Peripheral T-cell Lymphomas
Romidepsin Updates

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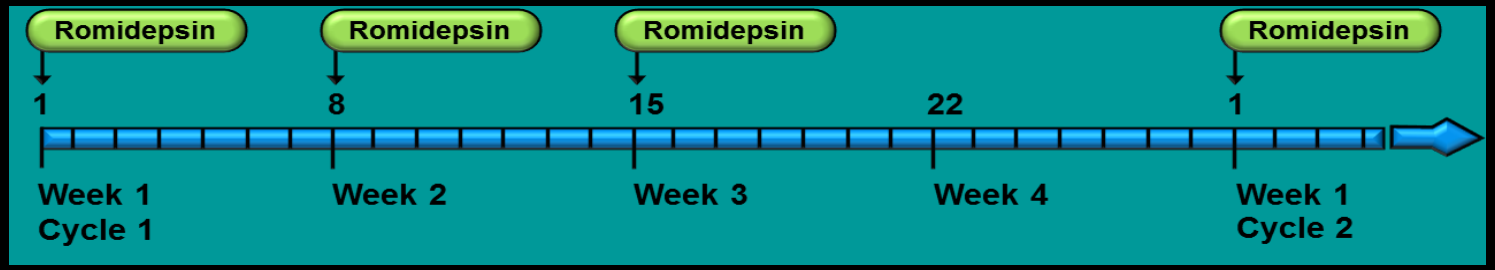
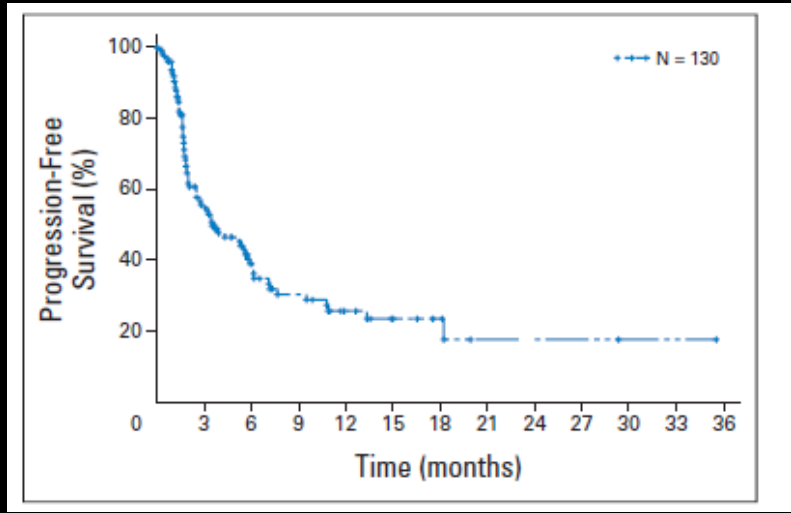
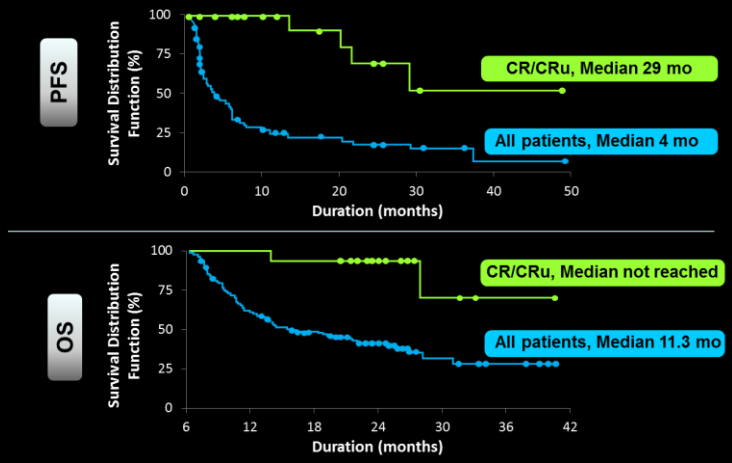
ROMIDEPSIN IN RELAPSED/REFRACTORY PTCL

Best Response	Central Review (IWC)	
	N (130)	%
Overall response (CR + PR)	33	25%
Complete response (CR+CRu)	19	15%
Partial response (PR)	14	11%







Coiffier B. et al. *J Clin Onc* 2012; 30:631-636

Romidepsin (2009): Where Do We Take It

- Palliative intent therapy
  - Combination with other single agent
    - Romidepsin and pralatrexate
    - Romidepsin and duvelisib
    - Romidepsin and 5-Azacytidine
- Curative intent therapy
  - Combination with multiagent platforms
    - Newly Dx PTCL
      - Ro-CHOP
    - Relapse-Refractory PTCL
      - Ro-ICE
  - Post-HCT maintenance

Frontline PTCL Therapy: Romidepsin + CHOP

Romidepsin in Combination with CHOP in Patients with Newly-Diagnosed PTCL: Phase 1b/2 dose-finding Study

Ro-CHOP: Patient and Disease Characteristics

	Total N=37
Age*, years	57 (30–77)
Gender, n	20 M / 17 F
aaIPI score >1, n (%)	27 (73)
Stage III/IV disease, n (%)	35 (95)
Diagnosis	
sALCL, ALK-, n (%)	2 (5)
cALCL, n (%)	1 (3)
Mycosis Fungoides, n (%)	1(3)
Peripheral T-cell lymphoma, follicular type, n (%)	1 (3)
Other peripheral T-cell lymphomas, n (%)	2 (6)
Peripheral T-cell lymphoma NOS, n	9 (24)
Angioimmunoblastic T-cell lymphoma, n	15 (41)
Precursor T-lymphoblastic lymphoma, n (%)	1 (3)
Enteropathy-associated T-cell lymphoma, n	1 (3)

Dupuis, J. et al. *Lancet Haematol.* 2015; 2:e160-65.

