

Phase I Analysis of the Safety and Pharmacodynamics of the Broad Spectrum Histone Deacetylase Inhibitor (HDACi) PCI-24781 in Relapsed and Refractory Lymphoma

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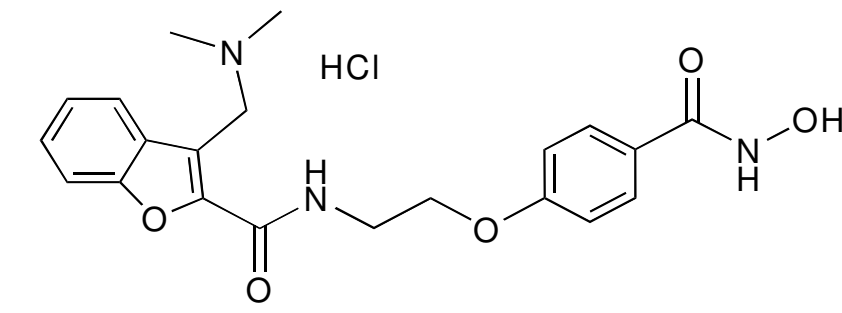
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INTRODUCTION

- Histone deacetylases (HDACs) are attractive drug targets due to their pleiotropic cellular activities essential for tumor cell growth
- PCI-24781 is an oral HDAC inhibitor with potent anti-tumor activity in lymphoma cell lines and animal models and has previously demonstrated safety and clinical activity in solid cancers (Undevia et al, ASCO 2008)
- In lymphoma cell lines, PCI-24781 causes increased oxidative stress and NF- κ B inhibition that results in caspase-dependent apoptosis (Bhalla S et al, Clin Cancer Res 2009)
- Based in part on this encouraging pre-clinical data, a phase I/II clinical trial was initiated in patients with relapsed/refractory lymphoma
- The Phase I portion of the trial evaluated safety, pharmacokinetics and pharmacodynamics of PCI-24781 administered orally as a single agent and determined the optimal dose and schedule for the Phase II part of the study

