Belinostat and Combo Therapies in T cell Lymphoma

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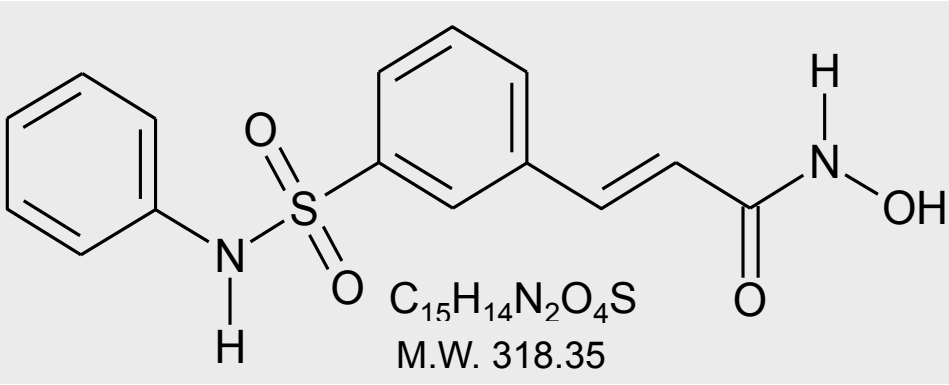
Belinostat Development

- Belinostat is a hydroxamic based pan Class I ,2 , and IV HDAC inhibitor.

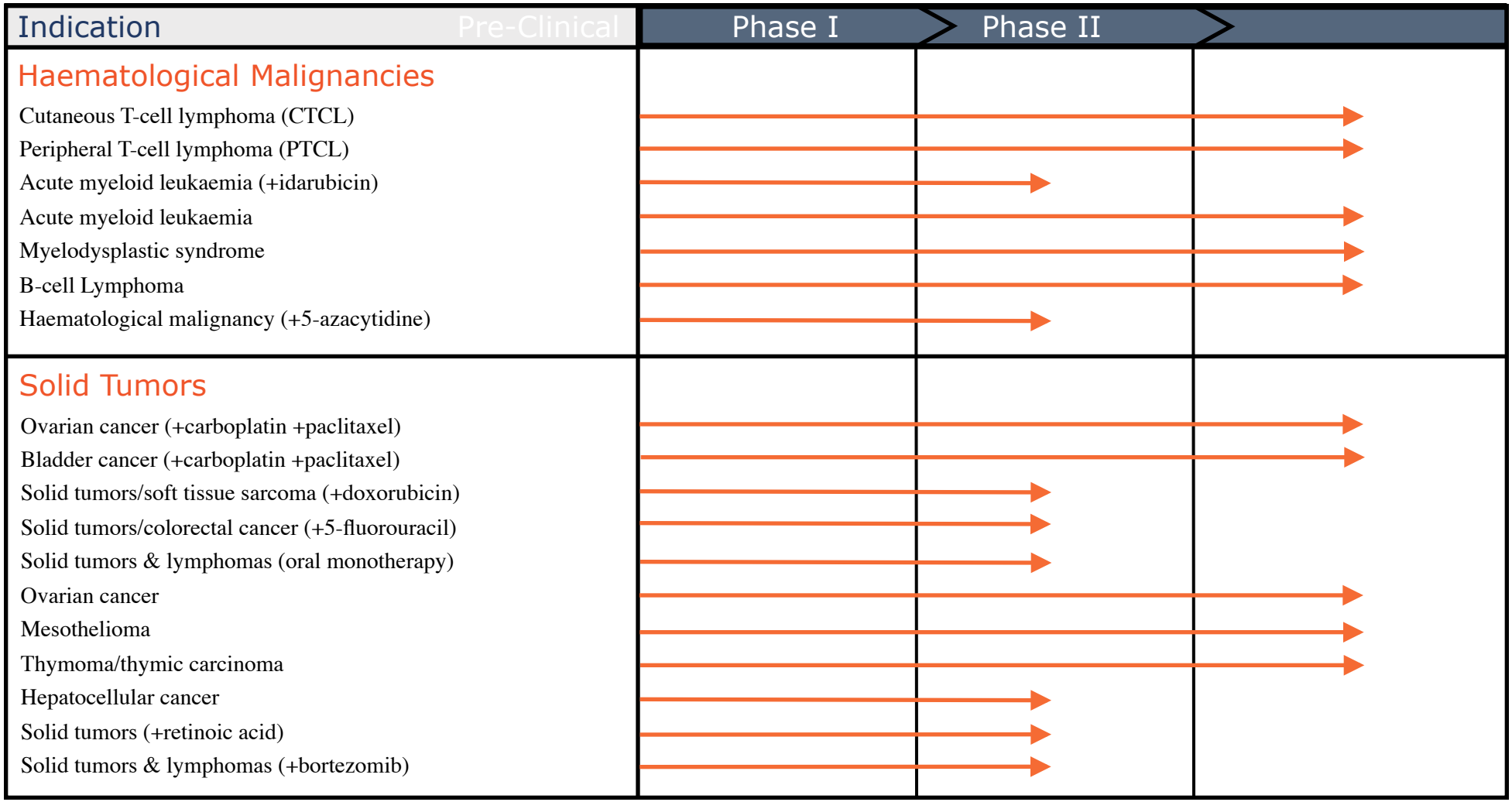


Selectivity of clinically advanced HDACi		
rhHDAC (Class)	Belinostat EC_{50} (nM)	Vorinostat EC_{50} (nM)
1 (I)	41	68
2 (I)	125	164
3 (I)	30	48
4 (I)	115	101
6 (II)	82	90
7 (II)	67	104
8 (I)	216	1524
9 (II)	128	107

Multi-targeted cellular effects

- Tumor suppressor genes
  - reactivation of p21 WAF & p19 ARF => cell cycle arrest
- DNA damage & repair
  - increased DNA acetylation => chromatin unfolding => increased access to DNA (synergy DNA targeted drugs, e.g. platinums, anthracyclines, trabectedin)
  - impact on repair mechanisms, e.g. ERCC1, RAD51, XPF => decreased expression due to double strand breaks and inter-strand cross-links (synergy DNA targeted drugs, e.g. platinums)
- Drug-targets (expression change)
  - thymidylate synthase (fluoropyrimidnes, antifolates)
  - EGFR (EGFR TKI's/Mab's)
  - aurora kinases A and B (Aurora inhib., vinca alkaloids)
  - topoisomerase II (anthracyclines, etoposide)
- α-tubulin (via HDAC6)
  - increased acetylation => stability (synergy taxanes)
- hsp90 (via HDAC6)
  - increased acetylation => promotes polyubiquitylation of misfolded client proteins (e.g Her-2, AKT, c-Raf, Bcr-Abl, mutant FLT-3) leading to proteasomal degradation (synergy bortezomib)
- Immunological effects
  - modulate activated T-cell responses (inhibit IL-2 release; induce apoptosis) and induce MHC class I-related chain A and B (MICA/B) expression on tumor cells and activated T-cells
- Anti-angiogenic effects
  - knockdown of HDAC6 causes down-regulation of VEGFR1/2

Belinostat: Active across a range of malignancies

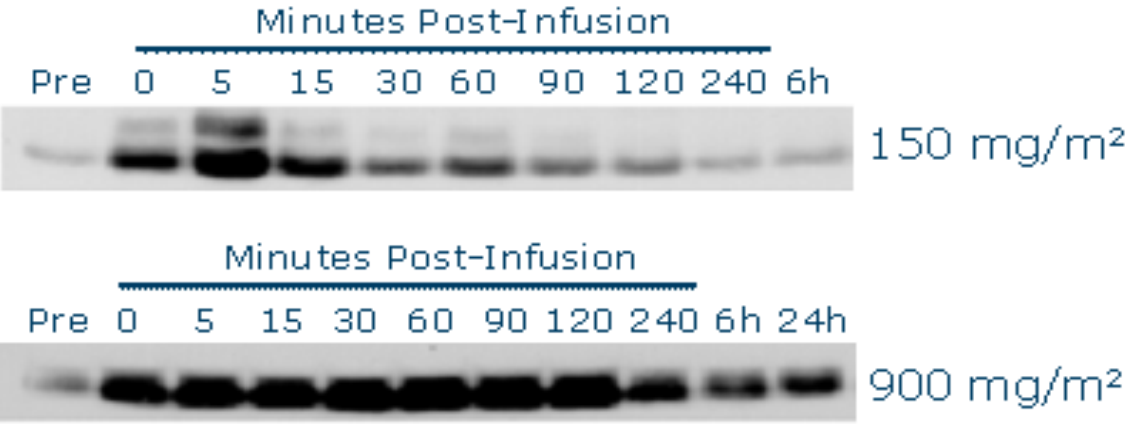


TopoTarget sponsored trials; NCI sponsored trials
IV administration unless otherwise indicated

