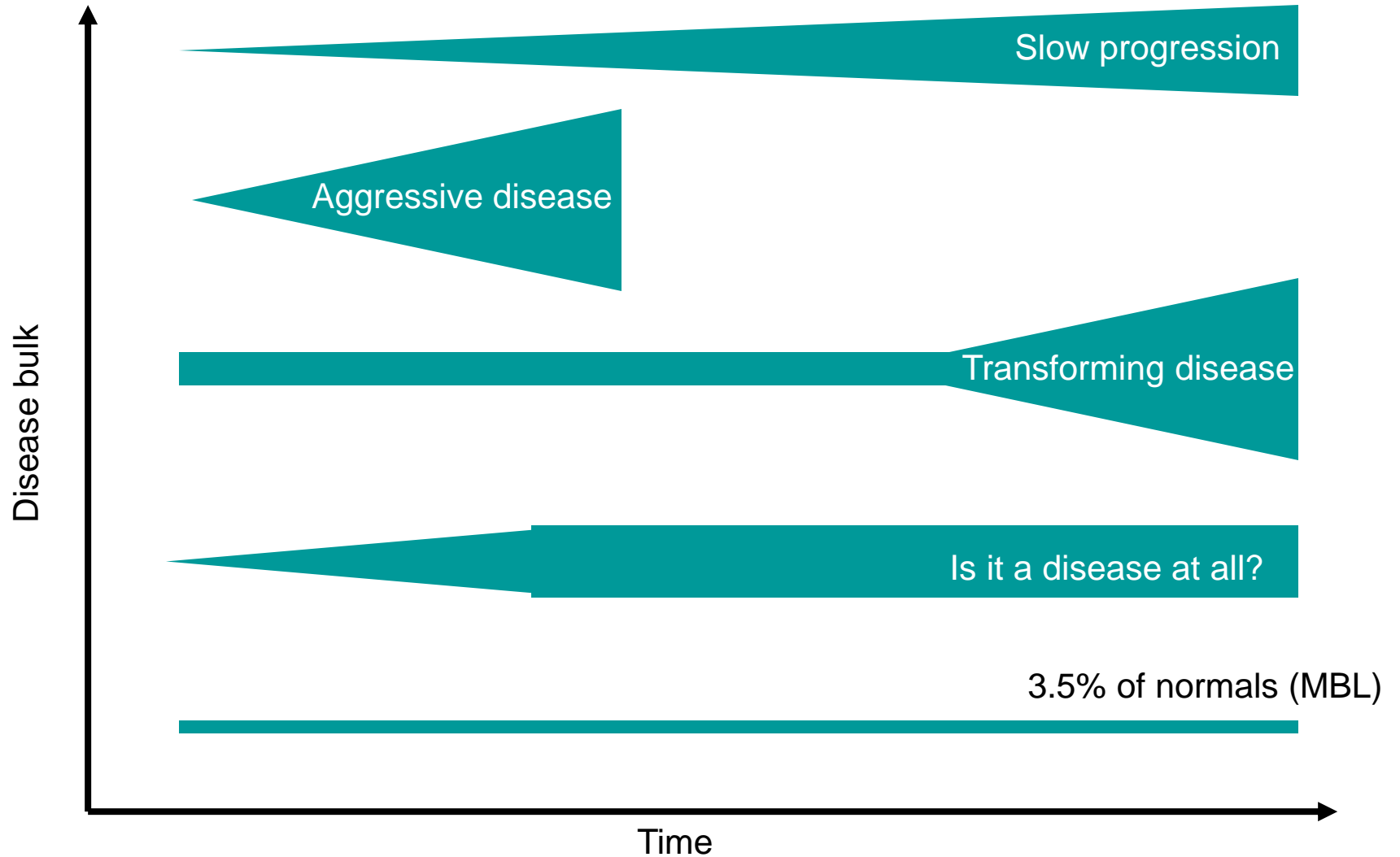


Prognostic Factors in CLL/SLL What to Use and What Do They Tell Us About Pathogenesis?

*George Ioannidis
Cambridge Lymphoma Forum
Nov 10th 2009*

Clinical Course of B-CLL



iWCLL Therapy Guidelines

Active or progressive disease defined as

1. Progressive BM failure
2. Massive/symptomatic splenomegaly (6cm LCM)
3. Massive (>10cm) or progressive lymphadenopathy
4. Progressive lymphocytosis: $LDT < 6\text{mo}$ or $LDT_{50} < 2\text{mo}$
5. AIHA/AITP poorly responsive to corticosteroids
6. Constitutional symptoms: Wt loss 10% <6mo, Fever $38^{\circ}\text{C} > 2\text{w}$, Unexplained sweats >4w, Fatigue $PS = < 2$

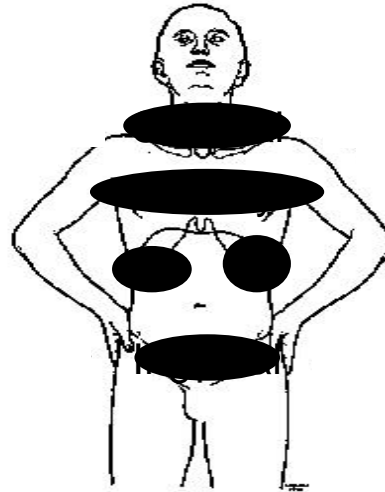
Prognostic Factors in CLL

- What can prognostic factors tell us?
 - Predict natural history of disease
 - Richters transformation
 - Pattern of disease
 - Patient information
 - Guide Therapy
 - When to start therapy
 - What therapy to choose
 - How do they predict prognosis?
 - Information about disease biology

CLL Clinical Staging Systems

Binet

Stage	OS (mo)
A. Hb > 10, PI > 100, < 3 LN	144
B. Hb > 10, PI > 100 3+ LN	60
C. Hb < 10 &/or PI < 100	24



Rai

Stage	OS
0. Lymphs > 15 (5) x 10 ⁹ /l	> 180
1. Lymphadenopathy	108
2. Spleen +/- Liver +/- LNs	60
3. Hb < 11g/dl	24
4. Platelets < 100 x 10 ⁹ /l	24



