Emerging Therapies in Relapsed and Refractory Peripheral T-Cell Lymphoma

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Abstract: The peripheral T-cell lymphomas (PTCLs) account for 5% to 10% of all non-Hodgkin lymphomas. In the up-front setting, approximately one-quarter of patients experience a long-term remission. In the setting of relapsed and refractory disease, the median progression-free survival and overall survival are reported to be only 3.7 and 6.5 months, respectively. Unfortunately, the molecular and genetic characterization of PTCL has lagged well behind that of the B-cell lymphomas, although several recent experiences are shedding light on the remarkable molecular heterogeneity that has come to define these diverse diseases. The need to identify new active drugs for patients with PTCL has been addressed in part over the last several years, as 4 drugs have now been approved by the US Food and Drug Administration for patients with relapsed or refractory disease, and a plethora of new studies exploring novel combinations have begun to emerge. More advanced techniques in molecular biology, such as next-generation sequencing, gene expression profiling, and comparative genomic hybridization, have helped identify subtleties among subtypes and potentially identify new targets. Many of these recent clinical advances have been based on the recognition that PTCL is a disease that may be broadly characterized by gross epigenetic dysregulation with sensitivity to histone deacetylase inhibitors. In this report, we discuss emerging new therapies in relapsed and refractory PTCL and try to place these new findings in the evolving biological understanding of the disease.

Keywords
Non-Hodgkin lymphoma, peripheral T-cell lymphoma, refractory, relapsed, therapies

Introduction

Peripheral T-cell lymphoma (PTCL) encompasses a diverse group of mature T-cell non-Hodgkin lymphomas (NHLs). PTCL does not refer to an anatomic site, but rather to the type of T lymphocyte responsible for the disease—namely, the more mature post-thymic T

cells. The World Health Organization classification system in 2008 identified 17 distinct types of PTCL, placing them into 1 of 4 general categories based on clinical and pathologic features.[1] In general, nodal, extranodal, and leukemic PTCLs present as aggressive disease, whereas cutaneous PTCLs tend to present in a more indolent fashion.

In Western countries, PTCL accounts for 15% to 20% of aggressive lymphomas and 5% to 10% of all NHLs.[2,3] Additionally, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database reports PTCL occurring in fewer than 1 per 100,000 people.[4] The incidence, geographic variability, and outcomes of PTCL were poorly described until the International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study was performed. This study demonstrated that the most common subtypes of PTCL are PTCL not otherwise specified (PTCL-NOS, 25.9%); angioimmunoblastic T-cell lymphoma (AITL, 18.5%); and anaplastic large cell lymphoma (ALCL, 12%).[5] PTCL-NOS is the most common subtype in both North America and Europe. Anaplastic lymphoma kinase (ALK)-positive ALCL is more common in North America, whereas enteropathy-associated T-cell lymphoma (EATL) is more common in Europe. Natural killer/T-cell lymphoma (NKTCL) and adult T-cell leukemia/lymphoma (ATLL) are notably more prevalent in Asia (22.4% and 25%, respectively) than in North America (5.1% and 2.0%, respectively), and AITL is more common in Europe.[5]

Patients who have PTCL have an overall inferior prognosis compared with patients who have aggressive B-cell lymphomas.[5] There are some exceptions, however, which include the primary cutaneous PTCLs, some indolent primary leukemic entities, and ALK-positive ALCL.[6] Patients with the other subtypes of PTCL frequently relapse, and many have disease refractory to initial therapy. Although there is no single agreed-upon standard of care for these patients, those who obtain a complete response (CR) with up-front therapy are increasingly consolidated by an autologous stem cell transplant.

Conventional frontline treatment paradigms used for patients with PTCL come from our experiences with the aggressive B-cell NHLs.[6] Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)-based chemotherapy is frequently used in the up-front setting, despite the observation that durable remissions are uncommon. Researchers from the British Columbia Cancer Agency demonstrated this when they evaluated 199 patients with relapsed or refractory PTCL, almost all of whom were treated with a CHOP-based chemotherapy regimen. Even though 64% of the patients had a CR, only 24% of patients were progression-free in the long term. Furthermore, many of these patients came from a low-risk group with no or only 1 risk factor.[7] Another case series used the International Prognostic Index (IPI) to evaluate the outcomes of 89 patients with PTCL receiving chemotherapy after relapse or progression. In this study, the median overall survival (OS) and median progression-free survival (PFS) after relapse or progression (second PFS) were 6.5 and 3.7 months, respectively.[8]

Because most patients undergoing treatment for PTCL do not achieve remission or ultimately relapse, new therapies are desperately needed. Studies evaluating novel treatments in the setting of relapsed or refractory PTCL have lagged well behind those for the B-cell lymphomas because of the rarity of the former disease and its biological heterogeneity. What further complicates drug development in PTCL is that this disease is an excellent model of acquired drug resistance; patients who receive conventional cytotoxic agents often respond within the first 4 cycles, only to relapse by completion of the sixth cycle and then typically exhibit a pattern of continued drug cross-resistance with subsequent lines of therapy. Therefore, it is a challenge to get and maintain these patients on standard phase 1 or 2 protocols. However, recent advances in next-generation sequencing, gene expression profiling, and comparative genomic hybridization, have helped identify new targets.[9-19] Below, we evaluate several of these newer agents.

Biological Rationales for Novel Therapies in Peripheral T-Cell Lymphoma

Targeting the Reduced Folate Carrier and Enhancing Cellular Internalization

The antifolates are among the earliest classes of drugs used for the treatment of cancer, dating back to the pioneering development of aminopterin for childhood acute leukemia by Farber and Diamond.[20] It is well established that antifolates kill cells through the inhibition of dihydrofolate reductase (DHFR).[21-23] DHFR reduces dihydrofolic acid (DHF) to tetrahydrofolic acid (THF), a metabolite required by dividing cells for the synthesis of thymidine. The antifolates are retained in the intracellular compartment via polyglutamylation catalyzed by folylpoly-γ-glutamate synthetase (FPGS).[24] Reduced folate carrier type 1 (RFC-1) mediates the cellular uptake of both natural folic acid analogues and antifolates. RFC is almost exclusively expressed on fetal and malignant tissue.[25,26] Pralatrexate (Folotyn, Spectrum Pharmaceuticals), a member of the 10-deazaminopterin class of antifolates, is far more efficiently internalized into the tumor cell via RFC-1, being incorporated at a rate nearly 14 times faster than that observed for methotrexate. It is also polyglutamylated 10 times more efficiently than methotrexate. These in vitro observations imply that pralatrexate may be a more potent antifolate and should overcome known mechanisms of resistance where downregulation of RFC-1 and/or FPGS leads to acquired methotrexate

resistance.[27] Indeed, in vitro testing has established that pralatrexate consistently yields IC_{50} (concentration that inhibits 50%) values that are 1 log below those usually seen for methotrexate in lymphoma cell lines, including T-cell lymphomas.[27,28] Quantitative reverse transcription polymerase chain reaction in murine and human models for a number of the determinants of antifolate activity, including RFC-1, FPGS, and γ-glutamyl hydrolase, has revealed a striking correlation between the level of RFC-1 expression and the incidence of CRs, noting that no CRs were ever appreciated in any methotrexate-treated mouse cohort.[29-31]

