



FORUM IN EMATOLOGIA:

BARI
6-7 OTTOBRE 2016
Villa Romanazzi Carducci

Il ruolo del microambiente nella terapia

**Lab of B Cell Neoplasia - Division of Experimental Oncology
Strategic Research Program on CLL – Department of Onco-Hematology**

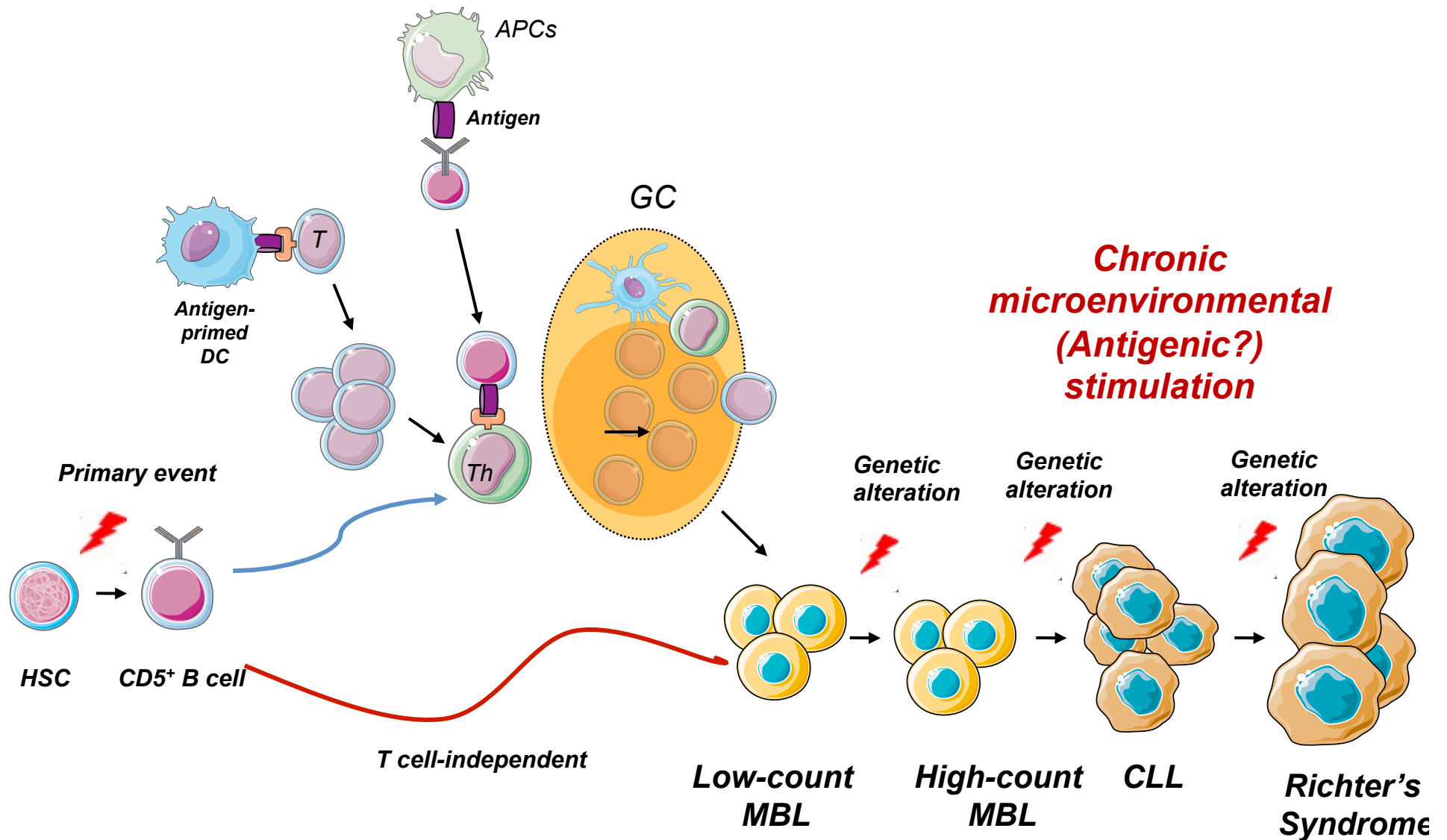


**Università Vita-Salute San Raffaele - Milano
IRCCS Istituto Scientifico San Raffaele - Milano**

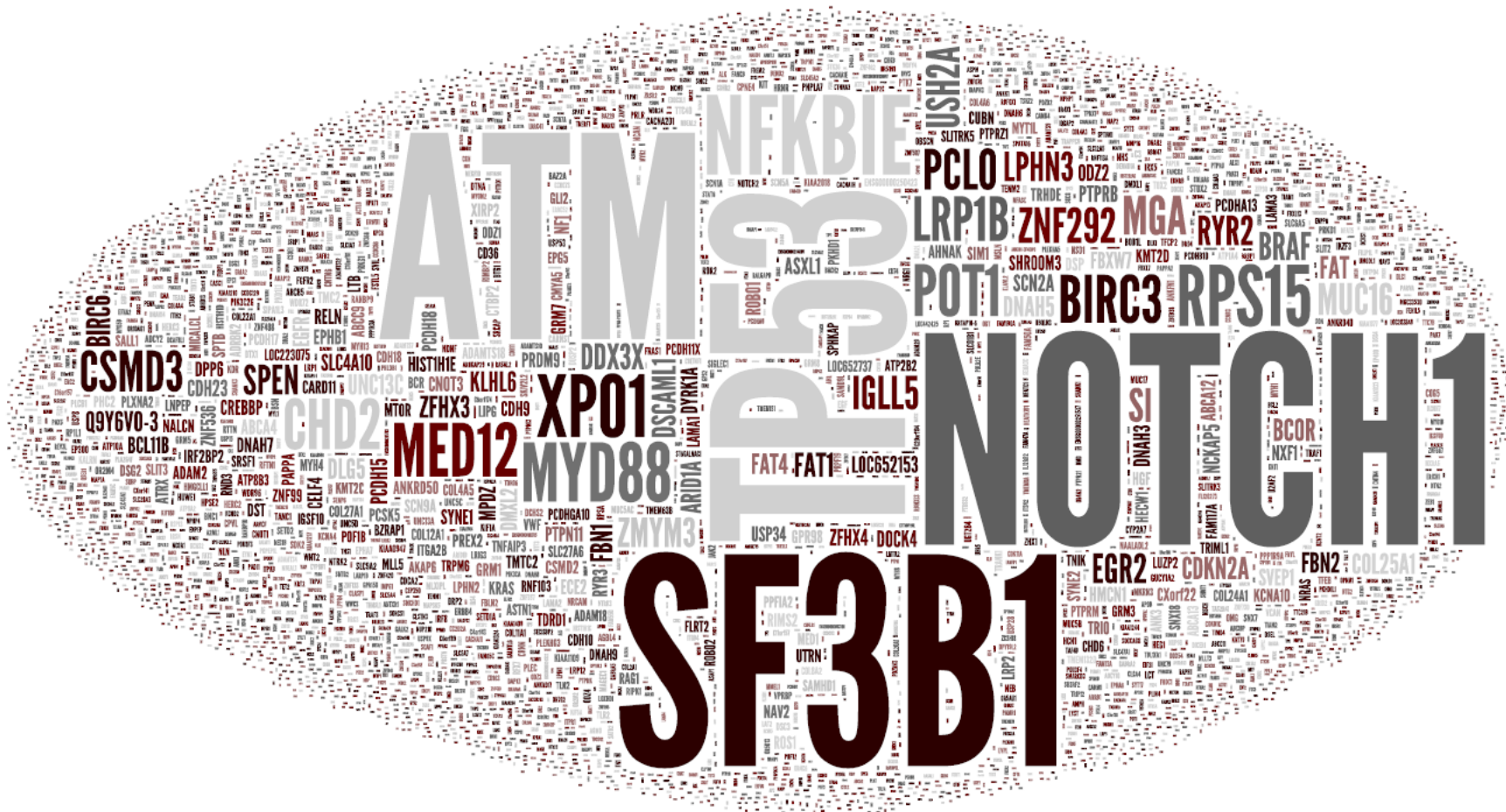
Paolo Ghia



A long path to CLL

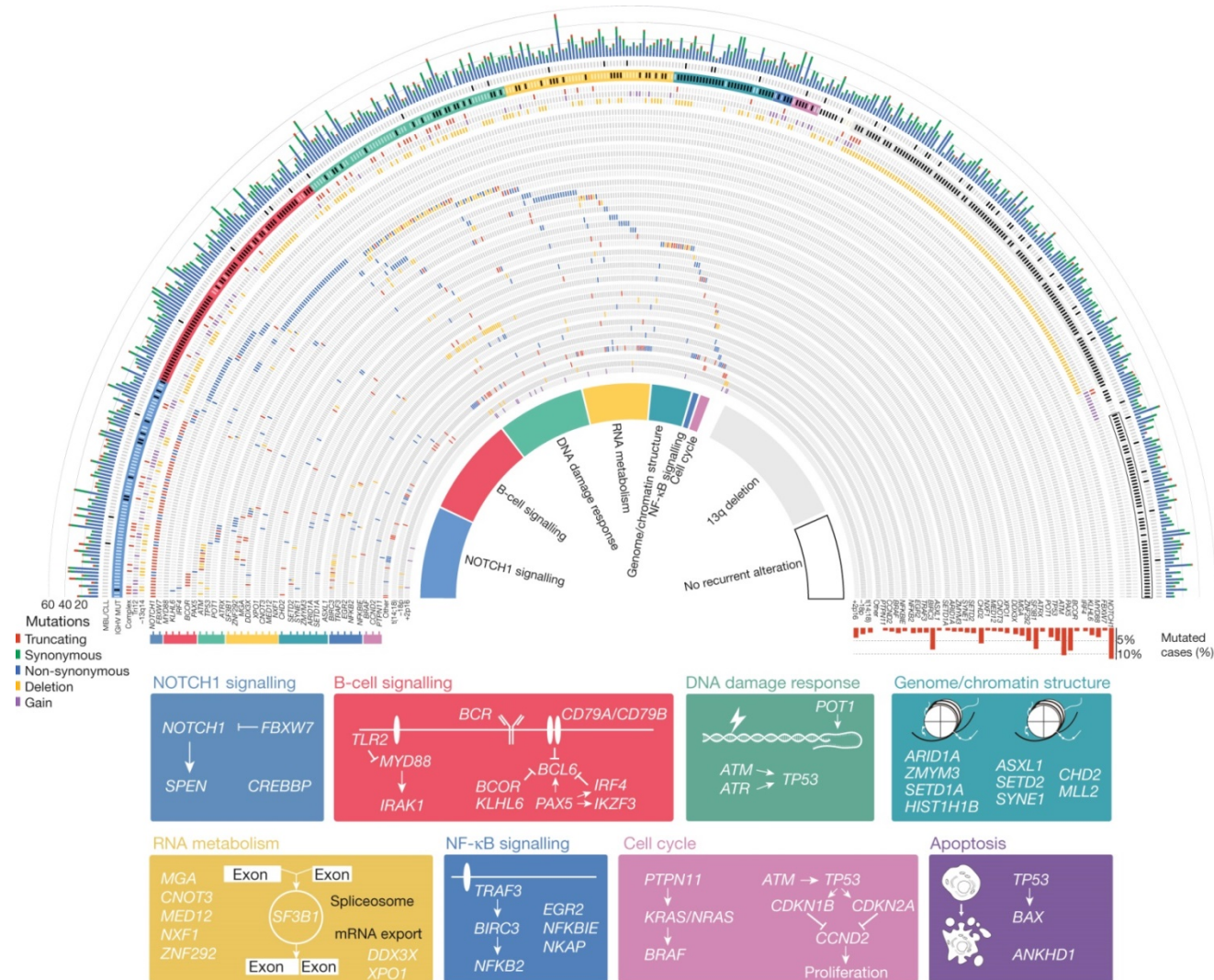


The mutational landscape of CLL

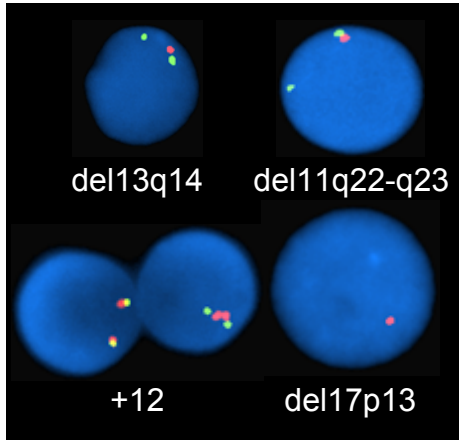


The wordcloud shows the genes that are reported as mutated in CLL by the v77 of the Catalogue of Somatic Mutations in Cancer (COSMIC). The size of the font is proportional to the mutation frequency

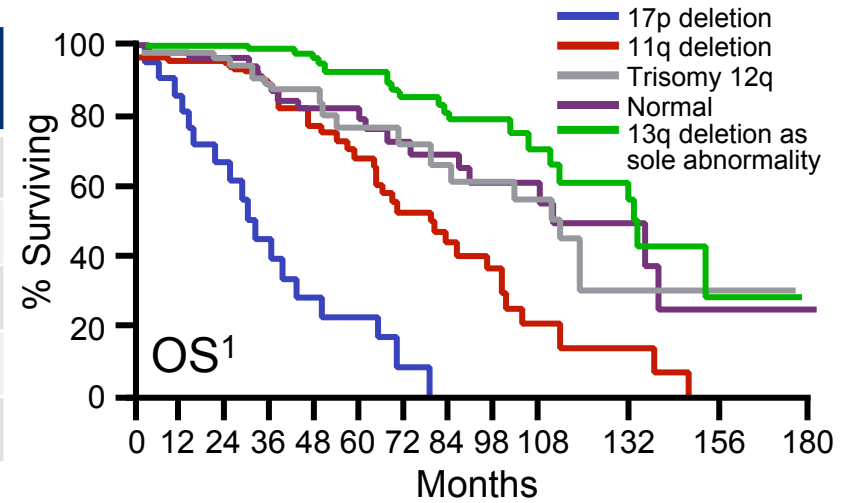
1000 pts - approaching completion?



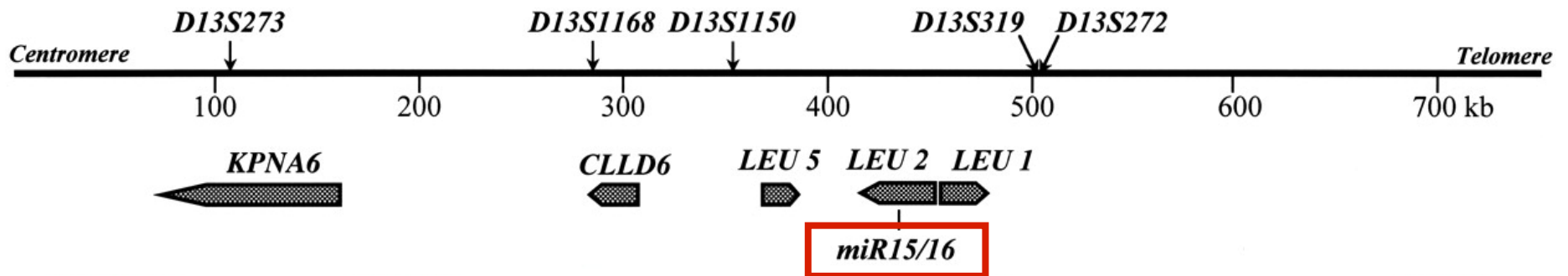
TP53 disruption is associated with poor prognosis



Aberration	Incidence (%) ¹	Median OS (months) ¹
17p del	7	32
11q del	18	79
+12	16	114
Normal	18	111
13q del	55	133

