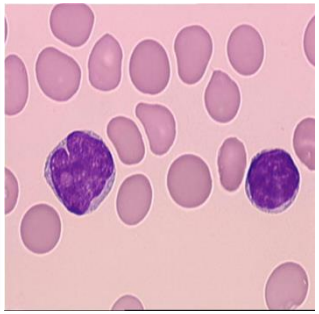
*ESMO 2014 * Haematological Educationals: Lymphoma in the elderly*

Follicular lymphoma:
Is it a boring disease ?



GLSG

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

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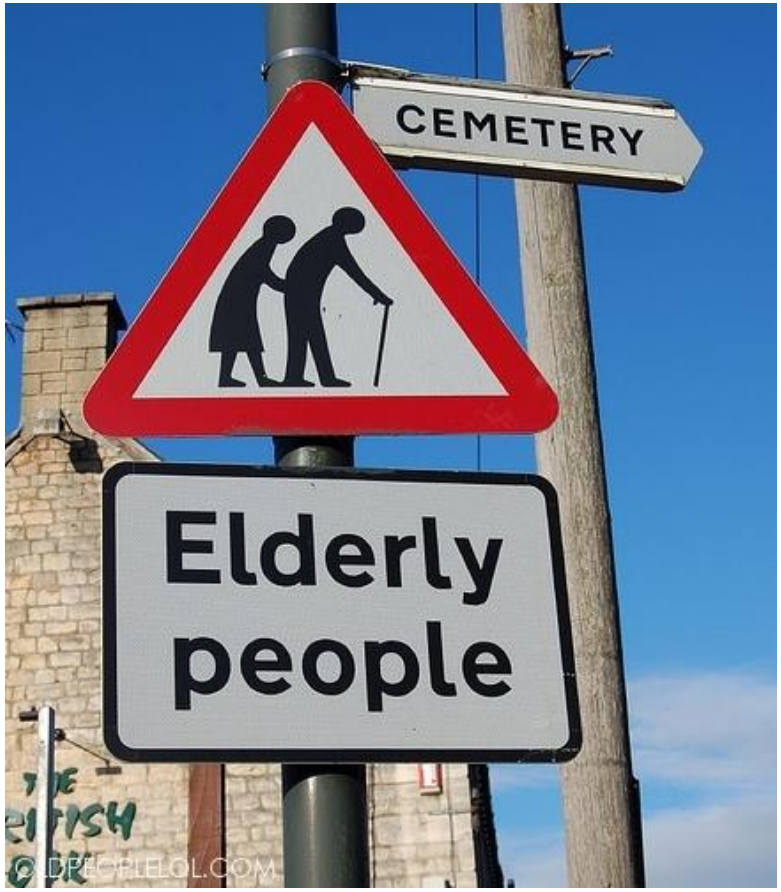
Medizinische Klinik III
LMU München

Disclosures

Research Support (institution)	**Celgene, Janssen, Mundipharma, Pfizer, Roche**
Employee	**-**
Major Stockholder	**-**
Speakers Bureau	**-**
Speakers Honoraria	**Celgene, Janssen, Gilead, Mundipharma, Pfizer, Roche**
Scientific Advisory Board	**Bayer, Celgene, Janssen**

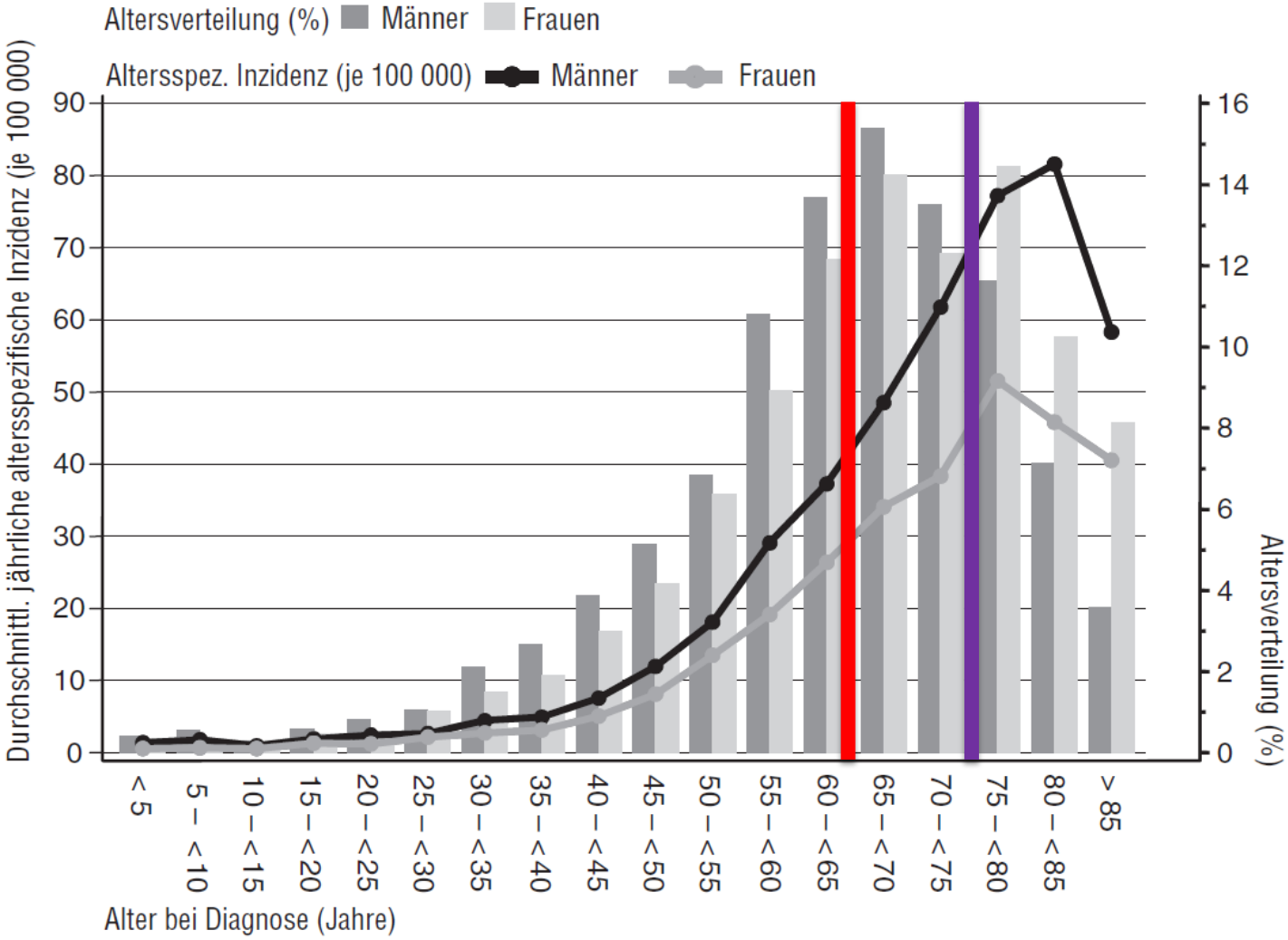
Definition

Elderly people



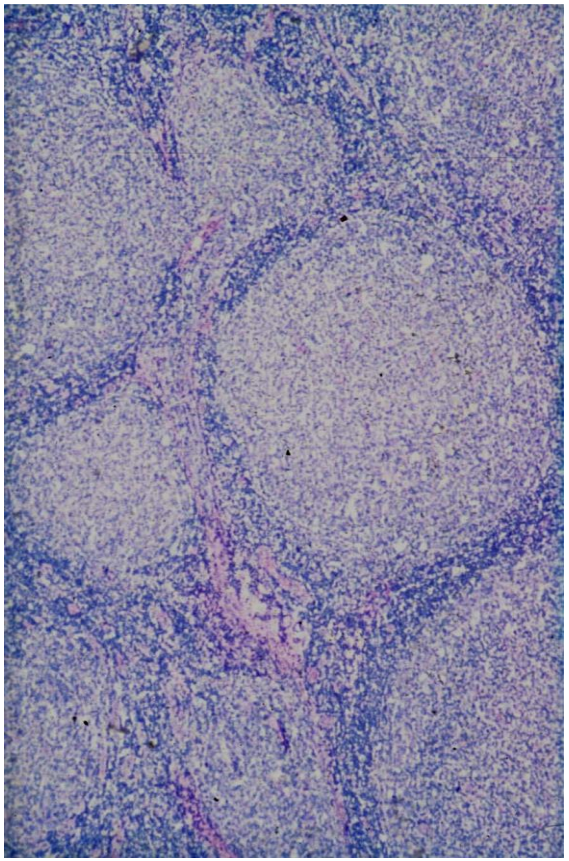
Elderly people

Incidence of lymphoma



Follicular lymphoma:

Clinical characteristics



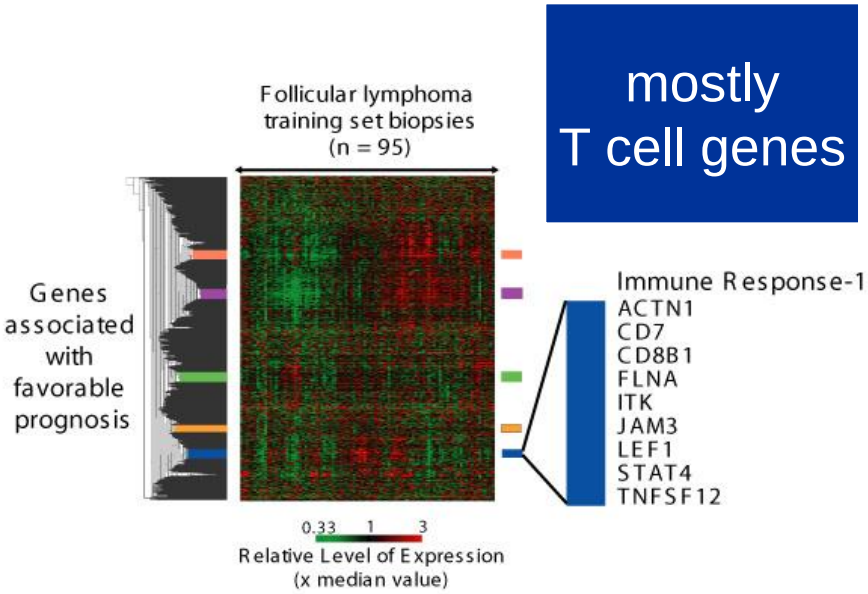
- about 25% of lymphoma
- Median age 60-65 years
- 85% advanced stage III/IV
- Indolent clinical course

  (median survival 15-20 years)
- In relapse still sensitive to therapy

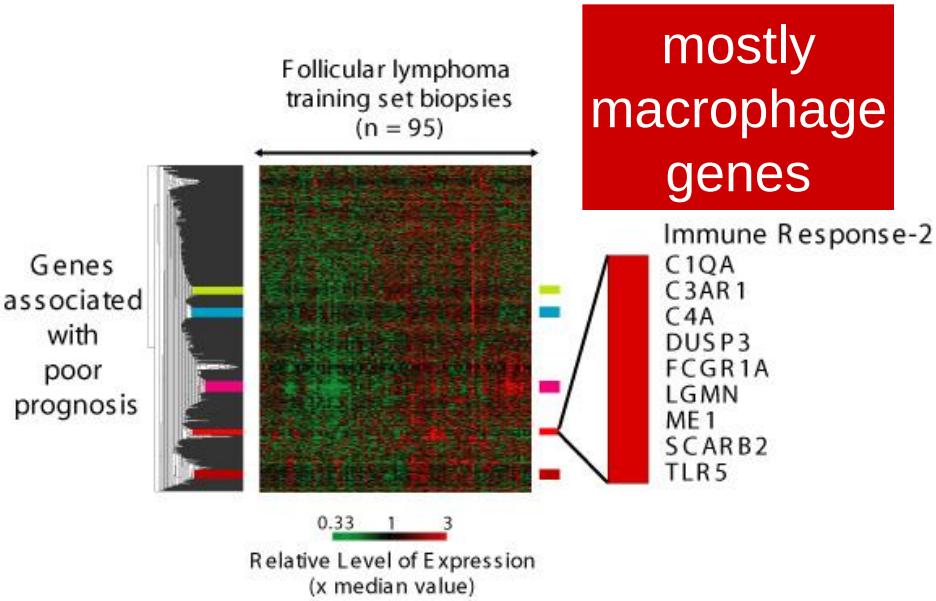
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 18, 2004 VOL. 351 NO. 21

Identification of gene expression signatures associated with favorable prognosis



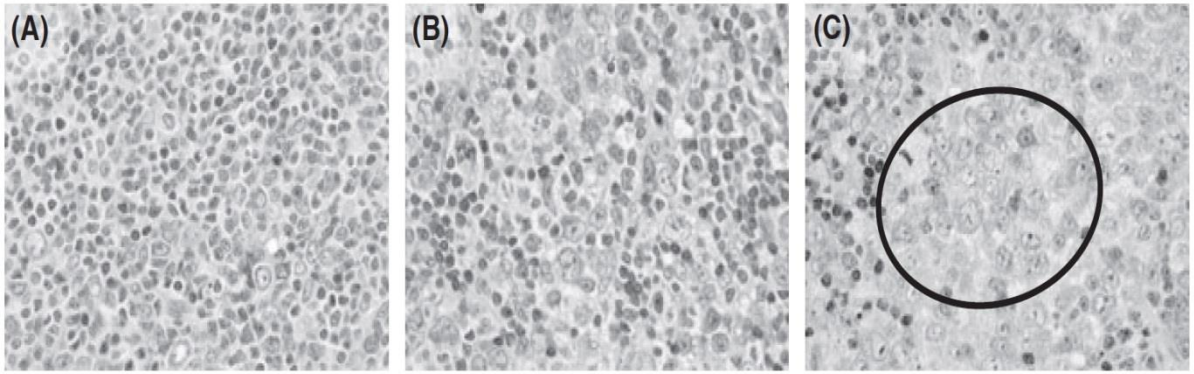
Identification of gene expression signatures associated with poor prognosis

