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CLINICAL TRIAL REPORT

A phase I study of oral panobinostat alone and in combination with docetaxel in patients with castration-resistant prostate cancer

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Abstract
Purpose Histone deacetylase inhibitors have demonstrated anticancer activity against a range of tumors. We aimed to define the maximum tolerated dose, toxicity, activity, and pharmacokinetics of oral panobinostat, a pan-deacetylase inhibitor, alone and in combination with docetaxel for the treatment of castration-resistant prostate cancer (CRPC).
Methods Sixteen patients were enrolled, eight in each arm. Eligible patients had CRPC and adequate organ function. In arm I, oral panobinostat (20 mg) was administered on days 1, 3, and 5 for 2 consecutive weeks followed by a 1-week break. In arm II, oral panobinostat (15 mg) was administered on the same schedule in combination with docetaxel 75 mg/m^2 every 21 days.
Results Dose-limiting toxicities were grade 3 dyspnea (arm I) and grade 3 neutropenia >7 days (arm II). In arm I, all patients developed progressive disease despite accumulation of acetylated histones in peripheral blood mononuclear cells. In arm II, five of eight patients (63%) had a ≥50% decline in prostate-specific antigen (PSA), including one patient whose disease had previously progressed on docetaxel.
Conclusions Oral panobinostat with and without docetaxel is feasible, and docetaxel had no apparent effect on the pharmacokinetics of panobinostat. Since preclinical studies suggest a dose-dependent effect of panobinostat on PSA expression, and other phase I data demonstrate that intravenous panobinostat produces higher peak concentrations (>20- to 30-fold) and area under the curve (3.5x–5x), a decision was made to focus the development of panobinostat on the intravenous formulation to treat CRPC.

Keywords Prostate cancer · Castration-resistant · Histone deacetylase inhibitor · Panobinostat · Docetaxel

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Introduction

Histone deacetylase inhibitors (HDACi) are a promising class of agents that target histone and nonhistone proteins and have demonstrated anticancer activity against a wide range of hematologic and solid tumors. The exact mechanism of action is unknown; however, there is evidence that key activities include induction of tumor cell apoptosis and differentiation, suppression of angiogenesis, and enhancement of host immune surveillance [1]. Preclinical studies

using HDACi in human prostate cancer models have confirmed decreased tumor proliferation and growth both in vitro and in vivo, [2–5] prompting further development of this class of agents, with the goal of increasing the therapeutic index of treatments used in the management of a wide array of clinical states ranging from localized tumors to castration-resistant metastatic disease.

Panobinostat is a potent HDACi belonging to the structurally novel cinnamic hydroxamic acid class of compounds, which has demonstrated antiproliferative activity at low nanomolar concentrations against a broad range of tumor cell lines. Treatment of LNCaP, an androgen receptor (AR)-positive prostate cancer cell line, with less than 100 nM panobinostat resulted in significant degradation of the AR as well as inhibition of cell growth, through acetylation and subsequent inhibition of Hsp90 chaperone function [6, 7]. In addition, panobinostat has demonstrated single-agent antitumor activity, at clinically attainable serum levels, in AR-positive, androgen-independent xenograft models, and such activity is potentiated by the addition of docetaxel [7]. This promising preclinical data have been supported by phase I studies of panobinostat demonstrating pharmacologic and clinical activity in patients with advanced solid tumors, including prostate cancer [8–10].

The phase IA/IB, two-arm, dose-escalation study was designed to characterize the safety, tolerability, biologic activity, and pharmacokinetic (PK) profile of oral panobinostat alone and in combination with docetaxel and prednisone, specifically for patients with metastatic castration-resistant prostate cancer (CRPC). The dosing schedule of Monday, Wednesday, and Friday every week for 2 consecutive weeks followed by a 1-week break was designed with the expectation that intermittent dosing of panobinostat would provide a sustained pharmacodynamic effect while reducing potential toxicities, compared to a schedule of continuous administration. Analyses of histone acetylation, circulating tumor cells (CTCs), and ^{18}fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) were performed as exploratory measures of pharmacodynamic response and antitumor activity.

