Phase II Study of Belinostat in Patients With Recurrent or Refractory Advanced Thymic Epithelial Tumors

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See accompanying article on page 2060

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ABSTRACT

Purpose

Thymic epithelial tumors are rare malignancies, and there is no standard treatment for patients with advanced disease in whom chemotherapy has failed. Antitumor activity of histone deacetylase (HDAC) inhibitors in this disease has been documented, including one patient with thymoma treated with the pan-HDAC inhibitor belinostat.

Patients and Methods

Patients with advanced thymic epithelial malignancies in whom at least one line of platinum-containing chemotherapy had failed were eligible for this study. Other eligibility criteria included adequate organ function and good performance status. Belinostat was administered intravenously at 1 g/m² on days 1 to 5 of a 21-day cycle until disease progression or development of intolerance. The primary objective was response rate in patients with thymoma.

Results

Of the 41 patients enrolled, 25 had thymoma, and 16 had thymic carcinoma; patients had a median of two previous systemic regimens (range, one to 10 regimens). Treatment was well tolerated, with nausea, vomiting, and fatigue being the most frequent adverse effects. Two patients achieved partial response (both had thymoma; response rate, 8%; 95% CI, 2.2% to 25%), 25 had stable disease, and 13 had progressive disease; there were no responses among patients with thymic carcinoma. Median times to progression and survival were 5.8 and 19.1 months, respectively. Survival of patients with thymoma was significantly longer than that of patients with thymic carcinoma (median not reached v 12.4 months; $P = .001$). Protein acetylation, regulatory T-cell numbers, and circulating angiogenic factors did not predict outcome.

Conclusion

Belinostat has modest antitumor activity in this group of heavily pretreated thymic malignancies. However, the duration of response and disease stabilization is intriguing, and additional testing of belinostat in this disease is warranted.

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INTRODUCTION

Thymic epithelial malignancies are rare tumors, with an incidence of 0.15 per million person-years,¹ yet they represent 50% of anterior mediastinal tumors.² Little is known about the biology of these tumors, which are usually relatively indolent, with overall 5-year survival rates higher than 50% in surgical series.² Surgery is the mainstay of treatment for these tumors, and stage and completeness of resection are major prognostic factors.³ WHO histologic classification has also been shown to be important in determining prognosis, with thymic carcinoma having a significantly worse prognosis than thymoma.³ Patients who present with advanced disease or large

inoperable mediastinal masses, in addition to the 10% to 30% who experience recurrence despite radical surgery, usually undergo chemotherapy. There are several active regimens, most of which contain cisplatin, with response rates varying from 30% to 70%.³ Unfortunately, patients with advanced disease are not cured by chemotherapy, even if response rates are high, and duration of responses is long. There is no standard treatment for thymic malignancies after failure of platinum-based chemotherapy. Few phase II studies have been performed in patients with this disease because of its rarity. A response rate of approximately 20% has been demonstrated with pemetrexed in patients with recurrent thymic malignancies,⁴ whereas epidermal

growth factor receptor and c-kit tyrosine kinase inhibitors have failed to show activity in phase II studies,³ which can be explained by the rarity of mutations in these genes.^{5,6}

There is a need to test novel agents in thymic malignancies, possibly on the basis of a better understanding of the biology of the disease. Histone deacetylases (HDACs) can regulate expression of tumor suppressor genes and activities of transcriptional factors involved in cancer initiation and progression through alteration of either DNA or the structural components of chromatin.⁷ Gene repression through acetylation has been clinically validated with several inhibitors of HDACs. Vorinostat and depsipeptide have recently been approved by the US Food and Drug Administration for the treatment of cutaneous T-cell lymphoma. Several other inhibitors are currently being developed. Belinostat is a hydroxamic acid pan-HDAC inhibitor presently undergoing phase II studies in several malignancies. In a phase I study of this agent, one patient with thymoma had a minor response that lasted for 17 months while receiving treatment.⁸ In general, the drug is well tolerated. We report results from a phase II study of belinostat in patients with recurrent or refractory thymic epithelial malignancies.

