Traditional and emerging therapies for anaplastic large cell lymphoma (Review)

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Abstract. Anaplastic large cell lymphoma (ALCL) is a rare and highly invasive non-Hodgkin's lymphoma. In the past few decades, traditional chemotherapy regimens, such as as the cyclophosphamide, vincristine, doxorubicin and prednisone regimen, have been recommended for first-line treatment. In order to improve the survival of patients, dose-intensive chemotherapy and hematopoietic stem cell transplantation have been deeply studied and some progress has been made. Recently, with the accumulation of clinical cases and the development of clinical trials, as well improvements to our in-depth understanding of the biological behavior of ALCL, the signaling pathways and the immunotherapy involved, research on this topic is in full swing. The emergence of several targeted drugs and immunotherapies, including anaplastic lymphoma kinase inhibitors, brentuximab vedotin, mTOR inhibitors, programmed cell death protein 1/programmed death ligand 1 inhibitors and chimeric antigen receptor-T cell therapy, seems to provide new opportunities for certain patients with ALCL. The present review focuses on the current use of traditional therapy and the treatment prospects of these new drugs in ALCL.

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1. Introduction

Anaplastic large cell lymphoma (ALCL) is a highly aggressive type of T cell lymphoma (TCL) that is characterized by CD30 expression and accounts for ~2% of adult non-Hodgkin's lymphoma (NHL) (1) and 15% of pediatric NHL cases (2). According to the 2017 World Health Organization classification (3), ALCL is divided into anaplastic lymphoma kinase-positive (ALK^+) ALCL, ALK-negative (ALK^-) ALCL, primary cutaneous ALCL and breast implant-associated ALCL; the first two types are collectively referred to as systemic ALCL (sALCL). ALK^+ ALCL accounts for 60-85% of all sALCL cases, and all express ALK fusion proteins, which are transcribed and translated by ALK fusion genes. The most common fusion gene is nucleophosmin (NPM)-ALK, which is formed by translocation of the ALK gene on chromosome 2p23 and the NPM gene on chromosome 5q35 (4). Another 10-20% of ALK^+ ALCL cases contain variant ALK fusions, such as 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase-ALK (5), TRK-fused gene-ALK (6), tropomyosin 3-ALK (7) and moesin-ALK (8). The majority of patients with ALCL are males presenting with B symptoms and advanced-stage disease. Patients with ALK^+ ALCL are usually aged <60 years and are younger than patients with ALK^- ALCL (9). Due to the rarity of the disease, most of the evidence describing the outcomes and various treatment options for patients with sALCL comes from retrospective studies of invasive lymphoma or TCL. The most effective therapeutic option for sALCL remains under investigation. Although the outcome of ALCL is more favorable than that of peripheral T-cell lymphoma (PTCL)-not otherwise specified (9), the overall survival (OS) rate and progression-free survival (PFS) rate have barely improved in the past 30 years (10), and the outcomes of relapsed or refractory (R/R) patients are not optimistic. With the deepening of our understanding of ALCL biology, an increasing number of potential therapeutic targets and immune checkpoints are being discovered and tested to improve the prognosis. The

traditional therapeutic strategies and emerging immunotherapies and targeted therapies of sALCL are presented in this review.

2. Chemotherapy

At present, sALCL is mostly treated with the anthracycline-based cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) regimen, but there is no consensus on the standard regimen for sALCL. With this treatment strategy, the prognosis of patients with ALK^+ ALCL is significantly superior to that of patients with ALK^- ALCL. The German High-Grade Non-Hodgkin Lymphoma Study Group evaluated the outcomes of 343 patients with TCL, including 191 patients with ALCL (113 ALK^- and 78 ALK^+). Patients were separated into CHOP and etoposide plus CHOP (CHOEP) regimen groups. For patients aged ≤60 and those with normal lactate dehydrogenase levels, the 3-year event-free survival (EFS) rate of the CHOEP regimen was significantly superior to that of the CHOP regimen, but OS rate was not improved. In elderly patients, the addition of etoposide had no obvious effect on prognosis (11). Another pooled analysis of 263 patients with ALK^+ ALCL found that CHOEP improved both PFS and OS rates. Furthermore, the 5-year cumulative incidence of relapse (IR)/progression was clearly decreased following etoposide-based induction (37 vs. 17%) (12). This study only included patients with ALK^+ ALCL and had a longer follow-up period, which may be the reason for the benefits observed in not only PFS rate, but also OS rate.

In addition to CHOP or CHOP-like regimens, a number of studies have been conducted on alternative therapies, such as hyperfractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone/methotrexate and cytarabine (hyper CVAD/MA) (13,14), hyper-CHOP (14) and etoposide, ifosfamide and cisplatin-reinforced doxorubicin, bleomycin, vinblastine and dacarbazine (15). Except for hyper CVAD/MA, which is controversial with regards to improving PFS rate (13,14), none of the other treatments exhibited better outcomes. Although intensive regimens may have a higher response rate, they also lead to a higher toxicity compared with traditional chemotherapy. In addition, due to the rarity of the disease, none of these studies analyzed the individual survival outcomes of ALCL, which needs to be verified by more rigorous randomized controlled trials.

To date, CHOP remains the recommended first-line treatment option for patients with sALCL. Young patients (≤60 years old) have a more favorable EFS following the CHOEP regimen, while dose-intensive CHOP or alternative treatments have not been reported to have superior outcomes (Table I). Although patients with ALCL have a more favorable OS and EFS than other patients with PTCL, the effect of traditional chemotherapy has seen little improvement over the past 30 years.

3. Hematopoietic stem cell transplantation (HSCT)

The complete remission (CR) rates of patients with ALK^+ and ALK^- ALCL following first-line treatment are 86 and 68%, respectively (16), but >40% of patients with ALCL relapse (9,17), and the outcomes of patients with recurrence remain poor. Studies have explored the effects of high-dose chemotherapy/autologous stem cell transplantation (HDC/ASCT) treatment in patients with ALCL to decrease relapse after the first remission (18-25). Due to the relatively favorable outcomes of first-line chemotherapy, ASCT is not recommended as the upfront consolidation for patients with ALK^+ ALCL.

Certain retrospective and prospective studies have shown that consolidative ASCT improves the outcomes of patients with PTCL, including those with ALCL (Table II) (18-25). In addition, based on the results of recent studies, the National Comprehensive Cancer Network (NCCN) guidelines (26) and the clinical practice recommendation of the American Society for Blood and Marrow Transplantation (27) recommend ASCT for most PTCL subtypes that reach the first CR (CR1), including ALK^- ALCL, but not ALK^+ ALCL. However, these studies have certain limitations, as all three prospective studies were single-arm phase II studies and did not use a contemporaneous control group. In addition, patients undergoing ASCT tend to be young and in a generally good condition, but with a more aggressive disease state. In addition, these studies had inconsistent responses to first-line chemotherapy [100% CR or partial response (PR)/CR] and different histological types (including or not including ALK^+ patients). Furthermore, several recent studies, including a retrospective study (28) and prospective cohort study (29), have shown that ASCT could not improve OS rate in patients with ALK^- ALCL, highlighting the need for randomized controlled studies to determine the role of ASCT as first-line consolidation therapy.

The role of ASCT and allogeneic HSCT (allo-HSCT) in patients with R/R ALCL remains unclear. Only a few studies have analyzed the impact of HSCT on the survival of patients with R/R ALCL (Table III). The effectiveness of HSCT as consolidation therapy in R/R ALCL was studied in two retrospective analyses conducted by the European Society for Blood and Marrow Transplantation (30,31). The 3-year cumulative IR, PFS and OS rates were 34, 64 and 73% for patients who had undergone ASCT (30), and 40, 53 and 74% for patients receiving allo-HSCT, respectively (31). The 5-year treatment-related mortality (TRM), IR, OS and EFS rates were 25, 28, 54 and 50%, respectively, in a retrospective study that enrolled 24 patients with R/R ALCL who had undergone allo-HSCT (32). In addition, the 5-year OS rate of patients receiving reduced-intensity condition (RIC) regimens (n=8) was reported to be superior to that of patients receiving myeloablative conditioning regimens (n=30) (100 vs. 49%; P=0.018), which may be associated with the lower TRM of the RIC regimen (33). In addition, the retrospective nature of the study and the small number of patients may have had an impact on the results.

One large multicenter retrospective study from the International Blood and Bone Marrow Transplantation Research Center compared the effect of ASCT and allo-HSCT in 112 patients with ALCL (61 ASCT and 51 allo-HSCT) (34). The results revealed that ASCT had a higher 3-year OS rate (62 vs. 33%; P=0.0088) and a lower TRM rate (5 vs. 32%; P<0.001) compared with allo-HSCT in patients beyond CR1, but PFS rate and recurrence/progression were not significantly different between the two groups. However, an important limitation of that study was that ALK status was indeterminate.

Table I. Studies on survival following chemotherapy in patients with ALCL.

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+ patients, n	ALK- patients, n	ALK status unknown, n	ORR (CR rate), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Escalon *et al*	/	2005	/	CHOP	50	26	7	11	8	/	/	3-year OS[a]: 62%	/	(14)
				Intensive therapy (hyper-CHOP, hyper-CVAD, etc.)	63	14	5	6	3	/	/	3-year OS[a]: 56%	/	
Simon *et al*	NCT00970385	2010	3	VIP-reinforced-ABVD	43	8	7	1	0	58 (44)	2-year EFS[a]: 45%; 5-yearEFS[a]: 32.5 months	Median OS[a]: 42 months	Neutropenia, thrombocytopenia	(15)
				CHOP/21	43	6	3	3	0	70 (35)	2-year EFS[a]: 41%, 5-year EFS[a]: 32 months	Median OS[a]: 42 months	/	
Schmitz *et al*	/	2010	/	CHOP/CHOEP	343	191	78	113	0	/	3-year EFS: ALK+ 75.8%; ALK- 45.7%	3-year OS: ALK+ 89.8%; ALK- 62.1%	/	(11)
Abramson *et al*	/	2014	/	CHOP-like therapy	237	/	/	/	/	69 (58)	3-year PFS[a]: 32%	3-year OS[a]: 55%	/	(13)
				Hyper CVAD/MA	20	/	/	/	/	85 (80)	3-year PFS[a]: 53%	3-year OS[a]: 49%	/	
Sibon *et al*	/	2019	/	CHOP	98	98	98	0	0	/	5-year PFS: 57%	5-year OS: 69%	/	(12)
				CHOEP	38	38	38	0	0	/	5-year PFS: 89%	5-year OS: 97%	/	

[a]Result is for all enrolled patients, not just patients with ALCL. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide and prednisone; hyper CVAD/MA, hyper fractionated cyclophosphamide, vincristine, Adriamycin, dexamethasone/methotrexate and cytarabine; VIP, etoposide, ifosfamide and cisplatin; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

Table II. Studies on survival following ASCT in patients with ALCL.

