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

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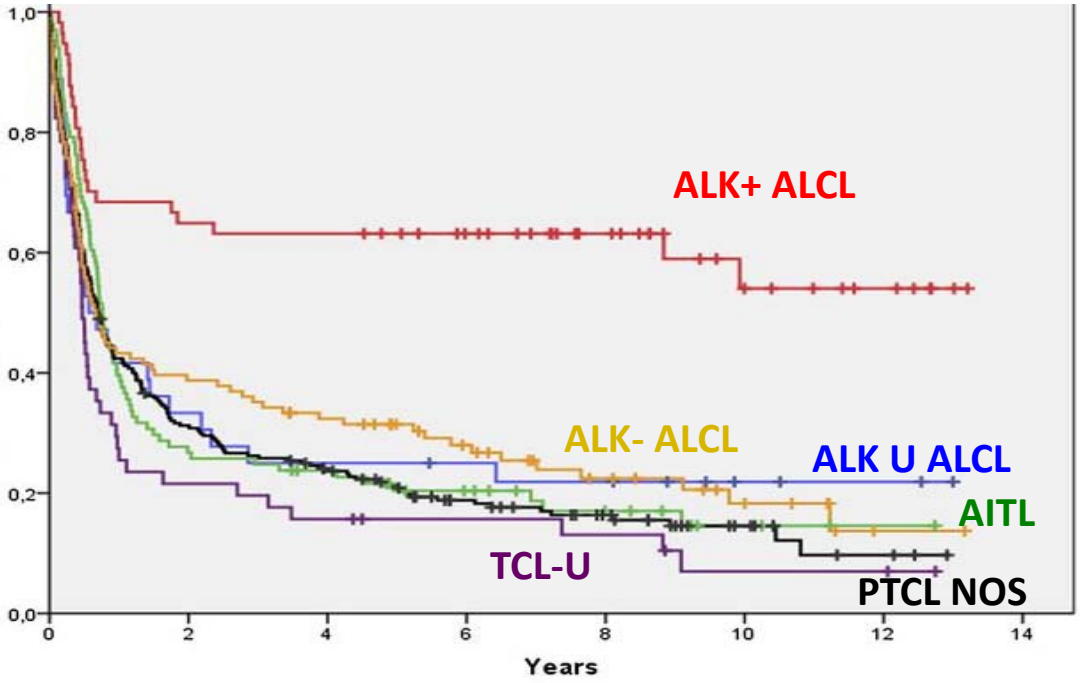
Unmet need for new strategies in T-cell lymphoma



FDA approved agents for R/R TCL

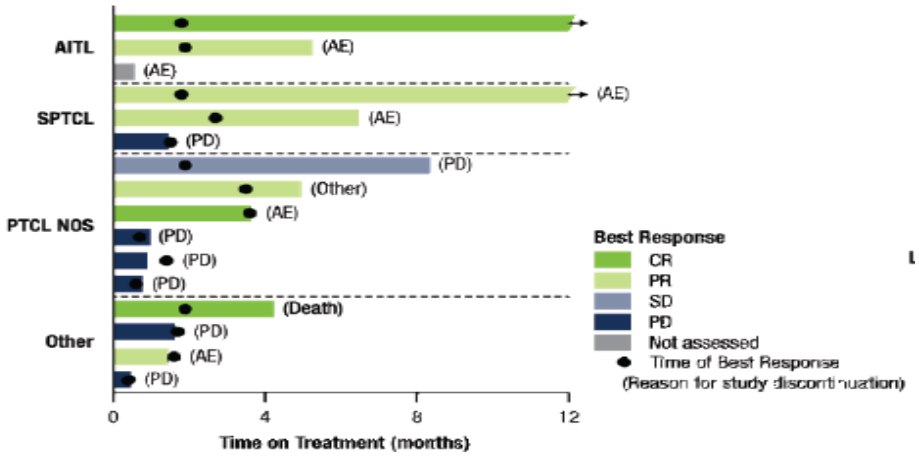
Drug	ORR
Pralatrexate	29%
Romidepsin	25%-38%
Belinostat	26%
Brentuximab vedotin	85% (ALCL)

