INCONTRO DI AGGIORNAMENTO SUI

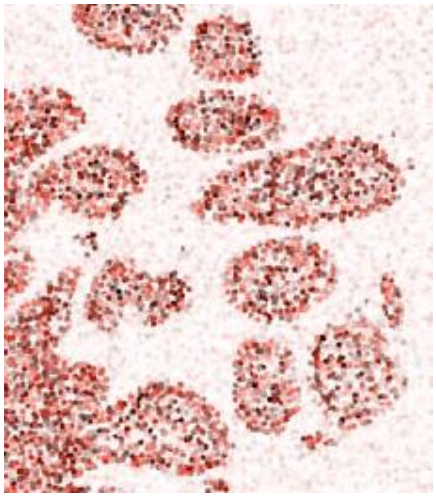
DISORDINI LINFOPROLIFERATIVI

E SUI PROTOCOLLI DELLA

FONDAZIONE ITALIANA LINFOMI

FONDAZIONE ITALIANA LINFOMI

rete oncologica
PIEMONTE | VALLE D'AOSTA
si prende cura di te



Torino
16 dicembre
2019

NOVITA' MOLECOLARI NEI LINFOMI MARGINALI

Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

DIVISIONE DI EMATOLOGIA
LABORATORIO DI BIOLOGIA MOLECOLARE
Prof. Mario Boccadoro

Simone Ferrero, MD

UNIVERSITA DEGLI STUDI DI TORINO

haematologica | 2010; 95(4)

Splenic marginal zone lymphoma: a hydra with many heads?

Luca Arcaini,[1] Marco Paulli[2]

[1]Division of Hematology, Department of Oncohematology and [2]Department of Pathology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Italy. E-mail: luca.arcaini@unipv.it *doi:10.3324/haematol.2009.021576*

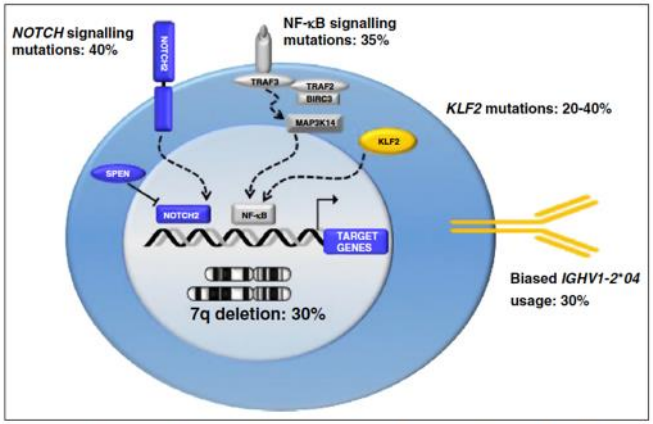
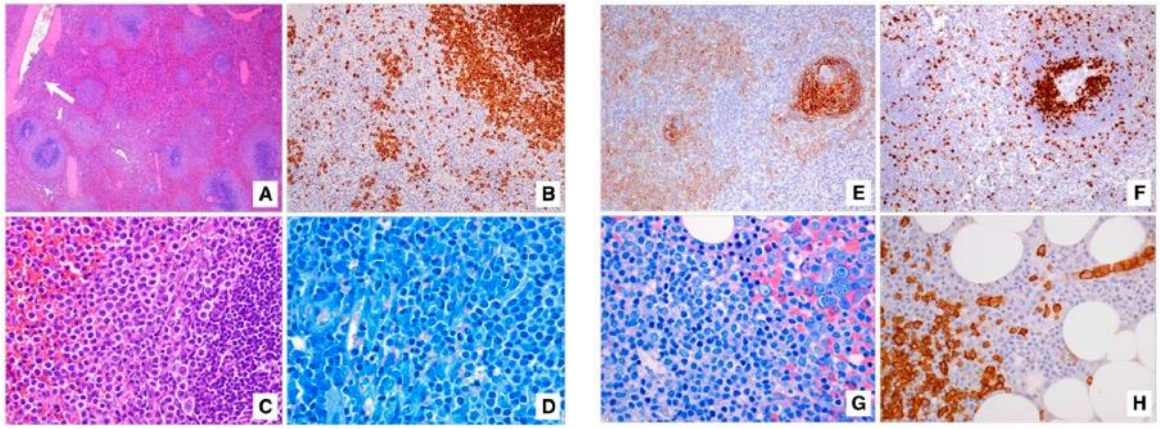


Figure 2. Key molecular alterations in SMZL. Schematic representation of genes and pathways that are molecularly deregulated in SMZL. The prevalence of molecular alterations in SMZL is shown as a percentage beside each gene or pathway.



BLOOD, 28 APRIL 2016 • VOLUME 127, NUMBER 17

INDOLENT B-CELL LYMPHOMA

Splenic marginal zone lymphoma: from genetics to management

Luca Arcaini,[1,2] Davide Rossi,[3] and Marco Paulli[1,4]

[1]Department of Molecular Medicine, University of Pavia, Pavia, Italy; [2]Department of Hematology Oncology, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; [3]Division of Hematology, Oncology Institute of Southern Switzerland and Institute of Oncology Research, Bellinzona, Switzerland; and [4]Unit of Anatomic Pathology, Fondazione Istituto Di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy

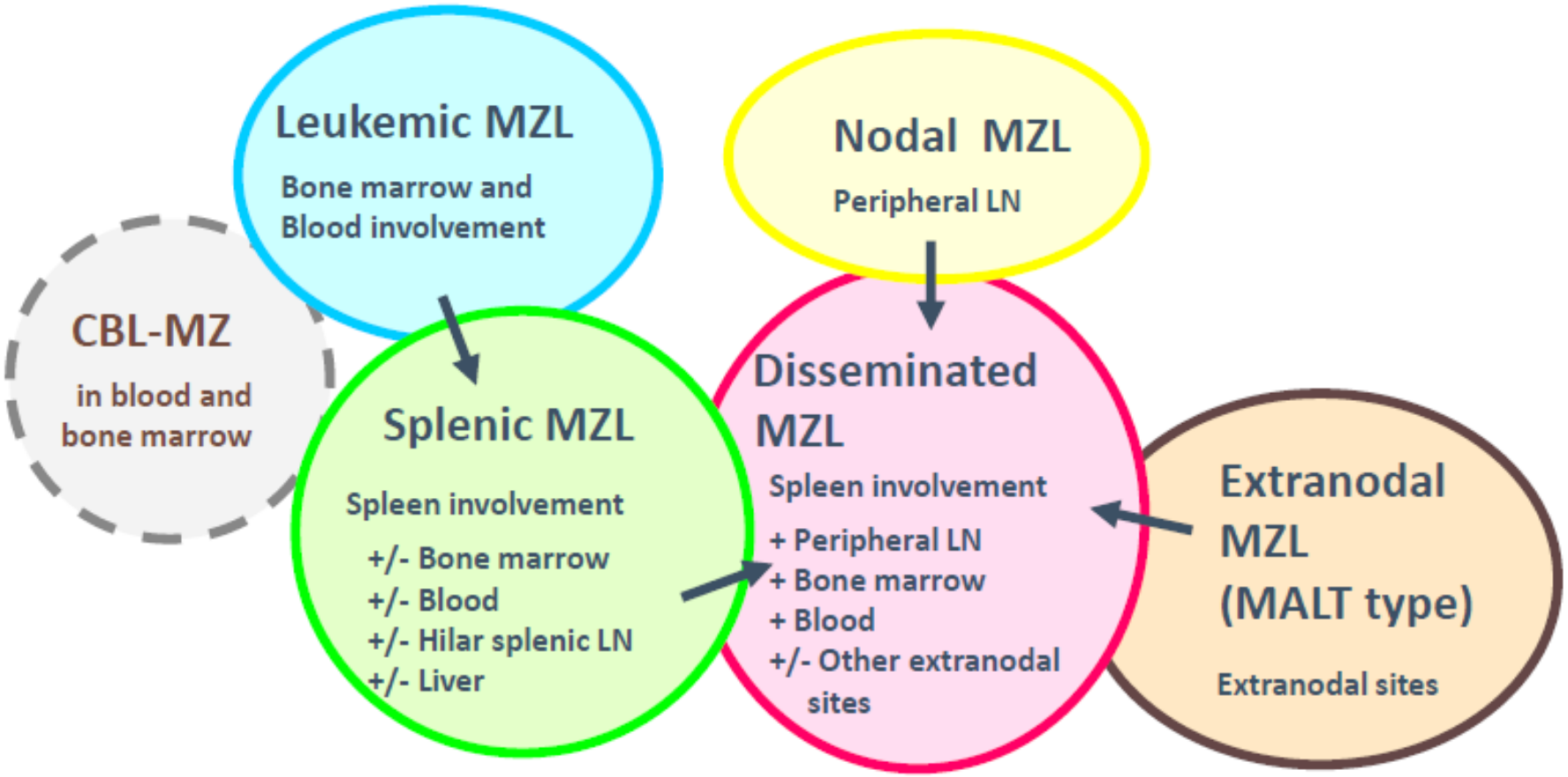
Marginal-Zone B-Cell lymphomas: WHO 17 subtypes

MZL WHO Subtypes	% of all lymphomas in SEER registries
Extranodal MZL of *Mucosa-Associated Lymphoid Tissue* (MALT-Lymphoma)	5%
Nodal MZL (NMZL)	2-3%
Splenic MZL (SMZL)	1-2%

Olszewski AJ and Castillo JJ. Cancer 2013

MZL: a group of related clinical entities

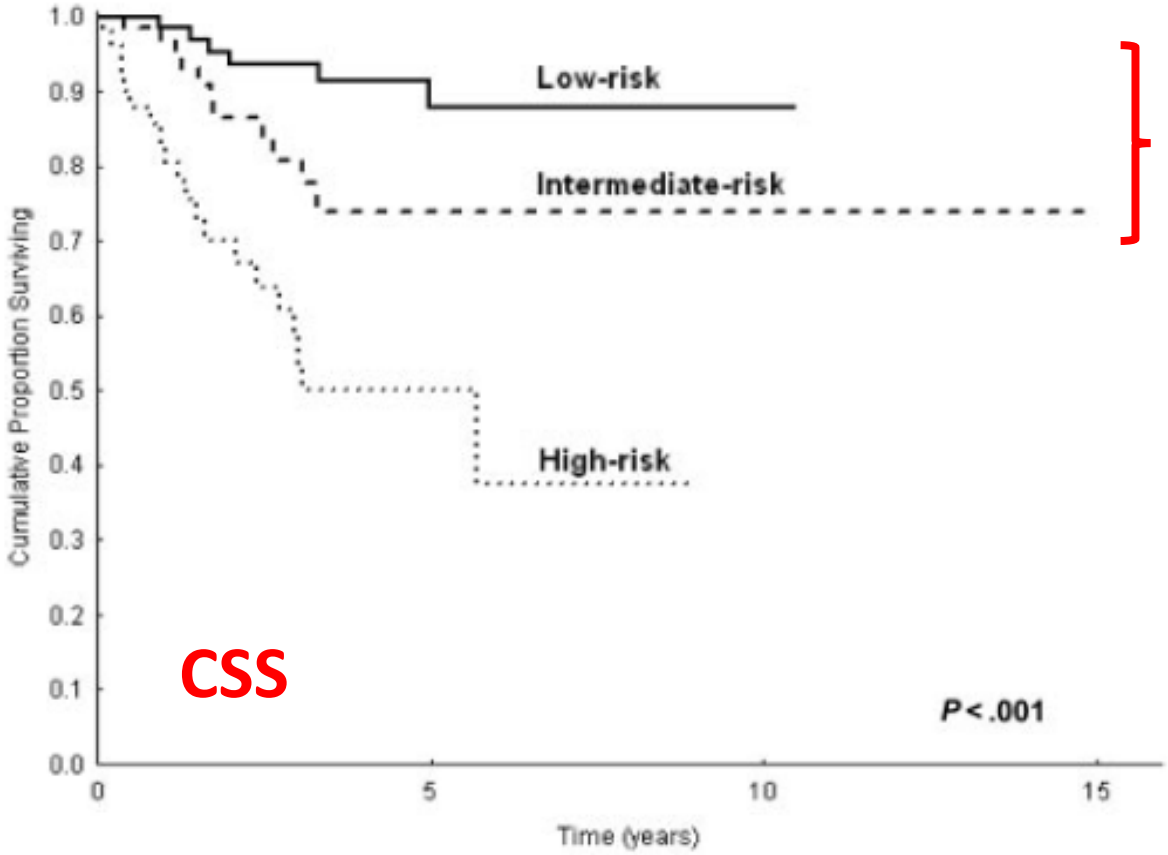
Differential diagnosis not always straightforward



SMZL prognostic score (IIL)

	OS		CSS	
	HR	*P*	HR	*P*
Hemoglobin level less than 12 g/dL	2.7	.005	2.5	.02
LDH level higher than normal	2.2	.008	3.0	<.001
Albumin level less than 3.5 g/dL	3.2	<.001	2.9	.005

SMZL score			5y-CSS
0	41%	Low	88%
1	34%	Int	73%
2-3	25%	High	50%



Generally indolent course with median survival 8-10ys

Arcaini et al, Blood 2006

SMZL prognostic score (IIL)

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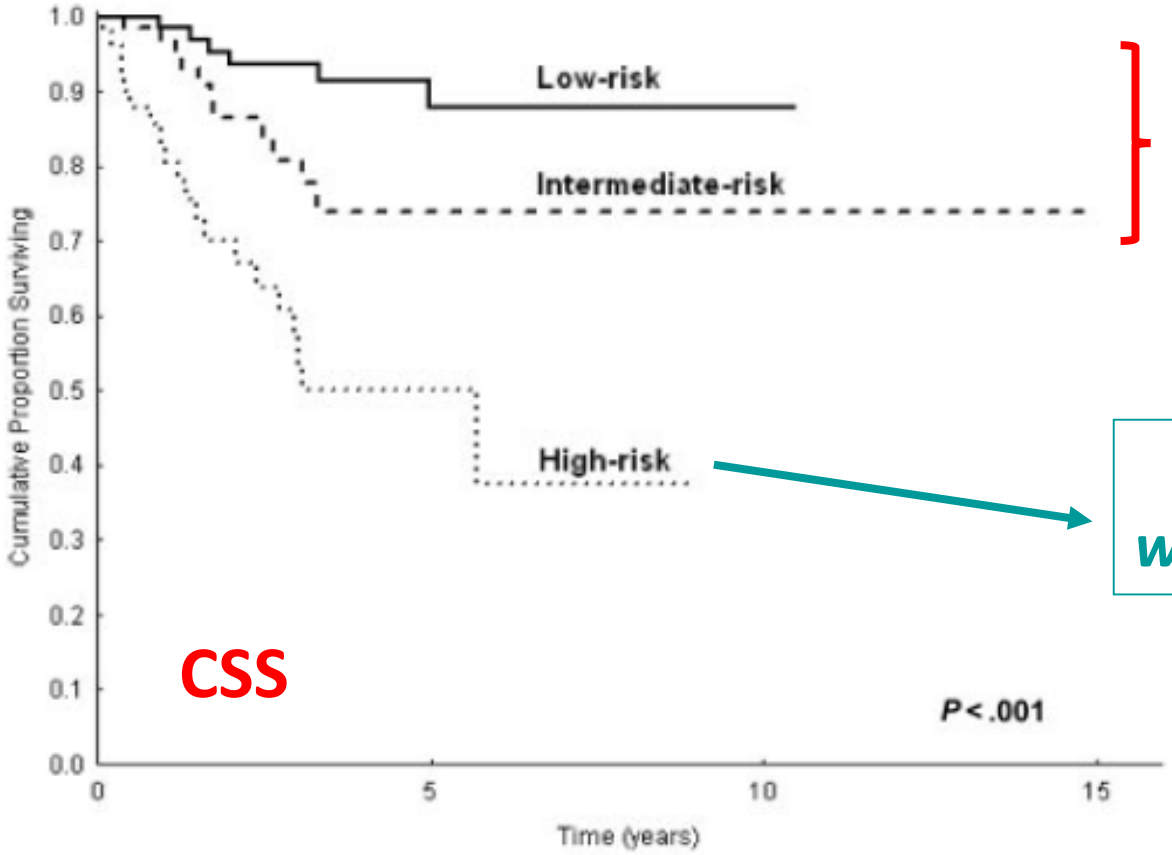


Generally indolent course with median survival 8-10ys

25-30% pts worse outcome

Arcaini et al, Blood 2006

REVIEW

Recent advances in understanding the biology of marginal zone lymphoma [version 1; peer review: 2 approved]

Francesco Bertoni[1,2*], Davide Rossi[1,2*], Emanuele Zucca[1,2]

[1]Università della Svizzera italiana, Institute of Oncology Research, Bellinzona, Switzerland
[2]Oncology Institute of Southern Switzerland (IOSI), Ospedale San Giovanni, Bellinzona, Switzerland

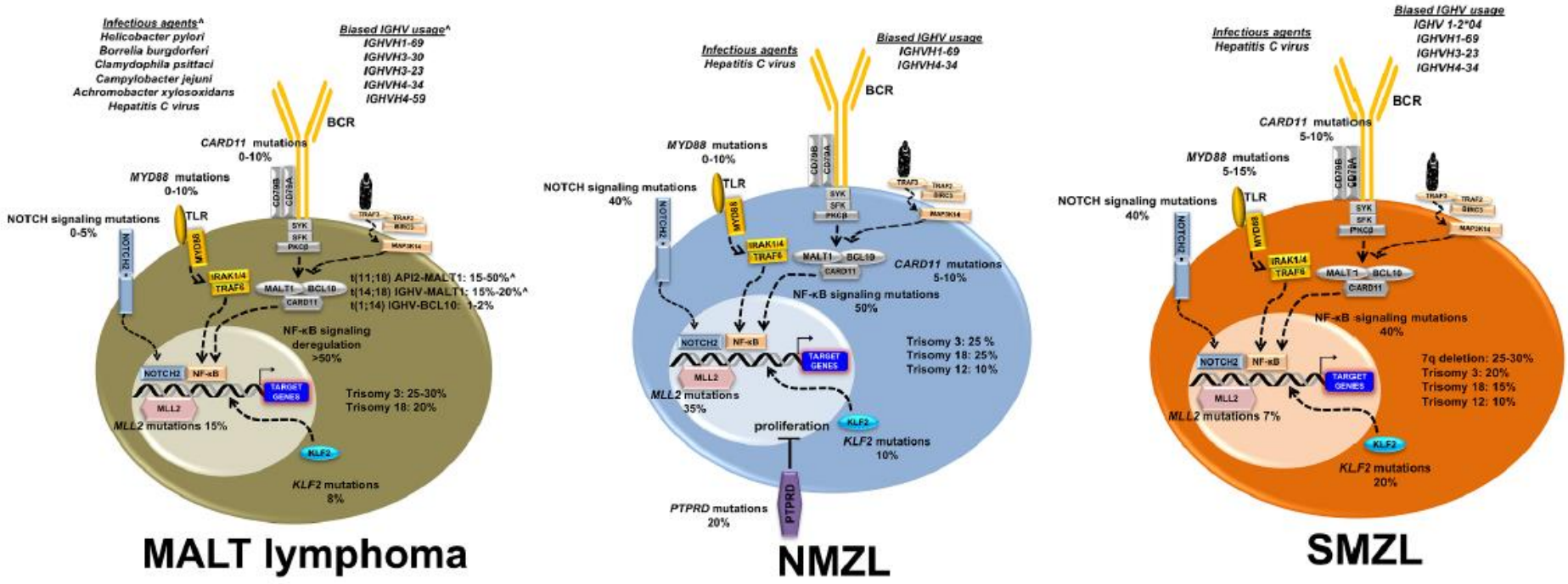


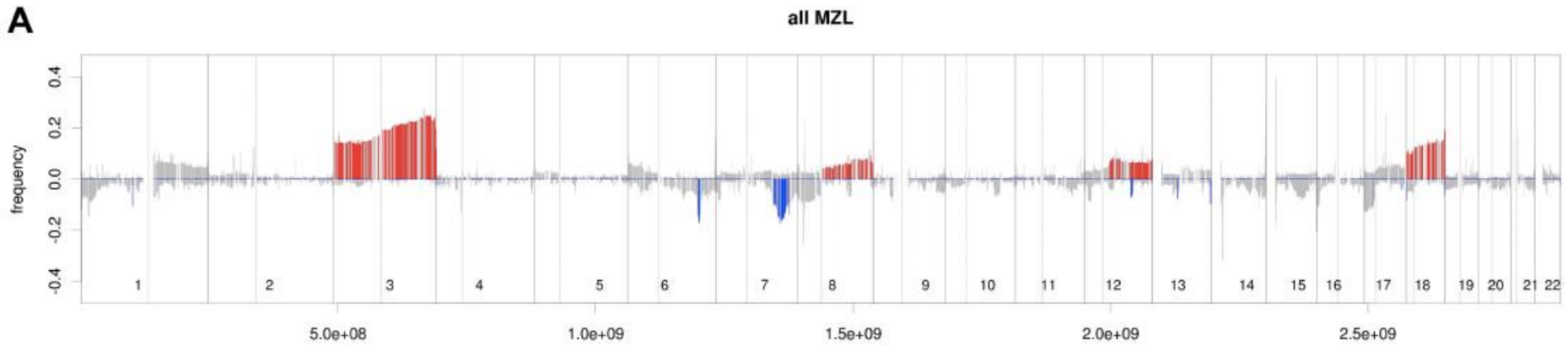
Figure 1. Summary of the main genetic and biologic features characterizing marginal zone lymphomas. ^Depending on the anatomical site. BCR, B-cell receptor; IGHV, immunoglobulin heavy variable; MALT, mucosa-associated lymphoid tissue; NF-κB, nuclear factor kappa B; NMZL, nodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma; TLR, Toll-like receptor.

blood
2011 117: 1595-1604
doi:10.1182/blood-2010-01-264275 originally published online November 29, 2010

Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome

Andrea Rinaldi, Michael Mian, Ekaterina Chigrinova, Luca Arcaini, Govind Bhagat, Urban Novak, Paola M. V. Rancoita, Cassio P. De Campos, Francesco Forconi, Randy D. Gascoyne, Fabio Facchetti, Maurilio Ponzoni, Silvia Govi, Andrés J. M. Ferreri, Manuela Mollejo, Miguel A. Piris, Luca Baldini, Jean Soulier, Catherine Thieblemont, Vincenzo Canzonieri, Valter Gattei, Roberto Marasca, Silvia Franceschetti, Gianluca Gaidano, Alessandra Tucci, Silvia Uccella, Maria Grazia Tibiletti, Stephan Dirnhofer, Claudio Tripodo, Claudio Doglioni, Riccardo Dalla Favera, Franco Cavalli, Emanuele Zucca, Ivo Kwee and Francesco Bertoni

Comprehensive analysis of genomic DNA copy number changes in a large series of **218 MZL patients** (25 nodal, 57 MALT, 134 SMZL and 2 NOS)



blood

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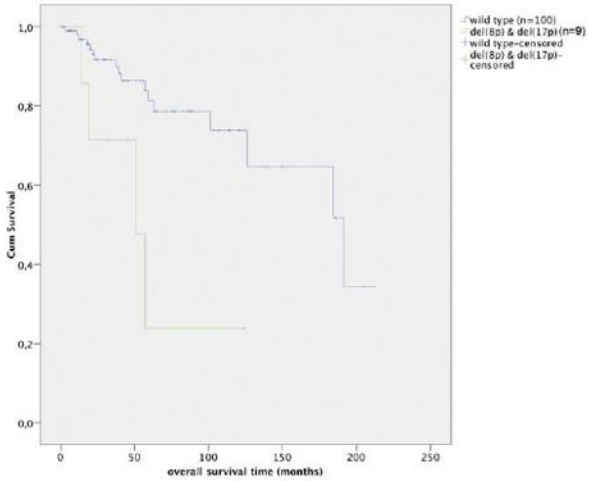
del(8p) and del(17p)