Randomized phase II study of BelCaP (belinostat/carboplatin/paclitaxel) vs carboplatin/paclitaxel in first line treatment of patients with Carcinoma of Unknown Primary (CUP) started Q4-08/Q1-09

Belinostat Schedule

- Belinostat efficacy increases with higher exposure pre-clinically
- Belinostat studies in vivo demonstrates that 5 day regimen is superior to 1 or 3 days and not inferior to 10 days
- Belinostat 30-min infusion produces a PD effect lasting 24 hrs in patients



PD activity (histone acetylation) up to 24 hr in pts using 30-min infusion

Schedule: i) IV administration maximizes exposure, ii) administration beyond 5 days not necessary for optimal belinostat efficacy (syngeneic P388 mouse survival model), iii) once daily short infusion possible => allows maximal patient exposure followed by sustained treatment free-intervals

Phase I Experience with Belinostat

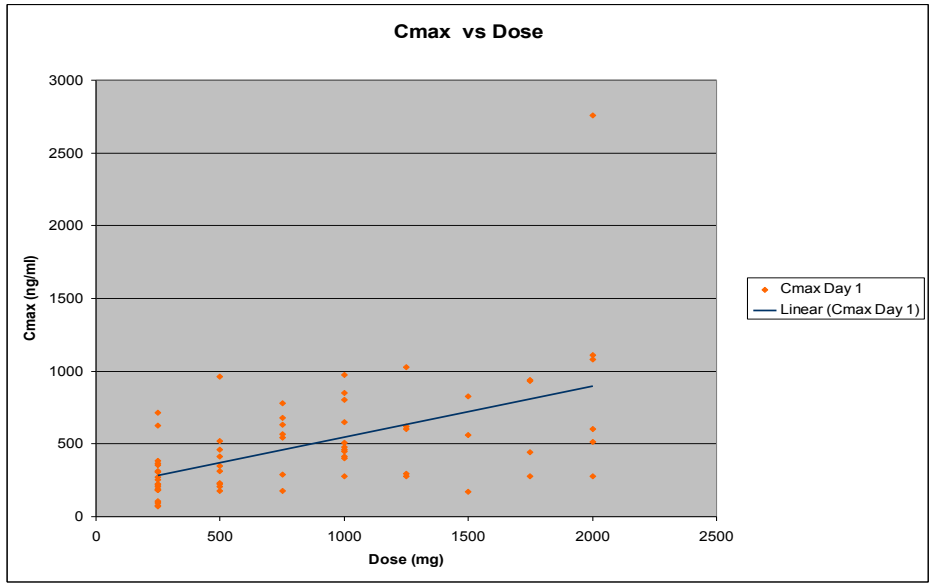
- Phase I study in refractory hematologic malignancies at doses of 600 mg/m2, 900 mg/m2, and 1000 mg/m2 for 5 days on 21 day cycle
  - no CR, 31% SD
  - Toxicities included grade 3 fatigue and neurologic symptoms
  - No MTD determined
- Parallel Phase I study in solid tumors determined MTD to be 1000 mg/m2
  - DLT was fatigue, diarrhea, atrial fibrlllation
- Oral study in 28 patients with hematologic malignancies determined MTD of **1500 mg daily**
  - Diarrhea and thrombocytopenia were DLT
  - Of 16 evaluable patients, 1CR, 1 PR
- Parallel Phase I oral study in refractory solid tumors had MTD of 750 mg daily

Belinostat: Phase I Oral Study

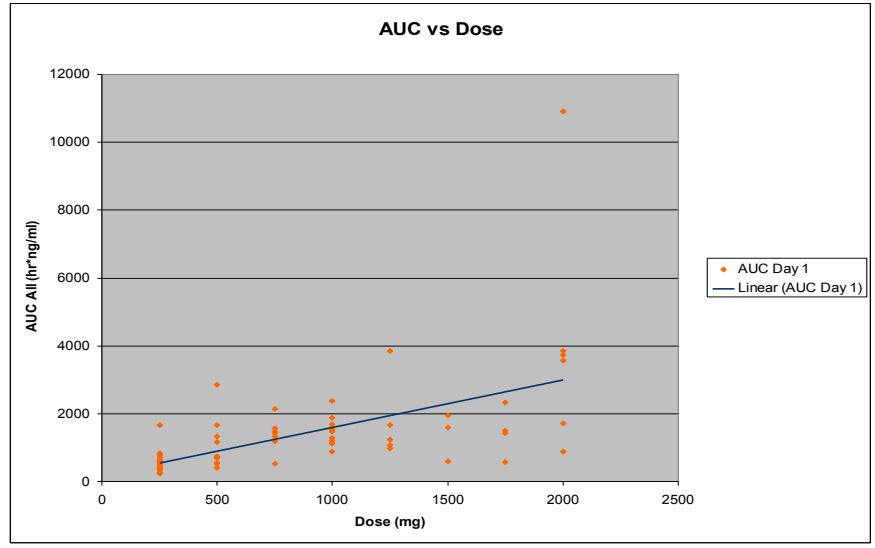
Schedules and number of treated patients per cohort

Cohort	1	2A	2B	1C	2C	2D	3C	4C	1E	2E	3E	4E	5E
Schedule	Continuous			Day 1 to 14, q3w					Day 1 to 5, q3w				
	QD	QD	BID	QD	QD	BID	QD	QD	QD	QD	QD	QD	QD
Dose (mg)	250	500	250 + 250	500	750	250 + 500	1000	1250	1000	1250	1500	1750	2000
# Pts	20	6	20	3	7	7	8	2	3	3	3	4	6
# DLTs	0	2	0	0	1	3	1	2	0	0	0	0	1

Pharmacokinetics: Phase I Oral Study



- **Cmax Day 1 *versus* Dose for all evaluable patients receiving belinostat QD**



- **AUC Day 1 *versus* Dose for all evaluable patients receiving belinostat QD**
- **The linear regression line is indicated by the blue line; R^2 is 0.3188 ($p<0.05$)**

CLN-6: A Phase II Clinical Trial of Belinostat in pts with Recurrent or Refractory T-Cell Lymphomas

Study Objectives

Study Objectives

Belinostat monotherapy

– Response rate, time to response, duration of

Patient Population

Patient Population

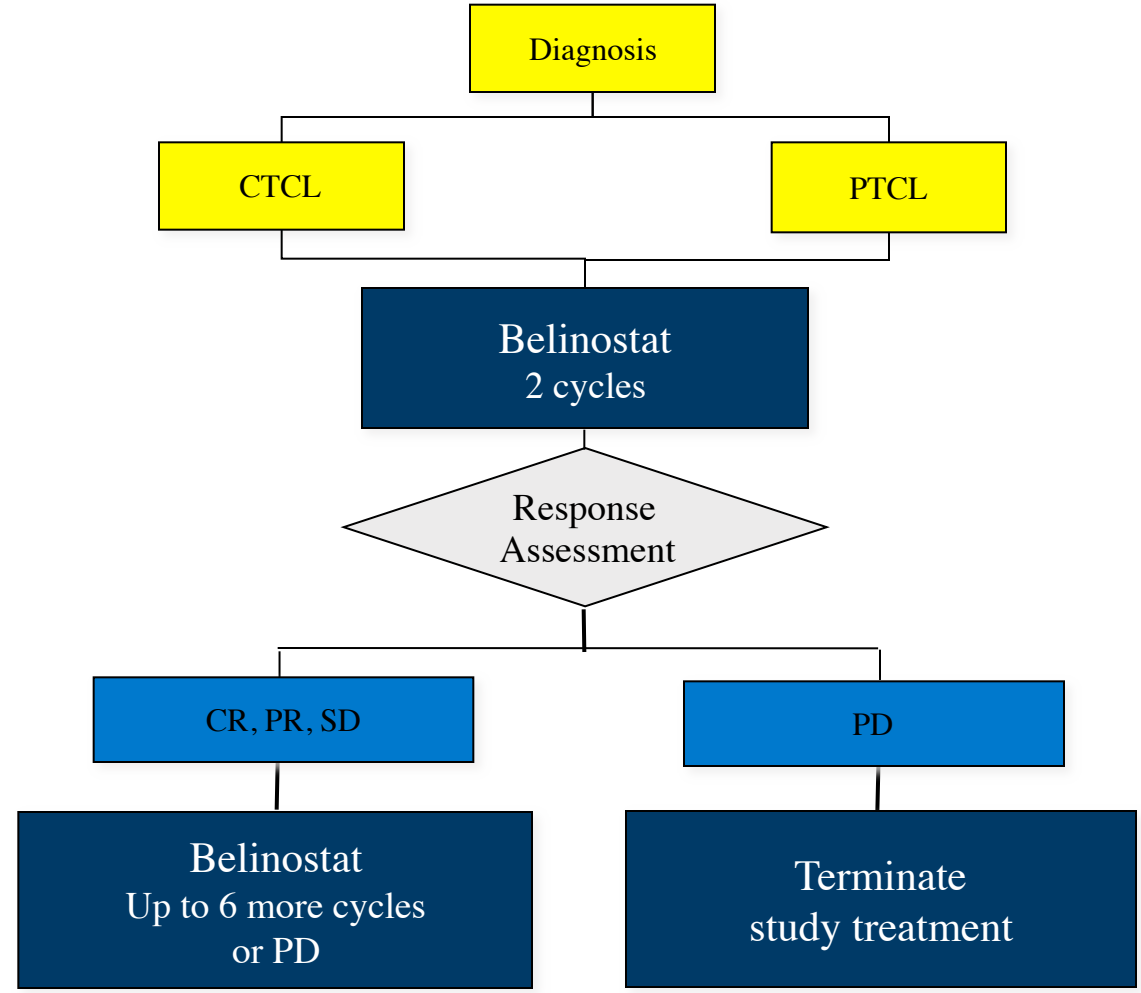
- CTCL or PTCL

30 min IV infusion once daily

30 min IV infusion once daily

on days 1-5 every 3 weeks

on days 1-5 every 3 weeks



Foss et al, Br J Hematol, 2015

Two-Stage Design (by study arm/diagnosis):