Fredrik Ellin et al. Blood 2014;124:1570-1577 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. Pro B, et al. *J Clin Oncol*. 2012;30:2190-2196

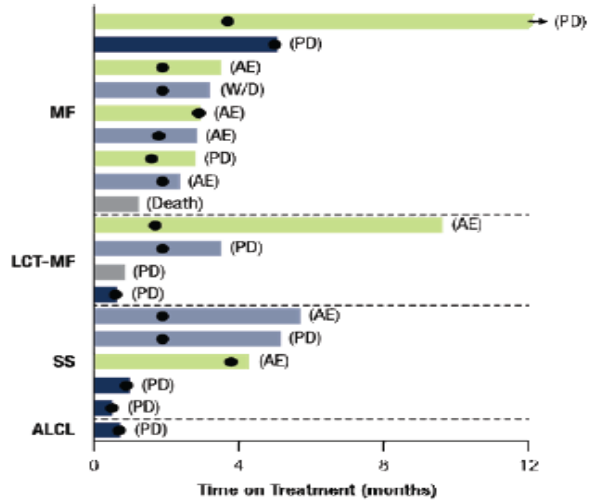
PI3K-δγ inhibition in T-cell lymphomas

- **Duvelisib**: an oral, dual inhibitor of PI3K-δ and PI3K-γ, demonstrated encouraging efficacy in TCL in a phase I study (**Horwitz, et al. Blood, in press**).

