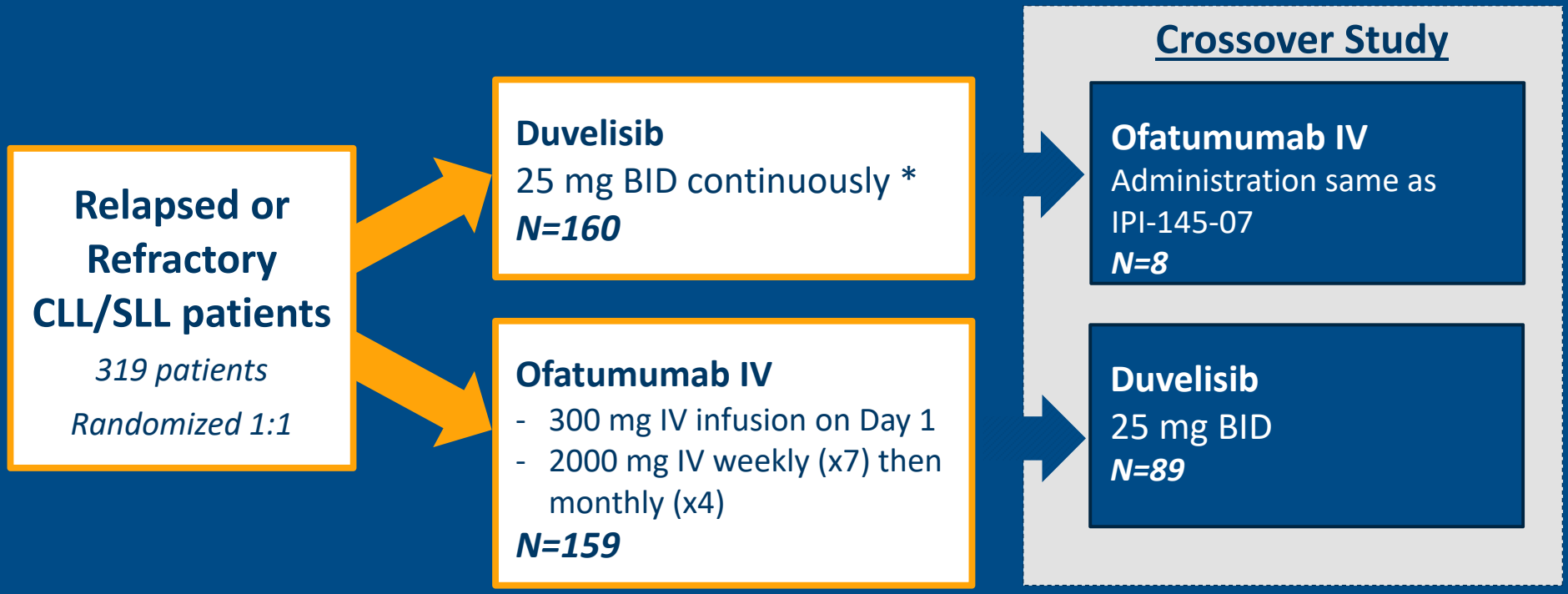
RESEARCH AND DEVELOPMENT EVENT AT ASH 2017

December 10, 2017

IAN FLINN, MD, PHD
SARAH CANNON RESEARCH INSTITUTE
TENNESSEE ONCOLOGY

DUO: A Phase 3 Randomized Study in Relapsed/Refractory CLL/SLL



Response per modified iwCLL/IWG Criteria **

- Assessed by blinded independent review committee (IRC)
- Cycle 3 (C3), C5, C7, C11, C15, C19, every 6 months thereafter
- CT scan, CBC , disease related symptoms, BM biopsy ***
- Survival assessment every 6 months

Endpoints

- PFS (primary)
- ORR, DOR, OS (secondary)
- Safety (AEs and lab abnormalities)

* Patients may have stopped treatment at C18 for CR/PR >3 months at discretion of Investigator

