A phase I pharmacokinetic study of belinostat in patients with advanced cancers and varying degrees of liver dysfunction

Naoko Takebe, National Cancer Institute, Bethesda
Jan H Beumer, UPMC Hillman Cancer Center
Shivaani Kummar, National Cancer Institute, Bethesda
Brian F Kiesel, UPMC Hillman Cancer Center
Afshin Dowlati, University Hospitals Seidman Cancer Center
Geraldine O Coyne, National Cancer Institute, Bethesda
Richard Piekarz, National Cancer Institute, Bethesda
Lawrence Rubinstein, National Cancer Institute, Bethesda
Laura K Fogli, National Cancer Institute, Bethesda
Bassel El-Rayes, Emory University

Journal Title: British Journal of Clinical Pharmacology
Volume: Volume 85, Number 11
Publisher: Wiley | 2019-11-01, Pages 2499-2511
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1111/bcp.14054
Permanent URL: https://pid.emory.edu/ark:/25593/vh0dj

Final published version: http://dx.doi.org/10.1111/bcp.14054

Copyright information:
© 2019 The Authors.
This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/).
Accessed October 21, 2024 6:41 PM EDT
A phase I pharmacokinetic study of belinostat in patients with advanced cancers and varying degrees of liver dysfunction

Naoko Takebe1 | Jan H. Beumer2,3,4 | Shivaani Kummar5 | Brian F. Kiesel2,3 | Afshin Dowlati6 | Geraldine O'Sullivan Coyne1 | Richard Piekars7 | Lawrence Rubinstein5 | Laura K. Fogli5 | Ulka Vaishampayan8 | Sanjay Goel9 | Cindy L. O'Bryant10 | Bassel F. El-Rayes11 | Vincent Chung12 | Heinz-Josef Lenz13 | Richard Kim14 | Chandra P. Belani15 | Joseph M. Tuscano16 | William Schelman17 | Nancy Moore1 | James H. Doroshow5,18 | Alice P. Chen1

1 Early Clinical Trials Development Program, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA
2 Cancer Therapeutics Program, UPMC Hillman Cancer Center, Pittsburgh, PA, USA
3 Department of Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA
4 Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
5 Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA
6 University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA
7 Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA
8 Wayne State University/Karmanos Cancer Institute, Detroit, MI, USA
9 Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY, USA
10 University of Colorado Cancer Center, Aurora, CO, USA
11 Winship Cancer Institute of Emory University, Atlanta, GA, USA
12 City of Hope, Duarte, CA, USA
13 Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA, USA
14 Department of Gastrointestinal Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL, USA
15 Penn State Cancer Institute, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA
16 Comprehensive Cancer Center, University of California Davis Medical Center, Sacramento, CA, USA
17 Carbone Cancer Center, University of Wisconsin, Madison, WI, USA
18 Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Correspondence
Naoko Takebe, MD, PhD, Early Clinical Trials Development Program, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH 31 Center Drive, Bldg. 31 Room 3A-44, Bethesda, MD 20892, USA.
Email: takeben@mail.nih.gov

Aims: The histone deacetylase inhibitor belinostat has activity in various cancers. Because belinostat is metabolized by the liver, reduced hepatic clearance could lead to excessive drug accumulation and increased toxicity. Safety data in patients with liver dysfunction are needed for this drug to reach its full potential in the clinic.
**Methods:** We performed a phase 1 trial to determine the safety, maximum tolerated dose (MTD) and pharmacokinetics of belinostat in patients with advanced cancer and varying degrees of liver dysfunction.

**Results:** Seventy-two patients were enrolled and divided into cohorts based on liver function. In patients with mild dysfunction, the MTD was the same as the recommended phase 2 dose (1000 mg/m²/day). Belinostat was well tolerated in patients with moderate and severe liver dysfunction, although the trial was closed before the MTD in these cohorts could be determined. The mean clearance of belinostat was 661 mL/min/m² in patients with normal liver function, compared to 542, 505 and 444 mL/min/m² in patients with mild, moderate and severe hepatic dysfunction. Although this trial was not designed to assess clinical activity, of the 47 patients evaluable for response, 13 patients (28%) experienced stable disease.

**Conclusion:** While a statistically significant difference in clearance indicates increased belinostat exposure with worsening liver function, no relationship was observed between belinostat exposure and toxicity. An assessment of belinostat metabolites revealed significant differences in metabolic pathway capability in patients with differing levels of liver dysfunction. Further studies are needed to establish formal dosing guidelines in this patient population.

**KEYWORDS**
anticancer drugs, drug metabolism, drug safety, histone deacetylase inhibitor, liver disease

---

**1 | INTRODUCTION**

**Histone deacetylase (HDAC) inhibitors** are a class of agents with the potential to exert antitumour effects through epigenetic modifications of histones. Histone deacetylation is associated with chromatin condensation and repression of transcription, notably of tumour suppressor genes. Preventing deacetylation with HDAC inhibition maintains chromatin in an open conformation and drives the expression of genes associated with cell cycle arrest, differentiation, and induction of cell death. HDAC inhibitors may also sensitize drug-resistant tumour cells to other antineoplastic agents by driving gene expression changes in relevant pathways. HDAC inhibitor-induced downregulation of the enzyme thymidylate synthase, for example, has been shown to sensitize cells to the antimetabolite fluorouracil, and changes in BRCA1/2 expression caused by the HDAC inhibitor vorinostat may confer susceptibility to poly ADP-ribose polymerase (PARP) inhibition. Furthermore, this class of agents may possess antiangiogenic properties, as HDAC inhibitor treatment depletes vascular endothelial cell growth factor and inhibits the proliferation of endothelial cells.

