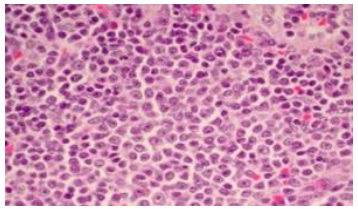
MOLECULAR ASPECTS IN SMALL LYMPHOCYTIC LYMPHOMA, LYMPHOPLASMACYTIC LYMPHOMA AND MANTLE CELL LYMPHOMA

Elias Campo

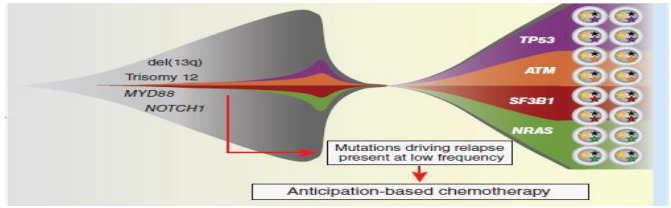
Hospital Clinic, Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), University of Barcelona

APOYO

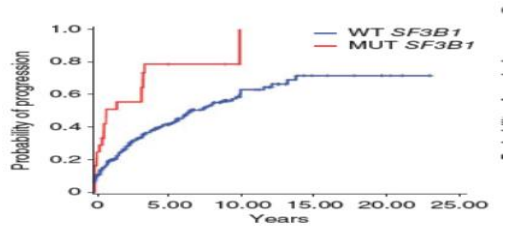
Molecular Studies in Small B cell Lymphomas



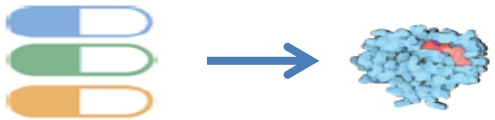
- Differential diagnosis of disease subtypes



- Understanding evolution of the disease

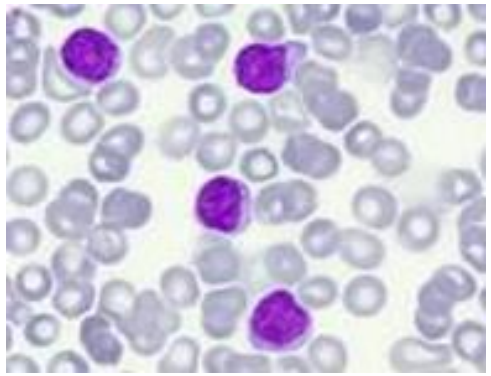


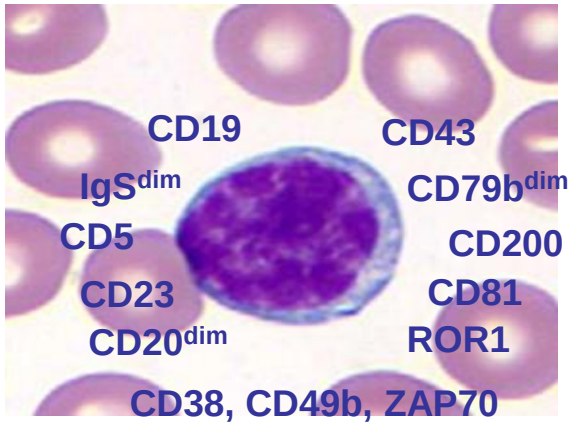
- Prognostic groups and risk stratification

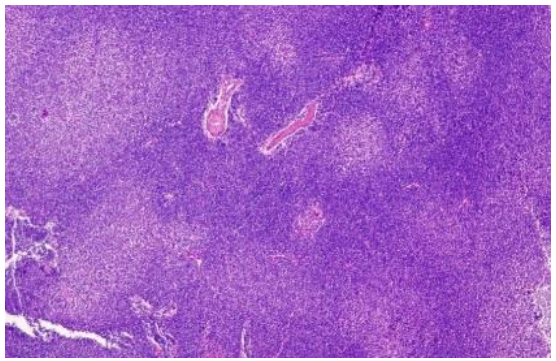


- Guide management estrategies

Chronic Lymphocytic Leukemia /Monoclonal B-cell Lymphocytosis







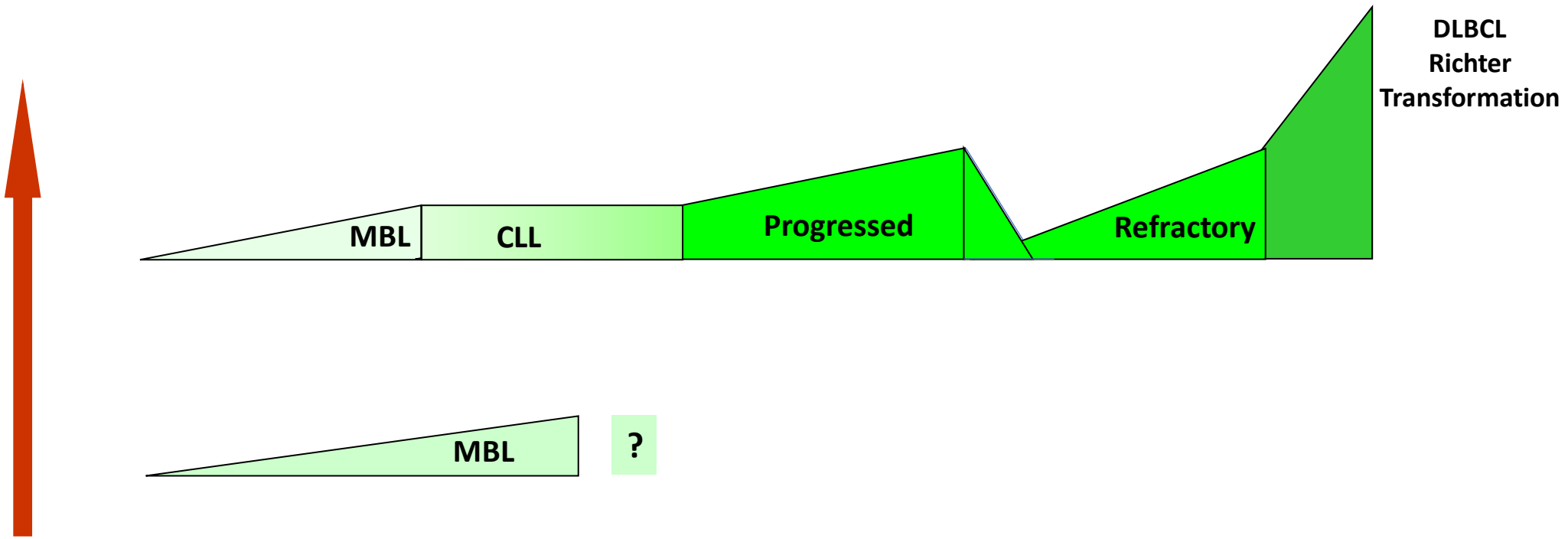
- **Diagnostic criteria**
  - CLL: ≥5 × 10^9/L clonal CD5+ B lymphocytes in blood, ≥ 3 months
  - SLL: Tissue involvement; **proliferation centers**

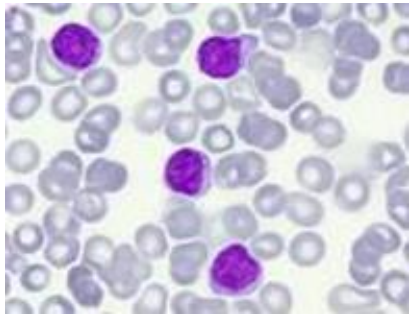
- **Genetic and Molecular**
  - **IGHV mutational status**
  - 11q, 12, 13q, **17p** (FISH)
  - ***TP53* mutations**
  - Others prognostic parameters need further studies (e.g. subclonal *TP53 mut*; BCR stereotypes, IGLV3-21R110; Complex karyotypes (≥ 3 or 5 in debate)

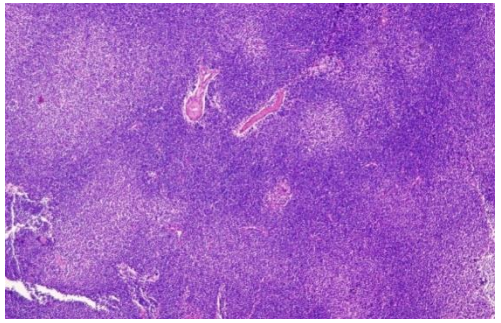
Hallek et al Blood 2018;131(25):2745-2760.

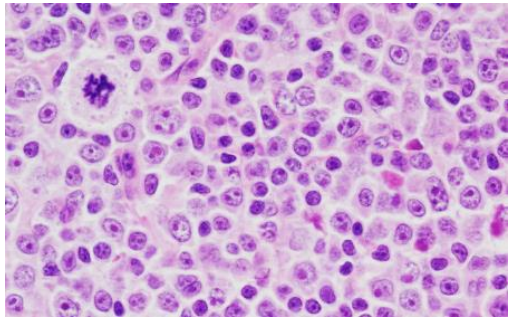
Disease Progression in CLL

Clonal B-cell selection and expansion



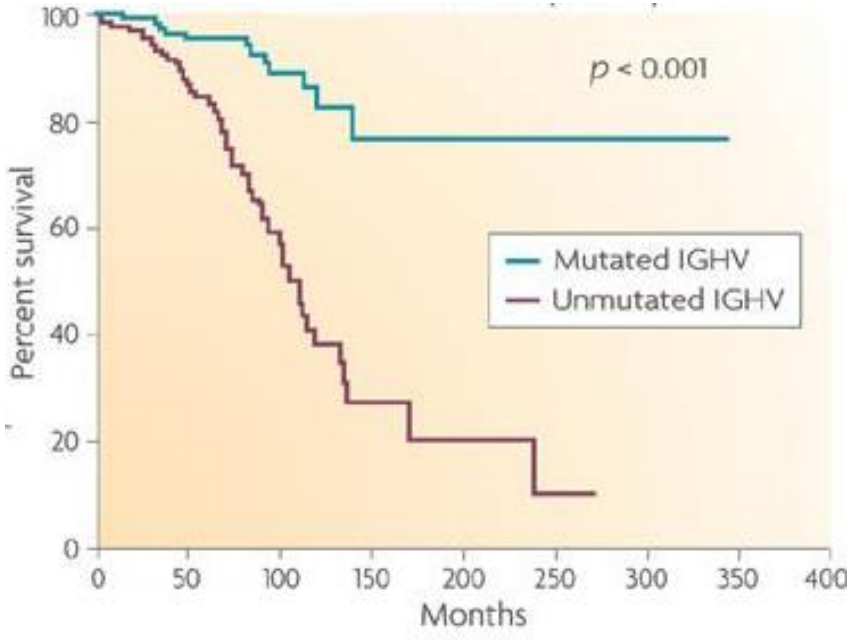






Chronic Lymphocytic Leukemia
Clinical Impact of Molecular and Genetic Subtypes

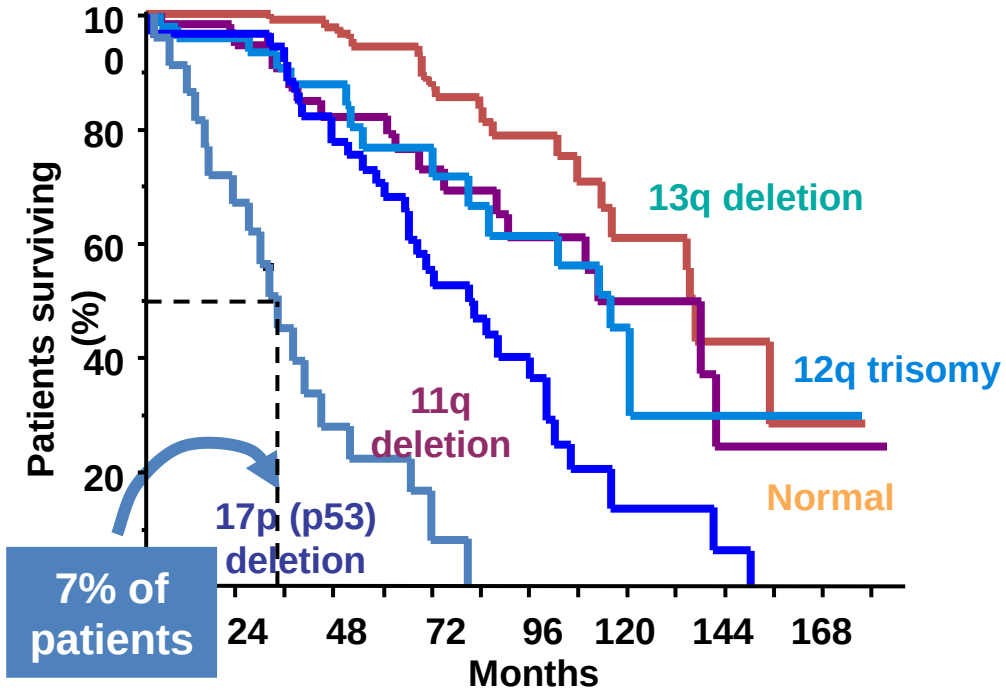
IGHV



- Cut-off 98% Homology with the germ line
- Unmutated CLL has shorter time to therapy initiation, shorter remission during therapy and shorter overal survival

Zenz et al., Nat Rev Cancer 2010

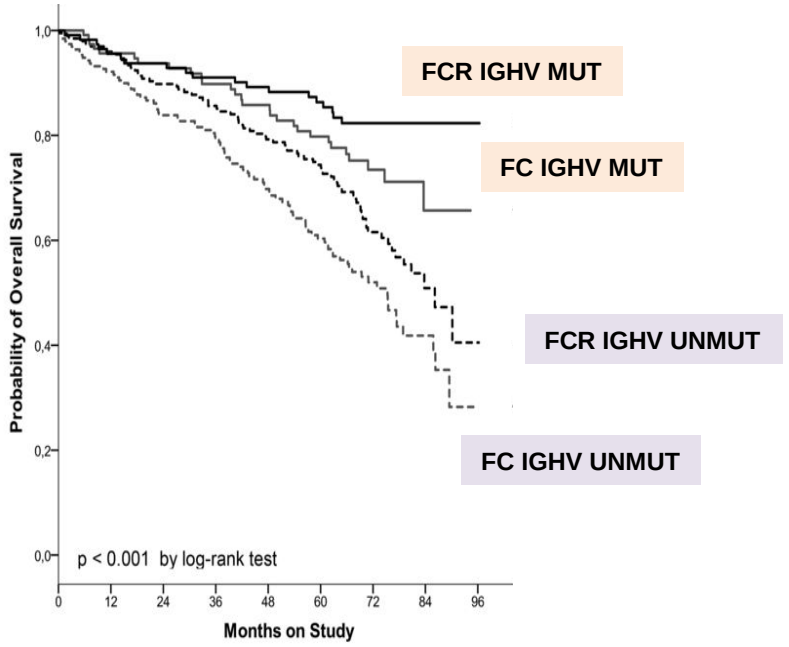
FISH



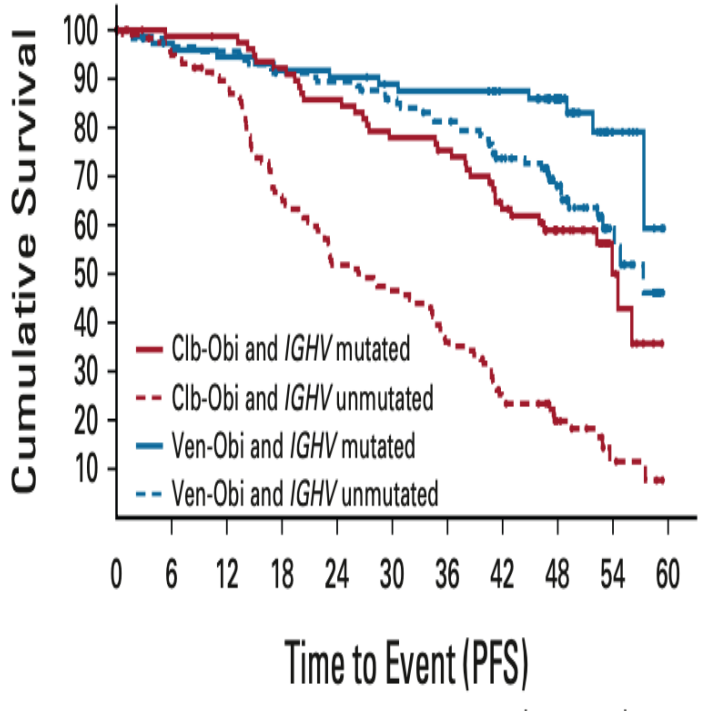
- Routinely detected by FISH del (11q), trisomy 12, del (13q) del (17p)