A, Prospective studies

First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support)	(Refs.)
Corradini *et al*, 2006	62	2	PTCL-NOS (n=28; 45%), AITL (n=10; 16%), ALK+ ALCL (n=19; 31%) ALK- ALCL (n=4; 6%)	ITT analysis	CR, 56; PR, 16; PD, 24	74	12-year OS, 34; 12-year EFS, 30	NA	ALK+ ALCL: 12-year OS, 62; 12-year EFS, 54; ALK-, NA	NA	Up-front HDT and ASCT are feasible, but could induce a high rate of long-term CR only in patients with ALK+ ALCL	Support	(18)
d'Amore *et al*, 2012	160	2	PTCL-NOS (n=62; 39%), ALK- ALCL (n=31; 19%), AILT (n=30; 19%), others (n=37; 23%)	ITT analysis	CR/Cru, 53; PR, 31; PD, 16	72	5-year OS, 51; 5-year PFS, 44	NA	5-year OS, 70; 5-year PFS, 61	NA	Dose-dense induction and HDT/ASCT are a rational up-front strategy in transplantation-eligible patients with PTCL	Support	(19)
Reimer *et al*, 2009; Wilhelm *et al*, 2016	111	2	PTCL-NOS (n=42; 38%), ALK- ALCL (n=16; 14%), AILT (n=37; 33%), others (n=16; 14%)	ITT analysis	CR, 62; PR, 20; PD, 18	68	5-year OS, 44; 5-year PFS, 39	5-year OS, 57%	NA	5-year OS, 23%	Up-front ASCT can result in long-term remissions in patients with all major subtypes of PTCL and therefore should be part of first-line therapy whenever possible	Support	(20,21)
Park *et al*, 2019	119	NA	PTCL-NOS (n=54; 45%), AILT (n=35; 29%), ALK- ALCL (n=30; 25%)	The first large prospective cohort study directly comparing the survival outcomes in CR1 with or without consolidative ASCT	CR, 100	30	2-year OS, 75; 2-year PFS, 63	2-year OS, 87.8%; median PFS, 57.6 months; median PFS, 47.5 months	2-y PFS=100% for ASCT group; 2-y PFS=84% for non-ASCT group; median OS (P=0.39) and PFS (P=0.27) not reached in either group	2-year OS, 70%; 2-year PFS, 67%; median PFS, 47.5 months	In nodal PTCL patients, no statistical difference in survival between the ASCT and non-ASCT groups. However, patients with AITL and/or high-risk features might benefit from consolidative ASCT in CR1	Not support	(28)

Table II. Continued.

B, Retrospective studies

First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support)	(Refs.)
Rodriguez *et al*, 2007	74	NA	PTCL-NOS (n=37; 50%), AILT (n=8; 11%), ALCL (n=23; 31%), others (n=6; 8%)	Study based on patients in CR after induction only	CR, 100	100	5-year OS, 68; 5-year PFS, 63		ALK status, NA; 5-year OS; 84; 5-year PFS, 80	NA	Consolidation with ASCT in CR patients increased the OS and PFS when compared with conventional chemotherapy	Support	(22)
He *et al*, 2012	64	NA	100% ALCL (ALK+ 33%, ALK- 22%, ALKu 45%)	48 patients undergoing conventional chemotherapy; 16 patients undergoing PBSCT	CR, 46; PR, 39; SD, 11; PD, 4	The PBSCT type was not explained (ASCT or allo-HSCT)	4-year OS, 90; 4-year EFS, 67e	4-year OS, 90%; 4-year EFS, 67% for all PBSCT patients; 4-year OS, 91%; 4-year EFS, 82% for patients undergoing PBSCT at CR1/PR1	NA	4-year OS, 88%; 4-year EFS, 71%	PBSCT improved the EFS of patients with specific adverse factors compared with conventional chemotherapy, OS was not improved	Partial support	(23)
Mehta *et al*, 2013	65	NA	PTCL-NOS (n=32; 49%), AILT (n=21; 32%), ALK- ALCL (n=12; 18%)	Retrospectively identified PTCL patients with the intention to transplant in CR1	CR, 51; PR, 32; PD, 12. For patients received ASCT: CR, 97; PR, 3	52 ASCT; 8 allo-HSCT	4-year OS, 52; 4-year PFS, 38	4-year OS, 67%; 4-year PFS, 55%	4-year OS, 66.7; 4-year PFS, 50 for HD-ASCT group (n=6); 4-year OS, 50; 4-year PFS, 33 for non-transplant group (n=6)	4-year OS, 67%; 4-year PFS, 30% for allo-HSCT group (n=5); 4-year OS, 27%; 4-year PFS, 17% for non-transplant group (n=26)	Support consolidation of CR1 with transplantation.	Support	(24)
Ellin *et al*, 2014	252	NA	PTCL-NOS (n=109; 43%), AILT (n=47; 19%), ALK- ALCL (n=52; 21%), others (n=44; 17%)	Subgroup ITT-based analysis of an initial real-world study	No data on this specific subgroup eligible for transplant	51 in ITT	No data on this specific subgroup eligible for transplant	5-year OS, 48%; 5-year PFS, 41% in the ITT-ASCT group	NA	5-year OS, 26%; 5-year PFS, 20% in the ITT-no ASCT group	Results support the role of ASCT consolidation for EATL and nodal PTCLs except ALK+ ALCL	Support	(25)

Table II. Continued.

B, Retrospective studies

First author, year	Number of patients available for analysis	Phase	Histological subtype	Design of the study/the significance of the research	Response rate after induction, %	ASCT rate, %	Survival for the entire cohort, %	Survival for patients treated with ASCT	Survival of patients with ALCL, %	Survival of patients of non-ASCT groups	Evaluation of ASCT as the first-line consolidation therapy	Conclusion (support/ not support)	(Refs.)
Fossard *et al*, 2018	269	NA	PTCL-NOS (n=78; 29%), AILT (n=123; 46%), ALK- ALCL (n=68; 25%)	ITT-based large multicentric retrospective study with PSM analysis and Cox proportional hazard model	CR, 81; PR, 19	50 in ITT	5-year OS, 60; 5-year PFS, 45	5-year OS, 59%; 5-year PFS, 46% in the ITT-ASCT group	ASCT ITT yes (n=31) vs. no (n=37): PFS: HR=1.02, P=0.89; OS: HR=1.08, P=0.74	5-year OS, 60%; 5-year PFS, 41% in the ITT-no ASCT group	Does not support the use of ASCT for up-front consolidation for all patients with PTCL-NOS, AITL, or ALK-ALCL with CR/PR after induction	Not support	(29)

ASCT, autologous stem cell transplant; ITT, intention-to-treat; CR, complete response; Cru, CR unconfirmed; PR, partial response; PD, progressive disease; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; OS, overall survival; PFS, progression-free survival; EFS, event-free survival; CR1, first CR; PR1, first PR; NA, not available; PSM, propensity score matching; ITT, intent-to-treat; ALKu, ALK status unknown; HDT, high-dose therapy; PBSCT, peripheral blood stem cell transplantation; HR, hazard ratio.

Table III. Studies on survival following HSCT in patients with R/R ALCL.

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR rate), %	PFS/EFS, %	OS, %	Adverse events 3-4 grade	(Refs.)
Smith *et al*	/	2013	/	ASCT	115	61	/	/	61	/	3-year PFS, 55	3-year OS, 68	/	(34)
				Allo-HSCT	126	51	/	/	51	/	3-year PFS, 35	3-year OS, 41	/	
Fukano *et al*	/	2015	/	ASCT	23	23	/	/	23	/	5-year EFS, 38	5-year OS, 51	/	(32)
				Allo-HSCT	24	24	/	/	24	/	5-year EFS, 50	5-year OS, 54	/	
Fukano *et al*	/	2019	/	MAC regimen	30	30	/	/	30	/	5-year EFS, 43	5-year OS, 49	/	(33)
				RIC regimen	8	8	5	2	1	100 (100)	5-year EFS, 88	5-year OS, 100	/	
Domingo-Domenech *et al*	/	2020	/	ASCT	65	65	38	24	3	/	3-year PFS, 64	3-year OS, 73	/	(30)
Domingo-Domenech *et al*	/	2020	/	Allo-HSCT	44	44	23	20	1	/	3-year PFS, 53	3-year OS, 74	/	(31)

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; ASCT, autologous stem cell transplantation; HDT, high-dose therapy; allo-HSCT, allogeneic hematopoietic stem cell transplantation; MAC, myeloablative conditioning; RIC, reduced-intensity condition.

According to the NCCN guidelines, allo-HSCT or HDC/ASCT can be used in patients with R/R ALCL who achieve PR/CR following second-line treatment. However, further in-depth studies comparing allo-HSCT and HDC/ASCT specifically in ALCL are necessary to prove their efficiency. In addition, decreasing the mortality rate and the incidence of side effects of HSCT is also a challenge that needs to be overcome.

4. Immunotherapy and targeted therapy

With the development of biomedicine and the reinvention of tumor therapy, targeted therapy and immunotherapy have gradually become the focus of tumor therapy research and are now playing an increasingly important role in the treatment of tumors, including ALCL. The role of drugs such as brentuximab vedotin (BV), histone deacetylase (HDAC) inhibitors, ALK inhibitors and programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors in ALCL have already been widely studied (Table IV), and the ongoing trials are summarized in Table V.

BV. BV (SGN-35) is an antibody-drug conjugate (ADC) against CD30 antigen, expressed in HL and ALCL. BV consists of three parts: An anti-CD30 monoclonal antibody cAC10, antimitotic drug microtubule polymerization monomethyl auristatin E (MMAE) and valine-citrulline dipeptide as a linker (35). CD30 is a member of the tumor necrosis factor receptor superfamily (36); its expression is limited in normal tissues but high in malignant tumors, such as ALCL and HL (37). Due to the targeting effect of antibodies, BV specifically binds to CD30 on the surface of malignant cells and induces cytotoxicity through MMAE-induced cell cycle arrest (38). This ADC combines the targeting selectivity of monoclonal antibodies with the high cytotoxicity of MMAE, achieving high antitumor activity and low toxicity and side effects compared with traditional chemotherapy (39).

BV was approved by the Food and Drug Administration (FDA) in August 2011 for the treatment of patients with sALCL who have experienced failure of first-line multiagent chemotherapy at least once (40). The NCCN guidelines also recommend BV as the preferred option as second-line treatment for R/R patients, regardless of whether a transplant is intended (26). A multicenter study conducted in Italy evaluated the effectiveness of BV in 40 patients with R/R sALCL (18 ALK^+ and 22 ALK^-). Of those, 31 (77.5%) achieved a favorable response after a median of four cycles of single-agent BV, with an overall response rate (ORR) of 62.5% (45% CR) (41). In addition to retrospective studies, prospective trials have also confirmed the efficacy of BV in ALCL. A phase 2 study (NCT00866047) showed a CR rate of 66% with an estimated 5-year OS and PFS rate of 60 and 39%, respectively (42). According to the present analysis, BV has good developmental and application prospects, with great potential to be used in the treatment of R/R ALCL.

Although patients with R/R ALCL have a high response rate to BV treatment and a good prognosis, disease progression still occurs in some patients following BV monotherapy-induced remission. The effect of BV retreatment has been explored in previous studies. A prospective study (NCT00947856) involving 8 patients with sALCL reported a ORR of 88% (63% CR) to BV retreatment and controllable safety (43). A retrospective multicenter study reported similar results (ORR, 70%; CR, 60%) (44). These two studies suggested that BV might be a promising option for the retreatment of patients with R/R ALCL.

