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Phase I trial of belinostat with cisplatin and etoposide in advanced solid tumors, with a focus on neuroendocrine and small cell cancers of the lung

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Abstract

The standard-of-care for advanced small cell lung cancer (SCLC) is chemotherapy with cisplatin +etoposide (C+E). Most patients have chemosensitive disease at the outset, but disease frequently relapses and limits survival. Efforts to improve therapeutic outcomes in SCLC and other neuroendocrine cancers have focused on epigenetic agents, including the histone deacetylase inhibitor belinostat. The primary objective was to determine the maximum tolerated dose of the combination of belinostat (B) with C+E. Belinostat was administered as a 48-h continuous intravenous infusion on days 1–2; cisplatin was administered as a 1-h intravenous infusion on day 2; and etoposide was administered as a 1-h intravenous infusion on days 2, 3, and 4. Twenty-eight patients were recruited in this single-center study. The maximum tolerated dose was belinostat 500 mg/m²/24 h, cisplatin 60 mg/m², and etoposide 80 mg/m². The combination was safe, although some patients were more susceptible to adverse events. Hematologic toxicities were most commonly observed. Objective responses were observed in 11 (39%) of 28 patients and seven (47%) of 15 patients with neuroendocrine tumors (including SCLC). Patients carrying more than three copies of variant *UGT1A1* (*28 and *60) had higher serum levels of belinostat because of slower clearance. DNA damage peaked at 36 h after the initiation of belinostat, as did global lysine acetylation, but returned to baseline 12 h after the end of infusion. The combination of B + C + E

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Conflicts of interest

There are no conflicts of interest.

is safe and active in SCLC and other neuroendocrine cancers. Future phase II studies should consider genotyping patients for *UGT1A1*28* and *UGT1A1*60* and to identify patients at an increased risk of adverse events.

Keywords

advanced carcinomas; histone deacetylase inhibitors; phase I; small cell lung cancer

Introduction

Small cell lung cancer (SCLC) accounts for ~12–13% of all lung cancer cases and has a 5-year survival rate of 6% compared with 21% for non-SCLC [1]. At the time of diagnosis, roughly 60% of patients have widespread metastases [2]. A combination of cisplatin and etoposide (C + E) is used to treat SCLC, extrapulmonary small cell cancers, and other advanced cancers with neuroendocrine differentiation. Therapy of neuroendocrine cancers has lagged behind that of most other solid tumors, in part because of their striking diversity – from indolent tumors to poorly differentiated, high-grade, aggressive cancers, including SCLC. Overall survival is poor in patients with advanced SCLC and other aggressive neuroendocrine carcinomas, varying between 6 and 18 months [3].

In the search for strategies to improve therapies for SCLC and other neuroendocrine tumors, in-vitro evidence has shown that SCLC is sensitive to histone deacetylase inhibitors (HDIs) [4–7], with more limited data in other neuroendocrine cancers [8–10]. HDIs increase histone acetylation, resulting in reversible alterations in gene expression. To date, four HDIs have been approved for the treatment of T-cell lymphomas and myeloma – vorinostat, romidepsin, belinostat, and panobinostat. A number of ongoing clinical trials are evaluating the activity of the HDIs in other solid tumors.

Belinostat is a second-generation HDI that is active *in vitro* against SCLC cell lines and HDIs are of interest in lung cancer for their ability to induce many components of the immune response [11]. Our study is based on data showing a synergistic effect of the combination of HDIs with topoisomerase inhibitors [12–15]. In addition, our laboratory has shown that simultaneous exposure to an HDI and cisplatin or etoposide is more effective than sequential exposure [13].

