POOLED ANALYSIS OF ROMIDEPSIN IN PATIENTS WITH RELAPSED OR REFRACTORY PERIPHERAL T CELL LYMPHOMA (PTCL) FOLLOWING INITIAL SYSTEMIC THERAPY.

S.Bates, F.Foss, R.Piekarz, S.Horwitz, B.Pro, M.Prince, L.Sokol,M.Greenwood, D.Caballero, P.Borchmann,F.Morschauser, M.Wilhelm,L.Pinter-Brown,S.Padmanabhan, A.Shustov,J.Wright, M.Kirschbaum,J.Zain, S.L.Allen, E.S.Jaffe, J.Nicholas, J.Wolfson, J.Baiser, B.Cioffier

I HAVE NOTHING TO DISCLOSE

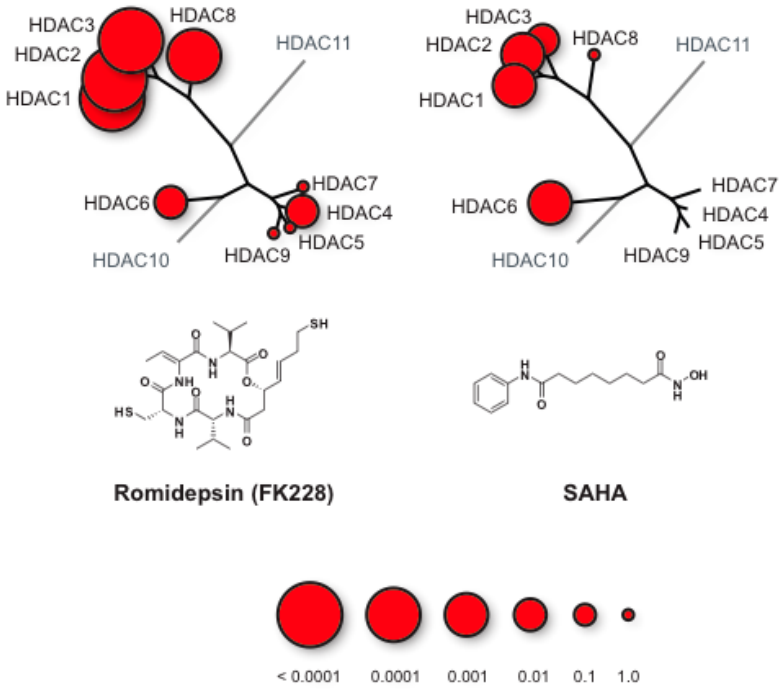
CLASSES OF HDACi

Hydroxamates
- Vorinostat (SAHA)
- Panobinostat (LBH589)
- Belinostat (PXD101)

Benzamides
- Entinostat (SNDX-275)
- MGCD-0103

Cyclic tetrapeptides
- Romidepsin

Comaprison of Ki of romidpesin with SAHA against different HDACs

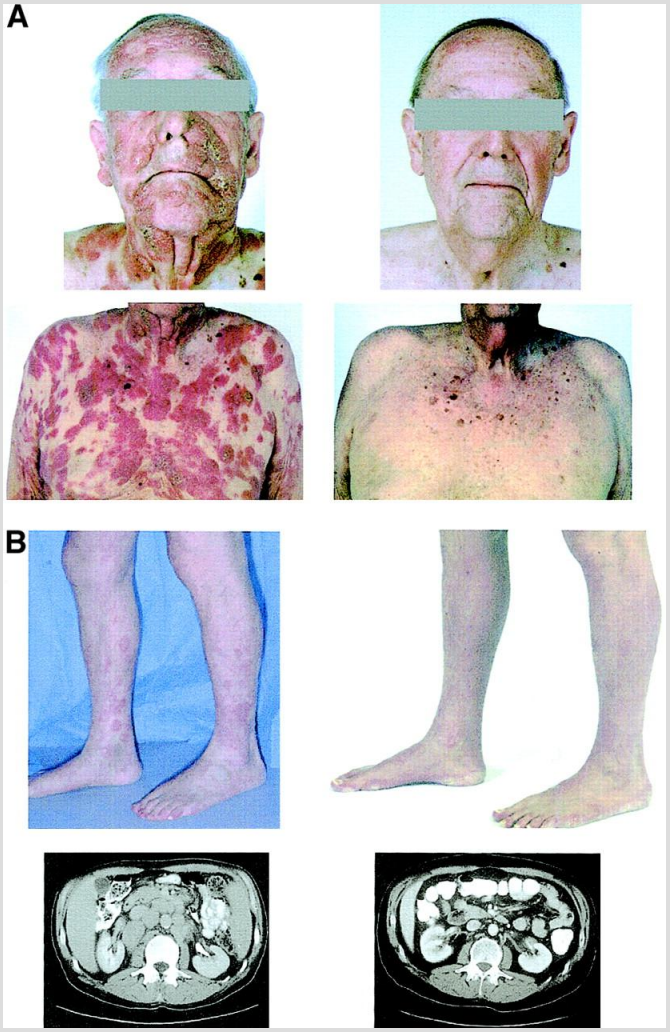


Bradner James et al: Nat Chem Bio 2010

Case Report on Patients on Phase I Romidepsin Study

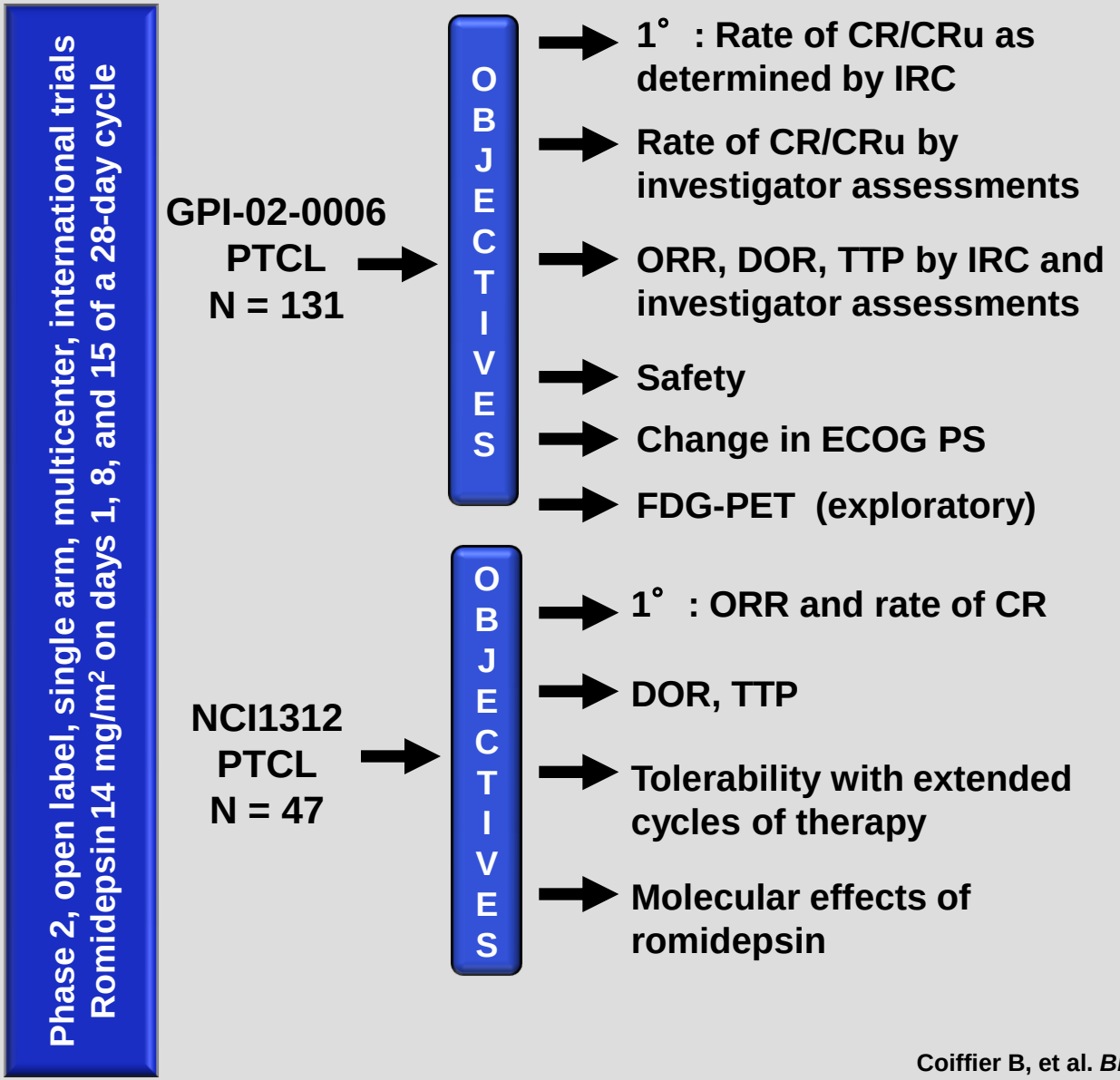
blood

JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Piekarz, R. L. et al. Blood 2001;98:2865-2868

