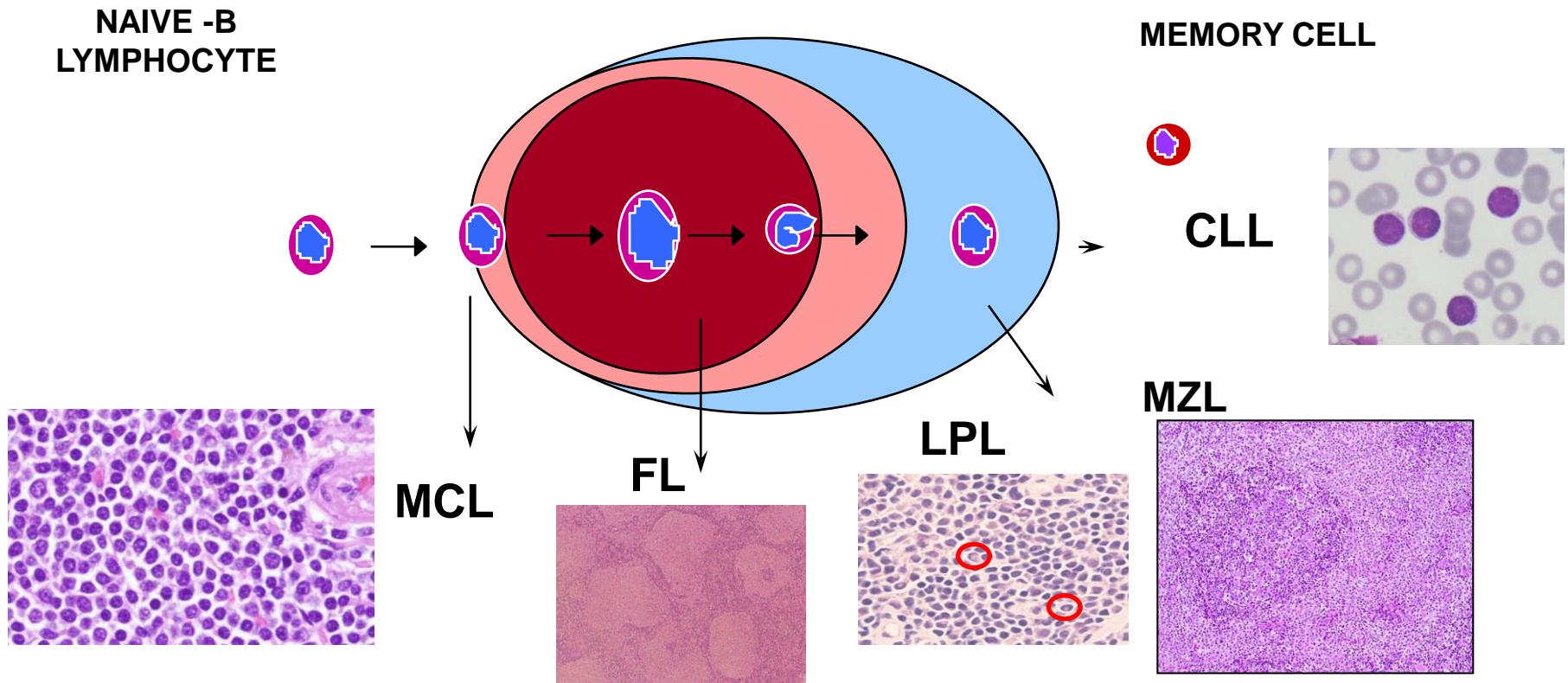


# *Pathology of Small B-cell lymphomas*

**Elias Campo**

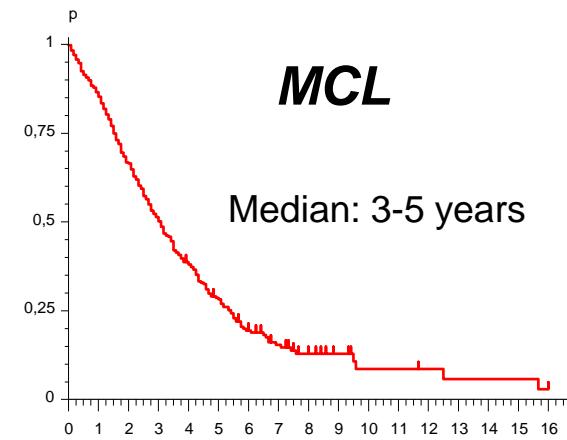
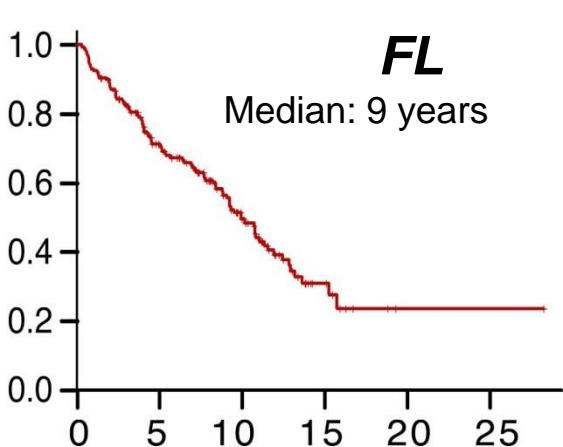
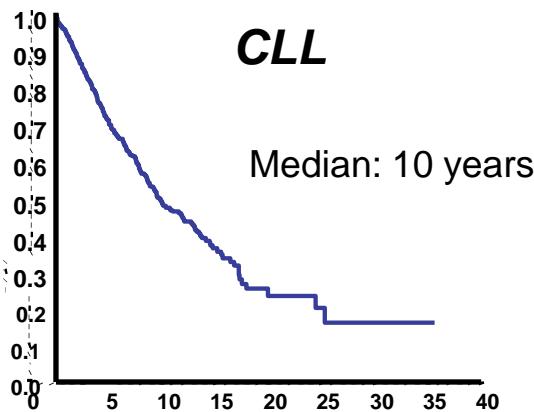
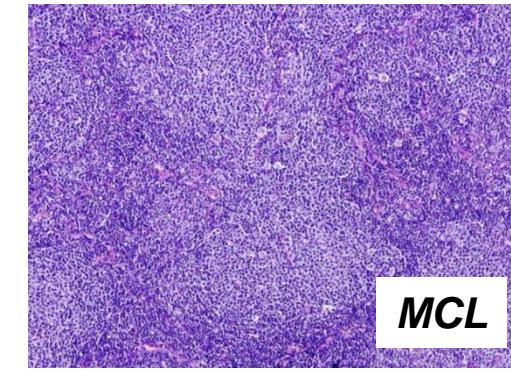
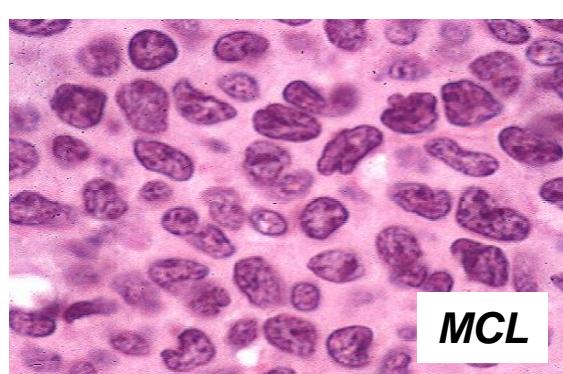
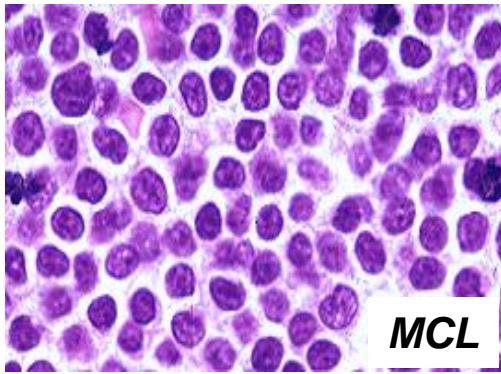
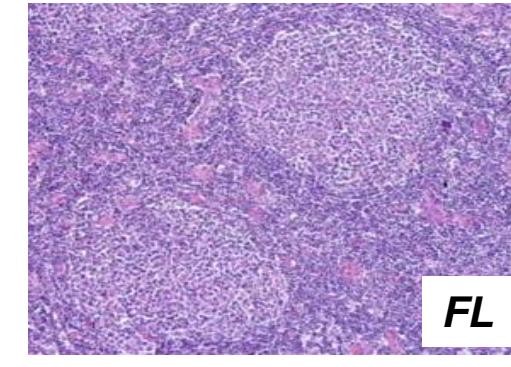
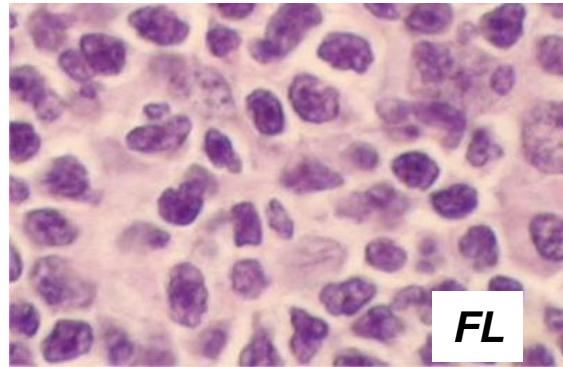
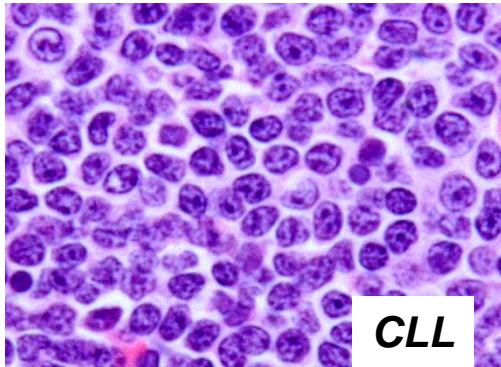
Hospital Clinic, University of Barcelona