PATIENTS AND METHODS

Eligibility criteria included histologically confirmed advanced thymoma or thymic carcinoma not amenable to potentially curative therapies, disease progression after failure of at least one prior line of platinum-based chemotherapy, age older than 18 years, life expectancy more than 3 months, measurable disease according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria,⁹ Eastern Cooperative Oncology Group performance status of 2 or greater, and adequate organ and bone marrow function. Repeated demonstration of a corrected QT (QTc) interval of more than 500 ms and long QT syndrome were exclusion criteria. No major surgery, radiotherapy, or systemic therapy was permitted up to 28 days before enrollment, and any residual toxicity had to have been resolved. Patients with stable and treated brain metastases and patients receiving steroids for myasthenia gravis or other autoimmune disorders were permitted to enroll. All patients provided written informed consent.

Belinostat was diluted in 250 mL normal saline and infused intravenously over 30 minutes through a central venous catheter on days 1 to 5, every 21 days. After 12 cycles of treatment, patients were offered treatment every 4 weeks. Treatment was continued until disease progression or development of intolerable toxicity. Dose modifications were performed if patients developed severe toxicities.

Assessment of disease extent at baseline was requested using computed tomography scans of the chest, abdomen, and pelvis; [¹⁸F]fluorodeoxyglucose-positron emission tomography scans and additional imaging were recommended as required for proper assessment. Electrocardiograms, blood cell counts, and chemistries were also performed before registration. Blood cell counts were initially repeated weekly, but because no hematologic toxicity was observed, the protocol was amended to allow performance of blood cell counts before every cycle (as with blood chemistries) after 19 patients had been recruited. An electrocardiogram was performed every cycle at the end of belinostat infusion on day 5, and the need for dose modification for the subsequent cycles was determined. Asymptomatic increase of QTc more than 500 ms required 25% dose reduction once QTc returned to less than 500 ms. Dose reductions were allowed twice. Assessment of response was performed every two cycles according to RECIST criteria.⁹ After 12 cycles, computed tomography scans were repeated every three cycles. Histology was determined according to WHO classification,¹⁰ and central review was required. Assessment of adverse effects was performed according to Common Terminology Criteria of Adverse Events (version 3.0).

Pharmacodynamic Analyses: Protein Acetylation and Peripheral Blood Mononuclear Cell Immune Subsets

Whole blood samples were collected in CPT tubes with sodium citrate (BD Vacutainer CPT Tubes; BD Biosciences, San Jose, CA) on day 1 of cycle one, 1 hour after belinostat dosing on day 3 of cycle one, and before belinostat dosing on day 1 of cycle two. Mononuclear cells were obtained by Ficoll density gradient centrifugation (Ficoll-Paque PREMIUM; GE Healthcare, Waukesha, WI), and the cells were viably frozen until analysis.

Analysis of global protein and tubulin acetylation was performed by multiparameter flow cytometry on an LSR II flow cytometer (BD Biosciences), and data were analyzed using FlowJo software (Tree Star, Ashland, OR), as described by Chung et al.¹¹ Peripheral blood mononuclear cells (PBMCs) were analyzed for immune subsets, including B cells (CD19), T cells (CD3), monocytes (CD14), and regulatory T cells (Tregs; CD4⁺25^{hi}Foxp3⁺). For determination of cell lineage-specific acetylation, the cells were first stained for the surface lineage marker and then fixed, permeabilized, and stained for acetylated lysine or acetylated tubulin.

Circulating Angiogenic Markers

Blood was collected in ethylenediaminetetraacetic acid-containing collection tubes at baseline, day 3 of cycle one, day 1 of cycle two, and end of study. The plasma samples were collected and tested in duplicates. After centrifugation, the plasma was aliquoted, immediately frozen, and stored at -80°C. Analyses were performed on vascular endothelial growth factor (VEGF), placental-derived growth factor (PlGF), basic fibroblast growth factor (bFGF), and VEGF receptor 1 (sVEGFR1) using assay plates from Meso-Scale Discovery (Gaithersburg, MD). The concentrations of cytokines were determined with recombinant standards and expressed as pg/mL. The data were subsequently entered into Prism (GraphPad, La Jolla, CA) to generate median values with interquartile ranges. Comparisons between different time points with pretreatment values were made using paired *t*-test.

