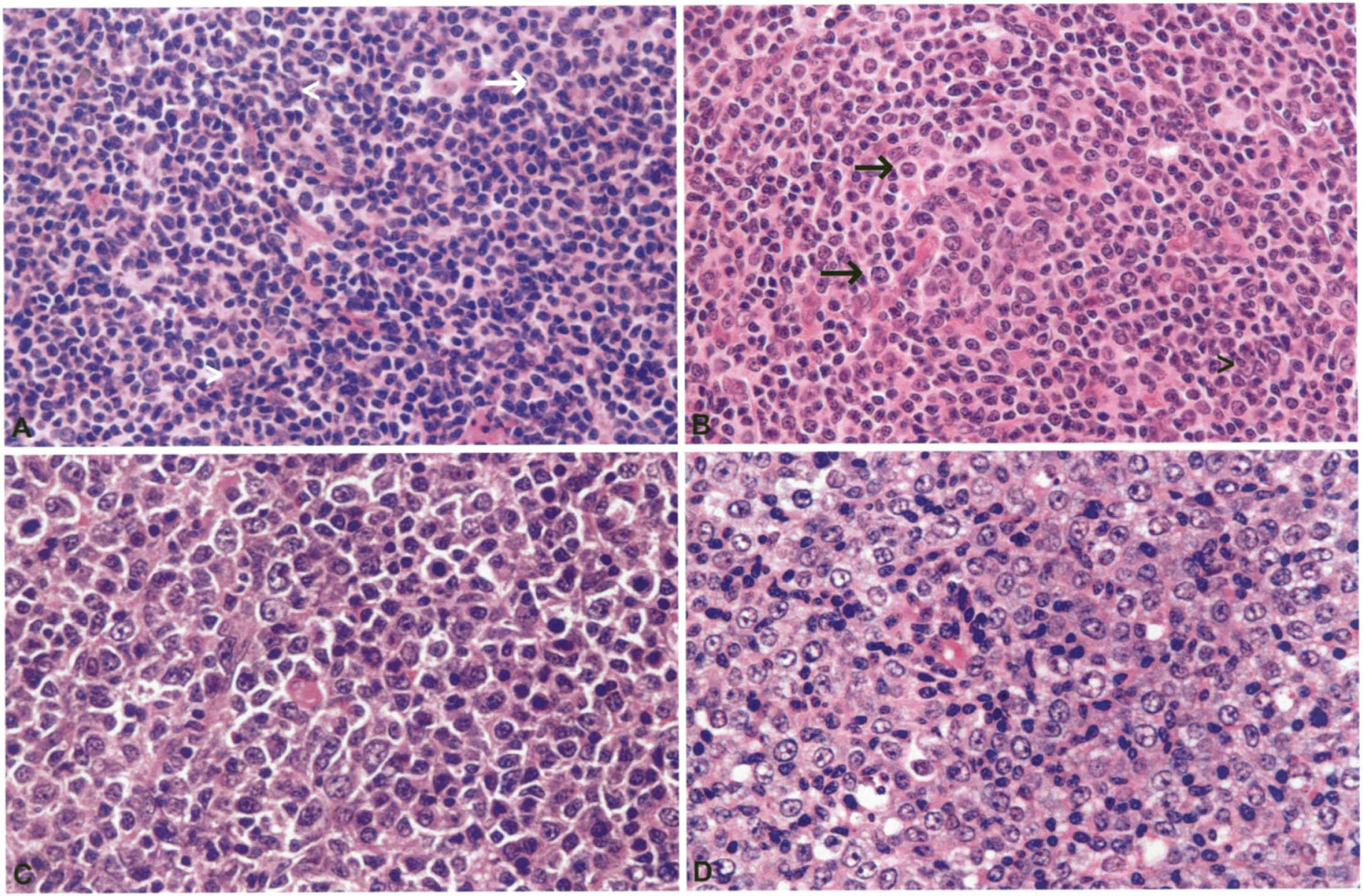
Optimal frontline treatment for symptomatic FL

- **Follicular lymphoma (FL) - 25% of all NHL B - represents the second most common type of lymphoma adults in Western countries. FL are B cell tumors typically follicular grade, with clonal B cells within the neoplastic follicles are specific and follicular reactive T cells, follicular dendritic antigen-presenting cells and macrophages (WHO 2008.)**

