

Splenic marginal zone NHL: Update on biology and therapy

Jonathan W. Friedberg M.D., M.M.Sc.

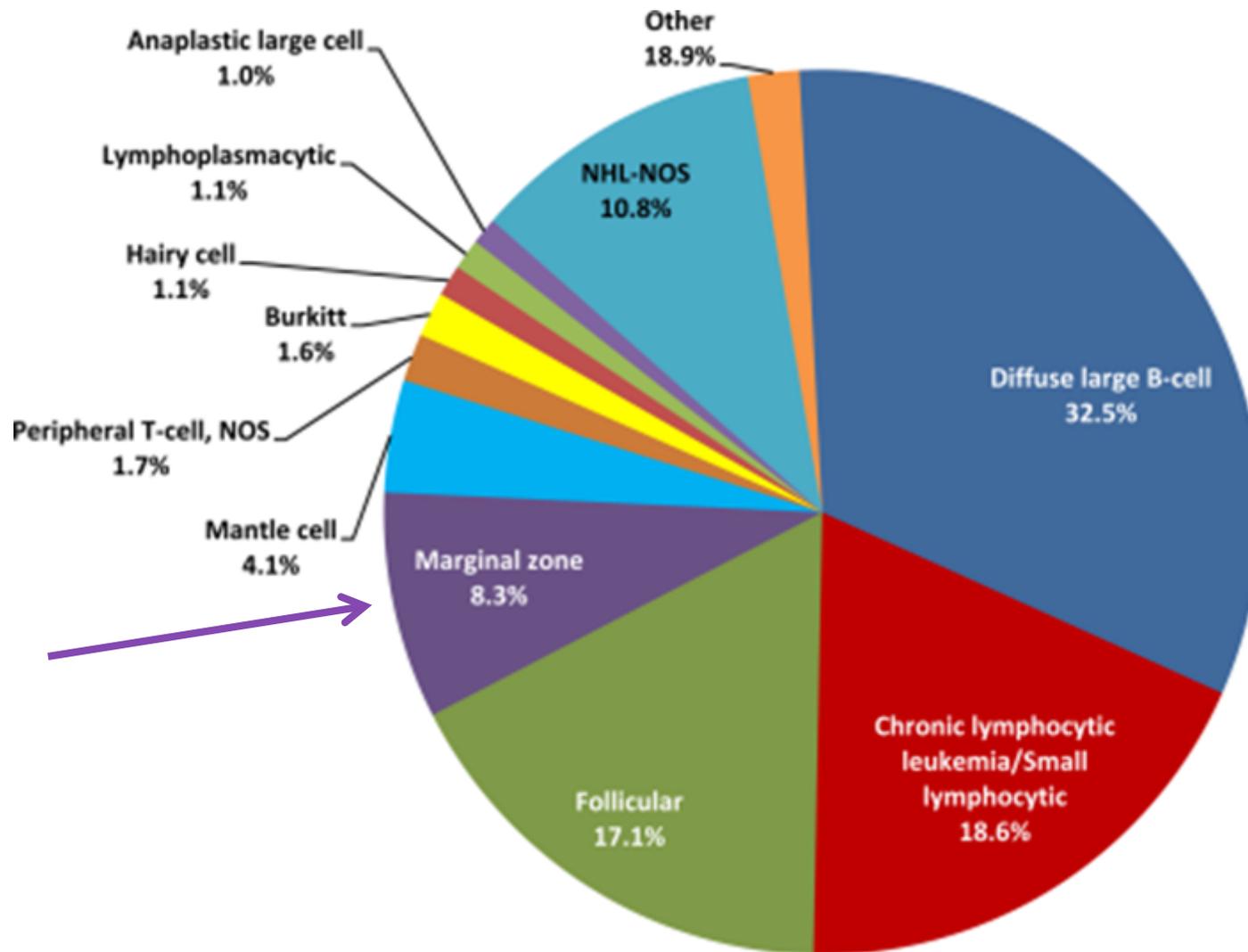


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Marginal zone NHL: A “Neglected” Lymphoma?

Marginal zone
NHL/MALT;
3rd most
common B-cell
NHL



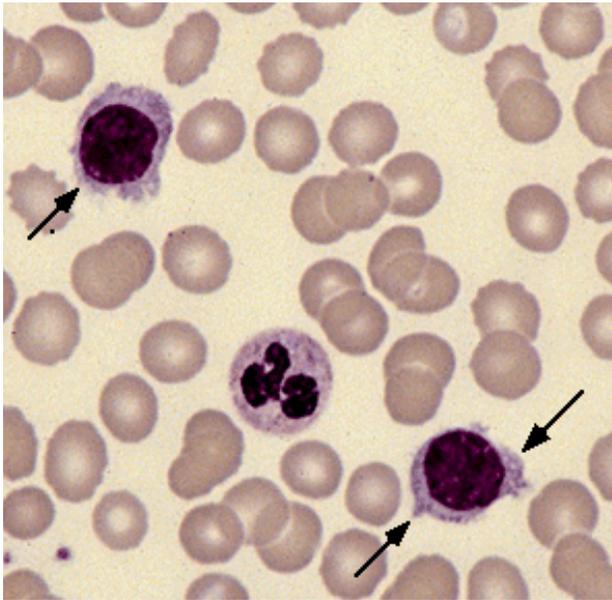
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Marginal zone lymphoma: Three distinct subtypes in WHO

- Extranodal marginal zone lymphoma of MALT (6%)
- Nodal marginal zone lymphoma (1-2%)
- Splenic marginal zone lymphoma (1-2%)

