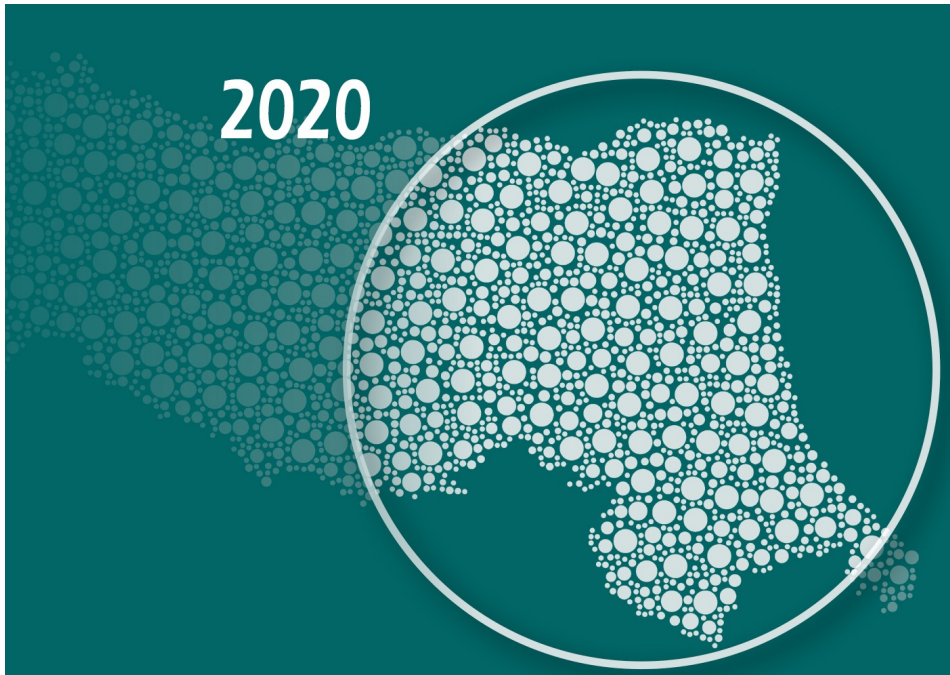


Progetto Ematologia Romagna

NOVITÀ NEI LINFOMI A BASSO GRADO
I linfomi della zona marginale
Faenza, 19 settembre 2020

Luca Arcaini
Divisione di Ematologia, Fondazione IRCCS Policlinico San Matteo e
Dipartimento di Medicina Molecolare, Università di Pavia

Posizione di dipendente in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**

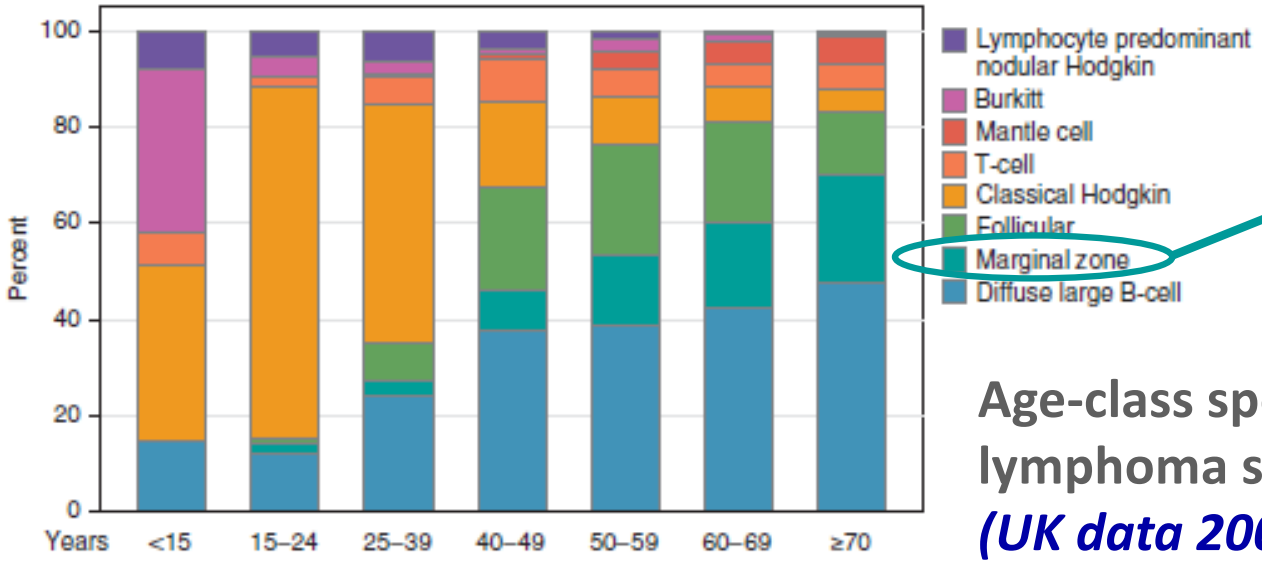
- Consulenza ad aziende con interessi commerciali in campo sanitario **Roche, Celgene, Janssen-Cilag, Gilead Sciences, Verastem, Sandoz**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **GILEAD**
- Partecipazione ad Advisory Board **CELGENE, JANSSEN-CILAG, VERASTEM**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Altro

Marginal-Zone B-Cell lymphomas: WHO 2017 subtypes

MZL WHO Subtypes	% of all lymphomas in SEER registries
Extranodal MZL of *Mucosa-Associated Lymphoid Tissue* (MALT-Lymphoma)	5%
Nodal MZL (NMZL)	2.4%
Splenic MZL (SMZL)	0.7%

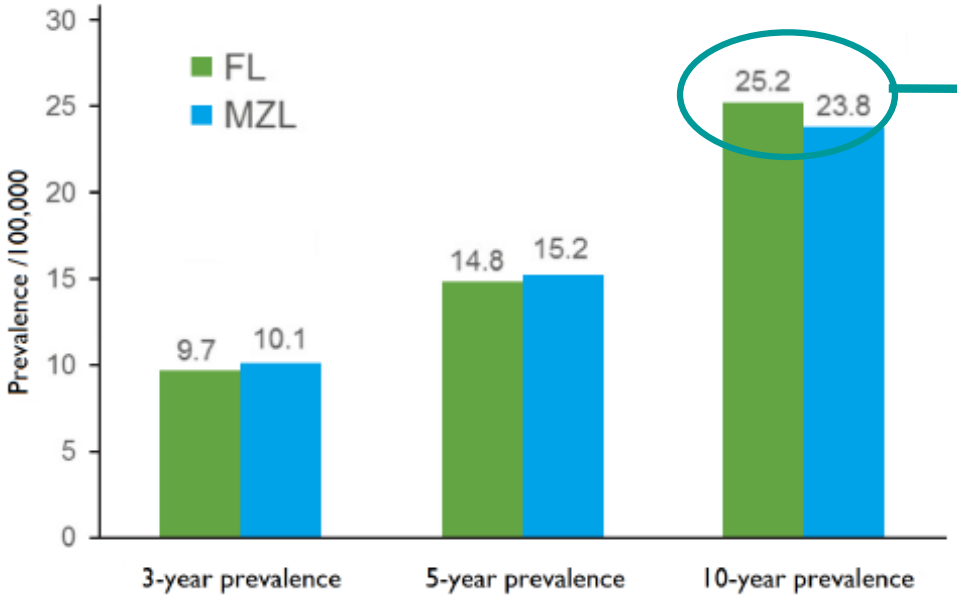
Olszewski and Castillo, Cancer 2013

Epidemiology of MZL



3rd most common B-NHL subtype

Age-class specific incidence by lymphoma subtype
(UK data 2004-2014)



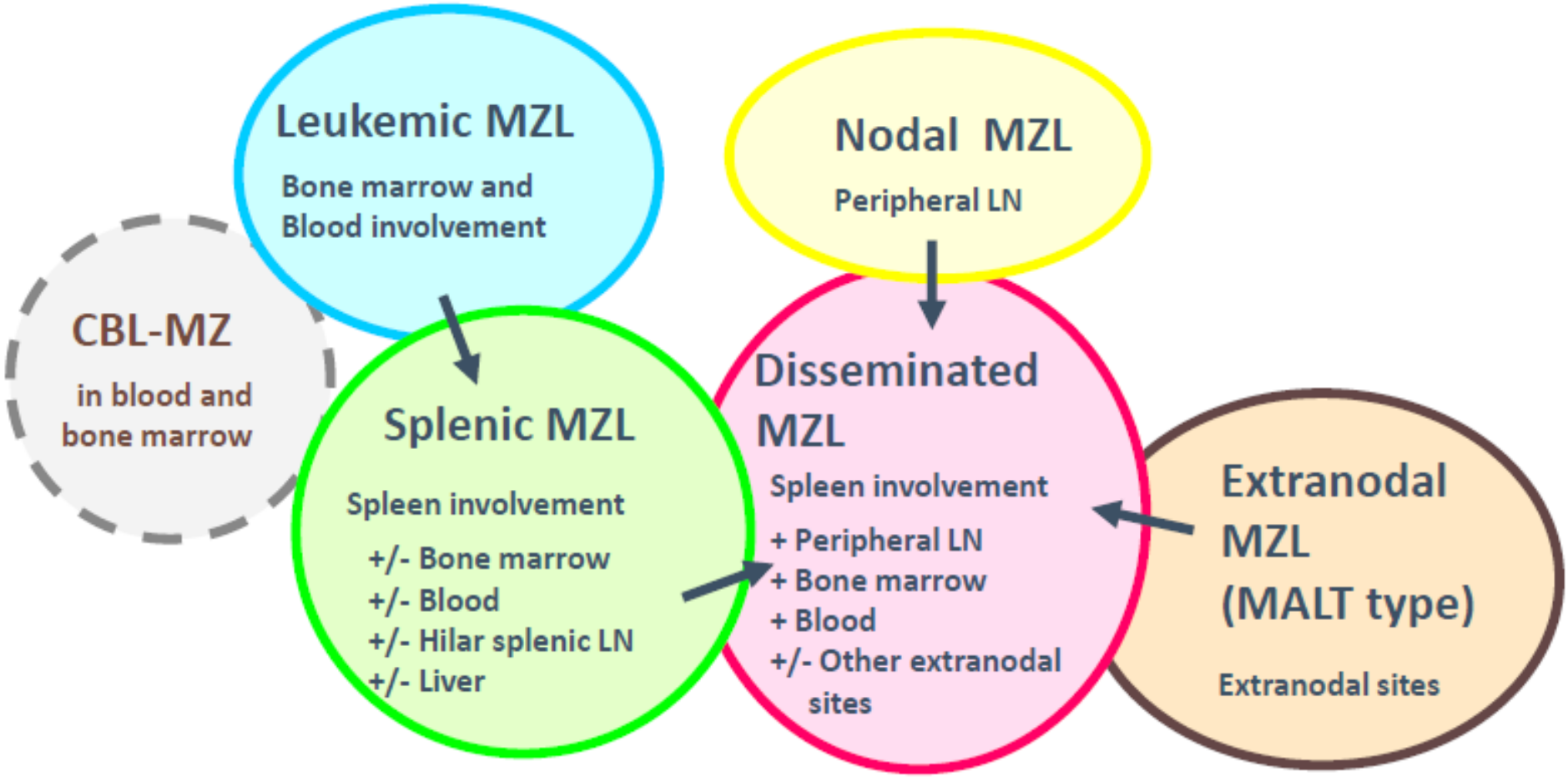
10y prevalence slightly inferior than FL

Prevalence of FL and MZL
(UK data 2004-2014)

Smith et al. BJC 2015
Monga et al. Ann Hematol 2019

MZL: a group of related clinical entities

Differential diagnosis not always straightforward



SPLENIC MARGINAL ZONE LYMPHOMA

Epidemiology

- NHL in the SEER: 763/116411 cases (0.7%) SMZL
- Median age at dg 69 years
- The overall age-adj incidence 0.13 per 100 000 persons per y
- Increasing trends among white, male, or age >70 years
- *International Lymphoma Epidemiology Consortium* NHL Subtypes Project (20 case-control studies, 17471 NHL cases, 23 096 controls): association with B-cell activating autoimmune conditions, asthma, and use of hair dye

Liu et al. Leukemia and Lymphoma 2013
Morton et al. J Natl Cancer Inst Monogr. 2014
Bracci et al. J Natl Cancer Inst Monogr. 2014

Minimal diagnostic criteria

1- Splenic histology + CLL score ≤2

in absence of spleen histology

2- Typical morphology (PB and BM) + FC

+ CD20+ intrasinusal infiltrate

Matutes et al. Leukemia 2008

Flow cytometry

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

SMZL: IgM+/IgD+, SIg +, CD20+, CD22+,CD24+, CD27+, FMC7+, CD79b+, CD103-, CD123-, CD10-, DBA44 + (75%), CD11c + (50%), CD23+ (30%), CD5 + (20%)

Arcaini et al. Blood 2016

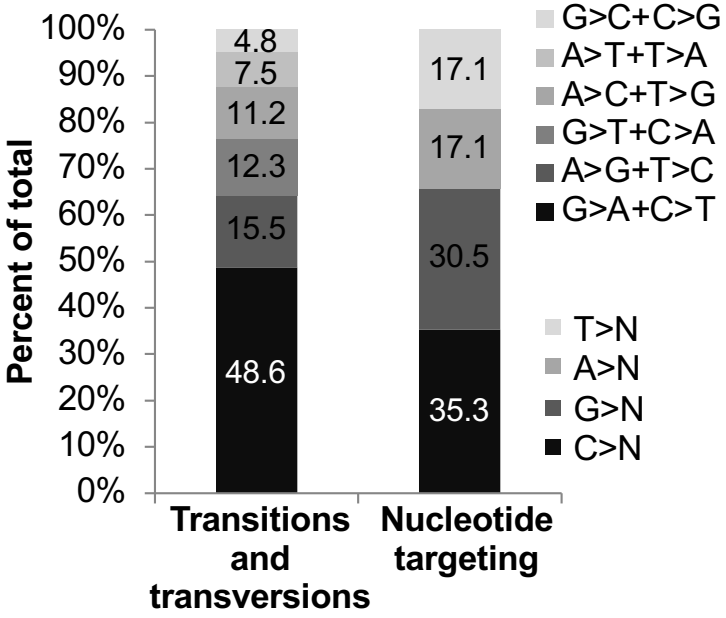
SMZL: IgM+/IgD+, SIg +, CD20+, CD22+,CD24+, CD27+, FMC7+, CD79b+, CD103-, CD123-, CD10-, DBA44 + (75%), CD11c + (50%), CD23+ (30%), CD5 + (20%)

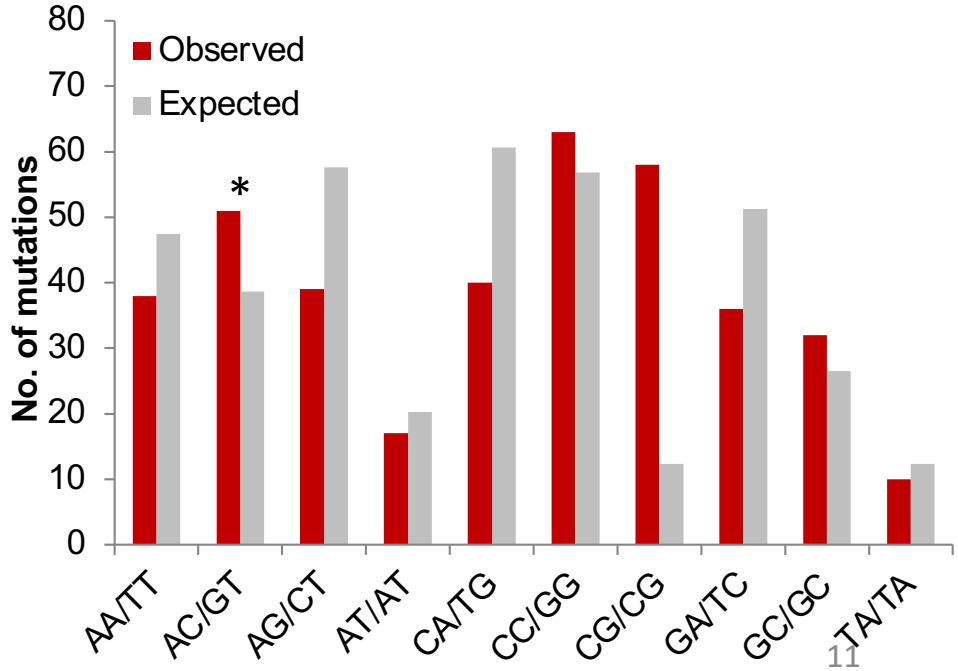
	SMZL	CLL	MCL	FL	HCL	HCL-v	MALT
Flow cytometry							
Strong SigM	+++	+/-	+++	+++	+++	+++	+++
CD5	+	+++	+++	-	-	-	-
CD23	+	+++	-	+	-	-	-
FMC7	+++	-	+++	+++	+++	+++	+++
CD11c	++	-	-	-	+++	+++	-
CD103	-	-	-	-	+++	++	-
CD123	-	-	-	-	+++	-	-
CD25	+	-	-	-	+++	-	-
CD27	++	+++	+++	+++	-	++	+
Immunohistochemistry							
DBA44	++	+	-	-	+++	+++	-
IgM, IgD	+++	+++	-	+	+++	+	+
CD10	-	-	-	+++	-	-	-
BCL6	-	-	-	+++	-	-	-
CCND1	-	-	+++	-	+	-	-
CD5	+	+++	+++	-	-	-	-
CD43	+	+++	+++	-	-	-	+
CD23	-	+++	-	+	-	-	-
CD27	++	+++	+++	+++	-	++	+
Annexin A1	-	-	-	-	+++	-	-

WES in SMZL

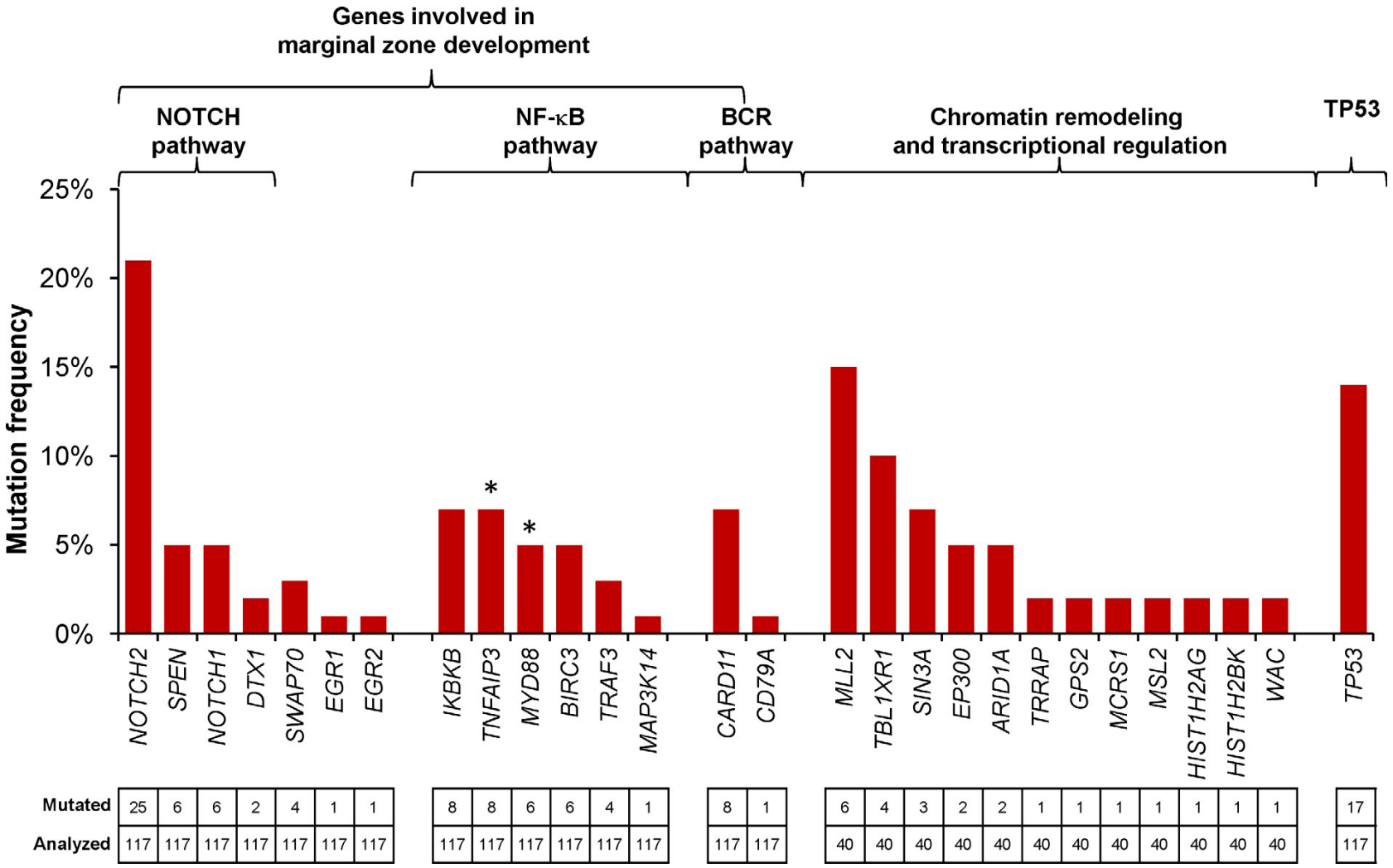
CLL:~ 10 lesions/exome
SMZL:~ 30 lesions/exome
DLBCL:~ 90 lesions/exome

Rossi et al, JEM 2012



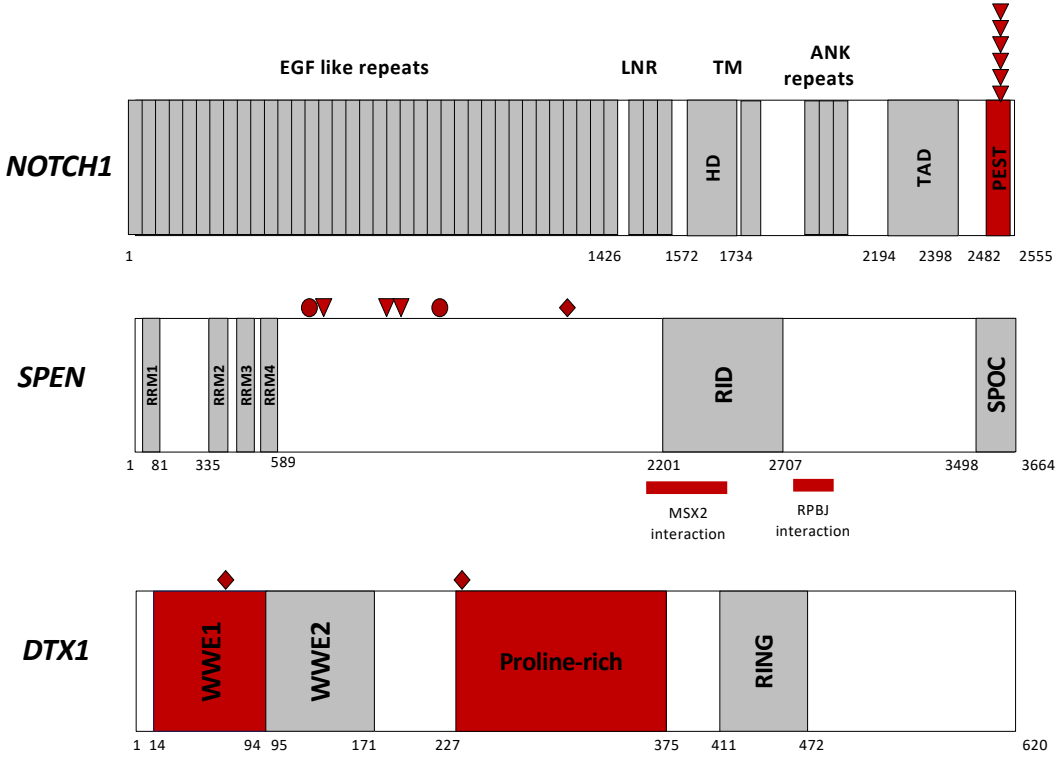


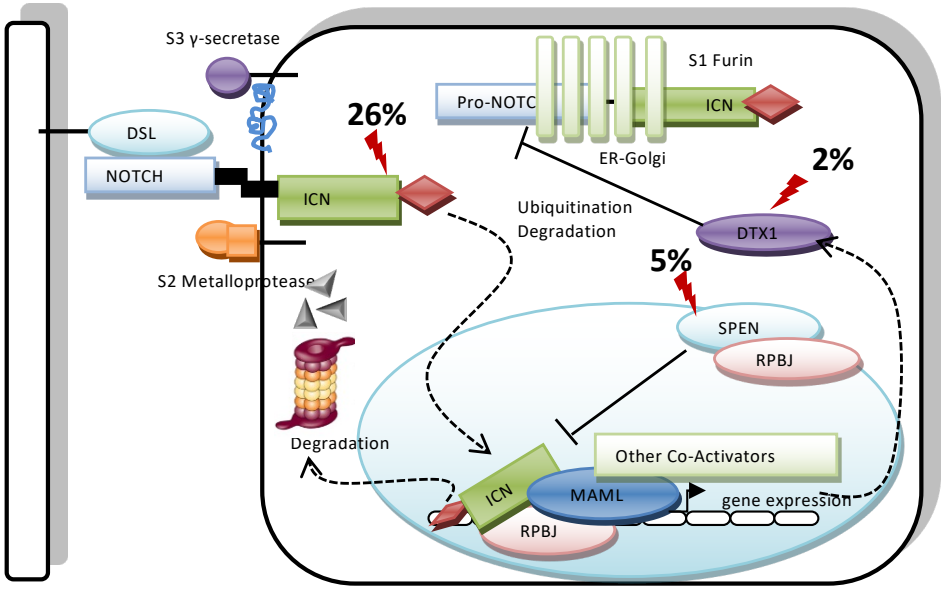
WES in SMZL

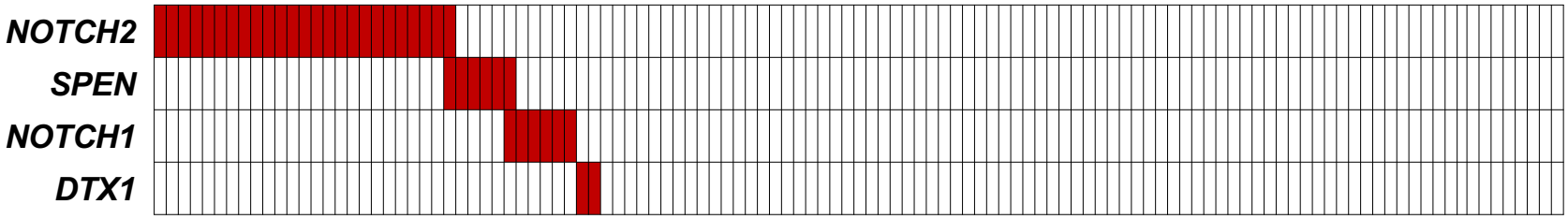


Rossi et al. JEM 2012

Mutations of NOTCH genes show a mutually exclusive pattern and account for 32% SMZL

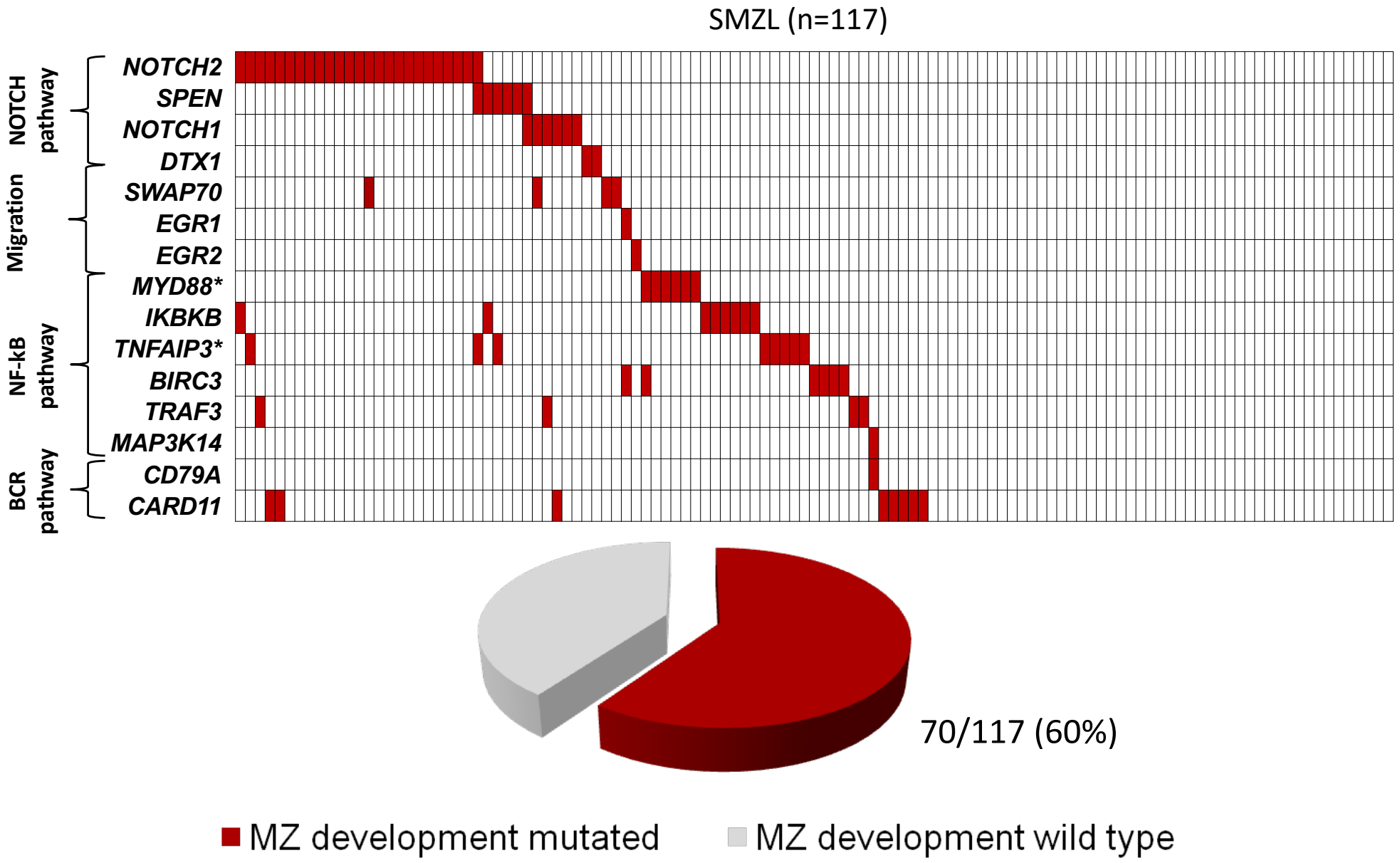




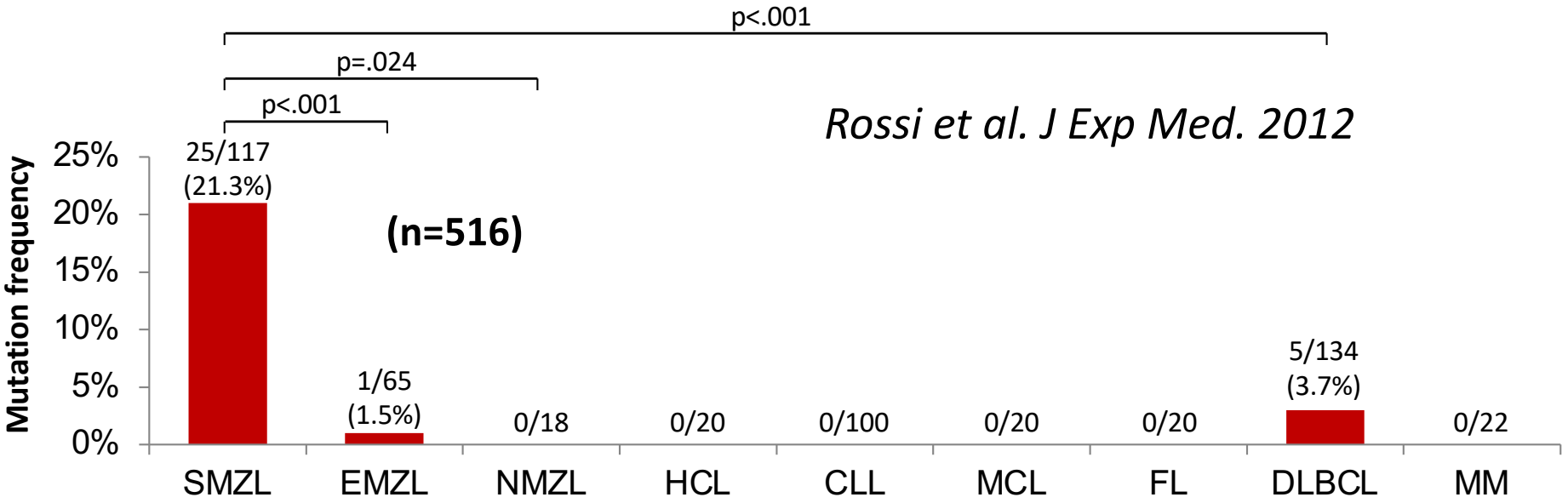


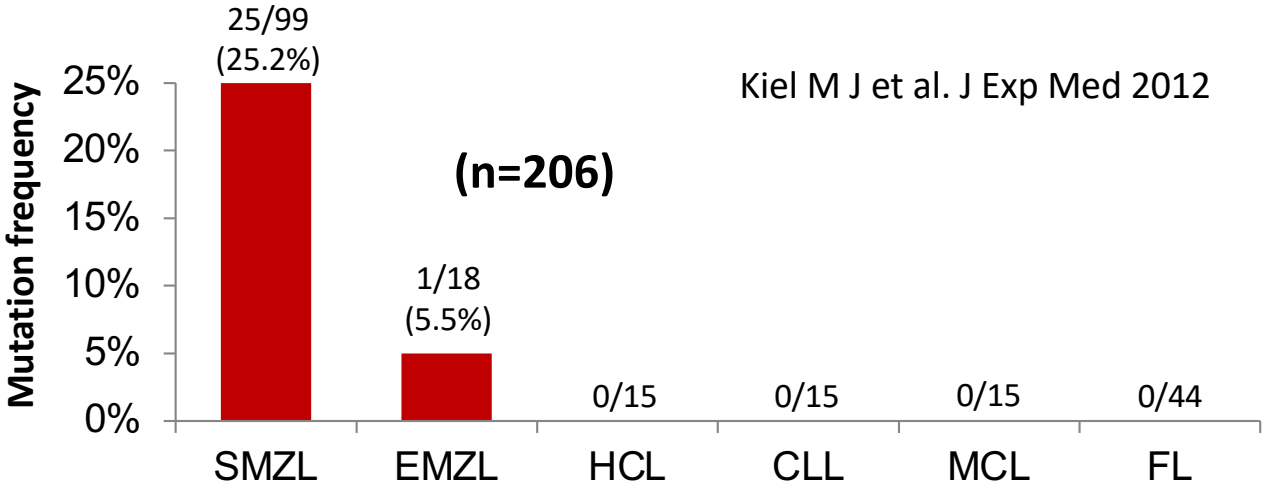
SMZL (n=117)

