Linfomi della zona marginale
Novita' in tema di terapia

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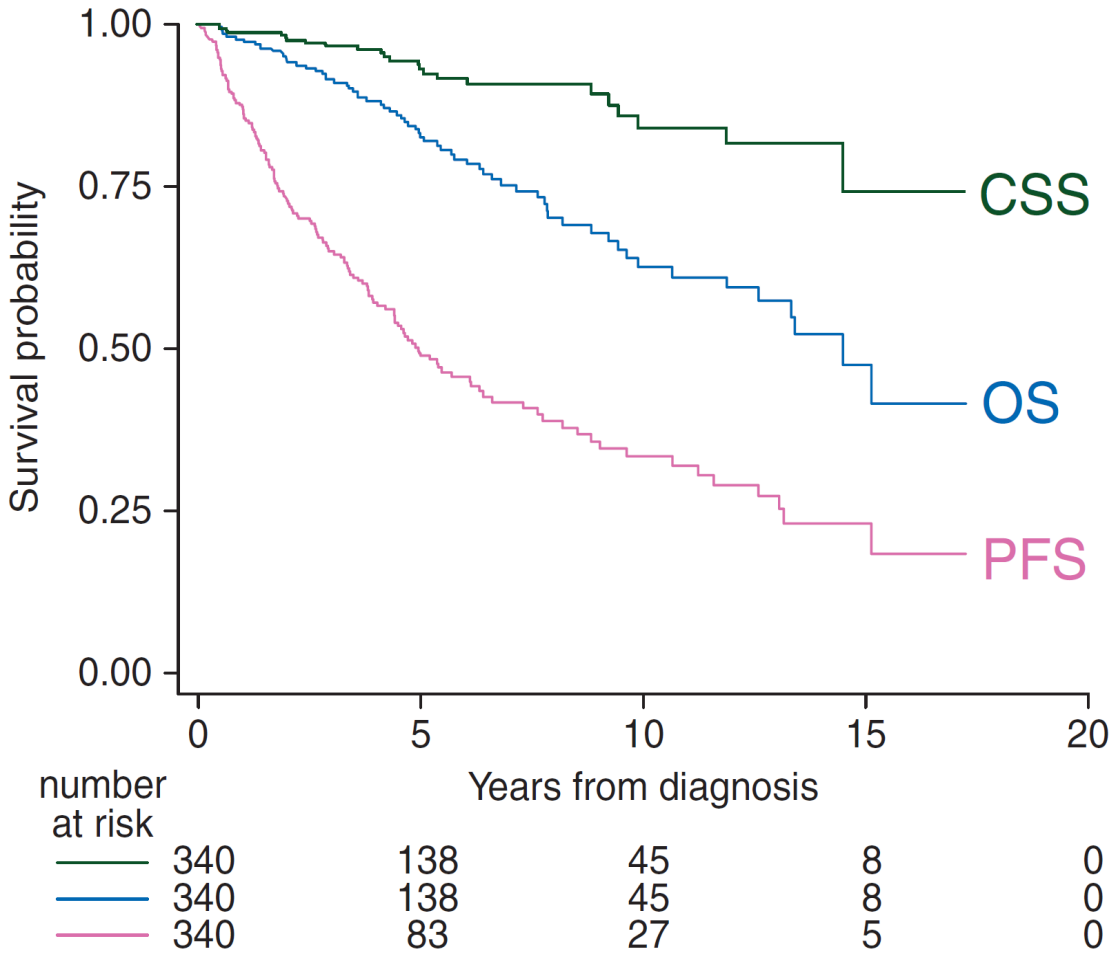
Marginal Zone B-Cell Lymphomas

NOT THE SAME	% of all lymphomas in SEER registries
▪ Splenic MZL	0.7%
▪ Nodal MZL	2.4%
▪ Extranodal MZL of Mucosa-Associated Lymphoid-Tissue (MALT Lymphoma)	5%

Olszewski AJ and Castillo JJ. *Cancer* 2013

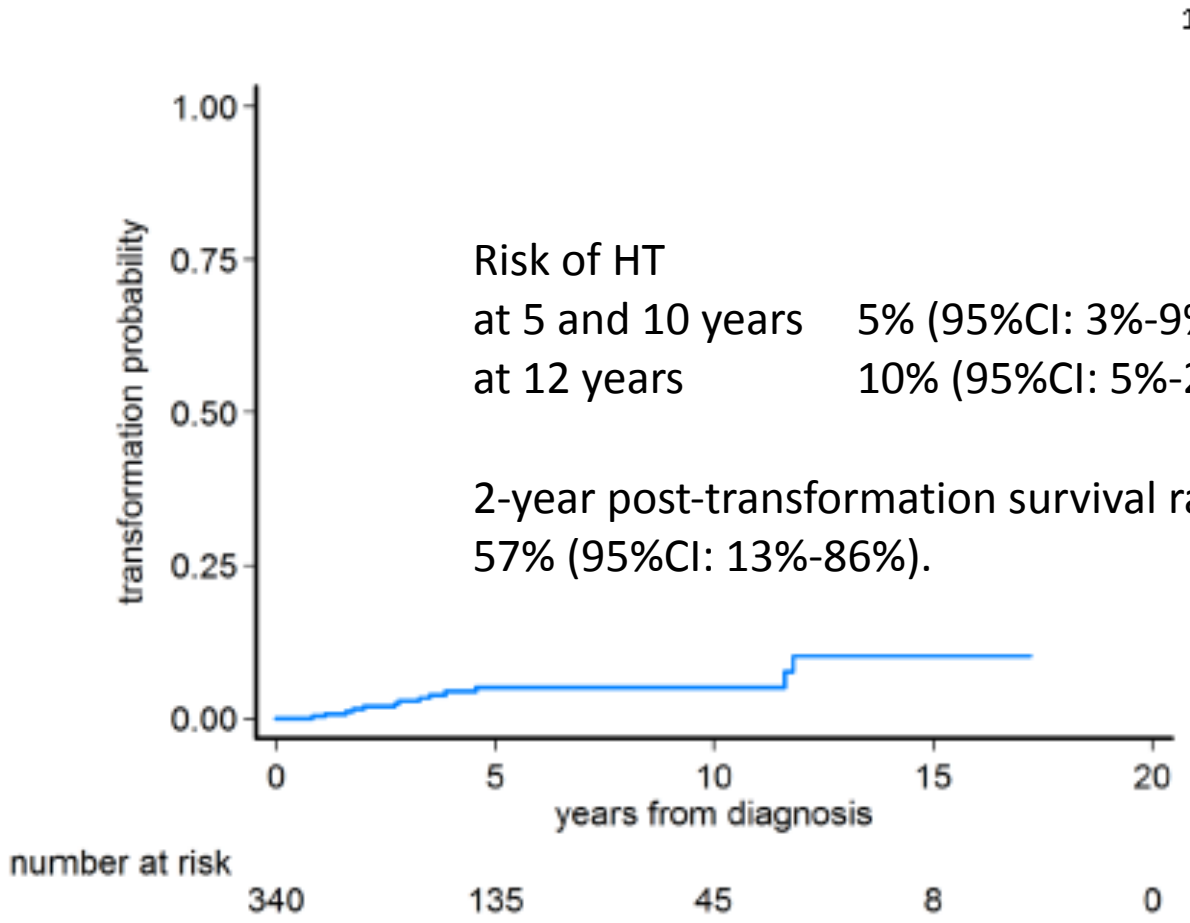
MZL outcome



MALT lymphoma, 157
Splenic MZL, 85
Nodal MZLs, 37
CBL-MZL, 61

A. Conconi et al. *Annals of Oncology* 26: 2329–2335, 2015

MZL transformation



Risk of HT

at 5 and 10 years	5% (95%CI: 3%-9%)
at 12 years	10% (95%CI: 5%-20%)

2-year post-transformation survival rate:
57% (95%CI: 13%-86%).

MALT lymphoma, 157
Splenic MZL, 85
Nodal MZLs, 37
CBL-MZL, 61

A. Conconi et al. *Annals of Oncology* 26: 2329–2335, 2015

Criteria to start and adapt treatment

- Not precisely defined

EMZL

- Symptomatic

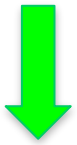
SMZL

- Symptomatic splenomegaly ✓
- Anemia : 10 g/L? 9.5 g/l? ✓
- Thrombocytopenia : 80 x10^9 G/L ✓
- Hyperlymphocytosis
- Immune disorders (AHAI, ITP…) —
- Nodal disease ✓
- Elevated LDH !?
- B symptoms !?

!?

NMZL

The same criteria as FL

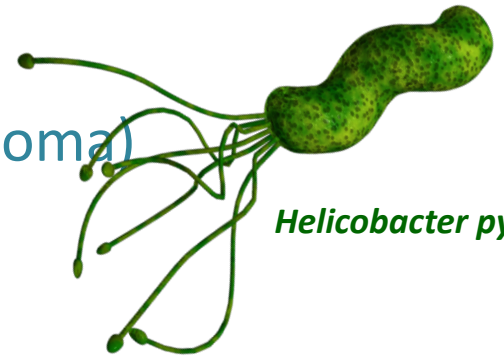


High tumor burden criteria

Evidence of antigen-driven growth of EMZL

- histological features
- somatic hypermutation of immunoglobulin gene (and intraclonal variation)
- association with chronic infectious conditions and auto-immune processes

  → “autoreactive” B cells in many cases
- therapeutic efficacy of antibiotics (75% lasting remissions in gastric lymphoma)

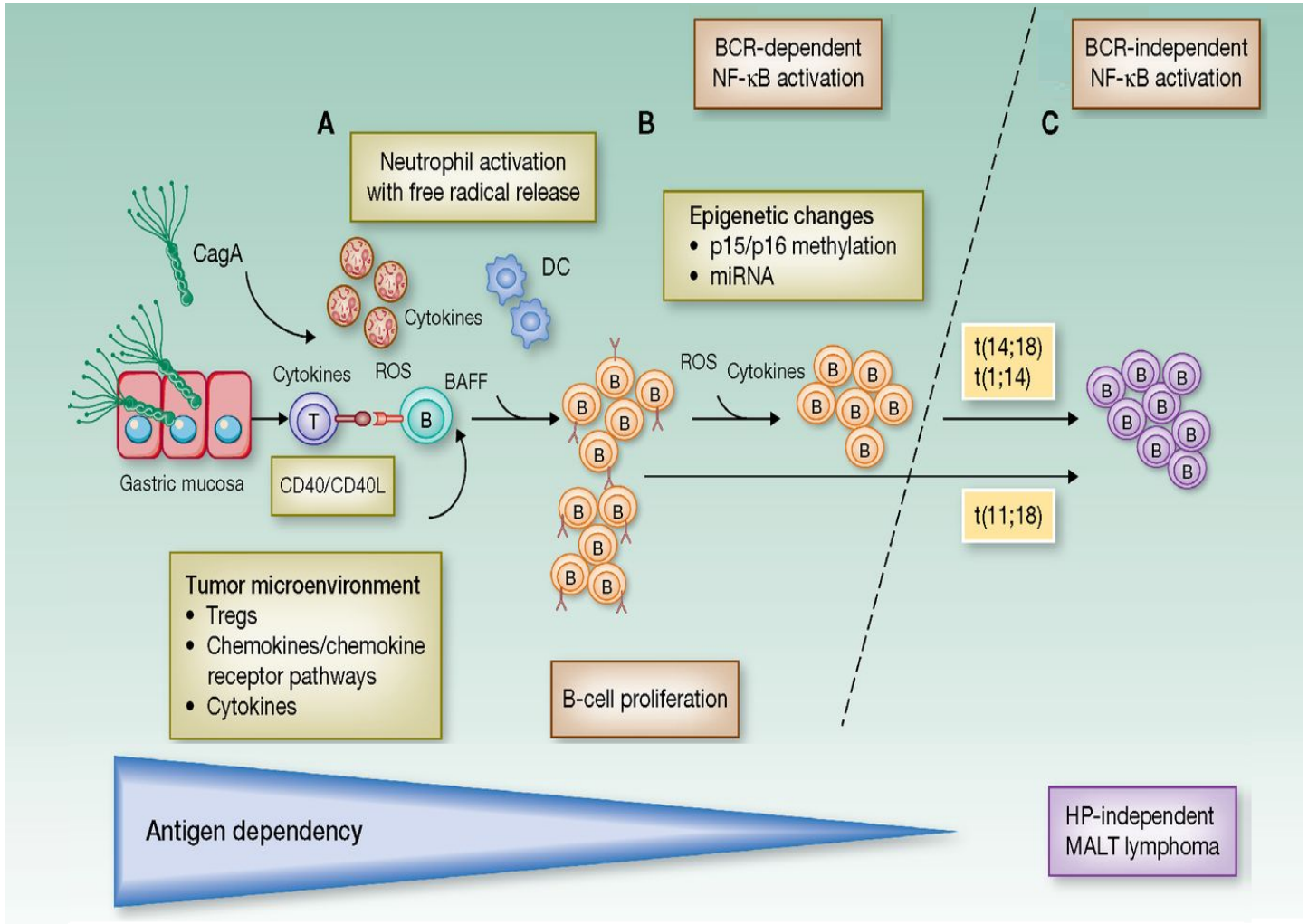


Helicobacter pylori

Zucca E, Bertoni F, Blood 2016; 127:2082

Helicobacter pylori and MALT lymphoma

A model of tumor progression



Zucca E, et al. Clin Cancer Res. 2014; 20:5207

Management of EMZL

1) Helicobacter pylori eradication for gastric EMZL
   - in localized HP+ disease
   - in localized HP- disease
   - in disseminated disease

