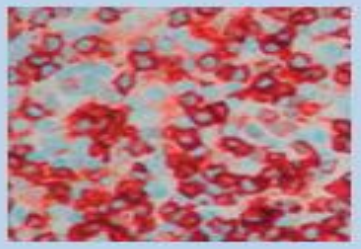
POLICLINICO DI SANT'ORSOLA

Belinostat: Past and Future



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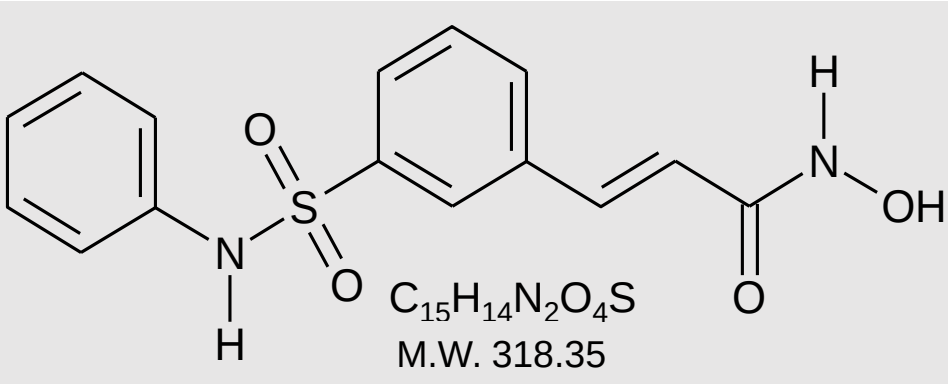
Belinostat Development

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



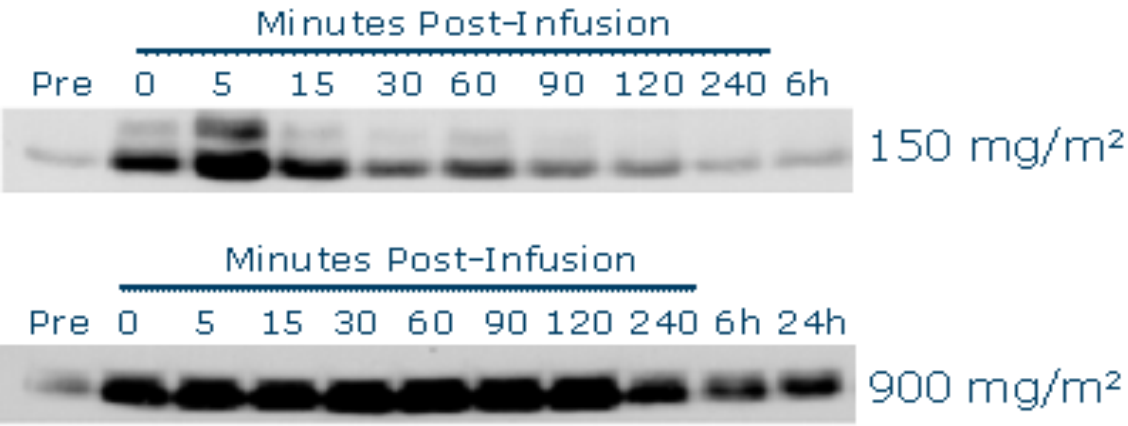
Selectivity of clinically advanced HDACi		
rhHDAC (Class)	Belinostat EC_{50} (nM)	Vorinostat EC_{50} (nM)
1 (I)	41	68
2 (I)	125	164
3 (I)	30	48
4 (I)	115	101
6 (II)	82	90
7 (II)	67	104
8 (I)	216	1524
9 (II)	128	107

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 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**
- **Clinical trials used 5 daily doses every 3 weeks**
- **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

Phase I Experience with Belinostat

- Phase I dose finding in refractory hematologic malignancies
  - 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 studies in hematologic malignancies and solid tumors determined MTD to be 1500 mg and 750 mg respectively
  - Response rate not robust with oral dosing…