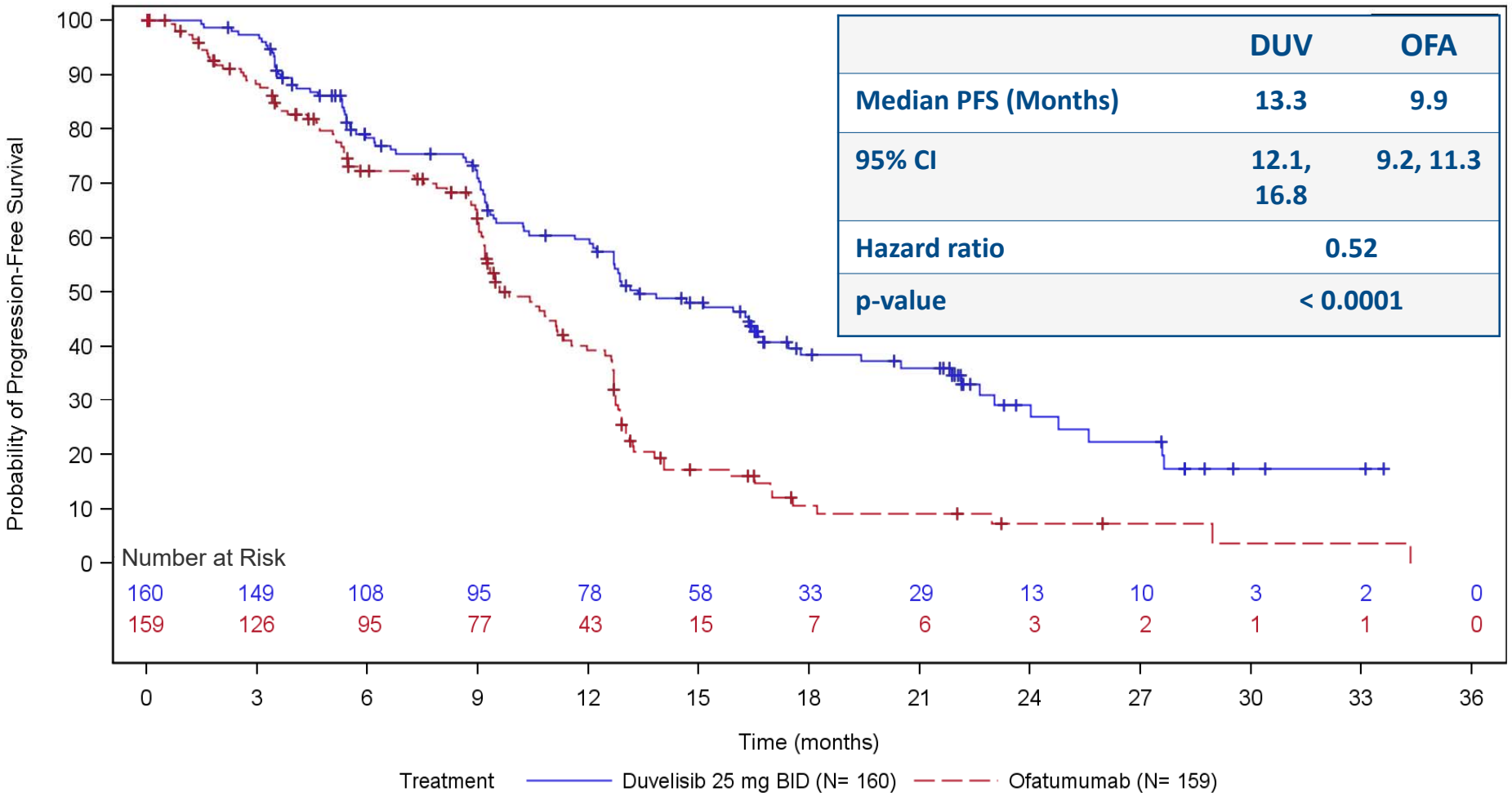
** Lymphocytosis not considered disease progression; PR = 2 Group A and 1 Group B Criteria

*** Required for confirmation of CR/CRi

Eligibility and Prophylaxis

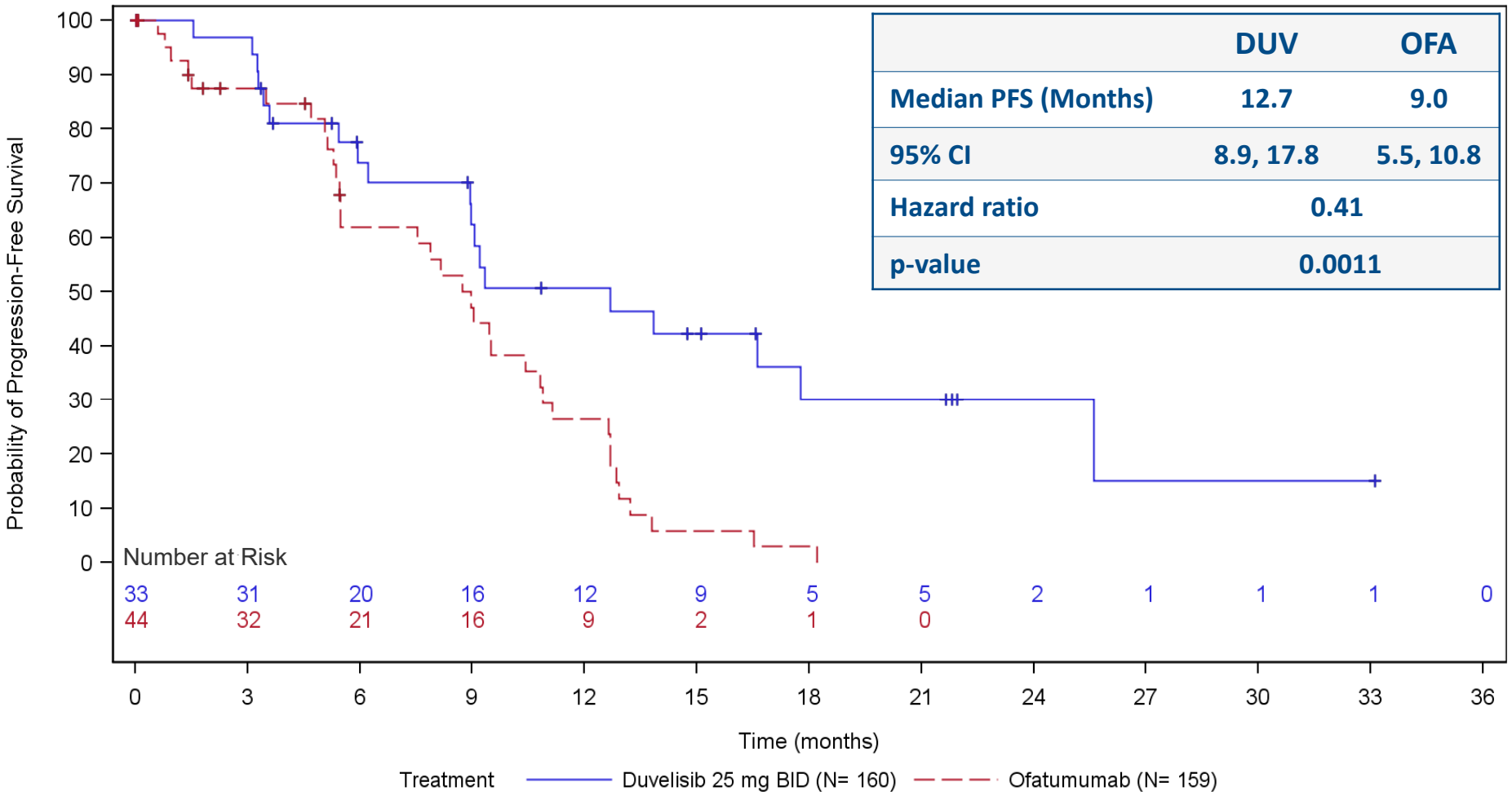
- **Key Eligibility Criteria**
  - Progressed on or relapsed after ≥ 1 prior anticancer therapy
  - Measurable lymph node disease (> 1.5 cm) per CT scan
  - Hemoglobin ≥ 8.0 g/dL and platelet count ≥ 10,000 µL with or without transfusion support
  - No minimum ANC required
  - Richter's transformation and prolymphocytic leukemia excluded
  - Prior treatment with BTK or PI3K inhibitors excluded
  - Patients with prior, current, or chronic hepatitis B infection excluded
- **Prophylaxis**
  - All patients required to receive *Pneumocystis* prophylaxis while on treatment
  - Prophylaxis for CMV infection/reactivation recommended but not required

