Marginal Zone Lymphomas. Prognostic Models

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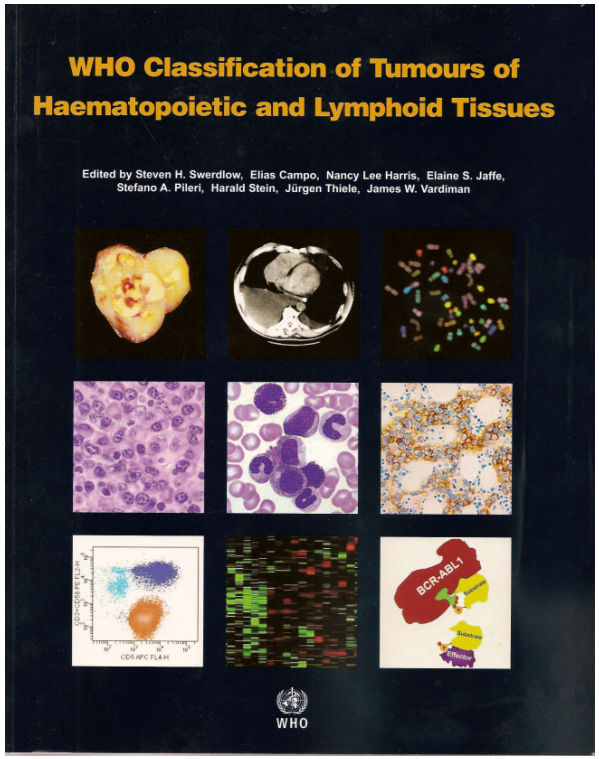
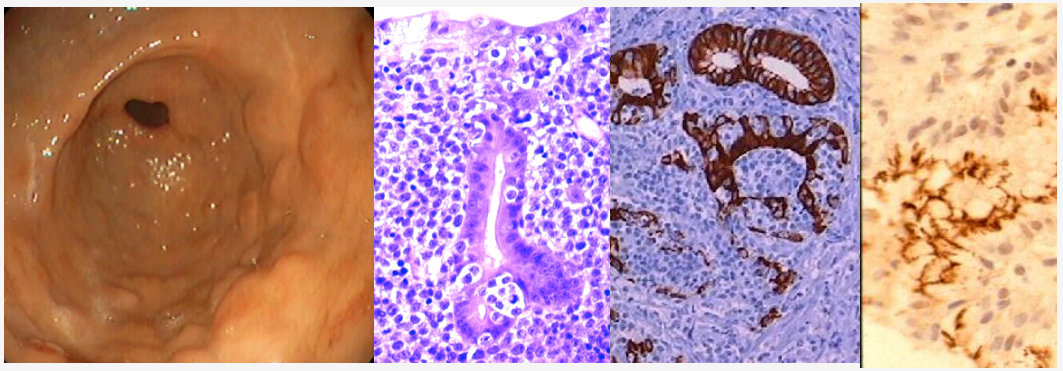


Histological types of MALT Lymphoma (WHO 2008,2016)

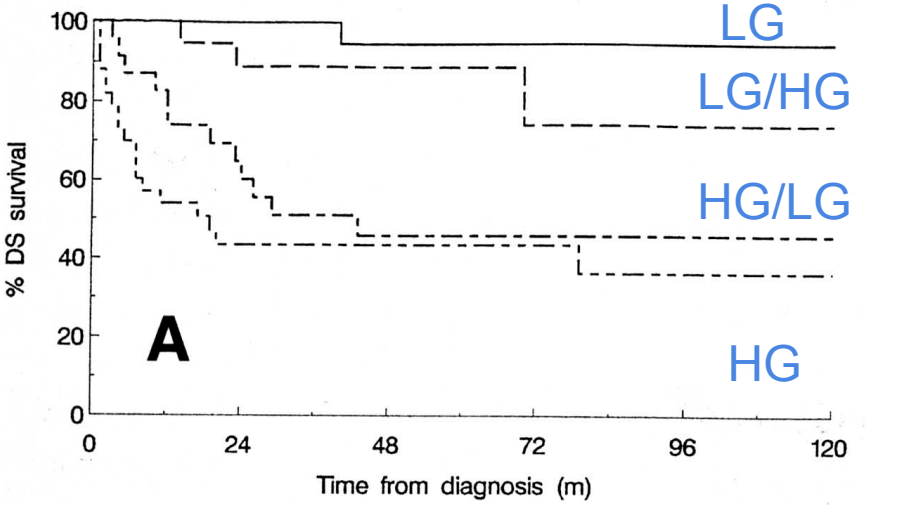
- MALT
- NMZL
- SMZL

Archeology of MALT Lymphoma:

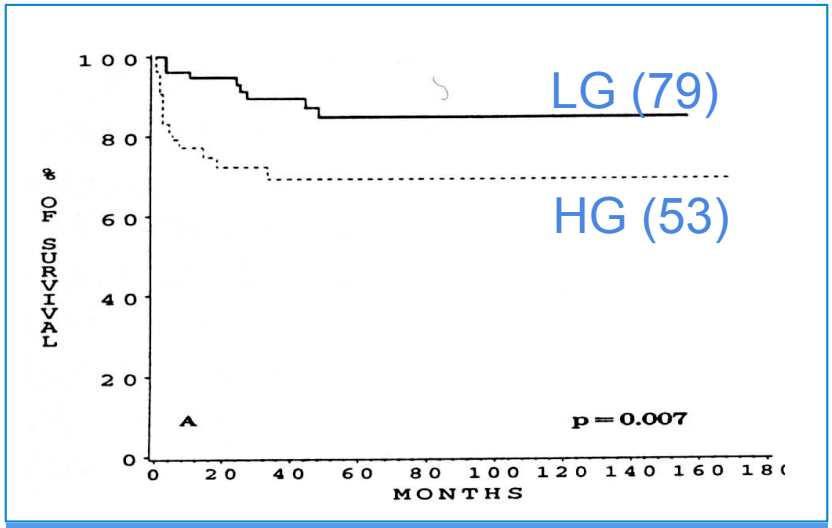
Practically only gastric MALT Lymphoma existed



Prognostic factors in the early days of Gastric MALT Lymphoma: **Stage and HG component**



De Jong. Gastroenterology, 97;112;1466



Montalban. Ann Oncol,95:6:355

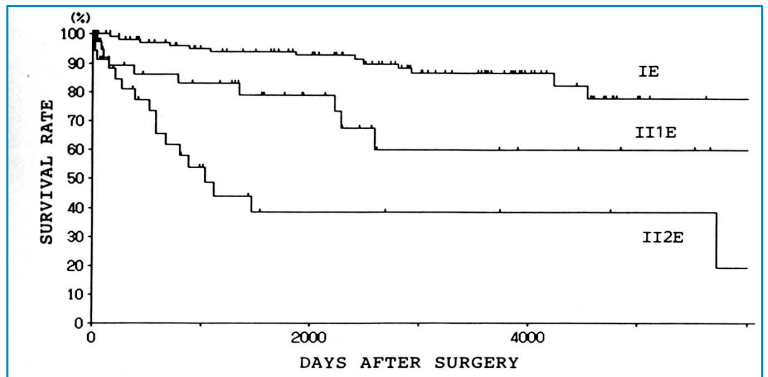


Figure 9. The survival curves of 199 patients with primary gastric lymphoma according to disease stage (log rank test, $P < 0.001$).

Nakamura. Cancer,1995;76;1313

Prognostic factors in the early days of Gastric MALT Lymphoma. Gastric MALT Lymphoma (LG/HG) in the Spanish series, 132 patients: **LDH, IPI, stage, treatment and response**

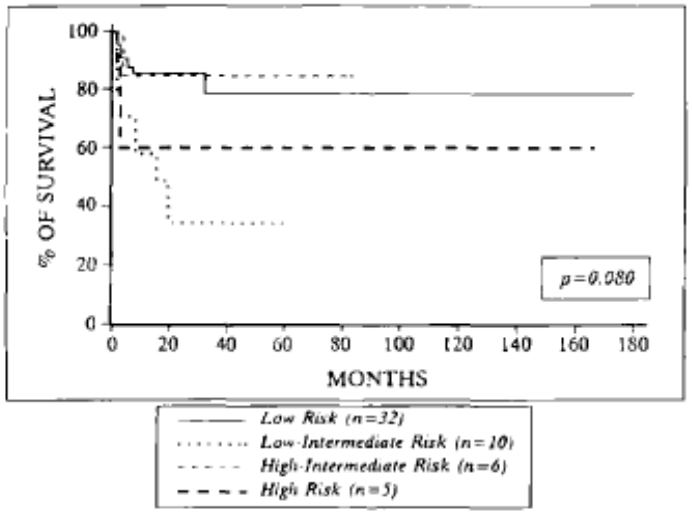


FIGURE 1 Survival of patients with high grade gastric MALT lymphoma according to the risk groups of the Modified International Prognostic Index.

The Modified IPI. Castrillo, Leukemia&Lymphoma,1996:24;159

Table 3. Factors influencing five-year survival in 132 treated and followed-up patients with gastric MALT lymphoma.

	n = 132	5-Year survival	CI 95%	p
Age				
≤60 Years	75	0.80	0.686–0.883	
>60 Years	57	0.76	0.599–0.864	0.732
LDH				
Elevated	20	0.50	0.271–0.691	
Normal	112	0.83	0.737–0.902	<0.001
Remission[a]				
Complete	108	0.94	0.870–0.980	
Partial	8	0	[b]	
No remission	15	0	[b]	<0.001
Grade				
Low-grade	79	0.84	0.721–0.919	
High-grade	53	0.69	0.537–0.804	0.007
Stage				
$I–II_{E1}–II_{E2}$	105	0.90	0.824–0.946	
III–IV	27	0.39	0.195–0.594	<0.001
Treatment[c]				
Surgery	49	0.91	0.796–0.968	
Chemotherapy	28	0.47	0.245–0.669	
Surgery + chemo-therapy	53	0.85	0.712–0.928	<0.001

Montalban, Ann Oncol, 1995:6:355

Prognostic influence of clinical factors in gastric and non-gastric MALT Lymphomas: **Site, IPI & Stage**

- Advanced Stage
- >60y or >64y
- B symptoms
- Nodal involvement
- Non-conjuctival sites
- >LDH

OAL(Revised in Decaudin, Blood 2006;108;1451)

- 247 pts.
- **IPI**

Salivary gland MALT. Jackson. The Oncologis, ;2015;20;1

- 180 patients
- Different treatments.
- **Stage**
- Nodal involvement
- **IPI**

: Mucosal+BM, Worst

Nongastric MALT Lymphoma. Zucca, Blood 2003;101;2489

- 75 pts.
- >LDH
- **IPI**
- **Lugano I-II$_2$ vs ≥II$_E$**

Gastric lymphoma. Wang. Medicine 2016;95;e4250

- 75 patients
- Different treatments.
- Outcome
  Thyroid, Better
  Mucosal+BM, Worst

Nongastric MALT Lymphoma. Zinzani JCO, 1999;17;1254

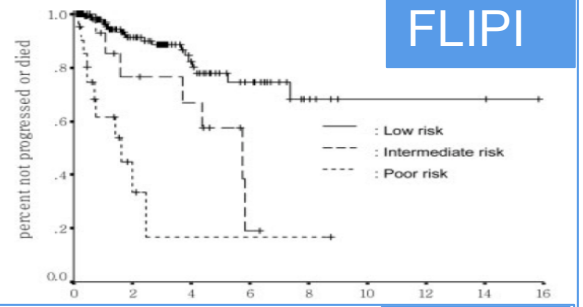
Key Questions

- Are different (or the same) factors playing in different sites?
- Retrospective studies
- Heterogenous treatments
- How to apply IPI (or FLIPI, or the Modified IPI & others) to Extranodal lymphomas?
- MALT is a different biological situation of FL/DLBCL: are IPI or FLIPI adequate??

