

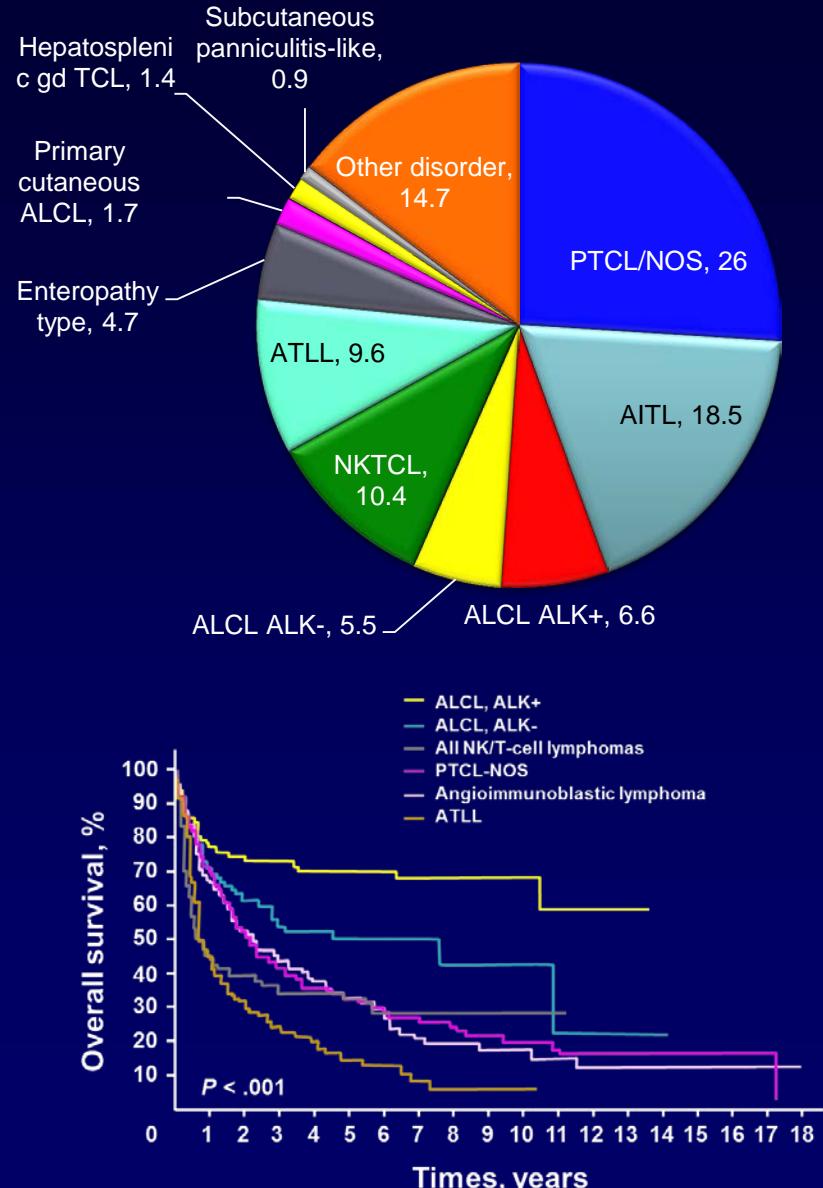
Progress and Pitfalls With Diagnosis in Peripheral T-Cell Lymphoma (PTCL)

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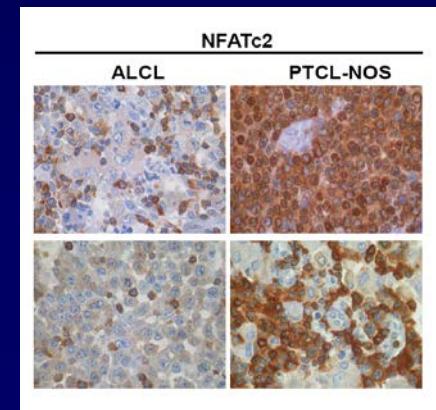
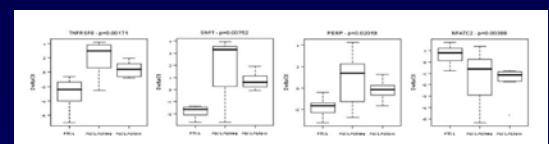
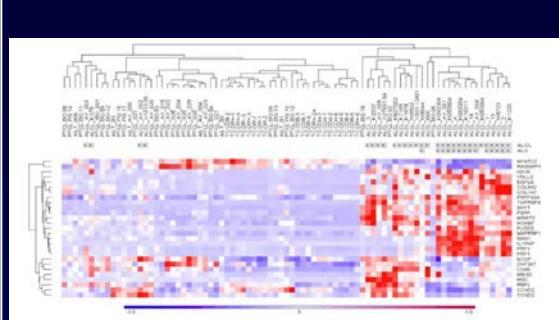
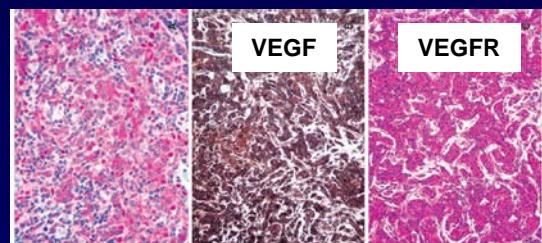
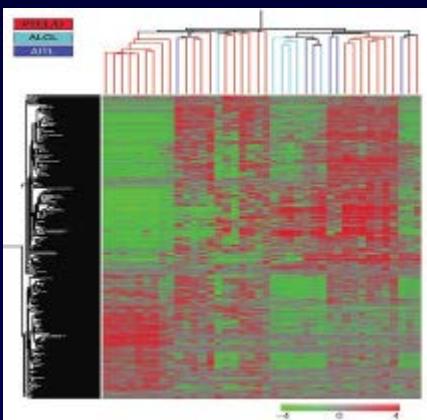
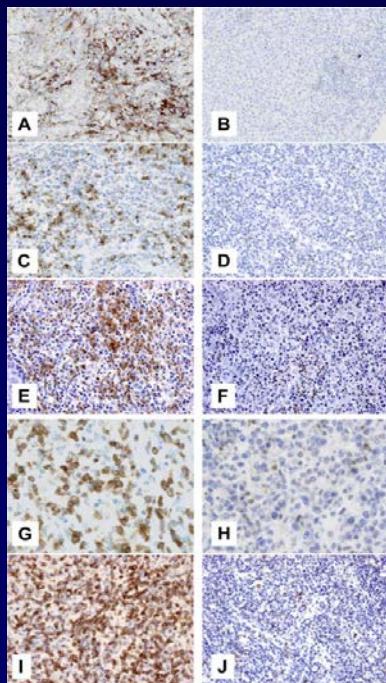
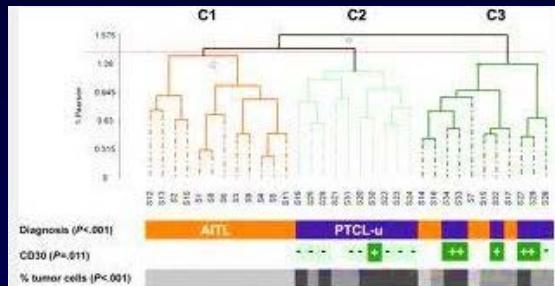
Peripheral T-Cell Lymphomas

- Rare tumors (10% NHL)
- Heterogeneous
- No diagnostic markers (but ALK⁺)
- Genetics
 - *RHOA, TET2, IDH2, DNMT3A/B*
 - *t(2;5), t(5;9), t(6;9)*
- Poor outcome



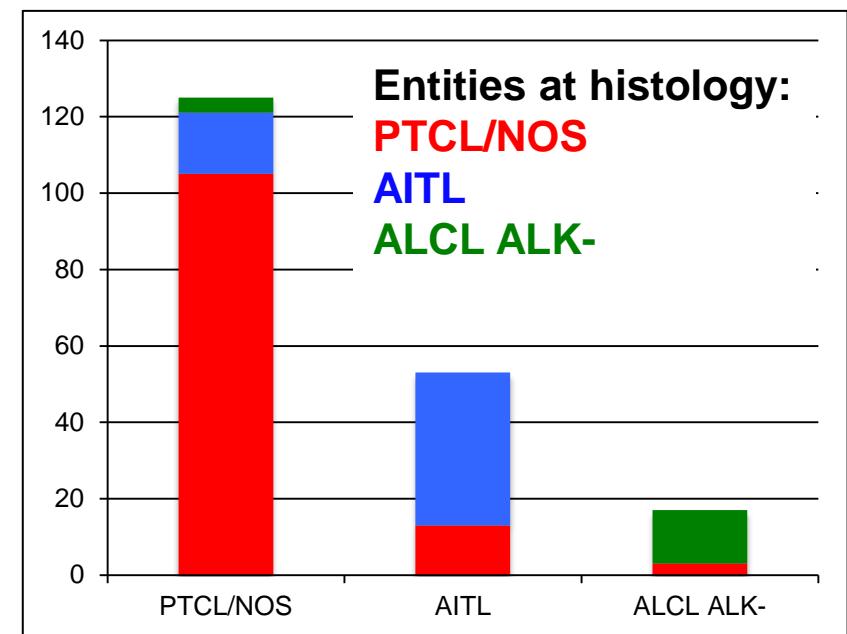
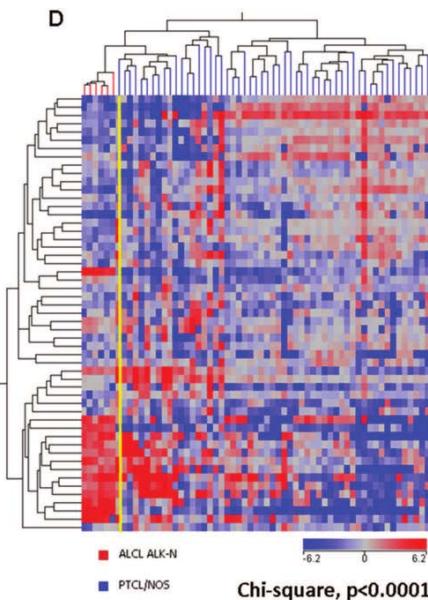
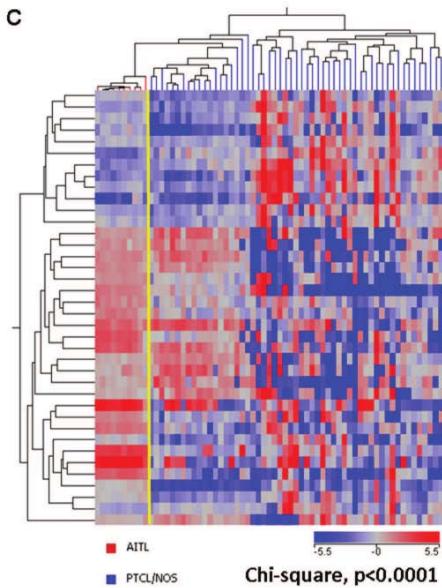
Can Molecular Diagnostic Improve Our Ability?

GEP Identified Specific Signatures for PTCLs/NOS, AITL and ALCLs



de Leval L, et al. *Blood*. 2007;109(11):4952-4963. Piccaluga PP, et al. *J Clin Invest*. 2007;117(3):823-834.
Piccaluga PP, et al. *Cancer Res*. 2007;67(22):10703-10710. Piva R, et al. *J Clin Oncol*. 2010;28(9):1583-1590.

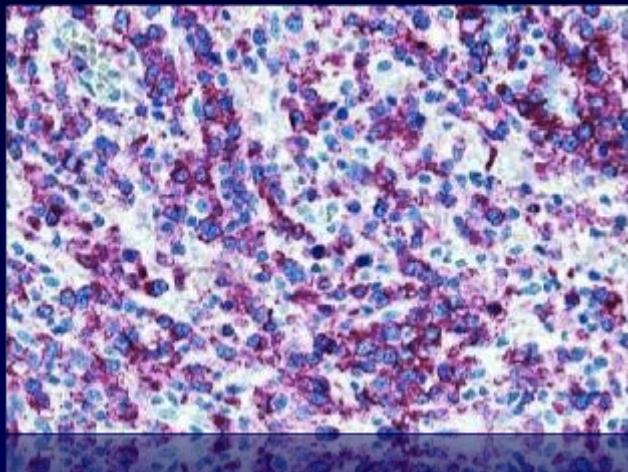
Molecular Profiling Improves Classification and Prognostication of Nodal Peripheral T-cell Lymphomas: Results of a Phase III Diagnostic Accuracy Study.