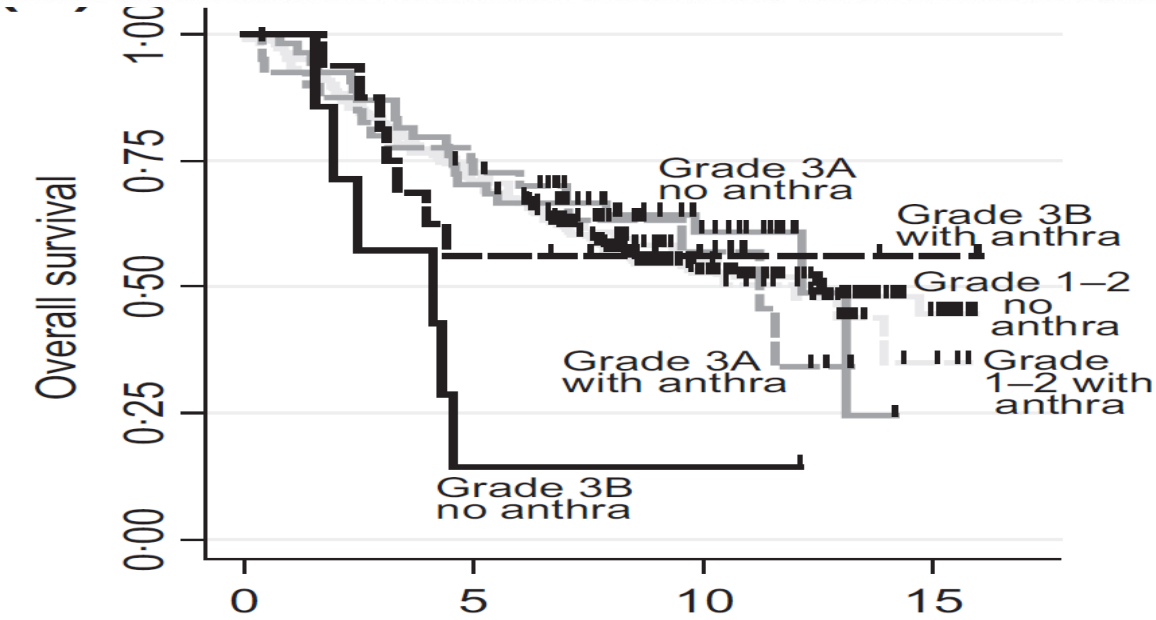


Dave, NEJM 2004

Follicular Lymphoma

Grade IIIa/IIIB





Wahlin, BJH 2011

Follicular Lymphoma

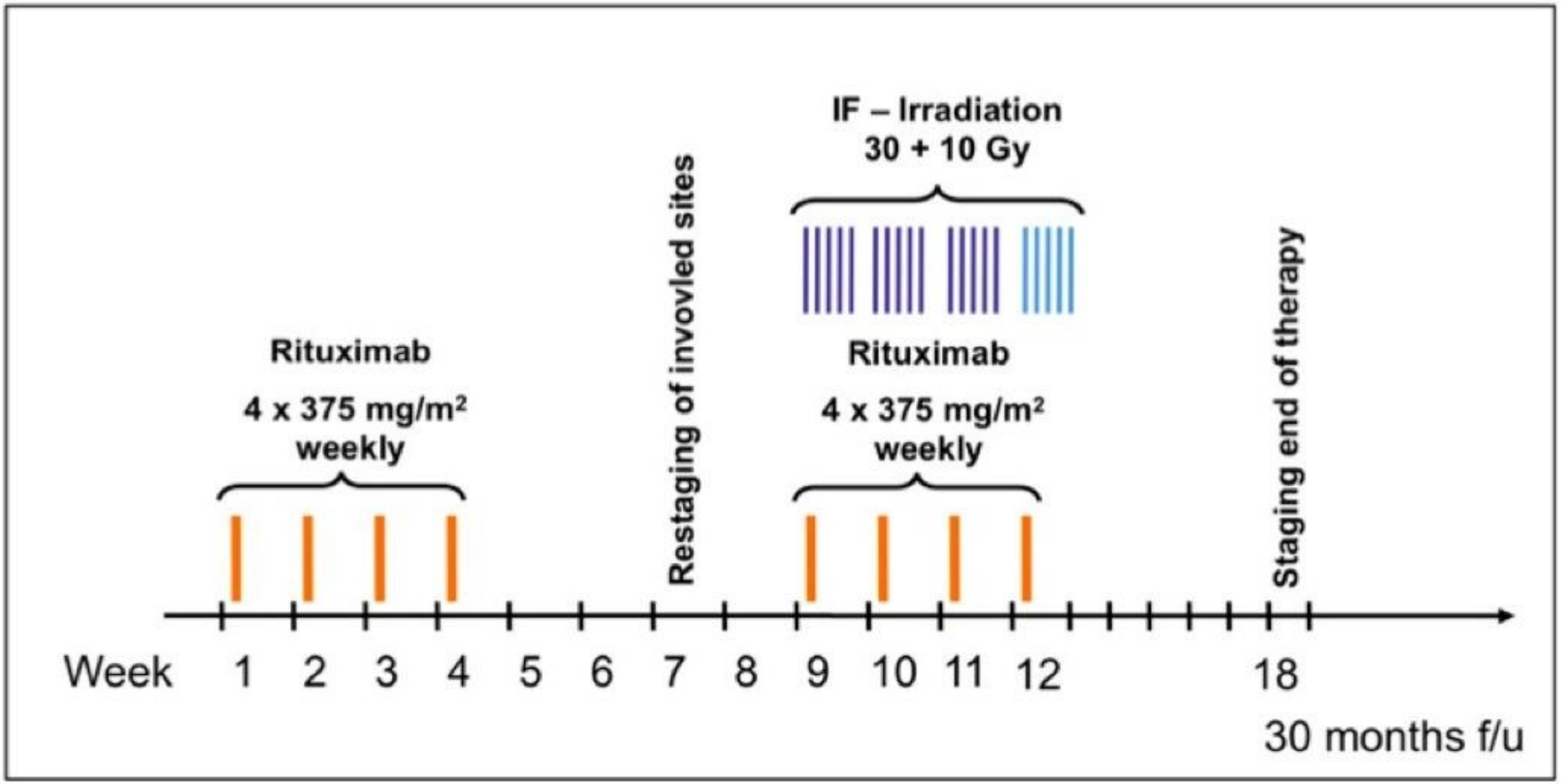
Therapeutic algorithm

Low tumour burden		High tumour burden	
Stage I/II	Stage III/IV	Stage III/IV (<65 years[a])	Stage III/IV (>65 years[a])
Front line			
Radiotherapy (involved field) 24–36 Gy In selected cases, watchful waiting	Watch and wait In symptomatic cases, consider rituximab monotherapy	Chemoimmunotherapy (e.g. R-CHOP, R-CVP, BR) In selected cases, rituximab monotherapy	Chemoimmunotherapy (e.g. R-CVP, BR, R-CHOP) or brief chemoimmunotherapy In selected cases, rituximab–chlorambucil rituximab monotherapy
–	–	CR/PR Rituximab maintenance (every 2 months, up to 2 years)[b]	CR/PR Rituximab maintenance (every 2 months, up to 2 years)
Relapse/progress			
Watch and wait Rituximab monotherapy In selected cases, palliative radiation (e.g. 2 × 2 Gy)	Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) In selected cases, rituximab monotherapy	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Discuss high-dose consolidation with ASCT • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy • In selected cases, discuss allogeneic transplantation	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy

Dreyling, ESMO CR 2014

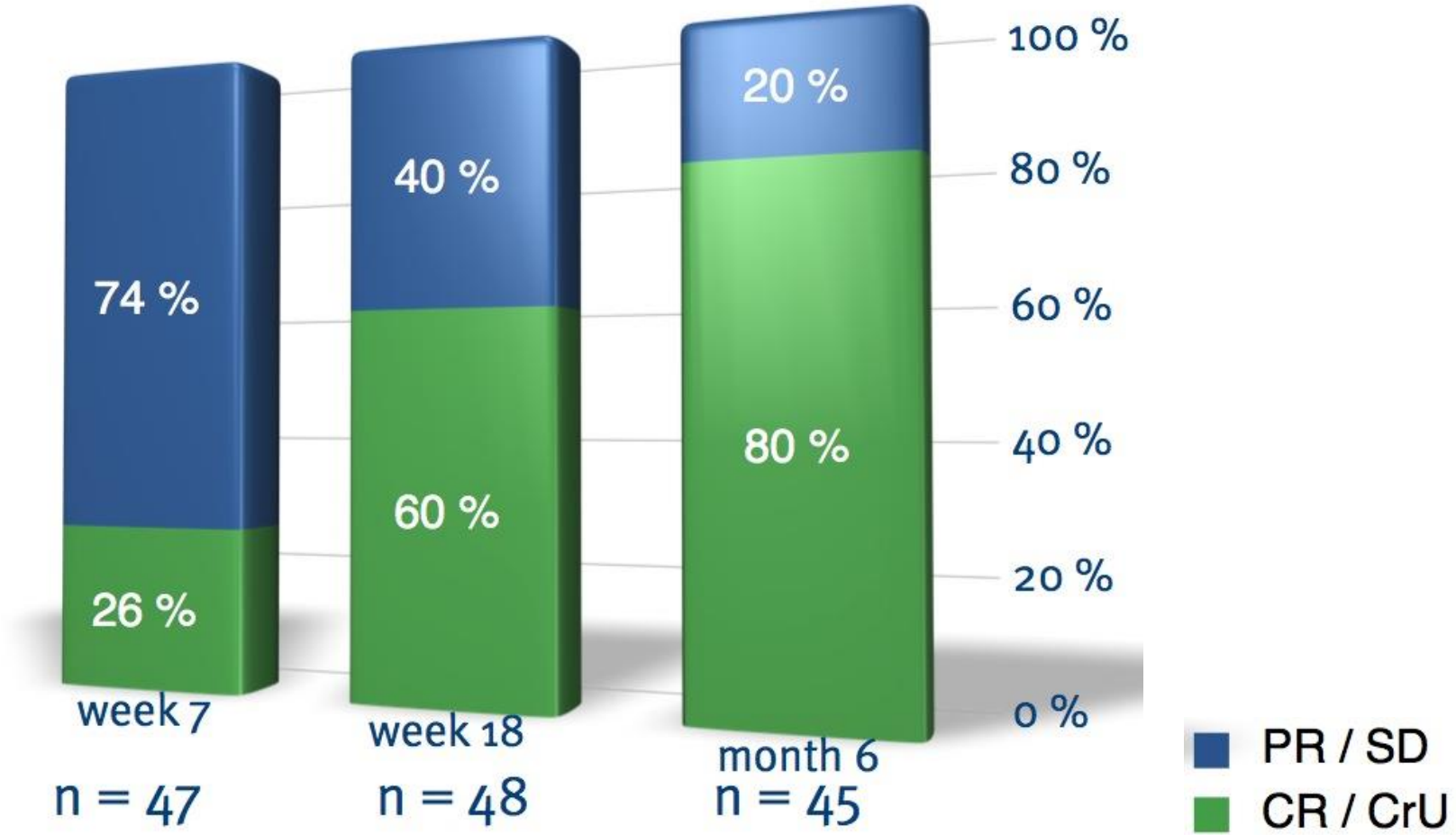
Follicular Lymphoma Stage I/II

MIR: : Rituximab + Radiation



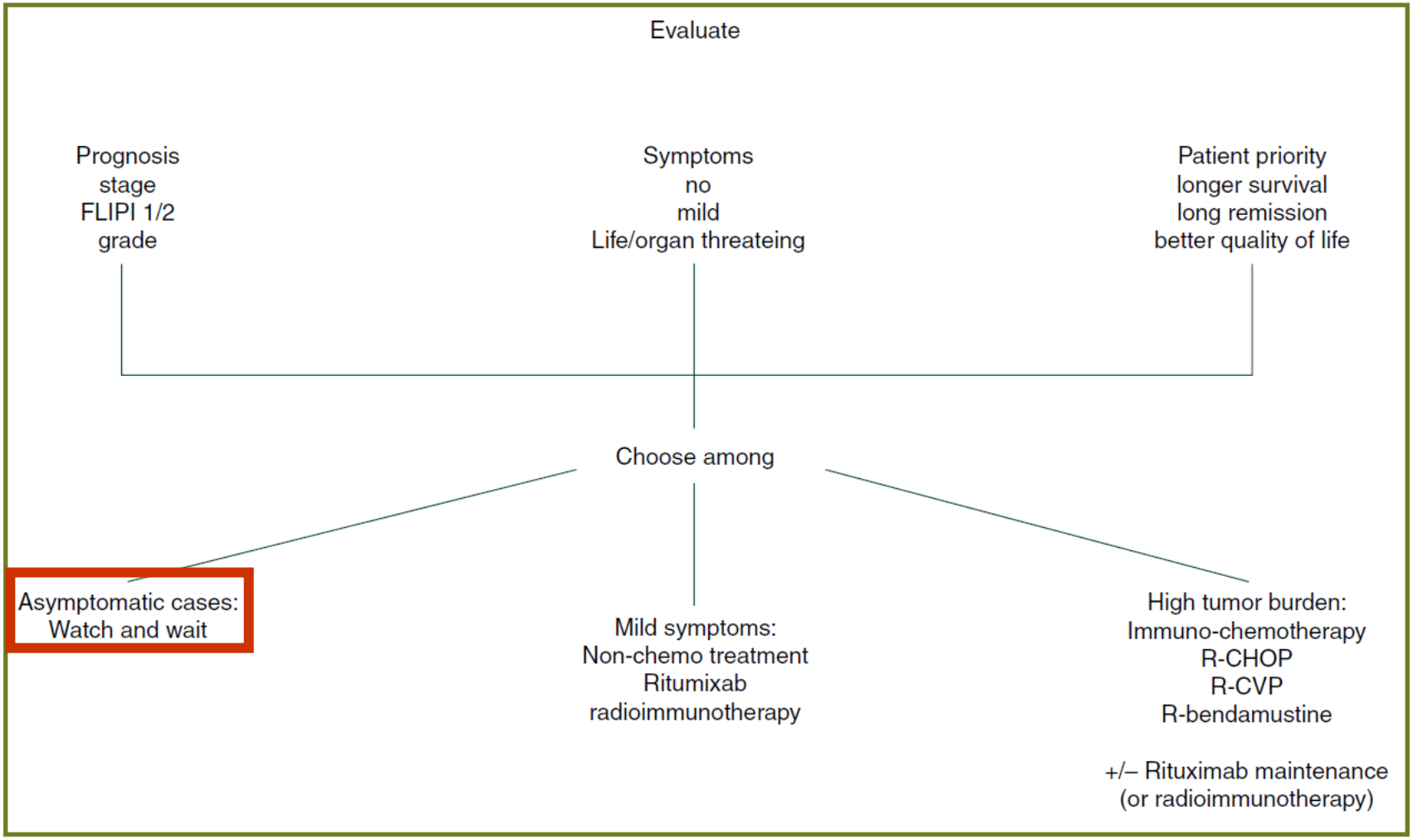
Herfarth, ASH 2012

Follicular Lymphoma Stage I/II
MIR: Response rates



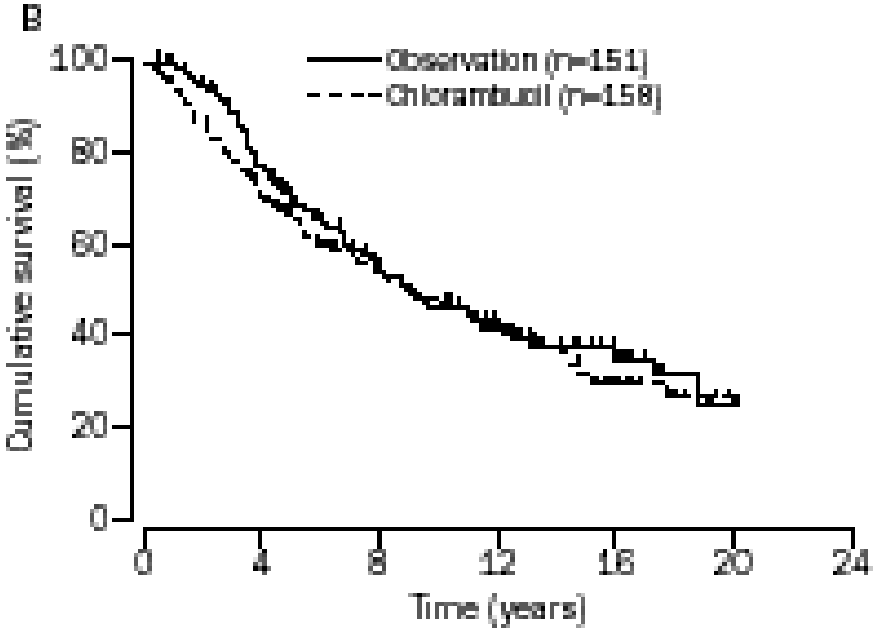
Herfarth, ASH 2012

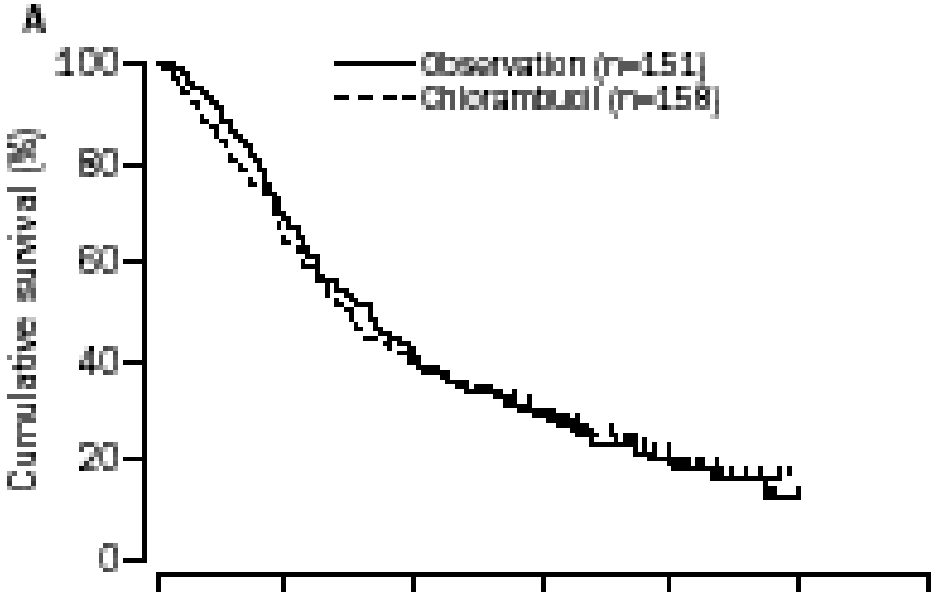
First line treatment in FL
Therapeutic algorithm



Dreyling, ESMO CR 2014

Long term effect watch & wait vs. chlorambucil for asymptomatic advanced stage (low grade) lymphoma



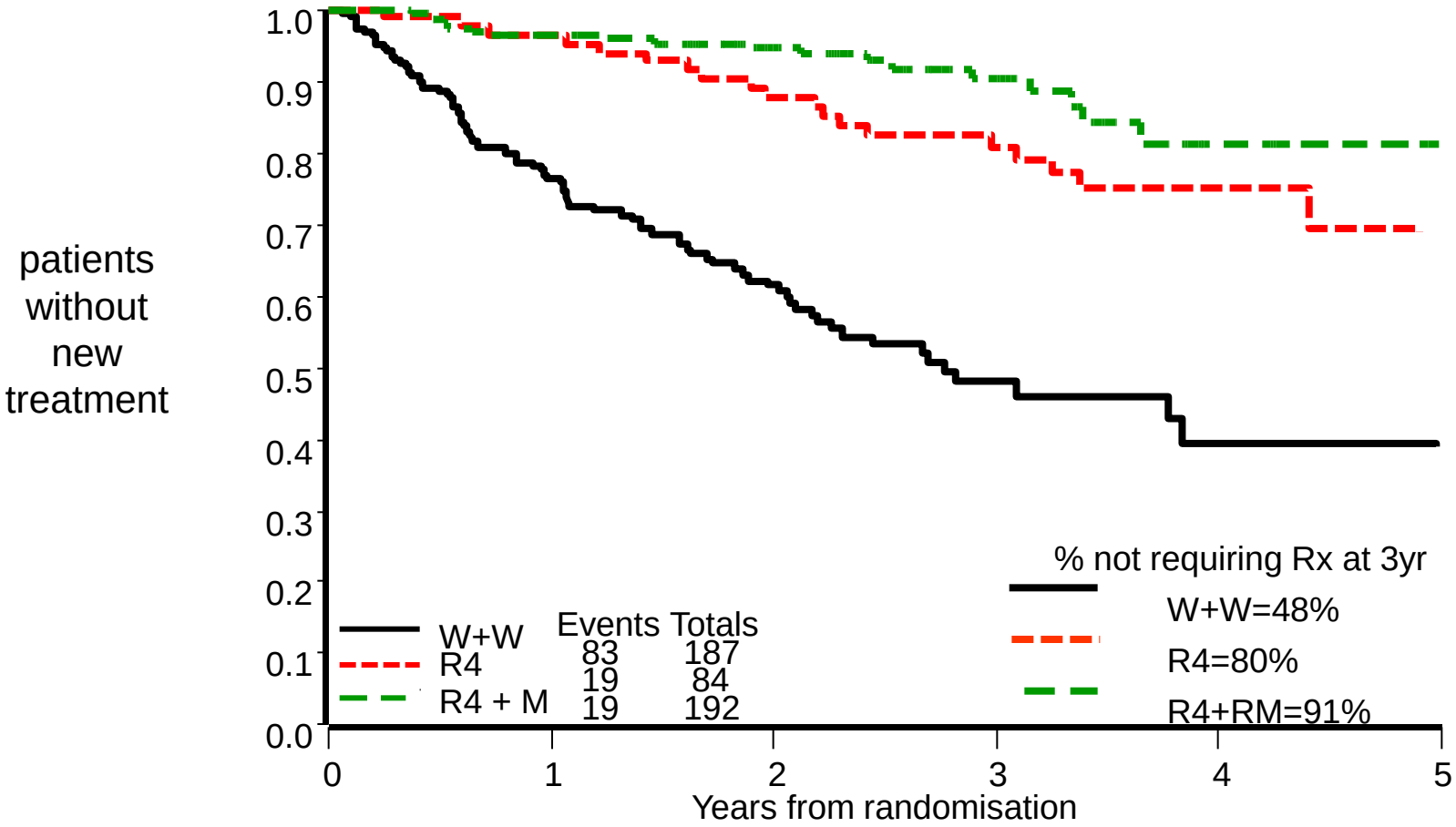


Prospective randomised study (follow-up 16 years) :
n=309; 65% follicular lymphoma

