

Un nou subtipus de limfoma de cèl.lules del mantell: *“El microscopi no enganya”*

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IDIBAPS/ CIBERONC

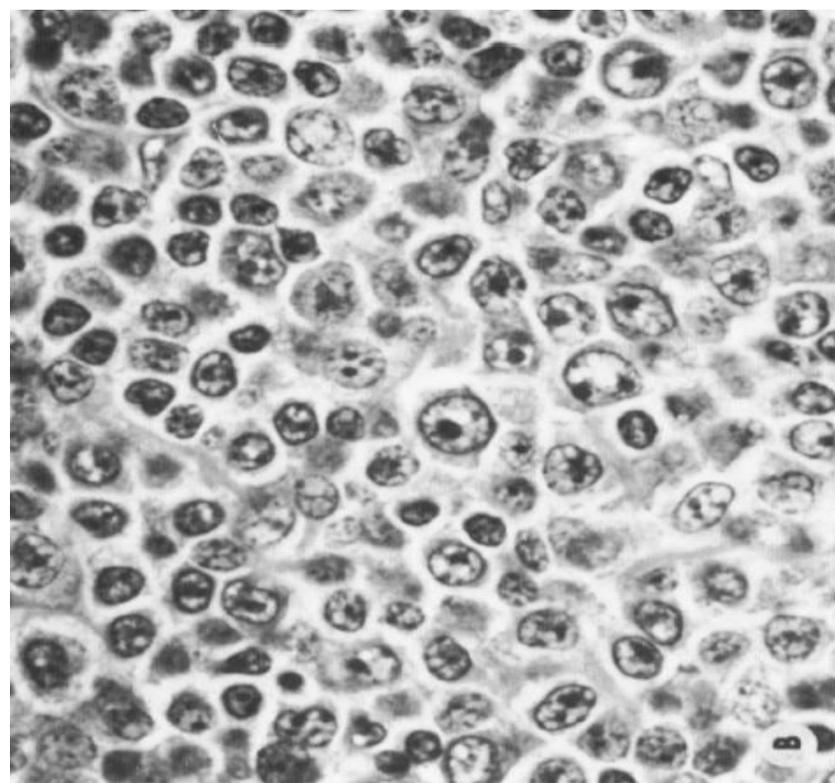
Sessions SCAP

“DESCOBRINT NOVES MALALTIES A PARTIR DE LA MORFOLOGIA. EL SOMNI FET REALITAT”

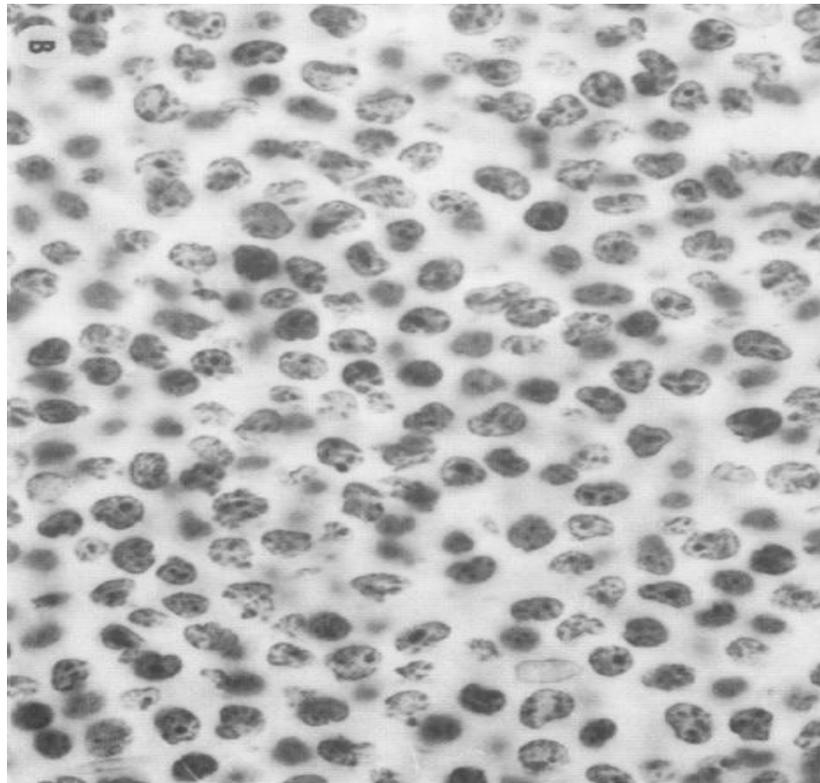
21 octubre 2021



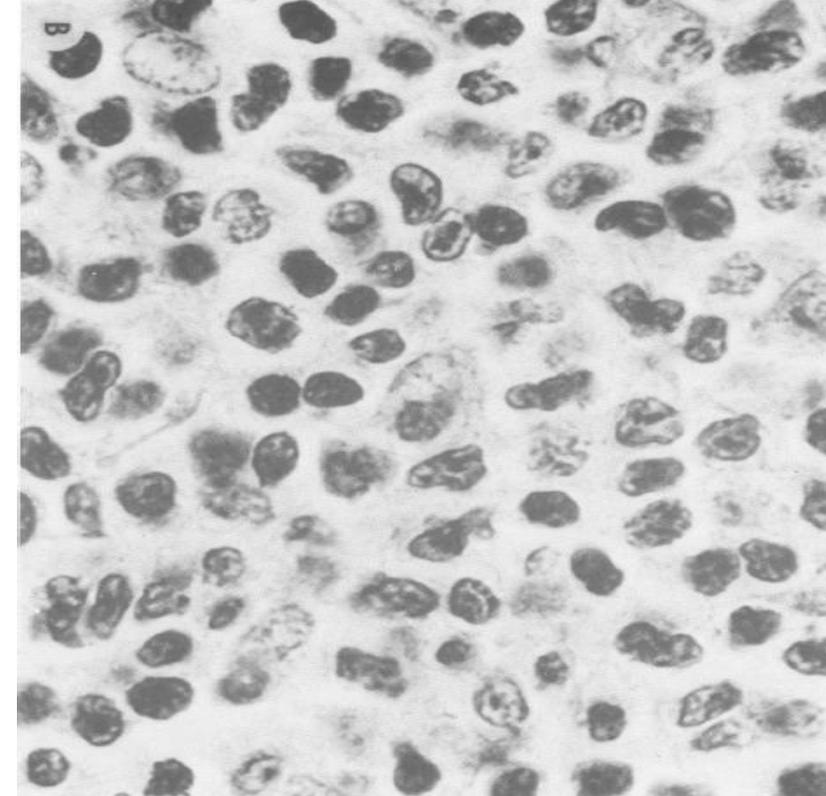
Mantle Cell Lymphoma: the genesis of a concept



Lymphocytic Lymphoma,
Well Differentiated

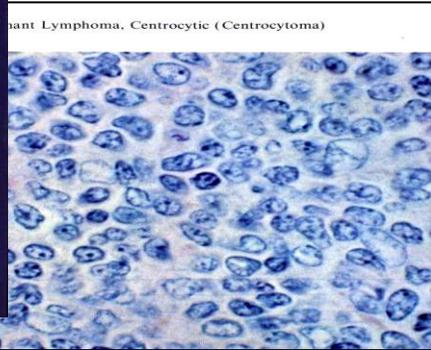
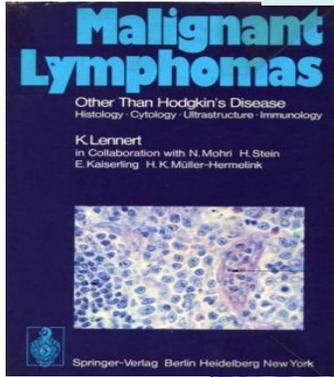


Lymphocytic Lymphoma,
Intermediate Differentiation

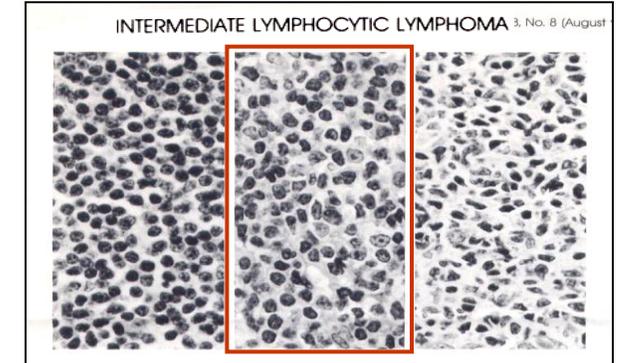


Lymphocytic Lymphoma,
Poorly Differentiated

Mantle Cell Lymphoma: the genesis of a concept



Centrocytic



Intermediate lymphocytic

EDITORIAL

Blood, Vol 78, No 2 (July 15), 1991: pp 259-263

***bcl-1*, *t(11;14)*, and Mantle Cell-Derived Lymphomas**

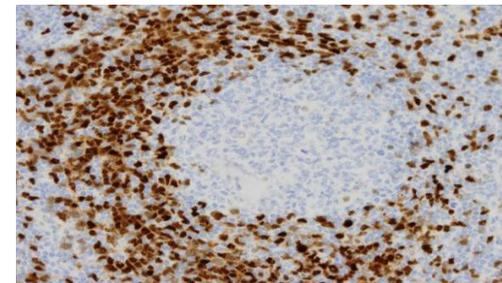
By Mark Raffeld and Elaine S. Jaffe

The American Journal of Surgical Pathology 16(7): 637-640, 1992

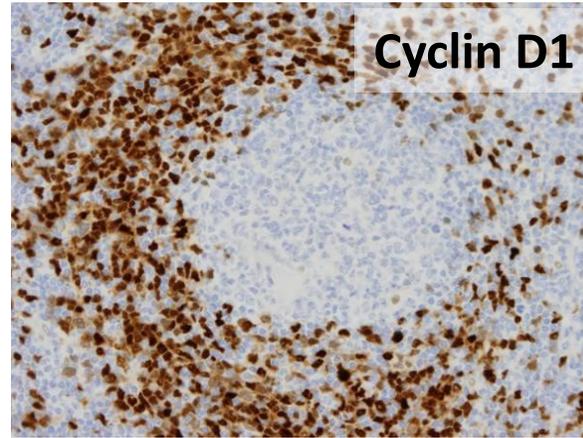
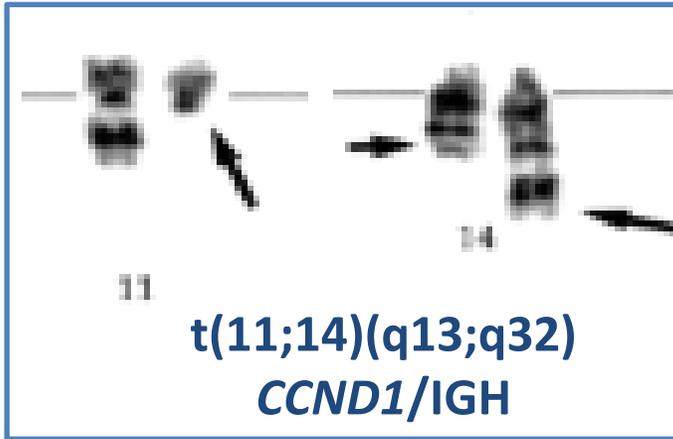
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Mantle Cell Lymphoma

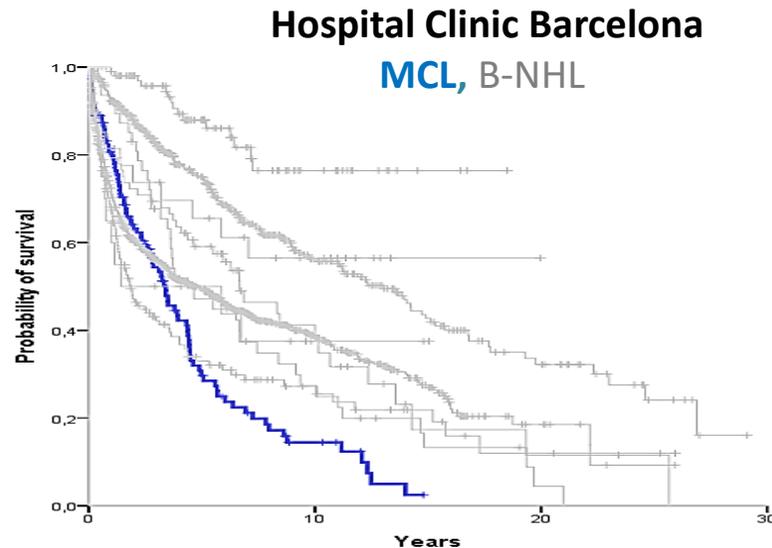
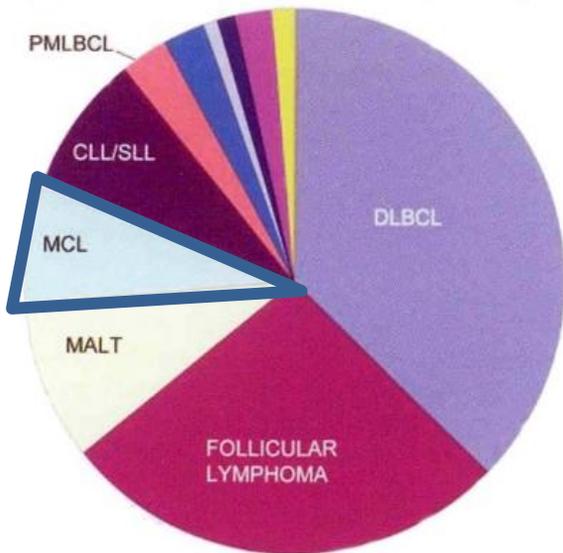
A Proposal for Unification of Morphologic, Immunologic, and Molecular Data