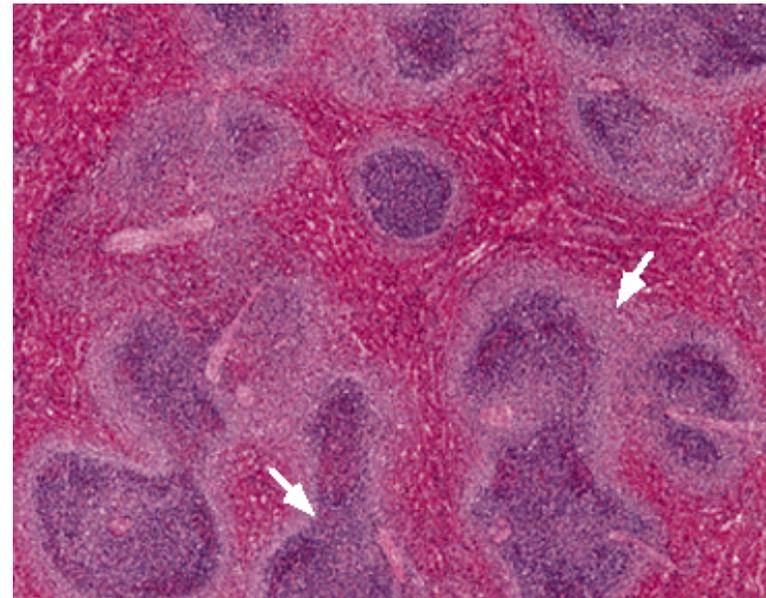


Splenic Marginal Zone NHL

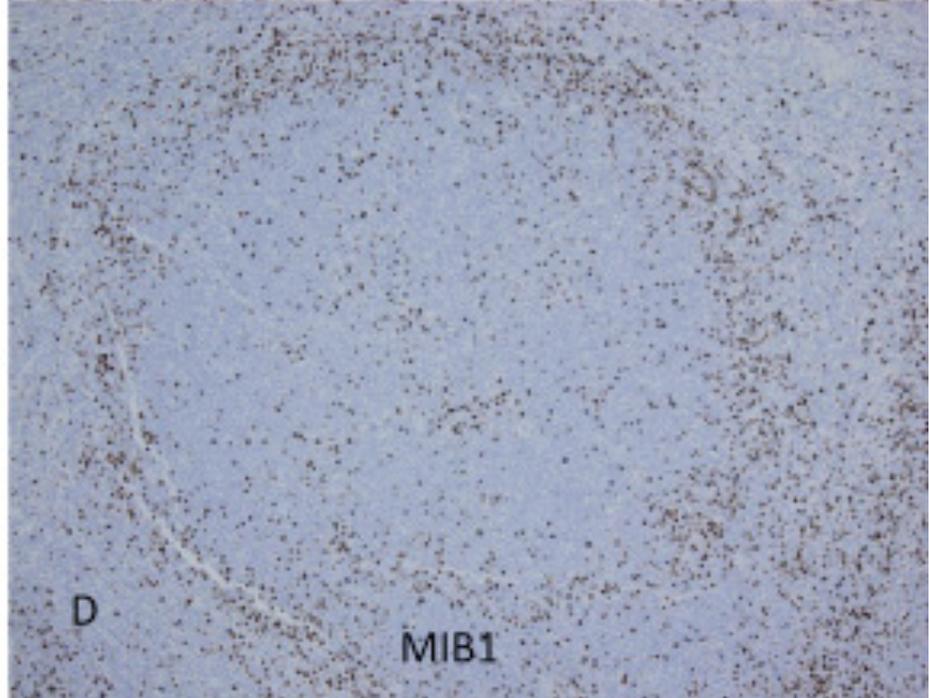
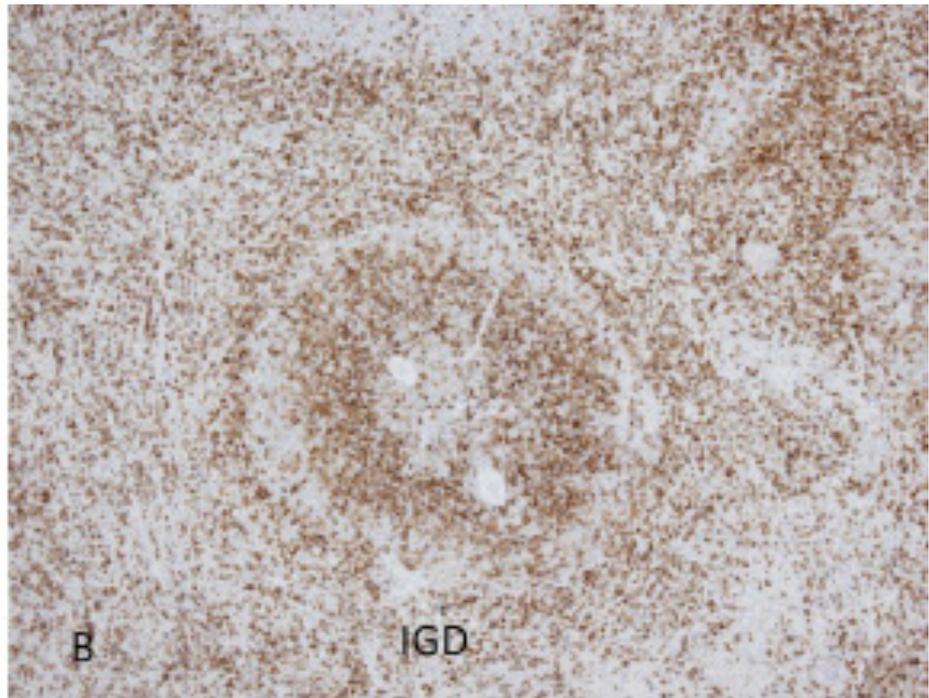
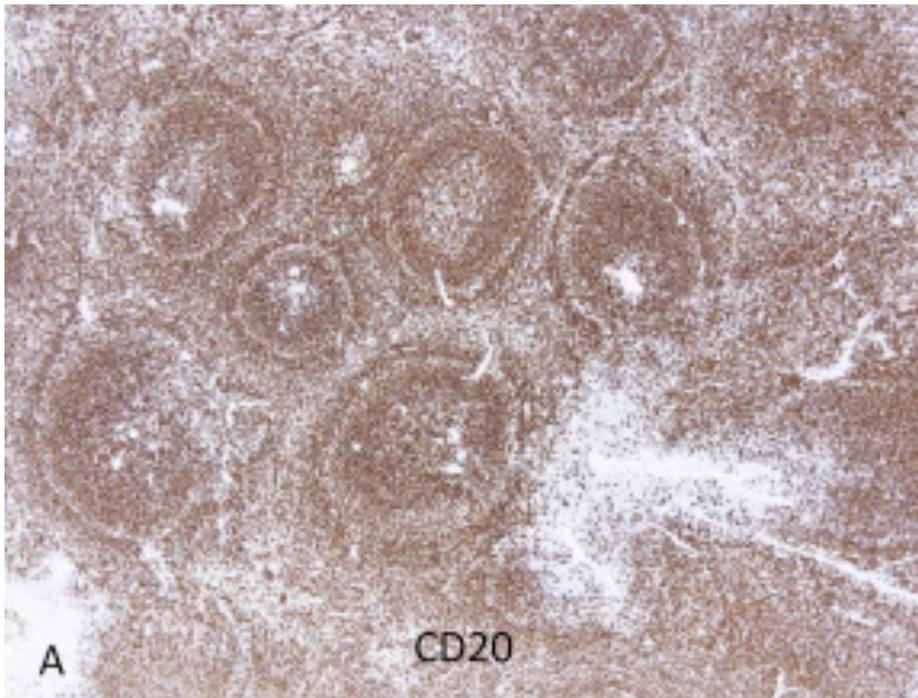


Villous Lymphocytes

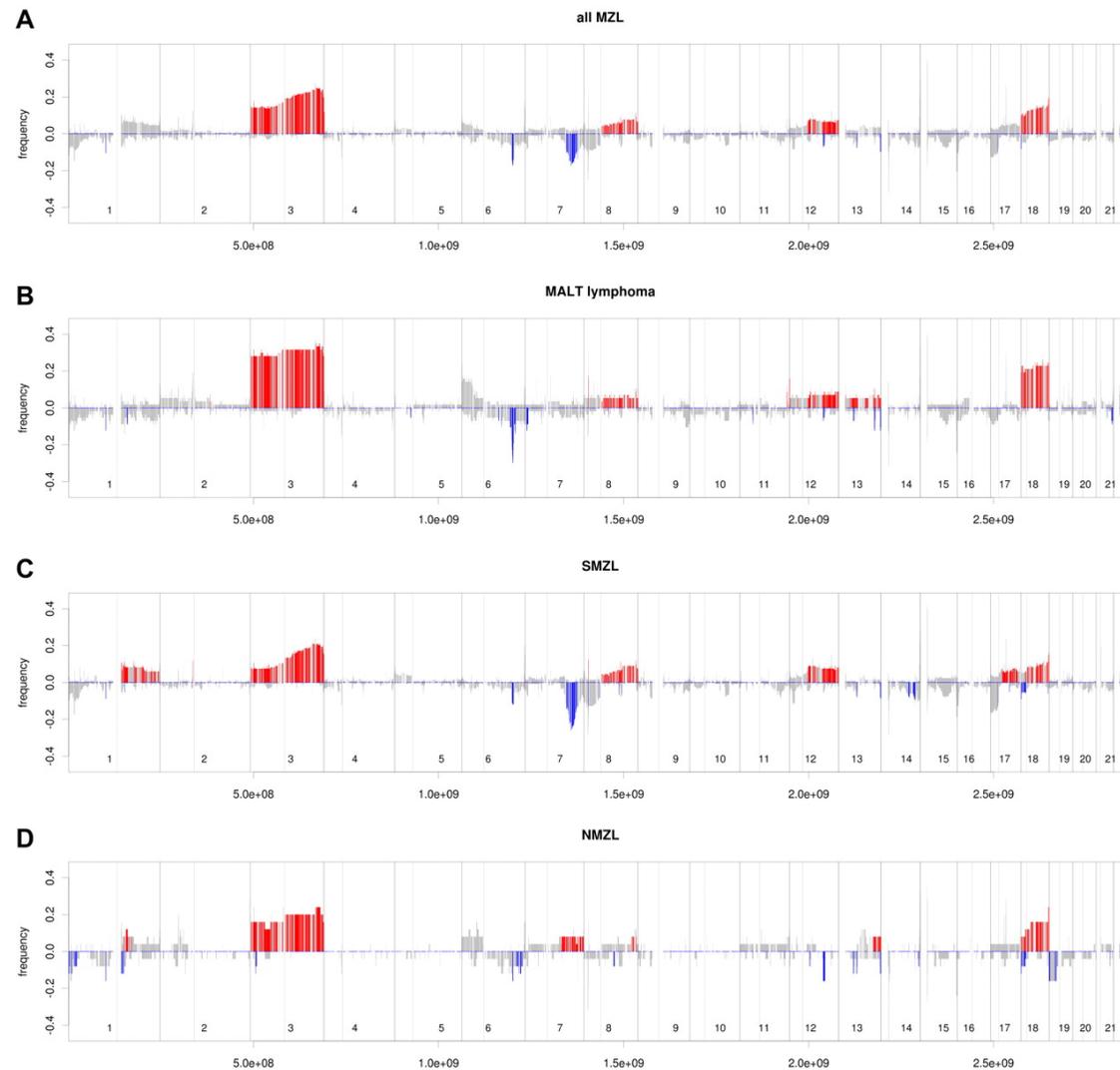
Splenic marginal zone expansion



CD5-, CD10-, CD43-, and CD23-. CD25- and CD103-.
B-cell antigens+ (CD19, CD20, CD22) and bcl-2+.



