Lymphomes folliculaires: questions actuelles et perspectives

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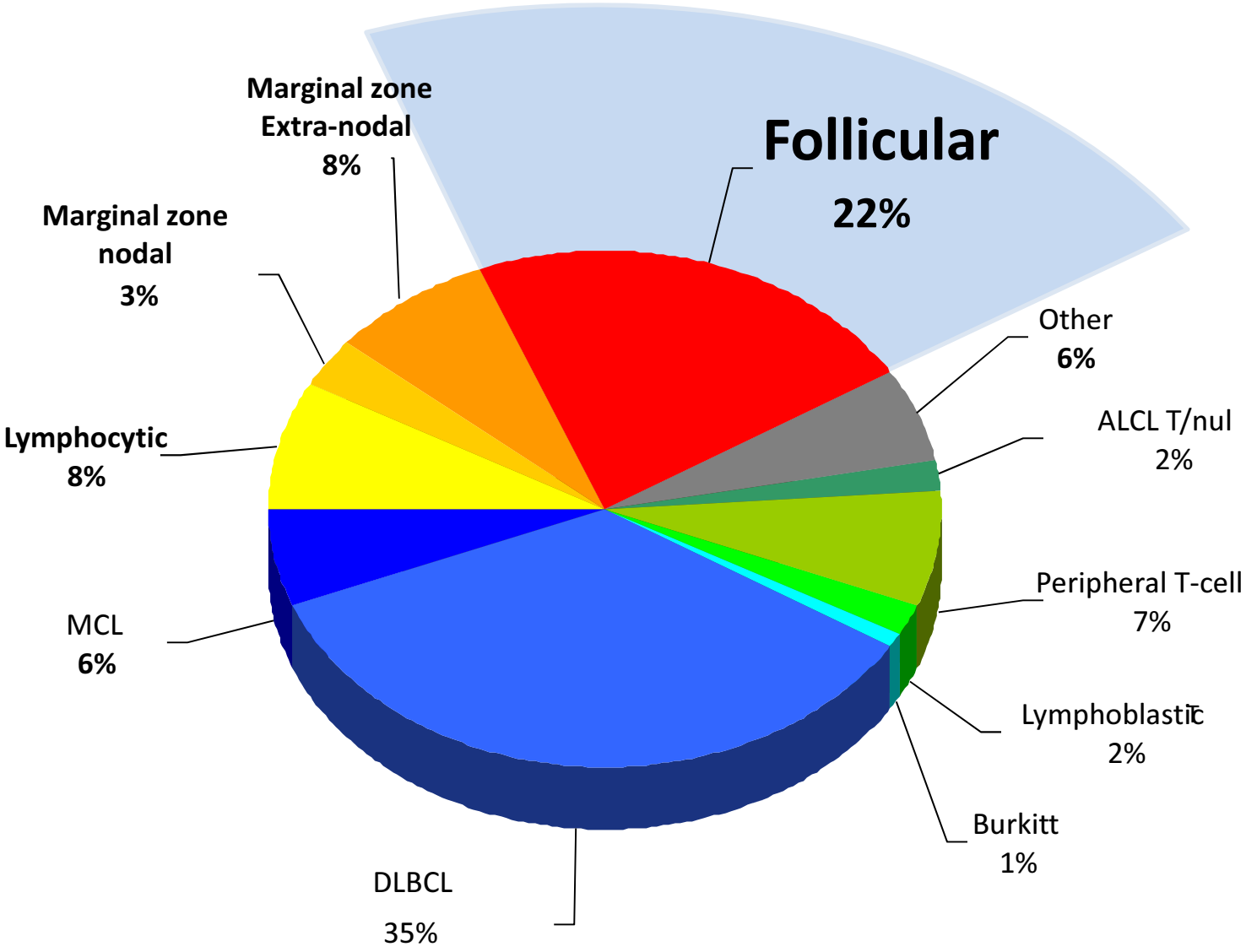
Non Hodgkin Lymphomas



(Non Hodgkin's Lymphoma Classification Project, Blood 1997)

WHO classification
Follicular lymphoma

Germinal center B cells

Small centrocytes

Large centroblasts

Follicular growth pattern

Grading

Grade 1: 0-5 centroblasts/hpf

Grade 2: 6-15 centroblasts/hpf

Grade 3: >15 centroblasts/hpf

3a: presence of centrocytes

3b: only centroblasts

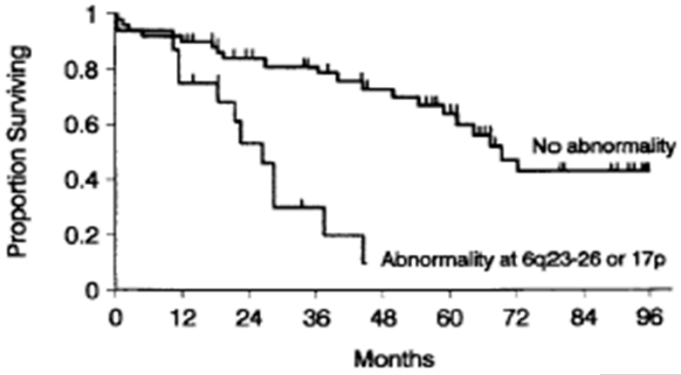
Paradoxes in follicular lymphoma

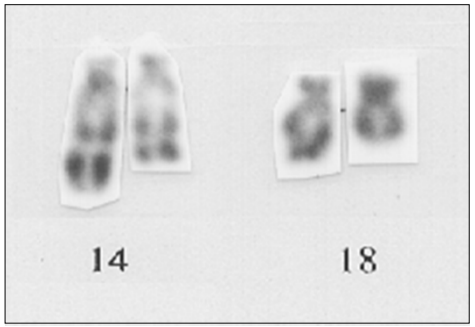
Indolent course, but incurable

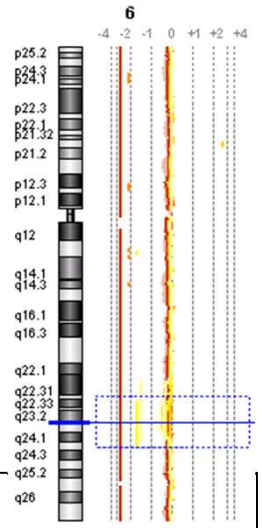
Treatment sensitive but always relapses

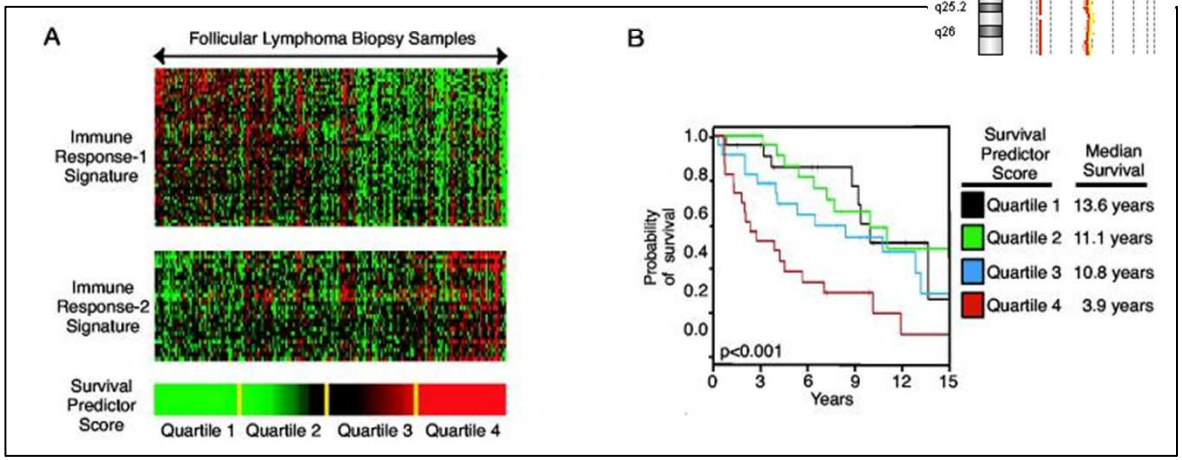
Homogeneous definition but variable outcome

t(14;18) as hallmark but genetic heterogeneity



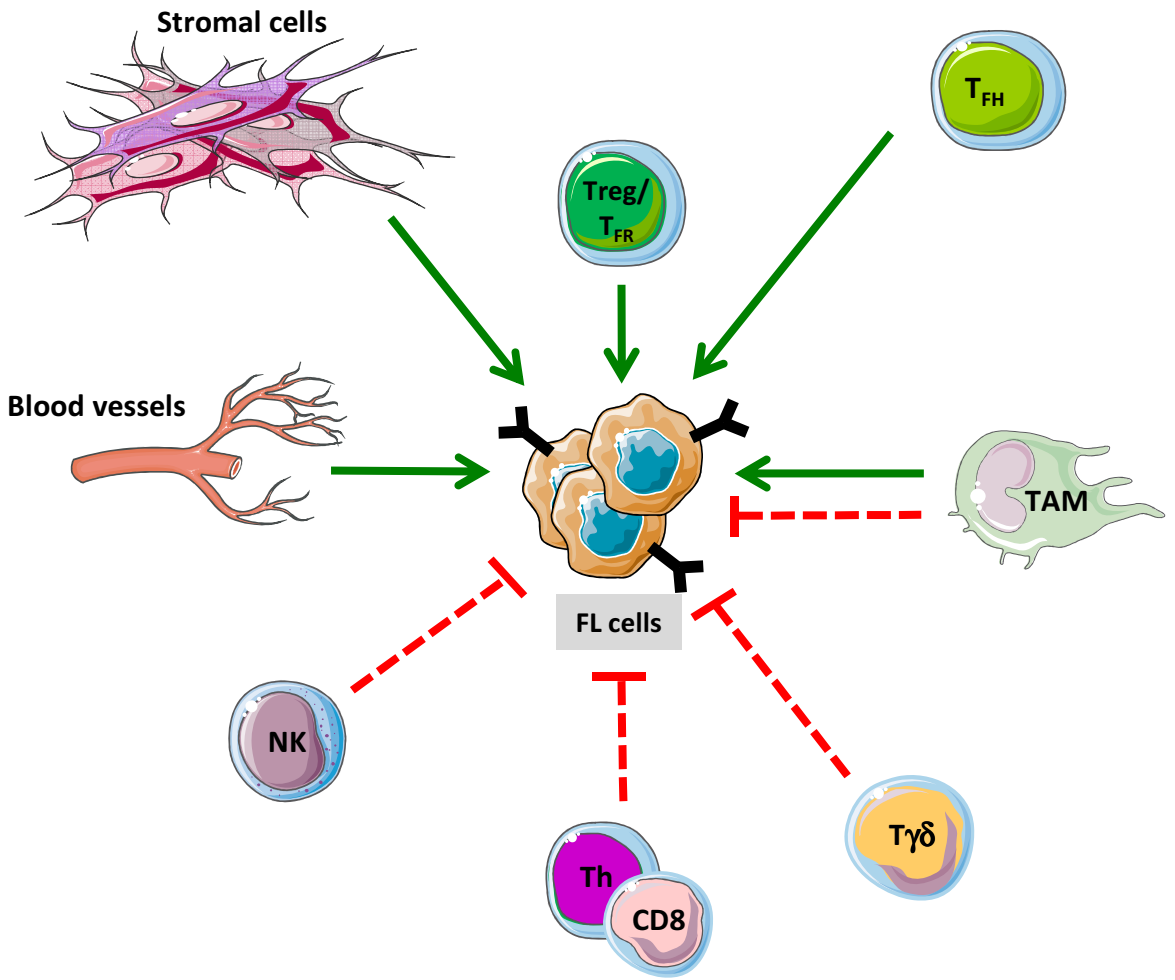






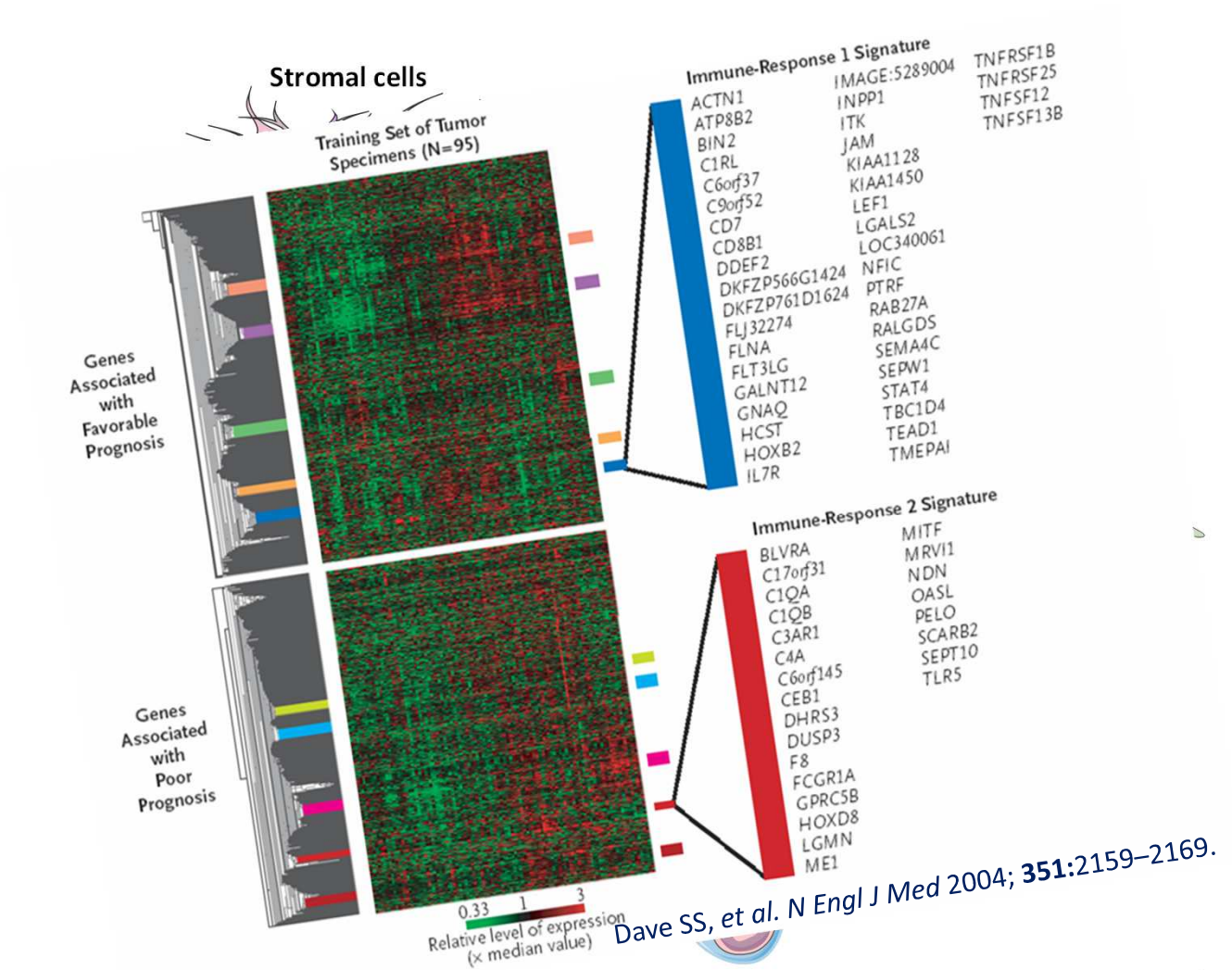
Staudt L.M. Adv. Immunol. 2005; 87 : 163-208

The importance of microenvironment



Adapted from K Tarte

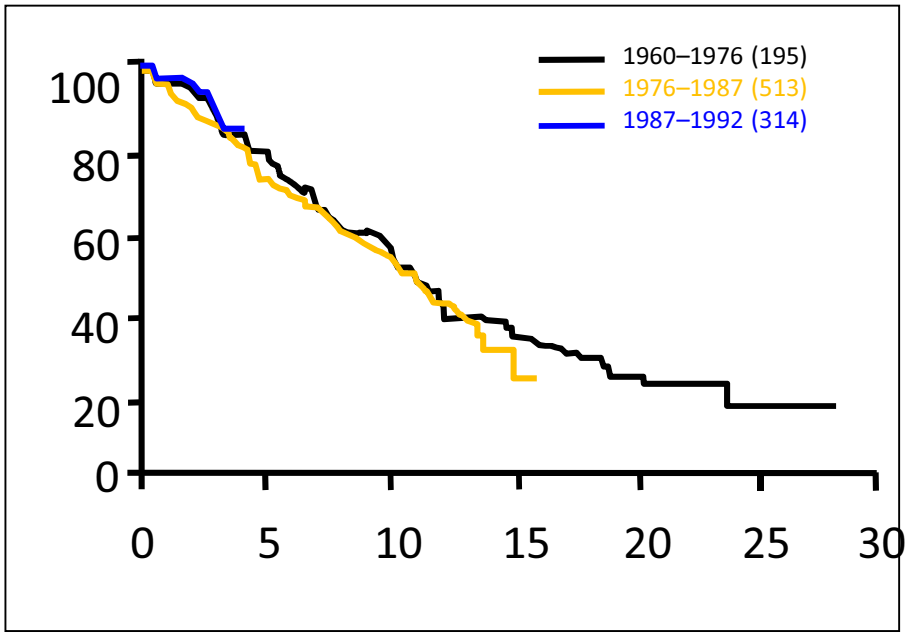
The importance of microenvironment

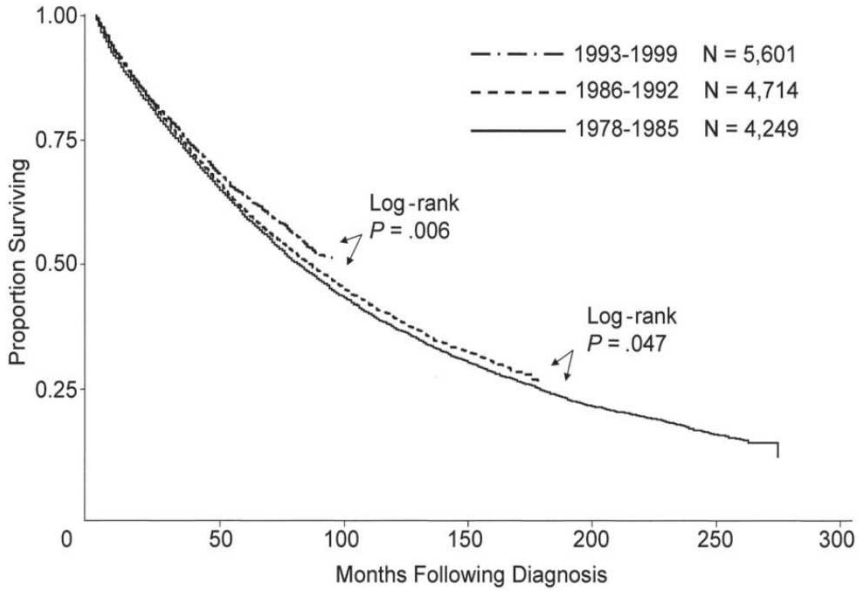


Dave SS, *et al. N Engl J Med* 2004; **351:**2159–2169.

Adapted from K Tarte

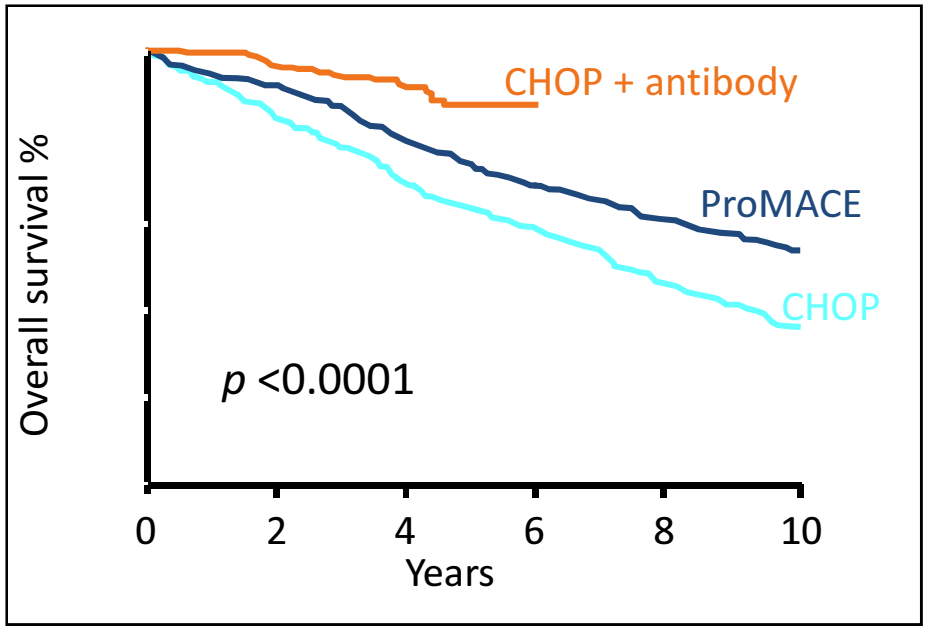
An irremediable natural history ?





1. Horning SJ. *Semin Oncol* 1993; 20 (Suppl. 5):75–88.
2. Swenson WT et al., *J Clin Oncol* 2005; *23:5019-5026.*
3. Lister TA, *J Clin Oncol,* 2005; 25:4830-31.

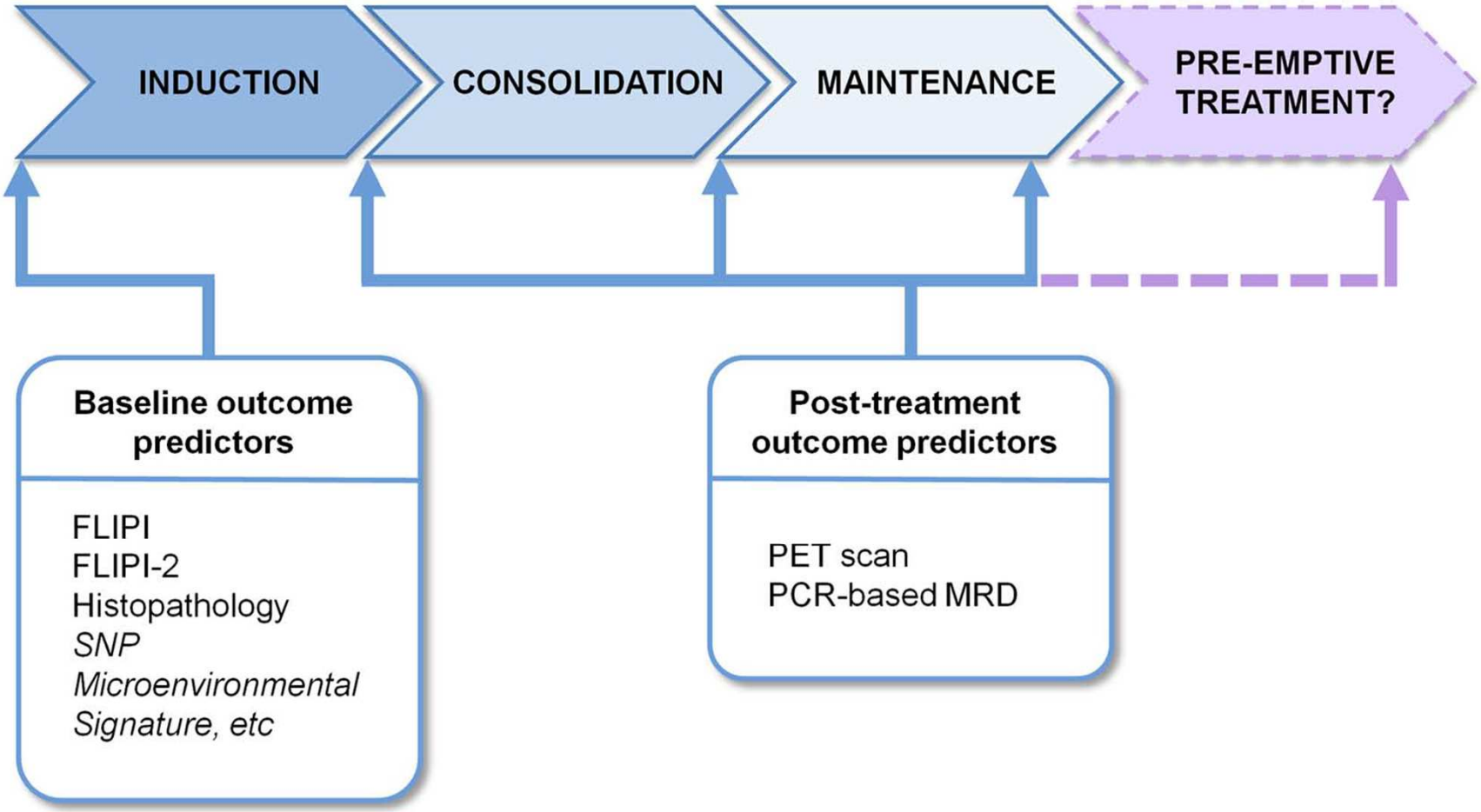
A new paradigm with immunochemotherapy



Observation period	5-year survival Probability (SD)	10-year Survival Probability (SD)
1992-1994	70.7 (1.3)	52.2 (1.6)
2002-2004	84.9 (0.9)	71.5 (1.4)

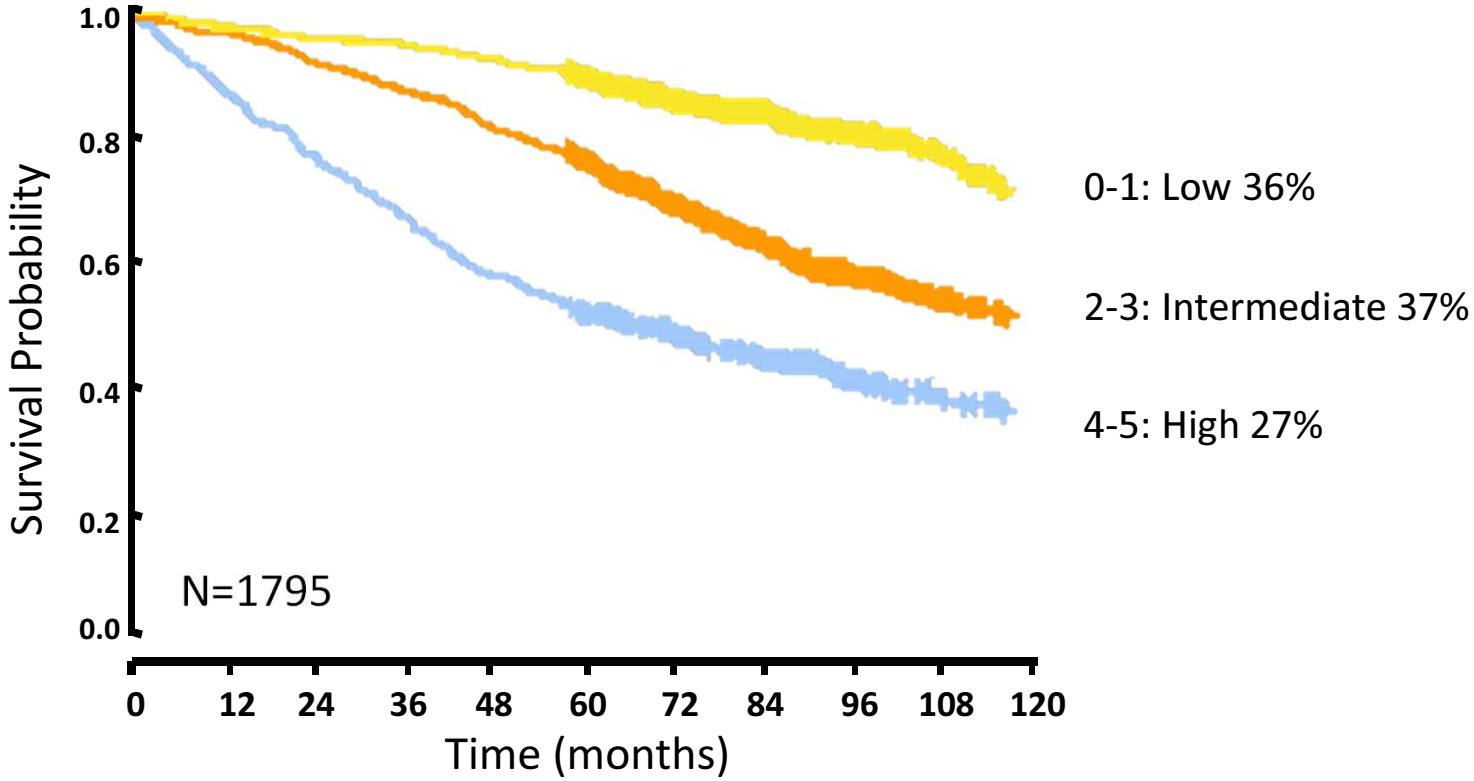
1. Fisher RI et al, J Clin Oncol 2005;23:8447–52
2. Schulz H et al., Cochrane Database of Systematic Reviews 2007; 4:CD003805.
3. Pulte D et al; Arch Intern Med. 2008;168:469-476.

