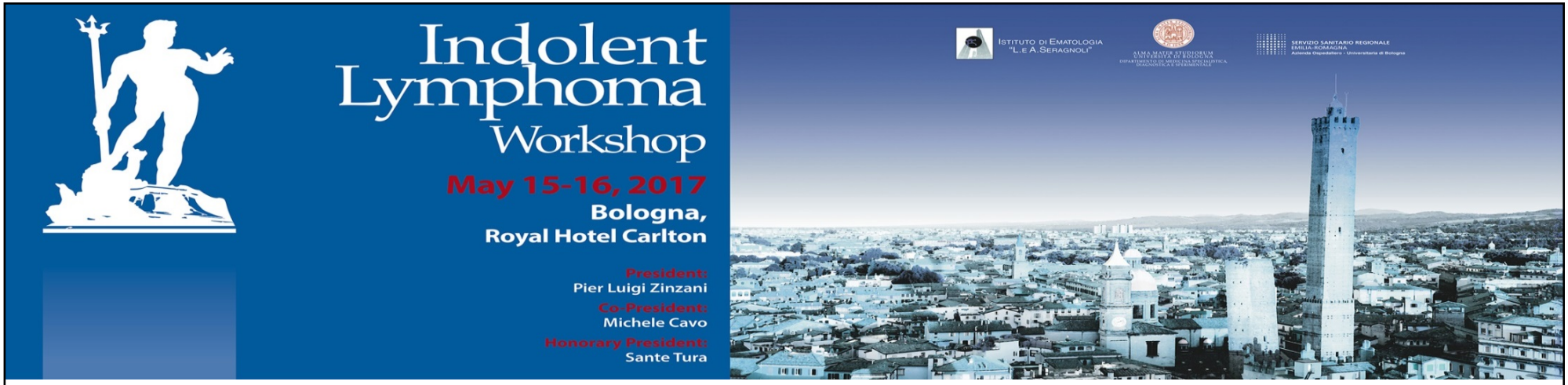

Treatment:
Gastric MALT lymphoma

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IOSI

ISTITUTO ONCOLOGICO DELLA SVIZZERA ITALIANA • ONCOLOGY INSTITUTE OF SOUTHERN SWITZERLAND

Gastric MALT lymphoma

- MALT lymphomas: approximately 7% of all NHLs
- At least 1/3 present as a primary gastric lymphoma
- 2/3 of cases associated with H. pylori infection

ESMO Clinical Practice Guidelines, 2013

Open questions in the management of gastric MALT lymphoma

- staging procedures
- H. *pylori* eradication to all patients?
- second line treatments

Open questions in the management of gastric MALT lymphoma

- **staging procedures**
- H. *pylori* eradication to all patients?
- second line treatments

Mandatory staging procedures in MALT lymphoma at any site

- History and physical exam
  (including lymph node regions, eye and ENT areas, liver and spleen)
- Complete blood counts and basic biochemical studies
  (including renal and liver function, LDH and β2MG, serum IFE, HIV, HCV and HBV serology)
- CT of the chest, abdomen and pelvis.
- bone marrow aspirate and biopsy recommended
- *The value of PET is controversial and has uncertain clinical utility*

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
ESMO Clinical Practice Guidelines

ESMO Consensus Conference, Ann Oncol 2013

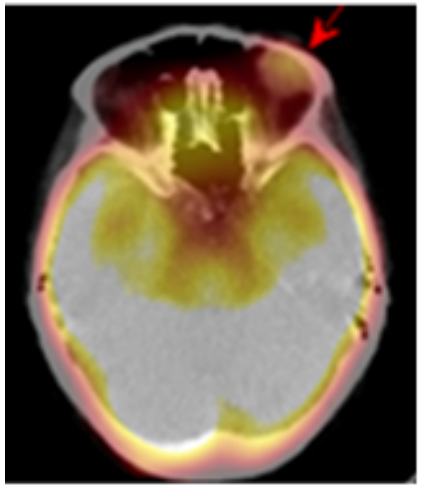
Recommended procedures in gastric MALT lymphoma

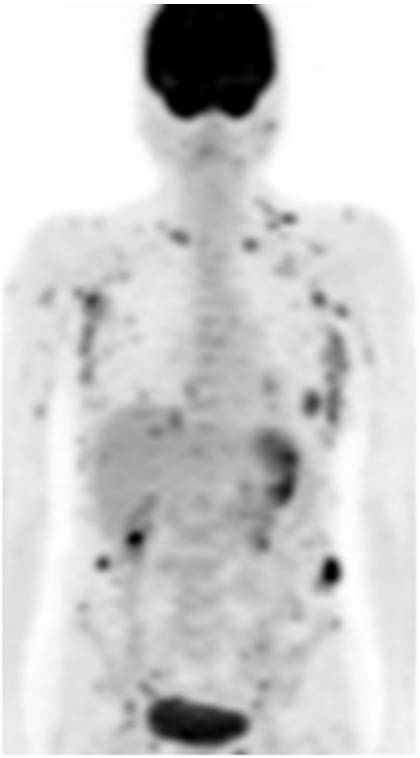
- EGD with multiple biopsies
- histochemical examination for *H. pylori* and serology studies if histology is negative
- endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration
- *optional*: FISH for the t(11;18) translocation

