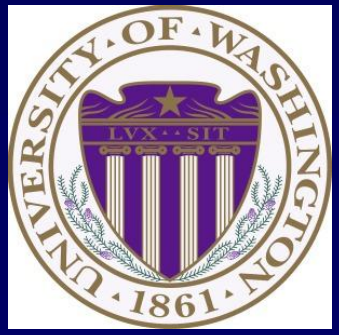
Converting Tumor Biology Into Effective Novel Therapies in T-Cell Lymphoma

Andrei Shustov, MD
University of Washington Medical Center
Seattle WA



prIME oncology

Classification of Mature T-cell Lymphomas (MTCL)

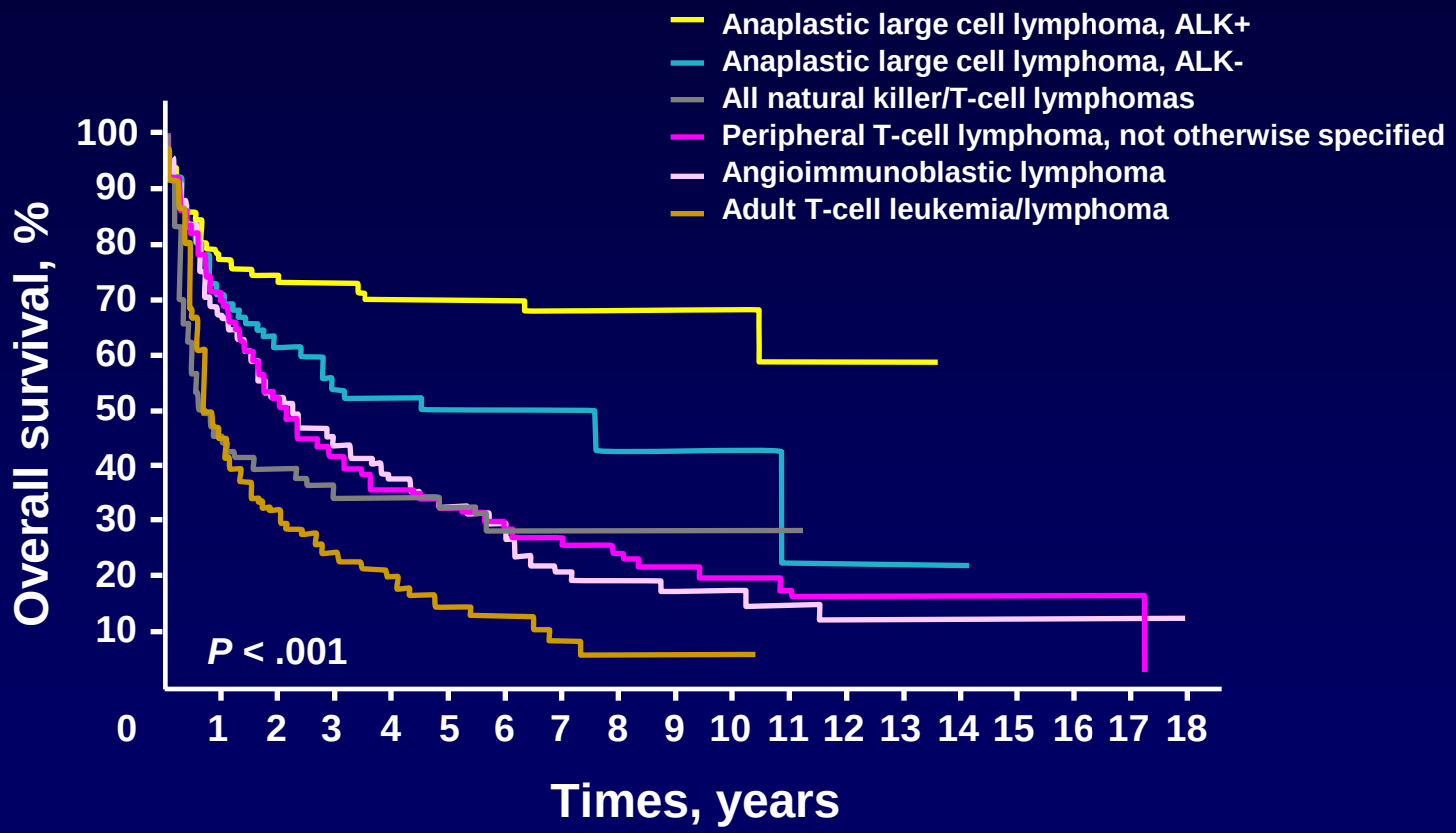
Mature T-/NK-cell lymphomas

CTCL	Extranodal	Nodal	Leukemic
Mycosis fungoides (MF)	NK/TCL nasal type	Peripheral TCL-NOS	Adult T-cell leukemia/ lymphoma
Transformed MF	Enteropathy-associated TCL	Anaplastic large cell lymphoma (ALK +/-)	Aggressive NK-cell leukemia
Sézary syndrome	Hepatosplenic TCL	Angioimmunoblastic TCL	T-cell prolymphocytic leukemia
Primary cutaneous CD30+ T-cell disorders	Subcutaneous panniculitis-like TCL		T-cell large granular lymphocytic leukemia
Primary cutaneous gamma/delta TCL			

Aggressive

Swerdlow SH, et al (eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, 4th Edition. International Agency for Research on Cancer/WHO Press; Geneva, Switzerland; 2008.

PTCL Prognosis Is Indicative of Diverse Biology

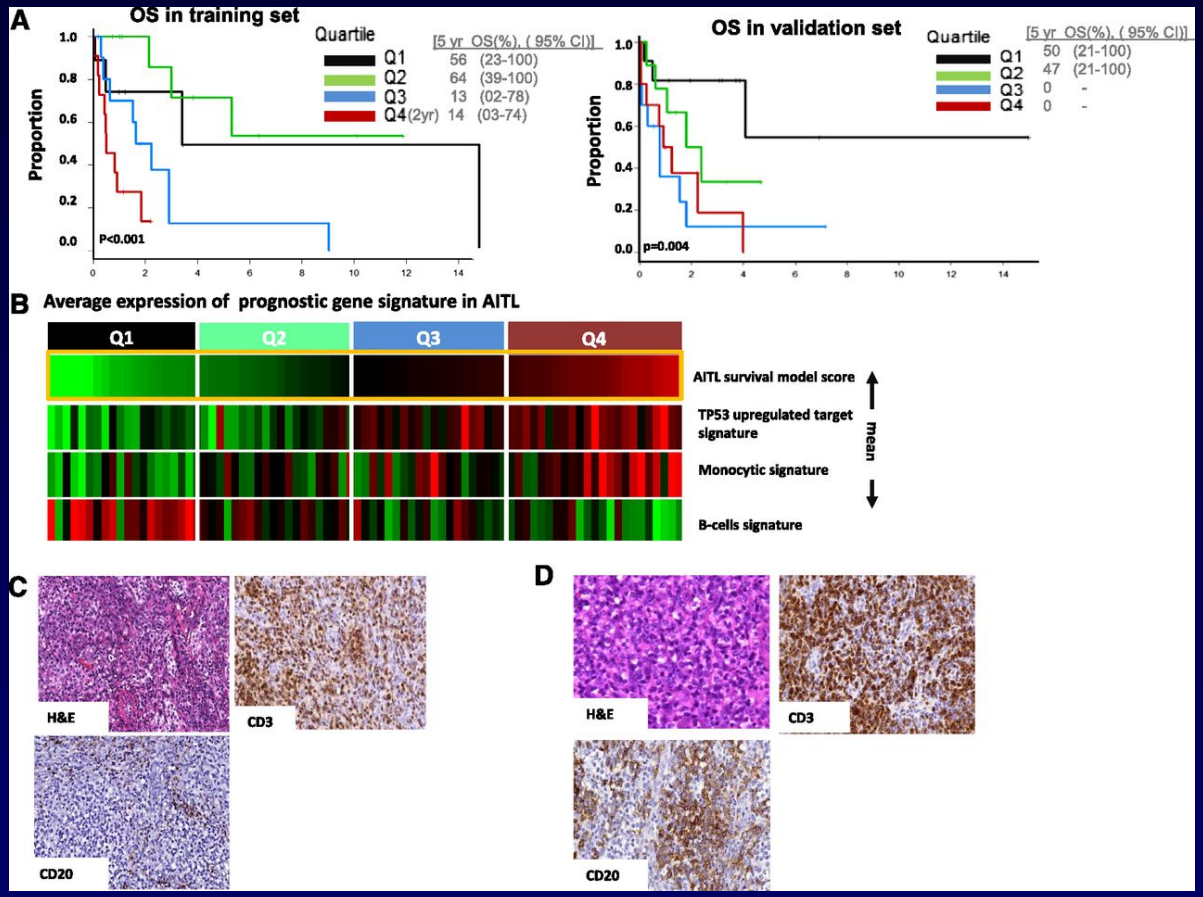


Vose J, et al. *J Clin Oncol.* 2008;26(25):4124-4130.