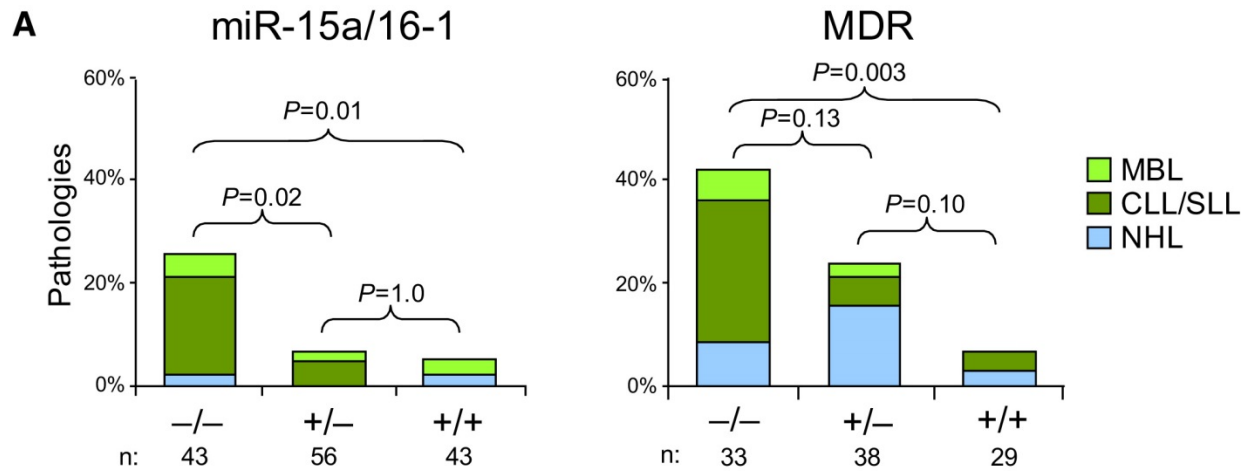


Döhner, *New Engl J Med* 2000



Calin et al. *PNAS* 2002

Del 13q in CLL and MBL

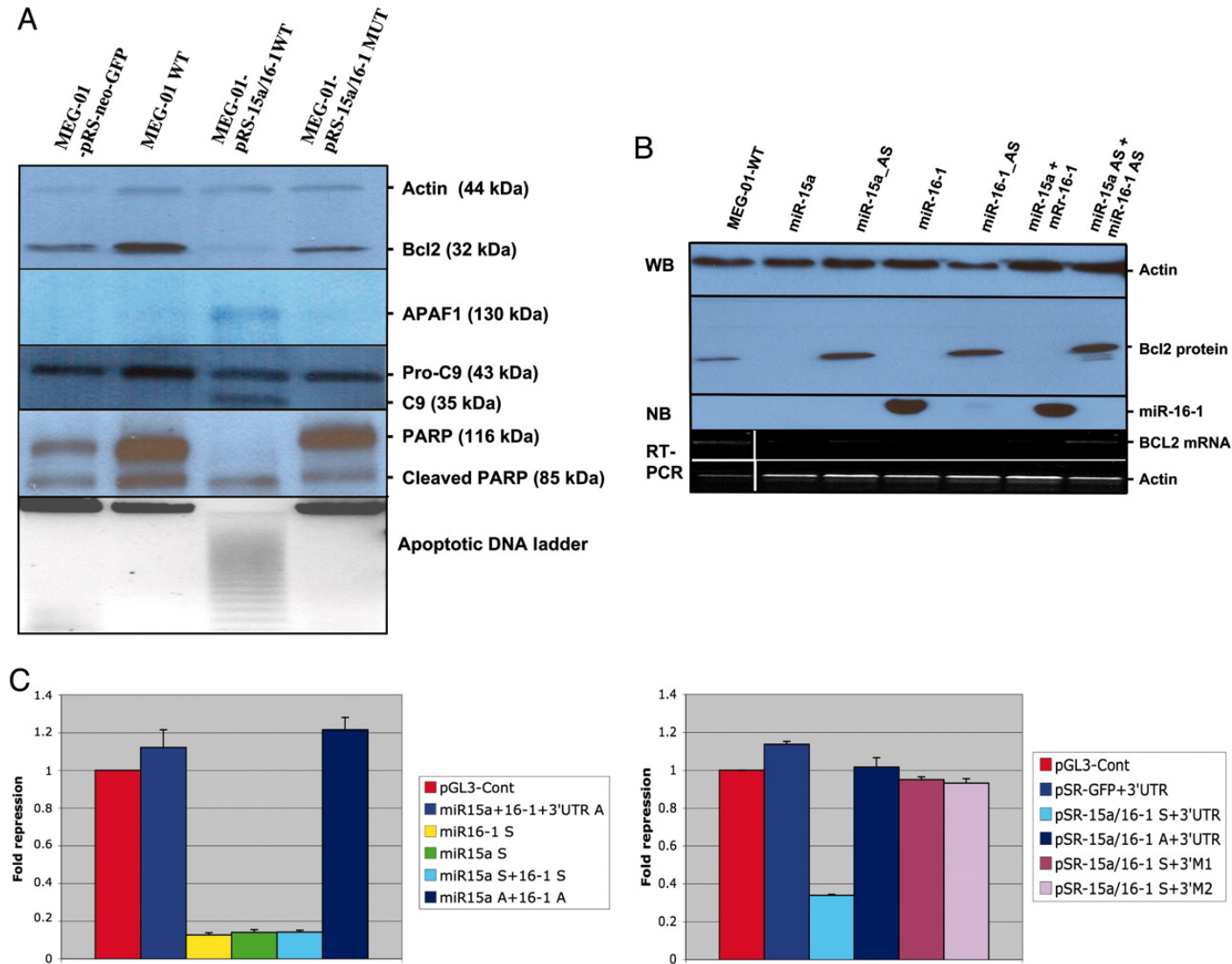


Del13q14.3

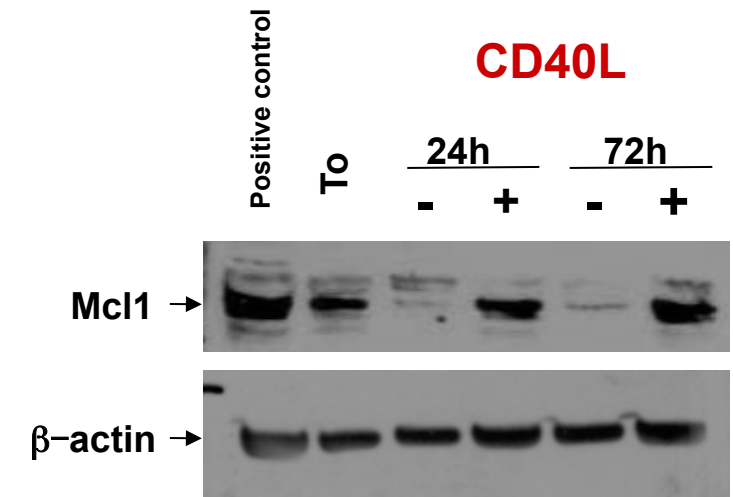
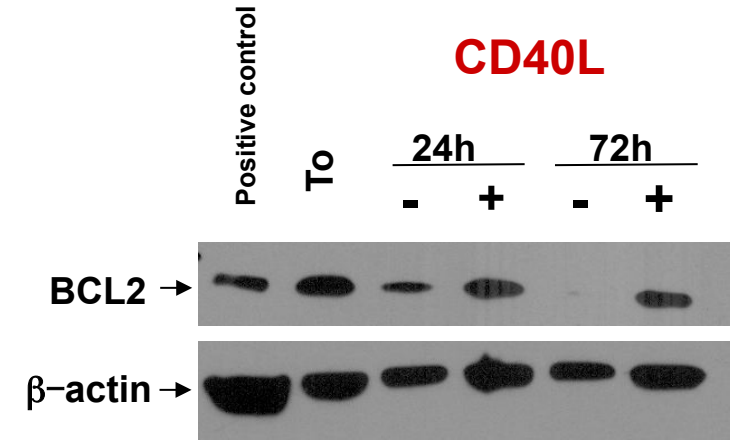
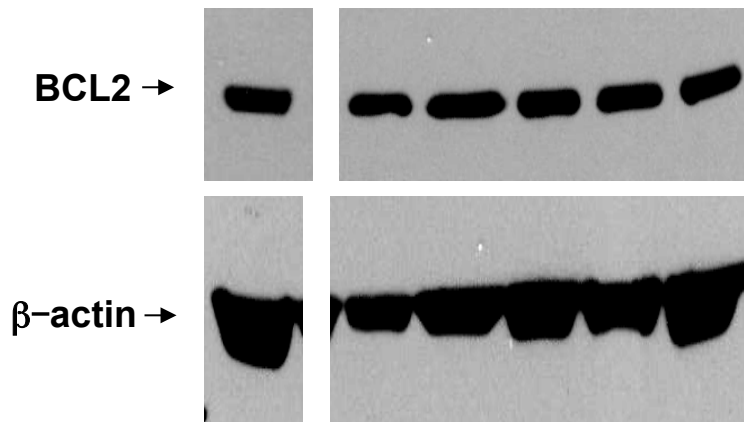
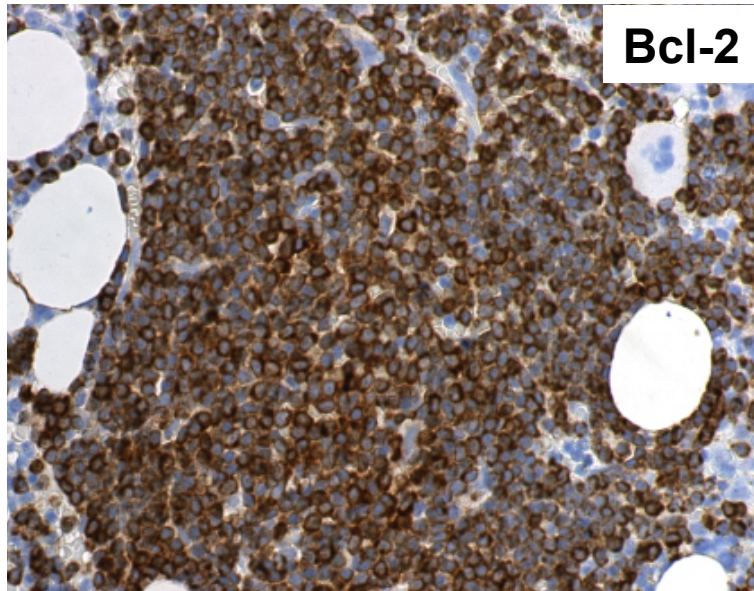


7/16 MBL cases
43.8%

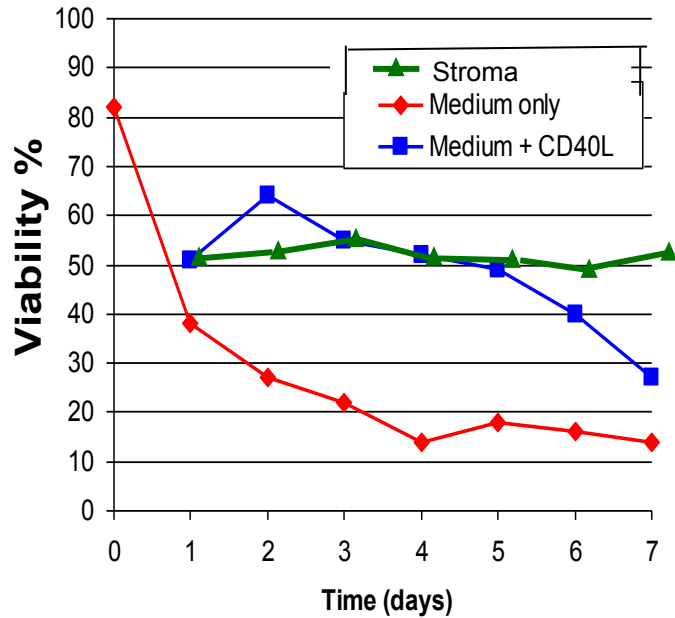
BCL2 is a target of miR-15 and miR-16



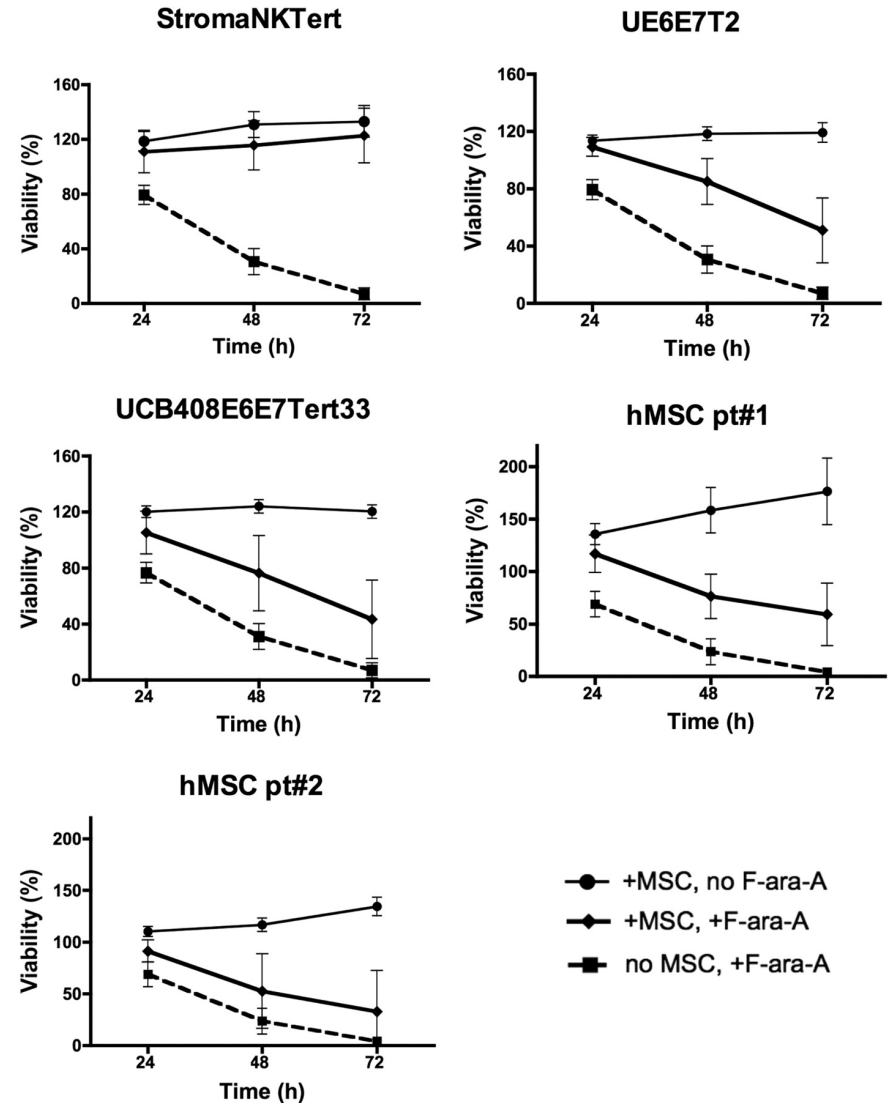
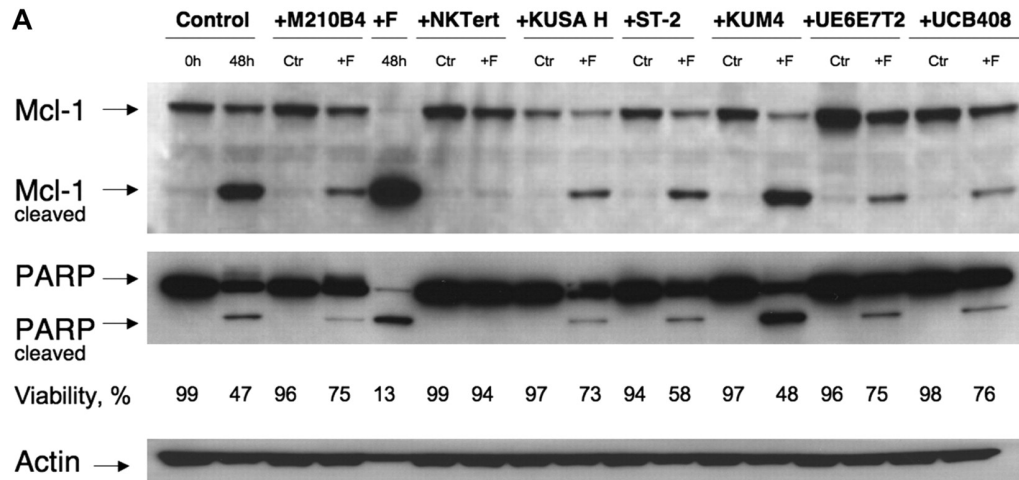
BCL2 is overexpressed in CLL



BCL2 is upregulated upon stroma interaction

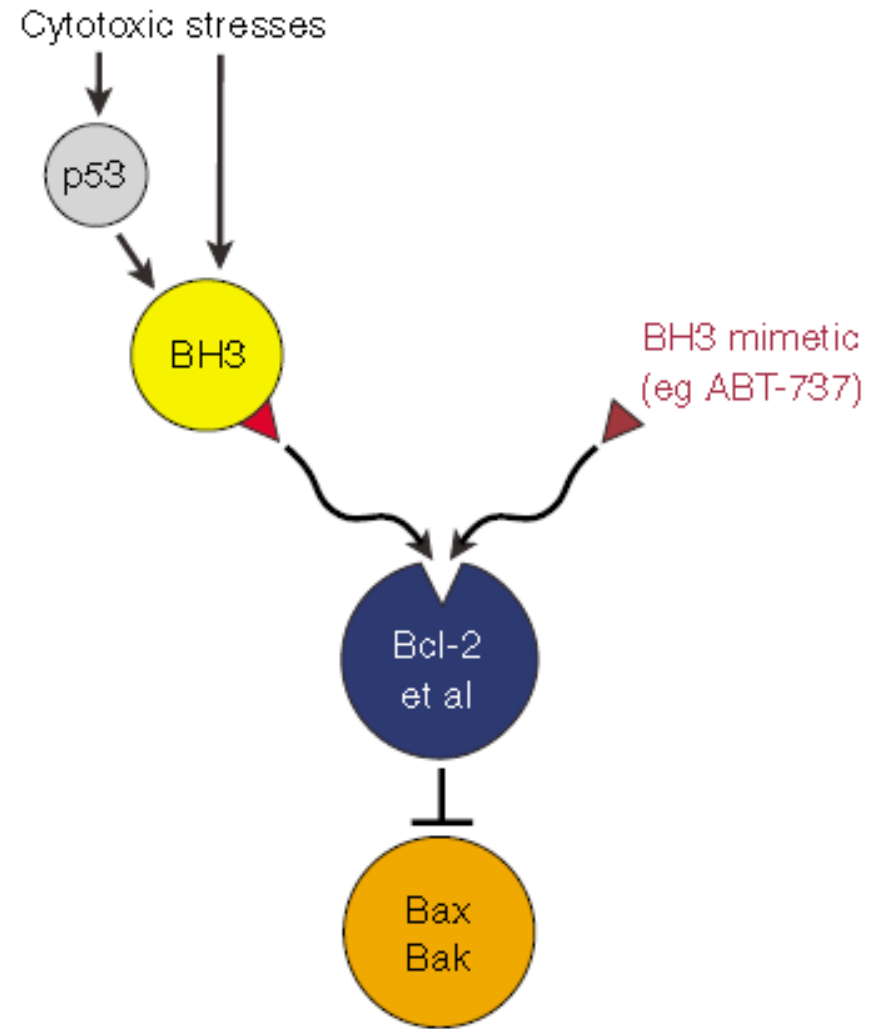
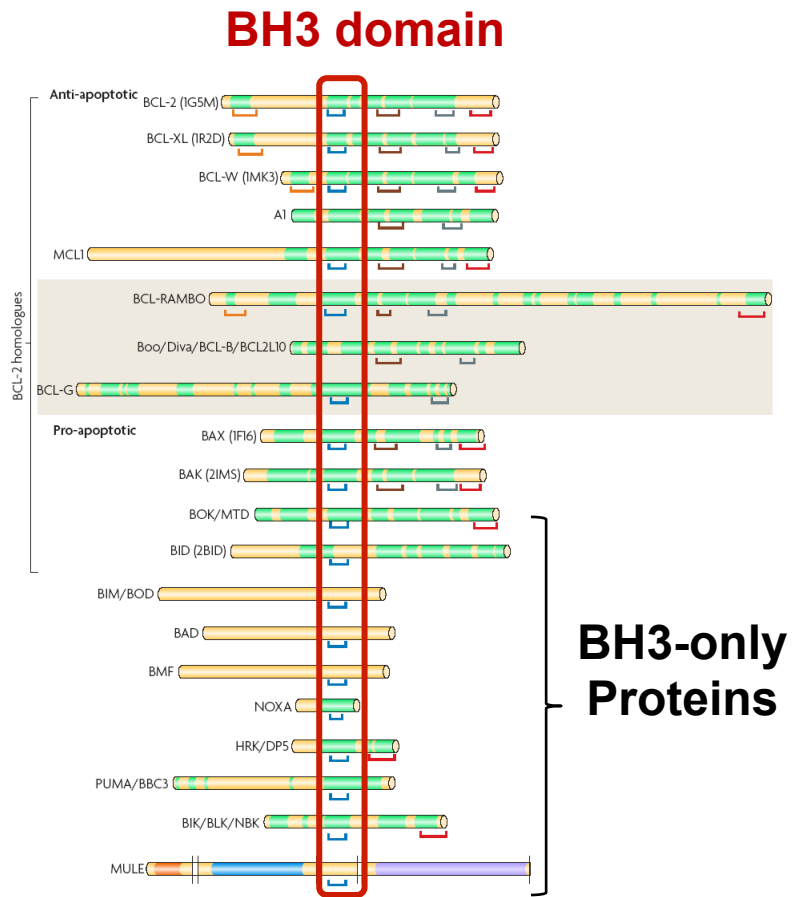