Prognostic tools
In follicular lymphoma



Lobetti-Bodoni C. Ther Adv Hematol 2013;3:189-98

FLIPI in follicular lymphoma



Parameter	Adverse factor	RR	95% CI
Age	≥60 y	2.38	2.04 – 2.78
Ann Arbor Stage	III–IV	2.00	1.56 – 2.58
Hemoglobin	<12 g/dL	1.55	1.30 – 1.88
Serum LDH level	>ULN	1.50	1.27 – 1.77
Number of nodal sites	>4	1.39	1.18 – 1.64

Solal-Céligny et al. Blood 2004;104:1258–65

Criteria for commencing therapy in FL
low *vs* high tumor burden

LYSA

"GELF" criteria

- Bulky disease : nodal/ extranodal mass > 7cm
- B symptoms
- Raised B2-microglobulin /LDH
- Involvement of 3 nodal sites (>3 cm)
- Splenic enlargement
- Compression syndrome
- Pleural/peritoneal effusion

BNLI

- Life threatening organ involvement
- "B" symptoms
- Bone marrow failure
- Rapidly progressive disease over any 3–6 month period

Première ligne
dans les lymphomes folliculaires

Dans les stages localisés

- **L’irradiation est-elle le standard ?**

Dans les faibles masses tumorales

- **Surveillance ou intervention précoce ?**

Dans les fortes masses tumorales

- **Quelle est la meilleure association ?**
- **Consolidation ou entretien?**

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Stage I-II patients

Radiation for Follicular Lymphoma/Pugh et al[5]

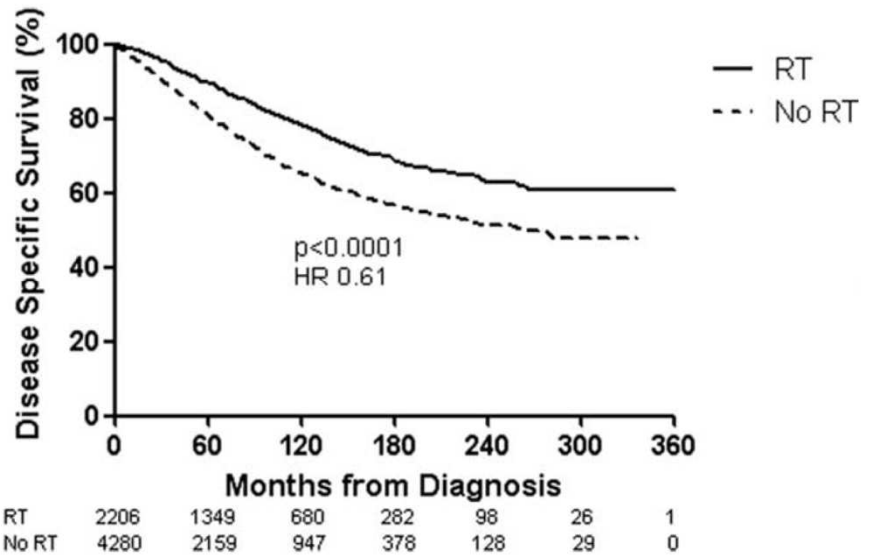

Figure 1. Non-Hodgkin lymphoma-specific survival with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.

1. Lowry et al. Radiother Oncol, 2011
2. NCCN & ESMO Guidelines
3. Friedberg , et al. JCO 2012
4. Plancarte et al. Eur J Haematol. 2006
5.Pugh et al. Cancer 2010

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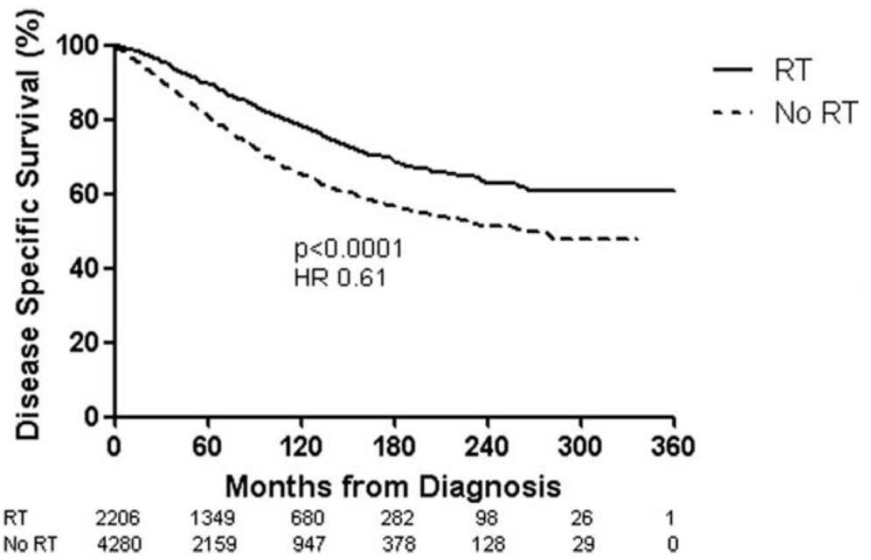

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Staging using CT/PET-CT and BM is recommended [3]

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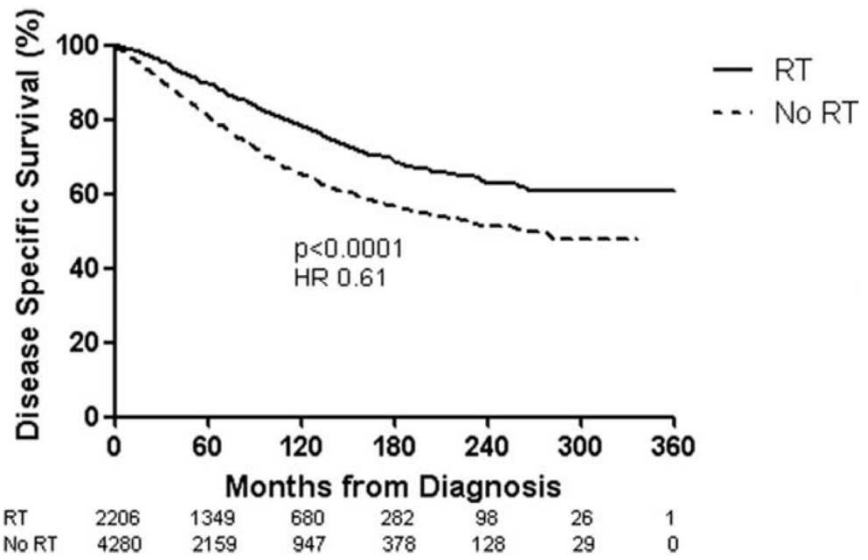

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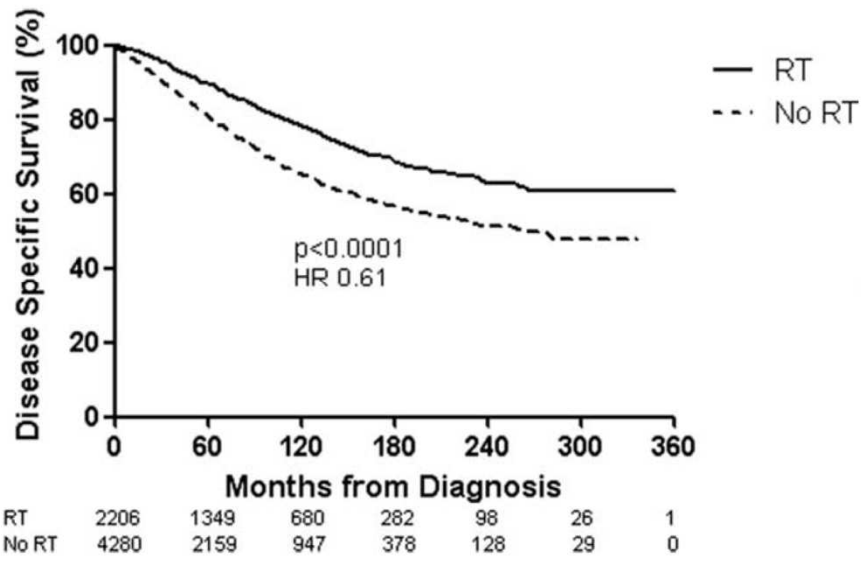

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A 24 Gy XRT dose provides equivalent results to 40-45 Gy [1]

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4. Plancarte et al. Eur J Haematol. 2006
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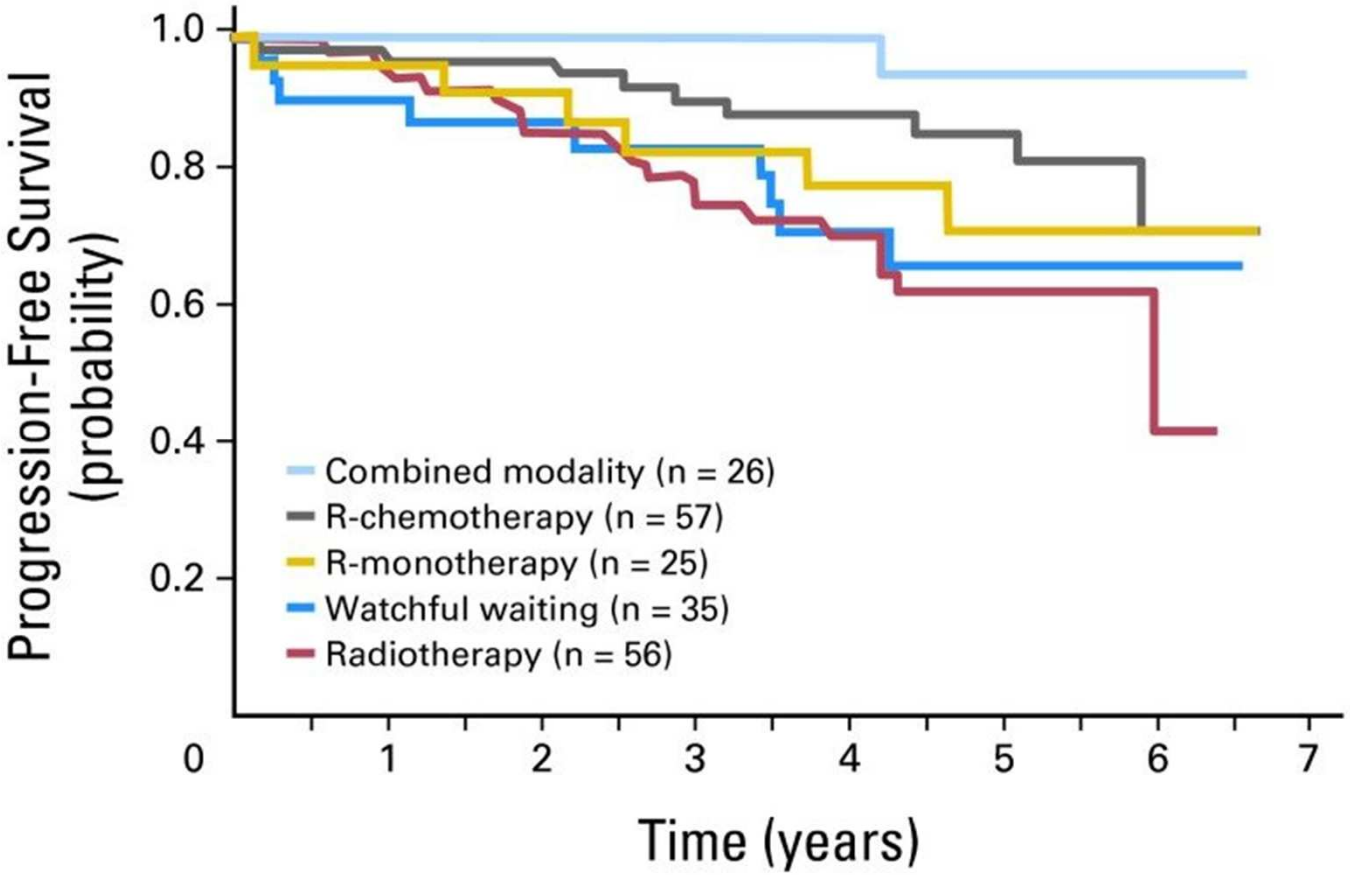
Results of different therapeutic strategies in FL pts with stage I

(Lymphocare study - 5 years PFS)



Friedberg JW. J Clin Oncol. 2012;30:3368-75

Michallet AS. J Hematol Oncol 2013;6:45.

Première ligne
dans les lymphomes folliculaires

Dans les stages localisés

L'irradiation est-elle le standard ?

Dans les faibles masses tumorales

Surveillance ou intervention précoce ?

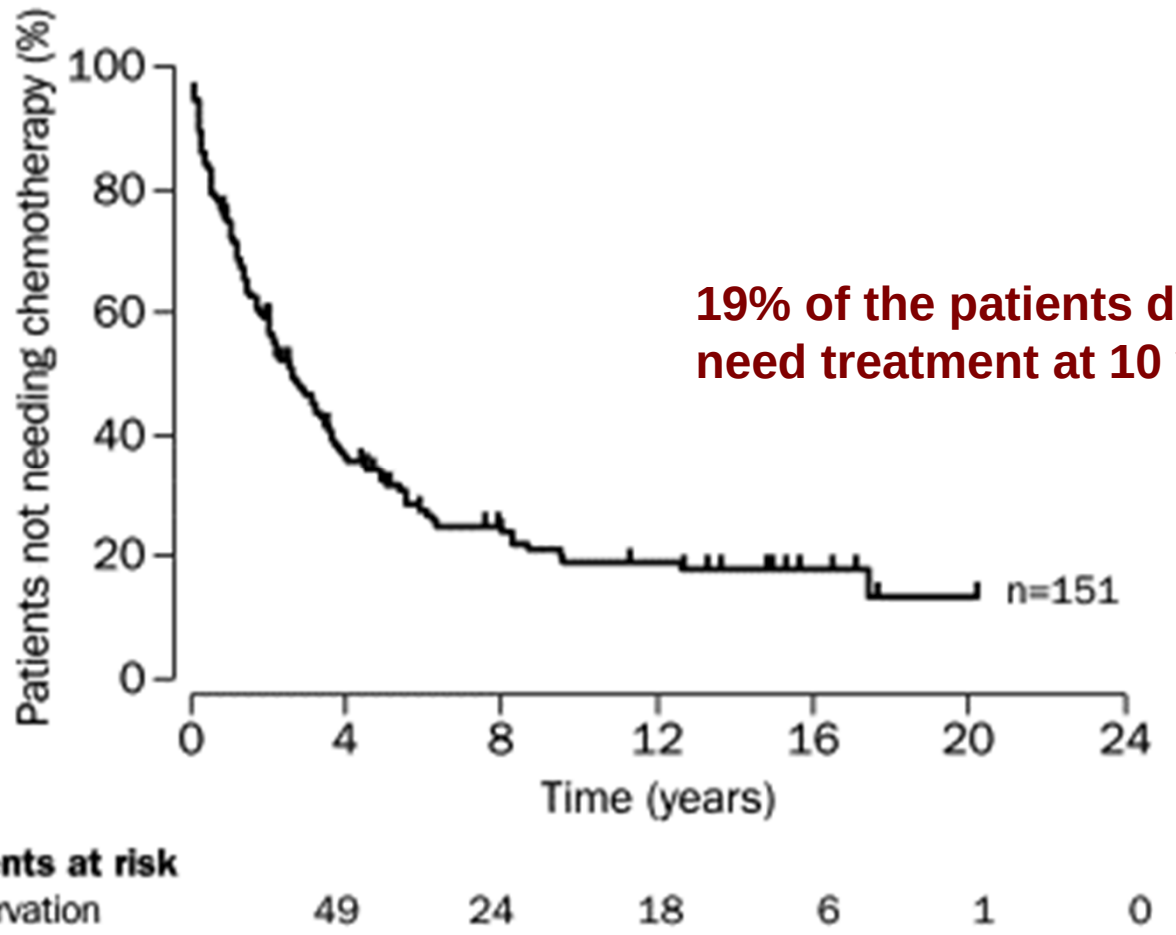
Dans les fortes masses tumorales

Quelle est la meilleure association ?

Consolidation or entretien?

Time to systemic treatment

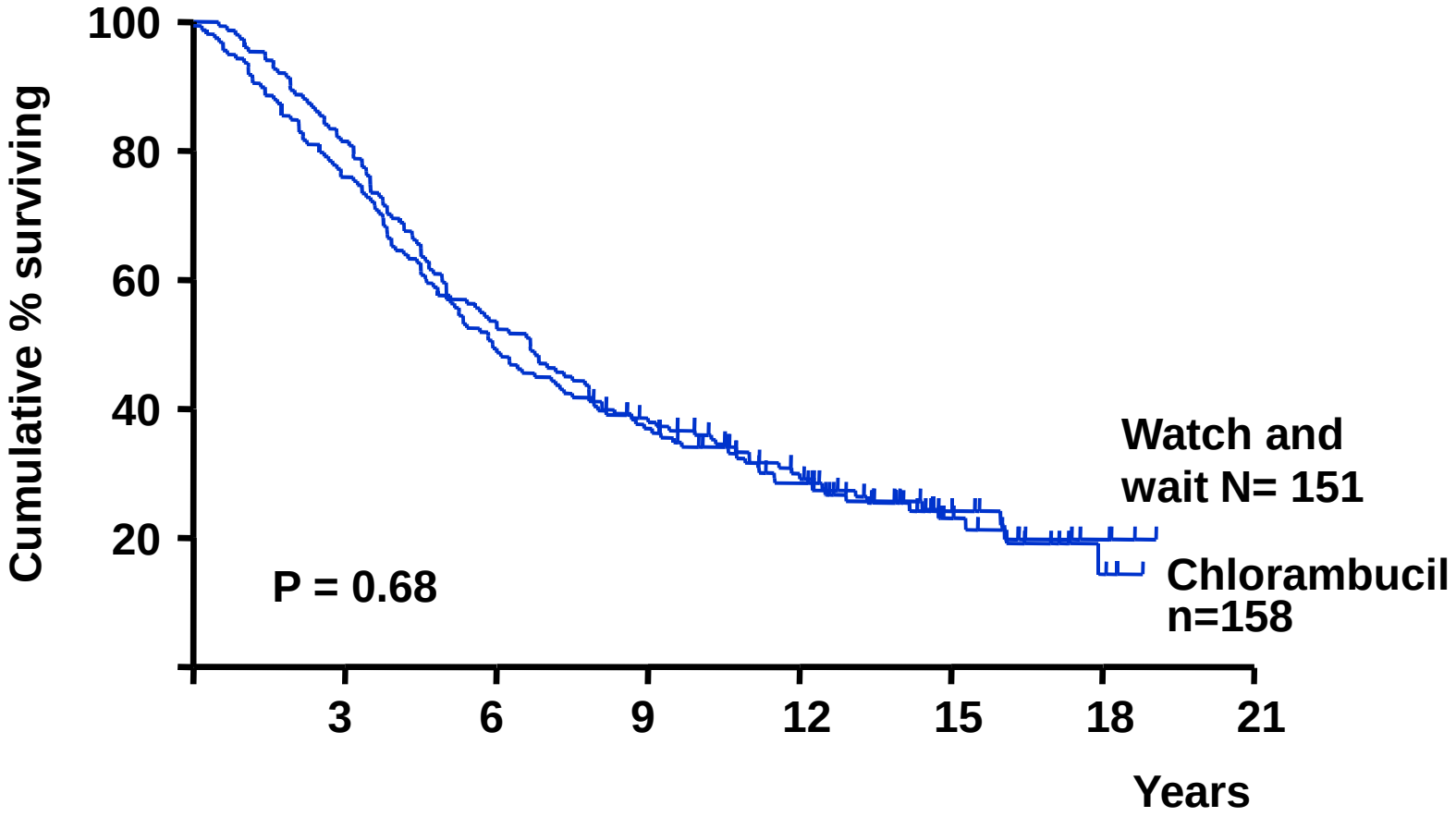
Observation group



19% of the patients do not need treatment at 10 years

Ardeshna et al., Lancet 2003;362:516-522.

Overall survival by treatment

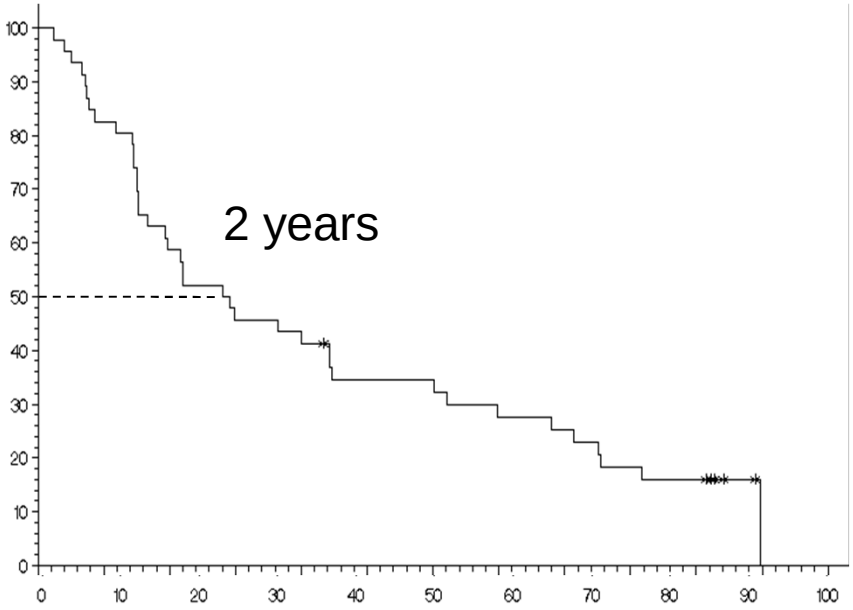


Ardeshna et al., Lancet 2003;362:516-522.

Studies of rituximab in follicular lymphoma patients eligible for observation

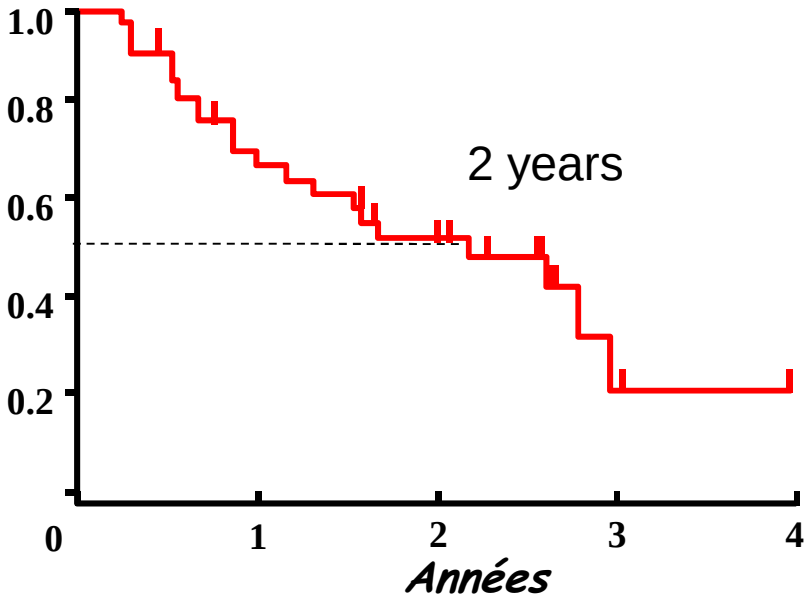
Time to next treatment

ORR: 80 %
CR: 50 %



Colombat P, et al.

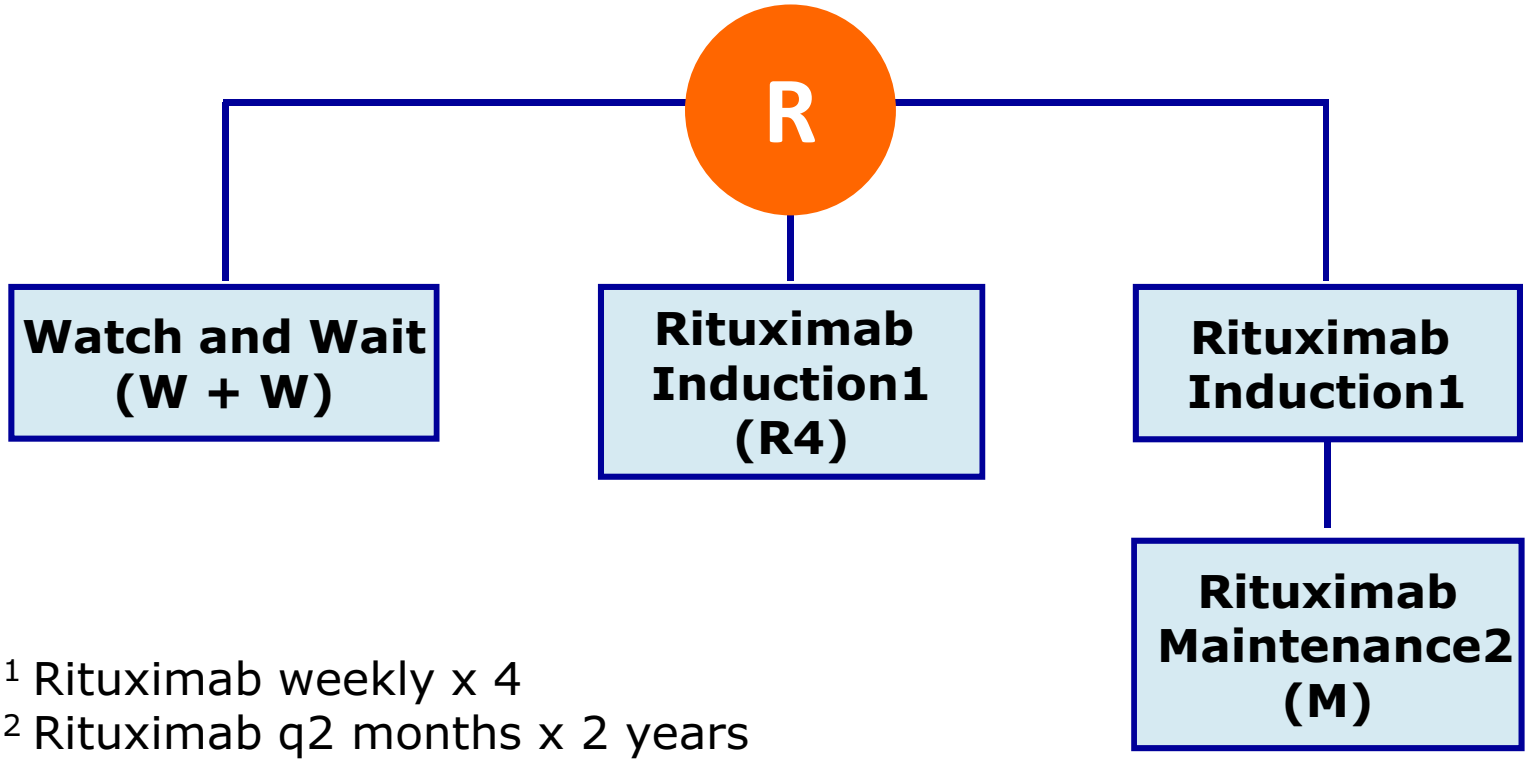
ORR: 72 %
CR: 36 %



Witzig TE, et al.