Ro-CHOP: Grade 3-4 TEAE >10%

TEAE per CTCAE 4.0	Total N=37
Anemia n (%)	16 (43)
Thrombocytopenia n (%)	29 (78)
Neutropenia	33 (89)
Lymphopenia	16 (43)
Nausea	7 (19)
Vomiting	4 (11)
Febrile neutropenia	6 (17)
Weight loss	4 (11)
Transaminase elevation	4 (11)
Hypophosphatemia	4 (11)
Asthenia	4 (11)

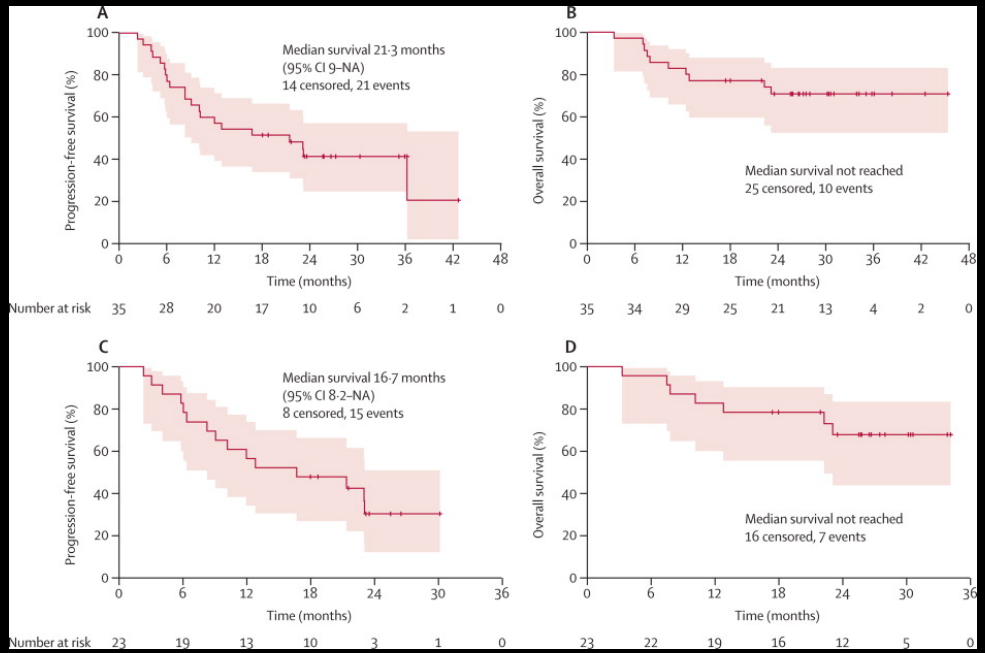
Dupuis, J. et al. *Lancet Haematol.* 2015; 2:e160-65.

Ro-CHOP: CLINICAL RESPONSE

	Total (N=35)
Objective Response, n (%)	24 (68%)
Complete Remission	18 (51%)
Partial Remission	6 (17%)

DLT reached at the dose of Romidepsin of 12 mg/sqm on days 1 and 8

Phase III trial of Ro-CHOP vs CHOP nears completion of accrual.



* Response per investigator at end of combination treatment (Cycle 6) or at latest assessment for 3 patients who discontinued prior to Cycle 6 (Cheson 2007)

Dupuis, J. et al. *Lancet Haematol.* 2015; 2:e160-65.

Relapsed/Refractory PTCL Therapy: Romidepsin + ICE

A Phase I Study of Romidepsin and Ifosfamide, Carboplatin, Etoposide (ICE) for the Treatment of Patients with Relapsed or Refractory Peripheral T-cell Lymphoma

Paolo Strati, MD

T-Cell Lymphoma Team

PI: Michelle Fanale, MD

Salvage Regimens in PTCL

REGIMEN	ORR (%)	CR rate (%)
Ifosfamide Carboplatin Etoposide	70	35
Gemcitabine Cisplatin Methylprednisolone	69	19
Gemcitabine Oxaliplatin Dexamethasone	38	8
Ifosfamide Methotrexate Etoposide	28	15

P. Strati ASH-2017

ENDPOINTS

- **Primary**
  - **Safety profile**
  - **MTD**

- **Secondary**
  - **ORR**
  - **CR**

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TREATMENT SCHEMA: "EVERYTHING IS BIG IN TEXAS"

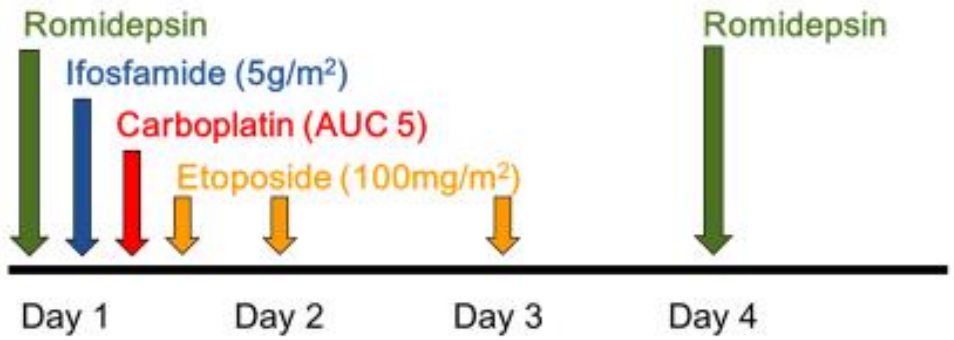
Treatment Schema

Romidepsin+ICE treatment dosing			
Day	**Drug**	**Dose Level**	**Infusion Time**
1 and 4	Romidepsin	Level 1 = 8 mg/m^2 Level 2 = 10 mg/m^2 Level 3 = 12 mg/m^2	IV over 4 hours
1	Ifosfamide + MESNA	5 gm/m^2 for both	IV infusion over 24 hrs
2	MESNA	2 gm/m^2	IV infusion over 12 hrs
1	Carboplatin	Target AUC = 5 mg/mL/min (Maximum dose of 750 mg)	IV over 1 hr
1 through 3	Etoposide	100 mg/m^2/day	IV over 2 hrs daily x 3 doses

Every 2 weeks
(ANC ≥ 1 , PLT ≥ 75)

2-6 cycles

Neulasta or Neupogen



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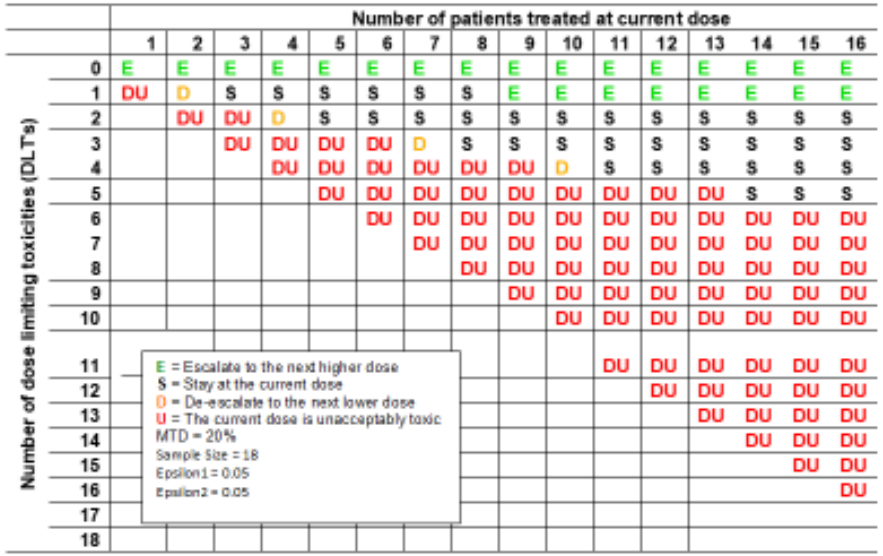
Dose Escalation (Bayesian CRM)

