The role of chemotherapy in follicular lymphomas

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WHO grading of follicular lymphoma

- **Follicular Lymphoma, grade 1**
  predominantly centrocytes (small cleaved B cells)
  with only a few (0- 5 per h.p.f.) scattered centroblasts
  (large B cells)

- **Follicular Lymphoma, grade 2**
- a mixture of centroblasts (6-15 per h.p.f.) and centrocytes

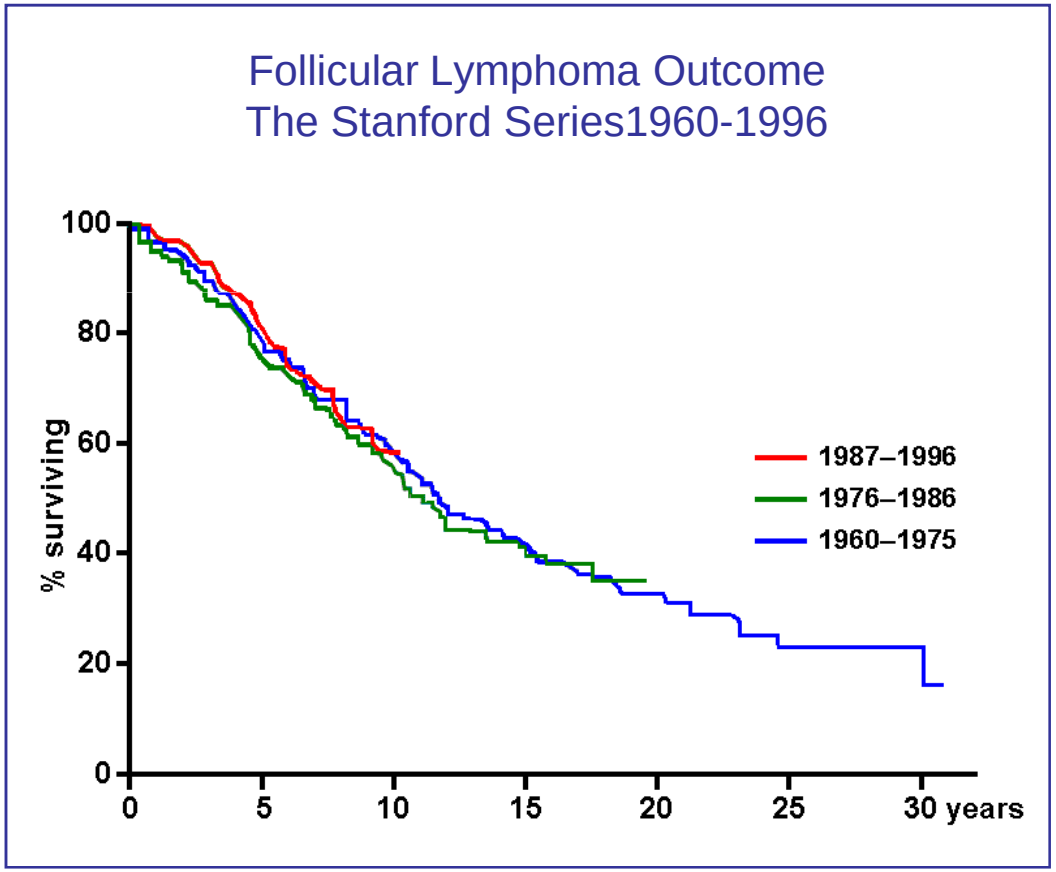
- **Follicular Lymphoma, grade 3A**
  predominantly centroblasts (>15 per h.p.f.)

- **Follicular Lymphoma, grade 3B**
  solid sheets of centroblasts
  (is considered a DLCL!)

<10% of FL

Natural history of FL over the last 3 decades of the 20th century

- most pts present with disseminated disease
- nearly all pts respond to first therapy, nearly all relapse and at relapse RR and PFS decrease,nearly all ultimately, die of FL (transformed?)
- median OS ~10 yrs in all historical series
- No radomised trial showed a survival advantage for any initial regimen

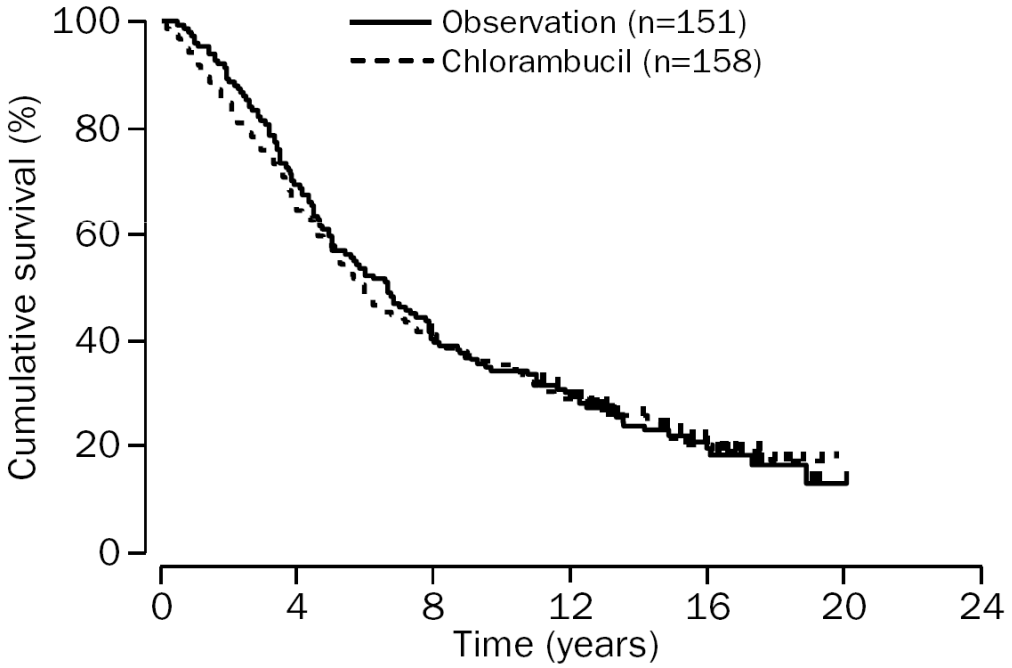


Historical Background

- up to ≥20% of FL patients have spontaneous remissions lasting longer than 1 year
  - *Horning SJ & Rosenberg SA. NEJM* 1984
    Gattiker HH, et al. Cancer 1980
    Krikorian JG, et al. Cancer 1980
- Stanford study of immediate vs delayed treatment:
  → median time to treatment 3 years
  → no survival advantage to upfront therapy

  Hoppe RT, et al. Blood 1981
- NCI randomized study comparing no initial therapy vs. immediate ProMACE-MOPP followed by TLI:
  → no survival advantage to upfront therapy
  - *Longo DL, et al. JCO* 1993

Patients without adverse parameters do not require immediate treatment



Patients at risk

Chlorambucil	105	60	42	15	2	0
Observation	103	65	43	17	0	0

Watch and wait is still an option!

- 3 randomized studies have shown an identical survival for the asymptomatic patients whether treated or untreated upfront

Brice et al, JCO 1997

Ardeshna et al, The Lancet 2003

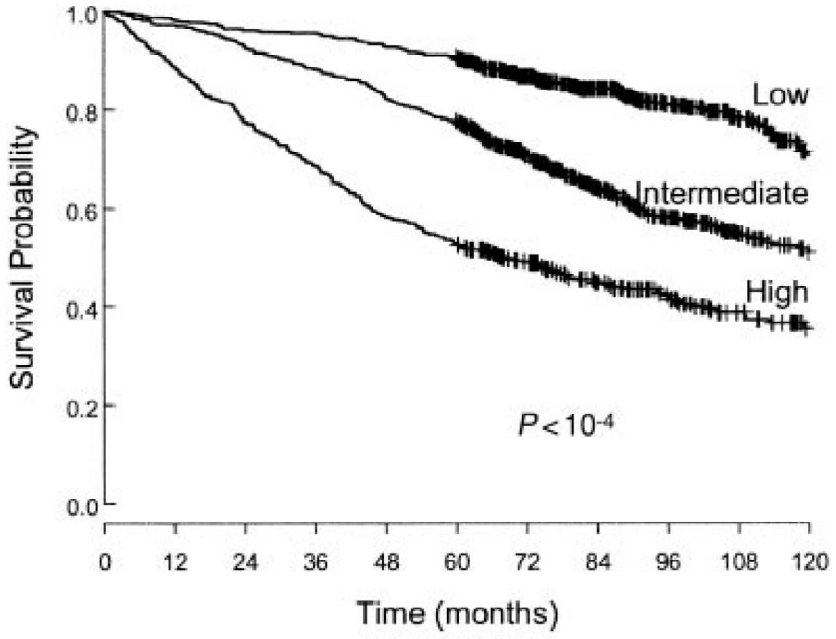
Most patients in FL trials were «in need of treatment»

GELF criteria†

- 3 nodes > 3 cm
- Single node > 7 cm
- Systemic symptoms or any symptoms
- Compression or risk of compression of vital organ
- Leukemic phase
- Cytopenias due to marrow infiltration
- Splenomegaly > 16 cm

† Presence of any one factor indicates that treatment should be considered.

FLIPI provides useful prognostic information



No. of Events											
Low	-	12	25	29	46	60	83	95	106	113	125
Intermediate	-	19	49	79	118	150	192	225	247	255	261
High	-	54	109	152	202	229	245	260	268	274	278
No. at Risk											
Low	641	629	616	612	595	581	450	337	241	157	93
Intermediate	670	651	621	591	552	519	385	263	178	108	68
High	484	430	375	332	282	255	193	139	98	56	33

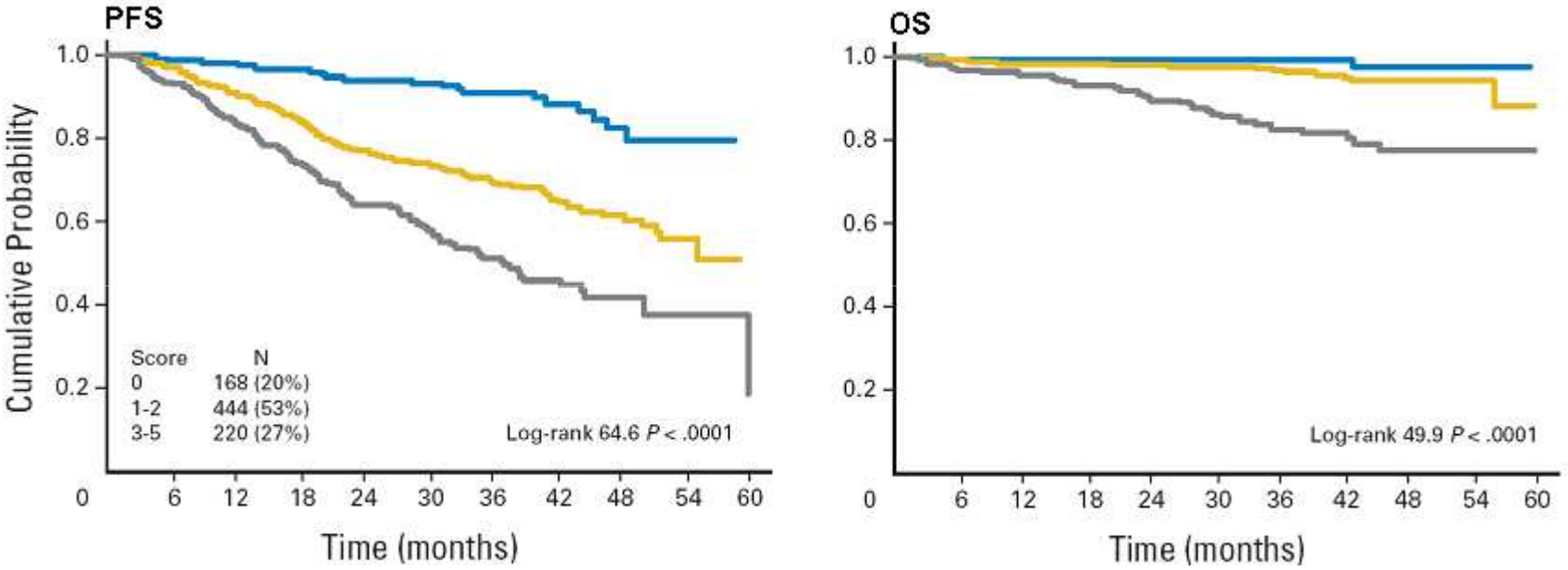
Figure 4. Survival of the 1795 patients according to risk group as defined by the Follicular Lymphoma International Prognostic Index.

