Biological identification of high-risk mantle cell lymphoma

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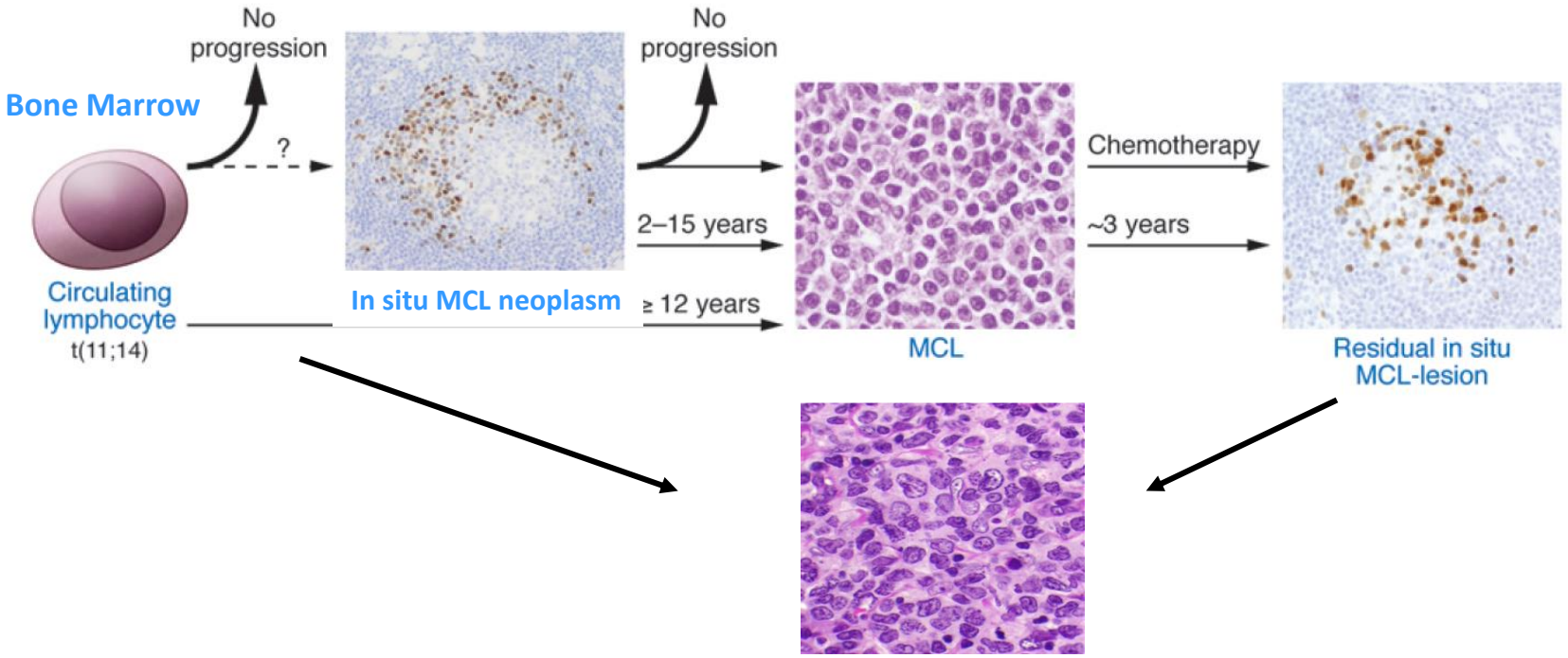
Disclosures

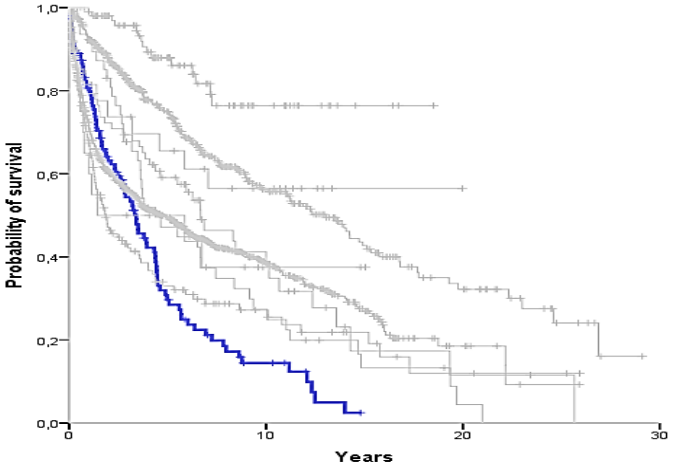
Roche	(Honoraria for educational activity)
Takeda	(Honoraria for educational activity)
Bristol Myers Squib	(Honoraria for educational activity)
Janssen	(Honoraria for educational activity)
EUSA Pharma	(Honoraria for educational activity)
GenMab	(Consultant)
AstraZeneca	(Research Support)
NanoString Technologies	(Patent licensed)
Diagnostica Longwood	(License of protected IgCaller algorithm)

MCL biological progression

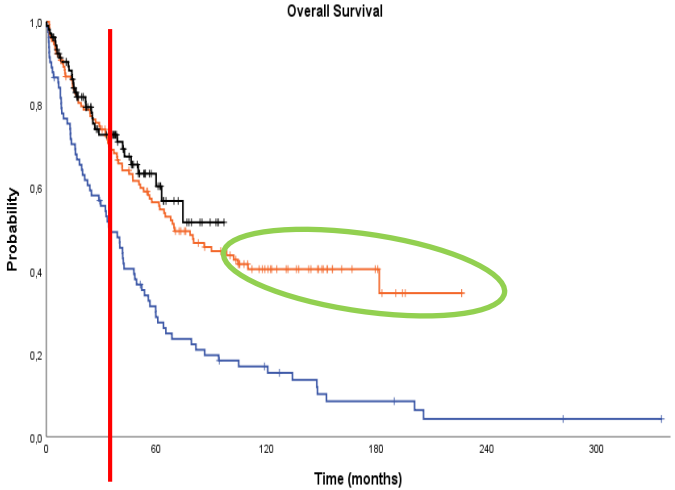


Jares P et al J Clin Invest 2012

Mantle Cell Lymphoma Clinical Evolution



Hospital Clinic of Barcelona, MCL, B-NHL



Median survival:
--- 1990-2001: **2.9 yr** (CI 1.9-3.7)
--- 2002-2013: **5.8 yr** (CI 3.8-7.8)
--- **2014-2022:** not reached

(Courtesy Dr. López-Guilllermo and E Giné)

Mantle cell lymphoma
Clinical Variants

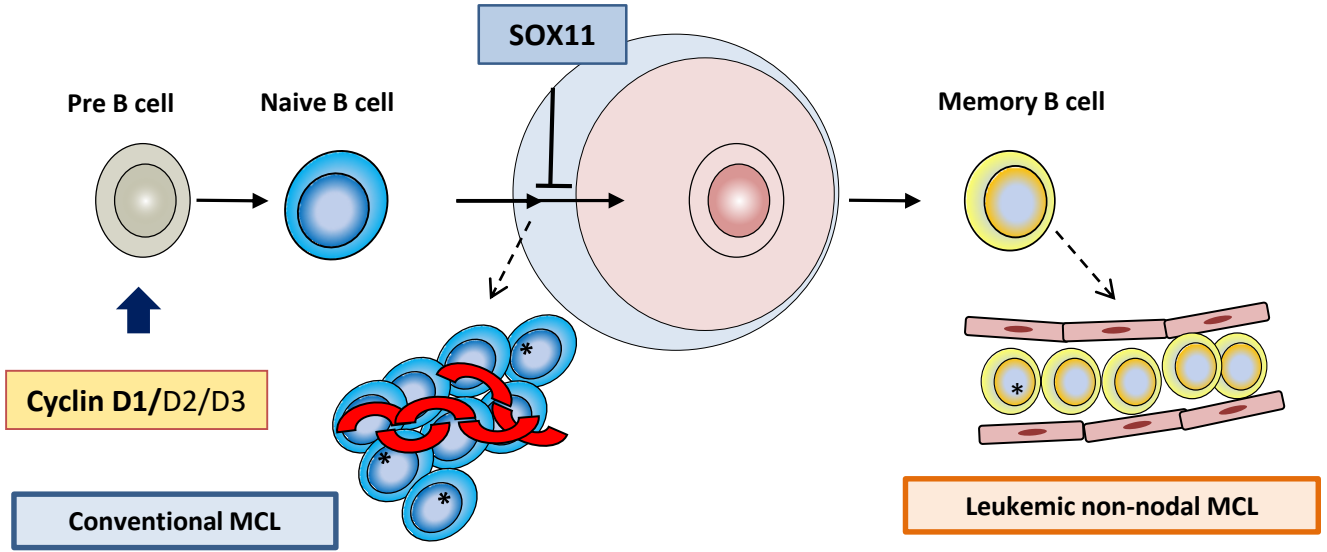
- **Indolent:**
  - **Stable disese, safely observed without therapy**

- **High-Risk /Very Aggressive:**
  - **Rapid clinical evolution, poor response to standard chemoimmunotherapy, high-risk MIPI, shorter survival**

What are the biological drivers underlying MCL evolution ?

