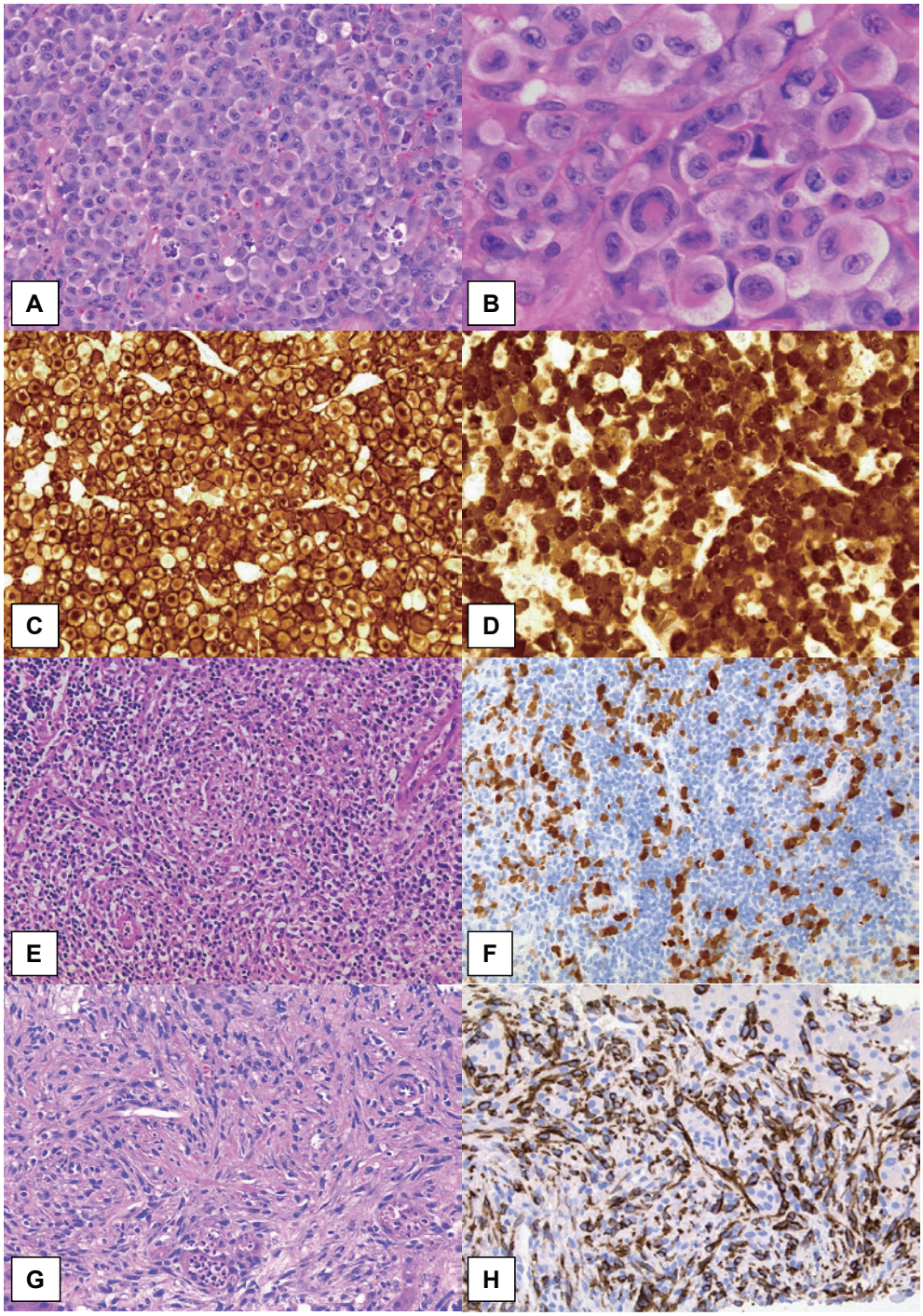

Fig. 1. Morphological patterns and immunostaining of ALK-positive ALCL.
The common pattern of ALK-positive ALCL comprises sheets of large, "hallmark" cell proliferation. Neoplastic cells exhibit variably shaped nuclei; invaginated, horseshoe- or kidney-shaped, donut-like, or Reed-Sternberg-like nuclei with abundant cytoplasm (***A, B***). Strong immunoreactivity for CD30 is generally observed both on the membrane and in the Golgi regions (***C***). In cases of ALCL with the t(2;5) translocation, as shown in this figure, the ALK protein has both nucleolar and cytoplasmic staining pattern (***E, F***). The lymphohistiocytic pattern of ALCL shows conspicuous infiltration of small lymphocytes and histiocytes with pale cytoplasm. Morphologically, neoplastic cells are not clear but are highlighted by ALK immunostaining (***F***). The sarcomatoid pattern of ALCL is characterized by atypical spindle-shaped cell proliferation with fascicular arrangement, simulating soft tissue sarcomas. Neoplastic cells are positive for CD30 (***H***) and ALK expression (***G, H***).

than ALCL; however, most cases of S-ALCL are associated with a component of the common pattern in the same lesion and are also mixed with a lymphohistiocytic variant of ALCL. Small neoplastic cells may or may not present strong CD30 expression, but exhibit positive ALK immunostaining with a nucleus-restricted pattern.[31]

Lymphohistiocytic pattern

The lymphohistiocytic variant of ALCL (LH-ALCL) comprises 10% of ALCL cases. In 1990, Pileri *et al.* first described this variant as "lymphohistiocytic T-cell lymphoma (anaplastic large cell lymphoma CD30+/Ki-1+ with a high content of reactive histiocytes)", and the authors suggested the possibility that this was a morphological variant of ALCL.[32] Due to the unique components of the tumor, however, LH-ALCL was still defined as a separate lymphoma entity, called lymphohistiocytic lymphoma, in the updated Kiel classification.[33] Subsequently, as the morphological spectrum of ALCL was expanded, LH-ALCL was described in the REAL classification as a subtype of ALCL. In 1997, the same group reported a case of LH-ALCL with ALK protein expression by immunohistochemistry, implying the presence of the t(2;5) translocation.[30] Then, in 1998, Ott *et al*. reported a similar case demonstrating the presence of the t(2;5)(p23;q35) translocation and NPM-ALK fusion product, which provided evidence that LH-ALCL belonged to the same spectrum as C-ALCL.[34]

In LH-ALCL, tumor cells often have a minor component with an inflammatory background, with a large number of histiocytes and lymphocytes (Figure 1). Moreover, the tumor cells are generally smaller in size than those of C-ALCL, and larger cells are usually found around blood vessels. From these findings, a diagnosis of ALCL may be difficult to make if pathologists do not recognize these features of such a rare variant of ALCL. The histiocytes in this variant have pale or eosinophilic cytoplasm and round nuclei, and do not resemble epithelioid macrophages, as observed in well-formed granulomas of the lymphoepithelioid variant of PTCL (so-called Lennert lymphoma). Plasma cells and small lymphocytes are present; however, neutrophils and eosinophils are rarely found. The neoplastic cells may cluster around blood vessels, as in S-ALCL, and can be recognized by CD30 and ALK immunostaining.

Hodgkin-like pattern

The Hodgkin-like variant of ALCL (HL-ALCL) is defined not only by morphological features resembling those in nodular sclerosis CHL (NSCHL) but also by the expression of ALK protein as a result of the *ALK* translocation. In the past, due to the striking morphological overlap between ALCL and CHL and the positivity of CD30 in neoplastic cells, cases of ALCL with features similar to those of CHL were originally reported as a variant of ALCL, referred to as "Hodgkin-related" or "Hodgkin-like" ALCL.[35,36] In these reports, certain clinical similarities between HL-ALCL and NSCHL were also described, with frequent mediastinal involvement with bulky mass and relatively limited disease stage. Moreover, in 1995, Orscheschek *et al*. reported the presence of NPM-ALK chimeric mRNA using reverse transcriptase polymerase chain reaction (PCR)-based assays, demonstrating that the t(2;5) translocation, reportedly exclusive to ALCL cases, also occurred in CHL cases and that CHL and ALCL had a common pathogenesis.[37]

However, after ALK immunostaining was developed, some cases thought to be HL-ALCL were shown to be negative for ALK and were subsequently reclassified as variants of CHL rich in tumor cells. Conversely, some histologically aggressive, prognostically poor subgroups of CHL,[38] including NSCHL grade II or lymphocyte-depleted CHL, were found to be within the morphological spectrum of ALCL if ALK expression was identified. Now that ALCL is recognized as a T/null-cell neoplasm with *ALK* translocation, whereas CHL is a B-cell neoplasm without *ALK* translocation, the identification of ALK expression/translocation is the most definitive criterion distinguishing ALCL from CHL.