Materials and methods

Eligibility criteria

From May 8, 2006, through August 1, 2007, 16 patients were accrued to the study, eight patients in each arm. Baseline characteristics are summarized in Table 1. All patients had CRPC. Arm I patients were no longer candidates for additional chemotherapy with docetaxel due to excessive toxicity or disease progression on prior docetaxel. Arm II patients were either docetaxel-naïve or previously treated with docetaxel and still appropriate candidates to receive additional docetaxel as determined by their treating physicians. Patients were required to have experienced disease progression with castrate (<50 ng/dL) levels of testosterone based on one or more of the following: (a) 2 consecutive increases in PSA levels at least 1 week apart greater than 5 ng/mL; (b) increase in unidimensionally measurable soft tissue lesions on computed tomography or magnetic resonance imaging; or (c) new metastatic lesions on bone scan. The protocol (06-031) was written at Memorial Sloan-Kettering Cancer Center and was approved by each center's Institutional Review Board, and all patients signed an informed consent form prior to their inclusion in the study.

Table 1 Patient characteristics

	Arm I (n = 8)	Arm II (n = 8)
Baseline characteristics		
Median age (range)	68 (60–80)	67 (53–72)
Median Gleason score (range)	7 (5–9)	8 (6–9)[a]
Median PSA level (ng/mL) (range)	67 (4–1350)	73 (8.4–278)
Median WHO performance status (range)	1 (0–2)	1 (0–1)
Median number of hormonal regimens (range)	3 (0–4)	2.5 (1–5)
Extent of disease		
Bone only	3 (37.5%)	2 (25%)
Soft tissue only	1 (12.5%)	5 (62.5%)
Both bone and soft tissue	4 (50%)	1 (12.5%)
Prior taxane treatment		
Taxane-naïve	0 (0%)	4 (50%)
Taxane-exposed	4 (50%)	3 (37.5%)
Taxane-refractory	4 (50%)	1 (12.5%)
Primary therapy		
Radical prostatectomy alone	3 (37.5%)	2 (25%)
Radiation therapy alone	3 (37.5%)	3 (27.5%)
Salvage radiation therapy	0 (0%)	0 (0%)
No prior prostatectomy or radiation therapy	2 (25%)	3 (38%)

[a] Includes data for 7 patients

Study design

This was a parallel, two-arm, open-label, dose-escalation multicenter phase IA/IB study of oral panobinostat alone and with docetaxel and prednisone. The study was designed to determine the maximum tolerated dose or optimal biologic dose, as well as safety, activity, and PK. The study was stopped after the first cohort of patients in each arm had been completed because emerging clinical and PK data on intravenous panobinostat suggested that acute higher

systemic exposure could be achieved with antitumor activity and similar toxicity.

Panobinostat was supplied by Novartis Pharmaceuticals Corporation in 5 or 20 mg hard gelatin capsules. Patients received panobinostat 20 mg on Monday, Wednesday, and Friday for 2 consecutive weeks followed by a 1-week break, or 15 mg on the same schedule in combination with docetaxel 75 mg/m^2 every 3 weeks and prednisone 5 mg orally twice a day. Twenty-one days were considered 1 treatment cycle. Dose-limiting toxicities (DLT) were determined from the safety profile of cycle 1. At least six patients entered each cohort, which was expanded upon the development of a DLT.

Patient evaluation

Patients were evaluated by a physician once weekly for 2 weeks out of every 3-week cycle. Toxicity assessment was based on standard National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0). Patient diaries were reviewed at each visit. A minimum of 6 sequential 12-lead electrocardiograms (ECGs), separated by 5–10 min, were performed before treatment on cycle 1 day 1. Additional ECG testing was performed during cycle 1 on days 1, 5, and 12 at 7 serial time points (pretreatment, 30 min, 1, 2, 4, 6, and 8 h after the first dose), and also at 1 time point (pretreatment) on days 3 and 8 of cycle 1. All ECGs were independently reviewed and sent electronically to a contract research organization for further processing, including storage and reconciliation.