Wilson MR et al. Br J Haematol 2023; 201:185-198; Scheubeck G et al. Leukemia 2023 Sep 37(9):1887-1894

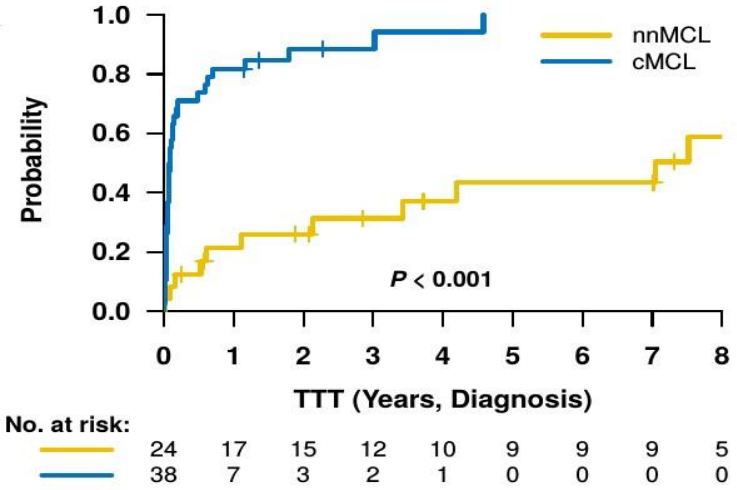
Molecular Subtypes of MCL



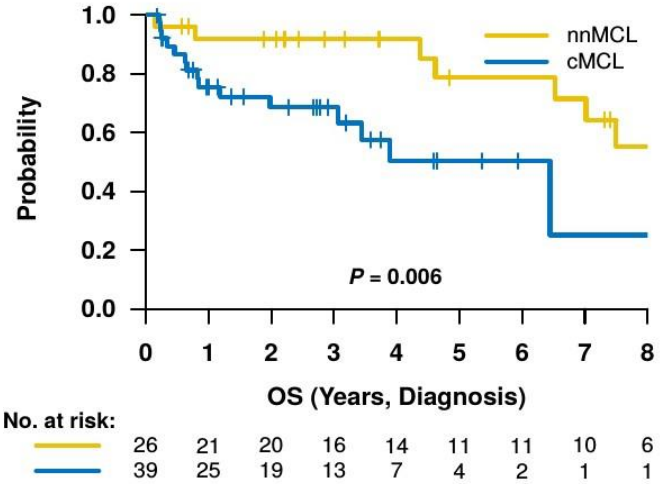
Puente et al Blood 2018; 131:2283-96

Outcome according to cMCL and nnMCL signatures

TTFT

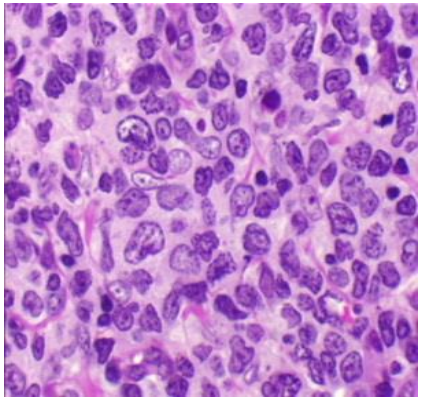


OS

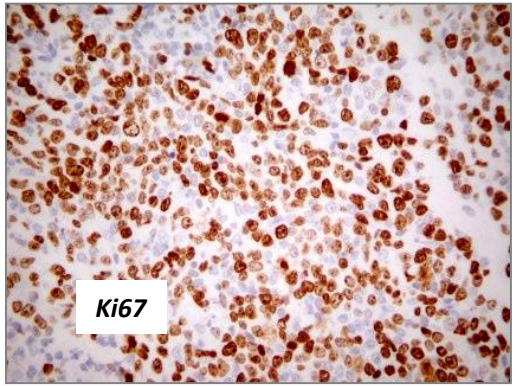


Clot G et al Blood 2018

Mantle cell lymphoma
Biological Drivers of Highly Aggressive variants

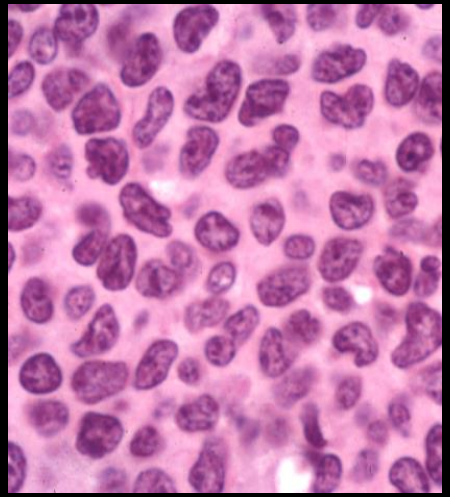


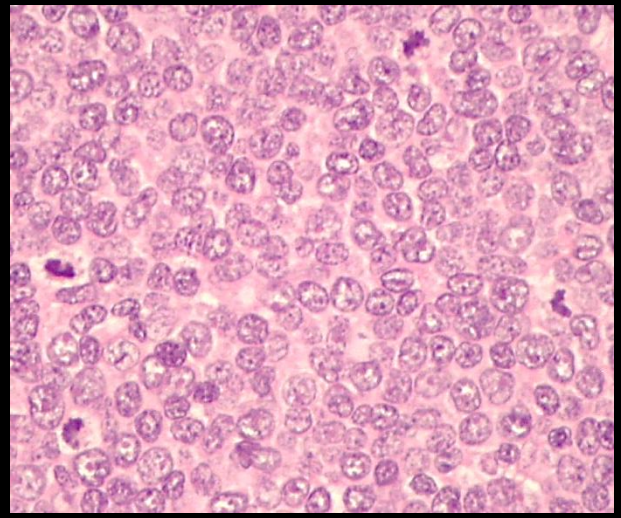
Blastoid MCL

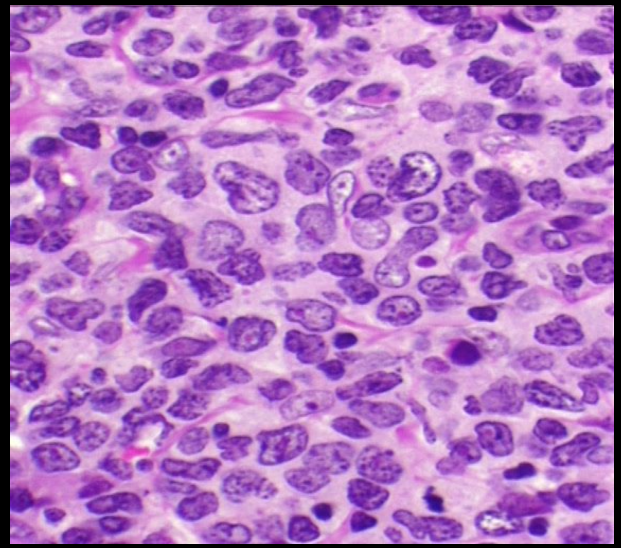


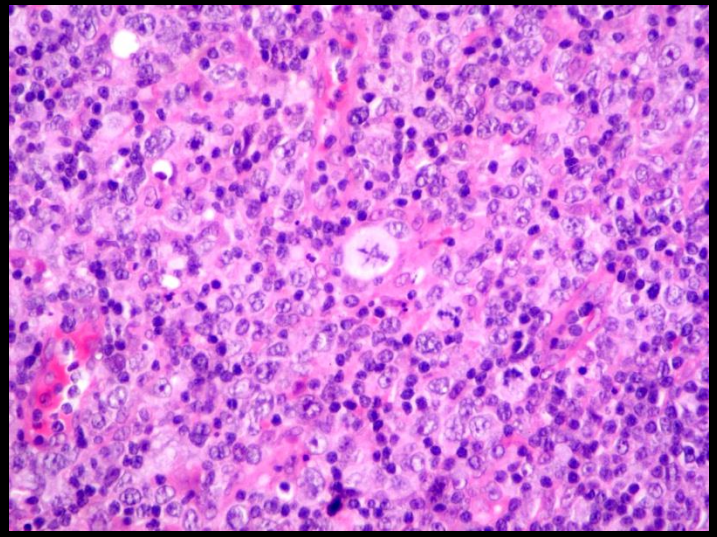
High proliferation

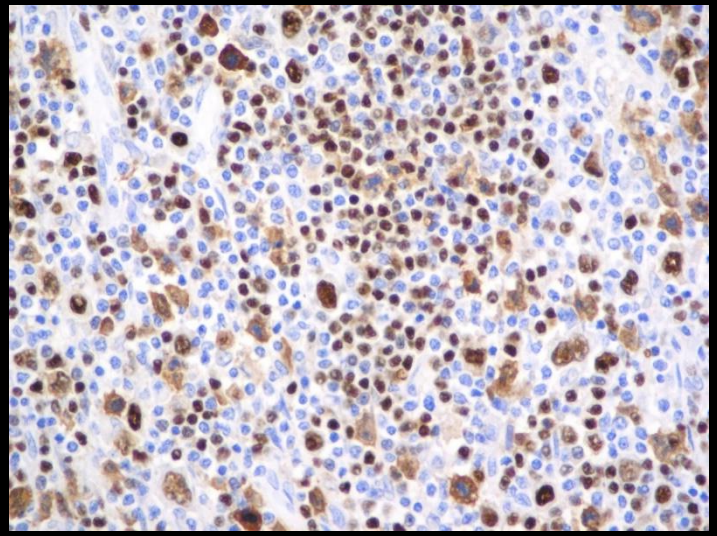
(Epi) Genomic alterations



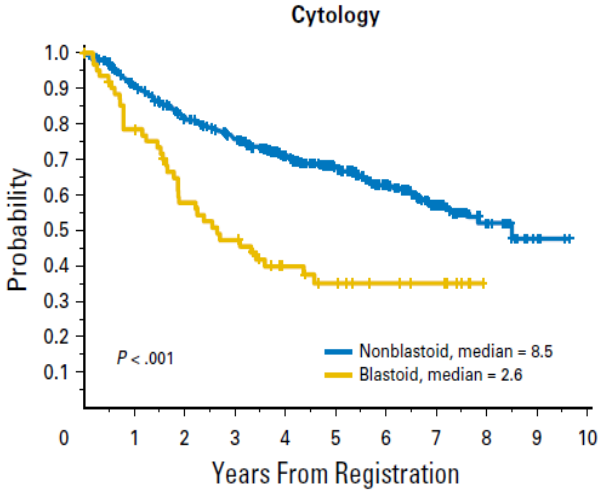


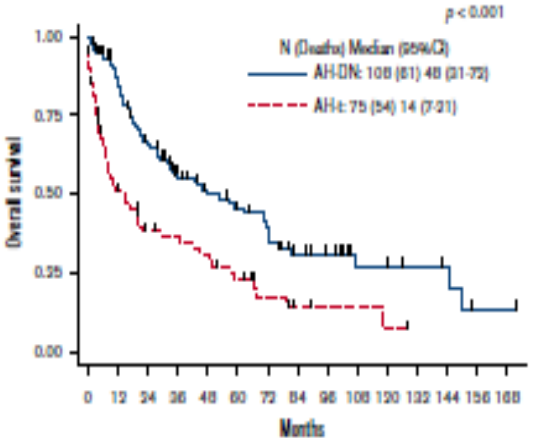




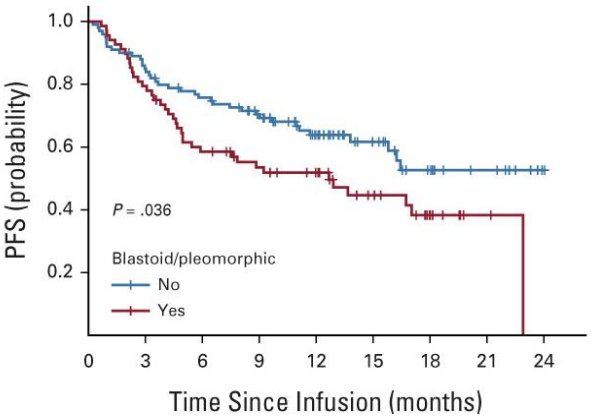