DUO Met Primary Endpoint of PFS
Significantly Longer Median PFS with Duvelisib per IRC



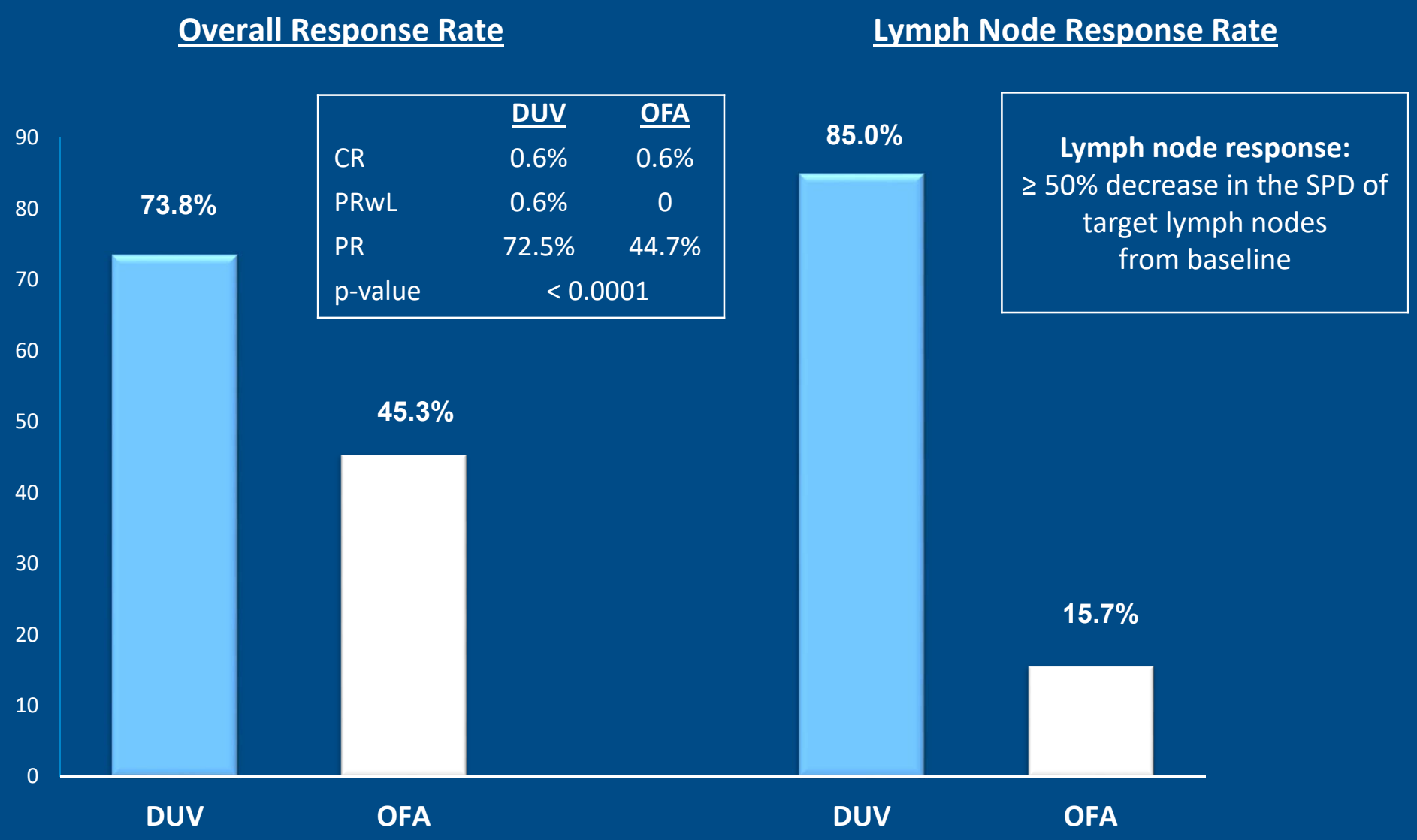
	DUV	OFA
Median PFS (Months)	13.3	9.9
95% CI	12.1, 16.8	9.2, 11.3
Hazard ratio	0.52	
p-value	< 0.0001	