Mutations of MZ genes show a mutually exclusive pattern and account for 60% SMZL

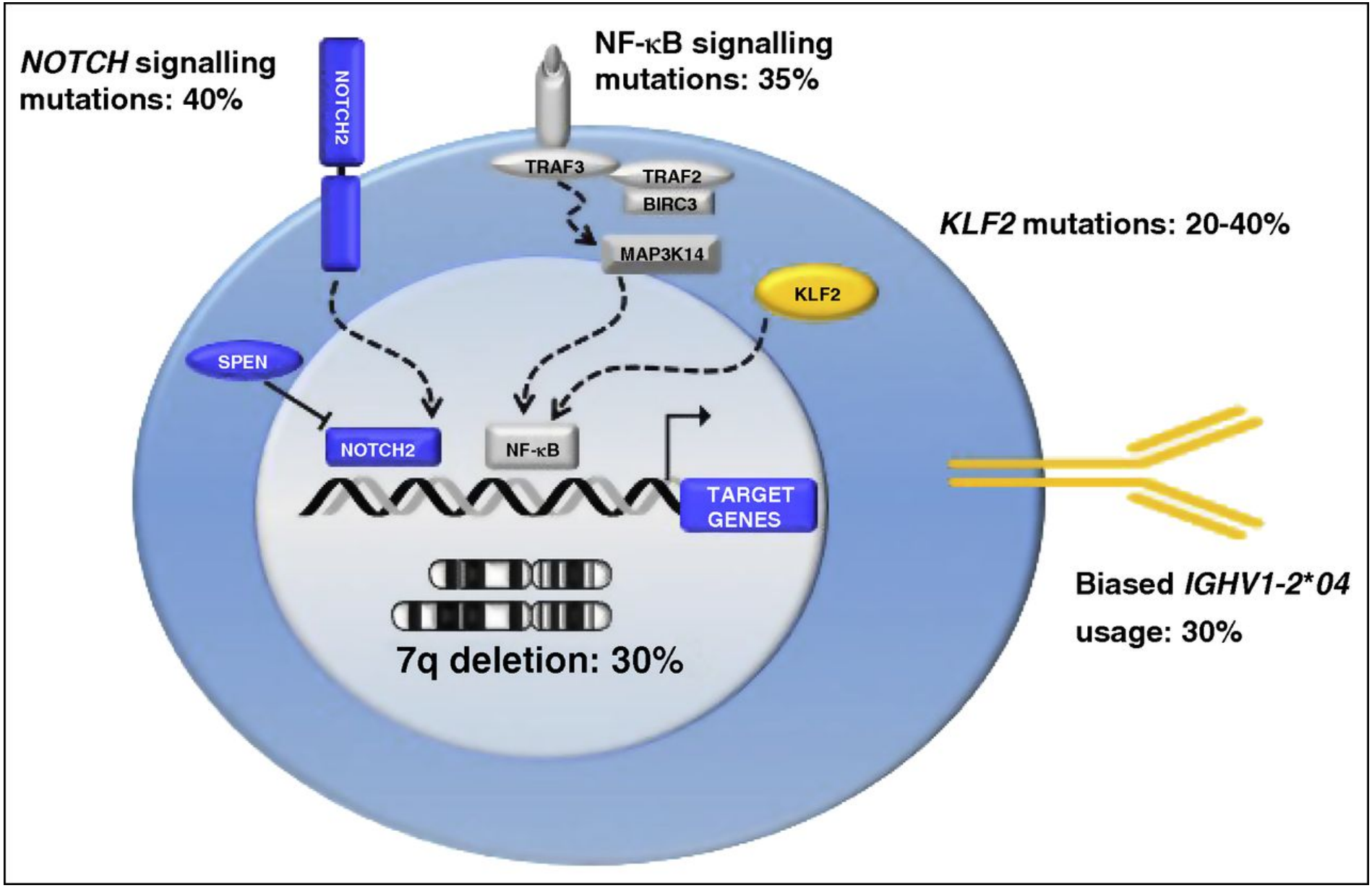


NOTCH2 mutations are selectively restricted to SMZL across mature B-cell tumors





Key molecular alterations in SMZL



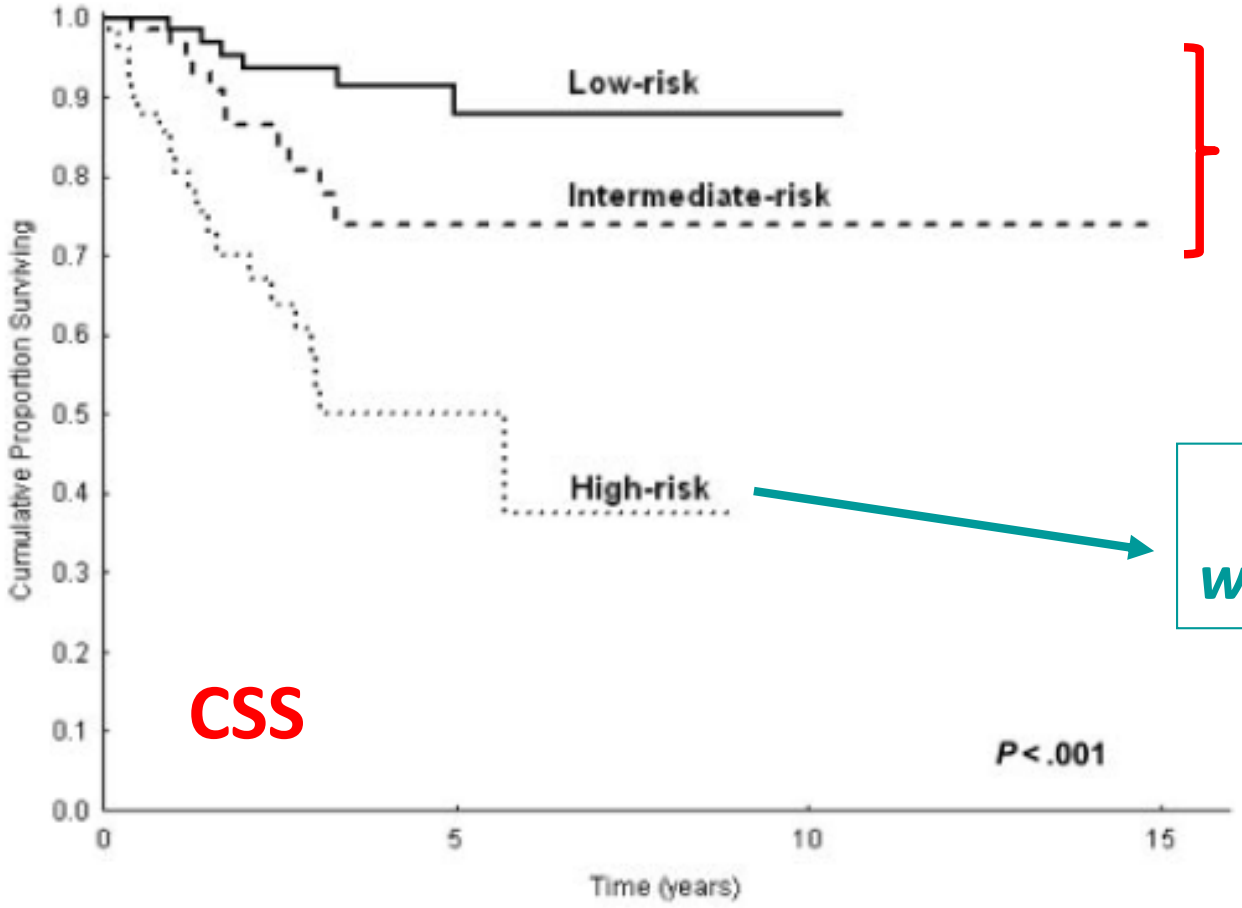
Arcaini et al. Blood 2016

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

0	41%	Low
1	34%	Int
2-3	25%	High



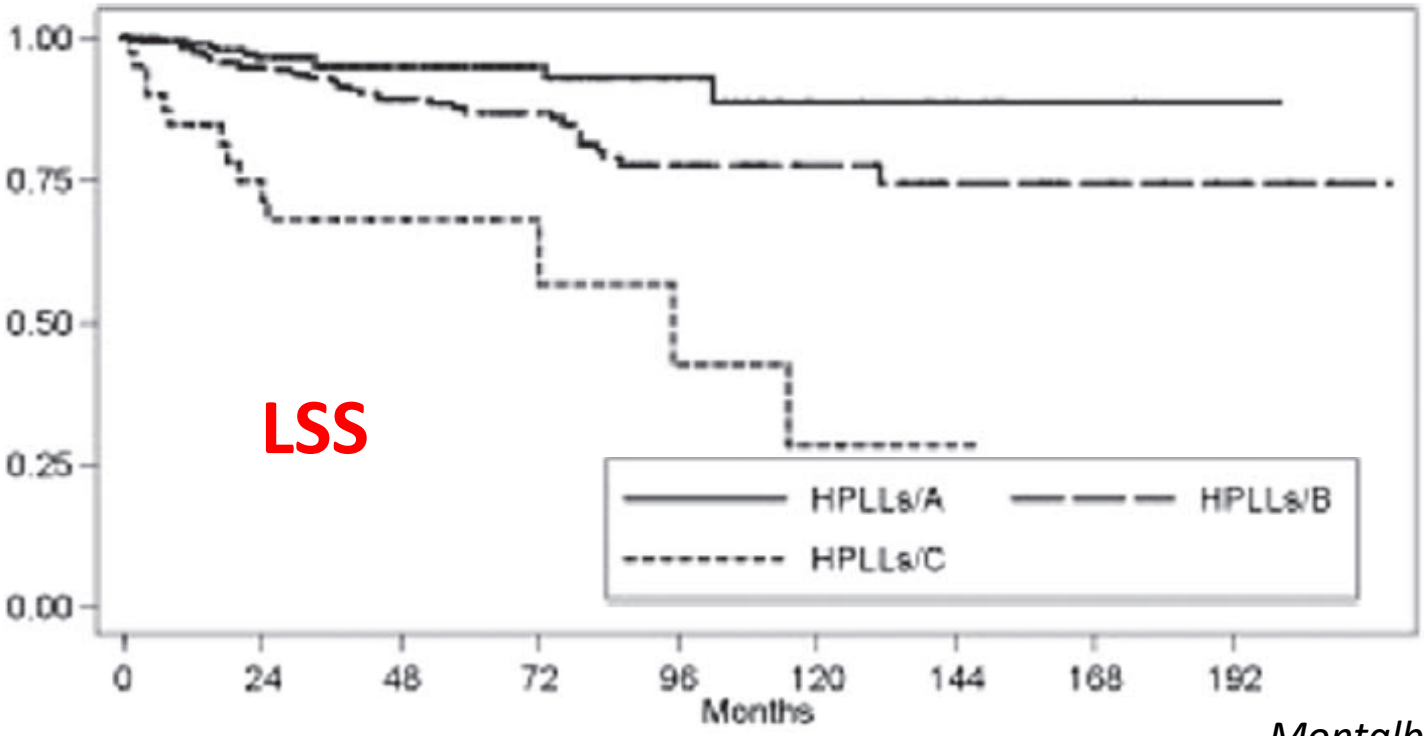
Generally indolent course with median survival 8-10ys

25-30% pts worse outcome

Arcaini et al. Blood 2006

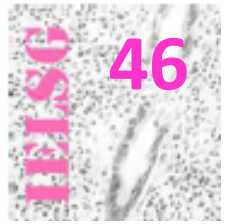
HPLL/ABC prognostic score

Risk factors HPLL/ABC score	HPLL/ABC score		
Hb < 9.5 g/dl	A	0	36%
Plt <80000/mmc	B	1-2	56%
high LDH	C	3-4	8%
extra-hylar Lymphoadenopathy			



Montalban et al, Leuk Lymph 2014

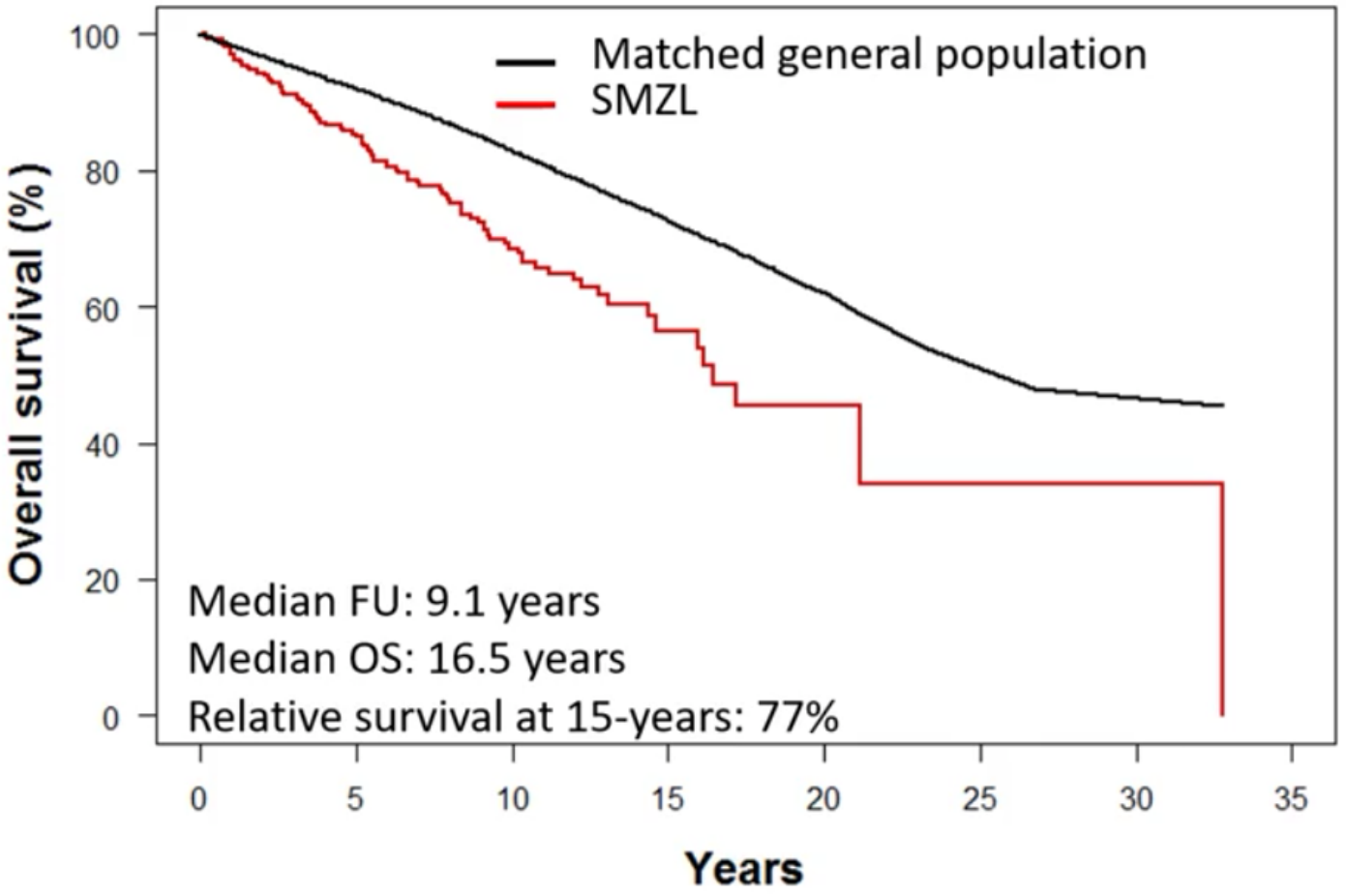
IELSG-46: molecular profiling in SMZL



- 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

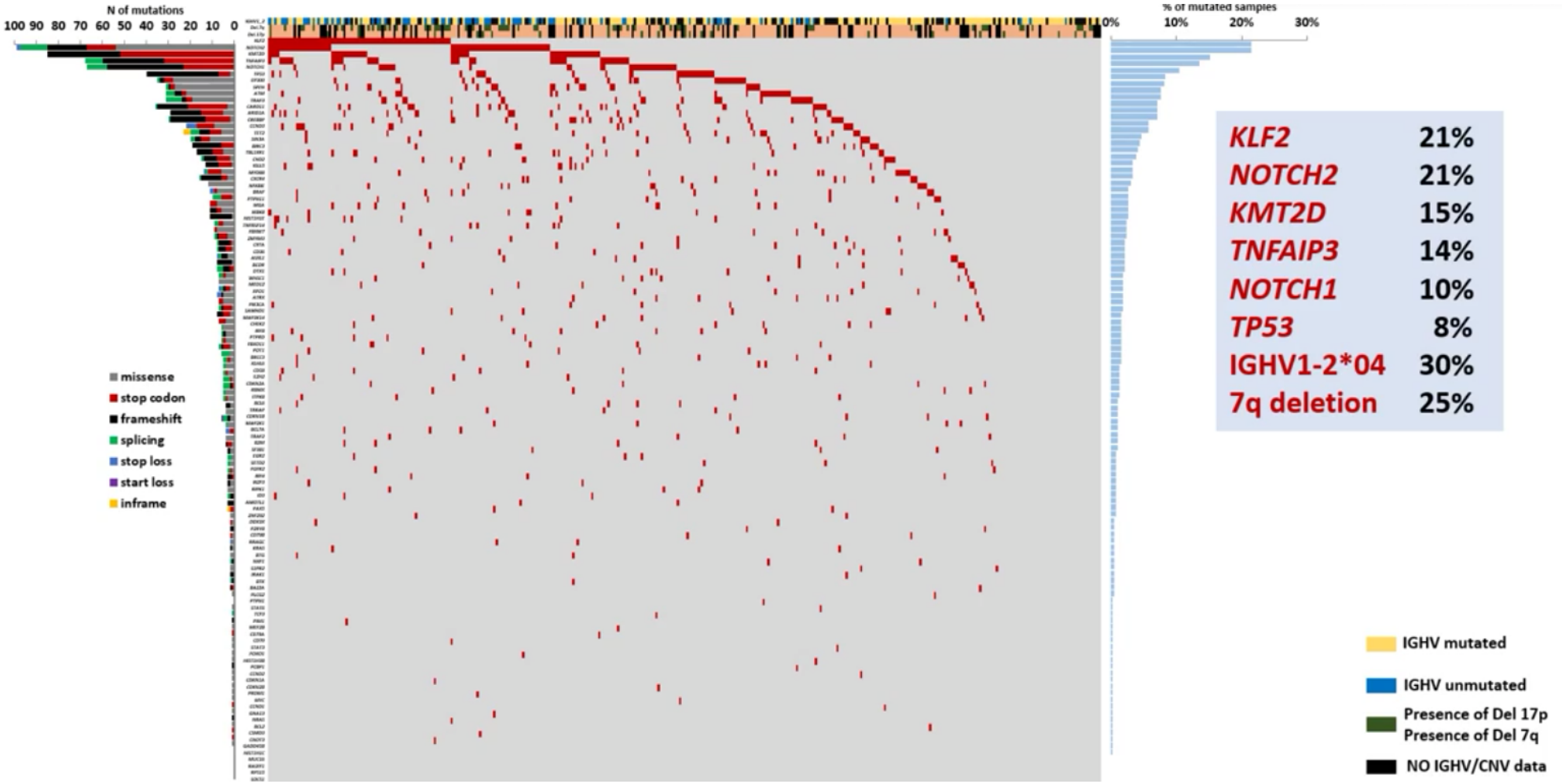


- **SMZL: -23% survival with respect to matched general population**

Bruscaggin A et al ICML 2019

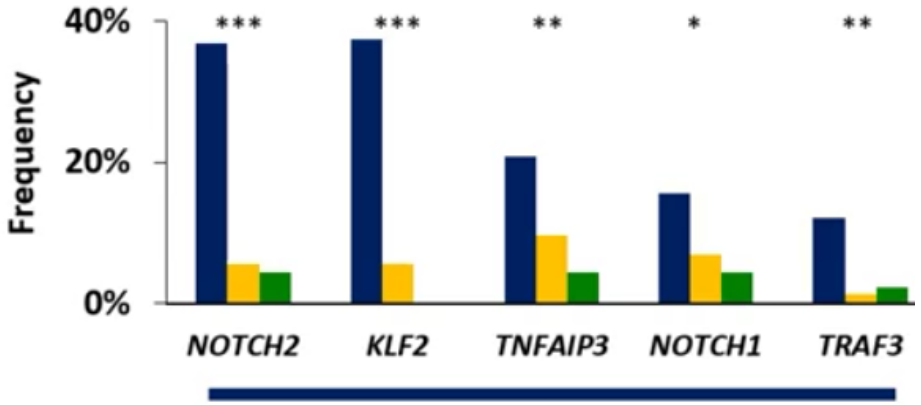
IELSG-46: SMZL mutational landscape

- N=404 fresh spleen samples (splenectomy before 2010)
- Targeted deep NGS, GEP, IGHV sequencing, machine-learning



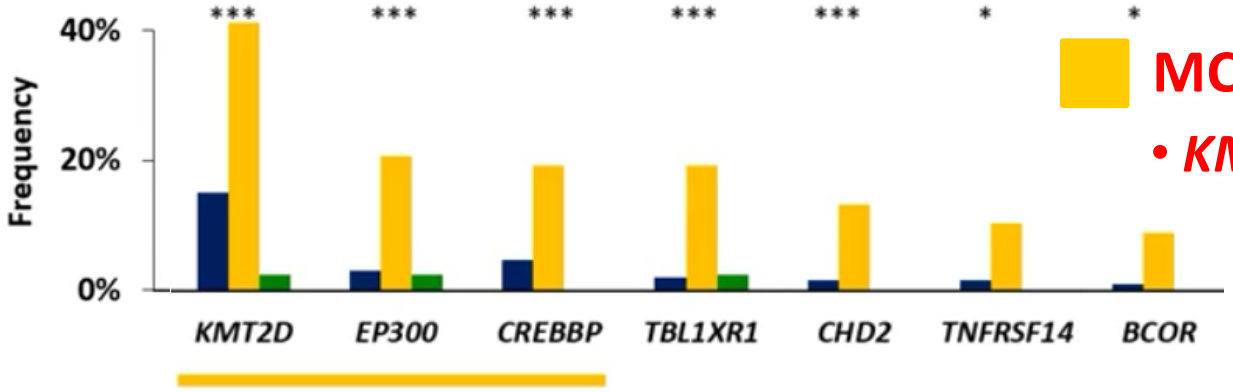
Bruscaggin A et al ICML 2019

IELSG-46: 3 molecular clusters



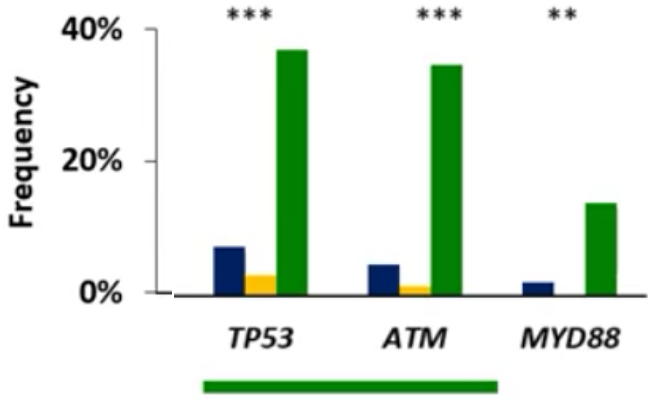
MC1: NOTCH-NF-kB genes (62%)

- ***NOTCH2, KLF2***



MC2: Epigenetic genes (21%)

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

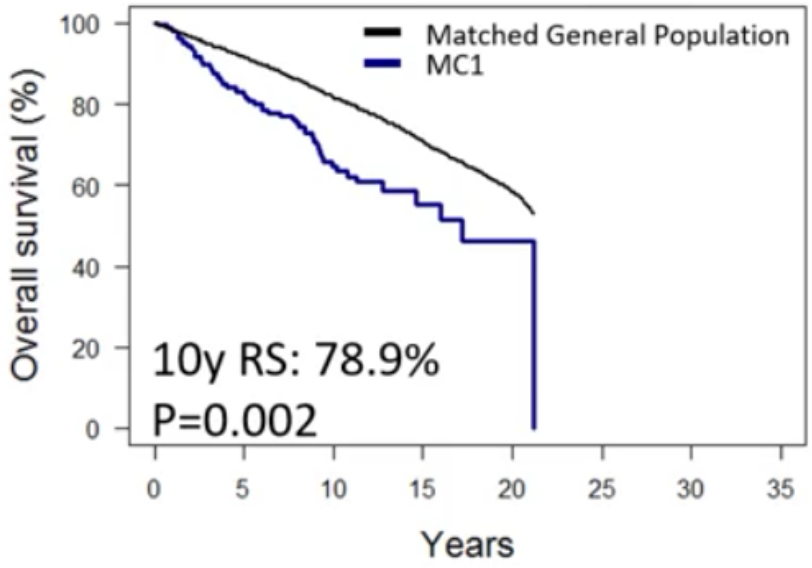


MC3: DNA damage genes (17%)

- ***TP53, ATM***

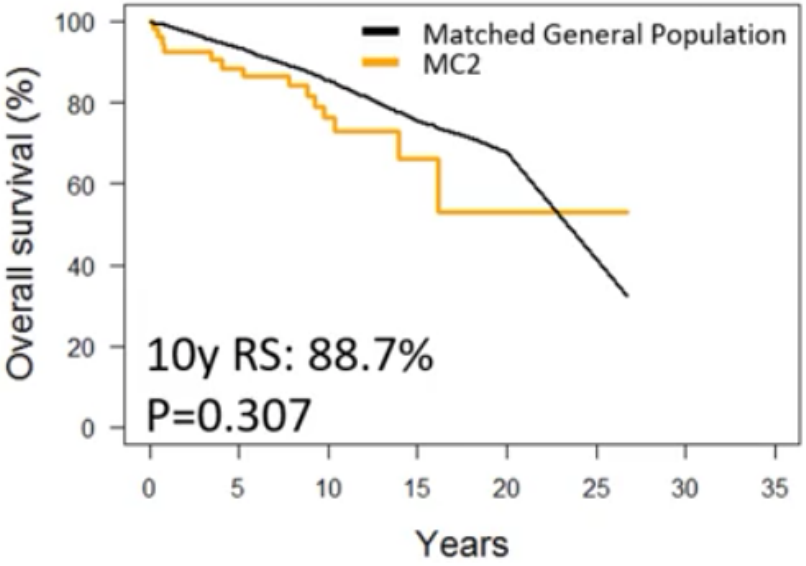
Bruscaggin A et al ICML 2019

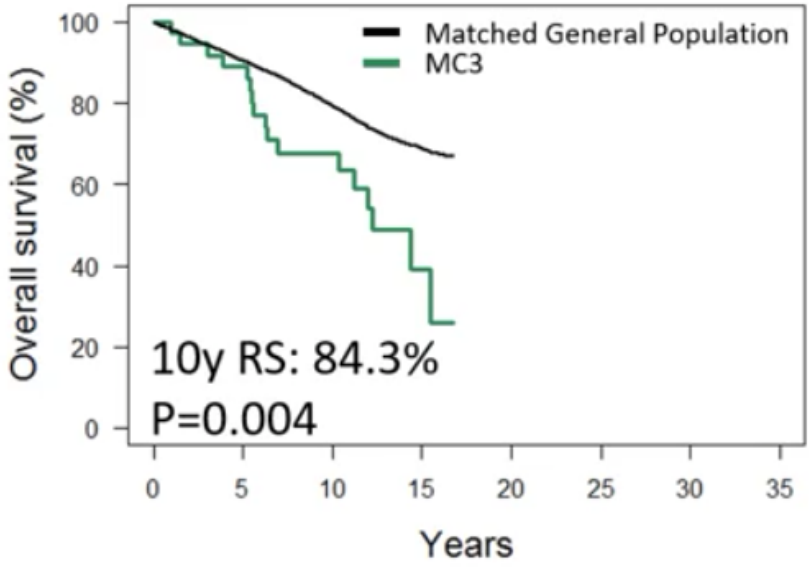
IELSG-46: molecular clusters survival



MC1 NOTCH-NF-kB genes

MC2 Epigenetic genes





MC3 DNA Damage genes

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

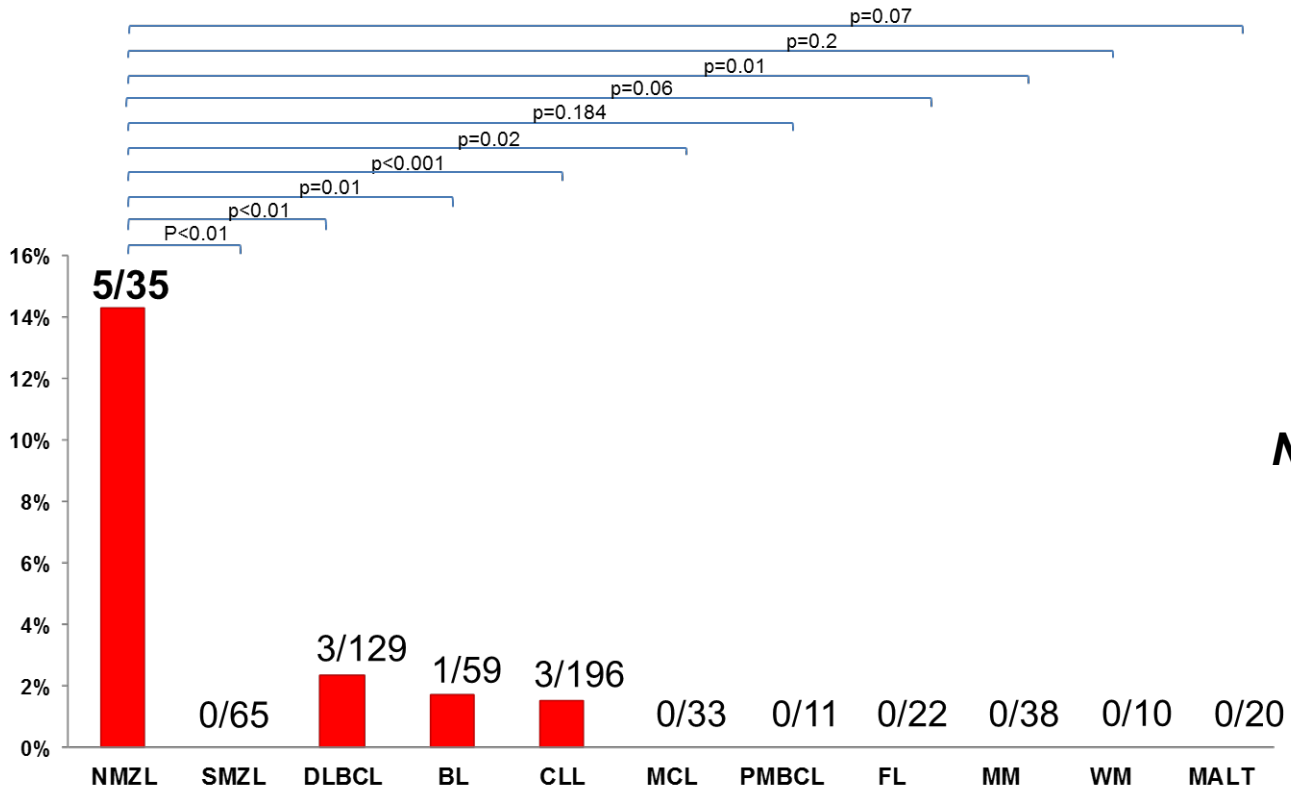
Bruscaggin A et al ICML 2019

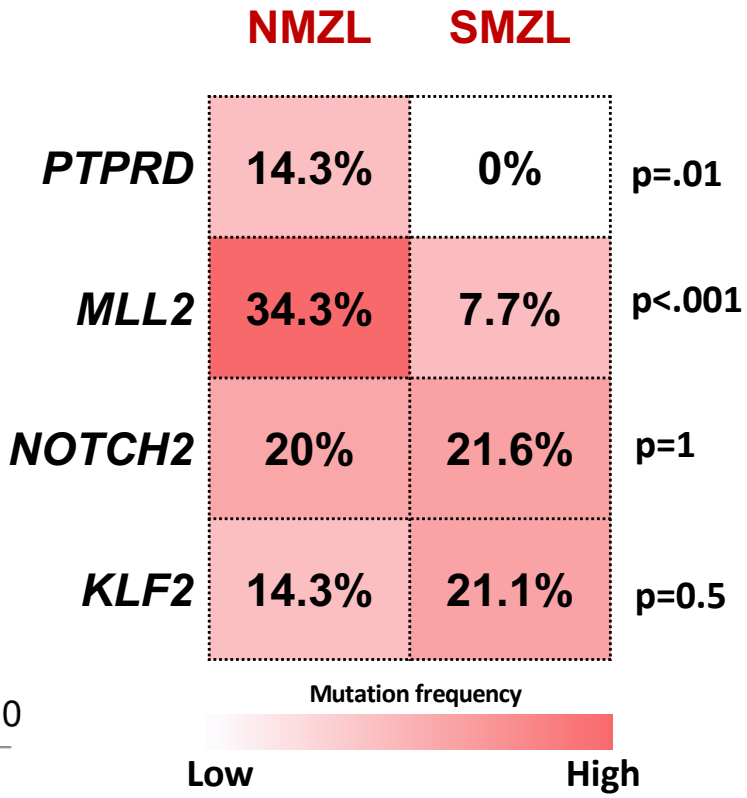
NODAL MARGINAL ZONE LYMPHOMA

Nodal marginal zone lymphoma

Definition: a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL of extranodal or splenic types, but without evidence of extranodal or splenic disease