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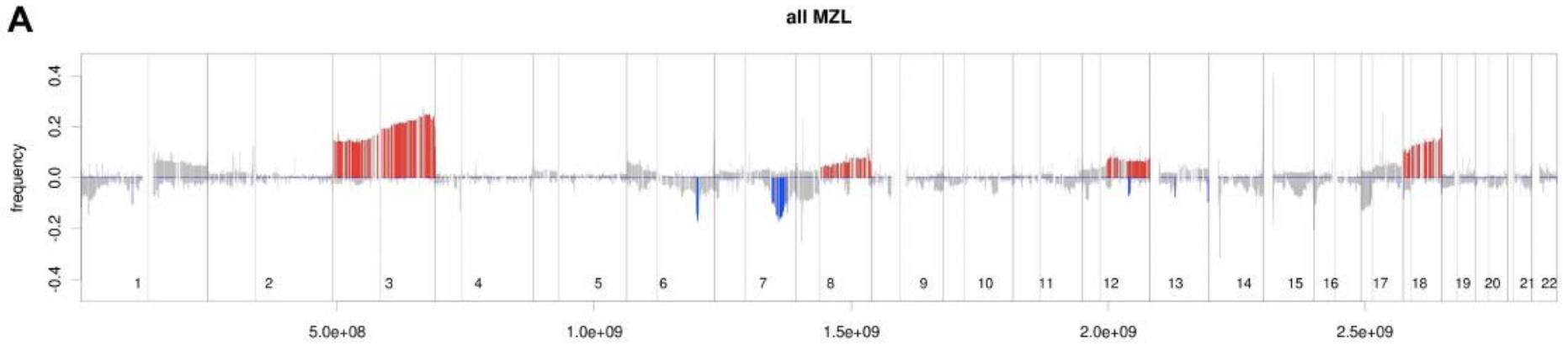
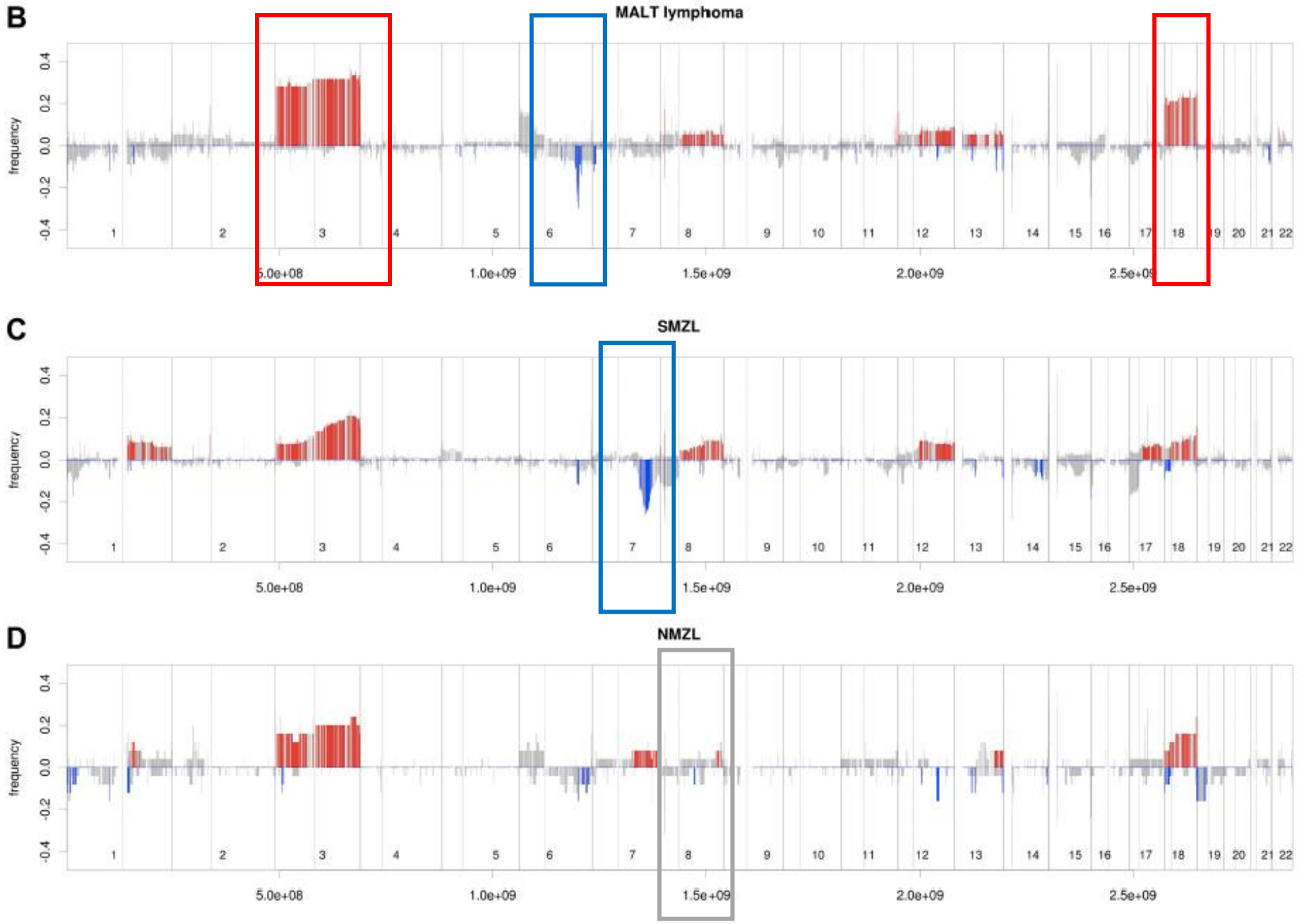
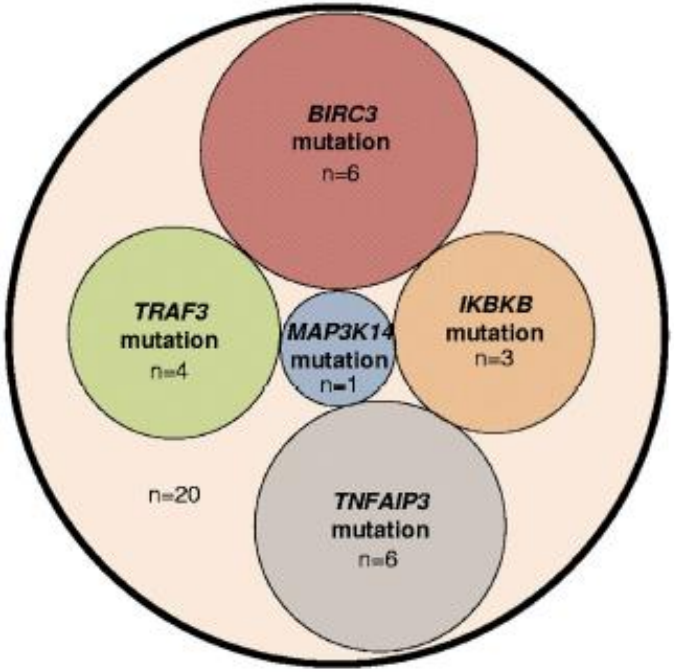


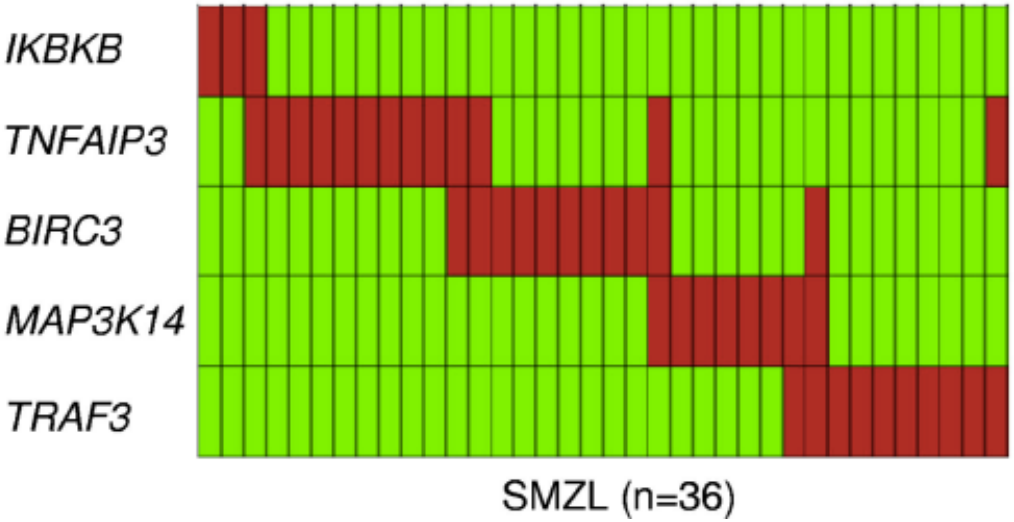

B
MALT lymphoma
frequency
0.4
0.2
0.0
-0.2
-0.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
5.0e+08
1.0e+09
1.5e+09
2.0e+09
2.5e+09
C
SMZL
frequency
0.4
0.2
0.0
-0.2
-0.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
5.0e+08
1.0e+09
1.5e+09
2.0e+09
2.5e+09
D
NMZL
frequency
0.4
0.2
0.0
-0.2
-0.4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
5.0e+08
1.0e+09
1.5e+09
2.0e+09
2.5e+09

blood
2011 118: 4930-4934
doi:10.1182/blood-2011-06-359166 originally published online August 31, 2011

Alteration of *BIRC3* and multiple other NF-κB pathway genes in splenic marginal zone lymphoma

Davide Rossi, Silvia Deaglio, David Dominguez-Sola, Silvia Rasi, Tiziana Vaisitti, Claudio Agostinelli, Valeria Spina, Alessio Bruscaggin, Sara Monti, Michaela Cerri, Stefania Cresta, Marco Fangazio, Luca Arcaini, Marco Lucioni, Roberto Marasca, Catherine Thieblemont, Daniela Capello, Fabio Facchetti, Ivo Kwee, Stefano A. Pileri, Robin Foà, Francesco Bertoni, Riccardo Dalla-Favera, Laura Pasqualucci and Gianluca Gaidano





NF-kB pathway mutations in SMZL

The coding genome of splenic marginal zone lymphoma: activation of *NOTCH2* and other pathways regulating marginal zone development

Davide Rossi,[1] Vladimir Trifonov,[2] Marco Fangazio,[1,3] Alessio Bruscaggin,[1] Silvia Rasi,[1] Valeria Spina,[1] Sara Monti,[1] Tiziana Vaisitti,[4] Francesca Arruga,[4] Rosella Famà,[1] Carmela Ciardullo,[1] Mariangela Greco,[1] Stefania Cresta,[1] Daniela Piranda,[1] Antony Holmes,[3] Giulia Fabbri,[3] Monica Messina,[3] Andrea Rinaldi,[5] Jiguang Wang,[2] Claudio Agostinelli,[6] Pier Paolo Piccaluga,[6] Marco Lucioni,[7] Fabrizio Tabbò,[8] Roberto Serra,[9] Silvia Franceschetti,[1] Clara Deambrogi,[1] Giulia Daniele,[10] Valter Gattei,[11] Roberto Marasca,[12] Fabio Facchetti,[13] Luca Arcaini,[14] Giorgio Inghirami,[8] Francesco Bertoni,[5] Stefano A. Pileri,[6] Silvia Deaglio,[4] Robin Foà,[15] Riccardo Dalla-Favera,[3,16,17] Laura Pasqualucci,[3,16,18] Raul Rabadan,[2] and Gianluca Gaidano[1]

The Rockefeller University Press $30.00
J. Exp. Med. 2012 Vol. 209 No. 9 1537-1551
www.jem.org/cgi/doi/10.1084/jem.20120904

The Journal of Experimental Medicine

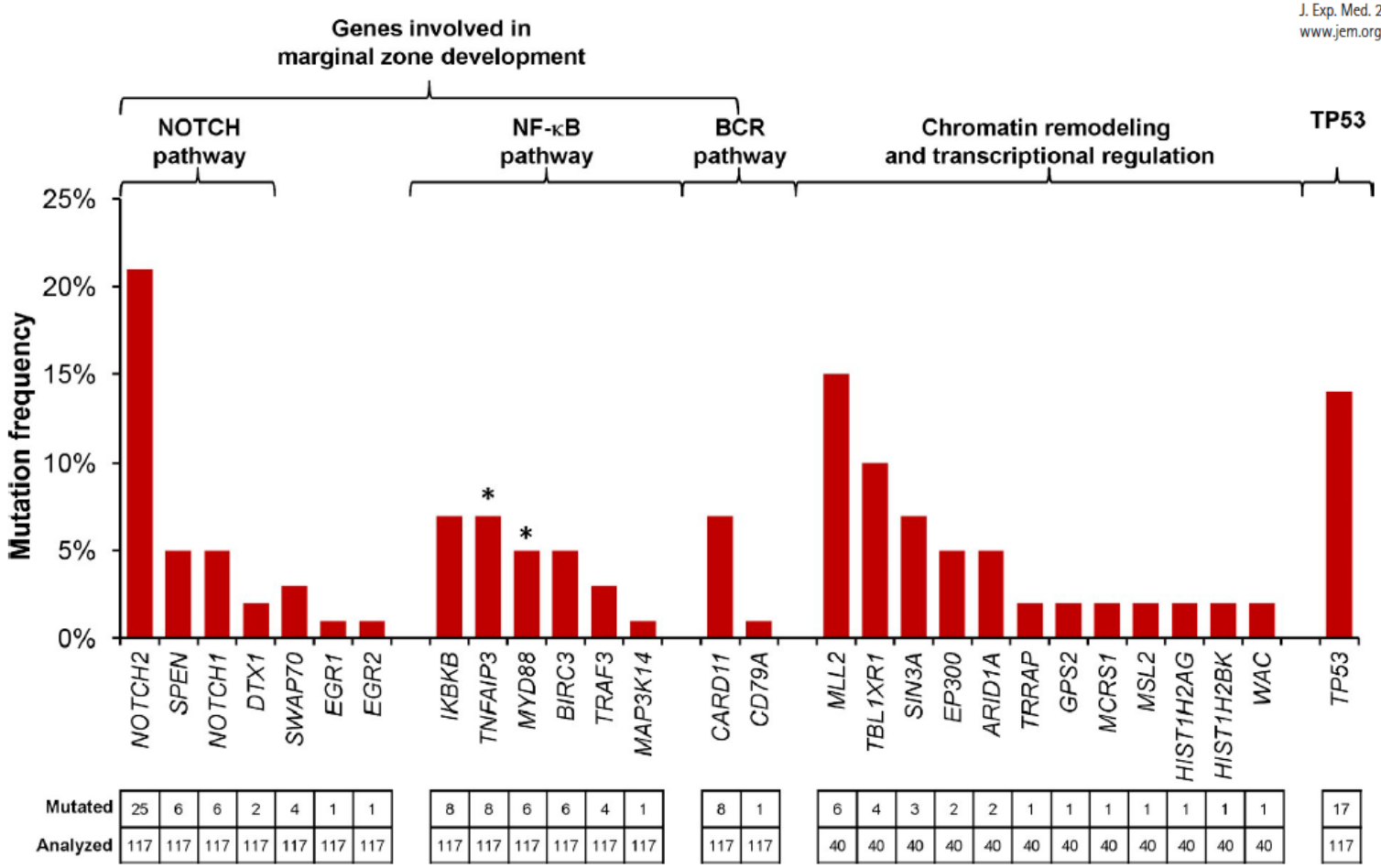


Figure 2. Recurrently targeted pathways in SMZL. Percentage of SMZL cases harboring mutations in selected genes belonging to cellular pathways that are recurrently altered in SMZL. Numbers at the bottom indicate the actual number of mutated cases over the total samples analyzed. Asterisks denote genes that are also implicated in Toll-like receptor responses. BCR, B cell receptor.

The Journal of Experimental Medicine

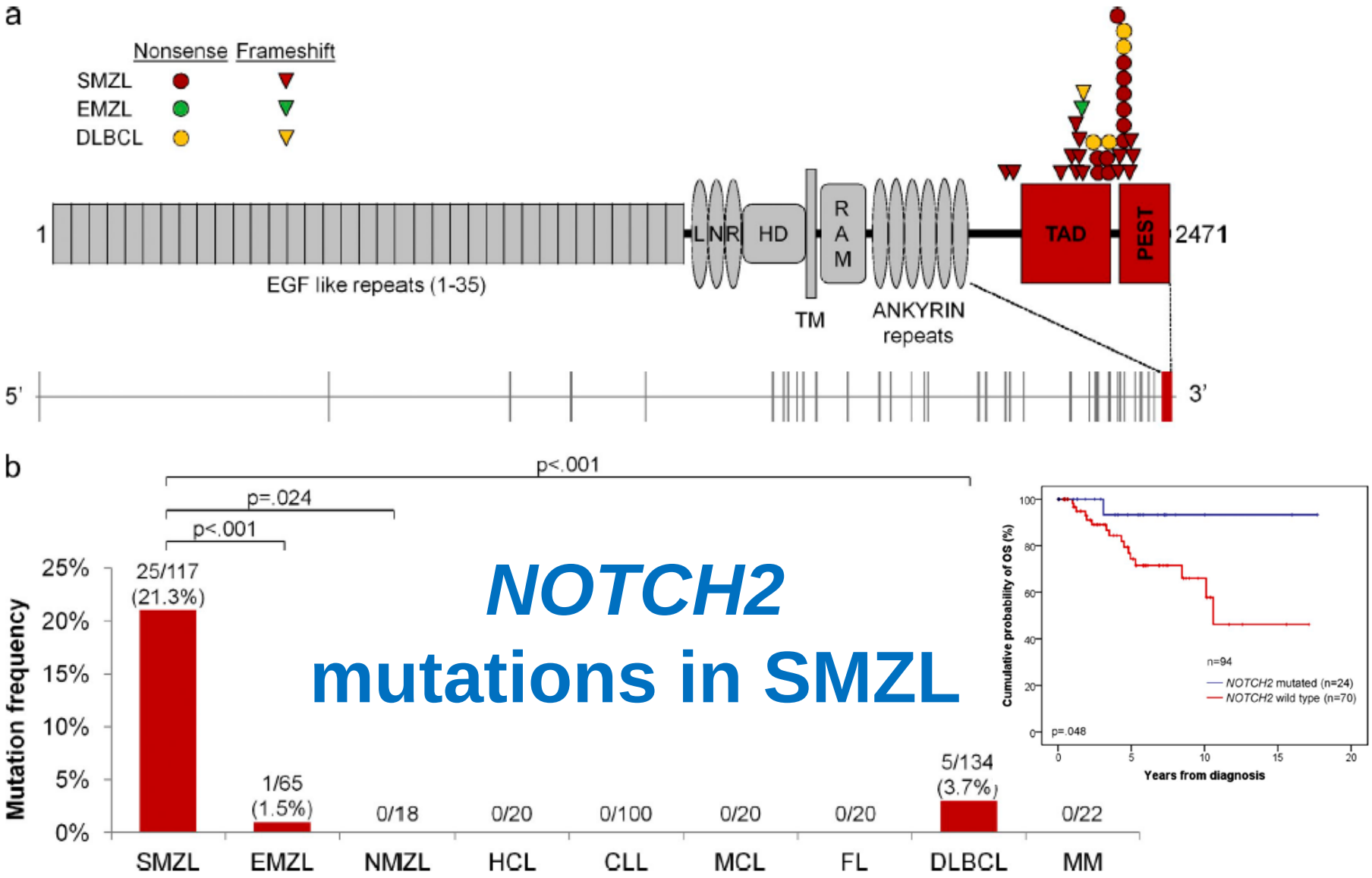


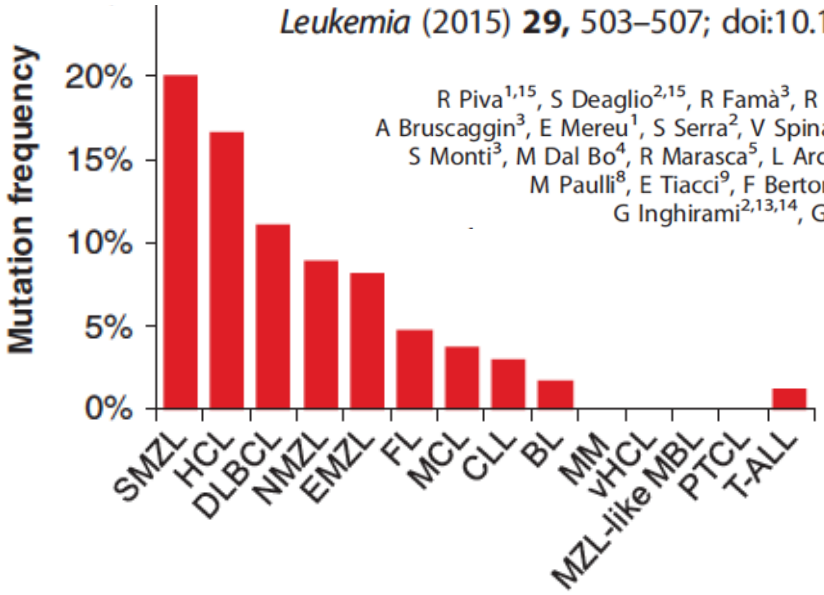
Figure 3. ***NOTCH2* is frequently mutated in SMZL.** (a) Schematic representation of the human NOTCH2 gene (bottom) and protein (top), with its key functional domains (EGF, epithelial growth factor; LNR, LIN-12/NOTCH repeats; HD, heterodimerization; TM, transmembrane; RAM, regulation of amino acid metabolism; TAD, transactivation domain). Color-coded symbols indicate the type and position of the mutations. (b) Prevalence of *NOTCH2* mutations among mature B cell tumors (EMZL, extranodal MZ lymphoma; NMZL, nodal MZ lymphoma; HCL, hairy cell leukemia; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma). Numbers on the top indicate the actual number of mutated cases over the total samples analyzed.