EGILS Consensus Report, 2011
ESMO Clinical Practice Guidelines, 2013

Staging of MALT Lymphoma

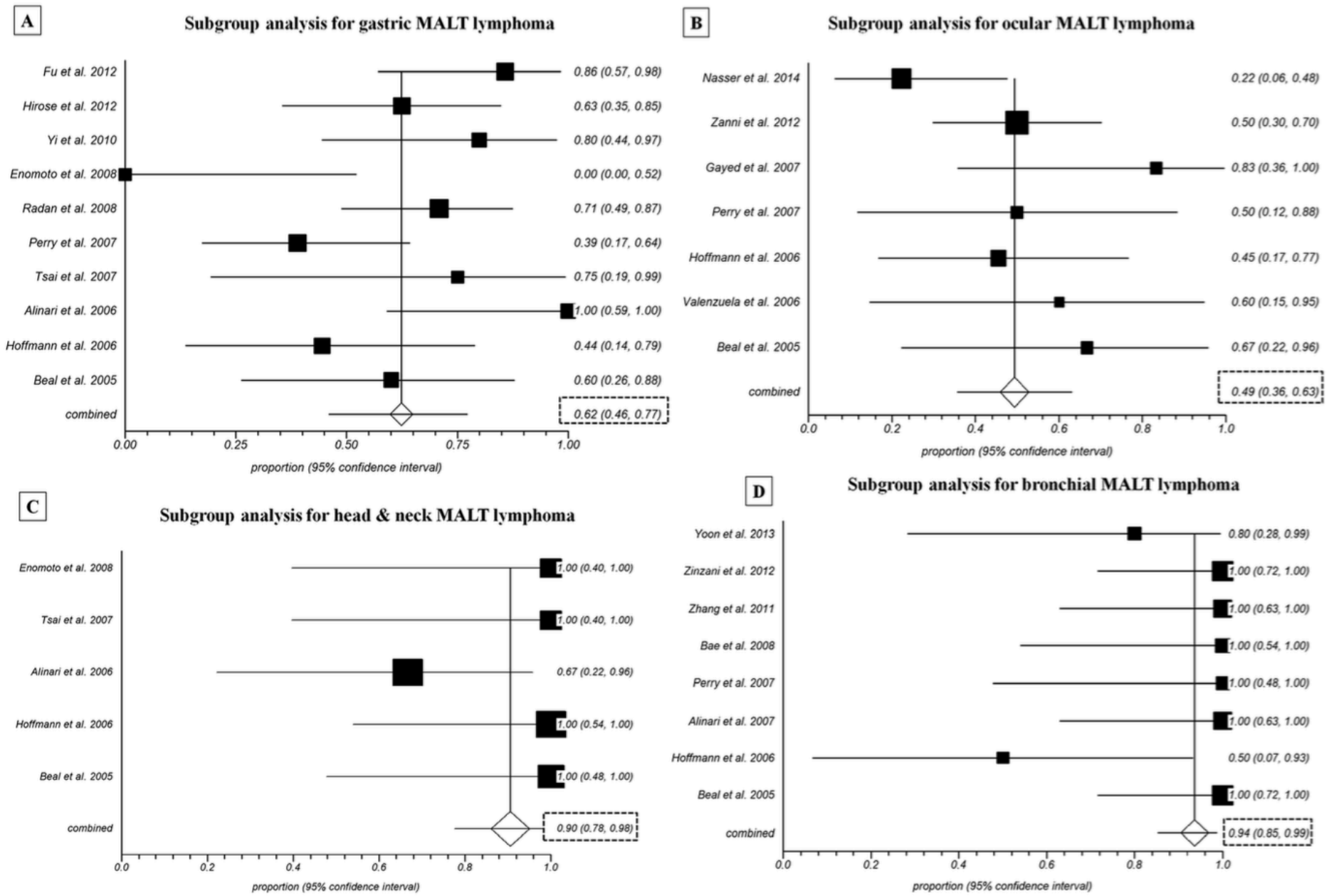
- The value of PET is controversial and has uncertain clinical utility
- multifocal disease in ≥25% of cases
- variable FDG-avidity (higher in non-gastric lesions!)
- pooled PET/CT detection rate, 71% (95% CI: 61-80%) in a literature meta-analysis





Treglia et al. Hematol Oncol. 2015

Lower FDG-avidity in gastric & OA lesions



Treglia et al. Hematol Oncol. 2015 Sep;33(3):113-24

Open questions in the management of gastric MALT lymphoma

- staging procedures
- **H. *pylori* eradication to all patients?**
- second line treatments

Most gastric MALT lymphomas regress after H. *pylori* eradication

Reference	No. of Patients	Complete Remission (CR) Rate	Time to CR (Months)	No. of Reported Relapses
Savio, 1996	12	84%	2-4	0
Pinotti, 1997	45	67%	3-18	2
Neubauer, 1997	50	80%	1-9	5
Nobre Leitao, 1998	17	100%	1-12	1
Steinbach, 1999	23	56%	3-45	0
Montalban, 2001	19	95%	2-19	0
Ruskone-Formestraux, 2001	24	79%	2-18	2
Hancock, 2009	231	46%	3-24	17

Bertoni & Zucca, Lymphomas: Essentials for Clinicians 2015: 55-60

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

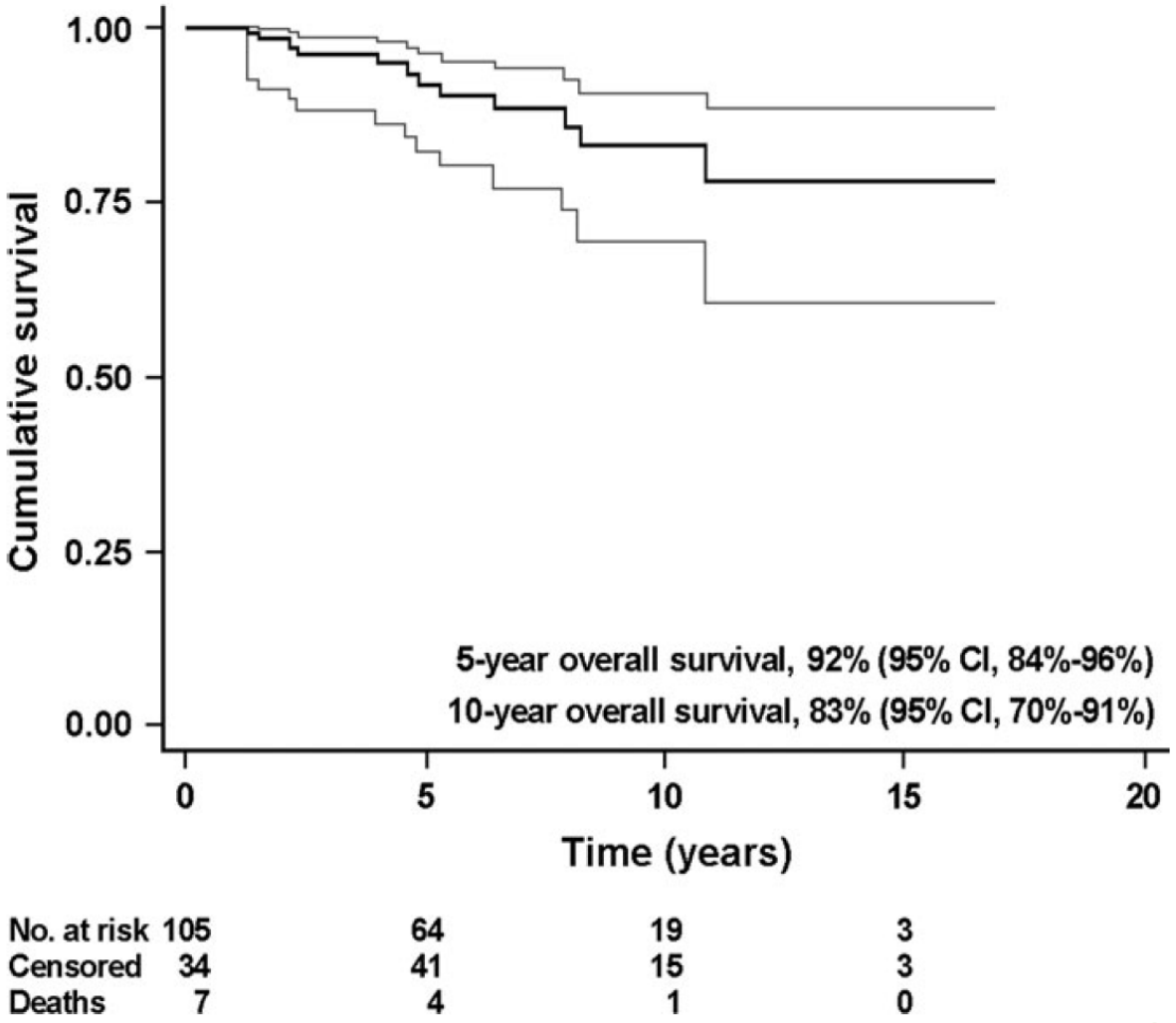
Copie-Bergman et al, Gut 2003; ***Copie-Bergman et al, Br J Haematol 2012***