Ardeshna, Lancet 2003

Rituximab vs watch & wait

Time to initiation of new therapy

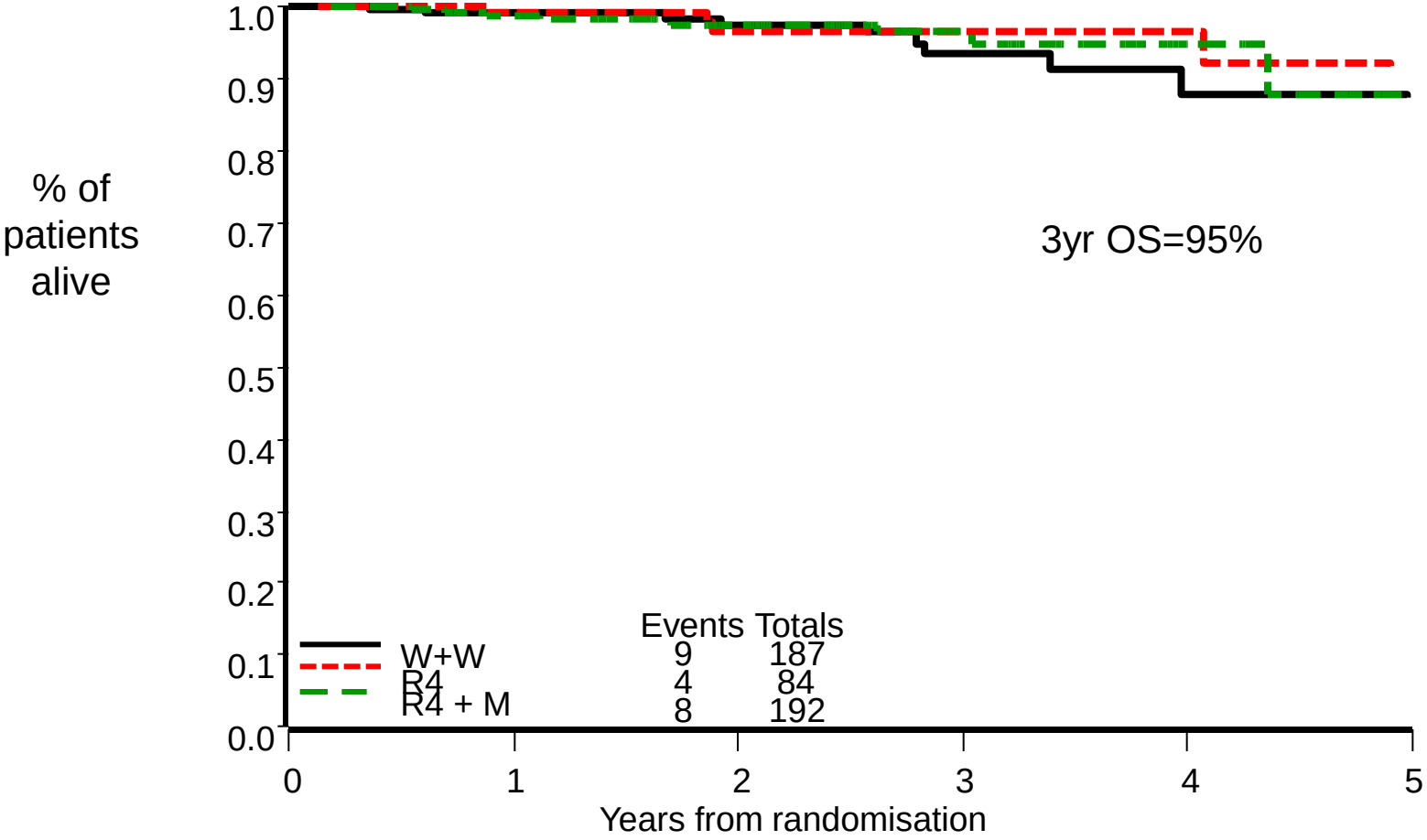


HR (Rituximab vs W+W) = 0.37, p<0.001
HR (Rituximab + M vs W+W) = 0.20, 0.29, p <0.001
HR (Rituximab + M vs Rituximab) = 0.57, p =0.10

Ardeshna, Lancet Oncol 2014

Rituximab vs watch & wait

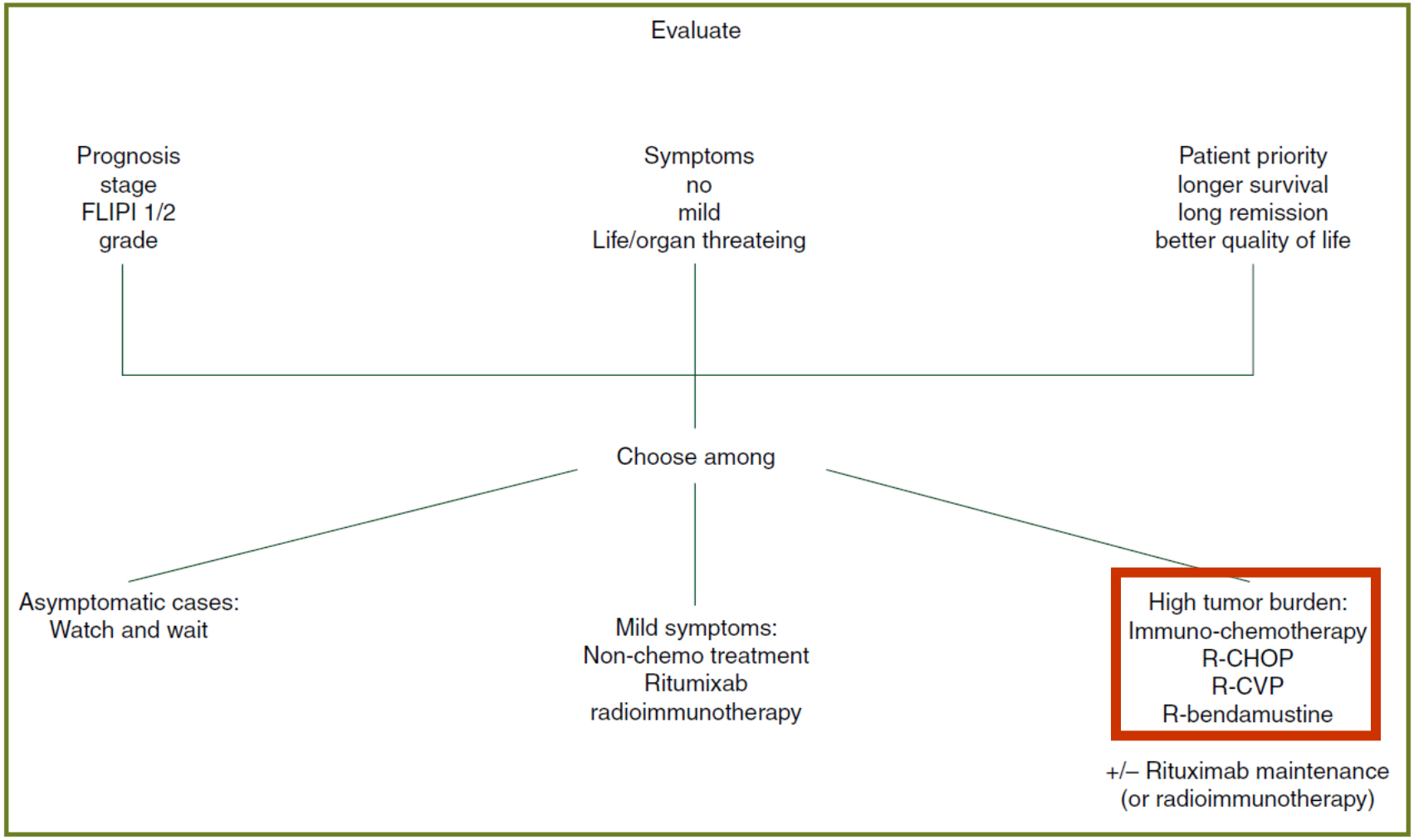
Overall survival



HR (Rituximab vs W+W) = 0.63, p=0.42
HR (Rituximab + M vs W+W) = 0.84, p=0.72
HR (Rituximab + M vs Rituximab) = 1.21, p=0.75

Ardeshna, Lancet Oncol 2014

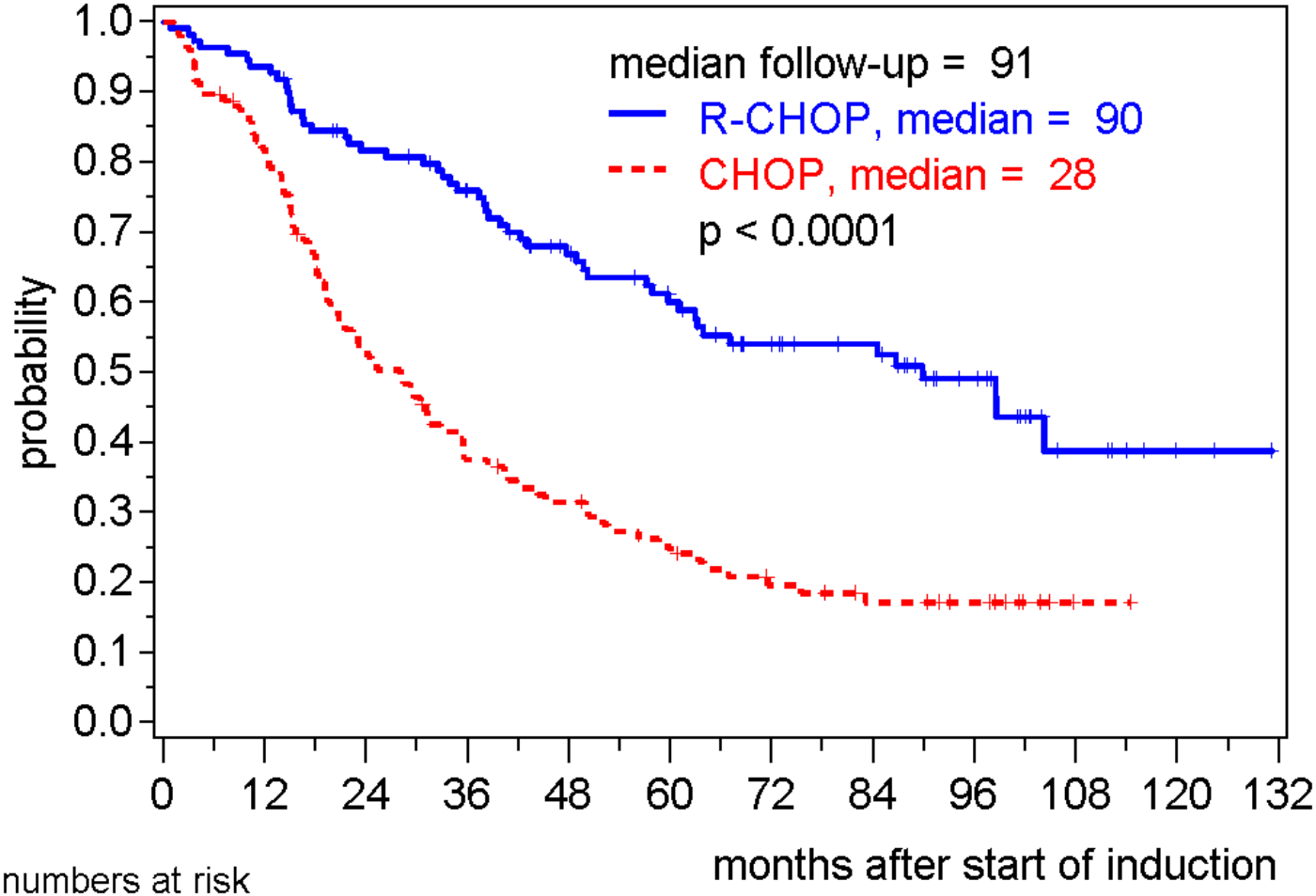
First line treatment in FL
Therapeutic algorithm



Dreyling, ESMO CR 2014

Follicular lymphoma (elderly patients)

Progression-free survival (R-CHOP)

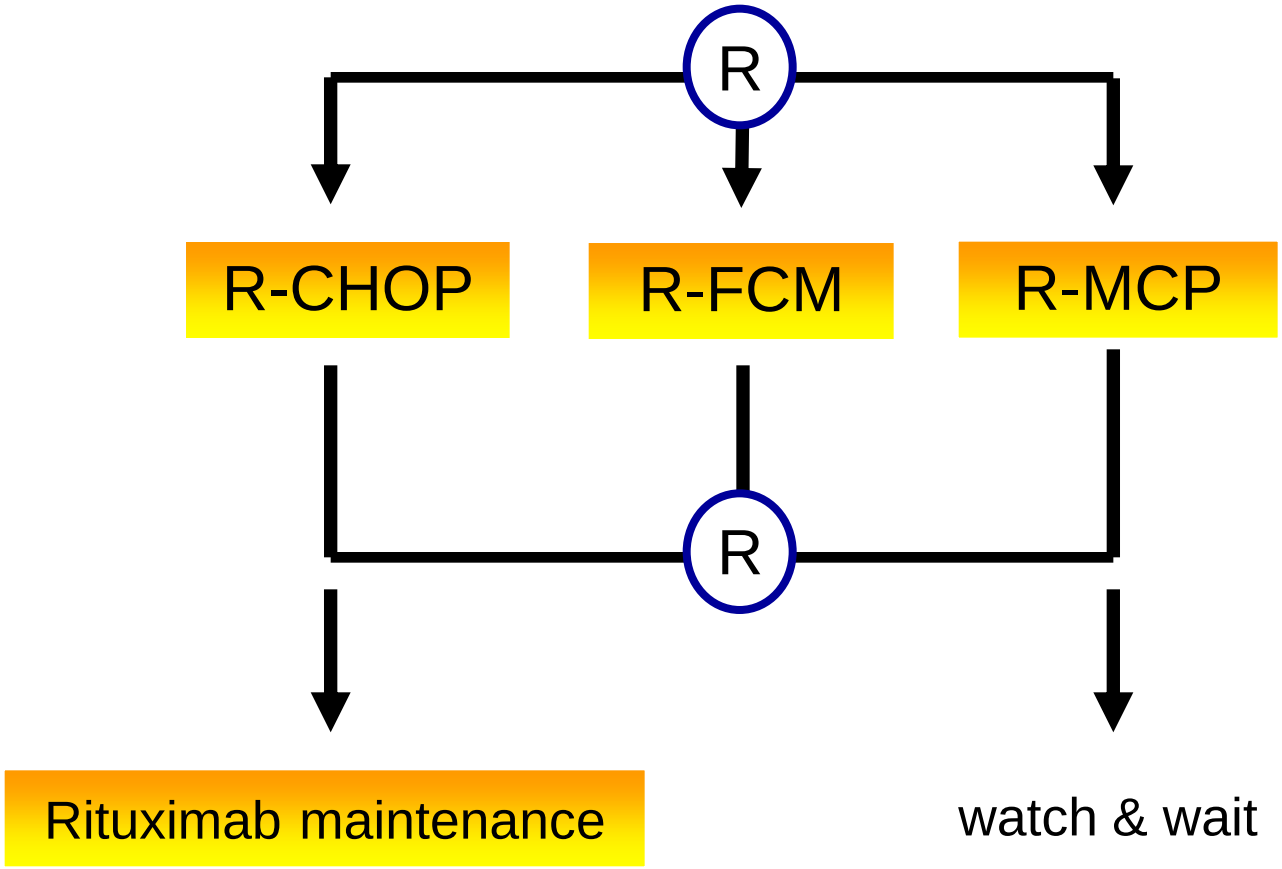


numbers at risk

R-CHOP	110	103	87	77	61	51	39	35	21	7	2	0
CHOP	107	86	55	38	31	23	17	13	10	1	0	

Follicular Lymphoma

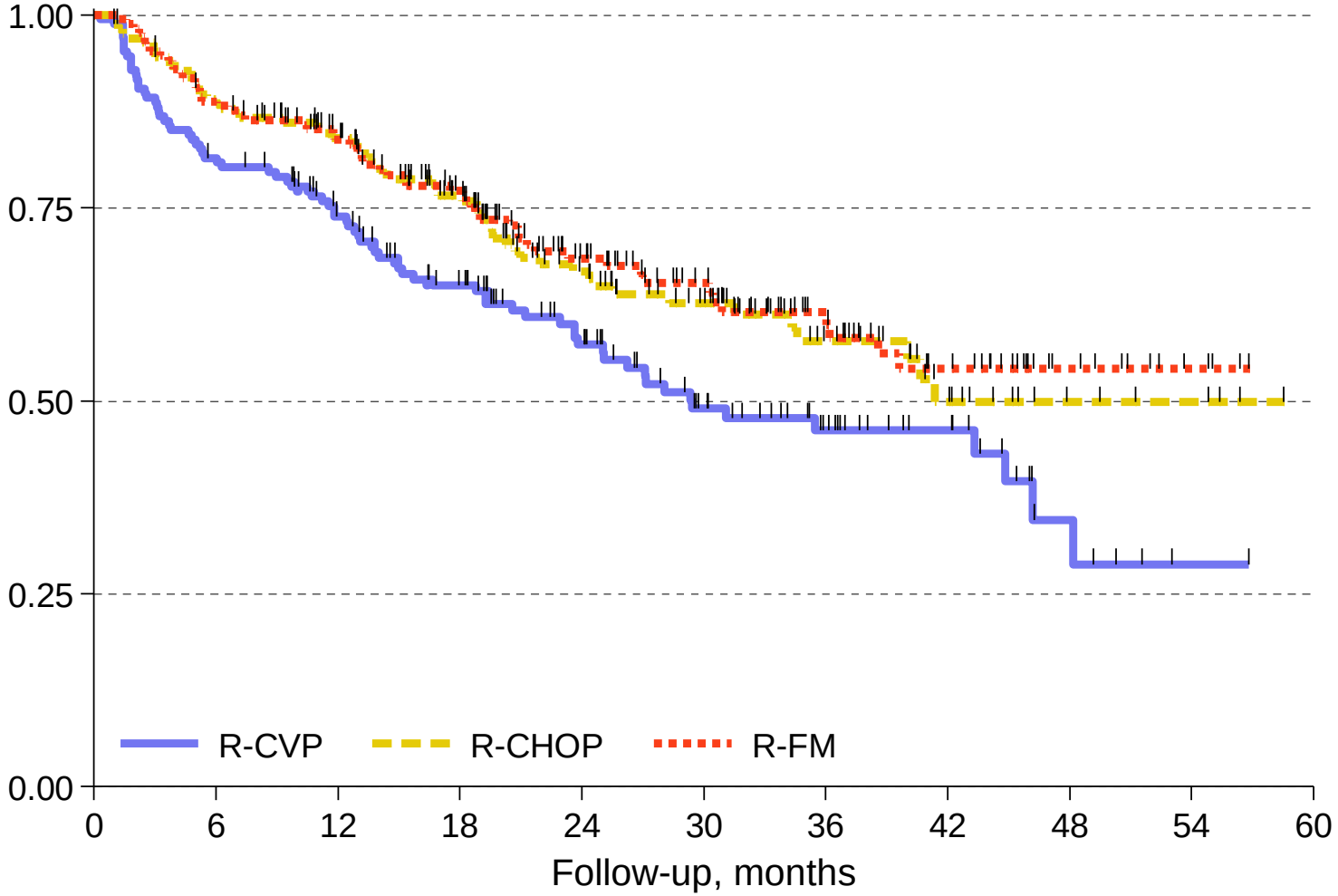
Immunchemotherapy



OSHO#70: maximum toxicity

	R-CHOP		R-FCM		R-MCP	
Hb						
Grade 1+2:	28	70%	22	59%	22	52%
Grade 3+4:	1	3%	2	5%	2	5%
Leukocytes						
Grade 1+2:	13	34%	1	3%	7	17%
Grade 3+4:	20	53%	34	92%	33	80%
Neutrophils						
Grade 1+2:	5	19%	1	5%	4	15%
Grade 3+4:	13	50%	17	85%	17	65%
Thrombocytes						
Grade 1+2:	7	18%	21	55%	17	40%
Grade 3+4:	2	5%	3	8%	1	2%