Significantly Longer PFS with Duvelisib in Patient with 17p Deletion per IRC



	DUV	OFA
Median PFS (Months)	12.7	9.0
95% CI	8.9, 17.8	5.5, 10.8
Hazard ratio	0.41	
p-value	0.0011	

Significantly Higher ORR with Duvelisib per Blinded IRC

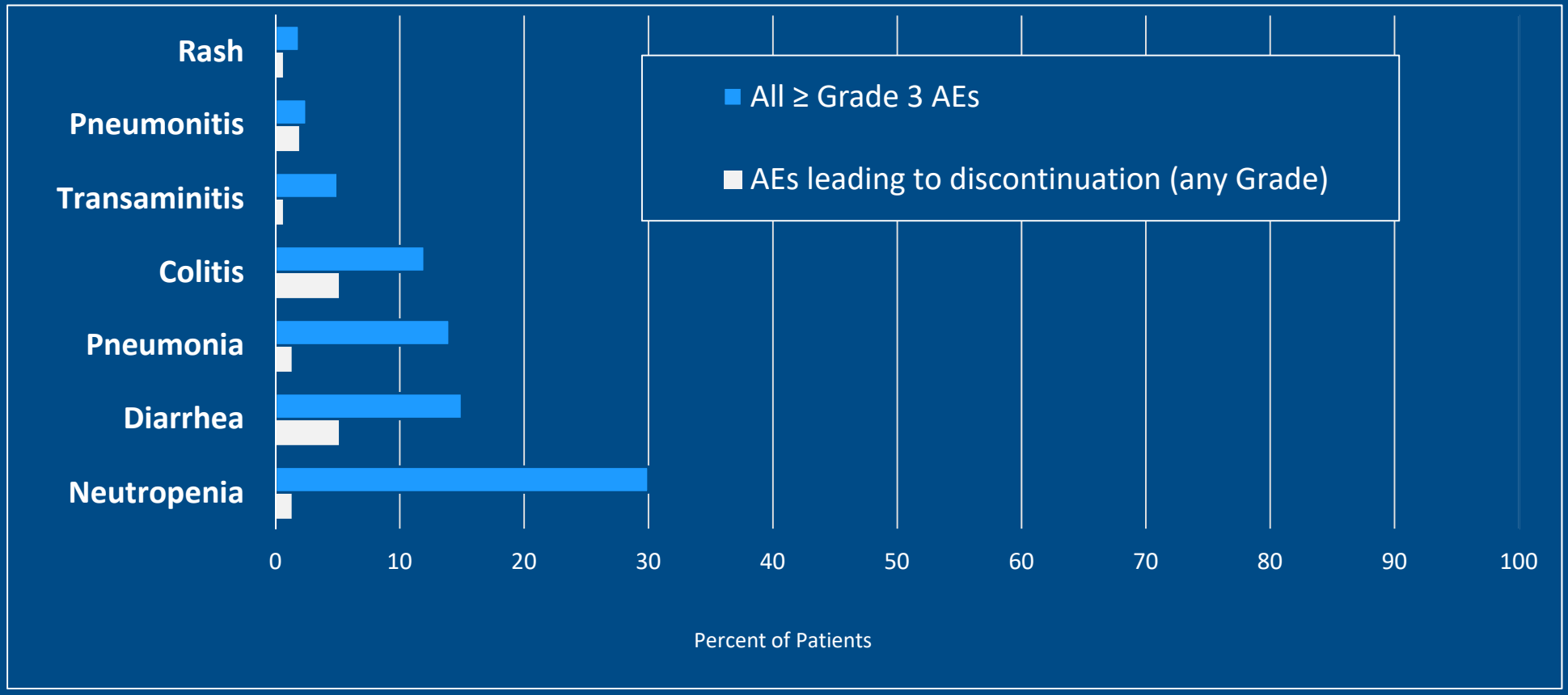


- ORR in patients with **17p deletion**: duvelisib 70% vs OFA 43% (p=0.0182)

Adverse Events (Percent of Patients)

		All Grades		≥ Grade 3	
		DUV N=158	OFA N=155	DUV N=158	OFA N=155
Median Observation Period (Weeks)		**50**	**23**	**50**	**23**
Hematologic	Neutropenia	33	20	30	17
	Anemia	23	10	13	5
	Thrombocytopenia	15	6	8	2
Nonhematologic	Diarrhea	51	12	15	1
	Pyrexia	29	10	3	1
	Nausea	23	11	0	0
	Cough	21	14	1	0
	Pneumonia	18	6	14	1
	Constipation	17	8	1	0
	Upper resp. tract infection	16	8	0	0
	Vomiting	15	7	0	0
	Bronchitis	13	8	3	1
	Colitis	13	1	12	1
	Decreased appetite	13	3	0	1
	Weight decreased	11	2	0	0
	Asthenia	11	11	2	3
	Abdominal pain	10	2	2	0
	Dyspnea	10	6	3	0
	Rash	10	12	2	1