PCI-24781

Structure of PCI-24781

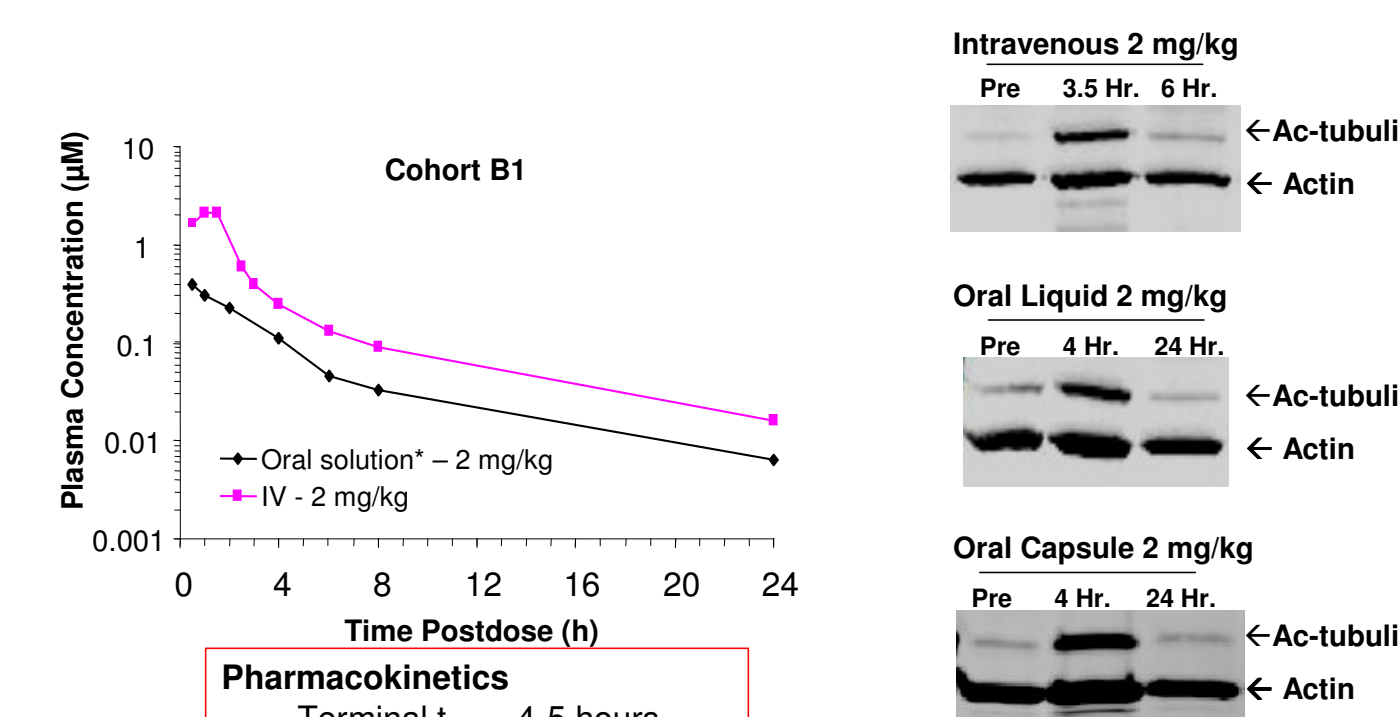


PCI-24781: Novel orally bioavailable broad-spectrum HDAC inhibitor in clinical trials at multiple sites.

Broad spectrum HDAC inhibition		Anti-tumor activity	
Isomorph	K _i (pM) ± Std. Dev.	Origin	Cell line
HDAC1	0.007 ± 0.001	Hematological	Jurkat 0.11
HDAC2	0.019 ± 0.002		HuT78 0.13
HDAC3/SMRT	0.0082 ± 0.001		DHL-4 0.11
HDAC6	0.017 ± 0.002	Colon	HCT-116 0.20
HDAC8	0.28 ± 0.05		DLD-1 0.6
HDAC10	0.024 ± 0.019	Breast	MCF-7 0.20
		Prostate	22Rv1 0.19
		Ovary	NCI-PC3 0.39
			SKOV-3 0.73
			OVCAR-3 0.20

Data from Buggy et al. Mol Cancer Ther 5, 1309-1317 (2006)

Human PK/PD data from previous trial



STUDY DESIGN

- Phase I/II, multicenter, open-label trial of PCI-24781 for patients with Non-Hodgkin's or Hodgkin's lymphoma
- PCI-24781 was given orally twice daily at escalating doses of 30-60mg/m² on a 4-week cycle on two treatment schedules: 5 days/week x 3 weeks (schedule 1) or 7 days/week every other week (schedule 2)
- A standard 3+3 phase I dose escalation scheme was used
- Tumor assessments occurred after each even-numbered cycle starting with Cycle 2
- Tubulin and histone acetylation were measured in peripheral blood mononuclear cells (PBMCs)

INCLUSION AND EXCLUSION CRITERIA

- Inclusion Criteria**
- Women and men age ≥ 18 years
 - Phase I: Any measurable, histologically confirmed, and previously treated lymphoma
 - Ability to swallow oral capsules without difficulty
 - Estimated life expectancy > 12 weeks
 - ECOG performance status ≤ 1
- Exclusion Criteria**
- More than four prior systemic treatment regimens (with 2 exceptions)
 - Allogeneic bone marrow transplant
 - Immunotherapy, chemotherapy, radiotherapy or experimental therapy within 4 weeks before first day of study drug dosing
 - Prior treatment with an HDAC inhibitor (unless for treatment of Mycosis fungoides or Sézary syndrome)
 - Laboratory abnormalities:
 - Creatinine > 1.5 x institutional upper limit of normal (ULN) or creatinine clearance ≤ 50 mL/min
 - AST and ALT > 2.5 x institutional ULN
 - Platelet count < 75,000/μL for Phase I and <100,000/μL for Phase II
 - Absolute neutrophil count (ANC) < 1500/μL
 - Corticosteroids > 20 mg prednisone equivalent per day (topical, inhaled, or nasal corticosteroids are permitted)
 - Concurrent therapeutic anticoagulation (Phase I only)
 - QTc prolongation (defined as a QTc ≥ 450 msec) or other significant ECG abnormalities
 - History of myocardial infarction, acute coronary syndromes, coronary angioplasty and/or stenting within the past 6 months
 - Pregnant or lactating women

