

Follicular Lymphoma: Will Our Approach in the Future Be Conservative or More Aggressive?

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« Pathologie des Cellules Lymphoïdes »
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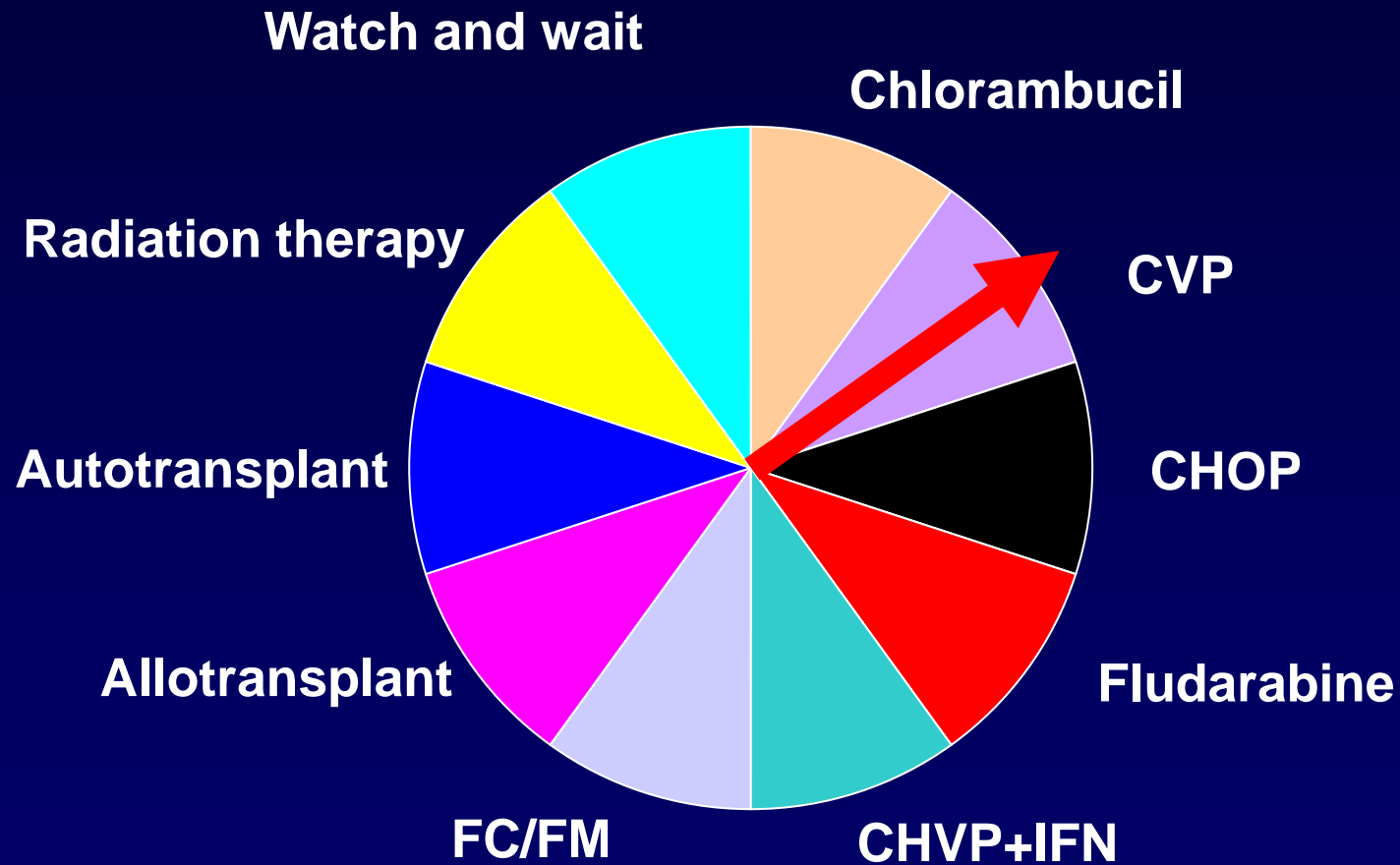
Groupe d'Etude des
Lymphomes de l'Adulte

Follicular Lymphoma Biological Aspects and Treatment

**Lessons learned
before the monoclonal Ab era**

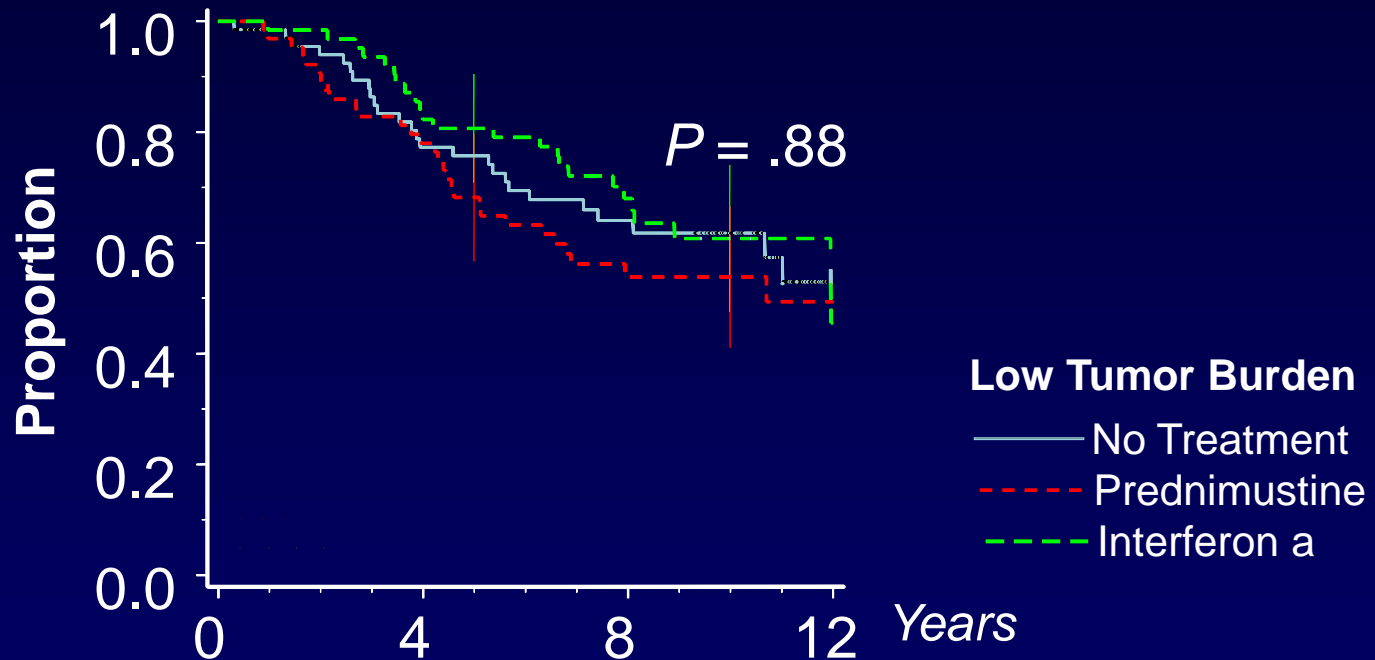
FL Treatment Choices

The Wheel of Fortune?