AEs of Special Interest:
Few Led to Duvelisib Discontinuation



- **Severe opportunistic infections (6%):** bronchopulmonary aspergillosis (n=4), fungal infection (n=2), PJP (n=2)*, and cytomegalovirus colitis (n=1)
  - No severe Herpes zoster infections
- **Treatment-related AEs leading to death** (n=4): general health deterioration (n=1); pneumonia staphylococcal (n=2); sepsis (n=1)

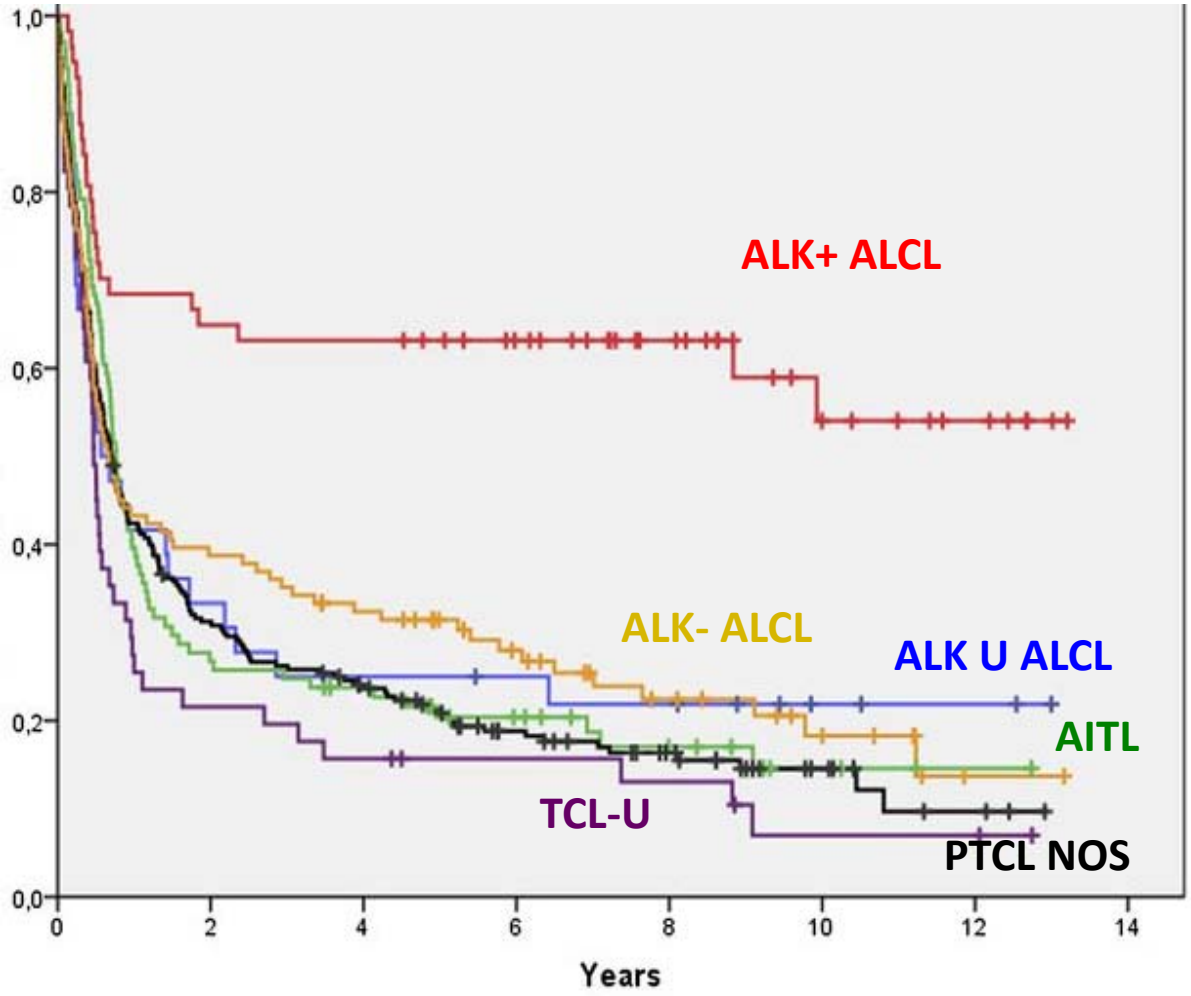
* Neither patient on prophylaxis at the time of the event

DUO Study Conclusions

- DUO met the primary endpoint for PFS: duvelisib monotherapy achieved significant improvement in PFS vs OFA (13.3 m vs 9.9 m; HR = 0.52; $p < 0.0001$) per IRC
  - PFS per investigator response assessment significantly favored duvelisib vs OFA (17.6 m vs 9.7 m; $p < 0.0001$)
  - Similar benefit in CLL/SLL patients with 17p deletion
  - Duvelisib achieved significant improvement in ORR vs OFA (74% vs 45%; $p < 0.0001$) per iwCLL/IWG
  - Duvelisib significantly reduced lymph node burden > 50% in most patients vs OFA (85% vs 16%)
- With a median exposure of 50 weeks, the AE profile of duvelisib was manageable and consistent to what has been previously observed
  - AEs of interest (neutropenia, diarrhea, pneumonia, colitis, transaminase elevations, pneumonitis, rash) infrequently led to discontinuation
- DUO results support duvelisib oral monotherapy as a potential new and convenient treatment option for previously treated CLL/SLL patients

