INCONTRO DI AGGIORNAMENTO SUI DISORDINI LINFOPROLIFERATIVI E SUI PROTOCOLLI DELLA FONDAZIONE ITALIANA LINFOMI

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Linfomi gastrici del MALT

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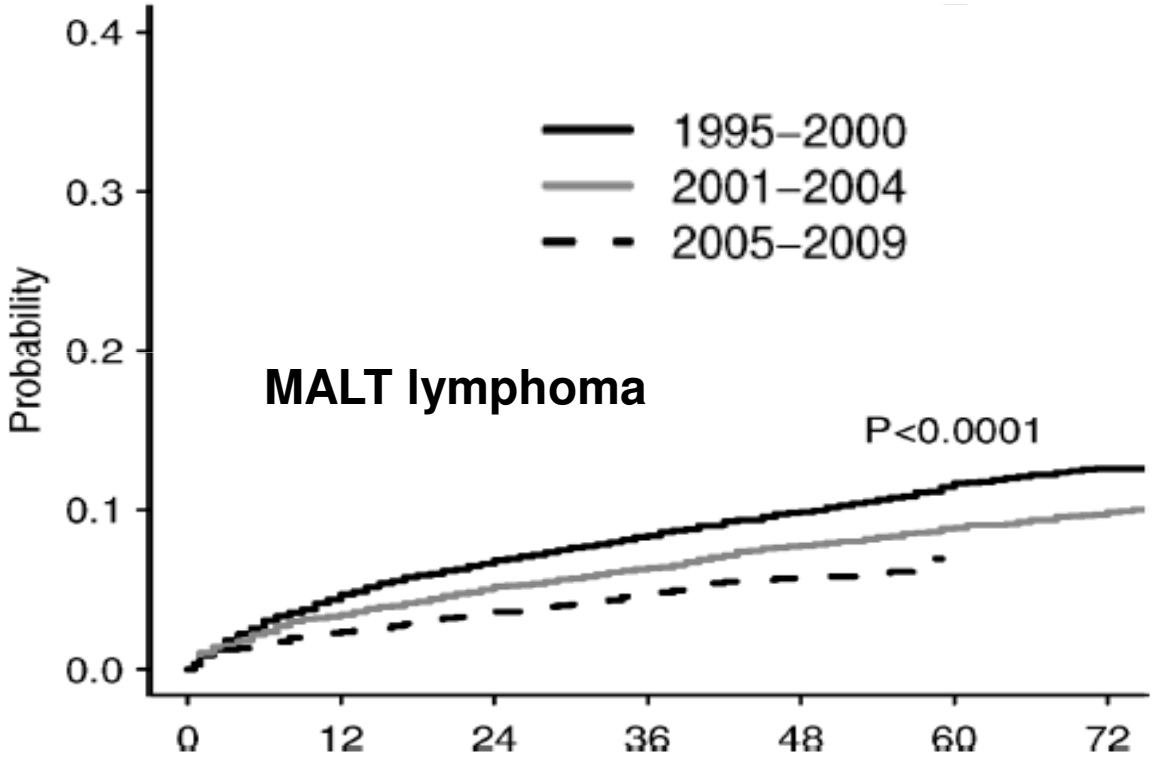
Marginal Zone B-Cell Lymphomas (MZLs)

WHO CLASSIFICATION

- Splenic MZL **~ 1% of all NHLs**
- Nodal MZL **~ 2% of all NHLs**
- Extranodal MZL (MALT Lymphoma) **~ 8% of all NHLs**

MALT lymphoma survival: analysis of the SEER database



Cumulative incidence of lymphoma related deaths

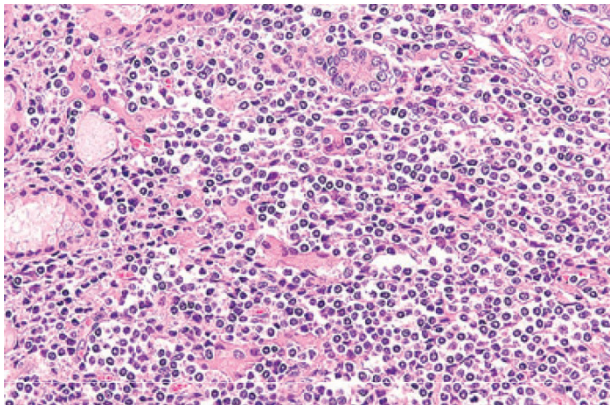
Olszewski AJ. Cancer 2013

Diagnosis of MALT lymphoma

(Extranodal Marginal Zone B-Cell Lymphoma of MALT)

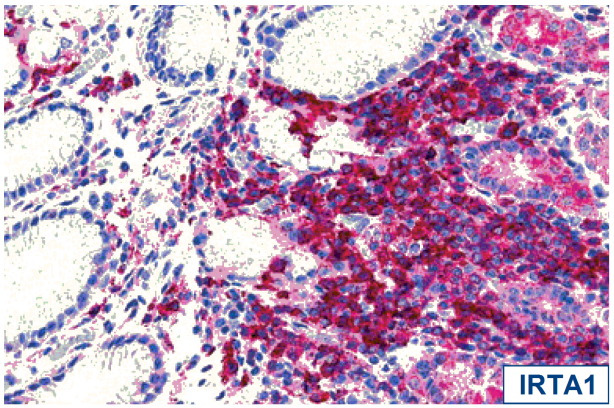
HISTOLOGICAL FEATURES

- centrocyte-like cells (usually)
- lymphoepithelial lesions
- plasma cell differentiation
- scattered transformed blasts
- admixed reactive T-cell
- follicular colonisation



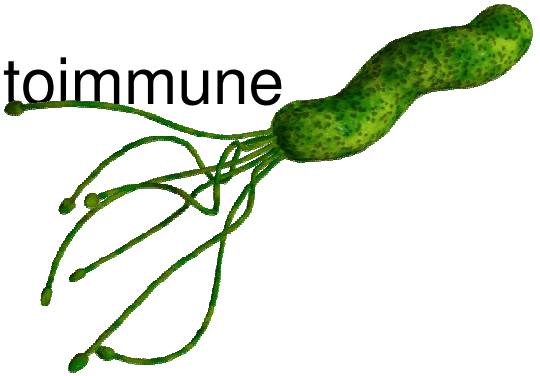
IMMUNOPHENOTYPE

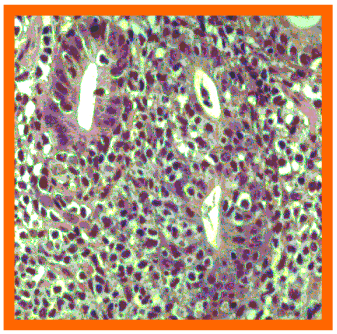
- CD5, CD10, CD23, cyclin-D1, IgD negative
- CD20, CD21, CD35, IgM positive
- IRTA1 positive



Isaacson et al. in *WHO Classification of Tumours of Haematopoietic &Lymphoid Tissues.* IARC, Lyon 2008; pp. 214-7
Falini et al. Histopathology. 2012 [Epub ahead of print]

Association with infection or autoimmune chronic inflammation

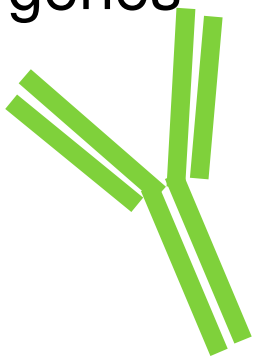




Histological features

Pathogenesis of MALT lymphoma: an antigen-driven process

Mutational status of the immunoglobulin genes



Efficacy of antibiotic therapy

Antigen-driven lymphoma development

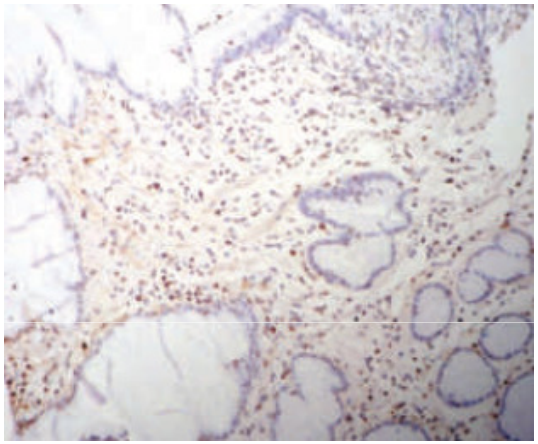
- ***Helicobacter pylori*** in gastric MZL
- ***Borrelia burgdorferi*** in cutaneous MZL
- ***Chlamydophila psittaci*** in some OALs
- ***Campylobacter jejuni*** in IPSID
- ***HCV*** association with some non-MALT MZL
- *Achromobacter (Alcaligenes) Xylosoxidans* in BALT-Lymphoma**?**
- **nevertheless,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

