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ORIGINAL ARTICLE

Phase I trial of belinostat in combination with 13-cis-retinoic acid in advanced solid tumor malignancies: a California Cancer Consortium NCI/CTEP sponsored trial

Thehang Luu[1] · Paul Frankel[2] · Jan H. Beumer[3] · Dean Lim[1] · Mihaela Cristea[1] · Leonard J. Appleman[3] · Heinz J. Lenz[4] · David R. Gandara[5] · Brian F. Kiesel[3] · Richard L. Piekarz[6] · Edward M. Newman[7]

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Abstract

Purpose The reported maximum tolerated dose (MTD) of single-agent belinostat is 1000 mg/m^2 given days 1–5, every 21 days. Pre-clinical evidence suggests histone deacetylase inhibitors enhance retinoic acid signaling in a variety of solid tumors. We conducted a phase I study of belinostat combined with 50–100 mg/m^2/day 13-cis-retinoic acid (13-cRA) in patients with advanced solid tumors.

Methods Belinostat was administered days 1–5 and 13-cRA days 1–14, every 21 days. Dose-limiting toxicity (DLT) was defined as cycle 1 hematologic toxicity grade ≥ 3 not resolving to grade ≤ 1 within 1 week or non-hematologic toxicity grade ≥ 3 (except controlled nausea and vomiting and transient liver function abnormalities) attributable to belinostat.

Results Among 51 patients, two DLTs were observed: grade 3 hypersensitivity with dizziness and hypoxia at 1700 mg/m^2/day belinostat with 100 mg/m^2/day 13-cRA, and grade 3 allergic reaction at 2000 mg/m^2/day belinostat with 100 mg/m^2/day 13-cRA. The MTD was not reached. Pharmacokinetics of belinostat may be non-linear at high doses. Ten patients had stable disease, including one with neuroendocrine pancreatic cancer for 56 cycles, one with breast cancer for 12 cycles, and one with lung cancer for 8 cycles. Partial responses included a patient with keratinizing squamous cell carcinoma of the tonsils, and a patient with lung cancer.

Conclusions The combination of belinostat 2000 mg/m^2 days 1–5 and 13-cRA 100 mg/m^2 days 1–14, every 21 days, was well-tolerated and an MTD was not reached despite doubling the established single-agent MTD of belinostat.

Keywords Histone deacetylase (HDAC) inhibitors · Retinoids · Phase I clinical trial · Pharmacokinetics

Other presentations This study was reported at the 2013 American Society for Clinical Oncology Annual Meeting.

✉ Edward M. Newman
enewman@coh.org

1 Department of Medical Oncology, City of Hope, Duarte, USA

2 Department of Biostatistics, City of Hope, Duarte, USA

3 UPMC Hillman Cancer Center, Pittsburgh, USA

4 University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA 90033, USA

5 University of California Davis Cancer Center, Sacramento, CA 95817, USA

6 Cancer Therapy Evaluation Program, National Cancer Institute, 9609 Medical Center Dr., MSC 9739, Bethesda, MD 20892, USA

7 Beckman Research Institute City of Hope, Duarte, CA 91010, USA

Introduction

Belinostat (PXD101, N-hydroxy-3-[phenylsulfamoylphenyl acryl amide) is a low molecular weight inhibitor of histone deacetylase (HDAC) activity [1] similar to trichostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA) [2]. In July 2014, the FDA approved belinostat for the treatment of relapsed or refractory peripheral T-cell lymphoma. Belinostat is currently being investigated in multiple solid tumors including non-small cell lung cancer, and thyroid cancer. Reports of the clinical activity of retinoids as treatment for both hematologic and solid malignancies have renewed interest in the class of agents [3]. In particular, 13-cRA with interferon-α2a has been reported to be active in squamous cell carcinomas [4–6]. Data from multiple cell lines indicate that sensitivity to retinoids depends in large part on the expression of RAR and RXR. HDAC inhibitors