Management of EMZL

1) Helicobacter pylori eradication for gastric EMZL
   in localized HP+ disease
   in localized HP- disease
   in disseminated disease
2) Role of antibiotics for extragastric EMZL

IELSG39 – BACKGROUND

Bacteria-Eradicating Therapy With Doxycycline in Ocular Adnexal MALT Lymphoma: A Multicenter Prospective Trial

Andrés J. M. Ferreri, Maurilio Ponzoni, Massimo Guidoboni, Antonio Giordano Resti, Letterio S. Politi, Sergio Cortelazzo, Judit Demeter, Francesco Zallio, Angelo Palmas, Giuliana Muti, Giuseppina P. Dognini, Elisa Pasini, Antonia Anna Lettini, Federico Sacchetti, Carlo De Conciliis, Claudio Doglioni, Riccardo Dolcetti

Journal of the National Cancer Institute, Vol. 98, No. 19, October 4, 2006

VOLUME 30 · NUMBER 24 · AUGUST 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Chlamydophila Psittaci Eradication With Doxycycline As First-Line Targeted Therapy for Ocular Adnexae Lymphoma: Final Results of an International Phase II Trial

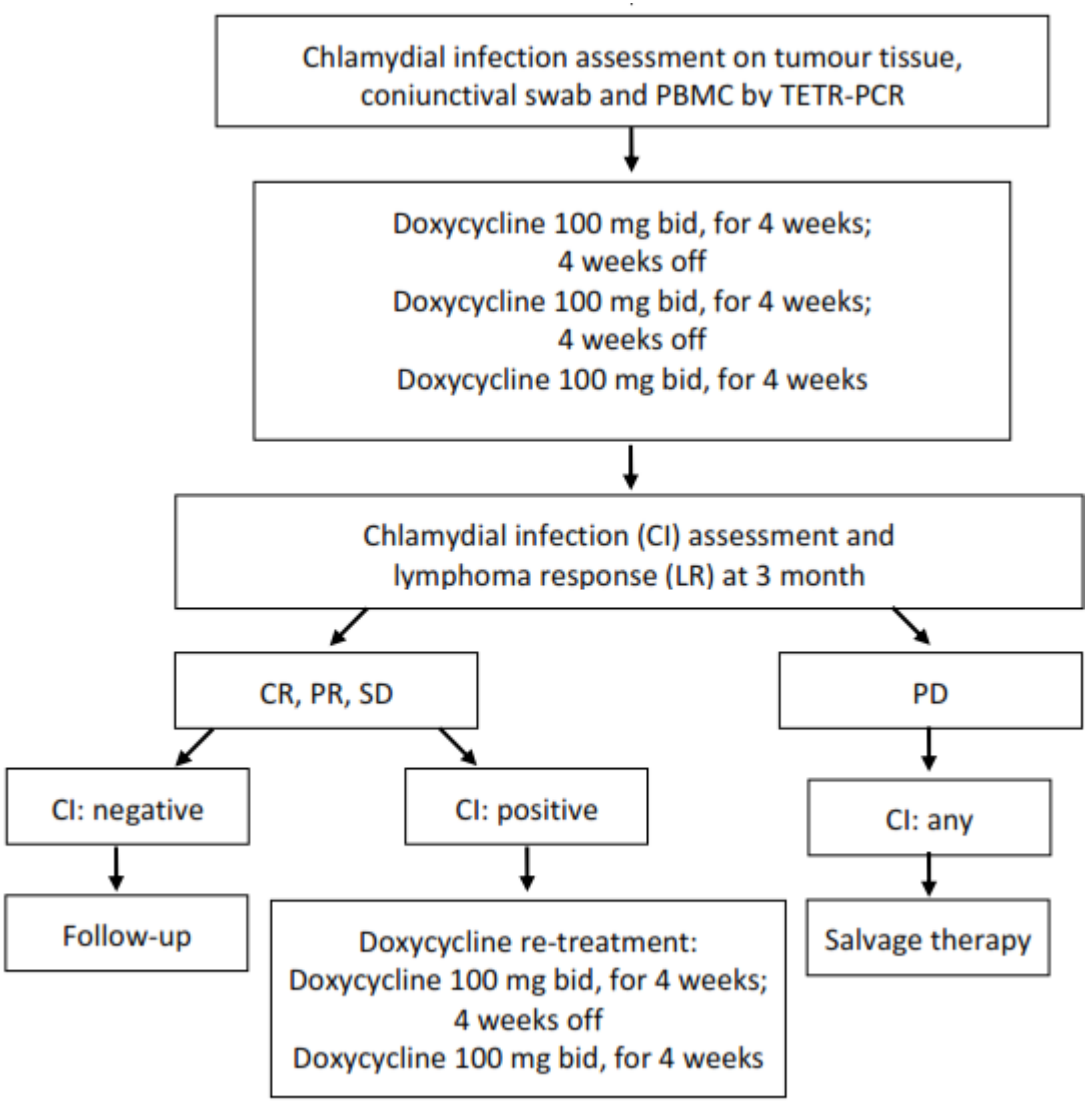
Andrés J.M. Ferreri, Silvia Govi, Elisa Pasini, Silvia Mappa, Francesco Bertoni, Francesco Zaja, Carlos Montalbán, Caterina Stelitano, Maria Elena Cabrera, Antonio Giordano Resti, Letterio Salvatore Politi, Claudio Doglioni, Franco Cavalli, Emanuele Zucca, Maurilio Ponzoni, and Riccardo Dolcetti

IELSG39 trial

multicentre phase 2 trial in patients with newly diagnosed OAMZL aimed to assess:

- the efficacy of upfront *Chlamydophila psittaci*-eradicating therapy with **prolonged administration of doxycycline**
- eradication **monitoring**
- **antibiotic re-treatment** at infection re-occurrence

IELSG39 – TRIAL DESIGN



Management of EMZL

1) Helicobacter pylori eradication for gastric EMZL
   in localized HP+ disease
   in localized HP- disease
   in disseminated disease
2) Role of antibiotics for extragastric EMZL
3) Role of radiotherapy for EMZL
   (optimal RT volume, dose and technique?)

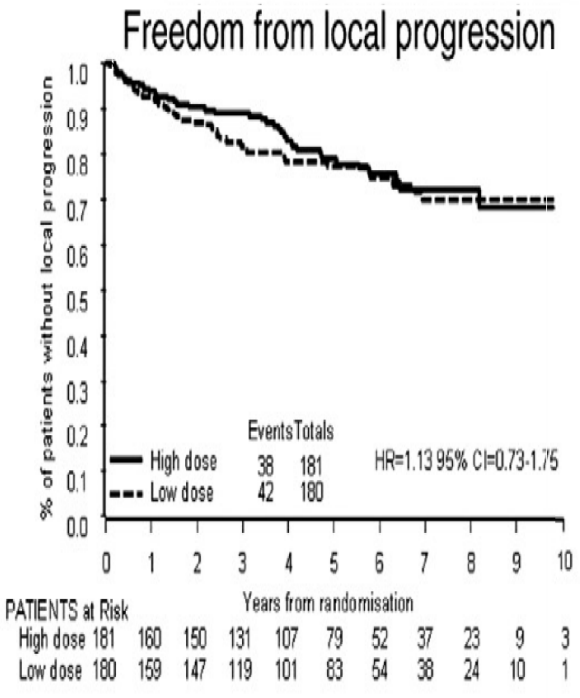
RT is very active in MALT lymphoma

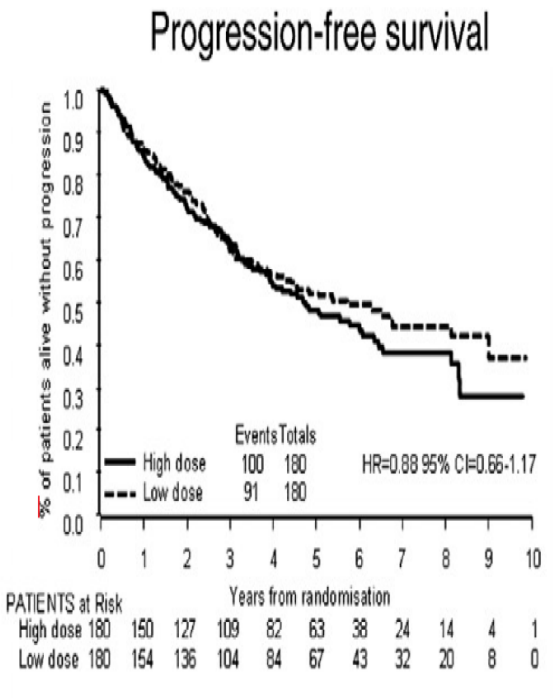
Radiotherapy Results in MALT Lymphoma				
Author	**No. of Patients**	**Site**	**RT dose (Gy)**	**Freedom from Treatment Failure**
Yahalom, 2002	51	Gastric	22.5-43.59	89% at 4 years
Goda, 2010	192	Gastric and non-gastric	17.5-35	95% at 10 years for thyroid 92% for stomach 68% for salivary glands 67% for orbit
Wirth, 2013	102	Gastric	26-46	88% at 10 years
Ohga, 2013	53	Orbit	24-30	91% at 5 years
Kim, 2013	64	Gastric	30-44	89% at 5 years
Nam, 2014	48	Gastric	30-45	84% at 5 years
Harada, 2014	86	Orbit	30-46	88% at 10 years

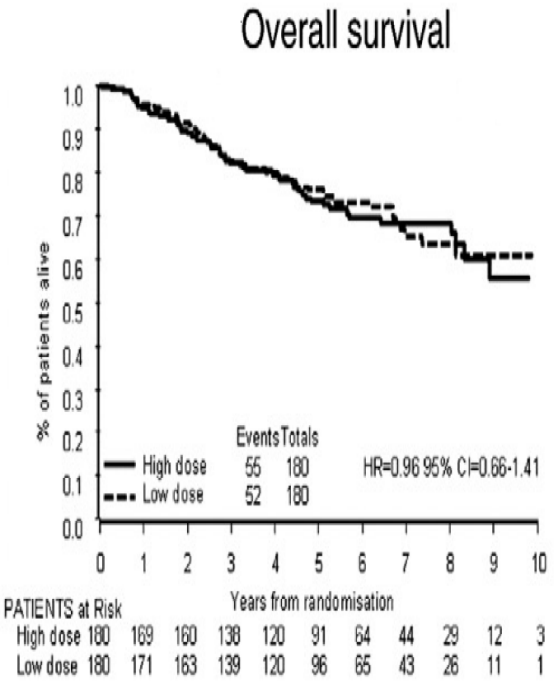
Bertoni & Zucca. *Lymphomas: Essentials for Clinicians* 2015

Randomized trial of reduced-dose RT in indolent NHL

N=289, mainly FL (65%) and including 56 MZL (19%)

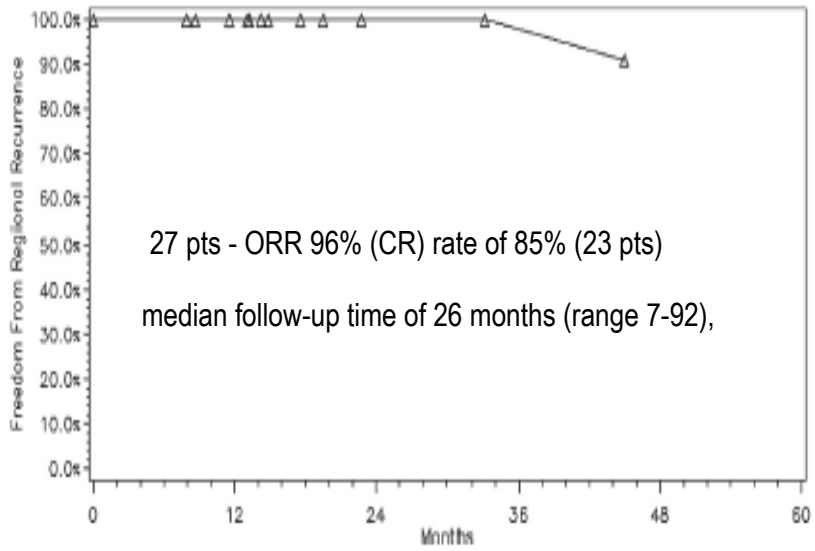






Lowry L, et al. Radiother Oncol 2011;100: 86-92

Gy 2 x 2 radiotherapy

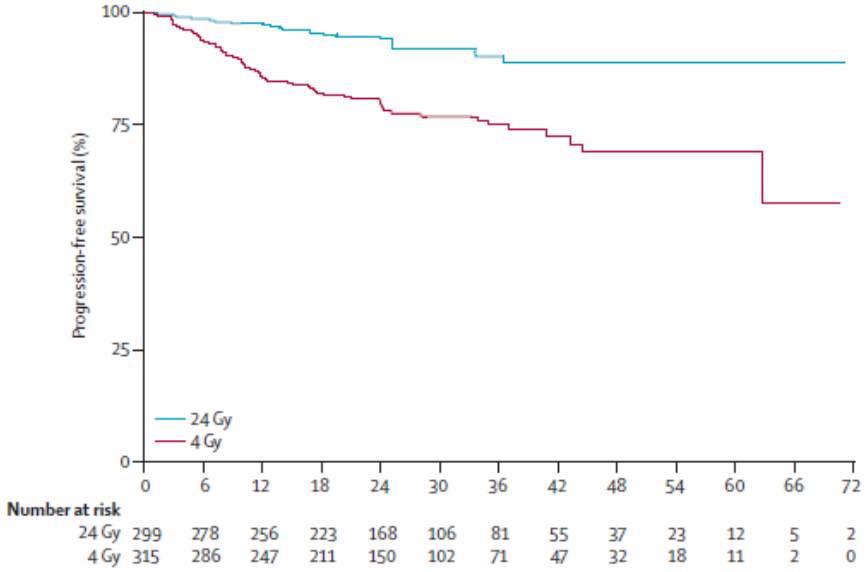


27 pts - ORR 96% (CR) rate of 85% (23 pts)

median follow-up time of 26 months (range 7-92),

Freedom from regional relapse for all sites with complete response treated with low-dose radiation therapy (N=23).