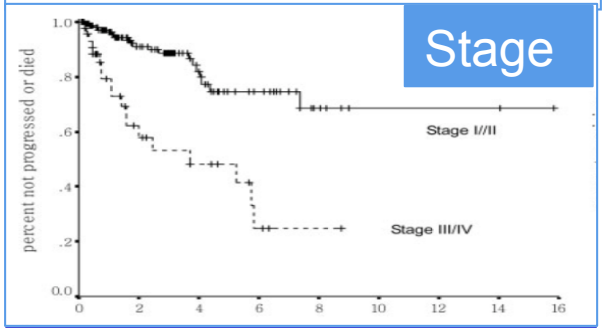
Prognostic clinical factors and FLIPI in non-gastric MALT and NMZL. PFS according to FLIPI

MZL 5y PFS according to Stage or FLIPI

FLIPI



Stage



96 ExtNMZL,
(+32 NMZL,16 SMZL)
Different Treatments

Heilgeist,
Cancer 2013;119:99

TABLE V. Analysis of Prognostic Factor for PFS and OS

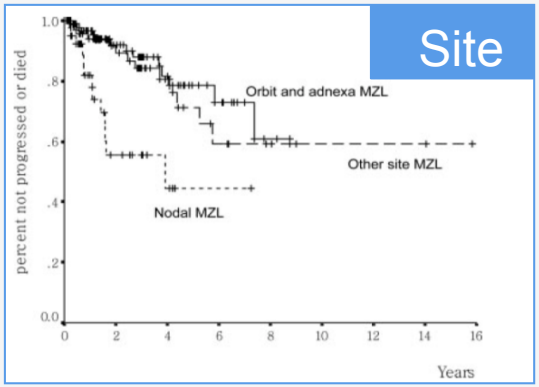
	PFS		OS	
Feature	Univariate	Multivariate	Univariate	Multivariate
Male	NS	–	NS	–
Age > 60	<0.001	NS	0.006	NS
B symptom (+)	NS	–	<0.001	NS
LDH > normal	NS	–	NS	–
Hemoglobin < 12 g/dl	0.001	0.036	NS	–
HCV Ab(+)	NS	–	NS	–
Nodal MZL	<0.001	0.004	NS	–
Bulky mass ≥ 10 cm	NS	–	NS	–
Bone marrow involvement	<0.001	NS	<0.001	NS
ECOG performance ≥ 2	0.002	0.039	0.002	0.003
Stage III/IV	<0.001	0.001	<0.001	0.006

Values in the table indicate *P*-value.
PFS, progression free survival; OS, overall survival; LDH, lactic dehydrogenase; HCV Ab, Hepatitis C virus antibody; MZL, marginal zone B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group.

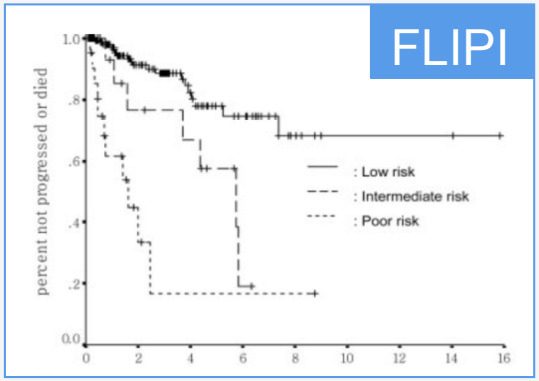
Oh, Am J Hematol, 2007;82;446

203 Extranodal nongastric
(+ 44 NMZL)

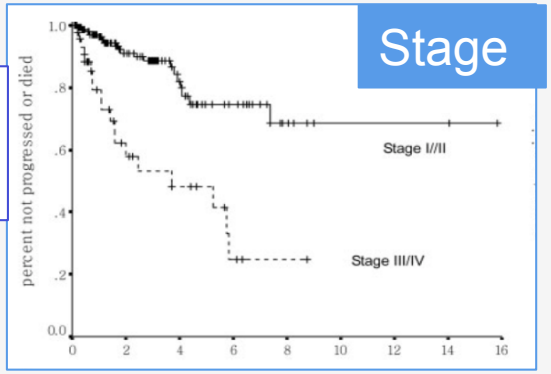
Site



FLIPI



Stage



Prognostic influence of clinical and biological factors in gastric&extragastric MALT Lymphomas

- >Treg FOXP3+ (**Gastric**): Better outcome [1]
- No impact of cytogenetics (**Gastric and Extra-gastric**)[2].
- Primary site: Non-gastric have a higher frequency of relapse [2].
- t(11;18) : (**Gastric**) - Resistance to H.pylori eradication [3,4]
  - Better outcome [3,4]
  - Long term persistance of residual population [5]
  - Resistence to Alkylating agents [6]Levy
  - Resistance to Rituximab (not to R-Chem).[7]
- HCV (**non-Gastric**) indolent course [8]
- More advanced disease,more aggresive bahavior , frequent systemic relapses (**OAL**)[9]
- Treatment with RadTX. (**OAL**) Age>60y and RT<30.6Gy [10]
- Expression of CagA /CagA signalin molecules predicts H.pylory dependence in early **gastric** DLBCL [11]

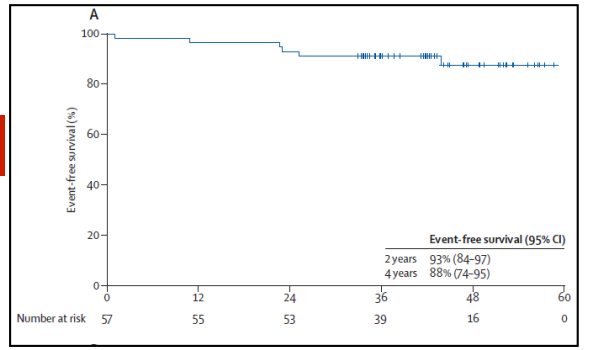
1. Garcia, Plos/one2012:7;e51681
2. Raderer Clin Cancer Res 2005;11;3349
3. Liu, Lancet;2001,357;39
4. Gastroenterology 2001;122;1286
5. Montalban, Leuk & Lymphoma, 2008;49;1561
6. Levy JCO 2005;23;5061
7. Levy 2. Leuk & Lymphoma, 2013;54:940
8. Arcaini, Ann Oncol, 2006;18;350
9. . Ferreri. Ann Oncol, 2006;17;769
10. Desai, Blood, 2017;129;324
11. Kuo S. Blood, 2017;129:188

The new era in MALT lymphomas: Prospective studies, homogeneous and effective treatments.

First-line response-adapted treatment with the combination of bendamustine and rituximab in patients with mucosa-associated lymphoid tissue lymphoma (MALT2008-01): a multicentre, single-arm, phase 2 trial

Lancet Haematol, 2014:1:e104

Antonio Salar, Eva Domingo-Domenech, Carlos Panizo, Concepción Nicolás, Joan Bargay, Ana Muntañola, Miguel Canales, José Luis Bello, Juan Manuel Sancho, José Francisco Tomás, María José Rodríguez, Francisco Javier Peñalver, Carlos Grande, José Javier Sánchez-Blanco, Luis Palomera, Reyes Arranz, Eulogio Conde, Mar García, Juan Fernando García, Dolores Caballero, Carlos Montalbán, for the Grupo Español de Linfomas/Trasplante de Médula Ósea (GELTAMO)



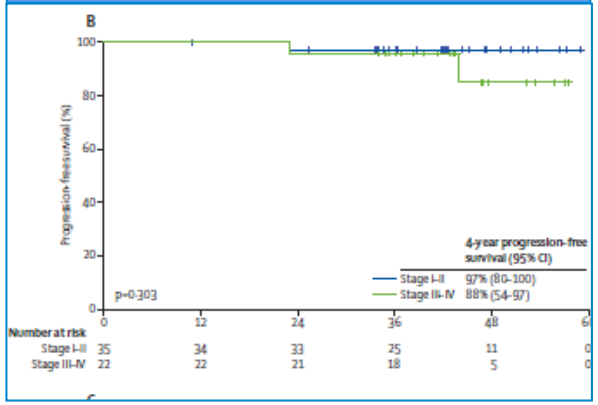
	After three cycles			At end of treatment		
	Complete response*	Partial response	Overall response	Complete response*	Partial response	Overall response
Age						
≤60 (n=25)	20 (80%)	5 (20%)	25 (100%)	24 (96%)	1 (4%)	25 (100%)
>60 (n=32)	23 (72%)	9 (28%)	32 (100%)	32 (100%)	0	32 (100%)
Ann Arbor Stage						
I–II (n=35)	27 (77%)	8 (23%)	35 (100%)	35 (100%)	0	35 (100%)
III–IV (n=22)	16 (73%)	6 (27%)	22 (100%)	21 (95%)	1 (5%)	22 (100%)
Primary extranodal site						
Gastric (n=19)	18 (95%)	1 (5%)	19 (100%)	19 (100%)	0	19 (100%)
Non-gastric (n=32)	20 (63%)	12 (38%)	32 (100%)	32 (100%)	0	32 (100%)
Multifocal (n=6)	5 (83%)	1 (17%)	6 (100%)	5 (83%)	1 (17%)	6 (100%)
Transloction t(11;18)						
Negative (n=44)	32 (73%)	12 (27%)	44 (100%)	43 (98%)	1 (2%)	44 (100%)
Positive (n=9)	8 (89%)	1 (11%)	9 (100%)	9 (100%)	0	9 (100%)
Unknown (n=4)	3 (75%)	1 (25%)	4 (100%)	4 (100%)	0	4 (100%)

*Complete response includes unconfirmed complete response.

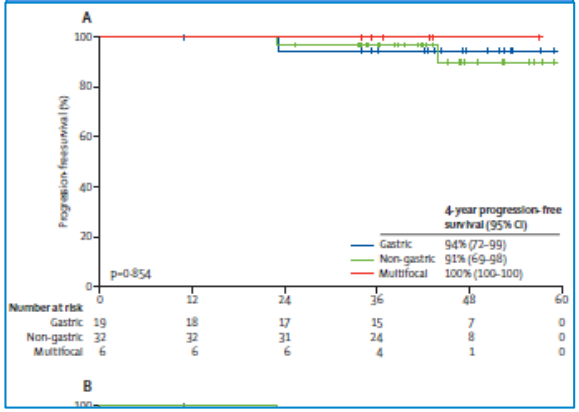
Table 2: Treatment response to bendamustine plus rituximab

- MALT Lymphoma (n=60)
- First line
- Any stage & Any site
- R/B Response-adapted: 4-6 cycles
  - RC 75% with only 4 cycles
  - RC 95-100% 4-6 cycles
- Active in all sites & stages
- No effect of t(11;18)