induce the expression of genes associated with cell cycle arrest and tumor suppression [7, 8]. These inhibitors, alone or in combination with DNA hypomethylating agents such as 5-azacytidine or decitabine, restore expression of silenced genes leading to cell differentiation and subsequent cell cycle arrest or apoptosis. In various tumor cell lines (ovarian, colon, lung, breast, prostate, and melanoma), belinostat induced apoptosis with IC_{50} values varying from 0.2 to 3.4 μM [1]. In a phase 1 study of single-agent belinostat administered as a 30-min IV infusion on days 1–5, every 21 days, 3 of 5 patients treated at a dose of 1200 mg/m^2/day experienced dose-limiting toxicities (DLT), 1 atrial fibrillation, 1 diarrhea with fatigue, and 1 fatigue [9]. In contrast, the single-agent MTD was not reached at 1400 mg/m^2/day in a separate trial in patients with hepatocellular carcinoma [10–13].

The retinoids include natural and synthetic analogues of retinol (vitamin A), and regulate growth and development by modulating transcription of genes essential to cellular differentiation and proliferation [14]. A major component of retinoid nuclear signaling occurs through intracellular binding to heterodimers of two classes of retinoic acid receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Each of these receptor classes has three isotypes and several major isoforms, increasing the complexity of signaling and leading to the pleiotropic effects of retinoids [15]. Although 13-cis-retinoic acid (13-cRA) is not as active as 9-cis-retinoic acid (9-cRA) or all-trans-retinoic acid (ATRA) in transcription assays, it clearly has clinical activity at pharmacologic doses, whether through in vivo isomerization to other RA isoforms or direct effects despite low potency; the longer half-life of 13-cRA suggests that it may serve as a depot from of ATRA, and perhaps 9-cRA [16, 17]. For example, 13-cRA has activity in recurrent malignant glioblastoma [18]. For this study, we chose off-label use of the commercially available oral formulation of 13-cRA (isotretinoin).

A number of pre-clinical studies suggest that HDAC inhibitors can enhance retinoic acid (RA) signaling with a synergistic impact in a variety of neoplastic cells [19]. HDAC inhibitors restore RA signaling and differentiation in primary blasts from patients with AML [20], and may enhance activity of RA on RA-responsive melanoma cell lines [21]. ER-negative breast cancer cell lines that express high RARα levels are sensitive to retinoids [22]. Trichostatin A (TSA) has been shown to activate RARβ in MDA-MB-231 cells [23]. Likewise, combined treatment with TSA and RA synergistically activated transcription from RA-responsive promoters in P19 embryonal carcinoma cells [24]. In MCF-7 xenografts, TSA reactivated RARβ and significantly increased tumor growth inhibition of RA [25].

A previous clinical trial demonstrated that oral 13-cRA can be safely administered at doses up to 4 mg/kg/day [26]. Our hypothesis was that the HDAC inhibitor belinostat can be safely combined with and increase the anti-neoplastic activity of 13-cRA. Based on this hypothesis, we undertook to assess the safety and feasibility of combining belinostat with 13-cRA in patients with advanced solid tumor malignancies. Our specific objectives were to establish the MTD of belinostat in combination with 13-cRA, to describe the toxicities at each dose studied, to describe any anti-tumor activity, and to evaluate the pharmacokinetics of belinostat when administered in combination with 13-cRA.

Materials and methods

Patients

Eligible patients were men and women aged ≥ 18 years with histologically confirmed advanced solid tumors, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 with life expectancy ≥ 3 months and adequate end organ and marrow function defined as follows: leukocytes ≥ 3000/mcL, absolute neutrophil count ≥ 1500/mcL, platelets ≥ 100,000/mcL, total bilirubin within normal institutional limits, AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal, creatinine within normal institutional limits, and creatinine clearance ≥ 60 mL/min. In addition, the principal investigator reviewed the cases of patients receiving medications or substances known to affect, or with the potential to affect, the activity or pharmacokinetics of belinostat, and eligibility was determined using a list of medications and substances known to, or with the potential to, interact with selected CYP450 isoenzymes. Women of child-bearing potential and men agreed to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. All patients were required to understand and be willing to sign a written informed consent document. Although not an eligibility criterion, it was recommended that patients have a central venous device (port-a-cath or PICC line).

