Memorial Sloan Kettering Cancer Center

Lenalidomide and… Combination studies in PTCL

Steven M. Horwitz M.D.
Associate Attending
Lymphoma Service
Memorial Sloan Kettering Cancer Center

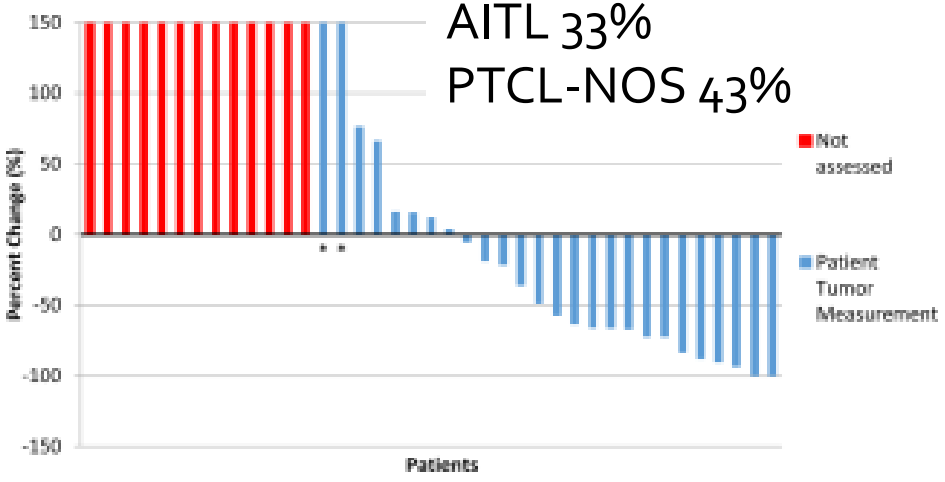
Associate Professor of Medicine
Weill Cornell Medical College

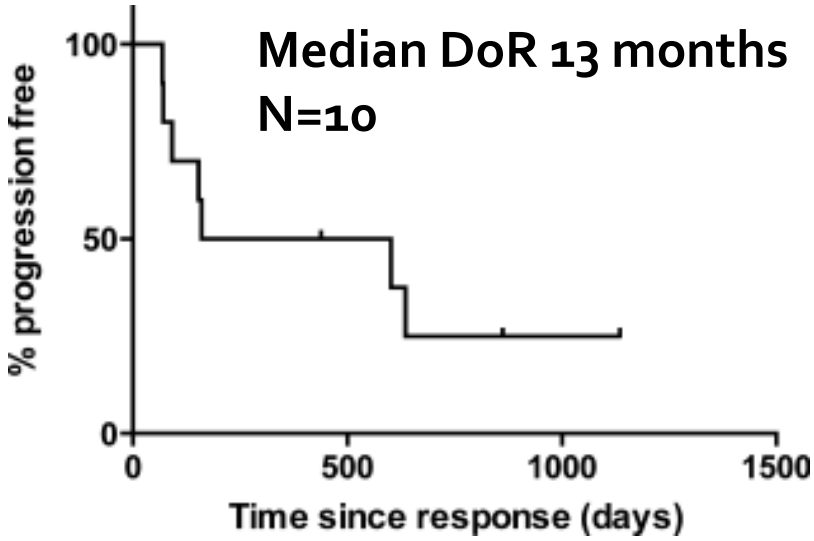
Lenalidomide in T-cell Lymphoma: Single Agent