Fasola E, In J Rad Oncol 2013



Hoskin PJ Lancet Oncol 2014

Management of EMZL

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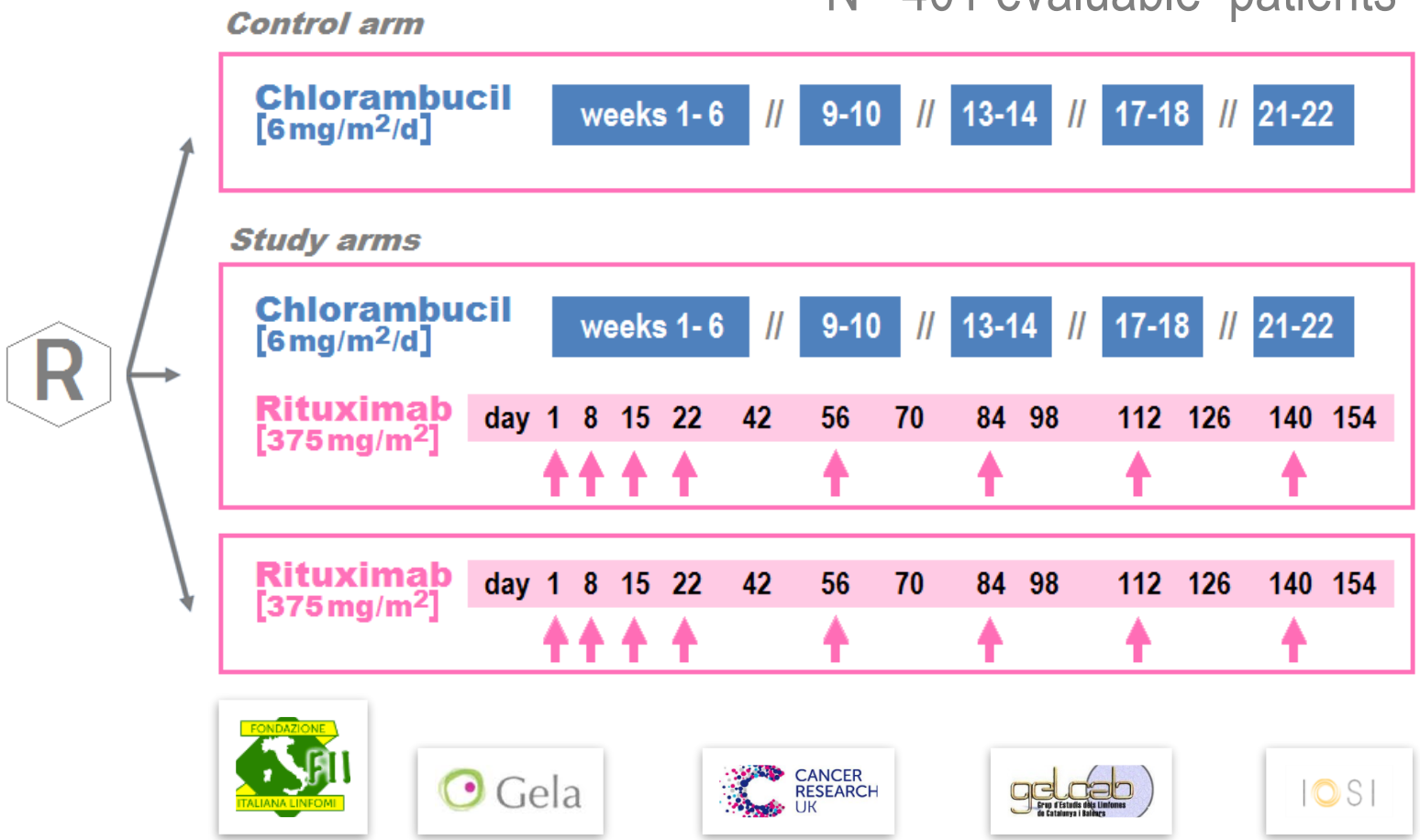
   in localized HP+ disease
   in localized HP- disease
   in disseminated disease
2) Role of antibiotics for extragastric EMZL
3) Role of radiotherapy for EMZL
   (optimal RT volume, dose and technique?)
4) Optimal treatment for disseminated disease

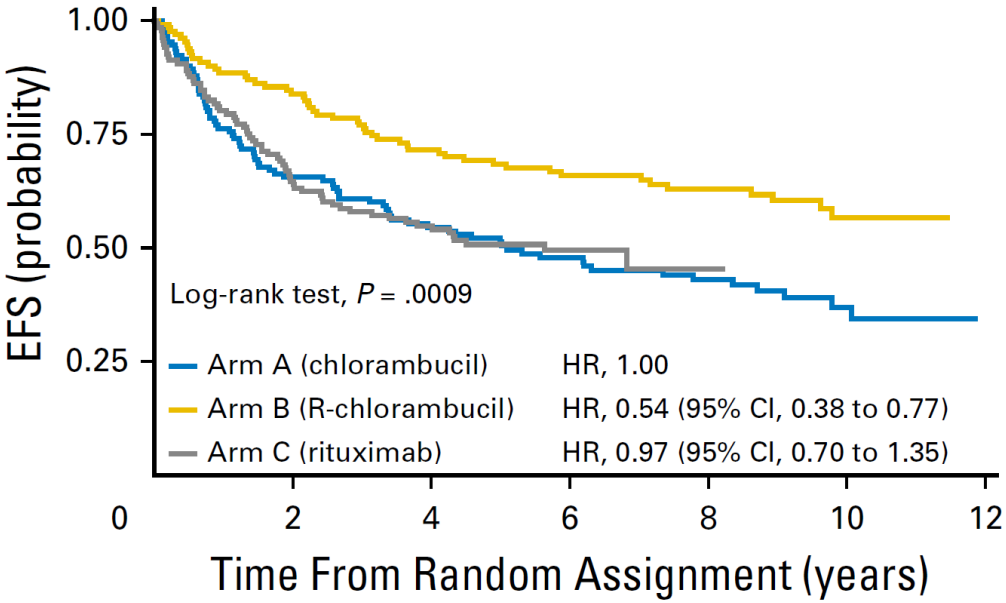
IELSG19 randomised study of MALT lymphoma

N= 401 evaluable patients



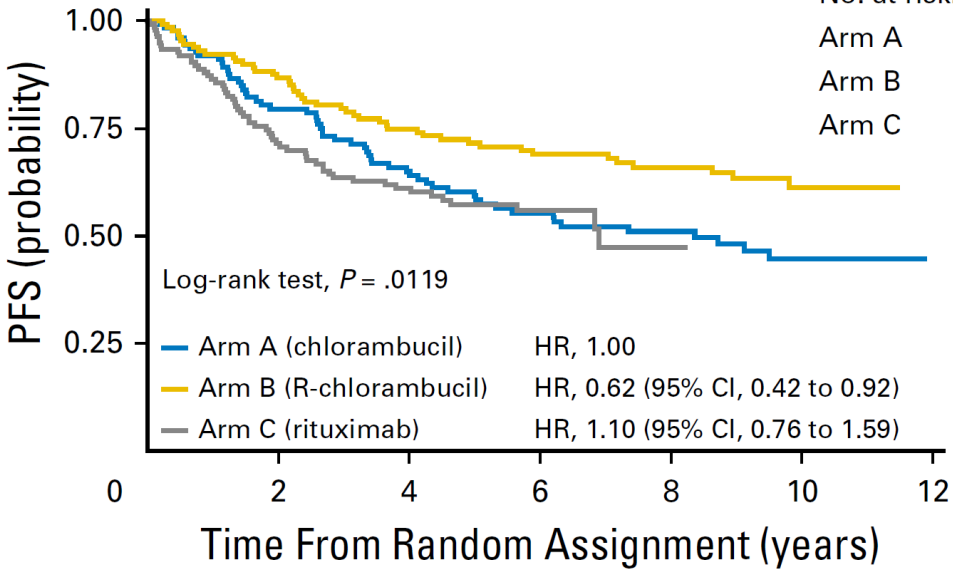
Zucca E, et al. JCO 2017; 35:1905-12

The IELSG19 results: EFS & PFS



No. at risk:

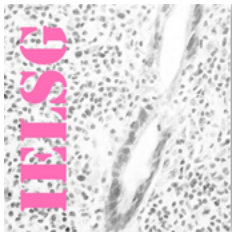
Arm A	131	85	68	53	41	16	0
Arm B	132	109	93	76	58	23	0
Arm C	138	87	69	30	2	0	0



No. at risk:

Arm A	131	89	70	53	42	16	0
Arm B	132	110	94	77	59	23	0
Arm C	138	90	71	31	2	0	0

Zucca E, et al. JCO 2017; 35:1905-12



The MALT-IPI

Prognostic Group	No. of Factors	No. of Patients in the IELSG-19 cohort (N=400)
Low risk	0	167 (42%)
Intermediate risk	1	165 (41%)
High risk	>1	68 (17%)

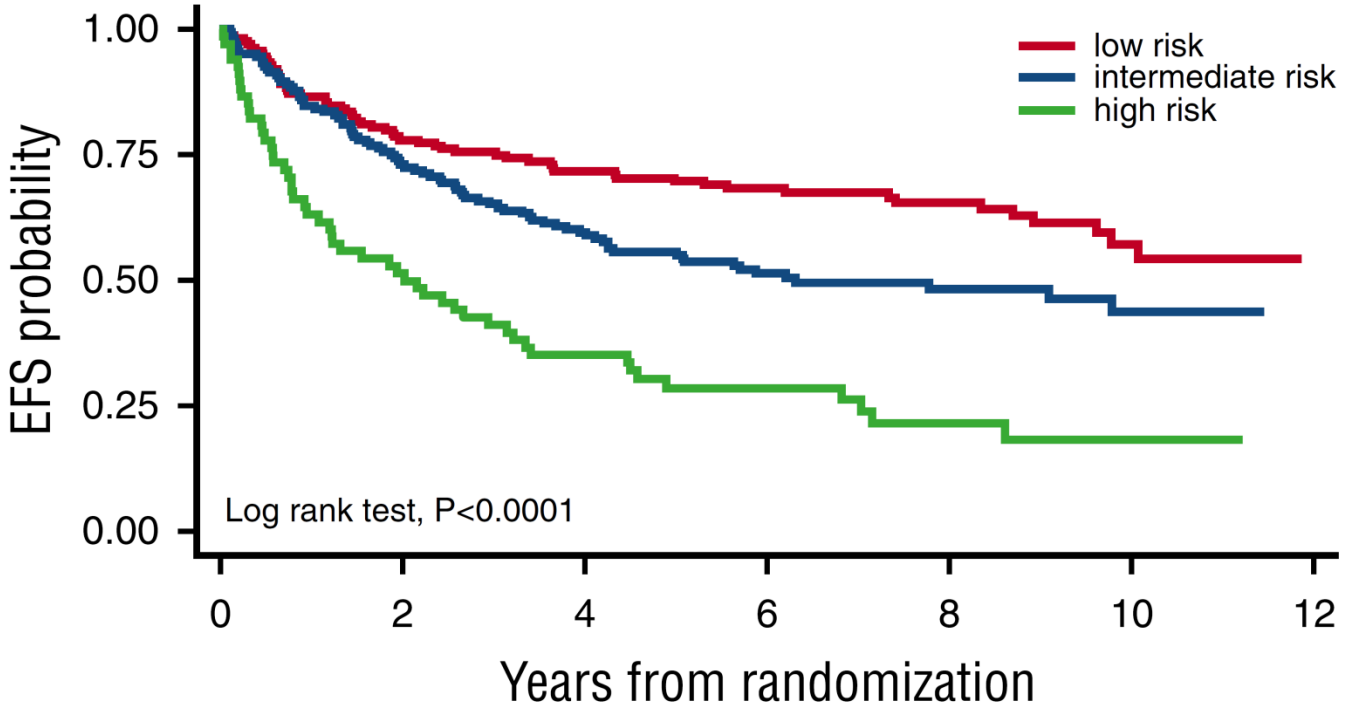
Risk Factors
Stage III-IV
Age>70 years
LDH >UNL