How Tumor Biology Will Drive Effective New Therapies

- Molecular classification
- Risk stratification
- Biology-based treatment choices
- Novel agents
- Novel platforms
- Trials based on biology

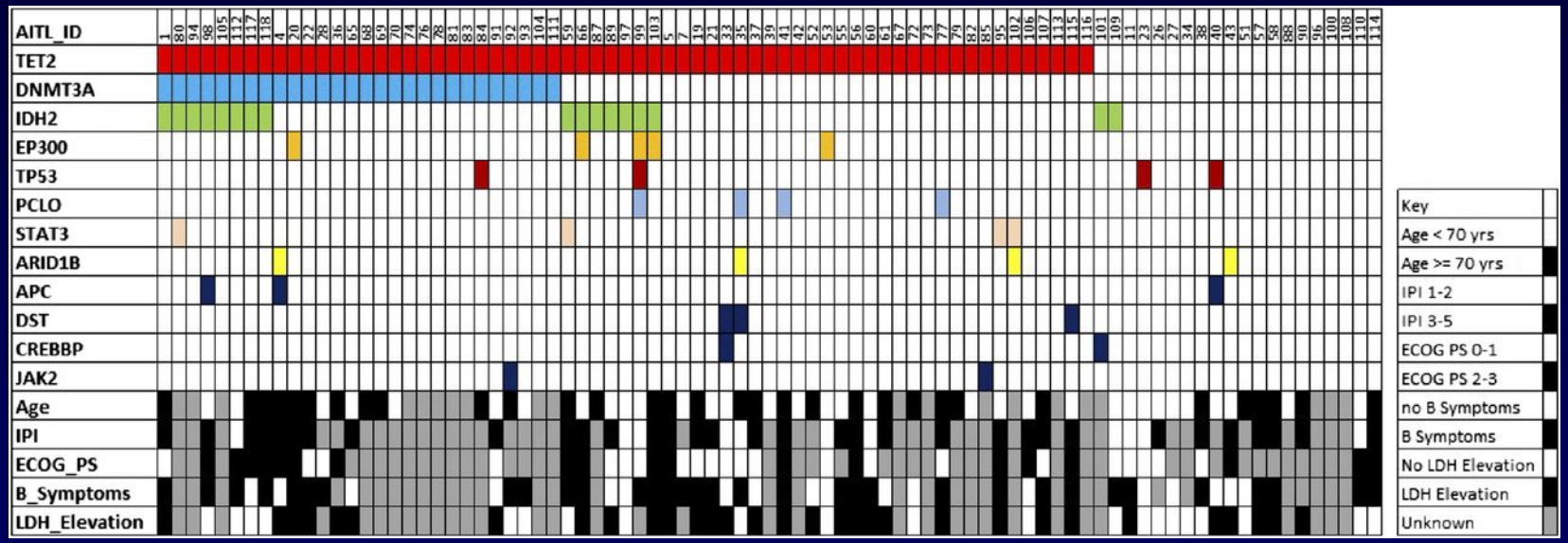
Survival Prediction in AITL



Iqbal J, et al. *Blood*. 2014;123:2915-2923.

blood

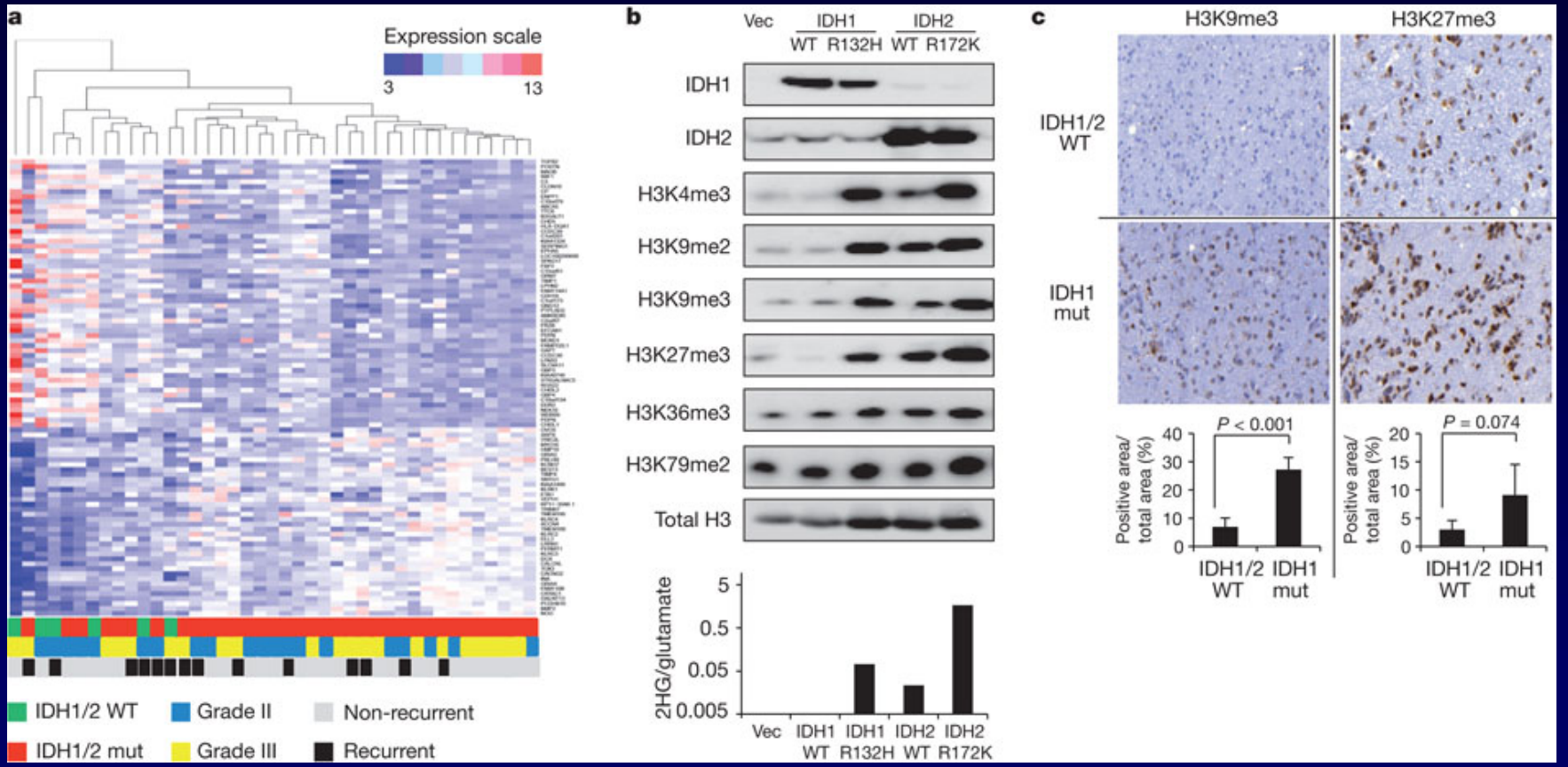
Distribution of Mutations in AITL



Odejide O, et al. *Blood.* 2014;123:1293-1296.

blood

IDH Mutations and Global Histone Methylation



nature

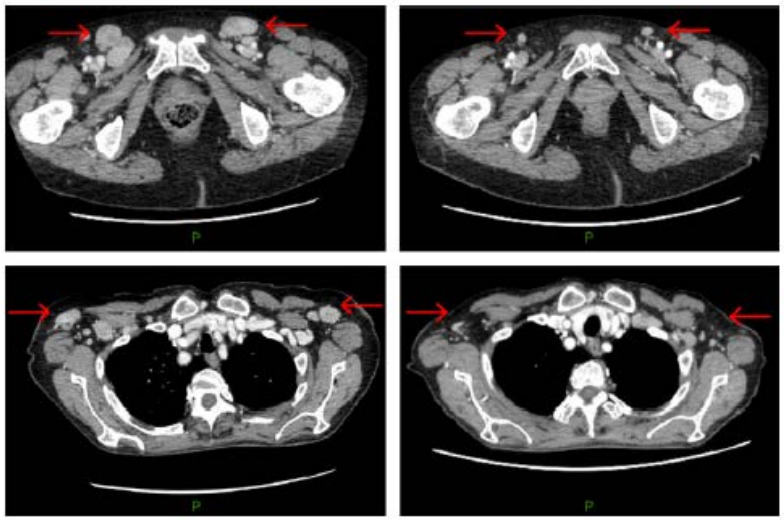
Lu C, et al. *Nature.* 2012;483(7390):474-478.

