Romidepsin and …

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2012…2015 T-Cell Lymphomas

We Are Illuminating The Darkest of Tunnels

Bologna, Italy

04/28/2015

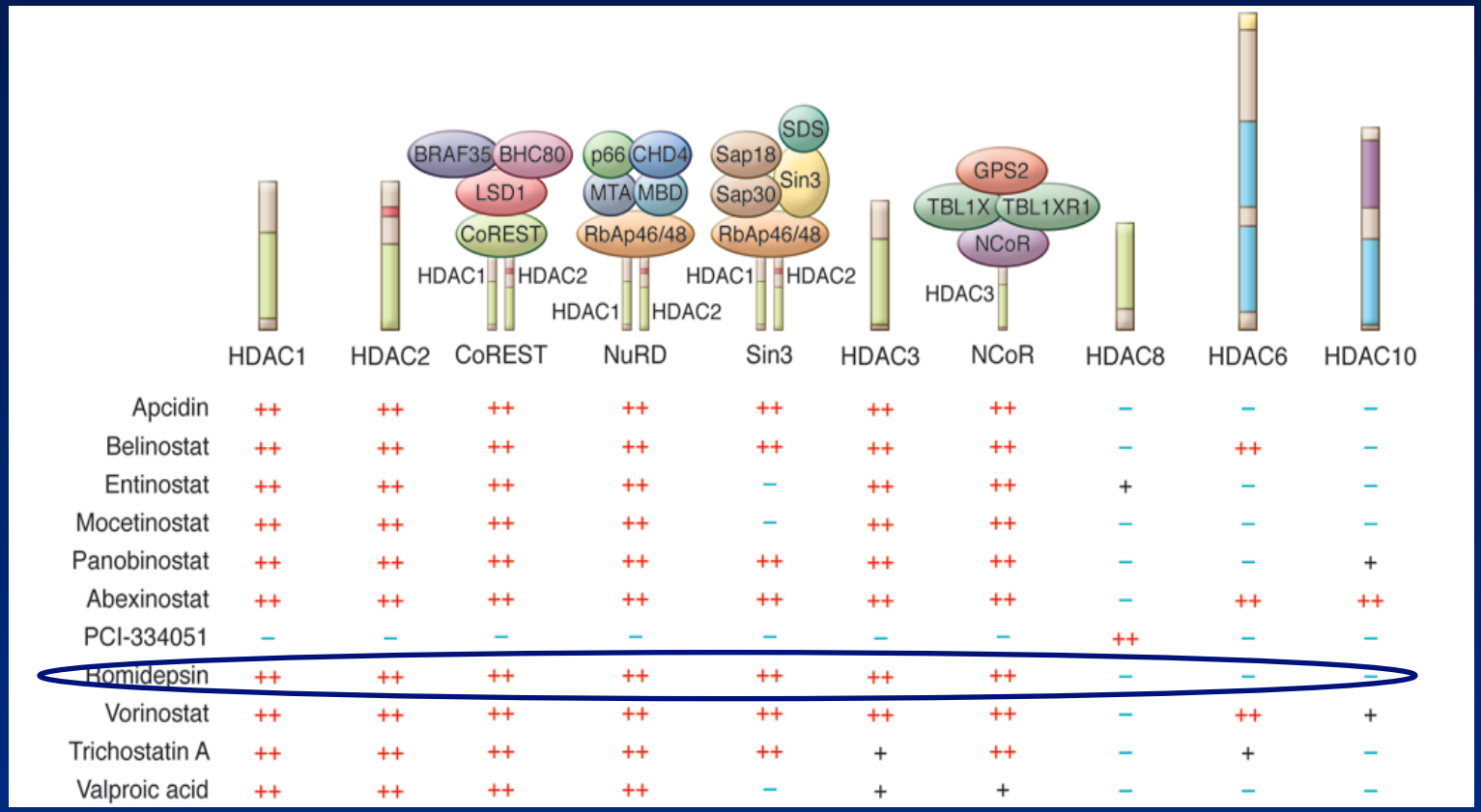
- Romidepsin in PTCL
  - Pivotal Trial and Follow-Up Data

- Romidepsin Combinations in PTCL
  - Romidepsin plus Traditional Chemotherapy
    - Gemcitabine
    - ICE (Ifosfamide, Carboplatin, Etoposide)
  - Romidepsin plus Novel Agents
    - Lenalidomide
    - Bortezomib/ Carfilzomib
    - Pralatrexate
    - 5-Azacytidine
    - Alisertib

Romidepsin Monotherapy

Comparison of Targets of Histone Deacetylase Inhibitors

- Romidepsin FDA approved in 2011 for relapsed PTCL.



