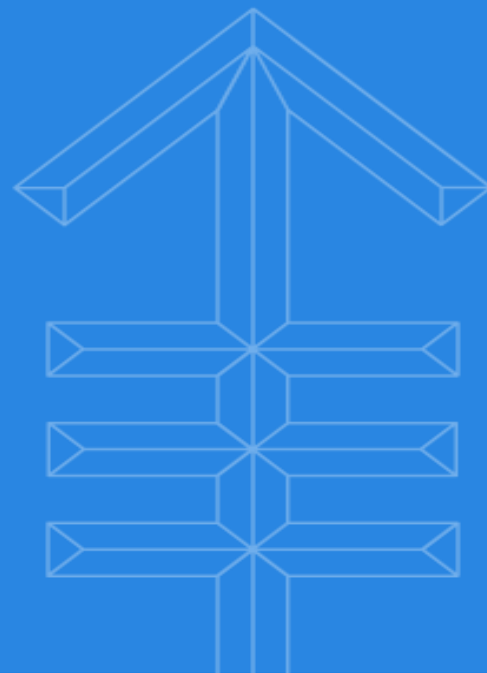




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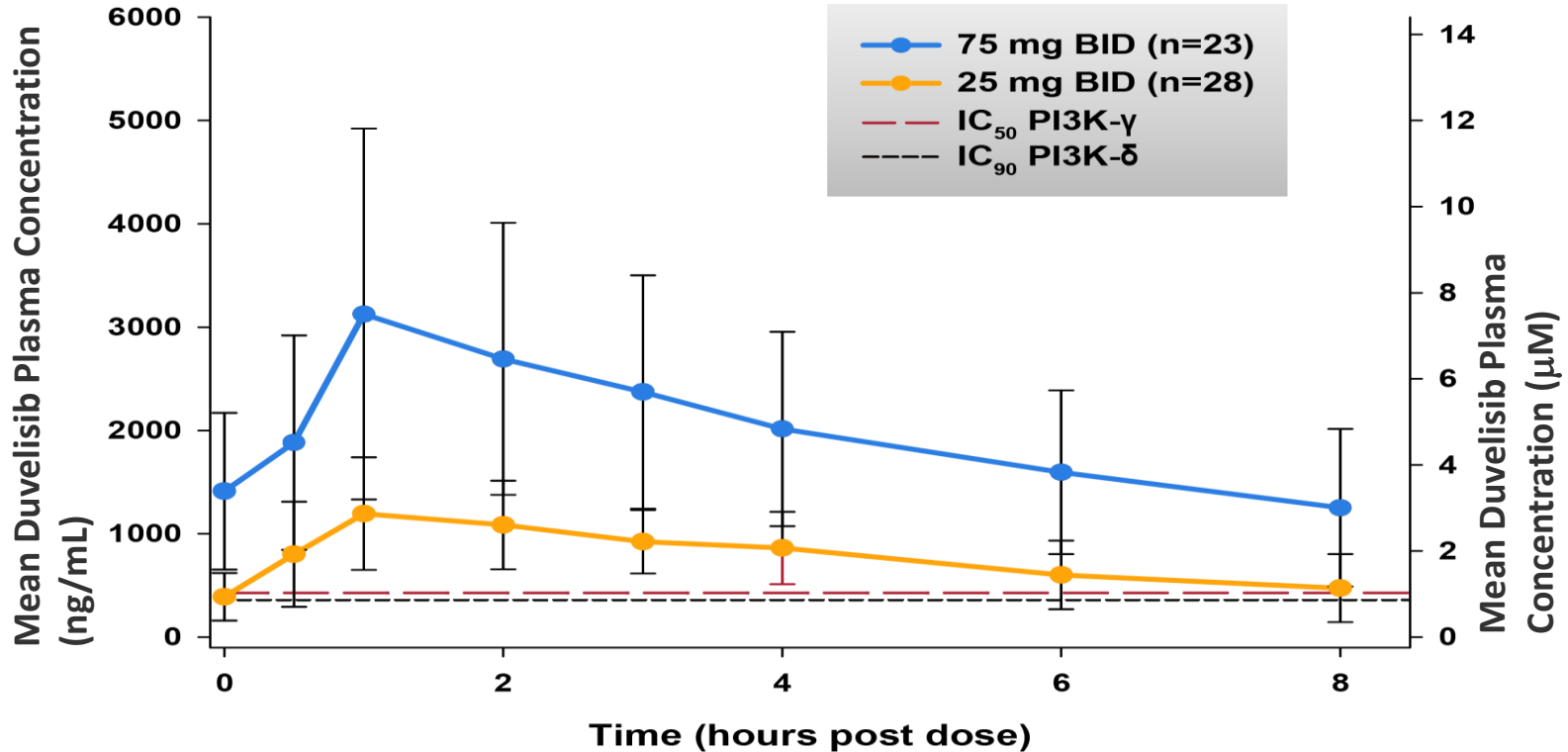
Duvelisib in T cell Lymphoma