The novel hydroxamic acid-type HDAC inhibitor belinostat has been shown to provide clinical benefit as a single agent in patients with various haematological malignancies, as well as in combination with chemotherapy in solid tumours. Durable complete responses have been observed with belinostat in patients with peripheral and cutaneous T-cell lymphomas, and, based on these data, belinostat (BELEODAQ, Spectrum Pharmaceuticals, Inc.) has been approved by the Food and Drug Administration for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Furthermore, in combination with carboplatin and paclitaxel chemotherapy, belinostat has demonstrated encouraging activity in different types of solid tumours, including platinum-resistant ovarian cancer.
Overall, belinostat is well tolerated, with the most common toxicities including nausea, fatigue, anaemia and vomiting. The recommended phase 2 dose is 1000 mg/m²/day on days 1–5 of a 21-day cycle.\textsuperscript{11,15}

While this agent possesses great promise for the treatment of various tumour types, questions remain regarding dosing guidelines for patients with organ dysfunction. With only up to 2% of total administered belinostat excreted unchanged in the urine, dose modifications are generally unwarranted for patients with kidney dysfunction.\textsuperscript{10,15} However, adjustments may be needed for patients with liver dysfunction. Belinostat is rapidly metabolized by the liver into metabolites, which are eliminated primarily through the kidneys.\textsuperscript{15–17} These resulting metabolites are inactive and not likely to be relevant to safety or tolerability. However, changes in enzyme activity and hepatic blood flow caused by liver disease can result in a reduction in hepatic metabolism and lead to increased parent belinostat exposure, potentially having a significant effect on drug-related toxicity.\textsuperscript{18} Therefore, the safety and dosing schedule of belinostat need to be established in patients with impaired liver function by a thorough evaluation of the drug’s pharmacokinetics (PK).\textsuperscript{15} The Food and Drug Administration emphasized the need for these data when issuing approval of the new drug application for belinostat, and the postmarketing study requirements included PK characterization of belinostat in patients with hepatic impairment.\textsuperscript{19}

To fulfill this postmarketing requirement, we performed a multicentre phase 1 study (NCT01273155) to evaluate the PK, establish the safety, and determine the maximum tolerated dose (MTD) of belinostat in patients with solid tumours or lymphomas and varying degrees of liver dysfunction. Patients with normal liver function were also included as a control cohort to enable a direct comparison with patients with liver dysfunction. This study was conducted by the Organ Dysfunction Working Group sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute.

2 METHODS

2.1 Eligibility criteria

Patients 18 years or older were eligible if they had solid tumours or lymphomas that were metastatic, unresectable, progressive or recurrent, and for which standard treatment measures that prolong survival did not exist or were no longer effective. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status \(\leq 2\); a life expectancy of \(>3\) months; and adequate organ and marrow function as defined by an absolute neutrophil count \(\geq 1500/\mu\text{L}\), leucocytes \(\geq 3000/\mu\text{L}\), platelets \(\geq 100\,000/\mu\text{L}\) and serum creatinine within normal institutional limits (or creatinine clearance \(\geq 60\text{ mL/min}/1.73\text{ m}^2\), as determined by a measured 24-hour creatinine clearance, for patients with creatinine levels above institutional normal).

Patients were excluded from the study if they had received prior therapy with belinostat, had uncontrolled intercurrent illness including ongoing or active untreated infection or active haemolysis, or had significant cardiovascular disease or cardiac illness. Patients were advised to avoid concomitant drugs that may cause QTc prolongation. Patients with brain metastases were eligible if the most recent brain irradiation was completed more than 4 weeks prior to entering the study. Patients were required to have completed chemotherapy or radiotherapy at least 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

Human immunodeficiency virus-positive patients on combination antiretroviral therapy were considered ineligible because of the potential for PK interactions with belinostat; human immunodeficiency virus-positive patients not on antiretroviral therapy were eligible for the normal liver function cohort only. Patients with chronic hepatitis B or C were eligible unless they required treatment with interferon. Pregnant women and women who were breastfeeding were excluded.

Patients with abnormal liver function were grouped into cohorts based on their level of liver dysfunction (cohort assignment criteria are defined in Table 1). Patients with biliary obstruction for which a stent has been placed were eligible, provided the stent had been in place for at least 10 days prior to the first dose of belinostat, and liver function had stabilized. Patients with normal liver function were eligible and grouped into a control cohort for comparison with the liver dysfunction cohorts.

2.2 Trial design

This study was a phase 1 dose escalation trial establishing the tolerability and evaluating the PK of belinostat in patients with varying

| TABLE 1 | Belinostat dose levels (mg/m²) based on liver function |
|---------|-------------------------------------------------|
| Dose level | \(\leq 1\) | 1 | 2 | 3 | 4 |
| Normal function | 750 | 1000 | No escalation | No escalation | No escalation |
| (bilirubin \(\leq\) ULN and AST \(\leq\) ULN) | | | | | |
| Mild dysfunction | 500 | 750 | 1000 | No escalation | No escalation |
| (bilirubin > ULN but \(\leq 1.5\times\) ULN and/or AST > ULN) | | | | | |
| Moderate dysfunction | 250 | 500 | 750 | 1000 | No escalation |
| (bilirubin >1.5 to \(\leq 3\times\) ULN and any AST) | | | | | |
| Severe dysfunction | 125 | 250 | 350 | 500 | 750 |
| (bilirubin >3 but \(\leq 10\times\) ULN and any AST) | | | | | |

AST, aspartate transaminase; ULN, upper limit of normal.
degrees of liver dysfunction. After discussions with the trial sponsor, a conventional 3 + 3 dose escalation method was chosen to best ensure patient safety. Belinostat was supplied by the National Cancer Institute’s Division of Cancer Treatment and Diagnosis under a Clinical Trials Agreement (CTA) with TopoTarget A/S (now Onxeo).

On days 1–5 of each 21-day cycle, patients received belinostat at a dose dependent on their liver dysfunction cohort and dose level. Belinostat was administered intravenously over 30 minutes. All patients received a single dose of 400 mg/m² of belinostat on Cycle 1 Day –7 for PK analysis (the total length of Cycle 1 was 28 days).

Table 1 shows the dose escalation for each cohort. The initial cohorts of patients began on dose level 1. Patients with normal liver function did not have their dose escalated. The mild liver dysfunction cohort were escalated according to a standard 3 + 3 design; moderate and severe cohorts had a similar dose escalation design, but with the flexibility to accru an additional 1 or 2 patients per dose level.

Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Dose-limiting toxicity (DLT) was based on events observed in the first cycle of therapy, and was defined as an AE deemed possibly, probably or definitely related to administration of study drugs and fulfilled 1 of the following criteria: grade ≥ 3 nonhaematological toxicity (except grade ≥ 3 diarrhoea, nausea, vomiting responsive to supportive therapy); grade ≥ 3 rise in creatinine (unless grade 3 able to be corrected to grade 1 or baseline within 24 hours); grade ≥ 3 electrolyte toxicities (except those able to be corrected to grade 1 or baseline within 48 hours); grade 4 thrombocytopenia; grade 4 neutropenia for >5 days or febrile neutropenia; any neurotoxicity grade ≥ 3 reversible to grade 1 or baseline within 48 hours); grade 4 thrombocytopenia; grade 4 neutropenia for >5 days or febrile neutropenia; any neurotoxicity grade ≥ 2 not reversible to grade 1 or baseline within 2 weeks; or any delay in treatment by ≥2 weeks due to treatment-related toxicity. Worsening liver function, as defined by a rise in serum bilirubin not related to tumour progression, was considered a DLT if a patient in the mild group progressed into the severe dysfunction range for 1 week, or if a patient in either the moderate or severe groups had a >1.5× increase in bilirubin lasting 1 week.

Radiological response assessments by computed tomography scans were performed at baseline and every 2 cycles to evaluate tumour response based on the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

This trial was conducted under a National Cancer Institute-sponsored investigational new drug application with institutional review board approval. Protocol design and conduct followed all applicable regulations, guidance, and local policies.

2.3 | Safety assessments

History and physical examination were performed at baseline and at the start of every cycle. Complete blood counts with differential and serum chemistries were performed at baseline, weekly during Cycle 1, and at the beginning of every subsequent cycle. Electrocardiograms were done prestudy, on Cycle 1 Day 5 within 5 hours after the belinostat dose, and prior to the dose at the beginning of Cycle 2. Serum magnesium was assessed at baseline and as clinically indicated.

Prothrombin time, international normalized ratio, and activated partial thromboplastin time were checked at baseline in all patients; patients requiring warfarin therapy were advised to have their prothrombin time/international normalized ratio monitored carefully by their local physicians.

2.4 | Pharmacokinetic evaluations

Blood samples for PK studies were collected in heparinized tubes prior to infusion; 15 and 25 minutes after the start of infusion; and 5, 10, 15, 30, 60 and 90 minutes, and 2, 4, 6, 8, and 24 hours after the end of infusion. Blood samples were centrifuged at 1000× g for 10 minutes to separate and collect plasma, which was stored at −70°C until analysis.

Quantitative determination of plasma concentrations of belinostat and 5 metabolites was performed with a previously validated assay. PK parameters were calculated noncompartmentally using PK Solutions 2.0 (Summit Research Services, Montrose, CO, USA). Effects of liver dysfunction on PK parameter values were evaluated with SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA), using the Jonckheere–Terpstra and Kendall’s τ test. Data was considered significantly different when P < .05. Metabolic ratios were calculated for both maximum plasma concentration (Cmax) and area under the plasma concentration–time curve extrapolated to infinity (AUC0–inf) by dividing the metabolite parameter value by the parent drug parameter value. The relationship of belinostat Cmax and AUC with grade ≥2 AE occurrence was analysed by cohort and in aggregate using nonparametric Mann–Whitney U tests.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18.

3 | RESULTS

3.1 | Patient characteristics

Seventy-two patients were enrolled in this study between March 2011 and August 2017. The median age was 60 years (range, 30–77), and the median number of prior treatments was 6 (range, 1–20). Except for 1 patient with lymphoma, all patients had solid tumours, with colorectal cancer being the most common. Only patients who received all 6 Cycle 1 doses of belinostat and remained on study until the end of Cycle 1 were considered evaluable for DLT (n = 40). The others came off study prior to the end of Cycle 1 (due to disease progression, intercurrent illness, toxicity, or withdrawal from study) and were not evaluable. Additional patient demographics are shown in Table 2.
Fourteen patients had normal liver function, while the remaining patients had some degree of liver dysfunction (30, 10, and 18 patients had mild, moderate and severe dysfunction, respectively, at time of enrollment). Patients were dosed with belinostat based on liver function cohort (see Table 1). All patients with normal liver function were placed on dose level (DL) 1 and were not eligible for dose escalation. All 3 liver function cohorts were escalated from DL 1 to DL 2. Three patients were switched from the mild to moderate cohort within the first week of Cycle 1 due to declining liver function; these patients were unevaluable for dose escalation and response, but were included in the safety analysis as part of the moderate cohort.

### 3.2 Toxicity

Patients who received at least 1 dose of belinostat were considered evaluable for toxicity (n = 66). Belinostat was generally well tolerated with most AEs being grade 1/2. The frequency of grade ≥3 events did not correlate with degree of liver dysfunction (Table 3); while 35.7% (5/14) of patients in the normal cohort had a grade ≥ 3 AE, 17.4% (4/23) and 25% (3/12) of patients in the mild and moderate cohorts, respectively, experienced grade ≥ 3 toxicity. Grade ≥ 3 events were less frequent in the severe cohort, although this may be due to the fact that these patients spent less time on study (Figure 1).

Fatigue, lymphopenia and anaemia were the most common AEs in the study overall and were not unexpected. Grade 2 or greater fatigue, lymphopenia or anaemia occurred and were attributed to the study drug in 21.9, 18.8 and 17.1% of all treated patients, respectively (Table 4). Increased bilirubin was also observed in patients on DL 2 and deemed to be possibly or probably related to the study drug. In the severe liver dysfunction cohort, 1 grade 5 lung infection (DL 1) considered to be possibly related to the study treatment occurred.

Overall, there were 6 patients in the mild cohort at DL 2 (1000 mg/m²) that were evaluable with no DLTs, establishing the MTD for patients with mild liver dysfunction at 1000 mg/m². The study was closed once adequate PK sampling had occurred; due to slow accrual, the MTD was not established for the moderate and severe cohorts prior to study closure. The moderate cohort had a total of 3 evaluable patients with no DLTs at DL 2 (750 mg/m²) but was not escalated to DL 3. The severe cohort was expanded at DL 1 (250 mg/m²) due to a possible DLT, but this event was later determined to be unrelated to study drug. In a total of 6 evaluable patients on DL 1, there was 1 true DLT (grade 5 lung infection, mentioned above). The severe cohort was then escalated to DL 2 (350 mg/m²), but because several patients experienced disease progression and went off study, the severe cohort had accrued only 1 evaluable patient at DL 2 before the study was closed.

