Marginal Zone Lymphomas
Clinical aspects

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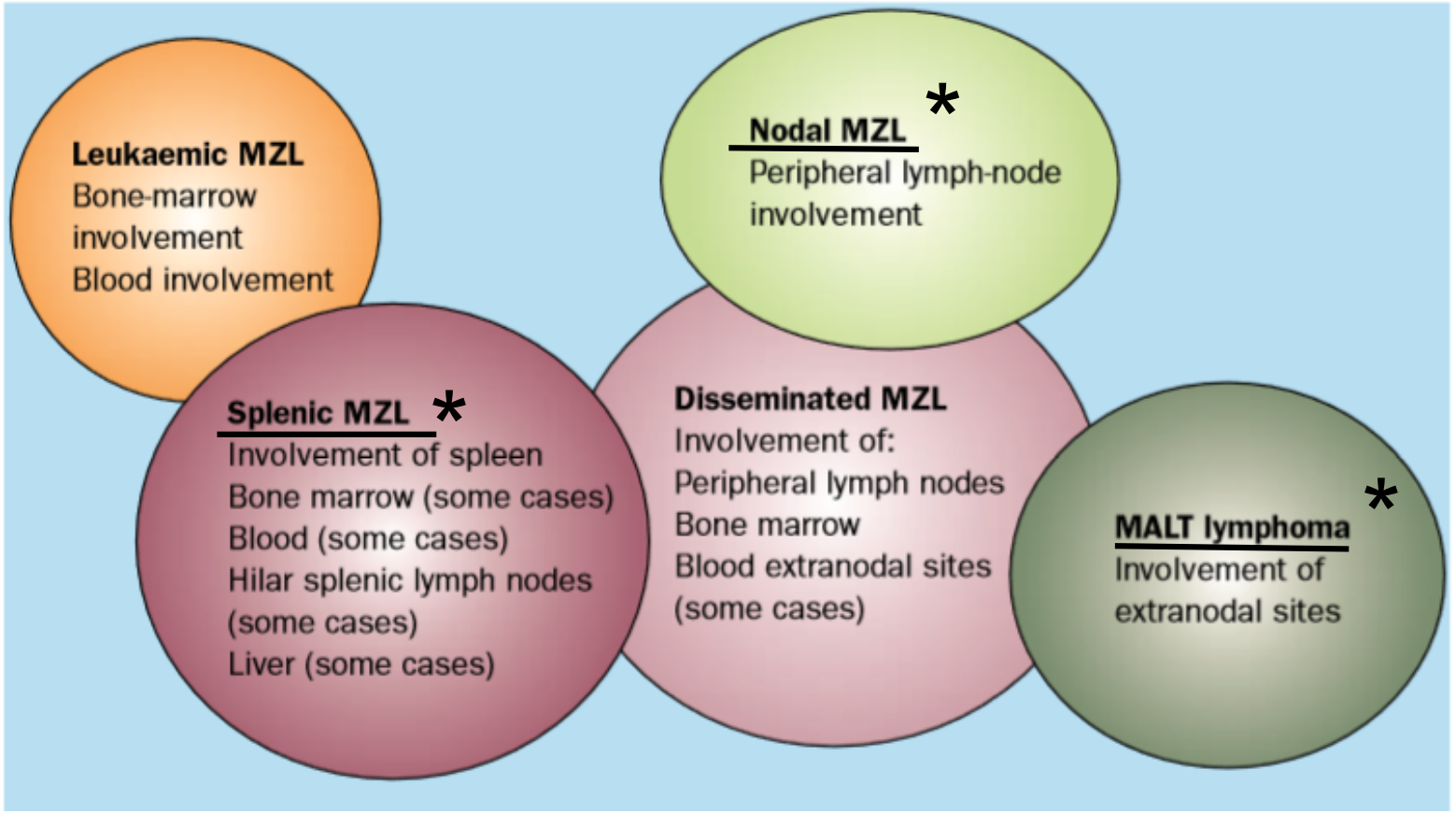
Bologna 16th, 2017

Marginal zone lymphomas (MZL)

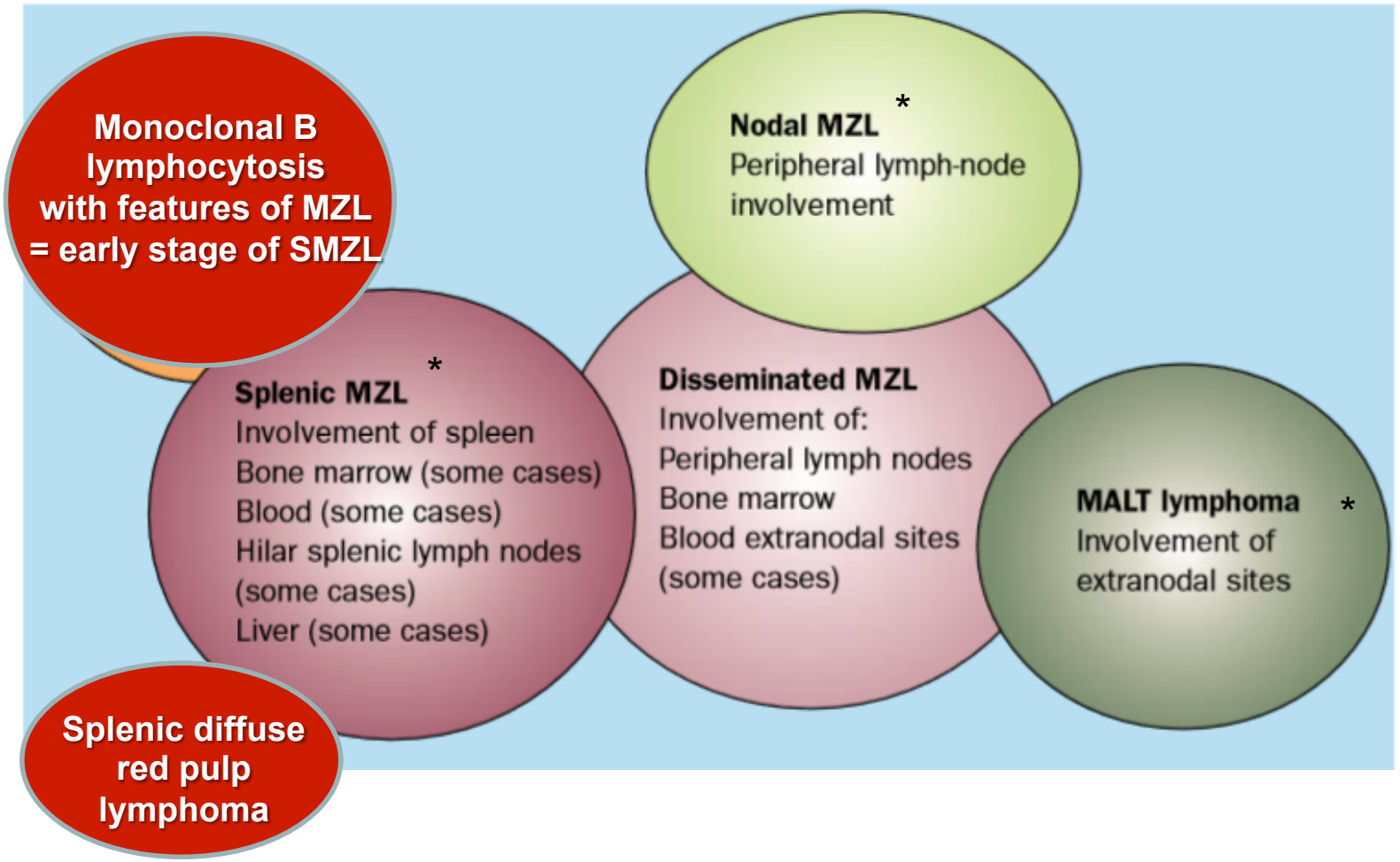
***Defined by the 2008 WHO classification**



Thieblemont C et al. Lancet Oncol 2003

Marginal zone lymphomas (MZL)