Most patients are still not treated at presentation

but FLIPI has never been validated as
a tool for deciding which patients
need therapy
and was not designed with this specific purpose

Solal-Céligny Blood 2004

FLIPI-2 a new promising tool in the Rituximab era



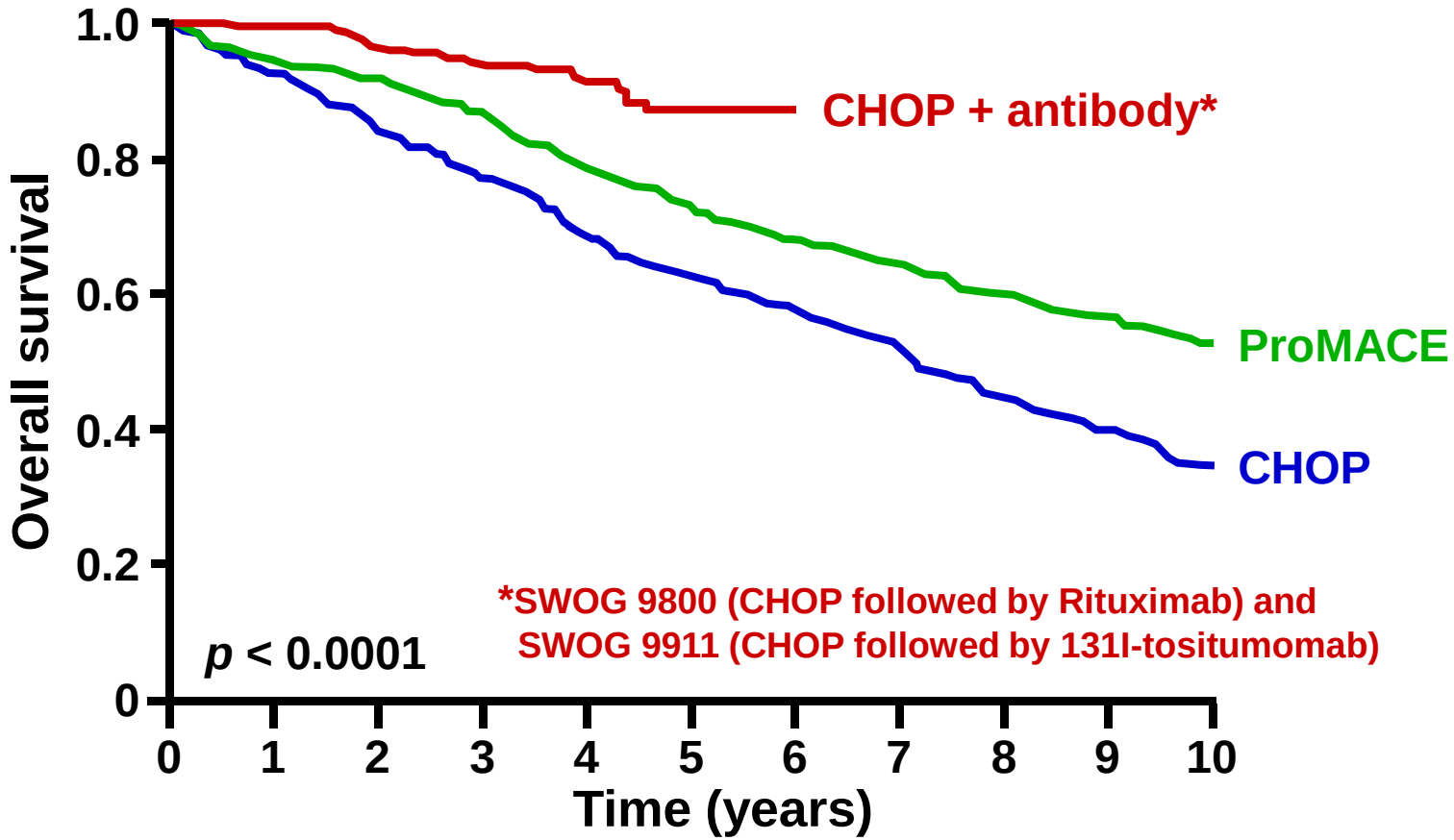
- Beta 2-microglobulin > normal
- longest diameter of the largest involved node > 6 cm
- bone marrow involvement
- hemoglobin level < 12 g/dL
- age > 60 years

Federico, JCO 2009

Improvement of FL mortality over the time in recent reports

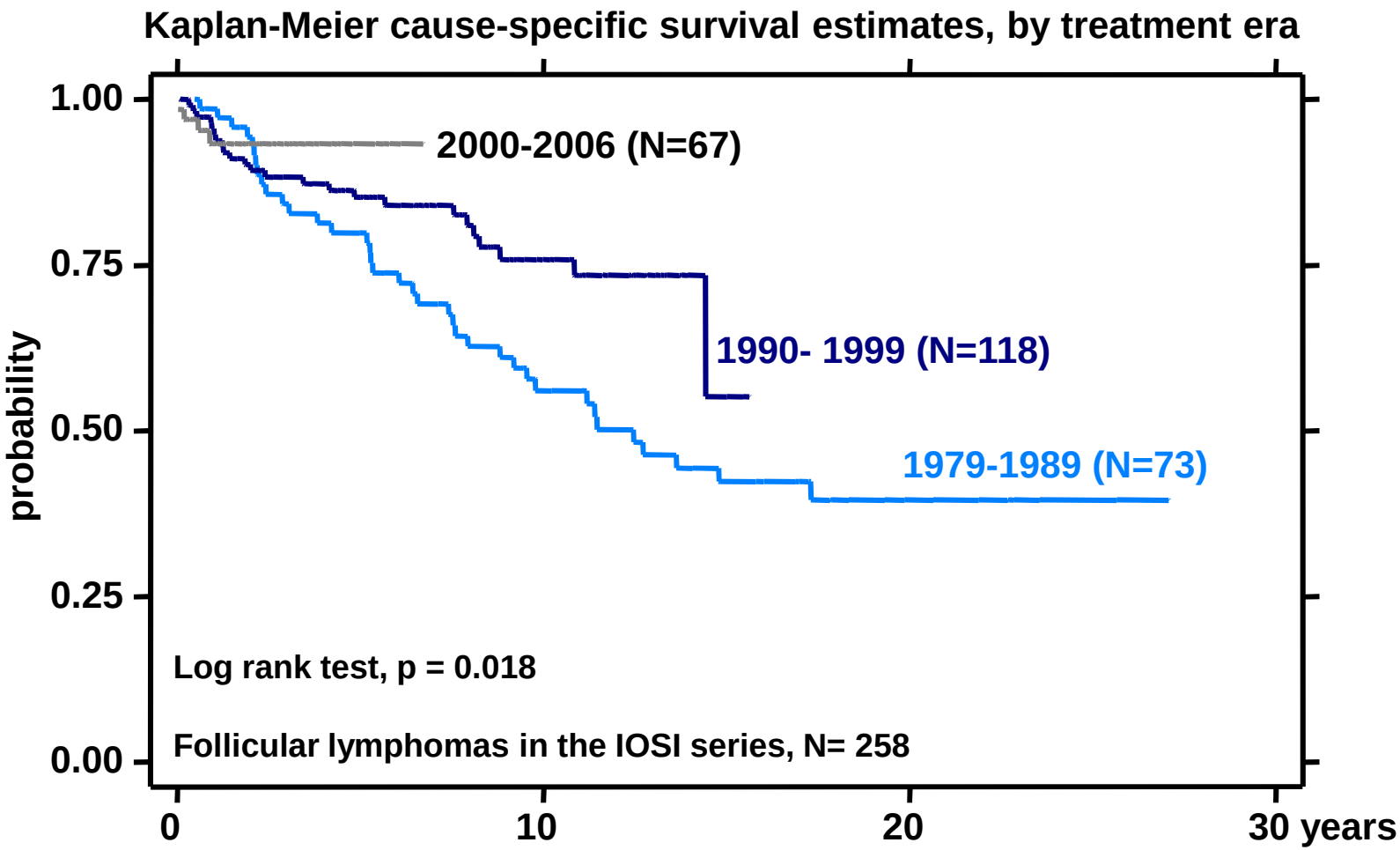
Author	Study population	Time span	N	Median age (y)
Swenson, JCO 2005	SEER cancer registries	1978-1999	14564	63
Fisher, JCO 2005	5 SWOG clinical trials	1974-2000	960	48-55
Liu, JCO 2006	5 MDACC clinical trials	1972-2002	580	72% <60
Sacchi, Cancer 2007	GISL clinical studies	1988-2004	438	69% <60
Tan, ASH 2007	Stanford consecutive pts	1969-2003	1334	49
Sebban, JCO 2008	2 GELA clinical studies	1986-2001	364	49-50
Zucca, ECCO 2007	IOSI consecutive pts	1979-2007	281	58

Rituximab has changed the FL clinical course



Fisher RI, *et al. J Clin Oncol* 2005; 23:8447–8452.

FL Lymphoma-Specific Survival



Conconi, *et al. Leuk Lymphoma 2010, in press*

Therapy of Follicular Lymphoma

- wait and see policy
- radiotherapy
- alkylating agents
- anthracycline-based chemotherapy
- purine analogs
- bendamustine
- unconjugated MoAbs
- radiolabelled MoAbs
- autologous SCT
- allogeneic SCT
- non-myeloablative allogeneic SCT
- DNA vaccination, antisense, etc

Follicular Lymphoma treatment

soft approaches

Palliation

Chronic disease

Repeat treatments

Histological transformation

Patient wishes

Quality of life

Healthcare costs

aggressive therapies

High response rate

Prolonged response

Long treatment-free intervals

Long term side-effects

prolong survival?