# Small B-cell lymphomas



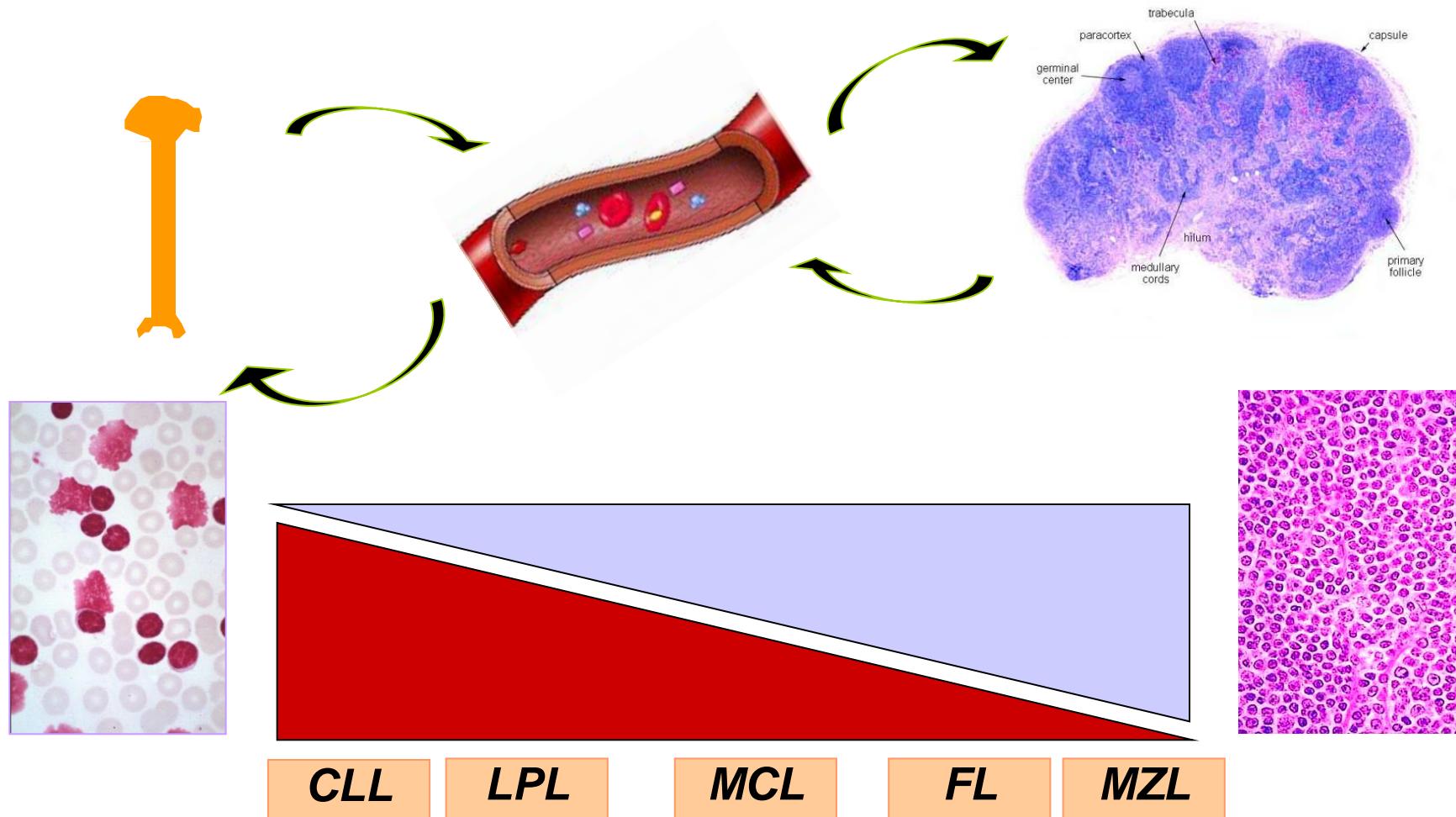
- Small cell size
- Low proliferation
- “Homing” growth patterns
- Immunomodulation by microenvironment
- Indolent clinical behavior

# Heterogeneity of Small B-cell Lymphomas

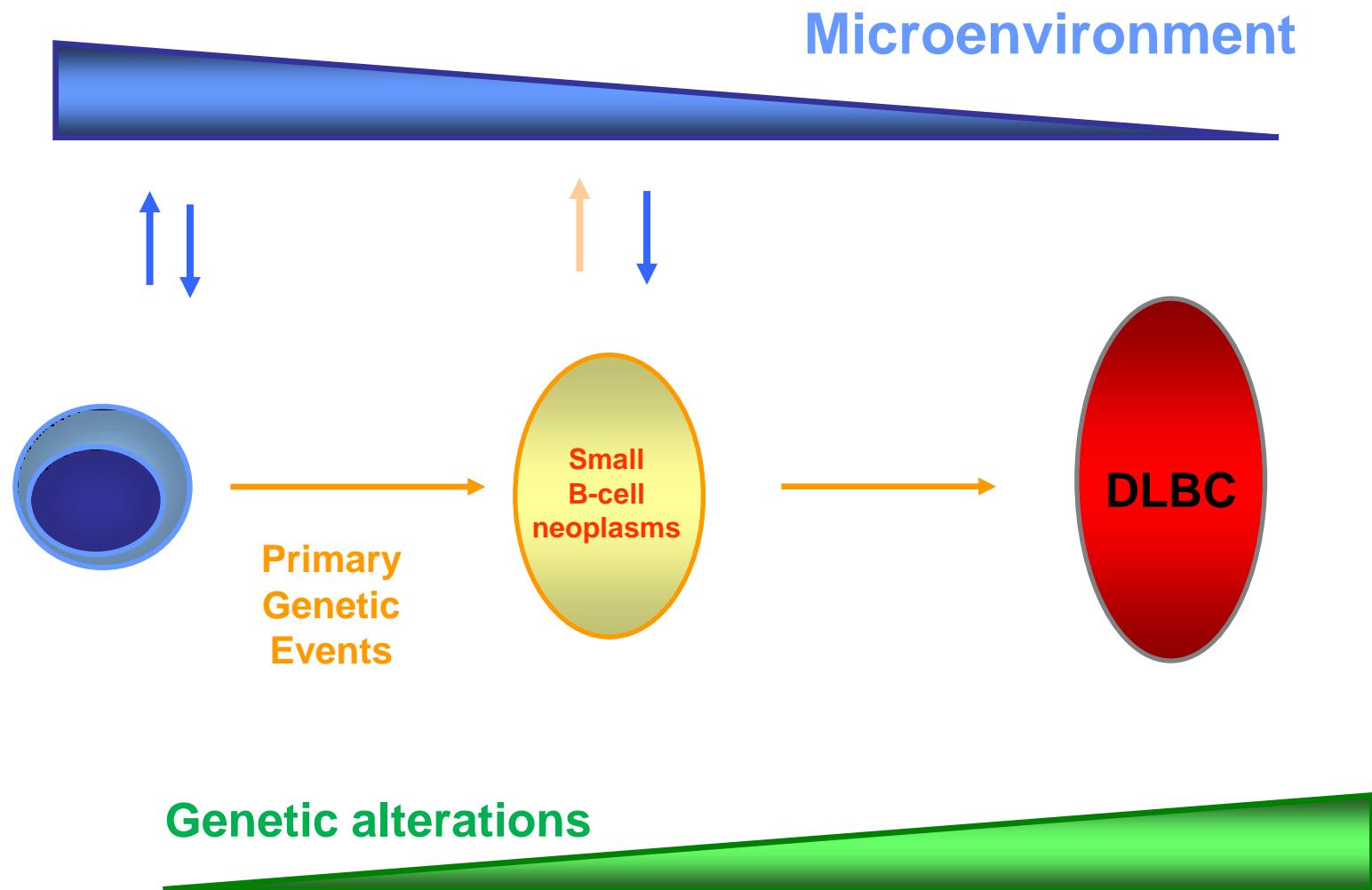


# Lymphoid Cell Circulation and Lymphoid Tissue Compartment

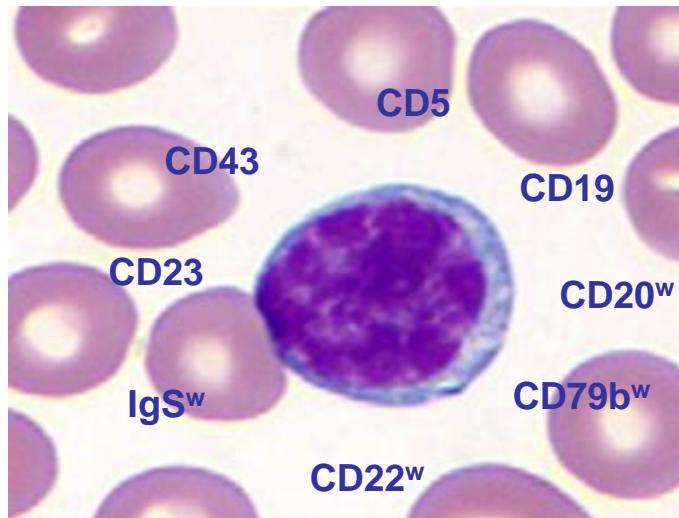
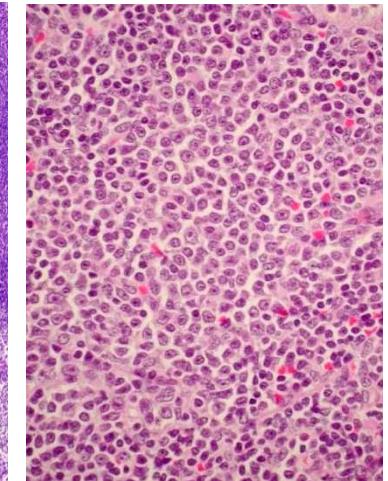
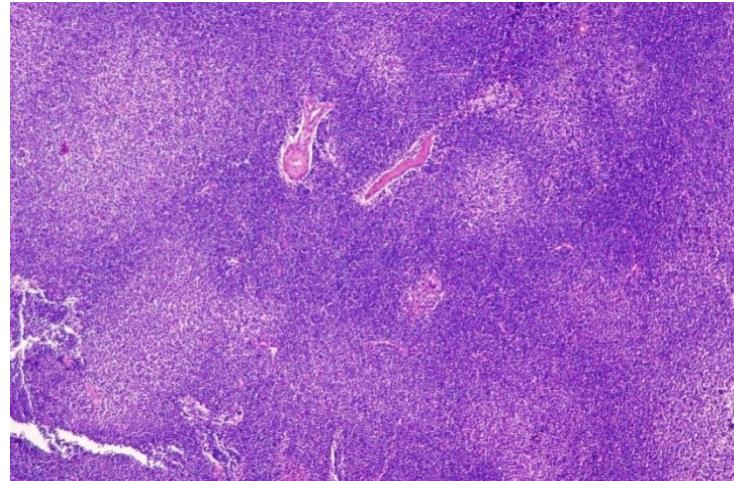
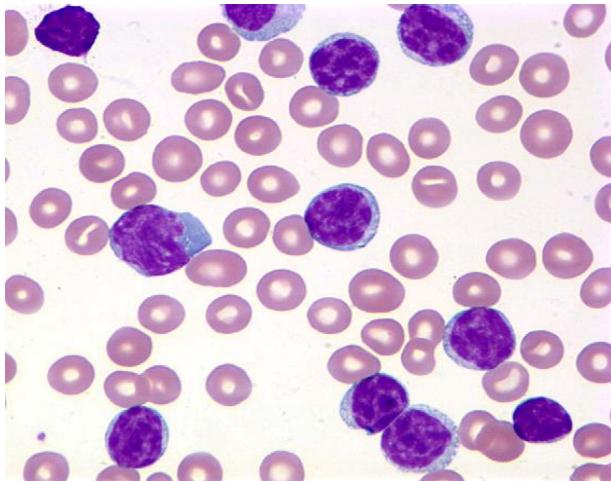
## *Key elements in Small B-cell lymphomas*