Frequency of DNA gains (up) and losses (down) in MZL



MZL
(N=218)

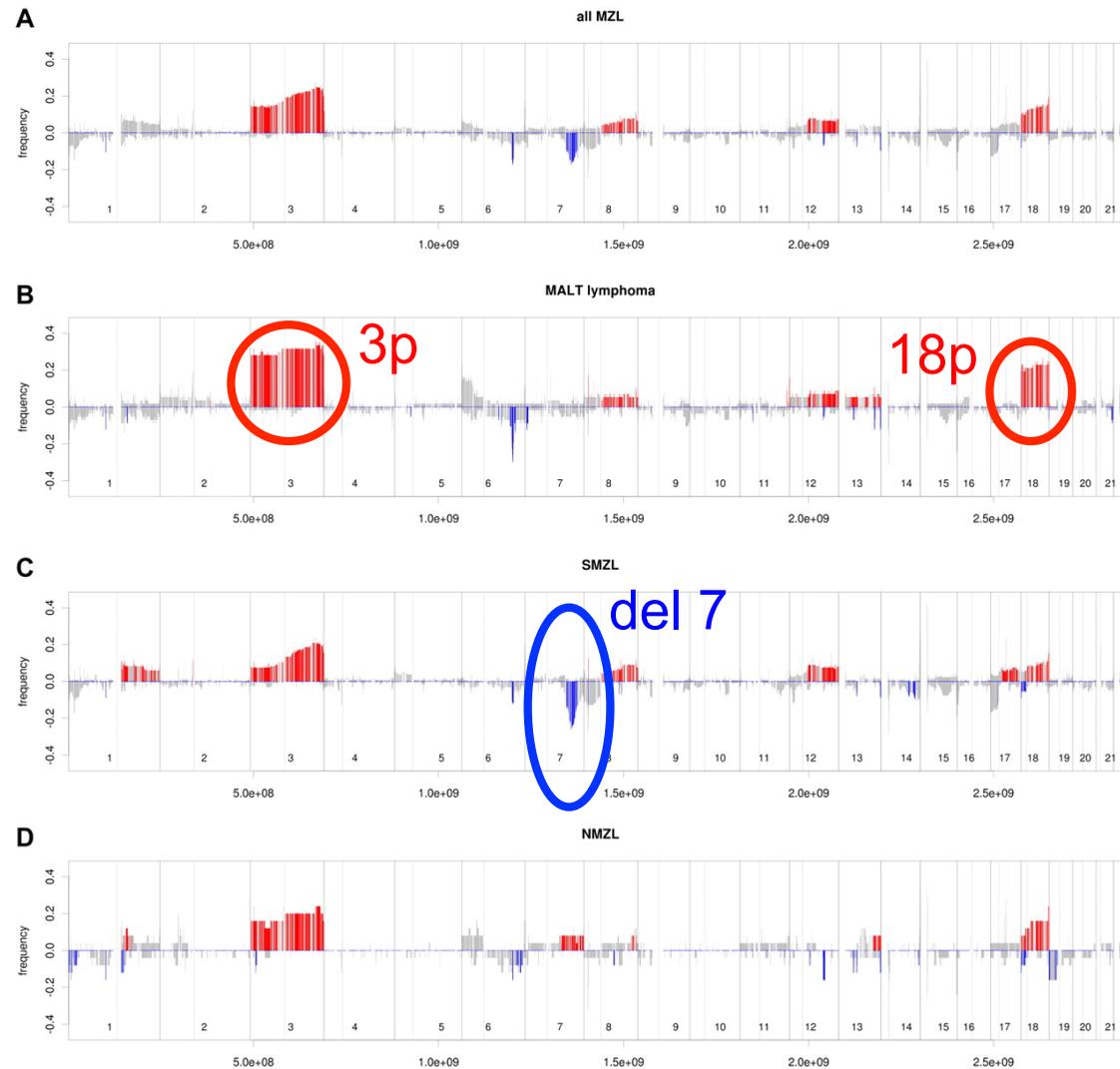
MALT
(N=57)

SMZL
(N=134)

Nodal MZL
(N=25)



Frequency of DNA gains (up) and losses (down) in MZL



MZL
(N=218)

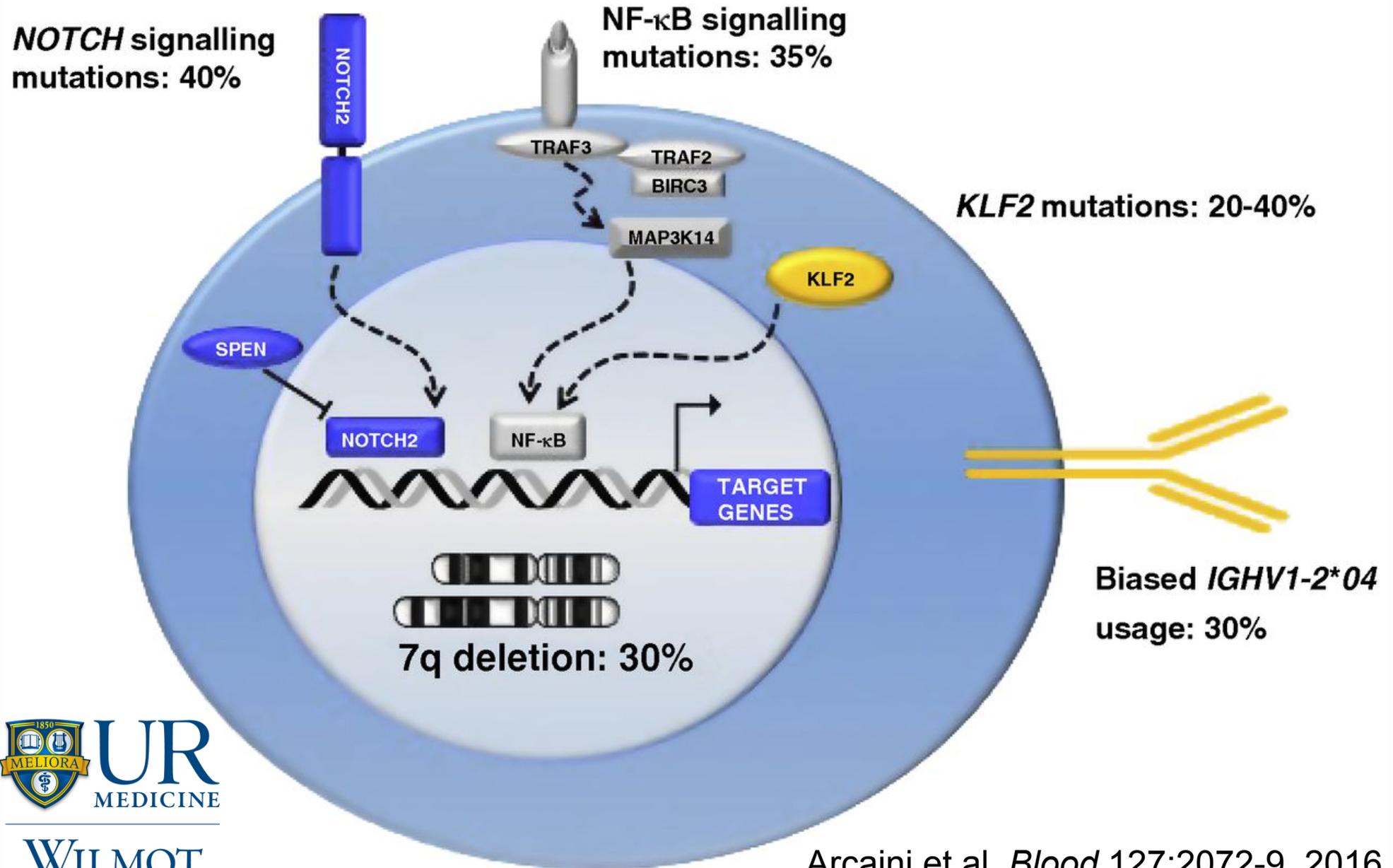
MALT
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SMZL
(N=134)