MCL: diagnostic and outcome



- t(11;14) initial event (virtually all), CCND1/IGH
- overexpression of cyclin D1 protein
- cell cycle deregulation
- disruption of DNA damage response pathway
- high genomic instability
- high proliferation

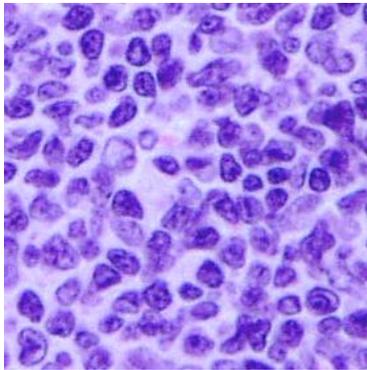


(Courtesy of Dr. A. López-Guillermo)

- 3-10% of NHL
- median age at diagnosis 60yr
- 3x more common in men
- affects LN frequently, and PB, BM, spleen, GI tract
- generally aggressive clinical course
- frequent relapses
- still an incurable disease

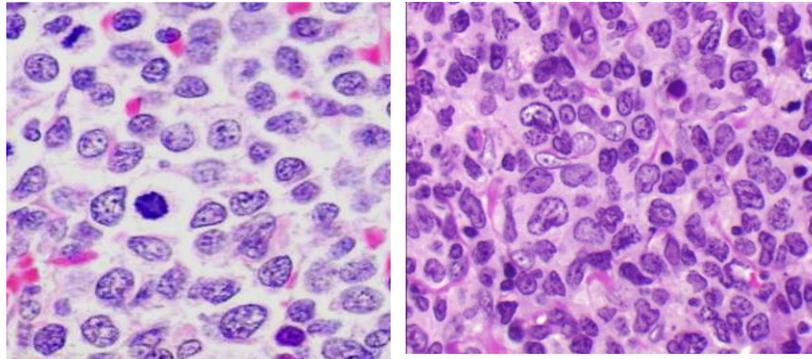
MCL: morphological variants

Classic MCL variant



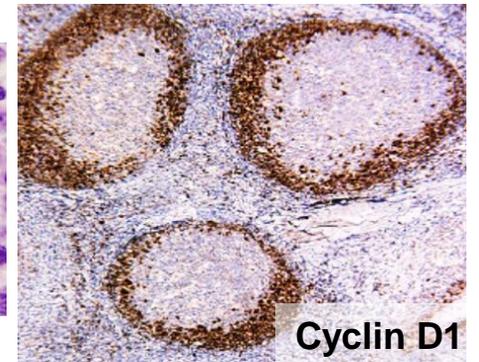
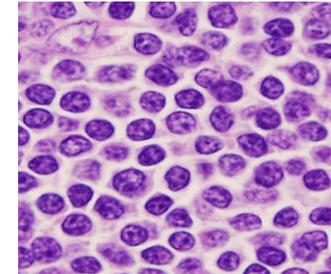
most common form
80-90%

Aggressive variants: Blastoid & Pleomorphic



highly proliferative
de novo or transformed from classic variant
highly proliferative
poor prognosis
treatment resistance

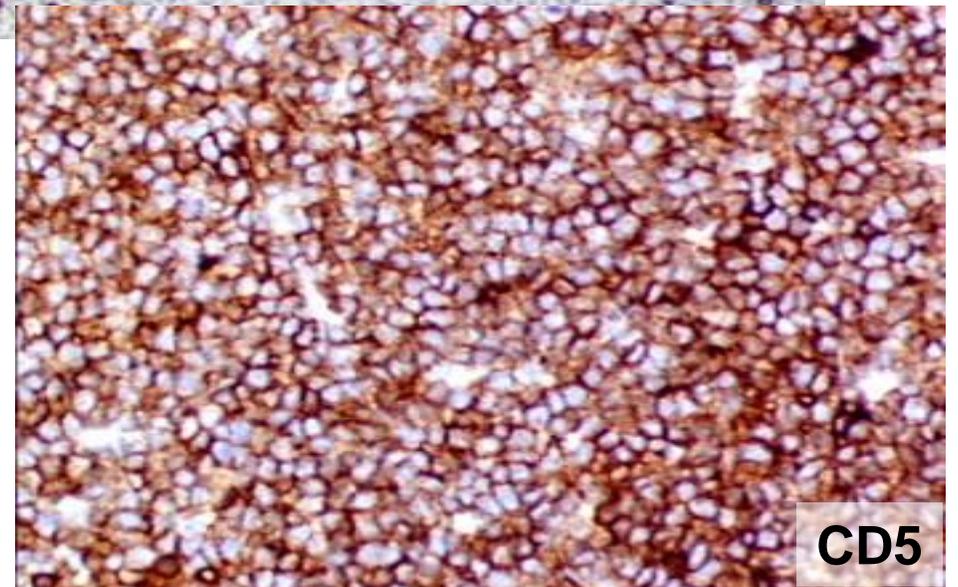
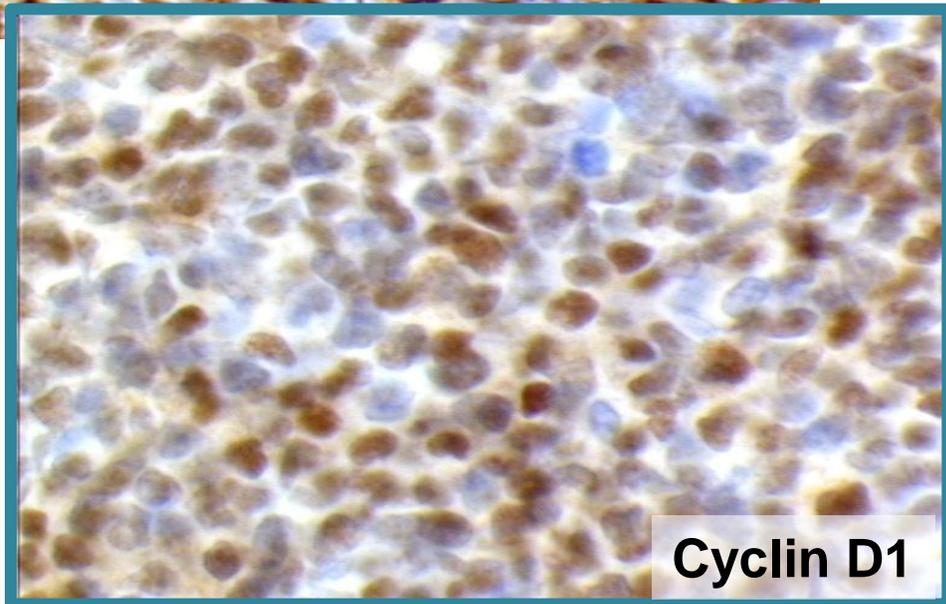
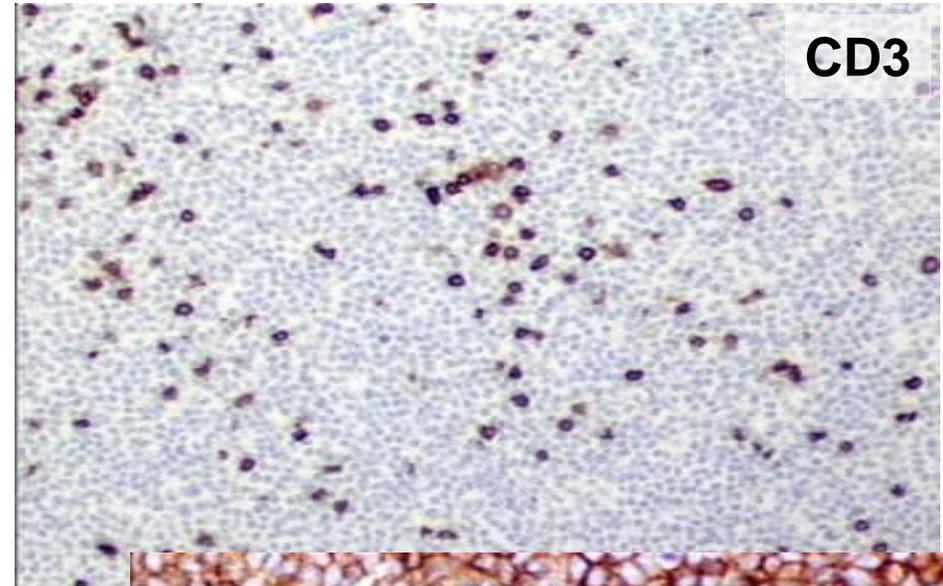
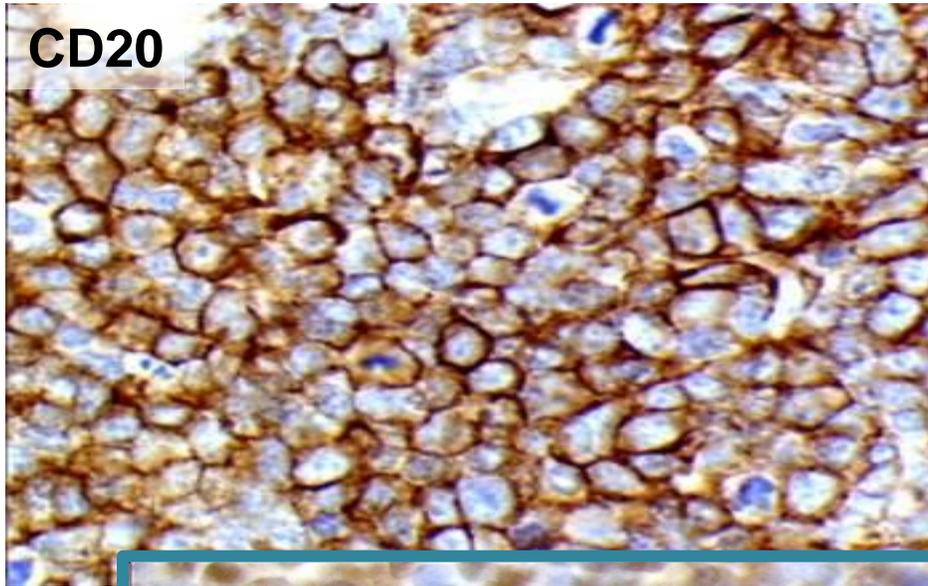
Other variants: Small-cell & Marginal-zone-like



Cyclin D1

may resemble other B-CLPD
good prognosis

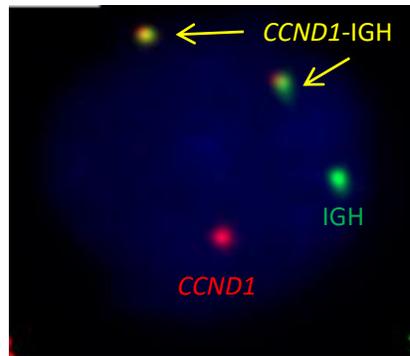
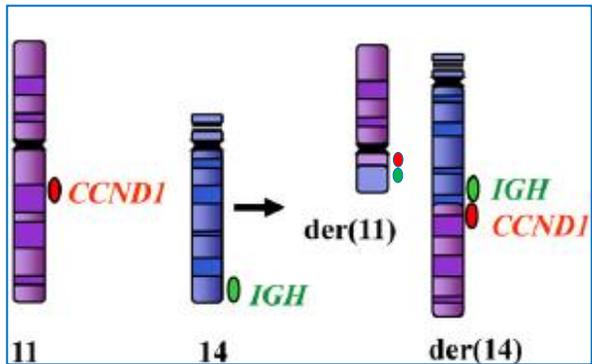
MCL: phenotype



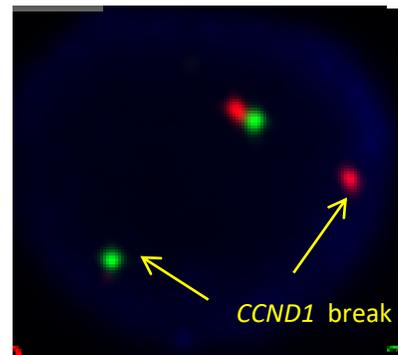
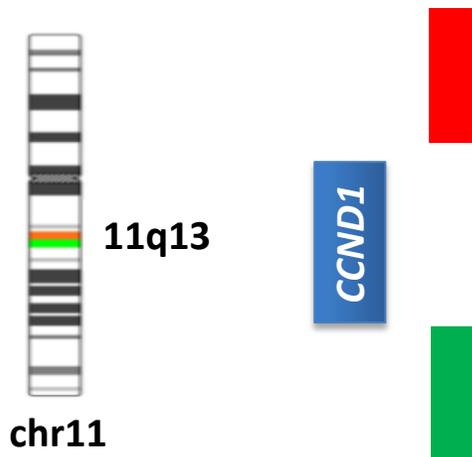
MCL: the diagnostic FISH strategy



