Belinostat in patients with refractory or relapsed peripheral T-cell lymphoma: a perspective review

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Abstract: Peripheral T-cell lymphoma (PTCL) is a disease with poor prognosis and limited treatment options. Recent advances in cancer biology suggest that PTCL may be characterized by gross epigenetic dysregulation, which may help explain its sensitivity to histone deacetylase (HDAC) inhibitors. HDAC inhibitors have demonstrated significant activity in T-cell neoplasms and recently, the BELIEF trial evaluated belinostat leading to its approval in the US. This review discusses the development of belinostat, its mechanism of action, pivotal clinical trials, drug toxicity and its recent approval for patients with relapsed or refractory PTCL. Key clinical trials covered include phase I/II evaluation of belinostat in hematologic malignancies, cutaneous T-cell lymphoma (CTCL) and PTCL. In addition, the BELIEF trial in PTCL leading to FDA approval of belinostat is reviewed in detail.

Keywords: belinostat, histone deacetylase inhibitors, peripheral T-cell lymphoma, PXD101

Introduction

The peripheral T-cell lymphomas (PTCLs) are a rare and heterogeneous group of mature T-cell lymphomas that are usually characterized by aggressive clinical behavior, and a paucity of salvage therapies, especially in contrast to their B-cell counterparts [Akagi *et al.* 2011; Puig *et al.* 2013; Hamadani *et al.* 2014]. The outcome of frontline chemotherapy regimens has been disappointing, with reported long-term survival of only 20–30% [Hamadani *et al.* 2014]. In one of the largest population registry studies in PTCL patients to date where 84% of patients received either CHOP or CHOEP as initial chemotherapy, 25% of patients developed primary refractory disease with a median overall survival of only 2.5 months [Ellin *et al.* 2014]. Of those who attained a response to induction chemotherapy, 53% relapsed with a median overall survival of only 6 months.

Because of this poor prognosis there is an urgent need to optimize induction and salvage therapies by identifying novel agents active in the disease, and incorporating them into conventional standards of care, or by developing novel platforms. To that end, belinostat recently became the fourth

agent approved for patients with relapsed or refractory PTCLs. Pralatrexate was the first drug approved by the US Food and Drug Administration (FDA) in 2009, followed by romidepsin in 2011, and brentuximab vedotin, which was approved exclusively for patients with relapsed or refractory anaplastic large T-cell lymphoma (Table 1) [Poole, 2014]

HDAC inhibition as a therapeutic target

Histone deacetylases (HDACs) are a group of enzymes which, along with histone acetyltransferases (HATs), regulate the acetylation of histone and nonhistone proteins [Bose *et al.* 2014]. The degree of histone acetylation affects the balance between euchromatin and heterochromatin, which directly affects transcriptional activation. While the steps involved in lymphomagenesis are a complex multistep process, dysregulation of the HAT–HDAC balance has been well established as a significant event in this process, and provides a rationale for utilizing HDAC inhibitors in PTCL [Glozak *et al.* 2005; O'Connor *et al.* 2014]. A total of 18 different HDACs are described, belonging to 4 different classes which can be further differentiated by their zinc dependency.

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Table 1. US Food and Drug Administration (FDA)-approved novel therapies in PTCL.

Drug	Disease	Pivotal Trial	Response Rate (ORR, CR)
Pralatrexate	PTCL	O'Connor <i>et al.</i> (2011)	29%, 11%
Romidepsin	PTCL	Piekarz <i>et al.</i> (2011)	38%, 18%
Brentuximab vedotin	ALCL	Pro <i>et al.</i> (2012)	86%, 57%
Belinostat	PTCL	O'Connor <i>et al.</i> (2013)	26%, 11%

ALCL, angioimmunoblastic T-cell lymphoma; CR, complete remission; ORR, overall response rate; PTCL, peripheral T-cell lymphoma.