Granziero et al, Blood 2003



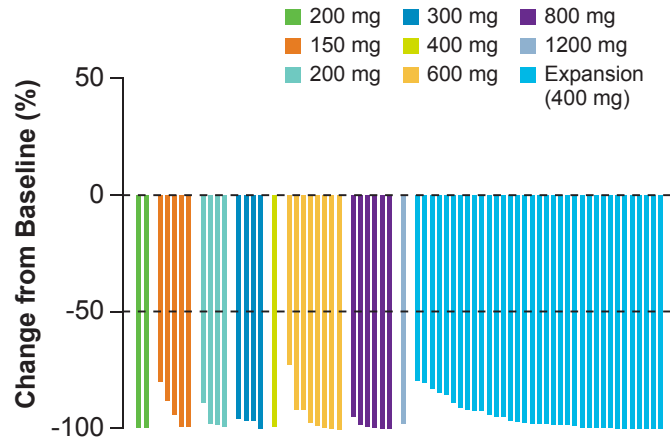
Kurtova A V et al. Blood 2009

BH3 Mimetics: BCL2-inhibitors



High responses in R/R CLL with ABT-199

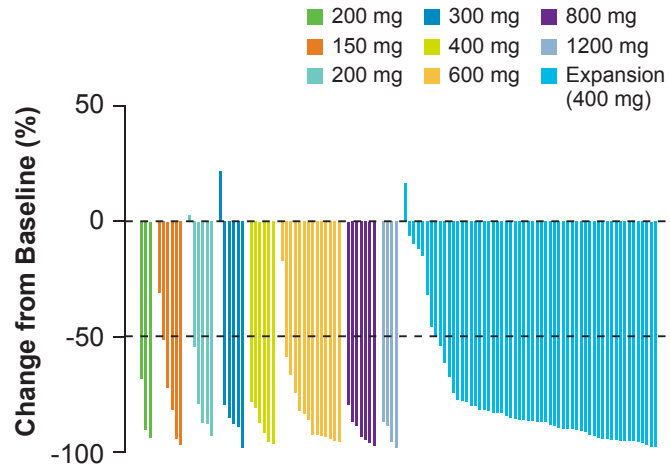
ABSOLUTE LYMPHOCYTE COUNT



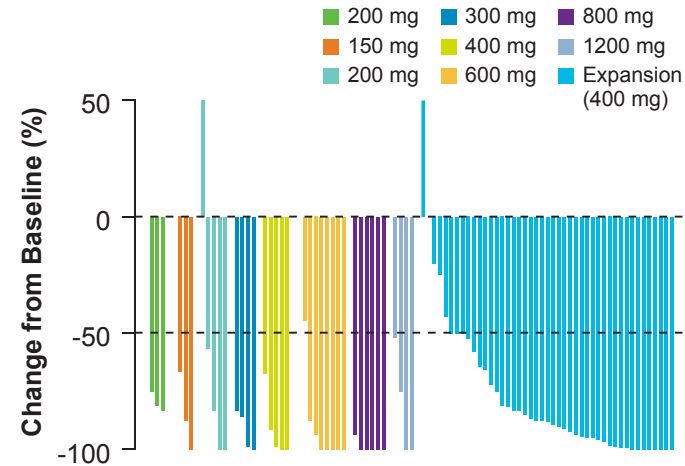
Median time to:	N	Median (range)
Lymphocytes <4000/mm ³	65	22 (1-451) days
50% reduction in nodal size	99	42 (20-417) days
Nodes <1.5 cm	34	8 (1-27) months
Complete clearance of bone marrow infiltrate	26	6 (2-22) months

Total number of R/R CLL and SLL patients = 116

NODAL MASS

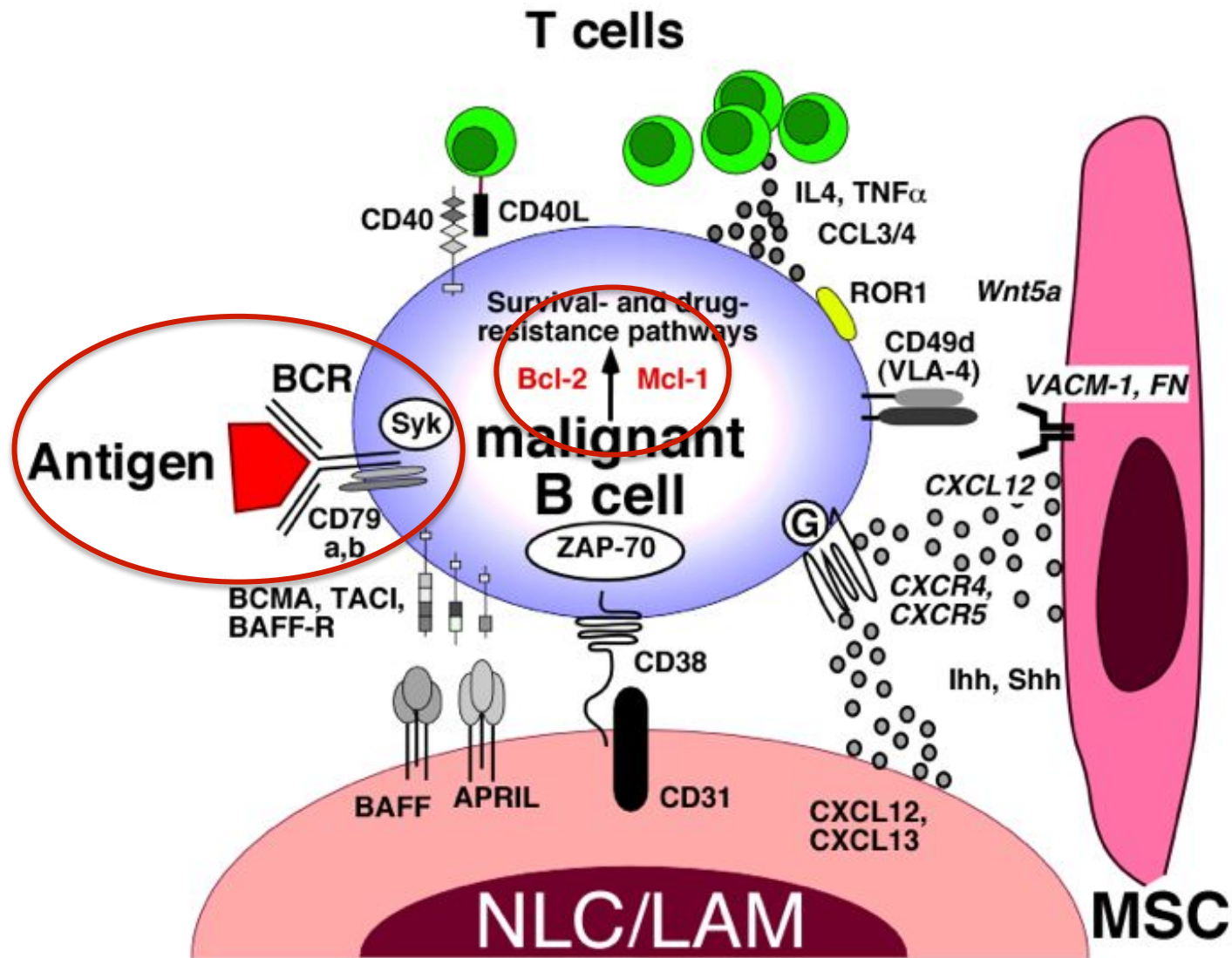


BONE MARROW INFILTRATE

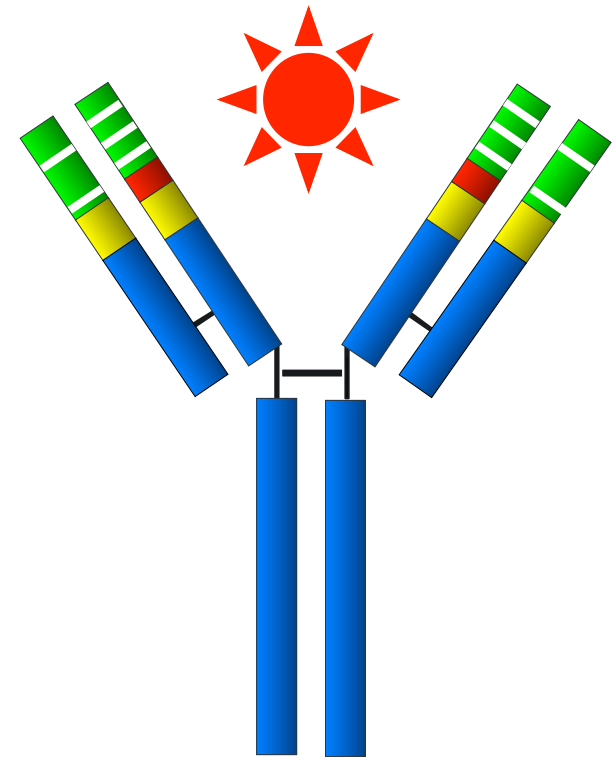
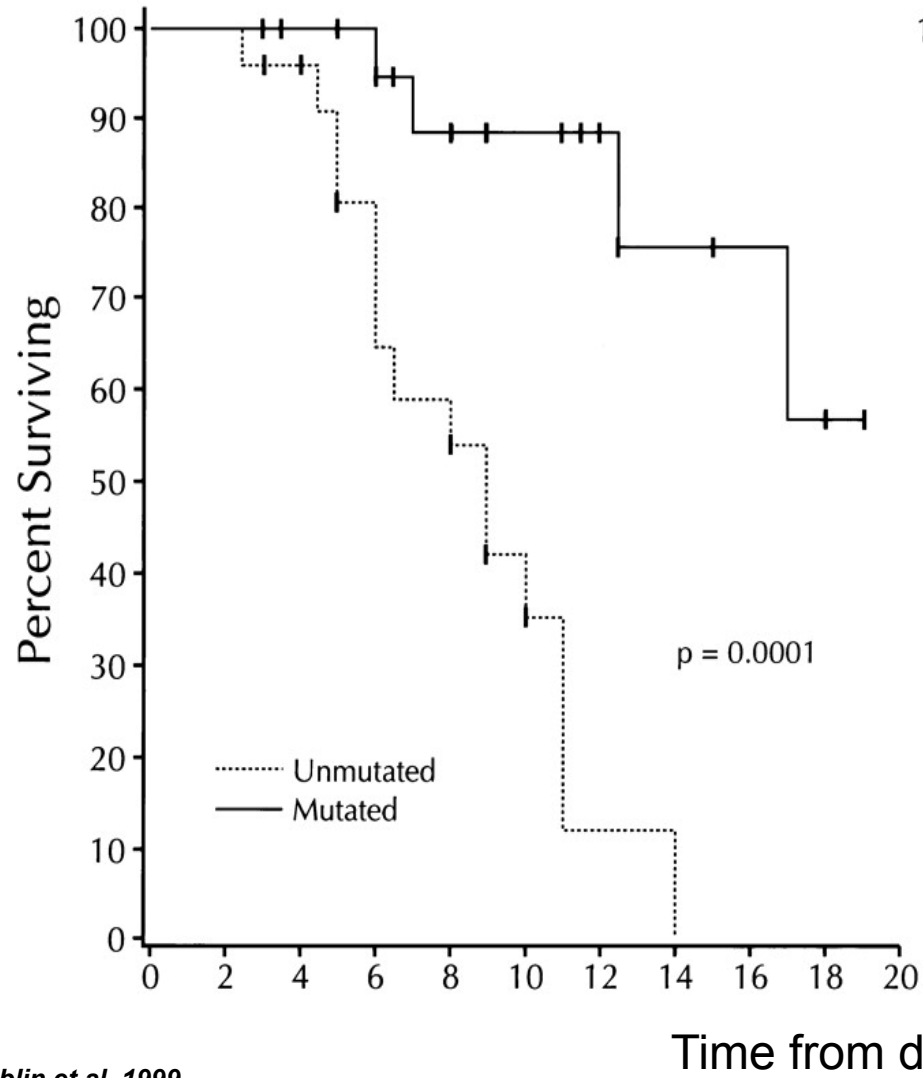


Note: Lymphocyte count in peripheral blood is reported only for the 66 patients who had lymphocytosis immediately before administration of ABT-199

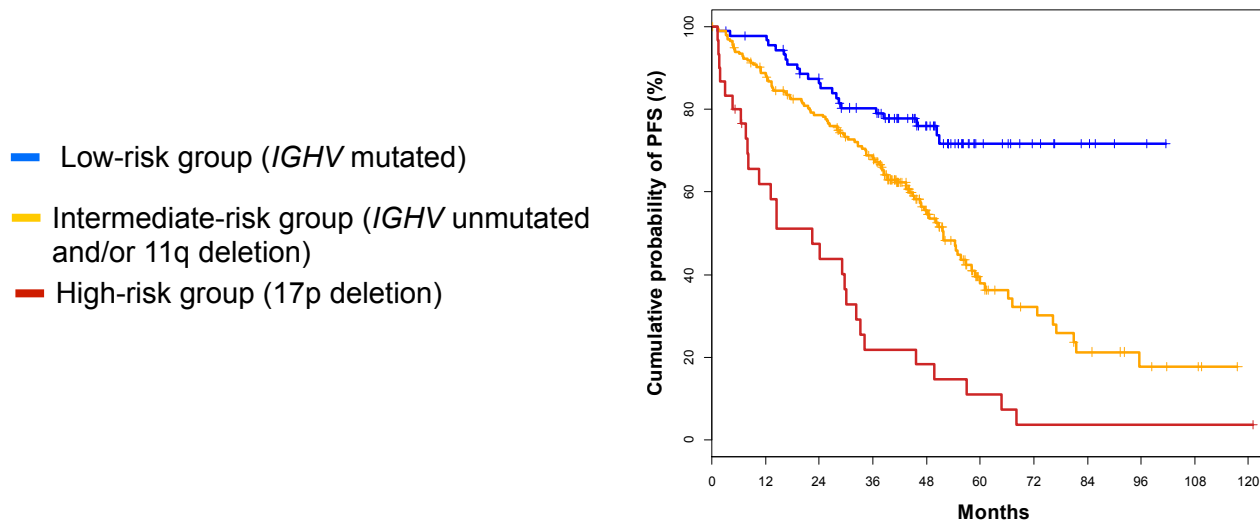
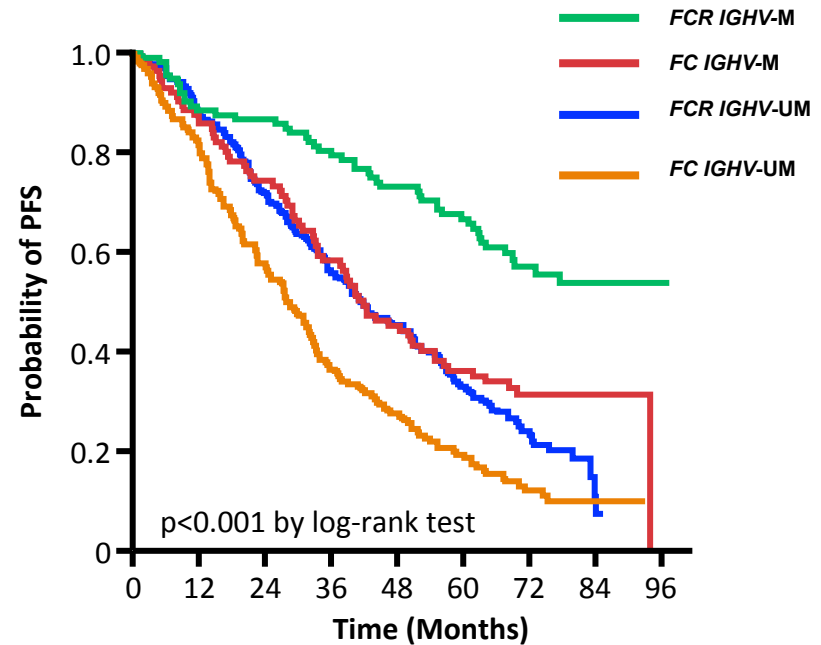
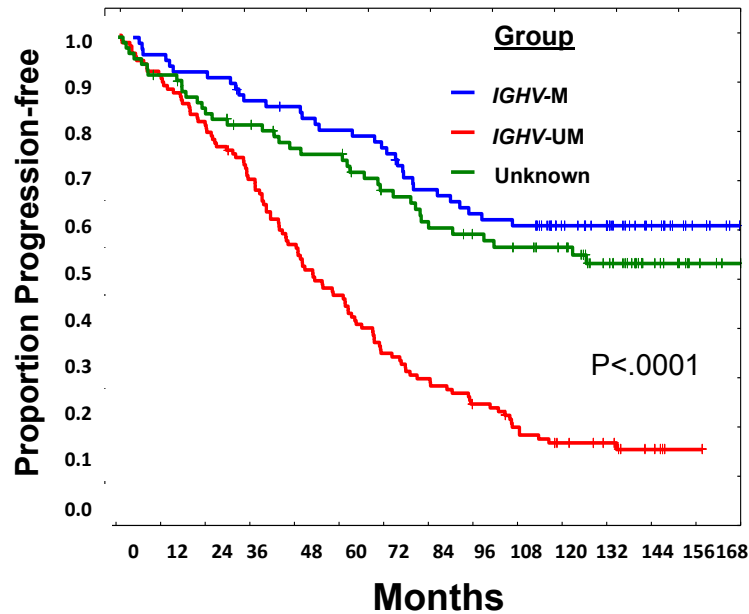
Microenvironmental stimuli in CLL