One possible explanation for the increased efficacy of the combination is accrued DNA damage because of HDI-mediated impairment of DNA repair. This could be because of the global hyperacetylation or downregulation of DNA repair proteins as reported previously [16,17]. An alternate mechanism of synergy could result from induced expression of topoisomerase II [15]. A recently reported phase 1/2 trial combined belinostat with chemotherapy including cisplatin, cyclophosphamide, and the topoisomerase II inhibitor doxorubicin in advanced or recurrent thymic epithelial tumors [18]. In-vitro data have shown that longer exposure durations render a more pronounced HDI effect; we thus sought to administer belinostat over a longer period of time and deliver overlapping exposure with cytotoxic chemotherapy. Given its short half-life (~1 h), similar to most other HDIs, the present study explored a 48-h continuous intravenous infusion (CIVI) schedule for the

administration of belinostat [19]. Thus, 48-h CIVI belinostat was combined with the topoisomerase II inhibitor etoposide and cisplatin in adults with advanced solid tumors, including SCLC and other neuroendocrine cancers. On the basis of the evidence of greater efficacy when an HDI is administered concurrently with chemotherapy [20], particularly topoisomerase inhibitors [15], etoposide and cisplatin infusions were started during the 48-h belinostat infusion.

Patients and methods

Patients

Eligible patients included those who had histologically or cytologically confirmed cancers for which there is no known standard therapy capable of extending life expectancy. Other eligibility criteria were age 18 + years, a life expectancy of 3 months or greater, an Eastern Cooperative Oncology Group performance status of 0–2, more than 4 weeks from cytotoxic chemotherapy, monoclonal antibody therapy, and previous experimental therapy, and acceptable organ and marrow function. Exclusion criteria were as follows: previous HDI within 2 weeks before enrollment, a history of central nervous system metastasis, persistence of an adverse event (AE) from previous therapy greater than grade 1 (except for alopecia, stable grade 2 tinnitus, or stable grade 2 sensory neuropathy), pregnancy, HIV-positive status, significant cardiovascular disease, or a prolonged baseline-corrected QT (QTc) interval.

Study design

This phase I, dose-escalation trial (NCT00926640) followed a traditional 3 + 3 design, with belinostat administered starting in the evening on day 1 by 48-h CIVI (days 1 and 2). Belinostat saline infusion bags were changed every 12 h to address pharmaceutical stability concerns. Cisplatin and etoposide were administered as 1-h intravenous infusions at 80 and 100 mg/m², respectively. Cisplatin was administered 12–14 h following the initiation of belinostat (day 2). Etoposide was administered immediately after cisplatin (day 2), and repeated on days 3 and 4. Therapy was repeated every 3 weeks and continued through six cycles. For patients continuing on the study, belinostat monotherapy was administered after cycle 6.

The primary objective was to determine a safe and tolerable phase 2 dose for the combination of belinostat, cisplatin, and etoposide. Secondary objectives included confirmation of increased protein lysine acetylation in peripheral blood mononuclear cells (PBMCs), evaluation of γ -H2AX, and evaluation of tumor response. Computed tomography scans were performed every two cycles, and response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Confirmatory scans were performed 3 weeks after the initial assessment. This clinical trial was approved by the institutional review board of the National Cancer Institute and all patients provided informed consent before trial enrollment.

Safety evaluations

Routine safety assessments were performed during every follow-up visit as indicated in the protocol. AEs were assessed per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. As HDIs are known to prolong the QTc interval [18,21,22], a 12-lead ECG was performed at baseline, at the start of the belinostat infusion; 12, 20–24, and 36 h into the belinostat infusion; and within 4 h before the end of infusion and 12 h after the end of belinostat infusion. QTc was calculated using the Fridericia method. Analysis of belinostat-induced QTc prolongation was stratified by the *UGT1A1* genotype and analyzed for differences using a Jonckheere–Terpstra trend test, where each patient's value was the average of their cycle 1 QTc measurements.

