Thérapeutiques ciblant le lymphocyte B dans les maladies systémiques

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Disclosures (LM)

- Consultant: Actelion, CSL Behring, Cytheris, GSK, LFB Biotechnologies, Lilly, Pfizer
  - Financial support to ARMIIC
- Investigator: Actelion, CSL Behring, Pfizer
- Financial support (grants): Actelion, CSL Behring, GSK, LFB Biotechnologies, Pfizer

Disclosures (rituximab)

- Roche has provided partly rituximab for the MAINRITSAN trial

Nomenclature des Ac monoclonaux

Espèce	Lettre	Suffixe	
Humain	U	umab	
Souris	O	omab	
Rat	E		
Hamster	E		
Primate	i		
Chimère	Xi	ximab	Rituximab
Humanisé	zu	zumab	Ocrelizumab

L Mouthon. Livre de l'interne en Médecine Interne. 2007

B-cell targeting therapies

Randomized controlled trials

Anti-CD20 and rheumatoid arthritis

Anti-CD20 and ANCA-associated vasculitis

Anti-CD20 and ITP

Anti-CD20 and cryoglobulinemia vasculitis

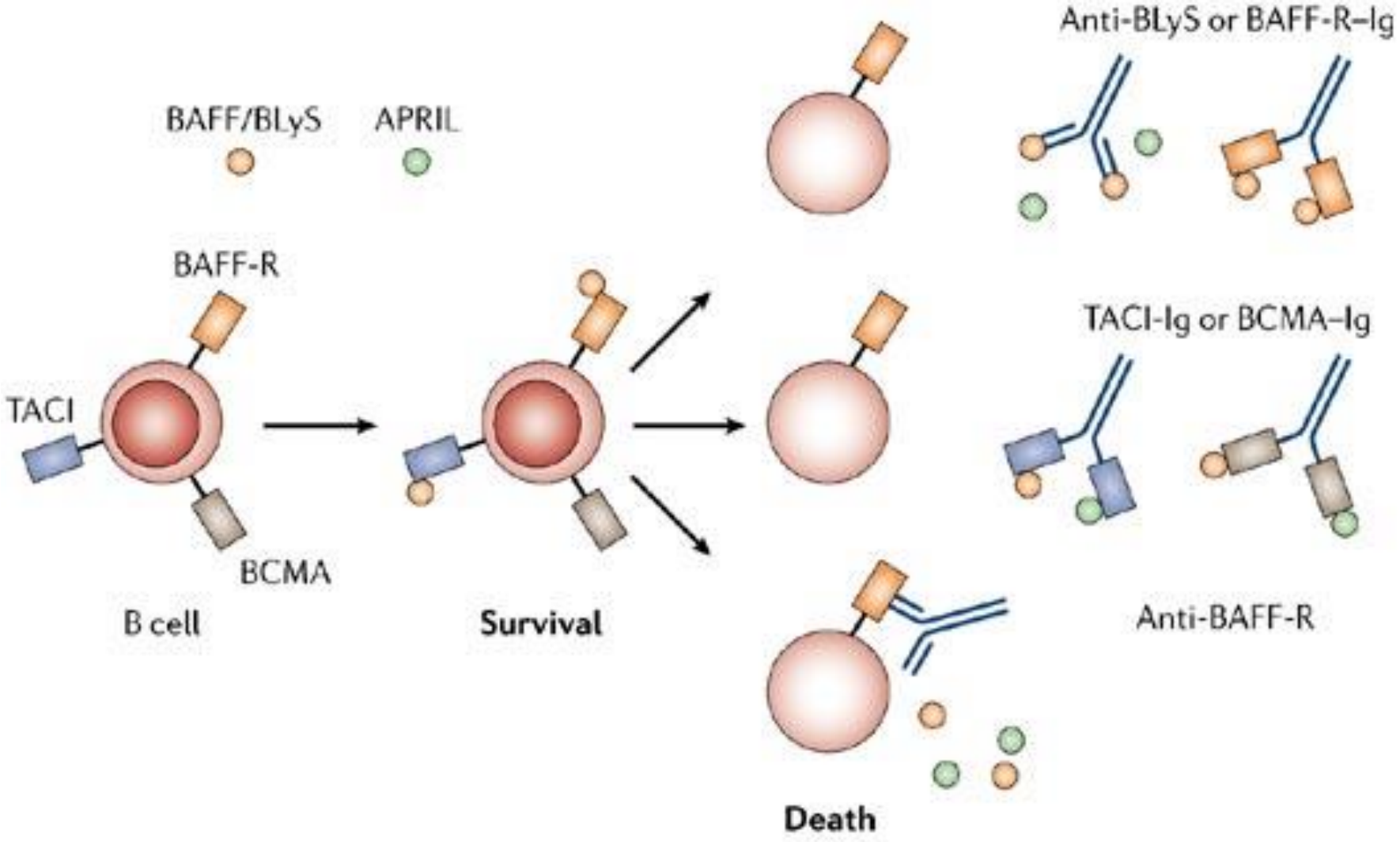
Anti-BAFF and systemic lupus

Other studies

Anti-CD20 and systemic lupus

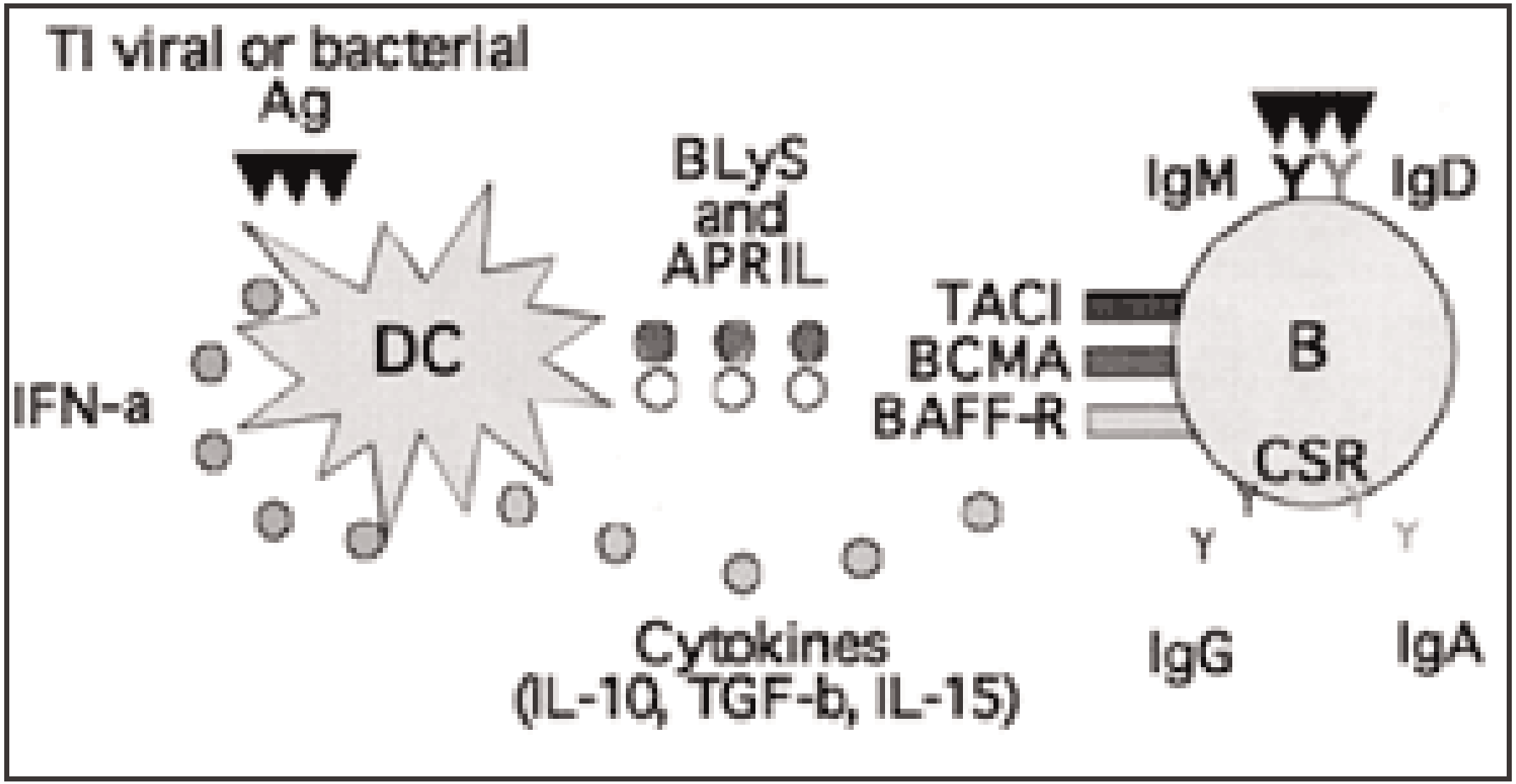
Anti-CD20 and Sjögren's syndrome

Anti-CD22 and systemic lupus



Nature Reviews | Drug Discovery

B lymphocyte stimulator (BLyS)



Litinskiy et al. Nat Immunol. 2002; 3:822-9

Effects of B-cell targeting therapies

<u>Induce total B-cell depletion</u>

Anti-CD20

<u>Decrease B-cell activation and proliferation</u>

Anti-BAFF (belimumab)

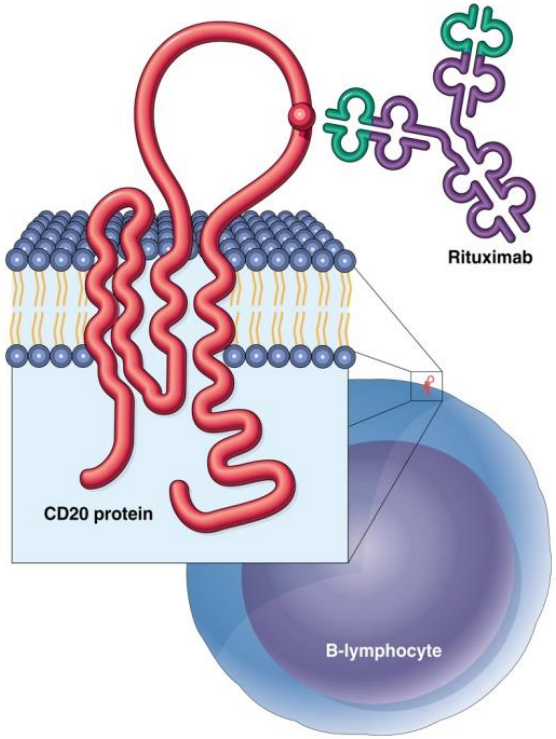
Anti-CD22 (épratuzumab)