Prognosis in CLL: LDT

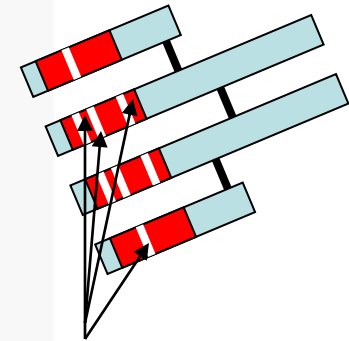
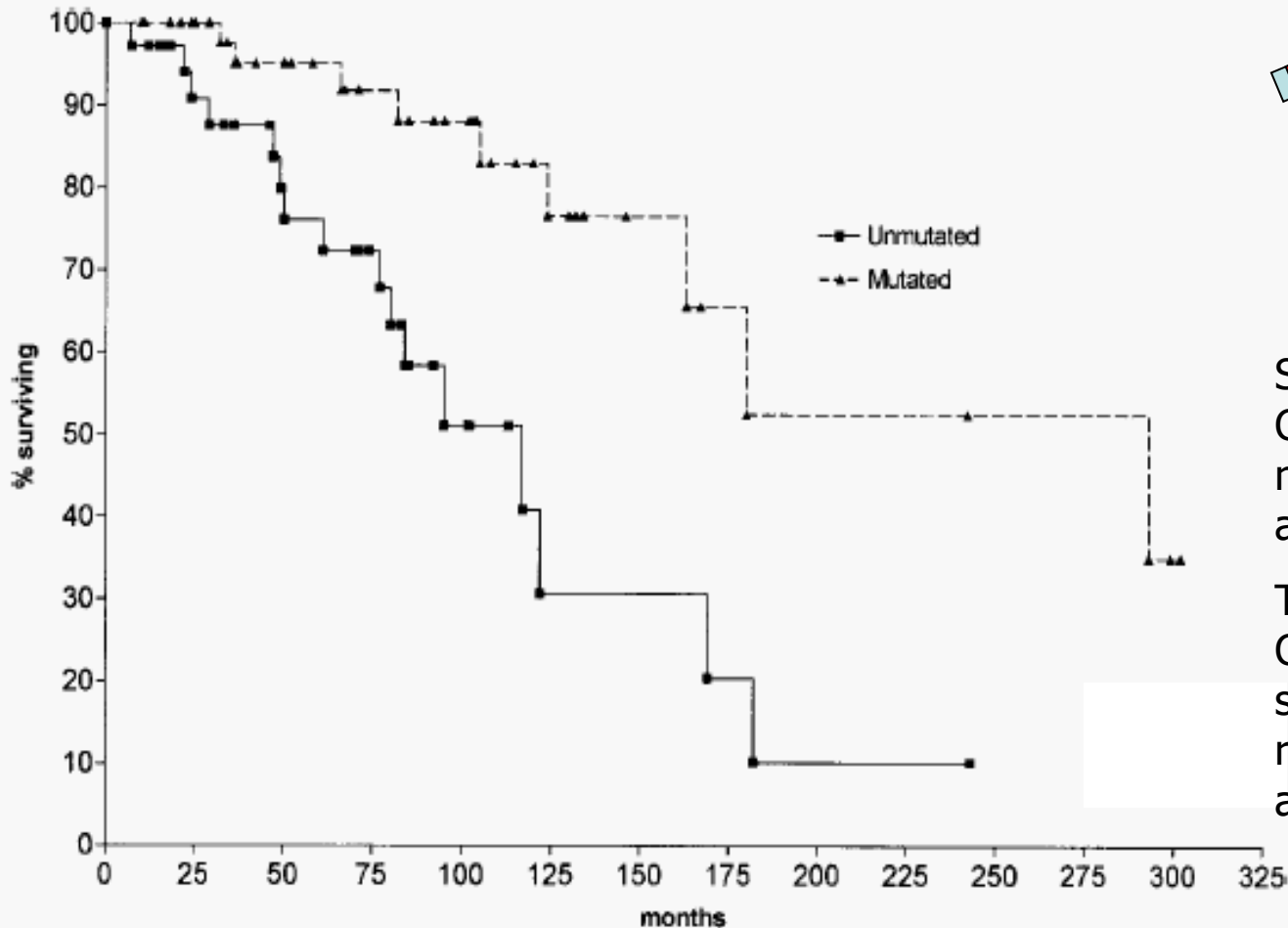
- Lymphocyte doubling time
 - < 1 year median survival 36 months
 - > 1 year median survival not reached
 - Not independent of clinical stage



Serum markers: CLL4

		5yr PFS	p	5yr OS	p
β2M	Low	24.9	0.001	72.8	<0.0001
	High	12		38.8	
sTK	Low	24.5	0.004	62.5	0.01
	High	12.6		50.6	
sFL	Norm.	27.5	0.03	66.2	0.04
	Abn.	15.5		53.2	
sCD23	Low	23.7	0.1	61.7	0.04
	High	13.6		50.4	

Prognosis: Vh gene Mutations

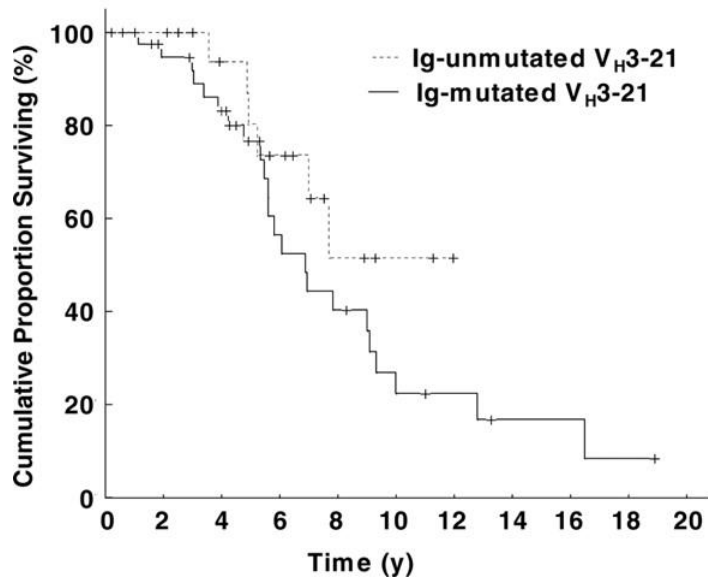


Somatic hypermutation in CDR of V_H and V_L genes normally occurs in GC after antigen exposure.

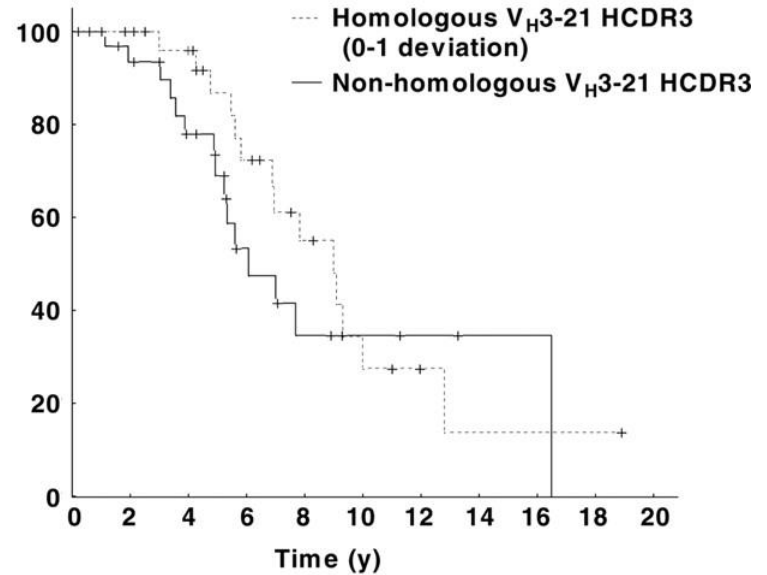
T cell help through CD40/40L mediated signals plays a central role in triggering SHM and class switching