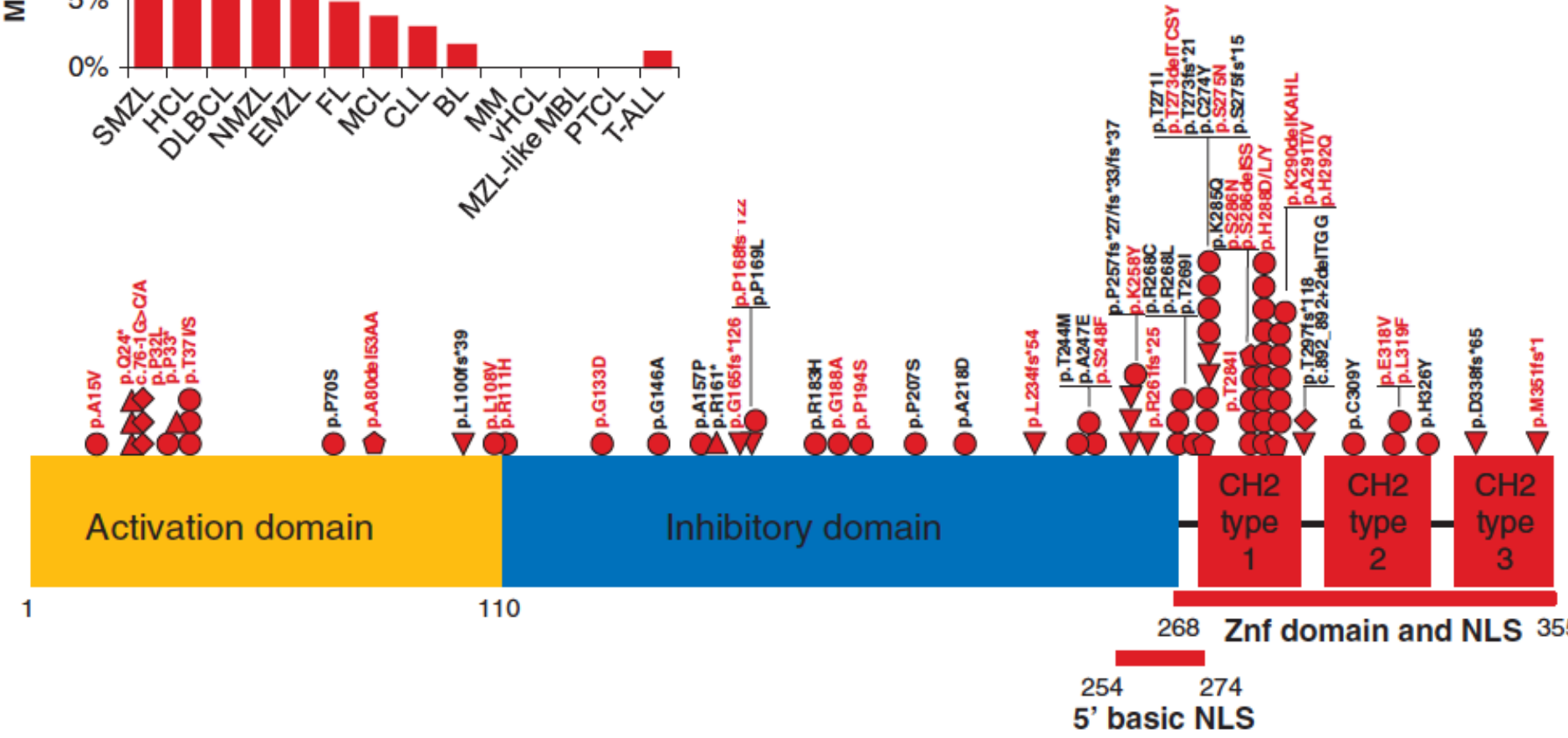
The Krüppel-like factor 2 transcription factor gene is recurrently mutated in splenic marginal zone lymphoma

Leukemia (2015) **29,** 503–507; doi:10.1038/leu.2014.294

R Piva[1,15], S Deaglio[2,15], R Famà[3], R Buonincontri[2], I Scarfò[1], A Bruscaggin[3], E Mereu[1], S Serra[2], V Spina[3], D Brusa[2], G Garaffo[1], S Monti[3], M Dal Bo[4], R Marasca[5], L Arcaini[6], A Neri[7], V Gattei[4], M Paulli[8], E Tiacci[9], F Bertoni[10], SA Pileri[11], R Foà[12], G Inghirami[2,13,14], G Gaidano[3] and D Rossi[3]

KLF2 mutations in SMZL

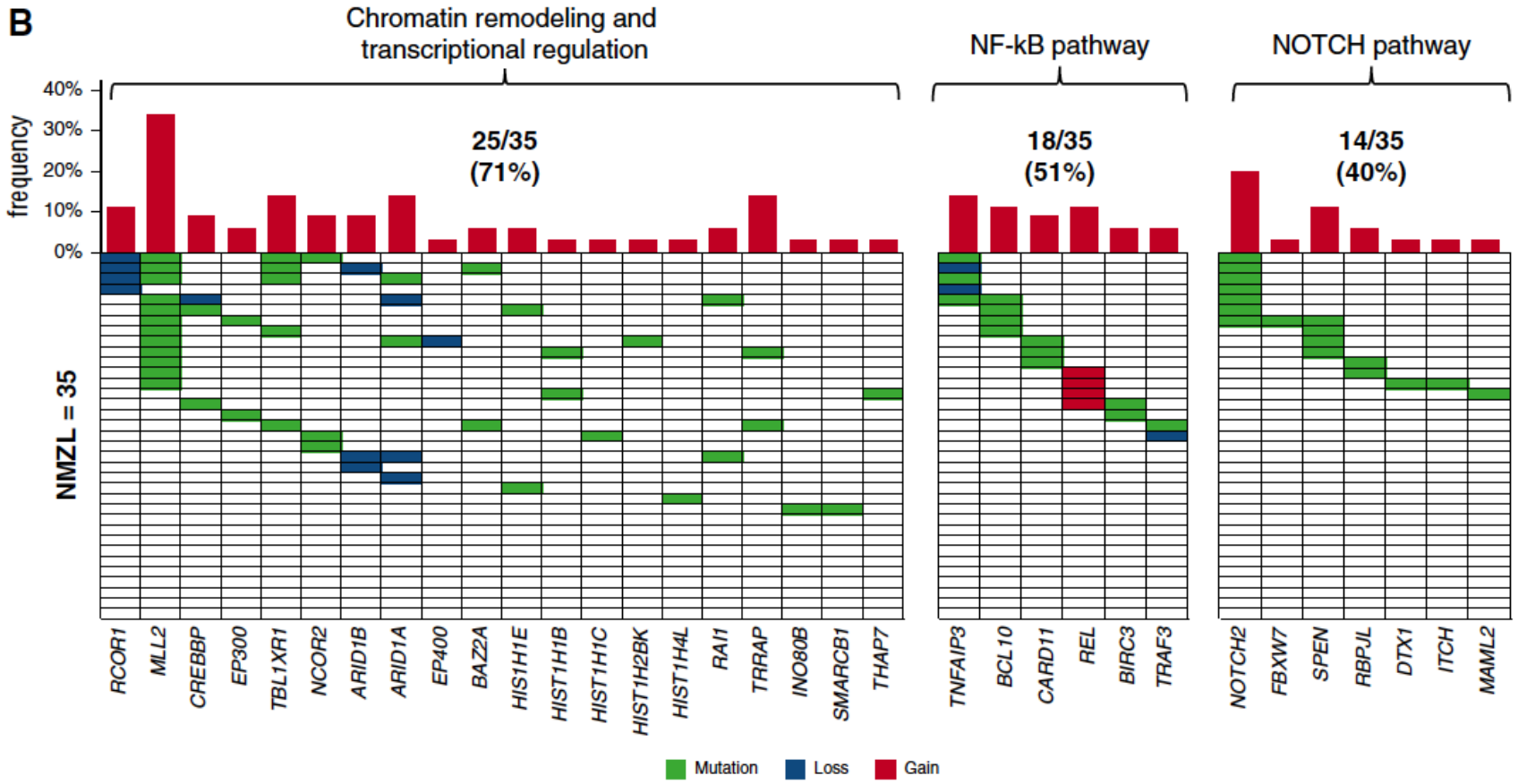




blood®
2016 128: 1362-1373
doi:10.1182/blood-2016-02-696757 originally published online June 22, 2016

The genetics of nodal marginal zone lymphoma

Valeria Spina, Hossein Khiabanian, Monica Messina, Sara Monti, Luciano Cascione, Alessio Bruscaggin, Elisa Spaccarotella, Antony B. Holmes, Luca Arcaini, Marco Lucioni, Fabrizio Tabbò, Sakellarios Zairis, Fary Diop, Michaela Cerri, Sabina Chiaretti, Roberto Marasca, Maurilio Ponzoni, Silvia Deaglio, Antonio Ramponi, Enrico Tiacci, Laura Pasqualucci, Marco Paulli, Brunangelo Falini, Giorgio Inghirami, Francesco Bertoni, Robin Foà, Raul Rabadan, Gianluca Gaidano and Davide Rossi

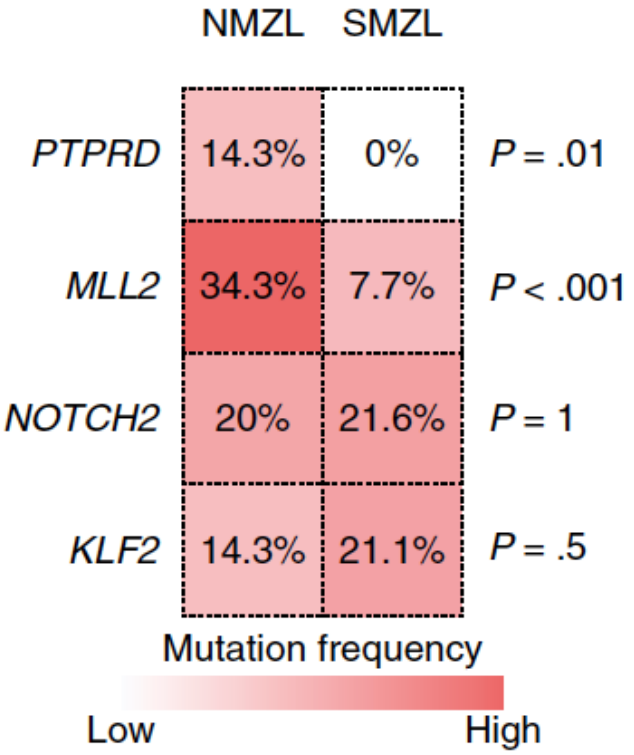


PTPRD mutations in NMZL

Key Points

- *PTPRD* lesions are among the most recurrent alterations in NMZL and appear to be enriched in this lymphoma type across mature B-cell tumors.
- NMZL and SMZL genetics overlap with the exceptions of *PTPRD* lesions, supporting their distinction as independent entities.

A



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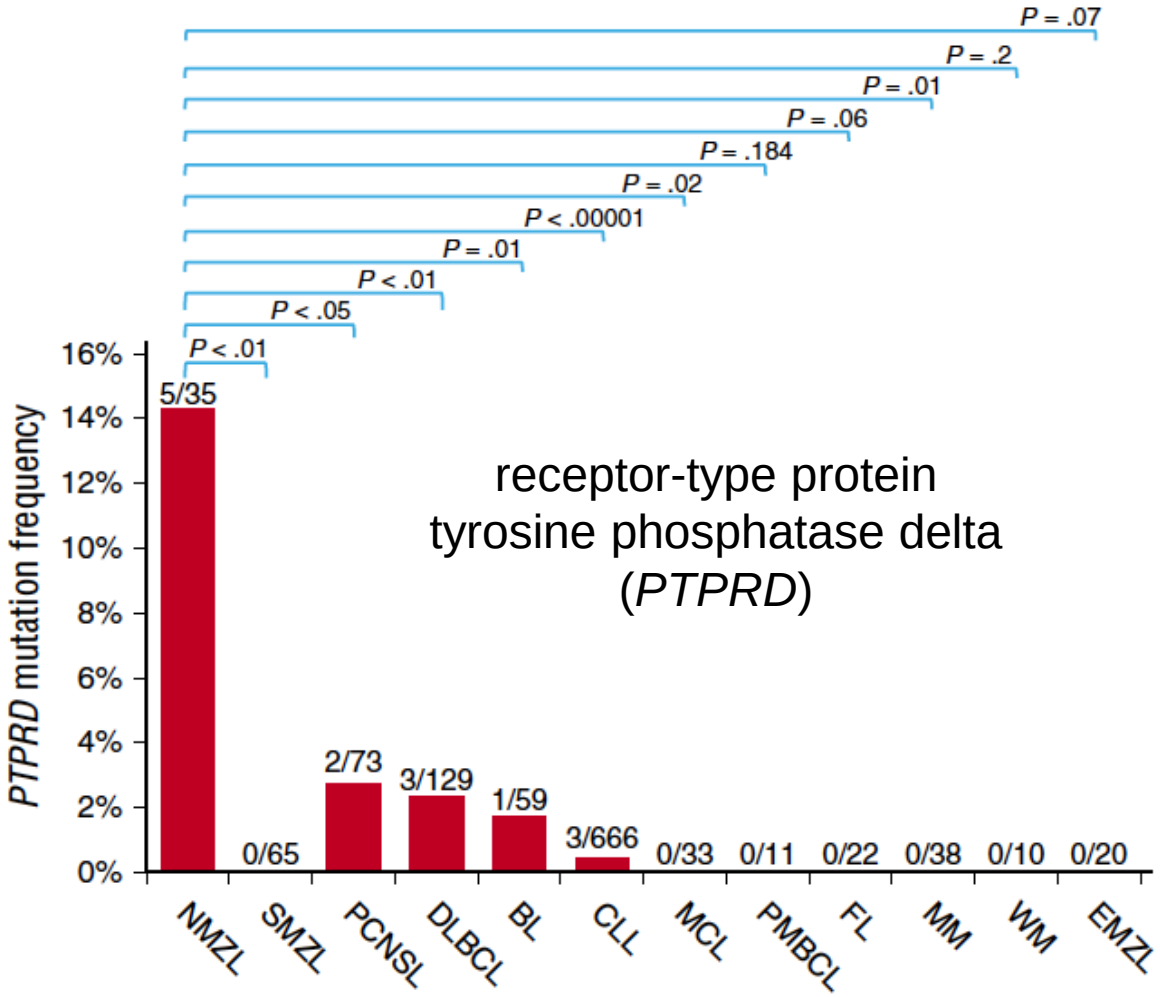

receptor-type protein tyrosine phosphatase delta (*PTPRD*)

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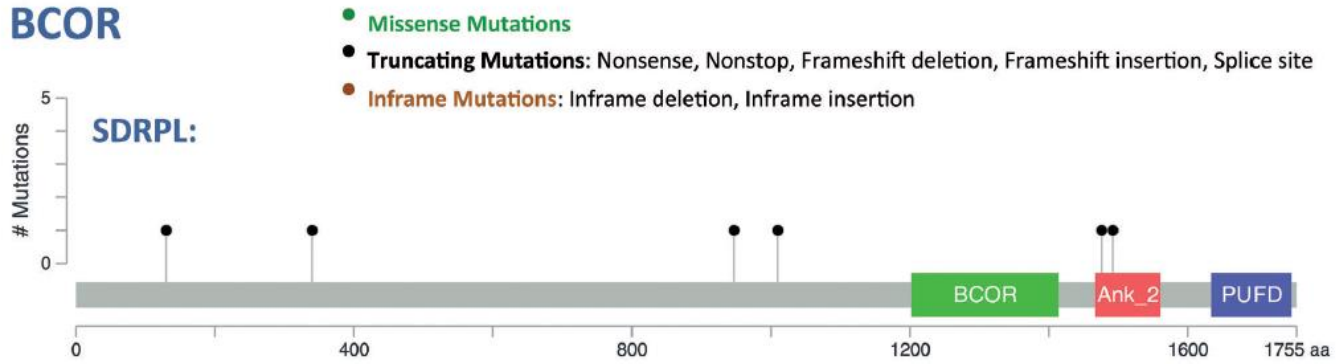
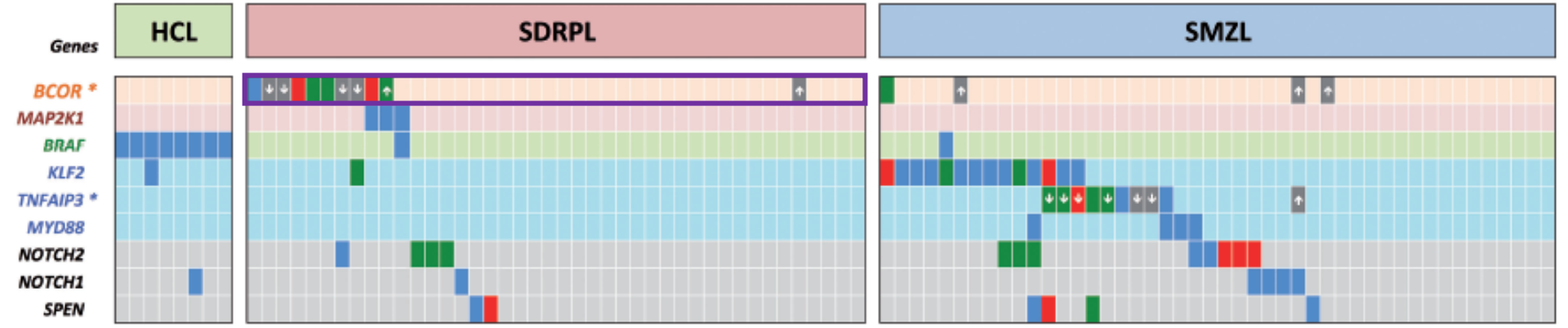
BCL6 corepressor (*BCOR*) in SDRPL

Exome sequencing identifies recurrent *BCOR* alterations and the absence of *KLF2*, *TNFAIP3* and *MYD88* mutations in splenic diffuse red pulp small B-cell lymphoma

Laurent Jallades,[1,2] Lucile Baseggio,[1,2] Pierre Sujobert,[1,2,3] Sarah Huet,[1,2,3] Kaddour Chabane,[1,2] Evelyne Callet-Bauchu,[1,2,3] Aurélie Verney,[2,3] Sandrine Hayette,[1,2] Jean-Pierre Desvignes,[4,5] David Salgado,[4,5] Nicolas Levy,[4,5,6] Christophe Béroud,[4,5,6] Pascale Felman,[1,2] Françoise Berger,[2,3,7] Jean-Pierre Magaud,[1,2,3] Laurent Genestier,[2] Gilles Salles[2,3,8] and Alexandra Traverse-Glehen[2,3,7]

Haematologica 2017
Volume 102(10):1758-1766





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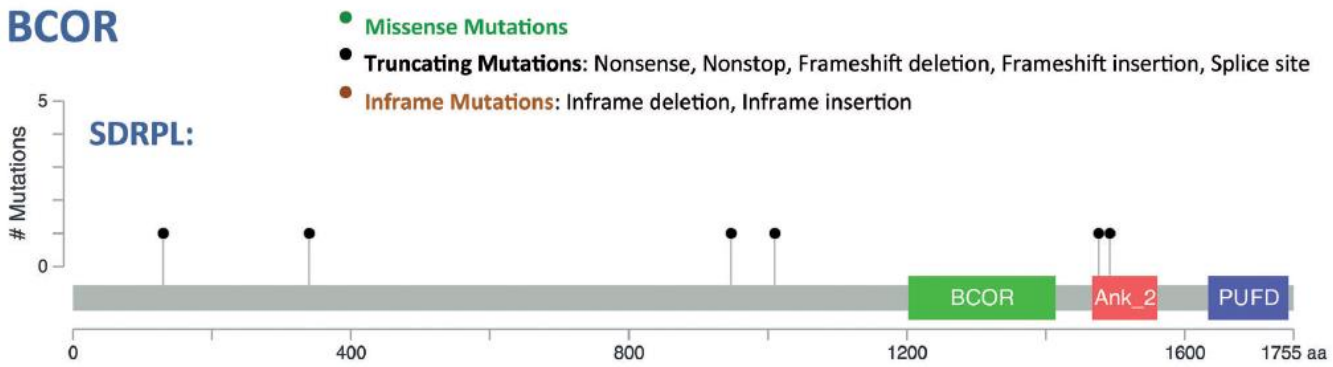
Haematologica 2017
Volume 102(10):1758-1766



Novel insights into the genetics and epigenetics of MALT lymphoma unveiled by next generation sequencing analyses

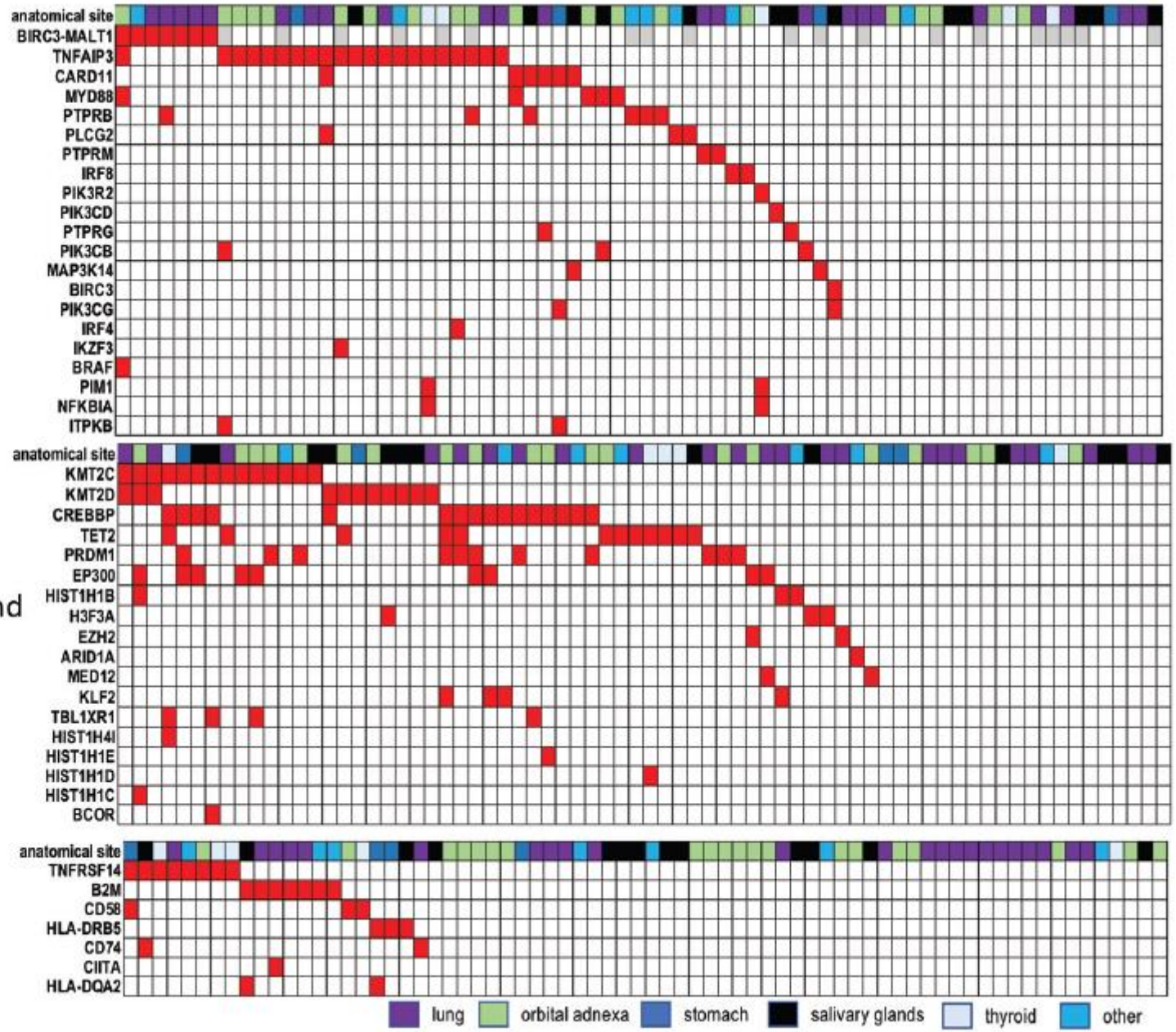
haematologica 2019; 104:e558

Luciano Cascione,[1,2] Andrea Rinaldi,[1] Alessio Bruscaggin,[1] Chiara Tarantelli,[1] Alberto J. Arribas,[1,2] Ivo Kwee,[1,3,5] Lorenza Pecciarini,[4] Afua A. Mensah,[1] Valeria Spina,[1] Elaine Y.L. Chung,[1] Lodovico Terzi di Bergamo,[1,2] Stephan Dirnhofer,[5] Alexandar Tzankov,[5] Roberto N. Miranda ,[6] Ken H. Young,[6] Alexandra Traverse-Glehen,[7] Gianluca Gaidano,[8] Steven H. Swerdlow,[9] Randy Gascoyne,[10] Raul Rabadan,[11] Maurilio Ponzoni,[4] Govind Bhagat,[12] Davide Rossi,[1,13] Emanuele Zucca[13] and Francesco Bertoni[1]

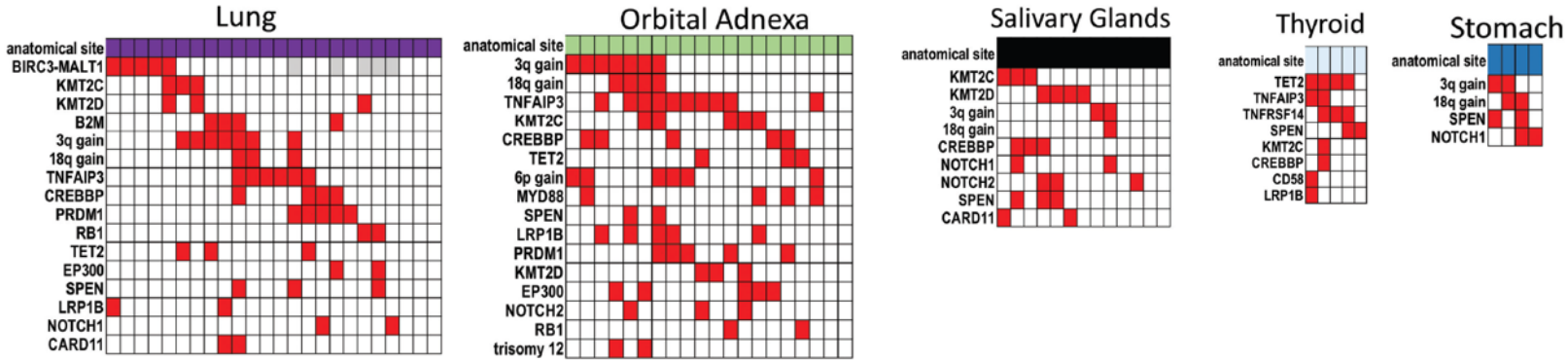
NFKB and BCR signaling

Chromatin remodeling and transcription regulation

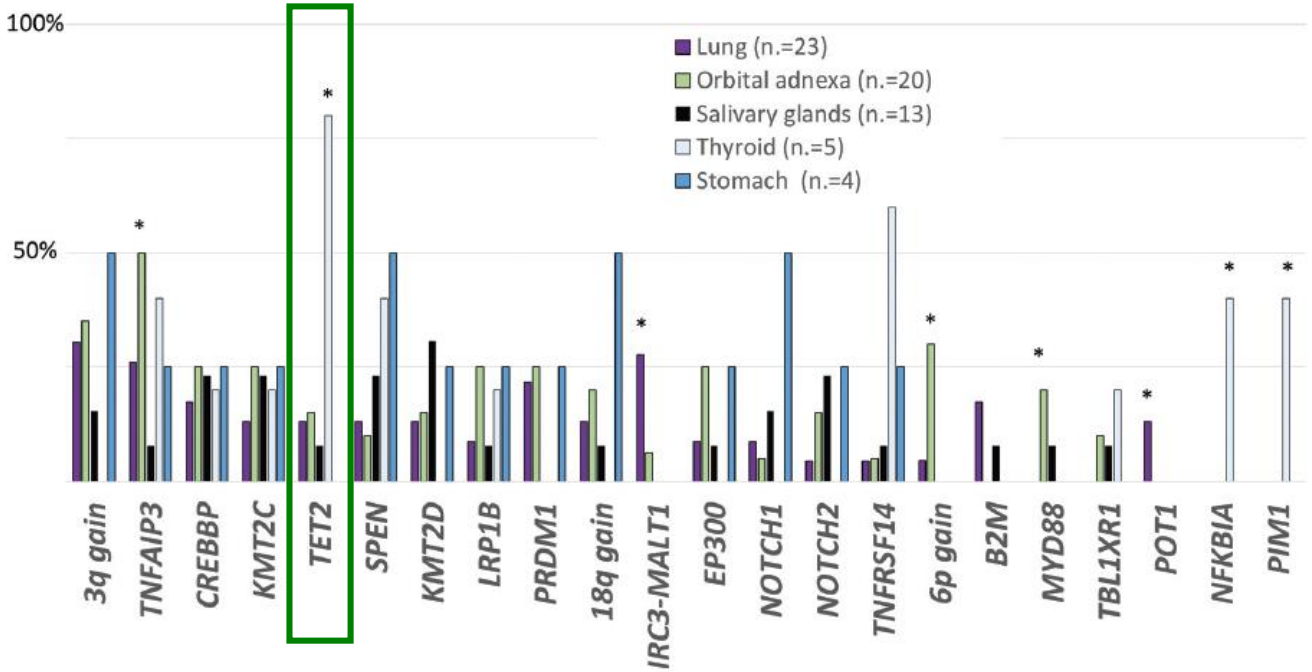
Immune surveillance



Lymphomas from different anatomic sites exhibit a different spectrum of genetic lesions