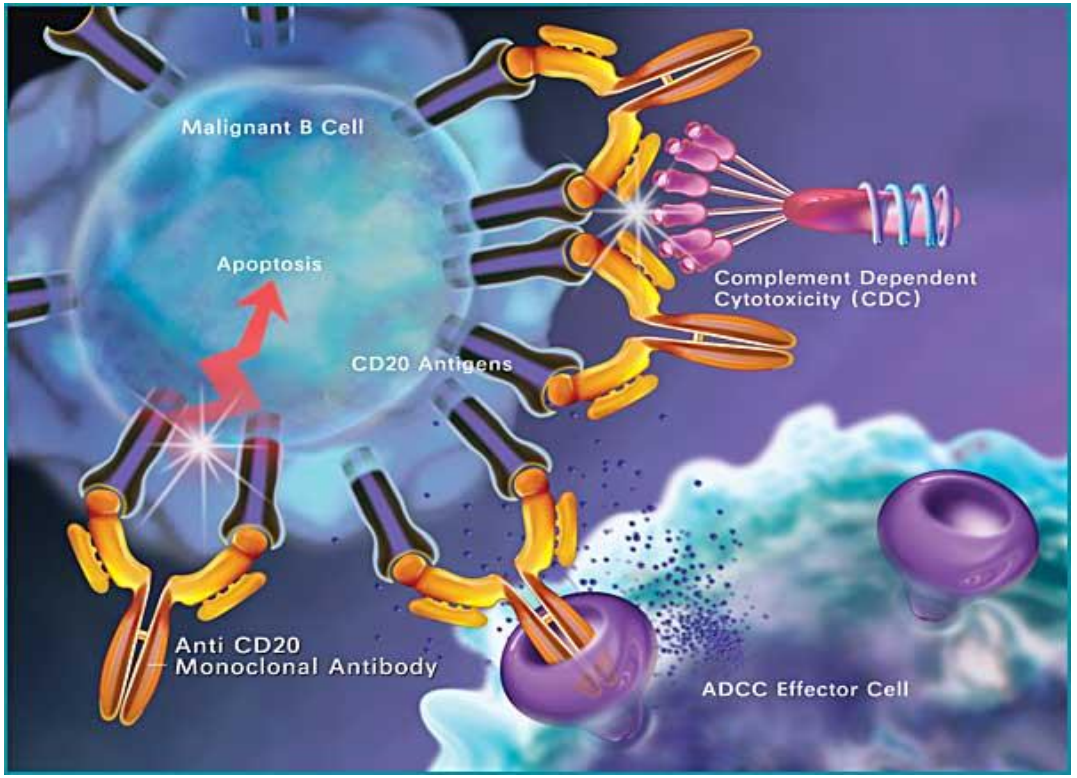
Anti-CD20 - Rituximab

Variables regions from murine anti-CD20 Ab: IDEC-2B8

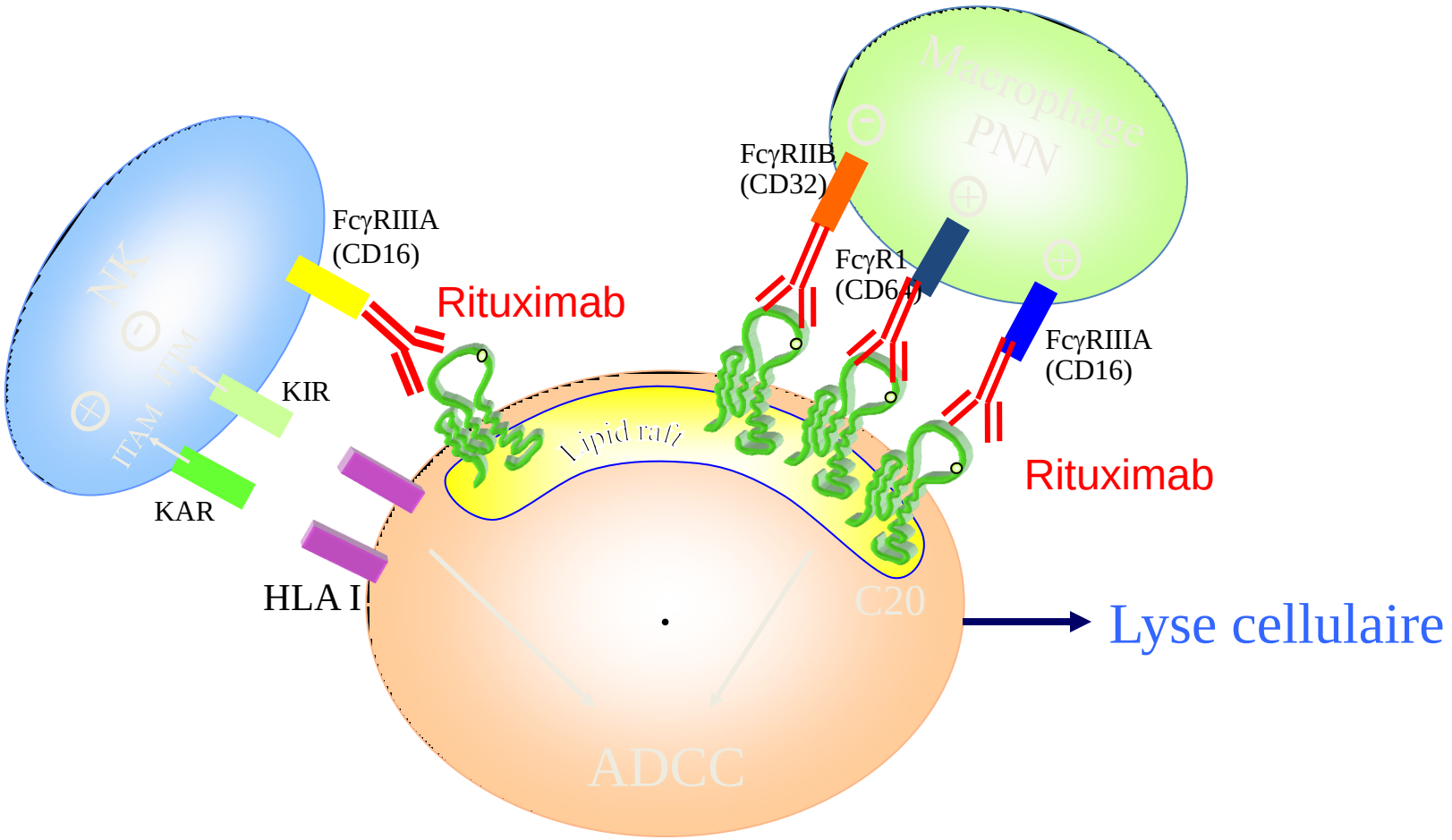
Constant regions: human IgG1k

First monoclonal antibody approved by the FDA (1997)





