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## Anti-Tumour Treatment

## Therapeutic options in relapsed or refractory peripheral T-cell lymphoma



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## ABSTRACT

Peripheral T-cell lymphoma (PTCL) represents a relatively rare group of heterogeneous non-Hodgkin lymphomas with a very poor prognosis. Current therapies, based on historical regimens for aggressive B-cell lymphomas, have resulted in insufficient patient outcomes. The majority of patients relapse rapidly, and current 5-year overall survival rates are only 10–30%. It is evident that new approaches to treat patients with PTCL are required. In recent years, prospective studies in PTCL have been initiated, mainly in patients with relapsed/refractory disease. In some of these, selected histologic subtypes have been evaluated in detail. As a consequence, numerous new therapies have been developed and shown activity in PTCL, including: agents targeting the immune system (e.g. brentuximab vedotin, alemtuzumab, lenalidomide); histone deacetylase inhibitors (romidepsin, belinostat); antifolates (pralatrexate); fusion proteins (denileukin difitox); nucleoside analogs (pentostatin, gemcitabine); and other agents (e.g. alisertib, plitidpsin, bendamustine, bortezomib). A variety of interesting novel combinations is also emerging. It is hoped that these innovative approaches, coupled with a greater understanding of the clinicopathologic features, pathogenesis, molecular biology, and natural history of PTCL will advance the field and improve outcomes in this challenging group of diseases. This review summarizes the currently available clinical evidence on the various approaches to treating relapsed/refractory PTCL, including the role of stem cell transplantation, with an emphasis on potential new drug therapies.

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## Introduction

Peripheral T-cell lymphoma (PTCL), a subset of non-Hodgkin lymphoma (NHL), comprises a spectrum of rare and usually aggressive T-cell disorders with a generally poor prognosis. The 2008 World Health Organization classification system contains 22 biologically and clinically different T-cell lymphoma subgroups, further subclassified as nodal, extranodal, cutaneous, or leukemic, which are distinct with respect to pathology, clinical presentation,

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**Table 1**  
Incidence and 5-year OS across PTCL subtypes [2].

Diagnosis	Incidence (%)	5-Year OS (%)
PTCL-NOS	25.9	32
AITL	18.5	32
NKTCL	10.4	
Nasal		42
Extra-nasal		9
ATLL	9.6	14
ALK-positive ALCL	6.6	70
ALK-negative ALCL	5.5	49
Enteropathy-type T-cell lymphoma	4.7	20
Primary cutaneous ALCL	1.7	90
Hepatosplenic T-cell lymphoma	1.4	7
Subcutaneous panniculitis-like-T-cell lymphoma	0.9	64

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; NKTCL, natural killer/T-cell lymphoma; OS, overall survival; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified.

response to therapy, and expression of surface markers [1]. The most common subgroups are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma (ATLL), and anaplastic large-cell lymphoma (ALCL) (Table 1) [2].

The treatment approach of PTCL has traditionally been similar to diffuse large B-cell lymphoma (DLBCL); however, outcomes are poor when PTCL is treated according to paradigms established for aggressive B-cell lymphomas [3]. Due to its rarity and the heterogeneity of subtypes, randomized controlled trials comparing different treatment approaches for PTCL are limited. Standard first-line therapy consists of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or a CHOP-like regimen. Therapeutic responses to this approach have been neither adequate nor durable, with rapid relapse in some subtypes [4,5]. Data collected by the International T-Cell Lymphoma Project over the past decade on over 1314 cases of PTCL revealed that survival rates were highly dependent upon disease subtype, with poor 5-year overall survival (OS) rates for most subtypes: 32% for PTCL-NOS and AITL, 49% for anaplastic lymphoma kinase (ALK)-negative ALCL, and 14% for ATLL (Table 1) [2]. Indeed, PTCL-NOS patients with multiple risk factors have been reported to have 5-year OS rates as low as 11% [6]. In general, the 5-year OS of PTCL patients is reported to be significantly lower than aggressive B-cell lymphoma patients (41% versus 53%;  $p = 0.0004$ ) [7].

Some phase II trials suggest that intensification with autologous stem cell transplantation (ASCT) could improve treatment outcomes, especially when patients are in first complete response (CR). However, many patients are not candidates for stem cell transplantation (SCT) because they do not reach stable remission after induction therapy—approximately 30% of the patients will progress before ASCT [8–10].

The generally poor outcomes observed in PTCL patients highlight the urgent need for alternative treatment strategies. Several novel approaches have been evaluated in single-arm phase I and II studies, mainly in patients with relapsed/refractory disease, who have a particularly poor prognosis. This review summarizes the currently available clinical evidence on the various approaches for treating relapsed/refractory PTCL, with an emphasis on potential new drug therapies.

## New treatment modalities

Recent research has led to the development of numerous agents, including: immunoconjugates, immunotherapies, and immunomodulators; histone deacetylase (HDAC) inhibitors; anti-folates; fusion proteins; and nucleoside analogs (Table 2) [11–37].

## Immunoconjugates, immunotherapies, and immunomodulators

### Anti-CD30 antibodies

Hodgkin lymphoma and ALCL are the most common CD30-expressing tumors [38]. However, monoclonal antibodies that target CD30, including MDX-060 [39], and SGN-30 [40,41], have shown minimal clinical activity.