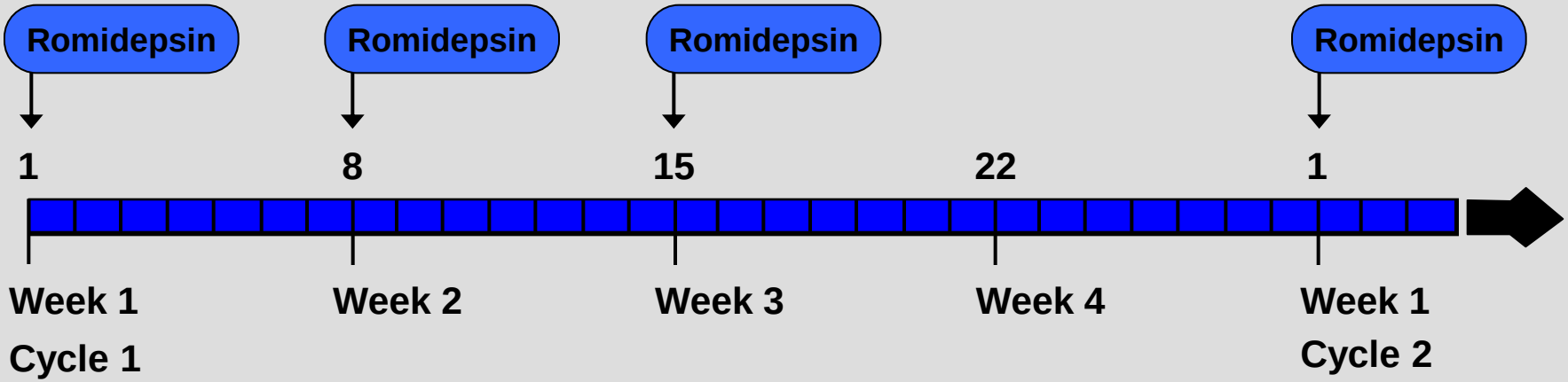
Romidepsin in Peripheral T-Cell Lymphoma



Piekarz R, et al. *Blood*. 2011 in press
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation

Study Treatment

- **Four-hour IV infusion of 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle**



Piekarz R, et al. *Blood*. 2009;114:1657, poster.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation.

IWC Response Criteria

Response Definition	Response Description
Complete response	• Disappearance of all signs and symptoms of tumor • Disappearance of all non-target lesions • All lymph nodes must have regressed to normal size: lymph nodes > 1.5 cm must decrease to ≤ 1.5 cm; lymph nodes 1.1-1.5 cm must decrease to ≤ 1 cm
Partial response	• ≥ 50% decrease in sum of the products of the greatest diameter in up to 6 largest nodes

- **On NCI 1312 responses were assessed by investigator; IWC criteria used for lymph nodes; skin involvement was assessed using Response Evaluation Criteria in Solid Tumors (RECIST)**
- **On GPI-06-0002, responses were determined by an independent review committee (IRC)**

Cheson BD, et al. J Clin Oncol. 1999;17:1244.
Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation.

PTCL Demographics and Baseline Characteristics

- **Patient demographics and baseline characteristics were similar across both studies; highly pretreated population with mostly advanced disease**

Characteristic	GPI-06-0002 (n = 130)[a]	NCI 1312 (n = 47)	Pooled (N = 177)
Age in years, median (range)	61 (20-83)	59 (27-84)	62 (20-84)
Gender, n (%)			
Male	88 (68)	25 (53)	113 (64)
Female	42 (32)	22 (47)	64 (36)
ECOG performance score, n (%)			
0	46 (35)	20 (43)	66 (37)
1	66 (51)	23 (49)	89 (50)
2	17 (13)	5 (11)	22 (12)
International prognostic index at study baseline, n (%)			
< 2	31 (24)	NA	NA
≥ 2	99 (76)	NA	NA

[a] Histologically-confirmed population; one enrolled patient found to have diffuse large B-cell lymphoma.

Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation
Celgene, data on file.

ECOG, eastern cooperative oncology group; NA, not assessed.

PTCL Demographics and Baseline Characteristics (cont.)

Characteristic	GPI-06-0002 (n = 130)[a]	NCI 1312 (n = 47)	Pooled (N = 177)
Number of prior systemic therapies, median (range)	2 (1-8)	3 (1-11)	2 (1-8)
Chemotherapy	129 (99)	47 (100)	176 (99)
Stem cell transplant	21 (16)	18 (36)	39 (22)
Radiation	31 (24)	19 (40)	50 (28)
Stage ≥ III at study entry	91 (70)	28 (60)	119 (67)
PTCL subtype, n (%)			
PTCL -NOS	69 (53)	27 (57)	96 (54)
Angioimmunoblastic T-cell lymphoma	27 (21)	7 (15)	34 (19)
ALK-1 negative Anaplastic large cell lymphoma	21 (16)	2 (4)	23 (13)
Other[b]	13 (10)	11 (23)	24 (14)

[a] Histologically-confirmed population; one enrolled patient found to most likely have diffuse large B-cell lymphoma.

[b] For GPI-06-0002 includes enteropathy-type TCL (6), subcutaneous panniculitis-type TCL (3), ALK-1+ ALCL (1), cutaneous γδ TCL (1), extranodal NK/TCL nasal type (1), transformed MF (1); for NCI1312 includes ALK-1+ ALCL (2), primary cutaneous anaplastic large cell lymphoma (2), cutaneous γδ TCL (2), hepatosplenic TCL (1), enteropathy associated TCL (1), PTCL NOS of the skin (1), primary cutaneous CD30-positive T-cell lymphoproliferative disorder (1), diffuse large B-cell lymphoma (1).

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NK, natural killer; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; TCL, T-cell lymphoma.

Clinical Responses

	GPI-06-0002 (n = 130)[a] IRC	GPI-06-0002 (n = 130)[a] Investigator	NCI 1312 (n = 45)[b]	Pooled (N = 175)

Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation

Overall Response Rates by PTCL Subtype

	Objective responses, n/N (%)			
Primary Diagnosis	**GPI-06-0002 IRC**	**GPI-06-0002 Investigator**	**NCI1312**	**Pooled**
PTCL NOS	20/69 (29)	21/69 (30)	11/27 (41)	32/96 (33)
AITL	9/27 (33)	11/27 (41)	1/6 (17)	12/33 (36)
ALK-1 negative ALCL	5/21 (24)	5/21 (24)	2/2 (100)	7/23 (30)
Other[a]	0/13 (0)	1/13 (8)	3/10 (30)	4/23 (17)

- **Responses seen across all major PTCL subtypes**
- **For patients with prior SCT, 5/21 (24%) and 6/18 (33%) achieved an objective response in the GPI-06-002 and NCI1312 trials, respectively**

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; SCT, stem cell transplant.

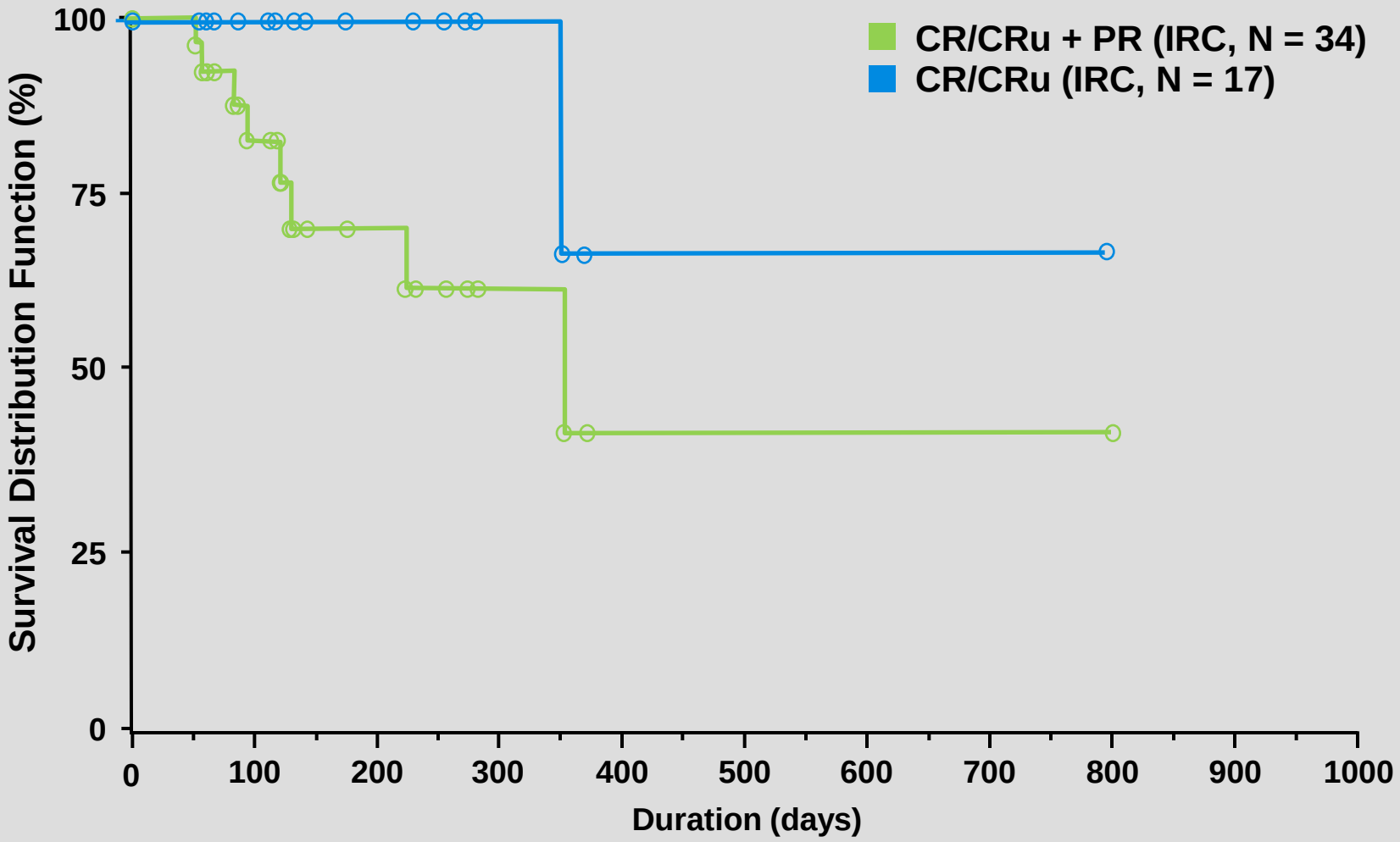
Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation
Celgene, data on file

