Marginal zone lymphomas:

biology and molecular genomics

Davide Rossi, M.D., Ph.D.

Hematology
IOSI - Oncology Institute of Southern Switzerland
IOR - Institute of Oncology Research
Bellinzona

Domains

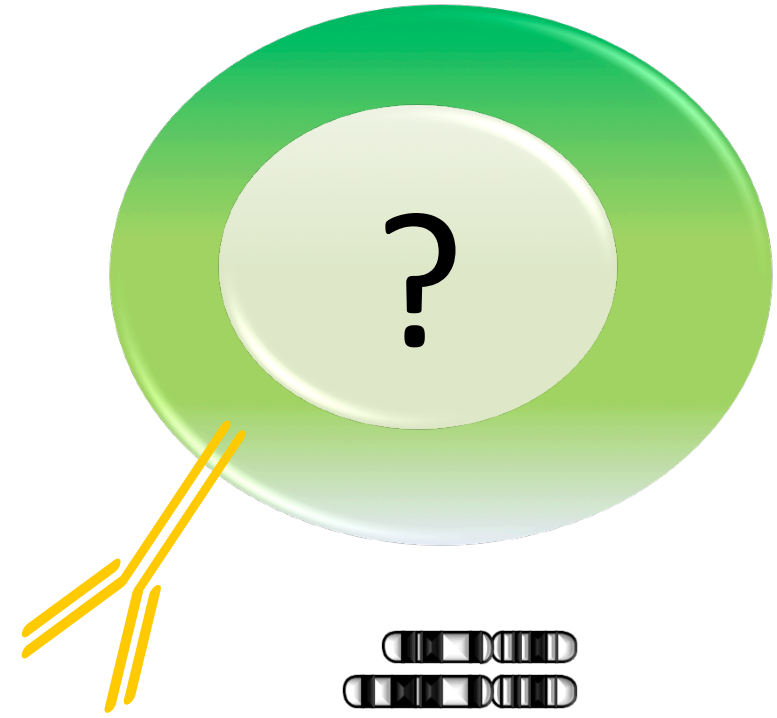
IOR Institute of Oncology Research

- Genetics of non-MALT MZL
  - SMZL
  - NMZL
- Clinical implications of non-MALT MZL genetics
  - Diagnosis
  - Prognosis
  - Therapy

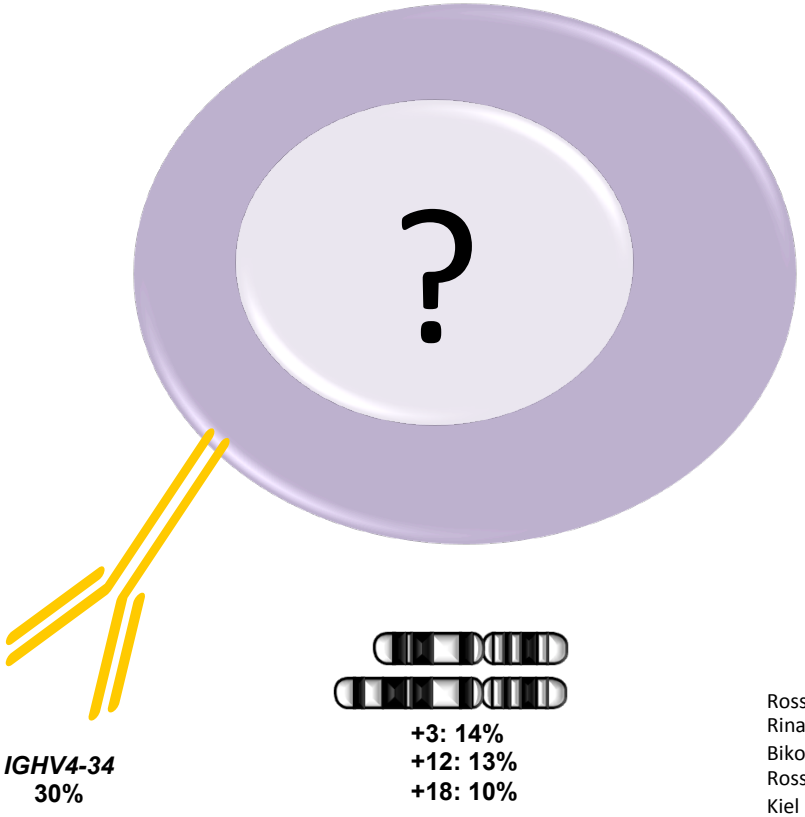
Molecular pathogenesis of non-MALT MZL

IOR Institute of Oncology Research

SMZL



NMZL

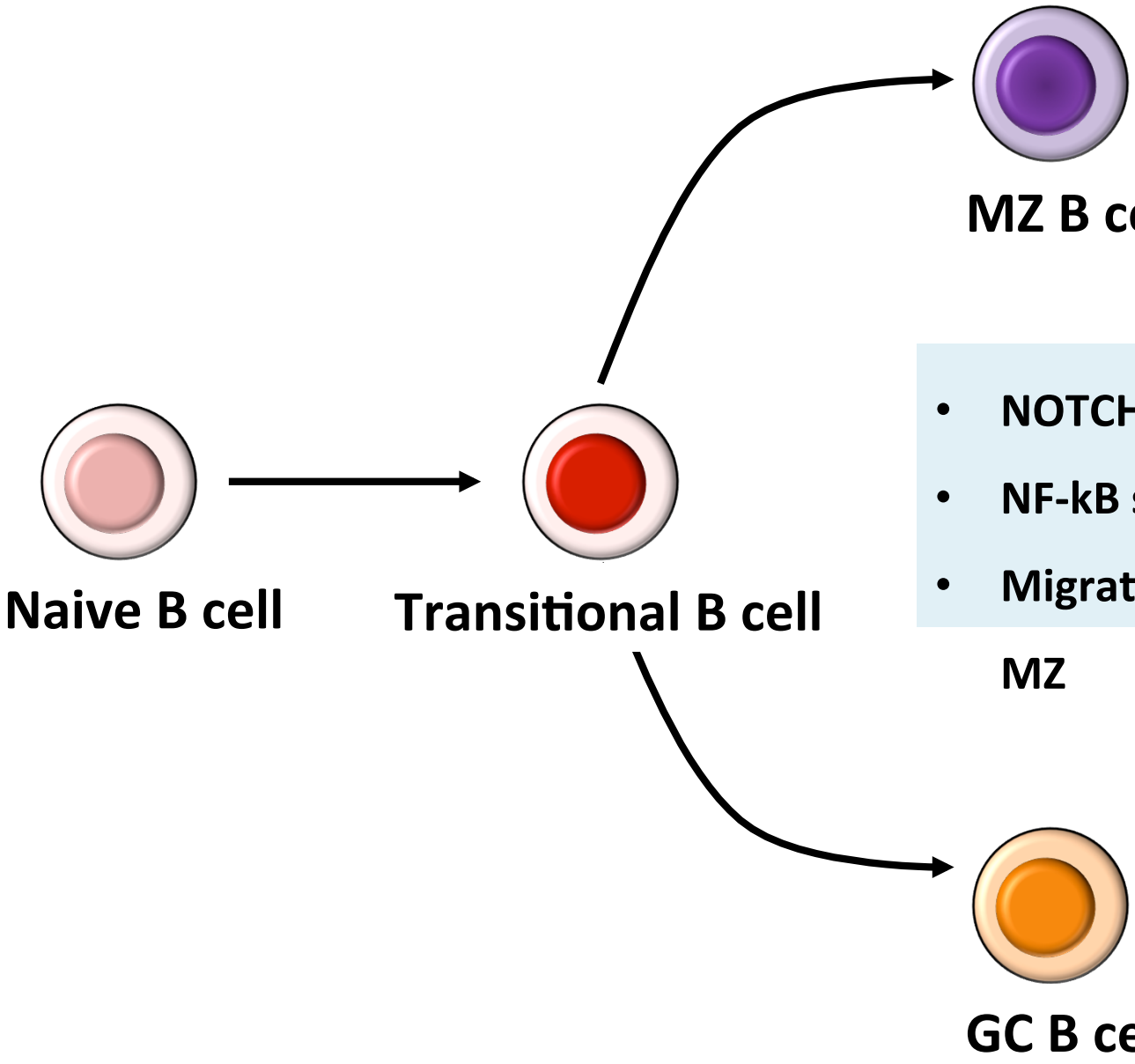


Rossi D, *Blood* 2011
Rinaldi A, *Blood* 2011
Bikos V, *Leukemia* 2012
Rossi D, *J Exp Med* 2012
Kiel MJ, *J Exp Med* 2012
Parry M, *PLoS One* 2013
Martinez N, *Leukemia* 2014
Piva R, *Leukemia* 2015
Clipson A, *Leukemia* 2015
Parry M, *Clin Cancer Res* 2015
Arribas A, *Blood* 2015

Spina V, Rossi D. *Semin Cancer Biol*. 2016

Pathways in the SMZL and NMZL signatures

IOR Institute of Oncology Research



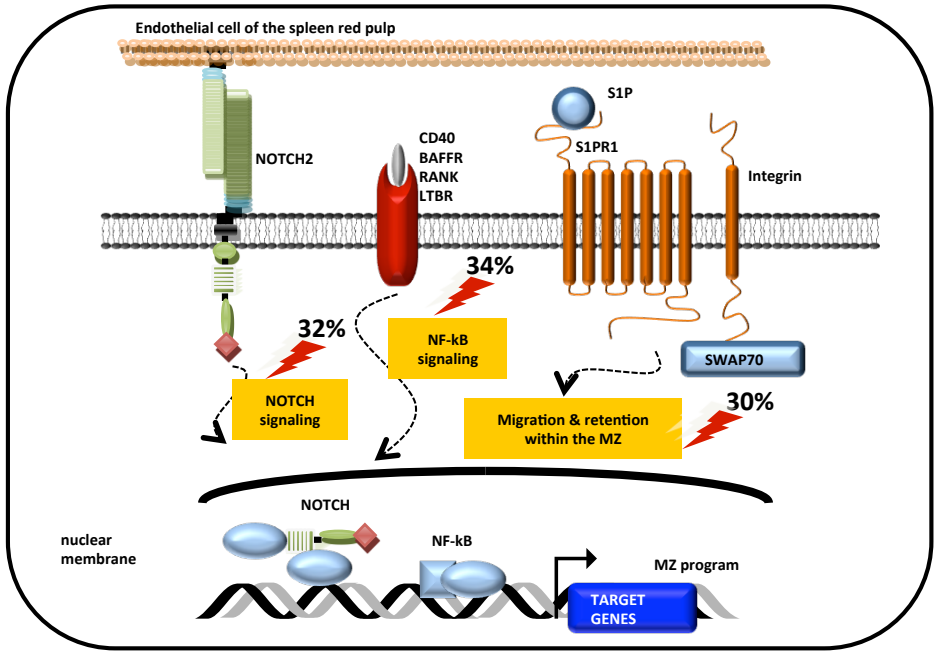
- NOTCH2 signals
- NF-kB signals
- Migration to and retention in MZ

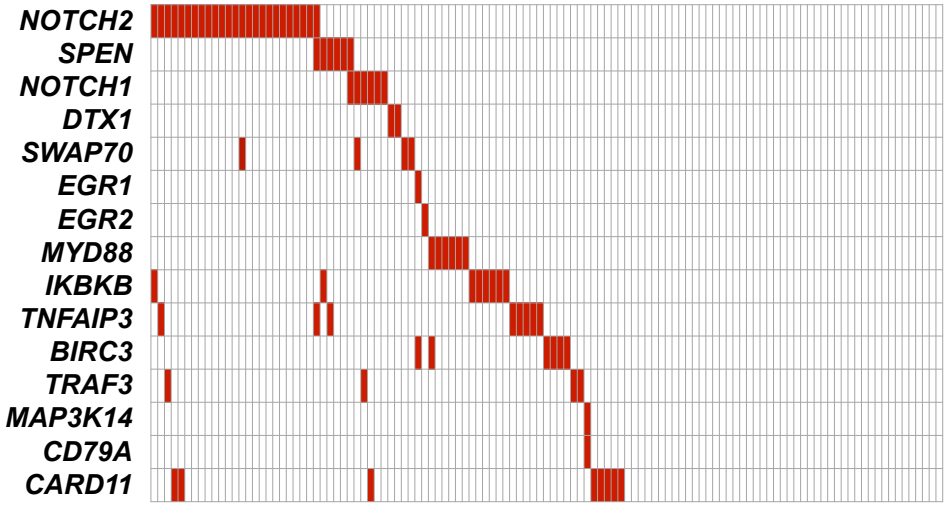
Trøen G, et al. J Mol Diag 2004
Ruiz-Ballesteros E, et al. Blood 2005

Pillai, et al. Nat Rev Immunol 2009

The coding genome of SMZL

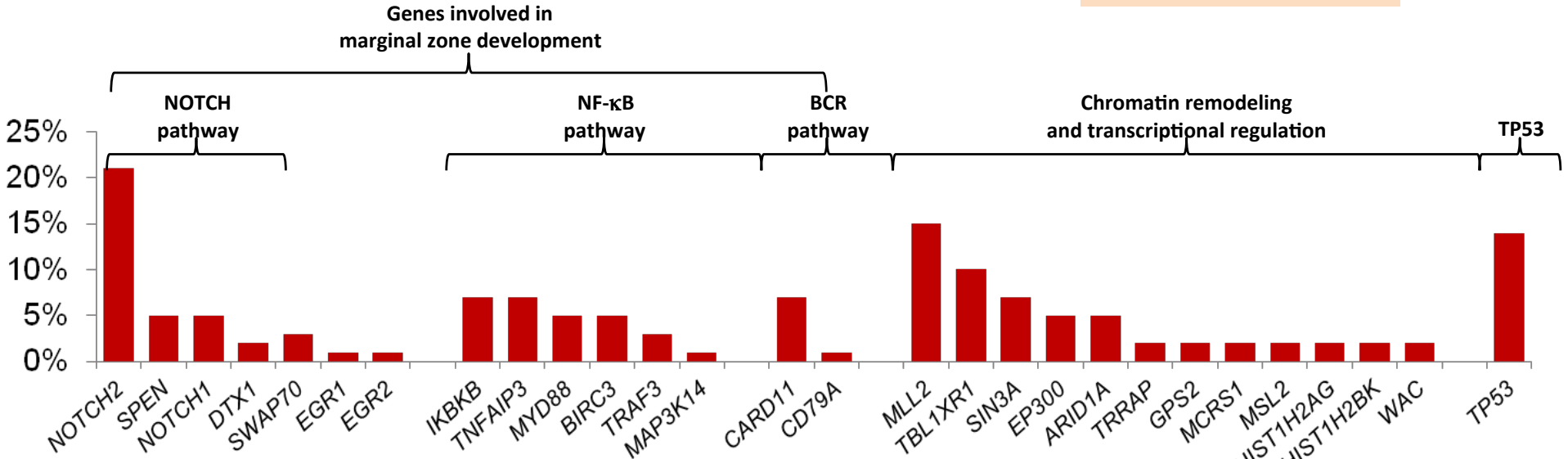
IOR Institute of Oncology Research





SMZL (n=117)