	HDAC1	HDAC2	CoREST	NuRD	Sin3	HDAC3	NCoR	HDAC8	HDAC6	HDAC10
Apcidin	++	++	++	++	++	++	++	–	–	–
Belinostat	++	++	++	++	++	++	++	–	++	–
Entinostat	++	++	++	++	–	++	++	+	–	–
Mocetinostat	++	++	++	++	–	++	++	–	–	–
Panobinostat	++	++	++	++	++	++	++	–	–	+
Abexinostat	++	++	++	++	++	++	++	–	++	++
PCI-334051	–	–	–	–	–	–	–	++	–	–
Romidepsin	++	++	++	++	++	++	++	–	–	–
Vorinostat	++	++	++	++	++	++	++	–	++	+
Trichostatin A	++	++	++	++	++	+	++	–	+	–
Valproic acid	++	++	++	++	–	+	+	–	–	–

Histones are the main target of HDAC1, 2, & 3, while HDAC6 targets tubulin and HSP 90.

West, A & Johnstone, R, *JCI*, 2014

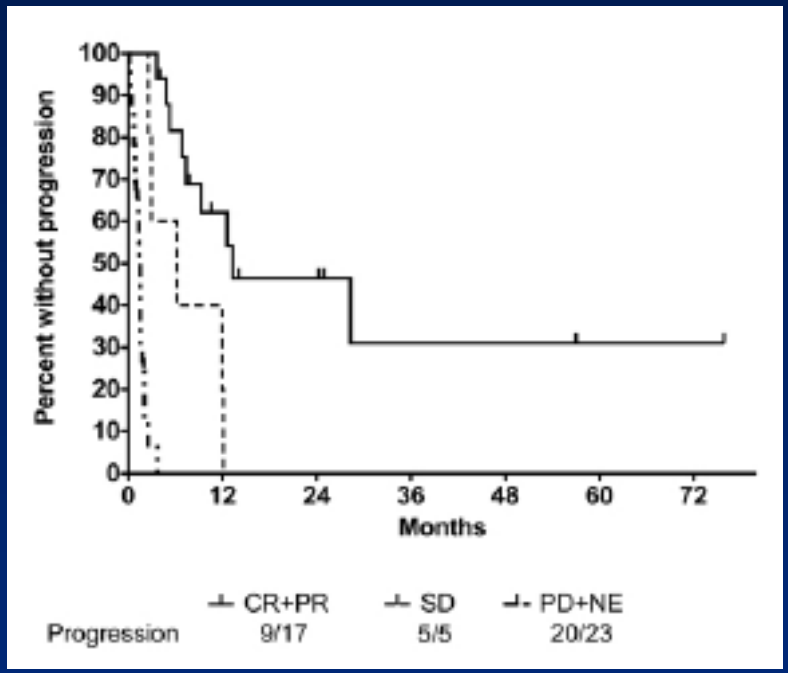
Romidepsin: Results From The NCI-Sponsored Phase II Trial

47 patients, median 3 prior tx (range, 1-11), 38% past SCT.

14 mg/m^2 as a 4-hour intravenous infusion on days 1, 8, and 15 every 28 days.

Efficacy	
ORR PTCL-NOS AITL ALCL	38% 41% 17% 33%
CR	18%
DoR	8.9 mo

Grade 3/4 AEs	
Neutropenia	26%
Thrombocytopenia	15%
Fatigue	9%
Anemia	6%



TTP:
13 mo (CR/PR), 4.6 mo (SD)