Therapeutic options at diagnosis for follicular lymphoma patients

- wait and see policy
- soft treatments
  - e.g. MoAbs only, (R)-chlorambucil…
- more intensive immunochemotherapy
  - e.g. R-CVP or R-CHOP (± R-maintenance)

Randomized Chemotherapy trials for FL

Regimen	References	CR Rates, %	Median Progression-Free Survival	Median Overall Survival
Chlorambucil/ cyclophosphamide	Peterson[49] Baldini[50]	66 34	4.2 yr 30 mo	8.7 yr >38 mo
Fludarabine	Coiffier[51] Hagenbeek[52]	34 38	1.5 yr 21 mo	2.7 yr Not reached
CVP	Klasa[53] Hagenbeek[52] Marcus[54]	7 15 10	9 mo 15 mo 15 mo	44 mo Not reached >30 mo
CHOP	Zinzani[55] Peterson[49]	51 60	>3 yr 3.6 yr	>3 yr 9.7 yr
FM	Zinzani[55] Foussard[56]	68 49	>3 yr 3 yr	>3 yr >53 mo
CHVP+INF	Solal-Celigny[9]	20	2.9 yr	>6 yr

B. Coiffier. Clinical Advances in Hematology & Oncology, 2005

Rituximab-based induction therapy is standard front-line treatment for FL

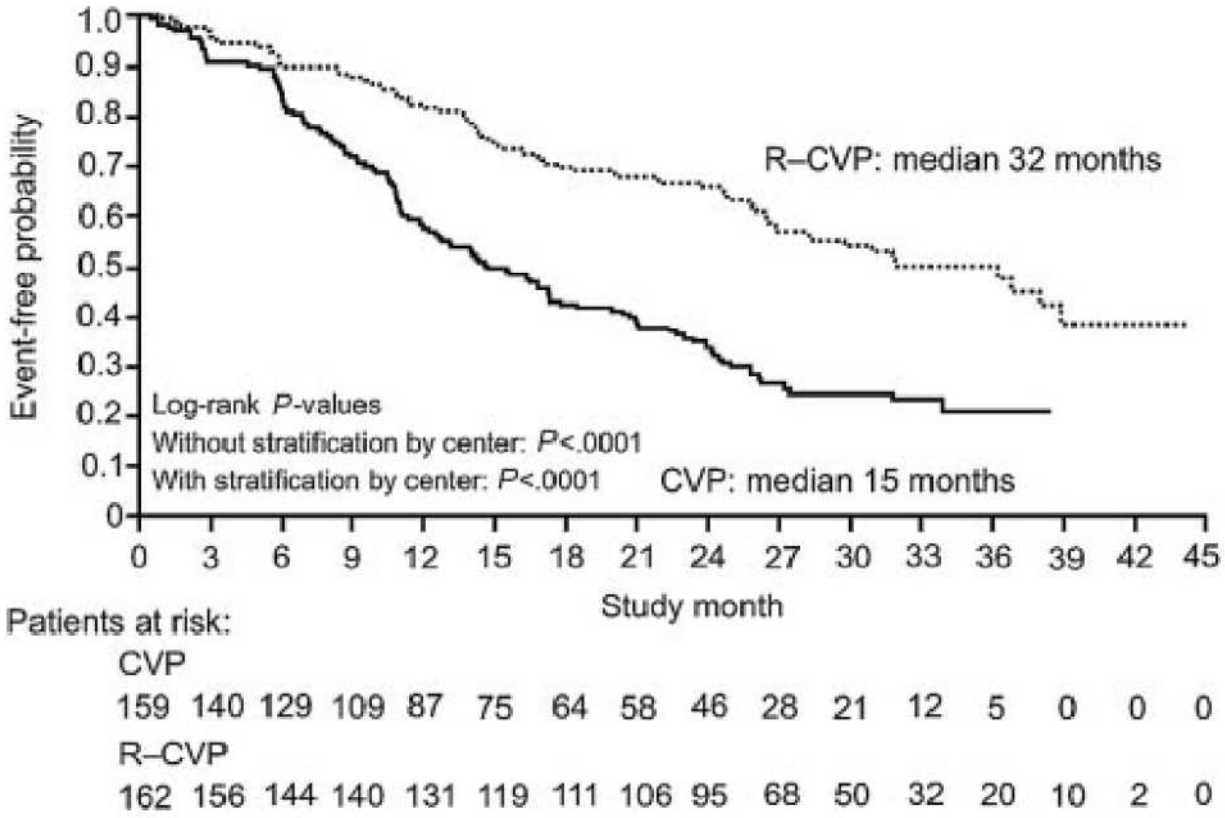


Figure 1. Time to disease progression, relapse or death after a median follow-up of 30 months among 321 patients assigned to chemotherapy with CVP or with R-CVP. Solid line represents CVP; dotted line, R-CVP.

Marcus et al. Blood 2005

Rituximab-based induction therapy is standard front-line treatment for FL

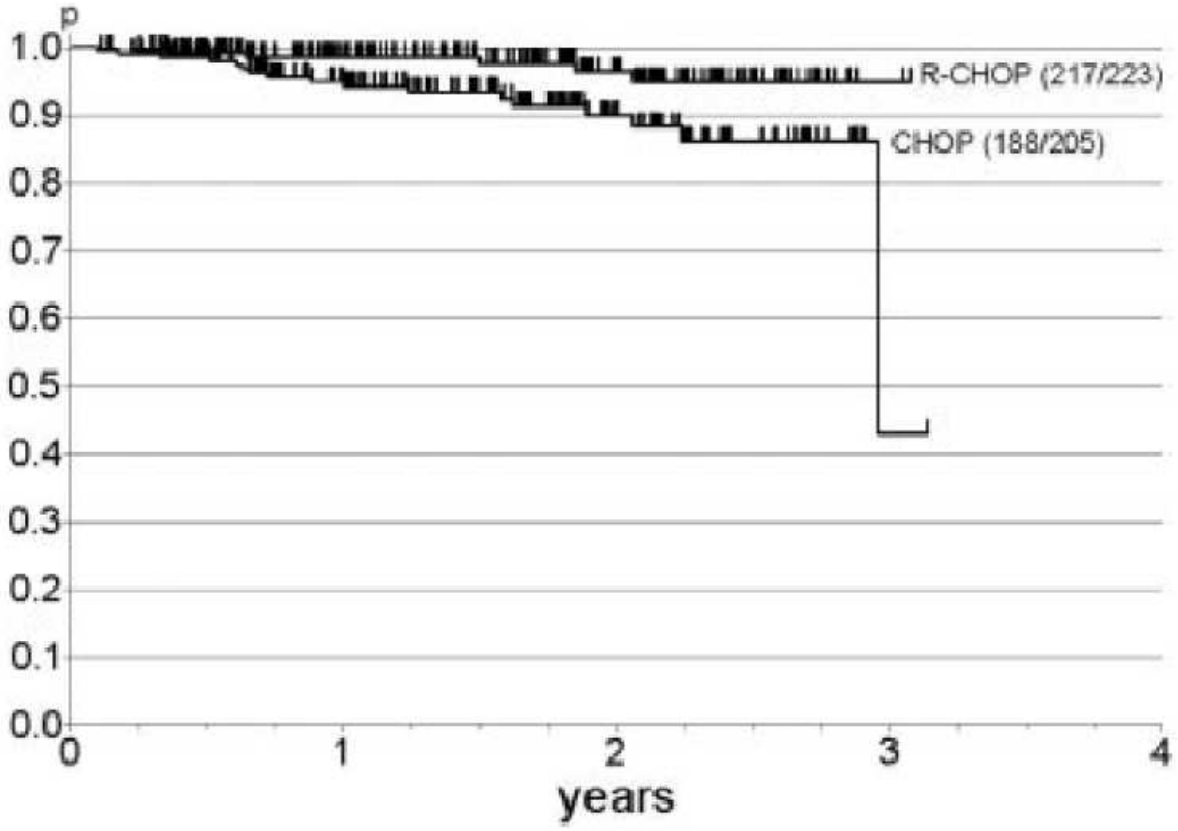
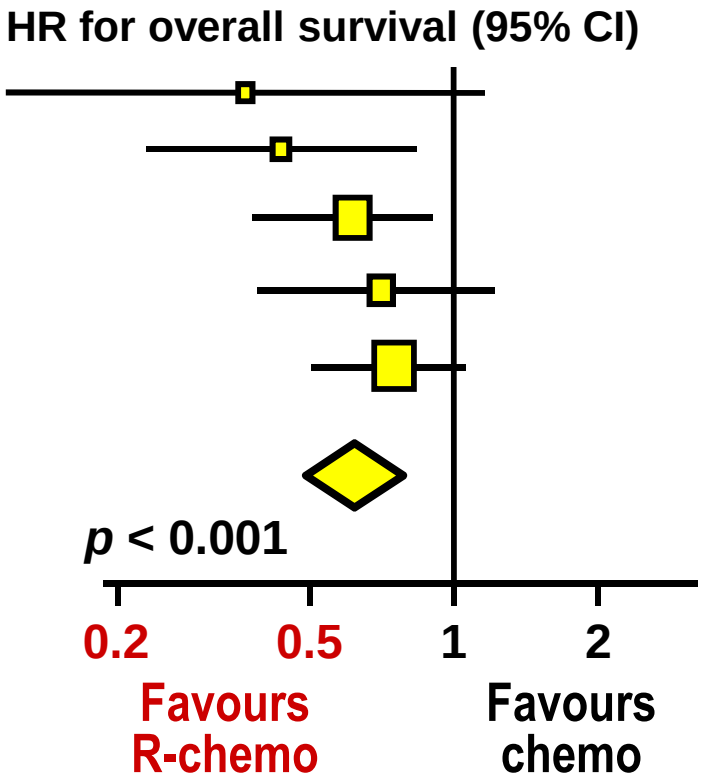


Figure 3. OS after start of therapy for CHOP and R-CHOP. Median OS has not been reached in either group. After 3 years, 6 patients in the R-CHOP arm have died compared with 17 patients in the CHOP arm ($P = .016$).

Hiddemann et al. Blood 2005

Rituximab-based induction in FL is superior to chemotherapy alone with respect to OS

R-chemo vs chemo induction

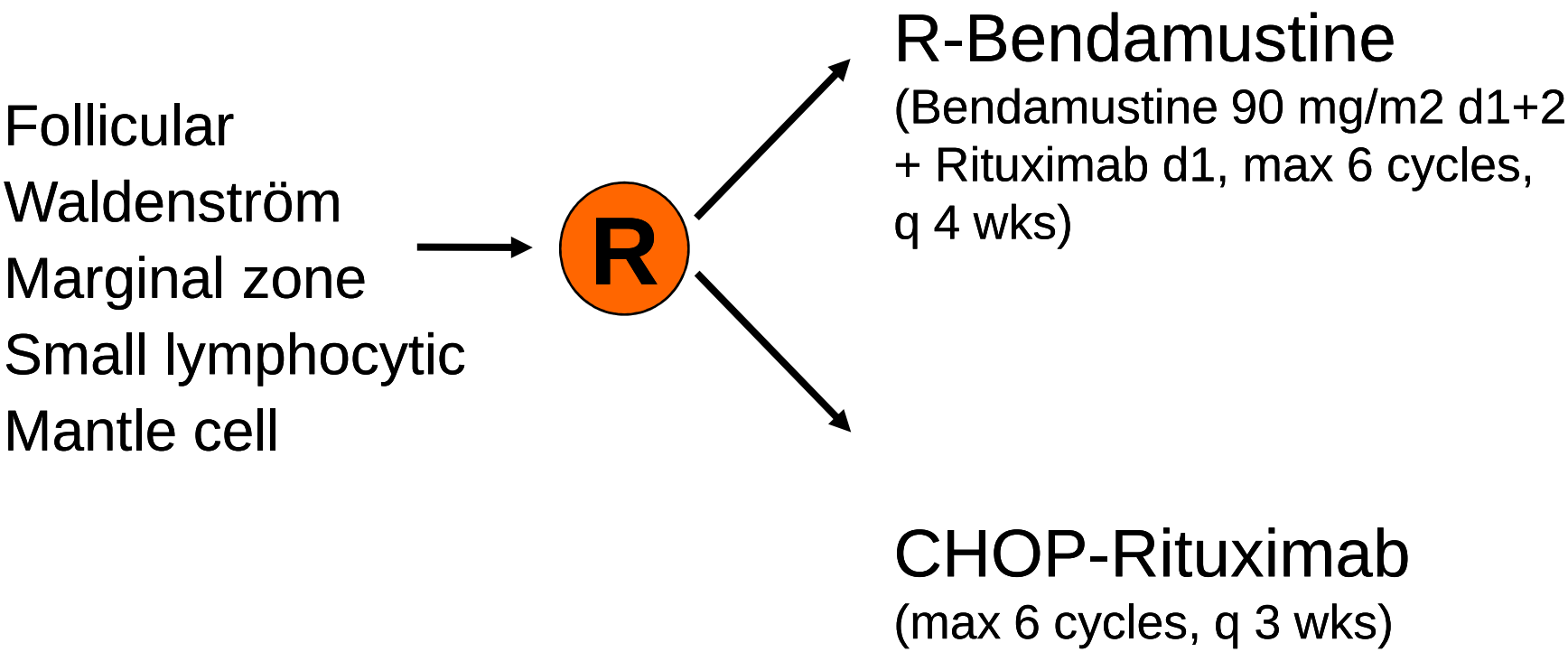


Patients treated with R-chemo had better overall survival, overall response, and disease control.