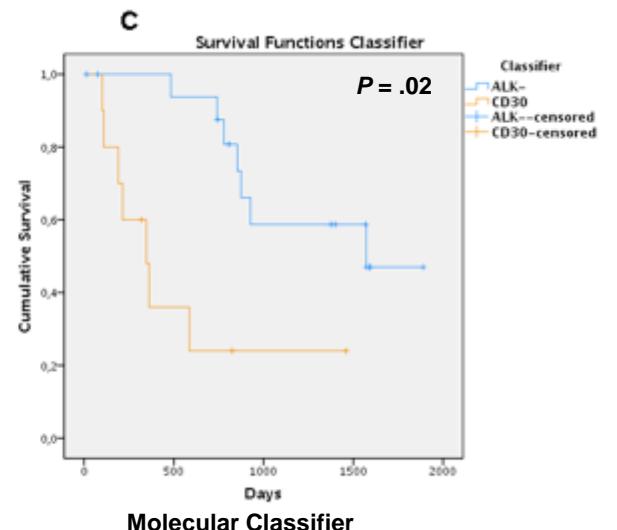
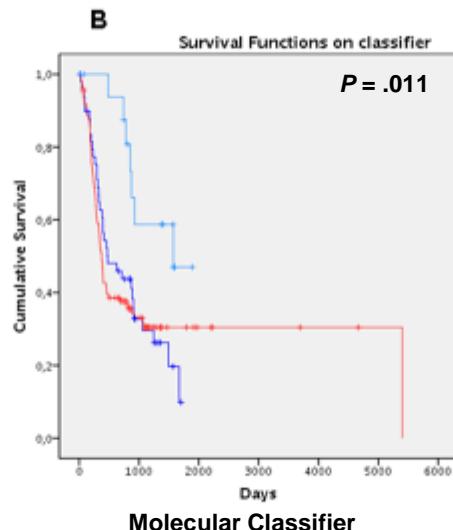
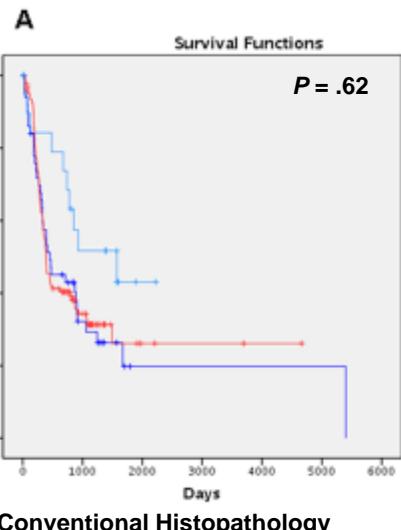
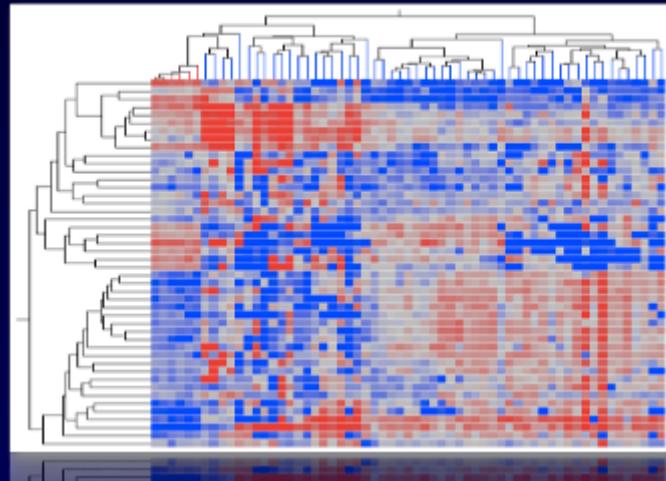
← *Molecularly defined entities* →

84% concordance for AITL
95% concordance for ALCL ALK-

Molecular Profiling Improves Classification and Prognostication of Nodal Peripheral T-Cell Lymphomas: Results of a Phase III Diagnostic Accuracy Study

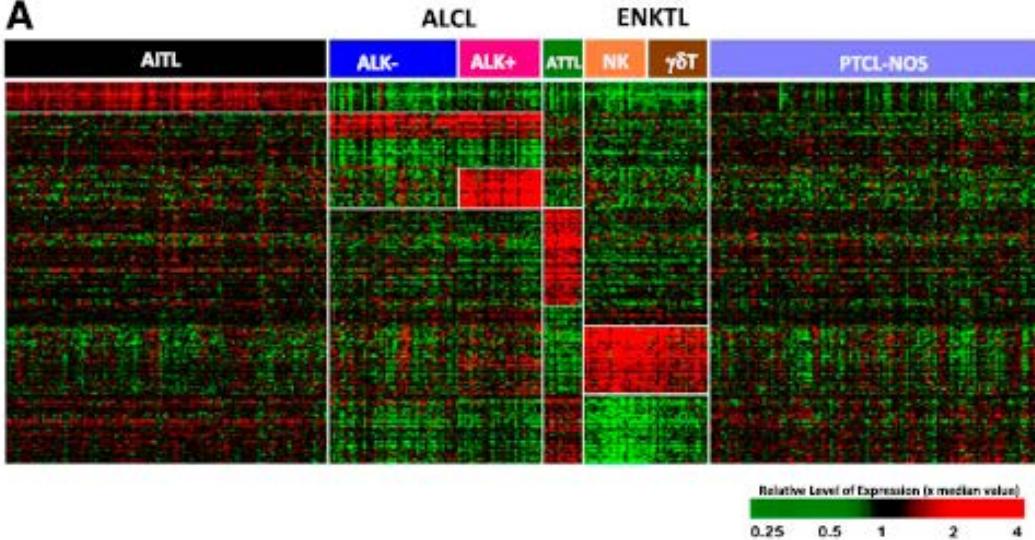


VS

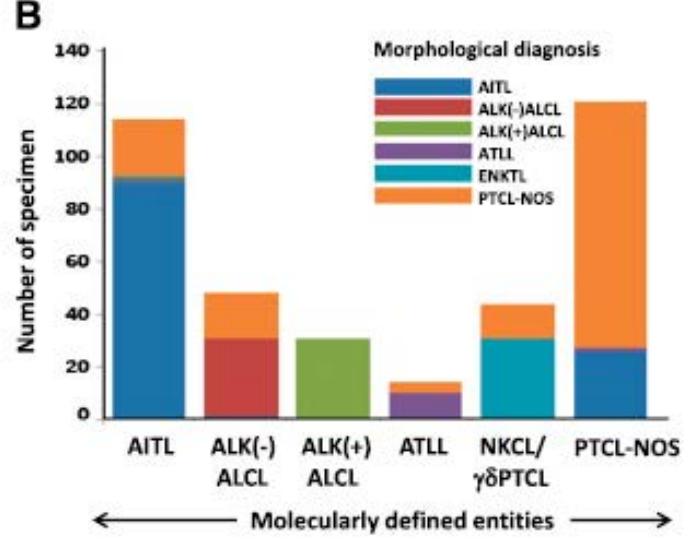


Gene Expression Signatures Delineate Biological and Prognostic Subgroups in Peripheral T-Cell Lymphomas

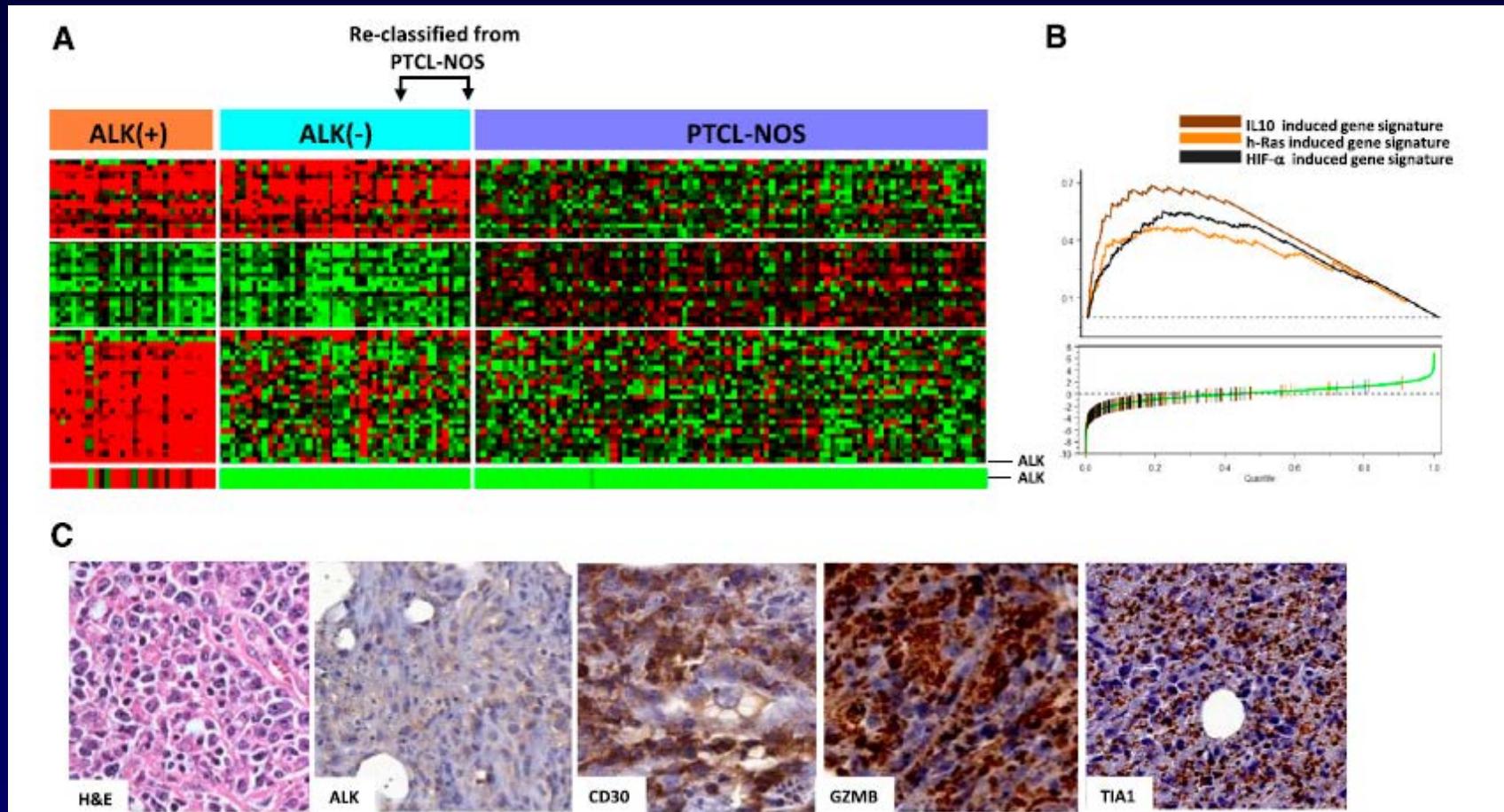
A



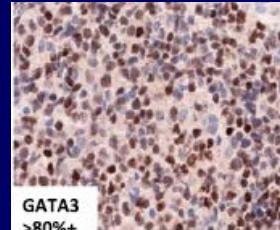
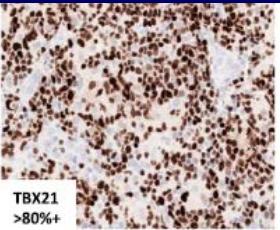
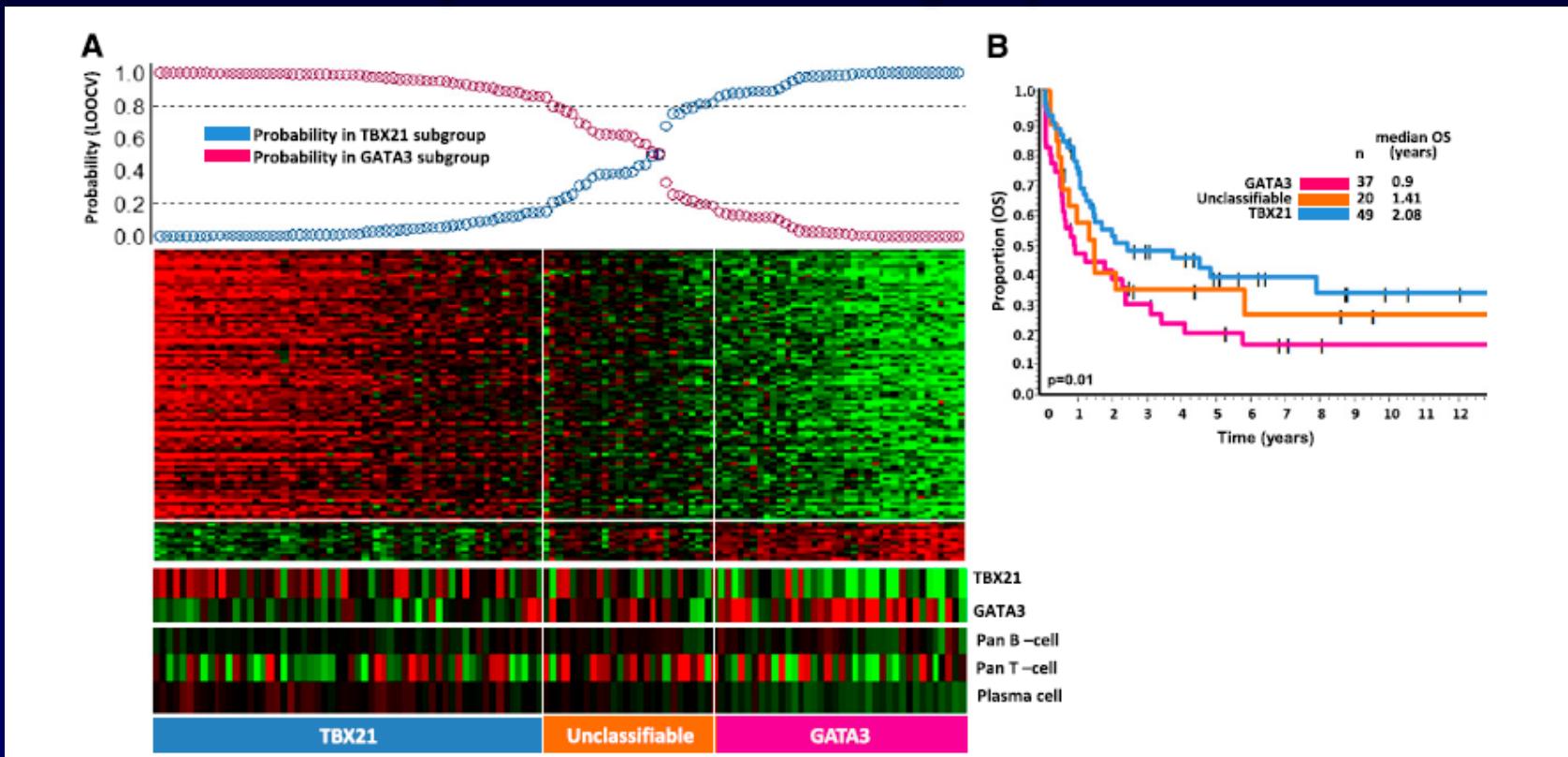
B