The new 2016 WHO classification



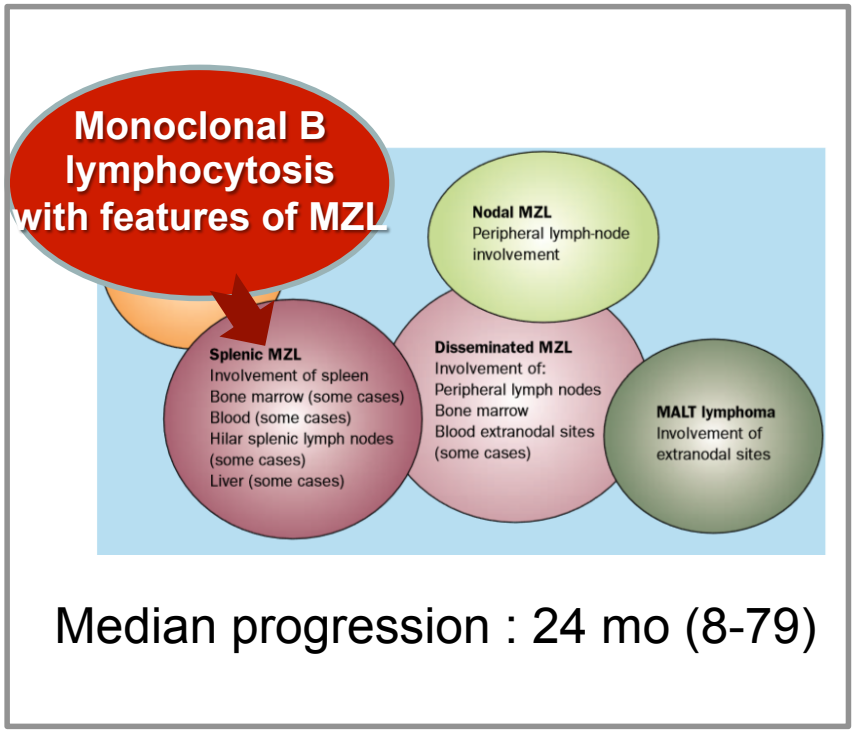
Swerdlow et al. Blood 2016

Monoclonal B lymphocytosis with features of MZL

Definition : monoclonal non CLL Lymphocytosis > 5 10^9/L

Swerdlow et al. Blood 2016

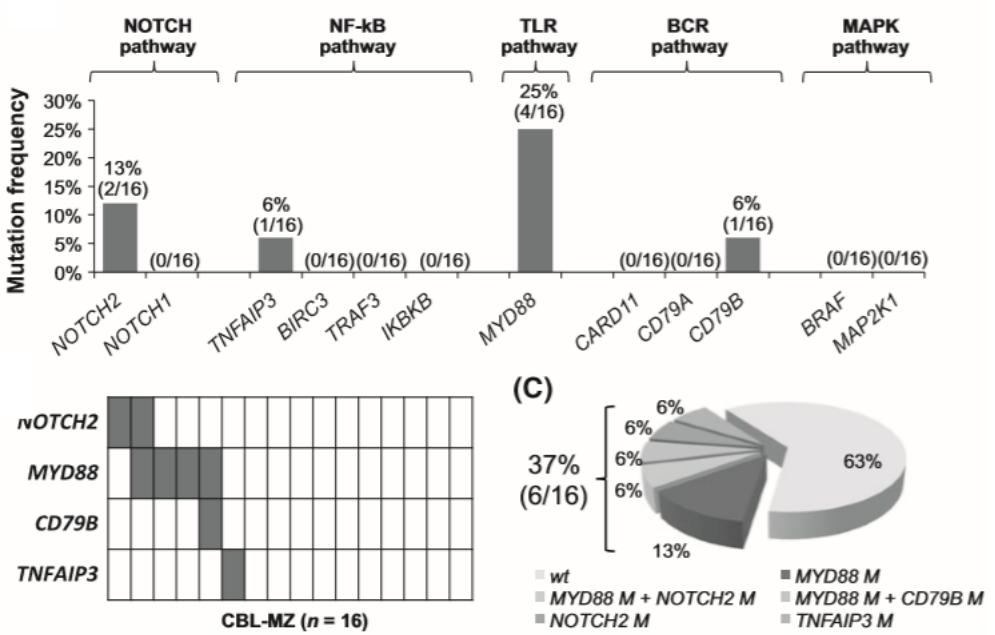
Clinical presentation



Median progression : 24 mo (8-79)

Xochelli A et al. Blood 2014

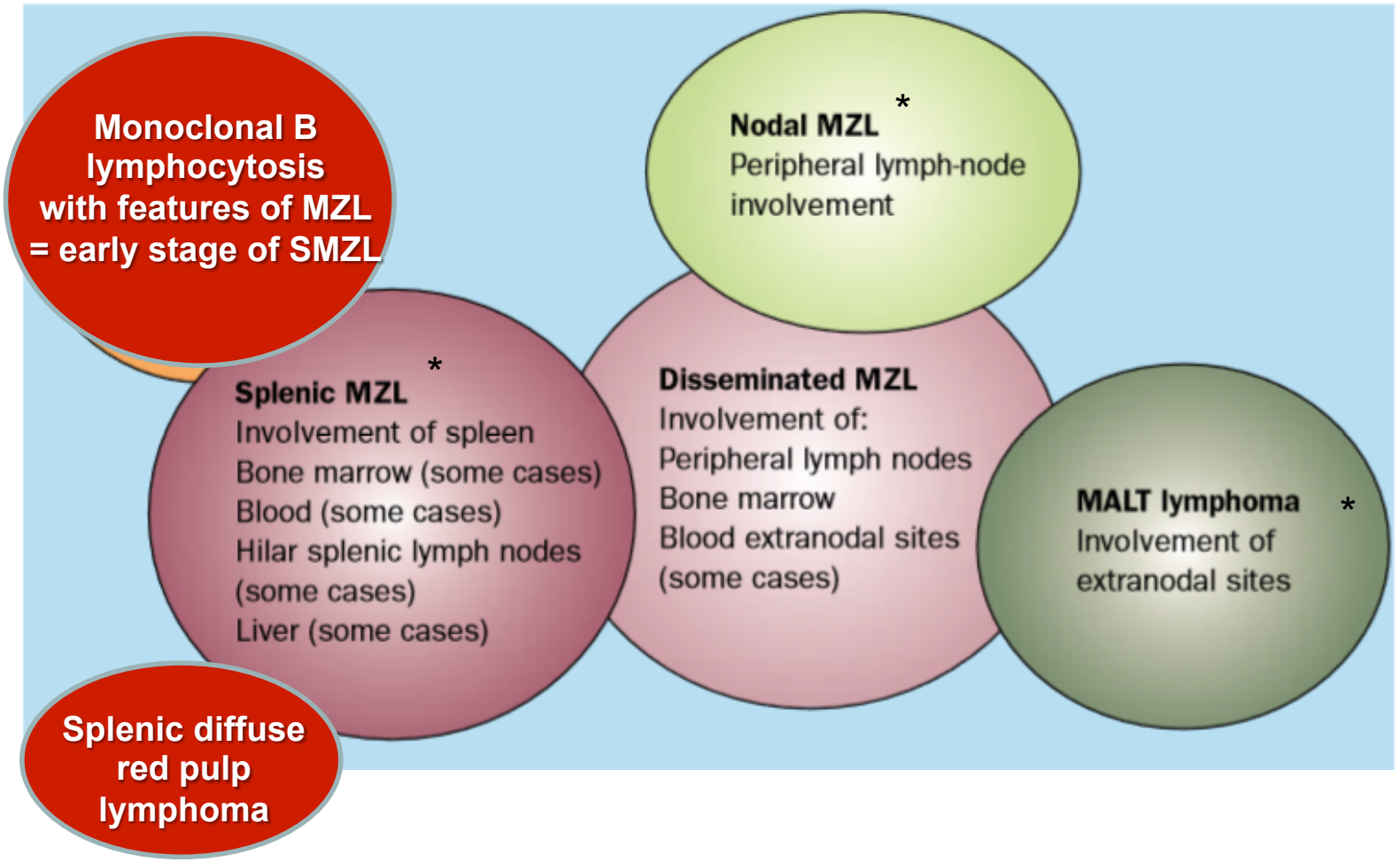
Biology



Bruscaggin A et al. Br J Haematology 2014

Marginal zone lymphomas (MZL)

The new 2016 WHO classification



Swerdlow et al. Blood 2016

Extranodal Marginal zone lymphoma

= MALT lymphoma

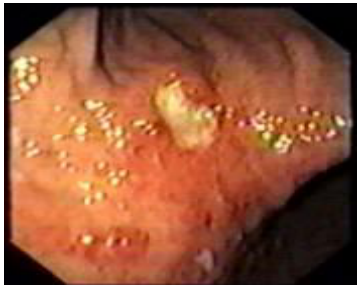
Very diverse sites of involvement

Mucosal sites	Non mucosal sites
Gastro-Intestinal tract - Stomach - Intestin Respiratory tract - lung - pharynx, larynx Urinary tract Breast Thyroid Salivary Gland	- Skin - Meninges - Orbit

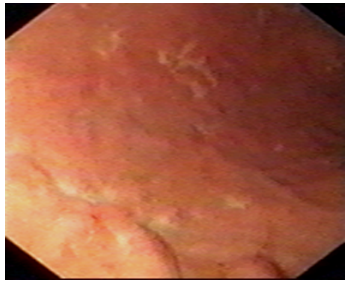
Thieblemont C. Hematology Am Soc Hematol Educ Program. ***2005***

MALT lymphoma : Sites of involvement

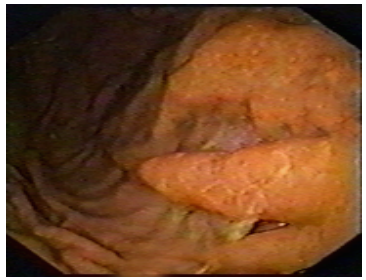
Gastric



Ulcer (20%)

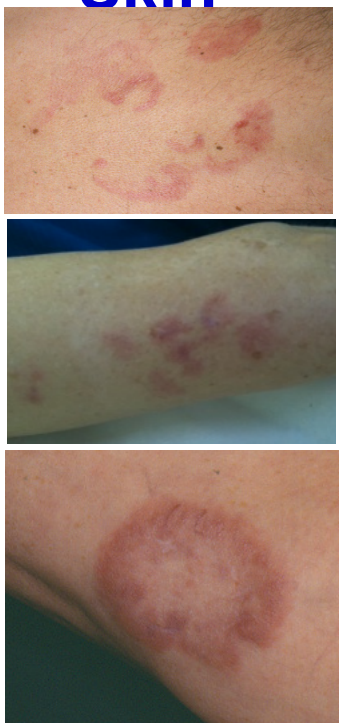


Pseudogastritis (25%)

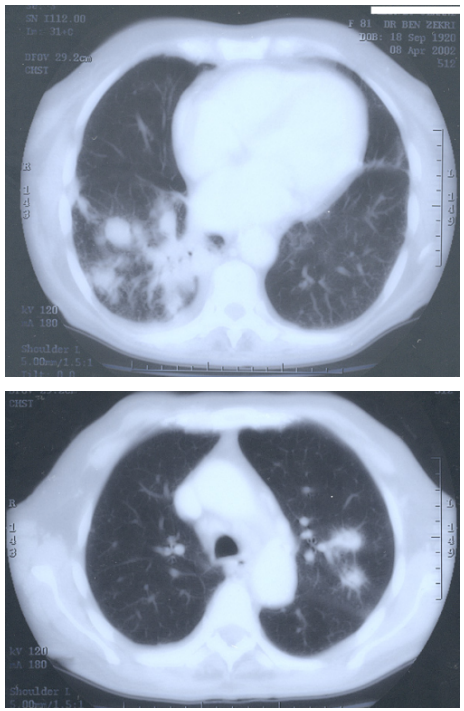


Nodular (25%)