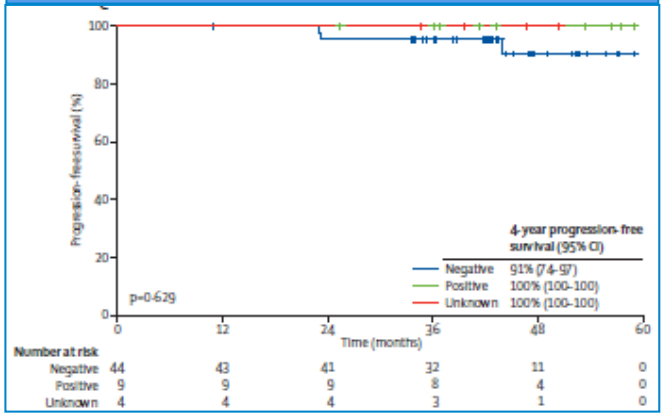
Stage I-II vs. III-IV



Gastric vs. non-G



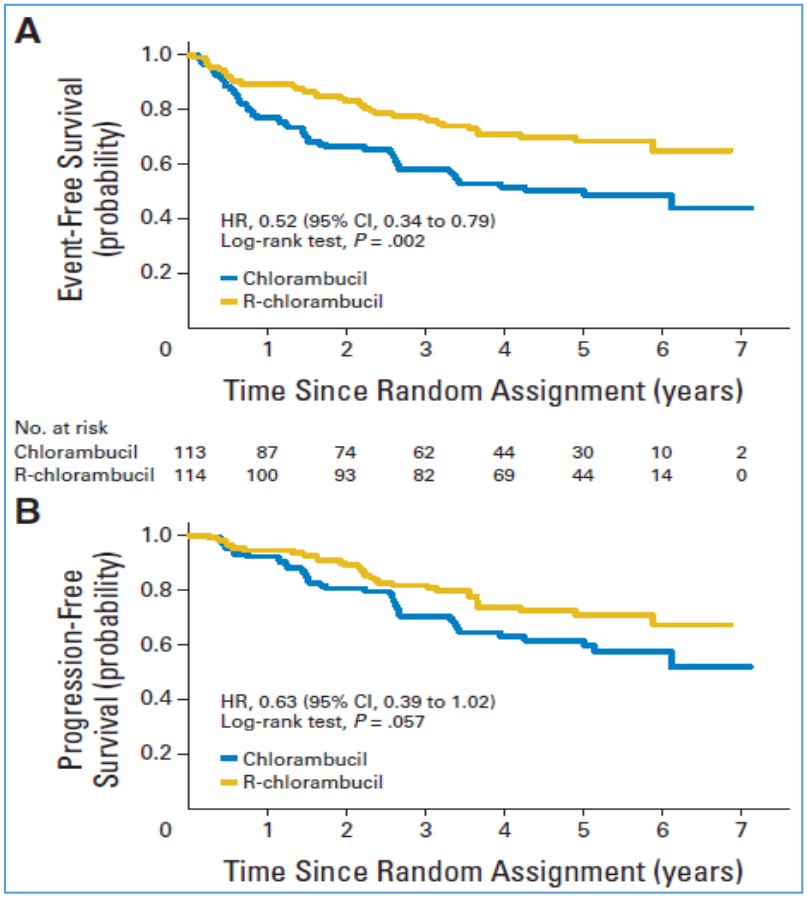
t(11;18) Neg vs. Pos



Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study

Emanuele Zucca, Annarita Conconi, Daniele Laszlo, Armando López-Guillermo, Reda Bouabdallah, Bertrand Coiffier, Catherine Sebban, Fabrice Jardin, Umberto Vitolo, Franck Morschhauser, Stefano A. Pileri, Christiane Copie-Bergman, Elias Campo, Andrew Jack, Irene Floriani, Peter Johnson, Maurizio Martelli, Franco Cavalli, Giovanni Martinelli, and Catherine Thieblemont

Zucca, JCO;2013;31;565 2015



Significant Prognostic Factors

- **IPI (MV)**
- **Treatmet arm (MV)**
- **>60y (UV)**
- **Bone Marrow + (UV)**
- **Stage III/IV (UV)**

Non-Significant Prognostic Factors

- Nodal Involvement **(MV)**
- Prior local therapy **(MV)**
- Primary non-gastric sites **(MV)**
- Sex (UV)
- PS≥2(UV)
- B symptoms(UV)
- >LDH(UV)

A simple and effective MALT Lymphoma: specific prognostic index generated from the database of the IELSG-19 controlled clinical trial. Thieblemont et al. 13 ICML. Lugano 2015 #124

393 patients. M FU 67 months	
Gastric	43%
Lymph Node inv.	34%
>LDH	10%
> Stage II	44%

Significant Factors
• **Age>70 y**
• **>LDH**
• **Stage> II**
Non-Significant factors
• PS
• Gastric vs non-gastric
• Nodal involvement
• >1 extranodal site

Exploratory analysis on the main study endpoint (EFS)

Generation of a MALT lymphoma-specific prognostic model

Cox regression

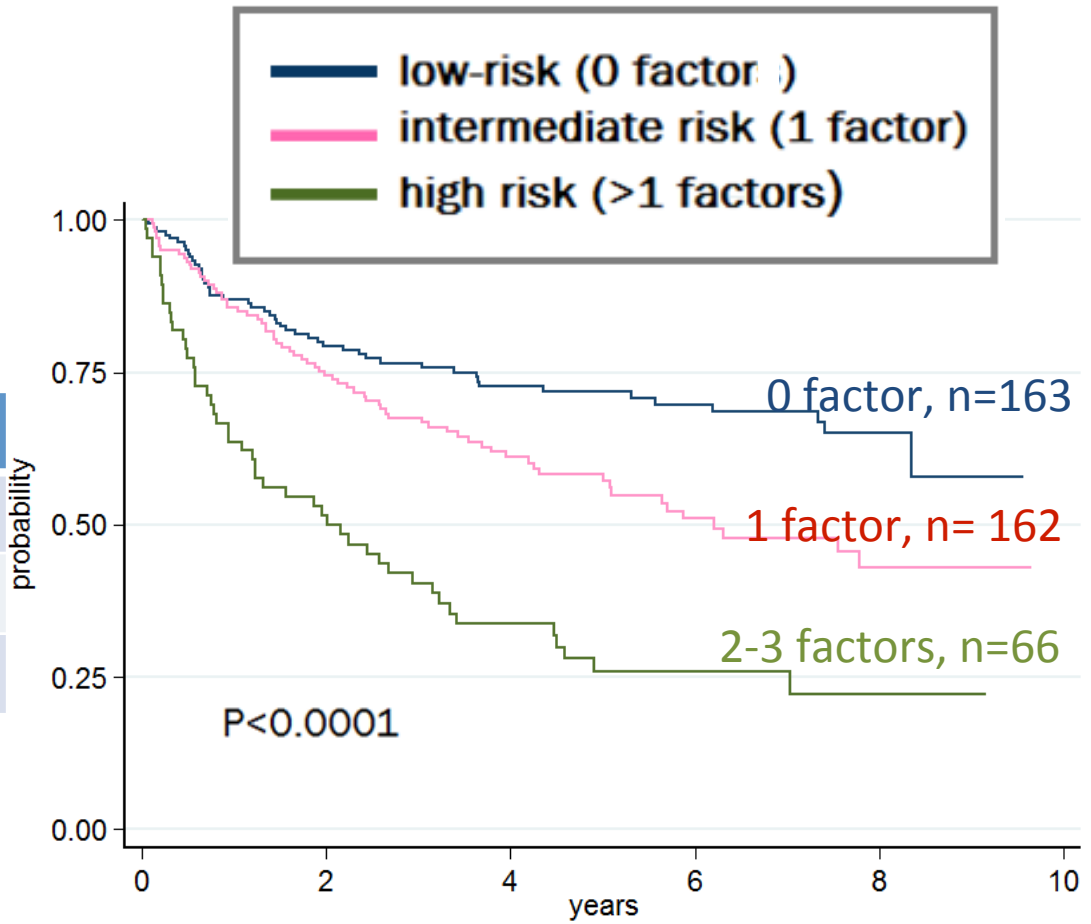
Backward selection using a p<0.05 cut-off

No. of subjects = 391 No. of failures = 168

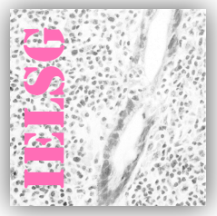
LR chi2(3)= 37.47 Log likelihood = -912.25 Prob > chi2 = 0.0000