DLT was defined as any of the following: (a) grade 3/4 nonhematologic toxicity with the exception of alopecia, drug-related fever, or nonsignificant electrolyte abnormalities; (b) grade 3/4 hematologic toxicity excluding grade 3 anemia, lymphopenia, neutropenia, or thrombocytopenia <7 days; (c) adverse events (AEs) likely attributable to docetaxel, unless there was an increase in severity and duration; or (d) any toxicity preventing the administration of 4 doses of panobinostat within 21 days. Patients' disease status was assessed at 12-week intervals using modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [11]. PSA was followed but not used as a formal response criterion because of conflicting results on the influence of HDACi on PSA levels in animal models [2].

Pharmacokinetics

Panobinostat's PK samples were obtained on day 1 of cycle 1, and on day 12 of cycle 4 for patients on both arms of the study. Blood samples (2 mL) were collected at pretreatment, 30 min, and 1, 2, 3, 4, 8, 24, and 48 h after the first panobinostat dose. Similarly, PK samples were obtained during cycle 4 day 12 at pretreatment, and 1, 2, 4, 6, 8, and 24 h after the day 12 panobinostat dose. Docetaxel plasma samples were not obtained in this study.

Plasma samples were assayed for panobinostat concentrations using a validated liquid chromatography–tandem mass spectrometry assay (LC–MS/MS). The lower limit of quantification (LLOQ) was approximately 0.5 ng/mL, and values below LLOQ were reported as 0.0 ng/mL.

Pharmacokinetic Analysis. The disposition of panobinostat was evaluated in patients who had a full concentration–time profile during cycle 1 day 1 and cycle 4 day 12 in arms 1 and 2. Noncompartmental analysis was used to generate PK parameters based on panobinostat concentration–time data, as implemented in WinNonlin® 5.01 software (Pharsight Corporation, Mountain View, CA). Area under the concentration versus time curves (AUC) were calculated using the linear trapezoidal method extrapolated to infinity or to 24 h.

Statistical analysis

The statistical model for dose escalation was based on a 3-parameter Bayesian logistic regression EWOC (escalation with overdose control) model [12]. Criterion for the selected next dose was the one that had the highest probability of target toxicity, given that the probability of excessive or unacceptable toxicity was less than 25%. After completion of a given dose cohort, the decision to dose escalate and the next dose chosen were based on a calculation of risk assessment using the EWOC model and a medical review of available clinical and laboratory data. The Mantel-Cox log-rank test was used to analyze time to progression associated with CTC counts.

Biomarkers

Histone Acetylation. Peripheral blood mononuclear cells (PBMC) were collected during cycle 1 prior to treatment on days 1, 5, and 8, and after treatment on days 5 (48-h postdose), and 8 (72-h postdose). Histone H3 and H4 acetylation were detected by Western blot [13].

Circulating Tumor Cells. CTCs were isolated from blood samples collected at baseline, cycle 1 day 8, cycle 2 day 1, and study completion. Samples were kept at room temperature and analyzed within 72 h at the Memorial Sloan-Kettering Cancer Center Clinical Chemistry laboratory using the semi-automated CellSearch System (Veridex, Raritan, NJ, USA) [13, 14].

^{18}FDG-PET. Acquisition of data was standardized across all sites and analyzed at an independent center by a single reviewer blinded to the clinical history [15–17]. All baseline scans were performed within 14 days of the first dose of panobinostat and at the end of cycles 2 and 4 in arm I, and at the end of cycles 4 and 8 in arm II. An end-of-study scan

was performed if the patient went off study earlier than specified in the protocol. Complete metabolic response required disappearance of all abnormal tracer activity; a decline of 25% or more in the maximal summation of standardized uptake value (sSUVmax) was considered a partial metabolic response; an increase of 25% or more was progressive metabolic disease; and all values in between were assessed as stable metabolic disease. The presence of an unequivocally new lesion was considered progressive metabolic disease irrespective of sSUVmax [18].