TTF by arm (N=504)



Events = 196	Logrank	P
R-CHOP vs R-CVP	5.22	0.022
R-FM vs R-CVP	7.03	0.008
R-CHOP vs R-FM:	0.10	0.758

Federico JCO 2013

Second malignancies

R-CVP (N=4)

- Breast
- GI tract
- Genitourinary
- Kaposi

R-CHOP (N=4)

- Genitourinary
- 2 x Lung
- Glioblastoma

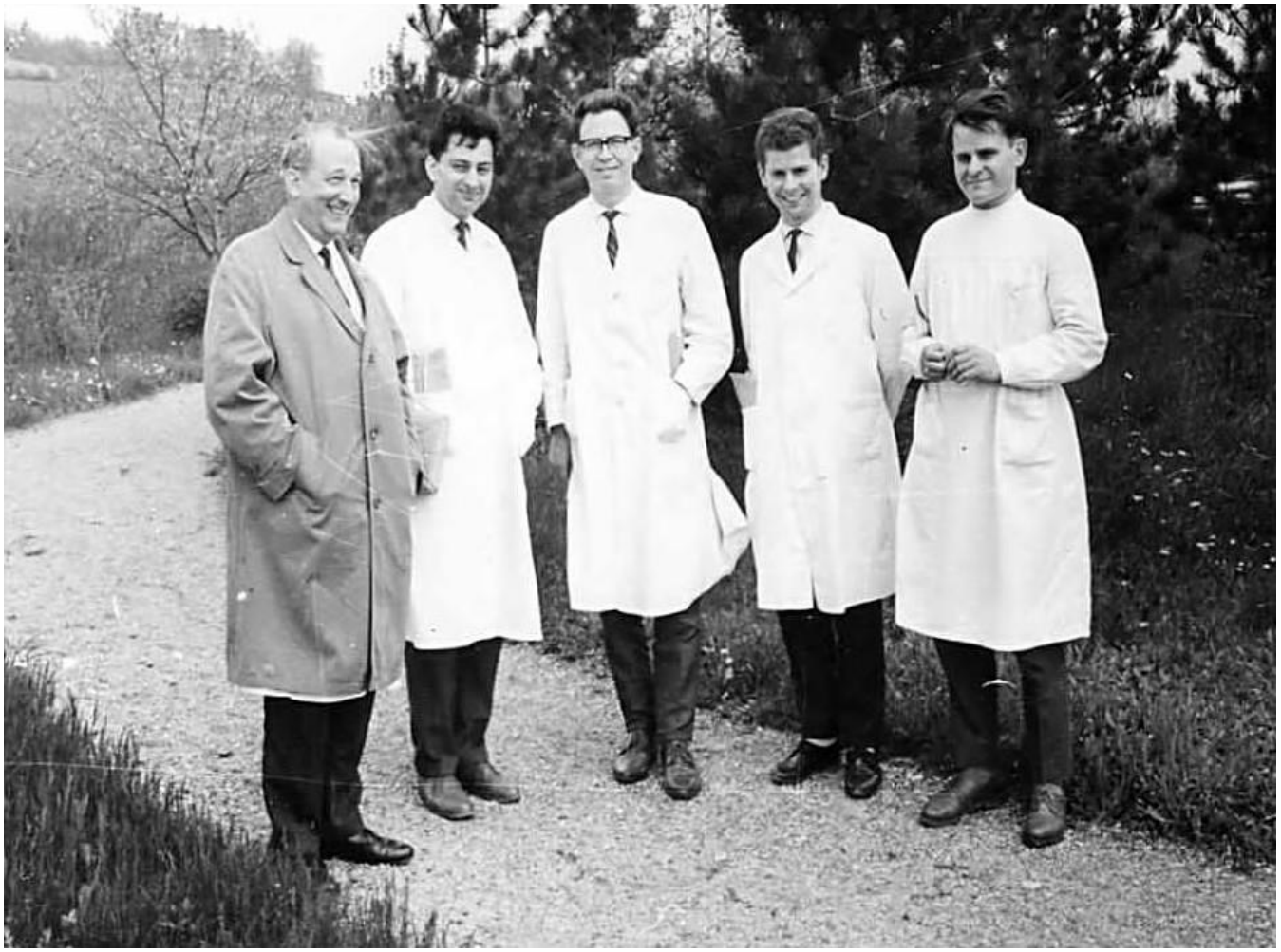
R-FM (N=13)

- 4 x AML/MDS (2 †)
- 3 x Genitourinary
- Lung
- Skin
- GI tract †
- Parotid
- Unknown primary
- Breast

Exact Fisher test for ITT P = 0.031

Federico JCO 2013

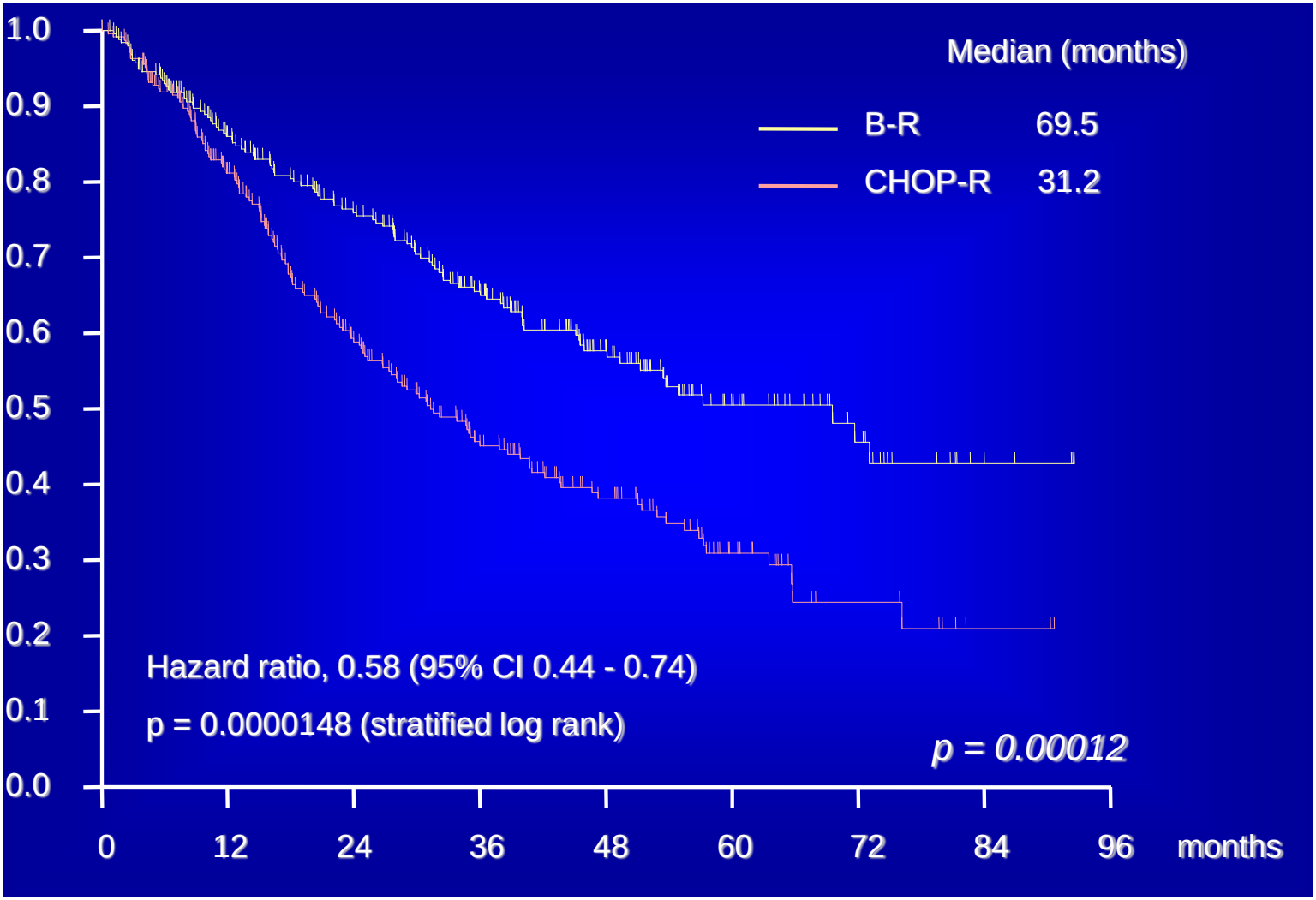
Bendamustine:
Back to the future



- synthesis : W.Ozegowski, D.Krebs, Institute of Microbiology and Experimental Therapy, Jena (1962)
- Published in Journal für Praktische Chemie, Vol. 20, issue 3-4, 1963
- IMET 3393 was developed by H. Knöll and later named Cytostasan

Follicular lymphoma

BR vs R-CHOP



Rummel, Lancet 2013

BR vs R-CHOP/R-CVP
Response rates

	CR		*CR + partial response*	
Histologic subtype, n/N (%)	*BR*	*R-CHOP/ R-CVP*	*BR*	*R-CHOP/ R-CVP*
Indolent NHL	49/178 (28)	43/174 (25)	173/178 (97)	160/174 (92)
Follicular	45/148 (30)	37/149 (25)	147/148 (>99)	140/149 (94)
Marginal zone	5/25 (20)	4/17 (24)	23/25 (92)	12/17 (71)
Lymphoplasmacytic	0/5	1/6 (17)	3/5 (60)	6/6 (100)
MCL	17/34 (50)	9/33 (27)*	32/34 (94)	28/33 (85)*

*

Flinn, Blood 2014

BR vs R-CHOP/R-CVP
Toxicity

	Preselected for R-CHOP		*Preselected for R-CVP*	
Characteristic	*BR (n = 103) no. (%)*	*R-CHOP (n = 98) no. (%)*	*BR (n = 118) no. (%)*	*R-CVP (n = 116) no. (%)*
Hematologic laboratory data (grade 3/4)				
White blood cell count	33 (32)	71 (72)[§]	51 (43)	44 (38)
Absolute neutrophil count	40 (39)	85 (87)[§]	58 (49)	65 (56)
Lymphocyte count	63 (61)	32 (33)[§]	74 (63)	32 (28)[§]
Hemoglobin	0	3 (3)	6 (5)	6 (5)
Platelet count	10 (10)	12 (12)	6 (5)	2 (2)
Infection[*]	57 (55)	56 (57)	63 (53)	58 (50)
Opportunistic infection[*]	10 (10)	7 (7)	14 (12)	10 (9)
Pneumonia/respiratory infection[*]	19 (18)	14 (14)	17 (14)	15 (13)

Flinn, Blood 2014

Annals of Oncology 22 (Supplement 6): vi59–vi63, 2011
doi:10.1093/annonc/mdr388

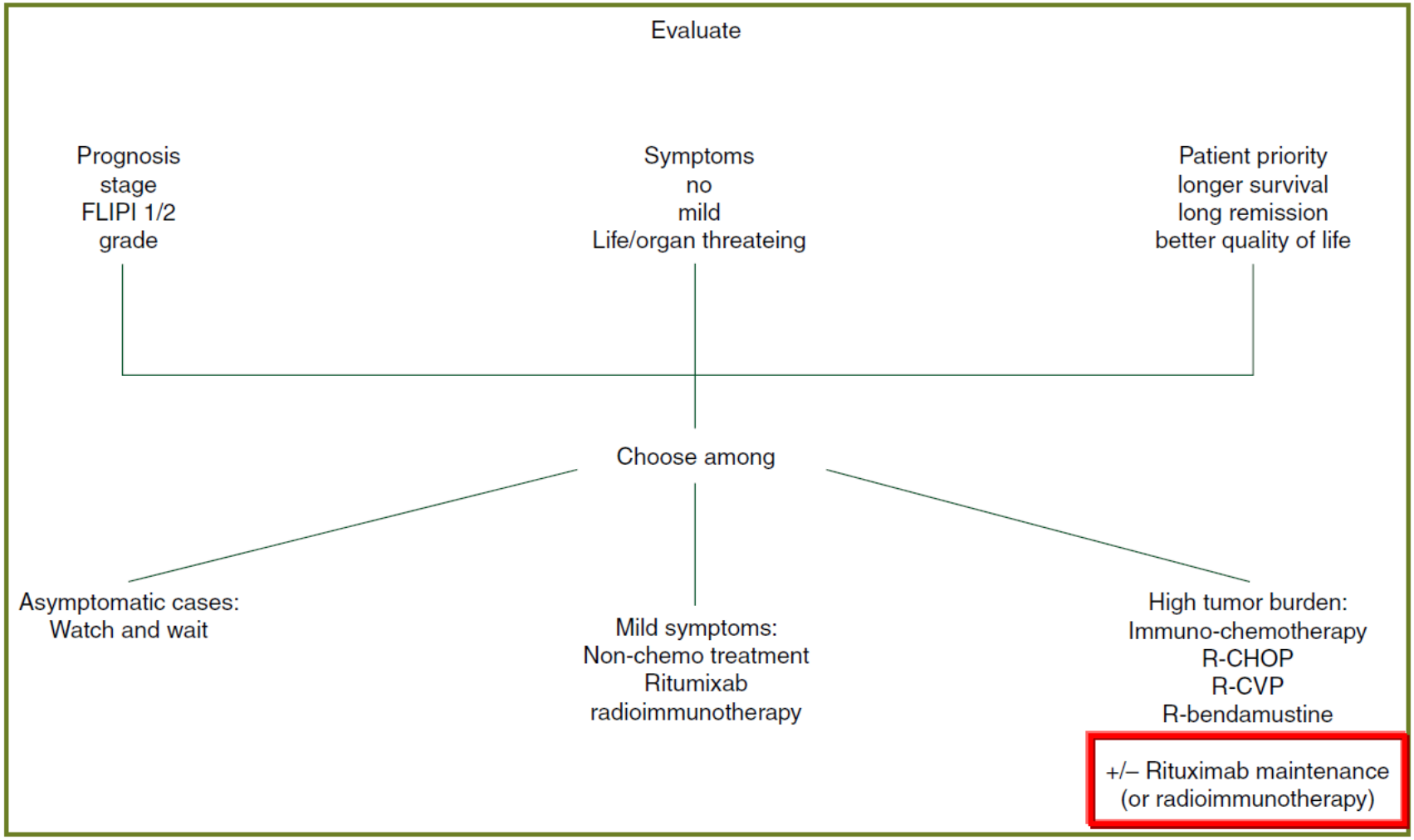
Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

- If complete remission and long PFS are to be achieved, rituximab in combination with chemotherapy [such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVP (cyclophosphamide, vincristine and prednisone), ~~purine analog-based schemes: FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone)~~ or Bendamustine] should be used [I, B] [11].

- Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remains an alternative in patients with low risk profile or contraindications for a more intensive chemoimmunotherapy [III, B] [17, 18].