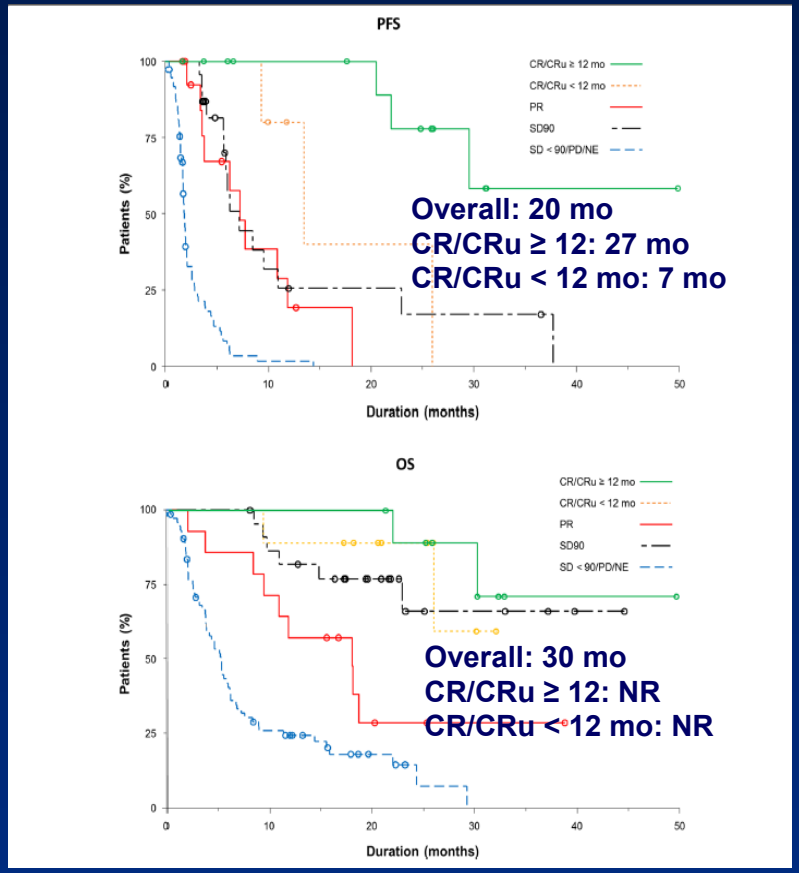
Piekarz, R, et al, *Blood*, 2011

Romidepsin: Results from The Pivotal Phase II Trial

131 patients, median number prior tx 2 (range, 1-8), 16% had prior ASCT.

Efficacy	Overall	PTCL -NOS	AITL	ALCL, ALK neg
ORR	25%	29%	30%	24%
CR/CRu	15%	14%	19%	19%
DoR	28 mo			

Grade 3/4 AEs	
Thrombocytopenia	24%
Neutropenia	20%
Infection	19%
Fatigue	5%



Coiffier, B, et al, *JCO*, 2012 and *J Hemat & Onc*, 2014

Romidepsin: Durable Remissions in Relapsed AITL

Patient characteristics for those with AITL were similar to rest of trial patients.

Amendment to allow for maintenance dosing of twice per cycle for patients treated for ≥ 12 cycles; dosing could be further reduced to once per cycle at ≥ 24 cycles in patients who had received maintenance dosing for ≥ 6 months.

Efficacy	All Patients	AITL
ORR	26%	33%
CR/CRu	15%	22%

Thrombocytopenia (n=2) was the only AE that led to discontinuation in >1 patient, both drug-related. AEs similar when compared to non-AITL patients.

5 of 9 patients who responded achieved long-term response ≥ 12 mo.
All 5 receive maintenance dosing.
Median DOR: Not evaluable (<1-56+).
Median PFS: 5.3 months (range, 1-57.9).
Median OS: 18.1 months (range, 2-58.1).

Pro, B, et al, *ASH*, 2014

Romidepsin Plus Traditional Chemotherapy

Gemcitabine in PTCL

- 30 pts across 2 trials
  - 1200 mg/m^2 on D 1, 8, 15 q 28 D
  - ORR 51-60%, CR 20-23%

Zinzani, PL, et al, *Ann Onc,* 2010; Sallah, S, et al, *BJH*, 2001

Romidepsin plus Gemcitabine

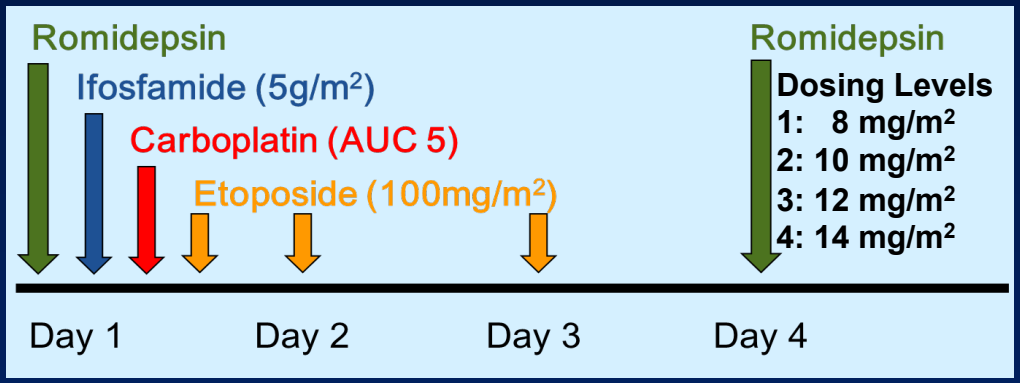
Sponsor	Phase	Regimen	Eligible Diagnoses	Treatment Schema
Fondazione Italiana Linformi ONLUS (Pier Luigi Zinzani)	IIa	Gemcitabine plus Romidepsin (GEMRO)	Refractory/ Relapsed PTCL	Romidepsin 12 mg/m^2 D 1,8,15 + Gemcitabine 800 mg/m^2 on D 1,15 x 6 cycles q 28 D → Romidepsin 14 mg/m^2 D 1,15 to PD (20 pts tx, enrollment completed, preliminary results at ICML)
National Cancer Institute of Canada (Anthony Reiman, Kerry Savage)	I	Romidepsin plus Gemcitabine, Dexamethasone, Cisplatin (GDP)	Refractory/ Relapsed PTCL and DLBCL	Romidepsin currently at dose level 10 mg/m^2 D1, D15; Gemcitabine 1000 mg/m^2 D1, D8; Dexamethasone 40 mg D1-D4; Cisplatin 75 mg/m^2 D1 x q 28D (increased from q 21D) x 6 cycles
Washington University School of Medicine (Kenneth Carson, Weiyun Ai)	I	Romidepsin, Gemcitabine, Oxaliplatin, Dexamethasone	Refractory/ Relapsed PTCL, Sézary Syn, MF, DLBCL, and HL	Romidepsin 8-12 mg/m^2 D2, D8; Gemcitabine 1000 mg/m^2 D1; Oxaliplatin 100 mg/m^2 D1; Dexamethasone 20 mg D1-D4 q 21D (recently opened, 1 pt tx)