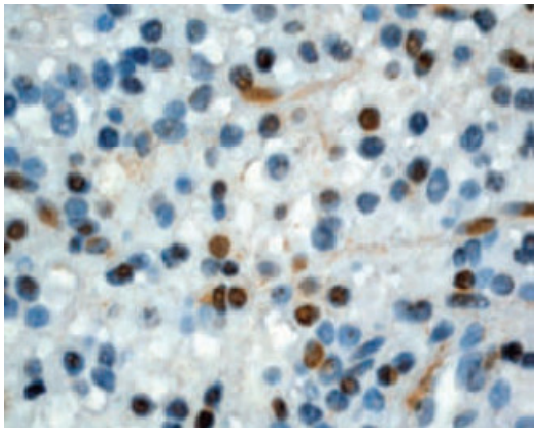
Evidence for linking specific microorganisms to MALT lymphoma pathogenesis at different sites

Koch's postulates (1882)	***H. pylori* & Gastric MZL**	***C. jejuni* & IPSID**	***B. burgdorferi* & Cutaneous MZL**	***C. psittaci* & Ocular adnexal MZL**
Organism found in the lesion.	**most cases**	some cases	variable	variable
Organism can be isolated and grown *in vitro*.	**yes**	not yet	not yet	**yes**
Organism inoculation causes lesions in animals	**yes**	unknown	unknown	unknown
Organism can be recovered from the experimental animal	**yes**	unknown	unknown	unknown
Lymphoma regression after bacteria eradication	**yes**	**yes**	**yes**	**yes**

modified from: MQ Du, J Clin Exp Hematopathol 2007

H. pylori translocates the bacterial protein CagA into gastric epithelial cells, and into MALT lymphoma B cells

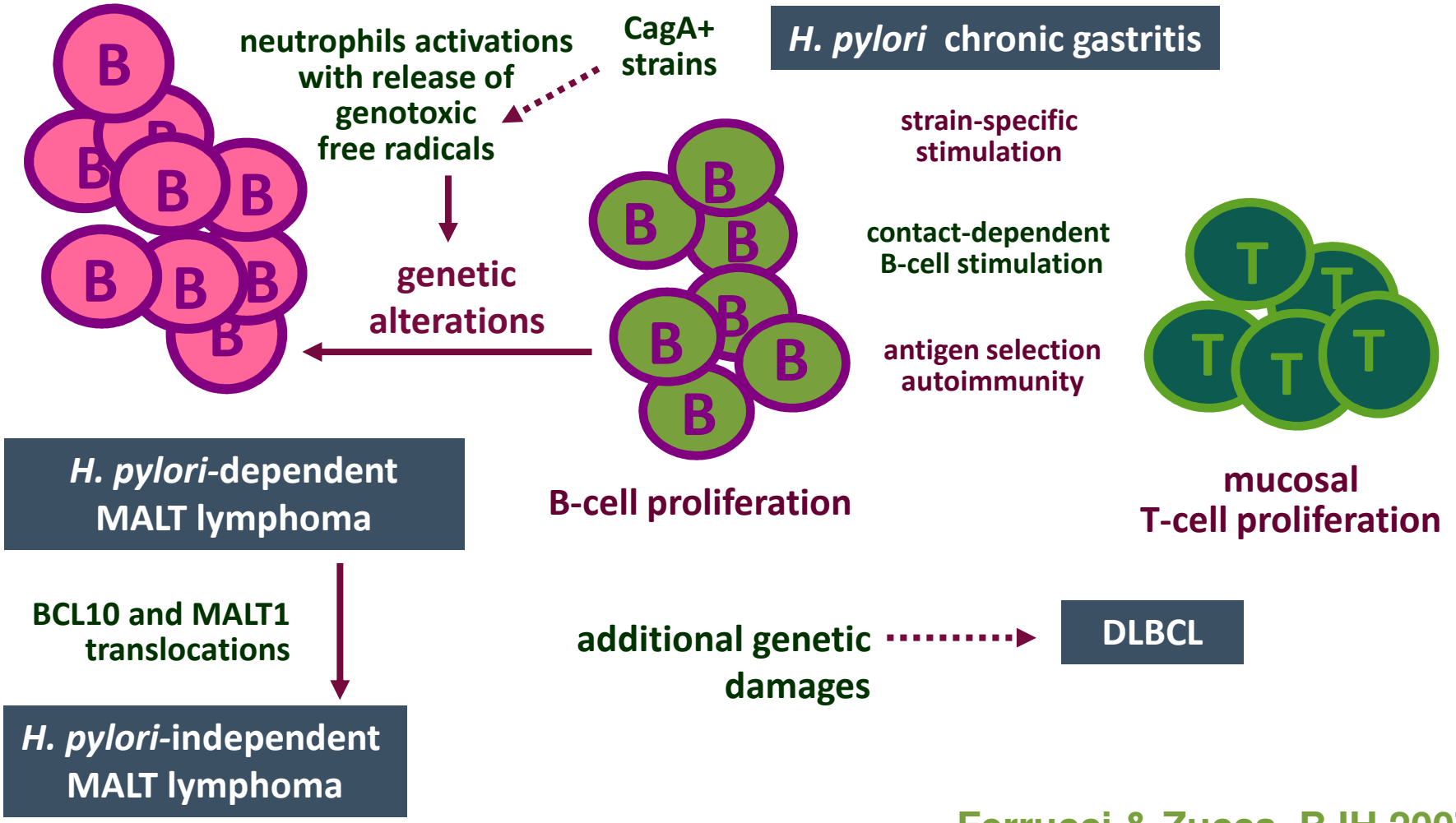




- CagA protein in gastric epithelial cells (where it deregulates intracellular signaling pathways) and the tumor B-cells within the gastric mucosa (×100)
- CagA undergoes tyrosine phosphorylation in tumor B-cells (×400), and binds to intracellular SHP-2
- during persistent *H. pylori* infection, the translocated CagA acts as a bacterium-derived oncoprotein in human B cells :
  - ✓ activates extracellular signal-regulated kinase and p38 mitogen-activated PK
  - ✓ upregulates the expressions of Bcl-2 and Bcl-XL, which prevents apoptosis