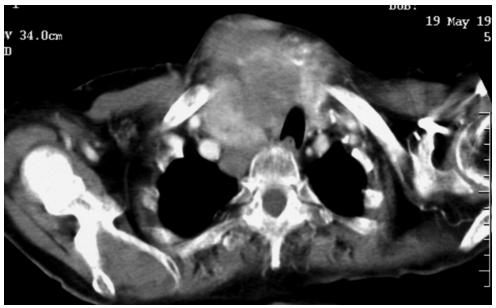
Skin



Lung

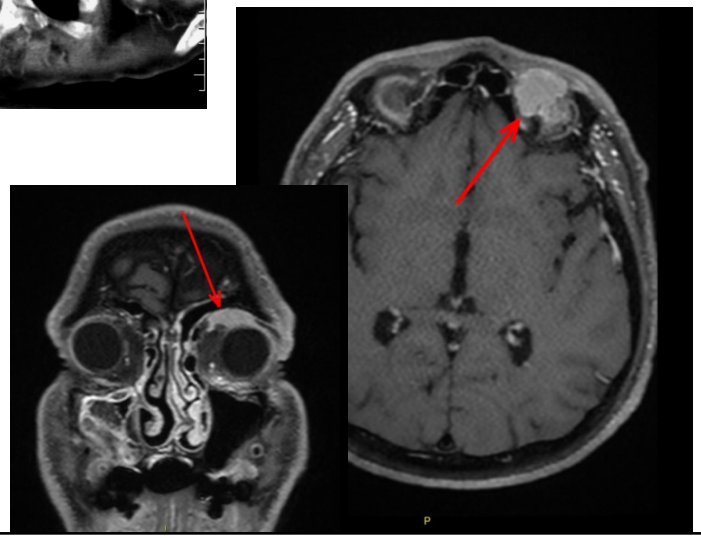


Thyroid



Orbit

- Conjonctiva
- Lacrymal gland
- Soft tissue



Very diverse sites of involvement

Non GIT: 50%

GIT : 50%

SKIN

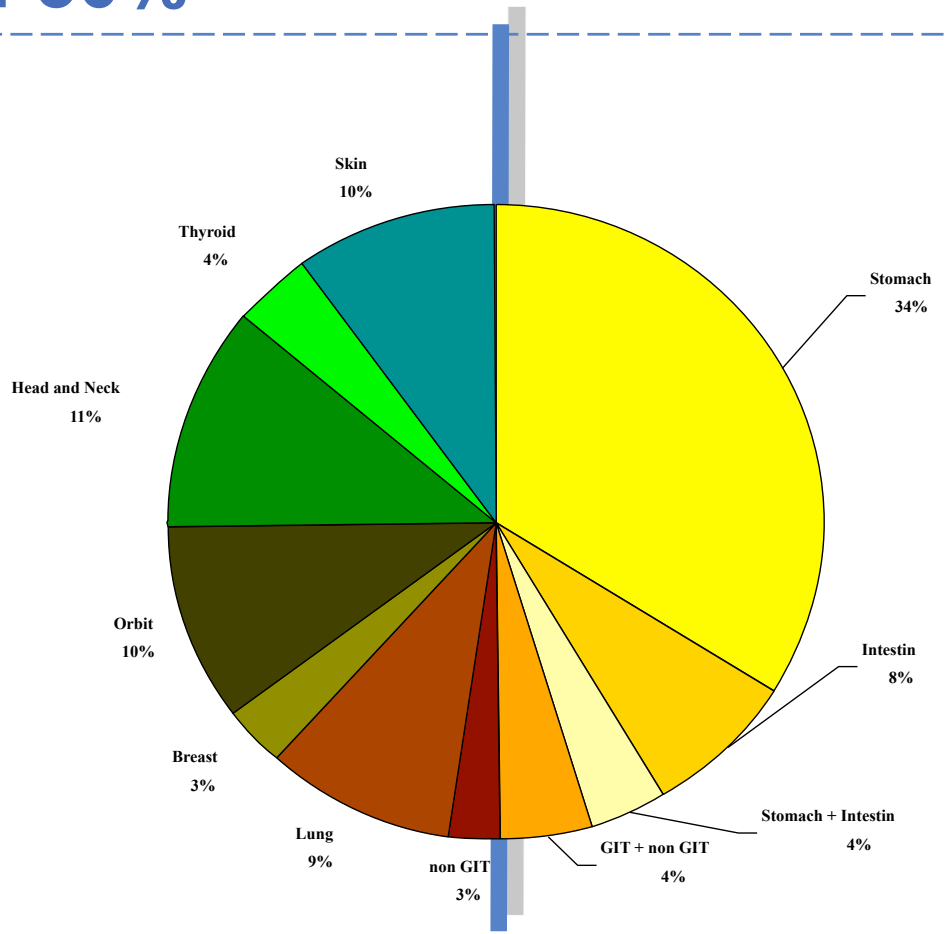
THYROID

ORBIT

LUNG

STOMACH

INTESTIN

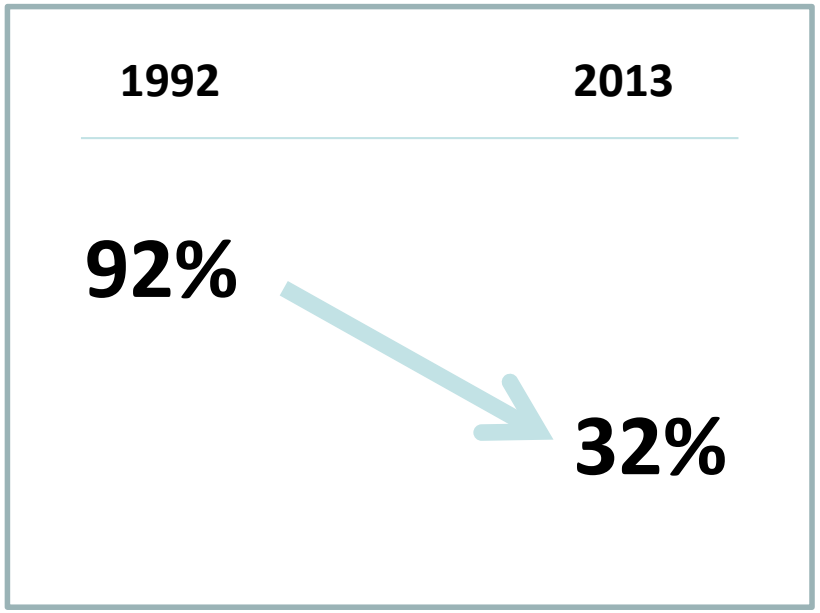


GIT = Gastro - Intestinal tract

Thieblemont C. et al. J Clin Oncol 1997

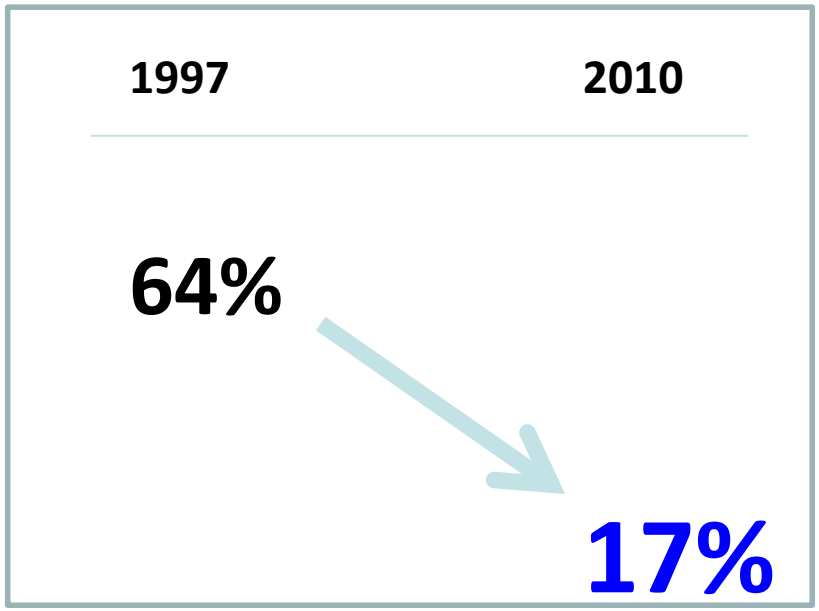
Prevalence HP

1343 gastric MALT lymphoma
London



Doglioni C, et al. Lancet. 1992
Wotherspoon A, Gut 2014

Gastric MALT lymphoma
Modena Cancer Registry

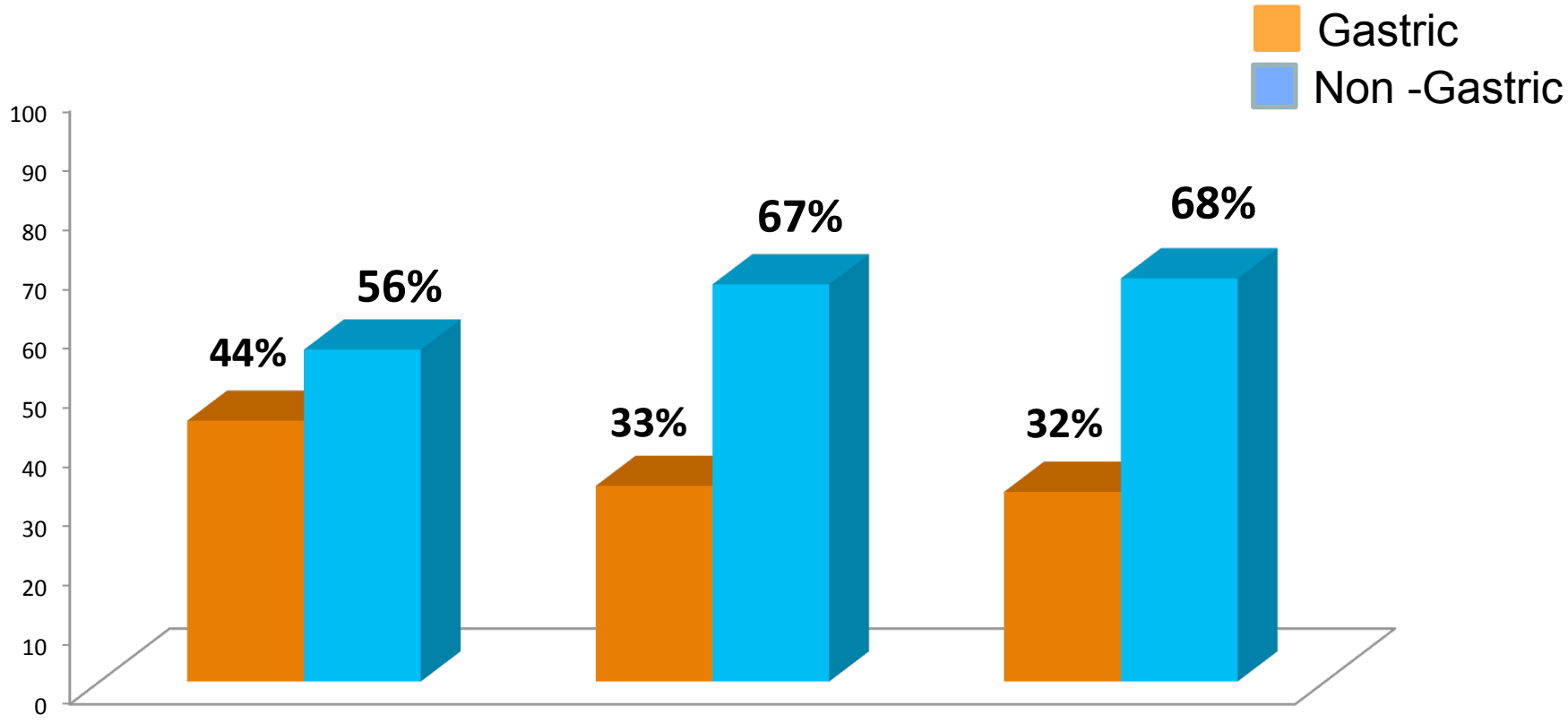


Luminari S, et al Ann Oncol 2010

Decrease incidence of gastric MALT L.:

1.4 to 0.2 /100 000 p.

Decreasis of Gastric MALT lymphoma in clinical trials



	IELSG19	MALT-2008-01	IELSG38
Time of inclusion	2003 – 2005 2006 - 2008	2009 - 2011	2013 - 2015
