Molecular Genetics of Small Mature B-cell Lymphomas

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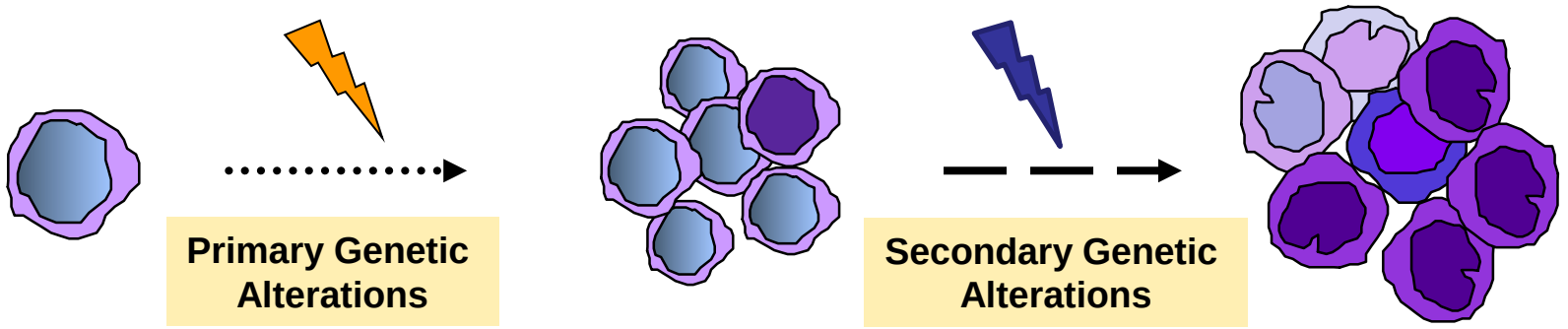
Genetic Drivers in Lymphomagenesis

Clonal Population

Overt Lymphoid Neoplasia

Progression/ Transformation



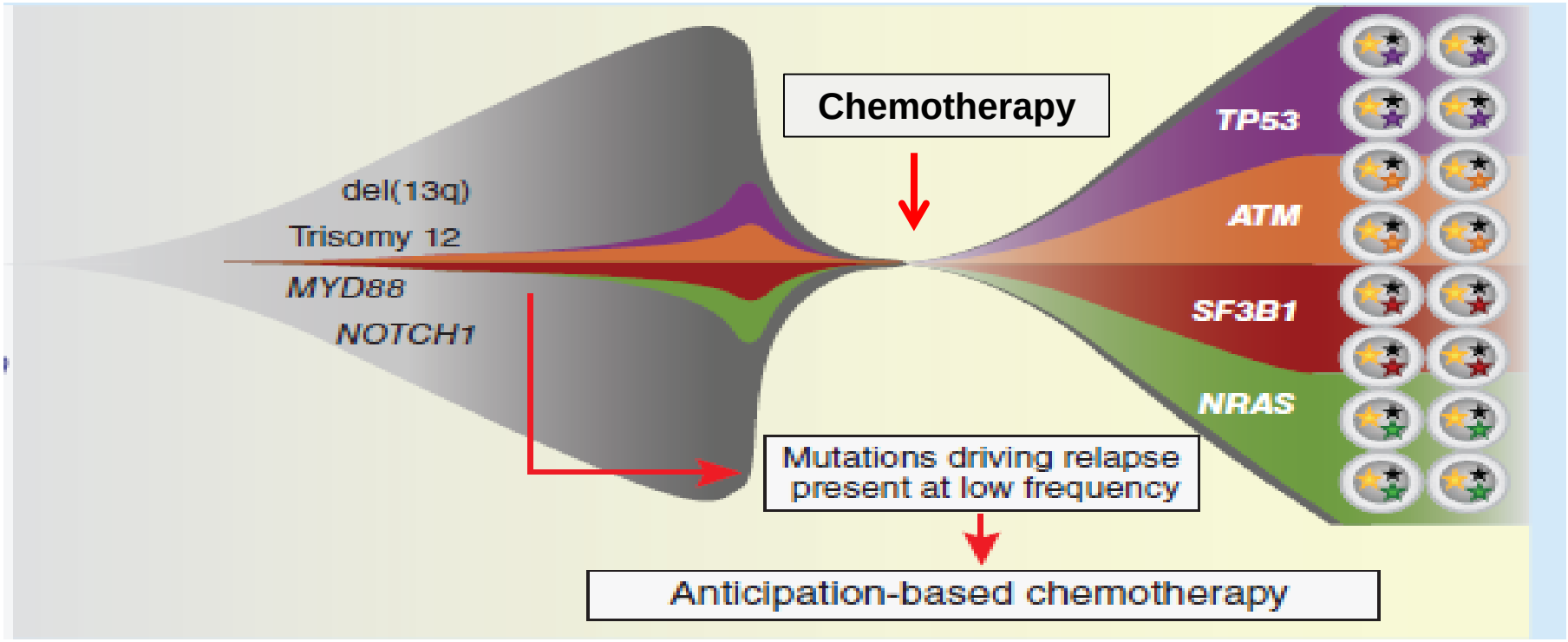
Primary Genetic Alterations

Secondary Genetic Alterations

Microenvironment

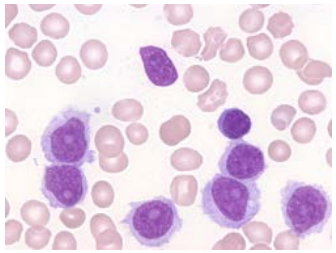
Genetic alterations

The mutational profile is a dynamic process

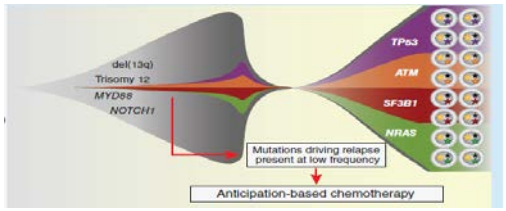


Puente X & Lopez-Otín C Nat Genet 2013

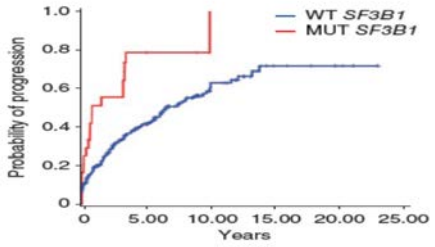
Impact of NGS in Small B-cell Neoplasms



- **Disease specific profiles**



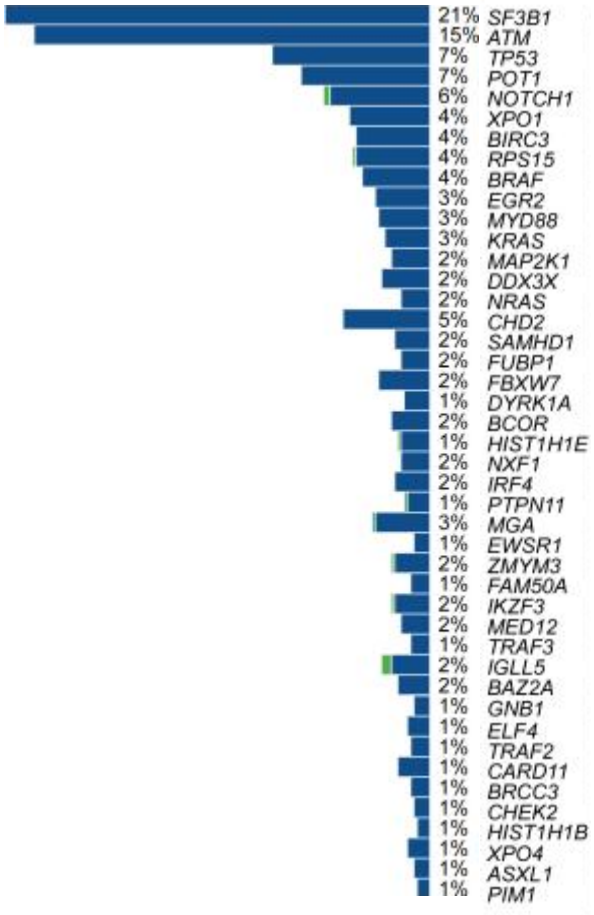
- **Understanding evolution of the disease**

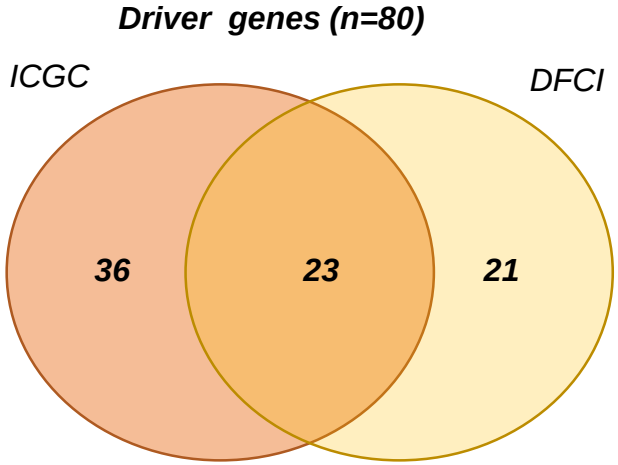


- **Prognostic groups and risk stratification**

- **Orient management estrategies**

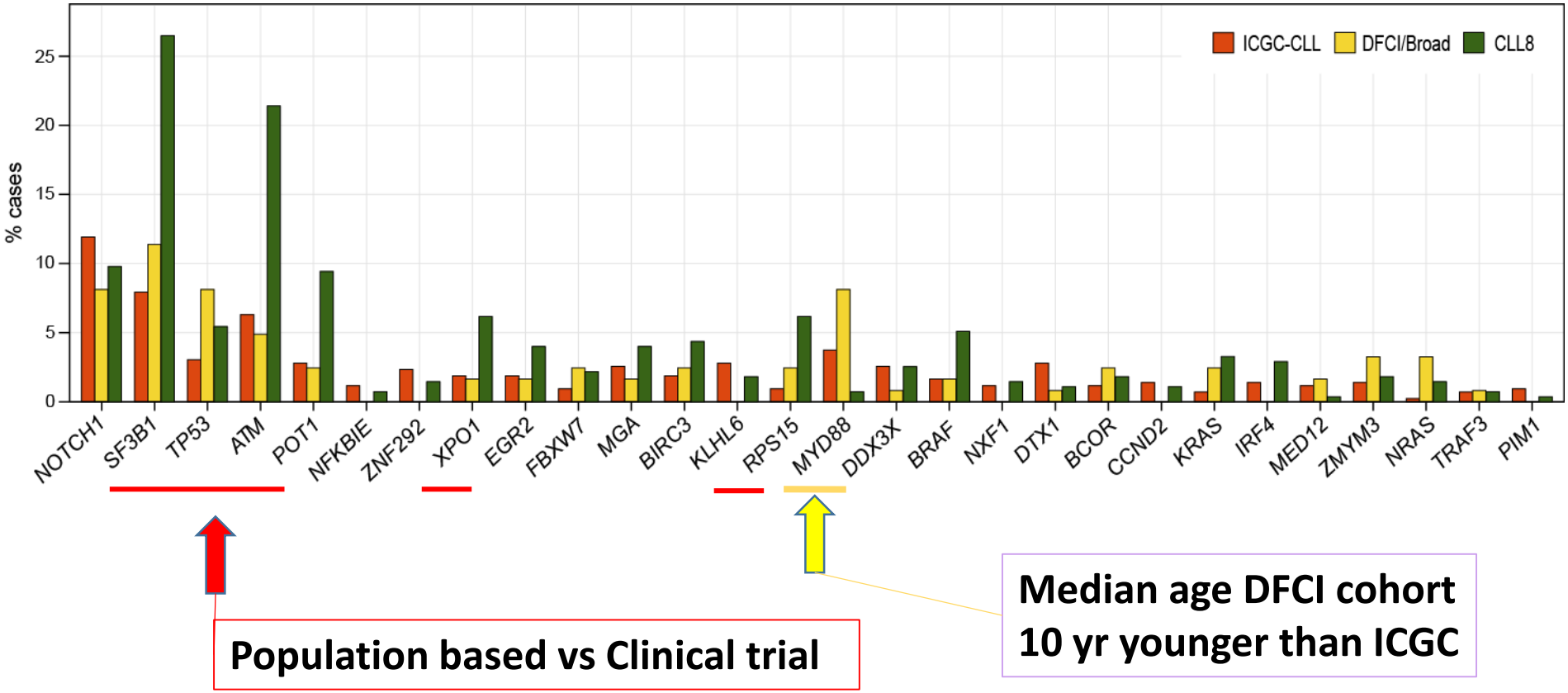
Driver mutated Genes and CNA in CLL
ICGC & Danna-Farber (DFCI)





ICGC: Puente *et al.* Nature. 2015, DFCI: Landau *et al.* Nature 2015,

Driver mutated Genes in CLL genomes (ICGC vs Danna Farber (DFCI)