Wei-Cheng et al. Cancer Res 2010

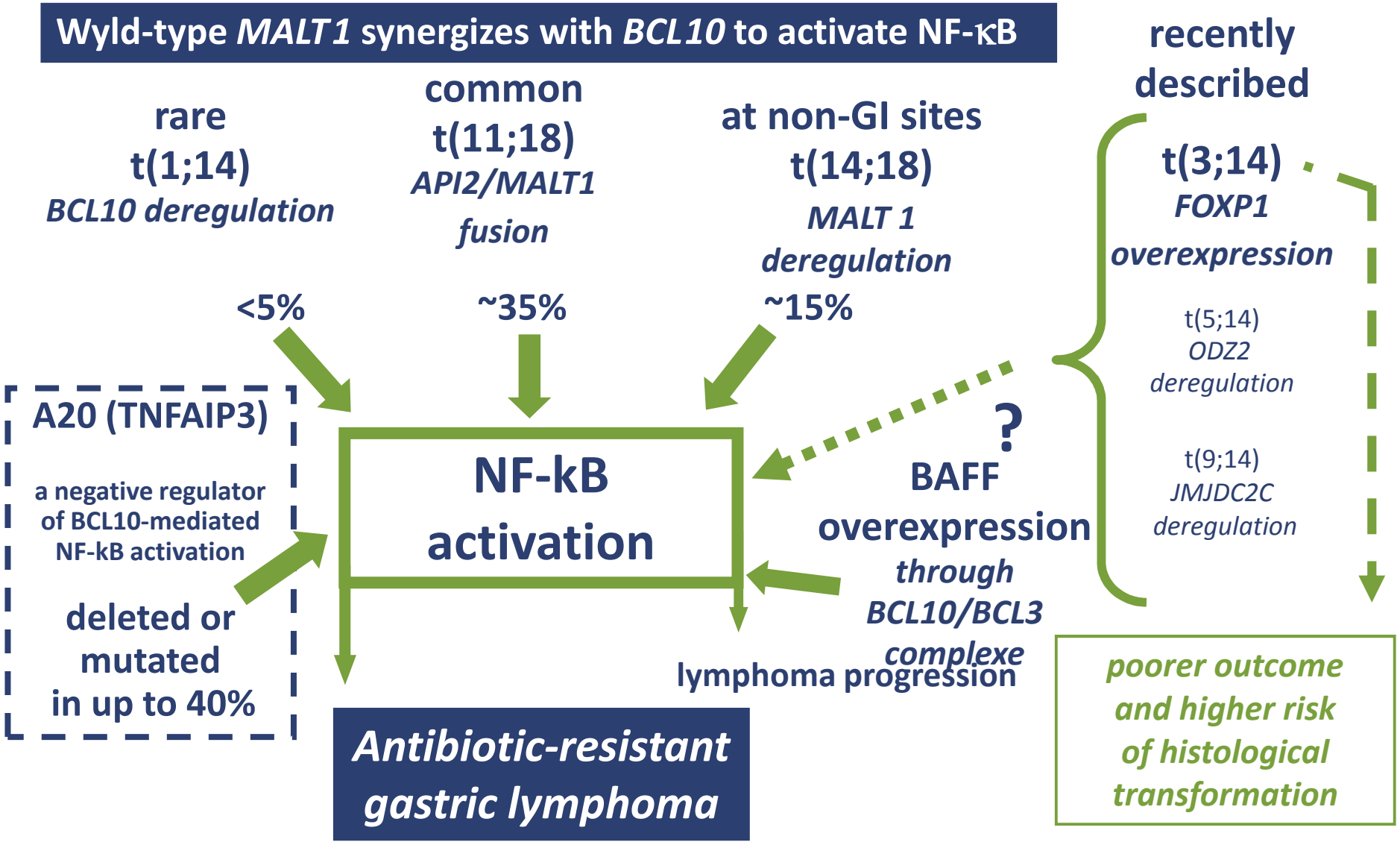
H. pylori and MALT lymphoma: a model of tumor progression



Ferrucci & Zucca, BJH 2007

Different chromosomal translocations

affecting the same signalling pathway in MALT lymphoma



Histological transformation

- The risk of HT is low across all MZL (3-4%)
- The incidence of HT in MZL is lower than that of other indolent B-cell malignancies
- As also observed in FL and CLL, HT in MZL occurs relatively early during the clinical course pointing to putative biological differences at diagnosis in MZL patients destined to transformed

Conconi et al. Ann Oncol, 2016

Controversial issues in the management of MALT lymphoma

- staging procedures
- who does not need antibiotics?
- evaluation of responses
- follow up policies
- treatment of *H. pylori*-negative and non-gastric cases
- second line treatments

Management of gastric MALT lymphoma:

attempts to overcome the controversies

- EGILS Consensus Report
  on gastric MALT lymphoma
  (Ruskone Formestraux et al. Gut 2011)

- ESMO Clinical Practice Guidelines
  (Zucca E et al. Ann Oncol 2013)

- SIE, SIES, GITMO guidelines for the management of non-follicular indolent lymphomas
  (Tarella C et al. Clinical Lymphoma Myeloma Leukemia 2015)

Mandatory procedures in gastric MALT lymphoma

- History and physical exam
  (including lymph node regions, eye and ENT areas, liver and spleen)
- Complete blood counts and basic biochemical studies (including evaluation of renal and liver function, LDH and β2MG, serum protein immunofixation, HIV, HCV and HBV serology)
- EGD with multiple biopsies taken from each region of the stomach, duodenum, gastro-esophageal junction and any abnormal-appearing site
- "If the presence of active H. pylori infection is not demonstrated by histochemistry, it must be ruled out by serology, urea breath test and/or stool antigen test"

ESMO Guidelines
SIE, SIES, GITMO Guidelines

Recommended procedures in gastric MALT lymphoma

- endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration at first local staging procedure
- CT of the chest, abdomen and pelvis.
- bone marrow aspirate and biopsy
- *The value of PET scan is controversial and has uncertain clinical utility*

ESMO Guidelines
SIE, SIES, GITMO Guidelines

Other investigations

- “In addition to routine histology and immunohistochemistry, fluorescence in situ hybridisation studies for detection of **t(11;18)** may be useful for identifying patients who are unlikely to respond to antibiotic therapy”

ESMO Guidelines

- “A molecular genetic analysis of lymphoma tissue for the detection of t(11;18) is recommended to identify the disease that is unlikely to respond to antibiotic therapy”