Brentuximab vedotin (SGN-35) is an antibody–drug conjugate that links an anti-CD30 antibody to a potent antimicrotubule agent, monomethylauristatin E (MMAE), enabling the delivery of the cytotoxic drug to the target malignant cell. Binding of MMAE to tubulin disrupts the microtubule network, induces cell-cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell [42]. A phase II study of brentuximab vedotin in 58 patients with ALCL showed an overall response rate (ORR) of 86%, including 57% CRs, with a median duration of response (DoR) of 12.6 months (Table 2) [17]. The most common ( $\geq 30\%$ ) adverse events (AEs) were peripheral sensory neuropathy (41%), nausea (40%), fatigue (38%), and pyrexia (34%). AEs led to treatment discontinuation in 24% of patients. Based on the results of this study, the US Food and Drug Administration (FDA) and European Medicines Agency approved the use of brentuximab vedotin for patients with systemic ALCL after failure of  $\geq 1$  multi-agent chemotherapy regimen. Another phase II trial of brentuximab vedotin in 34 patients with PTCL showed an ORR of 41% with a median progression-free survival (PFS) of 2.6 months (Table 2) [18].

### Alemtuzumab

The anti-CD52 monoclonal antibody alemtuzumab has been evaluated in two small phase II studies (Table 2) [11,12]. In the first study, 14 patients with PTCL received alemtuzumab (dose rapidly escalated to 30 mg) three-times-weekly for a maximum of 12 weeks [11], with an ORR of 36%. However, 10 patients discontinued treatment due to AEs or progressive disease; 5 patients experienced cytomegalovirus (CMV) reactivation after a median of 5 weeks. In a pilot study of 10 patients with PTCL-NOS or mycosis fungoides (MF) using a reduced-dose-intensity approach (10 mg three-times-weekly for 4 weeks), an ORR of 60% with a median DoR of 7 months was reported [12]. Fewer AEs and CMV reactivations were found; infusion-related AEs occurred in 3 patients (30%) and CMV reactivation in 1 patient (10%) [12]. Two phase III front-line trials were expected to finish recruitment at the end of 2013, and favorable safety data have been reported so far [43].

### Mogamulizumab

Mogamulizumab is a monoclonal antibody targeting CC chemokine receptor 4 (CCR4). A phase II study of weekly 1.0 mg/kg mogamulizumab infusions in 27 patients with relapsed, aggressive CCR4<sup>+</sup> T-cell lymphoma showed an ORR of 50%, including 31% CR (Table 2) [25]. Median PFS was 5.2 months and median OS was 13.7 months. The most common ( $\geq 15\%$ ) grade 3–4 AEs were lymphopenia (74%), leukocytopenia (30%), thrombocytopenia (19%), neutropenia (19%), and rash (19%). Another phase II study of mogamulizumab at the same dose in 38 patients (of which 37 were evaluable) with relapsed CCR4<sup>+</sup> PTCL or cutaneous T cell lymphoma (CTCL) showed an ORR of 35%, including 14% CR (Table 2); median PFS was 3 months [26]. The most common ( $\geq 15\%$ ) grade 3–4 AEs were lymphocytopenia (73%) and neutropenia (19%).

### Zanolimumab

The anti-CD4 monoclonal antibody zanolimumab was studied in a phase II study including 21 PTCL patients (Table 2) [37]. Weekly zanolimumab 980 mg infusions produced an ORR of 24% and 10% CR with no major toxicity. Five drug-related grade 3 AEs

**Table 2**  
Clinical trial efficacy results of novel single-agent treatment modalities.

Drug/regimen	Study	No. of evaluable patients	Type of patients	ORR (%)	Median DoR (months)	Median PFS (months)
Alemtuzumab	Enblad (2004) [11]	14	PTCL	36	NR	NR
	Zinzani (2005) [12]	10	PTCL-NOS and MF	60	7	NR
Alisertib	Friedberg (2014) [13]	48	NHL (including PTCL)	27	NR	NR
Belinostat	O'Connor (2013) [14]	120	PTCL	26	8.3	NR
Bendamustine	Damaj (2013) [15]	60	PTCL and CTCL	50	3.5	3.6
Bortezomib	Zinzani (2007) [16]	12	PTCL and CTCL	67	NR	NR
Brentuximab vedotin	Pro (2012) [17]	58	ALCL	86	12.6	13.3
	Horwitz (2014) [18]	34	PTCL	41	7.6	2.6
Denileukin diftitox	Dang (2007) [19]	27	PTCL	48	NR	6
Gemcitabine	Zinzani (1998) [20]	13	PTCL-NOS and MF	69	NR	NR
	Sallah (2001) [21]	10	PTCL-NOS and CTCL	60	13.5	NR
	Zinzani (2010) [22]	39	PTCL-NOS and MF	51	NR	NR
Lenalidomide	Dueck (2010) [23]	23	PTCL	30	NR	3.2
	Zinzani (2011) [24]	10	PTCL-NOS	30	NR	NR
Mogamulizumab	Ishida (2012) [25]	26	ATLL	50	NR	5.2
	Ogura (2014) [26]	37	CCR4 <sup>+</sup> PTCL/CTCL	35	NR	3.0
Pentostatin	Monfardini (1996) [27]	37	NHL (including PTCL)	13	8	NR
	Tsimberidou (2004) [28]	44	T-cell leukemias/lymphomas	55	4.3	2.1
	Dang (2003) [29]	14	T-cell NHL	50	NR	6
Plitidepsin	Ribrig (2013) [30]	29	PTCL	21	2.2	1.6
	O'Connor (2009) [31]	29	T-cell lymphoma	54	NR	NR
Pralatrexate	O'Connor (2011) [32]	109	PTCL	29	10.1	3.5
	Piekarz (2011) [33]	45	PTCL and CTCL	38	8.9	NR
Romidepsin	Coiffier (2012) [34]	130	PTCL	25	28	4
	(2014) [35]					
Tipifarnib	Witzig (2011) [36]	93	NHL (including PTCL)	20 (50 in PTCL-NOS)	7.5	NR
Zanolimumab	d'Amore (2010) [37]	21	PTCL	24	NR	NR