Dohner et al, NEJM, 2000

CLL Prognosis: Cytogenetic and IGHV Mutational status



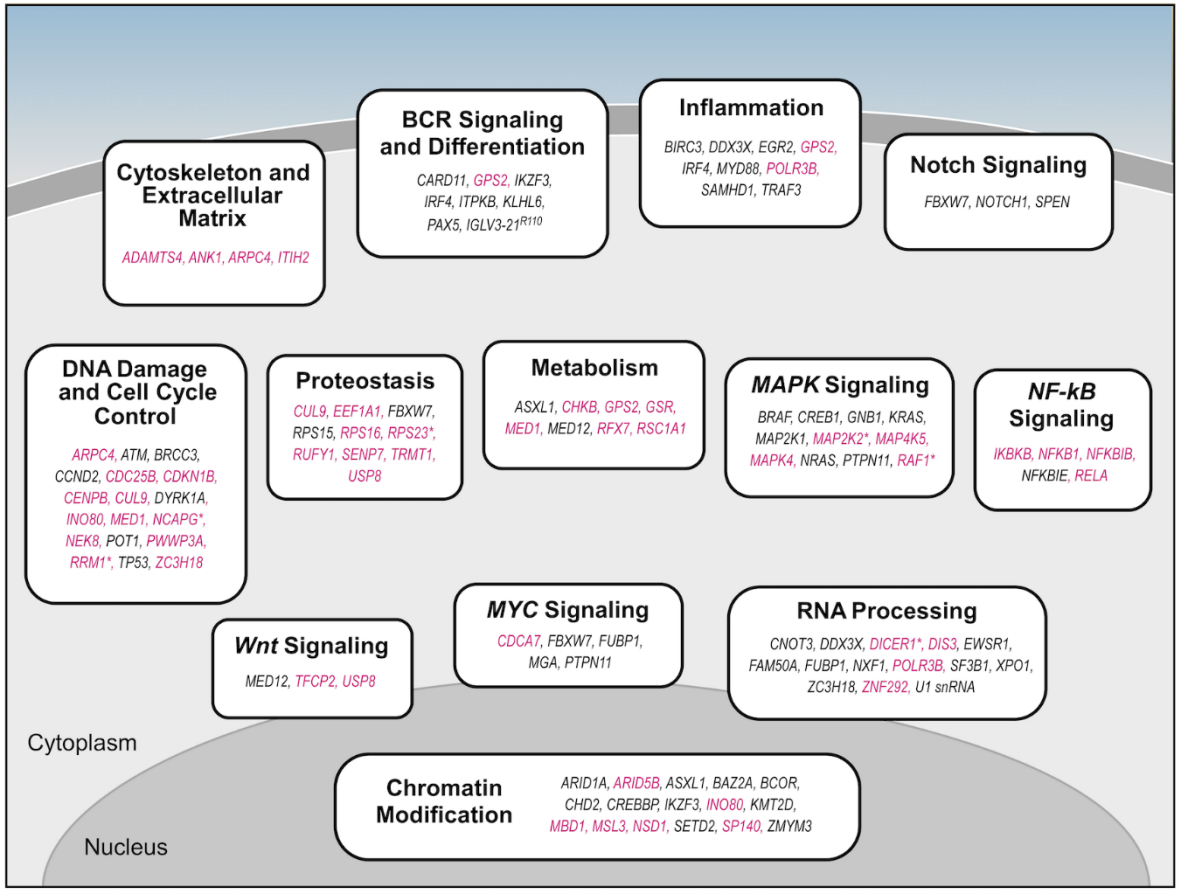
Fisher K et al Blood 2016 ;127:208-15



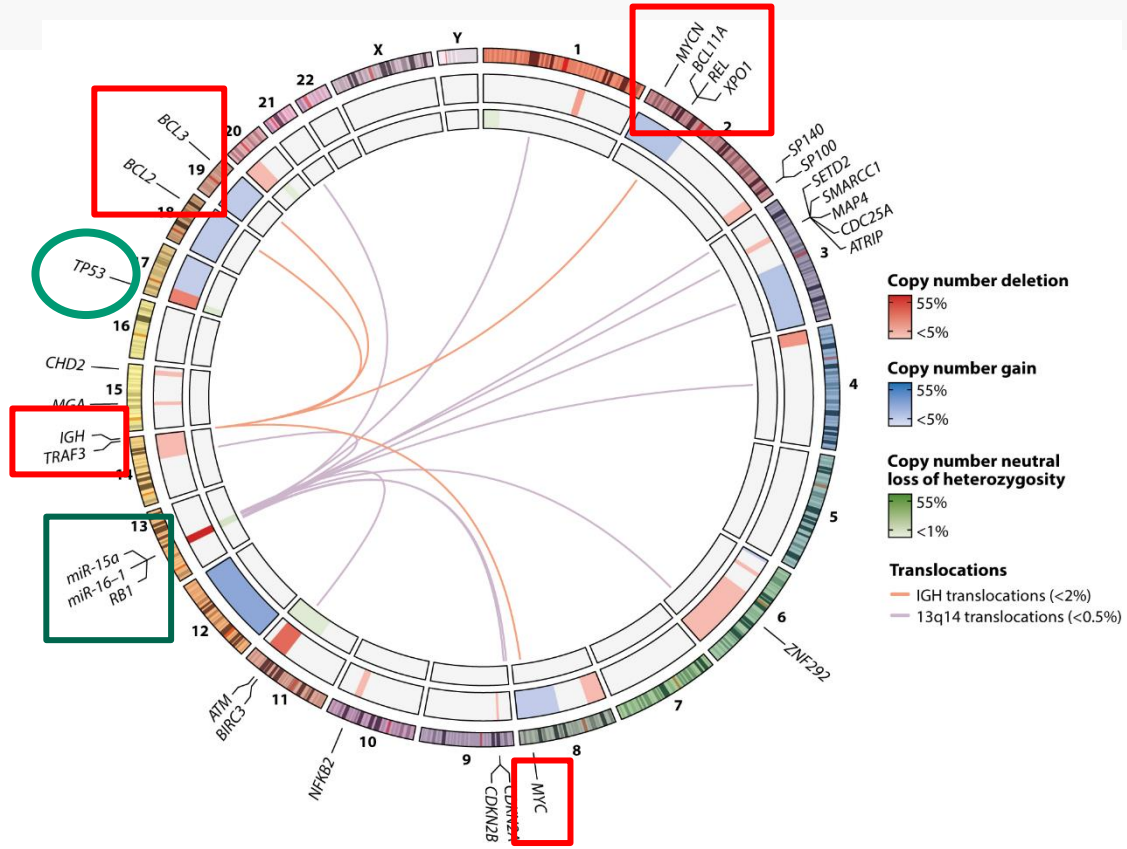
Al-Sawaf O et al J Clin Oncol 2021;39:4049-60

The Driver Genomic Landscape of CLL (WG/ES 1148 patients)

99 putative driver genes



105 recurrent CNA and few IGH translocations

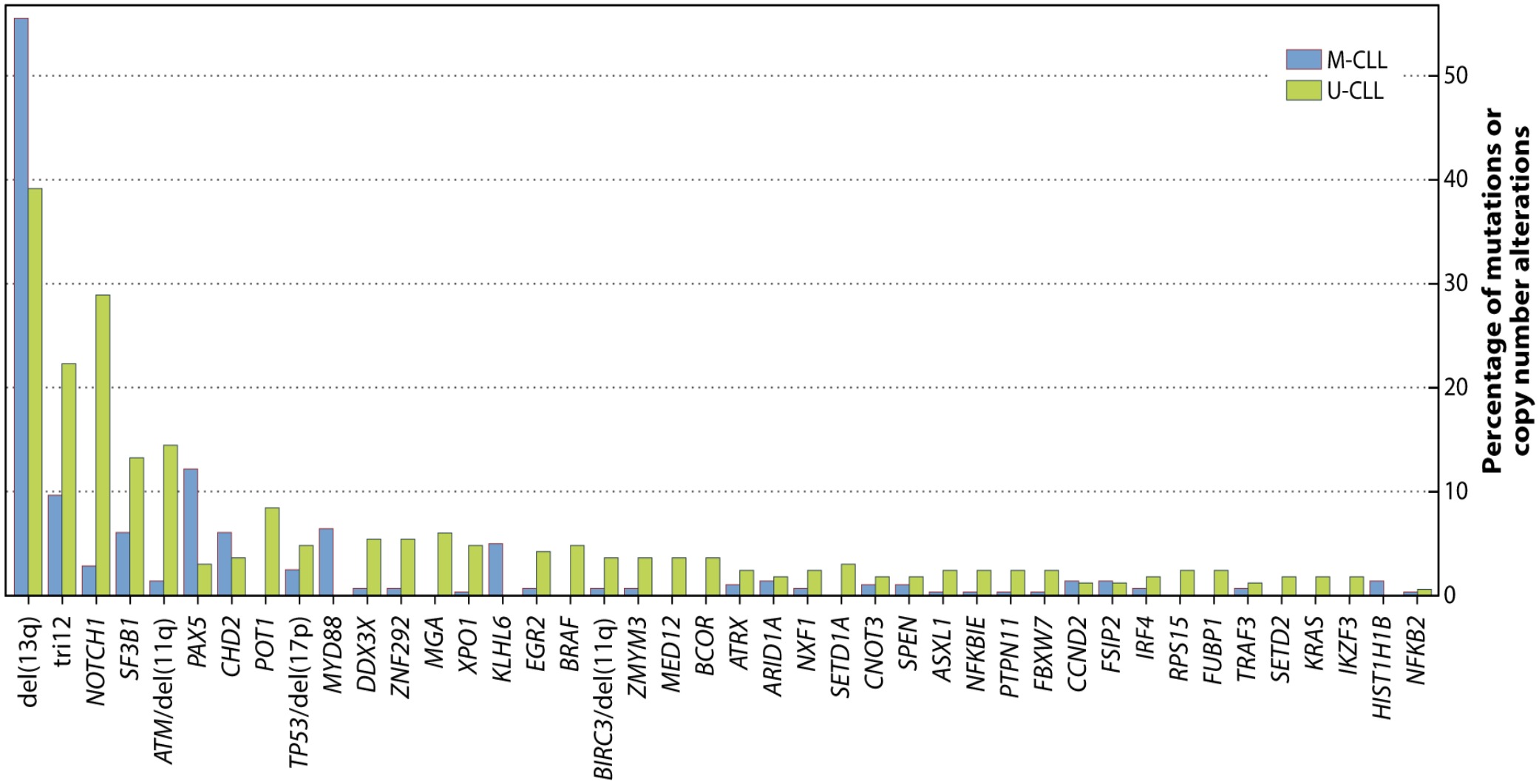


3.8% of patients lack a driver alteration!

Puente XA et al Nature 2015, Landau D et al Nature 2015;
Knisbacher, Lin, Hahn, Nadeu, Duran-Ferrer et al. Nat Genetics 2022

Numbers from Knisbacher, Lin, Hahn, Nadeu, Duran-Ferrer et al.Nat Genetics 2022
Image from Nadeu, Annu. Rev. Pathol. Mech. Dis. 2020.

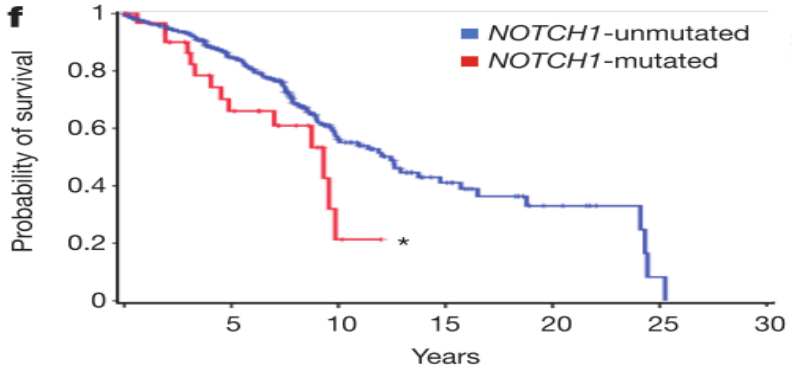
Inter- and intra-patient heterogeneity



Adapted from Nadeu, Annu. Rev. Pathol. Mech. Dis. 2020

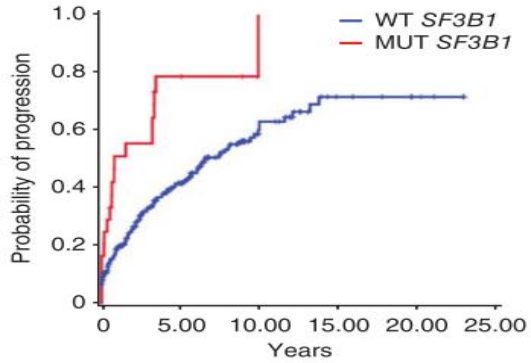
Clinical relevance of individual mutated genes in CLL

NOTCH1



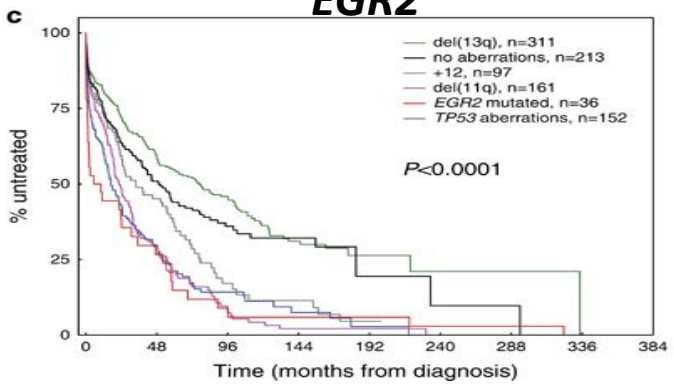
Puente *et al.* 2011, Nature

SF3B1



Quesada *et al.* 2011, Nat Genetics

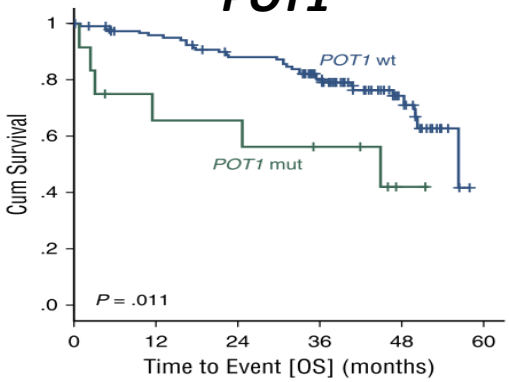
EGR2



Young *et al.* 2017, Leukemia

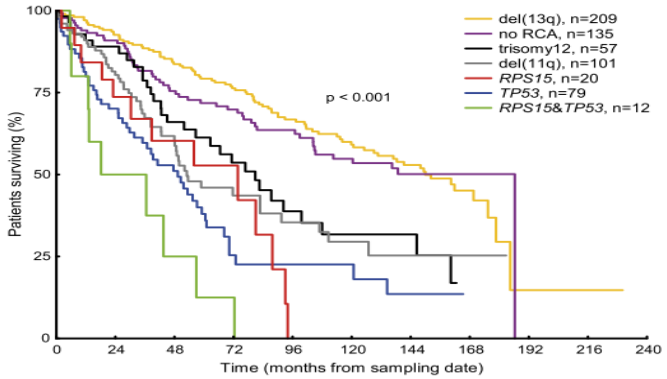
?