Based on these data and a phase 1 experience in patients with non–small cell lung cancer, a phase 1 study of pralatrexate in 20 patients with relapsed/refractory lymphoma was performed. Interestingly, all 4 patients with PTCL achieved a CR.[32] A subgroup analysis by lineage of an early phase 2-1-2 study demonstrated overall response rates (ORRs) of 54% and 10% in T-cell and B-cell lymphomas, respectively. Of the patients who achieved a CR, 8 had T-cell lymphoma, and two-thirds of the patients with PTCL who achieved a partial response (PR) had no evidence of disease by positron emission tomography–computed tomography (PET-CT).[33] These results led to the development of the PROPEL (Pralatrexate in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) trial and subsequent US Food and Drug Administration (FDA) approval of pralatrexate for relapsed/refractory PTCL (see below).[34]

The Epigenome and Peripheral T-Cell Lymphoma

The term *epigenetics* refers to genetic modifications that result in changes in gene expression and function without a corresponding alteration in DNA sequence.[35] To add further complexity, the process is governed by a long list of genes that also need to be expressed at the right time and place. These genes code for proteins that add, remove, and read post-translational modifications to nucleosomes that regulate gene expression. Functional mutations in these enzymes, in addition to the proteins that remodel chromatin and the histone proteins themselves, have been reported in many neoplastic diseases.[36] Modifiers of the epigenome have been established in diseases such as myelodysplastic syndrome and acute myelogenous leukemia.

Recently, mutations in epigenetic regulators, including *TET, DNMT3,* and *IDH,* have been reported in PTCL. For example, TET functions as a DNA demethylase, allowing the conversion of methylcytosine to hydroxycytosine, whereas DNMT functions as an adenine and cytosine methylator. IDH allows the conversion of isocitrate to α-ketoglutarate, which is a critical cofactor required for the normal functioning of TET (specifically TET2).[6] Several studies have shown mutations in *TET2, IDH2,* and *DNMT3A,* and in some patients, lymphoma specimens have shown mutations in all 3 genes.[37-41] Inactivating mutations in *TET* impair the conversion of methylcytosine to hydroxycytosine.[42] *IDH* mutations result in the production of 2-hydroxyglutarate rather than α-ketoglutarate,[43] which leads to the inhibition of TET2 and multiple lysine-specific demethylases, global DNA and histone methylation, and overall transcriptional silencing.[43] Recent data in AITL have shown this disease to harbor more mutations in epigenetic operations than any other PTCL subtype. Interestingly, one study showed that 73% of AITL cases with a *DNMT3A* mutation also harbored a *TET2* mutation, which suggests an oncogenic cooperation leading to dysregulation of methylation regulation.[37,39-41,44]

Drugs affecting various epigenetic operations appear to be active in PTCL, specifically the histone deacetylase (HDAC) inhibitors. These drugs inhibit HDAC and lead to an increase in the expression of genes that cause cell cycle arrest, or apoptosis.[6] Patients with PTCL who received HDAC inhibitors such as romidepsin (Istodax, Celgene) and belinostat (Beleodaq, Spectrum Pharmaceuticals) have shown high response rates, suggesting that the TCLs may be a disease characterized by the dysregulation of a wide range of epigenetic functions.[6,45-49] However, studies show that although HDAC inhibitors result in an overall increase in acetylation, this does not necessarily correlate with apoptosis or response.[50] Furthermore, some literature has demonstrated a crucial role for apoptosis in effecting cell death following exposure to HDAC inhibitors.[51-54] Therefore, it is speculated that HDAC inhibition can be augmented with the addition of a drug that increases the likelihood of apoptosis.[6] Examples include the addition of mitogen-activated protein kinase (MAPK) pathway inhibitors to increase the pro-apoptotic protein BIM, the use of pro-apoptotic BH3 mimetics, and supplementation with DNA-damaging agents, providing an impetus for the use of combination therapies in PTCL (see below).[54-59]

CD30 and Peripheral T-Cell Lymphoma

CD30 antigen is a transmembrane glycoprotein receptor and a member of the tumor necrosis factor superfamily.[60] Upon stimulation, CD30 exerts pleiotropic effects on cell growth and survival, which largely depend on nuclear factor κB pathway activation.[61] CD30 is heavily expressed on the cell surface in systemic ALCL and the Reed-Sternberg cell of classic Hodgkin lymphoma.[62-64]

Two lines of evidence support a role for targeting CD30 in PTCL. The first is recent evidence that CD30 is expressed to some degree in almost all subtypes of lymphoma, albeit to variable degrees. In addition to ALCL, CD30 expression has been demonstrated in a subset of primary cutaneous lymphoproliferative disorders,[65] EATL type 1,[66] nasal-type NKTCL,[67] mycosis fungoides (MF),[68] transformed MF,[69] and PTCL-NOS.[70] Interestingly, it also is variably expressed in diffuse large B-cell lymphoma,

and even some epithelial malignancies as well. In data obtained from a study that characterized cluster of differentiation (CD) markers in the disease of 319 patients with TCLs or NKTCLs, the rate of CD30 expression ranged from 0% to 64% in a variety of TCLs.[71] Another study demonstrated CD30 immunoreactivity in patient samples of AITL, ATLL, and hepatosplenic T-cell lymphoma (HSTCL), the expression of which correlated with mRNA expression.[72]

A second line of evidence supporting a role for targeting CD30 in PTCL stems from the activity of brentuximab vedotin (Adcetris, Seattle Genetics), a novel CD30 antibody-drug conjugate (see below) in PTCL. This drug was investigated in a proof-of-concept phase 2 trial of 58 patients with ALCL (Table 1).[73] The trial reported an ORR of 86%, which included a CR in 57% of patients and a median duration of response (DOR) of 12.6 months (13.2 months for patients with a CR).[74] A second study evaluated brentuximab vedotin in 35 patients who had AITL or PTCL-NOS with varying levels of surface and soluble CD30 expression. In this experience, 14 patients (41%) achieved an objective response, with 8 CRs and 6 PRs (Table 1). More than half of the patients with AITL (54%) achieved an objective response, including 5 CRs and 2 PRs, and one-third (33%) of the patients with PTCL-NOS achieved an objective response (3 CRs, 4 PRs). Despite the response rates, these responses did not tend to be very durable, with a median PFS and a median DOR of only 2.6 and 7.6 months, respectively.[75] There was no apparent correlation between response and CD30 expression. Several theories have been advanced to explain these and other, similar findings, including the sensitivity of the Ber-H2 immunohistochemistry (IHC) staining technique, the variability in performing the IHC, possible cross fire effects, and effects on the activated T cell in the stromal microenvironment. New companion diagnostics are being developed, and it is likely that with more sensitive assays, a correlation between some level of CD30 expression and response will be identified.