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





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

Spina et al Blood 2016

Series of nodal marginal zone lymphomas

	N	Extranodal disease except BM
ILSG *Blood 1997*	25	NA
Armitage et al *JCO 1998*	20	25%> 1 extran. site, 5% GI
Nathwani et al. (USA) *JCO 1999*	20	spleen 25%, 13% liver
Berger et al. (FR) *Blood 2000*	37	25%> 1 extran. site, 5% liver
Camacho et al. (E) *AJSP 2003*	27	0
Traverse-Glehen et al. (FR) *Histopathology 2006*	21	0
Oh et al. (Korea) *Ann Hematol 2006*	36	NA
Arcaini et al. (IT) *Br J Haematol 2007*	47	0
Kojima et al. (JPN) *Cancer Science 2007*	65	0

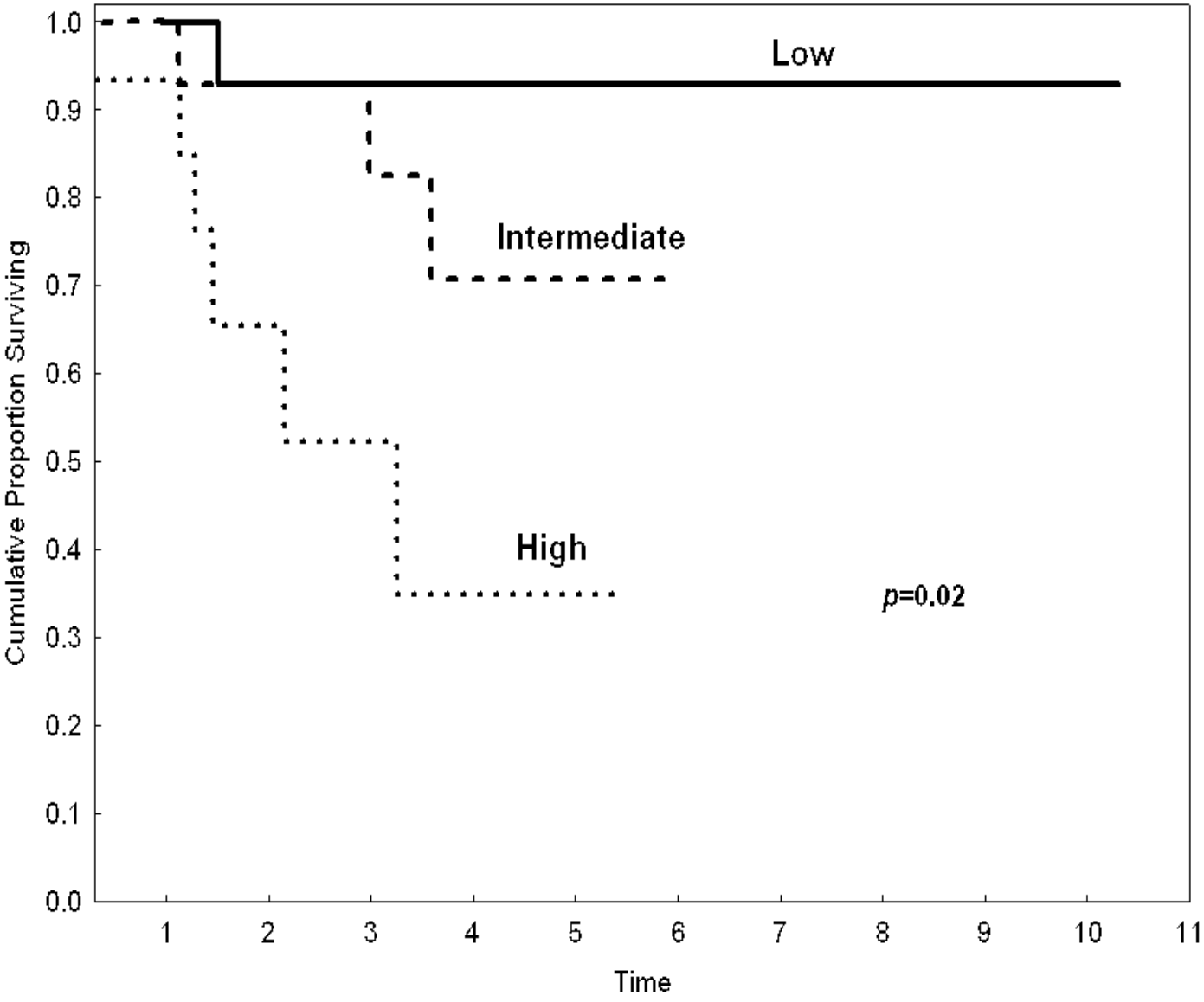
Presenting features (I)

	M/F	Median age (yrs)	Stage I/II (%)	BM+ (%)
ILSG *Blood 1997*	1:1.4	58	18	41
Armitage et al. *JCO 1998*	1:1.4	58	26	32
Nathwani et al. (USA) *JCO 1999*	1:1.3	59	29	28
Berger et al. (FR) *Blood 2000*	1:1.3	35% > 60 yrs	32	43
Camacho et al. (E) *AJSP 2003*	1:2.1	62	59	29
Traverse-G. et al. (FR) *Histopathology 2006*	2:1	57	24	62
Oh et al. (Korea) *Ann Hematol 2006*	2.6:1	50	50	19
Arcaini et al. (IT) *Br J Haematol 2007*	1:1.7	63	33	45
Kojima et al. (JPN) *Cancer Science 2007*	1:1.3	64	77	0

Outcome

	5-yrs OS	5-yrs PFS
ILSG *Blood 1997*	57	29
Armitage et al. *JCO 1998*	57	29
Nathwani et al. (USA) *JCO 1999*	56	28
Berger et al. (FR) *Blood 2000*	55	29
Camacho et al. (E) *AJSP 2003*	79	22
Traverse-G. et al. (FR) *Histopathology 2006*	70	35
Oh et al. (Korea) *Ann Hematol 2006*	83	47
Arcaini et al. (IT) *Br J Haematol 2007*	69	29
Kojima et al. (JPN) *Cancer Science 2007*	85	65

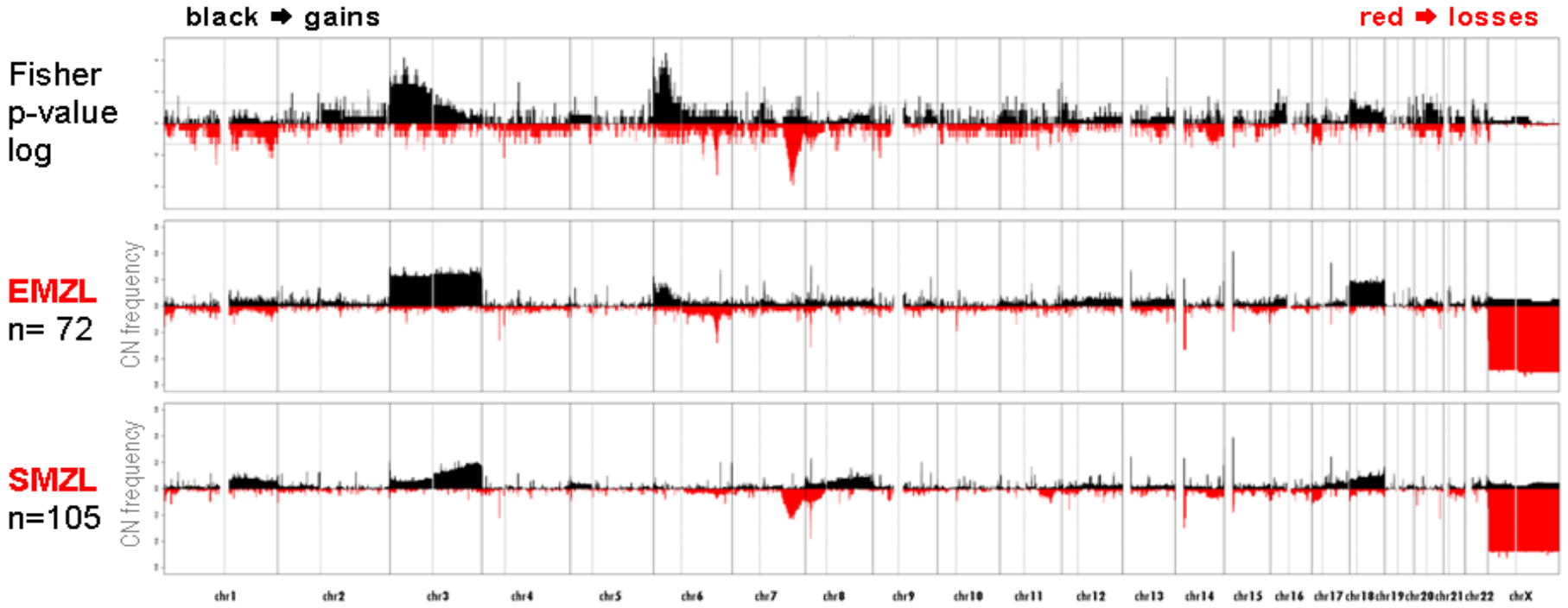
FLIPI score



Arcaini et al, BJH 2007

EXTRANODAL MARGINAL ZONE LYMPHOMA OF MALT

Array-CGH identifes both common or subtype-specific aberrations in MZL



- MZLs share 3q and 18q gains
- NMZL are more similar to EMZL than SMZL
- Extracopies of chr 3 and 18 are the same as in DLBCL

- EMZL and SMZL profiles show differences
  - 3p, 6p and 18p gains in EMZL
  - **6q losses in EMZL** (A20/TNFAIP3)
  - 7q, 8p, 14q and 17p losses in SMZL

Rinaldi et al, Blood 2011

MALT lymphoma: sites

- **Gastrointestinal tract** 50%
  - stomach 34%
  - intestine (inc IPSID) 5-8%
- **Salivary gland** 26%
- **Respiratory tract**
  - lung 9%
  - pharynx, larynx, trachea
- **Thyroid** 4-6%
- Ocular adnexa 10-17%
  - conjunctiva
  - lacrimal gland
  - orbit*
- **Thymus**
- **Liver** 3%
- **Genitourinary tract** 3%
  - bladder
  - prostate
  - kidney
- **Breast** 3%
- **Skin*** 10-12%
- **Dura***
- **Rare sites**

*not mucosal

Zucca et al. 2003, Thieblement & Coiffier 2004

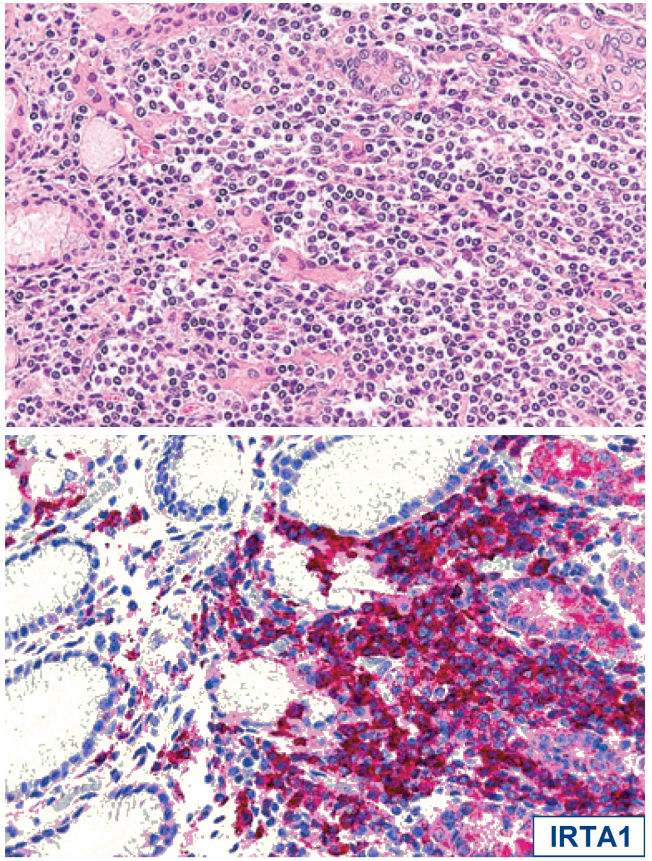
Diagnosis of MALT lymphoma

HISTOLOGICAL FEATURES

- Centrocyte-like cells (usually)
- Lymphoepithelial lesions
- Plasma cell differentiation
- Scattered transformed blasts
- Admixed reactive T-cell
- Follicular colonisation

IMMUNOPHENOTYPE

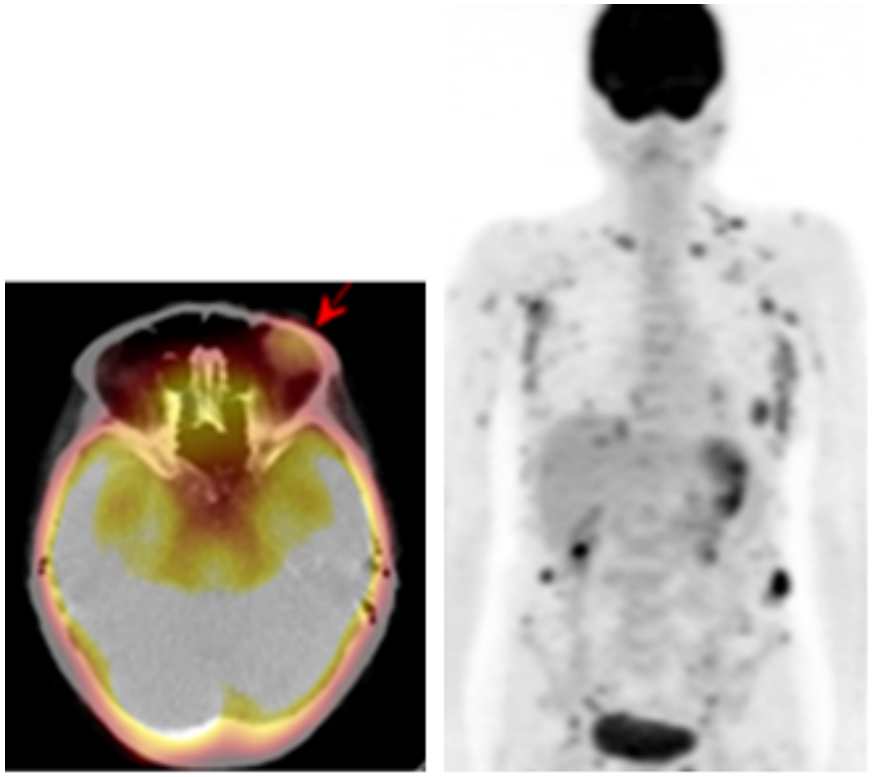
- CD5, CD10, CD23, IgD negative
- CD20, CD21, CD35, IgM, IRTA1 positive



Isaacson et al. in WHO Classification of Tumours of Haematopoietic &Lymphoid Tissues. IARC, Lyon 2008

Staging of MALT Lymphoma

- Multifocal disease in ≥25% of cases
- PET use is controversial and has uncertain clinical utility (*ESMO Guidelines*)
- Variable FDG-avidity
  (higher in non-gastric lesions!)
- Pooled PET/CT
  detection rate 71%
  (95% CI: 61-80%)
  in a literature meta-analysis



Treglia et al. Hematol Oncol. 2014

Evidence of antigen-driven growth in MALT lymphomas

- Histological features of MALT lymphoma
- Somatic hypermutation of immunoglobulin gene (and intraclonal variation)
- Association with chronic infectious conditions and auto-immune processes
- Therapeutic efficacy of antibiotics or antivirals

Antigen-driven lymphoma development

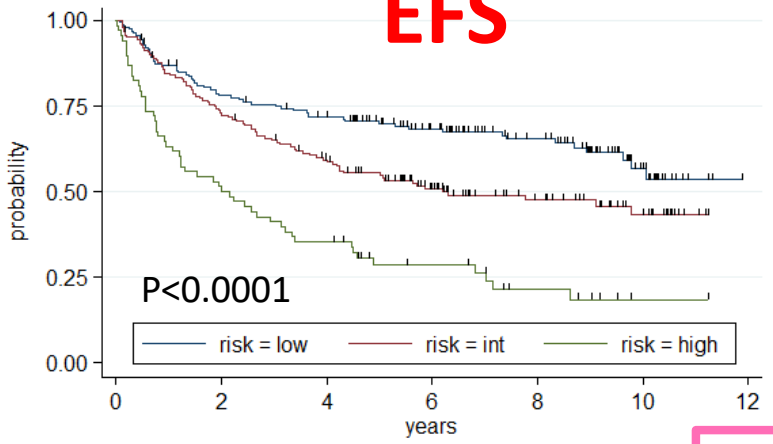
- ***Helicobacter pylori*** in gastric MZL
- ***Borrelia burgdorferi*** in cutaneous MZL
- ***Chlamydophila psittaci*** in some OALs
- ***Campylobacter jejuni*** in IPSID
- ***HCV*** association with some non-MALT MZL
- ***Achromobacter (Alcaligenes) Xylosoxidans*** in BALT-Lymphoma
- **Nevertheless, lymphoma cell are usually "autoreactive"**

IELSG MALT lymphoma score : LDH, Age, Stage

MALT score : 0 factor / 1 F / ≥ 2

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

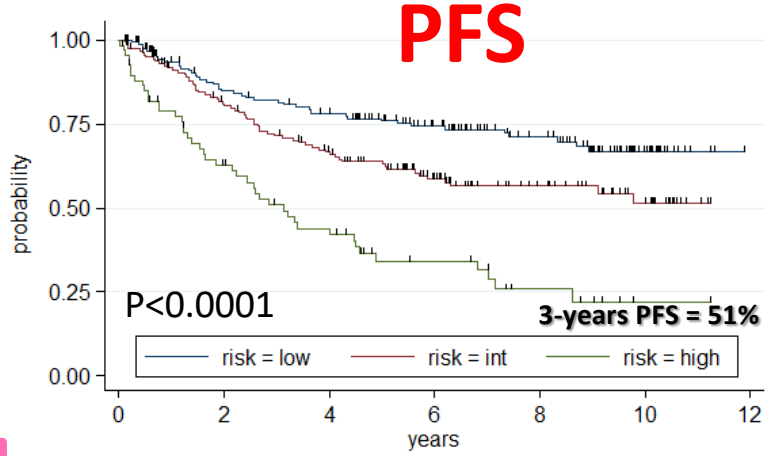
EFS



Number at risk

risk = low	167	126	112	84	57	20	
risk = int	164	119	92	59	34	16	
risk = high	68	35	24	14	7	1	

PFS

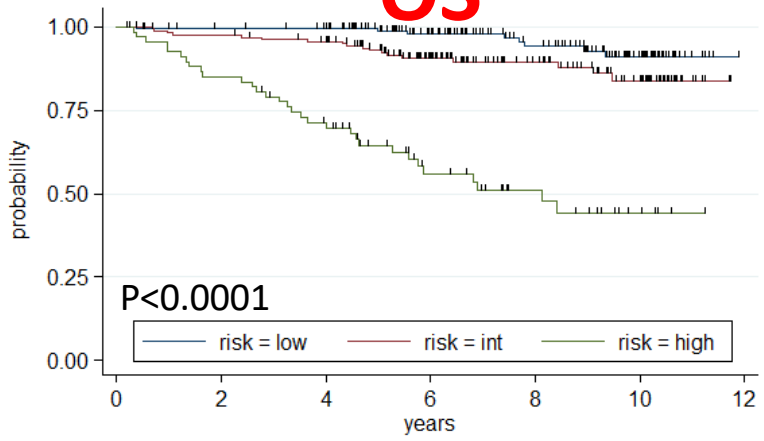


er at risk

isk = low	167	126	112	84	57	20	0
risk = int	164	120	93	60	35	17	0
sk = high	68	38	25	14	7	1	0

LDH >N
AGE >70
STAGE>2

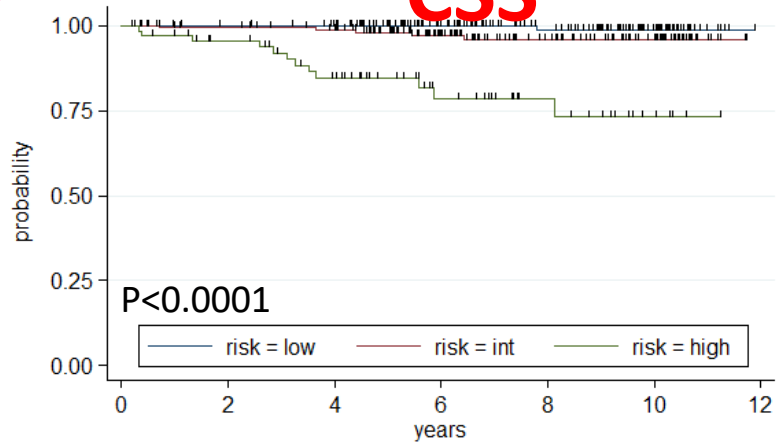
OS



Number at risk

risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

CSS

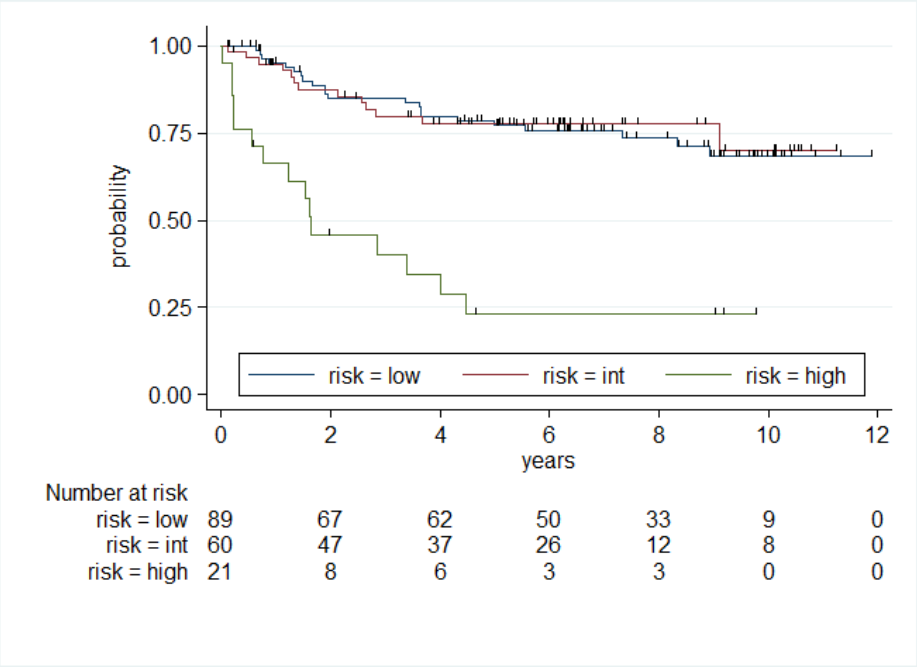


Number at risk

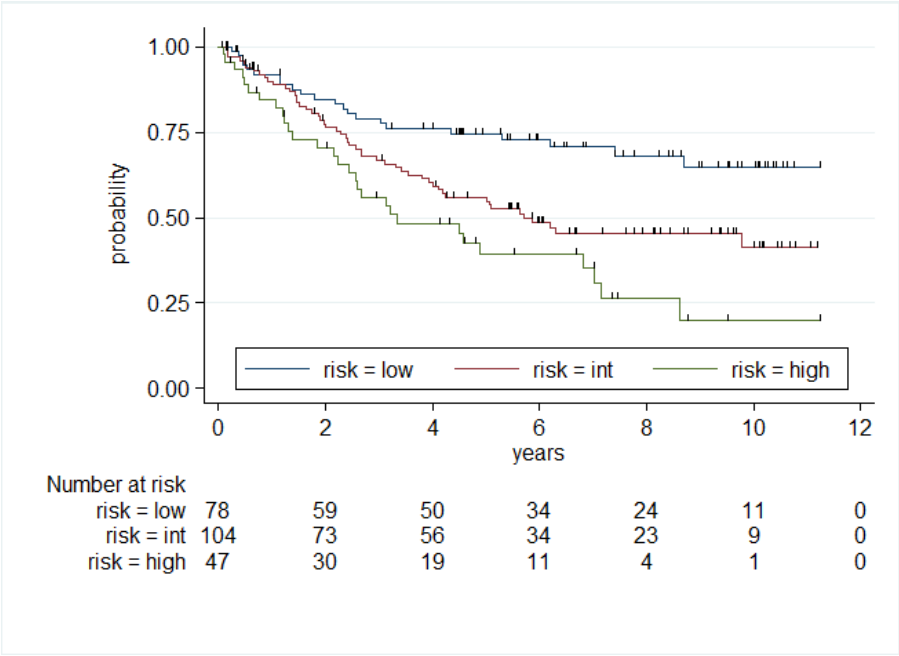
risk = low	167	159	154	113	78	31	0
risk = int	164	159	150	96	61	31	0
risk = high	68	57	45	25	15	6	0

PFS by MALT prognostic score

gastric MALT



Non-gastric MALT

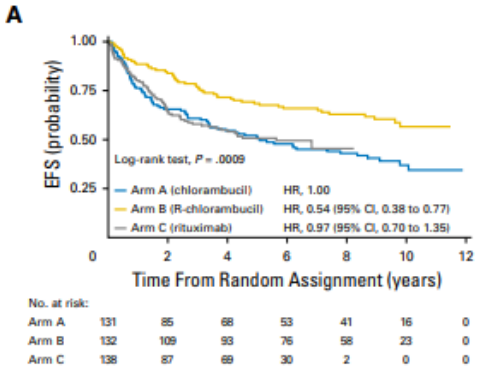


Thieblemont et al ICML 2015

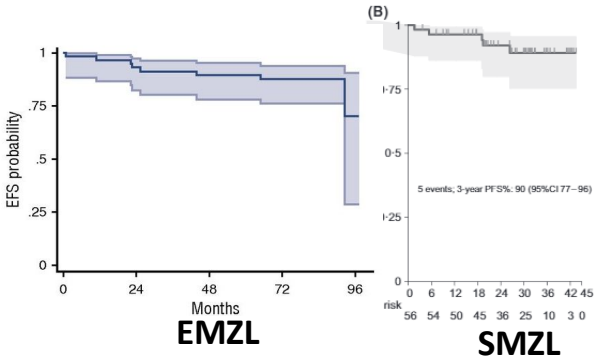
High risk Marginal Zone Lymphomas

- 6-9% of all NHLs
- Splenic, Nodal and Extranodal subtypes (SMZL, NMZL, EMZL)
- Indolent course improved in the Rituximab era
- Missing standard treatment but immunochemotherapy is generally used for symptomatic patients (R-Chl, R-Bendamustine)
- Subtype-specific prognostic scores (MALT-IPI, HPLL)

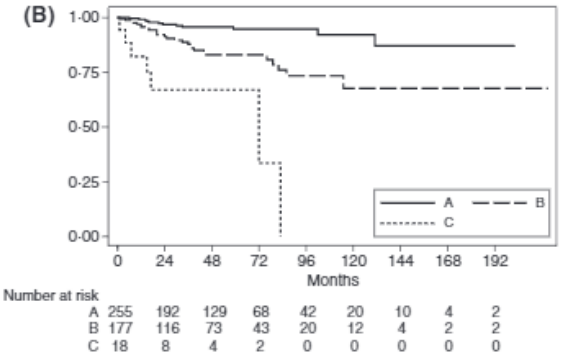
IELSG-19[1]



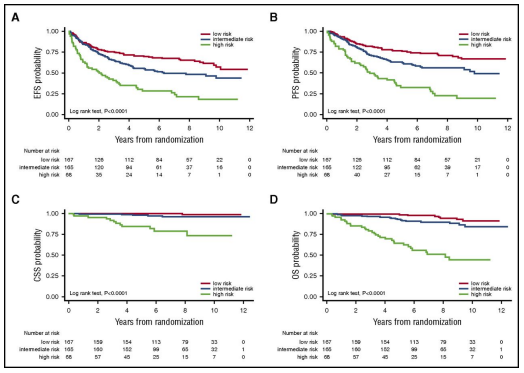
R-bendamustine[2-3]



HPLL for SMZL[4]



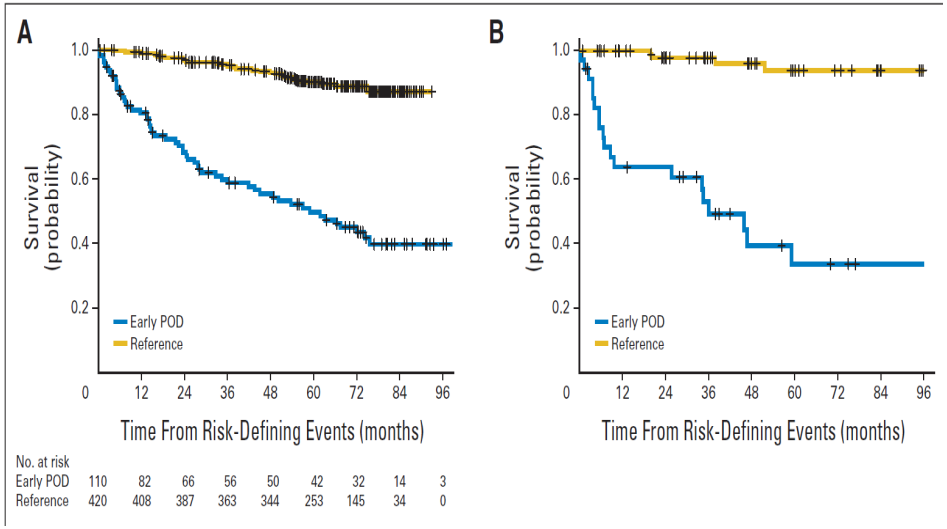
MALT-IPI for EMZL[5]



1. *Zucca E, JCO 2017*
2. *Salar A, Blood 2017*
3. *Iannitto, BJH 2018*
4. *Montalban, BJH 2012*
5. *Thieblemont, Blood 2018*

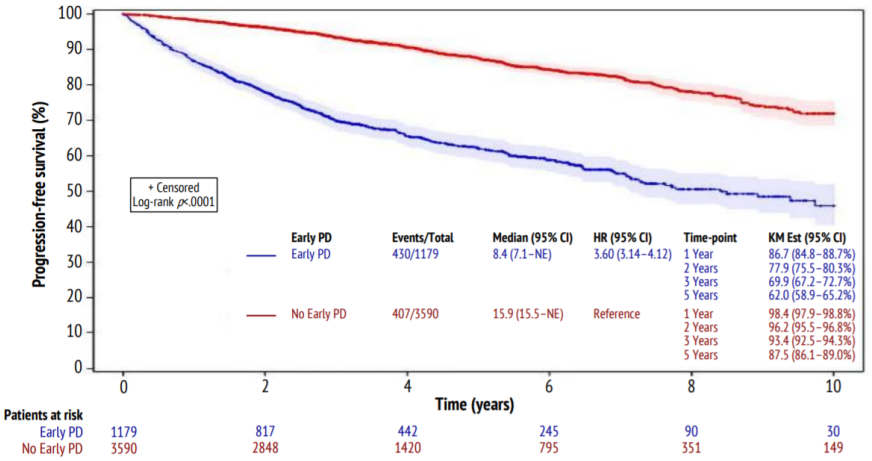
Early progressors in follicular lymphoma

National LymphoCare Study: early relapse after R-CHOP defines patients at high risk of death



	POD24 yes		POD24 no
2y-OS	68%	vs	97%
5y-OS	50%	vs	90%

FLASH study: landmark OS in FL patients with early POD



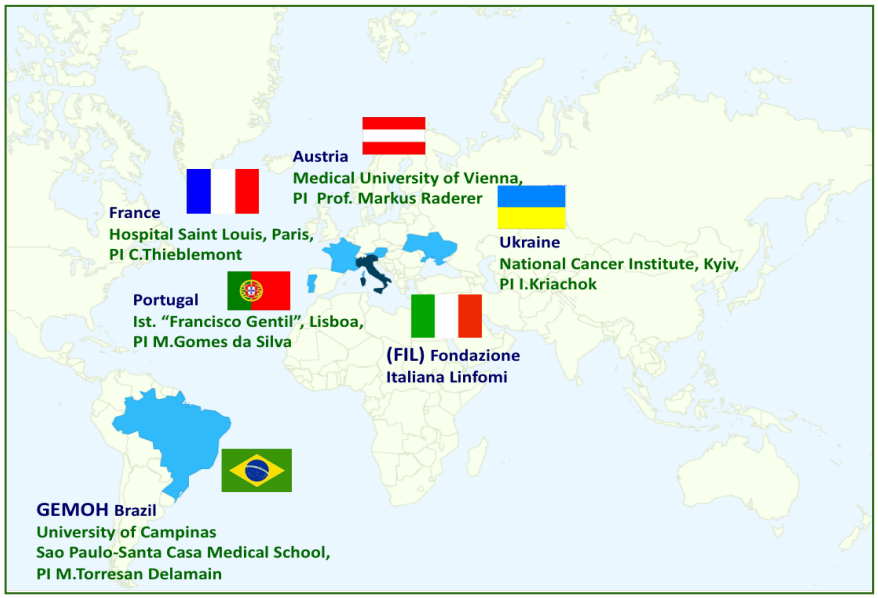
Association between POD24 and OS
HR (95%CI): 5.24 (4.63, 5.93); p<0.01

