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Research Article

Cancer Therapy: Clinical

A phase I/II multicenter, open-label study of the oral histone deacetylase inhibitor abexinostat in relapsed/refractory lymphoma

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Statement of translational relevance

Inhibition of histone deacytelases (HDACs) has emerged as a promising strategy in hematologic malignancies. Abexinostat is a novel, oral, broad-spectrum phenyl hydroxamic acid-based HDAC inhibitor that has demonstrated preclinical activity in lymphoma cell lines and animal models. This study established the appropriate dose and schedule for use in patients with non-Hodgkin lymphoma. An intermittent dosing schedule was used to achieve good tolerability even during prolonged drug administration. Incidence of higher grade hematologic adverse events and cardiac toxicities were modest and overall encouraging among established agents of this class. Additionally, abexinostat was particularly efficacious in relapsed/refractory follicular lymphoma with prolonged tumor control ≥18 months in most responders. Further evaluation of this agent as a single-agent therapy and in combination is warranted and underway in several tumor types.

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Abstract

Purpose: Additional targeted therapies are needed for the treatment of lymphoma. Abexinostat is an oral pan-histone deacetylase inhibitor (HDACi) displaying potent activity in preclinical models. We conducted a multicenter phase I/II study (N=55) with single-agent abexinostat in relapsed/refractory lymphoma.

Experimental Design: In phase I, 25 heavily pretreated patients with any lymphoma subtype received oral abexinostat ranging from 30-60 mg/m^2 twice daily 5 days/week for 3 weeks or 7 days/week given every other week. Phase II evaluated abexinostat at the maximum tolerated dose in 30 patients with relapsed/refractory follicular lymphoma (FL) or mantle cell lymphoma (MCL).

Results: The recommended phase II dose was 45 mg/m^2 twice daily (90 mg/m^2 total), 7 days/week given every other week. Of the 30 FL and MCL patients enrolled in phase II, 25 (14 FL, 11 MCL) were response-evaluable. Tumor size was reduced in 86% of FL patients with an investigator-assessed ORR of 64.3% for evaluable patients (intent-to-treat [ITT] ORR 56.3%). Median duration of response was not reached, and median progression-free survival (PFS) was 20.5 months (1.2-22.3+). Of responding FL patients, 89% were on study/drug >8 months. In MCL, the ORR was 27.3% for evaluable patients (ITT ORR 21.4%), and median PFS was 3.9 months (range, 0.1-11.5). Grade 3-4 treatment-related adverse events (phase II) with ≥10% incidence were thrombocytopenia (20%), fatigue (16.7%), and neutropenia (13.3%) with rare QTc prolongation and no deaths.

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Conclusions: The pan-HDACi, abexinostat, was very well tolerated and had significant clinical activity in FL, including highly durable responses in this multiply relapsed population.

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Introduction

Epigenetic modulation by histone deacetylation plays a critical regulatory role in normal cell processes and has been implicated in cancer development and progression.(1, 2) Histone deacetylases (HDAC) and histone acetylases can be aberrantly expressed or regulated in malignant tissues, resulting in inhibition of certain tumor suppressor genes and development of malignancy. HDAC inhibitors (HDACi) promote an open chromatin structure by allowing the continued presence of acetyl groups resulting in transcription of relevant tumor suppressor genes that may favor apoptosis. Clinically, inhibition of HDAC has shown promise for the treatment of B-cell (3) and T-cell lymphomas.(4) The HDAC inhibitors vorinostat, romidepsin, and belinostat are FDA-approved in cutaneous T-cell lymphoma (CTCL), CTCL or peripheral T-cell lymphoma (PTCL), and PTCL, respectively.(5, 6) There remains an unmet need for additional targeted therapeutic options for the treatment of patients with relapsed/refractory lymphoma.

The novel HDACi abexinostat is an oral broad-spectrum phenyl hydroxamic acid-based compound being evaluated in the treatment of neoplastic diseases. Abexinostat treatment of non-Hodgkin lymphoma (NHL) cell lines (7) resulted in dose-dependent apoptosis, G0/G1 arrest, and decreased S-phase and increased p21 protein expression. Abexinostat-induced cell death occurred through caspase-8 and the Fas-associated death domain, and was associated with a prominent increase in reactive oxygen species .(8) Similar apoptotic responses were observed in neuroblastoma and soft tissue sarcoma models.(9-11) Abexinostat also affects

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recombination by reducing RAD51, a recA homolog that binds single-stranded DNA-forming nucleoprotein filaments essential for recombination repair.(12, 13)

Based in part on these preclinical findings, a phase I/II clinical trial was initiated with abexinostat in patients with relapsed/refractory lymphoma. The phase I study examined safety, pharmacokinetics, and pharmacodynamics of different abexinostat treatment schedules in multiple lymphoma subtypes. Following identification of the appropriate dosing schedule, and based on early efficacy signals, a phase II extension component was completed in patients with relapsed/refractory follicular lymphoma (FL) and mantle cell lymphoma (MCL).

Materials and methods

Study design

This phase I/II study (NCT00724984) was conducted at seven centers across the United States in accordance with Good Clinical Practice guidelines, as provided by the International Conference on Harmonisation and principles of the Declaration of Helsinki. The institutional review board at each site approved the study. All patients provided written informed consent. S.B., L.I.G., J.Y., Y.L., T.G., and N.L.B analyzed the data and all authors had access to primary clinical trial data.