_t	HR	P>|z|	95% C.I.
LDH>N	1.702	0.014	1.111 - 2.608
AGE>70	1.832	0.000	1.324 - 2.535
STAGE>2	1.927	0.000	1.419 - 2.617

N Factors	5y EFS (%)	5y OS (%)
0	78	99
1	63	94
>1	29	74

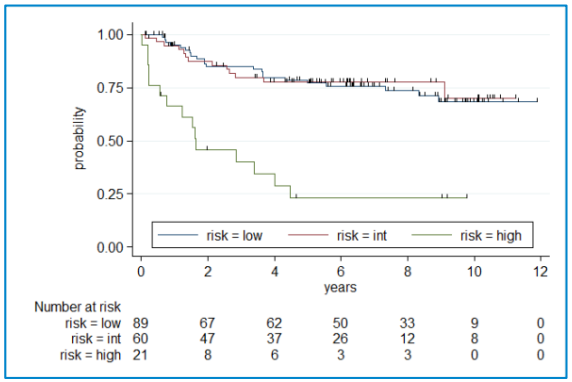


By courtesy of Dr. C. Thieblemont

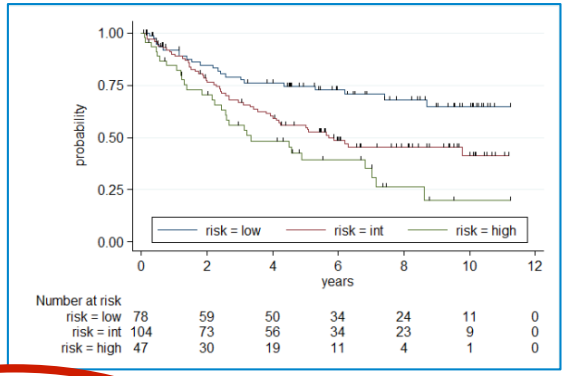


PFS by MALT prognostic score

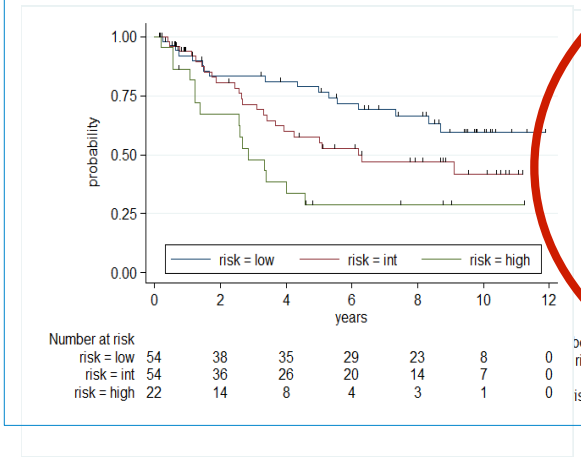
Gastric MALT



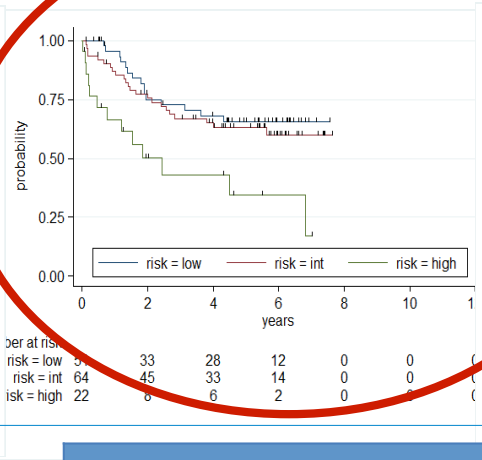
Non-gastric MALT



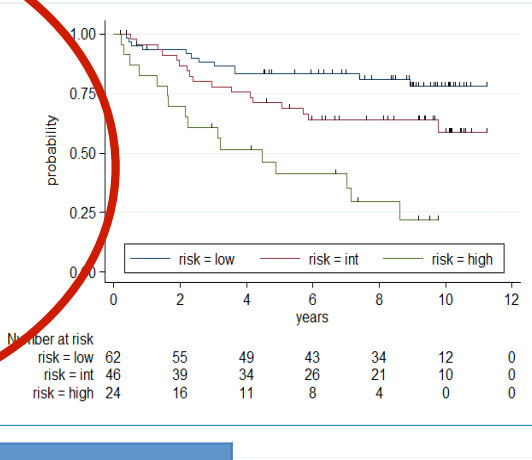
Chlorambucil arm



R-Chlorambucil arm



Rituximab arm



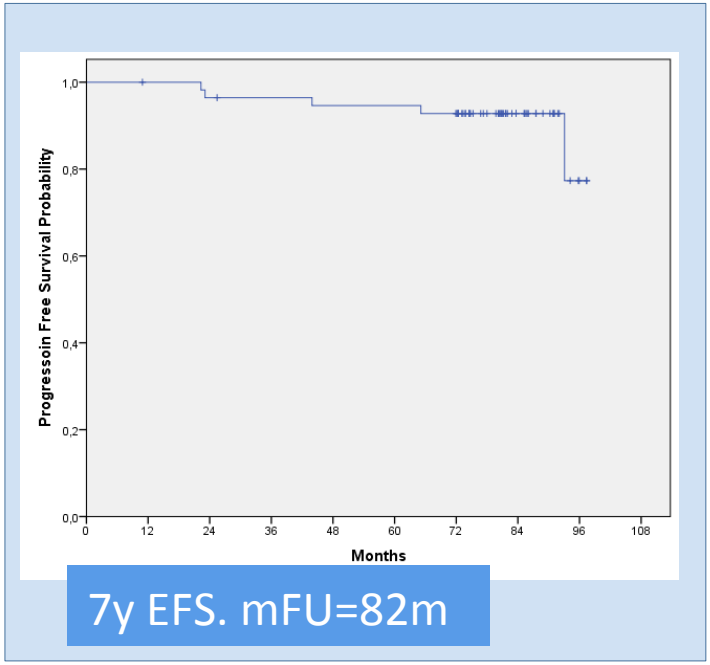
Endpoint	Harrel's C	
	MALT PS	IPI
EFS	0.61	0.58
PFS	0.62	0.61
CSS	0.84	0.76
OS	0.78	0.71

Comparison of MALRPS and IPI

By courtesy of Dr. C. Thieblemont

Long-term results of the Multicenter Phase II Trial with Bendamustine and Rituximab as First Line Treatment for Patients with MALT Lymphoma (MALT-2008-01) (EUDRACT 2008-007752-39). ICML 2017

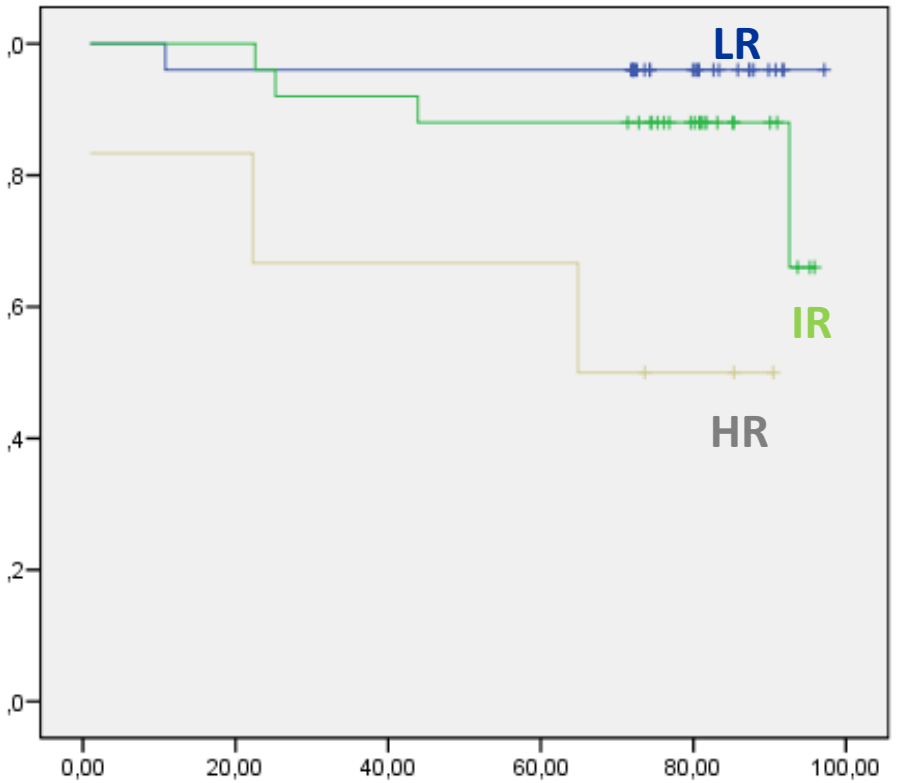
Prognostic effect of the MALT Score



7y EFS. mFU=82m

RF (n)	N (%)	EFS 7y	PFS 7y	OS 7y
0	25 (44.6)	96	100	96
1	25 (44.6)	68	73	77
>1	6 (10.7)	50	67	100

EFS at 7 years. FU 82 months.

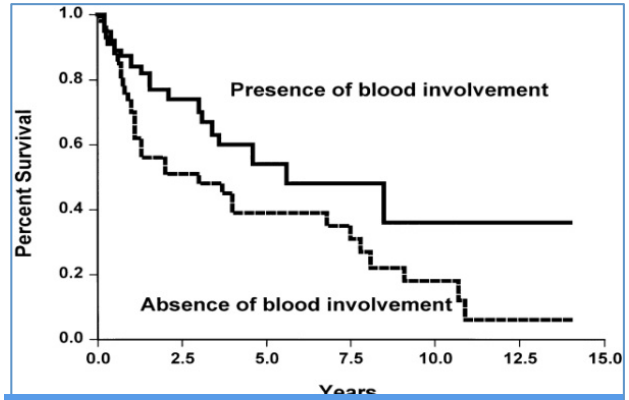


Global p=0.050

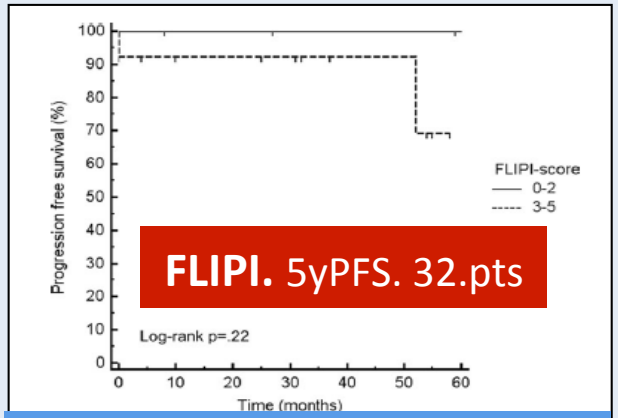
NMZL Factors with prognostic influence in published studies

- Age>60
- Male
- >LDH
- Hgb<12g/dl
- BM+
- ECOG≥2
- Stage III/IV
- B symptoms
- FLIPI 3-5
- HCV
- Survivin
- Caspase 3
- Cyclin E
- Ki67
- IRF4

Revised in Thieblemont, Blood 2016



NMZL. Berger, Blood, 2000



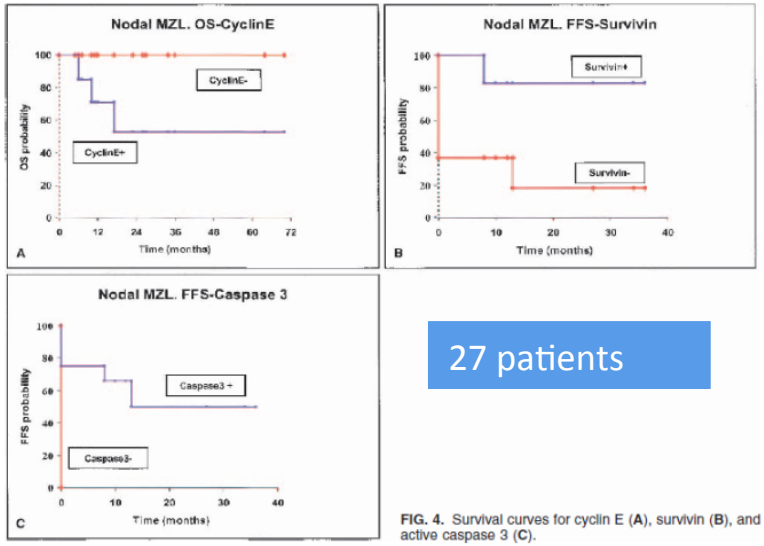
FLIPI. 5yPFS. 32.pts

Heilgeist et al. Cancer 2013;119:99

TABLE 7. *Prognostic relevance of immunohistologic markers*

	FFS	OS
CD5	NS	NS
CD43	NS	NS
CD23	NS	NS
CD38	NS	NS
IgD	NS	NS
Cyclin A	NS	NS
Cyclin B	NS	NS
Cyclin D3	NS	NS
Cyclin E	NS	p = 0.03
MUM1	NS	NS
Pax5	NS	NS
Survivin	p = 0.04	NS
Caspase 3 active	p = 0.04	NS
MIB1	NS	NS

NS, not significant; FFS, failure-free survival; OS, overall survival.



27 patients

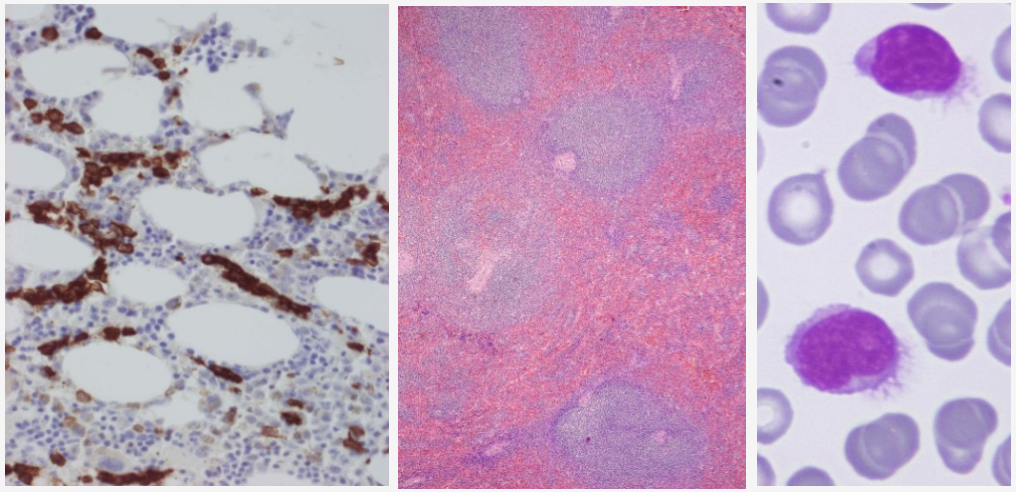
FIG. 4. Survival curves for cyclin E (A), survivin (B), and active caspase 3 (C).