Patients were ineligible if they met any of the following treatment criteria: chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or use of valproic acid (another histone deacetylase inhibitor) within 2 weeks prior to enrollment. Patients with known brain metastases, or who had a history of allergic reactions attributed to belinostat, another hydroxamic acid HDAC inhibitor, or a retinoid were excluded, as were patients who had uncontrolled intercurrent illness including, but not limited to the following: ongoing or active infection; psychiatric illness/social situations that would limit compliance with study requirements; marked baseline prolongation of QT/QTc interval, e.g., repeated

demonstration of a QTc interval > 500 ms, or long QT syndrome; the required use of concomitant medication on belinostat infusion days that may cause Torsade de Pointes; significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, congestive heart failure related to primary cardiac disease, a condition requiring anti-arrhythmic therapy, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry. HIV-positive patients on combination antiretroviral therapy were ineligible because of the potential for pharmacokinetic interactions with belinostat and increased risk of lethal infections when treated with marrow-suppressive therapy.

Prior to accruing patients, this study was approved by NCI-CTEP and the institutional review board of each institution that contributed patients (City of Hope; University of California, Davis; University of Southern California; and University of Pittsburgh). Written informed consent was obtained from each patient prior to initiating protocol-specific procedures or treatment.

Study design and treatment plan

This study was a phase I dose escalating multi-centered study employing a 3+3 design, escalating on 0/3 or 1/6 DLTs (dose-limiting toxicities), and de-escalating if 2 DLTs are encountered. There was no intra-patient escalation. To be evaluable for toxicity, a patient must either experience a DLT or receive at least one complete cycle of treatment. Any patient who was not evaluable for toxicity was replaced.

Dose-limiting toxicity (DLT) was based on toxicities at least possibly related to belinostat during the first cycle of therapy. DLT was defined as hematologic toxicity ≥ grade 3 that did not resolve to ≤ grade 1 within 1 week, or any non-hematologic toxicity ≥ grade 3, except grade 3 or 4 nausea and vomiting that responded to optimal anti-emetic therapy and grade 3 or 4 liver function abnormalities that resolved within 48 h. Toxicities were graded by NCI CTCAE 4.0.

Although measurable disease was not an eligibility criterion, tumor measurements were obtained every 6 weeks in patients with measureable disease at baseline. Response was assessed according to RECIST 1.0. Responses were considered "unconfirmed" if the tumor measurements met the criteria for response on only one occasion.

Initially, there were four dose levels based on the reported toxicity of the individual agents. The daily doses in mg/m^2 of PXD101 and 13-cRA, respectively, were (600, 50), (900, 50), (1200, 50) and (1200, 100). Because no DLTs were observed on any dose level, an additional dose level at (1400, 100) was added, followed by additional dose levels in increments of 100 mg/m^2/day of belinostat, up to 2000 mg/m^2/day.

Belinostat was administered as a 30–45 min infusion through an in-line 0.22-µm low protein binding filter, daily × 5 days every 21 days. 13-cRA was administered by mouth daily × 14 days every 21 days. Because belinostat is associated with nausea and vomiting, 13-cRA capsules were taken 2–3 h after belinostat infusion on days when both agents were administered and standard anti-nausea medications were recommended per National Comprehensive Cancer Network guidelines. The body surface area was based on actual body weight, and the dose of 13-cRA was rounded to the nearest 10 mg to match capsule size. Treatment was administered on an outpatient basis.

There were no dose modifications for 13-cRA. If a patient experienced ≥ grade 3 drug-related toxicity at any time in a cycle, the next cycle of belinostat was reduced by 25%, and all reductions were permanent. If the patient experienced another ≥ grade 3 toxicity, the dose of belinostat was reduced by an additional 25%. Treatment was allowed to hold up to 3 weeks. A third episode of ≥ grade 3 toxicity required the patient be removed from study. Because the non-fasting triglyceride level is not an appropriate medical assessment of the severity of hypertriglyceridemia, a fasting level was obtained as soon as possible when non-fasting triglyceride levels were elevated. Only the fasting triglyceride level was used in the determination of DLTs and dose reductions.