POT1



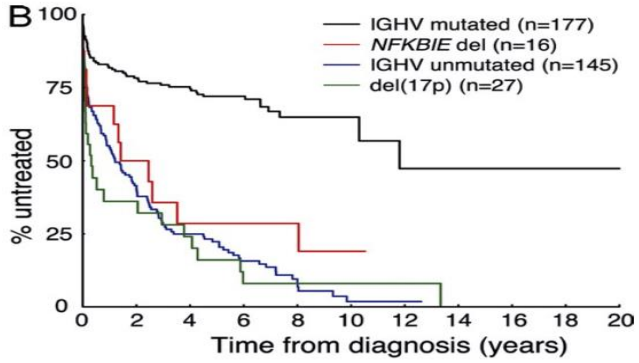
Herling *et al.* 2016, Blood

RPS15



Ljungström *et al.* 2015, Blood

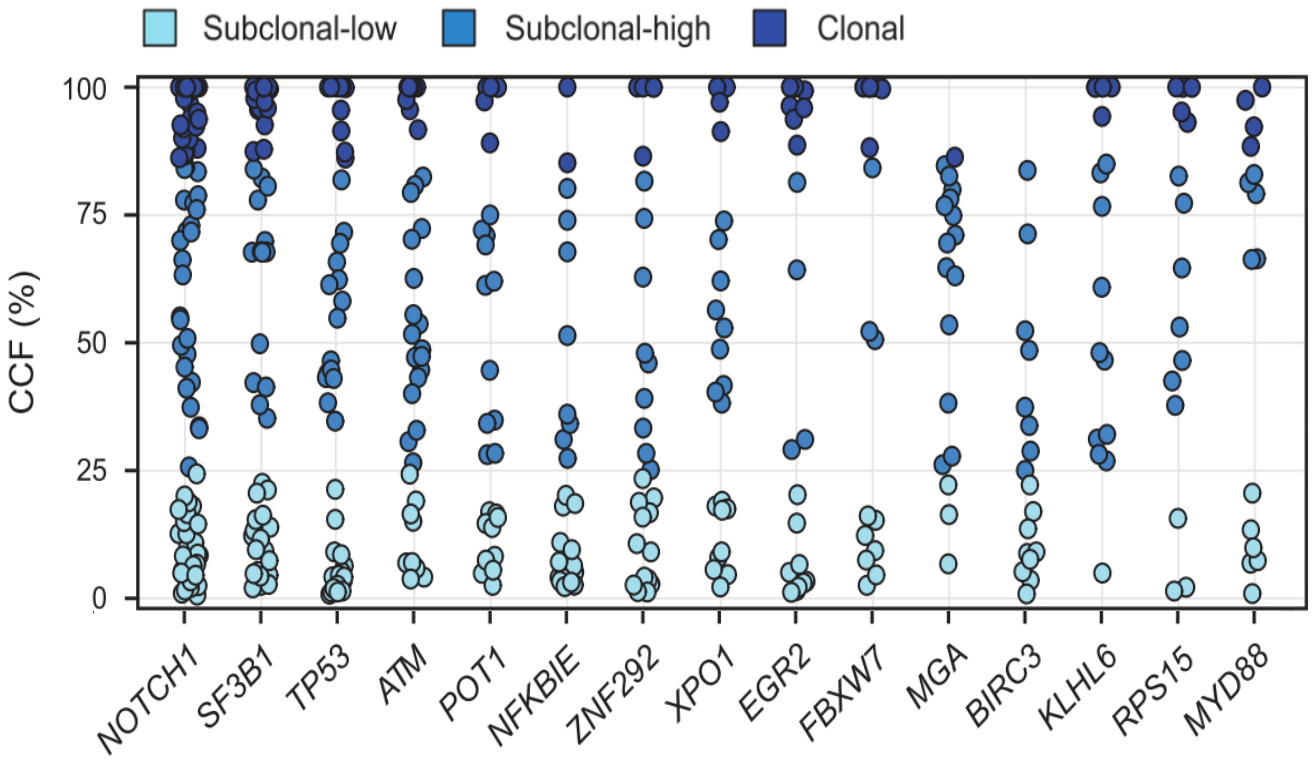
NFKBIE



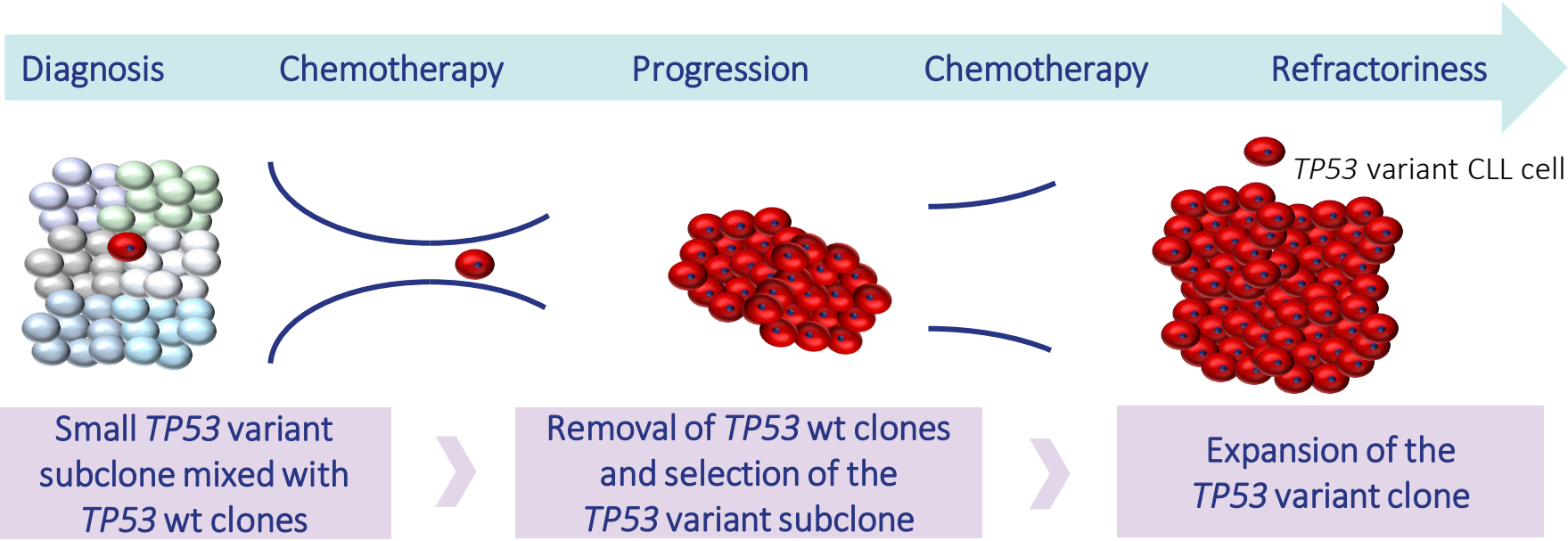
Mansouri *et al.* 2015, JEM

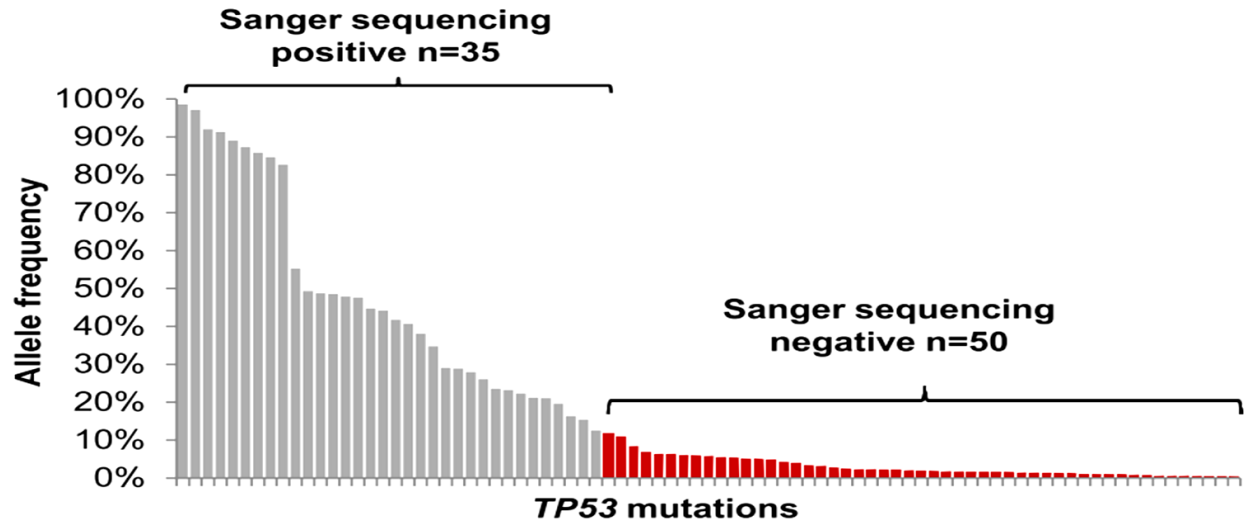
Inter- and intra-patient heterogeneity

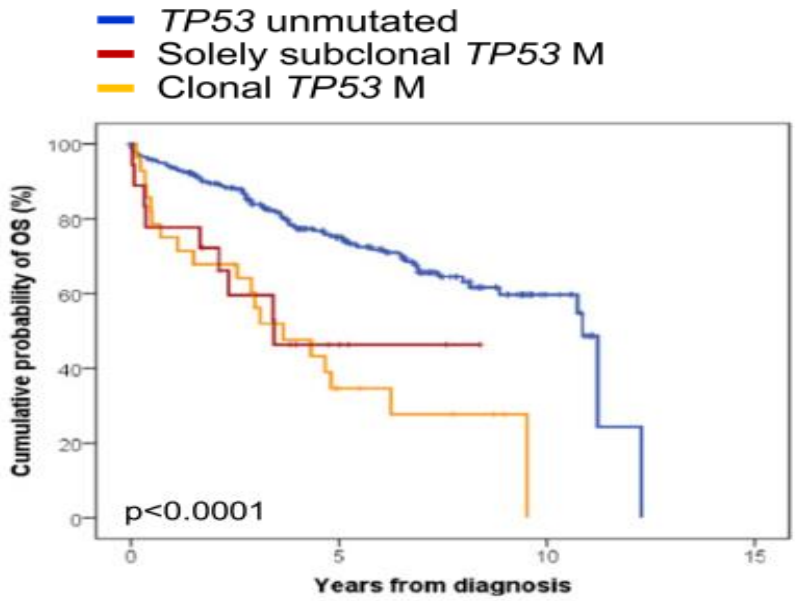
Trencadís on the staircase at Park Güell , Barcelona
(Antoni Gaudí)



Adapted from Nadeu, Leukemia 2018

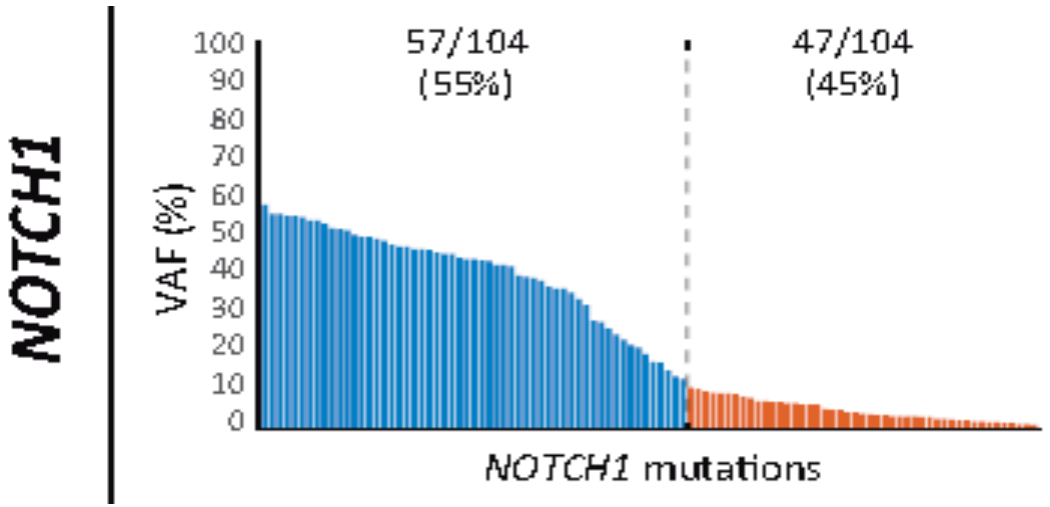


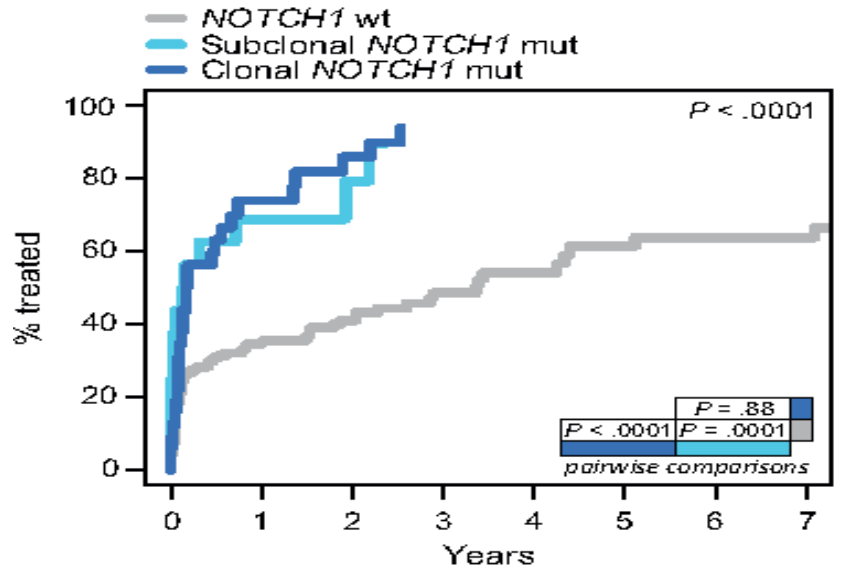


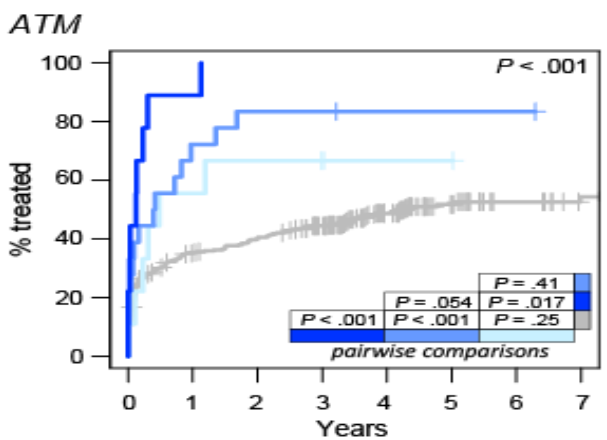


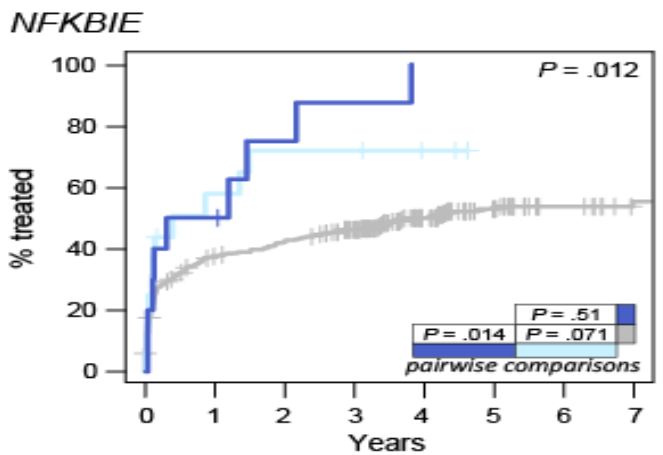
Rosi D et al Blood 2013

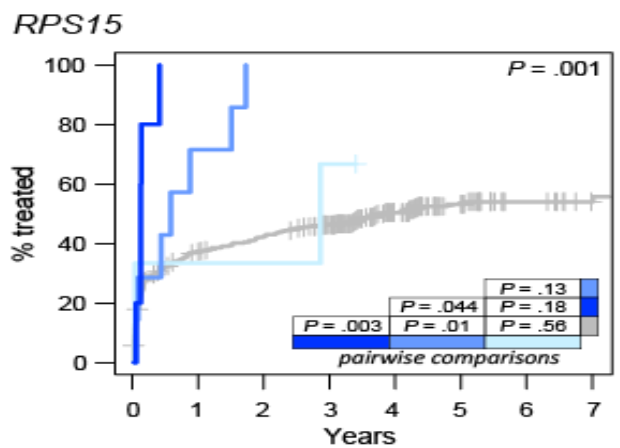
Clinical Impact of clonal and sublconal mutations in CLL







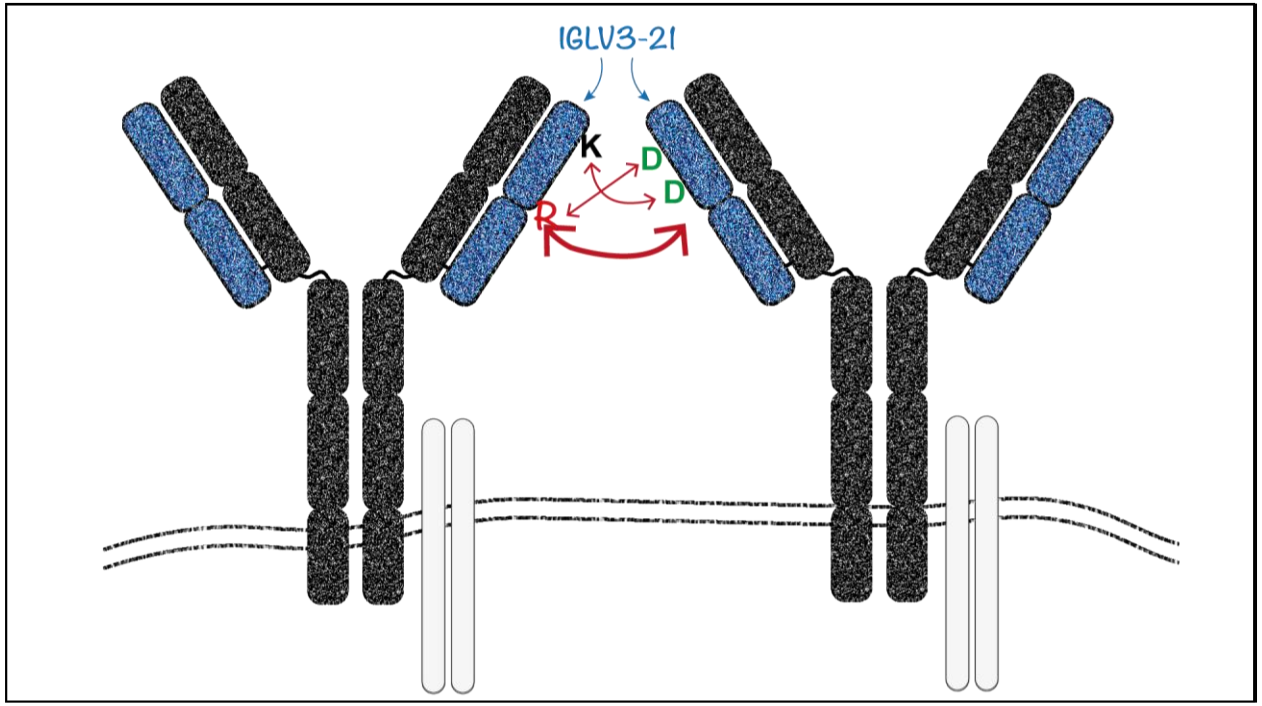




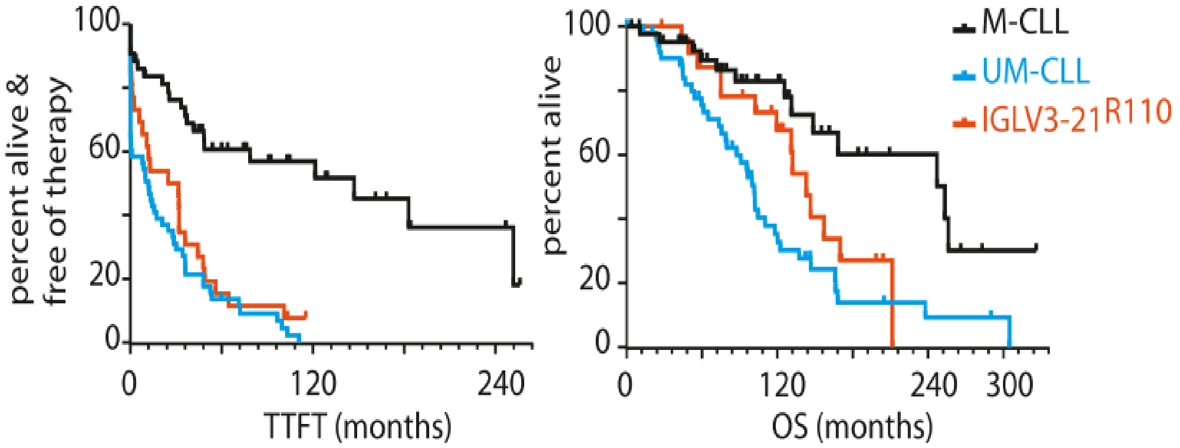
Nadeu F et al Blood 2016; Leukemia 2017

Beyond IGHV mutational status: IGLV3-21^{R110}

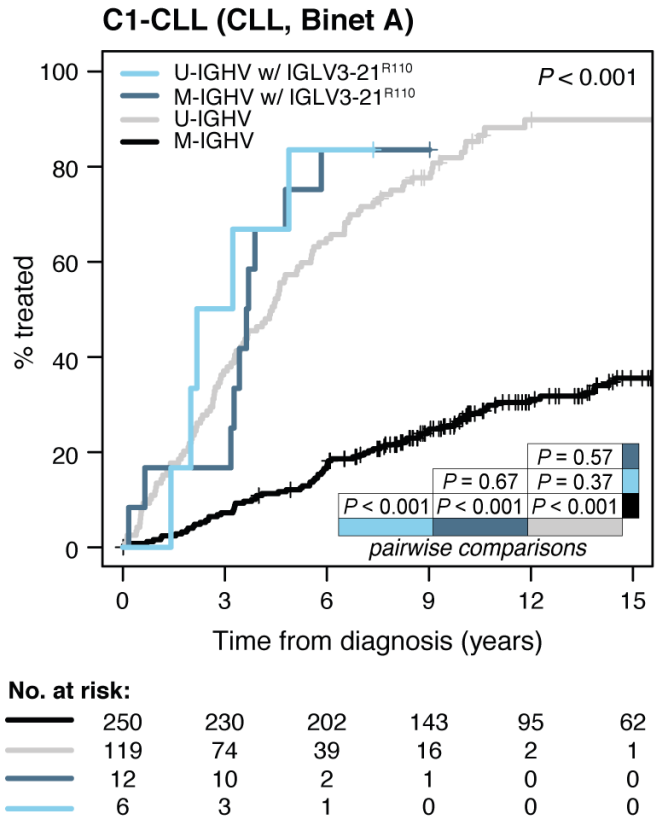
- 8-18% of cases carrying the IGLV3-21^{R110}.
- **50% M-IGHV, 50% U-IGHV**
- Poor outcome