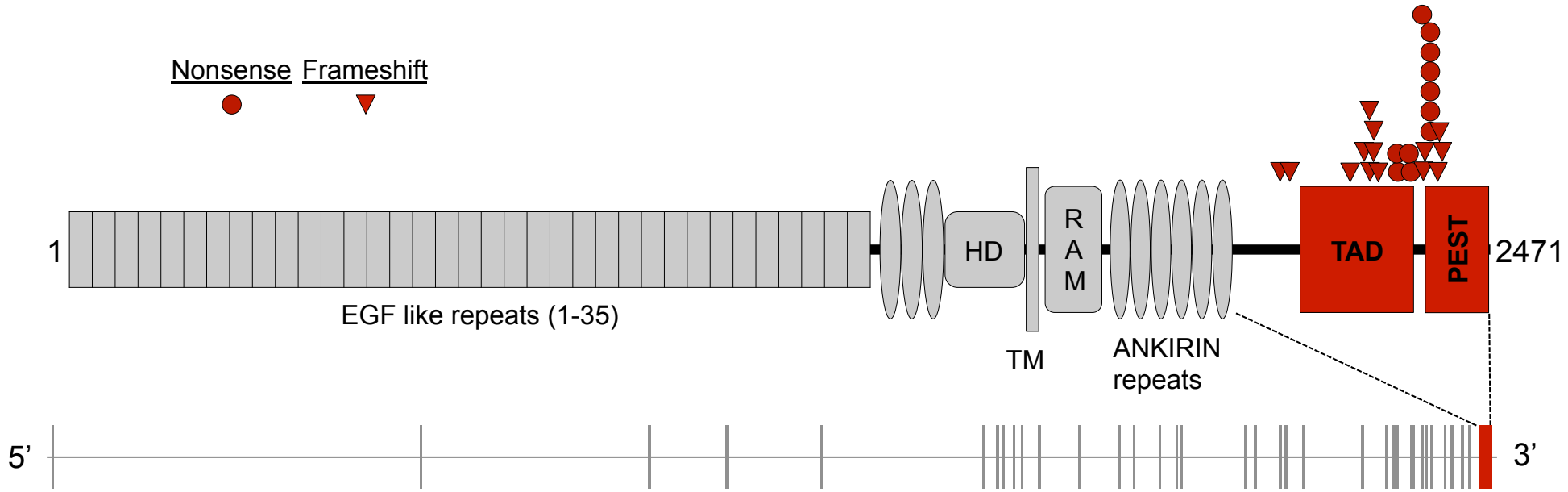
~60% of patients

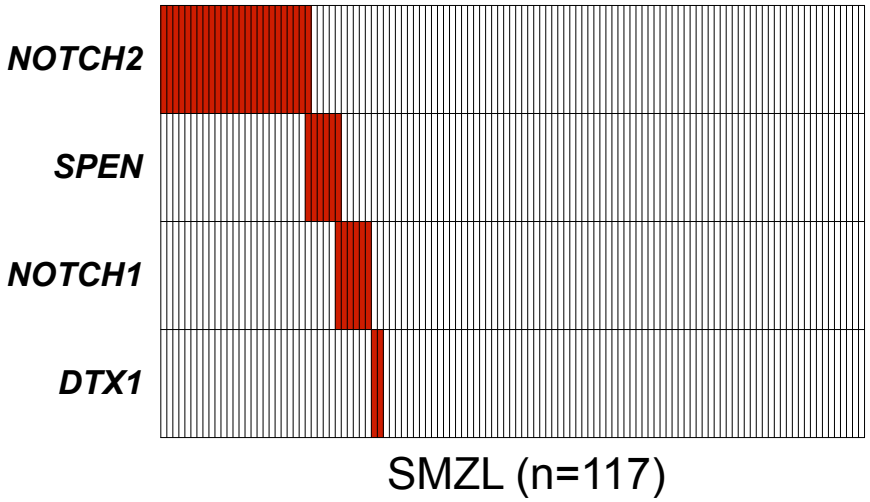


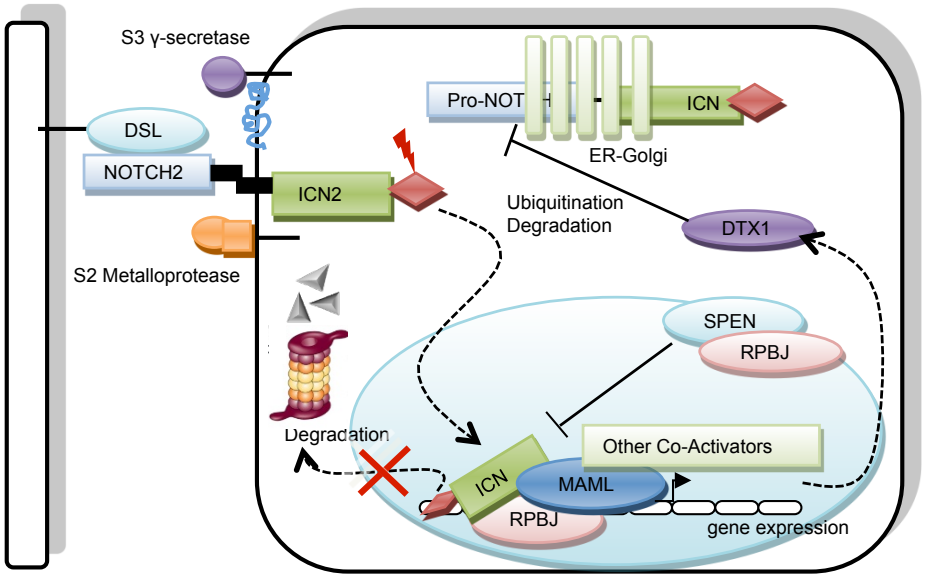
Rossi D, et al. J Exp Med 2012

NOTCH2 is the most frequently mutated gene in ~20% SMZL

IOR Institute of Oncology Research







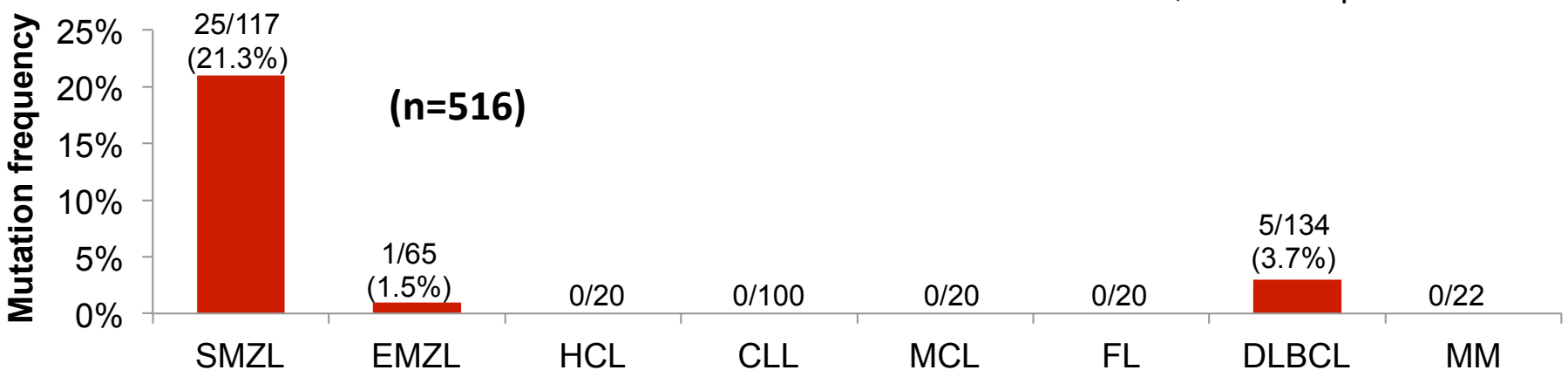
Rossi D, et al. J Exp Med. 2012

Predicted functional consequence of *NOTCH2* mutations

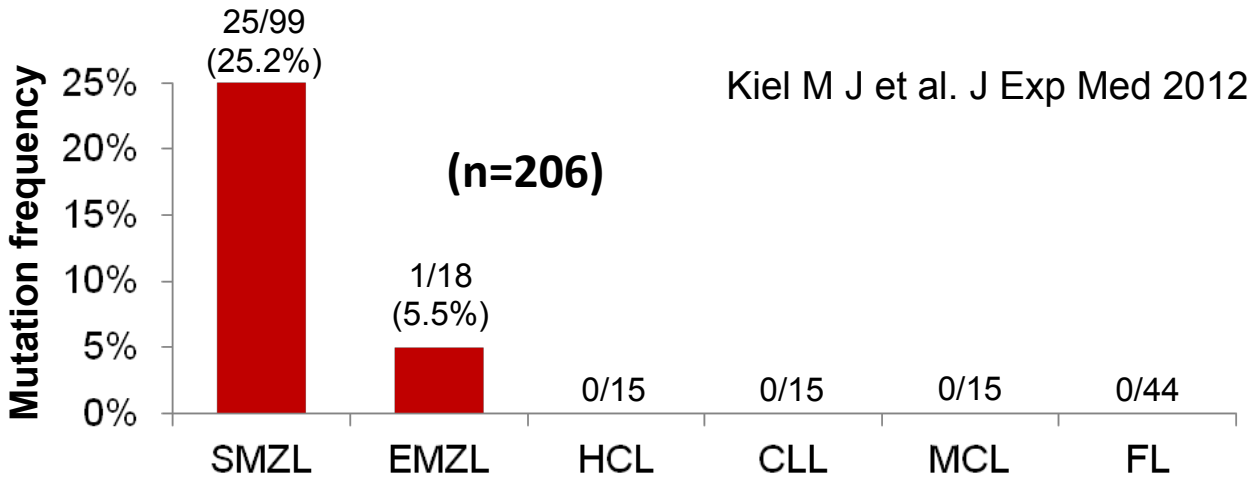
NOTCH2 mutations are restricted to SMZL across mature B-cell tumors