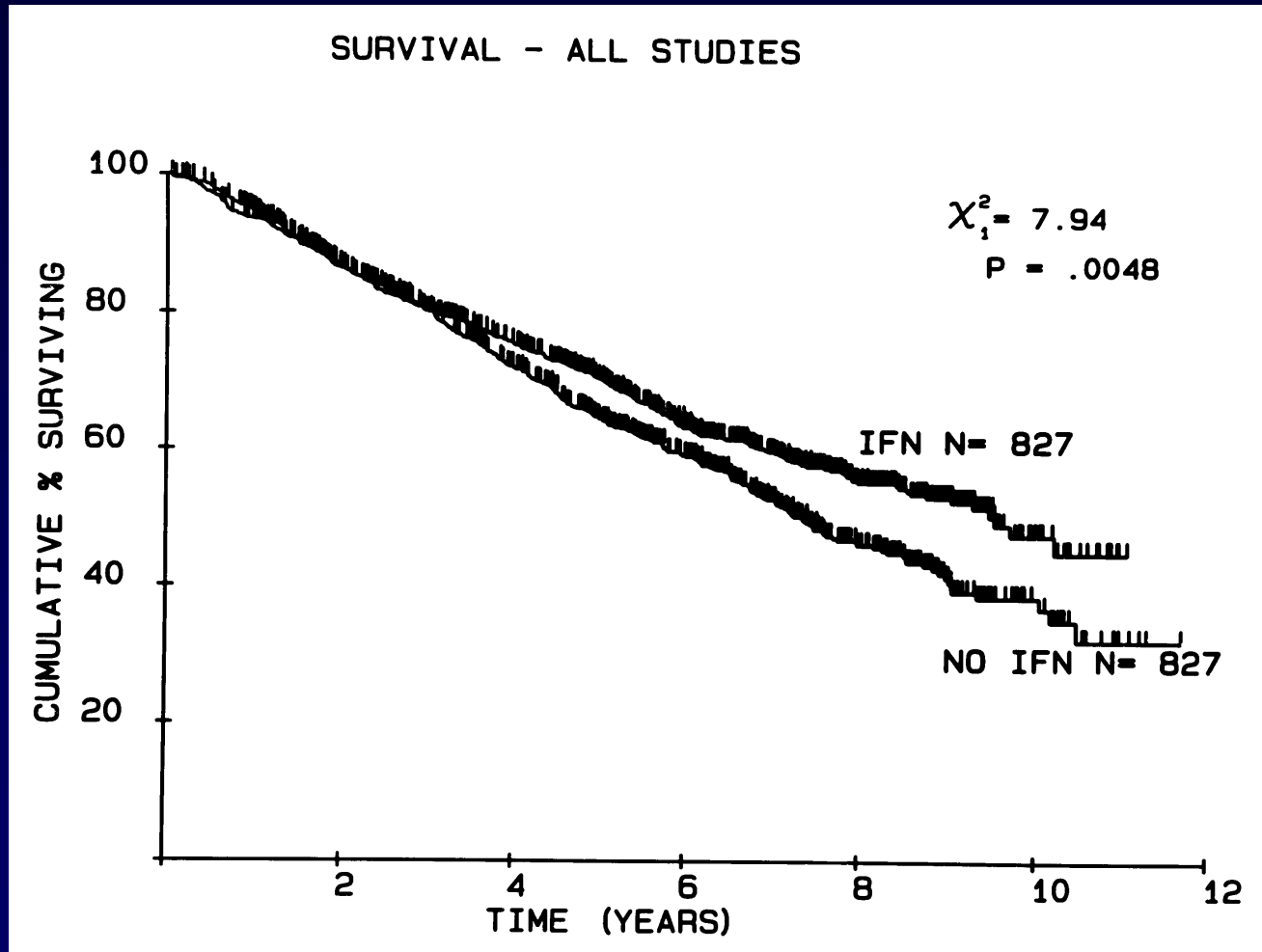
Watch and Wait Is an Acceptable Option in Selected Patients