Zinc-dependent HDACs encompass class I (HDACs 1, 2, 3 and 8), IIa (HDACs 4, 5, 7 and 9), IIb (HDACs 6 and 10) and IV (HDAC 11) while class III HDACs, otherwise known as sirtuins (SIRT1-7), are dependent on nicotinamide adenine dinucleotide (NAD) [Rosato and Grant, 2005; Bose *et al.* 2014]. HDAC inhibitors have demonstrated efficacy in peripheral and cutaneous T-cell lymphomas but also other hematological and solid organ malignancies [Bolden *et al.* 2006; Juergens *et al.* 2011; Munster *et al.* 2011; Coiffier *et al.* 2012]. While HDAC inhibitors are considered pleiotropic drugs, they have been shown to lower the apoptotic threshold of malignant cells through the down regulation of anti-apoptotic proteins, upregulation of pro-apoptotic proteins, inhibition of DNA repair and induction of DNA damage [Juergens *et al.* 2011]. In addition, they are known to play a role in mediating lethality through cytokinesis failure.

Beyond their effects on the histone–DNA complex, HDAC inhibitors affect the acetylation status of many nonhistone proteins such as chaperones, oncogenic transcription factors and other mediators of signal transduction likely contributing to their antineoplastic effects [Glozak *et al.* 2005].

Many HDAC inhibitors have been studied in hematologic malignancies to date. Amongst the first, was vorinostat, a hydroxamic acid that inhibits both class I and II HDAC enzymes. In a single-arm phase II multicenter trial in patients with relapsed/refractory cutaneous T-cell lymphoma (CTCL), vorinostat demonstrated an ORR of 29.7%, with duration of response of approximately 6 months [Olsen *et al.* 2007]. It was subsequently approved by the FDA for the treatment of patients with refractory and relapsed CTCL in October 2006 [O'Connor *et al.* 2006]. Romidepsin is a cyclic tetrapeptide pan-HDAC inhibitor which primarily functions by inhibiting class I

HDACs with only weak effects on the class IIb HDAC6 [Furumai *et al.* 2002; West and Johnstone, 2014]. It was approved by the FDA for the treatment of patients with relapsed and refractory CTCL in November 2009, and for patients with relapsed and refractory PTCL in June 2011 [Zain and O'Connor, 2010].

Belinostat, N-hydroxy-3-[3-(phenylsulfamoyl) phenyl] prop-2-enamide, is a low-molecular-weight HDAC inhibitor with a sulfonamide–hydroxamide structure. The hydroxamate region of belinostat chelates a zinc ion, which is necessary for activity of the histone deacetylase family of enzymes, similar to vorinostat. Belinostat is a pan-HDAC inhibitor, inhibiting class I, II and IV HDAC isoforms with nanomolar potency [Bolden *et al.* 2006; West and Johnstone, 2014]. In July 2014, the FDA granted accelerated approval to belinostat (BELEODAQTM, Spectrum Pharmaceuticals, Inc.) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) making it the latest HDAC inhibitor to be approved.

Phase I development of belinostat in hematological malignancies

A phase I clinical trial evaluated an intravenous belinostat infusion over 30 minutes on days 1–5 of a 21-day cycle in a sequential dose-escalation design in patients with hematological malignancies [Gimsing *et al.* 2008]. A total of 16 patients with a median of four prior therapies received belinostat at one of three dose levels: 600 mg/m²/day (*n* = 3), 900 mg/m²/day (*n* = 3) and 1000 mg/m²/day (*n* = 10). Except for one case of grade 3 lymphopenia, no other grade 3 or 4 hematological toxicities were noted. The most common grade 3 events were fatigue and neurological symptoms. Of note, and in contrast with other HDAC inhibitor experiences, no cardiac events were appreciated. While no complete remission (CR) or partial remissions (PR) were noted in these heavily pretreated

patients, five patients (31%) achieved stable disease (SD) having received two to nine cycles of treatment. None of the patients in this trial had a diagnosis of T-cell lymphoma.

Although this phase I clinical trial did not identify a maximum tolerated dose (MTD), an experience from a parallel dose-finding study in patients with solid tumors using the same schedule identified the MTD to be 1000 mg/m²/day [Steele *et al.* 2008]. The dose-limiting toxicities (DLTs) identified from the phase I trials in solid tumors were grade 3 fatigue, grade 3 diarrhea, grade 3 atrial fibrillation, and grade 2 nausea/vomiting. This dose became the recommended phase II dose (RP2D) for all future studies going forward.