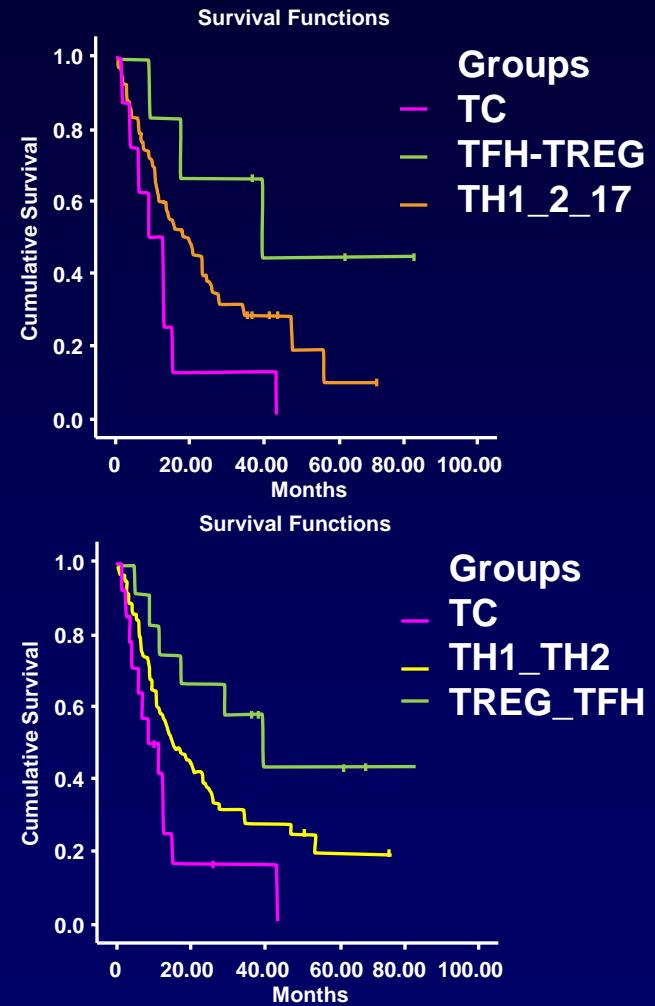
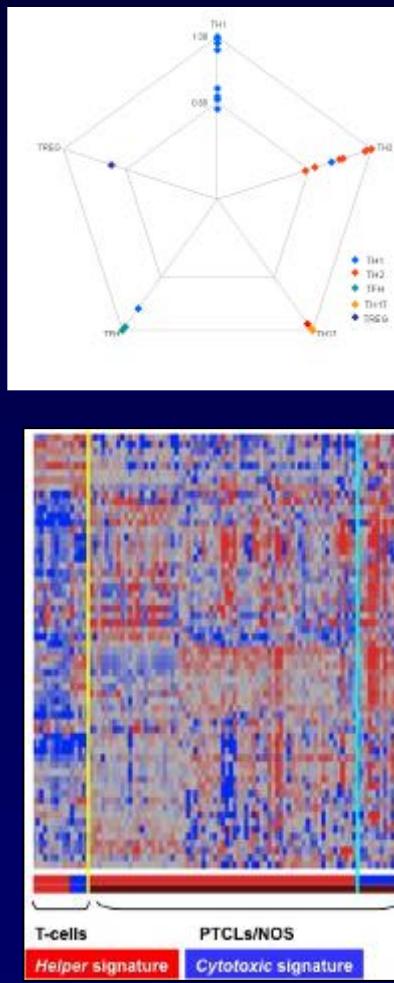
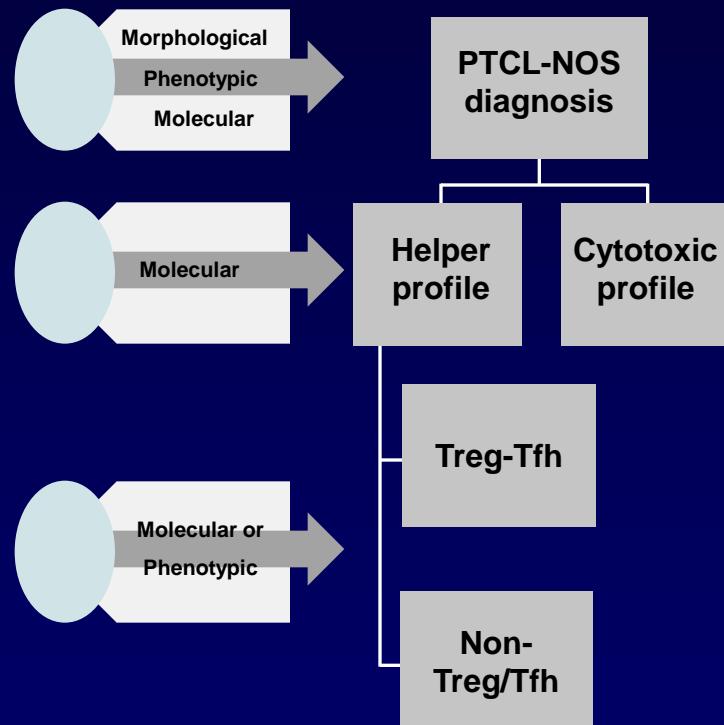
Gene Expression Signatures Delineate Biological and Prognostic Subgroups in Peripheral T-Cell Lymphomas



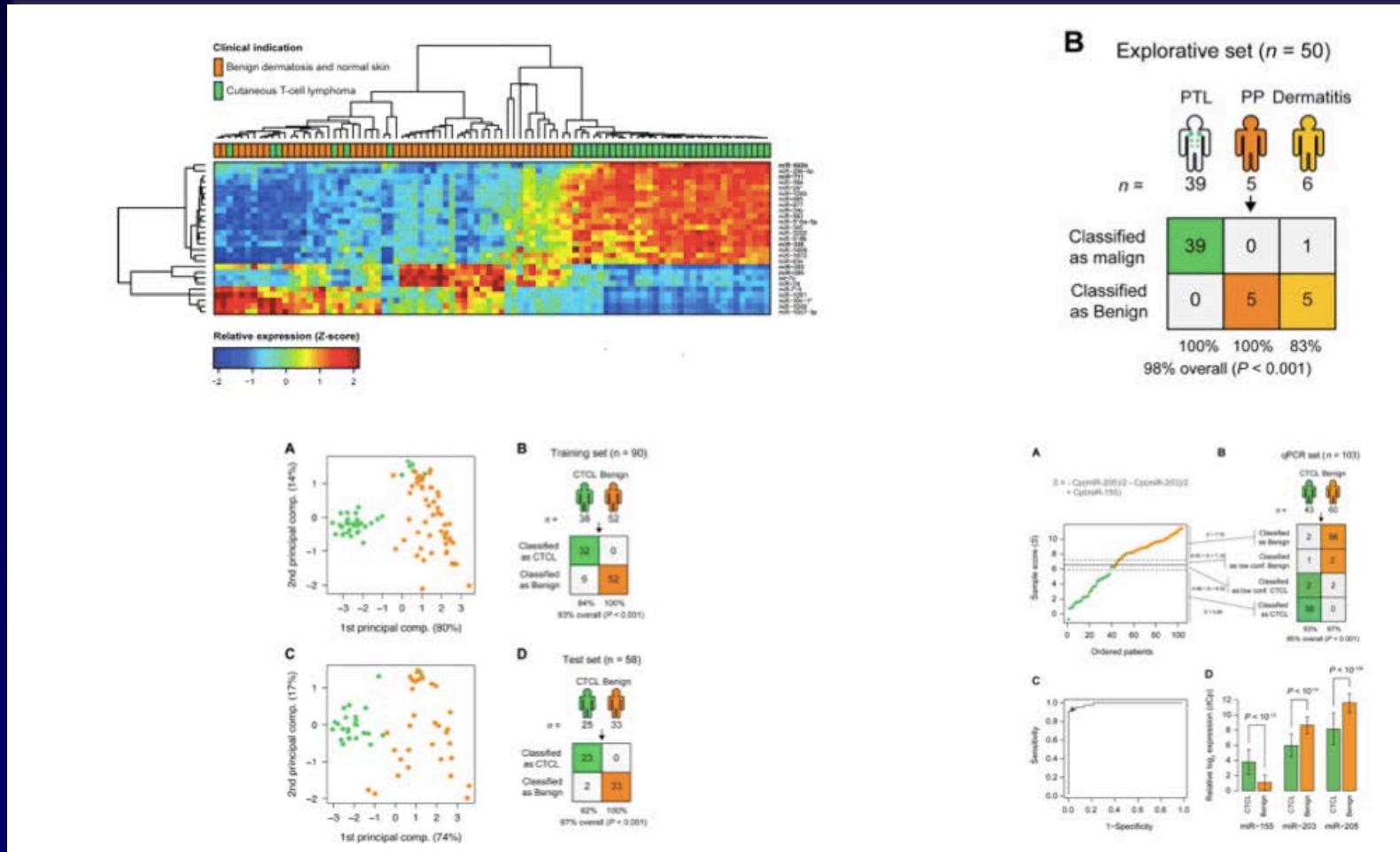
Gene Expression Signatures Delineate Biological and Prognostic Subgroups in Peripheral T-Cell Lymphomas



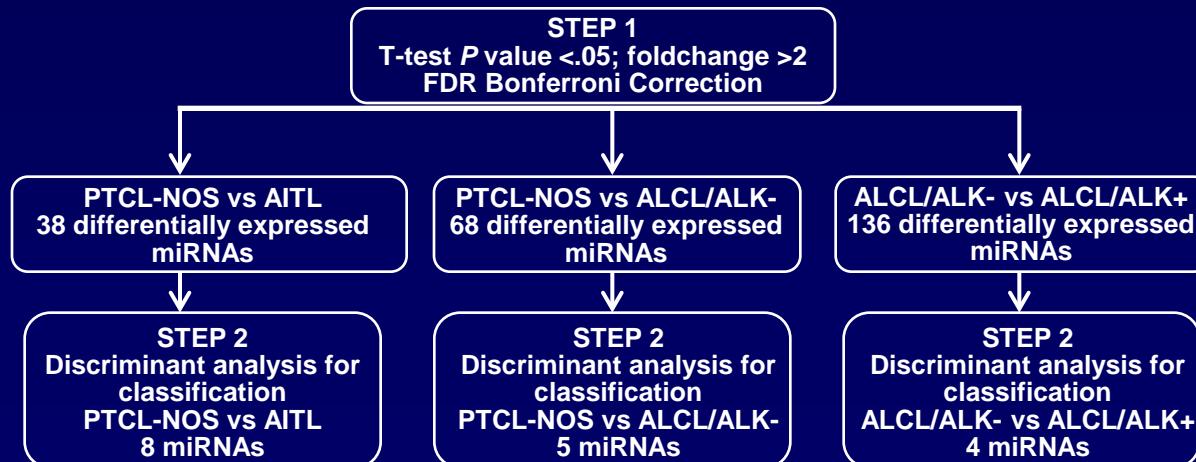
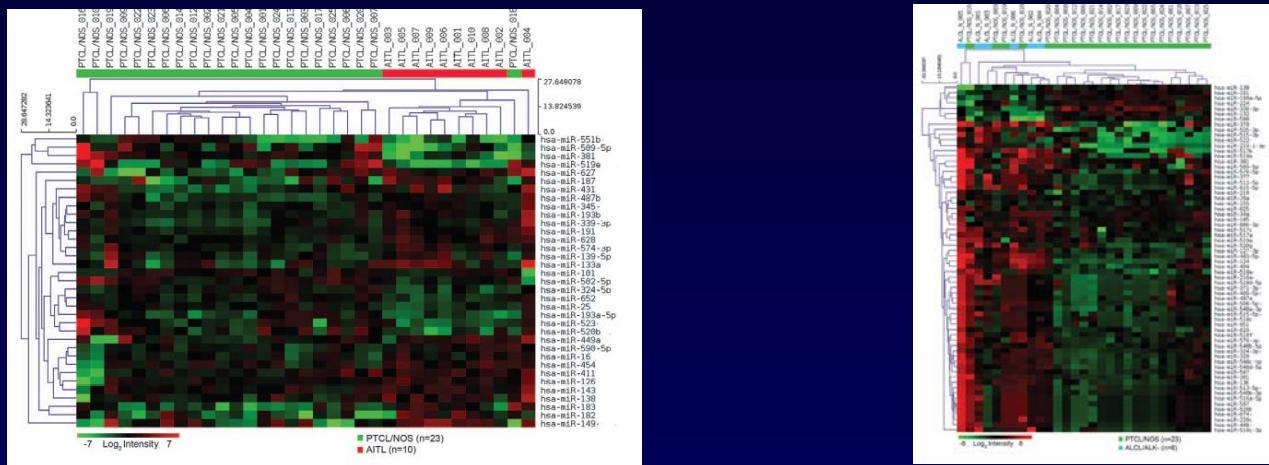
Classification of PTCLs-NOS According to Their Cellular Counterpart