- terminate study arm if ≤ 1/13 pts show response
- if ≥ 2/13 show response continue enrollment

CLN-6: Clinical Features of PTCL Patients

Male : female	14 (67%) : 7 (33%)
Age, median	61 (23-76) years
Karnofsky performance status, median	80% (30-100%)
Subtypes	
Peripheral, unspecified (PTCLu)	11 (52%)
Anaplastic large cell (ALCL)	3 (14%)
Angioimmunoblastic (AITL)	3 (14%)
Extranodal NK/T-cell (NK/T)	3 (14%)
Subcutaneous panniculitis-like (SPTCL)	1 (5%)
Stage III-IV at study enrollment	17 (81%)
IPI at study enrollment, median	2 (0-4)
Disease duration, median	20 (2-194) months
Prior systemic regimens, median	2 (1-10)
Specific treatments	
Chemotherapy	21 (100%)
CHOP	20 (95%)
Denileukin diftitox	5 (24%)
Monoclonal antibody (anti-CD20, 30, 52)	4 (19%)
Autologous stem cell transplantation	3 (14%)
Radiation therapy	3 (14%)
Bexarotene	1 (5%)
HDAC inhibitor	1 (5%)
Time to last treatment, median	102 (18-3057) days

CLN-6: PTCL Outcomes

Number of cycles, median	2 (1-8)
Evaluable patients	19*
Objective response	6 (29%)
Complete response	2 [2 PTCLu]
Partial response	4 [PTCLu, AITL, ALCL, NK/T]
Stable disease	4 [2 PTCLu, 2 NK/T, 1 ALCL]
Progressive disease	9

	Median (range)
Time to response (n=6)	67 (38-431) days
Time to complete response (n=2)	127 (114-140) days
Duration of response* (n=6)	268+ (99-847+) days
Duration of stable disease^ (n=4)	133+ (80-236+) days
Progression-free survival∞ (n=21)	40 (8-930+) days

CLN-6 -CTCL Characteristics

Male : female	15 (52%) : 14 (48%)
Age, median	69 (26-85) years
Karnofsky, median	90 (70-100)
Stage at enrollment MF/SS: Non-MF/SS	IB-II 8 III-IV 18 1(33%), 1(33%), 1 (33%)
Disease duration, median	35 (5-330) months

Prior systemic regimens, median	3 (1-9)
Specific treatments	
Chemotherapy	23 (79%)
Bexarotene	20 (69%)
Interferon	14 (48%)
Denileukin diftitox	11 (38%)
Radiation therapy	11 (38%)
HDAC inhibitor	4 (14%)
Time to last treatment, median	45 (0-850) days

CLN-6: CTCL Response

Cycles, median	2 (1-14)
Evaluable patients	29
Objective response	4 (14%)
Complete response	2 [MF, ALCL]
Partial response	2 [MF, SS]
Stable disease	18
Progressive disease	7

	Median, range
Time to response (n=4)	16 (14-35) days
Time to complete response (n=2)	128 (36-219) days
Duration of response* (n=2)	273 (48-469+) days
Duration of stable disease^ (n=18)	44+ (17-127+) days
Progression-free survival∞ (n=29)	44+ (16-483+) days

CLN-6: Hematological Toxicity

	Toxicity Grade without Consideration of Baseline Abnormalities			Shift from Baseline Toxicity Grade		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	5 (9%)	3 (6%)	0	5 (9%)	2 (4%)	0
Leukopenia	7 (13%)	1 (2%)	0	4 (8%)	0	0
Thrombo-cytopenia	1 (2%)	0	2 (4%)	2 (4%)	1 (2%)	0
Anemia	14 (26%)	2 (4%)	0	2 (4%)	0	0

ECG CHANGES

- Electrocardiographic (ECG) monitoring performed by central laboratory
  - In C1, D1-5, ECG pre-infusion & 1-hour post-infusion
  - In C2+, D1, ECG pre-infusion & 1-hour post-infusion

- Approximately 700 ECGs analyzed
  - Grade 2 (≥ 470 msec) QTcF prolongation – 7
  - Grade 3 (≥ 500 msec) QTcF prolongation – 0

CLN-6: Non-Hematological Toxicity

- **Most frequent drug-related adverse events of any grade**

nausea (50%)	**infusion site pain (14%)**	
vomiting (24%)	**fatigue (15%)**	**dizziness (10%)**

- **Infrequent grade 3 drug-related adverse events**

apraxia	cellulitis	ileus	peripheral edema
liver test abnormalities		pneumonitis	rash

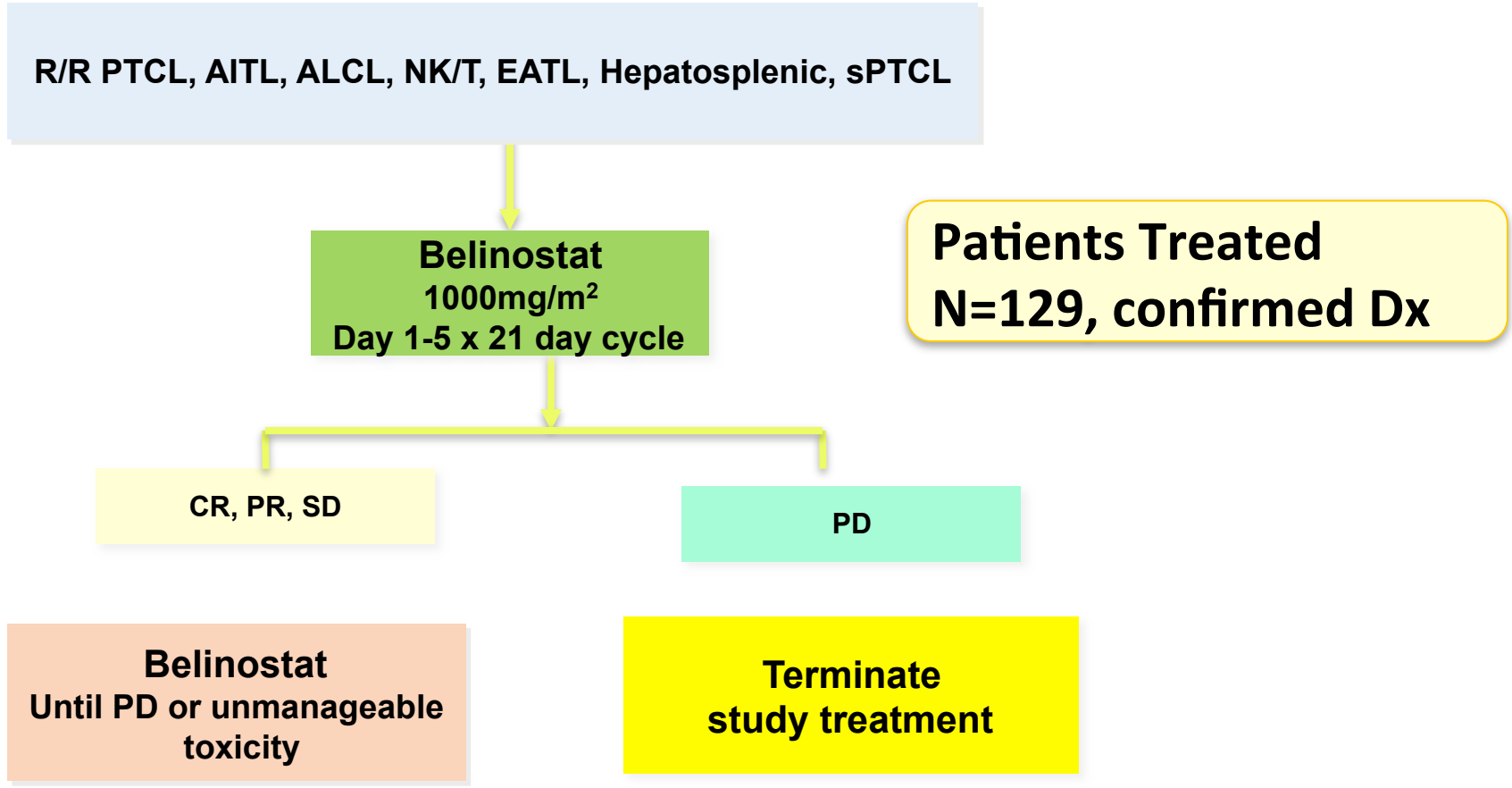
- **No grade 4 drug-related adverse events**
- **Deaths during study**