Trial of Rituximab *vs* a Watch & Wait in Patients with low burden follicularLymphoma

RWW trial



[1] Rituximab weekly x 4
[2] Rituximab q2 months x 2 years

Ardeshna KM et al. Lancet Oncol 2014; March 4

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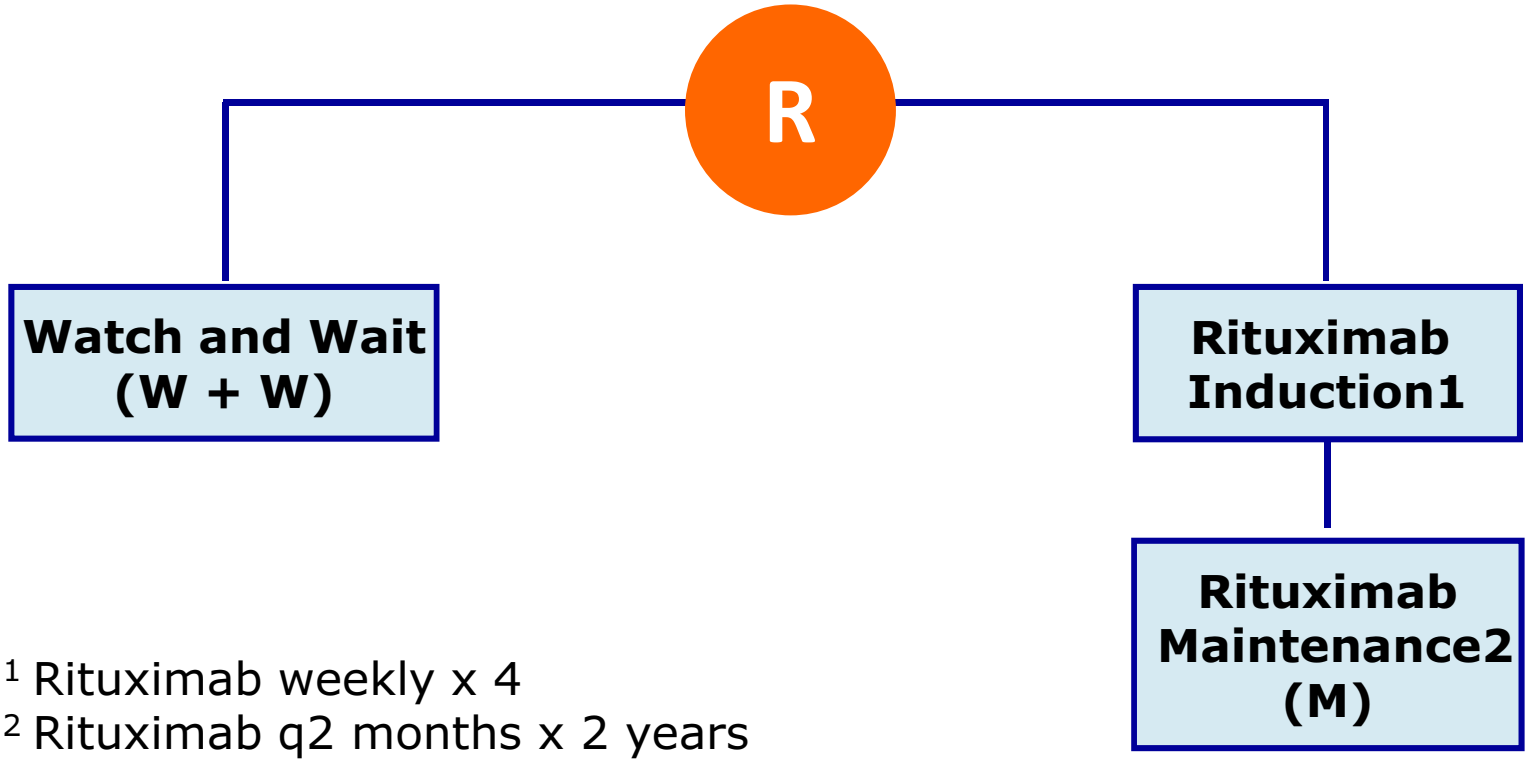

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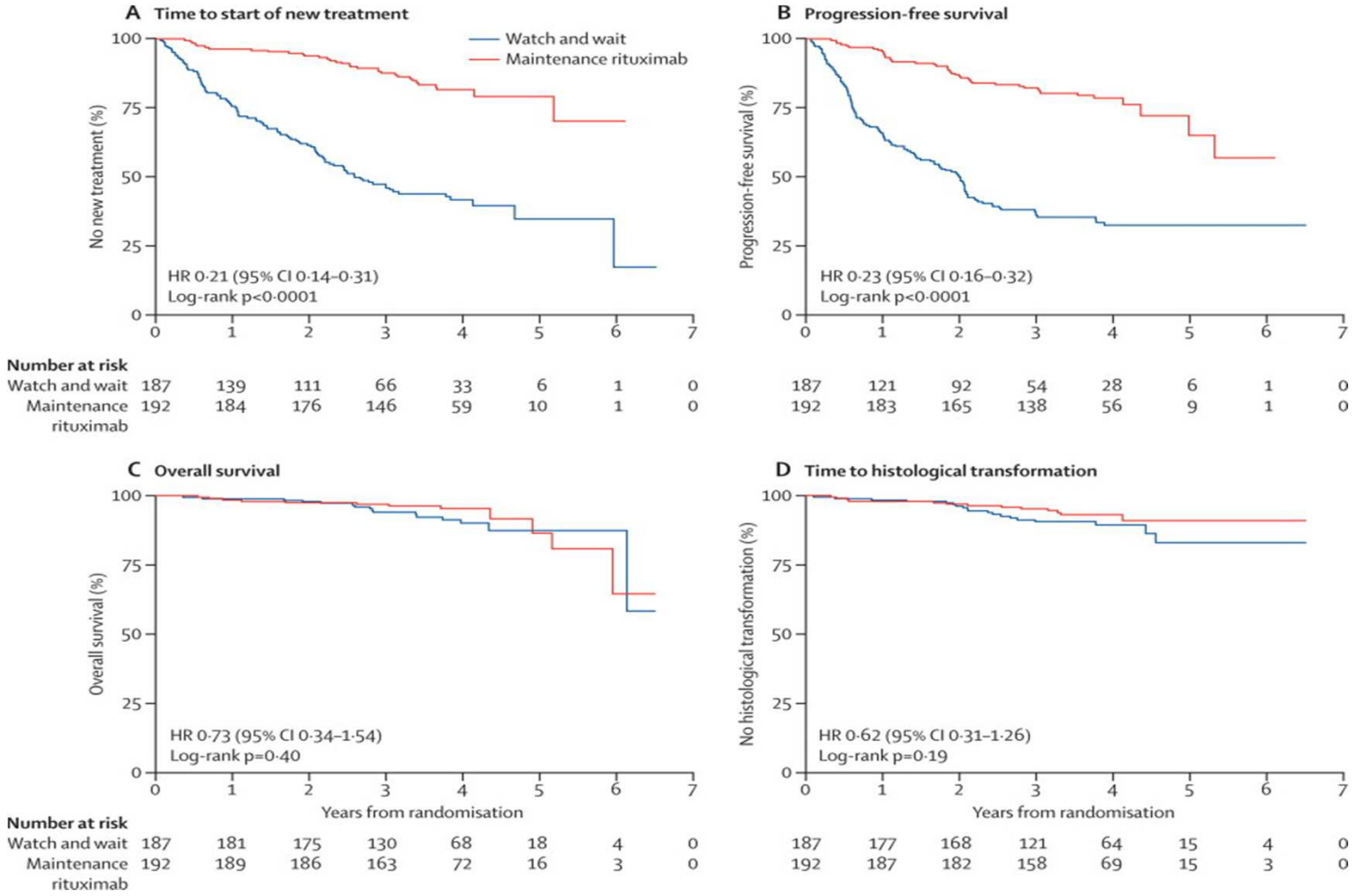
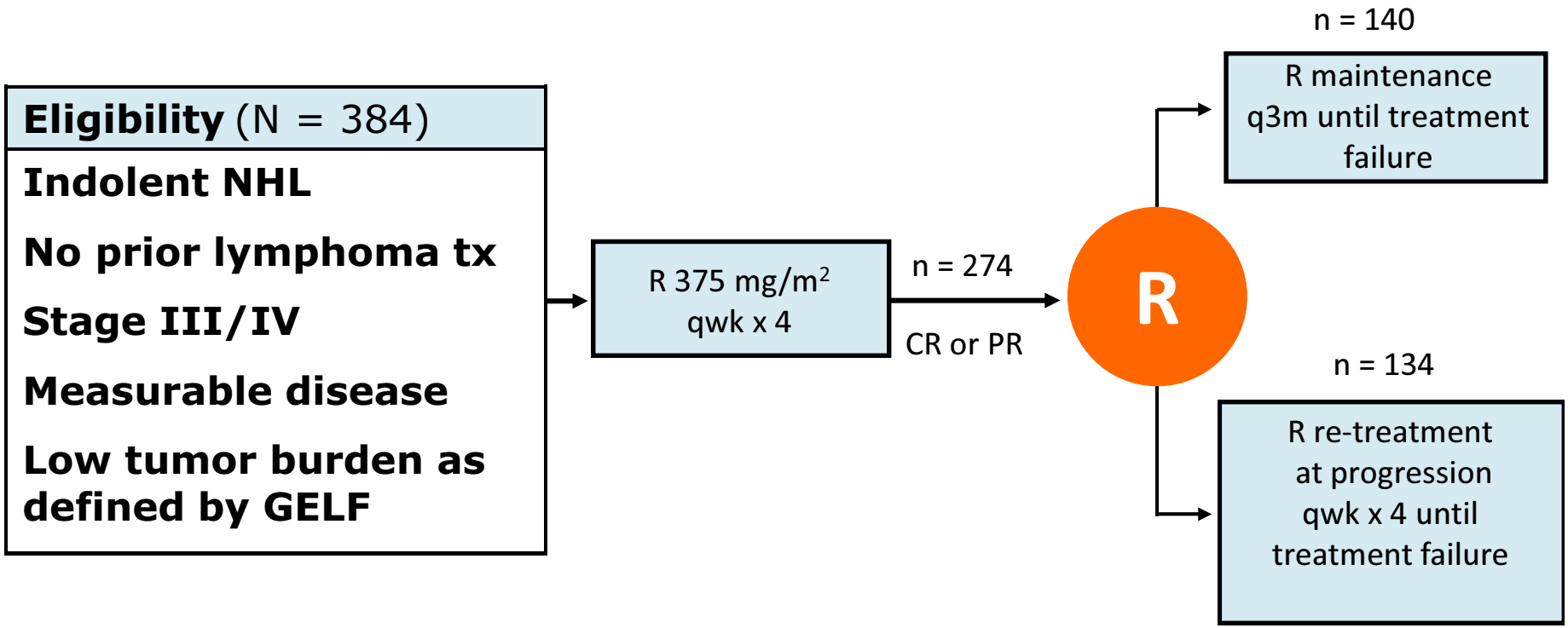


Ardeshna KM et al. Lancet Oncol 2014

E4402 (RESORT)
Scheme

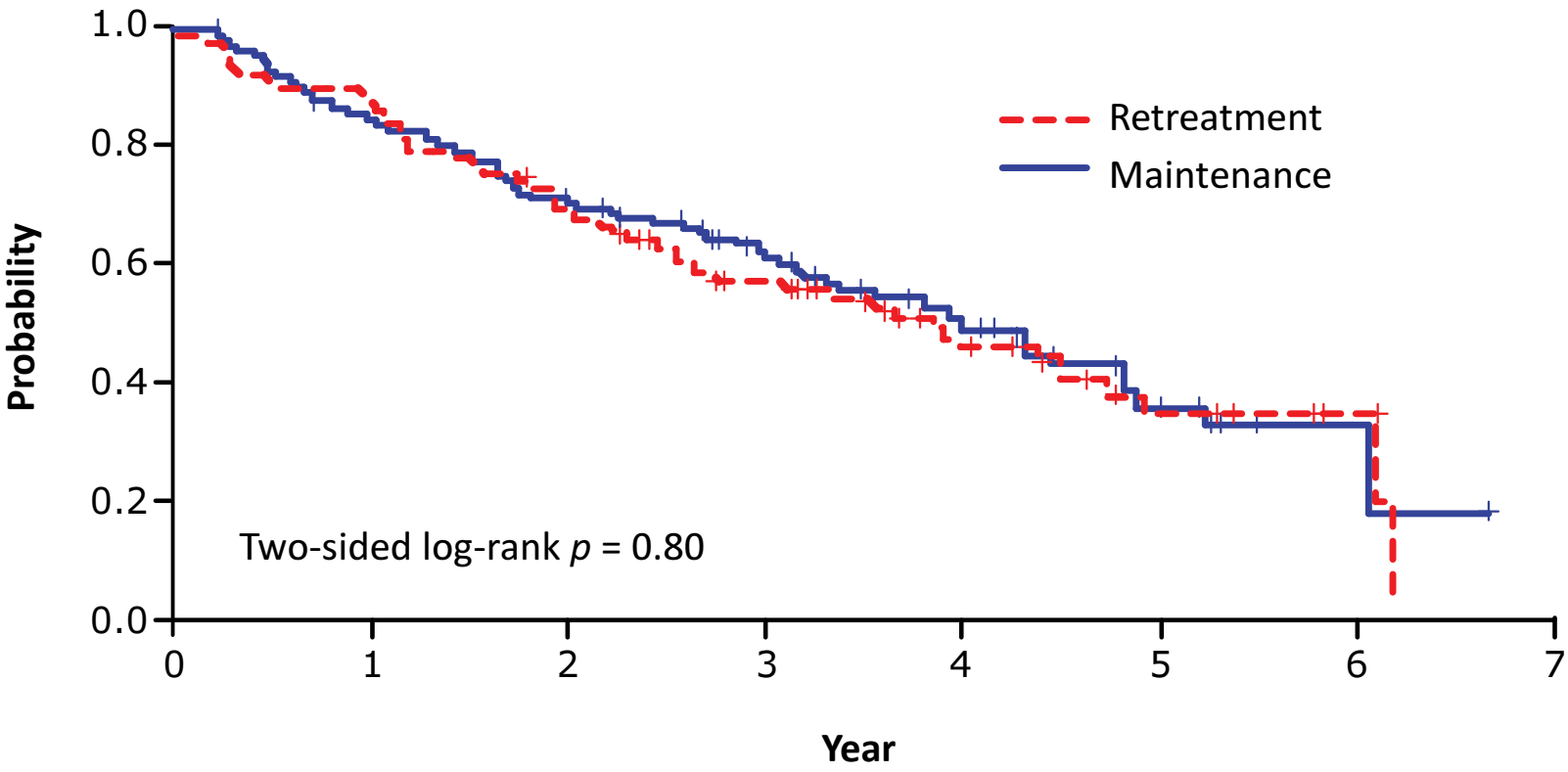


Primary Endpoint: Time to treatment failure (TTTF)

Secondary Endpoints: Time to first cytotoxic therapy (TTCT), quality of life (QOL) and safety

Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

E4402 (RESORT)
Time to Treatment Failure



Kahl BS et al. *Proc ASH* 2011;Abstract LBA-6.

Première ligne
Patients asymptomatiques / faible masse

- En 2014, il reste acceptable de retarder le début du traitement
- Le rituximab permet de retarder le début des agents cytotoxiques
- Le bénéfice d'un entretien n'est pas établi
- De nouvelles voies ?

Première ligne
dans les lymphomes folliculaires

Dans les stades localisés

L'irradiation est-elle le standard ?

Dans les faibles masses tumorales

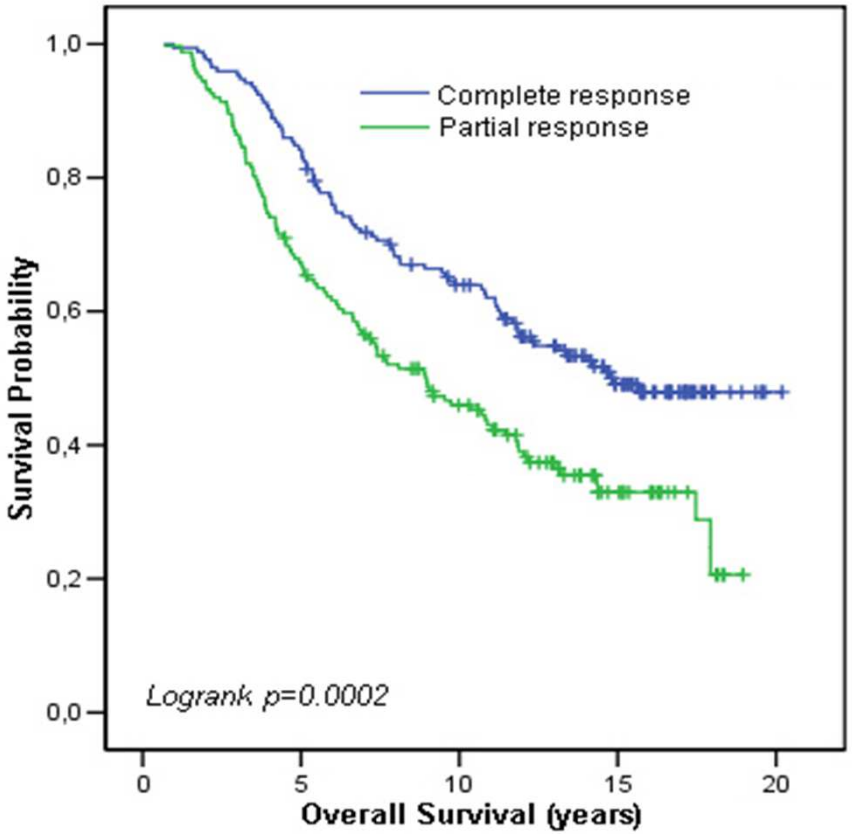
Surveillance ou intervention précoce ?

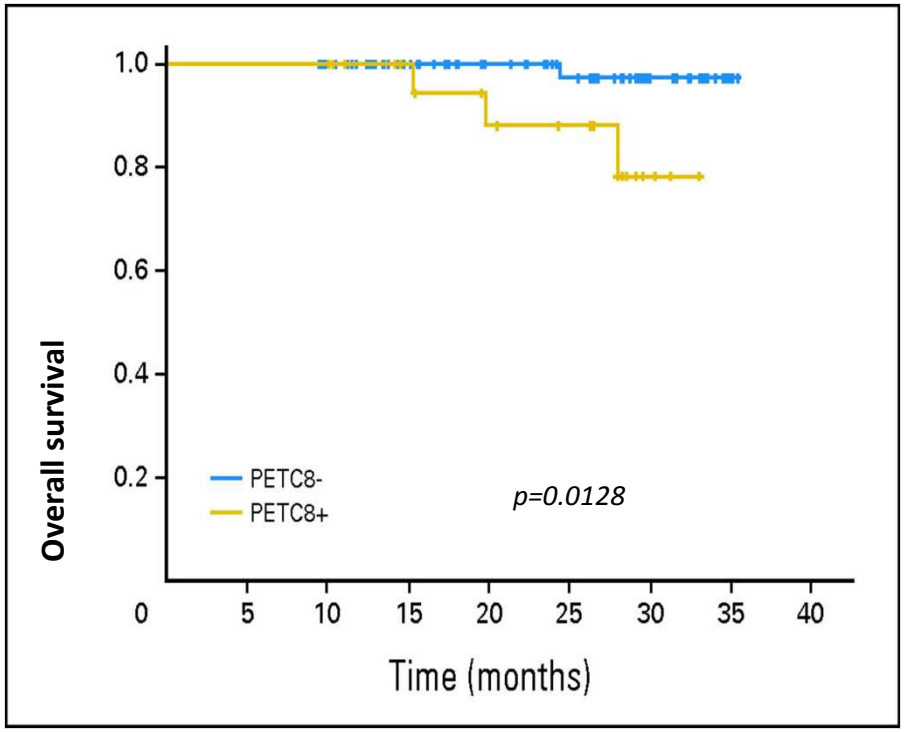
Dans les fortes masses tumorales

Quelle est la meilleure association ?

Consolidation ou entretien?

Is it necessary to achieve a complete response with first line treatment ?





E Bachy et al. J Clin Oncol. 2010;28:822-9

Dupuis J et al. J Clin Oncol 2012;30:4317-22.

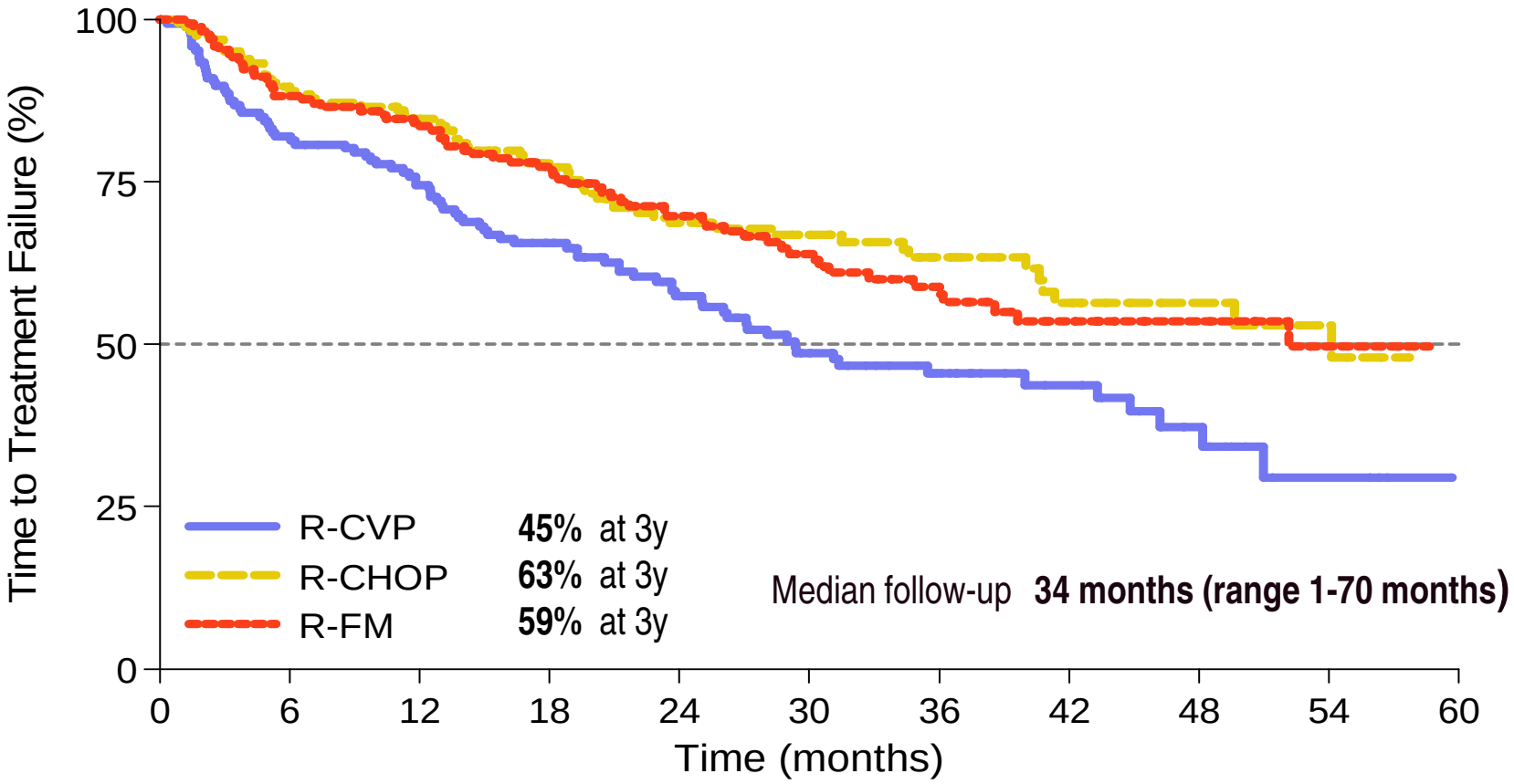
First line immunochemotherapy
Four randomised trials

Trial	Treatment		Survival (%)		P
	Control	Rituximab	Control	Rituximab	
M3902; Marcus	CVP	R-CVP	85	89	✓
GLSG; Hiddemann	CHOP	R-CHOP	90	95	✓
M39023; Herold	MCP	R-MCP	75	89	✓
FL2000; GELA GOELAMS	CHVP IFN	R-CHVP IFN	86	91	-

Marcus R et al. J Clin Oncol 2008;26:4537.
Hiddemann W et al. Blood 2005;106:3725.
Herold M et al. J Clin Oncol 2007;25:1986.
Salles G et al. Blood 2008;112:4824.

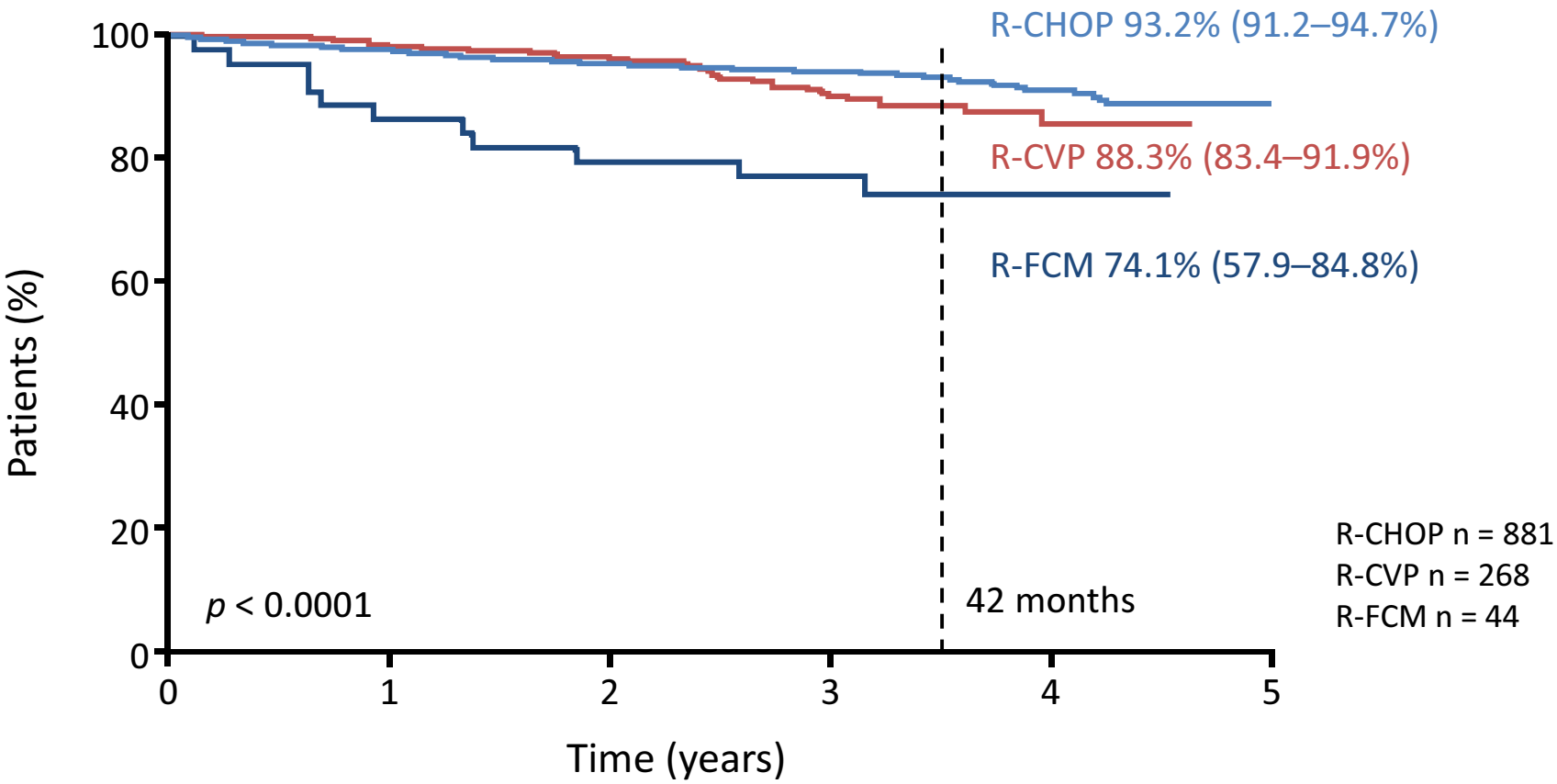
TTF by Arm

Events = 212	Logrank	P	P Adj
R-CHOP vs R-CVP	9.35	0.002	0.007
R-FM vs R-CVP	7.41	0.006	0.020
R-CHOP vs R-FM	0.16	0.692	0.971



R-CVP	168	136	119	95	74	51	36	23	13	5	1
R-CHOP	165	147	137	120	83	66	47	32	19	12	5
R-FM	171	150	139	120	95	68	50	32	20	12	4

Overall survival from registration by induction regimen



Morschhauser F 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)

514 pts

R

Bendamustine-Rituximab

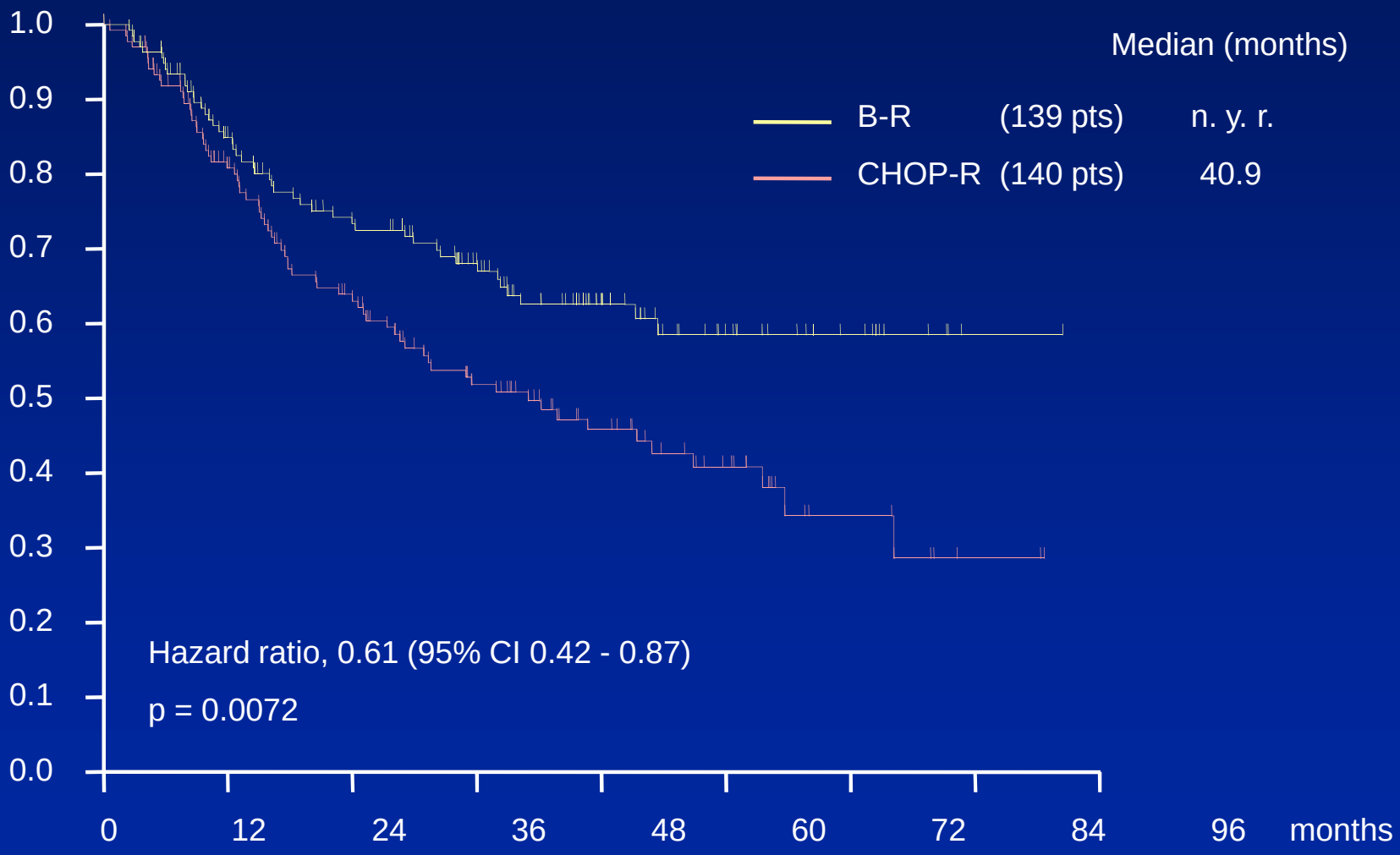
- Bendamustine 90 mg/m^2 day 1+2
- Rituximab 375 mg/m^2 day 1

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

Rummel M et al. Lancet 2013;381:1203-10.