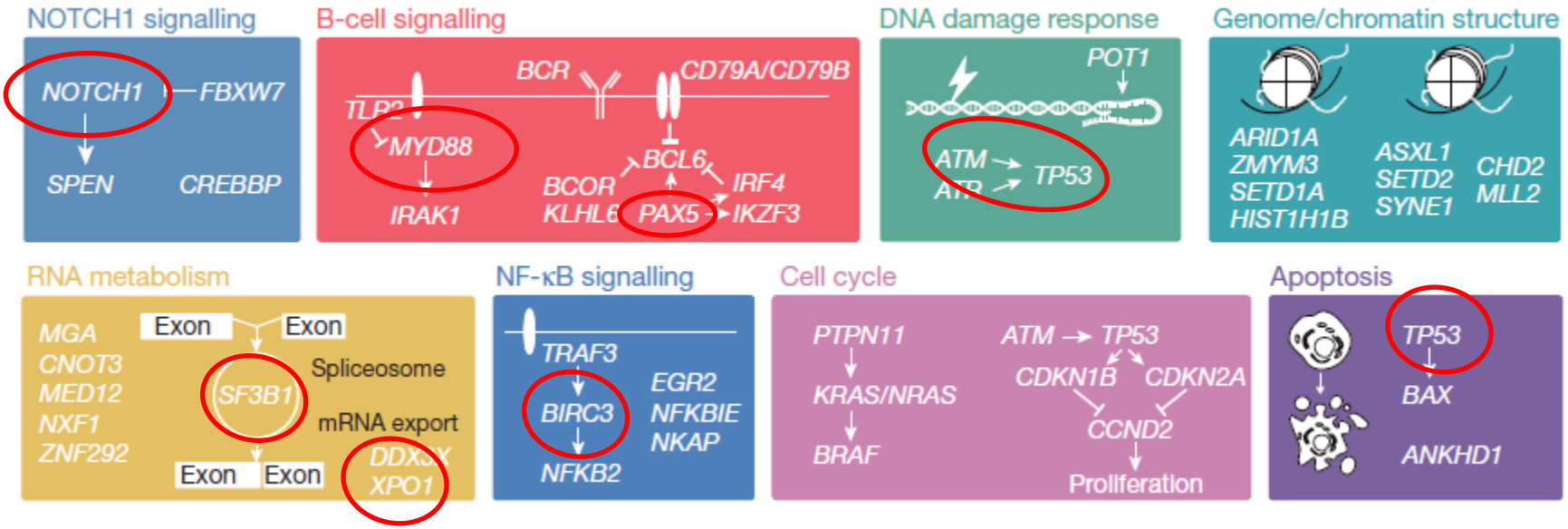


Population based vs Clinical trial

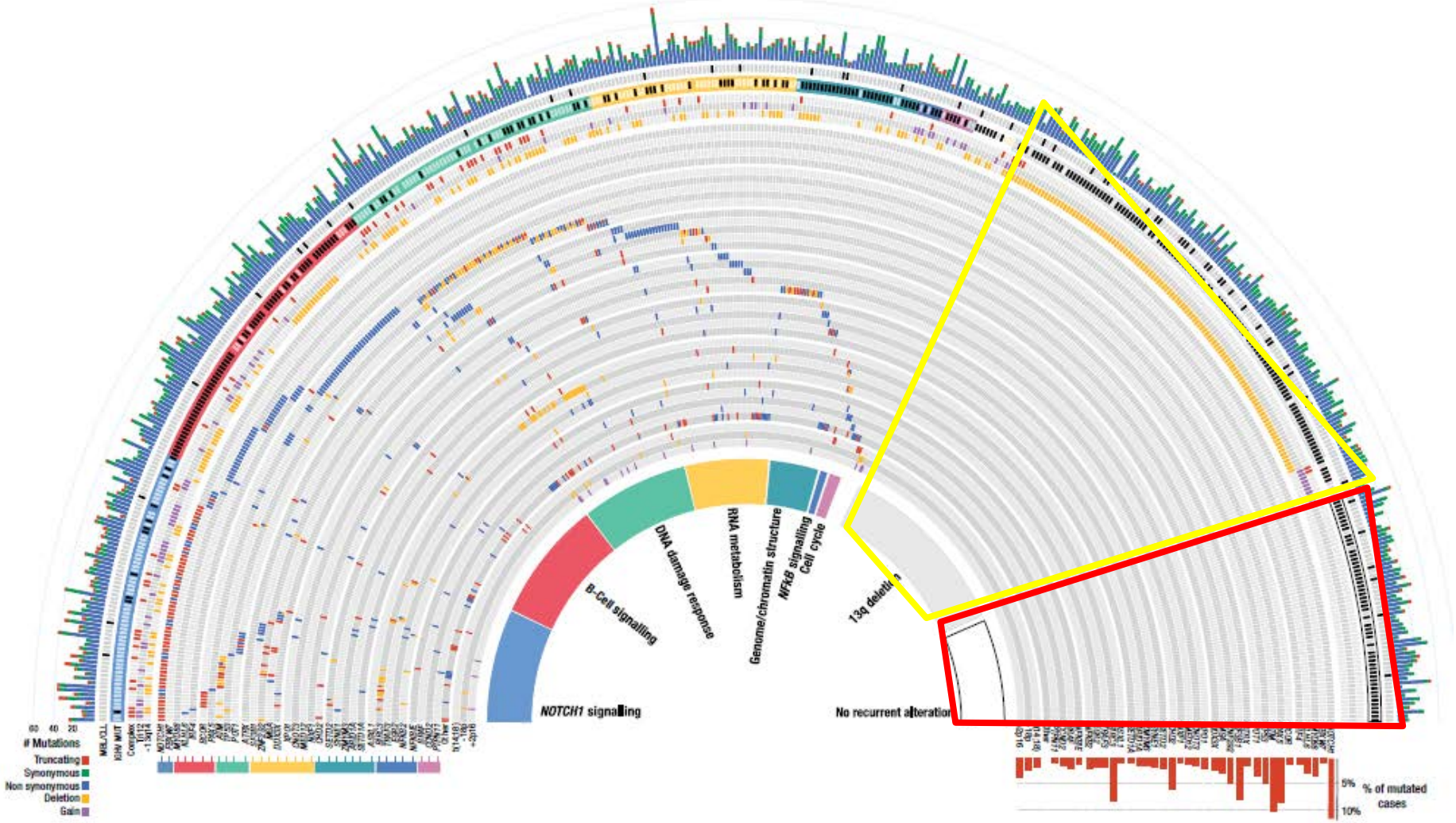
Median age DFCI cohort 10 yr younger than ICGC

ICGC (n=428): (Puente *et al.* Nature 2015).
DFCI/Broad (n=123) Only pretreatment cases considered
CLL8 (n=278): Clinical trial (Landau *et al.* Nature 2015)

Mutated Pathways in CLL



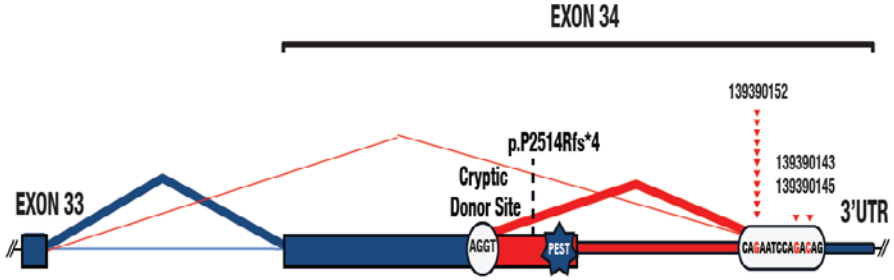
Genomic Heterogeneity and Driverless in CLL



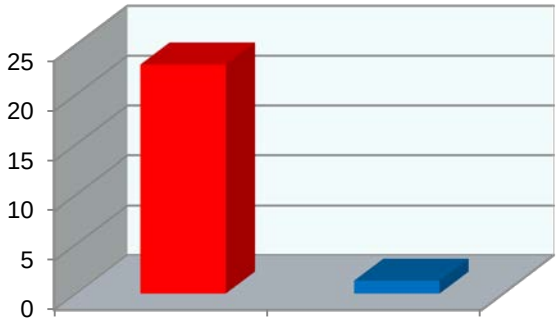
452 CLL & 54 MBL (150 whole genomes)
13.631 mut in coding genes: 27 per tumor
951 CNA (2 per tumor)
59 driver genes

