The Combination of Duvelisib, a PI3Kδ,γ Inhibitor, and Romidepsin Is Highly Active in Relapsed/Refractory Peripheral T-cell Lymphoma with Low Rates of Transaminitis: Results of Parallel Multicenter, Phase 1 Combination Studies with Expansion Cohorts

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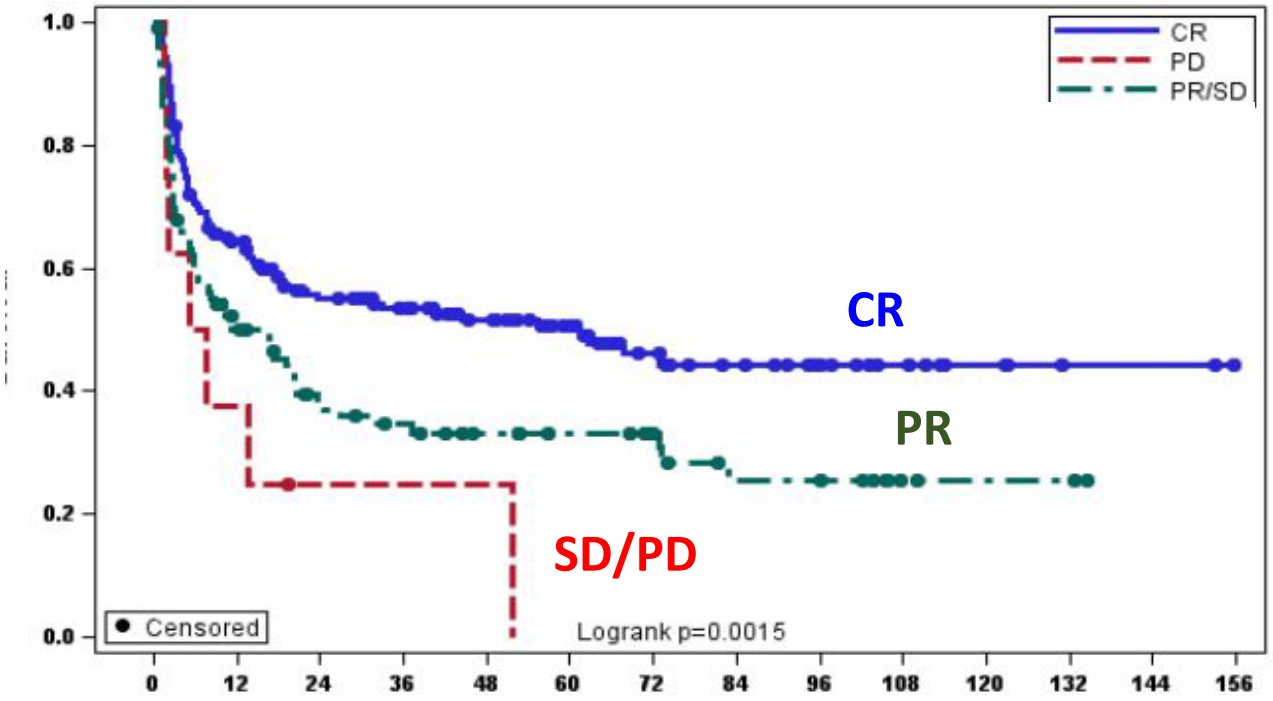
Relapsed/Refractory PTCL

Outcomes	ORR	CR	Median PFS
Pralatrexate N=109	29%	11%	3.5 mos
Romidepsin N=131	25%	15%	4 mos
Belinostat N=129	26%	11%	1.6 mos
Brentuximab (PTCL) N=34	41%	24%	6.7 mos
Brentuximab (ALCL) N=56	86%	59%	14.6 mos