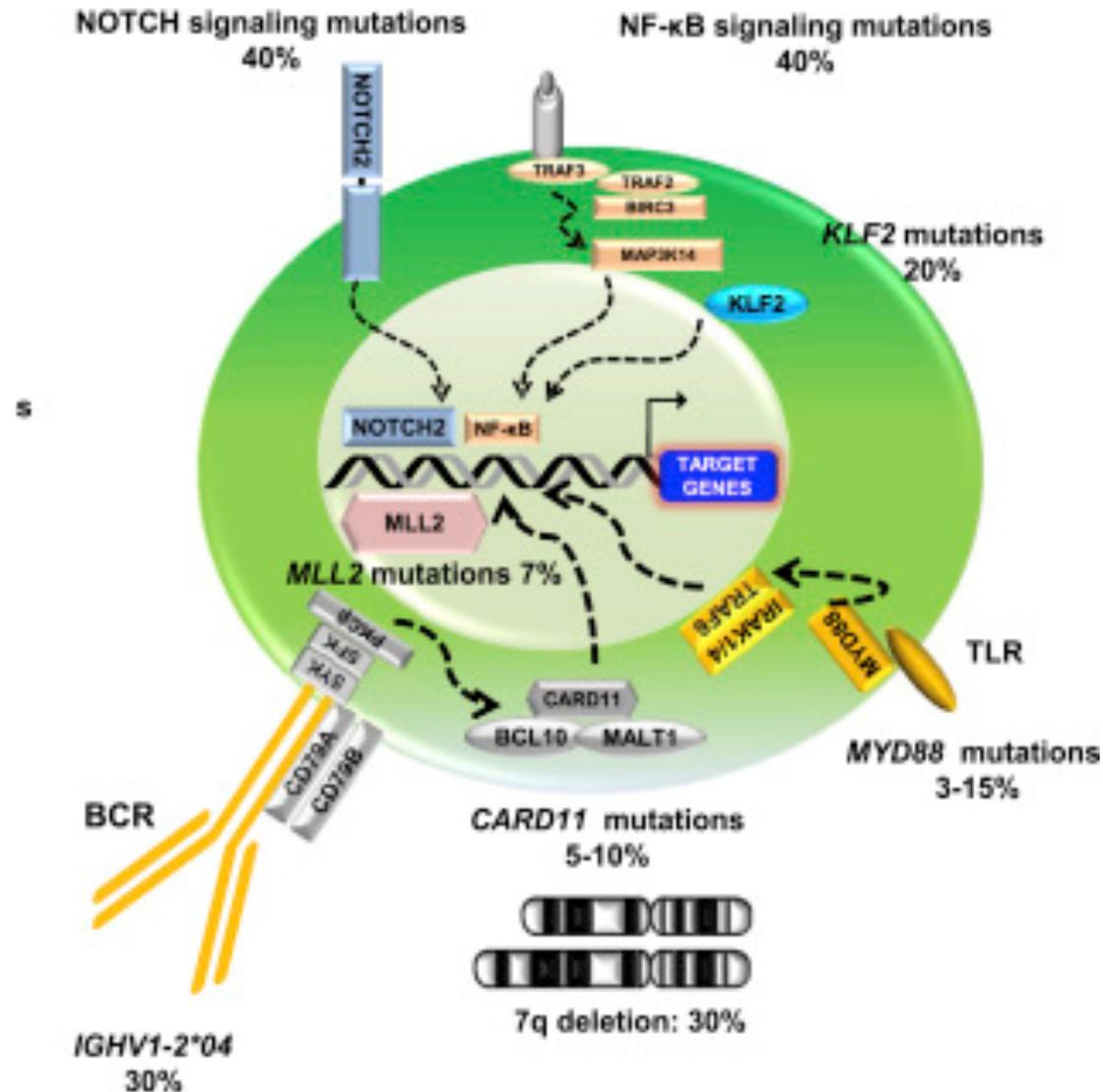
Nodal MZL
(N=25)



Key molecular alterations in SMZL



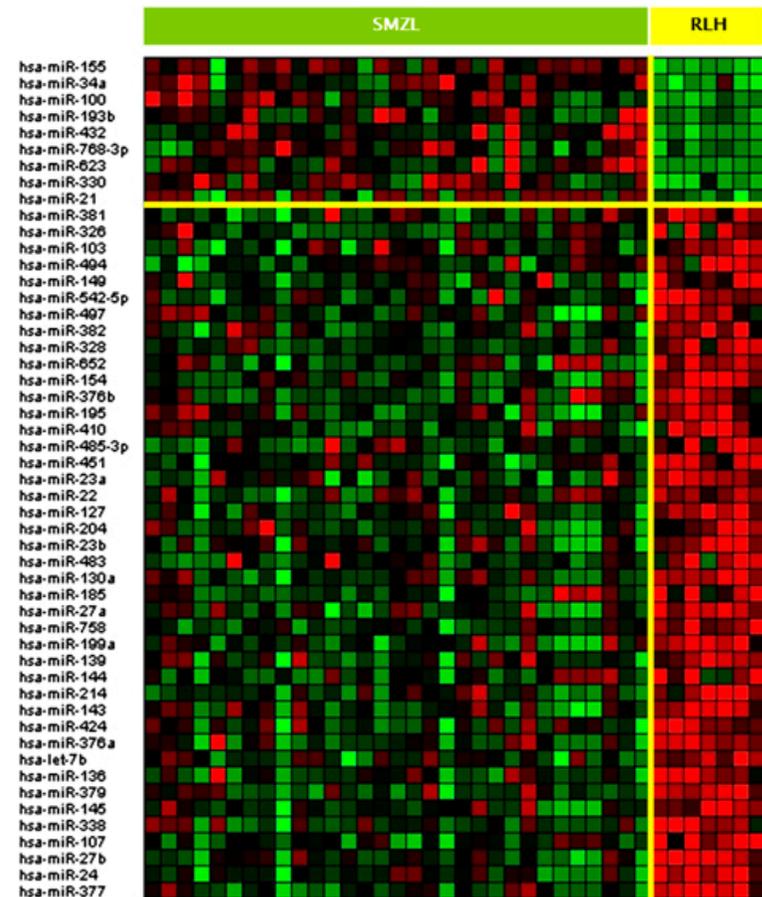
SMZL: Additional mutations



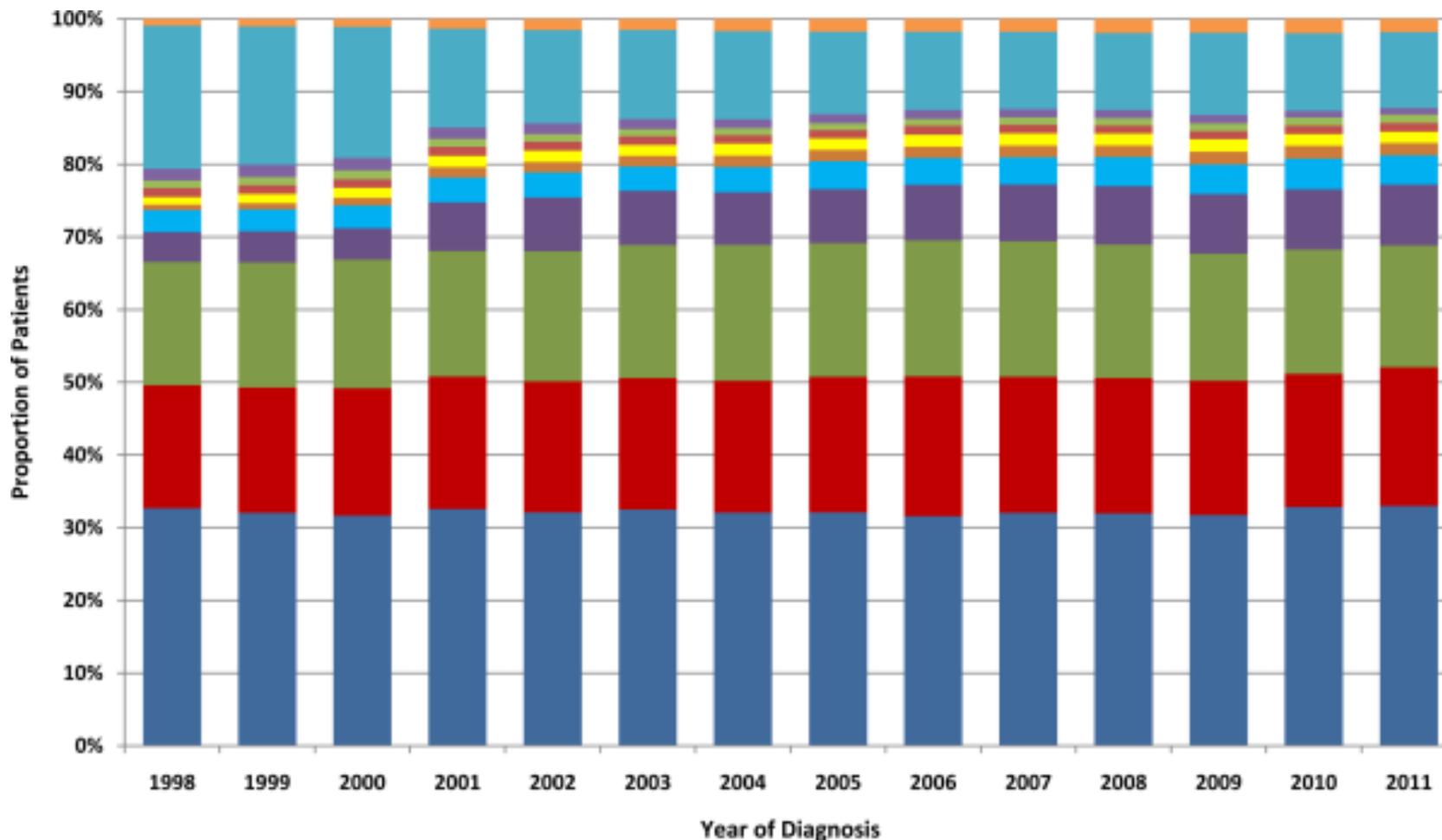
Splenic marginal zone lymphoma: Gene expression and mRNA profiling

The splenic marginal zone lymphoma miRNA signature contains 14 repressed miRNAs located in 14q32 chromosomal band (27% of the signature).

miRNA expression profile reproduces the *normal marginal zone* and *memory B-cell program*. The most relevant miRNAs of the signature have target genes involved in pathways such as NF- κ B and CD40 pathways.