Histologically, HL-ALCL exhibits nodular lesions separated by thick fibrosclerotic bands, highly suggestive of NSCHL. There are a significant number of neoplastic cells, present either sparsely or cohesively, and some of them have the morphology of H/RS or lacunar cells of CHL. Thus, it is almost impossible, even for expert hematopathologists, to differentiate among these subtypes based on morphology only, and routine surveys with a panel of antibodies, including anti-ALK antibodies, are needed, particularly for cases suggestive of NSCHL. Although hallmark cells and sinus involvement are usually observed, they may occasionally be found in CHL. Reactive inflammatory cells, including macrophages, neutrophils, eosinophils, and small lymphocytes, also infiltrate in HL-ALCL, as observed in CHL; however, the dominant component of the lesion is proliferation of large tumor cells.[35]

Composite pattern and other rare morphological patterns

Approximately 30% of cases of ALK-positive ALCL have a mixture of more than one morphological variant; this is referred to as a composite pattern and has the common pattern with small or lymphohistiocytic patterns, as described earlier. Other rare morphological patterns, such as sarcomatoid, giant cell-rich, and signet-ring cell patterns, are also recognized in the fourth edition of the WHO classification.

The sarcomatoid variant of ALCL is extremely rare, and pathologists have difficulty in identifying this variant as a lymphoid tumor because proliferating cells exhibit a spindle-shaped morphology, as typically observed in soft tissue sarcomas (Figure 1).[39] This feature was first reported by Chan *et al*. in 1990 as a rare case of ALCL with a sarcomatoid growth pattern involving subcutaneous tissue and a lymph node. The histology mimicked malignant fibrous histiocytoma (fibroblastic/myofibroblastic tumor), and the case had a partial highly cellular area consisting of pleomorphic round, oval tumor cells or spindle-shaped cells with a swirling/storiform pattern, and a partly myxoid component with tumor cells was found to form cuffs around the blood vessels, similar to rosette formation. A few small lymphocytes and eosin-

ophils were admixed.

CD30 AND ALK

The use of anti-CD30 and anti-ALK antibodies has facilitated the accurate identification of ALK-positive ALCL. Expression of CD30 and ALK is almost always strong and uniform in cases of C-ALCL; however, in some cases of other variants, including S-ALCL and LH-ALCL, strong staining may be observed only in a small number of admixed hallmark cells, which are often found around blood vessels. Furthermore, in S-ALCL, smaller tumor cells may be negative or only weakly positive for CD30. In contrast, many high-grade B- and T-cell lymphomas, particularly those with large pleomorphic cells or those associated with Epstein-Barr virus (EBV), may express CD30; however, these conditions can be distinguished from ALCL by analysis of a combination of other markers. Additionally, a rare form of large B-cell lymphoma, called ALK-positive large B-cell lymphoma (ALK-positive LBCL), which is positive for the ALK fusion, has been reported and described as a distinct entity in the current WHO classification.[11,40-43]

CD30 is a type 1 transmembrane protein (595 amino acids, 120 kDa) encoded by a gene located at chromosome 1p36 and is also known as tumor necrosis factor (TNF) receptor superfamily 8 (TNFRSF8). In the extracellular domain, CD30 has six cysteine-rich pseudo-repeat motives that show structural characteristics of TNFSF[44] and a TNF receptor-associated factor (TRAF)-binding motif in the C terminus, mediating activation of nuclear factor-κB (NF-κB).[45] Metalloproteinase-cleaved 85-kDa soluble CD30 (sCD30) is found in the peripheral blood of patients with CD30-positive lymphomas or autoimmune diseases.[46,47] The ligand of CD30 is a type II transmembrane protein, CD30L (CD153; 234 amino acids, 26 kDa) encoded by a gene located at chromosome 9q33.[44]

CD30 is expressed by activated B and T lymphocytes.[48] The expression of CD30 is also induced by mitogen stimulation such as phytohemagglutinin (PHA) and Epstein-Barr virus infection.[1,49] CD30 expression is usually observed in hematopoietic tumors, such as CHL and ALCL, and is uncommon in non-hematopoietic tumors, except embryonal carcinoma. CD30 expression is constitutively induced through the CD30/extracellular-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK)/JunB signaling cascade, which regulates the CD30 promoter.[50,51] The NPM-ALK fusion protein also induces JunB.[52]

CD30 activates the NF-κB pathway and MAPKs, including ERK, Jun N-terminal kinase (JNK), and p38.[53-55] CD30 signaling also induces differential responses depending on the cell type. Thymocytes and mature T cells undergo apoptosis through this signal,[56-59] which in turn induces the proliferation of activated T cells and other responses, including cell death, in several CD30-positive lymphoma-derived cell lines.[60] In NPM-ALK-positive ALCL cells, the CD30 signal induces apoptosis, activation of the NF-κB pathway, anti-apoptotic effects through the p38 MAPK pathway, and growth inhibition via the cyclin-dependent kinase inhibitor p21WAF/GIP.[60-64] In contrast, in CHL cell lines, growth inhibition by CD30 signaling is not observed,[61,62] and the NF-κB and ERK1/2/MAPK pathways are constitutively activated, independent of ligands.[50] The details of CD30 regulation and function remain unclear.

In humans, the *ALK* gene is located at chromosome 2p23 and encodes a protein consisting of 1,620 amino acids. Unmodified ALK protein (176 kDa) undergoes post-translational N-linked glycosylation and has a molecular weight of 220 kDa.[65] ALK is a classical receptor tyrosine kinase belonging to the insulin receptor superfamily. There are two meprin A5 protein and protein phosphatase μ (MAM) domains, a low-density lipoprotein class A (LDL-A) domain, and a glycine-rich region in the extracellular region. The MAM domain is thought to play a role in cell-cell interactions.[66] The function of the LDL-A domain is unclear; however, a previous study supported the idea that this domain functions as a ligand-binding site.[67]

In mice, ALK is strongly expressed in the nervous system during the embryonic stage and is then downregulated after birth;[65] therefore, ALK is thought to function in neural development. Immunohistochemical studies have demonstrated that ALK is weakly expressed in adult nerve cells.[68] Activation of ALK stimulates many signal pathways, including the RAS/RAF/MEK/ERK1/2, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphoinositol 3-kinase (PI3K)/AKT, and phospholipase C (PLC)-γ pathways.[69] The RAS/RAF/MEK/ERK1/2 and PLC-γ pathways are related to cell proliferation, whereas the JAK/STAT and PI3K/AKT pathways regulate cell survival and phenotypic changes.

The most common form of *ALK* aberration is fusion gene formation, reported in several types of human cancers (Table 1). Other aberrations include copy number gains and gain of function mutations in neuroblastomas.[70] In most cases of fusion gene formation, exons 1–19 of *ALK* (extracellular to transmembrane regions) are replaced with the 5′ side of a partner gene by chromosomal rearrangement. The ALK kinase domain is retained in the fusion product. The partner genes usually have a domain responsible for dimerization or oligomerization.[71]

In 1994, the first ALK fusion protein, NPM-ALK, was reported in ALCL with t(2;5)(p23;q35).[72,73] Other ALK fusion partners reported in ALCL include TRK fused gene (TFG), tropomyosin 3 and 4 (TPM3 and TPM4), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC), ring finger protein 213 (RNF213), clathrin heavy chain (CLTC), moesin (MSN), non-muscle myosin heavy chain (MYH9), and TRAF.[74-82] NPM-ALK is the most common ALK fusion in ALK-positive ALCL (70–80%), followed by TPM3-ALK (12-18%; Figure 2, Table 2). Other fusions are rare. Among hematopoietic neoplasms other than ALCL, the following partners have been reported: CLTC, NPM1, SEC31 homolog A (SEC31A), sequestosome 1 (SQSTM1), RAN binding protein 2 (RANBP2), echinoderm microtubule associated protein like

Table 1.