Results

Pharmacokinetic results

Oral panobinostat displayed rapid absorption, with maximum plasma concentrations being reached 0.5–3 h after dosing. Absorption was followed by biphasic elimination with a mean terminal half-life ($T_{1/2}$) of 14.6 h (Fig. 1). The mean (standard deviation) of C_{max} and $AUC_{0\text{-inf}}$ values was 14.3 (7.4) ng/mL and 134 (69) ng*hr/mL, respectively, following the single agent 20-mg panobinostat dose in arm I. PK parameters of C_{max} and AUC in patients receiving oral panobinostat with docetaxel (day 1) or without docetaxel (day 12) in arm II are summarized in Table 2. Mean panobinostat systemic exposure and C_{max} following co-administration with docetaxel did not appear to be different when compared with panobinostat administered alone, suggesting that docetaxel did not affect panobinostat's disposition. Analysis was limited by small patient numbers.

Toxicity

Arm I. AEs are outlined in Table 3. There were no episodes of grade 4 toxicity. One patient experienced grade 3 dyspnea within the first cycle, which was considered a DLT, prompting expansion of the cohort. No clear underlying etiology for the dyspnea was found. Another patient experienced grade 3 nausea and diarrhea but elected not to use supportive medications; therefore the episode was not considered to be a DLT.

Arm II. AEs are outlined in Table 3. Grade 3 toxicities on the combination arm included fatigue and febrile neutropenia. Neutropenia was the only grade 4 toxicity (six of eight patients, 75%; 95% confidence interval [CI], 44–100%). In prostate cancer, the incidence of grade 3/4 neutropenia with docetaxel alone is 32% (95% CI, 26–36%), [19] prompting us to include an amendment specifying that neutropenia lasting >7 days constituted an unexpected AE. One episode of grade 3 neutropenia in cycle 1 lasting >7 days was deemed a DLT, resulting in expansion of the cohort.

Clinical response

Overall response to treatment is outlined in Table 4A and B. With panobinostat alone, there was a suggestion of a more rapid rise in PSA posttherapy relative to rate of rise pretherapy (Fig. 2). One patient had stable disease by imaging after 3 cycles but elected to come off therapy due to a rising PSA. None of the eight responded by conventional criteria.

With the combination of panobinostat and docetaxel, two of seven evaluable patients had a partial response on imaging and a ≥50% decline in PSA, while an additional four patients had stable disease on imaging and remained on study for a median of 10 cycles (range 7–17 cycles). One of those four had previously experienced progressive disease on docetaxel alone.

Biomarker response

Histone Acetylation. In arm I, seven of seven evaluable patients on day 5 of cycle 1 demonstrated ≥twofold