Durability of Response

	Median (range) in months			
	GPI-06-0002 (N = 130) IRC	GPI-06-0002 (N = 130) Investigators	NCI 1312 (N = 45)	Pooled (N = 175)
Duration of complete response (CR/CRu)	NR (< 1-27+)	14 (< 1-28+)	30 (3-74)	17 (<1-74)
Duration of response (CR/CRu + PR)	12 (< 1-27+)	12 (<1+-28+)	9 (2-74)	12 (<1-74)
Time to response	2 (2-6)	2 (1-5)	2 (1 - 11)	2 (1 – 11)
Time to complete response	4 (2-10)	3 (2-10)		
Time to progression	6 (< 1+-28+)	3 (<1-28+)		

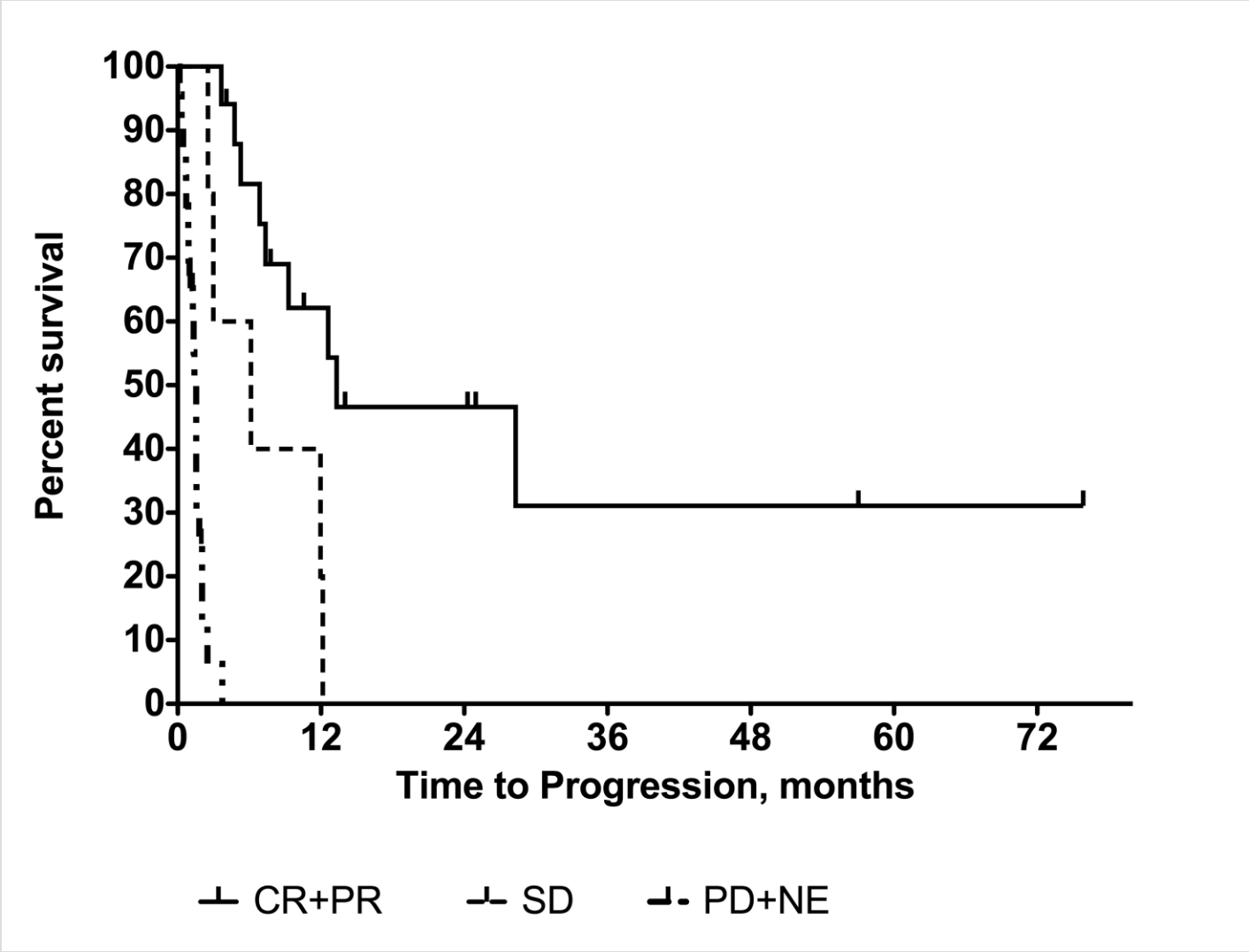
Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation
Celgene, data on file

GPI-06-0002: Duration of Response

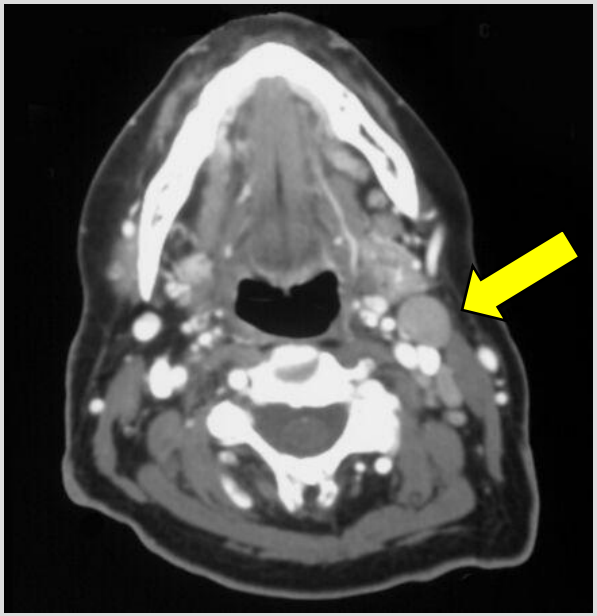


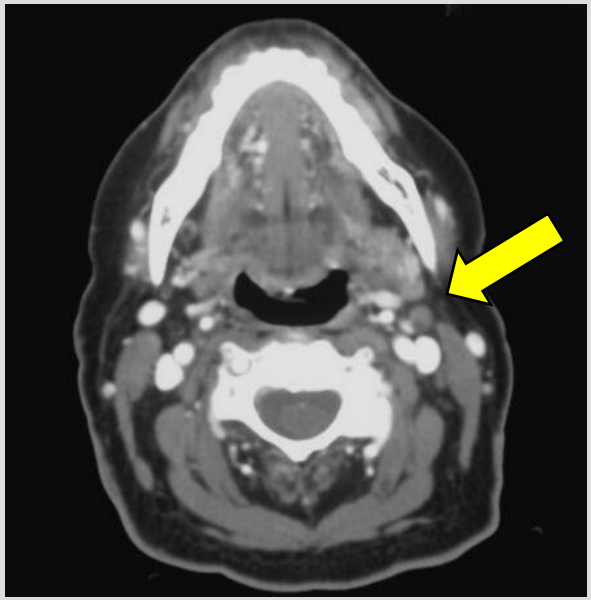
Horwitz S, et al. T Cell Lymphoma Forum 2010, poster and oral presentation.