R-chemo improved overall survival in patients with follicular lymphoma (HR for mortality = 0.63; 95% CI = 0.51 to 0.79)

Schulz H *et al. JNCI* 2007

StiL NHL 1-2003:
R-Bendamustine- *vs* R-CHOP



Rummel et al ASH 2009 Abs # 405

StiL NHL 1-2003 (B-R vs R-CHOP): Hematotoxicity grade 3+4

	B-R (n=1.450) (% of cycles)	**R-CHOP (n=1.408)** (% of cycles)	*P*-value
Leukocytopenia	12,1	38,2	< 0.0001
Neutropenia	10,7	46,5	< 0.0001
G-CSF administered	4,0	20,0	< 0.0001
Thrombocytopenia	0,7	1,2	
Anemia	1,4	1,9	

Rummel et al ASH 2009 Abs # 405

StiL NHL 1-2003 (B-R vs R-CHOP): Toxicity (all CTC grades)

	B-R (n=260) (No. of pts)	**R-CHOP (n=253)** (No. of pts)	*P*-value
Alopecia	-	+++	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin (erythema)	42	23	0.012
Allergic reaction (skin)	40	15	0.0003
Infectious complications	96	127	0.0025
Sepsis	1	8	0.019

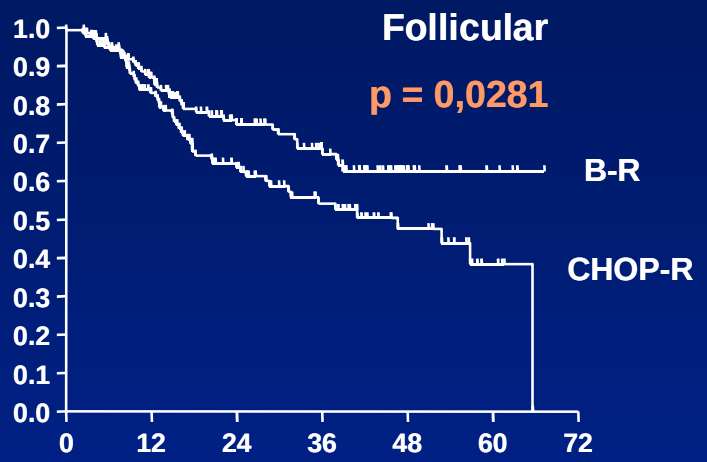
Rummel et al ASH 2009 Abs # 405

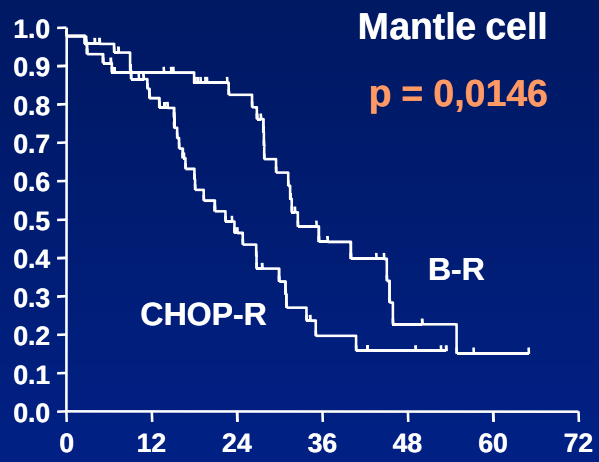
StiL NHL 1-2003 (B-R vs R-CHOP): Response rates

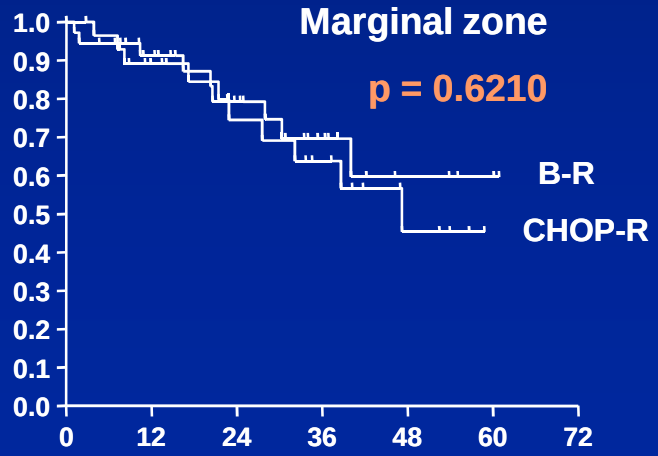
	B-R (n=260) (No. of pts)	**R-CHOP (n=253)** (No. of pts)	*P*-value
CR	39,6 %	30,0 %	= 0.0262
SD	2,7 %	3,6 %	
PD	3,5 %	2,8 %	
ORR	92,7 %	91,3 %	

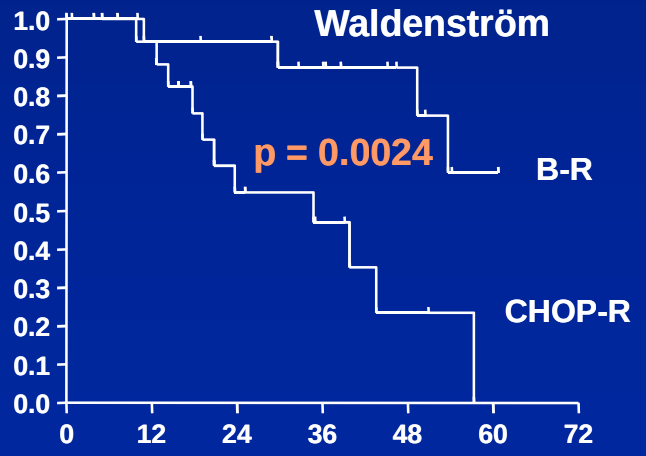
Rummel et al ASH 2009 Abs # 405

Progression free survival by histologic type









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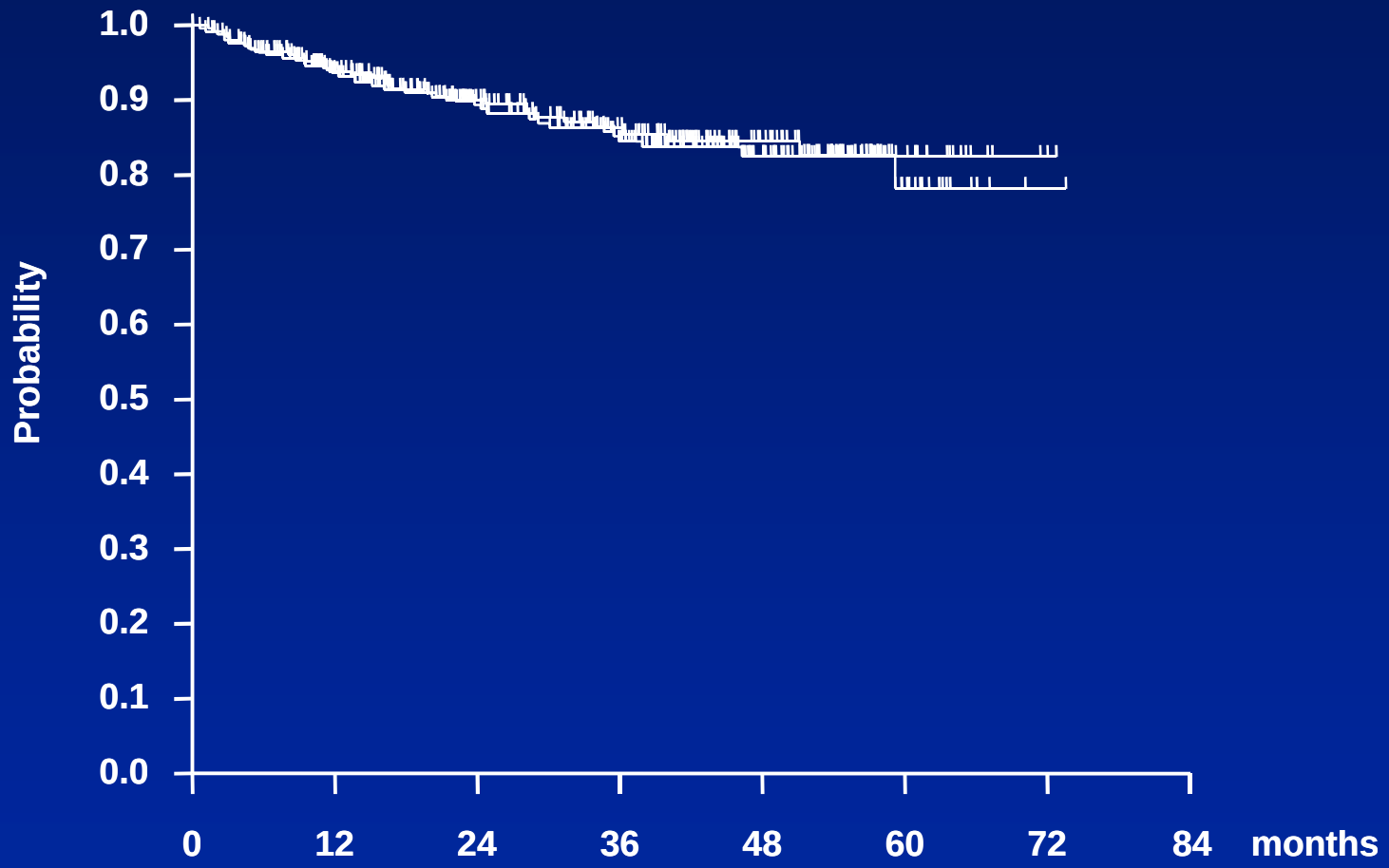
Overall Survival