Mantle Cell Lymphoma
Impact of Blastoid/Pleomorphic Cytology





Primary vs transformed

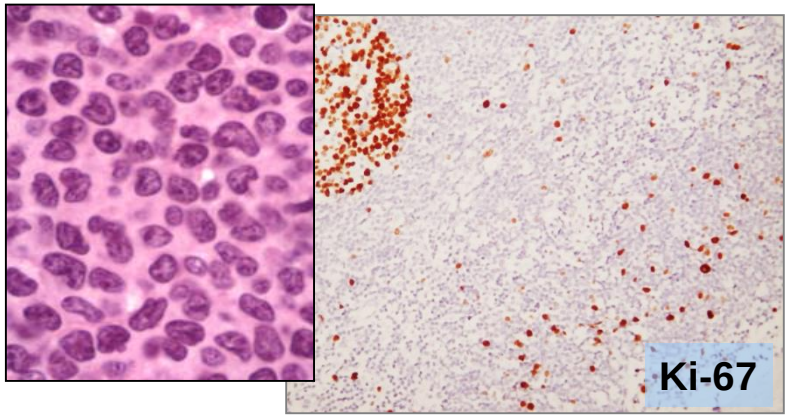


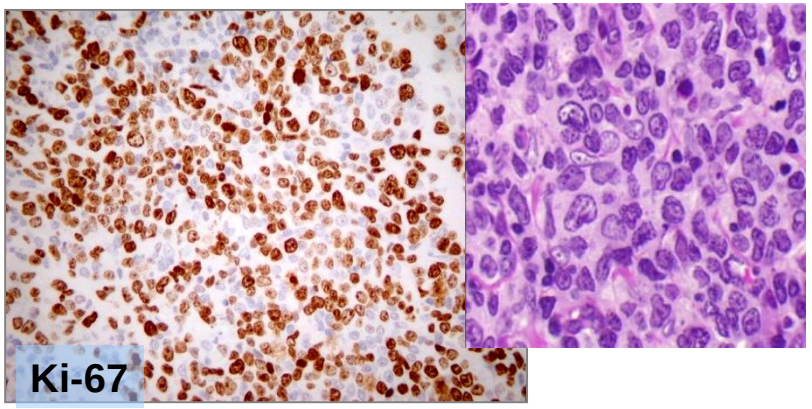
CAR-T

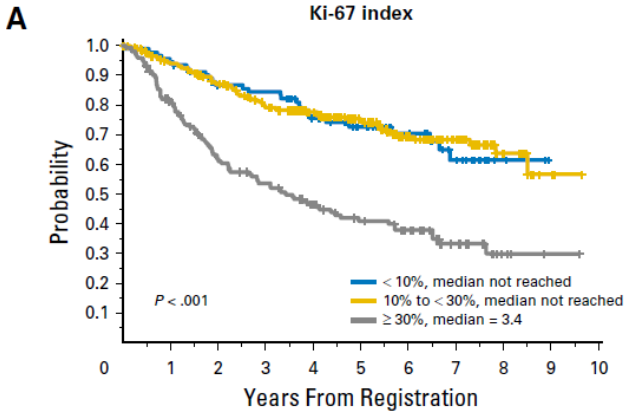
- Adverse impact of blastoid morphology explained in part by proliferación
- Still recomended to recognize it and consider a high-risk factor

Holster E et al J Clin Oncol 2016; Jain P et al Blood Adv 2020, Wang J et al J Clin Oncol 2023

Prognostic Value of Proliferation in MCL

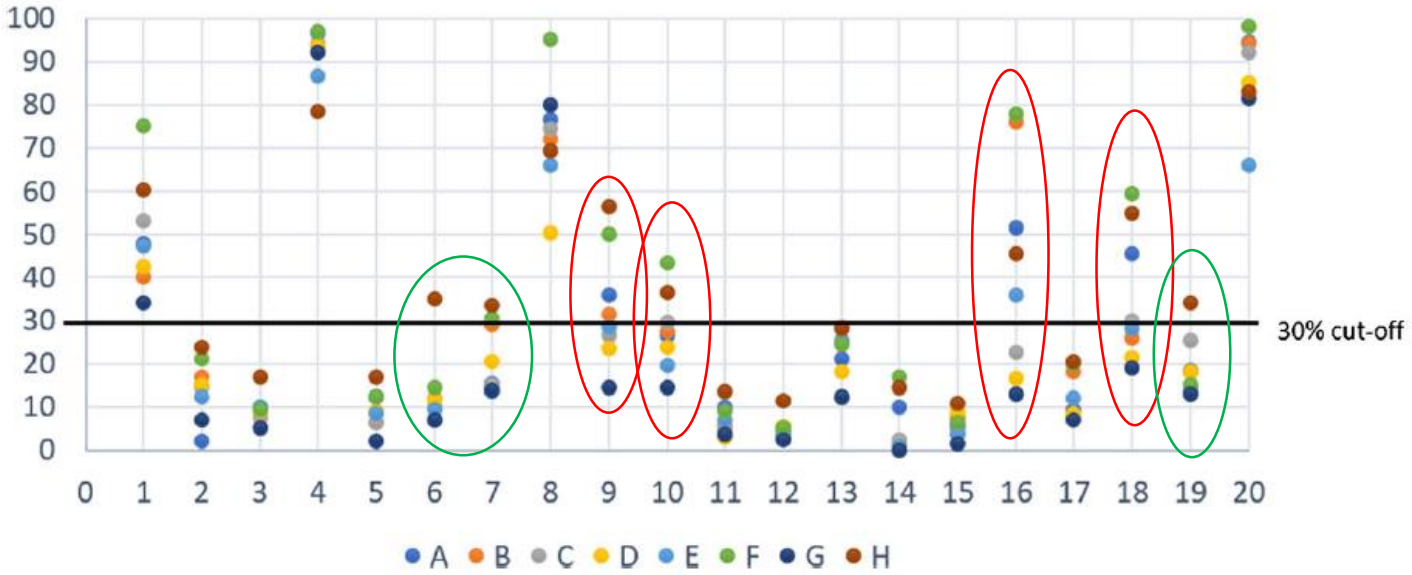






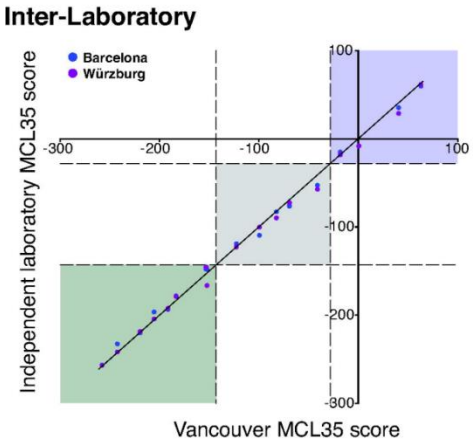
Holster E et al J Clin Oncol 2016

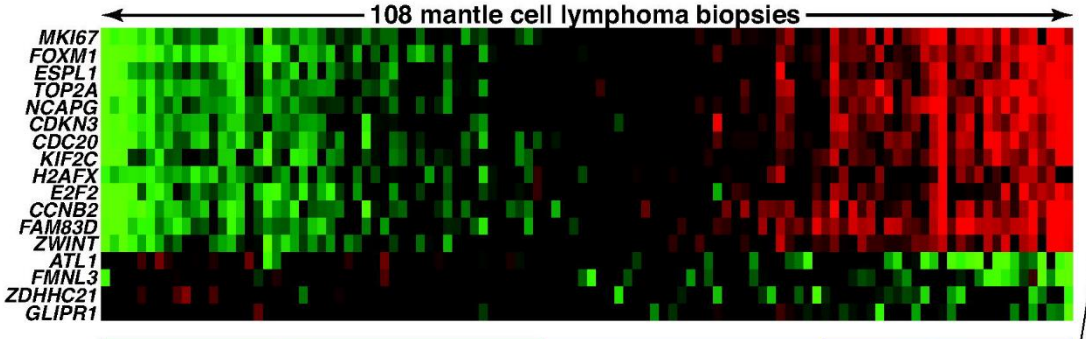
Ki67 Evaluation



Croci GA et al Virchows Arch 2020; 477: 259–267

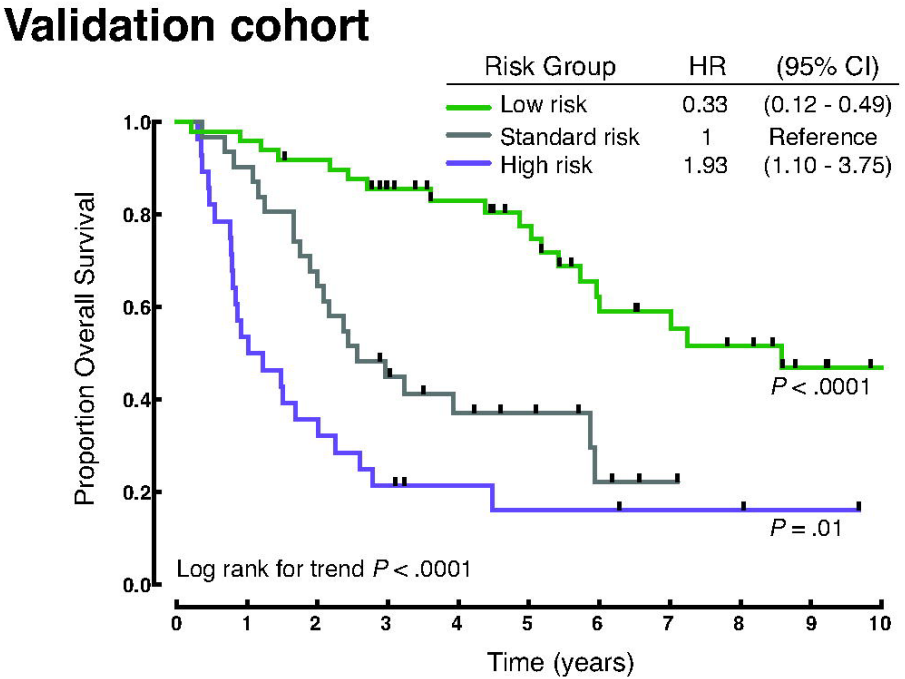
Molecular assay for proliferation signature in routine FFPE MCL samples





Scott DW et al JCO 2017 Mar 14:

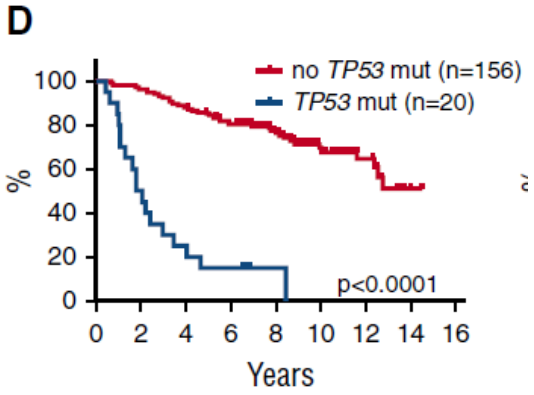
Molecular assay for proliferation signature in routine FFPE MCL samples



Scott DW et al JCO 2017 Mar 14:

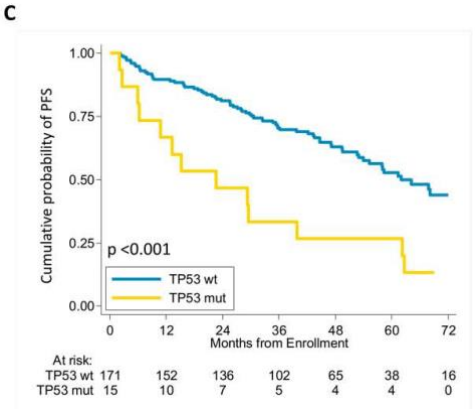
TP53 alterations in MCL

Nordic MCL2 and MCL3



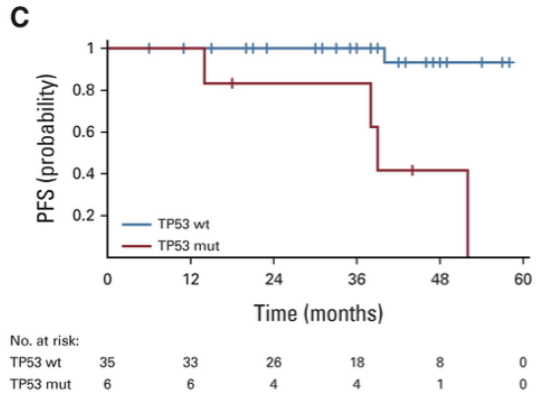
Eskelund, Blood, 2017

FIL-MCL0208 phase III trial



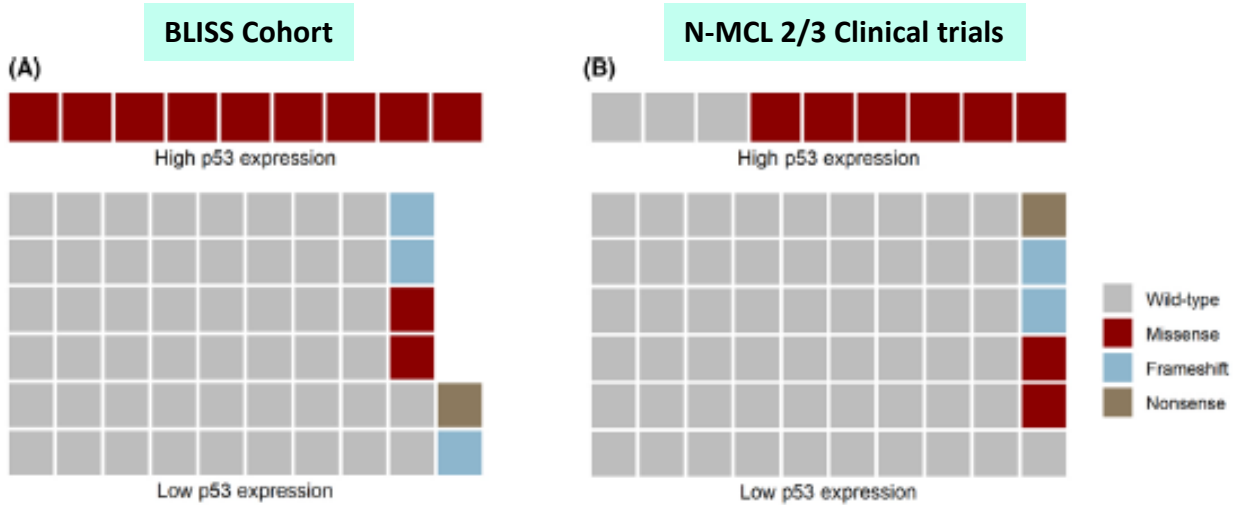
Ferrero, Haematologica,2020

IMCL-2015



Giné, JCO 2022

TP53 alterations in MCL should be studied by DNA sequencing
Immunohistochemistry vs Sequencing

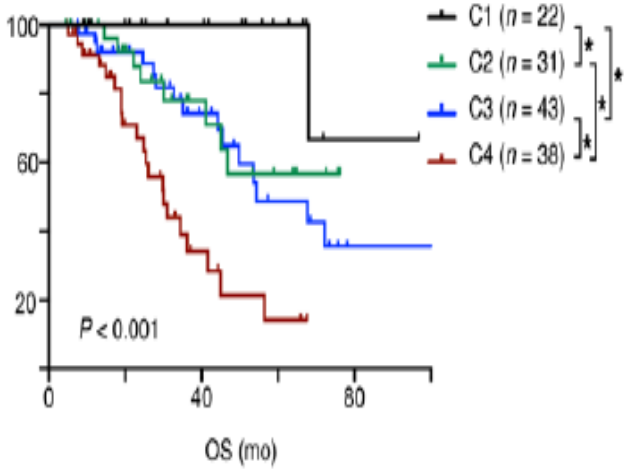


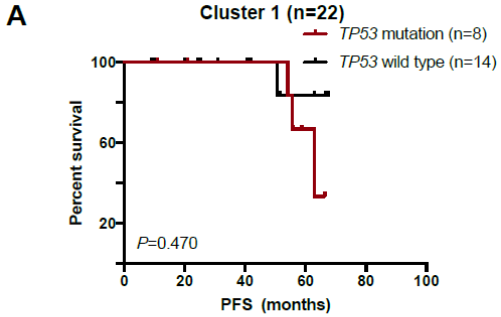
- **17% TP53 alterations by IHC were false positives**
- **40% all TP53 mutations may be missed by IHC**

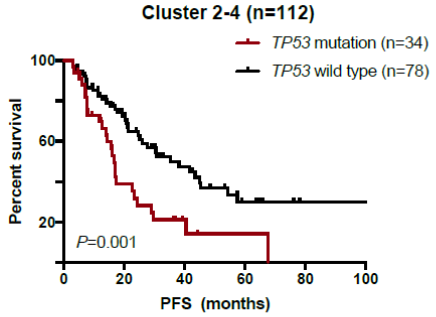
- **Frameshift and non-sense mutations not detected by IHC (27% of *TP53* mutations)**
- **18-25% Missense mutations missed by IHC**

Rodrigues JM et al Br J Haematol 2020; 191:796-805

TP53 Prognostic Impact and MCL Molecular Subtype



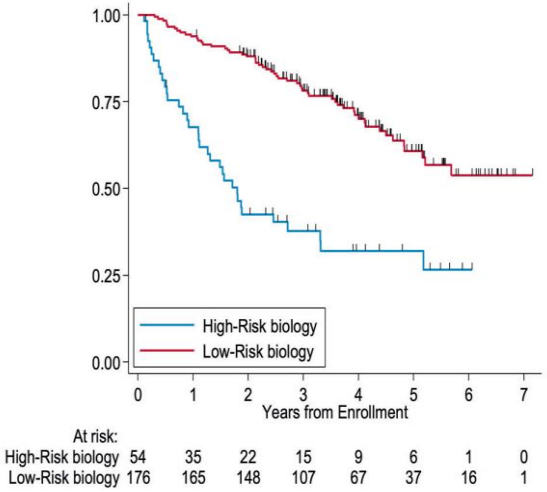




Yi S et al J Clin Invest 2022;132(3):e153283

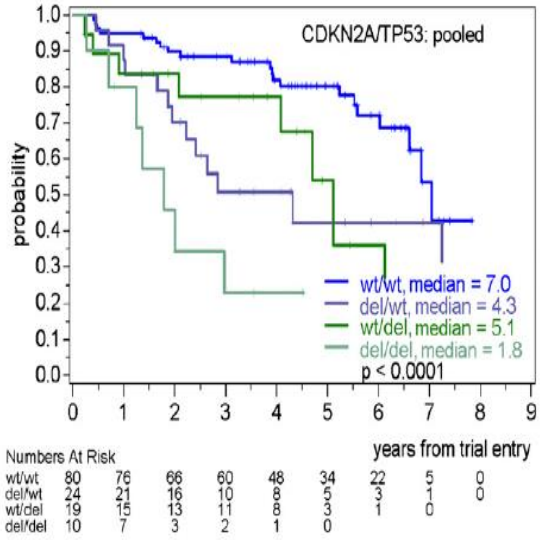
Increasing the prognostic Impact of *TP53* in MCL