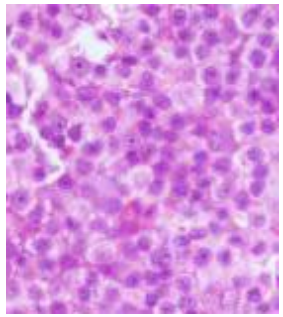
Puente et al Nature 2015

NOTCH1 Mutations in CLL

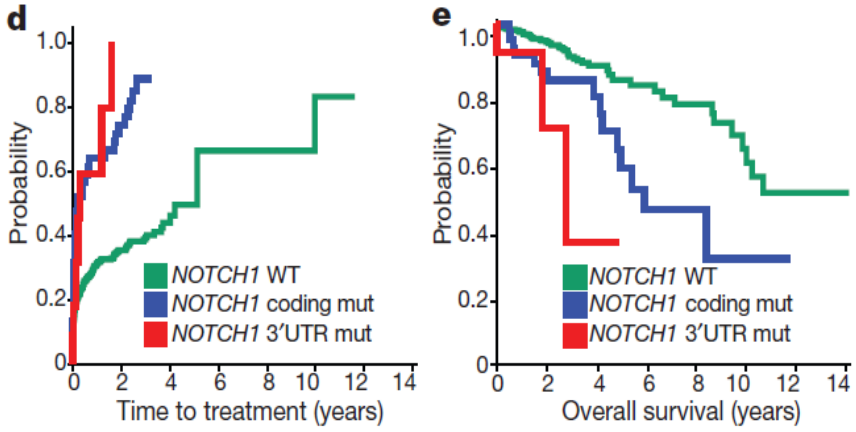


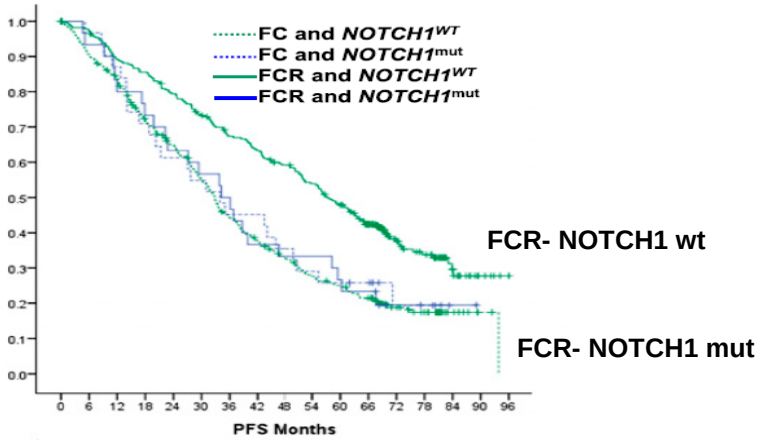
Richter Transformation





Mutated wt

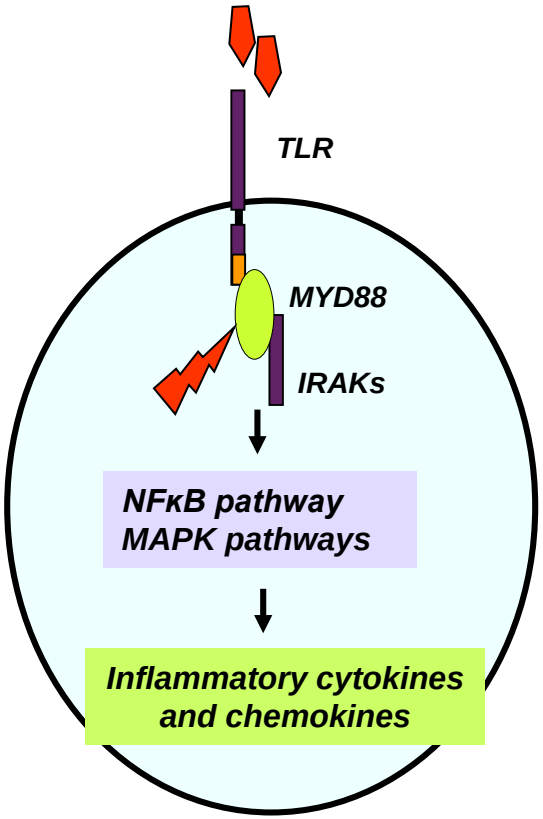


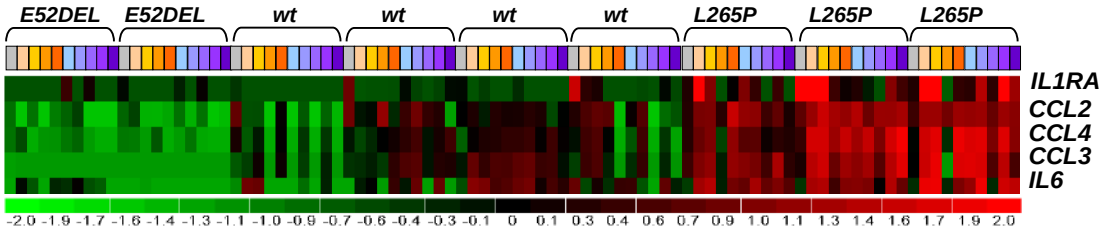


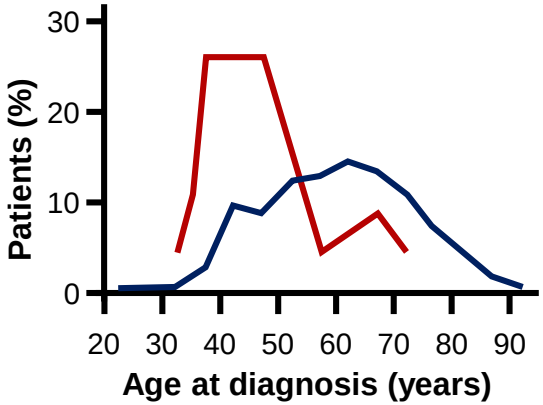
Puente et al, Nature 2011, 2015

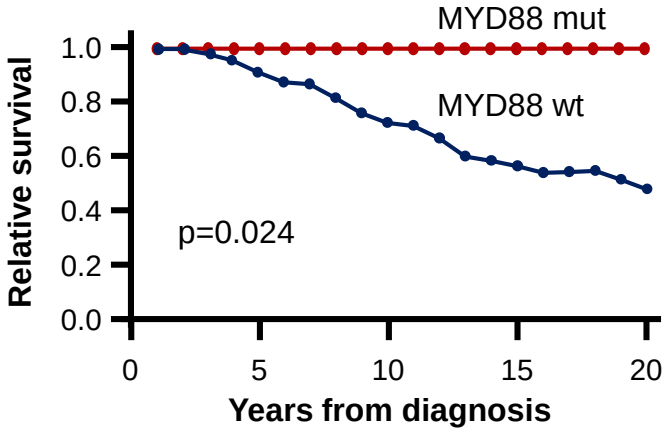
Stilgenbauer S et al. Blood 2014;123:3247-3254

TLR/MYD88 mutated pathway in CLL
A specific subgroup of patients?





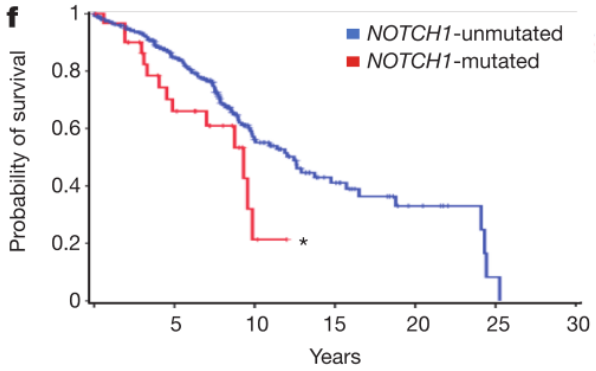




Martínez-Trillos A, et al. Blood 2014; 123:3790–3796.

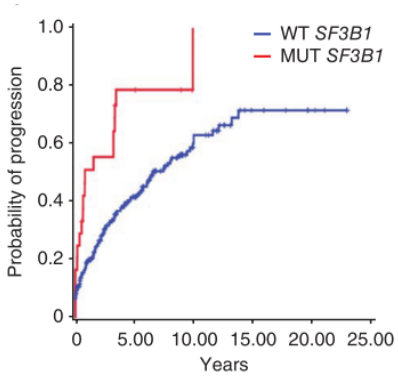
Clinical relevance of individual mutated genes in CLL

NOTCH1



Puente *et al.* 2011, Nature

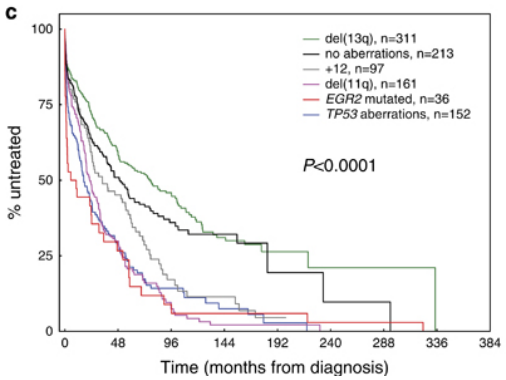
SF3B1



Quesada *et al.* 2011, Nat Genetics

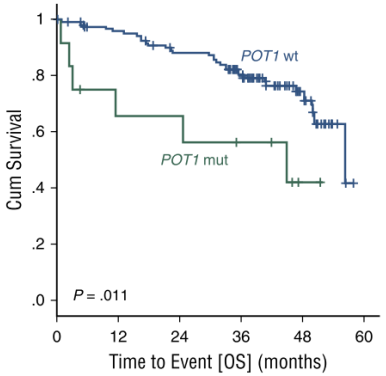
?

EGR2



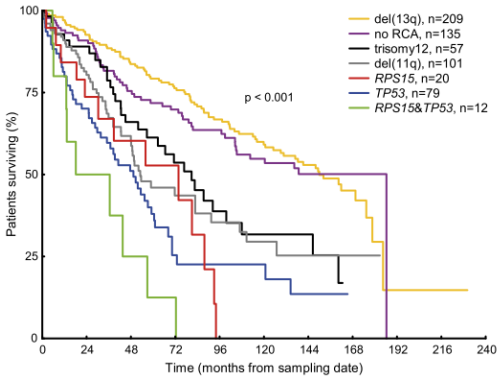
Young *et al.* 2017, Leukemia

POT1



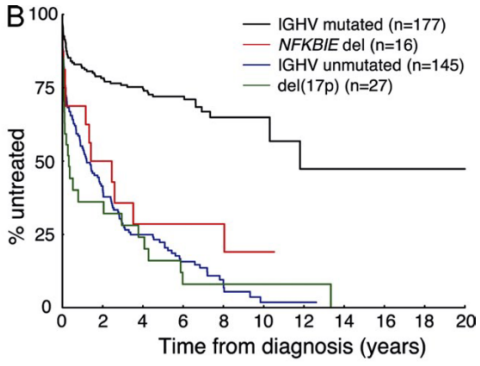
Herling *et al.* 2016, Blood

RPS15



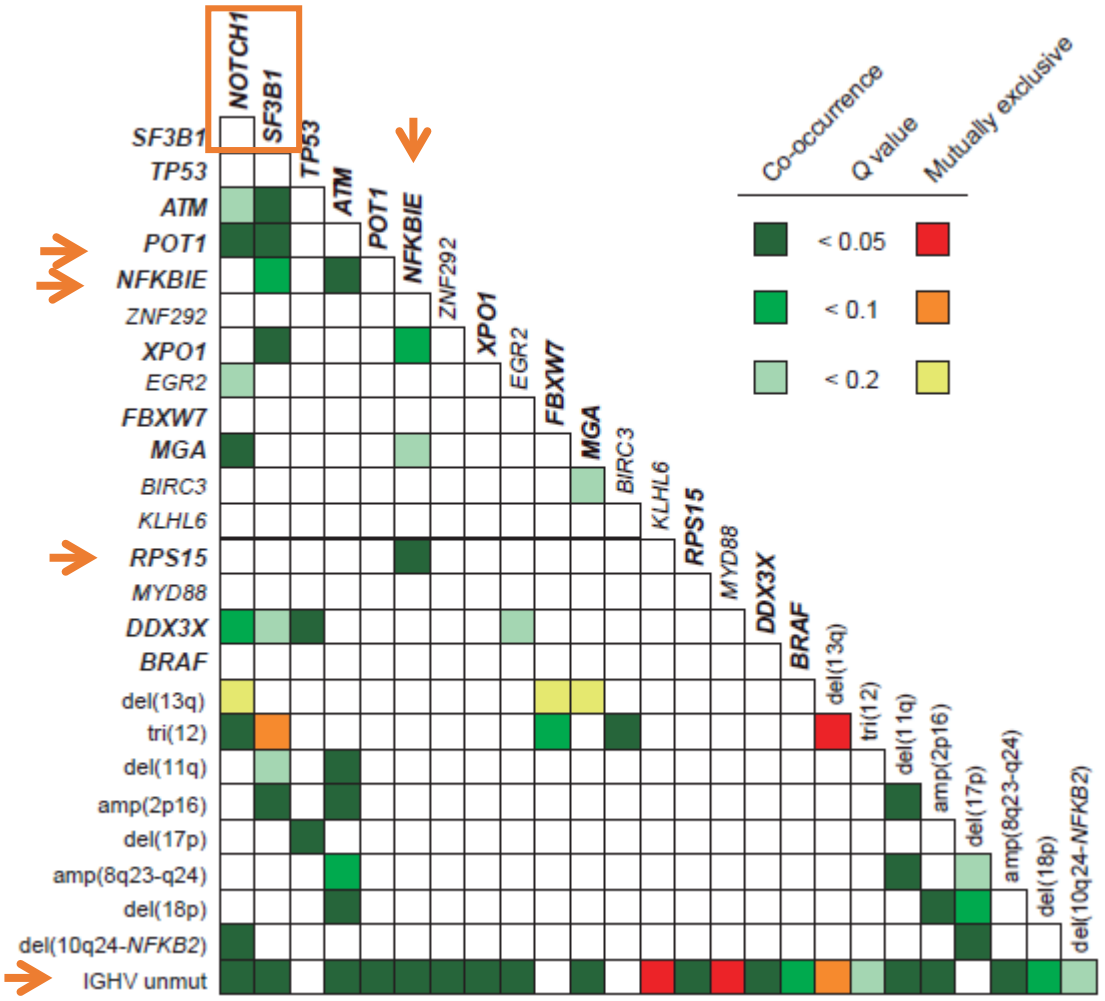
Ljungström *et al.* 2015, Blood

NFKBIE



Mansouri *et al.* 2015, JEM

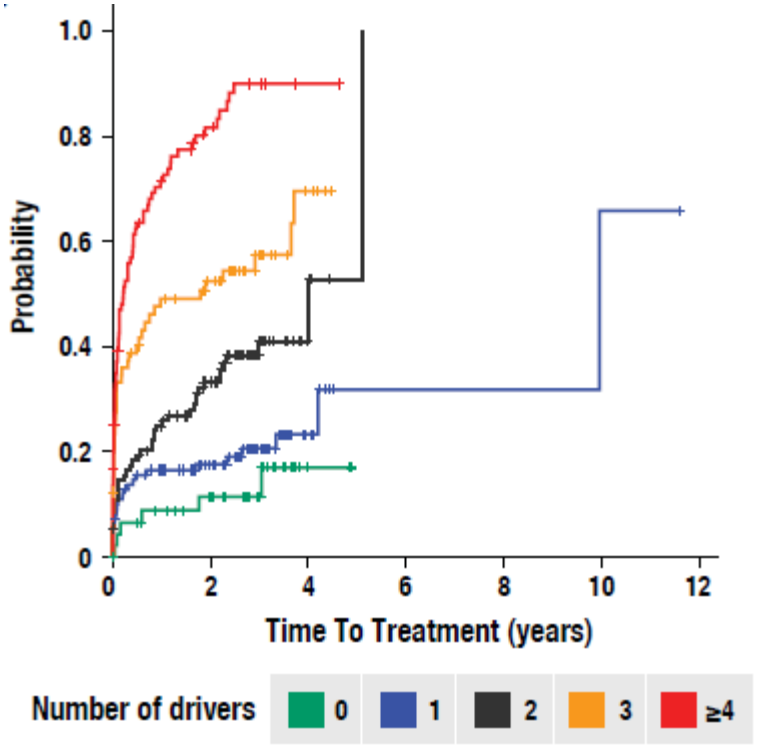
Co-occurrence of driver alterations in CLL



Nadeu F et al Leukemia 2017 (In press)

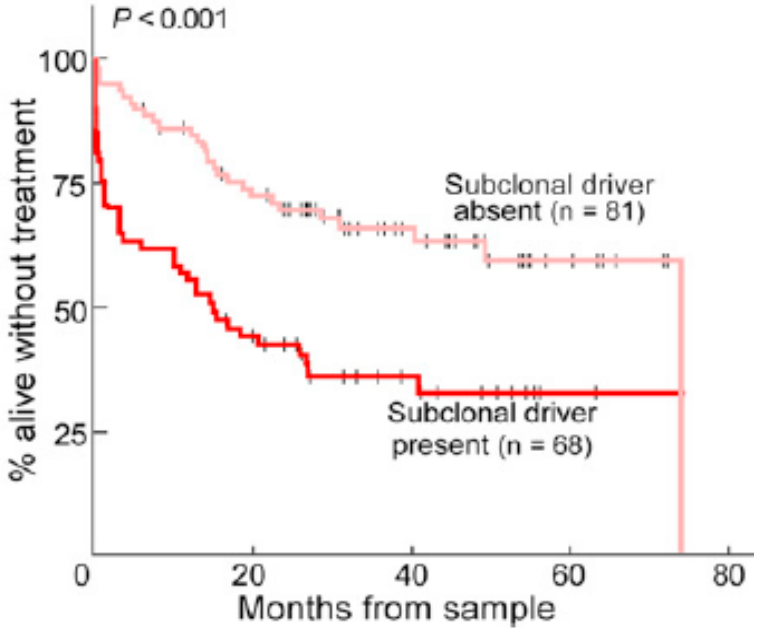
Prognostic impact of number of mutated drivers and subclonal alterations in CLL

