Memorial Sloan Kettering Cancer Center

Lenalidomide in PTCL

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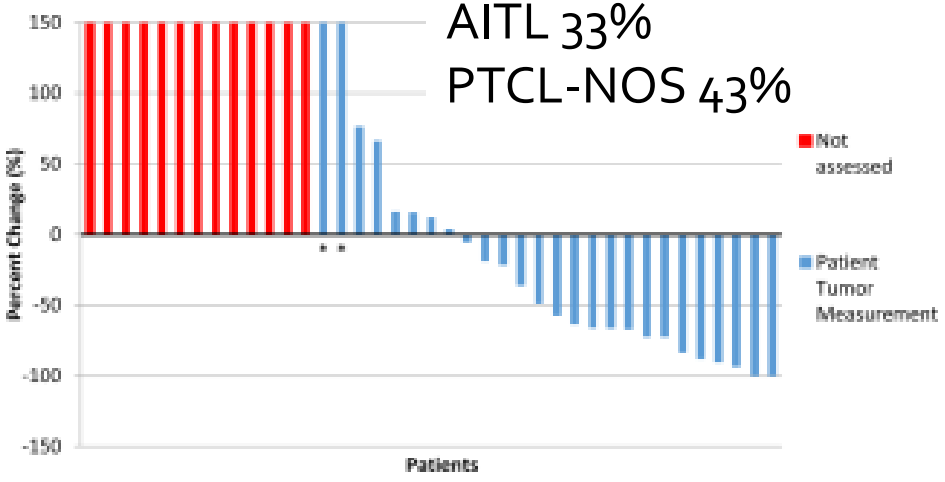
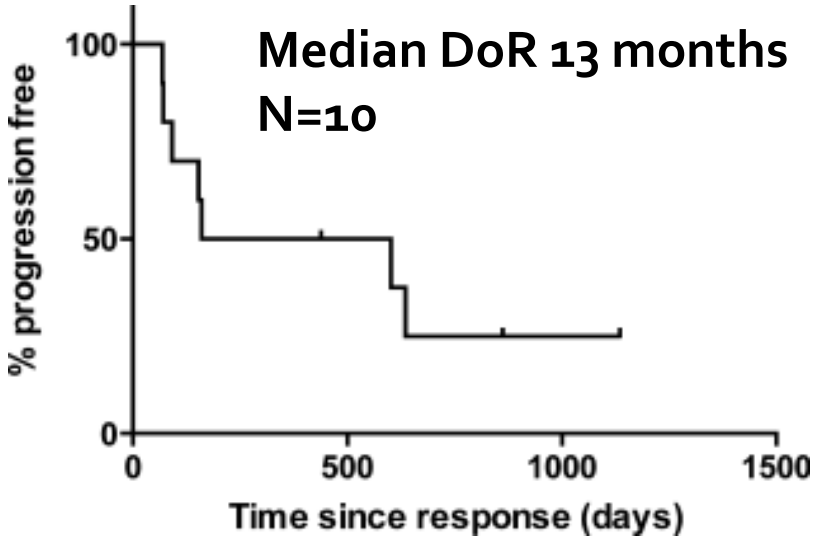
Lenalidomide in T-cell Lymphoma: Single Agent

Letter to Editor: **Zinzani et al** Leukemia & Lymphoma, August 2011;
Lenalidomide monotherapy for relapsed/refractory peripheral T-cell lymphoma not otherwise specified
ORR 30% (3/10)

Final Report of a Phase 2 Clinical Trial of Lenalidomide Monotherapy for Patients With T-Cell Lymphoma.
Toumishey et al. Cancer 2014; Volume 121, 5; pages 716-723