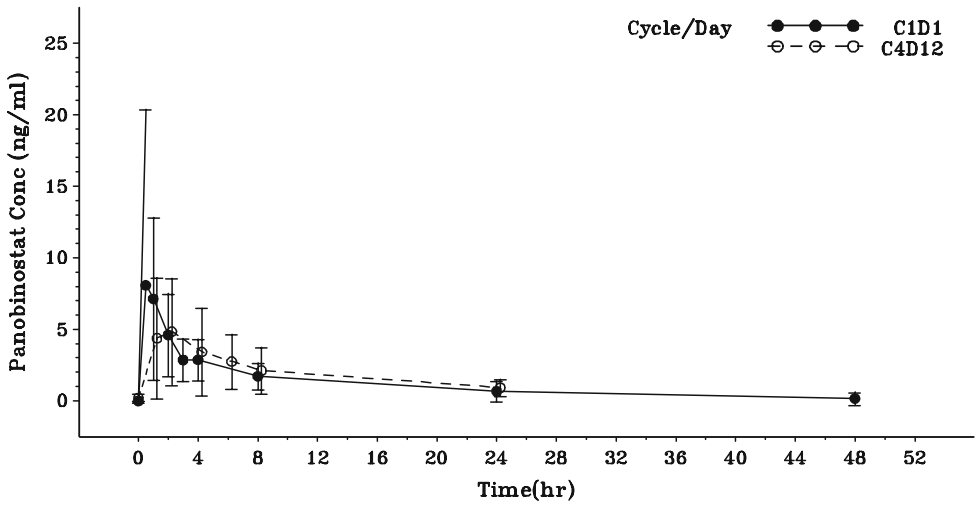

Fig. 1 Mean panobinostat plasma concentration–time profile following panobinostat + docetaxel (*closed circle*) versus panobinostat alone (*open square*) in arm II

Table 2 Pharmacokinetic parameters of panobinostat in arms I and II

	AUC_{0-24} (ng*h/mL)	$AUC_{0\text{-inf}}$ (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
Arm I: panobinostat 20 mg alone (cycle 1 day 1)				
Mean (SD)	81.2 (37.38)	134.3 (69.10)	14.3 (7.42)	–
CV% mean	46.1	51.5	51.8	–
Median	66.5	137.5	14.0	1.5
Min–Max	42.0–134.0	64.0–198.0	5.0–26.1	0.5–3.0
n	6	4	8	8
Arm II: panobinostat 15 mg and docetaxel (cycle 1 day 1)				
Mean (SD)	65.3 (19.22)	68.7 (18.15)	11.8 (11.15)	–
CV% mean	29.5	26.4	94.5	–
Median	66.5	66.0	5.6	1.0
Min–Max	43.0–85.0	52.0–88.0	3.4–33.7	0.5–4.0
n	4	3	7	7
Arm II: panobinostat 15 mg alone (cycle 4 day 12)				
Mean (SD)	96.0	115.0	5.1 (4.61)	–
CV% mean	–	–	91.4	–
Median	96.0	115.0	3.1	1.5
Min–Max	96.0–96.0	115.0–115.0	2.2–11.9	1.0–2.9
n	1	1	4	4

SD standard deviation

Table 3 Adverse events, regardless of study drug relationship

Adverse event[a]	Arm I panobinostat (20 mg) (*N* = 8) *n* (%)		Arm II panobinostat (15 mg) + docetaxel (*N* = 8) *n* (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Nausea	6 (75.0)	1 (12.5)	5 (62.5)	0 (0.0)
Diarrhea	4 (50.0)	1 (12.5)	3 (37.5)	0 (0.0)
Thrombocytopenia	4 (50.0)	0 (0.0)	1 (12.5)	0 (0.0)
Anemia	3 (37.5)	0 (0.0)	5 (62.5)	1 (12.5)
Anorexia	3 (37.5)	0 (0.0)	2 (25.0)	0 (0.0)
Fatigue	3 (37.5)	0 (0.0)	5 (62.5)	2 (25.0)
Asthenia	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)
Constipation	2 (25.0)	0 (0.0)	3 (37.5)	0 (0.0)
Dyspnea	2 (25.0)	1 (12.5)	1 (12.5)	0 (0.0)
Peripheral edema	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)
Pain in extremity	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	2 (25.0)	0 (0.0)	3 (37.5)	0 (0.0)
Dysphonia	1 (12.5)	0 (0.0)	2 (25.0)	0 (0.0)
Hyperglycemia	1 (12.5)	0 (0.0)	2 (25.0)	2 (25.0)
Hypokalemia	1 (12.5)	0 (0.0)	2 (25.0)	0 (0.0)
Leukopenia	1 (12.5)	0 (0.0)	2 (25.0)	2 (25.0)
Neutropenia	1 (12.5)	0 (0.0)	7 (87.5)	7 (87.5)
Abdominal pain	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Peripheral neuropathy	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Vision blurred	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)

[a] At least 25% in either arm. Includes all adverse events on treatment and up to 28 days after last dose