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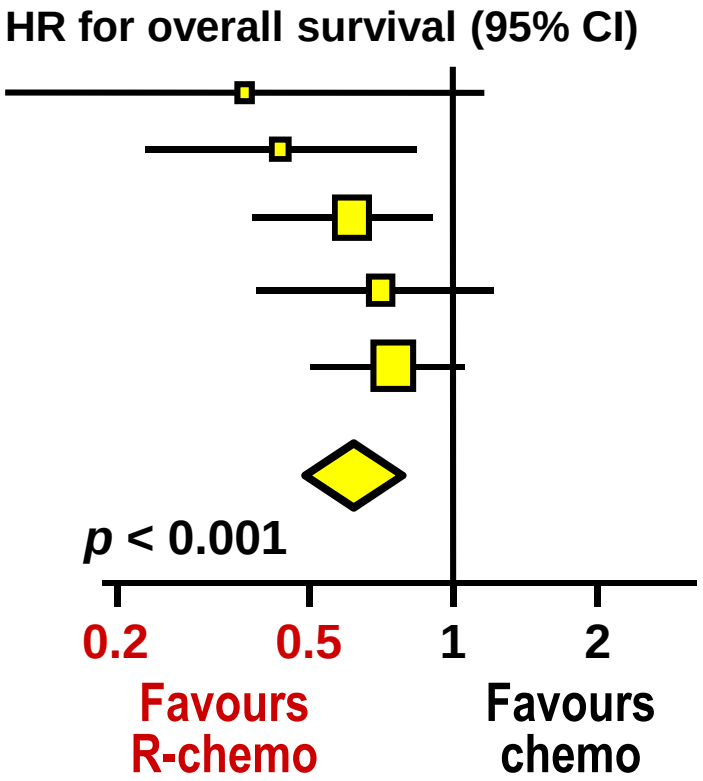
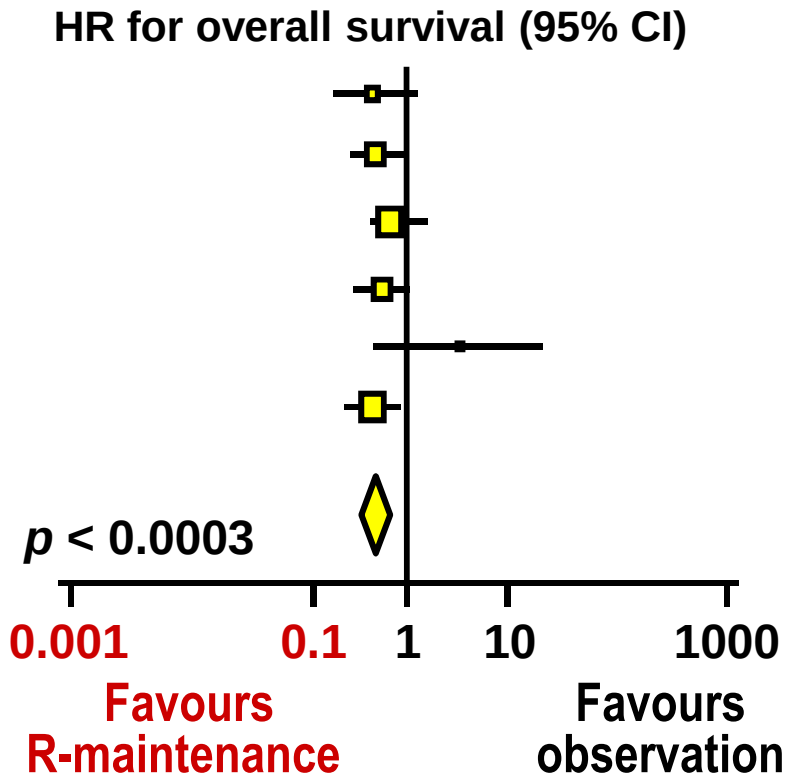
Follicular lymphoma: Rituximab-based induction and maintenance therapy is the standard of care

R-chemo vs chemo induction [1]



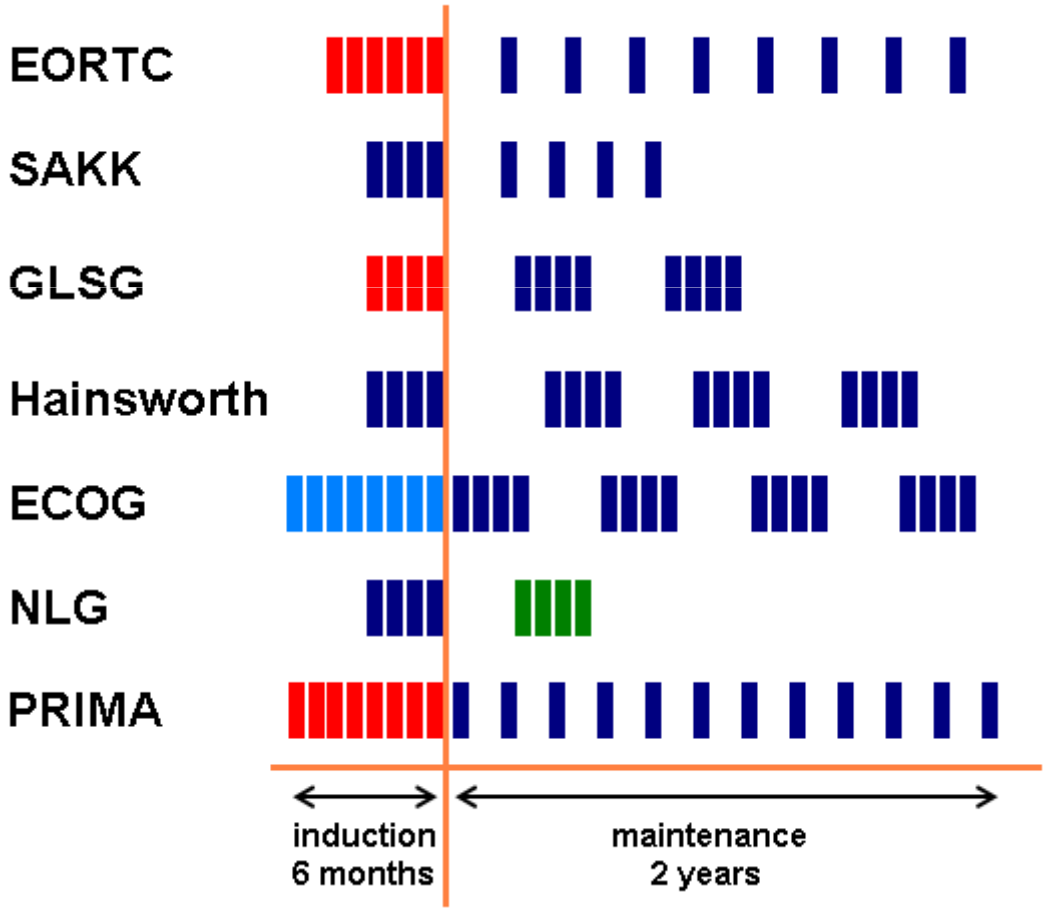
R-maintenance vs observation [2]



[1] Schulz H *et al. JNCI* 2007

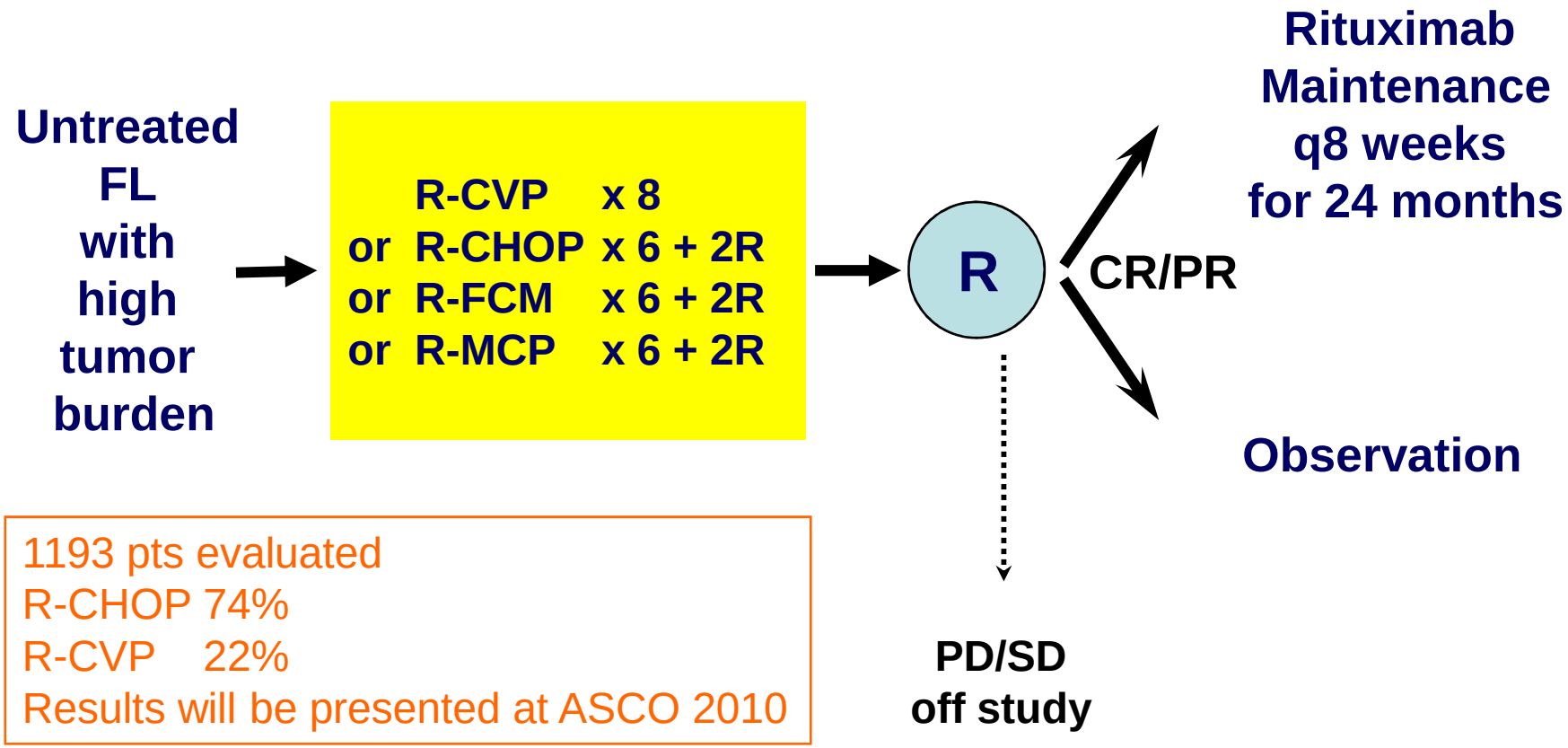
[2] Vidal L *et al. JNCI* 2009

Rituximab maintenance schedule



PRIMA Study

R-maintenance after front-line intensive R-chemo



1193 pts evaluated
R-CHOP 74%
R-CVP 22%
Results will be presented at ASCO 2010

An international intergroup trial coordinated by the GELA

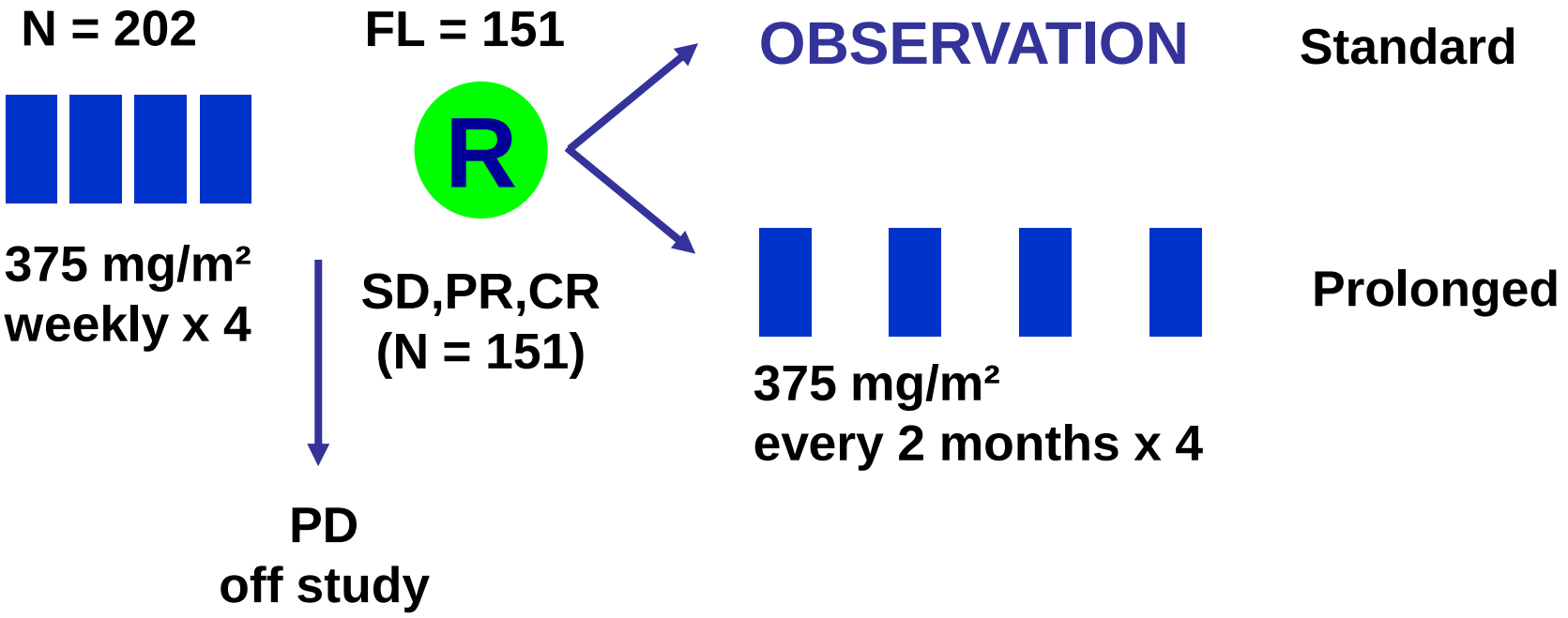
Gela

Phase III Study Showed Patients Lived Longer Without Lymphoma Progressing When Rituxan Was Used First-Line for Maintenance