Patients received abexinostat (PCI-24781/S78454) capsules orally twice daily (approximately 4-6 hours apart) at 30, 45, and 60 mg/m^2 (corresponding to total doses of 60, 90, and 120 mg/m^2 per day, respectively). Dosing at the 4-6 hour window was based upon observed improved preclinical effectiveness and the half-life of abexinostat. Two possible 4-week dosing cycle schedules were explored: 5

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days per week for the first 3 weeks [Days 1-5, 8-12, 15-19]) and an alternative dosing schedule, 7 days every other week [Days 1-7, 15-21]). Please see ***Supplemental Table 1*** on for details of the dosing schedule. Treatment continued until disease progression (PD), unacceptable toxicity, or patient or investigator decision to end therapy. Dose escalation continued until maximum tolerated dose (MTD) was achieved based on protocol-defined dose-limiting toxicities (DLTs), defined as the occurrence in cycle 1 of any of the following: a grade ≥3 nonhematologic adverse event (AE), grade ≥3 prolongation of the QTc interval, grade 4 neutropenia lasting >5 days on growth factors, grade 4 thrombocytopenia, or failure to restart abexinostat administration within 2 weeks. Dose escalation to next level proceeded after DLT assessment of patients at the end of cycle 1. Dose escalation followed a 3 + 3 principle.

Phase I and phase II enrolled different patients and responders who completed treatment were eligible to enroll in a separate long-term extension study. In the efficacy evaluation phase (phase II), dosing was based on MTD results from the initial dose escalation phase and included patients with relapsed/refractory FL and MCL based on phase I efficacy signals and historical data with other HDAC inhibitors. In phase II, the primary end point was overall response rate (ORR) as defined by disease-specific criteria. Secondary end points included duration of response (DOR); time to PD; progression-free survival (PFS); and safety and tolerability. Refractory disease was defined as no response to prior therapy or relapse within 3 months of completing prior therapy.

Patients

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Women and men aged ≥18 years with measurable, histologically confirmed, previously treated lymphoma were included. Phase I included patients with any lymphoma subtype; phase II included patients with FL or MCL. Patient requirements for both phases included receipt of prior therapies, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤1, adequate organ function, and estimated life expectancy of >12 weeks. Patients were excluded from the study if they had platelets <75,000/µL (phase 1) and <100,000/µL (phase 2) or if they had an absolute neutrophil count <1500/µL.

Patients were excluded if they had received prior HDACi (unless for treatment of mycosis fungoides or Sézary syndrome); allogeneic bone marrow transplantation; immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first study dose. Patients were also excluded for primary central nervous system lymphoma or a history of meningeal carcinomatosis.

Pharmacokinetic analyses

Plasma concentrations of abexinostat were determined by high performance liquid chromatography (HPLC) with tandem mass spectrometric (MS/MS) detection. Pharmacokinetic parameters including area under the drug concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration in hours ($AUC_{(0\text{-}t)}$), maximum observed drug concentration (C_{max}), time to maximum drug concentration (T_{max}), and terminal half-life ($T_{½}$) were summarized by phase I cohort.

Safety and efficacy assessments

Toxicity was graded using the NCI Common Terminology Criteria for Adverse

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Events, Version 4.0.(14) All AEs were recorded from the first abexinostat dose until 30 days after the last dose. Serious AEs (SAEs) were those events that were fatal, life threatening, required hospitalization, disabling, or judged to be medically significant. Electrocardiograms were performed at screening and both pre-first dose and 1-2 hours post-first dose on each of days 1, 8, and 15 of cycle 1, and day 1 of each additional cycle. In phase I, an additional electrocardiograms was obtained post-second dose in cycle 1.

Efficacy assessments

Patients were assessed for clinical response during days 22 to 28 of every even-numbered cycle beginning at cycle 2 using the modified International Workshop Lymphoma Response Criteria (IWLRC)(15) for ORR (complete response [CR] + partial response [PR]), stable disease (SD), and PD. Nodal changes relative to baseline were determined using the sum of the products of the perpendicular diameters (SPDs) for all measured nodal masses. Response was assessed by investigators according to the 1999 International Working Group criteria.(15) The efficacy-evaluable population was defined as all patients who received at least 1 dose of study drug and had a least 1 tumor assessment post-baseline.

Pharmacodynamic studies

Blood samples were collected for analysis of acetylated histones and acetylated tubulin in peripheral blood mononuclear cells (PBMCs). Blood samples for pharmacodynamic analyses were collected at cycle 1 day 1 pre-dose, 4 hours post-first dose, and pre-first dose on day 2. Pharmacodynamic methods of PBMC processing and protein quantification are shown in the supplemental material.

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Statistical Analysis

Phase I was an algorithm-based dose-escalation trial to find the MTD of abexinostat and characterize the most frequent AEs and DLTs with a planned enrollment of up to 30 patients. DLTs were evaluated on day 1 of cycle 2 and included all AEs experienced through week 4 of cycle 1. Experience from ≥6 DLT-evaluable patients was used to determine the MTD.