FDA–Approved Drugs

Pralatrexate

Pralatrexate was the first drug approved for patients with relapsed/refractory PTCL. The PROPEL trial evaluated pralatrexate in 115 heavily pretreated patients with relapsed/refractory PTCL (Table 1). The study population included patients with all aggressive subtypes of TCL, including challenging entities such as blastic NKTCL, transformed MF, and human T-cell lymphotropic virus type 1 (HTLV-1) ATLL, which are often excluded from other studies. In addition, the study population was the most heavily treated to date, with a median of 3 prior therapies (range, 1-12) and with 20% of patients having received 5 or more lines of prior treatment. Interestingly, responses were seen across all subtypes of PTCL; the ORR was 29% (39% by investigator review), with 18% of patients achieving a PR and 11% of patients attaining a CR or CR unconfirmed (CRu). In this study, 63% of patients responded after 1 cycle, the median time on therapy for all responders was 186 days, and the median DOR was more than 12 months. Notably, the median PFS and OS times were 3.5 and 14.5 months, respectively.[34]

A subset analysis was performed on 15 patients who received pralatrexate as their second-line treatment after CHOP. In these 15 patients, the ORR was 47% via central review, with 20% of patients attaining a CR. The median DOR was 12.5 months, and the median PFS was 7.4 months.[76] This experience suggests that an earlier use of pralatrexate in PTCL is likely to be associated with higher response rates, which is consistent with most treatment paradigms across cancer medicine. Of note, the continued administration certainly contributed to the reported response rates. Additionally, the number of cycles is not fixed, which can be thought of as a favorable feature in comparisons with the traditional cytotoxic agents.

Romidepsin

Romidepsin, a cyclic peptide originally isolated from *Chromobacterium violaceum*, is a pan-HDAC inhibitor with potent inhibitory activity against selected class 1 HDAC isoforms, such as HDAC-1, -2, and -3.[77-79] Romidepsin was approved for the treatment of patients with relapsed/refractory PTCL based on 2 separate phase 2 clinical trials. The National Cancer Institute NCI-1312 trial enrolled 47 patients with relapsed/refractory PTCL who had received a median of 3 prior therapies. This study reported an ORR of 38%, with 8 CRs (18%) and 9 PRs. The median DOR was 9 months.[49]

The pivotal phase 2 registration-directed trial evaluated romidepsin in 130 patients with PTCL whose disease had failed to respond to at least 1 prior systemic therapy (Table 1). Independent review revealed an ORR of 25%, including the 15% of patients who achieved a CR or CRu. Similar response rates were seen in a variety of subgroups, including those based on number of prior therapies, presence of a prior stem cell transplant, and refractoriness to the most recent therapy. The median DOR was 17 months, and of the 19 patients who achieved CR/CRu, 17 (89%) had not experienced disease progression at a median follow-up of 13.4 months. Although the study population was not as diverse or as heavily treated as the one reported in the PROPEL study, responses were seen across many of the subtypes, including PTCL-NOS (29%), AITL (33%), and ALK-negative ALCL (24%).[47] Just as with pralatrexate, continued administration had an effect on response rates, and the number of cycles was not fixed.

A follow-up study was published in 2014 (median follow-up, 22.3 months) to characterize patients who achieved long-term responses of 1 year or longer with romidepsin. Here, the median PFS and OS times were 4 and 11.3 months, respectively, with a DOR for all responders measured at 28 months (not reached for those who achieved a CR or CRu). Patients with a lack of response or a transient response to prior therapy achieved durable responses. None of the baseline characteristics examined, including heavy pretreatment, response to prior therapy, and advanced disease, barred long-term responses to romidepsin.[48]

Belinostat

Belinostat is a hydroxamic acid-based pan class 1 and 2 HDAC inhibitor.[80] It is currently approved for patients with relapsed or refractory PTCL who have received at least 1 line of prior therapy. The original phase 2 trial (CLN-6) included 24 patients with various subtypes of TCL and produced an ORR of 25% in relapsed/refractory PTCL.[46] This activity was the basis for initiating the BELIEF (CLN-19: Belinostat in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) study, in which 129 patients with relapsed/refractory disease received belinostat (Table 1). The median number of prior therapies was 2. The ORR was 26% (11% CR and 15% PR), with PFS and OS times of 1.6 and 7.9 months, respectively, and a median DOR of 13.6 months. Of the patients with AITL, 46% experienced a response.[45,81]

Brentuximab Vedotin

Brentuximab vedotin (SGN-35) is a novel anti-CD30 antibody linked to monomethyl auristatin E (MMAE), a potent antimicrotubule agent, via a protease-cleavable linker. MMAE is a mitotic spindle poison that induces G2-M cell cycle arrest and apoptosis.[82] Brentuximab vedotin is approved for relapsed Hodgkin lymphoma and relapsed/refractory systemic ALCL; results of the proof-of-concept trial were summarized above.[74] Also as previously noted, a subsequent experience in 35 patients with non-ALCL PTCL (essentially restricted to PTCL-NOS and AITL) revealed an ORR of 41% (24% with a CR). The median PFS and median DOR were 2.6 and 7.6 months, respectively (Table 1).[75]

Emerging Drugs

Single Agents

Alisertib. Alisertib (MLN8237) is an oral Aurora A kinase (AAK) inhibitor. AAK functions as a serine/threonine kinase by regulating G2-M transition and centrosome separation during mitosis. An initial phase 2 trial of alisertib in patients with B- or T-cell lymphoma demonstrated an ORR of 27% and, in 8 patients with aggressive TCL, a response rate of 50% (Table 2).[83] Recently, the Southwest Oncology Group's SWOG-1108 trial evaluated alisertib in 37 patients with PTCL in the relapsed/refractory setting. In this study, Barr and colleagues reported 2 CRs and 7 PRs, with an ORR of 24% (Table 2); the ORR was 33% for the most common subtypes (PTCL-NOS, AITL, and ALCL).[84] The LUMIERE trial (NCT01482962: A Phase 3, Randomized, Two-Arm, Open-Label, Multicenter, International Trial of Alisertib [MLN8237] or Investigator's Choice [Selected Single Agent] in Patients With Relapsed or Refractory Peripheral T-Cell Lymphoma) was recently closed. We eagerly await its results.[85]