High MIPIc or TP53 alt



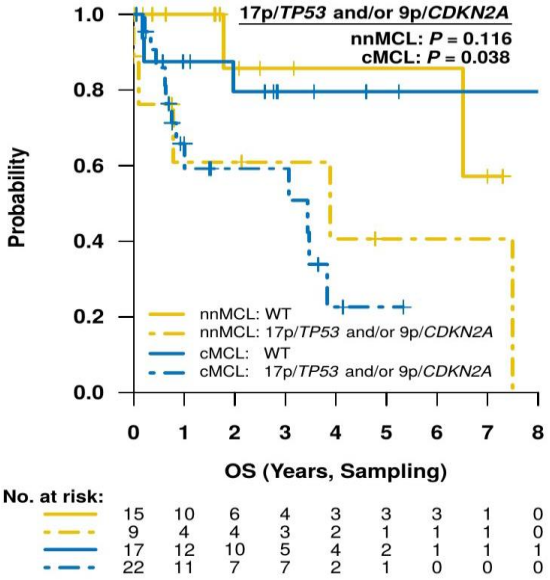
Scheubec G et al Leukemia 2023

TP53/CDKN2A
MCL younger



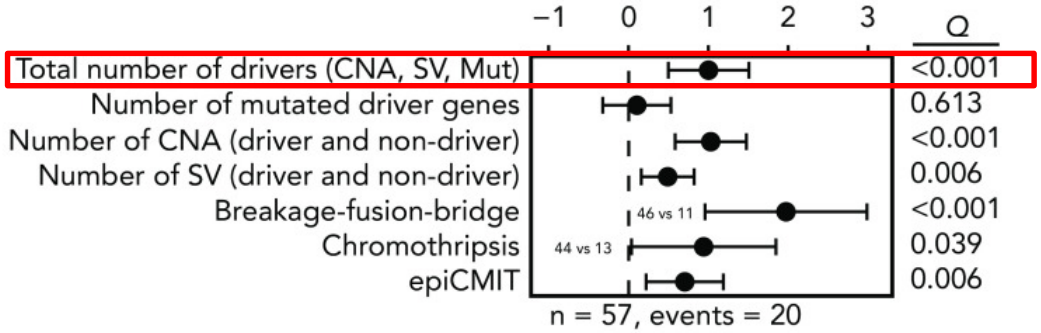
Delfau-Larue, Blood 2015

TP53/CDKN2A
cMCL and nnMCL



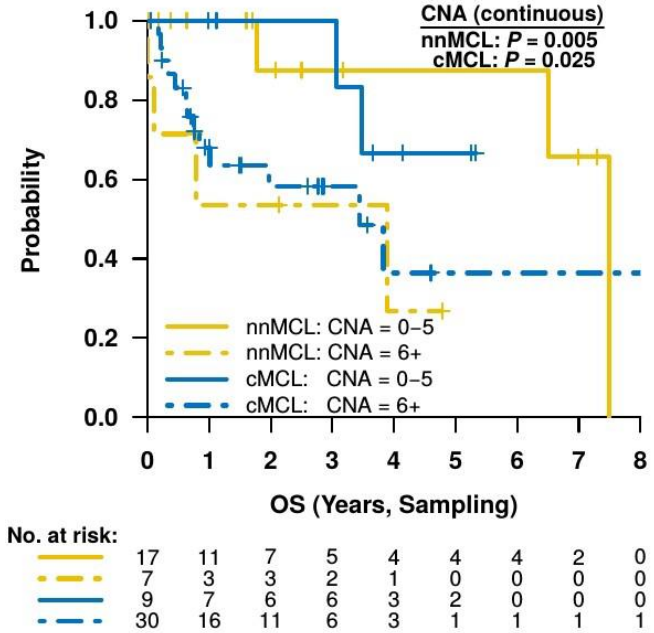
Clot G et al Blood 2018

Genomic Complexity in cMCL and nnMCL



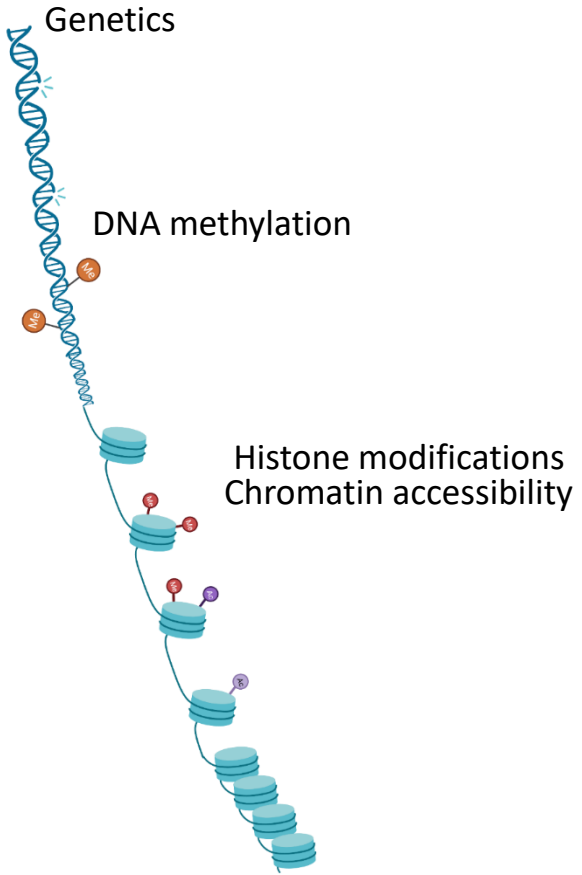
Nadeu F et al Blood 2020

Genomic Complexity



Clot G et al Blood 2018

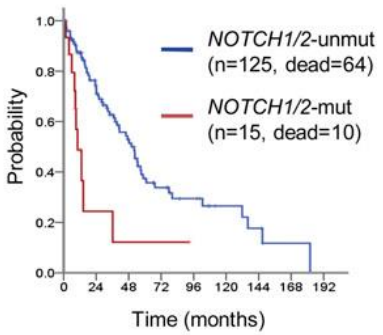
Multiple epigenetic layers regulate gene expression



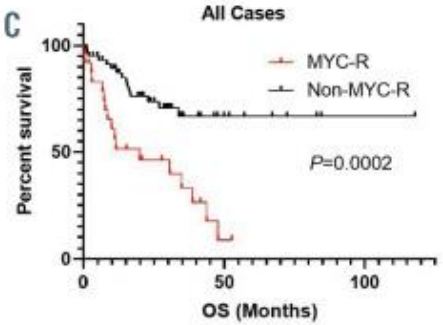
LAYER	FUNCTION
Genome	Information storage
DNA methylation	Context dependent
H3K4me3	Promoters
H3K4me1	Enhancers
H3K27ac	Active regulatory element
H3K36me3	Transcription Elongation
H3K27me3	Polycomb repression
H3K9me3	Heterochromatin
Chromatin accessibility	Transcription factor binding

Gene expression

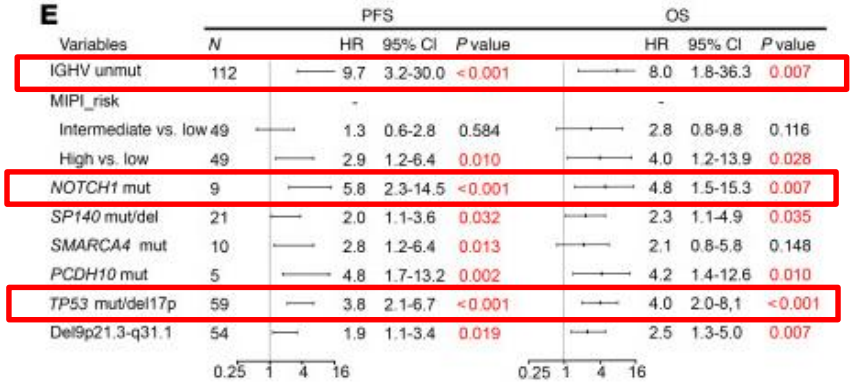
Adverse Genomic Alterations in MCL



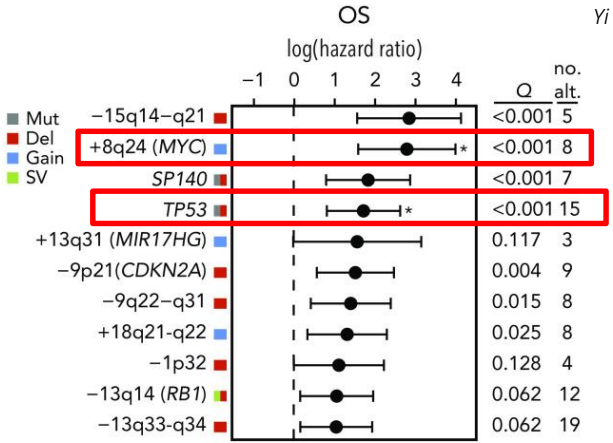
Bea S et al PNAS 2013



Wang L et al Haematologica 2021

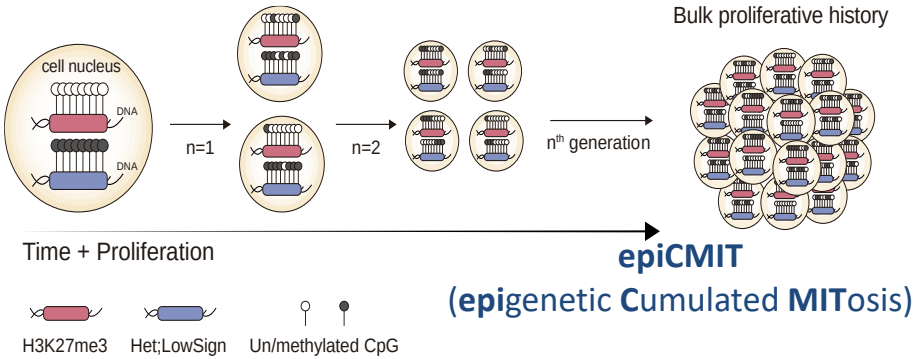


Yi S J Clin Invest 2022



Nadeu Blood 2020

DNA methylation changes accumulate upon cell division

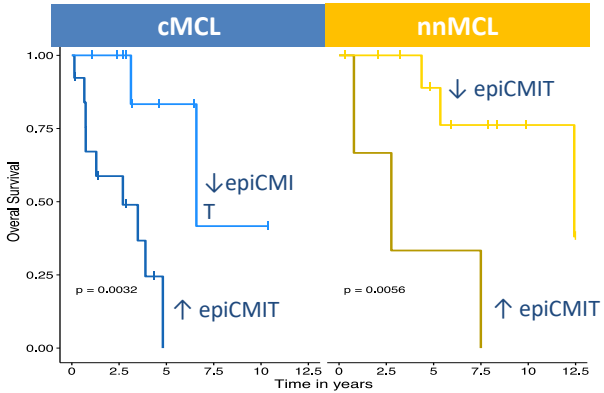


epiCMIT

(**epi**genetic **C**umulated **MIT**osis)

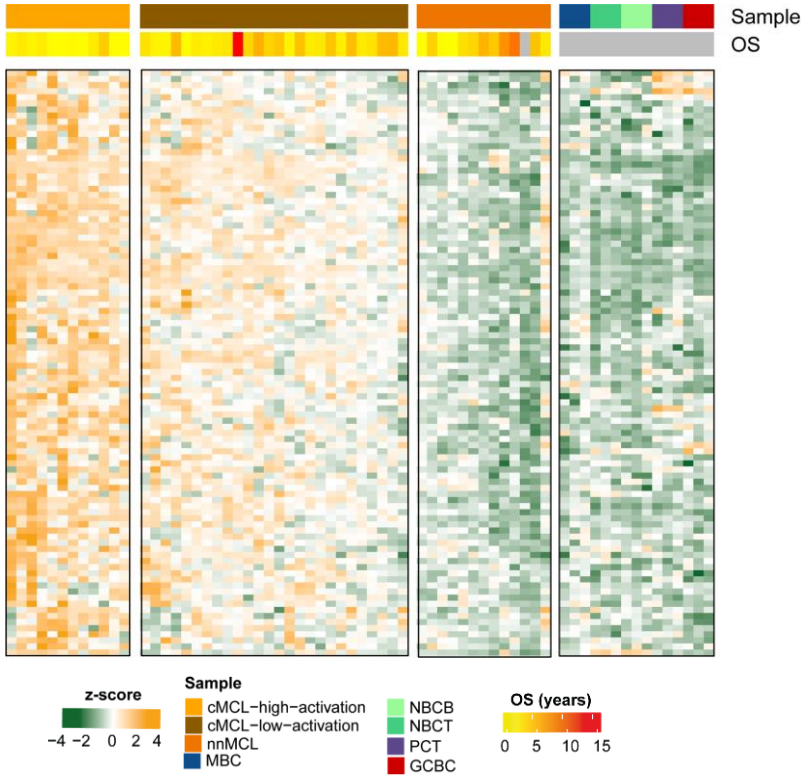
epiCMIT → reflects the proliferative history of a sample