Pharmacokinetics

Starting at dose level 9 (1800 mg/m^2/day belinostat, 100 mg/m^2/day 13-cRA), belinostat pharmacokinetics were studied in patients. For this pharmacokinetic cohort, the 13-cRA was started on day 2 of cycle 1 to allow determination of the pharmacokinetics of belinostat alone. Pharmacokinetic studies were repeated on day 5 to determine the disposition of belinostat following 4 daily doses of 13-cRA.

Heparinized blood was obtained on the day 1 (before 13-cRA) and 5 (following four doses of 13-cRA) of cycle 1 before and at 30, 60, 90 min, and at 2, 4, and 6 h after start of infusion. Samples were centrifuged at 1000×*g* for 10 min to separate plasma, which was stored at −20 °C or less until analysis.

Quantitative determination of plasma concentrations of belinostat was performed with a previously validated assay, as described [27]. Pharmacokinetic parameters were calculated non-compartmentally using PK Solutions 2.0 (Summit Research Services, Montrose, CO http://www.summitPK.com).

Any effects of 13-cis-retinoic acid on belinostat pharmacokinetics was evaluated with SPSS 21.0 for Windows (SPSS Inc., Chicago, IL), using the two-tailed exact Wilcoxon signed-rank test for related samples. Data were considered significantly different when $P < 0.05$. Within-subject

variability for $AUC_{0\text{-inf}}$ and C_{max} were calculated by calculating 100 × the square root of the mean square within groups obtained after ANOVA of log-transformed values of these parameters with subject as a factor.

Results

From June 2006 to September 2012, we enrolled 51 patients, with a median age of 61 years (range 40–80), 29 male, and tumor types including 13 lung, 11 breast, 8 colorectal, and 3 pancreatic cancer cases. A total of 39 patients were evaluable for toxicity. The 12 inevaluable patients had evidence of clinical progression, withdrew consent, or were unable to continue due to adverse events unrelated to the study drugs prior to completing cycle 1. Fifty-seven percent had performance status of ECOG 2. Baseline and demographic information are presented in Table 1.

Safety and tolerability

Two DLTs were observed, a grade 3 hypersensitivity reaction with dizziness and hypoxia on dose level 8 (belinostat 1700 mg/m^2/day with 13-cRA 100 mg/m^2/day), and a grade 3 allergic reaction on dose level 11 (belinostat 2000 mg/m^2/day with 13-cRA 100 mg/m^2). An MTD was not reached at the highest dose tested (see Table 2). Adverse event data from the first cycle and all cycles are summarized in Table 3, which includes grade 3 and 4 adverse events and grade 2 adverse events occurring in more than one patient that were possibly, probably, or definitely related to protocol treatment. Grade 4 adverse events included an elevated triglyceride and a low hemoglobin. Grade 3 adverse events included hemorrhage (trachea), elevated triglycerides, elevated cholesterol, fatigue, small bowel obstruction, dyspnea, allergic reaction (DLT), hypersensitivity (DLT), nausea/vomiting, palmar–plantar erythrodysesthesia syndrome, rash, left ventricular systolic dysfunction, and QT prolongation. No clinically significant cardiac adverse effects were observed at any of the dose levels.

Table 1 Baseline characteristics of patients

Total patients in study	51
Gender	29M/22F
Median age, years (range)	61 (40–80)
Median no. prior drug therapies (range)	4 (0–14)
Primary sites of disease	
Lung	13
Breast	11
Colorectal	8
Pancreas	3
Head and neck (squamous)	3
Mesothelioma	3
Kidney	2
Adenoid cystic	2
Cervix	1
Cholangiocarcinoma	1
Neuroendocrine	1
Ovary	1
Hemangiopericytoma	1
Small intestines	1
ECOG performance status	
0	1 (2%)
1	21 (41%)
2	29 (57%)

Pharmacokinetics

We did not observe significant reduction in belinostat maximum plasma concentration (C_{max}) or area under the concentration versus time curve (AUC) after combination with 13-cRA ($P > 0.32$); see Table 4 [27, 28]. The within-subject variability was 23% for C_{max} and 25% for $AUC_{0\text{-inf}}$ of belinostat. Because this study explored much higher doses than previously reported, we evaluated the linearity of belinostat pharmacokinetics of the patients studied in the higher cohorts with previously reported data [9, 29]. The C_{max} observed in our study appeared linear with previous reports, whereas AUC appeared to be slightly more than dose-proportionally increased in our study. The terminal half-life in our study was longer than that reported by Steele, but similar to that reported by Lassen (86 min versus 27–54 and 60–102 min, respectively) [9, 29]. This suggests that belinostat may exhibit non-linear pharmacokinetics at the high doses evaluated in the current study (Fig. 1).