O' Connor OA, et al. *J Clin Oncol*. 2011;29:1182-1189
Coiffier B, et al. *J Clin Oncol*. 2012;30 :631-636
O'Connor OA, et al. *J Clin Oncol*. 2015; 33:2492-2499.
Horwitz et al. Blood 2014 123:3095-3100
Pro B, et al. J Clin Oncol. 2012;30:2190-2196

Progression Free Survival post Allogeneic SCT



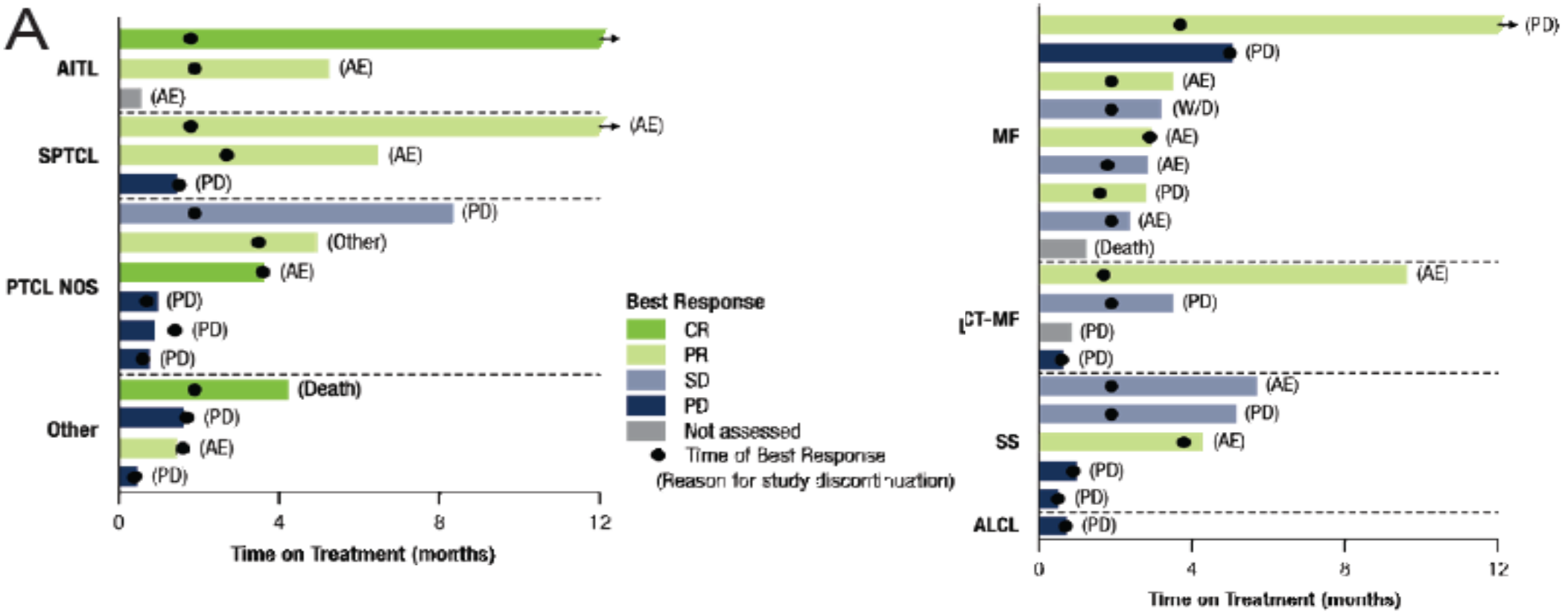
Median PFS (months)	
CR	**61.3**
PR/SD	**11.4**
PD	**6.4**

Mehta-Shah et al. ASH 2017

Duvelisib, PI3K-δγ Inhibitor, in T-cell Lymphoms

ORR in PTCL (N=16) : 50%
CR 3 (19%)
Median PFS 8.3 months

ORR in CTCL (N=19): 32%
CR 0
Median PFS 4.5 months



Most patients treated at 75 mg BID

Horwitz et al. Blood. 2018 Feb 22;131(8):888-898

Rationale

- Adding active agents to try to increase efficacy:
  - ORR, CR (bridge to transplant), durability of response
- Preclinical data suggests an epigenetic mechanism could mitigate the effects of PI3K inhibition in resistant lines.
- Cell line data demonstrates that PI3K-inhibitors may have a synergistic effect in inducing apoptosis when combined with HDAC inhibitors.
- Genomic data (largely in CTCL) supported combining PI3K and NF-κB inhibition.