IG genes can be mutated in CLL



Long term remissions in mutated IGHV with FCR

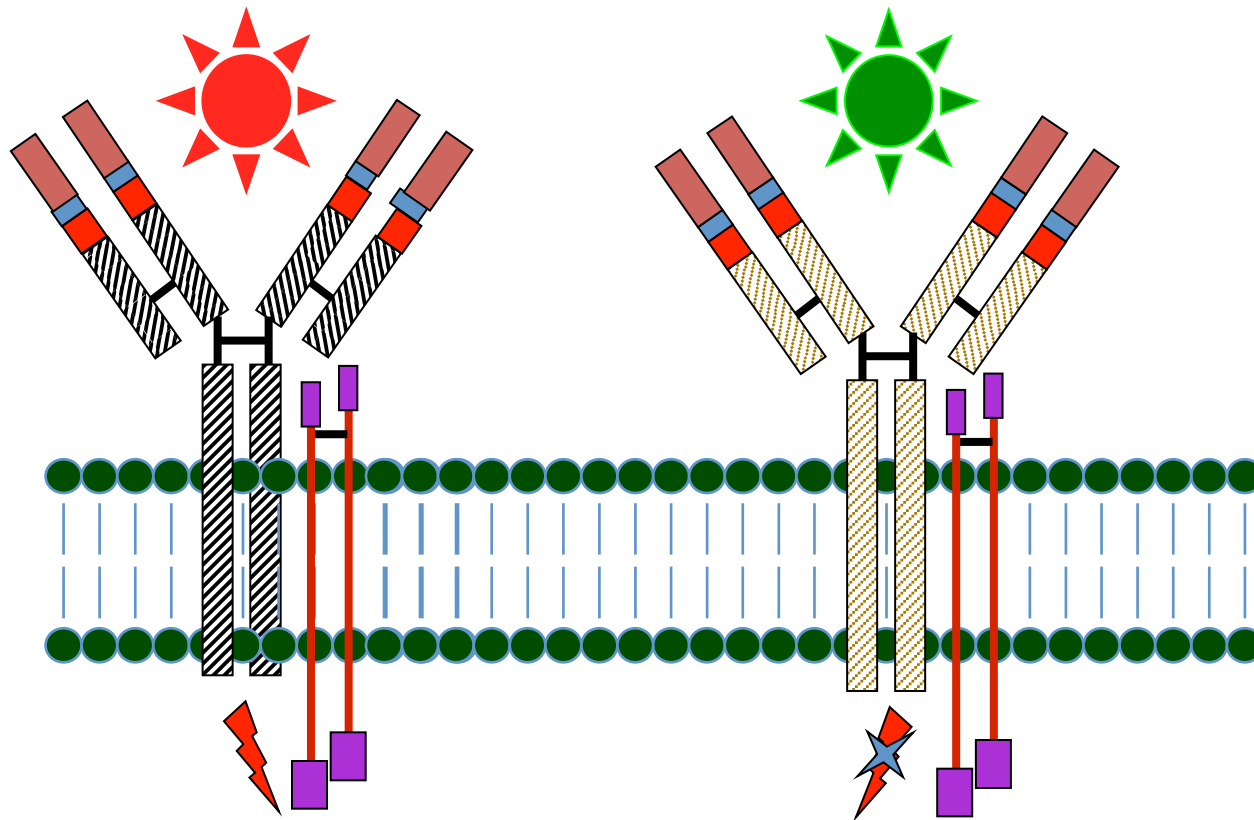


Fischer K, et al. Blood 2016
 Rossi et al, Blood 2015
 Thompson et al. Blood 2016

BCR signalling in CLL is heterogeneous

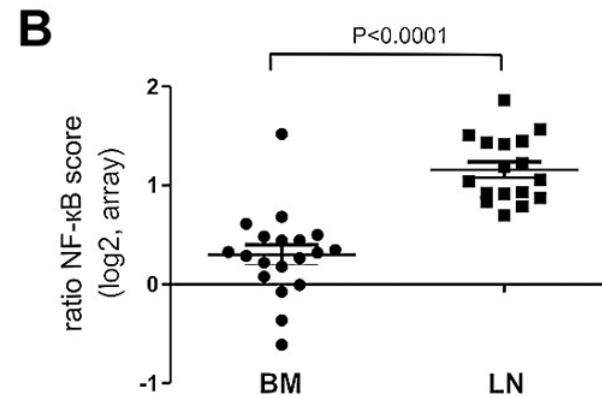
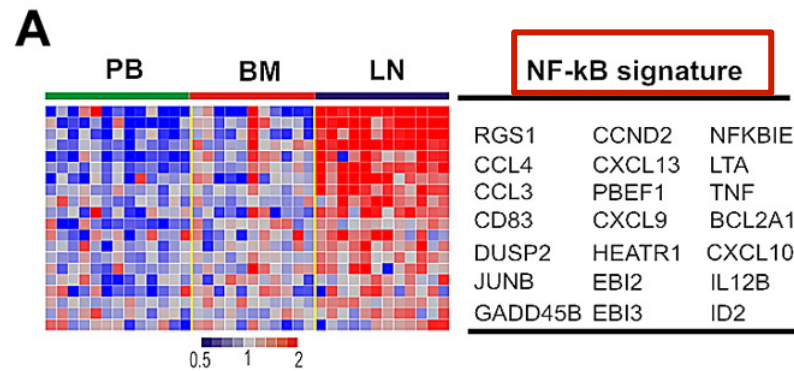
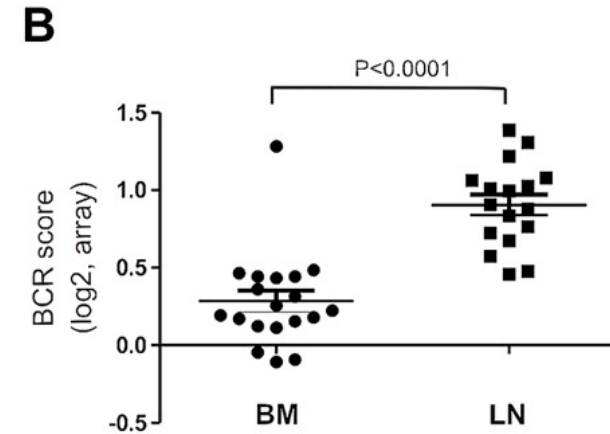
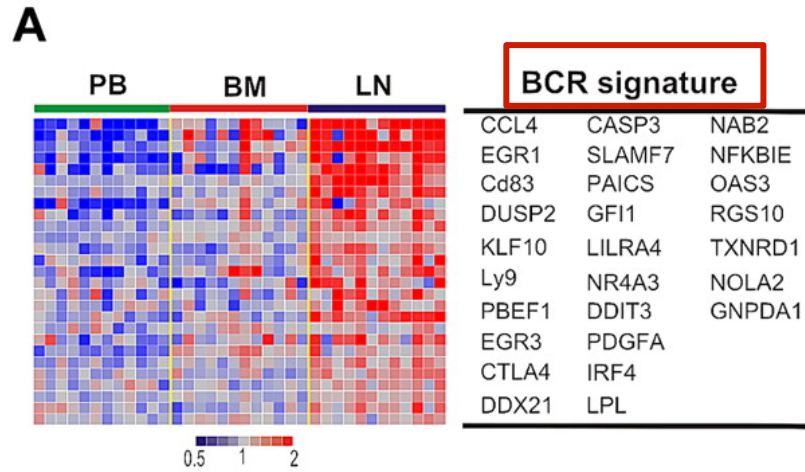
Bad prognosis

Good prognosis

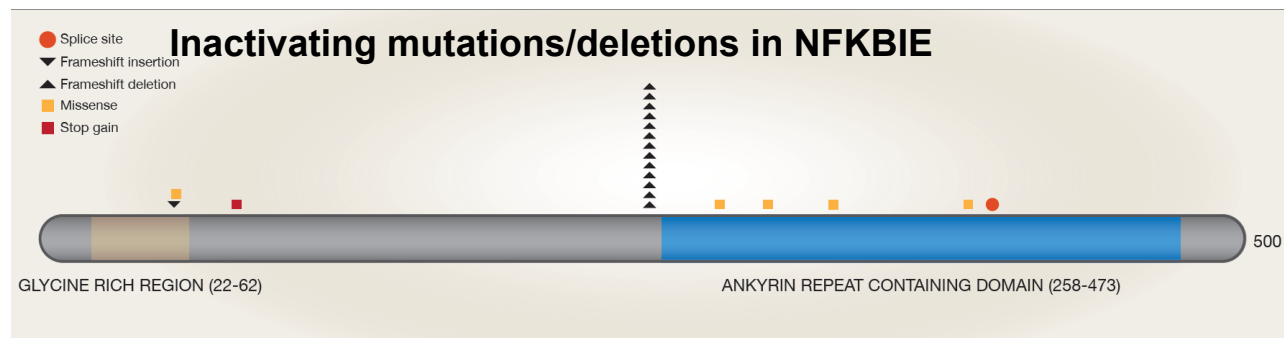
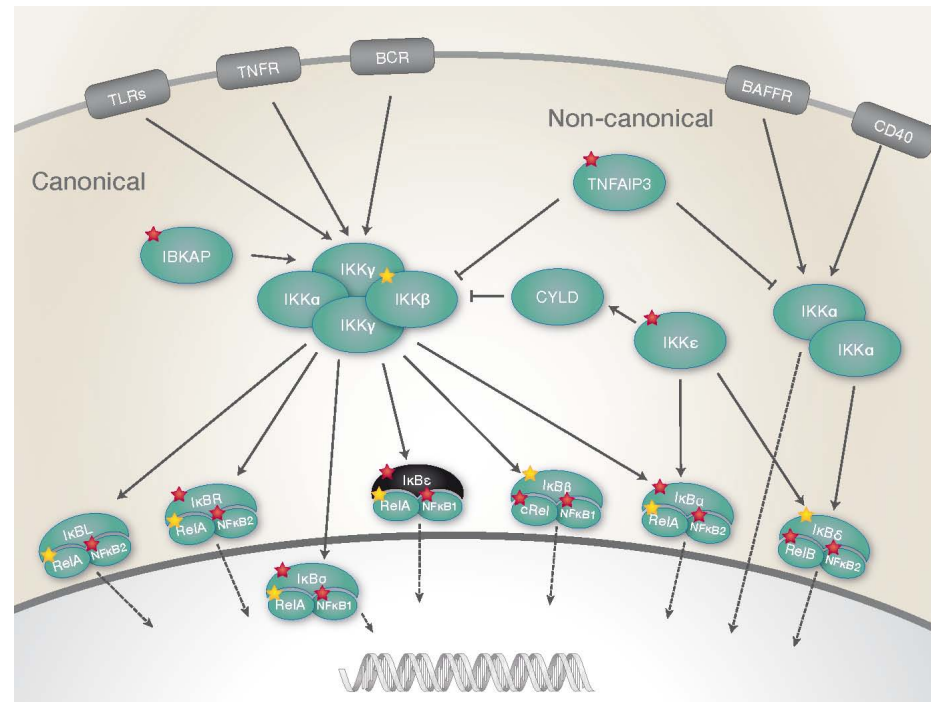


Survival
Proliferation

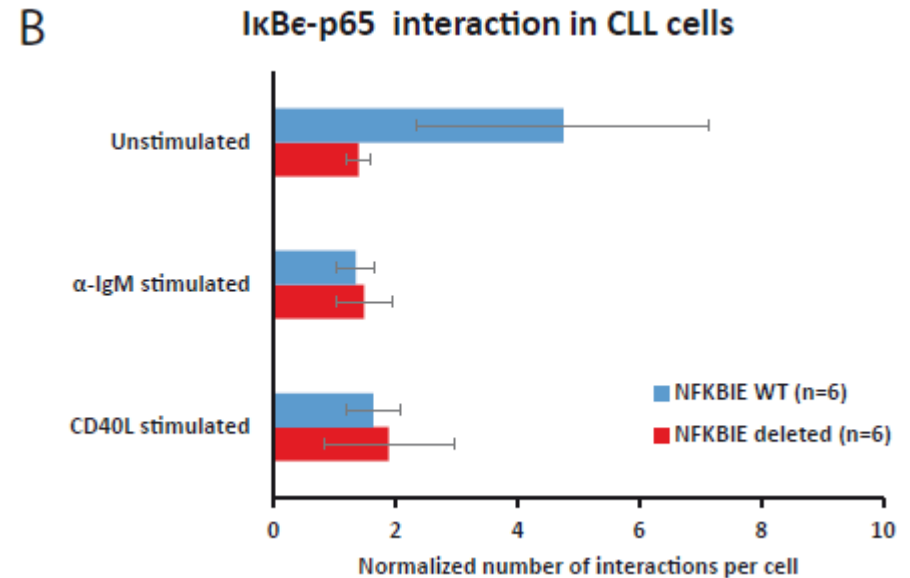
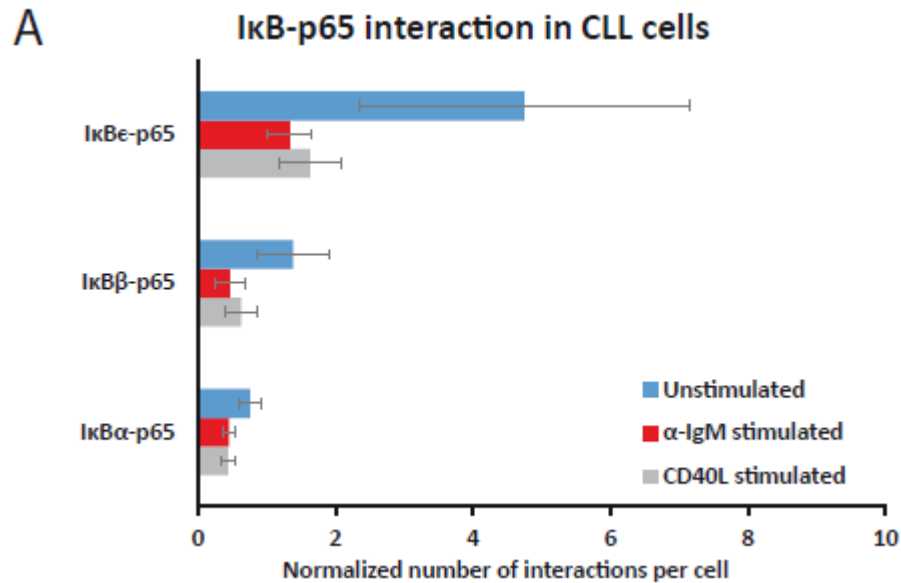
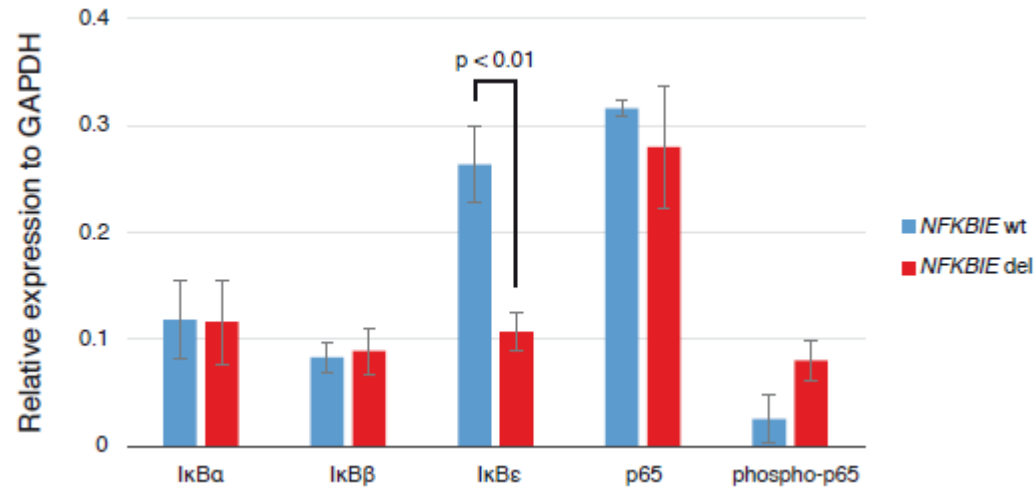
BCR is activated in the LN microenvironment



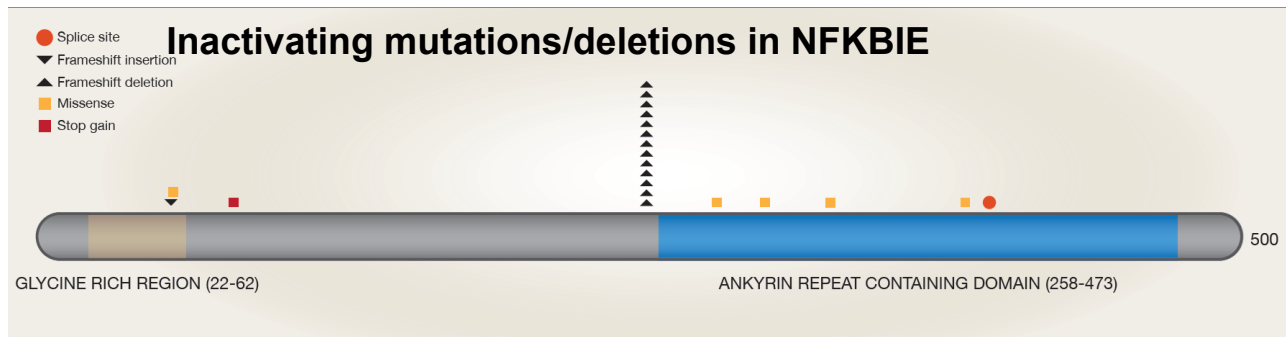
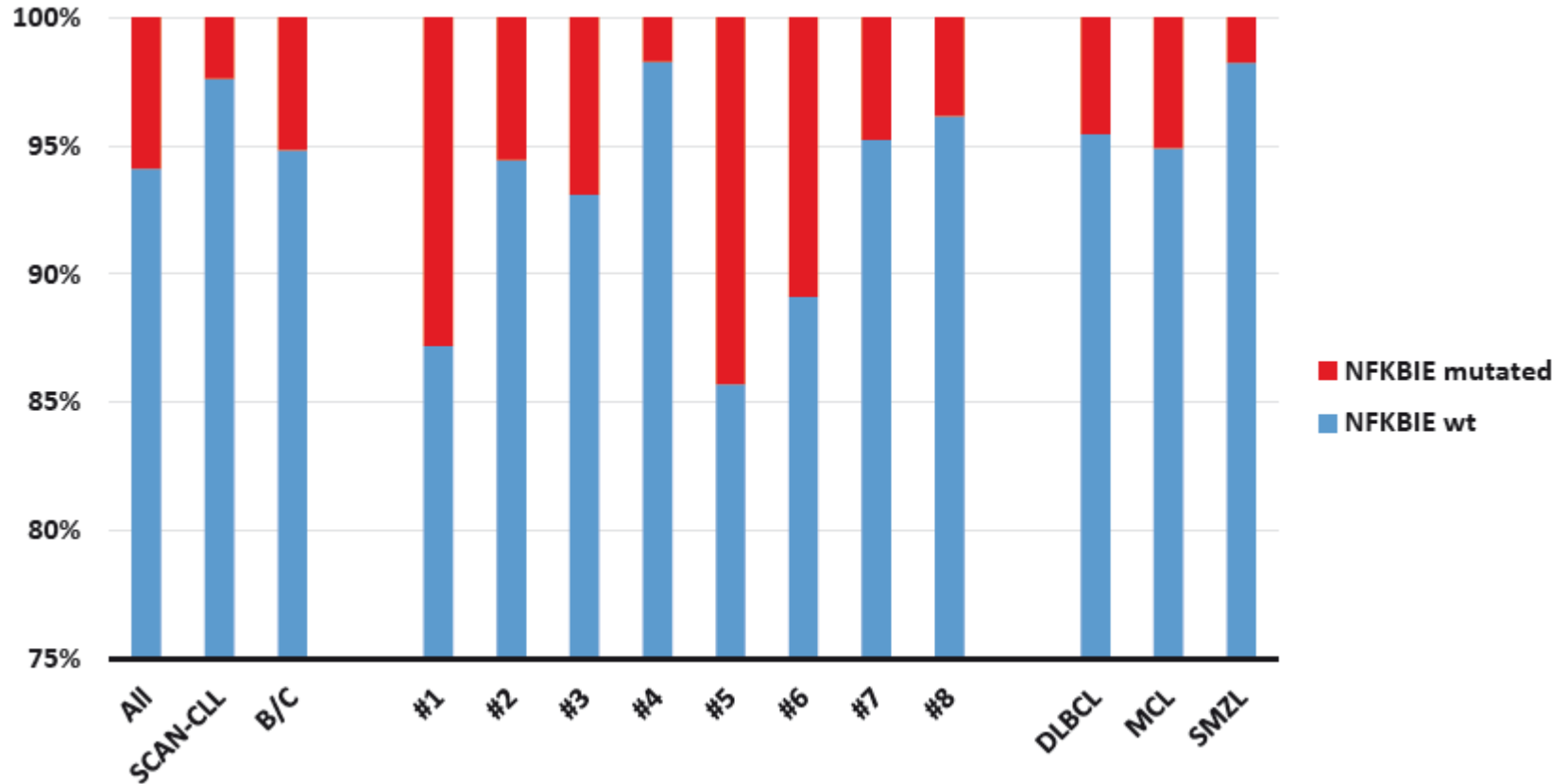
Recurrent mutations within the NF- κ B pathway