Statistics

The major end point of our study was response rate in patients with thymoma. Secondary end points were safety, duration of response, time to progression (TTP), progression-free survival, and overall survival (OS). Simon's minimax design was used. Sixteen patients with thymoma were to be treated initially; if at least two responses were observed, the plan was to continue accrual until 25 patients were enrolled. If there were two to four total responses among 25 patients, it would be concluded that belinostat did not demonstrate activity sufficient to continue with development. If five or more responses were observed among 25 patients, it would be concluded that belinostat demonstrated a response rate consistent with 30% and greater than 10%, and additional investigation would be warranted. No statistical considerations were made initially for thymic carcinoma, because tumors of this sort are exceedingly rare. However, we had an unexpectedly high accrual of patients with thymic carcinoma and decided to halt accrual after the first 16 patients did not show objective response. TTP and OS were calculated using the Kaplan-Meier method, starting from the first day of treatment to progression, death, or last contact. Survival curves were compared by log-rank test (SPSS for Windows version 15.0; SPSS, Chicago, IL).

RESULTS

Between December 2007 and January 2010, 41 patients were enrolled from two centers; 25 had thymoma, and 16 had thymic carcinoma. Patient characteristics are summarized in Table 1. Two significant differences between patients with thymoma and thymic carcinoma were that anthracyclines were administered less frequently to patients with thymic carcinoma (Fisher test *P* = .022), and four patients with thymoma versus none with thymic carcinoma had myasthenia gravis (likelihood ratio *P* = .040).

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Total No. of Patients (N = 41)	Patients With Thymoma (n = 25)	Patients With Thymic Carcinoma (n = 16)
Age, years			
Median	53	51	55
Range	23-83	23-73	36-83
Sex			
Male	20	10	10
Female	21	15	6
ECOG PS			
0	12	8	4
1	28	16	12
2	1	1	
Race			
White	35	22	13
Black	4	3	1
Asian	2	0	2
Metastatic sites			
Median	3	3	3.5
Range	1-8	1-7	1-8
Intrathoracic sites only	18	12	6
Extrathoracic sites (with or without intrathoracic sites)	23	13	10
Histology			
B1		4	
B2		7	
B2/B3		2	
B3		7	
B unspecified		1	
Not otherwise specified		4	3
Poorly differentiated			7
Squamous cell carcinoma			4
Basaloid			1
Neuroendocrine carcinoma			1
Paraneoplastic syndromes			
Myasthenia gravis	4	4	
Shulman syndrome	1	1	
Prior systemic therapy			
No. of regimens			
Median	2	2	2
Range	1-10	1-8	1-10
≥ 6 regimens	4	3	1
Anthracyclines	25	19	6
Prior chest radiotherapy	28	16	12
Prior surgery			
Radical	19	14	5
Debulking	6	3	3
Biopsy	16	8	8

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

Treatment Outcomes

At the time of this analysis (July 2010), three patients with stable disease (SD) were still receiving treatment (cycles 13, 16, and 18). Reasons for stopping treatment included progression in 28 patients, patient choice in seven, and complications in three (ie, polymyositis in one,¹² sepsis in one, and QTc prolongation in one). A total of 282 cycles have been administered to date (mean, 6.9 per patient; Table 2). Eleven patients received 12 or more cycles. Major adverse effects are listed in Table 3. Toxicity was mild; four patients had hypotension and required the infusion rate to be slowed; hypotension was symptomatic in two patients (ie, blood pressure decreased within minutes of start of infusion and normalized within 10 to 20 minutes after stopping infu-

sion). QTc prolongation was never clinically significant. Dose reductions were applied in seven patients (three as a result of QTc prolongation [per protocol] and one each as a result of dyspnea, nausea, syncope, and infusion reaction).

Forty patients were evaluable for response. One was not evaluable because the patient withdrew consent after only one cycle. Outcomes classified on the basis of histology are reported in Table 2. Partial responses were observed in two patients with thymoma; both were white men with performance status of 1 who had undergone debulking surgery, chest irradiation, and five and two prior lines of systemic therapy, respectively, and had intrathoracic disease only. Histology was B2/B3 in one patient and B3 in the other. They progressed at 391

Table 2. Major Treatment Outcomes

Outcome	Total No. of Patients	Patients With Thymoma	Patients With Thymic Carcinoma
Response			
Partial response	2	2	0
Stable disease	25	17	8
Progression	13	5	8
Not evaluable	1	1	0
Response rate, %	5	8	0
95% CI	1.4 to 16.5	2.3 to 25.9	0 to 19.4
Disease control, %	68	79	50
95% CI	53 to 82	59.5 to 90.8	25.5 to 74.5
Median time to progression, months	5.8	11.4	2.7
95% CI	2.8 to 8.8	2.2 to 20.6	0.9 to 4.6
Progression free at 6 months, %	46	61	25
Median survival, months	19.2	NR*	12.4
95% CI	14.9 to 23.4		9.8 to 14.9
1-year survival, %	69	77	55
2-year survival, %	42	66	0
Median No. of cycles	4	8	4
Range	1-21	1-21	1-16

Abbreviation: NR, not reached.