IOR Institute of Oncology Research

Rossi D, et al. J Exp Med. 2012



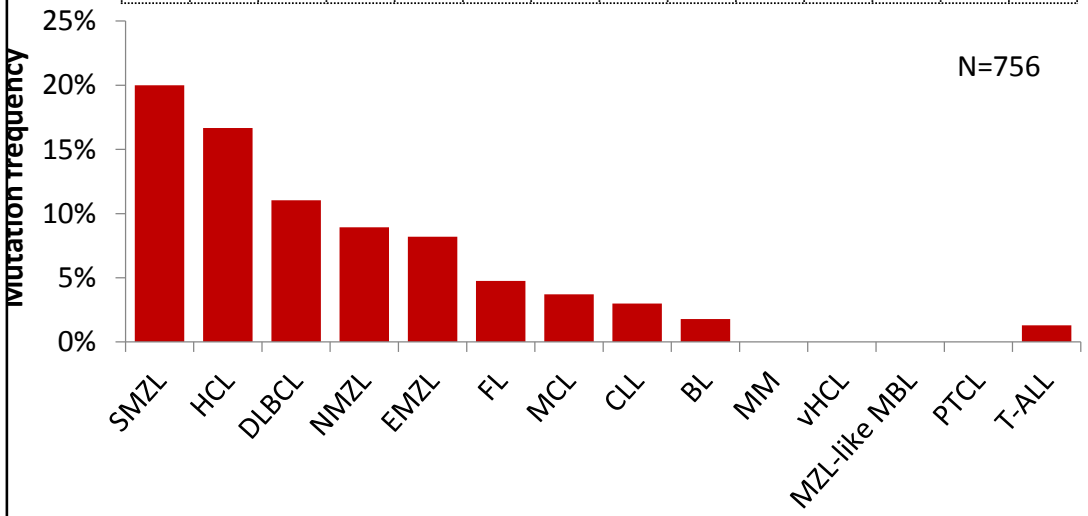
Kiel M J et al. J Exp Med 2012

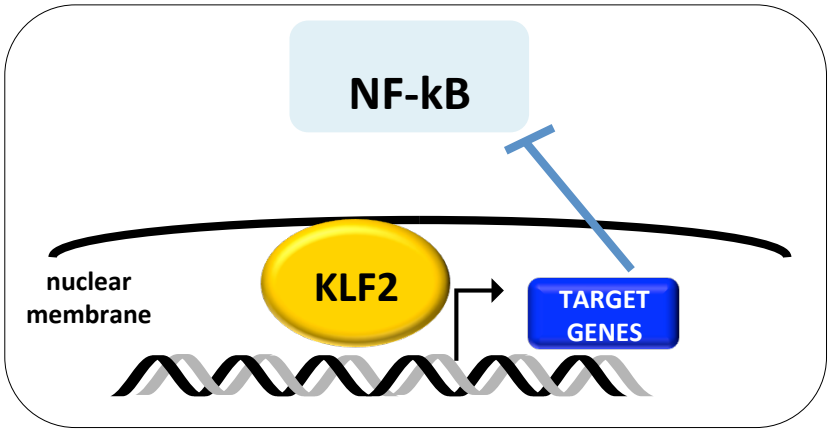


KLF2 mutations in SMZL

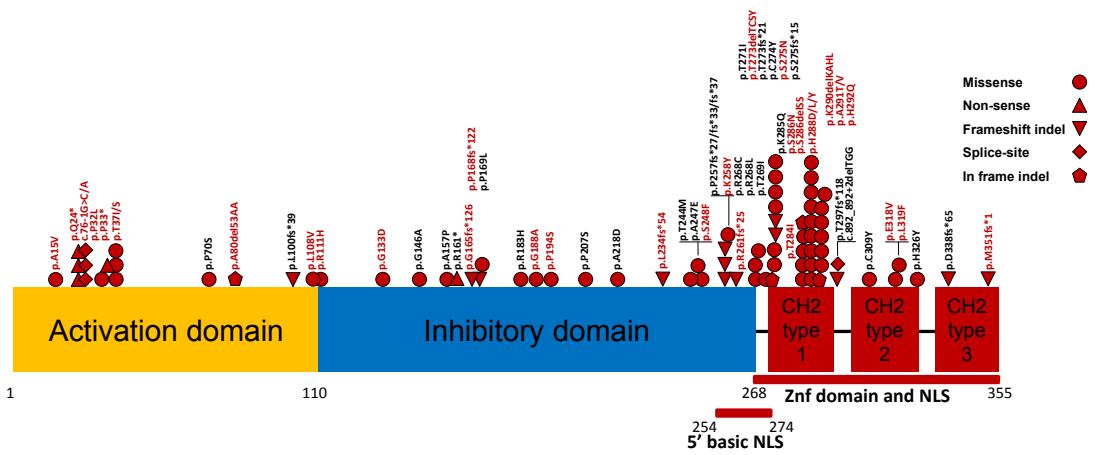
IOR Institute of Oncology Research

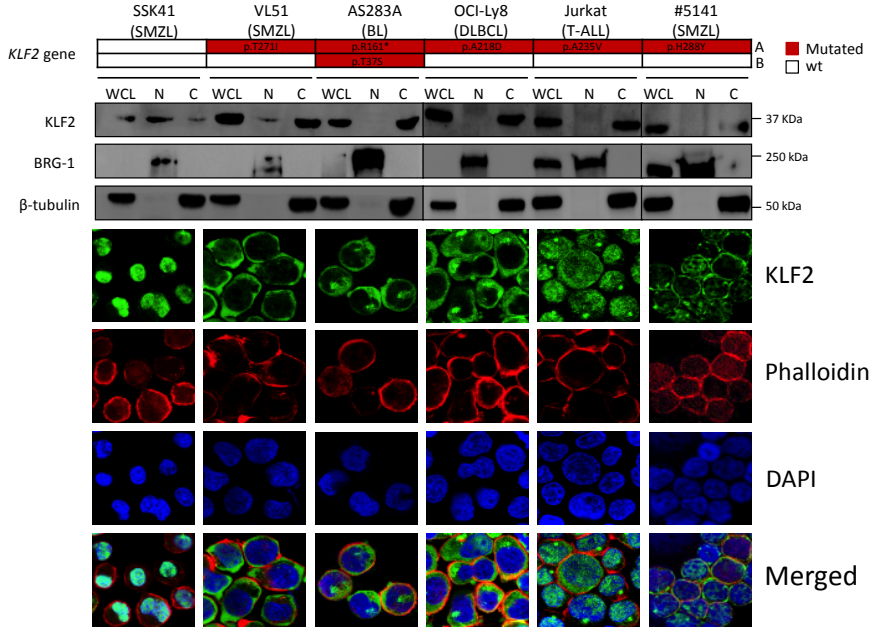
	SMZL	HCL	DLBCL	NMZL	EMZL	FL	MCL	CLL	BL	MM	vHCL	MZL-like MBL	PTCL	T-ALL
M	19	4	17	5	5	1	1	3	1	0	0	0	0	1
Tot	96	24	154	56	61	21	27	100	56	22	11	15	37	76
	20%	16%	11%	9%	8%	4%	4%	3%	2%	-	-	-	-	1%





Clipson A, *Leukemia* 2015



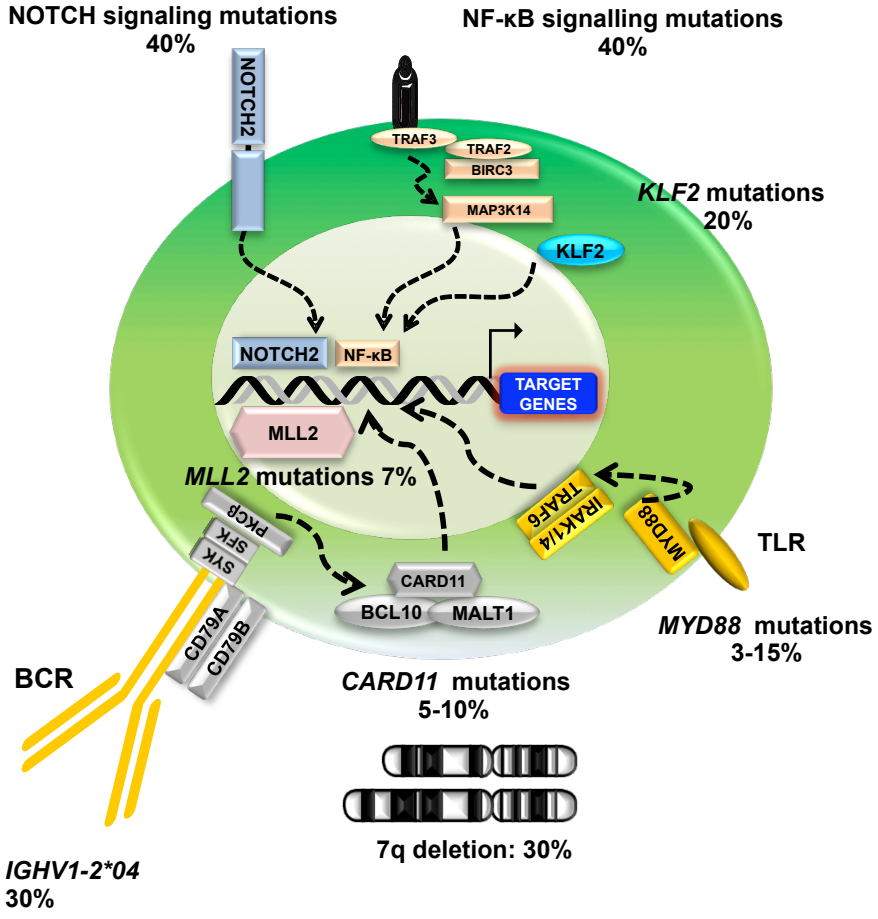


Piva R, *Leukemia* 2015

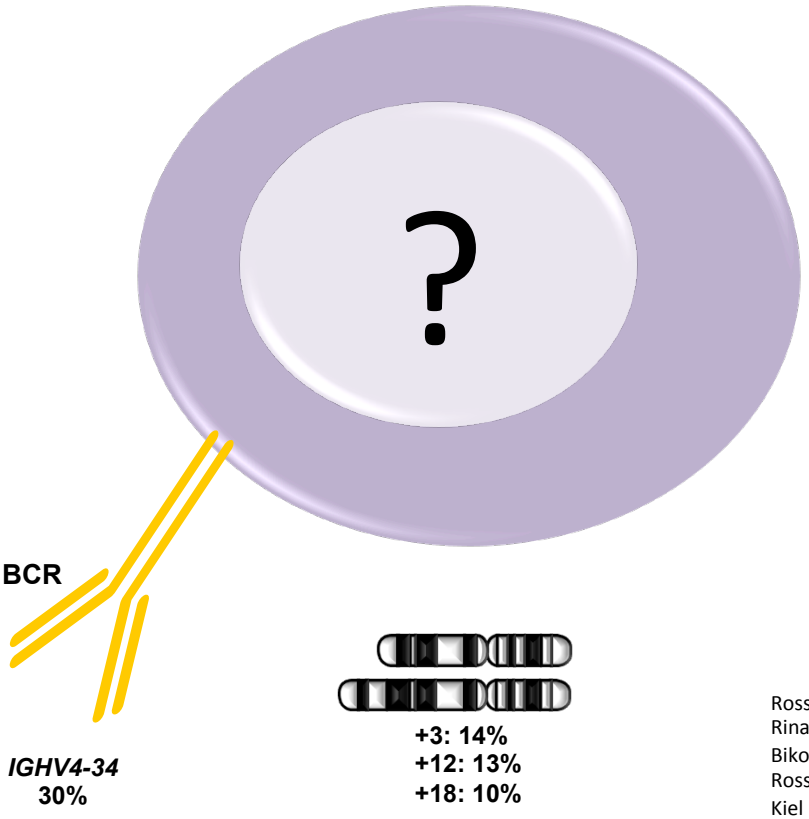
Molecular pathogenesis of non-MALT MZL

IOR Institute of Oncology Research

SMZL



NMZL

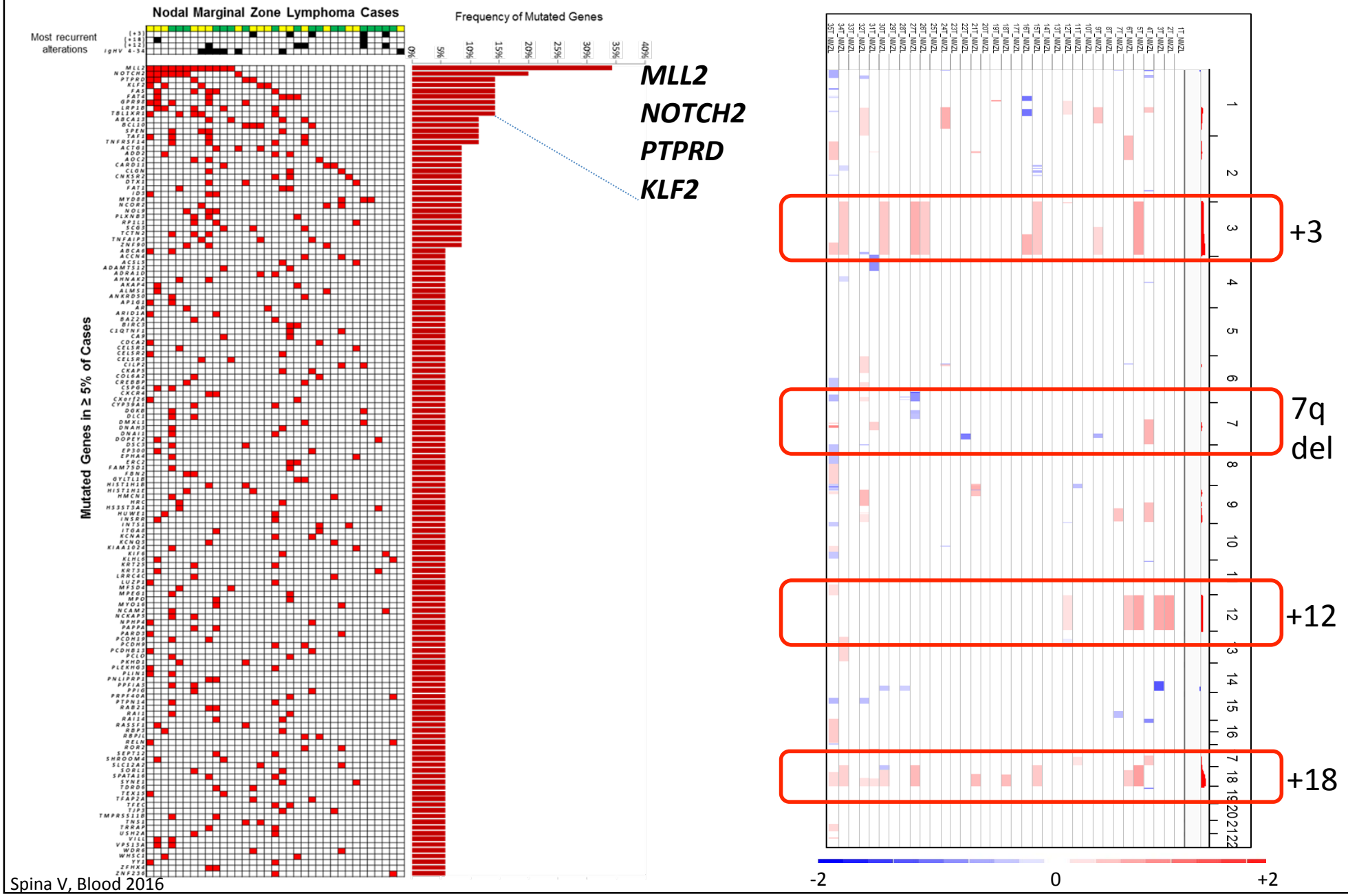


Spina V, Rossi D. *Semin Cancer Biol*. 2016

Rossi D, *Blood* 2011
Rinaldi A, *Blood* 2011
Bikos V, *Leukemia* 2012
Rossi D, *J Exp Med* 2012
Kiel MJ, *J Exp Med* 2012
Parry M, *PLoS One* 2013
Martinez N, *Leukemia* 2014
Piva R, *Leukemia* 2015
Clipson A, *Leukemia* 2015
Parry M, *Clin Cancer Res* 2015
Arribas A, *Blood* 2015