Dose Escalation

DLT (CTCAE v4.0)
- During cycle 1
- Non-heme: G ≥ 3 AE
- Heme: G4 AE for > 14 days

MTD
- dose at which 20% of pts have a DLT



Number of dose limiting toxicities (DLTs)	Number of patients treated at current dose															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	DU	D	S	S	S	S	S	S	E	E	E	E	E	E	E	E
2		DU	DU	D	S	S	S	S	S	S	S	S	S	S	S	S
3			DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
5					DU	DU	DU	DU	DU	DU	DU	DU	DU	S	S	S
6						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
7							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
8								DU	DU	DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU	DU	DU
11											DU	DU	DU	DU	DU	DU
12												DU	DU	DU	DU	DU
13													DU	DU	DU	DU
14														DU	DU	DU
15															DU	DU
16																DU
17																
18																

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 20%
Sample Size = 18
Epsilon1 = 0.05
Epsilon2 = 0.05

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PATIENTS' CHARACTERISTICS

Patients (n=22)	Number (percentage), median [range]
Median time from diagnosis (months)	6 [2-45]
Age (years)	58 [19-68]
Age ≥ 65 years	4 (18)
Males	15 (68)
Diagnosis: PTCL-NOS	9 (40)
AITL	8 (36)
ALK+ ALCL	3 (14)
NK/TCL	1 (5)
HSTL	1 (5)
Ann Arbor stage I	0 (0)
II	4 (18)
III	7 (32)
IV	11 (50)

Patients (n=22)	Number (percentage), median [range]
Previous regimens (n)	1 [1-2]
Previous regimen > 1	1 (5)
Latest regimen: CHOP	10 (45)
CHOEP	6 (27)
EPOCH	2 (9)
HCVAD	2 (9)
B-CHP	2 (9)
Previous autologous SCT	2 (10)
Previous radiation therapy	2 (10)
Response to previous regimen:	
CR	5 (23)
PR	3 (14)
SD	2 (9)
PD	12 (54)
Relapsed < 6 months	19 (86)

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Ro-ICE: Dose Level Distribution

Patients (n=18*)	Patients (n)	Total cycles (n)
Dose level 1 (8 mg/m2)	2	7
Dose level 2 (10 mg/m2)	15	39
Dose level 3 (12 mg/m2)	1	1

(*) 4 patients did not start treatment
consent withdrawal (2), lack of insurance (1), MI (1)

Median time between subsequent cycles was 21 days (range, 14-33 days)
Median time on study was 2 months (range, 1-13 months)

Reasons for Treatment Discontinuation

Patients (n=18)	Number (%)
SCT	12 (67)
Toxicity*	4 (23)
Lack of response	1 (5)
Withdrawal	1 (5)

(*): thrombocytopenia, AKI, allergy, ototoxicity

RO-ICE: GRADE 3-4 TEAE > 5%

Patients (n=18)	Number (%)
Hematological toxicity	
Thrombocytopenia	15 (83)
Anemia	9 (50)
Neutropenia	8 (44)
TTP	1 (5.5)
Febrile neutropenia	1 (5.5)

Patients (n=18)	Number (%)
Non-hematological toxicity	
Fatigue	6 (33)
Nausea/vomiting	6 (33)
Infections	5 (28)
Dyspnea	3 (17)
Transaminitis	2 (11)
Constipation	1 (5.5)
Arrhythmia	1 (5.5)
Confusion	1 (5.5)
Allergy	1 (5.5)
Acute renal insufficiency	1 (5.5)
Ototoxicity	1 (5.5)