Horwitz et al. Blood. 2018 Feb 22;131(8):888-898
Ungewickell et al., *Nature Genetics* 47, 1056–1060 (2015)

Study Objectives

Primary Endpoint:

- To define the MTD of the combinations of duvelisib + romidepsin, and duvelisib + bortezomib

Secondary Objectives:

- To characterize the safety and toxicity
- To assess the ORR, CR, TTR,DOR, PFS
- To collect tissue for exploratory and translational biologic studies

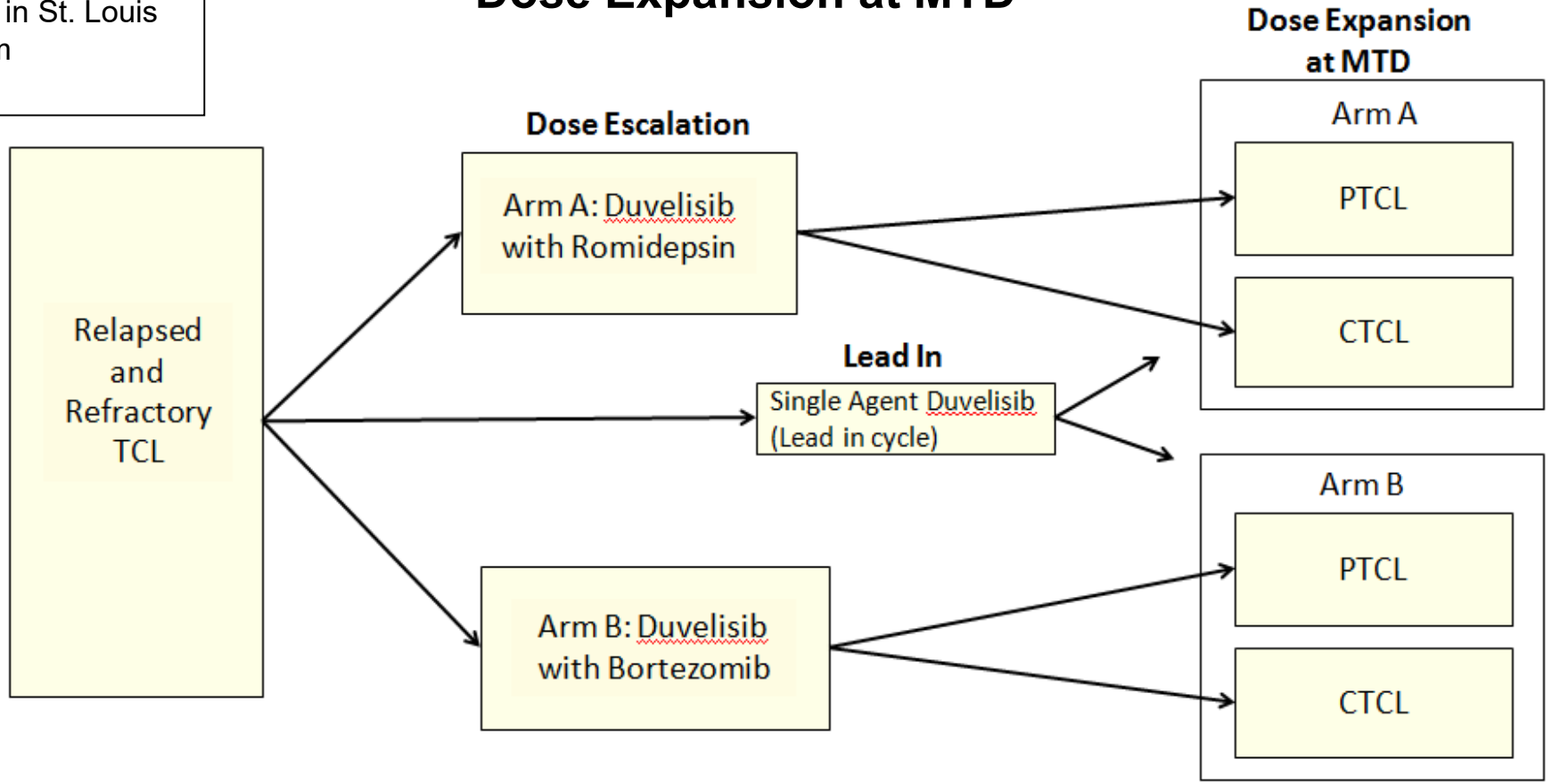
Exploratory Endpoints:

- Correlation of response with prior therapy
- Tissue collection for investigating predictors of response or resistance to therapy

SCOR IIT: A Phase I Trial of Duvelisib (IPI-145) in Combination with Either Romidepsin or Bortezomib in Relapsed/Refractory T-cell Lymphoma

Participating Institutions
Memorial Sloan Kettering
Dana Farber Cancer Institute
Stanford University
Washington University in St. Louis
Funding from Verastem
Support from the LLS

Parallel Phase I: 3+3 Design with Dose Expansion at MTD



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Patient Characteristics

Characteristics	n = 80
Median age (range)	64 (28-83)
Male, n (%)	46 (57%)
Prior # therapies, median (range)	3 (1-16)
Prior Transplants, n (%)	13 (16%)
Autologous	11 (14%)
Allogenic	2 (3%)
Race	
White	63
African-American or Black	10
Asian	3
Not Reported	4

Diagnosis	n = 80
Peripheral T-Cell Lymphoma	**51**
Cutaneous T-Cell Lymphoma	**29**

Phase 1 – Dose Escalation

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

MTD Arm B: Dose Level 1
Bortezomib (1.0mg/m2 SQ)
Duvelisib (25mg PO, BID)

ARM A – Duvelisib + Romidepsin

Dose Level	#pts treated	#pts evaluable for MTD	#pts with DLT
DL1 Romidepsin (10mg/m2 IV) + Duvelisib (25mg PO, BID)	4	3	0
DL2 Romidepsin (10mg/m2 IV) + Duvelisib (50mg PO, BID)	3	3	0
DL 3 Romidepsin (10mg/m2 IV) + Duvelisib (75mg PO, BID)	4	3	0