Casulo et al JCO 2015
Casulo et al Blood 2017

NF10 study by Fondazione Italiana Linfomi

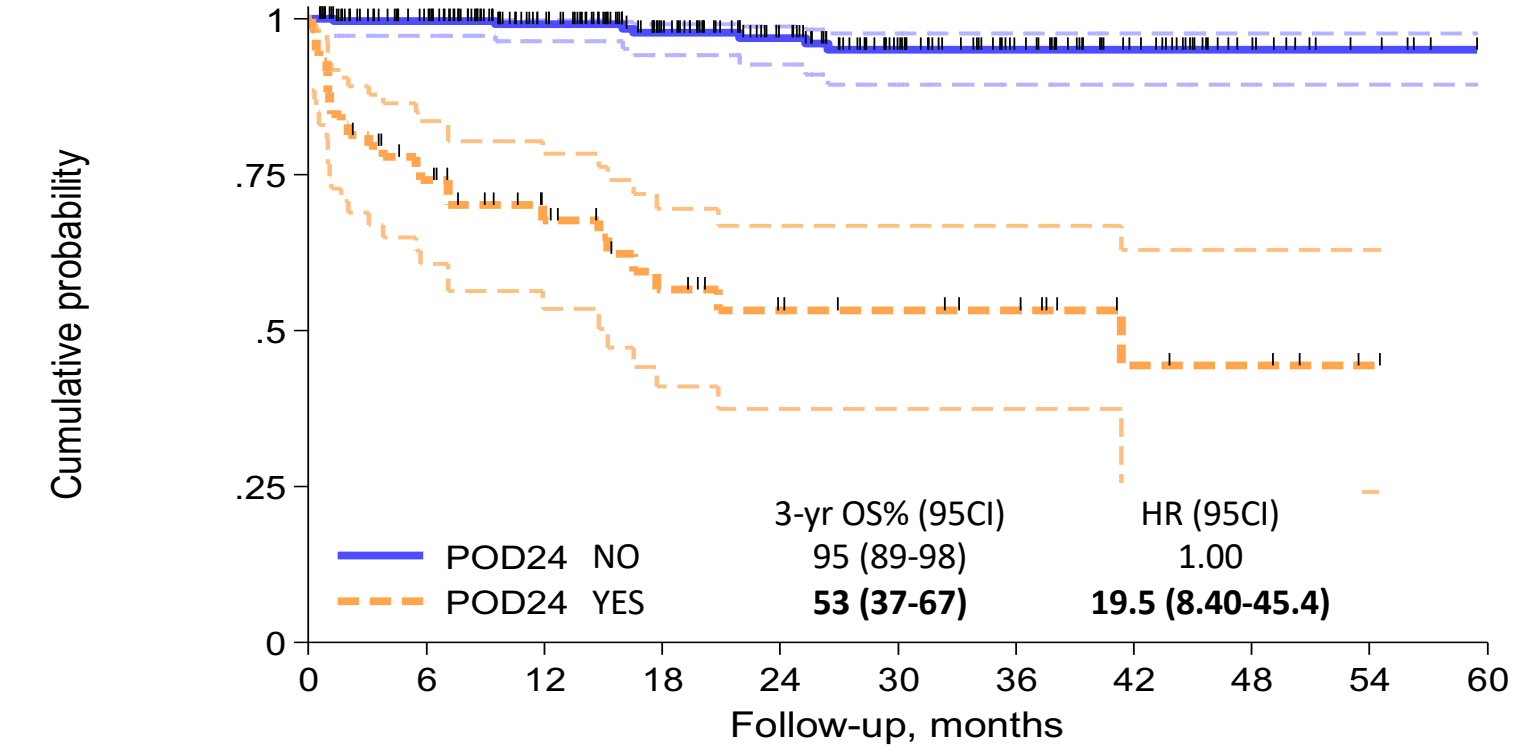
- Prospective observational study to investigate the prognosis of Indolent Non-Follicular B-Cell Lymphomas (INFL)
- Adult patients with biopsy-proven INFL
  - **SMZL** (bone marrow and/or splenic histology)
  - **ENMZL** (tissue biopsy)
  - **NMZL** (lymph node biopsy)
  - **Lymphocytic lymphoma** (lymph node biopsy)
  - **Lymphoplasmacytic lymphoma** (bone marrow histology or lymph node biopsy)
  - **CD5- lymphoproliferative disorder** (BM histology)
- No exclusion criteria

- Started in 2010
- 47 active centers in Europe and South America
- **1325 pts** eligible based on local pathology report



FONDAZIONE ITALIANA LINFOMI

Overall Survival by POD24



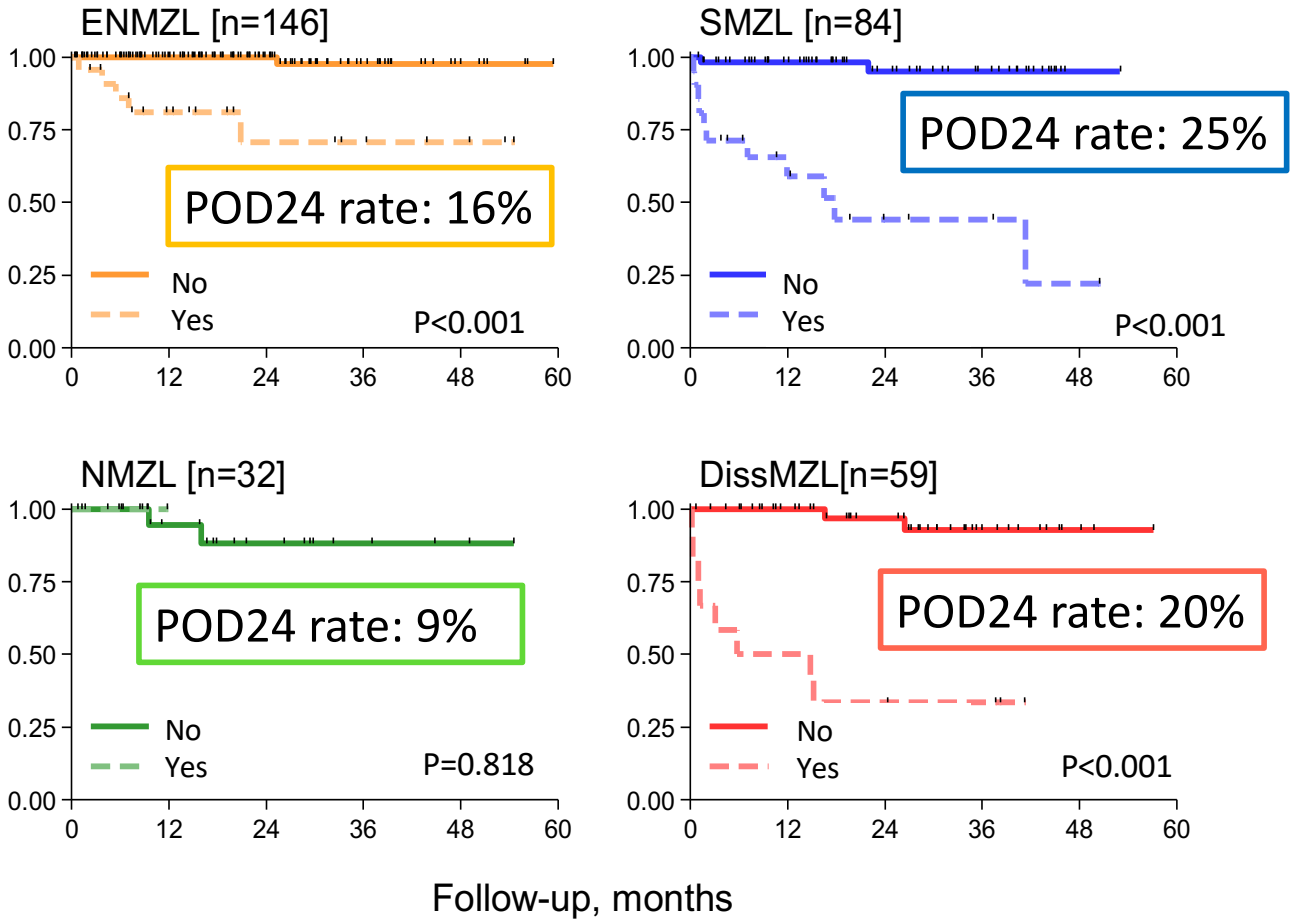
Patients at risk

POD24 No	262	224	179	138	108	74	52	33	14	7	1
POD24 Yes	59	40	28	20	15	13	11	5	4	1	0

POD24 rate: 59/321 (18%)

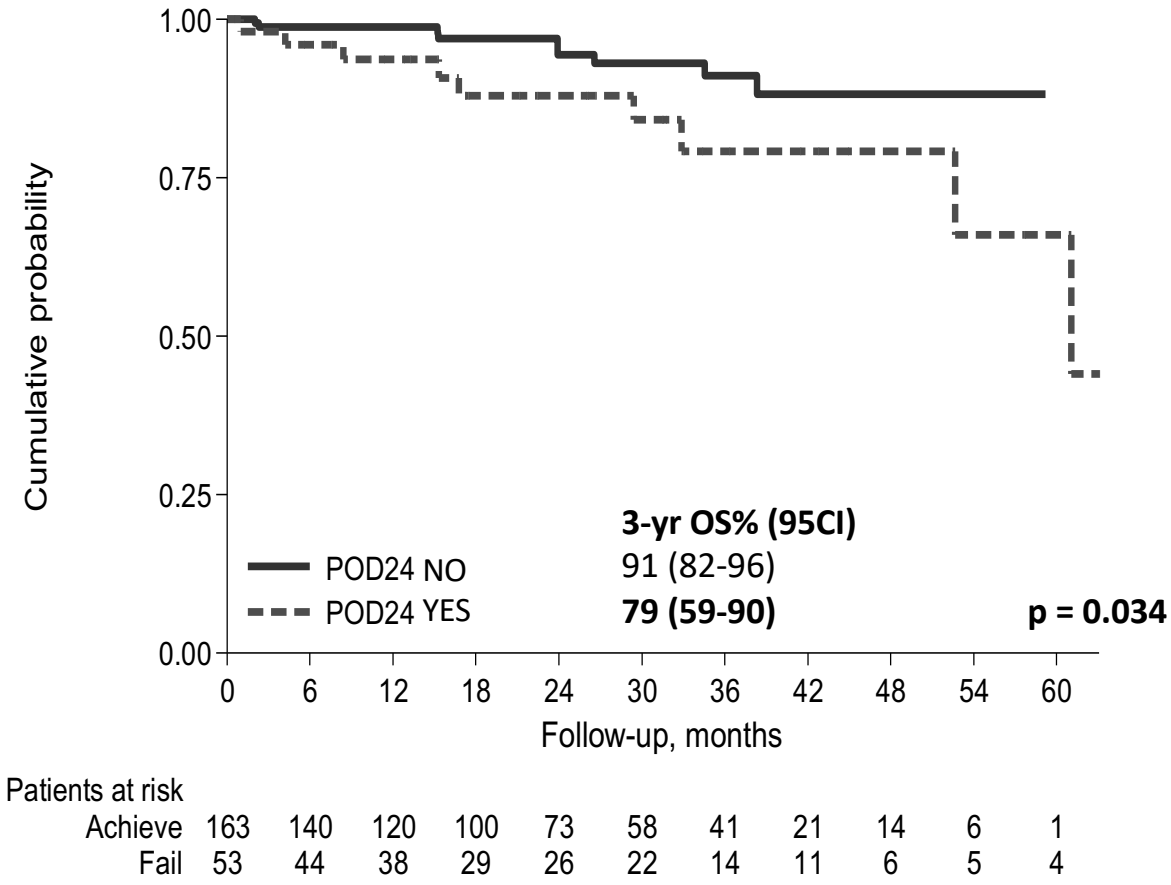
FONDAZIONE ITALIANA LINFOMI

Overall Survival by POD24 and MZL Subtypes



FONDAZIONE ITALIANA LINFOMI

Overall Survival by POD24 – W&W (n=286)



Patients at risk

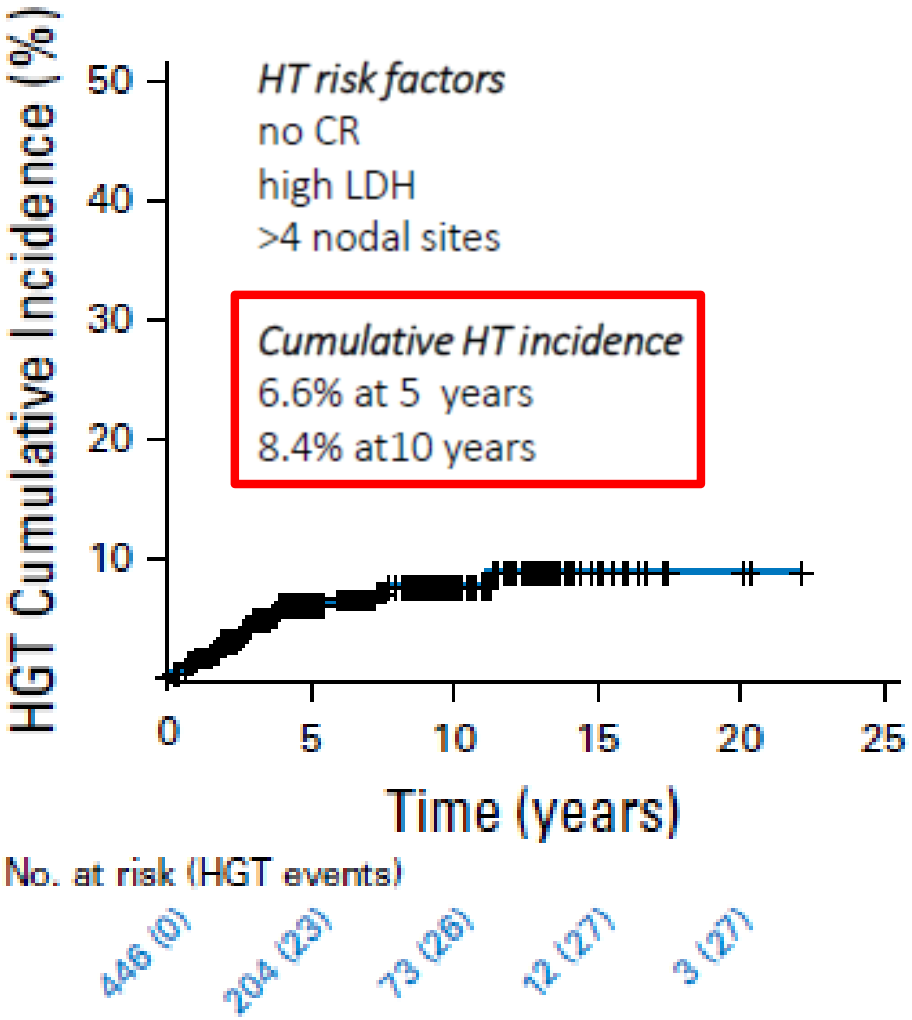
Achieve	163	140	120	100	73	58	41	21	14	6	1
Fail	53	44	38	29	26	22	14	11	6	5	4

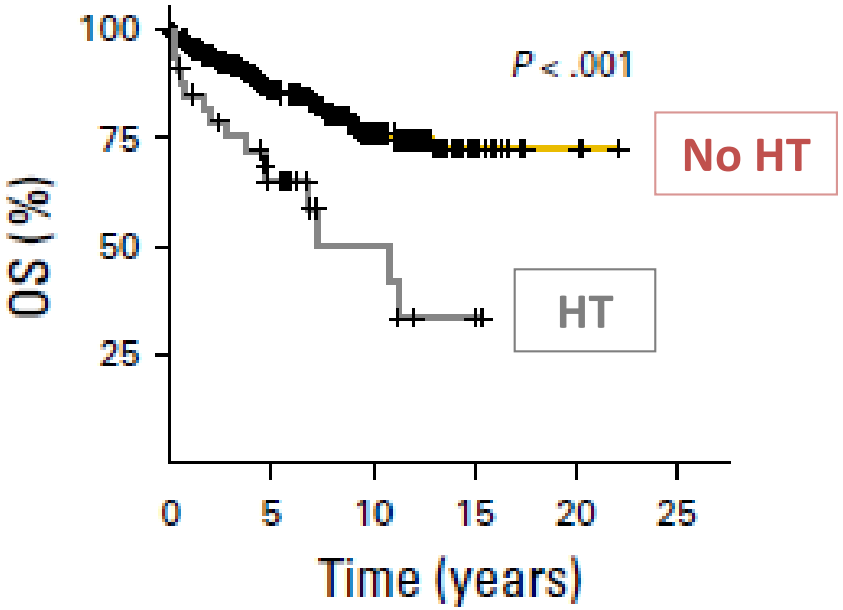
Cause of death (total =18)

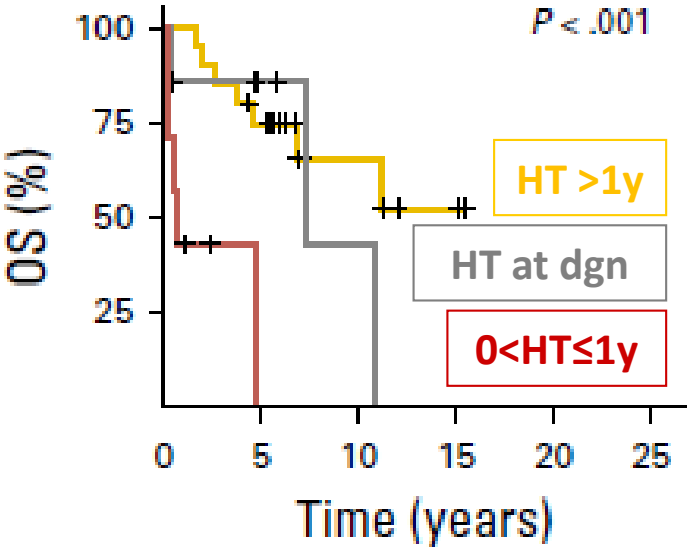
Lymphoma Progression 6 (33%)

Histologic Transformation (HT) in MZL

- 446 pts: 389 MALT, 29 NMZL, 35 SMZL



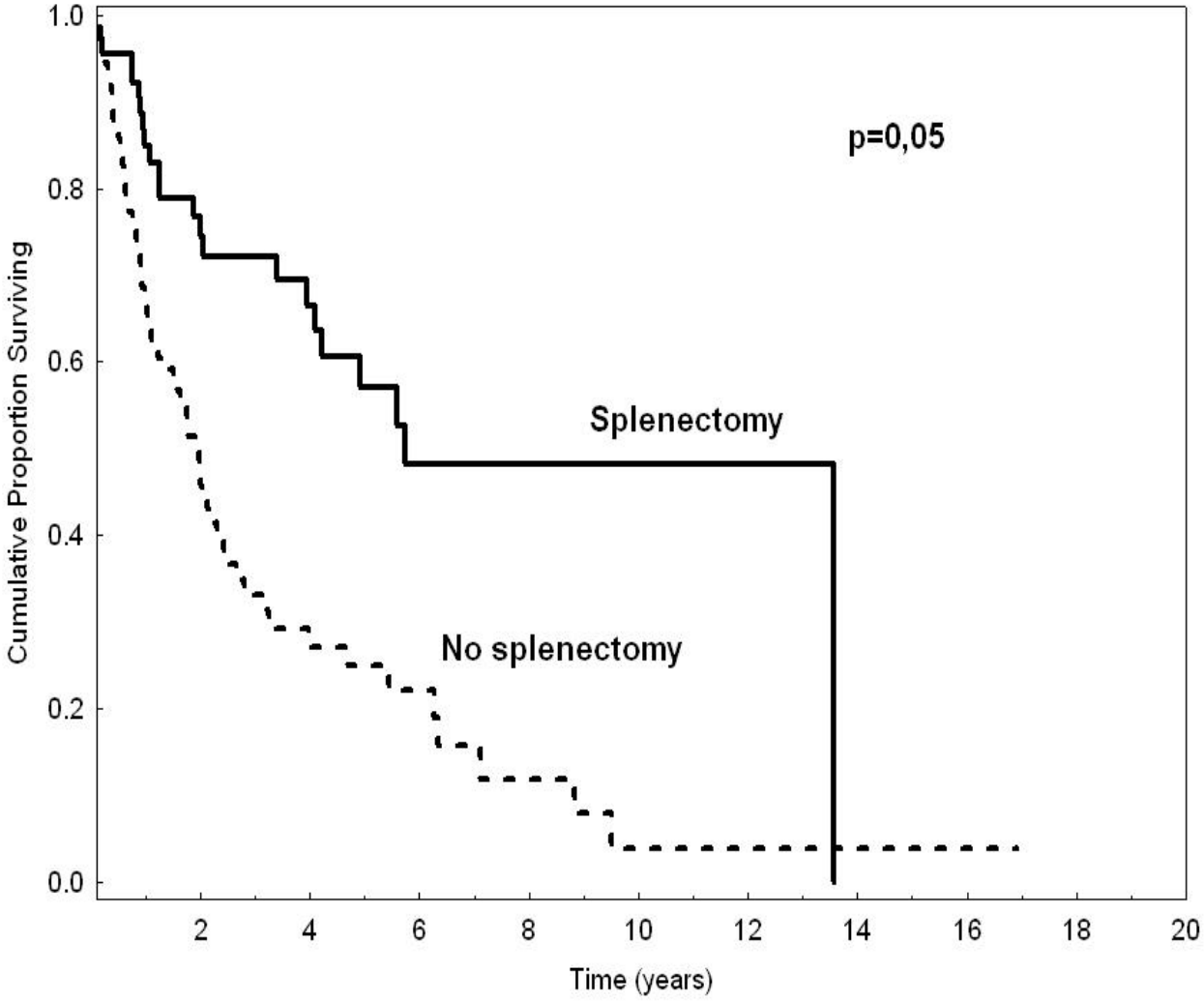




Alderuccio JP et al. JCO 2018

TREATMENT

Splenectomy



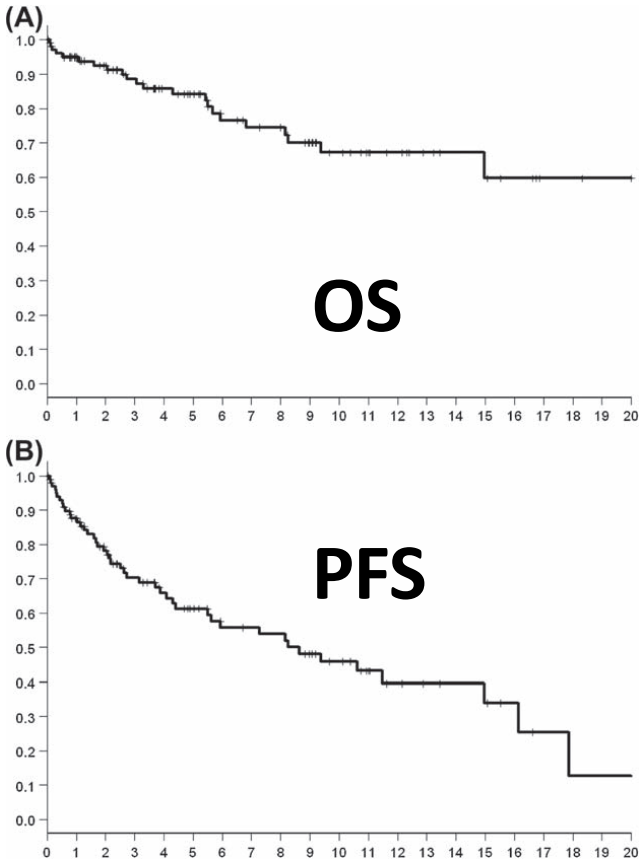
Arcaini et al. Blood 2006

Splenectomy

- 100 HCV- SMZL

treated by splenectomy

- Median PFS 8.25 yrs
- 5-y OS 84%
- 10-y OS 67%
- Hist. transformation in 11%



Lenglet et al, Leuk Lymph 2014

Splenectomy: series of SMZL

Reference	Year	N	Response		OS	Deaths due to surgery
			ORR (%)	Duration		
Mulligan et al[68]	1991	20	95	Median DOR 4 y	NR	1
Troussard et al[59]	1996	28	75	NR	71% at 5 y	1
Chacon et al[61]	2002	60*	93.3	Median FFS 40 mo	65% at 5 y	NR
Thieblemont et al[1]	2002	48†	100	PFS 48% at 5 y	NR	NR
Parry-Jones et al[60]	2003	33	NR	NR	LSS 95% at 10 y	NR
Iannitto et al[69]	2004	21	91	Median DOR 4 y	NR	NR
Tsimberidou et al[70]	2006	10	60	FFS 80% at 3 y	89% at 3 y	0
Olszewski et al[71]	2012	652	NR	NR	67.8% at 5 y‡	NR
Kalpadakis et al[73]	2013	27	85	PFS 58% at 5 y	77% at 5 y	1
Lenglet et al[7]	2014	100	97	PFS 61% at 5 y	84% at 5 y	0
Xing et al[62]	2015	52§	NR	FFS 39% at 10 y	61% at 10 y	0
Pata et al[89]	2015	41	90	PFS 35% at 5 y	75% at 5 y	0

DOR, duration of response; FFS, failure-free survival; LSS, lymphoma-specific survival; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

*Splenectomy alone in 29 patients.

†Splenectomy alone in 25 patients.

‡Survival of entire series of 1251 patients with no impact of splenectomy on OS.

§Splenectomy alone in 42 patients.

Arcaini et al Blood , 2016

Splenectomy: complications

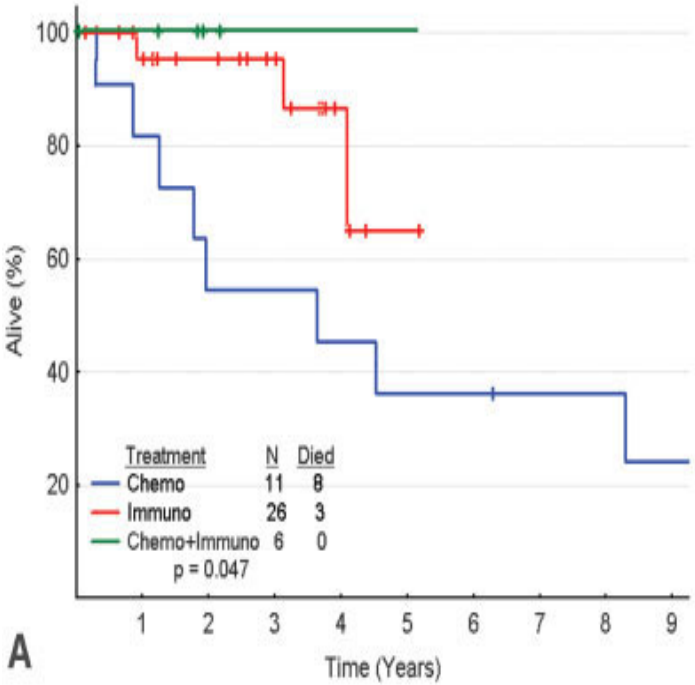
Perioperative complications in 41 splenectomized pts (*Pata et al, 2015*):

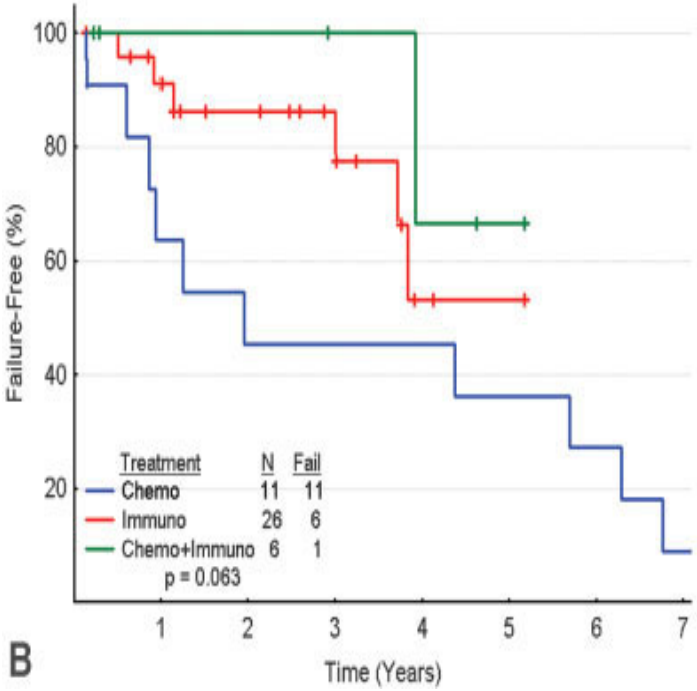
- Pulmonary dysfunction 20%
- Deep vein thrombosis 2%
- Portal vein thrombosis 2%
- Major bleeding 22%

Infections caused by encapsulated bacteria

In 2 recent series from France and British Columbia, about 5% of splenectomized patients died of infectious complications (*Langlet et al, 2014; Xing et al, 2015*)

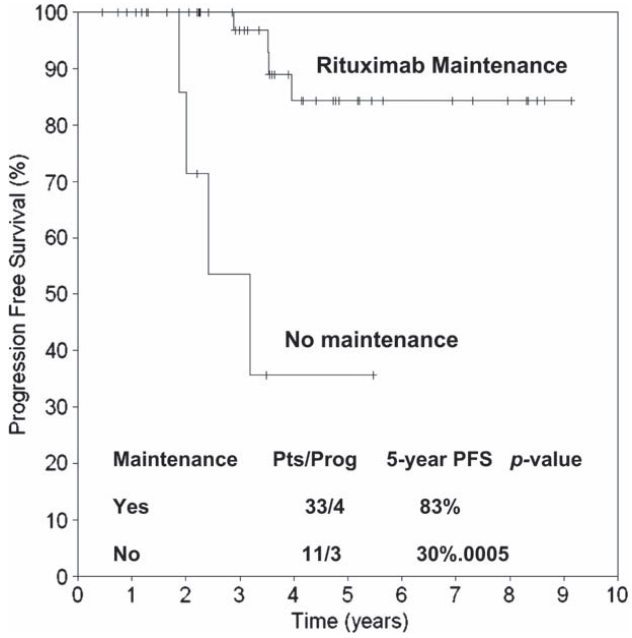
Rituximab





Tsimberidou et al, Cancer , 2006

Author	No. of patients	ORR, %	CR, %	PFS, % (at *n* years)	OS, % (at *n* years)
Bennett, 2005 [34]	11	91	NR	80 (6)	60 (4)
Tsimberidou, 2006 [26]	25	88	31	86 (3)	95 (3)
Kalpadakis, 2008 [36]	16	100	69	92 (2.4)	100 (2.1)
Else, 2012 [28]	10	100	90	89 (3)	98 (3)
Kalpadakis, 2013 [27]	58	95	45	73 (5)	92 (5)



Kalpadakis et al, Oncologist, 2013

R-COMP05

CR = 31 (64%)

PR = 10 (20%)

6-year PFS 54%

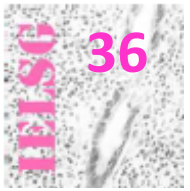
Grade >3 neutropenia 26%

Grade >3 infections 8%

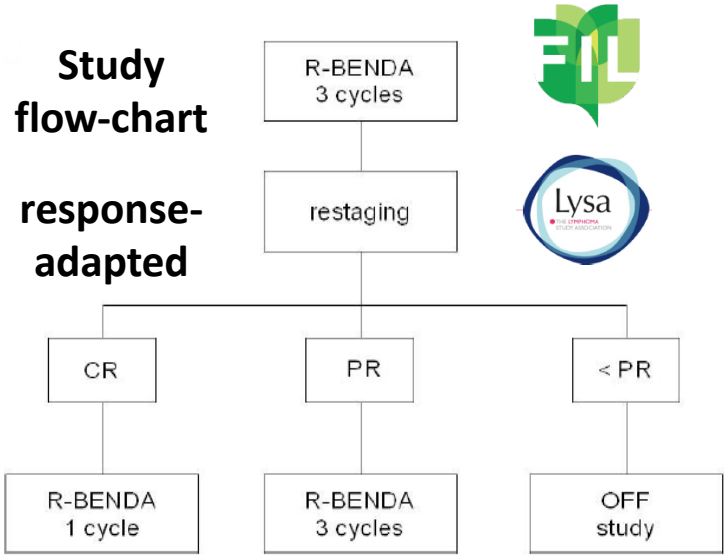
2 deaths as a result of infection

Iannitto et al, Leuk Lymphoma 2015

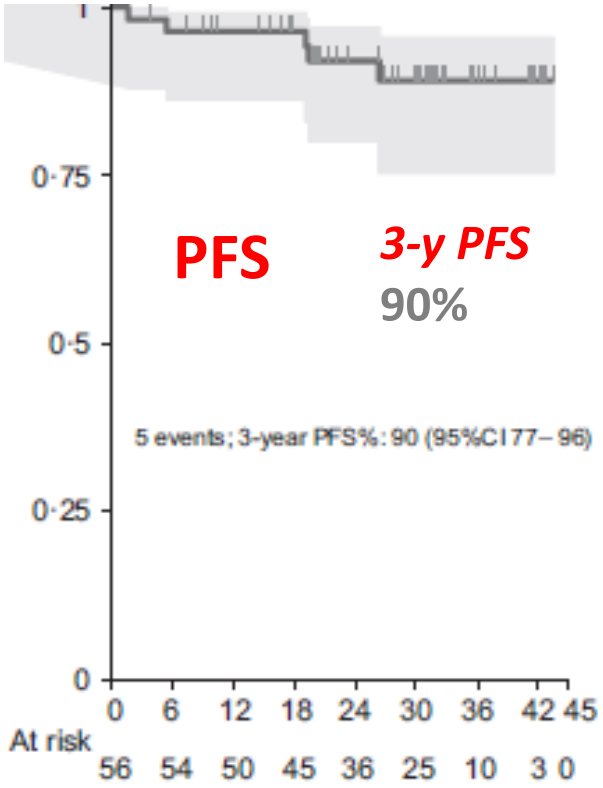
BR as 1st line tp in SMZL: BRISMA

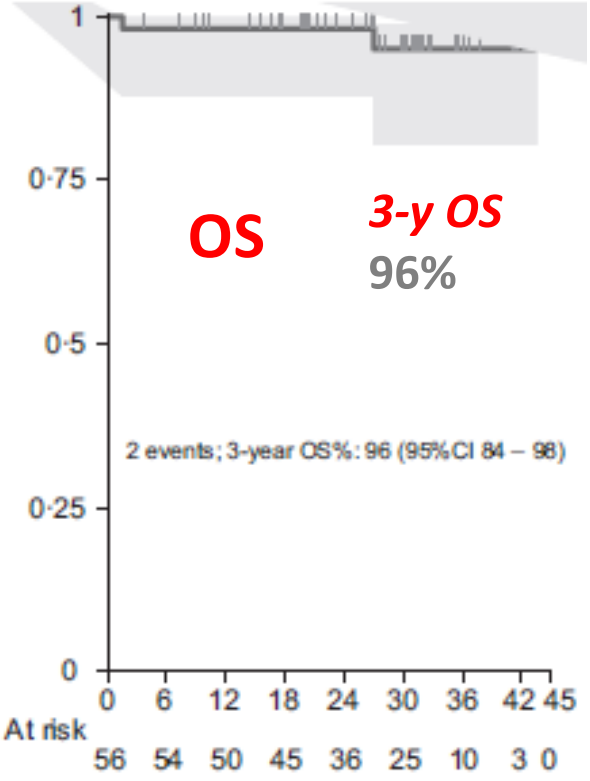


- **56 pts, SMZL**, symptomatic, diagnosis prospectively confirmed



- 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%**

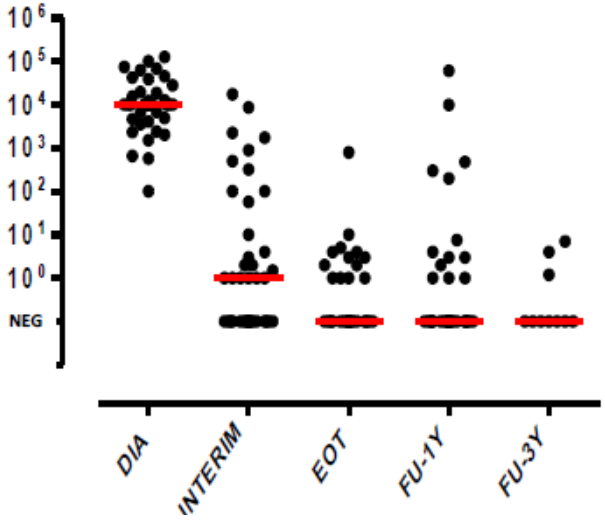
***Median follow-up:** **32 months** (2 - 52)