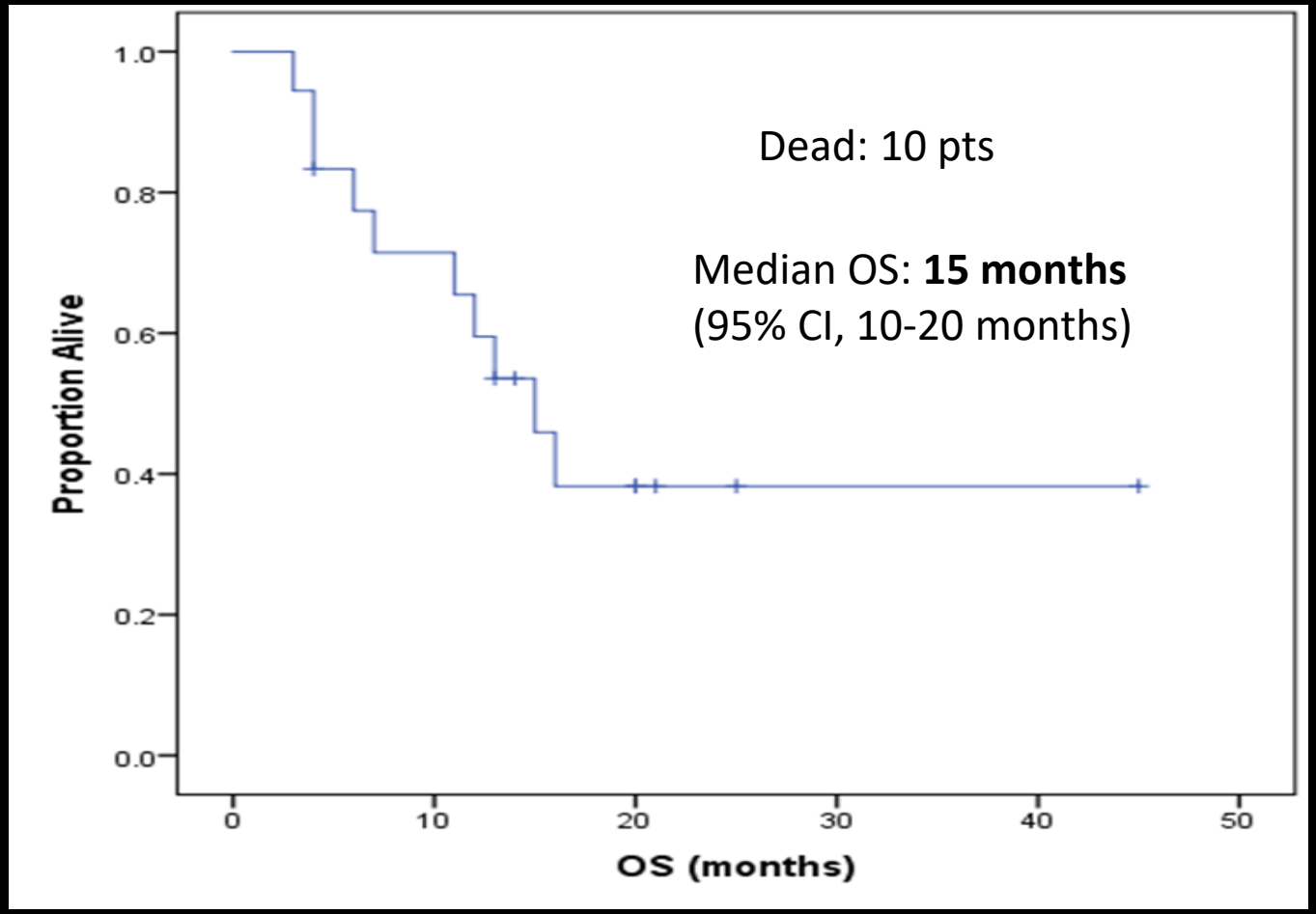
Ro-ICE: Efficacy Assessment

Patients (n=15*)	Number (%)
ORR	14 (93)
CR	12 (80)
PR	2 (13)
NR	1 (7)

(*) 3 pts stopped treatment before response assessment

Allergy, ototoxicity and thrombocytopenia

Overall Survival



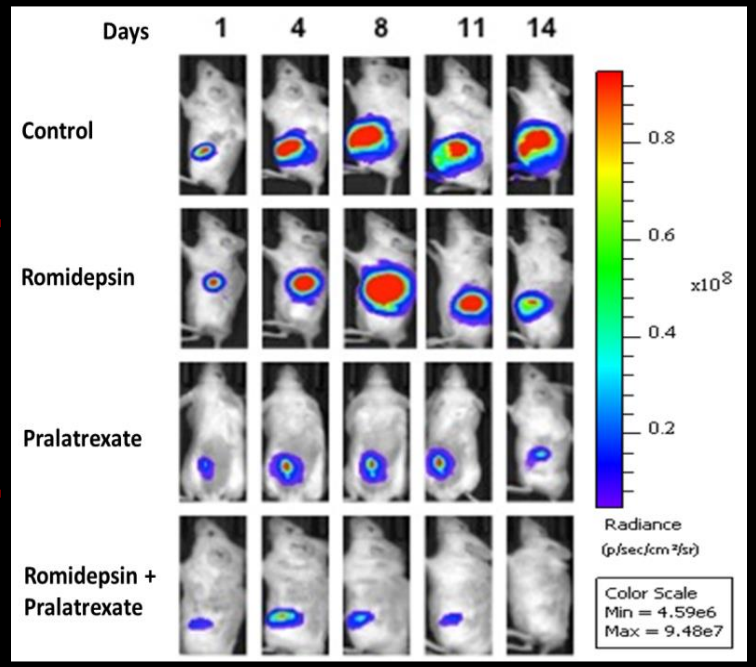
Patients (n=18)	Number (%)
Progression	6 (33)
Pneumomia (PD)	2 (10)
T-AML (CR)	1 (5)
AKI (CR)	1 (5)

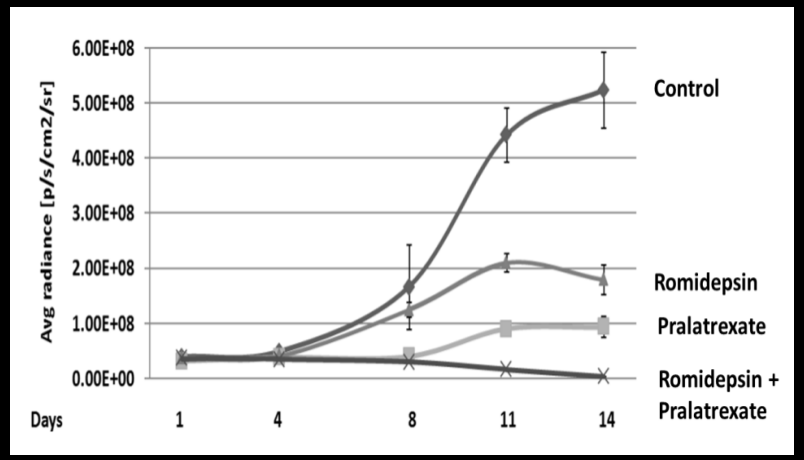
Ro-ICE vs. ICE vs. Romidepsin

REGIMEN	ORR (%)	CR rate (%)
ICE	70	35
Romidepsin	25	15
ICE + romidepsin	93	80

Toxicity ICE + romidepsin = ICE > romidepsin

Pralatrexate and Romidepsin are Highly Synergistic Across In Vivo Models of TCL





Synergy demonstrated by activity seen at lower doses of each drug compared to MTD of each

Treatment group	Estimated log-intensity (p-value)			
	4th day	8th day	11th day	14th day
Control	7.78 (<0.05)	8.09 (<0.05)	8.32 (<0.05)	8.55 (<0.05)
Romidepsin	7.75 (<0.05)	8.00 (<0.05)	8.20 (<0.05)	8.39 (<0.05)
Pralatrexate	7.58 (0.02)	7.74 (<0.05)	7.86 (<0.05)	7.98 (<0.05)
Romidepsin + Pralatrexate	7.49	7.24	7.06	6.87

Clinical Cancer Research

Jain, S. et al. Clinical Cancer Research, 2015. 21(9): 2096-2106

Evidence for Select Emerging Doublets in PTCL: Pure Targeting of Epigenetic Operations