Vh3-21 Prognosis

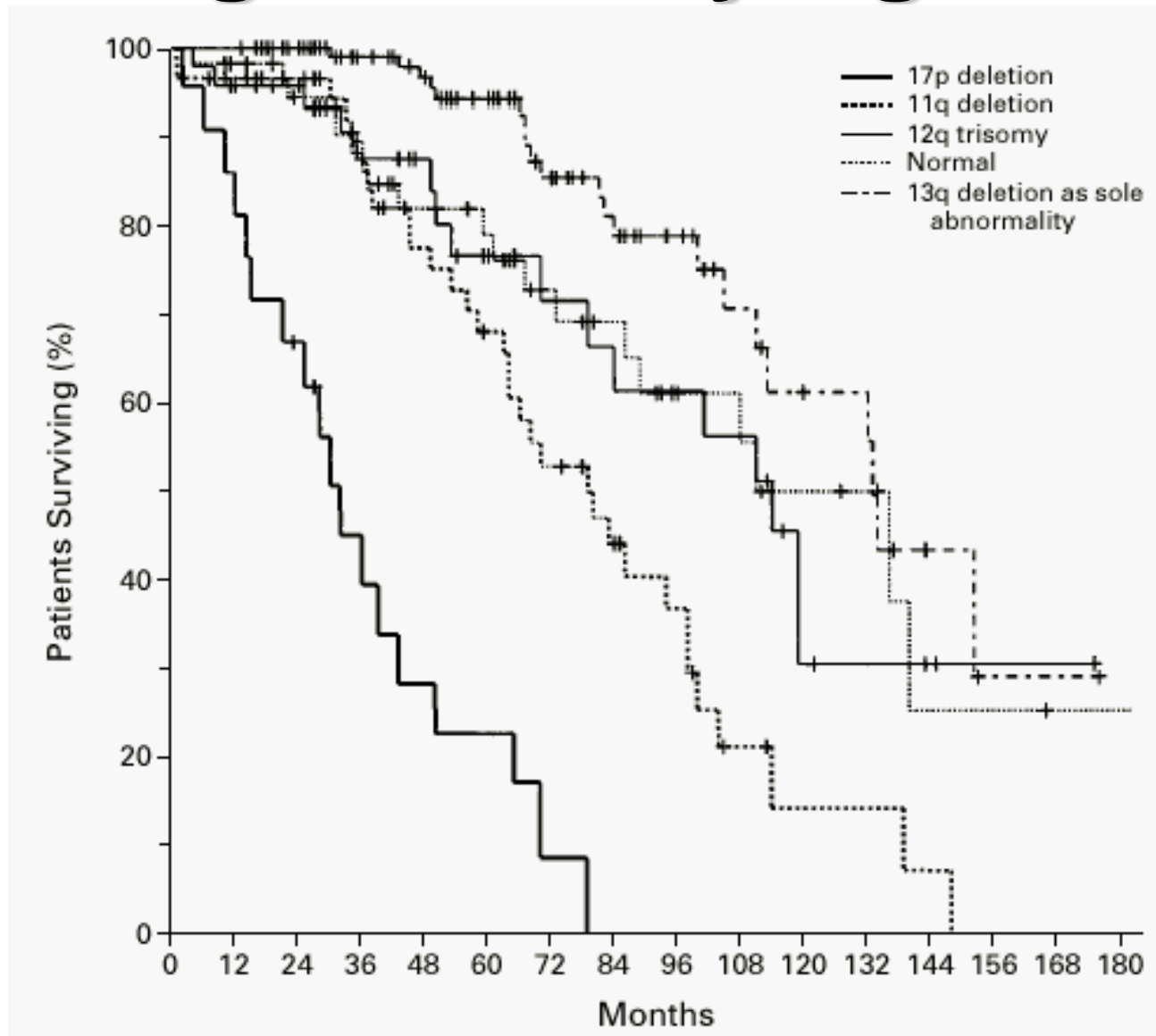
A



B

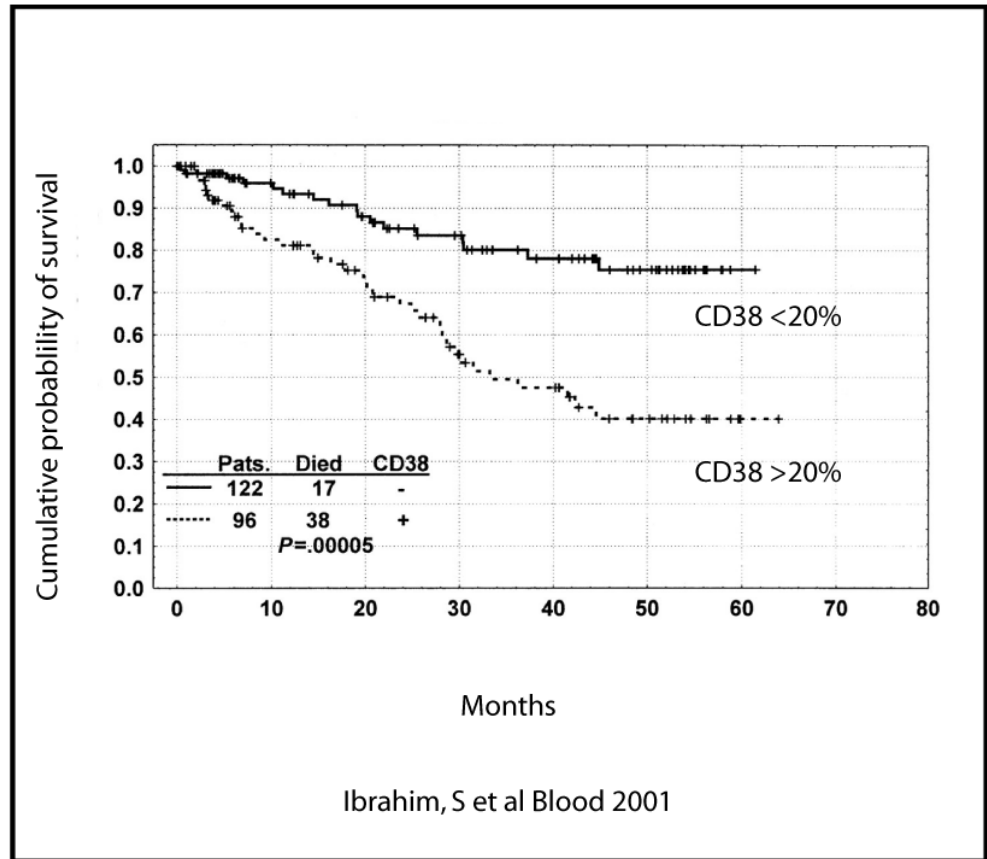
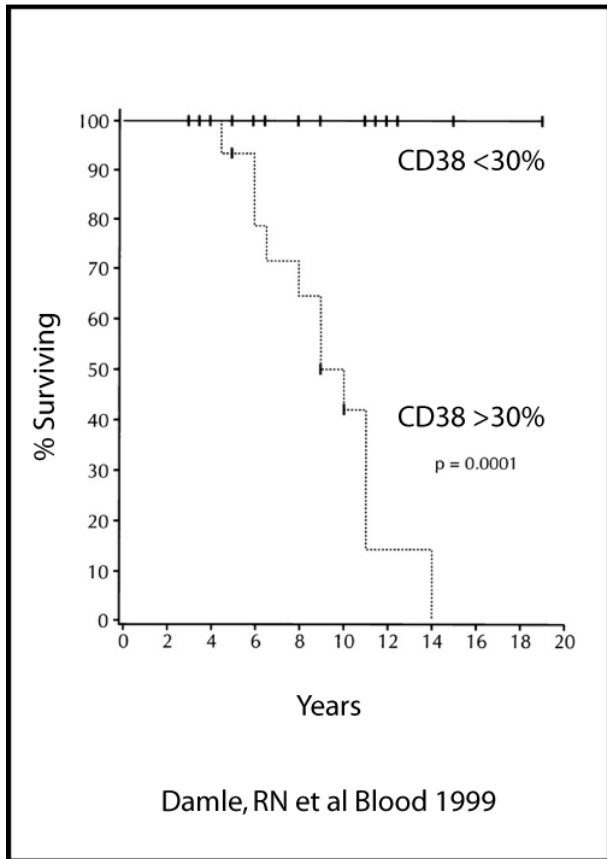