GELF-86 OVERALL SURVIVAL

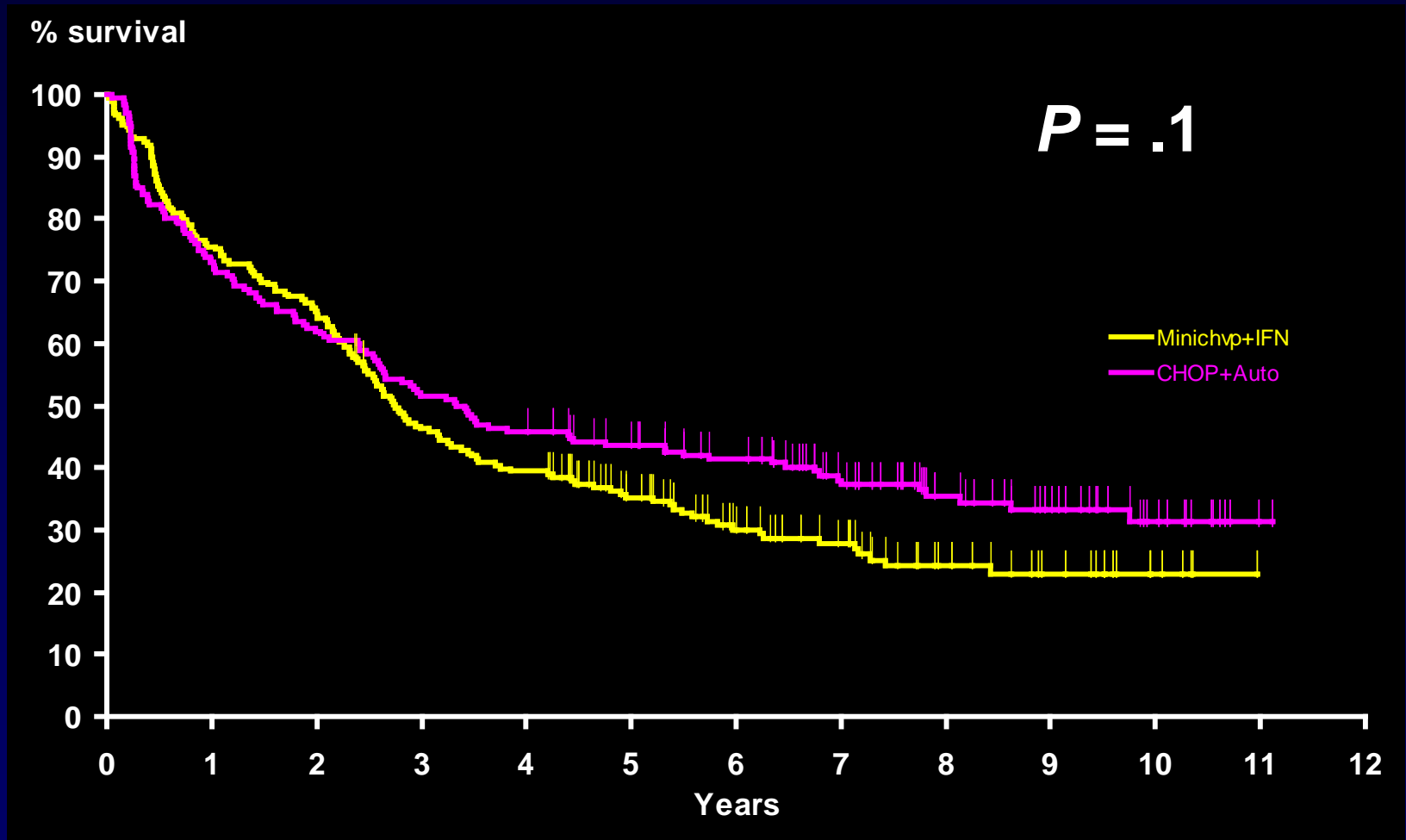


At risk	0	4	8	12
—	66	51	29	6
- - -	64	48	23	5
- - -	63	51	31	3

α -Interferon Meta-Analysis: Overall Survival



First Line ASCT: An Uncertain Benefit With Potential Long-Term Toxicities



Follicular Lymphoma Biological Aspects and Treatment

**Current treatments
for FL patients**

Clinical Criteria to Start a Cytotoxic Treatment

GELA criteria

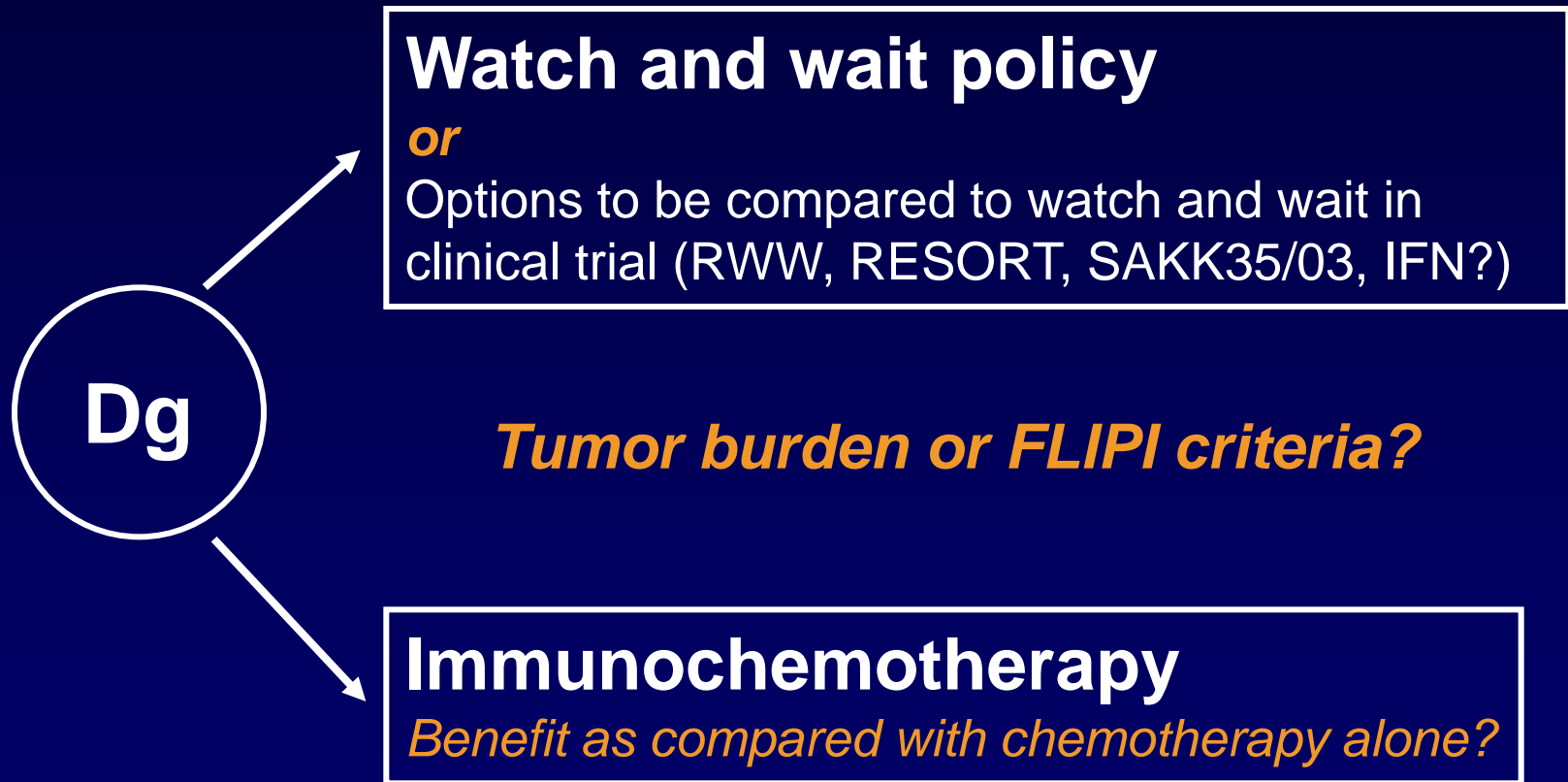
- ✓ High tumor bulk defined by either:
 - a tumor > 7 cm
 - 3 nodes in 3 distinct areas each > 3 cm
 - symptomatic splenic enlargement
 - organ compression
 - ascites or pleural effusion
- ✓ Presence of systemic symptoms
- ✓ Serum LDH or β 2-microglobulin above normal values

BNLI criteria

- ✓ Rapid disease progression in the preceding 3 months
- ✓ Life threatening organ involvement
- ✓ Renal or liver infiltration
- ✓ Bone lesions

- ✓ Systemic symptoms or pruritus
- ✓ Hb < 10 g/dL or WBC < $3.0 \times 10^9/L$ or Plat. < $100 \times 10^9/L$; related to marrow involvement

Therapeutic Options at Diagnosis in Follicular Lymphoma Patients



RWW = Rituximab versus watch and wait

RESORT trial = Rituximab maintenance versus rituximab retreatment as required

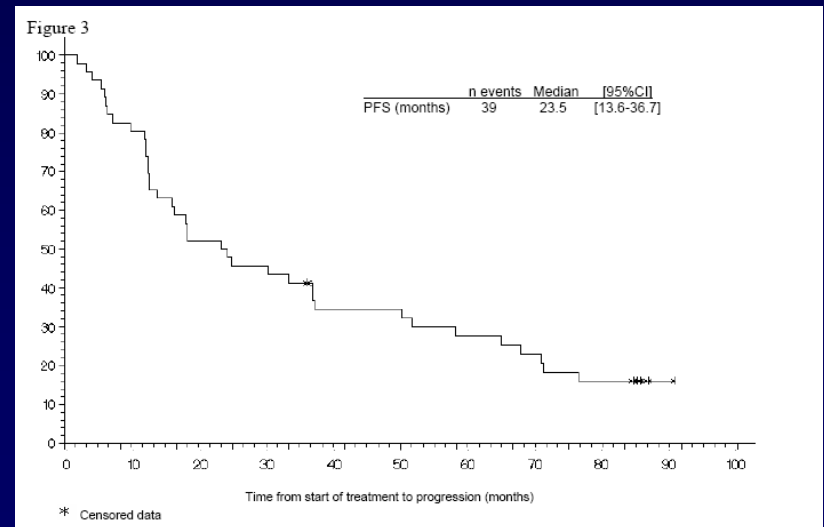
Rituximab as Single Agent

Summary of Phase II Studies in First Line

- ✓ **Good efficacy :**
 - about 3 out of 4 patients respond to therapy
- ✓ **Some long-term (molecular) responses**
- ✓ **Minimal toxicity**

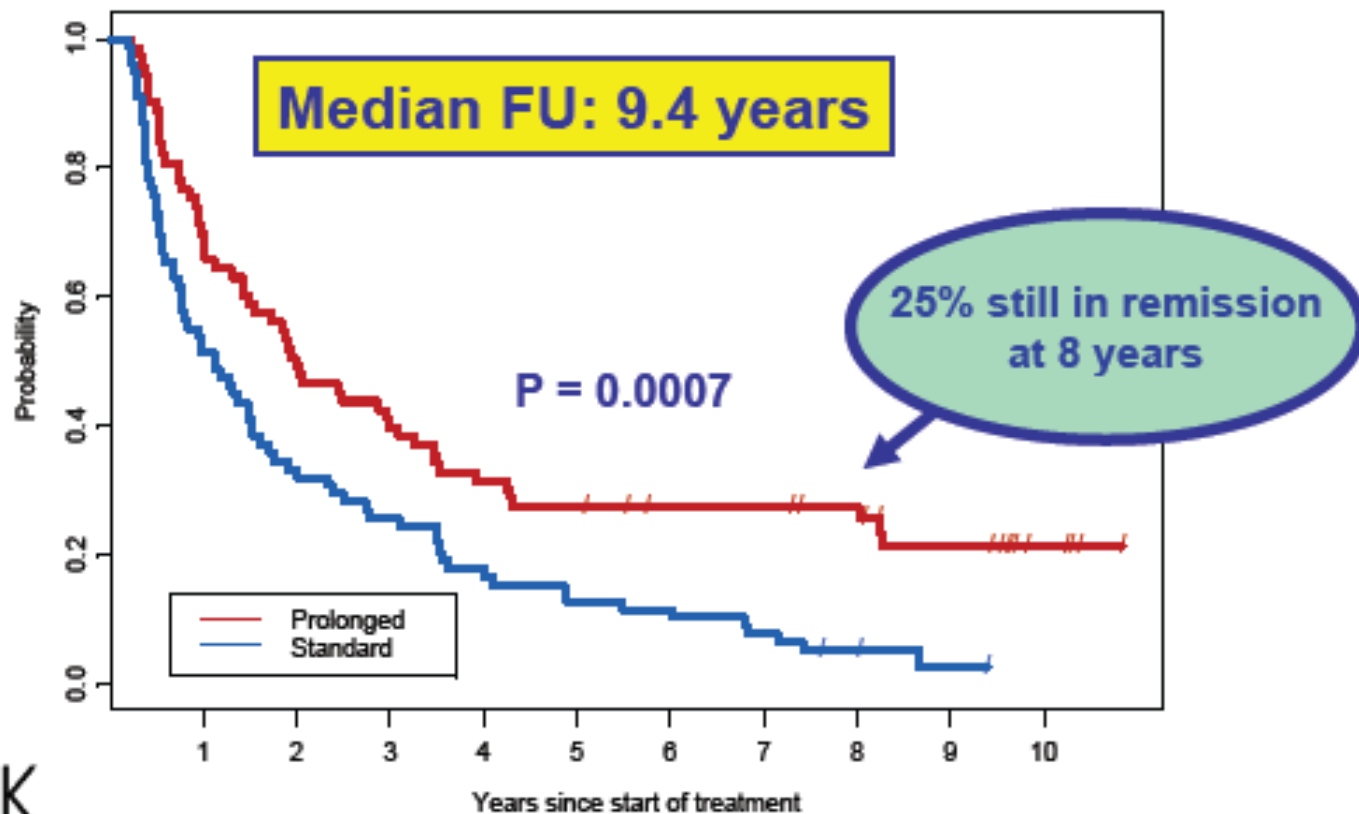
But:

- ✓ **short median PFS:**
 - 18 to 24 months
- ✓ **Cost**



SAKK 35/98 Long-Term Follow-up

Event-free survival in randomized follicular lymphoma patients

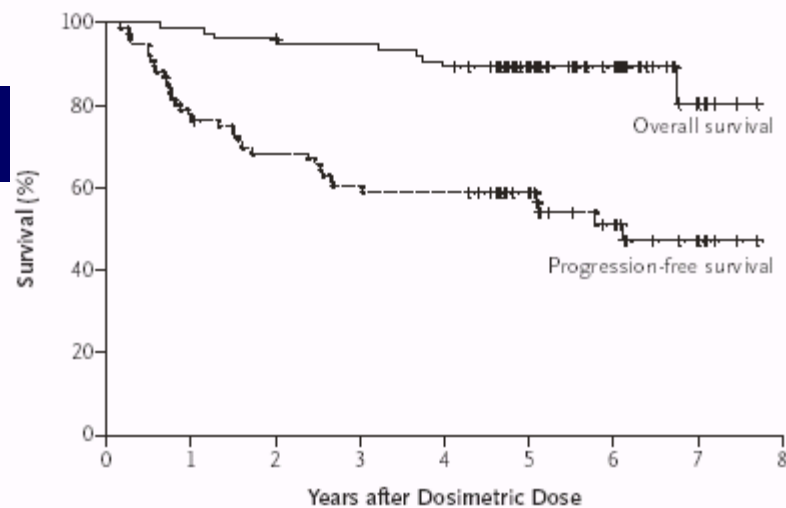


Is Prolonged Treatment with Rituximab Better Than a Short Course or Watch and Wait?