Pharmacokinetic evaluations

Pharmacokinetic (PK) and pharmacodynamic samples from this study were collected and partially reported previously [23,24]. Here, the average steady-state belinostat plasma concentration during the cycle one 48-h CIVI (C_{ss}) was calculated for each patient from 30 min after the start of infusion until the last sample taken just before the end of infusion. The mean belinostat C_{ss} at each dose level was then evaluated to assess exposure/response relationships with efficacy and AEs. In addition, model-predicted clearance values for these patients (on the basis of our previously published population PK model [24]) were used to assess differences on the basis of the number of variant copies of the polymorphic *UGT1A1*. Although included in that population model [24], these model-predicted clearance values were not explicitly depicted or tabulated.

Pharmacodynamic evaluations

The extent of global protein lysine acetylation in PBMCs was used as a surrogate indicator of histone deacetylase (HDAC) inhibitory activity for pharmacodynamic analysis. Peripheral blood was collected at baseline and at 12, 36, and 60 h after the start of belinostat infusion. PBMCs were isolated and viably frozen until analysis. Global protein lysine acetylation was assessed by multiparameter flow cytometry using a MACSQuant analyzer (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany) as described previously [25]. For the determination of cell lineage-specific acetylation, the cells were first stained for CD45 as a pan-hematopoietic marker together with lineage markers for T-cells (CD3) and B-cells (CD19). The cells were then fixed, permeabilized, and stained for acetylated lysine. The data were analyzed using FlowJo software (FlowJo LLC, Ashland, Oregon, USA) and the change in acetylation postdose relative to baseline was calculated. The following antibodies were used for the detection of cell lineage: anti-CD45 (HI30), anti-CD3 (UCHT1), and anti-CD19 (HIB19) from BioLegend (San Diego, California, USA). Acetylated lysine was detected by incubation with polyclonal rabbit anti-acetylated lysine antibody (Cat#9441) from Cell Signaling Technology (Danvers, Massachusetts, USA), followed by incubation with Alexa Fluor 488-conjugated goat anti-rabbit IgG (H + L) from Invitrogen/ThermoFisher (Waltham, Massachusetts, USA).

γ -H2AX detection

Assessment of DNA damage was performed by measurement of γ -H2AX levels in isolated PBMCs and in hair follicles from plucked scalp hairs. PMBCs were processed from blood collected at predose, 12, 36, and 60 h after the start of belinostat infusion. Hair follicles were collected at the same time points. Both samples (PBMCs and hair follicles) were subjected to the γ -H2AX phosphorylation assay as described previously [18].

Statistical considerations

Statistical evaluations on secondary objectives were completed without adjustment for multiple comparisons. Parametric data were analyzed using a two-tailed *t*-test. A value of *P* less than 0.05 was considered statistically significant. Data are presented as mean $\pm$ SD or mean $\pm$ SE, except for Supplementary Figs S2–S3, which are summarized by group as median with 95% confidence interval. For these data, a Jonckheere–Terpstra trend test was performed (*P* < 0.05, is significant). For global protein acetylation, a Wilcoxon matched-pairs signed-rank test was performed using GraphPad Prism, version 6.0 (GraphPad Software Inc., La Jolla, California, USA) to compare the baseline and post-treatment samples.

Results

Patients

Patient demographics are shown in Table 1. Fifteen (54%) of 28 patients had neuroendocrine tumors, including seven patients with SCLC and two patients with pheochromocytoma/paraganglioma. Patients remained in the study for a median of six cycles, 21/28 (75%) remaining on therapy for at least four cycles and 15/28 (54%) on therapy for at least six cycles. One patient with SCLC remained on study 15 cycles.

Safety and maximum tolerated dose determination

The primary objective of this study was to find the maximum tolerated dose (MTD) of the combination of belinostat, cisplatin, and etoposide. The dose-escalation schema is shown in Table 2. Criteria for exceeding the MTD were fulfilled on the first dose level at 400 mg/m²/24 h, and C + E doses were reduced in the remaining dose levels. One patient on the first dose level developed marked hyper-tension and posterior reversible encephalopathy syndrome, with the vision loss recovering after 5 days. Criteria were again fulfilled after escalation to 800 mg/m²/24 h (Table 2). The MTD was established at 500 mg/m²/24 h.