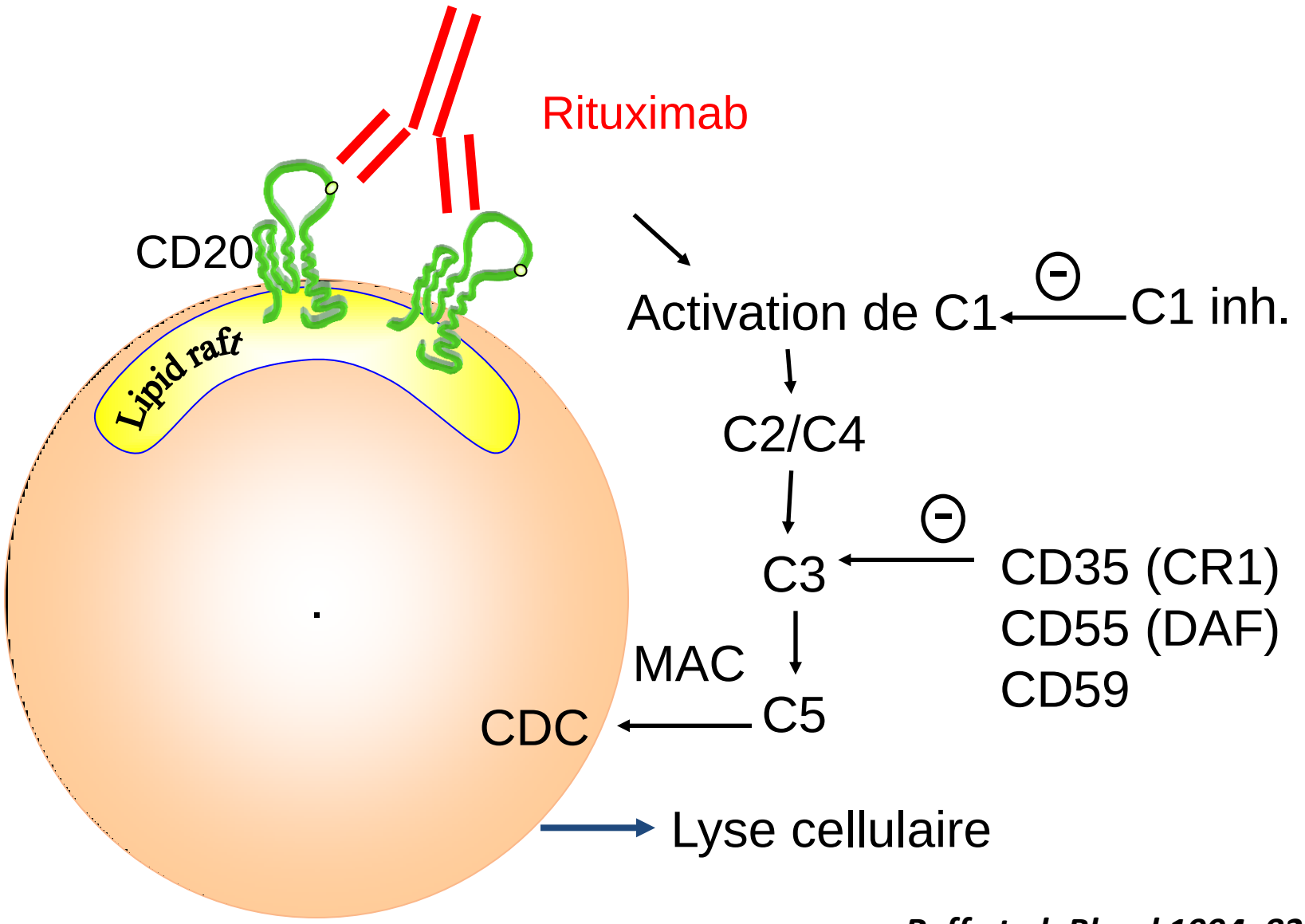
Rituximab: ADCC



ADCC: Antibody-dependant cellular cytotoxicity

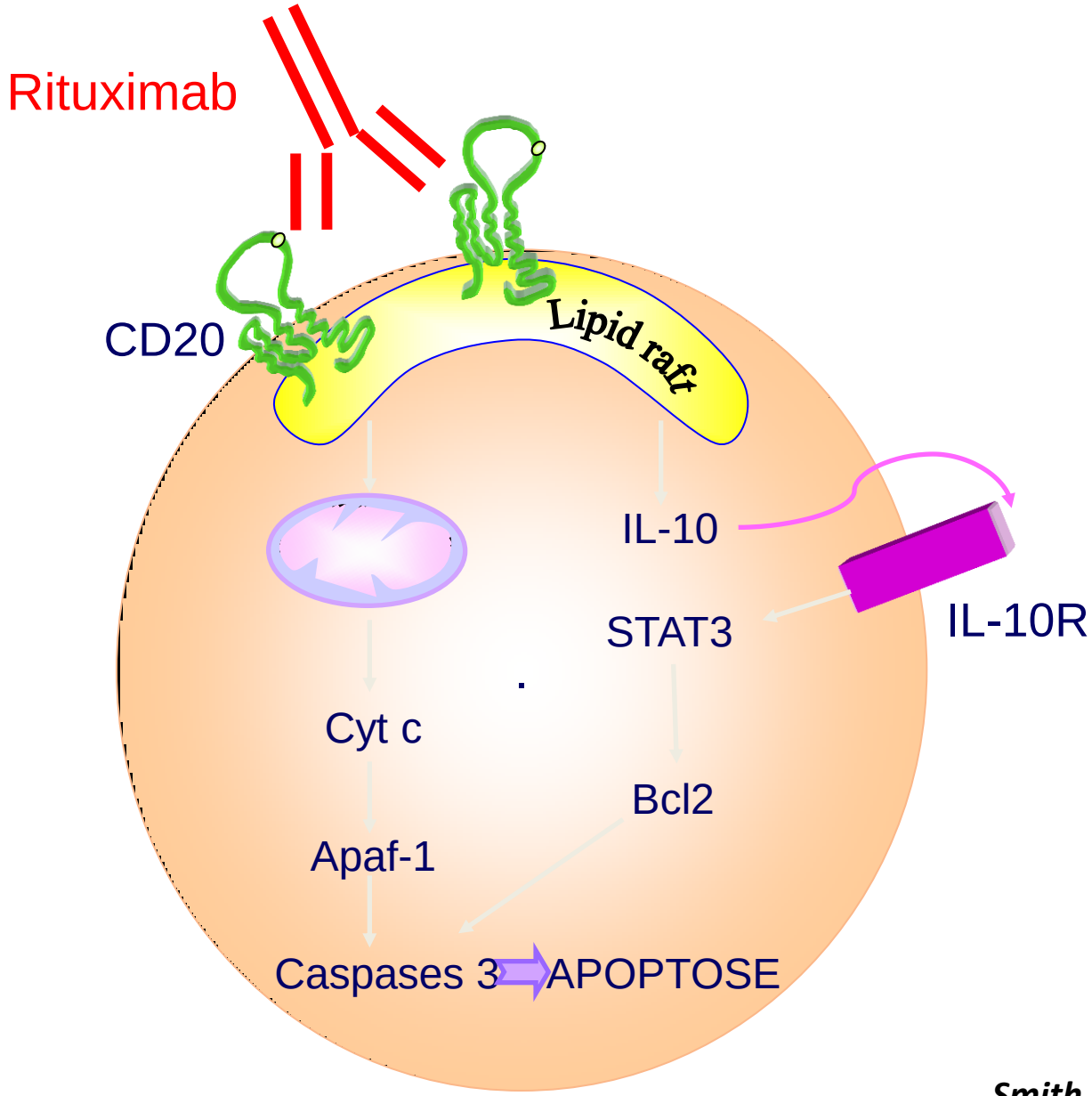
Anderson et al. Biochem Soc Trans 1997;25:705-8.
Clynes et al. Nat Med 2000; 6:443-6.