EFS Multivariate Analysis
(Stepwise Cox regression with backward selection using a $p<0.005$ cut-off)
N=400 (failures = 195)
P (Wald test) <0.0001

Thieblemont C, et al. Blood 2017;130:1409-17

EFS by MALT-IPI

in the testing set

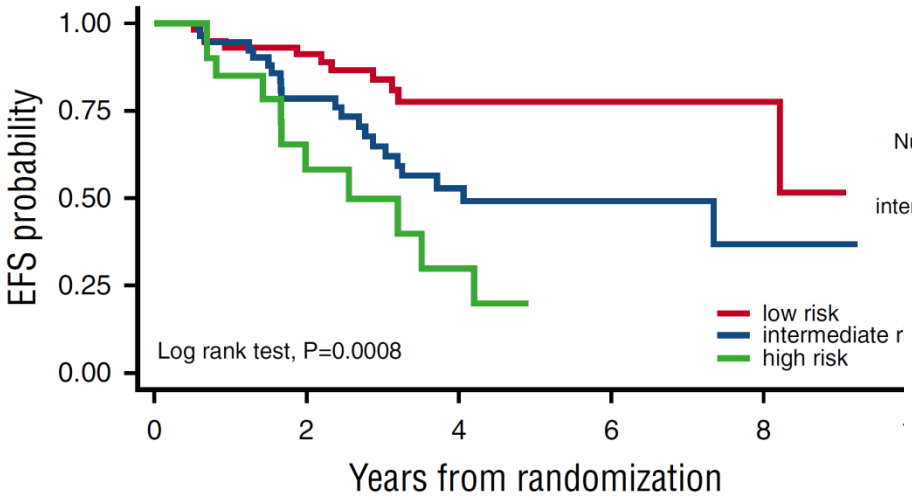


Number at risk							
low risk	167	126	112	84	57	22	0
intermediate risk	165	120	94	61	37	16	0
high risk	68	35	24	14	7	1	0

Thieblemont C, et al. Blood 2017 [Epub ahed of print]

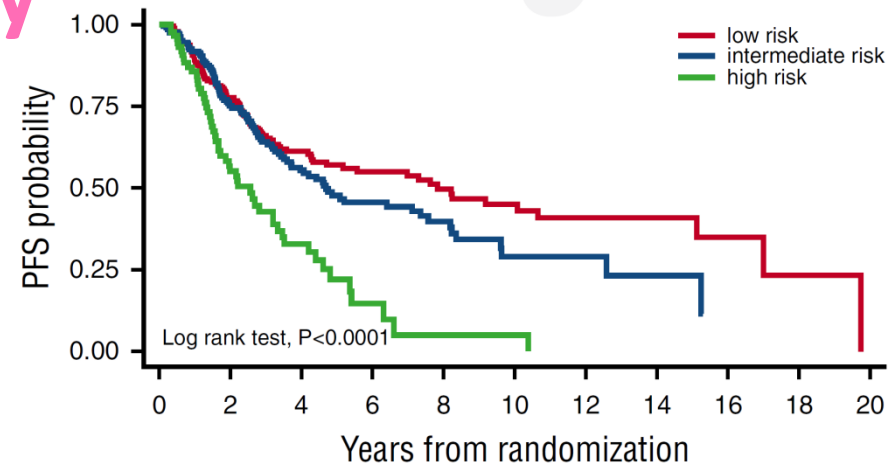
EFS, PFS and OS by MALT-IPI

in the validation set



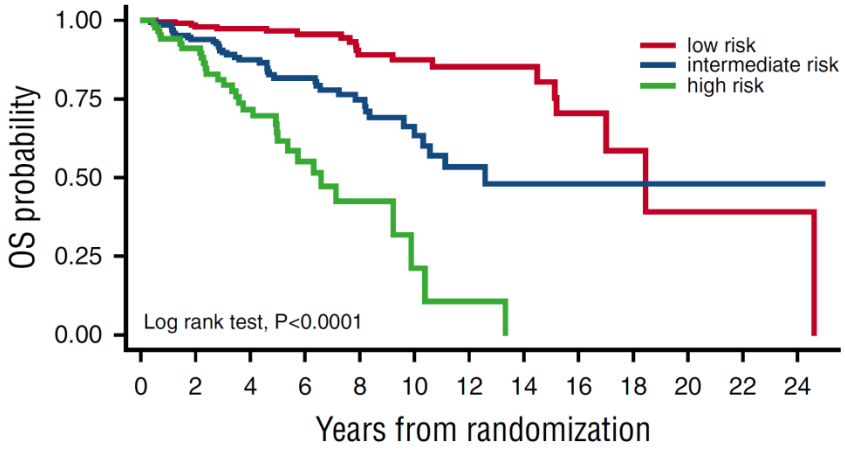
Number at risk

low risk	68	42	15	5	3
intermediate risk	57	31	14	6	2
high risk	22	8	3	0	0



Number at risk

low risk	251	147	79	49	34	24	15	9	3	1	0
intermediate risk	210	115	62	37	23	10	7	4	0	0	0
high risk	90	35	15	4	1	1	0	0	0	0	0



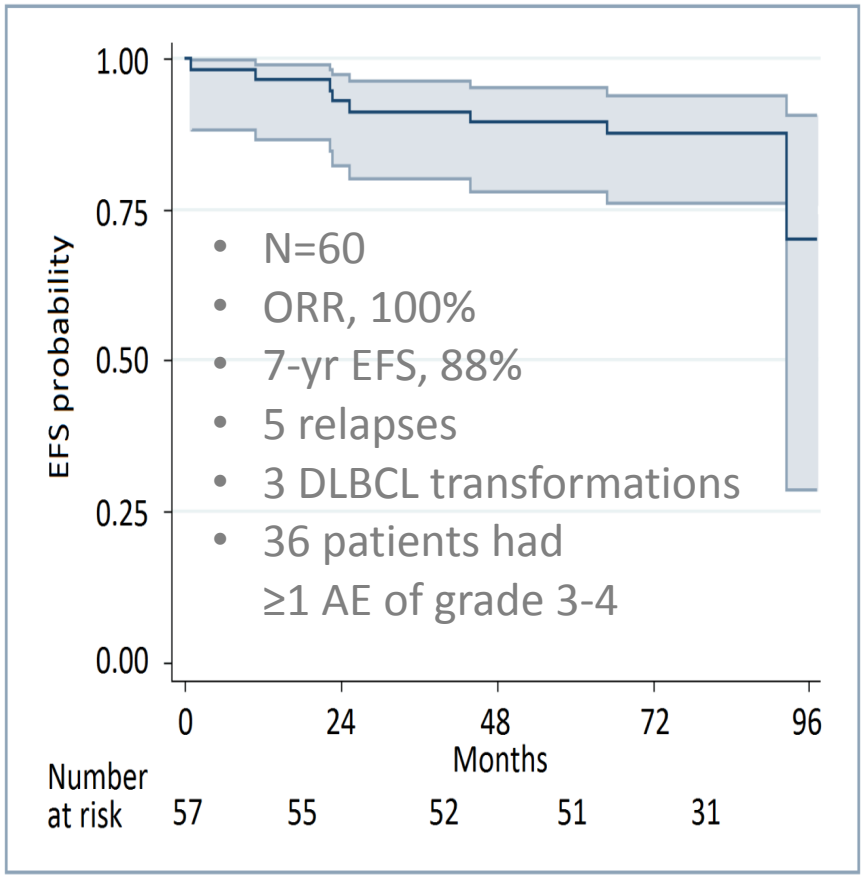
Number at risk

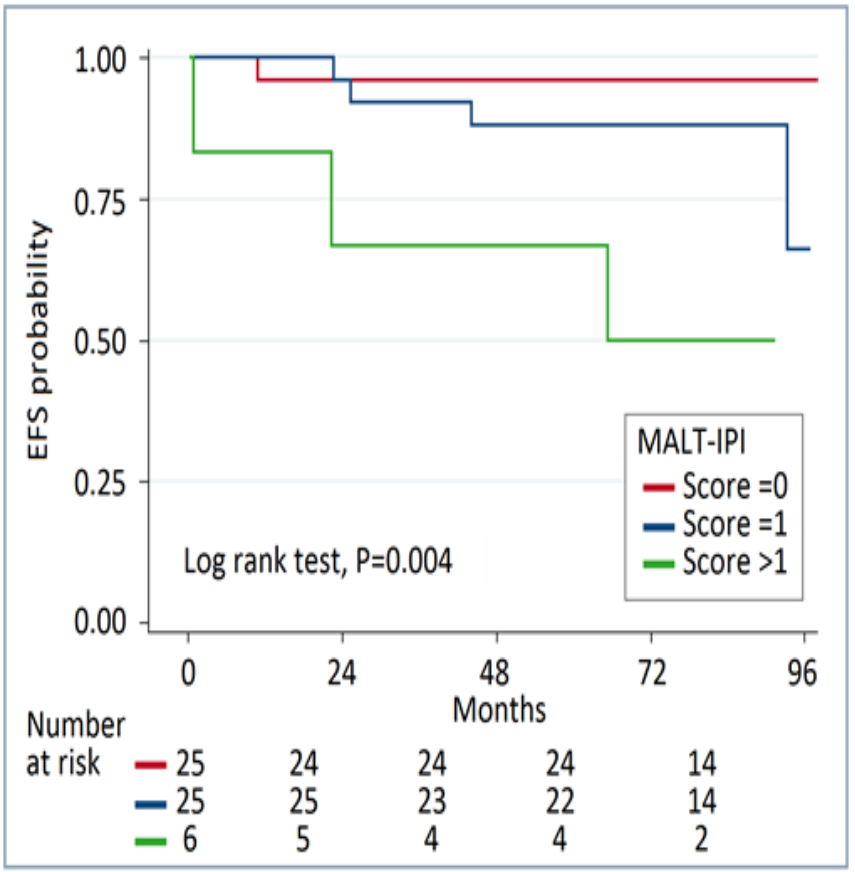
low risk	251	183	131	91	65	47	31	23	8	3	2	1	1
intermediate risk	210	146	102	67	41	22	14	7	2	1	1	1	1
high risk	90	60	36	16	7	2	1	0	0	0	0	0	0

Thieblemont C, et al. Blood 2017;130:1409-17

MALT-2008-01 GELTAMO phase-2 study

R-Bendamustine as 1st-line response-adapted therapy (4 to 6 cycles)