A second phase I study evaluated an oral formulation of the drug in 28 patients with a median of 5 prior regimens (range 0–13) [Zain *et al.* 2011]. The study included 12 Hodgkin lymphoma patients (HD), 5 mantle cell lymphoma patients, and 11 non-Hodgkin lymphoma patients. Toxicity was evaluated in 28 patients. Grade 3 diarrhea was the dose limiting toxicities which was observed in 9 patients at the 1500 and 2000 mg/day dose levels. Grade 3 thrombocytopenia was seen in 5 patients at doses of 1250 to 1750 mg/day. Of 16 patients evaluable for response, there was 1 CR in a non-Hodgkin lymphoma patient after 2 cycles, 1 PR after 8 cycles in a Hodgkin lymphoma patient, and stable disease was noted in 12 patients (duration: 1–24 cycles). Aside from the 1 CR and 1 PR, 8 patients had SD. The MTD of oral belinostat dose daily for 14 of 21 days among the lymphoma patients was 1500 mg. This was higher than the MTD achieved in patients with solid tumors which was 750 mg per day. These data distinguish belinostat as the only HDAC inhibitor that has multiple potential routes of administration, including intravenous administration, continuous intravenous infusion, and oral administration.

Clinical development in T-cell lymphoma

The first phase II trial was a single-arm study that evaluated the overall response rate (ORR) of belinostat at a dose of 1000 mg/m²/day administered as an intravenous infusion over 30 minutes on days 1–5 of a 21-day cycle in patients with refractory and relapsed CTCL and PTCL patients. The study enrolled a total of 53 patients with refractory and relapsed disease, which included 20 PTCL and 29 CTCL patients. The

20 patients with PTCL [10 PTCL-unspecified (PTCL-U), 3 ALCL, 3 AITL, 3 natural killer [NK]/T-cell lymphoma, and 1 subcutaneous panniculitis-like TCL (SPTCL)] had received a median of 3 prior systemic therapies (range 1–10), and 40% of them had stage IV disease. The ORR was 25% (5/20), which included 2 CR and 3 PR, and the median duration of response was 5 months. In addition, SD was observed in 5 patients with a median duration of 3.5 month. The 29 patients with CTCL [15 mycosis fungoides (MF), 7 Sezary syndrome (SS), 5 non-MF/SS, 2 unclassified] had received a median of 1 prior skin directed therapy (range 0–4) and 3 prior systemic therapies (range 1–9), with 55% of patients having stage IV disease. The ORR was 14% (4/29) among the CTCL patients with 2 CR and 2 PR, with a median duration of response of 9 month. In addition, SD was observed in 17 patients up to 4 months. Hematological toxicity was minimal without any grade 4 events (shift from baseline) with only one patient each experiencing grade 3 neutropenia and grade 3 thrombocytopenia, respectively. No grade 3 QTc prolongation was detected in more than 700 ECGs. Four Grade 3/4 drug-related adverse events (AEs) were reported, including: pruritus, rash/erythema, edema, and a dynamic ileus. These data established the activity of belinostat in PTCL and CTCL, which was felt to be comparable with what has been reported for other HDAC inhibitors in clinical practice. It also highlights the safety profile of the drug especially with regard to hematologic toxicity.

The BELIEF trial was a registration directed phase II study with the primary end point of ORR in patients with relapsed/refractory PTCL. It was a single arm study that evaluated belinostat at a dose of 1000 mg/m²/day administered as an intravenous infusion over 30 minutes on days 1–5 of a 21-day cycle [O'Connor *et al.* 2013]. The study included 129 patients who received a median of 2 prior therapies (1–8). Patients on study received a median of 2 cycles of therapy with belinostat (1–33). The median administered dose intensity was 98%. One and two dose reductions of 25% occurred in 12% and 1% of patients, respectively, due to AEs. Among the 120 evaluable patients with PTCL confirmed by central pathology review (CPGR) (Table 2), the ORR was 26%, which included a CR rate of 11% (*n*=13) and a PR rate of 15% (*n*=18). The median time to response was 5.6 weeks (range 4.3–50.4) with a median duration of response (DoR) of

Table 2. Response rates by T-cell subtype.

Diagnosis	ORR
PTCL-NOS (<i>n</i> = 77)	23%
AITL (<i>n</i> = 22)	46%
ALCL, ALK-negative (<i>n</i> = 13)	15%
ALCL, ALK-positive (<i>n</i> = 2)	0%
Enteropathy-associated TCL (<i>n</i> = 2)	0%
Extranodal NK/TCL, nasal type (<i>n</i> = 2)	50%
Hepatosplenic TCL (<i>n</i> = 2)	0%
PTCL, peripheral T-cell lymphoma; NOS, not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; ALCL, angioimmunoblastic T-cell lymphoma; TCL, T-cell lymphoma; NK, natural killer.	