### 3.3 Pharmacokinetics

PK was evaluated in 64 patients (Table 5). Moderate but statistically significant changes were observed in parent belinostat clearance and AUC as a function of the degree of liver dysfunction, although significant changes were not observed for C_max, half-life or apparent volume of distribution at steady state (Figure 2, Figure 3A-B, and Table 5). Mean clearance was 661 mL/min/m² in patients with normal liver function, compared to 542, 505 and 444 mL/min/m² in patients with mild, moderate and severe hepatic dysfunction, respectively, with a corresponding increase in AUC. Increases in belinostat exposure were moderately correlated with worsening liver function (r = 0.215), and there was no obvious relationship between exposure and DLTs during the first cycle of therapy. While there was a trend towards increased belinostat half-life with worsening liver function, this difference did
not reach statistical significance, probably due to the small effect size (33% increase from normal to severe) and large relative standard deviation.

Glucuronidation is the primary pathway for metabolism of belinostat, but other metabolic processes also play a role (Figure 4). Liver dysfunction affected patient disposition of belinostat and its metabolites, which represent distinct metabolic pathways. The predominant glucuronide metabolite had large within-cohort variation in exposure (Figure 3C,D) and no statistically significant difference in exposure with worsening liver function, although there was a statistically significant change in half-life (Table 5). A similar pattern was observed with M26 with no significant impact on \(C_{\text{max}}\) (Figure 3K).

**TABLE 3** Incidence of grade 3 or greater adverse events at least possibly related to study drug

| By liver function cohort\(^a\) | All patients |
|-------------------------------|-------------|
| **Dose level 1**              |             |
| Normal \((n = 14)\)           | Normal \((n = 9)\) | Moderate \((n = 6)\) | Severe \((n = 9)\) | \((n = 38)\) |
| (5 (35.7))                    | 1 (11.1)    | 1 (16.7)    | 1 (11.1)    | 8 (21.1) |
| **Dose level 2**              |             |
| Normal \((n = 14)\)           | Normal \((n = 6)\) | Moderate \((n = 8)\) | Severe \((n = 8)\) | \((n = 28)\) |
| (N/A)                         | 3 (21.4)    | 2 (33.3)    | 1 (12.5)    | 6 (21.4) |
| **All dose levels**           |             |
| Normal \((n = 14)\)           | Normal \((n = 23)\) | Moderate \((n = 12)\) | Severe \((n = 17)\) | \((n = 66)\) |
| (5 (35.7))                    | 4 (17.4)    | 3 (25)      | 2 (11.8)    | 14 (21.2) |

\(^a\)Data are shown as number (%) of patients with at least 1 grade \(\geq 3\) event within each liver function cohort and dose level.

\(^b\)All patients who received at least 1 dose of study drug were evaluable for assessment of toxicity.

![Graph](image_url)
but statistically significant increases in AUC (Figure 3L) and half-life (Table 5). M24, the proposed \( \beta \)-hydroxylation product of M26, showed a significant decrease in \( C_{\text{max}} \) (Figure 3I) but no discernible change in either AUC (Figure 3J) or half-life (Table 5). The most dramatic changes were observed in methyl belinostat and M21 (belinostat amide), both of which showed statistically significant increases in \( C_{\text{max}} \) (Figure 3E and G), AUC (Figure 3F and H), and half-life (Table 5) with worsening liver function.

Comparing metabolic ratios of metabolite-to-parent as a relative measure of metabolic pathway capability revealed several statistically significant differences between cohorts that were associated with degree of liver dysfunction (Table 6, Figure 5). The glucuronide to belinostat metabolic ratios of \( C_{\text{max}} \) (Figure 5A) but not AUC (Figure 5B) resulted in a statistically significant trend showing a decreased ability to produce the metabolite in patients with increasing liver dysfunction.

Methyl belinostat and M21 had statistically significant increases in metabolic ratios for \( C_{\text{max}} \) and AUC with worsening liver function (Figure 5C-F). M26 only showed a statistically significant increase in metabolic capability in AUC (Figure 5J), not \( C_{\text{max}} \) (Figure 5I). M24 had a statistically significant decrease in metabolic ratios for \( C_{\text{max}} \) and AUC with worsening liver function (Figure 5G-H). The largest change in metabolic ratio (approximately 2-fold) was observed for the AUCs of methyl belinostat to parent (Figure 5D) and M24/M26 (Figure 5L).

Statistical evaluation of belinostat \( C_{\text{max}} \) or AUC and grade \( \geq 2 \) AE occurrence revealed no relationship (determined by a \( P \)-value > .05, not corrected for multiple testing) for patients in aggregate or by cohort except for the AUC of the moderate cohort (\( P = .019 \); data not shown). However, patients who experienced grade \( \geq 2 \) toxicity had a lower AUC than patients that did not, which is counterintuitive and likely to be a spurious finding.

### 3.4 Clinical outcome

Patients were considered evaluable for response if they received at least 1 cycle of therapy, and either had their disease re-evaluated with interval imaging or exhibited objective disease progression prior to the end of Cycle 1 but after receiving all Cycle 1 doses. Of the 47 patients evaluable for response, 13 (27.7%) had stable disease after the first 2 cycles (Figure 1; 11 patients on DL 1, 2 patients on DL 2). No complete or partial responses were observed with belinostat treatment in any of the 4 cohorts.