Increasing incidence of MZL: National Cancer Data Base 1998 - 2011



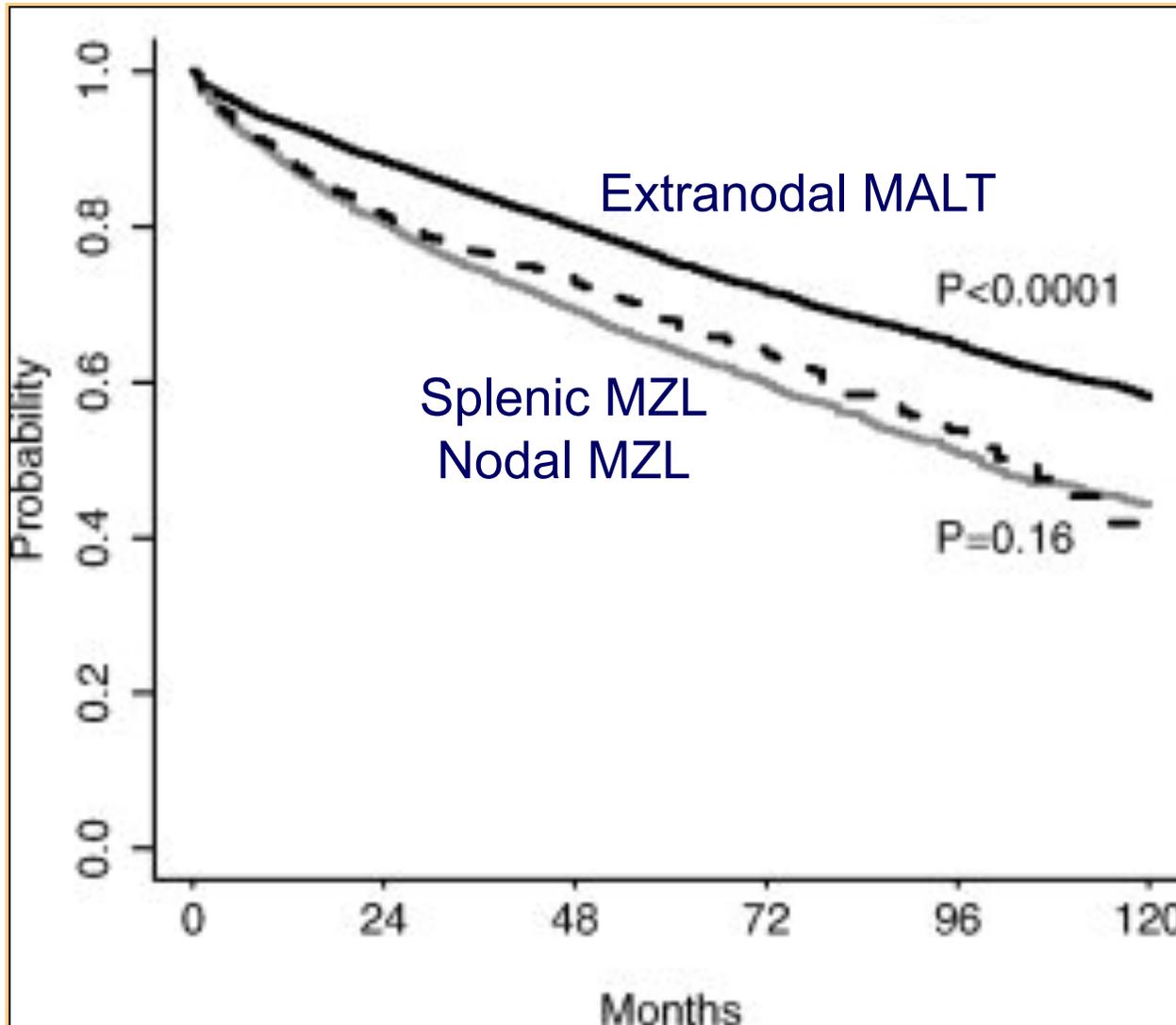
American Journal of Hematology
27 JUL 2015 DOI: 10.1002/ajh.24086

Marginal zone lymphoma in US

- SEER database, 1995-2009
- N=15,908; median age 68 years
- Key findings:
 - Increased incidence of NMZL 2001-2009
 - Most common sites of extranodal: gastric, ocular, bowel, pulmonary, salivary gland
 - Improvement in lymphoma survival for NMZL and MALT, **but no change for SMZL.**



Overall survival of patients Marginal zone NHL: SEER



SMZL: Prognosis

- Historically an indolent disease, but 30% of patients were not alive within 4 years of diagnosis; this is changing.
- IPI no value in SMZL
- Other proposed prognostic markers:
 - Beta-2 microglobulin
 - High circulating lymphocyte count

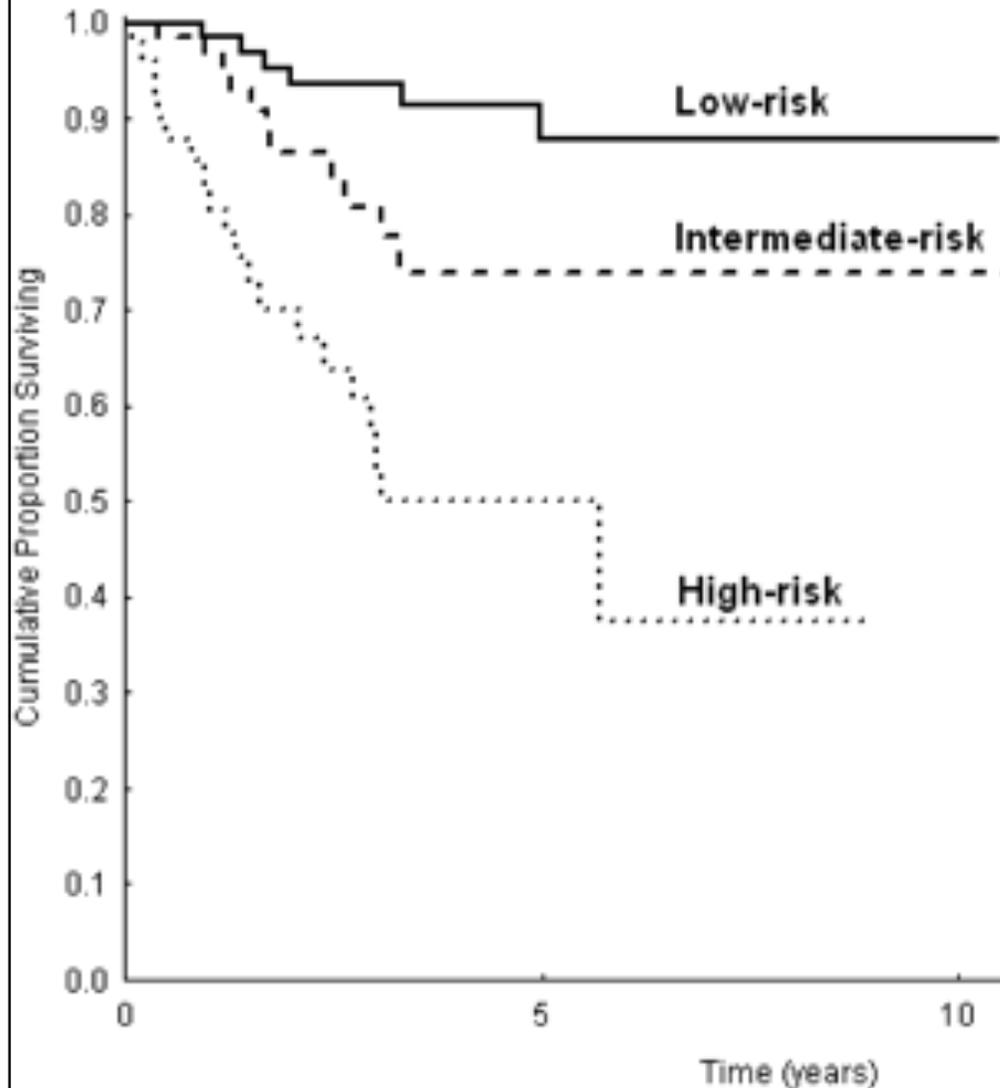


SMZL: Prognostic model

- *Intergruppo Italiano Linfomi* multicenter study (N=309)
- **Clinical parameters influencing OS and CSS in univariate analysis**
 - Hemoglobin level less than 12 g/dL
 - Albumin level less than 3.5 g/dL
 - IPI score 2-3
 - LDH level higher than normal
 - Age older than 60 y
 - HbsAg positivity
 - Platelet count below 100 000/ μ L
 - No splenectomy