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

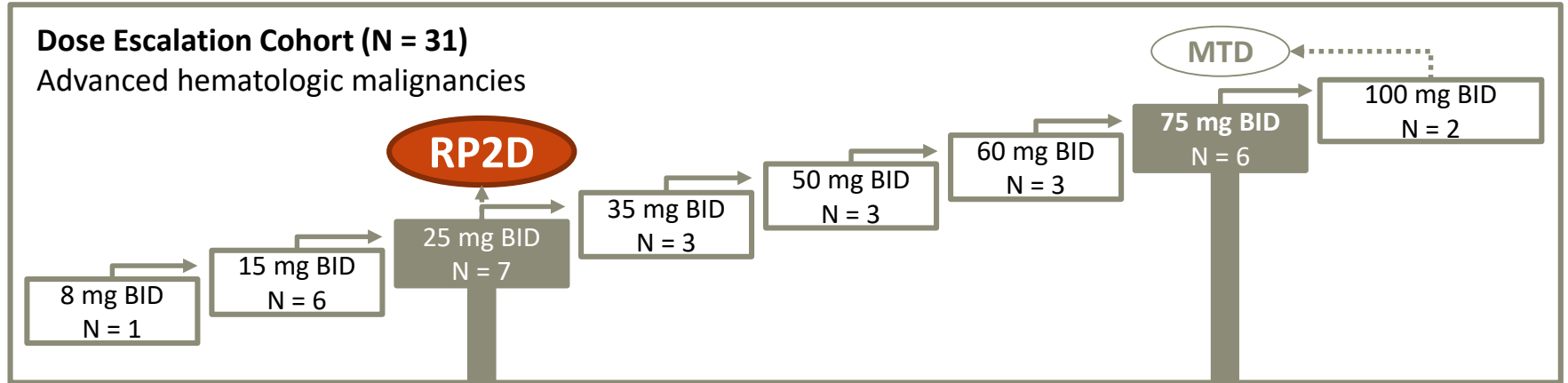


Duvelisib (IPI-145) is an Oral PI3K- δ , γ Inhibitor

Coverage of Both PI3K- δ and PI3K- γ at ≥ 25 mg BID



Duvelisib monotherapy studied across a wide range of B- and T-Cell malignancies



Expansion Cohorts: 25 mg BID (N = 59)

- CLL, iNHL, mantle cell lymphoma
- Treatment-naïve CLL

Expansion Cohorts: 75 mg BID (N = 118)