Prognosis : Cytogenetics

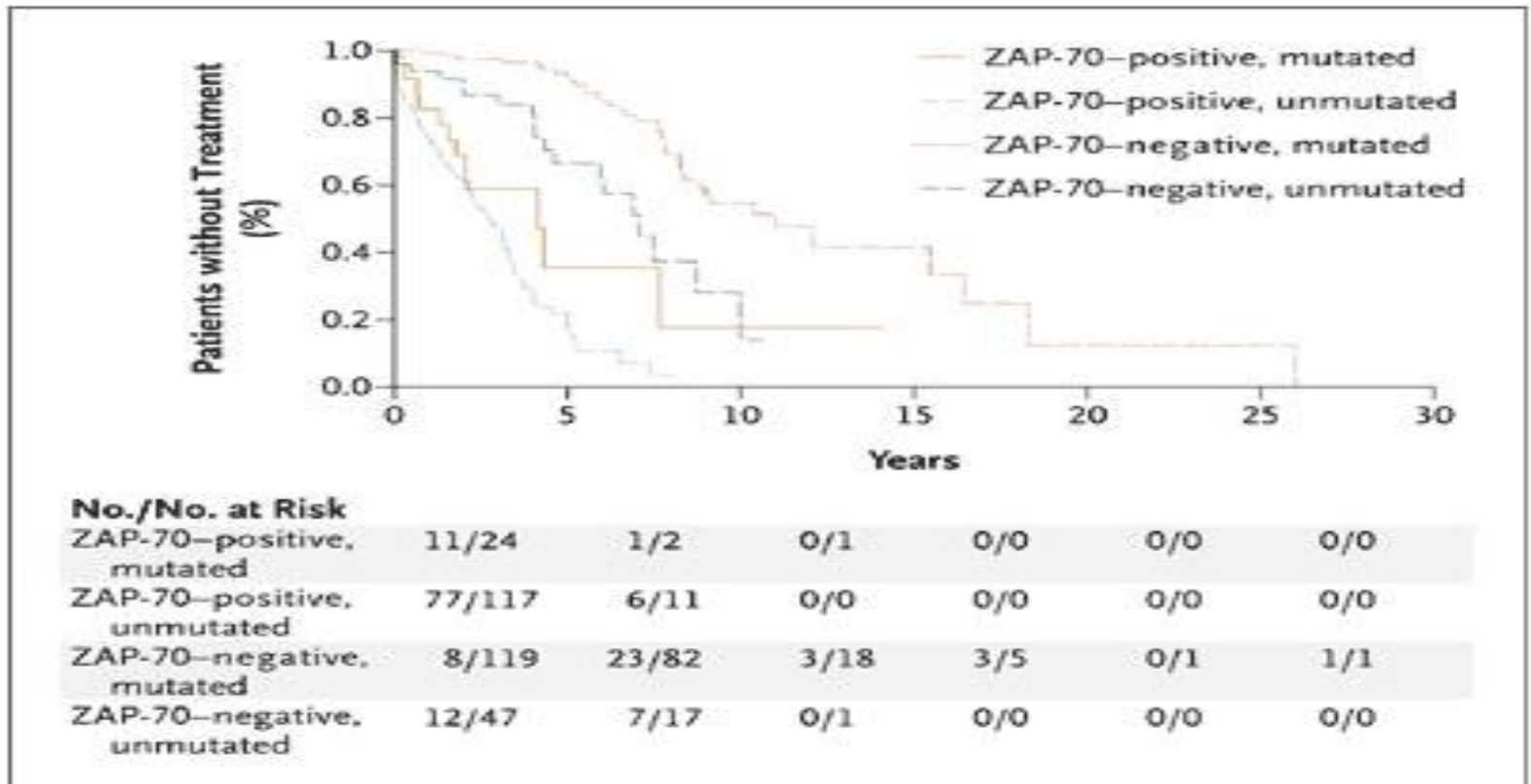


Dohner et al 2000

CD38: an independent prognostic marker in CLL



ZAP-70



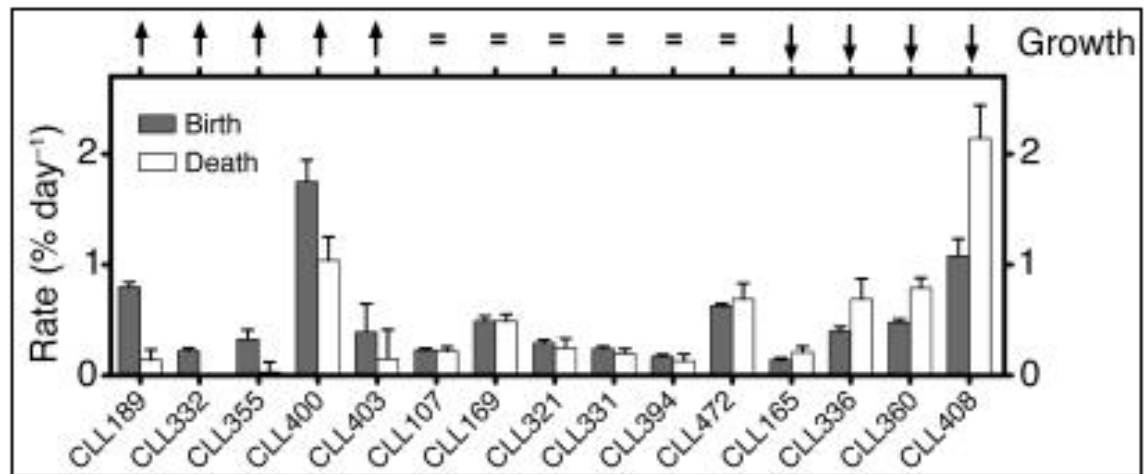
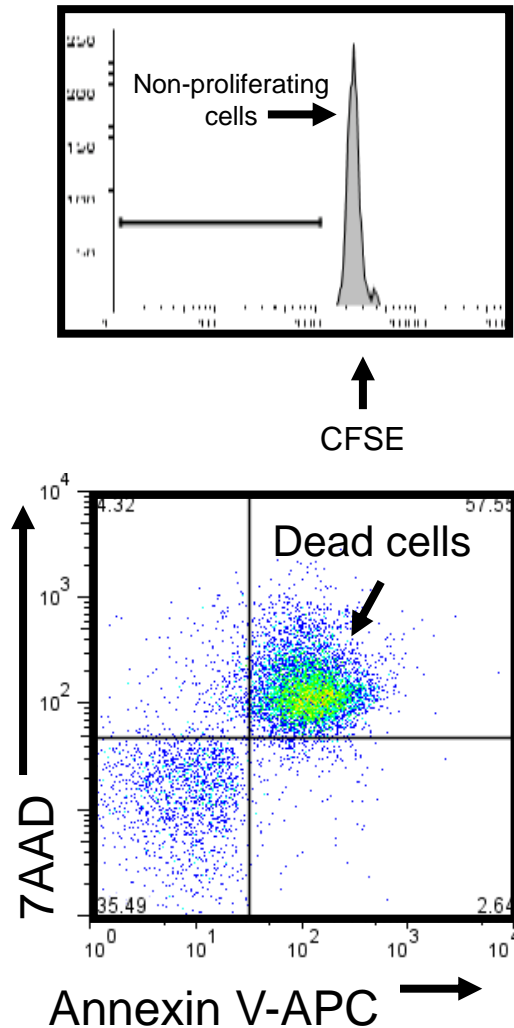
Prognostic factors

- What to do in everyday practice?
 - At diagnosis
 - Nothing required but patients often wish to have the information
 - Academic value in collecting information
 - Cytogenetics/FISH, V genes, CD38 (ZAP70)
 - Prior to (each) therapy
 - FISH +/- cytogenetics
 - TP53 deletion (mutations)
 - 11q deletions (ATM mutations)

How do prognostic factors influence outcome in CLL?