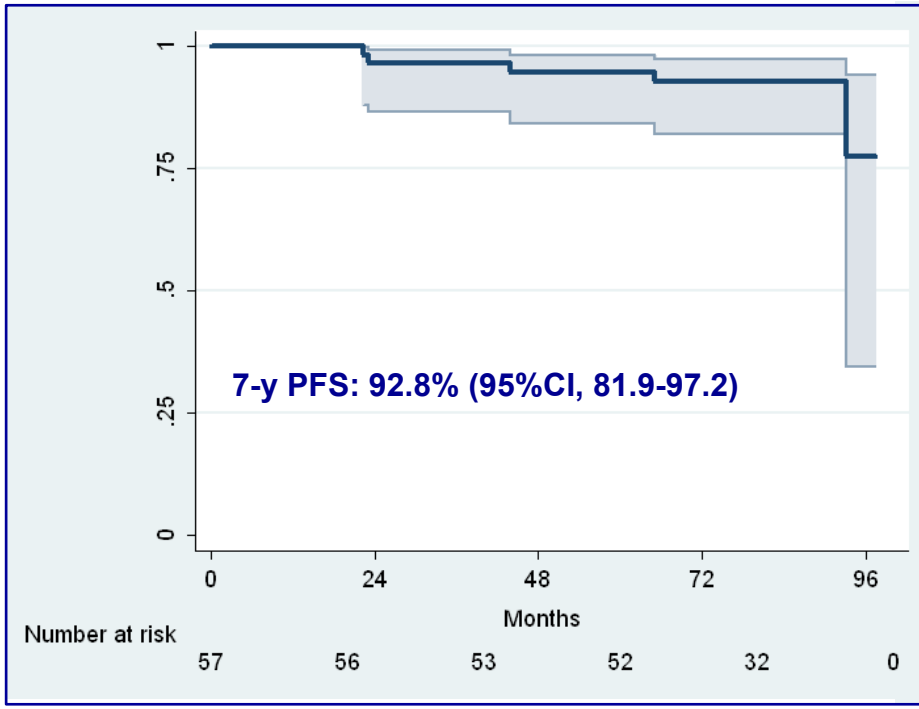




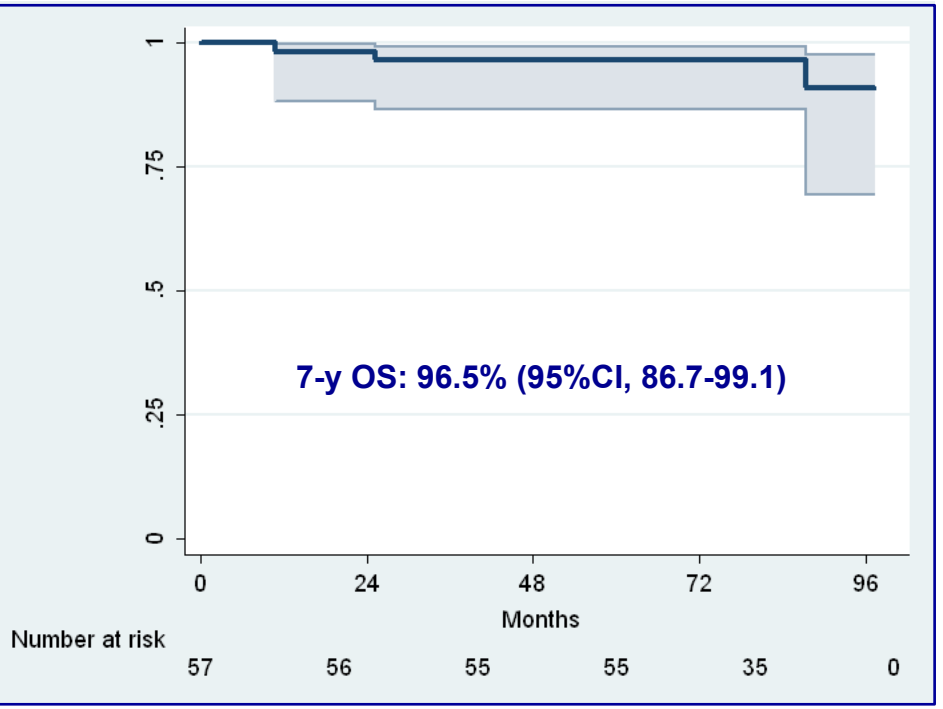
Salar A, et al. Blood 2017

Progression Free and Overall Survival

Progression free survival



Overall survival



Salar A, et al. Blood 2017

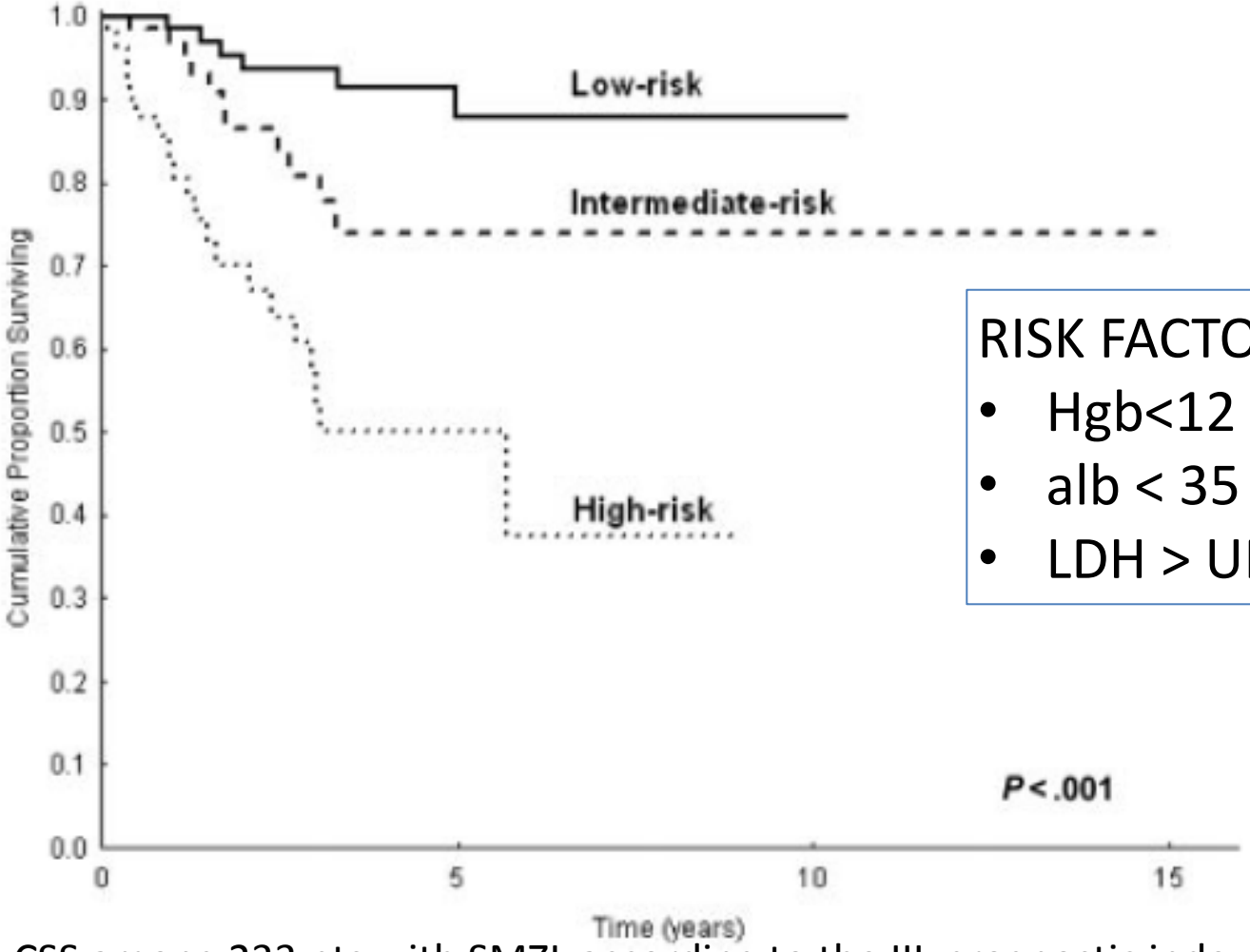
Toxicity beyond the first 2 years of follow-up

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

Salar A, et al. Blood 2017

Splenic Marginal Zone Lymphoma

Heterogeneous prognosis



RISK FACTORS

- Hgb<12 g/dl
- alb < 35 g/L
- LDH > UNL

CSS among 233 pts with SMZL according to the IIL prognostic index

Arcaini L et al. Blood 2006

IELSG46 retrospective study

Integrated Molecular and Clinical Profiling to Optimize Outcome Prediction in Splenic Marginal Zone Lymphoma

Multi-center, observational, training-validation analysis

Inclusion criteria

- SMZL diagnosis of on spleen histology before 2011
- Availability of tumor material and clinical annotations
- No therapy before splenectomy

Treatment of Splenic Marginal Zone Lymphoma (1)

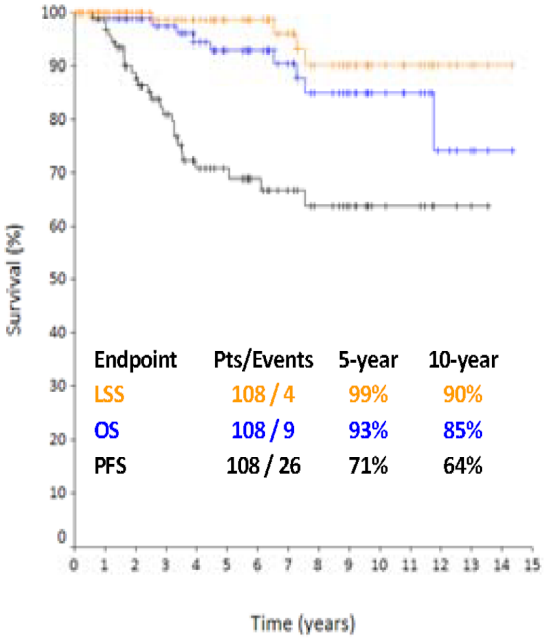
The case of:

Treatment against HCV infection
Splenectomy

Arcaini L, et al. Blood 2016

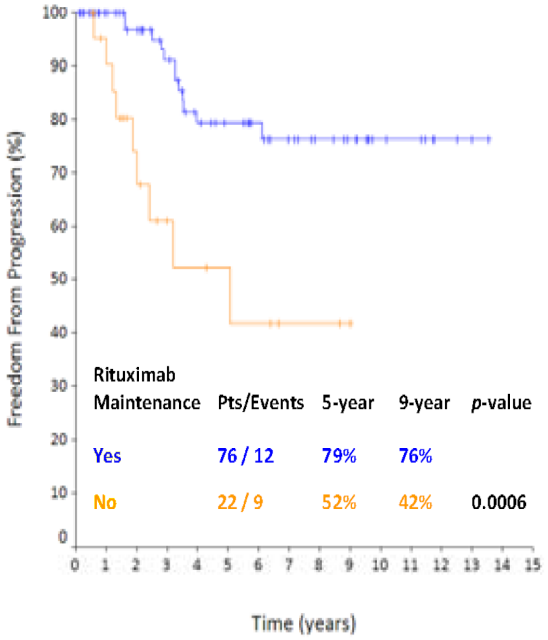
Rituximab monotherapy in SMZL: prolonged responses and potential benefit from maintenance

OS, LSS and FFP



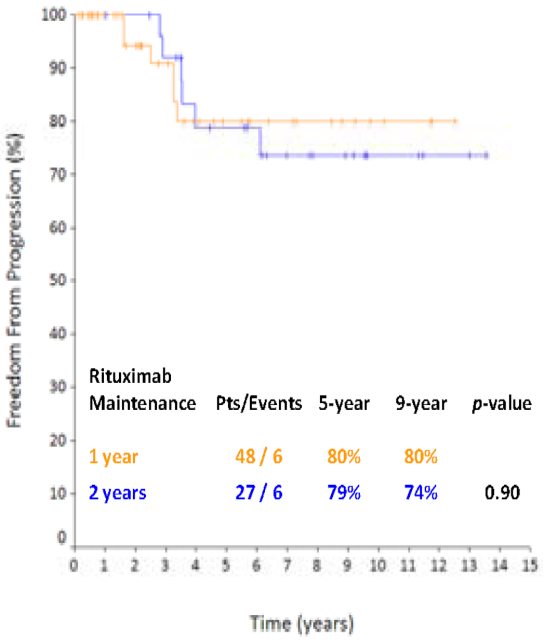
Endpoint	Pts/Events	5-year	10-year
LSS	108 / 4	99%	90%
OS	108 / 9	93%	85%
PFS	108 / 26	71%	64%

FFP according to Maintenance



Rituximab Maintenance	Pts/Events	5-year	9-year	*p*-value
Yes	76 / 12	79%	76%	
No	22 / 9	52%	42%	0.0006

FFP according to 1 or 2 yrs Maintenance



Rituximab Maintenance	Pts/Events	5-year	9-year	*p*-value
1 year	48 / 6	80%	80%	
2 years	27 / 6	79%	74%	0.90

Kalpadakis C, et al. Blood 2018

Treatment of Splenic Marginal Zone Lymphoma (2)

Series of SMZL patients treated with rituximab-based approach

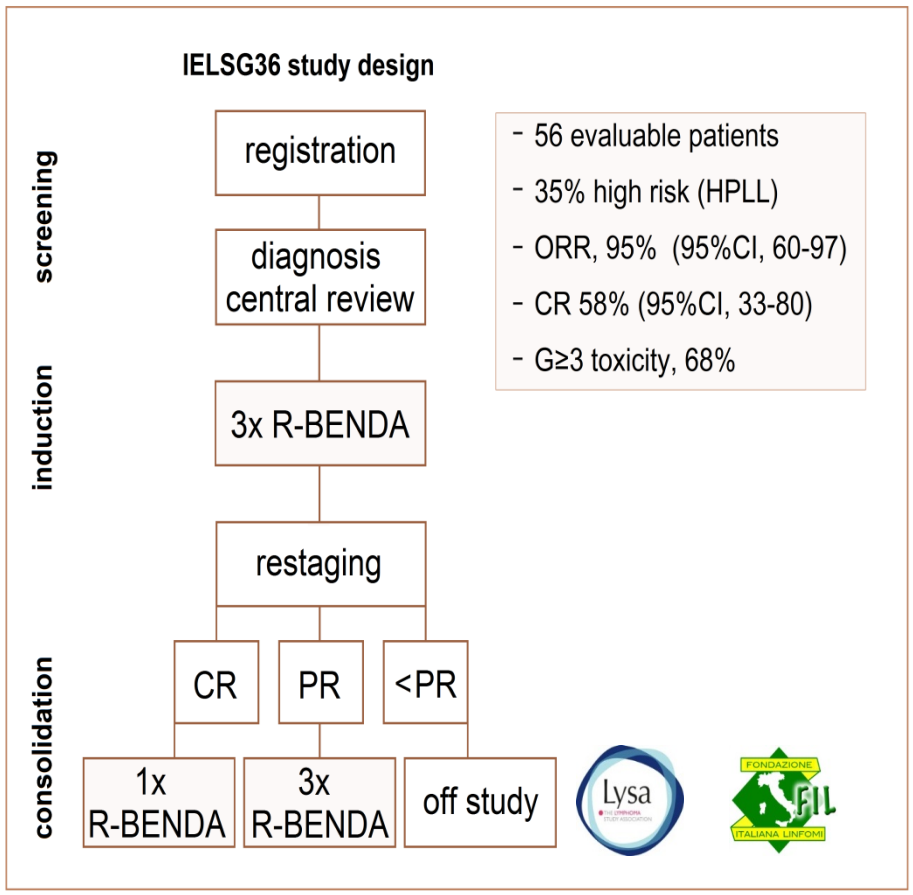
Reference	Year	Study type	Scheme	Patient status	N	Response		OS
						ORR	Duration	
Rituximab monotherapy								
Bennett et al	2005	Retrospective	R mono	RR	11	91%	PFS 60% at 5 y	70% at 5 y
Tsimberidou et al	2006	Retrospective	R mono	First line	25	88%	FFS 86% at 3 y	95% at 3 y
Kalpadakis et al	2007	Retrospective	R mono	First line	16	100%	PFS 92% at 2.4 y	100% at 2.1 y
Else et al	2012	Retrospective	R mono	First line and RR	10	100%	DFS 89% at 3 y	NR
Kalpadakis et al	2013	Retrospective	R mono	First line	58	95%	PFS 73% at 5 y	92% at 5 y
Rituximab + chemotherapy								
Tsimberidou et al	2006	Retrospective	R-chemo	First line	6	83%	FFS 100% at 3 y	100% at 3 y
Cervetti et al	2010	Retrospective	R-2CDA	First line and RR	47*	87%	PFS 80% at 5 y	86% at 5 y
Else et al	2012	Retrospective	R-chemo	First line and RR	33	100%	DFS 71% at 3 y	NR
Iannitto et al	2015	Prospective	R-COMP	First line	51	84%	PFS 54% at 6 y	72% at 6 y