ALCL, anaplastic large-cell lymphoma; ATLL, adult T-cell leukemia/lymphoma; CCR4<sup>+</sup>, CC chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; DoR, duration of response; MF, mycosis fungoides; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma.

<sup>a</sup> All studies were phase II, except for this phase I/II study.

occurred: lymphocytopenia (10%), infusion-related AEs (10%), and arthralgia (5%) [37].

### Lenalidomide

The immunomodulatory drug lenalidomide (25 mg on days 1–21 of each 28-day cycle) has shown efficacy in patients with relapsed/refractory PTCL (Table 2) [23,24,44]. A phase II study with 23 evaluable patients showed an ORR of 30% (all partial responses [PRs]) [23]. The median PFS and OS were 3.2 and 7.9 months, respectively. AEs were consistent with the known safety profile of lenalidomide: the most common grade 3–4 AEs ( $\geq 15\%$ ) were thrombocytopenia (42%), neutropenia (21%), dyspnea (17%), febrile neutropenia (17%), pain (17%), and pneumonitis (17%). Study discontinuation was mainly for progressive disease (PD; 46%); 4 patients (17%) discontinued due to AEs. A subsequent open-label phase II study in 10 patients with PTCL-NOS also found an ORR of 30% (all CRs) [24]. The most common grade 3–4 AEs ( $\geq 15\%$ ) included neutropenia (25%) and thrombocytopenia (15%). The multicenter, phase II EXPECT trial included 54 relapsed/refractory PTCL patients, mostly with AITL ( $n = 26$ ; 48%) and PTCL-NOS ( $n = 20$ ; 37%) [44]. The ORR was 22% (11% CR/unconfirmed CR [CRu]), 31% (15% CR/CRu) in AITL, and 20% in PTCL-NOS patients. The median PFS and DoR were 2.5 and 3.6 months, respectively. The most common grade 3–4 AEs ( $\geq 15\%$ ) included thrombocytopenia (20%), gastrointestinal disorders (17%), neutropenia (15%), infections (15%), and general disorders and administration site conditions (15%).

### Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors induce histone acetylation leading to increased expression of tumor suppressor genes. HDAC inhibition results in cell-cycle arrest, cell differentiation,

and apoptosis [45,46]. In vitro and ex vivo studies have reported synergy with targeted therapies (e.g. CD25-targeted therapy), radiation therapy, and chemotherapy [47–49].

### Romidepsin

Romidepsin (FK228; previously depsipeptide), an HDAC inhibitor isolated from *Chromobacterium violaceum* [50,51], is currently approved by the US FDA for the treatment of PTCL in patients who have received  $\geq 1$  prior therapy. In a phase II study of romidepsin (14 mg/m<sup>2</sup> administered as a 4-h infusion on days 1, 8, and 15 of a 28-day cycle) in separate cohorts of CTCL and relapsed PTCL patients, the ORR among the 45 PTCL patients was 38%, with 18% CR. Median DoR was 8.9 months; median duration of CR was 29.7 months. The most common ( $\geq 40\%$ ) AEs included nausea (51%), fatigue (40%), thrombocytopenia (47%), leukopenia (47%), granulocytopenia (45%), and anemia (40%) (Table 2) [33].

In a subsequent pivotal phase II trial, 130 patients with histologically confirmed relapsed/refractory PTCL were treated with romidepsin at the same dose for 6 cycles; patients with at least stable disease (SD) were allowed to continue until PD (Table 2) [34,35]. Fifty patients (38%) were treated for  $\geq 4$  cycles and 36 patients (28%) received  $> 6$  cycles. Most patients had PTCL-NOS ( $n = 69$ ), AITL ( $n = 27$ ), or ALK-negative ALCL ( $n = 21$ ). The ORR was relatively high (25%) considering that these patients had failed  $\geq 1$  prior therapies; 19 patients (15%) had CR, 10 of which had long-term ( $\geq 12$  months) response. At a median follow-up of 22.3 months, responders received a median of 8 treatment cycles (range  $< 1$ –54); patients with CR/CRu received a median of 19 treatment cycles (range 2–54). Romidepsin demonstrated clinically meaningful disease control in half of the patients. Similar CR/CRu rates were observed across the three major PTCL subtypes.