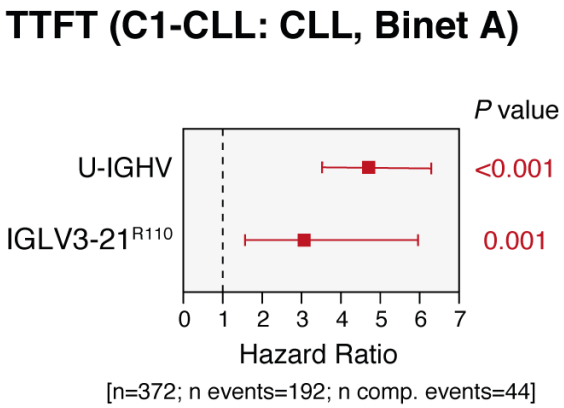


Minici, Nat Commun 2017 [drawing based on Maity, PNAS 2020]
Dühren-von Minden M, Nature 2012



IGVL3-21 ^{R110} CLL has a clinical evolution similar to IGHV-unmutated CLL independently of the IGHV mutational status

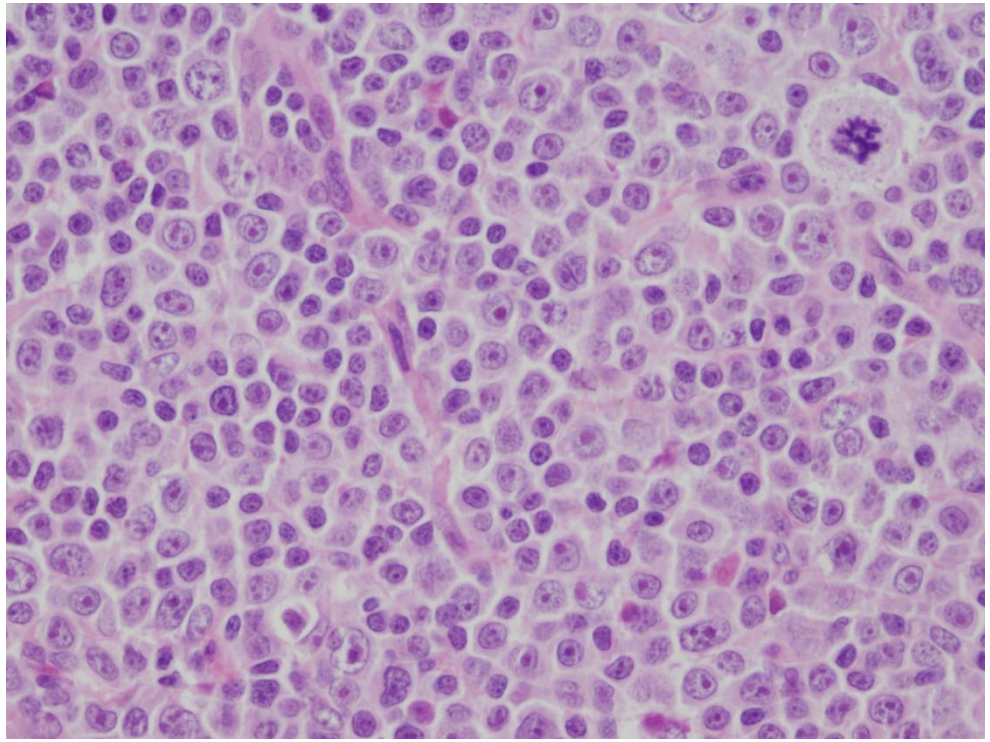




Nadeu F et al Blood 2020

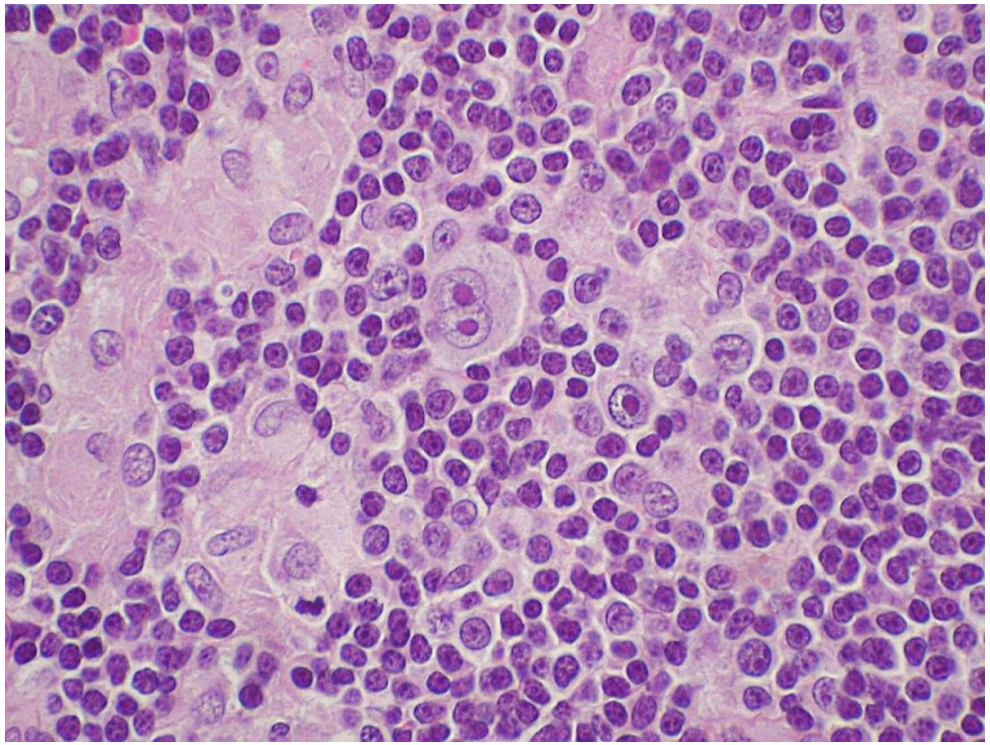
Richter's syndrome: Pathology

DLBCL



~ 90% of cases

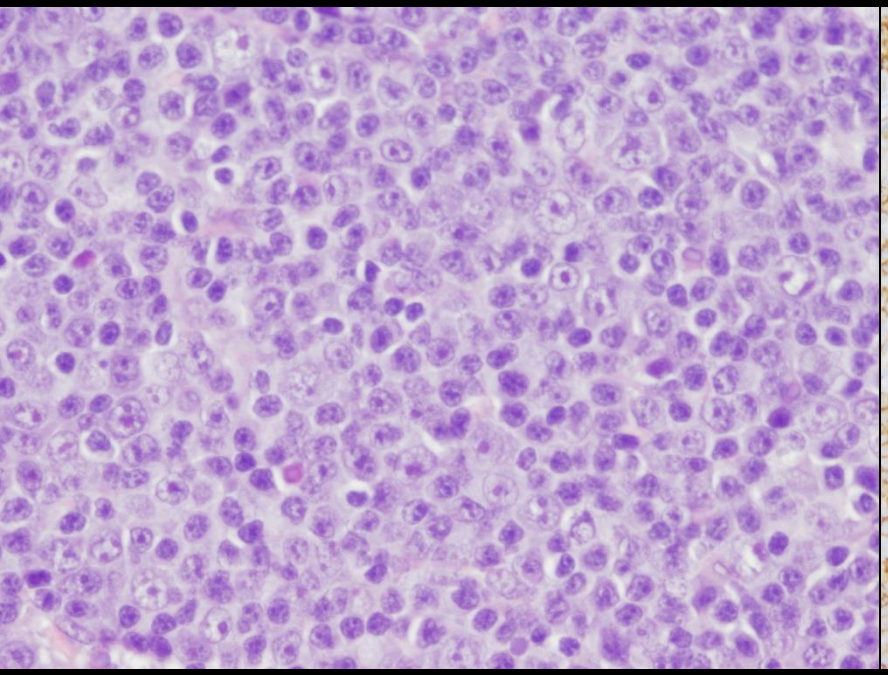
Hodgkin Lymphoma

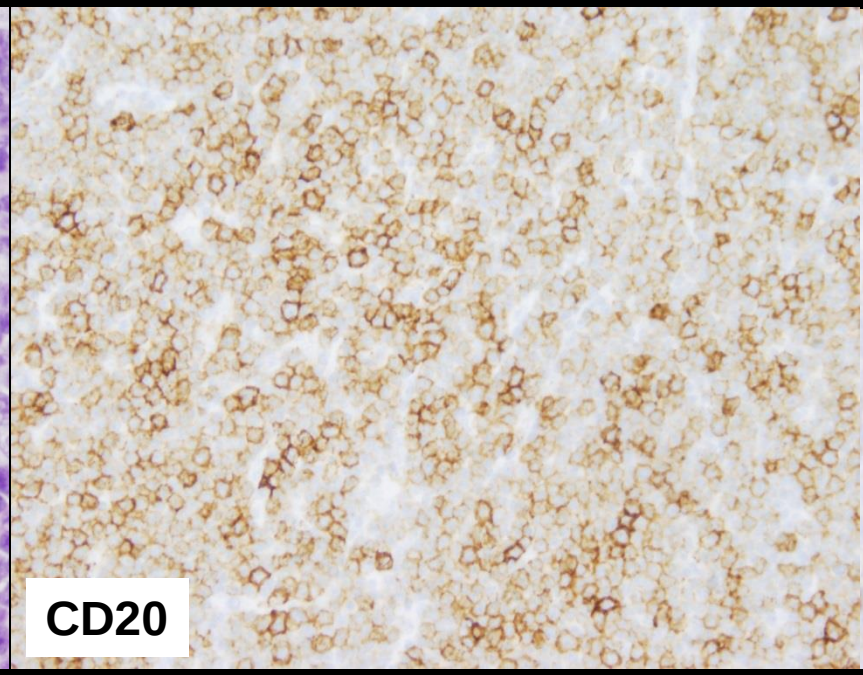


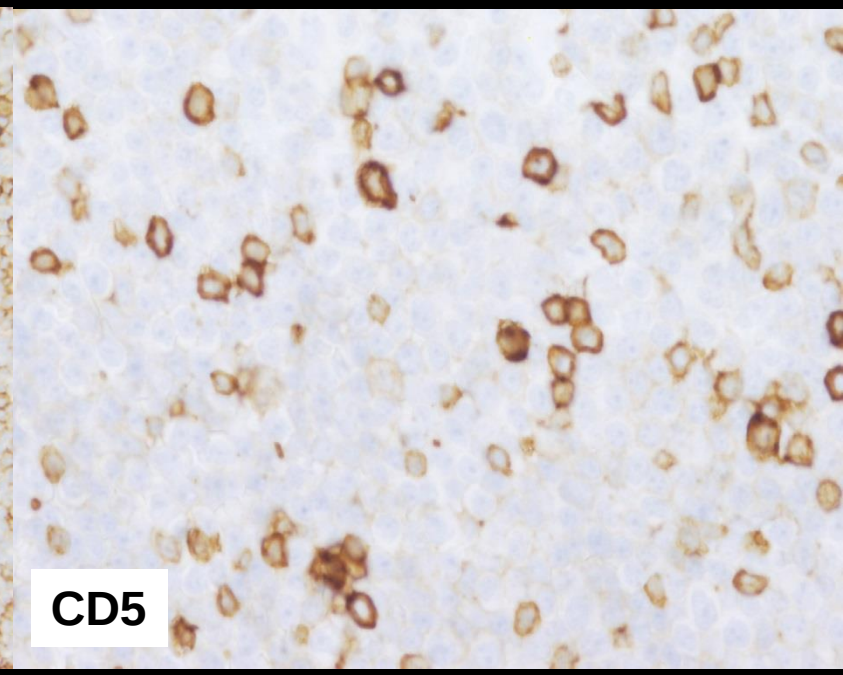
~ 10% of cases

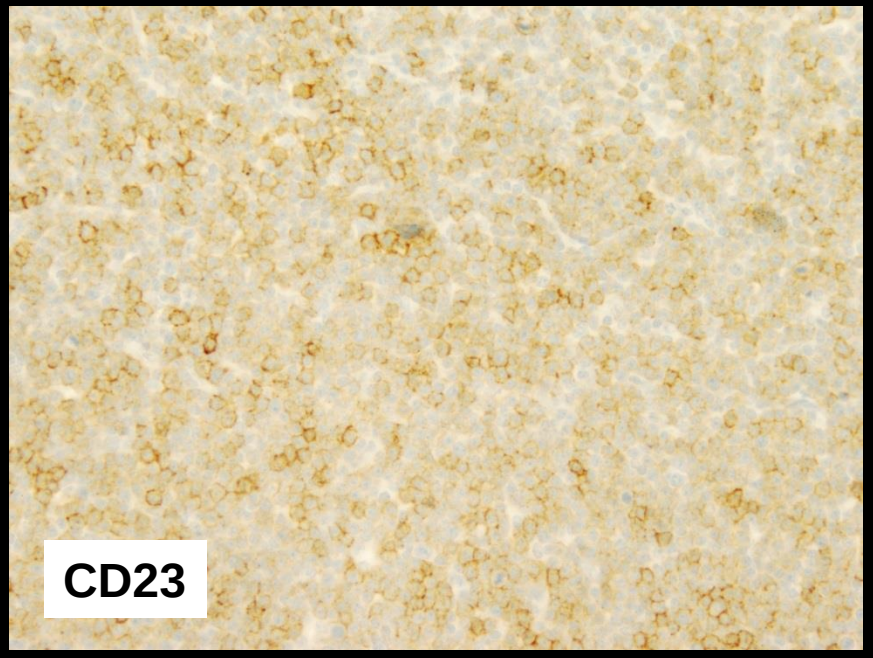
DLBCL: diffuse large B-cell lymphoma

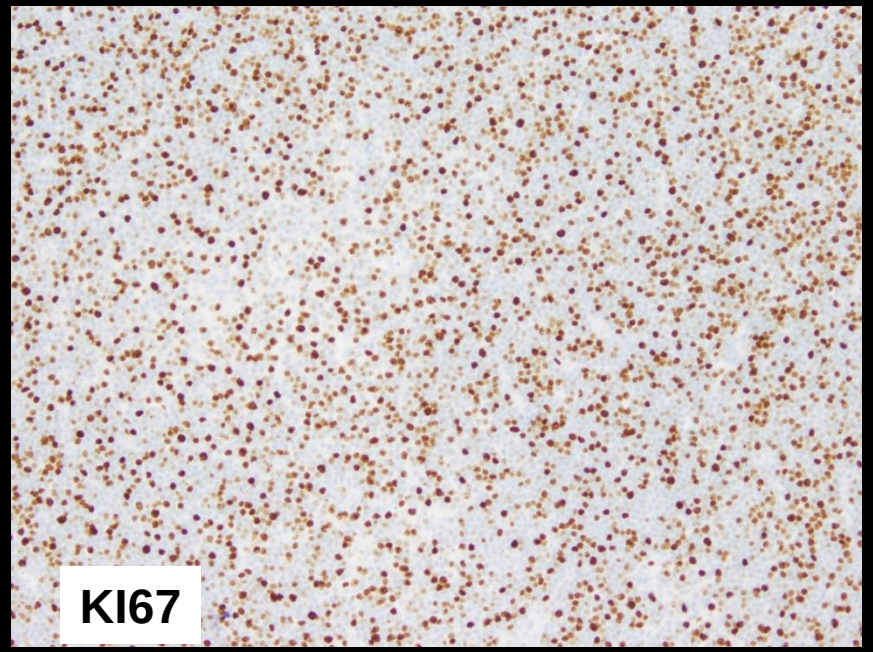
Rossi et al., Blood 2018; 131:2761-72





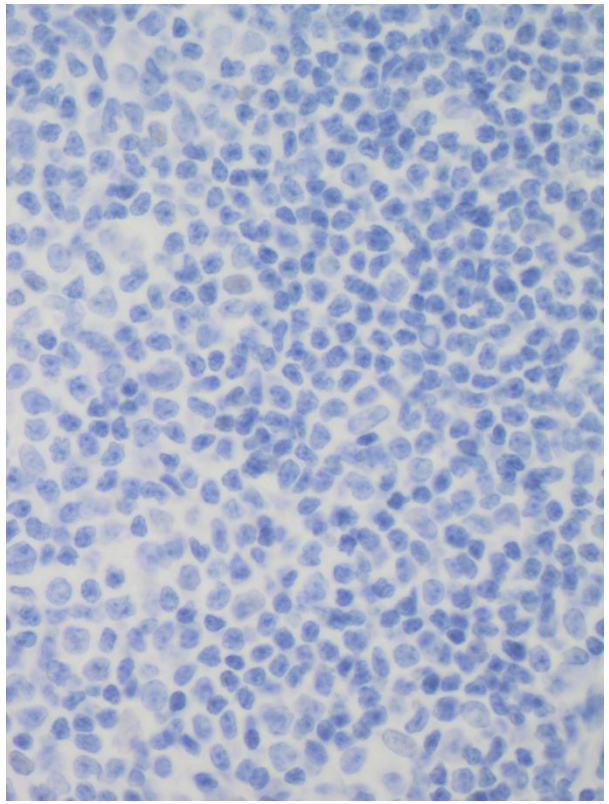


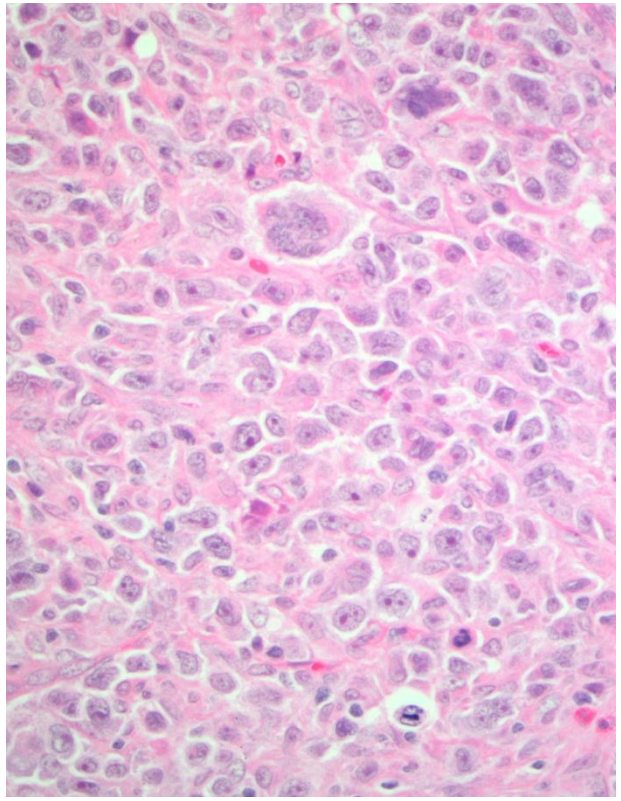


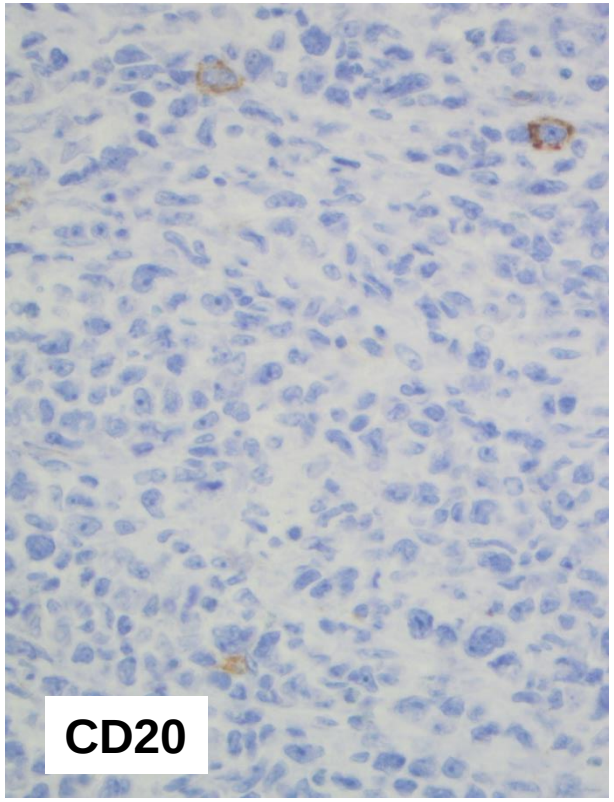


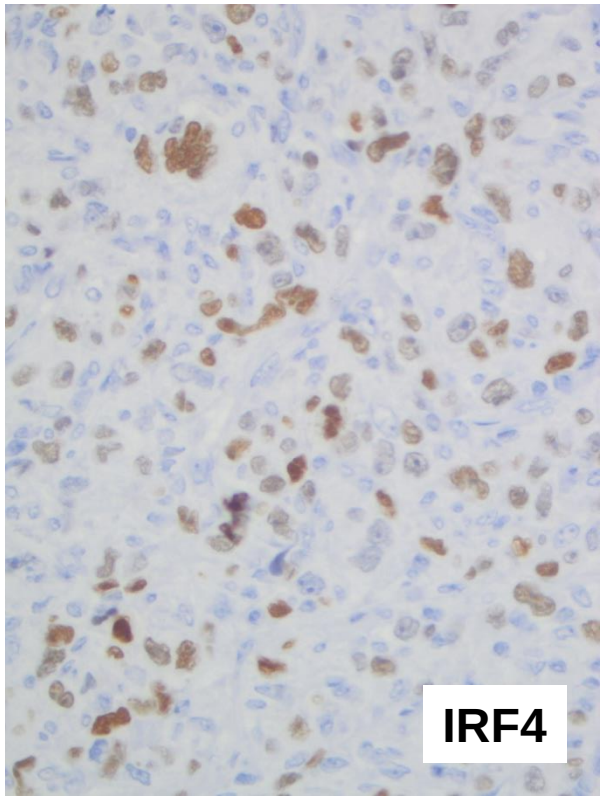
Unpublished data. Image provided by E Campo

Novel patterns of CLL transformation under ibrutinib: Terminal (Plasmablastic) differentiation