The coding genome of NMZL

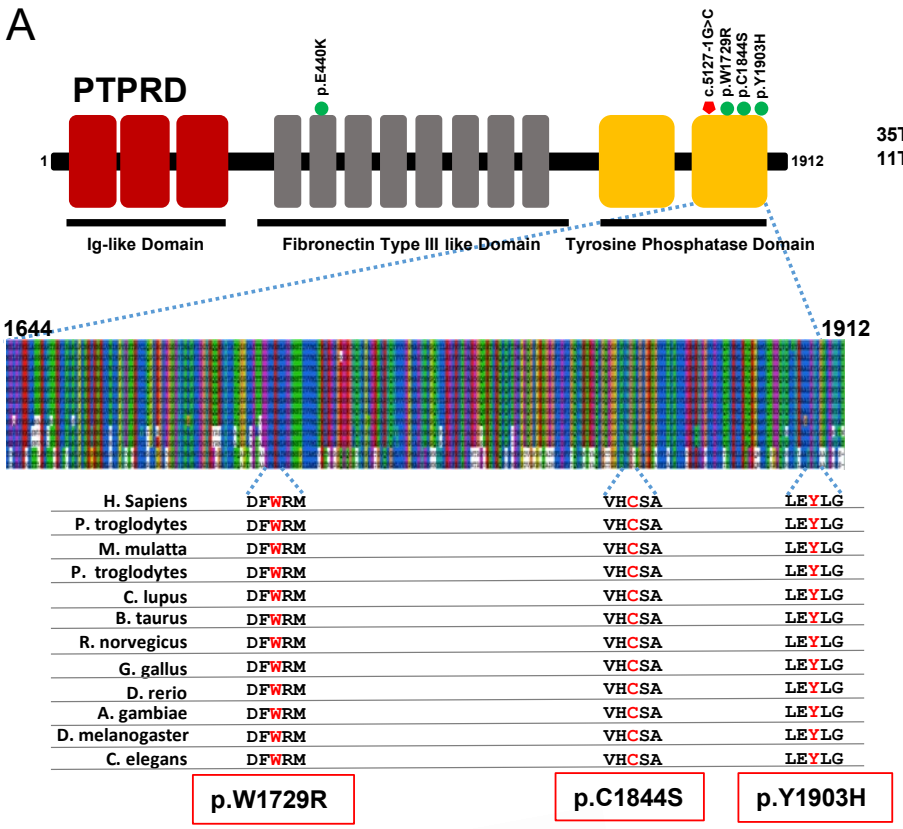
IOR Institute of Oncology Research

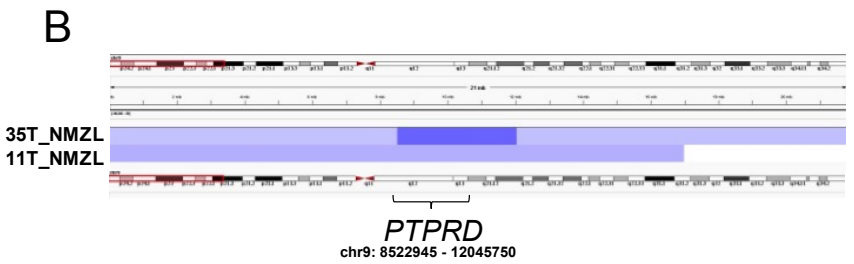


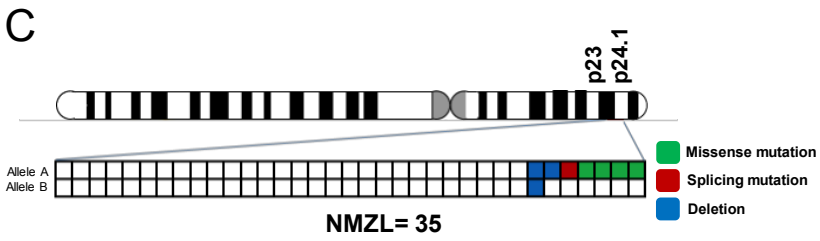
Spina V, Blood 2016

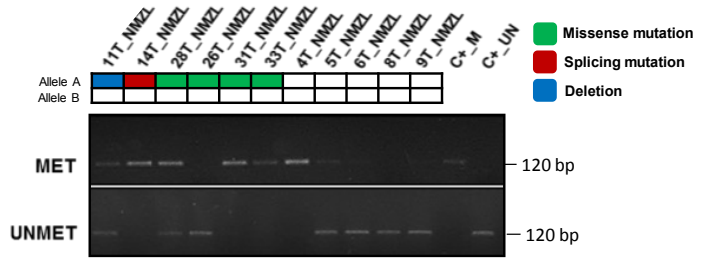
PTPRD in NMZL

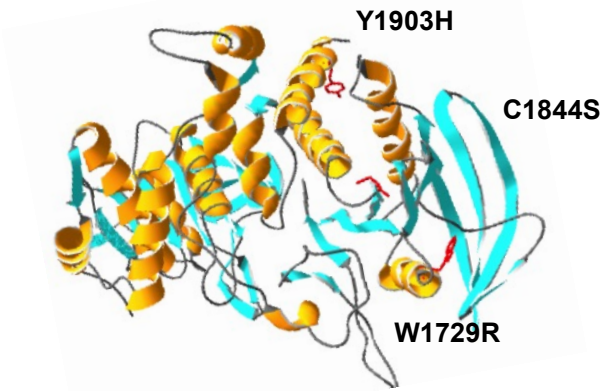
IOR Institute of Oncology Research

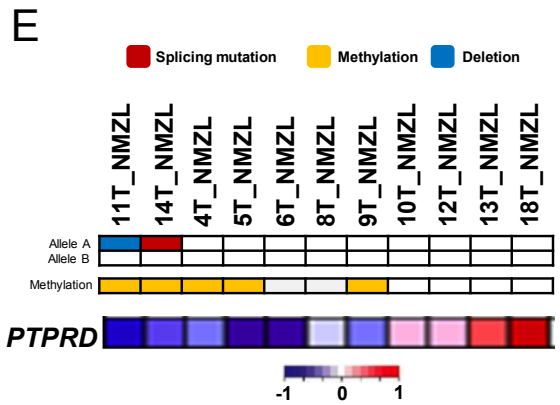


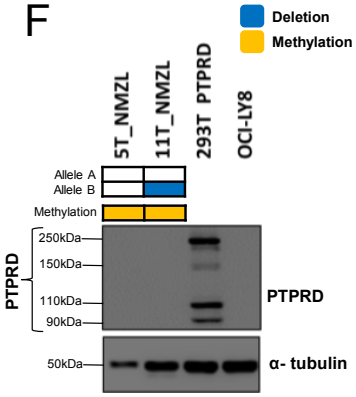








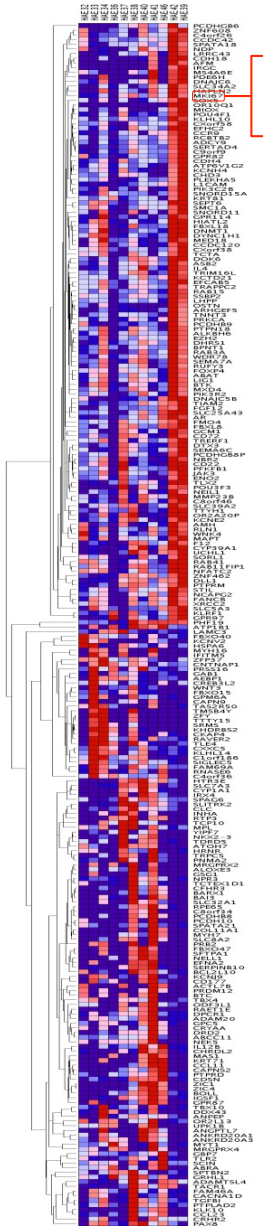




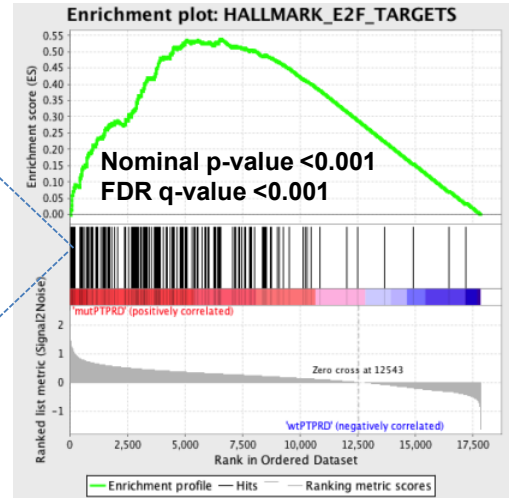
Spina V, Blood 2016

PTPRD mutations in NMZL associate with cell cycle signature and proliferation

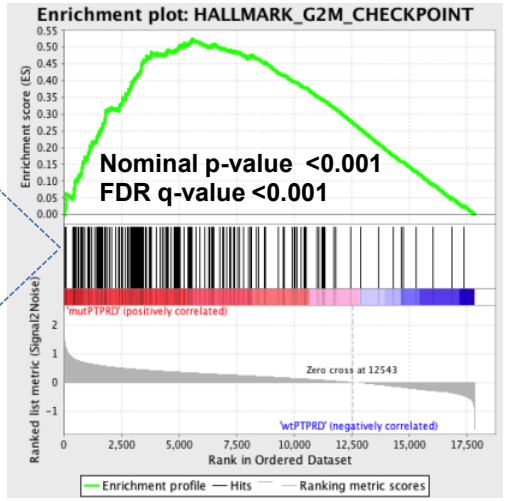
Institute of Oncology Research



EZH2
DNMT1
MKI67
SMC1A
LIG1
CIT
ING3
ILF3

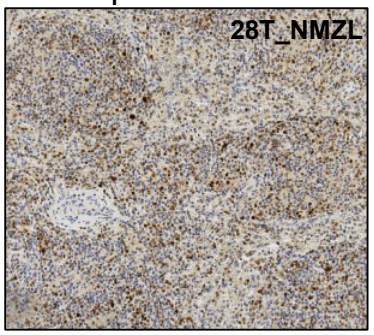


EZH2
STIL
MKI67
SMC1A
CDC7
ILF3
CENPE
E2F3
SUV39H1



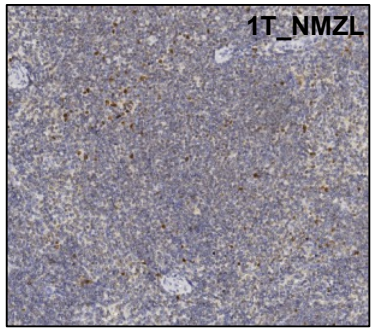
PTPRD

p.C1844S

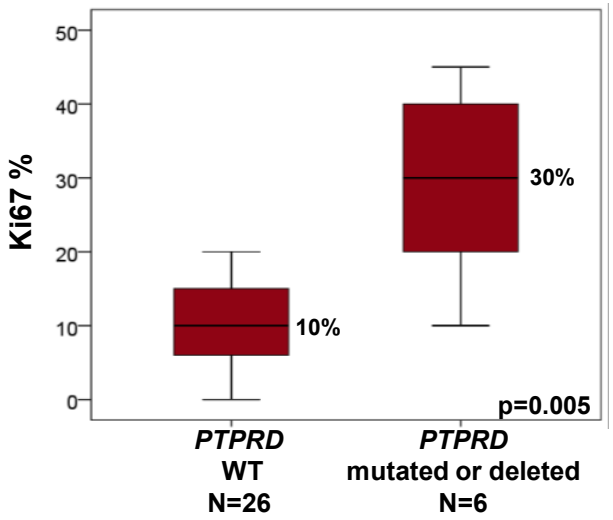


anti-Ki67

WT



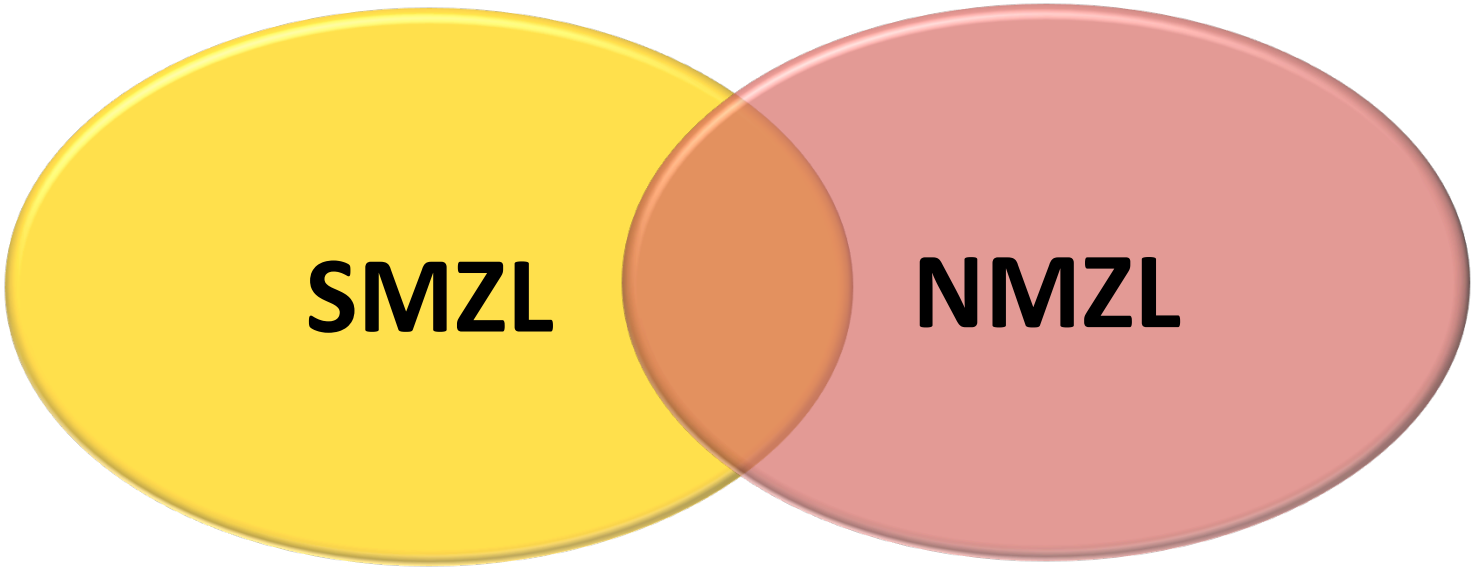
anti-Ki67



Spina V, Blood 2016

Splenic and nodal marginal zone lymphoma are distinguished by the different involved sites