STEVEN HORWITZ, MD
MEMORIAL SLOAN KETTERING CANCER CENTER

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

Duvelisib Clinical Activity in TCL

		Best Response, n (%)					Median Time to Response, months (Range)
	n	CR	PR	SD	PD	ORR	
All TCL	35	2 (6)	12 (34)	7 (20)	12 (34)	**14 (40)**	1.9 (1.5, 3.8)
CTCL	19	0	6 (31.6)	6 (31.6)	6 (33)	**6 (31.6)**	2.4 (1.6, 3.8)
PTCL	16	2 (18.8)	6 (31.3)	1 (6.3)	6 (37.5)	**8 (50)**	1.9 (1.5, 3.5)

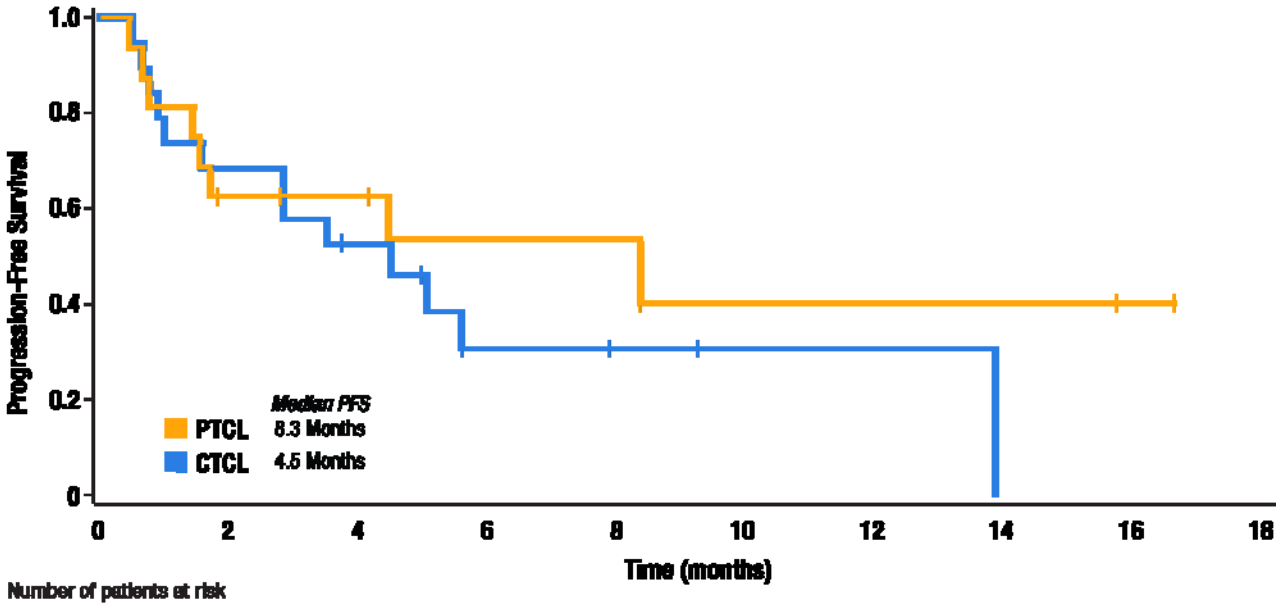
Includes evaluable patients = at least 1 on-treatment response assessment or PD without assessment
CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease
ORR = CR + PR

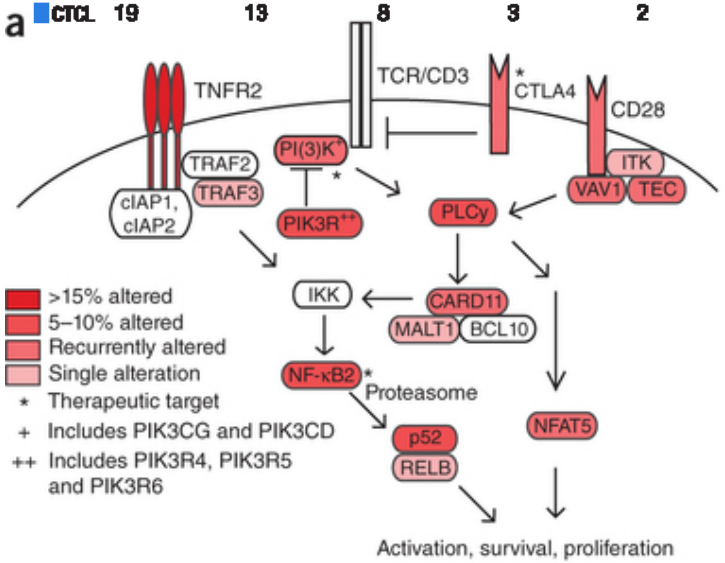
- Clinical activity observed across CTCL and PTCL subtypes
  - CTCL: PRs in 4 MF, 1 Sézary syndrome, and 1 MF-LCT
  - PTCL: CRs in 1 EATCL and 1 PTCL NOS
    PRs in 2 AITCL, 2 SPTCL, 1 PTCL NOS, 1 ALCL (ALK-negative)