PFS: follicular (n=279)

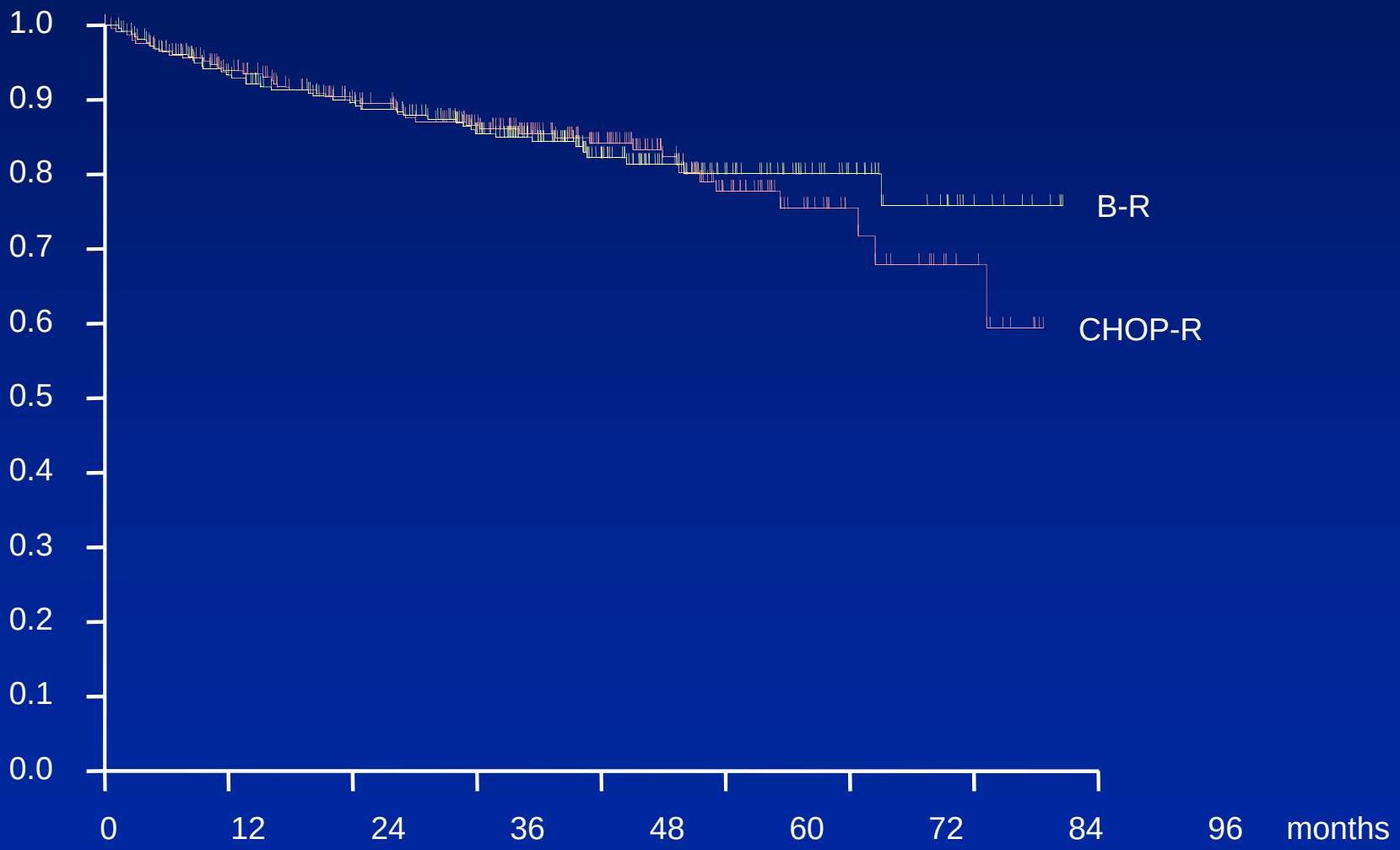


MJR

Toxicities (all CTC-grades)

	B-R (n=261) (no. of pts)	CHOP-R (n=253) (no. of pts)	*P* value
Alopecia	-	+++	
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Skin (erythema)	42	23	= 0.0122
Allergic reaction (skin)	40	15	= 0.0003
Infectious complications	96	127	= 0.0025
- Sepsis	1	8	= 0.0190

Overall survival



MJR

R-Bendamustine vs R-CHOP in follicular lymphoma
Conclusions

R-Bendamustine, nouveau standard ?

Questions:

- Bras contrôle
- Rechute après R-Benda ?
- Toxicité à long terme (MDS, …)
- Côuts

Première ligne
dans les lymphomes folliculaires

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Surveillance ou intervention précoce ?

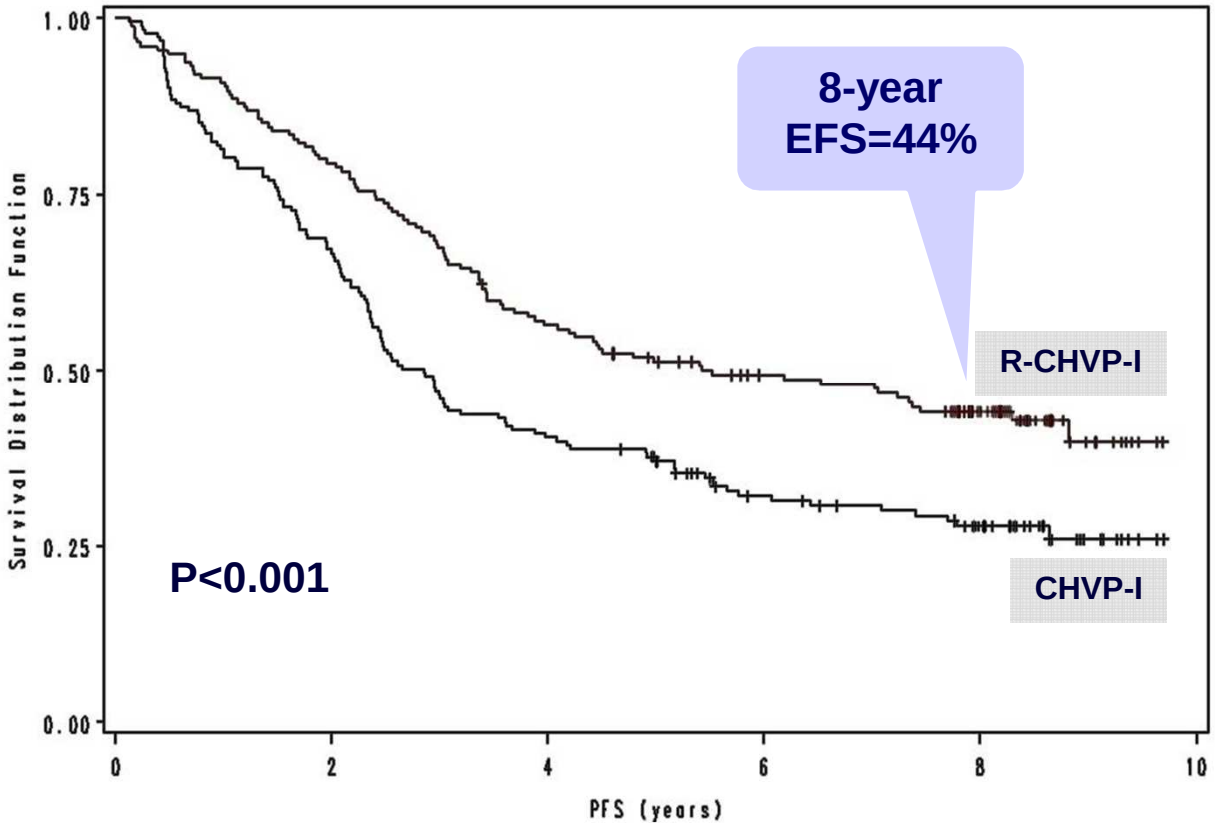
Dans les fortes masses tumorales

Quelle est la meilleure association ?

Consolidation ou entretien ou rien?

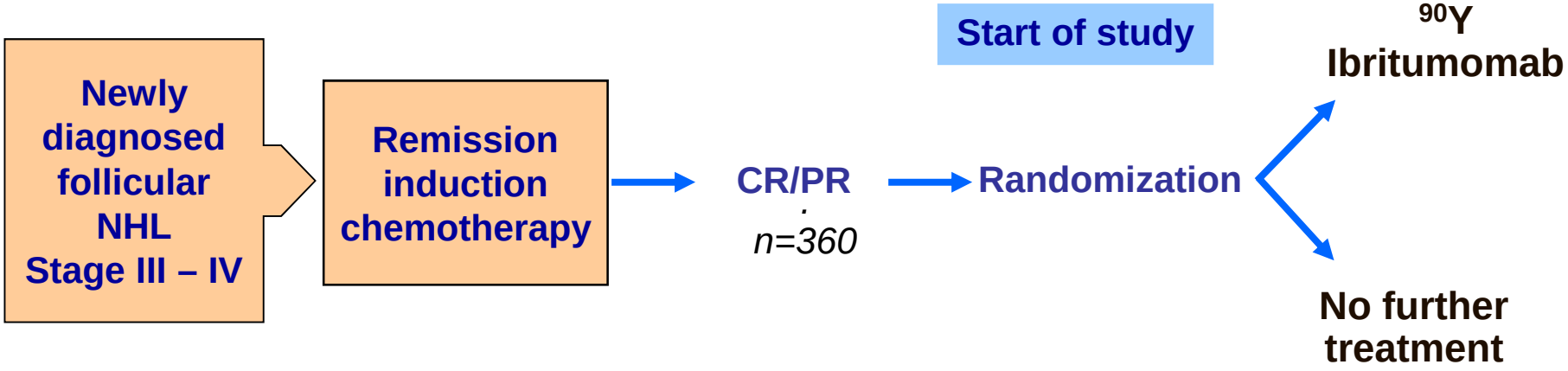
FL2000 GELA-GOELAMS study update
Event Free Survival

median follow-up = 8.3 years



Bachy et al, ICML 2011

FIT study
First line Follicular Lymphoma
Phase III Consolidation Study

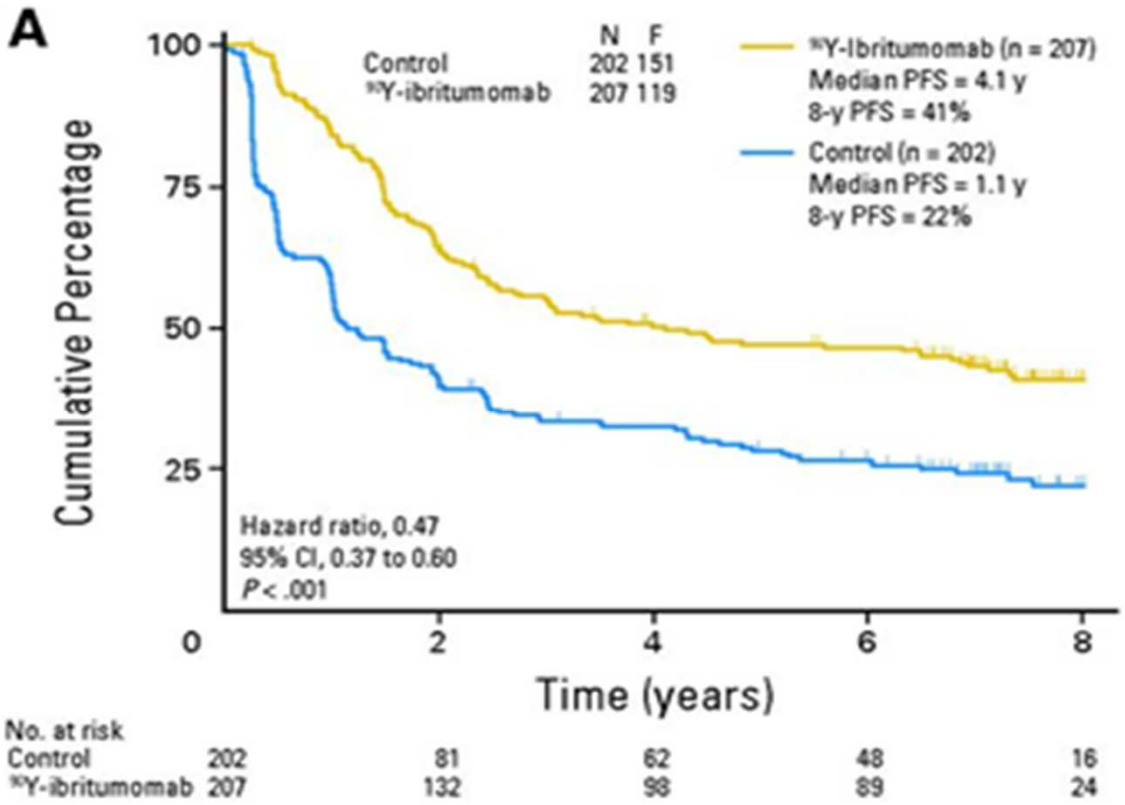


Morschhauser F et al. J Clin Oncol 2013;31:1977.

FIT study

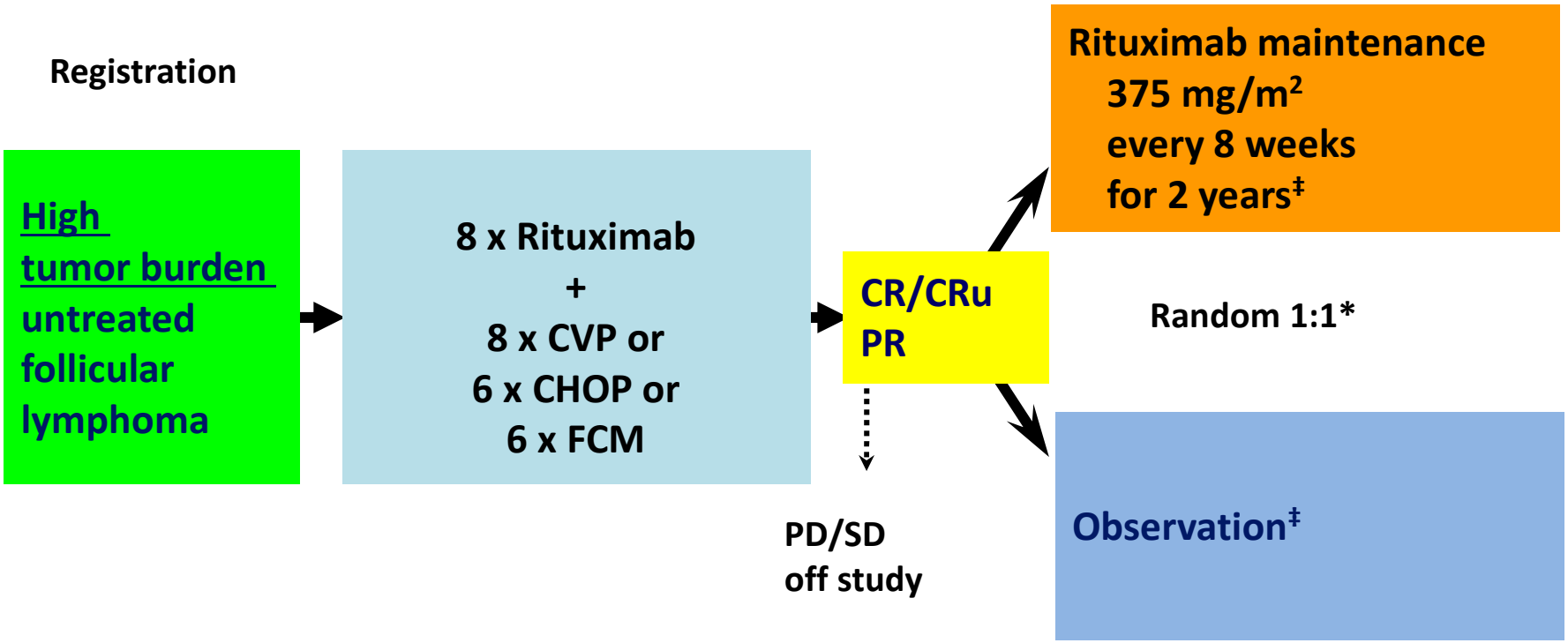
First line Follicular Lymphoma

PFS, 7 years of follow-up



Morschhauser F et al. J Clin Oncol 2013;31:1977.

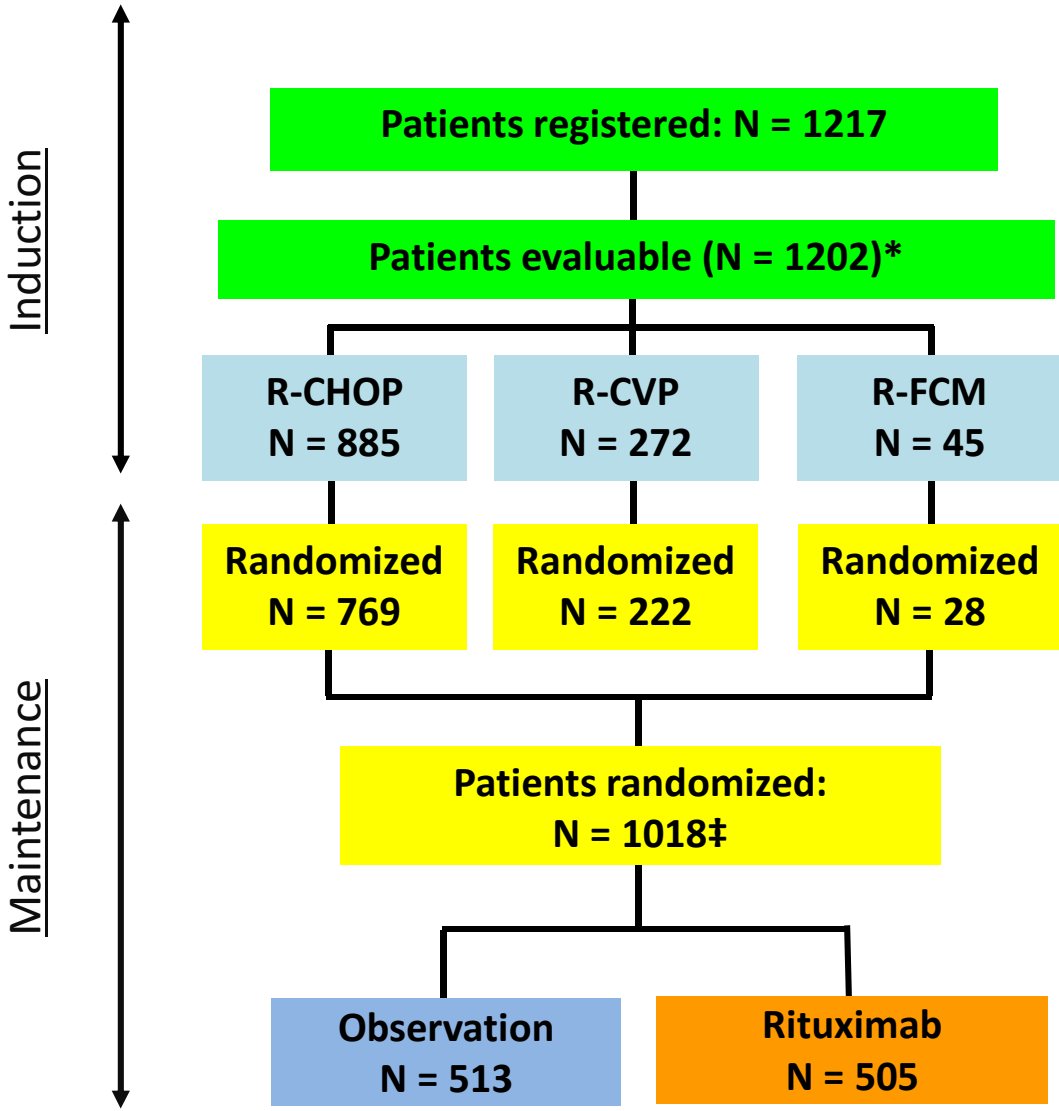
PRIMA: study design



* 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

Salles G et al. Lancet 2011;377: 42-51.

PRIMA: Patients disposition



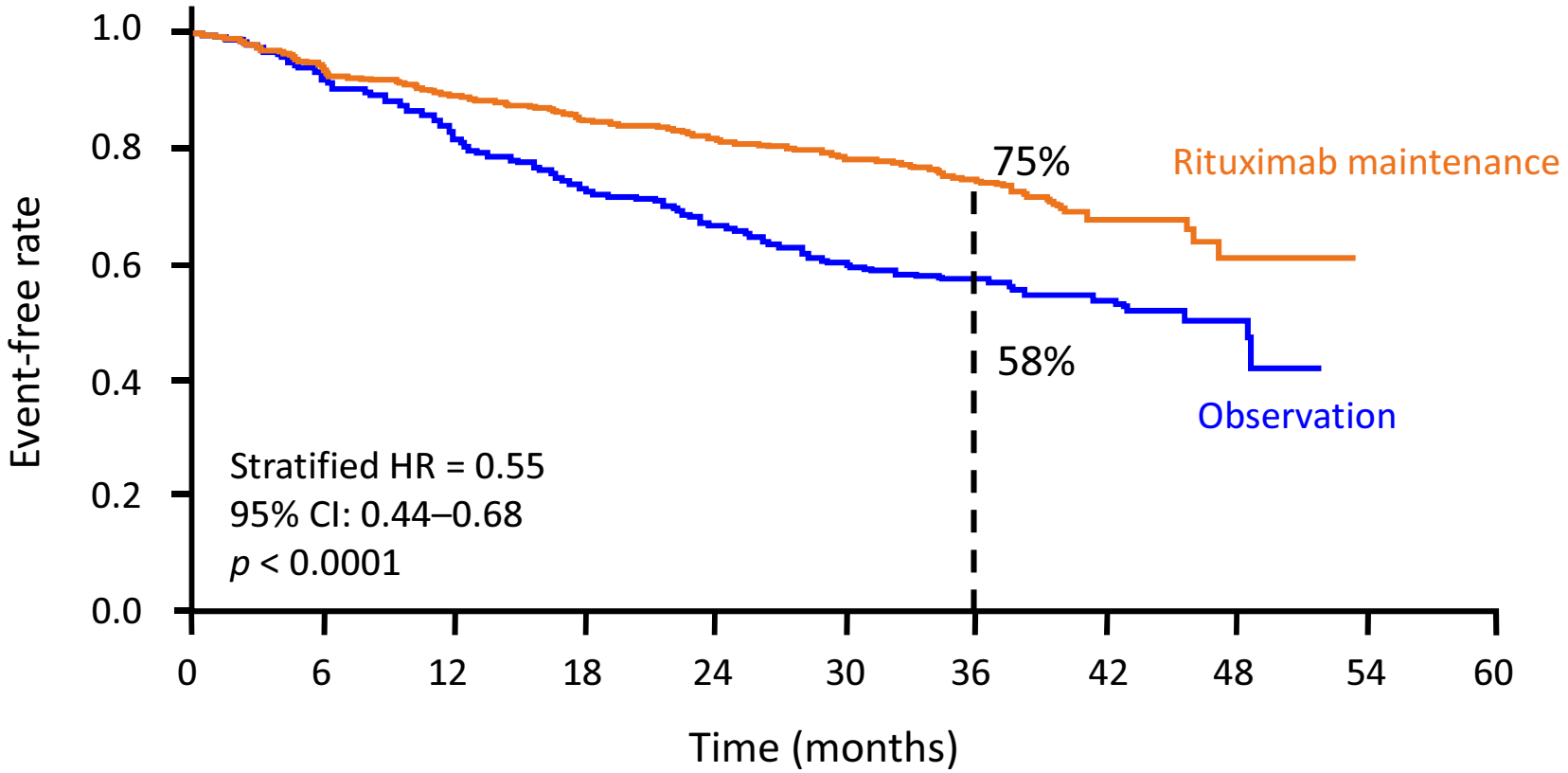
* *15 pts in 3 sites closed prematurely*

- *9 pts did not receive chemo*
- *147 pts withdrew during or at the end of induction (failure to respond; toxicity)*
- *28 pts failed to be randomized*

‡ *1 pt died during the randomization process*

Salles G et al. Lancet 2011;377: 42-51.