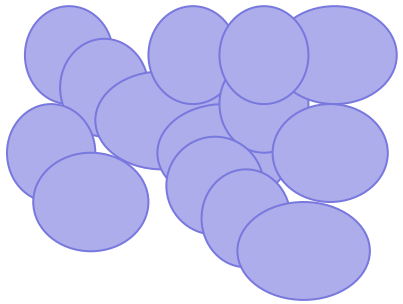




Unpublished data. Image provided by E Campo

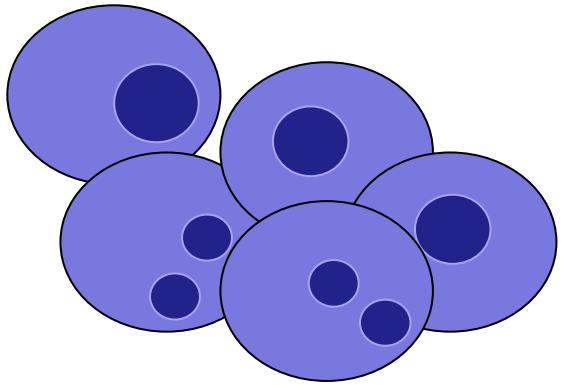
Richter's Transformation: Clonal Relationship

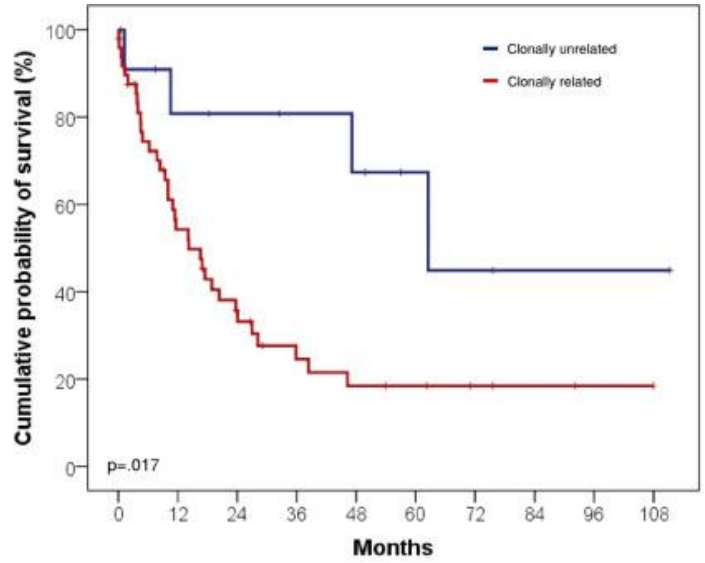
Clonally related



~ 80% DLBCL
~ 30% HL

80% IGHV Unmutated
Median Survival 14 months



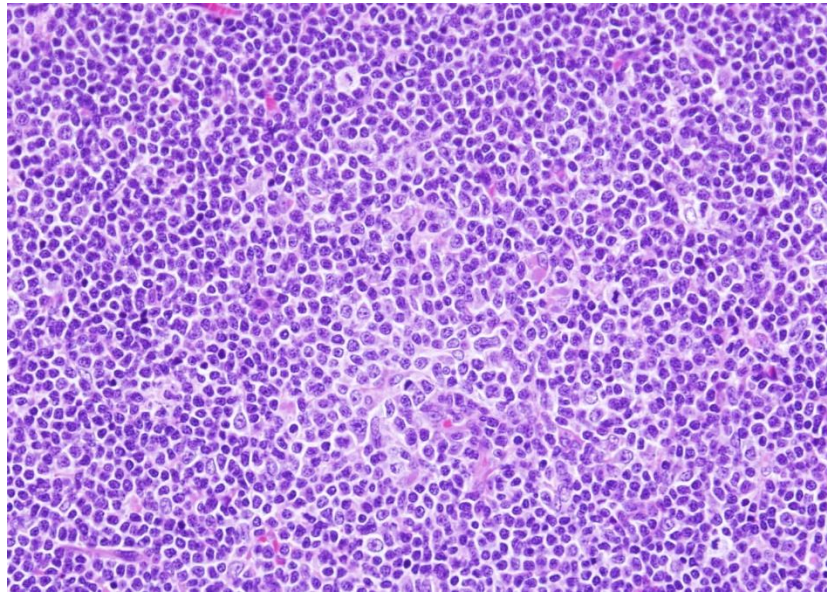


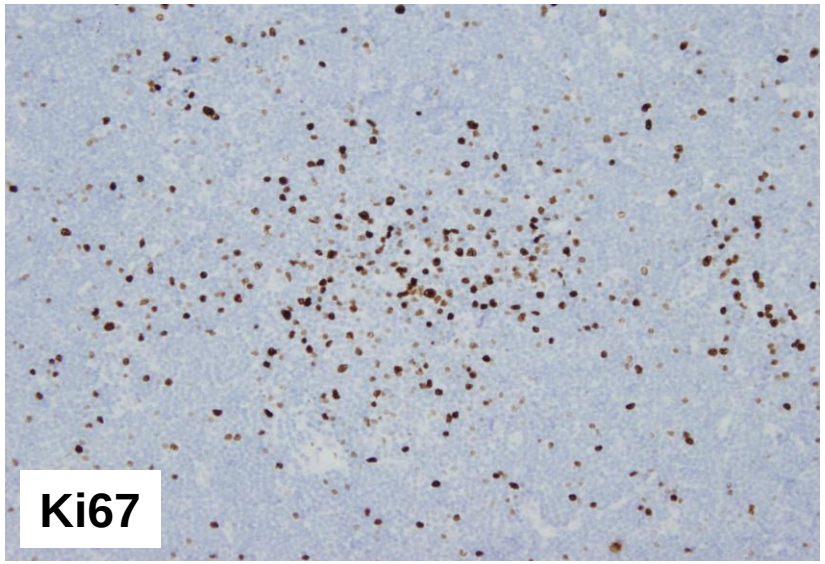
DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma

Mao et al Am J Surg Pathol 2007; 1605-14
Rossi D et al Blood 2011; 117:3391-401

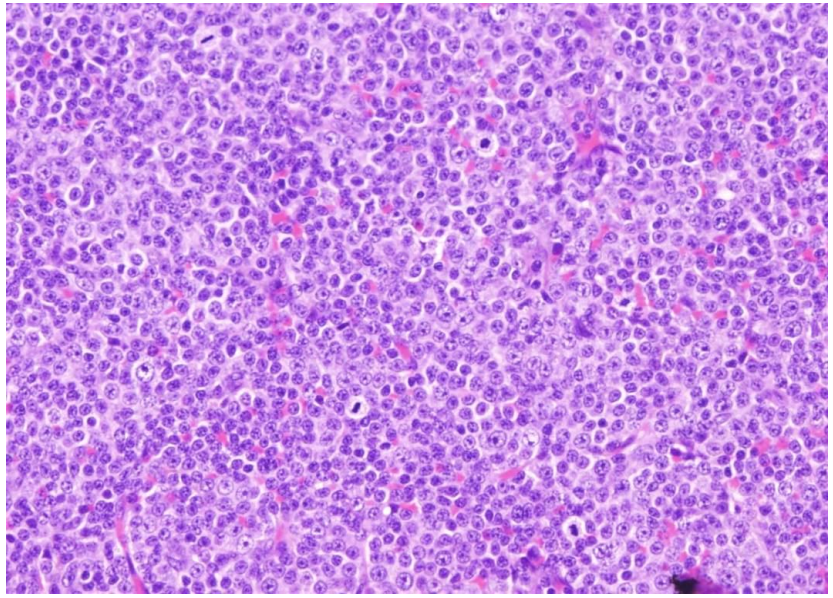
CLL with expanded proliferation centers: “Accelerated” CLL

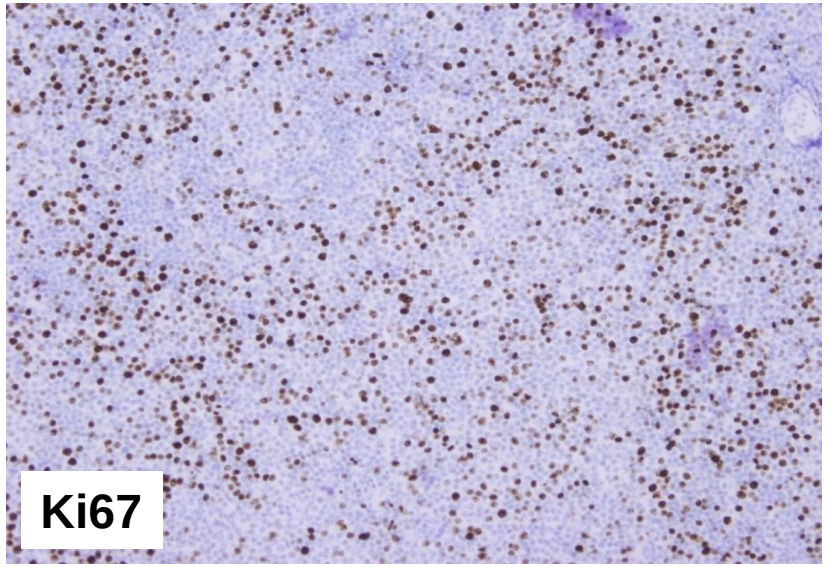
Conventional





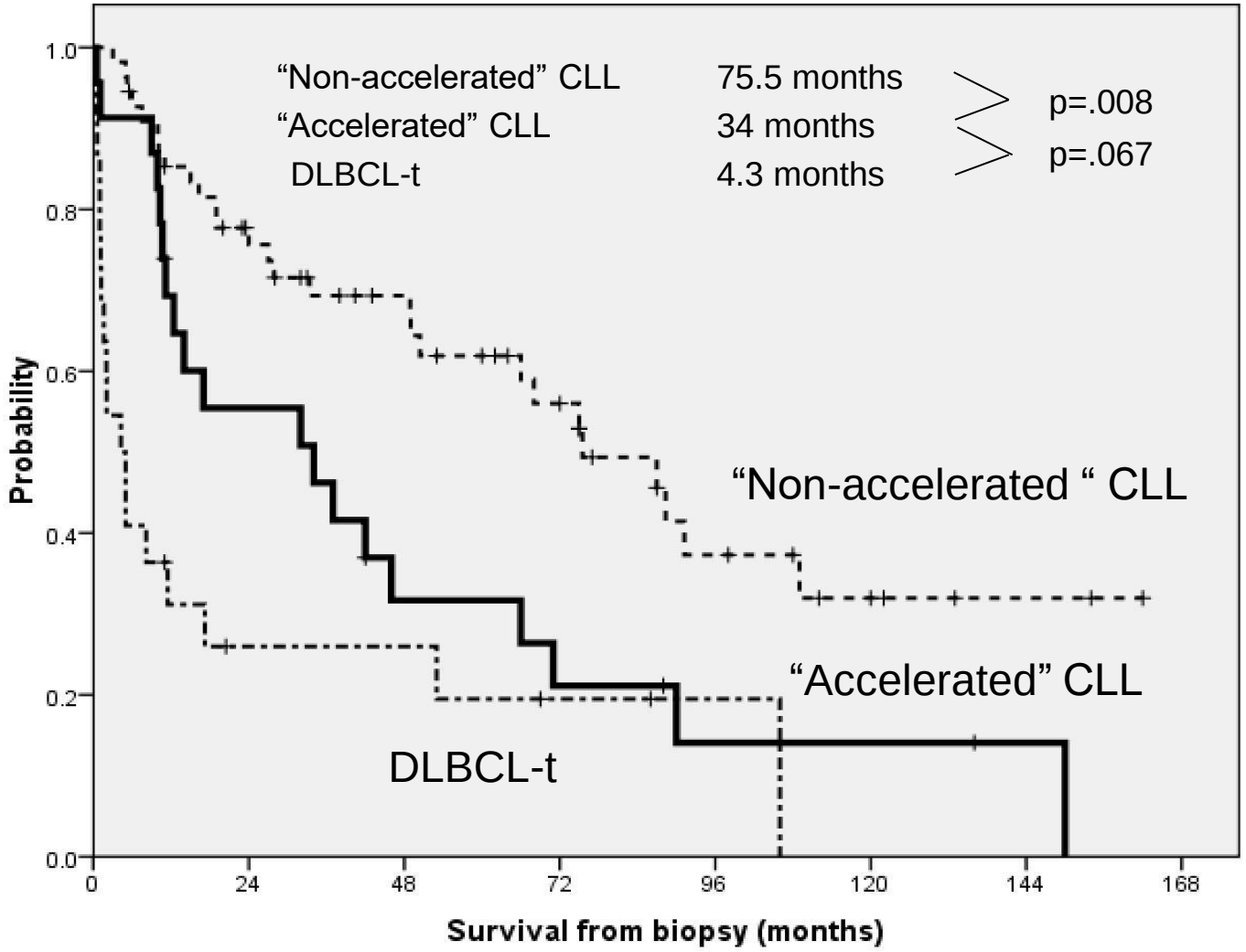
Accelerated





Unpublished data. Image provided by E Campo

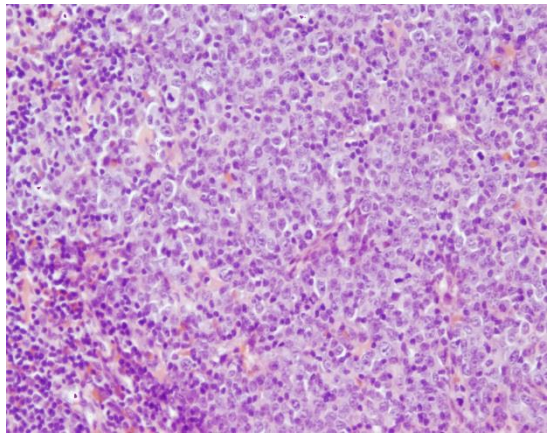
Overall Survival of Patients with Conventional and Accelerated CLL and DLBCL Transformation

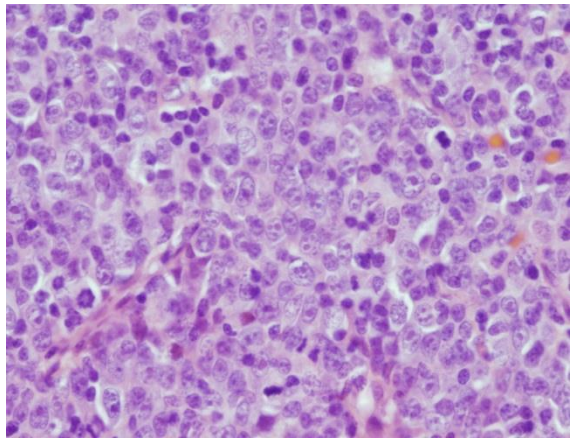


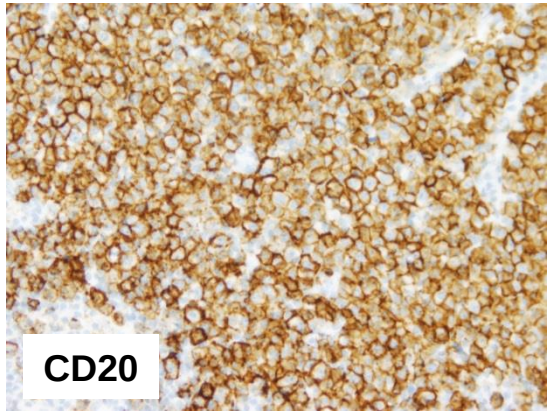
DLBCL-t: diffuse large B-cell lymphoma transformation