Given the side effects and unimproved efficacy of traditional chemotherapy, as well as the excellent results of BV in patients with R/R ALCL, Fanale *et al* (45) evaluated the efficacy of front-line BV in combination with cyclophosphamide, doxorubicin and prednisone (BV + CHP) in untreated patients with primary tumors. The study showed an estimated 5-year PFS and OS rate of 47 and 79%, respectively, and continued CR was maintained in 56% (9/16) of patients with ALCL until the end of the study, which indicated that frontline BV + CHP could yield durable benefits and might be a curative treatment option for some untreated patients with primary tumors. Given these promising results, ECHELON-2(NCT01777152), a large multicenter phase 3 double-blind randomized trial, was launched to compare the efficacy and safety of BV + CHP and CHOP in 452 untreated patients with $CD30^+$ PTCL (70% sALCL) (46). After 6 or 8 cycles of treatment, the CR rate and ORR of the BV + CHP group were superior to those of the CHOP group. In addition, BV + CHP also showed a higher 3-year PFS rate (57.1 vs. 44.4%) and a lower risk of death (hazard ratio, 0.66; P=0.0244). This favorable result prompted the FDA to approve BV for patients with previously untreated sALCL in combination with chemotherapy (47).

The most important adverse event (AE) of BV is peripheral neuropathy (PN), which has an incidence rate of >50%; however, in previous studies, a significant portion of patients showed regression or improvement, and there were no fatal AEs associated with BV during the treatment (42,45,46). Furthermore, ECHELON-2 showed that the incidence and severity of PN were similar between the BV + CHP and CHOP groups (46), which meant that BV may not increase the incidence of PN while still improving the curative effect.

Overall, the efficacy of BV in patients with R/R ALCL is considerable, and its retreatment effect on these patients is also worthy of further study. Compared with traditional chemotherapy, BV + CHP can achieve superior therapeutic outcomes without significantly increasing toxicity and it is emerging as a new treatment option for patients with newly diagnosed ALCL. There are several ongoing trials on BV in ALCL (NCT01909934, NCT03766516 and NCT03947255) (Table V).

Pralatrexate. In addition to BV, other US FDA-approved drugs for patients with R/R PTCL include pralatrexate, romidepsin and belinostat (48). Pralatrexate is a novel targeted folic acid agent that can competitively inhibit dihydrofolate reductase, ultimately leading to DNA replication error and tumor cell apoptosis (49).

In a large phase 2 study, PROPEL, patients with R/R PTCL who received a median of three previous systemic treatments achieved an ORR of 29% [11% CR/unconfirmed CR (CRu), 18% PR] and a median duration of response (DOR) of 10.1 months (50). Based on the relatively good and consistent reactivity, in 2009, pralatrexate became the first drug to be approved by the FDA for patients with R/R PTCL. In an international case-matched control analysis of the PROPEL study,

Table IV. Studies on survival following immunotherapy and targeted therapy in patients with ALCL.

A, BV

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Bartlett *et al*	NCT00947856	2014	2	BV	28	8	3	5	0	88 (63)	Median PFS, 12.9 months	Median OS, not reached	PN, fatigue, arthralgia and anemia	(43)
Broccoli *et al*	/	2017	/	BV	40	40	18	22	0	62.5 (45)	2-year PFS, 39.1%	2-year OS, 56.9%	Neutropenia and PN	(41)
Pro *et al*	NCT00866047	2017	2	BV	58	58	16	42	0	86 (66)	5-year PFS: ALK-, 39%; ALK+, 37%	5-year OS: ALK-, 61%; ALK+, 56%	PN	(42)
Fanale *et al*	NCT01309789	2018	1	BV + CHP	26	19	3	16	0	100 (92)[a]	5-year PFS, 47%	5-year OS, 79%	PN	(45)
Horwitz *et al*	NCT01777152	2019	3	BV + CHP	226	162	49	113	0	83 (68)[a]	Median PFS[a], 48.2 months; 3-year PFS[a], 57.1%	Median OS[a], not reached	Nausea, neutropenia, diarrhea, pyrexia, constipation, PN, anemia and fatigue	(46)
				CHOP	226	154	49	105	0	72 (56)[a]	Median PFS[a], 20.8 months; 3-year PFS[a], 44.4%	Median OS[a], not reached	Nausea, neutropenia, diarrhea, fatigue, constipation, PN, alopecia and anemia	
Fukuhara *et al*	/	2020	/	BV	28	10	/	/	10	70 (60)	Median PFS, 5.3 months	Median OS, not mentioned	Alanine aminotransferase increased, neutropenia and PN	(44)

B, Pralatrexate

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
O'Connor *et al*	NCT00364923	2011	2	Pralatrexate	115	17	/	/	/	29 (11)[a]; 35 for ALCL	Median PFS[a], 3.5 months	Median OS[a], 14.5 months	Thrombocytopenia, mucositis, neutropenia and anemia	(50)
Advani *et al*	NCT01336933	2016	2	Pralatrexate + CEOP	33	4	/	/	/	70 (52)[a]; 100 (75) for ALCL	2-year PFS[a], 39%	2-year OS[a], 60%	Anemia, thrombocytopenia, febrile neutropenia, mucositis, sepsis, increased creatinine and liver transaminases	(52)
O'Connor *et al*	/	2018	/	PROPEL group	80	13	/	/	/	/	/	Median OS[a], 15.2 months	/	(51)
				Control group	80	12	/	/	/	/	/	Median OS[a], 4.07 months	/	

Table IV. Continued..

C, HDAC inhibitors

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Coiffier *et al*	NCT00426764	2012	2	Romidepsin	130	22	1	21	0	25 (15)[a]; 24 (19) for ALCL	Median PFS[a], 4 months	Median OS[a], 11.3 months	Thrombocytopenia, neutropenia and infections	(53)
Coiffier *et al*		2014		Extension phase of romidepsin							Median PFS, 20 months for objective responders	Median OS, 30 months for objective responders		(57)
Dupuis *et al*	NCT01280526	2015	1b/2	Romidepsin + CHOP	37	3	0	3	0	68 (51)[a]	30-month PFS[a], 41.0%	30-month OS[a], 70.7%	Neutropenia, thrombocytopenia, anemia and nausea	(58)
O'Connor *et al*	NCT00865969	2015	2	Belinostat	120	15	2	13	0	25.8 (10.8)[a]; 13 for ALCL	Median PFS[a], 1.6 months	Median OS[a], 7.9 months	Anemia, thrombocytopenia, dyspnea and neutropenia	(54)
Johnston *et al*	NCT01839097	2021	1	Belinostat + CHOP	23	3	2	1	0	86 (71)[a] at MTD	/	/	Febrile neutropenia, pyrexia, nausea and neutropenia	(59)
Shi *et al*	/	2015	2	Chidamide	79	17	/	11	/	28 (14)[a]; 45 for ALK- ALCL	Median PFS[a], 2.1 months	Median OS[a], 21.4 months	Thrombocytopenia, leucopenia and neutropenia	(55)
Shi *et al*	/	2017	2	Chidamide monotherapy	256	35	/	/	/	39.06[a]	Median PFS[a], 129 days	Median DOR[a], 148 days	Thrombocytopenia and neutropenia	(56)
				Chidamide combined with chemotherapy	127					51.18[a]	Median PFS[a], 152 days	Median DOR[a], 169 days	Thrombocytopenia, neutropenia, anemia, and fatigue	
Zhang *et al*		2021	1b/2	Chidamide + CHOEP	128	?				60.2 (40.7)[a]	Median PFS[a], 10.7 months; 3-year PFS[a], 32.8%	/	/	(60)

D, ALK inhibitors

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Mossé *et al*	NCT00939770	2017	1/2	Crizotinib 165 mg/m^2	6	6	6	0	0	83 (83)	/	/	Neutropenia	(66)
				Crizotinib 280 mg/m^2	20	20	20	0	0	90 (80)	/	/	Neutropenia	
Gambacorti-Passerini *et al*	NCT01121588	2018	Ib	Crizotinib 250 mg twice daily	44	18	18	0	0	52.9 (47.1)	2-year PFS, 63.0%	Median OS, not reached	Nausea, elevated transaminases, vomiting, neutropenia, abdominal paim, leukopenia and fatigue	(67)

Table IV. Continued..

E, Everolimus

First author	Clinical trial ID	Year	Phase	Regimen	All patients, n	ALCL patients, n	ALK+, n	ALK-, n	ALK status unknown, n	ORR (CR), %	PFS/EFS	OS	Adverse events 3-4 grade	(Refs.)
Witzig *et al*	NCT00436618	2015	2	Everolimus	16	2	/	/	2	44[a]	Median PFS[a], 4.1 months	Median OS[a], 10.2 months	/	(94)
Kim *et al*	NCT01198665	2016	2	Everolimus + CHOP	30	7	0	7	0	90 (57)[a]	/	2-year OS[a], 70%	Neutropenia and thrombocytopenia	(95)

[a]Result is for all enrolled patients, not just ALCL patients. ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ORR, overall response rate; CR, complete remission; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; BV, brentuximab vedotin; PN, peripheral neuropathy; CHP, cyclophosphamide, vincristine and prednisone; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; CEOP, cyclophosphamide, etoposide, vincristine and prednisone; DOR, duration of response; MTD, maximum tolerated dose; CHOEP, cyclophosphamide, vincristine, doxorubicin, etoposide and prednisone; HDAC, histone deacetylase.

the median OS time of the PROPEL group was superior to that of the control group (15.24 vs. 4.07 months). In patients with ALCL, the OS curves of the two groups coincided, suggesting that pralatrexate might have a similar efficacy to that of treatment previously used in ALCL (51). The addition of new drugs to conventional cytotoxic drugs has the potential to yield unexpected clinical benefits for patients, such as the aforementioned successful discovery of CHOEP and BV + CHP; for that reason, some clinical centers are experimenting with different drug combinations. Advani *et al* (52) studied the effects of cyclophosphamide, etoposide, vincristine and prednisone alternating with pralatrexate as first-line treatment for patients with PTCL, but the results did not show a higher response rate or more favorable survival compared with the traditional CHOP regimen (NCT01336933).

HDAC inhibitors. Romidepsin, belinostat and chidamide are HDAC inhibitors that act at the epigenetic level to induce tumor cell cycle arrest and apoptosis. Results from three phase II clinical studies showed that among patients with R/R PTCL who had previously received a median of two or three systemic therapies, the ORR was 25% (15% CR), 25.8% (10.8% CR) and 28% (14% CR), and the median DOR was 17, 13.6 and 9.9 months, following treatment with romidepsin (53), belinostat (54) and chidamide (55), respectively. The most common AEs of grade 3 or higher were hematological toxicities (e.g., thrombocytopenia and neutropenia), with the lowest incidence observed following treatment with belinostat. Due to the poor survival of patients with R/R PTCL and the relatively effective and persistent reactivity of romidepsin and belinostat shown in those studies, these drugs were approved by the US FDA. Chidamide, a novel benzoamide-like HDAC inhibitor, was approved by the Chinese FDA in December 2014 for R/R PTCL and is currently only available in China. In a multicenter real-world study, the ORR of chidamide monotherapy was 39% and reached 51% when combined with chemotherapy (56). In addition, a long-term follow-up study of the romidepsin trial showed a median DOR of 28 months for patients who responded to treatment, and a median PFS time of 29 months for those who achieved CR/CRu, and the continuous application of romidepsin did not increase its toxicity (57). Therefore, romidepsin can enable patients to obtain an effective, long-lasting and relatively safe response, laying an important foundation for its further study in patients with PTCL.