Disease progression – 2
Sepsis (unrelated to study drug) – 1
Pneumonia (unrelated to study drug) – 1
Ventricular fibrillation – 1 (attributed to study drug; no QTc abnormality)

BELIEF Trial

- 120 patients with relapsed or refractory PTCL
- Dose: 1000 mg/m2 daily x 5 every 3 weeks until PD
- Primary endpoint: ORR > 20% is considered significant
- Eligibililty
  - ALCL
  - AITL
  - Enteropathy-associated T-cell lymphoma
  - Extranodal NK/T-cell lymphoma, nasal type
  - Hepatosplenic T-cell lymphoma
  - PTCL
  - Subcutaneous panniculitis-like T-cell lymphoma

BELIEF TRIAL DESIGN



BELIEF: Patient Characteristics

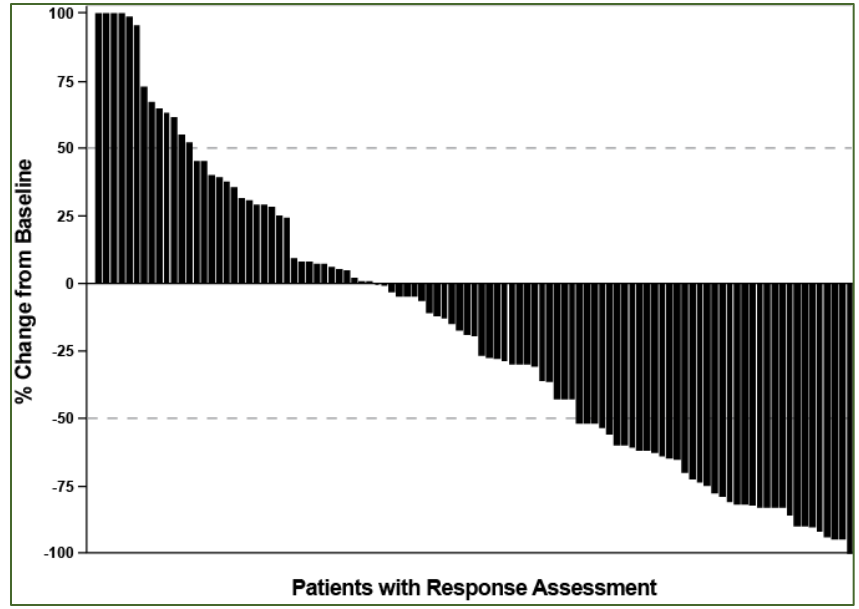
Gender	
Male	69 (54)
Female	60 (46)
Age	
<65	67 (52)
≥65	62 (48)
Median, yr (range)	63 (29-81)
Race	
White	111 (86)
Performance status, n (%)	
ECOG 0	44 (34)
ECOG 1	57 (44)
ECOG 2-3	28 (22)
Median time from last disease progression to study entry (mo)	1 (0.1-55)*
Bone marrow involvement	30%

PRIOR LYMPHOMA THERAPIES

Prior Therapy for PTCL	N = 129 n (%)
Median number of therapies (range)	2 (1-8)
Systemic therapy	**129 (100)**
CHOP or CHOP-like	125 (96)
Stem cell transplant	**29 (23)**
Autologous	27 (21)
Allogeneic	2 (2)
Radiation therapy	**28 (22)**

PTCL Response Assessed by Central Review

Response	Efficacy Analysis Set (N=120) n (%)	(95% CI)
ORR	31 (26)	(18-35)
CR	13 (11)	(6-18)
PR	18 (15)	
SD	18 (15)	
PD	48 (40)	
NE	23 (19)	



NE = not evaluable due to death (n=7), clinical progression (n=10), patient withdrawal (n=5) or lost to follow-up (n=1) prior to first radiologic assessment

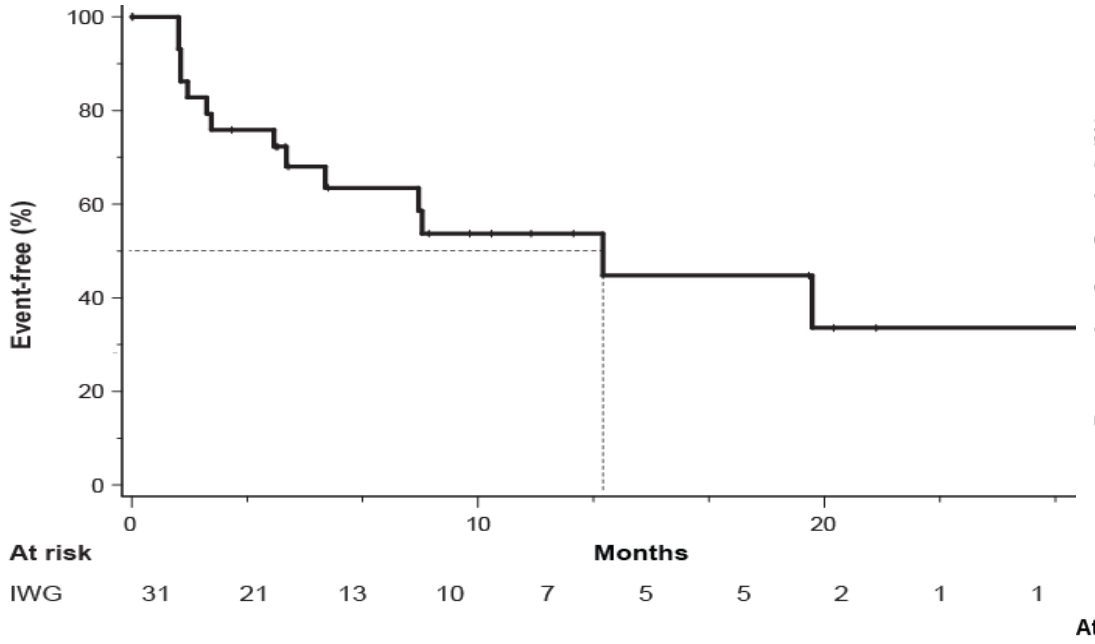
Response Rate by CPRG Lymphoma Diagnosis

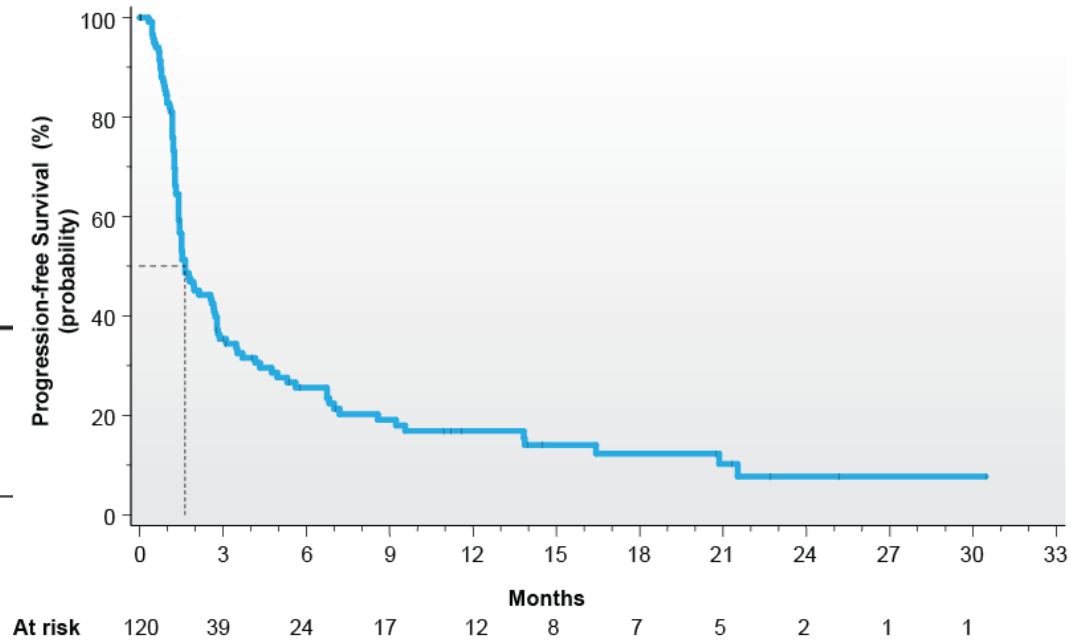
	Subset	Responders
CPRG lymphoma diagnosis	**n (%)**	**n (%)**
PTCL, NOS	**77 (64)**	**18 (23)**
AITL	**22 (18)**	**10 (46)**
ALCL, ALK-negative	**13 (11)**	**2 (15)**
ALCL, ALK-positive	**2 (2)**	**0 (0)**
Enteropathy-associated TCL	**2 (2)**	**0 (0)**
Extranodal NK/TCL, nasal type	**2 (2)**	**1 (50)**
Hepatosplenic TCL	**2 (2)**	**0 (0)**