Fusion partner	Locus	ALK+ ALCL	IMT	ALK+ LBCL	NSCLC	ALK+ histiocyt otis	Spitz tumor	RCC	CRC	Thyroid carcinoma	Bladder carcinoma	Ovarian cancer	Gastroint estinal leiomyoma	Myeloid leukemia	Ref
CLTC	17q23.1	+	+	+											Bridge JA *et al.* ***Am J Pathol***. 2001, Cools J *et al.* ***Genes Chromosomes Cancer***. 2002, Gascoyne RD *et al.* ***Blood***. 2003
NPM1	5q35.1	+		+			+								Shiota M *et al.* ***oncogene***. 1994, Morris SW. ***Science***. 1994, Van Roosbroeck K. ***Haematologica***. 2010, Yeh I. ***Am J Pathol***. 2015
TFG	3q12.2	+	+		+					+					Hernandez L *et al.* ***Blood***. 1999, Rikova K *et al.* ***Cell***. 2007, McFadden DG *et al.* ***J Clin Endocrinol Metab***. 2014, Lovly CM *et al.* ***Cancer Discov***. 2014
TPM3	1q21.3	+	+			+		+							Lamant L *et al.* ***Blood***. 1999, Lawrence B *et al.* ***Am J Pathol***. 2000, Chan JK *et al.* ***Blood***. 2008, Sugawara E *et al.* ***Cancer***. 2012, Wiesner T *et al.* ***Nat Commun***. 2014
TPM4	19p13.12	+	+												Lawrence B *et al.* ***Am J Pathol***. 2000, Meech SJ *et al.* ***Blood***. 2001
ATIC	2q35	+													Colleoni GW *et al.* ***Am J Pathol***. 2000, Debiec-Rychter M *et al.* ***Genes Chromosomes Cancer***. 2003
MSN	Xq12	+													Tort F *et al.* ***Lab Invest***. 2001
MYH9	22q12.3	+													Lamant L *et al.* ***Genes Chromosomes Cancer***. 2003
RNF213 (ALO17)	17q25.3	+													Cools J *et al.* ***Genes Chromosomes Cancer***. 2002
TRAF1	9q33.2	+													Feldman AL *et al.* ***Genes Chromosomes Cancer***. 2013
EML4	2q21		+	+	+			+	+	+					Soda M *et al.* ***Nature***. 2007, Lin E *et al.* ***Mol Cancer Res***. 2009, Sugawara E *et al.* ***Cancer***. 2012, Cancer Genome Atlas Research N. ***Cell***. 2014, Lovly CM *et al.* ***Cancer Discov***. 2014, Sakamoto K *et al.* ***Int J Hematol***. 2016
SEC31A (SEC31L1)	4q21.22		+	+	+										Panagopoulos I *et al.* ***Int J Cancer***. 2006, Van Roosbroeck K *et al.* ***Haematologica***. 2010, Kim RN *et al.* ***Cancer Res Treat***. 2016
RANBP2	2q13		+	+										+	Ma Z *et al.* ***Genes Chromosomes Cancer***. 2003, Lee SE *et al.* ***Hematol Oncol***. 2014, Maesako Y *et al.* ***Int J Hematol***. 2014
DCTN1	2p13.1		+		+		+								Wiesner T. ***Nat Commun***. 2014, Iyevleva AG. ***Cancer Lett***. 2015, Lee JC *et al.* ***J Pathol***. 2017
FN1	2q35		+									+	+		Ren H *et al.* ***Cancer Res***. 2012, Lovly CM *et al.* ***Cancer Discov***. 2014, Panagopoulos I *et al.* ***Mod Pathol***. 2016
PPFIBP1	12p11.23		+												Takeuchi K *et al.* ***Clin Cancer Res***. 2011
CARS	11p15.4		+												Cools J *et al.* ***Genes Chromosomes Cancer***. 2002, Debelenko LV *et al.* ***Lab Invest***. 2003
RRBP1	20p12.1		+												Lee JC *et al.* ***J Pathol***. 2017
LMNA	1q22		+												Lovly CM *et al.* ***Cancer Discov***. 2014
PRKAR1A	17q24.2		+												Lovly CM *et al.* ***Cancer Discov***. 2014
SQSTM1	5q35.3			+	+										Takeuchi K *et al.* ***Haematologica***. 2011, Iyevleva AG *et al.* ***Cancer Lett***. 2015
STRN	2p22.2				+			+	+	+					Majewski IJ *et al.* ***J Pathol***. 2013, Stransky N *et al.* ***Nat Commun***. 2014, Perot, G. *et al.* ***PLoS One***. 2014, Kelly LM *et al.* ***Proc Natl Acad Sci U S A***. 2014, Kusano H *et al.* ***Am J Surg Pathol***. 2016
TPR	1q31.1				+		+								Choi YL *et al.* ***J Thorac Oncol***. 2014, Yeh I *et al.* ***Am J Surg Pathol***. 2015
KIF5B	10p11.22				+										Takeuchi K *et al.* ***Clin Cancer Res***. 2009
KLC1	14q32.33				+										Togashi Y *et al.* ***PloS One***. 2012
PTPN3	9q31.3				+										Jung Y *et al.* ***Genes Chromosomes Cancer***. 2012
HIP1	7q11.23				+										Hong M *et al.* ***J Thorac Oncol***. 2014
CRIM1	2p22.2				+										Tan DS-W *et al.* ***J Clin Oncol***. 2016 (suppl; abstr 9064)
CLIP1	12q24.1						+								Yeh I *et al.* ***Am J Surg Pathol***. 2015
GTF3C2	2p23.3						+								Yeh I *et al.* ***Am J Surg Pathol***. 2015
VCL	10q22.2							+							Debelenko LV *et al.* ***Mod Pathol***. 2011, Marino-Enriquez A *et al.* ***Genes Chromosomes Cancer***. 2011
WDCP (C2orf44)	2p23.3								+						Lipson D *et al.* ***Nat Med***. 2012
CAD	2p23.3								+						Lee J *et al.* ***Oncotarget***. 2015
PPP1R21	2p16.3								+						Yakirevich E *et al.* ***Clin Cancer Res***. 2016
CENPF	1q41								+						Yakirevich E *et al.* ***Clin Cancer Res***. 2016
MAPRE3	2p23.3								+						Yakirevich E *et al.* ***Clin Cancer Res***. 2016
PRKAR1B	7p22.3								+						Yakirevich E *et al.* ***Clin Cancer Res***. 2016
PPP4R3B (SMEK2)	2p16.1								+						Stransky N *et al.* ***Nat Commun***. 2014
GTF2IRD1	7q11.23									+					Cancer Genome Atlas Research N, ***Cell***. 2014
GFPT1	2p13.3									+					Ji JH *et al.* ***PLoS Genet***. 2015
TPM1	15q22.2										+				Stransky N *et al.* ***Nat Commun***. 2014

ALK+ ALCL: ALK-positive anaplastic large cell lymphoma, IMT: Inflammatory myofibroblastiv tumor, ALK+ LBCL: ALK-positive large B-cell lymphoma, NSCLC: non-small cell lung cancer, RCC: renal cell carcinoma, CRC: colorectal carcinoma

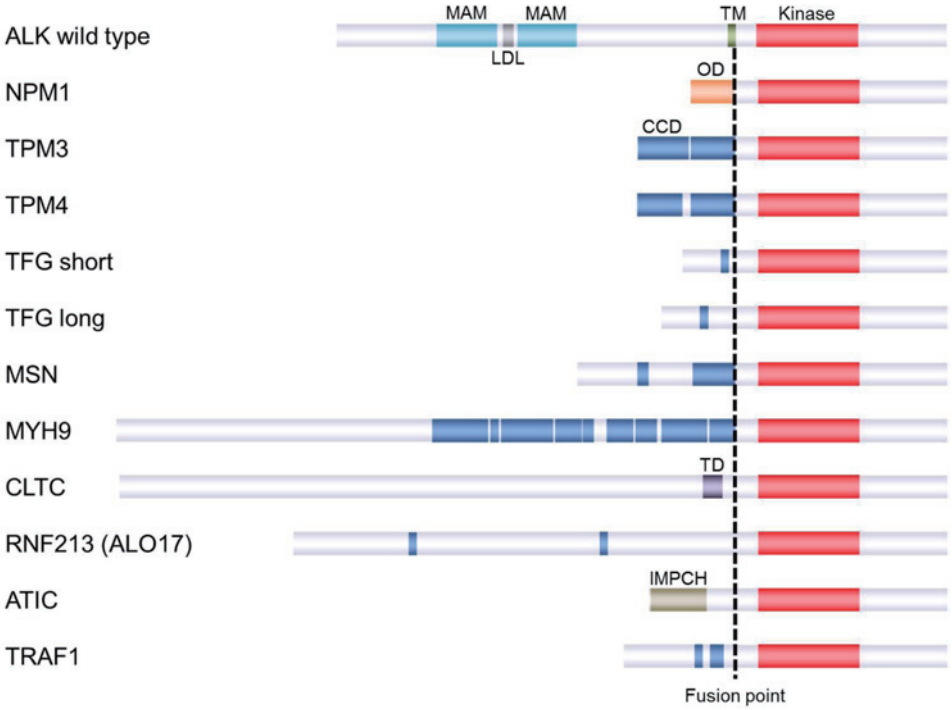

Fig. 2. ALK fusions reported in ALCL

Table 2. Genetic heterogeneity in anaplastic large cell lymphoma

ALK-positive ALCL		
NPM-ALK fusion gene	5q36.1	~80%
TPM3-ALK fusion gene	1p23	~15%
TFG-ALK fusion gene	3q12.2	rare
ATIC-ALK fusion gene	2q35	rare
CLTC-ALK fusion gene	17q23	rare
TPM4-ALK fusion gene	19p13	rare
MSN-ALK fusion gene	Xp11.1	rare
ALO17-ALK fusion gene	17q25.3	rare
MYH9-ALK fusion gene	22q13.1	rare
TRAF1-ALK fusion gene	9q33.2	rare
ALK-negative ALCL		
IRF4/DUSP22 locus rearrangements		30%
*TP63*locus rearrangements		8%
NFKB2-ROS1 fusion gene		-
NCOR2-ROS1 fusion gene		-
NFKB2-TYK2 fusion gene		-
PABPC4-TYK2 fusion gene		-
JAK1 and/or *STAT3* mutations		18%
truncated *ERBB4*		24%