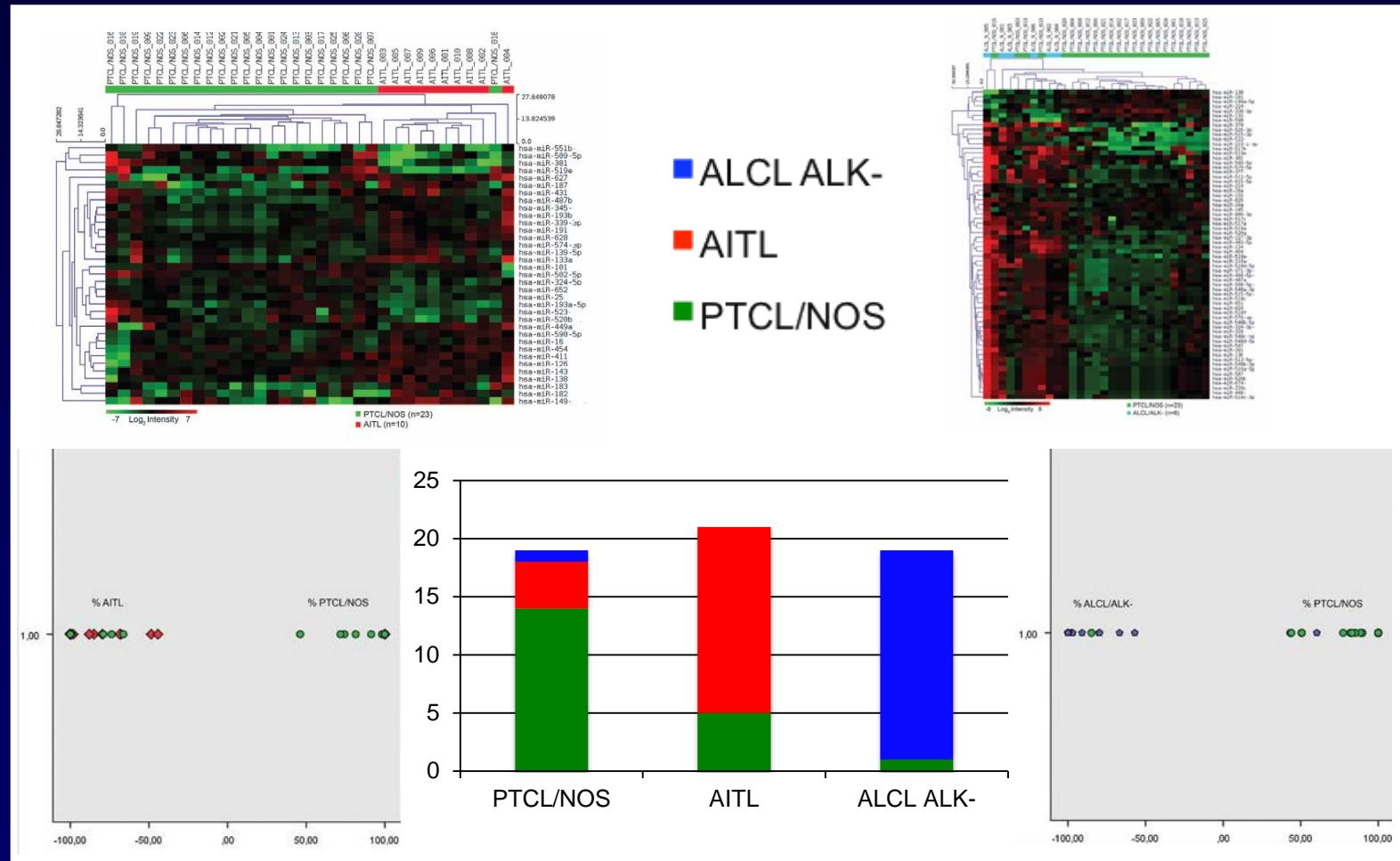
Diagnostic MicroRNA Profiling in Cutaneous T-Cell Lymphoma (CTCL)



Pathogenetic and Diagnostic Significance of MicroRNA Deregulation in Peripheral T-Cell Lymphoma Not Otherwise Specified



Pathogenetic and Diagnostic Significance of MicroRNA Deregulation in Peripheral T-Cell Lymphoma Not Otherwise Specified



Pathogenetic and Diagnostic Significance of MicroRNA Deregulation in Peripheral T-Cell Lymphoma Not Otherwise Specified

Diagnostic accuracy of PTCL-NOS vs AITL and PTCL-NOS vs ALCL/ALK-miRNA classifier evaluated in an independent set of cases

miRNA classification	Histopathology		Total
	PTCL-NOS	AITL	
PTCL-NOS	15	5	20
AITL	4	16	20
Accuracy			
	Value	95% CI	

ST 0.762 0.549-0.894

SP 0.789 0.567-0.915

PPV 0.8 0.584-0.919

NPV 0.75 0.531-0.888

LR+ 3.619 1.467-8.928

LR- 0.302 0.136-0.671

Overall accuracy 77.5% (31 of 40)

miRNA classification	Histopathology		Total
	PTCL-NOS	ALCL/ALK-	
PTCL-NOS	17	3	20
ALCL/ALK-	1	18	19
Accuracy			
	Value	95% CI	

ST 0.857 0.654-0.95

SP 0.944 0.742-0.999

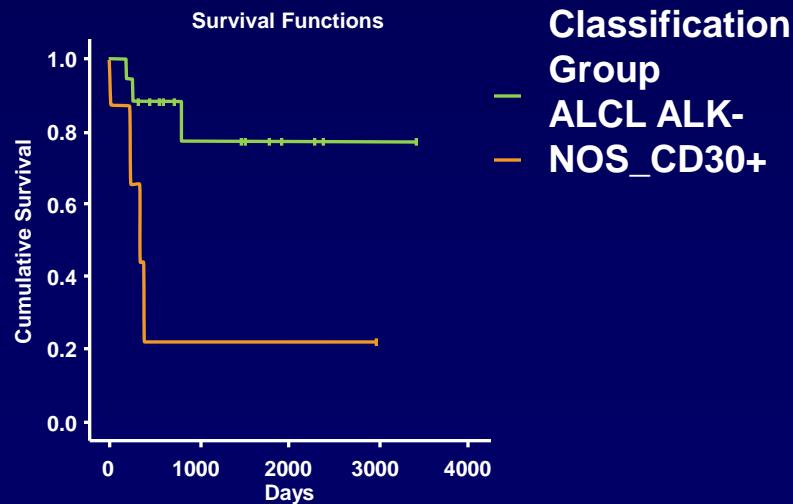
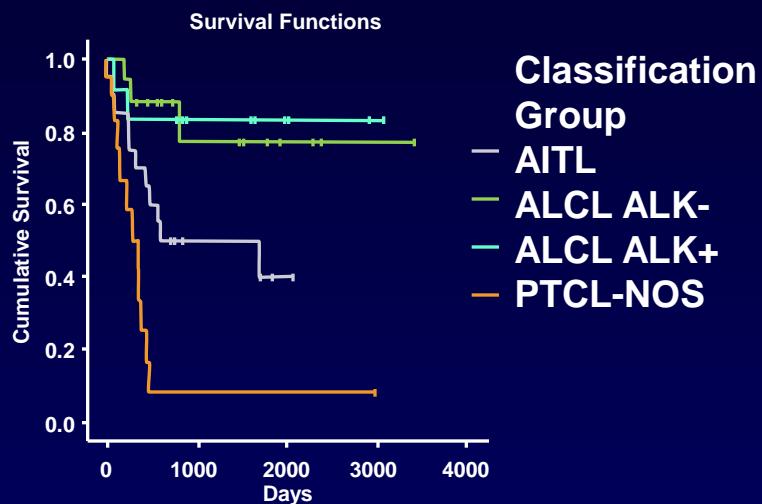
PPV 0.947 0.754-0.991

NPV 0.85 0.64-0.948

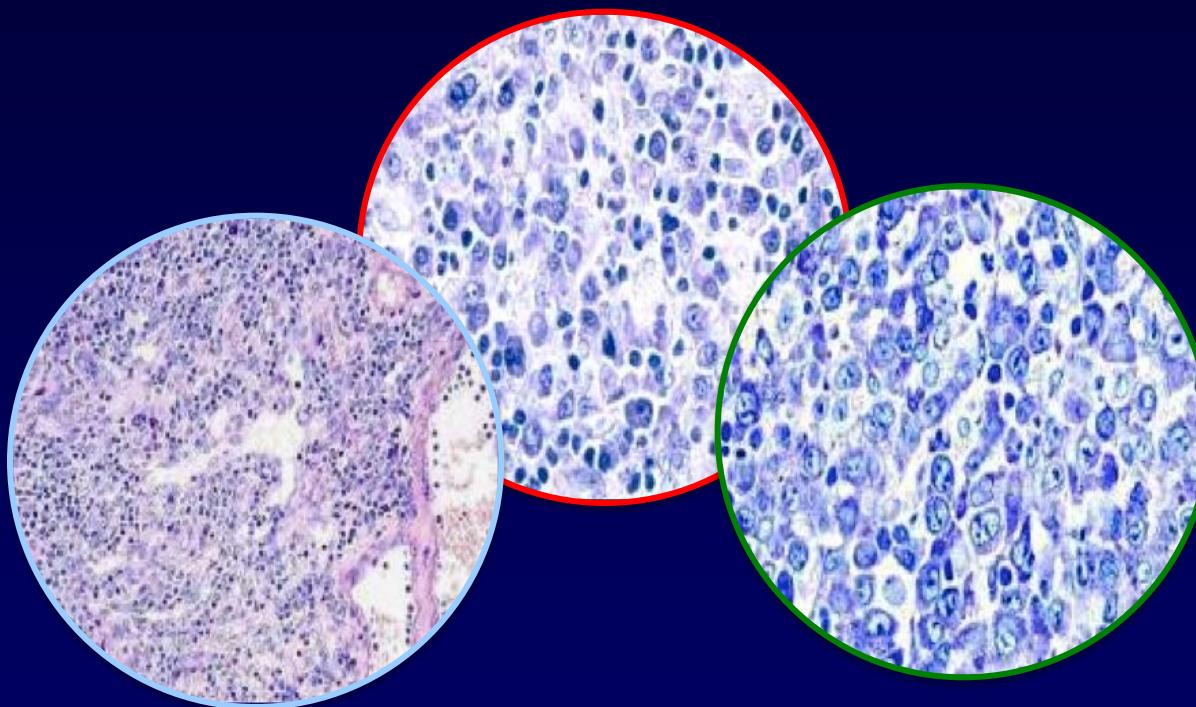
LR+ 15.429 2.278-104.475

LR- 0.151 0.053-0.434

Overall accuracy 89.74% (35 of 39)