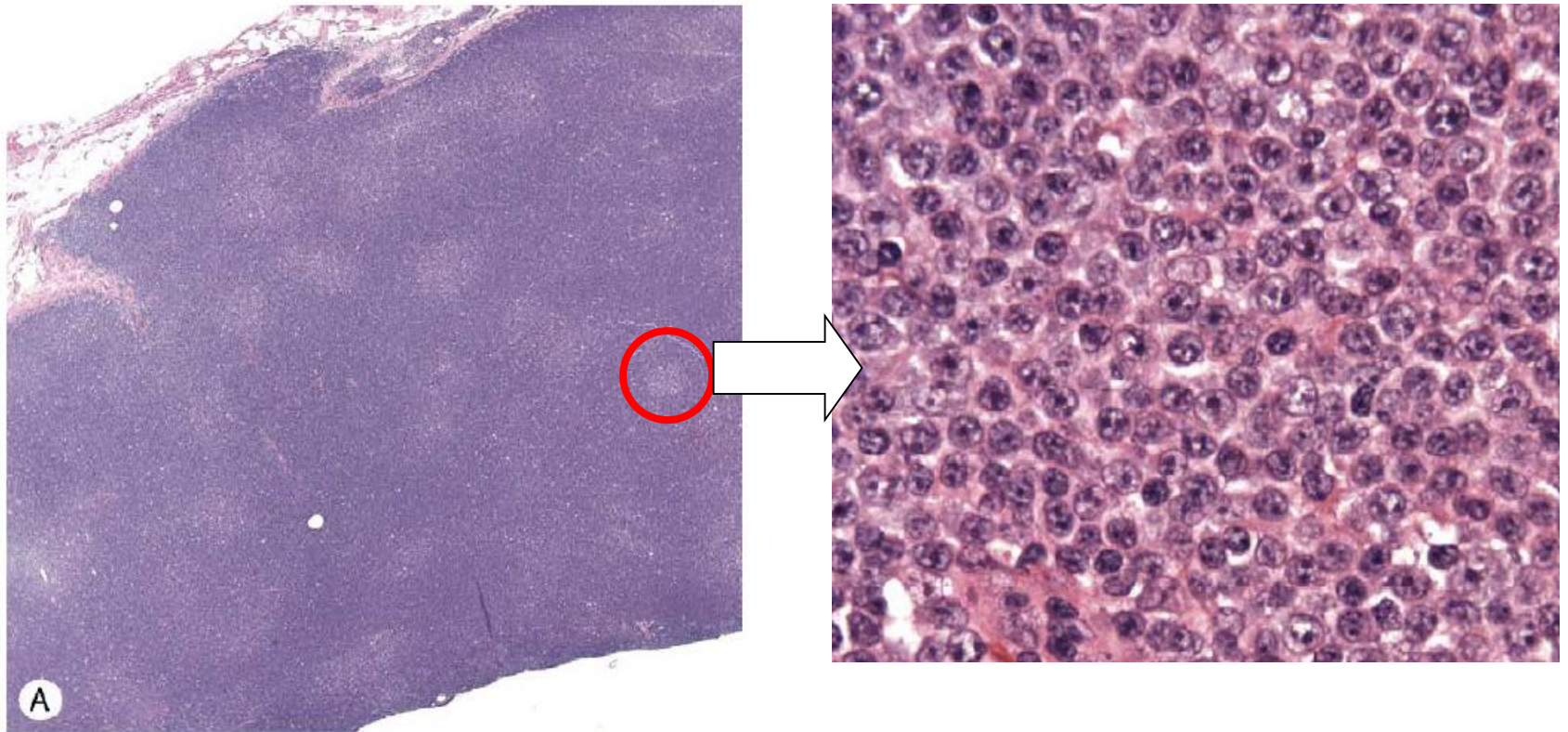
- Correlation with:
 - Disease progression
 - Increase in size of leukaemic clone
 - Tissue infiltration
 - Immune dysregulation
 - Response to therapy

In-vitro and in-vivo kinetics



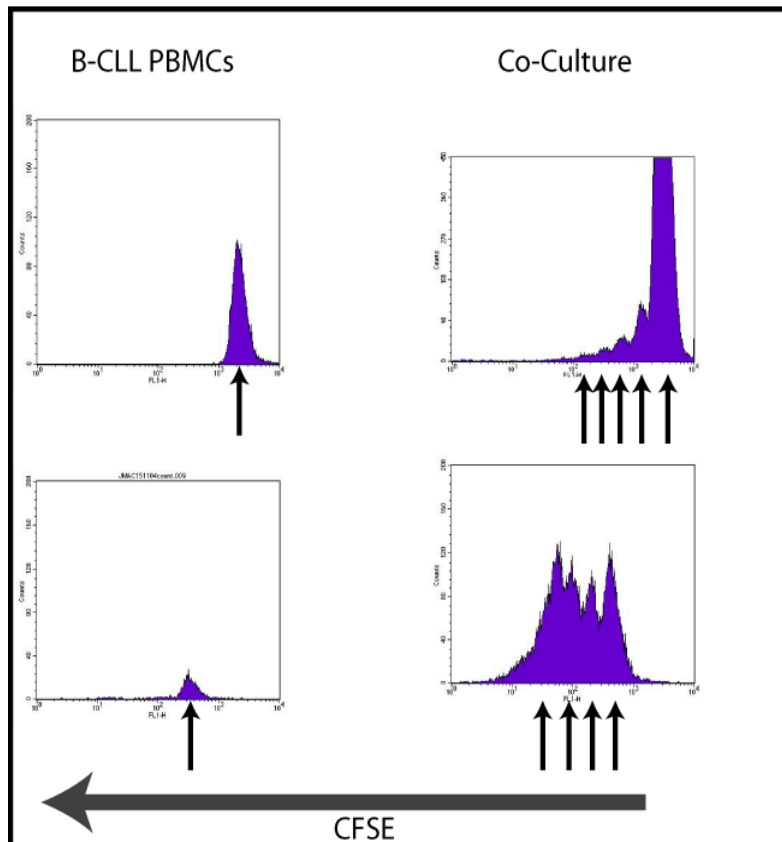
In-vivo deuterated water labelling
Messmer et al 2005

