

# FDA Approval: Belinostat for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma

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## Abstract

On July 3, 2014, the FDA granted accelerated approval for belinostat (Beleodaq; Spectrum Pharmaceuticals, Inc.), a histone deacetylase inhibitor, for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). A single-arm, open-label, multicenter, international trial in the indicated patient population was submitted in support of the application. Belinostat was administered intravenously at a dose of 1000 mg/m<sup>2</sup> over 30 minutes once daily on days 1 to 5 of a 21-day cycle. The primary efficacy endpoint was overall response rate (ORR) based on central radiology readings by an independent review committee. The ORR was 25.8% [95% confidence interval (CI), 18.3–34.6] in 120 patients

that had confirmed diagnoses of PTCL by the Central Pathology Review Group. The complete and partial response rates were 10.8% (95% CI, 5.9–17.8) and 15.0% (95% CI, 9.1–22.7), respectively. The median duration of response, the key secondary efficacy endpoint, was 8.4 months (95% CI, 4.5–29.4). The most common adverse reactions (>25%) were nausea, fatigue, pyrexia, anemia, and vomiting. Grade 3/4 toxicities (≥5.0%) included anemia, thrombocytopenia, dyspnea, neutropenia, fatigue, and pneumonia. Belinostat is the third drug to receive accelerated approval for the treatment of relapsed or refractory PTCL. *Clin Cancer Res*; 21(12); 2666–70. ©2015 AACR.

## Introduction

Peripheral T-cell lymphomas (PTCL) are a rare and heterogeneous group of disorders representing approximately 10% to 15% of all non-Hodgkin lymphomas in North America and have a poor prognosis (1, 2). According to the International T-Cell Lymphoma Project data (1,314 cases from 22 countries worldwide), the most common subtypes were PTCL not otherwise specified (PTCL-NOS, 25.9%), angioimmunoblastic T-cell lymphoma (AITL, 18.5%), natural killer (NK)/T-cell lymphoma (10.4%), adult T-cell lymphoma/leukemia (ATLL, 9.6%), and anaplastic large cell lymphoma [ALCL: anaplastic lymphoma kinase (ALK)-positive, 6.6% and ALK-negative, 5.5%; ref. 3]. PTCL

has an aggressive clinical course with inferior outcomes compared with aggressive B-cell non-Hodgkin lymphomas, and the overall 5-year disease-free survival is less than 30% (except for ALK-positive ALCL; ref. 4).

Although not specifically approved as regimens, commonly used first-line therapies for PTCL include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) and HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with high-dose methotrexate and cytarabine; ref. 5). Relapse is common after initial treatment, and there are few effective options for salvage therapy (6). Stem cell transplantation is a potentially curative treatment option for only a subset of patients. Until recently, pralatrexate and romidepsin were the only two drugs approved for the treatment of relapsed or refractory PTCL; however, from a regulatory standpoint, they are not considered as available therapy because they were approved under the accelerated approval regulations and have not been converted to regular approval (7).

This report summarizes the FDA review of the New Drug Application for belinostat for the treatment of patients with relapsed or refractory PTCL.

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**Note:** This is a U.S. Government work. There are no restrictions on its use.

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## Chemistry

Belinostat (Beleodaq; Spectrum Pharmaceuticals, Inc.) is a histone deacetylase (HDAC) inhibitor with a sulfonamide-hydroxamide structure. The chemical name is (2E)-N-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide. The drug is supplied as a

sterile lyophilized powder containing 500 mg belinostat in a single-use vial for reconstitution. Each vial also contains 1,000 mg L-Arginine, USP as an inactive ingredient. After reconstitution with 9 mL of Sterile Water for injection, it is further diluted with 250 mL of sterile 0.9% sodium chloride injection before intravenous infusion.

## Pharmacology and Toxicology

HDACs catalyze the removal of acetyl groups from the lysine residues of histones. While histones are a principal substrate for HDACs, other nonhistone proteins, including transcription factors, are also targeted by these enzymes. Functional outcomes of HDAC inhibition important to their anticancer mechanisms include apoptosis and cell cycle arrest of some transformed cells. Belinostat shows preferential cytotoxicity toward tumor cells compared with normal cells.