---

**TABLE 4** Grade \( \geq 2 \) adverse events (at least possibly related to study drug) reported by \( \geq 5 \% \) of all treated patients, shown as the number of patients per grade for each event (highest grade reported per patient)

| DOSE LEVEL 1 | Normal (n = 14) | Mild (n = 9) | Moderate (n = 6) | Severe (n = 9) |
|--------------|----------------|-------------|-----------------|--------------|
|              | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 |
| Anaemia      | 1      | 1       | 1      | -      | 3      | -       | -      | -       | -      | -      | -      | -      | -      | -      |
| Fatigue      | 2      | 1       | 1      | 1      | 1      | -       | -      | -       | -      | -      | -      | -      | -      | -      |
| Lung infection | -     | -       | -      | -      | -      | -       | -      | -       | -      | -      | -      | -      | -      | -      |
| Lymphocyte count decreased | 1      | 3       | -      | -      | 1      | 1       | -      | -       | -      | -      | -      | -      | -      | -      |
| Nausea       | 3      | -       | -      | -      | -      | -       | -      | -       | -      | -      | -      | -      | -      | -      |
| Vomiting     | 1      | -       | 1      | -      | -      | -       | 1      | -       | -      | -      | -      | -      | -      | -      |

| DOSE LEVEL 2 | Mild (n = 14) | Moderate (n = 6) | Severe (n = 5) |
|--------------|---------------|-----------------|---------------|
|              | Grade 2 | Grade 3 | Grade 2 | Grade 3 | Grade 2 | Grade 3 |
| Anaemia      | 3      | -       | 1      | -      | 1      | -       |
| Bilirubin increased | -     | -       | 1      | 2      | -      | -       |
| Fatigue      | 2      | 2       | 1      | 2      | -      | -       |
| Lymphocyte count decreased | 4      | -       | -      | -      | 2      | -       |
| Nausea       | 3      | -       | -      | -      | -      | -       |
| Vomiting     | 1      | 1       | -      | -      | -      | -       |

*All patients who received study drug were evaluable for adverse event assessment, with the exception of those who received only the Cycle 1 Day −7 dose.

*Only grade \( \geq 2 \) AEs considered to be at least possibly related to study drug are included.

*This event occurred in only 1 patient.
DISCUSSION

The HDAC inhibitor belinostat has been shown to have antitumour activity and a tolerable safety profile, but because belinostat is primarily eliminated via hepatic metabolism, safety information and PK data are needed for patients with liver dysfunction. The results reported here detail the assessment of belinostat safety, tolerability and PK in patients with advanced cancers and mild, moderate or severe liver dysfunction.

Belinostat was generally well tolerated in this study. We found the MTD in the mild cohort to be the same as in patients with normal liver function, indicating that no dose adjustment is necessary in patients with mild hepatic impairment. We could not formally determine the MTD in patients with more severe liver dysfunction, but our data suggest that increased belinostat exposure in these patients is not linked to significant differences in tolerability.

Patients with normal liver function demonstrated similar PK to previous reports, and the clearance of 661 mL/min/m² suggests a high extraction of drug at 76% of liver blood flow, which makes clearance of the drug especially susceptible to changes in blood flow, such as those associated with cirrhosis. Indeed, our results demonstrated moderately impaired clearance of belinostat in patients with hepatic dysfunction, indicating that no dose adjustment is necessary in patients with mild hepatic impairment. We could not formally determine the MTD in patients with more severe liver dysfunction, but our data suggest that increased belinostat exposure in these patients is not linked to significant differences in tolerability.

Table 5: Pharmacokinetic parameters shown as mean (standard deviation) for belinostat and metabolites on cycle 1 day −7 as a function of degree of liver dysfunction

|                  | Normal (n = 14) | Mild (n = 25) | Moderate (n = 10) | Severe (n = 15) | P-value | τ |
|------------------|----------------|--------------|------------------|----------------|---------|---|
| Belinostat       |                |              |                  |                |         |   |
| C(max) (μg/mL)   | 21.9 (8.7)     | 26.6 (9.5)   | 22.1 (5.7)       | 25.0 (7.4)     | .327    | .096 |
| AUC0−inf (μg/mL/min) | 719 (265)     | 859 (270)    | 834 (217)        | 1012 (408)     | .025    | .215 |
| t1/2 (min)       | 118 (90)       | 127 (57)     | 144 (86)         | 157 (118)      | .340    | .091 |
| Clearance (mL/min/m²) | 661 (346)     | 542 (214)    | 505 (114)        | 444 (137)      | .023    | −.216 |
| Vss (L/m²)       | 30.1 (16.1)    | 25.7 (17.4)  | 38.1 (40.4)      | 29.6 (15.4)    | .531    | .060 |
| Belinostat glucuronide |          |              |                  |                |         |   |
| C(max) (μg/mL)   | 80.8 (27.3)    | 90.8 (19.2)  | 67.2 (33.6)      | 72.8 (28.2)    | .063    | −.178 |
| AUC0−inf (mg/mL/min) | 15.1 (10.4)   | 18.4 (5.9)   | 18.4 (13.4)      | 23.4 (25.6)    | .548    | .057 |
| t1/2 (min)       | 280 (55)       | 246 (59)     | 238 (128)        | 267 (134)      | .023    | −.216 |
| Methyl belinostat|                |              |                  |                |         |   |
| C(max) (μg/mL)   | 2.10 (0.94)    | 2.99 (1.15)  | 3.26 (0.75)      | 3.35 (0.90)    | <.001   | .382 |
| AUC0−inf (μg/mL/min) | 354 (305)     | 483 (163)    | 829 (471)        | 930 (797)      | <.001   | .426 |
| t1/2 (min)       | 79.6 (38.9)    | 80.3 (19.1)  | 136.1 (96.0)     | 133 (98)       | .005    | .268 |
| M21              |                |              |                  |                |         |   |
| C(max) (μg/mL)   | 1.26 (0.75)    | 1.79 (0.70)  | 1.64 (0.32)      | 1.93 (0.59)    | .009    | .253 |
| AUC0−inf (μg/mL/min) | 647 (884)     | 840 (589)    | 1,058 (398)      | 1,295 (600)    | <.001   | .337 |
| t1/2 (min)       | 305 (337)      | 460 (324)    | 486 (191)        | 485 (205)      | .011    | .242 |
| M24              |                |              |                  |                |         |   |
| C(max) (μg/mL)   | 2.56 (0.77)    | 2.35 (0.96)  | 1.82 (0.65)      | 1.88 (0.96)    | .004    | −.278 |
| AUC0−inf (μg/mL/min) | 1009 (555)    | 916 (450)    | 885 (514)        | 970 (693)      | .524    | −.061 |
| t1/2 (min)       | 264 (106)      | 253 (97)     | 223 (119)        | 260 (133)      | .231    | −.114 |
| M26              |                |              |                  |                |         |   |
| C(max) (μg/mL)   | 1.68 (0.71)    | 1.80 (0.64)  | 1.83 (0.52)      | 2.24 (1.65)    | .312    | .098 |
| AUC0−inf (μg/mL/min) | 361 (193)     | 396 (164)    | 600 (292)        | 740 (576)      | .010    | .246 |
| t1/2 (min)       | 131 (115)      | 151 (194)    | 177 (95)         | 153 (83)       | .021    | .220 |