TET2 mutations in EMZL



haematologica 2019; 104:e558

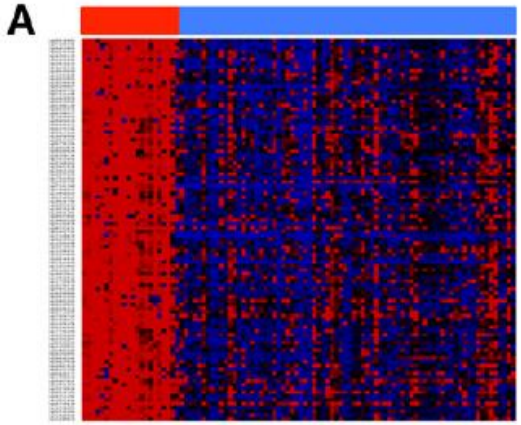
blood
2015 125: 1922-1931
doi:10.1182/blood-2014-08-596247 originally published online January 22, 2015

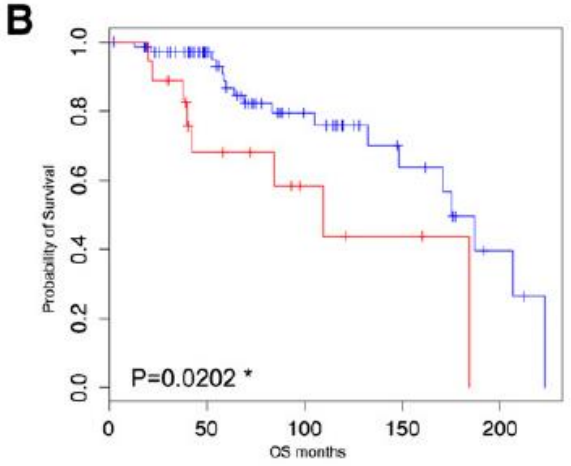
DNA methylation profiling identifies two splenic marginal zone lymphoma subgroups with different clinical and genetic features

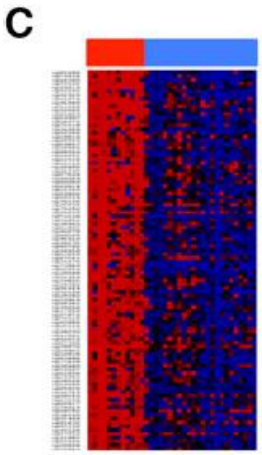
Alberto J. Arribas, Andrea Rinaldi, Afua A. Mensah, Ivo Kwee, Luciano Cascione, Eloy F. Robles, Jose A. Martinez-Climent, David Oscier, Luca Arcaini, Luca Baldini, Roberto Marasca, Catherine Thieblemont, Josette Briere, Francesco Forconi, Alberto Zamò, Massimiliano Bonifacio, Manuela Mollejo, Fabio Facchetti, Stephan Dirnhofer, Maurilio Ponzoni, Govind Bhagat, Miguel A. Piris, Gianluca Gaidano, Emanuele Zucca, Davide Rossi and Francesco Bertoni

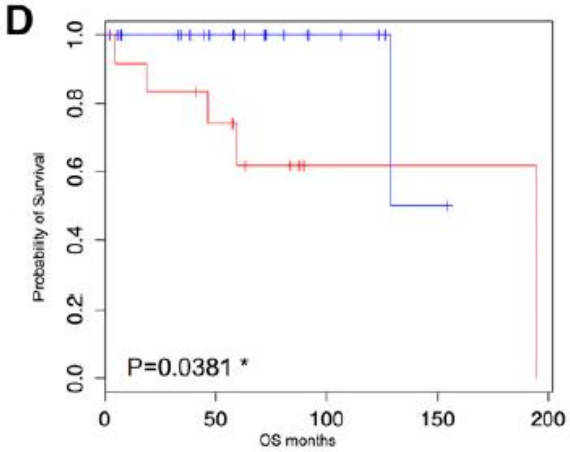
Key Points

- Methylation profiling identifies subgroups of SMZL with distinct biological features.
- Demethylating agents can reverse some of the adverse epigenetic alterations.

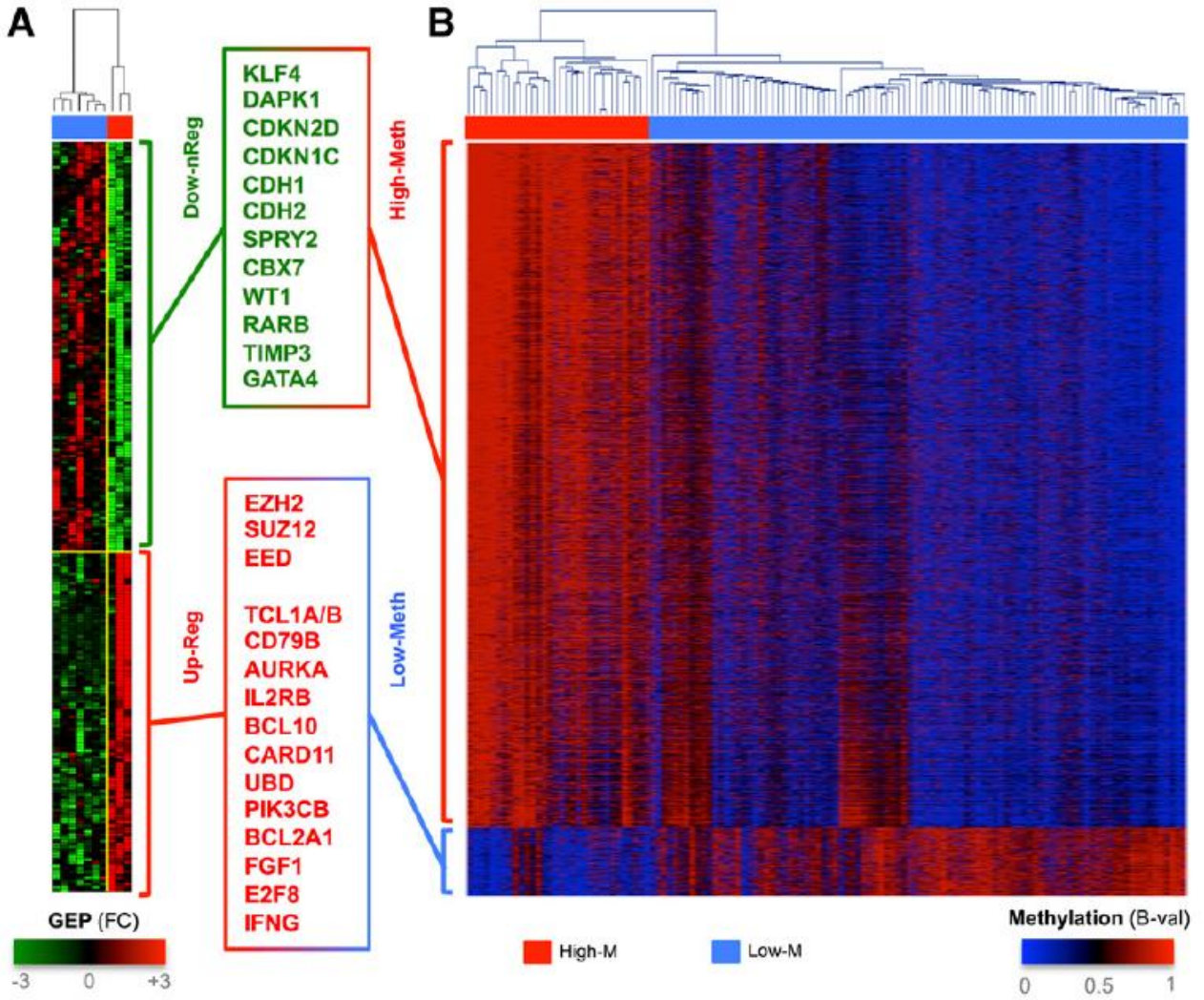








Distinct methylation profiles are linked to specific gene expression and risk features



The High-M phenotype is associated with:

IGHV1-02 usage, NOTCH2 mutations, 7q31-32 loss and histologic transformation

Many tumor-suppressor genes are methylated and repressed

Novel drugs in r/r MZL

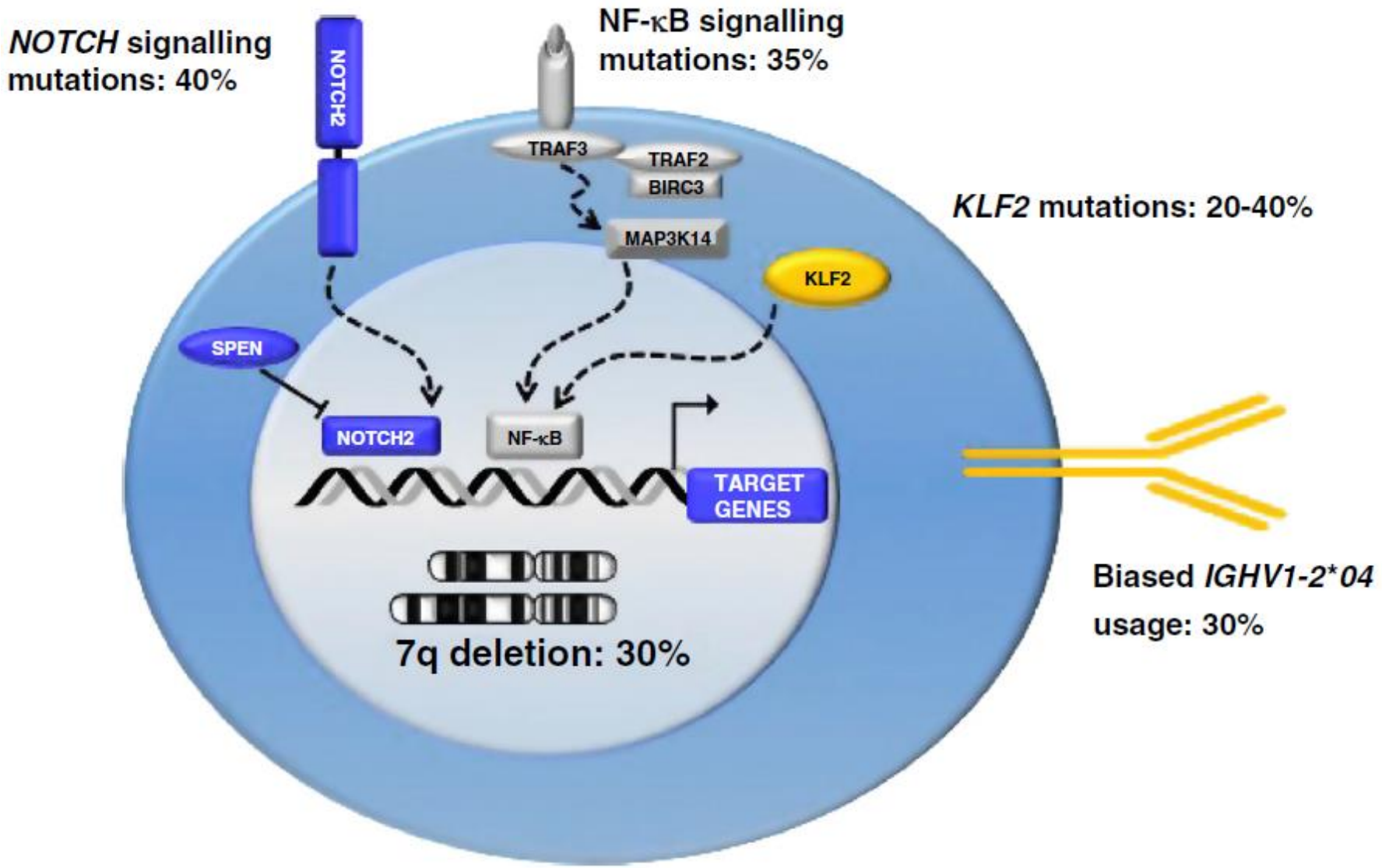
Signalling pathway	Target	Drug	N MZL pts	ORR %	DOR (mo)
Pi3K/AKT/mTOR	PI3K δ	Idelalisib	15	47	18
		Umbralisib	69	52	66% (12m)
	PI3K γ,δ	Duvelisib	18	39	>13
	PI3K α,δ	Copanlisib	23	78	NA
B-Cell receptor	BTK	Ibrutinib†	63	48	62% (18m)
		Zanubrutinib	9	78	NA
Apoptosis	BCL2	Venetoclax	3	66	2.3; 23.6
NF-κB	Cereblon	R-Lenalidomide	38	65	35.8

Demethylating agents?

†approved by FDA

Gopal et al, NEJM 2014; Zinzani et al ICML 2019; Jacobsen et al, SOHO 2019; Dreyling et al, ASH 2018; Noy et al, Blood 2017; TAM et al, ASH 2017; Davids et al, JCO 2017; Andorsky et al, ASCO 2019

SMZL: from genetics to management



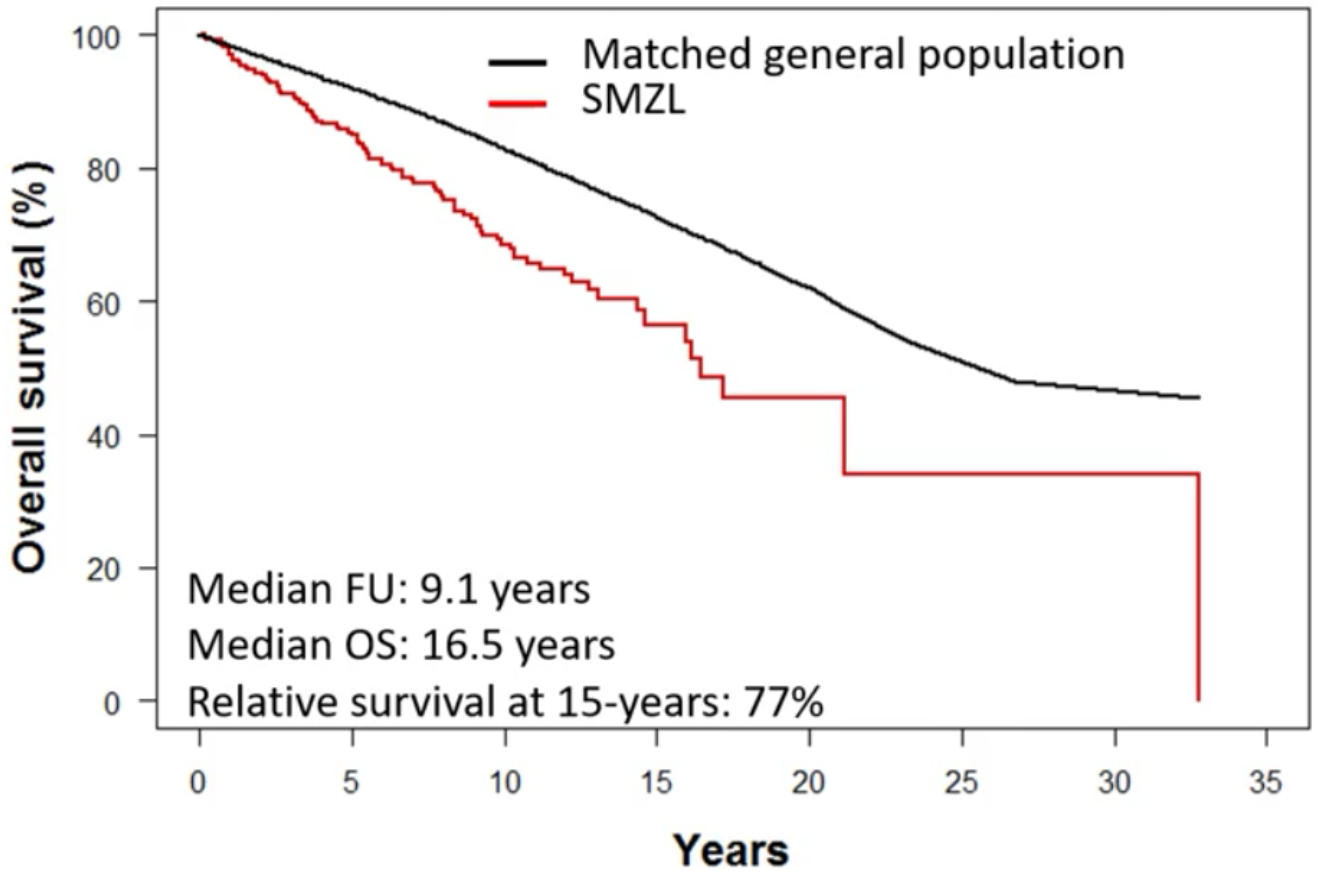
Arcaini L, Rossi D and Paulli M, Blood 2016

IELSG-46: molecular profiling in SMZL

- N=404 fresh spleen samples (splenectomy before 2010)
- SMZL diagnosis confirmed by pathologic revision
- Targeted deep NGS
  - mutations (CAPP-seq)
  - CNA
- Gene Expression Profiling (global and targeted mRNA seq)
- IGHV sequencing
- Clinical data (>8 years of follow-up)
- Machine-learning → molecular clusters

Bruscaggin A et al ICML 2019

IELSG-46: SMZL relative survival



- **SMZL: -23% survival with respect to matched general population**

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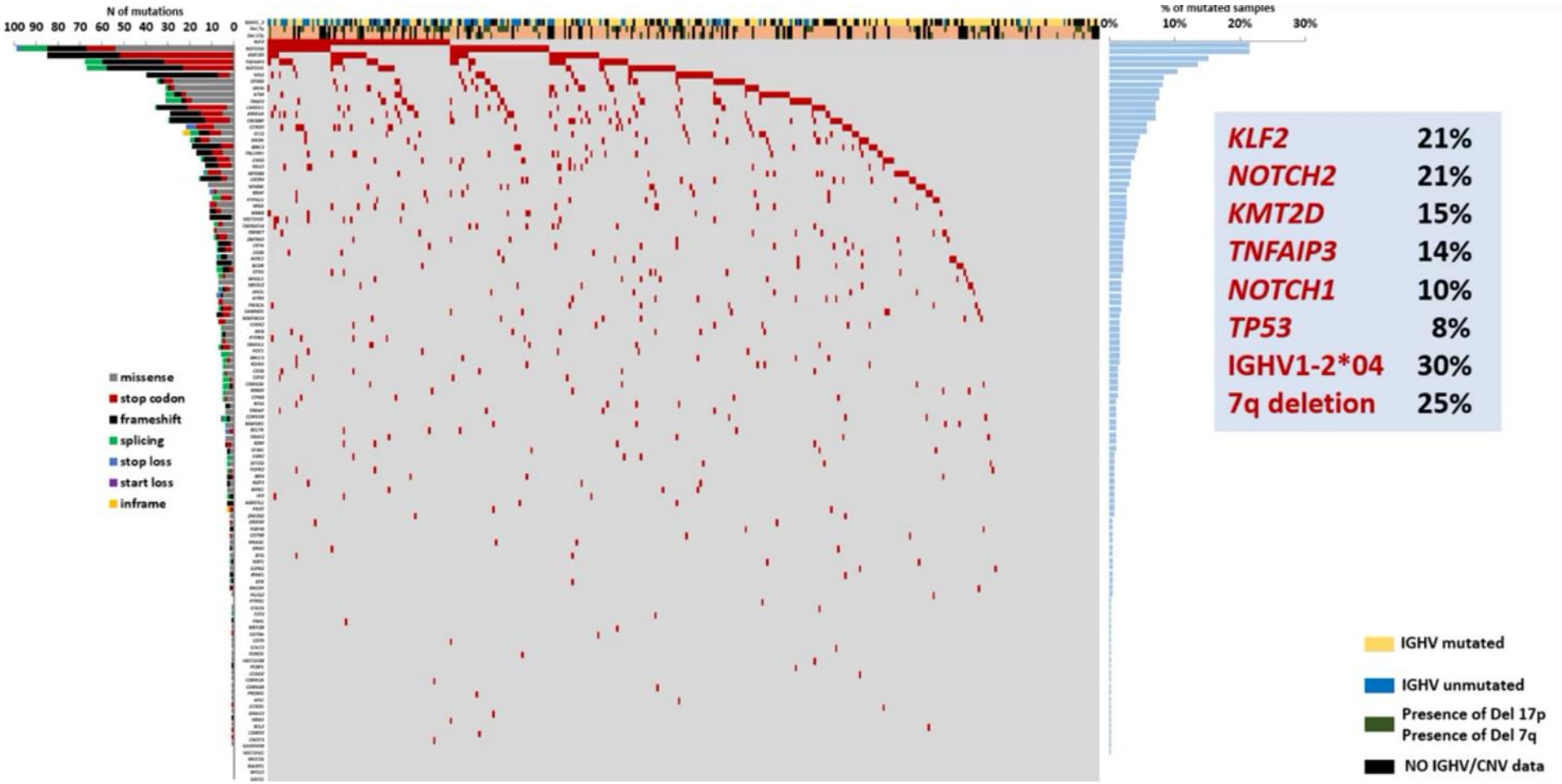
IELSG-46: SMZL mutational landscape

- N=404 fresh spleen samples (splenectomy before 2010)



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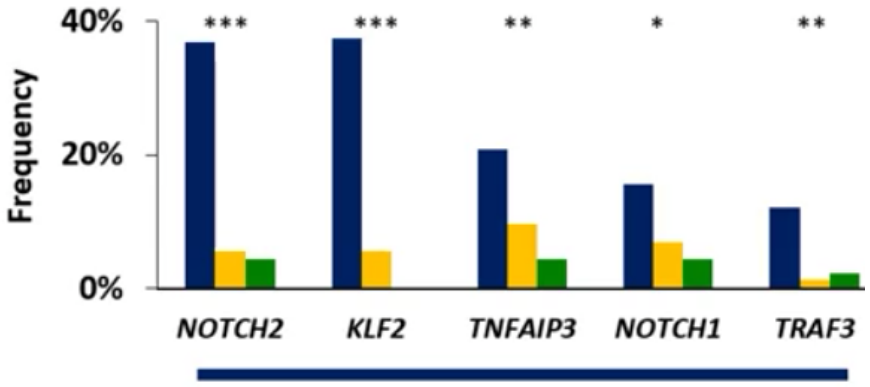
IELSG-46: 3 molecular clusters



MC1: NOTCH-NF-kB genes (62%)