Number of drivers

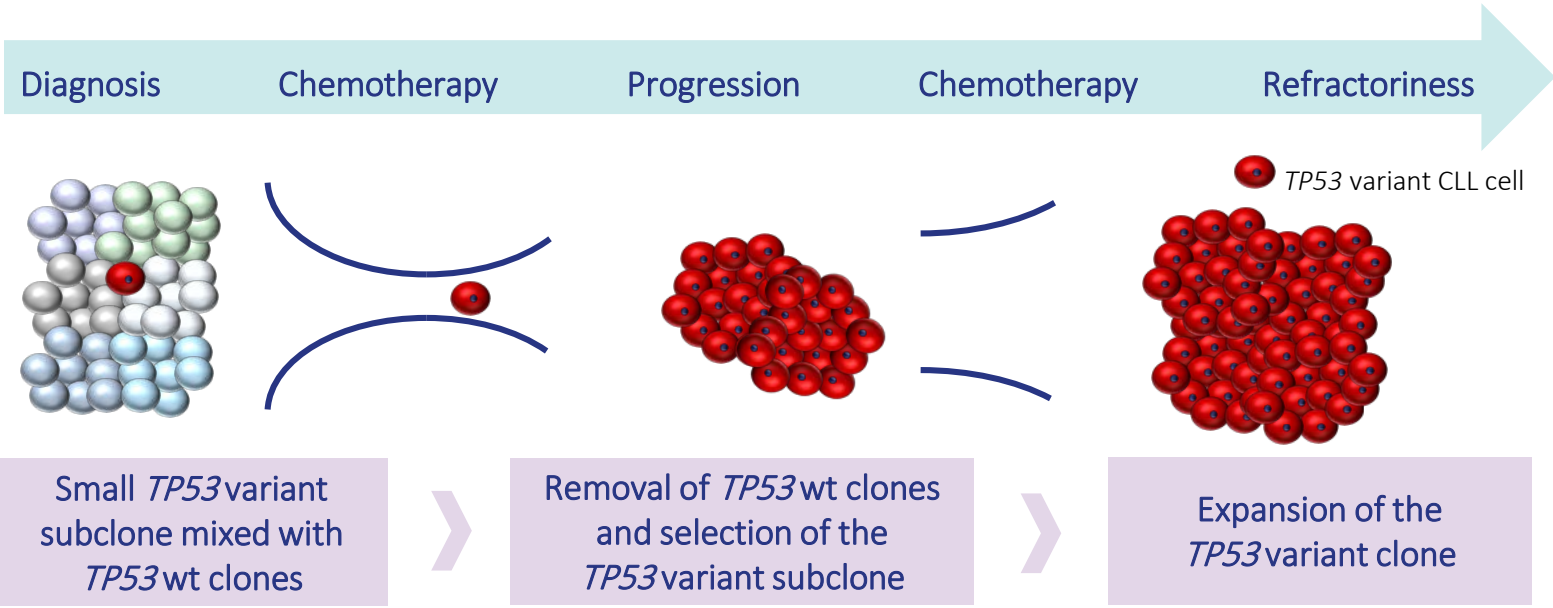


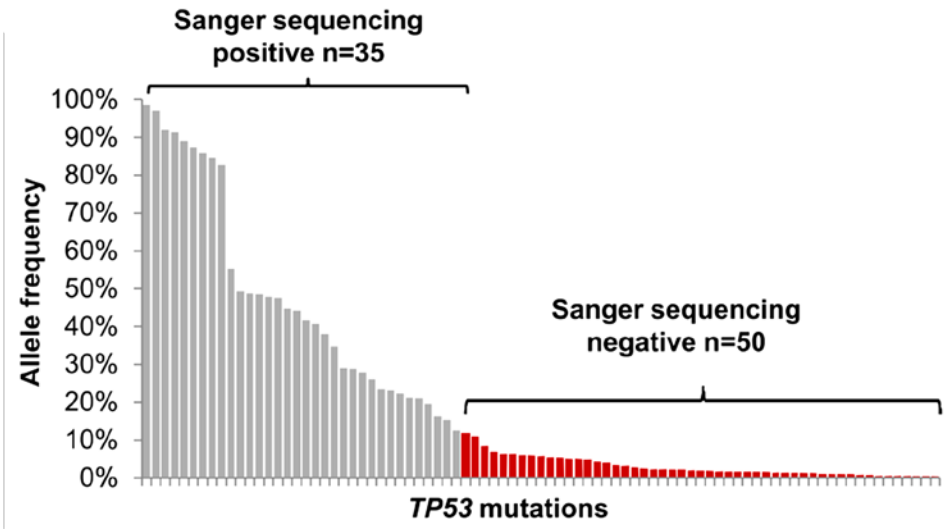
Puente X et al Nature 2015

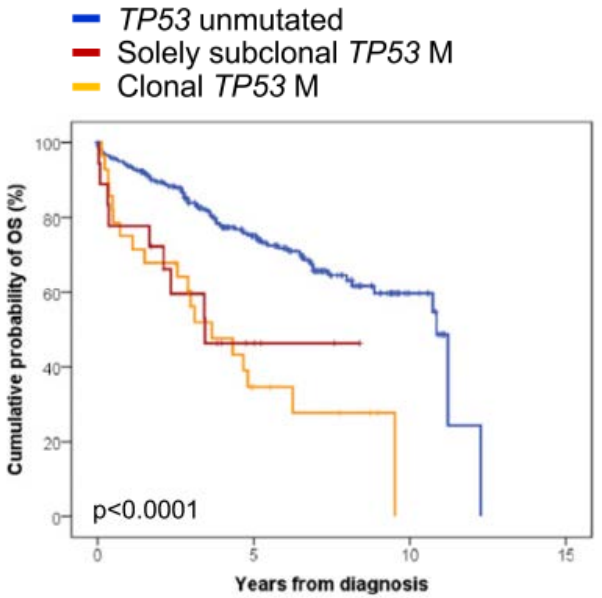
Clonal/subclonal heterogeneity



Landau DA et al Cell 2013

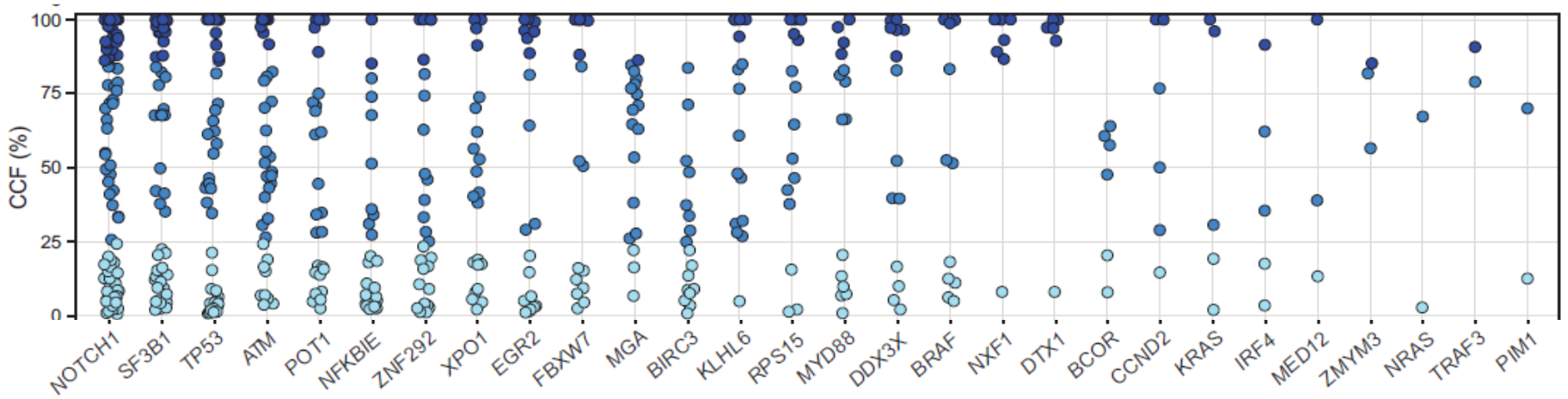






Rosi D et al Blood 2013

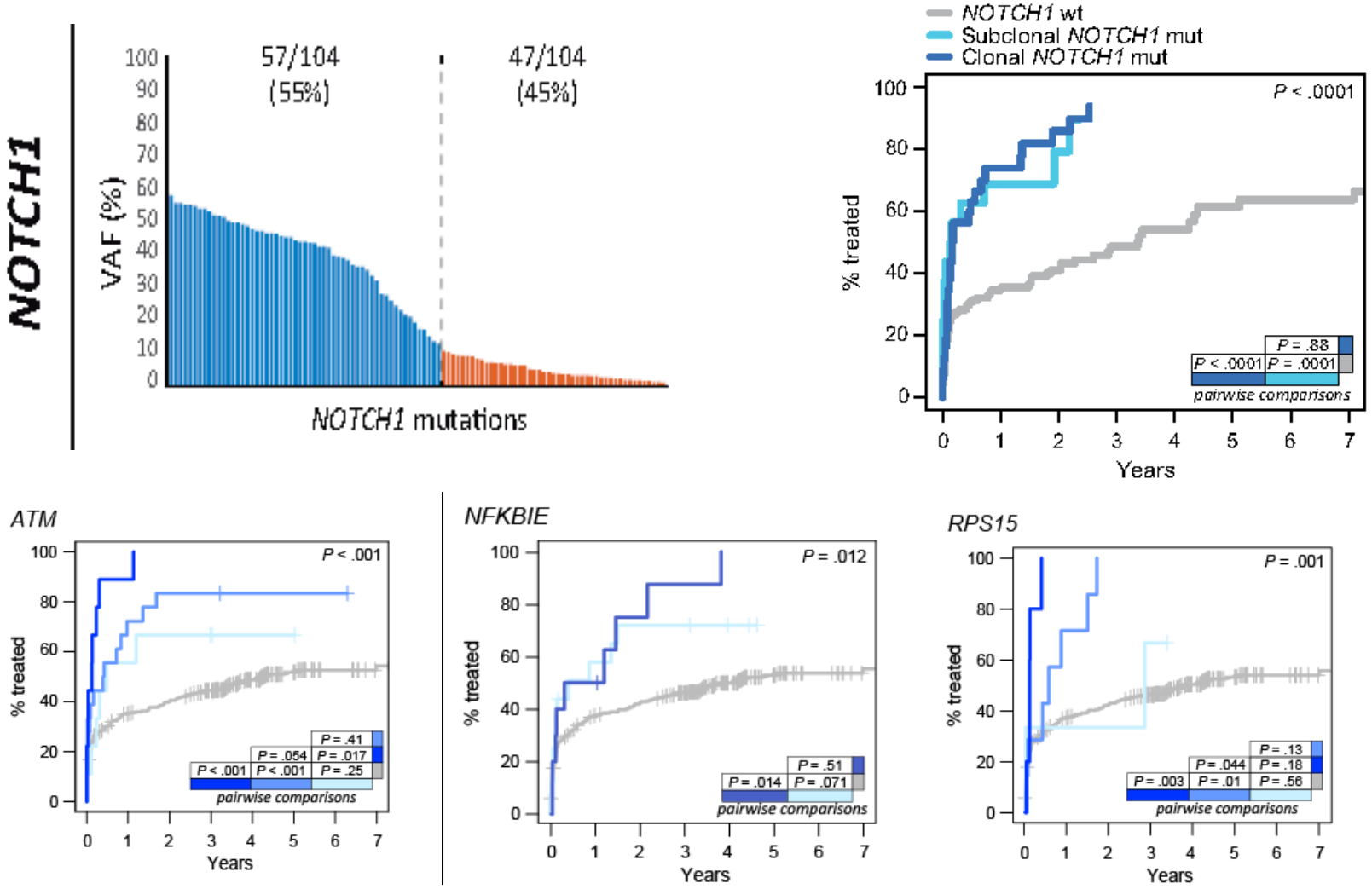
Small mutated subclones are identified in virtually all genes



- **406 untreated patients**
- **28 CLL driver genes**
- **Mean coverage 1500x NGS**
- **Sensitive pipeline 0.1% allelic frequency**