- Risk/benefit ratio of long-term rituximab maintenance?
- RWW in Europe/Australia
 - Watch and Wait versus 4 infusions followed by 2 years maintenance (every 2 months)
- RESORT in US
 - 4 infusions versus 4 infusions followed by prolonged maintenance (every 3 months)
- SAKK study
 - 4 + 4 infusions versus 4 infusions followed by 5 years maintenance (every 2 months)

Tositumomab (^{131}I -B1) As First Line Treatment of FL Patients

CR rate : 75%



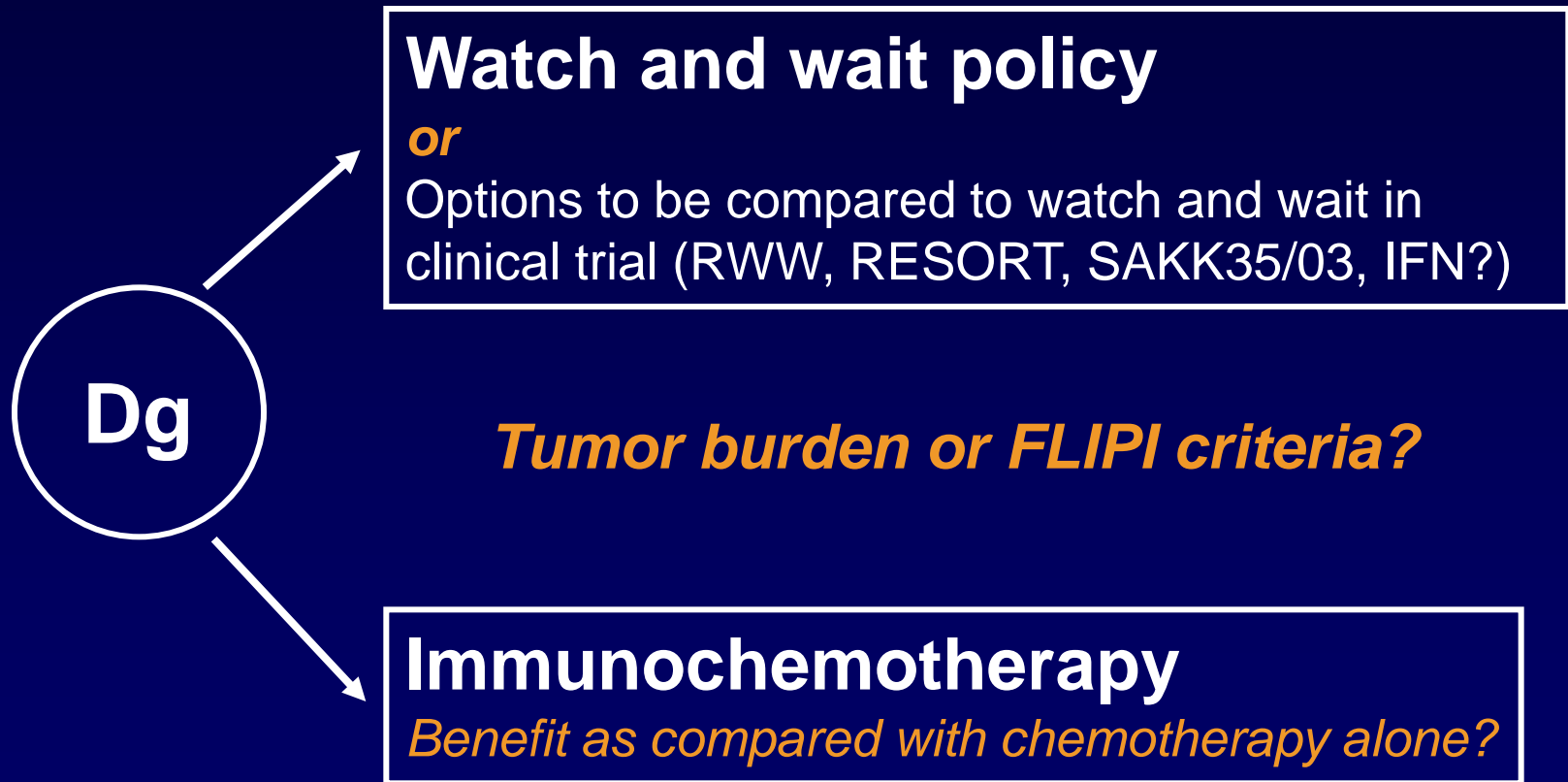
No. at Risk

Overall survival	75	73	71	67	50	25	7
Progression-free survival	59	51	45	44	33	16	7

Figure 2. Progression-free and Overall Survival for All Patients.

The data are for all 76 patients treated with ^{131}I -tositumomab therapy as initial treatment for advanced stage, follicular, low-grade, B-cell non-Hodgkin's lymphoma.

Therapeutic Options at Diagnosis in Follicular Lymphoma Patients



RWW = Rituximab versus watch and wait

RESORT trial = Rituximab maintenance versus rituximab retreatment as required

Immunochemotherapy in First-Line Indolent NHL: Four Randomized Trials

Study name and author	Randomized	Patients	Treatment
M39021; Marcus <i>et al.</i> ¹	321	FL	CVP vs R-CVP
GLSG; Hiddemann <i>et al.</i> ²	557	FL	CHOP vs R-CHOP *
M39023; Herold <i>et al.</i> ³	358	FL, MCL, LC	MCP vs R-MCP **
FL2000; Salles <i>et al.</i> ⁴	359	FL	CHVP IFN vs R-CHVP IFN

* autotransplant or */ ** interferon as consolidation

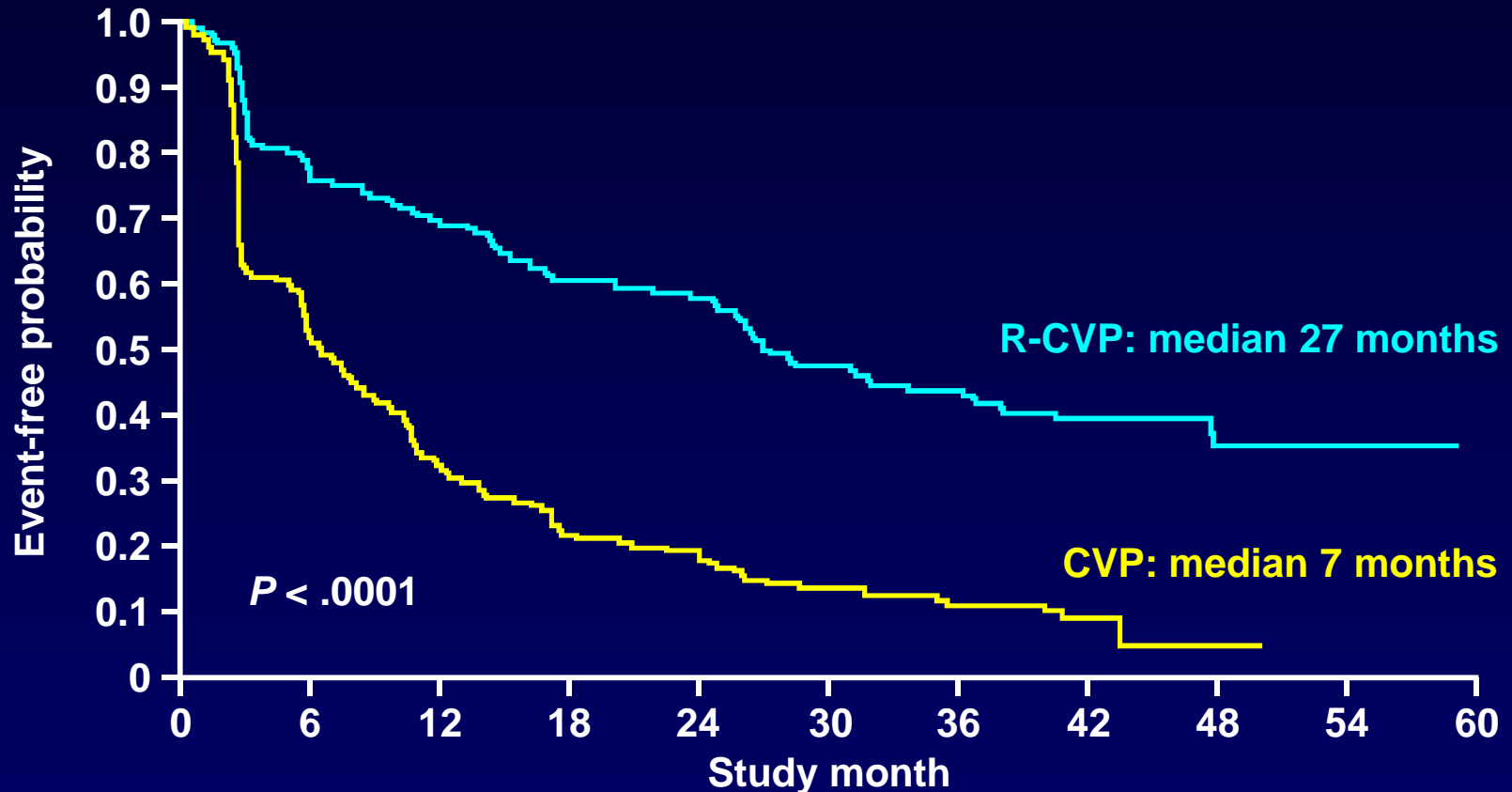
FL = follicular lymphoma
MCL = mantle cell lymphoma
LC = lymphoplasmacytic lymphoma