- The t(11;14) is detected by conventional cytogenetics (karyotype) only in 65%

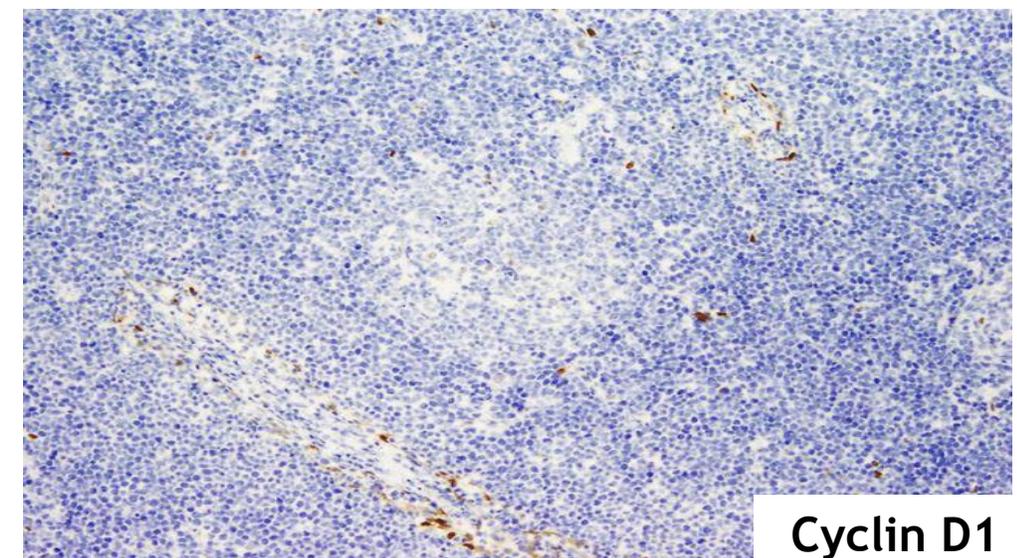
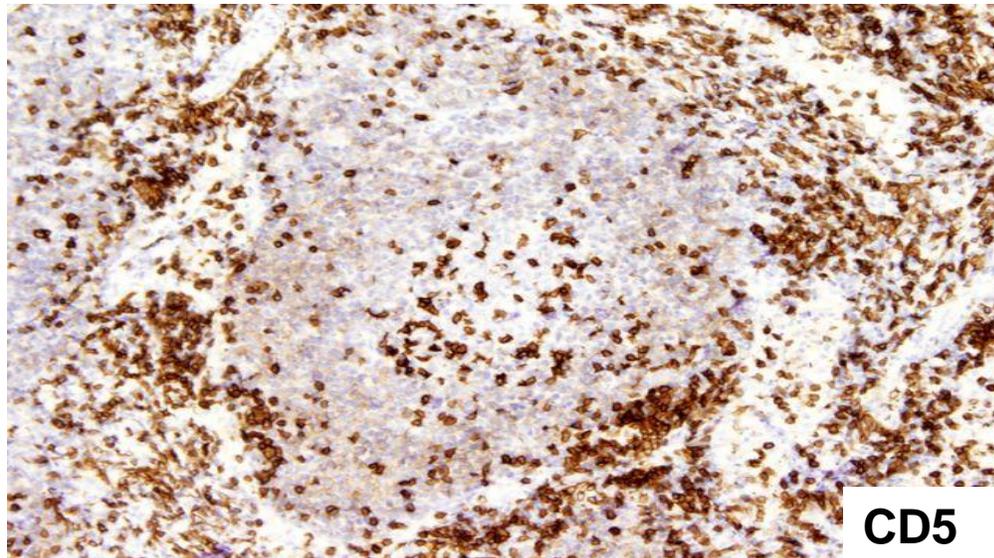
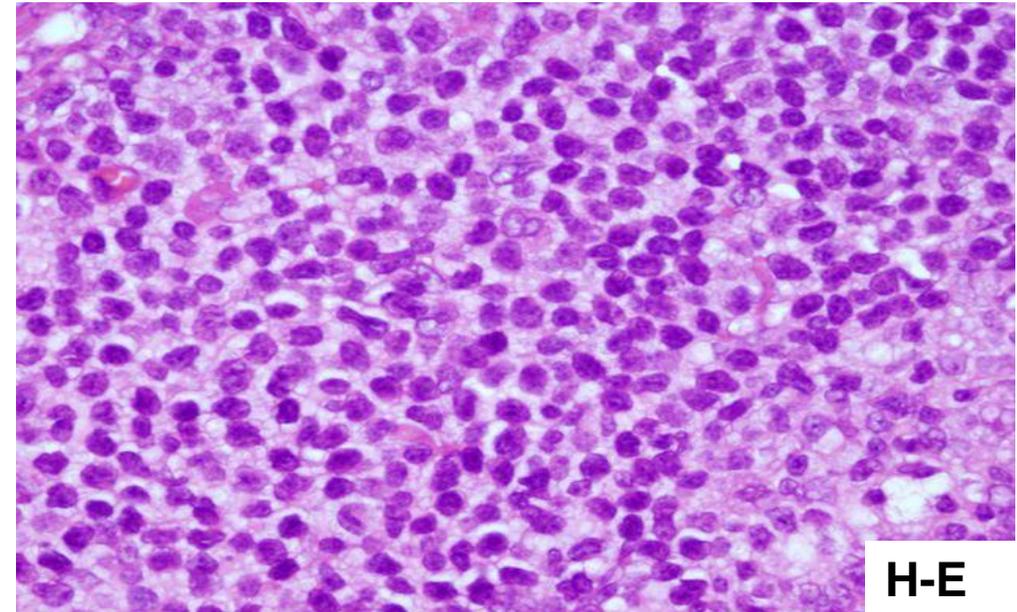
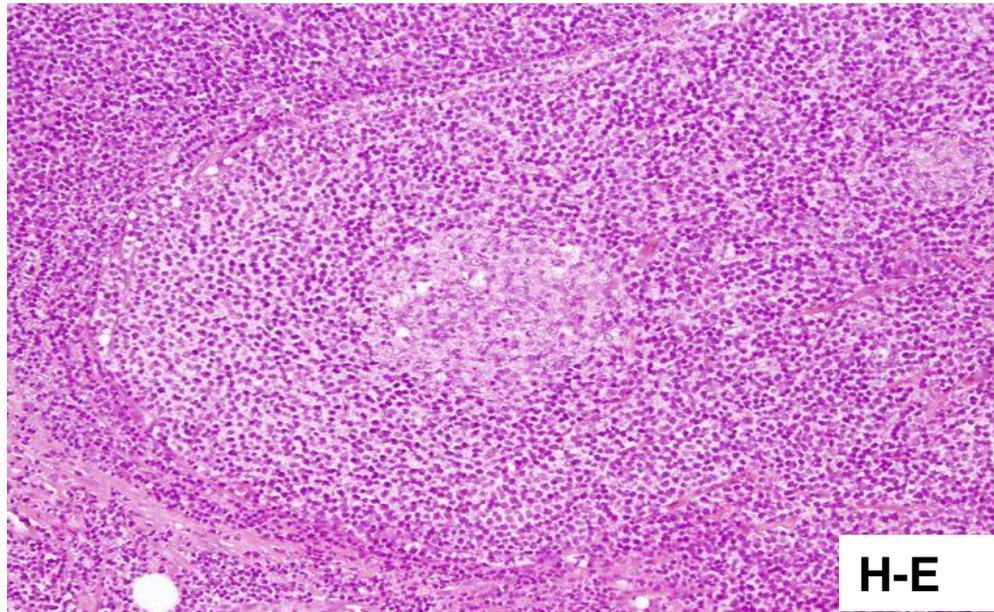


- using a commercial dual-color dual-fusion probe >95% MCL show *CCND1-IGH*



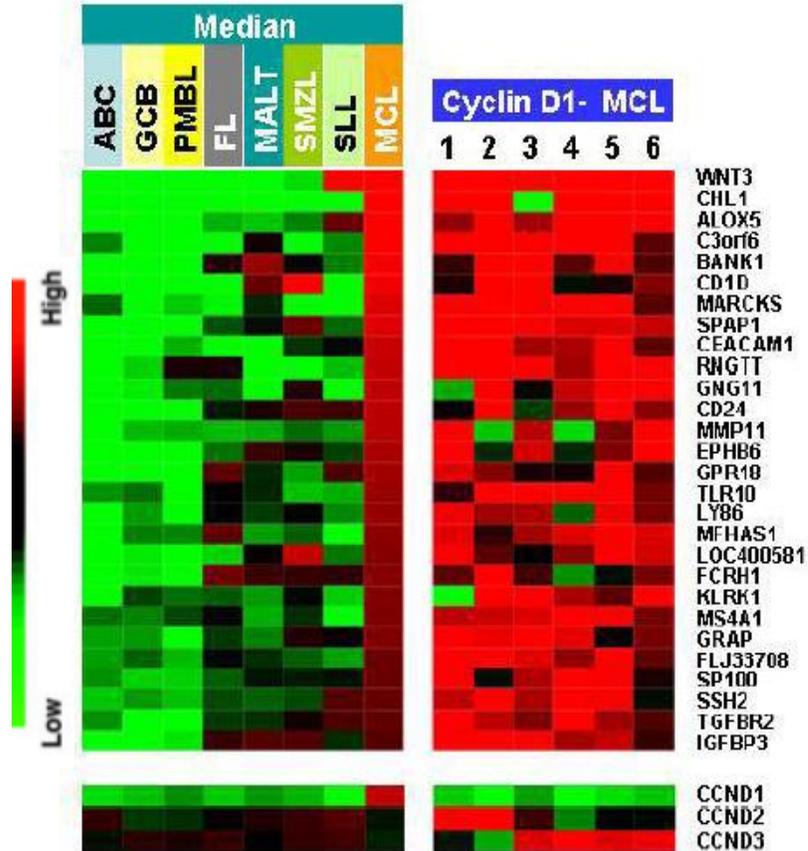
- A *CCND1* break-apart probe should be used for the few occasional MCL with *CCND1* gene rearranged with IG light chains (IGK or IGL)

MCL: Mantle zone pattern WITHOUT Cyclin D1 expression

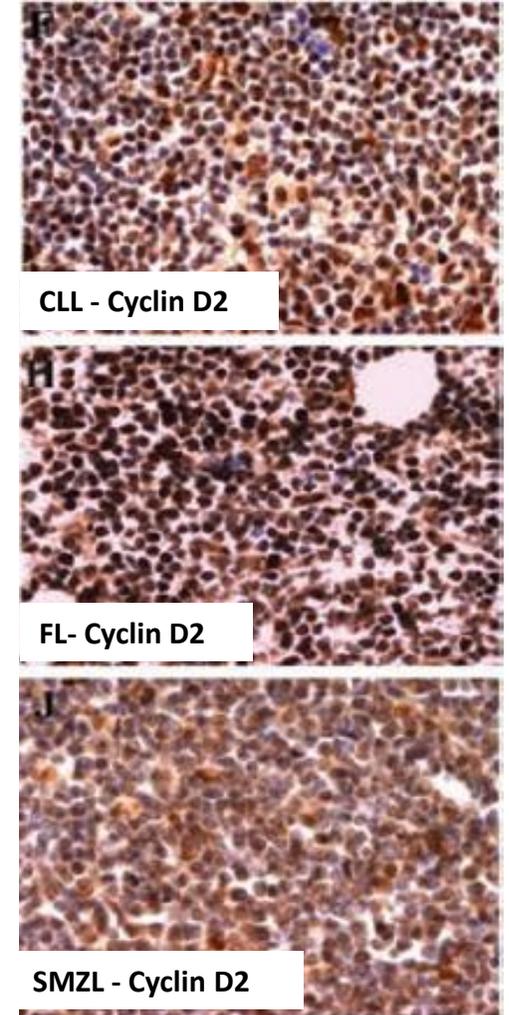
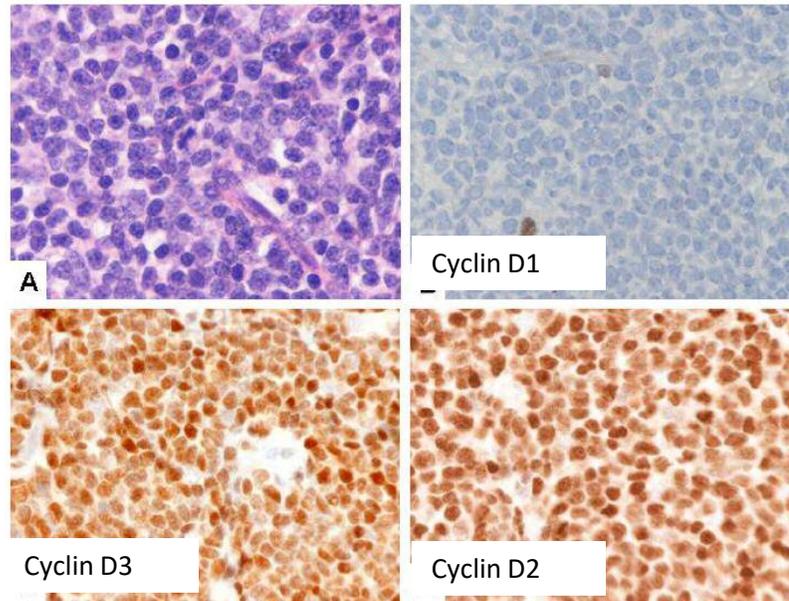


Cyclin D1-negative MCL subtype: first report

- LLMPP GEP: Overexpression of *CCND2/D3*
- FISH: No genetic *CCND2/D3* rearrangements