Rituximab: CDC



Reff et al. Blood 1994; 83 : 435.
Smith. Oncogene 2003; 22 : 735.

Rituximab: apoptosis



Smith. Oncogene 2003; 22 : 7359.

Utilisation du Rituximab dans les pathologies autoimmunes

Autorisation de mise sur le marché
- Polyarthrite rhumatoïde
- Vascularites associées aux ANCA

Études prospectives randomisées positives
- Purpura thrombopénique auto-immune
- Sclérose en plaques
- Vascularites associées aux cryoglobulinémies
- Anémies hémolytiques auto-immunes

Études prospectives randomisées négatives/ne permettant pas de conclure à une efficacité du rituximab
- Polymyosites et dermatomyosites
- Lupus érythémateux systémique
- Syndrome de Gougerot-Sjögren
- Neuropathies périphériques avec anticorps anti-MAG

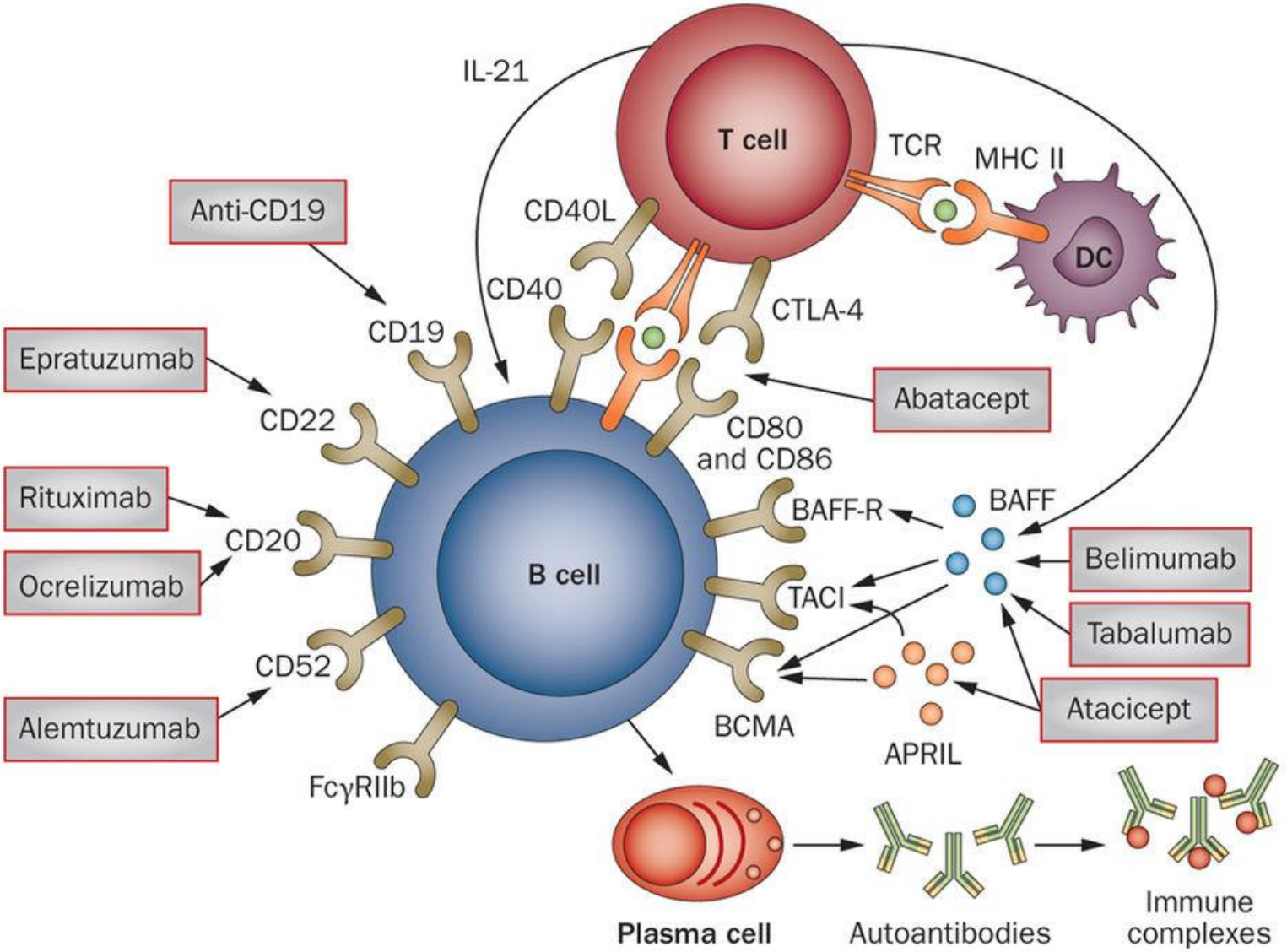
Études prospectives ouvertes
- Micro-angiopathies thrombotiques
- Auto-anticorps anti-facteur VIII
- Pemphigus vulgaire
- Myasthénie aiguë