ORR 26%
AITL 33%
PTCL-NOS 43%

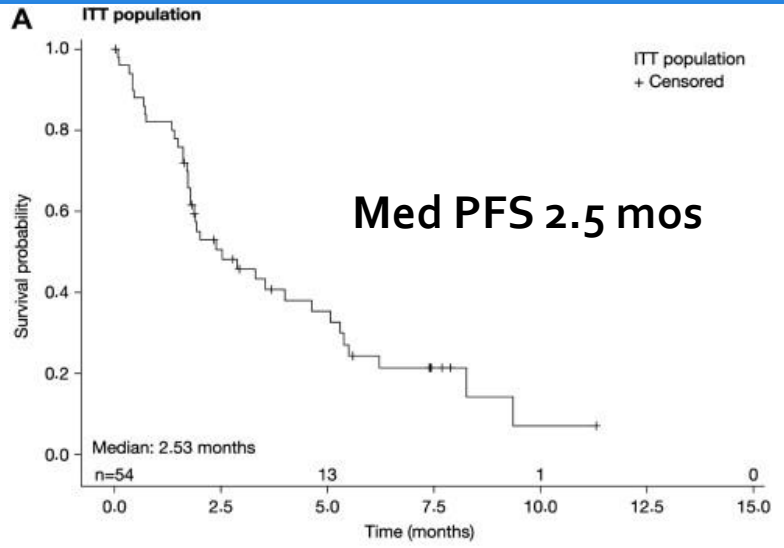


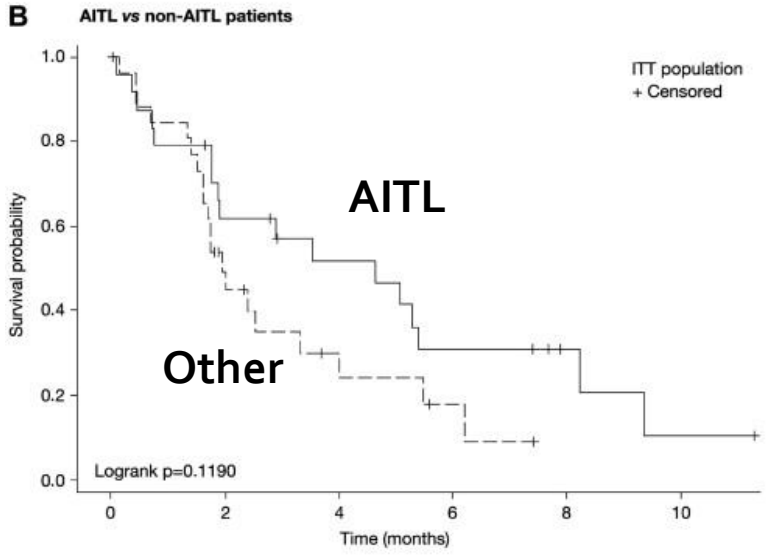


Lenalidomide 25 mg/day; D1-21 of a 28 day cycle

A phase 2, multicentre, single-arm, open-label study of lenalidomide in relapsed or refractory PTCL: The EXPECT trial

	ITT (N=54)	AITL (N=26)
Tumor Control	52% (28)	58% (15)
ORR	22% (12)	31% (8)
CR/Cru	11%(6)	15% (4)
PR	11%(6)	15% (4)
Stable disease	30% (16)	27%(7)
POD	33% (18)	23% (6)
D/C without response assesment	15% (8)	19% (5)

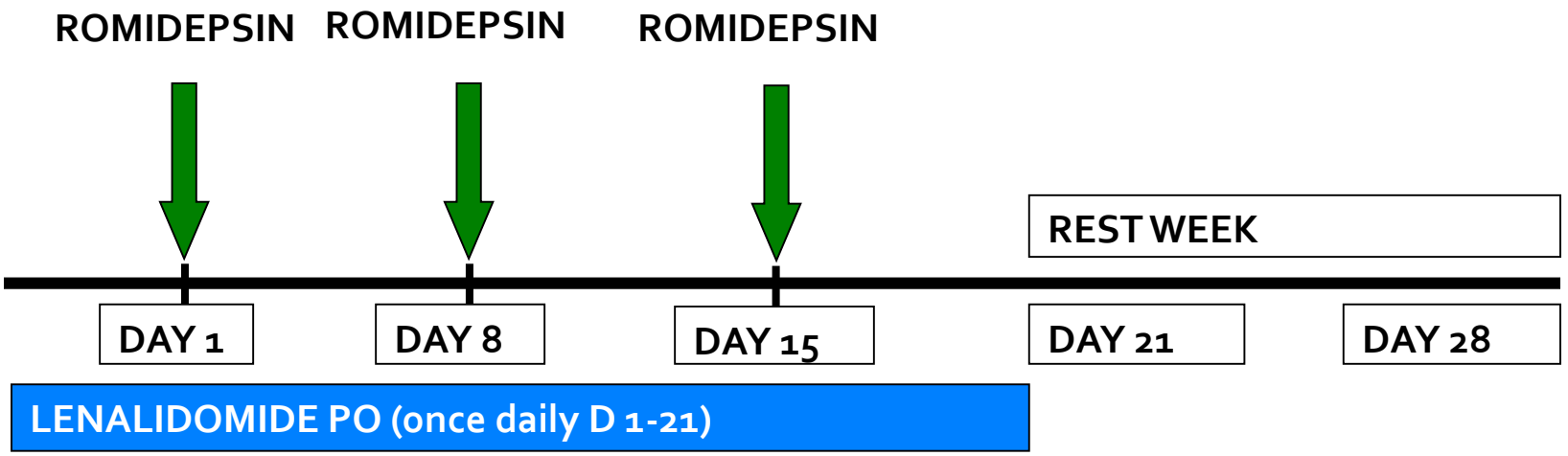




Morschhauser et al European Journal of Cancer, Volume 49, Issue 13, 2013, 2869

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

MSKCC:N. Mehta-Shah, A. Moskowitz, S. Horwitz
WCMC: J. Ruan, J. Leonard, UNMC: M. Lunning, J. Vose, StF: A. Boruchov



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 et al. ASCO 2014

A Phase Ib/IIa Study of Romidepsin in Combination with Lenalidomide: DLT

Cohort (Dose)	#pts (evaluable)	#pts with DLT	Dose reductions
1 (8mg/m^2/15mg)	3		1
2 (8mg/m^2/25mg)	7*	1 (pna)	5
3 (10mg/m^2/25mg)	3		2
4 (14mg/m^2/25mg)	7*	1 (syncope)	2

MTD from Phase Ib
Romidepsin 14mg/m^2 , Lenalidomide 25mg d 1-21

DLT definition in cycle 1

Non-heme tox of grade ≥3 (attributed to study drug)