Repeat-dose toxicology studies of up to 24-week duration were conducted in rats and dogs. Toxicities were primarily related to the gastrointestinal system, hematopoietic system (cytopenias), lymphoid system (lymphoid tissue atrophy), genitourinary system, and the site of injection. Cardiovascular toxicities included cardiomyopathy and tachycardia.

Belinostat was positive for genotoxicity in the three assays used. Animal studies to evaluate the reproductive and developmental potential of belinostat were not conducted because belinostat is genotoxic and targets rapidly dividing cells and, therefore, is expected to cause teratogenicity and/or embryo-fetal lethality.

## Clinical Pharmacology

The dose for the phase II PTCL trial was selected using data from two phase I dose-escalation trials in patients with solid tumors and advanced hematologic malignancies. The 1,000 mg/m<sup>2</sup> dose, given on days 1 to 5 of a 21-day cycle, was determined to be the MTD in these phase I trials. It was shown that body surface area–based dosing provides consistent exposure across all body sizes. Dose-dependent acetylation (a pharmacodynamic marker for HDAC enzymatic activity) was observed after the first dose and appeared to plateau at doses of 900 mg/m<sup>2</sup> and above.

*In vitro* studies showed that belinostat is primarily (80%–90%) metabolized by UGT1A1 and to a lesser extent by CYP2A6, CYP2C9, and CYP3A4. The sponsor did not conduct human drug–drug interaction studies to evaluate the influence of liver enzyme inhibitors of UGT1A1, CYP2A6, CYP2C9, and CYP3A4 on the systemic exposure of belinostat. Available data indicate that UGT1A1 inhibitors will likely produce meaningful belinostat exposure increases that could lead to dose-limiting toxicities. In addition, because UGT1A1 is a known polymorphic enzyme with allelic variants that influence enzymatic activity, subjects homozygous for UGT1A1\*28 may have up to 20% greater belinostat exposure than subjects with UGT1A1\*1. Other UGT1A1-reduced function alleles may have a similar impact on belinostat exposure.

Belinostat was shown to inhibit CYP2C8 and 2C9 in *in vitro* studies. However, a pharmacokinetic study in patients with cancer showed that the C<sub>max</sub> and AUC of the CYP2C9 substrate warfarin were similar in the absence and presence of belinostat, indicating that belinostat does not alter the pharmacokinetics of CYP2C8 and CYP2C9 substrates.

Limited data suggest that 40% of the administered belinostat dose was excreted in urine, mostly in the form of metabolites. Human mass balance and hepatic impairment studies are currently ongoing to fully characterize the disposition of belinostat.

## Clinical Trial

### Design

CLN-19 was a single-arm, open-label, multicenter trial in patients with relapsed or refractory PTCL who had received at least one prior systemic therapy. Patients with a platelet count of <50 × 10<sup>9</sup>/L, creatinine clearance < 45 mL/min/1.73 m<sup>2</sup>, or active infection were excluded. The primary efficacy endpoint was overall response rate (ORR), and secondary efficacy endpoints included time to response, duration of response, time to progression, progression-free survival (PFS), and overall survival (OS). Efficacy was determined by a central-blinded independent review committee (IRC) review.

Tumor assessments were made according to the International Working Group criteria. CT scans of the neck, chest, abdomen, and pelvis, and other documentation (i.e., skin lesions using a ruler) were conducted to assess tumor status. Assessments were performed at baseline and, using the same techniques, every 6 weeks for the first 12 months, then every 12 weeks until 2 years from the start of study treatment. Radiological assessments were discontinued at the time of tumor progression or initiation of new anticancer therapy. Patients were followed for survival every 3 months until 2 years from the start of belinostat treatment or until trial closure.