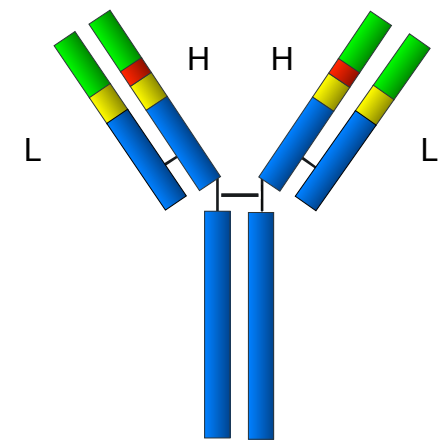
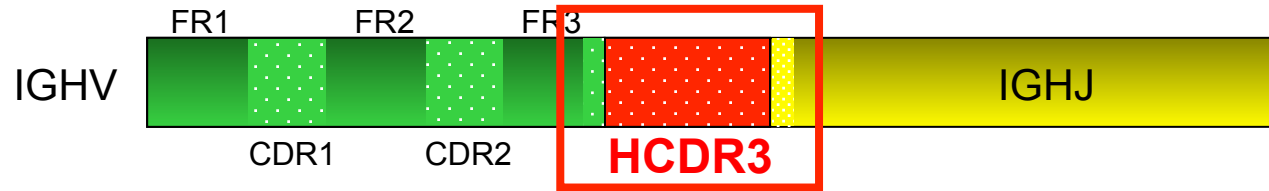
Mutated IκBe appear to lose its inhibitory capacity



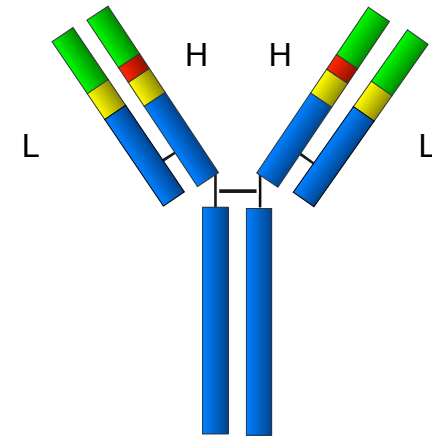
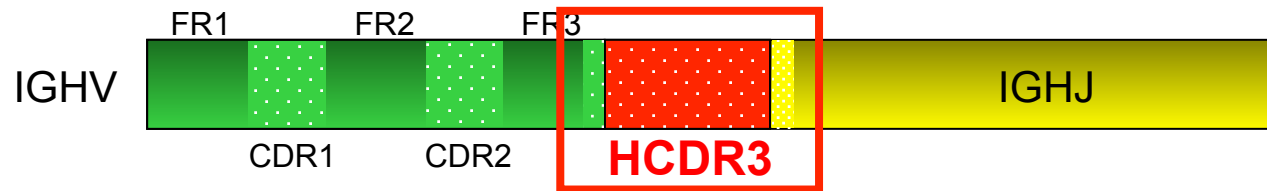
Recurrent mutations within the NF- κ B pathway



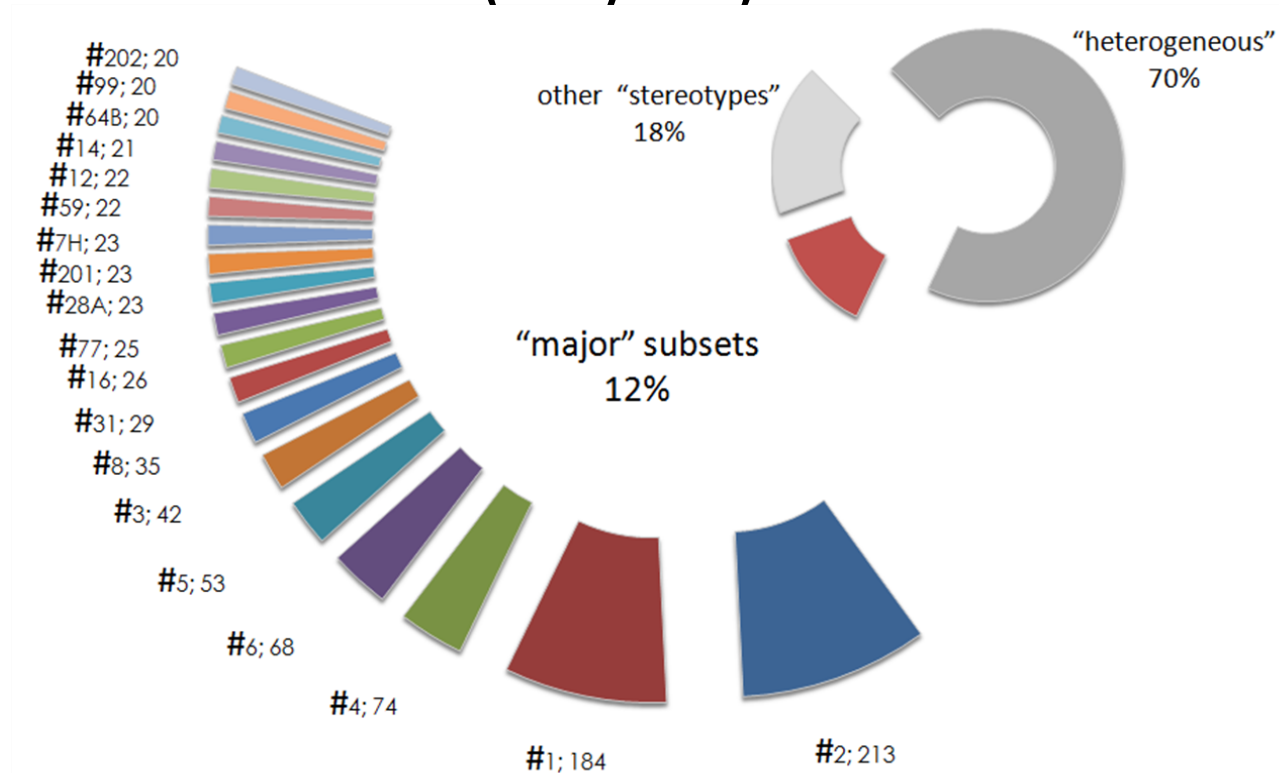
Stereotyped receptors in CLL



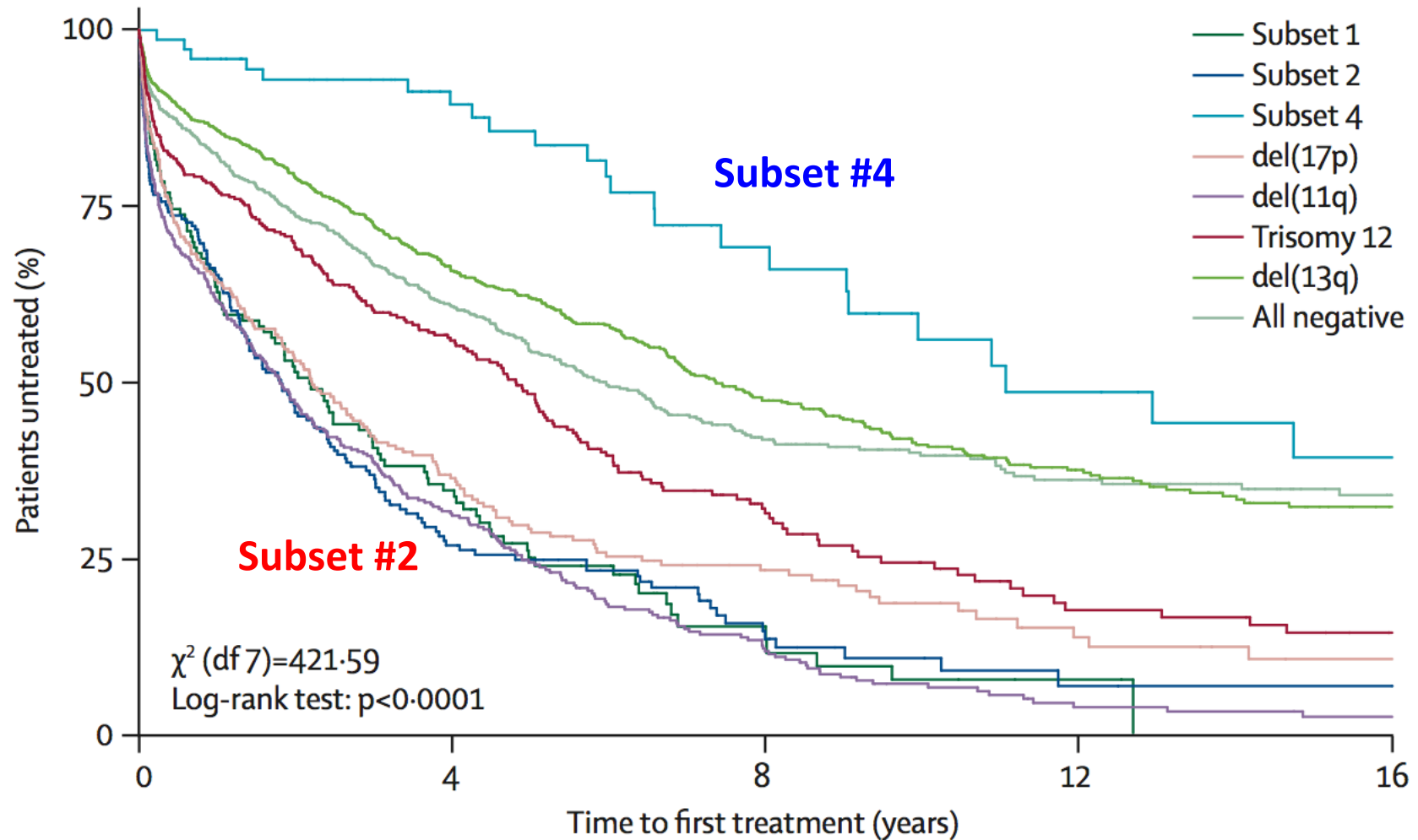
Stereotyped receptors in CLL



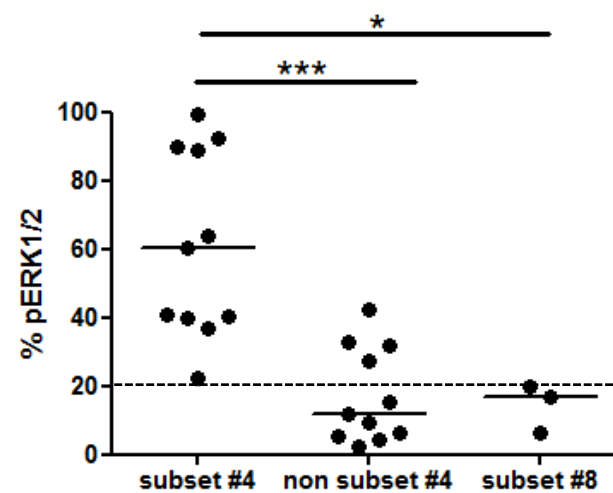
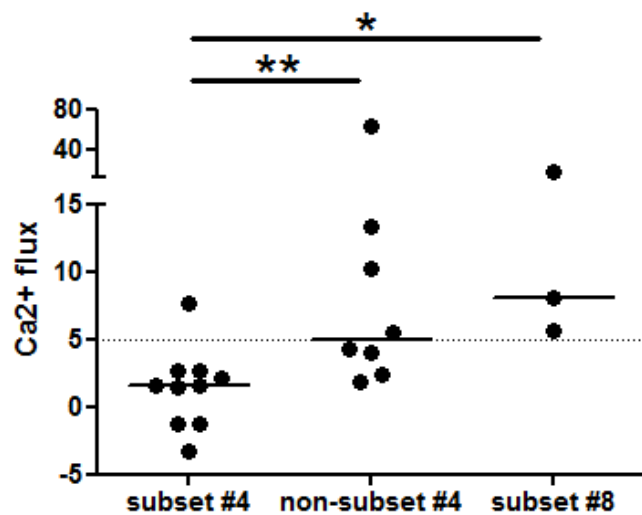
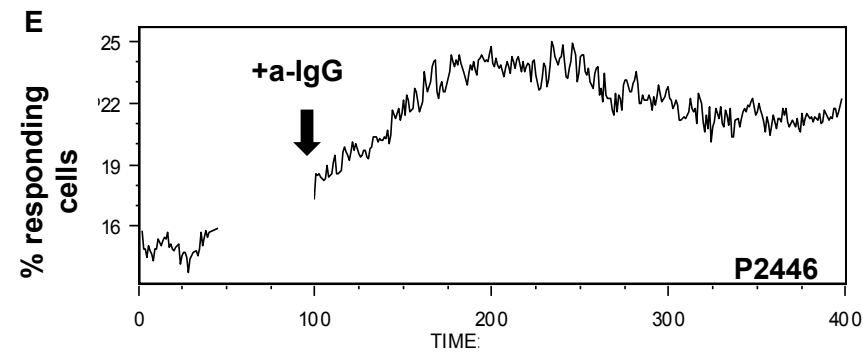
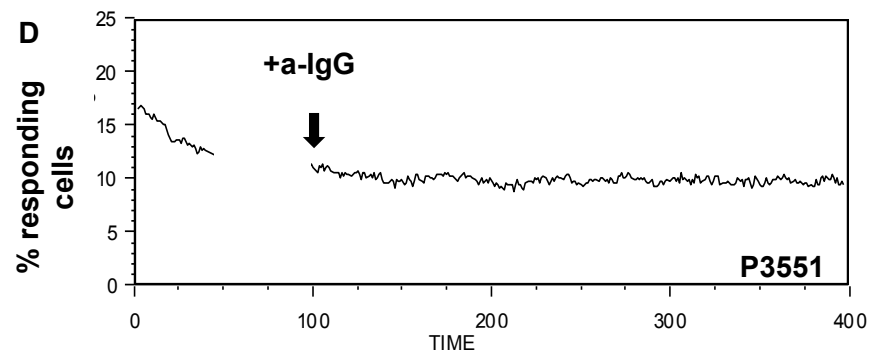
- **30.4%** of all CLL cases (2308/7596)



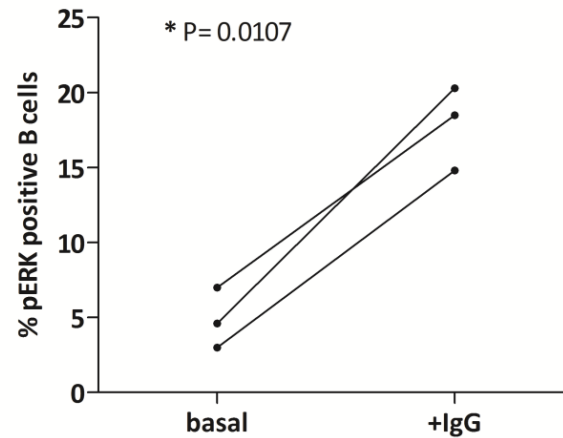
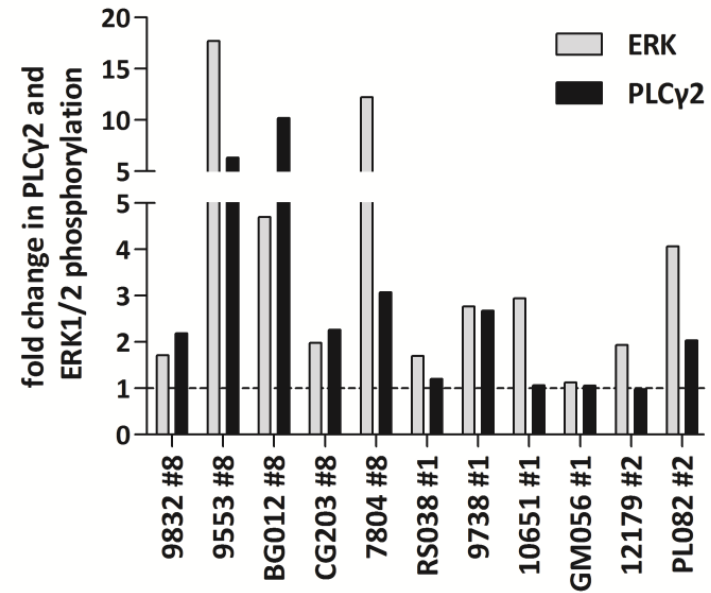
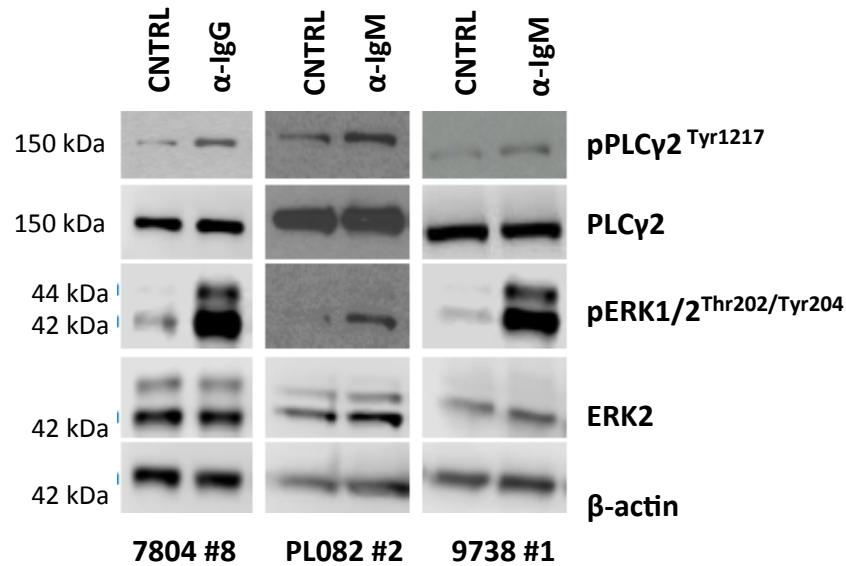
Stereotyped subsets have a distinct clinical course