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



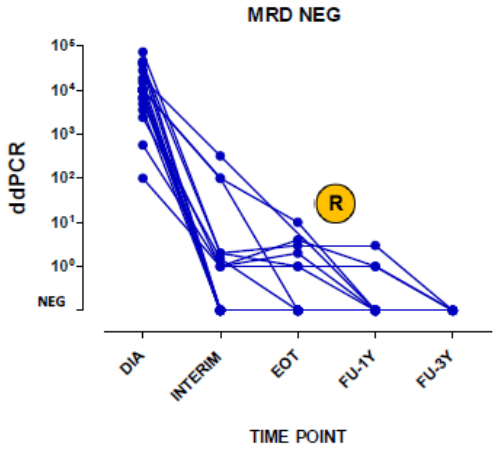
MRD neg rate	Overall	BM	PB
Interim	47%	41%	58%
EOT	54%	43%	82%
1 year	61%	64%	66%

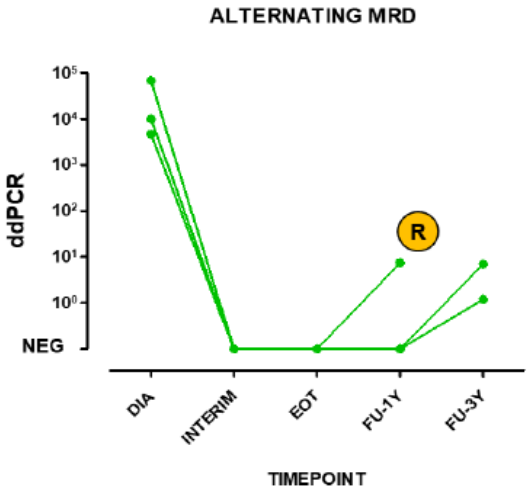
MRD KINETICS

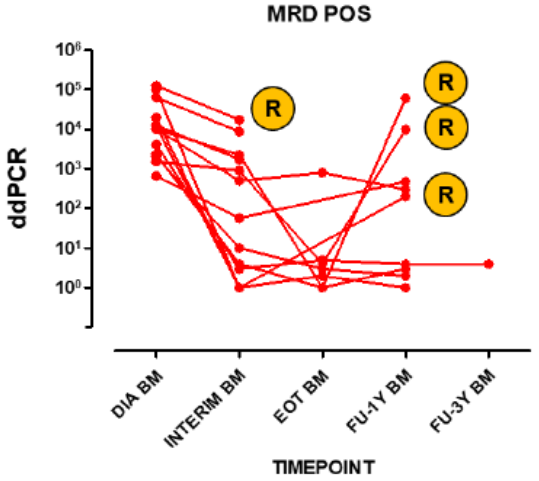
Persistent MRD negativity (41%)

Persistent MRD positivity (31%);

Alternating MRD (28%)





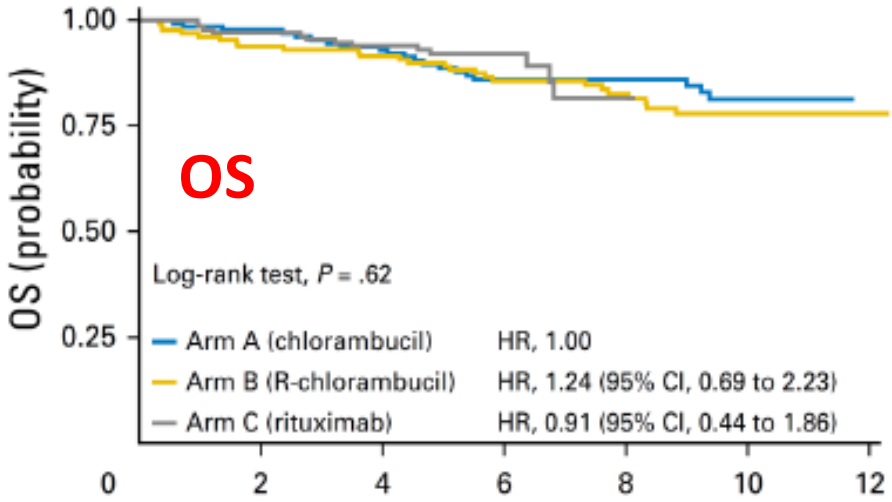


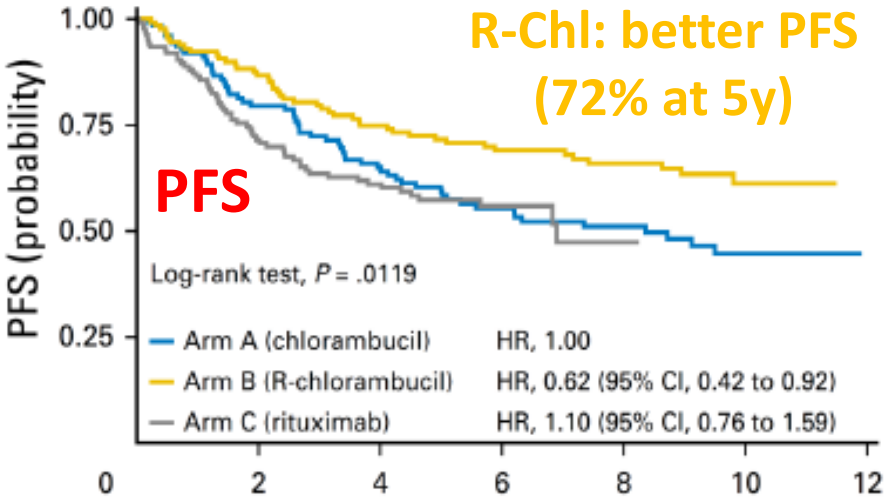
Ferrero S et al, ICML 2019

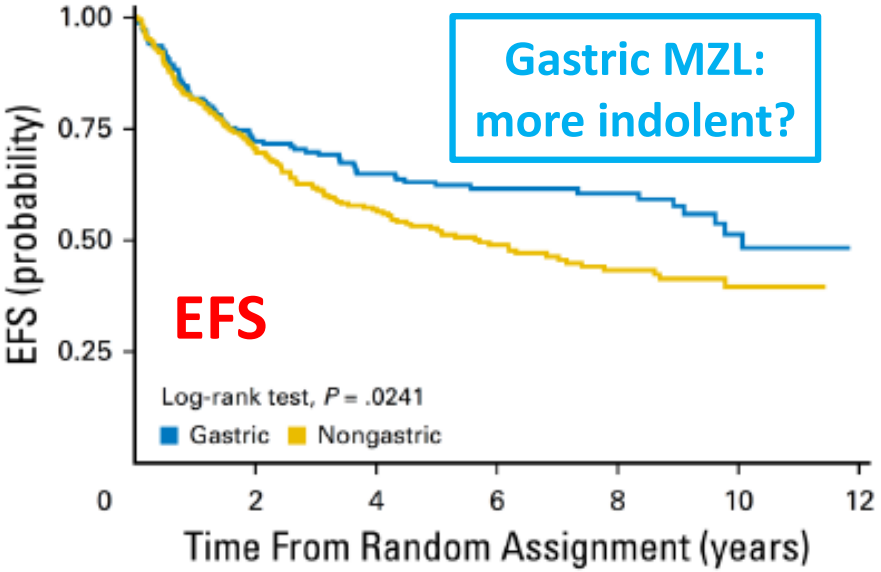
EXTRANODAL MARGINAL ZONE LYMPHOMA OF MALT

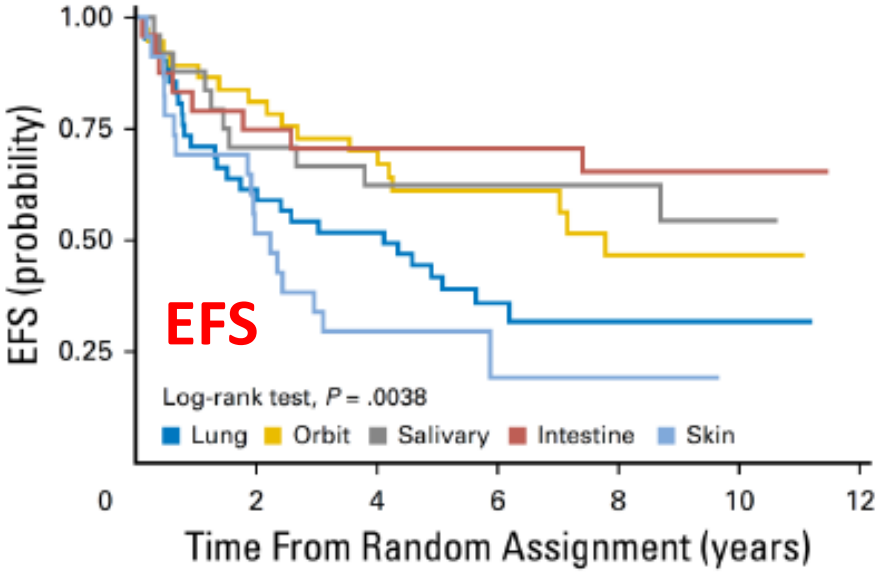
IELSG-19 randomized study in MALT MZL

- 401 pts: **Chlorambucil (Arm A)** *vs* **R-Chlorambucil (B)** *vs* **Rituximab (C)**







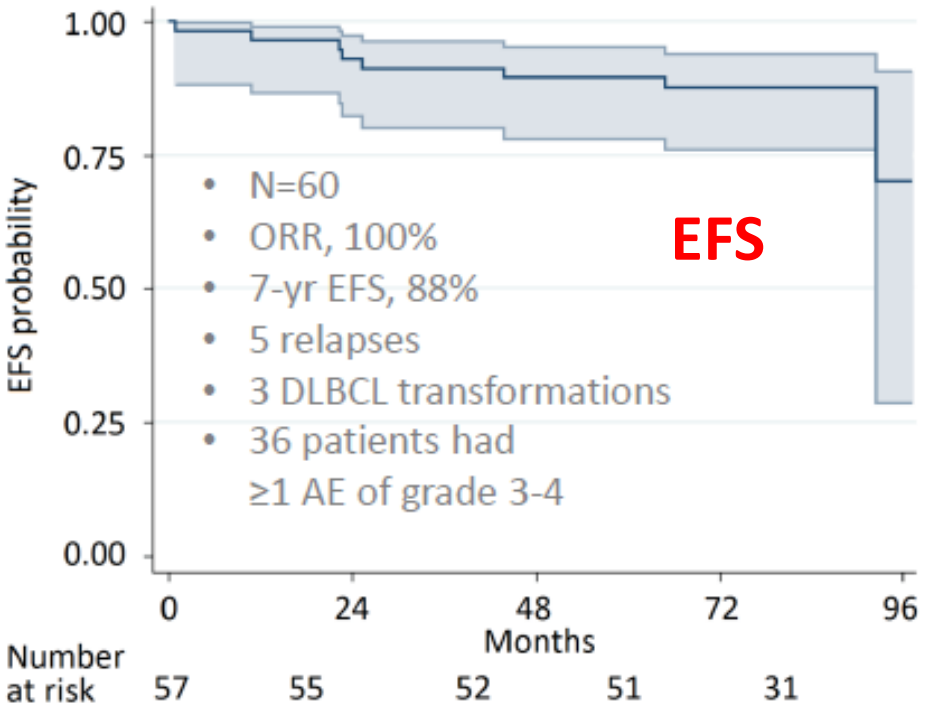


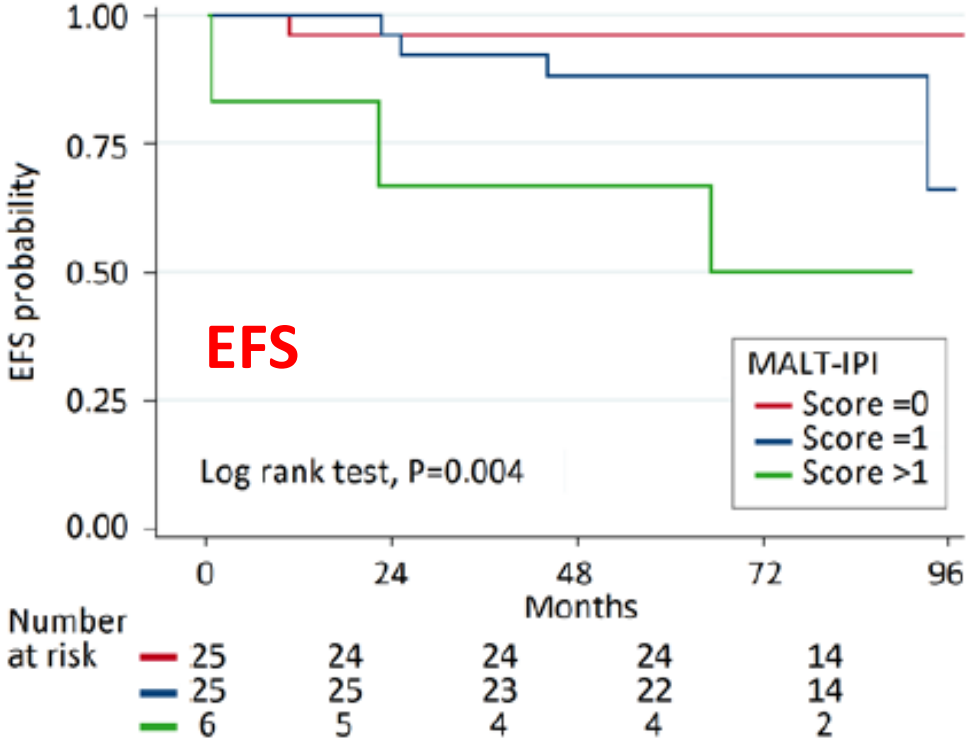
Zucca E et al, JCO 2017

BR as 1st-line therapy in MALT MZL

- GELTAMO phase 2 study (MALT-2008-01)
- R-Bendamustine as 1st-line response-adapted therapy (4 to 6 cycles)

7y EFS: 87.7% (95% CI, 76.0-94.0)





- No differences between gastric and non-gastric MALT MZL

7-y PFS: **92.8%** ***7-y OS:*** **96.5%**

Salar A et al, Blood 2017

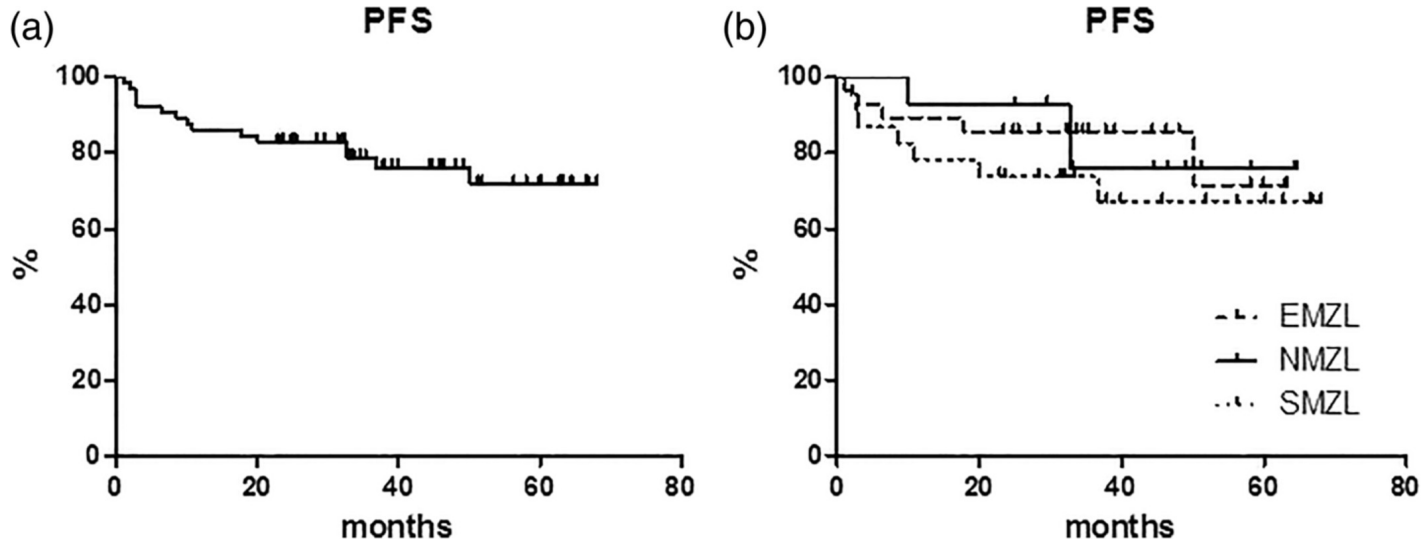
Toxicity beyond the first 2 years of follow-up

- 3 opportunistic infections:
  - 1 herpes zoster
  - 1 citomegalovirus
  - 1 lung infection by Nocardia
- No myelodysplastic syndrome or acute leukemia
- 3 neoplasia:
  - 1 epidermoid carcinoma of the tongue
  - 1 GIST
  - 1 granular lymphoproliferative disorder of NK-cells
- 3 non-melanoma skin cancers

R-bendamustine in MZL

- 65 MZL ts (28 EMZL, 23 SMZL, 14 nodal NMZL)
- 38 CR (58.5%)
- ORR 89.2%
- With a median f-up time of 44.6 mo estimated 6-year PFS 71.8%
- All toxicities quickly resolved and no treatment-related death occurred.

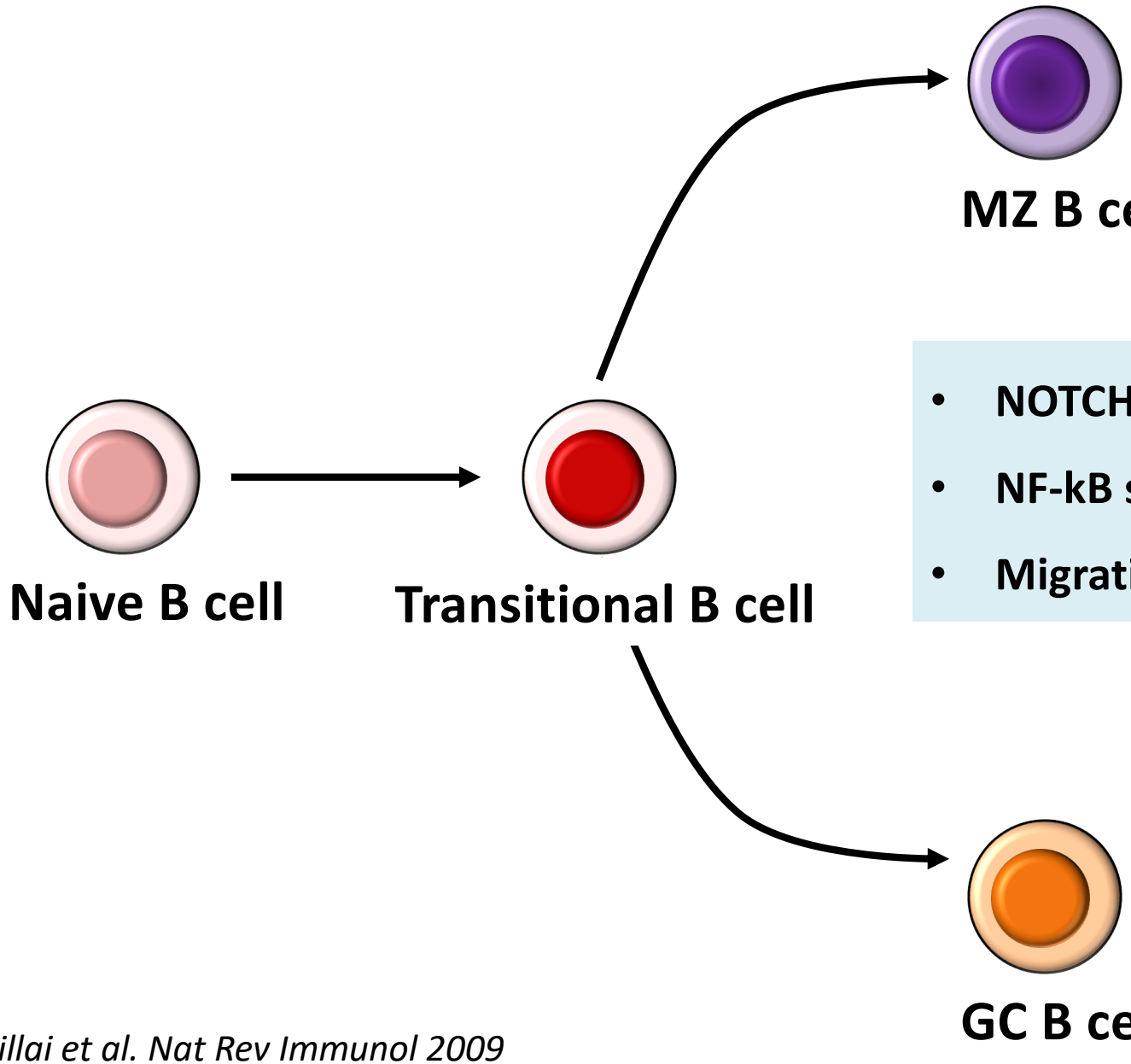
Morigi et al, Hematol Oncol 2020



Morigi et al, Hematol Oncol 2020

Biological rationale for innovative approach in MZL

Pathways in the SMZL and NMZL signatures

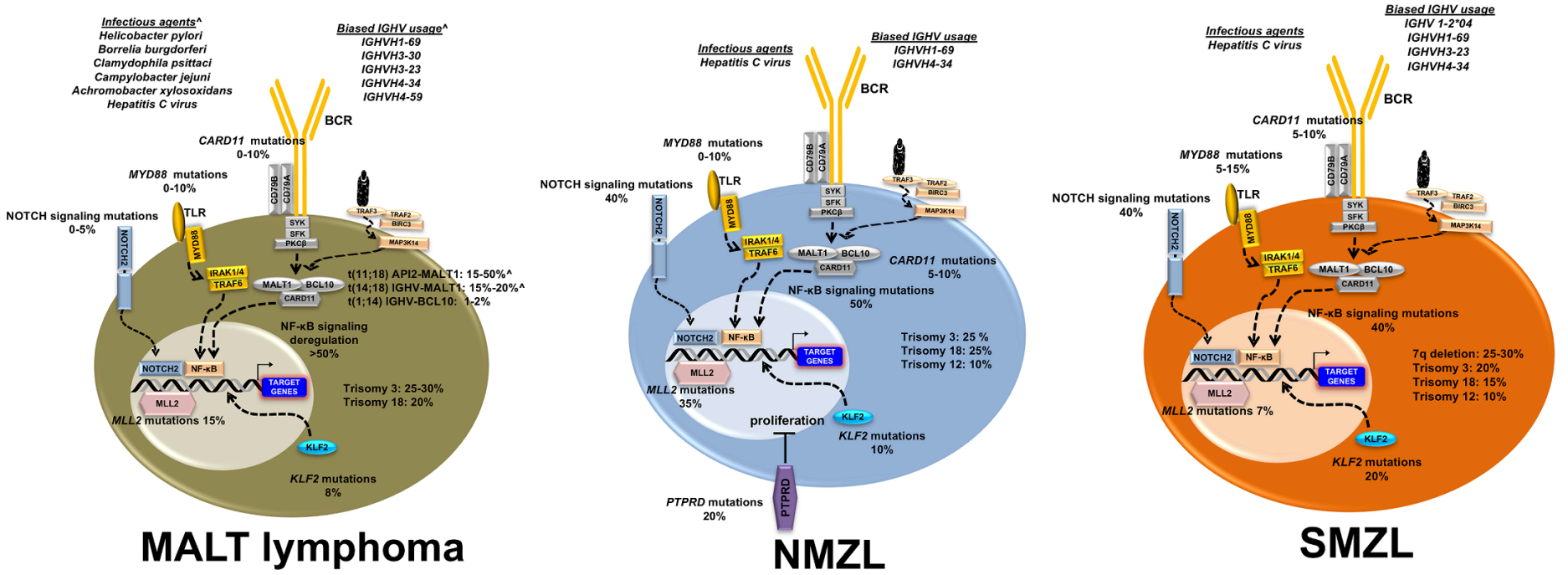


- NOTCH2 signals
- NF-kB signals
- Migration to and retention in MZ

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

Pillai et al. Nat Rev Immunol 2009

Molecular pathogenesis of MZL



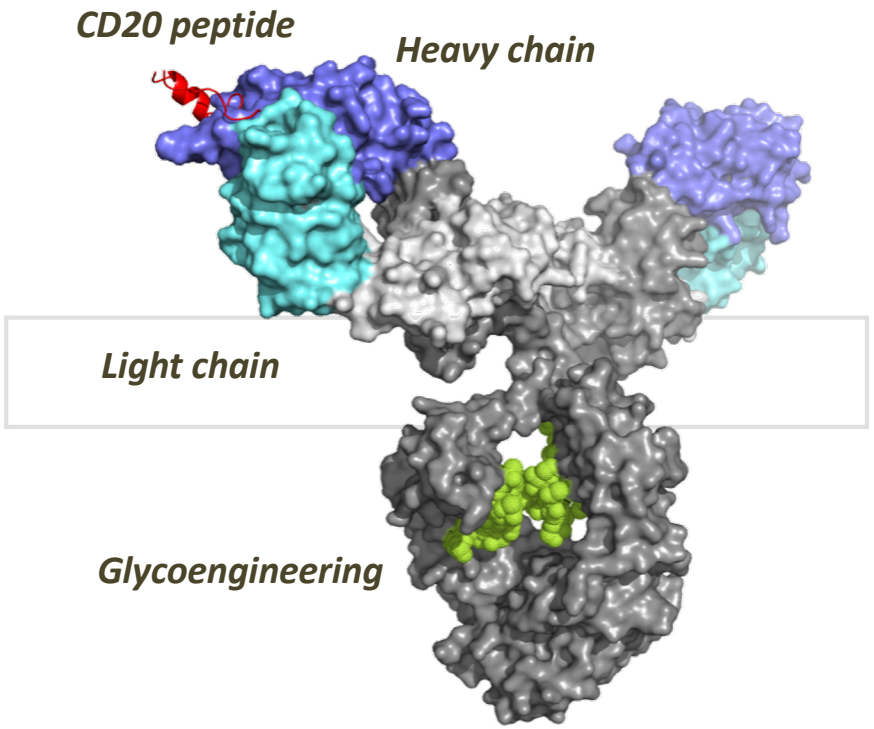
Bertoni et al F1000 Research 2018

GA101 glycoengineered, type II anti-CD20 monoclonal antibody (obinutuzumab)

Recognises a type II epitope

– Favour different CD20 conformations that are associated with different protein complexes and different mechanisms of action

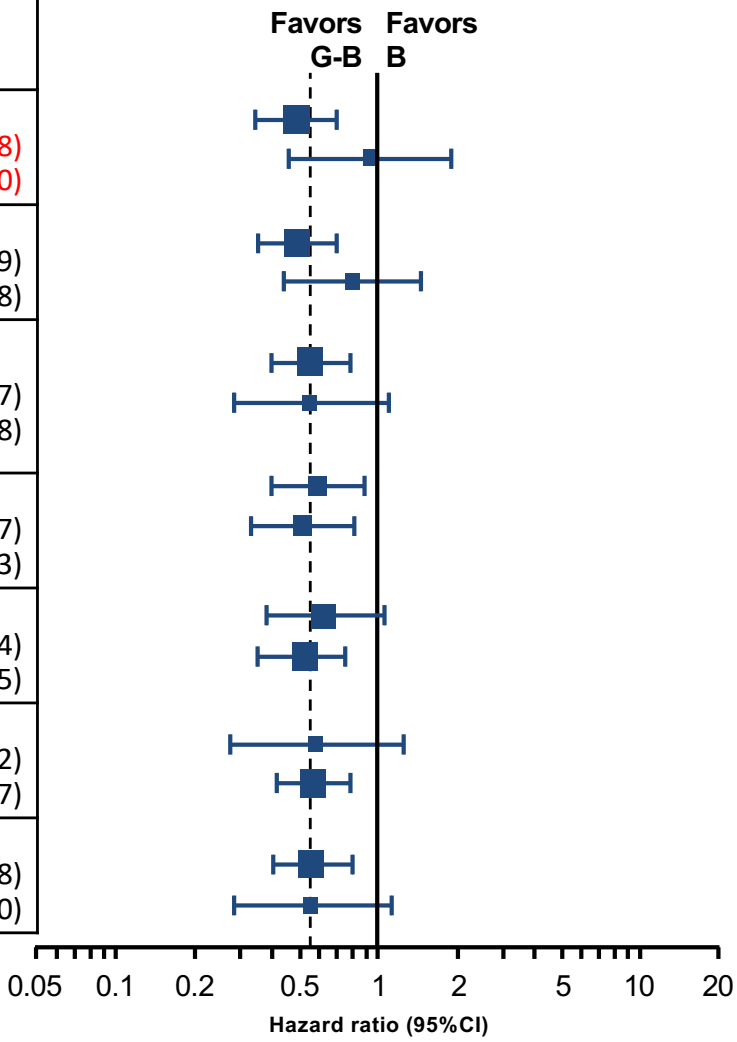
– Fc region of GA101 is glycoengineered to confer improved **antibody-dependent cell-mediated cytotoxicity**



Mössner et al Blood 2010
Niederfellner et al Blood 2011
Alduaij et al Blood 2011

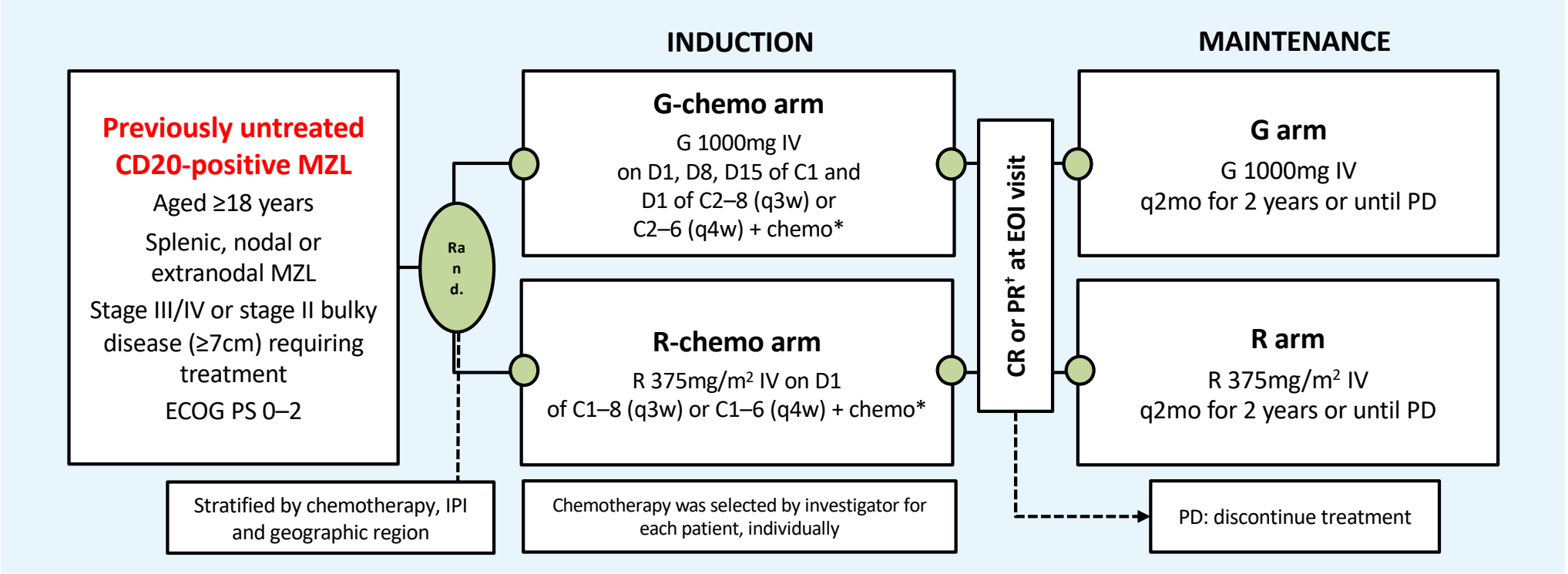
GADOLIN: PFS by subgroup

Subgroup	Total n	G-B (n=194) n	G-B (n=194) Events	B (n=202) n	B (n=202) Events	Hazard ratio (95%CI)
Follicular lymphoma						
Yes	321	155	54	166	90	0.49 (0.35–0.68)
No	**75**	39	17	36	14	0.94 (0.46–1.90)
No. of prior therapies						
≤2	312	154	51	158	83	0.49 (0.34–0.69)
>2	84	40	20	44	21	0.80 (0.43–1.48)
Refractory type						
Rituximab + chemotherapy	313	156	57	157	82	0.55 (0.39–0.77)
Rituximab monotherapy	83	38	14	45	22	0.55 (0.28–1.08)
Sex						
Male	228	110	41	118	57	0.58 (0.39–0.87)
Female	168	84	30	84	47	0.52 (0.33–0.83)
Bulky disease at BL						
Yes (>6 cm)	136	66	27	70	37	0.63 (0.38–1.04)
No (≤6 cm)	257	128	44	129	67	0.51 (0.35–0.75)
B symptoms at BL						
Yes	58	30	12	28	16	0.57 (0.27–1.22)
No	335	163	59	172	87	0.55 (0.40–0.77)
Double refractory status						
Yes	311	147	55	164	87	0.56 (0.40–0.78)
No	85	47	16	38	17	0.55 (0.28–1.10)