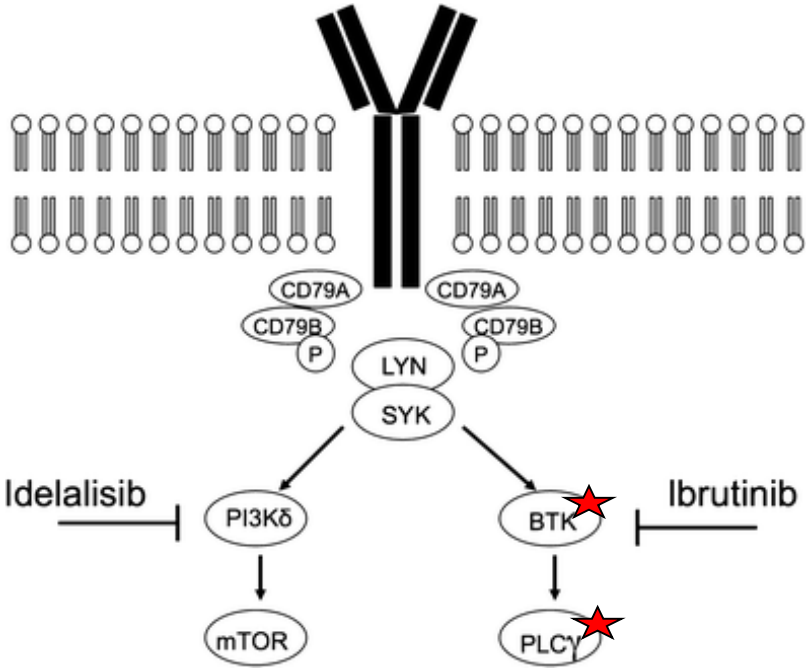
Nadeu F et al Leukemia 2017 (In press)

Clinical Impact of clonal and sublconal mutations in CLL



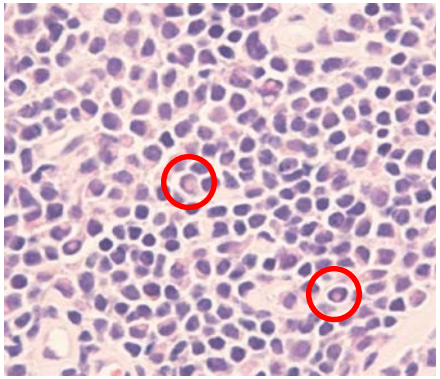
Nadeu F et al Blood 2016; Leukemia 2017 (In press)

Ibrutinib-resistant mutations may be detected before clinical relapse



Detection of mutated subclones may precede treatment
Median 8-9 months (3-15 months)

Ahn IE et al. Blood 2017;129:1469-1479; Woyach JA et al JCO 2017, 35, 1437-1443; Arnason & Brown Curr Oncol Report 2017



Somatic Mutations in 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

- **Useful information in the differential diagnosis of LPL**
- **Need to be interpreted in the global context of the disease**

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*

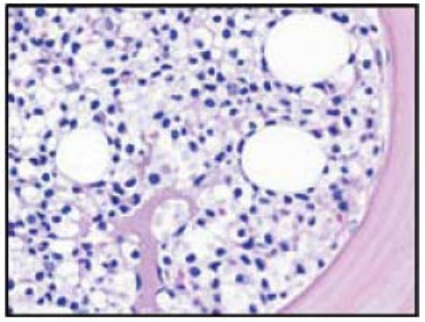
When should *MYD88* L265P mutations be studied in small B-cell neoplasms?

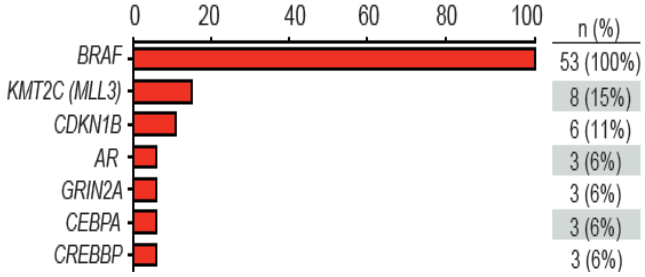
- **Differential diagnosis of LPL strongly considered but findings not conclusive**
- **Differential diagnosis between LPL and IgM PCM**
- **If LPL is not in the differential diagnosis MYD88 mutations may not be useful**

Swerdlow SH et al Virchows Arch. 2016;468(3):259-75

Somatic Mutations in HCL and HCLv

Hairy Cell Leukemia

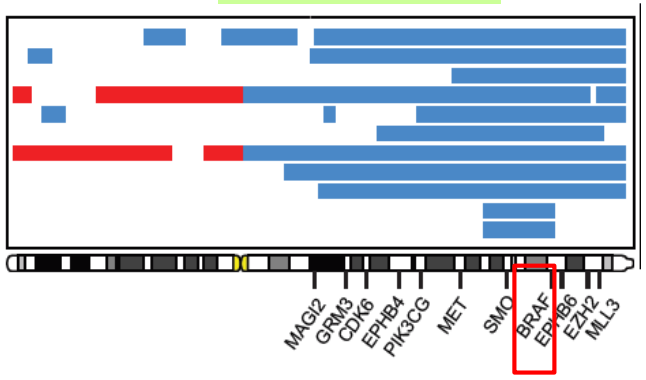




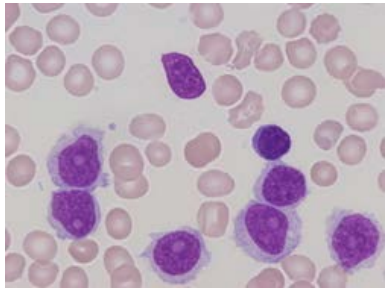
Vemurafenib Resistance

- NF1/NF2 downregulation
- KRAS mutation

7q deletion



HCL-v



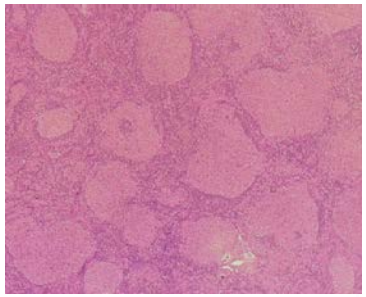
MAP2K1

- **50 % HCLv**

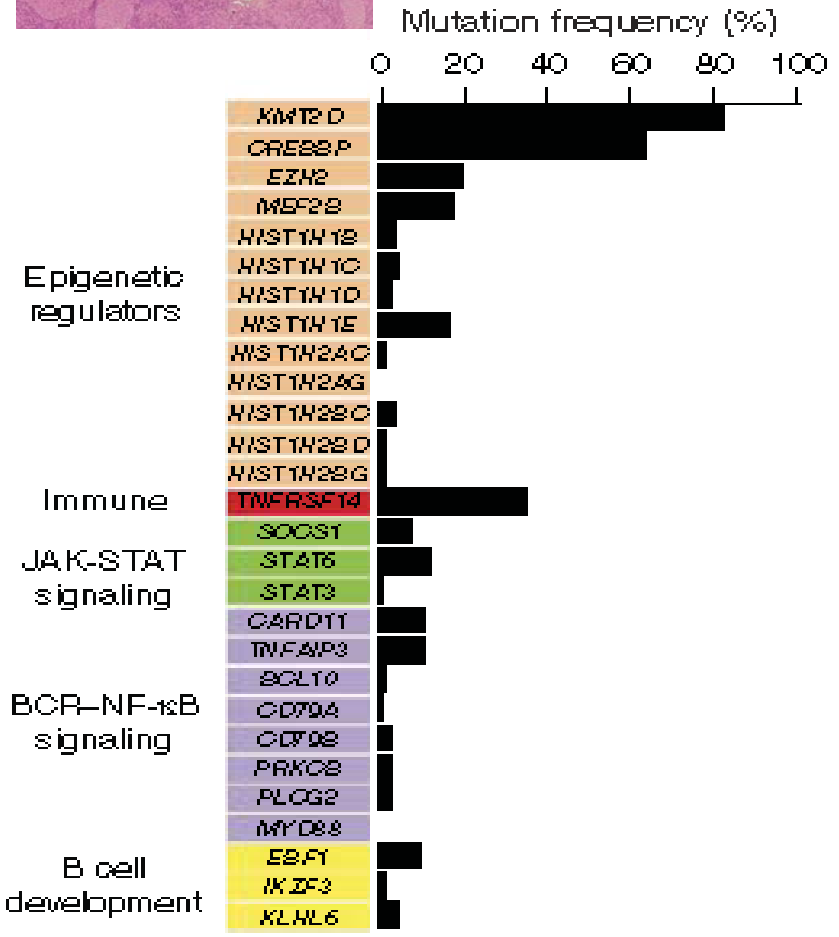
50% HCL IgH V4-34
50% Pediatric Type FL

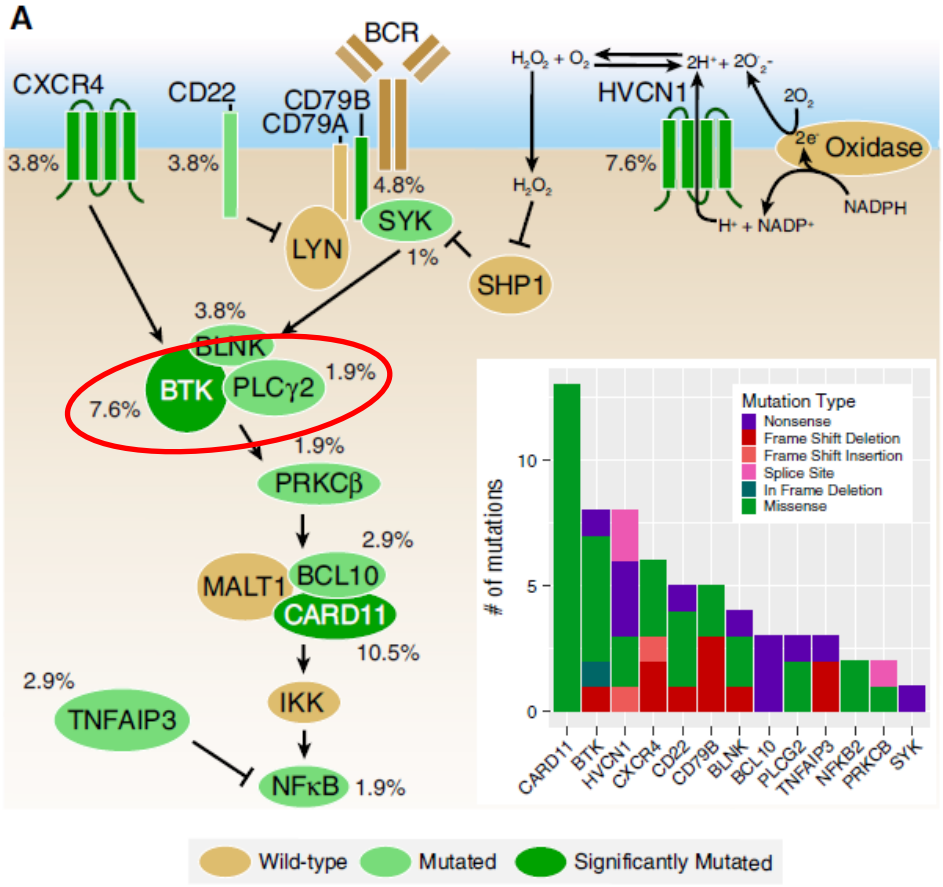
CCND3, U2AF1

Tiacci E, et al. N Engl J Med. 2011; Waterfall J et al Nat Genet. 2014; Durham BH et al Blood 2017



Follicular lymphoma Mutational Landscape

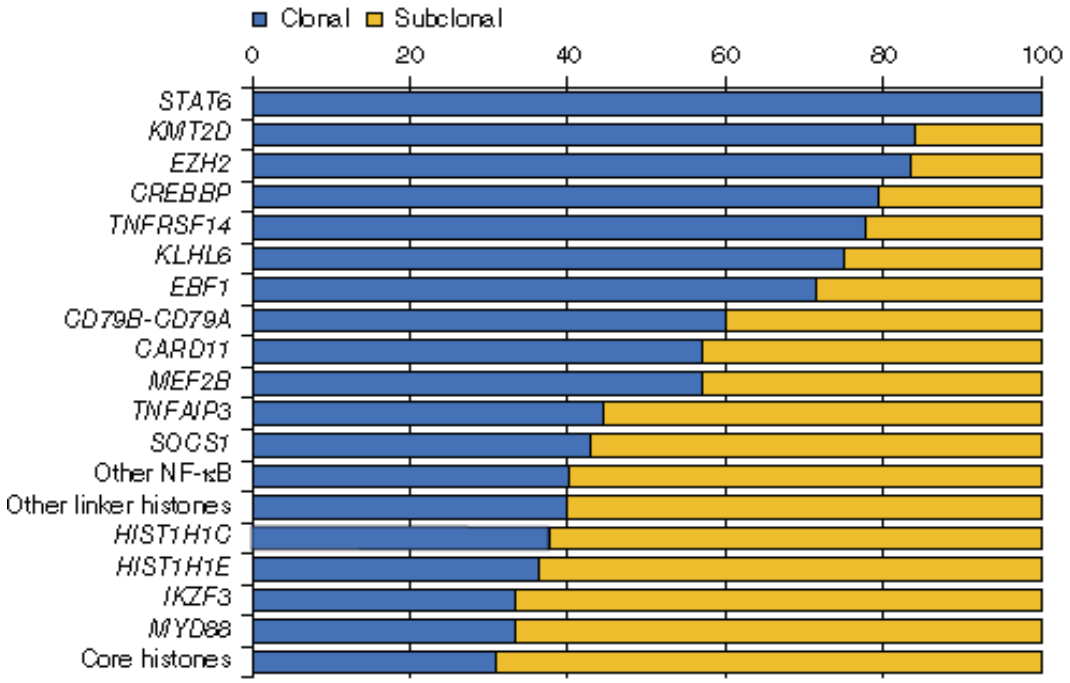




Okosun J et al Nat Genet. 2014 , 46:176-81.