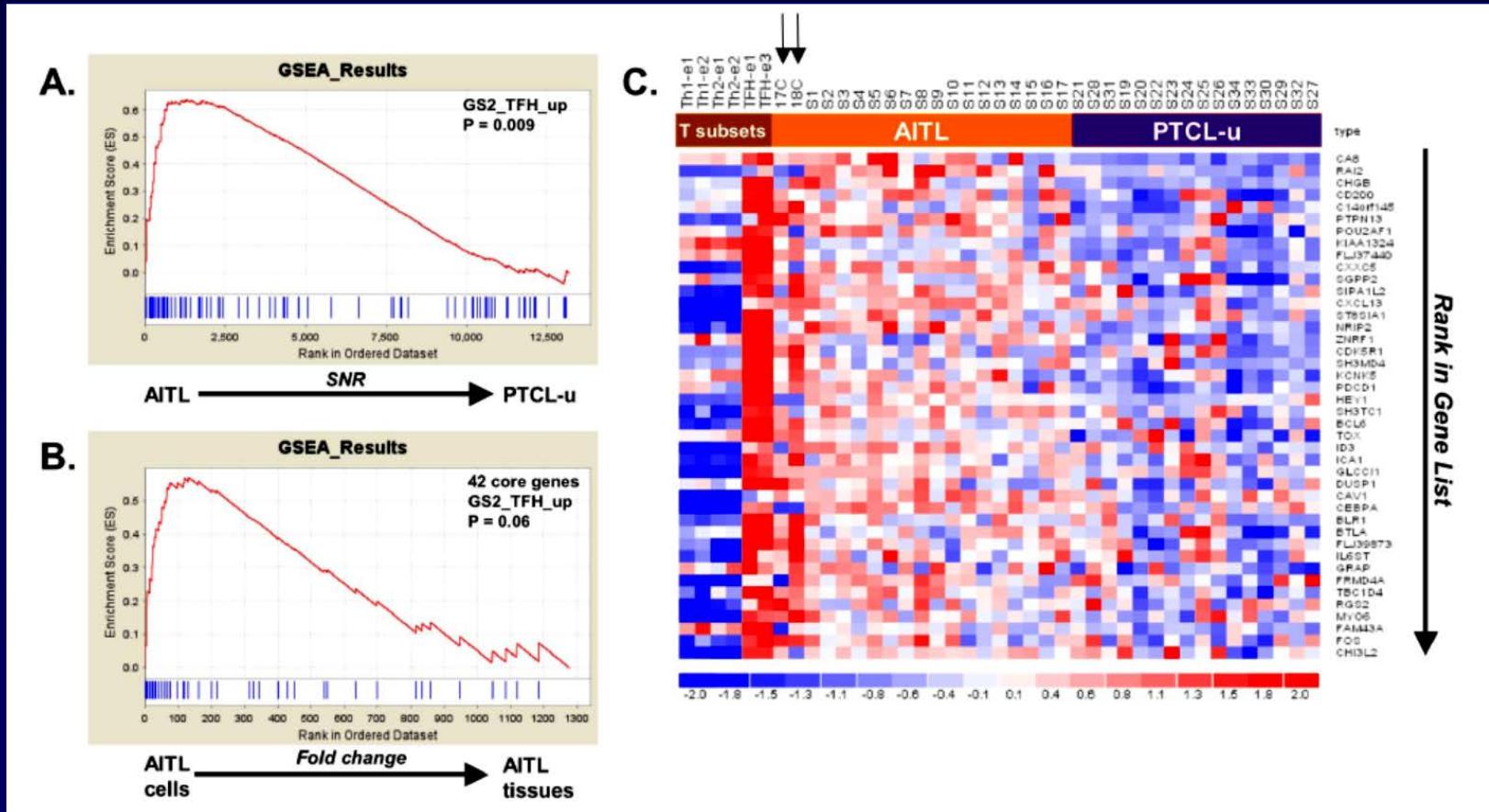
Molecular Diagnostic Can Improve the Distinction of Nodal “Grey Zone” PTCLs



Tfh PTCL/NOS
vs.
AITL

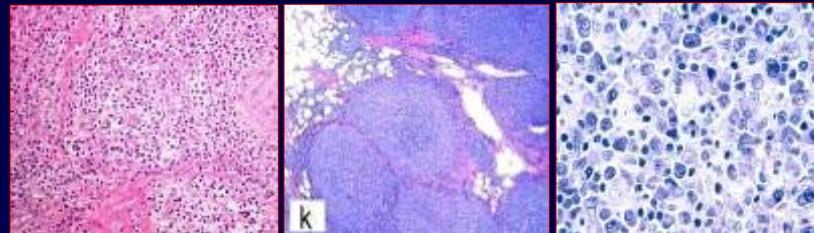
CD30+ PTCL/NOS
vs.
ALK- ALCL

A Fraction of PTCL/NOS Derives from TFH Cells



Peripheral T cell lymphomas with follicular T helper phenotype: a new basket or a distinct entity? Revising Karl Lennert's personal archive

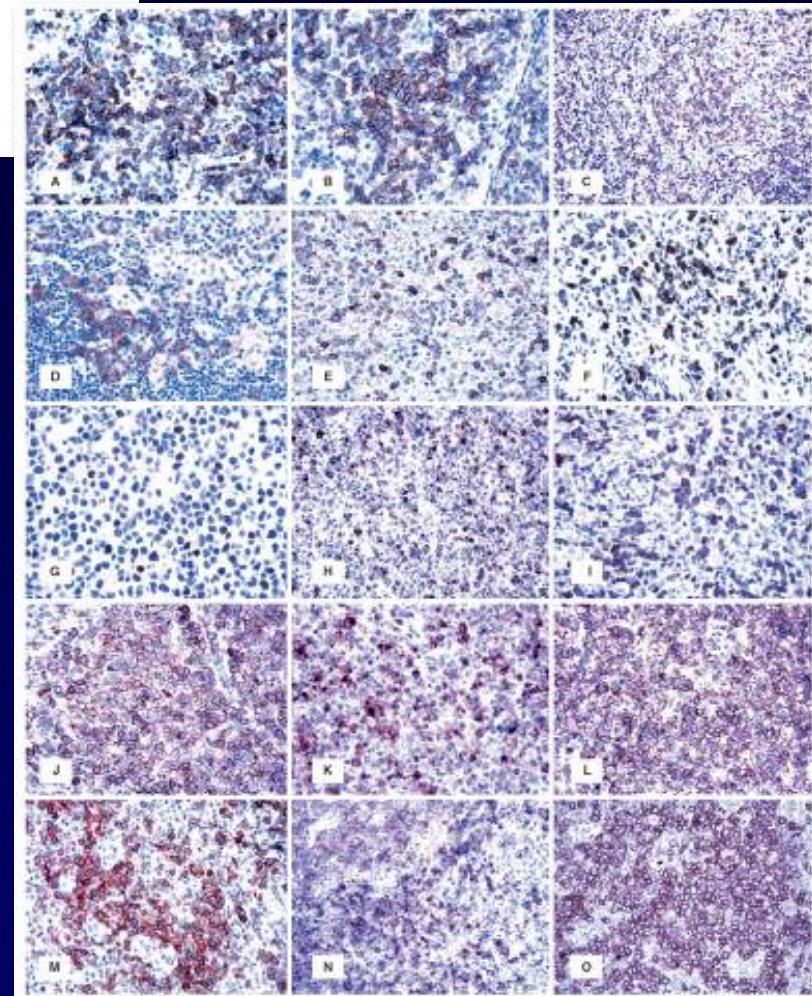
Claudio Agostinelli,¹ Sylvia Hartmann,² Wolfram Klapper,³ Penelope Korkolopoulou,⁴ Simona Righi,¹ Teresa Marafioti,⁵ Pier Paolo Piccaluga,¹ Efstratios Patsouris,⁴ Martin-Leo Hansmann,² Karl Lennert^{3,*} & Stefano A Pileri^{1,*}



Conclusions:

FTH-phenotype corresponds to a broad spectrum of PTCLs that might form a new category to be validated in future molecular and clinicopathological analyses.

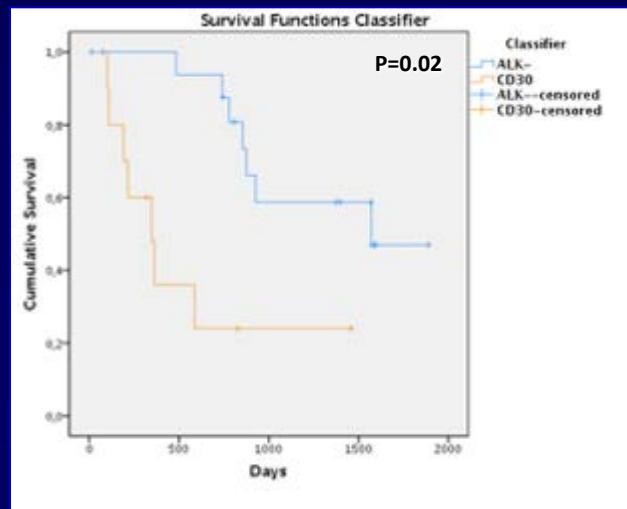
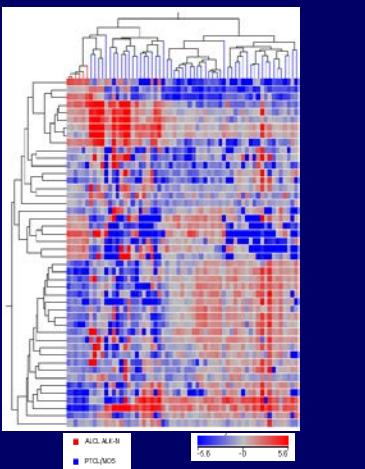
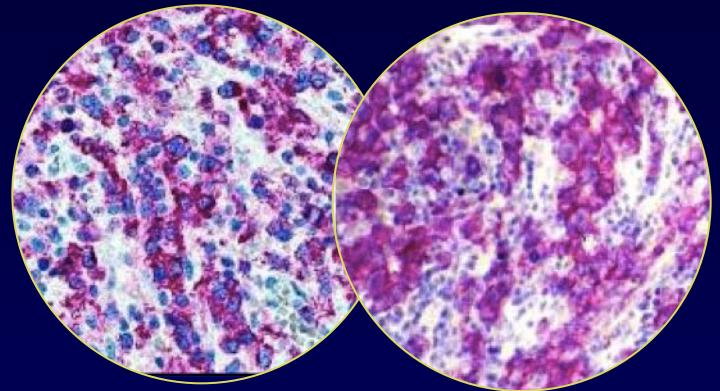
Genetics
TET2
RHOA
IDH2
T(5;9)-ITK/SYK



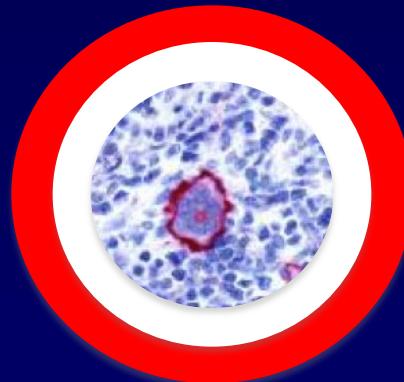
CD30⁺ PTCLs/NOS is different from ALCL

- CD30⁺ PTCL/NOS cases
 - No criteria for ALK- ALCL diagnosis
 - 16 cases
- Molecular classifier
 - 16/16 → PTCL/NOS