- CLL, iNHL, mantle cell lymphoma
- T-cell lymphomas

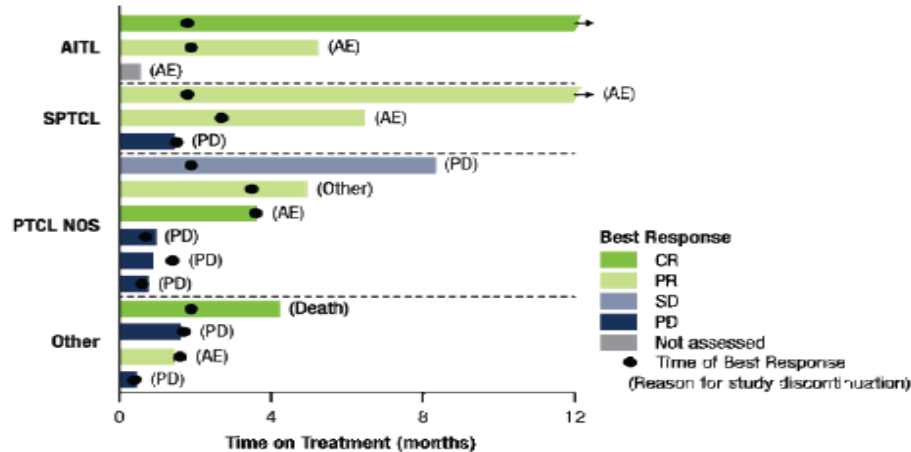
Exploratory cohorts

- Aggressive B-cell lymphomas
- T- or B-cell leukemia/lymphoma

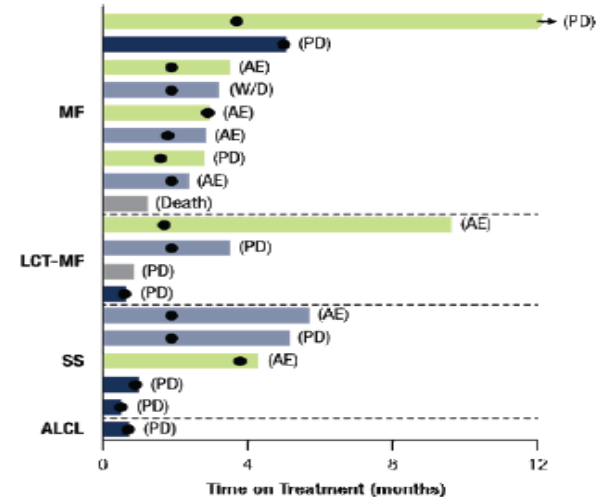
PI3K- $\delta\gamma$ inhibition in T-cell lymphomas

- **Duvelisib**: an oral, dual inhibitor of PI3K- δ and PI3K- γ , demonstrated encouraging efficacy in TCL in a phase I study.