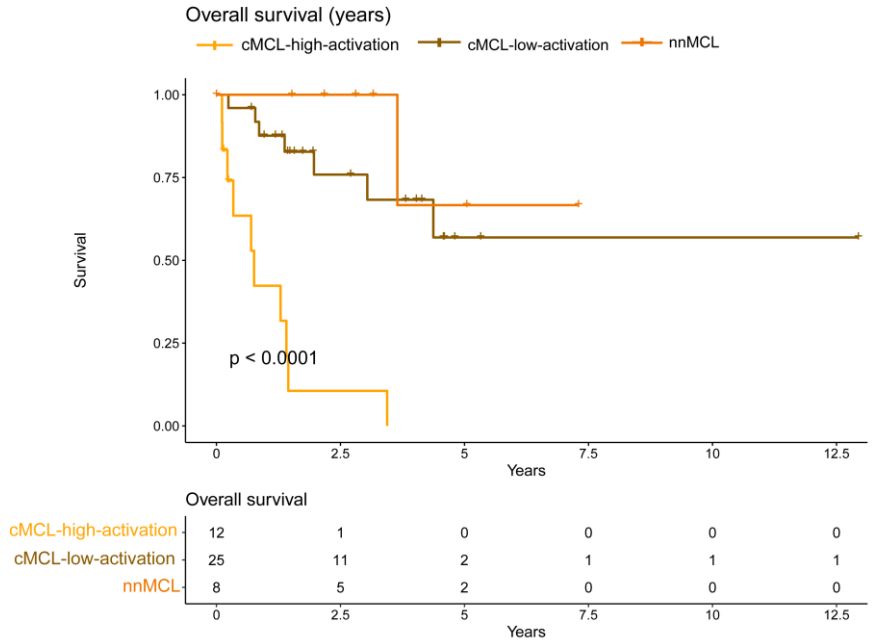
Most DNA methylation changes are due to proliferative history



Duran-Ferrer M et al, Nat Cancer 2020

Association of chromatin activation with clinical data

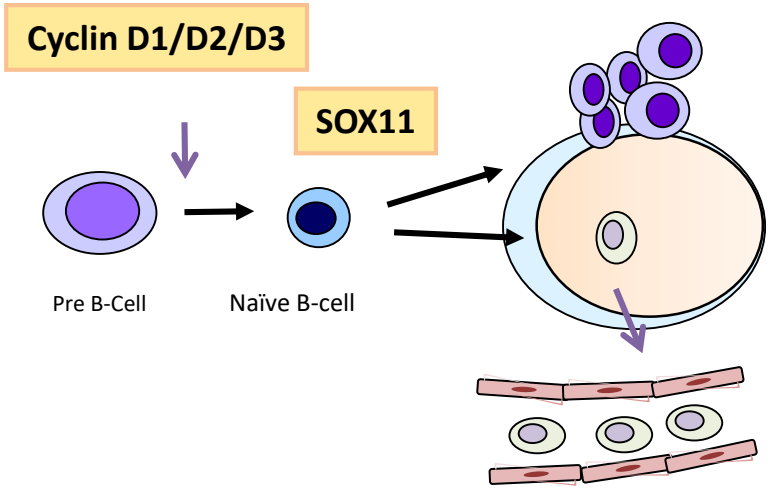




Level of chromatin activation seems to be related with the clinical outcome

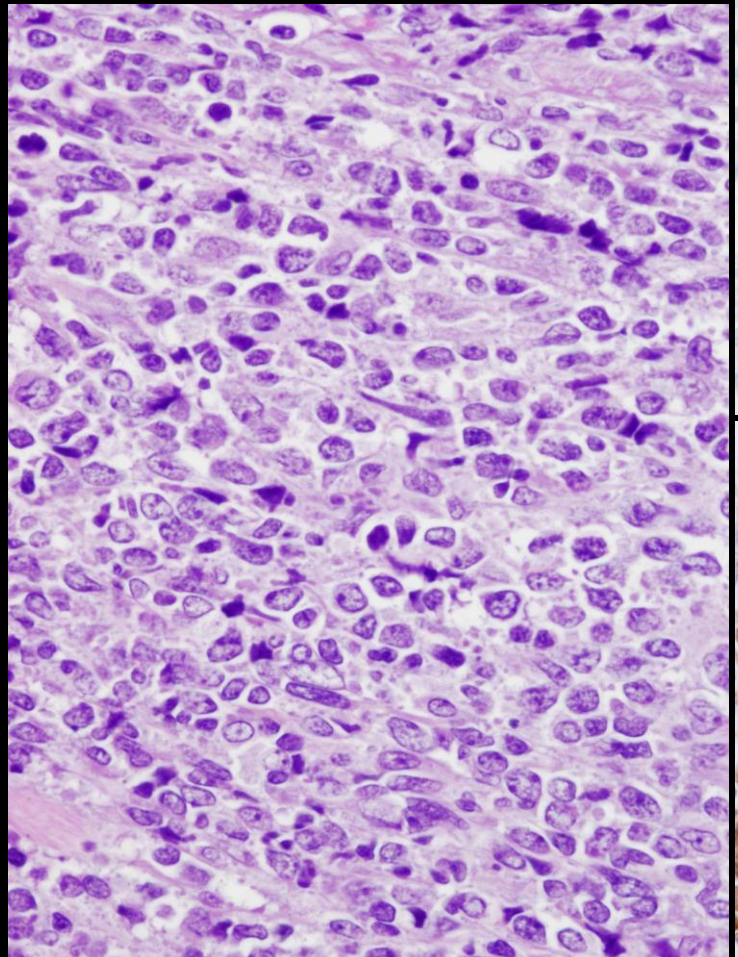
Biological Drivers of High-Risk MCL

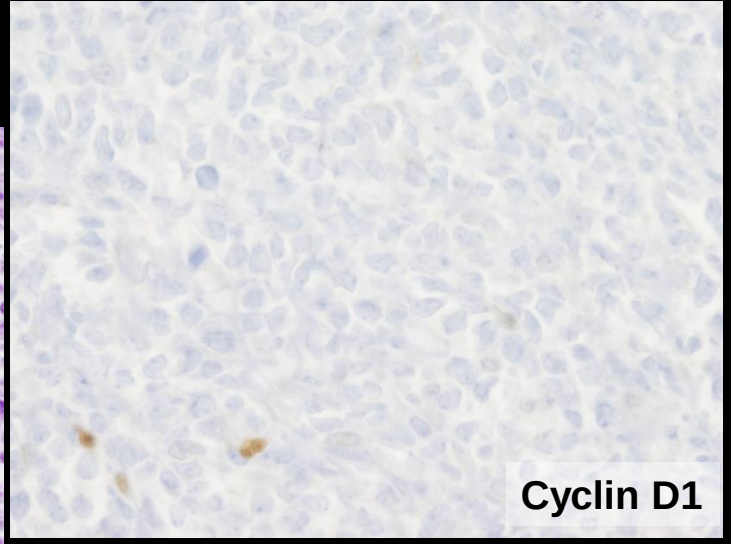
Conventional MCL (SOX11+)

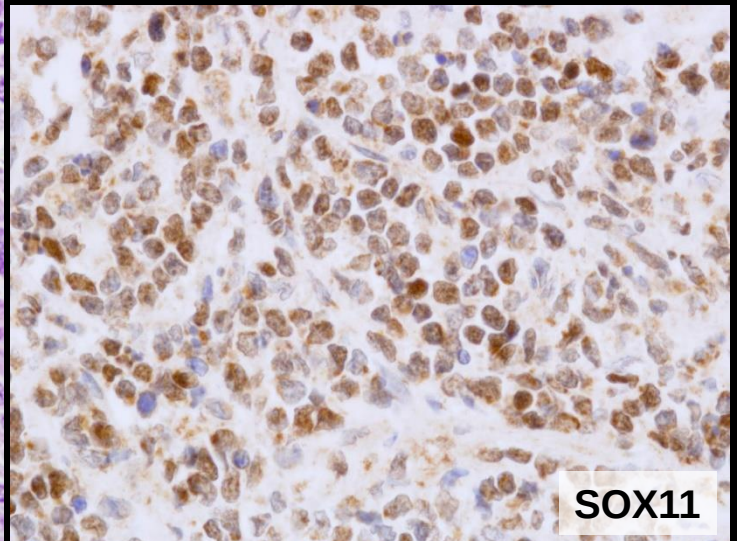


Leukemic non-nodal MCL (SOX11-)

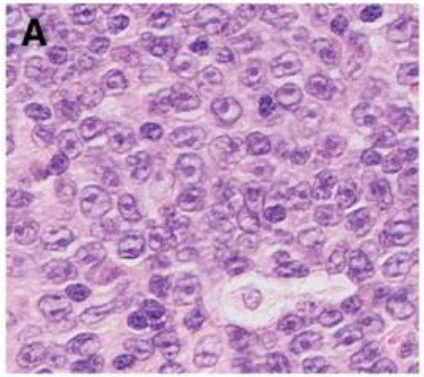
Pleomorphic MCL

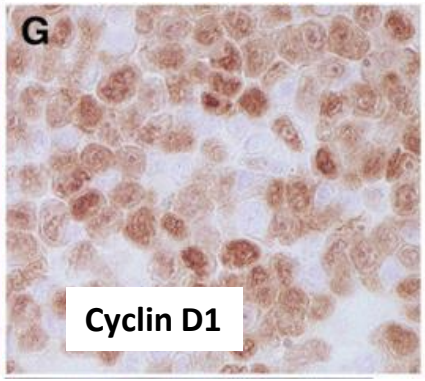


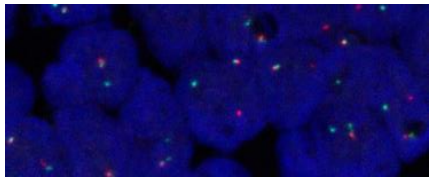




CCND1 Expression and Rearrangement as a Secondary Event in High Grade B-Cell Lymphoma and other B-cell neoplasms