The phase I secondary efficacy end point and phase II primary efficacy end point of response were defined by standard, disease-specific criteria. DOR was measured for responders from the first documentation of response to the date of disease progression or death and was calculated using the Kaplan-Meier procedure. In phase II, a sample size of 16 in two lymphoma categories was designed to achieve 80% power to detect an increase in ORR from 5% to 25% with abexinostat treatment.

Results

Patient characteristics and disposition

A total of 55 patients were enrolled and treated on this phase I/II study over 22 months. This included 25 patients in the phase I component and 30 patients in the phase II study who received one or more doses of abexinostat. The baseline patient characteristics for the phase I and II portions of the study are detailed in ***Table 1***. Sixteen patients with FL and 14 patients with MCL were enrolled and treated in phase II. The median age in the ITT phase II population was 67 years (range 36-81). The median number of prior therapies was 3 (range, 1-11) and 7 (range, 1-13) in FL and MCL, respectively, with most patients having received prior rituximab and CHOP chemotherapy. One-third of phase II patients had received prior autologous stem cell transplantation. Five patients (16.7%) were refractory to their last prior therapy, defined as PD < 3 months from completion of last prior therapy after responding.

The median follow-up time on drug for the phase II ITT population was 10.3 months for patients with FL and 2.4 months for those with MCL. Of the 30 patients enrolled in phase II, 11 (36.7%; 4 FL and 7 MCL) discontinued due to PD after cycle 1, 11 (36.7%) discontinued due to an AE, and 3 (10%) withdrew consent.

Pharmacokinetics and pharmacodynamics

The pharmacokinetic parameters of abexinostat are summarized by cohort in ***Table 2***. Approximate dose-proportional increases in abexinostat exposure were observed from 30 to 60 mg/m^2 after the first dose on Day 1. Abexinostat was rapidly absorbed with median time to maximum drug concentration values ranging from 1.00 to 1.08 hours across all doses. The PK samples were collected following the first dose of the day primarily for correlations with PD and thrombocytopenia for which the AUC is the primary parameter of interest. The true mean elimination half-life value could therefore not be calculated due to the 4 hour sampling window before the second dose but has been previously established as, 4-5 hours in two other phase I studies with sampling up to 24 hours.(16, 17) Data from 125 patients have been analyzed and modeled (18, 19) and the PK has been found to be very consistent between the two daily doses.

For pharmacodynamic studies, increased levels of acetylated tubulin were observed post-dose versus pre-dose in 11 patients treated with 45 mg/m^2 abexinostat twice daily (Cohorts 2 and 3 pooled) and significant increases in the 11

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patients treated with 60 mg/m^2 abexinostat twice daily, with the mean fold-increase of normalized acetylated tubulin being 1.48 and 1.46, respectively (***Figure 1A***). Increased levels of acetylated tubulin were not observed in the 5 patients receiving 30 mg/m^2 twice daily. In patients with FL, (phase II study), the mean fold-increase of normalized acetylated tubulin was 1.312; in patients with MCL, it was 0.7750. The difference between the two groups was not significant (P=.193) due to the high variability (***Figure 1B***).

MTD and DLT

No DLTs were observed at 30 mg/m^2 (cohort 1), and dose level 2 (45 mg/m^2, cohort 2) was initiated (DLTs are summarized in ***Supplemental Table 2***). Within cohort 2, 3/7 evaluable patients had at least one DLT, resulting in an MTD of the first dosing schedule (5 days/week for the first 3 weeks) of 30 mg/m^2. DLTs included grade 4 thrombocytopenia and 2 failures to restart abexinostat within 2 weeks of the first missed dose due to thrombocytopenia ≤grade 3. Dosing continued at 45 mg/m^2 with the alternative schedule (7 days/week every other week) (cohort 3). No patient in cohort 3 experienced a DLT and dosing was escalated to 60 mg/m^2 (cohort 4). Within cohort 4, 2/8 evaluable patients developed a DLT (grade 5 acute renal failure, and grade 3 prolonged diarrhea), resulting in an MTD at the alternative dosing schedule of 45 mg/m^2. In phase II, a sentinel group of 3 evaluable patients was treated at the MTD and assessed after the first cycle. No DLTs were observed, and the recommended phase II dose and schedule for single-agent abexinostat was established at 45 mg/m^2 twice daily, 7 days/week, every other week.

Safety

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AE data for phase I of the study by cohort are shown in ***Supplemental Table 3***. A summary of treatment-emergent AEs of any grade occurring in at least 20% of ITT patients and a summary of grade 3 or 4 AEs reported in more than 1 patient in phase II of the study are shown in ***Table 3***; AEs occurring in phase II are listed in ***Supplemental Table 4***. The most common phase II any-grade AEs were nausea (63%), fatigue (60%), diarrhea (50%), and thrombocytopenia (46.7%). The most common grade 3 or 4 treatment-emergent AEs reported in phase II were thrombocytopenia (20%), fatigue (16.7%), and neutropenia (13.3%). In 30 ITT patients, 3 (10%) reported a grade 4 thrombocytopenia event; grade 4 neutropenia, anemia, and decreased performance status were seen in one patient each.