Median PFS was 4 months and median OS was 11.3 months; in patients who achieved CR/CRu median, PFS was 29 months and OS was not reached. The most common ( $\geq 15\%$ ) grade  $\geq 3$  AEs were thrombocytopenia (24%), neutropenia (20%), and infections (19%). Discontinuation of therapy occurred in 19% of patients, mostly due to thrombocytopenia and pneumonia.

#### *Belinostat*

Belinostat is a potent hydroxamic acid-derived pan-HDAC inhibitor [52] that is currently evaluated in an open-label phase II study. A total of 129 relapsed/refractory PTCL patients received a 1000 mg/m<sup>2</sup> belinostat infusion on days 1–5 of every 3-week cycle (Table 2) [14]. Among 120 evaluable patients, the ORR was 26%, including 10% CR, and median DoR was 8.3 months. The most common ( $\geq 10\%$ ) grade 3–4 AEs were thrombocytopenia (13%), neutropenia (13%), and anemia (10%). Patients mainly discontinued due to PD (64%); 7% of patients discontinued due to AEs.

#### **Antifolates**

Folates are essential for DNA synthesis in any cell, including cancer cells. In the 1940s it was discovered that antifolates can be effective in cancer therapy. Currently, antifolates—including methotrexate—play an important role in the treatment of many types of cancers [53].

#### *Pralatrexate*

Pralatrexate is FDA approved for use in relapsed/refractory PTCL. The drug is a novel antifolate designed to selectively accumulate in malignant cells and block the biosynthesis of purines and pyrimidines. In an initial phase I/II study with 29 T-cell lymphoma patients, the ORR was 54%, with 31% CR and 23% PR (Table 2) [31]. In the pivotal phase II PROPEL study, 115 patients who progressed after  $\geq 1$  prior therapy received pralatrexate weekly for 6 weeks of each 7-week cycle (Table 2) [32]. Most patients had PTCL-NOS ( $n = 59$ ), although a significant proportion had systemic ALCL ( $n = 17$ ) or AITL ( $n = 13$ ). Among 109 evaluable patients, the ORR was 29%, including 11% CR/CRu, and the median DoR was 10.1 months. A low ORR (8%) was observed in AITL patients. The most common ( $\geq 15\%$ ) grade 3–4 AEs were thrombocytopenia (32%), neutropenia (22%), mucositis (22%), and anemia (18%); 71% of patients experienced some degree of mucositis. A total of 23% of patients discontinued pralatrexate due to AEs, mostly due to mucositis (6%) and thrombocytopenia (5%).

#### **Fusion proteins**

Fusion proteins are engineered to act as decoy receptors, increase the deliverability of an active substance into the cell, add stability, recruit immune effector cells, etc.; several fusion proteins are under investigation in oncology [54].

#### *Denileukin diftitox*

Denileukin diftitox is a fusion protein comprised of interleukin (IL)-2 and diphtheria toxin. It selectively targets IL-2 receptor-expressing cells, where the diphtheria toxin component inhibits protein synthesis leading to apoptosis. Denileukin diftitox is indicated for the treatment of persistent or recurrent CTCL expressing the CD25 component of the IL-2 receptor; it is no longer used in precursor T-cell lymphoblastic leukemia. A phase II study of 27 patients with relapsed/refractory PTCL showed single-agent activity at a dose of 18  $\mu\text{g}/\text{kg}/\text{day}$  (Table 2) with an ORR of 48% (13 patients; 6

CRs and 7 PRs) and median PFS of 6 months [19]. Patients with CD25<sup>+</sup> disease had a higher response rate than those with CD25<sup>-</sup> disease (62% versus 46%, respectively) [19]. The most common ( $\geq 50\%$ ) AEs were hypoalbuminemia (74%), transaminase elevation (74%), edema (63%), and skin reactions (59%); no hematologic AEs were observed and no responders discontinued treatment due to toxicity. Denileukin diftitox in combination with CHOP is currently studied as first-line treatment for patients with PTCL [55].

#### **Nucleoside analogs**

Purine nucleoside analogs are cytotoxic agents with strong immunosuppressive and antineoplastic activity. These agents are cytotoxic to both proliferating and non-proliferating cells, inhibiting DNA synthesis and repair, and inducing apoptosis [56].

#### *Pentostatin*

Three phase II studies have evaluated the antimetabolite pentostatin in PTCL (Table 2) [27–29]. An early trial studied pentostatin at an initial dose of 4 mg/m<sup>2</sup> weekly for 3 weeks, then every 2 weeks for 6 weeks, and thereafter every 4 weeks, leading to a low ORR of 13% in 37 patients with B- and T-cell NHL, including PTCL [27].