ICE in PTCL

- 26 PTCL pts
  - ICE q 2 wks x 3
  - ORR 54%, CR 31%

Zelenetz, AD, et al, *Ann Onc*, 2003

Phase I Romidepsin plus ICE in Refractory/ Relapsed PTCL



Cycles q 14 days
Maximum of 6 cycles

Median day to next cycle:
21 days (14-33 days)

Characteristics	N
Total pts enrolled	13
Median age (range)	60 (24-70)
Histologic dx	
PTCL-NOS	6
AITL	4
ALCL, ALK+, HSTCL, NKTCL	1, 1, 1
Primary refractory	8 (62%)

Response:
ORR 69%, CR 54%

Dose Level	Grade 3/4 Neutropenia	Grade 4 Thrombocytopenia
1	100%	86%
2	73%	91%
3	100%	100%

DLTs:
1 pt with persistent grade 4 thrombocytopenia in dose level 4
1 pt with grade 3 renal insufficiency in dose level 3

Chihara, D…Fanale,M, *ASH*, 2014

Romidepsin Plus Novel Agents

Lenalidomide in PTCL

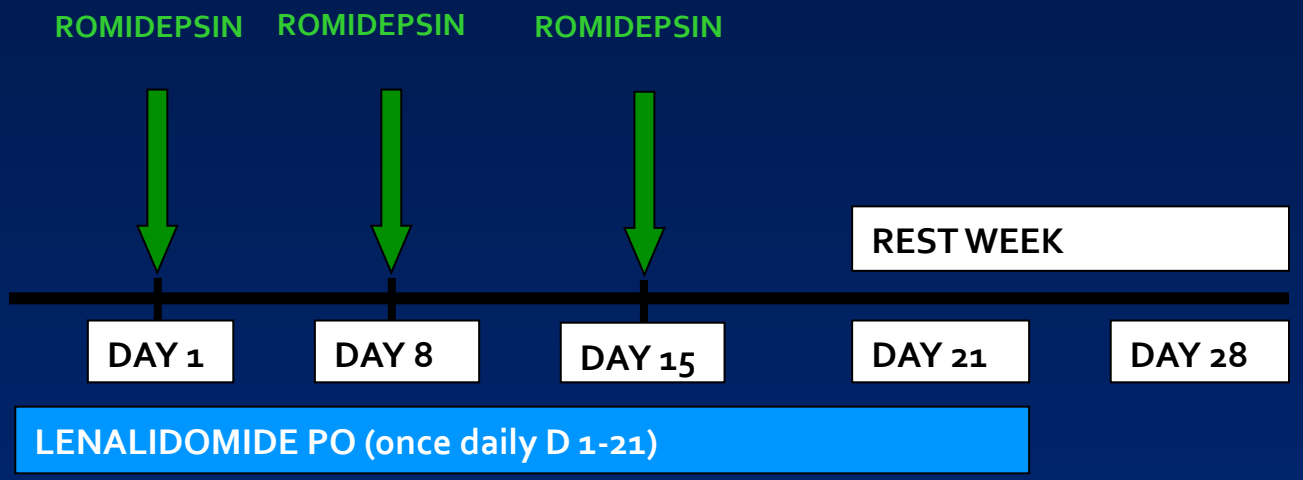
- 24 PTCL pts

  Lenalidomide 25 mg PO QD on days 1-21 of each 28-day cycle

  ORR of 30% (all PRs)