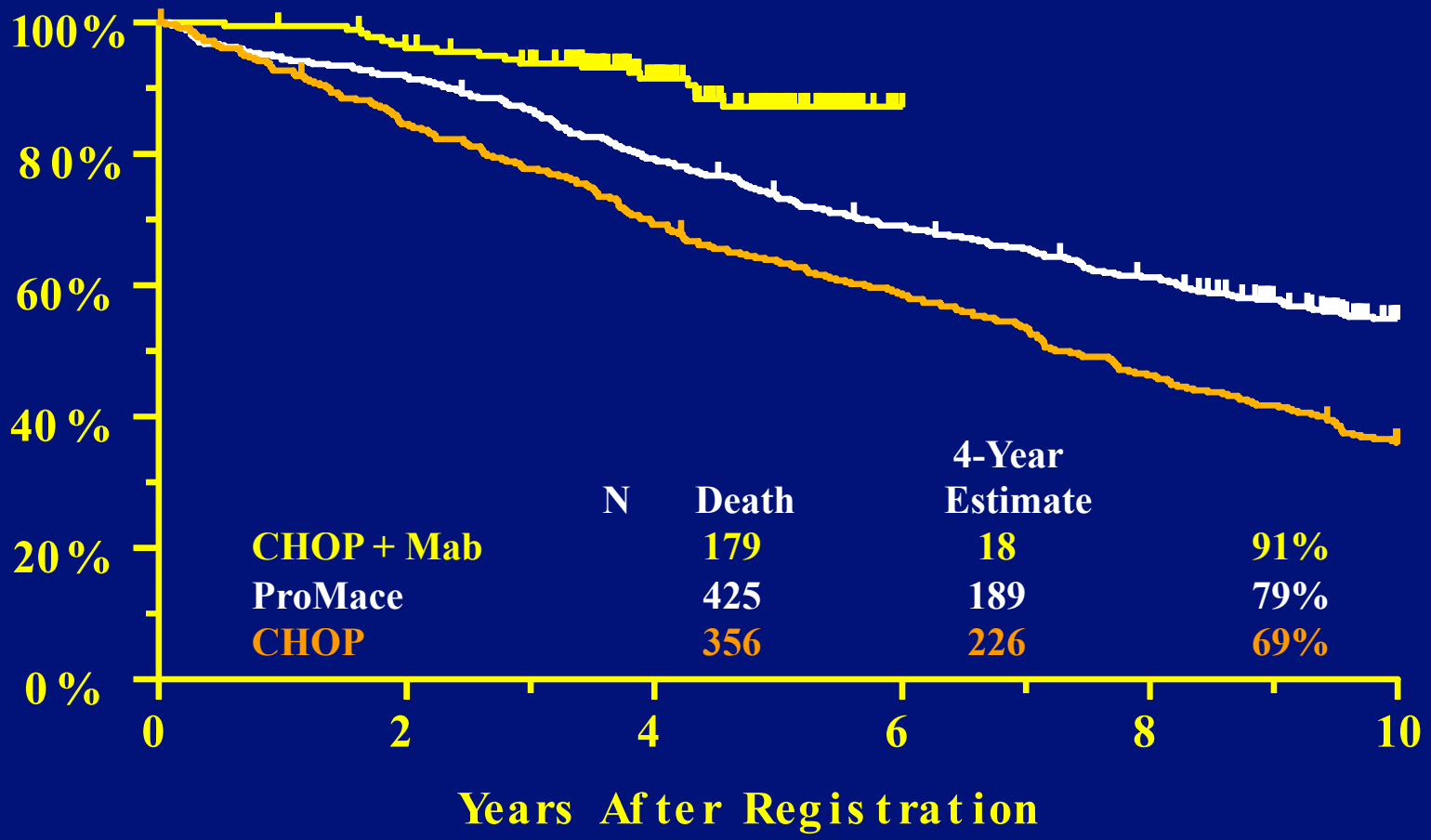
- WHO classification distinguishes three histological degree FL defines the predominant tumor growth, depending on the percentage of nodular and diffuse components of growth within the tumor.
- Step 1 and 2 (FL-1, -2) are typical centrocytic or centrocytic / centroblastic lymphomas with <5 and 5-10 centroblasts a large field of view.
- Step 3 (FL-3), with 17.8-28.9% of the frequency FL, according to the WHO classification can be divided into subtype
- FL-3A - centrocytic / centroblastic lymphoma with > 15 centroblasts in a large field of view and subtype
- FL-3B - centroblasts lymphoma present with diffuse component of growth



Follicular lymphoma grading. **A** Grade 1-2 of 3. There is a monotonous population of small cells with irregular nuclei (centrocytes) with only rare large cells (centroblasts) with 1 or more basophilic nucleoli and a moderate amount of cytoplasm (arrow). Most of the large nuclei present in this field are those of follicular dendritic cells (FDC) (arrowhead); these cells have more delicate nuclear membranes and violet-coloured nucleoli, and are often binucleate. **B** Grade 1-2 of 3. The majority of the cells are centrocytes, but more numerous centroblasts are present (arrows); several FDC with double nuclei are present (arrowhead). **C** Grade 3A. There are more than 15 centroblasts per high power field, but centrocytes are still present. **D** Grade 3B. The majority of the cells are centroblasts.