ARM B – Duvelisib + Bortezomib

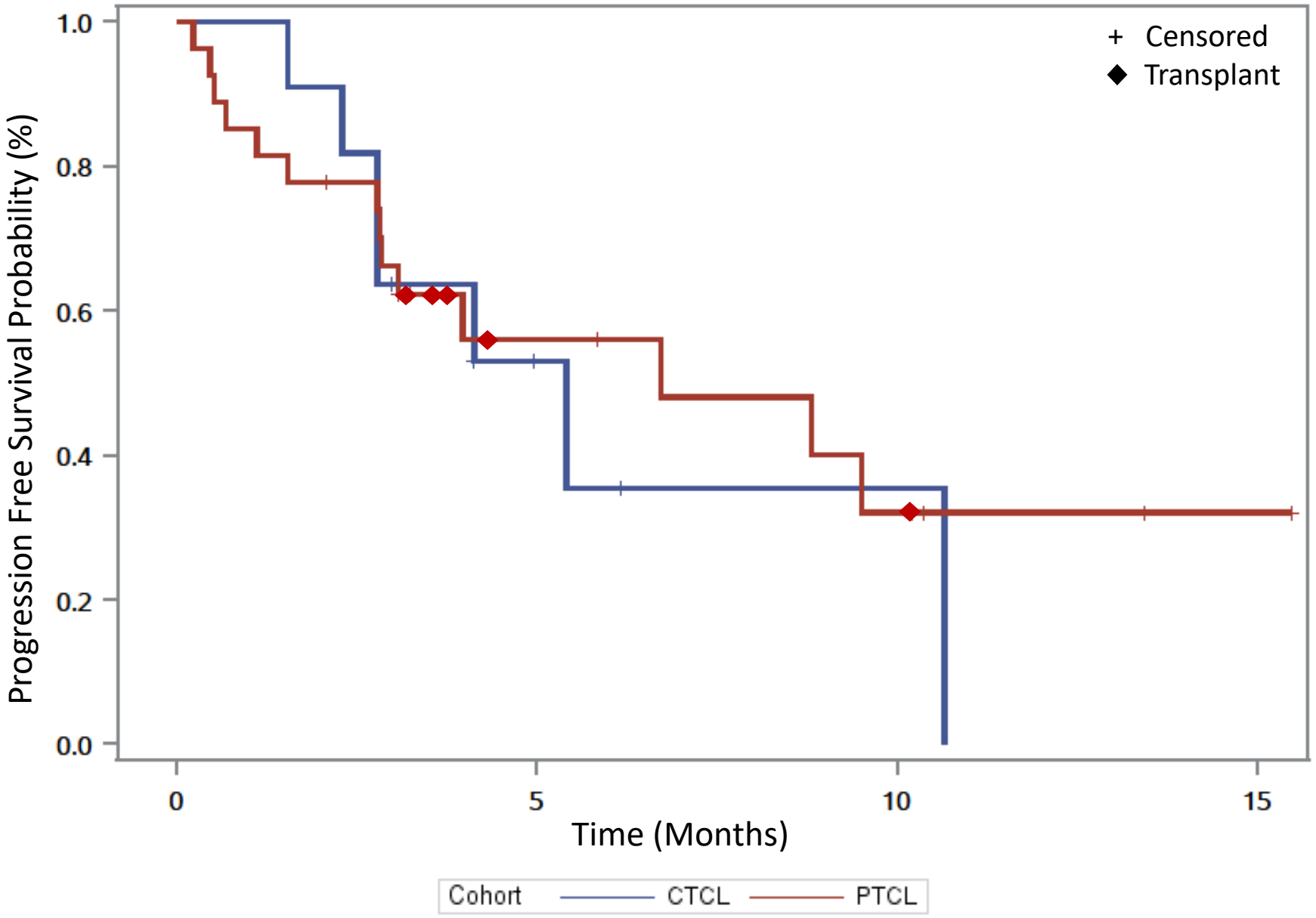
Dose Level	#pts treated	#pts evaluable for MTD	#pts with DLT
DL1 Bortezomib (1.0mg/m2 SQ) + Duvelisib (25mg PO, BID)	6	8	1*
DL2 Bortezomib (1.0mg/m2 SQ) + Duvelisib (50mg PO, BID)	3	3	0 (3**)
DL3 Bortezomib (1.0mg/m2 SQ) + Duvelisib (75mg PO, BID)	5	6	0 (3**)

**DLT: Grade 3 Neutropenia*
***experienced LFT toxicities after DLT reporting period*

Response: Duvelisib and Romidepsin (Arm A) by Histology
All Dose Levels

Histology	Patients	ORR	CR
Peripheral T-Cell Lymphoma	**27**	**16 (59%)**	**9 (33%)**
AITL/ TFH	8	6 (75%)	5 (63%)
PTCL, NOS	11	7 (64%)	4 (36%)
Hepatosplenic TCL	2	1 (50%)	0
Aggressive epidermotropic CD8+ TCL	2	1 (50%)	0
Primary cutaneous PTCL	1	1 (100%)	0
Primary cutaneous Gamma-delta (γδ)	2	0%	0
T-PLL	1	0%	0
Cutaneous T-Cell Lymphoma	**11**	**5 (45%)**	**0**
Sezary Syndrome	4	2 (50%)	0
Mycosis Fungoides	7	3 (43%)	0
*Large Cell Transformation**	*4*	*1 (25%)*	*0*
Overall	**38**	**21 (55%)**	**9 (24%)**