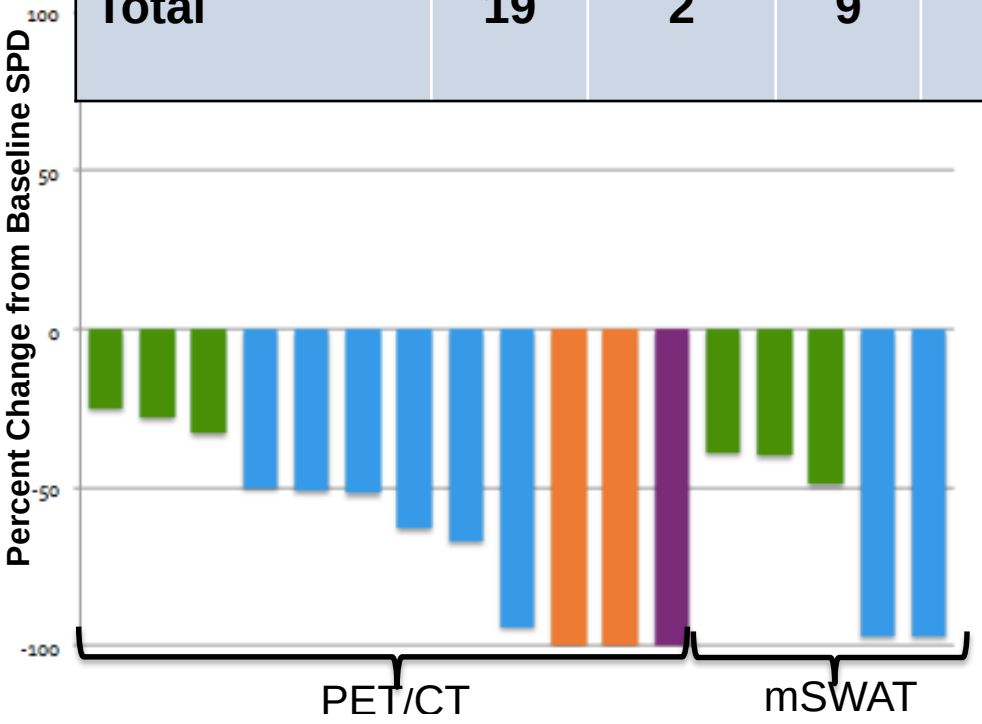
Heme tox grade 4 toxicity (attributed to study drug)

- Grade 4 thrombocytopenia of any duration,
- Failure of recovery of ANC≥ 1.0 K/µL or platelets to ≥ 50 K/µL in 14 days

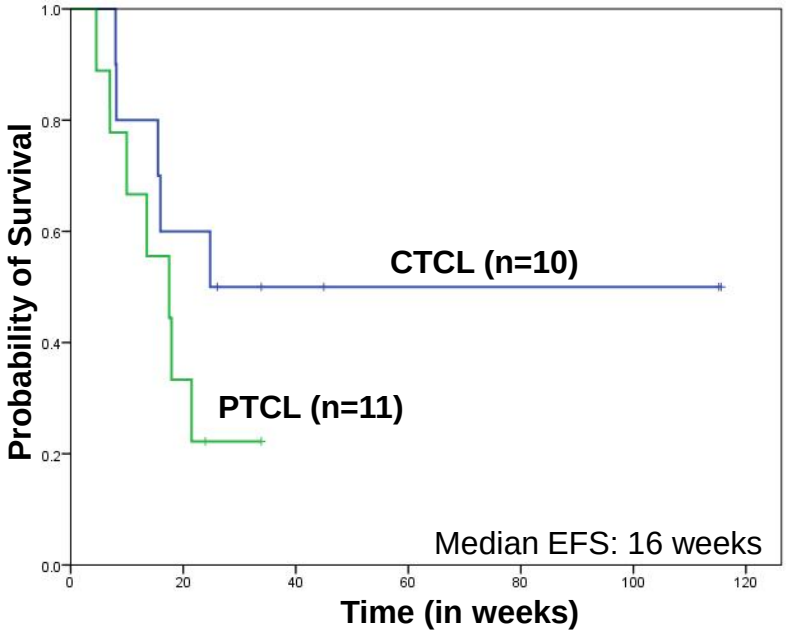
T-cell Responses

Histology	N	CR	PR	ORR
CTCL	9	2	3	5/9 (56%)
PTCL	10	-	6	6/10 (60%)
Total	**19**	**2**	**9**	**11/19 (58%)**

CR: MF (1), tMF (1)
PR: AITL (2), ATLL (1)
T-PLL (1), MF (3)



Event Free Survival



Not Shown:
- 1 subject w/ POD in non-measureable sites
- 1 subject with T-PLL (PR) not shown