Belinostat (1,000 mg/m<sup>2</sup>) was administered by intravenous infusion over 30 minutes once daily on days 1 to 5 every 3 weeks until disease progression or unmanageable treatment-related toxicities. The infusion time could be extended to 45 minutes if patients experienced pain at the infusion site or other symptoms attributable to the infusion. Belinostat dose delays or modifications were conducted for drug toxicities.

## Results

### Demographics

The trial enrolled a total of 129 patients from 62 sites in 16 countries. Efficacy analyses were based upon the 120 patients who had confirmed diagnoses of PTCL by the Central Pathology Review Group (CPRG) and had received at least one dose of belinostat. Approximately 90% of the patients were from the United States and Europe. The median age was 64 years (range, 29–81), approximately half of the patients were male, and most of patients were white and had Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1. The median number of prior systemic therapies was 2 (range, 1–8), and 37% of patients had received 3 or more prior therapies (Table 1). The majority of patients had PTCL-NOS (64%), followed by ATLL (18%) and ALK-negative ALCL (11%). A few patients had other PTCL subtypes. The majority of patients had stage III (35%) or stage IV (50%) disease.

### Efficacy

The IRC-assessed ORR was 26% with a complete response (CR) rate of 11% and partial response (PR) rate of 15%. The median duration of response (DoR) as evaluated from the first date of

Lee et al.

**Table 1.** Baseline demographics and disease characteristics

Category	Parameter	N = 120
Gender	Male	62 (51.7%)
	Female	58 (48.3%)
Age (years)	Median	64.0
	Range	29–81
	<65	61 (50.8%)
Race	≥65	59 (49.2%)
	White	105 (87.5%)
	Black	7 (5.8%)
	Asian	3 (2.5%)
	Latino	3 (2.5%)
Baseline ECOG score	Other	2 (1.7%)
	0	41 (34.2%)
	1	52 (43.3%)
	2	26 (21.7%)
Lymphoma diagnosis by CPRG	3	1 (0.8%)
	PTCL, NOS	77 (64.2%)
	AITL	22 (18.3%)
	ALCL, ALK-negative	13 (10.8%)
	ALCL, ALK-positive	2 (1.7%)
	Enteropathy-associated T-cell lymphoma	2 (1.7%)
	Extranodal NK/T-cell lymphoma, nasal type	2 (1.7%)
Stage	Hepatosplenic T-cell lymphoma	2 (1.7%)
	I	5 (4.2%)
	II	11 (9.2%)
	III	42 (35.0%)
	IV	60 (50.0%)
Prior systemic therapies	Unknown	2 (1.7%)
	Median (range)	2.0 (1.0–8.0)
	≥3 prior therapies	44 (36.7%)
	Prior CHOP or CHOP-like regimen	116 (96.7%)
	Platinum-containing regimens	38 (31.7%)
	Other multiagent regimens	44 (36.7%)
	Prior pralatrexate	10 (8.3%)
	Corticosteroids	4 (3.3%)
Prior stem cell transplant	Other single-agent regimens	20 (16.7%)
		25 (20.8%)

response to disease progression or death (based on the 31 responding patients) was 8.4 months [95% confidence interval (CI), 4.5–29.4]. Median time to response was 6 weeks (range, 4–50). As assessed by investigators, the ORR was 23% (95% CI, 15.4–31.0), and the CR and PR rates were 9% and 13%, respectively. Table 2 lists the results of the primary and key secondary endpoints.

In subgroup analyses, the ORRs were 35.6% and 16.4% for patients who were ≥65 and <65 years of age, respectively, and 31.0% and 21.0% in females and males, respectively. Among PTCL subtypes, the highest ORR was observed in patients with AITL (45.5%) followed by PTCL-NOS (23.4%). However, due to the small sample size of the subgroups and the nonrandomized design, the ORR in subgroups should be interpreted with caution.

PFS and OS results are not reported here as they are not interpretable in a single-arm trial. ORR generally is the only endpoint that can be reliably assessed in a single-arm trial because the observed effect on tumor size reduction is directly attributed to the drug and is generally not associated with the natural history of the disease (8). In addition, single-arm trials do not allow an evaluation of time-to-event endpoints (i.e., OS and PFS) because they lack information on when the event would have occurred in a group that did not receive the product being tested. In addition, because of variability in the natural history of many forms of cancer, a randomized study is necessary to evaluate time-to-event endpoints (9).