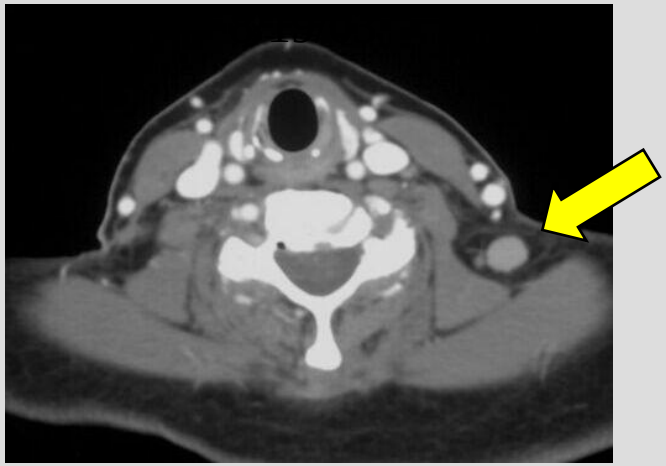
NCI 1312: Duration of Response

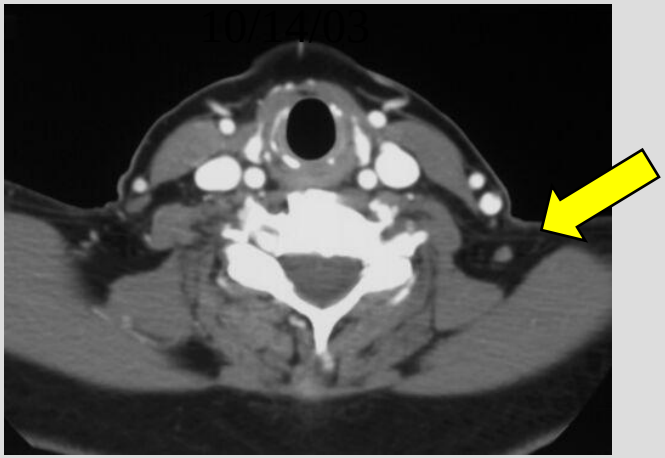


Peripheral T Cell Lymphoma: Clinical Results









8/19/03

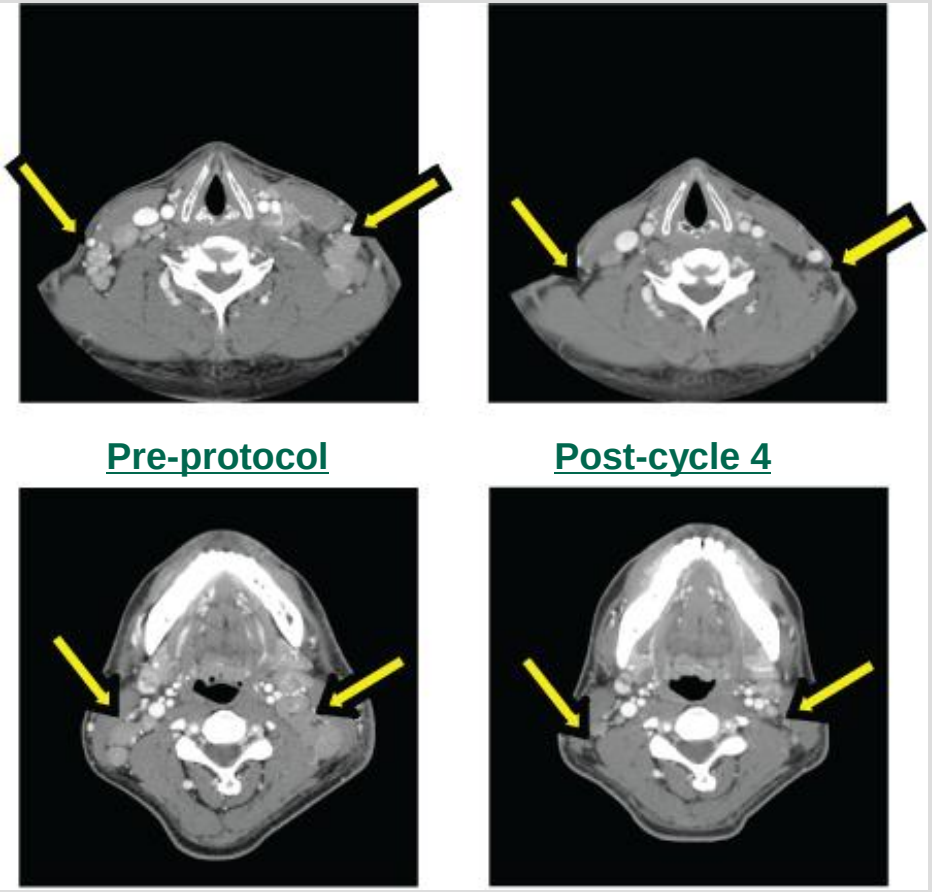
10/14/03

PTCL
dx 12/99
- CHOP
- ESHAP
- Stem Cell Transplant

Romidepsin
Aug 03

CR from
Dec 03 –
Dec 09

- **Patient with PTCL NOS who relapsed 1 year after prior CHOP chemotherapy**
- **The patient experienced a CR after the second cycle of therapy**
- **After being on therapy for 14 months, this patient developed and succumbed to an EBV-driven lympho-proliferative disorder**



Safety and Tolerability: Grade ≥ 3 Hematologic Events

Grade ≥ 3 Treatment-Related Treatment-Emergent Adverse Events (TEAEs), %			
	GPI-06-0002 (n = 131)	NCI 1312 (n = 47)[a]	Pooled (N = 177)
Anemia	6 (5)	7 (15)	13 (7)
Neutropenia	24 (18)	19 (40)	43 (24)
Thrombocytopenia	30 (23)	13 (28)	43 (24)

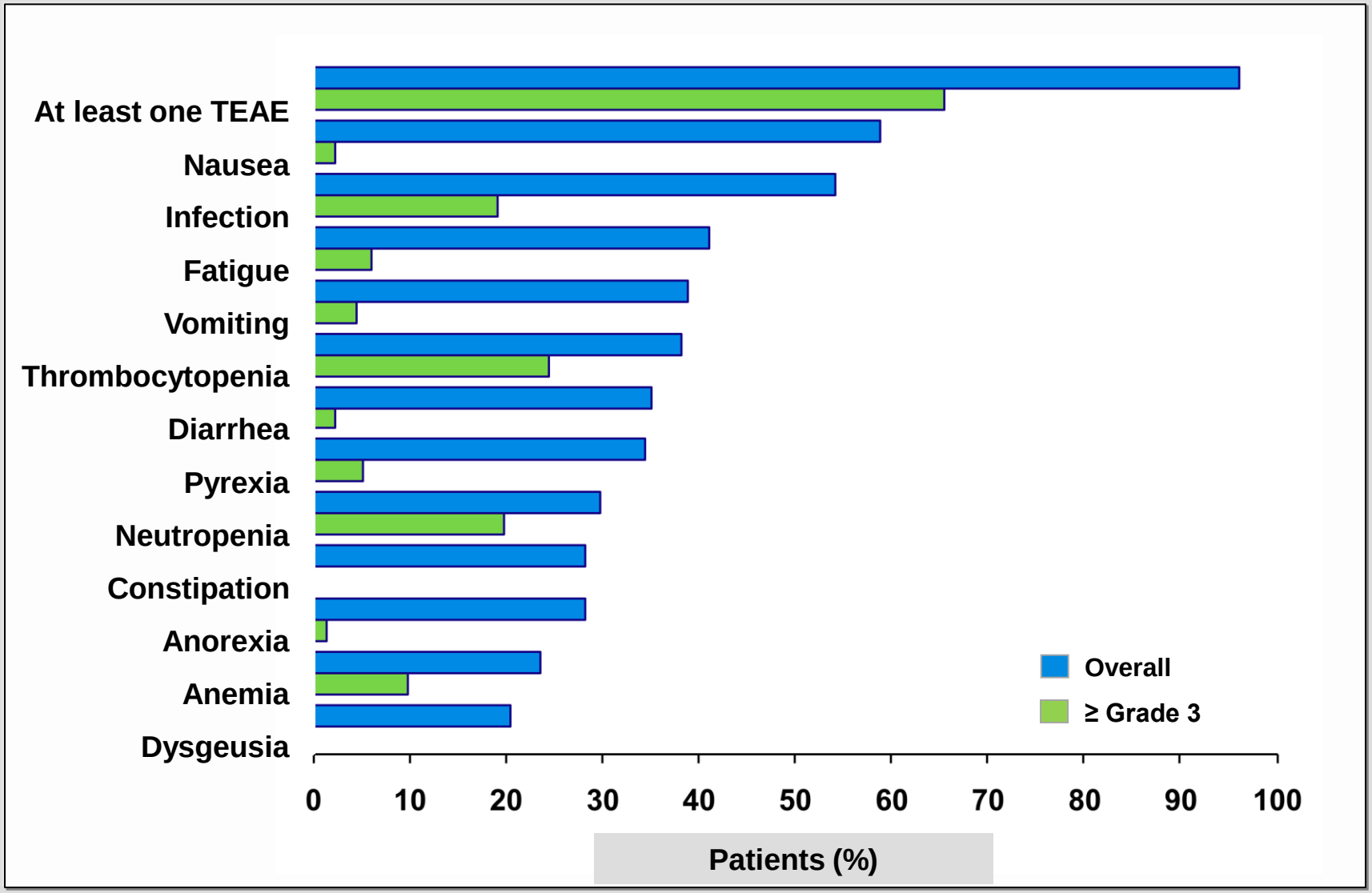
Piekarz R, et al. *Blood*. 2011, epub February 6, 2011.
Coiffier B, et al. *Blood*. 2010;116:114, oral presentation
Celgene, data on file