Bendamustine. Bendamustine is an alkylating agent with properties of the nitrogen mustard mechlorethamine and the purine analogue fludarabine. The BENTLY trial (Bendamustine in Patients With Refractory or Relapsed T-Cell Lymphoma) evaluated bendamustine in 60 patients with relapsed or refractory PTCL (Table 2). The ORR was 50%, including a CR rate of 28% and a PR rate of 22%. The drug showed consistent efficacy independently of major disease characteristics. The median PFS and median DOR were 3.6 and 3.5 months, respectively.[86]

Sorafenib. Sorafenib is a multikinase inhibitor that modulates multiple intracellular pathways, including platelet-derived growth factor receptor/vascular endothelial growth factor receptor (PDGFR/VEGFR) and MAPK signaling. A recent study evaluated sorafenib in 12 patients with TCL (3 with PTCL and 9 with CTCL) (Table 2). The median number of prior therapies for the patients with PTCL was 2. Of the patients with PTCL, 3 achieved a CR and 1 received an allogeneic stem cell transplant. The median event-free survival (EFS) for the entire cohort was 3.5 months. At a median follow-up of 11.2 months, 10 patients were alive (83%), and disease stabilization or reduction was noted in 75% of patients.[87]

Duvelisib. Duvelisib (IPI-145) is an oral inhibitor of phosphoinositide 3-kinase (PI3K)-δ and PI3K-γ. PI3K has been found to play key regulatory roles in many cellular processes, including cell survival, proliferation, and differentiation.[88-90] PI3K-δ and PI3K-γ isoforms are preferentially expressed in leukocytes with distinct roles in T-cell function.[91] A phase 1 trial of duvelisib included 16 patients with noncutaneous PTCL (Table 2). The median number of prior therapies was 4. Among the 33 evaluable patients (18 with CTCL and 15 with noncutaneous PTCL), an ORR of 42% was observed. In the patients with non-cutaneous PTCL, the ORR was 53%, with 2 CRs and 6 PRs.[92,93]

Table 1. Clinical Trial Results: Efficacy of FDA-Approved Monotherapies for Relapsed/Refractory PTCL

Drug	Evaluable Patients, n	Subtypes	ORR, %	Prior Therapies, Median, n	DOR, Median, mo	PFS, Median, mo
Pralatrexate[34,76]	115	- AITL - ALCL, primary systemic - ATLL (HTLV-1) - Blastic NKTCL - Extranodal PTCL/NKTCL - Nasal NKTCL - PTCL-NOS - Transformed MF	29	3	>12	3.5
Romidepsin[47,48]	130	- AITL - ALCL, ALK-negative - ALCL, ALK-positive - Cutaneous γ/δ TCL - EATL - Nasal NKTCL - PTCL-NOS - Subcutaneous panniculitis-like TCL - Transformed MF	25	3	17	4
Belinostat[45,46,81]	129	- AITL - ALCL, ALK-negative - ALCL, ALK-positive - EATL - Hepatosplenic TCL - Nasal NKTCL - PTCL-NOS	26	2	13.6	1.6
Brentuximab vedotin[74,75]	58 35	- ALCL only - AITL - PTCL-NOS	86 41	2 2	12.6 7.6	13.3 2.6

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; DOR, duration of response; EATL, enteropathy-associated T-cell lymphoma; FDA, US Food and Drug Administration; HTLV-1, human T-cell lymphotropic virus type 1; MF, mycosis fungoides; NKTCL, natural killer/T-cell lymphoma; NOS, not otherwise specified; ORR, overall response rate; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; TCL, T-cell lymphoma.

Plitidepsin. Plitidepsin is a cyclic depsipeptide originally isolated from the tunicate *Aplidium albicans* that is commercially produced by chemical synthesis. It displays a broad spectrum of anticancer activities, including induction of apoptosis and G1/G2 cell cycle arrest. Plitidepsin has shown activity against several human malignant cell lines, including leukemias and lymphomas.[94-97] A phase 2 trial evaluated plitidepsin in 67 patients, who included 34 patients with relapsed/refractory noncutaneous PTCL (Table 2). Of the 29 evaluable patients with noncutaneous PTCL, 6 demonstrated an objective response to plitidepsin (2 CRs and 4 PRs; ORR, 20.7%), with a median PFS and a median DOR of 1.6 and 2.2 months, respectively.[98]

Mogamulizumab. Mogamulizumab (KW-0761) is a humanized defucosylated monoclonal chemokine receptor 4 (CCR4) antibody with enhanced antibody-dependent cellular cytotoxicity. It has clinical efficacy in CCR4-expressing PTCL: namely, ATLL. In the initial phase 2 study, mogamulizumab was administered to 28 patients with relapsed ATLL (Table 2). An ORR of 50% was observed, with median PFS and OS of 5.2 and 13.7 months, respectively.[99] In 2014, another study evaluated 37 patients with relapsed CCR4-positive PTCL. The authors noted objective responses in 35% of the patients, including 14% with a CR. The ORR was 34% in patients with PTCL (3 of 16 with PTCL-NOS, 6 of 12 with AITL, and 1 of 1 with ALK-negative ALCL). The median PFS and OS for patients with PTCL were 2 months (8.2 months for PTCL responders) and 14.2 months, respectively. Interestingly, the total ORR did not significantly correlate with the level of CCR4 expression.[100]

Combination Therapies

Alisertib and romidepsin. Preclinical studies support the combination of alisertib with an HDAC inhibitor. For

Table 2. Clinical Trial Results: Efficacy of Emerging Monotherapies for Relapsed/Refractory PTCL

Drug	Evaluable Patients, n	Subtypes	ORR, %	Prior Therapies, Median, n	DOR, Median, mo	PFS, Median, mo
Alisertib[83,84]	8	- Aggressive TCL	50	3	NR	~19
	37	- AITL - ALCL - ATLL - Extranodal NKTCL - PTCL-NOS - Transformed MF	24	3	NR	NR
Bendamustine[86]	60	- AITL - ALCL - EATL - MF - PTCL-NOS	50	1	3.5	3.6
Sorafenib[87]	12	- AITL - CTCL - PTCL-NOS	42	2	NA	3.5 (reported as EFS)
Duvelisib[92,93]	18	- MF - Sézary syndrome - Transformed MF	33	6	NA	4.5
	15	- AITL - ALCL, ALK-negative - EATL - NKTCL - PTCL-NOS - Subcutaneous panniculitis-like TCL	53	2.5		8.3
Plitidepsin[98]	29	- AITL - ALCL, primary systemic - Extranodal NKTCL - PTCL-NOS	20.7	2	2.2	1.6
Mogamulizumab[99,100]	28	- ATLL	50	1	NA	5.2
	37	- CCR4-positive: AITL ALCL, ALK-negative PTCL-NOS	34	2	NA	2