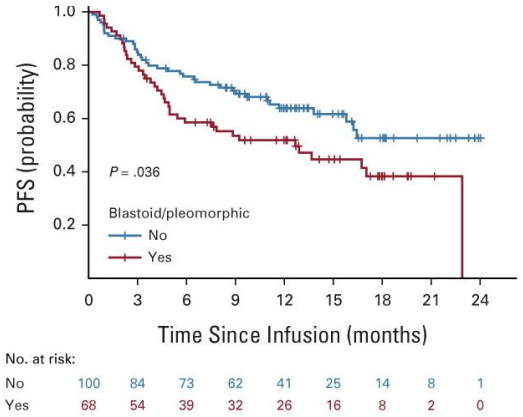


- **Large B cell morphology**
- **CD5 and SOX11-negative**
- **Usually CCND1 rearrangement negative but…**
- **Unusual cases *CCND1* rearranged**
- **Associated with multiple translocations (*BCL6, BCL2, MYC*)**
- **Unusual mutations (*KRAS* and *TNFRSF14)* in MCL**

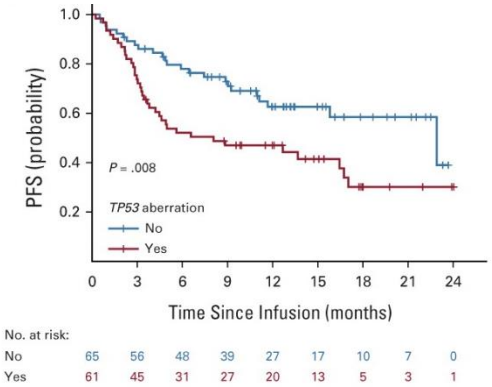
Hsiao et al Histopathology. 2012 Oct;61(4):685-93; Schliemann I et al Leuk Lymphoma. 2016;57(11):2672-6; Cheng J et al Hemasphere. 2021; 5(1): e505

Adverse Biological Factors in MCL CAR-T treatment

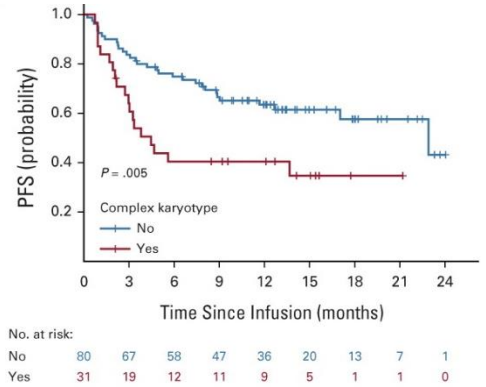
Blastoid/Pleomophic



TP53

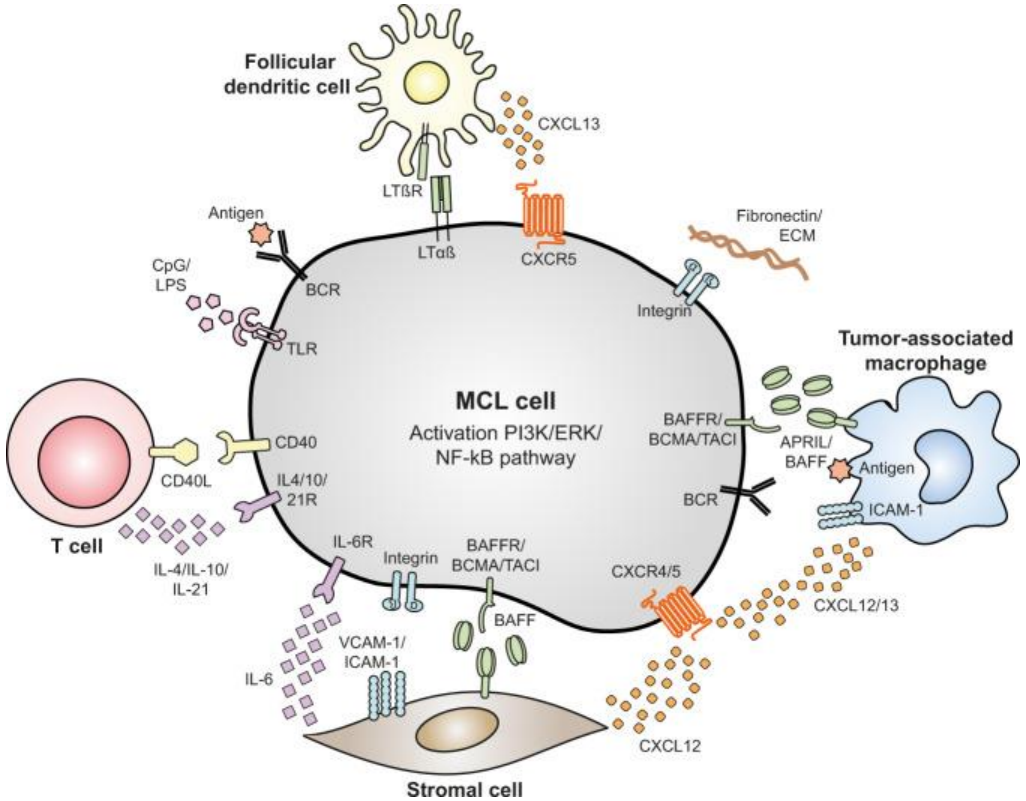


Complex Karyotypes



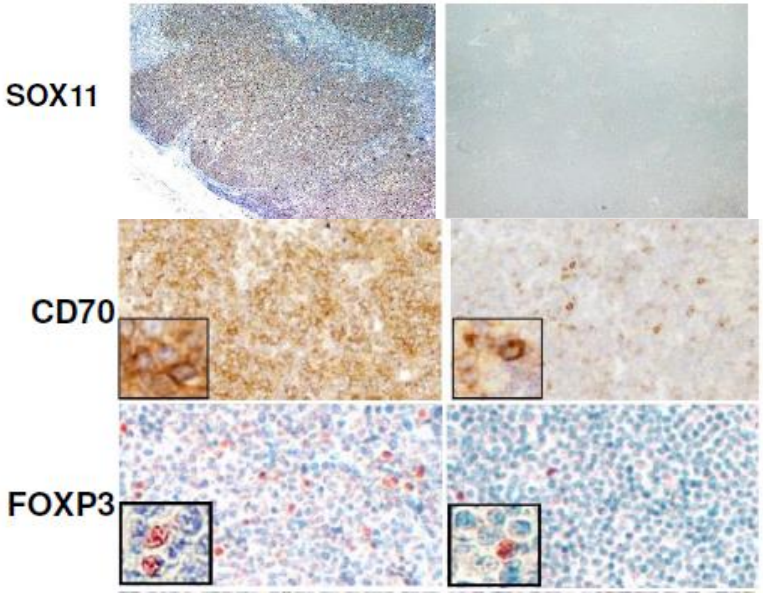
Wang Y et a J Clin Oncol 2023;41:2594-2606

Tumor and microenvionment interactions in MCL

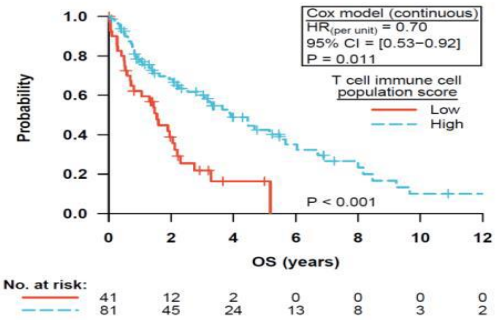


Thus YJ et al Leukemia 2022

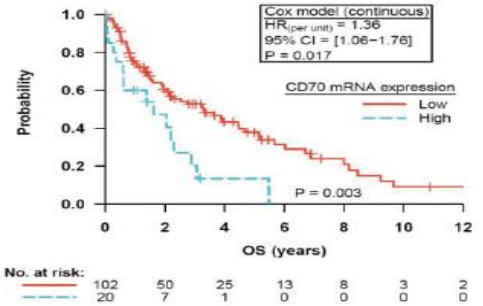
SOX11+ MCL overexpresses CD70 and has a tumor promoting microenvironment



T-cell score



CD70 expression



Balsas P & Veloza L et al Blood 2021

3rd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 21-22, 2023

Starhotels Majestic

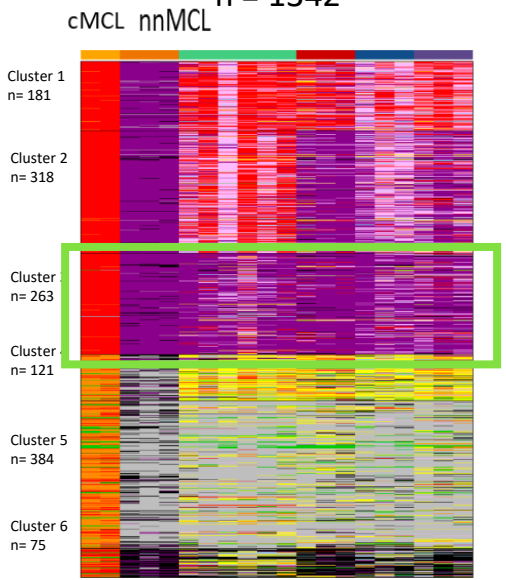
Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Disclosures of NAME SURNAME