*n represents the number of patients in a given cohort that received belinostat on Cycle 1 Day −7 and had blood samples successfully collected at the specified timepoints for pharmacokinetic analysis.

Statistically significant P-values (Jonckheere–Terpstra) and τ (Kendall’s tau) values are bolded.

Three patients with nonevaluable C(max).

The % of AUC0−inf extrapolated beyond AUC0−t was less than 9.0% (belinostat), 16.1% (glucuronide), 19.6% (methylbelinostat), 40.1% (M21, mean 14.5%), 30.2% (M24, mean 5.0%), and 19.7% (M26).

One patient with nonevaluable AUC.

AUC0−inf, area under the plasma concentration–time curve extrapolated to infinity; C(max), maximum plasma concentration; t1/2, half-life; Vss, apparent volume of distribution at steady state.

4 | DISCUSSION

The HDAC inhibitor belinostat has been shown to have antitumour activity and a tolerable safety profile, but because belinostat is primarily eliminated via hepatic metabolism, safety information and PK data are needed for patients with liver dysfunction. The results reported here detail the assessment of belinostat safety, tolerability and PK in patients with advanced cancers and mild, moderate or severe liver dysfunction.

Belinostat was generally well tolerated in this study. We found the MTD in the mild cohort to be the same as in patients with normal liver function, indicating that no dose adjustment is necessary in patients with mild hepatic impairment. We could not formally determine the MTD in patients with more severe liver dysfunction, but our data suggest that increased belinostat exposure in these patients is not linked to significant differences in tolerability.

Patients with normal liver function demonstrated similar PK to previous reports, and the clearance of 661 mL/min/m² suggests a high extraction of drug at 76% of liver blood flow, which makes clearance of the drug especially susceptible to changes in blood flow, such as those associated with cirrhosis. Indeed, our results demonstrated moderately impaired clearance of belinostat in patients with hepatic dysfunction.
dysfunction, although no distinction was made in aetiology of liver dysfunction (i.e. cirrhosis vs liver metastases, chronic hepatitis or other causes). While the presence of ascites can impact PK profiles, only a single patient with severe liver dysfunction had ascites on the day of PK sampling, and this patient was not an outlier in terms of the PK parameters within the severe cohort, eliminating ascites as a factor to explain PK variability in our dataset. Although even a small increase in exposure has the potential to cause toxicity, no relationship was observed between belinostat exposure and DLTs. This may be explained by the brief exposure period in the moderate and severe liver dysfunction cohorts, or by the tolerability of belinostat at the

**FIGURE 2** Geometric mean belinostat plasma concentration vs time for patients with normal (○), mild (□), moderate (△), and severe (▽) liver dysfunction. Error bars represent geometric standard deviation

**FIGURE 3** Plots showing maximum plasma concentration (C_max) and area under the plasma concentration–time (AUC) values for belinostat and its metabolites in patients with varying degrees of liver dysfunction. C_max and AUC are shown for belinostat (A, B), belinostat glucuronide (C, D), methyl belinostat (E, F), M21 (G, H), M24 (I, J) and M26 (K, L). The dots represent individual values; the bar indicates the mean of each group. Data are summarized and statistics are provided in Table 5. n = normal liver function; H1 = mild, H2 = moderate and H3 = severe liver dysfunction

**FIGURE 4** Metabolic pathways of belinostat and metabolites with putative enzymatic pathways involved. The schema includes observed statistical significance by Jonckheere–Terpstra (bold if P < .05) and direction of effects of liver dysfunction on metabolic ratios
doses used, supported by previous trials. In the phase 1 trial that
determined the MTD to be 1000 mg/m² days 1−5 every 21 days, only
3 of 24 patients (12.5%) experienced DLT at that dose. While 3 of
5 patients experienced DLT at 1200 mg/m²/day and did not reach the MTD. Furthermore, in a study of 13-cis-retinoic acid and belinostat, MTD was not
reached even at 2000 mg/m²/day. If belinostat is truly tolerable at
doses up to double 1000 mg/m², minor variability in exposure at 1000 mg/m² would not be expected to result in a meaningful impact on tolerability. Indeed, we could not detect an impact of belinostat exposure on the occurrence of grade ≥ 2 AEs. Higher doses may be
associated with excessive exposure and increased toxicity in patients with liver dysfunction, but our study closed before patients with moderate and severe liver dysfunction were enrolled on the highest dose levels (above 750 mg/m²).

All described metabolic changes to belinostat affect the hydroxamate moiety and inactivate the molecule, similar to related HDAC inhibitors such as vorinostat, trichostatin A and panobinostat; therefore, these resulting metabolites are not likely to be relevant to the tolerability of belinostat therapy. However, our study is unique in that, in addition to evaluating the safety of belinostat in patients with liver dysfunction, it also characterizes the impact of liver dysfunction on the generation of various belinostat metabolites. The predominant metabolic pathway for belinostat is
glucuronidation mediated by the UDP-glucuronosyltransferase
UGT1A1 and UGT2B7 (41.4% of dose by clinical mass balance), but methylation (1.9%), β-oxidation (6.1% M24) and metabolism by CYP450 (M21, M26) also contribute (Figure 4). We calculated Cmax and AUC metabolic ratios of the various metabolites to evaluate the impact of liver dysfunction on each of these different metabolic steps. We observed an impact on Cmax, but not AUC, metabolic ratios of glucuronidation, which is a metabolic step that is reportedly less sensitive to changes in liver function than those involving phase I enzymes, although some of these reports are based on studies with only mild to moderate liver dysfunction. Furthermore, UGT1A1 expression is not restricted to the liver, with the small intestine also expressing the enzyme. Possibly, the significant increase in belinostat glucuronide half-life with liver dysfunction is due to reduced efflux transporter expression associated with cholestatic disease, an effect that would prevent the significant decrease in Cmax metabolic ratio from translating to a decreasing AUC with liver dysfunction.