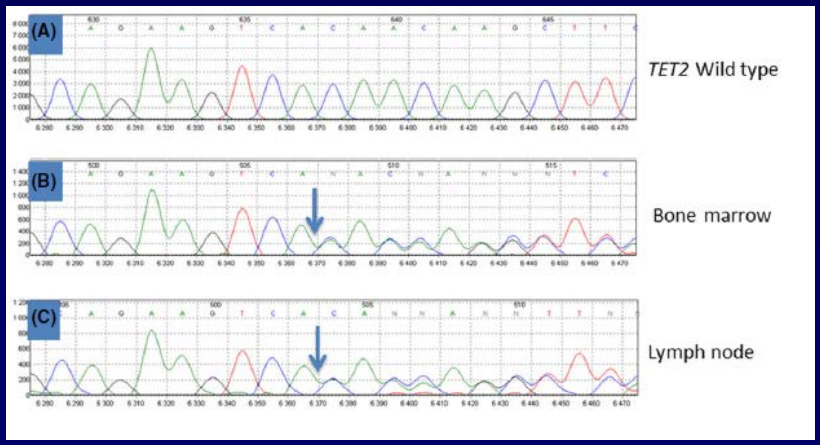
	Overall	TET2 mutated	TET2 WT	P[a]
Patients (*n*)	86	13	73	
CR	20 (23%)	5 (38%)	15 (21%)	0.17
PR	1 (1%)	0 (0%)	1 (1%)	
mCR	11 (13%)	4 (31%)	7 (10%)	
SD with HI	13 (15%)	2 (15%)	11 (15%)	
SD without HI	23 (27%)	1 (8%)	22 (31%)	
Progression	15 (17%)	1 (8%)	14 (19%)	
Early death (<4 cycles)	3 (4%)	0 (0%)	3 (4%)	
Overall response (CR, PR, mCR)	32 (37%)	9 (69%)	23 (31%)	0.01
Overall response including SD with HI	45 (52%)	11 (85%)	34 (47%)	0.01
Response duration, mos	9.3 (1.7–29.0)	9.2 (2.0–28.2)	7.1 (1.7–29.0)	0.7

Abbreviations: CR, complete remission; HI, hematological improvement; mCR, marrow CR; mos, months; PR, partial remission; SD, stable disease; TET2, ten-eleven-translocation 2.

Results are reported as *n* (%) or median.

[a] *TET2* mutated versus WT.





Itzykson R, et al. *Leukemia.* 2011;25(7):1147-1152.
Cheminant M, et al. *Br J Haematol*. 2014 Oct 14. [Epub ahead of print]

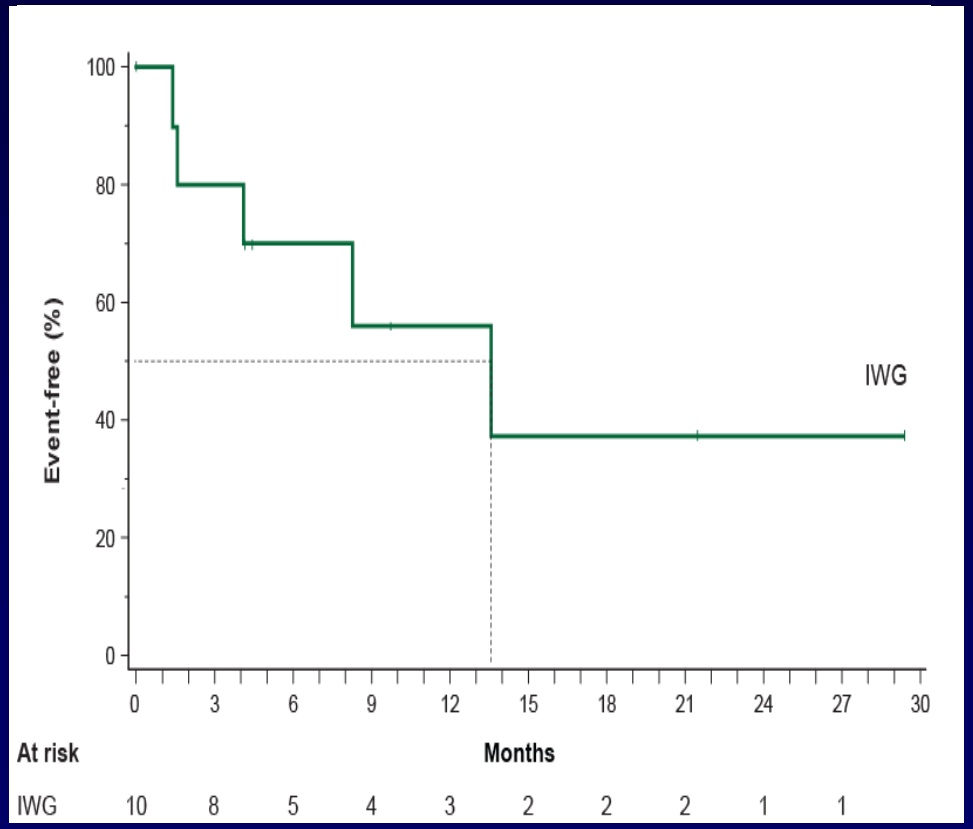
Belinostat in AITL: Results From the Belief Trial

	Efficacy analysis (N = 120)			
		Responders		
CPRG lymphoma diagnosis	N	ORR %	CR N (%)	PR N (%)
PTCL, NOS	77	23	7(9)	11 (14)
AITL	22	46	4 (18)	6 (27)
ALCL, ALK-negative	13	15	1(7)	1 (7)
ALCL, ALK-positive	2	0	-	-
Enteropathy-associated TCL	2	0	-	-
Extranodal NK/TCL, nasal type	2	50	1	-
Hepatosplenic TCL	2	0	-	-

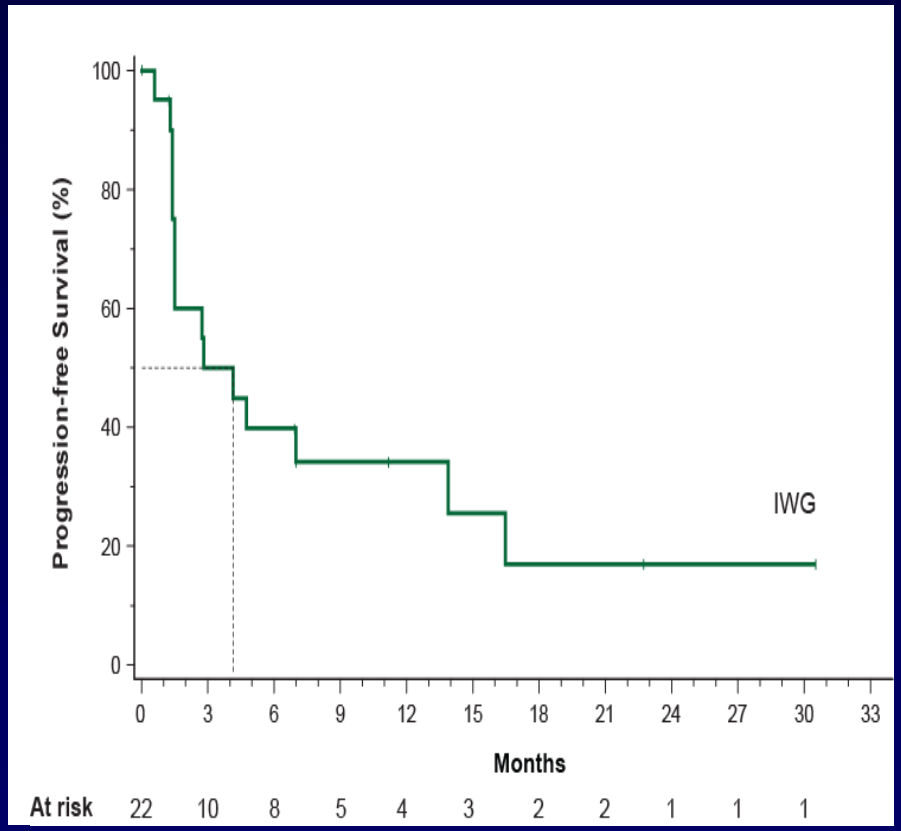
Horwitz S, et al. Presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 153.