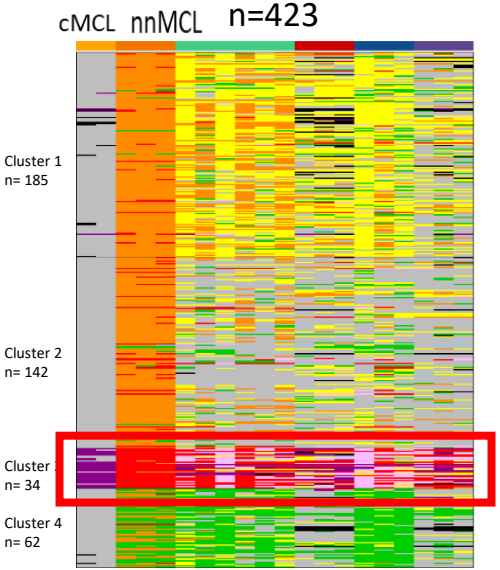
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

cMCL-nnMCL differences based on chromatin states

cMCL regulatory regions
n = 1342



nnMCL regulatory regions
n=423

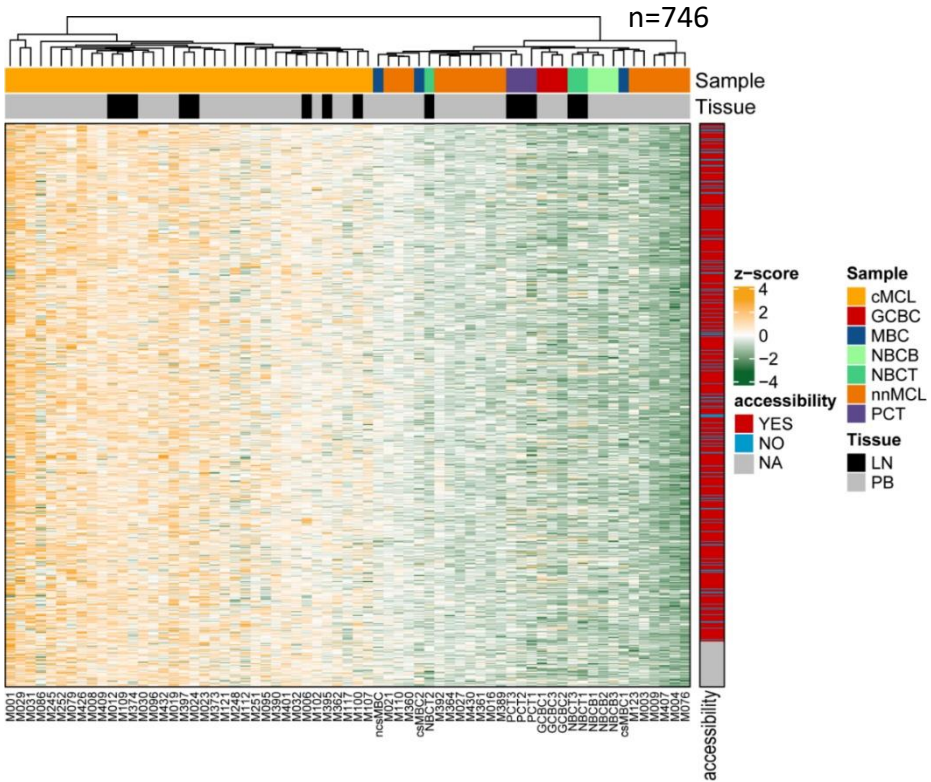


cMCL nnMCL NBCB NBCT GCBC MBC PC

Chromatin activation is more remarkable in cMCL.
Regions that are activated in nnMCL as compared to cMCL are in fact already active or partially-active in B cells.

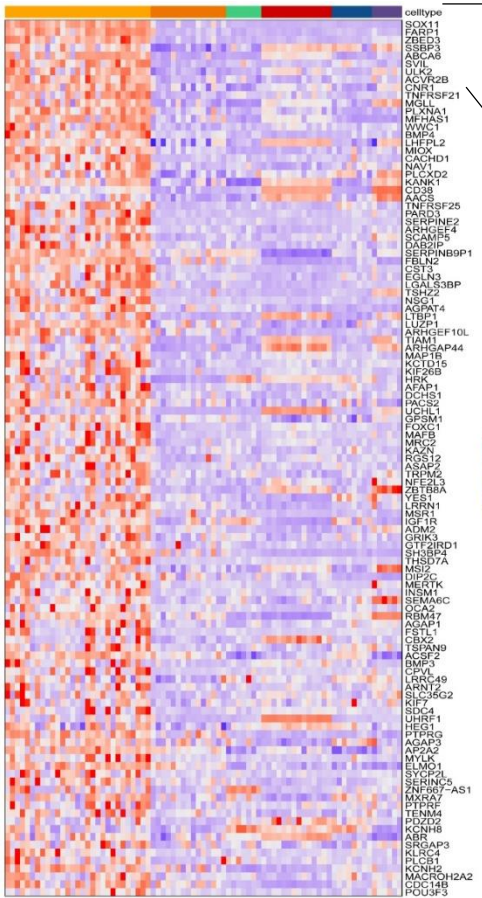
cMCL *de novo* regions

H3K27Ac



Gene Expression

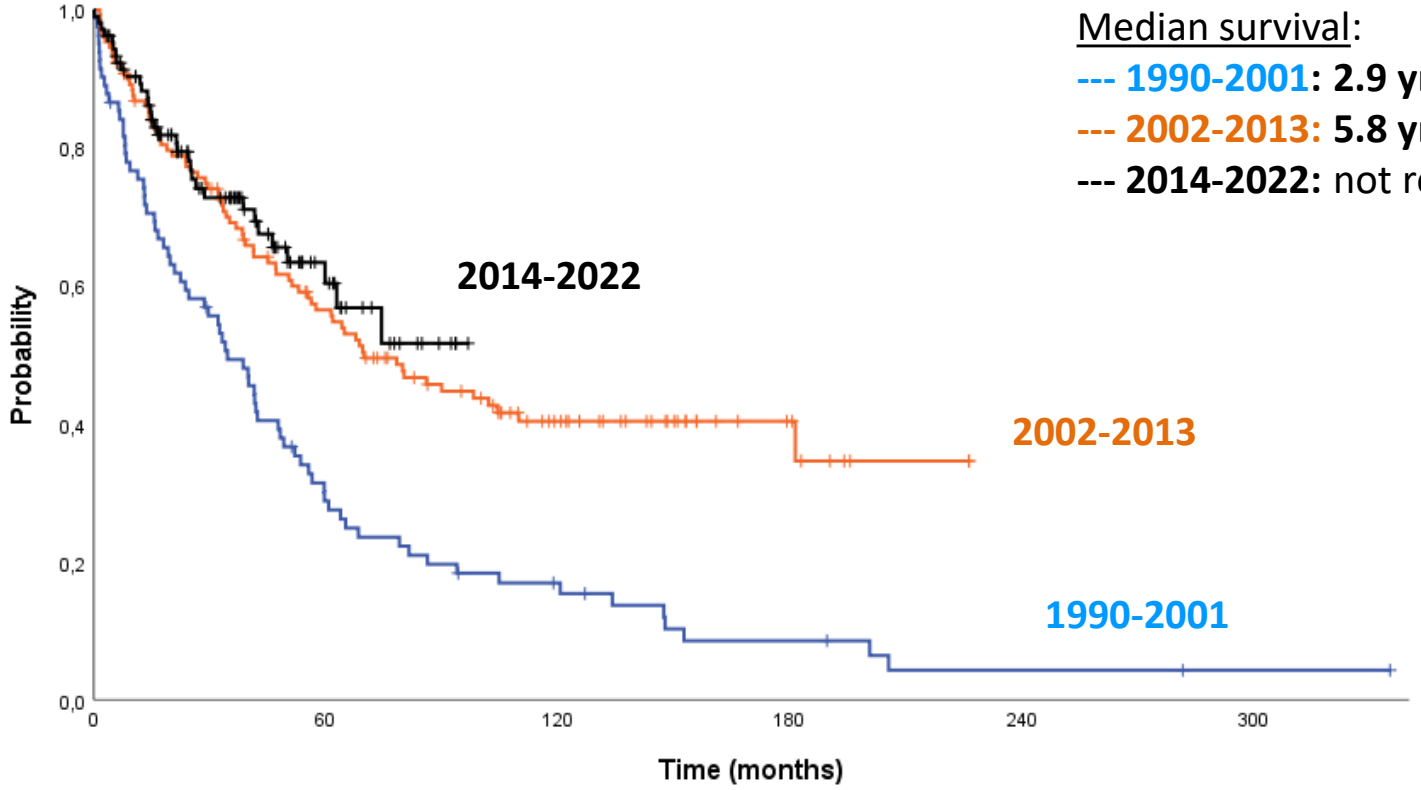
n=352



SOX11
FARP1
ZBED3
SSBP3
ABCA6
SVIL
ULK2
ACVR2B
CNR1
TNFRSF21

*data from U219 expression

Overall Survival in MCL



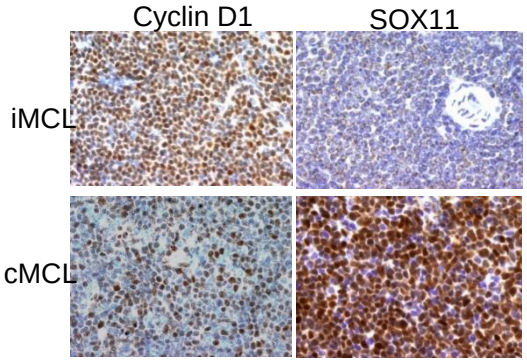
Median survival:

--- 1990-2001: **2.9 yr** (CI 1.9-3.7)

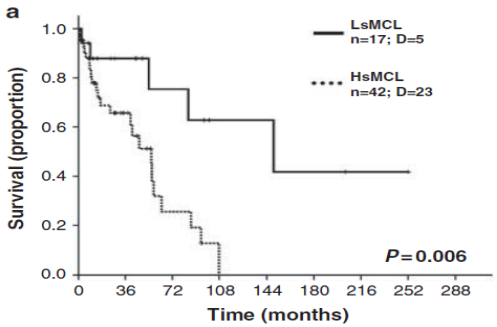
--- 2002-2013: **5.8 yr** (CI 3.8-7.8)

--- **2014-2022:** not reached

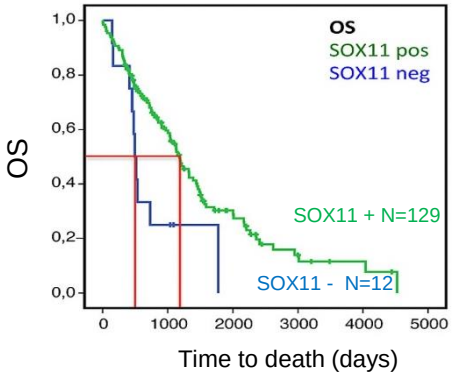
SOX11 as a marker for indolent MCL?

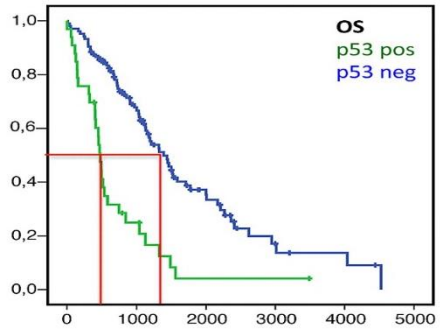


Fernàndez V., et al. Cancer Res. 2010



Royo C et al, Leukemia 2012





	p53 positive
SOX11-neg	9/13 (69%)
SOX11-post	24/152 (16%)

Nygren L et al, Blood 2012