Two subsequent studies investigated pentostatin at a dose of 3.75–5.0 mg/m<sup>2</sup> over 3 days every 3 or 4 weeks in T-cell NHL, and reported higher response rates [28,29]. Tsimberidou and colleagues reported an ORR of 55% with a median DoR of 4.3 months [28]. The most common ( $> 20\%$ ) AEs were infections (48%), granulocytopenia (36%), and fever (26%); no responders discontinued treatment because of toxicity. Dang and colleagues reported an ORR of 50% and a median PFS for responders of 6 months [29]. The most common ( $> 20\%$ ) AEs were fatigue (40%), fever, nausea, and edema (33% each); 1 patient discontinued the study due to AEs (severe nausea and vomiting).

In a 10-year retrospective analysis of 145 patients with PTCL treated with pentostatin, an ORR of 32% was reported [57]. Response rates were highest in patients with Sezary syndrome (62%) and prolymphocytic leukemia (45%), and were relatively low in patients with PTCL (19%).

#### *Gemcitabine*

Three phase II studies evaluated single-agent gemcitabine in T-cell lymphoma [20–22], mainly including patients with PTCL-NOS and MF (Table 2). Gemcitabine 1200 mg/m<sup>2</sup> was administered on days 1, 8, and 15 of a 28-day schedule for 3–6 cycles. ORRs in all patients ranged from 51–69%, with CR rates in PTCL-NOS patients ranging from 13–30%. Only one study specified the median DoR: 13.5 months [21]. In all three studies, gemcitabine was well tolerated and AEs were generally mild (grade 1–2) and manageable; more severe AEs included neutropenic fever requiring dose reductions in 2 of 10 patients [21] and a grade 3 transient increase of liver enzymes in 1 of 39 patients [22]. Gemcitabine is now suggested as monotherapy in the treatment of relapsed/refractory PTCL [58] and has been incorporated into several combination chemotherapy regimens (see following section).

#### **Other agents**

#### *Alisertib*

Aurora A kinase (AAK) plays a role in cell proliferation and is overexpressed in aggressive lymphoma; increased AAK levels are associated with a poorer prognosis [13]. Alisertib (MLN8237) is a



small-molecule inhibitor of AAK. A phase II trial of alisertib (50 mg twice daily on days 1–7 of each 21-day cycle) was conducted in 48 patients with relapsed/refractory aggressive NHL, including 8 patients with PTCL [13]. ORR was 27% in all patients and 50% in patients with PTCL. The sample size in this study was small; a phase III study of alisertib versus investigator's choice treatment in patients with relapsed/refractory PTCL is currently recruiting.

#### *Plitidepsin (aplidin)*

Plitidepsin, a cyclic depsipeptide isolated from the marine tunicate *Aplidium albicans*, displays a broad spectrum of antitumor activities, inducing apoptosis (through induction of early oxidative stress and activation of the Jun N-terminal kinase pathway), and G1 and G2 cell-cycle arrest. A phase II study assessed the effects of plitidepsin (3.2 mg/m<sup>2</sup> administered as a 1-h infusion on days 1, 8, and 15 every 4 weeks), in 34 patients with non-cutaneous PTCL (Table 2) [30]. Of the 29 evaluable patients, 6 responded (ORR 21%), including 2 CRs and 4 PRs; 6 patients had SD. Notably, 3 of 6 responders had AITL. The median DoR was 2.2 months; 1 patient achieved a long-term remission lasting for 28 months. The most common ( $\geq 20\%$ ) plitidepsin-related AEs were nausea (34%; all grade 1–2), fatigue (25%; grade 4 in 2%), and myalgia (22%; grade 3 in 2%). Severe laboratory abnormalities (mainly myelosuppression and increased liver transaminase levels) were transient and manageable; none resulted in treatment discontinuation.

#### *Bendamustine*

Bendamustine is an alkylating agent with antimetabolite properties that exhibits activity in several hematologic malignancies and solid tumors. In a recently reported phase II study, 60 patients with PTCL and CTCL (mainly AITL and PTCL-NOS) were treated with bendamustine 120 mg/m<sup>2</sup> infusions on days 1 and 2 every 3 weeks, for 6 cycles (Table 2) [15]. The ORR was 50% and the median DoR was 3.5 months, with 30% of responses lasting > 6 months. The most frequent ( $\geq 5\%$ ) grade 3–4 AEs were neutropenia (30%), thrombocytopenia (24%), and infections (20%); infections and hematologic AEs lead to discontinuation in 5 patients (8%).

#### *Bortezomib*

Bortezomib is a proteasome inhibitor with demonstrated activity in other hematologic malignancies, such as multiple myeloma and mantle cell lymphoma. In a small ( $n = 15$ ) phase II study in CTCL and PTCL patients, bortezomib (1.3 mg/m<sup>2</sup> intravenously on days 1, 4, 8, and 11, every 21 days for a total of 6 cycles) produced an ORR of 67%, including 1 patient with PTCL-NOS who achieved CR (Table 2) [16]. Grade 3 AEs comprised neutropenia (17%), thrombocytopenia (17%), and sensory neuropathy (8%); no grade 4 AEs occurred.