Endoscopic and histological remission does not mean "cure"

- 54 patients with monoclonality at diagnosis
- 42 (77%) histologic remission
  - 56% molecular remission (by PCR)
  - 44% sustained molecular remission (median f-up, 2 years)
  - 6 (14%) histologic relapses (4/6 in the presence of molecular disease)
- clinical and prognostic relevance of molecular remission still to be ascertained

Bertoni et al. Blood 2002

Long-term outcome after H. pylori eradication (IOSI and Varese series)



- N=105, stage IE
- f-up, 76 mos
- Remission rate, 76%
- Long-term clinical control in most cases:
  - 43% of responders had histological score fluctuations
  - 57% had stable MRD
  - 5-year OS is 92%.

A. Stathis et al. Ann Oncol , 2009

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

HP eradication is the standard initial treatment for localized disease

Recommendation

- PPI+clarithromycin-based triple therapy with either amoxicillin or metronidazole is the first choice for *H pylori* eradication. In case of failure, bismuth-based quadruple therapy is recommended.
- The outcome of *H pylori* eradication therapy should be checked by urea breath test at least 6 weeks after eradication therapy and at least 2 weeks after withdrawal of PPI medication.

EGILS Consensus Report, 2011
ESMO Clinical Practice Guidelines, 2013

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

HP eradication is the standard initial treatment for localized disease

- H. pylori eradication therapy must be given to all gastric MALT lymphomas, independently of stage
- Responses may require up to 12 months or more
- HP-negative patients with gastric MALT lymphoma may also receive anti-H pylori treatment
- Lymphomas with t(11;18) and those with lymph node involvement are unlikely to regress after HP eradication

EGILS Consensus Report, 2011
ESMO Clinical Practice Guidelines, 2013

Open questions in the management of gastric MALT lymphoma

- staging procedures
- H. *pylori* eradication to all patients?
- **second line treatments**

Same outcome after different treatments in stage IE gastric MALT lymphoma

Treatment	*N°of pts*	CR rate	5-years OS (95% CI)
Antibiotics	45	67%	94% (65-99)
Local treatment[a]	14	100%	92% (57-99)
Chemotherapy	8	50%	75% (32-93)
Combined modality[b]	5	100%	80% (20-97)
Total	72	74%	89% (76-96)

a surgery ± RT
b surgery+ adjuvant chemotherapy

Pinotti et al, Leuk Lymphoma 1997

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

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Radiotherapy Results in MALT Lymphoma

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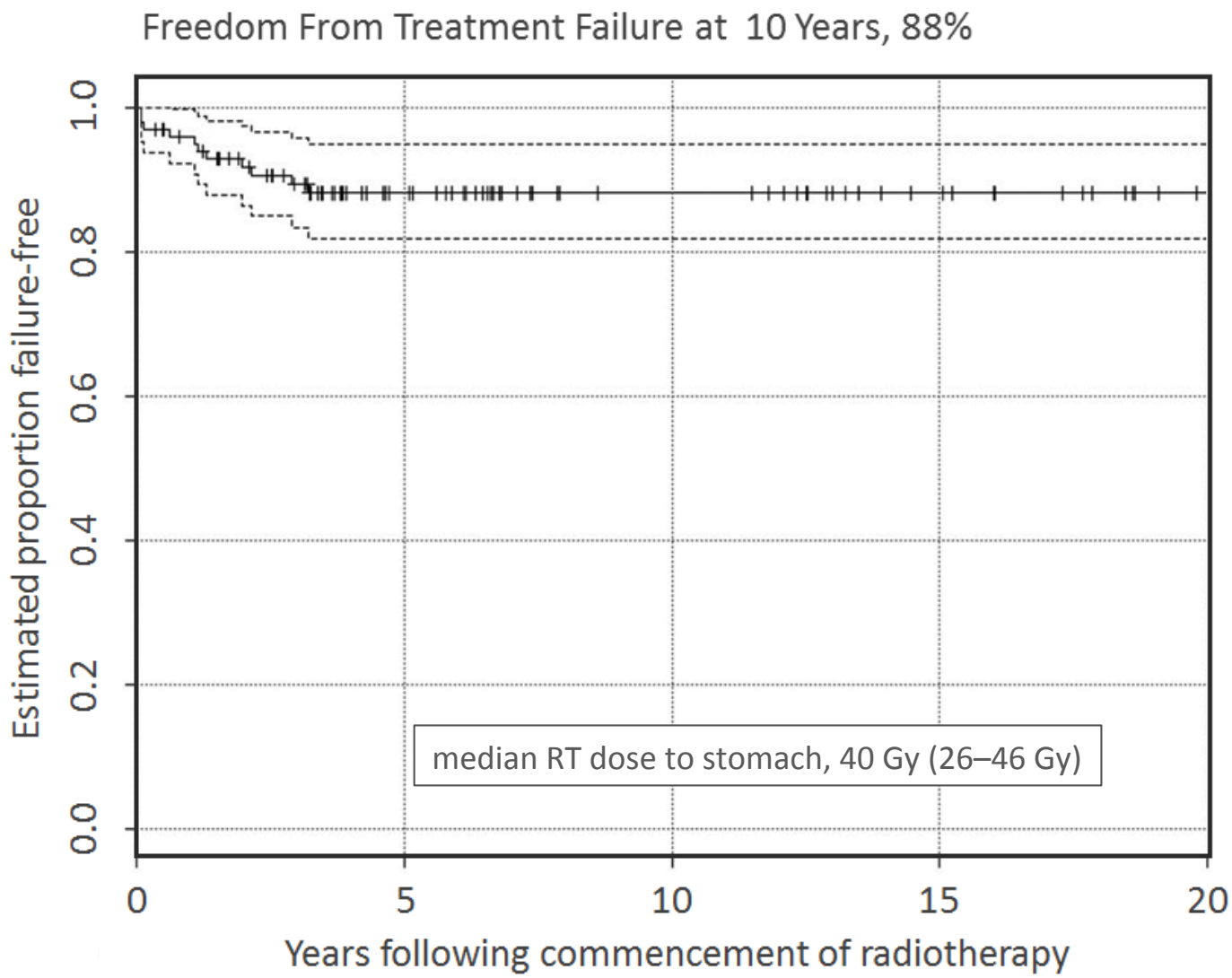
- optimal RT volume, dose and technique?
- does this really translate to cure?
- in a very indolent condition, is the potential toxicity acceptable?
- long term safety? (malignancy, gastric and renal toxicity)