Most Common (≥ 20% of Patients in Any Study) Nonhematologic Treatment-Related TEAEs, and Grade ≥ 3 Events

	PTCL			
	GPI-06-0002 (N=131)		NCI 1312 (N=47)[a]	
TEAE, n (%)	Related	Grade ≥3	Related	Grade ≥3
Nausea	70 (53)	3 (2)	32 (68)	2 (4)
Fatigue	51 (39)	8 (6)	30 (64)	6 (13)
Vomiting NOS	44 (34)	6 (5)	17 (36)	4 (9)
Anorexia	34 (26)	2 (2)	19 (40)	1 (2)
ECGT amplitude decreased	1 (1)	0	32 (68)	0
Hypocalcemia	NA	NA	22 (47)	4 (9)
Dysgeusia	27 (21)	0	13 (28)	0
Diarrhea NOS	30 (23)	3 (2)	11 (23)	1 (2)
Hypoalbuminemia	NA	NA	14 (30)	2 (4)
Hyperuricemia	NA	NA	13 (28)	3 (6)
Constipation	19 (15)	0	16 (34)	1 (2)
SGOT/AST increased	NA	NA	14 (30)	4 (9)
Hypomagnesemia	NA	NA	12 (26)	0
SGPT/ALT increased	NA	NA	13 (28)	4 (9)
Pyrexia	20 (15)	7 (5)	15 (32)	3 (6)
Bilirubin increased	NA	NA	10 (21)	1 (2)
Leukocytes increased	NA	NA	25 (53)	20 (43)

[a] NCI 1312 study reported all abnormalities as AEs, regardless of clinical significance.

GPI-06-0002: Treatment–Emergent Adverse Events (TEAEs) in ≥ 20% of Patients (N = 131)



Events with a missing toxicity grade are included.

Coiffier B, et al. *Blood*. 2010;116:114, oral presentation.

Deaths Within 30 Days of Last Dose of Romidepsin Treatment (n = 15)

GPI-06-0002[1]

- Disease progression (3 pts)
- Infection (4 pts)
- Multi-organ failure after sepsis (1 pt)

NCI 1312[2]

- Rapidly progressing diseases complicated by pericardial effusion (1 pt)
- Disease progression (4 pts)
- Hemophagocytosis syndrome (1 pt): Epstein-Barr virus-positive natural killer/T-cell lymphoma
- Sudden death* (1 pt): past cardiac history of extensive atherosclerotic disease, including hypercholesterolemia, hypertension, diabetes, myocardial infarction, carotid endarterectomy, and renal stents

*** As a result of this death on study, in the context of 5 others across several trials, protocol enrollment criteria were changed to exclude patients with significant cardiovascular disease, as well as other patients at risk for sudden death**

1. Coiffier B, et al. *Blood*. 2010;116:114
2. Piekarz R, et al. *Blood*. 2011, epub February 6, 2011

Assessment of Clinical Cardiac Safety (1)

- **ECG changes have been reported with the HDAC inhibitor-class of agents**
- **Romidepsin-treated patients were pooled and evaluated for ECG changes (n = 135; 113 CTCL, 15 PTCL, 7 solid tumor)**
- **Mild, clinically insignificant QTc effects were observed, which returned to baseline within 24 hours**
  - **5.0 ± 13.9 msec mean increase[1]**
  - **14 msec increase in NCI1312 study[2]**
- **No cases of torsades de pointes were observed**
- **No associated myocardial dysfunction**

1. Cabell C, et al. Blood. 2009;114:3709
2. Piekarz et al Clin Ca Res, 2006

Assessment of Clinical Cardiac Safety (2)

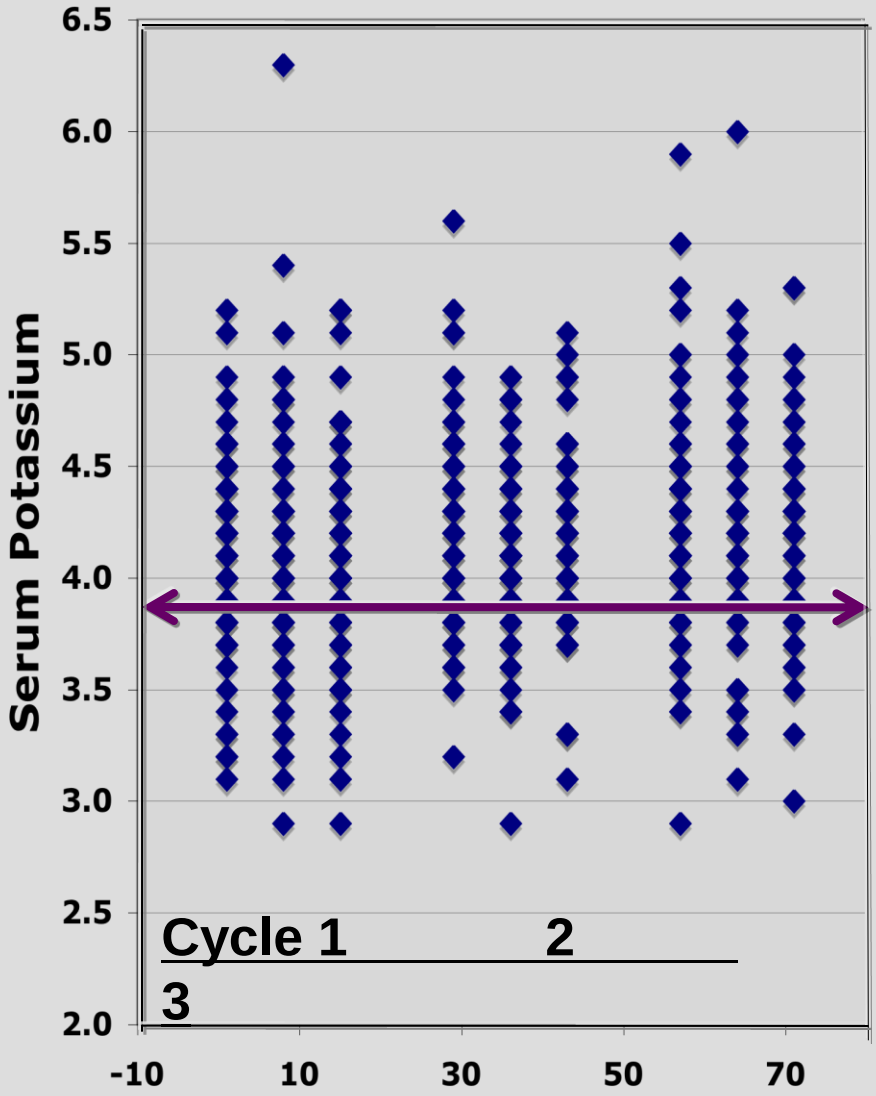
- **Morphologic changes observed were asymptomatic; no correlation with adverse events or cardiac function observed**
- **No evidence of relationship between plasma concentrations of romidepsin and changes in QTc interval**
- **Low levels of potassium and magnesium (can result from chemotherapy or underlying disease) can be associated with ECG abnormalities**
  - **Ensure levels are normalized prior to beginning romidepsin**
- **Six sudden deaths across romidepsin development program, all in patients with risk factors for sudden death.**