4 (EML4) in ALK-positive large B-cell lymphoma,[43,83-86] TPM3 in ALK-positive histiocytosis,[87] and RANBP2 in myeloid leukemia.[88]

In solid tumors, ALK fusions were first identified in IMT. In approximately 50% of IMT, ALK is fused to TPM3, TPM4, CLTC, ATIC, cysteiny1-tRNA synthetase (CARS), SEC31A, RANBP2, PPFIA binding protein 1 (PPFIBP1), fibronectin 1 (FN1), TFG, EML4, lamin A/C (LMNA), protein kinase cAMP-dependent type I regulatory subunit alpha (PRKAR1A), dynactin subunit 1 (DCTN1), or ribosome binding protein 1 (RRBP1).[78,89-97] FN1-has also been reported in gastrointestinal leiomyoma.[98]

In 2007, EML4-ALK was reported in non-small cell lung cancer (NSCLC);[99] this was the first description of an ALK-positive epithelial tumor. Although very rare, kinesin family member 5B (KIF5B), kinesin light chain 1 (KLC1), TFG, striatin (STRN), protein tyrosine phosphatase, non-receptor type 3 (PTPN3), Huntingtin interacting protein (HIP1), translocated promoter region protein (TPR), SEC31A, SQSTM1, DCTN1, and cysteine-rich transmembrane BMP regulator 1 (CRIM1) have also been reported to function as an ALK fusion partner in NSCLC.[100-109] After the discovery of EML4-ALK in NSCLC, ALK fusions were explored and identified in different epithelial tumors, including renal cancer,[110-113] colon cancer,[114-118] breast cancer,[114] ovarian cancer,[119] thyroid cancer,[116,120-124] and bladder cancer.[116] The frequencies of these fusions are 1–2% in thyroid cancer[120-123] and less than 1% in kidney and colon cancers.[112,118]

Recent studies have revealed that approximately 10% of Spitz tumors harbor ALK fusions.[125] CAP-Gly domain-containing linker protein 1 (CLIP1) and general transcription factor IIIC subunit 2 (GTF3C2) were identified as new partners in Spitz tumors.[126]

ALK immunohistochemistry plays a central role in the diagnosis of ALK-positive tumors. As ALK expression is

observed only in nerve cells, ALK immunohistochemistry-positive non-nerve cells are highly likely to have *ALK* rearrangements.

The ALK immunostaining pattern reflects the subcellular localization of the ALK fusion protein. This localization is dependent on the ALK fusion partner. Therefore, it may be possible to identify the ALK fusion partner in each case based on the staining pattern. For example, NPM-ALK-positive cases exhibit a nuclear and cytoplasmic staining pattern. NPM has a nuclear localization signal in its C-terminus, and heterodimers of wild-type NPM and NPM-ALK translocate to the nucleus, whereas NPM-ALK homodimers remain in the cytoplasm.[127] Currently, only NPM-ALK is known to exhibit nuclear positivity in ALK immunohistochemistry. Other characteristic ALK immunostaining patterns include a granular cytoplasmic pattern for CLTC-ALK, a cytomembrane and cytoplasmic pattern for TPM3-ALK, a cytomembrane pattern for MSN-ALK, and a nuclear membrane pattern for RANBP2-ALK.[79,93,128]

ALK immunohistochemistry is the gold standard for the diagnosis of tumors with ALK fusions. However, NSCLC with EML4-ALK is difficult to stain using standard ALK immunohistochemistry; indeed, in a study of 662 NSCLC cases in 2009, no tumors were immunostained for ALK.[129] Highly sensitive ALK immunohistochemistry allows for the detection of the EML4-ALK fusion protein and is used as a diagnostic tool for ALK-positive NSCLC.[101] Notably, highly sensitive ALK immunohistochemistry can also be used to detect low levels of wild-type ALK protein expressed in tumors with neuroendocrine differentiation, such as small cell carcinoma, although these tumors do not have ALK fusions.[130,131] Alveolar rhabdomyosarcoma and neuroblastoma may also be positive in highly sensitive ALK immunohistochemistry.[70,132]

There are generally two types of assays used for fluorescence *in situ* hybridization analyses of fusion genes, i.e., fusion assays and split (break-apart) assays. In fusion assays, the two genes involved are stained in different colors with the fluorescence-labeled probes. When a mixed-colored signal is observed, the case is recognized as positive for the fusion gene. In split assays, 5′- and 3′-sides of the gene of interest are stained different colors. The gene is observed in the mixed color when it is not rearranged, and individual 5′- and 3′-sides are observed when the sides are translocated by gene rearrangement. For genes that have many fusion partners, such as *ALK*, split assays are more appropriate for screening.

IMMUNOPHENOTYPE OTHER THAN CD30 AND ALK

Based on molecular evidence of the presence of clonal T-cell receptor (*TCR*) gene rearrangement, ALCL is now thought to originate from T cells.[133-135] However, in ALCL, many cases represent an extensive loss of T-cell antigens, and in some cases, none of the lineage-specific markers can be detected; this is called the null-cell phenotype.[15,133] The widely used pan-T-cell markers CD3, CD5, and CD7 are usually negative in the majority of cases, whereas CD2 and CD4 are most commonly preserved. CD8, a killer T-cell marker, is typically negative, whereas the cytotoxic molecules TIA-1 and granzyme B are positive.[133,136] Antibodies against TCR proteins, such as TCRβFl, are often negative in most cases, whereas rare cases have expression of TCRγM1 together with TCRβFl. Although exceptional cases of CHL may be positive for CD3 and CD4, staining for CD3 is usually not strong and exhibits cytoplasmic dot-like staining.

Some lymphoid or non-lymphoid markers are expressed in ALCL. Although not of diagnostic value, these markers are useful for discriminating between ALCL and other lesions. For example, epithelial membrane antigen (EMA), which is normally expressed on the surface of epithelial cells, is observed in the majority of ALCL cases but not in CHL or PTCL-NOS cases.[137] Neoplastic/non-neoplastic large cells with EBV-related markers are identified in some cases of CHL, PTCL-NOS, and large B-cell lymphoma; however, ALCLs are consistently negative for EBV detected either by *in situ* hybridization for EBV-encoded RNA or by immunostaining of latent membrane protein (LMP1) antigen. ALCL is typically negative for CD15 antigen, which is expressed in approximately 75% of CHL, but may be present in occasional cases of ALCL.[138] Myelomonocytic markers, such as CD13, CD33, and CD68 (KP-1), are occasionally expressed and should not be misinterpreted for myeloid or histiocytic neoplasms.[139]

No B-cell form of ALCL has been described in the current classification, and the expression of B-cell markers is a key finding in the differential diagnosis between ALCL and B-cell neoplasms, including CHL. However, rare cases of ALCL may aberrantly express the B-cell lineage transcription factor, PAX5, which is one of the most useful markers for making a diagnosis of CHL. Feldman *et al*. reported four cases of PAX5-positive ALCL, including one ALK-positive ALCL.[140] The authors revealed extra copies of the *PAX5* gene locus by fluorescence *in situ* hybridization analysis and identified the possible association of weak PAX5 immunostaining in rare ALCL cases.

MOLECULAR ALTERATIONS OTHER THAN ALK

In most ALCL cases (74–90%), *TCR* genes are clonally rearranged. However, TCRs and some related molecules are usually not expressed in ALK-positive or -negative ALCL.[133,141] Overexpression of NPM-ALK induces downregulation and/or epigenetic silencing of these molecules, including CD3ε, zeta-chain-associated protein kinase 70 (ZAP70), linker for activation of T cells (LAT), and lymphocyte cytosolic protein 2 (LCP2) via STAT3, whereas kinase-dead NPM-ALK K210R does not.[142] Deregulated tyrosine kinases, such as NPM-ALK, control the expression of molecules involved in T-cell identity and signaling.[142]

In 2016, Hassler *et al*. reported that DNA methylation patterns for genes involved in T-cell differentiation and

immune response, including TCRs and CTLA4, were similar between ALK-positive and -negative ALCL.[143] The DNA methylation patterns of ALCLs were similar to those of thymic progenitor T cells; ALK-positive ALCL resembled early thymic progenitors (CD34+/CD1a-) and ALK-negative ALCL more closely resembled pre-TCR and double-positive (CD4+/CD8+) T cells.[143]

Microarray-based gene expression profiling of 32 clinical samples and five ALCL cell lines was carried out.[144] Unsupervised analysis classified that these samples could be grouped into two clusters corresponding to the morphologic subgroups (common type versus small cell and "mixed" variants).[144] ALK-positive and -negative ALCLs were revealed to have different profiles; *BCL6*, *PTPN12*, *CEBPB*, and *SERPINA1* genes were overexpressed in ALK-positive ALCL, whereas *CCR7*, *CNTFR*, *IL22*, and *IL21* genes were overexpressed in ALK-negative ALCL.[144] Both types of ALCL expressed high levels of interferon regulatory factor 4 (IRF4), which induces MYC expression.[145]