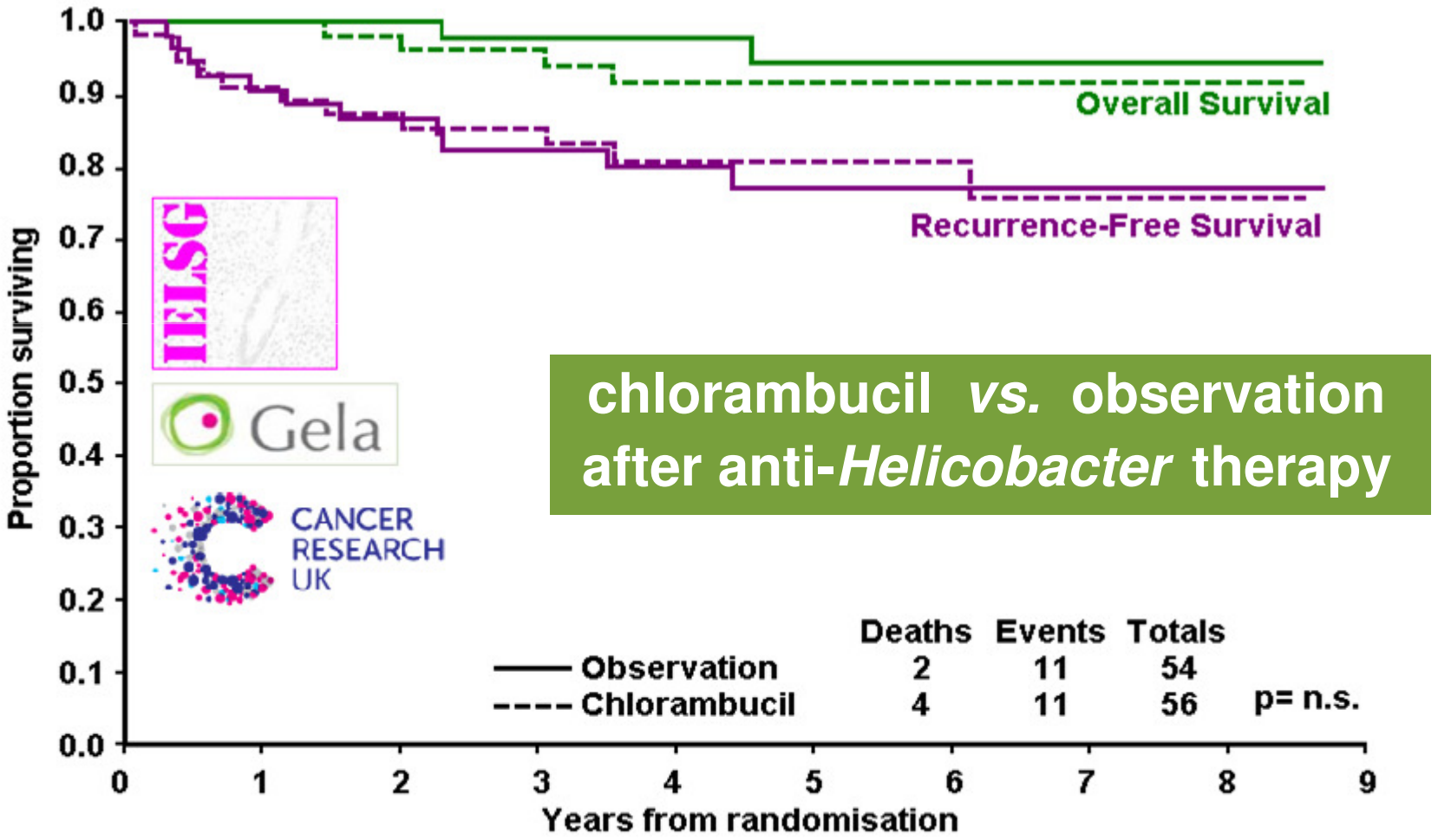
SIE, SIES, GITMO Guidelines

Most gastric MALT lymphomas regress after H. pylori eradication

Reference	n	staging procedure	CR rate (%)	time to CR (mos.)	relapses (n)
Savio, 1996	12	CT+EGD	84	2-4	0
Pinotti, 1997	45	CT+EGD	67	3-18	2
Neubauer, 1997	50	CT±EUS	80	1-9	5
Nobre Leitao, 1998	17	CT+EUS	100	1-12	1
Steinbach, 1999	23	CT±EUS	56	3-45	0
Montalban, 2001	19	CT±EUS	95	2-19	0
Ruskone-Formestraux, 2001	24	CT+EUS	79	2-18	2
Bertoni, 2002		CT+EGD	62	3-24	15
Zullo, 2010 (systematic review)	1408		77	5 (median)	72/994

Different definitions of lymphoma remission in different trials !

LY03 trial of gastric MALT lymphoma



chlorambucil *vs.* observation after anti-*Helicobacter* therapy

Hancock B. Br J Haematol, 2009

Gastric MALT lymphoma therapy: Helicobacter pylori eradication

- "Helicobacter pylori eradication therapy must be given **to all gastric MALT lymphomas**, independently of stage"

- "**Anti-Helicobacter regimens** combining PPI plus clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days are usually highly effective"

- "**The outcome of the eradication** therapy should be checked by a urea breath test (or by a monoclonal stool antigen test) at least 6 weeks after eradication therapy and at least 2 weeks after PPI withdrawal".

ESMO Guidelines
SIE, SIES, GITMO Guidelines

Localised Helicobacter pylori-positive gastric MALT lymphoma therapy

- “Eradication of H. pylori with **antibiotics should be the sole initial therapy** for a localised H. pylori-positive gastric MALT lymphoma [II, A]”.

- “It is reasonable to **wait for at least 12 months** before starting another treatment … [III, B]”.

- **consolidation chemotherapy is not indicated** (quality of evidence moderate; strength of recommendation, strong)

ESMO Guidelines
SIE, SIES, GITMO Guidelines

Why to treat HP-negative patients?

Recommendation

- *H pylori*-negative patients with gastric MALT lymphoma can also undergo anti-*H pylori* treatment.

- False negative diagnostic test
- Other microorganisms involved (*H. heilmannii*)
- Responses in 14 of 72 published cases (19%)

EGILS Consensus Report

Localised Helicobacter pylori-negative gastric MALT lymphoma therapy

- “In H. pylori-negative cases, a regression of the lymphoma after antibiotic treatment is unlikely and the **immediate start of oncological treatments** should be considered, but the administration of an anti-Helicobacter regimen may be worthwhile […]”.

ESMO Guidelines

- “HP-negative patients with localized gastric MALT lymphoma can also be treated with eradication therapy. However, the chance of a response is low, and **close monitoring** of the disease status is advisable during therapy (quality of evidence low, strength of recommendation weak”

SIE, SIES, GITMO Guidelines

The problem of the response definition

Helicobacter pylori-associated chronic gastritis

gastric MALT lymphoma

GELA score for lymphoma response evaluation after *H pylori* eradication

Score	Description	Histologic Features
CR	*Complete Remission*	Normal or empty LP and/or fibrosis with absent or scattered plasma cells and lymphoid cells in the LP; no LEL
pMRD	*Probable Minimal Residual Disease*	Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM; no LEL
rRD	*Responding Residual Disease*	Focal empty LP and/or fibrosis; dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP. Focal LEL or absent
NC	*No Change*	Dense, diffuse or nodular lymphoid infiltrate with LEL (LEL ‘‘may be absent’’)

LP=lamina propria; **LEL**= lymphoepithelial lesions; **MM**=muscularis mucosa; **SM**=submucosa

Copie-Bergman et al, Gut 2003; Copie-Bergman et al, Br J Haematol 2012

Long-term surveys after H. pylori eradication

- not only patients with molecular residual disease may remain stable but also those with minimal histological MALT lymphoma residuals

- A watch and wait policy seems safe in patients with minimal hRD or histological-only local relapse

Wundisch et al. JCO, 2005

Fischbach et al. Gut, 2007

Stathis et al. Ann Oncol , 2009

Nakamura et al. Gut 2012

EGILS recommendations for restaging and follow-up

- CR to be confirmed in 2 subsequent investigations
- PR and SD and relapses to be clinically managed on an individual basis:
  - if no signs of endoscopic or clinical progression are evident, a ‘watch and wait’ strategy can be adopted
  - patients with distant dissemination and/or gross endoscopic tumour should receive oncological treatment.

EGILS Consensus Report

How to follow up after antibiotics?

- Clear evidence of EUS utility as a staging procedure but less strong evidence in follow-up
- Breath test ±EGD at ~3 mos. after antibiotics then EGD with biopsies q 6 ms x 2 years, then q 12 mos
- Molecular studies not needed

EGILS Consensus Report

How long to follow up after antibiotics?

Life-long?

Patients with gastric MALT lymphoma have a 6 times higher risk for gastric adenocarcinoma in comparison with the general population and the risk is highest in patients younger than 60

Capelle et al . Eur J Cancer, 2008

Gastric MALT lymphomas failing anti-*HP* therapy or *HP*-negative

Radiotherapy in gastric MALT lymphoma

Author	n	RT dose (Gy)	FFP
Schechter, 1998	17	28-43	100% at 2 yr
Tsang, 2001	9	20-30	100% at 5 yr
Yahalom, 2002	51	30 median	89% at 4 yr
Hitchcock, 2002	9	34 median	78% (100% local)

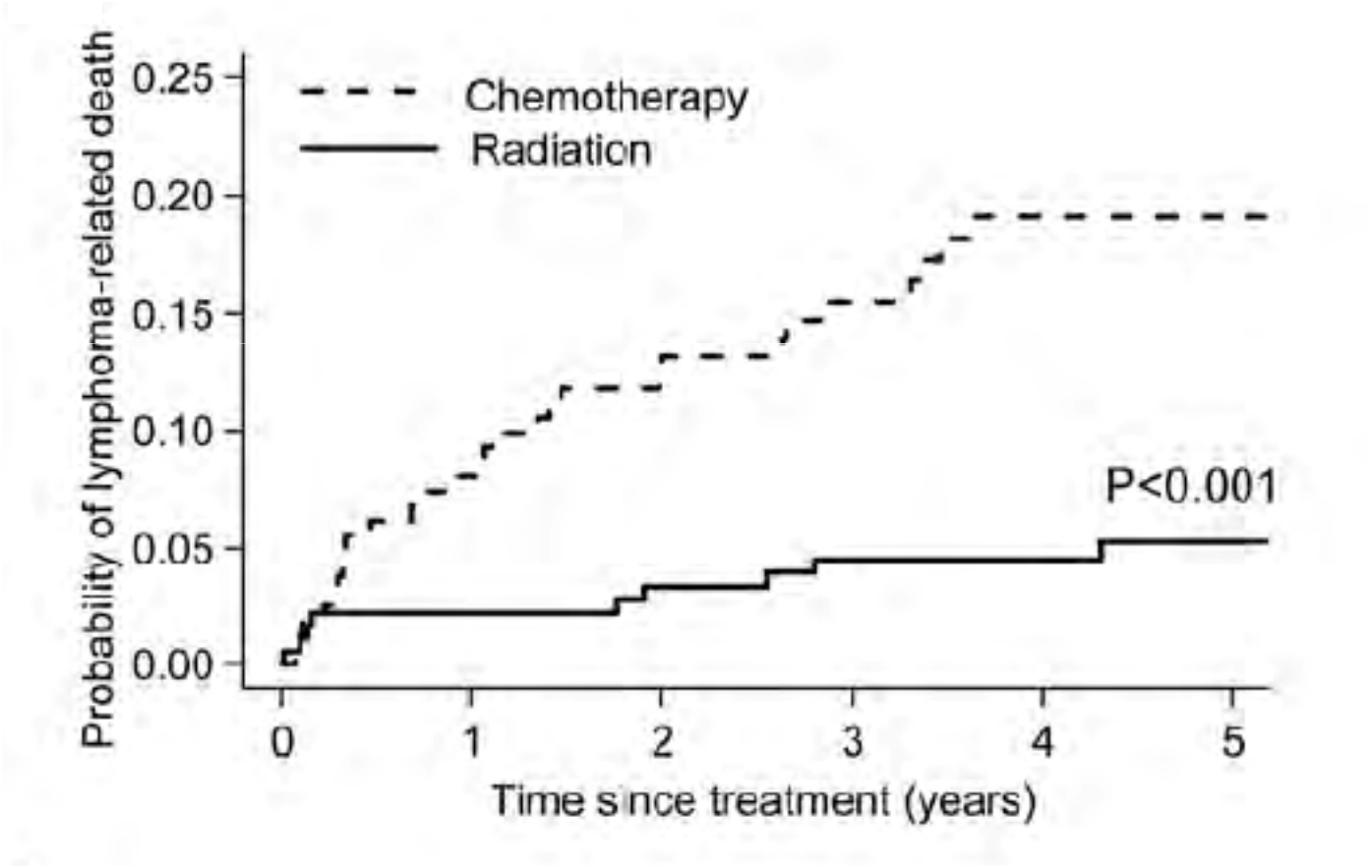
- **optimal RT volume, dose and technique?**
- **does this really translate to cure?**
- **in a very indolent condition, is the potential toxicity acceptable?**
- **long term safety? (malignancy, gastric and renal toxicity)**