Nber of patients	450	60	112

Zucca E et al.
Salar A. et al.
Stathis A. et al

Clinical presentation at initial diagnosis

- Indolent disease
- Good performance status
- Absence of B-symptoms
- Normal LDH and B2-microglobulin
- Localized disease : 70%
- Dissemination : 30%
  - multiple mucosal and non mucosal extranodal sites
  - Nodal involvement : 25%
  - Bone Marrow involvement : 20%
- Transformation : 3-18% of the MALT lymphomas

Thieblemont C et al. 1997 *Thieblemont C, Blood 2000*

IELSG-19 Randomised Study:
R-Chlorambucil vs chlorambucil vs R alone

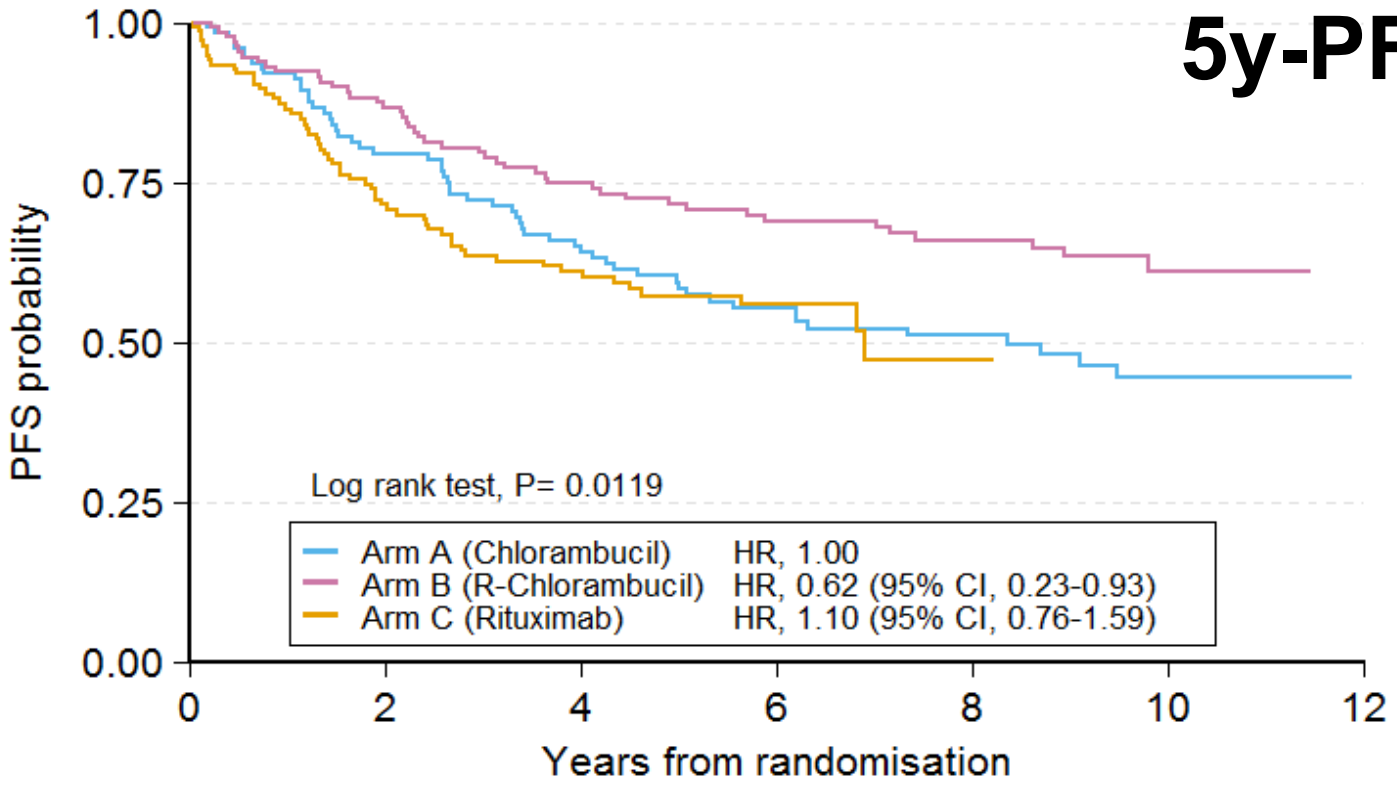
IELSG 19

median follow-up 7.4 years
range (5.6-9.7 years)

PFS

R-Chlorambucil

5y-PFS = 72%



Zucca E, et al J Clin Oncol 2017

IELSG-19 Randomised Study:
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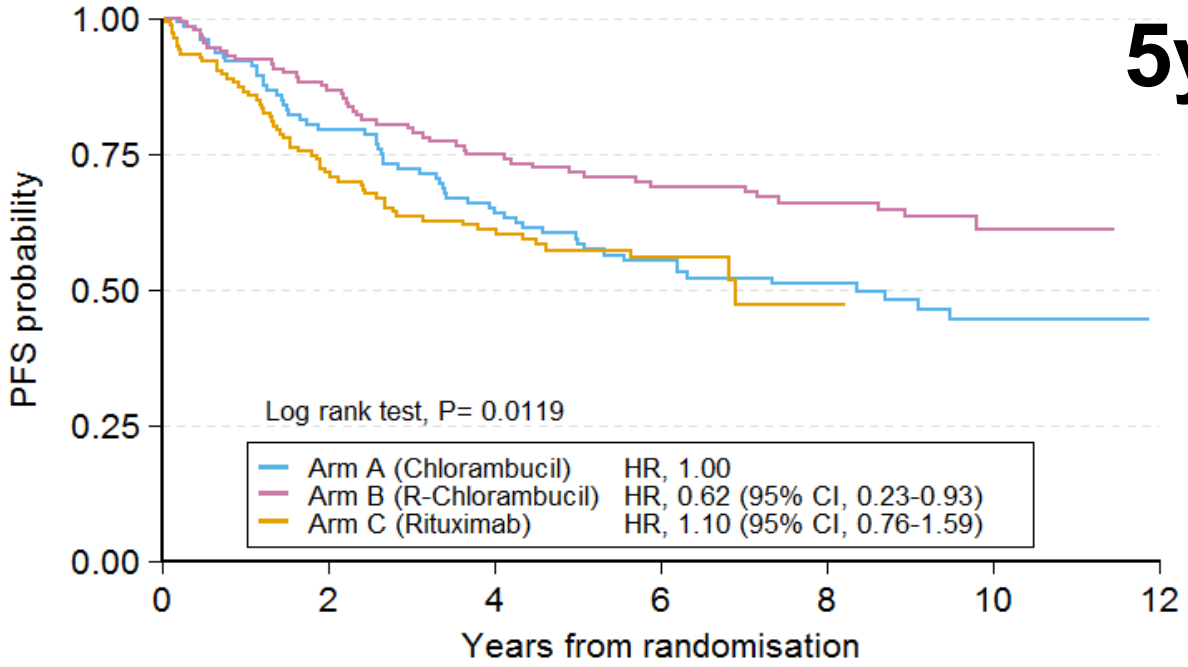
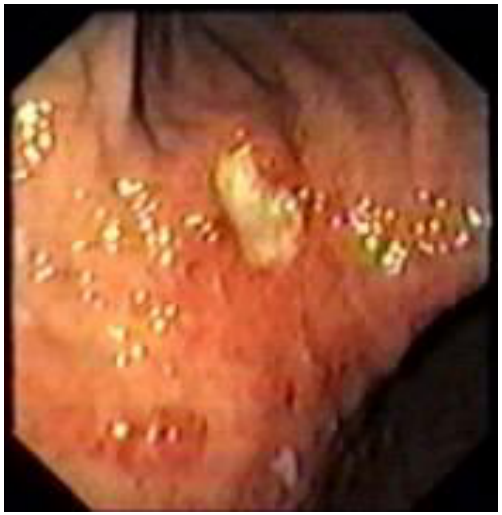