¹Marcus R, et al. *Blood*. 2005;105(4):1417-1423. ²Hiddemann W, et al. *Blood*. 2005;106(12):3725-3732.

³Herold M, et al. *J Clin Oncol*. 2007;25(15):1986-1992. ⁴Salles G, et al. *Blood*. 2008;112(13):4824-4831.

CVP versus R-CVP: Time to Treatment Failure

Median Follow-Up 42 months



Patients at risk:

CVP	159	86	51	34	30	21	16	5	1	0	0
R-CVP	162	123	113	98	93	76	66	36	15	5	0

Rituximab + Chemotherapy in First-Line FL: Effect on Overall Survival

Study name and author	Follow-up	Overall survival (%)		P
		Control	Rituximab	
M3902; Marcus <i>et al.</i> ¹	4 years	77	83	✓
GLSG; Hiddemann <i>et al.</i> ²	5 years	84	90	✓
M39023; Herold <i>et al.</i> ³	4 years	75	89	✓
FL2000; Salles <i>et al.</i> ⁴	5 years	79	84	✓

(high-risk pts)

Cochrane analysis:

HR = 0.63 [0.51–0.79]

Schulz H et al. Cochrane Database Syst Rev. 2007;(4):CD003805.

¹Marcus R, et al. *J Clin Oncol.* 2008;26:4579–4586. ²Buske C, et al. *Blood.* 2008;112:Abstract 2599.

³Herold M, et al. *J Clin Oncol.* 2007;25:1986–1992. ⁴Salles G, et al. *Blood.* 2008;112:4824–4831.

Follicular Lymphoma

Biological Aspects and Treatment

Next steps
for further improvements

Low-Risk Patients Next Steps?

1) Rituximab treatment:

- Prolonged treatment:

 - wait for RESORT, RWW and SAKK study results**

- Higher doses?

2) Radio-immunotherapy :

- Tositumomab¹

3) Combine rituximab with cytokines, other Abs or immunomodulatory agents?

- IFN, GM-CSF, IL-2²⁻⁶

- Anti-CD22, -CD40, -CD80, etc...

- Lenalidomide = R2 regimen ?

¹Kaminski MS, et al. *N Engl J Med*. 2005;352(5):441-449. ²Davis TA, et al. *Clin Cancer Res*. 2000;6(7):2644-2652.

³Sacchi S, et al. *Haematologica*. 2001;86(9):951-958. ⁴Kimby E. *Semin Oncol*. 2002;29(2 Suppl 6):7-10.

⁵Bosly A. *Pathol Biol (Paris)*. 2004;52(1):39-42. ⁶Cartron G, et al. *Crit Rev Oncol Hematol*. 2007;62(1):43-52.

High-Risk Patients

Next Steps?

Other chemotherapy
drugs?

Fludarabine, Bendamustine

6 – 8 x

R-CVP or R-CHOP

Consolidate with high-
dose or Rx-Ab?

**FIT, Ri-CHOP,
anti-CD22 ??**

Combine with
targeted therapies?

Bortezomib

New anti-CD20 mAbs?

Ofatumomab, GA101

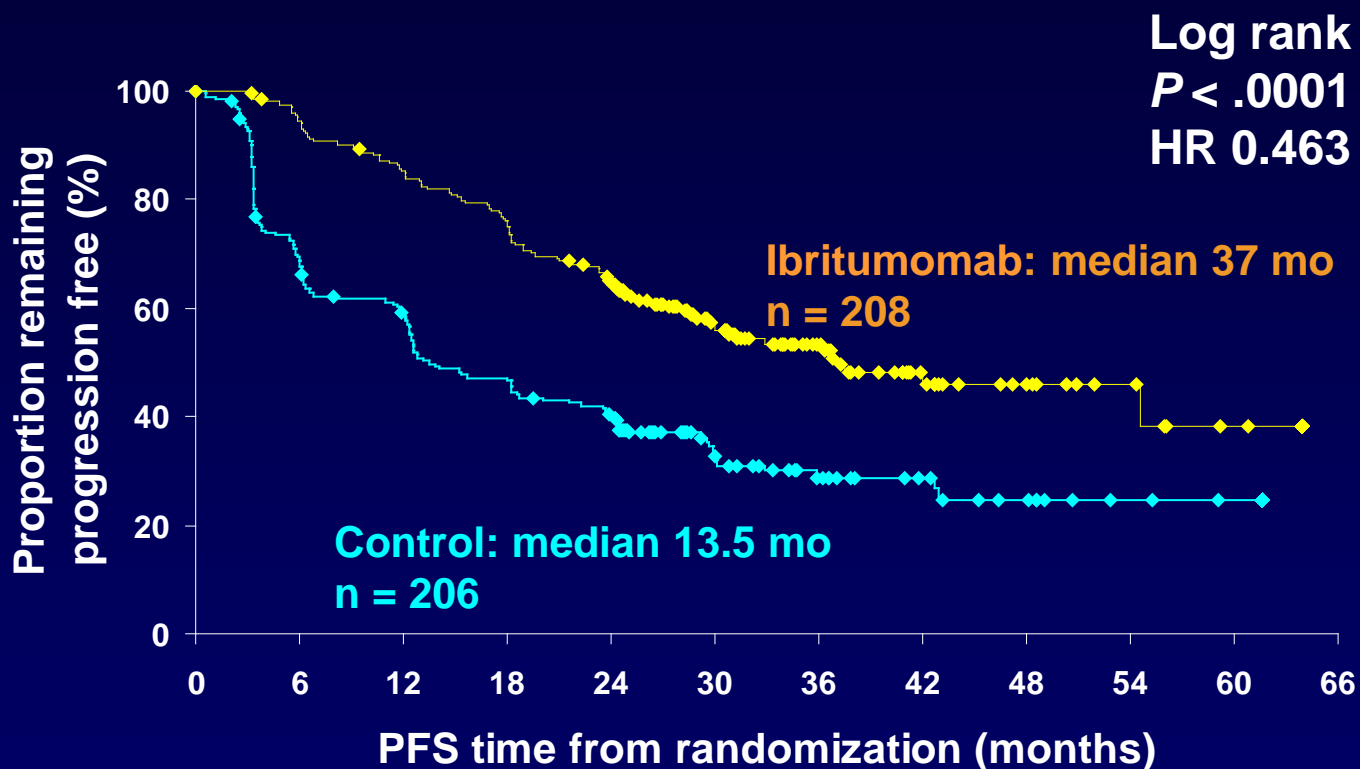
Maintenance with
rituximab?

PRIMA study

Combine with
immunomodulatory agents

GM-CSF, lenalidomide, ...