The efficacy of these three drugs in combination with conventional chemotherapy in first-line treatment was also studied separately. In the phase 2 trial of romidepsin in combination with CHOP, the ORR was 68% (51% CR), with a 30-month PFS and OS rate of 41.0 and 70.7%, respectively (NCT01280526) (58), indicating that the combination appears to be a feasible option. However, the higher toxicity of the romidepsin group, with grade 3-4 neutropenia in 89% of patients, and at least one serious AE in 68% of patients, should not be ignored. In addition, the existence of cardiotoxicity needs to be determined. An ongoing multicenter phase 3 randomized controlled study (NCT01796002) is currently comparing the efficacy of CHOP with that of romidepsin plus CHOP. In the belinostat combined with CHOP study, the ORR was 86% (71% CR) at the maximum tolerated dose of belinostat, and

Table V. Ongoing trials of ALCL.

Clinical trial ID	Status	Regimen	Phase	Patient diagnosis	Patient number
NCT01909934	Active, not recruiting	BV	4	R/R ALCL	50
NCT04306887	Recruiting	TQ-B3101	2	R/R ALCL	30
NCT03766516	Recruiting	BV	/	R/R ALCL or Classical HL	150
NCT03703050	Recruiting	Nivolumab	2	R/R ALK+ ALCL	38
NCT03443128	Recruiting	Vinorelbine	2	Child and adolescent R/R ALCL	20
NCT03505554	Recruiting	Lorlatinib	2	ALK+ R/R ALCL	12
NCT02419287	Active, not recruiting	Crizotinib	2	ALK+ ALCL resistant or refractory to standard cytotoxic treatment	12
NCT03947255	Recruiting	BV	2	HL, PTCL and ALCL	80
NCT01796002	Active, not recruiting	Romidepsin + CHOP	3	PTCL	421
NCT04526834	Recruiting	Anti-CD30 CAR T cells	1	ALCL, PTCL, DLBCL, Extranodal NK/T-cell Lymphoma and PMBCL	21
NCT04008394	Recruiting	Anti-CD30 CAR T cells	1	Adult TCL, ALCL, AITL, NK/T-cell Lymphoma, PTCL and HL	50
NCT03049449	Recruiting	Anti-CD30 CAR T cells	1	ALCL, EAT-CL, DLBCL, PTCL and Extranodal NK/T-cell Lymphoma	79
NCT04083495	Recruiting	Anti-CD30 CAR T cells	2	PTCL	20
NCT03383965	Recruiting	Anti-CD30 CAR T cells	1	HL and ALCL	20

BV, brentuximab vedotin; R/R, relapsed or refractory; ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; TCL, T-cell lymphoma; EAT-CL, Enteropathy-associated T-cell lymphoma; ALK+, anaplastic lymphoma kinase-positive; HL, Hodgkin's lymphoma; PTCL, peripheral T-cell lymphoma; CAR, chimeric antigen receptor; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; PMBCL, Primary Mediastinal Large B-Cell Lymphoma.

the incidence of AEs was similar to that following treatment with belinostat alone, suggesting that the combination would not cause additional toxicity (59). Chidamide, when combined with the CHOEP regimen, had an ORR of 60.2% (40.7% CR) and a 3-year PFS rate of 32.8% in 113 newly diagnosed PTCL patients who received 20 mg chidamide twice a week. The AEs were also at a controllable level (60).

However, all of these studies were non-randomized, single-arm trials, with a small patient population and without a separate analysis of the basic characteristics and survival outcomes of the patients with ALCL. Therefore, the efficacy of these drugs in ALCL needs to be further confirmed. At present, the drugs can be considered for patients who are R/R and have no response to treatment with BV; however, their role in combination with chemotherapy in first-line treatment needs to be further studied.

ALK inhibitors. ALK is a tyrosine kinase receptor that belongs to the insulin receptor superfamily. Under normal circumstances, the expression of ALK is limited to neurogenic cells in humans, while the translocation of the ALK chromosome leads to its expression and continuous activation. The expression of ALK can be found in ALK$^+$ ALCL, inflammatory myofibroblastoma and non-small cell lung cancer (NSCLC). Fusions of ALK have a clear carcinogenic potential, since their abnormal tyrosine kinase activity can promote cell proliferation and survival (61-63). The carcinogenic effect of ALK is mediated by triggering a large number of downstream molecules of the intracellular signaling cascade. Therefore, ALK can be used as an ideal therapeutic target for ALK$^+$ disease. At present, there are three generations of ALK inhibitors; the first generation is crizotinib, the second generation contains seritinib, alitinib and brigatinib, and the third generation is lorlatinib (64). In 2011, crizotinib was approved by the FDA for the treatment of patients with ALK$^+$ NSCLC (40); it has also been tried out in patients with ALCL and ALK$^+$ mutations in recent years and a series of clinical trials are underway.

Gambacorti Passerini *et al* (65) reported an ORR of 90.9% (10/11 cases) in R/R ALK$^+$ lymphoma following crizotinib treatment. Among the 9 patients with CR, 4 obtained continuous CR following long-term treatment with crizotinib, 2 experienced progression following CR, and 3 received allo-HSCT and remained in CR.

The efficacy and safety of crizotinib in patients with advanced or R/R ALCL have also been demonstrated in two clinical trials (66,67). One enrolled 26 patients with ALK$^+$ ALCL, aged 1-21 years, who received 280 or 165 mg/m^2 crizotinib twice daily and had an ORR of 88% (CR 81%) (66). The positive results led to the FDA approval of crizotinib for use in children aged ≥1 years old or young adults with R/R ALK$^+$ ALCL in 2021 (68). Another study showed that in 18 patients with R/R ALCL, ORR and CR were 52.9 and 47.1%, respectively, with a median DOR of 2.6 years (67). Although 88.6% of the patients experienced AEs, most were grade 1 and there were no fatal AEs.

Several case reports also reported that crizotinib alone or combined with HSCT had a good therapeutic effect in R/R ALCL (69-74). Alitinib, a second-generation ALK inhibitor, has also been reported to induce CR in patients with ALK$^+$ ALCL (75). All these studies suggested that ALK inhibitors could improve the prognosis of patients with ALK$^+$ ALCL, but there is also a report of rapid recurrence following the withdrawal of crizotinib (76); therefore, long-term follow-ups are still required to evaluate the efficacy and safety of these drugs.

Patients with R/R ALCL usually have a poor prognosis, and there is no consensus on the treatment that should be administered to these patients. Although research and clinical practice have confirmed that BV has a favorable effect on patients with R/R ALCL, its long-term AEs, such as PN, cannot be ignored. In recent studies, crizotinib has been shown to have significant and durable antitumor effects and a good tolerance in patients with R/R ALCL, which suggests its potential as a treatment option. However, it can only be used in ALK$^+$ patients and is currently only tentatively used in R/R patients. The matter of

recurrence following drug withdrawal, and whether crizotinib can be used as first-line treatment, require further study.

Platelet-derived growth factor receptor (PDGFR) inhibitors. Even following BV treatment or HSCT, the prognosis of patients with R/R ALCL has been reported to remain poor (77); for that reason, novel drugs have gradually started to be used for the treatment of these patients. In addition to the BV, pralatrexate, HDAC inhibitors and ALK inhibitors aforementioned, other emerging therapies, such as PD-1/PD-L1 inhibitors, PDGFRB inhibitors and other NPM-ALK fusion protein inhibitors, have also been widely studied and found to have potential benefits. The signal transduction pathways, immunotherapies and targeted therapies in ALCL are illustrated in Fig. 1.

PDGF is a peptide regulatory factor that stimulates tissue cell growth and plays a biological role by phosphorylating and activating PDGFR and initiating the PDGF/PDGFR signaling pathway. ALK can induce the expression of JunB and JUN through the PI3K/Akt/mTOR signaling pathways (78,79), and then bind to and activate the PDGFRB promoter. The expression and activation of PDGFR is a key event in lymphoma cell survival and proliferation. A previous study (80) showed that the therapeutic inhibition of PDGFR significantly prolonged the survival time of NPM-ALK transgenic mice. The study also reported the case of a 27-year-old patient with stage III ALK^+ ALCL, who was unresponsive to conventional chemotherapy and relapsed following ASCT (80). After 10 days of treatment with 400 mg/day imatinib, a kind of PDGFR inhibitor, the tumor marker levels decreased and the patient rapidly achieved CR, which was maintained for 22 months. A follow-up study showed that there was no recurrence 1 year after the withdrawal of imatinib (81). These results suggested that PDGFR inhibitors may be an effective treatment for NPM-ALK^+ ALCL. In addition, PDGFRs exists not only in NPM-ALK^+ TCL but also in ALK^- ALCL. Therefore, the application of PDGFR inhibitors is worthy of further study not only in patients with ALK^+ ALCL but also in those with ALK^- ALCL.

mTOR inhibitors. Most ALK^+ ALCL exhibit t(2;5)(p23;q35) translocation and mediate the expression of the NPM-ALK fusion protein. This fusion protein and its associated signaling pathways, such as the PI3K/Akt, JAK/STAT and RAS/MEK/ERK pathways, are potential targets for ALCL therapy (82-88). mTOR is an important downstream protein kinase of the PI3K-Akt and MEK/ERK signaling transduction pathways (89,90); it can accelerate the synthesis of intracellular proteins and provide the material basis for the growth of tumor cells. mTOR can be detected in 80% of patients with ALCL and is associated with the expression of ALK (91,92). mTOR inhibition can decrease the phosphorylation of mTOR and induce cell cycle arrest and apoptosis (93).

Everolimus is such an mTOR inhibitor (90). A phase II trial evaluating the efficacy of everolimus in patients with R/R TCL reported an ORR of 44% (PR in 1/2 patients with ALCL), with a median PFS and OS time of 4.1 and 10.2 months, respectively, following treatment with 10 mg everolimus daily (94). This indicated that everolimus had an antitumor effect in patients with TCL. Another phase II study of everolimus combined with CHOP as first-line treatment for patients with PTCL reported an ORR of 90% (27/30 cases; CR 57%). A total of 29% (2/7) of patients with ALK^- ALCL achieved CR (ALK^+ patients were not included in this study). However, the response duration was relatively short, suggesting that the value of this combination may be limited (95). A previous study reported the successful application of rapamycin (an mTOR inhibitor) in a patient with cutaneous ALCL (96). In the case of a 70-year-old woman who was unresponsive to treatment with a rituximab, etoposide, methylprednisolone, Adriamycin, cyclophosphamide and cisplatin regimen, a rituximab, etoposide, methylprednisolone, cytosine arabinoside and cisplatin regimen, or SGN-30, the tumor growth was halted following the use of rapamycin combined with local radiation for <6 weeks, and the patient had been taking rapamycin for 18 months and maintained a continuous CR.

In addition, studies have shown that the combination of alectinib and everolimus (97) or the combination of crizotinib and everolimus (98) can have a synergistic effect on the growth of ALK^+ ALCL cells, indicating that the combination of ALK inhibitors and mTOR inhibitors is worthy of further clinical investigation.

PD-1/PD-L1 inhibitors. PD-1 is a receptor protein on the surface of activated T cells and a member of the immunoglobulin superfamily. PD-L1 protein is the ligand of PD-1 and is expressed in a variety of tumor cells. The combination of the two proteins transmits a negative regulatory signal to T cells, inhibits T-cell activation, proliferation and cytokine production, induces T-cell apoptosis and enables the immune escape of tumor cells (99-101). The FDA has approved PD-1/PD-L1 inhibitors for the treatment of lung cancer, Hodgkin's lymphoma and other tumors (102-104).