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

Long-term outcome of gastric MALT lymphoma after RT: The retrospective multi-centre IELSG-22 study



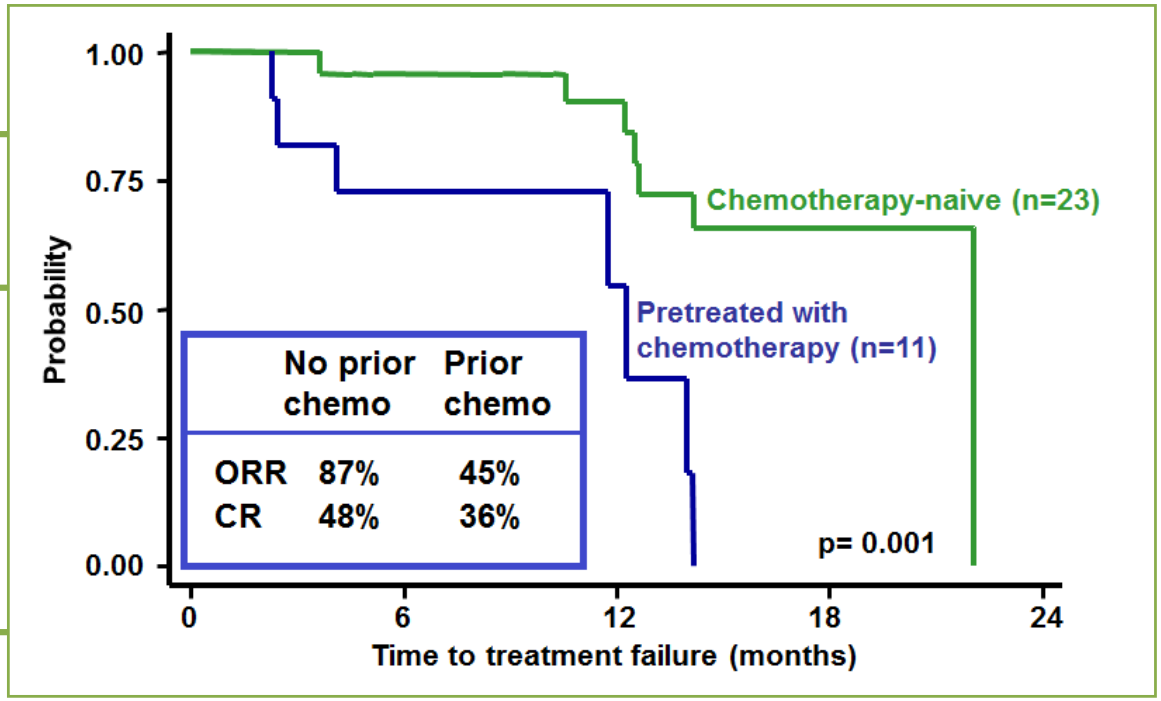
Wirth A et al. Ann Oncol 2013

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
R-cladribine	39 pts	81%	58%	Troch M. Haematologica 2013