Primary endpoint (PFS)

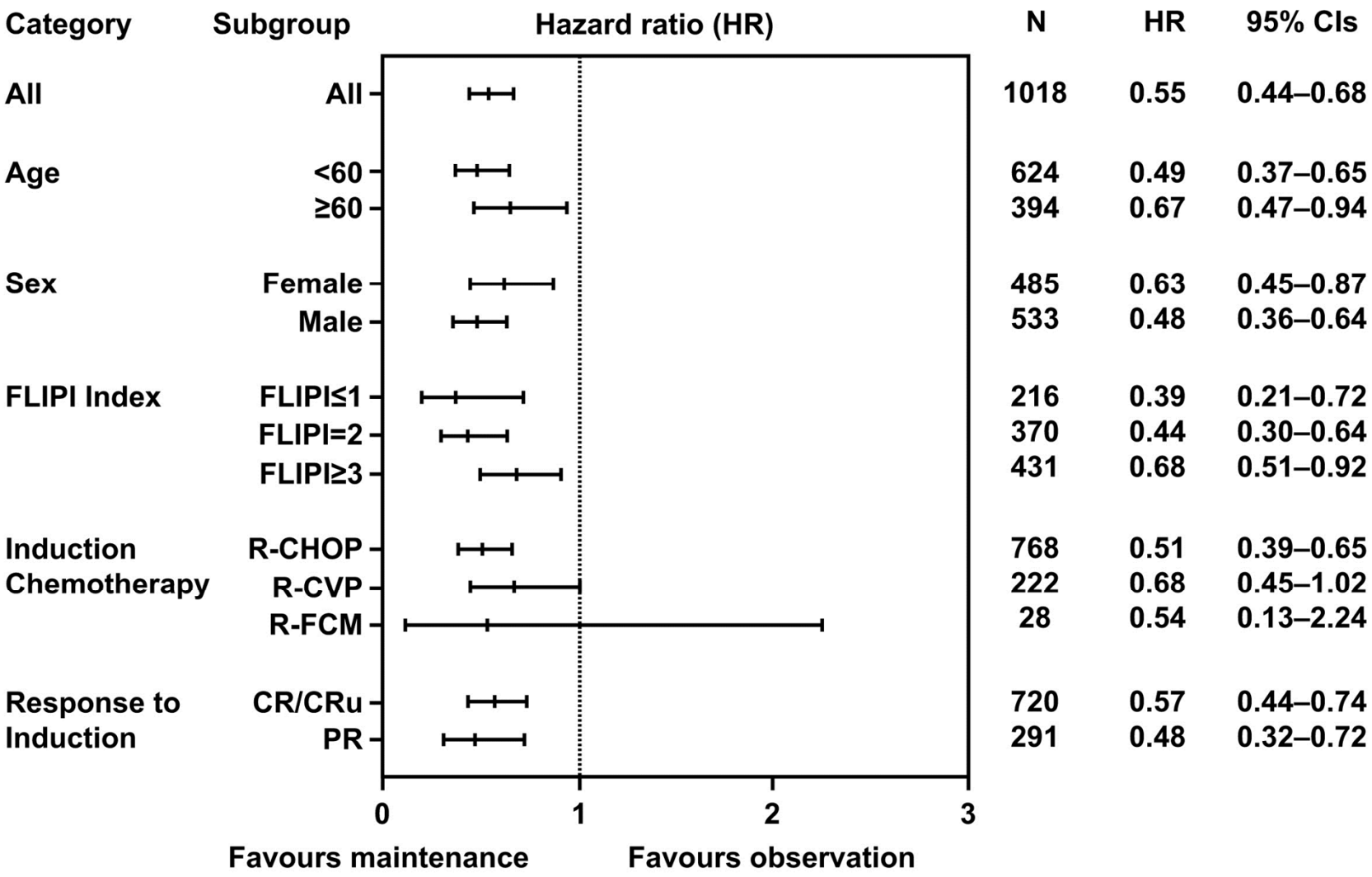


Patients at risk

505	472	445	423	404	307	207	84	17	0	–
513	469	415	367	334	247	161	70	16	0	–

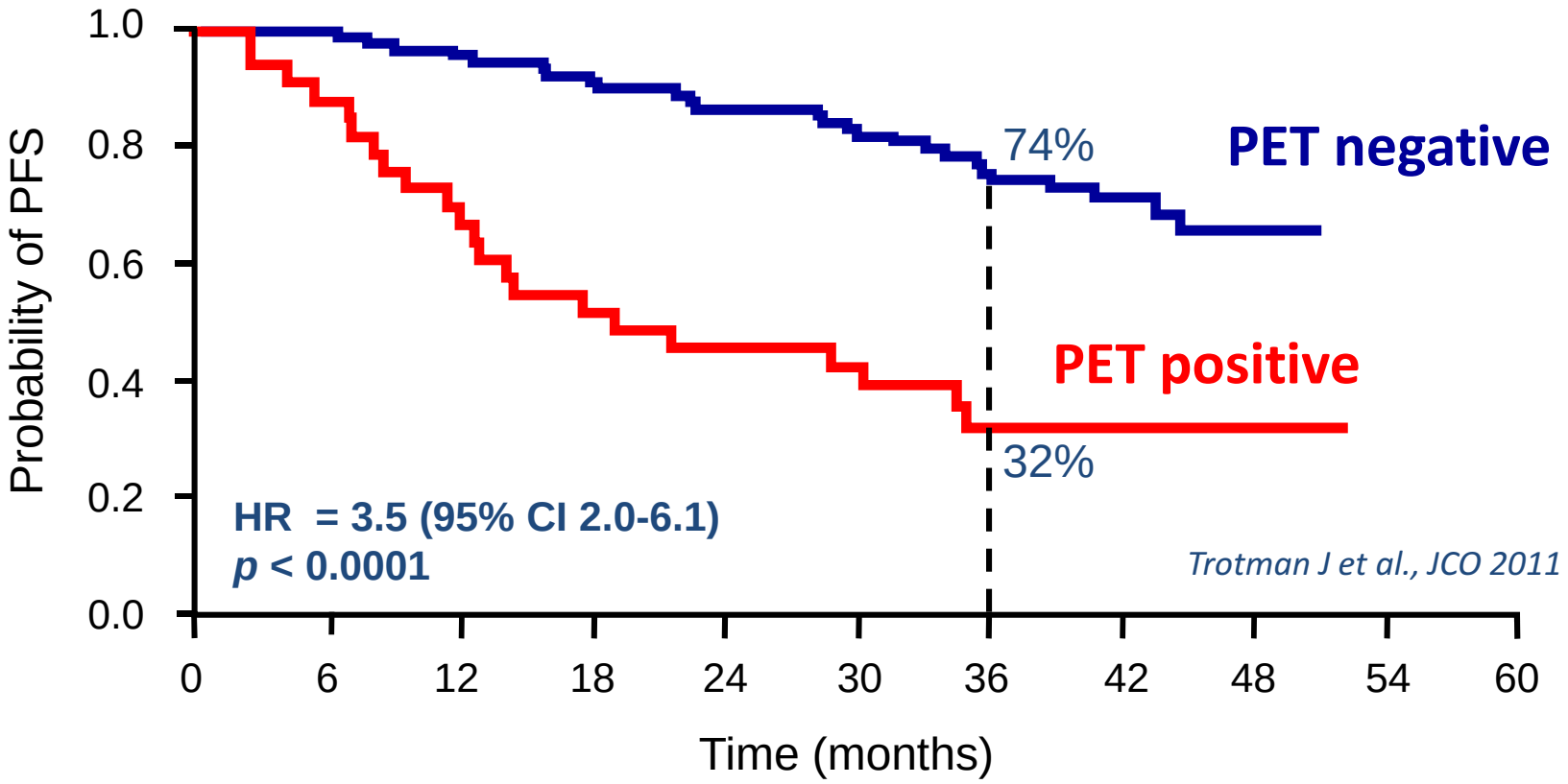
Salles G et al. Lancet 2011;377: 42-51.

Maintenance efficacy in predefined subgroups



Salles G et al. Lancet 2011;377: 42-51.

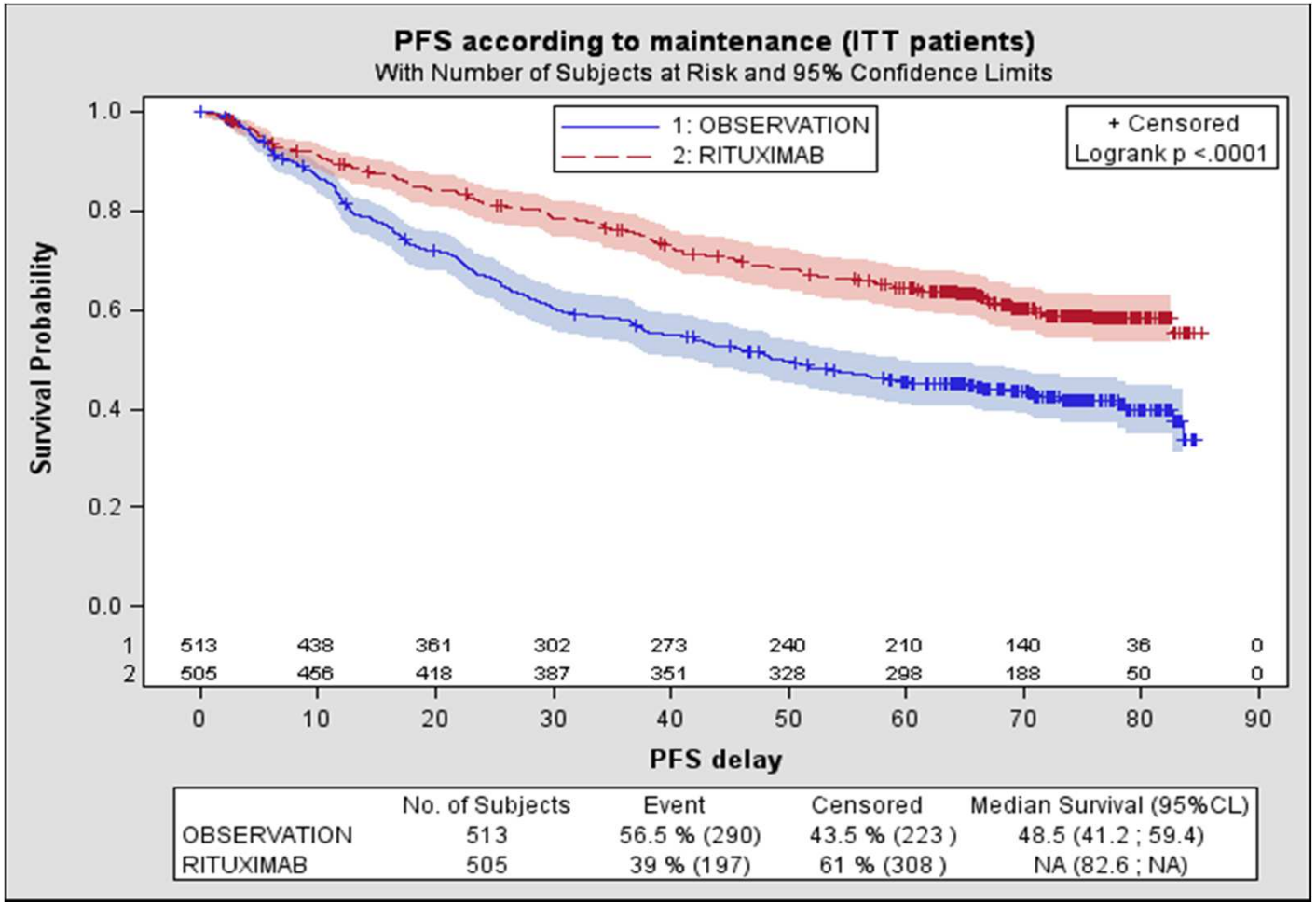
Assessment of response using PET-CT



- PET-CT results also predicted overall survival
- Results reproduced in a prospective study *(Dupuis et al, JCO, 2012)*

PRIMA 6 years follow-up

Progression free survival from randomization

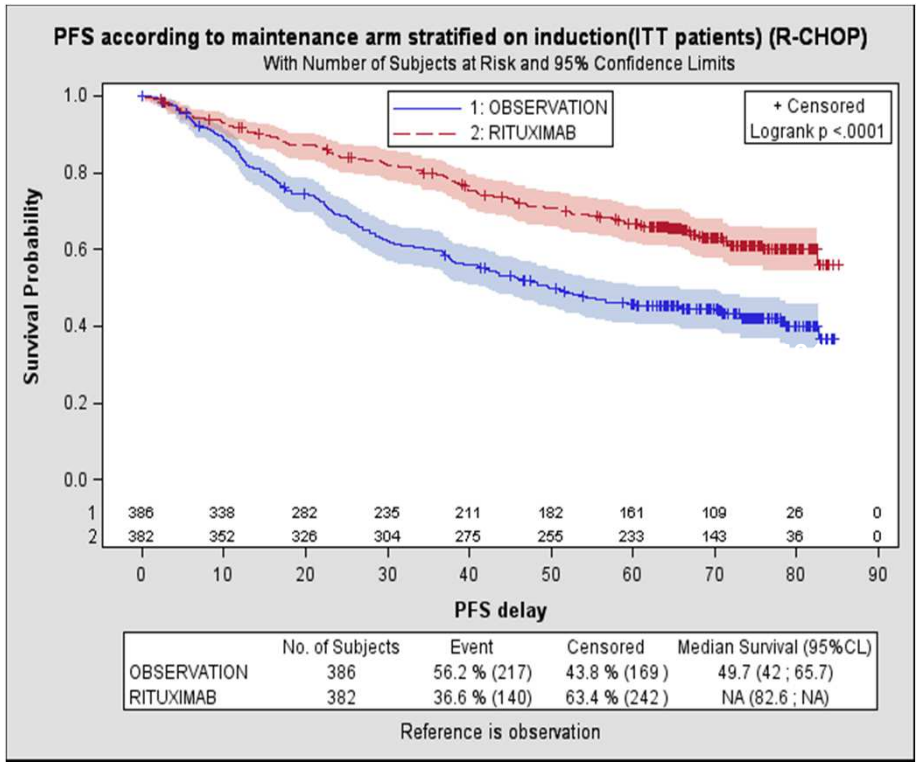


Median follow-up since randomization : 73 months

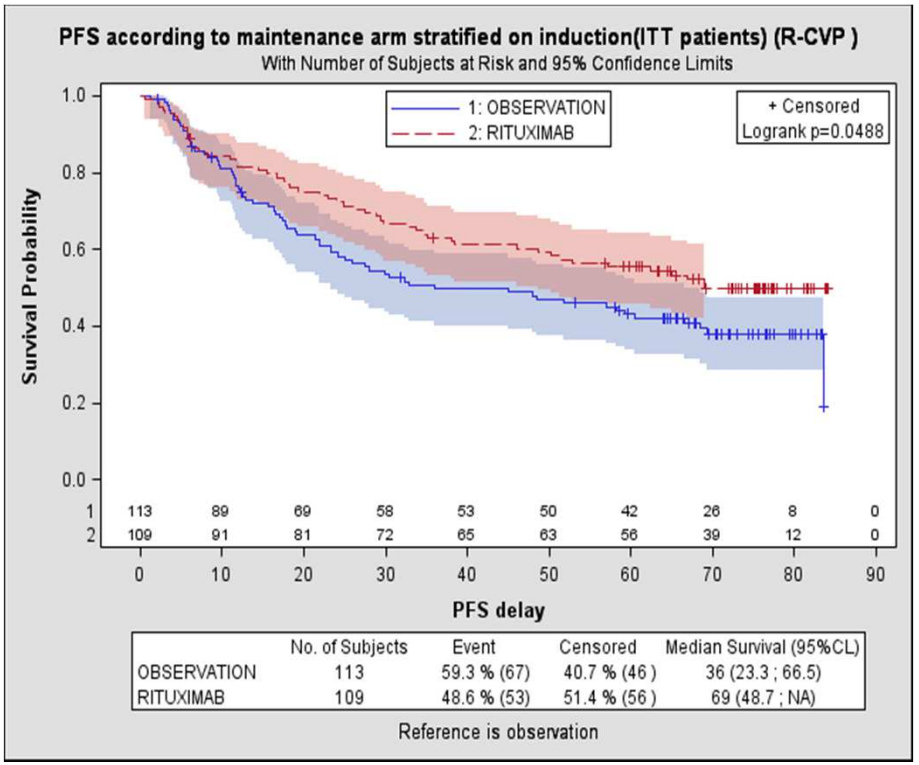
PRIMA 6 years follow-up

Progression free survival from randomization

R-CHOP induction



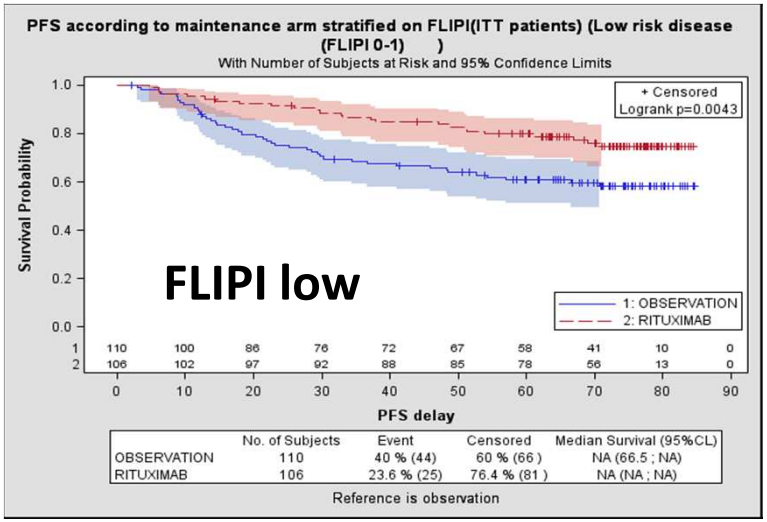
R-CVP induction

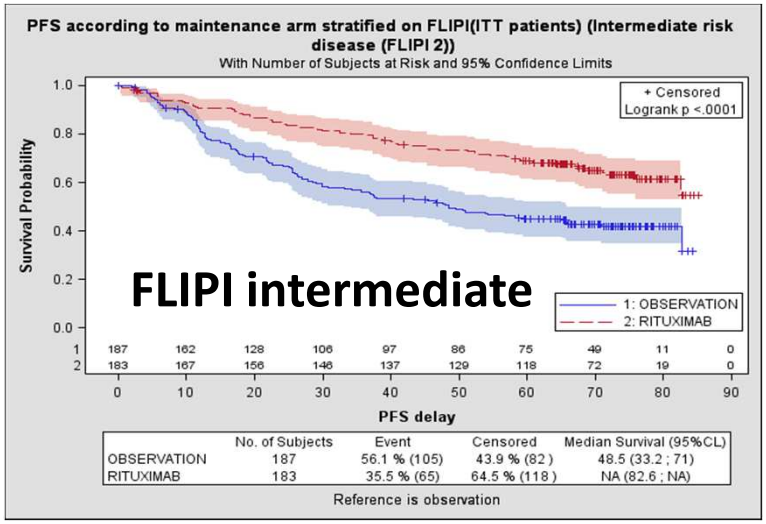


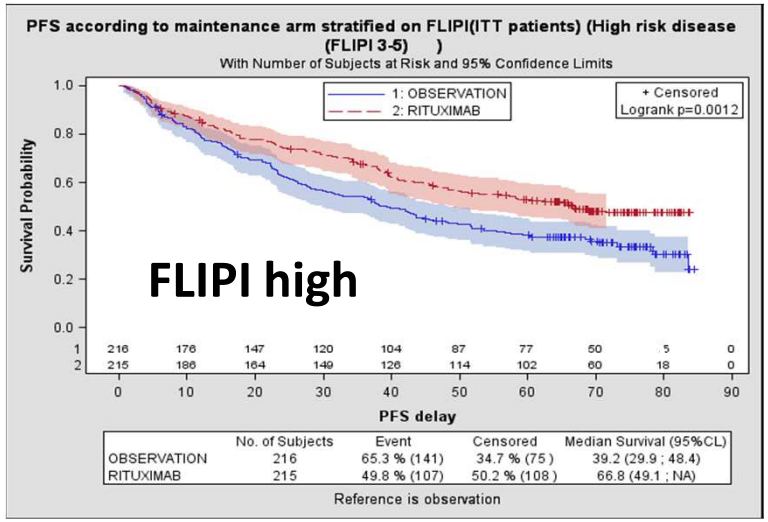
Median follow-up since randomization : 73 months

PRIMA 6 years follow-up

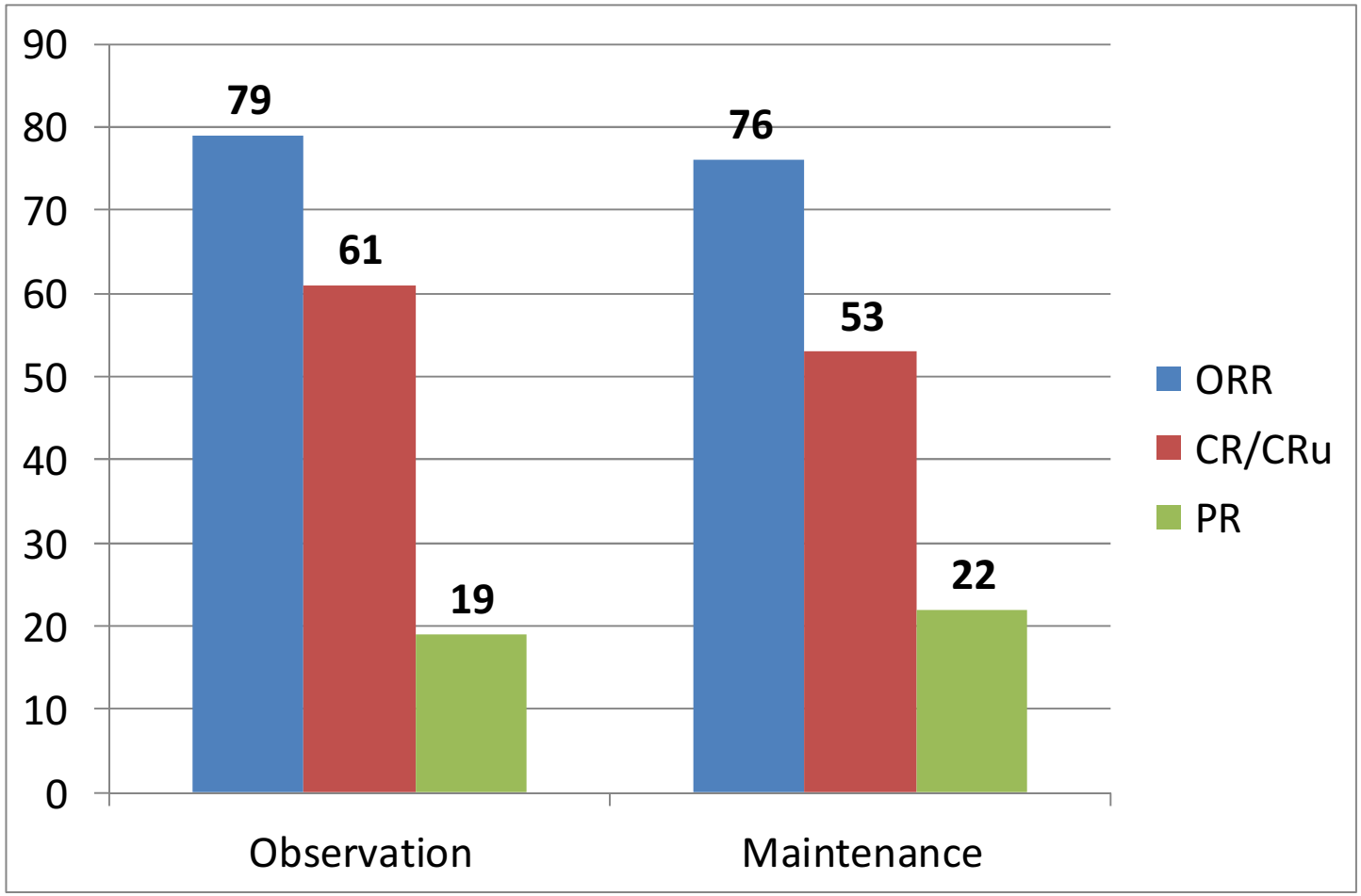
Progression free survival from randomization







PRIMA 6 years follow-up
Response to second line treatment



Responses reported by the investigators (percentage)

PRIMA = 6 years follow-up
Rate of histological transformation

	OBSERVATION	RITUXIMAB MAINTENANCE
Progression	278	186
With morphology documentation	114	80
Transformed histology	24 (21%)	16 (20%)

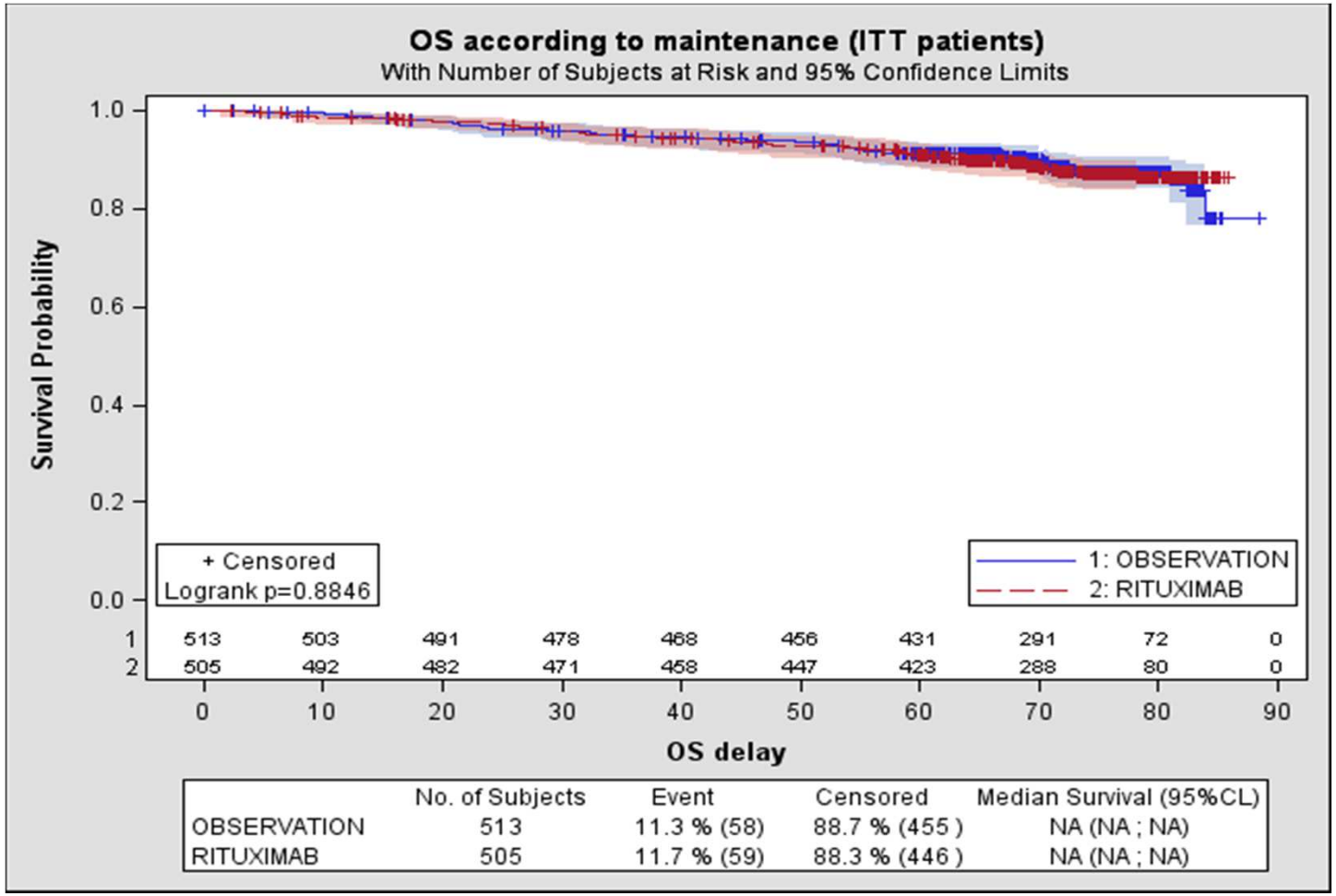
PRIMA = 6 years follow-up
Relevant causes of death

	OBSERVATION 58 / 518	RITUXIMAB MAINTENANCE 59 / 505
Lymphoma	28	28
2nd malignancies (MDS / AML)	19 (5)	6 (2)
Infections *	4	7
Others	7	18

* Infections include 1 case of PML in each arm and one case of hepatitis B in R-maintenance (both reported in 2011) and one case of aspergillosis in the observation arm.