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

Study Objectives

Belinostat monotherapy

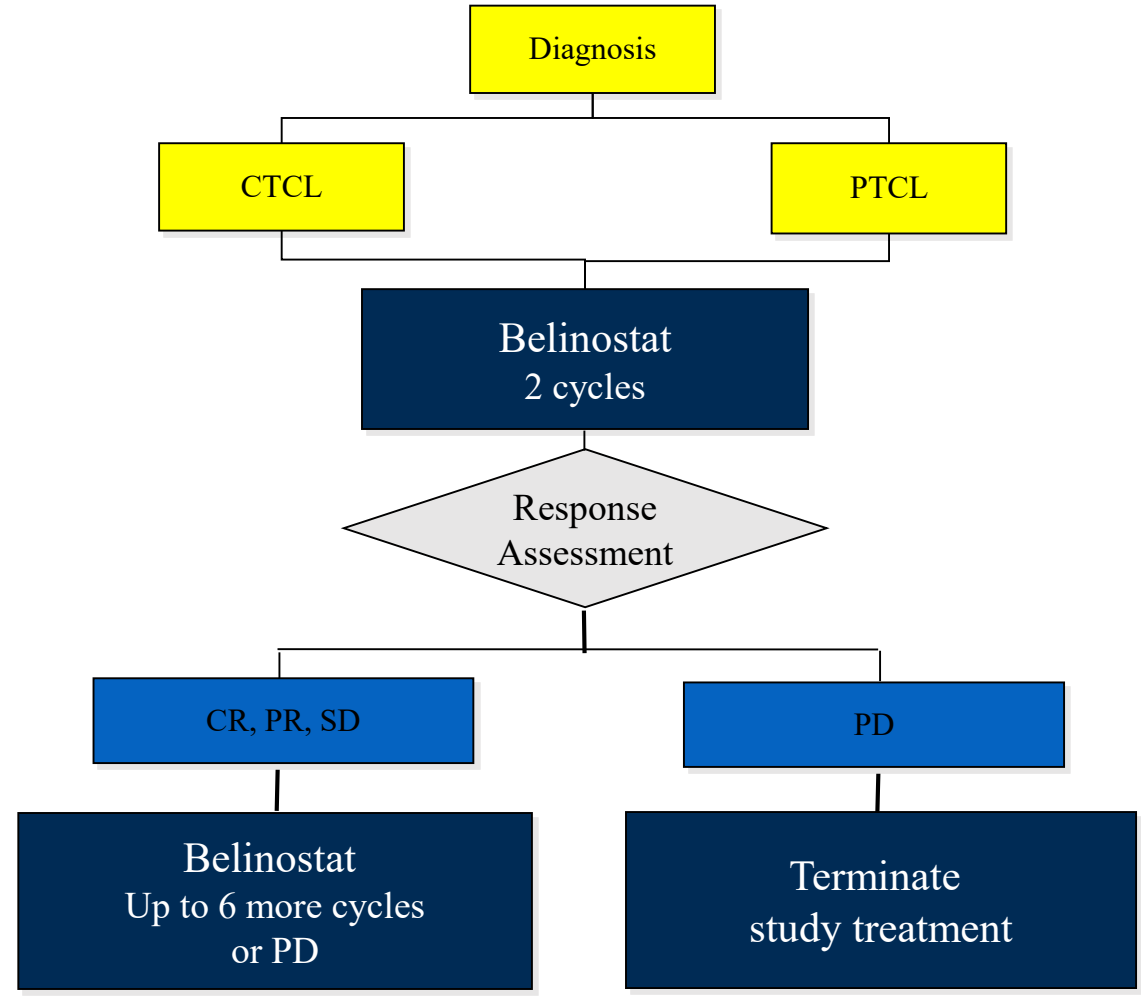
- Response rate, time to response, duration of response, time to progression
- Safety

Patient Population

- CTCL or PTCL
- Failed ≥ 1 prior line of therapy

Dosing

Belinostat 1000 mg/m^2 administered as a 30 min IV infusion once daily on days 1-5 every 3 weeks



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

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

Foss et al, Br J Hematol, 2015

CLN-6: Clinical Outcomes

	PTCL	CTCL
Number of cycles, median	2 (1-8)	2 (1-14)
Evaluable patients Objective response Complete response Partial response	19* 6 (29%) 2 [2 PTCLu] 4 [PTCLu, AITL, ALCL, NK/T]	29 4 (14%) 2 [MF, ALCL] 2 [MF, SS]
Time to response	67 (38-431) days	16 (14-35) days
Time to complete response	127 (114-140) days	128 (36-219) days
Duration of response	268+ (99-847+) days	273 (48-469+) days
Progression-free survival	40 (8-930+) days	44+ (16-483+) days

Belinostat- an active drug in CTCL?