#### *Tipifarnib*

Based on preclinical studies demonstrating induction of apoptosis in malignant lymphoid cells, the farnesyltransferase inhibitor tipifarnib (300 mg twice daily on days 1–21 of every 28-day cycle) was evaluated in a phase II study of 93 patients with a broad spectrum of hematologic malignancies, including PTCL (Table 2) [36]. The ORR was 20% in the total population and 50% (4 of 8 patients) in those with PTCL-NOS, including 3 CRs. Overall, the median DoR was 7.5 months and median time to progression was 3.6 months. The most common ( $\geq 15\%$ ) grade 3–4 AEs were neutropenia (37%) and thrombocytopenia (32%).

## Combination therapies

Several combination regimens have been evaluated in the treatment of PTCL, including conventional platinum-based regimens such as dexamethasone, high-dose cytosine arabinoside (Ara-C), and cisplatin (DHAP); etoposide, methylprednisolone, high-dose Ara-C, and cisplatin (ESHAP); ifosfamide, carboplatin, and etoposide (ICE); gemcitabine-based regimens (with or without platinum agents); and other non-platinum-containing combinations. Multi-agent regimens are generally associated with more toxicity than single-agent approaches and, in the absence of randomized controlled trials, it is unclear whether these regimens are more effective than single-agent therapies in the treatment of patients with PTCL.

### Platinum-based regimens

Conventional platinum-based regimens, such as DHAP, ESHAP, and ICE, have been studied in PTCL and are suggested by the National Comprehensive Cancer Network guidelines as salvage treatment options after first relapse [58].

Response rates are relatively high with DHAP and ESHAP (55% and 64%, respectively), at the expense of poor tolerability [59,60]. With DHAP, the major toxicities included severe neutropenia (53%), severe thrombocytopenia (39%), sepsis (31%), rise in serum creatinine of more than twice the baseline value (20%), and severe gastrointestinal toxicity (20%) [59]. With ESHAP, the primary AEs were neutropenic fever requiring admission (30%), rise in serum creatinine of more than twice the baseline value (22%), and grade 3 nausea/vomiting (8%) [60].

Carboplatin, included in the ICE regimen, is generally better tolerated than cisplatin, included in the DHAP and ESHAP regimens. A response rate of 72% was reported with the ICE regimen in a series of prospective clinical trials including a total of 222 patients [61]. Most of these patients ( $n = 176$ ) were diagnosed with DLBCL; 26 were diagnosed with PTCL. The ORR among PTCL patients was 54%, including 8 CRs and 6 PRs, and the 5-year PFS rate was 29%.

### Gemcitabine-based regimens

The combination of gemcitabine, dexamethasone, and cisplatin in relapsed/refractory lymphoma, including T-cell NHL, was evaluated in a phase I study with 22 patients [62]. Gemcitabine (800 mg/m<sup>2</sup>) and cisplatin (35 mg/m<sup>2</sup>) were administered on days 1 and 15 of a 28-day cycle, along with dexamethasone (20 mg/day) for 4 days. Dose escalation of gemcitabine was not possible due to poor tolerability; the ORR was 45%, including 1 CR and 1 PR in the 5 evaluable T-cell NHL patients. The GEM-P combination of gemcitabine (1000 mg/m<sup>2</sup> on days 1, 8, and 15), cisplatin (100 mg/m<sup>2</sup> on day 15), and methylprednisolone (1000 mg on days 1–5) every 28 days in PTCL patients was associated with an ORR of 69%, accompanied by high rates of grade 3–4 neutropenia and leukopenia (62% each) [63]. An open-label study, combining gemcitabine (1000 mg/m<sup>2</sup>) with vinorelbine (25 mg/m<sup>2</sup>) on days 1 and 8 of each 21-day cycle in 40 patients with relapsed/refractory lymphoma, produced an ORR of 53% in the total population and 70% in the 10 PTCL patients, including 4 CRs (40%) [64]. The most common ( $\geq 20\%$ ) non-hematologic AEs were fatigue (21% of cycles) and phlebitis (20% of cycles); grade 4 thrombocytopenia and neutropenia occurred in 15% and 13% of patients, respectively.

### L-Asparaginase-based regimens

The enzyme L-asparaginase hydrolyses asparagine, leading to anticancer effects in lymphoma cells that lack L-asparagine

synthetase, such as natural killer/T-cell lymphomas (NKTCL). In a retrospective study of 45 patients with relapsed/refractory extranodal NKTCL (nasal type) treated with L-asparaginase-based therapy, the response rate was 82% and the 5-year survival rate was 67% [65]. In another retrospective study of 15 patients with relapsed/refractory or disseminated extranodal NKTCL treated with L-asparaginase-based regimens, the response rate was 87%, with 33% ( $n = 5$ ) of patients alive without disease recurrence after a median follow-up of 1322 days (approximately 3.5 years) [66].

The combination of L-asparaginase, methotrexate, and dexamethasone was evaluated in a prospective phase II study of 18 patients with extranodal NKTCL (nasal type) [67]. The high ORR (78%) and median DoR (12 months) were offset by the high incidence of grade 3–4 AEs, including neutropenia (42%), anemia (21%), hepatic AEs (16%), febrile neutropenia (11%), and infections (11%).