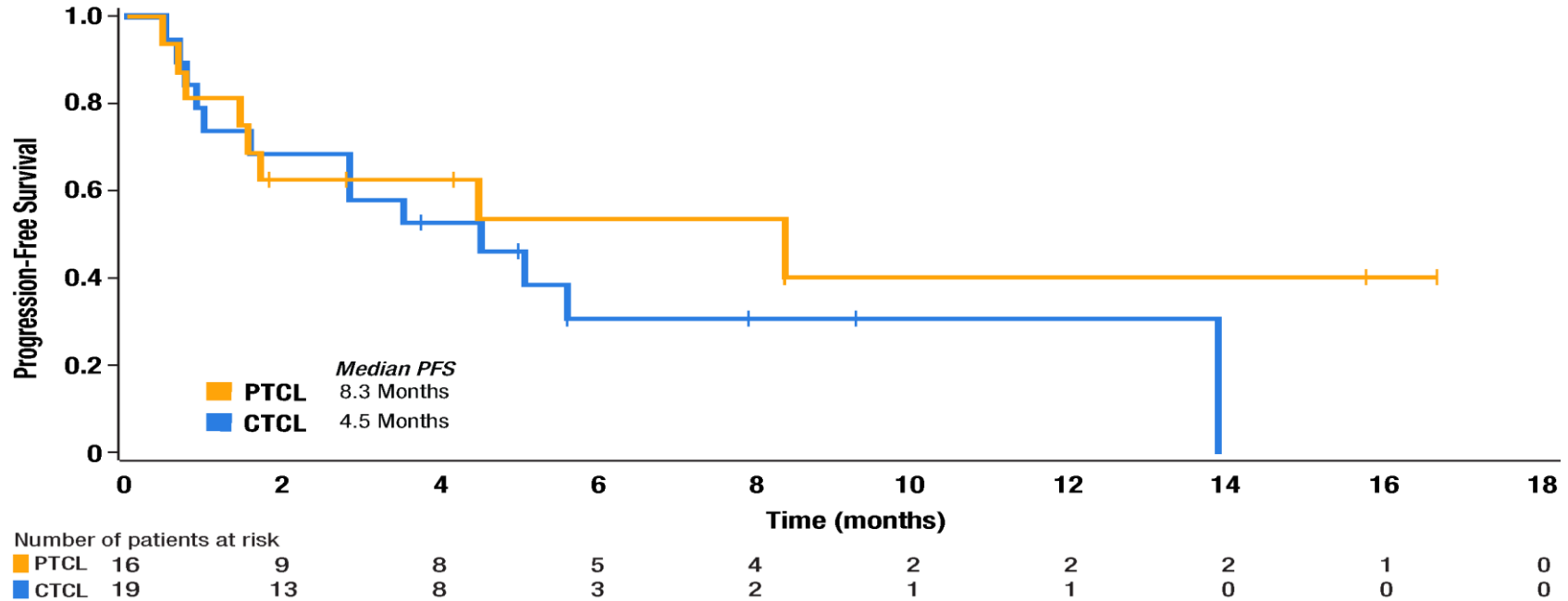
ORR in PTCL: 50%



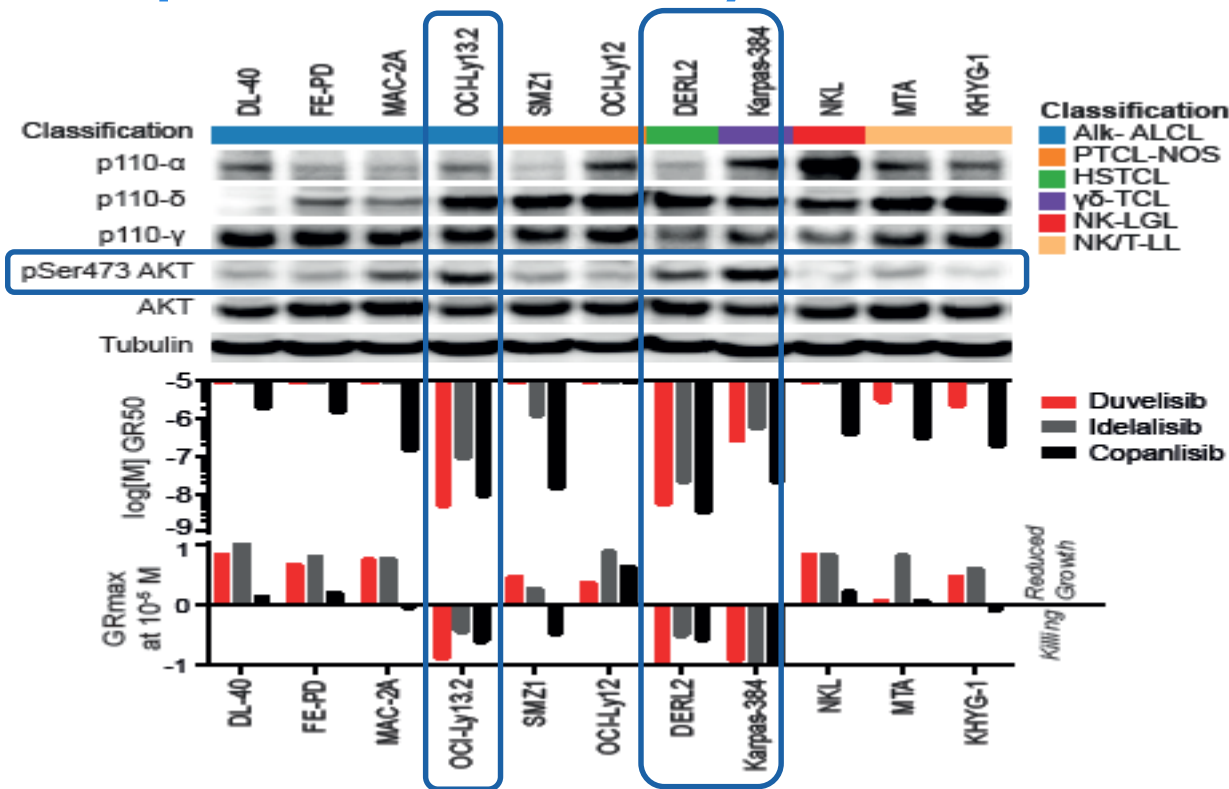
ORR in CTCL: 32%



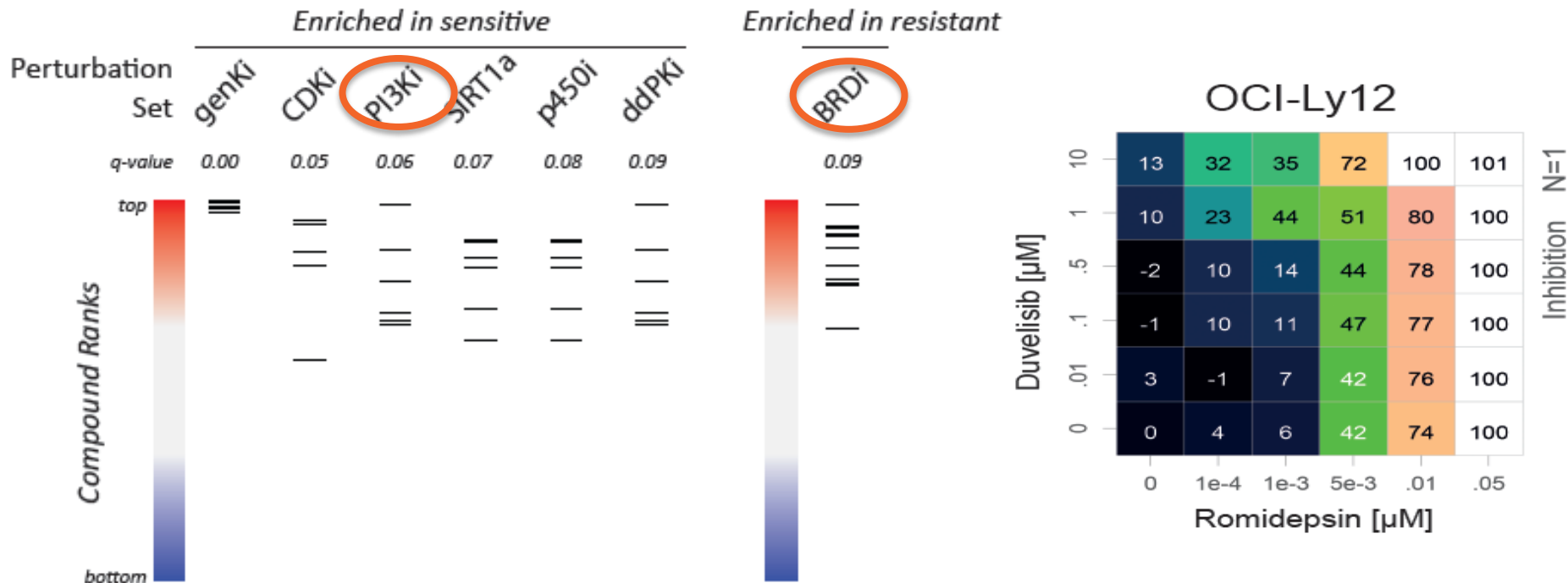
Duvelisib Phase I/Expansion TCL-PFS