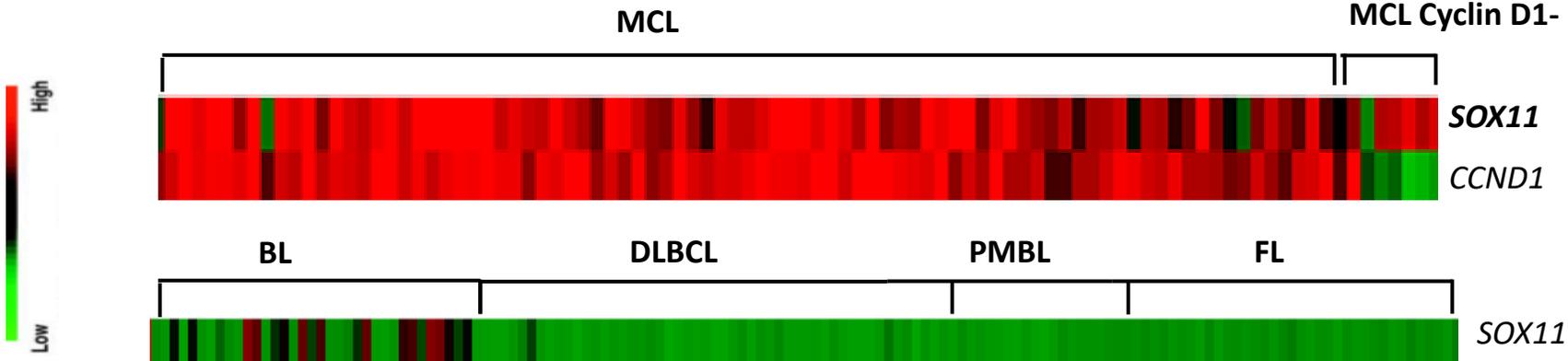


- IHC: Overexpression of cyclin D2/D3 but... not specific



Cyclin D1-negative MCL: SOX11 biomarker

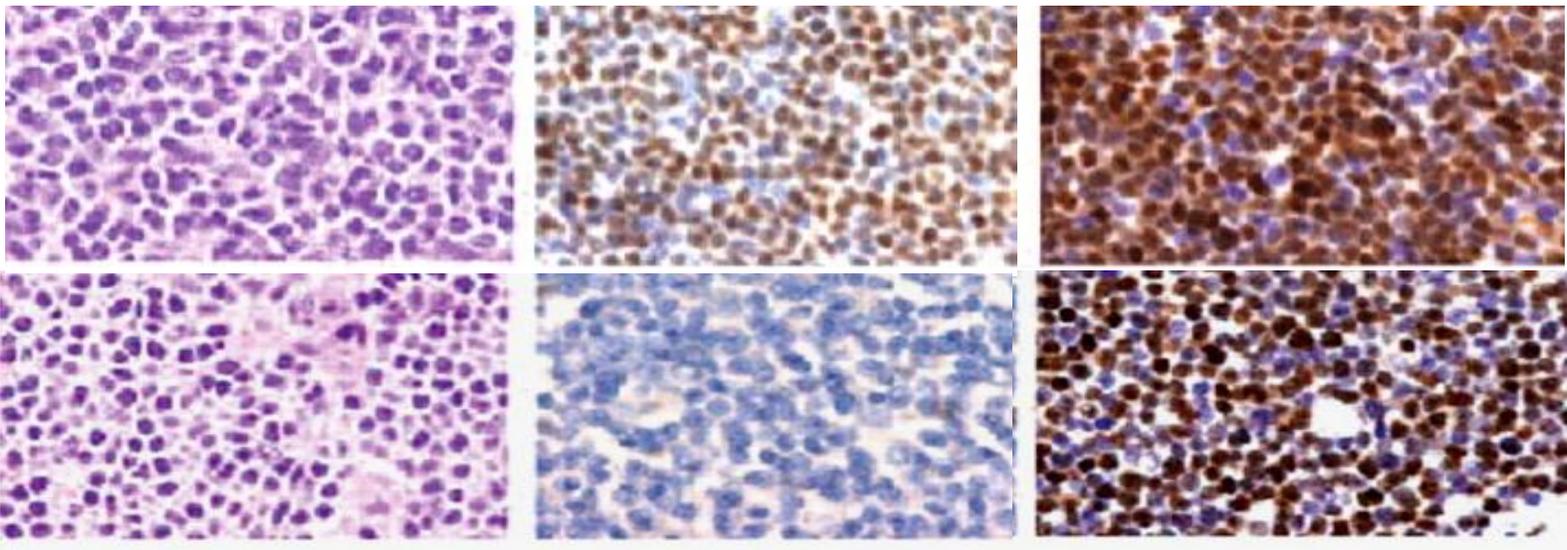
GEP



mRNA

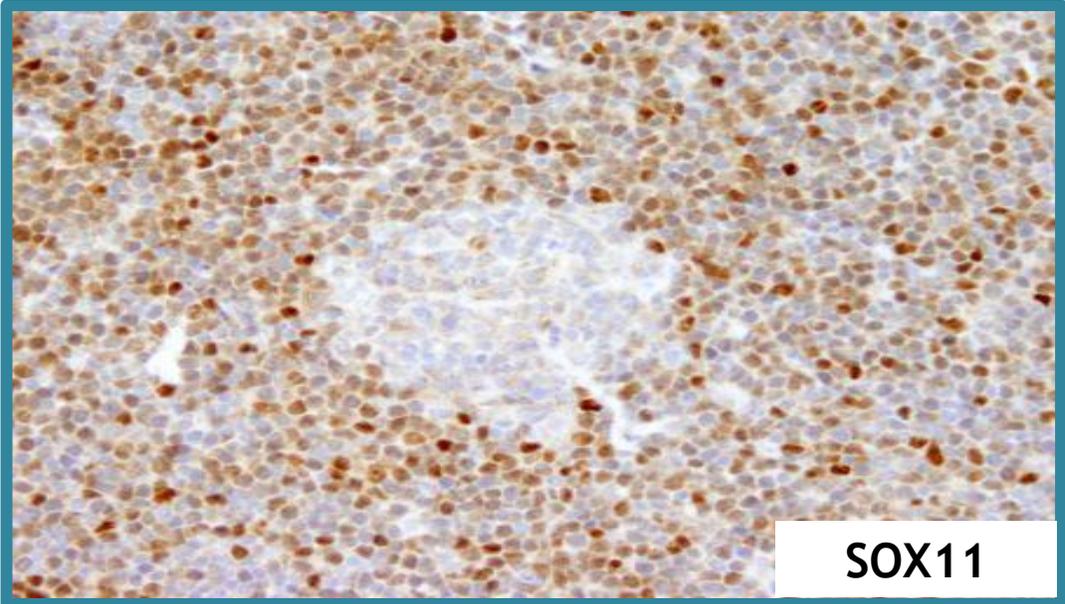
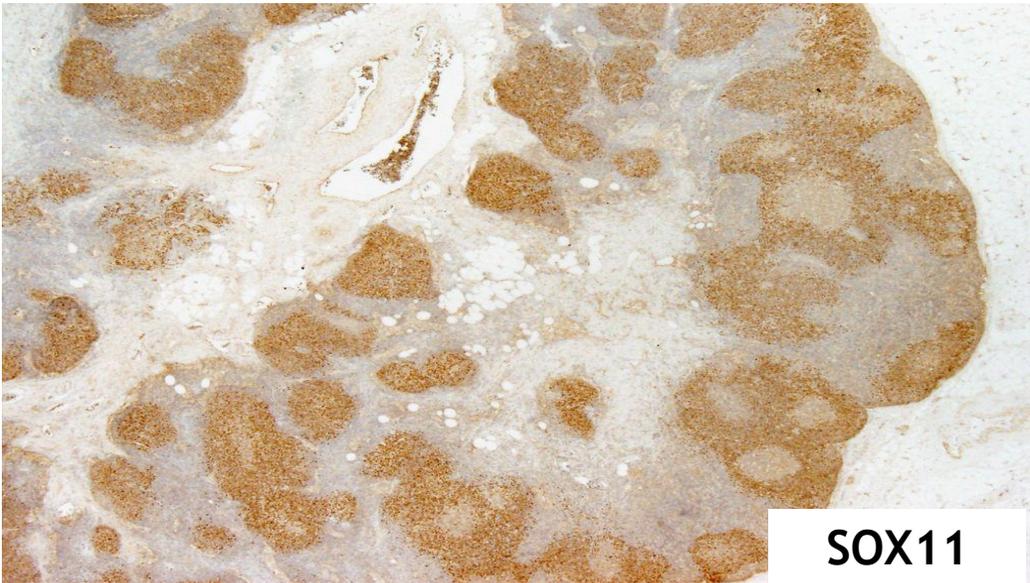
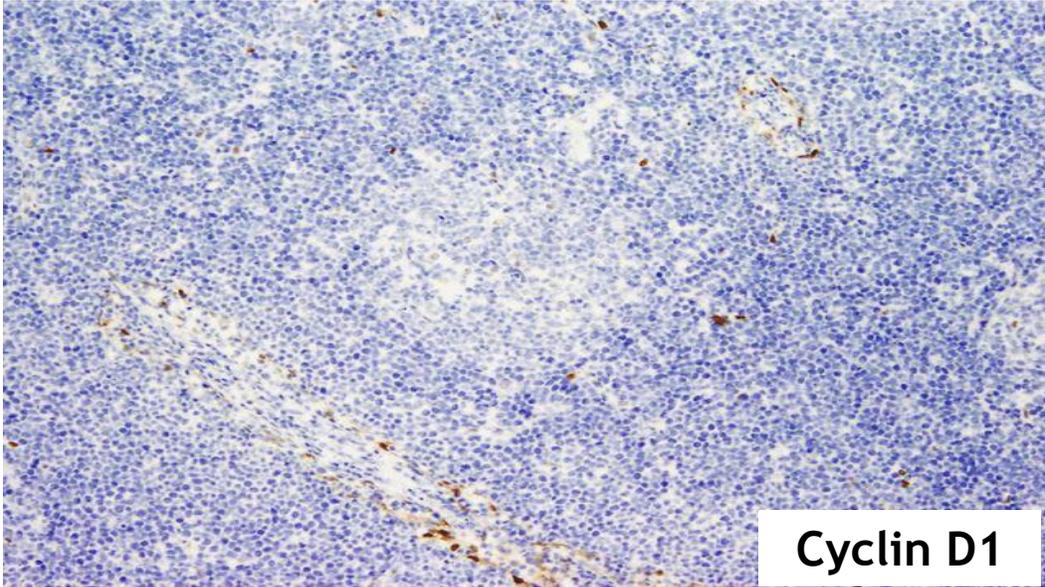
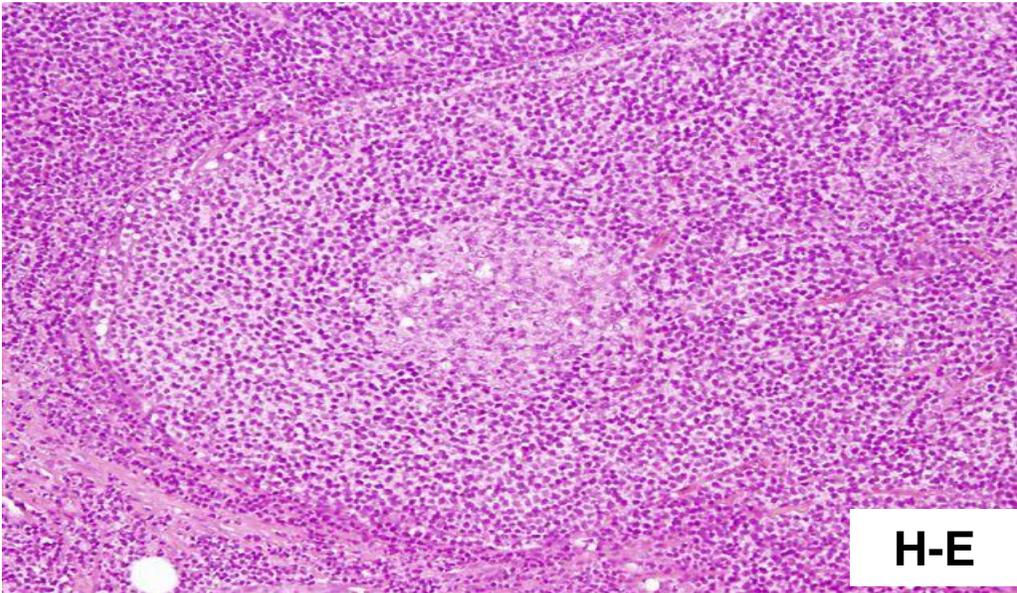
MCL Cyclin D1 Sox11