Études rétrospectives
- Déficit acquis en facteur Von Willebrand
- Neuromyélite optique (NMO)
- Glomérulonéphrite extra-membraneuse
- Érythroblastopénie auto-immune

ANCA : anticorps anti-cytoplasme de polynucléaire neutrophile ; MAG : glycoprotéine associée à la myéline.

Legendre P, Mouthon L Rev Med Int 2014

Emerging cell and cytokine targets in rheumatoid arthritis



Nature Reviews Rheumatology **10**, 77–88 (2014)

Essais prospectifs randomisés effectués avec le rituximab (Mabthera) dans la polyarthrite rhumatoïde

Étude	Nombre de patients	Critères d'inclusion	Principaux résultats
Edwards *et al.* [1]	161	Échec d'un traitement par MTX	• ACR50 à 24 semaines : 43 % rituximab (Mabthera®) 1 000 mg + méthotrexate 41 % rituximab (Mabthera®) 1 000 mg + cyclophosphamide (Endoxan®) 13 % méthotrexate • rituximab (Mabthera®) + MTX > rituximab (Mabthera®) seul
Emery *et al.* [2]	465	Échec d'au moins un traitement de fond autre que le MTX	• ACR20 à 24 semaines : 55 % rituximab (Mabthera®) 500 mg 54 % rituximab (Mabthera®) 1 000 mg 28 % placebo • ACR70 rituximab (Mabthera®) 1 000 mg > 500 mg • prémédication par corticoïdes : ↘ réactions liées à la perfusion de rituximab (Mabthera®)
Cohen *et al.* [3]	520	Échec d'au moins un traitement par anti-TNFα	• ACR20 à 24 semaines : 51 % rituximab (Mabthera®) 1 000 mg 18 % placebo • rituximab (Mabthera®) *vs* placebo : ↗ ACR50/70, DAS 28, EULAR amélioration fonctionnelle ↘ progression radiologique

Rituximab dans la PR

- PR avec critères ACR 1987
- Echec d'au moins un DMARD autre que le MTX
- Sous MTX seul depuis au moins 16 sem dont 4 à dose stable ≥10mg/sem
- PR active définie par:
  - NAG et NAD ≥ 8 à l'inclusion
  - 2 des critères suivants:
    - CRP ≥ 15 mg/L
    - VS ≥ 30 mm/h
    - Raideur matinale > 45 minutes
- Facteur rhumatoide ≥ 20 IU/mL

Edwards, NEJM, 2004

PR: initiation du Rituximab (II)

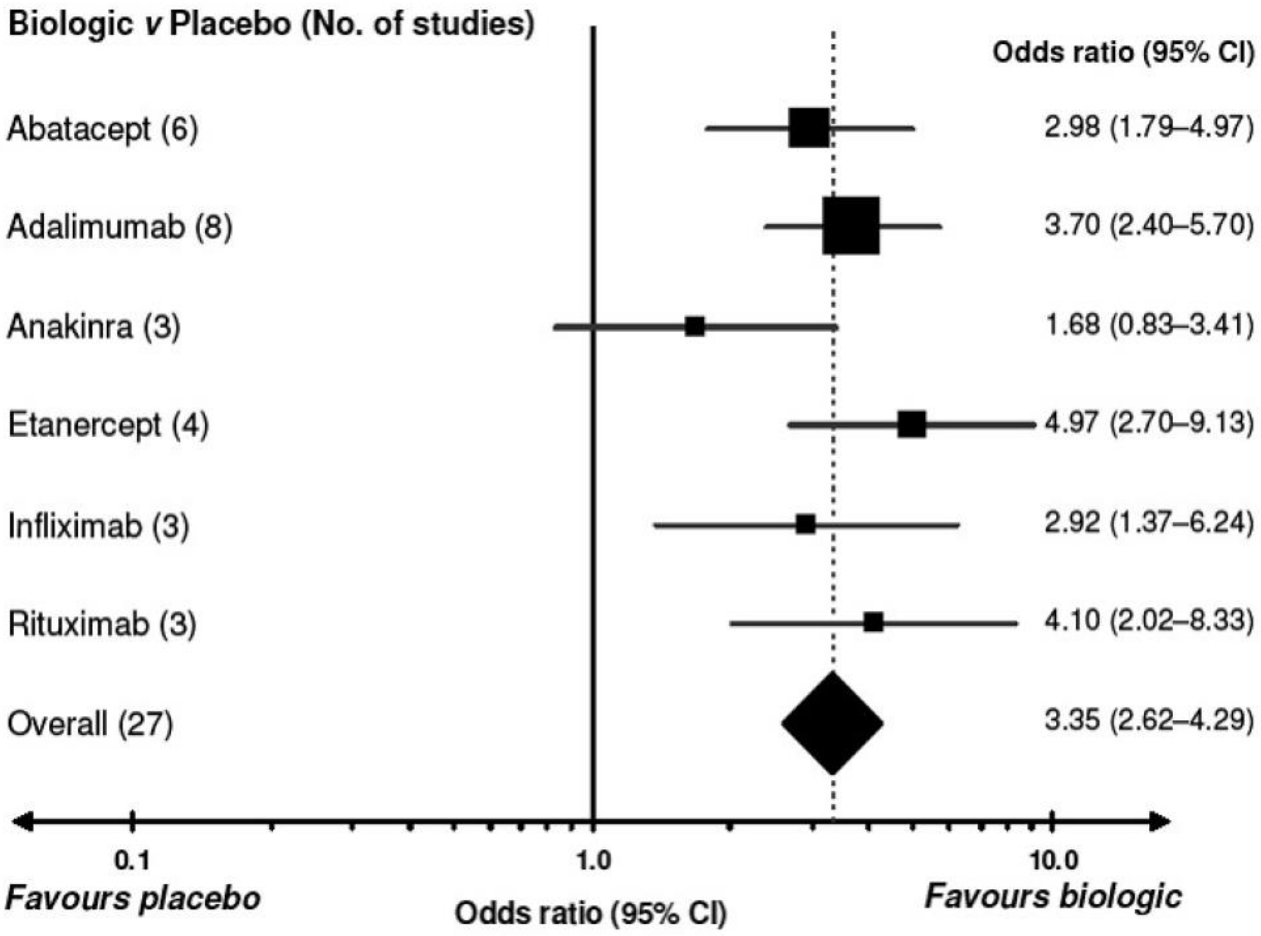
Fiches CRI. Revue Rhum. Dec 2007; 74 Hors série N°5