# Transformation in Small B-Cell Lymphomas

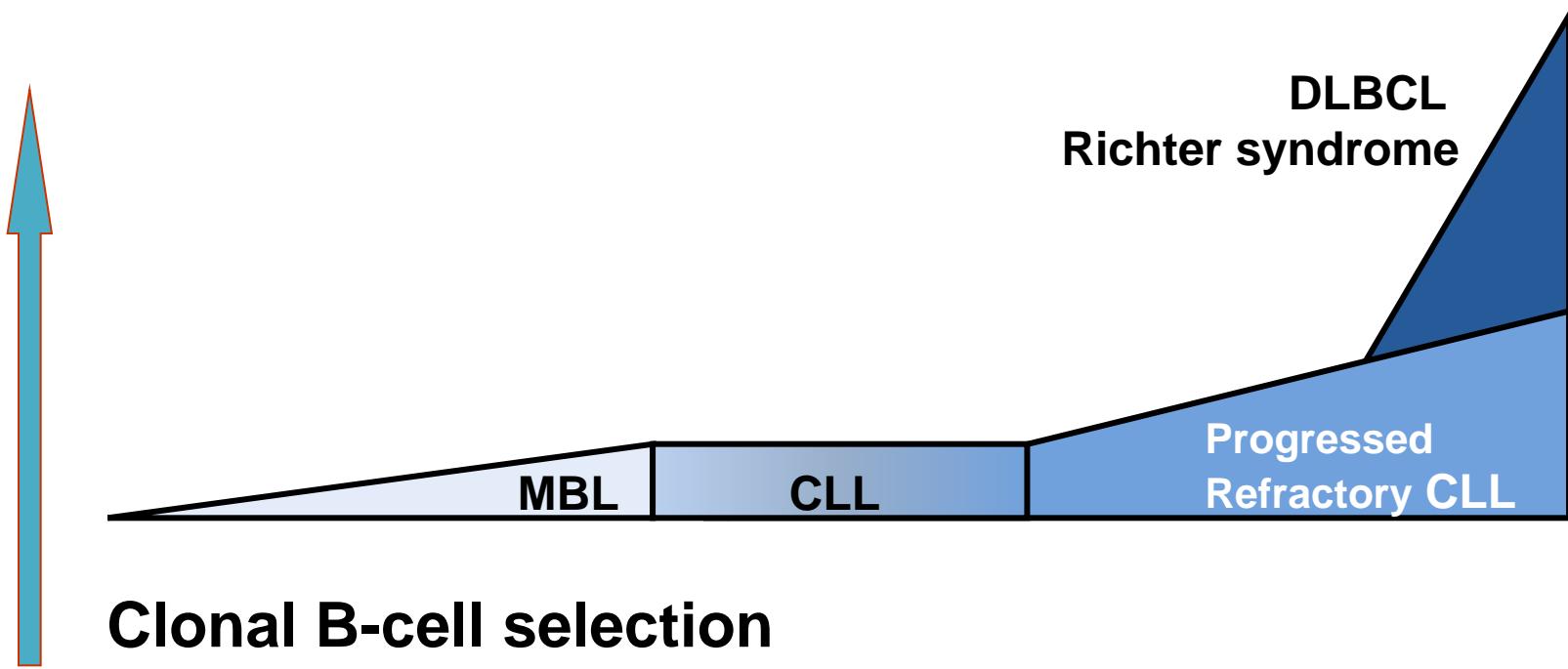


# Chronic lymphocytic leukaemia



- Presence of  $\geq 5 \times 10^9/L$  monoclonal lymphocytes with the CLL phenotype
- SLL is the same disease but restricted to tissues without evidence of leukemic involvement

# Disease progression in CLL

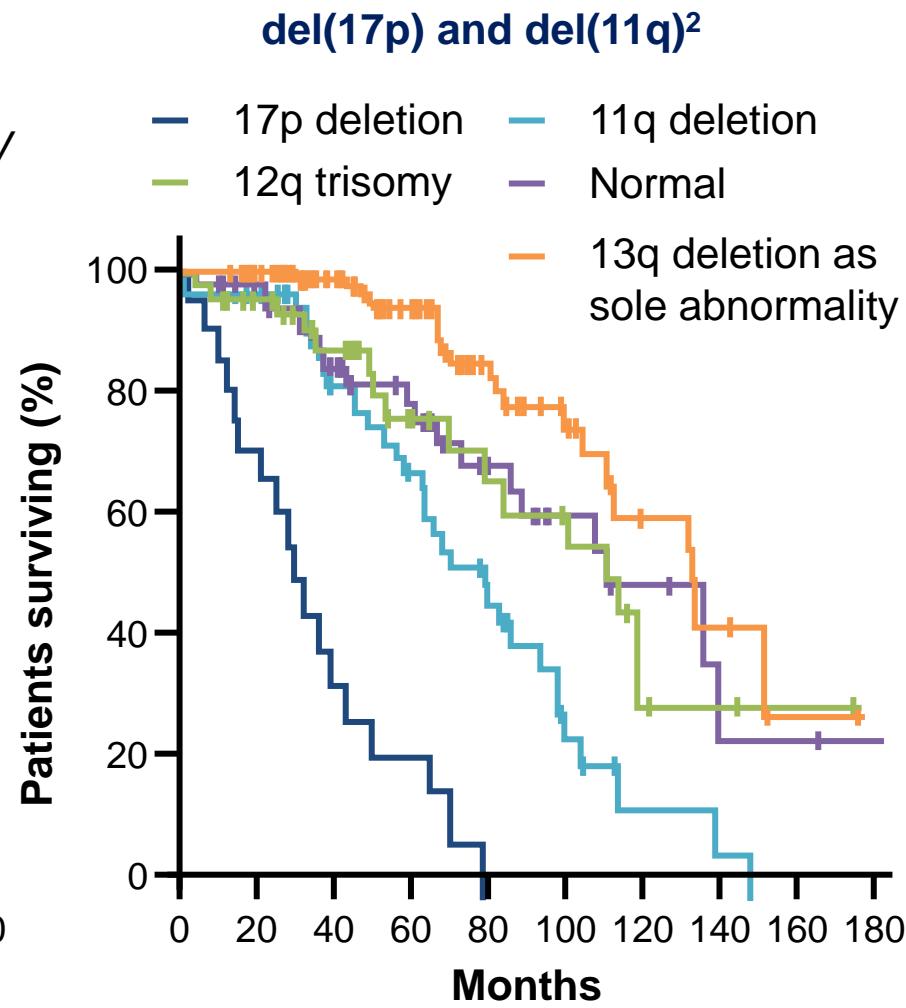
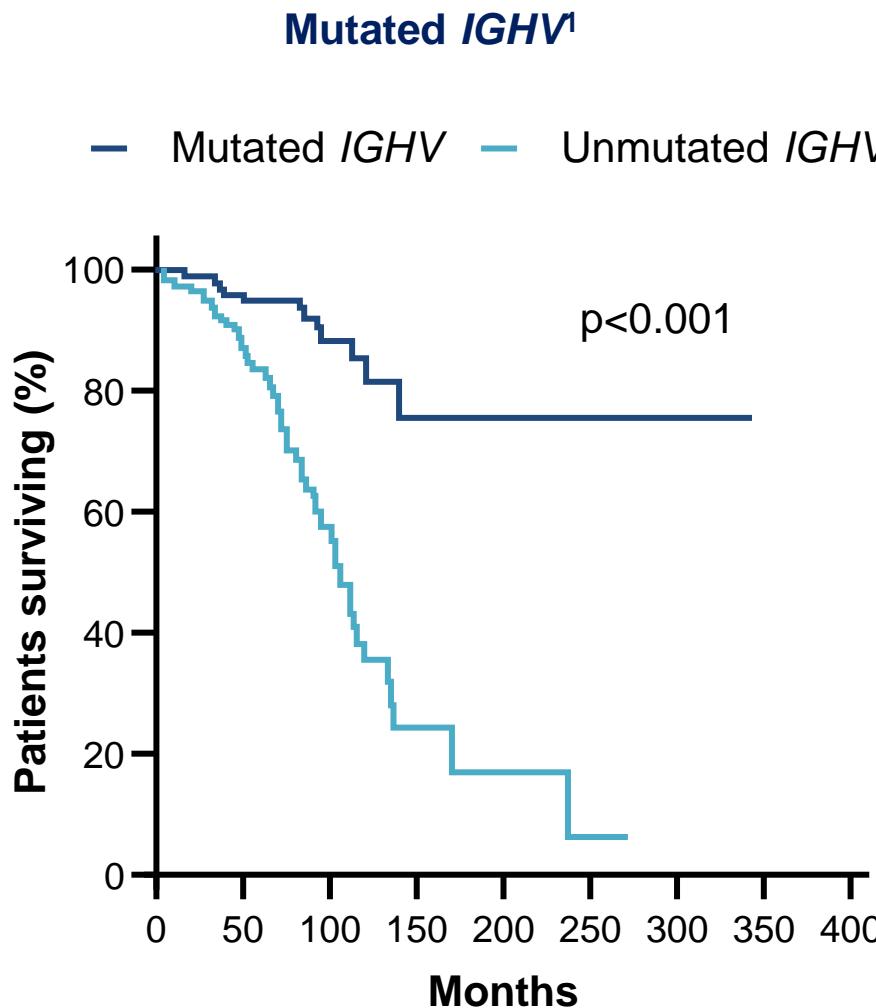