Arm A – Progression-Free Survival, all dose levels



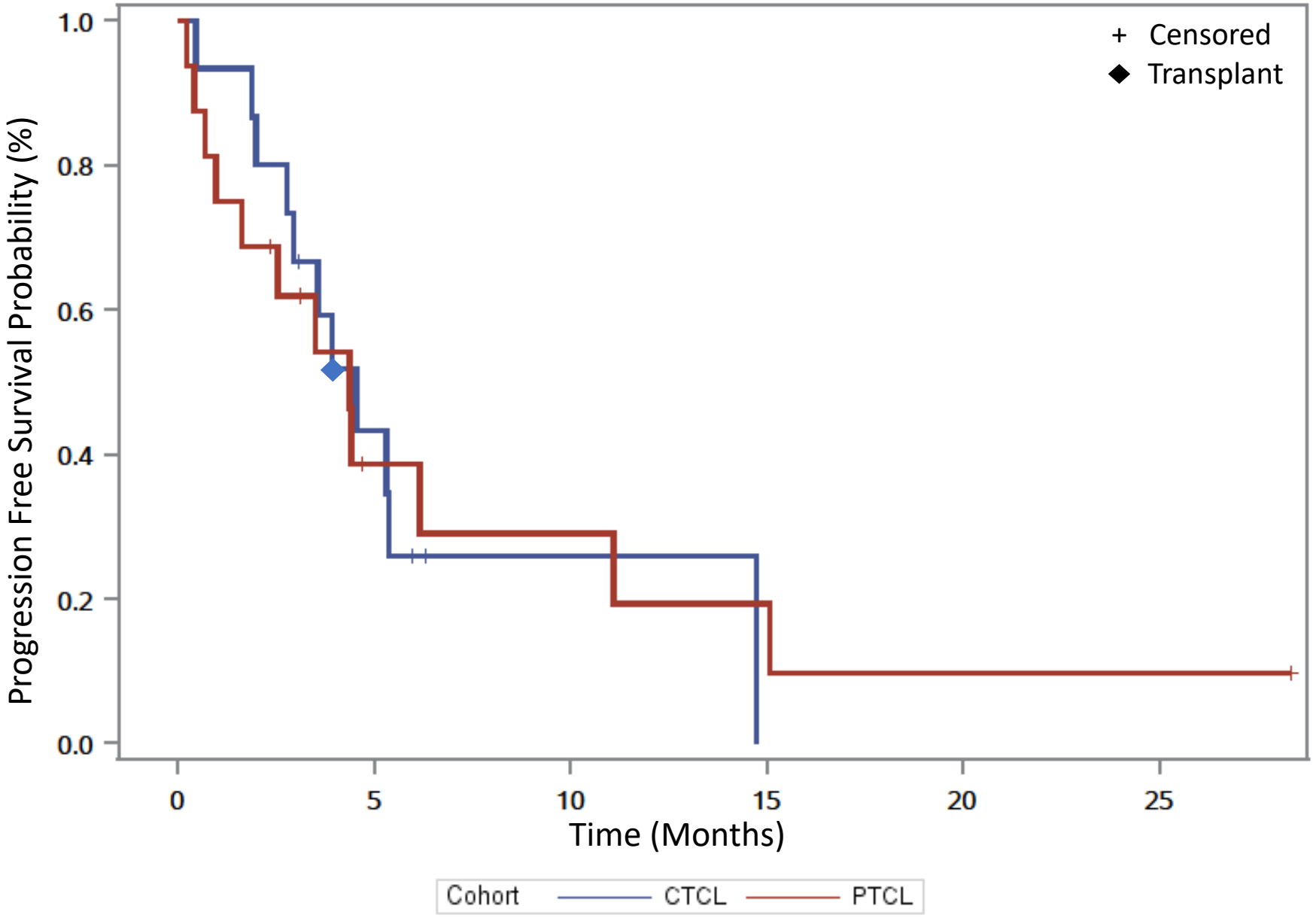
CTCL
n=11; censored=4
Median PFS: 5.41 Mos
CI: 2.30-10.66