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



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



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

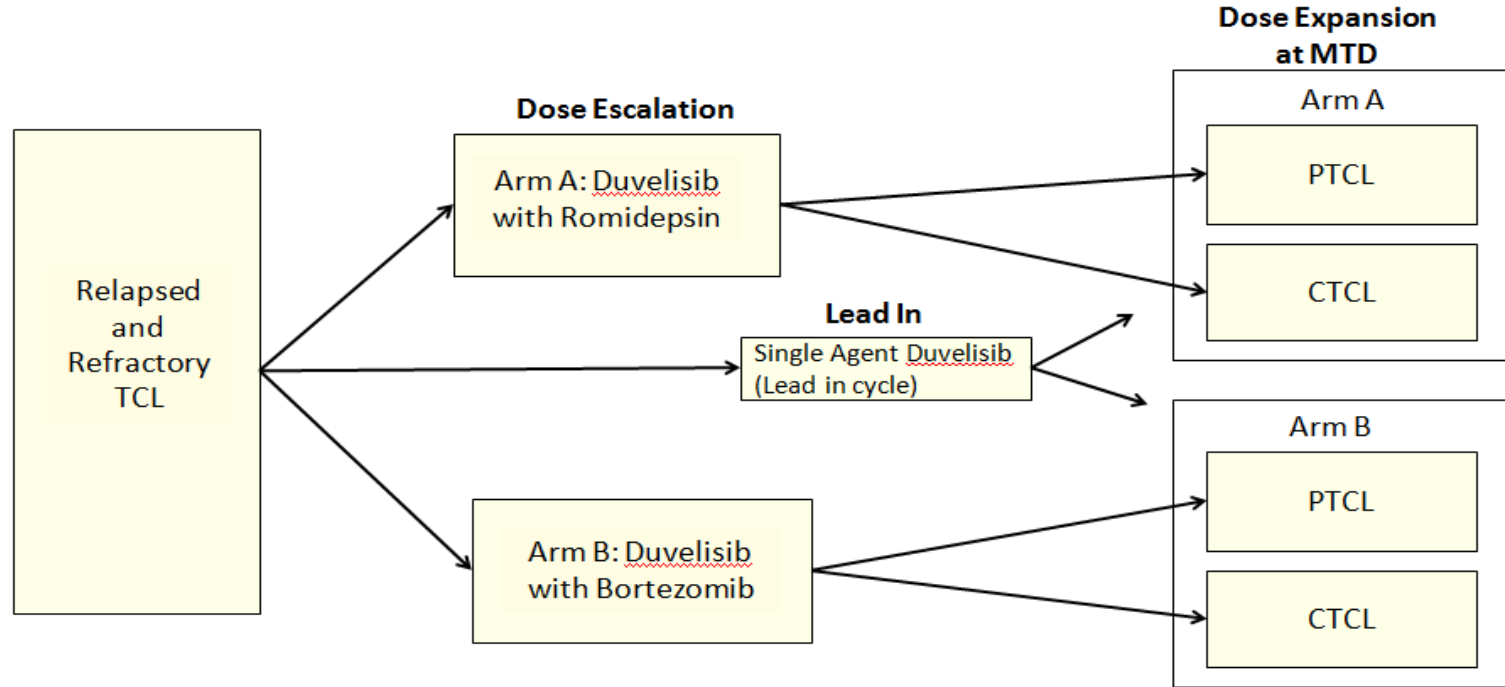


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Parallel Phase I studies of Duvelisib plus Romidepsin or Bortezomib

3+3 design with dose expansion at MTD



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ARM A: dose escalation and expansion