RT Toxicity can be reduced using modern 3D techniques and minimizing the RT dose to the kidneys and the liver

excellent local control in non-gastric sites , too!

Comparative outcomes of oncologic therapy in gastric MALT lymphoma

The SEER-Medicare experience

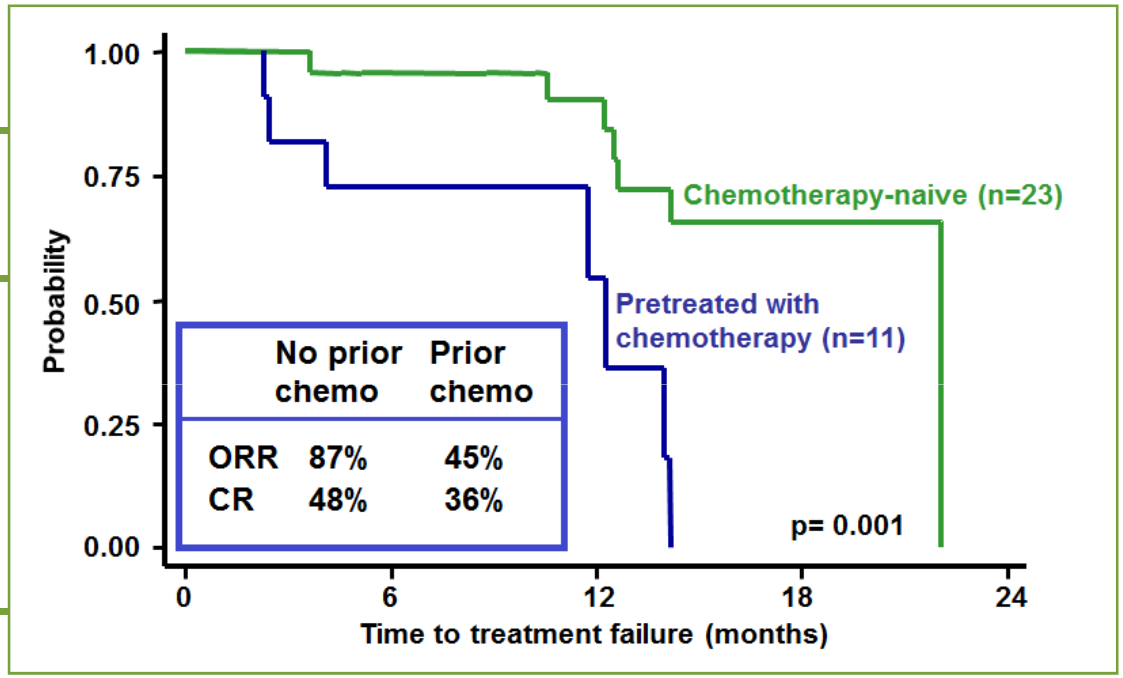


Cumulative incidence of lymphoma related death by arm of treatment in stage I disease

Olszewski AJ. Ann Oncol 2013

Rituximab activity in MALT lymphoma

response	*n*	*%*
ORR	**25**	**73**
SD	**6**	**18**
PD	**3**	**9**



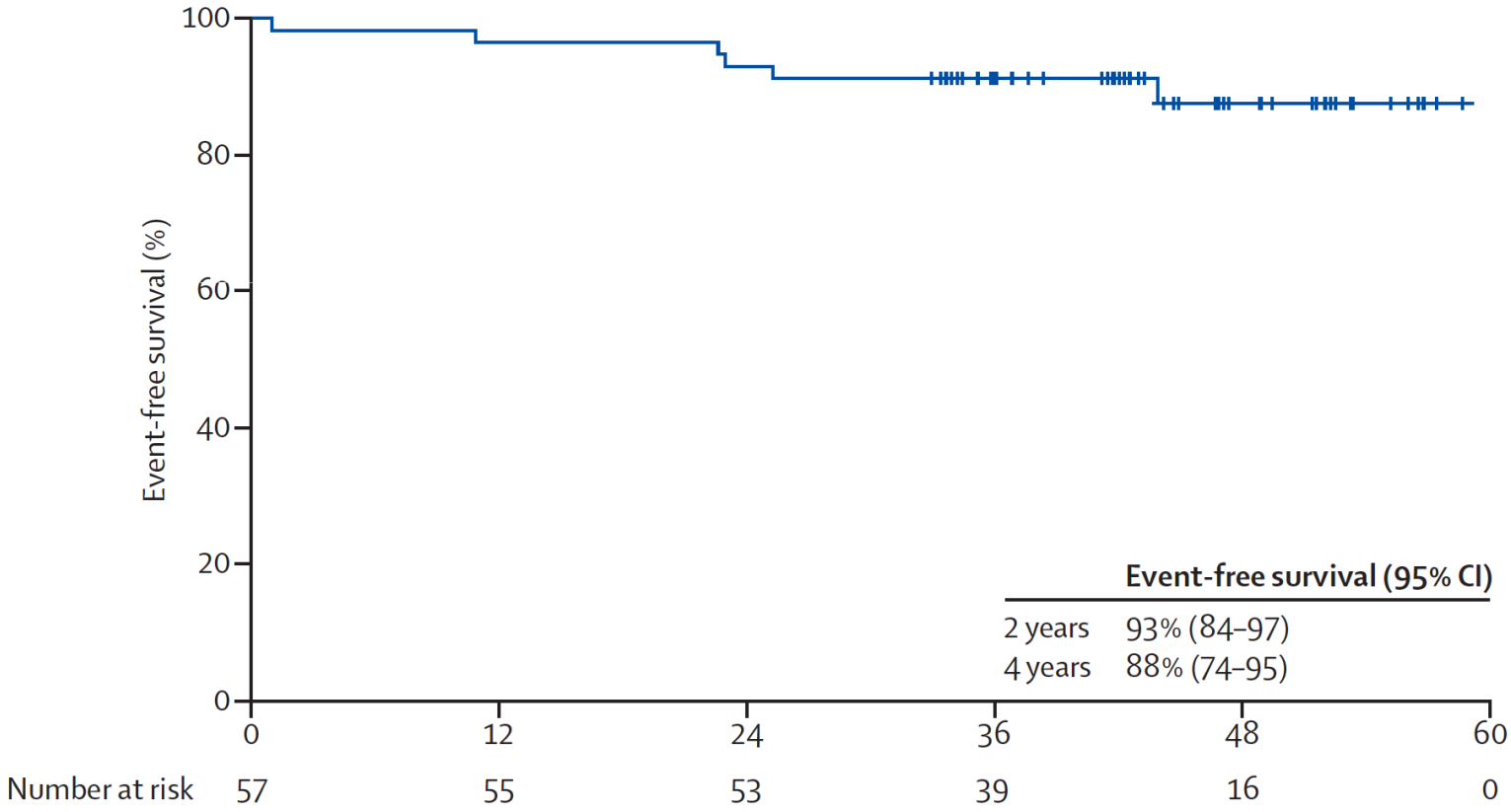
34 pts, 11 with prior chemotherapy,
15 gastric, 20 stage IV