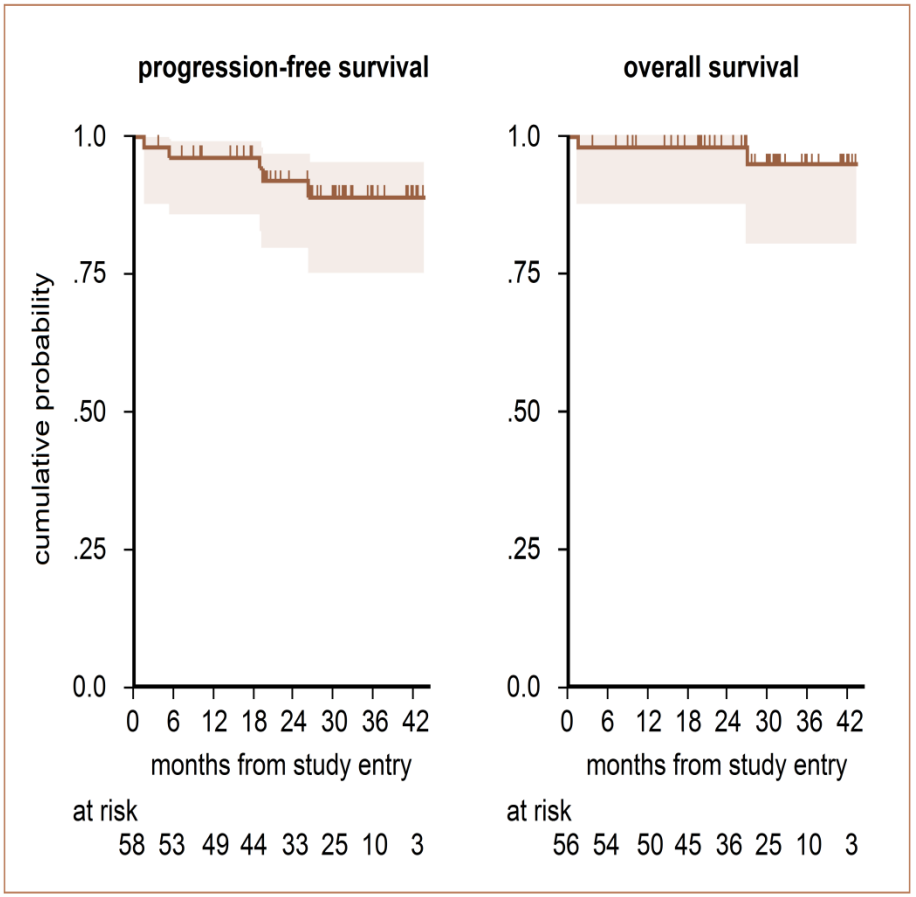
2CDA, 2-chlorodeoxyadenosine; chemo, chemotherapy; DFS, disease-free survival; R, rituximab; RR, relapsed/refractory.
*Rituximab in 32 patients.

Arcaini L, et al. Blood 2016

IELSG36 BRISMA Phase II trial

*B*endamustine and *R*ituximab for Untreated *S*plenic *Mar*ginal Zone Lymphoma





Iannitto et al. BJH 2018

IELSG36 BRISMA Phase II trial: toxicity (*i*)

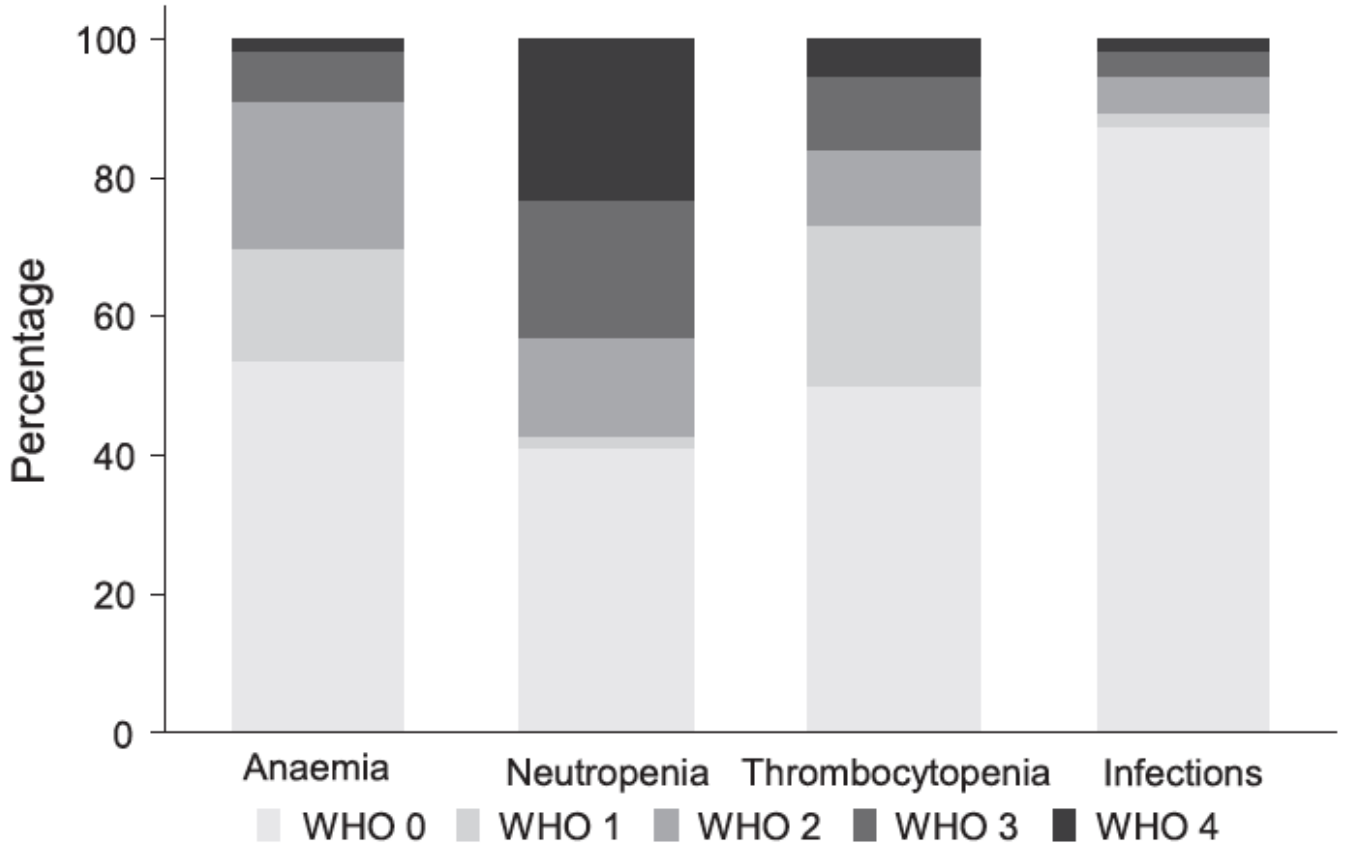


Fig 3. Overall haematological toxicities (World Health Organization [WHO] grades].

Iannitto et al. BJH 2018

IELSG36 BRISMA Phase II trial: toxicity (*ii*)

Table IV. Non haematological toxicity. Maximum grade during/after therapy.

Non haematological AE category	Adverse events Grade 1–2		Adverse events Grade 3–4	
	n (%)	Adverse event term	n (%)	Adverse event term
Blood and lymphatic system disorders	1 (1·8)	Disseminated intravascular coagulation	–	
Cardiac disorders	–		1 (1·8)	Angioplasty
Endocrine disorders	1 (1·8)	Diabetes imbalance	–	
Gastrointestinal disorders	22 (39·3)	Nausea/vomiting (14) Diarrhoea (6) Acute abdominal pain (splenic stroke) Constipation	3 (6·3)	Nausea/vomiting Constipation Mucositis oral
General disorders and administration site conditions	12 (21·4)	Infusion reaction (6) Fatigue (6)	2 (3·6)	Infusion reaction Fatigue
Immune system disorders	–		1 (1·8)	Allergic reaction*
Infections	4 (7·1)	Lung infection Vaginal infection Pharyngitis Abdominal infection	2 (3·6)	Lung infection Erysipelas
Investigations	4 (7·2)	Weight loss (2) Creatinine increased Blood bilirubin increased	–	
Metabolism and nutrition disorders	1 (1·8)	Anorexia	1 (1·8)	Tumour lysis syndrome
Musculoskeletal and connective tissue disorders	2 (3·6)	Chest wall pain Bone pain	–	
Nervous system disorders	3 (5·3)	Paresthesia (3)	–	
Renal and urinary disorders	–		1 (1·8)	Urinary tract obstruction
Reproductive system and breast disorders	1 (1·8)	Testicular pain	–	
Respiratory, thoracic and mediastinal disorders	2 (3·6)	Bronchospasm Cough	2 (3·6)	Pleural effusion Pneumonitis
Skin and subcutaneous tissue disorders	8 (14·3)	Rash maculo papular (7) Pruritus	1 (1·8)	Rash maculo papular
Surgical and medical procedures	1 (1·8)	Transurethral resection	–	
Vascular disorders	1 (1·8)	Oedema	1 (1·8)	Hypotension