Krysiak K et al Blood 2017; 129: 473-483

Early and Late Mutations in Follicular Lymphoma

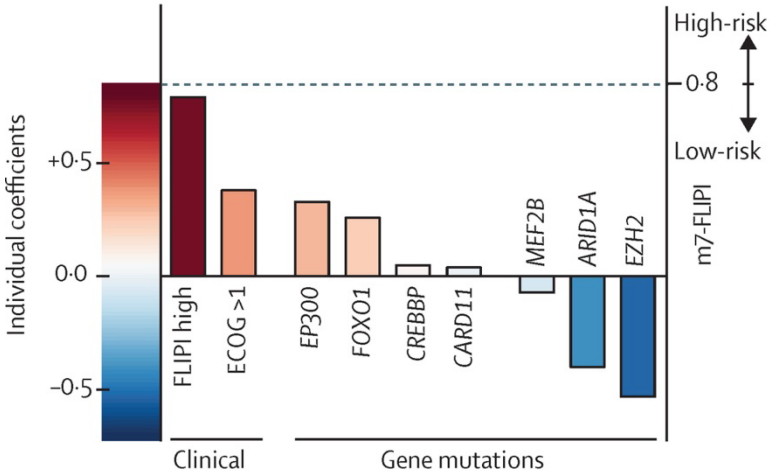


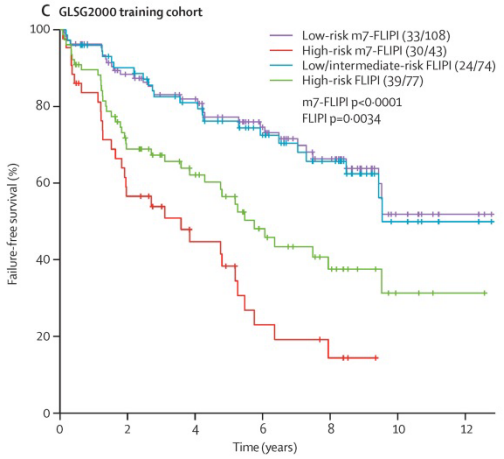
Early driver mutations in chromatin regulator genes
(*CREBBP*, *EZH2* and *KMT2D* (MLL2)),
Gained at transformation : *EBF1* and regulators of NF-κB signaling
(*MYD88* and *TNFAIP3*)

Okosun J et al Nat Genet. 2014 , 46:176-81.

Clinical Impact of FL Mutations

Risk Stratification





Pastore et al Lancet Oncol. 2015 Sep;16(9):1011-1012

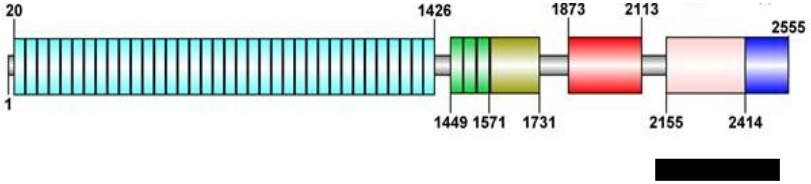
Target Therapy

EZH2 inhibitor (Tazemetostat) in Refractory/Relapsed FL

- OR: 63% in patients with EZH2 mutations (*N* = 8)
  28% in with wild type EZH2 (*N* = 46)

Morschhauser F et al Hematol Oncol 2017; 35, S2: 24–25

NOTCH1/2 Mutations in FL

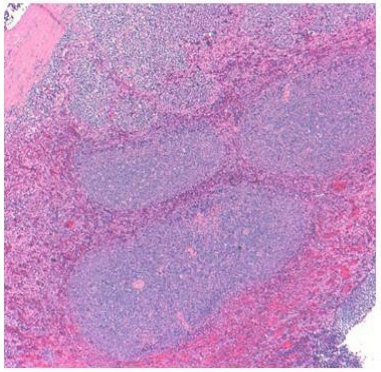


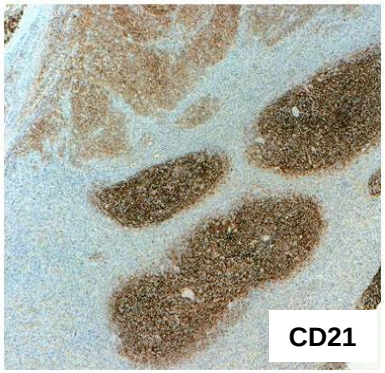
PEST/TADD domain
Truncanting mutations

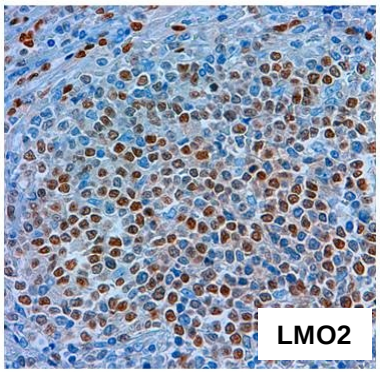
7/112 FL cases (6.3%)

5 *NOTCH1*
2 *NOTCH2*

NOTCH3/4 (4%)



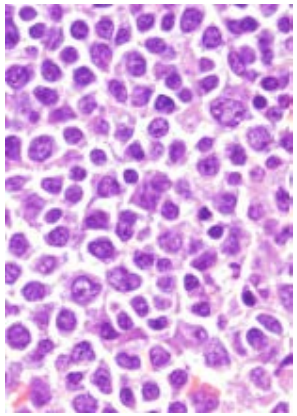


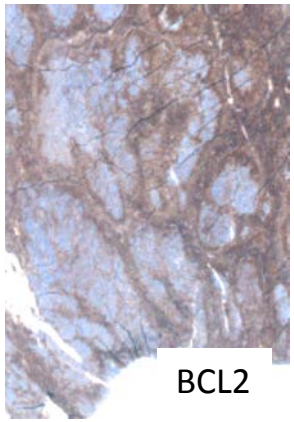


Female
Splenic/extranodal involvement
Negative for t(14;18)
DLBCL component

Karube K et al J Pathol 2014; 234:423-30
Krysiak K et al Blood 2017; 129: 473-483

Pediatric Type Follicular Lymphoma



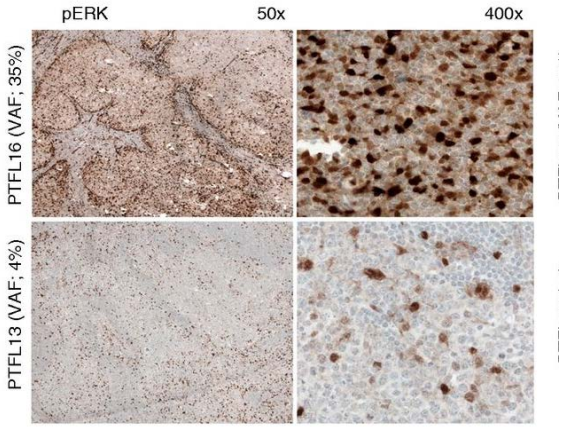


BCL2

Genes	PTFL (n=71) (%)	t(14;18)-neg FL (%)	t(14;18)-pos FL (%)	P-value
TNFRSF14	33-51	36	18-46	Ns
KMT2D	14-16	36	67-82	Ns
CREBBP	3*	45	33-64	0.001
FOXO1	5	27	-	Ns
GNA13	11	0	-	Ns
EZH2	3*	18	7-20	0.0049

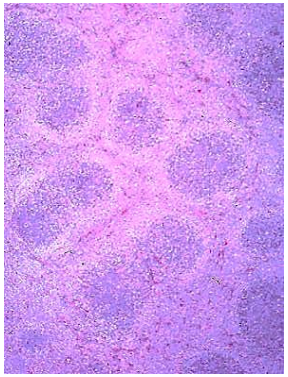
* >18yr

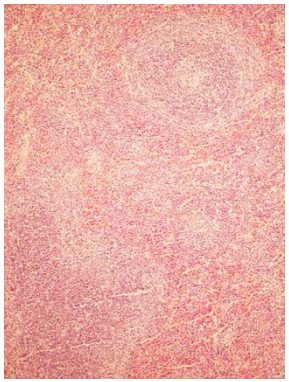
Genes	PTFL
MAP2K1	38-49%
MAPK1	10%
IRF8	15-50%



Louissaint A et al Blood 2016; Ozawa et al Mod Pathol 2016; Schmidt J et al Blood 2016 & 2017

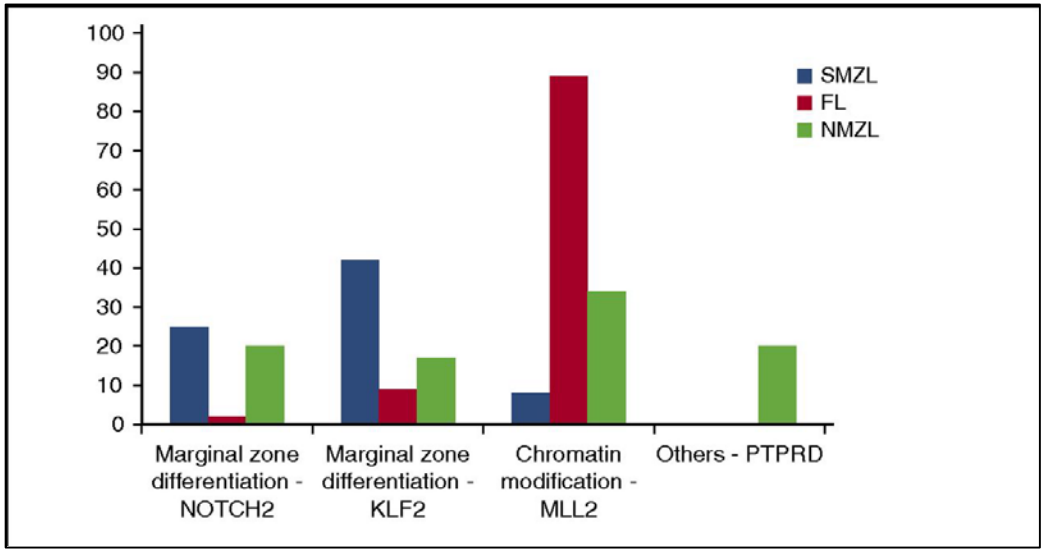
Mutational Profile of Nodal and Splenic Marginal Zone Lymphoma





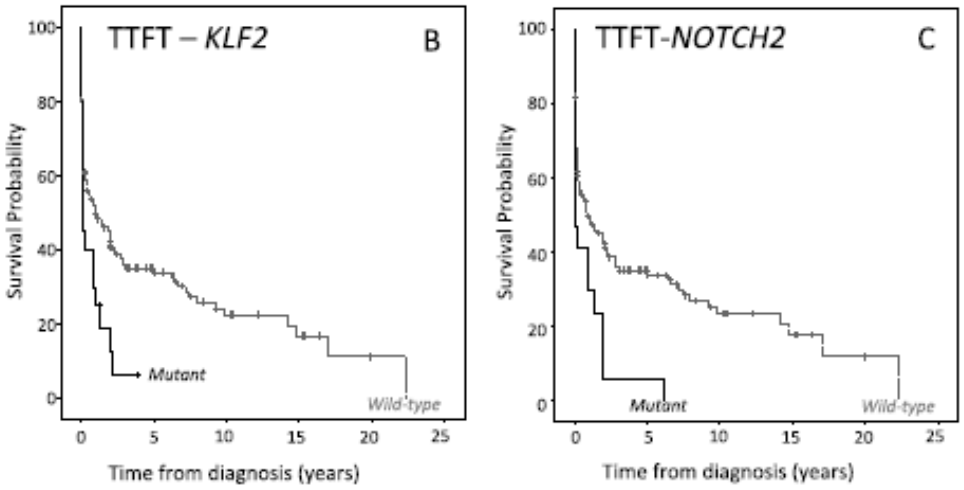
Targeted Pathways

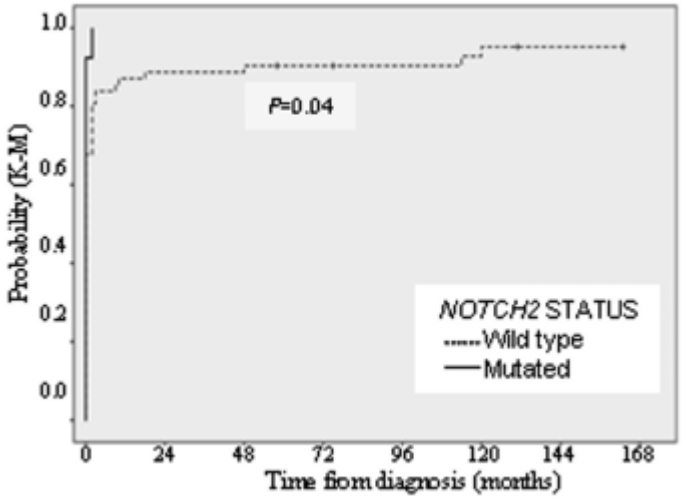
- **KLF2, NOTCH2, activation** (40-25%)
- **NFkB activation** (36-51%)
- **BCR signaling** (SMZL 8%)
- **PTPRD (NMZL 20%)**