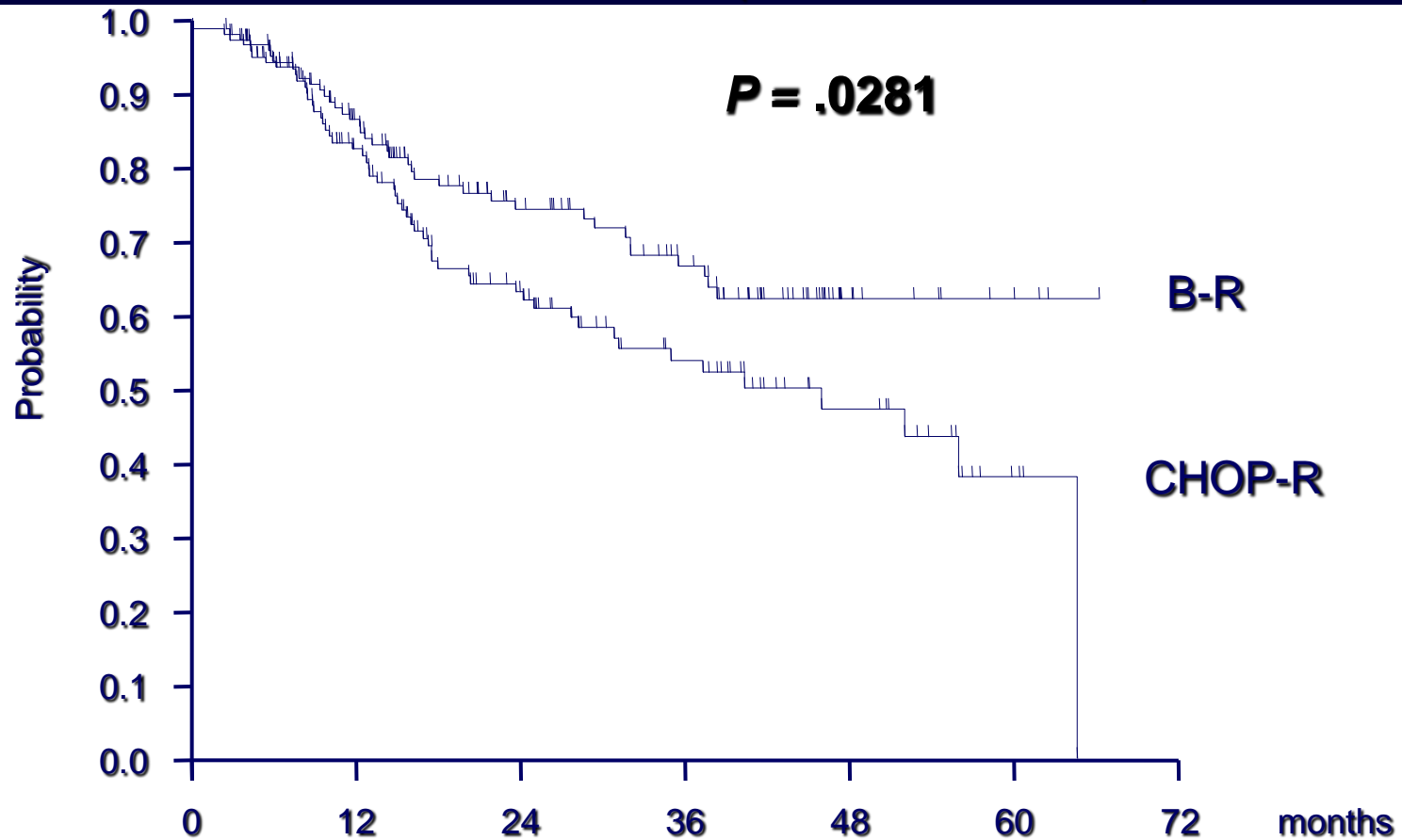
FIT Primary End Point: Median PFS in All Patients*



R-Bendamustine versus R-CHOP Progression-Free Survival Follicular Lymphoma

B-R: not reached vs CHOP-R: 46,7 months (median)

HR = 0.63 (95% CI: 0.42 - 0.95)