**Clonal B-cell selection  
and expansion**



# Chronic lymphocytic leukaemia

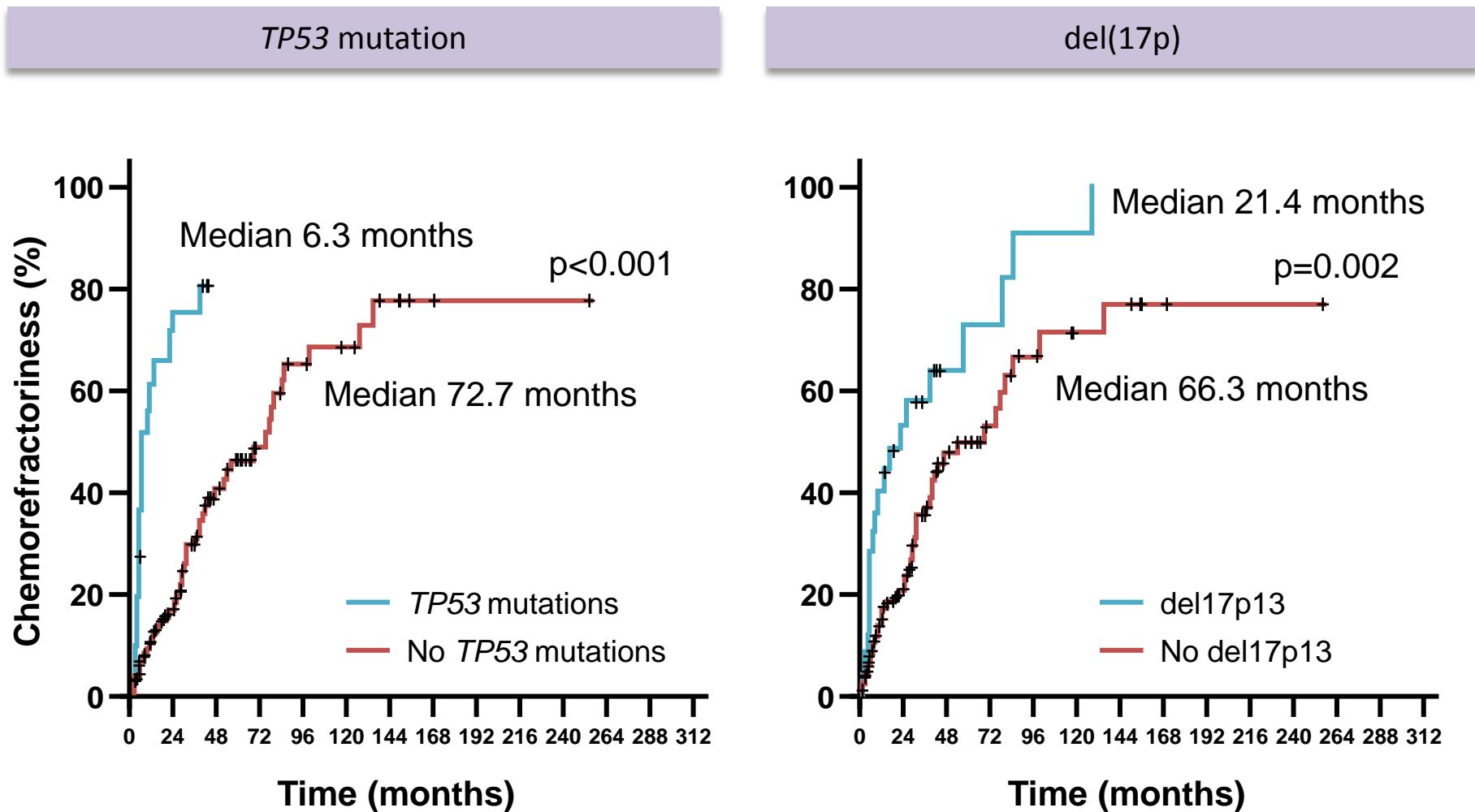
## Clinical impact of molecular and genetic subtypes



1. Zenz T, et al. *Nat Rev Cancer* 2010; 10:37–50.

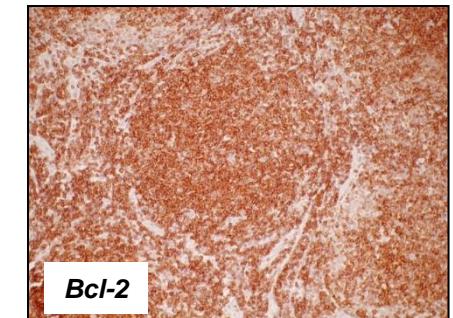
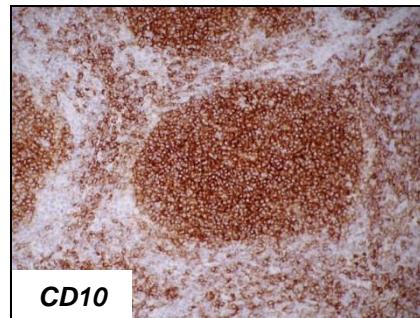
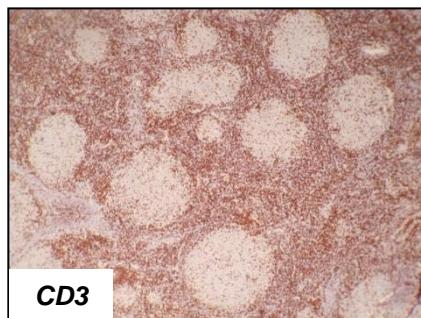
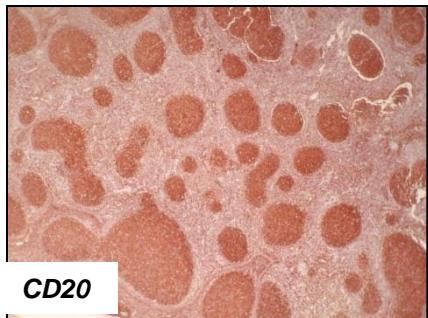
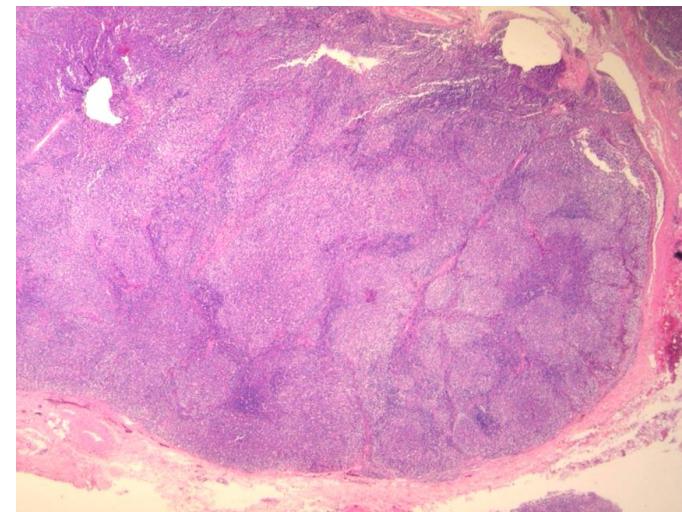
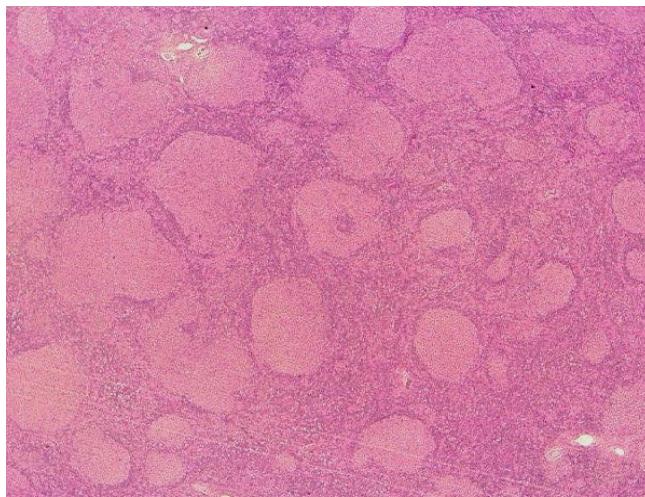
2. Döhner H, et al. *N Engl J Med* 2000; 343:1910–1916.

# **del(17p)/TP53 mutations significantly reduce time to chemotherapy-refractory disease**



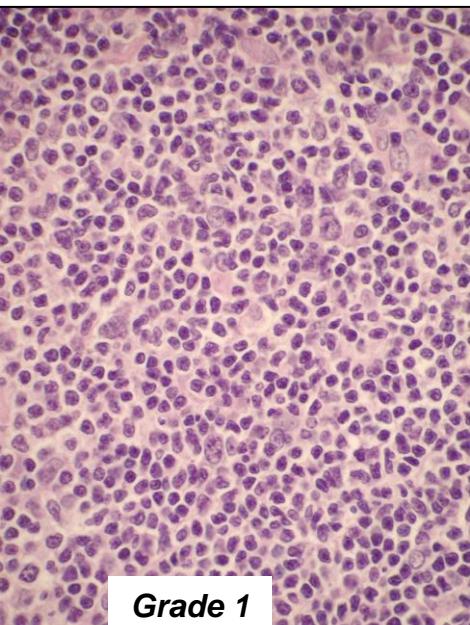
# Follicular Lymphoma

- Usually follicles of similar size/shape but some variation may occur
- Cytologically monotonous with cleaved nuclei and no tingible body macrophages
- Polarisation of normal follicles absent

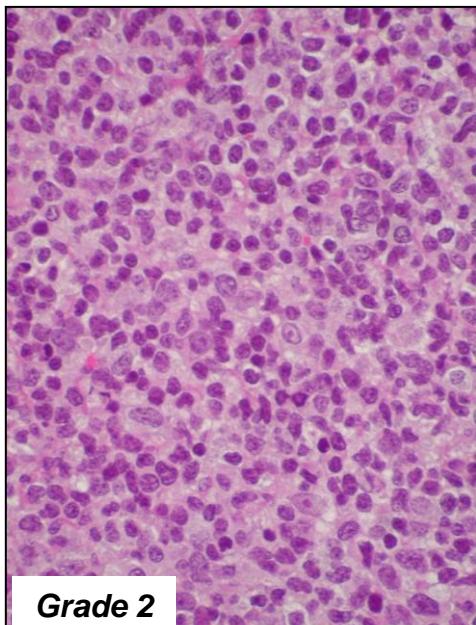


# WHO classification: Grading in FL

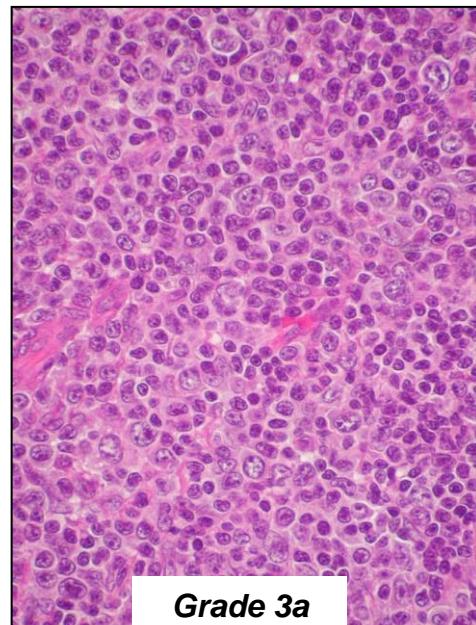
Grade	Centroblasts/high power field	Characteristics
1	≤5	—
2	6–15	—
3A	>15	Centroblasts with intermingled centrocytes
3B	>15	Pure sheets of blasts