Belinostat in AITL: Results From the Belief Trial

DOR median 13.6 months
(95% CI, 1.4-29.4)
(8.3 months for overall study)

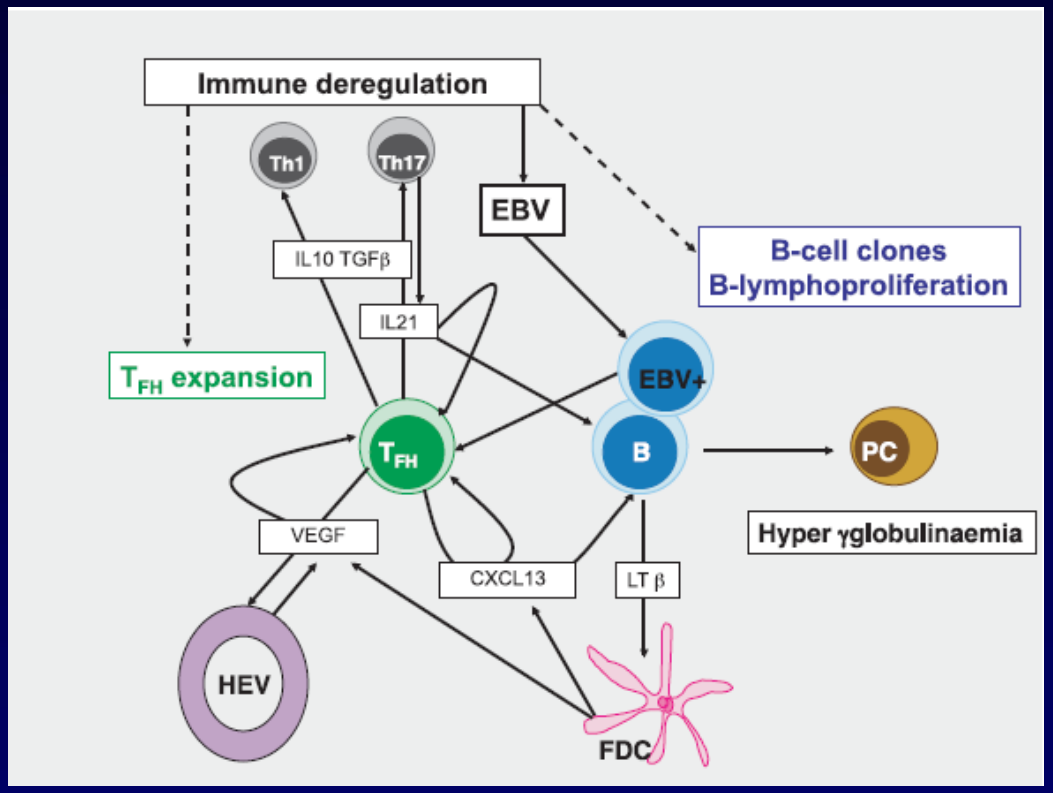


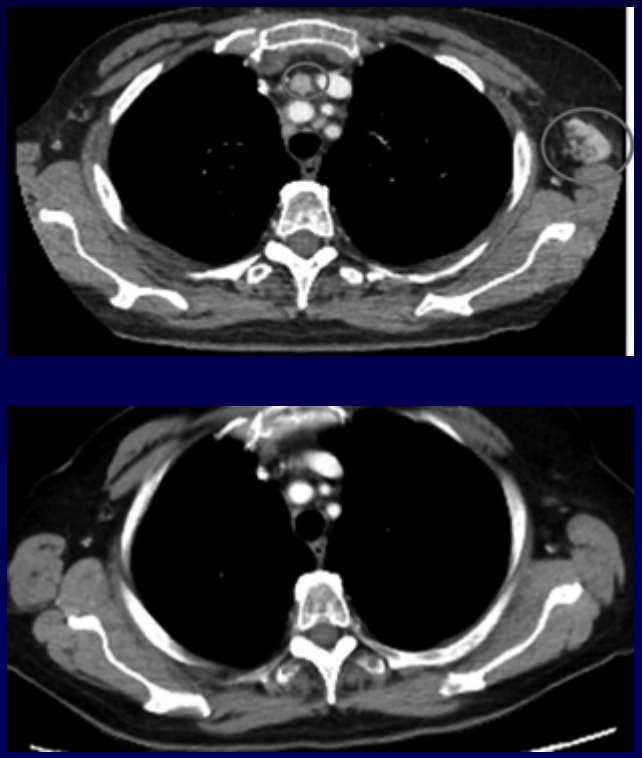
PFS median 4.2 months
(95% CI, 1.5-13.9)
(1.6 months for overall study)



Horwitz S, et al. Presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 153.