The association between NPM-ALK and PD-L1 was recently clarified (105-107). The signalosome containing growth factor receptor-bound protein 2 (GRB2)/SOS Ras/Rac guanine nucleotide exchange factor 1 (SOS1) and STAT3 can induce the expression of PD-L1, in which GRB2/SOS1 plays a role by activating the MEK-ERK and PI3K-Akt signaling pathways (106). These signaling networks induce the expression of PD-L1 through the action of the transcription factors interferon regulatory factor 4 and basic leucine zipper ATF-like transcription factor 3 on the PD-L1 gene (106). In addition, targeting the carcinogenic signaling pathway in ALK^+ ALCL could suppress the PD-L1-mediated ability of tumor immune escape (106).

Shen *et al* (108) examined the expression of PD-L1 in 95 patients with ALCL and found that PD-L1 expression was higher in ALK^+ ALCL than that in ALK^- ALCL (76 vs. 42%; P=0.002), but that there was no difference in OS between patients with PD-$L1^+$ ALCL and those with PD-$L1^-$ ALCL (P=0.44). This suggested that the prognostic predicting ability of PD-L1 expression for ALCL was not significant, but this an area that requires further research (107). Kong *et al* (109) deemed that being PD-$L1^+$ is associated with a poor prognosis in ALK^- ALCL. Among 44 patients with ALK^- ALCL, patients with PD-$L1^+$ had an inferior median survival time (38 vs. 262 months; P=0.03); Kong *et al* (109) analyzed the reasons for this phenomenon and concluded that it may have been due to the difference in the PD-L1 positivity rate between

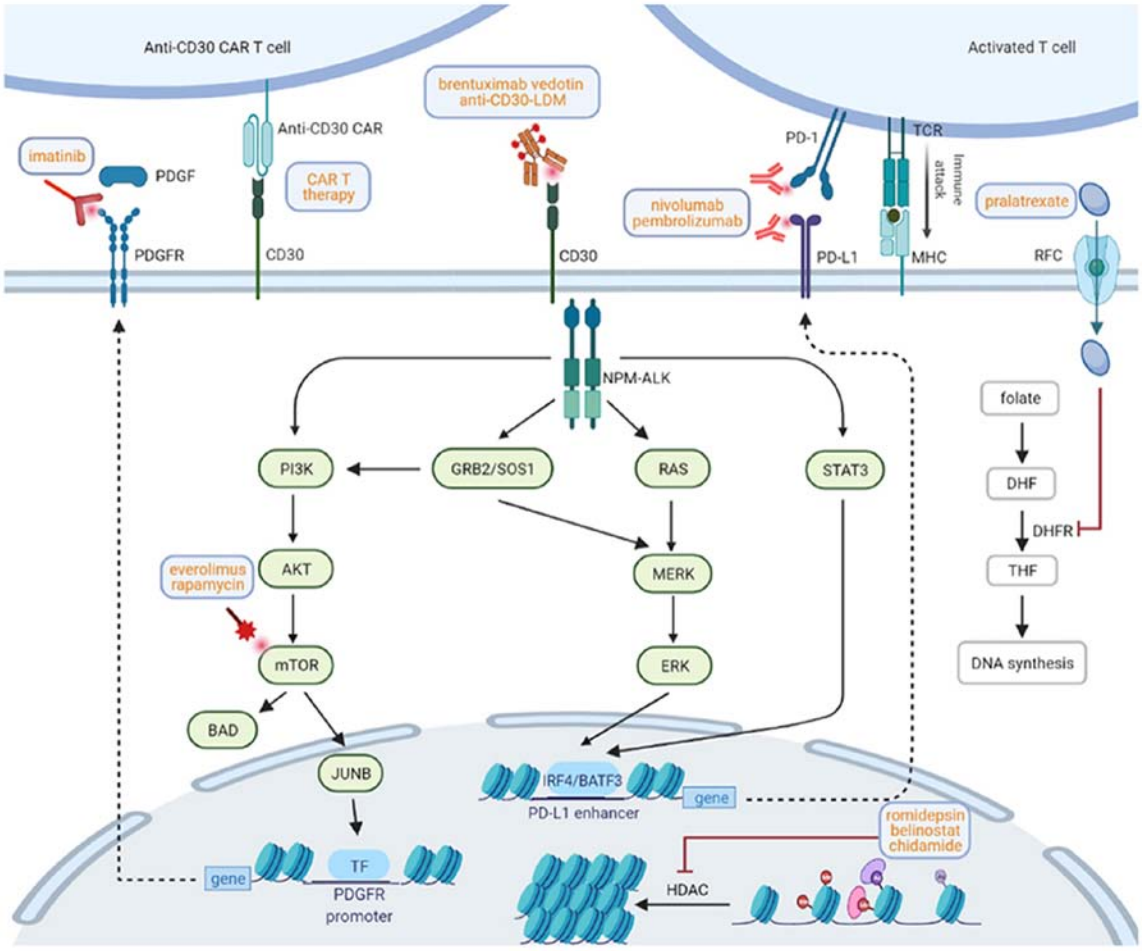

Figure 1. Signal transduction pathways, immunotherapies and targeted therapies in anaplastic large cell lymphoma. PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; CAR, chimeric antigen receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; MHC, major histocompatibility complex; RFC, reduced folate carrier; DHF, dihydrofolate; DHFR, dihydrofolate reductase; THF, tetrahydrofolate; HDAC, histone deacetylase; NPM-ALK, nucleophosmin-anaplastic lymphoma kinase; mTOR, mammalian target of rapamycin; TF, transcription factor; Grb2, growth factor receptor-bound protein 2; SOS1, SOS Ras/Rac guanine nucleotide exchange factor 1; IRF4, interferon regulatory factor 4; BATF3, basic leucine zipper ATF-like transcription factor 3; ADC, antibody-drug conjugate; LDM, lidamycin; TCR, T cell receptor; BAD, B-cell lymphoma 2-associated death promoter; JUNB, recombinant Jun B Proto Oncogene.

the two studies and the more aggressive disease experienced by patients in the previous study by Shen *et al* (108).

These studies provide a theoretical basis for the application of PD-1/PD-L1 inhibitors in R/R ALCL. In two previous case reports, 2 patients with ALK$^+$ ALCL who relapsed after chemotherapy and ALK inhibitor treatment (one of whom also underwent allo-HSCT) obtained a sustained CR following treatment with nivolumab (3 mg/kg/2 weeks) (110,111). Another patient (112) with stage IV ALK$^-$ ALCL who experienced relapse following chemotherapy, ASCT, allo-HSCT and BV treatment, was administered pembrolizumab (2 mg/kg; 1 dose of each at weeks 1 and 6, then once every 3 weeks) and obtained a CR after the third dose. These reports provide a clinical basis for the application of anti-PD1/PD-L1 therapy in R/R ALCL. A clinical trial (NCT03703050) evaluating the response of patients with progressive R/R ALK$^+$ ALCL to nivolumab or its use as consolidative therapy in patients with a CR after relapse is currently recruiting.

Chimeric antigen receptor T cells (CAR-T) therapy. As a major breakthrough in immunology, the emergence of CAR-T therapy has significant implications for the treatment of R/R B-cell NHL (113,114). However, its development in T-cell malignancies is fraught with difficulties and challenges, due to targetable antigens, cell fratricide and other issues (115). The presence of CAR-T cells that could recognize CD30 offers hope for patients with ALCL. As previously described, CD30 is widely expressed in ALCL cells. Several clinical trials on the efficacy, safety or optimum dose of CD30 CAR-T therapy in patients with R/R CD30$^+$ lymphocyte malignancies (including ALCL) are ongoing (NCT04526834, NCT04008394, NCT03049449, NCT04083495 and NCT03383965) (Table V).

Others. The MYC proto-oncogene, basic helix-loop-helix transcription factor gene family and its products can promote cell proliferation, differentiation and transformation, and play an important role in a variety of tumors, while ALCL can induce the expression of MYC protein in several ways (116,117). In addition, MYC can regulate antitumor immunity by controlling the expression of PD-L1 in ALCL (118,119). The inhibition of MYC had a toxic effect on the DEL ALK$^+$ ALCL cell line,

suggesting that use of the MYC inhibitor may be an effective breakthrough in the treatment of ALCL in the future (117).

Lidamycin (LDM) is a highly effective enadiyne antitumor antibiotic that kills tumor cells by directly acting on DNA chains to cause DNA damage (120). The LDM molecule is composed of an apoprotein and highly active enadiyne chromophore (121). Anti-CD30-LDM, obtained by coupling LDP with CD30 by genetic engineering, is a new type of ADC that has exhibited strong tumor-targeting and antitumor effects in $CD30^+$ ALCL cells and a Karpas299 mouse model, with no obvious toxicity to normal tissue (122). Further experiments showed that the combination of crizotinib and anti-CD30-LDM had a significant synergistic inhibitory effect on ALK^+ ALCL cells *in vitro* and *in vivo* (123).

Other agents, such as KRCA-0008 (a co-inhibitor of wild-type ALK and crizotinib-resistant ALK mutant) (124), ZYY (a novel ALK inhibitor) (125) and tyrosine kinase 2 (a member of the JAK family of tyrosine kinases) (126) inhibitors, have been studied in ALCL and achieved good responses in a series of *in vivo* and *in vitro* trials, providing new options for the treatment of ALCL and the potential to improve patient prognosis.

5. Conclusions

ALCL is a type of lymphoma with a low incidence, which makes carrying out clinical research challenging. Traditional chemotherapy, such as the CHOP regimen, is still recommended for the first-line treatment of ALCL due to its acceptable AEs and relatively satisfactory treatment effects and survival rate compared with intensive chemotherapy. HSCT can be administered to certain patients and improve their survival, but the increased AEs and TRM cannot be ignored, particularly with regard to allo-HSCT. Targeted therapy and immunotherapy, such as ALK inhibitors, HDAC inhibitors, and BV, have exhibited high response rates and favorable survival rates for patients with ALK^+ or $CD30^+$ R/R ALCL, but their application as first-line therapy requires further exploration. In addition, other novel drugs, such as mTOR inhibitors, PDGFR inhibitors and PD-1/PD-L1 inhibitors, have been proven to be effective in certain case reports, offering options for R/R patients. However, the relatively high price is an important reason to limit the widespread application of immunotherapy. In addition, how to evaluate and determine which immunotherapy regimen to use and how to predict its effectiveness, as well as the AEs and drug resistance of immunotherapy, all need further research.