PRIMA 6 years follow-up

Overall survival



Median follow-up since randomization : 73 months

PRIMA 6 years follow-up

Conclusions

Bénéfice durable de la maintenance en PFS et délai d'un autre traitement

Pas de signe de toxicité nouvelle

Pas de bénéfice en survie

Le traitement de la rechute doit être amélioré dans les deux groupes

A la rechute

At the time of relapse: Many options

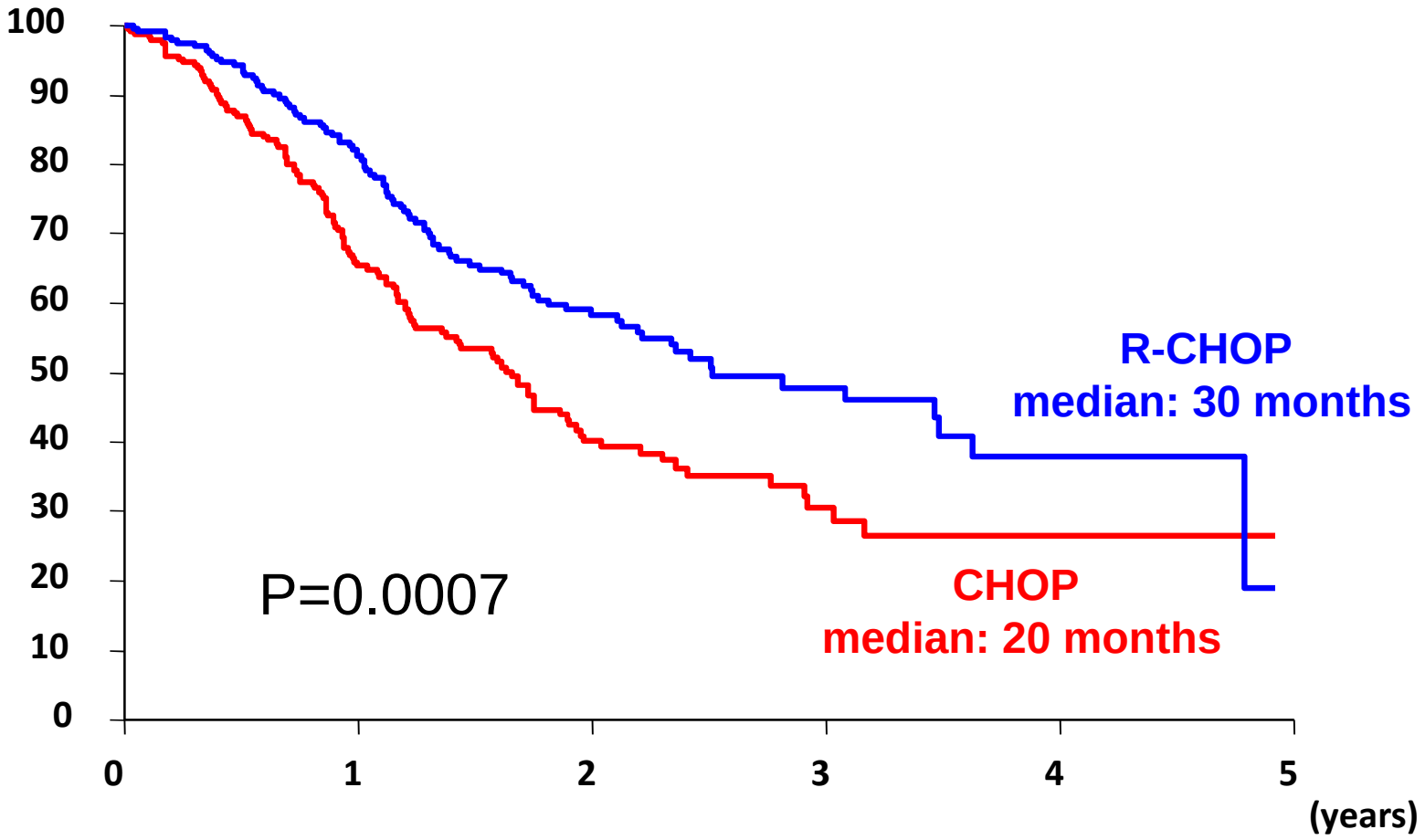
- Watch and wait
- Rituximab alone
- Radiolabelled antibody
- Various immuno-chemotherapy regimen
  - R-Bendamustine/R-CHOP
  - R-DHAP
  - R-FCM, …
- Autologous transplant
- Allogeneic transplant
- New agents in development

Treatment of first relapse

- Patient status
  - Age
  - Performance status
  - Co-morbidities
- Characteristics of relapse
  - On/off therapy
  - Delay from first treatment
  - FLIPI / Bulk
  - Transformation
  - Aggressiveness
- Initial therapy
  - Components
  - Maintenance
  - Toxicities
- Patient wishes

Immunochemotherapy

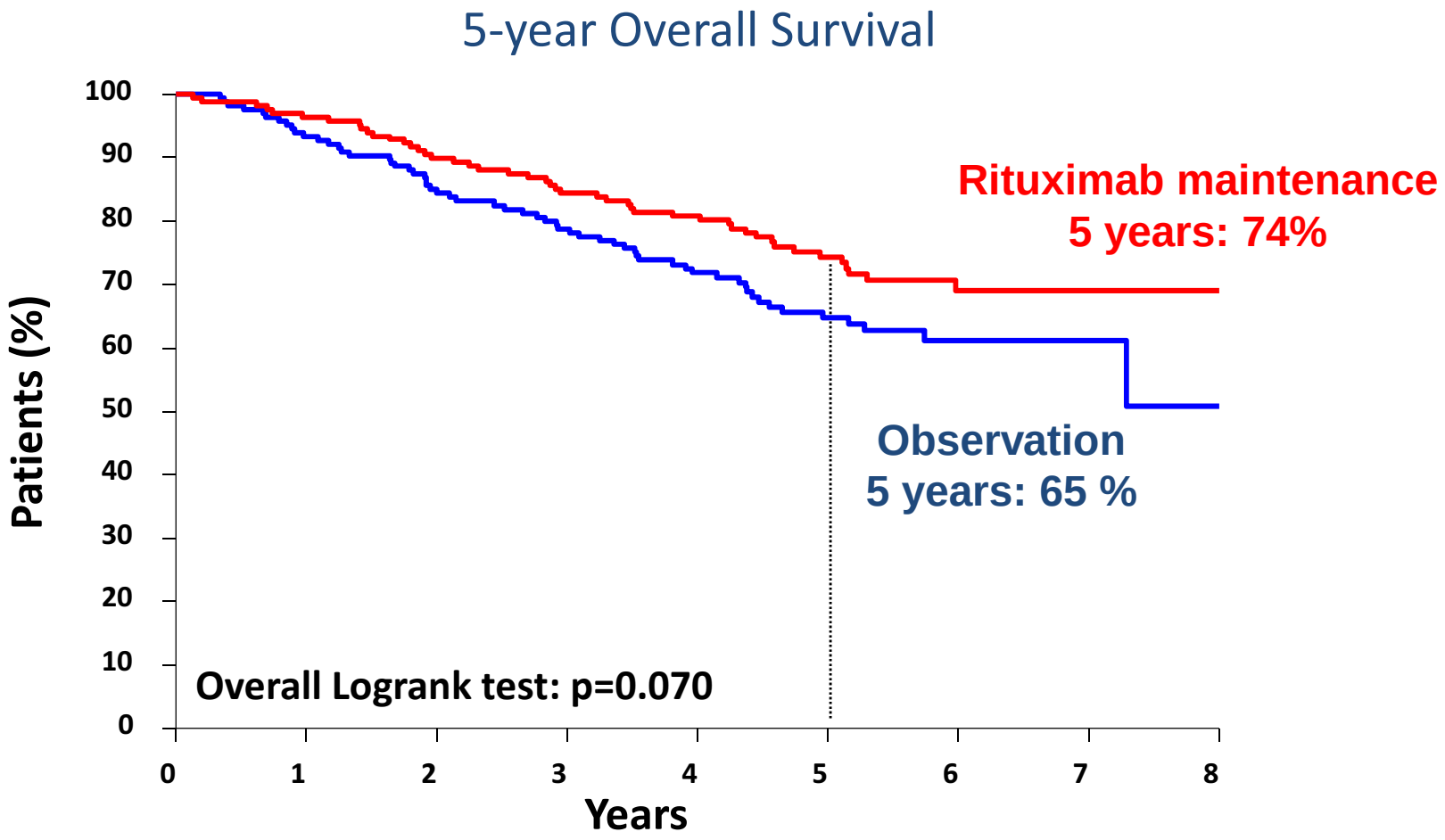
If the patient did not receive anthracyclins, R-CHOP appears as a standard



Van Oers Blood 2006;108:3295

Rituximab maintenance at time of relapse

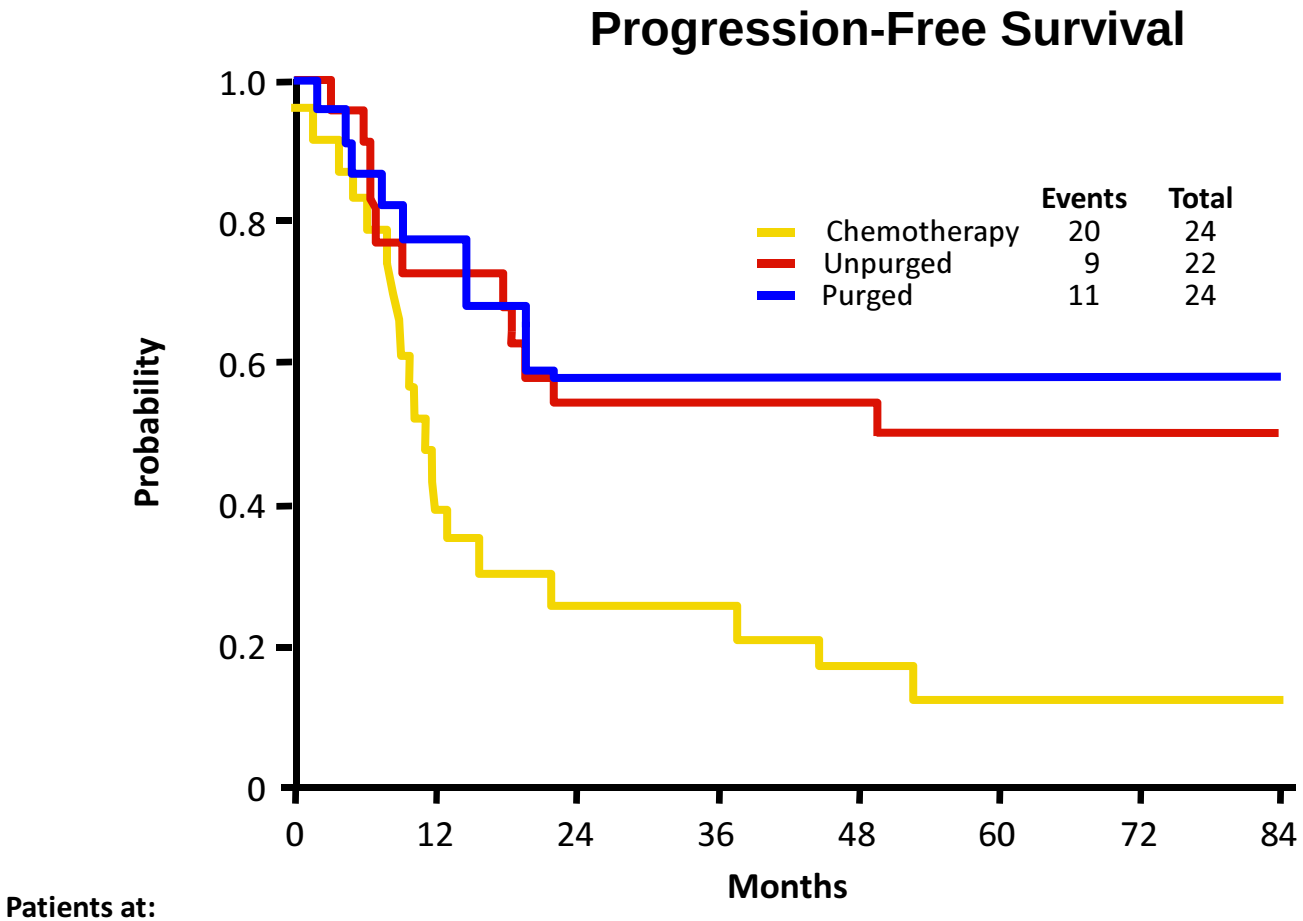
EORTC 20981 Intergroup phase III trial



van Oers M, *et al.* J Clin Oncol. 2010 Jun 10;28(17):2853-8.

The CUP trial

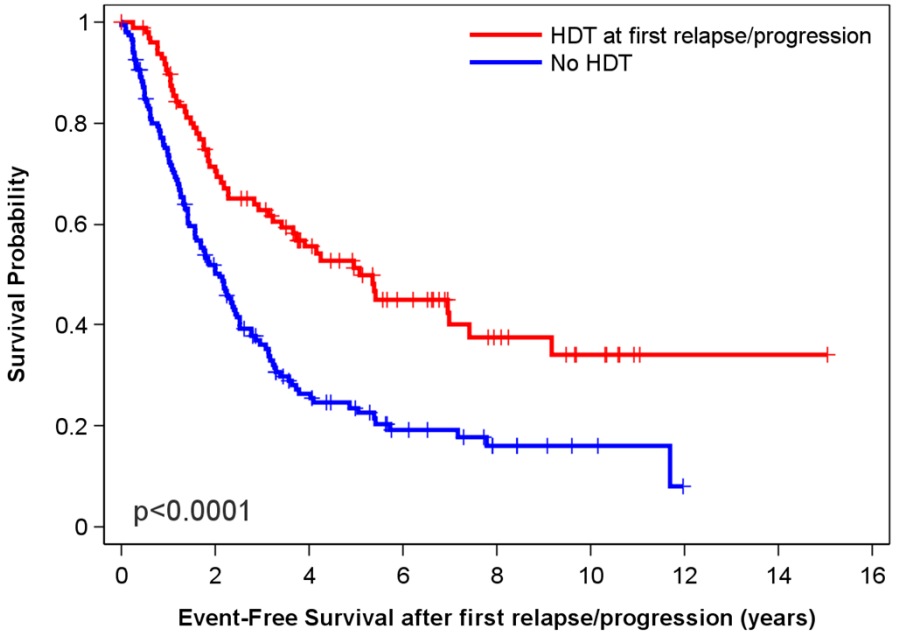
In the pre-rituximab era



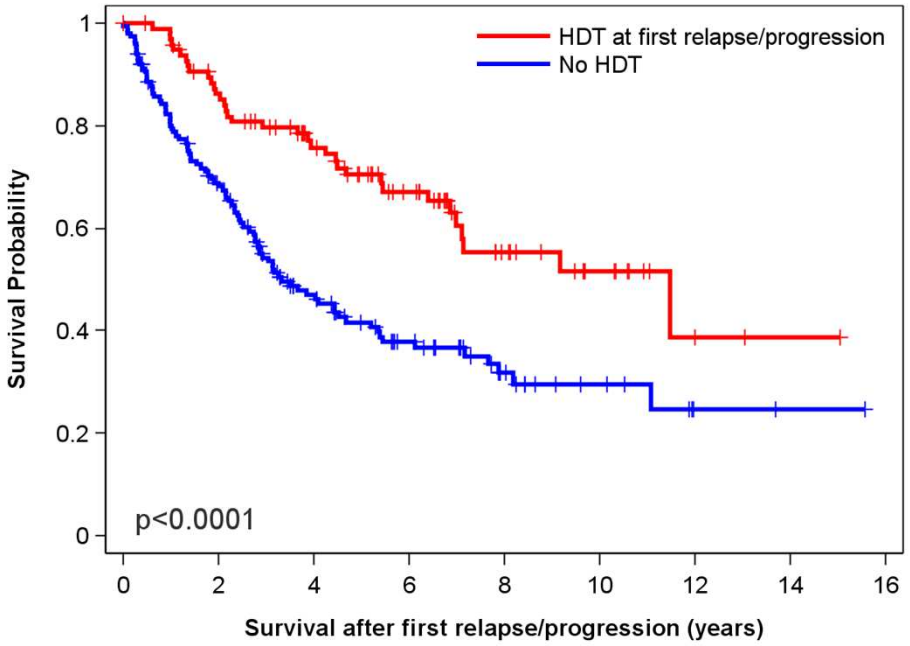
Schouten, H. C. et al. J Clin Oncol; 21:3918-3927 2003

HDT with ASCT compared with other approaches after 1st relapse

Event-free survival after relapse

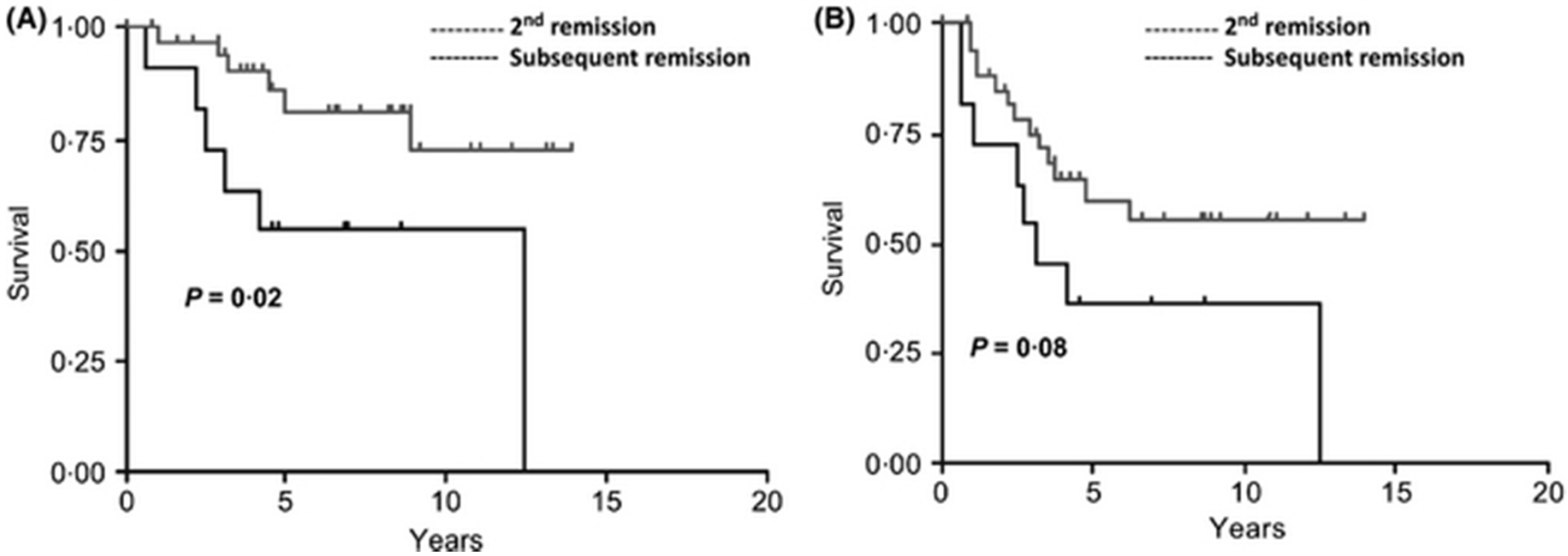


Overall survival after relapse



Sebban C et al. J Clin Oncol. 2008;26:3614-20

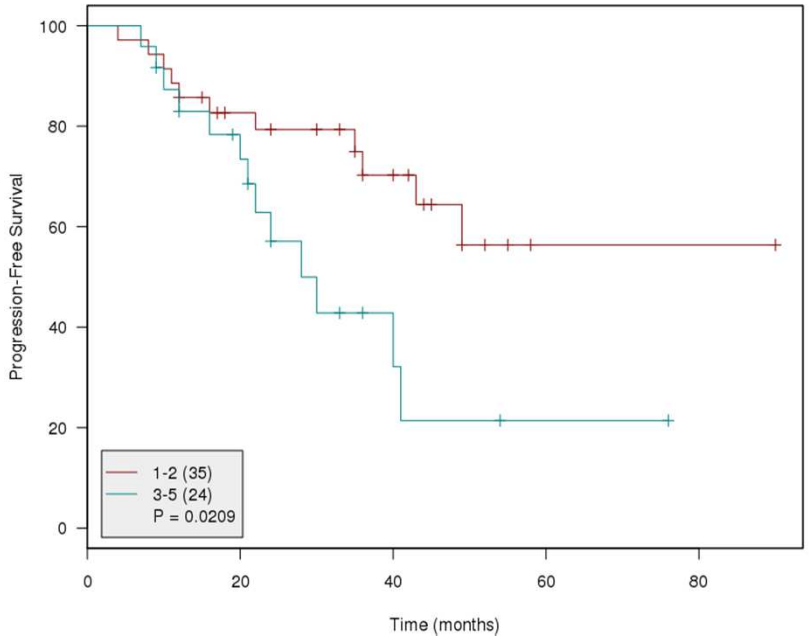
Autologous stem cell transplantation for follicular lymphoma is of most benefit early in the disease course



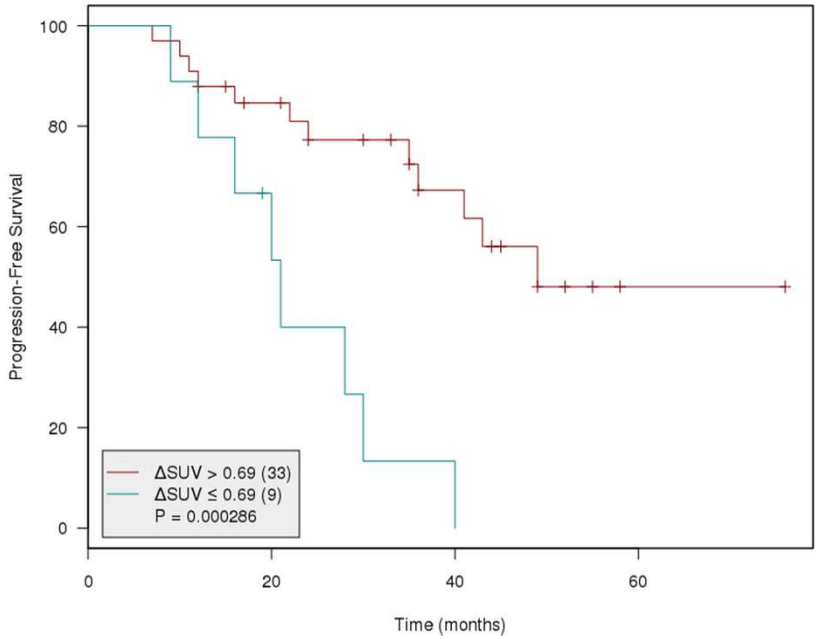
Kothari J et al. Br J Haematol 2014; doi 10.1111

Importance of chemosensitivity

Deauville scale

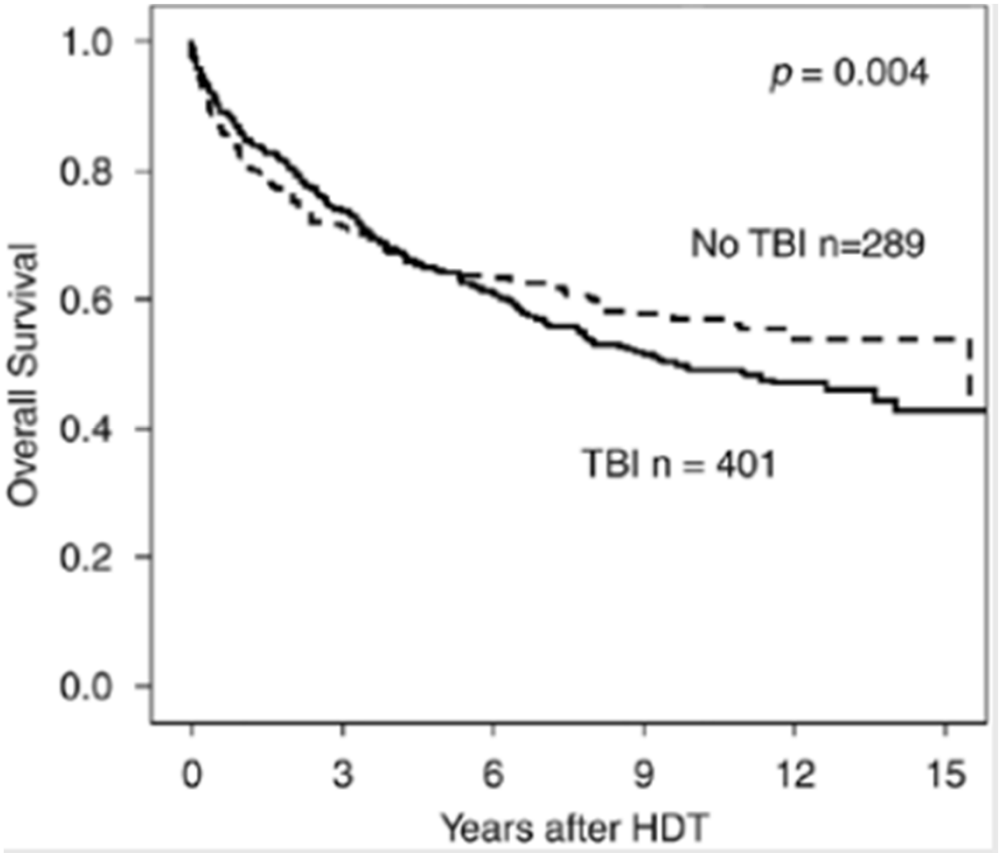


ΔSUV



Alcantara M et al. ASH 2013

Importance of conditioning regimen

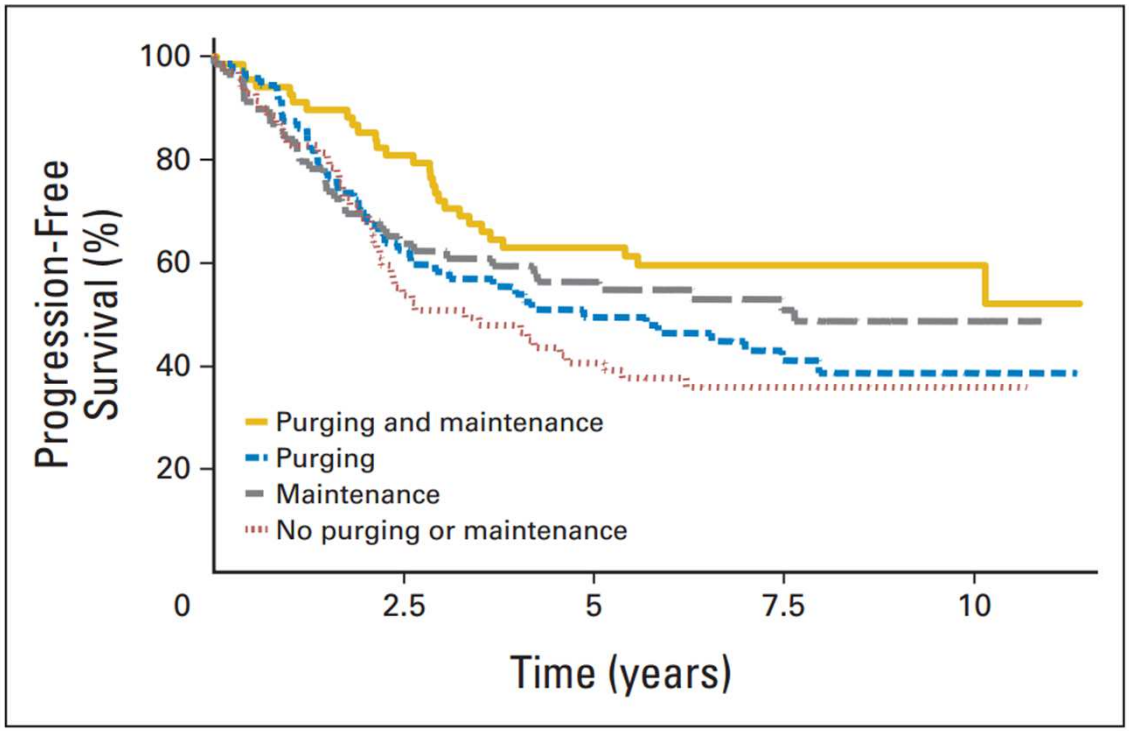


EBMT Registry
693 patients

MDS: 39 pts
in TBI: 34

Montoto S et al. Leukemia (2007) 21, 2324–2331

ASCT with or without rituximab in relapsed follicular lymphoma: the EBMT Trial



Progression-free survival by treatment arm.

10-years Overall Survival estimates > 65%

Pettengel R et al. J Clin Oncol. 2013 Apr 1.