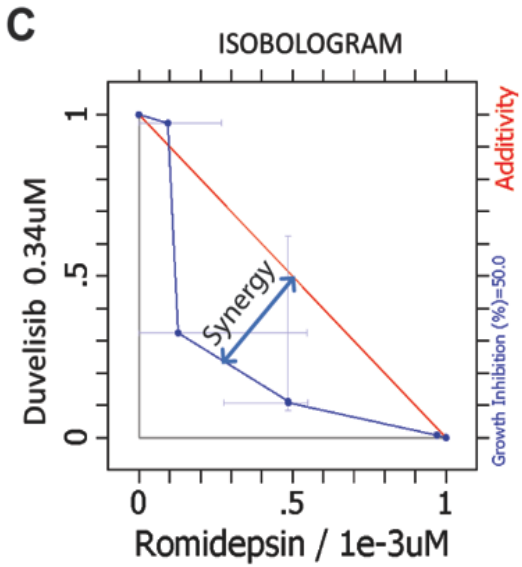
Horwitz et al, Blood in press 2017

Targeting PI3K in PTCL

Duvelisib Phase I TCL Expansion







Duvelisib (IPI-145)

- ORR 53% (8/15) in phase I trial of patients with relapsed/refractory PTCL
- Exhibits in vitro synergy with romidepsin (HDACi approved for PTCL)

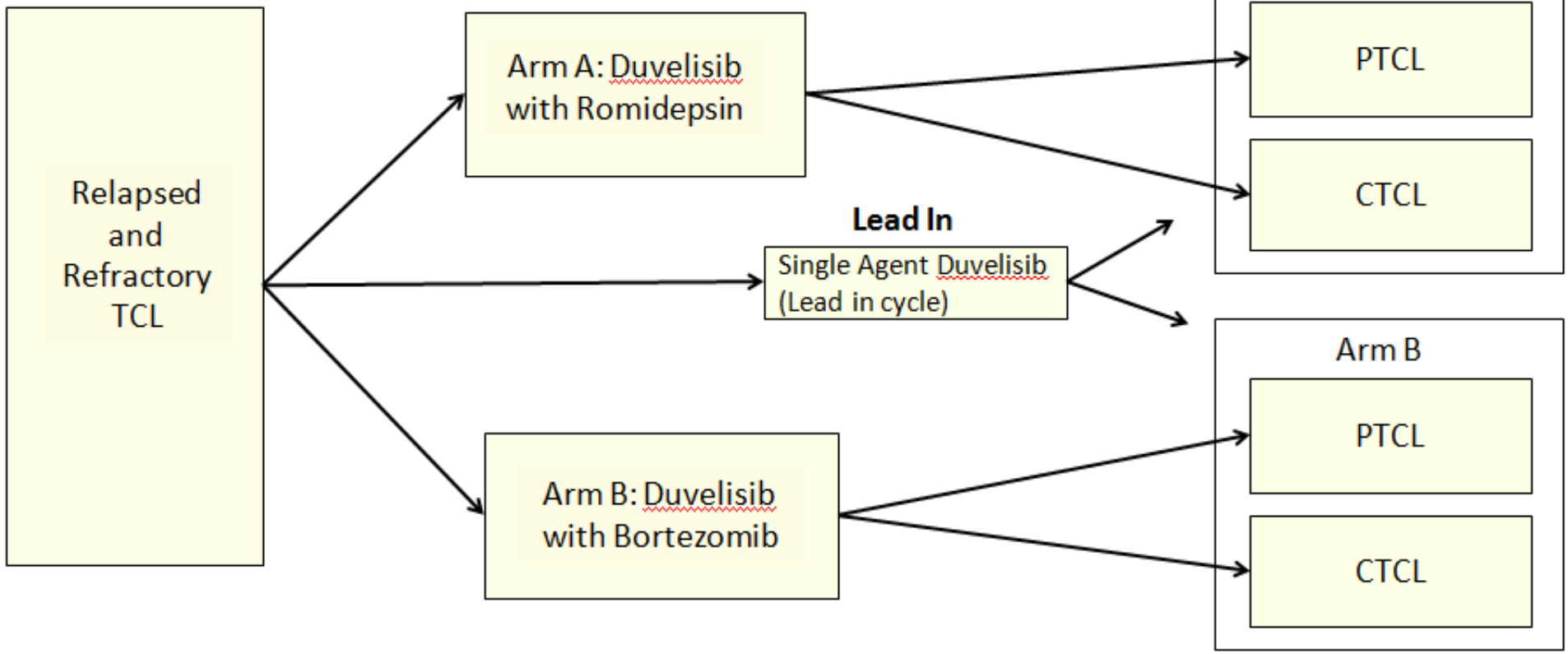
- Combinations in TCL
- (IST Infinity)
  - Bortezomib
  - Romidepsin

Horwitz et al, ASH 2014; Ungewickell et al. ,*Nature Genetics* 47, 1056–1060 (2015)