Conconi et al. Blood 2003

Chemotherapy in MALT lymphomas

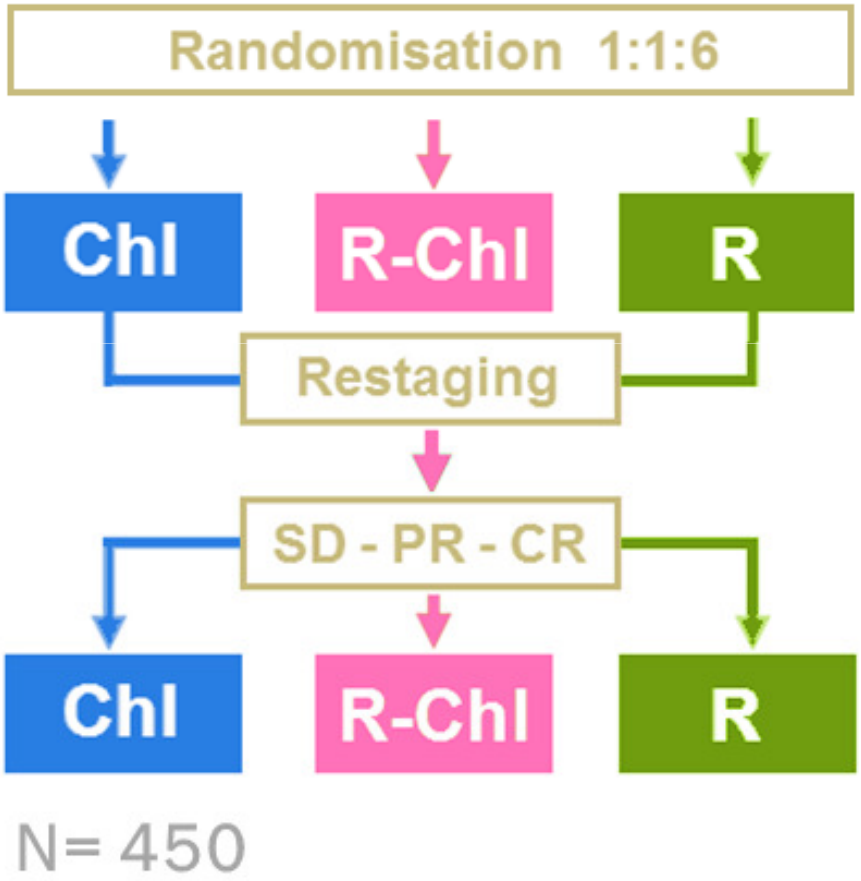
Treatment	Nr. pts	ORR	CR	Author
Alkylators	24 pts	100%	75%	Hammel P. J Clin Oncol 1995
R-CHOP/CNOP	7 pts	100%	100%	Raderer M. Ann Oncol 2002
Cladribine	26 pts	100%	84%	Jäger G. J Clin Oncol 2002
Oxaliplatin	16 pts	93%	56%	Raderer M. J Clin Oncol 2005
Fluda-Mito	20 pts	100%	100%	Zinzani PL. Cancer 2004
CLB-Mito-Pred	15 pts	93%	53%	Wohrer S. Ann Oncol 2003
R-cladribine	39 pts	81%	58%	Troch M. Haematologica 2013
R-bendamustine	60 pts	98%	98%	Salar A. Lancet Haematol 2014

Response-adapted 1st line R-Bendamustine in MALT



Salar et al, Lancet Oncol, 2014

IELSG-19 trial study design



Strata

- **IPI** (lo/lo-int *vs.* int-hi/hi)
- **nodal involvement** (yes *vs.* no)
- **site** (gastric *vs.*non-gastric)
- **prior local treatment** (yes *vs.* no)

Main Endpoint, EFS

Zucca E, Conconi A et al, Submitted to J Clin Oncol

IELSG-19: response to treatment

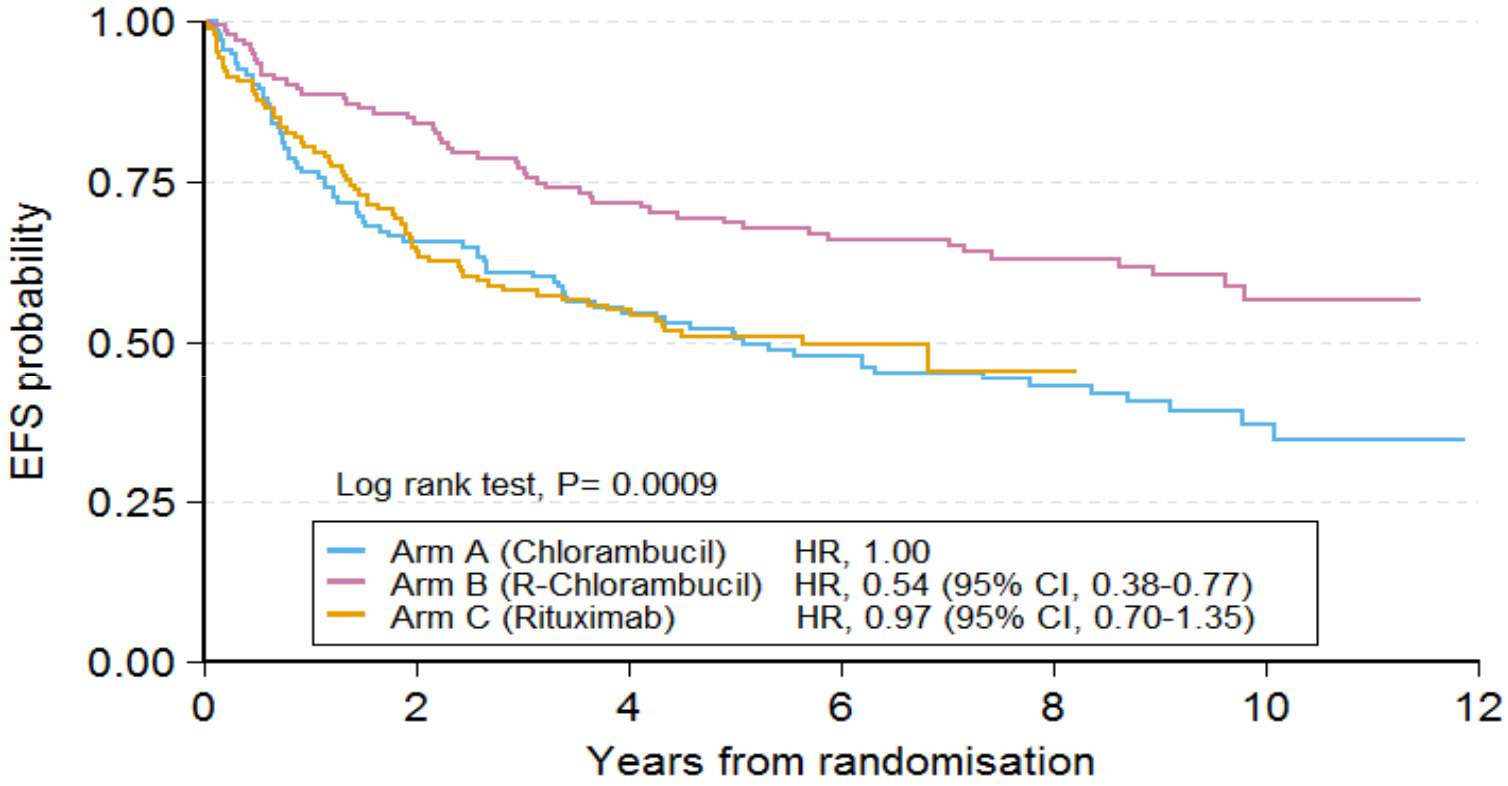
response	All	CLB	R-CLB	R
ORR	345 (86%)	112 (85.5%)	125 (94.7%)	108 (78.3%)
CR	264 (65.8%)	83 (63.4%)	104 (78.8%)	77 (55.8%)
PR	81 (20 2%)	29 (22.1%)	21 (15.9%)	31 (22.5%)
SD	28 (7%)	11 (8.4%)	1 (0.8%)	16 (11.6%)
PD	23 (5.7%)	7 (5.3%)	4 (3.0%)	12 (8.7%)
NA	5 (1.3%)	1 (0.8%)	2 (1.5%)	2 (1.5%)