IOR
Institute of Oncology Research



Shared features

Cytologic: clonal expansion of centrocyte-like and monocytoid-like B-cells

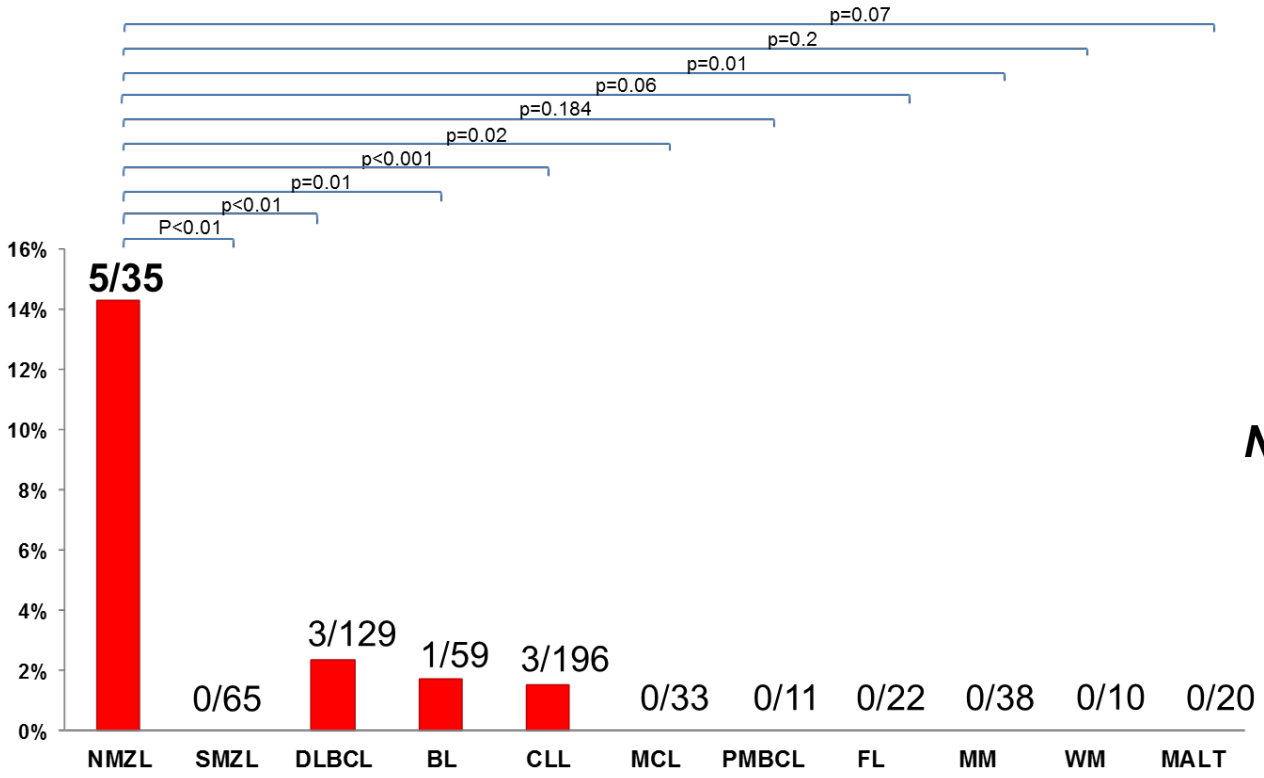
Histologic: marginal zone colonization with interfollicular expansion

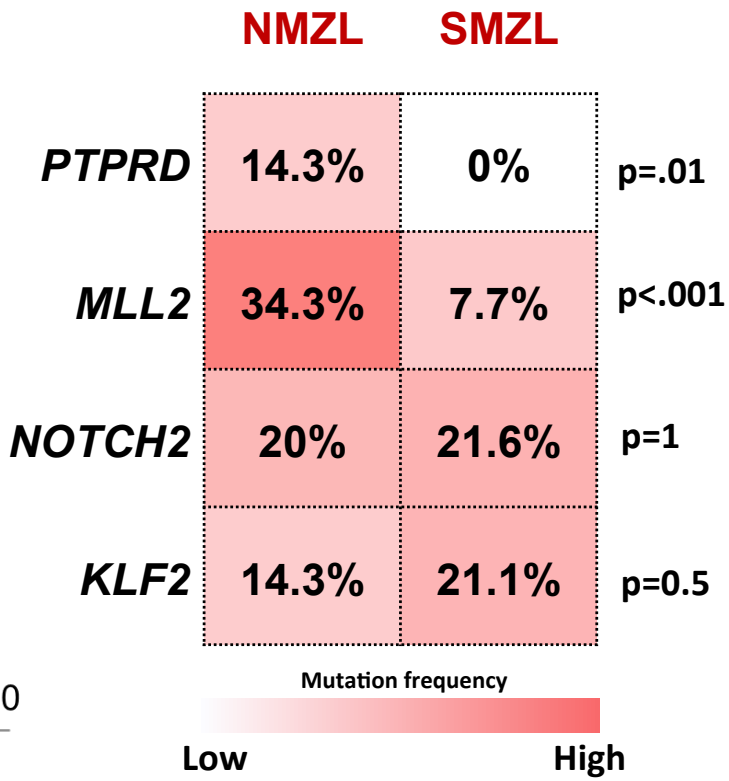
Phenotypic: CD19+, CD20+, CD79a+, CD5-, CD10-, CD23-, BCL6-, cyclin D1-

2008 WHO Classification

PTPRD mutations are enriched in NMZL across mature B-cell tumors (n=619)

IOR Institute of Oncology Research



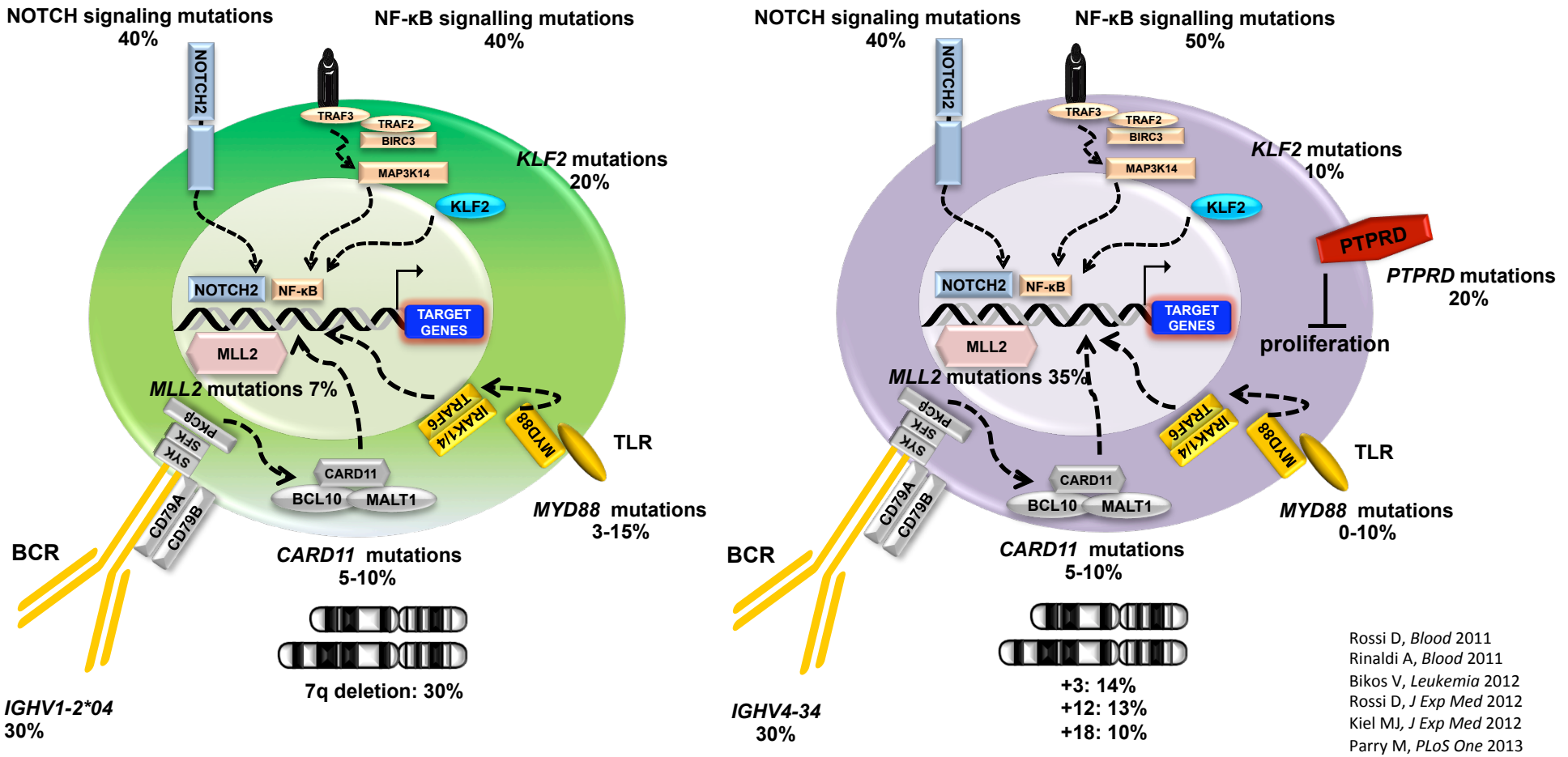


Genes mutated in ≥15% of NMZL and/or SMZL

Spina V, Blood 2016

Molecular pathogenesis of non-MALT MZL

IOR Institute of Oncology Research



Spina V, Rossi D. *Semin Cancer Biol*. 2016

Rossi D, *Blood* 2011
Rinaldi A, *Blood* 2011
Bikos V, *Leukemia* 2012
Rossi D, *J Exp Med* 2012
Kiel MJ, *J Exp Med* 2012
Parry M, *PLoS One* 2013
Martinez N, *Leukemia* 2014
Piva R, *Leukemia* 2015
Clipson A, *Leukemia* 2015
Parry M, *Clin Cancer Res* 2015
Arribas A, *Blood* 2015
Spina V, *Blood* 2016

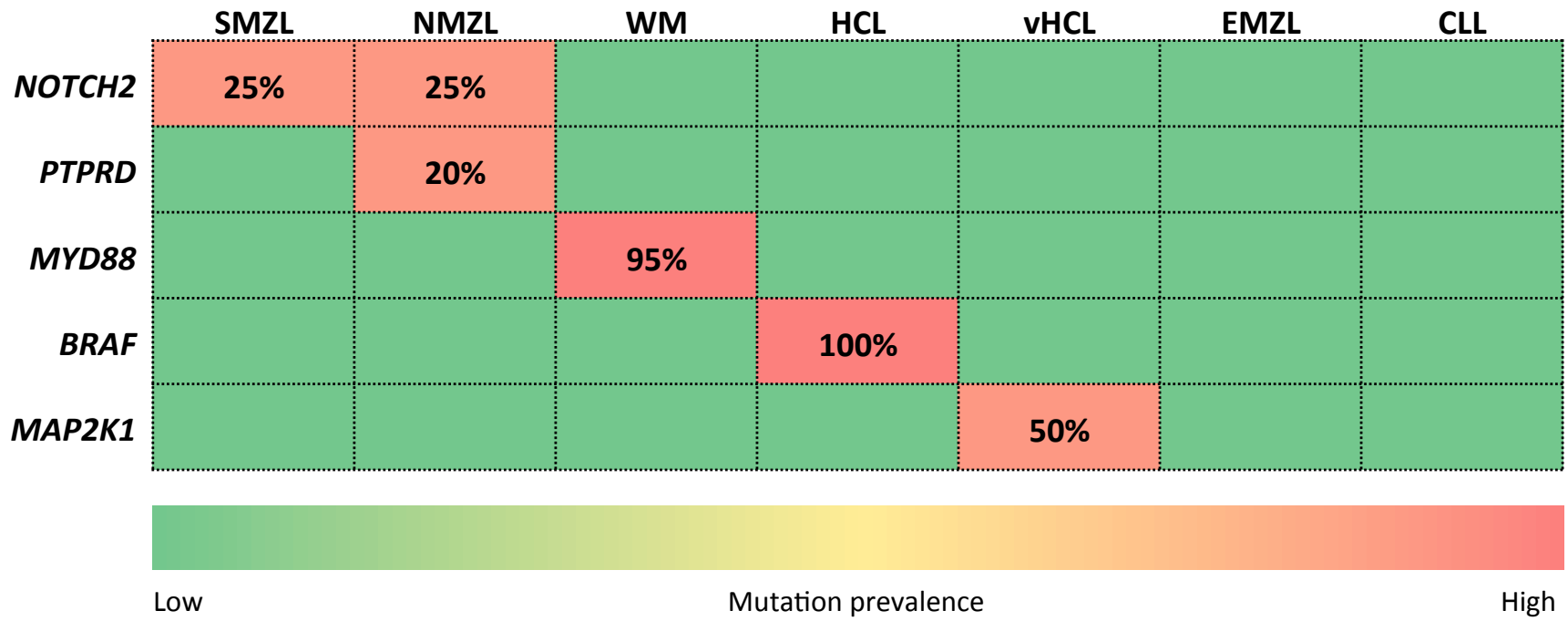
Domains

IOR Institute of Oncology Research

- Genetics of non-MALT MZL
  - SMZL
  - NMZL
- Clinical implications of non-MALT MZL genetics
  - Diagnosis
  - Prognosis
  - Therapy

Genetics can assist in the specification of histopathologically challenging B-cell LPDs

IOR Institute of Oncology Research



Tiacci et al, New Engl J Med 2011
Treon et al, New Engl J Med 2012
Landau et al, Cell 2013
Rossi et al, J Exp Med 2013
Rossi et al, ASH 2013
Waterfall et al, Nat Genet 2013
Spina et al, Blood 2016