Romidepsin

+

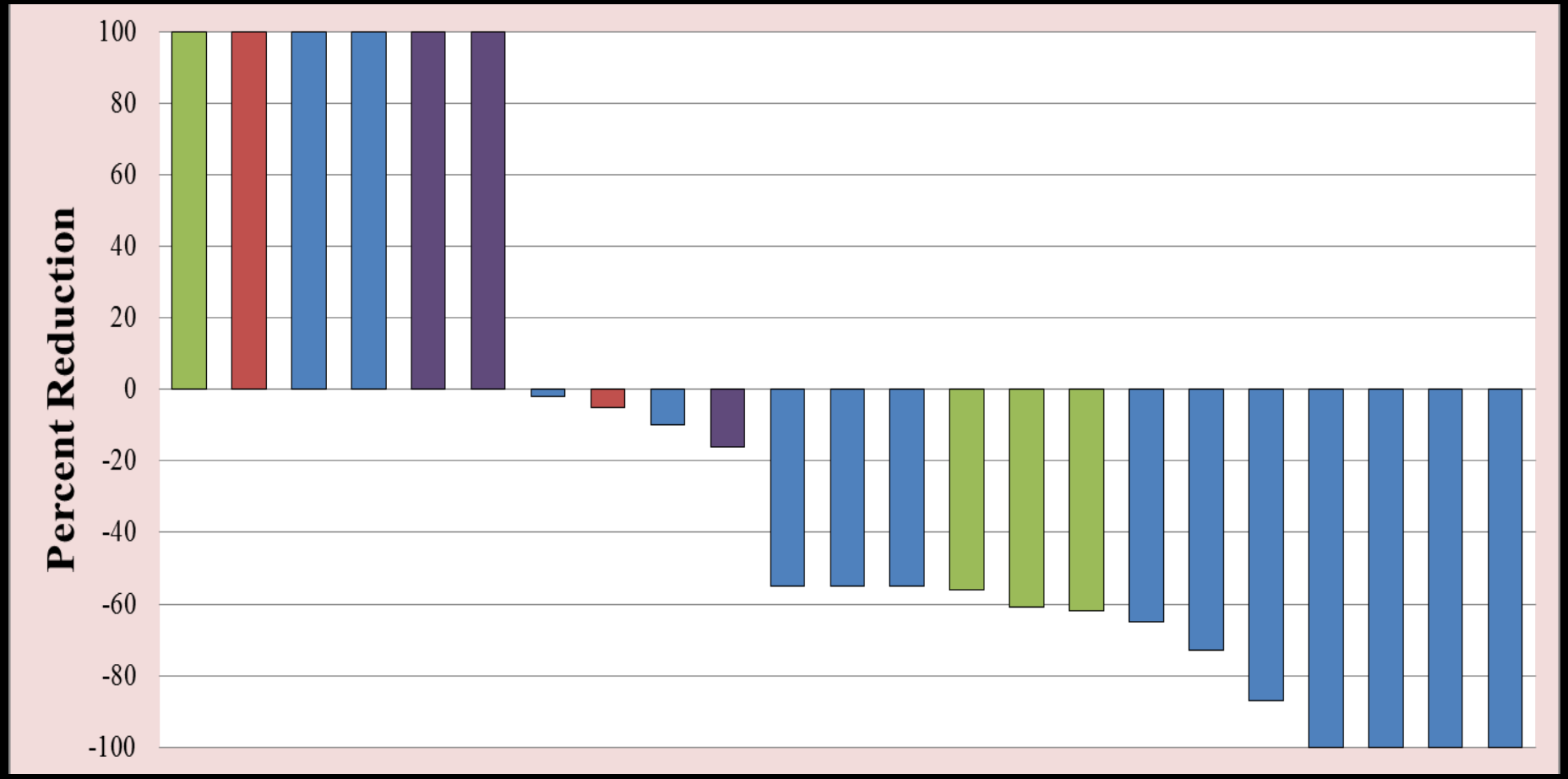
Pralatrexate

Summary of Response Data: Pralatrexate Romidepsin Phase 1

Parameter	Number
Total # of Patients (evaluable)	29 (23)
ORR (all)	13/23 (57%)
ORR non-TCL	3/9 (33%)
ORR T-Cell	**10/14 (71%)**
T-Cell CR	**4/10 (40%)**
T-Cell PR	**6/10 (60%)**