Methyl belinostat and M21 (belinostat amide) had counterintuitive
increases in Cmax and AUC with worsening liver function. Although cirrhosis has been shown not to impair the efficiency of nicotinamide methylation, the exact enzyme responsible for belinostat methylation is not known. M21 is reportedly produced by CYP2A6/3A4/2C9. While the expression of CYP enzyme genes and corresponding nuclear receptors is generally decreased in end-stage liver diseases,
the impact of liver dysfunction on specific CYP enzymes is not uniform. CYP2A6 and CYP3A4 activity is reportedly decreased with increasing liver dysfunction, while CYP2C9 is not affected. Possibly, the contribution of methyl belinostat and M21 to the metabolic clearance is increased indirectly by a decreased contribution of the other metabolic pathways. Interestingly, the M24/M26 metabolic ratios displayed a significant decline of more than a factor of 2 with increasing liver dysfunction, suggesting that \( \beta \)-hydroxylation is a metabolic process relatively sensitive to impaired liver dysfunction. M26 can be generated either directly from belinostat or upon amide hydrolysis of M21. In the latter case, assuming amide hydrolases are ubiquitous in the body, the ratio of M26/M21 would not be affected. We found a significant change in M26/M21 metabolic ratio in AUC, not \( C_{\text{max}} \) (Table 6), although this was driven by a difference between the normal cohort and all 3 dysfunction cohorts, without a progressive trend as dysfunction increases in severity.

While the primary objectives of this trial were to assess the safety and PK of belinostat in patients with reduced hepatic function, the study also provided an opportunity to evaluate the clinical activity of the drug in this patient population. While no objective responses were observed, 13 heavily pretreated patients experienced stable disease, with 1 patient remaining on study for 12 cycles. The lack of clinical response may be partially due to the high rate of study discontinuation, associated with the advanced nature of disease in these patients. Belinostat may also have limited clinical utility as a monotherapy in patients with solid tumours, as its most marked single agent activity has been seen in lymphoid malignancies, specifically T cell lymphoma.

This phase I study evaluated the effect of liver dysfunction on belinostat PK and tolerability and found that small increases in exposure due to mildly impaired hepatic drug clearance were not associated with increased toxicity. Patients with mild liver dysfunction tolerated belinostat at normal doses. However, an in-depth assessment of disposition of belinostat and its metabolites in patients with different levels of liver dysfunction revealed significant differences in metabolic pathway capability among liver function cohorts. Although formal dose adjustment guidance cannot be projected from this study, we can recommend that when using this drug in patients with advanced liver dysfunction, clinicians exercise caution and monitor patients closely. Additional studies would be required to evaluate higher doses of belinostat in patients with liver dysfunction and to determine whether dosing adjustments are needed in patients with moderate or severe hepatic impairment.

ACKNOWLEDGEMENTS

This project has been funded in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract Number HHSN261200800001E. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government. This study was also supported by Topotarget A/S (Topotarget A/S has since merged with BioAlliance Pharma SA to form Onxeo) and by the following grants: U01-CA099168, UM1-CA186690 (NCI-CTEP), R50 CA211241 (NCI). The PK study was
performed using the UPMC Hillman Cancer Center Cancer Pharmacokinetics and Pharmacodynamics Facility (CPPF) and was supported in part by award P30-CA47904 and by Spectrum Pharmaceuticals.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.H.B., S.K., R.P. and J.H.D. were involved in the conception and trial design. N.T., S.K., A.D., G.O.C., U.V., S.G., C.L.O., B.F.E., V.C., H.L., R.K., C.P.B., J.M.T., W.S., N.M. and A.P.C. were responsible for patient care and data acquisition. N.T., J.H.B., S.K., B.F.K., L.K.F., N.M., J.H.D. and A.P.C. performed data analysis and interpretation. J.H.B., B.F.K., and L.R. performed statistical analysis. N.T., J.H.B., B.F.K., L.K.F., J.H.D., and A.P.C., wrote the manuscript with input from all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at ClinicalTrials.gov, reference number NCT01273155.

ORCID

Jan H. Beumer https://orcid.org/0000-0002-8978-9401

REFERENCES

1. Glaser KB, Staver MJ, Waring JF, Stender J, Ulrich RG, Davidsen SK. Gene expression profiling of multiple histone deacetylase (HDAC) inhibitors: defining a common gene set produced by HDAC inhibition in T24 and MDA carcinoma cell lines. Mol Cancer Ther. 2003;2:151-163.

2. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. Nat Rev Drug Discov. 2002;1(4):287-299.

3. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet. 2002;3(6):415-428.

4. Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. J Natl Cancer Inst. 2000;92(15):1210-1216.

5. Lee JH, Park JH, Jung Y, et al. Histone deacetylase inhibitor enhances 5-fluorouracil cytotoxicity by down-regulating thymidylate synthase in human cancer cells. Mol Cancer Ther. 2006;5(12):3085-3095.

6. Monks A, Zhao Y, Hose C, et al. The NCI pharmacosensitive murine leukemia benchmark: a tool to examine dynamic expression profiling of therapeutic response in the NCI-60 cell line panel. Cancer Res. 2018;78(24):6807-6817.

7. Kim MS, Kwon HJ, Lee YM, et al. Histone deacetylases induce angio genesis by negative regulation of tumor suppressor genes. Nat Med. 2001;7(4):437-443.

8. Gimsing P, Hansen M, Knudsen LM, et al. A phase I clinical trial of the histone deacetylase inhibitor belinostat in patients with advanced hematological neoplasia. Eur J Haematol. 2008;81(3):170-176.