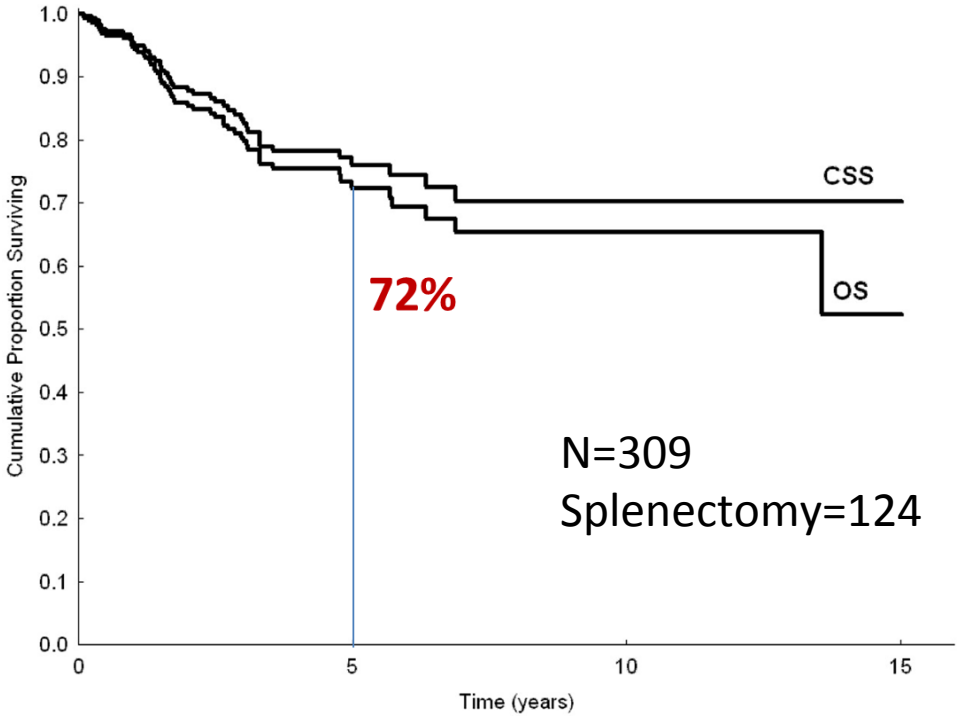
Domains

IOR Institute of Oncology Research

- Genetics of non-MALT MZL
  - SMZL
  - NMZL
- Clinical implications of non-MALT MZL genetics
  - Diagnosis
  - Prognosis
  - Therapy

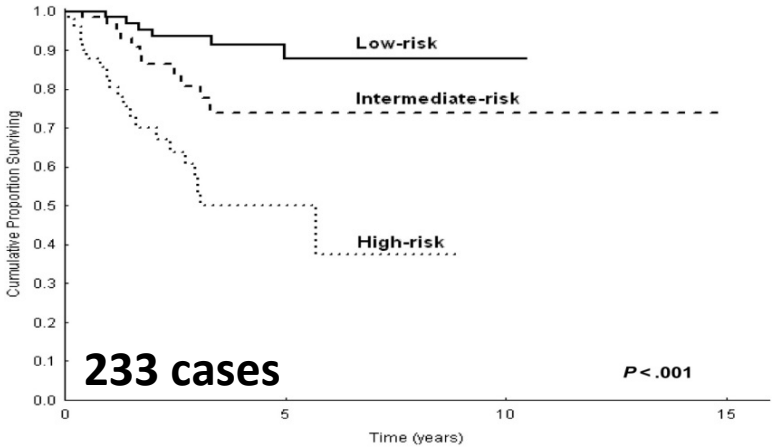
Background
SMZL shows an heterogeneous clinical course

IOR Institute of Oncology Research



N=309
Splenectomy=124

LSS



IIL score
Hemoglobin
LDH
Albumin

	Deaths	5-year LSS
Low	16%	88%
Int	30%	73%
High	54%	50%

Arcaini, Blood 2006

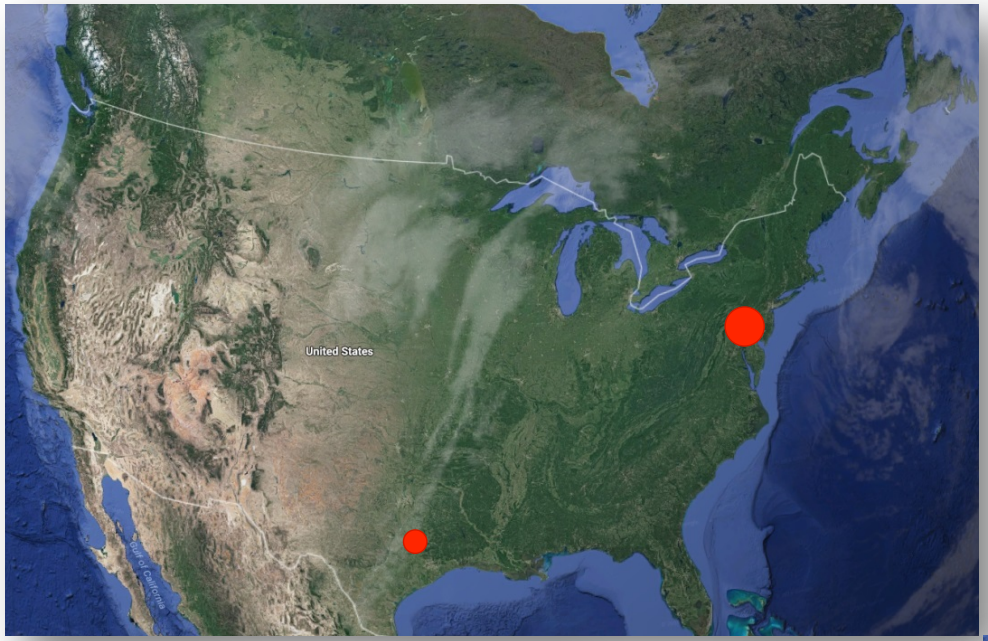
Molecular features of SMZL associated with prognosis

IOR Institute of Oncology Research

- *NOTCH2* mutations
- *KLF2* mutation
- *TP53* disruption
- *IGHV1-2*04* usage
- 7q deletion

Salido M, *Blood* 2010
Kiel MJ, *J Exp Med* 2012
Parry M, *Clin Cancer Res* 2015
Arribas A, *Blood* 2015

IELSG 46: INTEGRATED MOLECULAR AND CLINICAL PROFILING TO OPTIMIZE OUTCOME PREDICTION IN SMZL



New York
- Columbia University Medical Center
- Weill Cornell Medicine

Houston

ClinicalTrial.gov: NCT02945319

Basel
Bellinzona
Bern
St. Gallen

London
Bournemouth

Lisbon

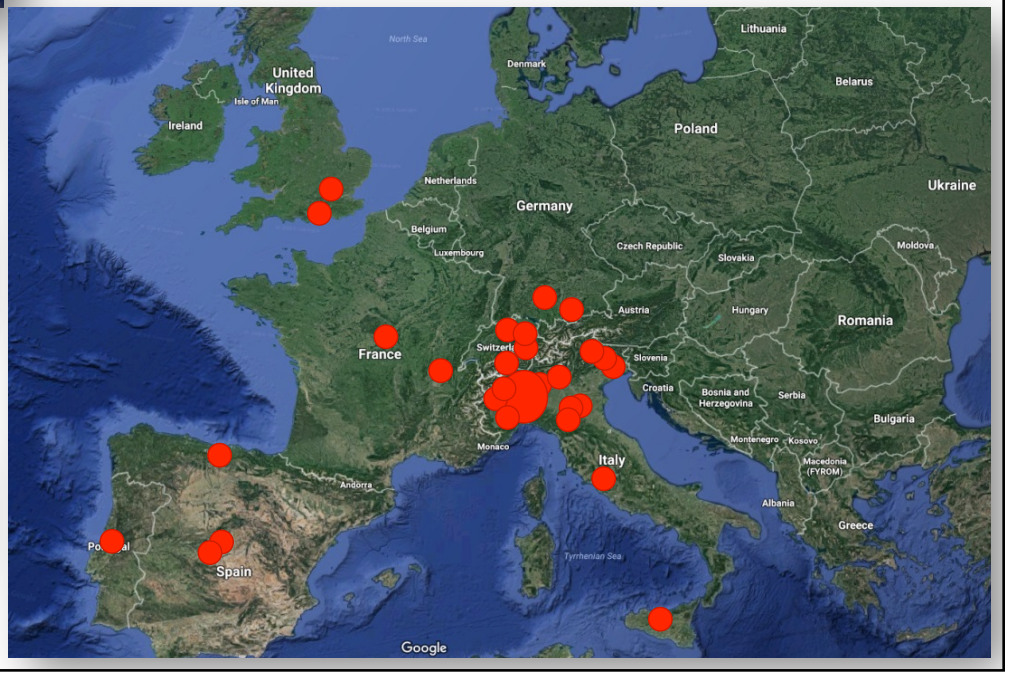
Milano
- Ist tumori
- Niguarda
- San Raffaele
- Policlinico

Aviano
Alessandria
Bergamo
Bologna
Brescia
Modena
Novara
Pavia
Roma
Torino
Udine
Varese
Verona
Vicenza

Lyon
Paris

Heidelberg
Kiel
Munich
Ulm

Barcelona
Madrid
Santander
Toledo



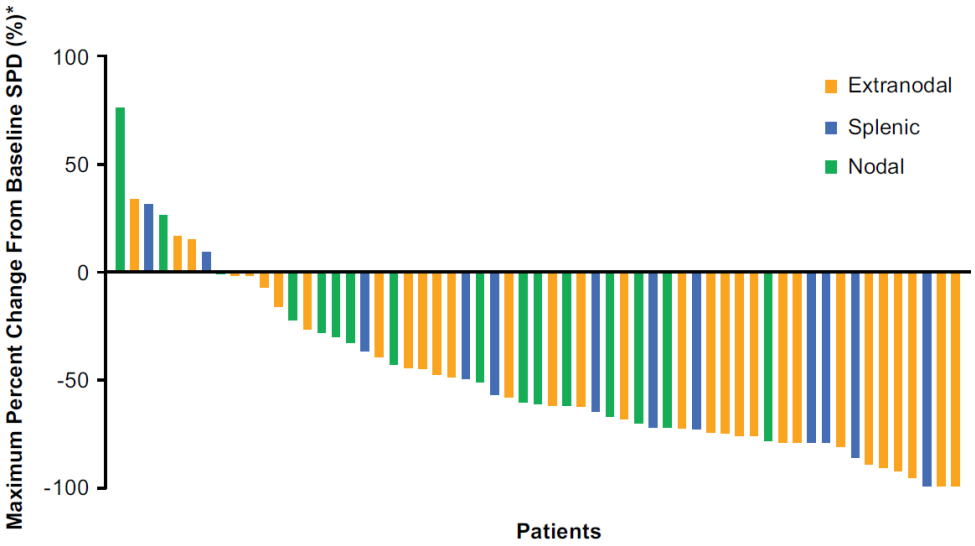
Domains

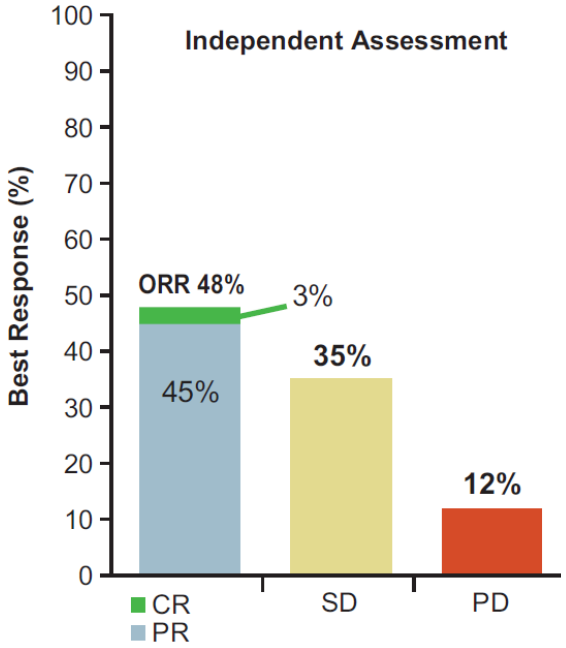
IOR Institute of Oncology Research

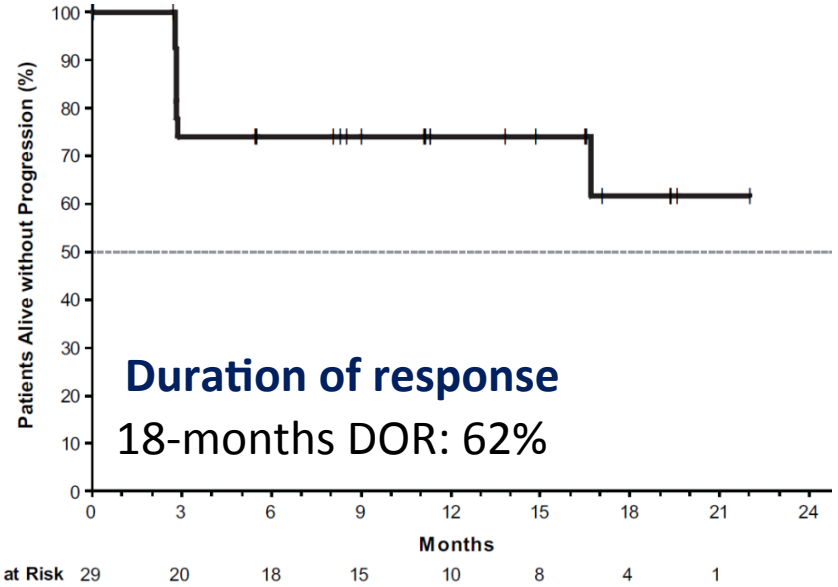
- Genetics of non-MALT MZL
  - SMZL
  - NMZL
- Clinical implications of non-MALT MZL genetics
  - Diagnosis
  - Prognosis
  - Therapy