8.3 months. The longest reported duration of response (DOR) was 29.4 months. Seven patients remained on study in complete response at time of abstract presentation.

An interesting analysis from the BELIEF trial included an analysis of patients with variable platelet counts. In patients who had a platelet count $\geq 100,000/\mu\text{l}$ (*n* = 100), the ORR was 28% including 11% of the patients who attained a CR. Notably, the most frequent ($\geq 5\%$) grade 3–4 treatment emergent AEs were thrombocytopenia (13%), neutropenia (13%), anemia (10%), dyspnea (6%), pneumonia (6%), and fatigue (5%). Discontinuations were due to progression of disease (64%), death (11%), AEs (7%), and patient request (8%). Interestingly, 20 patients with platelet counts between 50,000 and 100,000 were also enrolled. Among these patients, the ORR for this group was 15%. This particular finding demonstrates that even patients with poor marrow reserve and low platelet counts tolerated and benefited from belinostat treatment. Other studies with HDAC inhibitors typically required platelet counts of 100,000 or greater. Another interesting finding from the BELIEF study was the response rate in patients with angioimmunoblastic T-cell lymphoma (AITL). Among 22 patients with

AITL, the ORR was 46% (Table 3). This observation raises the prospect that belinostat may be targeting some discrete biology in AITL that is not being targeted by other HDAC inhibitors. Despite the magnitude of this response, it is important to point out this is still a small number of patients, and the study was not powered to describe differences in response rate between the different subtypes of PTCL.

The BELIEF trial reaffirmed that HDAC inhibitors have a unique single-agent class effect in PTCL. The study supported the finding that this class of drugs produces an ORR in the range of 25–30%, with a highly favorable safety profile

Safety profile

Belinostat was approved as an outpatient intravenous infusion over 30 minutes. No infusion reactions were reported. Common side effects included nausea, fatigue, pyrexia, anemia, and vomiting. The most common serious adverse reactions were pneumonia, pyrexia, infection, anemia, increased creatinine, thrombocytopenia, and multi-organ failure. QTc prolongation is reported at a rate of 11% with grade 3 or 4 reported at a rate of 4%.

Table 3. BELIEF trial efficacy.

All patients	<i>n</i> = 120
Overall response rate	26%
Complete Response	11%
Median progression-free survival	1.6 months
Patients with AITL	
Overall response rate	46%
Median progression-free survival (<i>n</i> = 22)	4.2 months
AITL, angioimmunoblastic T-cell lymphoma.	

Belinostat may cause teratogenicity and thus is not recommended in patients who are pregnant.

While fatal events were rare, three were reported, including: one associated with hepatic failure, one associated with tumor lysis syndrome, and one associated with ventricular fibrillation. It is noted that for the latter case ECG analysis did not identify QTc prolongation [Bosshart, 2003].

Overall, because the BELIEF trial included patients with moderate thrombocytopenia, there is an impression that belinostat may have a more favorable hematologic toxicity, which may bode well when studied in combinations. In the absence of a direct head-to-head comparison between the agents approved for PTCL however, definitive conclusions about the relative safety cannot be made. Clearly, additional clinical experience will clarify the drug's safety profile among the broader spectrum of patients with T-cell lymphoma.

Combination trials

Because HDAC inhibitors appear to synergize with a variety of drugs, HDAC inhibitors lend themselves to combinations with targeted therapies and traditional cytotoxic agents. Paoluzzi and colleagues have demonstrated synergistic cytotoxicity of romidepsin and belinostat in combination with bortezomib in a panel of mantle cell lymphoma cell lines [Paoluzzi *et al.* 2010]. In addition, preclinical experiences have also evaluated the combination of different HDACIs and the DNA methyltransferase (MTase) inhibitor, decitabine, in *in vitro* and *in vivo* models of diffuse large B-cell lymphoma (DLBCL) and PTCL [Kalac *et al.* 2011]. A class effect of the combination was observed, with HDAC inhibitors potently synergizing with decitabine across the spectrum of DLBCL lines studied. This effect was observed even in the cell lines considered relatively resistant to decitabine [Kalac *et al.* 2011]. Clinical trials are now underway to evaluate the combination of various proteasome inhibitors, DNA MTase inhibitors and HDAC inhibitors for the treatment of lymphoma, and PTCL in particular.