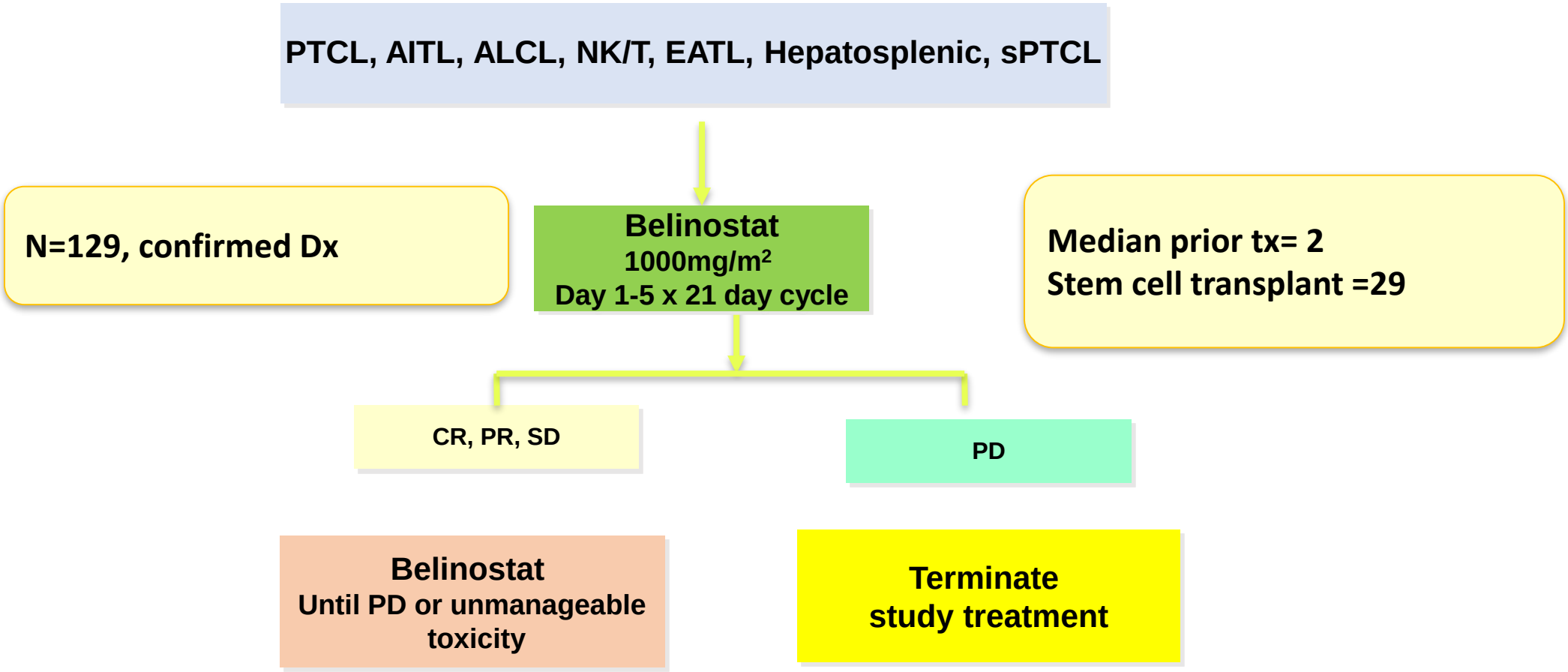
- **ORR belinostat 14% , Vorinostat 30%, romidepsin 34%**
- **17 MF and 7 SS patients enrolled , Median age 69**
- **18 pts were stage III/,IV, median MSWAT was 60**
- **82% of patients had prior chemotherapy**
- **7 of 15 pts with baseline pruritis had improvement**
- **10pts (34%) had stable disease**

Table V. Clinical characteristics of responders – ITT population.