- La réponse thérapeutique observée est supérieure lorsque l'administration de rituximab est combinée au méthotrexate, à des posologies entre 10 et 25mg/semaine, comparée au rituximab seul.
- Même si le rituximab n'a reçu l'AMM qu'en association avec le méthotrexate, il faut noter que le rituximab en monothérapie a démontré une efficacité supérieure à celle du placebo.

Edwards JC, NEJM 2004

Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)

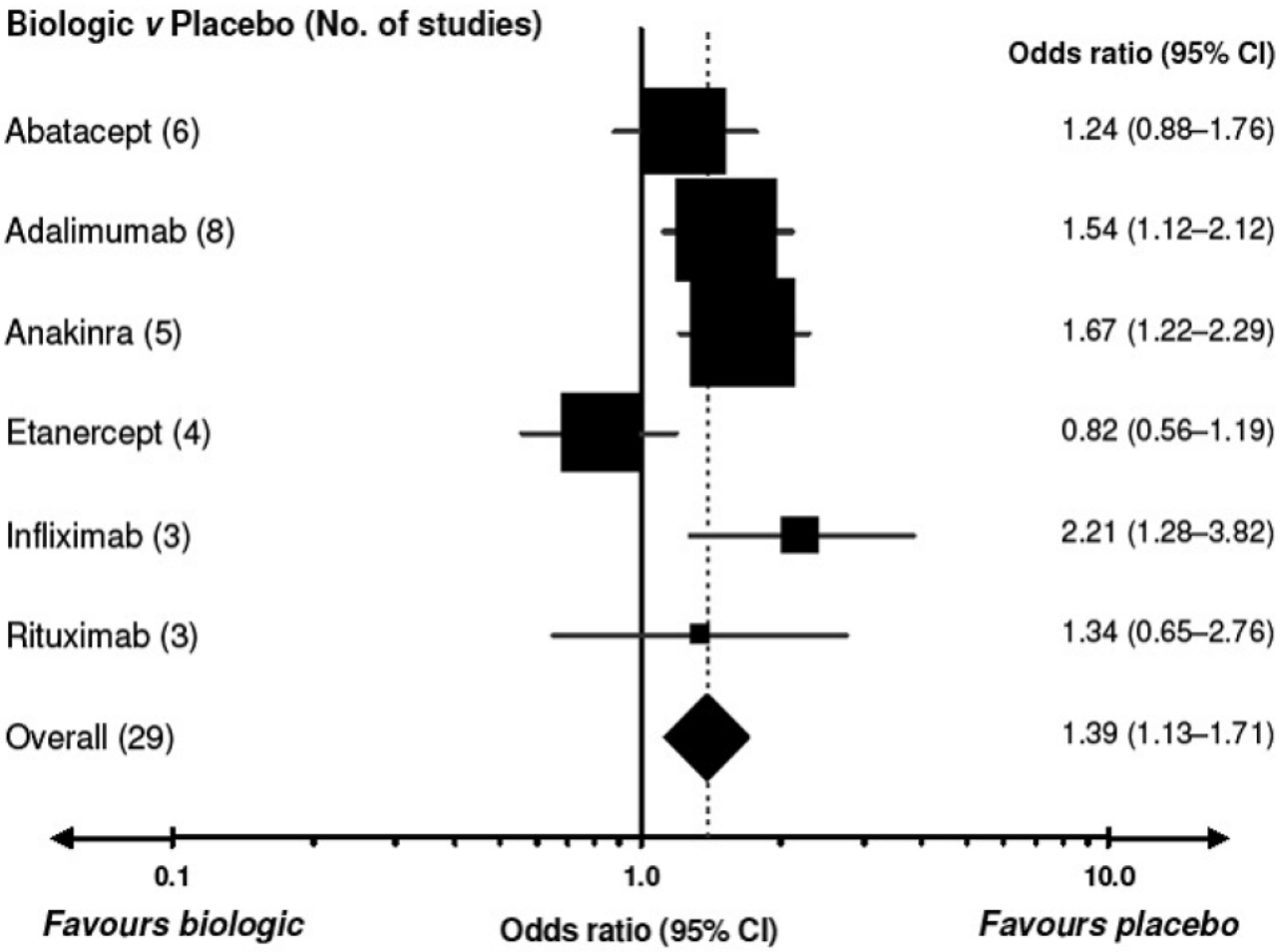
Comparison of each biologic to placebo for benefit (ACR 50)



Singh JA et al. Cochrane 2009

Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Review)

Comparison of each biologic to placebo for safety



Singh JA et al. Cochrane 2009

OPEN ACCESS Freely available online

PLOS ONE

Safety with Ocrelizumab in Rheumatoid Arthritis: Results from the Ocrelizumab Phase III Program

Paul Emery[1,2*], William Rigby[3], Paul P. Tak[4¤], Thomas Dörner[5], Ewa Olech[6], Carmen Martin[7], Laurie Millar[7], Helen Travers[7], Elena Fisheleva[7]

Objective: The objective was to determine the safety of ocrelizumab (OCR) in patients with rheumatoid arthritis (RA).