Proliferation Centres



Number of proliferation centres correlates with prognosis

In-vitro Model of Pseudofollicle

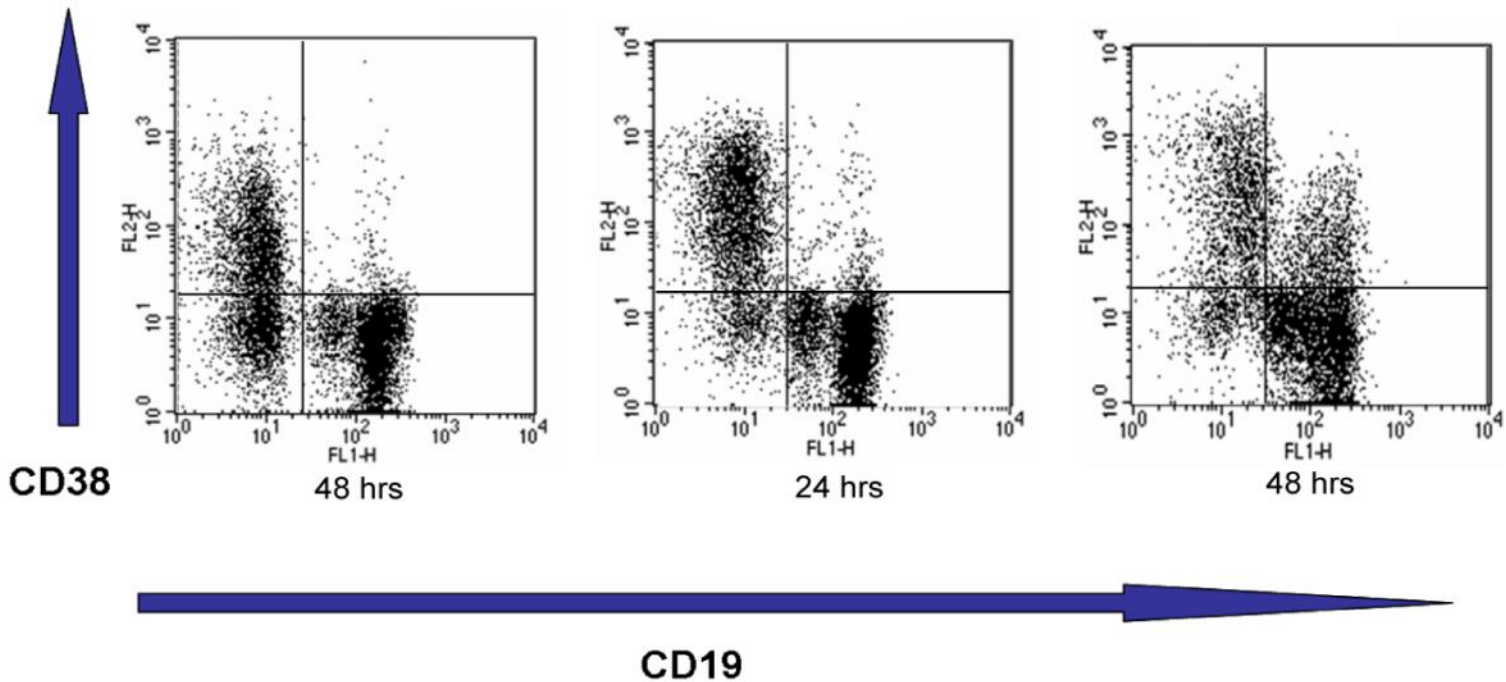


Contact with activated T cells causes proliferation of CLL cells

Activated T-cells Upregulate CD38

Unstimulated T cells
with B-CLL Cells

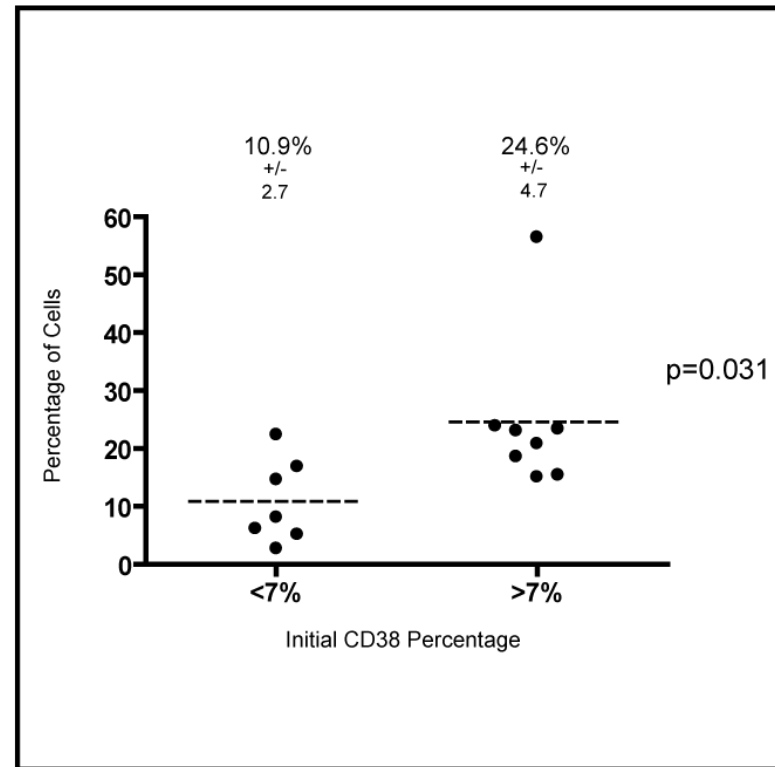