Results from a recent phase II study indicated that the SMILE regimen (steroid [dexamethasone], methotrexate, ifosfamide, L-asparaginase, and etoposide) was active in patients with extranodal NKTCL (nasal type) [68]. Of the 38 patients evaluated, 71% with stage III or IV disease, 20 received SMILE as first-line therapy and 18 had relapsed/refractory disease. The ORR was 79% and did not differ significantly between first-line and relapsed/refractory patients. The PFS and OS rates at 1-year were 53% and 55%, respectively. Hematologic toxicities were common; grade 4 neutropenia and leukopenia occurred in 92% and 76% of patients, respectively. A total of 61% of patients developed a grade 4 infection; 10 patients (26%) did not complete the planned treatment, including 6 patients who discontinued due to AEs.

### Interferon and retinoids

Recombinant interferons have previously demonstrated antitumor activity in several types of malignant lymphoma, and retinoids have shown efficacy in CTCL and a PTCL pilot study. The combination of interferon- $\alpha$  (3 mega units/day) and isotretinoin (1 mg/kg/day) was assessed in a phase II study of 54 patients, including 6 with PTCL-NOS, 1 with human T-cell leukemia virus (HTLV)-ATLL, and 1 with ALCL [69]. The response rate was 39% in all patients and 67% in PTCL-NOS patients, including 3 CRs (50%); the patients with HTLV-ATLL and ALCL both achieved PR. The most common ( $\geq 50\%$ ) AEs were flu-like syndrome (91%), fever (91%), dry skin (57%), fatigue (55%), and hypertriglyceridemia (50%).

### Topoisomerase inhibitors

The topoisomerase inhibitors irinotecan and mitoxantrone are both under evaluation for the treatment of solid tumors and NHL. After showing signs of efficacy in a small pilot study in relapsed/refractory NHL patients, the CMD combination of irinotecan (25 mg/m<sup>2</sup> on days 1 and 2), mitoxantrone (8 mg/m<sup>2</sup> on day 3), and dexamethasone (40 mg/day on days 1–3), administered every 3 weeks for 6 cycles, was assessed in a phase II study of 30 patients with relapsed/refractory PTCL [70]. The ORR was 60%, with 37% CR; 3-year PFS and OS were 18% and 28%, respectively. Grade 3–4 hematologic AEs were observed in 60% of patients, mostly grade 4 neutropenia (27%) and grade 3–4 thrombocytopenia (17%). The only grade  $\geq 3$  non-hematologic AE was febrile neutropenia (27%).

### CHOP-based regimens

Several trials are assessing if the addition of a novel agent, such as romidepsin, denileukin diftitox, alemtuzumab, or bortezomib, can enhance the efficacy of CHOP as first-line therapy [71]. A

detailed discussion of first-line CHOP-based regimens is beyond the scope of this review.

### Other combinations

Few trials have assessed the combination of novel agents with established chemotherapy regimens in relapsed/refractory patients. In a recent study, 24 patients with relapsed/refractory PTCL received alemtuzumab plus DHAP (A-DHAP), with responders subsequently undergoing ASCT [72]. The ORR was 50%, including 5 CRs. Median OS was 6 months and the median DoR was 2.9 months. The most common AE was grade 3–4 leukopenia (79%).

### Stem cell transplantation

Treatment guidelines for PTCL in the US and the UK include SCT as a treatment option for patients in first remission [58,73]. However, the role of SCT in relapsed/refractory PTCL is unclear. A comprehensive discussion of SCT is beyond the scope of this review; recent reviews by Reimer [74], Schmitz and colleagues [75], and Hosing and Champlin [76] have explored the role of SCT in patients with PTCL in more detail.

### Autologous stem cell transplantation

Evidence exists for the use of ASCT in transplant-eligible patients with previously untreated PTCL [77–79]. However, initial studies evaluating ASCT in relapsed/refractory PTCL patients were disappointing, particularly in patients with ALK-negative disease [80,81].

The Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea (GEL-TAMO) registry of 115 patients with untreated and relapsed/refractory PTCL treated with ASCT showed 5-year disease-free survival and OS rates of 60% and 56%, respectively [82]. The authors concluded that results with salvage ASCT in PTCL are similar to those in aggressive B-cell lymphoma.

In a retrospective analysis assessing the efficacy of ASCT in 53 patients with PTCL, median PFS and OS in the 10 evaluable refractory patients were 0.3 and 0.8 years, respectively [83]. The investigators concluded that ASCT may be beneficial when used as consolidation therapy following first response, but has minimal durable benefit in patients with relapsed/refractory PTCL [83]. When outcomes in 36 patients with chemosensitive relapsed PTCL undergoing ASCT were compared with those from a similar, historical control group of 97 patients with DLBCL, 3-year event-free survival rates were not significantly different (37% versus 42%) [84].

In AITL, ASCT has been recommended as consolidation therapy for suitable patients with chemosensitive relapse; it appears to have limited efficacy in patients with refractory disease [85]. Among 76 patients with AITL who underwent ASCT as salvage therapy, 4-year PFS rates for patients with chemosensitive ( $n = 56$ ) and chemorefractory disease ( $n = 20$ ) were 30% and 23%, respectively [85].