Ibrutinib monotherapy in R/R MZL

IOR Institute of Oncology Research

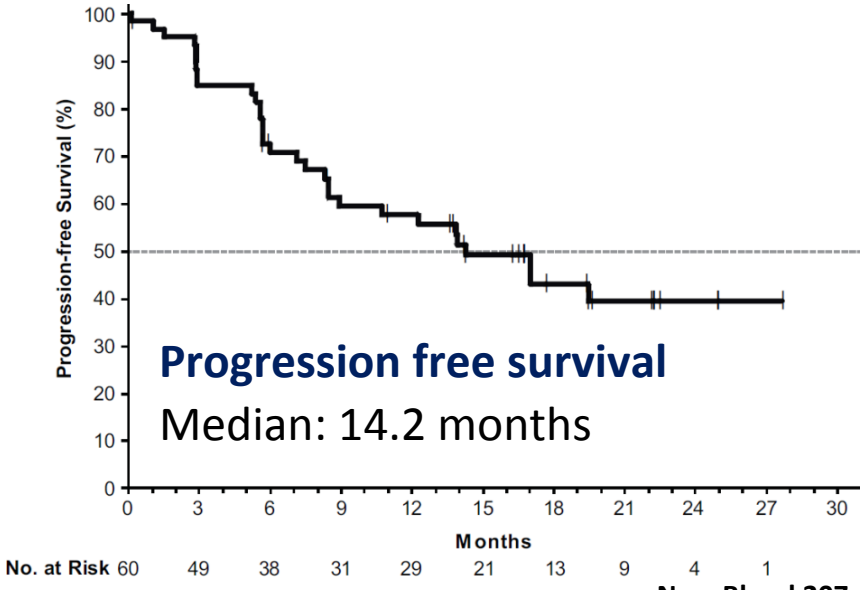






Duration of response

18-months DOR: 62%



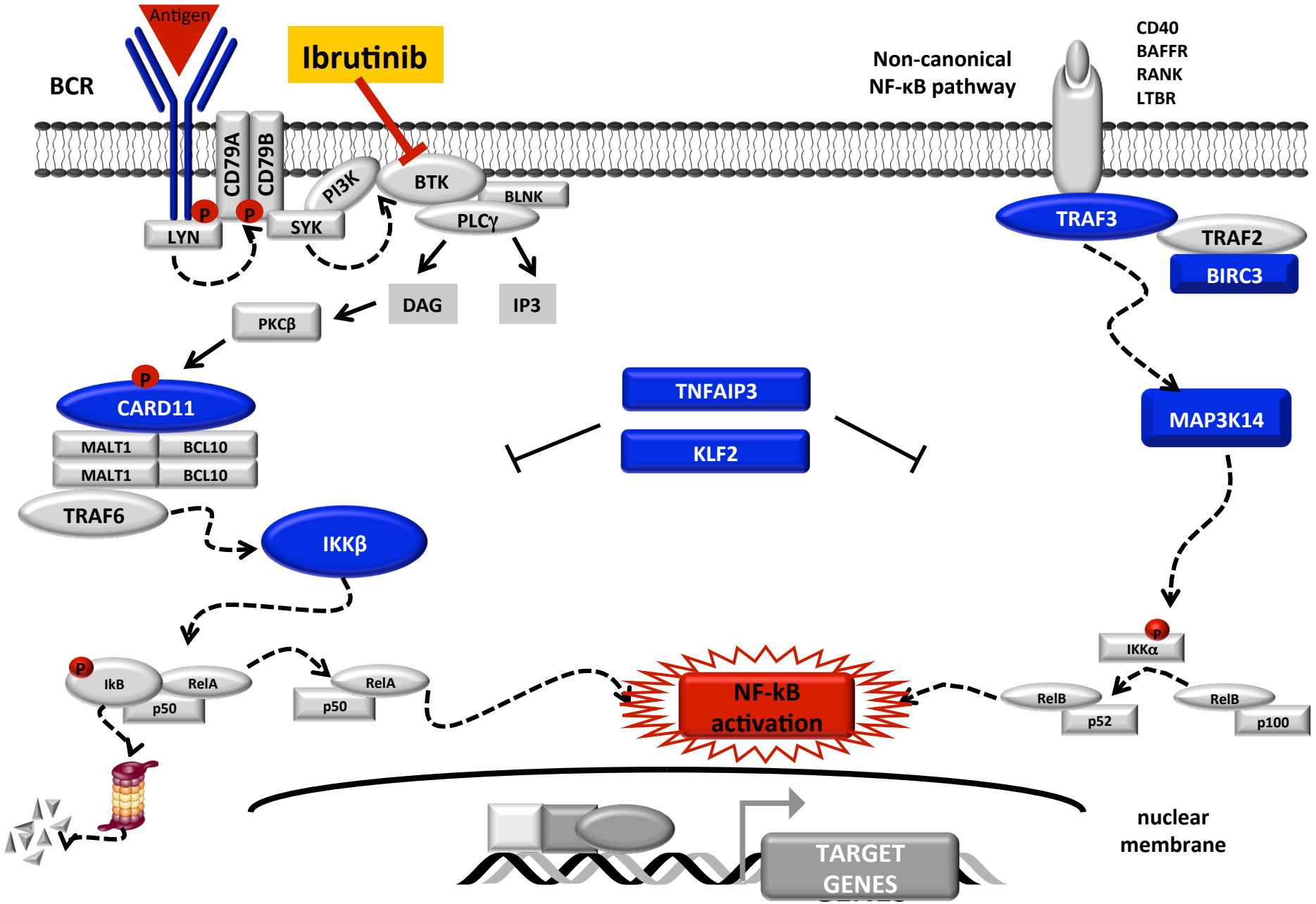
Progression free survival

Median: 14.2 months

Noy, Blood 207

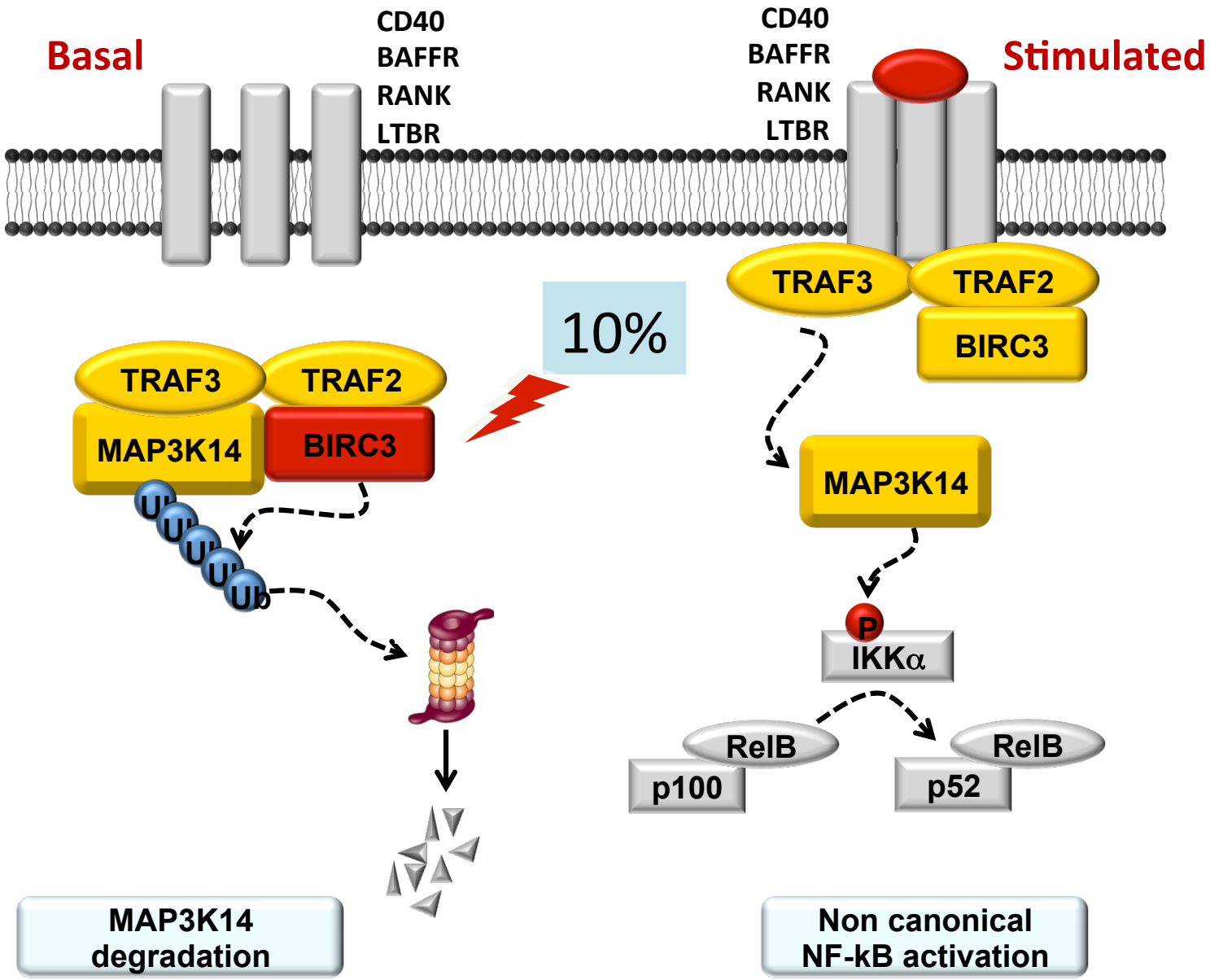
Signaling activation in MZL

IOR
Institute of Oncology Research



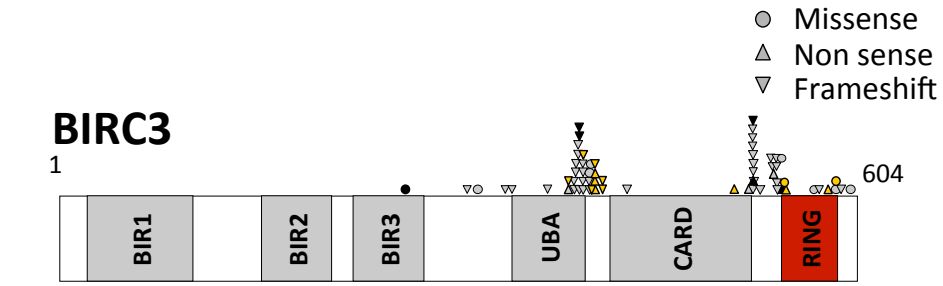
BIRC3 mutations in SMZL

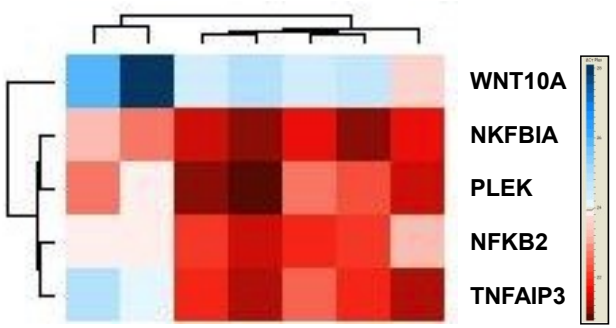
IOR Institute of Oncology Research

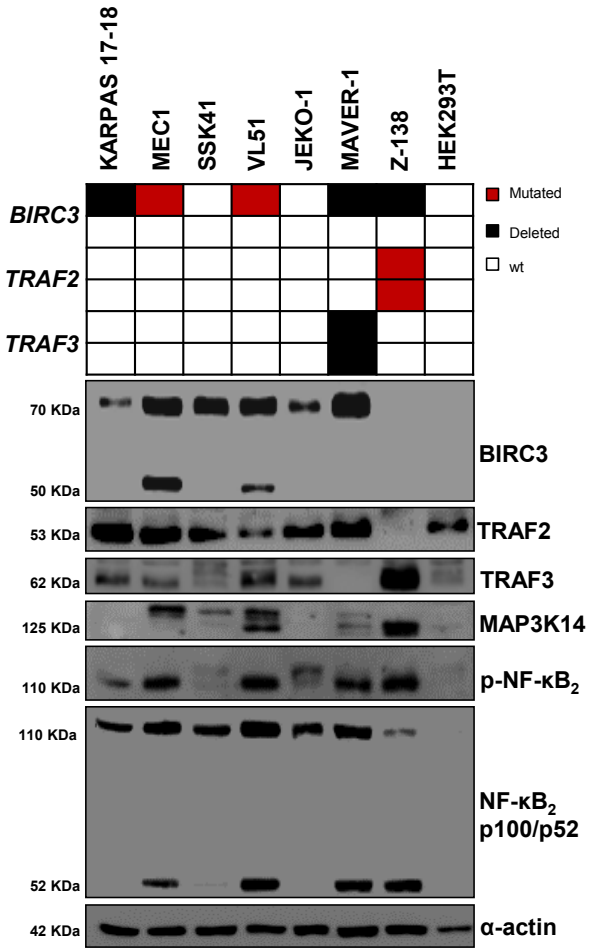


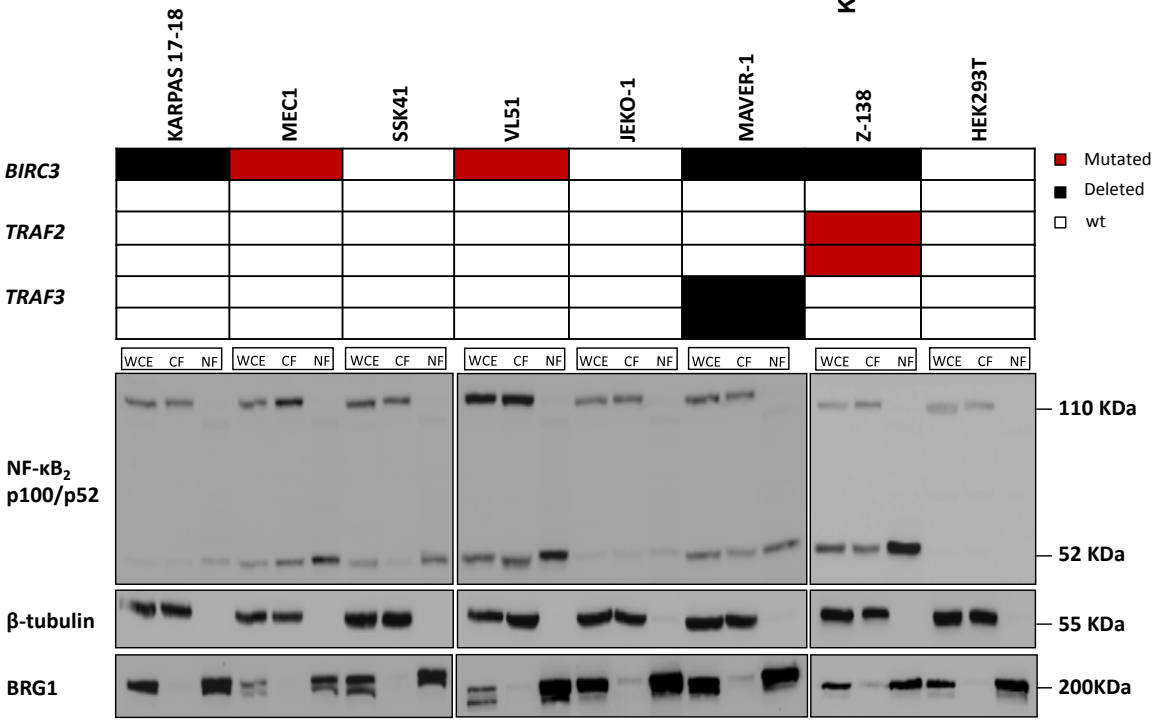
BIRC3 mutations activate non-canonical NF-kB