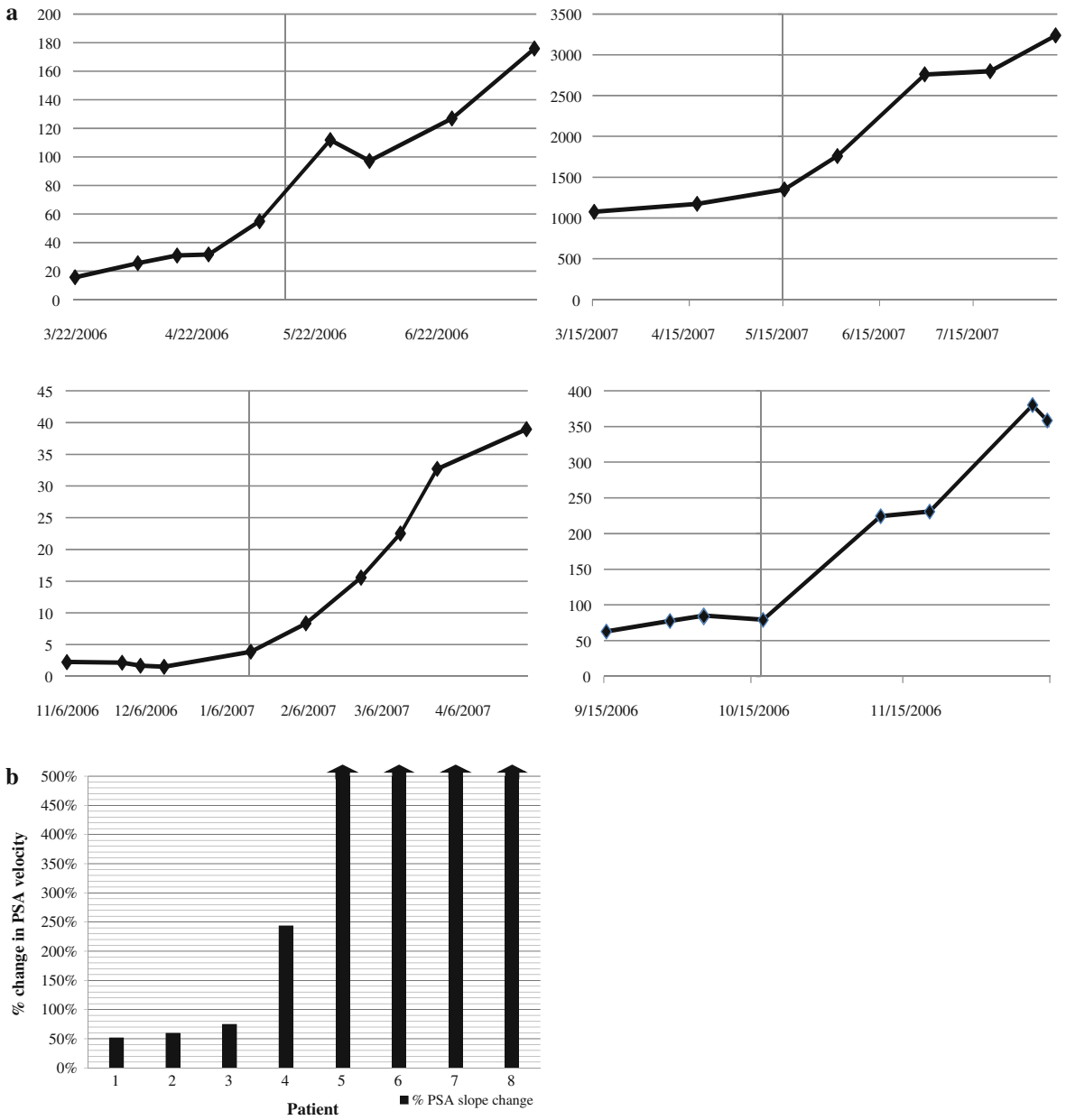

Fig. 2 Pretreatment and posttreatment PSA trends in arm I (panobinostat 20 mg/m^2). **a** Examples of pretreatment and posttreatment PSA rise in arm I. KEY: *Vertical line* indicates initiation of panobinostat treatment. **b** Posttreatment percent change in PSA velocity in arm I

increase in PBMC histone acetylation compared with day 1. On day 8, one patient's histone acetylation status reverted to baseline. In arm II, two of four evaluable patients showed an increase in PBMC histone acetylation (Table 4B).