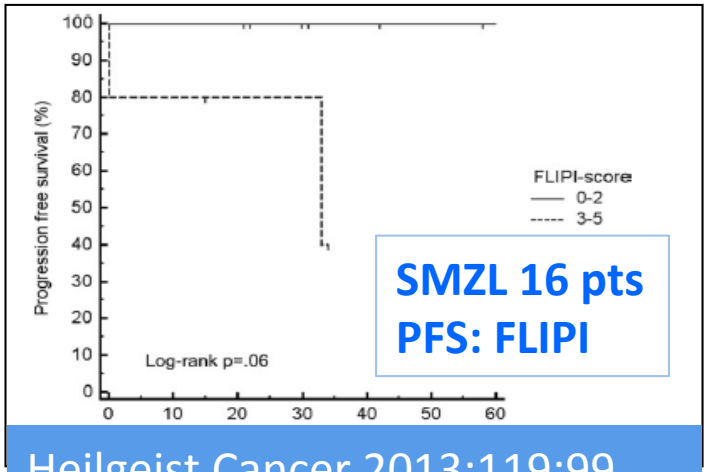
Camacho, Am J Surg Pathol, 2003:27;762

NMZL Factors with prognostic influence in published studies

- No valid prognostic models
- Only isolated factors
- Series with few cases (27-47)
- Heterogeneous treatments
- Different factors in the series
- Factors influencing PFS or OS
- Low statistical significance

SMZL: Problems in the evaluation of prognostic factors





Heilgeist Cancer 2013;119:99

- No established criteria for starting treatment
- No standard treatment
- Treatments in diferent clinical situations
- Diagnostic splenectomy: diagnostic, but also a form of treatment
- Some studies in only splenectomized patients
- Studies with treated and non treated patients
- Large number of patients and events (relapse, death, etc) are required to get consistent results.
- IPI & FLIPI are not adequate (most stage IV)

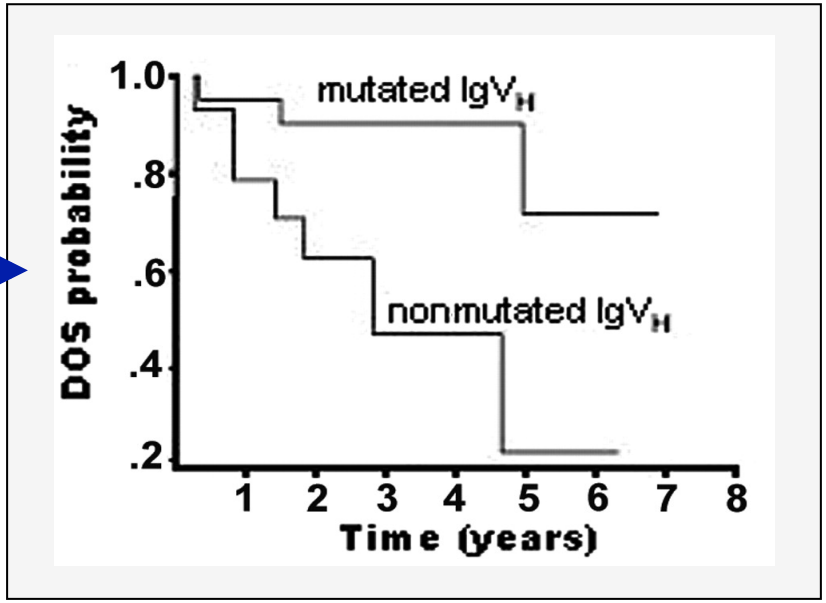
Clinical prognostic factors: Not Consistent

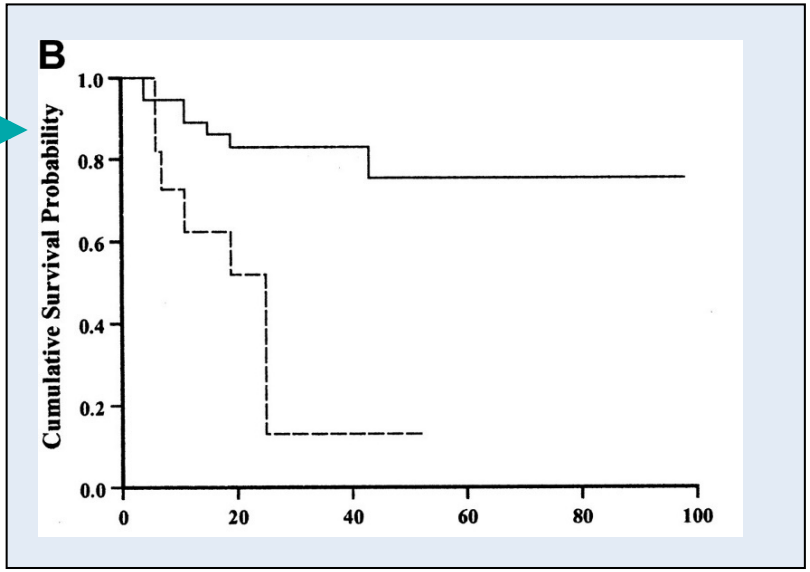
- Lymphocitosis >16.000-30.000/mm^3 (1)
- Monoclonal spike(3)
- > β2 microglobulina(3)
- Active immunologic complications (3)
- Extranodal Involvement (6)
- Lymphadenopathy? (6)
- **Anemia** (1,2,4,7)

(1) Parry-Jones. Br J. Haematol, 2003;120;75
(2) Arcaini , Cancer:2004;100;107
(3) Thieblemont, Lancet Oncol,2003;4;95
(5) Troussard, Br J Haematol, 1996;93:731
(6) Chacon, Blood,2002;100;1648
(7) Salido, Blood, 2010

Biological prognostic factors: Not consistent

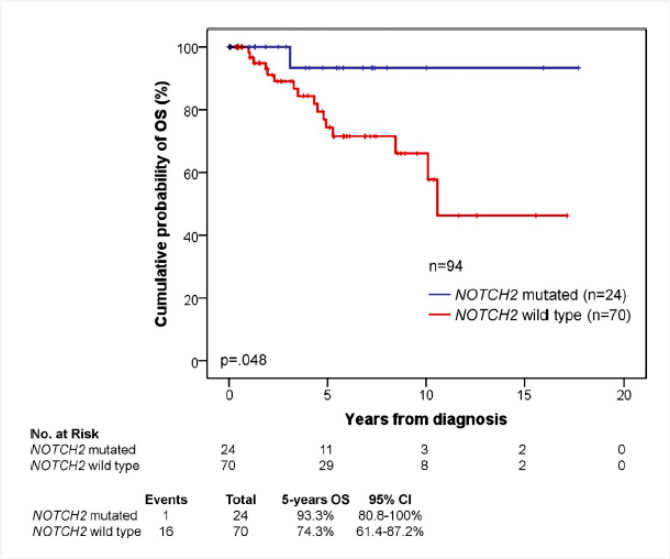
- Unmutated IgV_H (1,2,3,5)
- 7q- (1)
- Ki 67(2)
- CD38+ (2)
- Genes of NF-kB pathway(1)
- P53 alterations (3,5)





(1) Algara, 2002;99;1299
(2) Ruiz Ballesteros, Blood ,2005;106;1831
(3) Gruszka, Blood;2001;97;3552
(4) Chacon, Blood,2002;100;1648
(5) Hockley, BJH, 012;158;347

SMZL: Influence of NOTCH2 mutations in the outcome of SMZL: Contradictory results

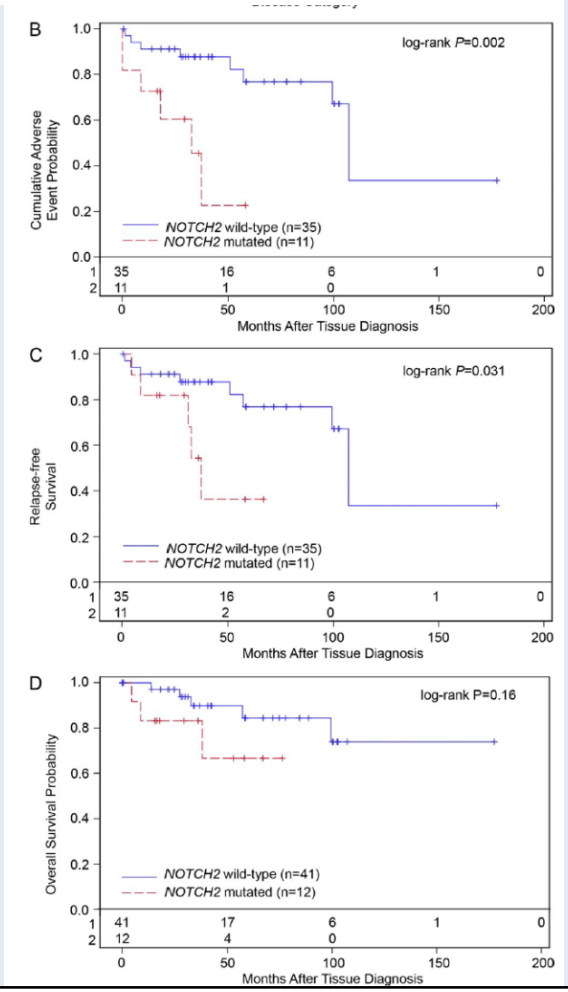


The coding genome of splenic marginal zone lymphoma: activation of *NOTCH2* and other pathways regulating marginal zone development

Rossi. JAM, 2012;209:9:1537

Whole-genome sequencing identifies recurrent somatic *NOTCH2* mutations in splenic marginal zone lymphoma

Kiel. JAM, 2012;209:9:1553



Prognostic effects of Cytogenics in SMZL

Cytogenetic aberrations and their prognostic value (330 pts).

Salido et al. Blood, 2010,116;1497

- 7q -, no effect
- UniV: 2 cytogenetic aberrations, TP35 delection, 14q aberrations, 14q del
- Multivariate study: No cytogenetic factor. **Only Anemia and age**

High-resolution genome-wide array comparative genomic hybridization in splenic marginal zone B-cell lymphoma.

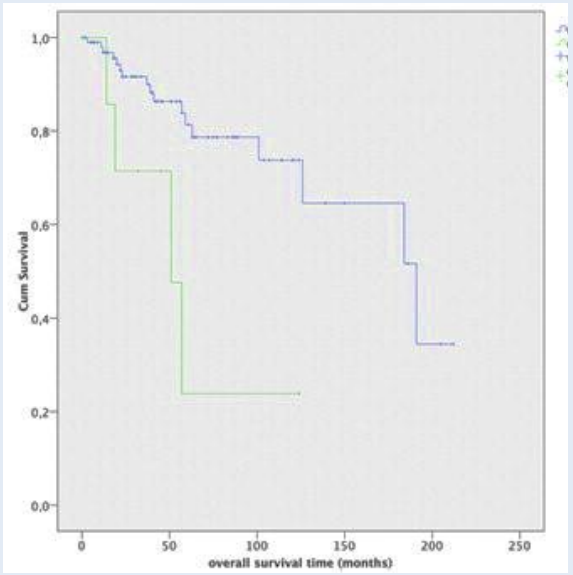
Novara et al. Human Pathology 2009;40;1628

- ILI high risk group associated with del(7q) and del(17p)

Genome-wide DNA profiling

Rinaldi et al. Blood,2011;117;1595

- del(8p) only (P = .068),
- del(17p) only (P = .256),
- del(8p) plus del(17p) (P = .004)



Clinical Cancer Research

2015:21:4174

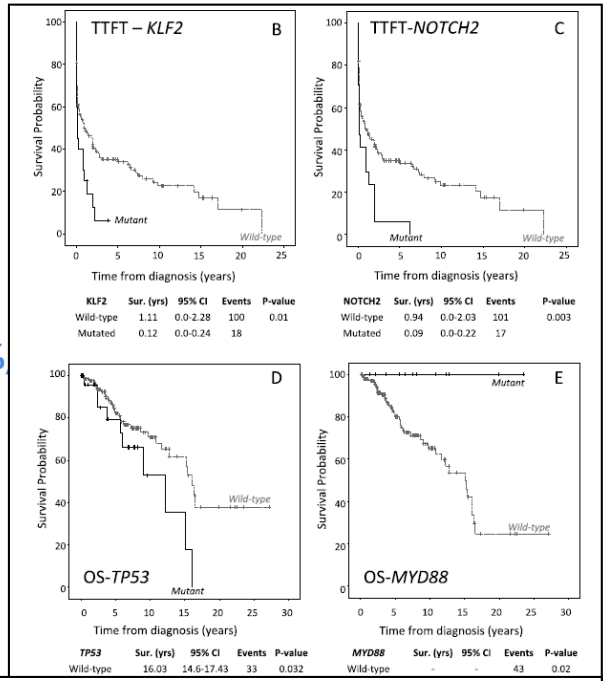
Genetics and Prognostication in Splenic Marginal Zone Lymphoma: Revelations from Deep Sequencing

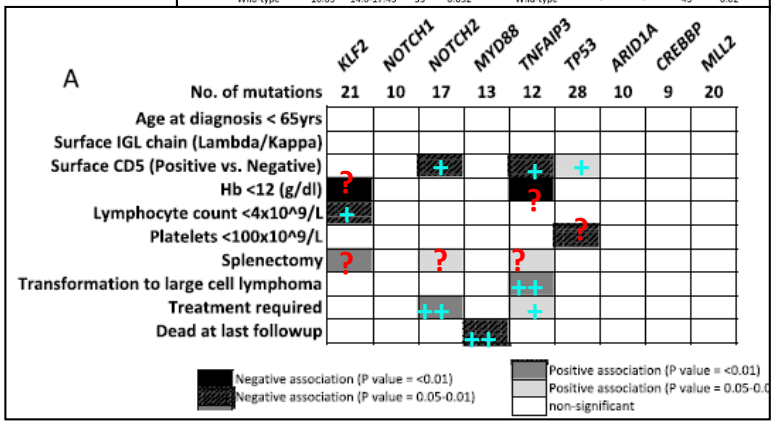
Marina Parry, Matthew J Rose-Zerilli, Viktor Ljungström, et al.