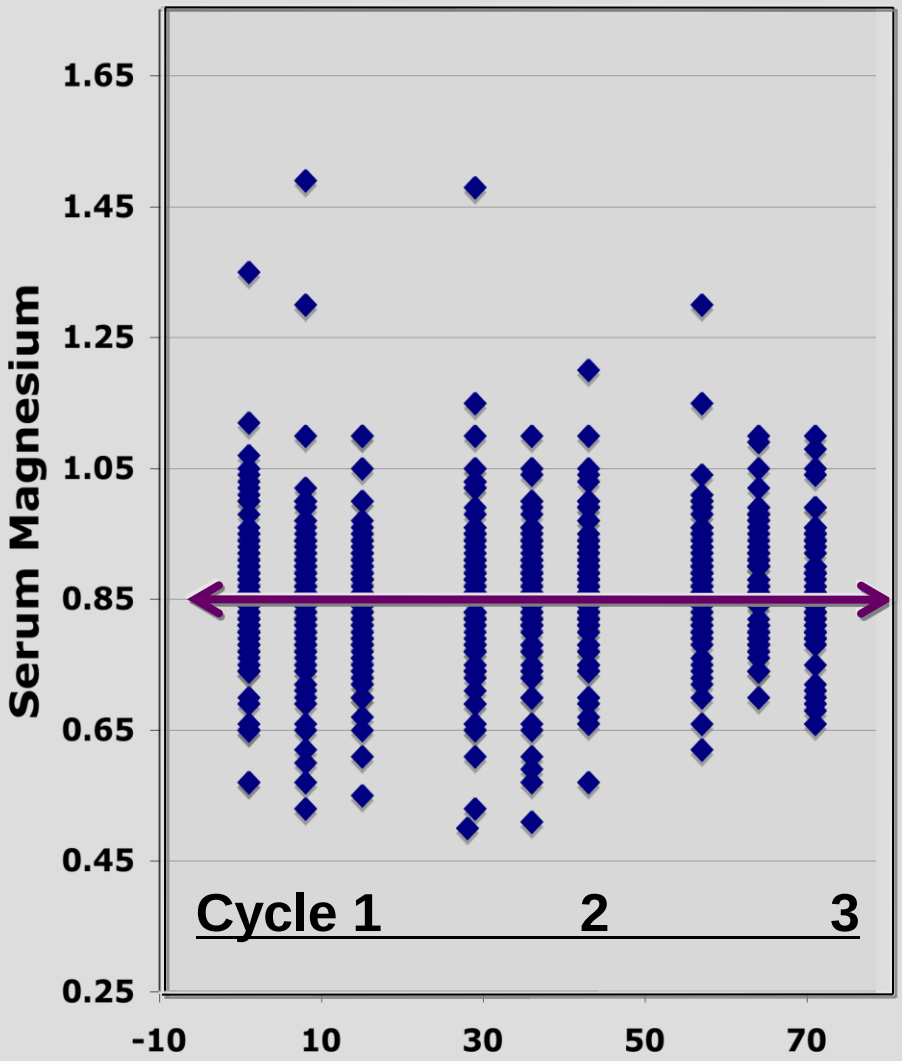
Cabell C, et al. Blood. 2009;114:3709, poster.

Cardiac Safety

- **Associated protocol requirements**
  - **Repletion of potassium and magnesium to the normal range prior to therapy**
  - **Avoidance of medications known to significantly prolong QTc or strongly inhibit CYP3A4 metabolism**
  - **Exclusion of patients with risk factors for sudden death**

Replacement Recommended Per Protocol: Potassium < 4.0 mmol/L, Magnesium < 0.85 mmol/L





Romidepsin: Days 1, 8, and 15 of Cycles 1, 2, and 3

Histone Deacetylase Inhibitors in Lymphoma

	Vorinostat (SAHA)	Romidepsin (Depsipeptide)	Panobinostat (LBH589)	Belinostat (PDX 101)	Mocetinostat ((MGCD0103)
CTCL	24 - 30%	34% (24/71) 35% (33/96)	16% (15/95) 60% (6/10)	25%	—
PTCL	—	38% (17/45)	—	18%	—
HL	4% (1/25)	—	21% (11^{1}/53) 35% (10/28)	—	35% (9^{2}/26)
DLBCL	5.5% (1^{1}/18)	—	—	—	23% (4^{1}/17)
FL	40% (8^{4}/20) 75% (3/4)	—	—	—	10.5% (2^{1}/19)

HDI Efficacy in Peripheral T-cell Lymphoma

- **Activity in PTCL**
  - **Likely a Class Effect for HDIs**
  - **Clinical Trials Ongoing - Romidepsin, Panobinostat, and Belinostat**
  - **Supplemental NDA filed for romidepsin**
- **Pooled Data in PTCL show an overall response rate of 31% and a 15% CR rate for romidepsin, based on two trials:**
  - **ORR: NCI 1312 38% GPI 06-002 29%**
  - **CR: NCI1312 18% GPI 06-002 16%**

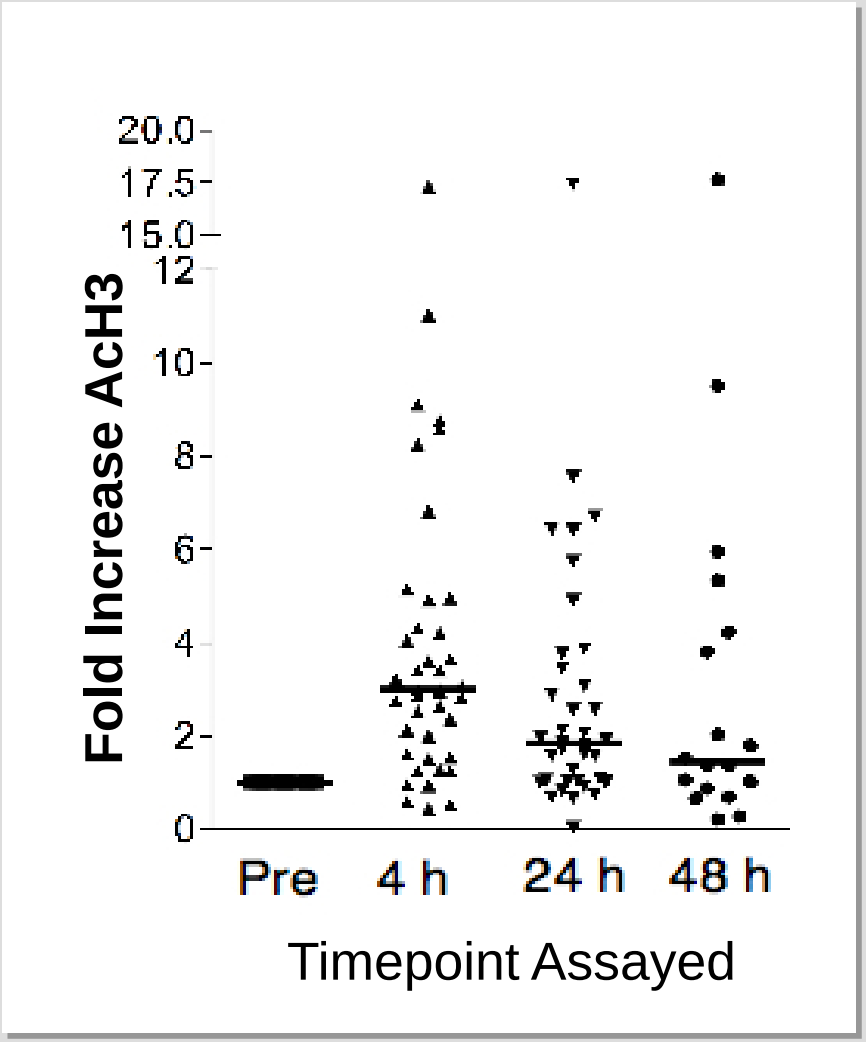
Clinical Activity of HDIs in T-cell Lymphoma

What have we learned about HDIs in T-cell lymphoma?

Are there biomarkers of activity?
What about toxicities?
Differences between agents?

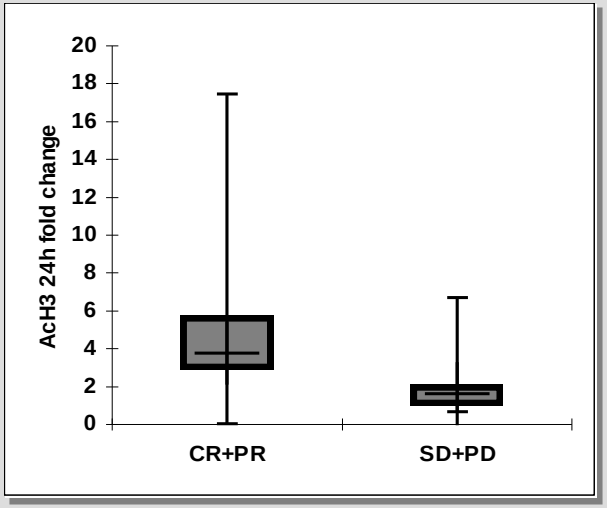
What is the mechanism of exquisite sensitivity of T-cell lymphomas?