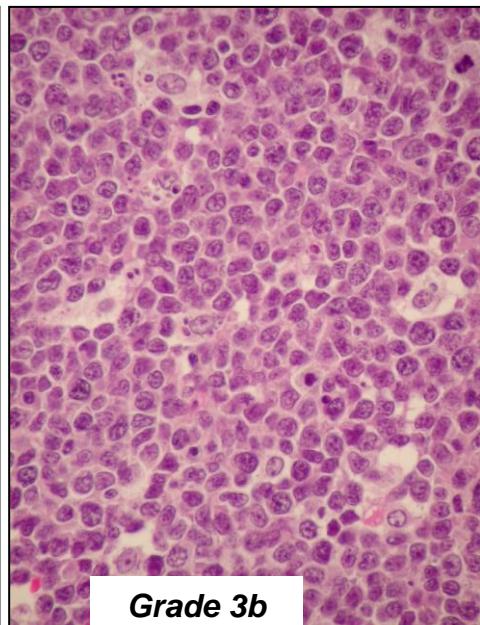
Grade 1



Grade 2

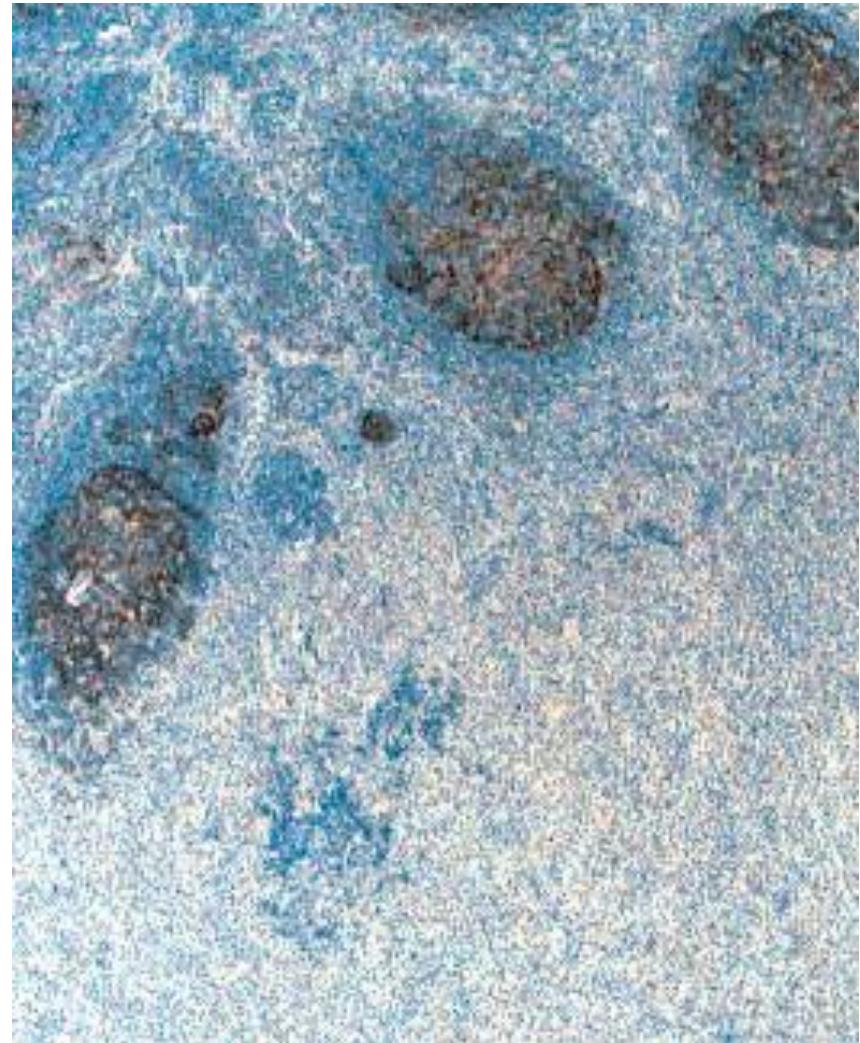
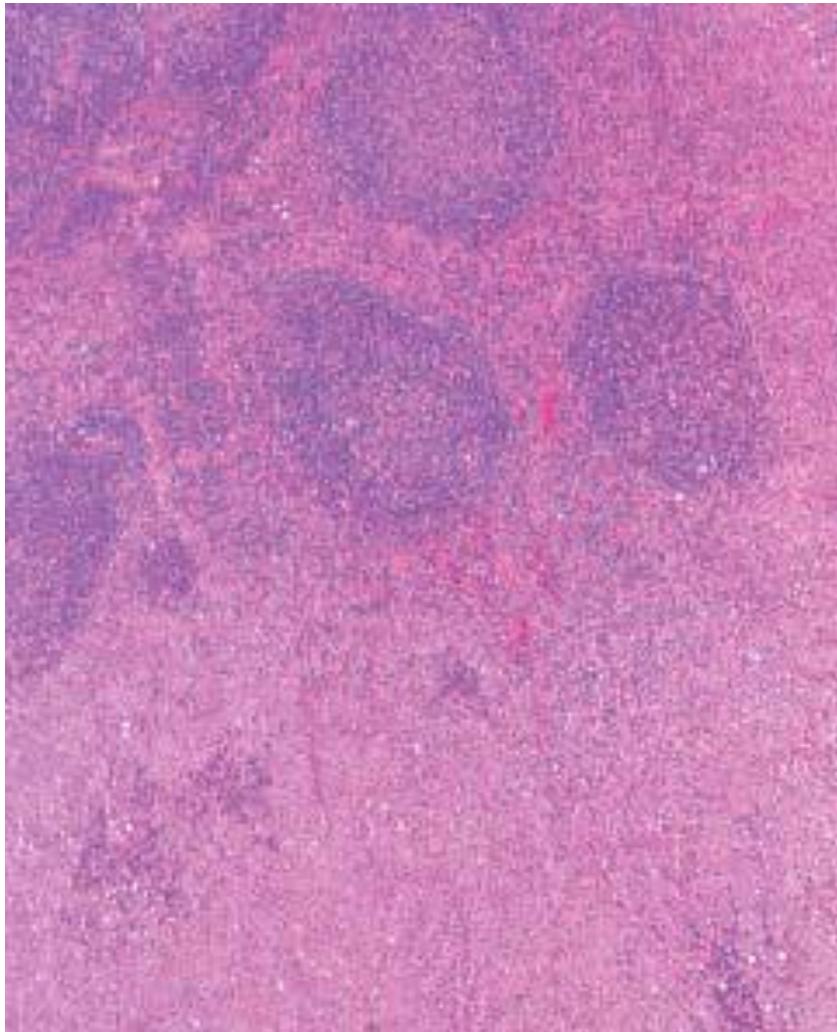


Grade 3a



Grade 3b

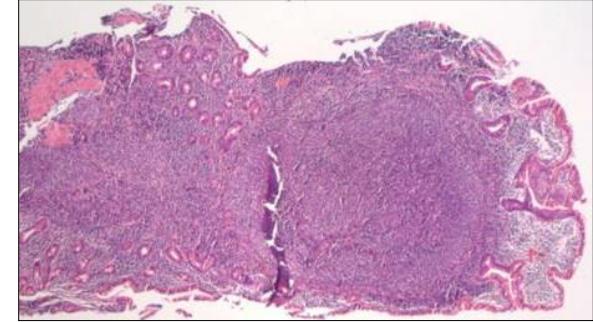
# Diffuse component in FL



# Follicular Lymphoma: A single disease?

## *FL subtypes*

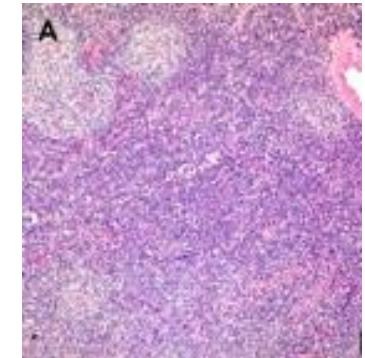
- Paediatric follicular lymphoma
- Primary duodenal follicular lymphoma
- Primary cutaneous follicular centre lymphoma
- Diffuse variant of follicular lymphoma
- Follicular lymphoma negative for the t(14;18)



# Different subtypes of t(14;18) negative FL

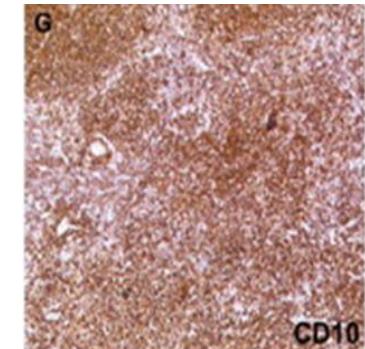
- **FL with conventional morphology** <sup>1</sup>

- 30% BCL2 protein positive
- Lower GC expression signature (CD10 negative)
- Higher proliferation
- No clinical impact



- **Diffuse variant of FL** <sup>2</sup>

- Large nodal tumors in inguinal region
- Localized disease
- CD10, BCL2, BCL6, CD23 positive
- Del 1p36