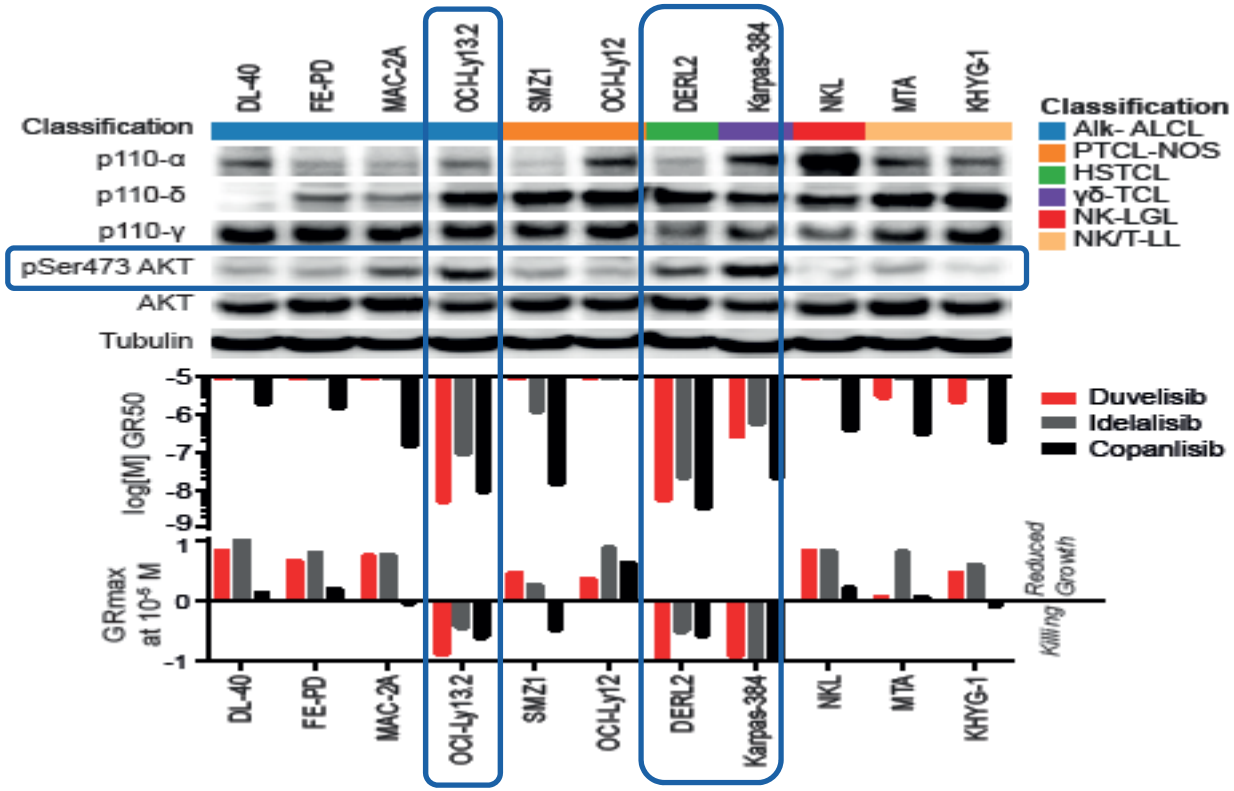
ORR in PTCL: 50%



ORR in CTCL: 32%

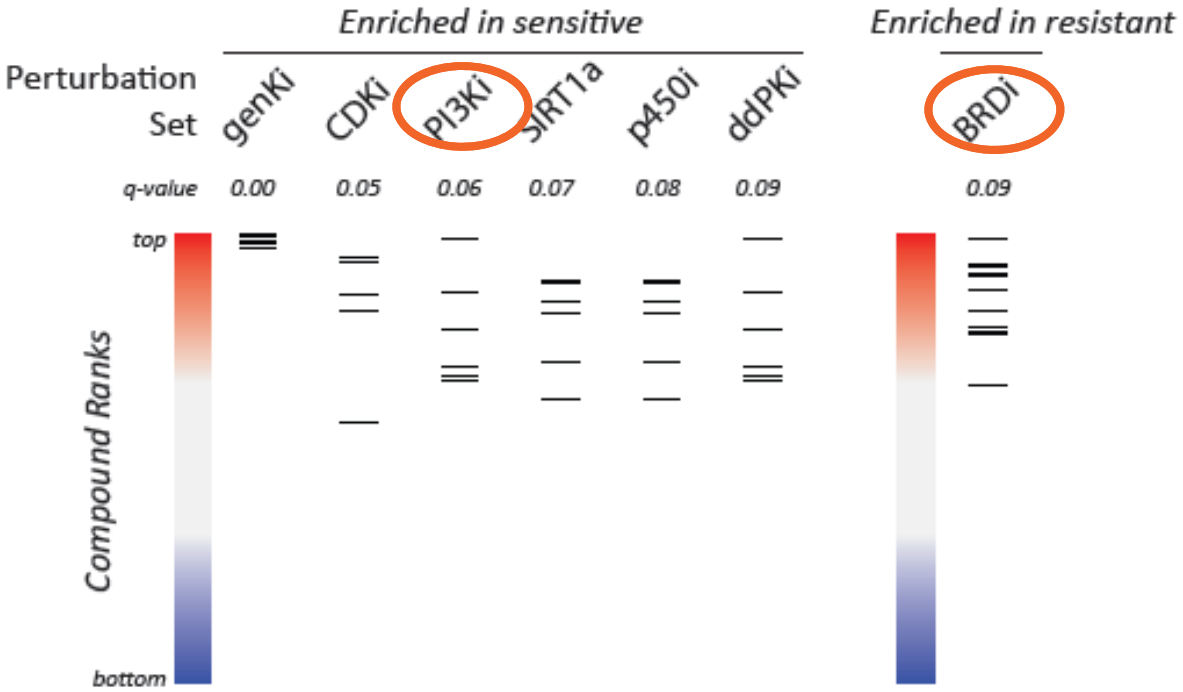


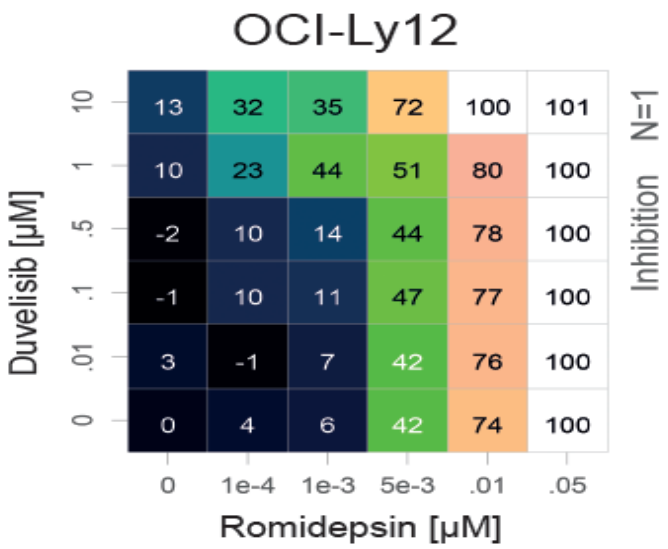
Constitutive activity of pAKT T-cell lymphoma cell lines predicts sensitivity to duvelisib



Horwitz, et al. Blood, in press

Phosphoproteomic profile indicates on-target affects of duvelisib and suggests mechanism of resistance