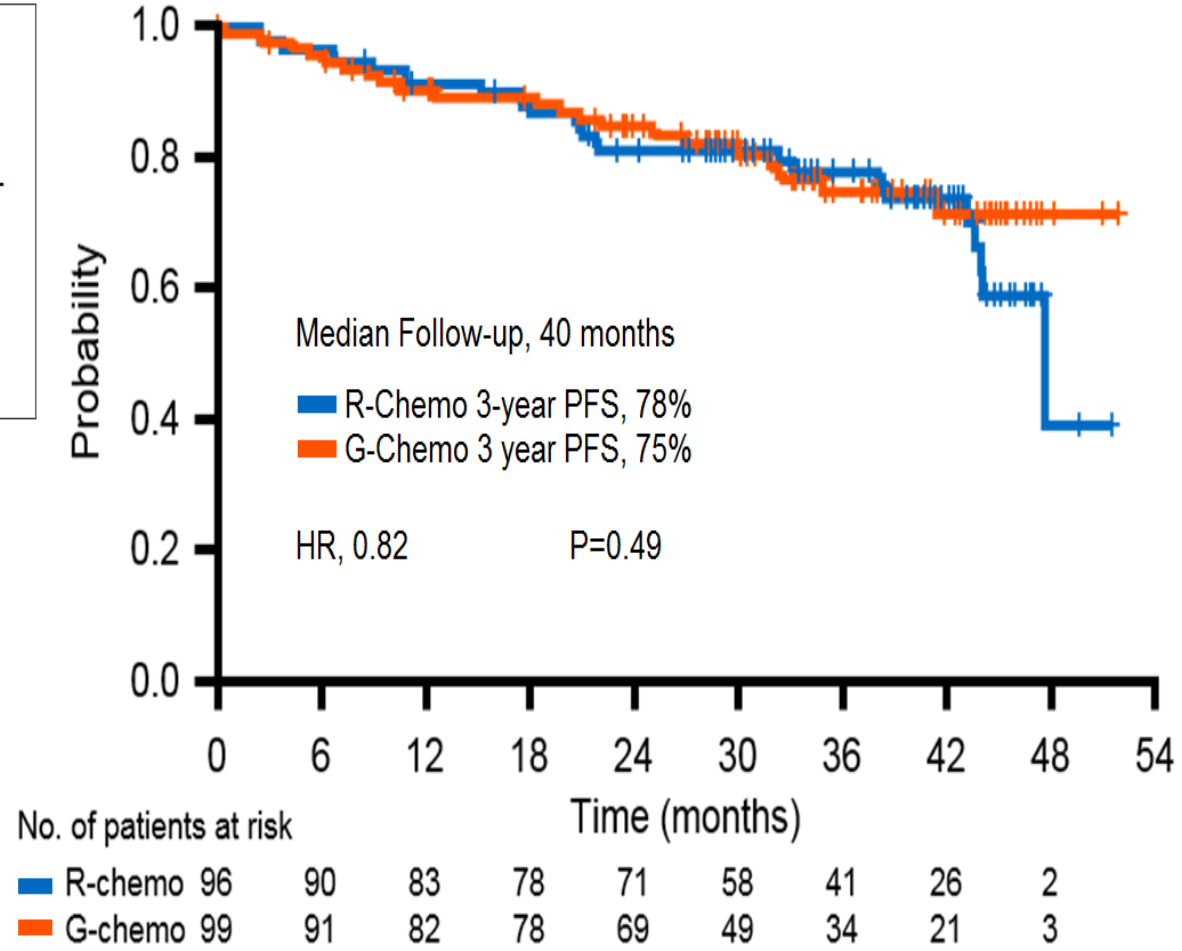
Iannitto et al. BJH 2018

Chemotherapy plus obinutuzumab or rituximab in MZL

GALLIUM Trial

195 untreated MZL

- 61, extranodal
- 66, nodal
- 68, splenic



Herold et al. Hematol Oncol 2017; 35 (S2):146-7

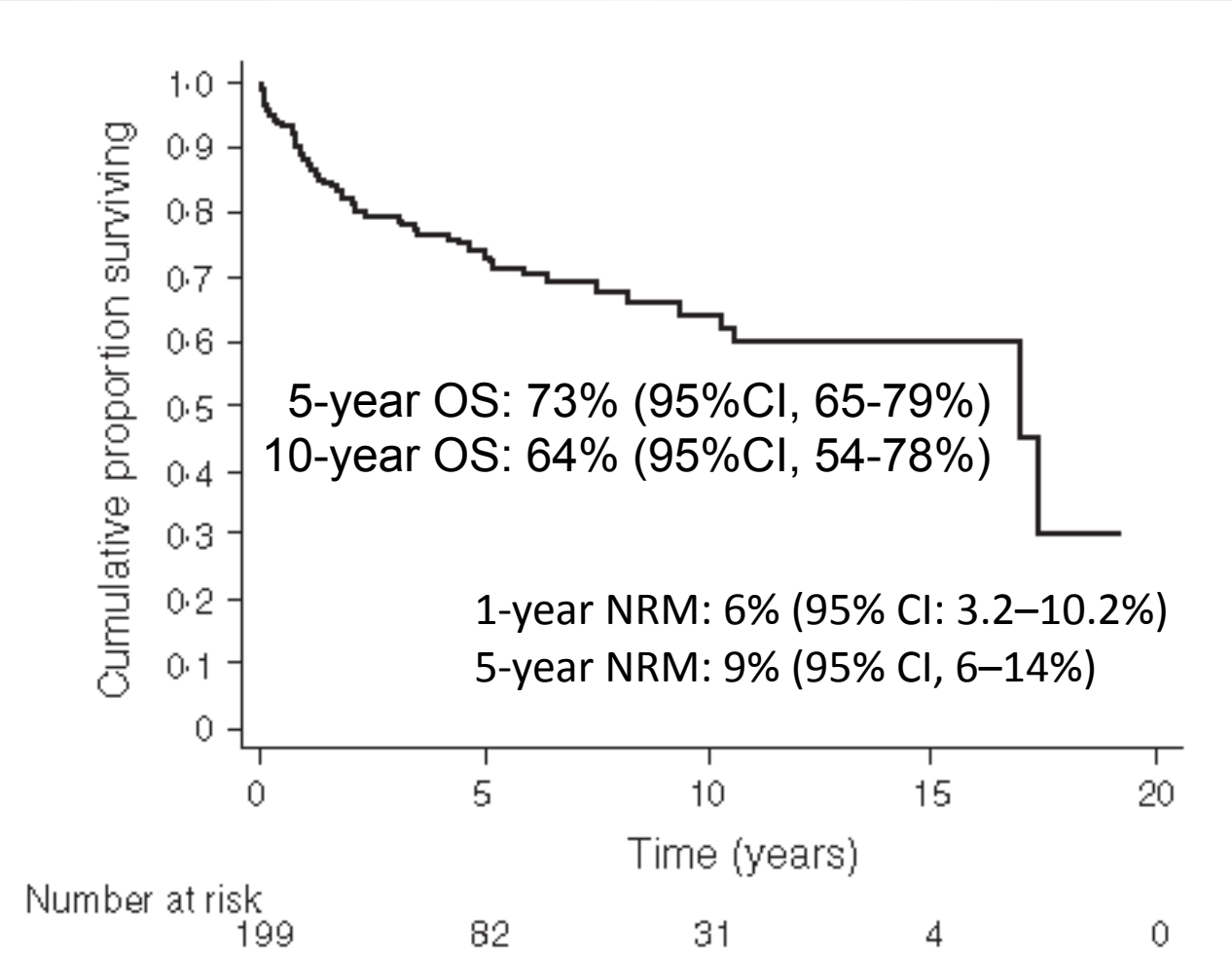
Chemotherapy plus obinutuzumab or rituximab in MZL

adverse events in the GALLIUM randomized trial

n (%) of pts with ≥1 one event	R-chemo, n=93	G-chemo, n=101
Any AE	93 (100)	101 (100)
Grade 3–5 AEs	72 (77)	83 (82)
SAE	48 (52)	65 (64)
Infections†	62 (67)	84 (83)
Second neoplasms‡	8 (9)	7 (7)
AE leading to treatment discontinuation	19 (20)	27 (27)
Grade 5 (fatal) AE	6 (6)	12 (12)

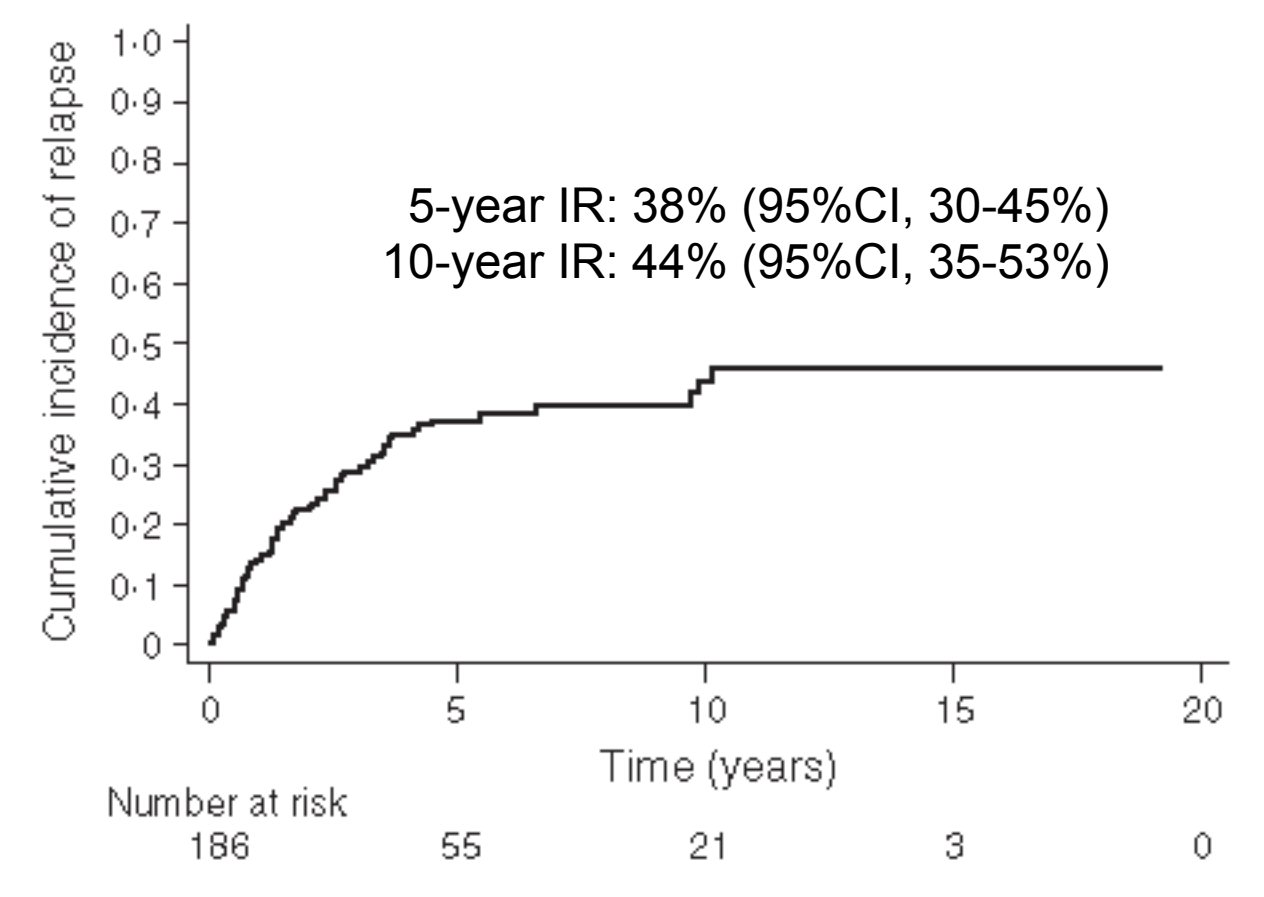
Herold et al. Hematol Oncol 2017; 35 (S2):146-7

Overall survival in 199 pts with MZL lymphoma undergone ASCT – the EBMT & FIL/GITMO series



Median follow-up 5 years (IQR, 2.4-7.5)

Cumulative incidence of relapse/progression



Median follow-up 5 years (IQR, 2.4-7.5)

A future of targeted treatments?

Phase II studies in relapsing MALT lymphoma

	ORR	Study	
Everolimus	20%	IELSG	Conconi et al, Br J Haematol 2014
Bortezomib	48%	IELSG	Conconi et al, Ann Oncol 2011
Lenalidomide	61%	Vienna	Kiesewetter et al, Haematologica 2013
Rituximab	45%	IELSG	Conconi et al, Blood 2003
Idelalisib	47%	Gilead	Gopal et al, N Engl J Med 2014
Ibrutinib	51%	Pharmacyclics	Noy et al, Blood 2017

The CLEO trial (IELSG40)

A PHASE II TRIAL ADDRESSING FEASIBILITY AND ACTIVITY OF CLARITHROMYCIN + LENALIDOMIDE COMBINATION: A FULL ORAL TREATMENT FOR PATIENTS WITH RELAPSED/REFRACTORY EXTRANODAL MARGINAL ZONE LYMPHOMA

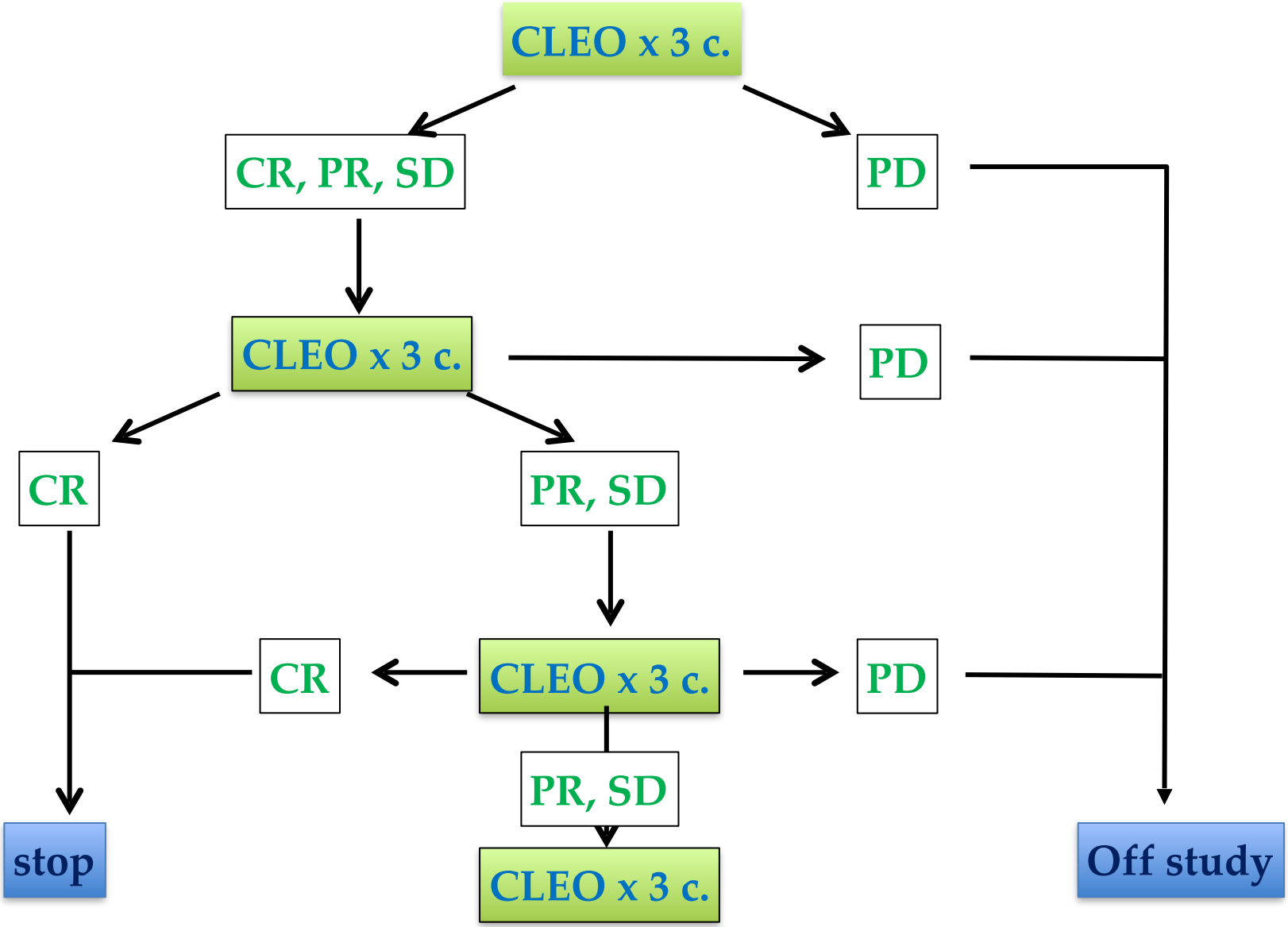
Primary endpoint: ORR
Secondary endpoints: PFS & safety

Main inclusion criteria:

- Histological diagnosis of MALT lymphoma arising at any extranodal site
- Disease refractory to or in first or greater relapse after prior radiotherapy and/or chemotherapy and/or immunotherapy

Study medication :
Lenalidomide 20 mg once daily for 21 days;
Oral Clarithromycin 500 mg twice daily for 28 days.
Courses will be repeated every 28 days.