Arcaini L, Rossi D. Haematologica. 2012; Rossi et al J Exp Med 2012; Clipson et al Leukemia 2015; Parry et al Clin Cancer Res 2015; Spina V et al; 2016; Piris MA Blood 2016;

Clinical Impact of Somatic Mutations in SMZL

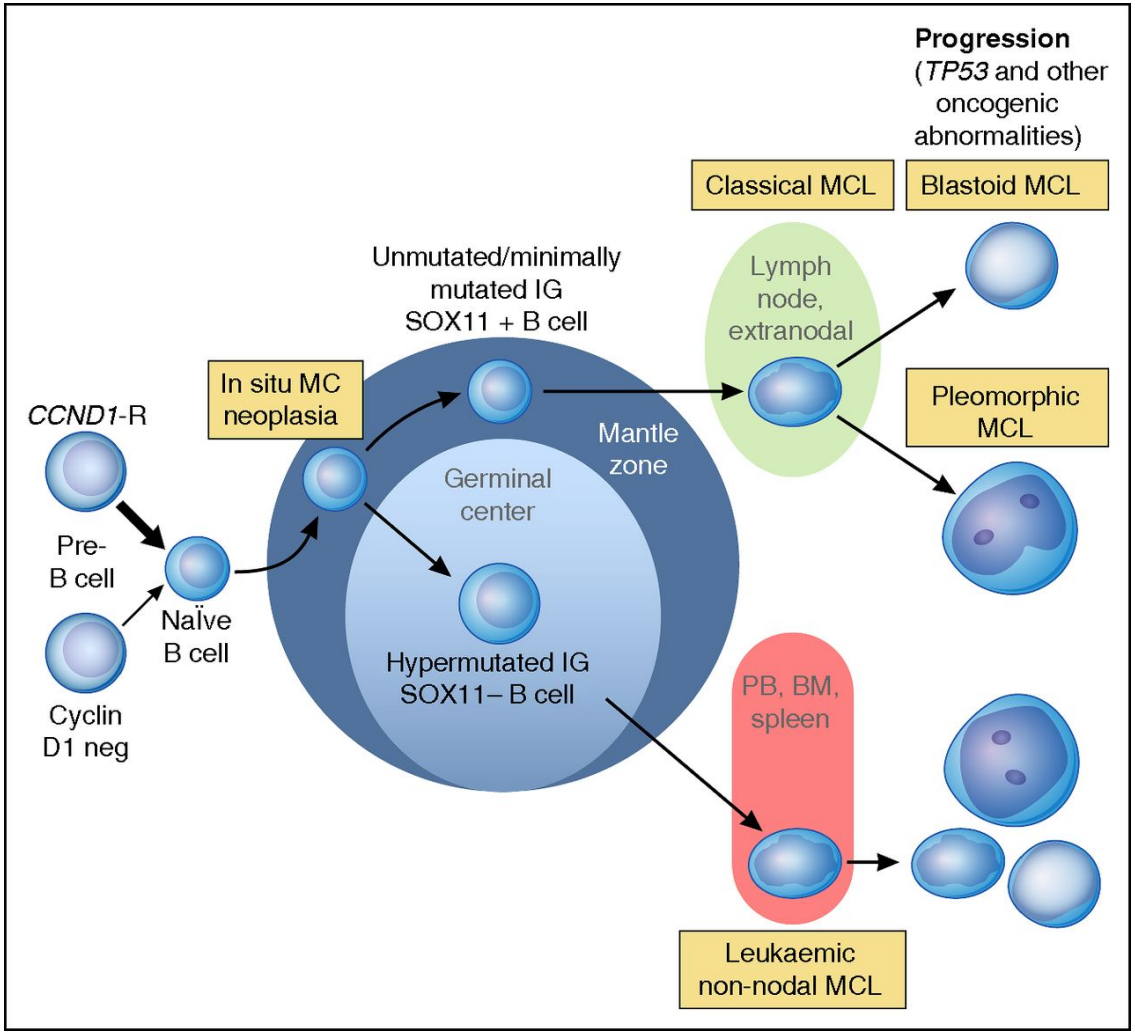




Parry et al Clin Cancer Res 2015

Campos-Martin Y et al Haematologica 2017

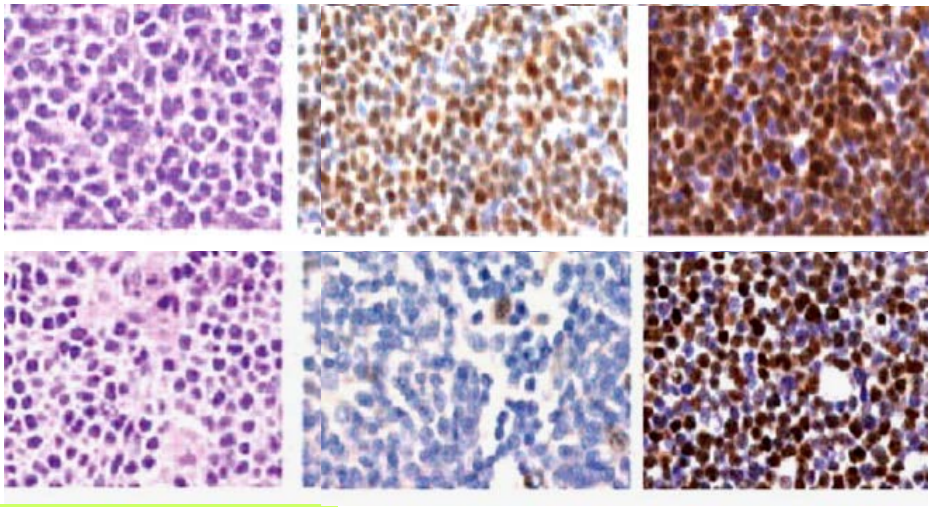
Molecular Pathogenesis and Clinical Subtypes of MCL



Steven H. Swerdlow et al. Blood 2016;127:2375-2390

Mantle cell lymphoma
CCND1-negative variant

Classic MCL

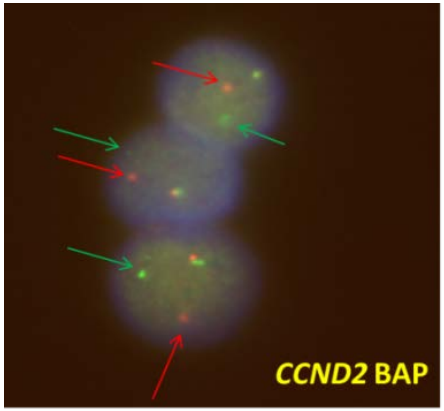


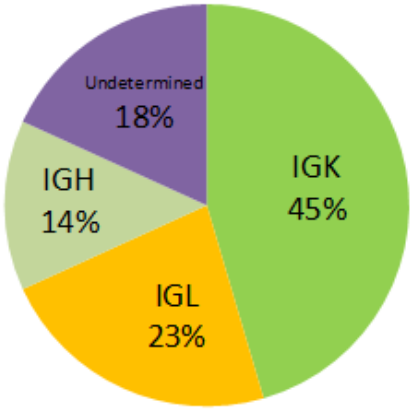
CCND1 neg MCL

Cyclin D1

Sox11

Rearrangements	No. (%)
CCND2	22 (55%)
CCND3	0
No Cyclin D gene translocation	18 (45%)

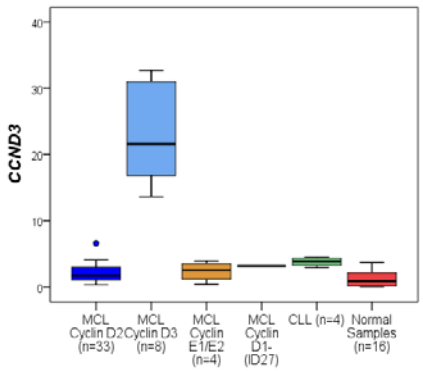


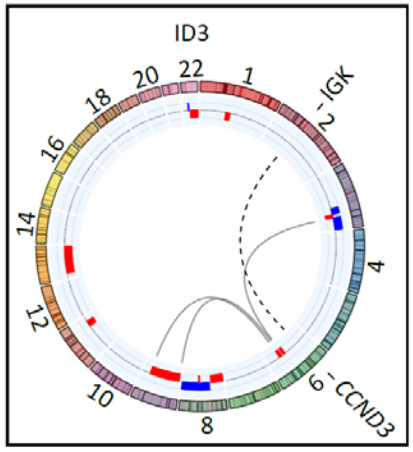


Mozos et al Haematologica 2009; Salaverria et al Blood 2013

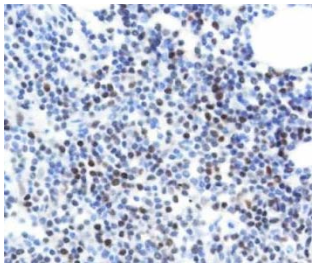
Cryptic IG-*CCND1/2/3* rearrangements in MCL