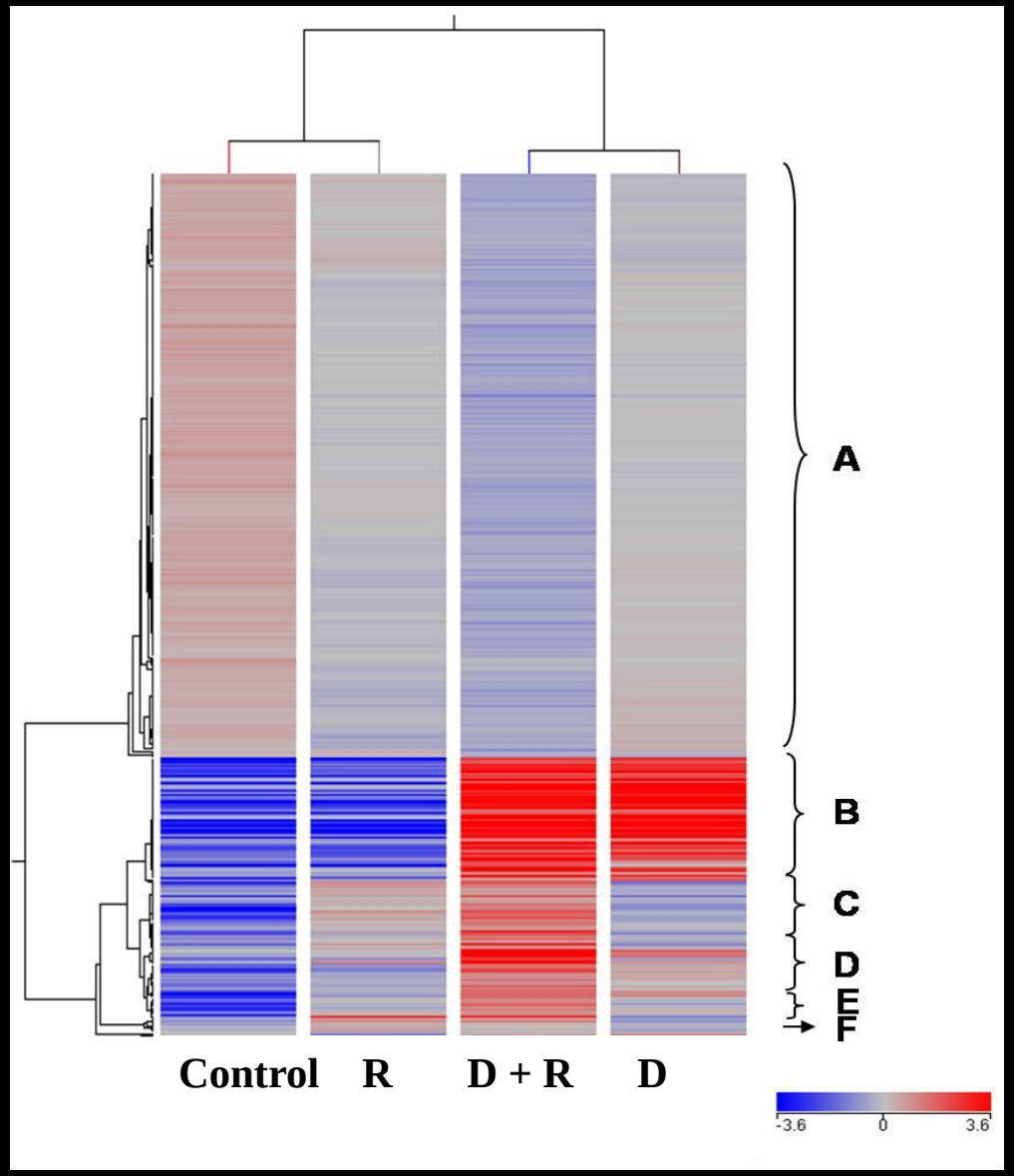
Amengual JA et al; Blood 2017

Waterfall Plot of Patients with Measurable Disease on Pralatrexate / Romidepsin



Amengual JA et al; Blood 2017

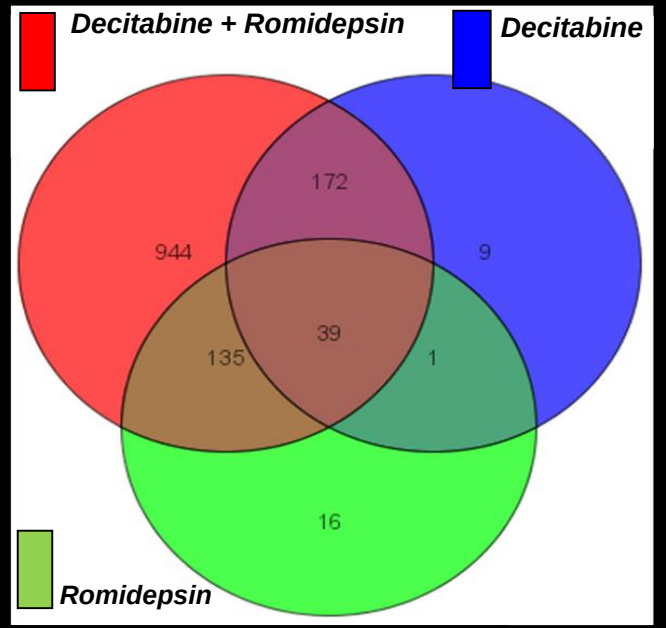
EPIGENETIC DRUGS SIGNIFICANTLY AFFECT THE MALIGNANT PHENOTYPE



Illumina Human HT-12 v4
Expression BeadChip microarrays

>47,000 probes
Cell lines: HH, H9, P12, PF 382
Treatment schedules: D, R, R+D
GEP timing: 48 hours of incubation

Data analysis: *GeneSpring GX 11.0*



Marchi E. et al; BJH 2015 Kalac M. et al; Blood 2011

Columbia University Medical Center

Evidence for Select Emerging Doublets in PTCL: Pure Targeting of Epigenetic Operations

Romidepsin

+

(Oral) 5-Azacytidine

Phase 1-2 Study of Oral 5-Azacytidine and Romidepsin in Lymphoma

Parameter	Number
Total # of Pts. (evaluable)	26 (23)
ORR (all)	7/23 (30%)
ORR non-PTCL	3/18 (17%)
ORR T-Cell	4/5 (80%)

- Most significant toxicity is Grade 1-2 nausea due to azacytidine
- One DLT in cohort 7 led to expansion
- Albeit early, responses in PTCL appear more than what is seen in BCL
- PK analysis pending
- Methylation assays being conducted on all patients (PBL) and select tissue

Courtesy of O. O'Connor

In Vitro, *In Vivo*, and Parallel Phase I Evidence Support the Safety and Activity of Duvelisib, a PI3K δ,γ Inhibitor, in Combination with Romidepsin or Bortezomib in Relapsed/Refractory T-Cell Lymphoma

Alison J. Moskowitz MD, Raphael Koch MD, Neha Mehta-Shah MD, Patricia Myskowski MD, Meenal Kheterpal MD, Ahmet Dogan MD PhD, Theresa Davey MPAS, Natasha Galasso BA, Marzouk Evan BA, Monica Shah BA, Nivetha Ganesan BS, Lakeisha Lubin BS, Youn H. Kim MD, Michael Khodadoust MD PhD, Timothy Almazan MD, Julia Dai MD, Eric D. Jacobsen MD, David M. Weinstock MD, and Steven M. Horwitz MD