Targeting Microenvironment in AITL

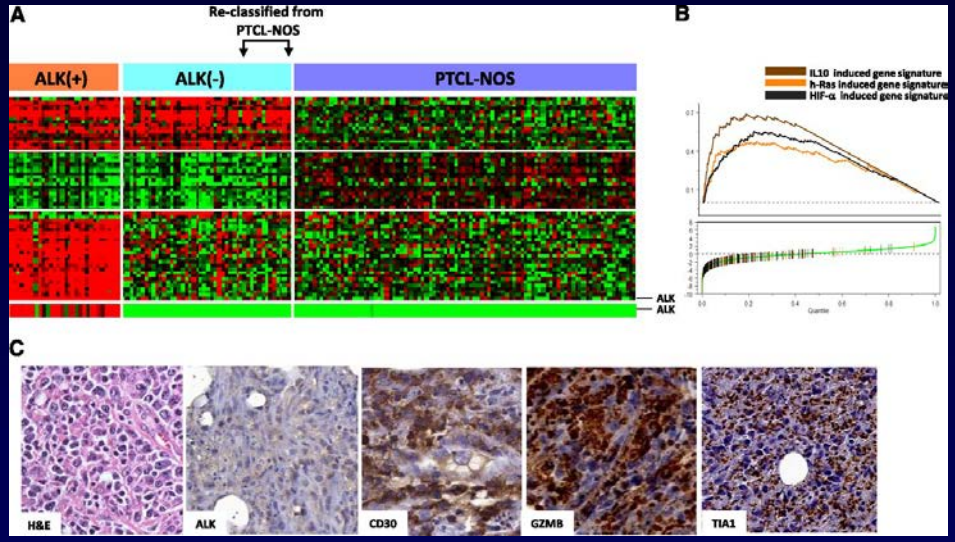


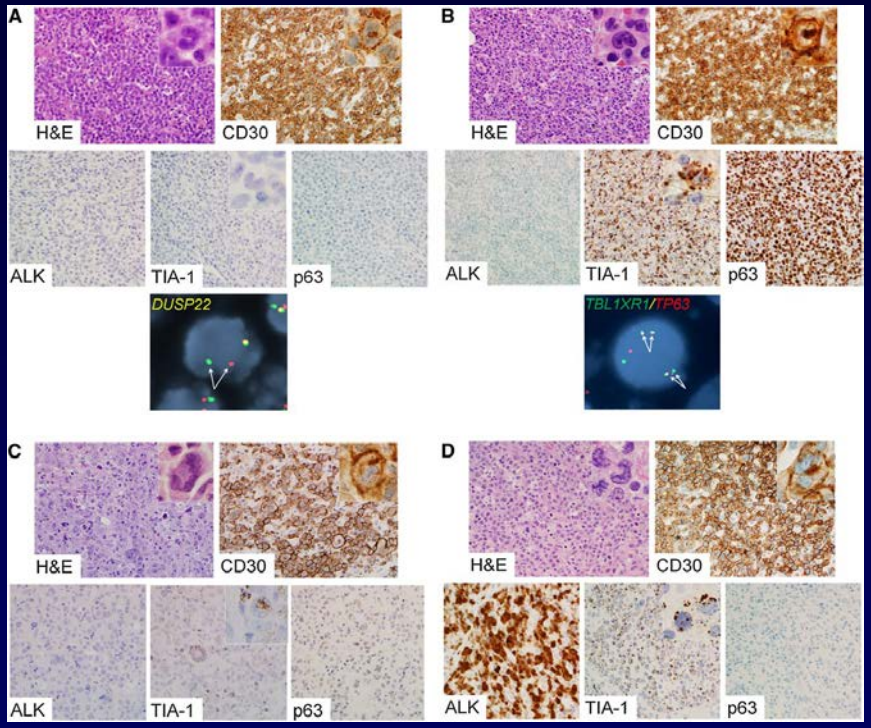


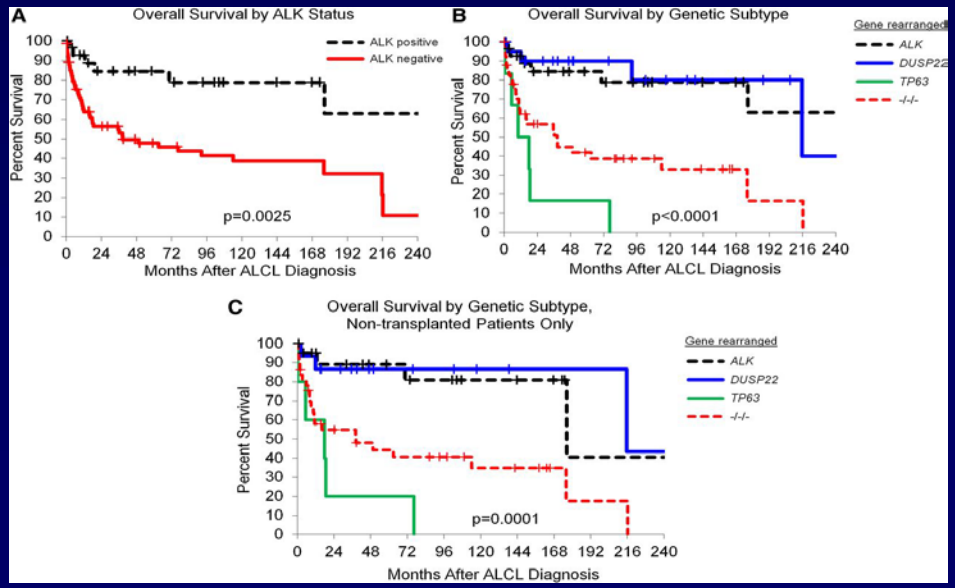
de Leval L, et al. Br J Haematol. 2010;148(5):673-689.

Chaoui D, et al. *Br J Haematol*. 2014;164(5):750-752.

Molecular Distinction of ALK-Negative ALCL



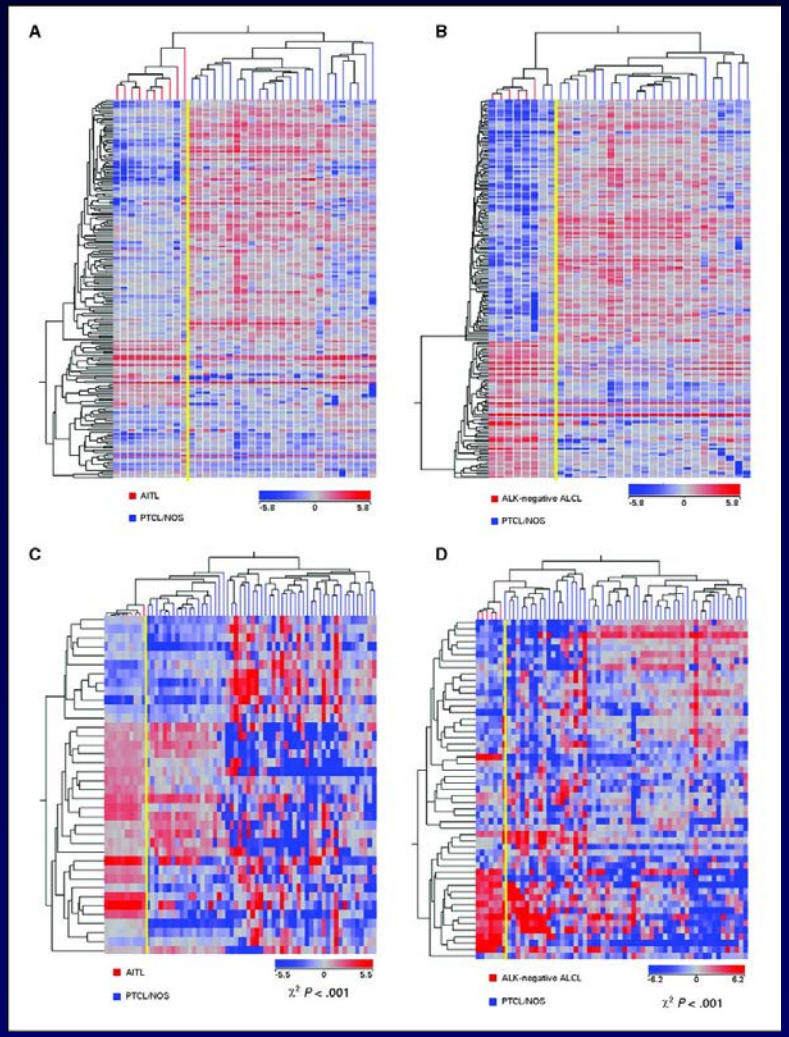




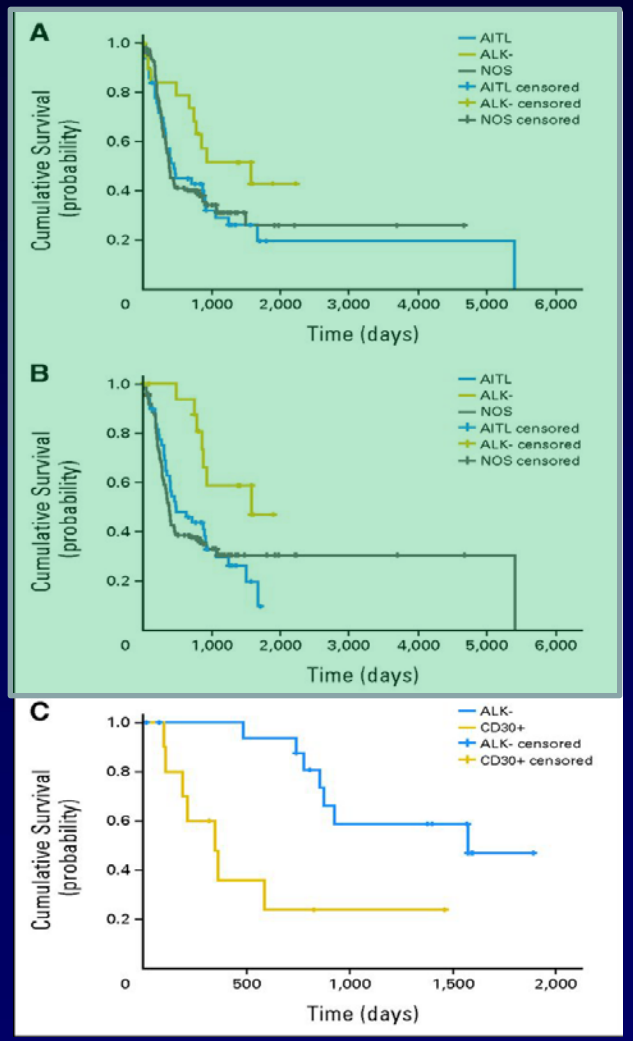
Iqbal J, et al. *Blood*. 2014;123:2915-2923.

blood

Supervised analyses identified genes differentially expressed in (A) angioimmunoblastic T-cell lymphoma (AITL) versus peripheral T-cell lymphoma (PTCL) not otherwise specified (NOS) and (B) ALK-negative anaplastic large-cell lymphoma (ALCL) versus PTCL



Survival curves according to peripheral T-cell lymphoma (PTCL): (A) histopathologic subtype, (B) molecular subtype, and (C) molecular distinction of CD30+ PTCL not otherwise specified (NOS) and ALK-negative anaplastic large-cell lymphoma (ALK-).