No ALCL morphology; CD30 > 75%



CD30: One Target, More Than One Disease

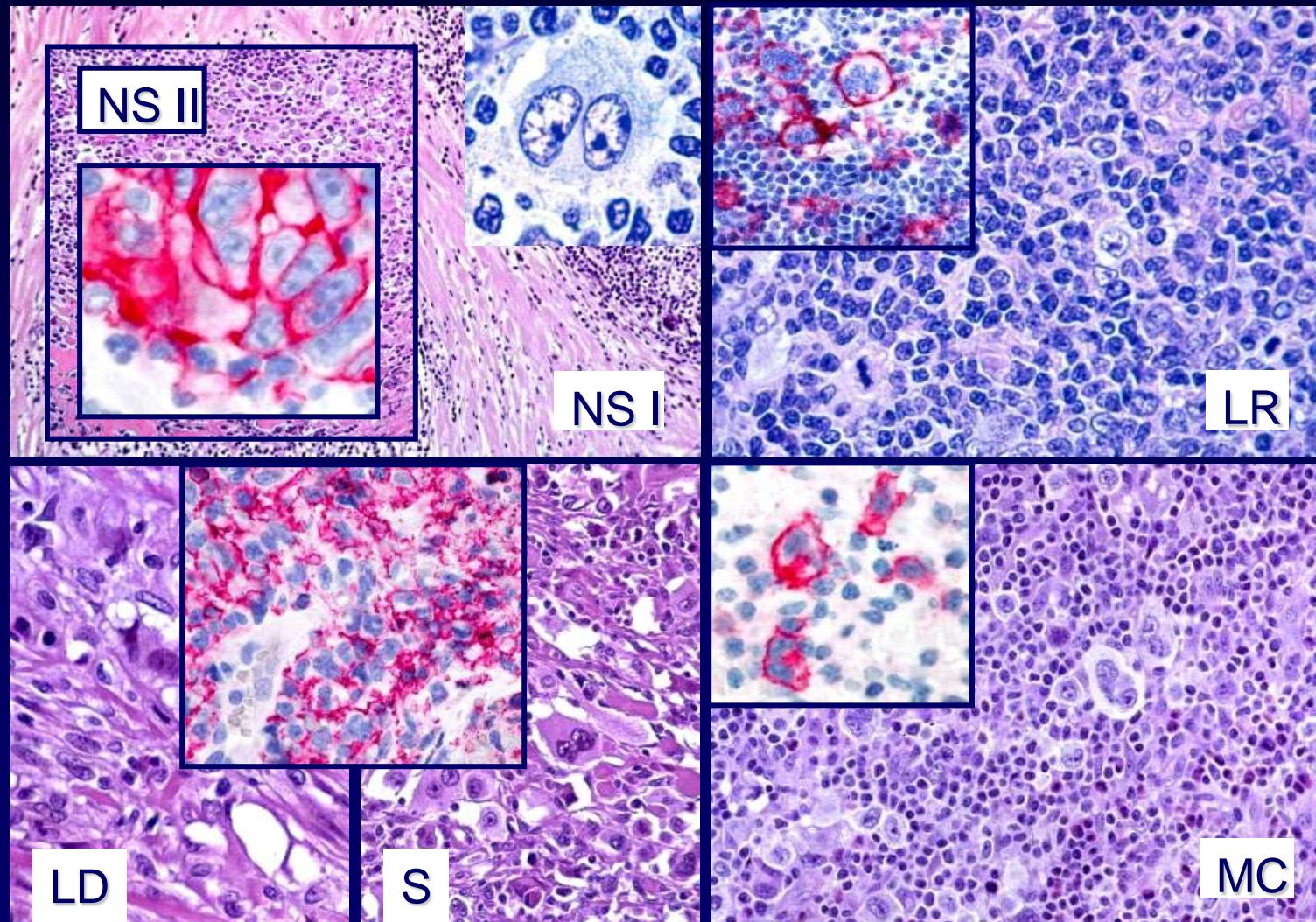


Current Diagnostic by Anti-CD30 Staining

- Hodgkin lymphoma
- Anaplastic large cell lymphoma

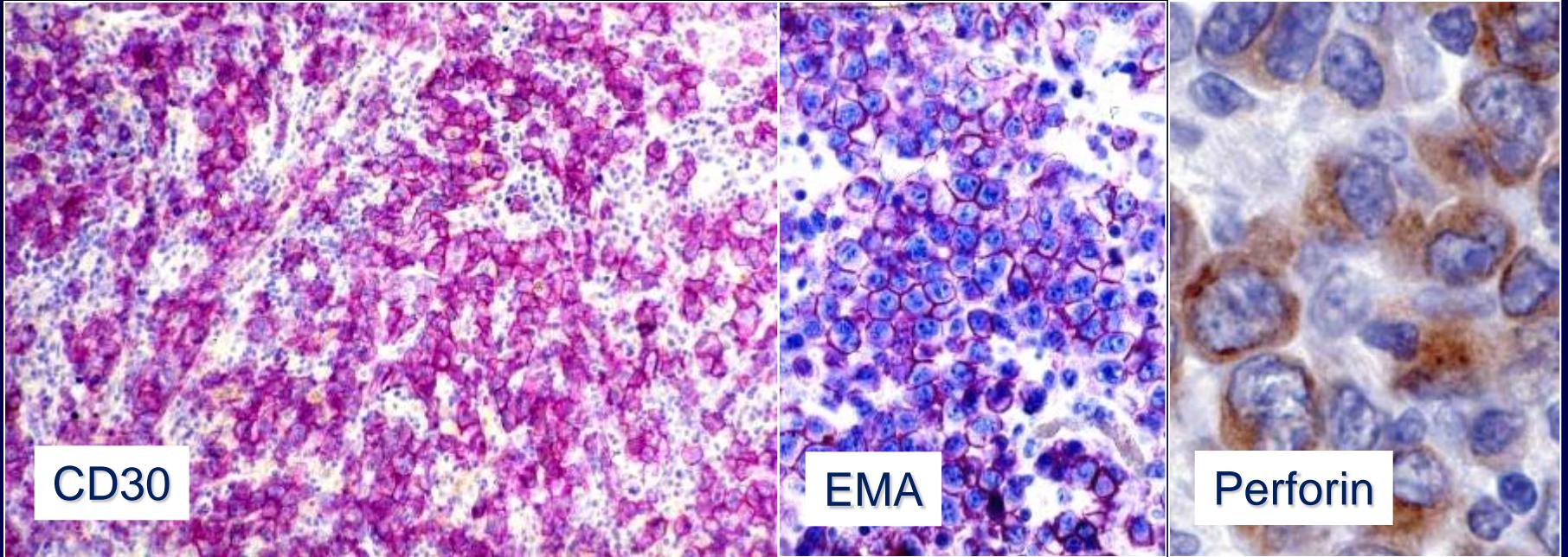
- B-cell lymphomas
 - PMBCL
 - DLBCL
- Peripheral T-cell lymphomas
 - CD30⁺ PTCL/NOS

CD30 Expression in cHL



LD, lymphocyte depletion; LR, lymphocyte rich; MC, mixed cellularity; NS, nodular sclerosis; S, sarcomatoid.

Anaplastic Large Cell Lymphoma



Phenotype:

CD30⁺

T/null (**PAX5⁻**)

CD45^{+/-}

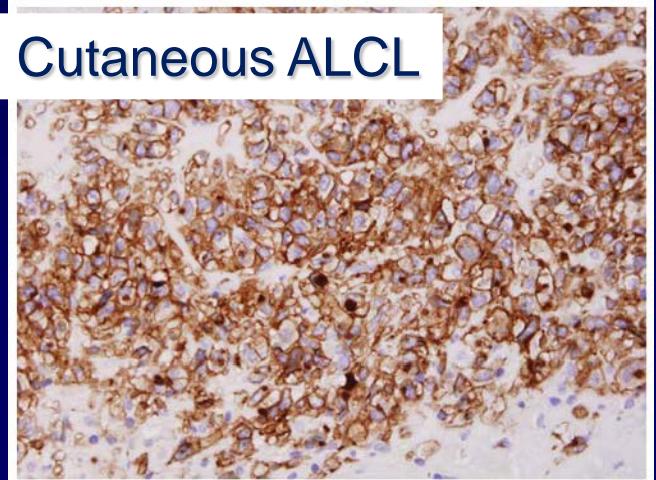
EMA^{+/-}

CD15⁻⁽⁺⁾

Cytotoxic markers⁺

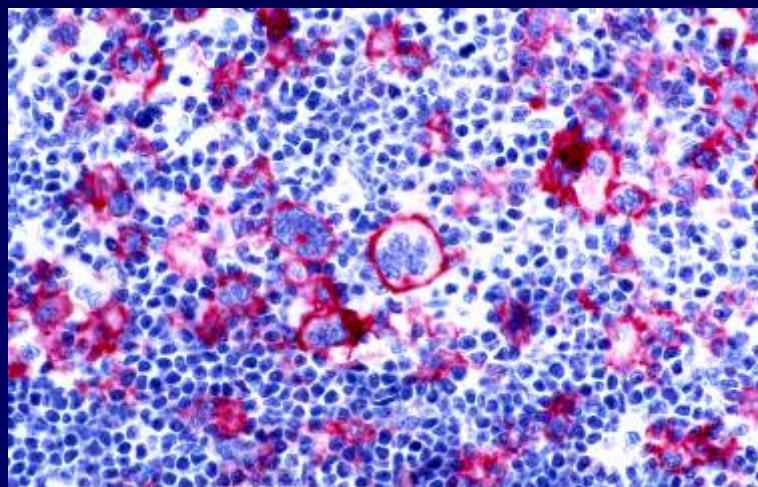
EBV⁻

Cutaneous ALCL

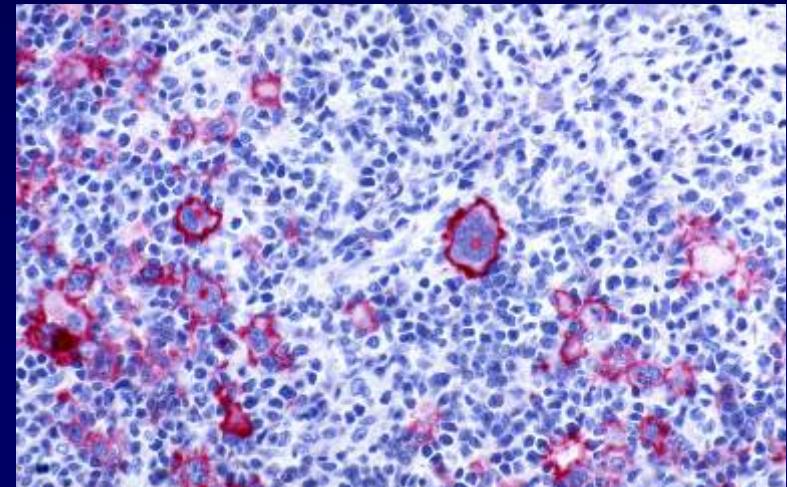


CD30 Expression Is Stable During Disease Natural History

- ASCO 2012: Retreatment with brentuximab vedotin in CD30-positive hematologic malignancies: A phase II study (# 8027)
- EHA 2012: Persistence of cd30 expression in CD30-positive lymphomas following treatment with brentuximab vedotin (SGN-35)(# 0203)



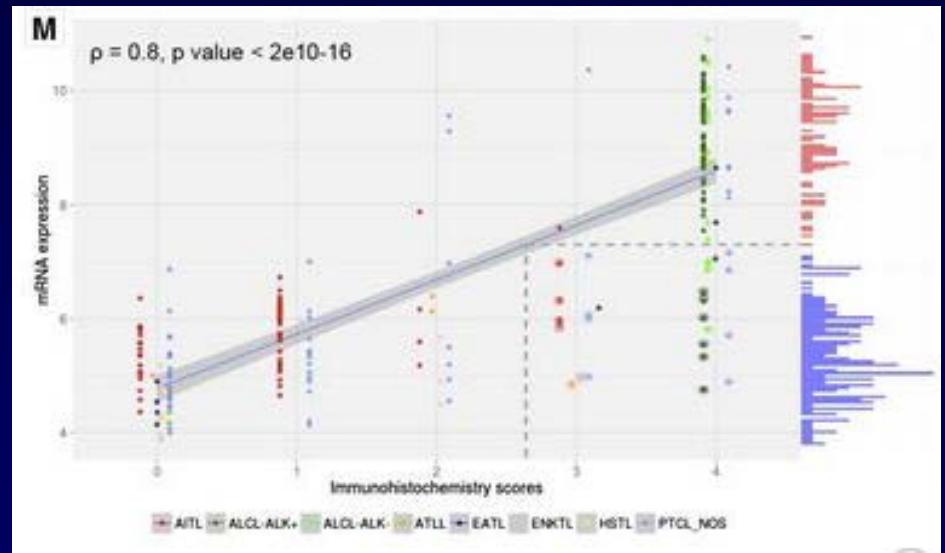
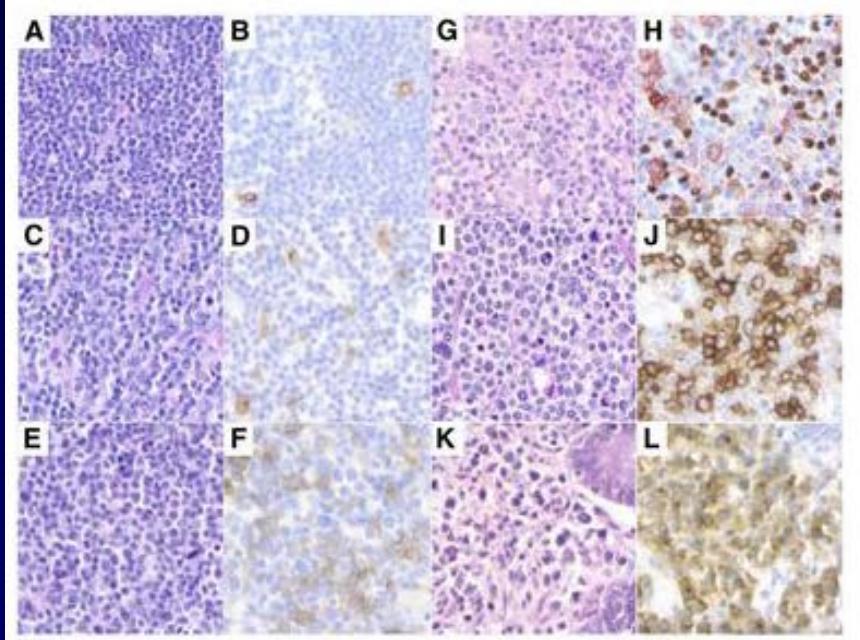
Before