		Prior therapy					
Patient	Stage	Stem cell transplant	Systemic	Radiation	Response	Response	No. treatment cycles
PTCL							
1	IIIA	No	CHOP	No	PR	CR	9
2	IIIB	No	denileukin diftitox, CHOP	No	CR	CR	4
3	IVB	Autologous	*	No*	CR	PR	2
4	IVB	No	Prednisone, CHOP	No*	PR	PR	6
5	IIA	No	*	No	CR	PR	8
6	IVA	No	CHOP, EPOCH	No	PD	PR	6
CTCL							
7	IIB	No	CHOP, Interferon	Yes	NA	CR	5
8	IIB	No	Prednisone, Methotrexate,Soriante, PUVA	No	PD	CR	14
9	IIA	No	Denileukin diftitox, Zolinza, Gemzar, Doxil	No*	PD	uCR	4
10	IVA	No	CHOP, Interferon,Targretin, Isotrenitoin	No	SD	PR	6

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, CR, complete response, CTCL, cutaneous T-cell lymphoma, EPOCH, CHOP plus etoposide, ITT, intent to treat, No, number, NA, not assessable, PD, disease progression, PR, partial response, PTCL, peripheral T-cell lymphoma, PUVA, psoralen plus ultraviolet A, SD, stable disease, uCR, unconfirmed complete response.
*Received systemic treatment and/or radiation therapy prior to 2003.

BELIEF Registration Study in relapsed/refractory PTCL



BELIEF: Patient Characteristics

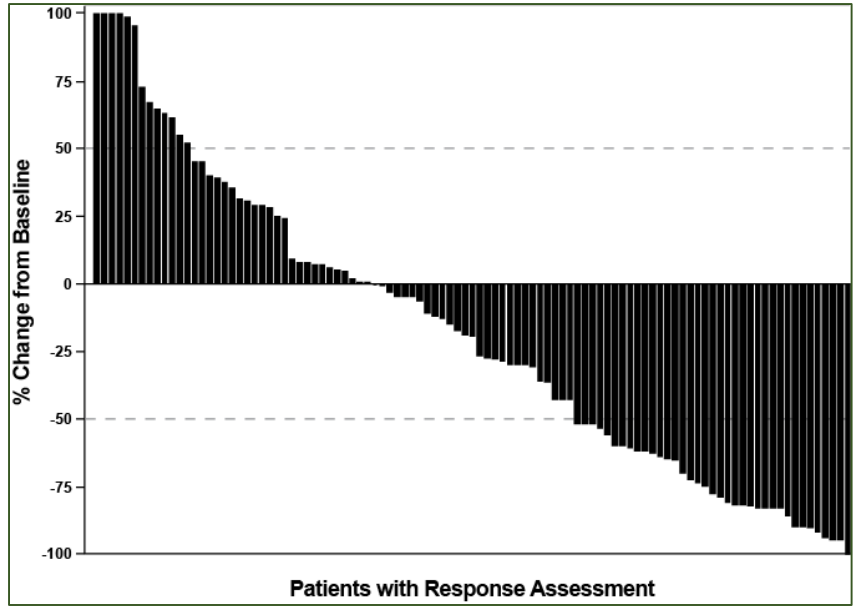
Gender	
Male	69 (54)
Female	60 (46)
Age	
<65	67 (52)
≥65	62 (48)
Median, yr (range)	63 (29-81)
Race	
White	111 (86)
Performance status, n (%)	
ECOG 0	44 (34)
ECOG 1	57 (44)
ECOG 2-3	28 (22)
Median time from last disease progression to study entry (mo)	1 (0.1-55)*
Bone marrow involvement	30%

Belief Study: Prior 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)	