Comparative genomic hybridization analysis of 43 ALK-positive and 31 ALK-negative ALCLs revealed that ALK-positive (58%) and -negative (65%) ALCLs had chromosomal imbalances.[146] ALK-positive ALCL demonstrated more frequent gains in 17p and 17q24-qter and losses of 4q13-q21 and 11q14, whereas ALK-negative ALCL showed gains in 1q and 6p21.[146]

To the best of our knowledge, the results of next-generation sequencing analyses for ALK-positive ALCL are not yet available; however, those for ALK-negative ALCL are providing insights into the oncogenic mechanisms of this alteration (Table 2). *JAK1* and/or *STAT3* mutations were identified in 18% of ALK-negative ALCL by whole-exome sequencing.[147] *STAT3* mutants were found to exhibit constitutive phosphorylation and tumorigenicity, and *JAK1* mutants were reported to stimulate the phosphorylation of wild-type STAT3.[147] RNA sequencing identified the new fusion tyrosine kinase genes NFKB2-ROS1, NCOR2-ROS1, NFKB2-TYK2, and PABPC4-TYK2, which were mutually exclusive of *JAK1*/*STAT3* mutations, and activated the JAK/STAT3 pathway as well as ALK fusions.[147,148] STAT3-mediated oncogenic mechanisms may be shared by both ALK-positive and -negative ALCLs; therefore, JAK/STAT pathway inhibitors, such as ruxolitinib, may have applications in the treatment of ALCLs.[149]

Among73 ALK-negative ALCLs, 22 (30%) and six (8%) had rearrangements at *DUSP22/IRF4* (6p25.3) and *TP63* (3q28) loci, respectively.[150] The two events were mutually exclusive and were not observed in ALK-positive ALCL.[150] These rearrangements are regarded as prognostic factors; ALK-negative ALCLs with rearrangements at the *DUSP22/IRF4* locus had good prognoses comparable with ALK-positive ALCLs, whereas those with rearrangements at the *TP63* locus had poorer outcomes.[150]

Oncogenic truncated Erb-B2 receptor tyrosine kinase 4 (ERBB4) was expressed in 24% of ALK-negative ALCL, but not in ALK-positive ALCL or PTCL-NOS.[151] ERBB4-positive cases recurrently exhibited a Hodgkin-like morphology with prognoses typical of ALK-negative ALCL.[151] Preliminary data suggest ERBB4 expression may be mutually exclusive of *TP63*, *DUSP22/IRF4*, *ROS1*, and *TYK2* rearrangements, indicative of the presence of an ERBB4-positive subgroup, although further validation studies are required.[151]

PROGNOSIS AND PROGNOSTIC FACTORS

ALK-positive ALCL has been reported to have a better prognosis than ALK-negative ALCL or other PTCL.[9-11,13,14,16,152,153] The long-term overall survival (OS) rates were 70–90% in patients with ALK-positive ALCL and 40–60% in patients with ALK-negative ALCL.[9-14,16] Although these findings do not challenge the concept that ALK-positive ALCL is a distinct disease entity, several research groups have discussed the prognostic importance of ALK status over age in patients with systemic ALCL. In two retrospective studies analyzing a relatively large number of cases,[12,14] ALK expression was not identified as an independent prognostic factor in multivariate analysis mainly because of the correlation between younger age and ALK positivity. One of the studies demonstrated that ALK expression is a prognostic factor only in patients older than 40 years.[14] In the report of the IPTL project, when the comparison of ALK-positive and -negative patients was limited to those at least 40 years old or those less than 40 years old, no significant difference in failure-free survival or OS was found.[9] Furthermore, in addition to age distribution, the genetic heterogeneity of the ALK-negative ALCL cohort may have complicated the analysis of the prognostic difference between ALK-positive and -negative ALCLs. For example, the proportion of patients harboring *DUSP22* or *TP63* rearrangements in the ALK-negative ALCL cohort in each study may have altered the prognostic results.[150]

The International Prognostic Index (IPI) is a useful tool for predicting outcomes of ALK-positive ALCL,[9,11-13,17] similar to the Prognostic Index for PTCL-U (PIT).[9,14] The IPTL project reported estimated OS rates of 90%, 68%, 23%, and 33% in patients with ALK-positive ALCL with IPI scores of 0–1 (low), 2 (low-intermediate), 3 (high-intermediate), and 4–5 (high), respectively.[9] Similarly, in a report on patients with ALCL treated within the Groupe d'E´tude des Lymphomes de l'Adulte (GELA) trials, 8-year OS rates were 86%, 66%, 46%, and 39% in the respective groups within the entire ALCL cohort.[14] Although ALK-positive ALCL is generally associated with a good prognosis, it should be noted that outcomes in patients with ALK-positive ALCL having IPI scores of 3 or more are rather poor and similar to those of patients with other types of PTCL (5-year progression-free survival [PFS] of 20–30%).[9,14,23]

Among morphological variants, patients with the small cell variant, who often present with disseminated disease, may not have favorable outcomes, similar to those of patients with other ALK-positive ALCLs.[5] With regard to the clinical impact of the difference in partner genes of *ALK*, no significant differences in prognosis have been observed for

NPM-ALK and other translocations in ALK-positive ALCL,[12,154] although the prognosis of ALK-positive large B-cell lymphoma (LBCL) differs depending on the *ALK* fusion partner.[43] In addition, some case reports have described patients with ALK-positive ALCL with concurrent rearrangement of *MYC* and aggressive clinical behavior.[155,156]

Some additional factors have been suggested to predict poor outcomes in patients with systemic ALCL, including CD56 expression,[12] elevated pretreatment serum soluble CD30 levels,[157] and beta-2-microglobulin (≥ 3 mg/L).[14] Anemia or more than 1 extranodal site of involvement have also been reported to be prognostic in patients with ALK-positive ALCL in some studies.[9,14] In pediatric patients with NPM-ALK-positive ALCL, a risk stratification model using minimal disseminated disease (MDD) in bone marrow or peripheral blood detected by RT-PCR for NPM-ALK fusion and anti-ALK antibody titers in plasma was proposed.[158] Both MDD (detected at diagnosis) and minimal residual disease detected during treatment have been demonstrated to have prognostic value.[159,160]

CONVENTIONAL THERAPIES

First-line therapy

No randomized trials focusing on adult ALK-positive ALCL or both types of ALCLs have been reported. Therefore, the data are limited to those from retrospective analyses or subgroup analyses of previously conducted trials. In addition, data from the era in which the definitions of ALCL or ALK-positive ALCL had not been established should be interpreted carefully because they tend to include patients with Hodgkin lymphoma or ALK-positive LBCL. Some groups conducted prospective studies on pediatric patients.[19,161-166] The pediatric data have been thoroughly reviewed elsewhere.[18] Thus, in this review, we will focus on therapeutic approaches for adult patients.

Generally, patients with ALK-positive ALCL are treated with anthracycline-based regimens, such as combination cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) or CHOEP (CHOP plus etoposide), which provide a favorable prognosis, except for those with multiple IPI factors. For patients with limited stages, six cycles of CHOP/CHOP-like chemotherapy or 3–4 cycles of this therapy plus localized radiotherapy are generally recommended. A retrospective study evaluating doxorubicin-based chemotherapy in combination with radiotherapy in early-stage ALCL reported favorable outcomes in patients with ALK-positive ALCL (5-year OS rate, 92.9%; 5-year PFS rate, 69.2%).[167] In contrast, another retrospective study that analyzed the survival of patients with limited stage PTCLs found no significant benefit in patients who underwent consolidative radiotherapy.[168] A specific analysis on patients with ALCL was not performed in this study. Similar results have been reported in an analysis of Swedish registry data on patients with PTCL.[17] Among 118 patients with stage I/II PTCL, including ALCL, 32 cases received consolidative local radiotherapy at a median dose of 40 Gy. A trend of superior survival in patients who underwent irradiation was observed, but no risk reduction associated with the addition of radiotherapy was found by multivariate analysis. Survival data of patients treated with 3 or 4 courses of CHOP/CHOEP plus radiotherapy and those treated with at least six courses without radiotherapy were not significantly different. Although the number of cases analyzed was small in each study, and no apparent conclusions were reached, there was no definitive evidence demonstrating the benefit of combined or consolidative radiotherapy for patients with limited-stage ALK-positive ALCL. In patients who cannot tolerate multiple courses of chemotherapy, however, abbreviated CHOP combined with radiotherapy may be a reasonable choice.

For adult patients with advanced ALK-positive ALCL, six cycles of CHOP or CHOP-like regimens are generally recommended. The results of major retrospective studies are summarized in Table 3 with information on first-line treatments for patients with ALK-positive ALCL. For PTCLs, some studies have examined the effects of intensified regimens, such as hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate and cytarabine), ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone), or VIP-reinforced-ABVD (etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine, dacarbazine), to improve outcomes. Specific analyses of ALK-positive ALCL and ALCL have not been performed, and obvious benefits of intensification of the therapy have not been observed for PTCLs.[13,14,153,169,170] Adding etoposide to CHOP may improve the prognosis of a subset of patients with PTCL. A report of patients with PTCL, including 78 ALK-positive ALCL and 113 ALK-negative ALCL, treated within the trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) found that the addition of etoposide to CHOP was associated with improved 3-year event-free survival (EFS; 91.2% versus 57.1%) in patients with ALK-positive ALCL who were younger than 60 years old and with LDH of less than or equal to the upper normal value, although OS was not significantly different and adjustment with IPI or other factors was not performed.[13] The value of adding etoposide to CHOP/CHOP-like regimens in ALK-positive ALCL still needs to be evaluated in further studies.