Dueck, G, et al, *Cancer*, 2010

A Phase Ib/IIa Study of Romidepsin in Combination with Lenalidomide in Relapsed or Refractory Lymphomas and Myeloma



DOSE LEVEL	ROMIDEPSIN	LENALIDOMIDE
-1	8 mg/m^2	10 mg
1	8 mg/m^2	15 mg
2	8 mg/m^2	25 mg
3	10 mg/m^2	25 mg
4	14 mg/m^2	25 mg

Lunning, MA….Horwitz, S, *ASCO*, 2014

Phase Ib results:
MTD of Romidepsin 14 mg/m^2 and Lenalidomide of 25 mg D1-21
ORR of 55%, CR 13%
PTCL ORR of 66%

Front-line PTCL phase II trial to commence (PIs: Adam Petrich, Steve Rosen, Francine Foss, Andrei Shustov)

A Phase Ib/IIa Study of Romidepsin, Lenalidomide, and Carfilzomib (PIs: Steven Horwitz, Matthew Lunning)

Relapsed and Refractory B- and T-cell Lymphoma Patients (n~18)

↓

Romidepsin (8-10mg/m^2), D 1,8

Lenalidomide (10-20 mg), D 1-15

Carfilzomib (20-70mg/m2), D 1,8

↓

Determine MTD

↙ ↘

T-cell Lymphoma Cohort (n=10)

B-cell Lymphoma Cohort (n=10)

Phase Ib: Dose Finding

- 3+3 design, 21 day cycle
- Objectives:
  - •Determine Maxmium Tolerated Dose (MTD)
  - •Determine Toxicity and Safety

Phase IIa: Expansion Phase

- Two cohorts treated at MTD, 21 day cycle
- •Objectives:
  - •Confirm safety and estimate efficacy

Bortezomib in PTCL

- 15 patients with cutaneous TCL
  - 2/15 PTCL unspecified (PTCLU) w/ isolated skin involvement
  - ORR 67%, CR 17% (1/2 PTCLU had disease response)

Zinzani, PL, et al, *JCO*, 2007

Phase I Trial of Bortezomib plus Romidepsin (PI: Steven Grant and Beata Holkova)

Bortezomib plus romidepsin on D1, 8, 15 of q 28D cycles

Dose Levels	Bortezomib (mg/ m^2)	Romidepsin (mg/ m^2)
1	1.3	8
2A	1.3	10
2B	1.6	8

Eligible histologies included relapsed CLL/SLL, indolent B-cell lymphomas, PTCL, CTCL
Preclinical data had shown highest levels of apoptosis in CLL cell lines

18 pts enrolled (2 PTCL, 1 CTCL)
Dose level 2A was the MTD, DLTs of grade 3 vomiting, fatigue, cytokine release syndrome
ORR of 6% (1 PR in CLL pt)

Holkova, B, et al, *ASH*, 2014

Pralatrexate: Results from Pivotal PROPEL Study

FDA approved in 2009 for relapsed PTCL.

Antifolate that is well internalized by the reduced folate carrier (RFC) and is also an excellent substrate for folylpolyglutamyl synthetase.

111 patients, median prior tx 3 (range, 1-12), 16% prior ASCT.

30 mg/m^2/wk for 6 weeks in 7-week cycles.