Mehta-Shah et al. ICML 2015

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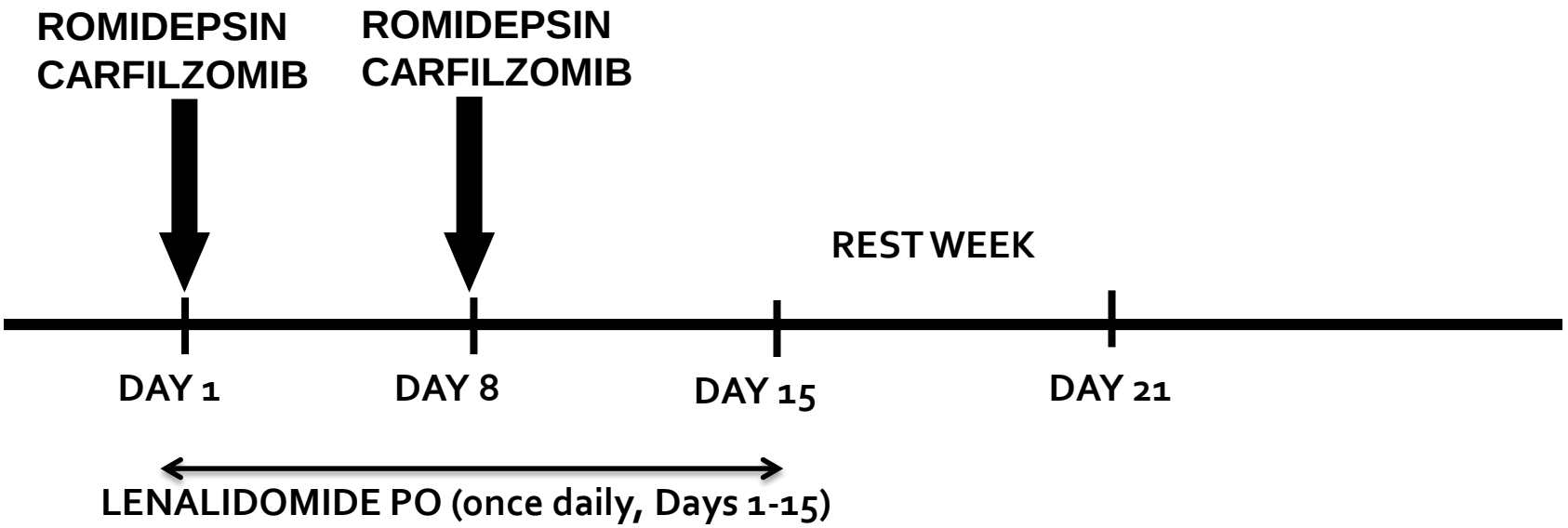
A Phase Ib/IIa Trial of the Combination of Romidepsin, Lenalidomide and Carfilzomib in Patients with Relapsed/Refractory Lymphoma Shows Complete Responses in Relapsed and Refractory B- and T-Cell Lymphomas

Neha Mehta-Shah, MD[1,2], Alison J. Moskowitz, MD[2], Matthew A. Lunning, DO[3], Peggy Lynch[2*], Mark Scheuerman[2*], Veenna Minnal[2*], Natasha Galasso, BA[2*], Anita Kumar, MD[4], John Gerecitano, MD, PhD[5], Andrew D. Zelenetz, MD, PhD[4], Paul A. Hamlin, MD[6], Ariela Noy, MD[4], Matthew J. Matasar, MD[4], Maria Lia Palomba, MD[7], Anas Younes, MD[2], Wendy Schaffer, MD[8*], Ravinder Grewal, MD[9*], Jurgen Rademaker, MD[9*], Craig S. Sauter, MD[10], Parastoo B. Dahi, MD[10*], Patricia Myskowski, MD[11*], Meenal Kheterpal, MD[11*], Ahmet Dogan, MD, PhD[4], Melissa Pulitzer, MD[12*], Lakeisha Lubin, BS[4*], Laura Tang, Pharm. D[13*], Nivetha Ganesan, BS[2*], Ai Ni, PhD[14*] and Steven M. Horwitz, MD[2]

Schedule and Dose Levels



Dose Level	Romidepsin	Lenalidomide	Carfilzomib (mg/m^2)
-1	8 mg/m^2	10 mg	20
1	8 mg/m^2	15 mg	36
2	8 mg/m^2	15 mg	45
3	10 mg/m^2	20 mg	45
4	10 mg/m^2	20mg	56

Treated until progression or intolerance

Patient Characteristics (n=27)

Age	
Median (Range)	57 (37-83)
Gender	
Male	21 (78%)
Female	6 (22%)

Prior systemic therapies	
Median (Range)	2 (1-7)
Prior transplants	
Autologous	6
Allogeneic	1

Disease Subtype	
B-cell NHL	**11**
DLBCL*	7
Follicular	2
Mantle Cell	2
T-cell NHL	**16**
PTCL-NOS	7
AITL*	5
MF/SS	2
tMF	1
ENKTCL	1

*One patient had concurrent DLBCL and AITL

Dose Limiting Toxicities/Maximum Tolerated Dose

Cohort (Dose)	#pts (evaluable)	#pts with DLT
1 (8mg/m²/10mg/36mg/m²)	6	
2 (8mg/m²/15mg/45mg/m²)	6	2* (thrombocytopenia)
3 (8mg/m²/15mg/45mg/m²)	--	
4 (14mg/m²/25mg/56mg/m²)	--	

Maximum Tolerated Dose:
Romidepsin 8mg/m², Lenalidomide 10mg, Carfilzomib 36mg/m²

Related and Unrelated Toxicities (Grade 3 or 4)

Toxicity	Grade 3	Grade 4
Hematologic Toxicity		
Neutropenia	2 (17%)	1 (8%)
Thrombocytopenia	2 (17%)	3 (25%)
Febrile Neutropenia	1 (8%)	
Diarrhea	1 (8%)	
Vomiting	1 (8%)	
Weight Loss	1 (8%)	
Peripheral Motor Neuropathy	1 (8%)	
Generalized Muscle Weakness	1 (8%)	
Back Pain	1 (8%)	
Pneumonia	1 (8%)	

Response Rates by Disease Subtype
All Treated Patients

T-cell Cohort (n=16)