Anti-tumor activity

The median number of courses was 2 (range 1–56). One patient with a neuroendocrine pancreatic tumor had stable disease (SD) for 56 cycles, 1 breast cancer patient for 12 cycles, and 1 lung cancer patient for 8 cycles. Unconfirmed partial responses (PR) were observed in one patient with keratinizing squamous cell carcinoma of the tonsil, and one with lung cancer. The patients with SD or PR, regardless of duration, are listed in Table 5. In this heavily pretreated advanced solid tumor patient population, 2 PR (4%) and 10 SD were observed in 51 patients. As documented in Table 5, the responses were often short-lived. There was no clear dose-related pattern to the responses and the median time to treatment failure for the whole group was 4 months (range 2–40 months).

Table 2 Toxicity and response at each dose level

PXD101/13-cRA (mg/m^2/day)	No. pts	No. cycles median (range)	No. first cycle DLT (description)	Cardiac AEs (all cycles)	Response
Level 1 600/50	5	2 (1–4)	None		1 SD 3 Prog 1 Ineval
Level 2 900/50	4	2 (2–2)	None		4 Prog
Level 3 1200/50	4[a]	2.5 (2–4)	None		1SD 2 Prog 2 Ineval
Level 4 1200/100	4	4.5 (3–56)	None	1 gr2 arrhythmia	2 SD 1 PR 1 Ineval
Level 5 1400/100	3	2 (1–4)	None		2 Prog 1 Ineval
Level 6 1500/100	5	3(1–4)	None		4 Prog 1 PR
Level 7 1600/100	4	2 (2–4)	None	1 gr3 left vent dysf 1 gr2 infarct 1 gr2 arrhythmia	3 Prog 1 Ineval
Level 8 1700/100	7	4 (1–6)	1 (hypersensitivity with hypoxia and dizziness)	1 gr2 QTc prolong	4 SD 1 Prog 2 Ineval
Level 9 1800/100	3	8 (2–12)	None	2 gr2 QTc prolong	2 SD 1 Prog
Level 10 1900/100	5	2(1–2)	None	1 gr3 QTc prolong	4 Prog 1 Ineval
Level 11 2000/100	6	2(1–3)	1 (allergic reaction)	1 gr2 sinus tachy 1 gr2 QTc prolong	4 Prog 2 Ineval

[a]Excludes one patient found to be ineligible 2 days after initiating treatment

Discussion

Pre-clinical investigations have implicated growth inhibition and induction of differentiation and apoptosis as mechanisms by which retinoids can inhibit tumor cells, as reviewed previously [3, 30, 31]. It is not clear which mechanisms predominate clinically; nonetheless, the retinoids exert their actions mainly through the common element of binding to retinoic acid receptors, which is the proposed site of interaction with HDAC inhibitors [19]. In some cases, the receptor gene is not absent or mutated; rather the chromatin structure is inhibiting expression. Treatment with HDAC inhibitors can restore expression, along with sensitivity to retinoids [20, 21, 23, 25]. These pre-clinical data suggest a role a role for HDAC inhibitors in extending the utility of 13-cRA, especially in combination with other anti-neoplastic agents. As a first step, we undertook a dose-escalation study to determine a safe dose of belinostat to combine with high-dose 13-cRA (50–100 mg/m^2/day).