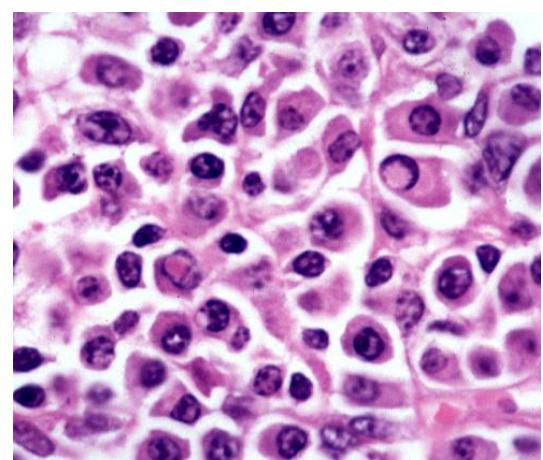
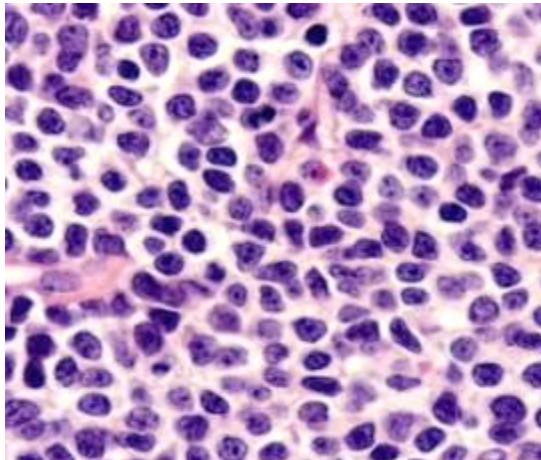
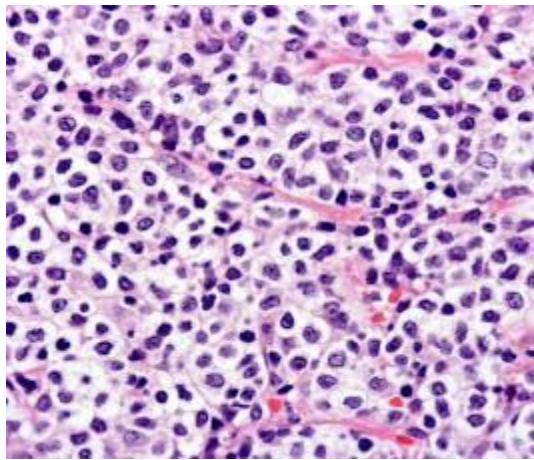
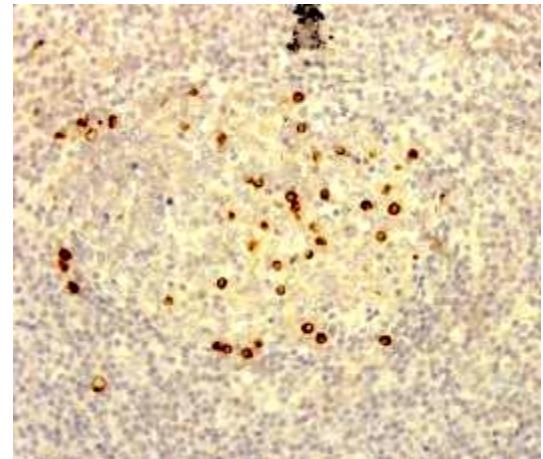
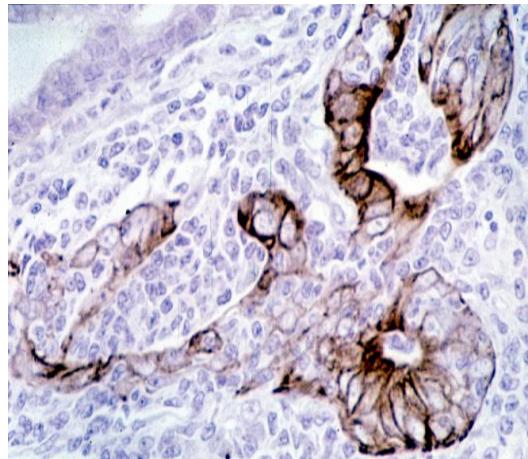
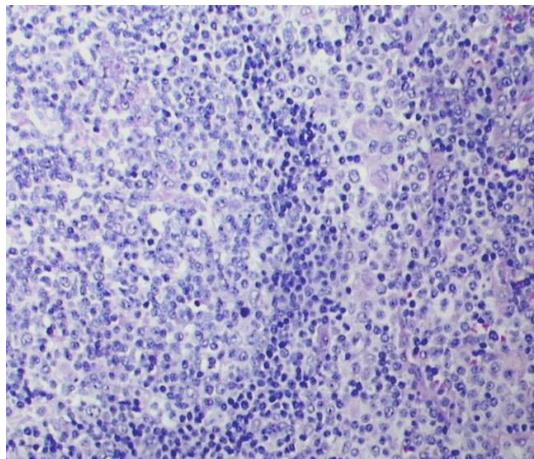


<sup>1</sup> Leich et al. *Blood* 2009;114:826-34

<sup>2</sup> Katzeberger T et al *Blood* 2009;113:1053-61

# Extra Nodal MZL: Morphology

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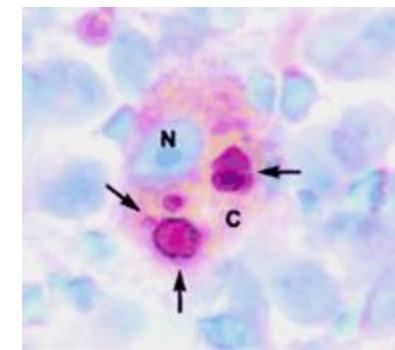
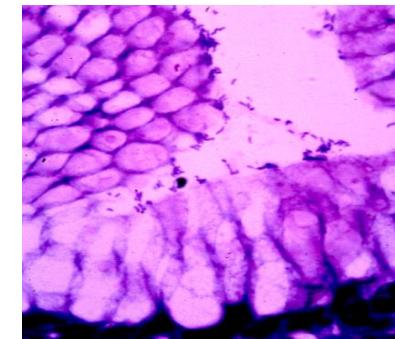


# Extra Nodal MZL: Etiological Factors

## Chronic Inflammatory Response

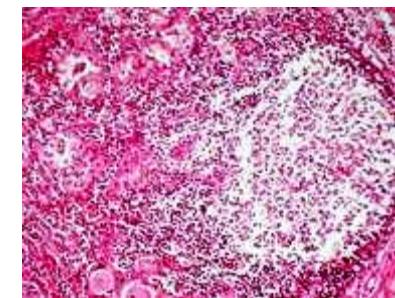
Stomach  
Ocular  
Salivary Gland  
Thyroid  
Skin  
Other

H pylori →  
Chlamydia Psittaci  
Sjogren's  
Hashimoto's  
Borrelia  
?  
HCV?

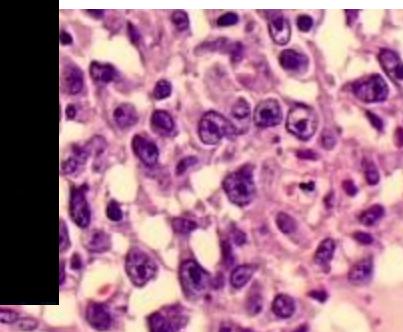
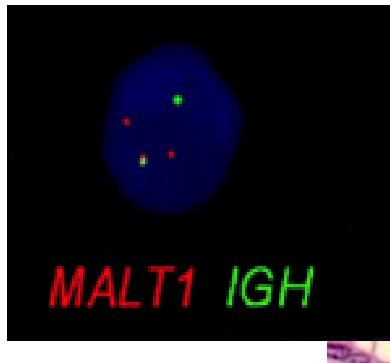
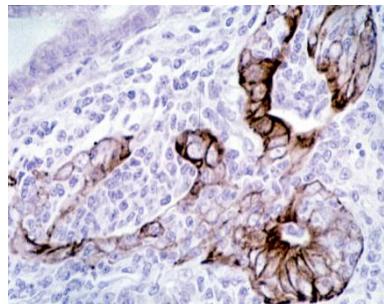
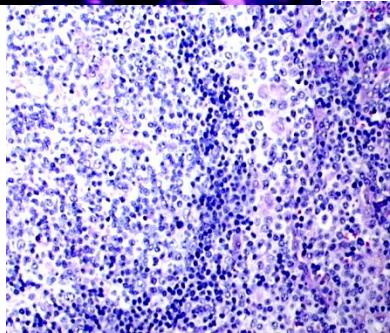
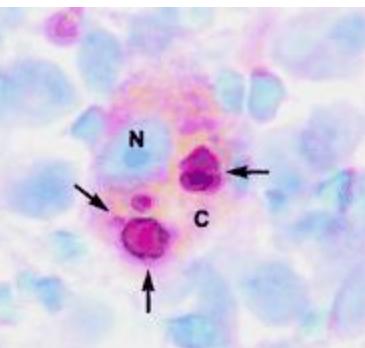
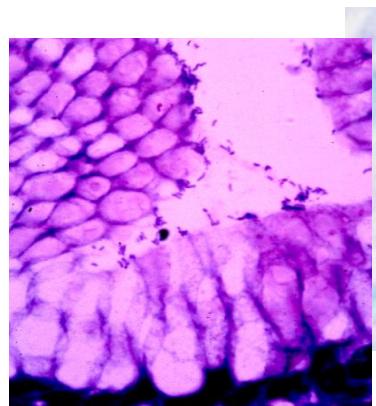


## Genetic and environmental background

Polymorphisms  
Thymic MZL  
Asians



# Tumor Site, Etiology, and Tumor Progression in MALT Lymphomas



Normal Cell



Oligoclonal Expansion



MALT Lymphoma  
*HP dependent*

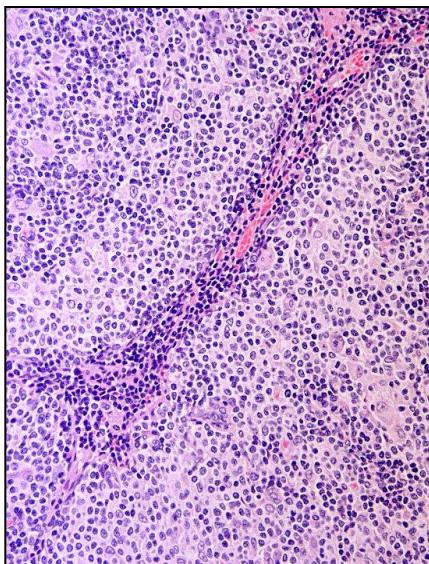
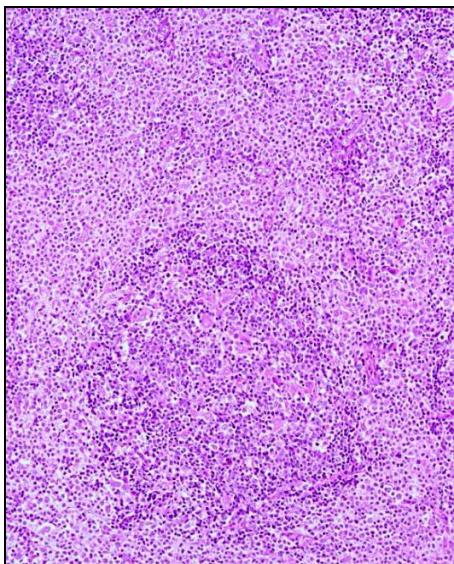
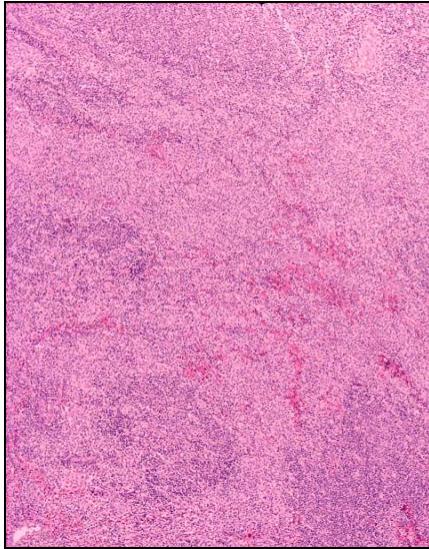
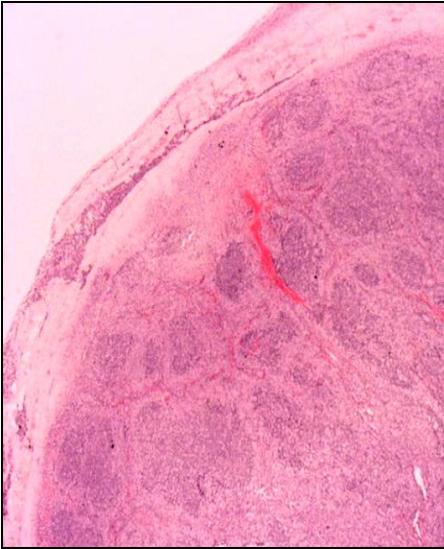