Response By Subgroup

Characteristic	Belinostat (N=120)	
	Subset	Responders
	n (%)	n (%)
Bone Marrow involvement		
No	65 (54)	20 (31)
Yes	35 (29)	8 (23)
Indeterminate	8 (7)	2 (25)
Not assessed	12 (10)	1 (8)
Platelets		
≥100,000/μL	100 (83)	28 (28)
<100,000/μL	20 (17)	3 (15)

Response Duration and Progression Free survival





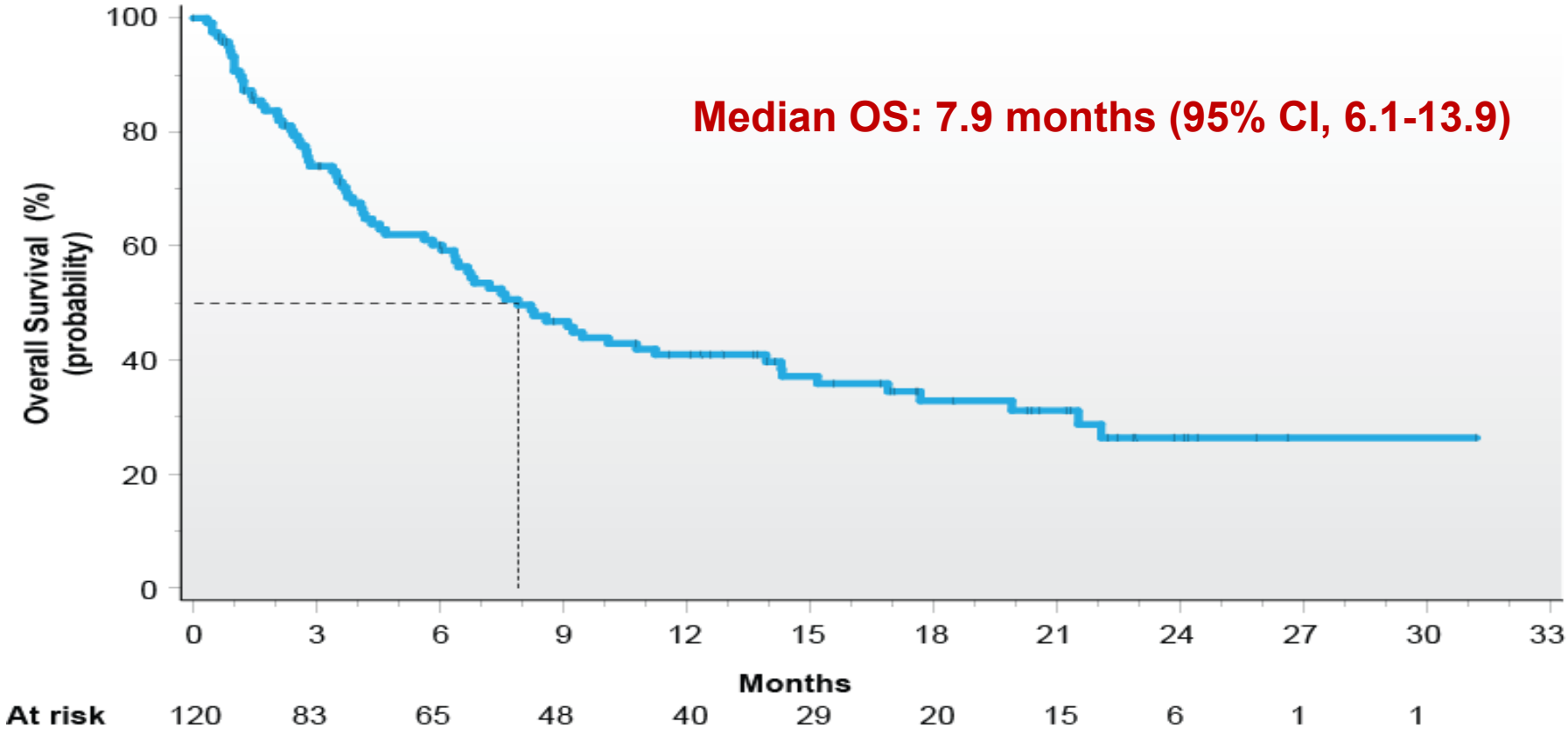
Median DoR: 13.6 months (95% CI, 4.5-29.4)

Median PFS:1.6 months (95% CI, 1.4-2.7)

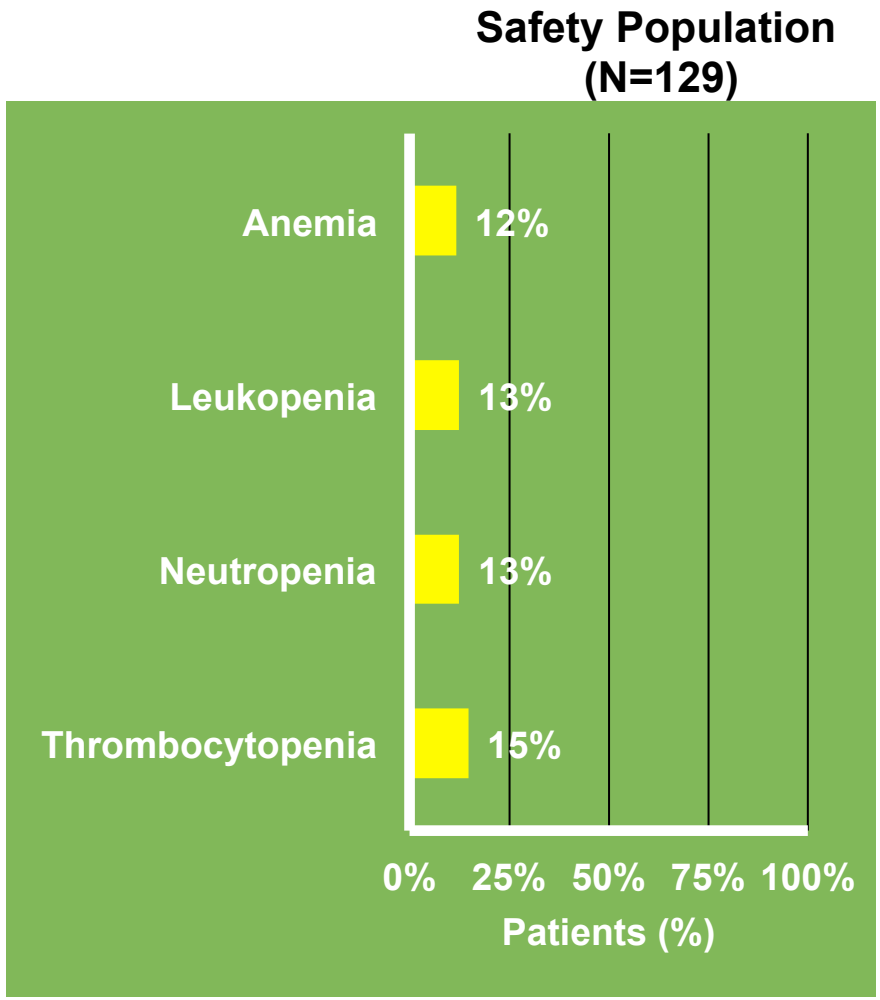
Belinostat Drug Exposure and Dose Reductions