### Allogeneic stem cell transplantation and reduced-intensity conditioning

After allogeneic SCT, a significant, immune-mediated, graft-versus-lymphoma antitumor effect has been observed in T-cell lymphomas, suggesting that allogeneic SCT may be effective in this setting [86,87]. A retrospective study of allogeneic SCT in relapsed/refractory PTCL patients demonstrated PFS and OS rates of 40% and 50% at 5 years, respectively [88].

The high treatment-related mortality rates (around 30%) associated with the use of standard-intensity conditioning have been attributed primarily to the advanced age of patients with relapsed/refractory PTCL and to the effects of prior therapy [87,89]. Therefore, reduced-intensity conditioning with allogeneic SCT was examined [86,88,90,91].

A phase II study of reduced-intensity conditioning with allogeneic SCT in 17 patients with relapsed/refractory PTCL showed 3-year OS and PFS rates of 81% and 64%, respectively, with low treatment-related mortality (non-relapse mortality probability at 2 years: 6%) [86].

In a study of 10 patients with relapsed PTCL who received alemtuzumab-based induction therapy, followed by reduced-intensity fludarabine, busulfan, and cyclophosphamide conditioning with allogeneic SCT, 6 patients achieved remission; however, extensive graft-versus-host disease was observed in 5 of the 10 patients [90].

## Conclusions

Current patient outcomes suggest the need for novel regimens and alternative strategies to improve disease management and extend the duration of response. New compounds with novel mechanisms of action, such as the ones described in this review, may help to improve patient outcomes. Treatment can be individualized based on the histopathologic PTCL subtype, and regimens can be tailored to patient characteristics. Furthermore, biomarkers should be further explored.

Although numerous trials have evaluated novel therapies for the treatment of relapsed/refractory PTCL, prospective phase III trials are lacking. The absence of comparative trials hinders making impartial clinical recommendations for individual treatment regimens.

Development of novel therapies necessitates the development of paradigms for combining these agents, to improve response rates and durability of responses. Romidepsin may be particularly suitable for combination therapy because of its favorable toxicity profile compared with pralatrexate. A phase III trial assessing romidepsin combined with CHOP versus monotherapy is currently ongoing. Brentuximab vedotin has shown to be very effective in CD30<sup>+</sup> ALCL and may also prove useful for the treatment of other T-cell lymphomas. It is of great interest whether brentuximab vedotin adds to the effect of other drugs or regimens: a phase II clinical trial of brentuximab vedotin in combination with CHOP has been completed recently and several studies are currently underway, including a large international phase III trial comparing CHOP versus CHP plus brentuximab vedotin. The combination of alemtuzumab with other drugs also warrants further exploration: two international phase III trials (ACT-1 and ACT-2) comparing CHOP versus CHOP plus alemtuzumab have just completed enrollment. Bendamustine is also amenable for use in numerous combination regimens.

Having several new agents available with demonstrated activity in refractory T-cell lymphoma will provide additional therapeutic approaches for patients, lead to development of new combination approaches, and improve treatment options and long-term outcomes for these difficult-to-treat patients.

Additional studies are needed to determine the relative value of these novel therapies, as monotherapy or in combination, in the different subtypes of PTCL and to continue to evaluate the role of other treatment modalities, including SCT, conventional chemotherapy, and radiotherapy for optimizing responses and long-term outcomes in PTCL. The development of new and effective treatment strategies will improve overall outcomes in patients with PTCL.

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## Contributors

B.C., M.F., D.C., C.D., F.M., U.J., L.T., E.Z., M.G.daS., R.P., E.W., F.d'A., H.T., and P.L.Z contributed to the review, discussion, and classification of available evidence. B.C., M.F., D.C., C.D., F.M., U.J., L.T., E.Z., M.G.daS., R.P., E.W., F.d'A., H.T., and P.L.Z participated in the preparation of the manuscript. B.C., M.F., D.C., C.D., F.M., U.J., L.T., E.Z., M.G.daS., R.P., E.W., F.d'A., H.T., and P.L.Z approved the final manuscript before submission.

## Conflict of interest statement

B.C. has received honoraria from Celgene, Spectrum, and Millennium for advisory boards. M.F. has received honoraria from Celgene, Allos, Millennium, and Mundipharma for advisory boards; and paid expert testimony for Mundipharma. D.C. has received honoraria from Celgene, Pharmamar, Janssen, and Mundipharma for advisory boards. C.D. received honoraria for advisory boards from Celgene, Mundipharma, Seattle Genetics, and Genzyme. F.M. received honoraria and paid expert testimony from Celgene. U.J. has received honoraria from Celgene and participates in Celgene advisory boards. L.T. has participated in advisory boards for Celgene. E.Z. received research grants from Roche, Celgene, and Mundipharma. M.G.daS. has received honoraria from Celgene for participation in advisory boards. R.P. has received honoraria from Celgene and Mundipharma for advisory boards. E.W. has received honoraria from Celgene and Mundipharma for advisory boards. F.d'A. has been a consultant for Millennium-Takeda and Kyowa-Kirin; received honoraria from Millennium-Takeda; and received grants from Sanofi and Amgen. H.T. has participated in advisory boards for Celgene. P.L.Z. has received honoraria from Celgene, Mundipharma, Spectrum, and Millennium for advisory boards.

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