- ***NOTCH2, KLF2***

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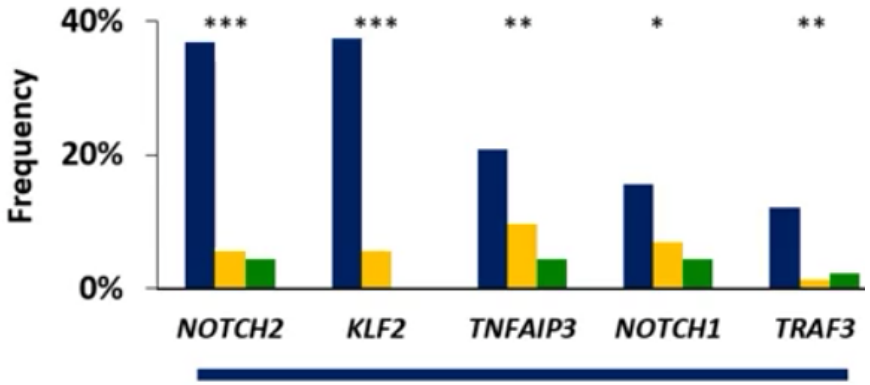
IELSG-46: 3 molecular clusters



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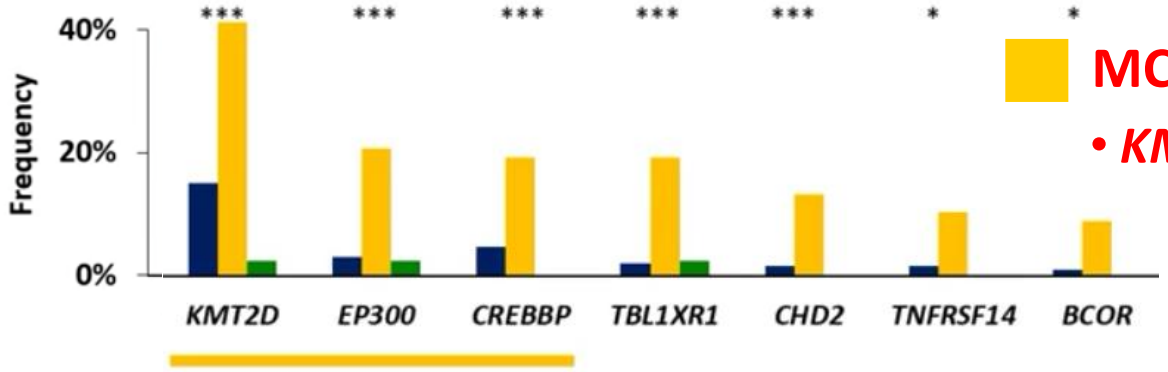
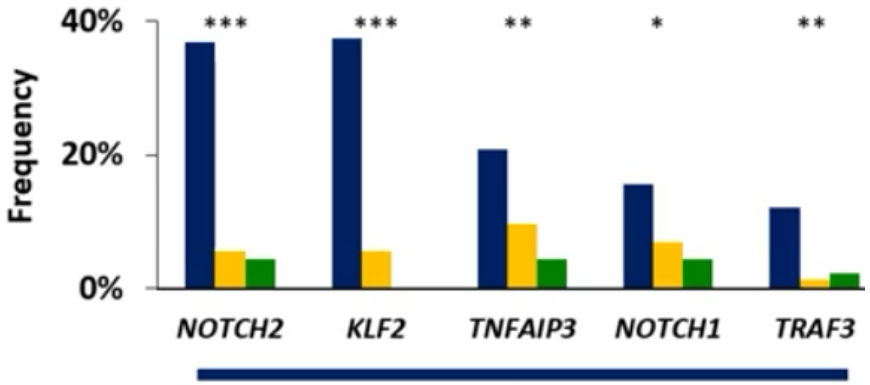


MC2: Epigenetic genes (21%)

- ***KMT2D, EP100, CREBBP***

Bruscaggin A et al ICML 2019

IELSG-46: 3 molecular clusters



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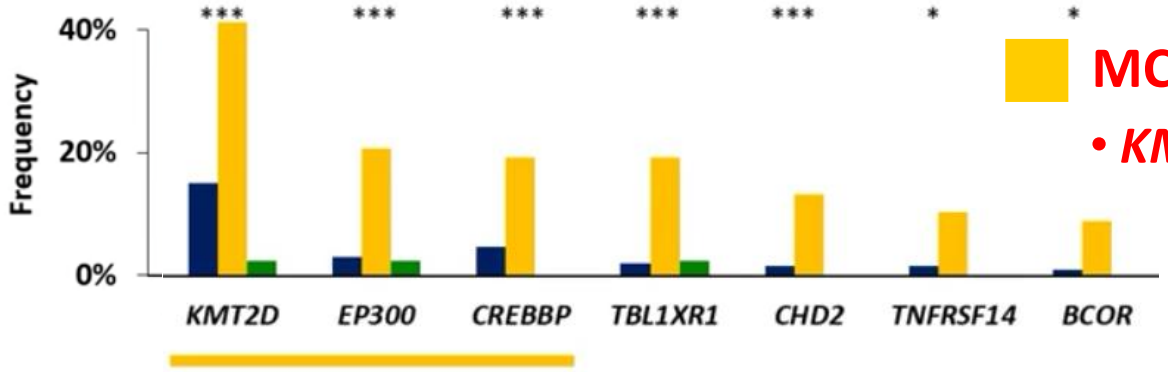

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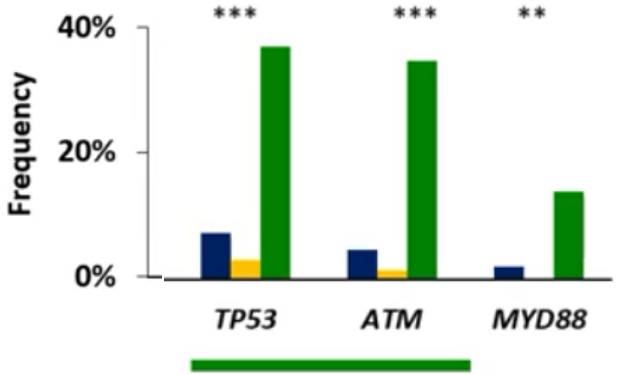

MC3: DNA damage genes (17%)

- *TP53, ATM*

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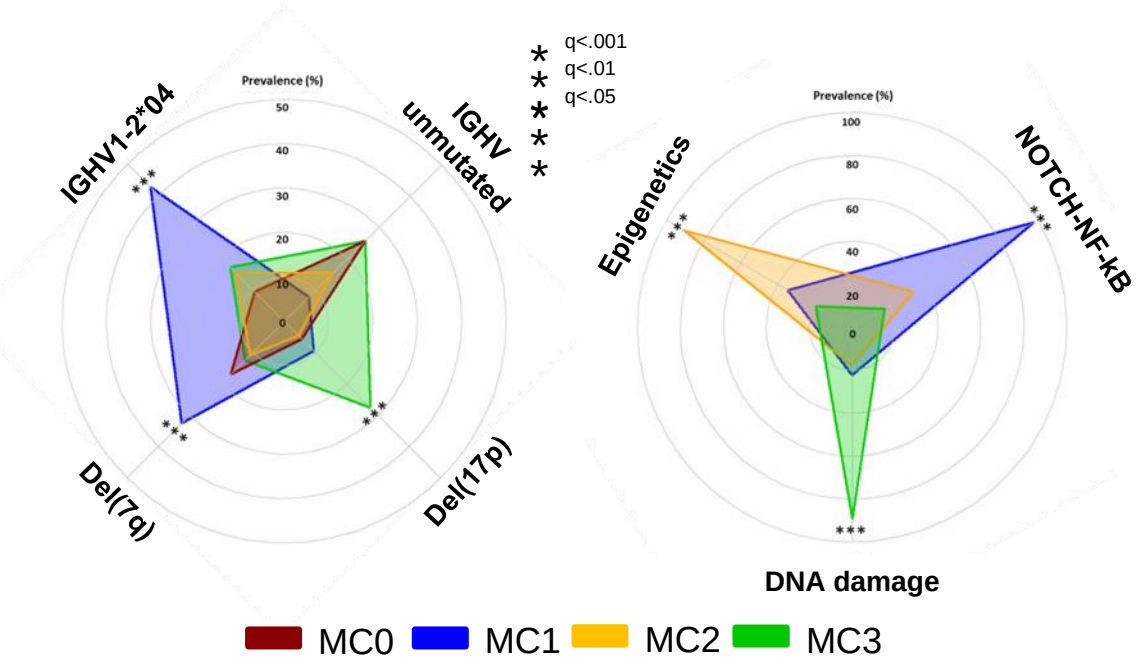
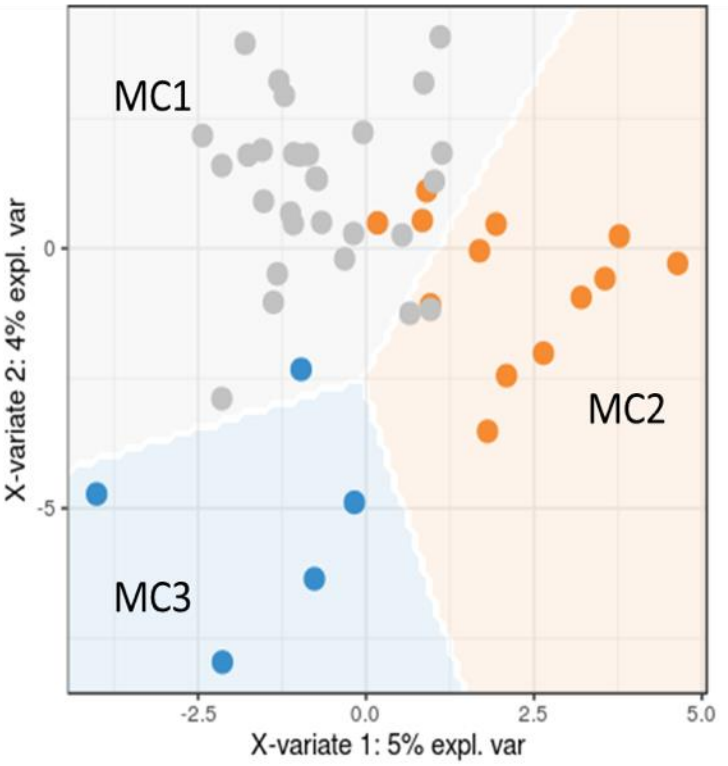
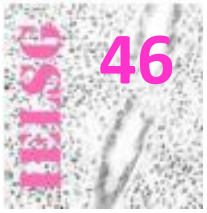
Molecular Clusters in SMZL have underling biological differences







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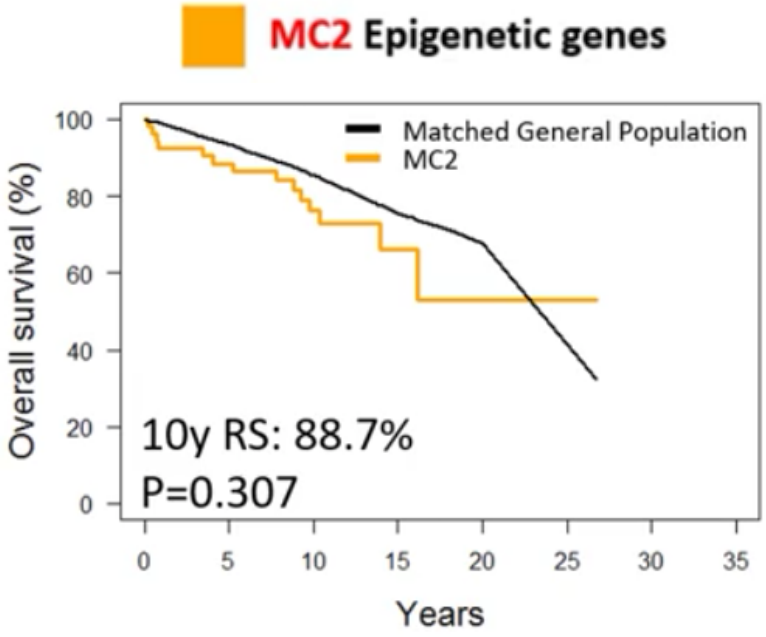
IELSG-46: molecular clusters survival



Bruscaggin A et al ICML 2019

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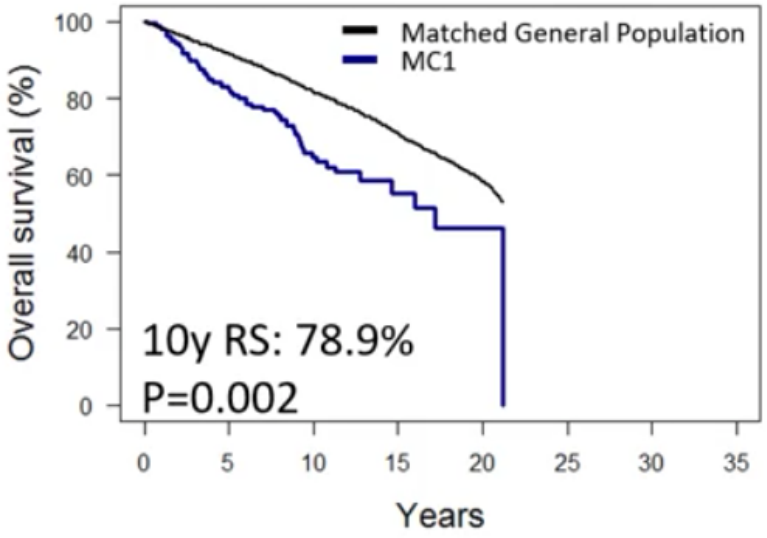
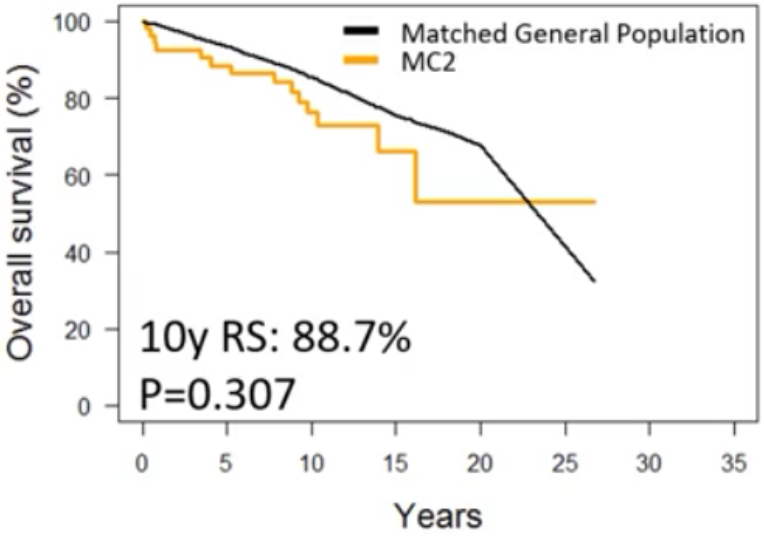


MC1 NOTCH-NF-kB genes

MC2 Epigenetic genes



Bruscaggin A et al ICML 2019

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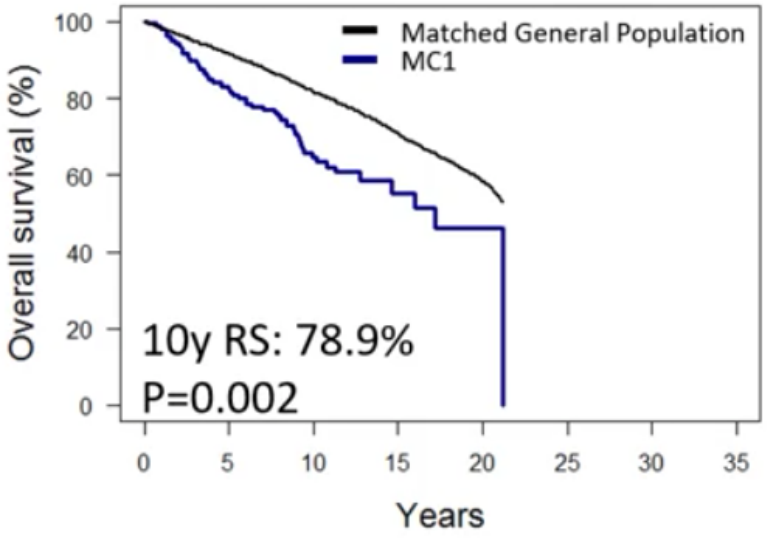

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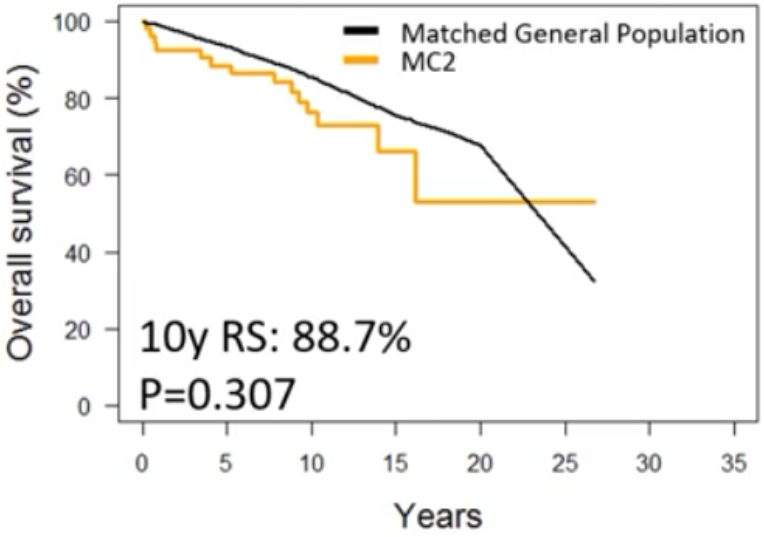
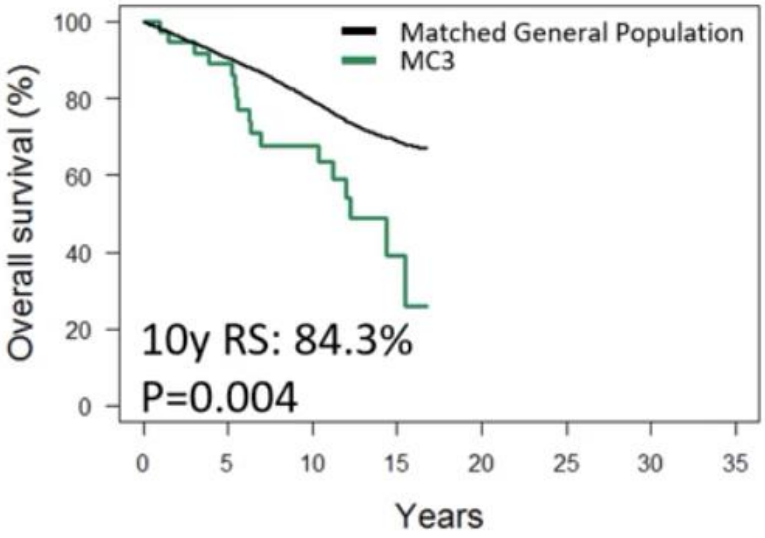




MC3 DNA Damage genes

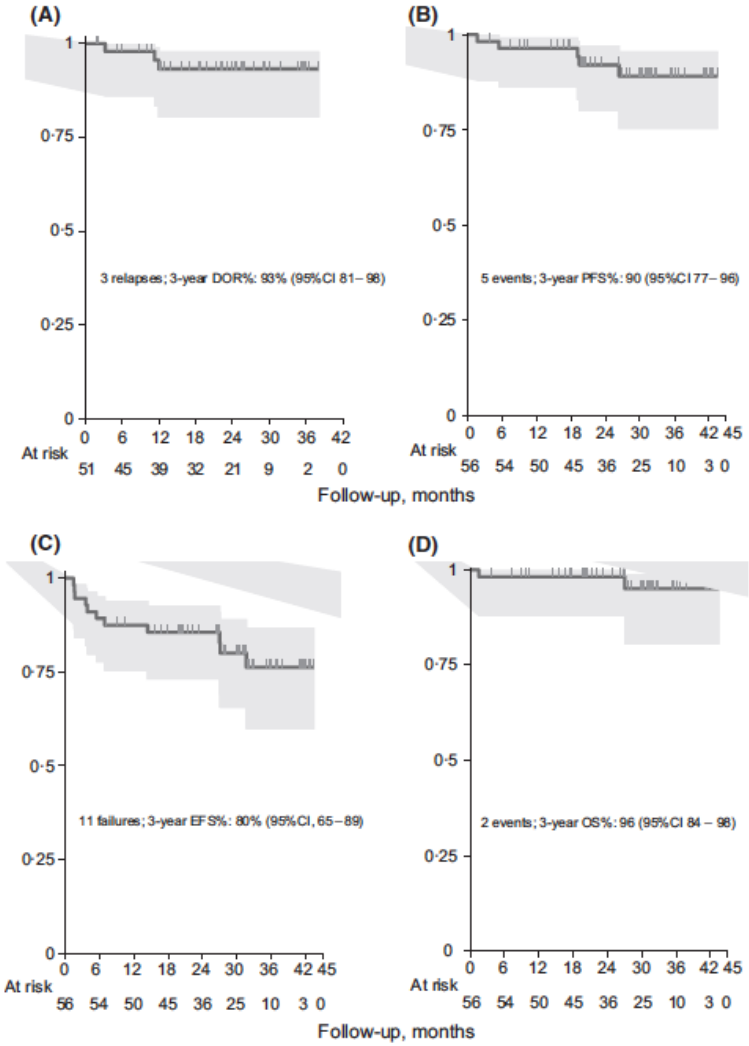
- *TP53* mutations (8%): lower survival (10y OS 46% vs 76.9%, p<0.01)

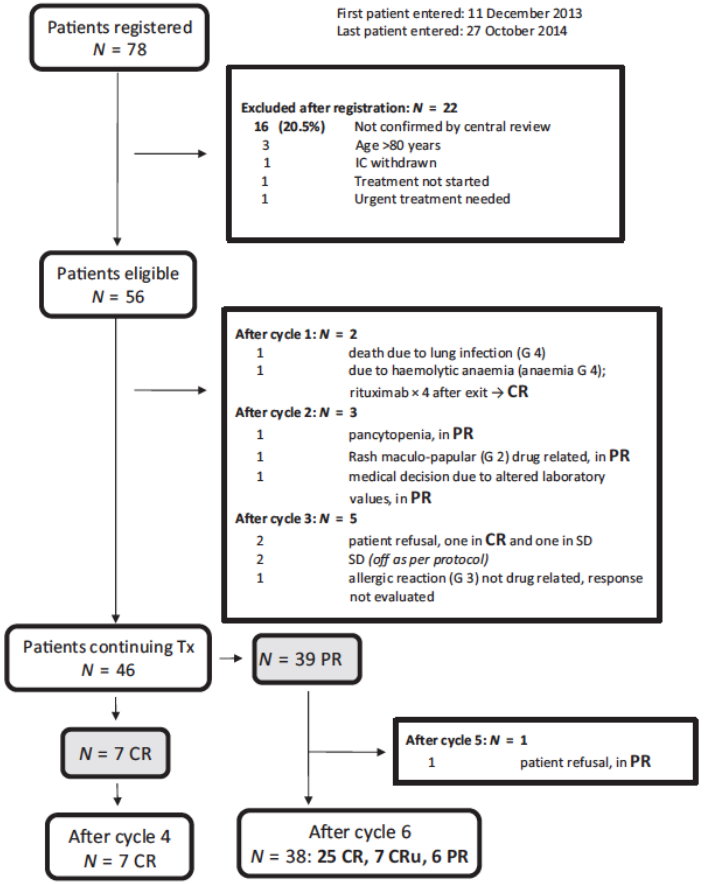
Bruscaggin A et al ICML 2019

bjh research paper

Efficacy of bendamustine and rituximab in splenic marginal zone lymphoma: results from the phase II BRISMA/IELSG36 study