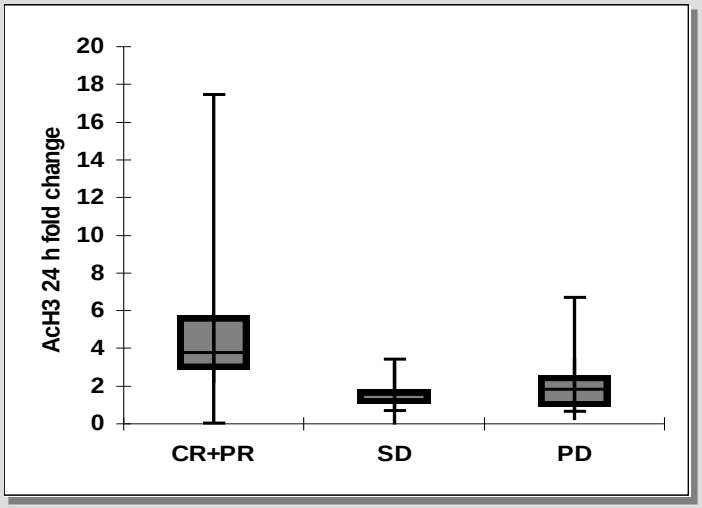
Global Histone Acetylation Increased in PBMCs Obtained from Patients on Romidepsin



24 Hr Histone Acetylation in PBMCs Associated with Response to Therapy

	CR/PR			PD/SD			
	(n)	Mean	Std Error	(n)	Mean	Std Error	p-value
AcH3 24h	(9)	5.052	1.721	(23)	1.991	0.335	0.026

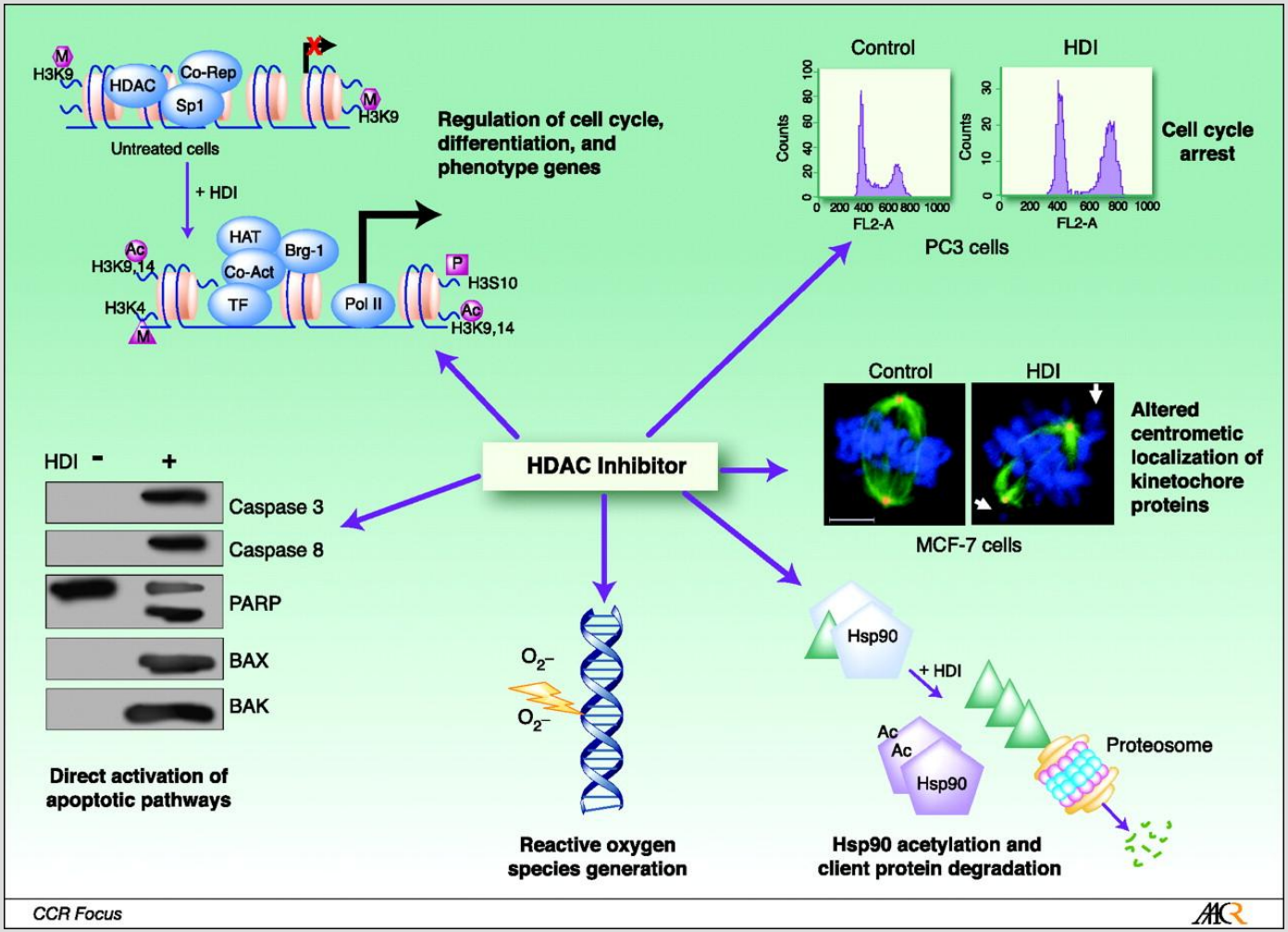




Wilcoxon rank sum test, p = 0.026

Bates et al. Br J Hematology 2009

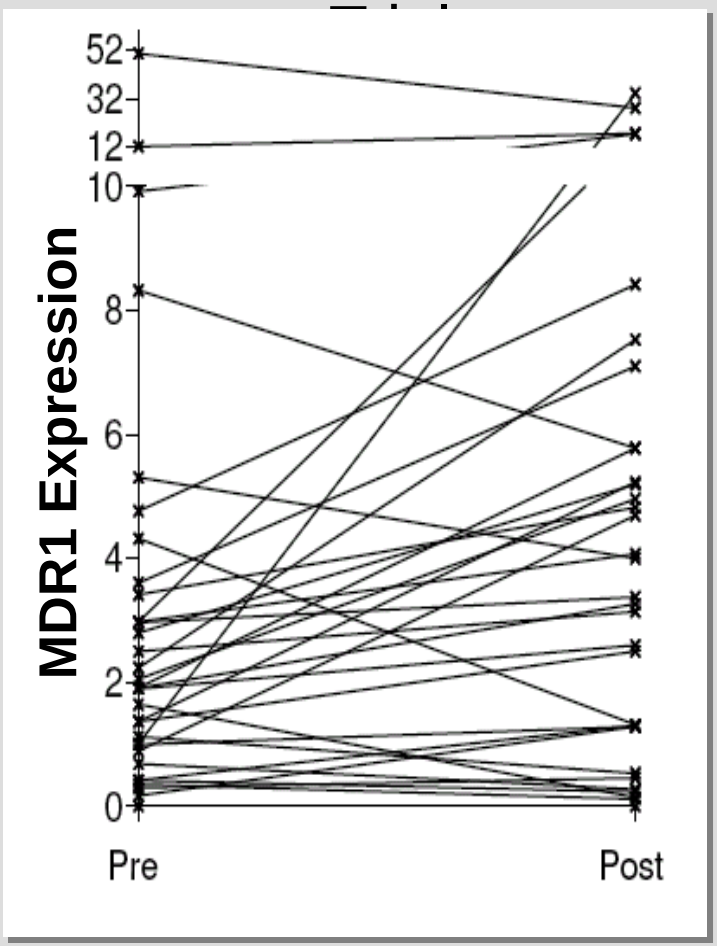
What is the Mechanism of Exquisite Sensitivity in T-cell Lymphomas?