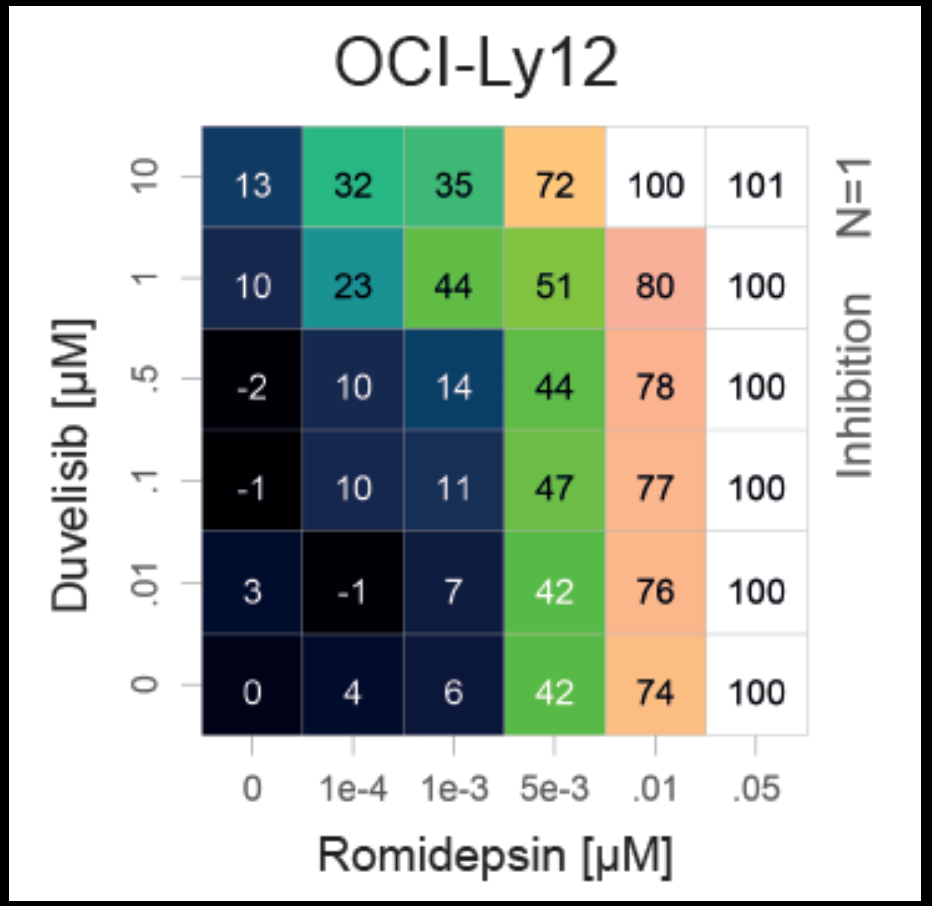
Memorial Sloan Kettering Cancer Center

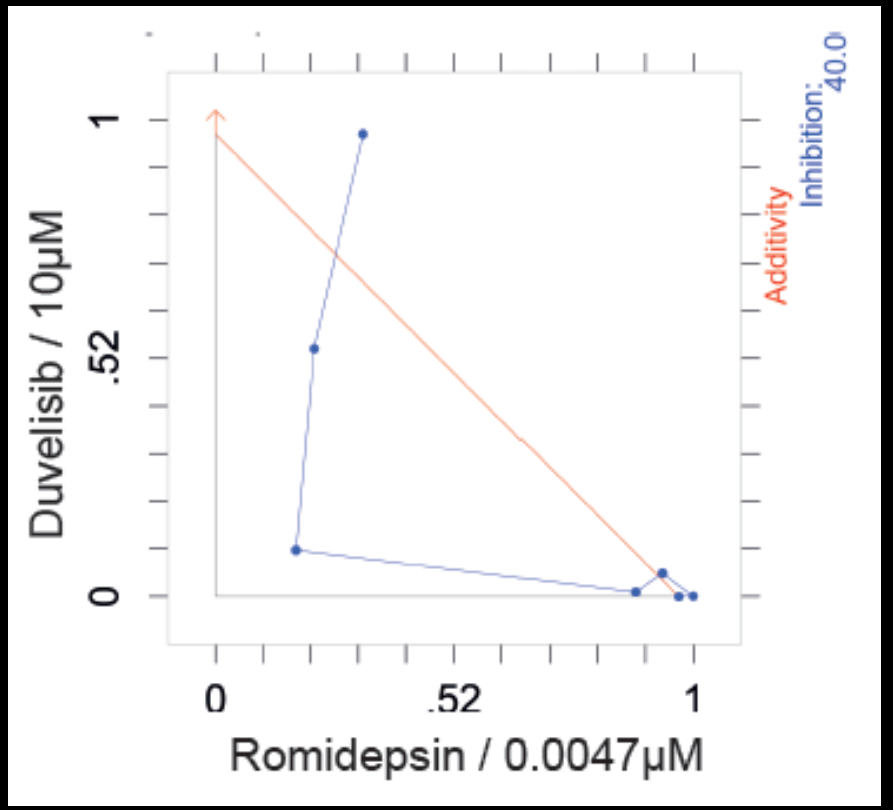
DANA-FARBER CANCER INSTITUTE

Stanford SCHOOL OF MEDICINE

Washington University in St. Louis SCHOOL OF MEDICINE

Synergy demonstrated between duvelisib and romidepsin in duvelisib-resistant cell line

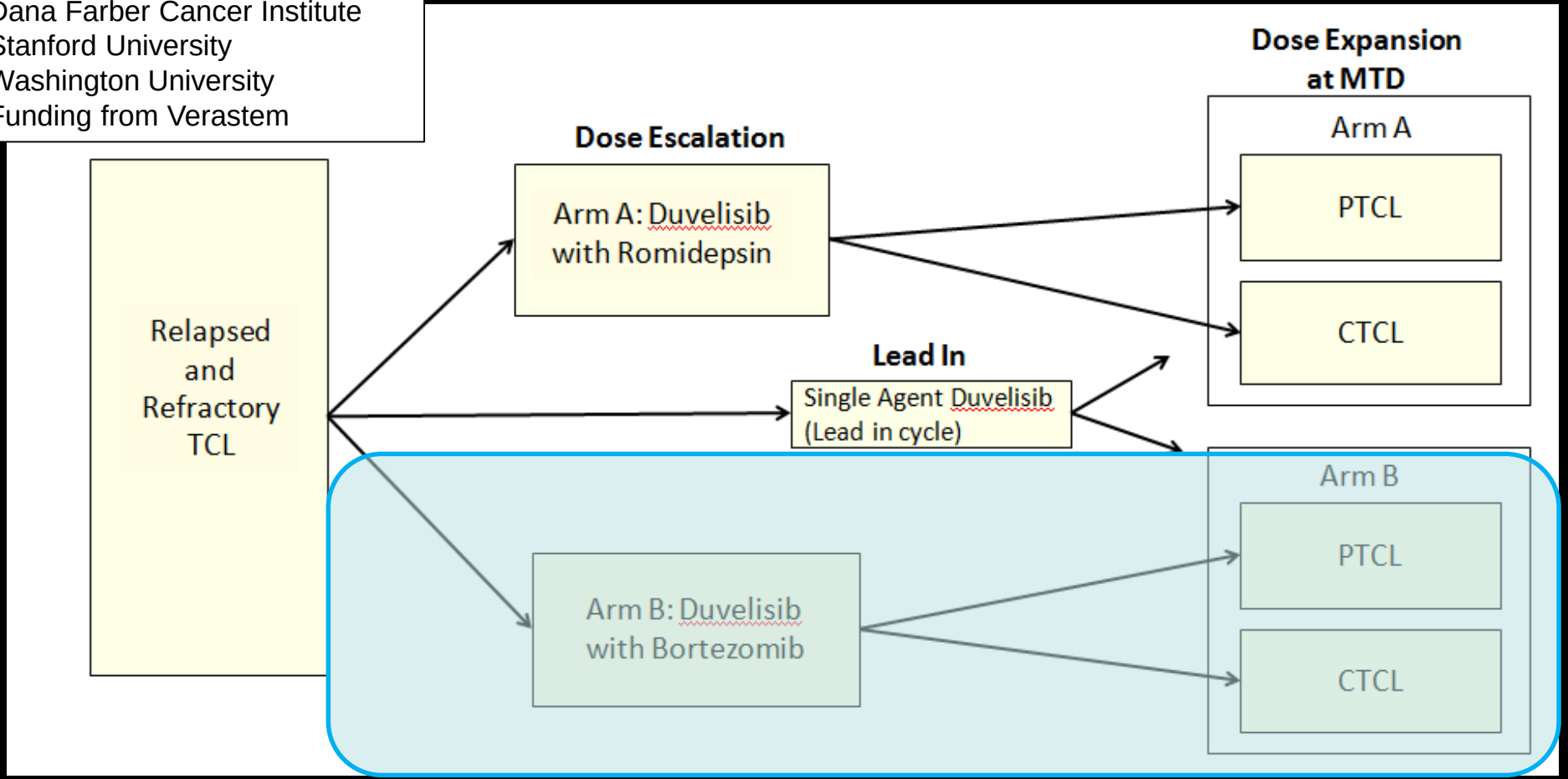




Courtesy of S. Horwitz ASH-2017

Parallel Phase I studies of duvelisib plus romidepsin or bortezomib
3+3 Design with Dose Expansion at MTD