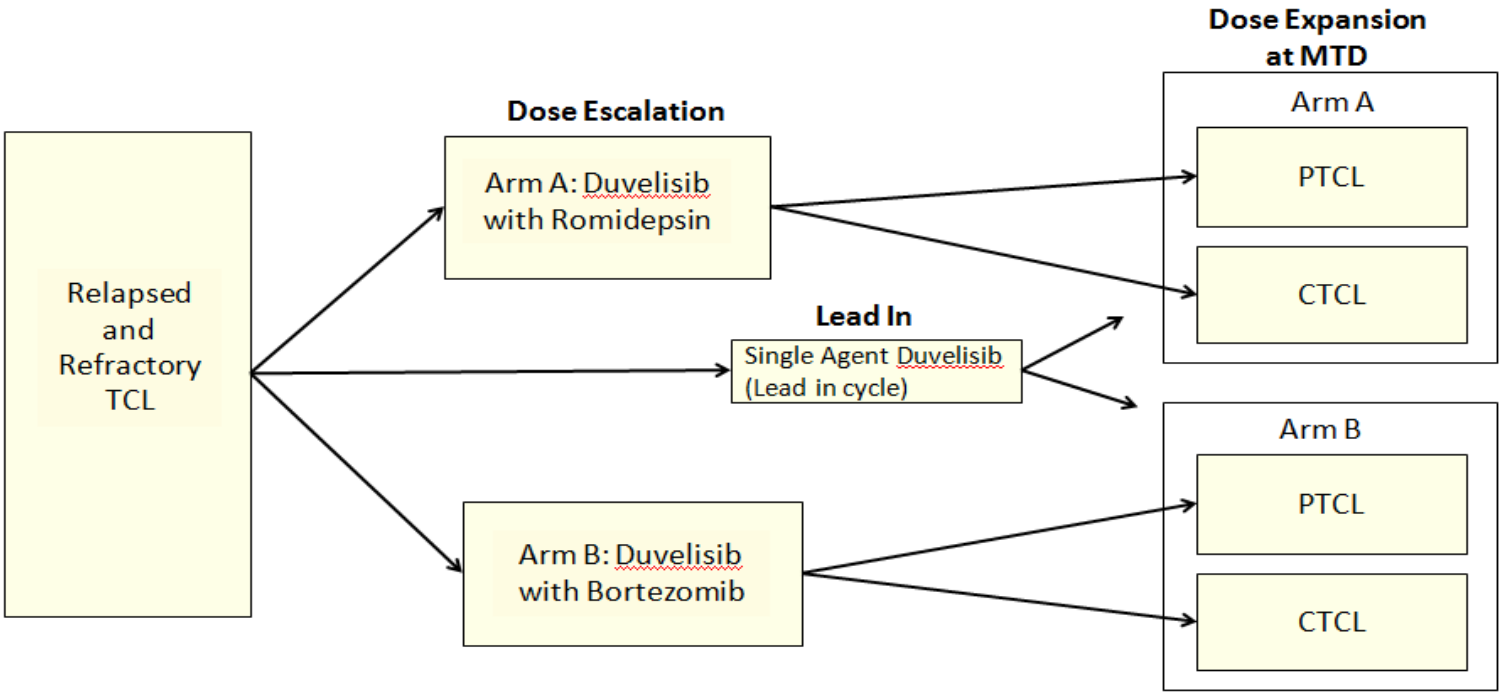




Horwitz, et al. Blood, in press

Parallel Phase I studies of Duvelisib plus Romidepsin or Bortezomib

3+3 design with dose expansion at MTD



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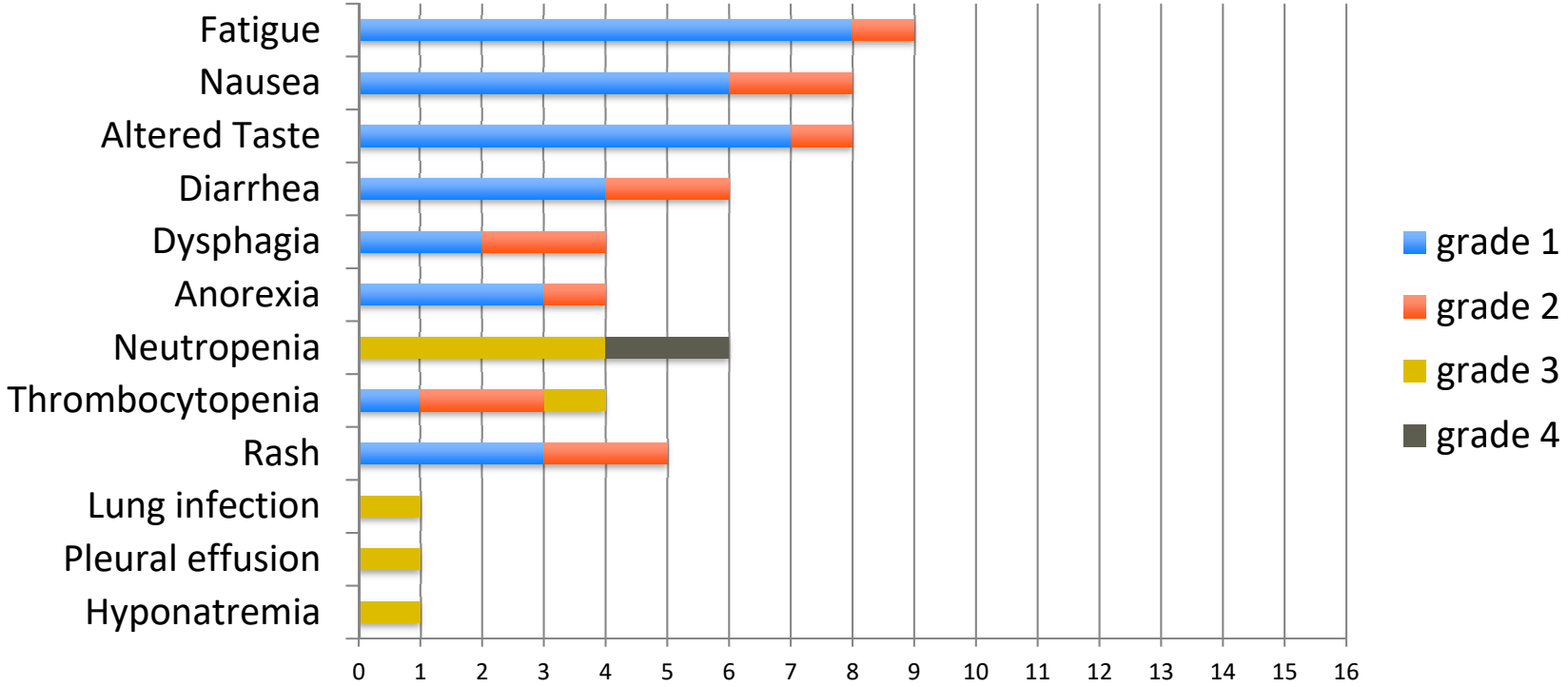
ARM A: dose escalation and expansion