Dreyling, ESMO CR 2014

First line treatment in FL
Therapeutic algorithm

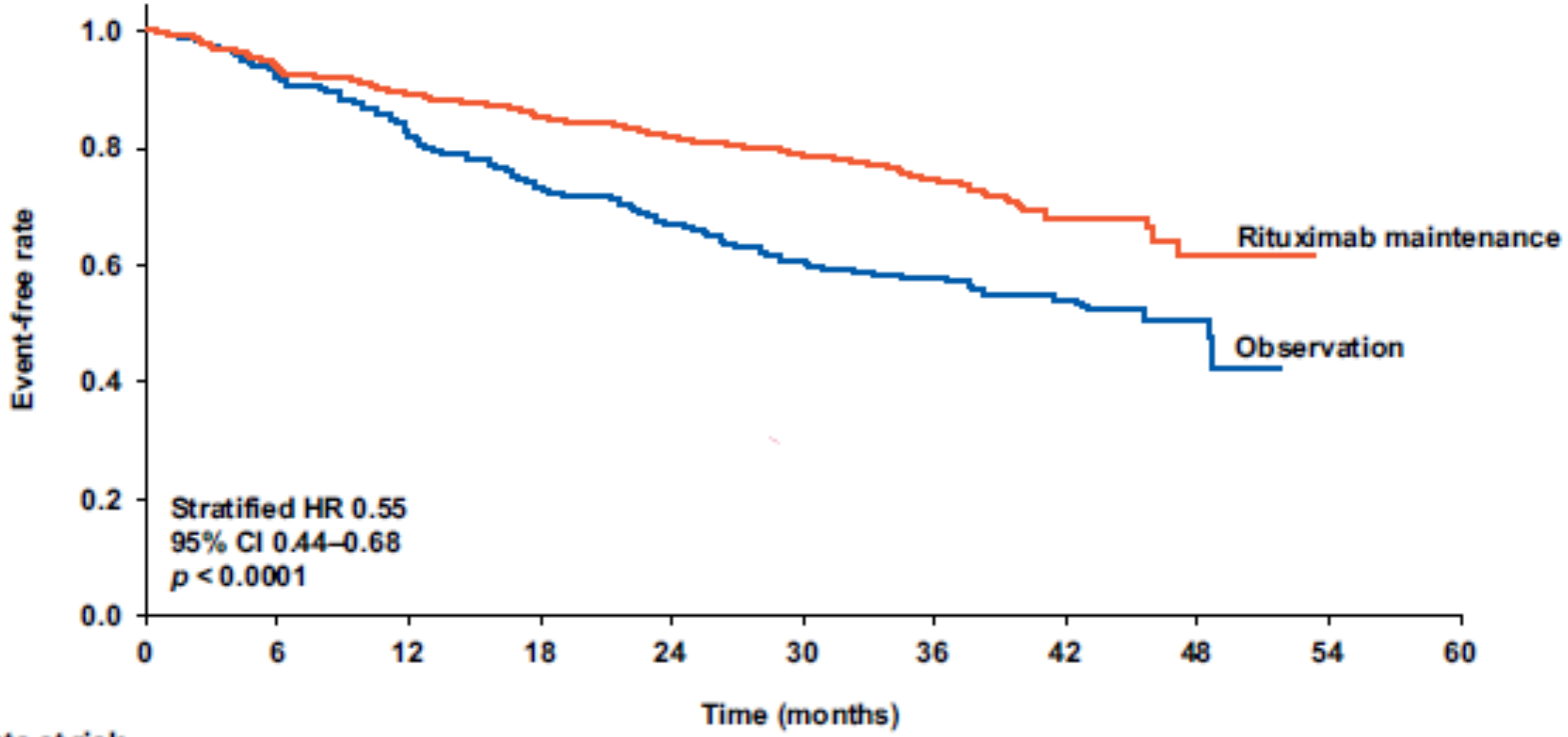


Dreyling, ESMO CR 2014

Follicular Lymphoma

Rituximab Maintenance

Figure 2. Progression-free survival

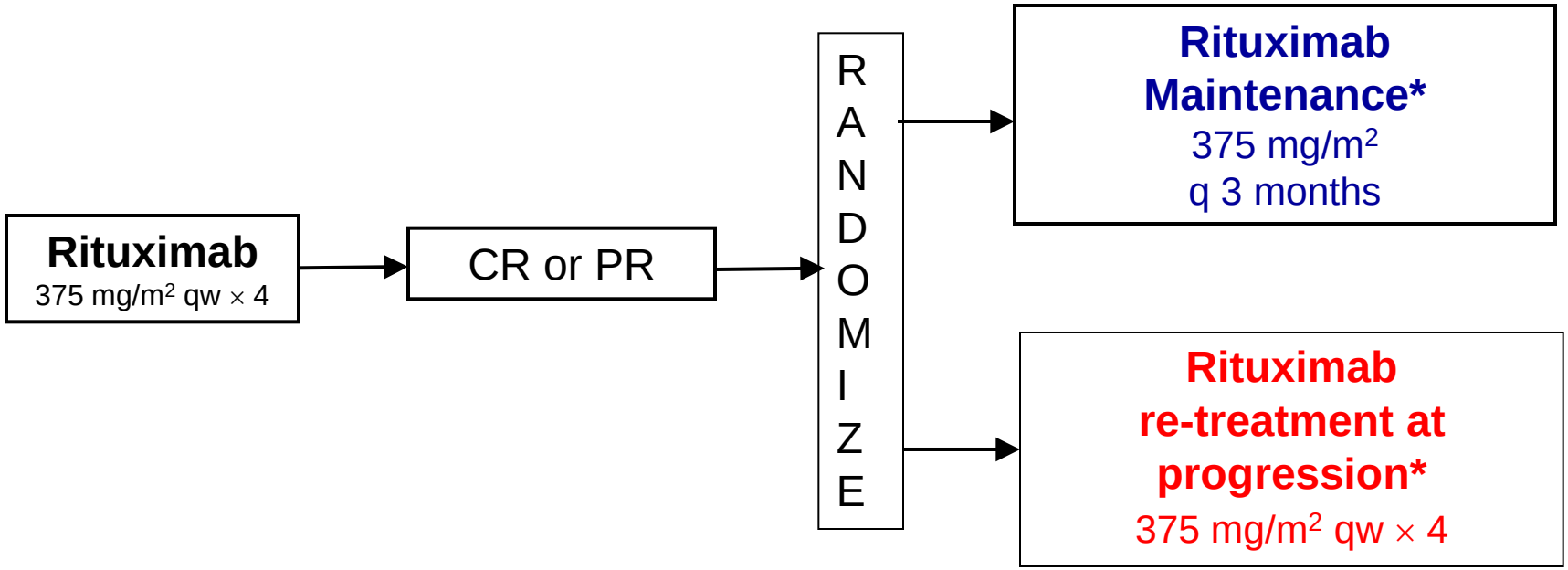


Patients at risk

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

Salles, Lancet Oncology 2011

E4402 (RESORT)
Schema

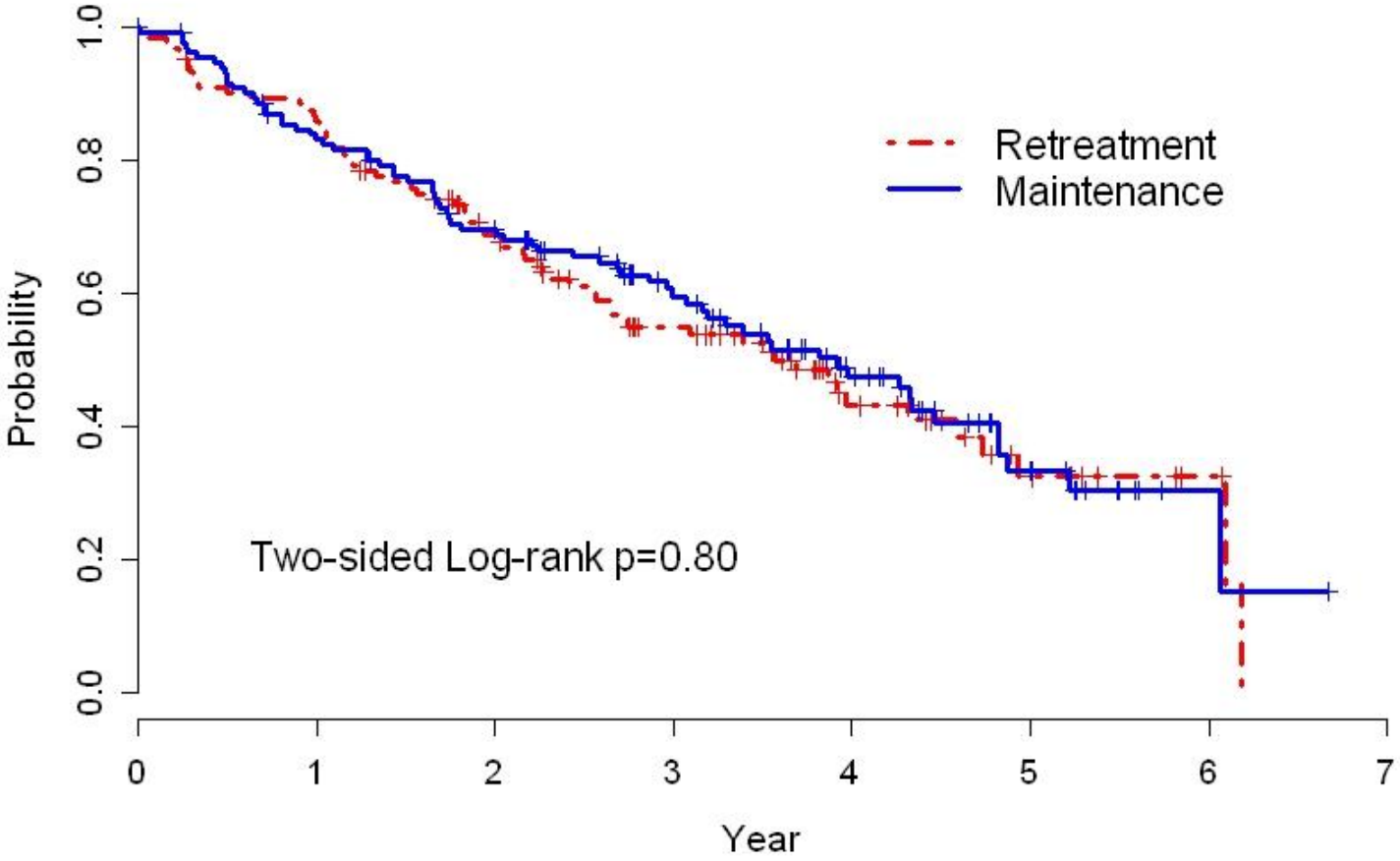


*Continue until treatment failure
No response to retreatment or PD within 6 months of R
Initiation of cytotoxic therapy or Inability to complete rx

Kahl, JCO 2014

E4402 (RESORT)

Progression-free survival



Kahl, JCO 2014

Annals of Oncology 22 (Supplement 6): vi59–vi63, 2011
doi:10.1093/annonc/mdr388

MADRID 2014

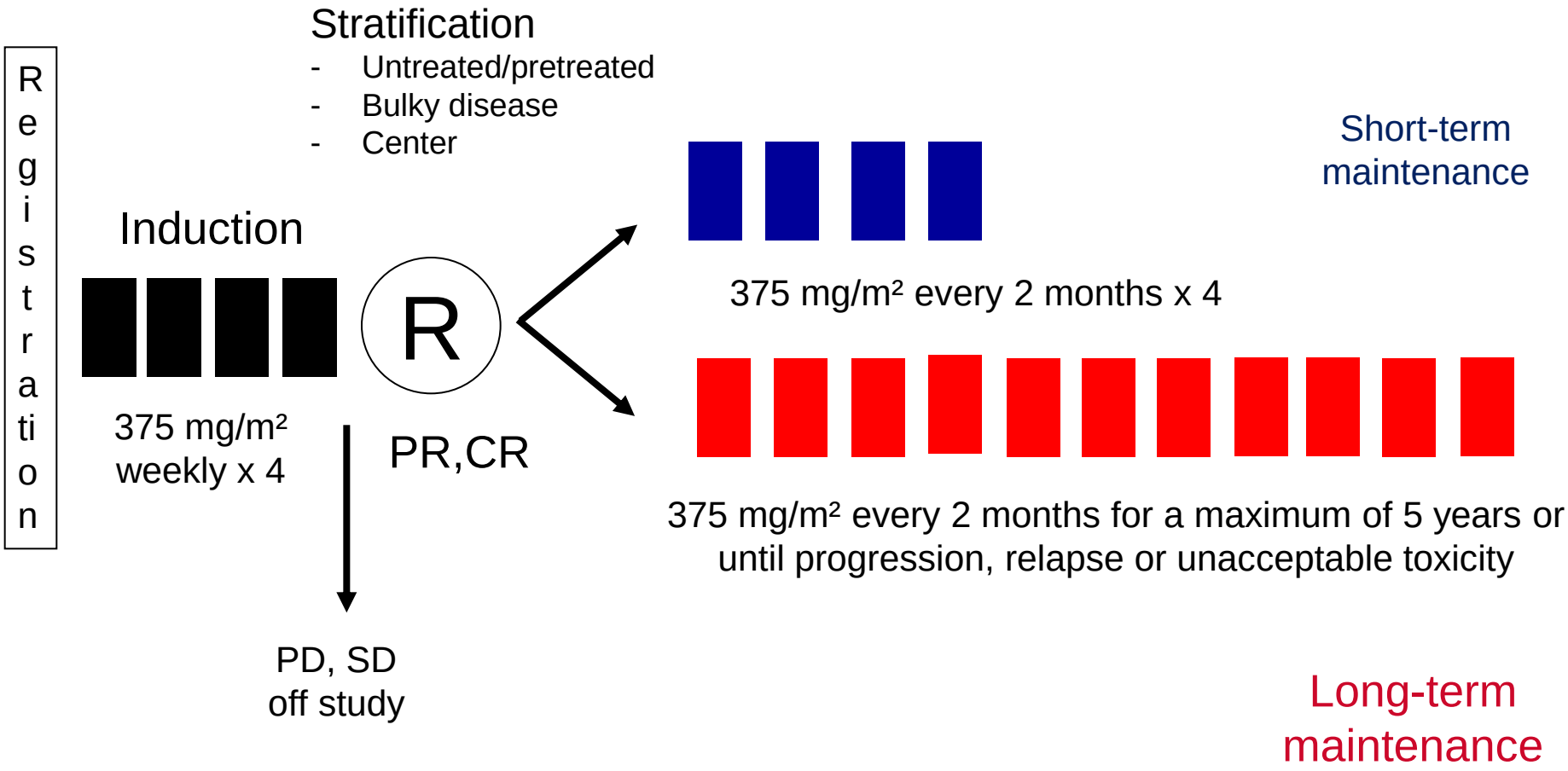
Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

consolidation/maintenance.

- ~~Meta-analysis of the pre-rituximab era suggests a potential benefit of interferon α maintenance therapy that has to be balanced against toxicity~~ [20].
- Rituximab maintenance for 2 years improves PFS (75% vs 58% after 3 years, $P < 0.0001$) [I, B] [21].
- Radioimmunotherapy consolidation prolongs PFS after chemotherapy but its benefit following rituximab combinations has not been established [I, B] [22].
- ~~Myeloablative radiochemotherapy followed by autologous stem cell transplantation prolongs PFS but not OS in four randomized trials and therefore represents no standard of care outside of trials [I, A]~~ [23–26]