PATIENT CHARACTERISTICS

- Patients enrolled in the Phase I dose-escalation portion

Baseline Patient Data	
N	=25
Median Age	= 66 (32-79)
Gender	
Male	= 15
Female	= 10
Prior Therapies	
Median Number of Prior Therapies	= 3 (range 2-6)
Prior Rituximab	=19/25
Prior CHOP	= 17/25
Prior Autologous Stem Cell Transplantation	= 9/25

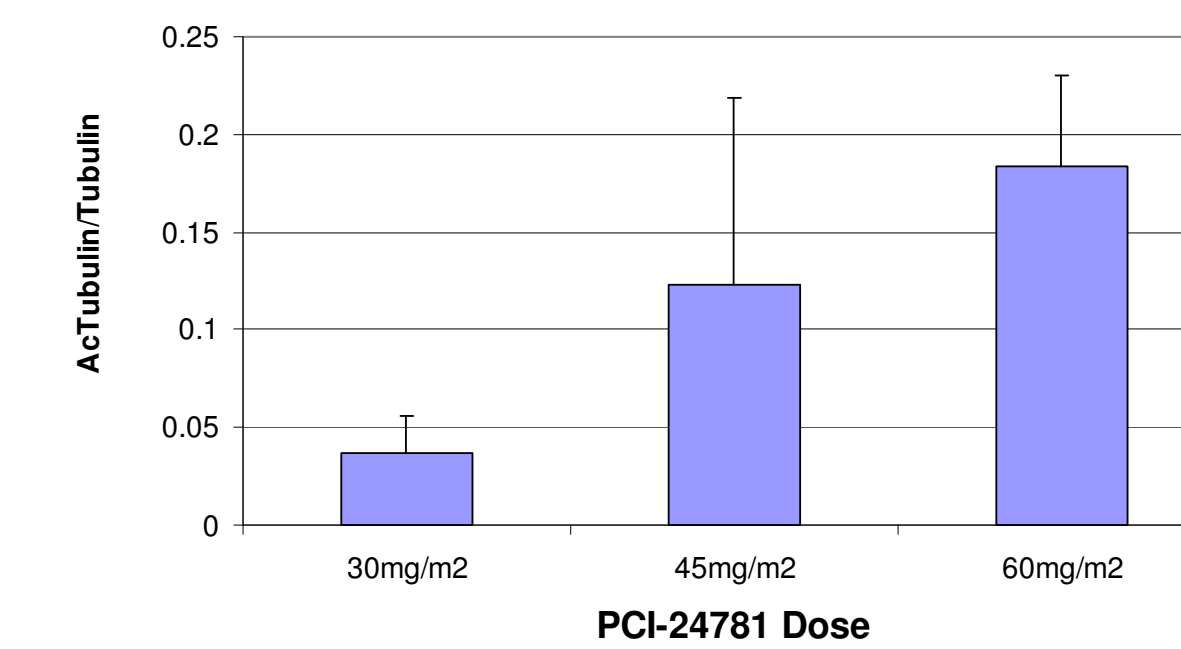
CHOP=cyclophosphamide, adriamycin, vincristone, prednisone