No difference in OS : ~90% in the three arms

Zucca E, et al J Clin Oncol 2017

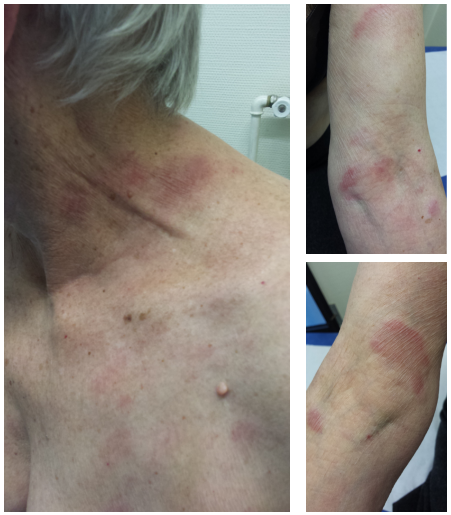
MALT lymphoma : Heterogeneous disease

Case 1
Gastric MALT HP-lymphoma
42 y



RT
Cured after local 1rst line?
Probably…

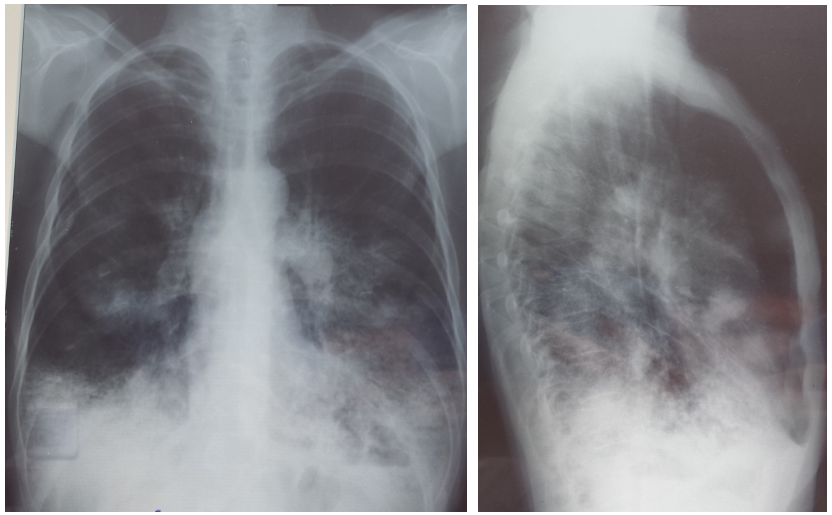
Case 2
Cutaneous MALT lymphoma
72 y



R-clb
A disseminated disease

Case 3
Mrs L. Pulmonary MALT lymphoma

58 y



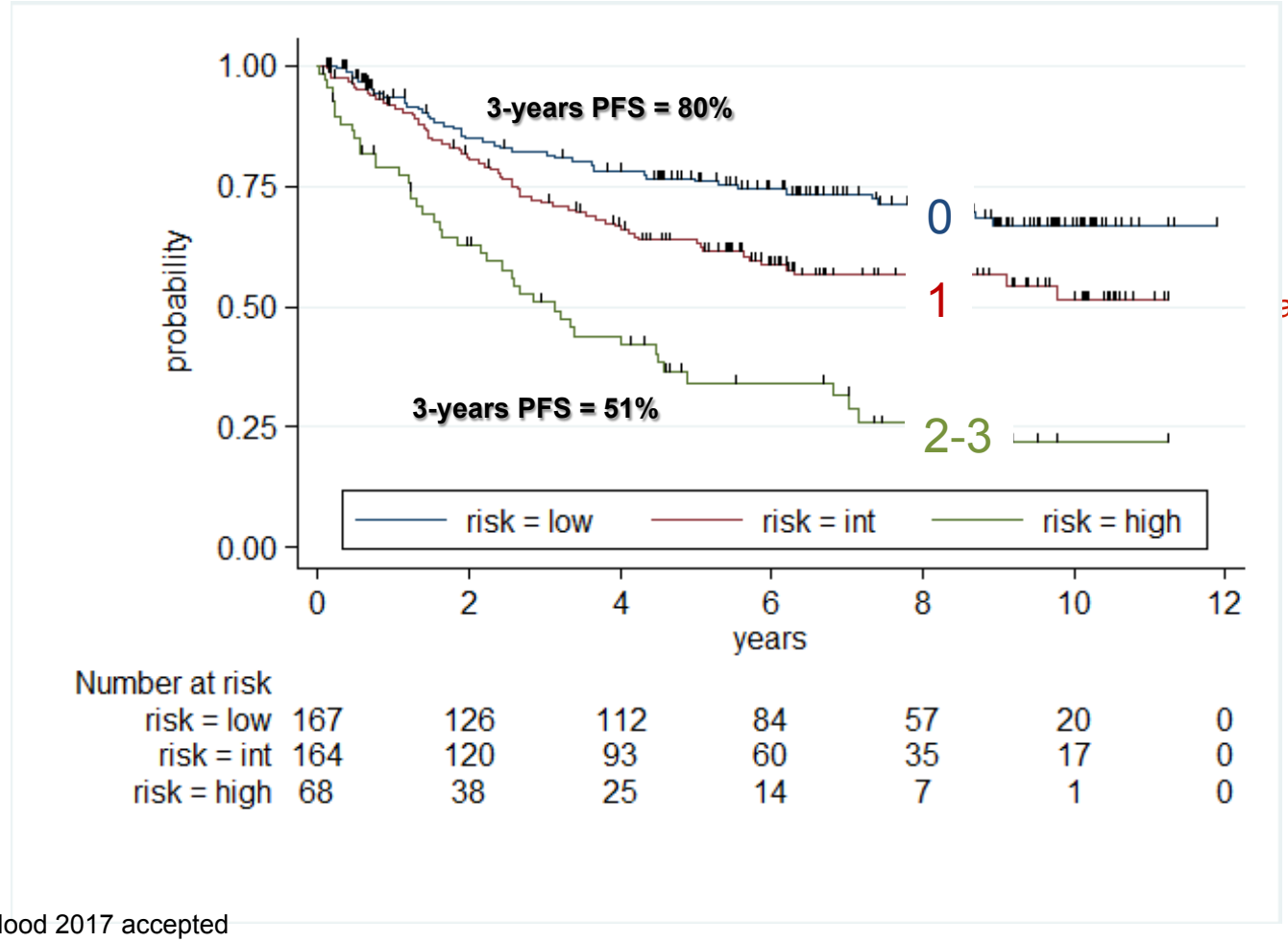
R- Fludarabine x 6 - 2007 . RC
Pulmonary Aspergillosis
Viral infections
2017 – in CR but still in need of oxygen

MALT lymphoma : LDH, Age, Stage
MALT score : 0 factor / 1 F / ≥ 2

IELSG 19 n = 401

LDH >N
AGE >70
STAGE>2

PFS



0 factor, n=167

actor, n= 164

2-3 factors, n=68

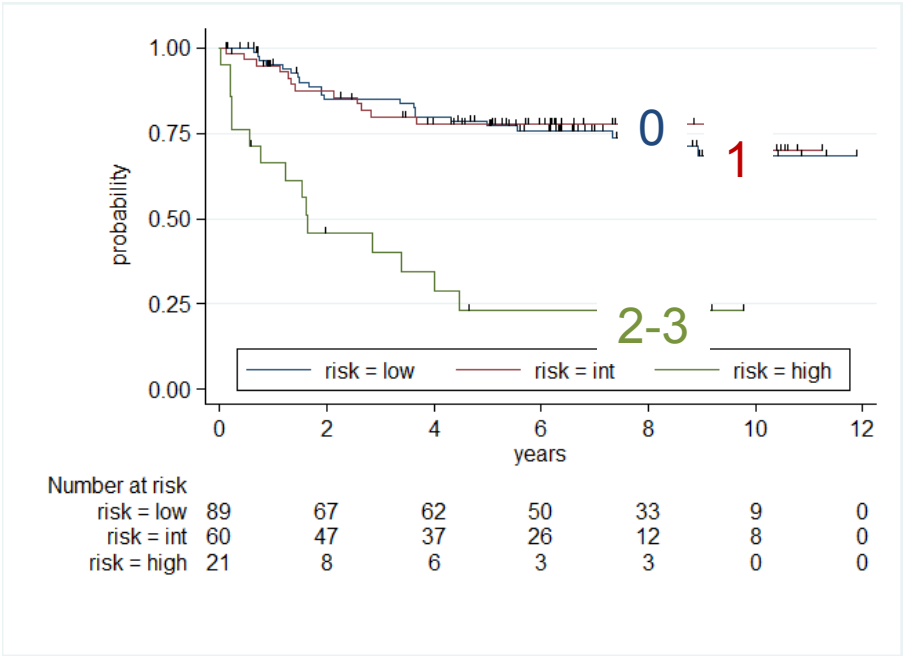
P<0.0001

Thieblemont C et al. Blood 2017 accepted

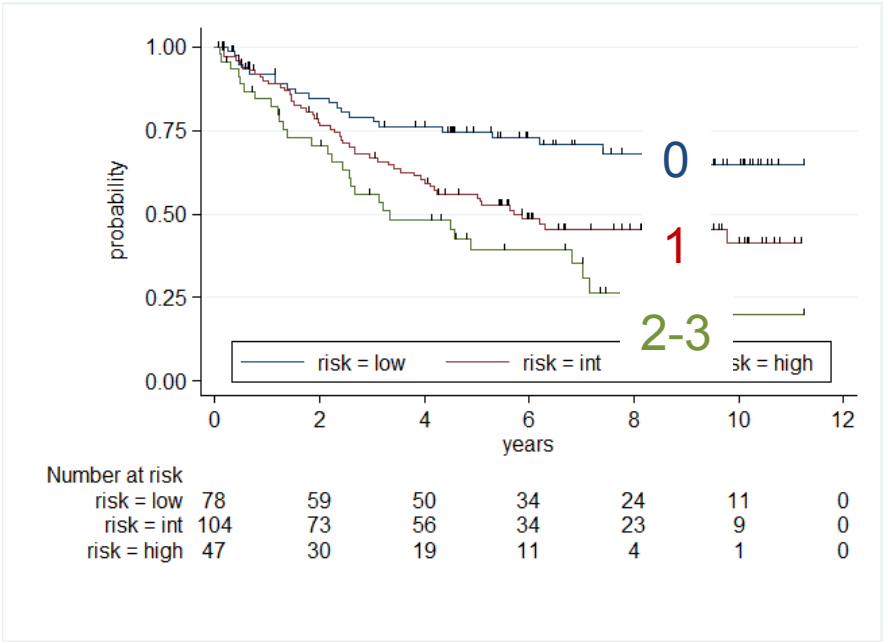
IELSG 19

PFS by MALT prognostic score

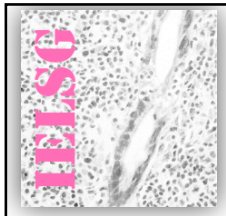
gastric MALT



Non-gastric MALT



Thieblemont C et al. Blood 2017 accepted



IELSG 19

PFS by MALT prognostic score

Elevated LDH	**42**	**(10.2%)**
age >70 years	**90**	**(22.9%)**
stage III-IV	**172**	**(43.8%)**
EN sites>1 (BM not included)	120	(30.5%)
lymph node involvement	136	(34.6%)
ECOG PS>1	5	(1.3%)