Rituximab activity in MALT lymphoma

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

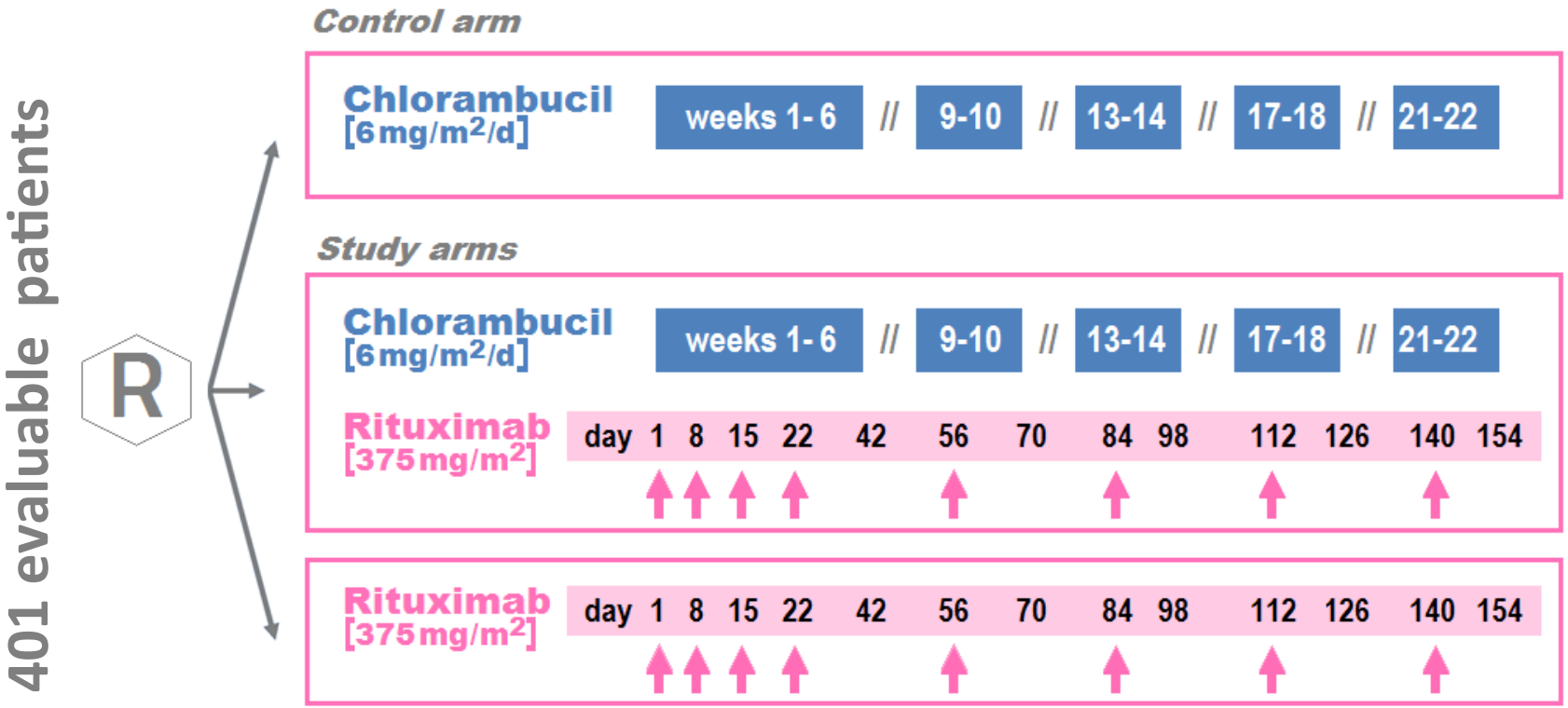


34 pts, 11 with prior chemotherapy,
15 gastric, 20 stage IV

IELSG phase II study, Conconi et al. Blood 2003

IELSG-19 Randomised Study

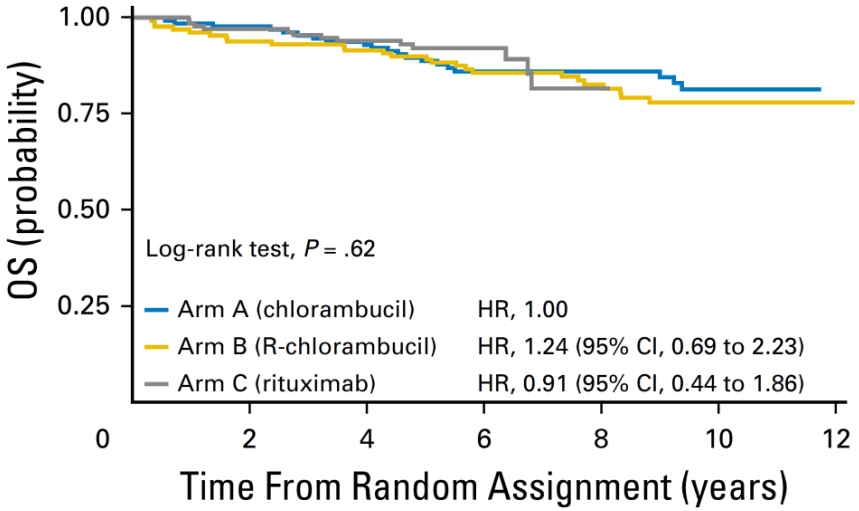
Treatment Schedule



E. Zucca E et al. *J Clin Oncol* 2017 Epub

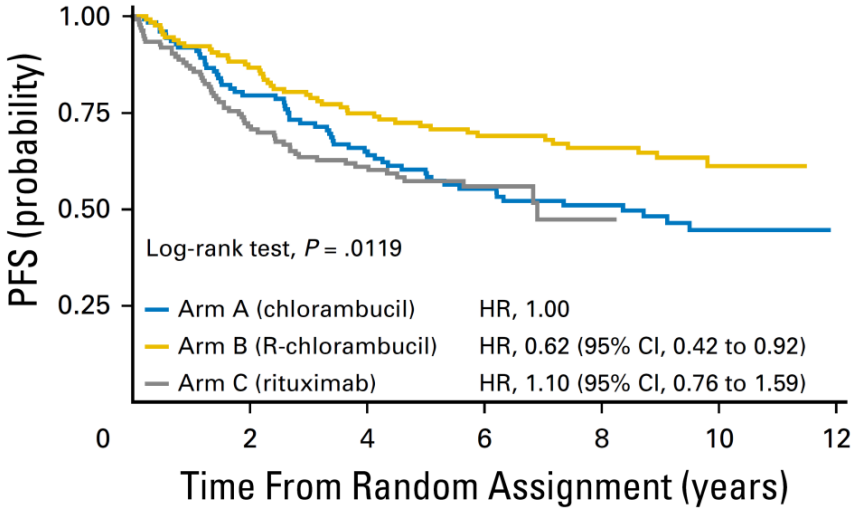
IELSG-19 Randomised Study

Final Results



No. at risk:

Arm A	131	126	116	92	79	37	0
Arm B	132	121	118	95	77	35	1
Arm C	138	130	118	50	3	0	0