IOR Institute of Oncology Research



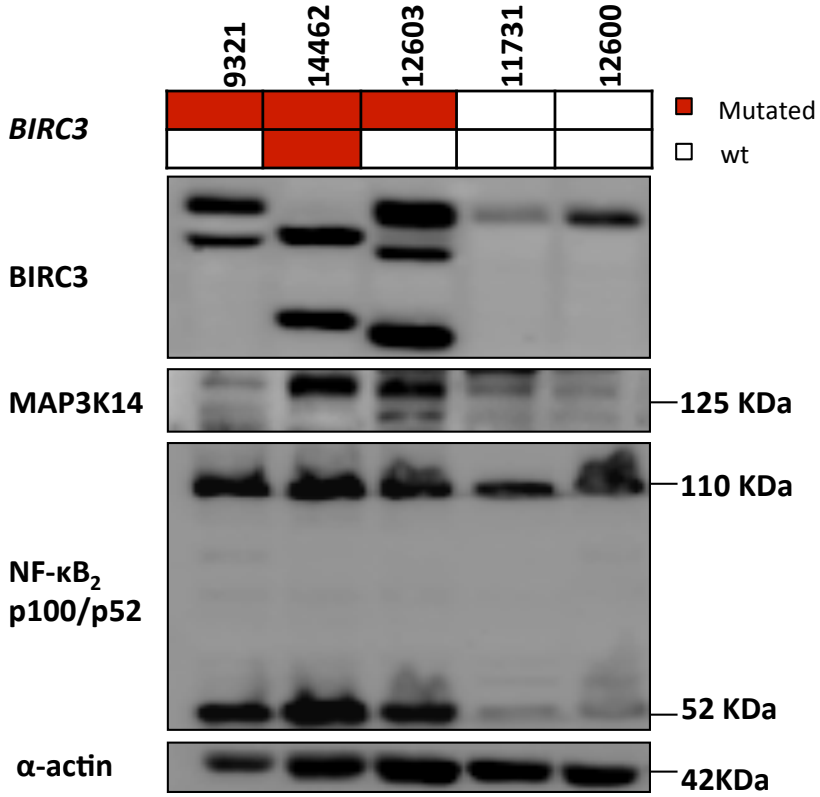


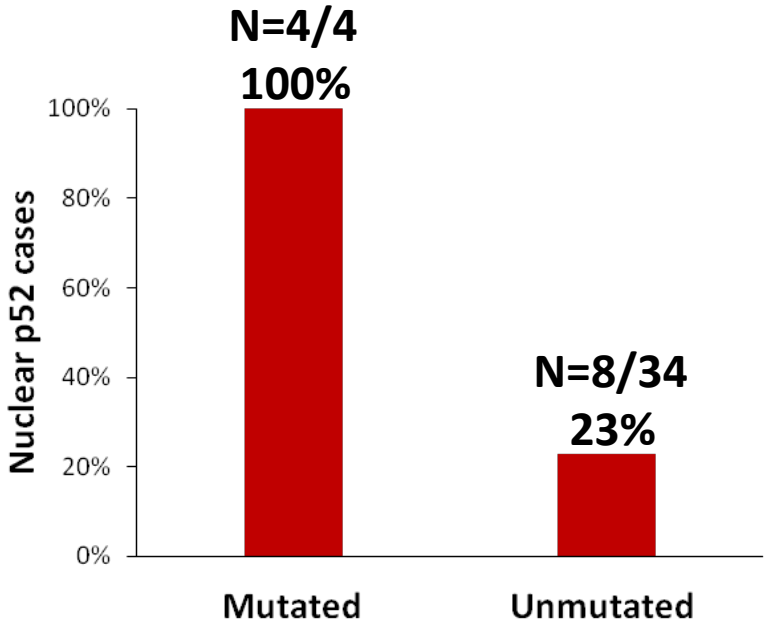


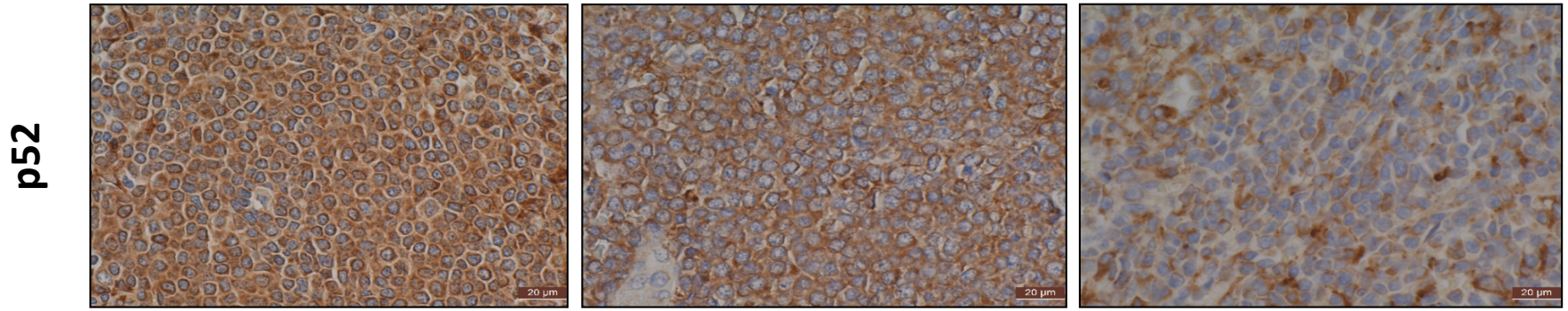


Non-canonical NF-κB pathway is active in *BIRC3* mutated primary samples

IOR Institute of Oncology Research

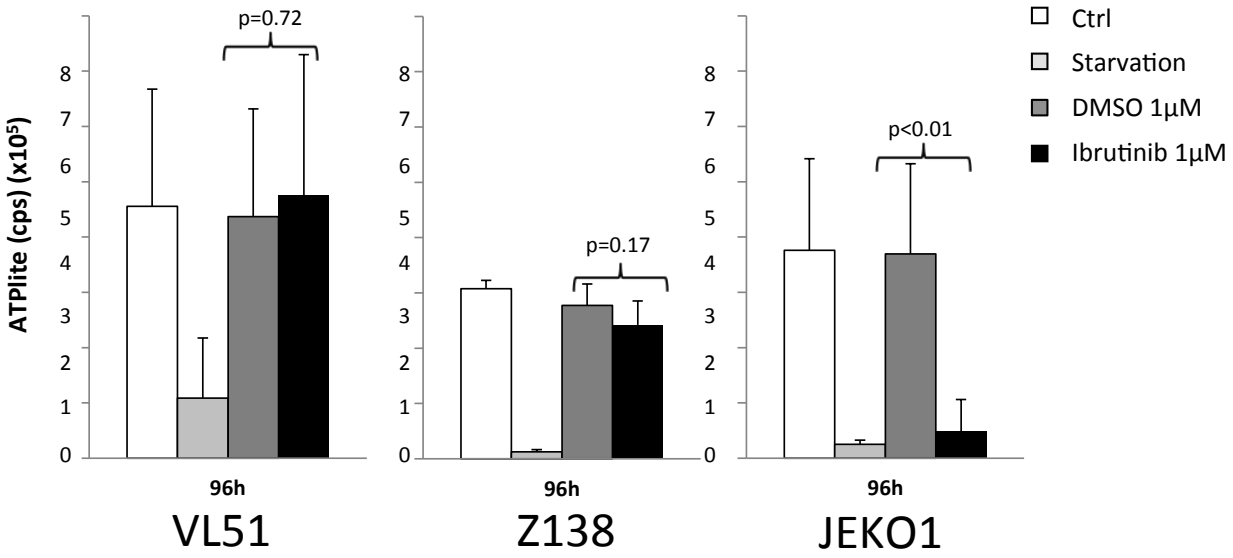


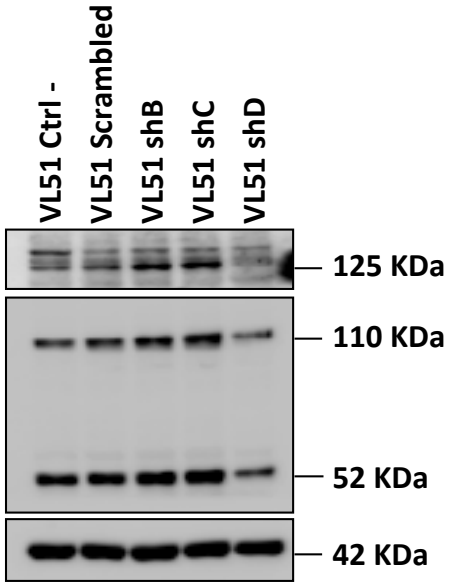


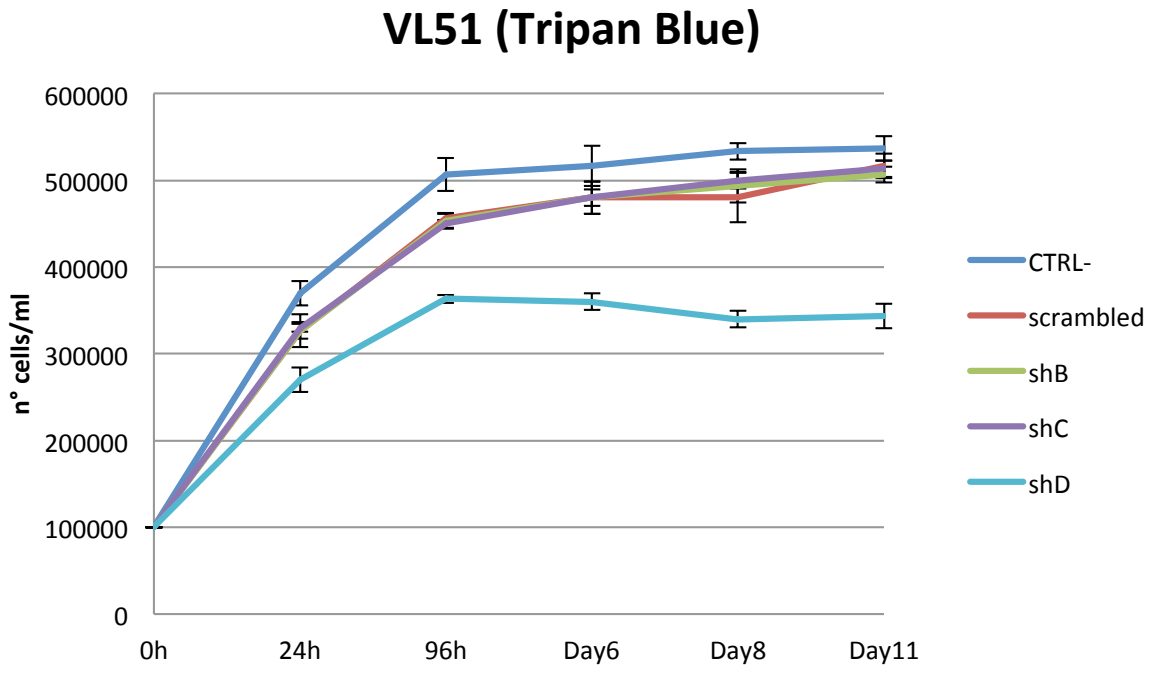


BIRC3 mutated cells are addicted of NIK

IOR Institute of Oncology Research







Conclusions

IOR Institute of Oncology Research

- NMZL and SMZL are enriched of mutations in genes involved in the physiological development of MZ B-cells
- *NOTCH2* mutations are specific for SMZL and NMZL across mature B-cell tumors (diagnostic implications)
- *PTPRD* mutations are specific for NMZL across mature B-cell tumors (diagnostic implications)
- Signals on the prognostic implications of mutations prompt the development of molecular biomarker-based score systems (pts counseling, clinical trial design)
- NF-kB mutations may mark resistance to ibrutinib (treatment tailoring)

IOSI

IOR Institute of Oncology Research

UPO Università del Piemonte Orientale

Sapienza Università di Roma

Francesco Bertoni
Bernhard Gerber
Anastasios Stathis
Georg Stüssi
Emanuele Zucca

Franco Cavalli
Michele Ghielmini

Alessio Bruscaggin
Adalgisa Condoluci
Gabriela Forestieri
Valeria Spina

Clara Deambrogi
Fary Diop

Gianluca Gaidano

Monica Messina

Robin Foà

ICH

Carmelo Carlo-Stella

Università Cattolica del Sacro Cuore

Stefan Hohaus
Luigi Larocca

Luca Arcaini
Marco Lucioni

Institute For Cancer Genetics
Columbia University Health Sciences Division

Laura Pasqualucci

Riccardo Dalla Favera

Weill Cornell Medical College

Giorgio Inghirami

Studium Generale Civitatis Perusini A.D. MCCCVIII

Enrico Tiacci

Ospedale San Raffaele

Maurilio Ponzoni

IEO Istituto Europeo di Oncologia

Stefano Pileri

FNSNF
Swiss National Science Foundation

krebsliga schweiz
Gemeinsam gegen Krebs

fidinam