Thu Sep 17, 2009 1:03am EDT
SOUTH SAN FRANCISCO, Calif. & CAMBRIDGE, Mass.
--(Business Wire)--
Genentech, Inc., a wholly-owned member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY) and Biogen Idec (Nasdaq:BIIB), today announced that a Phase III study (PRIMA) showed that patients with follicular lymphoma who continued receiving Rituxan (rituximab) alone after responding to Rituxan and chemotherapy lived longer without their disease worsening (progression-free survival or PFS) than those who did not continue to receive Rituxan. Because PRIMA met its endpoint during a pre-planned interim analysis, the study was stopped early on the recommendation of an independent data and safety monitoring board. The safety profile of Rituxan observed in the study was consistent with that previously reported.

Single agent rituximab in FL: The SAKK35/98 study

FL pretreated/untreated in need oftreatment



Ghielmini et al. Blood 2004

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SAKK35/98 - Patients' Characteristics

	Included (n = 202)	Randomised (n = 151)
Median age	57	57
PS 0-I	94 %	97 %
Stage III-IV	85 %	85 %
Involved BM	52 %	50 %
Bulky (≥ 5 cm)	53 %	48 %
Elevated LDH	37 %	30 %
Previous chemotherapy	68 %	66%

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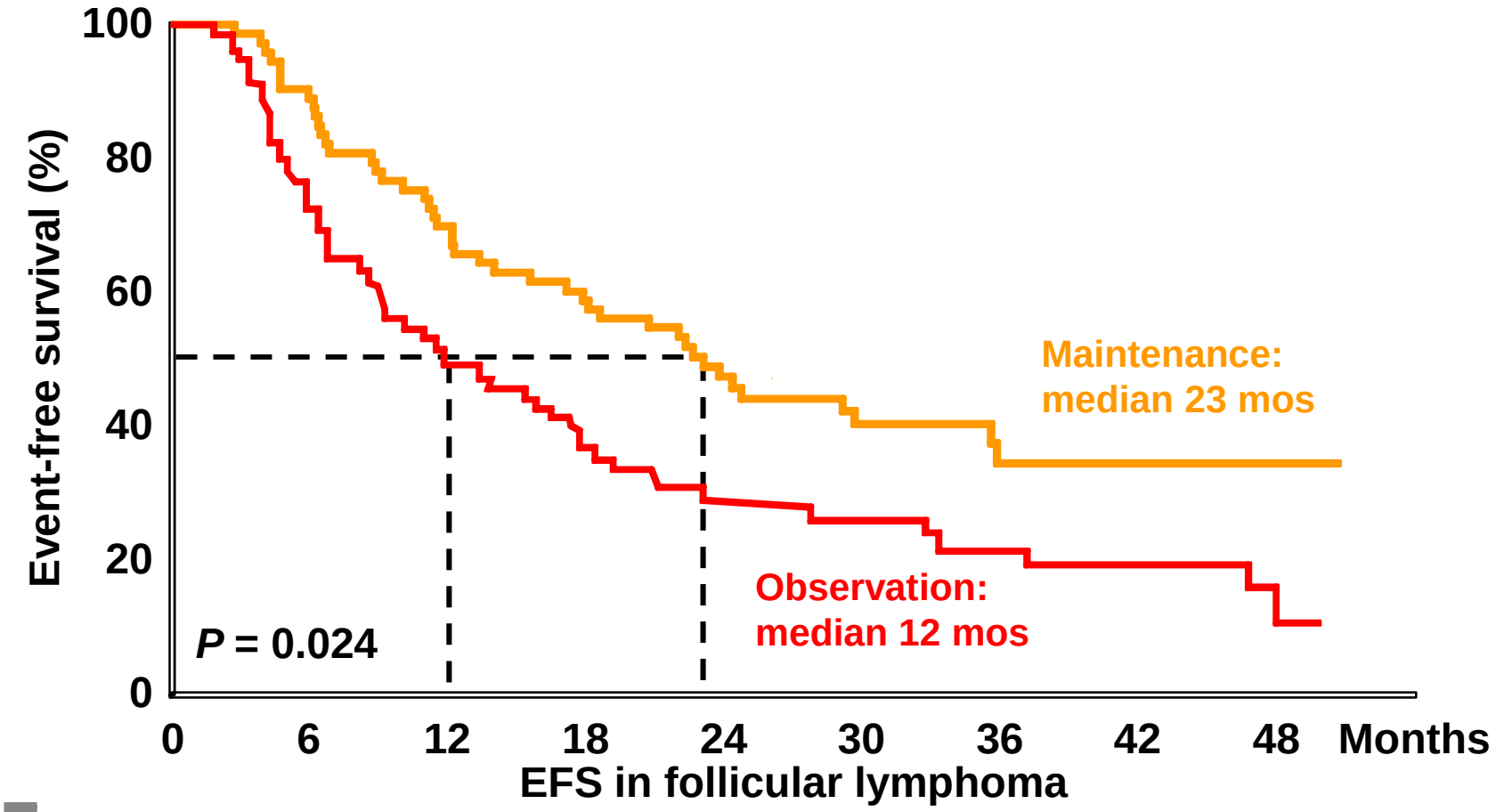
Ghielmini et al. Blood 2004

SAKK 35/98
R-maintenance after single agent Rituximab



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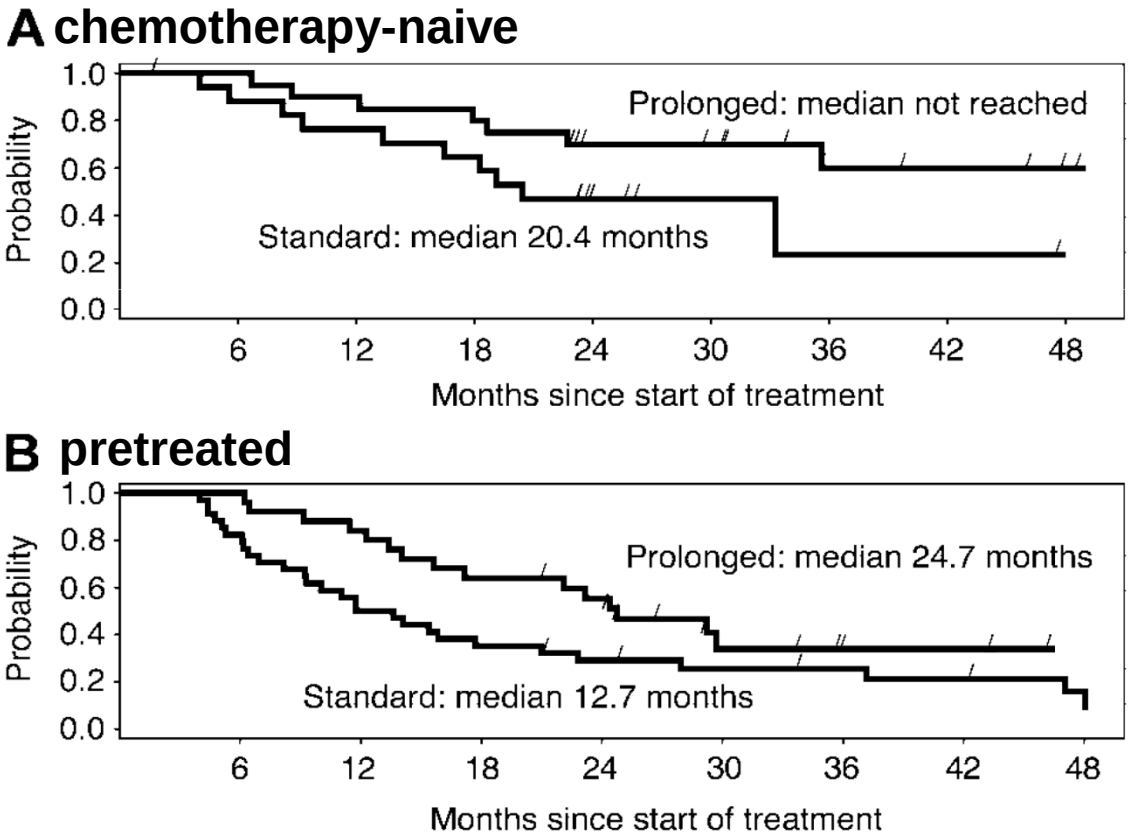
Ghielmini M, *et al. Blood* 2004; 103:4416–4423.