Stimulated T cells with B-CLL
Cells



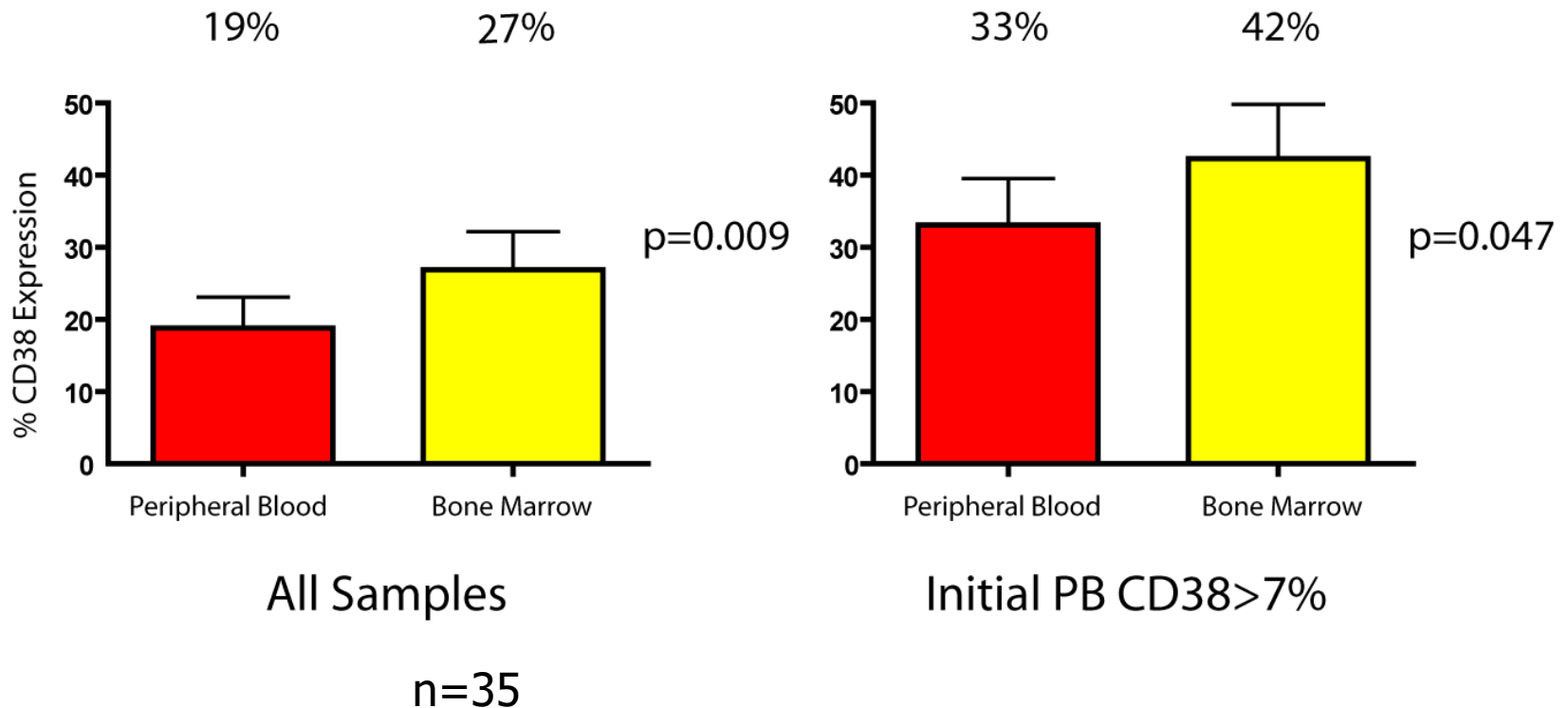
Activated T-cells Upregulate CD38

Proliferation of B-CLL cells compared to peripheral blood CD38%

CD38^{hi} cells are primed for in-vitro proliferation



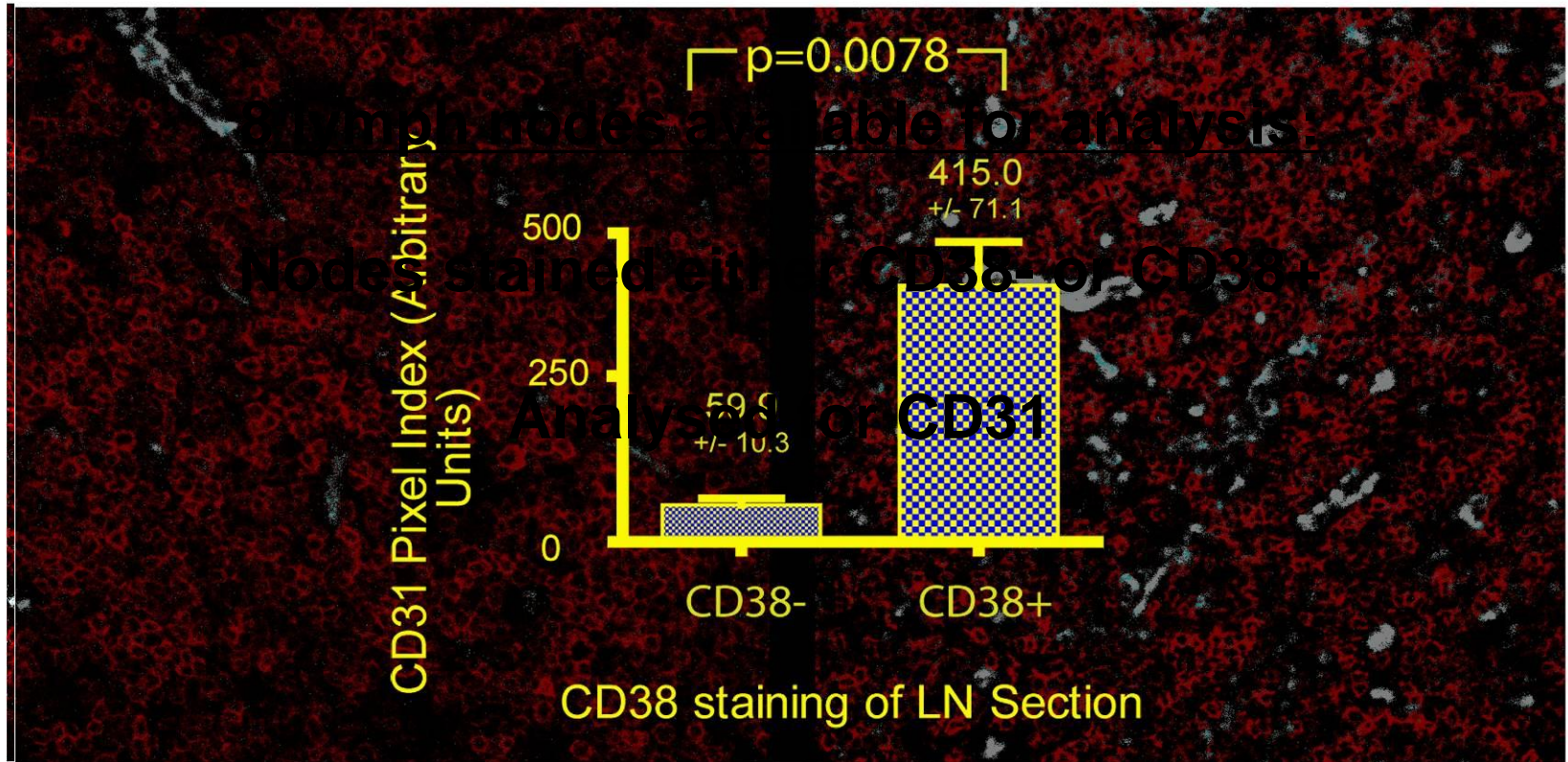
CD38 expression on B-CLL cells is higher in bone marrow than peripheral blood