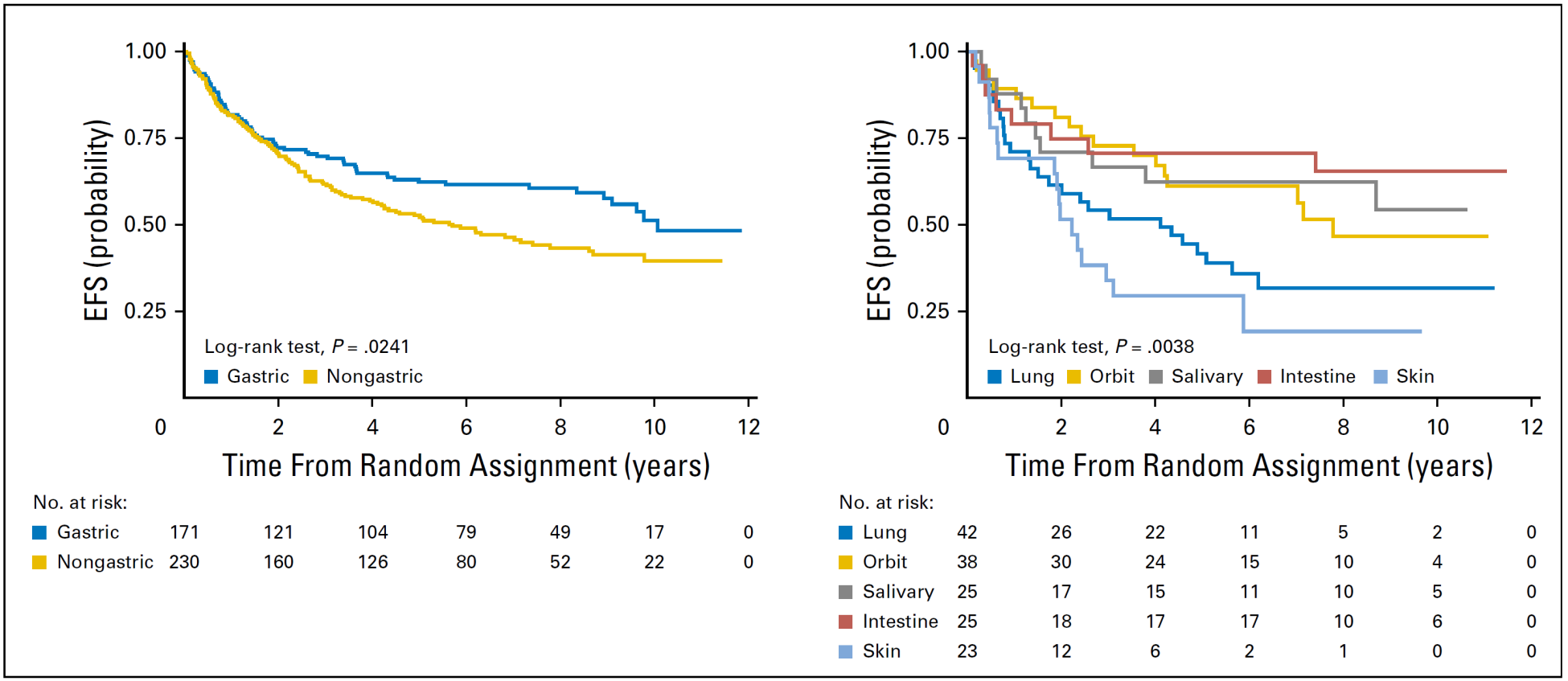
No. at risk:

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

E. Zucca E et al. *J Clin Oncol* 2017 Epub

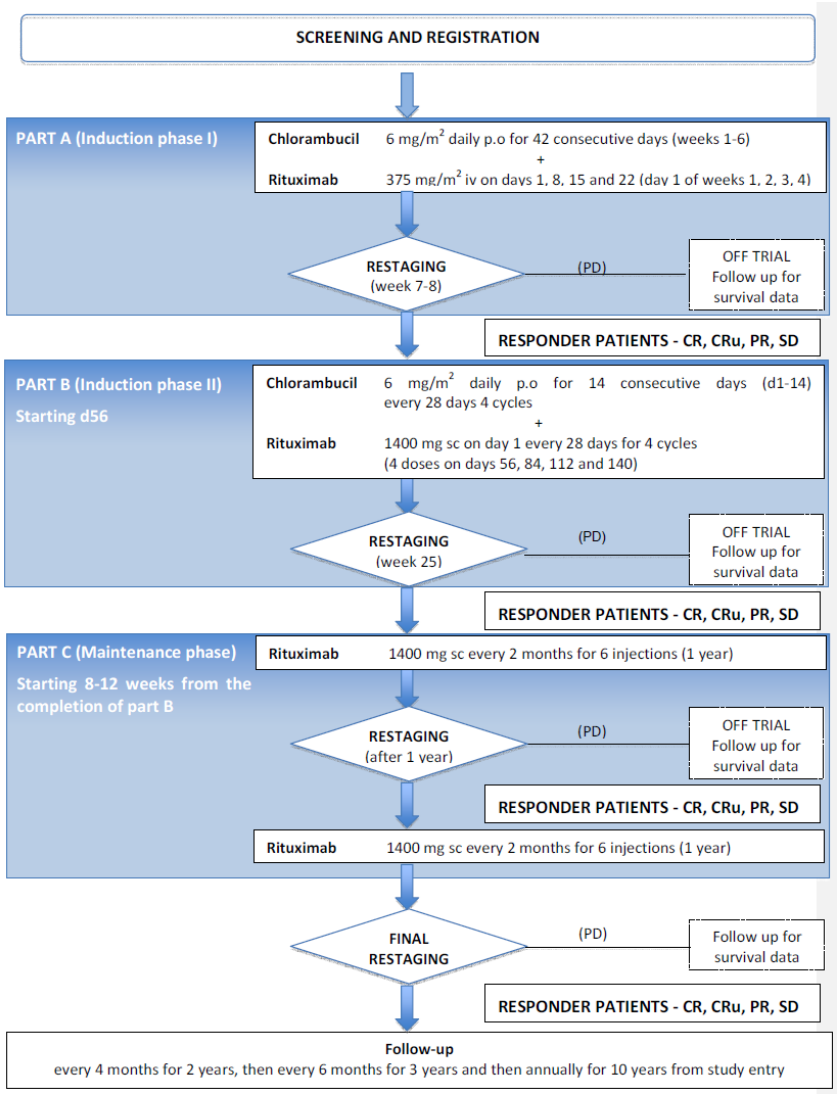
IELSG-19 Randomised Study

Outcome by Primary Site



E. Zucca E et al. *J Clin Oncol* 2017 Epub

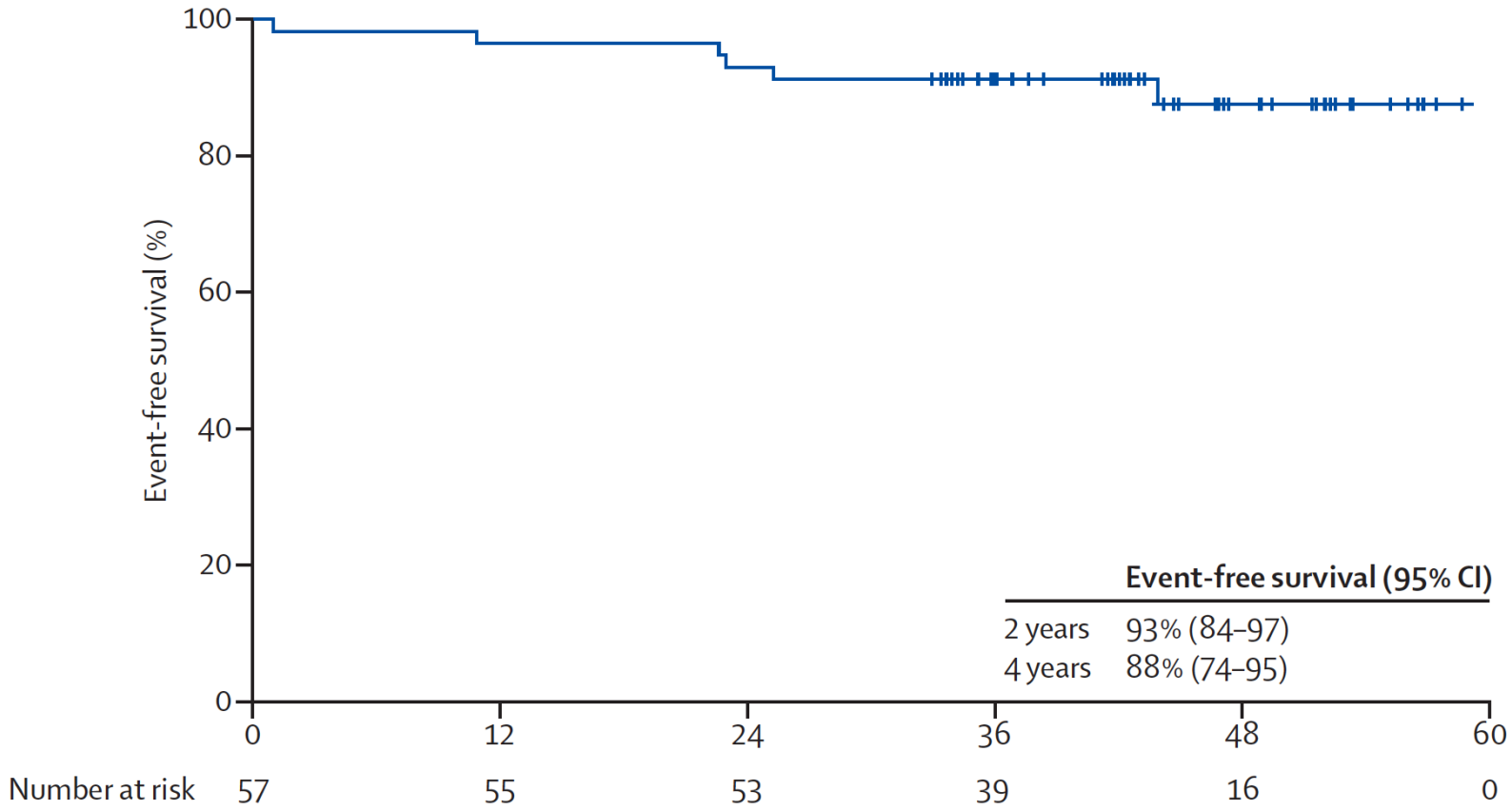
Any role for R-maintenance? IELSG-38: study design