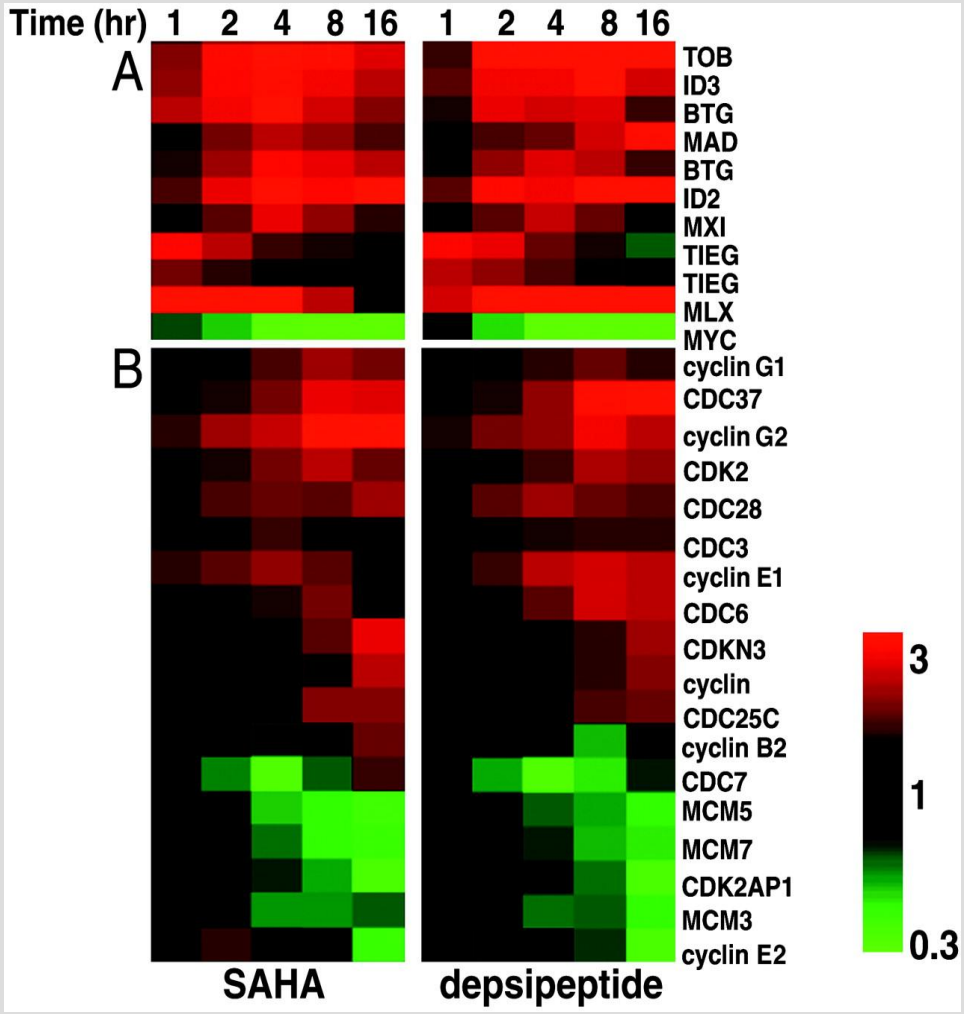
Schrump, D. S. Clin Cancer Res 2009;15:3947-3957

MDR-1 Evaluated as a Marker of Gene Induction

Biopsy Samples Patients on Romidepsin

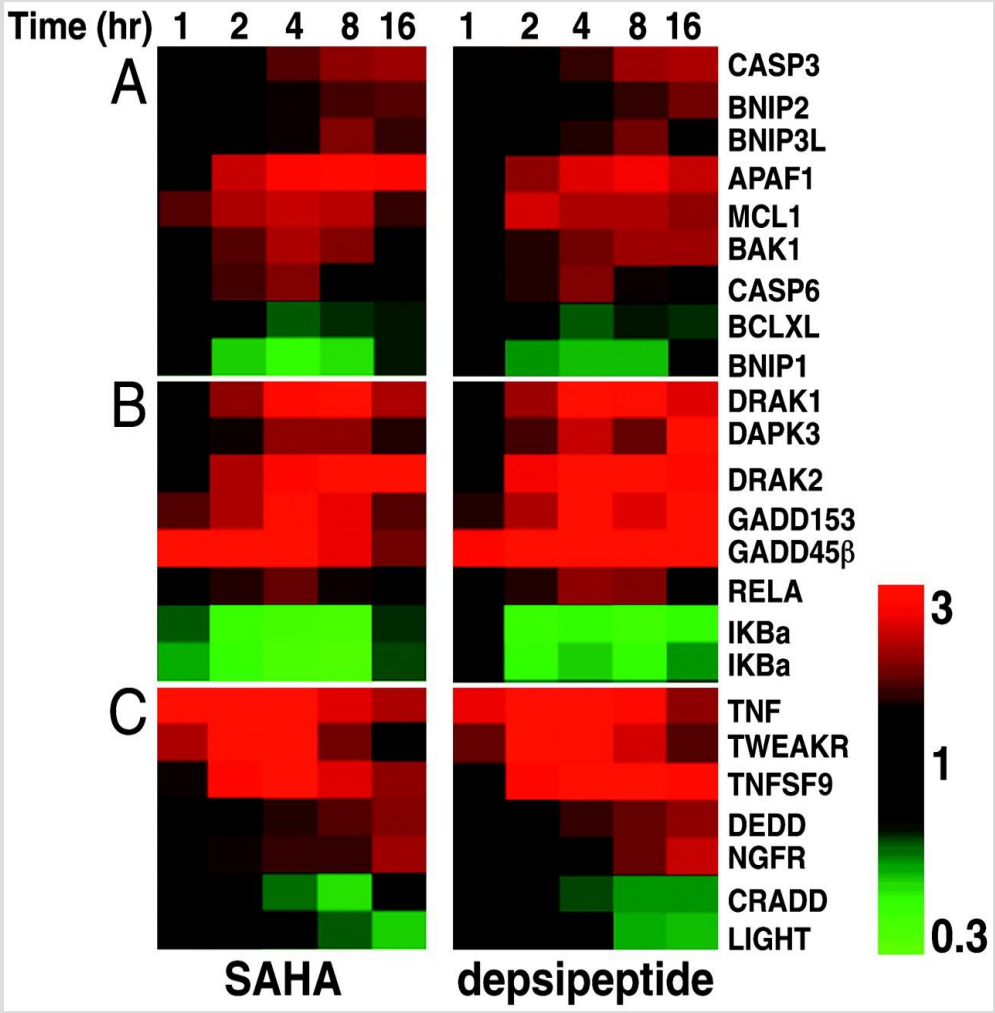


Clustering of Vorinostat- and Depsipeptide-regulated Cell Proliferation Genes



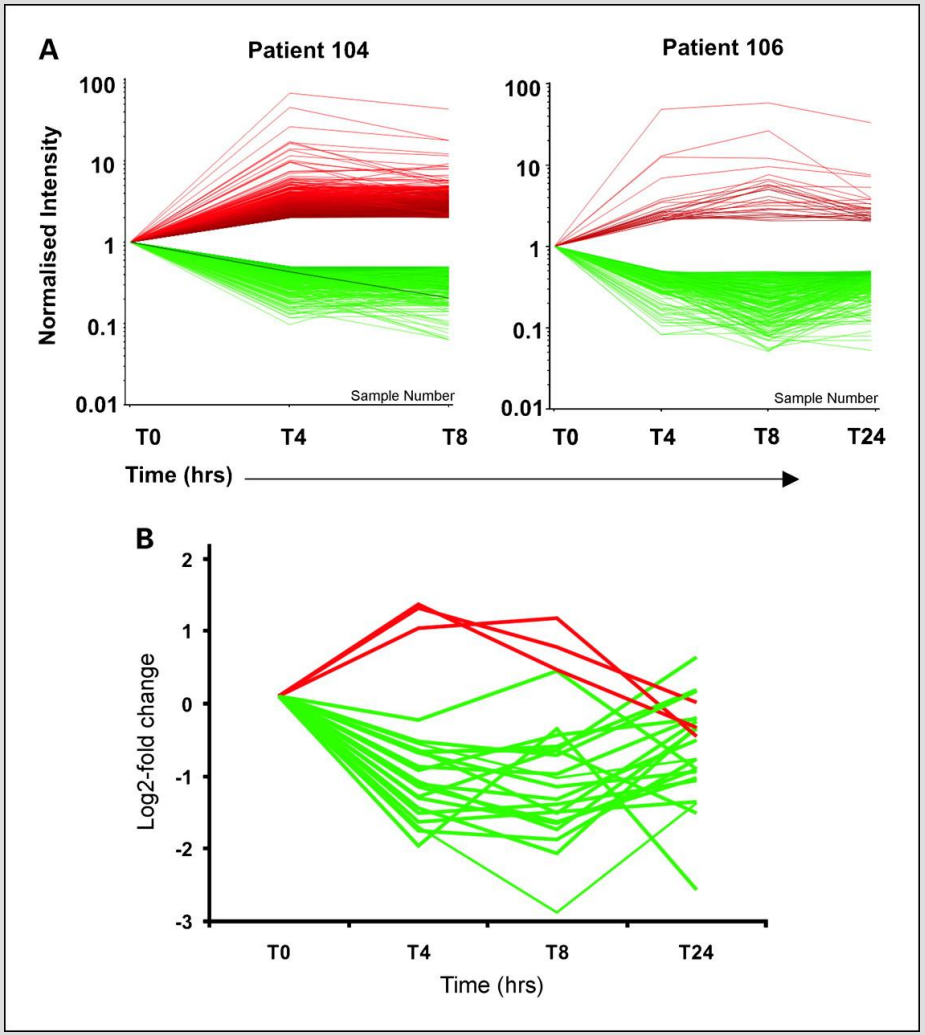
Peart, Melissa J. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 3697-3702

Vorinostat- and Depsipeptide-Regulated Apoptosis Genes



Peart, Melissa J. et al. (2005) Proc. Natl. Acad. Sci. USA 102, 3697-3702

Effects Of Panobinostat On Histone Acetylation.



Ellis L et al. Clin Cancer Res 2008;14:4500-4510
Johnstone R, Prince, M et al

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Orsolya Polgar*
Akina Tamaki*
Ken Steadman*
Marius Dohse*
Tom Obruzt*
John Deeken*

Gloucester Pharmaceuticals + NCI Partnership

If you want to go fast go alone.

If you want to go far go together.

African Proverb