*At 29.2 months.

and 378 days from start of treatment, received 17 and 19 cycles of belinostat, and were alive at more than 829 days from start of treatment, respectively. One response is shown in Appendix Figure A1 (online only). Overall SD was observed in 25 patients and progressive disease in 13. Among patients with thymoma, the response rate was 8% (95% CI, 2.2% to 25%) and median TTP was 11.4 months; OS was not reached at 29.3 months. At 6 months, 61% of patients had not

progressed, and at 12 months, 46% had not progressed. Patients with thymic carcinoma had significantly shorter TTP and OS than those with thymoma. TTP and OS curves for the whole population and by histology are depicted in Figures 1A to 1F.

Clinical Predictors of Response and Survival

Of all potential predictors of response and survival analyzed (ie, sex, performance status, paraneoplastic syndromes, disease extent, prior surgery, and prior chest irradiation), the only factor that predicted significantly for better disease control (partial response plus SD) was the presence of intrathoracic disease only, which also significantly predicted longer TTP and survival (Table 4). This was true for patients with thymoma and thymic carcinoma for both TTP ($P = .009$) and OS ($P = .012$). Patients with a performance status of 0 survived significantly longer than those with worse performance status, but TTP was not significantly better. Figures 1E and 1F show TTP and OS for patients with only intrathoracic disease versus those with extrathoracic disease (with or without intrathoracic disease).

Pharmacodynamic Analyses

No marker has yet been shown to predict response to HDAC inhibitors. We measured total protein and tubulin-specific hyperacetylation as markers of target modulation in PBMCs.¹¹ Because thymic epithelium is critical for T-cell maturation, including maturation of natural Tregs, and HDAC and protein deacetylase inhibitors increase the suppressive functions of Foxp3⁺Treg,¹³ and because of the increased incidence of autoimmunity in patients with thymoma and the critical role of Tregs in regulation of autoimmunity,¹⁴⁻¹⁶ we measured Treg number and surface phenotype. HDAC inhibitors have been shown to inhibit angiogenesis by repressing hypoxia-induced VEGF^{17,18}; therefore, we also assessed plasma angiogenic factors.

Table 3. Adverse Effects Grade 2 or Higher*

Adverse Effect	Grade		
	2	3	4
Injection site irritation	4		
Hypotension	2	2	
Thrombocytopenia	1		
Allergy	1		
Vomiting	1		
Nausea	3		
Anorexia	3		
Fatigue	1		
QTc prolongation	8	5	
Leukopenia	3		
Neutropenia	2		
Lymphopenia	4	4	1
Anemia	3		
Infection	2	1	
Fever	2		
Transaminases	1		
Hypophosphatemia	1		
Hyperesthesia	1		
Weight gain	1		
Pain	1		

Abbreviation: QTc, corrected QT.

*Worst toxicity per patient over all cycles.

Fig 1. Time to progression (TTP) in (A) the overall population and (B) patients with thymoma and thymic carcinoma. Overall survival (OS) in (C) the overall population and (D) patients with thymoma and thymic carcinoma. (E) TTP and (F) OS in patients with intrathoracic disease only v patients with extrathoracic disease (with or without intrathoracic sites).

Protein Acetylation

As shown in Figure 2A, 37 of 37 patients responded with global protein hyperacetylation. Response was higher 1 hour after infusion on day 3 of cycle one than on day 1 of cycle two before infusion. This result is consistent with belinostat pharmacokinetics.⁸ When analyzed for tubulin acetylation, 35 of 37 patients responded, with the same kinetics (Fig 2B). Maximum-fold increase and median-fold increase in acetylated lysine was nine-fold and two-fold ($P < .001$), respectively, and maximum-fold increase and median-fold increase in acetylated tubulin was 18-fold and four-fold ($P < .001$), respectively. Degree of hyperacetylation did not correlate with response, survival, or toxicity. In addition, there were variations in acetylation among the immune subpopulations (ie, monocytes generally had higher basal acetylation and lower magnitude of response than lymphocyte populations [data not shown]).