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; CCR4, chemokine receptor 4; CTCL, cutaneous T-cell lymphoma; DOR, duration of response; EATL, enteropathy-associated T-cell lymphoma; EFS, event-free survival; MF, mycosis fungoides; NA, not available; NKTCL, natural killer/T-cell lymphoma; NOS, not otherwise specified; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PTCL, peripheral T-cell lymphoma; TCL, T-cell lymphoma.

instance, high-throughput screening has shown alisertib to be synergistic with romidepsin, and not to be synergistic with pralatrexate or ixazomib. During simultaneous exposure to alisertib and romidepsin at their IC_{10}, IC_{20}, and IC_{30} values, marked synergy was observed only in T-cell lymphoma–derived cell lines, and not B-cell lymphoma–derived cell lines.[101] Evidence for apoptosis was confirmed in TCL cell lines, evidenced by increased expression of PUMA, caspase 3–mediated cleavage of poly(ADP-ribose) polymerase (PARP), and decreased expression of BCL-xL and BCL-2. Alisertib was also found to induce a G2-M arrest, whereas the combination of the 2 agents appeared to induce polyploidy and a failure of cytokinesis. In vivo, alisertib and romidepsin showed synergy after a TCL cell line was inoculated into severe combined immunodeficiency (SCID) mice.[101,102]

Based on this rationale, a phase 1 trial evaluating the combination of alisertib and romidepsin in relapsed/refractory PTCL (in addition to BCL) has been initiated (NCT01897012). Although early, 9 patients to date

have been enrolled. Of these, 3 had relapsed/refractory PTCL (the median number of prior therapies was 4). Of the patients with PTCL, 1 attained a CR, 1 had stable disease, and 1 had progression of disease. Of note, the patient with a CR had received 7 prior lines of treatment, remains in remission at 5 months of follow-up, and has declined transplant.[103]

Azacitidine/decitabine and romidepsin. The single-agent efficacy and synergistic interaction of a panel of HDAC inhibitors and DNA methyltransferase (DNMT) inhibitors (including decitabine and 5-azacitidine) have recently been evaluated in preclinical models of TCL. Cell viability was not affected by treatment with decitabine or 5-azacitidine as monotherapy. Although romidepsin was successful at inhibiting cell viability as a single agent, simultaneous exposure to combinations of decitabine plus romidepsin produced marked synergy in all TCL models; decitabine plus romidepsin produced the deepest synergy at 72 hours, with synergy coefficients in the range of 0.3.

The molecular basis for the synergistic effect of HDAC inhibitors and DNMT inhibitors was also evaluated by gene expression profiling (GEP) and CpG methylation. A significant downregulation of genes involved in biosynthetic pathways, including protein and lipid synthesis, and a significant upregulation of genes responsible for cell cycle arrest were seen. Of the genes modulated by single agents, 92% were similarly modulated by the combination, but the combination induced a further significant change in the transcriptome that affected an additional 390 genes. Decitabine in combination with romidepsin decreased the number of demethylated gene regions, and when GEP and methylation data were compared, a significant inverse relationship (R^2 = 0.657) was found, with genes differentially expressed in the GEP and methylation analyses.[59]

Based on these data, a phase 1/2a dose escalation study (NCT01998035) is currently accruing patients with relapsed/refractory lymphoma, including TCL, to evaluate the combination of oral 5-azacitidine and romidepsin.

Pralatrexate and romidepsin. A high-throughput screening approach and multimodality imaging approach of surface bioluminescence and three-dimensional ultrasound were used in a xenograft murine model of TCL to explore the in vitro and in vivo activity of pralatrexate and romidepsin in combination. In vitro, the combination of pralatrexate and romidepsin exhibited concentration-dependent synergy against a panel of TCL cell lines. In a murine model of TCL, the group of mice treated with pralatrexate plus romidepsin demonstrated a statistically significant reduction in bioluminescent intensity compared with the romidepsin-alone, pralatrexate-alone, and control groups after 21 days. A CR was observed by day 18 only in the combination cohort, in which all 6 mice exhibited a CR. Additionally, the fraction of actively proliferating cells was lower in the combination-treated mice (20%), and these mice demonstrated a statistically significant reduction in three-dimensional tumor volumes compared with the other 3 mouse cohorts. Furthermore, the median OS time was statistically superior to that observed in the other cohorts.[104] Based on these preclinical findings, a phase 1/2 study of the combination has been launched and is actively accruing patients (NCT01947140).

Conclusions

Data from the British Columbia Cancer Agency show that only 24% of patients with PTCL treated with traditional CHOP chemotherapy are progression-free in the long term; therefore, newer therapies are absolutely needed.[7] Lineage-specific drugs can change our current paradigms for treating PTCL. Data from the BELIEF trial with belinostat show no evidence of a unique subgroup effect, in addition to showing activity in more than 60% of patients.[81] These data, in addition to the previously described preclinical combination data, suggest that combination therapies with HDAC inhibitors may show much promise in the treatment of relapsed/refractory PTCL, and such therapies are likely what is in store for the future. Whether improvements in rates or duration of response come from other epigenetic modifiers, DNA-damaging agents, or modulators of apoptosis remains to be determined.

References

1. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. *Blood*. 2011;117(25):6756-6767.
2. Ascani S, Zinzani PL, Gherlinzoni F, et al. Peripheral T-cell lymphomas. Clinico-pathologic study of 168 cases diagnosed according to the R.E.A.L. Classification. *Ann Oncol*. 1997;8(6):583-592.
3. Anderson JR, Armitage JO, Weisenburger DD. Epidemiology of the non-Hodgkin's lymphomas: distributions of the major subtypes differ by geographic locations. Non-Hodgkin's Lymphoma Classification Project. *Ann Oncol*. 1998;9(7):717-720.
4. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*. 2006;107(1):265-276.
5. Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124-4130.
6. O'Connor OA, Bhagat G, Ganapathi K, et al. Changing the paradigms of treatment in peripheral T-cell lymphoma: from biology to clinical practice. *Clin Cancer Res*. 2014;20(20):5240-5254.
7. Savage KJ, Chhanabhai M, Gascoyne RD, Connors JM. Characterization of peripheral T-cell lymphomas in a single North American institution by the WHO classification. *Ann Oncol*. 2004;15(10):1467-1475.
8. Mak V, Hamm J, Chhanabhai M, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *J Clin Oncol*. 2013;31(16):1970-1976.
9. Nagel S, Leich E, Quentmeier H, et al. Amplification at 7q22 targets cyclin-dependent kinase 6 in T-cell lymphoma. *Leukemia*. 2008;22(2):387-392.