9. Mackay HJ, Hirte H, Colgan T, et al. Phase II trial of the histone deacetylase inhibitor belinostat in women with platinum resistant epithelial ovarian cancer and micropapillary (LMP) ovarian tumours. Eur J Cancer. 2010;46(9):1573-1579.

10. Steele NL, Plumb JA, Vidal L, et al. A phase I pharmacokinetic and pharmacodynamic study of the histone deacetylase inhibitor belinostat in patients with advanced solid tumors. Clin Cancer Res. 2008;14(3):804-810.

11. Lee HZ, Kwitkowski VE, Del Valle PL, et al. FDA approval: Belinostat for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Clin Cancer Res. 2015;21(12):2666-2670.

12. O’Connor OA, Horwitz S, Masszi T, et al. Belinostat in patients with relapsed or refractory peripheral T-cell lymphoma: results of the pivotal phase II BELIEF (CLN-19) study. J Clin Oncol. 2015;33(23):2492-2499.

13. Dizon DS, Damstrup L, Finkler NJ, et al. Phase II activity of belinostat (PXD-101), carboplatin, and paclitaxel in women with previously treated ovarian cancer. Int J Gynecol Cancer. 2012;22(6):979-986.

14. Lassen U, Molife LR, Sorensen M, et al. A phase I study of the safety and pharmacokinetics of the histone deacetylase inhibitor belinostat administered in combination with carboplatin and/or paclitaxel in patients with solid tumours. Br J Cancer. 2010;103(1):12-17.

15. BELEODAQ® (belinostat) Package Insert. Irvine, CA: Spectrum Pharmaceuticals, Inc.; 2014.

16. Calvo E, Reddy G, Boni V, et al. Pharmacokinetics, metabolism, and excretion of (14)C-labeled belinostat in patients with recurrent or progressive malignancies. Invest New Drugs. 2016;34(2):193-201.

17. Bailey H, McPherson JP, Bailey EB, et al. A phase I study to determine the pharmacokinetics and urinary excretion of belinostat and metabolites in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2016;78(5):1059-1071.

18. Verbeek RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147-1161.

19. US Food and Drug Administration. Belinostat. http://www.fda.gov/drugsatfda. Accessed September 15, 2018.

20. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 2009;101(10):708-720.

21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

22. Kiesel BF, Parise RA, Tjornelund J, et al. LC-MS/MS assay for the quantitation of the histone inhibitor belinostat and five major metabolites in human plasma. J Pharm Biomed Anal. 2013;81:82-89.

23. Harding SD, Sharmar JL, Faccenda E, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. Nucl Acids Res. 2018;46:D1091-D1106.

24. Alexander SPH, Fabbro D, Kelly E, et al. The Concise Guide to PHARMACOLOGY 2017/18: Enzymes. Br J Pharmacol. 2017;174(Suppl 1): S272-S539.

25. Yeo W, Chung HC, Chan SL, et al. Epigenetic therapy using belinostat for patients with unresectable hepatocellular carcinoma: a multicenter phase I/II study with biomarker and pharmacokinetic analysis of tumors from patients in the Mayo phase II consortium and the cancer therapeutics research group. J Clin Oncol. 2012;30:3361-3367.

26. Luu TH, Franken PH, Lim D, et al. Phi-S3(NCI# 7251): Phase I trial of belinostat (PXD101) in combination with 13-cis-retinoic acid (13c-RA) in advanced solid tumor malignancies—A California Cancer Consortium NCI/CTEP sponsored trial. American Society of Clinical Oncology; 2013.

27. Parise RA, Holleran JL, Beumer JH, Ramalingam S, Egorin MJ. A liquid chromatography-electrospray ionization tandem mass spectrometric assay for quantitation of the histone deacetylase inhibitor, vorinostat (suberoylanilide hydroxamic acid, SAHA), and its metabolites in human
serum. J Chromatogr B Analyt Technol Biomed Life Sci. 2006;840(2):108-115.

28. Elaut G, Laus G, Alexandre E, et al. A metabolic screening study of trichostatin a (TSA) and TSA-like histone deacetylase inhibitors in rat and human primary hepatocyte cultures. J Pharmacol Exp Ther. 2007;321(1):400-408.

29. Clive S, Woo MM, Nydam T, Kelly L, Squier M, Kagan M. Characterizing the disposition, metabolism, and excretion of an orally active pan-deacetylase inhibitor, panobinostat, via trace radiolabeled 14C material in advanced cancer patients. Cancer Chemother Pharmacol. 2012;70(4):513-522.

30. Wang LZ, Ramirez J, Yeo W, et al. Glucuronidation by UGT1A1 is the dominant pathway of the metabolic disposition of belinostat in liver cancer patients. PLoS One. 2013;8(1):e54522.

31. Dong D, Zhang T, Lu D, Liu J, Wu B. In vitro characterization of belinostat glucuronidation: demonstration of both UGT1A1 and UGT2B7 as the main contributing isozymes. Xenobiotica. 2017;47:277-283.

32. Ohno S, Nakajin S. Determination of mRNA expression of human UDP-glucuronosyltransferases and application for localization in various human tissues by real-time reverse transcriptase-polymerase chain reaction. Drug Metab Dispos. 2009;37(1):32-40.

33. Cuomo R, Dattilo M, Pumpo R, Capuano G, Boselli L, Budillon G. Nicotinamide methylation in patients with cirrhosis. J Hepatol. 1994;20(1):138-142.

34. Chen H, Shen ZY, Xu W, et al. Expression of P450 and nuclear receptors in normal and end-stage Chinese livers. World J Gastroenterol. 2014;20(26):8681-8690.

35. Rodighiero V. Effects of liver disease on pharmacokinetics. An update. Clin Pharmacokinet. 1999;37(5):399-431.

How to cite this article: Takebe N, Beumer JH, Kummar S, et al. A phase I pharmacokinetic study of belinostat in patients with advanced cancers and varying degrees of liver dysfunction. Br J Clin Pharmacol. 2019;85:2499-2511. https://doi.org/10.1111/bcp.14054