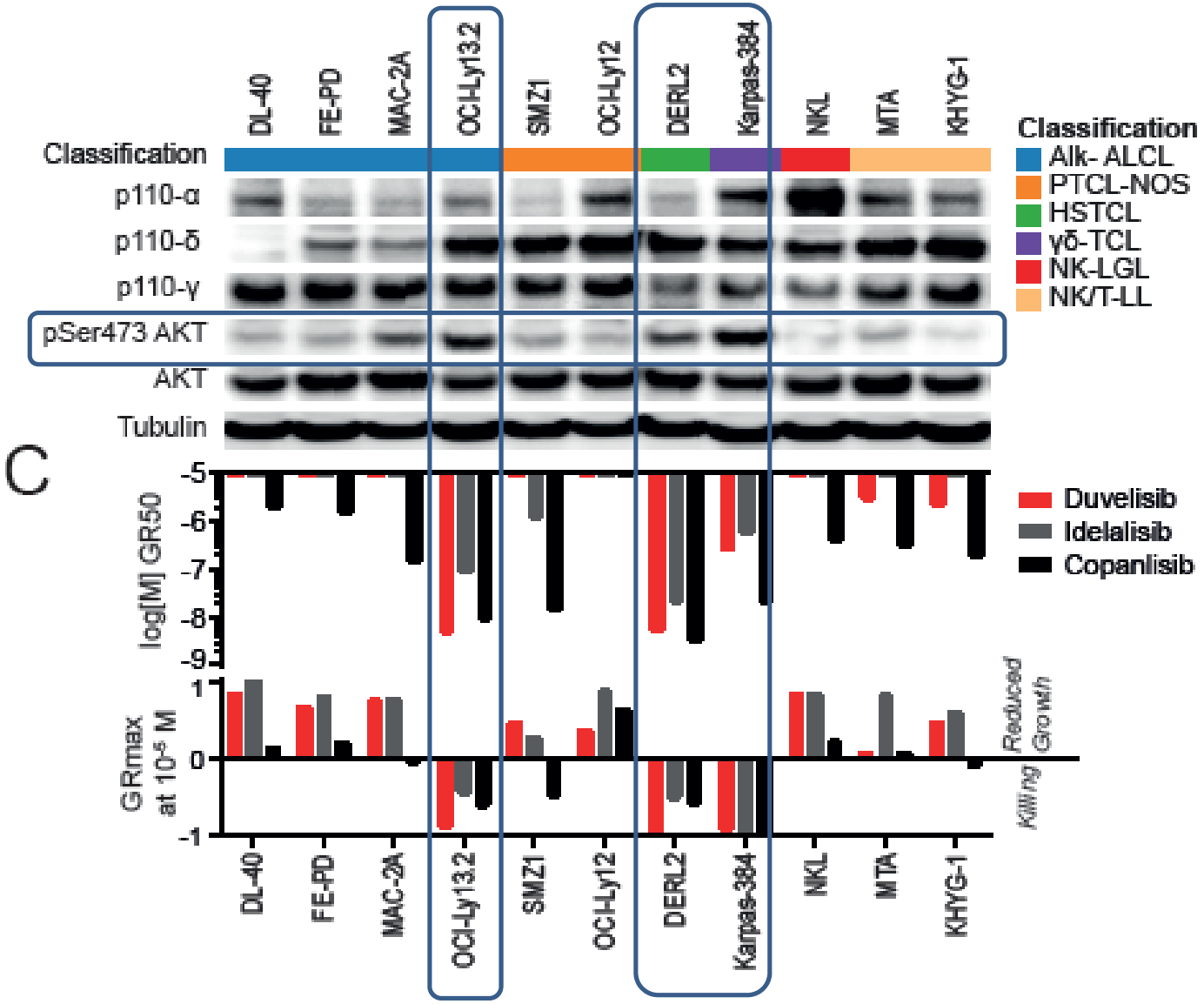
Parallel Phase I studies of duvelisib plus romidepsin or bortezomib

3+3 Design with Dose Expansion at MTD

Participating Institutions
Memorial Sloan Kettering*
Dana Farber Cancer Institute
Stanford University
Washington University
Funding from Verastem



Constitutive activity of pAKT TCL cell lines predicts sensitivity to duvelisib



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

Conclusions

- Preclinical studies elucidated mechanisms of response and resistance to duvelisib which will be further evaluated in this present phase I study
- Safety and tolerability of duvelisib plus bortezomib and duvelisib plus romidepsin was observed
- Incidence of AST/ALT elevations limited tolerability of duvelisib plus bortezomib upon dose escalation but did not limit dose escalation of duvelisib plus romidepsin
- Responses of least 50% were observed across the most common PTCL histologies with both regimens
- Expansion cohorts of patients with peripheral and cutaneous T-cell lymphoma are currently enrolling.

PRESENTATIONS AT ASH 2017

Oral Presentations

Title: **Results from the Phase 3 DUO™ Trial: A Randomized Comparison of Duvelisib Vs Ofatumumab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma**
Presenter: Ian Flinn, M.D., Ph.D., Sarah Cannon Research Institute
Abstract Number/Publication ID: 493
Date and Time: **Sunday, December 10, 2017 at 4:30 PM ET**

Title: **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**
Presenter: Steven Horwitz, M.D., Memorial Sloan Kettering Cancer Center
Abstract Number/Publication ID: 819
Date and Time: **Monday, December 11, 2017 at 5:00 PM ET**

Posters

Title: **The Dual PI3K-δ,γ Inhibitor Duvelisib Stimulates Anti-Tumor Immunity and Enhances Efficacy of Immune Checkpoint and Co-Stimulatory Antibodies in a B Cell Lymphoma Model**
Presenter: Jonathan Pachter, Ph.D., Verastem
Abstract Number/Publication ID: 1541
Date and Time: **Saturday, December 9, 2017 from 5:30-7:30 PM ET**

Title: **Combinatorial Inhibition of Focal Adhesion Kinase and BCL-2 in AML**
Presenter: Xiangmeng Wang, Ph.D., MD Anderson Cancer Center
Abstract Number/Publication ID: 2653
Date and Time: **Sunday, December 10, 2017 from 6:00-8:00 PM ET**