For patients with PTCL at a high risk of relapse, consolidative high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) for the first complete response (CR) has been evaluated for improvement of outcomes.[170-173] Currently, the role of consolidation therapy in ALCL is controversial. A prospective study to evaluate upfront ASCT in patients with PTCL (N = 62) included 19 patients with ALK-positive ALCL.[174] In an intent-to-treat analysis, 74% of the entire cohort completed the program. A separate analysis for patients with ALK-positive ALCL demonstrated a 12-year OS and EFS of 62 and 54%, respectively. In one retrospective study focusing on newly diagnosed ALCL treated with the combination of carmustine, etoposide, cytarabine, and melphalan (BEAM), and ASCT (N = 15), seven of 12 patients with T/null type had ALK-positive ALCL.[175] All

Table 3. Retrospective studies in ALK+ALCL

Reference	B cell type (N)	ALCL (T/null) (N)	ALK status			Age			Sex	median follow-up (year)	Stage (ALK+)				IPI (ALK+)				Progression/disease/event/ failure free survival				Overall survival				regimen (N)	prognostic factors (in ALCL, including ALK+ALCL)
			ALK+ ALCL (N)	ALK- ALCL (N)	ALK unknown (N)	adult	children	median age (range) (ALK+)	median age (range) (ALK-)	Male/ Female (ALK+)		I	II	III	IV	0-1 (Low)	2 (Low-intermediate)	3 (High-intermediate)	4-5 (High)	year	ALK+ ALCL (%)	ALK- ALCL (%)	p-value	year	ALK+ ALCL (%)	ALK- ALCL (%)	p-value		
Nakamura S, Am J Surg Pathol 1997	B=3, mixed=1 (ALK-)	67	43‡	24	-	+	+	17 (2-73)	60 (12-85)	1.9	3.8 (ALK+), 1.8 (ALK-)	18%	38%	28%	18%	NR				NR				5	72	30	<0.05	Doxorubicin-containing (CHOP, VEPA, VEPA + methotrexate), RT only, RT + chemotherapy	
Gascoyne RD, Blood 1999	5 (ALK+), 8 (ALK-)	57	31	26	-	+	-	30 (15-64)*	61 (27-75)*	3*	4.2	17 (47%)*		19 (53%)*		27 (47%)†	10 (18%)†	8 (14%)†	11 (19%)†	5*	88	32	<0.0001	5**	93	37	<0.00001	Doxorubicin-containing	IPI ≤3, ALK+, normal LDH (favorable)
Falini B, Blood 1999	-	78	53	25	-	+	+	mean 22 (3-52)	mean 43	3.1	2.1	15 (28%)		38 (72%)		25 (50%)		25 (50%)		10	82	28	<0.0001	5	71	15	<0.0007	Doxorubicin-containing (68/78), ALL-like (8 in ALK+)	aaIPI < 2, ALK+ (favorable)
Suzuki R, Blood 2000	-	143	83	60‡	-	+	+	21 (1-73)	57 (8-85)	1.7	NR	10 (12%)	17 (21%)	25 (30%)	31 (37%)	40 (50%)	22 (28%)	13 (16%)	5 (6%)			NR		5	70	40	0.0009	Doxorubicin-containing (129), without Doxorubicin (9), RT/ resection (5), none (1)	IPI ≥3, CD56+ (poor)
ten Berge RL, Histopahtology 2003	-	74	28	46	-	+	+	24 (2-69)	55 (13-90)	1.6	NR	5 (19%)	12 (46%)	5 (19%)	4 (15%)	18 (64%)	6 (21%)	2 (10%)	0 (0%)	5**	85	45	0.007	5	90	40	0.0001	mostly CHOP. RT (5), none (5)	
Escalon, Cancer 2005	-	40	12	19	9	+	-	49 (17-76)†		1.7†	3.1	30%†	20%†	15%†	35%†	17 (43%)†	11 (28%)†	12 (30%)†				NR		3	100	66	0.04	CHOP 65% (ALK+ 7, ALK- 11, ALK unknown 8)	
Savage KJ, Blood 2008	-	159	87	72	-	+	-	34	58	1.7	3.5 (ALK+), 1.7 (ALK-)	-	30 (35%)	25 (29%)	31 (36%)	40 (49%)	18 (22%)	12 (15%)	12 (14%)	5	60	36	0.015	5	70	49	0.016	Anthracycline-based (95% in ALK+, 88% in ALK-)	(controlled for IPI)(in ALK+ALCL) anemia
Schmitz N, Blood 2010	-	191	78	113	-	+	-	37 (18-74)	50 (18-77)	1.3	3.7	37 (47%)		41 (53%)		45 (57.7%)	21 (26.9%)	10 (12.8%)	2 (2.6%)	3	75.8	45.7	NR	3	89.8	62.1	<0.001	in ALK+ALCL: CHOP (21) or CHOEP (36), Hi-CHOEP (9), MegaCHOEP + SCT (12)	use of etoposide
Sibon D, J Clin Oncol 2012	-	138	64	74	-	+	-	32 (15-75)	56 (19-87)	1.6	8	28 (44%)		36 (56%)		30 (55%)	12 (22%)	10 (18%)	3 (5%)	8	72	39	<0.001	8	82	49	<0.001	Anthracycline-based. (most frequently used: ACVBP + consolidation)	age>=40, beta 2-microglobulin ≥ 3mg/L (In ALK+ALCL, only >1 extranodal site remained.)
Zhang X, Eur J Haematol 2013	-	46	15	20	11	+	-	38 (18-70)†		1.4†	4.6	20 (43.5%)†	26 (56.5%)	-	-	35 (76%)†	11 (24%)†		0 (0%)†	5	69.2	57.1	0.622	5	92.9	84.4	0.249	CHOP or CHOP-like (median number of cycles = 6) + RT 96%	
Parilla Castellar ER, Blood 2014	-	105	32	73	-	+	+	28 (6-77)	58 (22-94)	1.9	6.5	7 (26%)	6 (22%)	0 (0%)	14 (52%)	20 (69%)	6 (21%)	3 (10%)	0 (0%)			NR		5	85	52	0.0025	CHOP/CHOP-like 76%	
Ellin F, Blood 2014	-	177	68	115	69	+	-	41 (18-81)	67 (19-93)	1.2	7.9	35 (51%)		33 (49%)		36 (53%)	26 (38%)		4 (6%)	5	63.2	31.4	0.01	5	79.4	38.4	<001	CHOP/CHOEP 83%***	

†, in ALCL; **, estimated from Kaplan-Meier curve; ‡, including EBV positive cases
*, including B cell type patients; ***, including other T cell lymphoma patients
ALCL, anaplastic large cell lymphoma; IPI, International prognostic index; aaIPI, age adjasted IPI; NR, not reported; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; VEPA, vincristine, cyclophosphamide, prednisolone, and doxorubicin; RT, radiotherapy
CHOEP, CHOP plus etoposide; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; SCT, stem cell transplantation

patients achieved CR, and the 5-year EFS was 87% for the entire cohort. However, it is not clear whether ASCT improved outcomes because all but two patients had low or low-intermediate IPI risk. A number of other retrospective studies examined the benefit of ASCT in the frontline setting and reported good outcomes in PTCL, including ALCL. Notably, these results should be interpreted carefully because the number of analyzed patients was small, and selection bias was an issue.[176,177] In general, upfront ASCT is not included in the standard therapeutic approach for patients with ALK-positive ALCL.