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

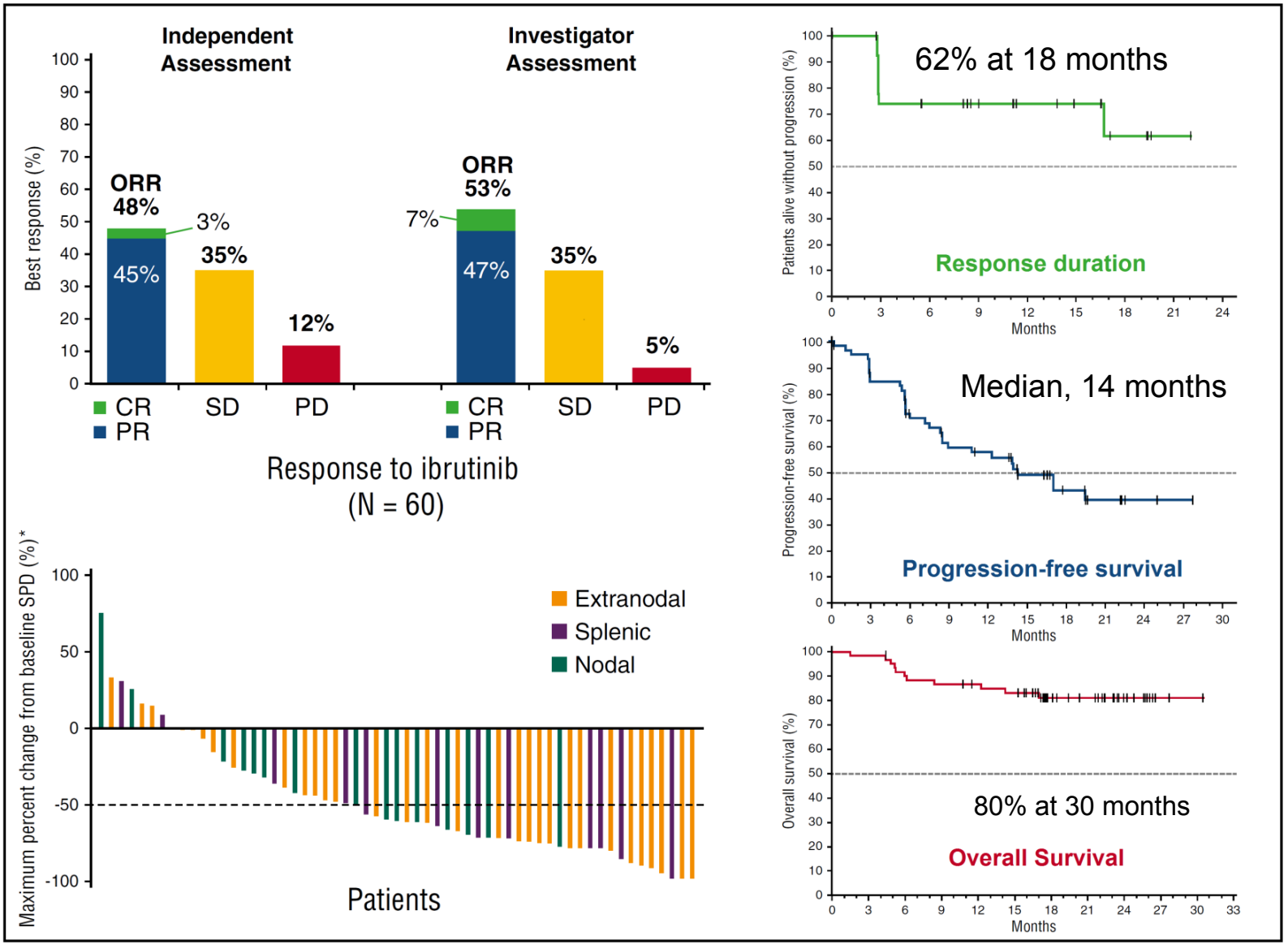
Response-adapted 1st line R-Benda

(GELTAMO MZL phase-2 trial)



A. Salar et al, Lancet Oncol, 2014

Targeting BTK with ibrutinib in r/r MZL



Noy A et al. *Blood* 2017

Phase II studies in MALT lymphoma

	ORR	Study
Everolimus	20%	IELSG
Bortezomib	48%	IELSG
Lenalidomide	61%	Vienna
Rituximab	45%	IELSG
Idelalisib	47%	Gilead
Ibrutinib	51%	J&J
R-Lenalidomide	89%	Mayo
R-Benda	93%	Vienna

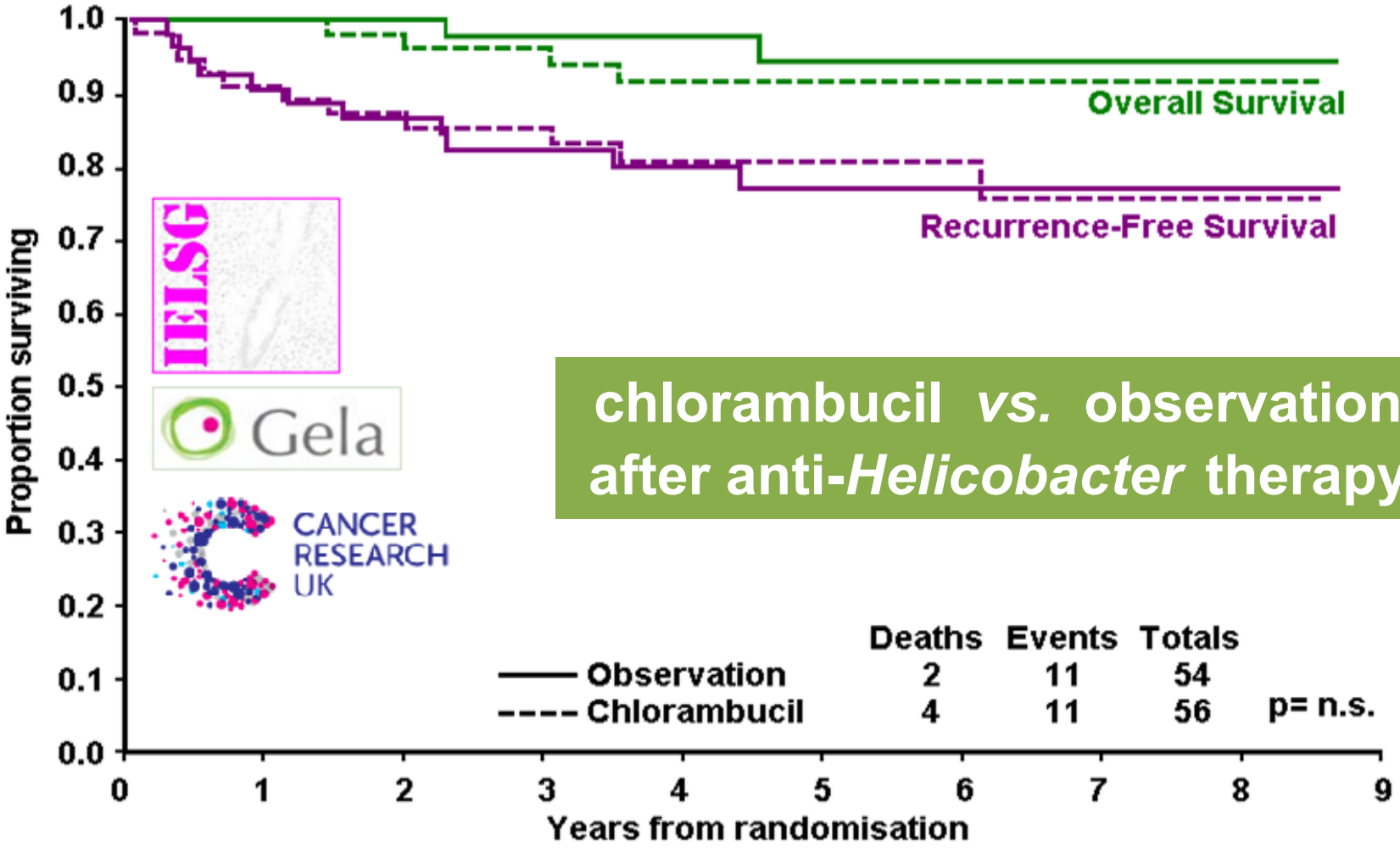
Take-home messages

- H.pylori eradication is standard front-line treatment
- Persistent MRD not clearly associated with progression
- Watchful waiting is safe in case of stable MRD or transient local histological relapses
- The best treatment not yet defined for HP-negative cases and antibiotic failures


14-ICML
14th International Conference on Malignant Lymphoma
Palazzo dei Congressi
Lugano (Switzerland)
www.lymphcon.ch
SAVE THE DATE: June 14-17, 2017


15-ICML
15th International Conference on Malignant Lymphoma
Palazzo dei Congressi
Lugano (Switzerland)
www.lymphcon.ch
SAVE THE DATE: June 18-22, 2019

LY03 trial of gastric MALT lymphoma



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

B. Hancock, et al. Br J Haematol, 2009

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