GALLIUM study design (MZL)

International study with open-label, randomised design



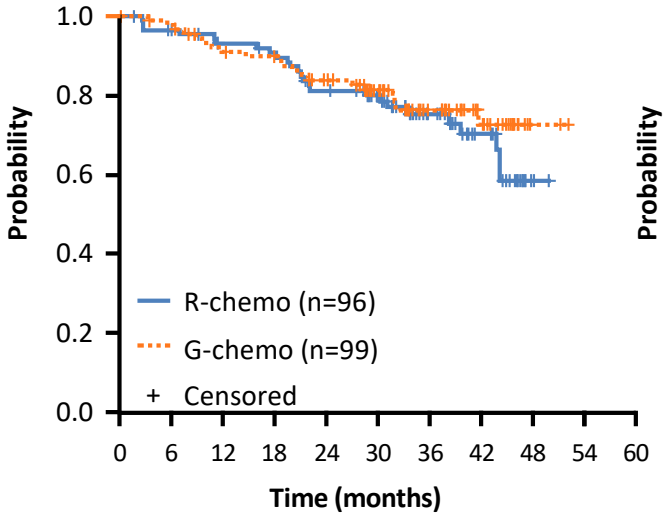
Exploratory endpoints

- PFS (INV-assessed)
- PFS (IRC-assessed)
- OS
- TTNT
- ORR/CR at EOI (+/– FDG-PET)
- Safety

*CHOP q3w × 6 cycles, CVP q3w × 8 cycles, bendamustine q4w × 6 cycles
†Pts with stable disease (SD) at EOI entered observation for up to 2 years or until progressive disease (PD) if earlier
CR, complete response; IPI, International Prognostic Index; ORR, overall response rate; PR, partial response; TTNT, time to next treatment

Other time-to-event endpoints*

IRC-assessed PFS

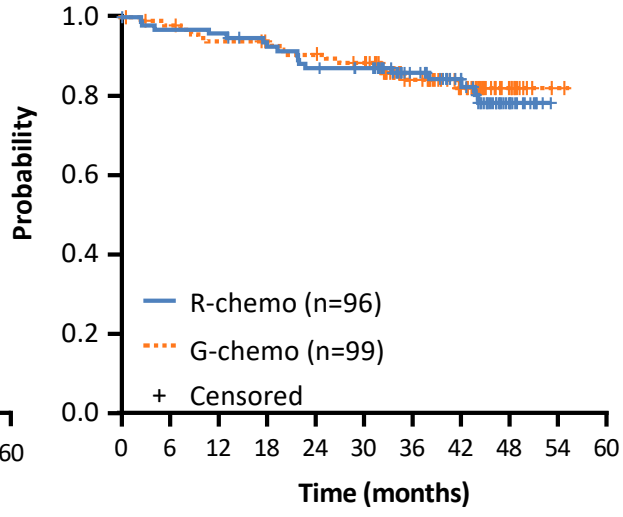


No. of patients at risk

R-chemo	96	85	80	76	68	56	35	21	1
G-chemo	99	89	80	77	68	52	36	19	2

HR (95% CI), p-value†	0.83 (0.46, 1.51), p=0.55

OS

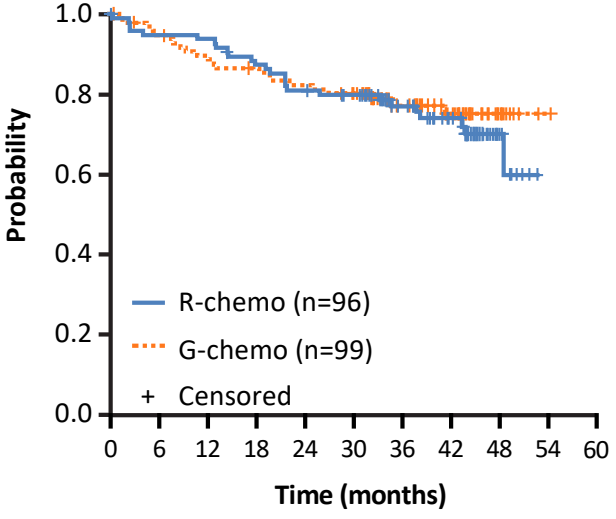


No. of patients at risk

R-chemo	96	92	91	86	81	78	59	44	12	
G-chemo	99	95	90	88	85	81	50	35	12	1

HR (95% CI), p-value†	0.90 (0.45, 1.81), p=0.78

TTNT



No. of patients at risk

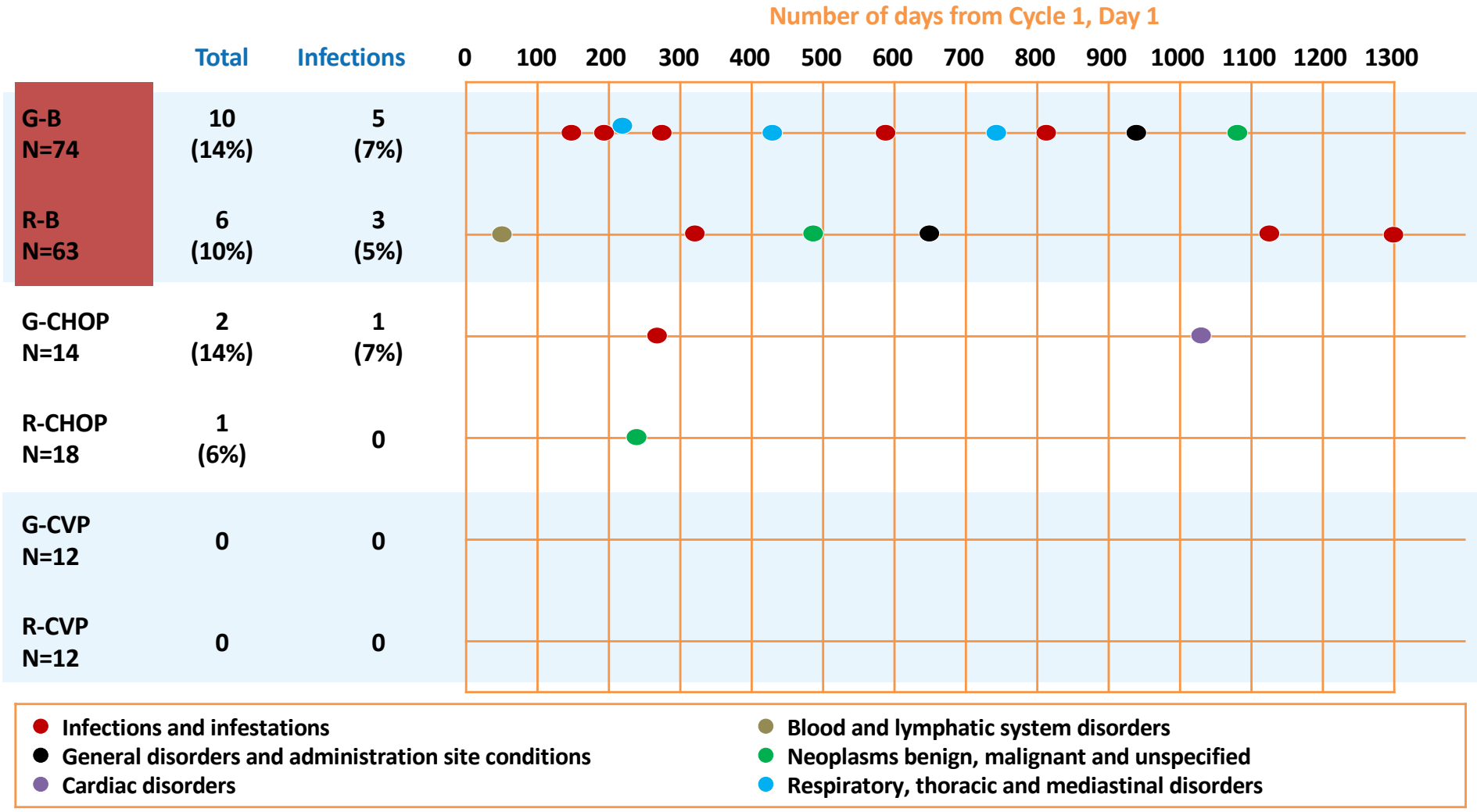
R-chemo	96	90	89	82	76	72	52	40	10
G-chemo	99	92	86	82	78	75	46	33	12	1

HR (95% CI), p-value†	0.85 (0.48, 1.50), p=0.57

*ITT population

†Stratified analysis; stratification factors: IPI and chemotherapy regimen

Grade 5 (fatal) AEs*



Note: no patient had PD or had started new anti-lymphoma treatment at the time of the grade 5 AE

*Safety population (all randomised pts who received at least one dose of study drug; note: 3 pts randomised to R-chemo received G [n=2] or no antibody [n=1])

Bortezomib

NFkB - targeted therapies

IELSG-25 and Austrian phase II trials of bortezomib for MALT Lymphoma

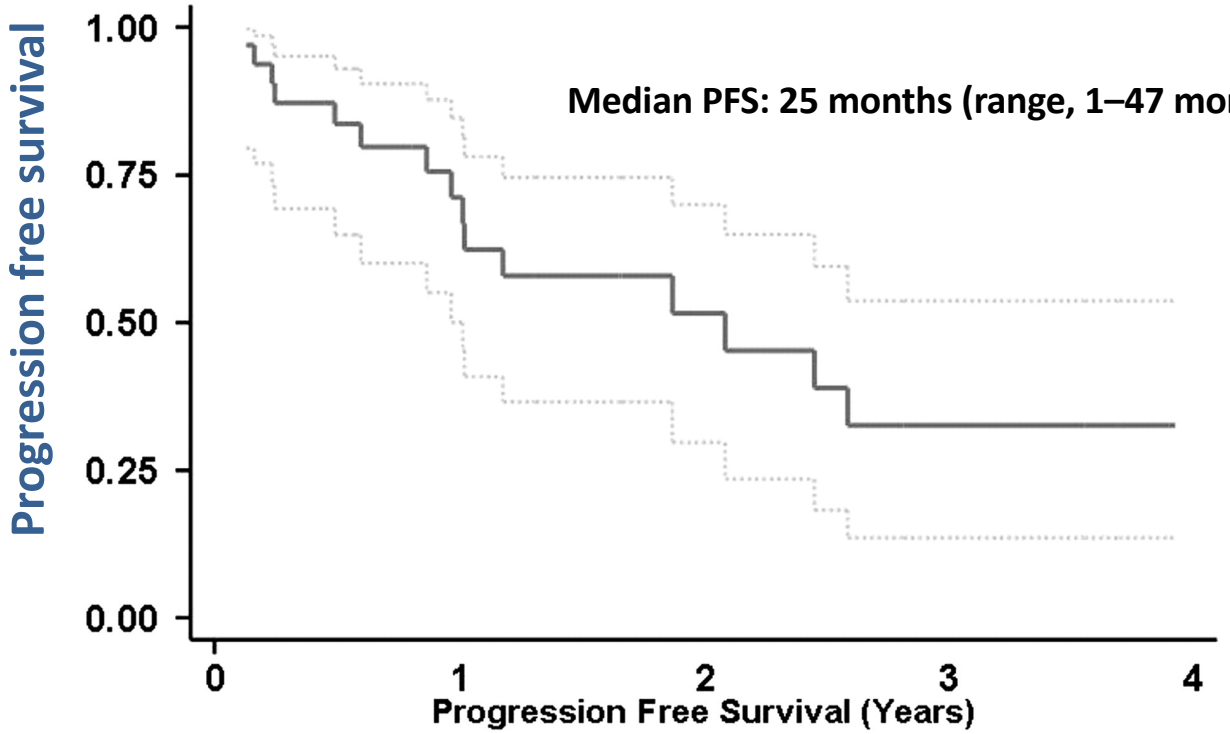
- 1.3 mg/m^2 days 1, 4, 8, 11 q21
- 21 pts with **R/R** MALT lymphoma,
- 52% stage IV
- 52% primary gastric
- Median follow up 17 mos
- CR 27%, PR 37%
- Toxicity similar to that observed in multiple myeloma and other NHL (peripheral neuropathy and fatigue)
- 3 deaths, non-related to treatment, observed during the early follow up.

Conconi et al Ann Oncol 2010

- 1.5 mg/m^2 days 1,4,8,11 q21
- 16 pts **front-line**, 4 primary gastric
- median follow up 23 mos
- ORR 80%, CR 43%
- Fifteen patients required dose reductions due to either neuropathy (7 patients) or diarrhea (8 patients).

Trosch et al Haematologica 2010

Phase II study of bortezomib in relapsed/refractory MALT lymphomas



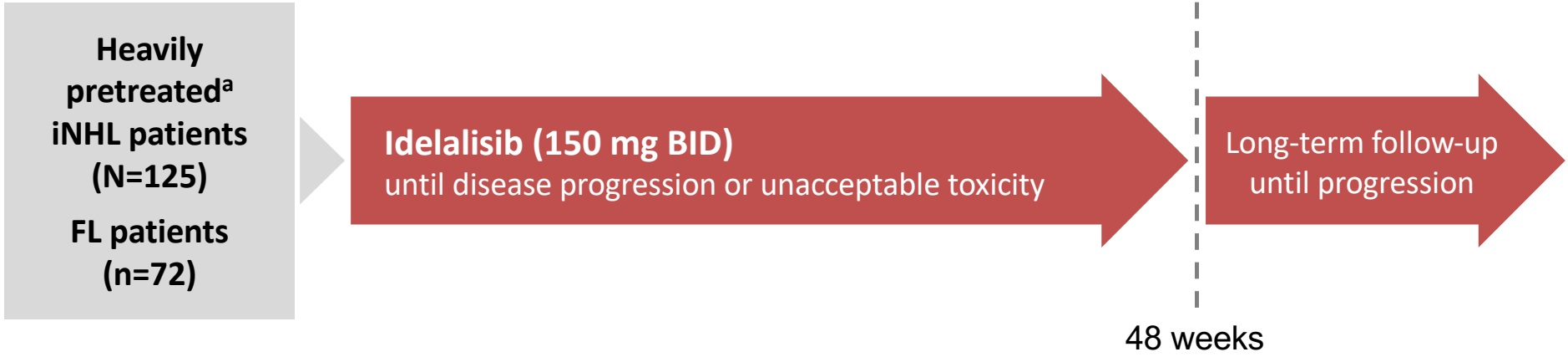
Interval	Entered	Relapsed	Censored	Survival	[95% Conf. Int.]
0 - 1 yr	31	10	7	0.64	0.43 - 0.79
1 - 2 yr	14	2	4	0.53	0.32 - 0.71
2 - 3 yr	8	3	1	0.32	0.12 - 0.54
3 - 4 yr	4	0	4	0.32	0.12 - 0.54

IELSG 25

Conconi et al Ann Oncol 2011

PI3K inhibitors

Study 101-09: single-group open-label Phase II study



Key endpoints

Primary: ORR

Secondary: DoR, PFS, OS and safety

Refractory was defined as less than partial response or progression of disease within 6 months after completion of a prior therapy

Gopal et al NEJM 2014

Clinical features

Baseline characteristics	Patients (N=125)
Median age (range), y	64 (33–87)
Subtype of iNHL, n (%)	
Follicular lymphoma	
Small lymphocytic lymphoma	28 (22)
Marginal zone lymphoma	15 (12)
Lymphoplasmacytic lymphoma with/without Waldenström's macroglobulinaemia	10 (8)
Disease status, n (%)	
Stage III or IV	111 (89)
Elevated LDH	38 (30)
Bulky disease (≥7 cm in one dimension)	33 (26)

LDH: lactate dehydrogenase

Gopal et al NEJM 2014

Clinical features

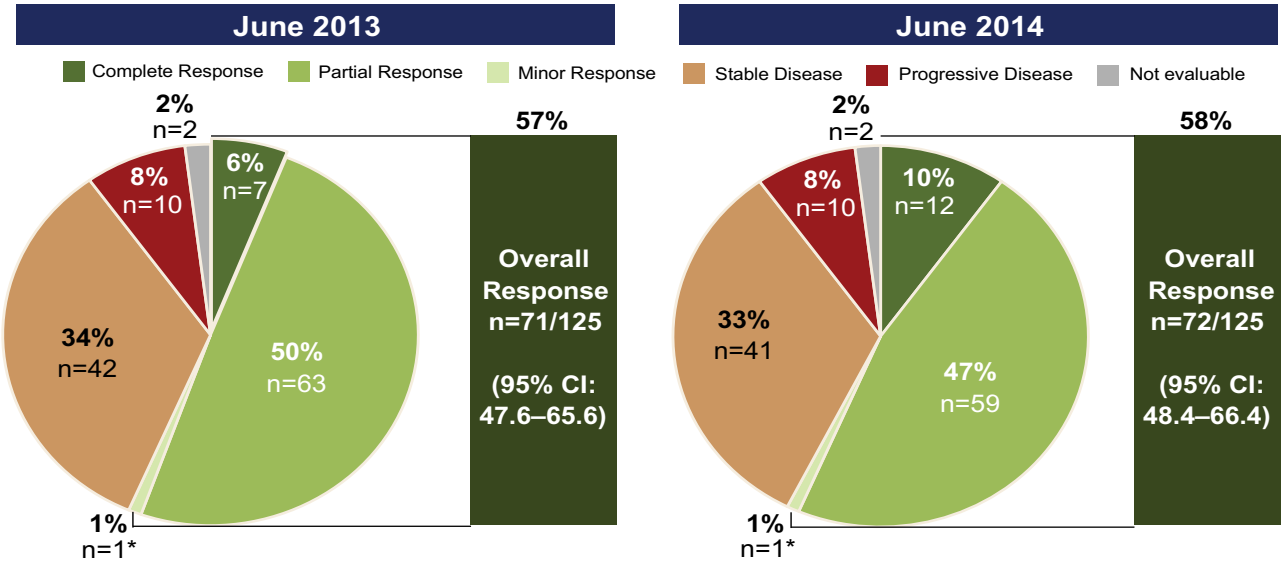
Prior therapy exposure[1,2]	Patients (N=125)
Median (range) prior regimens, n	4 (2–12)
Prior therapy, n (%)	
Rituximab	125 (100)
Alkylating agent	125 (100)
R + alkylating agent	114 (91)
Bendamustine	81 (65)
Anthracycline	79 (63)
Purine analogue	42 (34)
Stem cell transplantation	14 (11)
Median time from last regimen to study entry, months	3.9

Prior therapy refractoriness, n/n (%)[1,2]	Patients (N=125)
Rituximab	125/125 (100)
Alkylating agent	124/125 (99)[a]
R + alkylating agent	108/114 (95)
R-CVP	29/36 (81)
R-bendamustine	47/60 (78)
Bendamustine	61/81 (75)
R-CHOP	40/56 (71)
Refractory to ≥2 regimens	99/125 (79)
Refractory to last regimen	112/125 (90)

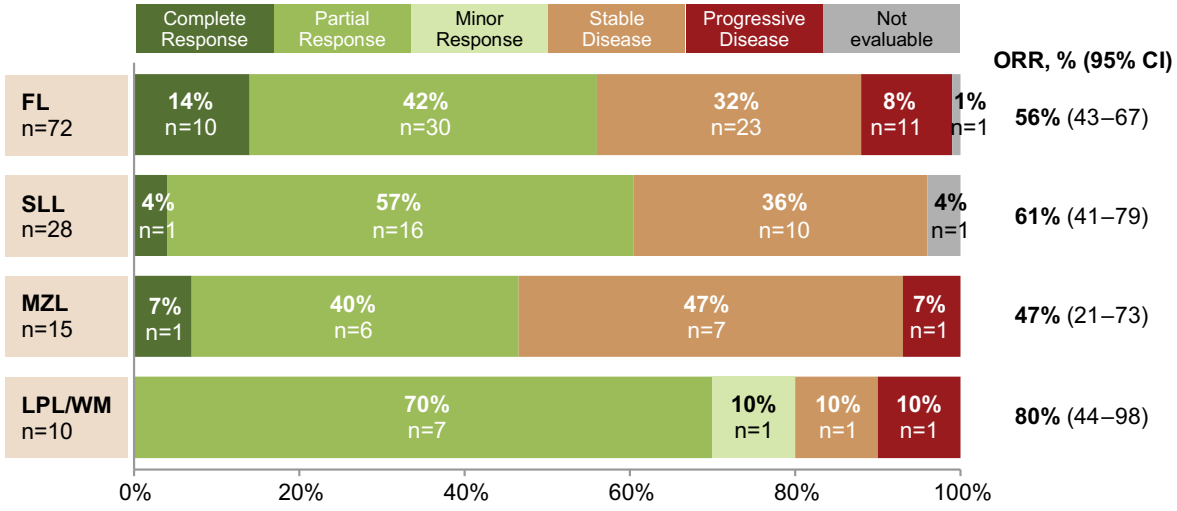
[a] Refractoriness to two cycles required to meet definition but one patient received only one cycle, with no response after that cycle.
CHOP: cyclophosphamide, vincristine, doxorubicin and prednisone; CVP: cyclophosphamide, vincristine and prednisone; R: rituximab

Gopal et al NEJM 2014

Response

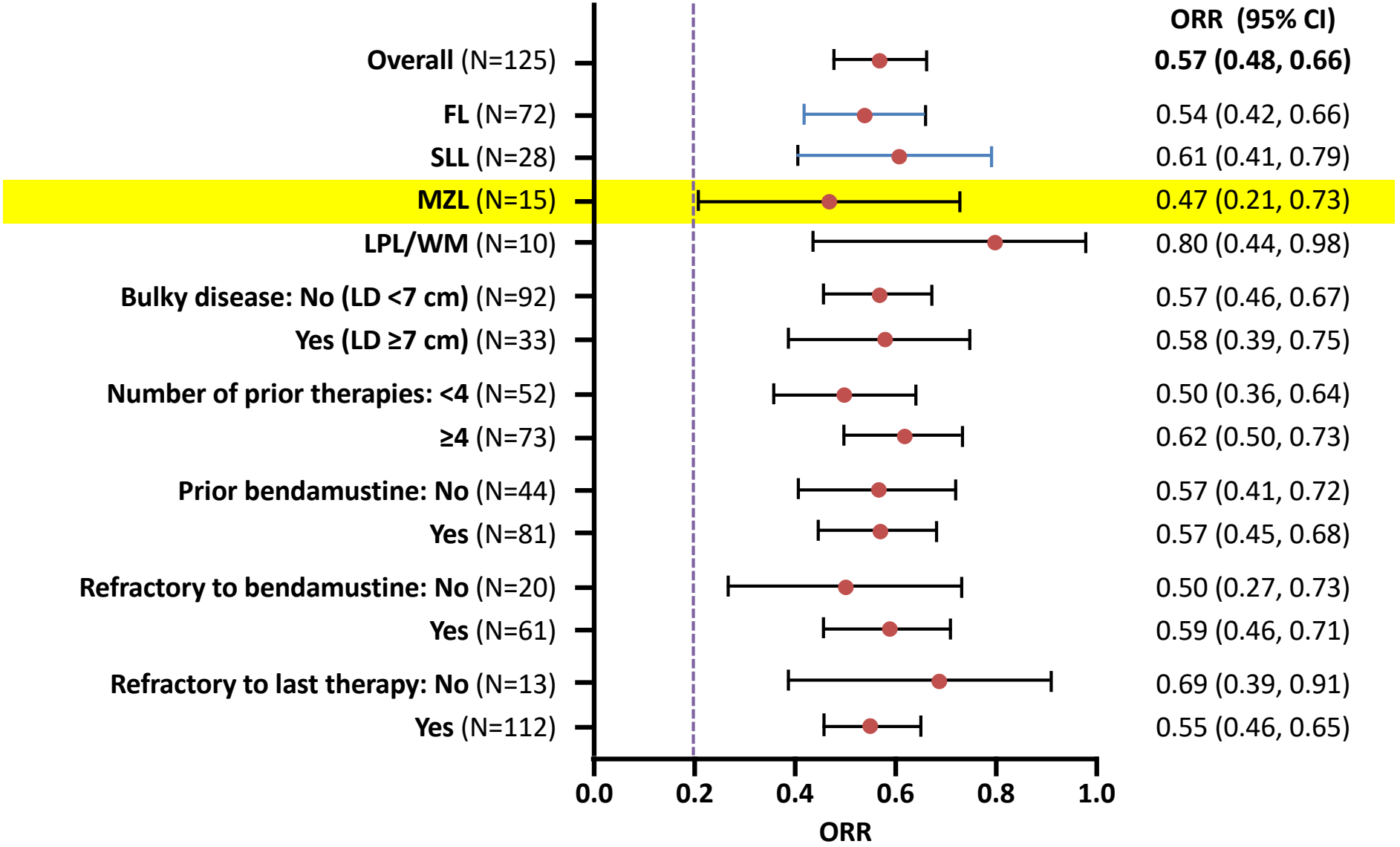


Overall Response Rate By Disease Subgroups: 2014



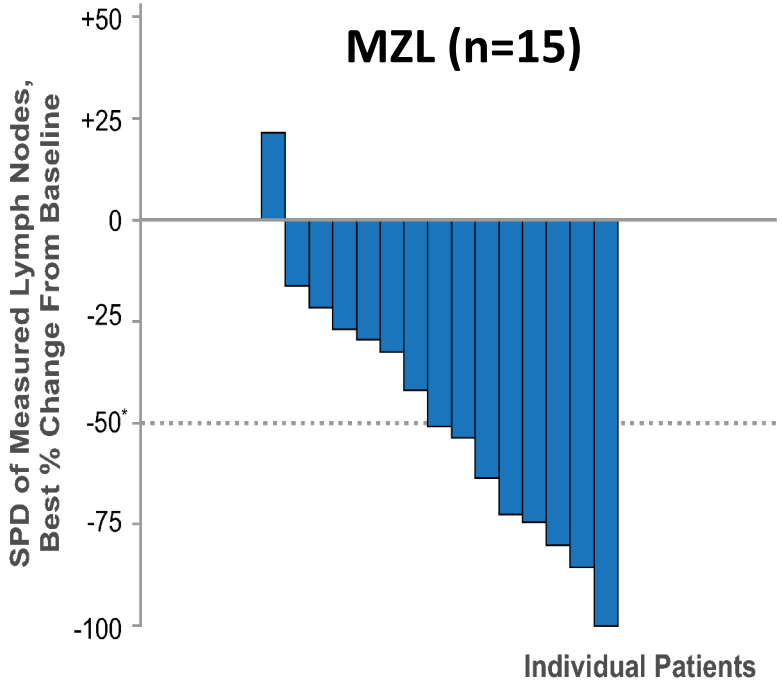
Gopal et al NEJM 2014
Gopal et al ASH 2014

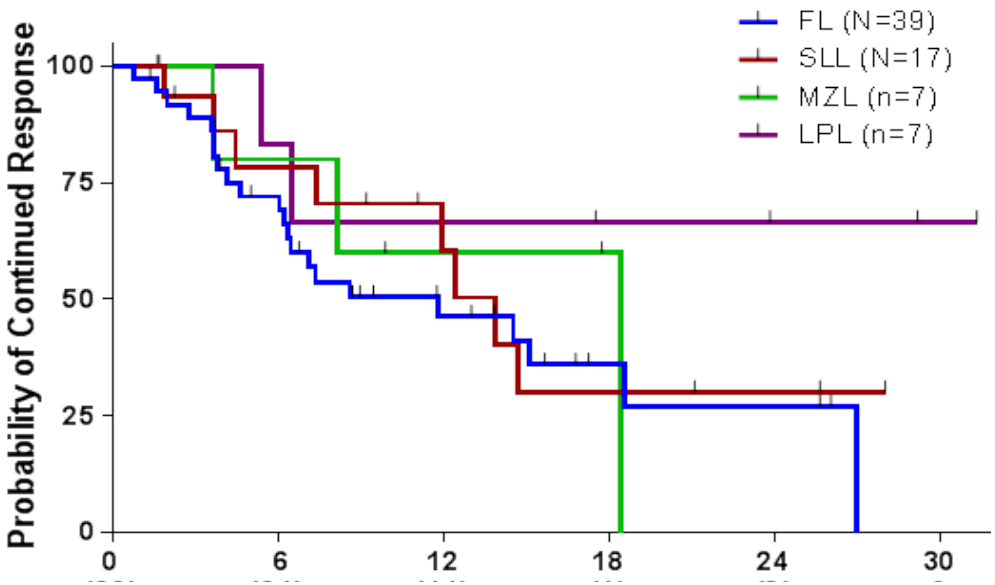
ORR across double-refractory iNHL subgroups

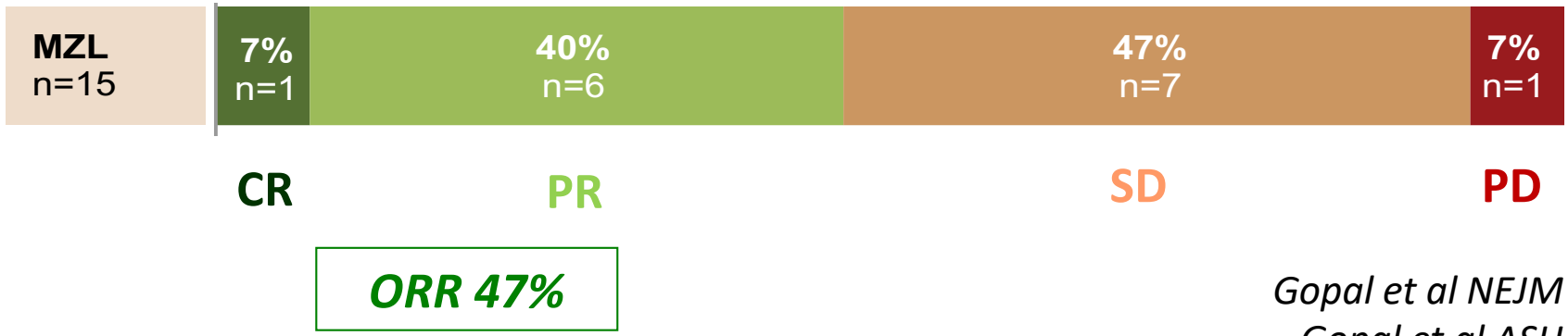


Dotted line: null hypothesis response rate of <20%

Idelalisib in double-refractory iNHL







ORR 47%

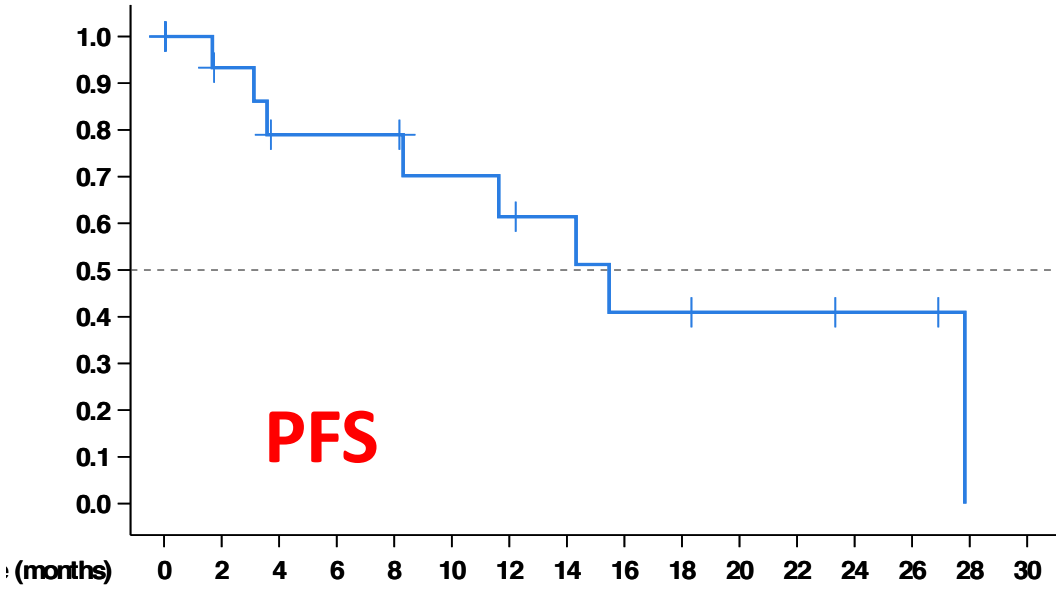
Gopal et al NEJM 2014
Gopal et al ASH 2014

Duvelisib in double refractory MZL

- DYNAMO: Phase 2 study in iNHL
- Duvelisib dual PI3Ki ($\gamma\delta$)
- 18 MZL pts (9 MALT, 4 NMZL, 5 SMZL)
- 2 median prior tp (1-8)
- Median exposure: 8.4 months