Tregs

Comparing day 3 of cycle one with baseline, there was no consistent trend in Treg number; in contrast, a majority of patients

showed an increase in human leukocyte antigen (HLA) –DR⁺Treg (data not shown). Although there was no correlation with response, higher Treg numbers were significantly associated with poorer performance status ($P = .006$), thymic carcinoma histology ($P = .006$), extrathoracic disease ($P = .009$), and shorter TTP ($P = .001$). High Treg numbers were significantly correlated with lower lymphocyte count ($P < .001$).

Circulating Angiogenic Markers

Previous preclinical studies have suggested that HDAC inhibitors may inhibit tumor angiogenesis.¹⁹ Our results show that belinostat treatment had significant effect on plasma PlGF and b-FGF (Appendix Table A1, online only). Higher plasma VEGF and b-FGF were associated with poorer performance status ($P = .007$ and $P < .001$, respectively) and extrathoracic disease ($P = .028$ and $P = .042$, respectively), but there was no correlation with response, survival, or toxicity.

Table 4. Parameters Affecting Response, TTP, and OS

Characteristic	Disease Control Rate	Median TTP (months)	Median OS (months)
Sex			
Female	15 of 20	6	19.2
Male	12 of 20	3.3	17.1
<i>P</i>	.311	.679	.481
Histology			
Thymoma	19 of 24	11.4	NR*
Thymic carcinoma	8 of 16	2.7	12.4
<i>P</i>	.054	.006	.001
ECOG PS			
0	8 of 11	14.2	NR*
1-2	19 of 29	3.3	16.7
<i>P</i>	.189	.144	.040
Disease extension			
Intrathoracic	16 of 18	12.6	NR†
Extrathoracic (± intrathoracic)	11 of 22	1.9	12.4
<i>P</i>	.009	.008	.021
Prior surgery			
Biopsy	9 of 15	2.8	20.1
Debulking	3 of 6	1.9	NR‡
Resection	15 of 19	7.3	17.1
<i>P</i>	.308	.139	.694
Prior chest radiotherapy			
Yes	7 of 12	1.6	19.1
No	20 of 28	6	NR‡
<i>P</i>	.657	.452	.478

Abbreviations: TTP, time to progression; OS, overall survival; NR, not reached; ECOG PS, Eastern Cooperative Oncology Group performance status.

*At 29.2 months.

†At 27.8 months.

‡At 27.9 months.

DISCUSSION

To our knowledge, this is one of the largest phase II studies of a novel agent ever tested in advanced recurrent thymic epithelial malignancies. Treatment with belinostat resulted in only two objective responses among patients with thymoma but none among those with thymic carcinoma. Treatment was well tolerated, and 27% of patients received 12 or more cycles. The large number of patients with SD may be partially explained by the relatively indolent nature of

thymoma; however, it should be noted that all patients had demonstrated progressive disease at enrollment, and in most patients, multiple lines of prior systemic treatment had failed. In future trials in recurrent and refractory disease, use of progression-free survival may be more appropriate.

In our initial statistical considerations, we aimed for a high response rate. However, this class of agents does not produce as high response rates in solid tumors as single agents; rather, this class has a disease-stabilizing effect. Indeed, TTP was almost 1 year in patients

Fig 2. Global protein and tubulin acetylation in patient peripheral blood mononuclear cells (PBMCs). PBMCs were isolated at day 1 of cycle one preinfusion (C1D1 pre), day 3 of cycle one 1 hour postinfusion (C1D3 post), and day 1 of cycle two preinfusion (C2D1 pre). PBMCs were viably frozen, thawed, and stained for (A) acetylated lysine and (B) acetylated tubulin and analyzed by flow cytometry. Fluorescence intensity was normalized to C1D1 preinfusion. Line graphs show fold change at C1D3 and C2D1 for (A) global protein acetylation and (B) tubulin acetylation.