CCND1/2 neg MCL

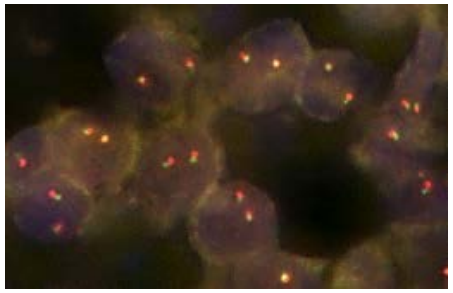




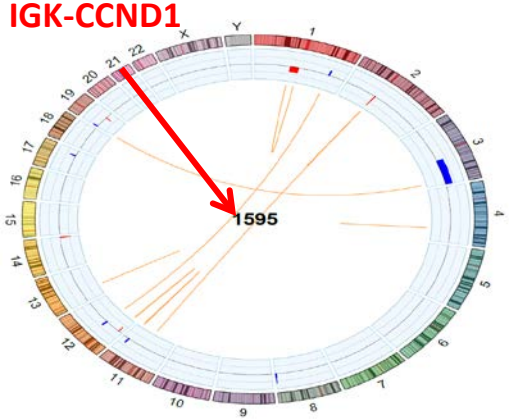
IHC CCND1+

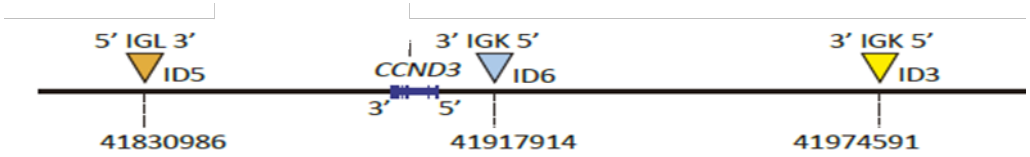


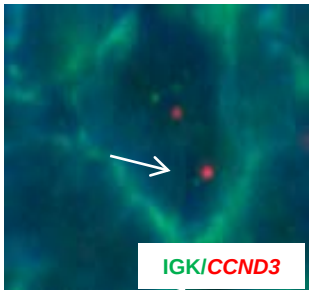
Break apart CCND1 neg

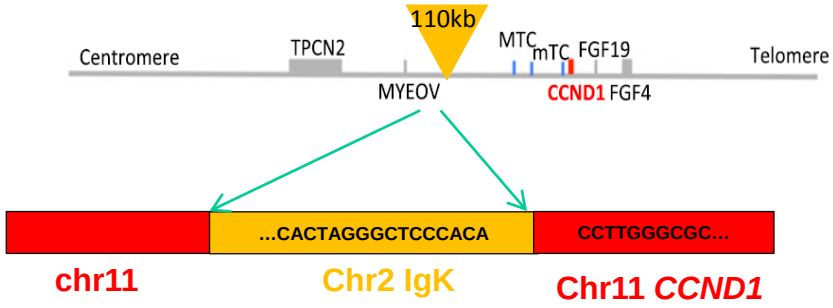


Cryptic IGK-CCND1



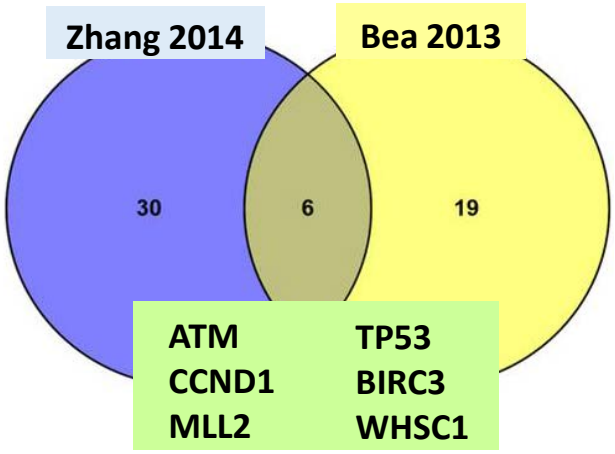


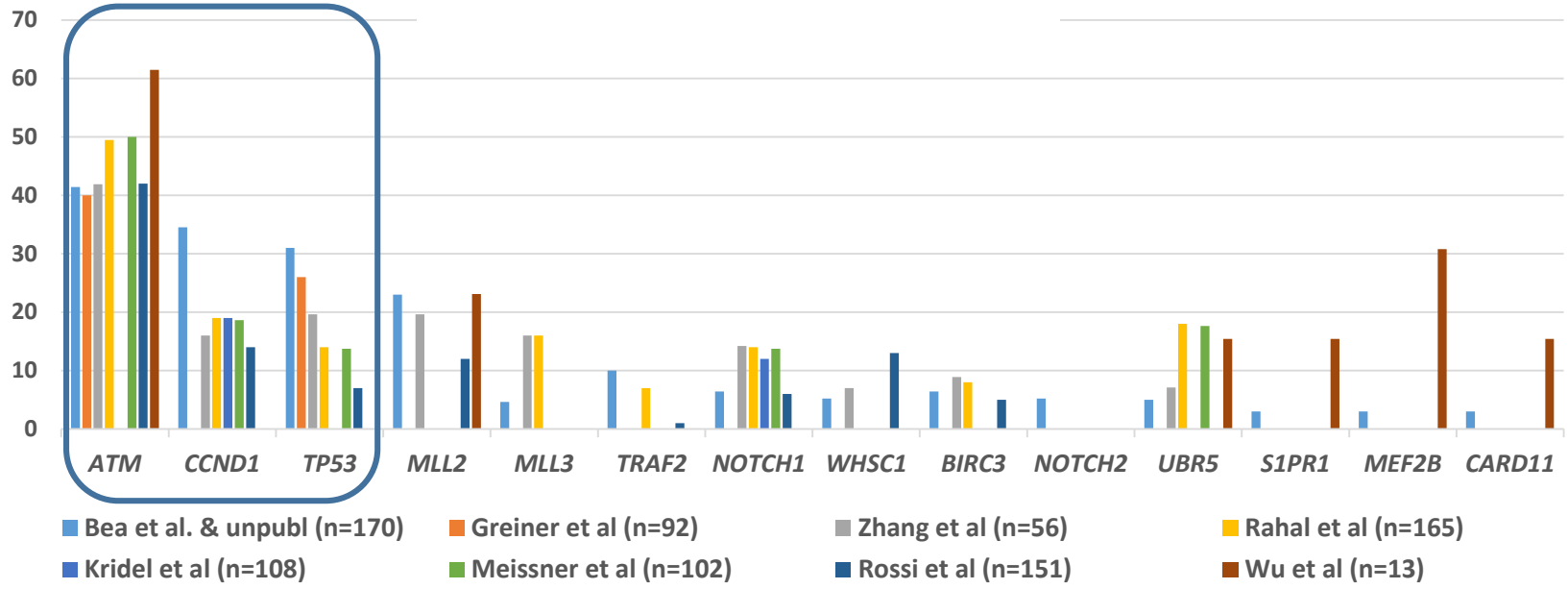




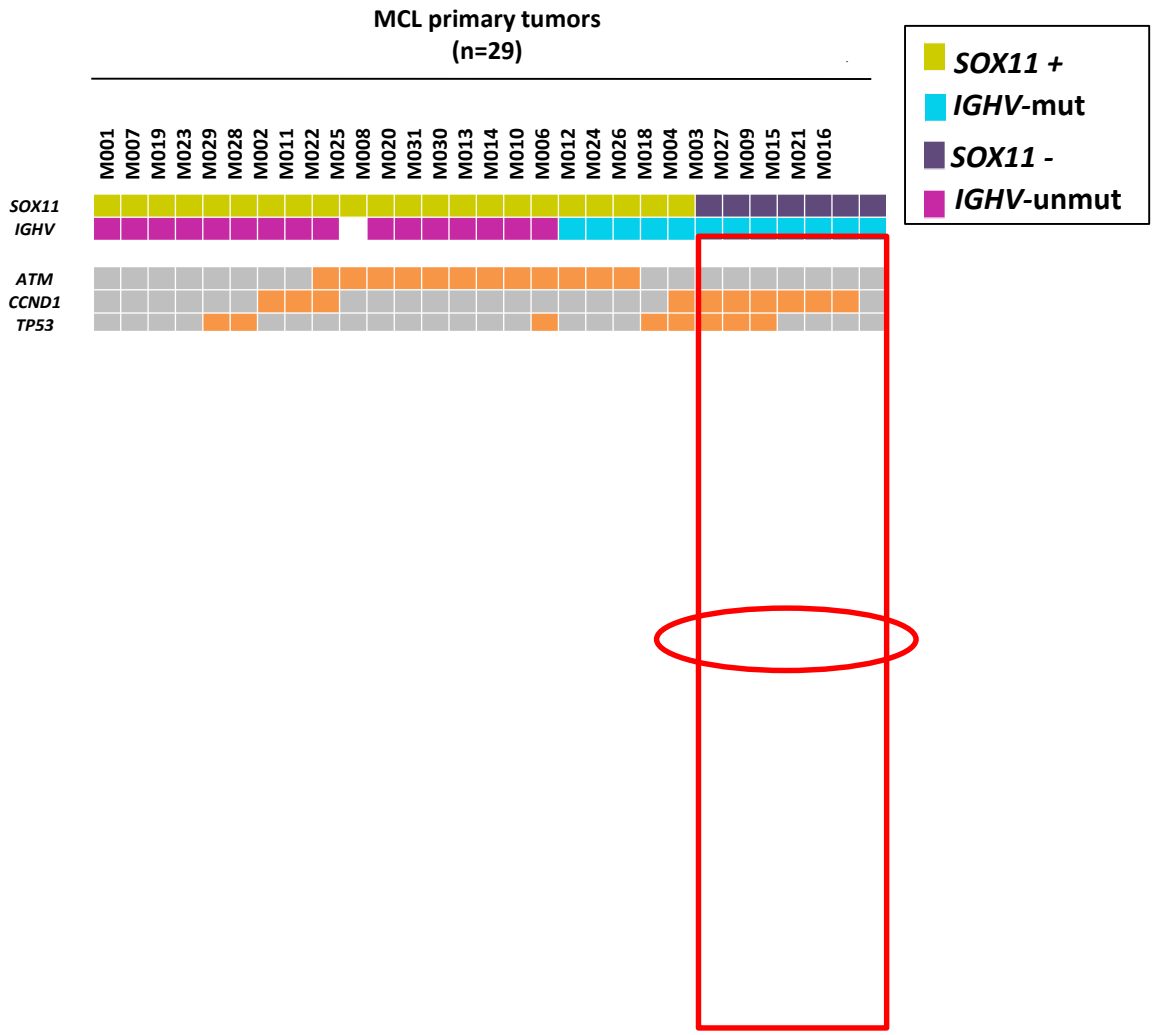
Bea S et al unpublished

Recurrent gene mutations in MCL





Somatic Mutations in MCL



SOX11 +
ATM (55%)
Chromatin (10%)

NOTCH1/2 (5%)
TP53 23%)
BIRC3 (7%)

High CNA

SOX11 -
TLR2 (29%)

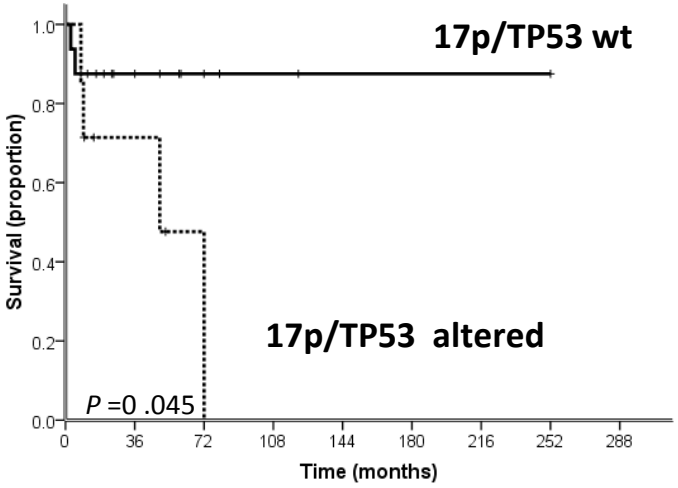
NOTCH1/2 (5%)
TP53 23%)
BIRC3 (14%)

Low CNA

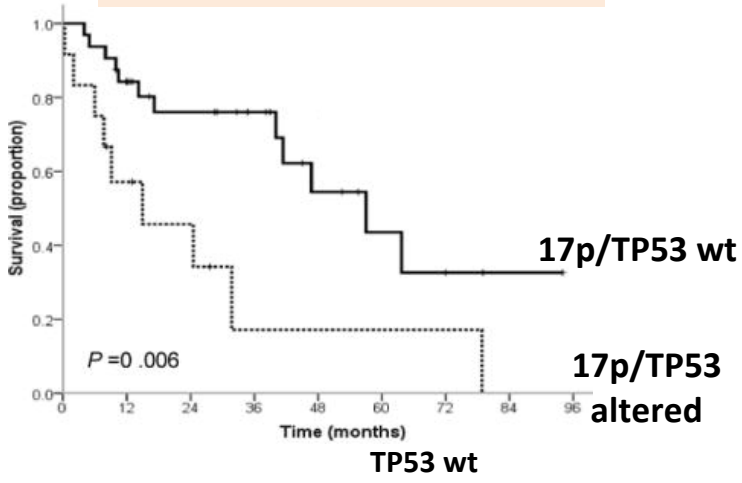
Bea S et al PNAS 2013

Prognostic impact of 17p*TP53* aberrations in MCL

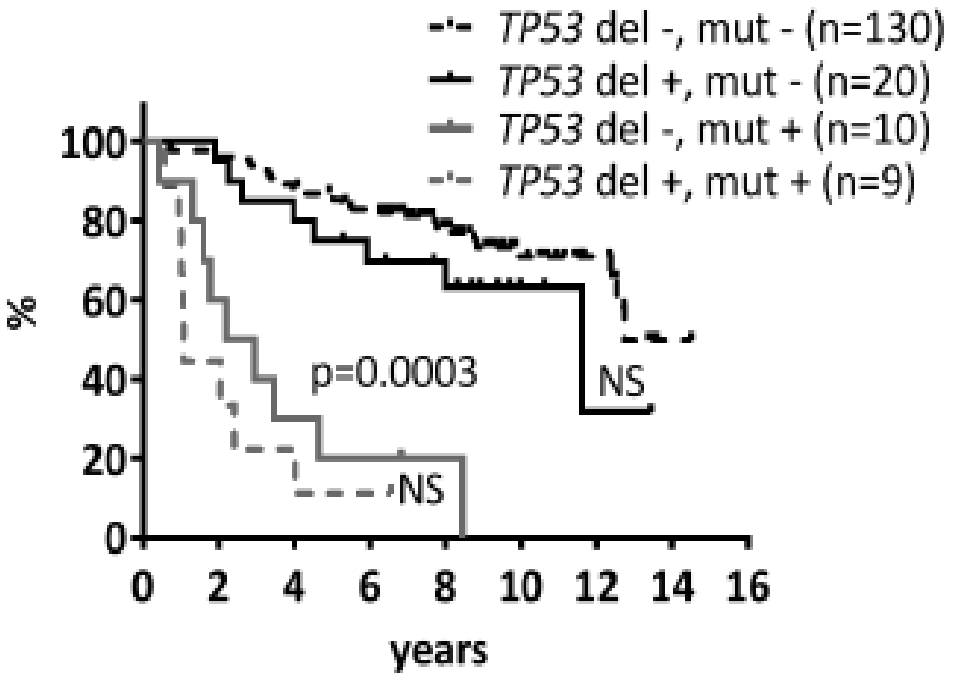
SOX11-negative MCL



SOX11 +



Royo C et al, Leukemia 2012



Eskelund CW et al Blood 2017

Clinical Relevance of Mutational Profiles in Lymphoid Neoplasms

- **Diagnostic criteria to refine entities**
- **Identification of subsets of patients**
- **Prognostic and predictive significance**
- **Monitoring disease evolution: Dynamic evolution of mutational landscape**
- **Targets for therapy decisions:**
  - **Selection of patients**
  - **Actionable mutations**

M Chagall, Tossa de Mar, 1933

Recurrently Mutated Pathways in Small B-cell Neoplasms

Pathway	U-CLL	M-CLL	cMCL	nnMCL	FL	PTFL	LPL	MZL	HCL
DNA-damage	+		+						
SF3B1	+	+/-							
NOTCH1/2	+	+/-	+		+/-			+	
Chromatin Remodeling			+		+				
BCR-signaling					+			+/-	
NFkB	+		+					+/-	
TLR/MYD88		+/-		+/-			+		
MAPK						+			+