SMZL: Prognostic model



Multivariate analysis

Hb < 12

LDH > normal

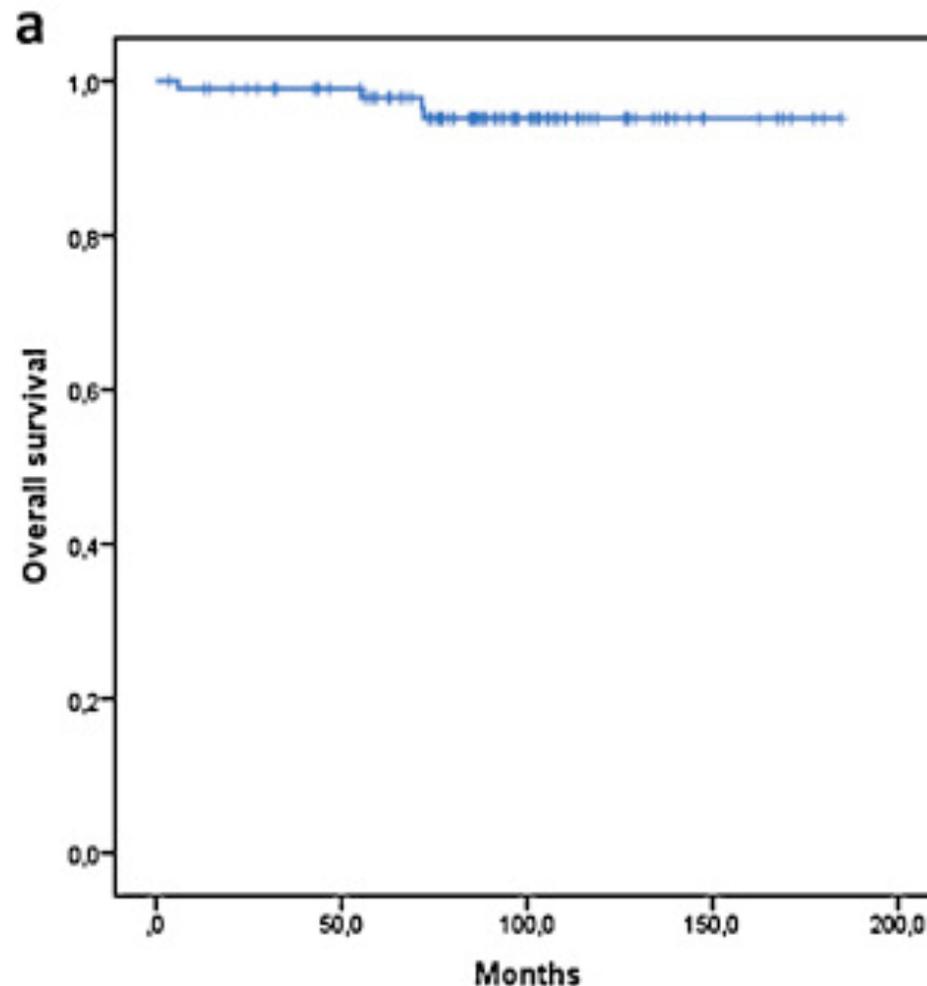
Albumin < 3.5

Splenectomy did not maintain significance in multivariate analysis

SMZL: Improving survival in rituximab era: Rome experience 2000-2012

10 year OS 95%, similar to
age-matched controls

Italian score remained
prognostic of outcome;
very few high-risk patients



SMZL: Improving survival in rituximab era: Cleveland US experience 2000-2012

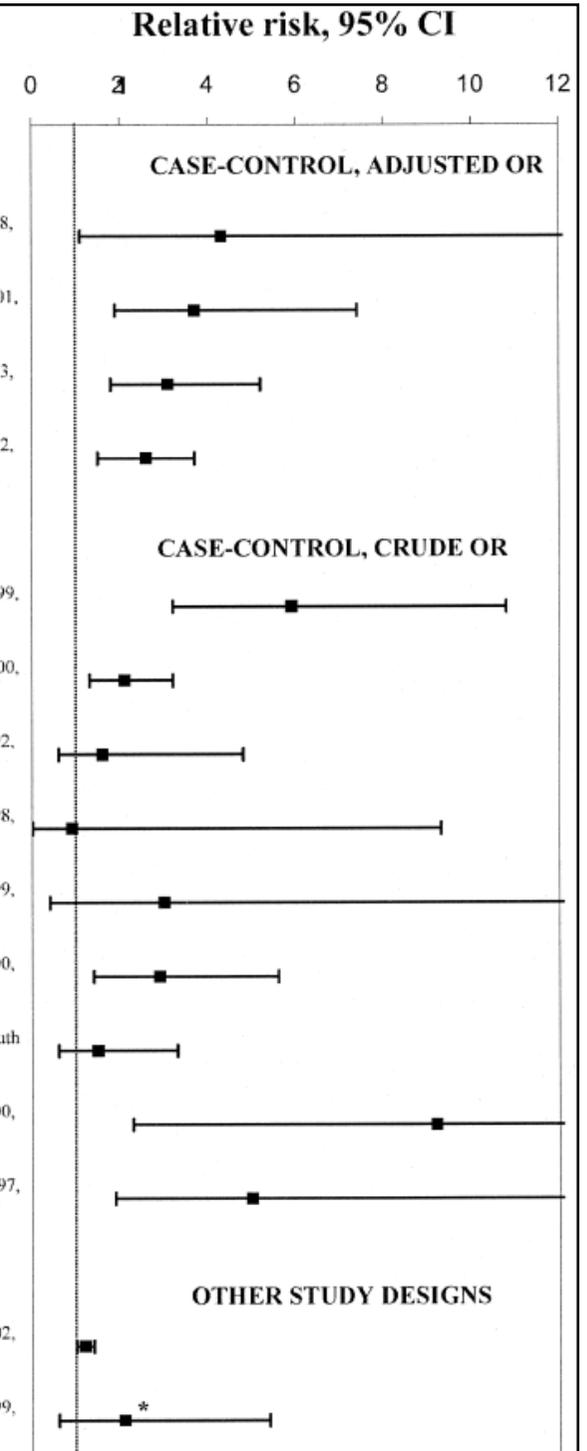
Median OS of >13 years; splenectomy did not predict for favorable outcome.

Low hemoglobin and high-risk FLIPI were associated with inferior outcomes.



Is SMZL associated with *Hepatitis C*?

- Association between HCV and NHL (MZL)
 - RR in the 2-4 range
 - Geographic variability:
 - Italy: 20% HCV-positive.
 - If prevalence of HCV is 1%, NHL attributable to HCV would be <1%



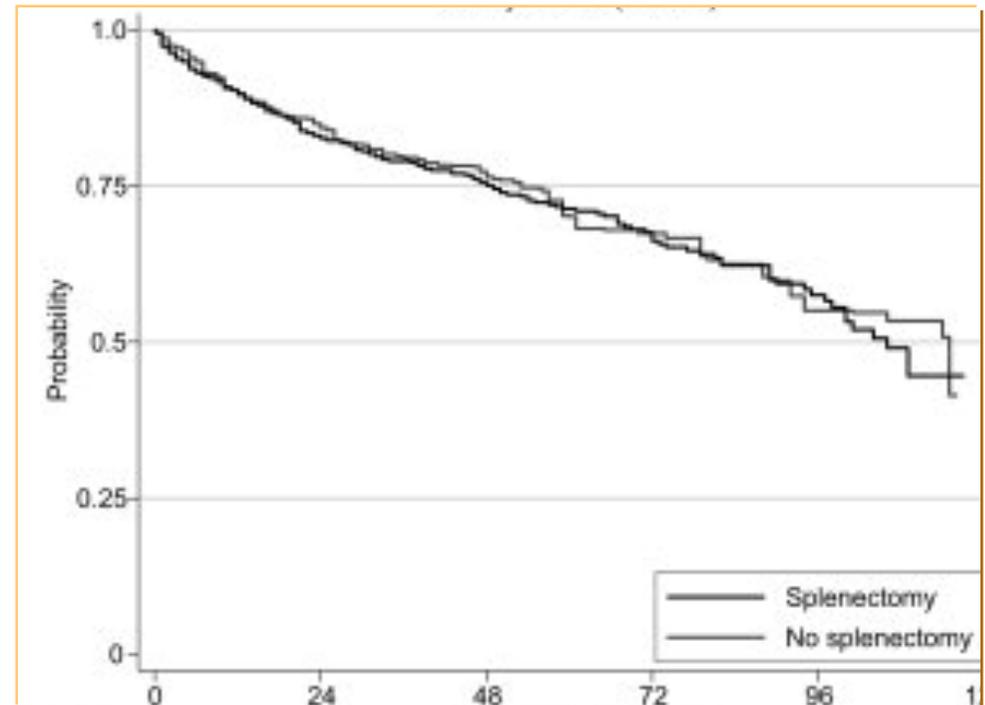
Is marginal zone lymphoma associated with *Hepatitis C?*

- Likely indirect role of antigenic stimulation
 - NHL identified that expresses antigen receptor for HCV
- Treatment of HCV with ribavirin plus IFN can result in regression of indolent NHL