### Safety

The safety analysis population was comprised of 129 patients. The median duration of belinostat treatment was 7 weeks (range, 3–135), the median number of cycles was 2 (range, 1–33), and the median number of belinostat doses received by patients was 10 (range, 1–165). Eighty-eight percent of patients received the drug without dose reductions. Nineteen percent of patients experienced an adverse reaction resulting in belinostat discontinuation. Nine patients (7.0%) died during the trial or within

**Table 2.** Summary of efficacy results

	Efficacy analysis set (N = 120)
Primary endpoint	
ORR by IRC	31 (25.8%)
95% CI	18.3–34.6
CR	13 (10.8%)
95% CI	5.9–17.8
PR	18 (15.0%)
95% CI	9.1–22.7
Secondary endpoints	
Median duration of response (n = 31)	8.4 months
95% CI	4.5–29.4
Median time to response (n = 31)	5.6 weeks
Range	4.3–50.4
Median time to progression (n = 120)	2 months
95% CI	1.5–2.8

**Table 3.** Treatment-emergent adverse reactions occurring in  $\geq 10\%$  of patients by preferred term

MedDRA-preferred term	Full analysis set (N = 129)		
	All grades N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
All TEAEs	125 (96.9)	124 (96.1)	79 (61.2)
Nausea	54 (41.9)	53 (41.1)	1 (0.8)
Fatigue	48 (37.2)	41 (31.8)	7 (5.4)
Pyrexia	45 (34.9)	42 (32.6)	3 (2.3)
Anemia	41 (31.8)	27 (20.9)	14 (10.9)
Vomiting	37 (28.7)	36 (27.9)	1 (0.8)
Constipation	30 (23.3)	29 (22.5)	1 (0.8)
Diarrhea	29 (22.5)	27 (20.9)	2 (1.6)
Dyspnea	28 (21.7)	20 (15.5)	8 (6.2)
Peripheral edema	26 (20.2)	26 (20.2)	0 (0)
Rash	26 (20.2)	25 (19.4)	1 (0.8)
Cough	24 (18.6)	24 (18.6)	0 (0)
Chills	21 (16.3)	20 (15.5)	1 (0.8)
Pruritus	21 (16.3)	17 (13.2)	4 (3.1)
Thrombocytopenia	21 (16.3)	12 (9.3)	9 (7.0)
Increased LDH	20 (15.5)	18 (14.0)	2 (1.6)
Decreased appetite	19 (14.7)	16 (12.4)	3 (2.3)
Headache	19 (14.7)	19 (14.7)	0 (0)
Infusion site pain	18 (14.0)	18 (14.0)	0 (0)
Hypokalemia	16 (12.4)	11 (8.5)	5 (3.9)
Abdominal pain	14 (10.9)	13 (10.1)	1 (0.8)
QT prolongation	14 (10.9)	9 (7.0)	5 (3.9)
Dizziness	13 (10.1)	13 (10.1)	0 (0)
Hypotension	13 (10.1)	9 (7.0)	4 (3.1)
Phlebitis	13 (10.1)	12 (9.3)	1 (0.8)

Abbreviations: LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse reaction.

30 days of the last dose of belinostat unrelated to disease progression: multiorgan failure (2 patients), cardiac failure (2), hepatic failure (1), lung infection (1), gastrointestinal hemorrhage (1), euthanasia (1), and shock (1). However, only the death due to hepatic failure was assessed as related to the study treatment.

The most frequently reported adverse reactions ( $>25\%$ ) were nausea, fatigue, pyrexia, anemia, and vomiting (Table 3). Grade 3/4 toxicities ( $\geq 5.0\%$ ) included anemia (10.9%), thrombocytopenia (7.0%), dyspnea (6.2%), neutropenia (6.2%), fatigue (5.4%), and pneumonia (5.4%). A total of 55 patients (43%) experienced adverse reactions indicative of myelosuppression. The highest incidence overall occurred in the decreased hemoglobin/anemia (33.3%) and decreased platelet count/thrombocytopenia (23.3%) categories. Tumor lysis syndrome occurred in 4 patients (3.1%).