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Authors' contributions

XS wrote the manuscript, XF provided the main outline and direction of the manuscript, and helped to revise the content of the manuscript. DL and YL summarized the data and tables, and helped to revise the manuscript. XW provided the latest ideas and polished the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ and Go RS: Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: A longitudinal analysis of the National cancer data base from 1998 to 2011. Am J Hematol 90: 790-795, 2015.
2. Alessandri AJ, Pritchard SL, Schultz KR and Massing BG: A population-based study of pediatric anaplastic large cell lymphoma. Cancer 94: 1830-1835, 2002.
3. Swerdlow SH, Harris NL, Jaffe ES, Pileri SA, Stein H and Thiele J (eds): WHO classification of tumours of hematopoietic and lymphoid tissues. Vol 2. 4th edition. International Agency for Research on Cancer (IARC), Lyon, 2017.
4. Morris SW, Kirstein MN, Valentine MB, Dittmer KG, Shapiro DN, Saltman DL and Look AT: Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 263: 1281-1284, 1994.
5. Ma Z, Cools J, Marynen P, Cui X, Siebert R, Gesk S, Schlegelberger B, Peeters B, De Wolf-Peeters C, Wlodarska I and Morris SW: Inv(2)(p23q35) in anaplastic large-cell lymphoma induces constitutive anaplastic lymphoma kinase (ALK) tyrosine kinase activation by fusion to ATIC, an enzyme involved in purine nucleotide biosynthesis. Blood 95: 2144-2149, 2000.
6. Hernández L, Pinyol M, Hernández S, Beà S, Pulford K, Rosenwald A, Lamant L, Falini B, Ott G, Mason DY, *et al*: TRK-fused gene (TFG) is a new partner of ALK in anaplastic large cell lymphoma producing two structurally different TFG-ALK translocations. Blood 94: 3265-3268, 1999.
7. Lamant L, Dastugue N, Pulford K, Delsol G and Mariamé B: A new fusion gene TPM3-ALK in anaplastic large cell lymphoma created by a (1;2)(q25;p23) translocation. Blood 93: 3088-3095, 1999.

8. Tort F, Pinyol M, Pulford K, Roncador G, Hernandez L, Nayach I, Kluin-Nelemans HC, Kluin P, Touriol C, Delsol G, *et al*: Molecular characterization of a new ALK translocation involving moesin (MSN-ALK) in anaplastic large cell lymphoma. Lab Invest 81: 419-426, 2001.
9. Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, Rimsza L, Pileri SA, Chhanabhai M, Gascoyne RD, *et al*: ALK-anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: Report from the International peripheral t-cell lymphoma project. Blood 111: 5496-5504, 2008.
10. Larose H, Burke GAA, Lowe EJ and Turner SD: From bench to bedside: The past, present and future of therapy for systemic paediatric ALCL, ALK. Br J Haematol 185: 1043-1054, 2019.
11. Schmitz N, Trumper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, Peter N, Loeffler M, Rosenwald A and Pfreundschuh M: Treatment and prognosis of mature T-cell and NK-cell lymphoma: An analysis of patients with T-cell lymphoma treated in studies of the German high-grade non-hodgkin lymphoma study group. Blood 116: 3418-3425, 2010.
12. Sibon D, Nguyen DP, Schmitz N, Suzuki R, Feldman AL, Gressin R, Lamant L, Weisenburger DD, Rosenwald A, Nakamura S, *et al*: ALK-positive anaplastic large-cell lymphoma in adults: An individual patient data pooled analysis of 263 patients. Haematologica 104: e562-e565, 2019.
13. Abramson JS, Feldman T, Kroll-Desrosiers AR, Muffly LS, Winer E, Flowers CR, Lansigan F, Nabhan C, Nastoupil LJ, Nath R, *et al*: Peripheral T-cell lymphomas in a large US multicenter cohort: Prognostication in the modern era including impact of frontline therapy. Ann Oncol 25: 2211-2217, 2014.
14. Escalon MP, Liu NS, Yang Y, Hess M, Walker PL, Smith TL and Dang NH: Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: The M D Anderson cancer center experience. Cancer 103: 2091-2098, 2005.
15. Simon A, Peoch M, Casassus P, Deconinck E, Colombat P, Desablens B, Tournilhac O, Eghbali H, Foussard C, Jaubert J, *et al*: Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 151: 159-166, 2010.
16. Sibon D, Fournier M, Brière J, Lamant L, Haioun C, Coiffier B, Bologna S, Morel P, Gabarre J, Hermine O, *et al*: Long-term outcome of adults with systemic anaplastic large-cell lymphoma treated within the groupe d'etude des lymphomes de l'adulte trials. J Clin Oncol 30: 3939-3946, 2012.
17. Brugières L, Quartier P, Le Deley MC, Pacquement H, Perel Y, Bergeron C, Schmitt C, Landmann J, Patte C, Terrier-Lacombe MJ, *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 11: 53-58, 2000.
18. Corradini P, Tarella C, Zallio F, Dodero A, Zanni M, Valagussa P, Gianni AM, Rambaldi A, Barbui T and Cortelazzo S: Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia 20: 1533-1538, 2006.
19. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, Holte H, Österborg A, Merup M, Brown P, *et al*: Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol 30: 3093-3099, 2012.
20. Reimer P, Rudiger T, Geissinger E, Weissinger F, Nerl C, Schmitz N, Engert A, Einsele H, Müller-Hermelink HK and Wilhelm M: Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: Results of a prospective multicenter study. J Clin Oncol 27: 106-113, 2009.
21. Wilhelm M, Smetak M, Reimer P, Geissinger E, Ruediger T, Metzner B, Schmitz N, Engert A, Schaefer-Eckart K and Birkmann J: First-line therapy of peripheral T-cell lymphoma: Extension and long-term follow-up of a study investigating the role of autologous stem cell transplantation. Blood Cancer J 6: e452, 2016.
22. Rodriguez J, Conde E, Gutierrez A, Arranz R, León A, Marín J, Bendandi M, Albo C and Caballero MD: The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (PTCL) in first complete remission: The Spanish lymphoma and autologous transplantation group experience. Ann Oncol 18: 652-657, 2007.
23. He XH, Li B, Zou SM, Dong M, Zhou SY, Yang JL, Xue LY, Yang S, Liu P, Qin Y, *et al*: Efficacy of peripheral blood stem cell transplantation versus conventional chemotherapy on anaplastic large-cell lymphoma: A retrospective study of 64 patients from a single center. Chin J Cancer 31: 532-540, 2012.
24. Mehta N, Maragulia JC, Moskowitz A, Hamlin PA, Lunning MA, Moskowitz CH, Zelenetz A, Matasar MJ, Sauter C, Goldberg J and Horwitz SM: A retrospective analysis of peripheral T-cell lymphoma treated with the intention to transplant in the first remission. Clin Lymphoma Myeloma Leuk 13: 664-670, 2013.
25. Ellin F, Landstrom J, Jerkeman M and Relander T: Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: A study from the Swedish lymphoma registry. Blood 124: 1570-1577, 2014.
26. Horwitz SM, Ansell S, Ai WZ, Barnes J, Barta SK, Clemens MW, Dogan A, Goodman AM, Goyal G, Guitart J, *et al*: NCCN Guidelines Insights: T-Cell Lymphomas, Version 1.2021. J Natl Compr Canc Netw 18: 1460-1467, 2020.
27. Kharfan-Dabaja MA, Kumar A, Ayala E, Hamadani M, Reimer P, Gisselbrecht C, d'Amore F, Jantunen E, Ishida T, Bazarbachi A, *et al*: Clinical practice recommendations on indication and timing of hematopoietic cell transplantation in Mature T cell and NK/T cell lymphomas: An International collaborative effort on behalf of the guidelines committee of the American society for blood and marrow transplantation. Biol Blood Marrow Transplant 23: 1826-1838, 2017.
28. Park SI, Horwitz SM, Foss FM, Pinter-Brown LC, Carson KR, Rosen ST, Pro B, His ED, Federico M, Gisselbrecht C, *et al*: The role of autologous stem cell transplantation in patients with nodal peripheral T-cell lymphomas in first complete remission: Report from COMPLETE, a prospective, multicenter cohort study. Cancer 125: 1507-1517, 2019.
29. Fossard G, Broussais F, Coelho I, Bailly S, Nicolas-Virelizier E, Toussaint E, Lancesseur C, Le Bras F, Willems E, Tchernonog E, *et al*: Role of up-front autologous stem-cell transplantation in peripheral T-cell lymphoma for patients in response after induction: An analysis of patients from LYSA centers. Ann Oncol 29: 715-723, 2018.
30. Domingo-Domenech E, Boumendil A, Climent F, Sengeloev H, Wahlin B, Wattad W, Arat M, Finel H, Schapp N, Ganser A, *et al*: Autologous hematopoietic stem cell transplantation for relapsed/refractory systemic anaplastic large cell lymphoma. A retrospective analysis of the lymphoma working party (LWP) of the EBMT. Bone Marrow Transplant 55: 796-803, 2020.
31. Domingo-Domenech E, Boumendil A, Climent F, Socié G, Kroschinsky F, Finel H, Vandenbergue E, Nemet D, Stelljes M, Bittenbring JT, *et al*: Allogeneic hematopoietic stem cell transplantation for patients with relapsed/refractory systemic anaplastic large cell lymphoma. A retrospective analysis of the lymphoma working party of the European society for blood and marrow transplantation. Bone Marrow Transplant 55: 633-640, 2020.
32. Fukano R, Mori T, Kobayashi R, Mitsui T, Fujita N, Iwasaki F, Suzumiya J, Chin M, Goto H, Takahashi Y, *et al*: Haematopoietic stem cell transplantation for relapsed or refractory anaplastic large cell lymphoma: A study of children and adolescents in Japan. Br J Haematol 168: 557-563, 2015.
33. Fukano R, Mori T, Fujita N, Kobayashi R, Mitsui T, Kato K, Suzuki R, Suzumiya J, Fukuda T, Shindo M, *et al*: Successful outcome with reduced-intensity condition regimen followed by allogeneic hematopoietic stem cell transplantation for relapsed or refractory anaplastic large-cell lymphoma. Int J Hematol 110: 723-728, 2019.
34. Smith SM, Burns LJ, van Besien K, Lerademacher J, He W, Fenske TS, Suzuki R, Hsu JW, Schouten HC, Hale GA, *et al*: Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 31: 3100-3109, 2013.
35. Katz J, Janik JE and Younes A: Brentuximab Vedotin (SGN-35). Clin Cancer Res 17: 6428-6436, 2011.
36. Smith CA, Farrah T and Goodwin RG: The TNF receptor superfamily of cellular and viral proteins: Activation, costimulation, and death. Cell 76: 959-962, 1994.
37. Younes A and Kadin ME: Emerging applications of the tumor necrosis factor family of ligands and receptors in cancer therapy. J Clin Oncol 21: 3526-3534, 2003.
38. Ansell SM: Brentuximab vedotin: Delivering an antimitotic drug to activated lymphoma cells. Expert Opin Investig Drugs 20: 99-105, 2011.
39. Shustov A and Soma L: Anaplastic large cell lymphoma: Contemporary concepts and optimal management. Cancer Treat Res 176: 127-144, 2019.