Participating Institutions
Memorial Sloan Kettering*
Dana Farber Cancer Institute
Stanford University
Washington University
Funding from Verastem



Courtesy of S. Horwitz ASH-2017

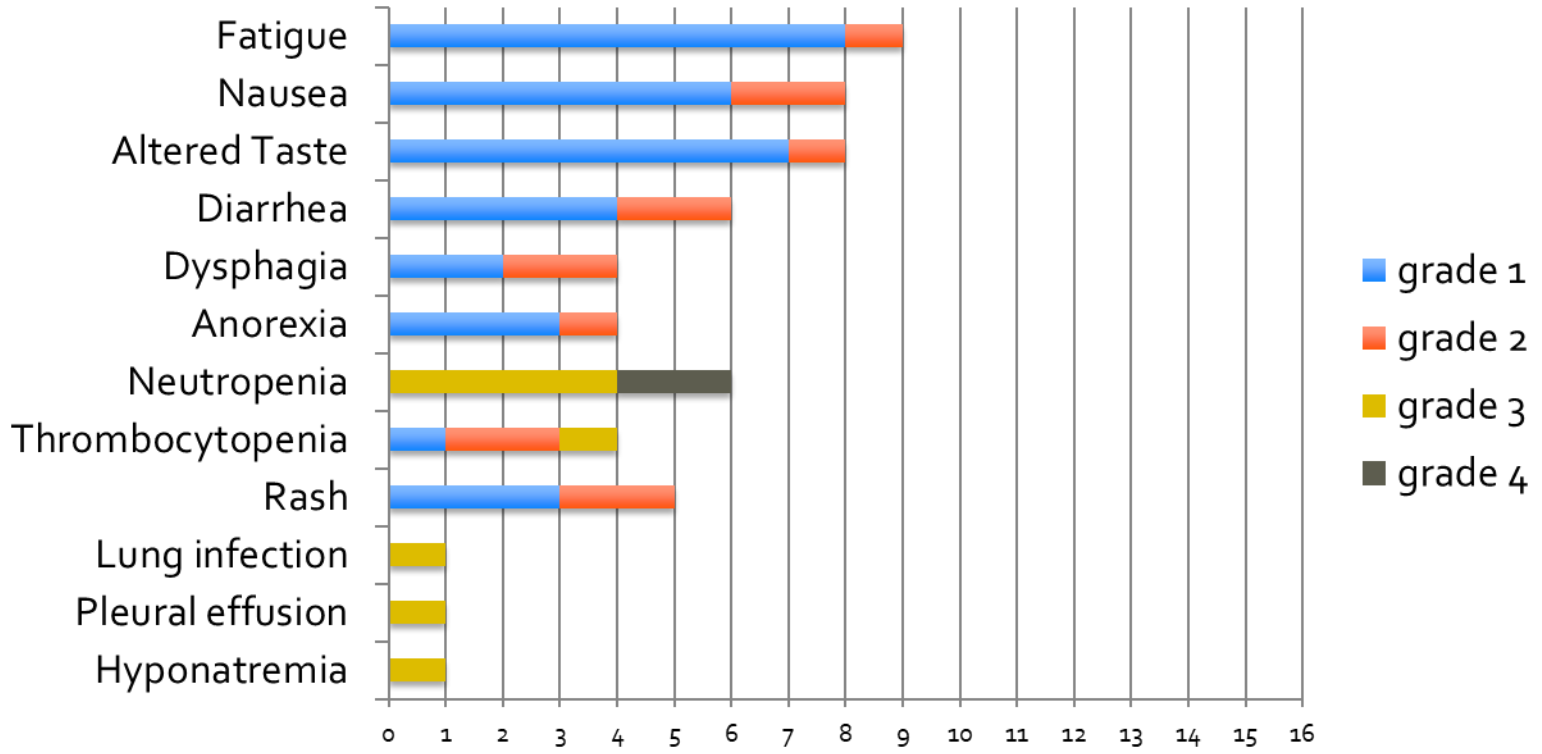
ARM A: DOSE ESCALATION AND EXPANSION

ARM A – Duvelisib + Romidepsin		
Dose Level	Romidepsin days 1, 8, 15	DUV PO days 1-28
1	10 mg/m^2	25mg BID
2	10 mg/m^2	50mg BID
3	10 mg/m^2	75mg BID

MTD Arm A Dose Level 3; Romidepsin (10mg/m2 IV) + Duvelisib (75mg PO, BID)

Courtesy of S. Horwitz ASH-2017

ROMIDEPSIN + DUVELISIB: ALL GRADE 3,4 AND >20% ALL



2 deaths unrelated to treatment:

- Diffuse alveolar hemorrhage following allogeneic stem cell transplant
- Sepsis in setting of disease progression

Courtesy of S. Horwitz ASH-2017

Romidepsin + Duvelisib: Efficacy

ARM A – Duvelisib + Romidepsin - Response				
Dose Level	# pts Evaluable for Response/Total	Overall response	Complete Response	Partial Response
1	4/4	2	0	2
2	3/4	2	1	1
3	8/8	5	3	2
TOTAL	15/16	9 (60%)	4 (27%)	5 (33%)

CTCL vs. PTCL	#pts Evaluable for Response	Overall Response Rate	Complete Response	Partial Response
CTCL	4	2 (50%)	0	2 (50%)
PTCL	11	7 (64%)	4 (36%)	3 (27%)
(AITL)	5	3 (60%)	2 (40%)	1 (20%)
(PTCL-US)	4	3 (75%)	2 (50%)	1 (25%)

Courtesy of S. Horwitz ASH-2017

Adverse Events of Special Interest (LFTs)

Duvelisib + Romidepsin		
AE	n=16	
	Any grade	Gr. 3 & 4
ALT	2 (12.5)	0 (0)
AST	2 (12.5)	0 (0)

Courtesy of S. Horwitz ASH-2017

Single Agent Duvelisib		
AE	n=210	
	Any grade	Gr. 3 & 4
ALT	81 (38.6)	41 (19.5)
AST	79 (37.6)	32 (15.2)

Flinn et al., Bood 2017

Romidepsin (2009): Where Did We Take It

- No new label or a combination a decade later; lesson learned?
- Ro-CHOP phase I: increased toxicity of CHOP, added efficacy unknown; phase III final trial results pending
- Ro-ICE phase I: minimal added toxicity to ICE, promising CR rate; need confirmatory trial
- Novel doublets with pralatrexate, 5-azacytidine, and duvelisib increased ORR and CR rates; confirmatory studies needed; might be the initial step towards new multiagent platform for newly Dx and R/R PTCL

THANK YOU