Piccaluga PP, et al. *J Clin Oncol*. 2013;31(24):3019-3025

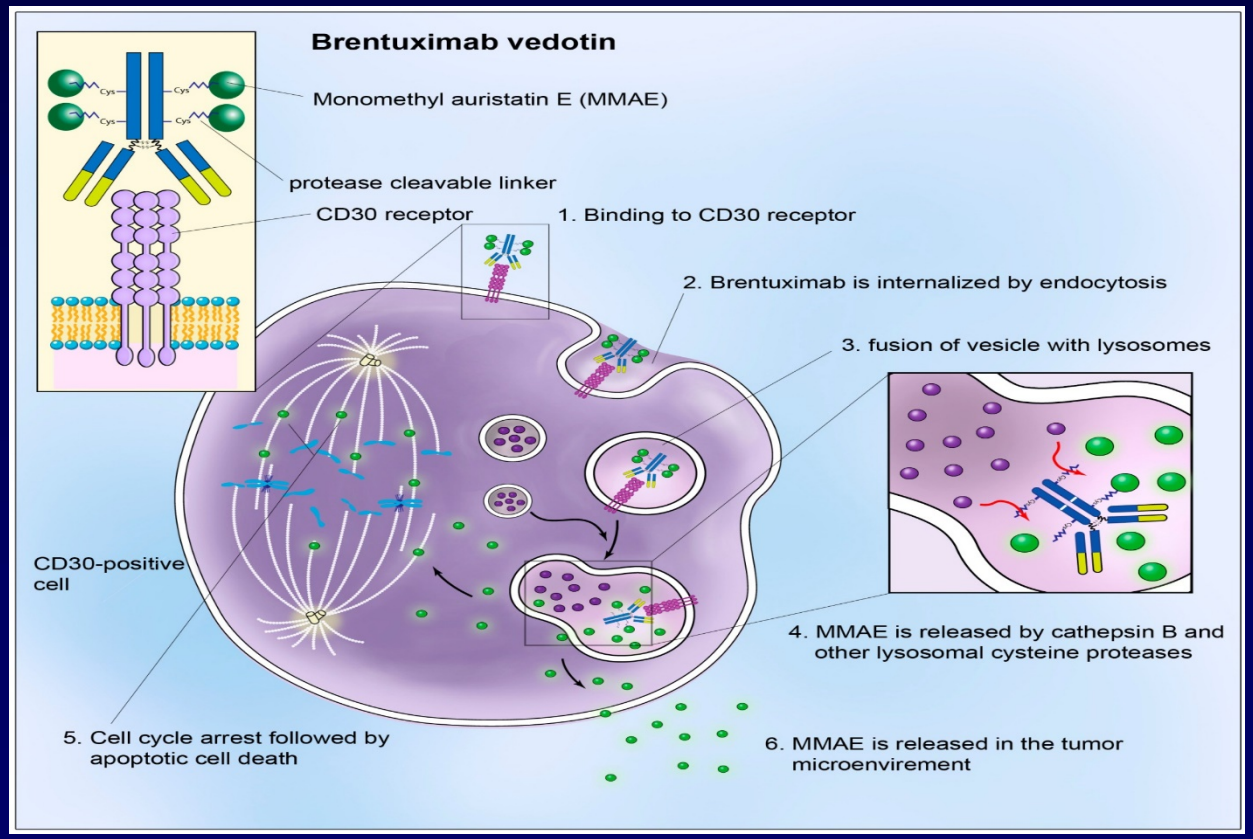
VOLUME 30 · NUMBER 18 · JUNE 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study

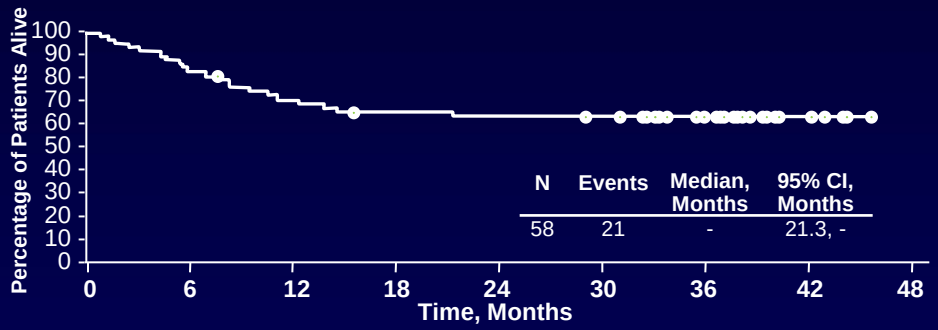
Barbara Pro, Ranjana Advani, Pauline Brice, Nancy L. Bartlett, Joseph D. Rosenblatt, Tim Illidge, Jeffrey Matous, Radhakrishnan Ramchandren, Michelle Fanale, Joseph M. Connors, Yin Yang, Eric L. Sievers, Dana A. Kennedy, and Andrei Shustov



Shustov A. *Ther Adv Hematol*. 2013;4(3):173-187.

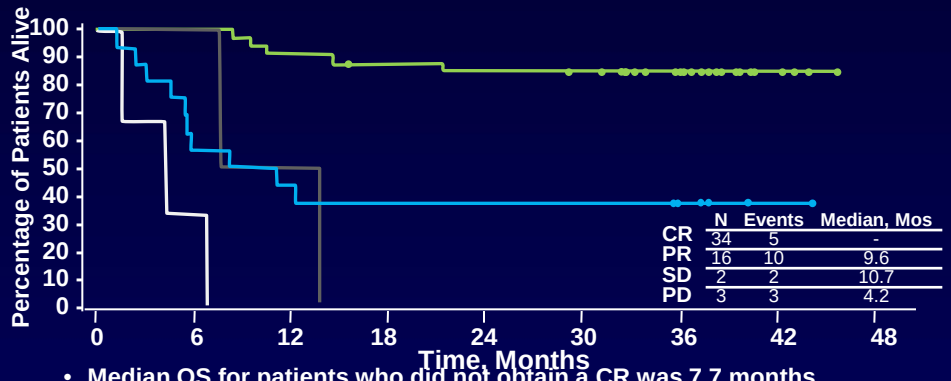
SGN-35-004: Updated Results

Overall Survival



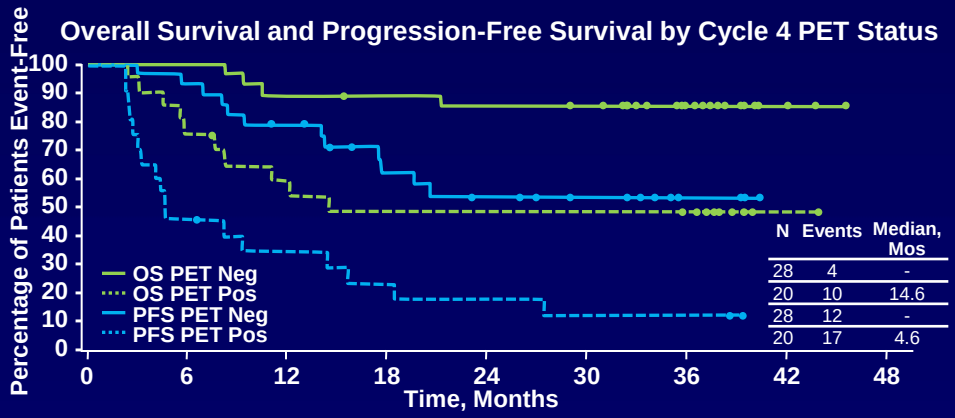
- 37 of 58 patients (64%) were alive at time of last follow-up
- Estimated overall survival rate at 3 years = 63% (95% CI: 51%, 76%)
- 12 patients were retreated with brentuximab vedotin (N = 8) or received extended treatment (>16 cycles) with brentuximab vedotin (N = 4)

Overall Survival by Best Response



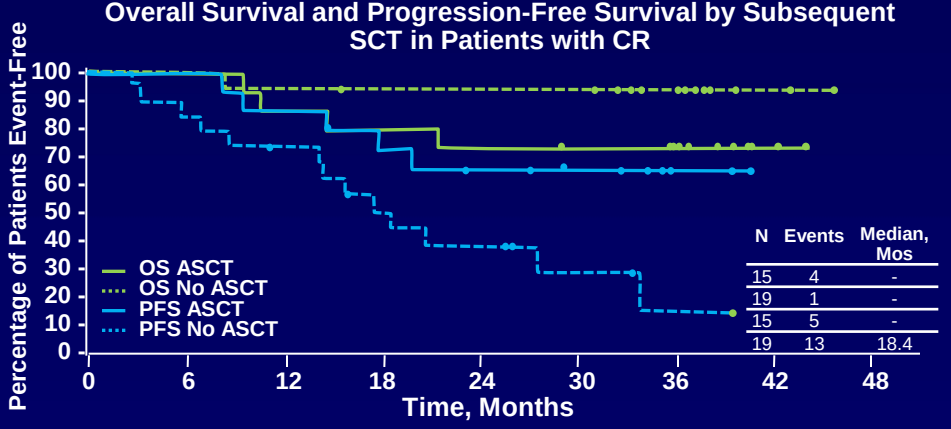
- Median OS for patients who did not obtain a CR was 7.7 months (95% CI: 4.5, 13.7)
- Median OS for patients who obtained a CR has not yet been reached