The main AEs were consistent with the known effects of HDIs, including belinostat in the approved dose and schedule [18] (Supplementary Table S1, Supplemental digital content 1, <http://links.lww.com/ACD/A245>). All laboratory abnormalities were captured, irrespective of clinical significance or attribution. Hematologic toxicities were most common, with thrombocytopenia and neutropenia most frequent. Elevated aspartate aminotransferase and alanine aminotransferase were also noted with relative frequency – of unknown cause. Some patients were observed to be particularly sensitive to the combination.

The cardiac effects of HDIs have been investigated carefully and ECGs were monitored in this study. Most patients had reversible grade 1 or 2 QTc increase (median 29.5 ms QTc increase for all patients in cycle 1), with corrected intervals generally not exceeding 500 ms. Two patients developed grade 3 (QTc > 501 ms on repeated ECGs). One of these patients concurrently had sinus bradycardia associated with hypocalcemia. One patient had a single QTc more than 500 with every cycle of treatment, with the greatest QTc interval change from baseline (QTc) occurring on cycle 5 (95 ms). During the first two cycles (QTc = 71 ms), this patient was on concurrent trazadone, an agent associated with QTc elevation when overdosed [26,27]. With a median increase of 7 bpm, there was no consistent increase in heart rate as observed previously for romidepsin [28].

Efficacy

All 28 patients enrolled on the study were evaluable for response. The details of responses are shown in Tables 3 and 4. Objective responses were observed in 11 (39%) of 28 patients; 13 (46%) of 28 patients had stable disease and four (14%) patients had progressive disease (PD). Among patients with neuroendocrine cancers, including SCLC, seven (47%) of 15 patients achieved an objective response, seven (47%) patients had stable disease, and one (7%) patient had PD. There were no complete responses. Figure 1 shows a waterfall plot depicting best response to treatment. In some cases, responses were dramatic. In one such patient with a neuroendocrine malignancy and previous treatment with standard chemotherapy, imaging showed marked tumor shrinkage in the liver after two cycles of therapy (by MRI; Fig. 2). This patient previously had six cycles standard carboplatin and etoposide, a 12-week break, and disease progression before enrollment in our study.

Pharmacogenomics and pharmacokinetics

Overall, this CIVI of belinostat (with C + E) was unevenly tolerated, where some patients experienced routine toxicities at the MTD that were easily managed, and others showed more significant toxicity. We evaluated *UGT1A1* variants to evaluate the etiology of increased sensitivity. Steady-state plasma concentrations of belinostat (C_{ss}) generally increased with dose from 400 mg/m² to 800 mg/m² and within each dose level; patients categorized as extensive metabolizers had lower C_{ss} compared with impaired metabolizers (Supplementary Fig. S1-A, Supplemental digital content 1, <http://links.lww.com/ACD/A245>). Using model-predicted clearance values from a previously published population model [24], Supplementary Fig. S1-B (Supplemental digital content 1, <http://links.lww.com/ACD/A245>), shows a decreasing trend with the number of variant copies of *UGT1A1*. These data are consistent with *UGT1A1* genotype-dependent trends in grade and toxicity, namely, thrombocytopenia [23].

We also analyzed the association of genotype with QTc prolongation. Overall, there was a statistically significant trend of increasing QTc interval with number of variant copies. Elevated QTc intervals were noted in patients with at least three variant copies of *UGT1A1* ($P = 0.016$) compared with patients with 0 variant copies (Mann–Whitney), suggesting that patients with at least three variant alleles could have greater belinostat exposure that induced longer QTc intervals (Supplementary Fig. S2-A, Supplemental digital content 1, <http://links.lww.com/ACD/A245>). There was no difference in the delta heart rate (Supplementary

Fig. S2-B, Supplemental digital content 1, <http://links.lww.com/ACD/A245>) or the PR interval (not shown) by genotype, nor was there a correlation ($r^2 > 0.5$) between either C_{ss} versus QTc interval or model-predicted clearance versus the QTc interval (not shown).