SAKK 35/98 - response duration by arm



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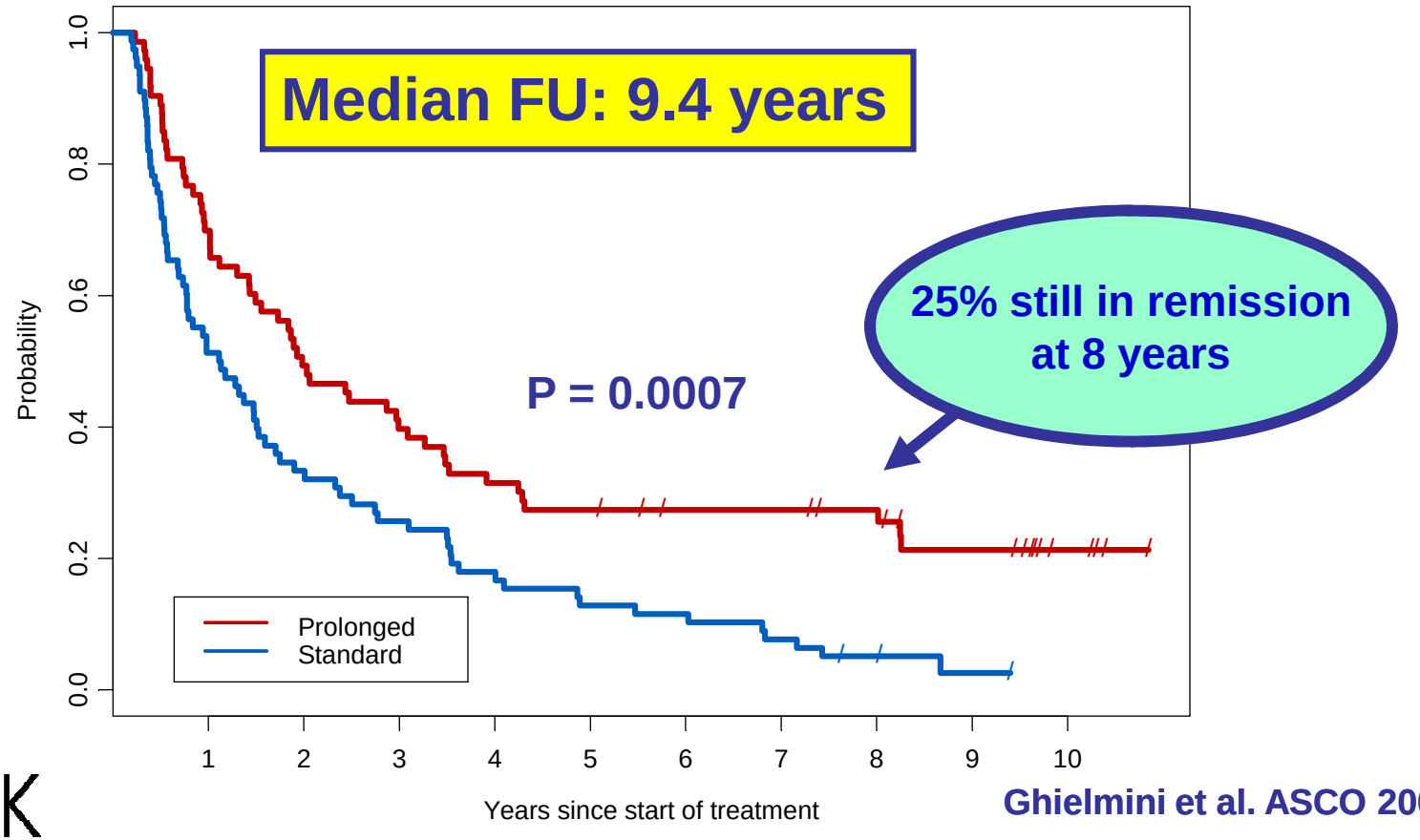
Ghielmini M, *et al. Blood* 2004; 103:4416–4423.

SAKK 35/98 Long-Term Follow-up

Event-free survival in randomized follicular lymphoma patients



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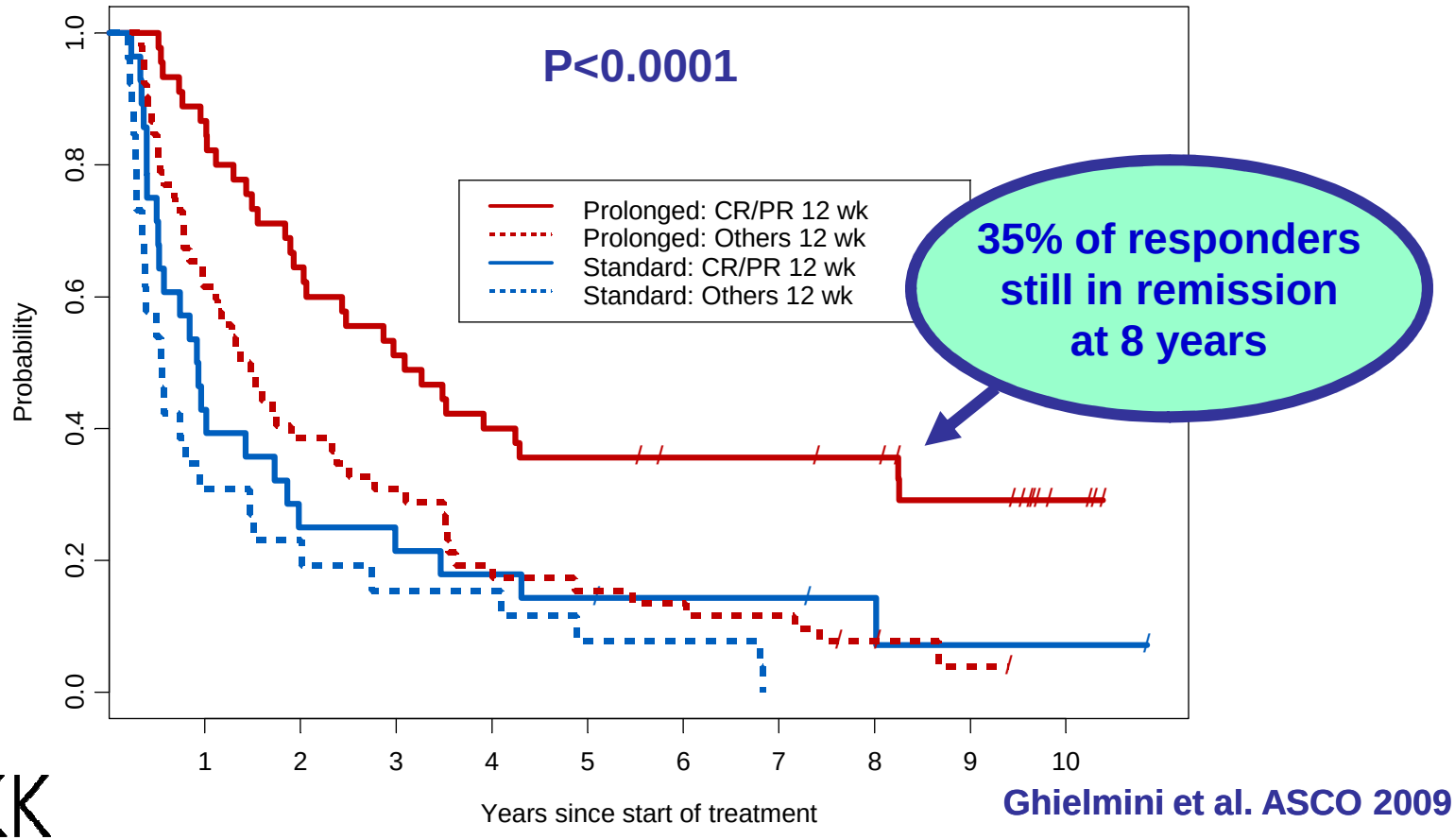
Ghielmini et al. ASCO 2009

SAKK 35/98 Long-Term Follow-up

EFS according to response to rituximab

Event-free survival in randomized follicular lymphoma patients



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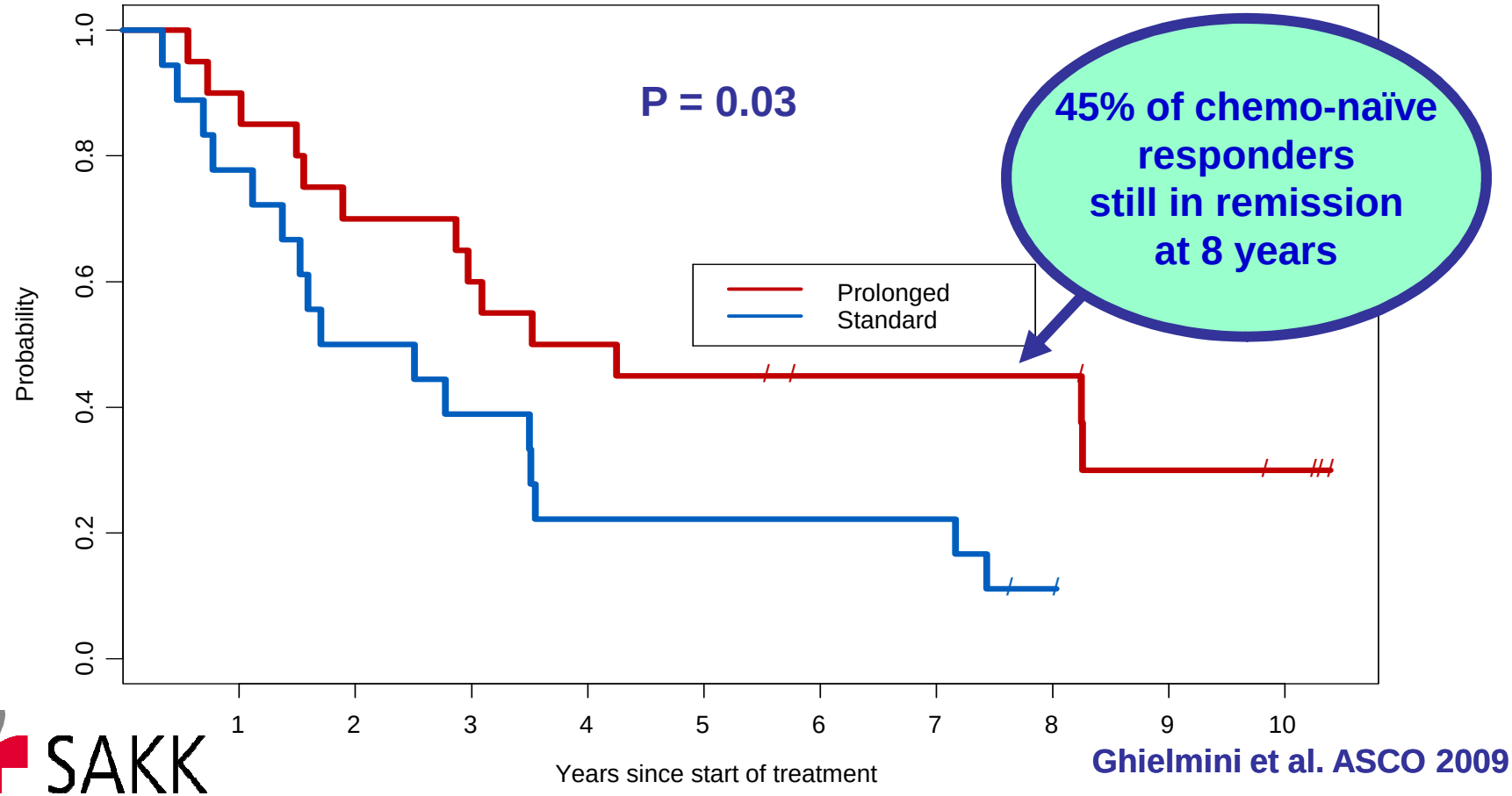
Ghielmini et al. ASCO 2009

SAKK 35/98 Long-Term Follow-up

EFS in chemo-naïve responders (n=38)