MALT Lymphoma  
*HP independent*



Transformation

# Nodal Marginal Zone Lymphoma



**NMZL resembles extranodal or splenic MZL but is only localized in lymph nodes**

**Adults median age 60, M=F**

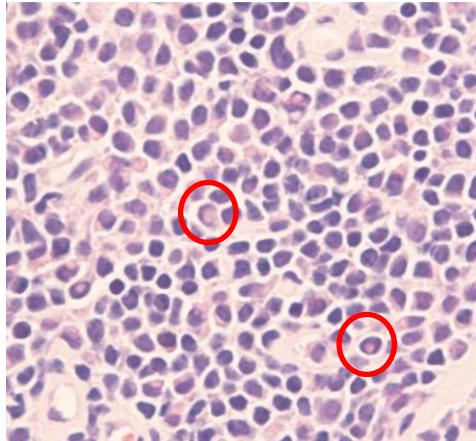
**Need to rule out extranodal site**

**Hepatitis C virus?**

**Tri 3, 18, 7**

**50-60% have 5 year survival**

# Somatic Mutations in Waldenstrom Macroglobulinemia /LPL



## MYD88 L265P

- **95% WM/LPL**
- 29% DLBCL-ABC
- 6% MZL
- 3% CLL

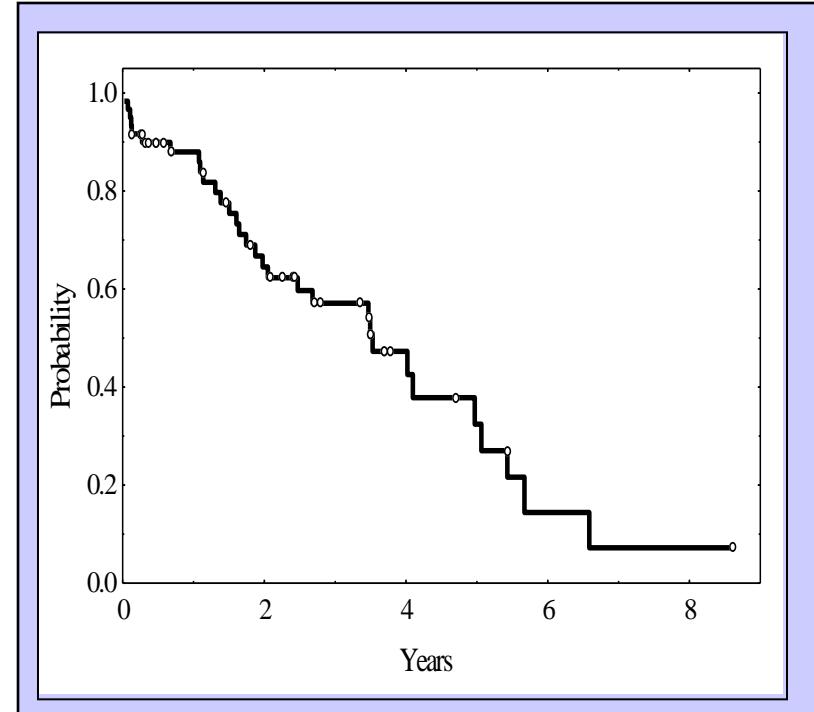
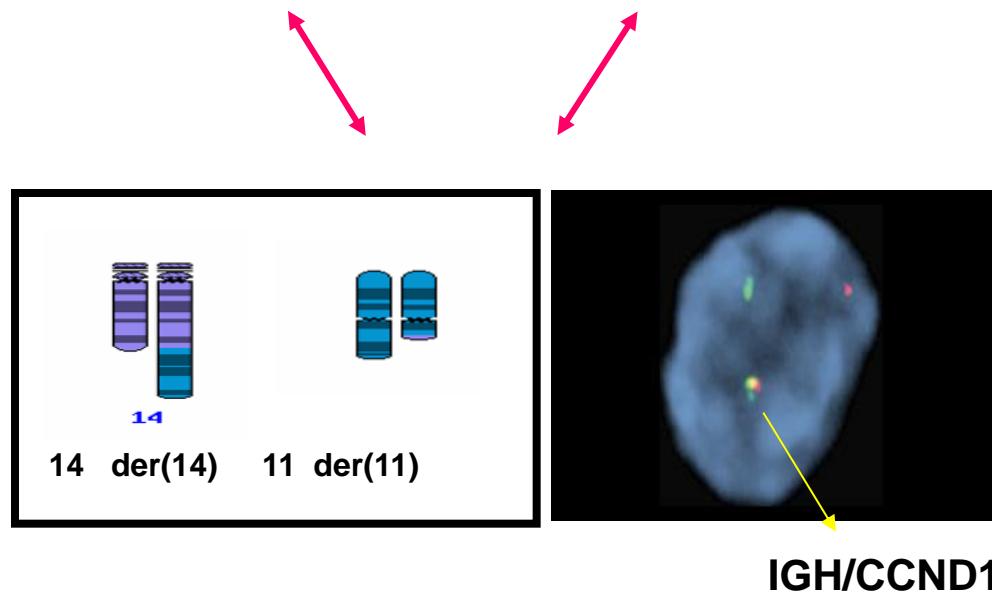
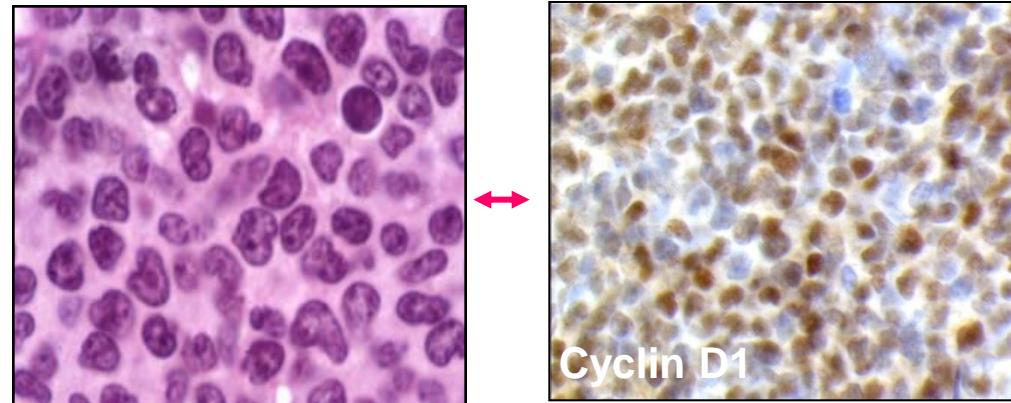
## CXCR4

- **25-35% WM/LPL**
- Associated with MYD88
- More active disease
- Less lymphadenopathy
- More resistant disease to new drugs

- Useful information in the differential diagnosis of LPL
- Other entities with plasmacytic differentiation are negative (e.g gamma heavy chain disease).
- Need to be interpreted in the global context of the disease

Tacci et al NEJM 2011 Ngo Nature 2011; Puente Nature 2011; Xi L et al Blood 2012;  
Schmidt et al Br J Haematol 2015; Cao et al Leukemia, 2015 **29**, 169–176.

# Mantle Cell Lymphoma

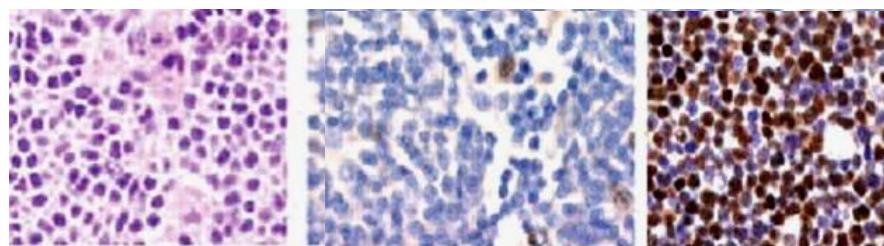
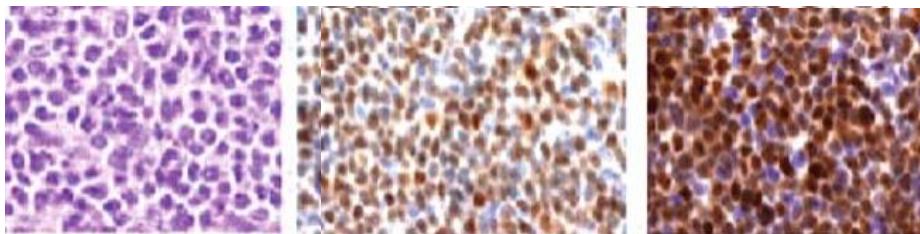


**Complete Response** 25% (6-50%)  
**Duration of CR** 1.5 yrs (0.5-2.5 yrs)  
**Median Survival** 3-4 years

# *Mantle cell lymphoma*

## *CCND1-negative variant*

**Classic MCL**

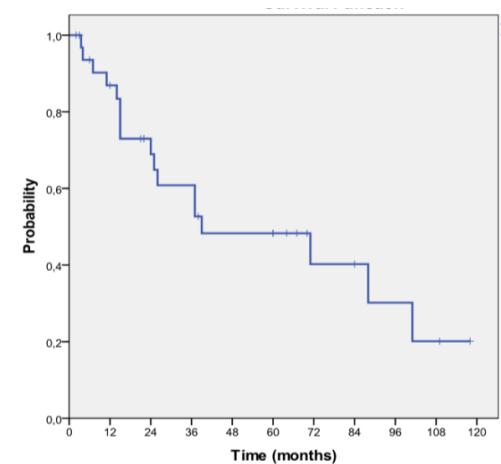
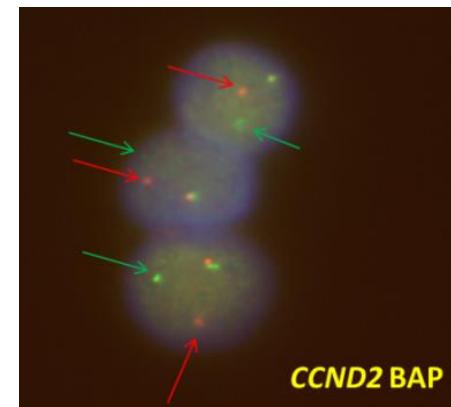