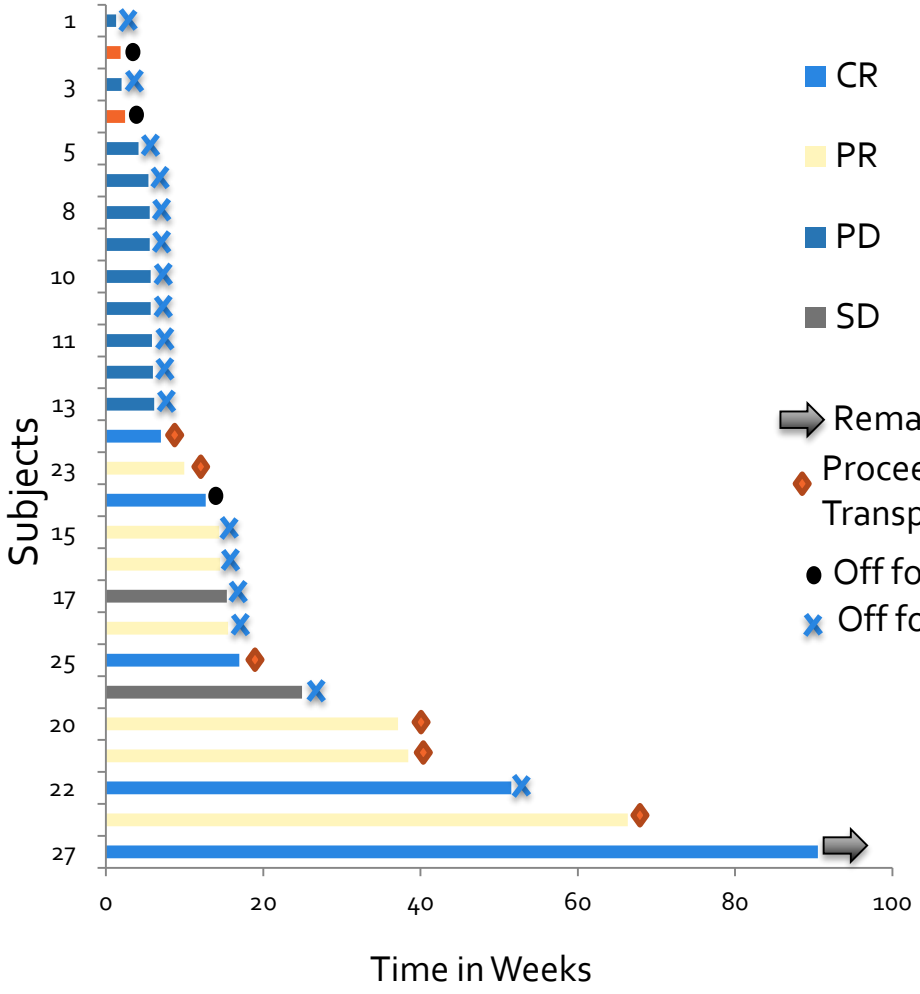
	N	CR	PR	ORR
T-cell NHL	**16**	**5**	**3**	**8/16 (50%)**
PTCL-NOS	7	1	1	2/7 (29%)
AITL*	5	4	1	5/5 (100%)
CTCL	3	-	1	1/3 (33%)
NK/T	1	-	-	0/1 (0%)

- 2 patients were evaluable for toxicity alone (stopped for toxicity in cycle 1 without evidence of progression)
- One patient with concurrent AITL and DLBCL was evaluated for efficacy in both BCL and TCL cohorts

Event Free Survival

- Median time to best response: 5.7 weeks
- Median duration of response: 38.7 weeks (95% CI: 9.7 to NR)
- Median duration of follow up: 56.0 weeks (2.4-102.1 w)

Swimmer's Plot (n=27)



- 6 patients proceeded to allogeneic transplant
  - 2 PTCL-NOS
  - 2 DLBCL
  - 1 Mantle Cell
  - 1 with concurrent AITL and DLBCL
- Sustained CRs in TCL:
  - 1 AITL for 11.7 months
  - 1 PTCL-NOS on treatment at 17 months.