40. 2011 Notifications. https://www.fda.gov/drugs/resources-information-approved-drugs/2011-notifications. Journal 2021: U.S. Food and Drug Adminstration, 2018.
41. Broccoli A, Pellegrini C, Di Rocco A, Puccini B, Patti C, Gini G, Mannina D, Tani M, Rusconi C, Romano A, *et al*: Italian real-life experience with brentuximab vedotin: Results of a large observational study of 40 cases of relapsed/refractory systemic anaplastic large cell lymphoma. Haematologica 102: 1931-1935, 2017.
42. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, *et al*: Five-year results of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood 130: 2709-2717, 2017.
43. Bartlett NL, Chen R, Fanale MA, Brice P, Gopal A, Smith SE, Advani R, Matous JV, Ramchandren R, Rosenblatt JD, *et al*: Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol 7: 24, 2014.
44. Fukuhara N, Yamamoto G, Tsujimura H, Chou T, Shibayama H, Yanai T, Shibuya K and Izutsu K: Retreatment with brentuximab vedotin in patients with relapsed/refractory classical Hodgkin lymphoma or systemic anaplastic large-cell lymphoma: A multicenter retrospective study. Leuk Lymphoma 61: 176-180, 2020.
45. Fanale MA, Horwitz SM, Forero-Torres A, Bartlett NL, Advani RH, Pro B, Chen RW, Davies A, Illidge T, Uttarwar M, *et al*: Five-year outcomes for frontline brentuximab vedotin with CHP for CD30-expressing peripheral T-cell lymphomas. Blood 131: 2120-2124, 2018.
46. Horwitz S, O'Connor OA, Pro B, Illidge T, Fanale M, Advani R, Bartlett NL, Christensen JH, Morschhauser F, Domingo-Domenech E, *et al*: Brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma (ECHELON-2): A global, double-blind, randomised, phase 3 trial. Lancet 393: 229-240, 2019.
47. U.S. Food and Drug (FDA): FDA approves first-line treatment for peripheral T-cell lymphoma under new review pilot. FDA, Silver Spring, MD, 2018. https://www.fda.gov/news-events/press-announcements/fda-approves-first-line-treatment-peripheral-t-cell-lymphoma-under-new-review-pilot. Accessed November 16, 2018.
48. Vu K and Ai W: Update on the treatment of anaplastic large cell lymphoma. Curr Hematol Malig Rep 13: 135-141, 2018.
49. Malik SM, Liu K, Qiang X, Sridhara R, Tang S, McGuinn WD Jr, Verbois SL, Marathe A, Williams GM, Bullock J, *et al*: Folotyn (pralatrexate injection) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma: U.S. food and drug administration drug approval summary. Clin Cancer Res 16: 4921-4927, 2010.
50. O'Connor OA, Pro B, Pinter-Brown L, Bartlett N, Popplewell L, Coiffier B, Lechowicz MJ, Savage KJ, Shustov AR, Gisselbrecht C, *et al*: Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study. J Clin Oncol 29: 1182-1189, 2011.
51. O'Connor OA, Marchi E, Volinn W, Shi J, Mehrling T and Kim WS: Strategy for assessing new drug value in orphan diseases: An international case match control analysis of the PROPEL study. JNCI Cancer Spectr 2: pky038, 2018.
52. Advani RH, Ansell SM, Lechowicz MJ, Beaven AW, Loberiza F, Carson KR, Evens AM, Foss F, Horwitz S, Pro B, *et al*: A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): Final results from the T-cell consortium trial. Br J Haematol 172: 535-544, 2016.
53. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, Caballero D, Borchmann P, Morschhauser F, Wilhelm M, *et al*: Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 30: 631-636, 2012.
54. O'Connor OA, Horwitz S, Masszi T, Van Hoof A, Brown P, Doorduijn J, Hess G, Jurczak W, Knoblauch P, Chawla S, *et al*: Belinostat in patients with relapsed or refractory peripheral T-Cell Lymphoma: Results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol 33: 2492-2499, 2015.
55. Shi Y, Dong M, Hong X, Zhang W, Feng J, Zhu J, Yu L, Ke X, Huang H, Shen Z, *et al*: Results from a multicenter, open-label, pivotal phase II study of chidamide in relapsed or refractory peripheral T-cell lymphoma. Ann Oncol 26: 1766-1771, 2015.
56. Shi Y, Jia B, Xu W, Li W, Liu T, Liu P, Zhao W, Zhang H, Sun X, Yang H, *et al*: Chidamide in relapsed or refractory peripheral T cell lymphoma: A multicenter real-world study in China. J Hematol Oncol 10: 69, 2017.
57. Coiffier B, Pro B, Prince HM, Foss F, Sokol L, Greenwood M, Caballero D, Morschhauser F, Wilhelm M, Pinter-Brown L, *et al*: Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: Pivotal study update demonstrates durable responses. J Hematol Oncol 7: 11, 2014.
58. Dupuis J, Morschhauser F, Ghesquières H, Tilly H, Casasnovas O, Thieblemont C, Ribrag V, Bossard C, Le Bras F, Bachy E, *et al*: Combination of romidepsin with cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated patients with peripheral T-cell lymphoma: A non-randomised, phase 1b/2 study. Lancet Haematol 2: e160-e165, 2015.
59. Johnston PB, Cashen AF, Nikolinakos PG, Beaven AW, Barta SK, Bhat G, Hasal SJ, De Vos S, Oki Y, Deng C and Foss FM: Belinostat in combination with standard cyclophosphamide, doxorubicin, vincristine and prednisone as first-line treatment for patients with newly diagnosed peripheral T-cell lymphoma. Exp Hematol Oncol 10: 15, 2021.
60. Zhang W, Su L, Liu L, Gao Y, Wang Q, Su H, Song Y, Zhang H, Shen J, Jing H, *et al*: The combination of chidamide with the CHOEP regimen in previously untreated patients with peripheral T-cell lymphoma: A prospective, multicenter, single arm, phase 1b/2 study. Cancer Biol Med: Mar 23, 2021 (Epub ahead of print).
61. Jäger R, Hahne J, Jacob A, Egert A, Schenkel J, Wernert N, Schorle H and Wellmann A: Mice transgenic for NPM-ALK develop non-Hodgkin lymphomas. Anticancer Res 25: 3191-3196, 2005.
62. Chiarle R, Gong JZ, Guasparri I, Pesci A, Cai J, Liu J, Simmons WJ, Dhall G, Howes J, Piva R and Inghirami G: NPM-ALK transgenic mice spontaneously develop T-cell lymphomas and plasma cell tumors. Blood 101: 1919-1927, 2003.
63. Kuefer MU, Look AT, Pulford K, Behm FG, Pattengale PK, Mason DY and Morris SW: Retrovirus-mediated gene transfer of NPM-ALK causes lymphoid malignancy in mice. Blood 90: 2901-2910, 1997.
64. Waqar SN and Morgensztern D: Lorlatinib: A new-generation drug for ALK-positive NSCLC. Lancet Oncol 19: 1555-1557, 2018.
65. Gambacorti Passerini C, Farina F, Stasia A, Redaelli S, Ceccon M, Mologni L, Messa C, Guerra L, Giudici G, Sala E, *et al*: Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 106: djt378, 2014.
66. Mossé YP, Voss SD, Lim MS, Rolland D, Minard CG, Fox E, Adamson P, Wilner K, Blaney SM and Weigel BJ: Targeting ALK with crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: A children's oncology group study. J Clin Oncol 35: 3215-3221, 2017.
67. Gambacorti-Passerini C, Orlov S, Zhang L, Braiteh F, Huang H, Esaki T, Horibe K, Ahn JS, Beck JT, Edenfield WJ, *et al*: Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. Am J Hematol 93: 607-614, 2018.
68. U.S. Food and Drug (FDA): FDA approves crizotinib for children and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma. FDA, Silver Spring, MD, 2021. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-crizotinib-children-and-young-adults-relapsed-or-refractory-systemic-anaplastic-large. Accessed January 15, 2021.
69. Mahuad CV, Repáraz Mde L, Zerga ME, Aizpurua MF, Casali C and Garate G: Three years sustained complete remission achieved in a primary refractory ALK-positive anaplastic T large cell lymphoma treated with crizotinib. Rare Tumors 8: 6266, 2016.
70. John TD, Naik S, Leung K, Sasa G, Martinez C and Krance RA: Allogeneic hematopoietic cell transplant following crizotinib monotherapy for relapsed/refractory anaplastic large cell lymphoma. Pediatr Transplant 22: e13210, 2018.
71. Ordemann R, Stöhlmacher J, Beuthien-Baumann B, Platzek I, van den Hoff J, Kroschinsky F, Middeke JM, Platzbecker U, Zietz C, Bornhäuser M and Ehninger G: Use of targeted therapy for refractory ALK-positive anaplastic large cell lymphoma as a bridging strategy prior to allogeneic transplantation. Ann Hematol 92: 125-127, 2013.
72. Cleary JM, Rodig S, Barr PM, Shinagare AB, Clark JW, Shapiro GI and Armand P: Crizotinib as salvage and maintenance with allogeneic stem cell transplantation for refractory anaplastic large cell lymphoma. J Natl Compr Canc Netw 12: 323-326, 2014.
73. Shelikhova LN, Fominykh VV, Abramov DS, Myakova NV, Maschan MA and Maschan AA: Use of crizotinib for refractory ALK-positive lymphomas. Ter Arkh 89: 51-56, 2017.