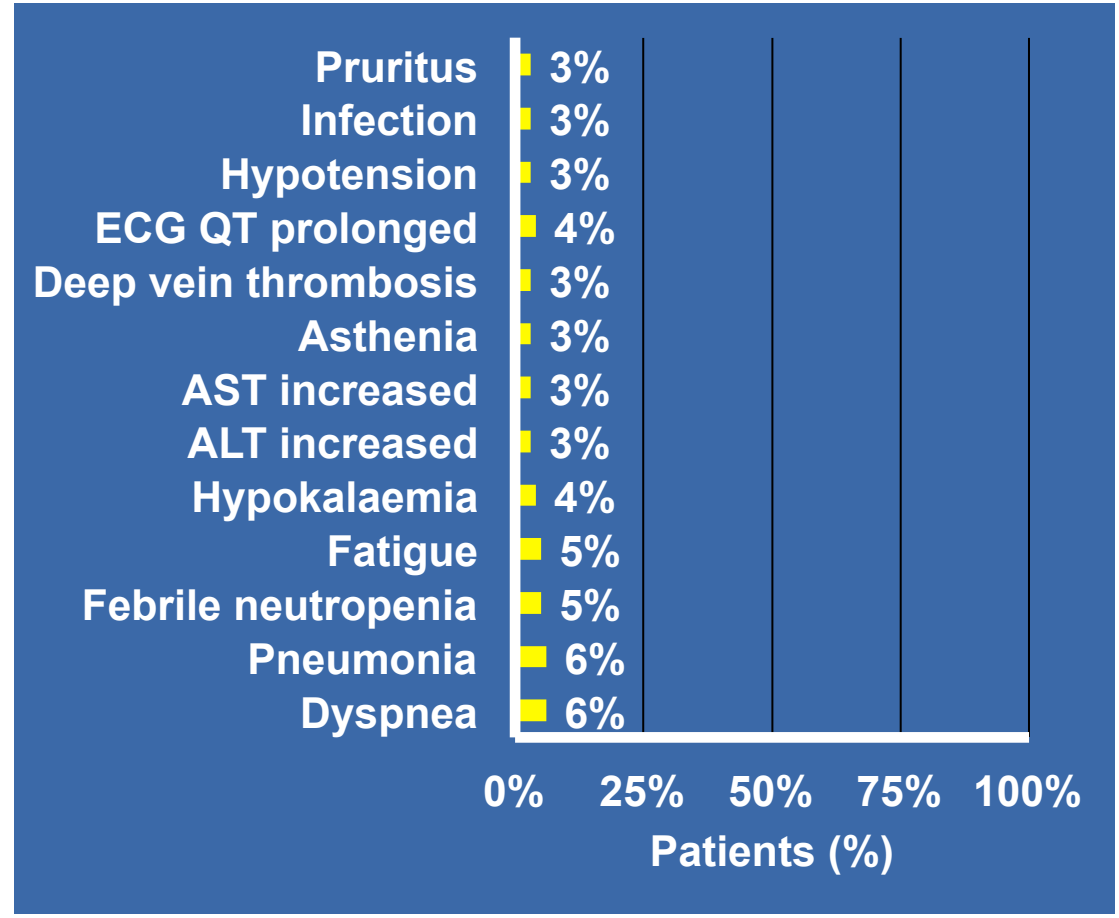
Extent of Exposure	All Patients N = 129	Platelets <100K N = 24
Median duration of treatment, wk	7 (3-135)	6 (3-55)
Median number of cycles	2 (1-33)	2 (1-18)
Median cumulative dose (g/m^2)	10.5 (1-164)	9.3 (3-91)
Relative dose intensity,%	**98.3 (20-105)**	**98.5 (55-103)**
Patients with dose reduction, n (%)	17 (13)	4 (17)
1 reduction to 750 mg/m^2	16 (12)	4 (17)
2 reductions to 560 mg/m^2	1 (1)	-
Cycles delayed by ≥7 days, n (%)	37 (29)	6 (25)
For adverse events	19 (15)	4 (17)
For other reasons	18 (14)	2 (8)

Kaplan-Meier Estimate of Overall Survival*



Grade ≥3 Adverse Events





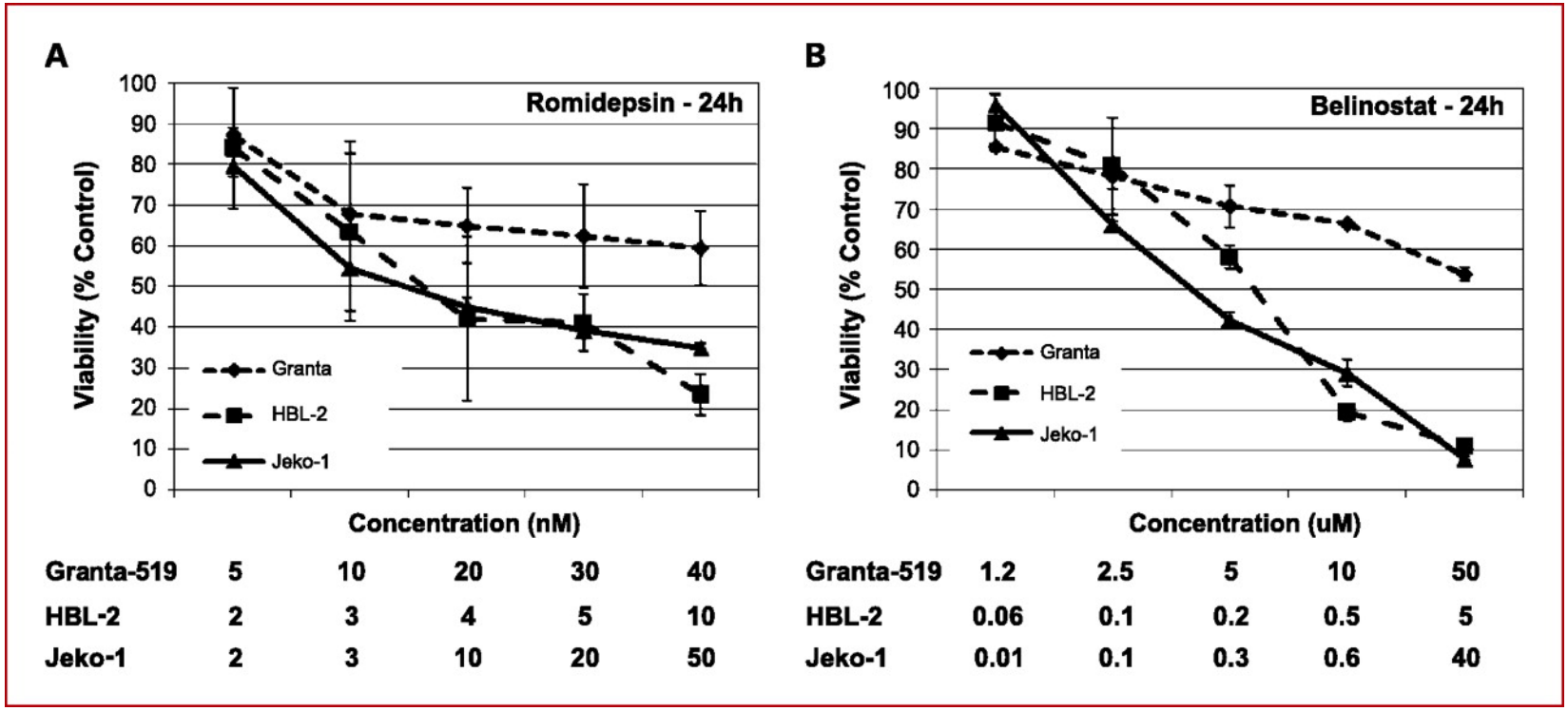
Conclusions: Belief Trial

- Single agent response rate in relapsed/refractory setting of 26%, comparable to romidepsin and pralatrexate
- Safety profile was acceptable with expected HDAC associated Aes
- Significant activity in AITL
- Further investigation of belinostat in combination with other therapies is warranted to develop new treatment paradigms for PTCL

Combination Studies with Belinostat

- **BelCaP (belinostat + carboplatin + paclitaxel)**
- Relapsed Ovarian Cancer (PXD101-CLN-8; n=35)
  37% progression-free rate at 6 months, 5.5 mo median PFS
  - Bladder Cancer (after cis/gem)
  - 29% OR (n=14)
- **BelFU (belinostat + 5-FU; n=35)**
  - 26% SD with duration up to 41 weeks (median 3 prior regimens; majority ≥2 FU-based)
- **BelAza (belinostat + azacitidine)**
  - 2 CR, 1 PR & 4 hem. improvement (n=21)
  - Expansion to randomised phase started by NCI
- **BelIda (belinostat + idarubicin)**
  - 2 CR & 3 CRi using IV or CIV (n=34)
- **BelDex (belinostat + dexamethasone)**
  - 44% OR (2 PR, 2 MR; duration of 6 to +16w)
  - 56% SD with duration up to 58w

HDAC Synergy with Bortezomib in MCL cell lines.