	N=18
ORR per IRC, n (%)	
ORR	7 **(39)**
CR	1
PR	6
95% CI	(17, 64)
Time to response per IRC, months	
Median (min, max)	3.7 (1.8, 8.4)
Duration of response per IRC, months	
Median (50th percentile)	NE (1.3, NE)

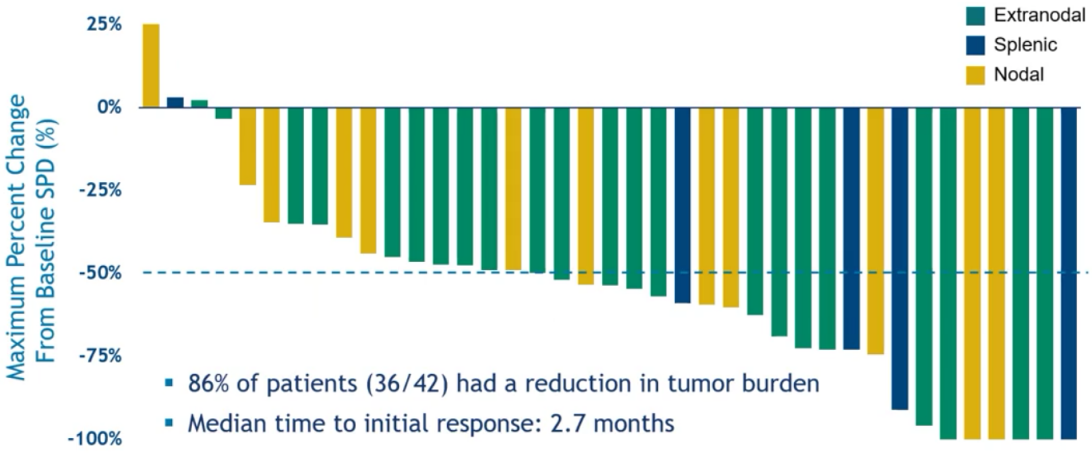
Toxicity, n (%)		
	All Gr.	**Gr>3**
Diarrhea	9 (50)	3 (17)
Colitis	3 (17)	2 (11)
Neutropenia	6 (33)	5 (28)
Cough	6 (33)	0

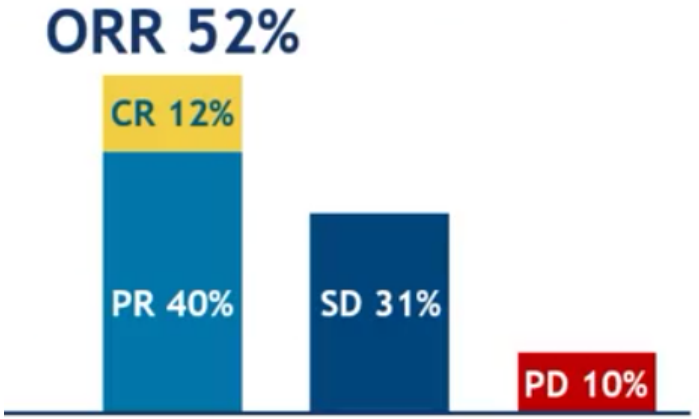


Jacobsen E et al, SOHO 2019

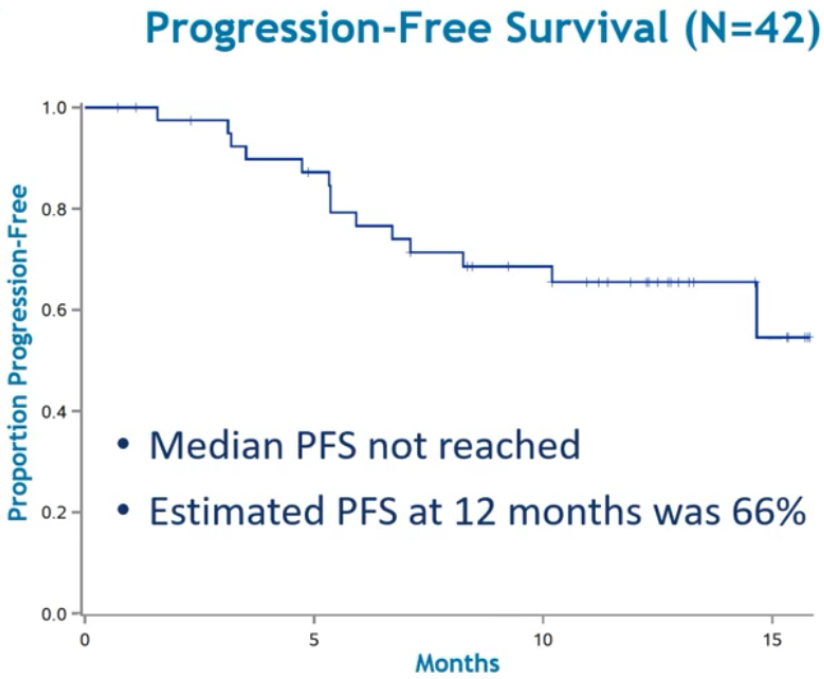
Umbralisib phase 2 study in r/r MZL

- Unity-NHL, MZL cohort
- Umbralisib: next gen PI3Kδ inh, 800 mg QD
- 72 pts, 2 median prior tp





	All Grades		Grade 3/4	
	N	%	N	%
Diarrhea	10	24%	2	5%
ALT increased	1	2%	-	-
AST increased	-	-	-	-
Pneumonitis	1	2%	1	2%
Pneumonia	-	-	-	-



Zinzani P et al, ICML 2019

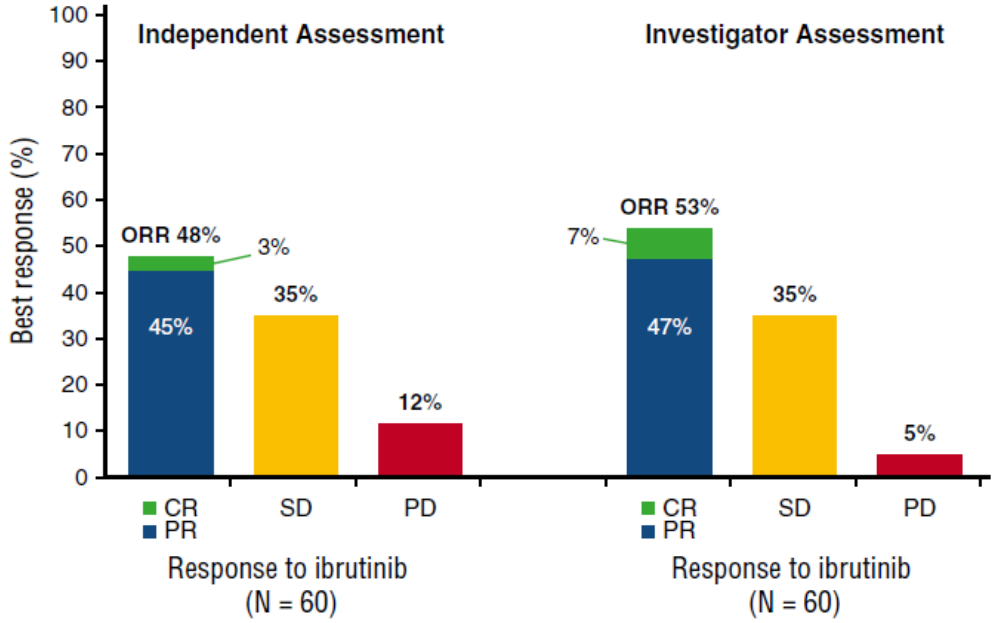
Ibrutinib

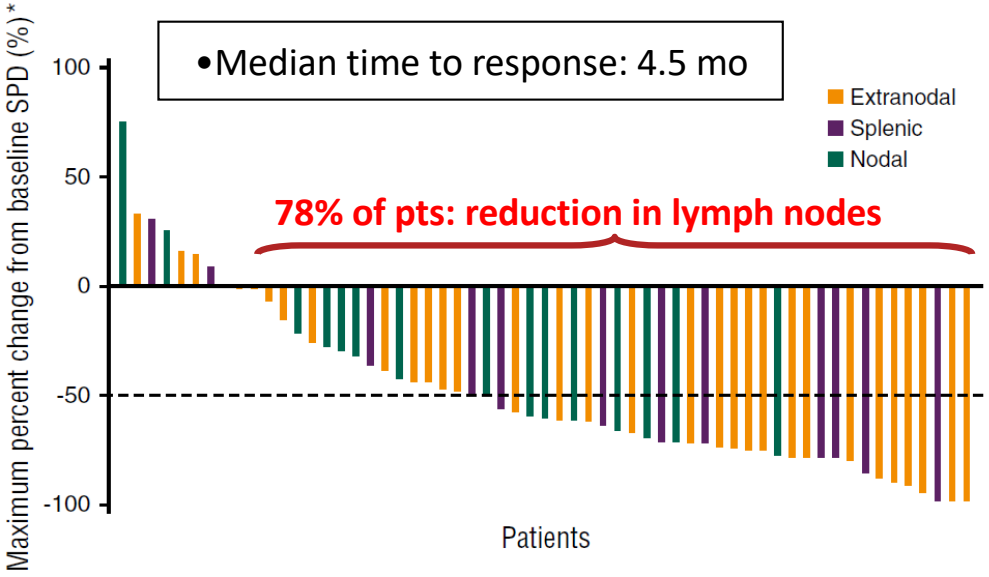
Ibrutinib in r/r MZL, phase 2 study

- 63 pts (32 MALT, 14 SMZL, 17 NMZL), median 2 prior tp

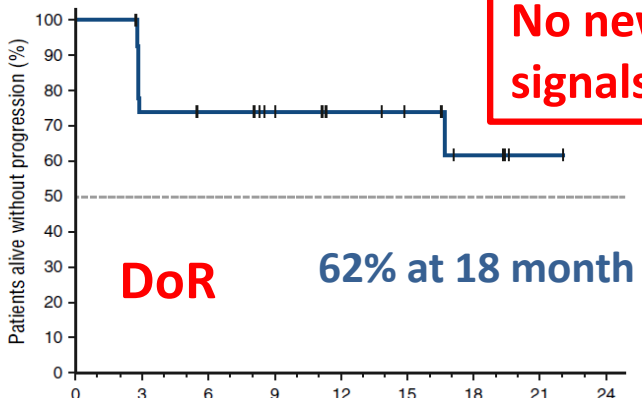
560 mg QD

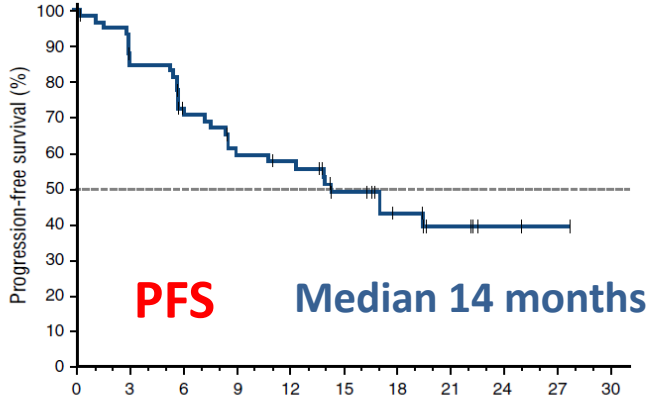
No new toxicity signals in MZL

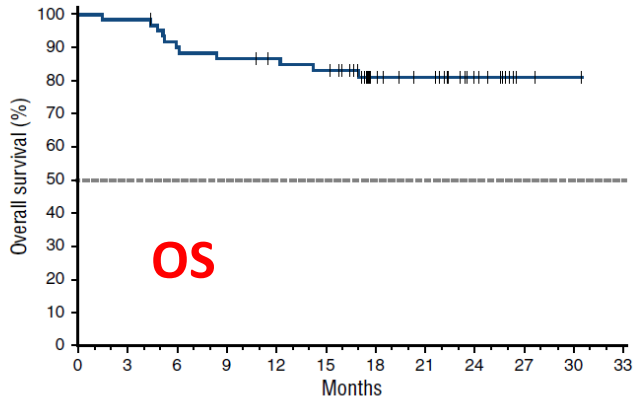




- Median time to response: 4.5 mo







Noy A et al, Blood 2017

Toxicity

- Rates of discontinuation and dose reductions due to AEs were 17% and 10%, respectively

- Median duration of exposure 11.6 mo

- At a median f-up of 19.4 mo for the all treated population (n=63), 38% continue study treatment

Noy et al. Blood 2017

Toxicity

- Fatigue (44%)
- Diarrhea (43%)
- Anemia (35%)
- Nausea and thrombocytopenia (25%)
- Grade ≥3 AEs occurred in 40 pts (63%)
- AF occurred in 4 pts (6%; all grade 1/2)
- Any-grade bleeding events occurred in 57% of pts, with 1 grade 3 event of hematemesis and 1 grade 5 cerebral hemorrhage

Noy et al. Blood 2017

MALIBU study: Ibrutinib + R as 1st-line tp in MZL

MALT-MZL 120 pts

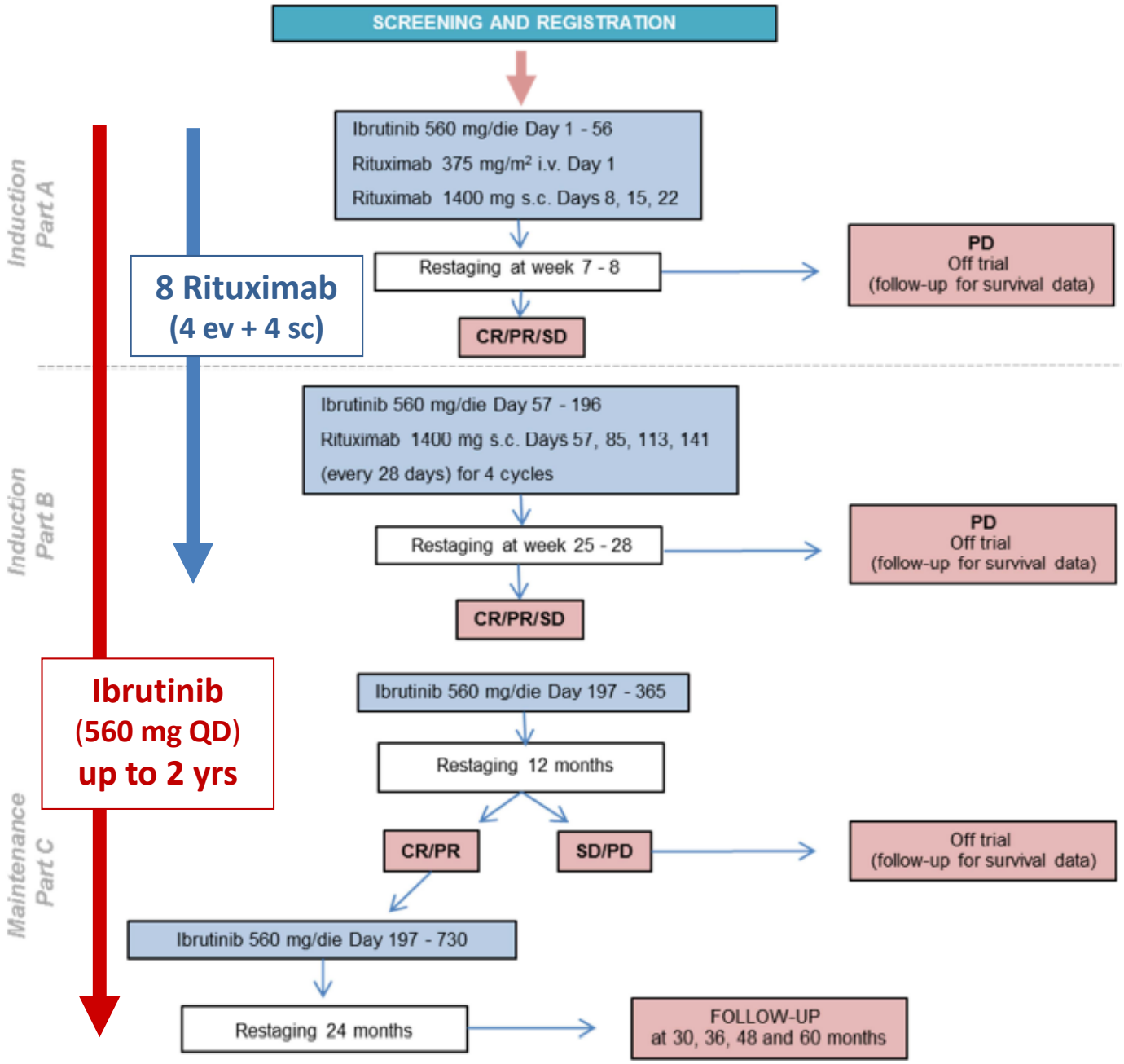
- MALT-IPI≥1
- need of therapy
- not eligible for local tp
- de novo or relapsed after local tp or antibiotics

NMZL 15 pts

SMZL 15 pts

Primary endpoints

- CR 12 months
- PFS 5 years



Lenalidomide

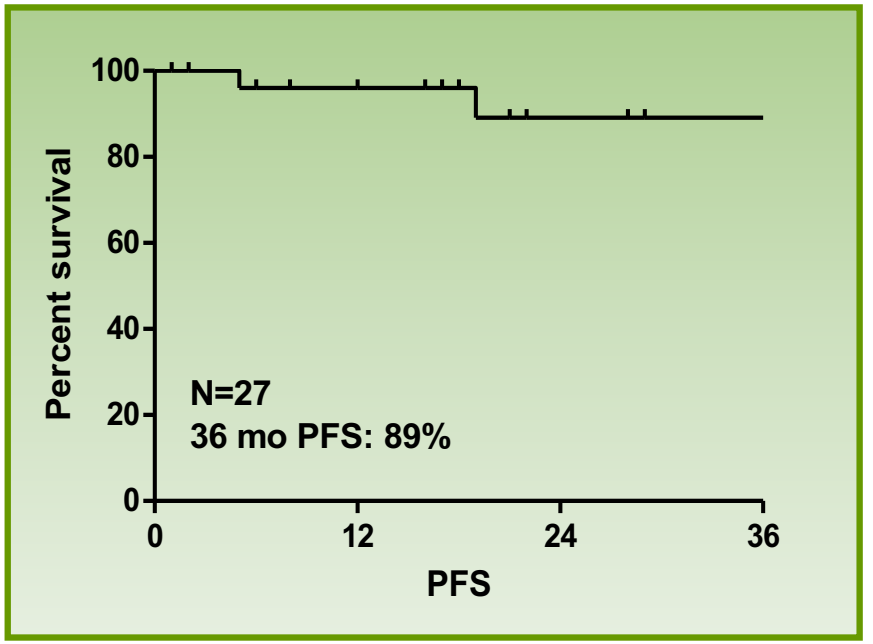
Lenalidomide + Rituximab as Initial Therapy in Indolent NHL (R^2)

- **Treatment**
  - **Lenalidomide** 20 mg/day on days 1-21
  - **Rituximab** 375 mg/m^2 on Day 1 of each 28-day cycle for 6 cycles; up to 12 cycles if clinical benefit observed
  - Restaging at 4, 6, 9, 12 mos
- **Primary endpoint: ORR**
- **Secondary endpoints**
  - Rates of PR and CR, PFS, OS, safety, tolerability in previously untreated patients, effect on tumor and immune microenvironment

Fowler et al ASH 2012

R-Lenalidomide in MZL: Response Rates and PFS

n (%)	SLL (N=30)	MZL (N=27)*	FL (N=46)*
ORR	24 (80)	**24(89)**	45(98)
CR/Cru	8(27)	**18(67)**	40(87)
PR	16(53)	**6(22)**	5(11)
SD	4(13)	**3(11)**	1(2)
PD	2(7)	**0**	0



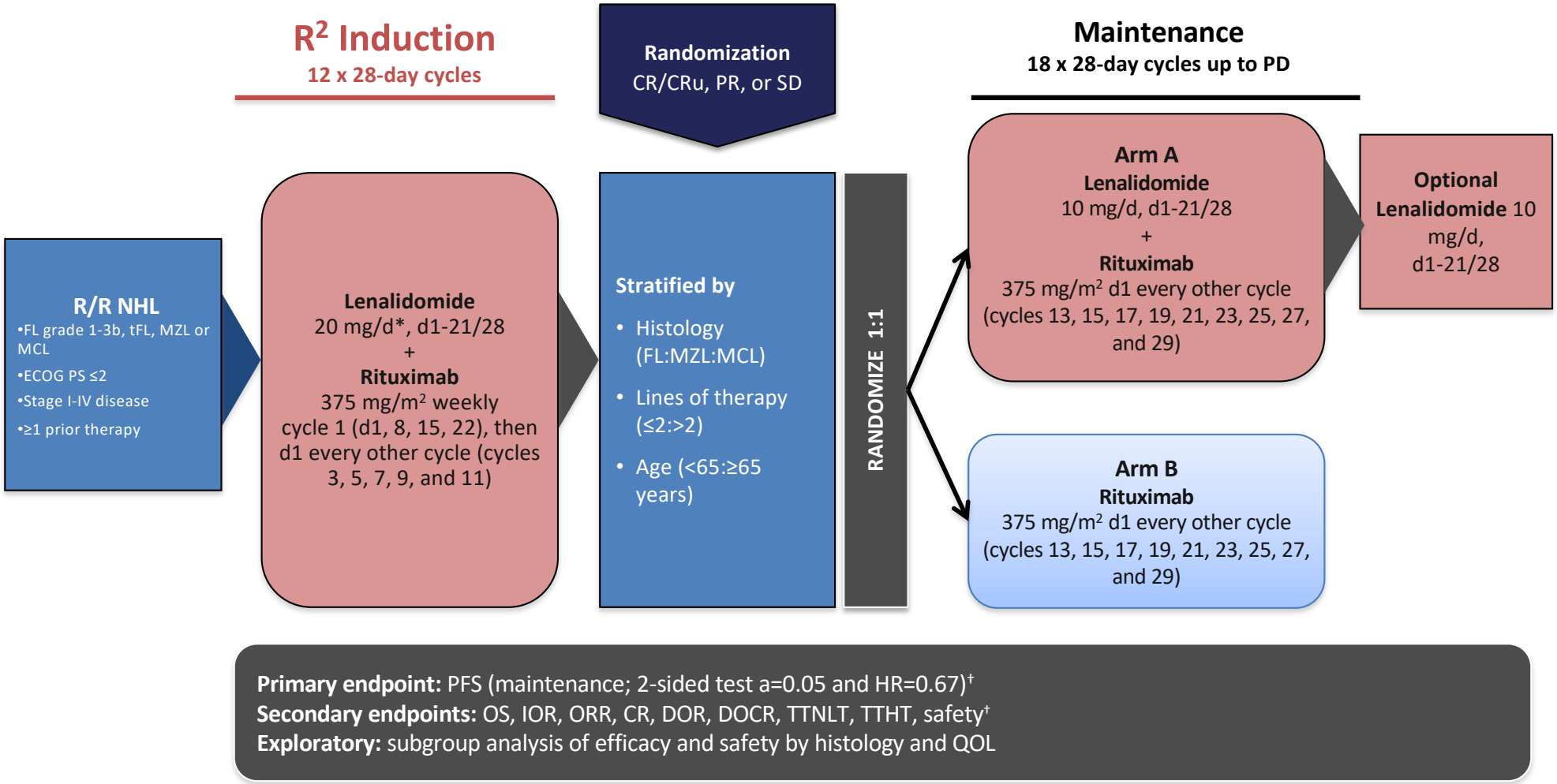
*7 pts not evaluable for response:

- 5 due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

MZL – Nodal and Extranodal

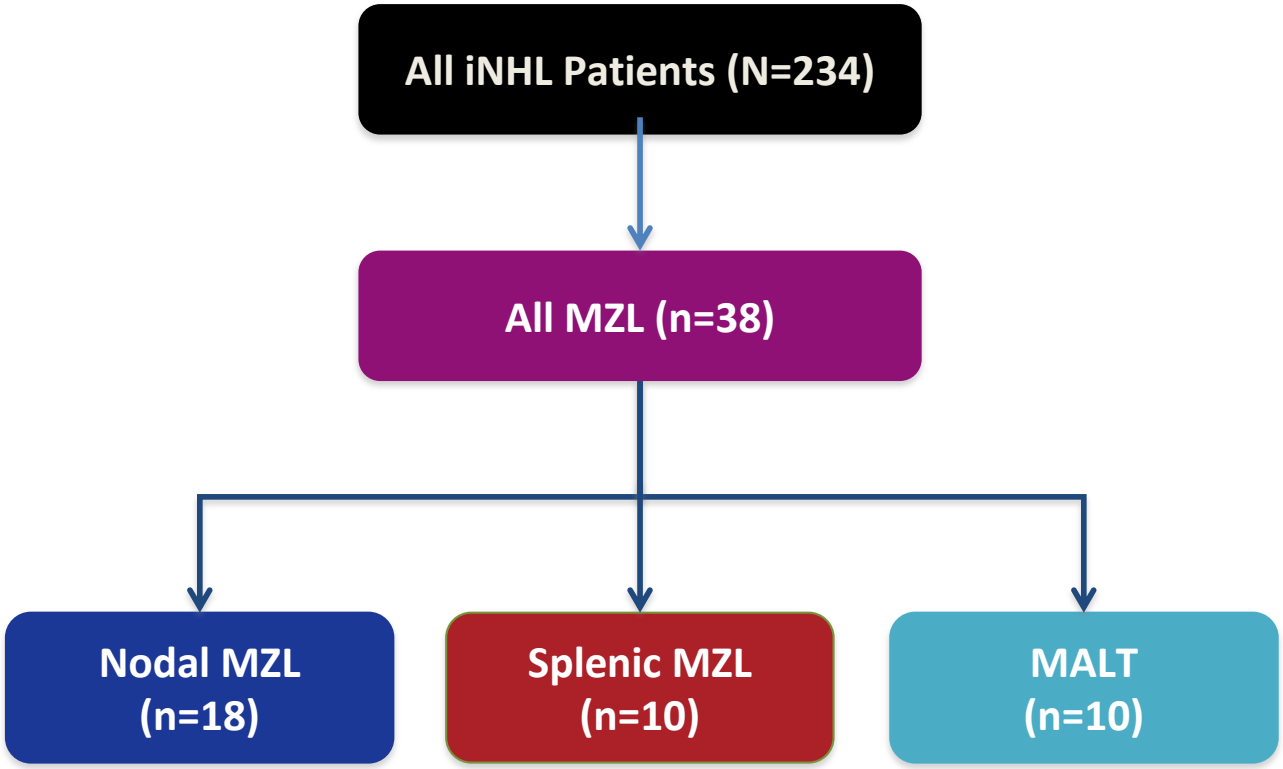
Fowler et al Lancet Oncology 2014

Phase III randomized, open-label, multicenter study of R^2 induction therapy followed by R^2 maintenance vs. rituximab (R) maintenance in patients with R/R NHL, including MZL - NHL-008 study (MAGNIFY)



Coleman et al ICML 2017

MAGNIFY: MZL Patients



- As of January 9, 2017, 234 patients with indolent NHL were enrolled and received treatment, including 38 (16%) patients with MZL

Baseline Characteristics and Prior Treatment

Characteristic, n (%)		All MZL (n=38)
Median age, years (range)		66 (58-72)
Age ≥65 years		20 (53)
Male		23 (61)
ECOG PS*	0	17 (48)
	1	21 (52)
Disease stage*	I	1 (3)
	II	4 (11)
	III	7 (18)
	IV	26 (68)
Positive bone marrow involvement		21 (55)

Characteristic, n (%)	All MZL (n=38)
Median number of prior systemic anti-cancer therapies	1 (1-5)
Number of prior systemic anti-cancer therapies	
1	22 (58)
2	7 (18)
3	5 (13)
≥4	4 (11)
Prior rituximab-containing therapy	38 (100)
Rituximab-refractory	13 (34)
Most common prior treatment regimens	
Rituximab	19 (50)
BR	10 (26)
R-CHOP-like	7 (18)

- 34% were refractory to rituximab (defined as SD/PD to or PR/CR lasting fewer than 6 months following the last rituximab dose)

MAGNIFY: Best Response During R^2 treatment (32 pts)

	Nodal MZL (n=14)	Splenic MZL (n=8)	MALT (n=10)	Evaluable MZL (n=32)
Best Response, n (%)				
ORR (CR+CRu+PR)	8 (57)	5 (63)	8 (80)	21 (66)
[95% CI]*	[29%-82%]	[25%-92%]	[44%-98%]	[47%-81%]
CR/CRu	8 (57)	2 (25)	4 (40)	14 (44)
PR	0	3 (38)	4 (40)	7 (22)
SD	5 (36)	3 (38)	1 (10)	9 (28)
PD†	1 (7)	0	1 (10)	2 (6)
Median treatment duration, mo (range)	8.3 (1.3-20.4)	9.7 (0.2-25.8)	11.8 (3.5-25.8)	9.4 (0.2-25.8)
Median TTR, mo (range)	2.9 (2-11)	2.7 (2-11)	3.4 (3-11)	3.1 (2-11)

Median follow-up of 13.8 mo

Median treatment duration was 9.4 mo and median TTR was 3.1 mo

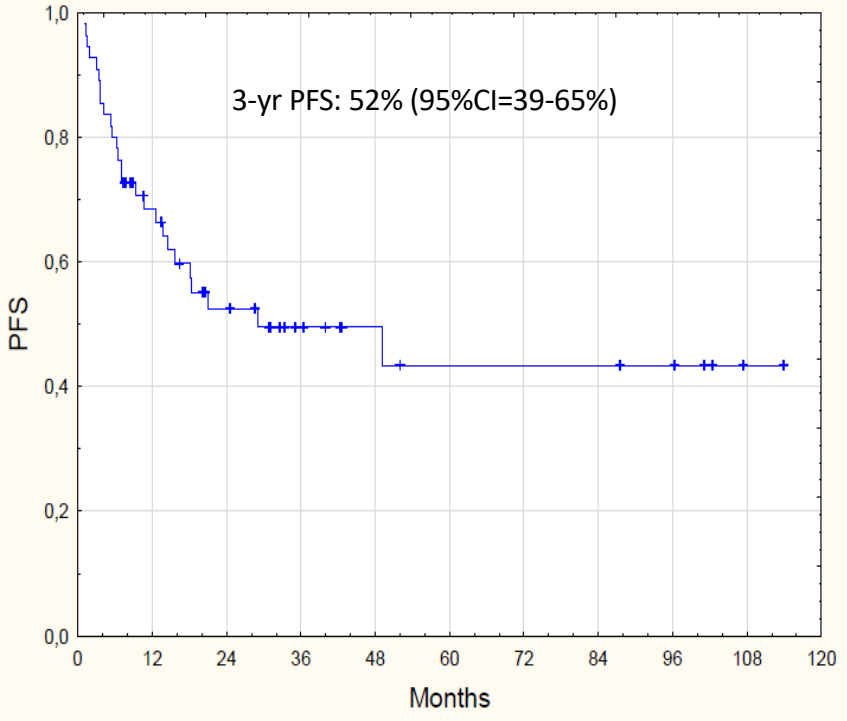
Median DOR has not been reached for any subgroup

Efficacy

Median f-up: 33 mo

29 (53%) pts remain progression-free

No cases of high-grade transformation.



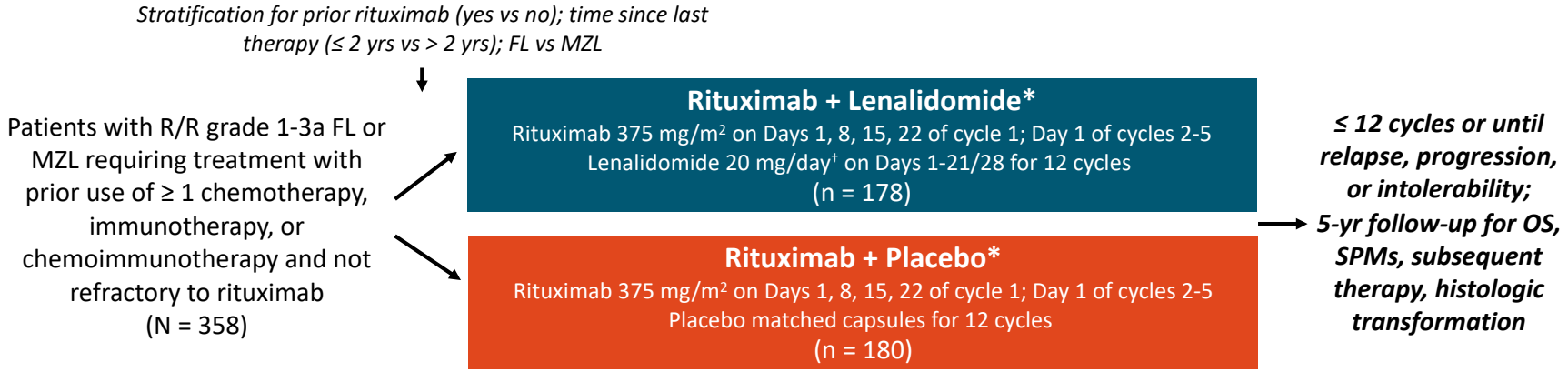
52 pts are alive ; no pt died of lymphoma

3-year OS of 96% (95%CI=91-100%).

Deaths: HCV-related cirrhosis, stroke, NSCLC.