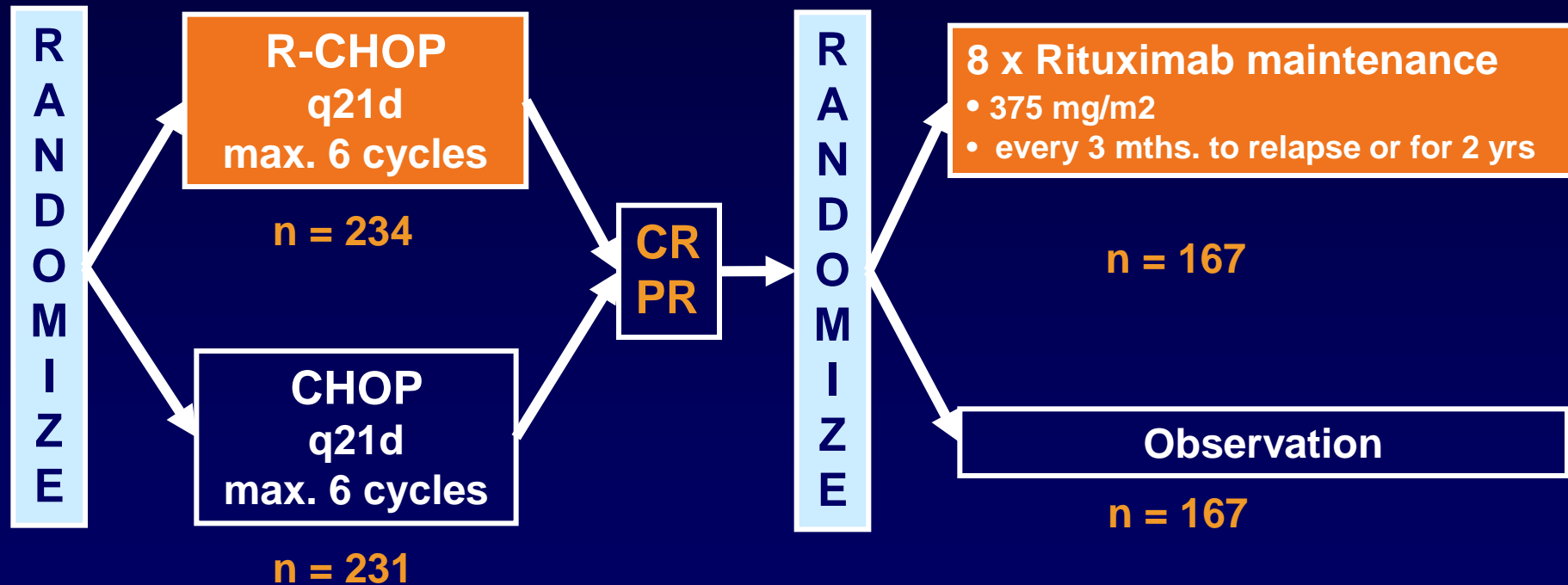


Rationale for Rituximab Maintenance

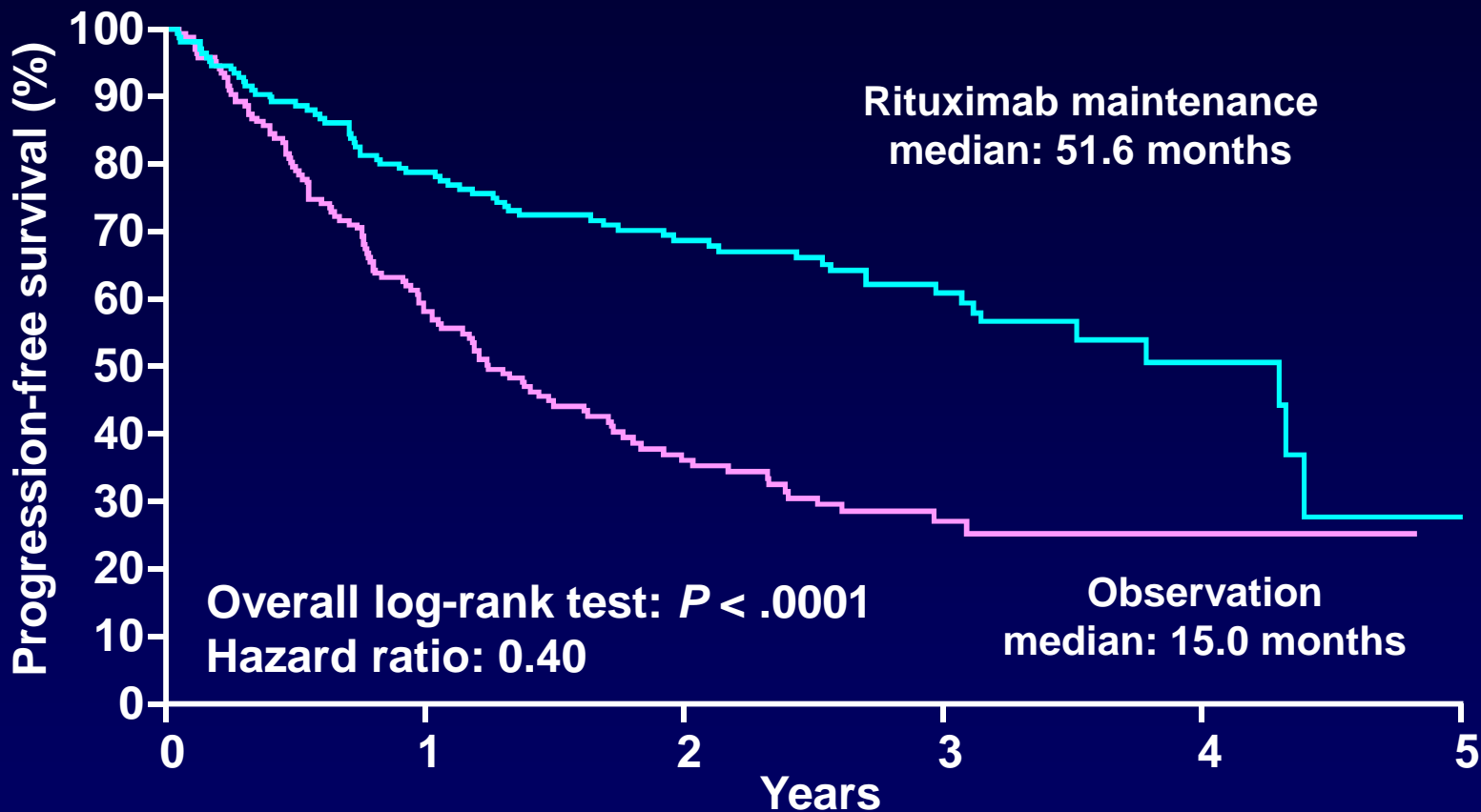
- Maintenance therapy against lymphoma more efficient in a state of minimal residual disease
- Long half life of the antibody in vivo allows to space the infusions for 2 – 3 months (Kahl BS, et al. *Blood*. 2007;110:Abstract 3420.)
- Rituximab immunological mediated actions (ADCC for instance) may be more effective at a period distinct from chemotherapy administration
- Good safety profile of the antibody