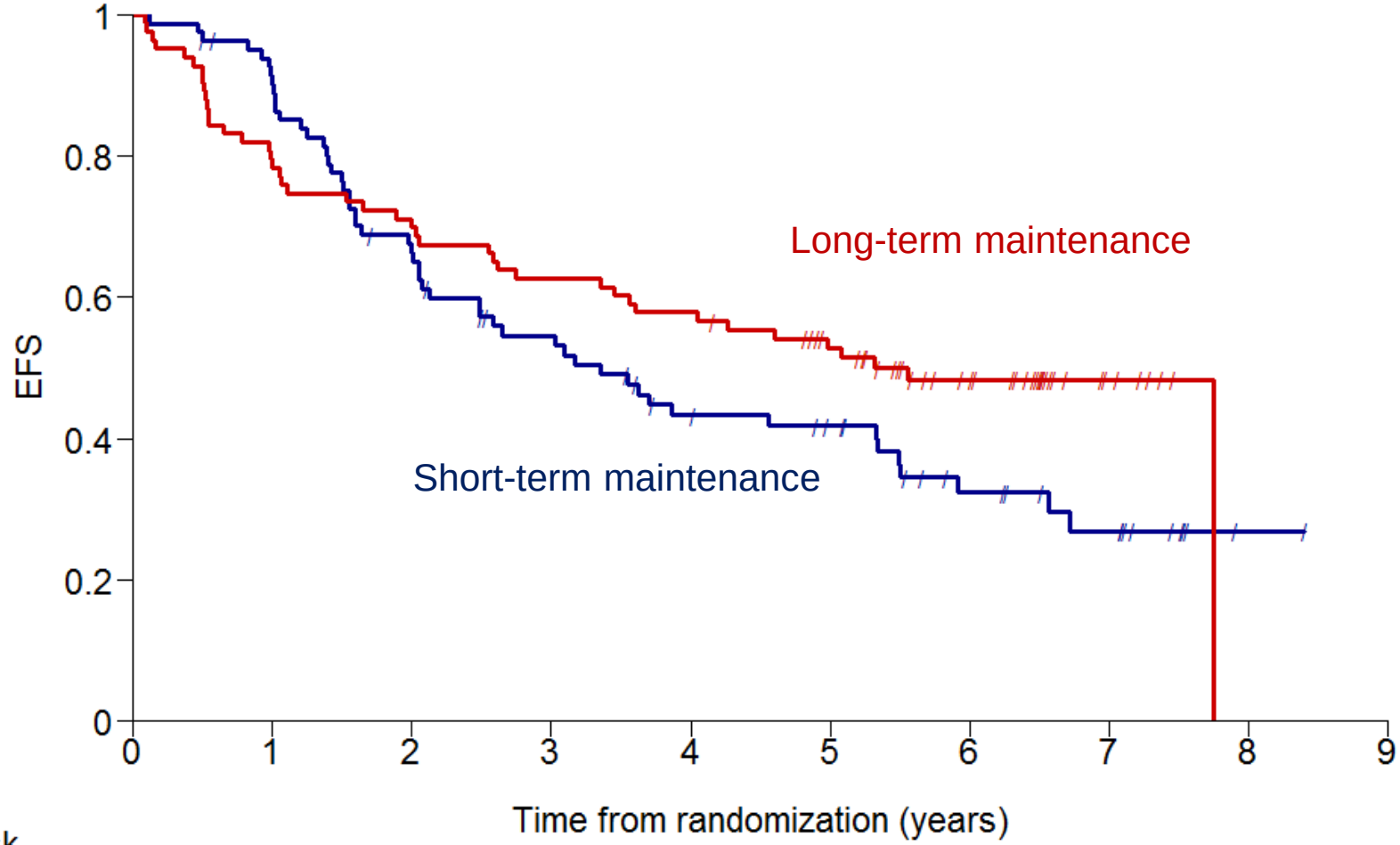
Dreyling, ESMO CR 2014

Study design SAKK 35/03



Taverna, ASH 2013

Event-free survival

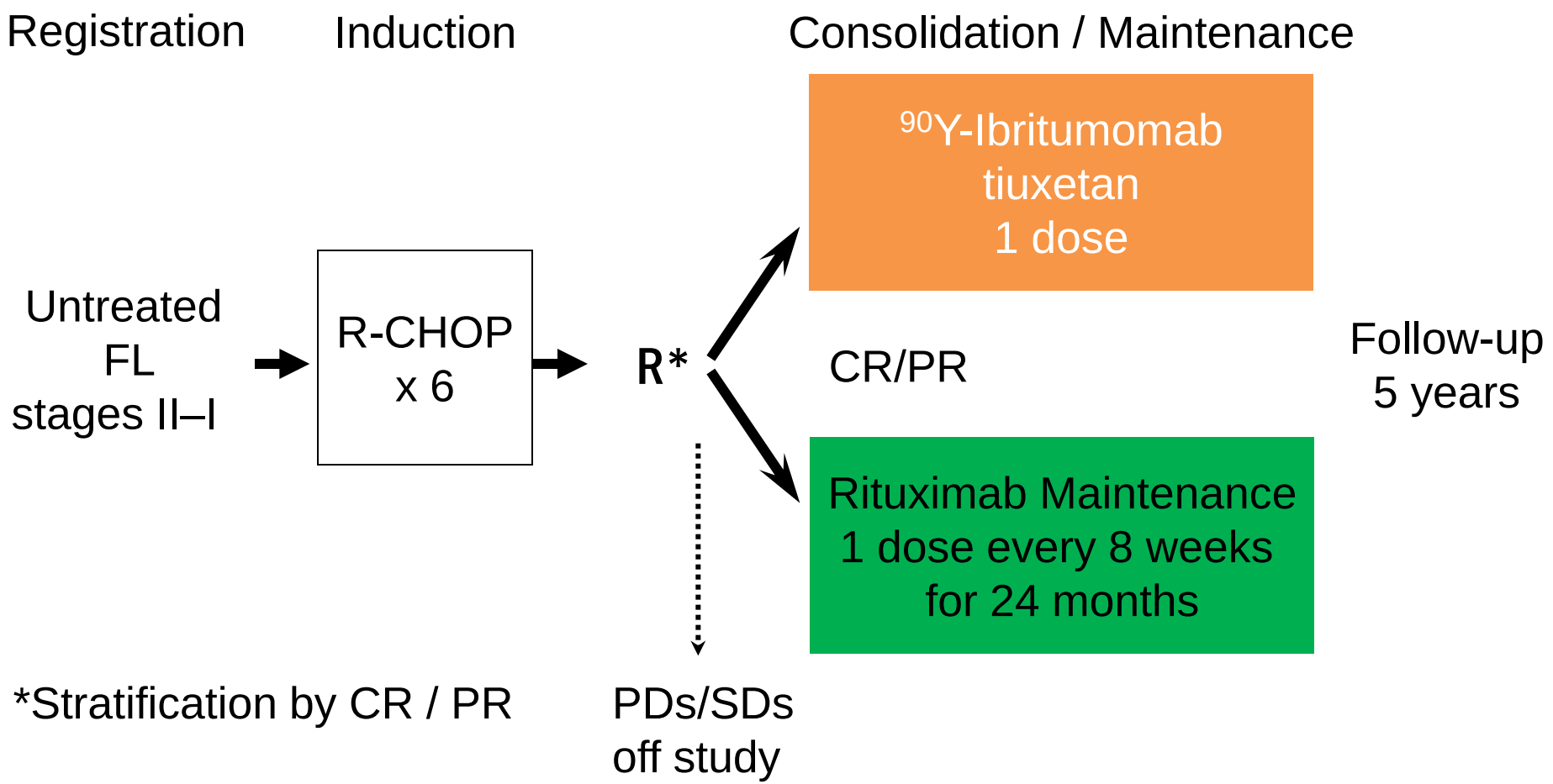


# at risk										
Short-term	82	73	53	40	29	25	15	10	1	0
Long-term	83	65	58	52	48	39	25	6	0	0

Median (95% CI) 3.4 (2.1, 5.3) versus 5.3 (3.5, NA) years; p=0.14

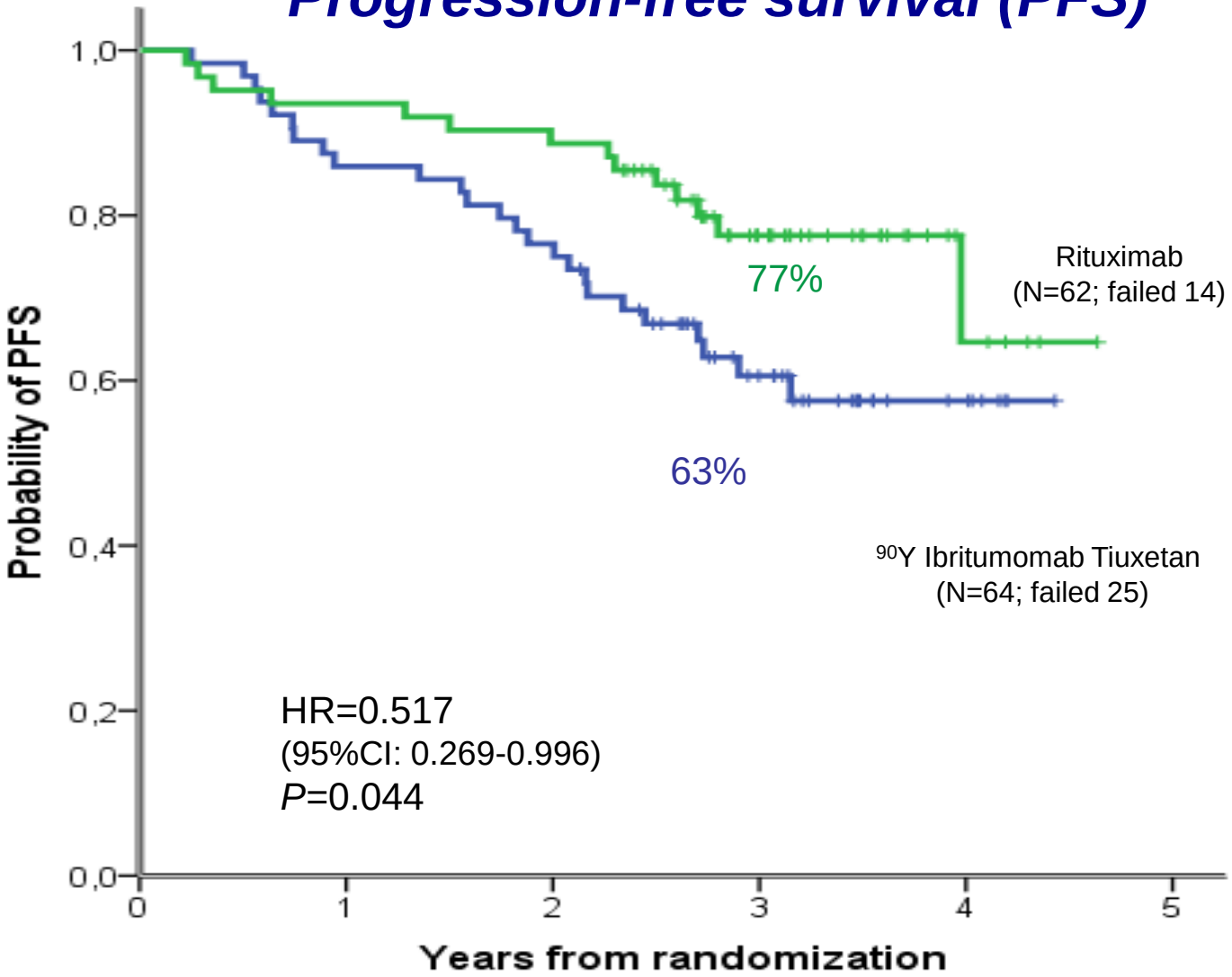
Taverna, ASH 2013

ZAR study: Design



Lopez-Guillermo, ASH 2013

Primary endpoint:
Progression-free survival (PFS)



Lopez-Guillermo, ASH 2013

Obinutuzomab

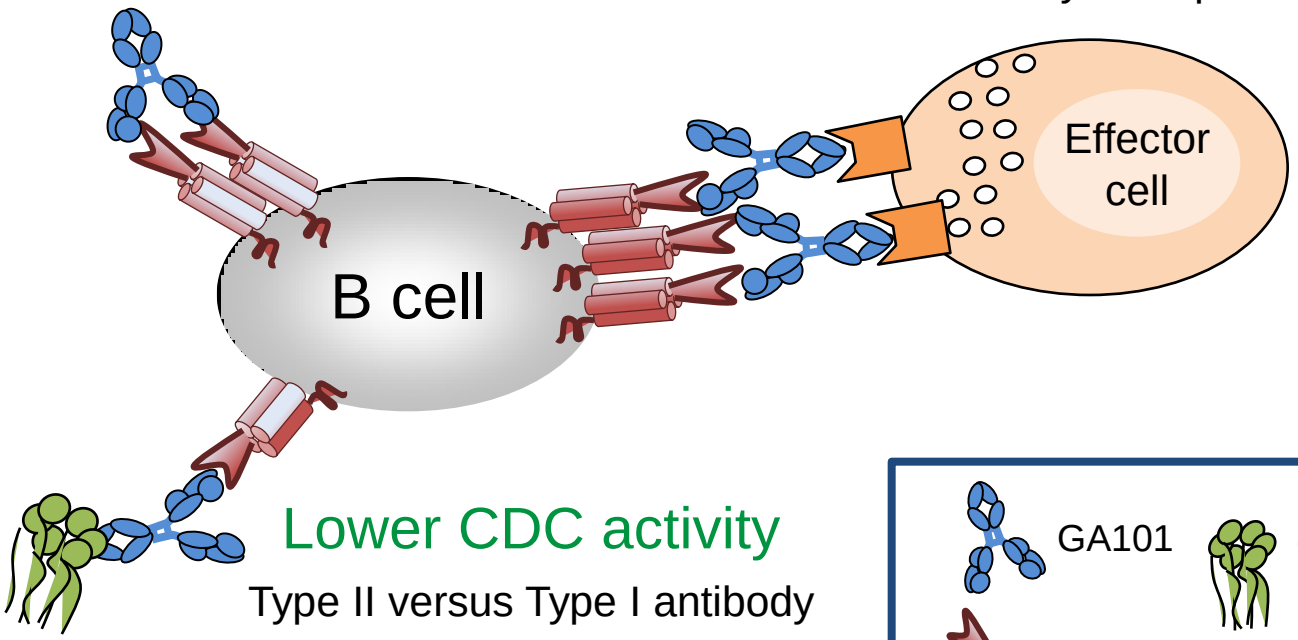
Mechanisms of action

Increased direct cell death

Type II versus Type I antibody

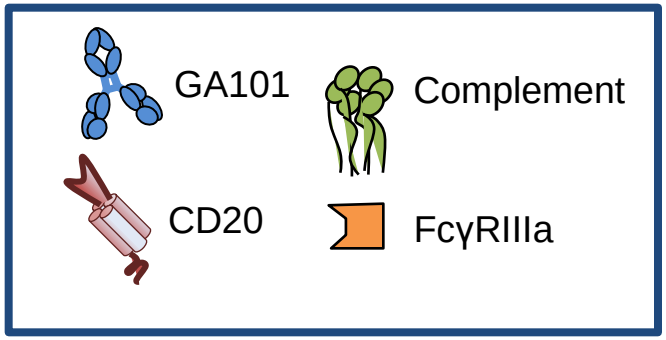
Enhanced ADCC

Glycoengineering for increased affinity to FcγRIIIa



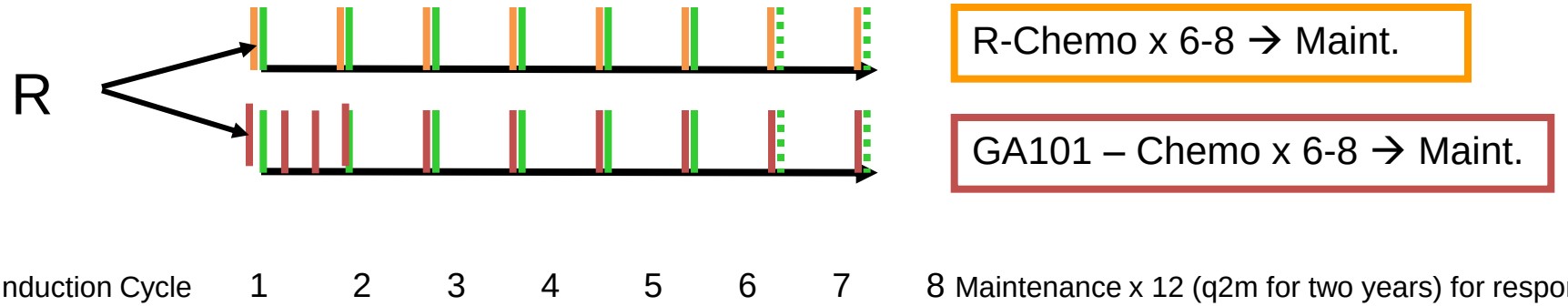
Lower CDC activity

Type II versus Type I antibody



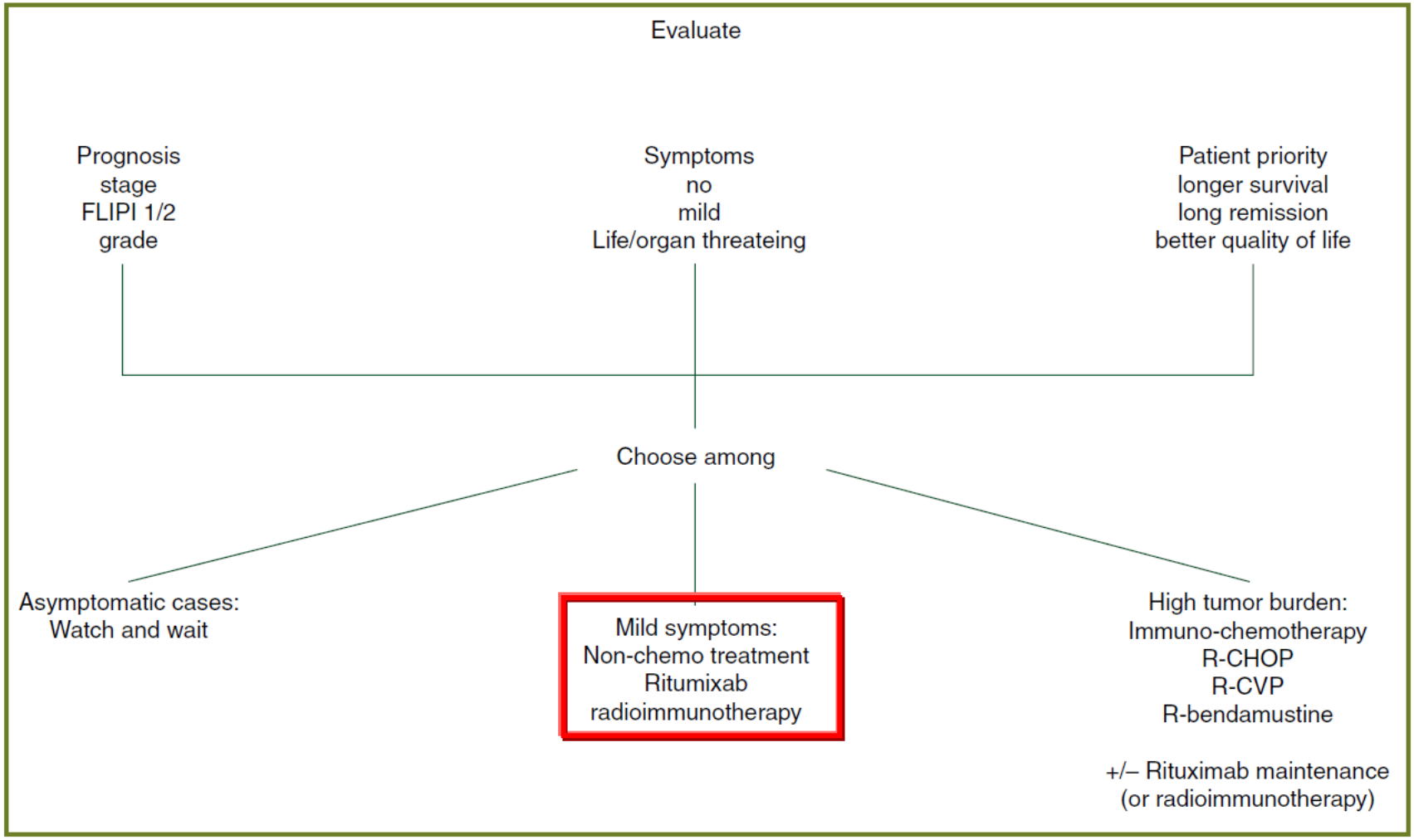
Mössner, Blood 2010

First line trial in follicular lymphoma



Phase III	**Open label study with induction and 2 years maintenance therapy** • **Primary Endpoint: PFS; HR 0,74; ⇑ median PFS from 72m to 97m** • **Secondary Endpoints: OS, EFS, ORR, CR, TNLT, safety and other** • **One futility analysis based on 33% PFS events; one IA based on 67% of PFS events** • **1200 patients from 250 sites, study duration approx. 6.1 years from FPI to final clinical data cutoff** • **200 additional patients with MZL, MALT, or SMZL**

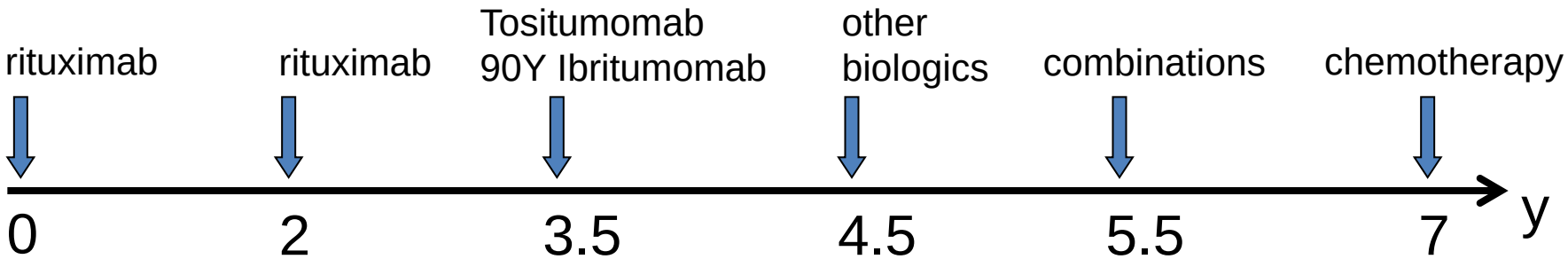
First line treatment in FL
Therapeutic algorithm