The natural history of follicular has changed in the last 10 years

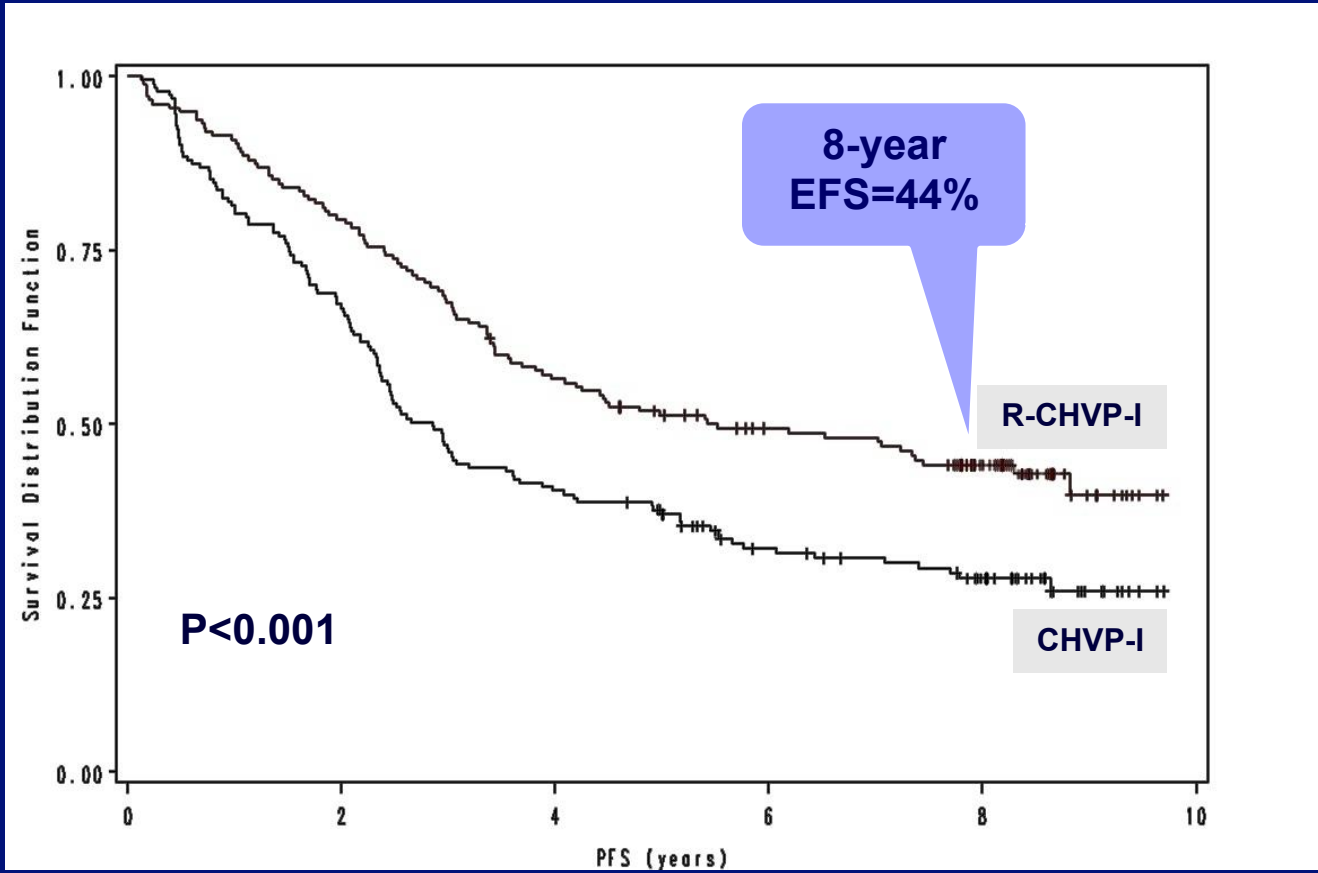
OS by Treatment



Fisher, et. al. J. Clin. Oncol. 23: 8447-8452, 2005

FL2000 GELA- study update
Event free survival

median follow-up = 8.3 years



Lysa
THE LYMPHOMA STUDY ASSOCIATION

Bachy et al, Lugano 2011

Indolent lymphoma: best first line strategy
In patient requiring immediate therapy

1. **Rituximab plus chemotherapy represents the standard of care:**
   - **New anti-CD20 antibodies (ofatumomab, obinutuzumab-GA101) are being evaluated (GALLIUM study)**

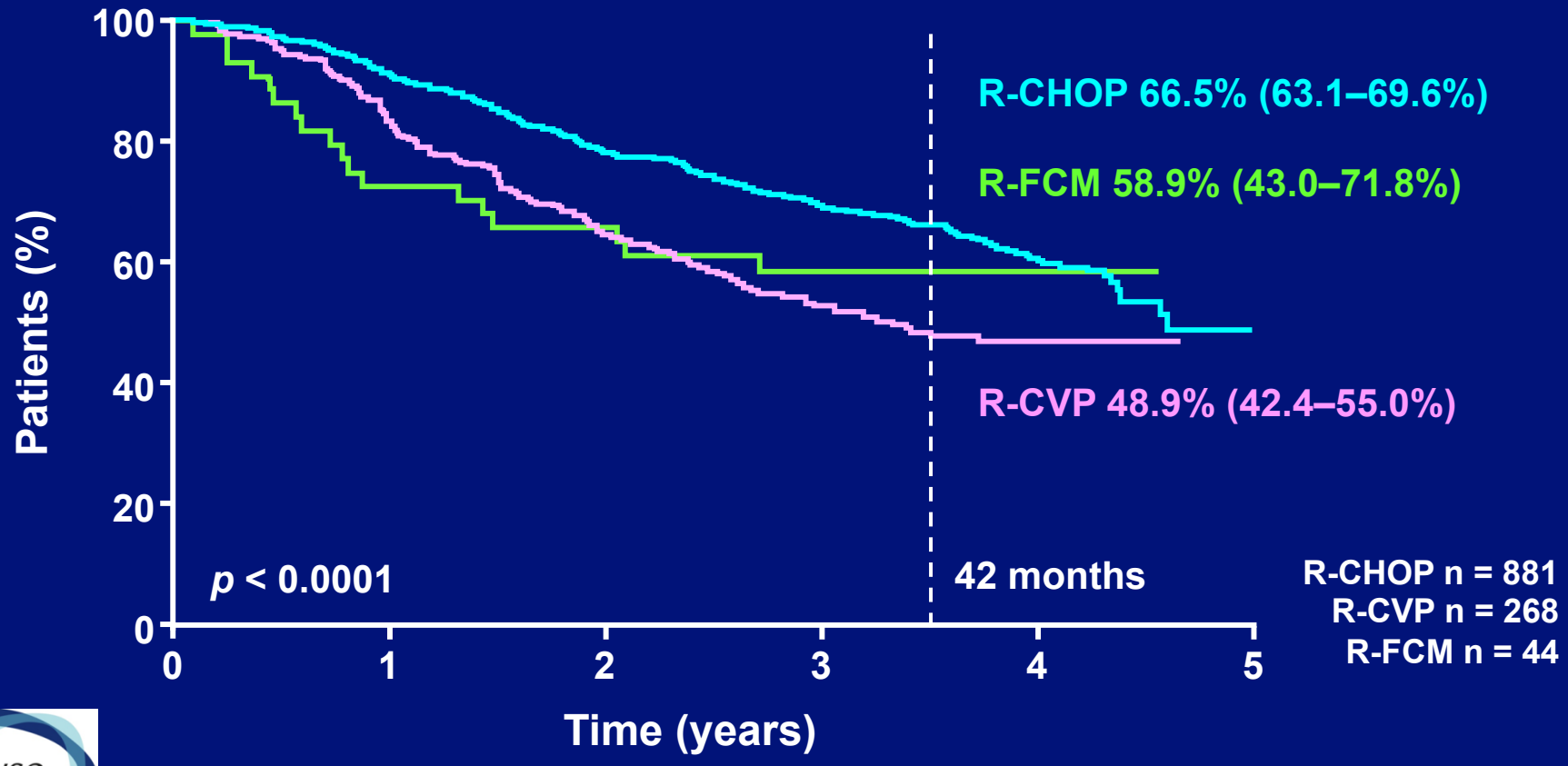
2. **Is there an optimal chemotherapy regimen ?**
   - **R-CVP, R-CHOP, R-FC/FM/FCM or R-Benda..**

3. **What is the benefit of further consolidation ?**
   - **radioimmunotherapy, rituximab maintenance**

All chemo regimen are not equal:

PRIMA study :

PFS from registration by induction regimen



Morschhauser et al., ICML 2011

All chemo regimen are not equal:

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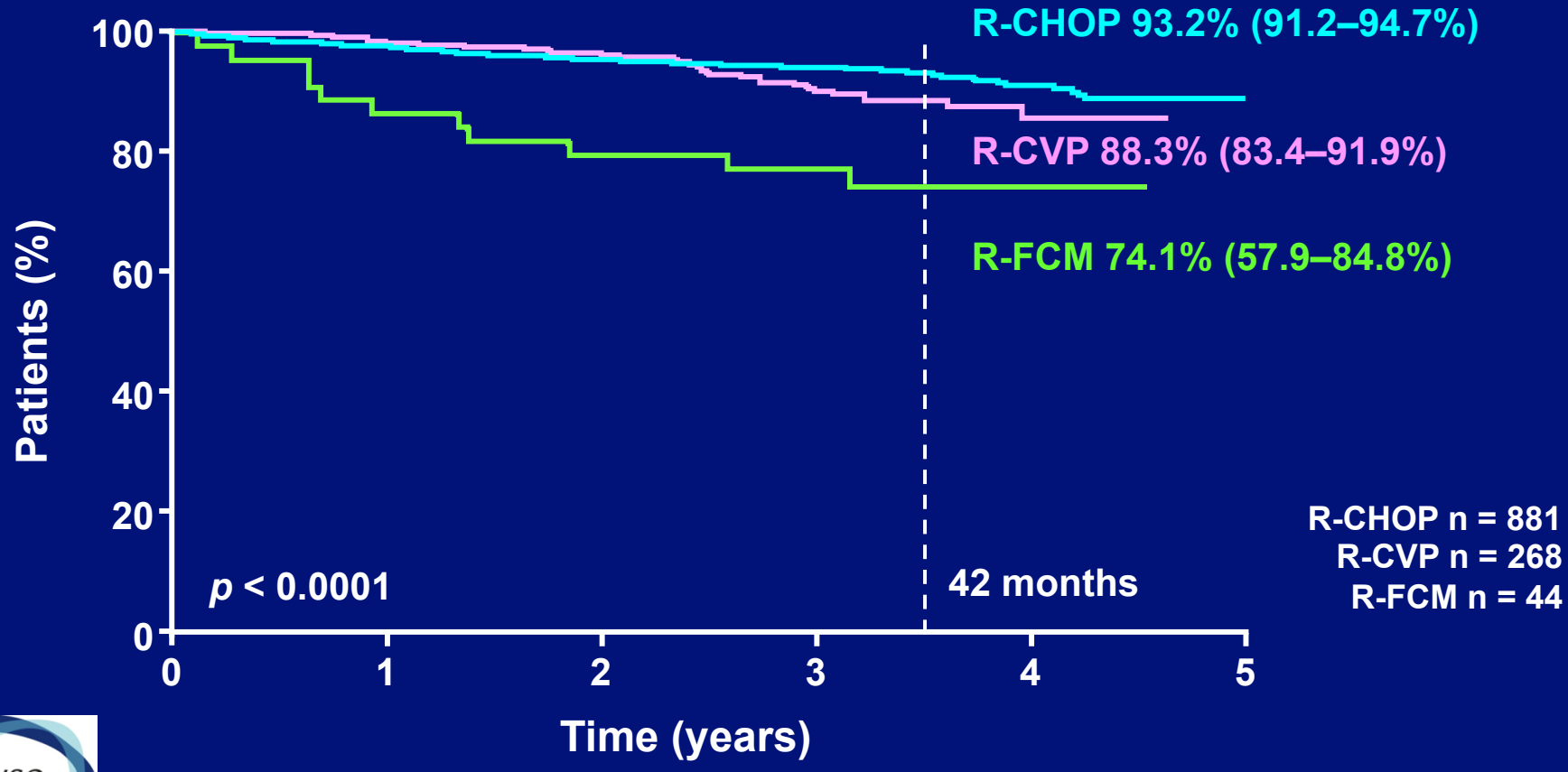
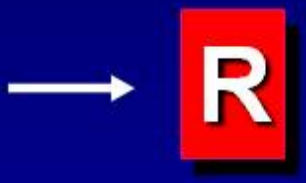


Morschhauser et al., ICML 2011

Bendamustine-Rituximab (B-R) vs CHOP-R

StiL NHL 1-2003

Follicular
Waldenström's
Marginal zone
Small lymphocytic
Mantle cell (elderly)