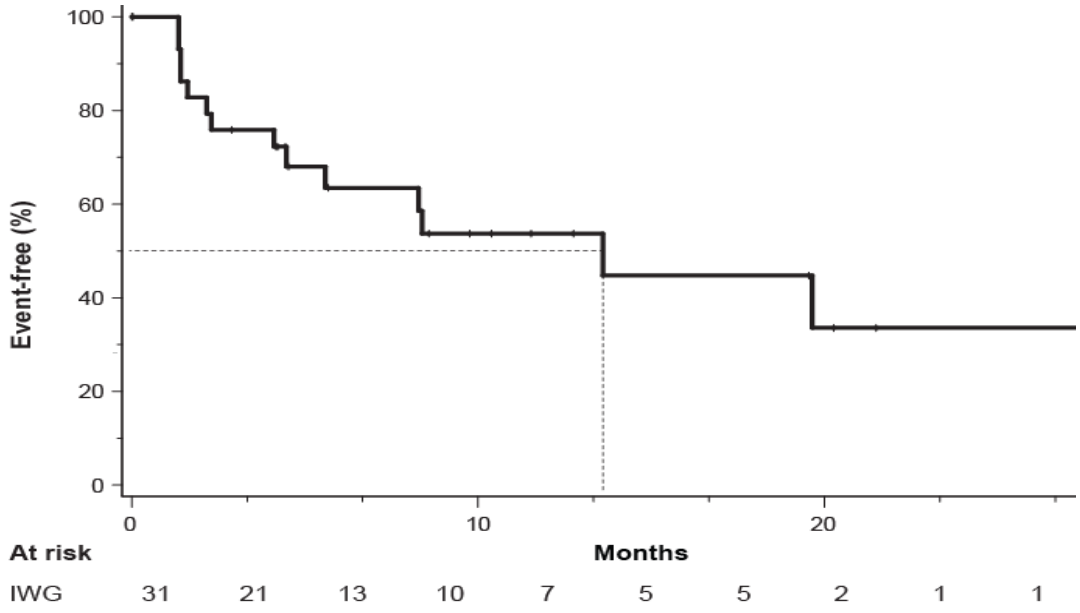


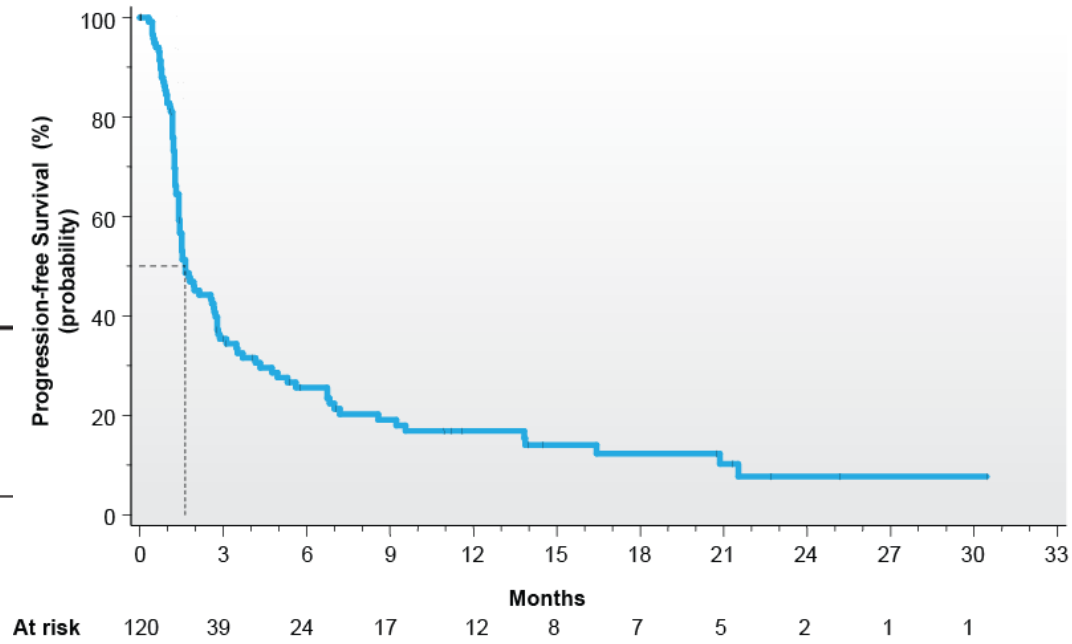
NE = not evaluable due to death (n=7), clinical progression (n=10), patient withdrawal (n=5) or lost to follow-up (n=1) prior to first radiologic assessment

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 Duration and Progression Free survival