Overall Survival and Progression-Free Survival by Cycle 4 PET Status



Note: 10 pts did not have a PET scan at C4 because of AEs (3 pts), progressive disease (5 pts), investigator decision (1 pt), and patient decision (1 pt); PFS was censored at the IRF's last radiologic assessment that determined lack of progression

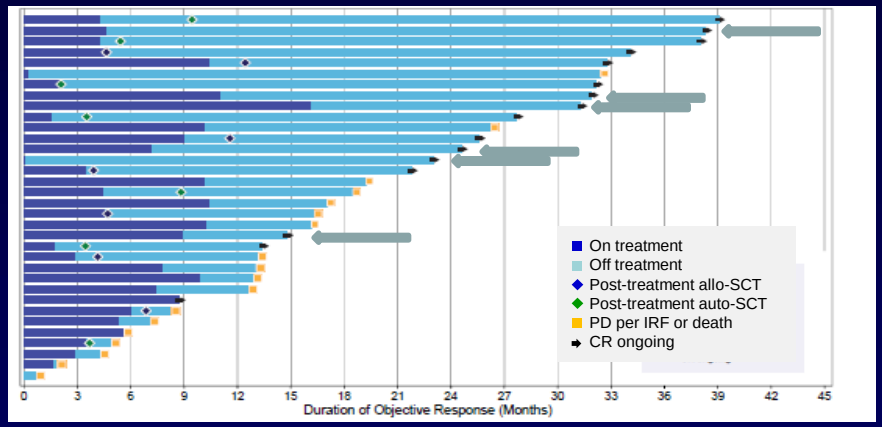
Overall Survival and Progression-Free Survival by Subsequent SCT in Patients with CR



Note: Allo-SCT (8 pts) and auto-SCT (7 pts); 3 non-disease-related deaths occurred in post-allo SCT patients; PFS was censored at the IRF's last radiologic assessment that determined lack of progression

SGN-35-004: Updated Results

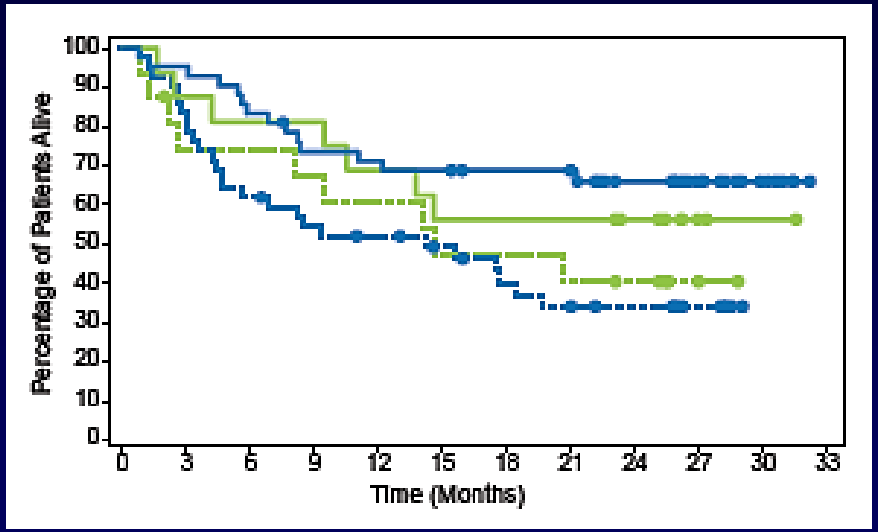
Duration of Response in Patients with CR



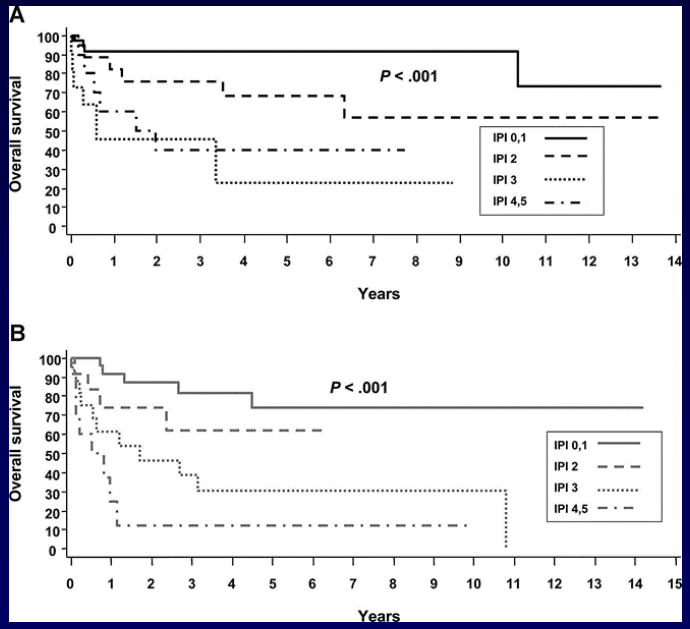
Of the 34 patients who achieved a CR, 16 (47%) remained in remission at the time of last follow-up:

- **10/16 have received SCT following brentuximab vedotin**
- **6/16 have had no new anti-cancer therapy following brentuximab vedotin**

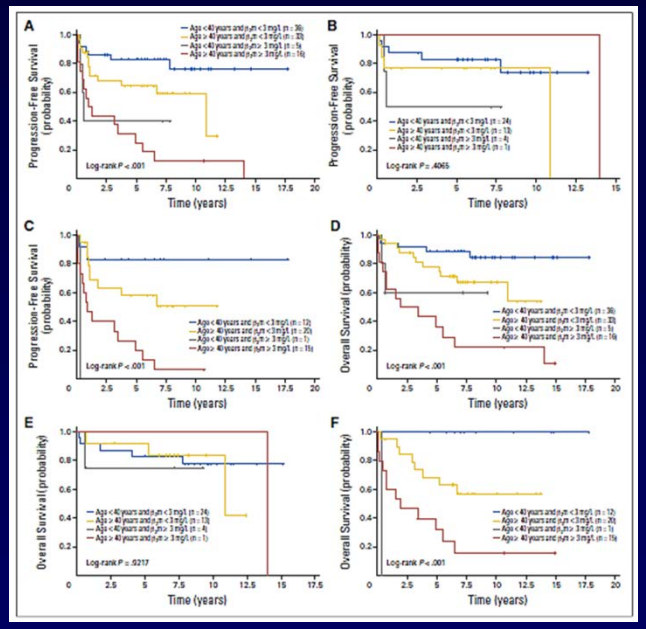
OS and PFS by ALK status



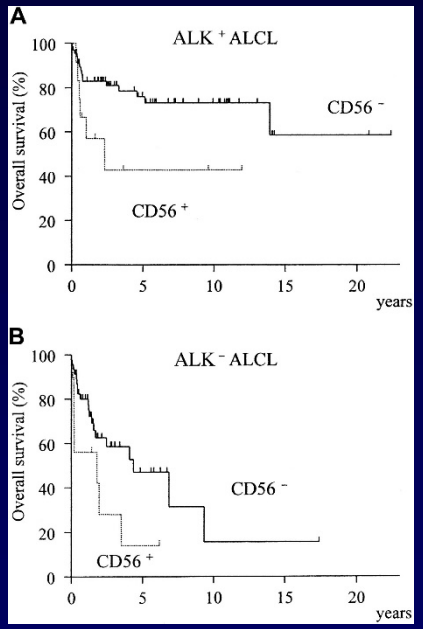
ALK-Positive ALCL: Not All Born Equal



Savage KJ, et al. *Blood.* 2008;111:5496-5504.