Thieblemont C et al. Blood 2017 accepted

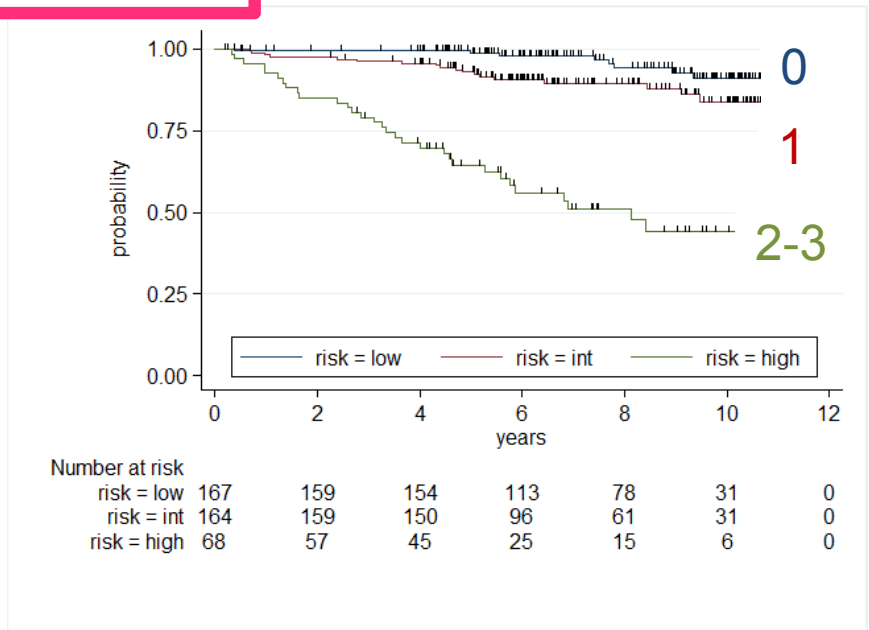
MALT - IPI

0 factor, n=167
1 factor, n= 164
2-3 factors, n=68

IELSG19

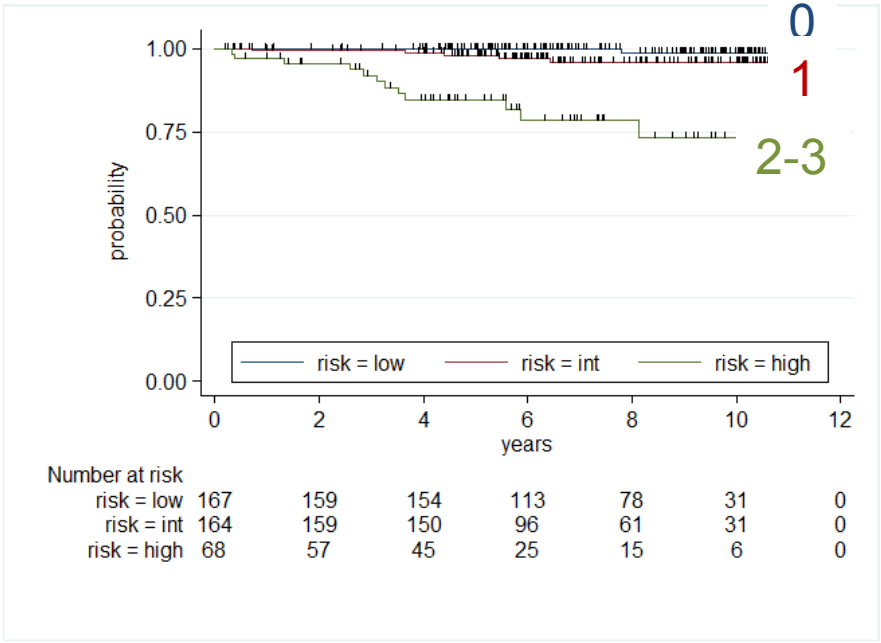
LDH >N
AGE >70
STAGE >2

OS



P<0.0001

CSS



P<0.0001

Thieblemont C et al. Blood 2017 accepted

Splenic Marginal zone lymphoma

Clinical presentation

Most of the patients

- **Asymptomatic**
- **Abnormal blood cells count**
  - ° Lymphocytosis
  - ° Cytopenia (autoimmune or by hypersplenism)

- **No B symptoms**
- **Good performance status (PS <2) : 85%**
- **Median age : 65**
- **Clinical examen : SPLENOMEGALY**

C. Thieblemont et al. , 2003 – K Viala et al., 2008 – Troussard X et al., 1996 – J Chacon et al. 2002 – N Parry-Jones et al., 2003

Clinical presentation

In case of advanced disease :

- **Asthenia : PS > 2**
- **Cachexia**
- **Pain of left hypochondrium : large splenomegaly**

- **Abnormal blood cell count**

  - **Lymphocytosis**
  - **Cytopenia +++ (autoimmune or by hypersplenism)**

C. Thieblemont et al. , 2003 – K Viala et al., 2008 – Troussard X et al., 1996 – J Chacon et al. 2002 – N Parry-Jones et al., 2003

Associated with Immune disorders

M component (IgM) 46%

- Marked hyperviscosity and hyperglobulinemia = uncommon

Immune disorders 20%

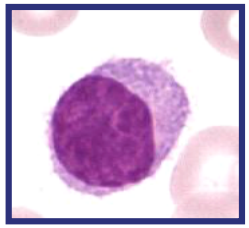
- Hemolytic anemia 10%
- Positive Coombs test 16%
- Thrombocytopenia 5%
- Coagulation (VW, Cardio lupic) 3%
- cold agglutinin
- Angioedema: acquired deficit in C1-esterase inhibitor
- Neuropathy (radiculopathy, axonal, demyelinating)

C. Thieblemont et al. , 2003 – K Viala et al., 2008 – Troussard X et al., 1996 – J Chacon et al. 2002 – N Parry-Jones et al., 2003

Procedures for the diagnosis SMZL lymphoma

Mandatory

- Full blood count and Blood cytology
- Blood Flow cytometry : CD5−, CD10−, CD19+, CD23−
  CD27+, CD43−, FMC7±, kappa / lambda



Optional

- Caryotype
- FISH CCND1
- IgV_H Mutated 2/3 - Biased usage **IGHV1-2*04**

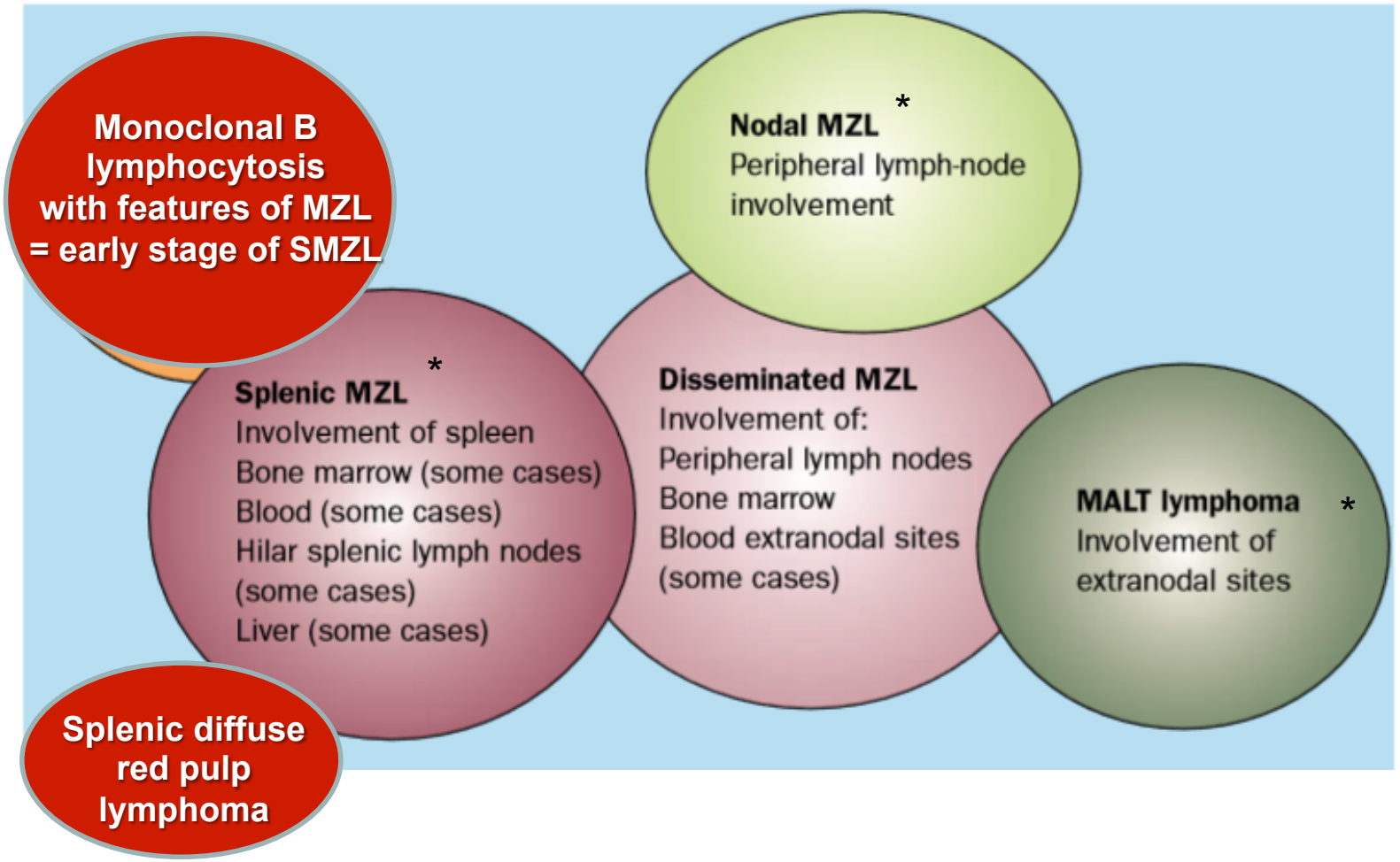
- **BRAF mutation 0% - MYD88 : 0% - NOTCH2 : 10-30% - KLF2 : 20%**