We were able to treat patients with intravenous doses of belinostat up to 2000 mg/m^2/day on days 1–5 in combination with oral 13-cRA at 100 mg/m^2/day on days 1–14 every 21 days without reaching the MTD. Thus, belinostat in combination with oral 13-cRA was well-tolerated at twice the reported belinostat single-agent MTD. The DLT observed at the highest dose level of belinostat 2000 mg/m^2 was hypersensitivity to belinostat. The metabolic fate of belinostat is complex; belinostat is primarily metabolized by hepatic UGT1A1 and also undergoes hepatic metabolism by CYP2A6, CYP2C9, and CYP3A4 enzymes [27, 32]. The potential effects of 13-cRA and its metabolic products on these enzymes is also complex, but would be expected primarily to affect CYP3A4 [28]. As the primary metabolic enzyme is UGT1A1, a drug–drug interaction was not anticipated. However, there were no DLTs at dose level 8 (1.4-times the reported single-agent MTD). The protocol was amended to add pharmacokinetic studies beginning at dose level 9 (1800 mg/m^2/day belinostat, 100 mg/m^2/day 13-cRA) before and after four daily doses of 13-cisRA to confirm that belinostat plasma concentrations continued to increase at the higher doses and that there was not a significant decrease in belinostat plasma concentrations after the addition of 13-cRA. Induction of UGT1A1 would be expected to have resulted in an increased belinostat clearance on day 5, even if

Table 3 Treatment-related toxicity (grade 2+)[a] on 51 patients (199 cycles), maximum per patient

Toxicity	Cycle 1			All cycles		
Grade	2	3	4	2	3	4
Hypertriglyceridemia	3	1		3	2	1
Hemoglobin	3		1	6	1	1
Dyspnea	1			1	1	1
Fatigue	8			10	3	
Dehydration		1			2	
Hypoxia		1			2	
Nausea	4	1		6	1	
Vomiting	2	1		4	1	
QTc prolonged	1			3	1	
Dizziness		1		1	1	
Hypercholesterolemia	1			1	1	
Allergic reaction		1			1	
Rash/desquamation		1			1	
Diarrhea					1	
Tracheal hemorrhage					1	
Left ventricular dysf					1	
Obstruction, small bowel					1	
Palmar–plantar syndrome					1	
Anemia	4			6		
Dry skin	2			5		
Hypoalbuminemia	1			3		
Anorexia	1			3		
Fever	1			3		
Hyperglycemia	2			3		
ALT, SGPT	1			2		
Flushing	2			2		
Hypertension	1			2		
Injection site reaction	1			2		
INR	1			2		
Phlebitis	2			2		
Platelets	2			2		
Atrial fibrillation				2		

[a]Excludes lymphopenia and toxicities with maximum grade 2 in only one patient

Table 4 Pharmacokinetics of belinostat on day 1 (D1) and day 5 (D5, after three doses of 13cRA)

Dose (mg/m^2)	C_{max} (μg/mL)	$AUC_{0\text{-inf}}$ (μg/mL·h)	$AUC_{0\text{-t}}$ (μg/mL·h)	$t_{½}$ (min)	Cl (L/h/m^2)	Vss (L/m^2)	C_{max} D5/D1	$AUC_{0\text{-inf}}$ D5/D1
1800 ($N=3$)	76.8 (9.3)	55.2 (9.9)	54.7 (9.8)	88 (23)	33.4 (6.6)	30.1 (4.1)	0.89 (1.19)	0.86 (1.30)
1900 ($N=5$)	106 (23)	72.8 (18.3)	72.1 (17.9)	86 (21)	28.0 (9.4)	24.3 (6.2)	0.77 (1.43)	0.76 (1.58)
2000 ($N=5$)	112 (12)	86.4 (5.7)	85.2 (6.0)	85 (19)	23.2 (1.5)	20.3 (10.3)	0.95 (1.40)	0.95 (1.35)
Total ($N=13$)	–	–	–	86 (19)	27.1 (6.9)	25.7 (5.0)	0.87* (1.36)	0.86** (1.41)

Means (SD); D5/D1 ratios as geometric means (geometric SD factor)

% of $AUC_{0\text{-inf}}$ extrapolated beyond $AUC_{0\text{–t}}$ was less than 5.4% in all cases