Circulating Tumor Cells. Favorable CTC counts (<5 cells per 7.5 ml of blood) posttherapy were associated with a longer time to progression (27 weeks), compared with unfavorable (≥5 cells) posttherapy counts (13 weeks; $P = 0.063$ in log-rank analysis) [20].

^{18}FDG-PET. Percent changes in sSUVmax and overall metabolic response were evaluable in nine patients (arm I = 4, arm II = 5). There was no change in sSUVmax for patients in arm I. In arm II, three patients achieved a complete metabolic response and two additional patients achieved a partial metabolic response. These PET results corresponded with a PSA decline of ≥50% in three of five evaluable patients, one of whom also achieved a change from an unfavorable baseline CTC value (63 cells per 7.5 mL of blood) to a favorable posttreatment CTC status (<5 cells per 7.5 mL).

Table 4 Overall clinical response to treatment

Patient number	Duration (cycles)	Prior taxane treatment	Baseline CTC (#/7.5 mL)	≥50% Decline in PSA[a]	Best response (RECIST)[a]	Best % change in sSUVmax	Histone acetylation in PBMC
A. Arm I, panobinostat 20 mg (n = 8)							
1	3	TE	2	No	SD	3	Yes
2	4	TE	–	No	PD	−18	Yes
3	2	TR	–	No	[c]	−64	Yes
4	4	TE	12	No	PD	–	Yes
5	1	TR	1,055	No	PD	–	Yes
6	2	TE	35	No	PD	–	–
7	1	TR	–	No	[c]	–	Yes
8	3	TR	4	No	PD	19	Yes
B. Arm II, panobinostat 15 mg and docetaxel 75 mg/m^2 (n = 8)							
1	4	TE	26	No	PD	−100	–
2	7	TR	316	No	SD	−47	–
3	10	TE	3	Yes	SD	−100	Yes
4	8	TE	3	Yes	PR	–	Yes
5	15	None	0	Yes	PR	−100	No
6	1	None	79	No	[c]	–	No
7	9	None	63[b]	Yes	SD	−76	–
8	17	None	0	Yes	SD	–	–

CTC circulating tumor cells; *PSA* prostate-specific antigen; *RECIST* response evaluation criteria in solid tumors; *sSUVmax* maximal summation of standardized uptake value; *PBMC* peripheral blood mononuclear cells; *TE* taxane exposed; *TR* taxane refractory; *PD* progression of disease; *SD* stable disease; *PR* partial response; – not available

[a] Result is based on investigator's assessment

[b] Posttreatment CTC declined to <5

[c] No postbaseline scan performed before start of other antineoplastic therapy

Discussion

The interest in the development of HDACi for the treatment of prostate cancer is based on promising in vitro and in vivo data demonstrating that AR-dependent cell lines are particularly sensitive to HDACi [21]. These agents regulate AR-mediated transcriptional activation of a number of critical genes involved in tumorigenesis, including *TMPRSS2*, the 5′ partner of a series of *ETS* fusion genes implicated in 70% of human prostate cancers [22]. Independent of AR protein levels, HDACi also interfere with AR complex assembly and function in castration-resistant tumor models [23].