PTCL
n=27; censored=13
Median PFS: 6.72 Mos
CI: 2.82-NR
6 (22%) → Transplant

Response: Duvelisib and Bortezomib (Arm B) by Histology
All Dose Levels

Histology	Patients	ORR	CR
Peripheral T-Cell Lymphoma	**16**	**7 (44%)**	**4 (25%)**
AITL/TFH	4	3 (75%)	2 (50%)
PTCL, NOS	8	4 (50%)	2 (25%)
ALCL	2	0%	0
Extranodal Nasal NK/TCL	1	0%	0
ATLL	1	0%	0
Cutaneous T-Cell Lymphoma	**15**	**4 (27%)**	**0**
Sezary Syndrome	6	3 (50%)	0
Mycosis Fungoides	9	1 (11%)	0
*Large Cell Transformation**	*6*	*0*	*0*
Overall	**31**	**11 [35%]**	**4 (13%)**

Arm B – Progression-Free Survival, all dose levels



CTCL
n=15; censored=4
Median PFS: 4.56 Mos
CI: 2.00-14.75
1 patient → Transplant

PTCL
n=16; censored=4
Median PFS: 4.39 Mos
CI: 0.98-11.11

Response: Single Agent Duvelisib Lead In Cycle

Pts LEAD IN cycle	
Dose	N
DL 3; Duvelisib (75mg PO, BID)	14
DL1 Duvelisib (25mg PO, BID)	12

Response: Single Agent Duvelisib Lead In Cycle

Pts LEAD IN cycle	
Dose	N
DL 3; Duvelisib (75mg PO, BID)	14
DL1 Duvelisib (25mg PO, BID)	12

Response post lead in cycle - Arm A	
CR	29% [4/14]
PR	21% [3/14]
ORR - single agent lead in	50% [7/14]

Response: Single Agent Duvelisib Lead In Cycle

Pts LEAD IN cycle	
Dose	N
DL 3; Duvelisib (75mg PO, BID)	14
DL1 Duvelisib (25mg PO, BID)	12

Response post lead in cycle - Arm A	
CR	29% [4/14]
PR	21% [3/14]
ORR - single agent lead in	50% [7/14]

Response to Arm A Duv + Romi	
CR	10% [1/10]
PR	30% [3/10]
ORR - Combo	40% [4/10]

Response: Single Agent Duvelisib Lead In Cycle

Pts LEAD IN cycle	
Dose	N
DL 3; Duvelisib (75mg PO, BID)	14
DL1 Duvelisib (25mg PO, BID)	12

Response post lead in cycle - Arm A	
CR	29% [4/14]
PR	21% [3/14]
ORR - single agent lead in	50% [7/14]

Response to Arm A Duv + Romi	
CR	10% [1/10]
PR	30% [3/10]
ORR - Combo	40% [4/10]

Response post lead in cycle - Arm B	
CR	25% [3/12]
PR	17% [2/12]
ORR - single agent lead in	41% [5/12]

Response: Single Agent Duvelisib Lead In Cycle

Pts LEAD IN cycle	
Dose	N
DL 3; Duvelisib (75mg PO, BID)	14
DL1 Duvelisib (25mg PO, BID)	12

Response post lead in cycle - Arm A	
CR	29% [4/14]
PR	21% [3/14]
ORR - single agent lead in	50% [7/14]