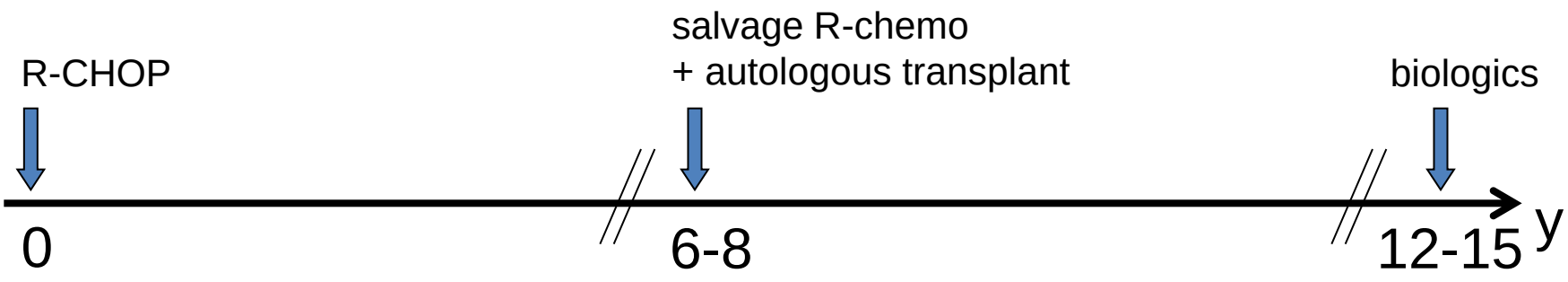
Dreyling, ESMO CR 2014

Different philosophies to treat FL

- avoid chemotherapy as long as possible



- try to reach a CR and have a long duration of CR

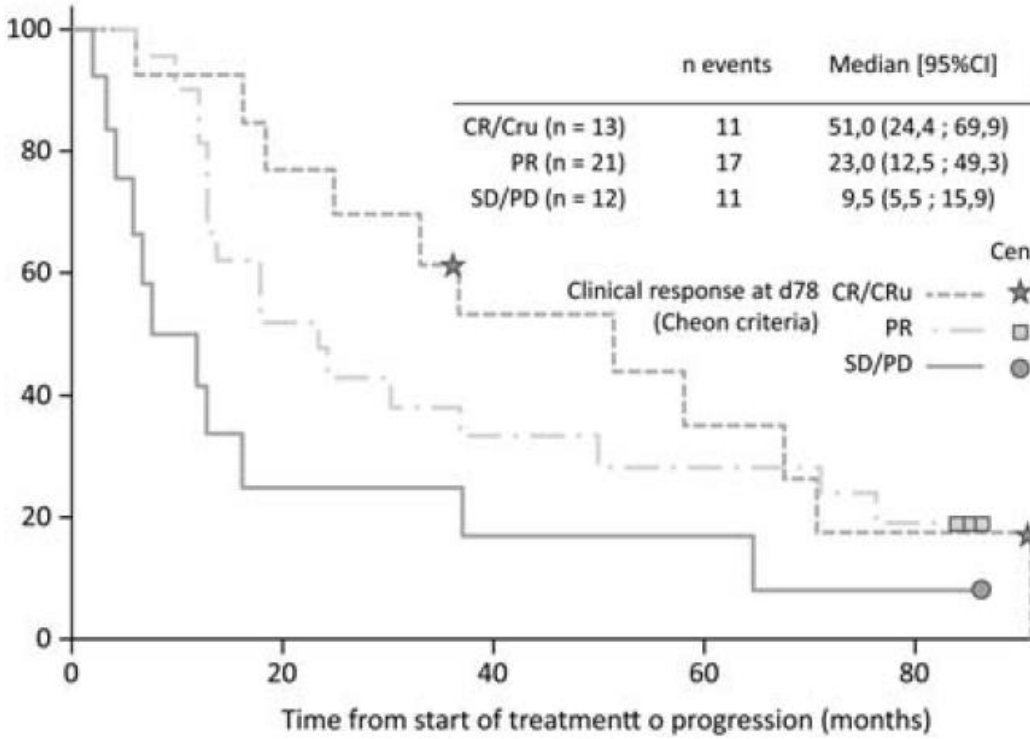


courtesy of B. Coiffier

Follicular lymphoma

Rituximab Monotherapy

Patients characteristics	N	%
Follicular histology	46	100
Age (years)		
Median	52	
Range	41–58	
Gender		
Male	24	52
Female	22	48
WHO grade		
1	21	46
2/3a	25	54
Ann Arbor stage		
II	3	6
III	11	30
IV	32	70
FLIPI		
Low	20	43.5
Intermediate	20	43.5
High	6	13

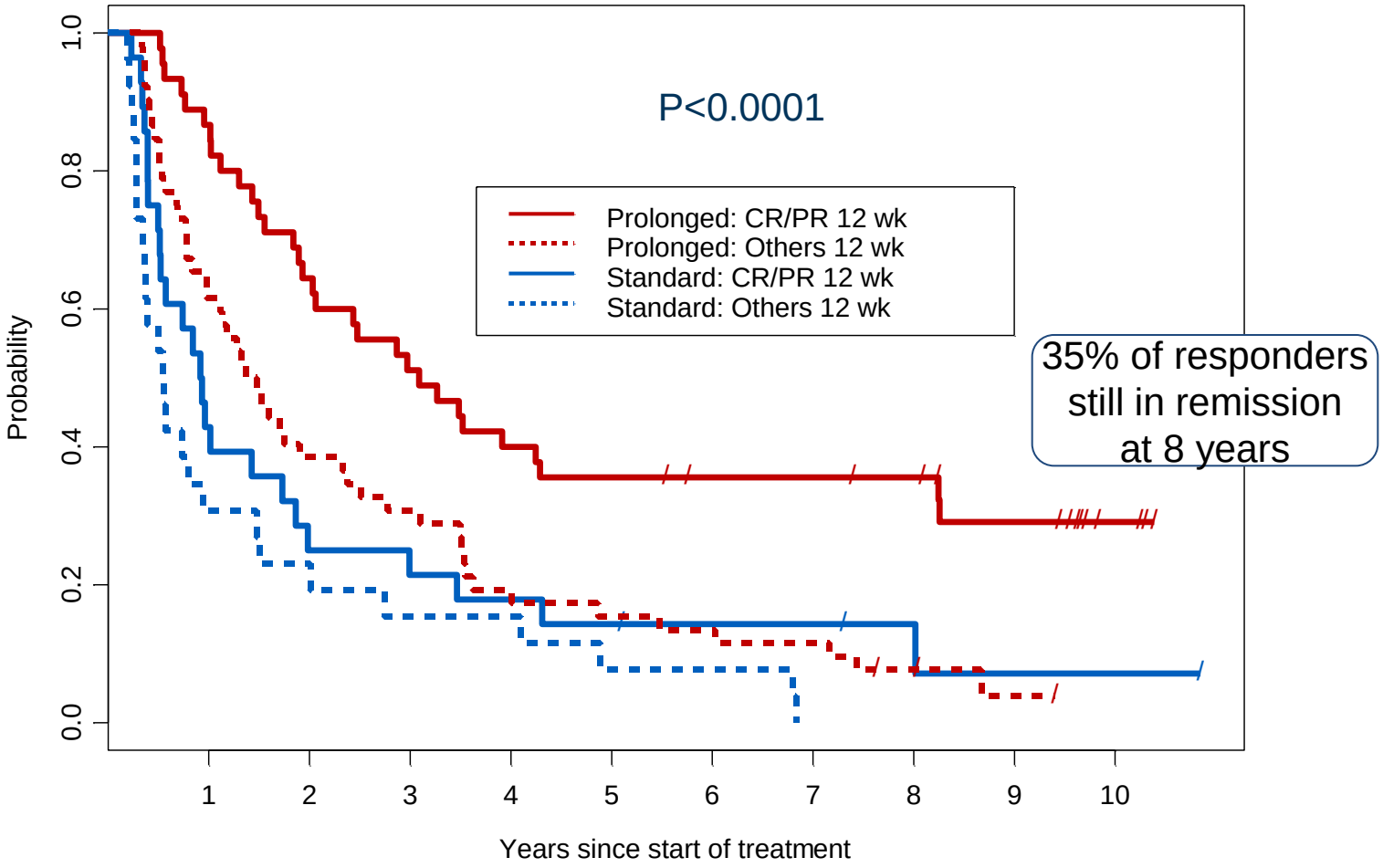


Colombat, Ann Oncol 2012

Follicular Lymphoma

Rituximab monotherapy

Event-free survival in randomized follicular lymphoma patients



Martinelli, JCO 2010

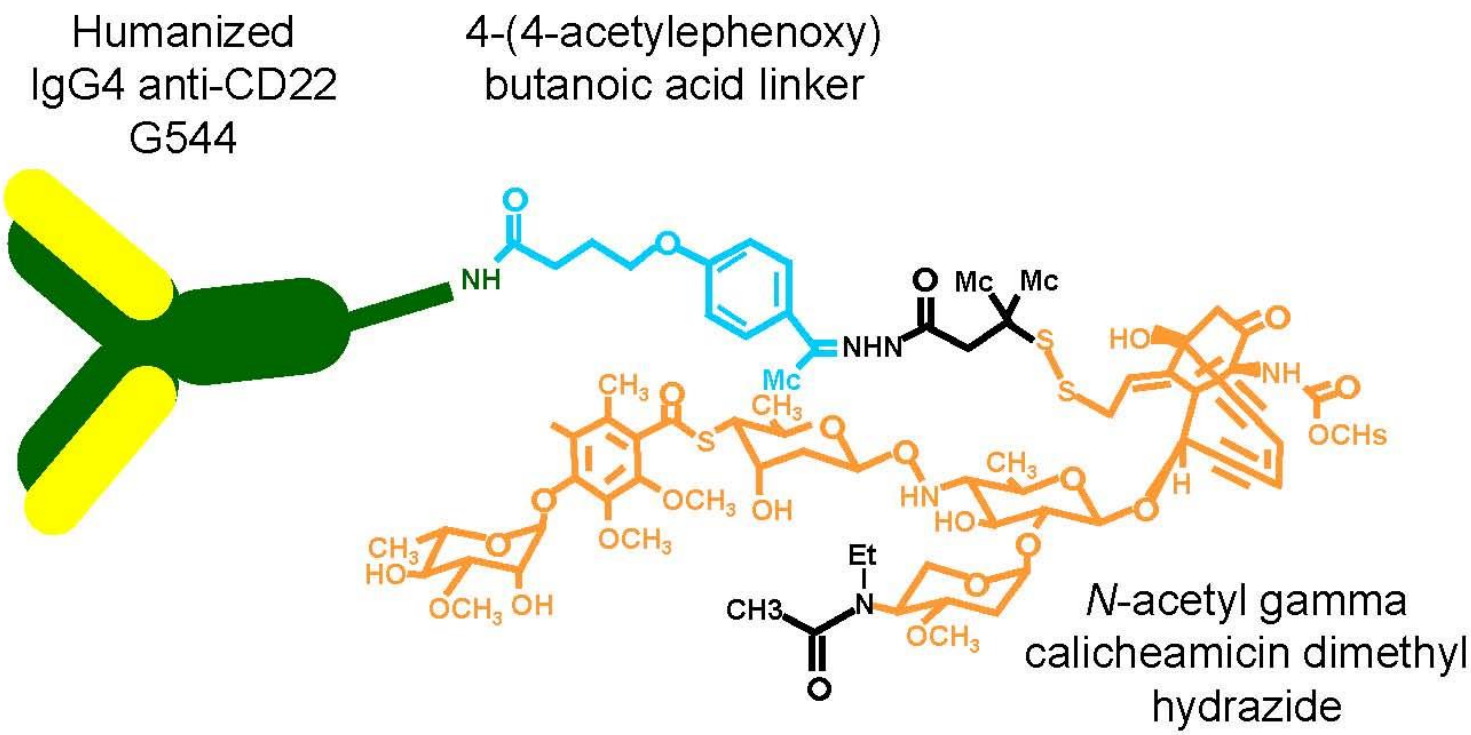
Monoclonal antibodies

- Naked MAb
  - Rituximab anti-CD20
  - humanized (ocraluzumab, ofatumumab)
  - Alemtuzumab anti-CD52
  - Epratuzumab anti-CD22
  - Galiximab anti-CD80
  - Bevacizumab anti-VEGF

- MAb + radionucleide
  - ^{90}Y ibritumomab tiuxetan anti-CD20
  - ^{131}I tositumomab anti-CD20