Event-free survival in chemo-naive patients with CR/PR at 12 weeks



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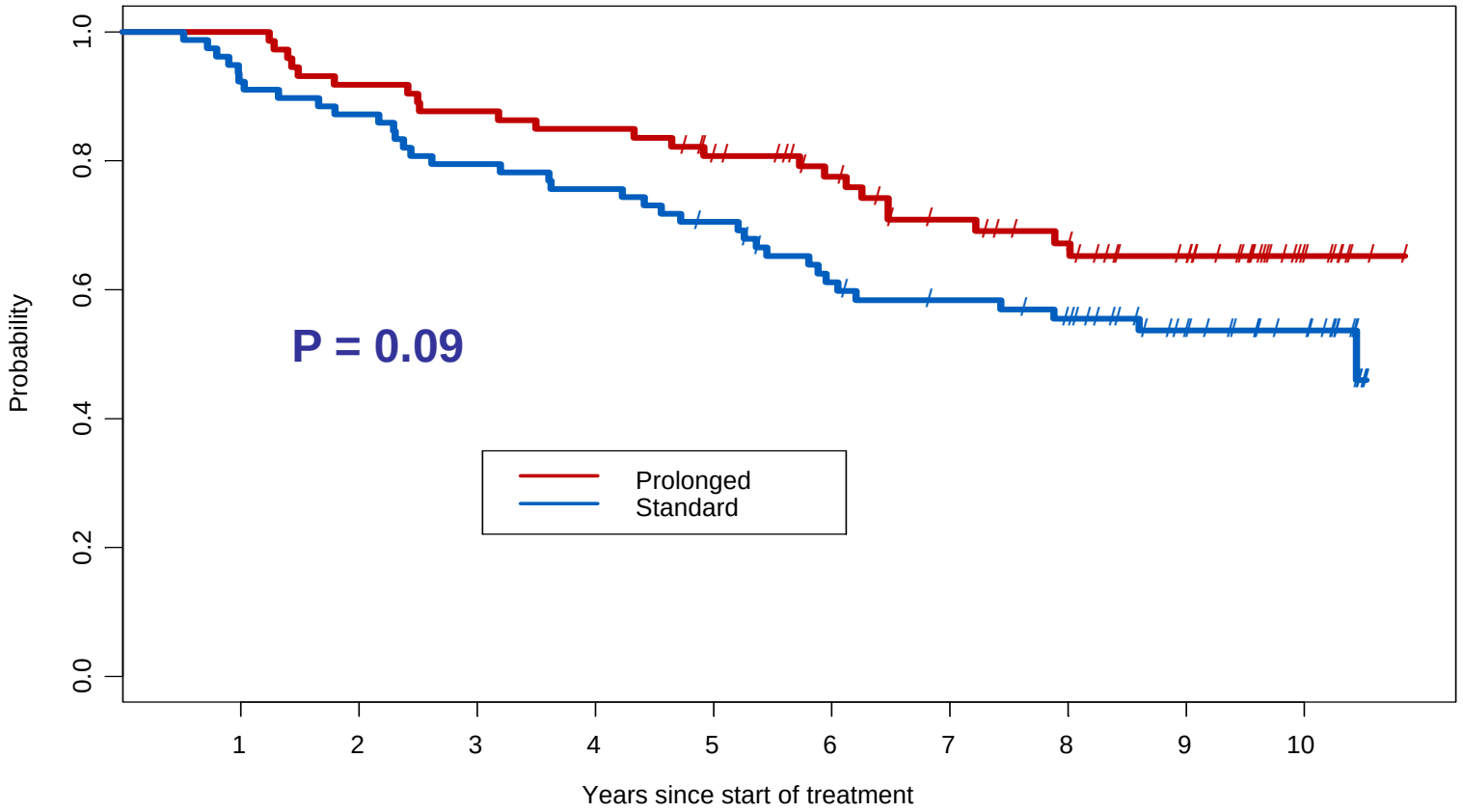
Ghielmini et al. ASCO 2009

SAKK 35/98 Long-Term Follow-up

Overall Survival

Overall survival in randomized follicular lymphoma patients



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Ghielmini et al. ASCO 2009

Multivariate analysis of EFS (n = 151)

Prognostic factor	Hazard ratio	P-value
Prolonged schedule	0.6	0.007
Bulky (≥ 5 cm)	1.4	0.09
Previous chemotherapy	1.4	0.18
Fcγ receptor VV	0.7	0.27
Stage IV	1.1	0.76

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Ghielmini et al. ASCO 2009

SAKK 35/98 Long-Term Results

- The optimal way to give rituximab is at a prolonged schedule
- When treated this way, the chance of being still in remission at 8 years is ~25%
- For chemotherapy naive patients responding to induction, the chance is ~ 45% at 8 years
- Schedule is the only and most potent prognostic factor for response duration
- Prolonged rituximab treatment is safe and might prolong survival

Ghielmini et al. ASCO 2009

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Questions on prolonged rituximab

- **when?**
  - **scheduled *vs.* as needed**
  - **front-line vs second-line**
- **how long?**
- **is the induction needed?**
- **is chemotherapy always needed?**

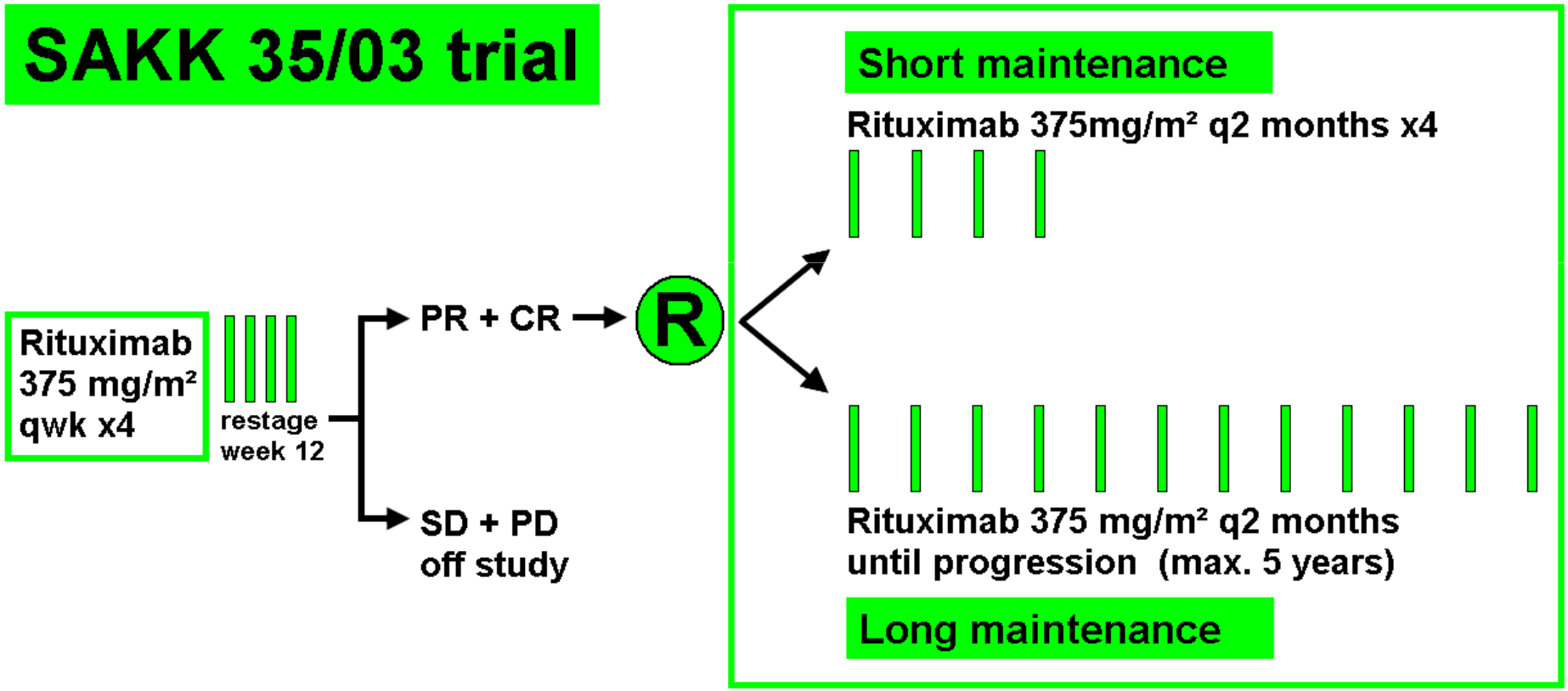
Questions on prolonged rituximab

- **ongoing studies with no cytotoxic treatment**

- **RWW (UK and Australia)**
  - W&W vs Rituximab (4xR vs 4xR + maintenance)
- **RESORT**
  - 4xR vs 4xR + maintenance
- **SAKK 35/03**
  - Short vs prolonged maintenance (up to 5 yr)

Questions on prolonged rituximab treatment

how prolonged?



Taverna et al Abstr. 8534 - ASCO 2009

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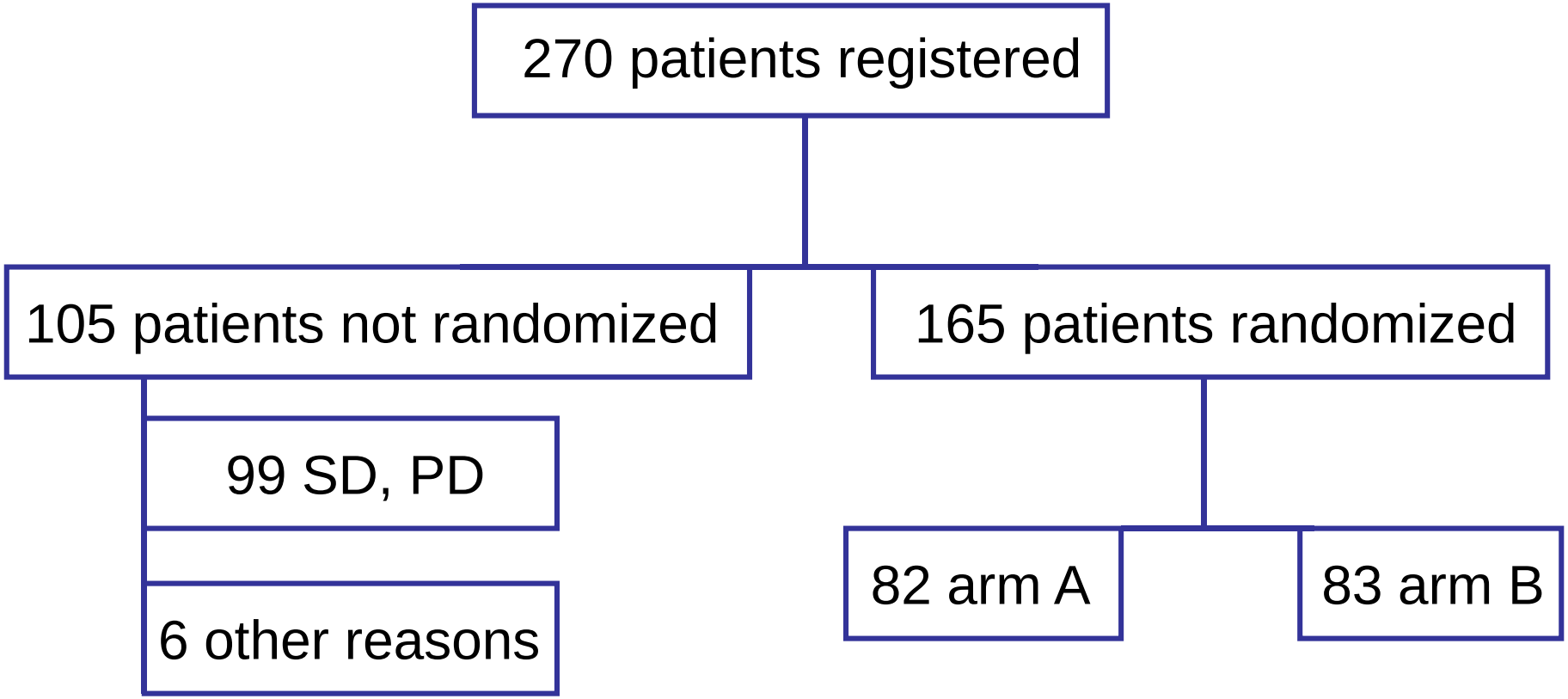
SAKK 35/03 - Study flow chart



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Front Line Treatment of FL

- **FL patients in need of therapy should receive Rituximab with and after chemotherapy**
- **However, is chemotherapy always needed?**

Conclusions

- R-chemo + R-maintenance may not be alway the standard
- The long term results of SAKK 35/98 together with few available data from other studies indicate immunotherapy alone can have a role in indolent lymphomas
  - prolonged PFS if short IFN consolidation is given with Rituximab in a NLG study
  - ~90% CR with R-Lenalidomide in a MDACC phase 2 study
- This should be specifically addressed in controlled trials

FL: “transformation … of the physicians”

- “the current generation of oncologists rarely observe these patients without treatment, many are receiving R-CHOP and virtually all rituximab…
- ...the experience and skill of the physician in recognising ***which*** patients should be treated ***when*** and ***how*** is the major factor in the quality and length of survival of patients with FL”

Saul A. Rosenberg, J Clin Oncol, 2008