HDAC inhibitors have also been shown to modulate a number of pro- and anti-apoptotic proteins. Through the lowering of the apoptotic threshold, HDAC inhibitors also lend themselves

to combination with conventional cytotoxic chemotherapeutic agents as well, a strategy that is being explored in solid tumors and other malignancies, including lymphoproliferative malignancies. Several trials are now underway looking at the combination of HDAC inhibitors with cytotoxic agents and other targeted therapies, including bexarotene and CHOP. The post-marketing commitment of belinostat requires completion of a dose-finding trial of belinostat administered as an intravenous infusion with CHOP chemotherapy, as well as follow-on randomized phase III trials to characterize the comparative efficacy and safety of belinostat in combination with CHOP *versus* CHOP alone.

Conclusion

Belinostat is a next-generation hydroxamic acid HDAC inhibitor. Like other HDAC inhibitors it has demonstrated promising activity in patients with heavily treated PTCL, which has begun to firmly establish the merits of targeting epigenetic functions in these diseases. In comparison to other HDAC inhibitors, belinostat appears to have a highly favorable safety profile, with minimal grade 3 and grade 4 toxicity. It is especially well tolerated in patients with thrombocytopenia with clinical benefit. Although there have been a number of novel therapies approved for patients with relapsed/refractory PTCL, each has its own strengths and limitations. Thus, clinical decisions need to be made on a case-by-case basis after evaluation of the patient's comorbidities and potential toxicity.

Interestingly, in comparison to other HDAC inhibitors, belinostat produced a response rate of 46% in patients with AITL [O'Connor *et al.* 2013]. While the numbers are small, and the study was not powered to determine with confidence belinostat's activity in this sub group of patients, it may be worth pursuing studies of belinostat in patients with AITL. Ongoing combination studies are evaluating the safety and efficacy of integrating belinostat into the upfront CHOP-based treatment platform. The potential for synergy with cytotoxic or targeted agents may guide the way to establish new frontline platforms for the treatment of PTCL and/or superior salvage regimens. Irrespectively, belinostat represents another valuable therapy for patients with refractory or relapsed PTCL.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