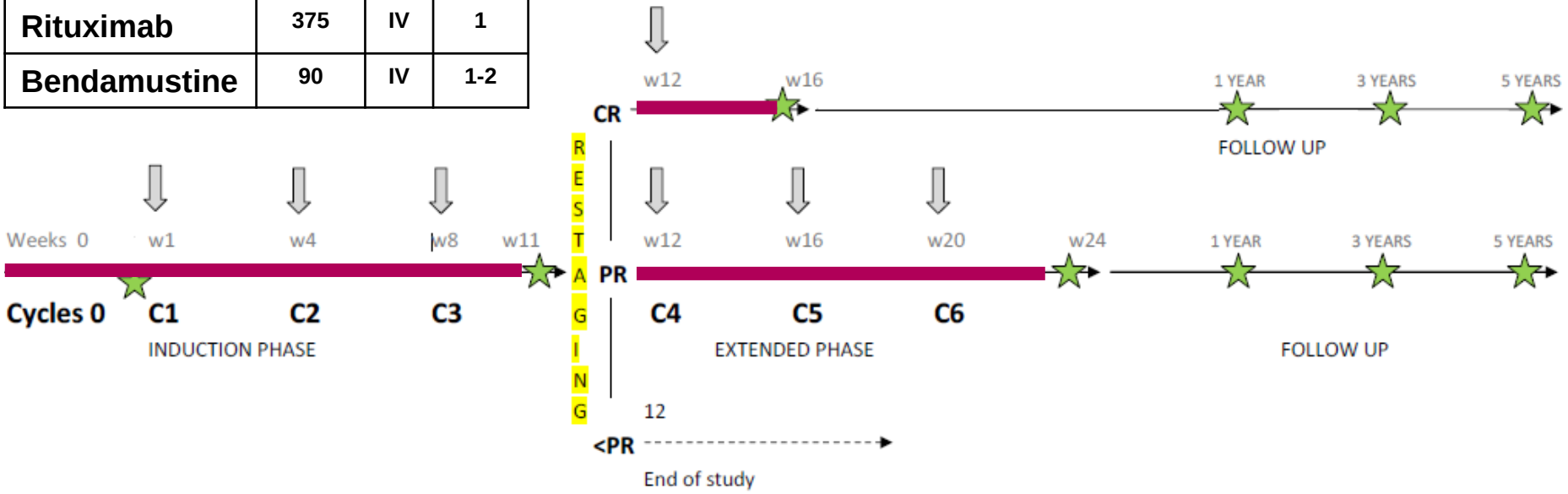
Emilio Iannitto,[1] Monica Bellei,[2] Sandy Amorim,[3] Andrés J. M. Ferreri,[4] Luigi Marcheselli,[2] Marina Cesaretti,[2] Corinne Haioun,[5] Salvatrice Mancuso,[1] Krimo Bouabdallah,[6] Remy Gressin,[7,8] Claudio Tripodo,[9] Alexandra Traverse-Glehen,[10] Lucile Baseggio,[11] Simonetta Zupo,[12] Caterina Stelitano,[13] Barbara Castagnari,[14] Caterina Patti,[15] Isabel Alvarez,[16] Anna Marina Liberati,[17] Michele Merli,[18] Guido Gini,[19] Maria Giuseppina Cabras,[20] Jean Dupuis,[21] Benoit Tessoulin,[22] Aurore Perrot,[23] Francesca Re,[24] Francesca Palombi,[25] Alessandro Gulino,[9] Emanuele Zucca,[26] Massimo Federico[27] and Catherine Thieblemont[28]





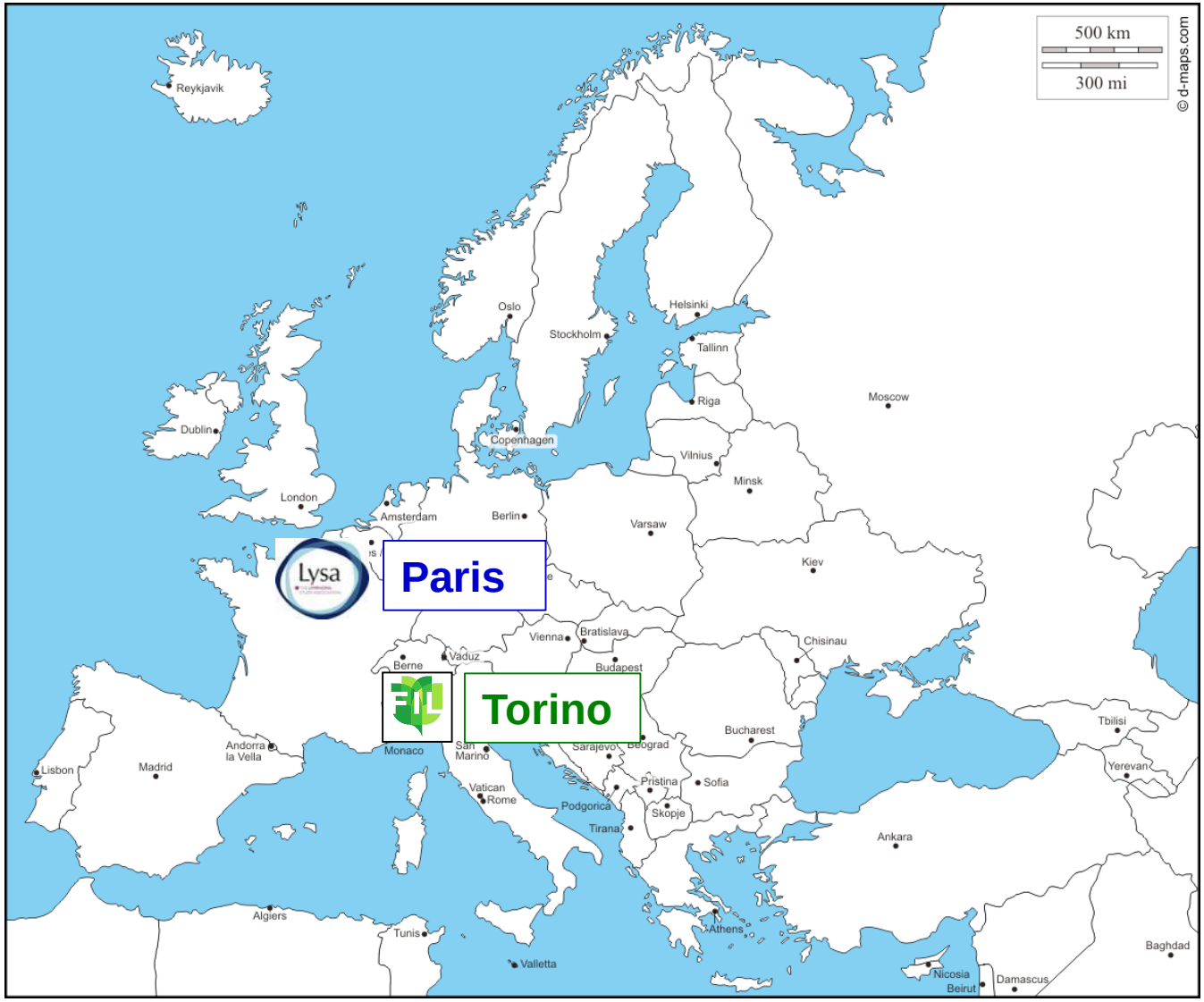
MRD in BRISMA timepoints

	Dose (mg/m²)		Days
Rituximab	375	IV	1
Bendamustine	90	IV	1-2



★ **MRD = IgH MRD: droplet digital PCR**
Biomed 2 - EuroMRD
consensus guidelines

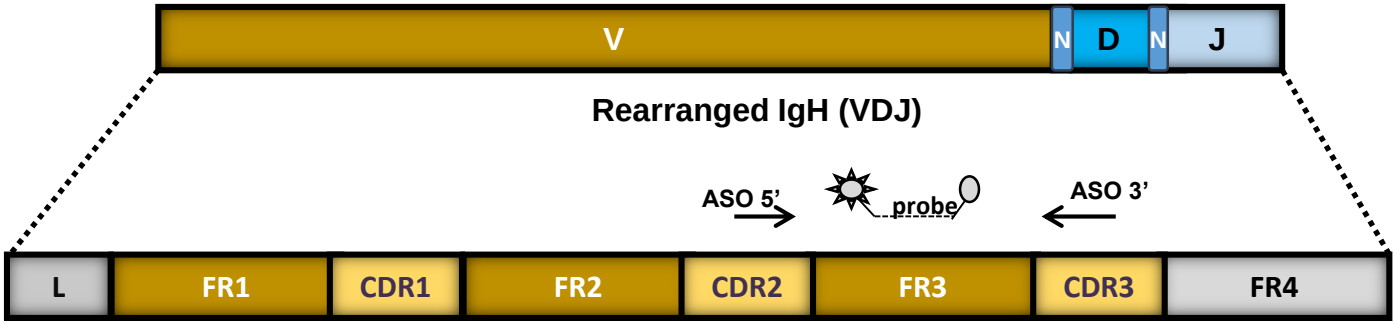
MRD in BRISMA labs

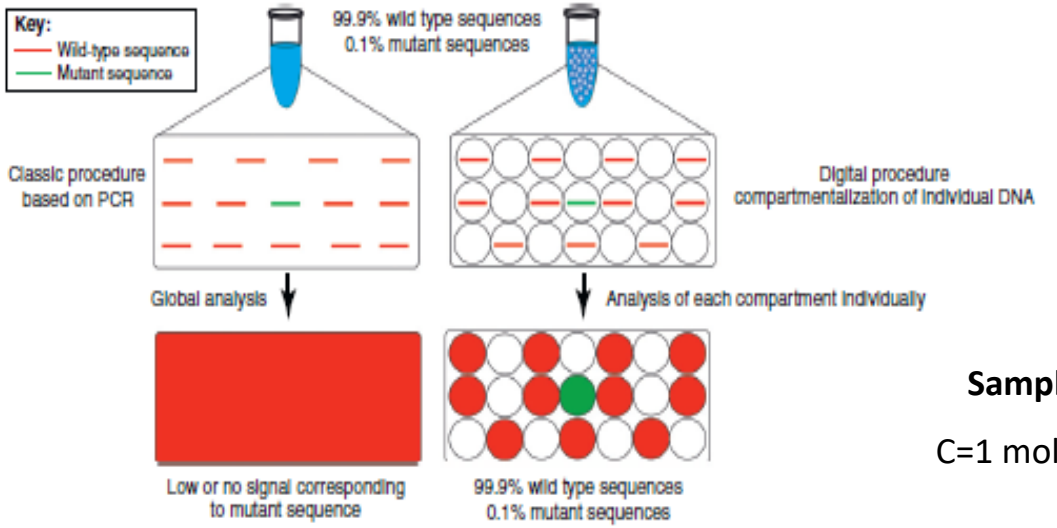


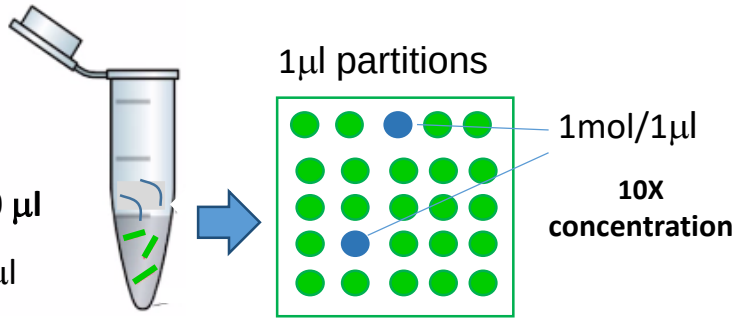
METHODS
droplet digital PCR

EuroMRD

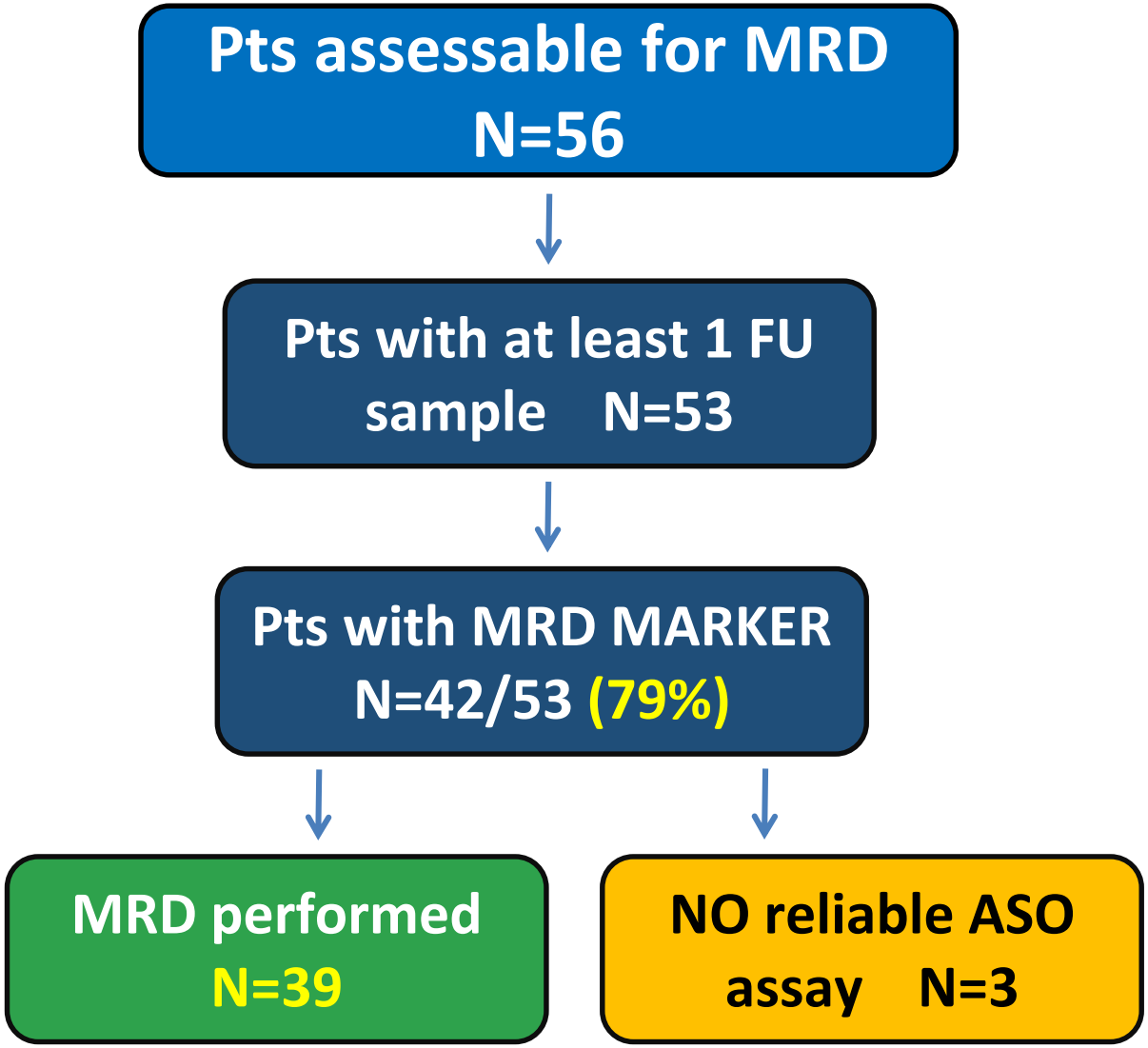
STRATEGY FOR IgH MRD DETECTION



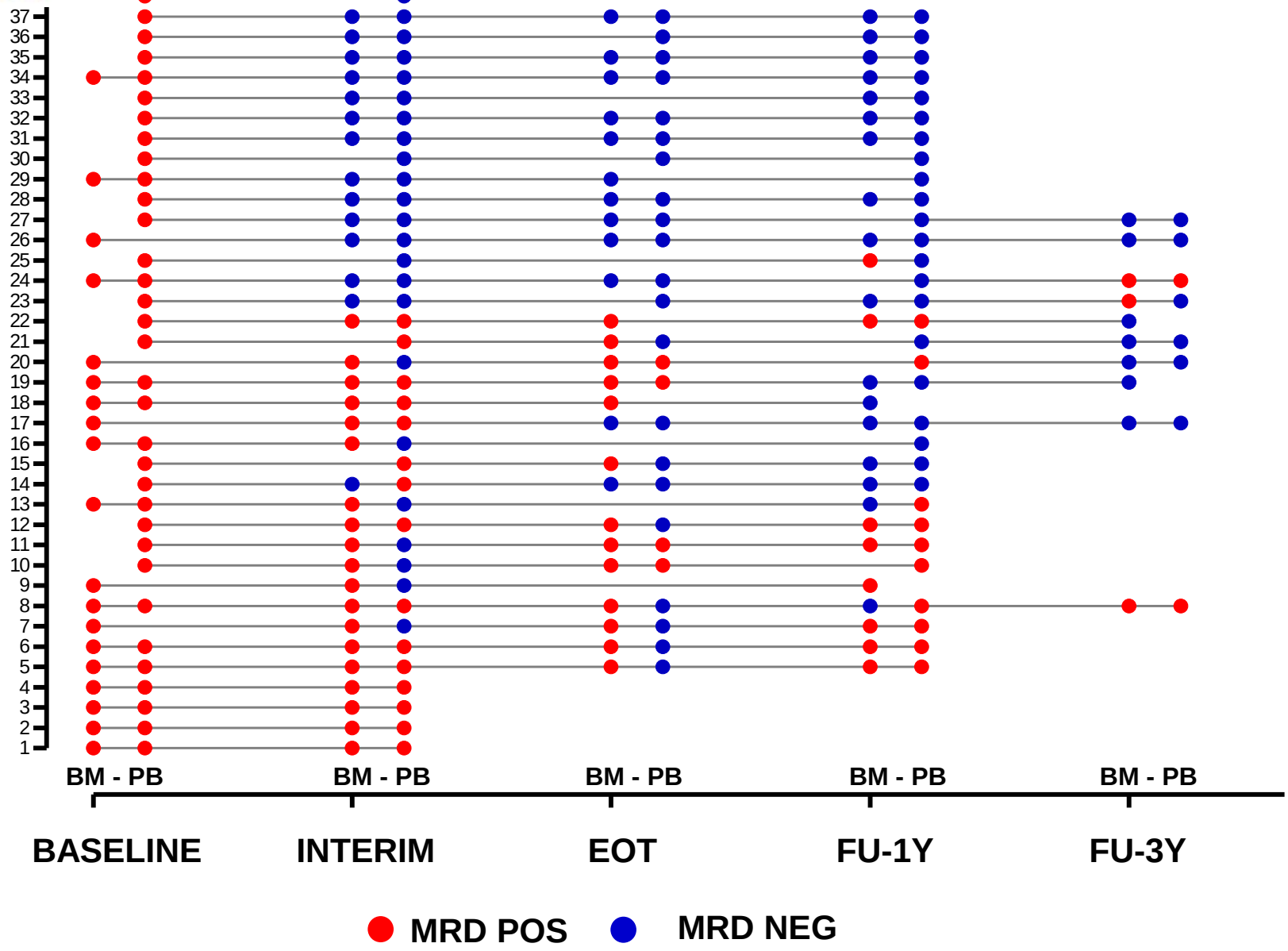




BRISMA: MRD flow



RESULTS: MRD ANALYSIS PLOT



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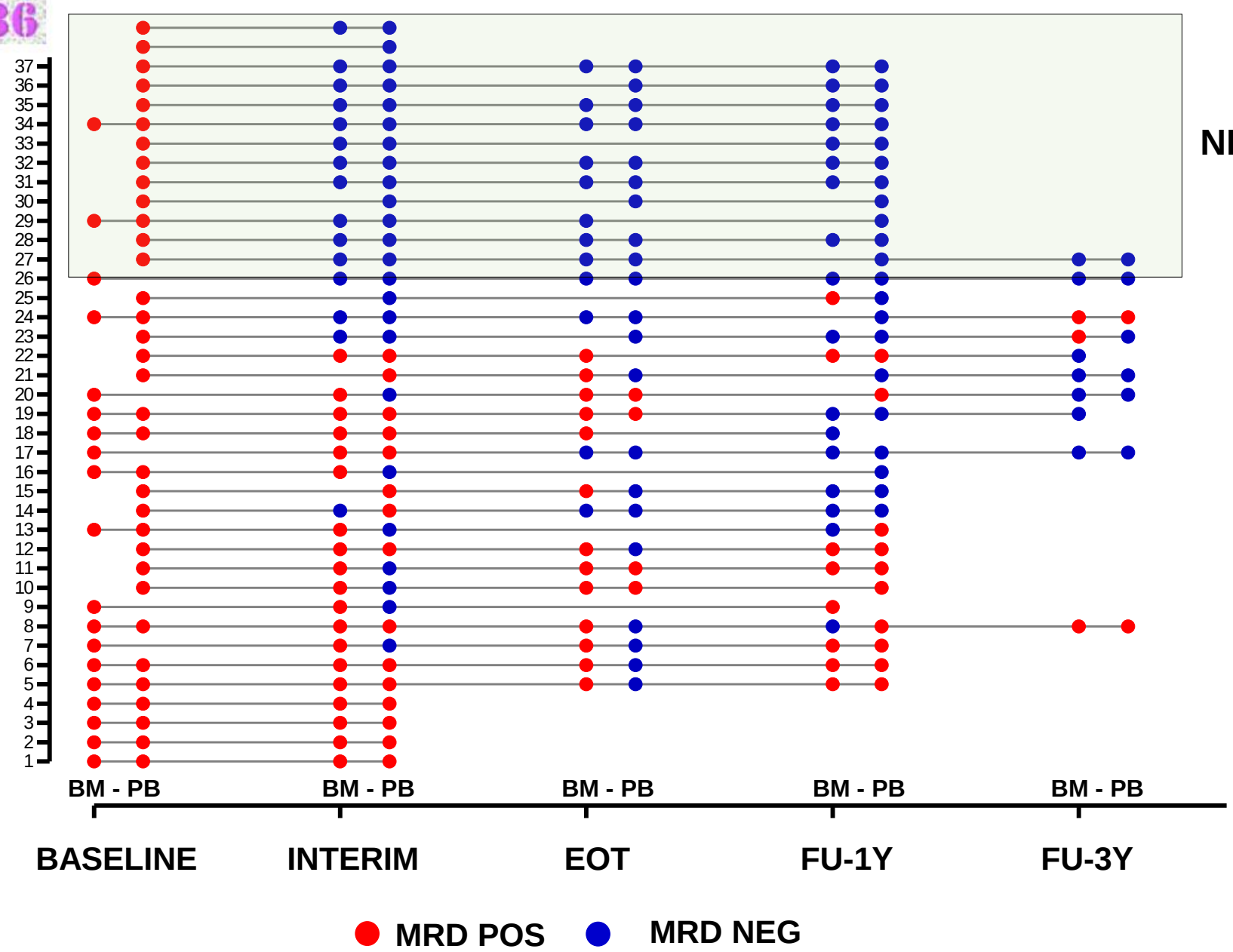

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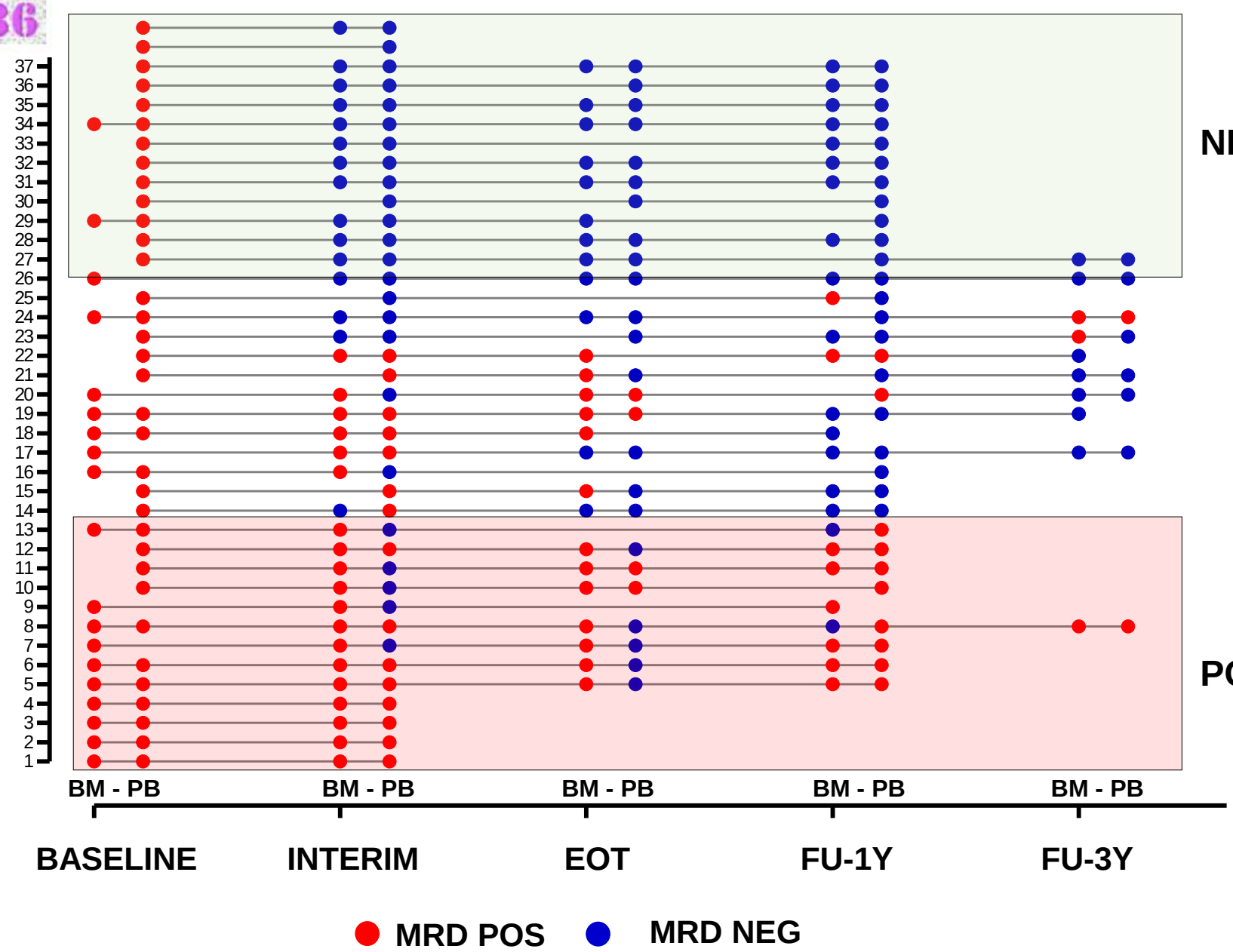