Response to Arm A Duv + Romi	
CR	10% [1/10]
PR	30% [3/10]
ORR - Combo	40% [4/10]

Response post lead in cycle - Arm B	
CR	25% [3/12]
PR	17% [2/12]
ORR - single agent lead in	41% [5/12]

Response to Arm B Duv + Bortez	
CR	10% [1/9]
PR	20% [2/9]
ORR - Combo	33% [3/9]

ARM A (Duvelisib + Romidepsin): Gr. 3-4 Adverse Events

occurring in ≥10% of patients

Event	Total # of patients at MTD n=31
Transaminase	**7 (23%)**
ALT	**5 (16%)**
AST	**2 (6%)**
Diarrhea	**6 (19%)**
Hyponatremia	4 (13%)
Neutrophil count decreased	10 (32%)
Platelet count decreased	3 (10%)

ARM B (Duvelisib + Bortezomib): Gr. 3-4 Adverse Events

occurring in ≥10% of patients

Event	Total # of patients at MTD n=23	initiated with single agent lead in cycle n=10	initiated with combination at MTD n=13
Transaminase*	2 (8%)	2 (20%)	0%
Alanine aminotransferase increased (ALT)	2 (4%)	1 (10%)	0%
Aspartate aminotransferase increased (AST)	1 (4%)	1 (10%)	0%
Neutrophil Count Decrease	5 (22%)	3 (30%)	2 (15%)

Conclusions

- MTD of Duvelisib in combination with Romidepsin was 75 mg bid vs 25 mg bid when combined with Bortezomib.
- Combination show reasonable safety and tolerability at MTDs
  - Not apparently in excess of single agents at MTD
  - Duvelisib in combination with Romidepsin *may* have less transaminitis when started simultaneously-allowing higher doses to be given for a longer duration of time
- Duvelisib in combination with Romidepsin is active with ORR 55% and CR 24%, (? PTCL>CTCL)
  - Median PFS 6 months, confounded by 6 subjects proceeded to allogeneic SCT
- Duvelisib in combination with Bortezomib ORR 35% and CR 14%, (? PTCL>CTCL)
- Single agent Duvelisib led to responses and CRs at both 75 mg bid and 25 mg bid

Further Questions

Samples avail # of patients	Baseline	On Tx	EOT/POD	Total
66	58	43	20	121

Translational biomarker component (Dave Weinstock)

- Multi-target immunofluorescence for immune subset analysis and macrophage polarization
- RNAseq
- Exome sequencing
- Quantitative Phosphoproteomics

Clinical Trials

- Further expansion of Duvelisib and Romidepsin for PTCL (phase 2; N=50)
- PRIMO Study (Verastem sponsor)
  - Phase 2 Single agent Duvelisib
  - Dose optimization in Cohort 1 (ongoing) allowing intra-patient dose escalation
  - Cohort 2, N=100 at “optimal” dose

Acknowledgments

Lymphoma DMT at MSK
Alison Moskowitz
Andrew Zelenetz
Lia Palomba
Anita Kumar
Paul Hamlin
Andy Intlekofer
Matt Matasar
Ariela Noy
David Straus
Gottfried von Keudell
Anas Younes
Connie Batlevi
Santosh Vardhana
Donald Colbourn
Ildefonso Rodriguez-Rivera
Paola Ghione
Joachim Yahalom
Ahmet Dogan
Oscar Lin
Travis Holmann
Patricia Myskowski
Sarah Noor

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Jasmine Zain, COH
Andrei Shustov, FHCRC
Pierluigi Porcu,TJU
Farhad Khimani, Moffit

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Jessie Schweiterman
Kristen McDaniels
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This is an investigator-sponsored trial (NCT02783625) with research support from the Leukemia & Lymphoma Society, Infinity Pharmaceuticals (Cambridge, MA) and Verastem, Inc. (Needham, MA)

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