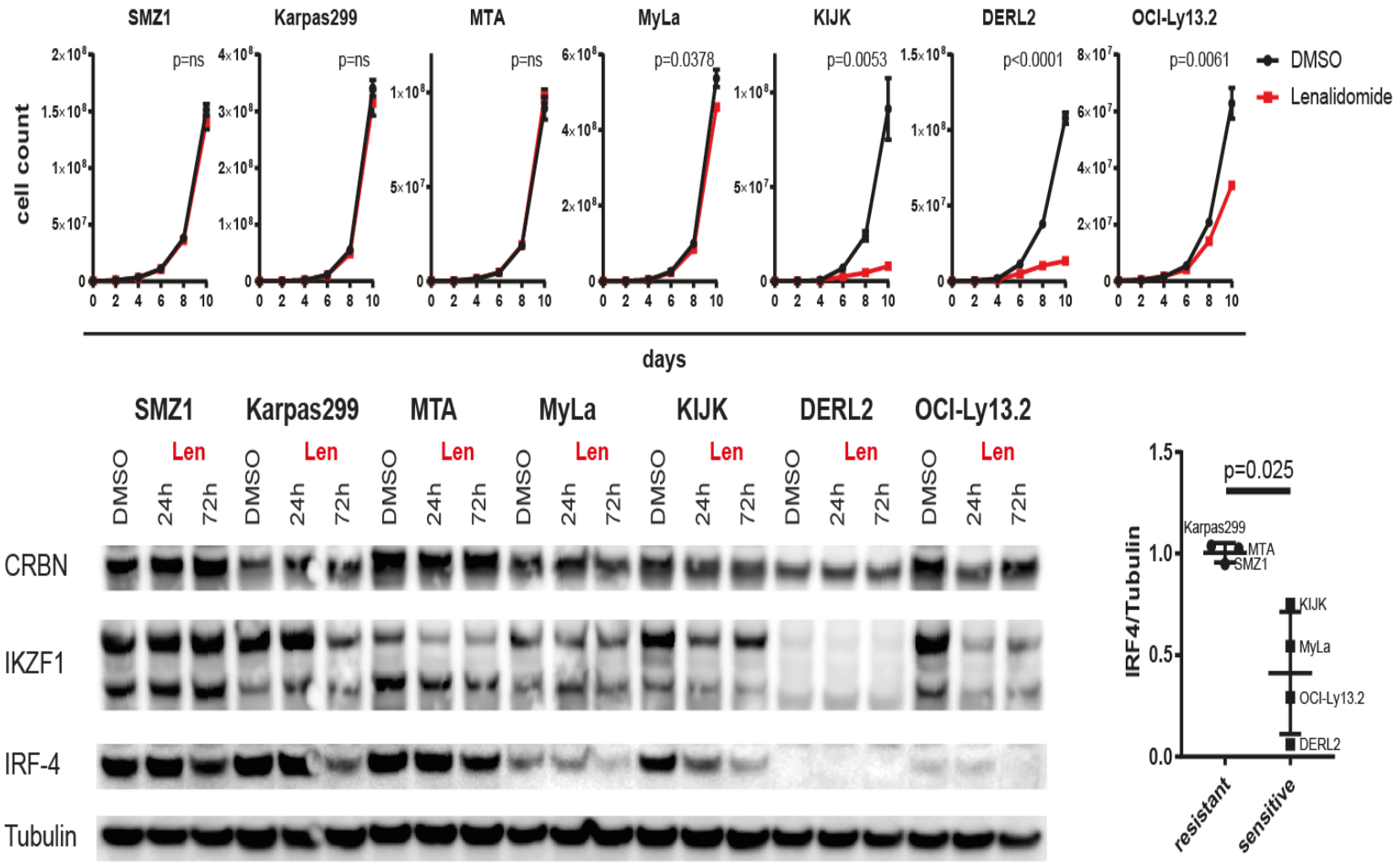
Differential Responses in PTCL

Combined Data Romidepsin + Lenalidomide +/- Carfilzomib

	N	CR	PR	ORR
PTCL-NOS	13	1	3	4/13 (31%)
AITL*	7	4	3	7/7 (100%)

Mehta-Shah et al. ASH 2017

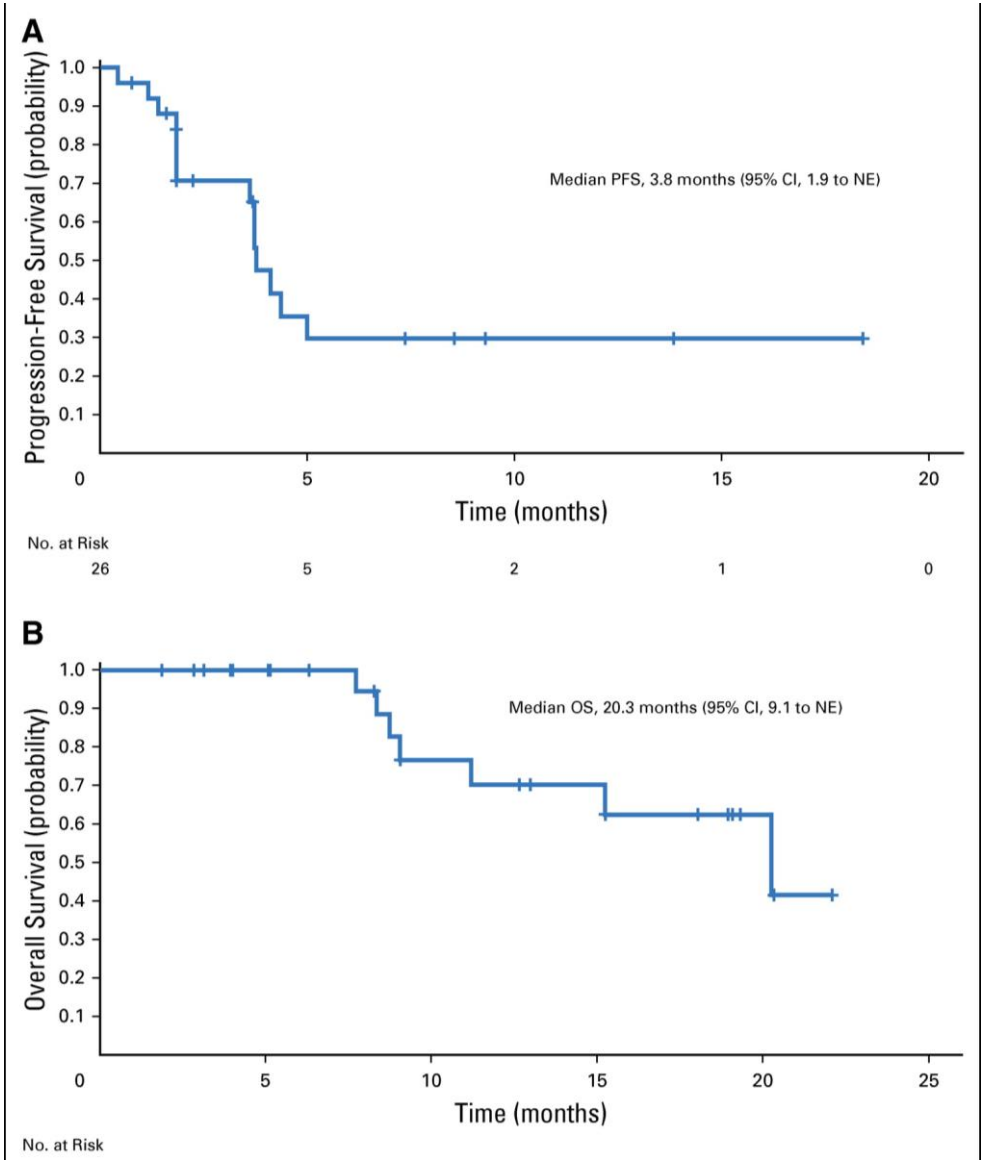
Lenolidamide activity in TCL lines associates with low IRF4 expression