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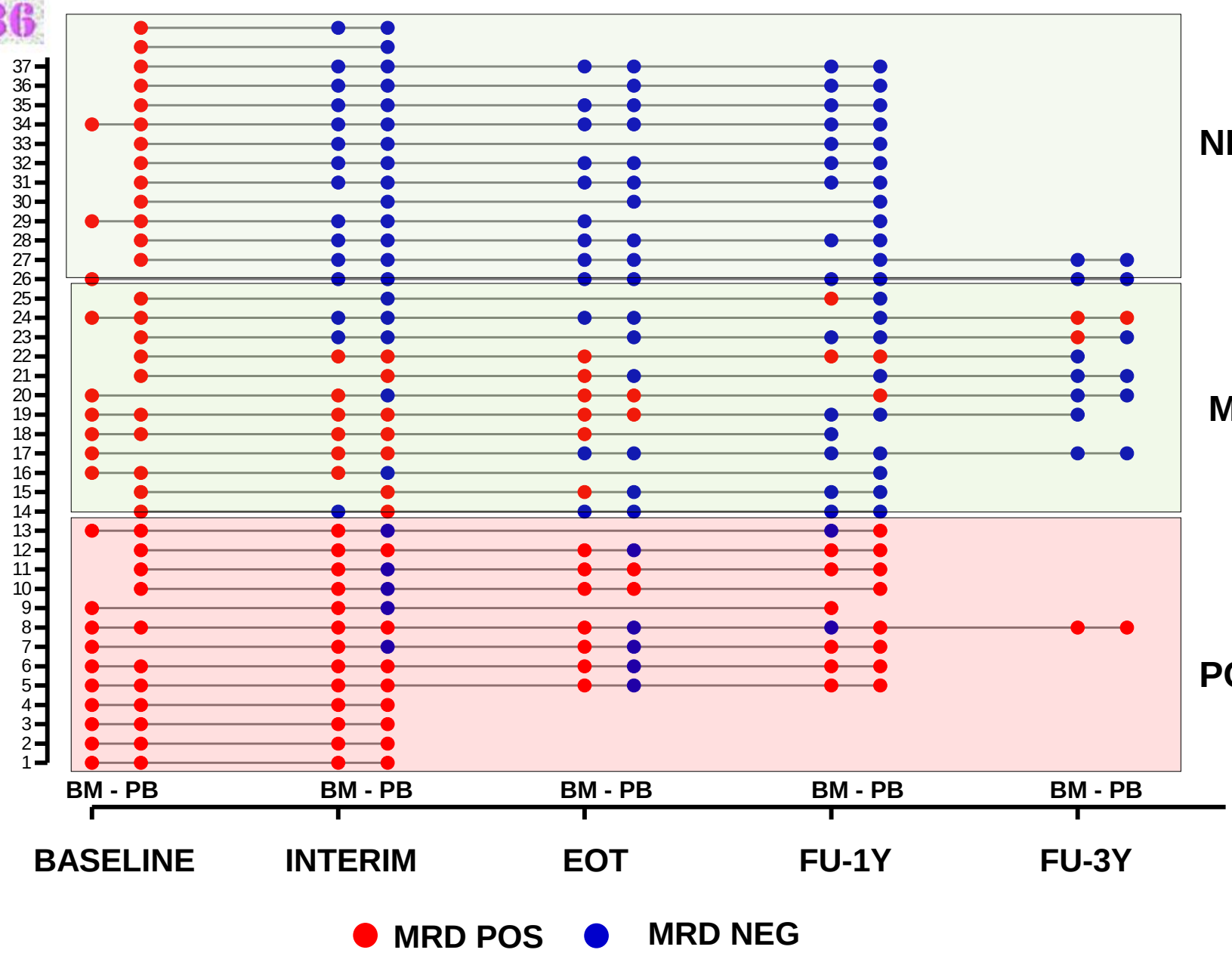

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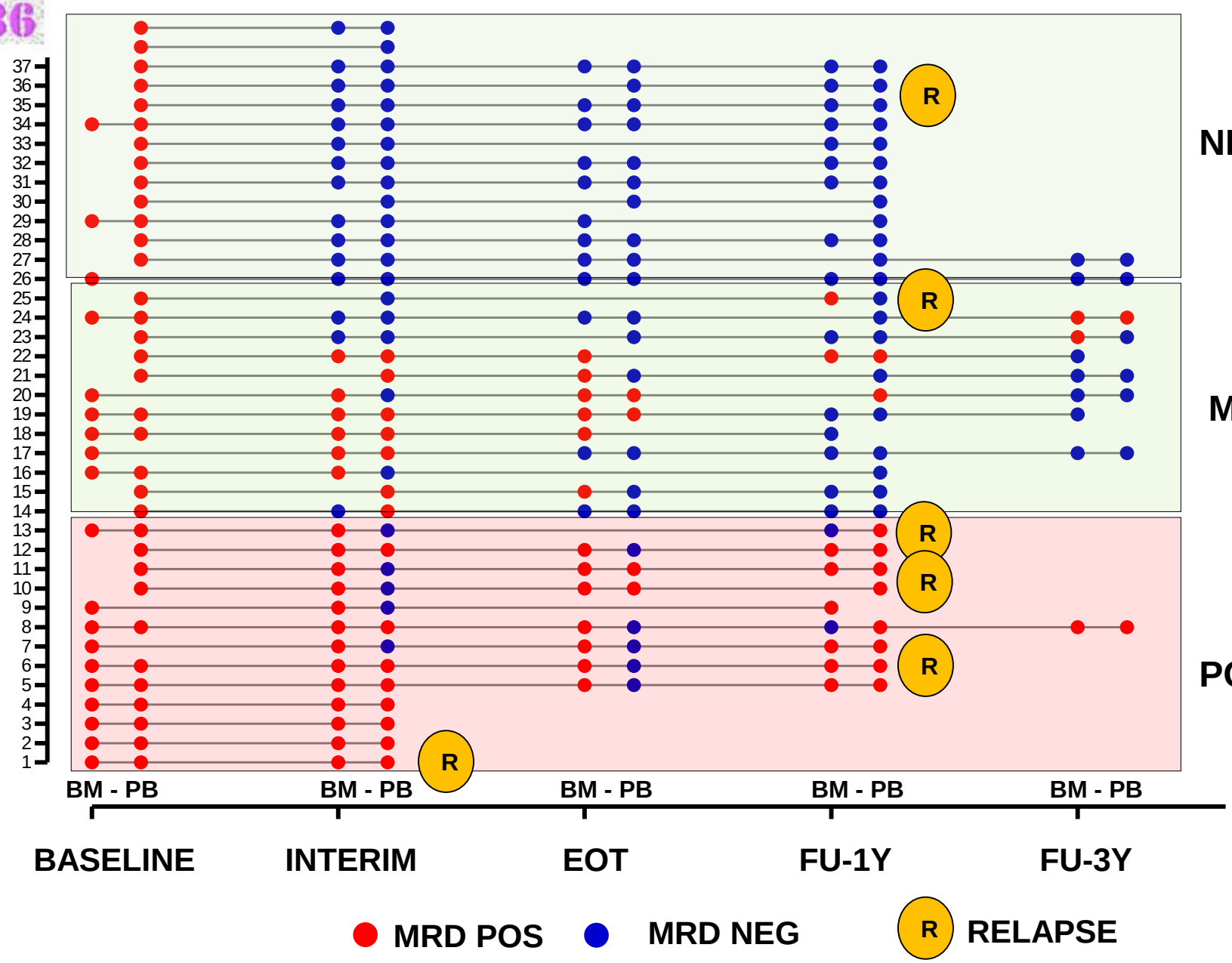
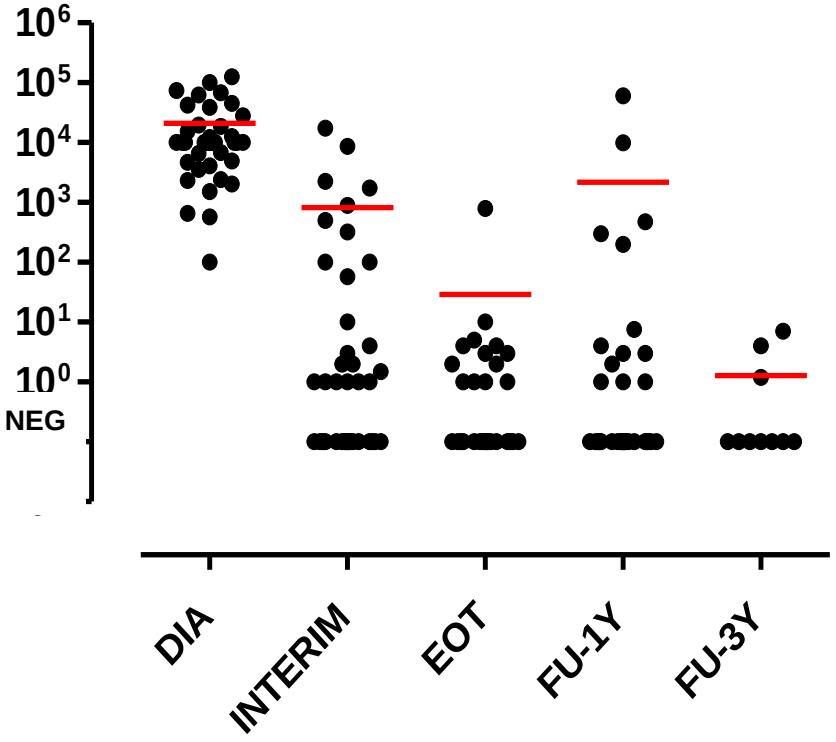
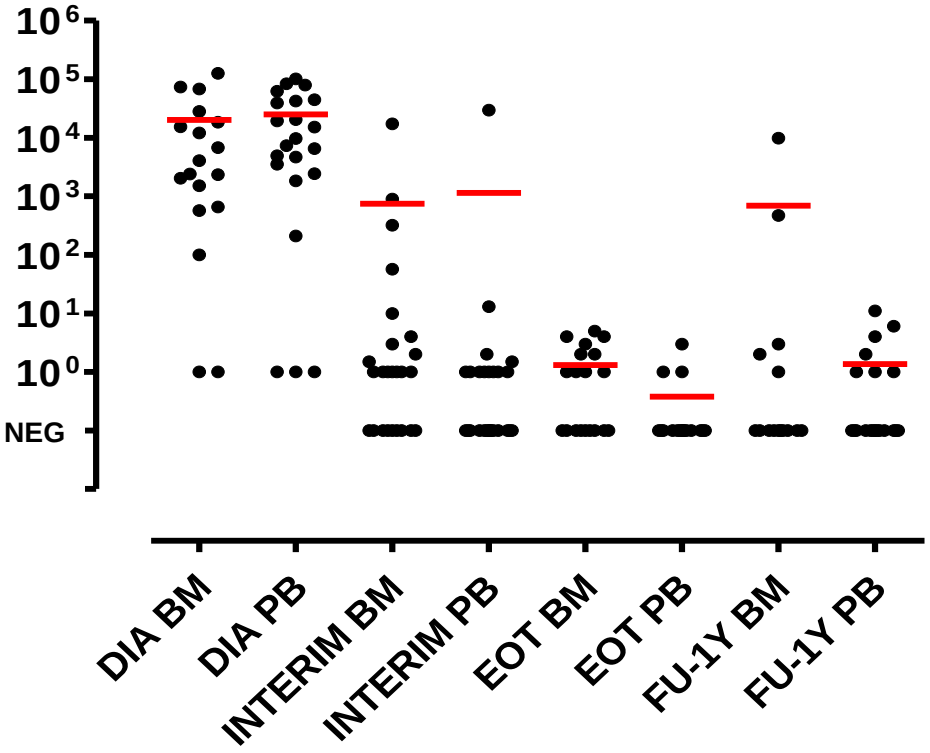


RESULTS: MRD SHRINKAGE





TUMOR BURDEN AT BASELINE

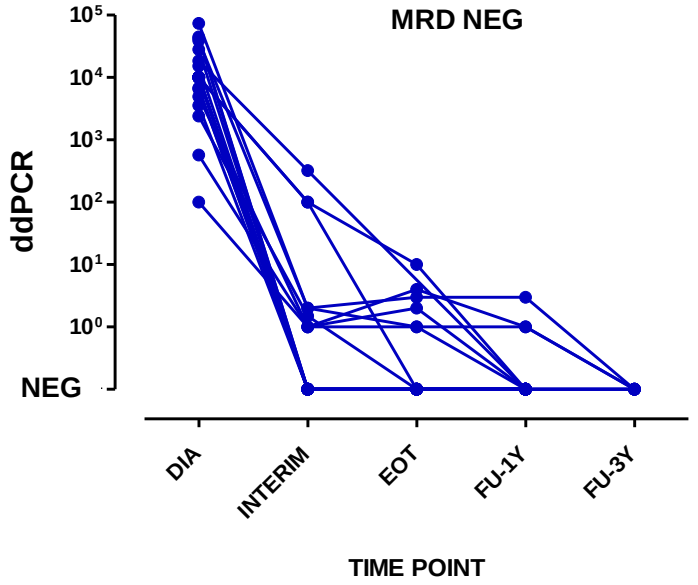
- **BM** 1.45E-01 (1 - 2.67E-03)
- **PB** 4.04xE-01 (1 - 5.60E-03)

MRD NEGATIVIZATION RATES

- 47% at **interim** (BM: 13/32; PB: 21/36)
- 54% at **EOT** (BM: 10/23; PB: 18/22)
- 61% **after one year** (BM: 14/22; PB: 19/29)

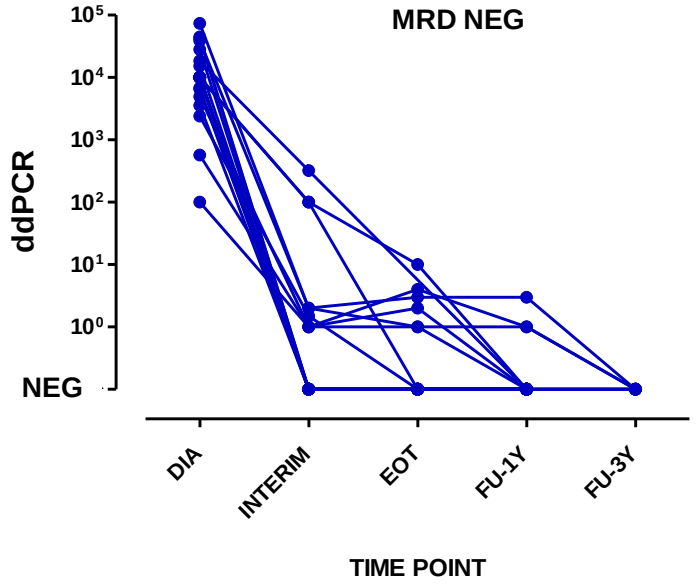
RESULTS: MRD KINETICS

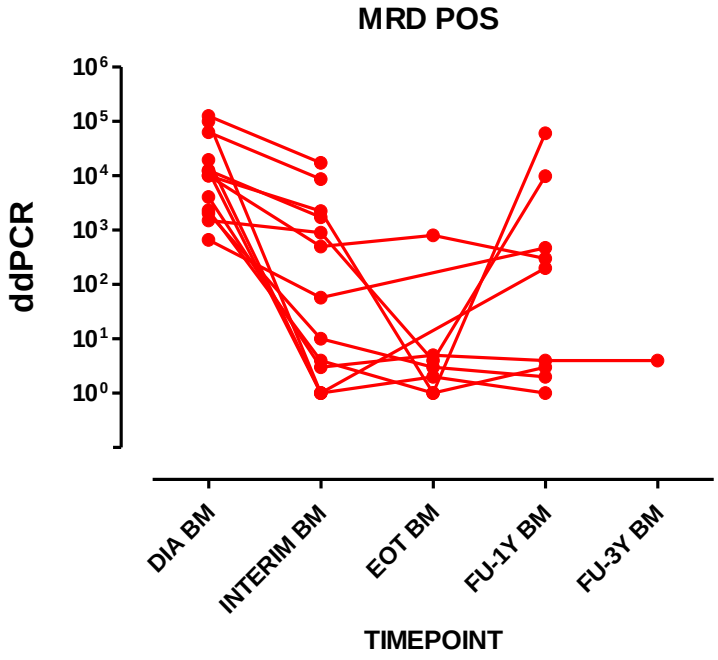
- Persistent MRD negativity (41%)



RESULTS: MRD KINETICS

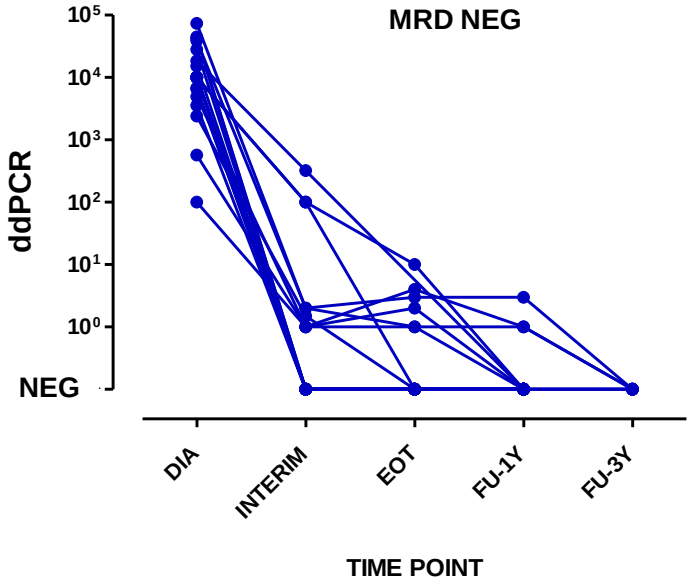
- Persistent MRD negativity (41%)
- Persistent MRD positivity (31%);

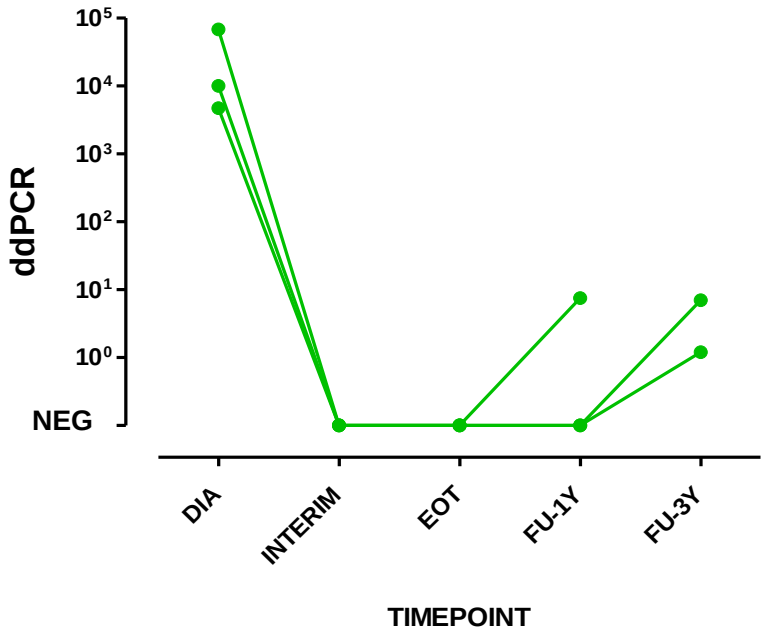


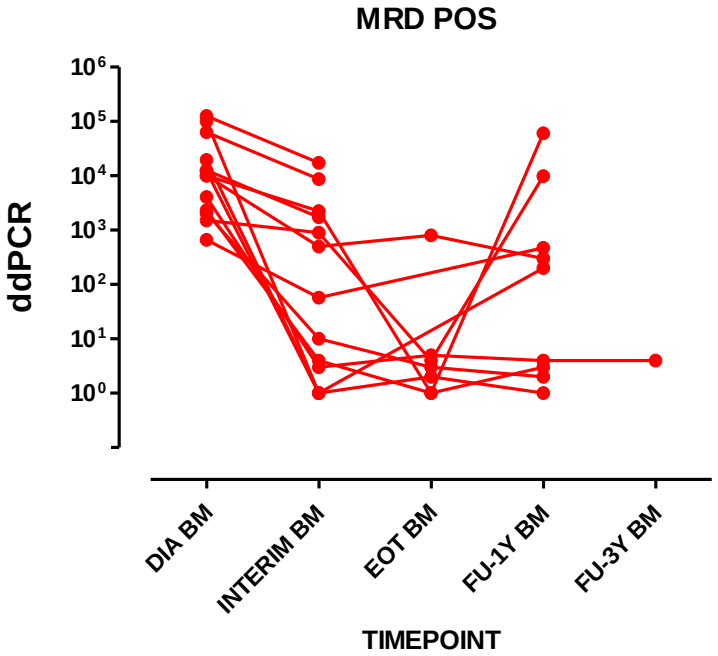


RESULTS: MRD KINETICS

- Persistent MRD negativity (41%)
- Persistent MRD positivity (31%);
- Alternating MRD (28%)







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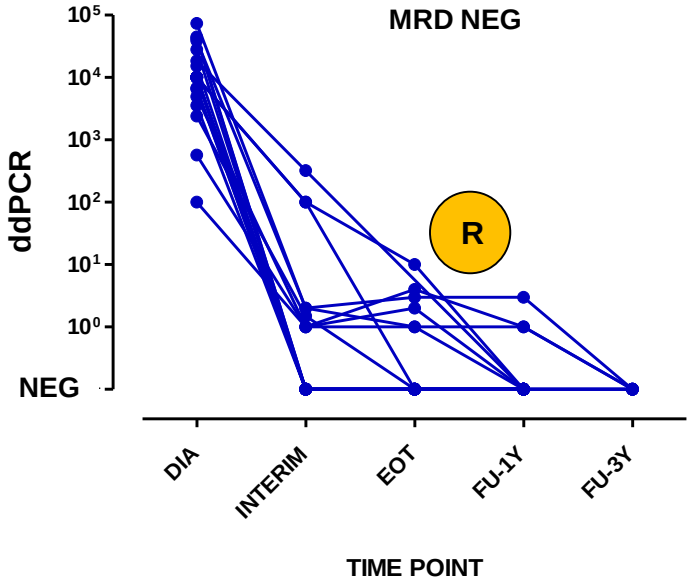