PK and PD RESULTS

Cohort	Dose (mg/m ²)	Dose Frequency	C _{max} (μM)	T _{max} (h)	Daily AUC _{0-24h} (μM·h)	t _{1/2} [*] (h)
1	30	BID	0.185 (0.073) ^{**}	1.20 (0.45)	1.48 (0.84)	1.38 (0.28)
2	45	BID	0.339 (0.245)	1.00 (0.50)	1.44 (0.89)	1.34 (0.27)
3	45	BID	0.526 (0.088)	1.33 (0.58)	1.48 (0.84)	2.57 (2.14)
4	60	BID	0.295 (0.150)	1.11 (0.30)	2.27 (1.69)	3.34 (4.24)

*Terminal half-life, last time point available in this study = 4 hours postdose
**Standard Deviation

- Orally administered PCI-24781 was rapidly absorbed
- Mean T_{max} values ranged from 1.00 to 1.33 hours
- Increases in exposure were generally less than dose-proportional
- Mean C_{max} and daily AUC values were 59% and 53% higher, respectively, in patients dosed at 120 mg/m²/day when compared to patients dosed at 60 mg/m²/day



- Pharmacodynamic monitoring revealed a dose-dependent increase in tubulin acetylation at 4 hours following the first dose, however, this did not correlate with response or toxicity

CLINICAL RESULTS

Patients with possibly or definitely drug-related adverse events*

AE	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	2 (8%)		4 (16%)	2 (8%)
Anemia	1 (4%)	1 (4%)	3 (12%)	
Diarrhea	7 (28%)	2 (8%)	1 (4%)	
Neutropenia		1 (4%)	1 (4%)	
Hypertension			1 (4%)	
Fatigue	8 (32%)	2 (8%)		
Nausea	6 (24%)	1 (4%)		
Abdominal Pain	2 (8%)	1 (4%)		
Vomiting	2 (8%)	1 (4%)		
Anal Infection		1 (4%)		
Influenza		1 (4%)		
Muscle spasms		1 (4%)		
Perianal Infection		1 (4%)		
Pyrexia		1 (4%)		
Dyspnea	2 (8%)			
Mucosal Inflammation	2 (8%)			

*Additional AEs not shown in table
One patient with history of renal insufficiency had a DLT of acute renal failure
Grade 1 AEs occurring in one patient each

DISCLOSURES

- SB, MS, CMannem, CMani, MG, NS, DL, JJB & AH are employees of and shareholders in Pharmacyclics, Inc., a publicly owned biotechnology company.

CLINICAL RESULTS (continued)

Results from 20 evaluable patients

By Histology				
Histology	n	Response	DLT	Mean # days on study
DLBCL	7	1 PR	2	36
Follicular	4	1 CR 2 PR 1 SD	1	197
Hodgkins	2	1 SD		42
CLL/SLL	2	2 SD		88
ALT	2	1 SD	2	29
MCL	1	1 PR		63
CTCL	1	1 SD		102
MALT	1	1 SD		44