protein

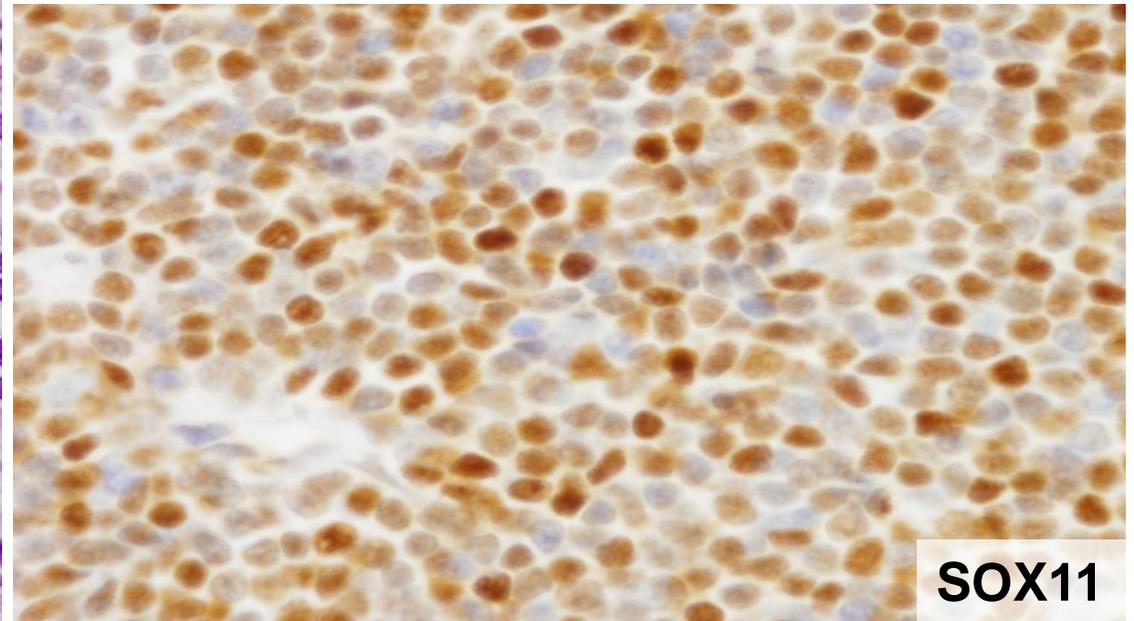
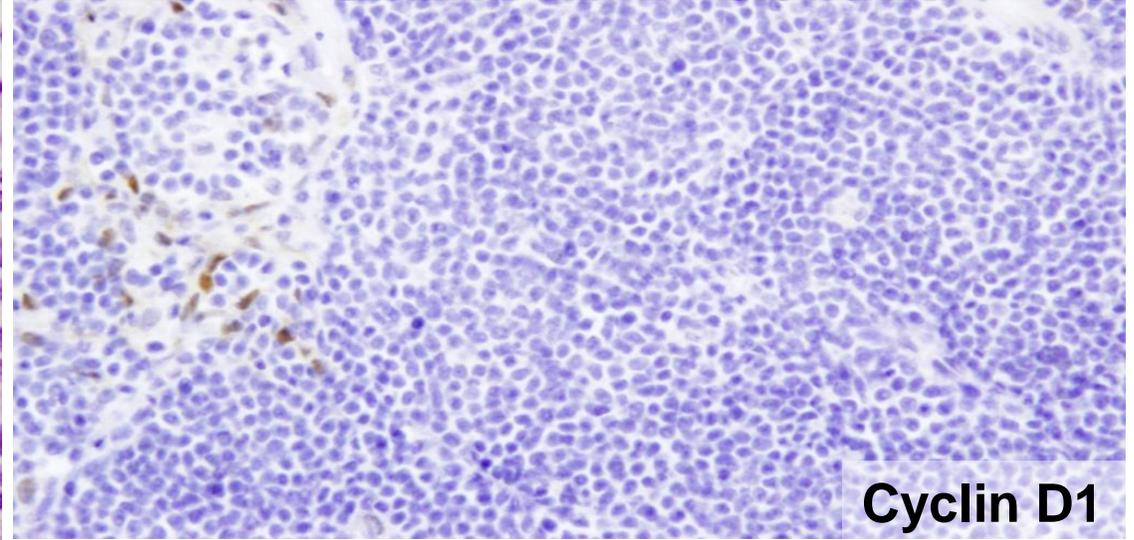
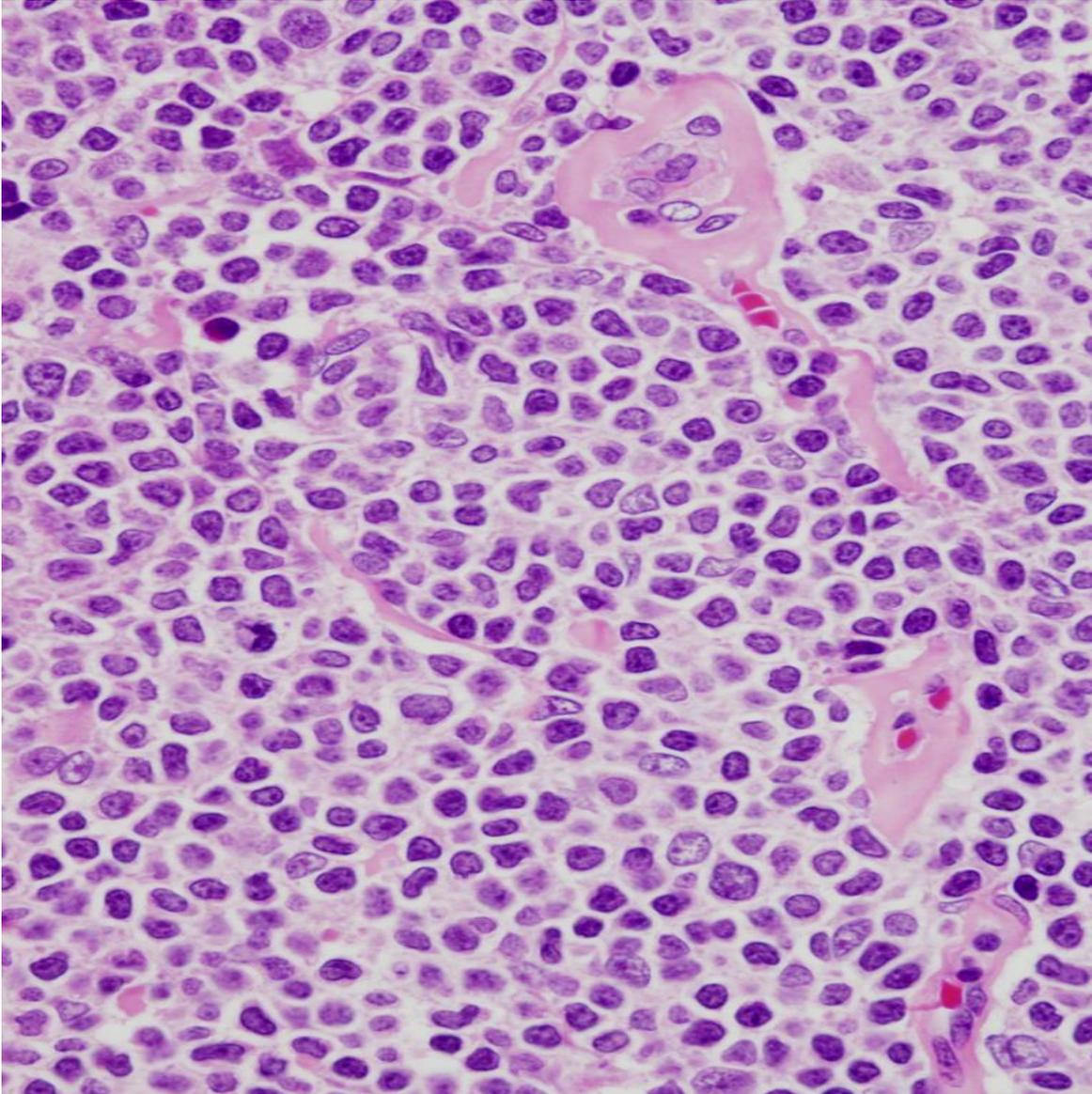


(Mozos, Haematologica 2009)

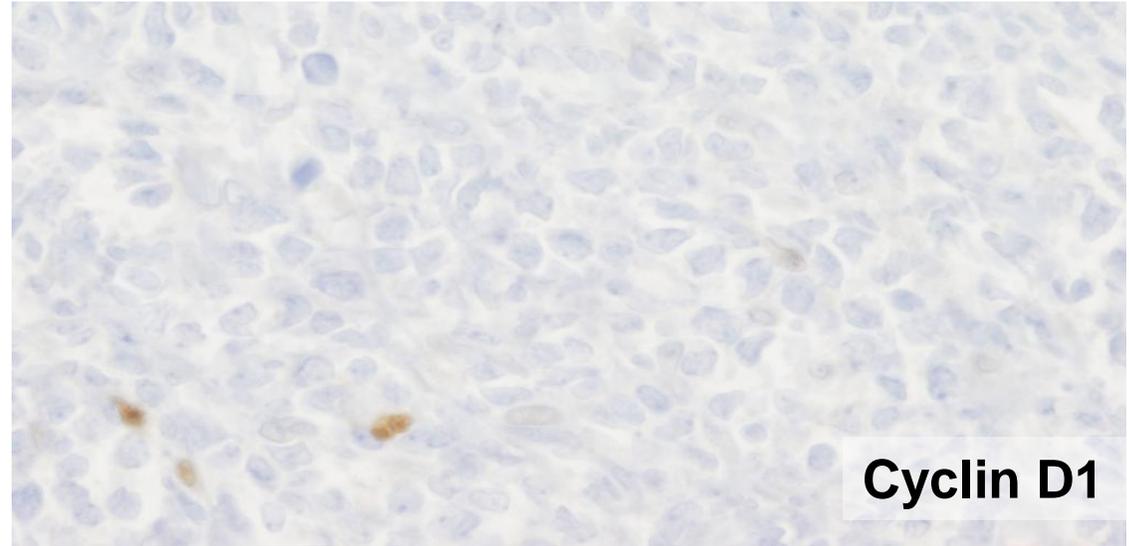
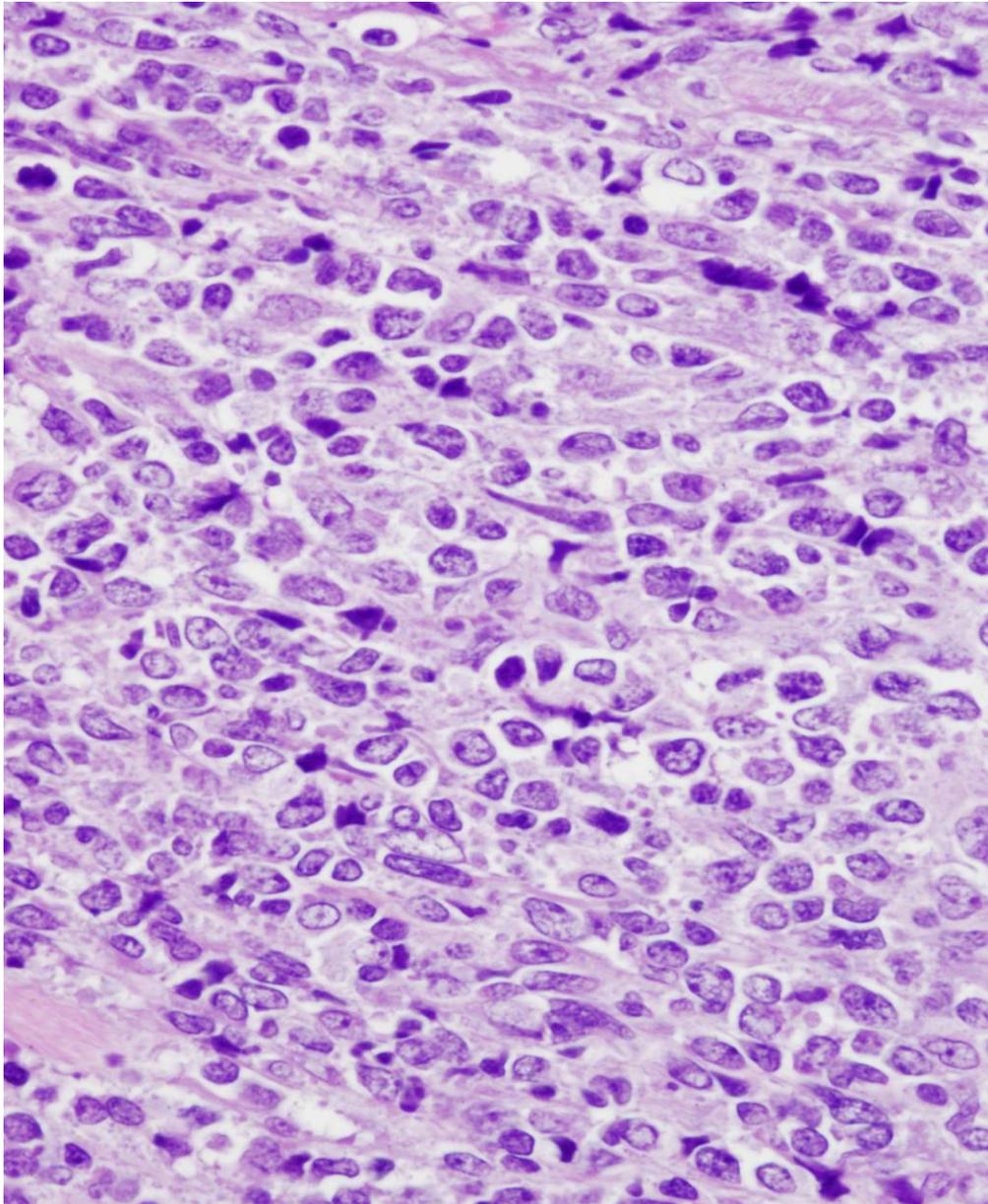
Cyclin D1-negative MCL: Mantle zone pattern AND Sox11+



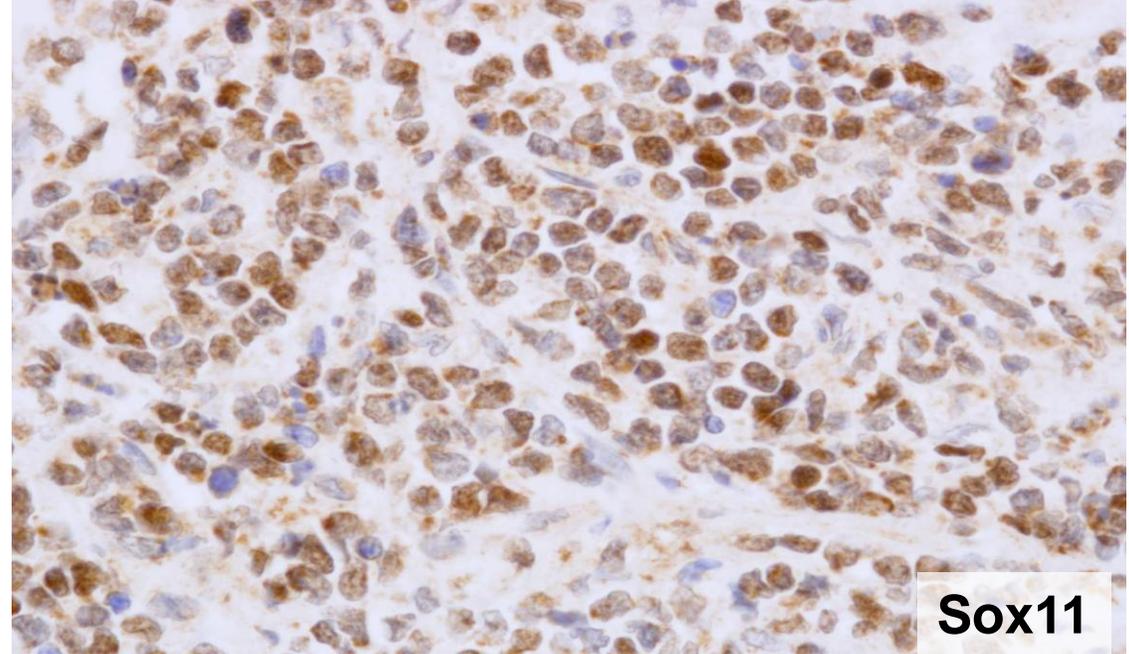
Cyclin D1-negative MCL: Classical MCL (at diagnosis)