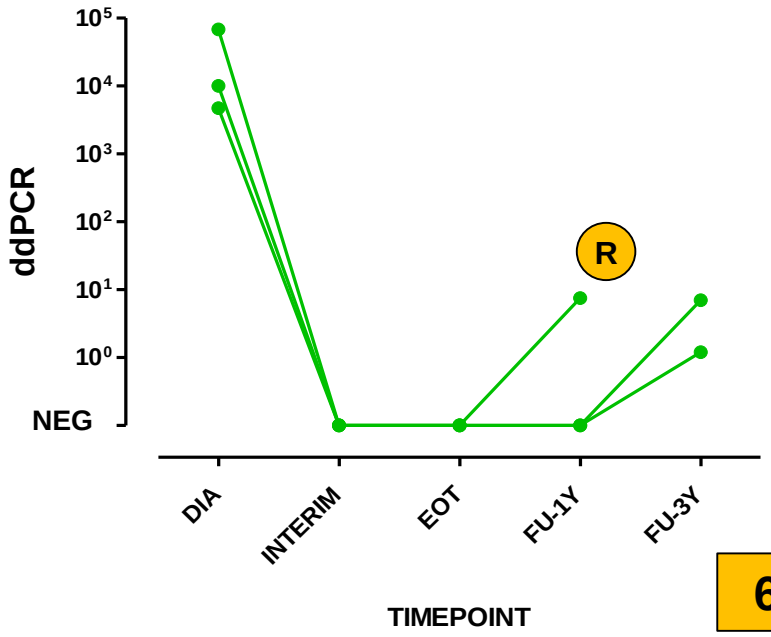

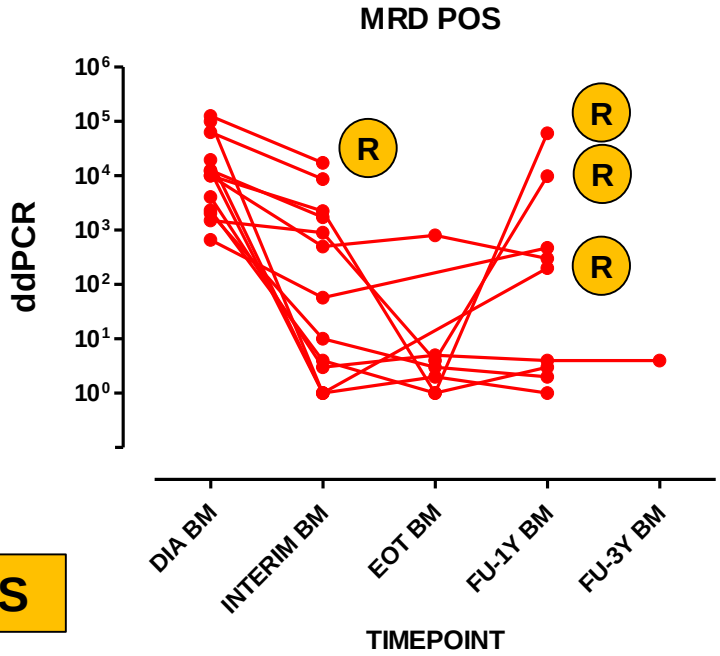

6 RELAPSES

CONCLUSIONS

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- **MRD is feasible in MZL**, describes the activity of anti-lymphoma drugs and might early identify high-risk patients

ACKNOWLEDGEMENTS

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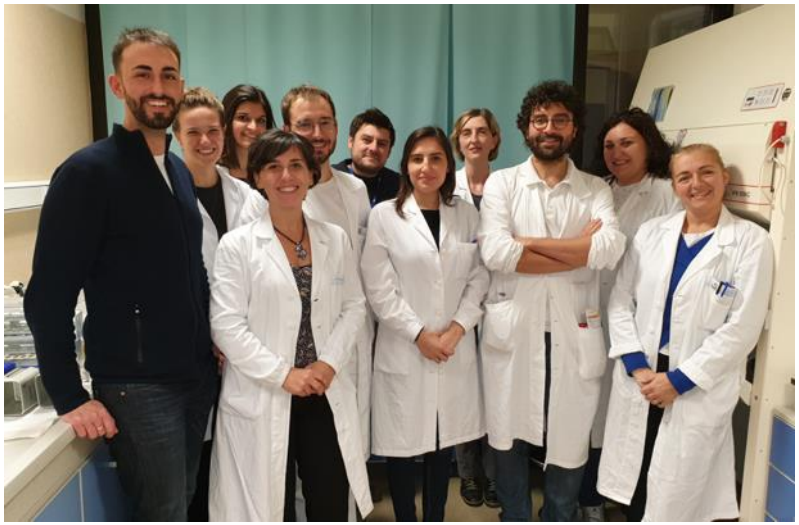

FIL Committee for biological studies

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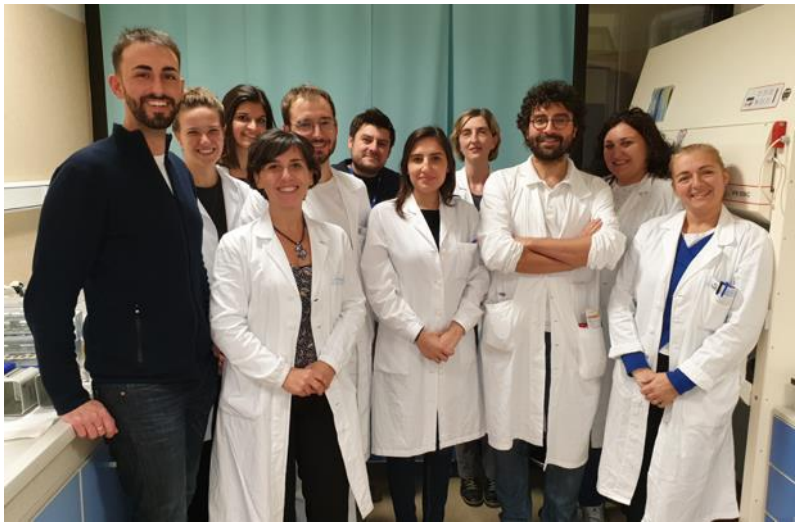

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Lab technician position available in Torino, please refer to: *simone.ferrero@unito.it*

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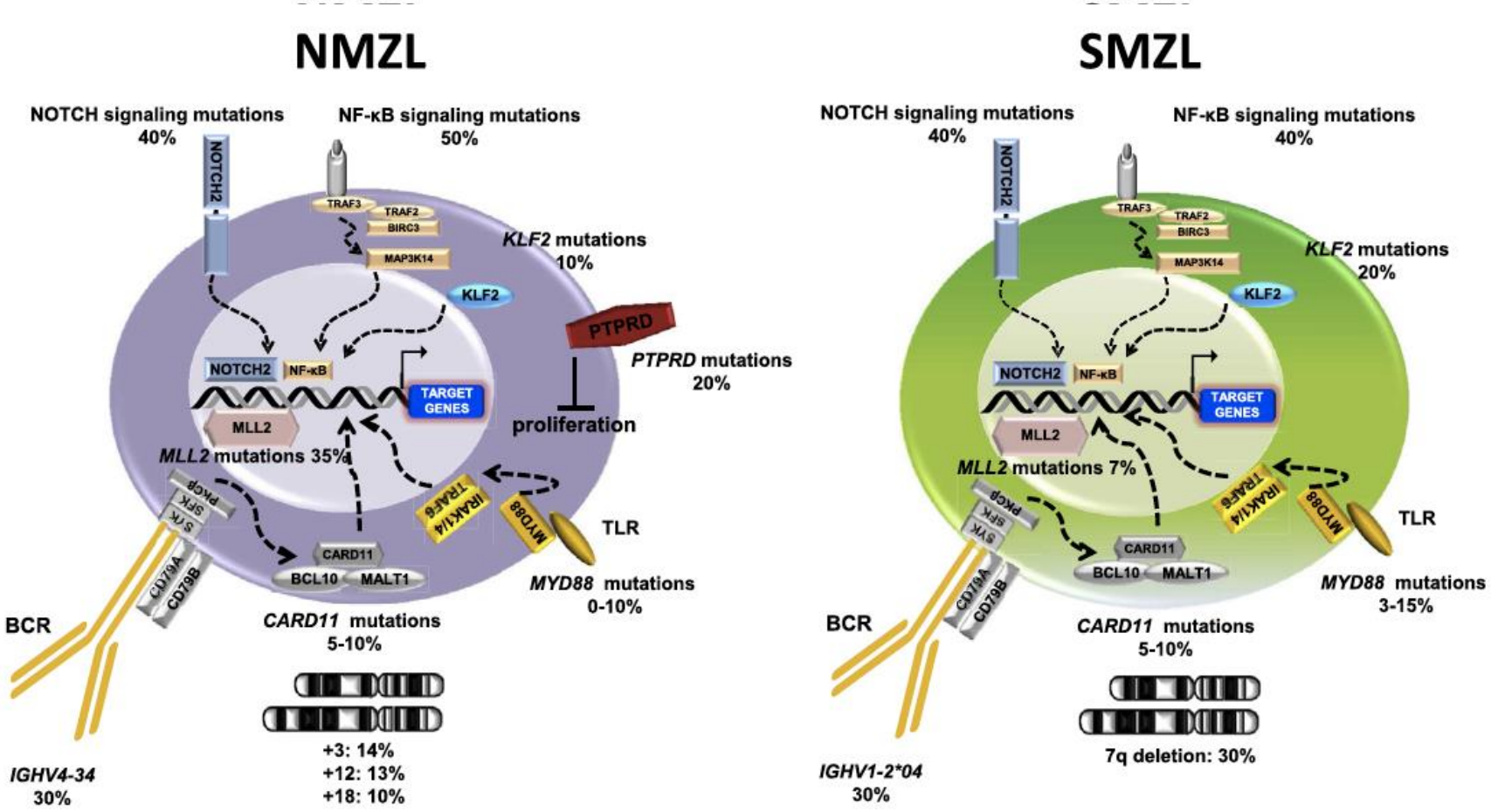


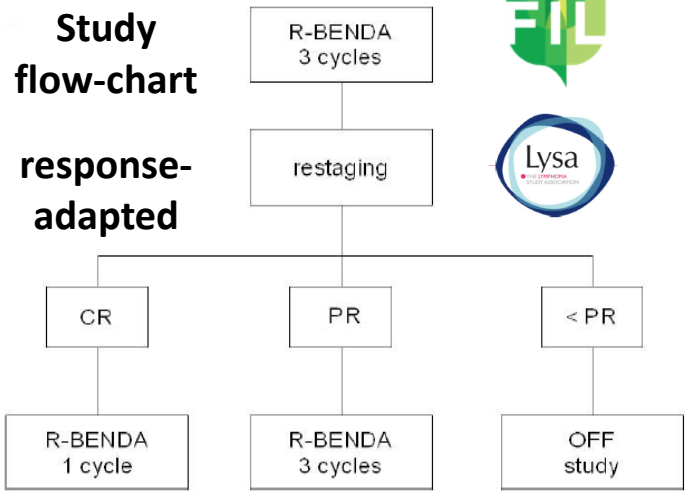
Fig. 1. Key molecular alterations of SMZL and NMZL. Genes and pathways that are molecularly deregulated are schematically represented. The prevalence of molecular alterations is reported beside each gene or pathway.

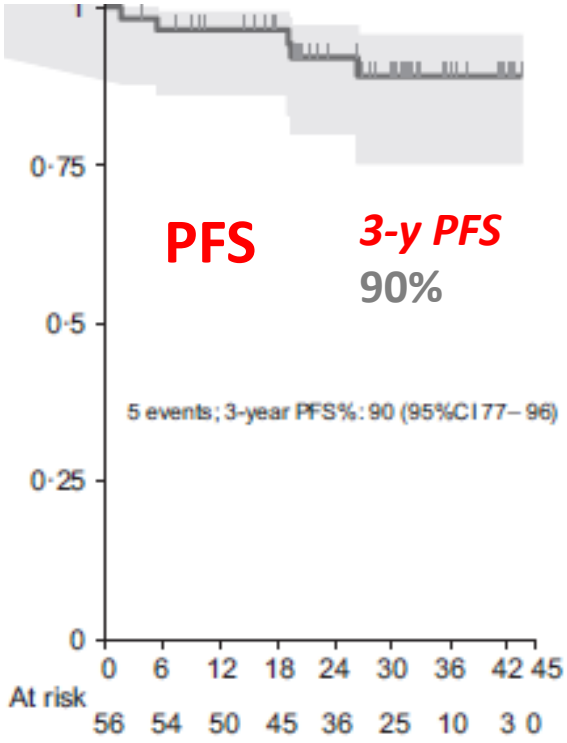
BR as 1st line tp in SMZL: BRISMA

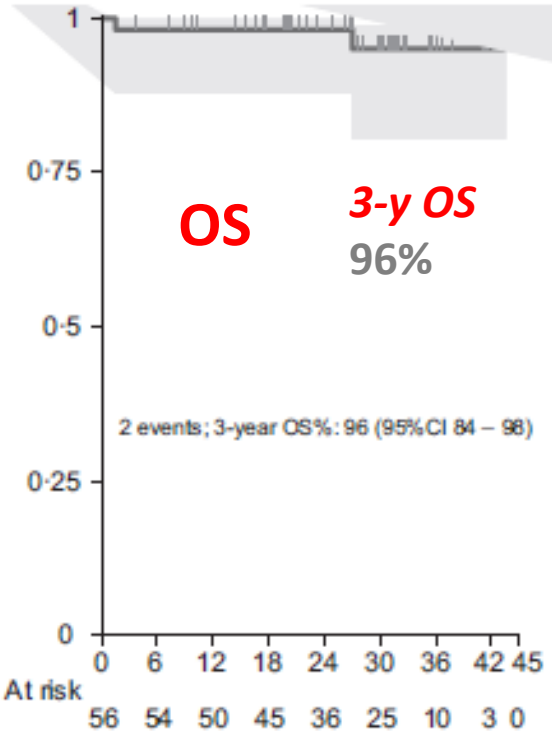
- **56 pts, SMZL**, symptomatic, diagnosis prospectively confirmed

Study flow-chart

response-adapted







- 35% high risk HPLL
- **ORR 91%**
- **CR 73%**
- Gr≥3 toxicity 68% (neutropenia 43%; infections 3.6%, FN 5.3%)

3-y EFS: **80%**

3-y DoR **93%**

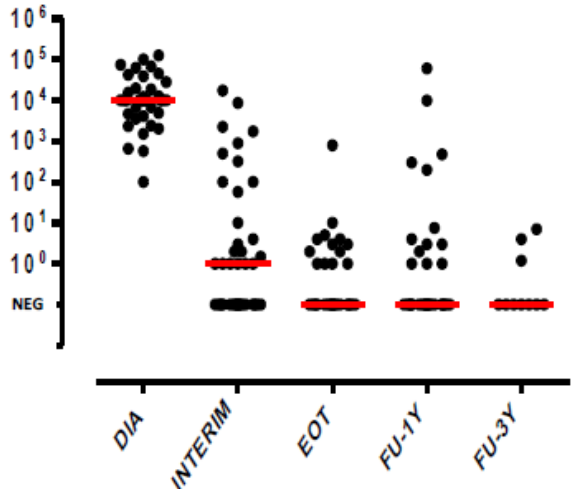
***Median follow-up:** **32 months** (2 - 52)

Iannitto E et al, BJH 2018

BRISMA: 1st MRD analysis in SMZL

- **42/53 pts (79%): MRD marker (IgH)** with **ddPCR** → **good feasibility**

MRD SHRINKAGE



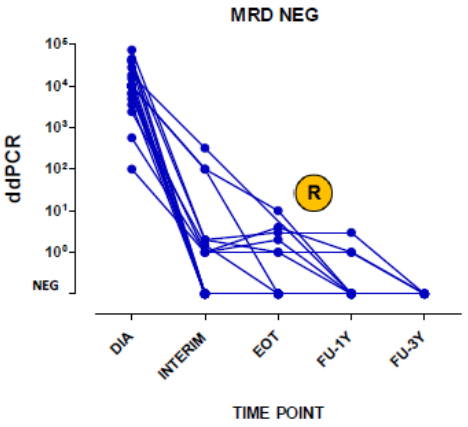
MRD neg rate	Overall	BM	PB
Interim	47%	41%	58%
EOT	54%	43%	82%
1 year	61%	64%	66%

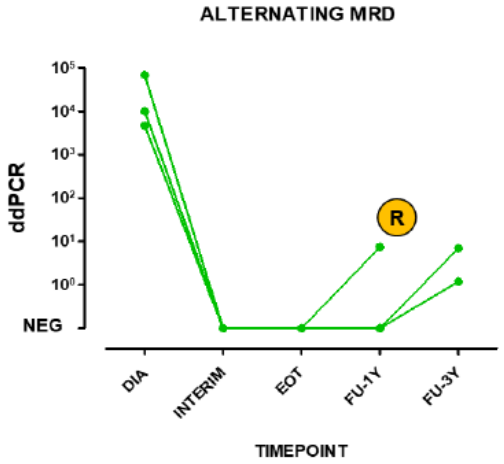
MRD KINETICS

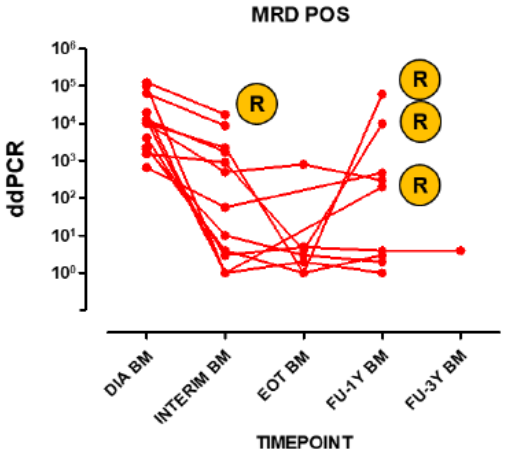
Persistent MRD negativity (41%)

Persistent MRD positivity (31%);

Alternating MRD (28%)







Ferrero S et al, ICML 2019

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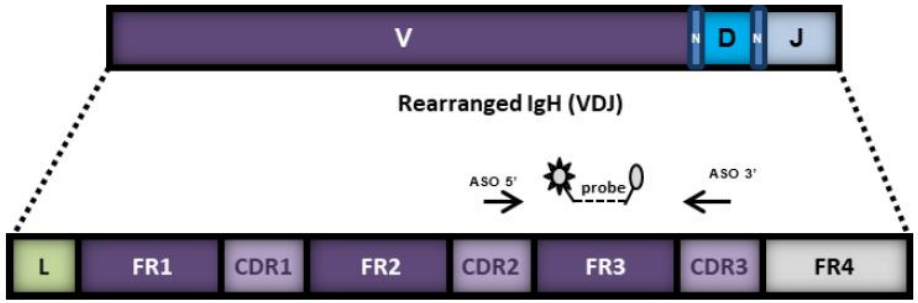

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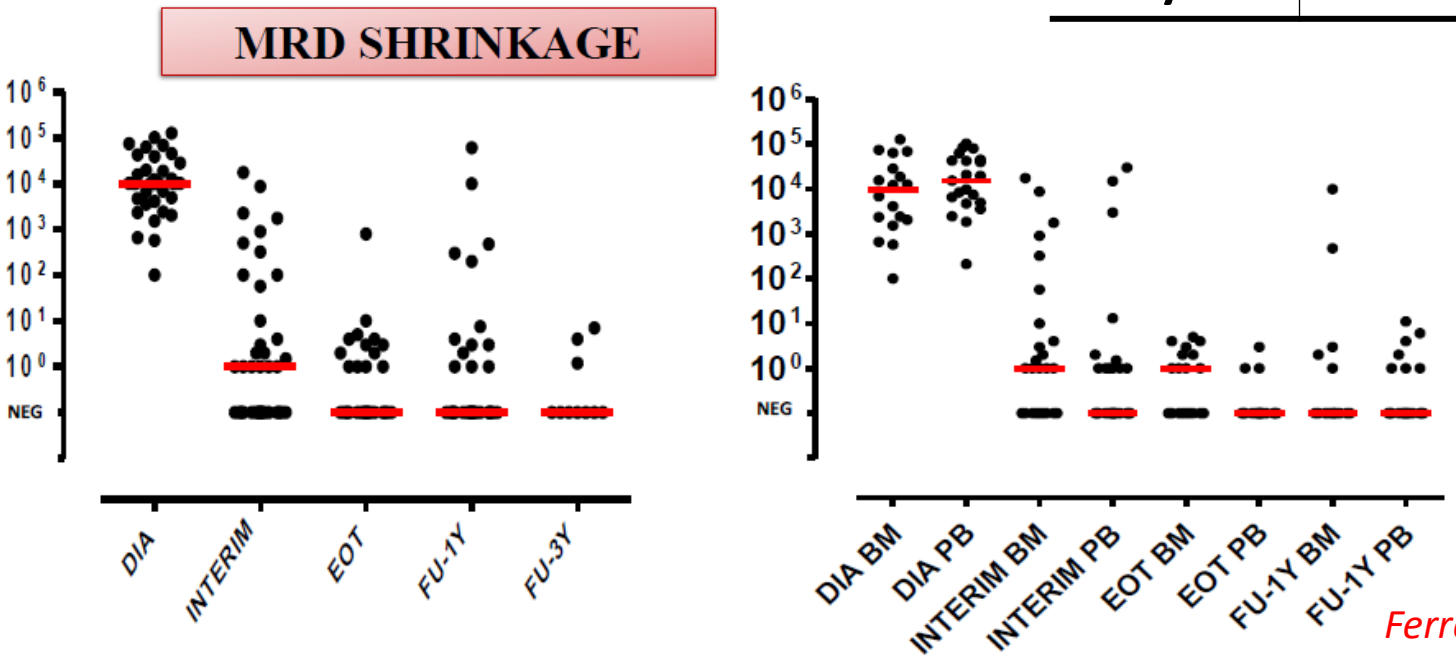

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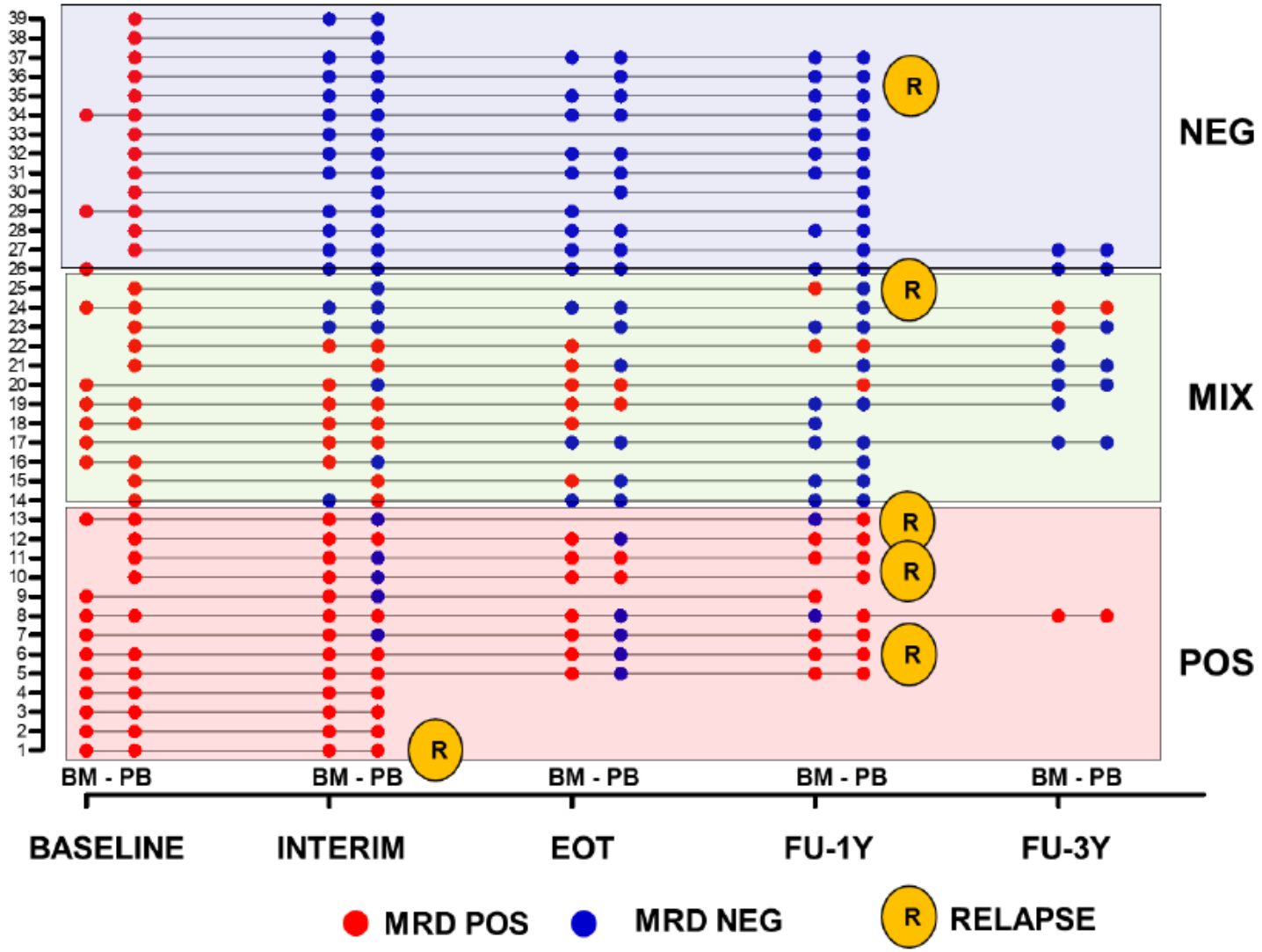

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