In phase II, a total of 13 findings of QTc <480 ms but >450 ms by the site were observed in 7 patients. Seven findings were not confirmed upon central review, whereas 2 of the findings were confirmed. The central review data for 4 of the findings were missing. The 2 patients with centrally confirmed QT prolongation did not experience cardiac-related AEs other than QT prolongation during the study. The 3 patients with QTc >450 ms who were not centrally reviewed had no cardiac-related adverse events during the study.

Efficacy

In the phase I efficacy evaluable population (n=21), 61.9% of patients achieved SD or better, and the ORR was 19.0%, including 1 CR in FL grade 1, and 3 PRs in patients with DLBCL, FL, and MCL. The ORR in the ITT population (n=25) was 16%. In phase II, full response assessments were not available for 5 patients (2 FL; 3

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MCL). The ORR was 48%, with 1 CR and 11 PRs (***Table 4***). The ORR for the ITT population (n=30) was 40%.

Among the 14 evaluable patients with FL (***Table 4***), with a median time on study of 11.9 months (range, 1.2-24.8), 9 (64.3%; ITT ORR 56.3%) responded, including 1 patient with a CR, and 12 (86%) had reductions in lymph node diameter, including 5 with >75% reduction (***Figure 2A***). The median DOR was not reached. Among the 9 responding patients with FL, 8 were on study more than 8 months, and 5 were treated for more than 18 months (***Figure 2B***). The median PFS for FL patients was 20.5 months (range, 1.2-22.3+) as shown in ***Figure 2C***. There were no differences in response or DOR based on prior treatments, including refractoriness to prior therapies (data not shown).

Among the 11 evaluable phase II patients with MCL, there were 3 responses (27.3%; ITT ORR 21.4%), all of them PRs per investigator assessment. The DORs in responding patients were 2+, 2.8, and 6.1+ months (***Figure 2B***) and the median PFS was 3.9 months (0.1-11.5+) (***Figure 2C***).

Discussion

Inhibition of HDAC has emerged as a promising strategy in hematologic malignancies. A recent phase II study of panobinostat in Waldenström macroglobulinemia reported a partial remission rate of 22% and minimal response in 25% of the 36 patients.(20) Vorinostat, approved for the treatment of cutaneous T-cell lymphoma, provided a 47% ORR in patients with relapsed/refractory FL in a phase II trial, with good tolerability and a median PFS of 15.6 months, but no

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responses in 9 MCL patients in this study.(3) In a recent Asian multicenter phase II study of vorinostat in 56 patients with relapsed/refractory indolent B-cell NHL, sustained antitumor activity was reported in relapsed patients with FL (n=39), with an ORR of 49% and a median PFS of 20 months.(21) However, with a median prior therapy of 1 (1-4), the FL patients were less heavily pretreated than in the current study, and both the previous studies used a twice daily regimen that differs from the FDA-approved label for vorinostat. In the present phase I/II multicenter study, we demonstrated that single-agent oral abexinostat had rapid oral absorption, was overall well tolerated, and had significant clinical activity in patients with heavily pretreated relapsed/refractory FL.

In early phase clinical trials, the safety profiles of HDACi agents have been mostly favorable, particularly in comparison with cytotoxic chemotherapy.(22) The most common toxicities of HDACi are fatigue, nausea, diarrhea, which were also observed in this study. Grade ≥3 cytopenias (mostly thrombocytopenia) occurred infrequently despite a number of patients receiving prolonged treatment courses during this study (i.e., >12-15 months).

One particular safety concern with HDACi is cardiac toxicity, including ventricular arrhythmia and QT/QTc prolongation, which is a safety issue seen with an increasing number of agents.(23-29)

In the phase I component of the present study, there were no occurrences of prolonged QT intervals or other cardiac abnormalities. Additionally, in the 30-patient phase II study, only 1 patient had a confirmed grade 3 QTc prolongation in conjunction with atrial fibrillation, both of which were transient and resolved within 24 hours of abexinostat discontinuation. This is consistent with the initial findings from an ongoing phase I/II trial in patients with relapsed/refractory Hodgkin lymphoma, NHL, or CLL receiving oral abexinostat in an alternative schedule in which prolonged QTc intervals were not observed.(16)

The potential risk for QTc prolongation is generally driven by drug concentration. To minimize this potential risk for abexinostat, twice-daily oral administration (versus intravenous or once-daily oral administration) was selected to lower peak concentrations while maintaining similar overall daily exposure (AUC) as compared to once-daily dosing for the equivalent total daily dose. A schedule of twice-daily dosing 4-6 hours apart was utilized based on preclinical findings demonstrating its superior efficacy over 12-hour apart dosing. This dosing regimen is consistent with previous work showing a minimum of 6-8 hours continuous exposure with HDACi is needed for inducing ROS and apoptosis in tumor cells, (30, 31) and is made possible by the unique PK profile of this drug which has a terminal half life of 4-5 hours.(16, 17) This regimen also allows for longer recovery time off drug per day, and may account for the better tolerability and efficacy profile of abexinostat relative to other HDACi agents.(18)