- Akagi, T., Takahashi, N., Yamaguchi, K., Ishizawa, K., Murai, K., Tajima, K. *et al.* (2011) Comparison of long-term clinical outcomes of CHOP chemotherapy between Japanese patients with nodal peripheral T-cell lymphomas and those with diffuse large B-cell lymphoma in the study group of the Tohoku Hematology Forum. *J Clin Exp Hematop* 51(1): 29–35.
- Bolden, J., Peart, M. and Johnstone, R. (2006) Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov* 5(9): 769–784.
- Bose, P., Dai, Y. and Grant, S. (2014) Histone deacetylase inhibitor (HDACi) mechanisms of action: emerging insights. *Pharmacol Ther* 143(3): 323–336.
- Bosshart, H. (2003) Interleukin-3 receptors in Hodgkin's disease. *Am J Pathol* 162(1): 355–356; author reply 356–357.
- Coiffier, B., Pro, B., Prince, M., Foss, F., Sokol, L., Greenwood, M. *et al.* (2012) Results from a pivotal, open-label, phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. *J Clin Oncol* 30(6): 631–636.
- Ellin, F., Landstrom, J., Jerkeman, M. and Relander, T. (2014) Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood* 124(10): 1570–1577.
- Furumai, R., Matsuyama, R., Kobashi, N., Lee, K., Nishiyama, M., Nakajima, H. *et al.* (2002) FK228 (depsipeptide) as a natural prodrug that inhibits class I histone deacetylases. *Cancer Res* 62(17): 4916–4921.
- Gimsing, P., Hansen, M., Knudsen, L., Knoblauch, P., Christensen, I., Ooi, C. *et al.* (2008) A phase I clinical trial of the histone deacetylase inhibitor belinostat in patients with advanced hematological neoplasia. *Eur J Haematol* 81(3): 170–176.
- Glozak, M., Sengupta, N., Zhang, X. and Seto, E. (2005) Acetylation and deacetylation of non-histone proteins. *Gene* 363: 15–23.
- Hamadani, M., Abu Kar, S., Usmani, S., Savani, B., Ayala, E. and Kharfan-Dabaja, M. (2014) Management of relapses after hematopoietic cell transplantation in T-cell non-Hodgkin lymphomas. *Semin Hematol* 51(1): 73–86.
- Juergens, R., Wrangle, J., Vendetti, F., Murphy, S., Zhao, M., Coleman, B. *et al.* (2011) Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. *Cancer Discov* 1(7): 598–607.
- Kalac, M., Scotto, L., Marchi, E., Amengual, J., Seshan, V., Bhagat, G. *et al.* (2011) HDAC inhibitors and decitabine are highly synergistic and associated with unique gene-expression and epigenetic profiles in models of DLBCL. *Blood* 118(20): 5506–5516.
- Munster, P., Thurn, K., Thomas, S., Raha, P., Lacevic, M., Miller, A. *et al.* (2011) A phase II study of the histone deacetylase inhibitor vorinostat combined with tamoxifen for the treatment of patients with hormone therapy-resistant breast cancer. *Br J Cancer* 104(12): 1828–1835.
- O'Connor, O., Bhagat, G., Ganapathi, K., Pedersen, M., D'Amore, F., Radeski, D. *et al.* (2014) Changing the paradigms of treatment in peripheral T-cell lymphoma: from biology to clinical practice. *Clin Cancer Res* 20(20): 5240–5254.
- O'Connor, O., Heaney, M., Schwartz, L., Richardson, S., Willim, R., MacGregor-Cortelli, B. *et al.* (2006) Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol* 24(1): 166–173.
- O'Connor, O., Masszi, T., Savage, K., Pinter-Brown, L., Foss, F., Popplewell, L. *et al.* (2013) Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial. *J Clin Oncol* 31(15): abstract 8507.
- O'Connor, O., Pro, B., Pinter-Brown, L., Bartlett, N., Popplewell, L., Coiffier, B. *et al.* (2011) Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *J Clin Oncol* 29(9): 1182–1189.
- Olsen, E., Kim, Y., Kuzel, T., Pacheco, T., Foss, F., Parker, S. *et al.* (2007) Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol* 25(21): 3109–3115.
- Paoluzzi, L., Scotto, L., Marchi, E., Zain, J., Seshan, V. and O'Connor, O. (2010) Romidepsin and belinostat synergize the antineoplastic effect of bortezomib in mantle cell lymphoma. *Clin Cancer Res* 16(2): 554–565.
- Piekarz, R., Frye, R., Prince, H., Kirschbaum, M., Zain, J., Allen, S. *et al.* (2011) Phase 2 trial

of romidepsin in patients with peripheral T-cell lymphoma. *Blood* 117(22): 5827–5834.

Poole, R. (2014) Belinostat: first global approval. *Drugs* 74(13): 1543–1554.

Pro, B., Advani, R., Brice, P., Bartlett, N., Rosenblatt, J., Illidge, T. *et al.* (2012) Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol* 30(18): 2190–2196.

Puig, N., Wang, L., Seshadri, T., al-Farsi, K., Keating, A., Crump, M. and Kuruvilla, J. (2013) Treatment response and overall outcome of patients with relapsed and refractory peripheral T-cell lymphoma compared to diffuse large B-cell lymphoma. *Leuk Lymphoma* 54(3): 507–513.

Rosato, R. and Grant, S. (2005) Histone deacetylase inhibitors: insights into mechanisms of lethality. *Expert Opin Ther Targets* 9(4): 809–824.

Steele, N., Plumb, J., Vidal, L., Tjornelund, J., Knoblauch, P., Rasmussen, A. *et al.* (2008) A phase 1 pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. *Clin Cancer Res* 14(3): 804–810.

West, A. and Johnstone, R. (2014) New and emerging HDAC inhibitors for cancer treatment. *J Clin Invest* 124(1): 30–39.

Zain, J., Foss, F., Diefenbach, C., Petrylak, D., Narwal, A., Neylon, E. *et al.* (2011) Preliminary results of an ongoing phase I trial of oral belinostat a novel histone deacetylase inhibitor in patients with lymphoid malignancies. *Blood (ASH Annual Meeting)* 118(21): Abstr 3710.

Zain, J. and O'Connor, O. (2010) Targeted treatment and new agents in peripheral T-cell lymphoma. *Int J Hematol* 92(1): 33–44.