*$P=0.332$ by 2-sided exact Wilcoxon test

**$P=0.320$ by 2-sided exact Wilcoxon test

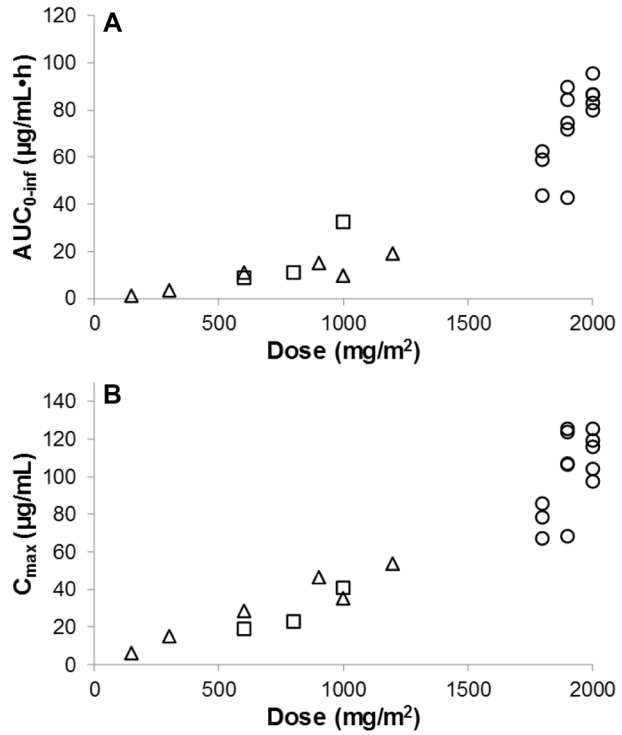

Fig. 1 Belinostat area under the plasma concentration versus time curve (**a**) and maximum plasma concentration (**b**) in the current study (circle) as compared to previously published results by Steele (triangle, [9]) and Lassen (square, [29])

it may not have been at its maximal effect. Increased mRNA levels in rats could be seen within 12 h of dosing [33]. While the reason the higher doses were tolerated is unclear, we effectively ruled out an immediate pharmacokinetic interaction. In particular, the plasma concentrations of belinostat in our study were not lower than expected as compared with single-agent belinostat pharmacokinetics. We can hypothesize that 13-cRA might mitigate the adverse effects of belinostat, but the complex and multiple biological effects of both drugs make it difficult to postulate a specific mechanism. A pharmacodynamic interaction, which could affect efficacy, as well as toxicity, cannot be ruled out.

The most common observed toxicities ≥ grade 2 were fatigue 19.6%, nausea 11.7%, vomiting 7.8%, and anemia 11.7%. There was a 4% partial response and a median time to treatment failure of 4 months (range 2–40 months). The duration of response in this trial was brief, as expected for this heavily pretreated patient population with a median of four prior therapies (range 0–14). We did observe a long period of stable disease (56 cycles) in a patient with neuroendocrine pancreatic cancer. A clinical study using fixed doses of belinostat and 13-cRA in a more uniform patient population will be required to assess potential efficacy of this combination.

Table 5 Characteristics of PR and SD patients

PXD101/13-cRA (mg/m^2/day)	Response	Disease	TTF (months)
Level 4 1200/100	PR	Sq. cell carcinoma, keratinizing/tonsil	2.0
Level 6 1500/100	PR	Adenocarcinoma/lung	2.6
Level 1 600/50	SD	Adenoid cystic carcinoma/supraglottis	3.1
Level 3 1200/50	SD	Non-small cell carcinoma/lung	3.2
Level 4 1200/100	SD	Squamous cell carcinoma/lung	4.0
Level 4 1200/100	SD	Neuroendocrine carcinoma/head of pancreas	40.5
Level 8 1700/100	SD	Mesothelioma, peritoneum	4.0
Level 8 1700/100	SD	Hemangiopericytoma, peritoneum	3.5
Level 8 1700/100	SD	Adenocarcinoma/small intestine	4.0
Level 8 1700/100	SD	Adenocarcinoma/cecum	4.1
Level 9 1800/100	SD	Adenocarcinoma/lung	5.4
Level 9 1800/100	SD	Infiltrating duct carcinoma/breast	8.4

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Compliance with ethical standards

Conflict of interest Jan H. Beumer received research support from Spectrum Pharmaceuticals.

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