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%

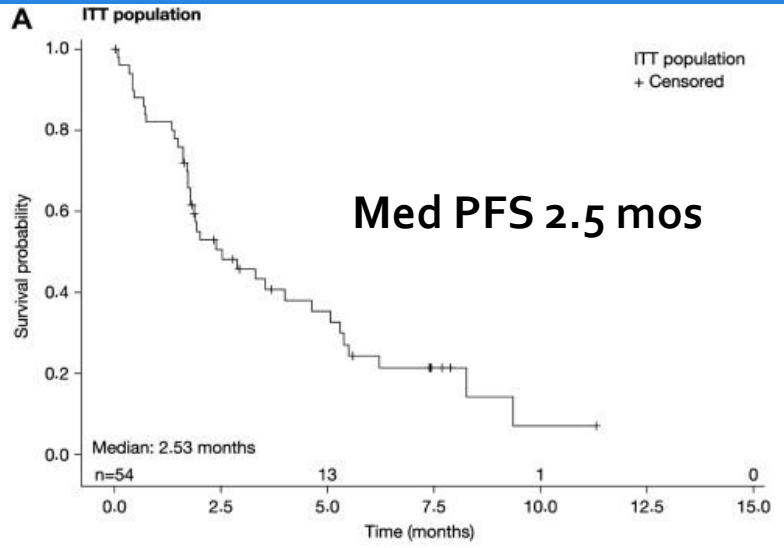


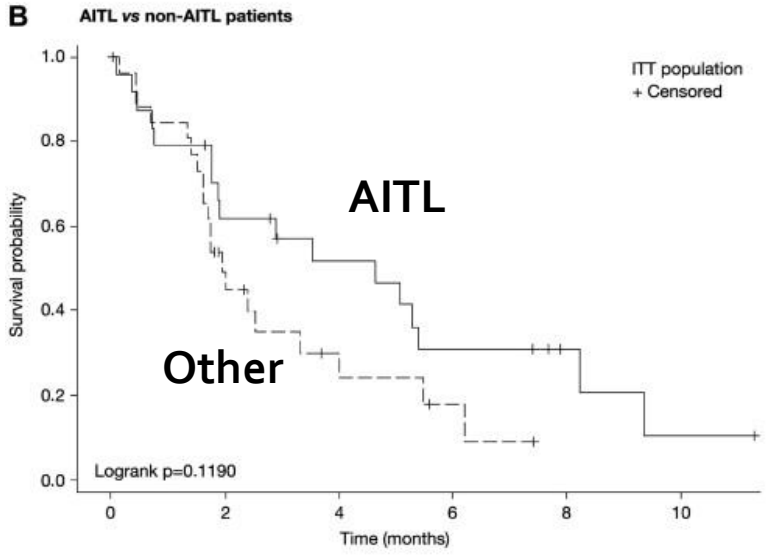


Lenalidomide 25 mg/day; D1-21 of a 28 day cycle

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

Lenalidomide with vorinostat and dexamethasone for relapsed/refractory peripheral T cell lymphoma (PTCL): phase I/II trial

Phase 1

- Vorinostat at 400 mg/day (fixed dose, days 1–21),
- Dexamethasone at 40 mg/day (fixed dose, days 1, 8, and 15),
- Lenalidomide (dose escalation, days 1–21),

Dose escalation on lenalidomide was planned- 3+3 dose design

- level I: 10 mg
- level II, 15 mg
- level III, 20 mg
- level IV, 25 mg per daywas applied.

MTD of lenalidomide was found to be 5 mg/day (level -I)

- DLTs (thrombocytopenia grade 3, stroke grade 4).

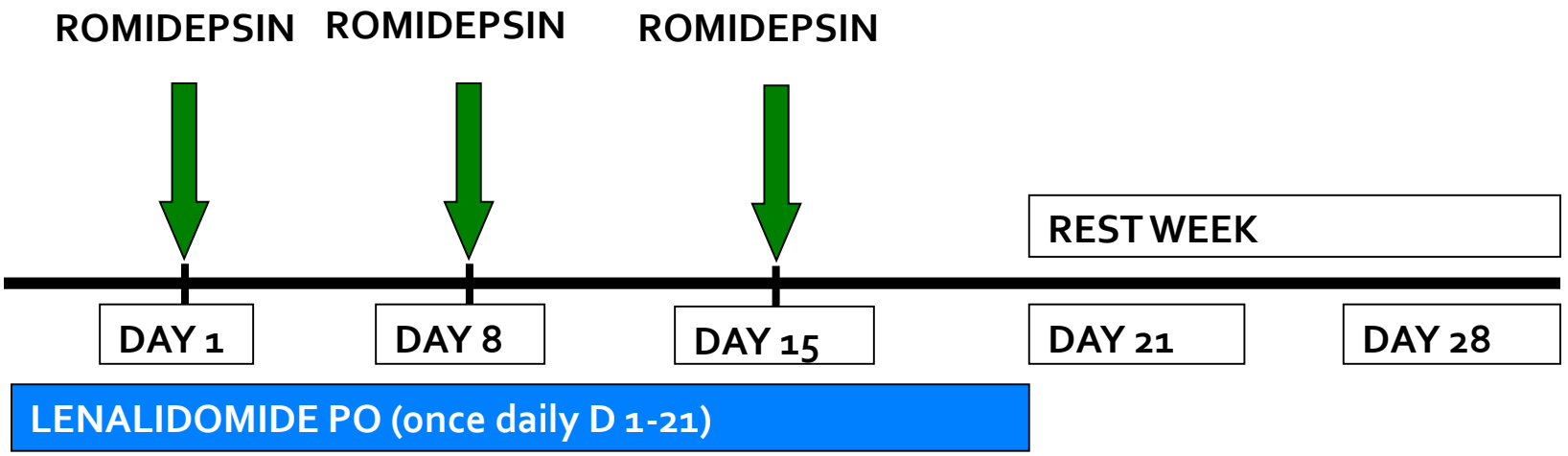
ORR of 25 %.