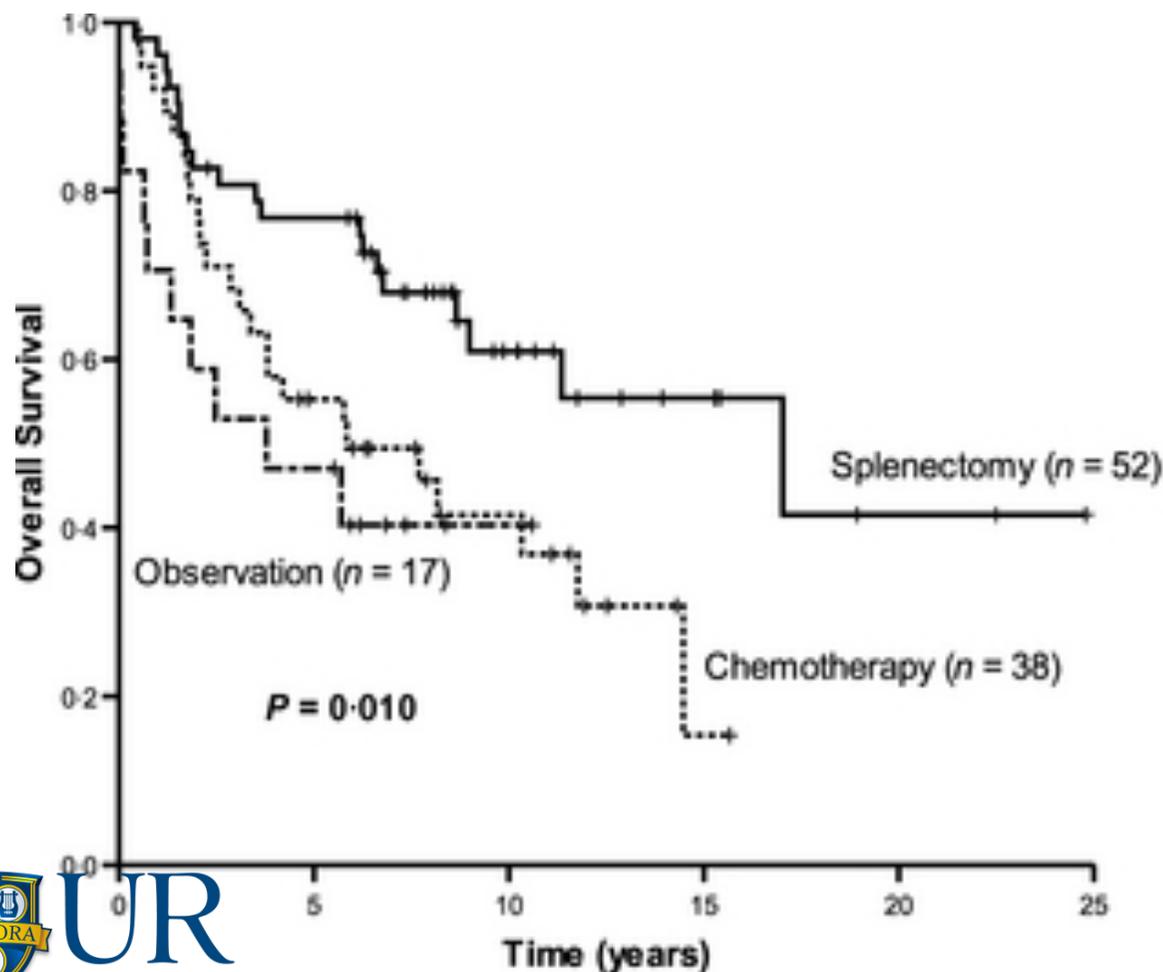


Overall survival with and without splenectomy in SMZL: SEER

- N=1251
- 52% splenectomy
- Propensity score, splenectomy or no splenectomy:
 - No difference in survival
 - No difference in lymphoma-specific survival



Vancouver experience: Improved OS with splenectomy for SMZL



Similar transformation rates to other indolent lymphomas

Survival of FL is now better than this experience.



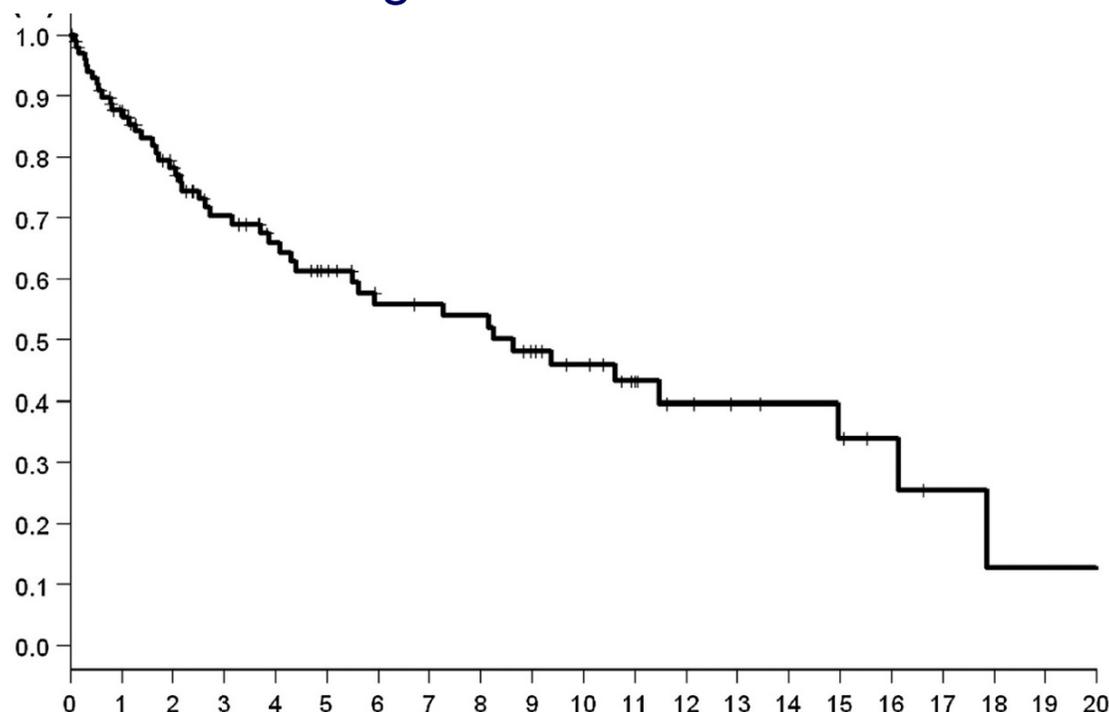
Long-term follow-up analysis of 100 patients with splenic marginal zone lymphoma treated with splenectomy as first-line treatment

Median PFS was 8.25 years.

The 5-year and 10-year overall survival (OS) rates were 84% and 67%, respectively.

Histological transformation occurred in 11% of patients

Progression-free survival

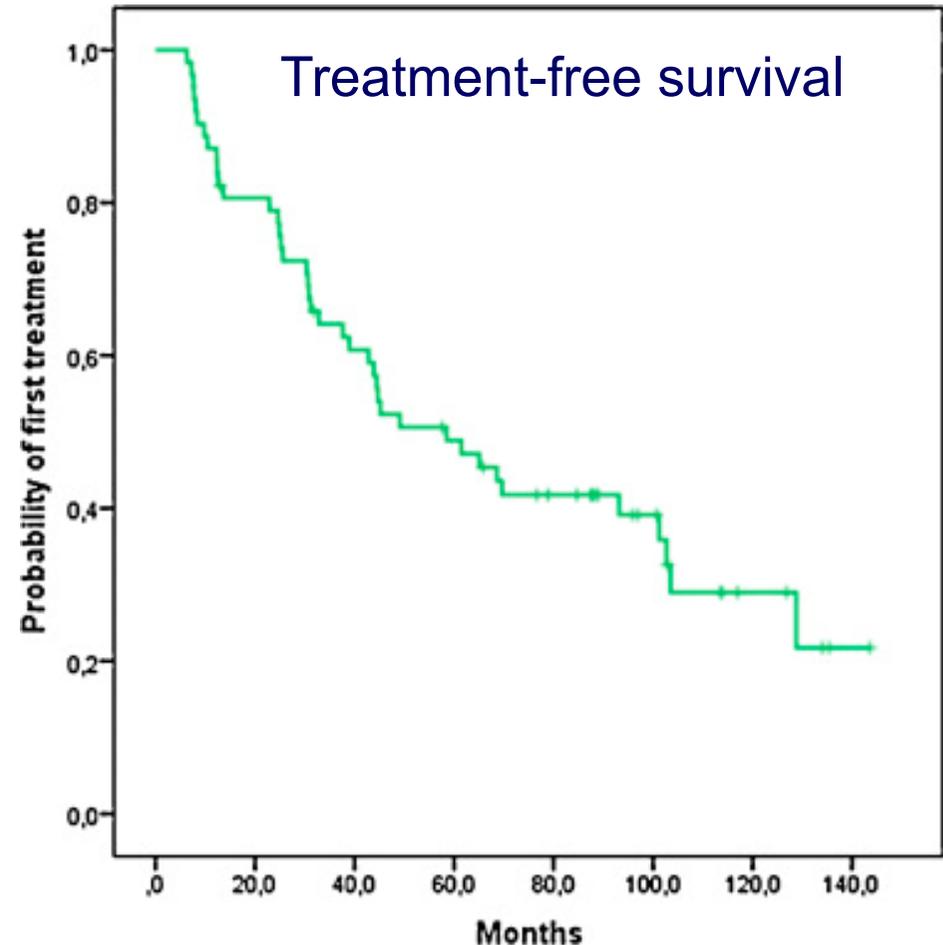


Watch and wait a viable option in SMZL: Rome experience

62 asymptomatic patients were observed at diagnosis.