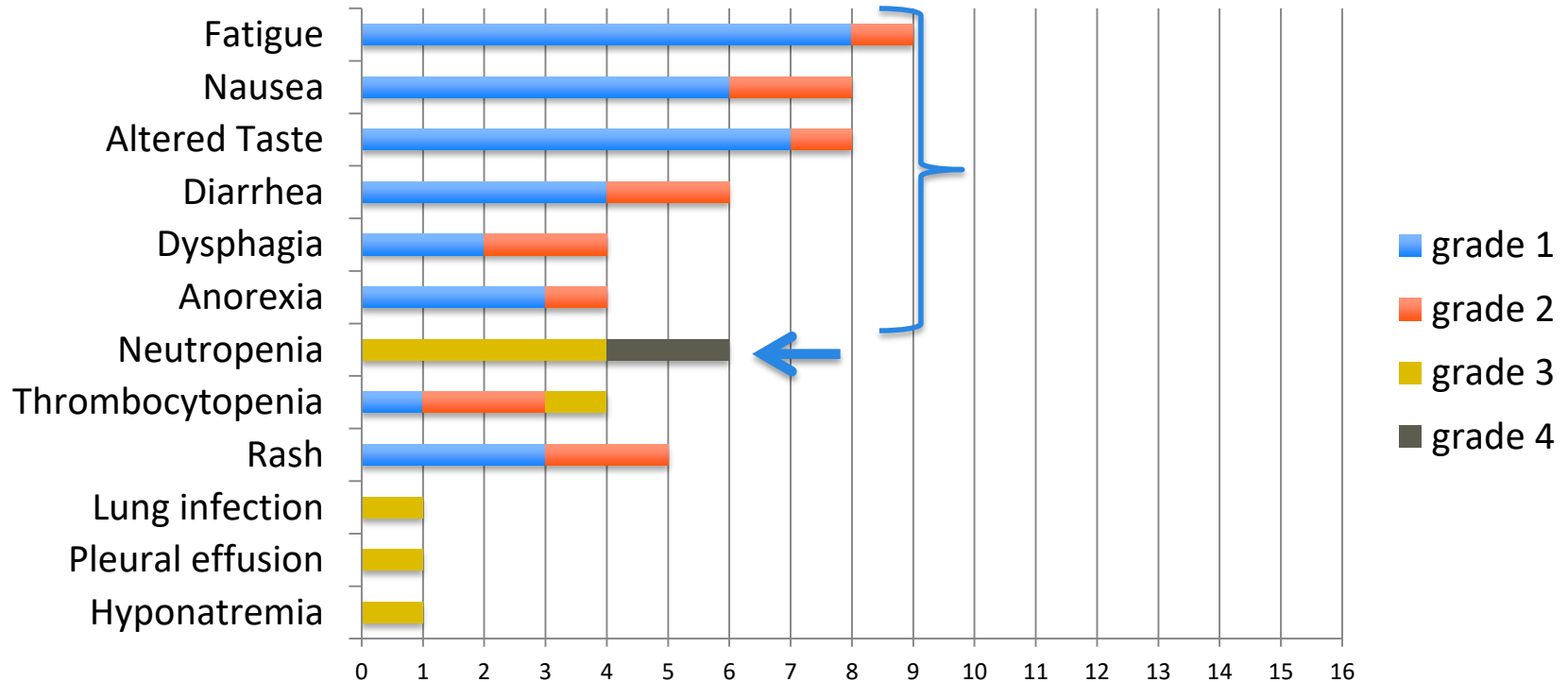
ARM A – Duvelisib + Romidepsin

Dose Level	Romidepsin days 1, 8, 15	DUV PO days 1-28
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)

Duvelisib + Romidepsin adverse events

Showing events affecting $\geq 20\%$ 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%)