Based on the poor response, the trial was stopped when phase I was completed.

Hopfinger et al. Ann Hematol (2014) 93:459–462

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

A Phase Ib/IIa Study of Romidepsin-Lenalidomide: Toxicity: Related in ≥2 Subjects

Toxicity (Related)	Grade 1	Grade 2	Grade 3
Anorexia	4 (20%)		
Blood bilirubin increase	3 (15%)		
Constipation	5 (25%)		
Creatinine increase	3 (15%)		
Diarrhea	3 (15%)		
Dysgeusia	9 (45%)		
Fatigue	7 (35%)		
Nausea	6 (30%)		
Neutropenia		3 (15%)	6 (30%)
Thrombocytopenia	7 (35%)	4 (20%)	5 (25%)
Weight loss	7 (35%)		

No thromboembolic events to date, subjects recommended but not required to take ASA

A Phase Ib/IIa Study of Romidepsin-Lenalidomide: Toxicity: Grade 3-4, Any

Toxicity (related and unrelated)	Grade 3	Grade 4
Electrolyte Abnormalities	12 (60%)	1 (5%)
LFT Abnormalities	2 (10%)	
Neutropenia	8 (40%)	2 (10%)
Anemia	10 (50%)	
Lymphopenia	11 (55%)	5 (25%)
Thrombocytopenia	11 (55%)	3 (15%)
Amylase/Lipase	1 (5%)	
INR increase	1 (5%)	
Anorexia	1 (5%)	
Dehydration/Syncope	1 (5%)	
Fatigue	1 (5%)	
Pneumonia	1 (5%)	
Leukopenia	6 (30%)	3 (15%)

A Phase Ib/IIa Study of Romidepsin-Lenalidomide: Response Phase Ib

Cohorts	# pts (evaluable/ total)	Complete Response	Partial Response
1	3/4	1	2
2	7/7	0	3
3	2/5	0	0
4	6/7	1	1
TOTAL	18/23*	2	8

Disease	# pts (evaluable)	Overall response rate	Complete Response	Partial Response
Hodgkin	4	2/4 (50%)	0	2
B-cell	8	4/8 (50%)	2	2
T-cell	6	4/6 (66%)	0	4
TOTAL	18	10/18 (55%)	2	8

A Phase Ib/IIa Study of Romidepsin-Lenalidomide:

- Final results (lymphoma) to be presented this summer
- N=43
- TCL 21 (10 CTCL, 11 PTCL)

- Of the 30 pts treated at the MTD
- 17 required subsequent dose reductions.
- Most common reason for dose reduction were:
  - Neutropenia
  - Thrombocytopenia
  - Fatigue.

- Of the 25 pts (58%) on therapy for ≥4 cycles, the median maintenance dose was romidepsin 8mg/m^2 and lenalidomide 15mg.