Therapy for refractory or relapsed cases

Relapses are not uncommon (30% of cases), and ASCT after salvage chemotherapy has been widely applied for patients with relapsed ALCL. Although evidence from randomized trials is lacking, ASCT or allogeneic stem cell transplantation (SCT) may provide long-term survival benefits in patients who respond to salvage therapy. There are multiple retrospective reports of ASCT in patients with relapsed/refractory PTCL, which have been exhaustively reviewed elsewhere.[176,177] Briefly, the long-term PFS rate has been reported to be 25–75%, and some studies have demonstrated that the salvage rate is similar to that of DLBCL, particularly for ALCL.[23] However, data on transplantation in ALK-positive ALCL is scarce. The following are the examples of studies that included patients with relapsed/refractory ALCL. In one retrospective study, patients with ALCL had a better 3-year EFS than patients with other PTCLs (67% versus 37%, respectively).[178] Another retrospective study with 28 patients with PTCL reported that patients with ALCL had a superior 3-year OS compared with patients having other PTCLs (86% versus 47%, respectively), and ALK-positive ALCL was associated with a better EFS than ALK-negative ALCL (100% versus 0%, respectively).[179] An analysis of data from the Center for International Blood and Marrow Transplantation Research (CIBMTR) database demonstrated that 39 patients with ALCL who underwent ASCT beyond CR1 had 3-year PFS and OS rates of 50% and 65%, respectively.[180]

Data on allogeneic SCT for relapsed/refractory ALCL are very limited. The 2–5-year PFS rate is 30–60%, with a treatment-related mortality rate of approximately 30% in selected patients.[176] In an analysis of data from the CIBMTR database, 51 patients with ALCL (for whom information on ALK status is lacking) who received allogeneic SCT were identified, and the 3-year PFS and OS rates were 35 and 41%, respectively, with non-relapse mortality of 31%.[180] Another retrospective study analyzed 77 recipients of allogeneic SCT who had PTCLs, including 27 with ALCL, and at least eight of these had ALK-positive ALCL. Although heavily treated patients were not included, some benefit was demonstrated for patients with chemorefractory PTCL (5-year OS of 29%).[181]

For both transplant-eligible and -ineligible patients with ALCL, the discovery of novel agents, including belinostat, pralatrexate, and romidepsin, has changed the standard therapeutic approach. The following two targeted therapies have attracted much attention.

TARGETED THERAPIES WITH NEW AGENTS

Brentuximab vedotin

Owing to its high expression on tumor cells and limited expression in normal tissues, CD30 has become an attractive target for antibody-based immunotherapy, particularly for Hodgkin lymphoma and ALCL.[182] Brentuximab vedotin (BV) is an antibody-drug conjugate containing an anti-CD30 monoclonal antibody (cAC10) linked to the synthetic antimitotic agent monomethyl auristatin E (MMAE) via a protease cleavable dipeptide linker. In CD30-positive cells, the conjugate is internalized through receptor-mediated endocytosis, and MMAE is released by lysosomal proteases such as cathepsin B.[183-185] The antitumor activity of BV has been confirmed in preclinical models, including xenograft mouse models with tumors derived from Karpas 299 cells, a cell line harboring the NPM-ALK fusion.[186]

Clinically, several early phase studies have reported excellent results using BV. In a phase I study for relapsed or refractory CD30-positive lymphomas, two patients with ALK-positive ALCL were evaluated, and both achieved CR. The durations of response were 17.3 and 5.0 months in the two patients.[187] Another phase I study enrolled five patients with relapsed or refractory ALCL, including one patient with ALK-positive ALCL. The CR rate was 80% (4/5) in ALCL patients; one patient who received the lowest dose of BV achieved only stable disease (SD).[188] Subsequently, a multinational, open-label phase II study for relapsed or refractory systemic ALCL was conducted, and 58 patients were treated (16 patients were positive for ALK). The overall response rate (ORR) was 86% (CR rate, 57%) for the entire cohort and 81% (CR rate; 69%) for patients with ALK-positive ALCL. The median duration of response was 12.6 months, and the median PFS was 13.3 months, with no significant difference between ALK-positive and -negative patients.[189] In terms of treatment-emergent adverse events, peripheral sensory neuropathy (PSN) was most commonly observed (24/58, 41%), including seven (12%) patients with grade 3 disease. BV received accelerated approval from the US Food and Drug Administration in 2011 for the treatment of relapsed or refractory Hodgkin lymphoma and systemic ALCL based on the results of two phase II studies, including the above study. Follow-up data at 3 and 4 years have been published,[190] and with a median observation time of 46.3 months, and 62% (36/58) of patients were alive at the last follow-up. The estimated 4-year survival rate was 64%. The median PFS was 20.0 months for all patients and 25.5 months for patients with ALK-positive ALCL. Notably, 47% (17/36) of patients with CR, including seven without further treatment, remained in follow-up with no evidence of progression. This suggested that BV had curative effects in some patients, although further studies are needed to confirm these findings. In Japan, a phase 1/2 study was performed, and similar results were obtained.[191] Retreatment with BV for relapsed CD30+ lymphomas (21 Hodgkin lymphoma and eight ALCL) has been

evaluated in a phase II study, and the ORR in patients with ALCL was 88%.[192]

BV was also tested in the initial treatment of ALCL. Fanale *et al.* reported a phase I study conducted in the US and Europe. Thirty-nine patients with CD30-positive T-cell lymphoma, mostly ALCL, were enrolled and received one of two regimens: a sequential treatment (two courses of BV followed by six cycles of CHOP) or a combination treatment (six cycles of BV plus CHP). In the latter regimen, vincristine was omitted due to an overlapping adverse effect (PSN) with BV. Responders could receive additional BV for 8–10 cycles. Among 32 patients with ALCL, six (19%) had ALK-positive ALCL and were at intermediate risk (IPI 2–3). The ORRs were 85% (CR, 62%) and 100% (CR, 88%) in the sequential and combination groups, respectively. In the combination group, the estimated 1-year PFS rate was 71% without consolidative ASCT. PSN (69%) was the most frequently experienced adverse event, and grade 3/4 events were experienced by 73% of patients; febrile neutropenia (31%), neutropenia (23%), anemia (15%), and pulmonary embolism (12%) occurred in at least 10% of patients. Based on the observations in this study, a phase III randomized study comparing CHOP and BV+CHP in CD30-positive T-cell lymphomas was planned and is now ongoing (ECHELON-2, NCT01777152).

ALK inhibitors

ALK inhibitors have already been used in the treatment of *ALK*-rearranged non-small cell lung cancer.[193,194] Some *in vitro* and *in vivo* studies have demonstrated that inhibition of ALK suppresses tumor growth in ALK-positive ALCL.[195-197] Crizotinib was confirmed to be effective in an ALK-positive ALCL xenograft model.[198] Although data regarding the efficacy of ALK inhibitors in patients with ALK-positive ALCL are still limited, encouraging results have been obtained.

Including the first report of two patients with relapsed ALK-positive ALCL who achieved a rapid CR using crizotinib,[199] several case reports and studies with small numbers of heavily pretreated patients have been published (Table 4).[200-206] In a pediatric phase I trial evaluating crizotinib for refractory solid tumors or ALCL, seven of nine (78%) patients with ALK-positive ALCL achieved CR.[207] Gambacorti-Passerini *et al.* reported nine adult patients with refractory ALK-positive ALCL treated with crizotinib.[201] All patients obtained response, and, at the time of the report, four of the patients were on crizotinib and in CR without stem cell transplantation (duration of response: > 21, > 30, > 35, and > 40 months). The estimated 2-year PFS and OS rates were 63.7% and 72.7%, respectively. A preliminary report of a phase I study (NCT01121588) had a good objective response rate (60%; five CRs and four partial responses) for pretreated ALK-positive lymphomas (14 ALK-positive ALCL and one ALK+LBCL) at a median duration of treatment of 33 weeks.[208] Recently, abrupt relapses following discontinuation of crizotinib in patients who were in CR with crizotinib for 1 year or 4 years were reported.[209] The appropriate timing to discontinue ALK inhibitors in responding patients is still unclear.

Ceritinib is a second-generation ALK inhibitor that has greater potency than crizotinib *in vitro* and has been reported to have strong antitumor effects in an ALK-positive ALCL xenograft model.[210] Moreover, ceritinib has been shown to be effective in patients with crizotinib-resistant NSCLC.[211] In a phase I trial evaluating ceritinib in patients with advanced or metastatic ALK-altered tumors (ASCEND-1), three patients with relapsed ALK-positive ALCL were enrolled.[211] Two achieved CR, and one had partial response with maximal tumor reduction of 94.8%. All three patients had maintenance of CR or partial response longer than 20 months.[212]

A number of trials evaluating ALK inhibitors are ongoing. The Children's Oncology Group is conducting a randomized phase II study to evaluate the feasibility and efficacy of combining BV or crizotinib with multi-agent chemotherapy (ALCL99 regimen) in pediatric newly diagnosed stage II to IV ALK-positive ALCL (NCT01979536).[213] Another randomized trial with risk stratification by minimal disseminated disease and anti-ALK antibody titers[158] is ongoing. The ALCL99 regimen with crizotinib or vinblastine will be evaluated in combination.[213] In addition to crizotinib and ceritinib, alectinib is also in clinical evaluation for ALK-positive ALCL in Japan. Alectinib is a potent second-generation ALK inhibitor that is effective even in NSCLC harboring crizotinib-resistance mutations[214] and has demonstrated promising results in clinical settings.[215,216] Ongoing clinical trials for ALK-positive ALCL are listed in Table 5.

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NT (History, Epidemiology and etiology, Histopathology, and Immunophenotype other than CD30 and ALK), KS (Clinical features, Prognosis, Prognostic factors, Conventional therapies, and Targeted therapies with new agents), SS (CD30 and ALK), and AD (Other molecular alterations) wrote the manuscript drafts. KT edited the sections and organized them into the review article.

CONFLICT OF INTEREST

The authors do not have any conflicts of interest to declare.