CD31 staining

CD20: Red

CD31: White



x200

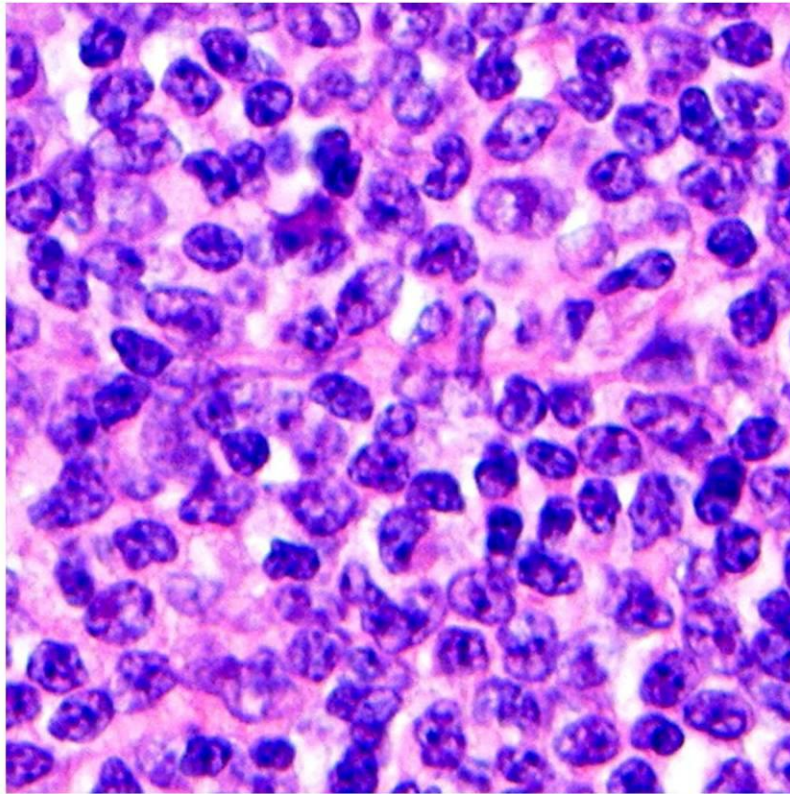
x200

CD38-

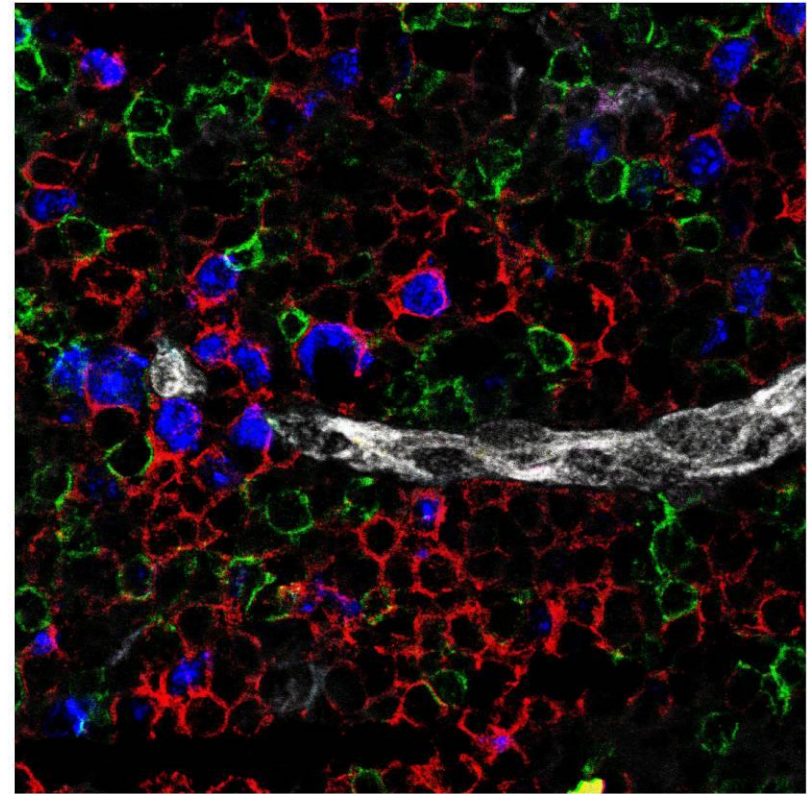
CD38+

Pseudofollicle microenvironment

H&E



CD23: Red CD3: Green
Ki67: Blue CD31: White

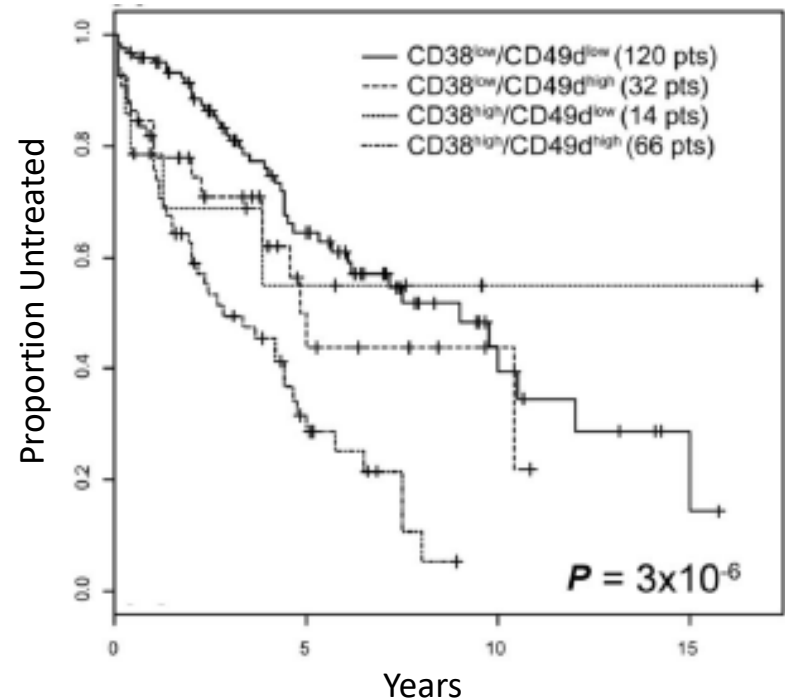


Summary

CD38 influences outcome through effects on the tumour microenvironment that involve interaction with non-malignant cells including T-lymphocytes and the vascular endothelium

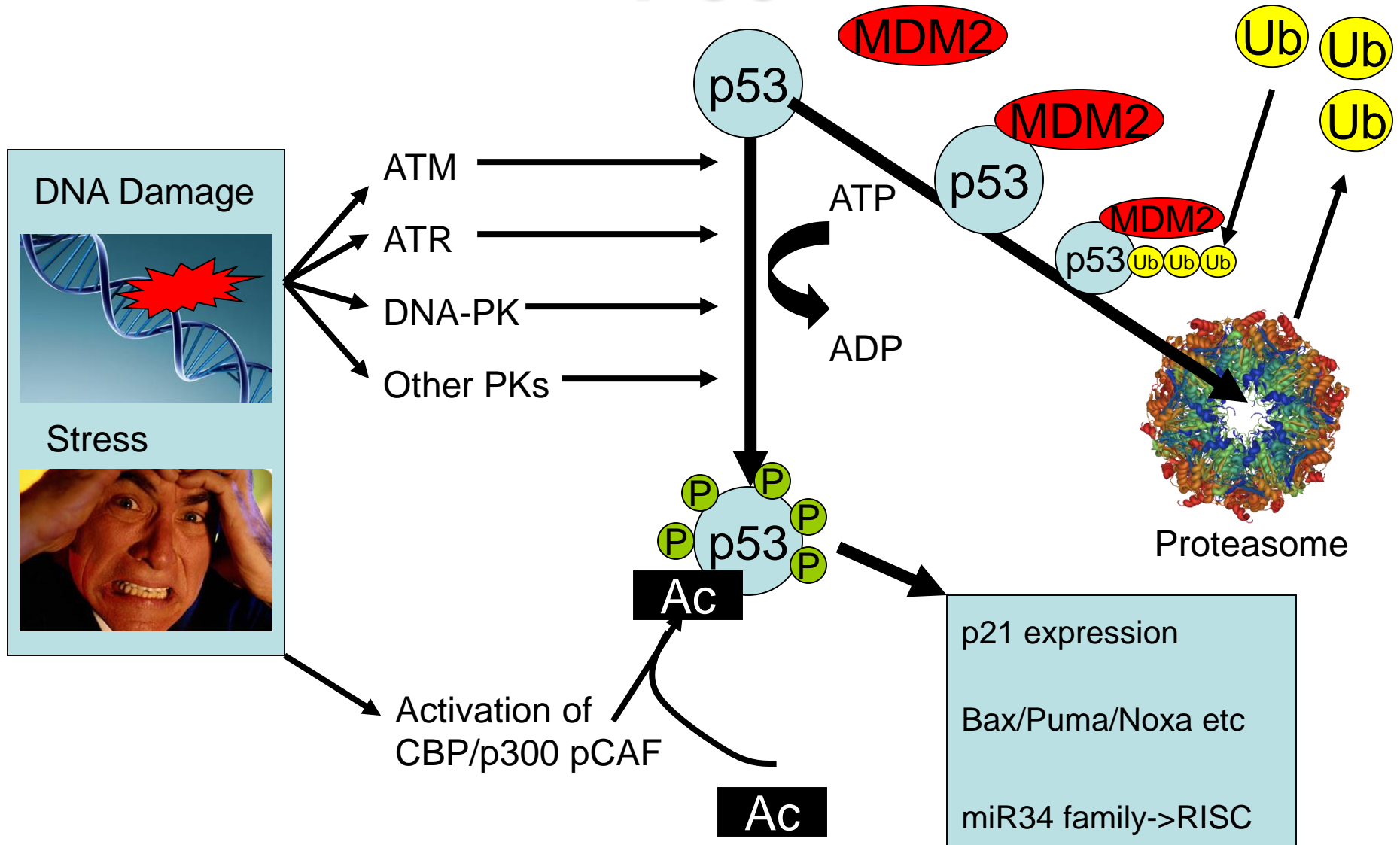
Clinical Interaction Between CD49d & CD38

- Both independent negative prognostic markers
- Combined use of CD38 & CD49d identifies highly aggressive disease and poor prognosis cases



Gattei, V et al. Blood (2008)

P53



Prognostic factors & Pathogenesis