A Phase Ib/IIa Study of Romidepsin-Lenalidomide-Carfilzomib

NCCN Supported collab w/UNMC: M. Lunning, J. Vose,

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 Maximum Tolerated Dose

↙ ↘

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

The Effect of Lenalidomide Combined with R-CHOP (R2CHOP) on Negative Prognostic Impact of non-Germinal Center (non-GCB) Phenotype in Newly Diagnosed Diffuse Large B-cell Lymphoma: A phase 2 Study

Grzegorz S. Nowakowski, Betsy LaPlant, Craig B. Reeder, James M. Foran, Luis F. Porrata, William R. Macon, Patrick B. Johnston, Candido E. Rivera, Thomas M. Habermann, David J. Inwards, Ivana N. Micallef, Patrick B. Johnston, Carrie Thompson, Garth D. Nelson, Stephen M. Ansell and Thomas E. Witzig

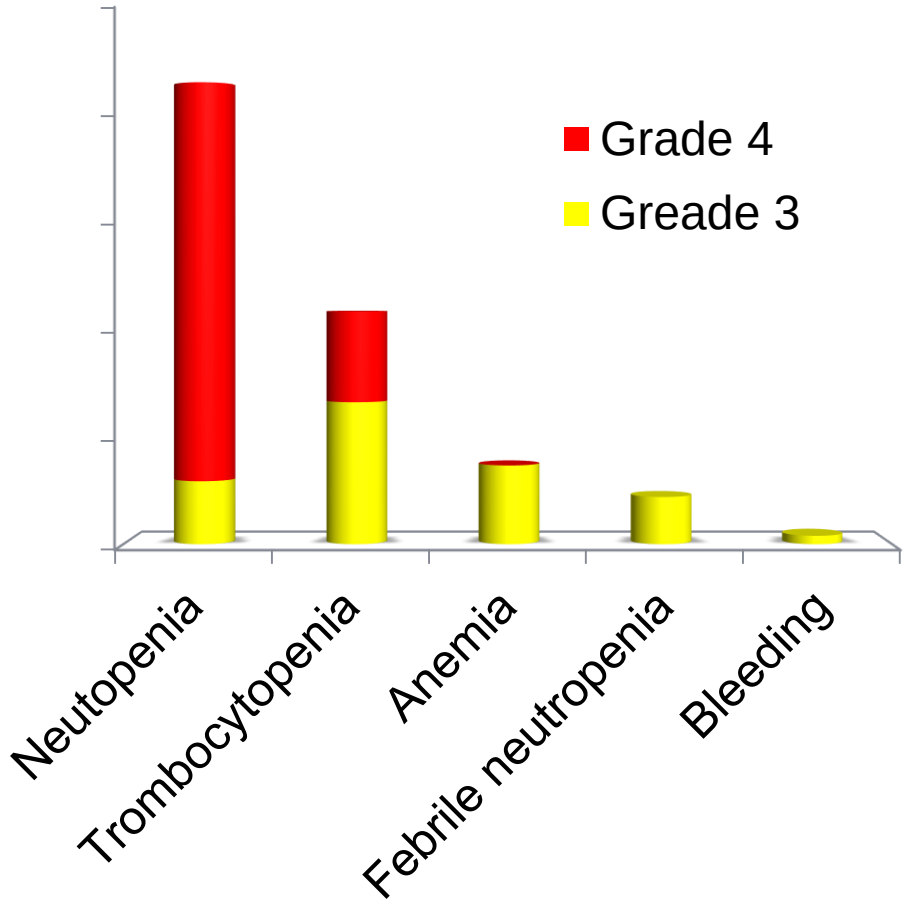
Mayo Clinic, USA

Presented at ASCO 2014

R2CHOP Treatment Schedule
MTD phase 1; Toxicity

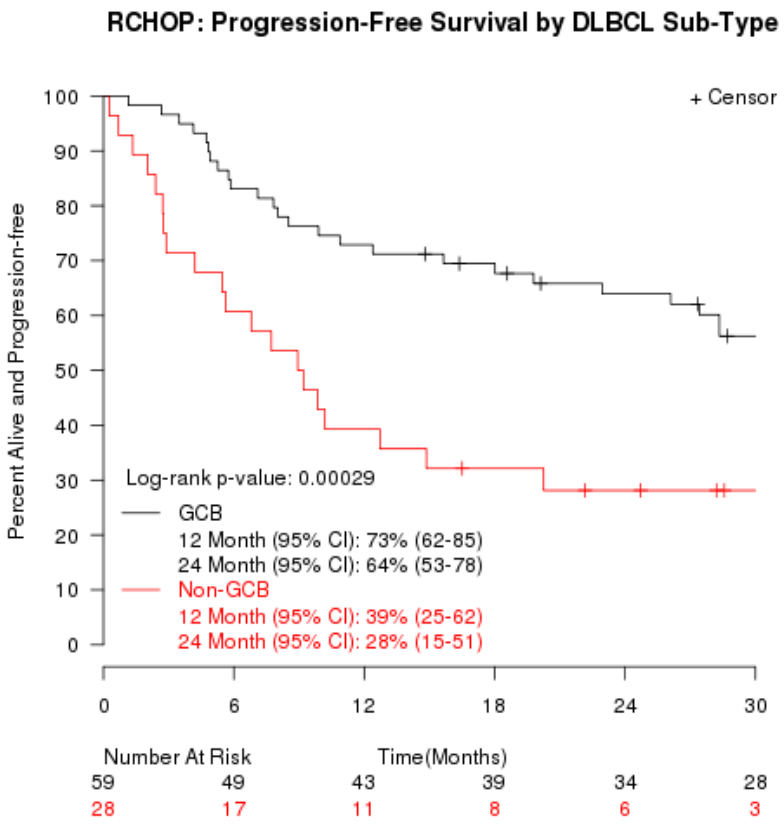
Cycle = 21 days; 6 Cycles of Treatment

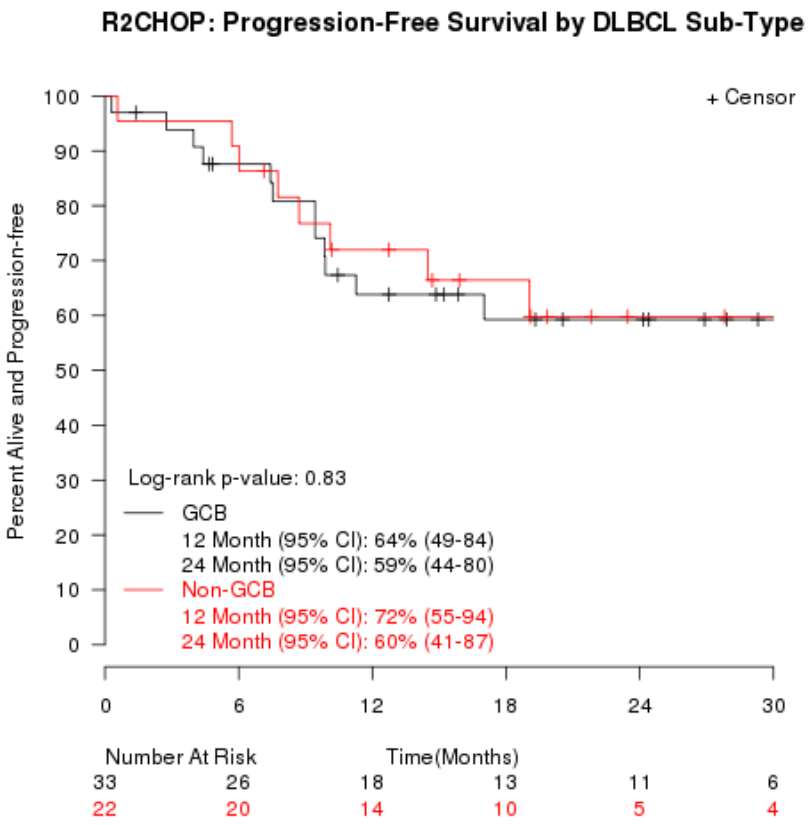
Agent	Dose	Route	Day
Lenalidomide	**25 mg**	**po**	**1-10**
Rituximab	375 mg/m^2	IV	1
Cyclopho	750 mg/m^2	IV	1
Doxorub	50 mg/m^2	IV	1
Vincristine	1.4 mg/m^2	IV	1
Pred	100 mg/m^2	po	1-5
Peg-G	*6 mg*	*SC*	*2*
Aspirin	*325 mg*	*po*	*daily*



Presented by: Nowakowski et al ASCO 2014.