- MAb + toxin
  - *CMC-544 (calicheamicin)* anti-CD22

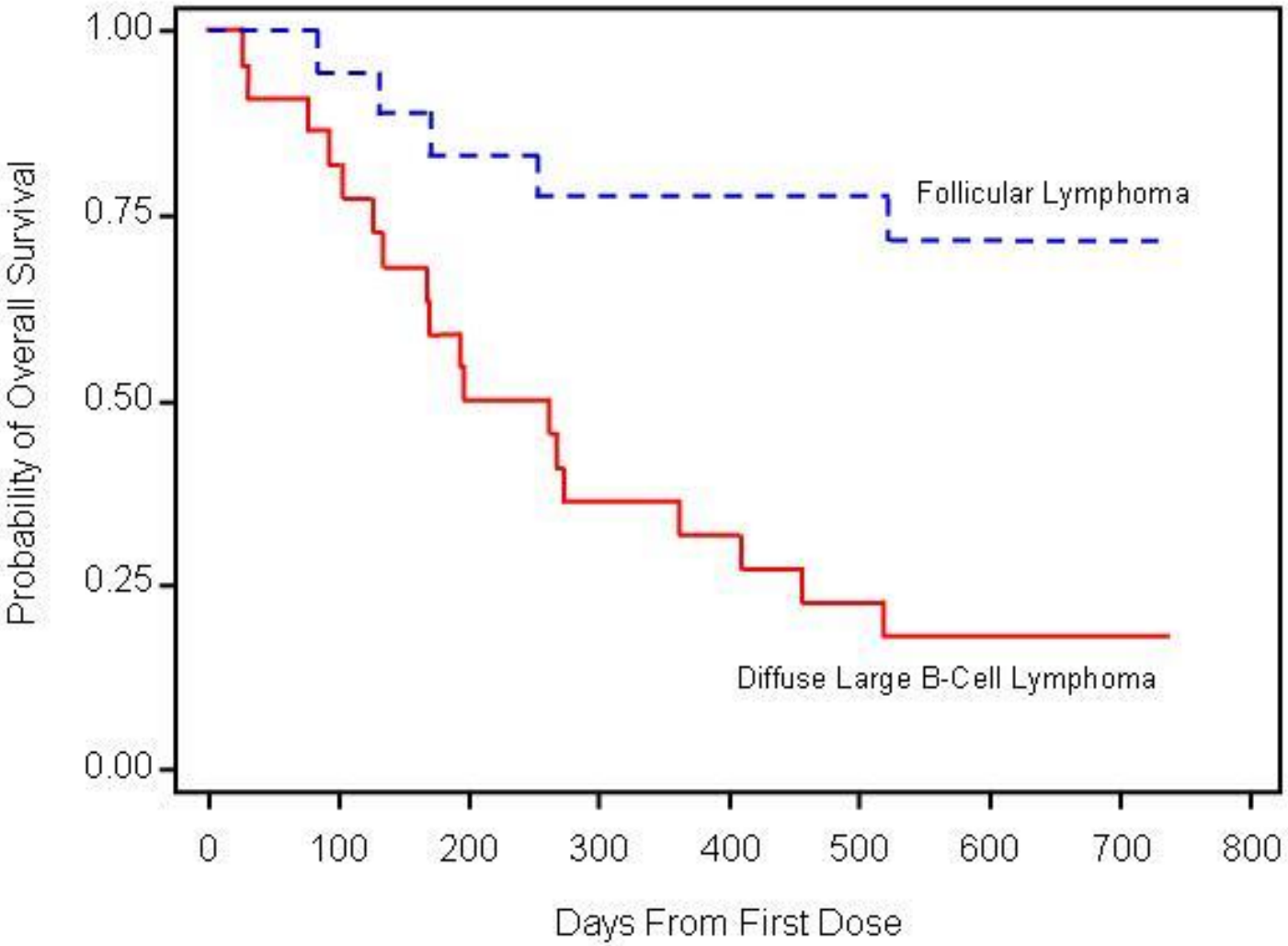
Follicular lymphoma
chemo-immunotherapy



Advani JCO 2010

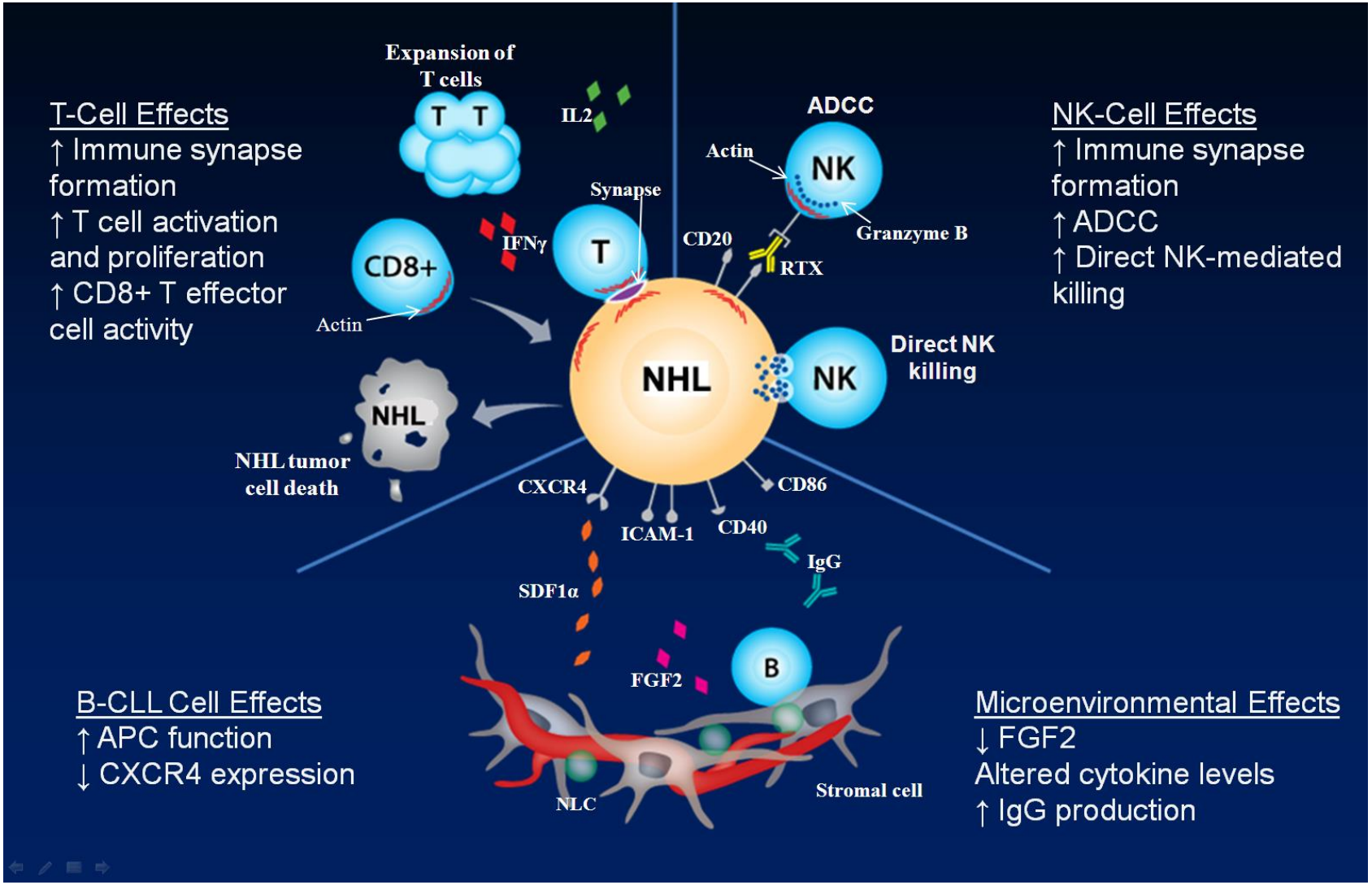
Follicular lymphoma

chemo-immunotherapy



Advani JCO 2010

Lenalidomide
Mechanism of action



Comparison of frontline FL therapies

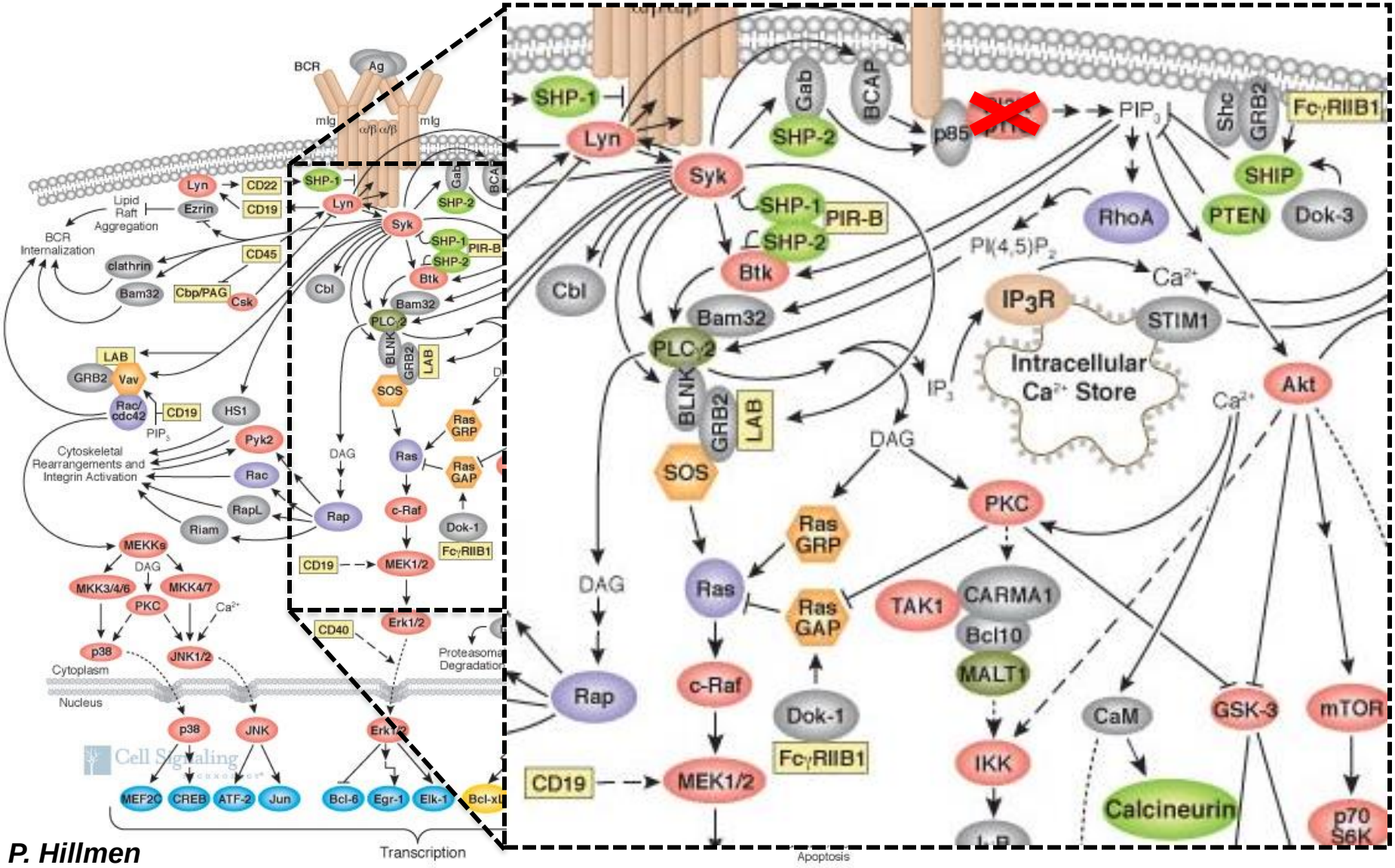
	Colombat et al	R[2]	Rummel et al.	Hiddemann et al	Marcus et al
Regimen	Rituximab	Lenalidomide + Rituximab	Bendamustine + Rituximab	CHOP + Rituximab[†]	CVP + Rituximab
Stage III/IV, %	**50 (II+)**	**100**	**100**	**100**	**100**
Grade 3	**No**	**No**	**No**	**No**	**9%**
GELF Criteria for treatment, %	**0**	**49**	**100**	**NR**	**80[±]**
FLIPI ≥ 3, %	**NR**	**29**	**46**	**NR**	**38**
Bulky disease, %	**0%**	**29**	**28**	**NR**	**39**
ORR, %	**73**	**98**	**94***	**96**	**80**
CR, %	**26**	**85**	**41***	**20**	**41**
PFS	**1 year 80%**	**2 year 83%**	**2 year 78%***	**2 year ≈ 85%**	**32 mo 50%**

Fowler, Lancet Oncology (in press)

MADRID 2014 ESMO congress

B-cell receptor pathway

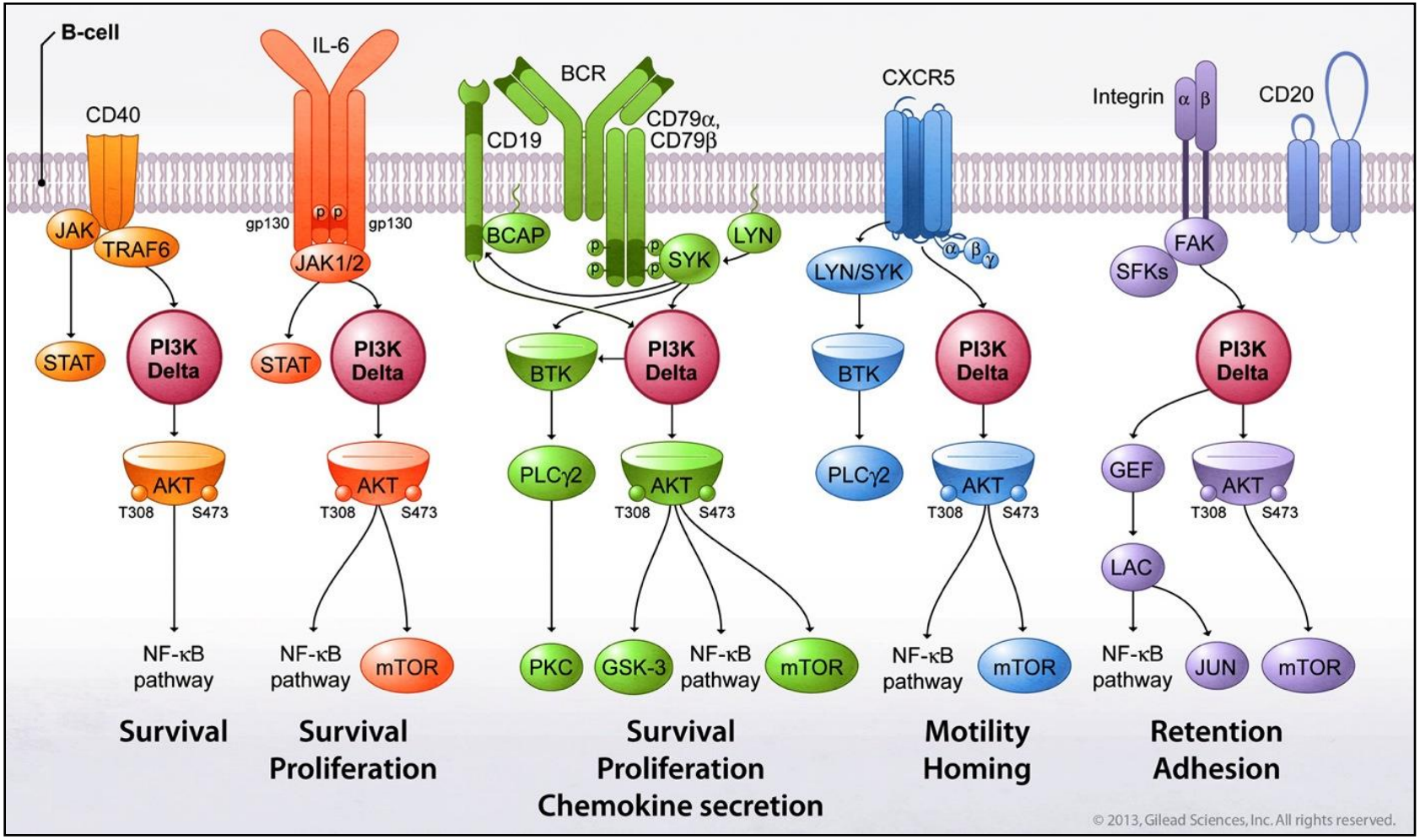
Targeting a critical pathway



P. Hillmen

Follicular Lymphoma

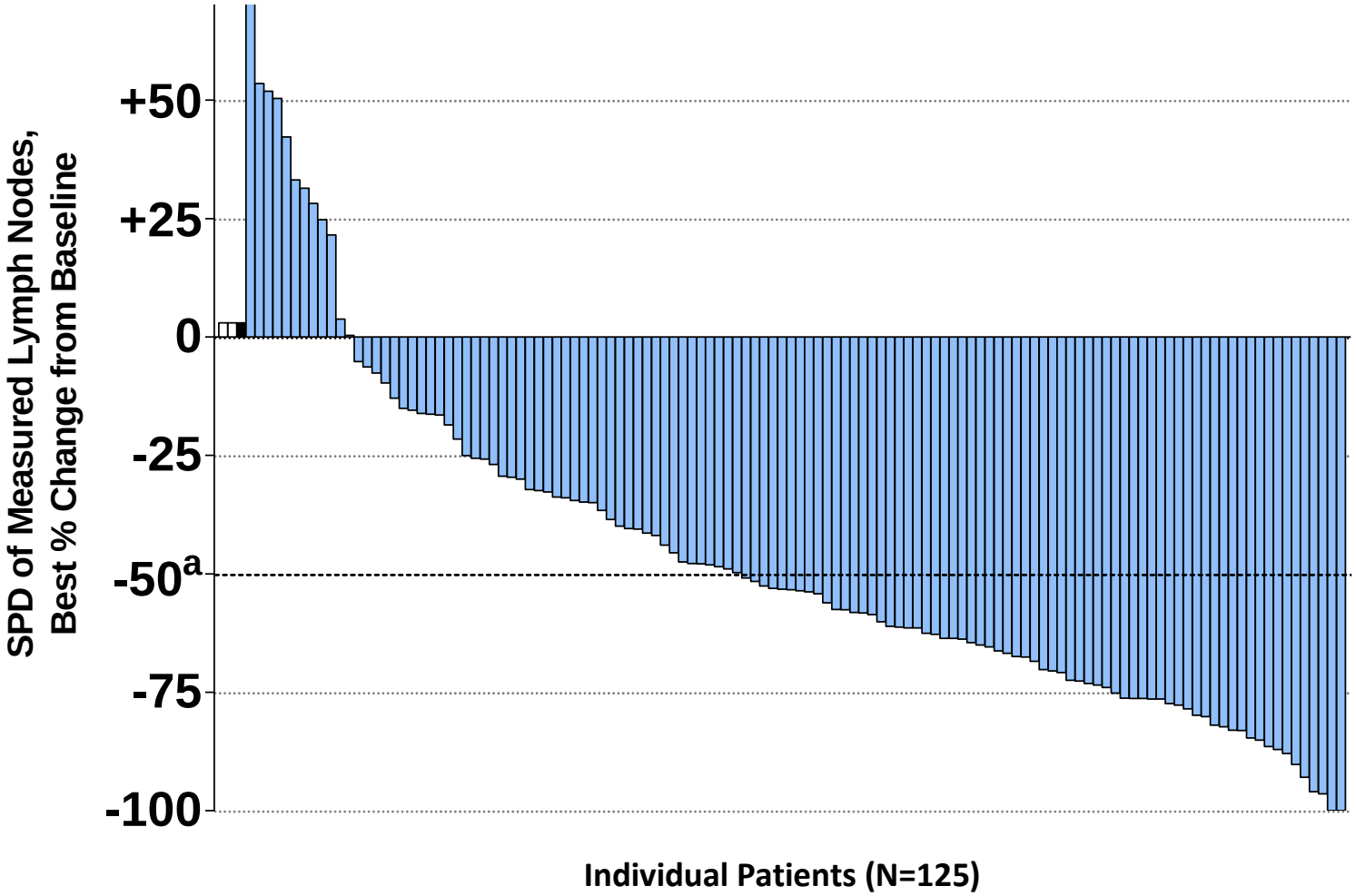
PI3Kδ inhibition in FL



Gopal, NEJM 2014

Double refractory Follicular Lymphoma

PI3Kδ inhibition



Gopal, NEJM 2014

Follicular lymphoma

GLSG studies 2014

medically non-fit

R-CHOP/B vs. G-CHOP/B

↓

R vs G maintenance

R-CHOP vs. R2

↓

Ritux maintenance (+/- lenalidomide)

R+/- Bendamustine

↓

Ritux maintenance

Relapse

FLAZ:

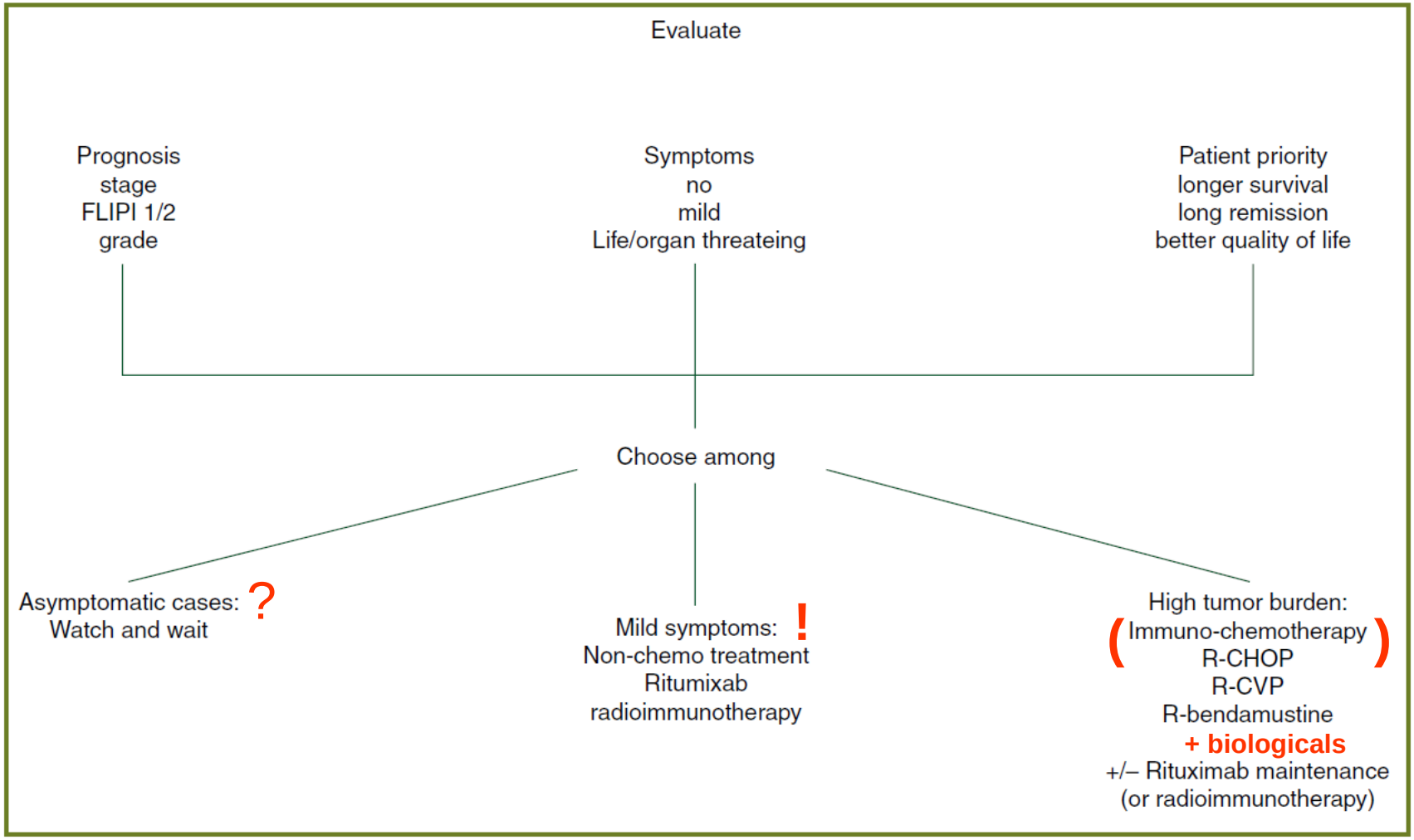
ASCT vs. RIT

R-Benda Temsirolimus

(BeRT)

R- Lenalidomide +/- Benda R-maintenance

First line treatment in FL 2020
Therapeutic algorithm



Oktoberfest
Mainzer Spring
Messe
Mainz Spring