175 patients. Recurrent mutations in TP53 (16%), KLF2 (12%), NOTCH2 (10%, TNFAIP3 (7%) MLL2 (11%), MYD88 (7%), ARID1A (6%)

Table 3: Multivariate survival analysis of recurrently mutated genes

Variable	TTFT		
	HR	95% CI	P-Value
Hb<12g/dl	2.28	1.32-3.96	0.003
IGHV 100% identity	2.19	1.05-4.55	0.036
NOTCH2	2.12	1.02-4.40	0.044
	EFS		
	HR	95% CI	P-Value
Plts<100x10^{9}L	3.75	1.68-8.41	0.001
Lymphocytes <4x10^{9}L	0.41	0.17-0.96	0.04
Age at diagnosis <65yrs	0.45	0.21-0.96	0.038
	OS		
	HR	95% CI	P-Value
Hb<12gdl	2.18	1.12-4.23	0.02
Lymphocytes <4x10^{9}L	2.35	1.11-4.97	0.03
Age at diagnosis <65yrs	0.09	0.03-0.27	<0.001
TP53	2.36	1.08-5.20	0.03

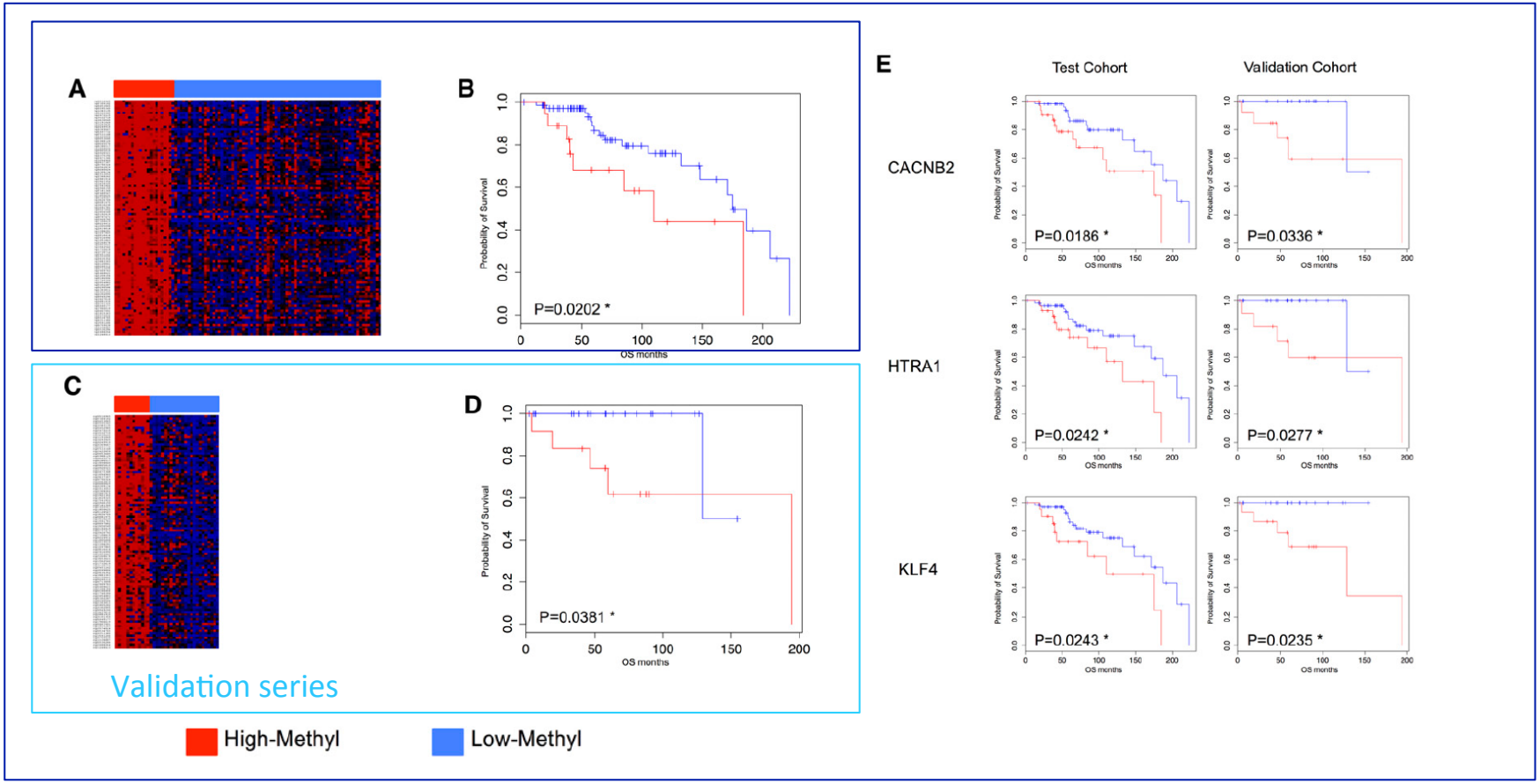




- Mutation have different effect in closely related end points???
- Heterogeneous population and treatments
- Problems with the endpoints:
  - Criteria for starting treatment are not uniform
  - Heterogeneous treatment
  - TTFT and EFS depends of criteria for treatment
- **No conclusive or practical data**

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

Alberto J. Arribas,[1] Andrea Rinaldi,[1] Afua A. Mensah,[1] Ivo Kwee,[1,2] Luciano Cascione,[1,3] Eloy F. Robles,[4] Jose A. Martinez-Climent,[4] David Oscier,[5] Luca Arcaini,[6] Luca Baldini,[7] Roberto Marasca,[8] Catherine Thieblemont,[9] Josette Briere,[9] Francesco Forconi,[10,11] Alberto Zamò,[12] Massimiliano Bonifacio,[12] Manuela Mollejo,[13] Fabio Facchetti,[14] Stephan Dirnhofer,[15] Maurilio Ponzoni,[16] Govind Bhagat,[17] Miguel A. Piris,[18] Gianluca Gaidano,[19] Emanuele Zucca,[3] Davide Rossi,[19] and Francesco Bertoni[1,3] (*Blood*. 2015;125(12):1922-1931)



- Methylation profiling identifies groups with different biological features and outcome
- High-M phenotype is asociated with IGHV1-02 usage, 7q- and transformation
- A model based on methiyation of 3 genes (CACNB2, HTRA1, KLF4) identifies a poor suvival group
- Demethylating agents (Azazitidine) can reverse adeverse alterations

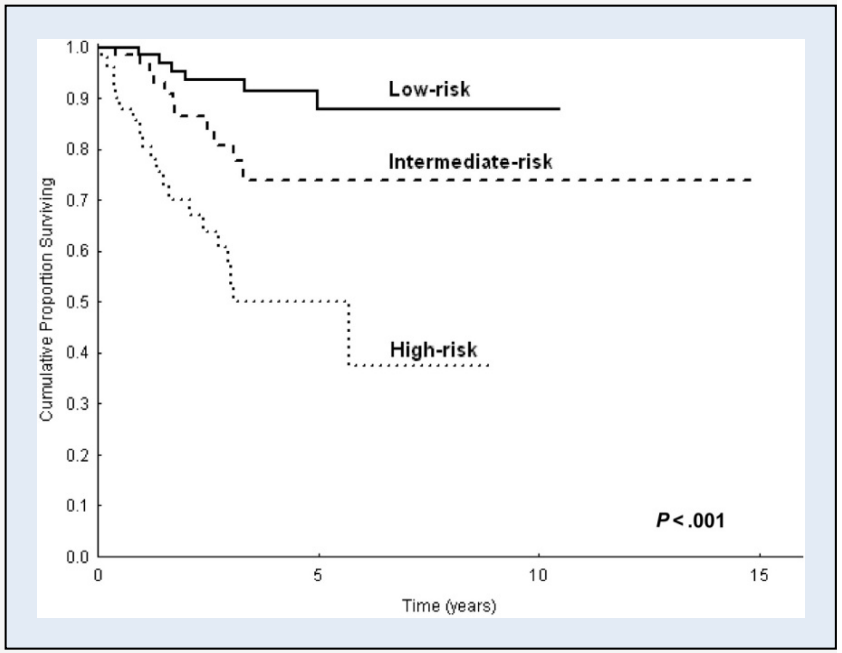
SMZL. IIL Prognostic groups.

Arcaini et al. Blood, 2006;107;4643

- 309 patients
- IIL prognostic factors:

  Hgb<12gr/dl; Albumin <3.5 gr/dl; >LDH

- 3 risk groups with **LSS** at 5 years
  - **LR (1 factor) 88%**
  - **IR (2 factors) 73%**
  - **HR (3 factors) 50%**



- HR group
  - 53% of lymphoma related deaths
  - del(7q) and del(17p)

SMZLSG Score Project.

Montalban & SMZLSG. BJH 2012;159:164

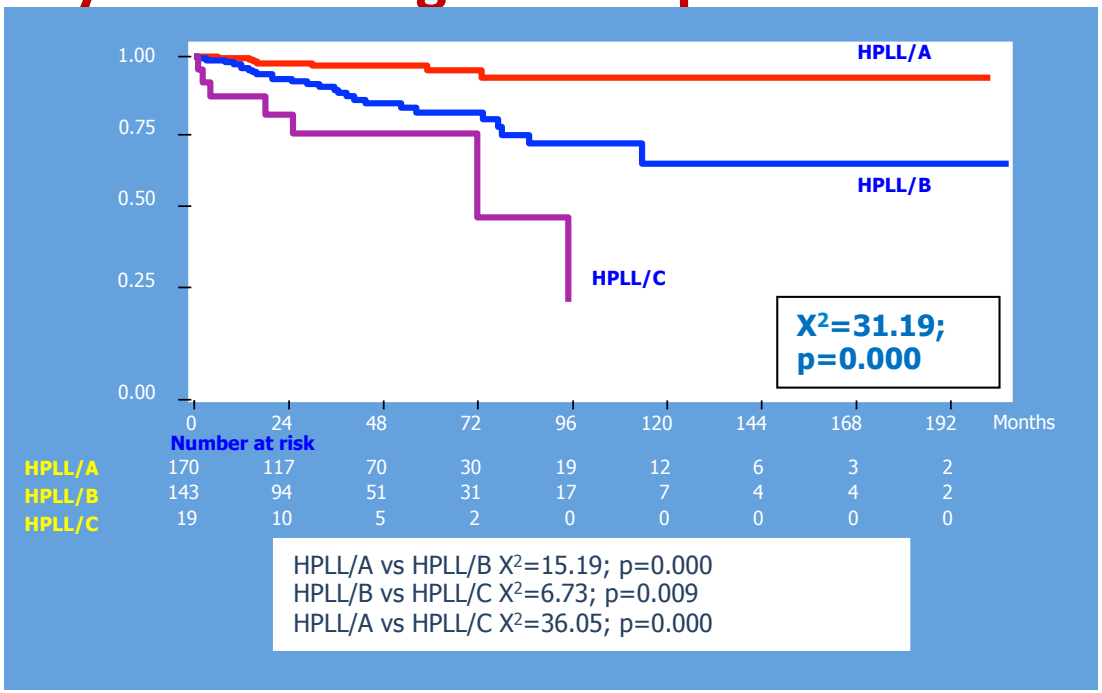
- Retrospective International SMZSG study
- 596 pts. Traning and validation series (336, 227 pts.)
- Hgb & platelet numbers were used **as continuous** variables to get a better accuracy.
- Multivariate Analysis. Statistically significant variables
  - Haemoglobin (p=0.003)
  - Platelets (p=0.043)
  - >LDH (p=0.011)
  - Extrahilar Lymphadenopathy (0.020)