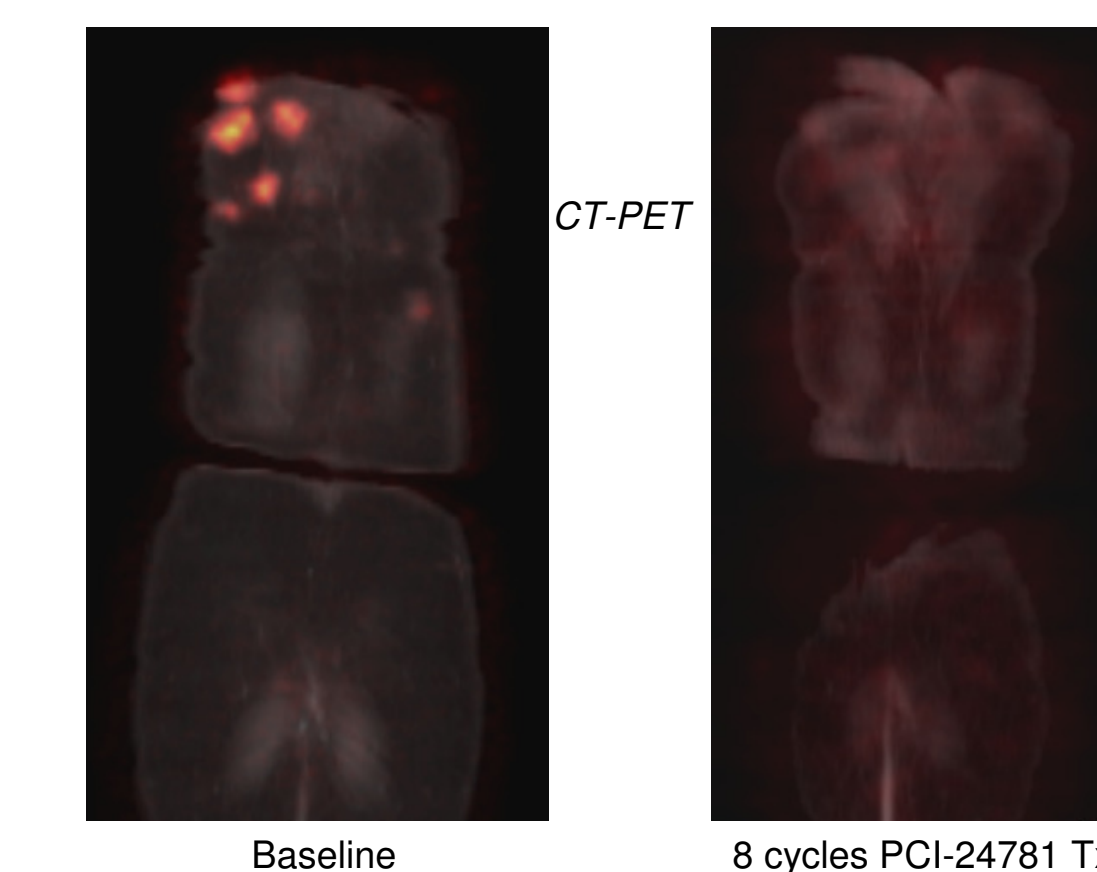
By Cohort

Cohort #	Dose	Schedule	n	Response	DLT	Mean # days on study
1	30 mg/m ²	1	3	1 PR 2 SD		93
2	45 mg/m ²	1	7	1 CR 2 SD	3	78
3	45 mg/m ²	2	3	1 PR 1 SD		127
4	60 mg/m ²	2	7	2 PR 2 SD	2	98

DLBCL= diffuse large B-cell lymphoma; MCL= mantle cell lymphoma; CLL= chronic lymphocytic leukemia; SLL= small lymphocytic lymphoma; ALT = Angioimmunoblastic T-cell lymphoma; MALT= extranodal marginal zone lymphoma

FOLLICULAR LYMPHOMA PATIENT

- Heavily pretreated follicular lymphoma patient (72 yo female)
- 5 prior treatments: 1) CHOP 2) FAUID (vaccine) 3) SL 11047 4) doxorubicin, and 5) rituximab/doxorubicin/fludarabine
- Started 12/15/08 (with soft tissue disease), still on treatment
- PR at cycle 4, CR at cycle 8



CONCLUSIONS

- PCI-24781 is well tolerated, including complete absence of prolonged QT intervals or other cardiac abnormalities
- Preliminary clinical benefit in heavily pre-treated relapsed/refractory lymphoma patients in the phase I portion of this study with 1 CR, 4 PR and 7 SD in 20 evaluable patients
- Thrombocytopenia was the most common Grade 3/4 adverse event; rapidly reversed in nondosing week of schedule 2
- The recommended dose and schedule for Phase II were established as 45 mg/m² BID 7d/wk every other week
- Accrual will continue to the phase II component of the trial