ARM A – Duvelisib + Romidepsin						
Dose Level	Romidepsin days 1, 8, 15	DUV PO days 1-28	#pts enrolled	#pts evaluable for DLT	#pts with DLT	Expansion arm
1	10 mg/m^2	25mg BID	4	3	0	0
2	10 mg/m^2	50mg BID	4	3	0	0
3	10 mg/m^2	75mg BID	4	3	0	4

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

Duvelisib + Romidepsin adverse events

Showing events affecting ≥ 20% of patients and all grade 3 or 4 events



2 deaths unrelated to treatment:

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

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/Tfh)	5	3 (60%)	2 (40%)	1 (20%)
(PTCL-NOS)	4	3 (75%)	2 (50%)	1 (25%)

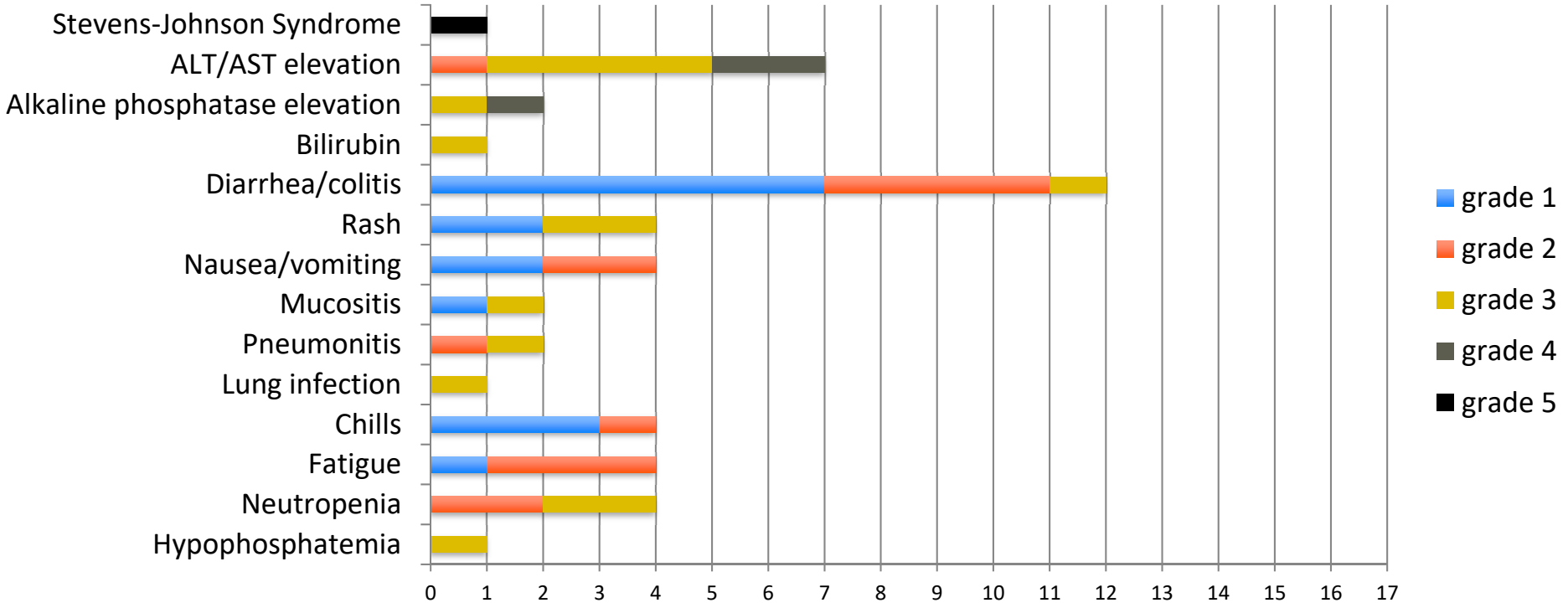
ARM B: dose escalation and expansion

ARM B – Duvelisib + Bortezomib					
Dose Level	Bortezomib (SQ) Days 1,4,8,11	DUV PO days 1-28	#pts enrolled	#pts evaluable for DLT	#pts with DLT
1	1.0 mg/m^2	25mg BID	8	6	1
2	1.0 mg/m^2	50mg BID	3	3	0
3	1.0 mg/m^2	75mg BID	6	5	0