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Table 4. Cases of relapsed/refractory ALK+ALCL patients treated with ALK inhibitors

No.	Author	Reference	Agent	Age/ Sex	Stage	Previous therapy line	Previous SCT	SCT after treatment with crizotinib	Best response	Duration of response (month)	Status at last observation
1	Gambacorti-Passerini C	J Natl Cancer Inst. 2014 (#1,2: New Engl J Med. 2011)	Crizotinib	26F	IIIB	CHOP, DHAP, HD-VP16	No	No	CR	>40	CR, on crizotinib
2				20M	IVB	CHOP, DHAP, BEAM	autologous	No	CR	2	relapsed, dead
3				22	IIB	CHOP, VAD, HyperCVAD/MA	No	No	CR	>35	CR, on crizotinib
4				20	IIB	CHOP, DHAP, BEAM	autologous	No	CR	2	relapsed after 2 months, alive in CR on BV
5				47	IIIBe	IEV, DHAP, CHOP	No	No	CR	>30	CR, on crizotinib
6				28	IIIB	CHOP, DHAP, mini-BEAM	No	allogeneic	CR	2	Crizotinib was used as bridge to SCT. CR with cGVHD
7				34	IVBe	CHOP, ESHAP	No	allogeneic	CR	3	Crizotinib was used as bridge to SCT and restarted upon relapse after SCT. It was stopped again 10 months after SCT. CR with cGVHD
8				38	IVB	CHOP, DHAP, VIM	allogeneic	No	CR	8	Crizotinib was stopped. CR with cGVHD
9				55	IIIB	CHOP	No	No	CR	>21	CR, on crizotinib
10-18	Mossé YP	Lancet Oncol. 2013	Crizotinib	median 10	NR	multiagent chemotherapy	autologous in 1	SCT in 3	CR: 7, PR: 1, SD: 1		5 patienes were on crizotinib
19	Ordemann R	Ann Hematol. 2013	Crizotinib	29M	IVB	CHOP, DHAP, Dexa-BEAM	No	allogeneic	PR?	1	relapsed and treated with BV and donor lymphocyte infusion
20	Cleary JM	J Natl Compr Canc Netw. 2014	Crizotinib	34M	IV	CHOP, gemcitabine-based therapy, pralatrexate, high-dose MTX	No	allogeneic	CR	3	Crizotinib was stopped. alive in CR for 30 months
21	Conyers R	Eur J Haematol. 2014	Crizotinib	22M	IIIB	CHOP, RT	No	allogeneic	CR	>21	Crizotinib was stopped, but restarted upon relapse after SCT. CR for >21 months on crizotinib
22	Lawrence K	BMC Res Notes. 2015	Crizotinib	32M	IV	CHOP, GDP, BV	No	allogeneic	PD	-	died 6 months after SCT
23	Richly H	Blood. 2015	Ceritinib	40M	IV	HyperCVAD	No	NR	CR	>26	CR, on ceritinib
24				48F	IIIB	CHOP	No	NR	CR	>24	CR, on ceritinib
25				24M	IIIA	CHOP	No	NR	PR	>20	PR, on ceritinib
26	Kothari S	J Med Case Rep. 2016	Crizotinib	48M	IVB	CHOP, splenectomy, ICE	No	No	CR	>29	CR, on crizotinib
27	Mahuad CV	Rare Tumors 2016	Crizotinib	16F	IVBe	CHOP, ESHAP	autologous	No	CR	>36	CR, on crizotinib

SCT, stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP, dexamethasone, cisplatin, cytarabine; HD-VP16, high-dose etoposide; BEAM, carmustine, etoposide, cytarabine, melphalan; VAD, vincristine, doxorubicin, high-dose dexamethasone; HyperCVAD/MA, alternate regimens of 1) cyclophosphamide, vincristine, doxorubicin, dexamethasone; 2) methotrexate and cytarabine; IEV, Ifosfamide, epirubicin, etoposide; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; VIM, ifosfamide, mitoxantrone, etoposide; Dexa, dexamathasone; RT, radiotherapy; GDP, gemcitabine, dexamethasone, cisplatin; BV, brentuximab vedotin; ICE, ifosfamide, carboplatin, and etoposide; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NR, not reported
cGVHD, graft versus host disease

Table 5. Clinical trials for ALK+ALCL (Jan. 2017)

NCT/EudraCT/ Other Number	status	Condition	Agent/Intervention	Age	Phase
NCT02729961	newly diagnosed	ALK+ALCL	Brentuximab vedotin, Ceritinib	child/adult	1/2
NCT02462538	relapsed/refractory	ALK+ALCL	Brentuximab vedotin, Imatinib	adult	1/2
NCT00939770	relapsed/refractory	Solid tumors, ALK+ALCL	Crizotinib	child/adult	1/2
NCT02419287	relapsed/refractory	ALK+ALCL	Crizotinib	adult	2
NCT02572453	relapsed/refractory	ALK+ALCL, diffuse large B-cell lymphoma, Mantle cell lymphoma	Onalespib (AT13387) (HSP90 inhibitor)	adult	2
NCT01742286	relapsed/refractory	ALK altered malignancy	Ceritinib	child	1
NCT01979536	newly diagnosed	ALK+ALCL	Brentuximab vedotin or crizotinib and ALCL99*	child/adult	2
NCT01524926		Solid tumors, ALCL	Crizotinib	child/adult	2
NCT00585195		NSCLC (ALK+, c-Met dependent, ROS+), sALCL, Advanced Malignancies	Crizotinib, Rifampin, Itraconazole	adult	1
NCT02568267		Solid tumors, ALCL	Entrectinib (TrkA/B/C, ROS1, ALK inhibitor)	adult	2
NCT02561273	newly diagnosed	ALK-ALCL, ALK+ALCL (IPI 3-5), other TCL	Lenalidomide, CHOEP, autologous stem cell transplantation	adult	1/2
NCT01777152	newly diagnosed	CD30-positive mature TCL	Brentuximab vedotin + CHP vs CHOP	adult	3
UMIN000016991	relapsed/refractory	ALK+ALCL	Alectinib	child/adult	2
JMA-IIA00229	relapsed/refractory	HL, ALCL	Brentuximab vedotin	child	1
NCT01657331	relapsed/refractory	HL, ALCL	Brentuximab vedotin, Bendamustine	adult	1/2
NCT02169505	undergone allogeneic SCT	HL, ALCL	Brentuximab vedotin	adult	2
NCT01909934	relapsed/refractory	ALCL	Brentuximab vedotin	adult	4
NCT01309789	newly diagnosed	CD30+ mature T-cell and NK-cell neoplasms	Brentuximab vedotin with CHOP	adult	1
NCT02978625		Non-melanoma skin cancer or lymphomas other than B-cell lymphomas	Talimogene Laherparepvec, Nivolumab	adult	2
NCT02939014	relapsed/refractory	HL, ALCL	Brentuximab vedotin	adult	2
NCT02419287	relapsed/refractory	ALK+ALCL	Crizotinib	adult	2
2010-022978-14		ALK altered malignancy (not NSCLC)	Crizotinib	adlescents/adult	1B
2015-000814-23		ALK altered malignancy	Ceritinib	adult	2
2016-001396-69	relapsed/refractory	TCL (including ALK+ALCL)	Tipifarnib	adult	2
2010-022230-81	Achieved an objective response following initial treatment with CHOP-based chemotherapy	TCL (ALCL, excluding ALK+ with IPI < 2 at initial diagnosis and CR after completion of CHOP-based therapy)	Pralatrexate	adult	3
2011-004151-39	relapsed/refractory	TCL (including ALK+ALCL)	Mogamulizumab	adult	2
2008-005843-40	relapsed/refractory	PTCL	Belinostat	adult	2
2013-003505-26	relapsed/refractory	ALK+ALCL	Brentuximab vedotin, Imatinib	adult	1
2011-001240-29	relapsed/refractory	HL, ALCL	Brentuximab vedotin	child	1/2
2010-021091-28	relapsed/refractory	TCL (including ALK+ALCL)	masitinib + dexamethasone, gemcitabine + dexamethasone, masitinib + gemcitabine + dexamethasone	adult	2/3
2013-000885-13	relapsed/refractory	Solid tumors, hematological malignancy	Crizotinib	child/adult	2
NCT1121588	relapsed/refractory	ALK altered malignancy (not NSCLC)	Crizotinib	child/adult	1
NCT02465528	relapsed/refractory	ALK altered malignancy (not NSCLC)	Ceritinib	child/adult	2

ALCL, anaplastic large cell lymphoma; ALK+ALCL, ALCL, ALK-positive; ALK-ALCL, ALCL, ALK-negative; NSCLC, non-small cell lung cancer; TCL, T cell lymphoma; HL, Hodgkin lymphoma; IPI, international prognostic index; CR, complete response; PTCL, peripheral T cell lymphoma
CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOEP, CHOP plus etoposide; CHP, CHOP minus vincristine
*: ALCL99 contains cyclophosphamide, cytarabine, dexamethasone, doxorubicin, etoposide, ifosfamide, and methotrexate

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