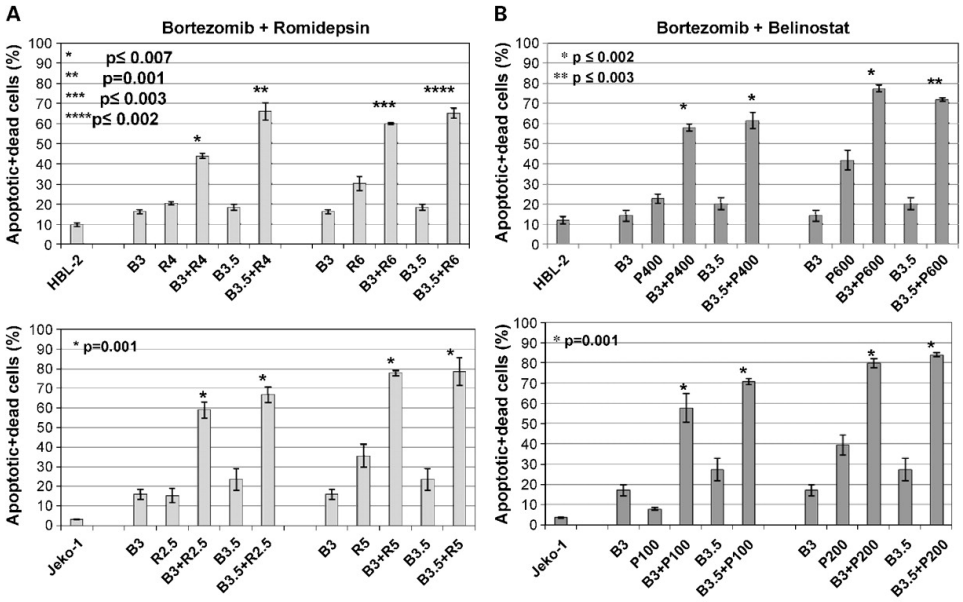


Luca Paoluzzi et al. Clin Cancer Res 2010;16:554-565

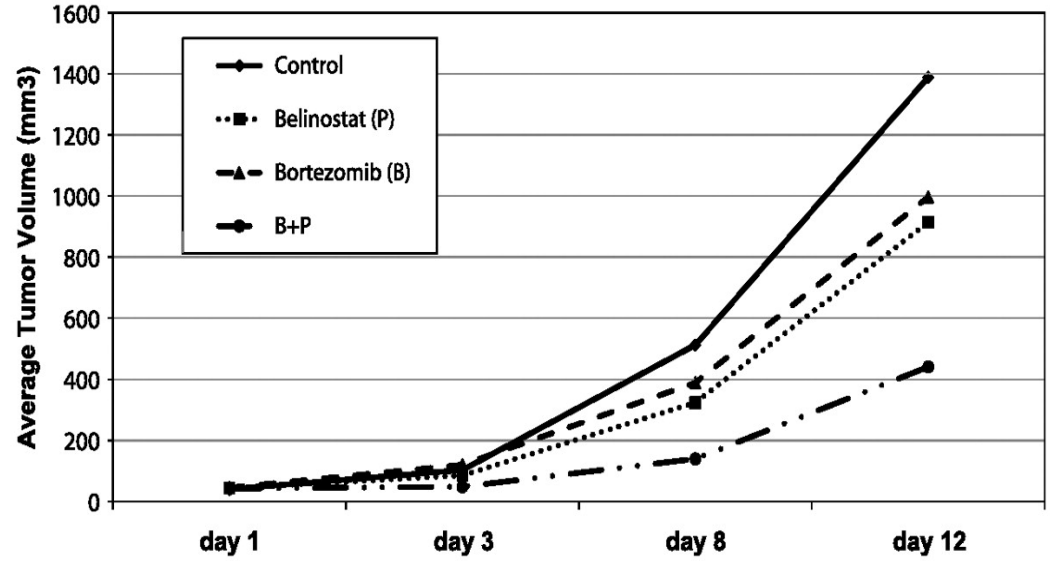
Clinical Cancer Research
AACR American Association for Cancer Research

HDAC Synergy with Bortezomib in MCL cell lines.

Enhanced apoptosis of bortezomib (B) combined to an HDACI in MCL cell lines.



Enhanced activity of belinostat combined to bortezomib in a xenograft SCID beige mouse model of MCL (HBL-2).



Luca Paoluzzi et al. Clin Cancer Res 2010;16:554-565

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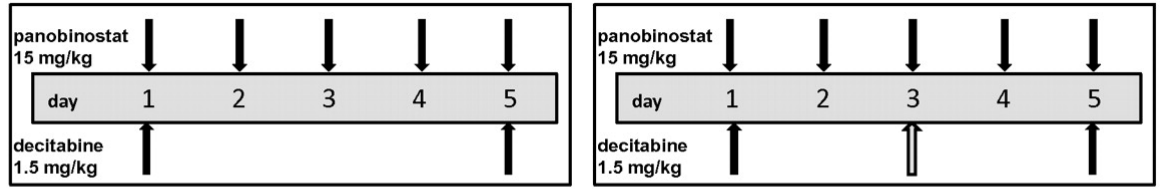
Phase I study of bortezomib and belinostat in relapsed acute leukemia, MDS, or CML

- PRIMARY OBJECTIVES
  - To determine the recommended phase II doses for the combination of bortezomib and belinostat
- SECONDARY OBJECTIVES
  - Safety and tolerability
  - Effects on NF-kB (nuclear RelA by immunofluorescence microscopy), NF-kB dependent proteins XIAP and Bcl-xL, and BIM.
- THERAPY
  - belinostat days 1-5 and 8-12 of 21 day cycle
  - bortezomib IV on days 1, 4, 8, and 11

Panobinostat and decitabine synergize in the SCID beige DLBCL xenograft model.

A



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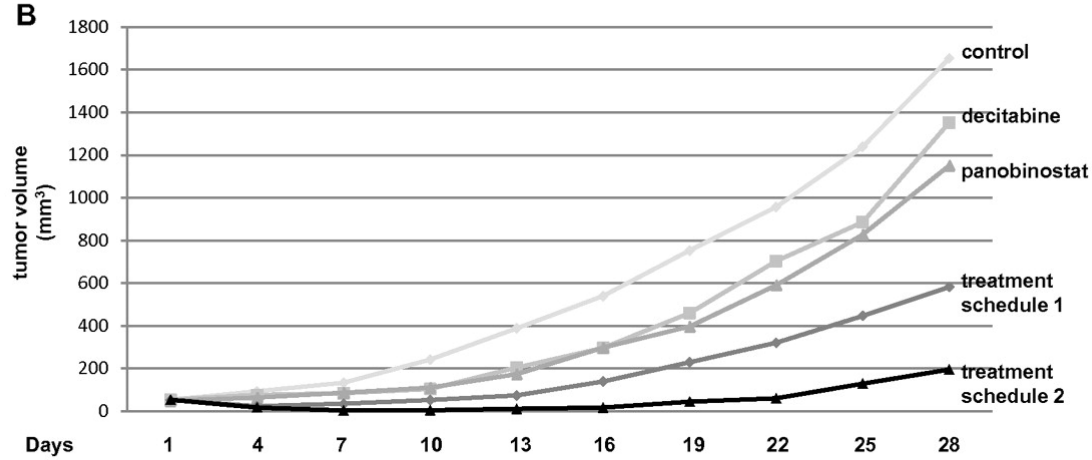


C

	control	panobinostat	decitabine	treatment schedule 1	treatment schedule 2
control	N.A.	0.1606	0.1049	0.0047	0.0004
panobinostat	0.2787	N.A.	0.7210	0.0148	0.0004
decitabine	0.0282	1.0000	N.A.	0.0207	0.0004
treatment schedule 1	0.0002	0.0105	0.0004	N.A.	0.0004
treatment schedule 2	0.0004	0.0004	0.0004	0.0007	N.A.

Matko Kalac et al. Blood 2011;118:5506-5516

blood

Phase I study of belinostat and azacitidine in myeloid malignancies

- AZA 75 mg/m2 daily x 5 with belinostat in Part 1
- Randomized to combo vs AZA in part 2 for cycle 1, then combo for subsequent cycles

- **18 of 56 patients responded**
- **MTD of belinostat 1000 mg/m2**

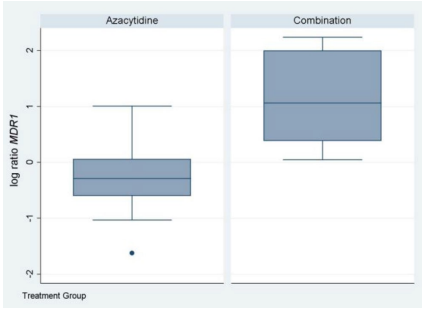


Table 4 Nine responders in Dose Escalation Phase (n=24)

ID #	Age	Diagnosis	Stage of disease	Cytogenetic risk group	No. prior regimens	Dose BEL	±No. cycles	Best responses	Time to initial response (days)	Response duration (days)
2	49	AML	Relapsed	Intermediate	5§	150	9	HI-N	102	147
3	75	CMML-1	Refractory	Favorable	1	150	64	PR	27	1860
9	54	MDS-RCMD	Relapsed	Favorable	4§*	300	11	HI-P	28	279
13	56	AML	Relapsed	Unfavorable	2§	300	4	HI-N	59	41
14	67	AML	Refractory	Intermediate	2	300	6	CR^	49	239
15	67	PMF	Refractory	Intermediate	1*	1000	2	HI-P	21	35
17	70	MDS-RAEB-1	Relapsed	Unfavorable	2§	1000	6	HI-P	86	42
22	76	t-MN	Prev. untreated	Unfavorable	0	1000	4	CR^	21	399
24	68	MDS-RAEB-2	Prev. untreated	Favorable	1	1000	15	CR^	245	534