In the phase I component, we observed preliminary clinical benefits with abexinostat in 21 heavily pretreated relapsed/refractory lymphoma patients (i.e., 1 CR, 3 PRs, and 9 SDs). In phase II, the ORR was 64.3% in 14 evaluable FL patients and 56.3% in the ITT population. Of these 14 patients, 86% had reductions in tumor burden and durable responses, with 64% remaining on the study for >8 months. Rapid and marked reductions in lymphadenopathy were also seen in patients who

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were refractory to their last prior therapy (18.8%). The clinical response in FL is comparable to the ORR in 57 rituximab-refractory FL patients treated with ibritumomab tiuxetan radioimmunotherapy (32), and in 76 rituximab-refractory patients with B-cell NHL treated with bendamustine;(33) however it should be acknowledged that the sample size in the current study was smaller and needs to be confirmed in larger cohorts. It is important to note that positron emission tomography (PET) scanning was not utilized for the FL patients enrolled in the phase II study, which may have led to an underestimation of the ORR and CR rates.(15) Regarding time-to-event analyses, results with abexinostat appear favorable. With a median follow-up of 10.3 months for FL patients, the dedian duration of response was not reached with abexinostat .

In conclusion, this phase I/II study demonstrated that the pan-HDACi, abexinostat, is clinically active in patients with relapsed/refractory FL and MCL, particularly in FL patients, who achieved durable tumor control for periods ≥18 months. With a unique intermittent dosing regimen, abexinostat showed good tolerability during prolonged drug administration and little evidence of the cardiac concerns observed with other HDACi. The safety profile of abexinostat allows for combination approaches with other immuno-chemotherapy regimens and/or novel agents (34). Abexinostat is currently being tested in a variety of clinical trial settings and further examination in NHL is indicated.

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Table 1.

Characteristic	Phase I* (n = 25)	Phase II FL (n = 16)	Phase II MCL (n = 14)	Phase II Total (N = 30)
Age, years				
Median	66	62	67	67
Range	32-79	36-81	59-77	36-81
Gender, n (%)				
Female	10 (40)	8 (50)	2 (14.3)	10 (33.3)
Male	15 (60)	8 (50)	12 (85.7)	20 (66.7)
Baseline ECOG Performance Status, n (%)				
0	13 (52)	8 (53.3)	5 (35.7)	13 (44.8)
1	12 (48)	7 (46.7)	8 (57.1)	15 (51.7)
2	0	0	1 (7.1)	1 (3.4)
Prior treatments				
Median (Range)	9 (2-16)	3 (1-11)	7 (1-13)	5 (1-13)
Rituximab, n (%)	19 (76)	14 (87.5)	14 (100)	28 (93.3)
CHOP, n (%)	16 (64)	10 (62.5)	7 (50.0)	17 (56.7)
Auto-SCT, n (%)	9 (36)	5 (31.3)	5 (35.7)	10 (33.3)

Abbreviations: Auto-SCT, autologous stem cell transplantation; CHOP, cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), prednisone/prednisolone; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; MCL, mantle cell lymphoma.

*Histologies: Diffuse large B-cell lymphoma (n = 10), FL (n = 4), Hodgkin lymphoma (n = 3), angioimmunoblastic T-cell lymphoma (n = 2), chronic lymphocytic leukemia/small lymphocytic lymphoma (n = 2), MCL (n = 2), cutaneous T-cell lymphoma (n = 1), and

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extranodal marginal zone B-cell lymphoma, malt type (n = 1).

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Table 2.

BID Dose Level[a] (schedule)	**30 mg/m^2 (days 1-5, 8-12, 15-19)**	**45 mg/m^2 (days 1-5, 8-12, 15-19)**	**45 mg/m^2 (days 1-7, 15-21)**	**60 mg/m^2 (days 1-7, 15-21)**
Cohort	**1 (n=5)**	**2 (n=7)**	**3 (n=3)**	**4 (n=9)**
T_{max} (h)				
Median (min, max)	1.00 (0.917, 2.00)	1.08 (1.00, 1.18)	1.03 (1.00, 2.08)	1.00 (0.667, 2.17)
C_{max} (µM)				
Mean (SD)	0.185 (0.075)	0.339 (0.245)	0.226 (0.088)	0.295 (0.155)
$AUC_{(0-4)}$ (µM·h)				
Mean (SD)	0.409 (0.085)[b]	0.630 (0.424)	0.440 (0.107)	0.693 (0.427)

[a] Administered within 28-day cycles.

[b] N=4.

T_{max} = time to maximum drug concentration, C_{max} = maximum observed drug concentration, $AUC_{(0-4)}$ = drug concentration-time curve from 0 to 4 hours

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Table 3.