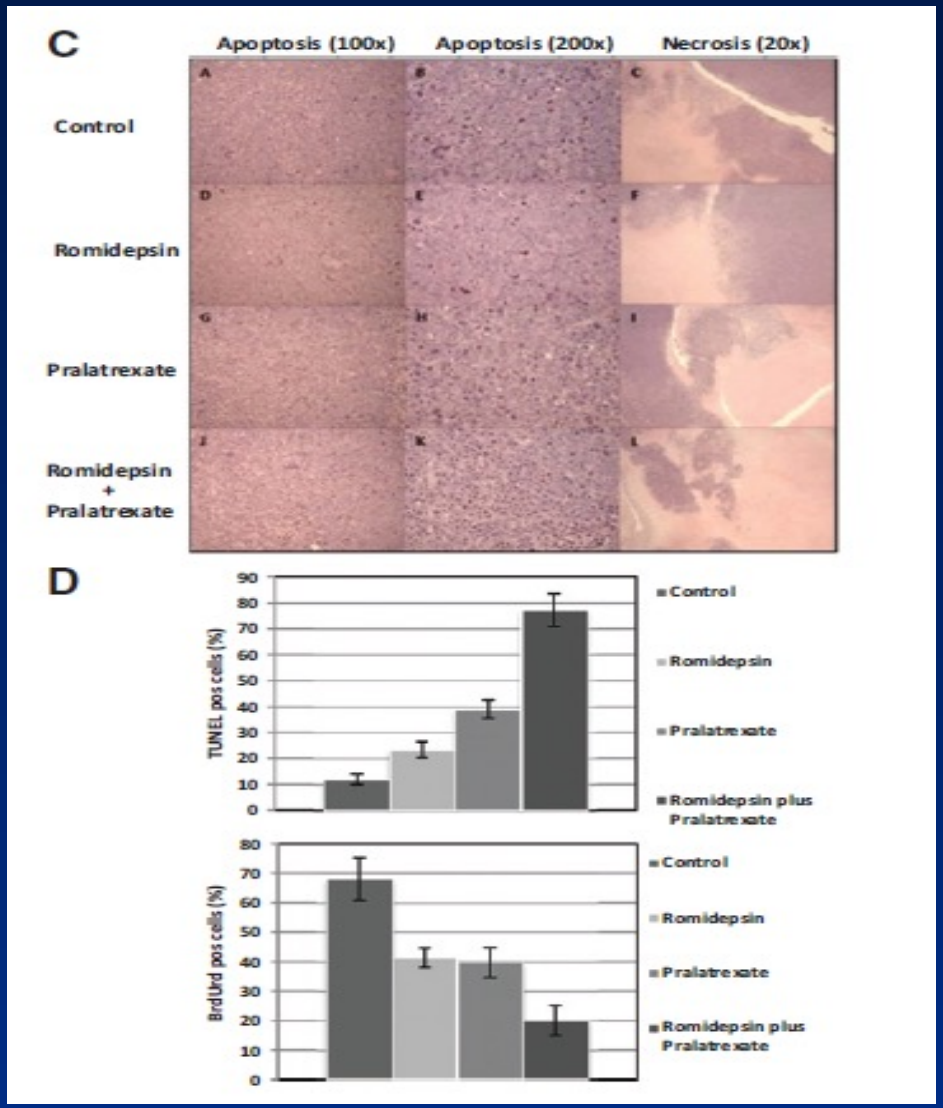
Efficacy	
ORR	29%
PTCL-NOS	32%
AITL	8%
ALCL	35%
Transformed MF	25%
CR	11%
DoR	10.1 mo

Grade 3/4 AEs	
Thrombocytopenia	32%
Mucositis	22%
Neutropenia	22%
Anemia	18%

Mucositis: 71% have some degree.
Median time of grade ≥ 2 14 d.

O'Connor, O, et al, *JCO*, 2011

Preclinical Data Supporting Romidepsin plus Pralatrexate



Xenograft tumor harvested from mice 7 days after 1 cycle of treatment

Photomicrographs demonstrated higher apoptosis and necrosis with combination compared with single agent treatment.

Levels of apoptosis assessed by TUNEL staining and proliferation inhibition assessed by BrdUrd staining were also respectively higher with romidepsin plus pralatrexate.

Jain, S … O'Connor, O, *CCR*, 2015

Phase I/II Trial of Pralatrexate plus Romidepsin in Relapsed Lymphoma (PIs: Owen O'Connor and Jennifer Amengual)

Dosing intervals:

q *21D* dosing of D1, D8

or

q *28D* dosing of D1, D8, D15 *or* D1, D15

Dosing range:

Pralatrexate	Romidepsin	
10 mg/m^2	12 mg/m^2	D 1, 8, 15
Pralatrexate	Romidepsin	D 1, 15 (*cont dose escalation*)
20 mg/m^2	12 mg/m^2	

Results:

To date in PTCL x 7 pts, 100% ORR, 57% CR

DLTs mainly cytopenias

5-Azacytidine in PTCL

- No significant level of clinical data in PTCL as monotherapy
- 5-azacytidine is oral agent while azacytidine is IV/SubQ

  Azacytidine FDA approved in 2004 for treatment of MDS

  Cytidine analog

- Decitabine is 5-aza-2′deoxycytidine also used in treatment of MDS

- 5-azacytidine and decitabine have differing mechanisms of action

  5-azacitidine is incorporated into RNA

  Decitabine is exclusively incorporated into DNA and sensitivity correlates with ara-C sensitivity

  Both drugs induced DNA methyltransferase (DNMT) depletion, DNA hypomethylation, DNA damage

  5-azacytidine has greater effect on reducing cell viability and protein synthesis