Ng et al. Nature Comm 2018 (in press)

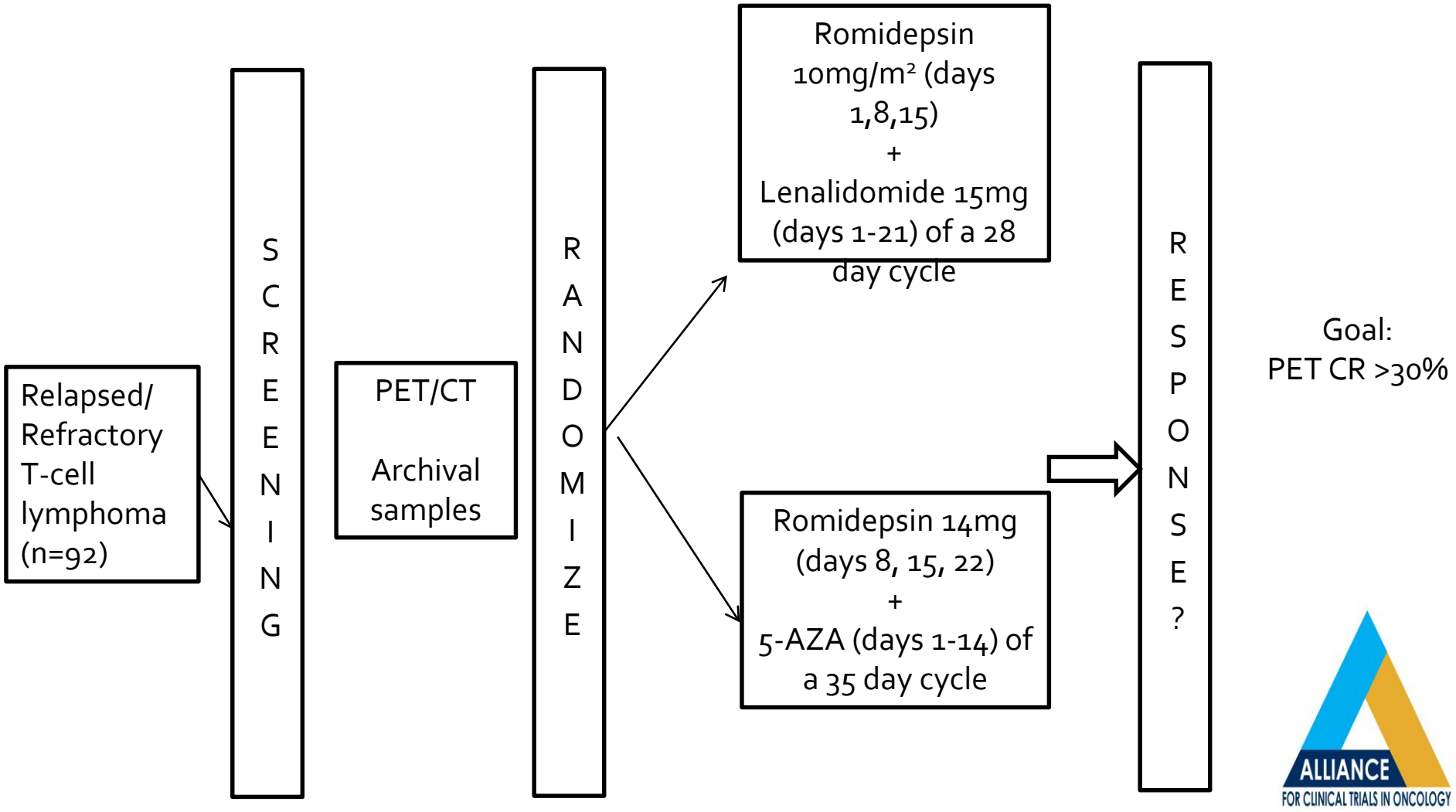
Lenalidomide in ATL

- lenalidomide 25 mg/d continuously
- overall response rate, 42% (11/26)
- PFS 3.8 months
- OS were 20.3 months



Ishida, et al. JCO 34, no. 34, 2016 4086-4093.

Proposed Trial



ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Memorial Sloan Kettering Cancer Center

Protocol Title: A Phase I/II Trial of CHOEP Chemotherapy plus Lenalidomide as Front Line Therapy for Patients with Stage II, III and IV Peripheral T-Cell Non-Hodgkin's Lymphoma

Lenalidomide-CHOEP in Untreated PTCL-T-cell Consortium

PI: S. Ansell, Mayo , Coord Center: UNMC: J. Vose, M. Lunning

- Newly diagnosed
- Stage II, III and IV
- PTCL-NOS ALK- ALCL, (ALK+ if IPI 3, 4, or 5), AITL, EATL, HSTCL

Phase 1: 3+3

Dose level	Dose	Day of the 21-day cycle
-1	Lenalidomide 5 mg	Day 1-10
1 (starting dose level)	Lenalidomide 10 mg	Day 1-10
2	Lenalidomide 15 mg	Day 1-10
3	Lenalidomide 20 mg	Day 1-10