Any-grade adverse events occurring in >20% of patients			
Patients with event, n (%)	**FL (n=16)**	**MCL (n=14)**	**Total (N=30)**
Nausea	12 (75.0)	7 (50.0)	19 (63.3)
Fatigue	10 (62.5)	8 (57.1)	18 (60.0)
Diarrhea	8 (50.0)	7 (50.0)	15 (50.0)
Thrombocytopenia	10 (62.5)	4 (28.6)	14 (46.7)
Cough	6 (37.5)	7 (50.0)	13 (43.3)
Vomiting	8 (50.0)	3 (21.4)	11 (36.7)
Constipation	7 (43.8)	3 (21.4)	10 (33.3)
Decreased appetite	5 (31.3)	3 (21.4)	8 (26.7)
Headache	5 (31.3)	3 (21.4)	8 (26.7)
Peripheral edema	3 (18.8)	5 (35.7)	8 (26.7)
Anemia	4 (25.0)	4 (28.6)	8 (26.7)
Neutropenia	4 (25.0)	3 (21.4)	7 (23.3)
Dysgeusia	4 (25.0)	3 (21.4)	7 (23.3)
Sinusitis	3 (18.8)	4 (28.6)	7 (23.3)
Insomnia	5 (31.3)	1 (7.1)	6 (20.0)
Chills	1 (6.3)	5 (35.7)	6 (20.0)
Grade 3 or 4 adverse events occurring in more than one patient			
Thrombocytopenia	3 (18.8)	3 (21.4)	6 (20.0)
Fatigue	2 (12.5)	3 (21.4)	5 (16.7)
Neutropenia	2 (12.5)	2 (14.3)	4 (13.3)
Hyperglycemia	0 (0)	2 (14.3)	2 (6.7)
Performance status decrease	1 (6.3)	1 (7.1)	2 (6.7)
Arthralgia	1 (6.3)	1 (7.1)	2 (6.7)

Treatment-emergent adverse events (AEs) are events with onset dates on or after the start of treatment and up to 30 days after the last dose date, or continuing AEs diagnosed before the start of treatment and getting worse in grade or relationship to treatment after the start of treatment. Counts and percentages are of patients, not events.

Abbreviations: FL, follicular lymphoma; MCL, mantle cell lymphoma.

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Table 4.

Category, n (%)	**FL (n = 14)**	**MCL (n = 11)**	**Total (N = 25)**
ORR 95% CI	9 (64.3) 35.1, 87.2	3 (27.3) 6.02, 61.0	12 (48) 27.8, 68.7
CR	1 (7.1)[a]	0	1 (4)
PR	8 (57.1)	3 (27.3)	11 (44)
SD	3 (21.4)	4 (36.4)	7 (28)
PD	2 (14.3)	4 (36.4)	6 (24)
Median time to progression, days (range)	625 (36-679+)	120 (4-349+)	625 (4-679+)

[a] CR was confirmed by positron emission tomography.

Abbreviations: FL, follicular lymphoma; MCL, mantle cell lymphoma; CI, confidence interval; ORR, overall response rate (CR+PR); CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

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Table and Figure Legends

Table 1. Patient characteristics.

Table 2. Plasma PCI-24781 PK parameters following oral administration of PCI 24781 on day 1 by cohort (phase 1 pharmacokinetics evaluable population).

Table 3. Treatment-emergent adverse events in phase II.

Table 4. Clinical responses in efficacy-evaluable patients, phase II.

Figure 1. Abexinostat pharmacodynamic correlative analyses. Mean fold-increase of normalized acetylated tubulin post-dosed compared with pre-dose in ***(A)*** Phase I, and, ***(B)*** Phase II. * indicates statistically significant increase relative to the 30 mg/m^2 twice-daily dose (*P*=.0053)

Figure 2. Patient outcomes in phase II. (*A)* Best on-treatment percent changes in the sum of greatest perpendicular diameters (SPD) of measured lymph nodes. Asterisks indicate values outside of the plot. ***(B)*** Time on study with best responses, phase II ITT population. Asterisks represent patients with >75% reduction in SPD. CR, complete response; IND, ongoing; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease. ***(C)*** Kaplan-Meier plot for progression-free survival, phase II efficacy-evaluable population

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Figure 1.