Cyclin D1-negative MCL: Pleomorphic MCL (at relapse)



Cyclin D1



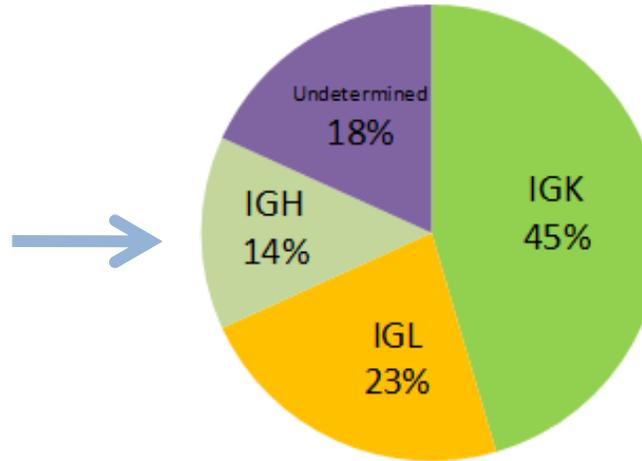
Sox11

Cyclin D1-negative MCL: genetics

Estudy of 40 Cyclin D1-neg MCL

- **CCND2** rearrangement by FISH in 55% cases

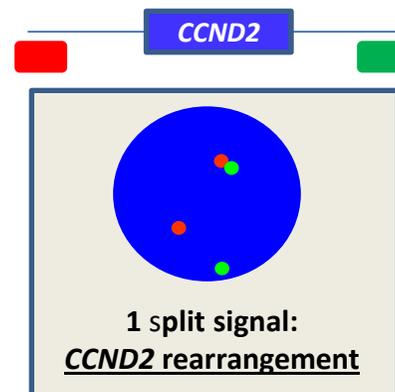
Rearrangements	No. (%)
<i>CCND1</i>	0
<i>CCND2</i>	22/40 (55%)
<i>CCND3</i>	0
No Cyclin D gene translocation	18 (45%)



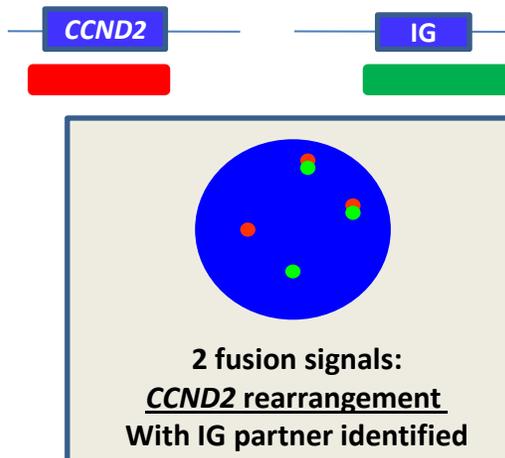
CCND2 translocation partners: frequently IG light chains

No *CCND1/D2 /D3* mutations in the phosphorylation site

CCND2 breakapart probe

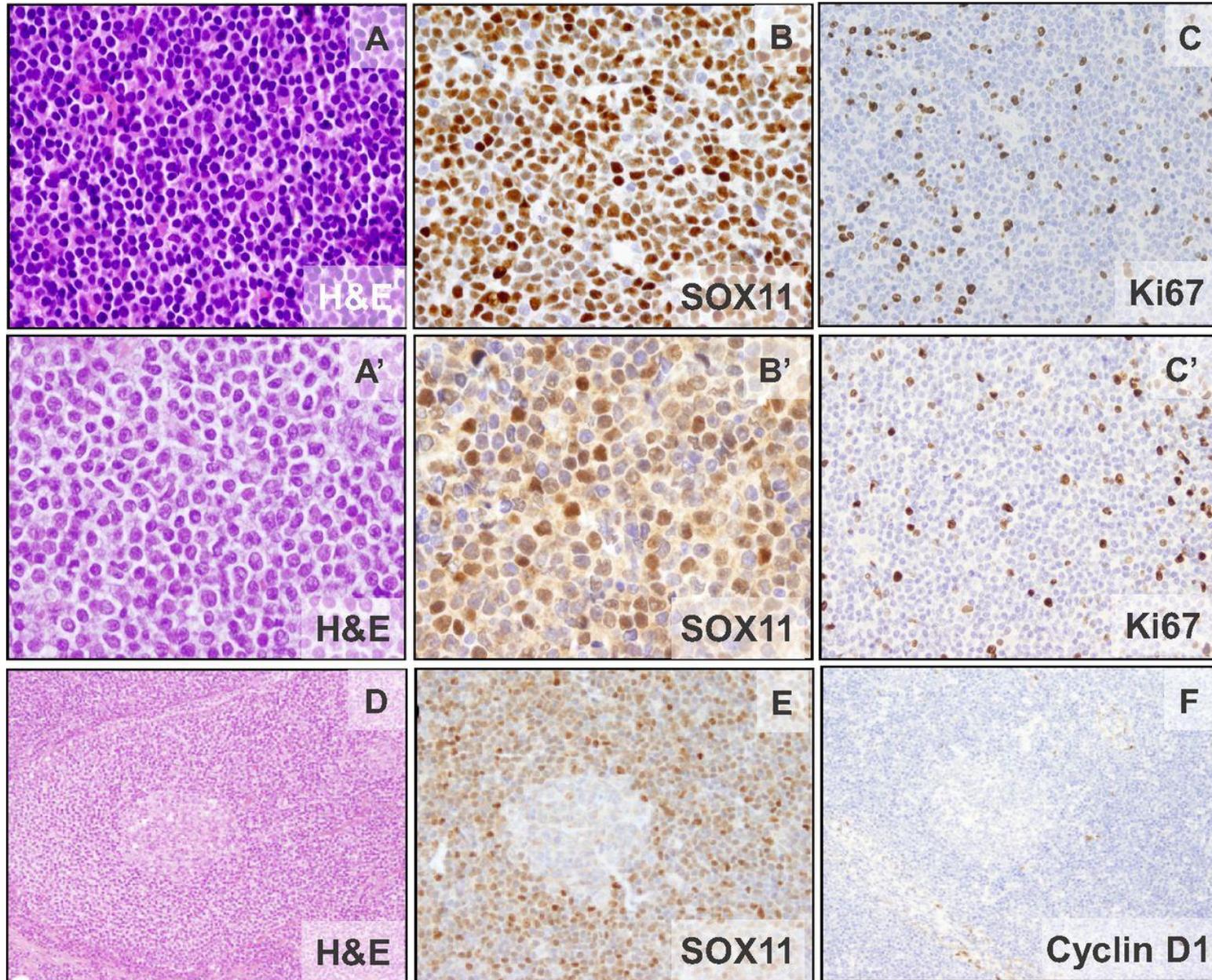


CCND2 fusion probes (IGH, K, L)



(Salaverria, Blood 2013)

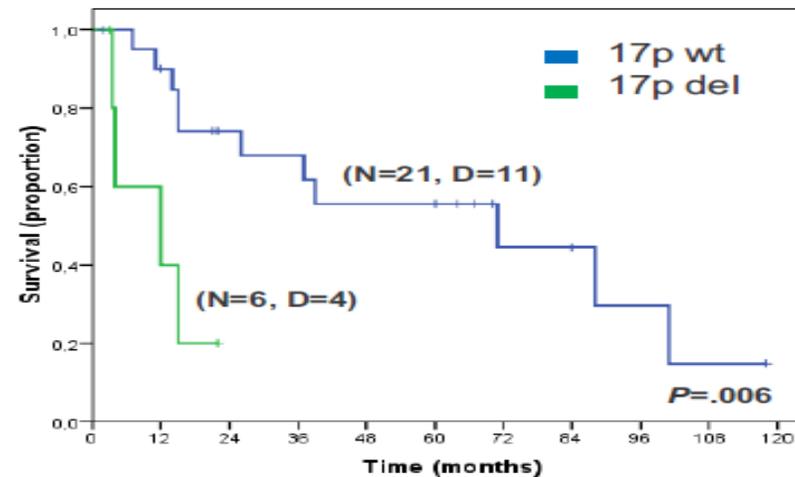
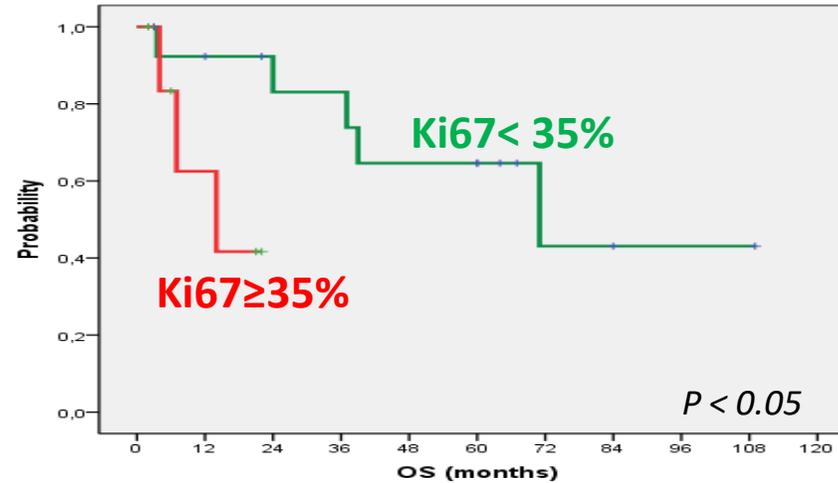
Cyclin D1-negative MCL: Morphology and IHC



Cyclin D1-negative MCL: clinico-pathological features

40 Cyclin D1-neg MCL

- SOX11+
- Male/Female ratio: 3/1
- Advanced stage (IV): 73%
- Extranodal involvement: 87%
- Leukemic involvement: 69%
- High proliferation (Ki67) has prognostic impact
- 17p/TP53 deletion has prognostic impact



Cyclin D1-negative MCL: next step

• **Aim:** To identify other potential mechanisms driving the pathogenesis of cyclin D1–/cyclin D2– MCL (45%), especially regarding primary genetic events

Material 56 cases, MCL morphology

Gender	2.6:1
Age	65 yr
Growth pattern	45 nodular and/or diffuse 2 mantle-zone
Morphology	70% classical 30% blastoid
Immunophenotype	100% SOX11+ 98% CD5+
Proliferation	38% Ki67 (≥30%)
Treated	100%

Methods

- **FISH:** probes breakpoint for cyclins and IG

Next-generation sequencing with FT DNA

- **Mate-pair whole-genome seq** T (4 cases)
- **Whole-genome seq** T/N (1 case)
- **Whole-exome seq** T (3 cases)

Molecular techniques with FFPE DNA/RNA

- **Gene expression profiling** (n=14)
- **qPCR:** cyclins (n=56)
- **Copy-number arrays** (n=42)

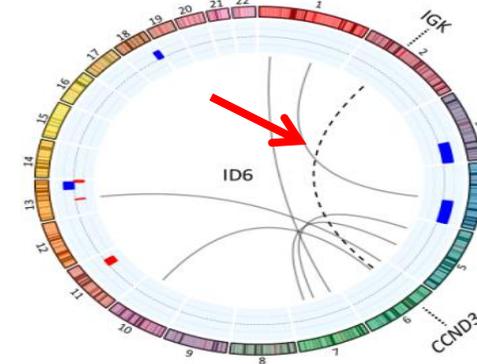
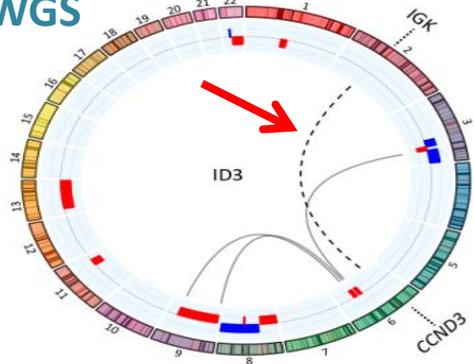
New cryptic IGK/L enhancer insertions near *CCND3*

- 3 cases *CCND3*+ GEP

1 2 (3) 4 5 (6)