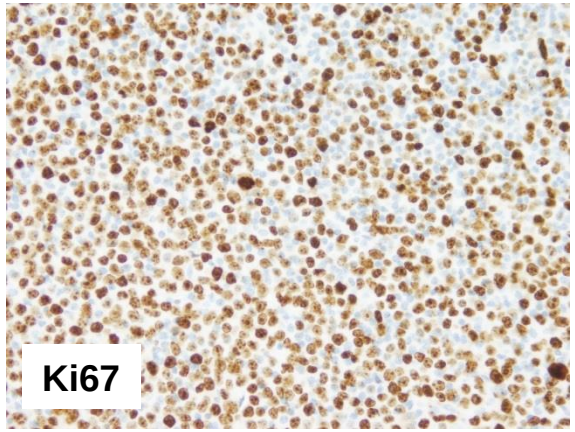
Giné et al Haematologica 2010; 1526-33

“Pseudo-Richter”
A pitfall in CLL treated with ibrutinib









- Unmutated IGHV CLL
- Adverse genetic alterations: TP53
- Multiple prior lines of therapy

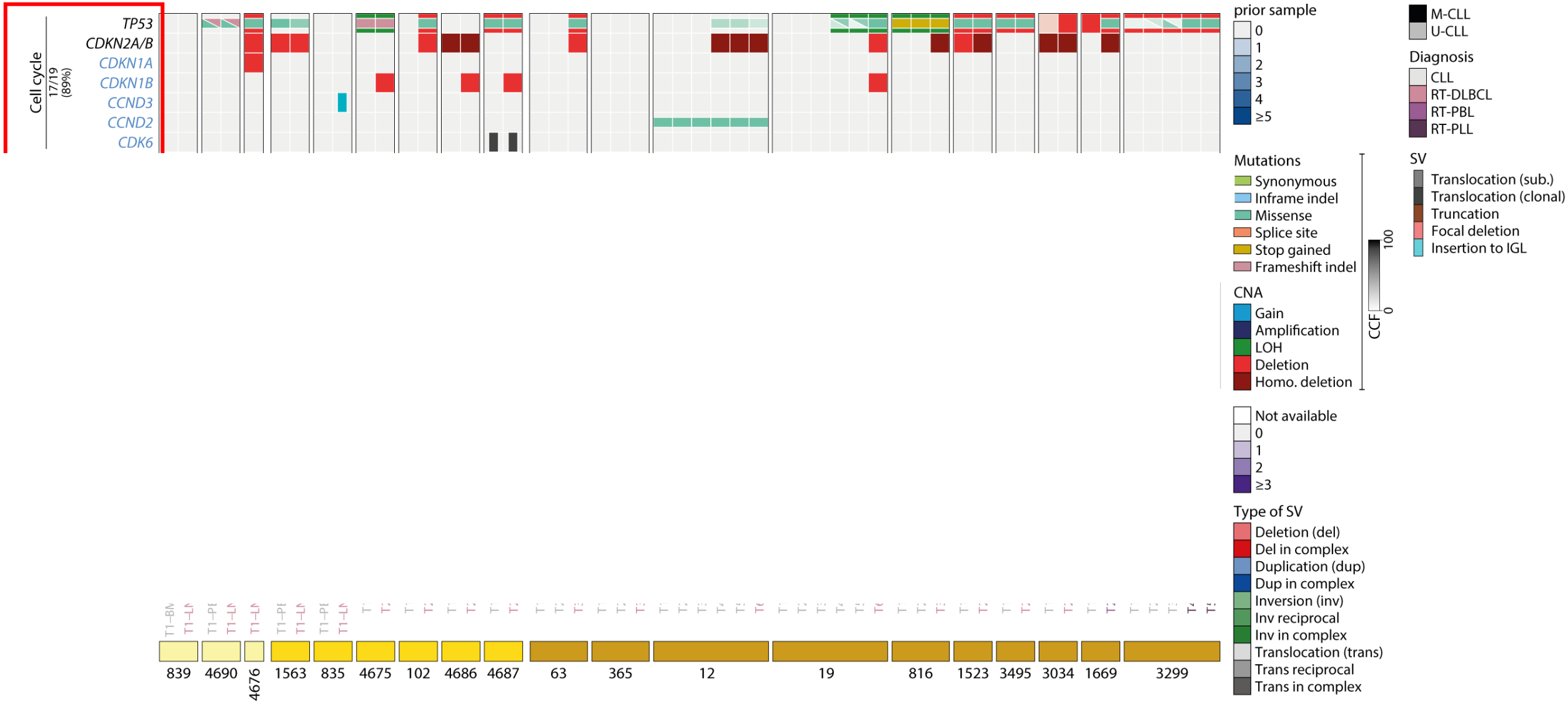
- Ibrutinib for 10-48 months
- Ibrutinib hold (10-40 days) for different reasons: Surgery
- Evidence of progression: Nodal enlargement
- **Morphology of highly proliferative “DLBCL”**

- Re-introduction of ibrutinib led to clinical response
- Re-biopsy 3-6 months: CLL
- Follow-up without evidence of progression **7-30 months**

DLBCL: diffuse large B-cell lymphoma

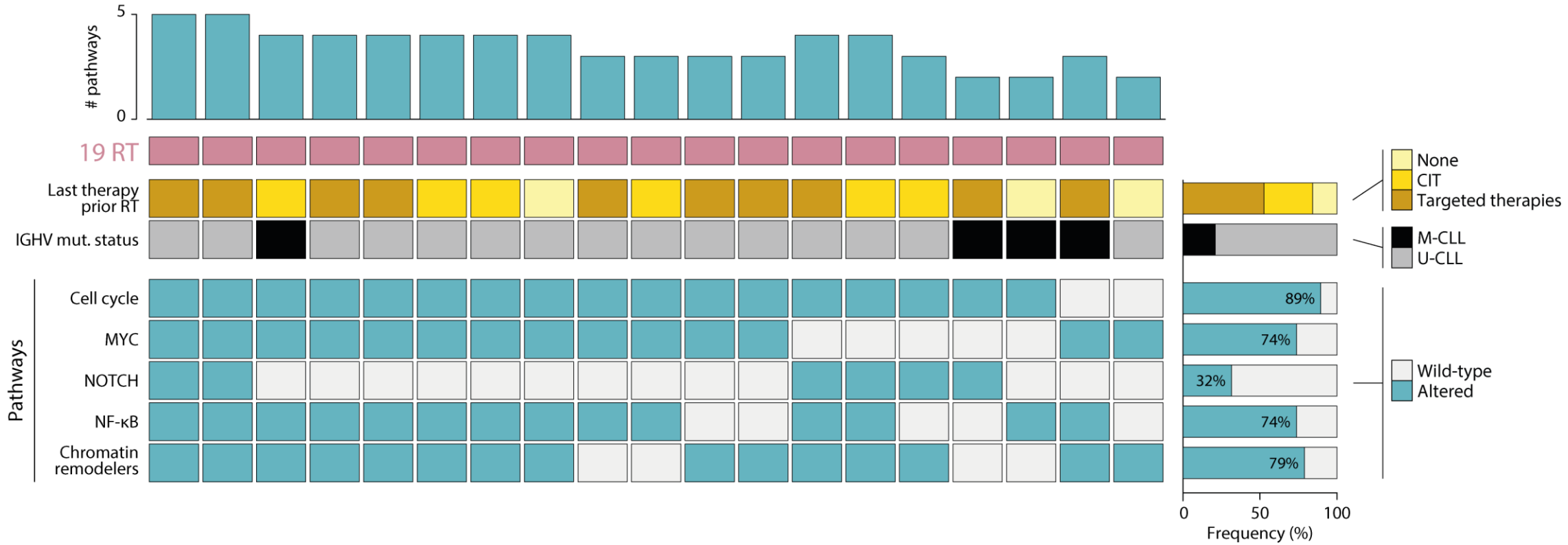
Slonim et al. Br J Haematol 2020; 191(1):e22-e25; Hample et al. Blood Adv 2020; 4(18):4508-4511

Similar chromosomal landscape of RT after different treatment modalities



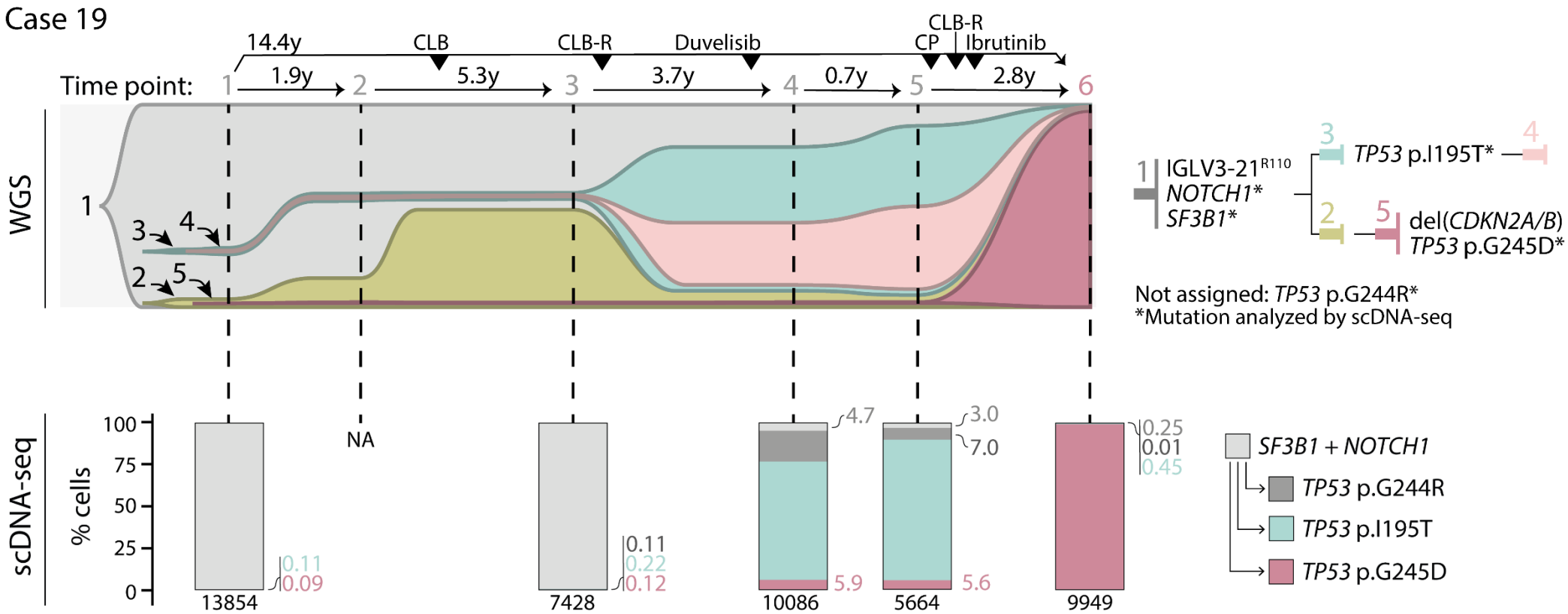
Nadeu F, Royo R, et al, Massoni-Badosa R, Playa-Albinyana H, Garcia B et al *Nat Medicine* 2022

Pathways Genetically Altered in RT



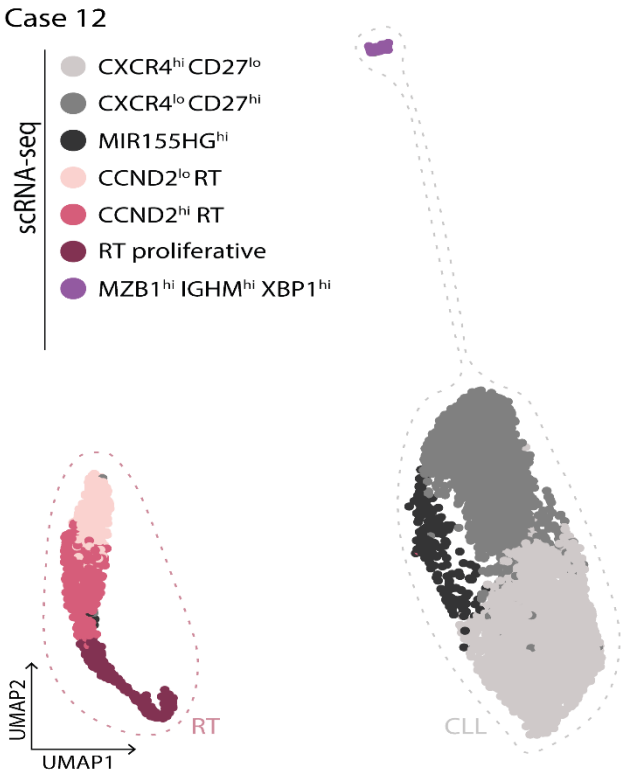
Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

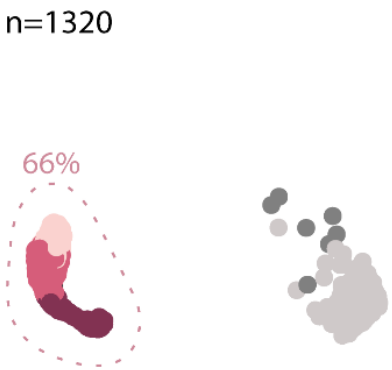
Early seeding of RT: tracking driver mutations by scDNA-seq



Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

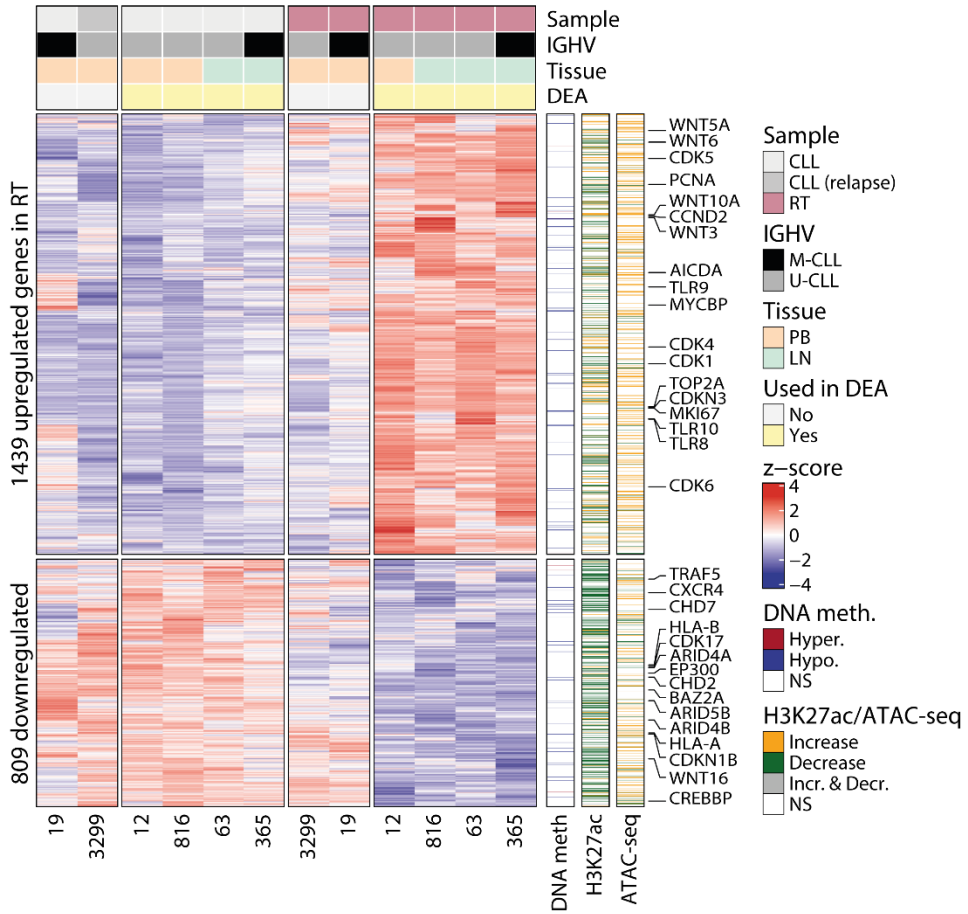
Single cell analysis detects early seeding of subclonal relapses and transformation in CLL

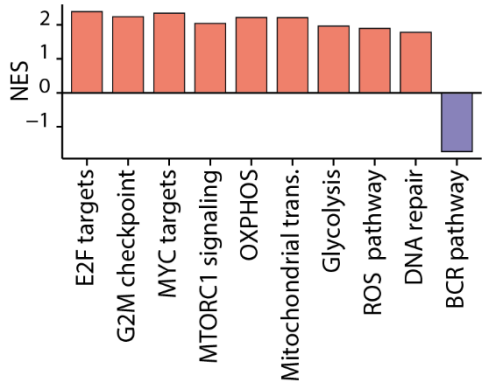


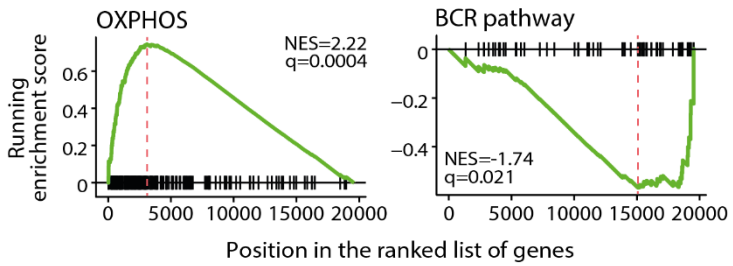


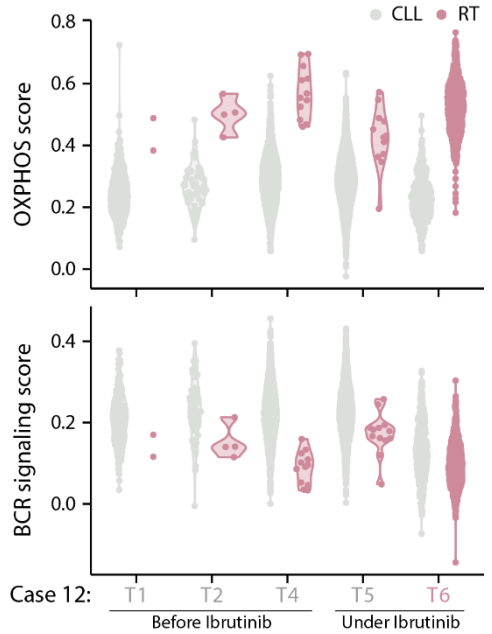
Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