After

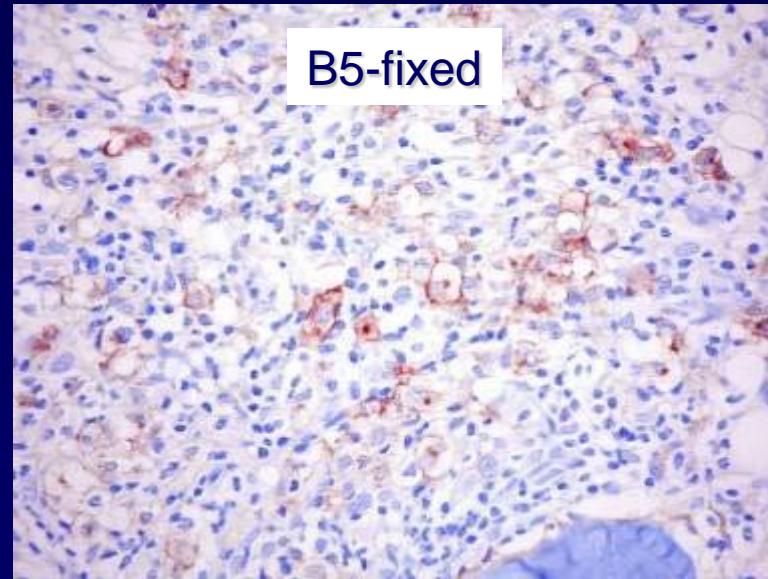
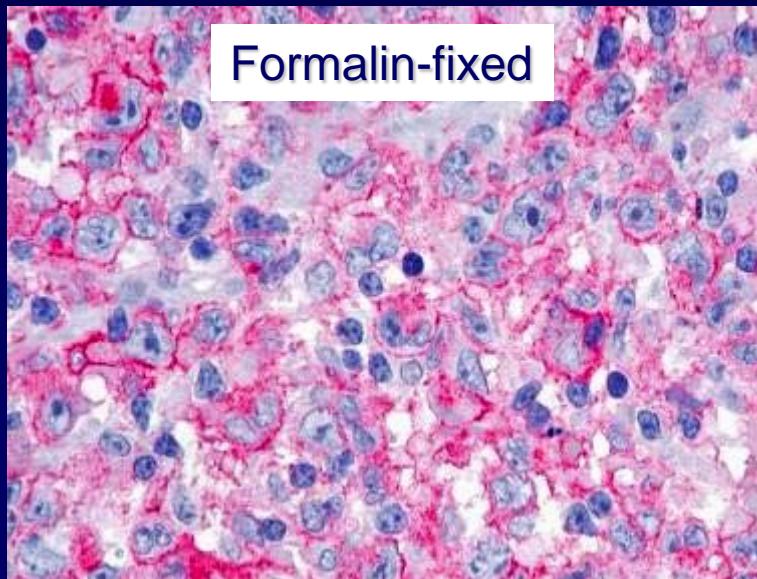
**Is CD30 Staining (Always)
Reliable?**

Immunohistochemistry as a Valuable Tool to Assess CD30 Expression in Peripheral T-cell Lymphomas: High Correlation Between Protein and mRNA Expression

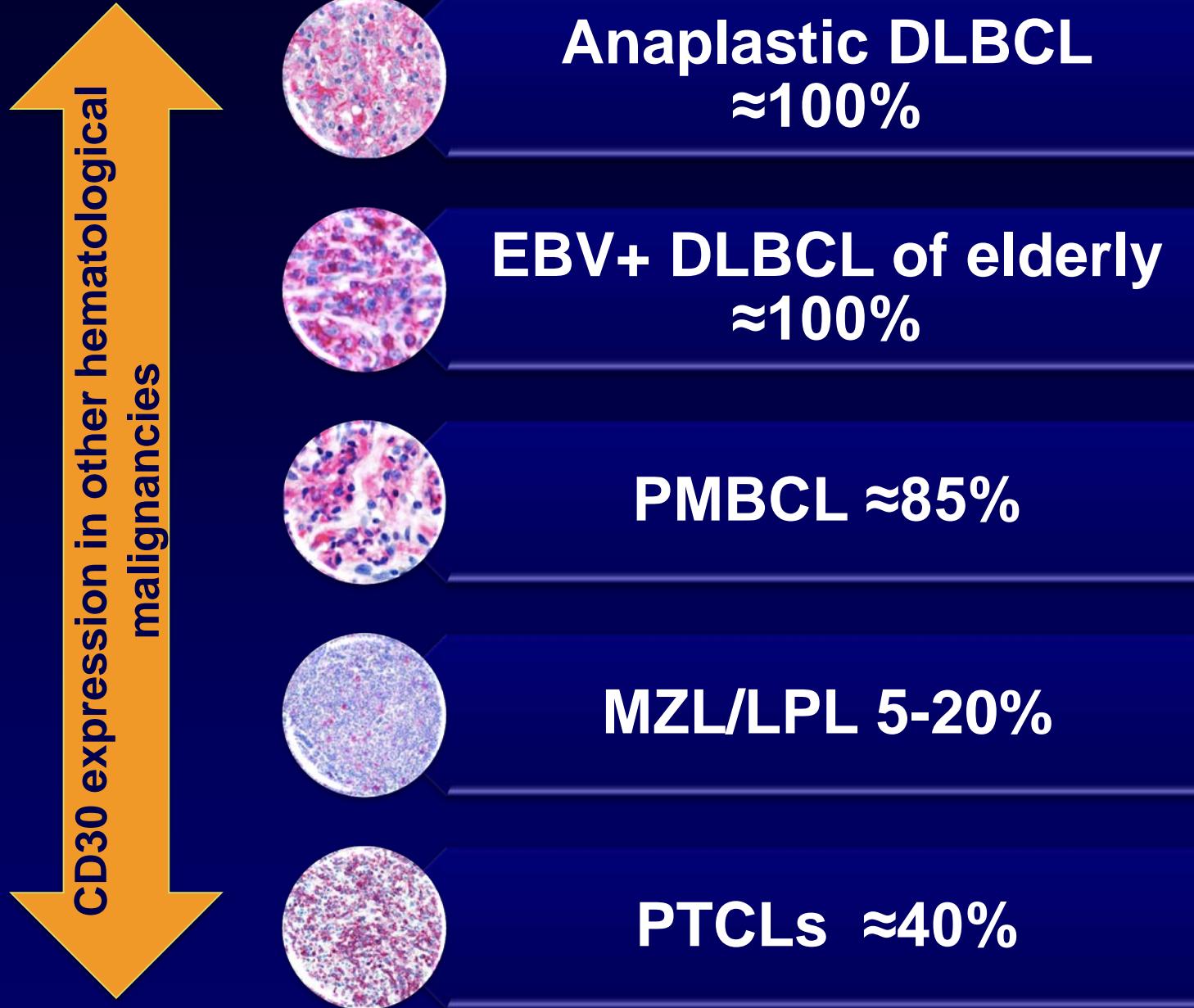


Fixation

- 10% buffered formalin (Lillie's) 24h: optimal
- Bouin 4-6h: acceptable
- B5 2-3h: suboptimal



Targeting CD30 in Other CD30+ Hematological Malignancies

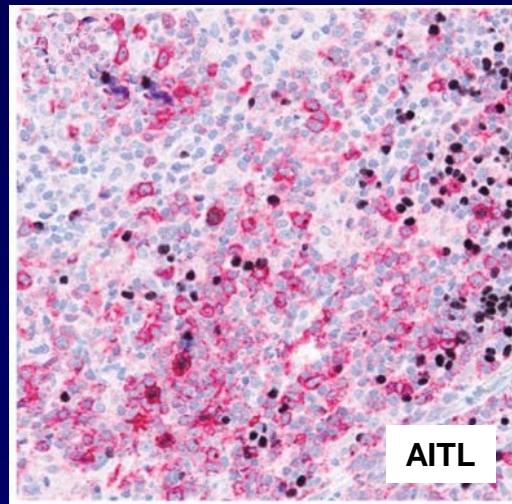
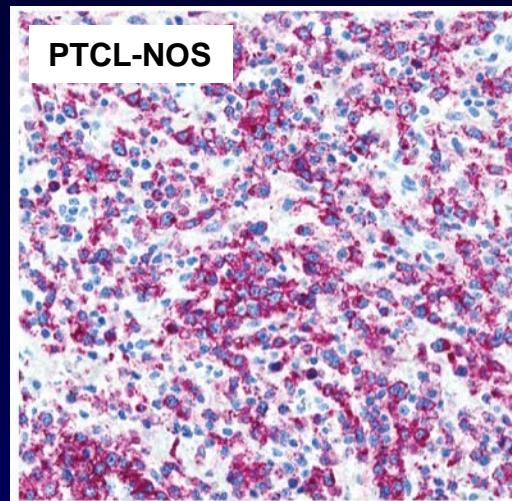


CD30 Expression in T-cell Lymphomas

Sabattini E, et al. *Haematologica*. 2013;98(8):e81-82.

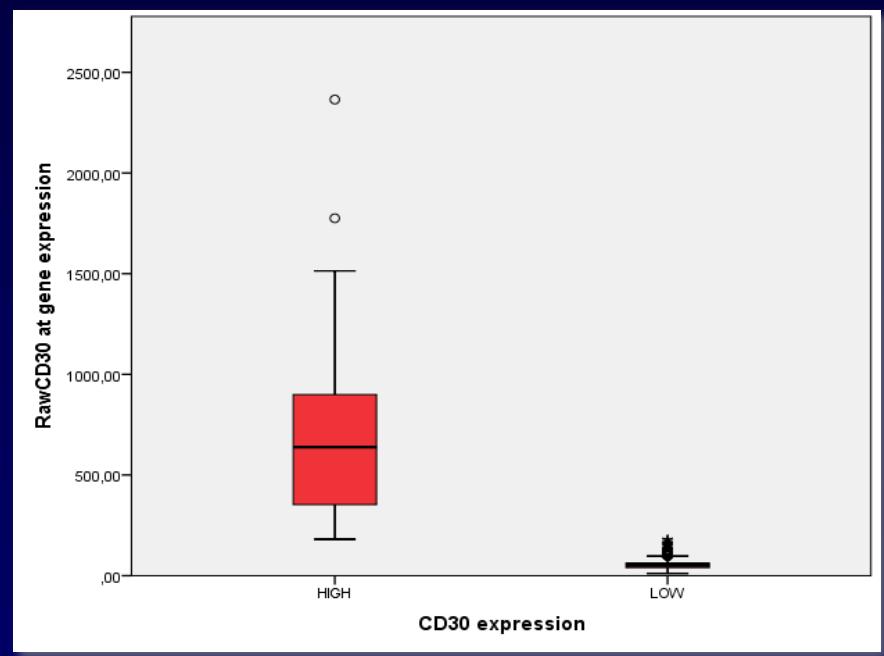
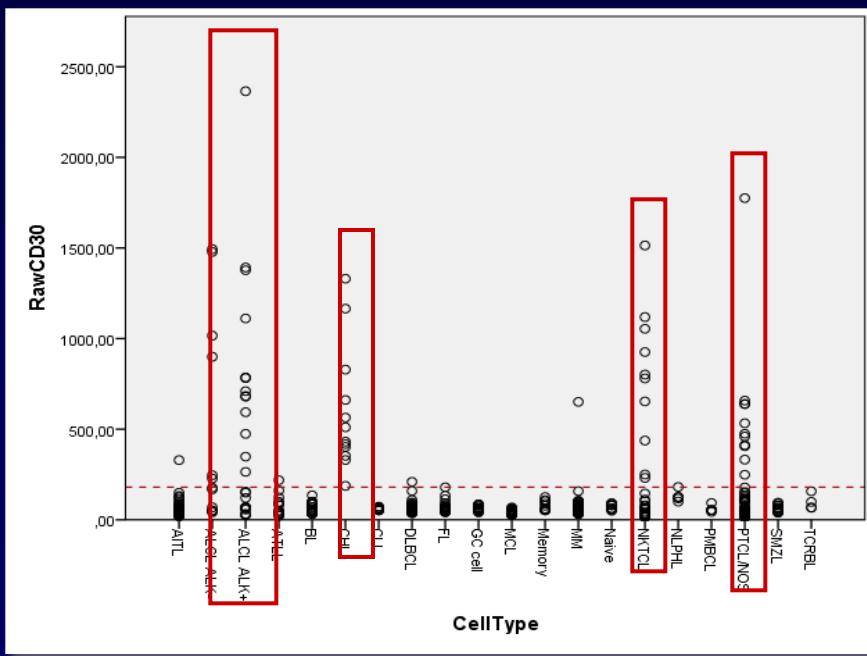
	CD30 IHC SCORE					
	0	1+	2+	3+	4	Score >2+
PTCL, NOS (87 cases)	31 (35.63%)	11 (12.64%)	18 (20.69%)	11 (12.64%)	16 (18.39%)	45/87 (51.72%)
AITL (42 cases)	24 (51.14%)	9 (21.42%)	5 (11.90%)	4 (9.52%)	—	9/42 (21.42%)
ENTL (10 cases)	2 (20.00%)	1 (10.00%)	3 (30.00%)	1 (10.00%)	3 (30.00%)	7/10 (70.00%)
MF (32 cases)	13* (40.63%)	15** (46.88%)	2 [§] (6.25%)	—	2 ^{§§} (6.25%)	4/32 (12.50%)
Transformed MF (9 cases)	—	—	3 (33.33%)	6 (66.67%)	—	9/9 100%
EATL type 1 (9 cases)	—	—	2 (22.22%)	—	7 (77.78%)	9/9 (100.00%)
EATL type 2 (3 cases)	3 (100%)	—	—	—	—	—
All types (192 cases)	73 (38.02%)	36 (18.75%)	33 (17.18%)	17 (8.85%)	28 (14.58%)	83/192 (43.22%)

PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified;
AITL: angioimmunoblastic T-cell lymphoma; ENTL: extranodal NK/T-cell lymphoma, nasal type;
MF: mycosis fungoides; EATL: enteropathy-associated T-cell lymphoma; *2 cases in tumoral phase;
**1 case in tumoral phase; [§]folliculotropic variant; ^{§§}pagetoid reticulosis subtype.