Bendamustine-Rituximab

- Bendamustine 90 mg/m^2 day 1+2
- Rituximab 375 mg/m^2 day 1

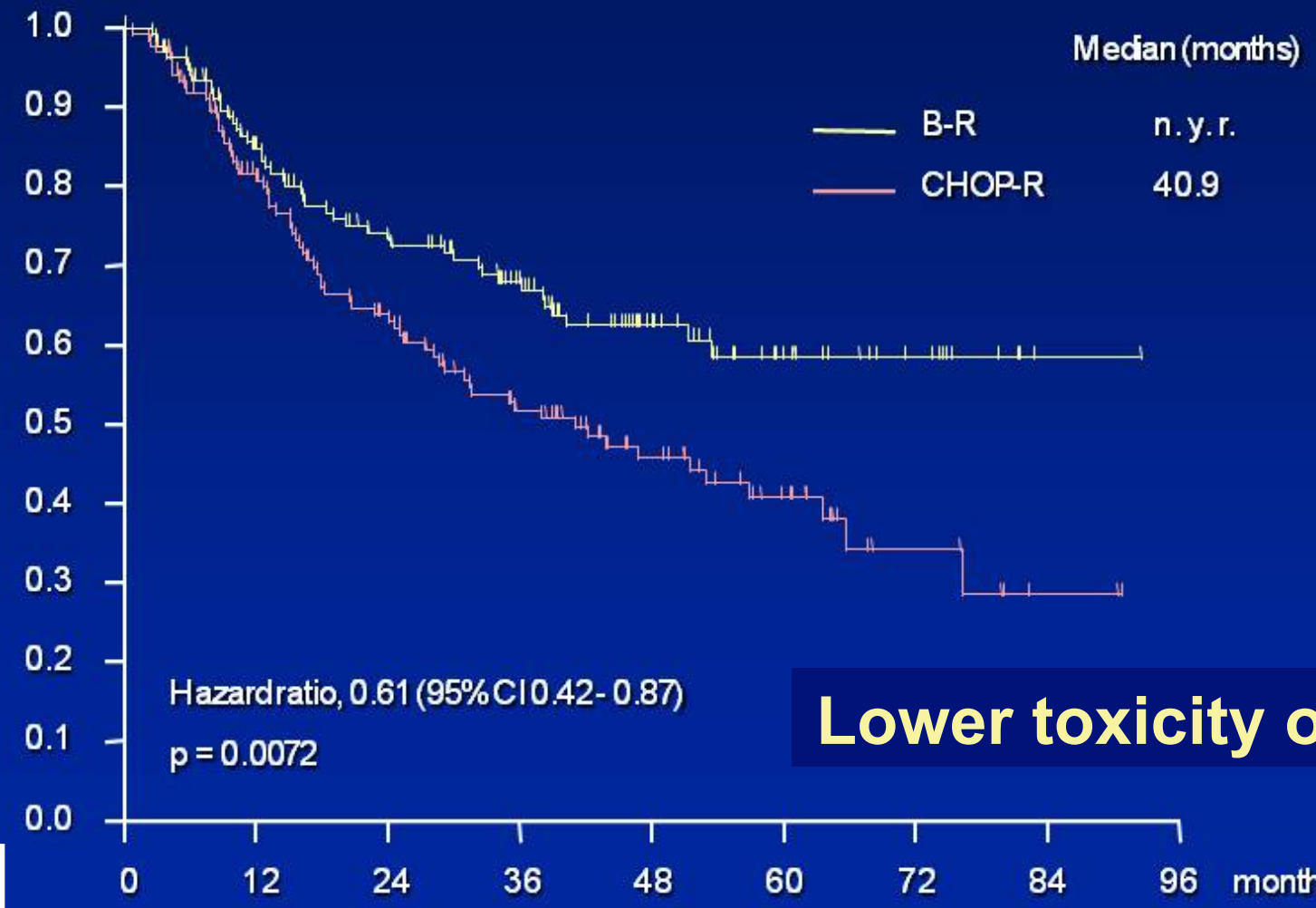
CHOP-Rituximab

- Cyclophosphamide 750 mg/m^2 day 1
- Doxorubicin 50 mg/m^2 day 1
- Vincristine 1.4 mg/m^2 day 1
- Prednisone 100 mg days 1-5
- Rituximab 375 mg/m^2 day 1

StiL
Studiengruppe indolente Lymphome

R-Bendamustine versus R-CHOP

Progression free survival follicular lymphoma (n=279 pts)



Lower toxicity of B-R

Mathias J Rummel et al. www.thelancet.com **Published online February 20, 2013 http://dx.doi.org/10.1016/S0140-6736(12)61763-2**

R-Bendamustine versus R-CHOP

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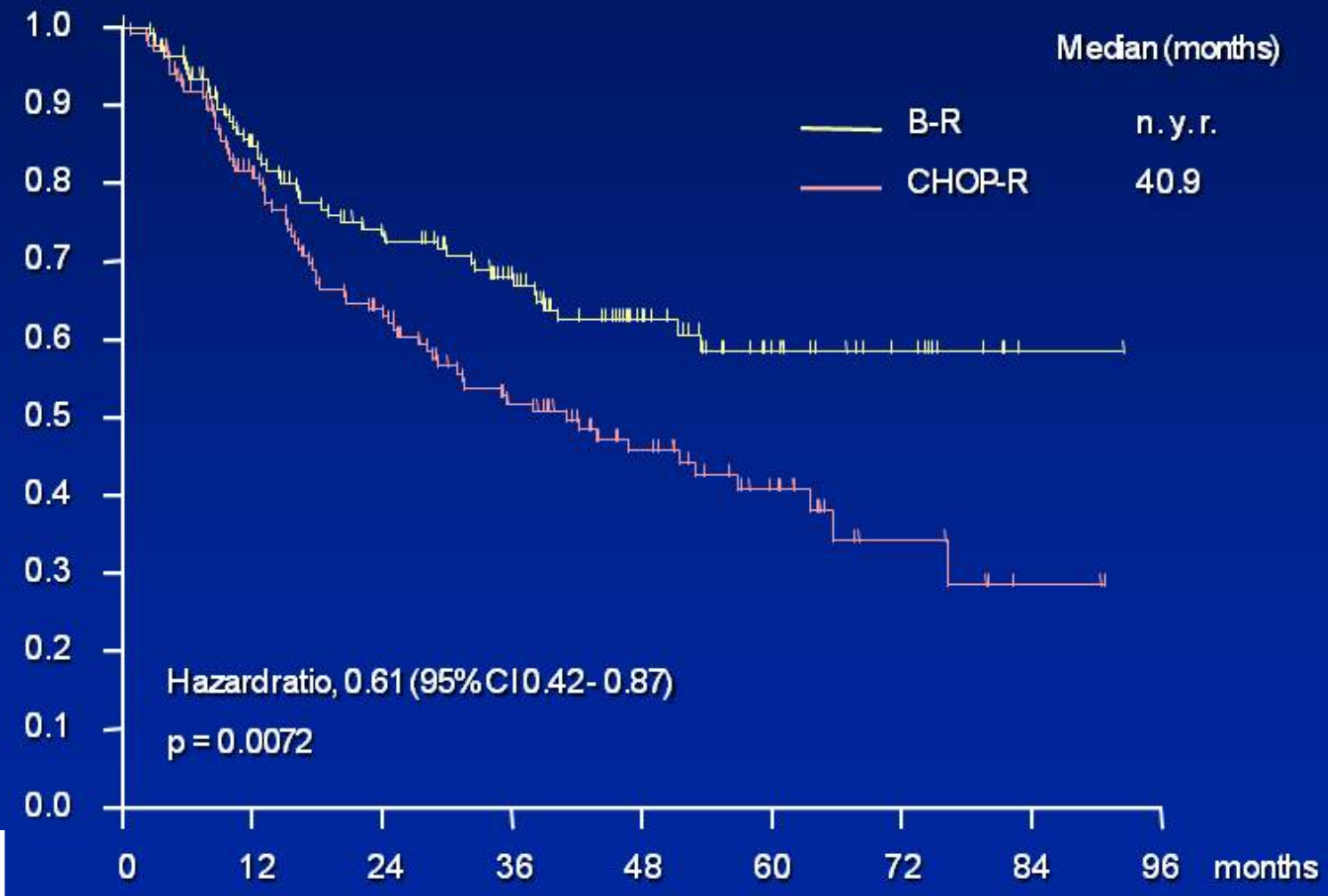


StiL
Studiengruppe indolente Lymphome

MJR

Some questions

- Early results reported at ASH 2007 ?
- Poor results of the R-CHOP arm ?
- Long term toxicity of benda ??
- OS benefit ?