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

Duvelisib + Bortezomib treatment related AEs

Showing events affecting ≥ 20% of patients and all grade 3 or 4 events



ARM B – Duvelisib + Bortezomib – Response

Dose Level	# pts (Evaluable for Response/ Total	Overall responses	Complete Response	Partial Response
1	8/8	3	1	2
2	3/3	2	1	1
3	6/6	1	1	0
TOTAL	17	6 (35%)	3 (18%)	3 (18%)

CTCL vs. PTCL	# pts Evaluable for Response	Overall responses (%)	Complete Response	Partial Response
CTCL	7	1 (14%)	0	1 (14%)
PTCL	10	5 (50%)	3 (30%)	2 (20%)
(AITL)	4	3 (75%)	2 (50%)	1 (25%)
(PTCL-NOS)	4	2 (50%)	1 (25%)	1 (25%)

Adverse Events LFTs

Duvelisib + Romidepsin		
AE	n=16	
	Any Grade	Gr. 3 & 4
ALT	**2 (13%)**	**0**
AST	**2 (13%)**	**0**

Duvelisib + Bortezomib		
AE	n=17	
	Any Grade	Gr. 3 & 4
ALT	**7 (41%)**	**6 (35%)**
AST	**5 (29%)**	**4 (24%)**

Single Agent Duvelisib		
AE	n=210	
	Any Grade	Gr. 3 & 4
ALT	**81 (39%)**	**41 (20%)**
AST	**79 (38%)**	**32 (15%)**

(Flinn et al., Bood 2017)

Conclusions

- Preclinical studies elucidated potential mechanisms of response and resistance to Duvelisib which are being further evaluated in this present phase I study
- Safety, tolerability, and responses of least 50% were observed with both regimens in systemic TCL
- AST/ALT elevations limited tolerability of Duvelisib plus Bortezomib upon dose escalation but did not limit dose escalation of Duvelisib plus Romidepsin
- Expansion cohorts of patients with PTCL and CTCL are almost complete and further expansion of the Duvelisib plus Romidepsin cohort is planned to more precisely define the activity of this combination

Acknowledgements

MSKCC Lymphoma
Steve Horwitz
Andrew Zelenetz
Craig Moskowitz
Lia Palomba
Anita Kumar
Paul Hamlin
Andy Intlekofer
Matt Matasar
John Gerecitano
Ariela Noy
Carol Portlock
David Straus
Anas Younes
Connie Batlevi
Santosh Vardhana
Joachim Yahalom
Ahmet Dogan
Oscar Lin
Patricia Myskowski

Clinical Research Staff
Theresa Davey
Natasha Galasso
Monica Shah
Evan Marzouk
Obadi Obadi
Nivetha Ganesan
Lakeisha Lubin
Veenna Minnal
Chris Joong
Somia Sohail

Tissue Collection
Marissa Mattar
Janine Pichardo

LLS SCOR
Dave Weinstock –DFCI, PI
John Aster-DFCI
Giorgio Inghirami-WCMC
Craig Thompson
Andy Intlekofer
Ahmet Dogan

The patients and their families!

Clinical Trial Collaborators
Eric Jacobsen- DFCI
Raphael Koch - DFCI
Youn Kim-Stanford
Ranjana Advani-Stanford
Michael Khodadoust- Stanford
Jia Ruan-WCMC
Julie Vose-UNMC
Matt Lunning-UNMC
Neha Mehta-Shah- Wash U
Jasmine Zain-COH
Andrei Shustov-FHCRC
Pierluigi Porcu-Jefferson
Jonathan Schatz-U Miami

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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