Pharmacodynamics

We confirmed increased protein lysine acetylation in the circulating blood cell compartments (Supplementary Fig. S3, Supplemental digital content 1, <http://links.lww.com/ACD/A245>). Treatment-mediated DNA damage because of therapy was measured by γ -H2AX phosphorylation in PBMCs and hair follicles at 12, 36, and 60 h after the start of belinostat. Figure 3 shows the time course of γ -H2AX formation in PBMCs, with 36 h postbelinostat start showing the highest γ -H2AX, indicating the greatest level of DNA double-strand breaks. This time course is consistent with the amount of global lysine acetylation observed in a previous PK/PD analysis of this dataset [24]. γ -H2AX formation is observed in hair follicles in a time-dependent manner, showing that drug therapy can target solid tissues. Different from the PBMCs, hair follicle analysis showed that 60 h postbelinostat start corresponded to the highest γ -H2AX phosphorylation (Fig. 3). Differences in γ -H2AX kinetics may be linked to differential drug exposure or DNA repair responses among different cell types and tissues.

Discussion

Platinum and etoposide have been the standard-of-care for SCLC, extrapulmonary small cell cancers, and a variety of other advanced neuroendocrine cancers. The addition of the HDI belinostat to cisplatin and etoposide is based on in-vitro evidence of SCLC sensitivity to single-agent belinostat, especially with prolonged exposure, and synergy between topoisomerase inhibitors and HDIs [7,12–15]. This phase I dose-escalation trial combined cisplatin and etoposide with a CIVI of belinostat and established the MTD at 60 mg/m² cisplatin, 80 mg/m² etoposide, and 500 mg/m²/24 h belinostat. Differential sensitivity to AEs was observed at the MTD, which appeared to be related to the *UGT1A1* genotype. On the basis of PK modeling [24], we conclude that the recommended phase 2 dose would be 600 mg/m²/24 h belinostat for extensive *UGT1A1* metabolizers and 400 mg/m²/24 h belinostat for impaired *UGT1A1* metabolizers [24], with 60 mg/m² cisplatin and 80 mg/m² etoposide.

Criteria for defining ‘extensive’ versus ‘impaired’ *UGT1A1* metabolizers are based on two *UGT1A1* genotypes (*28 and *60). There are over 100 *UGT1A1* polymorphic variants and for many, the functional significance is unknown. *UGT1A1**28 has been the most studied (an additional ‘TA’ in the promoter region reduces expression), particularly for its impact on irinotecan [29] and bilirubin [30] metabolism. Similar observations have been made for belinostat [31], as well as other *UGT1A1* substrates including bilirubin, where the presence of *28 causes Gilbert’s syndrome. Our data showed that *60(–3279T > G) was also associated with lower clearance of belinostat. The impact of the *28 and *60 polymorphisms was most evident at greater doses, where both the frequency and the grade of thrombocytopenia were significantly associated with the *UGT1A1* genotype at a belinostat dose greater than 400 mg/m²/24 h [23]. A similar scenario was also reported for neutropenia

in patients following irinotecan [32,33]. Although efficacy could not be correlated with PK data, any such associations may have been confounded by dose reductions that were undertaken in patients showing more signs or symptoms of toxicity. Occasional patients were noted to have QTc prolongation, possibly related to carriers of the *UGT1A1* variants. It should be noted that QTc intervals are particularly difficult to measure accurately in the context of the ST-T effects of HDIs.