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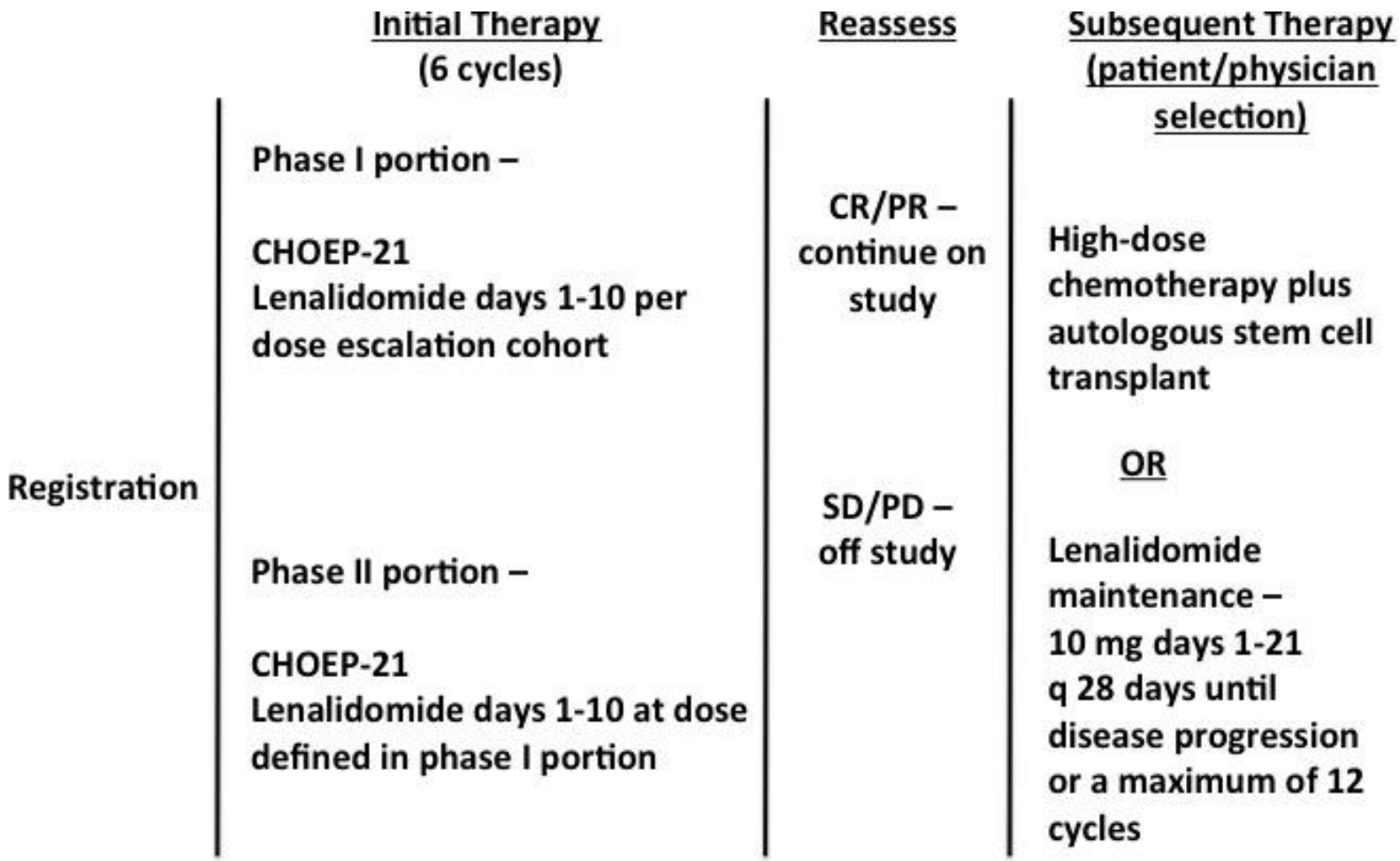

CHOEP-Len: Phase I-II: Phase I Results

(n = 12)	AE's Occurring in ≥ 15% of Patients		AE's Occurring in ≥ 15% of Patients	
Adverse Events	*Grade 3/4*		*Grade 3/4 in Cycles 4-6*	
	N	%	N	%
Lymphopenia	**8**	**67**	**8¥**	**67**
Neutropenia	**9**	**75**	**8¥**	**67**
Anemia	**6**	**50**	**4**	**33**
Leukopenia	**8**	**67**	**7**	**58**
Platelets	**5**	**42**	**4**	**33**
F & N	**4**	**33**	**2**	**17**

Subject	Histology	Dose	Response Cycle 6
1	PTCL-NOS	10 mg	CR
2	AITL	10 mg	PR
3	AITL	10 mg	PR
4	AITL	10 mg	PR
5	AITL	10 mg	CR
6	PTCL-NOS	10 mg	POD
7	AITL	10 mg	CR
8	AITL	10 mg	PR
9	PTCL-NOS	15 mg	CR
10	PTCL-NOS	15 mg	PR*
11	PTCL-NOS	15 mg	CR
12	AITL	15 mg	CR*

***Responses were after cycle 4**

ORR 92%, CR 40%

Len at a dose of 10 mg days 1-10 was R2P2 when combined with CHOEP.

Lunning et al TCF 2018

Lenalidomide in peripheral T cell lymphoma

Single agent

- Modest/Moderate activity –20-30% ORR
- May be higher activity in AITL
- May be higher in ATL
- Optimal use in TCL yet undefined

Combinations

- Attractive combination partner, activity, toxicity, route of administration
- HDACs, Proteasome Inhibitors, chemotherapy, etc.

Biomarker

- IRF_4