74. Sun X, Fang X and Jiang Y: Successful combination of crizotinib and hematopoietic stem cell transplantation in relapsed ALK-positive ALCL. Indian J Cancer 58: 108-111, 2021.
75. Reed DR, Hall RD, Gentzler RD, Volodin L, Douvas MG and Portell CA: Treatment of refractory ALK rearranged anaplastic large cell lymphoma with alectinib. Clin Lymphoma Myeloma Leuk 19: e247-e250, 2019.
76. Gambacorti-Passerini C, Mussolin L and Brugieres L: Abrupt relapse of ALK-Positive lymphoma after discontinuation of crizotinib. N Engl J Med 374: 95-96, 2016.
77. Chihara D, Wong S, Feldman T, Fanale MA, Sanchez L, Connors JM, Savage KJ and Oki Y: Outcome of patients with relapsed or refractory anaplastic large cell lymphoma who have failed brentuximab vedotin. Hematol Oncol 37: 35-38, 2019.
78. Mathas S, Hinz M, Anagnostopoulos I, Krappmann D, Lietz A, Jundt F, Bommert K, Mechta-Grigoriou F, Stein H, Dörken B and Scheidereit C: Aberrantly expressed c-Jun and JunB are a hallmark of Hodgkin lymphoma cells, stimulate proliferation and synergize with NF-kappa B. EMBO J 21: 4104-4113, 2002.
79. Staber PB, Vesely P, Haq N, Ott RG, Funato K, Bambach I, Fuchs C, Schauer S, Linkesch W, Hrzenjak A, *et al*: The oncoprotein NPM-ALK of anaplastic large-cell lymphoma induces JUNB transcription via ERK1/2 and JunB translation via mTOR signaling. Blood 110: 3374-3383, 2007.
80. Laimer D, Dolznig H, Kollmann K, Vesely PW, Schlederer M, Merkel O, Schiefer AI, Hassler MR, Heider S, Amenitsch L, *et al*: PDGFR blockade is a rational and effective therapy for NPM-ALK-driven lymphomas. Nat Med 18: 1699-1704, 2012.
81. Laimer-Gruber D: Blockade of the PDGF receptor: A new and effective therapy option for NPM-ALK-dependent lymphoma. Pathologe 35 (Suppl 2): S185-S186, 2014.
82. Slupianek A, Nieborowska-Skorska M, Hoser G, Morrione A, Majewski M, Xue L, Morris SW, Wasik MA and Skorski T: Role of phosphatidylinositol 3-kinase-Akt pathway in nucleophosmin/anaplastic lymphoma kinase-mediated lymphomagenesis. Cancer Res 61: 2194-2199, 2001.
83. Bai RY, Ouyang T, Miething C, Morris SW, Peschel C and Duyster J: Nucleophosmin-anaplastic lymphoma kinase associated with anaplastic large-cell lymphoma activates the phosphatidylinositol 3-kinase/Akt antiapoptotic signaling pathway. Blood 96: 4319-4327, 2000.
84. Slupianek A and Skorski T: NPM/ALK downregulates p27Kip1 in a PI-3K-dependent manner. Exp Hematol 32: 1265-1271, 2004.
85. Rassidakis GZ, Feretzaki M, Atwell C, Grammatikakis I, Lin Q, Lai R, Claret FX, Medeiros LJ and Amin HM: Inhibition of Akt increases p27Kip1 levels and induces cell cycle arrest in anaplastic large cell lymphoma. Blood 105: 827-829, 2005.
86. Chiarle R, Simmons WJ, Cai H, Dhall G, Zamo A, Raz R, Karras JG, Levy DE and Inghirami G: Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. Nat Med 11: 623-629, 2005.
87. Zhang Q, Raghunath PN, Xue L, Majewski M, Carpentieri DF, Odum N, Morris S, Skorski T and Wasik MA: Multilevel dysregulation of STAT3 activation in anaplastic lymphoma kinase-positive T/null-cell lymphoma. J Immunol 168: 466-474, 2002.
88. Marzec M, Kasprzycka M, Liu X, Raghunath PN, Wlodarski P and Wasik MA: Oncogenic tyrosine kinase NPM/ALK induces activation of the MEK/ERK signaling pathway independently of c-Raf. Oncogene 26: 813-821, 2007.
89. Marzec M, Kasprzycka M, Liu X, El-Salem M, Halasa K, Raghunath PN, Bucki R, Wlodarski P and Wasik MA: Oncogenic tyrosine kinase NPM/ALK induces activation of the rapamycin-sensitive mTOR signaling pathway. Oncogene 26: 5606-5614, 2007.
90. Vega F, Medeiros LJ, Leventaki V, Atwell C, Cho-Vega JH, Tian L, Claret FX and Rassidakis GZ: Activation of mammalian target of rapamycin signaling pathway contributes to tumor cell survival in anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. Cancer Res 66: 6589-6597, 2006.
91. Gao J, Yin M, Zhu Y, Gu L, Zhang Y, Li Q, Jia C and Ma Z: Prognostic significance and therapeutic potential of the activation of anaplastic lymphoma kinase/protein kinase B/mammalian target of rapamycin signaling pathway in anaplastic large cell lymphoma. BMC cancer 13: 471, 2013.
92. Li JF, Li GD, Gu L, Liu WP, Li FY, Liao DY and Ma ZG: Study on activation of AKT/mTOR pathway in anaplastic large cell lymphoma. Zhonghua Xue Ye Xue Za Zhi 29: 649-653, 2008 (In Chinese).
93. Jundt F, Raetzel N, Müller C, Calkhoven CF, Kley K, Mathas S, Lietz A, Leutz A and Dörken B: A rapamycin derivative (everolimus) controls proliferation through down-regulation of truncated CCAAT enhancer binding protein {beta} and NF-{kappa}B activity in Hodgkin and anaplastic large cell lymphomas. Blood 106: 1801-1807, 2005.
94. Witzig TE, Reeder C, Han JJ, LaPlant B, Stenson M, Tun HW, Macon W, Ansell SM, Habermann TM, Inwards DJ, *et al*: The mTORC1 inhibitor everolimus has antitumor activity in vitro and produces tumor responses in patients with relapsed T-cell lymphoma. Blood 126: 328-335, 2015.
95. Kim SJ, Shin DY, Kim JS, Yoon DH, Lee WS, Lee H, Do YR, Kang HJ, Eom HS, Ko YH, *et al*: A phase II study of everolimus (RAD001), an mTOR inhibitor plus CHOP for newly diagnosed peripheral T-cell lymphomas. Ann Oncol 27: 712-718, 2016.
96. Chumsri S, Zhao M, Garofalo M, Burger A, Hamburger A, Zhao F and Rapoport A: Inhibition of the mammalian target of rapamycin (mTOR) in a case of refractory primary cutaneous anaplastic large cell lymphoma. Leuk Lymphoma 49: 359-361, 2008.
97. Kim D, Koh Y and Yoon SS: Synergistic effect of alectinib and everolimus on ALK-positive anaplastic large cell lymphoma growth inhibition. Anticancer Res 40: 1395-1403, 2020.
98. Xu W, Kim JW, Jung WJ, Koh Y and Yoon SS: Crizotinib in combination with everolimus synergistically inhibits proliferation of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. Cancer Res Treat 50: 599-613, 2018.
99. Butte MJ, Keir ME, Phamduy TB, Sharpe AH and Freeman GJ: Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 27: 111-122, 2007.
100. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, Fitz LJ, Malenkovich N, Okazaki T, Byrne MC, *et al*: Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 192: 1027-1034, 2000.
101. Sun C, Mezzadra R and Schumacher TN: Regulation and function of the PD-L1 checkpoint. Immunity 48: 434-452, 2018.
102. U.S. Food and Drug (FDA): FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%). FDA, Silver Spring, MD, 2019. https://www.fda.gov/drugs/fda-expands-pembrolizumab-indication-first-line-treatment-nsclc-tps-1. Accessed April 11, 2019.
103. U.S. Food and Drug (FDA): FDA extends approval of pembrolizumab for classical Hodgkin lymphoma. FDA, Silver Spring, MD, 2020. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-extends-approval-pembrolizumab-classical-hodgkin-lymphoma. Accessed November 10, 2020.
104. Durvalumab (Imfinzi). https://www.fda.gov/drugs/resources-information-approved-drugs/durvalumab-imfinzi. Journal, 2017.
105. Yamamoto R, Nishikori M, Tashima M, Sakai T, Ichinohe T, Takaori-Kondo A, Ohmori K and Uchiyama T: B7-H1 expression is regulated by MEK/ERK signaling pathway in anaplastic large cell lymphoma and Hodgkin lymphoma. Cancer Sci 100: 2093-2100, 2009.
106. Zhang JP, Song Z, Wang HB, Lang L, Yang YZ, Xiao W, Webster DE, Wei W, Barta SK, Kadin ME, *et al*: A novel model of controlling PD-L1 expression in ALK$^+$ anaplastic large cell lymphoma revealed by CRISPR screening. Blood 134: 171-185, 2019.
107. Marzec M, Zhang Q, Goradia A, Raghunath PN, Liu X, Paessler M, Wang HY, Wysocka M, Cheng M, Ruggeri BA and Wasik MA: Oncogenic kinase NPM/ALK induces through STAT3 expression of immunosuppressive protein CD274 (PD-L1, B7-H1). Proc Natl Acad Sci USA 105: 20852-20857, 2008.
108. Shen J, Li S, Medeiros LJ, Lin P, Wang SA, Tang G, Yin CC, You MJ, Khoury JD, Iyer SP, *et al*: PD-L1 expression is associated with ALK positivity and STAT3 activation, but not outcome in patients with systemic anaplastic large cell lymphoma. Mod Pathol 33: 324-333, 2020.
109. Kong J, Dasari S and Feldman AL: PD-L1 expression in anaplastic large cell lymphoma. Mod Pathol 33: 1232-1233, 2020.
110. Rigaud C, Abbou S, Minard-Colin V, Geoerger B, Scoazec JY, Vassal G, Jaff N, Heuberger L, Valteau-Couanet D and Brugieres L: Efficacy of nivolumab in a patient with systemic refractory ALK+ anaplastic large cell lymphoma. Pediatr Blood Cancer 65: e26902, 2018.
111. Hebart H, Lang P and Woessmann W: Nivolumab for refractory anaplastic large cell lymphoma: A case report. Ann Intern Med 165: 607-608, 2016.

112. Chan TS, Khong PL and Kwong YL: Pembrolizumab for relapsed anaplastic large cell lymphoma after allogeneic haematopoietic stem cell transplantation: Efficacy and safety. Ann Hematol 95: 1913-1915, 2016.
113. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, *et al*: Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377: 2531-2544, 2017.
114. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, Jäger U, Jaglowski S, Andreadis C, Westin JR, *et al*: Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 380: 45-56, 2019.
115. Rogers AM and Brammer JE: Hematopoietic cell transplantation and adoptive cell therapy in peripheral T cell lymphoma. Curr Hematol Malig Rep 15: 316-332, 2020.
116. Lollies A, Hartmann S, Schneider M, Bracht T, Weiß AL, Arnolds J, Klein-Hitpass L, Sitek B, Hansmann ML, Küppers R and Weniger MA: An oncogenic axis of STAT-mediated BATF3 upregulation causing MYC activity in classical Hodgkin lymphoma and anaplastic large cell lymphoma. Leukemia 32: 92-101, 2018.
117. Weilemann A, Grau M, Erdmann T, Merkel O, Sobhiafshar U, Anagnostopoulos I, Hummel M, Siegert A, Hayford C, Madle H, *et al*: Essential role of IRF4 and MYC signaling for survival of anaplastic large cell lymphoma. Blood 125: 124-132, 2015.
118. Casey SC, Tong L, Li Y, Do R, Walz S, Fitzgerald KN, Gouw AM, Baylot V, Gütgemann I, Eilers M and Felsher DW: MYC regulates the antitumor immune response through CD47 and PD-L1. Science 352: 227-231, 2016.
119. Atsaves V, Tsesmetzis N, Chioureas D, Kis L, Leventaki V, Drakos E, Panaretakis T, Grander D, Medeiros LJ, Young KH and Rassidakis GZ: PD-L1 is commonly expressed and transcriptionally regulated by STAT3 and MYC in ALK-negative anaplastic large-cell lymphoma. Leukemia 31: 1633-1637, 2017.
120. Shao RG and Zhen YS: Enediyne anticancer antibiotic lidamycin: Chemistry, biology and pharmacology. Anticancer Agents Med Chem 8: 123-131, 2008.
121. Shao RG and Zhen YS: Relationship between the molecular composition of C1027, a new macromolecular antibiotic with enediyne chromophore, and its antitumor activity. Yao Xue Xue Bao 30: 336-342, 1995 (In Chinese).
122. Wang R, Li L, Zhang S, Li Y, Wang X, Miao Q and Zhen Y: A novel enediyne-integrated antibody-drug conjugate shows promising antitumor efficacy against $CD30^+$ lymphomas. Mol Oncol 12: 339-355, 2018.
123. Wang R, Li L, Duan A, Li Y, Liu X, Miao Q, Gong J and Zhen Y: Crizotinib enhances anti-CD30-LDM induced antitumor efficacy in NPM-ALK positive anaplastic large cell lymphoma. Cancer Lett 448: 84-93, 2019.
124. Hwang J, Song I, Lee K, Kim HR, Hong EH, Hwang JS, Ahn SH and Lee J: KRCA-0008 suppresses ALK-positive anaplastic large-cell lymphoma growth. Invest New Drugs 38: 1282-1291, 2020.
125. Shen J, Wang J, Du J, Wang L, Zhou X, Chang X, Li Z, Zhai X, Zuo D and Wu Y: A novel ALK inhibitor ZYY inhibits Karpas299 cell growth in vitro and in a mouse xenograft model and induces protective autophagy. Toxicol Appl Pharmacol 383: 114781, 2019.
126. Prutsch N, Gurnhofer E, Suske T, Liang HC, Schlederer M, Roos S, Wu LC, Simonitsch-Klupp I, Alvarez-Hernandez A, Kornauth C, *et al*: Dependency on the TYK2/STAT1/MCL1 axis in anaplastic large cell lymphoma. Leukemia 33: 696-709, 2019.