Indications for Hematopoietic Stem Cell Transplantation in patients with FL:

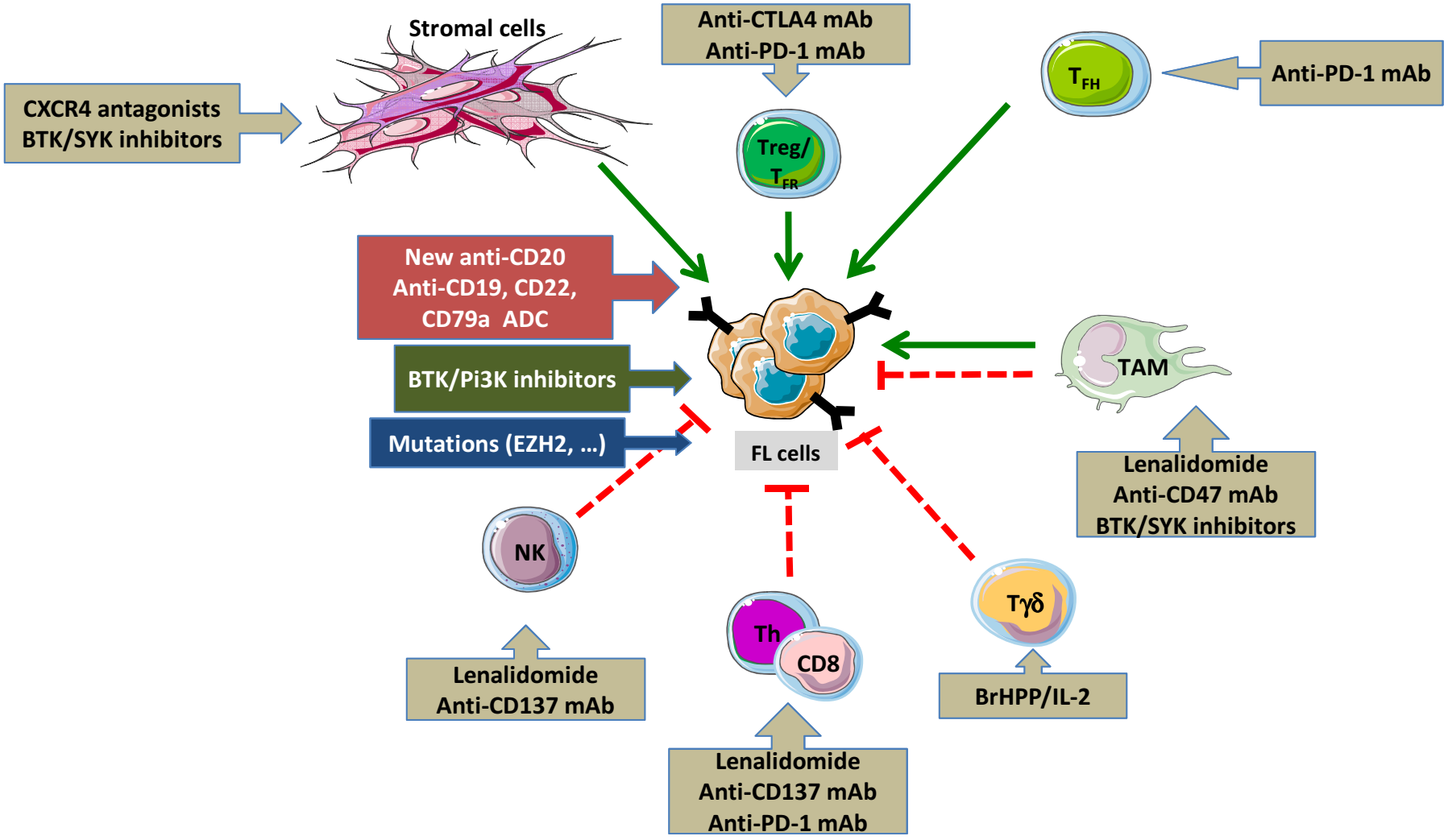
A consensus project of the EBMT-Lymphoma Working Party

Consensus	Agreed statement
YES	In patients in first relapse with **chemo-sensitive** disease HDT- ASCR is an appropriate treatment option to consolidate remission: - after a short response duration - with a high-risk FLIPI
YES	Allogeneic transplantation should be considered in patients with **relapse after HDT-ASCR**.

Montoto S et al., Haematologica 2013;98:1014

Quelques perspectives

Some targets in follicular lymphoma



Adapted from K Tarte

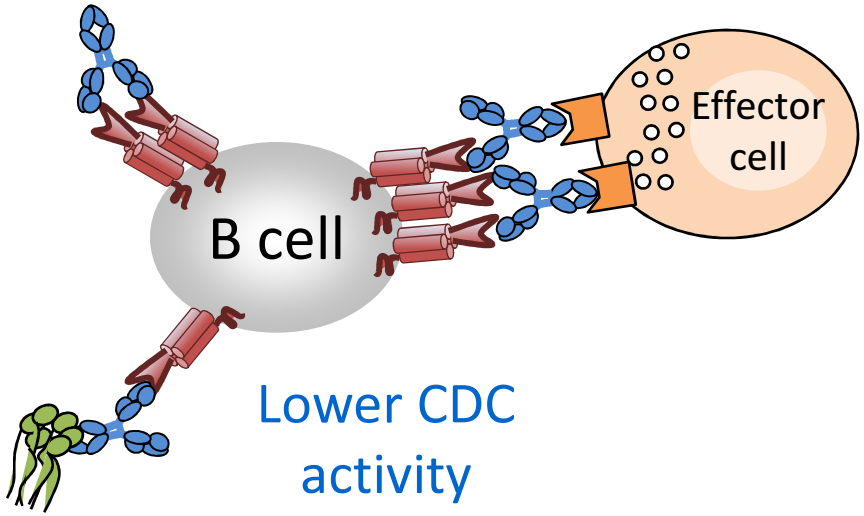
GA101: Mechanisms of action

Increased direct cell death

Type II versus type I antibody

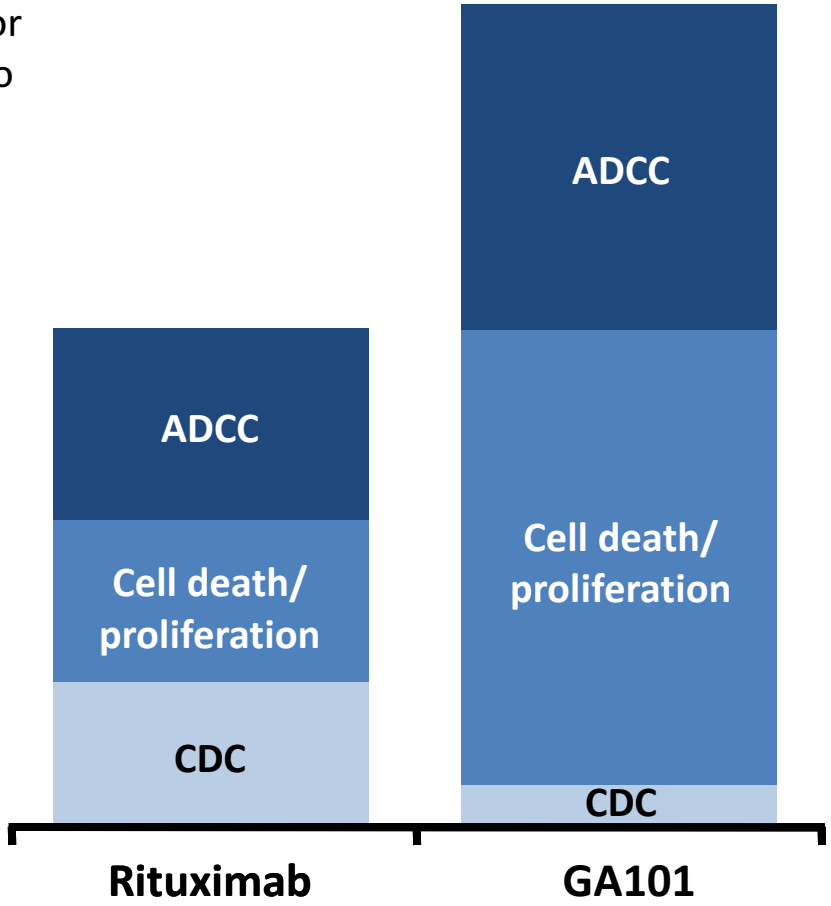
Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



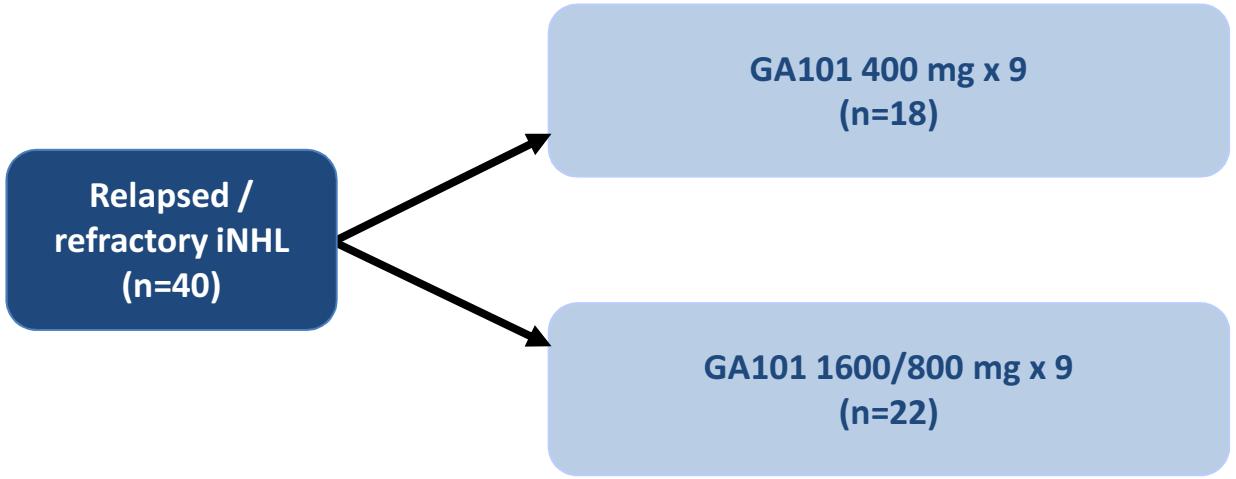
Lower CDC activity

Type II versus type I antibody



Mössner E, *et al*. *Blood* 2010;115:4393–4402

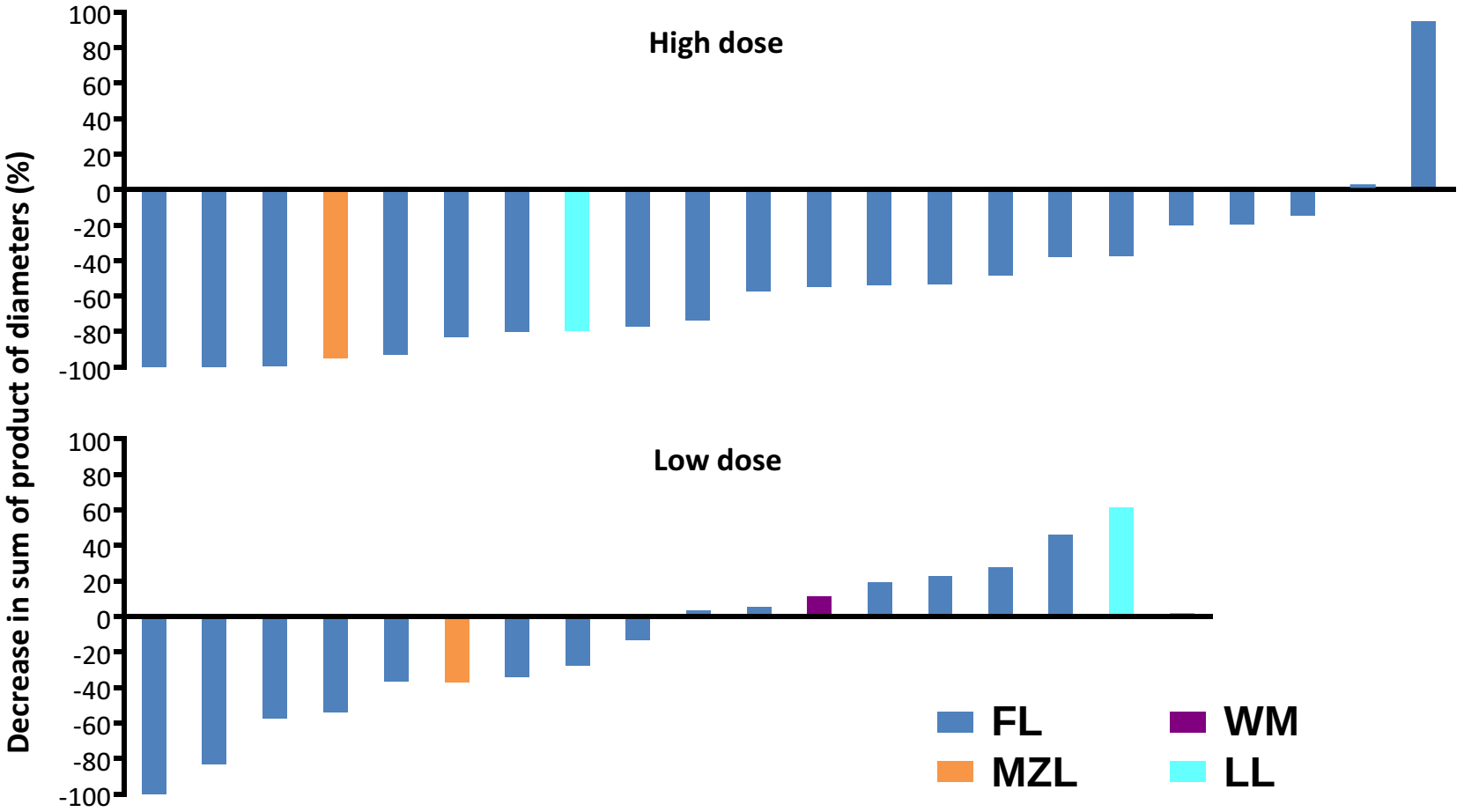
GAUGUIN Phase II: Indolent lymphomas



Arm 1:	GA101 400 mg d1, d8 cycle 1; d1 cycles 2–8
Arm 2:	GA101 1600 mg d1, d8 cycle 1; 800 mg d1 cycles 2–8
Primary endpoint	End of treatment response in relapsed/refractory iNHL, assessed 4 weeks after the last infusion (28 weeks after treatment start)

Salles G, *et al*. *Blood* 2010;116:Abstract 2868, taken from poster presentation at ASH, Dec. 2010

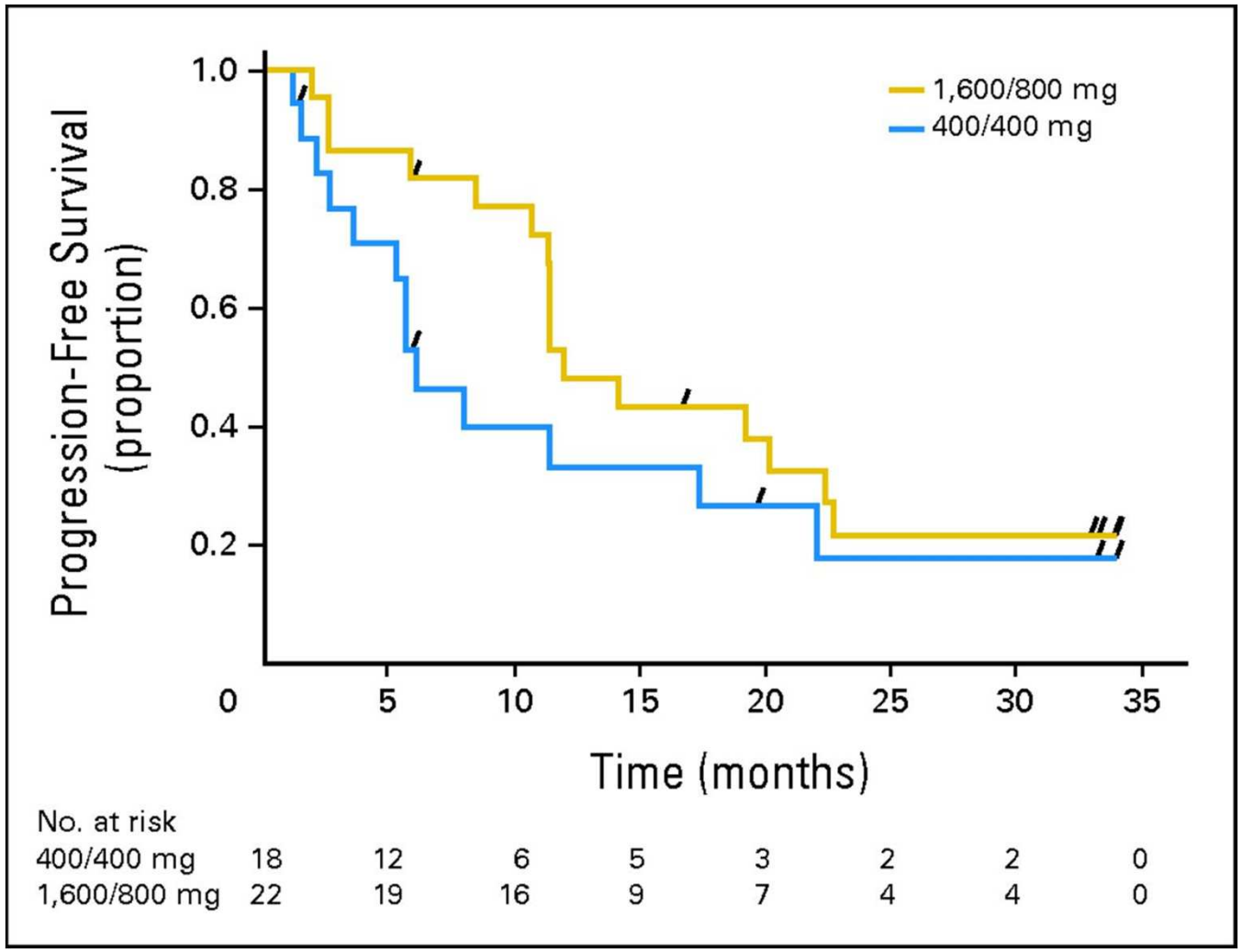
GAUGUIN iNHL Phase II: Tumour assessment



FL, follicular lymphoma; MZL, marginal zone lymphoma; WM, Waldenström's macroglobulinemia; LL, lymphoplasmacytic lymphoma

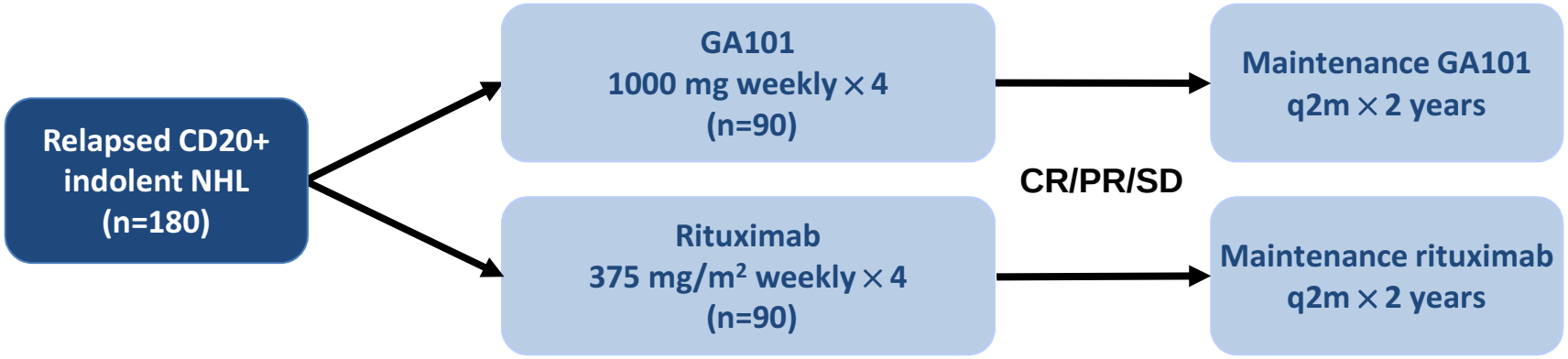
Salles G A et al. JCO 2013;31:2920-2926

GAUGUIN iNHL Phase II: PFS



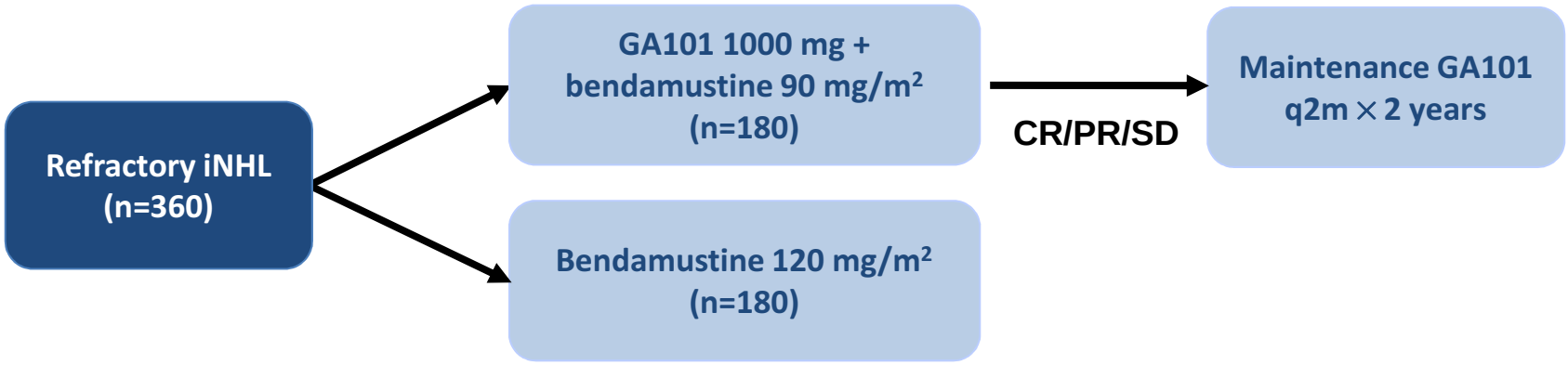
Salles G A et al. JCO 2013;31:2920-2926

GAUSS Phase II: Study design



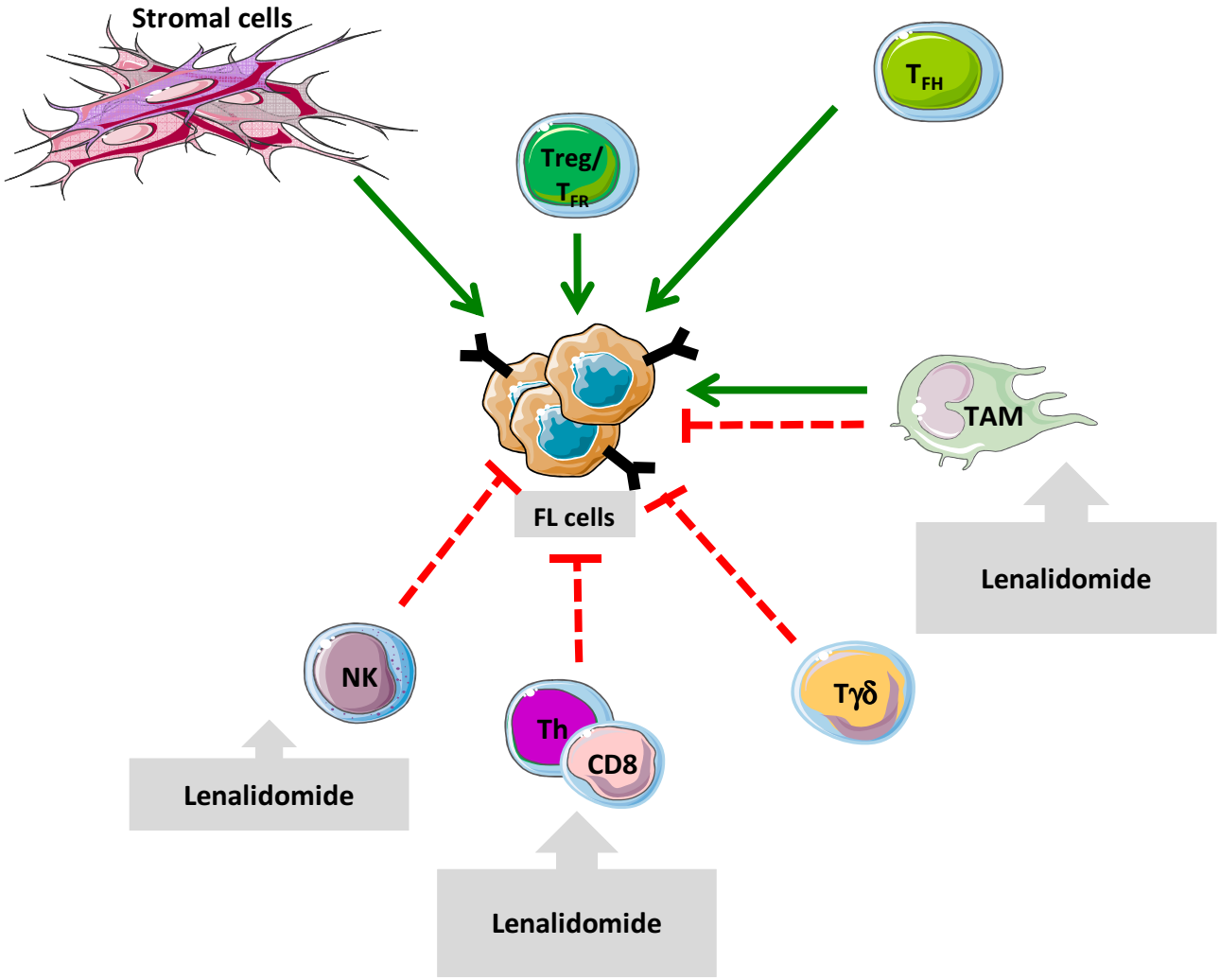
Experimental arm	GA101 1000 mg d1 q28d
Control arm	Rituximab 375 mg/m^2 on d1 q28d
Patient population	70 follicular NHL, 20 other indolent per arm
Primary endpoint	ORR after four infusions in follicular NHL patients
Extended treatment	Patients achieving CR, PR or SD, may continue induction therapy every 2 months for up to 2 years

GADOLIN Phase III: Study design



Experimental arm	Bendamustine 90 mg/m^2 d1, d2 q28d + GA101 d1, d8, d15 cycle 1; d1 q28d cycles 2–6
Control arm	Bendamustine 120 mg/m^2 on d1, d2 q28d for 6 cycles
Evaluation	CT prior to cycle 4 and 28 days following cycle 6
Primary endpoint	IRC-assessed PFS
Extended treatment (experimental arm only)	Patients achieving CR, PR or SD may continue GA101 every 2 months for up to 2 years

Some targets in follicular lymphoma



Adapted from K Tarte

Lenalidomide and rituximab in follicular lymphoma

- Lenalidomide has single agent activity in relapsed indolent lymphoma.[1]
- Lenalidomide enhances rituximab induced apoptosis in preclinical models.[2]
- Lenalidomide in combination with rituximab has an important activity in relapsed follicular lymphoma.[3,4]

1. Witzig T et al. J Clin Oncol 2009:32;5404-9.
2. Ramsay AG et al. Blood 2009:114:4713-20.
3. Fowler N et al. ICML 2011. Abst#137.
4. Martin P et al. ICML 2013. Abst#63.