The OXPHOS^{high}-BCR^{low} transcriptional axis of RT









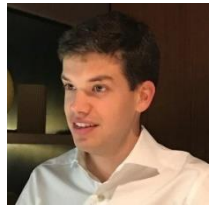
This axis might explain the selection and rapid expansion of small RT subclones under therapy with BCR inhibitors

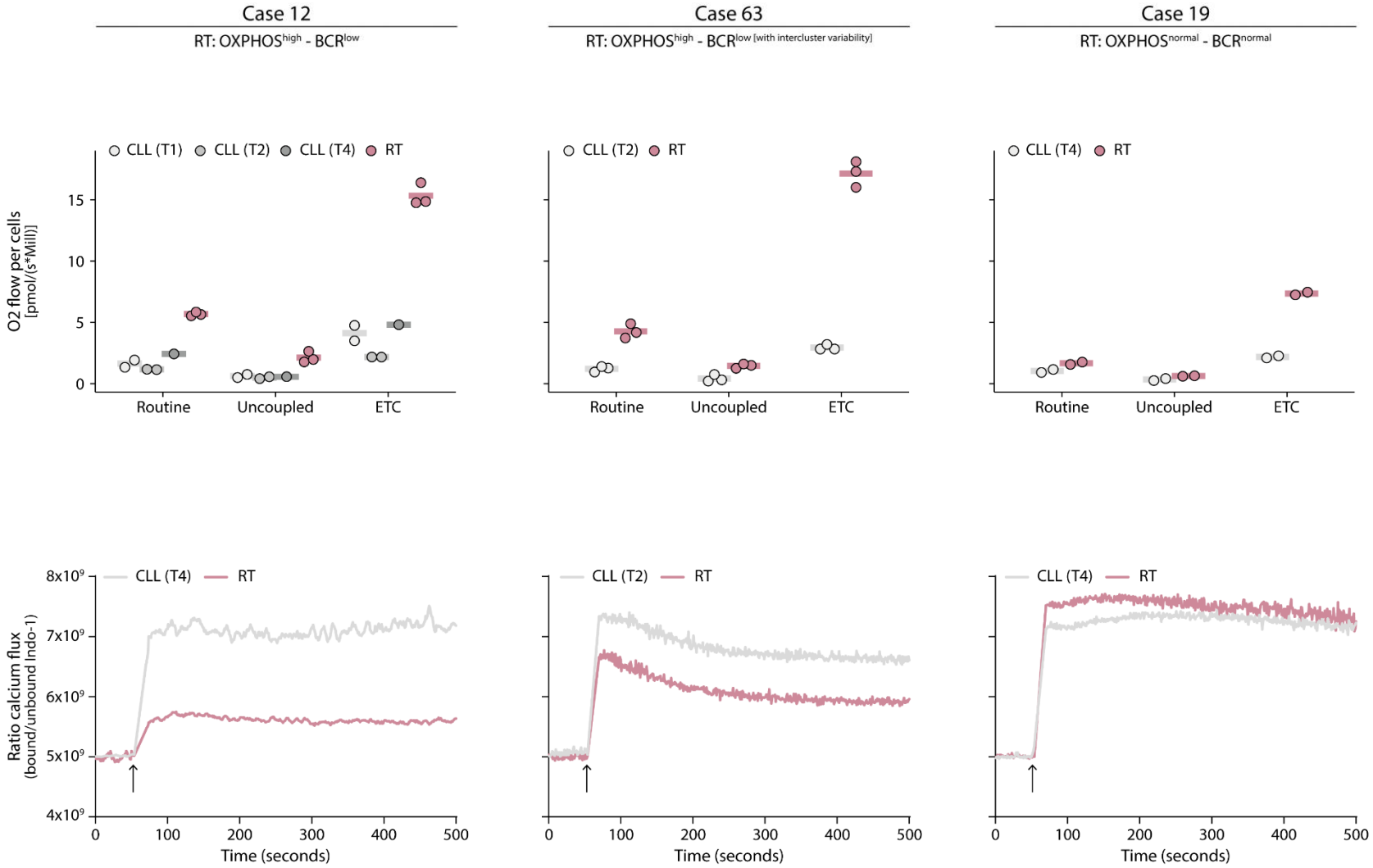
Monti Blood 2005; Caro Cancer Cell 2012; Norberg Cell Death Differ 2017.

RT: Richter transformation; BCR: B-cell receptor

Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

Cellular respiration and BCR signaling in RT cells





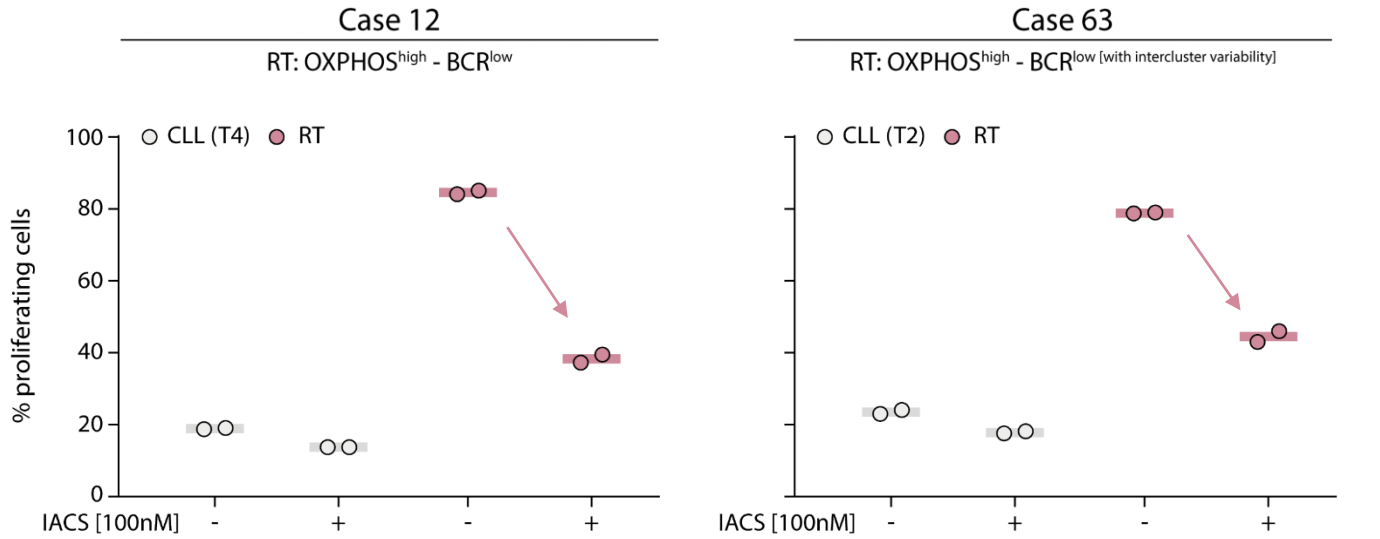
RT: Richter transformation; BCR: B-cell receptor

Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

The OXPHOS^{high} phenotype of RT is of potential therapeutic value

OXPHOS pathway can be exploited therapeutically.

Caro Cancer Cell 2012; Norberg Cell Death Differ 2017; Molina Nat Med 2018;
Vangapandu Oncotarget 2018; Zhang Sci Transl Med 2019; Ravera Sci Rep 2020; Chen Nat Commun 2021.



RT: Richter transformation

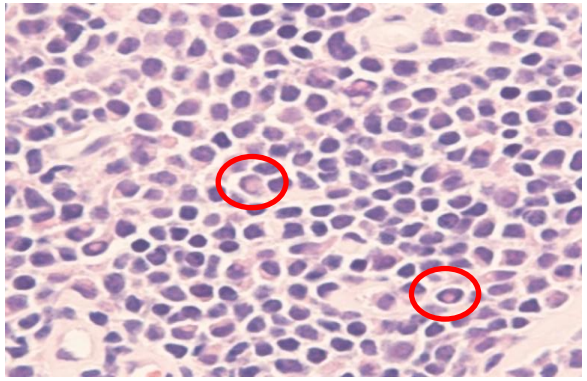
Nadeu et al. Nat Medicine 2022; 28(8):1662-1671

Lymphoplasmacytic lymphoma (LPL)

IgM (Waldenström's macroglobulinemia) and non-IgM (IgG, IgA)

- **Neoplasm of small B-lymphocytes, plasmacytoid cells and plasma cells in bone marrow and sometimes lymph nodes and spleen.[1]**
- **IgM paraprotein frequent but not required for diagnosis[1]**
- **Diagnosis requires abnormal lymphoplasmacytic aggregates in the bone marrow and evidence of clonal B-cells and plasma cells:**
  - Even when the aggregates represent **<10%** of cellularity of the bone marrow (ICC)[2]
  - **≥10%** of the bone marrow cellularity (WHO-5ed) [3]

1. Swerdlow SH, et al. Blood. 2016;127(20):2375-90.
2. Campo E, Jaffe ES, et al. Blood. 2022; 140(11):1229-1253.
3. Alaggio R et al Leukemia 2022; 36(7):1720-1748



Lymphoplasmacytic Lymphoma

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

BTK

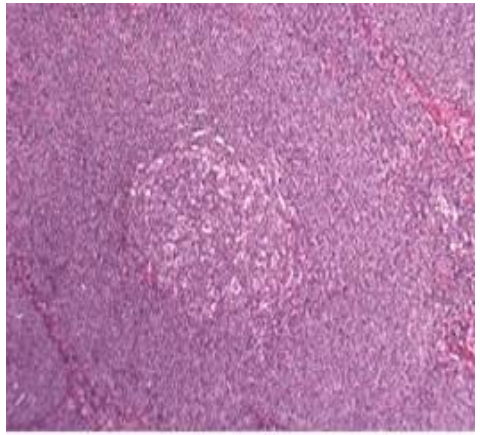
Patients treated with Ibrutininb

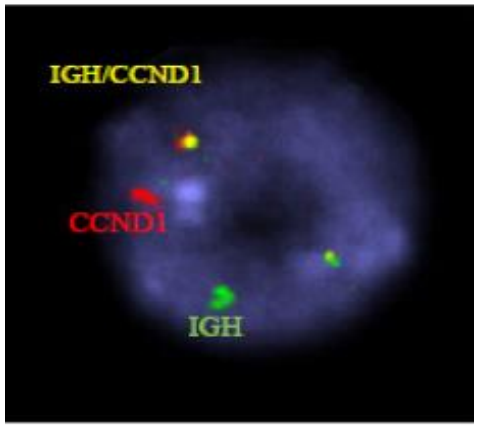
Mutations before clinical progression

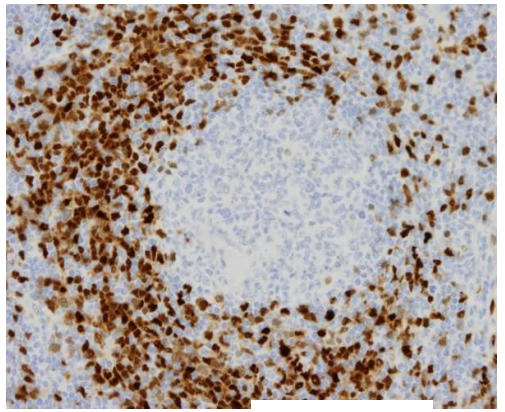
- Molecular studies for *MYD88* and *CXCR4* mutations are strongly encouraged in the workup of suspected LPL
  - Need to be interpreted in the global context of the disease
    - Absence of a *MYD88* mutation does not exclude the diagnosis of LPL (even IgM)

Tiacci 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.; Xu L et al Blood 2017*

Mantle Cell Lymphoma



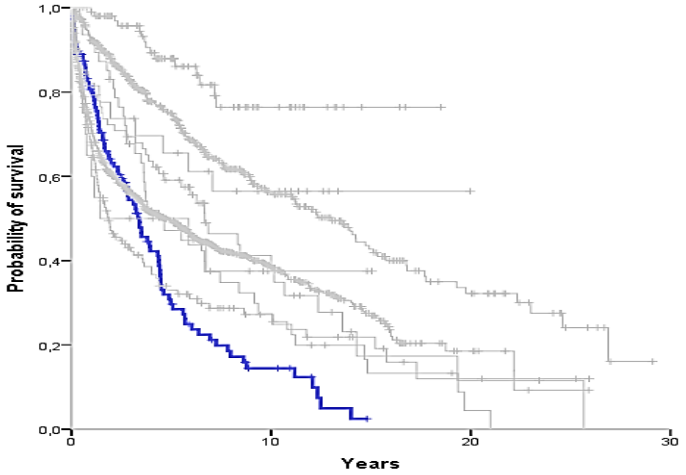




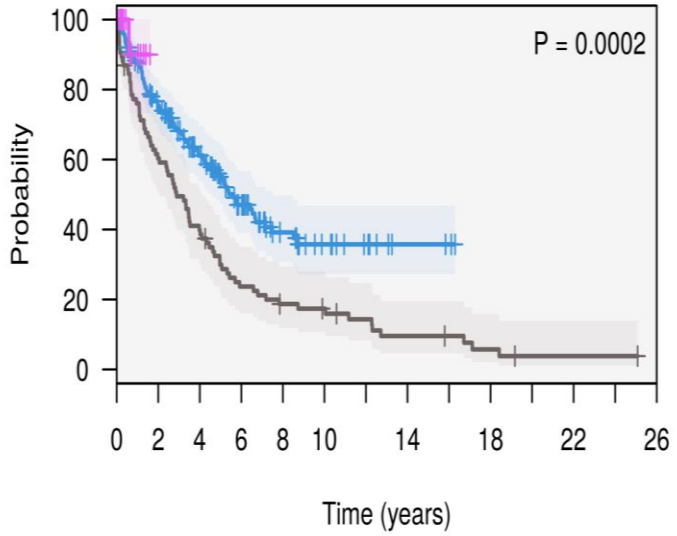
Cyclin D1

Hospital Clinic of Barcelona

MCL, B-NHL

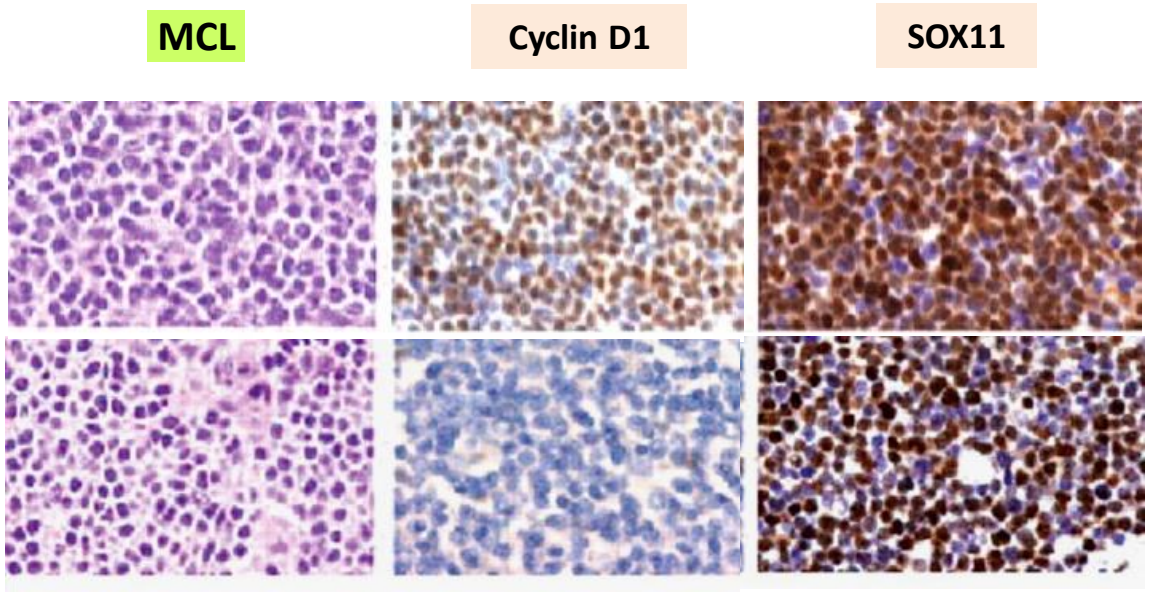


(Courtesy Dr. López-Guilllermo)



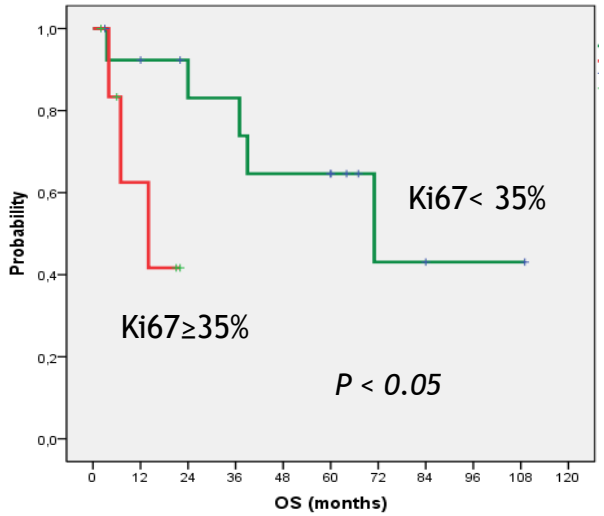
Median survival:
1990-2001: 3.2 yrs
2002-2017: 5.6 yrs
2018: not reached