Garcia-Manero, G, et al, *ASH*, 2009; Kantarjian, H, et al, *Cancer*, 2006

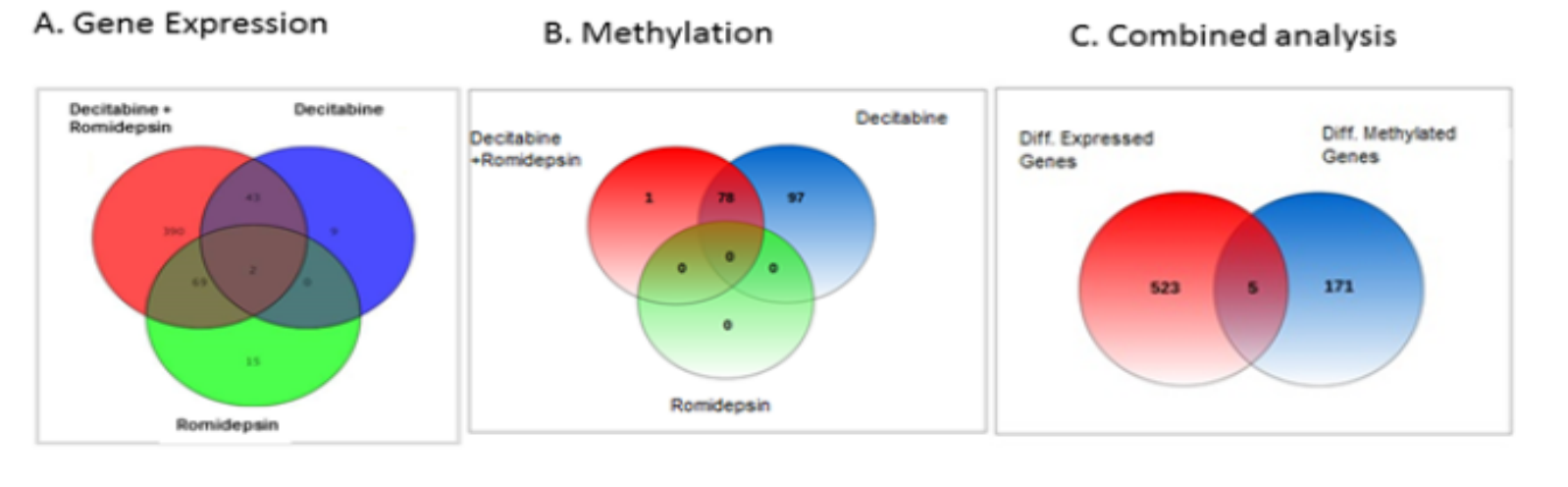
Preclinical Data of Hypomethylating Agents Plus HDACi in TCL

- Combination based treatment strategies have been evaluated in high risk MDS and AML.
- HDACi plus decitabine was previously evaluated in DLBCL cell lines and demonstrated synergistic growth inhibition and induction of apoptosis.
- In vivo activity of decitabine plus belinostat and/or romidepsin was analyzed in a xenograft model of CTCL via GEP and methylation arrays.

  Combination reverse malignant phenotype

  Up-regulation of genes that control cell cycle arrest

  Down-regulation of protein and lipid synthesis genes



Kalac, M.…O'Connor, O, *Blood*, 2011; O'Connor, O…Piccaluga, PP, *ASH*, 2013

Phase I/II Study of 5-Azacytidine and Romidepsin in Relapsed Lymphomas (PI: Owen O'Connor)

Dosing intervals:

q *21D* dosing of D1-D14 5-azacytidine plus romidepsin D 8,15

or

q *28D* dosing of D1-D14 5-azacytidine plus romidepsin D 8,15

Dosing range for current pts tx:

5-Azacytidine	Romidepsin
100 mg D1-D14	12 mg/m^2 D 8, 15 q 21D
5-Azacytidine	Romidepsin D 1, 15 (*cont dose escalation*)
300 mg D1-D14	14 mg/m^2 D 8, 15 q 28D

Results:

To date in TCL x 4 pts, 100% ORR, 50% CR

Few DLTs

Alisertib in PTCL

Aurora A kinase inhibitor

Orally at 50 mg twice daily for 7 days in 21-day cycles.

Phase II trial with 48 patients with DLBCL, transformed FL, PTCL, and BL.

Efficacy	Overall	PTCL (8 pts)
ORR	27%	50%
CR	10%	25%

Grade 3/4 AEs	
Neutropenia	63%
Anemia	35%
Thrombocytopenia	33%

SWOG 1108, TCL focused phase II trial, 37 patients

Efficacy	
ORR (PTCL-NOS, AITL, ALCL)	33%

Phase III randomized trial of alisertib vs doc's choice (praltrexate, romidepsin, or gemcitabine)