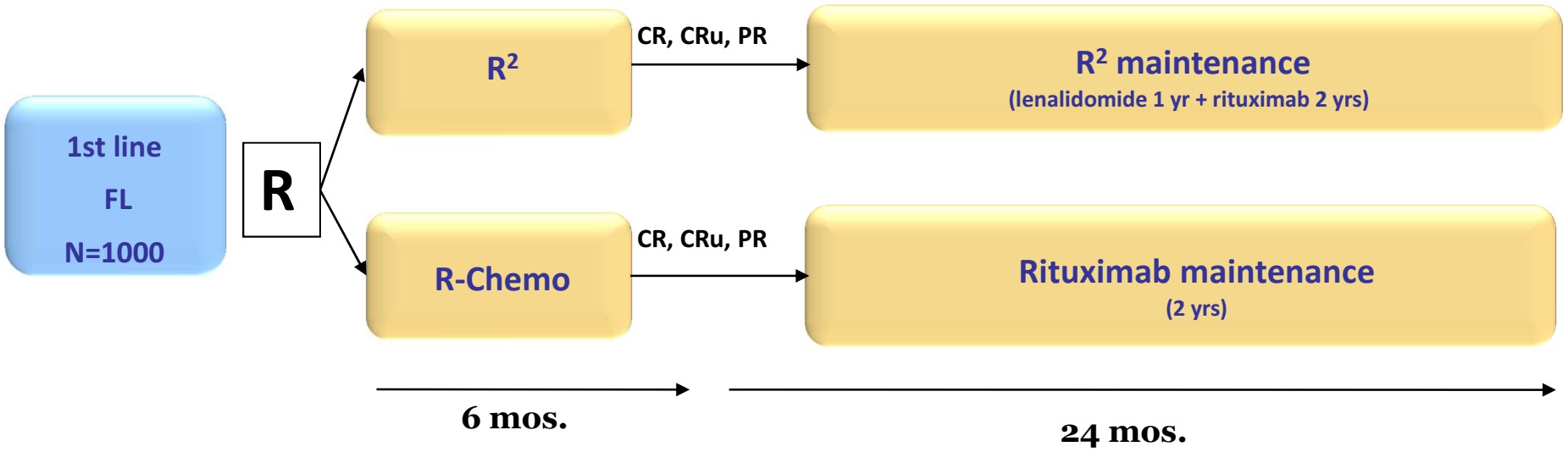
Frontline Combination of Lenalidomide and Rituximab for Follicular Lymphoma: Clinical Response

BY GELF CRITERIA N=45							
GELF (+) N=22 (49%)				GELF (-) N=23 (51%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1 (5%)	21(95%)	100%	1(5%)	4(17%)	18 (78%)	95%

BY BULK OF DISEASE N=45							
BULKY N=13 (29%)				NON-BULKY N=32 (71%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1(8%)	12(92%)	100%	1(3%)	4 (13%)	27 (84%)	97%

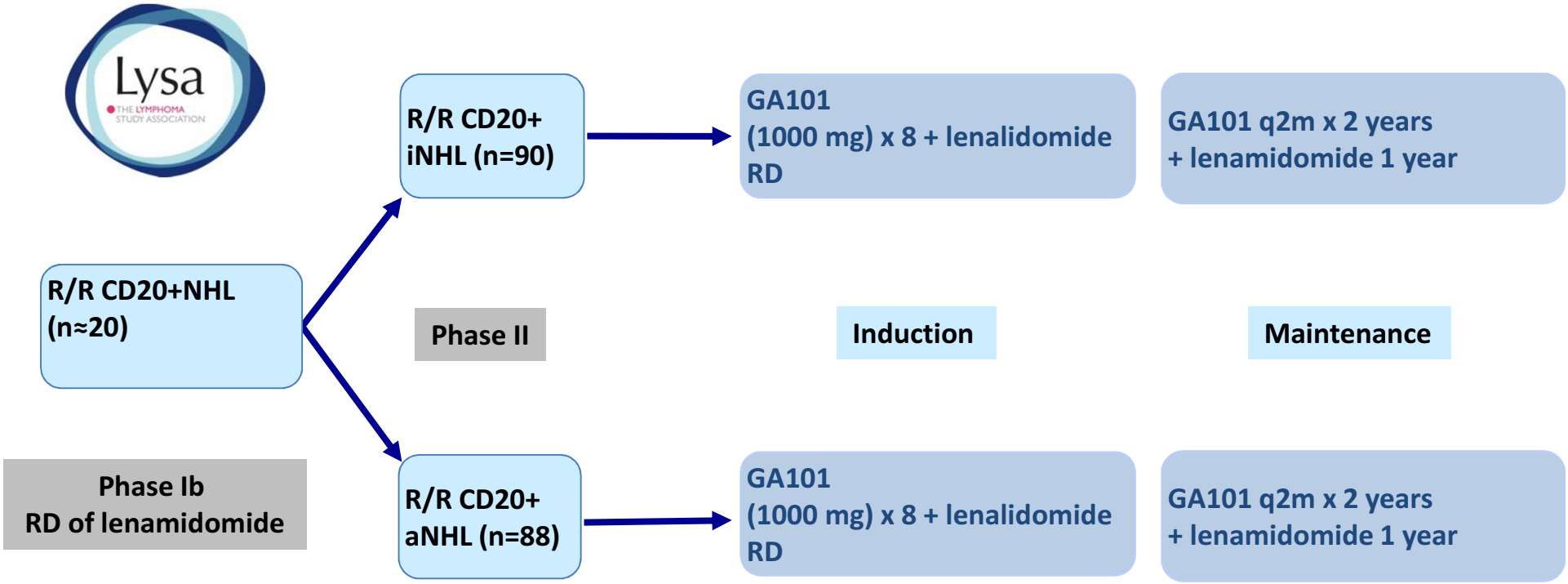
Fowler, N. et al. ICML 2011. Abst#137.

RELEVANCE – Study Design



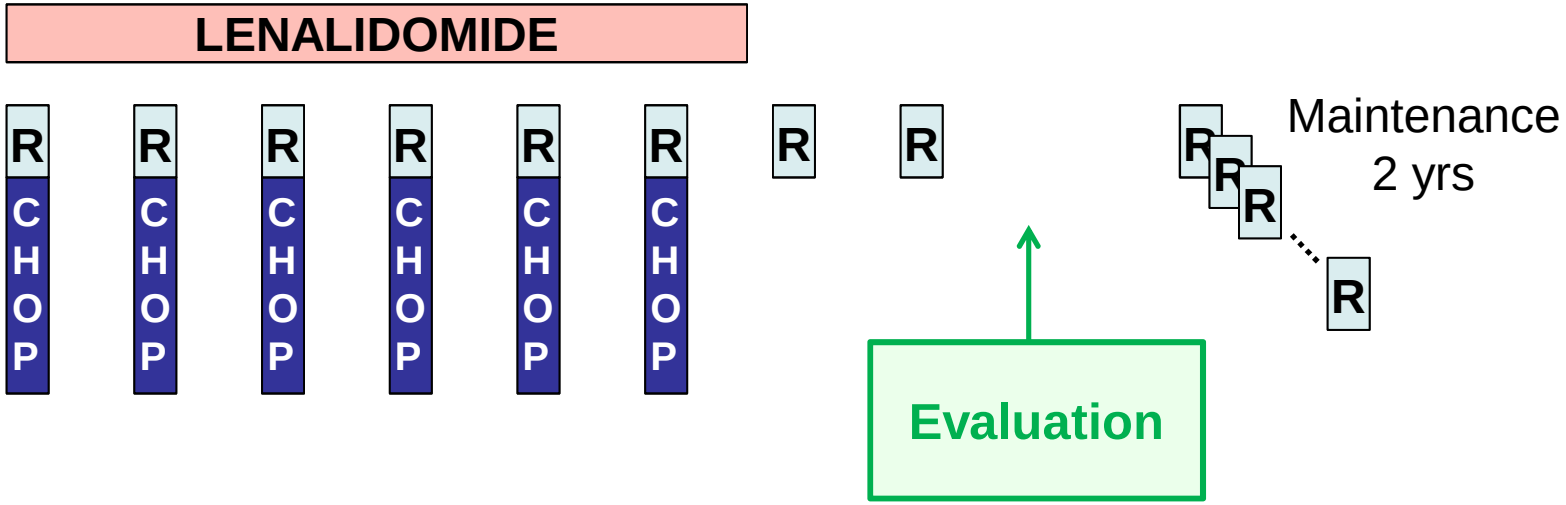
- Inclusion: GELF criteria
- R-Chemo arm: Investigator choice of R-CHOP, R-CVP or R-Benda

GALEN study: Phase Ib/ II



Experimental treatment	GA101 (d8, d15,D22 cycle 1; d1 cycles 2–6) in combination with Lenalidomide once daily at the RD on days 1-21 (cycle 1) and days 2-22 (cycles 2-6) of a 28-day cycle
Extended treatment	Patients achieving CR or PR may receive GA101 at the induction dose every 2 months for up to 2 years and lenalidomide(10mg on days 2-22 of a 28-day cycle during a maximum of 1 year)

R2-CHOP Phase 2: Scheme



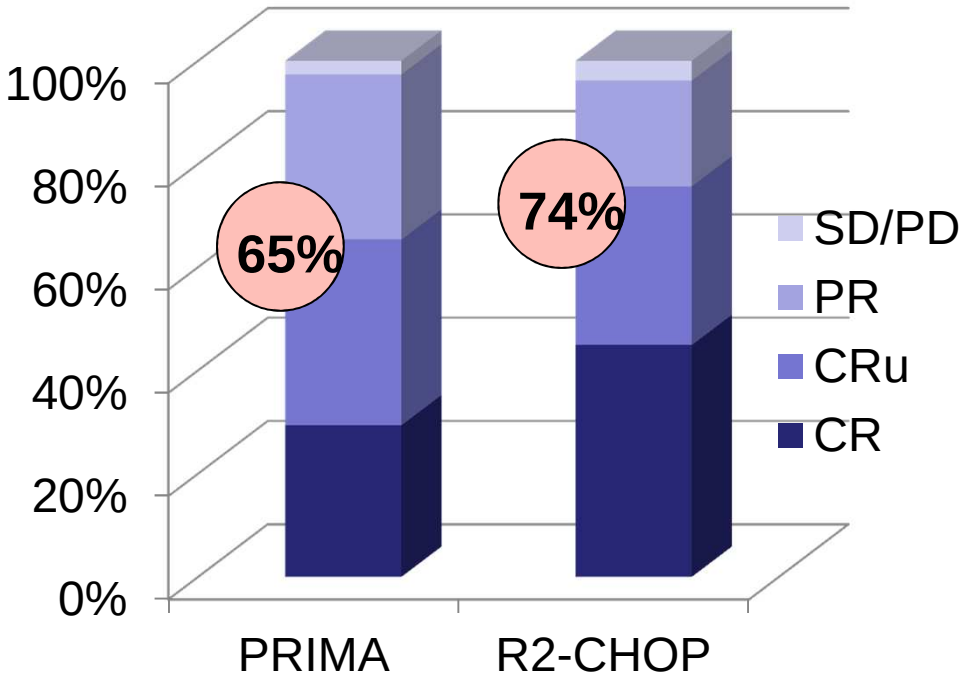
		Dose	Days
CYCLOPHOSPHAMIDE	IV	750 mg/m^2	1
DOXORUBICIN	IV	50 mg/m^2	1
VINCRISTINE	IV	1.4 (Max 2mg)	1
PREDNISONE	PO	40 mg/m^2	1-5
RITUXIMAB	CI	375 mg/m^2	1
LENALIDOMIDE	**PO**	**25 mg**	**1-14**

Pegfilgrastim 6mg
Aspirin 100 mg
Pneumocystis prophylaxis

Exploratory analysis: matched with PRIMA trial

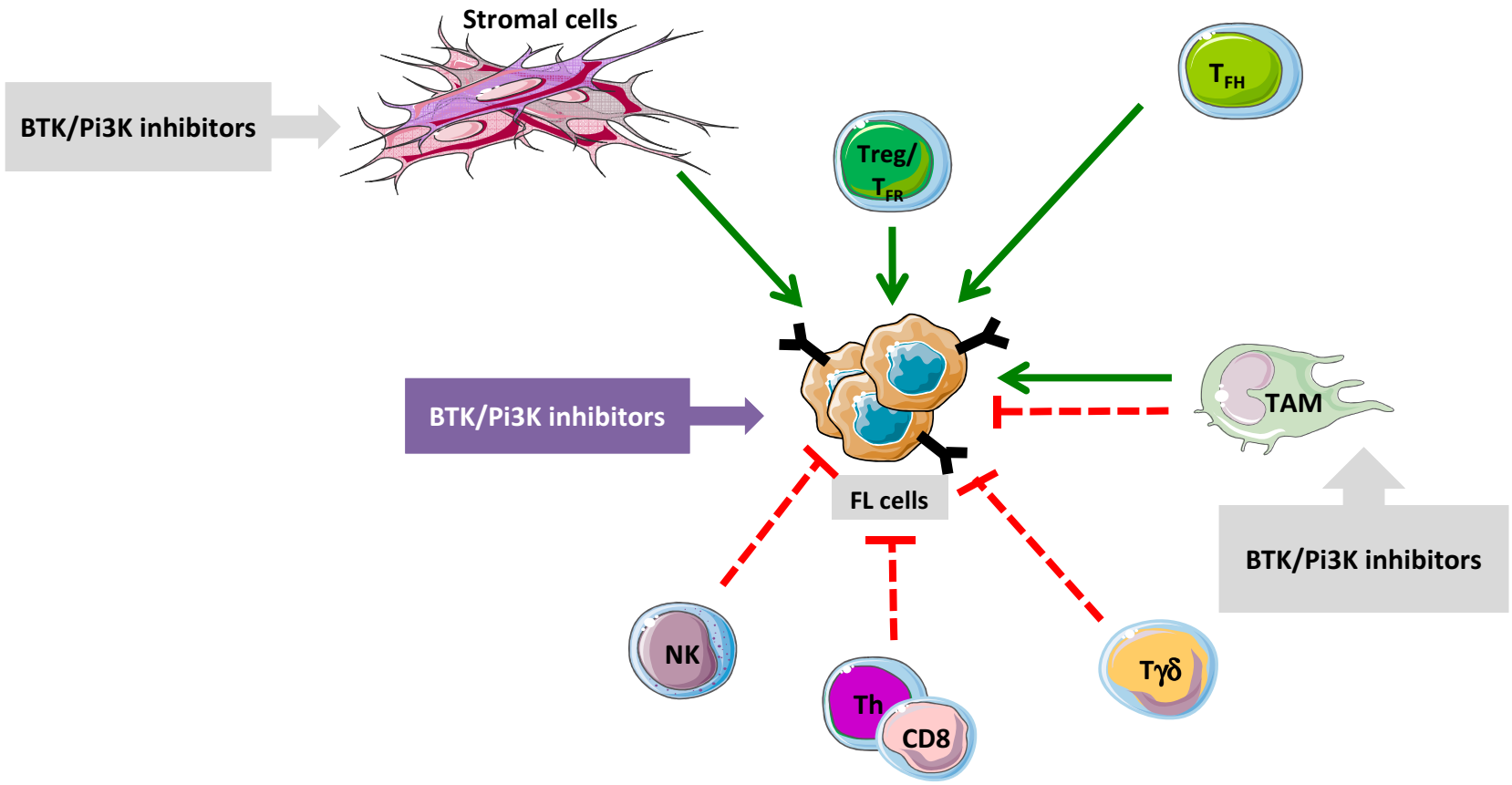
	R-CHOP PRIMA n=80	R2-CHOP n=80
Age >60	42	42
Sex M/F	40/40	40/40
FLIPI 3-5	50	50
Stage III-IV	74	75
Hb <12 g/dl	13	20
LDH > N	32	36

Response at the end of induction (IWG 1999)



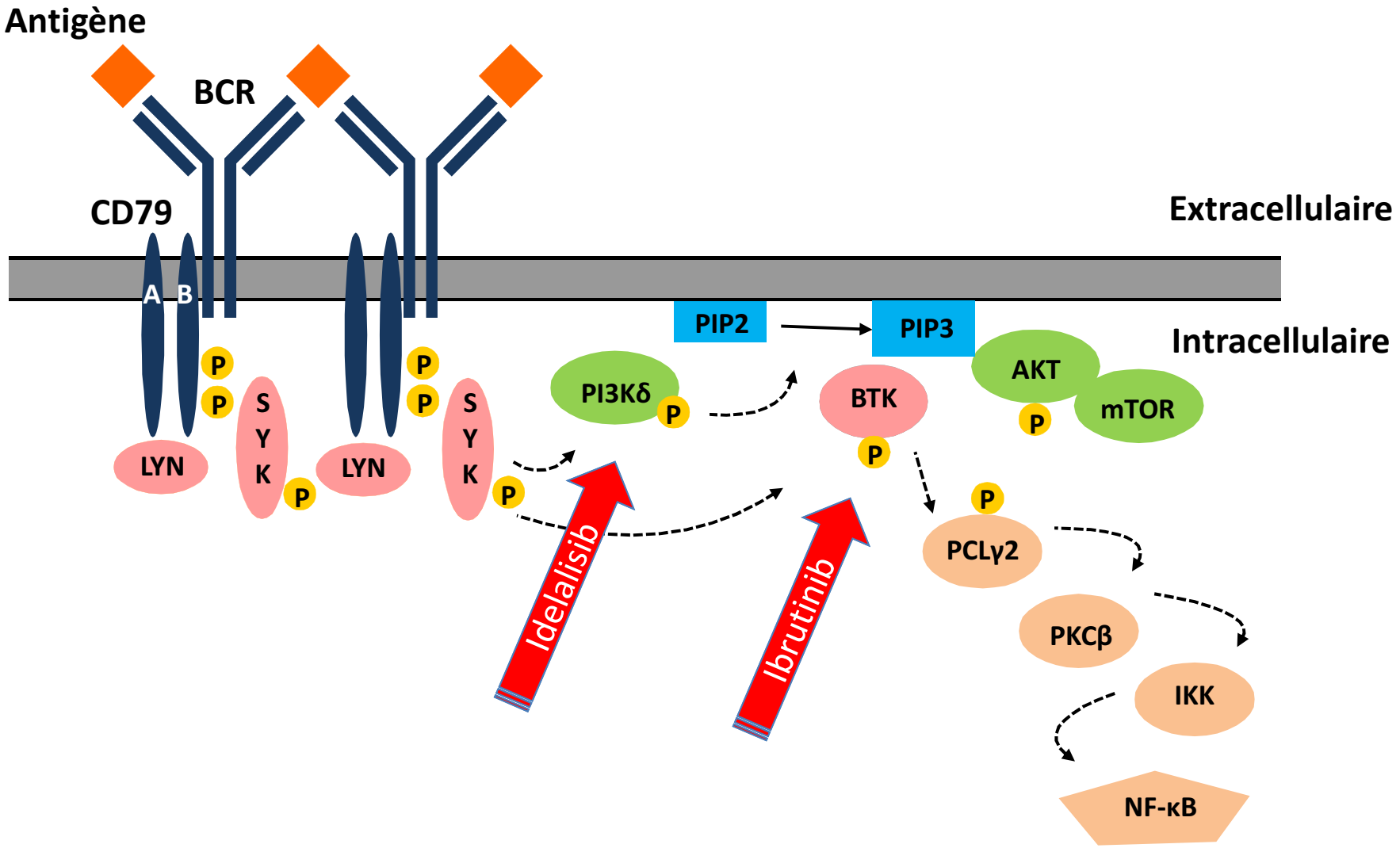
Salles G et al. Lancet 2011;377:42-51.
Morschhauser F et al. ICML 2011

Some targets in follicular lymphoma



Adapted from K Tarte

Voies d'activation du BCR



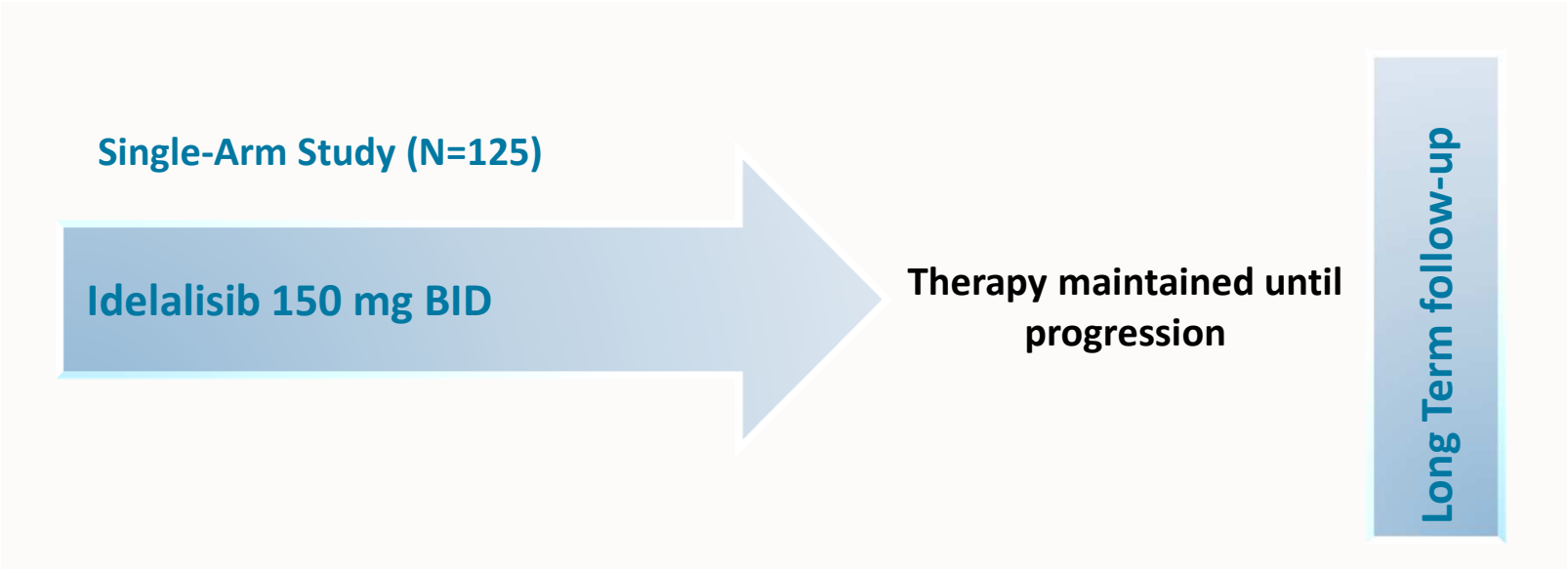
PI3Kδ Inhibition in B-cell malignancies

- **PI3Kδ**
  - Is critical for activation, proliferation and survival of B lymphocytes
  - Plays a critical role in homing and retention of B-cells in lymphoid tissues
  - Is hyperactive in many B-cell malignancies and drives proliferation, survival and trafficking to lymphoid
- **Idelalisib**
  - Is a first in class, targeted, highly selective, oral inhibitor of PI3K δ
  - Inhibits proliferation and induces apoptosis in many B-cell malignancies
  - Inhibits homing and retention of malignant B-cells in lymphoid tissues reducing B-cell survival

Phase 2 Study in Patients with Double Refractory

Eligibility Criteria

- Previously treated iNHL: (FL, SLL, MZL, LPL/WM)
- Refractory to **BOTH** rituximab and an alkylating agent:
- Measureable disease - minimum ≥ 2 cm lymph node diameter
- ECOG 0-2/Karnofsky PS ≥ 60



A, Gopal et al, DOI: 10.1056/NEJM/2014

Study 101-09
Patient characteristics

Characteristic	Patients N=125
Age — yr	
Median	64
Range	33–87
Male sex — no. (%)	80 (64)
Subtype of indolent non-Hodgkin's lymphoma — no. (%)	
Follicular lymphoma	72 (58)
Small lymphocytic lymphoma	28 (22)
Marginal-zone lymphoma	15 (12)
Lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia	10 (8)
Disease status — no. (%)	
Stage III or IV	111 (89)
Elevated LDH	38 (30)
Bulky disease†	33 (26)

Study 101-09

Response rate

Characteristic	N=125
Overall Response Rate, n (%)	71 (57%)
Complete Response	7 (6%)
Partial Response	63 (50%)
Minor Response[1]	1 (1%)
Stable Disease	42 (34%)
Progressive Disease	10 (8%)
Not Evaluated	2 (2%)
Time to response, months (N=71)	
Median (interquartile range)	1.9 (1.8, 3.7)

[1]-LPL/WM patients

Study 101-09

Adverse events

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

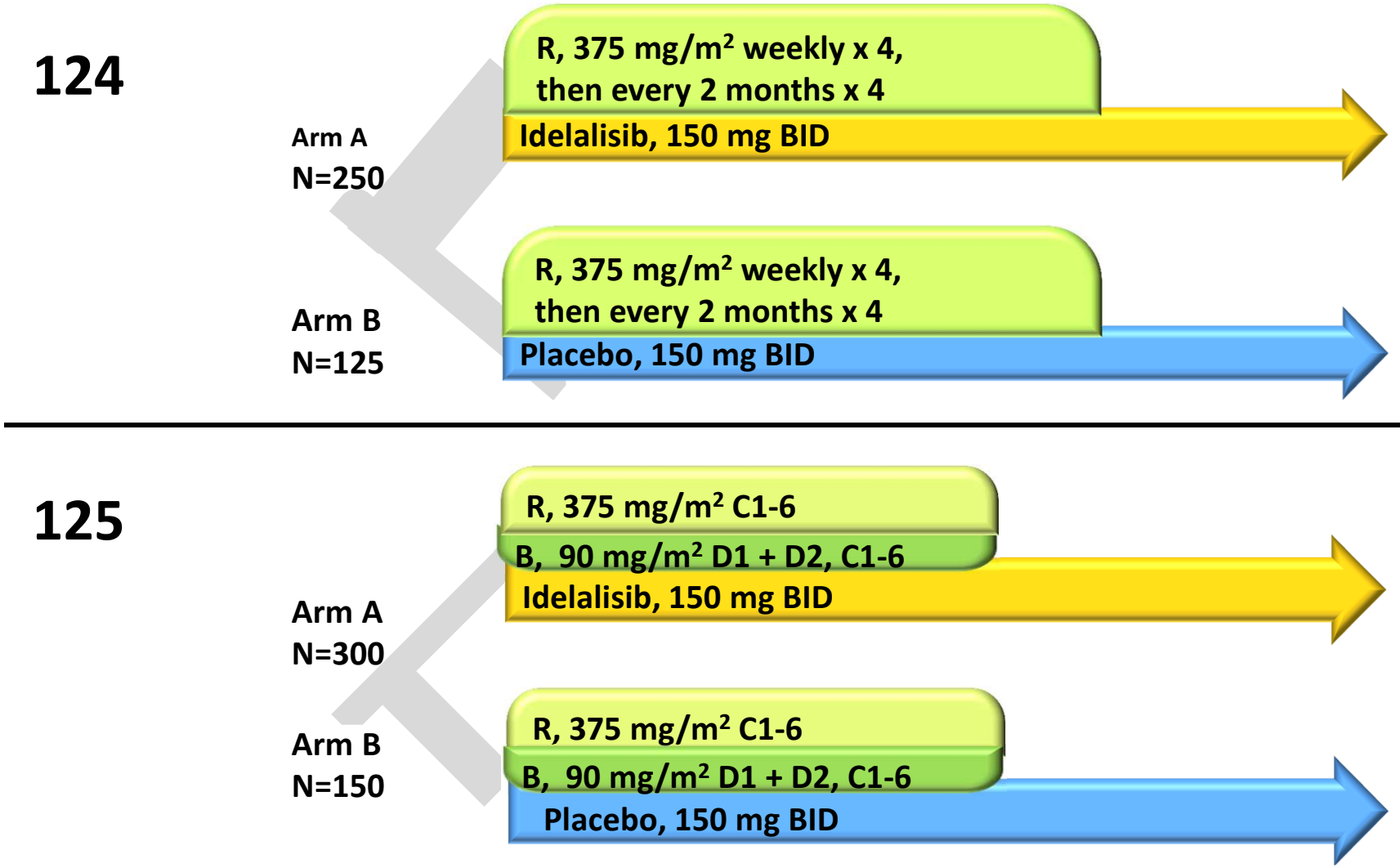
ALT/AST Elevations:

- 14/16 patients rechallenged
- 10 (71%) with no recurrence

10% or more of the 125 patients

Phase 3 Studies 124/125

Combinations of Idelalisib in recurrent indolent lymphoma



Conclusions

- L'immunochimiothérapie a changé l'évolution des lymphomes folliculaires

- La surveillance simple peut toujours être proposée aux patients de faible masse tumorale mais la monothérapie par rituximab permet de retarder les cytotoxiques et d'améliorer la QdV avec une bonne sécurité à long terme

- Chez les patients de forte masse, les agents non cytotoxiques pourront peut-être concurrencer ou épargner les chimiothérapies

- La TEP devient un outil nécessaire

Merci

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New agents in development for the treatment of relapsed FL

- **New anti-CD20 antibodies:**

  - Veltuzumab, ofatumomab, obinotuzumab (GA101)

- **Antibody drug conjugates:**

  Antibodies against CD19, CD22, CD79a coupled with anti-microtubule agents (calicheamicin, maytansine or monomethyl auristatin E) : Inotuzumab Ozogamicin, SAR3419, etc…

- **Immunomodulatory** agents to potentiate the activity of anti-CD20 monoclonal antibodies

  - Imids, anti-KIR, anti PD1

- **Kinase inhibitors** (against mTOR, PI3K, BTK , SYK, …)

  - Temsirolimus, everolimus, idelalisib, ibrutinib, etc…

- **Pro-apoptotic agents:**

  - BCL-2 antagonists (ABT-199), death receptor agonists