- **Therefore, these data strongly support use of bendamustine plus rituximab for first-line treatment of patients with indolent non-Hodgkin's and mantle-cell lymphomas, whether this use affects the long natural history of these diseases remains to be seen.**

CA Jacobson, AS Freedman

www.thelancet.com Published online February 20, 2013

How to consolidate the results after rituximab plus chemotherapy ?

R-CVP
or R-CHOP
or R-Benda

Consolidate with ASCT ?

Consolidate with RIT ?
FIT, SWOG study

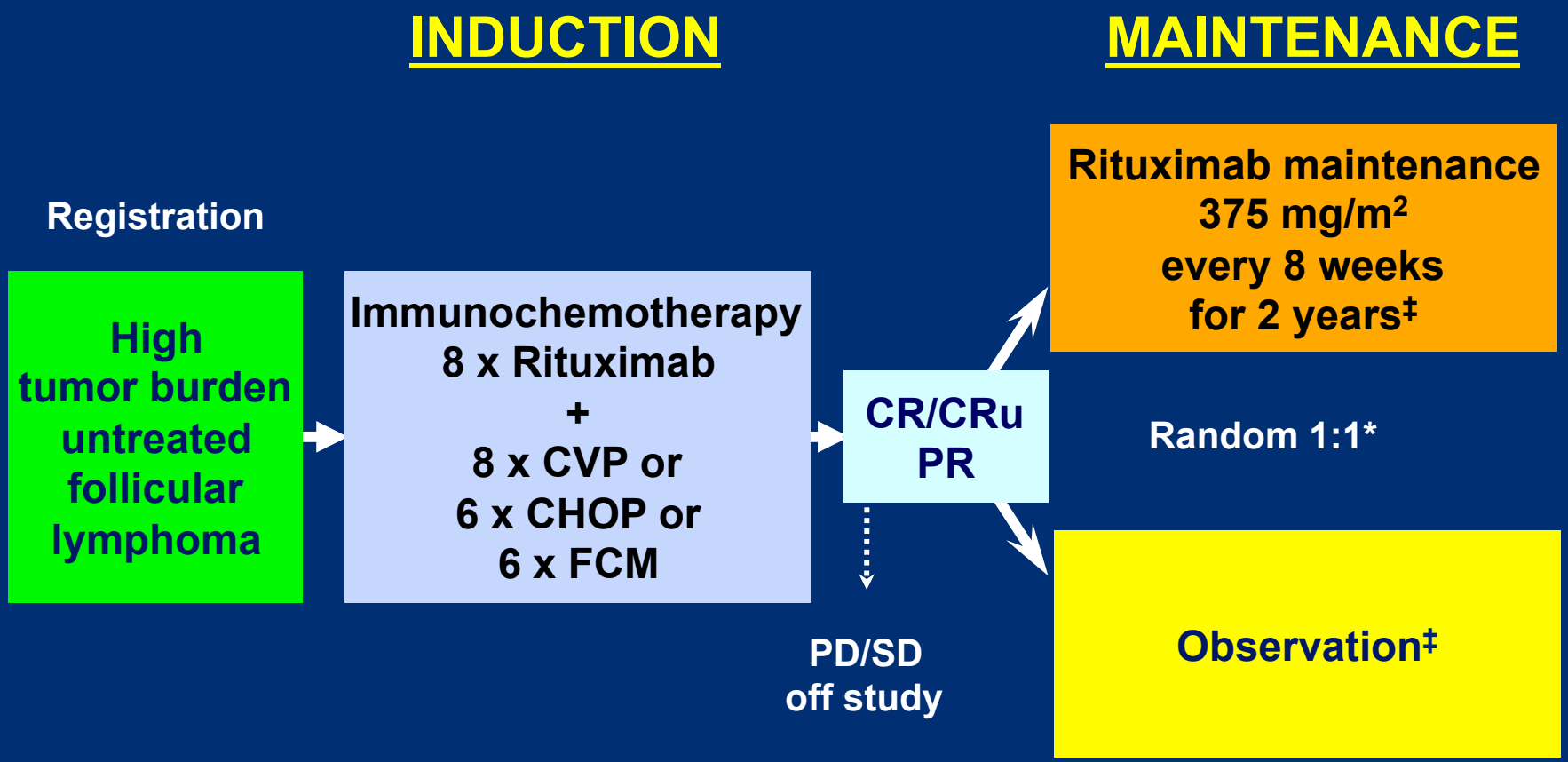
Maintenance with rituximab ?
PRIMA study

Rationale for anti-CD20 Ab maintenance

- Maintenance therapy is more efficient against lymphoma responding to induction therapy
- Long half life of the antibody;
  - *in vivo* infusions to be spaced every 2–3 months [1,2]
  - ECOG data suggest that every 2 months is optimal [2]
  - ALG PK data also in favor of 2 months intervals [3]
- Immunological-mediated actions of rituximab (e.g. ADCC) may be more effective at a period distinct from chemotherapy administration [4-6]
- Good safety profile of the antibody