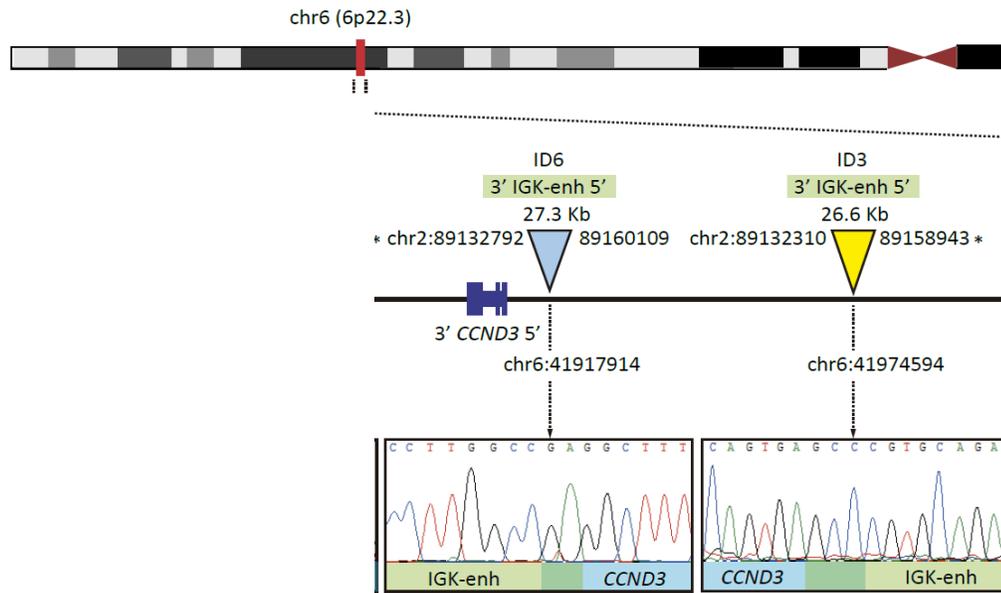


MP-WGS

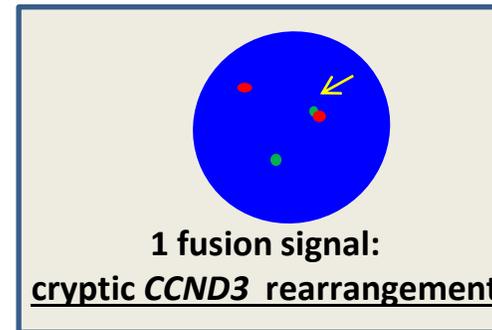
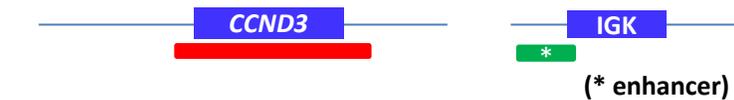


Chr2/Chr6
IGK/*CCND3* cryptic

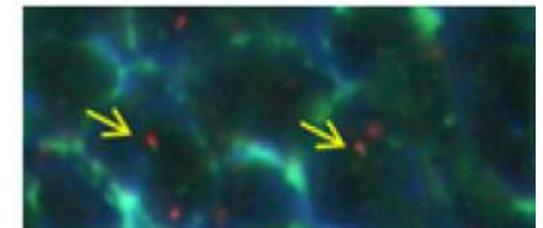
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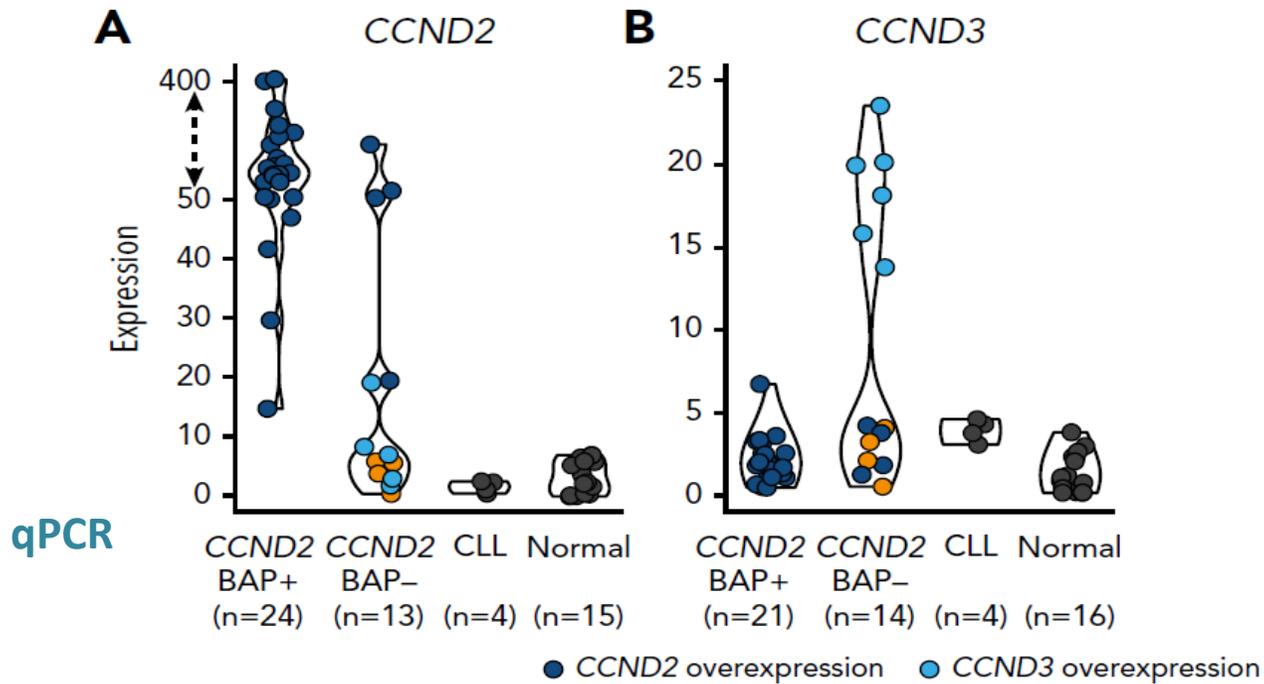
FISH



ID3 IGK-enh/*CCND3*



mRNA expression of *CCND2* and *CCND3* and cryptic rearrangements



28 *CCND2* overexpression

- 24 FISH *CCND2* breaks

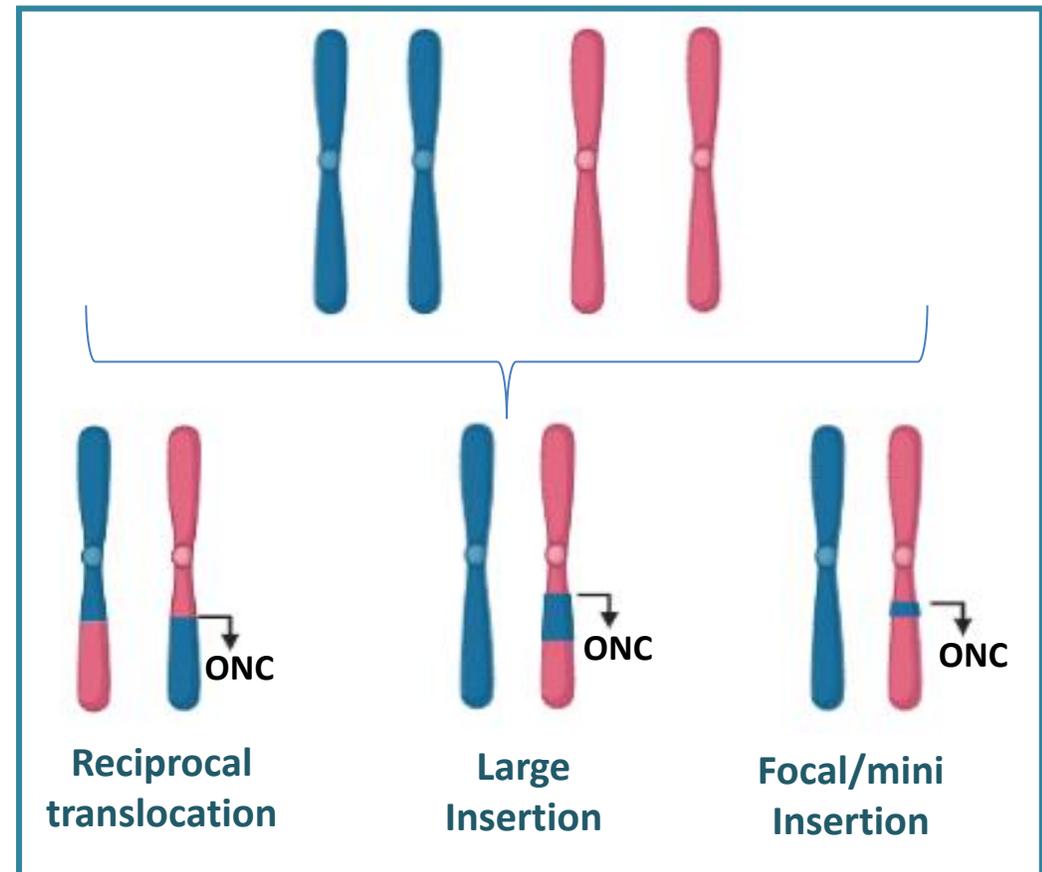
- 4 cryptic *CCND2*/IGK-enh

9 *CCND3* overexpression

- No FISH *CCND3* breaks

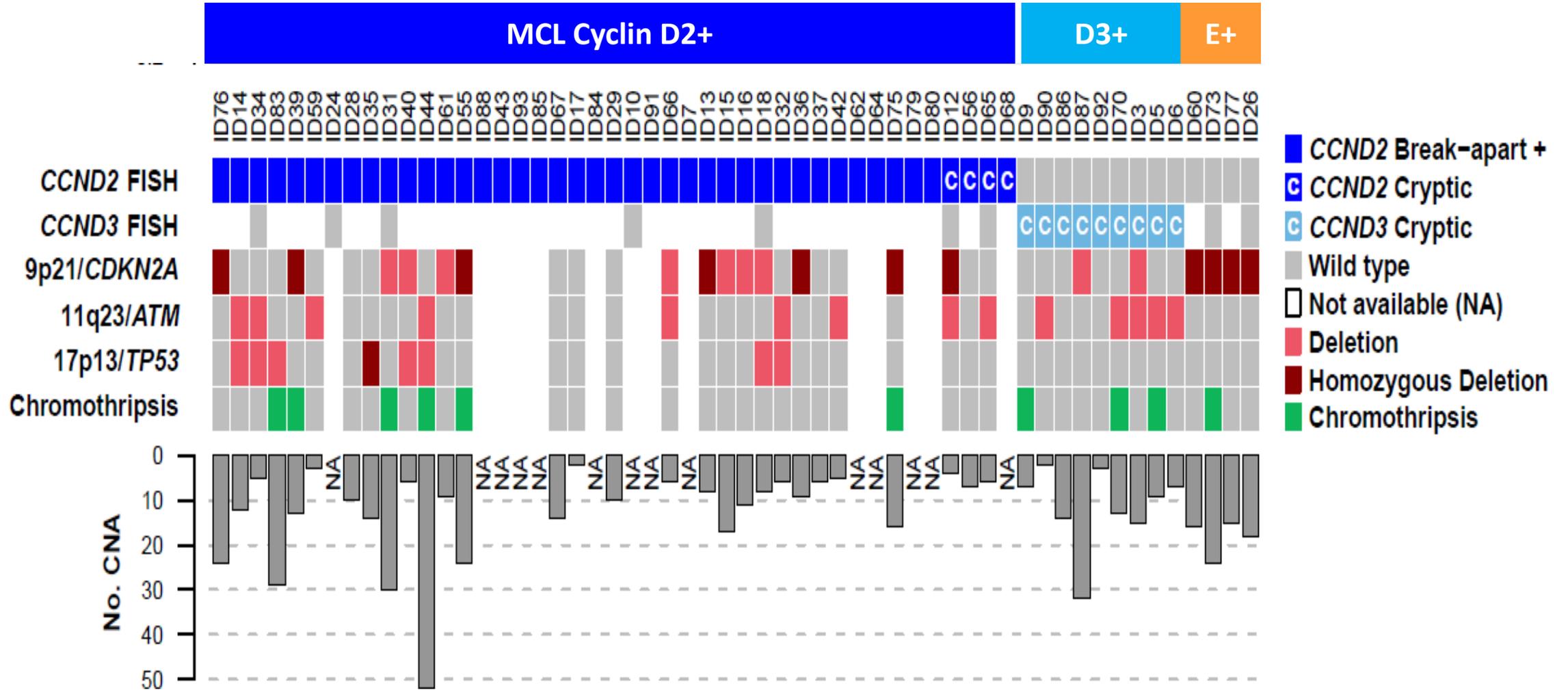
- 9 cryptic *CCND3*/IGK/L-enh

Cryptic enhancer insertions near oncogenes: a novel mechanism alternative to reciprocal translocation



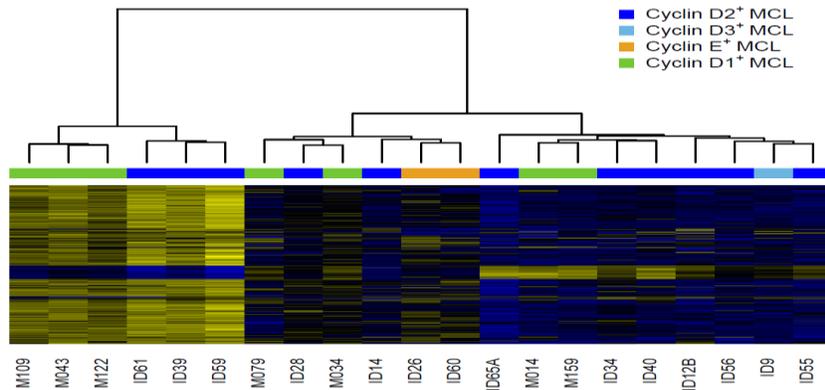
(Martin-Garcia, Blood 2019)