**CCND1 neg MCL**

*Cyclin D1*

*Sox11*

*CCND2 trans 55%*



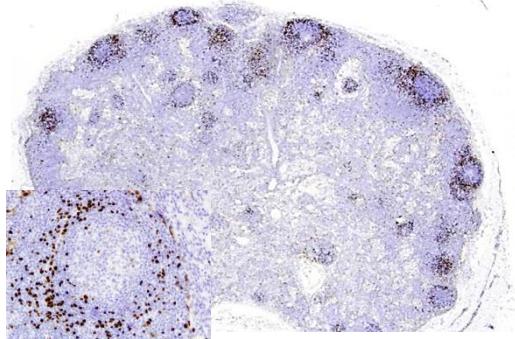
Mozos et al *Haematologica* 2009  
Salaverria et al *Blood* 2013

# Mantle cell lymphoma

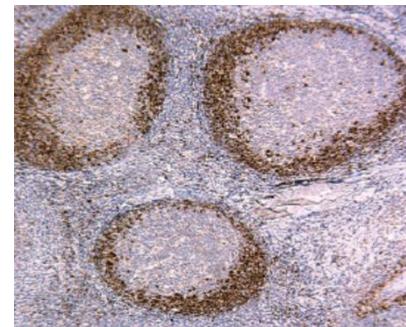
## Indolent Variants

- Clinical concept with different pathological conditions
  - In situ MC neoplasia, Mantle zone pattern, low proliferation index (SOX11+ or SOX11-)

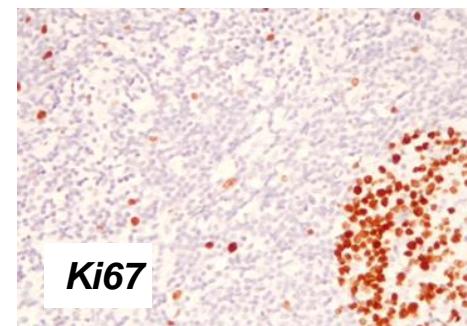
In situ MC neoplasia



Mantle Zone MCL



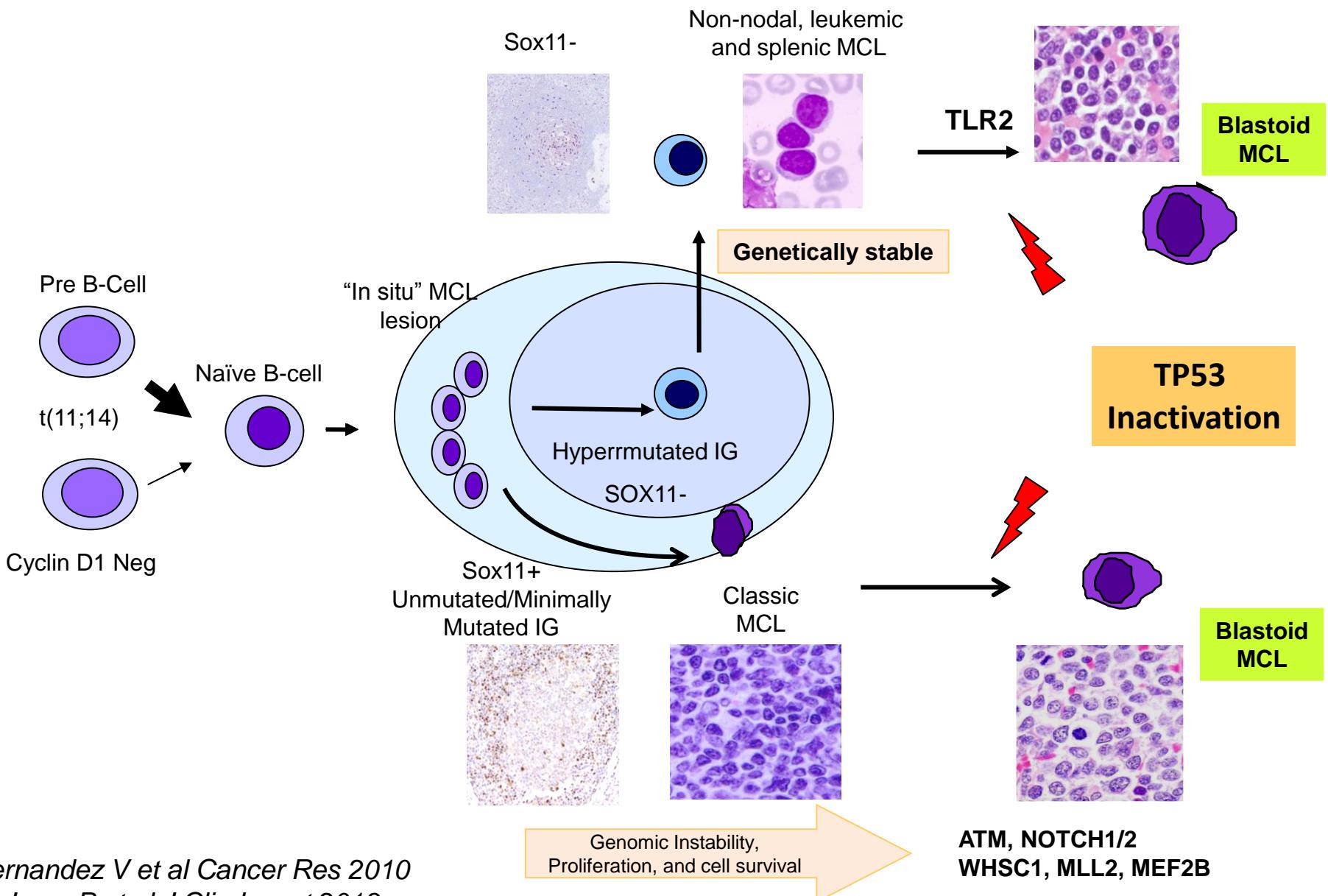
Low proliferation



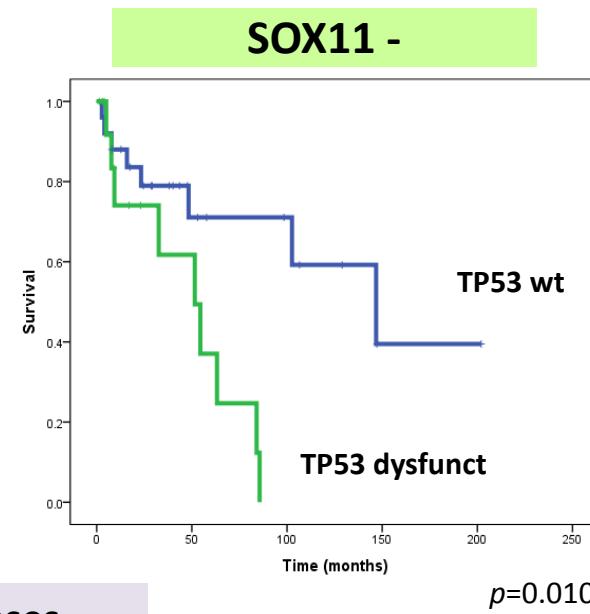
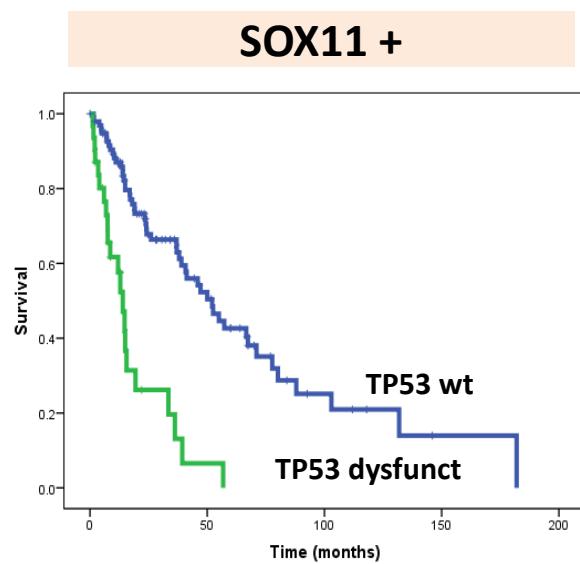
### – Non-nodal leukemic subtype of MCL

- Non-nodal leukemic (splenomegaly) disease
- SOX11-negative
- Hypermutated *IGHV*
- Simple karyotypes
- May transform into blastoid MCL (*TP53* mut)

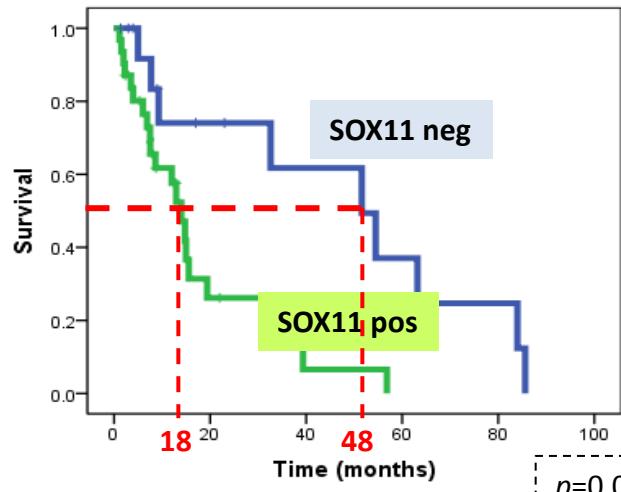
# Molecular Pathogenesis and Clinical Subtypes of MCL



# Prognostic impact of 17p del and *TP53* mutations in MCL



**TP53 dysfunctional cases  
(17pdel/TP53 mut)**



**Median Surv**  
SOX11 neg 48 m  
SOX11 pos 18 m

# **Small B-cell Lymphomas**

- **A heterogeneous group of lymphoid neoplasms with different clinico-pathological characteristics**
- **Increasing recognition of early or “in situ” lesions (Multi-step pathogenesis in NHL)**
- **Specific variants in each disease with particular clinical and pathologic characteristics**