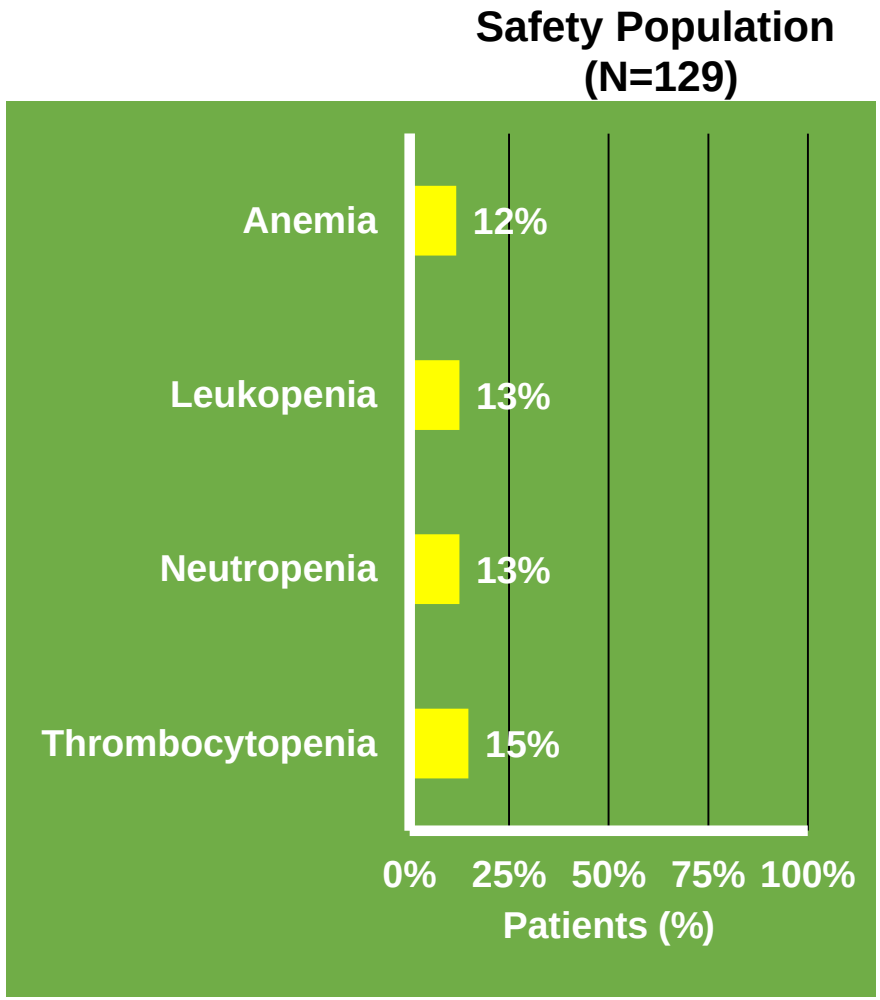


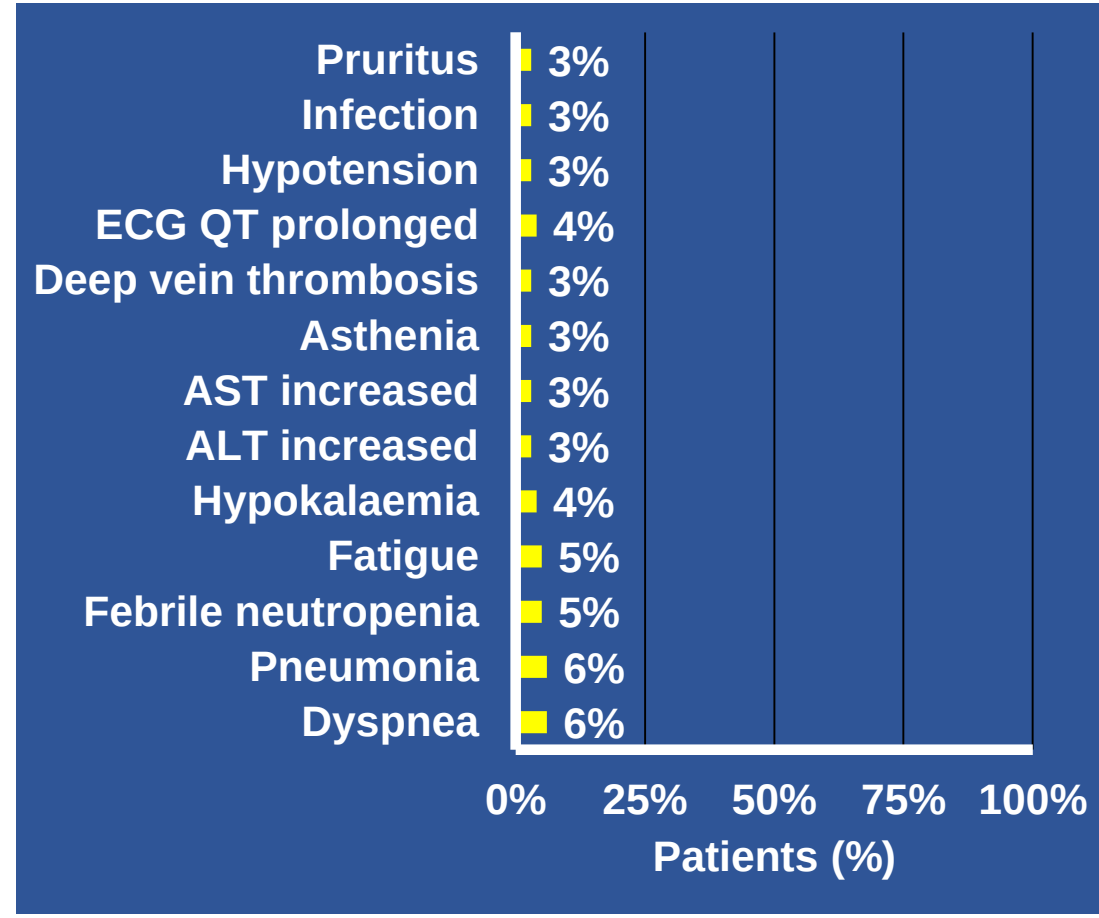


Median DoR: 13.6 months (95% CI, 4.5-29.4)

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

Grade ≥3 Adverse Events





Conclusions from Belief Trial

- 26% ORR in all patients with R/R PTCL (N=120)
- Belinostat was well tolerated with a favorable safety profile, including patients with a previous autologous or allogeneic stem cell transplant
- Further investigation of belinostat in combination with other therapies is warranted to develop new treatment paradigms for PTCL

BEL- CHOP Study

- Phase I Study to find MTD of Belinostat with CHOP in patients with PTCL who had no treatment
  - 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…

Phase 1 Bel-CHOP Study Design

3 + 3 Design (6 × 21-day cycles)

Cohort	Belinostat 1000 mg/m² (IV)	CHOP
3 *(starting regimen)*	Day 1-3	Day 1
5	Day 1-5	Day 1
4	Day 1-4	Day 1
2	Day 1-2	Day 1
1	Day 1	Day 1
Dose Expansion (n=10) at MTD/MAD		

- **Primary Endpoint:** Maximum Tolerated Dose (**MTD**) of belinostat in combination with CHOP (Bel-CHOP)
- Key Secondary Endpoints: Safety and ORR

[a] Maximum 2 mg; [b] Prednisone administered Day 1 with CHOP and Days 2-5 after belinostat.
G-CSF, granulocyte colony-stimulating factor; IV, intravenous; MAD, maximum administered dose; ORR, overall response rate; PK, pharmacokinetics; PO, oral.

Bel-CHOP Phase 1: Dose-Limiting Toxicities

- Part B expansion consisted of **Cohort 5** dosing:
  - Belinostat Days 1-5 + CHOP

Adverse Event, n (%)	(N=23)
Any Event	**18 (78)**
Neutrophil Count Decreased	7 (30)
Anemia	5 (22)
Neutropenia	5 (22)
Febrile Neutropenia	4 (17)
Lymphocyte Count Decreased	4 (17)