P <0·001 for both CR and ORR

Zucca E, Conconi A et al, Submitted to J Clin Oncol

IELSG 19

IELSG-19: event-free survival



Number 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

Zucca E, Conconi A et al, Submitted to J Clin Oncol

A MALT lymphoma-specific prognostic index generated from the dataset of the IELSG-19 trial

Generation of a MALT lymphoma-specific prognostic model

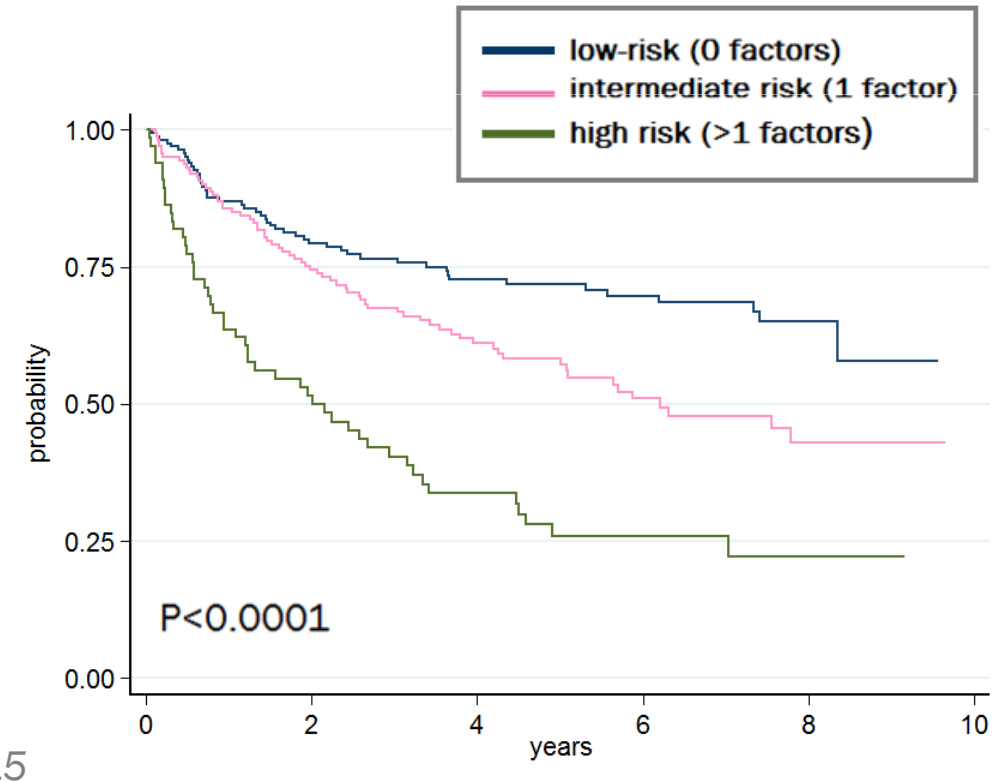
Cox regression

Backward selection using a p<0.05 cut-off

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

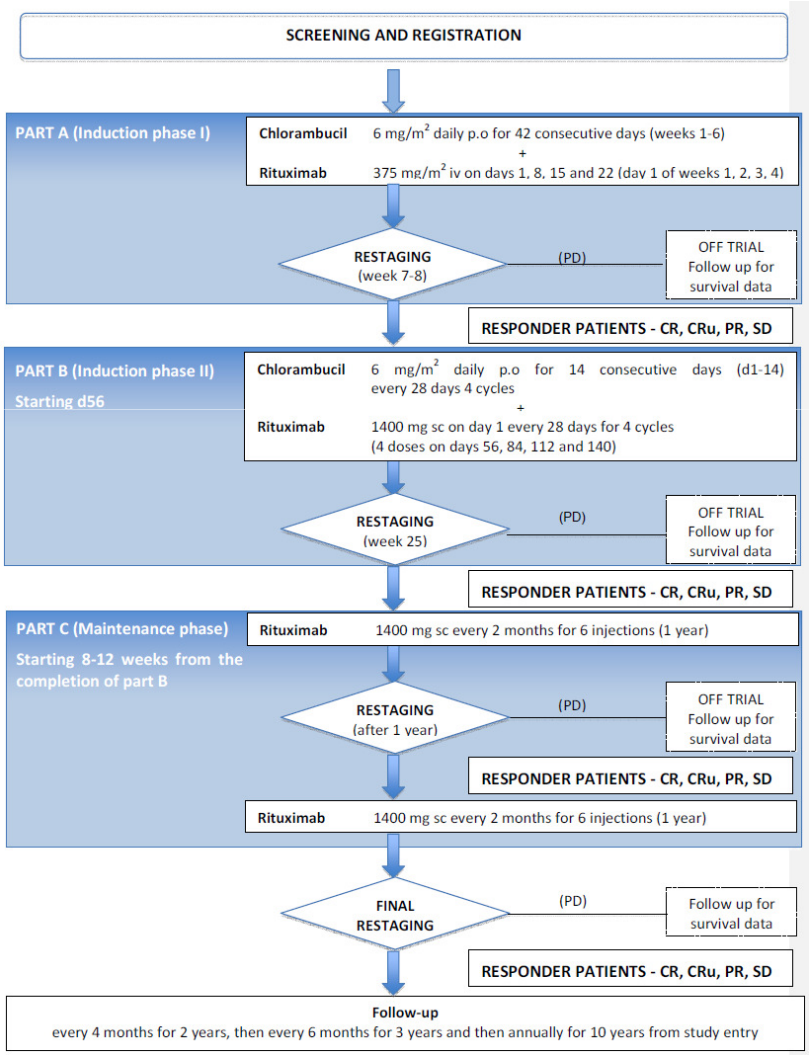
LR chi2(3)= 37.47 Log likelihood = -912.25 Prob > chi2 = 0.0000

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



C. Thieblemont et al, 13-ICML, Lugano, 2015

Any role for R-maintenance? IELSG-38: study design



- Single arm phase II study
- R-Chlorambucil for 6 mos followed by 2-yrs maintenance with Rsc
- Accrual just completed with 112 newly diagnosed MALT pts in need of systemic treatment