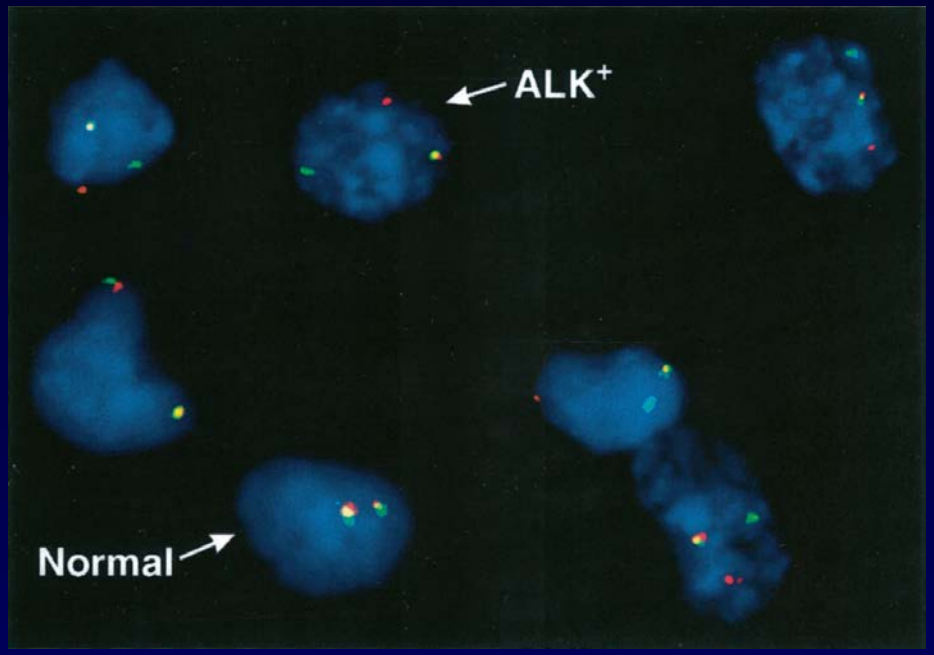


Sibon D, et al. *J Clin Oncol.* 2012;30:3939-3946.

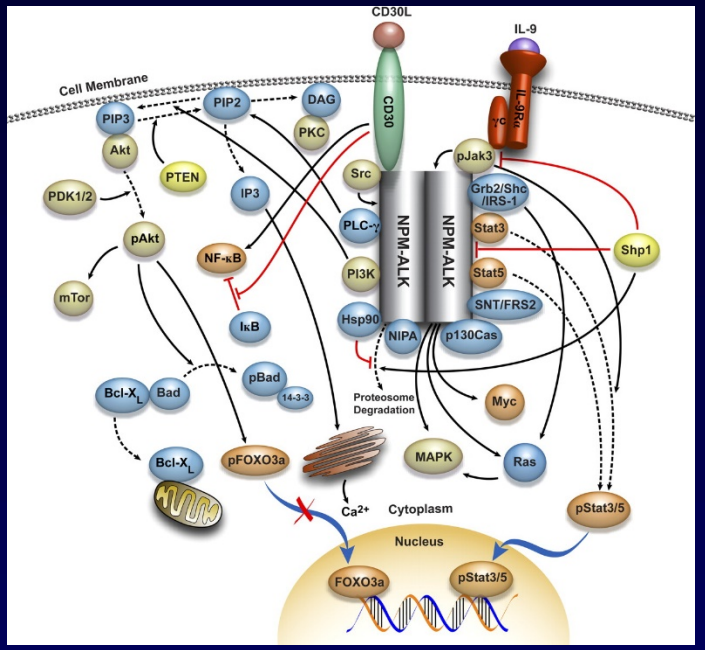


Suzuki R, et al. *Blood.* 2000;96:2993-2900.

ALK+ ALCL



Kutok JL, et al. *J Clin Oncol*. 2002;20(17):3691-3702.

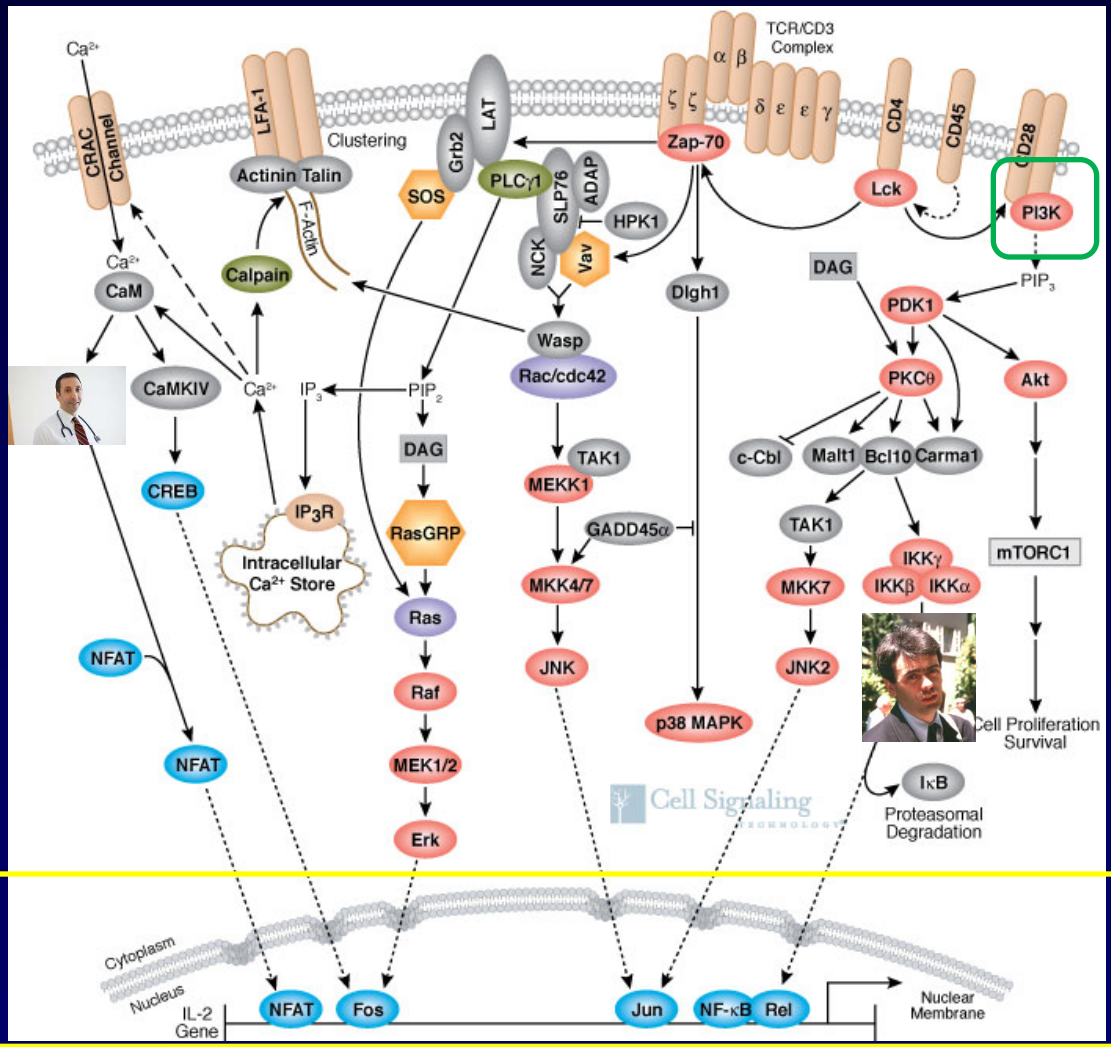


Amin HM, et al. *Blood*. 2007;110(7):2259-2267.

	N	ORR/CR	PFS
Passerini, et al	11	91%/64%	63% (2 years)
Mosse, et al	8	88%/75%	NR

PTCL-NOS:
Where Do We Go From Here?

Collateral pathway blockade



Targeted therapy

Cell cycle/ Apoptosis modulation

Epigenetic modulation

S-phase blockade

Novel Agents in PTCL

Study	N	ORR (%)	CR (%)	PFS (months)	DOR (months)	OS (months)
Romidepsin[1]	130	25	15	4	28	11.3
Pralatrexate[2]	111	29	11	3.5	10.1	14.5
Belinostat[3]	129	26	11	1.6	13.6	7.9
Bendamustine[4]	60	50	28	3.6	3.5	6.2

1. **Coiffier B, et al. *J Clin Oncol* 2012; 30:631-636.**
2. **O'Connor OA, et al. *J Clin Oncol* 2011; 29:1182-1189.**
3. **O'Connor OA, et al. *J Clin Oncol* 2014; In review.**
4. **Damaj G, et al. *J Clin Oncol* 2013; 31:104-110.**

“If we knew what it was we were doing, it would not be called research, would it?”

Albert Einstein