➢ **The diagnosis of SMZL at present does not strictly require a splenectomy**

Dreyling M, Thieblemont, C. ESMO guidelines 2013
Matutes E et al. Leukemia 2007. Bikos V et al. Leukemia 2012 Kalpadakis etal Anticancer Res2009

Marginal zone lymphomas (MZL)

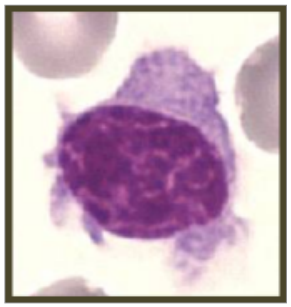
The new 2016 WHO classification



Swerdlow et al. Blood 2016

Splenic diffuse red pulp lymphoma

- Uncommon lymphoma with diffuse pattern of involvement of splenic red pulp
- Involvement of the spleen + BM + peripheral blood = same as SMZL
- Peripheral blood : - monomorphous lymphocytes
  - villous morphology
  - CD11++ / CD22++



- May require the examination of the spleen for differential diagnosis with SMZL and HCLv
- Mutations NOTCH2, KLF2, MYD88 = 0, mutations in MAP2K1 and NOTCH1 more frequent, but analysed in less than 10 cases
- In need of molecular studies
- Treatment : not specific

Swerdlow et al. Blood 2016

Flow cytometry in SMZL

- **No characteristic marker**
- **Matutes score : ≤ 3 / 5**

	SMZL	CLL	MCL	HCL	HCL-v
sIg	Strong	Weak	Strong	Strong	Strong
CD5	+	+++	+++	–	–
CD23	+	+++	–	–	–
FMC7	+++	+	+++	+++	+++
CD11c	++	–	–	+++	+++
CD103	–	–	–	+++	++
CD123	–	–	–	+++	–
CD25	+	–	–	+++	–
CD27	++	+++	+++	–	++
CD200	–	+++	–	+++	–

–, <10% of cases positive; +, 11%-35% positive cases; ++, 36%-75% positive cases; +++, >75% positive cases.

Arcaini L et al. Blood 2016

Differential diagnosis with other small B-cell lymphomas

	Immunophenotype	Cytogenetic	Immuno genetic	Mutations
MZL	CD20+ CD19+ CD79a+ CD5- CD23- CD10-CD43v BCL2+ Matutes Score ≤ 3 CCND1 negative (IHC)	7q (del) 45% +3/+3q MALT L. t(11;18), t(14;18), t(1;14), t(3;14) SMZL +3, +18, + 12, del 6q NMZL +3, +19, -7, +12, del 6q No t(11;14)	IGHV1-2*04	NOTCH2 10-20% NOTCH1, BIRC3, TNFAIP3, TRAF3, IKBKB, MYD88… KLF2 20% SMZL PTRPD 15% NMZL
LPL/Waldenström	CD22+f CD25+ CD103-	del6q +4 +3 +18		MYD88 90% L265P
Hairy cell leukemia	CD103 CD11c CD25 (HC-2/) CD123 (=IL-3R) Score RMN 3 ou 4 / 4	5q13 +5 del(5) del(7)(q32) del(17)(q25) t(11;20) t(2;8)	IGVH4-34	BRAF 100% V600E
LLC/ SLL	CD20+ CD5+ CD23+ CD43+ CD10- FMC7- CD79b- Matutes Score 4 ou 5 / 5	13q(del) 60% +12 15-20% 11q (del) 30% 17pdel 2-30%		-
MCL	CD20 CD5 CCDN1+ SOX11+ except indolent MCL	t(11;14)(q13;q32) 95%		-

Swerdlow SH. et al. IARC 2008; Kiel et al. 2012; Rossi D et al. 2012; Tiacci E et al. 2011; Treon SP. et al.

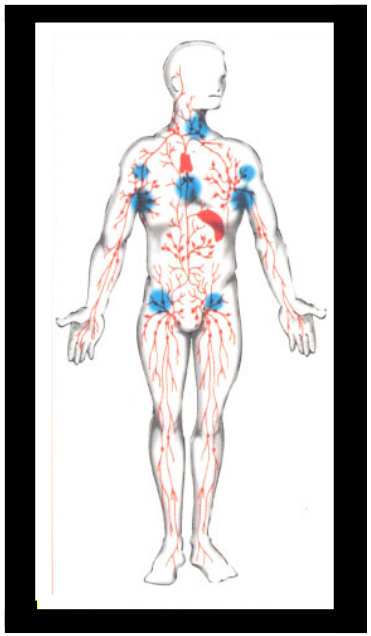
Nodal Marginal Zone lymphoma

Nodal Marginal Zone Lymphoma

➢ **Very rare lymphoma :** 1.5% to 15% of the NHL series

➢ **Clinical presentation**

- Median age : 50-62 years
- Disseminated nodal involvement (peripheral and visceral)
- Bone marrow 28% - 44%
- M-component unfrequent < 10%
- Rare cytopenia



Sheibani et al. Am J Pathol 1986 - Cousar et al. Am J Clin Pathol - 1987 Piris M et al. Histopathology. 1988
Lennert K, Feller AC. Berlin: Springer Verlag; 1990 – Jaffe E. et al. REAL classification 1990 -Swerdlow et al WHO classification

Outcome

Study	No. of patients	5-y OS rate, %	Median OS, y	Median progression, y
Armitage et al (1998)[15]	25	57	ND	ND
Nathwani et al (1999)[44]	20	56	ND	ND
Berger et al (2000)[11]	37	55	ND	ND
Camacho et al (2003)[16]	22	79	ND	ND
Arcaini et al (2004)[13]	9	ND	Not reached	2.8
Traverse-Glehen et al (2006)[12]	21	64	ND	1.3
Oh et al (2006)[18]	36	83	5.5	1.3
Arcaini et al (2007)[14]	47	69	Not reached	2.6
Kojima et al (2007)[45]	65	85	ND	ND
Orciuolo (2010)[46]	89	96	ND	ND
Heilgeist et al (2012)[20]	32	89	ND	ND
Olszewski & Castillo (SEER) (2013)[10]	4724	77*	ND	ND

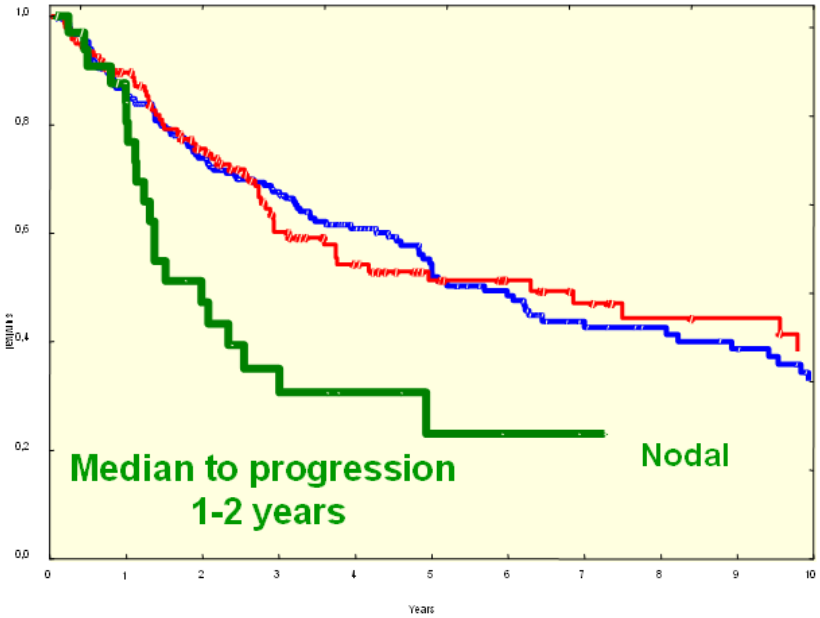
Median PFS : 1.3 to 2.6 years

5-y OS : 56 – 96%

Thieblemont C et al. Blood 2016 for review

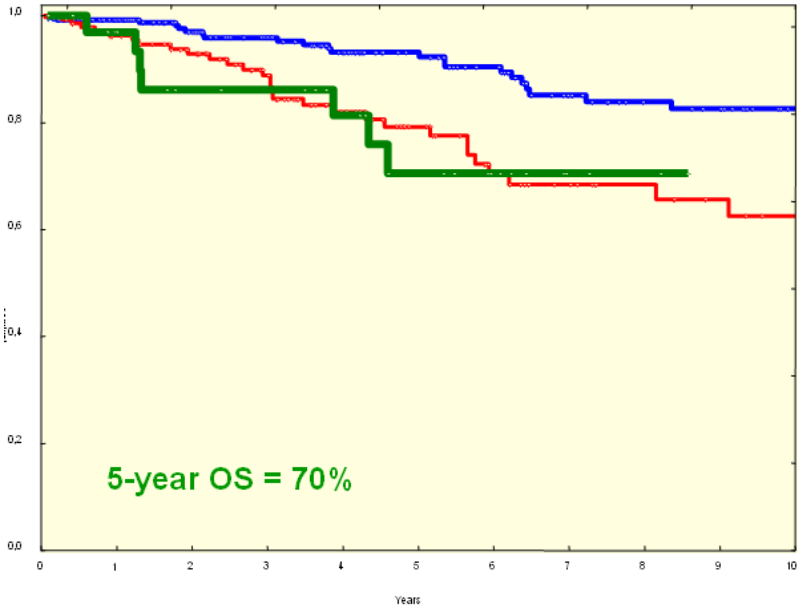
A more aggressive disease but a good outcome