Global genetic landscape of Cyclin D1-negative MCL

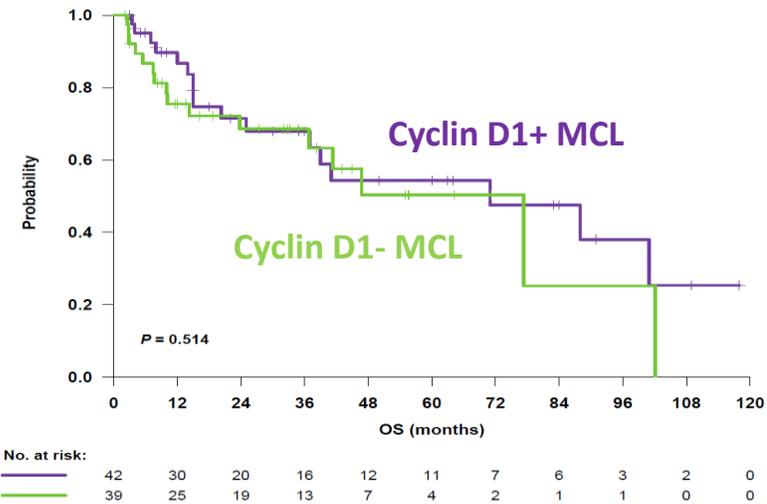


Cyclin D1- MCL are indistinguishable from cyclin D1+ MCL

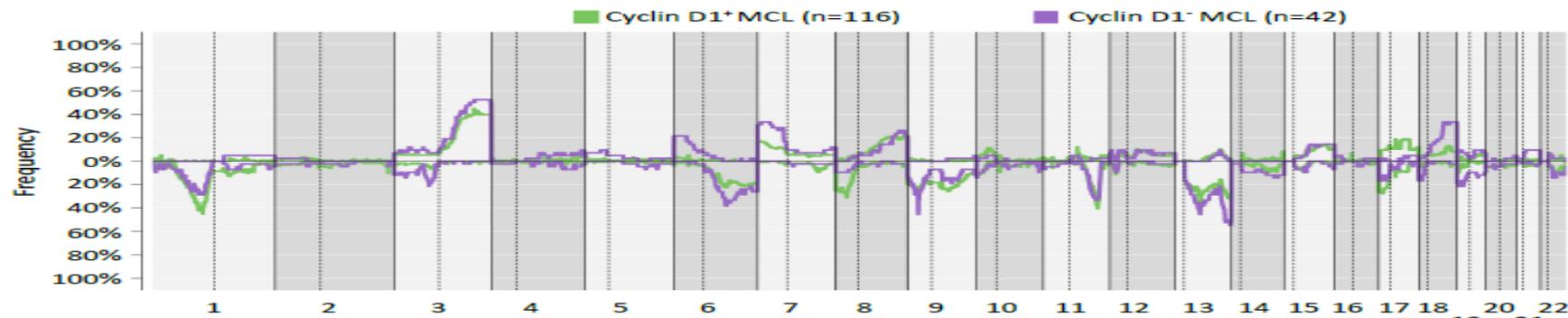
Expression: no separate cluster



Same poor overall survival, 3 yr

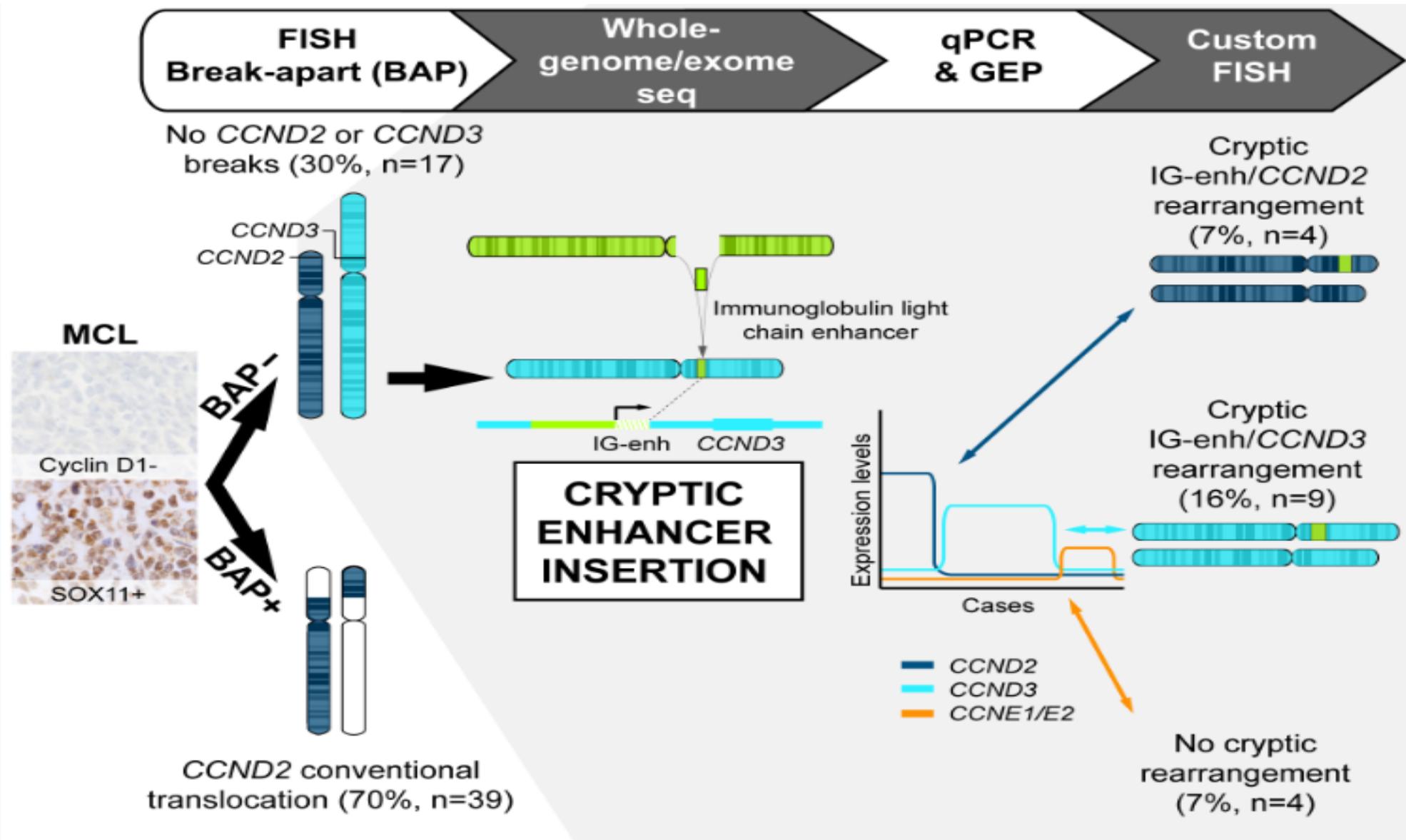


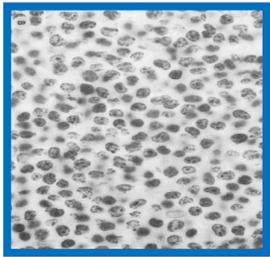
High genetic instability, same CNA pattern



(Martin-Garcia, Blood 2019)

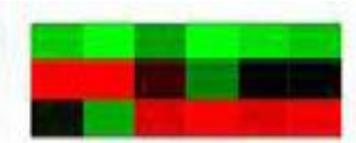
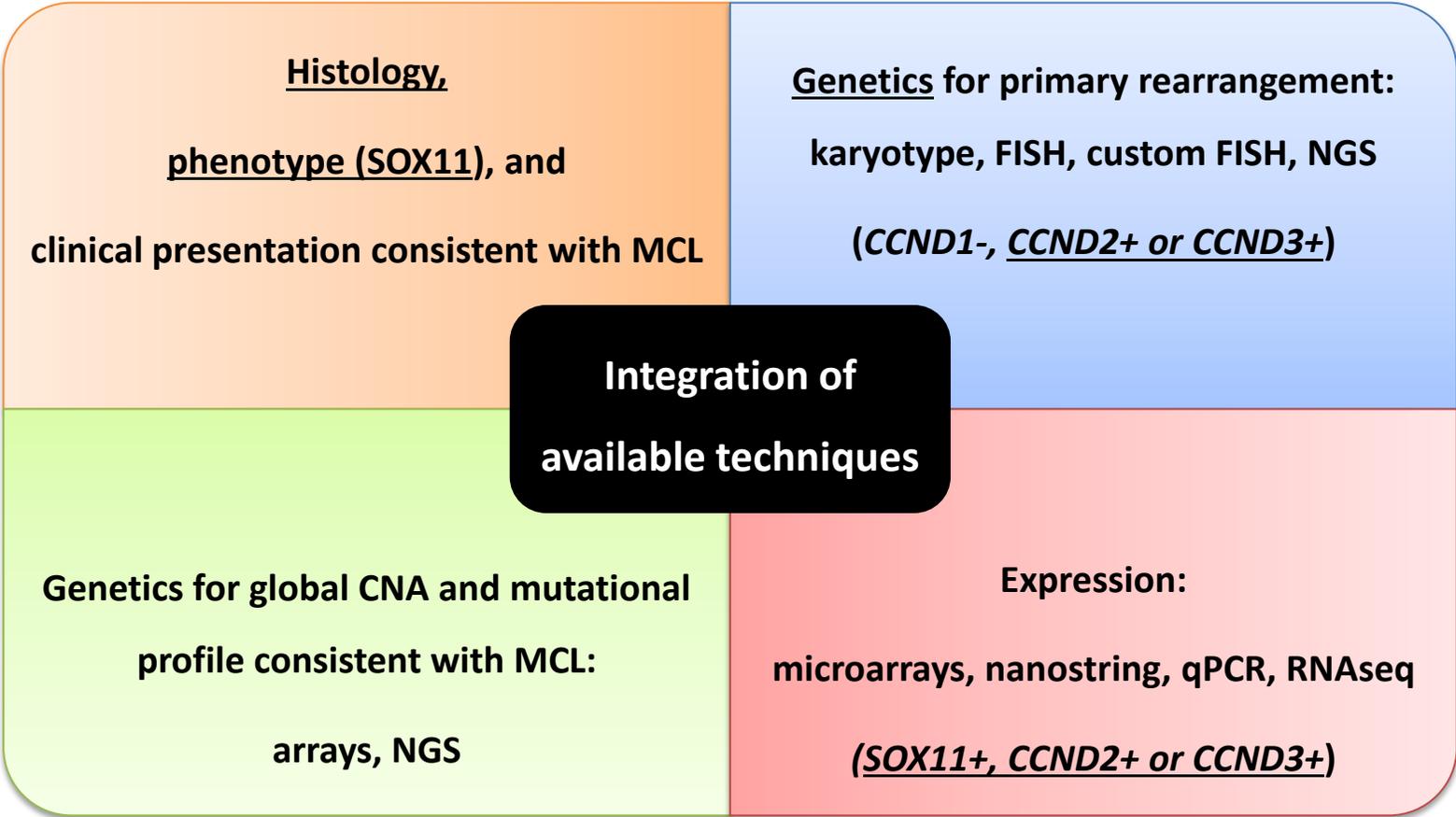
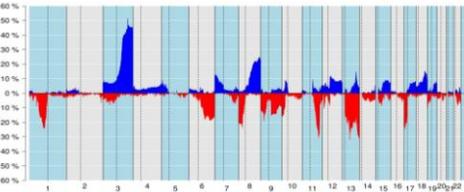
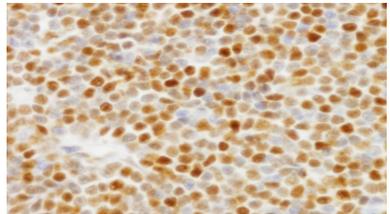
Cyclin D1- MCL study overview





Cyclin D1- MCL: how to identify them in the real life?

MCL Crosstalk between the Microscopy and Molecular Pathology



Take-home messages: an MCL subtype identification

- The microscope won't trick you: if it seems a MCL... it may be a MCL
- Crucial contribution of Molecular Biology and Integration to diagnostic/prognostic
- Cyclin D1-neg MCL have similar clinico-biological characteristics as conventional MCL and can be recognized by SOX11 expression
- CCND2 translocations are the most frequent event in cyclin D1-neg MCL
- By NGS we identified cryptic insertions of IGK enhancers near CCND3
- Up to 23% cyclin D1-neg MCL have cryptic insertions in *CCND3* or *CCND2*
- Specific *CCND2/D3* FISH probes or high mRNA levels may be useful in the differential diagnosis of Cyclin D1-neg MCL (or NGS, OGM...)

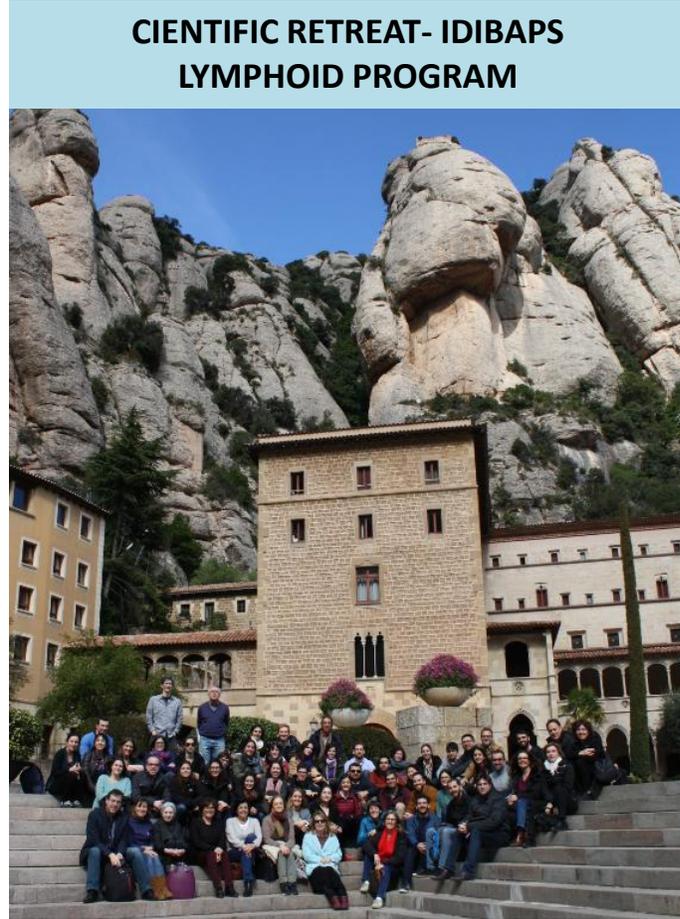
Acknowledgements



SBEA'S TEAM



ELIAS CAMPO & HIS MICROSCOPE



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& WORLWIDE COLLABORATORS



Hospital Universitari