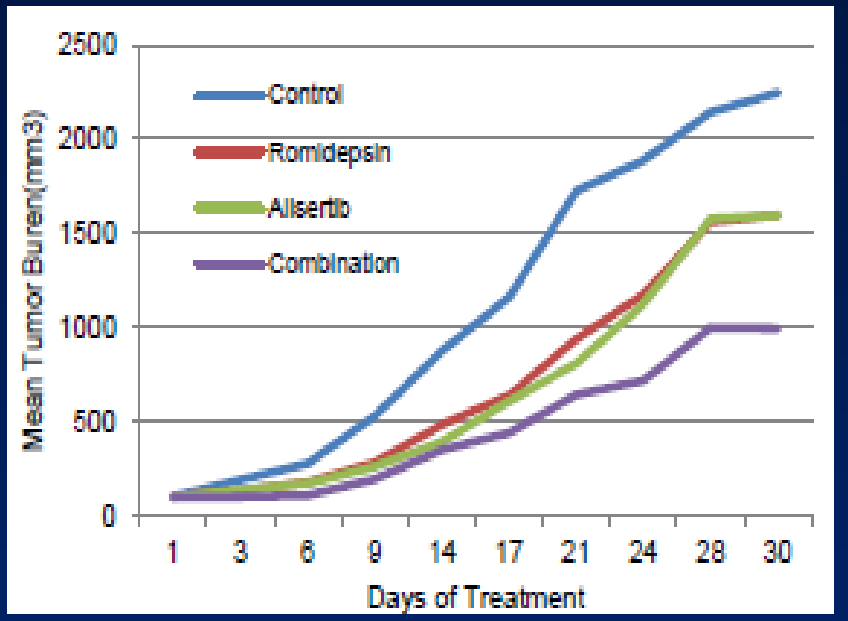
Friedberg, J, et al, *JCO*, 2014, Barr, P, et al, *ASCO*, 2014

Preclinical Support of Alisertib plus Romidepsin

Synergy Coefficients at 72 hours in TCL Cell Lines					
Drug Combination	**DND41 (T-ALL)**	**J.Cam1.6 (T-ALL)**	**HH (CTCL)**	**H9 (CTCL)**	**C5M (HTLV-1)**
Romidepsin [IC_{10-20}] + Alisertib 50 nM	0.96	0.81	1.05	1.1	1.53
Romidepsin [IC_{10-20}] + Alisertib 100 nM	0.51	0.56	0.68	0.66	0.58
Romidepsin [IC_{10-20}] + Alisertib 1000 nM	0.40	0.20	0.40	0.46	0.70

No synergy in BCLs or with pralatrexate or ixazomib. Romidepsin causes a mild increase in % of cells in G1 and alisertib significantly increases the % of cells in G2/M arrest. Live cell imaging demonstrated marked cytokinesis failure.

Zullo, K …O'Connor, O, *ASH*, 2014 and *CCR*, 2015



In an in vivo xenograft model alisertib plus romidepsin was statistically better than monotherapy or the control group.

Phase I Trial of Romidepsin plus Alisertib in Aggressive BCLs and TCLs

Dose Level	Alisertib	Romidepsin
Level -1	20 mg orally BID on days 1-7	6 mg/m^2 IV on days 1 and 8
Level 1	20 mg orally BID on days 1-7	8 mg/m^2 IV on days 1 and 8
Level 2	20 mg orally BID on days 1-7	10 mg/m^2 IV on days 1 and 8
Level 3	40 mg orally BID on days 1-7	10 mg/m^2 IV on days 1 and 8
Level 4	40 mg orally BID on days 1-7	12 mg/m^2 IV on days 1 and 8
Level 5	40 mg orally BID on days 1-7	14 mg/m^2 IV on days 1 and 8

Fanale, M et al, *ASH*, 2014

12 patients enrolled to date (3 PTCL, 3 DHL, 3 DLBCL, 1 DPL, 1 BL, 1 PTCL/DLBCL) up to dose level 4 with 92% having primary refractory disease with a median of 3.5 (range 1 to 7) prior lines of therapy and no patients having undergone a past SCT. To date the best responses have been seen in patients with PTCL which is supported also by preclinical data and includes 1 patient with CR lasting 9.9 months and 2 with SD including 1 patient with divergent histology.

In 24 cycles administered the incidence of reversible grade 3 or 4 neutropenia, anemia, and thrombocytopenia respectively are 62.5%, 29%, and 48%. MTD has not been reached.

Amendment underway to add D15 of romidepsin and to change alisertib dosing for better overlap with romidepsin with plans for 3 days of alisertib to be given around each dose of romidepsin, based on gyn onc data w/ wkly paclitaxel from Coleman, R, et al.

Conclusions

Multiple romidepsin doublets have shown efficacy and now introduction of triplets.

Challenges remain in defining what outcomes have the highest significance when determining which regimen to consider for front-line trial.

Potential to consider randomized trials in the relapsed setting to select the preferred treatment but need cooperative effort in the setting of rare diagnoses.

Need to better define predictive biomarkers for patient selection.