Time to progression



Splenic
MALT

Overall survival



MALT
Splenic
Nodal

CHLS data

Thieblemont, C. 2005

Prognostic factors in NMZL

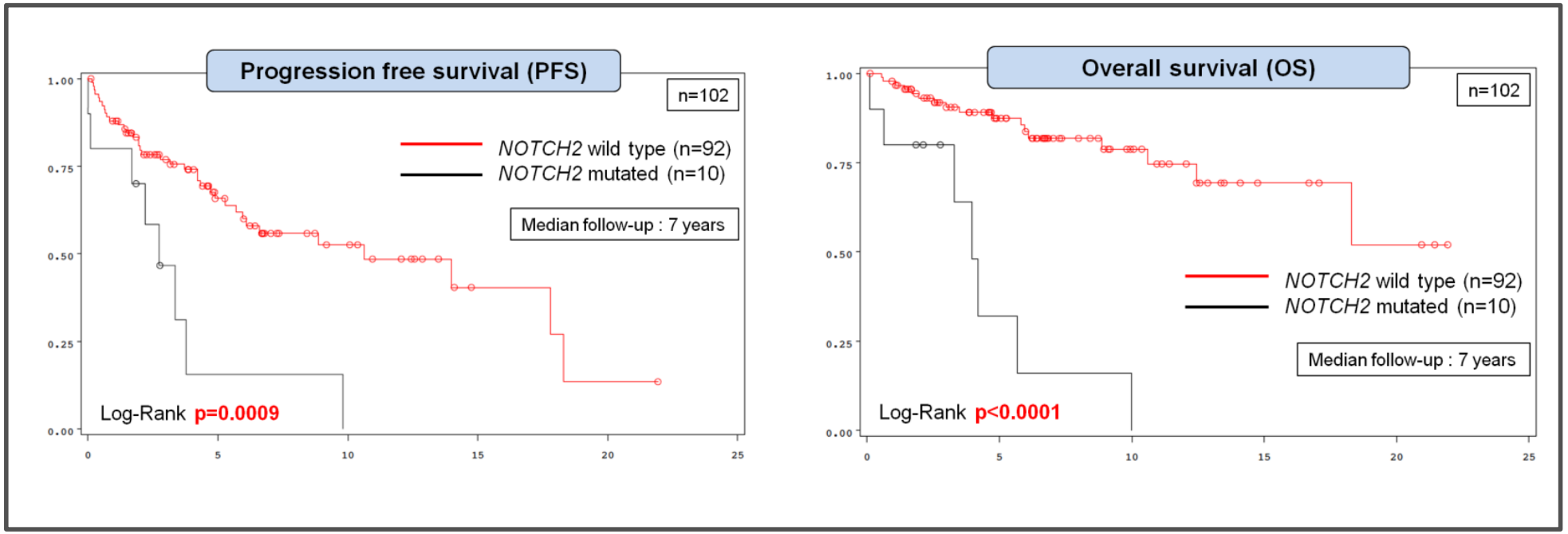
	PFS	OS
Factor	N=	N=
Age >60 y	36	47; 65; 4188*
Elevated LDH	36	47
Hb <12 g/dL	36; 47	36
BM+	36	36; 47
ECOG ≥2	36	36
Stage III/IV	36	36; 4188*
B symptoms	47	36; 4188*
No anthracycline	36	
Survivin	27	
Caspase 3	27	
FLIPI 3-5	32	
Male		4188*
HCV+		47
Cyclin E		27
Ki67		12
IRF4		12
FLIPI 3-5		32

Thieblemont C et al. Blood 2016 for review

Biomarkers and Clinical impact

Notch2 mutations

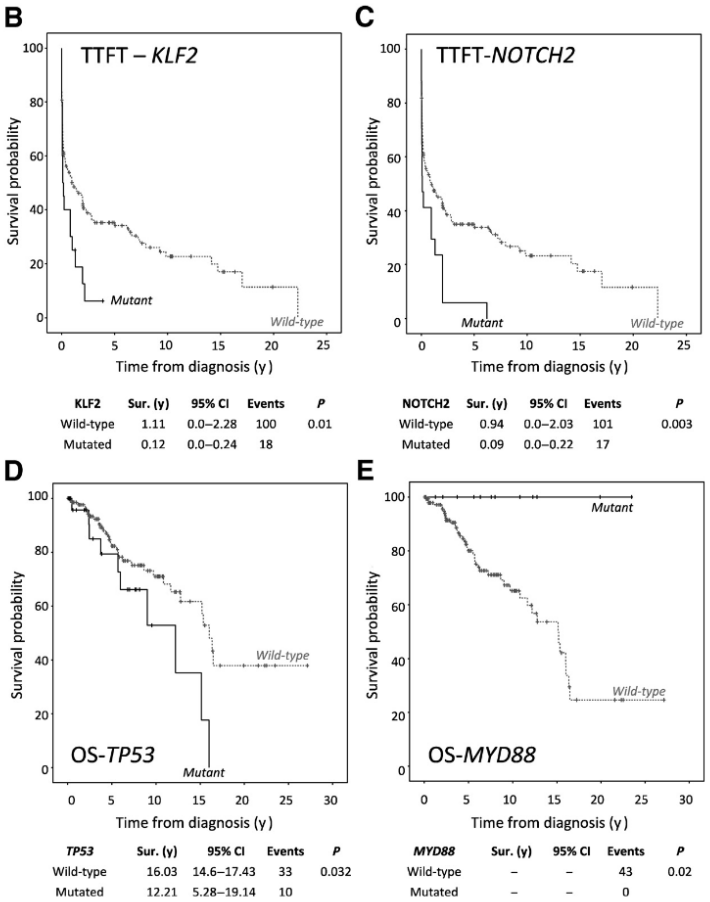
SMZL, n=100
Splenectomy



- Increased risk to transformation 16% vs 66% (p = . 0008)

Algrin C, et al. ASH 2012

Biomarkers and Clinical impact



KLF2	Sur. (y)	95% CI	Events	P
Wild-type	1.11	0.0–2.28	100	0.01
Mutated	0.12	0.0–0.24	18	

NOTCH2	Sur. (y)	95% CI	Events	P
Wild-type	0.94	0.0–2.03	101	0.003
Mutated	0.09	0.0–0.22	17	

TP53	Sur. (y)	95% CI	Events	P
Wild-type	16.03	14.6–17.43	33	0.032
Mutated	12.21	5.28–19.14	10	

MYD88	Sur. (y)	95% CI	Events	P
Wild-type	–	–	43	0.02
Mutated	–	–	0	

n=175 patients with SMZL

	Variable	Description	Total	Events	Median, y (95% CI)	HR (95% CI)	P
TTFT	*KLF2*	Mutated	20	18	0.12 (0.0–0.24)	1.93 (1.16–3.23)	**0.01**
		Unmutated	140	100	1.11 (0.0–2.28)		
	NOTCH2	Mutated	17	17	0.09 (0.0–0.22)	2.13 (1.26–3.58)	**0.003**
		Unmutated	143	101	0.94 (0.0–2.03)		
	Hb	<12 g/dL	70	63	0.1 (0.04–0.17)	2.75 (1.87–4.02)	**<0.001**
		>12 g/dL	84	51	2.73 (0.0–7.14)		
	Lymphocytes	<4 × 10^9/l	40	33	0.15 (0.07–0.24)	1.76 (1.16–2.68)	**0.007**
		>4 × 10^9/l	101	69	1.43 (0.50–2.37)		
	IGHV identity	100%	12	11	0.14 (0.0–0.38)	2.06 (1.07–3.74)	**0.027**
		<100%	78	50	1.98 (0.98–2.99)		
EFS	*TP53*	Mutated	15	8	0.98 (0.04–12.22)	2.17 (1.00–4.74)	**0.05**
		Unmutated	84	32	3.11 (2.35–6.20)		
	Age	>65 y	53	26	6.82[a] (4.45–9.20)	2.09 (1.07–4.08)	**0.028**
		<65 y	45	14	12.69[a] (9.19–16.18)		
	Platelet count	<100 × 10^9/L	19	11	2.92 (2.03–3.80)	1.99 (0.98–4.02)	**0.052**
		>100 × 10^9/L	78	28	6.91 (4.47–9.34)		
OS	*TP53*	Mutated	26	10	12.21 (5.28–19.14)	2.16 (1.05–4.43)	**0.032**
		Unmutated	134	33	16.03 (14.64–17.43)		
	MYD88	Mutated	12	0	—[b]	—[c]	**0.02**[d]
		Unmutated	148	43	—		
	Age	>65 y	103	37	10.36[a] (9.0–11.76)	6.37 (2.55–15.87)	**<0.001**
		<65 y	56	6	22.65[a] (19.38–25.91)		
	Hb	<12 g/dL	68	24	9.01 (2.90–15.12)	2.69 (1.45–4.99)	**0.001**
		>12 g/dL	87	18	16.35 (14.99–17.70)		

- **KLF2, NOTCH2 mutations, IGHV genes lacking SHM : short time-to-first treatment**
- **TP53 abnormalities : short overall survival**
- **MYD88 mutations : long overall survival**

Parry et al, 2015

Take home messages

- **Heterogeneous presention**
- **Specific physiopathology**
- **Very indolent disease**
- **Clinical trials should be based on new prognostic index and include biomarkers**

International Splenic Lymphoma Study Group

Paris, October 9-10th, 2015

Next meeting 2017 in Pavia

And the IELSG