At the first dose level, belinostat dosed at 400 mg/m²/24 h in combination with cisplatin 80 mg/m² and etoposide 100 mg/m² was difficult to tolerate. We hypothesize that this resulted from a PK interaction between etoposide and belinostat on the basis of competition for UGT1A1 metabolism (*albeit* a minor pathway for etoposide), which is supported by the pharmacogenomics associations presented. Most of the etoposide dose is excreted unchanged renally (56%); thus, we did not initially expect a belinostat–etoposide interaction. Although etoposide has other metabolic pathways such as demethylation and hydroxylation by CYP3A4 [34], UGT1A1-mediated glucuronidation [35] appeared to be important in this study. Overall, the proportion of patients requiring dose reduction or modification in our trial is consistent with observations from similar previously carried out studies of cytotoxic chemotherapy in combination with HDIs [36–40].

We also evaluated biomarkers for HDAC inhibition, namely, global lysine acetylation, to ensure that sufficient belinostat exposure was being achieved to induce a pharmacological effect. As shown in our population PK/pharmacodynamic model [24], there was a sustained fold-change increase in global lysine acetylation during the 48-h CIVI that was reversible, consistent with an epigenetic effect. Further, PK data correlated well with toxicity data [23]. In addition, γ -H2AX in PBMCs followed the same reversible time course as global lysine acetylation, whereas hair follicles showed a similar, albeit delayed trend.

Conclusion

Our study shows the safety and clinical activity of belinostat administered as a 48 h infusion with C + E in patients with advanced solid tumors, including SCLC and other neuroendocrine cancers. By using a novel 48-h CIVI, we more closely approximated synergistic laboratory studies [12–15]. An alternative strategy for prolonged HDAC inhibition may be to use an HDI with a very long half-life, such as the benzamides entinostat or chidamide. A subset of patients was particularly sensitive to AEs related to treatment and increased sensitivity appeared to be related to the UGT1A1 genotype. DNA damage related to treatment can be assessed by measuring γ -H2AX in hair follicles. Larger studies are needed to validate our findings and confirm clinical activity at the recommended phase 2 doses ascertained by our study. The data presented here argue for further study, particularly in light of the few therapeutic options available for SCLC and neuroendocrine cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Waterfall plot of best response to treatment. GI, gastrointestinal; SCLC, small cell lung cancer.

Fig. 2.

Response of metastatic neuroendocrine tumor. A 49-year-old man with metastatic cancer of unknown primary site with poorly differentiated neuroendocrine features presented with progressive disease 2 months after receiving six cycles of carboplatin/etoposide. Contrast-enhanced MRI of liver metastases before (left) and after two cycles of infusional belinostat, cisplatin, and etoposide (right) shows a major response to treatment.

Fig. 3.

Pharmacodynamic assessment of γ -H2AX formation in peripheral blood mononuclear cells (PBMCs) and plucked hairs. (a) Diagram depicting sample collection (PBMCs and hairs, arrows) before (pre), and 12, 36, and 72 h during belinostat, cisplatin, and etoposide (BCE) infusions. Time course of drug infusions (red, belinostat; gold, cisplatin; blue, etoposide) is illustrated. γ -H2AX foci per cell (fpc) in PBMCs (b) and hair follicles (c) from individuals plotted as average fpc $\pm$ SEs. Data plotted as average fpc $\pm$ SDs in PBMCs ($n = 24$) (d) and hair follicles ($n = 8$) (e). (d) Representative images of γ -H2AX staining in patients' PBMCs (f) and hair follicles (g) collected before and during the indicated times of BCE infusions. The stereomicroscope image on the left of (g) indicates the region on plucked hairs (white rectangle) where both image capture and γ -H2AX quantification were performed. Insets on the right of (g) show enlarged regions of hairs from the right panels (white squares) and show the γ -H2AX staining pattern in cells at different time points. Note the specific γ -

H2AX panstaining pattern at 60 h (white arrow) that may be indicative of accrued DNA damage and/or apoptosis. Green, γ -H2AX; red, DNA stained with PI. ***A statistically significant difference with the pretreatment samples (pre) ($P < 0.001$).