Cyclin D1 Negative MCL Variant



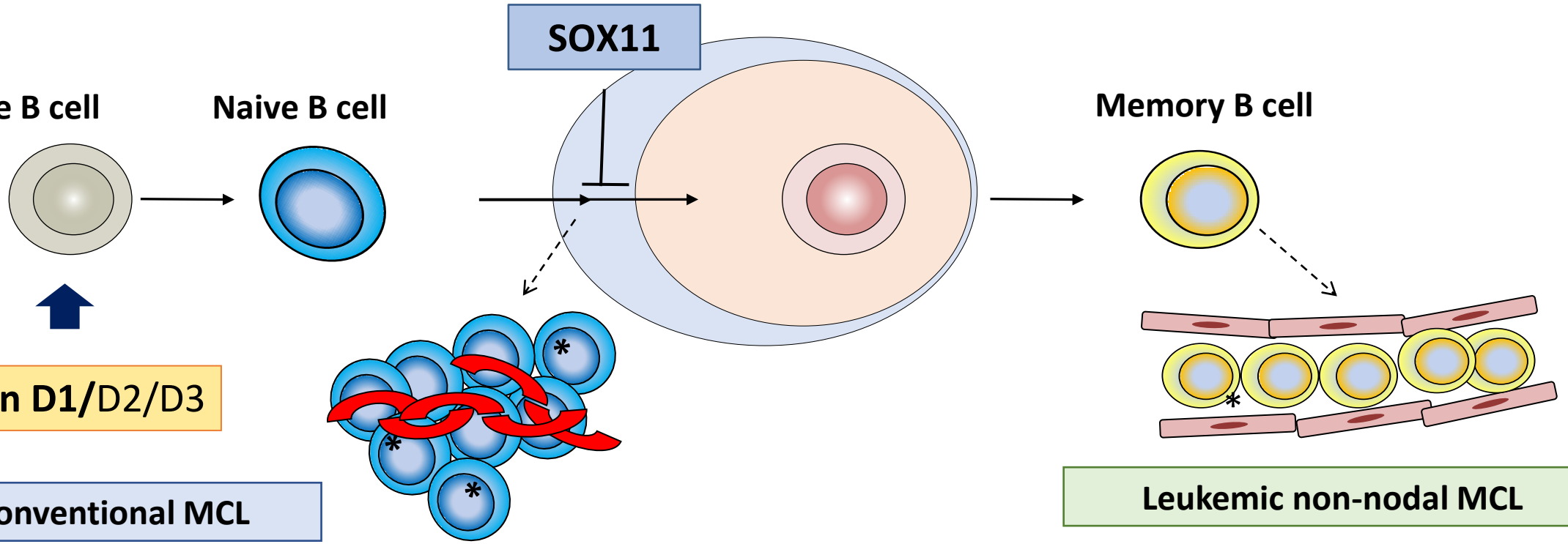
Rearrangements	No. (%)
CCND1	0
CCND2	43 (83%)
CCND3	9 (17%)*

* They may be cryptic with conventional FISH probes



Mozos et al Haematologica 2009; Salaverria I et al Blood 2013; Martin-Garcia et al Blood 2018

Molecular Pathogenesis and Clinical Subtypes of MCL



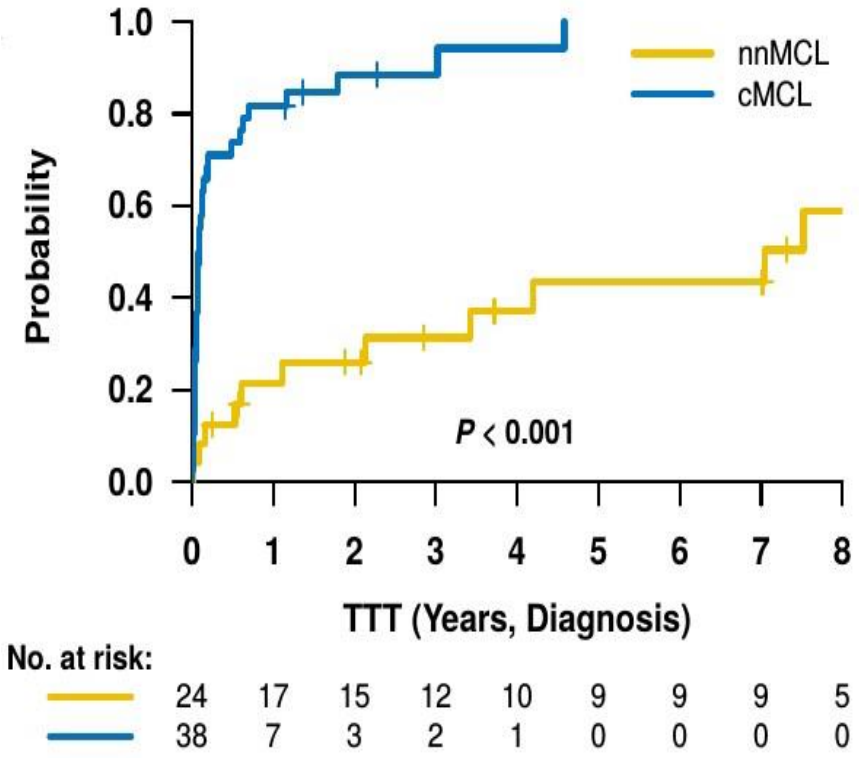
IGHV-unmutated
Genomic instability
Nodal & Extranodal involvement
↑ECOG, ↑MIPI
Need of treatment

IGHV-mutated
Genomic stability
Leukemic, splenomegaly
Non-nodal
↓ECOG
Delay Chemotherapy

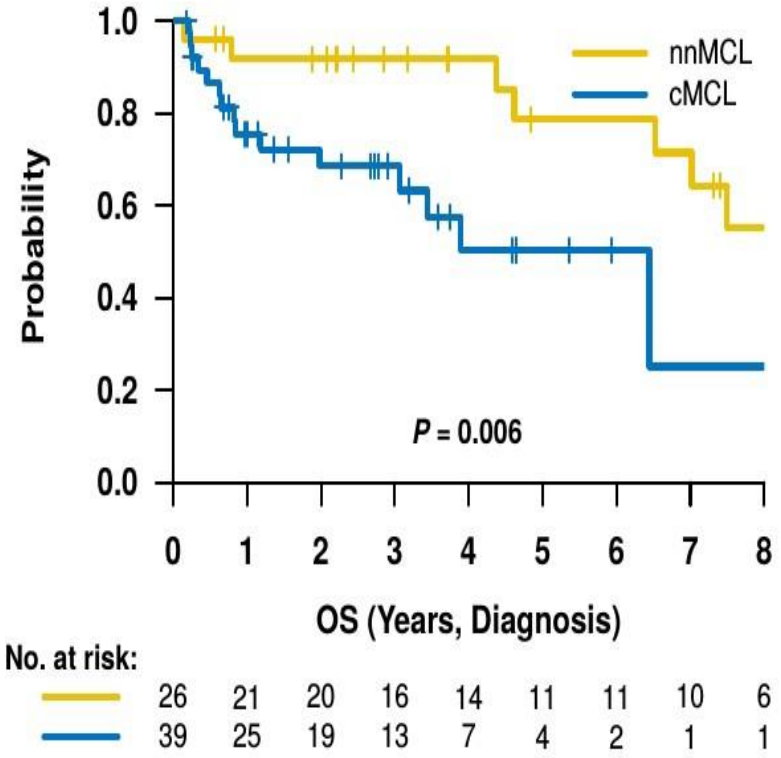
Puente et al Blood 2018; 131:2283-96

Outcome according to cMCL and nnMCL signatures

TTFT

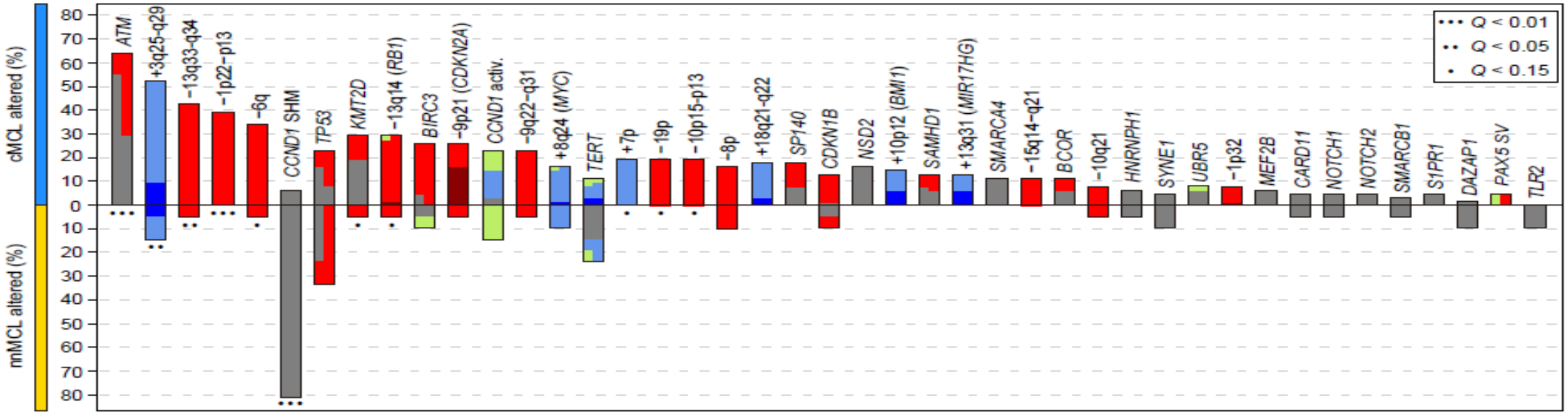


OS



Clot G et al Blood 2018

Different distribution of driver alterations in MCL subtypes

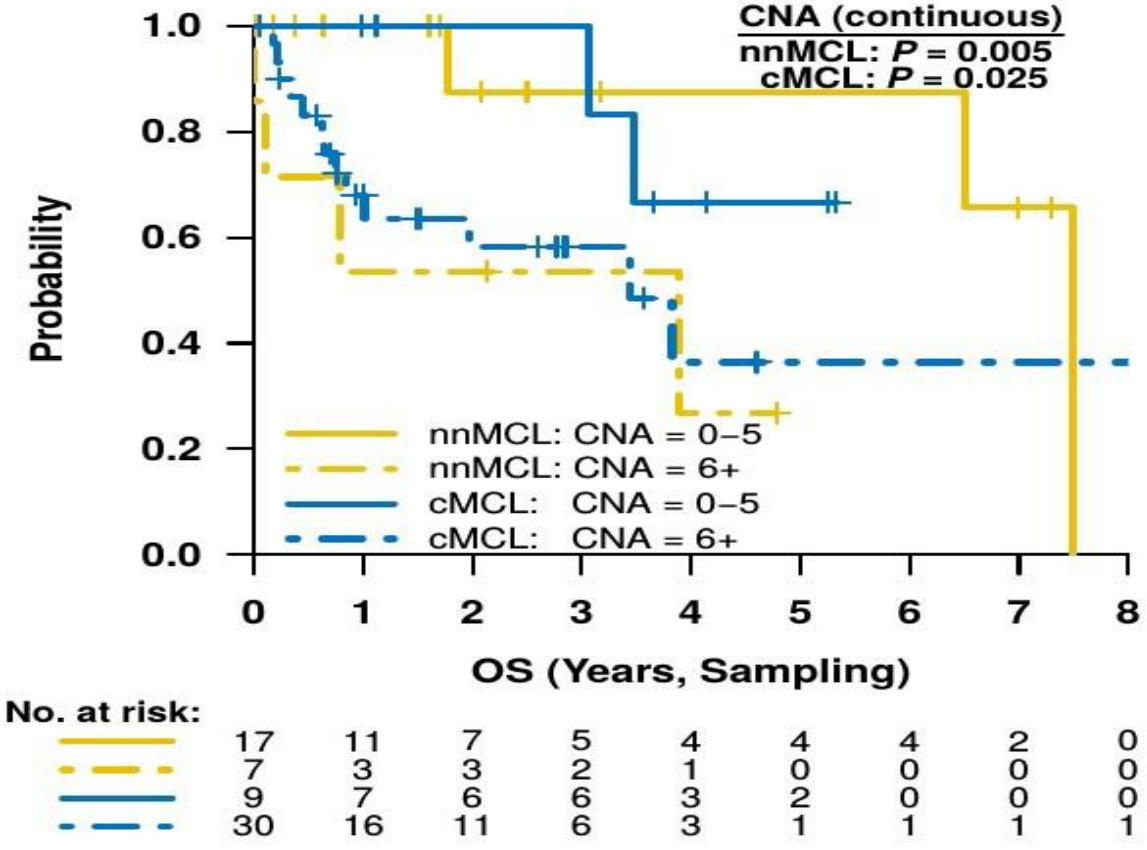


- **Early drivers: *ATM*, *TP53* loss, -13q3**
- **Late drivers: -6q, -19p, +8q (*MYC*), +18q**

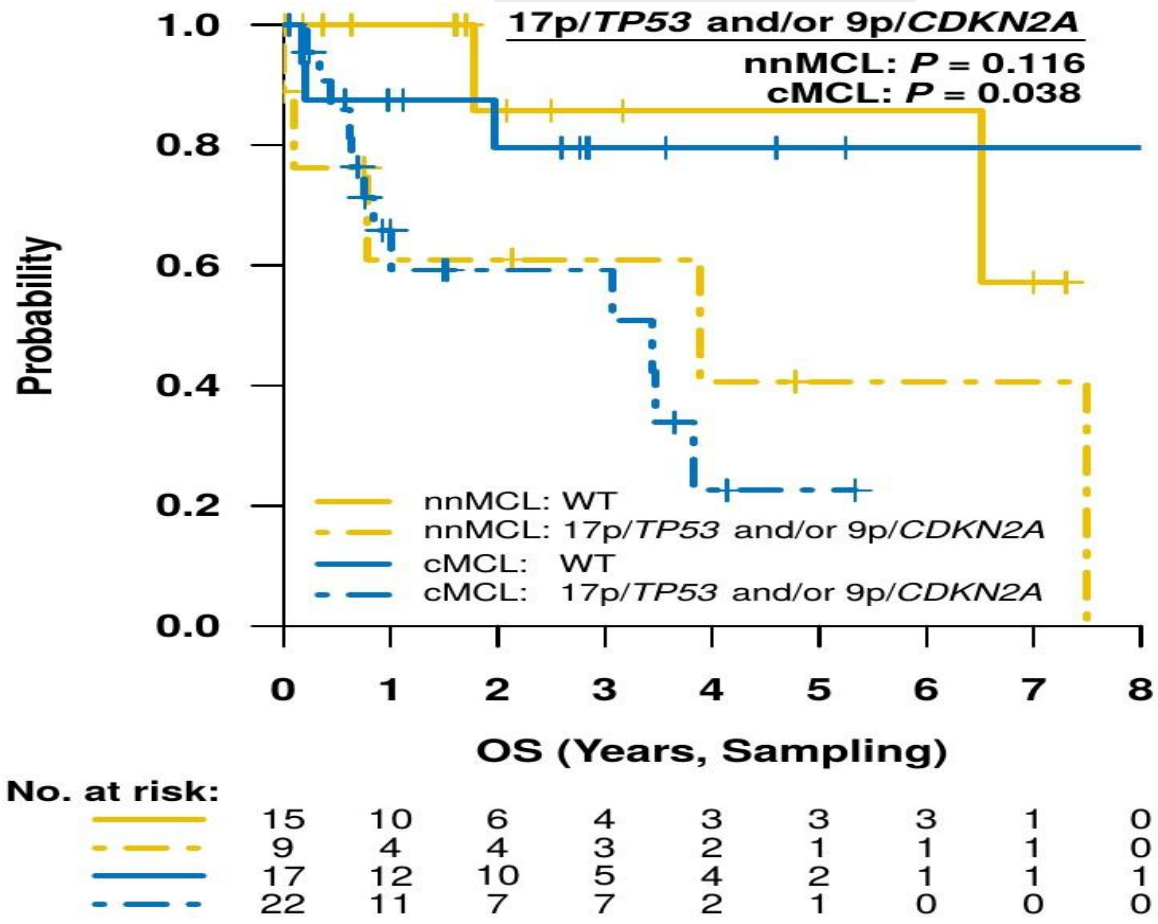
Nadeu F & Martin-Garcia D et al Blood 2020

Genomic alterations confer adverse outcome in both cMCL and nnMCL

Genomic Complexity

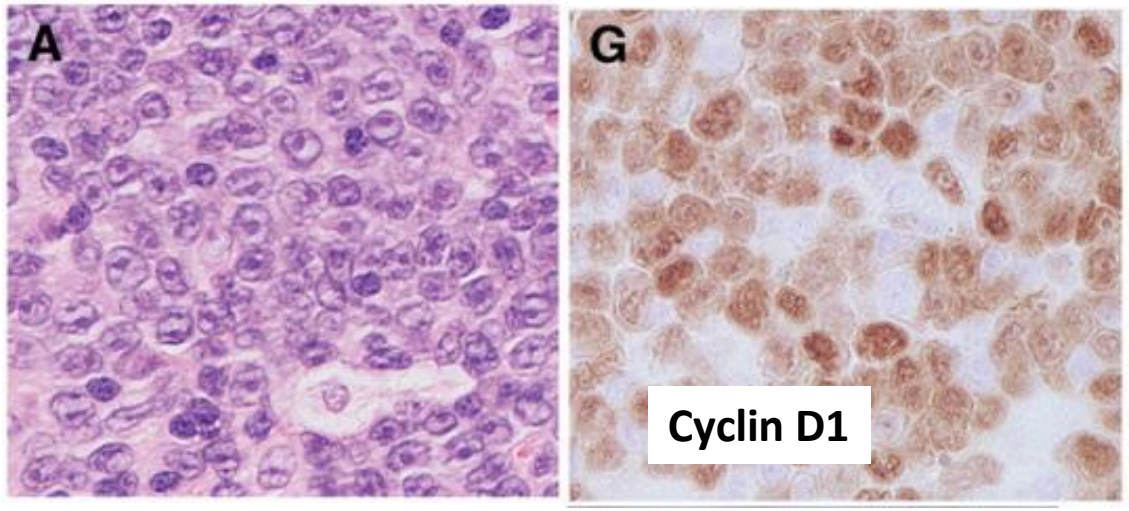


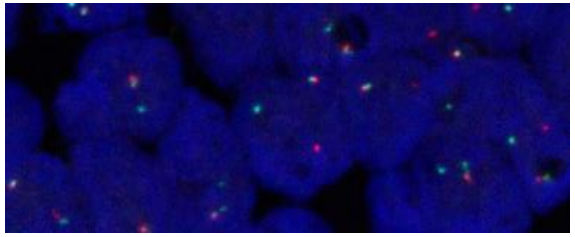
TP53/CDKN2A



Clot G et al Blood 2018

CCND1 Expression and Genomic 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.
Cheng J et al Hemasphere. 2021; 5(1): e505
Schliemann I et al Leuk Lymphoma. 2016;57(11):2672-6

Conclussions and Practical approach

CLL

- Need to study IGHV and *TP53* alterations (FISH, Sequence) before treatment
- Future perspective: TP53 Subclonal mutations, IGL V3-21 R110, NOTCH1 and other drivers, complex karyotypes
- Richter Transformation: Define clonal relationship

LPL

- MYD88 and CXCR4

MCL

- Consider FISH and NGS in cases SOX11-negative with blastoid/large cells cyclin D1+
- Posibly *TP53* alterations in the near future

3° CONGRESO
LATINOAMERICANO DE
HEMATOPATOLOGÍA
SÃO PAULO | 2023

REALIZACIÓN

SOLAHP Sociedad Latinoamericana de Hematopatología

Sociedade Brasileira de PATOLOGIA

EA4HP European Association for Haematopathology

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RECORDATI RARE DISEASES GROUP

AstraZeneca

NOVARTIS

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

A.C.Camargo Cancer Center Especializado em Vida

Agilent Dako