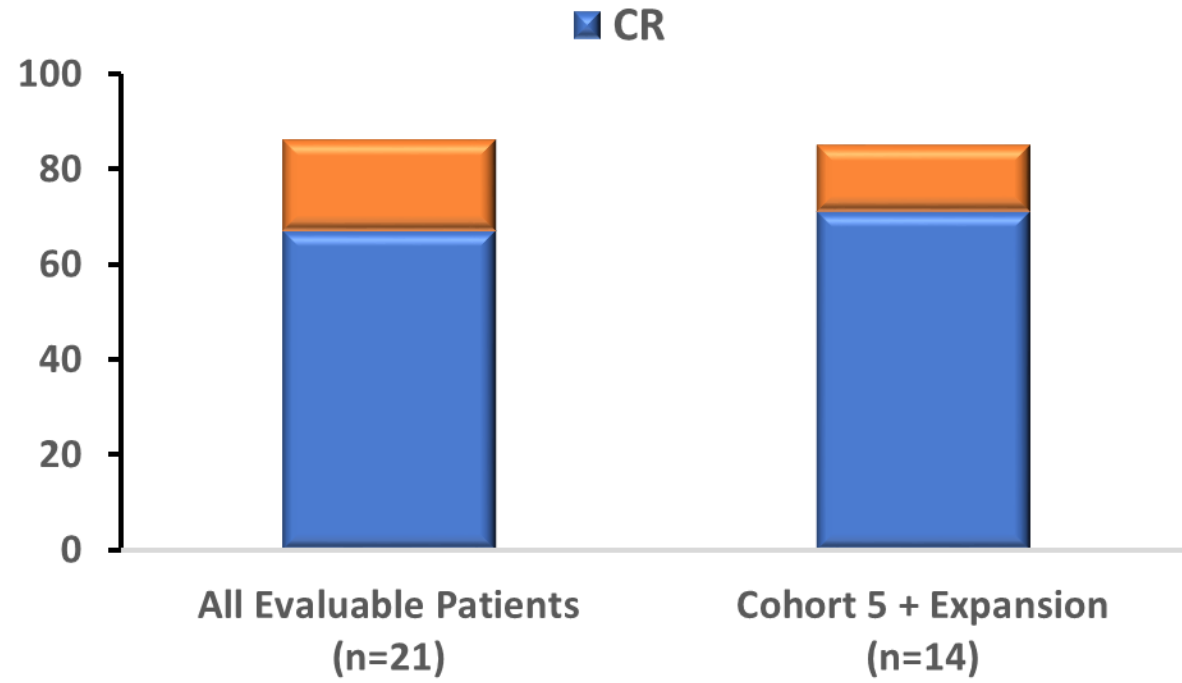
3 + 3 Design (6 × 21-day cycles)

Cohort	Belinostat 1000 mg/m² (IV)	CHOP
3 *(starting regimen)*	Day 1-3	Day 1
5	Day 1-5	Day 1
4	Day 1-4	Day 1
2	Day 1-2	Day 1
1	Day 1	Day 1
Dose Expansion (n=10) at MTD/MAD		

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DLT, dose-limiting toxicity.

Summary of Best Response

- 21 patients evaluable for efficacy
  - **Cohort 3** = 7 out of 8 patients
  - **Cohort 5** + Expansion Phase = 14 out of 15 patients
- ORR: 86% (18/21)
  - CR 67% (14/21)
  - PR 19% (4/21)



CR, complete response; ORR, overall response rate; PR, partial response.

Conclusions

- **Belinostat + CHOP combination was well tolerated**
  - All agents administered at standard therapeutic doses and schedules
- **AE rates were consistent with those observed with CHOP alone**
- **Encouraging clinical activity observed:**
  - 86% ORR with 67% CR rate
- ? Benefit in Ro/CHOP, BelCHOP vs CHOP randomized trial planned

AE, adverse event; Bel-CHOP, combination of belinostat + cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; ORR, overall response rate; PTCL, peripheral T-cell lymphoma.

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

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**

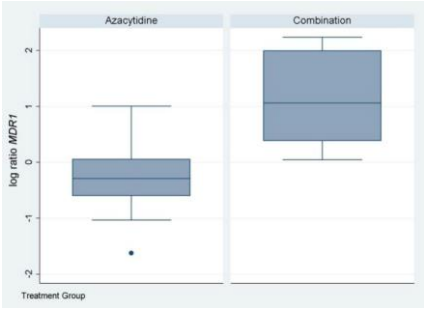


Table 4 Nine responders in Dose Escalation Phase (n=24)

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

Phase I study of belinostat and AZD1775 in myeloid malignancies

- HDACIs disrupt the DNA damage response (DDR), including checkpoints and repair (e.g., HR and NHEJ).
- AZD1775 is an oral Wee-1 inhibitor tha7 interacts synergistically with pan- HDACIs (e.g., Belinostat) to kill human leukemia cells independently of p53 status, including those bearing FLT3-ITD.
- HDACI co-administration induced pronounced Wee1 and Chk1 inactivation, resulting in DNA damage and apoptosis.
- Phase I clinical trial of AZD1775 Belinostat in patients with R/R AML/MDS/CML-BC

Belinostat : The future

- Active in PTCL, more active in follicular helper subtype
- Toxicities easy to manage, no cardiac warning
- Combines well with several agents and with combination chemotherapy
- +short infusion time/- 5 day dosing schedule
- Synergistic interaction with multiple agents being exploited in clinical trials