with thymoma. This compares favorably with other studies in this patient population. However, there are inherent limitations when making comparisons with other phase II studies, because there are only sparse data on TTP, and there is substantial heterogeneity in disease histology, burden of disease, and prior treatment between studies. A phase II study of octreotide with or without prednisone reported a response rate of 10.5% with octreotide alone and 31.6% in 38 evaluable patients with octreotide-positive imaging, who were subsequently treated with octreotide and prednisone. TTP for thymoma and thymic carcinoma was 8.8 and 4.5 months, respectively, and OS was not reached at 50 and 23.4 months, respectively.²⁰ In this study, however, eight (21%) of 38 patients had received more than two prior treatment regimens, and seven patients had received no prior systemic therapy. Furthermore, there were only five patients with thymic carcinoma, and extrathoracic disease was present in a minority of cases. In a phase II study of pemetrexed, four responses were observed in patients with thymoma out of 23 evaluable patients (11 had thymic carcinoma). TTP and OS were 45.4 and 5.1 weeks in patients with thymoma and thymic carcinoma, respectively.⁴ Our results compare favorably with this series, in which patients had baseline characteristics similar to our patients. In our study, despite heterogeneity in terms of histology, prior therapy, and presentation, we were able to demonstrate a significant impact on outcome on the basis of histology (thymoma *v* thymic carcinoma) and localization of disease (intrathoracic only *v* extrathoracic).

Patients with thymic carcinoma have worse prognosis than patients with thymoma,²¹ but it is of interest to be able to demonstrate this difference in patients whose disease is far advanced. This study demonstrates that intrathoracic localization of disease is more favorable than disease localization outside the chest cavity. Thymoma tends to remain localized in the chest for a long time and rarely metastasizes to extrathoracic organs. Pleural localization and dissemination into the lung at a later time are the most common manifestations of thymoma progression.²¹ In contrast, thymic carcinoma is more aggressive and tends to metastasize to extrathoracic organs more frequently.²²

Treatment with belinostat was well tolerated, and only a few patients needed dose reductions. QTc prolongation was the reason for dose reduction in three patients, but this was not symptomatic and did not require treatment. Cardiotoxicity has been an important adverse effect in this class of agents, particularly with depsipeptide.²³ In follow-up studies with belinostat, QTc prolongation will need to be monitored carefully.

We assessed a number of pharmacodynamic markers to help identify patients who may derive the most benefit from treatment with HDAC inhibitors. HDAC inhibitors induce hyperacetylation of more than 100 proteins; therefore, we used multiparameter flow cytometry, which detects global protein acetylation rather than just histone acetylation.¹¹ All patients demonstrated protein and tubulin hyperacetylation in PBMCs at the day 3 time point. Unfortun-

nately, hyperacetylation was not correlated with response, TTP, or OS.

Treg suppressor function is heightened in response to HDAC inhibitors *in vitro* and *in vivo* in mice and *in vitro* in humans.¹³ Recently, it was observed that human Tregs are functionally and phenotypically diverse. Expression of HLA-DR has been described as a marker of enhanced Treg suppressive function. Both *ex vivo*-isolated and *in vitro*-generated HLA-DR⁺Tregs are more efficient at suppressing immune response than HLA-DR⁻Tregs.²⁴ In our study, in a majority of patients, expression of HLA-DR was upregulated on the Treg population. Of interest is our finding of a correlation of high Treg numbers with patient characteristics of poor prognosis and shorter TTP. We also showed evidence of changes in circulating PlGF and b-FGF after treatment with belinostat and an association of higher VEGF and b-FGF levels with poor prognostic characteristics. However, no angiogenesis marker was associated with treatment outcome.

In conclusion, our study demonstrates a potential stabilizing effect of belinostat in patients with thymoma, which cannot solely be explained by the relatively indolent behavior of thymoma. Although the number of objective responses is low, we believe that this agent deserves additional investigation, perhaps in combination with chemotherapy. Synergy between belinostat and several chemotherapeutic agents has been demonstrated in preclinical models, and clinical studies of combinations with chemotherapy are under way in various malignancies.²⁵ We recently initiated a phase I/II study of the cyclophosphamide, doxorubicin, and cisplatin regimen plus belinostat in patients with advanced thymic malignancies who have not received prior chemotherapy (ClinicalTrials.gov identifier: NCT01100944).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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