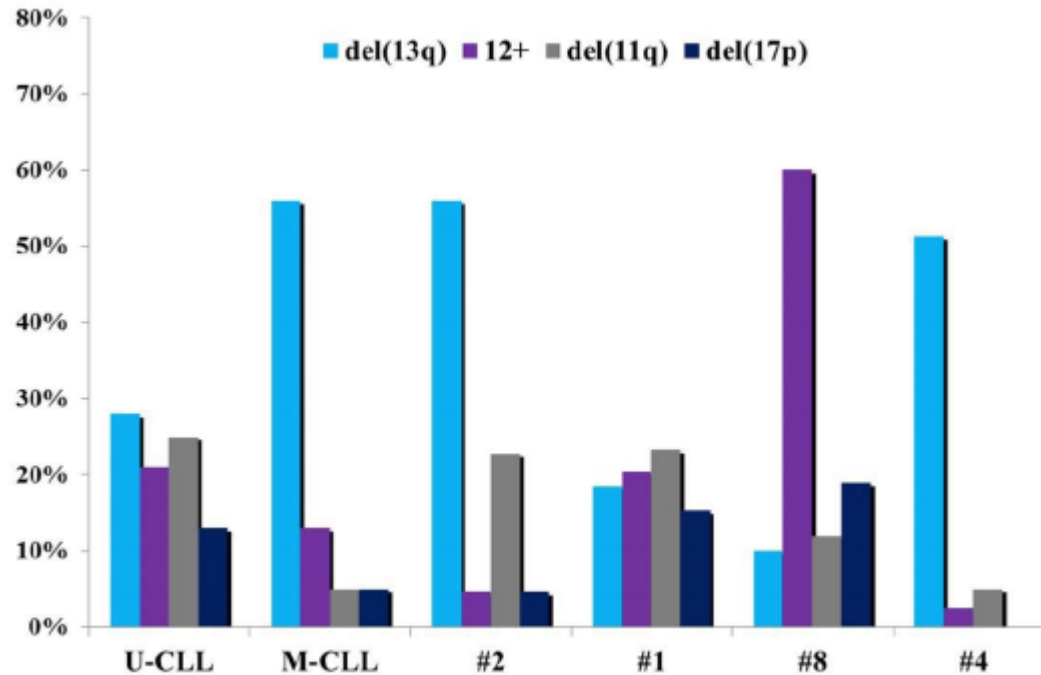
Subset 4 CLL is anergic to BCR stimulation



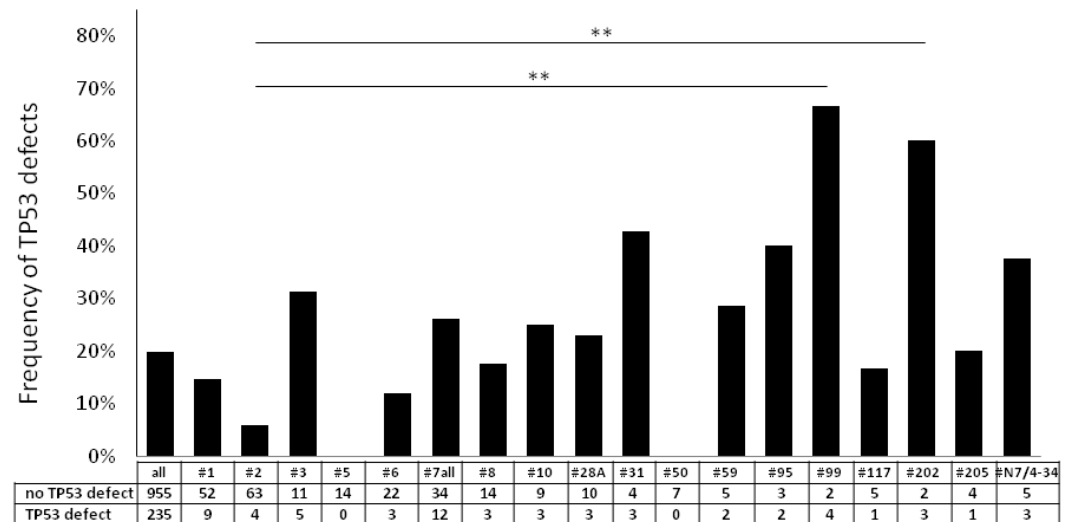
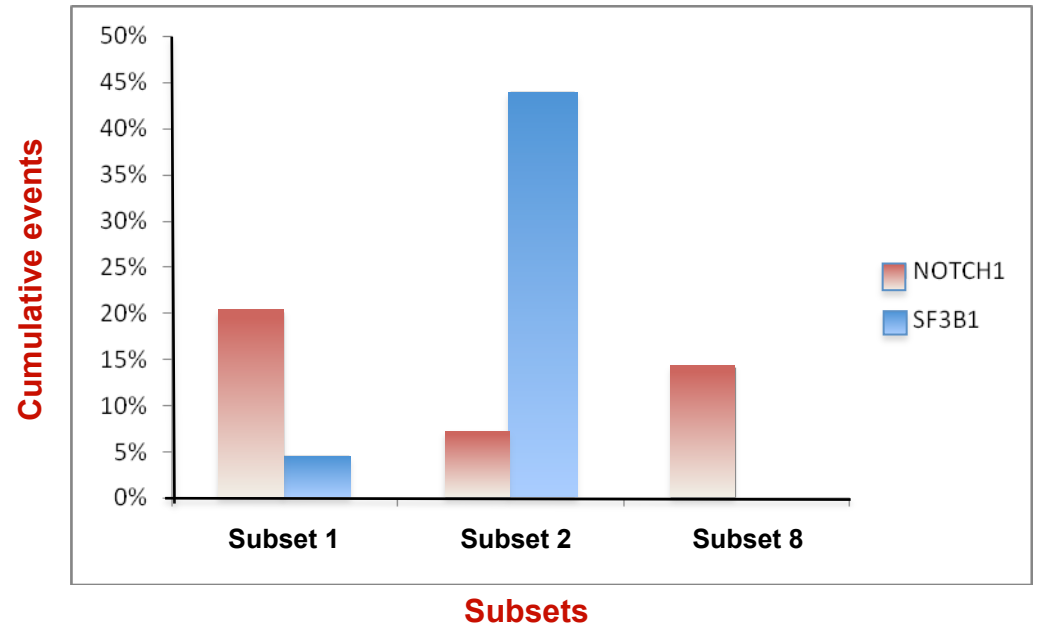
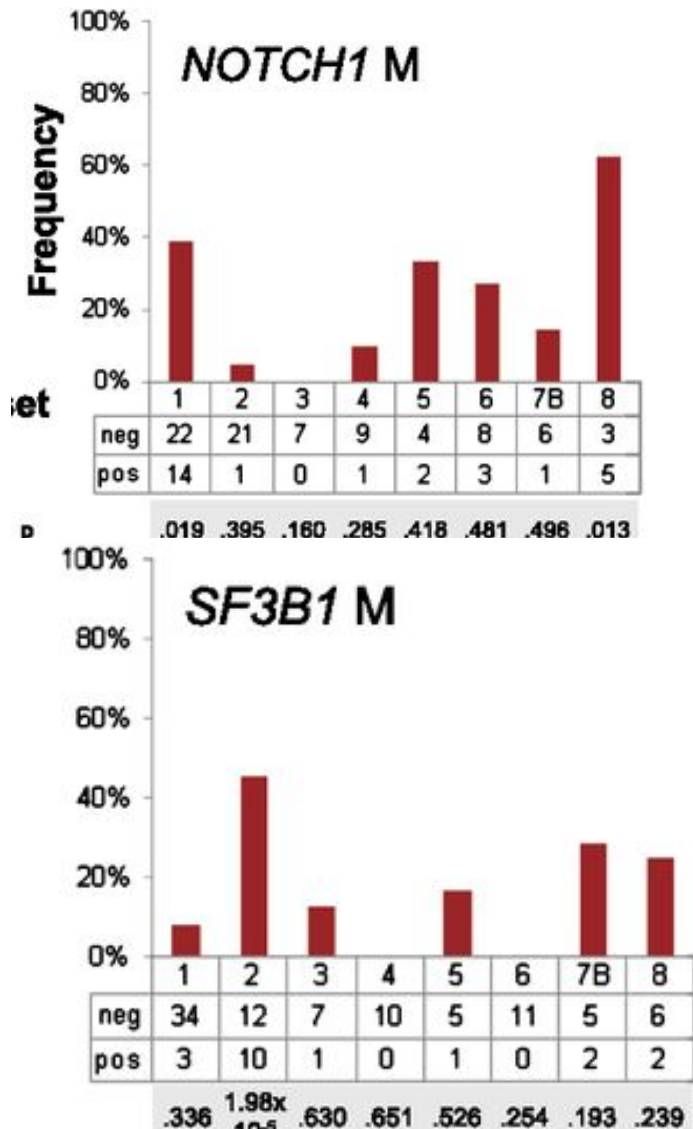
Aggressive subsets respond avidly via the BcR

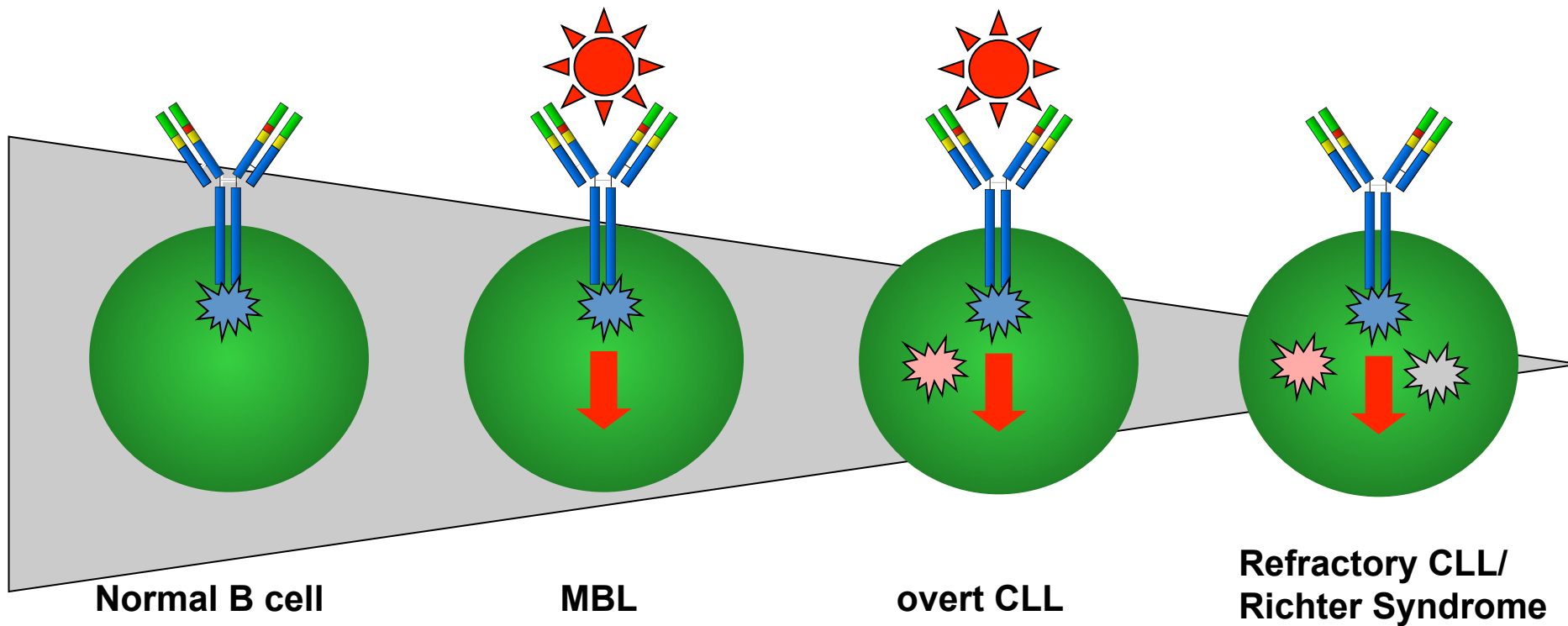


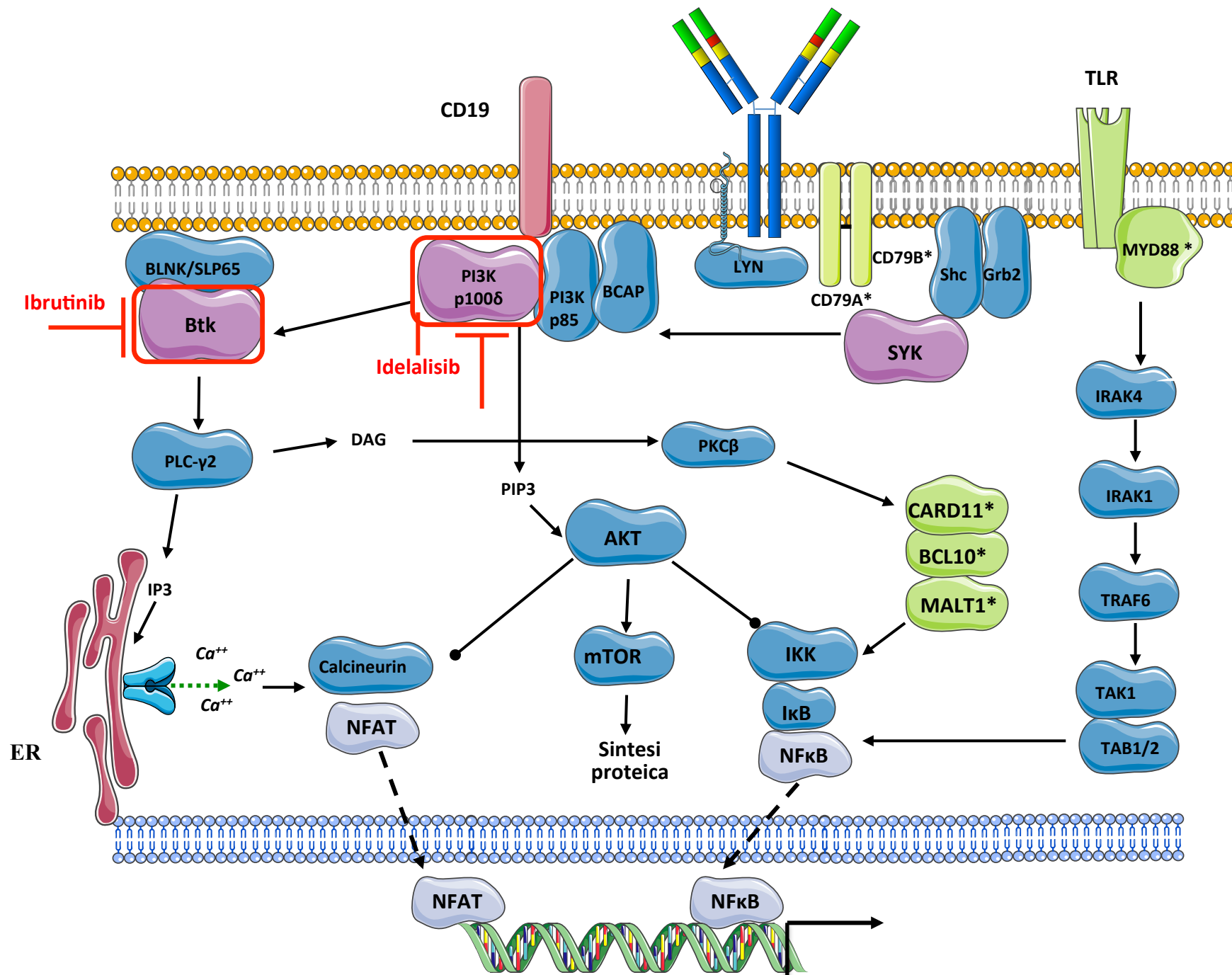
Poor clinical course is independent of cytogenetics