Relapsed/Resistant FL: EORTC 20981 Trial Design

Pivotal phase III Trial Using Rituximab Maintenance

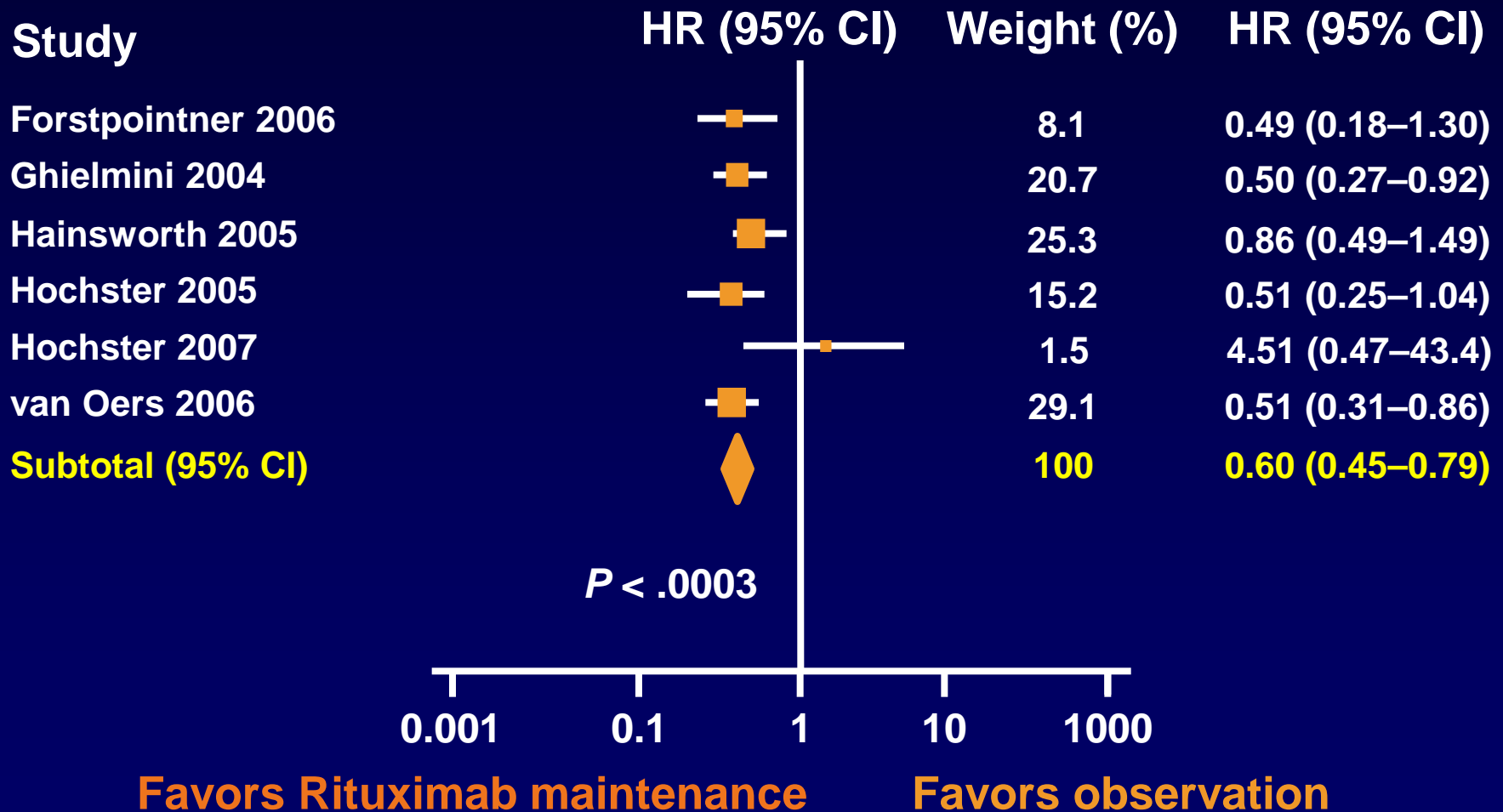


Intergroup Phase III Trial: PFS from Second Randomization – All Patients

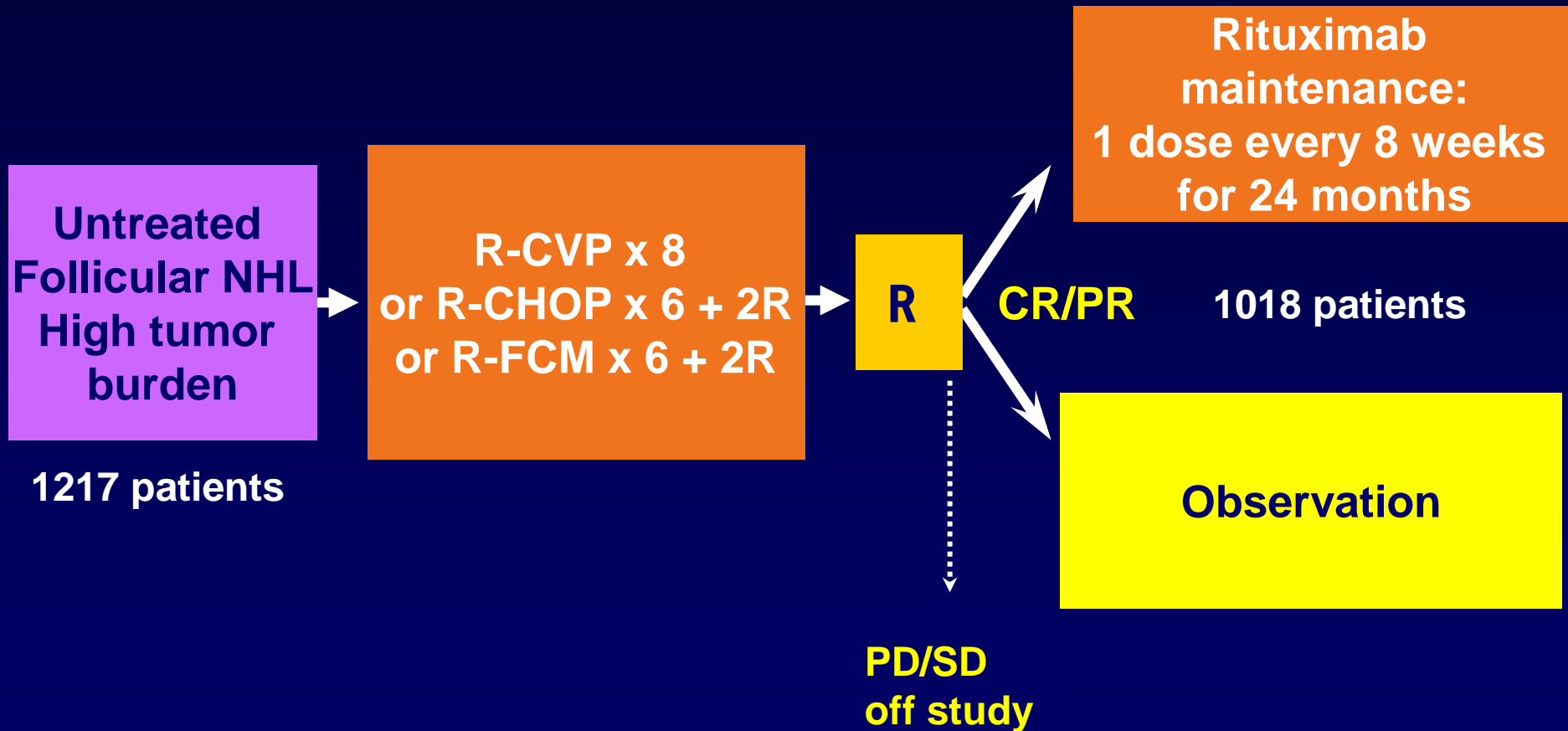


O	N	Number of patients at risk				Treatment
110	167	90	42	17	5	— Observation
66	167	126	86	47	12	— Rituximab

Meta Analysis: Rituximab Maintenance in FL



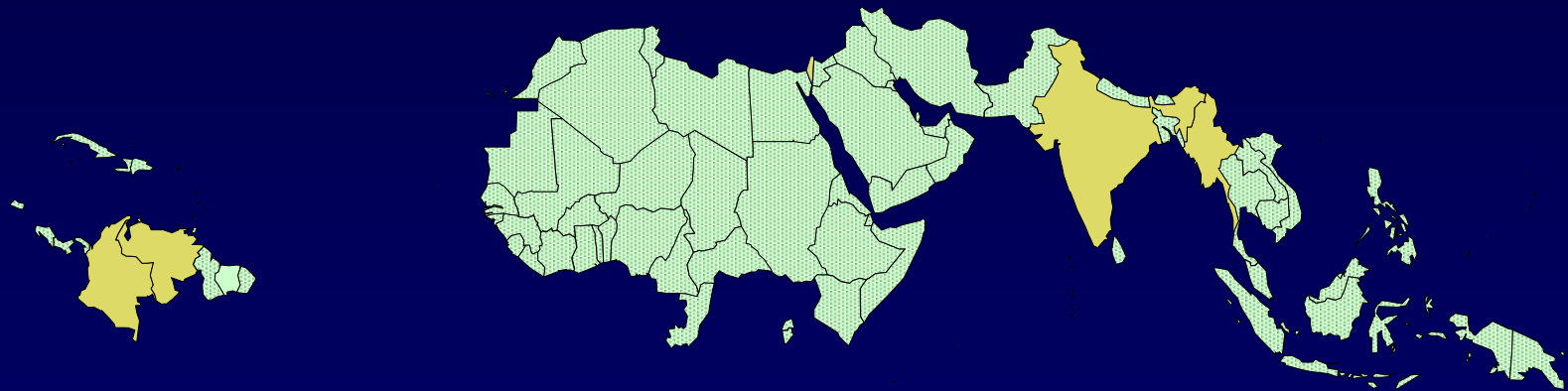
PRIMA Study



An international Intergroup study conducted by the GELA



PRIMA: An International Collaborative Effort



PRIMA Study

The DSMC had declared the first interim analysis positive

Results presented at ASCO and EHA meetings

Rituximab Maintenance: Open Questions

- **Optimal length?**
- **Safety of rituximab maintenance?**
- **Characteristics of relapses during/after maintenance? How to treat those relapses?**
- **Can we further improve the efficacy of maintenance with immunotherapy?**

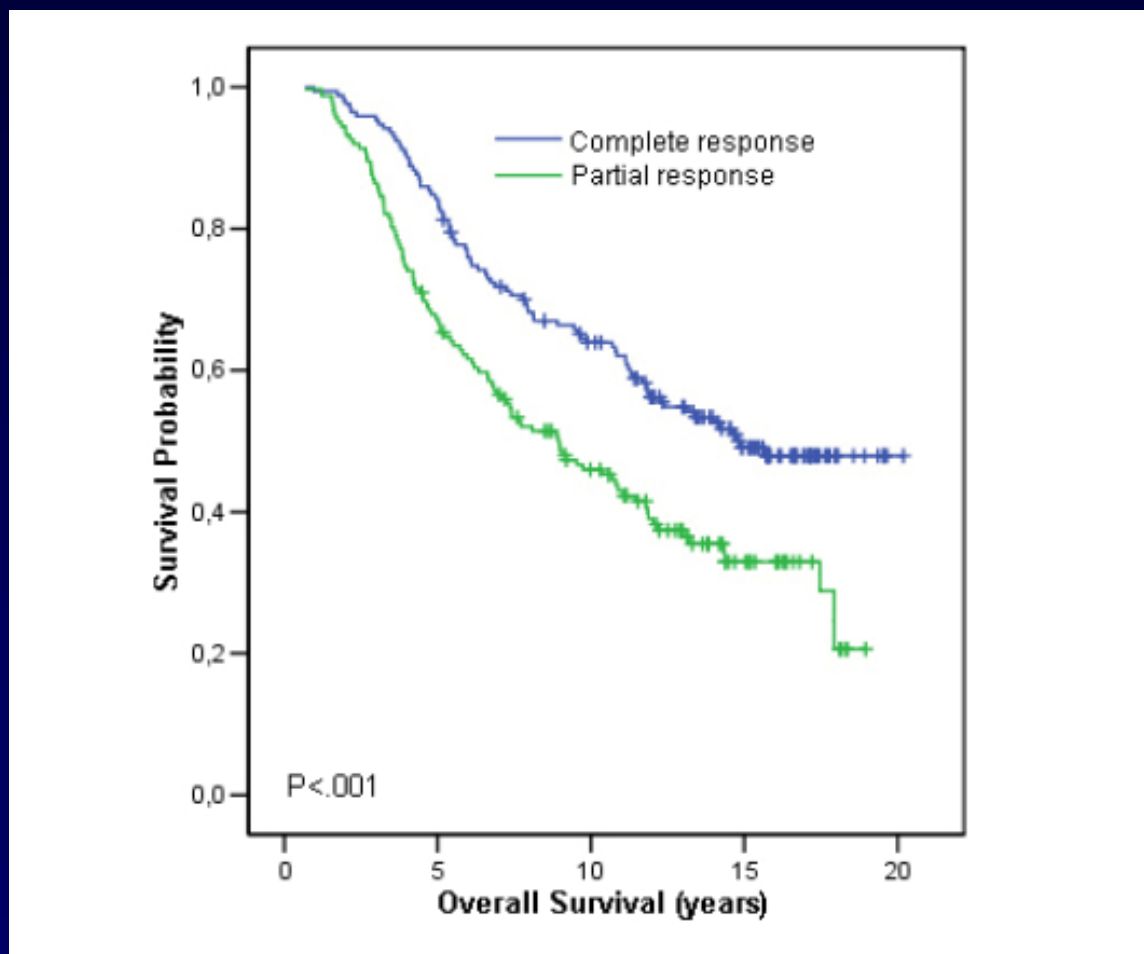
Follicular Lymphoma

Biological Aspects and Treatment

**What are our
treatment goals?**

Is it Necessary to Achieve A Complete Response with First-Line Treatment?

Long-term results of the GELF-86 trials



Follicular Lymphoma Treatment Being Conservative or Aggressive?

- The natural history has already changed
- We can then attempt to make further progress:
 - Earlier / more efficient intervention in low-risk patients
 - Use strategies that produce the highest CR rates or more prolonged PFS
 - Identify patients with a high risk of failure
 - Upfront with prognostic markers?
 - At the end of induction therapy (MRD, PET)?
 - Towards “intensification” with chemo? Immuno?
- Long term toxicities are worrisome when life expectancy > 15 years:
 - Careful evaluation always needed

Follicular Lymphoma: What do We Want to Achieve?

Improved survival

Patient wishes

Palliation

Chronic disease

Repeat treatments

High response rate

Long treatment-free intervals

Prolonged response

Quality of life

Healthcare costs

Histological transformation

Long-term side effects

Improving Patient Survival in FL