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Table 1

Patient demographics

Parameters	Mean (range) or <i>N</i>
Age (years)	54.6 (39.8–78.2)
Performance status	
ECOG 0	1
ECOG 1	25
ECOG 2	2
Sex	
Male	18
Female	10
Primary site	
SCLC	7
Neuroendocrine/SCC	6
Pheochromocytoma	2
Carcinoma of Unknown Primary	2
NSCLC	2
Cervical	2
Other	7

Other, one each, adrenocortical cancer, mesothelioma, Leydig cell, endometrial, hepatoid lung, Merkel cell, pancreatic ductal adenocarcinoma.

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer; PGL, paraganglioma; SCC, small cell carcinoma; SCLC, small cell lung cancer.

Table 2

Dose-escalation table

Dose level	n	Belinostat (mg/m ² /24 h)	Cisplatin (mg/m ²)	Etoposide (mg/m ²)	C _{ss} (mean ± SD) (µmol/l)	Dose-limiting toxicities ^a
-1	0	200	80	100	NA	NA
1	3	400	80	100	0.97 ± 0.59	Gr 4 CPK Gr 4 WBC Gr 4 WBC, Gr 4 HTN, Gr 4 Vision
1A	7	400	60	80	0.89 ± 0.32	Gr 3 AST, ALT
2	2	800	60	80	1.61 ± 0.07	Gr 4 Pneumonitis Gr 3 HTN, Gr 3 AST, ALT
1B	6	600	60	80	1.66 ± 0.44	Gr 3 Bradycardia, Gr 3 QcF
1C	10	500	60	80	1.67 ± 0.32	Gr 3 Hypokalemia Gr 3 QTcF

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; C_{ss}, average steady-state belinostat concentration between 30 min from the start to the end of infusion; CPK, creatine phosphokinase; Gr, grade; HTN, hypertension; WBC, white blood cell.

IC₅₀ for histone deacetylase inhibition *in vitro* was 1 µmol/l.

^aDose-limiting toxicities for individual patients listed on separate rows.

Table 3

Summary of best responses

Response data: belinostat + cisplatin + etoposide (N = 28)				
Response	Total (N = 28)	SCLC (N = 7)	NETs (N = 6) ^a	Pheo (N = 2)
CR	0	-	-	-
PR	11	4	3	-
SD	13	3	3	1
PD	4	-	-	1

CR, complete response; NET, neuroendocrine tumor; PD, progressive disease; Pheo, pheochromocytoma; PR, partial response; SCLC, small cell lung cancer; SD, stable disease.

^aNET = two small cell carcinoma prostate; four gastrointestinal NETs.

Table 4Results in patients with small cell lung cancer and neuroendocrine histologies ($N = 15$)

Patient nos	Histology	Previous cytotoxic regimen	Belinostat dose (m ² /24 h)	Best response	Number of cycles
4	SCLC	2 ^a	400	SD	4
6	Prostate (SCC)	1 ^a	400	PR	8
7	SCLC	0	400	PR	6
13	SCLC	1 ^a	600	PR	8
16	SCLC	0	600	PR	6
19	SCLC	2 ^a	500	PR	5
20	Pheochromocytoma	2	500	PD	2
21	Pheochromocytoma	2	500	SD	4
22	Neuroendocrine	1 ^a	500	PR	6
23	SCLC	2 ^a	500	SD	6
24	SCLC	1 ^a	500	SD	4
25	Prostate/neuroendocrine	0	500	SD	3
26	Pancreatic neuroendocrine	0	500	SD	8
27	Prostate (SCC)	0	500	PR	8
28	Gastric neuroendocrine	0	500	SD	4

PD, progressive disease; PR, partial response; SCC, small cell carcinoma; SCLC, small cell lung cancer; SD, stable disease.

^aPlatinum-based.