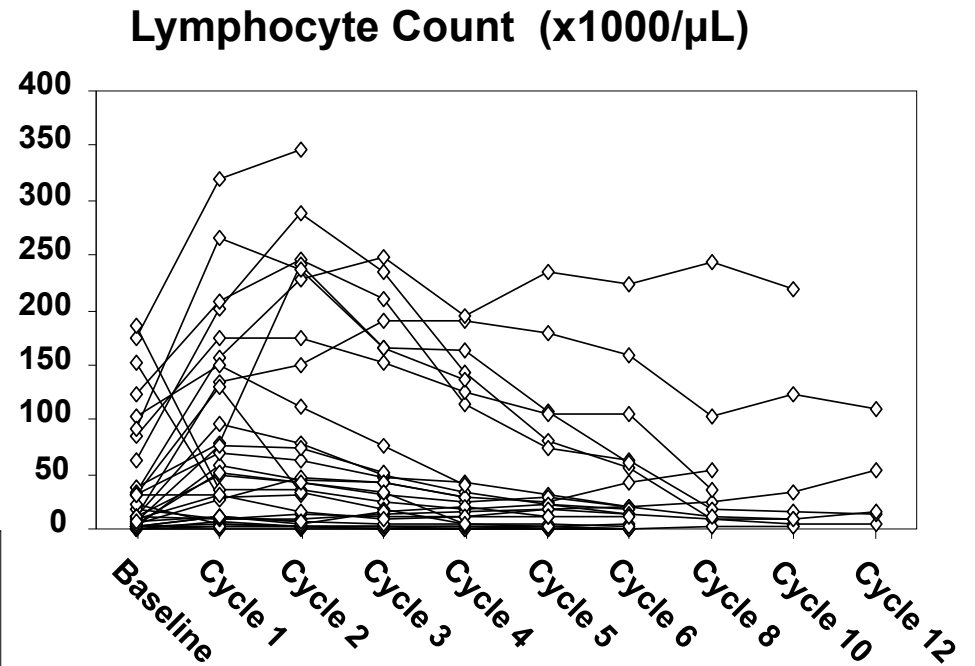
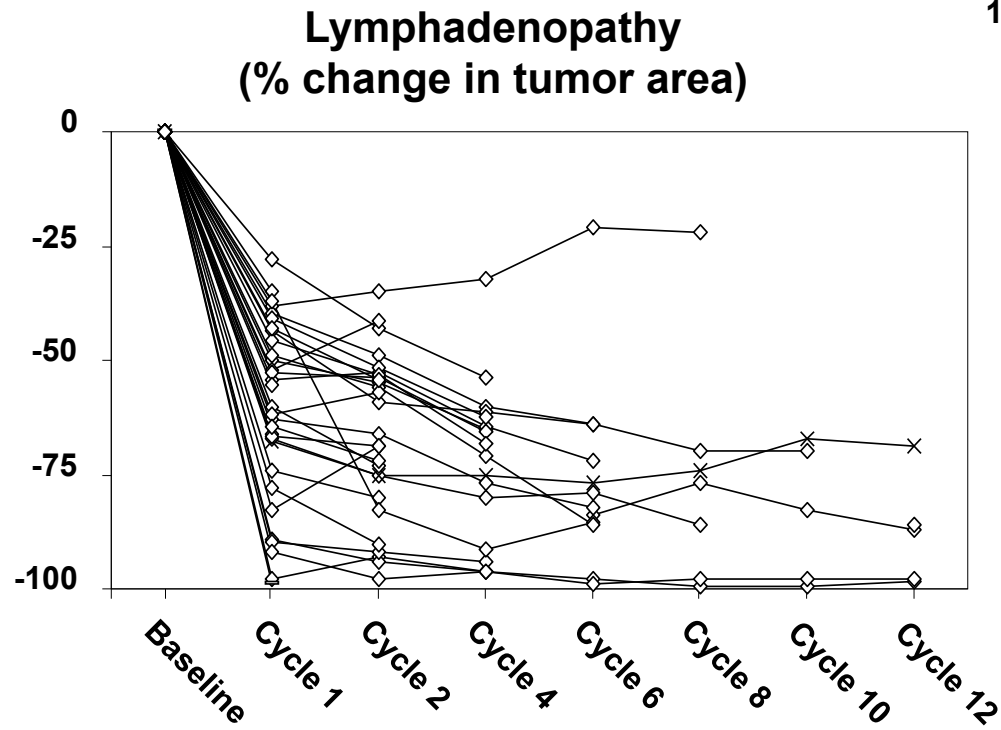
Gene mutations and IG stereotypy





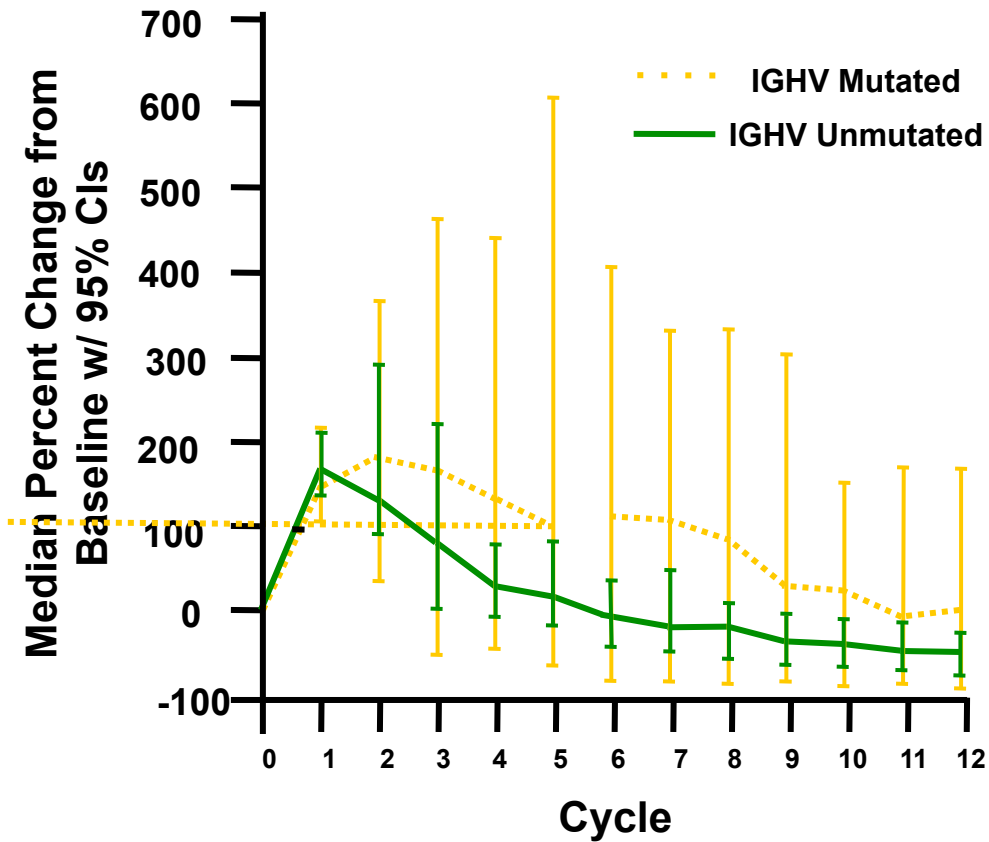


Response Pattern in CLL Patients with Idelalisib

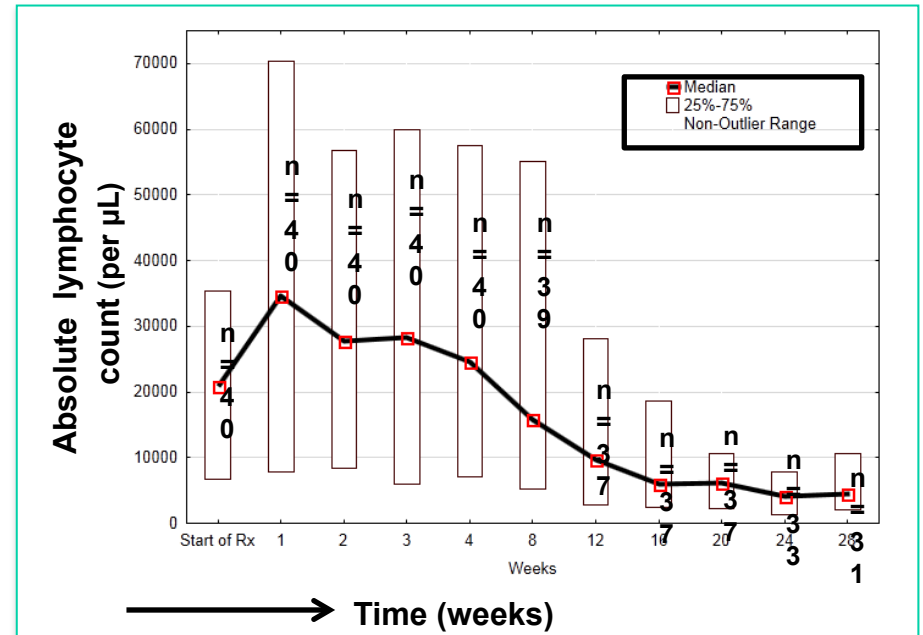


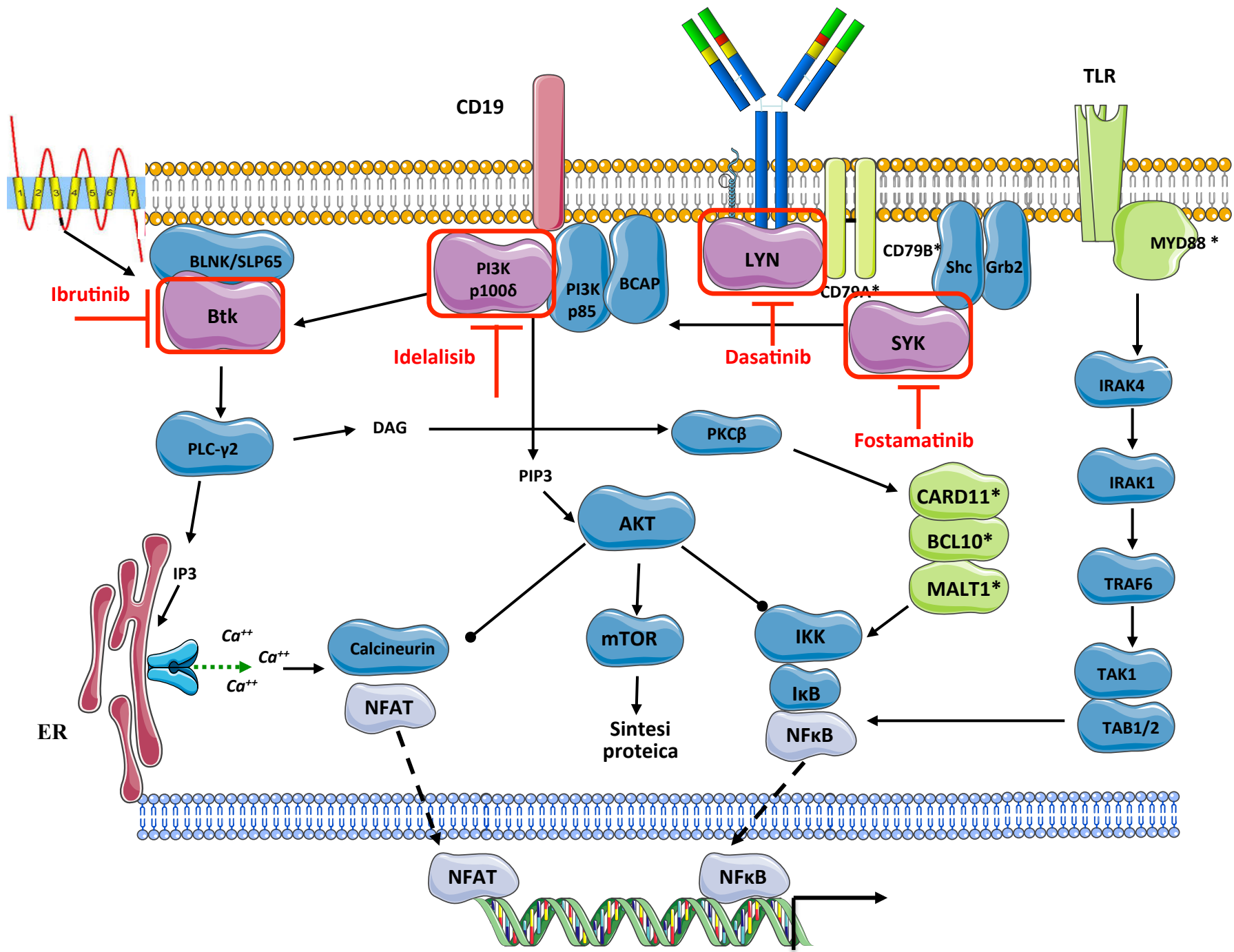
Prolonged lymphocytosis in IG-mutated CLL

BTK inhibitors



Ibrutinib + R





○



Università Vita-Salute San Raffaele
Istituto Scientifico San Raffaele
Department of Onco-Hematology
Division of Experimental Oncology



Laboratory of B Cell Neoplasia

**Lydia Scarfò, Andreas Agathangelidis, Maria Gounari,
Alessandra Rovida, Tania Veliz-Rodriguez, Engin Bojnik,
Pamela Ranghetti, Federica Barbaglio, Cristina Scielzo**

Biocrystallography Unit

Claudia Minici, Massimo Degano

Laboratory of Cell Signaling

**Eleonora Maria Fonte, Maria
Giovanna Vilia, Marta Muzio**

CERTH, Thessaloniki

**Anna Vardi, Stavroula Ntoufa,
Anastasia Hadzidimitriou,
Kostas Stamatopoulos**

Uppsala University, Uppsala

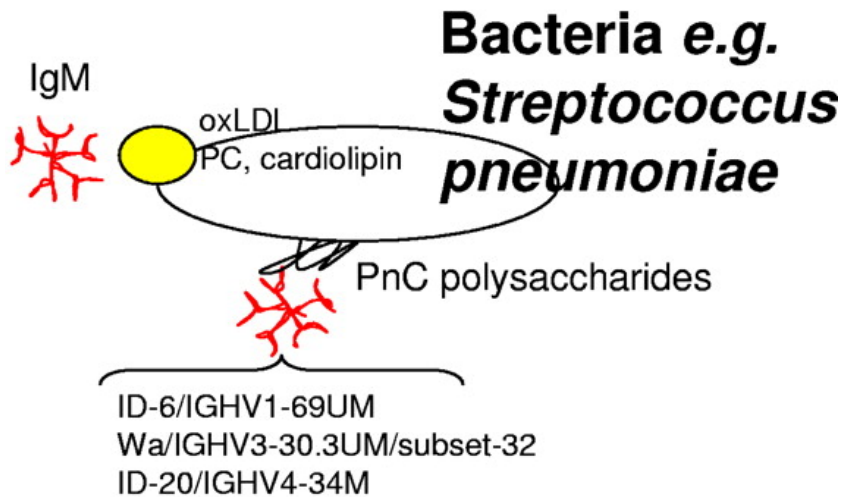
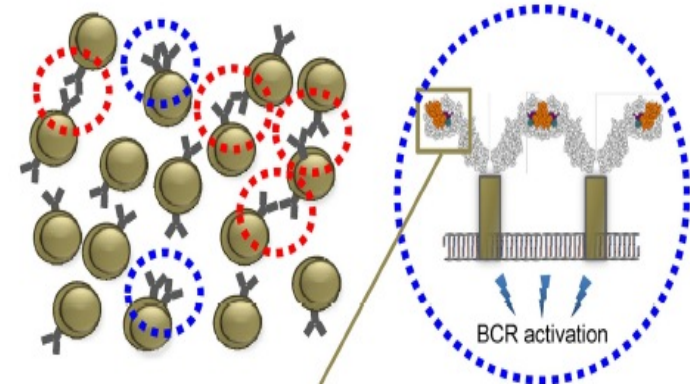
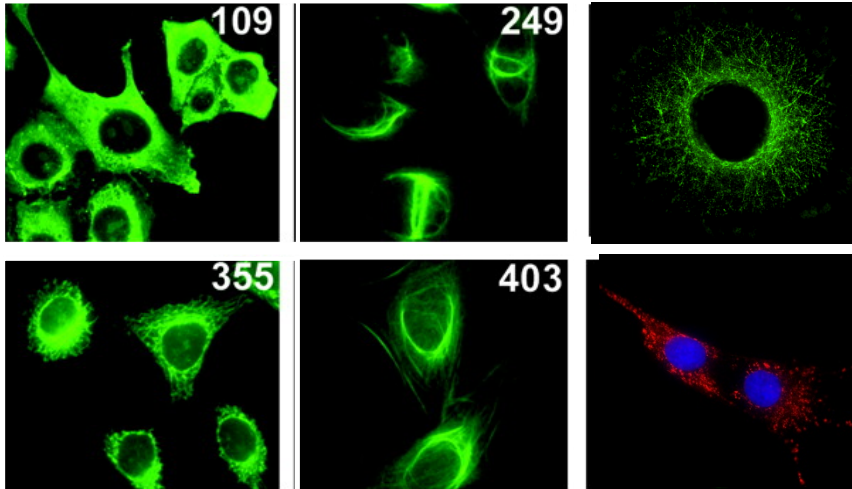
**Lesley Ann Sutton, Viktor
Ljungstrom, Richard Rosenquist**

Strategic Research Program on CLL

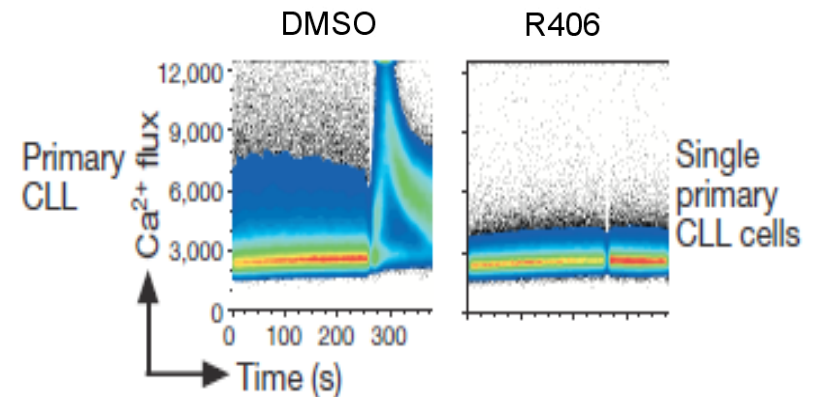
**Lydia Scarfò, Piera Angelillo, Maria Colia,
Stefania Cresta, Eloise Scarano**