* Prior therapy included hypomethylating agent § Prior therapy included allogeneic stem cell transplant ± Number of cycles administered ^Response was ongoing at the time of discontinuation of study treatment; HI-N, HI-P denote hematologic improvement in neutrophils or platelets

Table 5 Nine responders in Randomized Phase (n=32)

ID #	Age	Diagnosis	Stage of disease	Cytogenetic risk group	No. prior regimens	Randomization arm (Cycle 1)	±No. cycles	Best response	Time to initial response (days)	Response duration (days)
31	57	MDS: RAEB-2	Refractory	Intermediate	1*	0	14	CR-marr	50	349
34	74	t-MN	Prev. Untreated	Unfavorable	0	1000	7	CR	59	161
36	63	AML	Relapsed	Intermediate	1	1000	5	CR^	98	59
48	69	CMML	Prev. Untreated	Intermediate	0	1000	6	HI-P/HI-E	28	141
49	77	MDS: RAEB-2	Refractory	Favorable	2*	1000	28	HI-E^	161	682
50	72	t-MN	Prev. Untreated	Unfavorable	0	1000	28	CR	41	753
51	53	AML	Relapsed	Intermediate	3§	0	5	CR^	44	99
54	64	MDS	Refractory	Unfavorable	1	1000	6	HI-P	91	56
55	79	MDS	Relapsed	Unfavorable	1	0	5	HI-P	28	91

*Prior therapy included hypomethylating agent § Prior therapy included allogeneic stem cell transplant ± Number of cycles administered
^Response was ongoing at the time of discontinuation of study treatment; CR-marr denotes complete response in the marrow
HI-N, HI-P, HI-E denote hematologic improvement in neutrophils, platelets or erythroid lineage

Odenike et al, Invest New Drugs 2015

Combination trials in solid tumors

Authors	Tumor Type	Belinostat Dose	Other chemotherapy agents	
Thomas et al, Clin Can Res 2014	Thymic epithelial cancer	1000	Cytoxan, Adriamycin.platinim	Decreased T regs and exhausted CD8+ cells
Haibnsworth et al, Cancer 2015	Unknown primary Carcinoma	1000	Carboplatin, paclitaxel	Randomized, higher response rate with belinostat but no PFS difference
Dizon et al, Int J Gynecol Cancer	Ovarian cancer	1000	Carboplatin, paclitaxel	ORR 44% in platinum resistant patients 63% in platinum sensisive
Lassen et al, Br J Cancer 2010	Solid tumors Phase I study	600-1000, no DLT	Paclitaxel, carboplatin	No alteration in AUC of any drug; 2 PR in rectal and pancreatic cancer pts

BEL- CHOP Study

- Phase I Study to find MTD of Belinostat with CHOP in patients with PTCL
  - Cohort 1: belinostat 1000 mg/m2 IV on Day 1
  - Cohort 2: belinostat 1000 mg/m2 IV on Day 1-2
  - Cohort 3: belinostat 1000 mg/m2 IV on Day 1-3
  - Cohort 4: belinostat 1000 mg/m2 IV on Day 1-4
  - Cohort 5: belinostat 1000 mg/m2 IV on Day 1-5
- Expansion cohort at MTD
  - Cohort 5 expansion just completed

Study Objectives

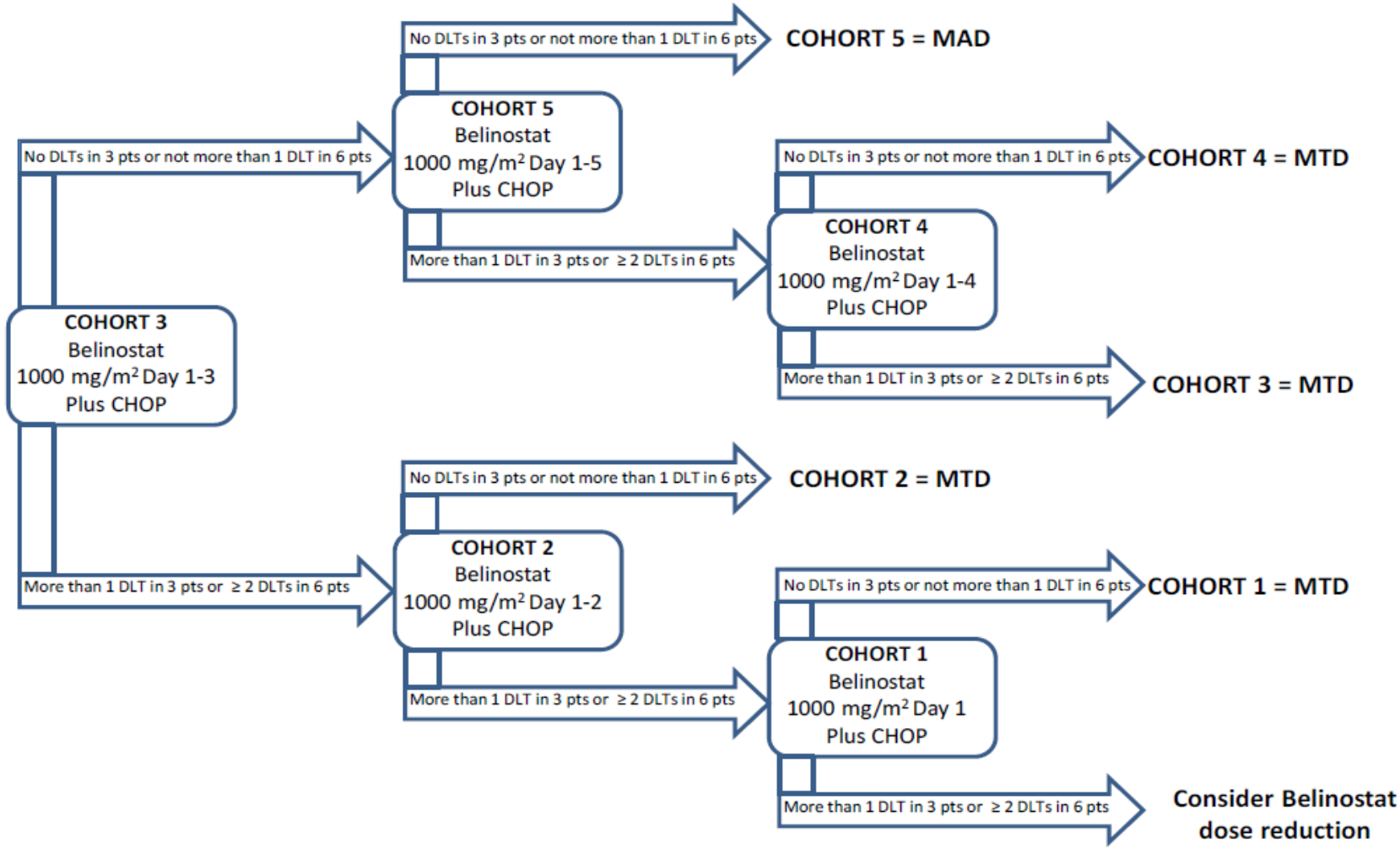
Primary Objective:

To determine the MTD (Maximum Tolerated Dose) for Belinostat when combined with CHOP regimen *and* establish the Phase 3 recommended Belinostat dose

Secondary Objectives:

- To assess safety and tolerability of belinostat when given in combination with CHOP regimen
- Objective response rate (ORR) after 6 cycles of Bel-CHOP regimen
- Pharmacokinetics of belinostat when co-administered with CHOP regimen

Bel-CHOP Study Design



BEL-CHOP Patient Population

- Inclusion Criteria:
  - Age 18 years or above
  - Life Expectancy > 3 months
  - Histologically confirmed diagnosis of PTCL
  - Patients with transformed CTCL eligible for CHOP regimen
  - Measurable disease based on Cheson 2007 criteria
  - Eastern Cooperative Oncology Group (ECOG) performance status < 2
- Exclusion Criteria:
  - Known active Hepatitis B/ Hepatitis C/ HIV infection
  - Known, uncontrolled CNS metastases or primary CNS lymphoma
  - Deep vein thrombosis diagnosed within 3 months
  - Ongoing treatment for pre-existing cardiovascular disease
  - Neuropathy Grade 3 or more
  - Previous extensive radiotherapy except limited field RT for locally advanced nasal NK PTCL or for pain palliation
  - Prior therapy with severely myelotoxic regimens, including autologous and allogenic stem cell transplantation
  - Prior therapy with HDAC inhibitors (except for CTCL)
  - Inadequate hematological, hepatic, or renal function

Belinostat Conclusions

- Active in PTCL, minimal activity in CTCL in small Phase II trial
- Toxicities are similar to other HDAC inhibitors
- Oral belinostat has activity in lymphoma and is well –tolerated
- No significant EKG changes noted
- Results of BELIEF trial were recently accepted for publication in the Journal of Clinical Oncology
- Analysis of the Phase 1 Bel-CHOP study is ongoing
- Other combo trials should be explored in T cell NHL