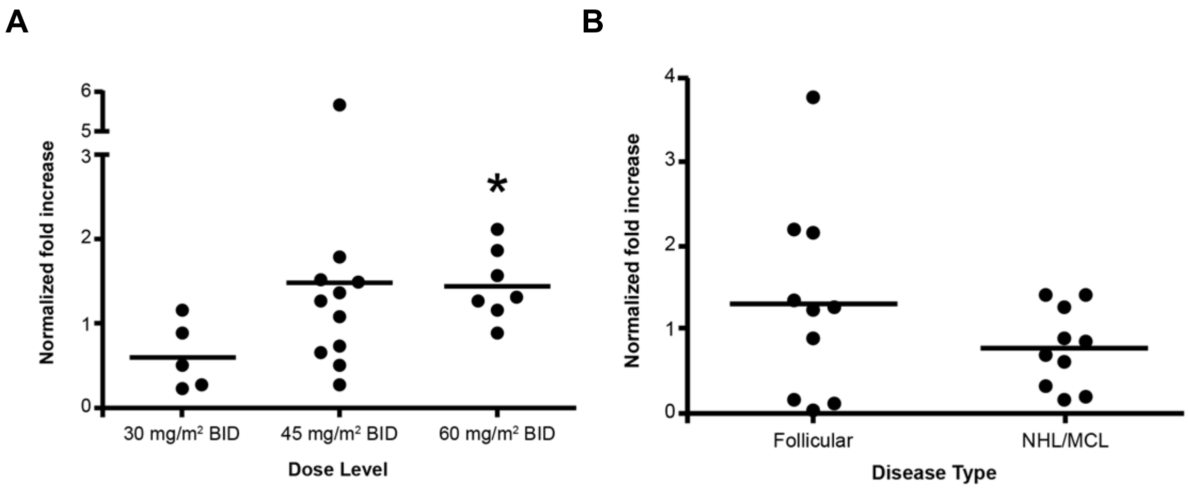

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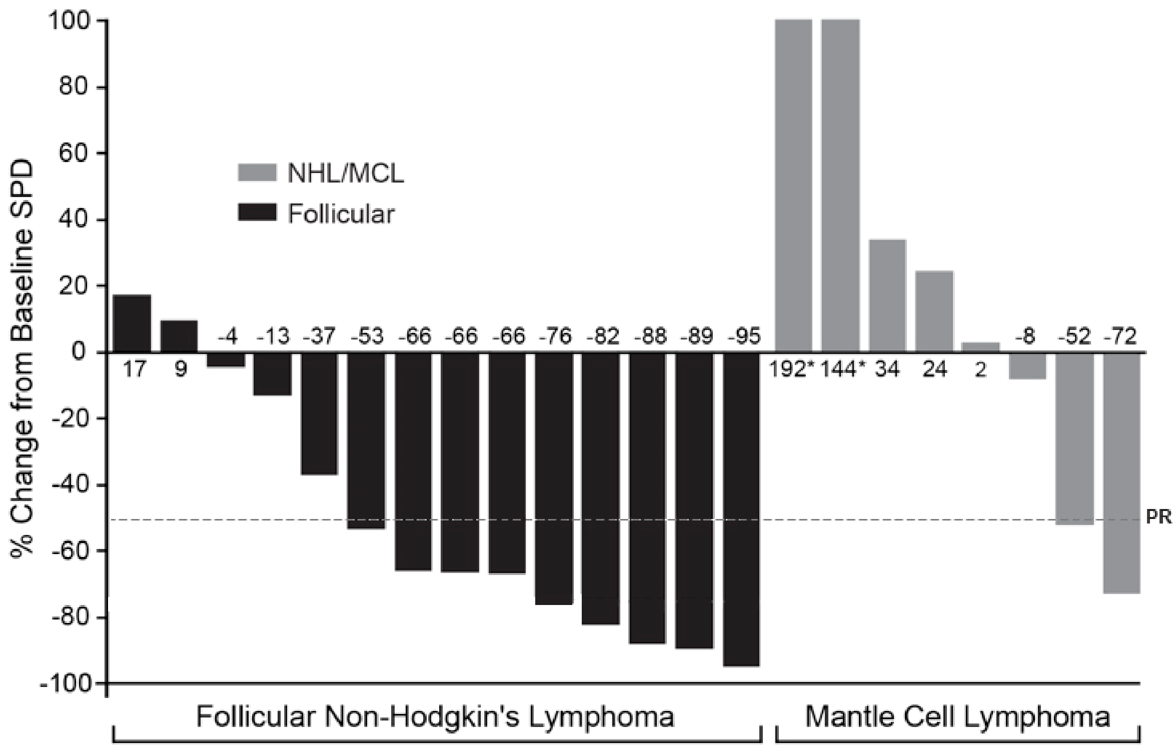
Figure 2.

A



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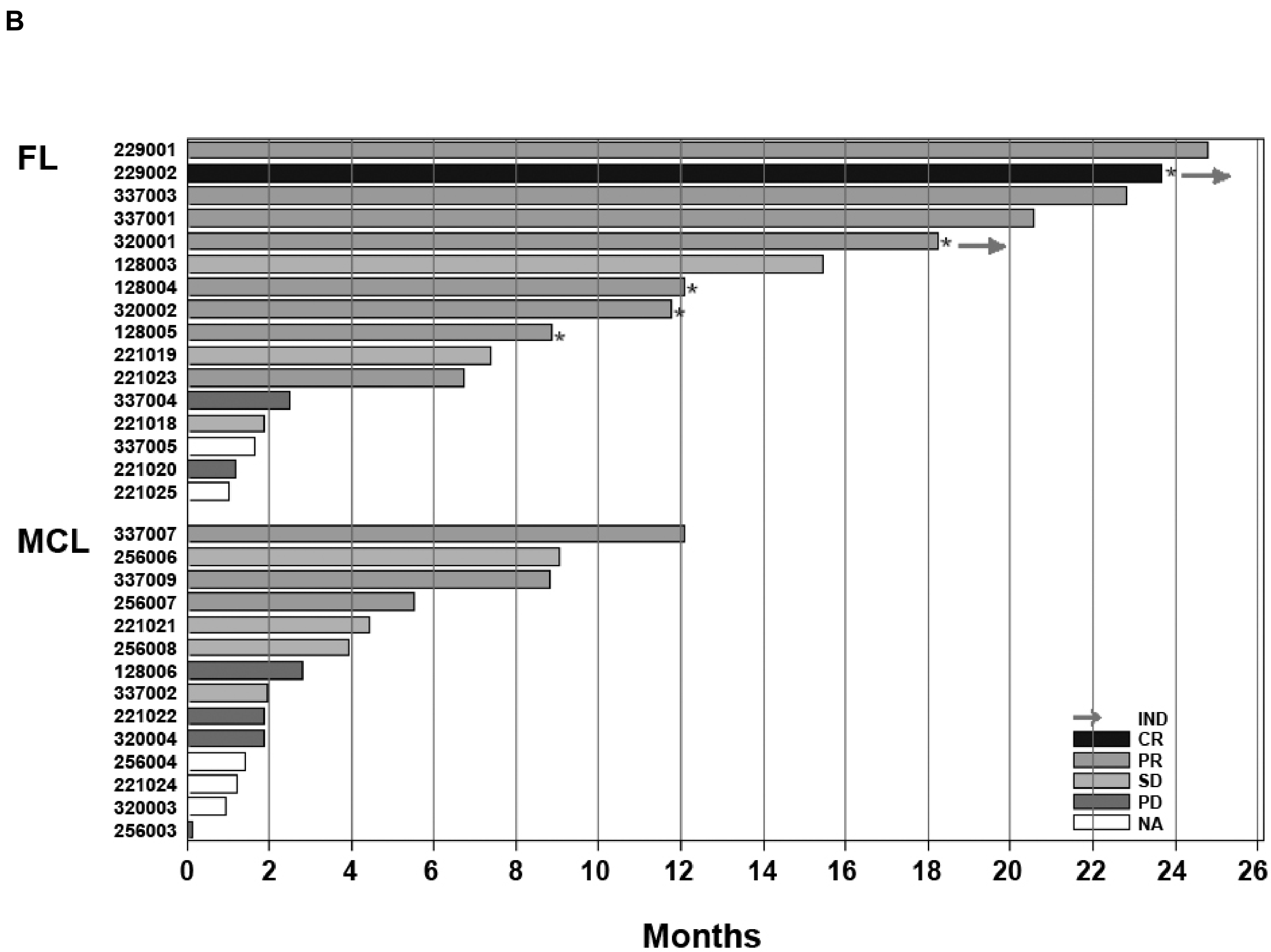