PI: **0.02 x hemoglobin** (g / l) **+ 0.006 x platelet count** (10^9 / l) **- 1 x high LDH** (1> high, 0 normal) **- 1 x extrahilar lymphadenopathy** (1 present, 0 absent)

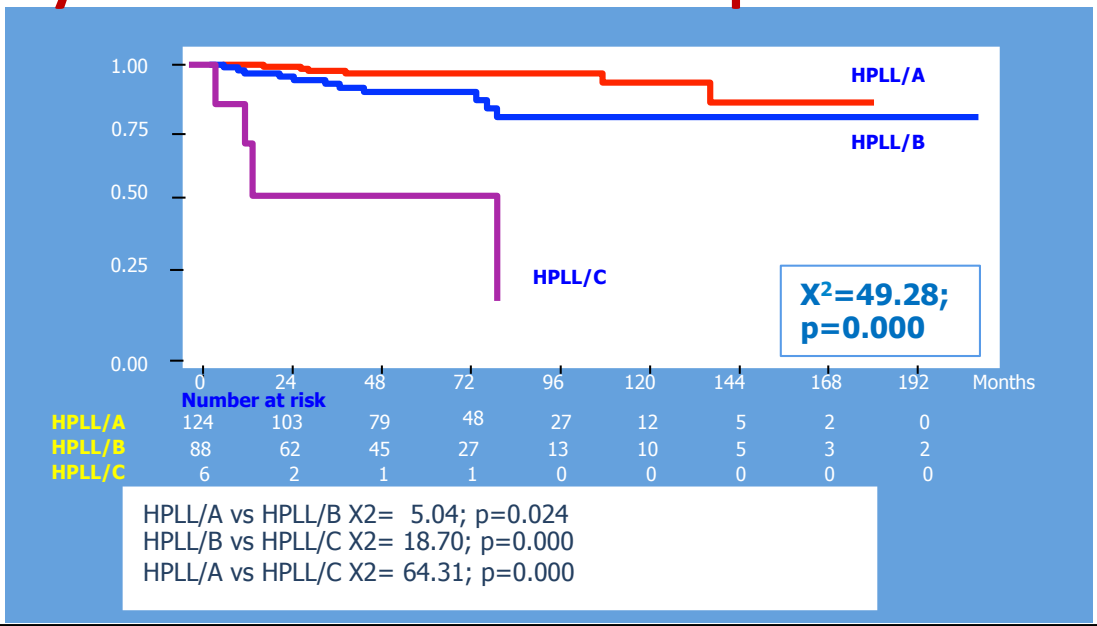
- Cut points (2.6 and 0.9) separate three groups with significantly different 5y LSS, 0.94, 0.78 and 0.67.

H(Hemoglobin) **P**(Platelets) **L**(LDH) **L**(Lymphadenopathy extrahilar):**HPLL/ABC Score**

5-y LSS Training set 336 patients

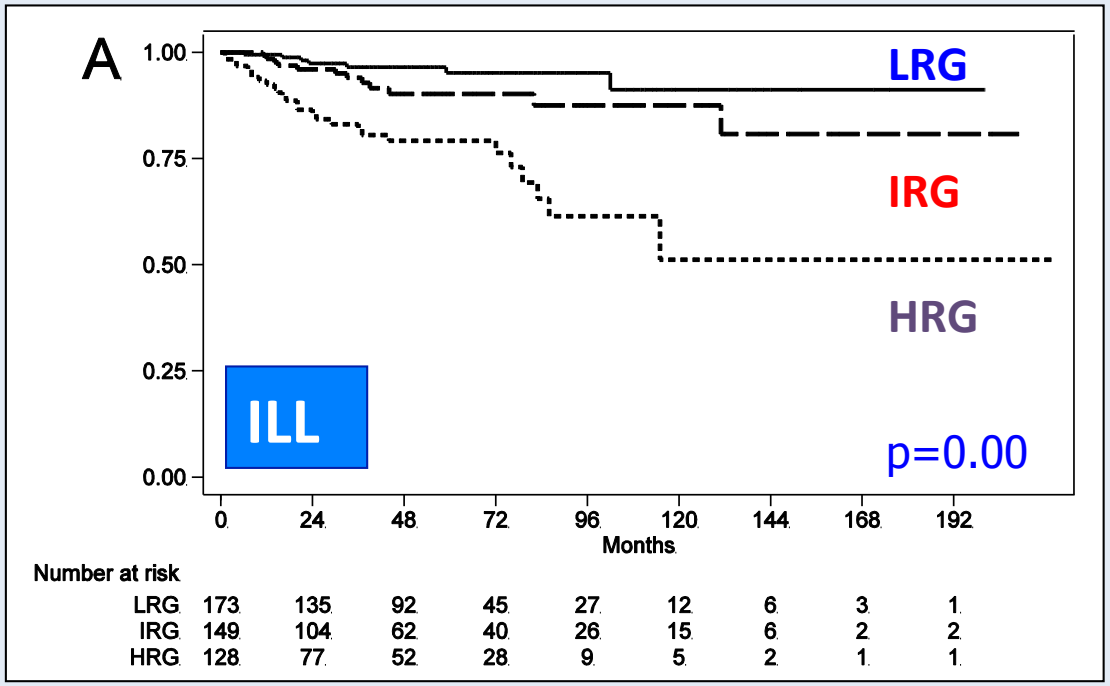


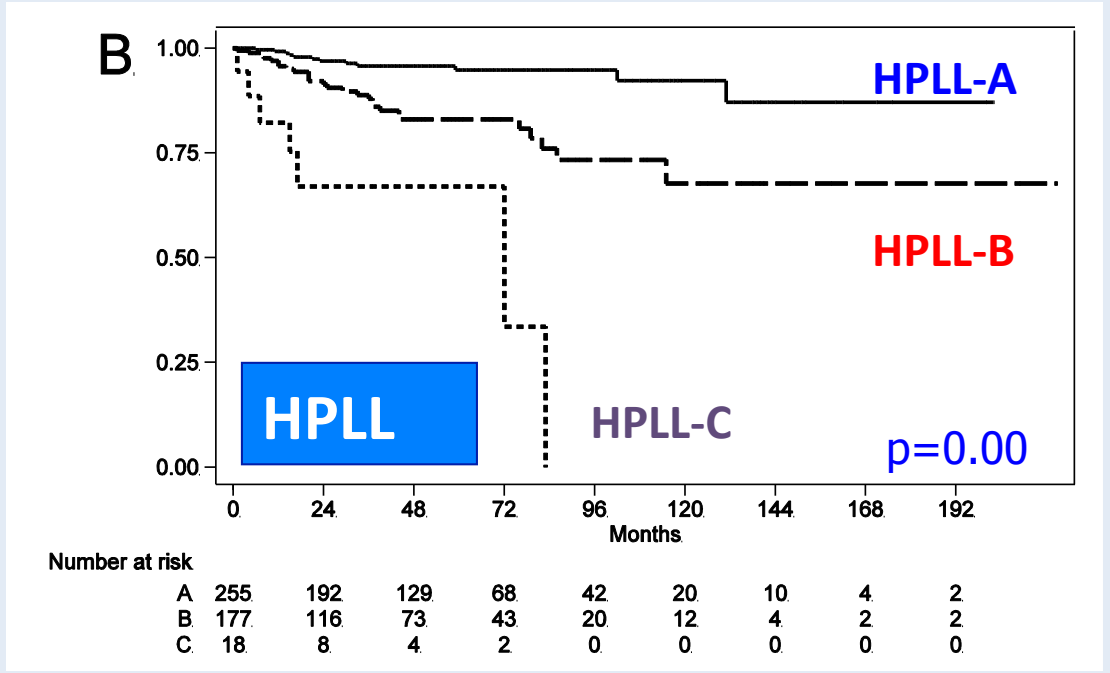
5y LSS. Validation set 227 patients



HPLL Stratification & ABC Risk Groups: Training and validation series

Comparison of HPLL vs. IIL. 5-y LSS in 450 pts.





LRG vs IRG X^2 =2.67; p=0.102
IRG vs HRG X^2 =11.97; p=0.005
LRG vs HRG X^2 =25.90; p=0.000

Hosmer-Lemeshow test:
IIL (p=0.18); HPLL (p=0.475):
the higher p value indicates that HPLL better discriminates the risk groups.

- **HPLL better than IIL**
- **HPLL Major problem:**

An equation is required

HPLL/A vs HPLL/B X^2=16.23; p=0.000
HPLL/B vs HPLL/C X^2=12.75; p=0.000
HPLL/A vs HPLL/C X^2=53.90; p=0.000

Point score simplification for practical use of the risk stratification for SMZ lymphoma: PLL/sABC-

Montalban & SMZLSG Project. Leukemia Lymphoma, 2014; 55:929

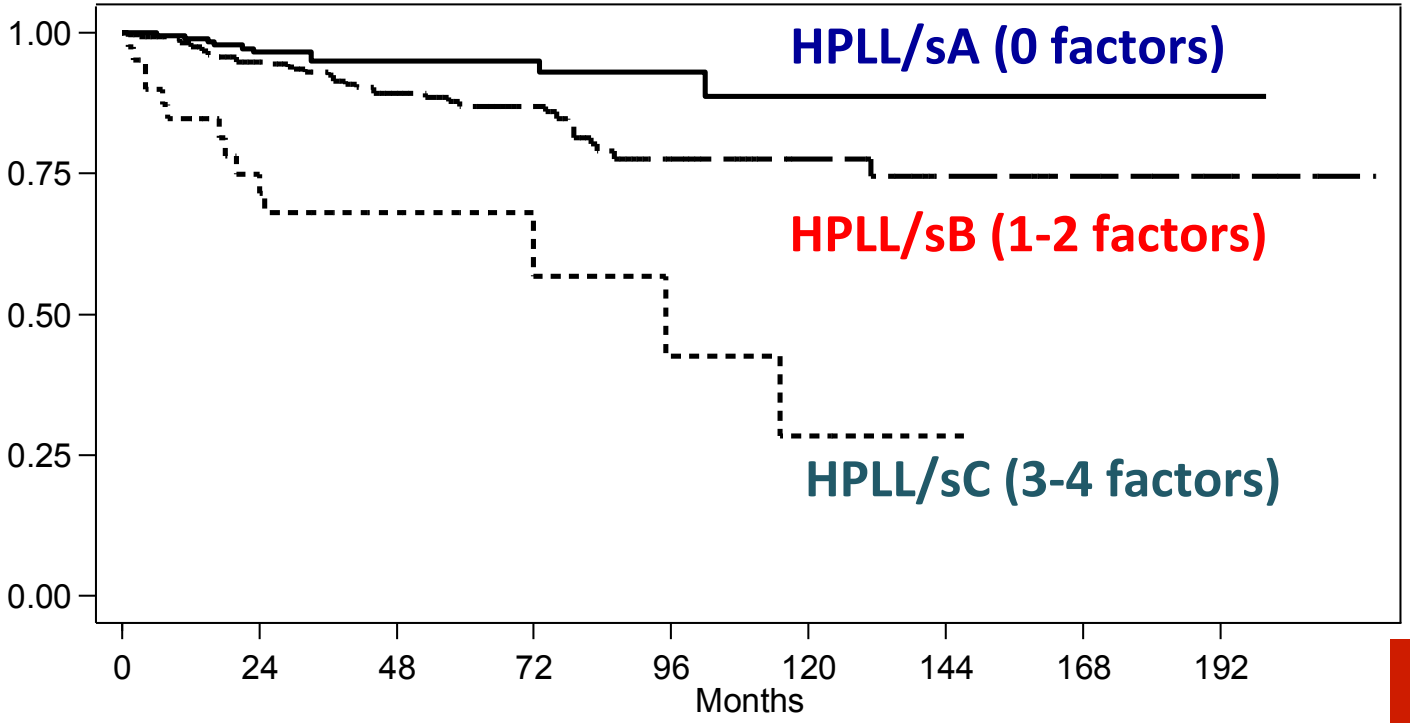
- **550 patients from HPLL Study**
- **Hgb and platelet count used as categorized variables**
- **Cut points** (*)
  - Hgb < 9,5 g/dl
  - Platelets <80x10^3/µl
- **Adverse factors**
  - Hgb <9,5 g/dl
  - Platelet count <80x10^3/µl
  - High LDH
  - Extrahilar lymphadenopathy
- **Groups**
  - **HPLL/A**: No adverse factors
  - **HPLL/B**: 1-2 adverse factors
  - **HPLL/C**: ≥3 adverse factors