ARM B: dose escalation and expansion

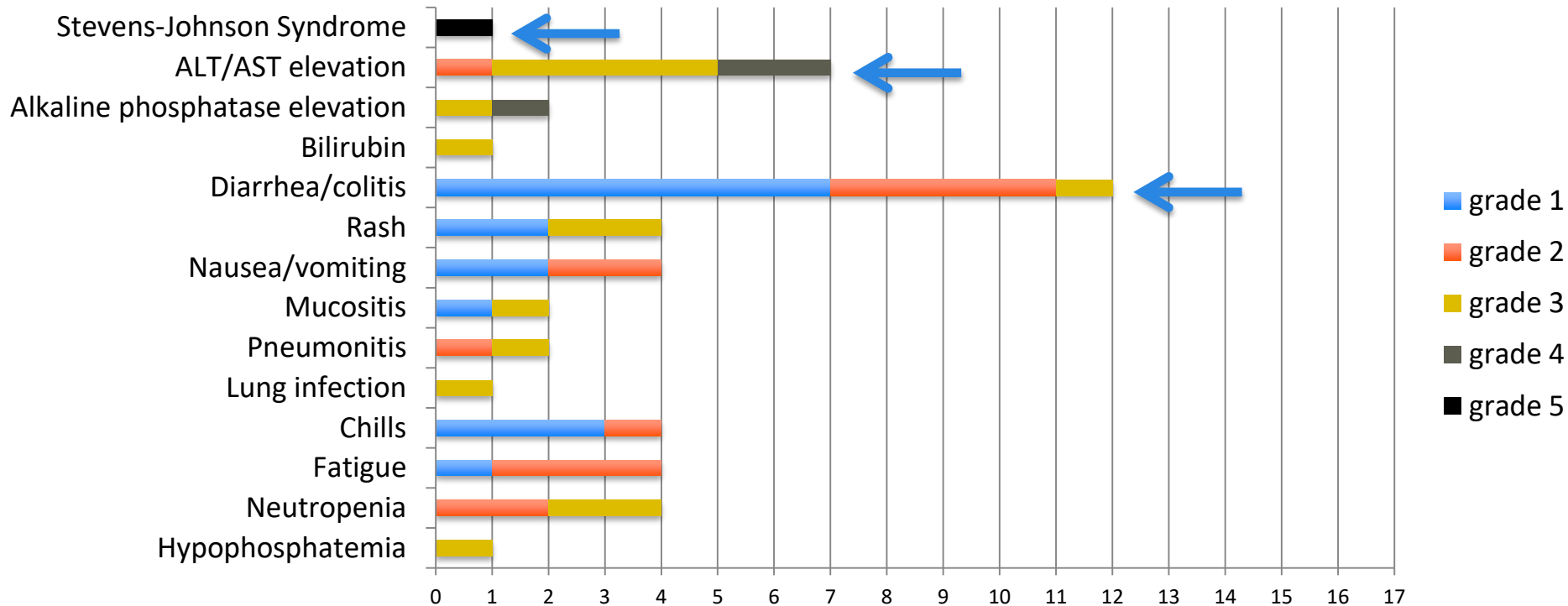
ARM B – Duvelisib + Bortezomib

Dose Level	Bortezomib (SQ) Days 1,4,8,11	DUV PO days 1-28
1	1.0 mg/m ²	25mg BID
2	1.0 mg/m ²	50mg BID
3	1.0 mg/m ²	75mg BID

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

Duvelisib + Bortezomib treatment related AEs

Showing events affecting $\geq 20\%$ of patients and all grade ≥ 3 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%)

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%)

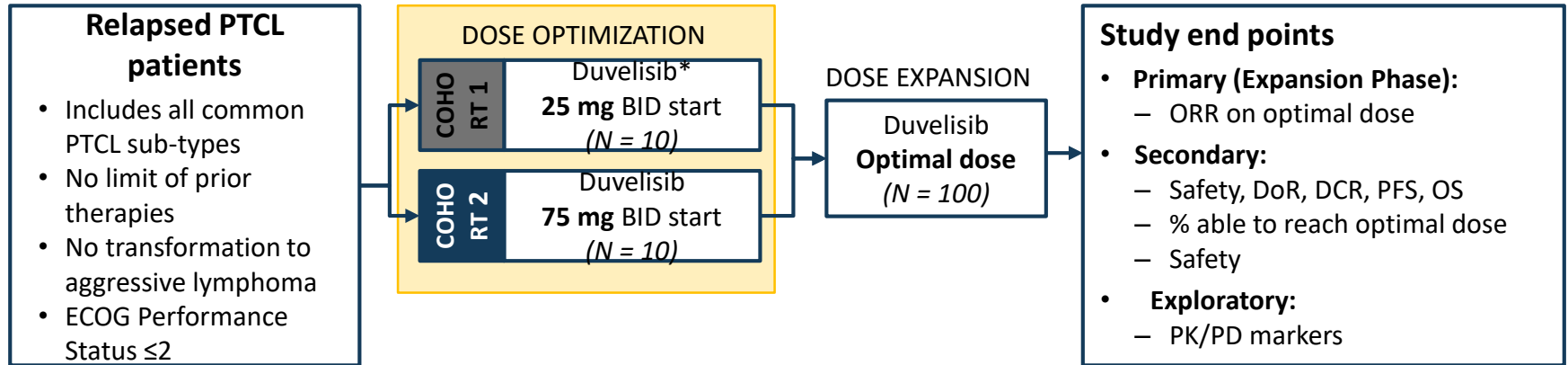
Single Agent Duvelisib		
AE	n=210	
	Any Grade	Gr. 3 & 4
ALT	81 (39%)	41 (20%)
AST	79 (38%)	32 (15%)

(Flinn et al., Bood 2017)

Conclusions

- Duvelisib has single agent activity in PTCL and CTCL
- Preclinical studies identified potential mechanisms of response and resistance
- Combination studies with romidepsin and bortezomib showed safety, tolerability, and responses of least 50% were observed with both regimens in systemic TCL
- AST/ALT elevations limited dose escalation of Duvelisib plus Bortezomib 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 ongoing to more precisely define the activity of this combination

Phase 2: Confirm and extend activity of Duvelisib monotherapy in RELAPSED/REFRACTORY PTCL



Goal: Establish optimal dose and confirm monotherapy activity

Trial design details:

- At least one prior therapy for PTCL
- Intra-patient dose escalation in Cohort 1 is allowed

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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

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