10. Thorns C, Bastian B, Pinkel D, et al. Chromosomal aberrations in angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma unspecified: A matrix-based CGH approach. *Genes Chromosomes Cancer*. 2007;46(1):37-44.
11. Martinez-Delgado B, Meléndez B, Cuadros M, et al. Expression profiling of T-cell lymphomas differentiates peripheral and lymphoblastic lymphomas and defines survival related genes. *Clin Cancer Res*. 2004;10(15):4971-4982.
12. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of angioimmunoblastic lymphoma indicates derivation from T follicular helper cells and vascular endothelial growth factor deregulation. *Cancer Res*. 2007;67(22):10703-10710.
13. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. *J Clin Invest*. 2007;117(3):823-834.
14. de Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood*. 2007;109(11):4952-4963.
15. Ballester B, Ramuz O, Gisselbrecht C, et al. Gene expression profiling identifies molecular subgroups among nodal peripheral T-cell lymphomas. *Oncogene*. 2006;25(10):1560-1570.
16. Zettl A, Rüdiger T, Konrad MA, et al. Genomic profiling of peripheral T-cell lymphoma, unspecified, and anaplastic large T-cell lymphoma delineates novel recurrent chromosomal alterations. *Am J Pathol.* 2004;164(5):1837-1848.
17. Salaverria I, Beà S, Lopez-Guillermo A, et al. Genomic profiling reveals different genetic aberrations in systemic ALK-positive and ALK-negative anaplastic large cell lymphomas. *Br J Haematol*. 2008;140(5):516-526.
18. Cuadros M, Dave SS, Jaffe ES, et al. Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. *J Clin Oncol.* 2007;25(22):3321-3329.
19. Iqbal J, Weisenburger DD, Greiner TC, et al; International Peripheral T-Cell Lymphoma Project. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood*. 2010;115(5):1026-1036.
20. Farber S, Diamond LK. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid. *N Engl J Med*. 1948;238(23):787-793.
21. Osborn MJ, Huennekens FM. Enzymatic reduction of dihydrofolic acid. *J Biol Chem*. 1958;233(4):969-974.
22. Rueda A, Casanova M, Quero C, Medina-Pérez A. Pralatrexate, a new hope for aggressive T-cell lymphomas? *Clin Transl Oncol*. 2009;11(4):215-220.
23. Gangjee A, Jain HD, Kurup S. Recent advances in classical and non-classical antifolates as antitumor and antiopportunistic infection agents: part II. *Anticancer Agents Med Chem*. 2008;8(2):205-231.
24. Assaraf YG. Molecular basis of antifolate resistance. *Cancer Metastasis Rev*. 2007;26(1):153-181.
25. Visentin M, Zhao R, Goldman ID. The antifolates. *Hematol Oncol Clin North Am*. 2012;26(3):629-648, ix. ix.
26. Zhao R, Goldman ID. Resistance to antifolates. *Oncogene*. 2003;22(47):7431-7457.
27. O'Connor OA. Pralatrexate: an emerging new agent with activity in T-cell lymphomas. *Curr Opin Oncol*. 2006;18(6):591-597.
28. Wang ES, O'Connor O, She Y, Zelenetz AD, Sirotnak FM, Moore MA. Activity of a novel anti-folate (PDX, 10-propargyl 10-deazaaminopterin) against human lymphoma is superior to methotrexate and correlates with tumor RFC-1 gene expression. *Leuk Lymphoma*. 2003;44(6):1027-1035.
29. Schmid FA, Sirotnak FM, Otter GM, DeGraw JI. New folate analogs of the 10-deaza-aminopterin series: markedly increased antitumor activity of the 10-ethyl analog compared to the parent compound and methotrexate against some human tumor xenografts in nude mice. *Cancer Treat Rep*. 1985;69(5):551-553.
30. Sirotnak FM, DeGraw JI, Moccio DM, Samuels LL, Goutas LJ. New folate analogs of the 10-deaza-aminopterin series. Basis for structural design and biochemical and pharmacologic properties. *Cancer Chemother Pharmacol*. 1984;12(1):18-25.
31. Sirotnak FM, DeGraw JI, Schmid FA, Goutas LJ, Moccio DM. New folate analogs of the 10-deaza-aminopterin series. Further evidence for markedly increased antitumor efficacy compared with methotrexate in ascitic and solid murine tumor models. *Cancer Chemother Pharmacol*. 1984;12(1):26-30.
32. O'Connor OA, Hamlin PA, Portlock C, et al. Pralatrexate, a novel class of antifol with high affinity for the reduced folate carrier-type 1, produces marked complete and durable remissions in a diversity of chemotherapy refractory cases of T-cell lymphoma. *Br J Haematol*. 2007;139(3):425-428.
33. O'Connor OA, Horwitz S, Hamlin P, et al. Phase II-I-II study of two different doses and schedules of pralatrexate, a high-affinity substrate for the reduced folate carrier, in patients with relapsed or refractory lymphoma reveals marked activity in T-cell malignancies. *J Clin Oncol*. 2009;27(26):4357-4364.
34. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol*. 2011;29(9):1182-1189.
35. Piekarz RL, Bates SE. Epigenetic modifiers: basic understanding and clinical development. *Clin Cancer Res*. 2009;15(12):3918-3926.
36. Plass C, Pfister SM, Lindroth AM, Bogatyrova O, Claus R, Lichter P. Mutations in regulators of the epigenome and their connections to global chromatin patterns in cancer. *Nat Rev Genet.* 2013;14(11):765-780.
37. Couronné L, Bastard C, Bernard OA. TET2 and DNMT3A mutations in human T-cell lymphoma. *N Engl J Med*. 2012;366(1):95-96.
38. Palomero T, Couronné L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet*. 2014;46(2):166-170.
39. Quivoron C, Couronné L, Della Valle V, et al. TET2 inactivation results in pleiotropic hematopoietic abnormalities in mouse and is a recurrent event during human lymphomagenesis. *Cancer Cell*. 2011;20(1):25-38.
40. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood*. 2012;119(8):1901-1903.
41. Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood*. 2014;123(9):1293-1296.
42. Losman JA, Looper RE, Koivunen P, et al. (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. *Science.* 2013;339(6127):1621-1625.
43. Losman JA, Kaelin WG Jr. What a difference a hydroxyl makes: mutant IDH, (R)-2-hydroxyglutarate, and cancer. *Genes Dev.* 2013;27(8):836-852.
44. Lemonnier F, Couronné L, Parrens M, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood*. 2012;120(7):1466-1469.
45. O'Connor OA, Masszi T, Savage KJ, et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): results from the BELIEF trial [ASCO abstract 8507]. *J Clin Oncol*. 2013;31(15)(suppl).
46. Pohlman B, Advani R, Duvic M, et al. Final results of a phase II trial of belinostat (PXD101) in patients with recurrent or refractory peripheral or cutaneous T-cell lymphoma [ASH abstract 920]. *Blood.* 2009;114(22)(suppl).
47. Coiffier B, Pro B, Prince HM, 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*. 2012;30(6):631-636.
48. Coiffier B, Pro B, Prince HM, et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. *J Hematol Oncol*. 2014;7:11.
49. Piekarz RL, Frye R, Prince HM, et al. Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma. *Blood*. 2011;117(22):5827-5834.
50. Luchenko VL, Litman T, Chakraborty AR, et al. Histone deacetylase inhibitor-mediated cell death is distinct from its global effect on chromatin. *Mol Oncol*. 2014;8(8):1379-1392.
51. Chen S, Dai Y, Pei XY, Grant S. Bim upregulation by histone deacetylase inhibitors mediates interactions with the Bcl-2 antagonist ABT-737: evidence for distinct roles for Bcl-2, Bcl-xL, and Mcl-1. *Mol Cell Biol.* 2009;29(23):6149-6169.
52. Ierano C, Chakraborty AR, Nicolae A, et al. Loss of the proteins Bak and Bax prevents apoptosis mediated by histone deacetylase inhibitors. *Cell Cycle.* 2013;12(17):2829-2838.
53. Jona A, Khaskhely N, Buglio D, et al. The histone deacetylase inhibitor entinostat (SNDX-275) induces apoptosis in Hodgkin lymphoma cells and synergizes with Bcl-2 family inhibitors. *Exp Hematol.* 2011;39(10):1007-1017e1.
54. Wiegmans AP, Alsop AE, Bots M, et al. Deciphering the molecular events necessary for synergistic tumor cell apoptosis mediated by the histone deacetylase inhibitor vorinostat and the BH3 mimetic ABT-737. *Cancer Res.* 2011;71(10):3603-3615.
55. Ozaki K, Minoda A, Kishikawa F, Kohno M. Blockade of the ERK pathway markedly sensitizes tumor cells to HDAC inhibitor-induced cell death. *Biochem Biophys Res Commun*. 2006;339(4):1171-1177.
56. Fiskus W, Sharma S, Qi J, et al. Highly active combination of BRD4 antagonist and histone deacetylase inhibitor against human acute myelogenous leukemia cells. *Mol Cancer Ther*. 2014;13(5):1142-1154.
57. Fiskus W, Sharma S, Shah B, et al. Highly effective combination of LSD1 (KDM1A) antagonist and pan-histone deacetylase inhibitor against human AML cells. *Leukemia*. 2014;28(11):2155-2164.
58. Fiskus W, Wang Y, Sreekumar A, et al. Combined epigenetic therapy with the his-