Median treatment-free interval was 58 months.

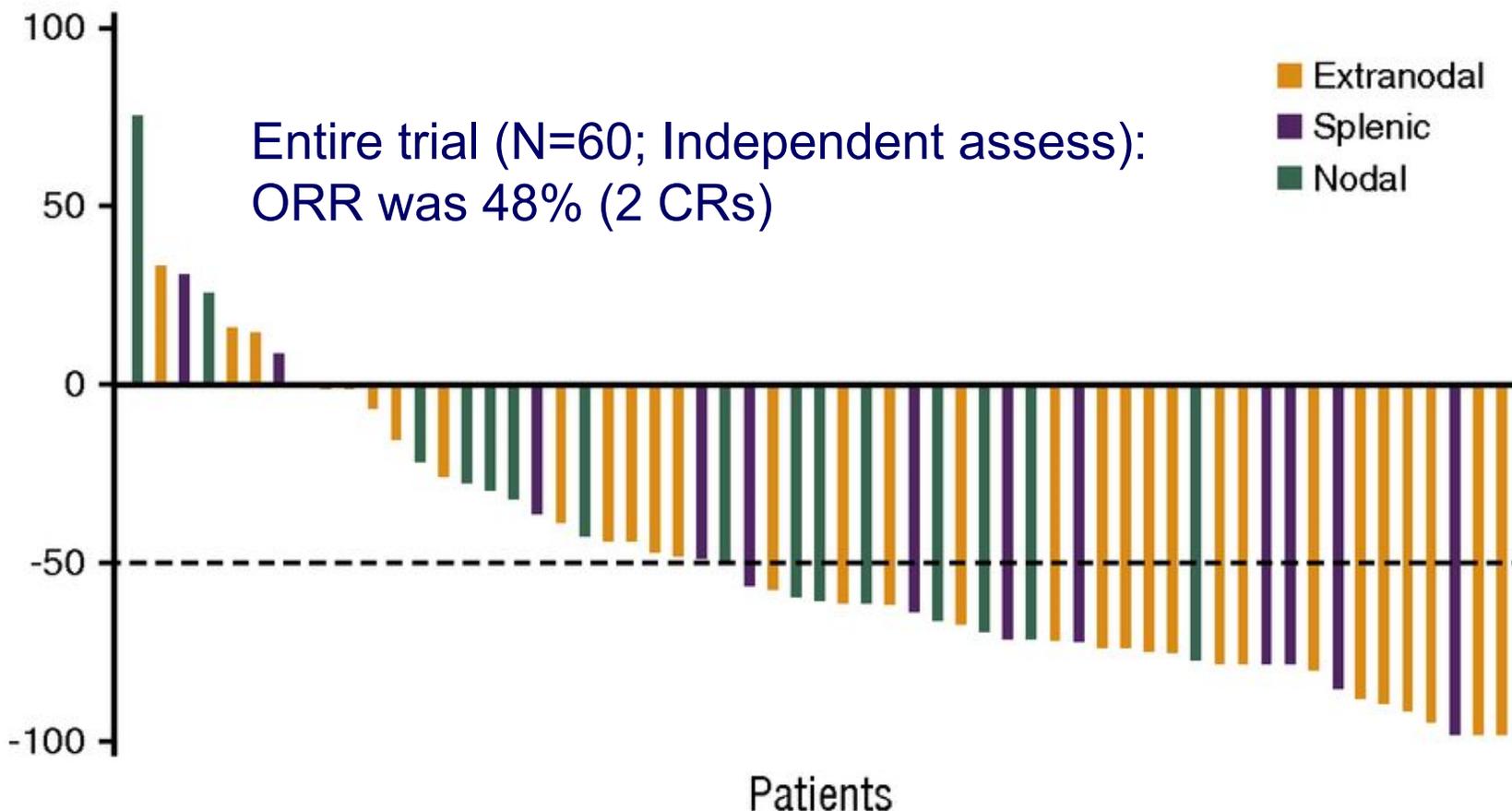
At 10 years, 30% of patients still did not require therapy.



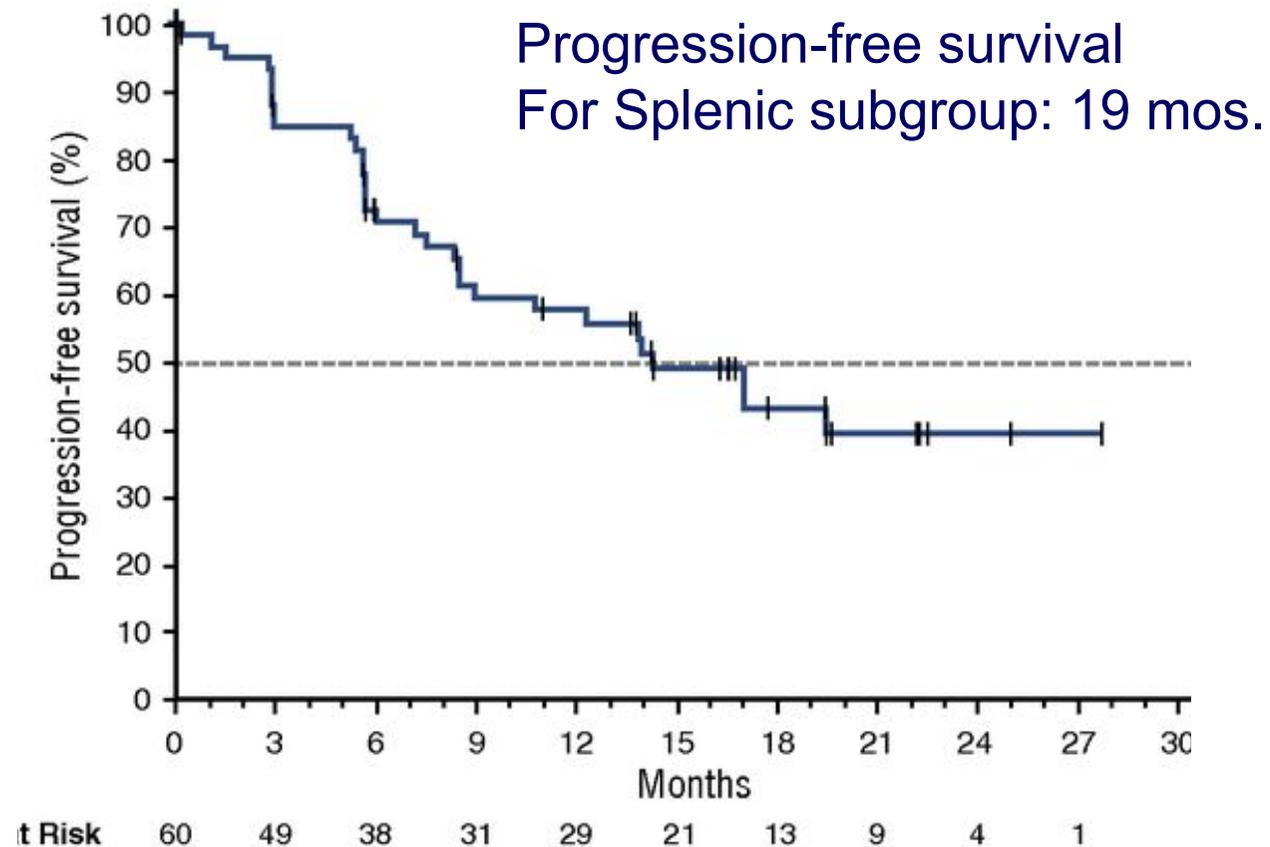
Outcomes of rituximab in SMZL

<u>Author</u>	<u># of pts</u>	<u>ORR (%)</u>	<u>CR (%)</u>	<u>PFS (%) (years)</u>	<u>OS (%) (at n years)</u>
Bennett et al.	11	91		60 (5)	70 (5)
Tsimberidou et al.	25	88	31	86 (3)	95 (3)
Kalpadakis et al.	16	100	69	92 (2.4)	100 (2.1)
Else et al.	10	100	90	89 (3)	NR
Kalpadakis et al.	58	95	45	73 (5)	92 (5)
Kalpadakis et al.	76	95	42	69 (7)	87 (7)

New therapeutic option: Ibrutinib in MZL



New therapeutic option: Ibrutinib in MZL



SMZL: Management approach

- Hepatitis C-associated
 - Antiviral therapy/Hepatology evaluation
- Non Hepatitis C-associated
 - Observation
 - Rituximab
 - Splenectomy
 - Novel agents



Acknowledgments

Mentors

Wilmot Lymphoma team

SWOG lymphoma team

International Collaborators

Patients



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