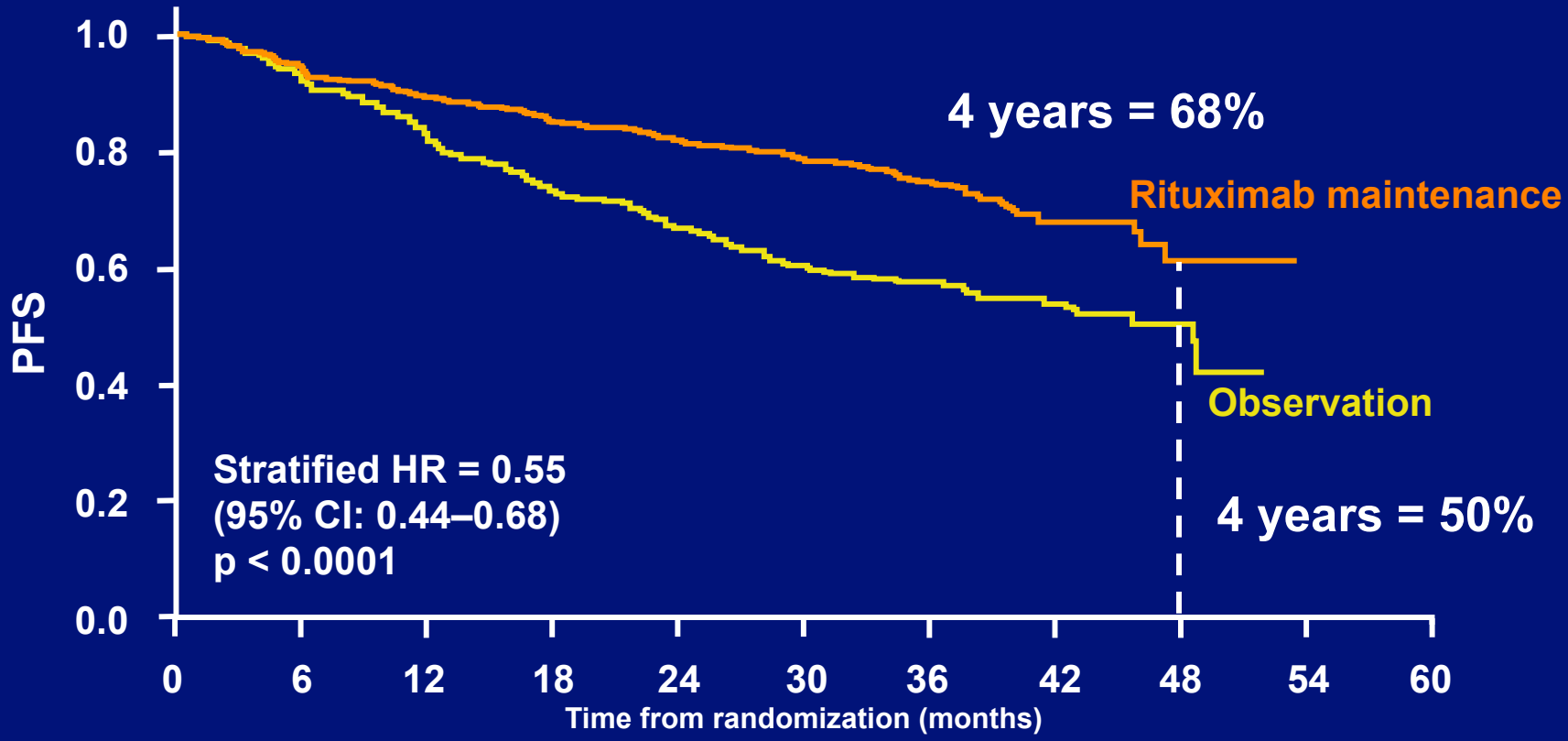
1. Gordan LN, *et al. J Clin Oncol* 2005; 23:1096–1102. 2. Kahl B, *et al. Blood* 2007; 110:Abstract 3420. 3. Jäger U, *et al. Blood* 2008; 112:Abstract 1997. 4. Cartron G, *et al. Blood* 2004; 104:2635–2642. 5. Hilchey P, *et al. Blood* 2009; 113:3809–3812. 6. Abes, at al, *Blood*. 2010;116(6):926-934)

PRIMA: study design



* Stratified by response after induction, regimen of chemo, and geographic region
‡ Frequency of clinical, biological and CT-scan assessments identical in both arms
Five additional years of follow-up

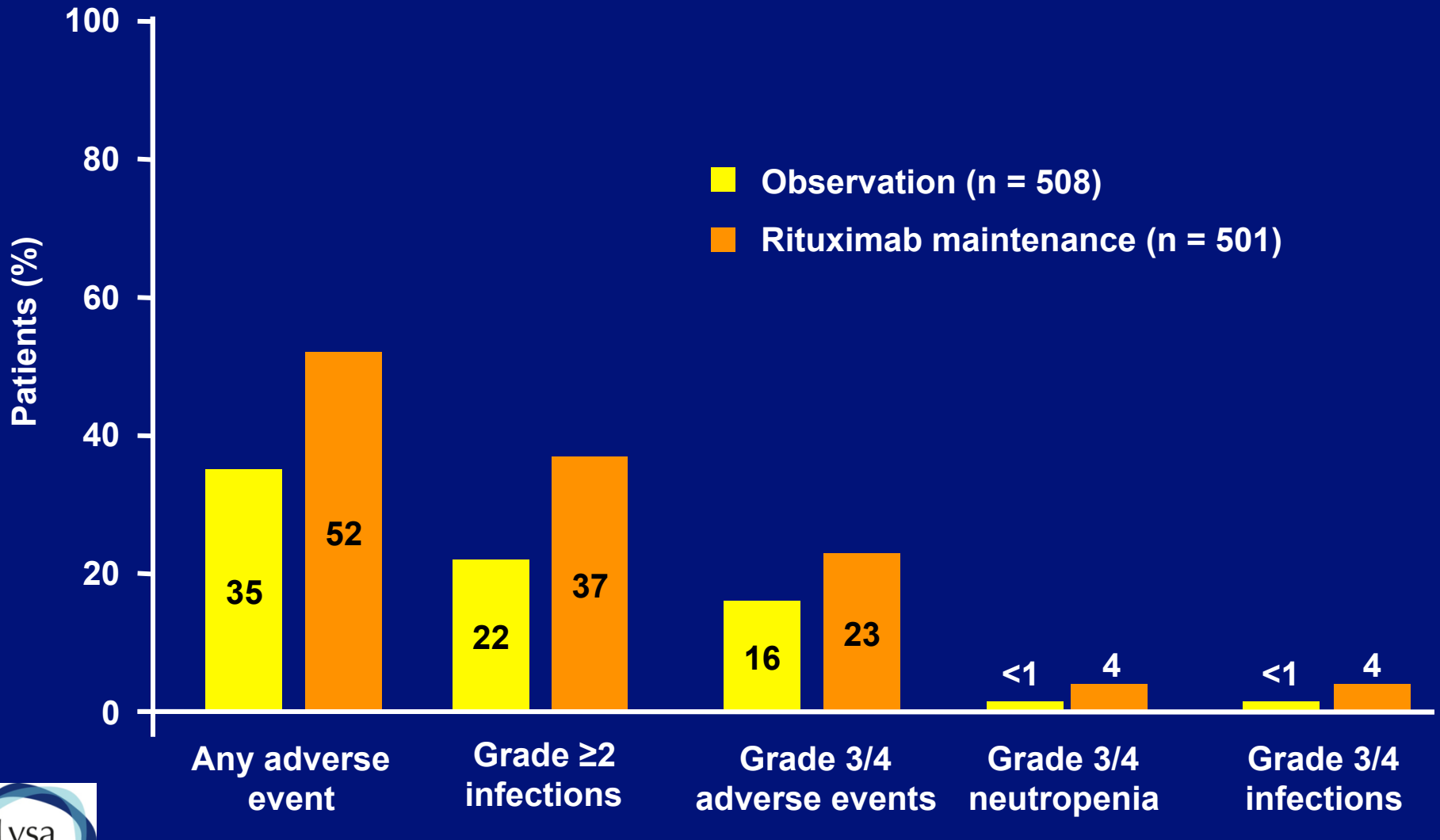
Rituximab maintenance for 2 years: PRIMA study 4 years follow-up