tone methyltransferase EZH2 inhibitor 3-deazaneplanocin A and the histone deacetylase inhibitor panobinostat against human AML cells. *Blood*. 2009;114(13):2733-2743.
59. Marchi E, Zullo K, Scotto L, et al. The combination of hypomethylating agents and histone deacetylase inhibitors (HDACi) are synergistically cytotoxic and reverse the malignant phenotype in preclinical models of T-cell lymphoma [ASH abstract 646]. *Blood.* 2013;122(21)(suppl).
60. Chiarle R, Podda A, Prolla G, Gong J, Thorbecke GJ, Inghirami G. CD30 in normal and neoplastic cells. *Clin Immunol*. 1999;90(2):157-164.
61. Buchan SL, Al-Shamkhani A. Distinct motifs in the intracellular domain of human CD30 differentially activate canonical and alternative transcription factor NF-κB signaling. *PLoS One*. 2012;7(9):e45244.
62. Falini B, Bolognesi A, Flenghi L, et al. Response of refractory Hodgkin's disease to monoclonal anti-CD30 immunotoxin. *Lancet*. 1992;339(8803):1195-1196.
63. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. *Blood*. 1985;66(4):848-858.
64. Tazzari PL, de Totero D, Bolognesi A, et al. An Epstein-Barr virus-infected lymphoblastoid cell line (D430B) that grows in SCID-mice with the morphologic features of a CD30+ anaplastic large cell lymphoma, and is sensitive to anti-CD30 immunotoxins. *Haematologica*. 1999;84(11):988-995.
65. Duvic M. CD30+ neoplasms of the skin. *Curr Hematol Malig Rep*. 2011;6(4):245-250.
66. Cheson BD, Horwitz SM, Weisenburger DD. Peripheral T-cell lymphomas: diagnosis and treatment options. Proceedings from a live roundtable, August 17, 2011, Kauai, Hawaii. *Clin Adv Hematol Oncol*. 2011;9(11)(suppl 26):1-14.
67. Pongpruttipan T, Sukpanichnant S, Assanasen T, et al. Extranodal NK/T-cell lymphoma, nasal type, includes cases of natural killer cell and αβ, γδ, and αβ/γδ T-cell origin: a comprehensive clinicopathologic and phenotypic study. *Am J Surg Pathol*. 2012;36(4):481-499.
68. Nikoo A. The expression of CXCR3 and CD30 in mycosis fungoides. *Arch Iran Med*. 2012;15(3):146-150.
69. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. *Blood*. 2012;119(7):1643-1649.
70. Went P, Agostinelli C, Gallamini A, et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. *J Clin Oncol*. 2006;24(16):2472-2479.
71. Karube K, Aoki R, Nomura Y, et al. Usefulness of flow cytometry for differential diagnosis of precursor and peripheral T-cell and NK-cell lymphomas: analysis of 490 cases. *Pathol Int*. 2008;58(2):89-97.
72. Bossard C, Dobay MP, Parrens M, et al. Immunohistochemistry as a valuable tool to assess CD30 expression in peripheral T-cell lymphomas: high correlation with mRNA levels. *Blood*. 2014;124(19):2983-2986.
73. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med.* 2010;363(19):1812-1821.
74. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol.* 2012;30(18):2190-2196.
75. Horwitz SM, Advani RH, Bartlett NL, et al. Objective responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood*. 2014;123(20):3095-3100.
76. Shustov A, Pro B, Gisselbrecht C, et al. Pralatrexate is effective as second-line treatment following cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) failure in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) [ASH abstract 4882]. *Blood.* 2010;116(21)(suppl).
77. Furumai R, Matsuyama A, Kobashi N, et al. FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. *Cancer Res*. 2002;62(17):4916-4921.
78. Ueda H, Nakajima H, Hori Y, et al. FR901228, a novel antitumor bicyclic depsipeptide produced by Chromobacterium violaceum No. 968. I. Taxonomy, fermentation, isolation, physico-chemical and biological properties, and antitumor activity. *J Antibiot (Tokyo)*. 1994;47(3):301-310.
79. Nakajima H, Kim YB, Terano H, Yoshida M, Horinouchi S. FR901228, a potent antitumor antibiotic, is a novel histone deacetylase inhibitor. *Exp Cell Res*. 1998;241(1):126-133.
80. Khan N, Jeffers M, Kumar S, et al. Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. *Biochem J*. 2008;409(2):581-589.
81. O'Connor OA, Horwitz S, Masszi T, 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*. 2015;33(23):2492-2499.
82. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. *Blood*. 2003;102(4):1458-1465.