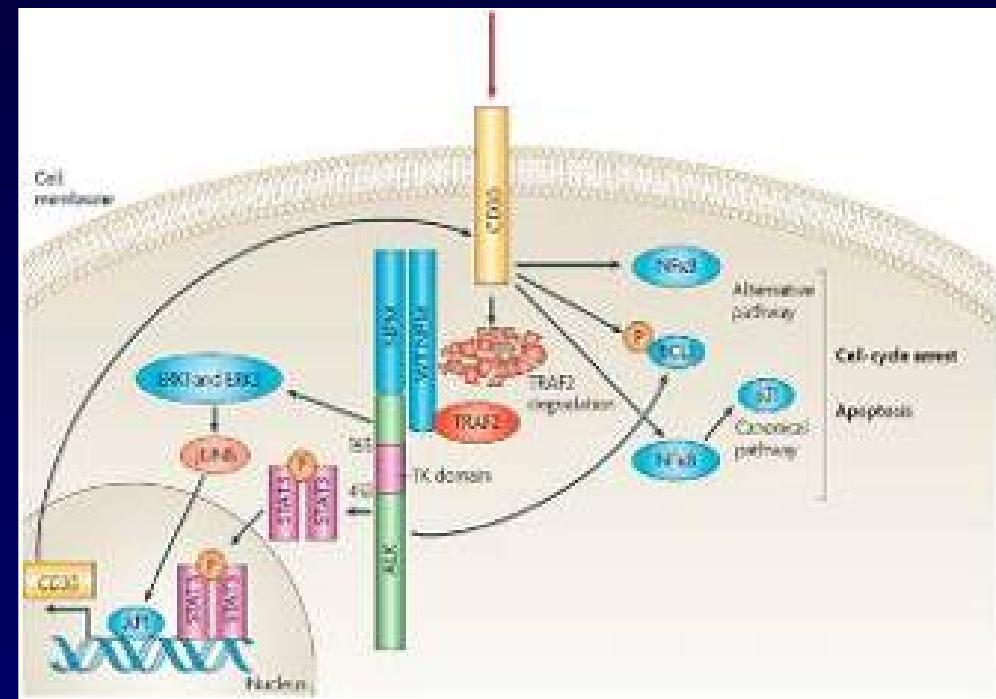
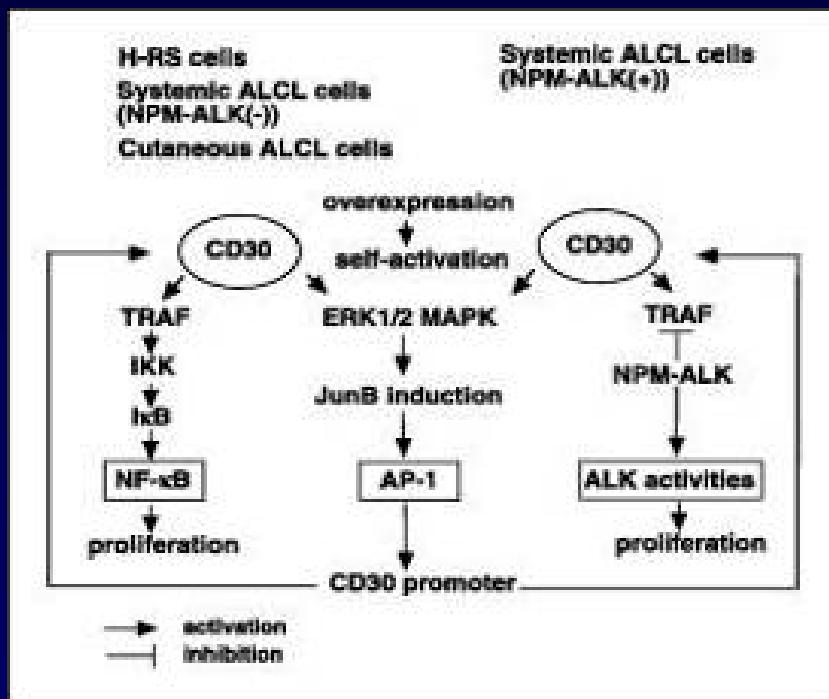


0 no staining; 1+ <25% positive cells; 2+ 25–50% positive cells; 3+ >50–75% positive cells; 4+ >75% positive cells

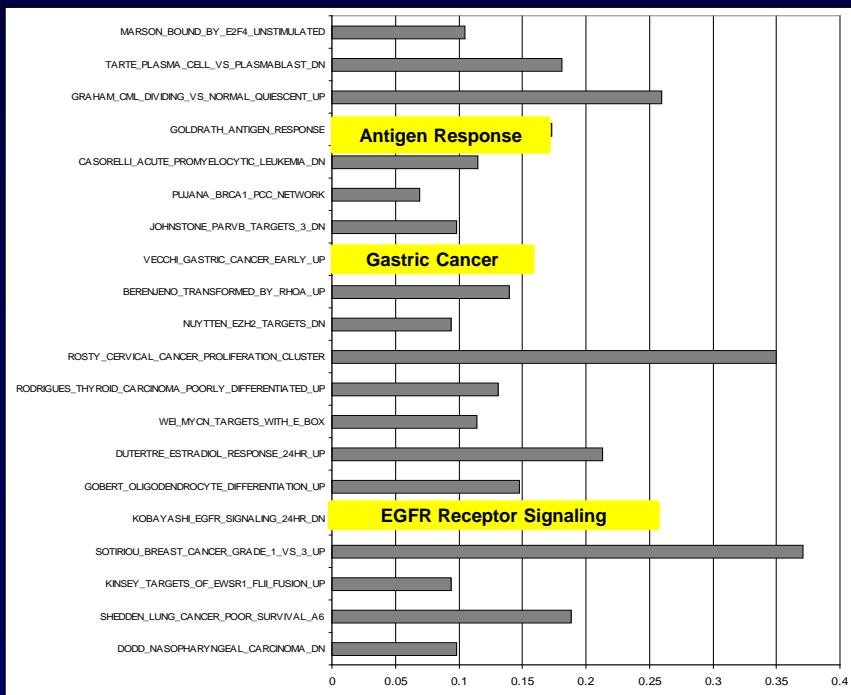
CD30 Expression in Human Lymphomas (N=693)



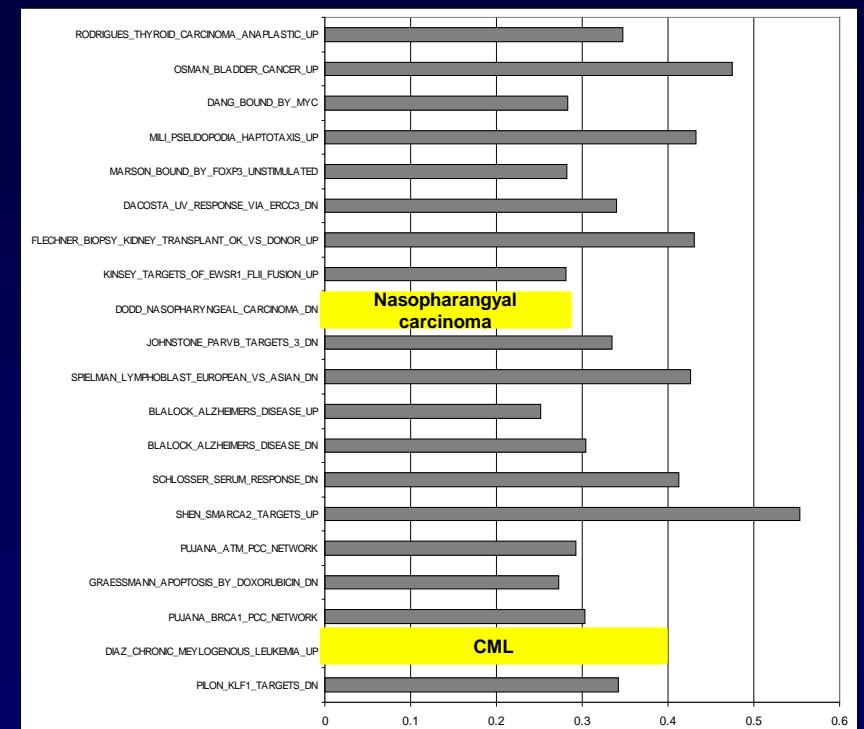
CD30/CD30L Signaling



CD30 Expression is Associated with Cancer-Related Programs in Both B- & T-cell Lymphomas

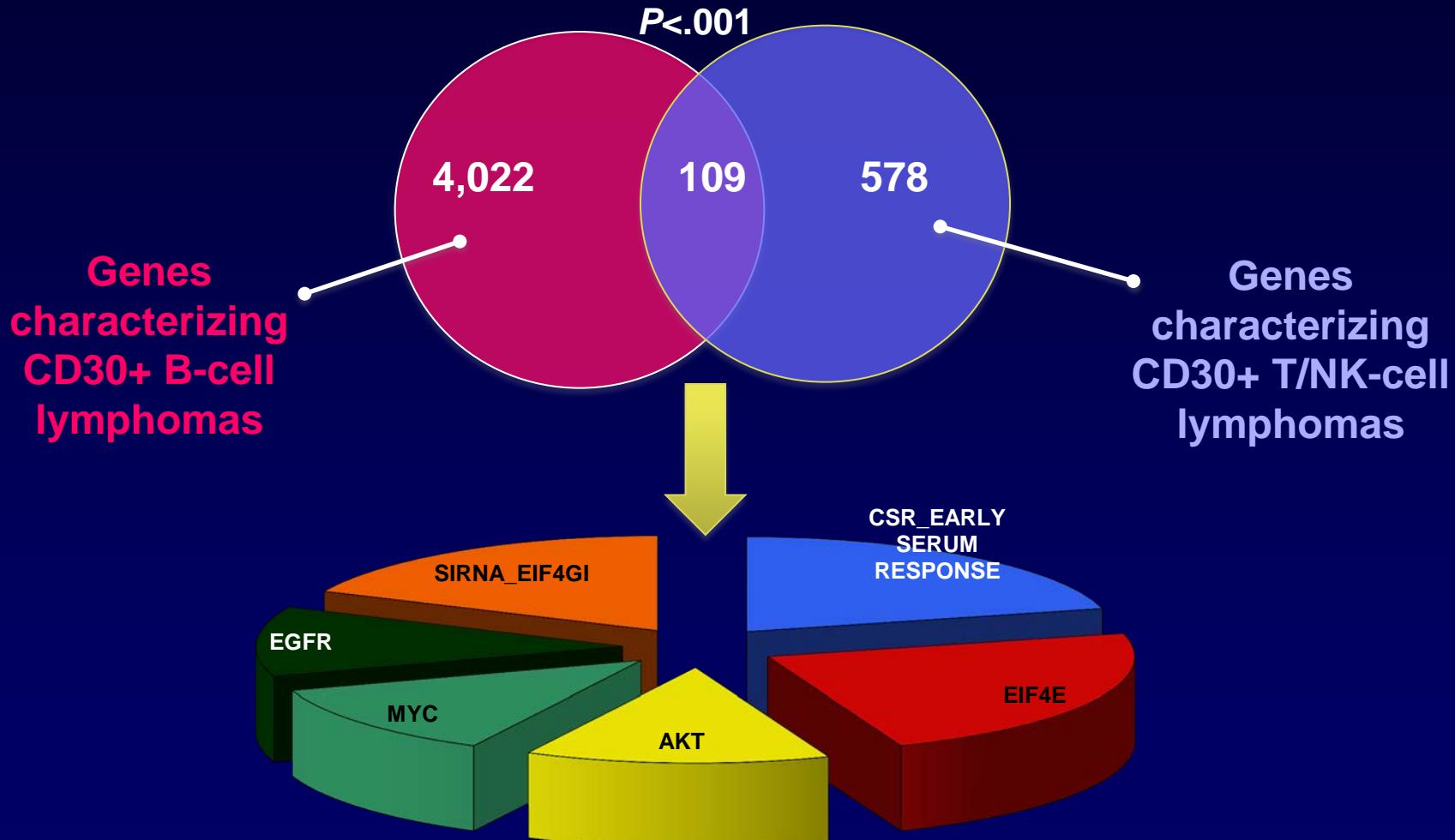


Pathways enriched in CD30+ PTCLs



Pathways enriched in CD30+ B-cell lymphomas

CD30 Triggers Common Molecular Events in B- & T-cell Lymphomas



Summary

- Molecular diagnostic can improve current standards in PTCL
- CD30 is consistently and stably expressed in different PTCL subtypes
- CD30 expression is associated with cancer-related pathways in both B- & T-cell lymphomas