	Subjects (n)	Event n (%)	Censored n (%)	Median survival (95% CL)
Observation	513	254 (50)	259 (50)	48.36 (41.17–54.21)
Rituximab	506	160 (32)	346 (68)	NA (NA –NA)

Salles G, et al. unpublished data

Safety during rituximab maintenance

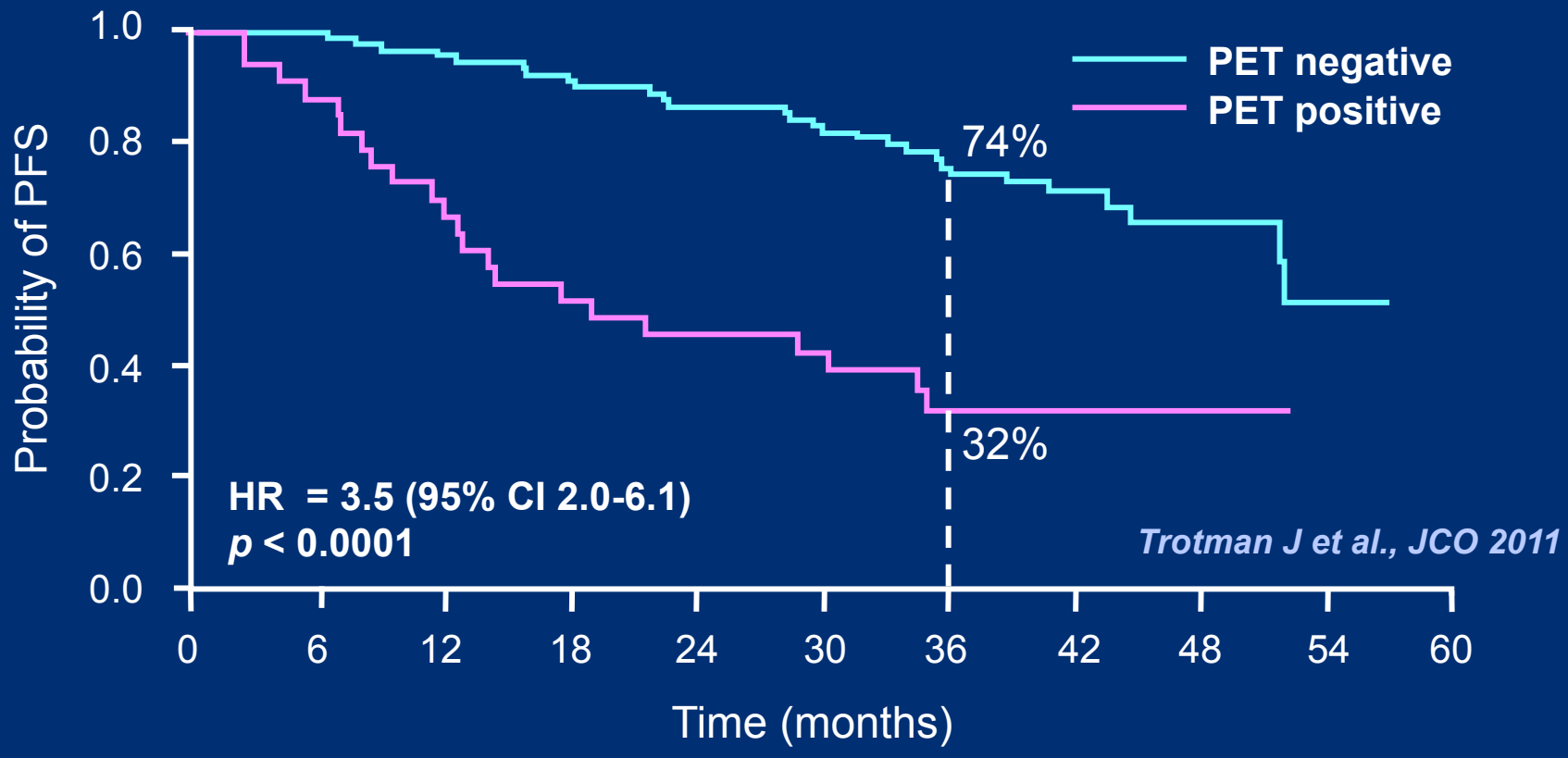


Salles et al., Lancet 2011

Indolent lymphoma
best first line strategy

Future directions

Assessment of response using PET-CT provides useful prognostic indication



- PET-CT results also predicted overall survival
- Results reproduced in a prospective study

(Dupuis et al, JCO, 2012)

The increase in patients survival implies new challenges for first line strategy

Lymphoma progression still representing the leading cause of patient deaths, we should continue to evaluate new treatment options

Important endpoints for future/ongoing studies:

- **Quality of response**
- **Surrogate for PFS ?**
- **Quality of life**
- **Ability to deliver second line treatments**
- **Long term toxicities**

… and Overall survival