83. Friedberg JW, Mahadevan D, Cebula E, et al. Phase II study of alisertib, a selective Aurora A kinase inhibitor, in relapsed and refractory aggressive B- and T-cell non-Hodgkin lymphomas. *J Clin Oncol*. 2014;32(1):44-50.
84. Barr PM, Li H, Spier CM, et al. U.S. Intergroup phase II trial (SWOG 1108) of alisertib, an investigational aurora A kinase (AAK) inhibitor, in patients with peripheral T-cell lymphoma (PTCL; NCT01466881) [ASCO abstract 8523]. *J Clin Oncol.* 2014;32(15)(suppl).
85. O'Connor O, Leonard EJ, Benaim E. Phase III study of investigational MLN8237 (alisertib) versus investigator's choice in patients (pts) with relapsed/refractory (rel/ref) peripheral T-cell lymphoma (PTCL) [ASCO abstract TPS8110]. *J Clin Oncol.* 2012;30(15)(suppl).
86. Damaj G, Gressin R, Bouabdallah K, et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: the BENTLY trial. *J Clin Oncol*. 2013;31(1):104-110.
87. Gibson JF, Foss F, Cooper D, et al. Pilot study of sorafenib in relapsed or refractory peripheral and cutaneous T-cell lymphoma. *Br J Haematol*. 2014;167(1):141-144.
88. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet*. 2006;7(8):606-619.
89. Bader AG, Kang S, Zhao L, Vogt PK. Oncogenic PI3K deregulates transcription and translation. *Nat Rev Cancer*. 2005;5(12):921-929.
90. Vivanco I, Sawyers CL. The phosphatidylinositol 3-Kinase AKT pathway in human cancer. *Nat Rev Cancer*. 2002;2(7):489-501.
91. So L, Fruman DA. PI3K signalling in B- and T-lymphocytes: new developments and therapeutic advances. *Biochem J*. 2012;442(3):465-481.
92. Horwitz SM, Porcu P, Flinn I, et al. Duvelisib (IPI-145), a phosphoinositide-3-kinase-δ,γ inhibitor, shows activity in patients with relapsed/refractory T-cell lymphoma [ASH abstract 803]. *Blood.* 2014;124(21)(suppl).
93. Horwitz SM, Porcu P, Flinn I, et al. Duvelisib (IPI-145), a phosphoinositide-3-kinase-δ,γ inhibitor, shows activity in patients with relapsed/refractory T-cell lymphoma: updated phase 1 data [ASH abstract 803]. *Blood.* 2014;124(21)(suppl).
94. Aplidin increases sensitivity to treatment in leukemia and lymphoma cells. *Expert Rev Anticancer Ther*. 2003;3(2):133-134.
95. Erba E, Serafini M, Gaipa G, et al. Effect of aplidin in acute lymphoblastic leukaemia cells. *Br J Cancer*. 2003;89(4):763-773.
96. Depenbrock H, Peter R, Faircloth GT, Manzanares I, Jimeno J, Hanauske AR. In vitro activity of aplidine, a new marine-derived anti-cancer compound, on freshly explanted clonogenic human tumour cells and haematopoietic precursor cells. *Br J Cancer*. 1998;78(6):739-744.
97. Coiffier B, Federico M, Caballero D, et al. Therapeutic options in relapsed or refractory peripheral T-cell lymphoma. *Cancer Treat Rev*. 2014;40(9):1080-1088.
98. Ribrag V, Caballero D, Fermé C, et al. Multicenter phase II study of plitidepsin in patients with relapsed/refractory non-Hodgkin's lymphoma. *Haematologica*. 2013;98(3):357-363.
99. Ishida T, Joh T, Uike N, et al. Defucosylated anti-CCR4 monoclonal antibody (KW-0761) for relapsed adult T-cell leukemia-lymphoma: a multicenter phase II study. *J Clin Oncol*. 2012;30(8):837-842.
100. Ogura M, Ishida T, Hatake K, et al. Multicenter phase II study of mogamulizumab (KW-0761), a defucosylated anti-cc chemokine receptor 4 antibody, in patients with relapsed peripheral T-cell lymphoma and cutaneous T-cell lymphoma. *J Clin Oncol.* 2014;32(11):1157-1163.
101. Zullo KM, Guo Y, Cooke L, et al. Aurora A kinase inhibition selectively synergizes with histone deacetylase inhibitor through cytokinesis failure in T-cell lymphoma. *Clin Cancer Res*. 2015;21(18):4097-4109.
102. Zullo K, Guo Y, Cooke L, et al. The investigational Aurora A kinase inhibitor alisertib exhibits broad activity in preclinical models of T-cell lymphoma and is highly synergistic with romidepsin [ASH abstract 4493]. *Blood.* 2014;124(21)(suppl).
103. Fanale MA, Hagemeister FB, Fayad L, et al. A phase I trial of alisertib plus romidepsin for relapsed/refractory aggressive B- and T-cell lymphomas [ASH abstract 1744]. *Blood.* 2014;124(21)(suppl).
104. Jain S, Jirau-Serrano X, Zullo KM, et al. Preclinical pharmacologic evaluation of pralatrexate and romidepsin confirms potent synergy of the combination in a murine model of human T-cell lymphoma. *Clin Cancer Res*. 2015;21(9):2096-2106.