Rituximab + Lenalidomide vs Rituximab + Placebo for R/R Indolent NHL (AUGMENT)

- Multicenter, double-blind, placebo-controlled, randomized phase III trial

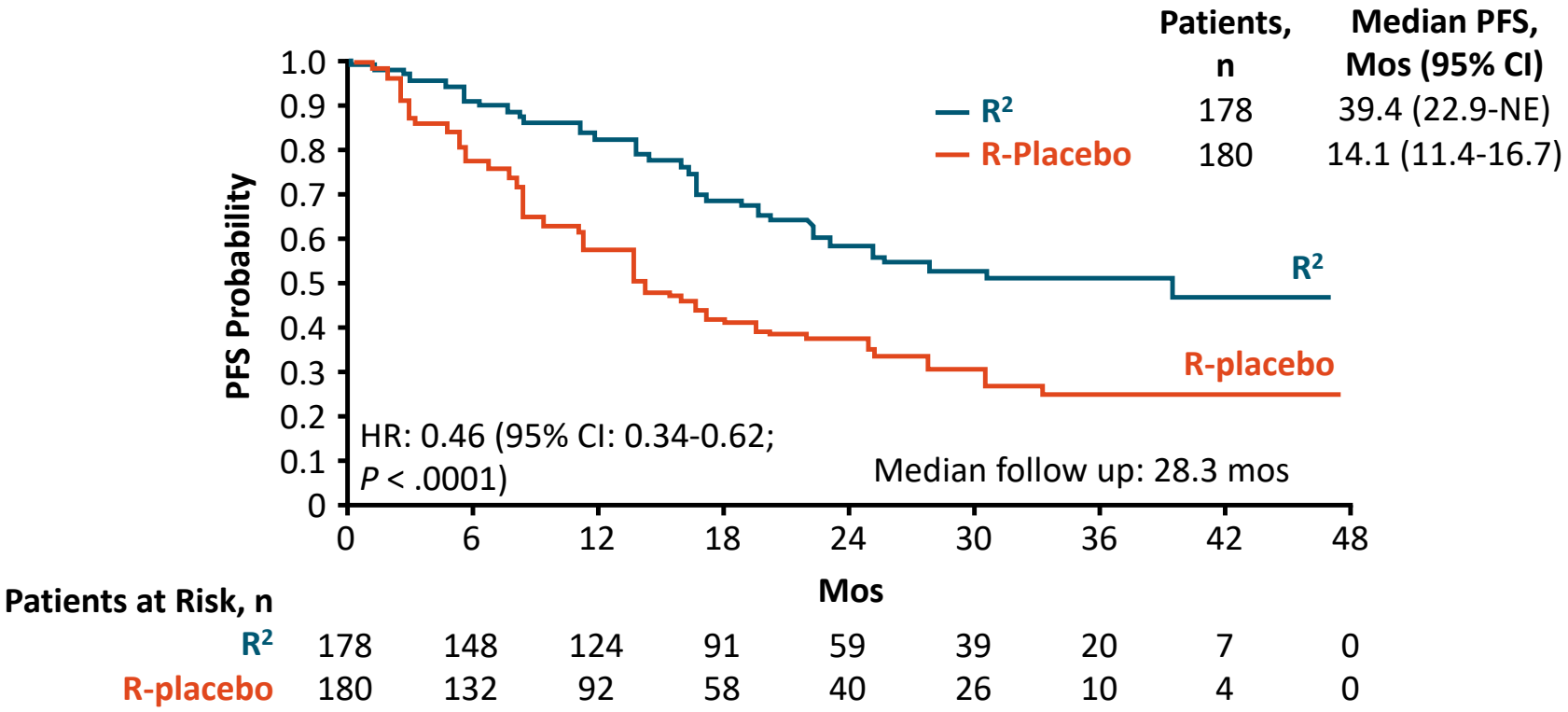


*Anticoagulation or antiplatelet therapy recommended for patients at risk. Growth factor use in line with ASCO/ESMO guideline permitted. †10 mg if CrCl is 30-59 mL/min.

- Primary endpoint: IRC-assessed PFS in ITT population
- Secondary endpoints: ORR, OS, histologic transformation, safety

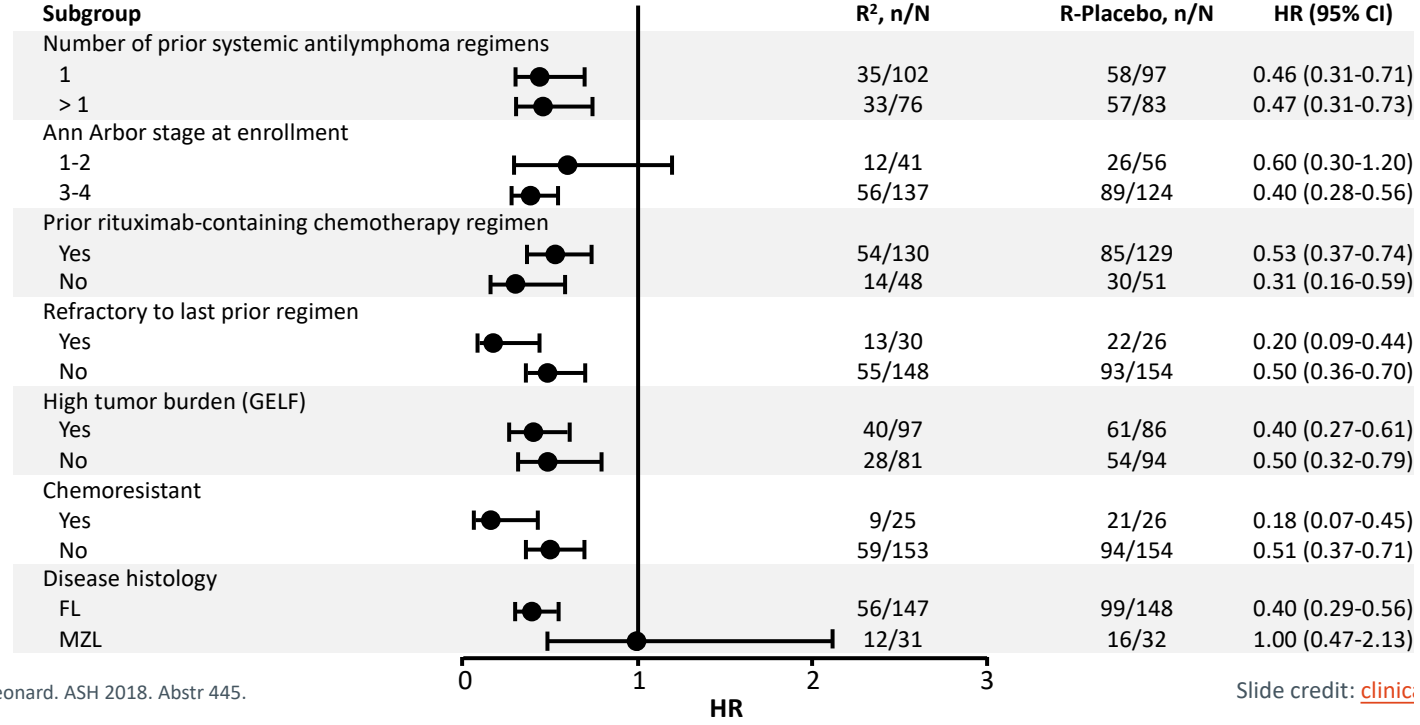
Leonard et al ASH 2018

AUGMENT: IRC-Assessed PFS in ITT Population (Primary Endpoint)



- Comparable results obtained by investigator assessment (HR: 0.51; *P* < .0001)

AUGMENT: IRC-Assessed PFS by Subgroup (ITT)



Leonard. ASH 2018. Abstr 445.

Slide credit: clinic

- Median IRC-assessed PFS (ITT): 39.4 vs 14.1 mo ($P < .0001$)
- PFS benefit observed across subgroups, except for MZL
- ORR median DoR improved with R^2
- OS improved with R^2 in FL

Hepatis C virus

Splenic and Nodal Marginal Zone Lymphomas Are Indolent Disorders at High Hepatitis C Virus Seroprevalence with Distinct Presenting Features but Similar Morphologic and Phenotypic Profiles

Arcaini et al Cancer 2004

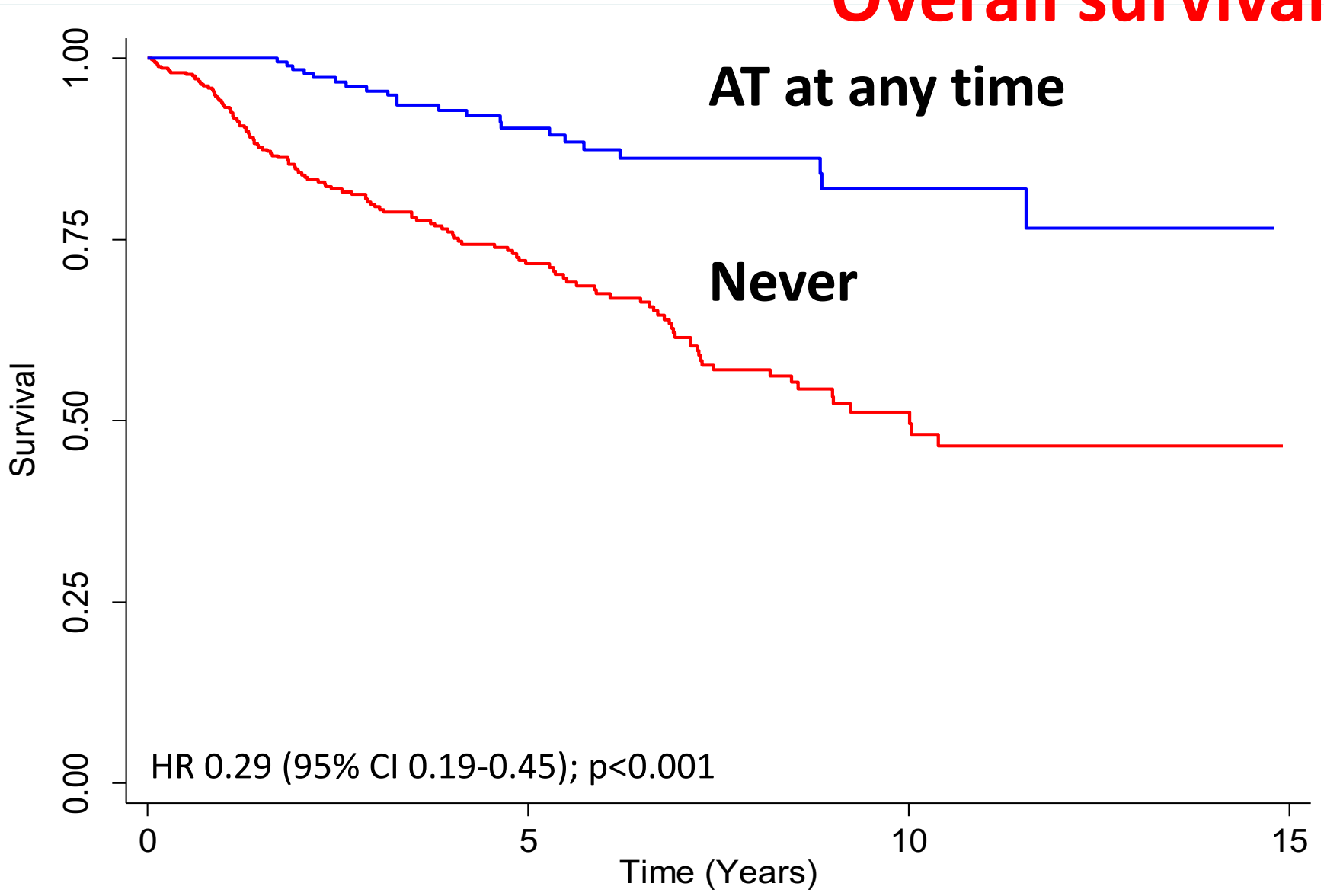
Brief report

Splenic lymphoma with villous lymphocytes, associated with type II cryoglobulinemia and HCV infection: a new entity?

Saadoun et al Blood 2004

Arcaini et al Ann Oncol 2014

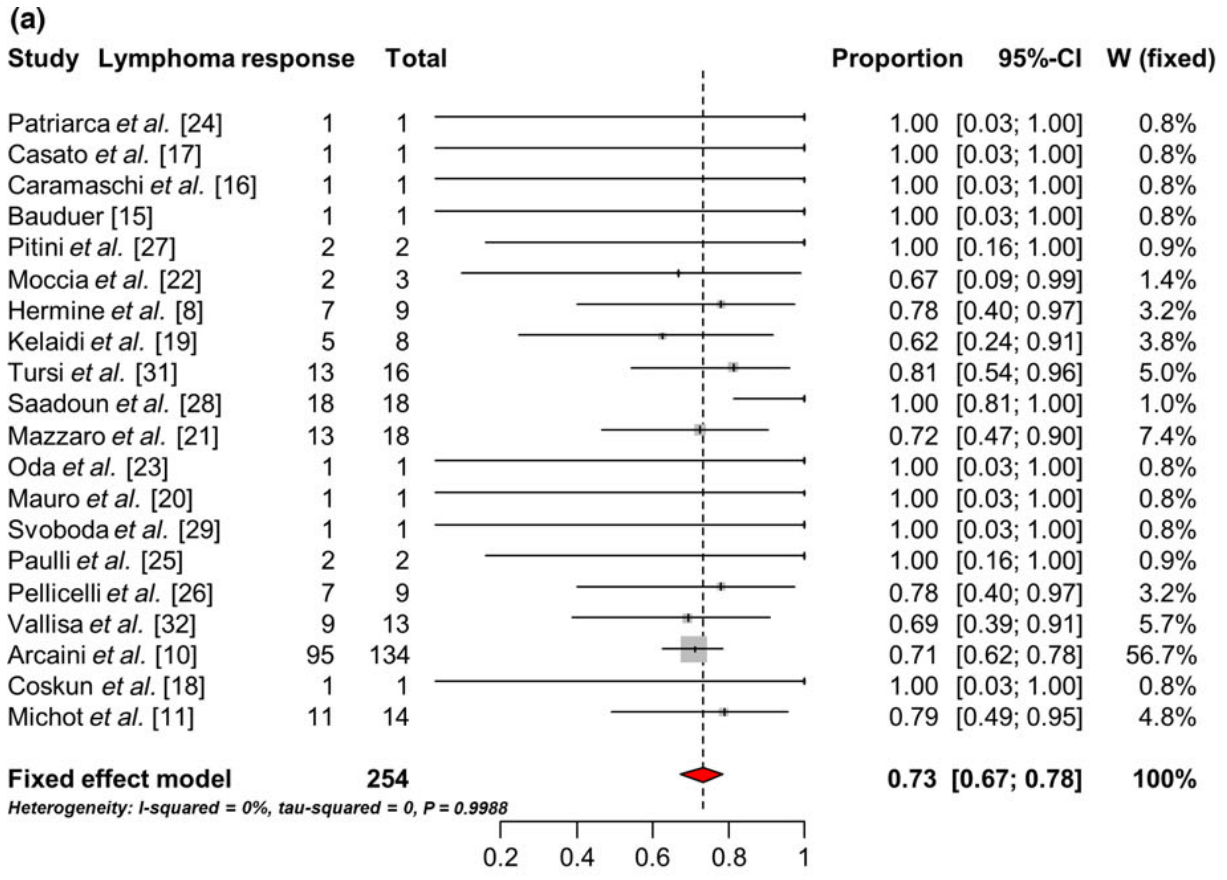
Overall survival

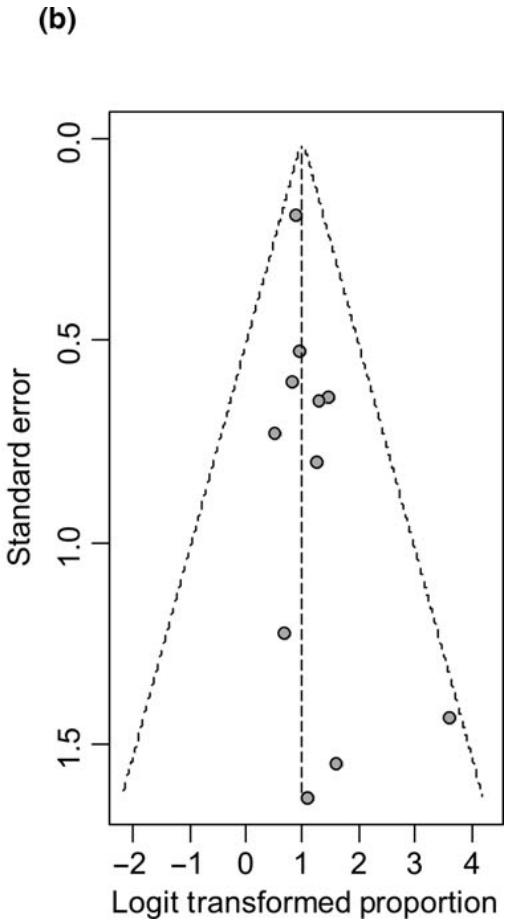


N at risk

AT	222	102	33	7
never	465	154	34	10

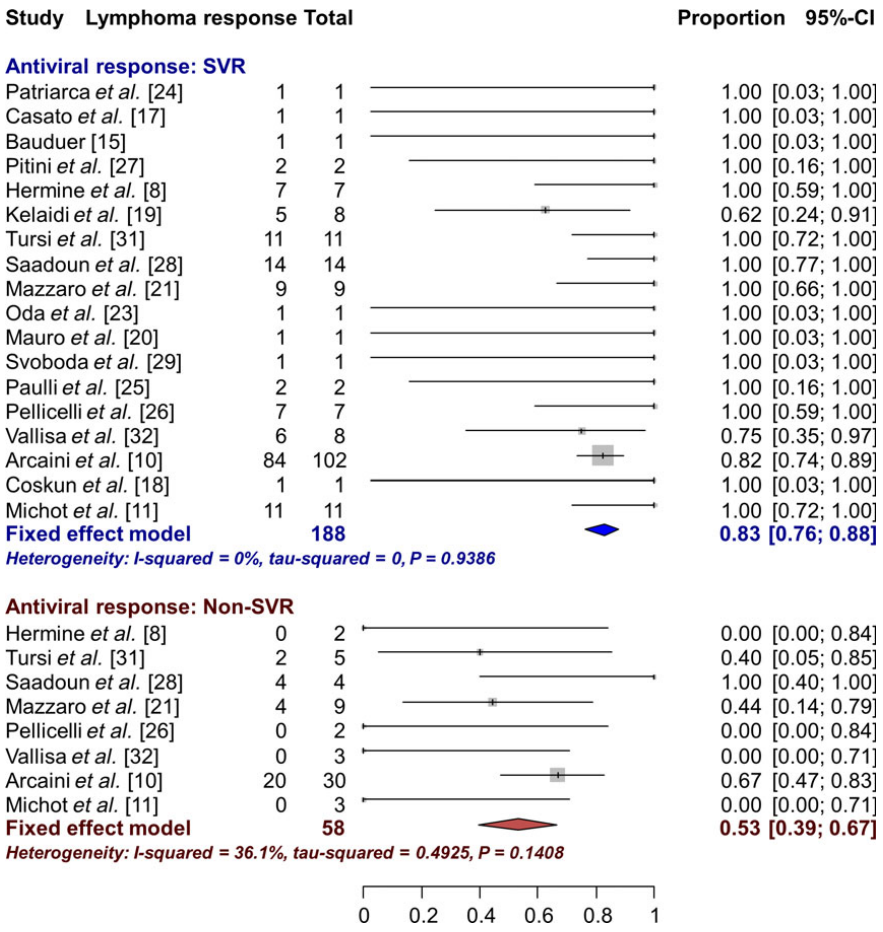
Lymphoma response





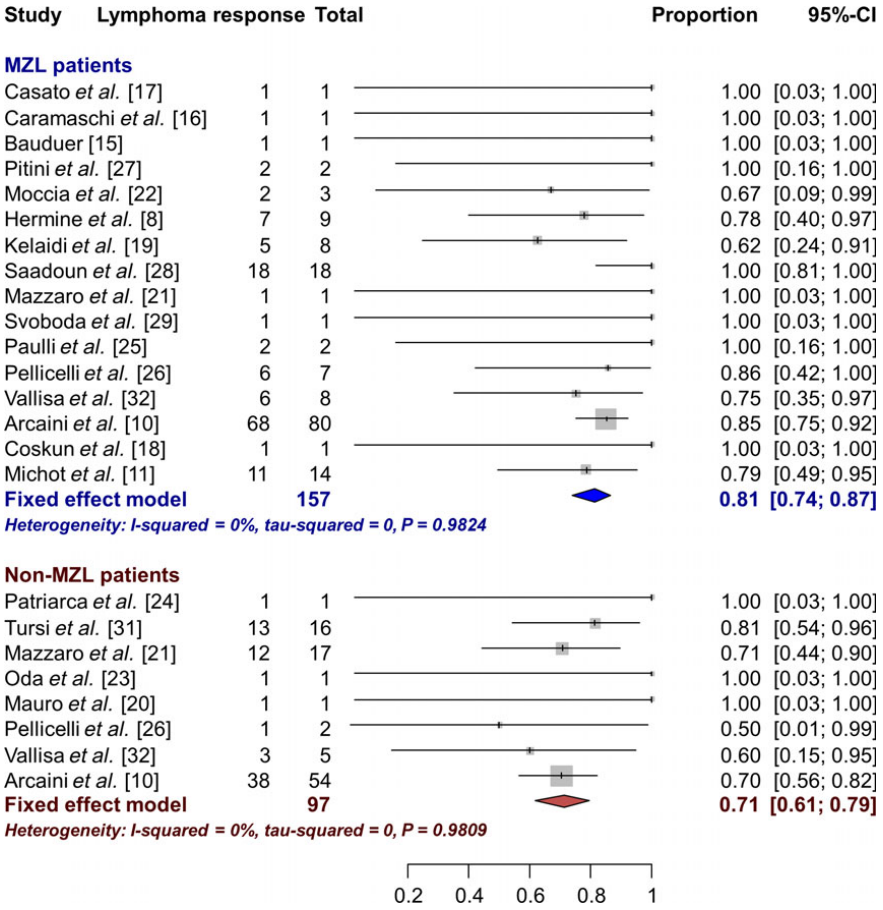
ORR 73%

SVR and histotype



83 % vs 53%

157 MZL



81 % vs 71%

Antiviral therapy and risk of lymphoma

- 501 HCV+ pts never treated
- 2,708 HCV+ pts treated with IFN
- Cumulative rates at 5, 10 and 15 yrs:
- **Non-IFN group**: 0.6%, 2.3% and 2.6%
- **IFN-group with SVR**: 0%, 0% and 0%
- **IFN-group with persistent infection**: 0.4%,1.5% and 2.6%

Kawamura et al AJM 2007

Regular Article

blood

LYMPHOID NEOPLASIA

Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection

Luca Arcaini,[1,2,*] Caroline Besson,[3,*] Marco Frigeni,[1] Hélène Fontaine,[4] Maria Goldaniga,[5] Milvia Casato,[6] Marcella Visentini,[6] Harrys A. Torres,[7] Veronique Loustaud-Ratti,[8] Jan Peveling-Oberhag,[9] Paolo Fabris,[10] Roberto Rossotti,[11] Francesco Zaja,[12] Luigi Rigacci,[13] Sara Rattotti,[2] Raffaele Bruno,[14,15] Michele Merli,[16] Céline Dorival,[17] Laurent Alric,[18] Arnaud Jaccard,[8] Stanislas Pol,[4] Fabrice Carrat,[17,19] Virginia Valeria Ferretti,[1] Carlo Visco,[20,†] and Olivier Hermine[21,22,†]

	CR, n	PR, n	SD, n
All (N = 46)	12	19	11
MZLs (n = 37)	11	16	6
Splenic (n = 17)	4	7	5
Nodal (n = 1)	1	0	0
Extranodal (n = 15)	5	7	0
Leukemic (n = 4)	1	2	1
Follicular lymphoma (n = 2)	0	2	0
Lymphoplasmacytic lymphoma (n = 2)	0	1	1
Low-grade B-NHL NOS (n = 1)	1	0	0
CLL/SLL (n = 4)	0	0	4

ORR 67%: 26 % CR, 41% PR - ORR in MZL 73%; no response in CLL

100 pts treated with DAAs

	CR (n)	PR (n)	SD (n)	PD (n)
All (n=100)	23	43	26	8
Marginal zone lymphomas (n=71)	21	31	13	6
Splenic (n=35)	7	20	6	2
Nodal (n=3)	2	0	1	0
Extranodal (n=25)	9	8	4	4
Leukemic (n=8)	3	3	2	0
Follicular lymphoma (n=6)	0	4	1	1
Lymphoplasmacytic lymphoma (n=7)	0	5	1	1
Low-grade B-cell NHL NOS (n=6)	2	3	1	0
CLL/SLL (n=10)	0	0	10	0

Frigeni et al Leukemia 2019

IFN vs DAAs

	DAA (n=66)	IFN (n=100)	*P*
Sex – n (%) Male Female	 29 (44) 37 (56)	 41 (41) 59 (59)	0.642
Age (years), median (range)	61 (40-83)	62 (24-77)	0.170
Age < 60 / ≥ 60 – yr (%)	31 (47) / 35 (53)	41 (41) / 59 (59)	0.523
Diagnosis – n (%) MZL Non MZL	 53 (80) 13 (20)	 60 (60) 40 (40)	0.007
Stage – n (%) Limited (I-II) Advanced (III-IV)	 7 (11) 59 (89)	 10 (10) 90 (90)	>0.900
Nodal involvement – n (%)	36 (55)	55 (55)	>0.900
Extranodal involvement* – n (%)	27 (41)	38 (38)	0.747
N° of involved extrnodal sites, n (%) 1 ≥2	 21 (78) 6 (22)	 33 (87) 5 (13)	0.504
ECOG performance status ≥ 1 – n (%)	22 (34)	24 (24)	0.214
Hemoglobin <12 g/dl – n (%)	21/65 (32)	31/96 (32)	>0.900
Platelets <100 x 10^9/L – n (%)	8/65 (12)	14/96 (15)	0.816
LDH > UNL – n (%)	10/58 (17)	17/96 (18)	>0.900
β_2-microglobulin > UNL – n (%)	30/42 (71)	31/59 (52)	0.066
Serum monoclonal component – n (%)	23 (35)	35 (35)	>0.900
Cryoglobulin – n (%)	27 (41)	34 (34)	0.412
Albumin less than 3.5 g/dl – n (%)	6/58 (10)	10/90 (11)	>0.900
HCV genotype – n (%) 1 2 3-4	 38/65 (59) 19/65 (29) 8/65 (12)	 37 (39) 52 (55) 6 (6)	0.005

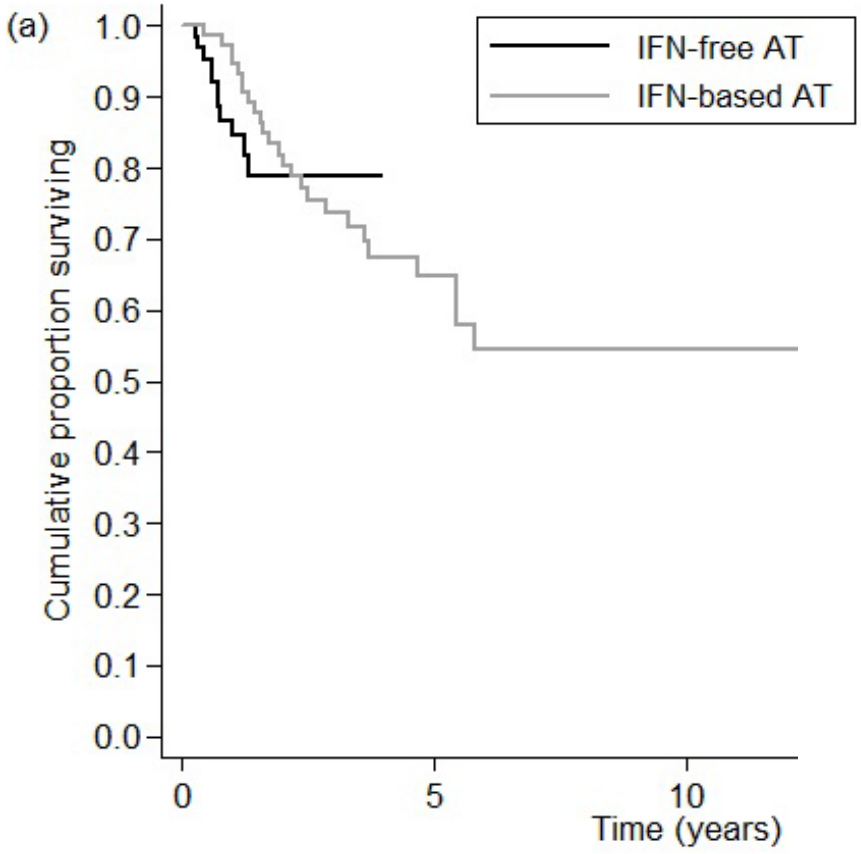
Frigeni et al Leukemia 2019

IFN vs DAAs

- Duration of therapy longer with IFN (median 28 w vs 12, p<0.001)
- SVR rate higher among pts treated with DAAs (98% vs 81%, p<0.001).
- In the IFN group, six pts discontinued treatment due to toxicity vs 0 with DAA
- ORR was similar in the two groups
- 18 the pts treated with IFN obtained a higher rate of CR than pts treated with DAAs (48% vs 19 21%, p=0.001)

Frigeni et al Leukemia 2019

IFN vs DAAs



3-year PFS : 79% (64% – 88%) DAAs
74% (61% – 83%) IFN
p=0.45

3-year OS: 97% (82% – 100%) DAAs
96% (87% – 99%) IFN
p=0.94

Frigeni et al Leukemia 2019

Guidelines

ESMO Consensus guidelines marginal zone lymphoma

Dreyling et al, Ann Onc 2013

1.11 *Consensus statement*

In patients with NMZL or SMZL and concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral treatment with pegylated interferon and ribavirin should be considered as first treatment

NCCN National Comprehensive Cancer Network® **2018**

"the panel recommends initial antiviral therapy in asymptomatic patients with low-grade HCV-positive indolent B-cell NHL"

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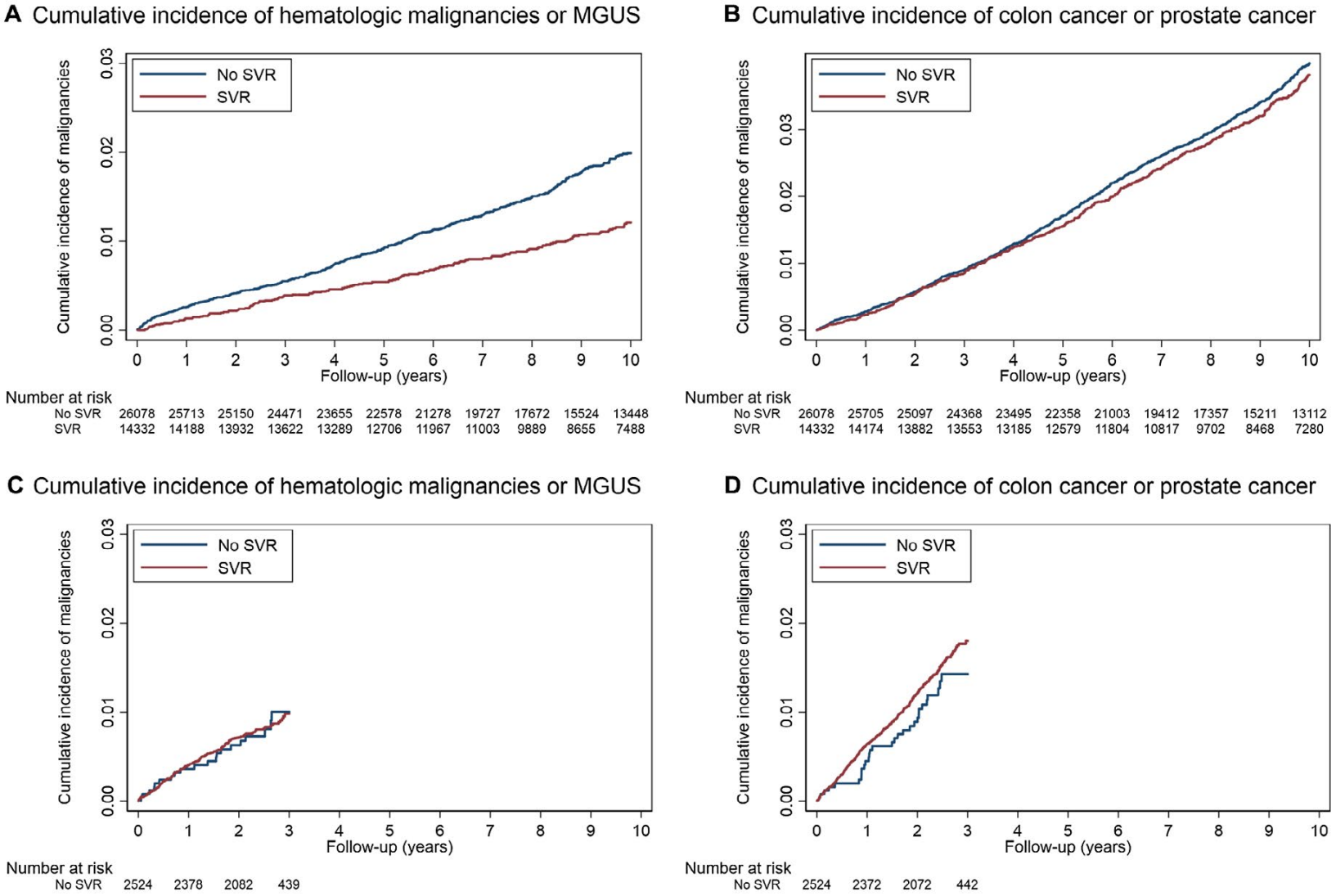
Review

International therapeutic guidelines for patients with HCV-related extrahepatic disorders. A multidisciplinary expert statement☆

Anna Linda Zignego [a,*], Manuel Ramos-Casals [b], Clodoveo Ferri [c], David Saadoun [n,o,p,q], Luca Arcaini [d], Dario Roccatello [e,f], Alessandro Antonelli [g], Anne Claire Desbois [n,o,p,q], Cloe Comarmond [n,o,p,q], Laura Gragnani [a], Milvia Casato [h], Peter Lamprecht [i], Alessandra Mangia [j], Athanasios G Tzioufas [k], Zobair M Younossi [l,m], Patrice Cacoub [n,o,p,q], on behalf of the ISG-EHCV:

SRV and hematological maligancies



Ioannou et al Hepatol Comm 2019

A multicenter study to evaluate the anti-viral activity of an interferon-free treatment with ledipasvir/sofosbuvir (G1 and G4) and sofosbuvir/velpatasvir (G2 and G3) for patients with hepatitis C virus-associated indolent B-cell lymphomas

ID Study: FIL_BArT (B-cell lymphoma **A**ntivi**r**al **T**reatment**)**

EudraCT number: 2015-004830-81

STUDY COORDINATOR

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