*SPD reduction >75%

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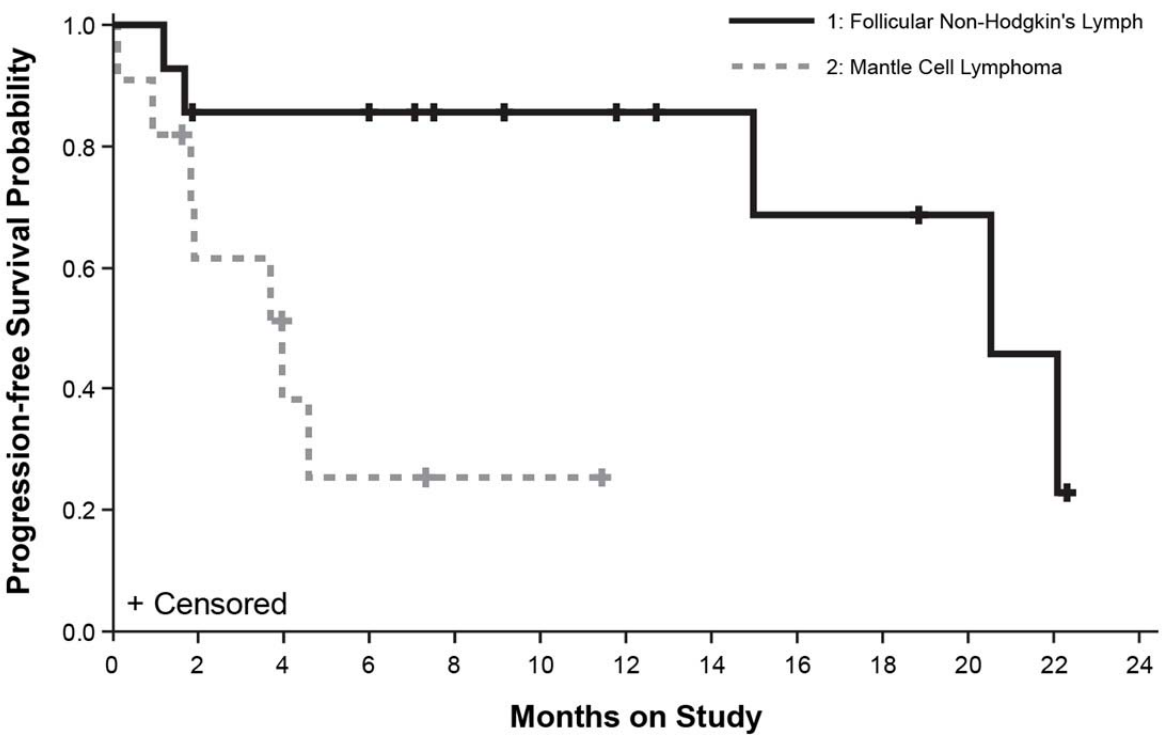
C



Number At Risk

1	14	11	11	11	8	7	6	5	4	4	3	2	0
2	11	6	3	2	1	1	0						

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A phase I/II multicenter, open-label study of the oral histone deacetylase inhibitor abexinostat in relapsed/refractory lymphoma

Andrew M. Evens, Sriram Balasubramanian, Julie M Vose, et al.

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