Treatment of patients who failed antibiotics and nongastric cases

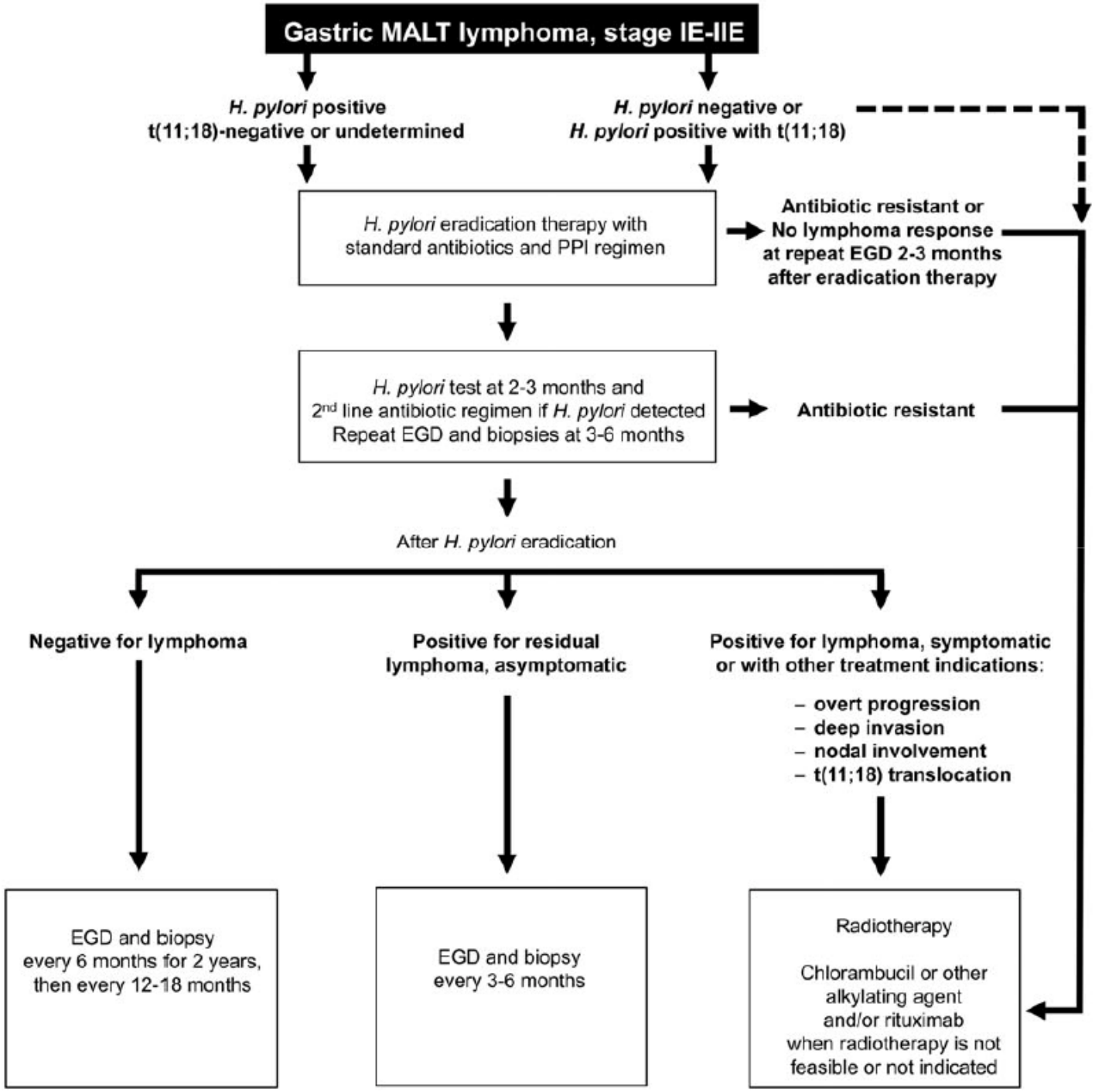
- Radiotherapy might be the preferred option for localised stage. (24–30 Gy radiation to the stomach and perigastric nodes given in 3 to 4 weeks).
- Chemotherapy and/or immunotherapy are effective in patients with MALT lymphoma of all stages.
- Surgery restricted to the treatment of complications

EGILS Consensus Report
ESMO Guidelines Consensus Conference
SIE, SIES, GITMO Guidelines

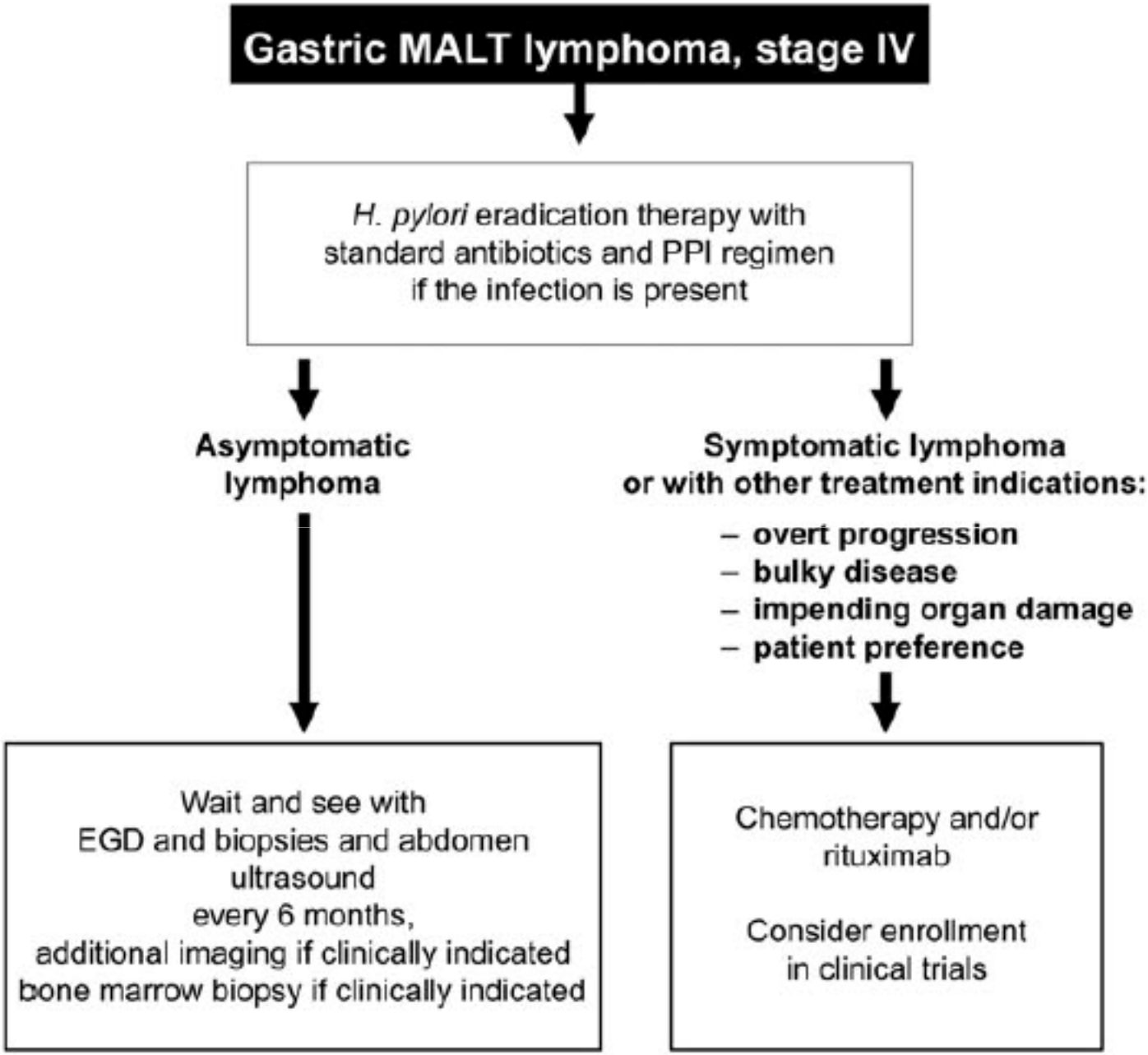
Phase II studies in MALT lymphoma

Agent	pts	ORR	CR	Author
Bortezomib	29	48%	31%	*Conconi et al. Ann Oncol 2011*
Everolimus	24	25%	4%	*Conconi et al. Br. J Haematol 2014*
Lenalidomide	16	69%	37%	*Kiesewetter et al. Haematologica 2013*
R-Lenalidomide	27	89%	67%	*Fowler et al, Lancet Oncol 2014*
R-Lenalidomide	46	80%	54%	*Kiesewetter et al. Blood 2016*
Ibrutinib	63	51%	10%	*Noy et al. ASH 2016*

Localized Gastric MALT lymphoma: treatment algorithm (1)



Advanced stage Gastric MALT lymphoma: treatment algorithm (2)



Take-home messages

- antigen-driven process associated with chronic infections
- NF-kB pathway activation
- indolent course with limited tendency to distant spreading and histological transformation,excellent prognosis
- *H.pylori* eradication is standard front-line therapy for gastric MZL
- no treatment should be initiated after antibiotics in case of transient local histological relapses (they tend to be self-limiting)
- best treatment not fully defined for HP-negative cases, antibiotic failures and nongastric cases