## Discussion

Several HDAC inhibitors have been studied in clinical trials for non-Hodgkin lymphoma. However, only three HDAC inhibitors (romidepsin, vorinostat and belinostat) have received approval. Vorinostat was granted regular approval for third-line cutaneous T-cell lymphoma based on two open-label trials (one was a single-arm trial and the other assessed several dosing regimens) achieving ORRs of 30% (median DoR was not reached but estimated to exceed 6 months) and 24% (median DoR of 106 days).

The accelerated approval of belinostat was based on efficacy and safety data from a single-arm phase II trial. With the approval of belinostat, three drugs are now approved for the treatment of relapsed or refractory PTCL under the accelerated approval regulations: pralatrexate in 2009, romidepsin in 2011, and belinostat in 2014. Although cross-study comparisons must be interpreted with caution, the ORRs were similar for the three drugs: belinostat

(ORR: 26%, CR: 11%, DoR: 8.4 months), pralatrexate [ORR: 27%, CR + CRu (Complete Response unconfirmed): 8%, median DoR: 9.4 months], and romidepsin (ORR: 25%, CR + CRu: 15%, DoR:  $>9.2$  months with responses in 11 of the 19 patients achieving CR + CRu  $>9.2$  months). There are no controlled trials comparing any of these three drugs. Ten patients (8%) in the belinostat trial had been previously treated with pralatrexate and among these patients, only 1 patient (10%) achieved a response (PR).

As noted above, currently there are no therapies that have received full approval for patients with relapsed/refractory PTCL. Given the aggressive nature of PTCL, which has a poor prognosis, this patient population represents an unmet medical need. The key efficacy results of the CLN-19 trial for belinostat were similar to those of pralatrexate and romidepsin that led to accelerated approval. The FDA is willing to approve more than one product under accelerated approval in a specific disease setting, because should one of the products fail to demonstrate clinical benefit in the confirmatory trial, there would be treatments available for patients with relapsed/refractory PTCL. Therefore, accelerated approval was granted for belinostat.

The safety profile of belinostat was considered to be acceptable for a serious and life-threatening disease such as PTCL where there are limited treatment options. In general, the major toxicities of belinostat appeared to be similar to those observed with romidepsin, another HDAC inhibitor. Again, although cross-study comparisons must be interpreted with caution, grade 3/4 hematologic toxicities occurred less often in the belinostat trial than in the romidepsin and pralatrexate trials. It is important to note that CLN-19 was a single-arm trial and therefore the safety profile of belinostat could not be fully evaluated. As a postmarketing requirement (PMR), the safety profile and efficacy of belinostat will be further evaluated in a randomized trial intended to confirm clinical benefit.

Lee et al.

At this time, none of the three drugs approved for PTCL under the accelerated approval regulation have been converted to regular approval. As both pralatrexate and belinostat are marketed by the same company, it was determined that a single trial would be the optimal path forward to expedite the fulfillment of PMRs for both drugs. Thus, the FDA replaced the existing PMRs for pralatrexate with the following clinical trial that could also fulfill the PMR for belinostat: "A Phase 3, Randomized, Open-Label, Study Comparing the Efficacy and Safety of Beleodaq-CHOP or Foflotyn-CHOP versus CHOP Regimen Alone in Newly Diagnosed Patients with Previously Untreated Peripheral T-Cell Lymphoma." In this trial, the primary efficacy endpoint is PFS, and the key secondary efficacy endpoints are OS, ORR, and DoR comparing the clinical activity of each of the drug combinations relative to a shared control arm and not the relative activity of each of these drug combinations to one another. A separate phase I dose escalation trial with each drug combination will be conducted before the phase III trial to establish the optimal and safe dose of each drug to be used in combination with the CHOP regimen.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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