Panobinostat is one of the most potent nonselective HDACi and has demonstrated encouraging activity in hematologic malignancies, prompting further development for the treatment of solid tumors. This trial demonstrated that oral panobinostat can be administered safely at doses that inhibit HDAC activity, both alone and in combination with cytotoxic chemotherapy, in patients with CRPC. The combination of oral panobinostat (15 mg) and standard docetaxel resulted in a ≥50% reduction in PSA in five of eight patients, including two patients who also achieved a partial response by modified RECIST criteria [24]. Two additional patients showed a decline in PSA of <50%, which corresponded with a reduction in sSUVmax on PET imaging; one of these patients had previously progressed on standard docetaxel.

The observation of a high frequency of grade 3/4 neutropenia with the combination, higher than observed with docetaxel alone, [19] was not anticipated. First, although docetaxel is known to be a CYP3A4 substrate, panobinostat does not induce or competitively inhibit CYP3A4 in vitro. As a result, alterations in docetaxel levels were not expected. Formal study of potential interactions was planned in the dose expansion phase which was never opened. Second, the observed mean panobinostat AUC0-24 value (65.3 ng*h/mL) in combination with docetaxel was slightly lower than the single agent panobinostat AUC0-24 value (81.2 ng*hr/mL), rendering a pharmacokinetic interaction between docetaxel and panobinostat unlikely. These findings do not exclude the possibility of an additive effect of the two agents on granulocyte counts, as panobinostat alone is known to be myelosuppressive. Since the number of patients treated with the combination was small, additional experience with this combination will be needed to characterize its myelosuppressive potential.

There were no objective responses in arm I despite the demonstration of histone acetylation in all seven evaluable patients treated with 20 mg of oral panobinostat alone. The dissociation between acetylation status and clinical outcome, which was demonstrated in this study, is well recognized [25] and underscores the importance of developing additional measures of clinical benefit. To address this we explored pretherapy and posttherapy CTC number and serial ^{18}FDG-PET imaging [14, 20]. Although the small patient cohort in this trial limits a meaningful association between CTC number and duration of treatment, there was a suggestion that posttreatment CTC values of <5 were associated with a longer time to progression.

A more rapid rise in PSA posttherapy versus pretherapy in patients on arm I (Fig. 2) is noteworthy, although whether this represented a favorable (differentiating) or unfavorable (paradoxical disease stimulation) effect of the drug is unknown. To address this we studied the effect of panobinostat dose on AR function in LNCaP cells. The results showed a biphasic response, with lower doses stimulating endogenous PSA production while higher doses were inhibitory [23]. While we recognize the limitations of extrapolating cell line to in vivo data, the maximal exposures achieved with oral panobinostat were similar to the concentrations that resulted in stimulation in vitro. Consistent with the lack of a favorable change in PSA, no declines in sSUVmax were observed in patients treated in arm I.

With these findings, and in the absence of a single-agent antitumor effect on the patients treated, dose escalation of oral panobinostat was halted in favor of the IV formulation of the drug, which produces higher peak concentrations (20- to 30-fold) and exposure (fivefold), and has demonstrated clinical activity including a patient with prostate cancer who achieved a partial response on imaging and a >50% decline in PSA [26]. Although oral formulations are preferable to those that are parenterally administered, the absence of clinical efficacy, the more rapid posttreatment rise in PSA—suggesting possible disease stimulation—and our demonstration in prostate cancer laboratory models that the effects of panobinostat are dose dependent led us to redirect resources in favor of the IV formulation. IV panobinostat has demonstrated antitumor activity in phase I exploration and allows for the achievement of plasma concentrations that have been shown in prostate cancer model systems to decrease PSA and AR levels and to inhibit tumor growth. Ongoing trials of IV panobinostat, alone and in combination with docetaxel, include further exploration of the role CTCs, ^{18}FDG-PET, and a novel AR imaging agent, [18F]-fluorodihydrotestosterone, can play in demonstrating in vivo the effects of the drug on the AR itself, which is known to undergo oncogenic changes that directly contribute to the growth of CRPC [27, 28]. It is hypothesized that direct changes in AR expression in the tumor may be more predictive of a favorable clinical outcome than changes in histone acetylation in mononuclear cells.

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