PFS by GCB vs. non-GCB Subtype* in RCHOP Case-matched Control and R2CHOP Patients





* As defined by Hans et Al. Blood 2004

Presented by: Nowakowski et al ASCO 2014.

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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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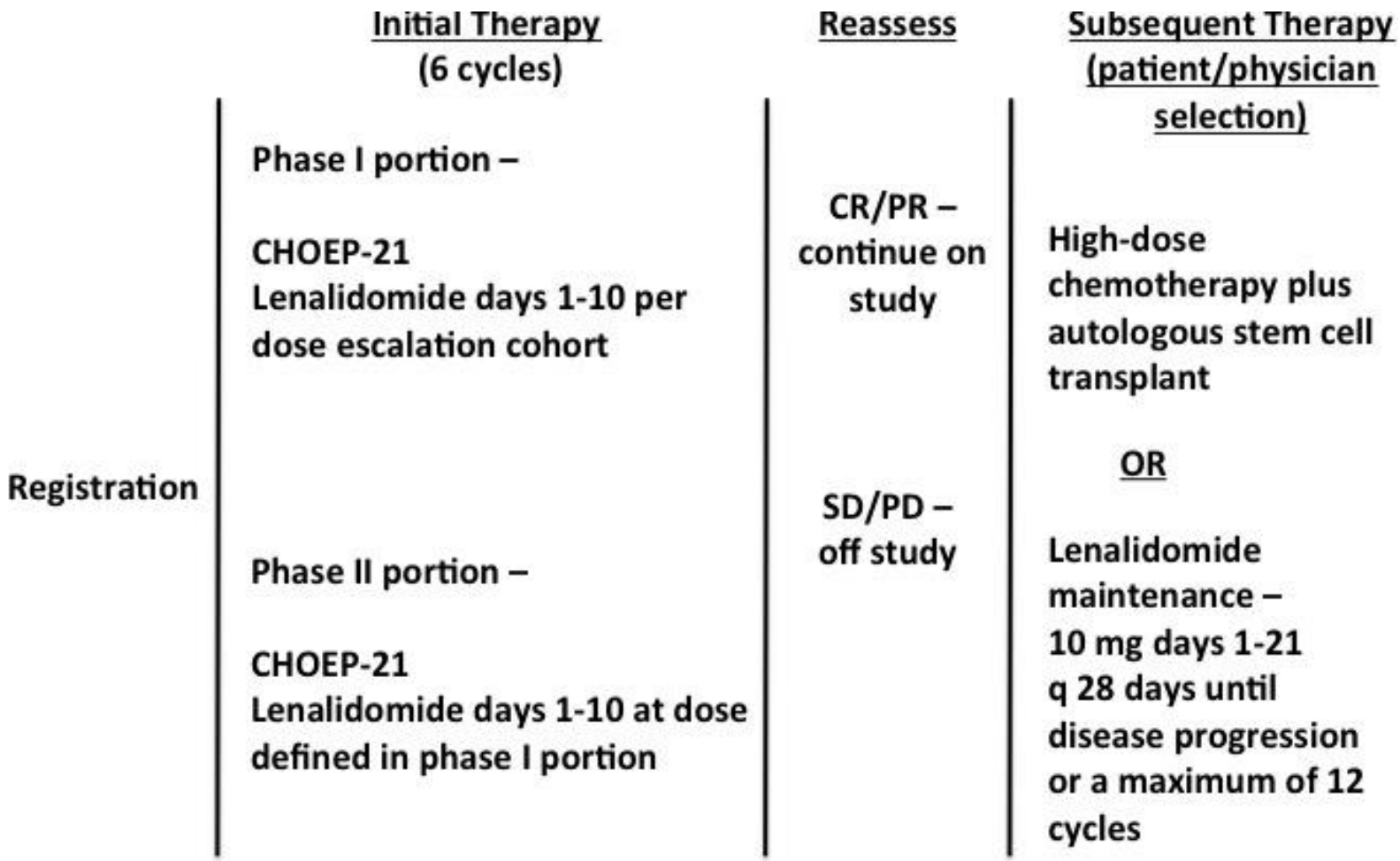

Lenalidomide in peripheral T cell lymphoma

Single agent

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

Combinations

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

Strategies

- Novel combination regimen
- Addition to standard upfront therapy