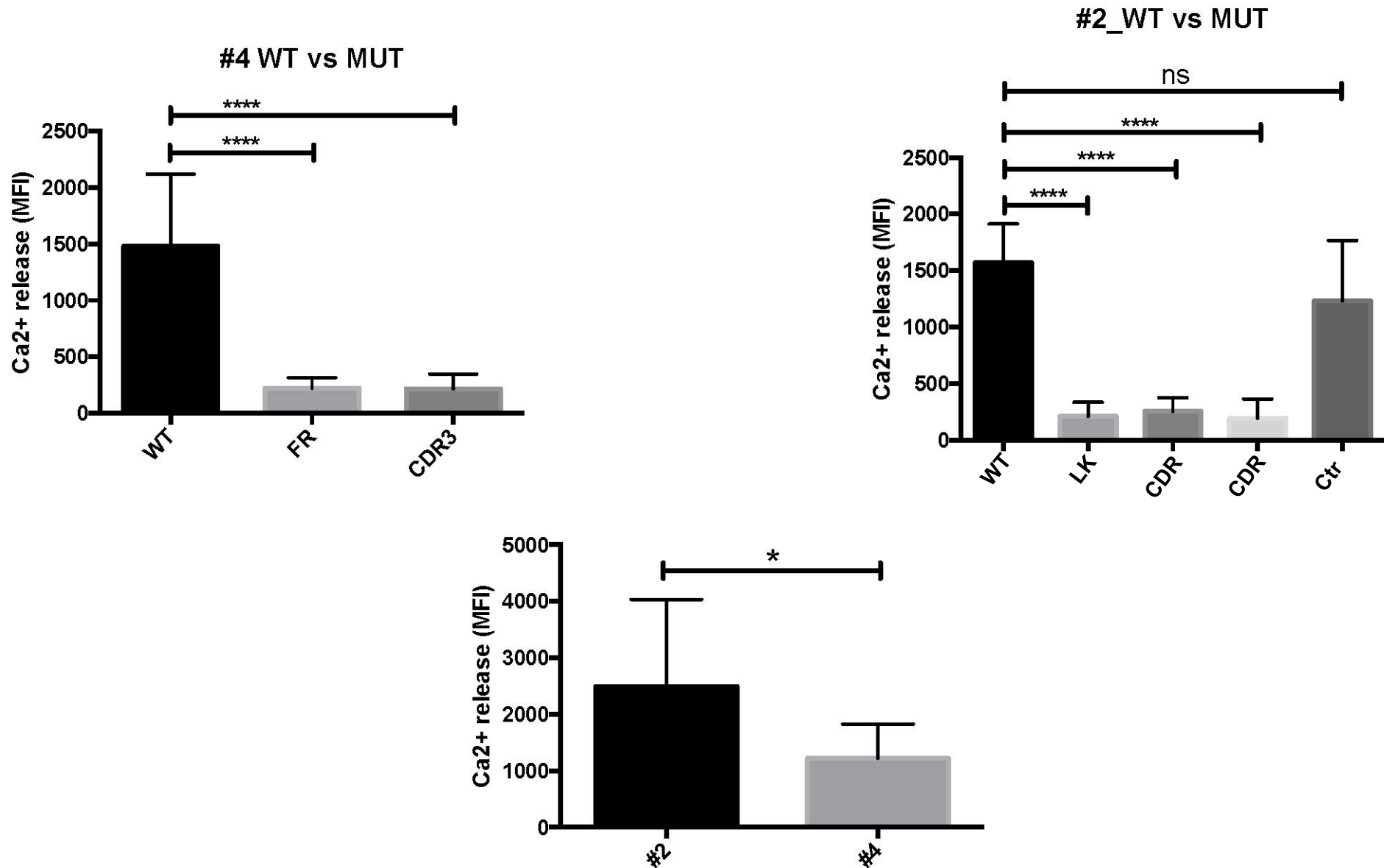
BCR reactivity in CLL: self and foreign antigens



CLL binding peptide	W N W P L P P V R Q F S
hVH consensus	X X W V R Q X P G
mVH consensus	X X W V K Q X P G



Stereotyped subsets have distinct calcium fluxes



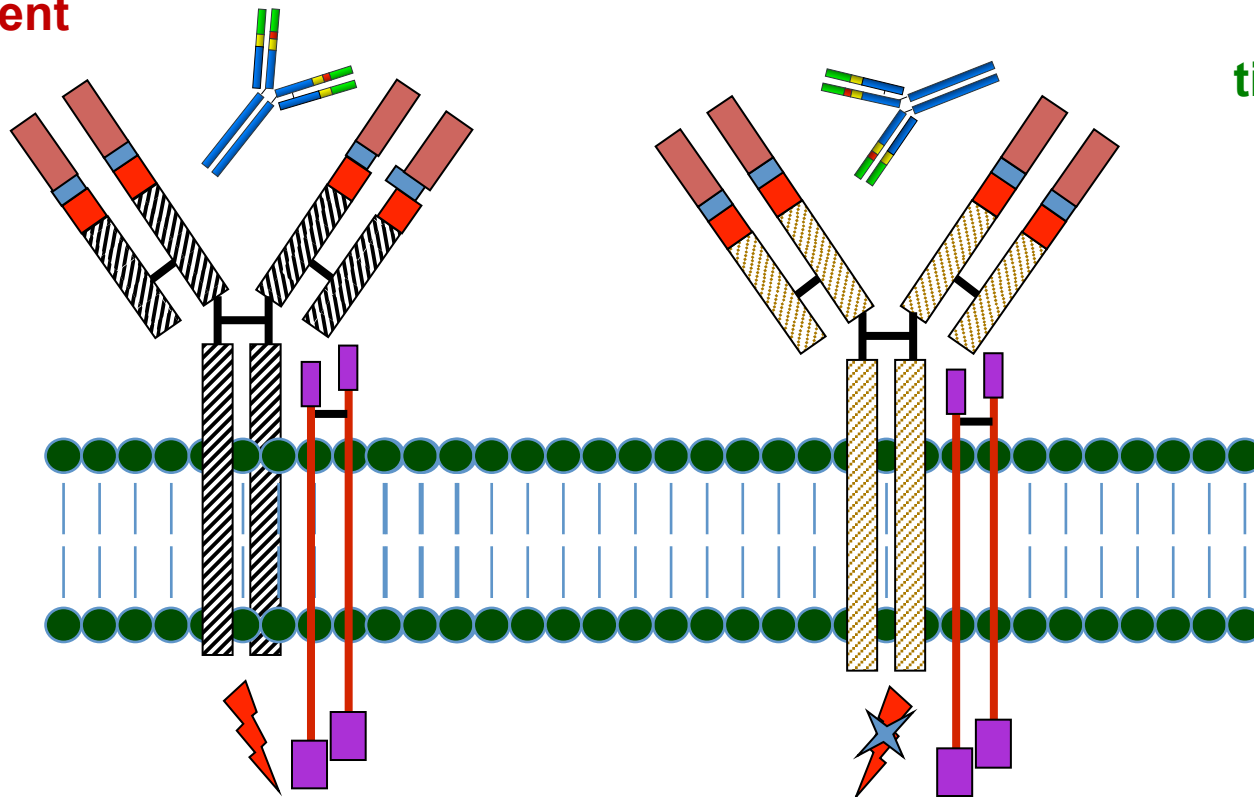
BCR signalling in CLL is heterogeneous

Aggressive

Indolent (anergic)

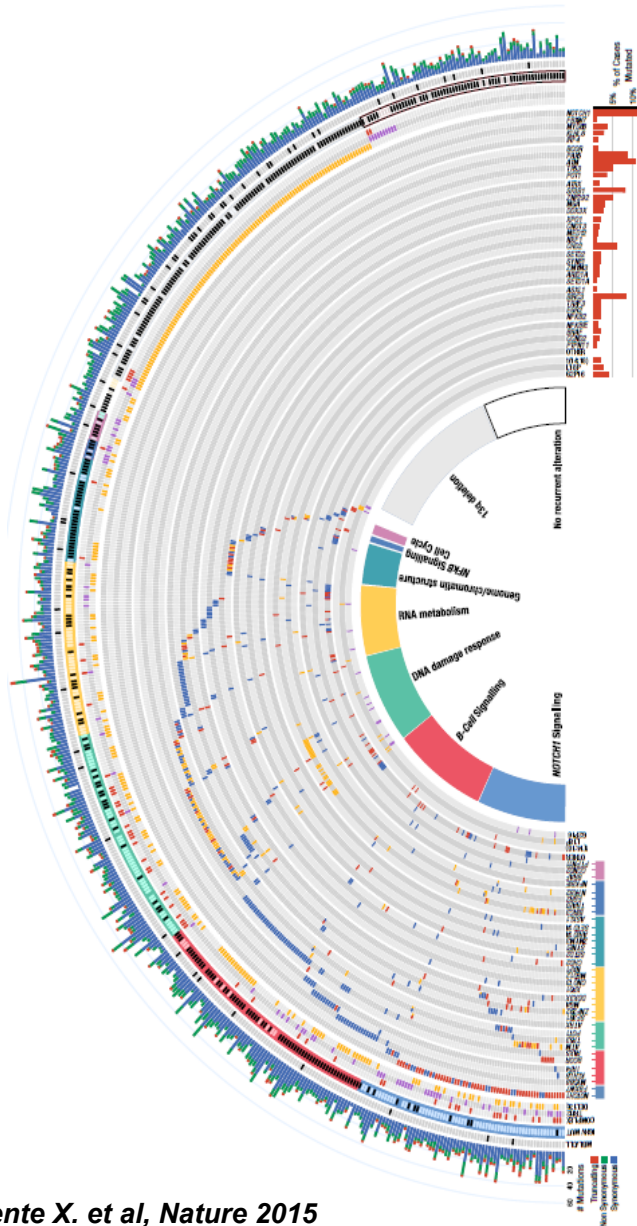
**weak, transient
binding**

**tight, stable
binding**

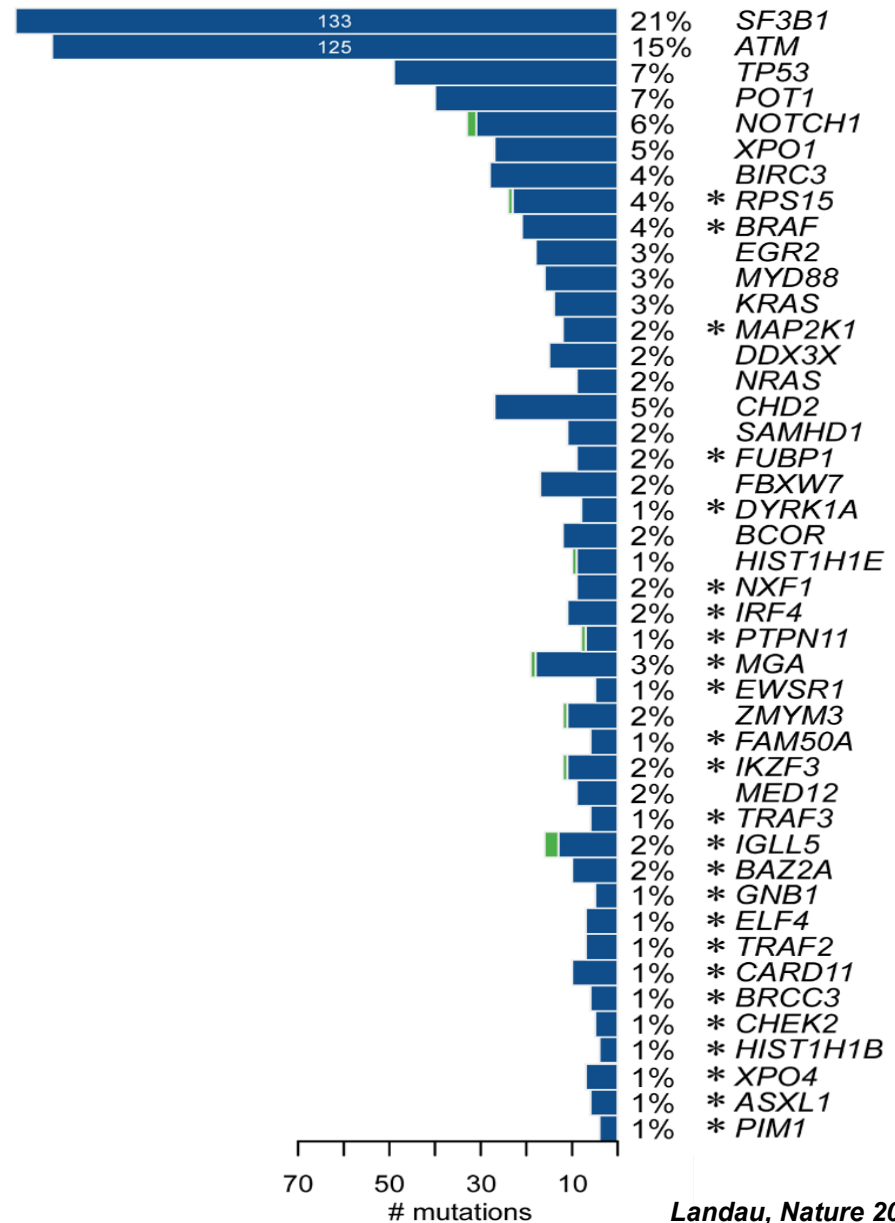


**Survival
Proliferation**

Novel driver mutations

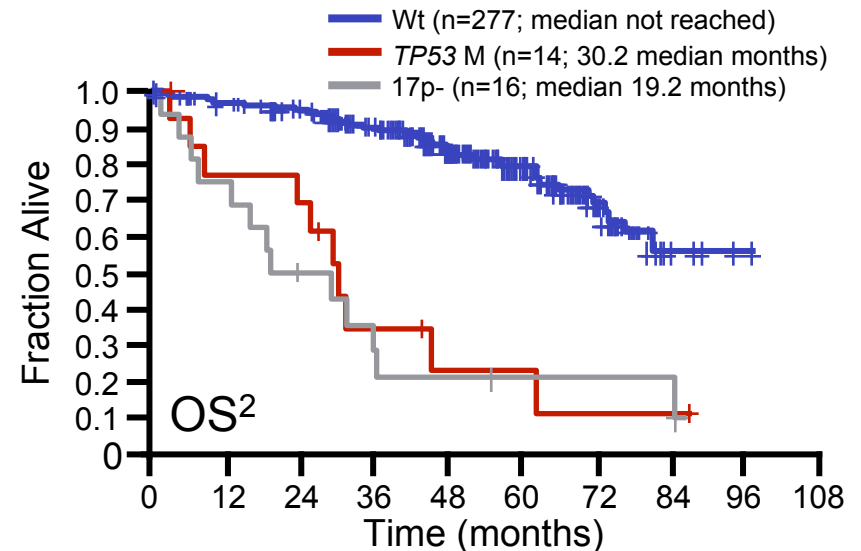
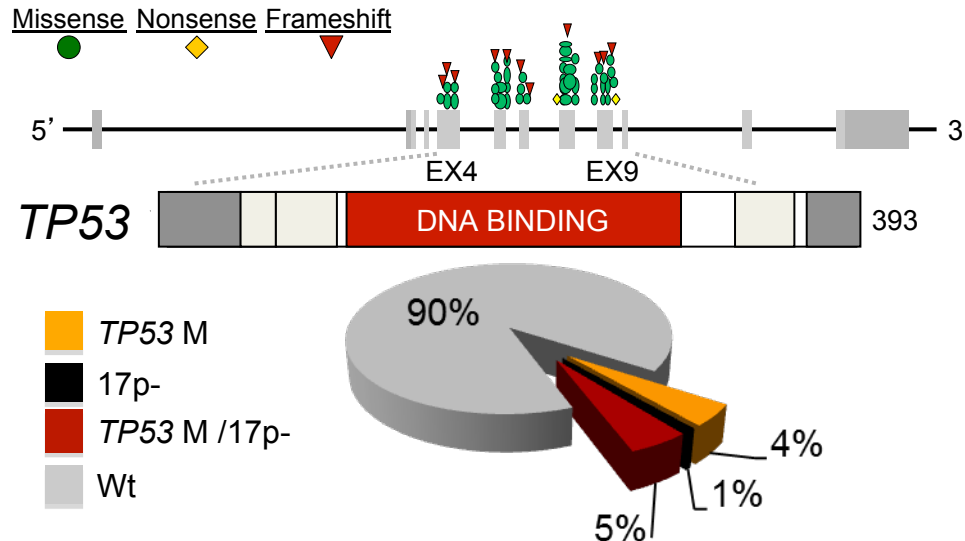
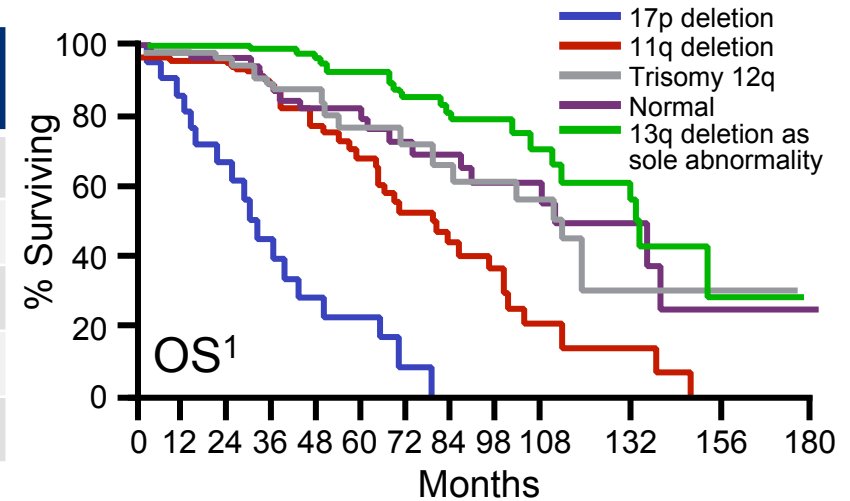
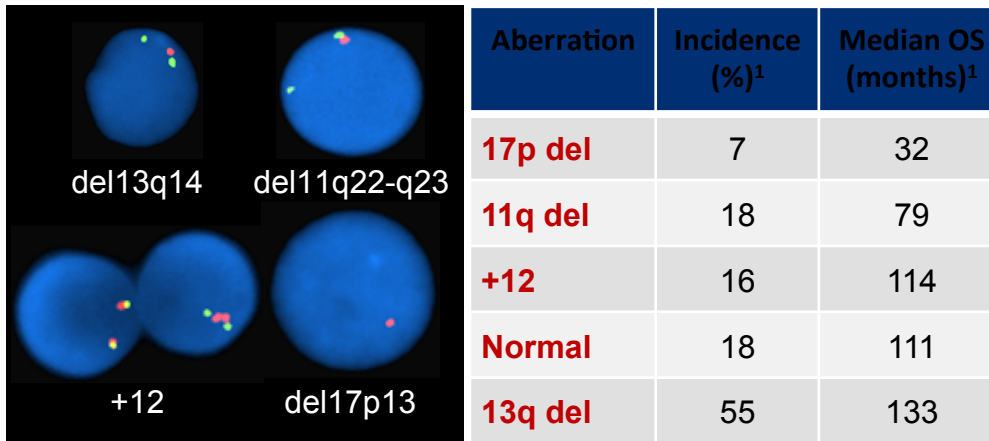


Puente X. et al, Nature 2015



Landau, Nature 2015

TP53 disruption is associated with poor prognosis



Nt: wildtype; OS: overall survival

1. Döhner H, et al. *N Engl J Med* 2000;343:1910-6; 2. Zenz T, et al. *J Clin Oncol* 2010;28:4473-9.