Trial Design

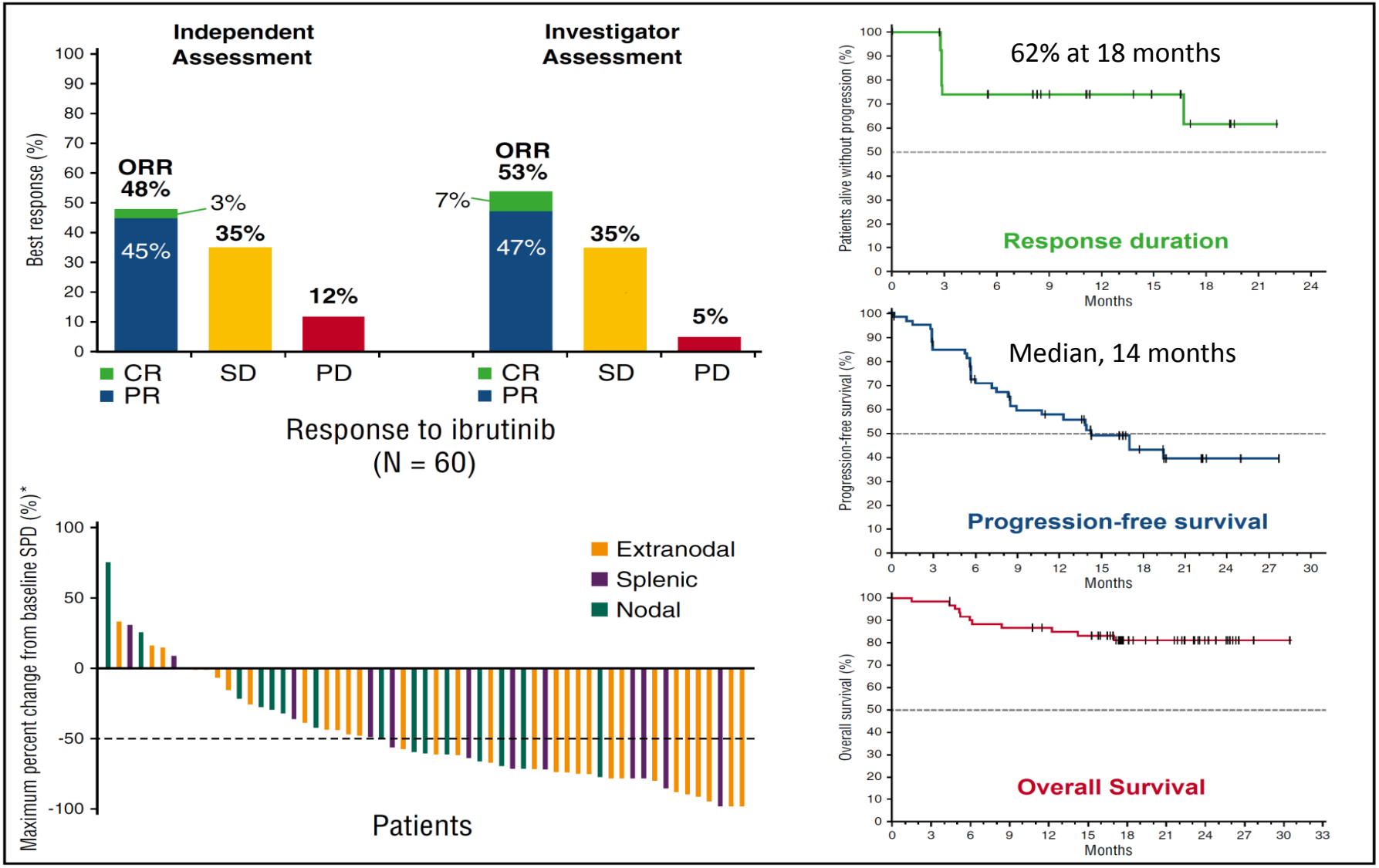


CLEO trial: Statistics

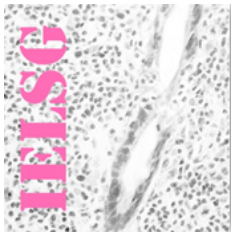
- Two-stage Simon minimax design
- Background:
  - ORR lenalidomide alone= 61%[1] - clarithromycin alone 52%[2]
- Hypothesis: the addition of clarithromycin will increase ORR from 60% (P0) to 75% (P1)
- With an α level of 0.05 and β of 0.80, 62 pts are needed
- Drop-out 10%: 68 pts
- First step: 30 pts (≥18 responses)
- Second step: 62 pts (≥44 responses)
- Expected duration: 36 months

[1]**Kiesewetter B, *et al.* Haematologica 2013**
[2]**Ferreri AJM, *et al*. Ann Oncol 2015**

Targeting BTK with ibrutinib in r/r



Noy A, et al. Blood 2017



MALIBU TRIAL

Clinical evaluation of activity and safety of combination **rituximab-ibrutinib** in

previously untreated and symptomatic patients with histologically proven CD20-positive **marginal zone B-cell lymphoma (MZL)**
in need of systemic treatment

FONDAZIONE FIL ITALIANA LINFOMI

Gela

CANCER RESEARCH UK

Primary endpoints

1/ Complete Response (CR) rate at 12 months

2/ PFS at 5 years

assessed by the investigators,

according to revised response criteria for malignant lymphomas,
from study entry to death from any cause or PD

Secondary endpoints

- Acute and long-term safety -NCI CT Criteria, V 4.0
- CR rate at 24 months
- Overal Response Rate (ORR) at 12 and 24 months
- Duration of Response (DOR)
- Duration of Complete Response (DCR)
- Event-Free Survival (EFS)
- Overall Survival (OS) Time To Next Treatment (TTNT)
- Histological Transformation (HT) rate
- Assessment of the prognostic role of the quantitative measures of FDG-PET/CTscan

Inclusion criteria

1/ Previously untreated and symptomatic patients with histologically proven diagnosis of CD20-positive marginal zone B-cell lymphoma (MZL) not eligible for local therapy, including :

EMZL

1. **MALT-IPI 1 or 2 in need of treatment**
2. Either de novo, or relapsed following local therapy (RT, surgery or ATB)
2. Measurable disease
3. Any stage (Ann Arbor I-IV)

SMZL

- either de novo or relapsed following local therapy (surgery and anti- HCV)
- symptomatic disease
- cytopenias : Hb < 10 g/dL, or Platelets < 80 000/µL, or neutrophil count < 1000/µL

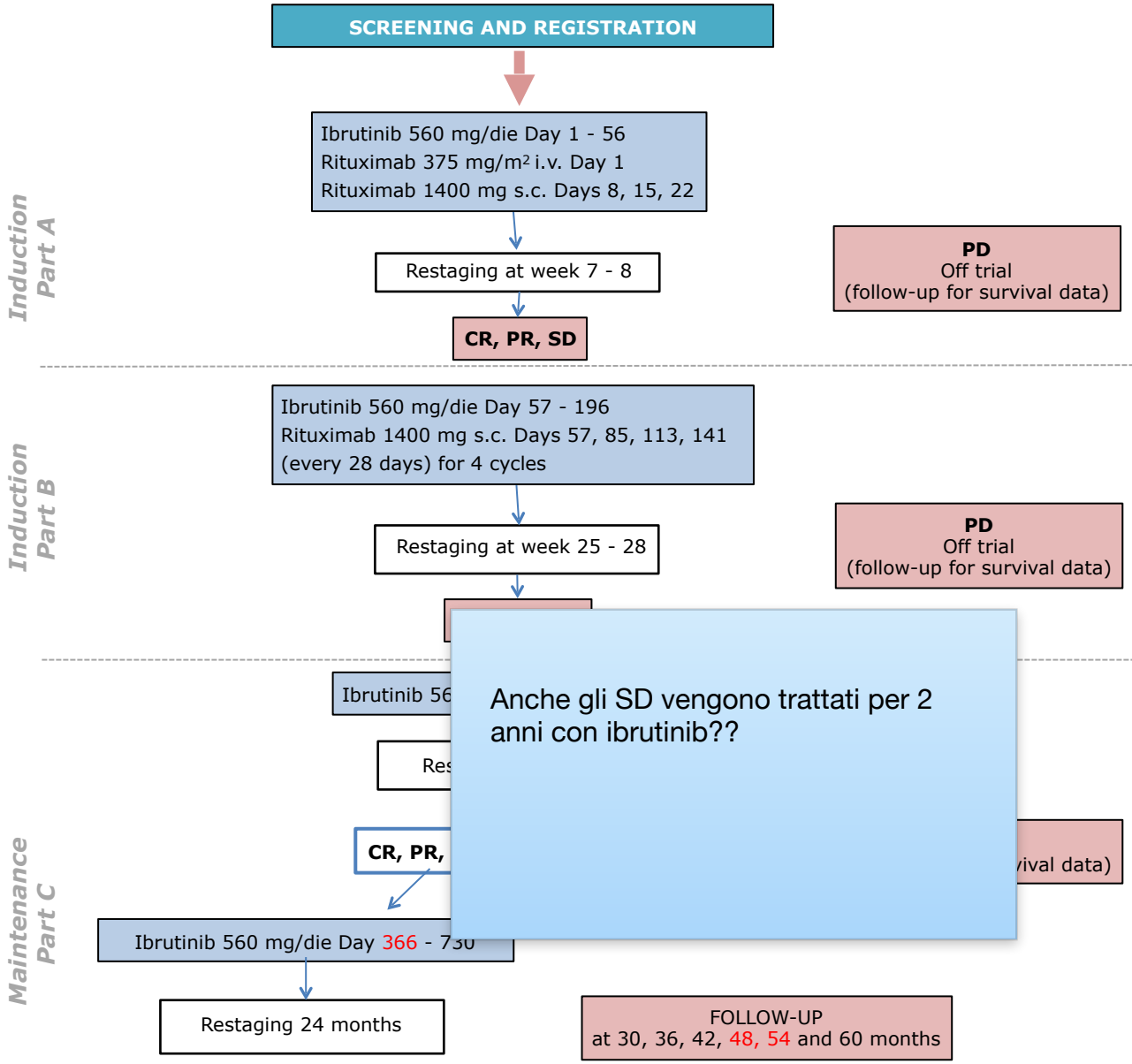
NMZL

- de Novo
- Disseminated

- Measurable or evaluable disease.
- Ann Arbor II-IV Stage I disease may be eligible only if not candidate to local therapy (surgery or radiotherapy)
- ECOG Performance status 0-2

n= 130 **n=15** **n=15**

IELSG47 - MALIBU trial
Study flow chart



*patients in SD will continue study treatment at discretion of the investigator, if of clinical benefit

MALIBU TRIAL: sample size

For the purpose of the study, the proportion of patients able to achieve a CR is considered primary endpoint, while PFS is a co-primary endpoint.

In order to preserve a family-wise error $\alpha=0.05$ one-sided, the associated α error for primary and co-primary endpoint will be $\alpha1=0.025$ and $\alpha2=0.025$.

If the primary endpoint is significant at the $\alpha1=0.025$ level, PFS will be tested at $\alpha2+\alpha1=0.05$ level, otherwise, PFS will be tested at $\alpha2=\alpha2^{i}=0.025$ level

Wiens BL. Pharmaceutical Statistics, 2003

MALIBU TRIAL: sample size

The statistical hypothesis is based on an improvement of the CR rate at 12 months from 72.9 % (as observed with the combination of Rituximab and Chlorambucil in the IELSG19 study in patients with MALTIPI>0) to 85%

Ho: p = 0.7290 and alternative p = 0.8500
alpha = 0.0250 (one-sided)
power = 0.9000
n = 120

Taking into account exclusion of cases after central histology review and non-evaluable patients, 130 patients with EZML (MALT lymphoma) will be enrolled

Grazie per l’attenzione