Similar weight:
One point each

(*) Cut points chosen to get the best fit

Point score simplification for practical use of the risk stratification for SMZ lymphoma: HPLL/sABC

Montalban & SMZLSG. Leukemia Lymphoma. 2014; 55:929



LSS

Global p=0.000;
HPLLs/A vs. HPLLs/B: p=0.0159; HPLLs/B vs. HPLLs/C: p=0.000;
HPLLs/A vs. HPLLs/C: p=0.000

Net Reclassification Improvement: -9.6 (HPLLs vs HPLL 9.6% loss of accuracy)

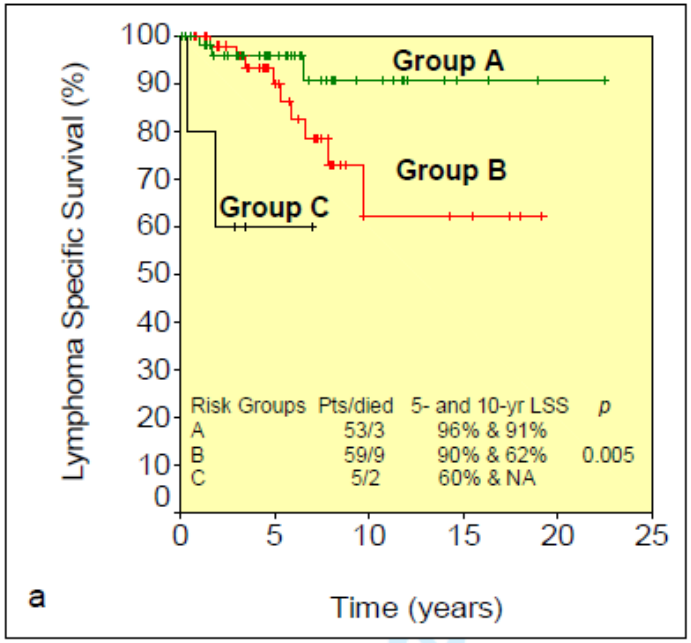
Validation of the simplified Prognostic Score for SMZL of the Splenic Marginal Zone Lymphoma Study Group

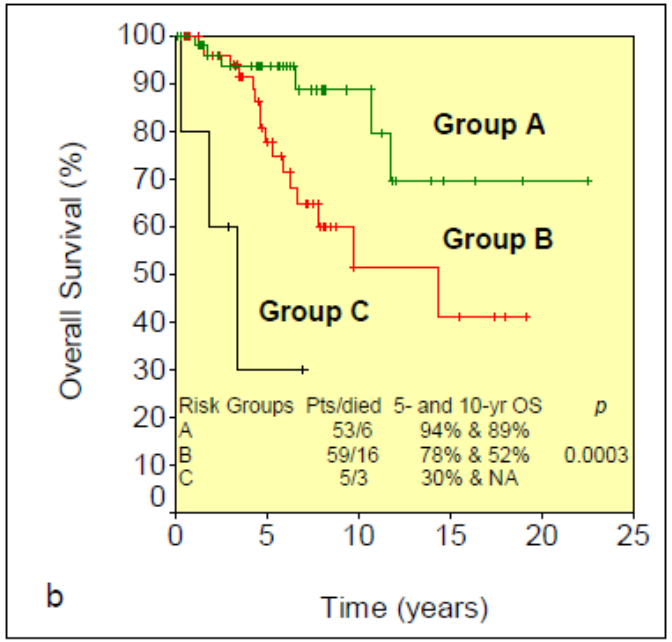
Kalpadakis et al. Leukemia Lymphoma 2014; 55: 2640

117 pts.	
Anemia	24/117 (53%)
Thrombop.	7/117 (6%)
>LDH	46/117 (39%)
Lymph. EXt	23/117 (20%

	A%	B%	C%
RitX	70	54	60
Splec	8	36	

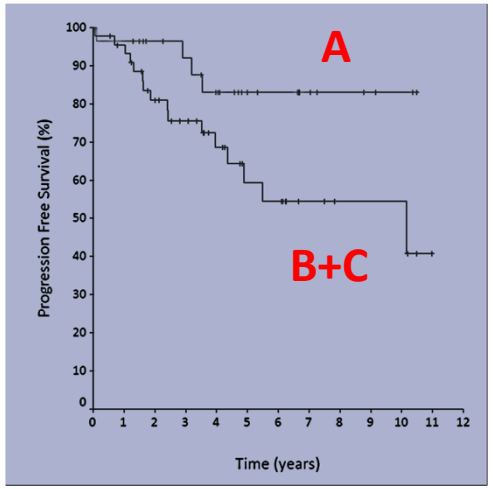
Groups	SMZLSG (%)	Present (%)	5-yr LSS (%)	
			SMZLWG	Present
A	36	45	95	96
B	56	50	87	90
C	7.4	4	68	60





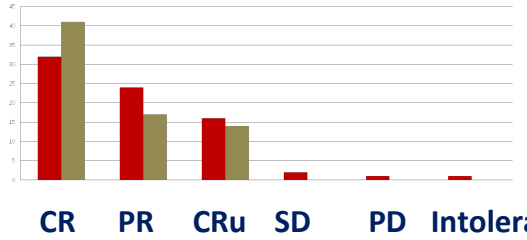
VALIDATION OF THE SIMPLIFIED PROGNOSTIC SCORE FOR SMZL OF THE SMZLSG (SMZL STUDY GROUP) IN A SERIES OF PATIENTS TREATED HOMOGENEOUSLY WITH RITUXIMAB MONOTHERAPY AND LONG TERM OUTCOME OF RITUXIMAB RESPONDERS C. Kalpadakis et al. EHA 20th. Viena 2015. #P861

CHARACTERISTICS	AT DIAGNOSIS	AT TREATMENT INITIATION
MALE	33/76 (43)	33/76 (43)
AGE (M-range)	65 (41-91)	65 (41-91)
Hb <9,5 g / dl	14/76 (18)	16/76 (21)
PLTs <80 × 10^3 / µl	6/76 (8)	9/76 (12)
LDH> N	23/74 (31)	28/74 (38)
EXTRAHILAR LYMPHADENOPATHY	20/75 (27)	21/75 (28)
GROUP A	34/73 (47)	27 (37)
GROUP B	36/73 (49)	42 (58)
GROUP C	3/73 (4)	4 (5)



7-YEAR PFS	(%)
GROUP A	83
GROUP B	48
GROUP C	50

RESPONSE TO RITUXIMAB AFTER INDUCTION AND MAINTENANCE TREATMENT



RESPONSE TO RITUXIMAB TREATMENT

AFTER INDUCTION	AFTER MAINTENANCE
CR=32 (42%)	CR= 41 (57%)
PR=24 (32%)	PR= 17 (24%)
CRu-=16 (21%)	Cru= 14 (19%)
Failure= 3 (4%)	
Intolerance =1 (1%)	
Overall Response = 72 (95%)	

- This study validates the applicability of the SMZLSG prognostic system regarding PFS, in a series of 73 patients homogeneously treated with rituximab monotherapy.
- The long-term disease-specific survival exceeded 90%.
- Our findings confirm the efficacy of Rituximab monotherapy as first line treatment in SMZL and demonstrate the potential for a long-term disease control, beyond the initial 5 years, in a substantial patient subgroup.

How to progress in SMZL risk stratification and treatment

- BRISMA study (Response-adapted treatment with RB (FIL & GELA). E. Iannitto, C. Thieblemont
- Indolent Non-Follicular lymphoma Prognostic Project NF10 Protocol (FIL). L. Arcaini, E Luminari
- GELTAMO Risk adapated Treatment Project.
  C. Montalban, E. Domingo, A. Salar
- Incorporate Biological studies to prospective trials with homogeneous criteria of diagnosis and treatment. The IELS 46 Study. D.Rossi & L. Arcaini

Indolent Non-Follicular lymphoma. Prognostic project NF10 Protocol

L. Arcaini, S. Luminari (FIL)

- Indolent non-follicular lymphomas
- Mostly SMZL
- Multicenter and international
- Prospective study with registered clinical data and response to treatment
- 2012-2016
- Results pending

Articulating Treatment and risk. Risk-adapted treatment of SMZL. The GELTAMO Project.

C.Montalban, E. Domingo, A. Salar

- Nation-wide diagnostic, stratification & Treatment Recomendations for SMZL
- 40 Hospitals of the GELTAMO Network in Spain
- (2014) To be followed in the next 4 years
- Standarization of diagnosis, work-up, diagosis, response and follow-up criteria(1)
- Centralized Review of PathologyDiagnosis (MAP, MM& EM)
- Uniform stratification: HLLLs/ABC(2)
- Splenectomy is not recomended for diagnosis or standard treatment
- Risk-Adapted treatment

(1) SMZL Guidelines, Leukemia 2008, Dreyling ESMO Guidelines 2013, NCCN Guidelines 2011
(2) Montalban, Leukemia Lymphoma 2014, Kalpadakis 2014

Risk-adapted Treatment
HPLLs/ABC Factors and Risk Groups

Risk Groups HPLLs/ ABC	Number of factors	Treatment
A. Low Risk	0 factors	No treatment
B. Intermediate Risk	1-2 factors	Rituximab
C. Hig Risk	3-4 factors	Rituximab + ChT(*)

Factors: One poin for each fator

- Hemoglobin <9.5 g/dL
- Platelets <80 x103/µL
- LDH serum over normal locallevels
- Lymphadenopathy out of splenic and hepatic hila

(*) QT: CVP-R, F-R, B-R at the discretion of investigators

IELSG46 study. Integrated Molecular and Clinical Profiling to Optimize Outcome Prediction in Splenic Marginal Zone Lymphoma. D. Rossi, L. Arcaini

- To develop a Molecular&Clinic prognostic model
- 300 patients
- Retrospective study
- 44 Centers
- Spleen histology
- Central Pathologic Review
- Biological studies
  - Mutation analysis by NGSequencing
  - Immunoglobulin gene analysis
  - DNA methylation analysis
  - FISH analysis
- Develop of an accurate and validated Prognostic System
- Started 2017