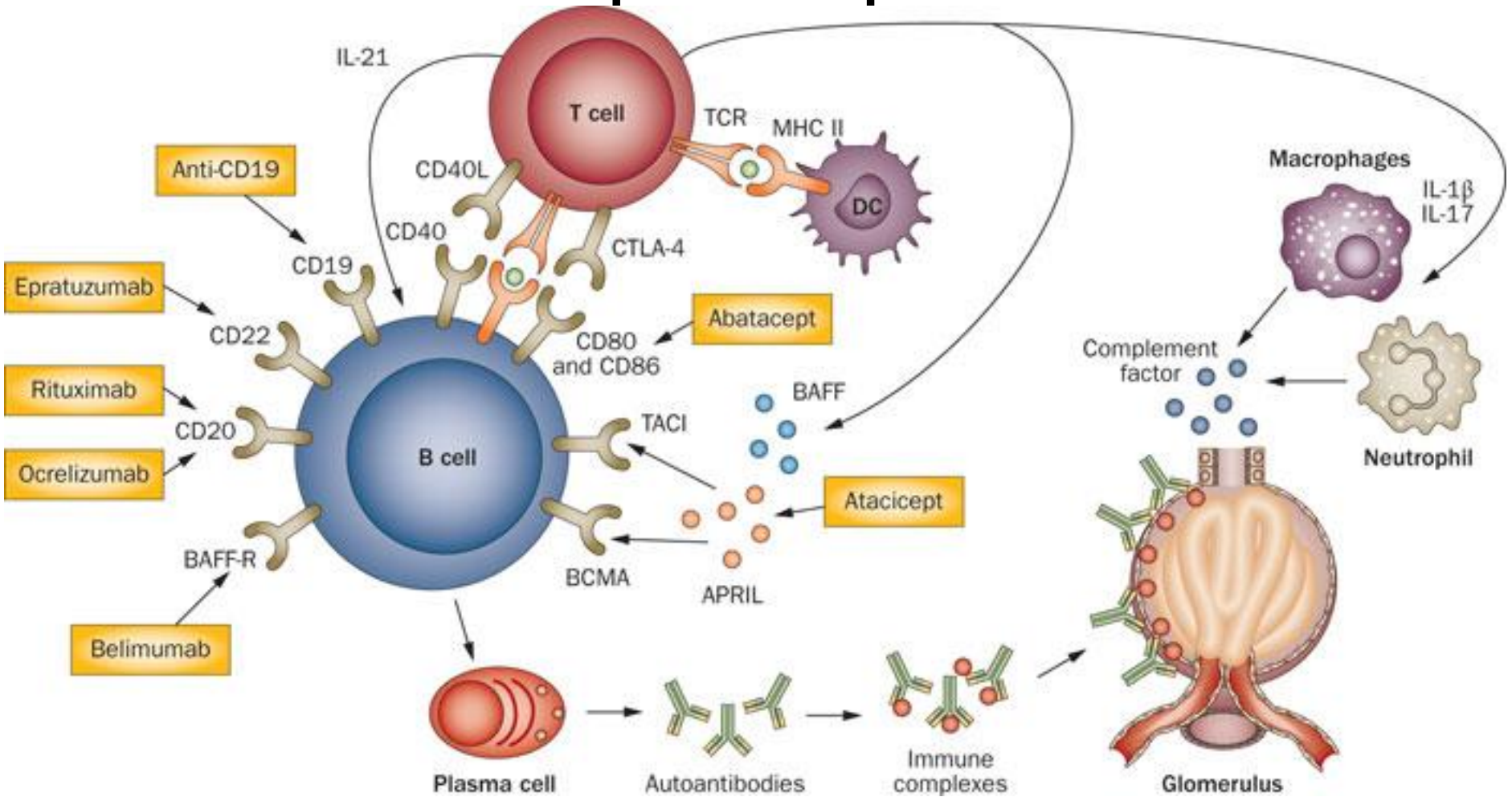
Methods: This was an analysis of the double-blind, placebo-controlled periods and long-term follow-up of 4 OCR phase III trials in RA (SCRIPT, STAGE, FILM and FEATURE). Safety data per study and the results of a meta-analysis of serious infectious events (SIEs) are presented.

Results: Overall, 868 patients received placebo, 1064 patients OCR 200 mg×2 (or 400 mg×1) (OCR200), and 827 patients OCR 500 mg×2 (OCR500) plus background methotrexate (MTX) at baseline and 24 weeks. During the double-blind, placebo-controlled periods, the incidence of adverse events and serious adverse events was comparable between the OCR+MTX and placebo +MTX groups. Infusion-related reactions were more common with OCR+MTX and decreased in frequency with subsequent infusions. Serious infusion-related reactions were rare (0.1%). Serious infections occurred more frequently with OCR500+MTX. In the meta-analysis, a statistically significant difference from placebo +MTX in incidence of SIEs per 100 patient-years of 2.4 (95% CI, 0.3–4.5) was observed with OCR500+MTX, but not with OCR200+MTX (0.6; 95% CI, −1.3 to 2.4). Patients recruited in Asia exhibited a higher risk of serious infections (hazard ratio, 1.78; 95% CI, 1.03–3.06). The incidence of human anti-human antibodies was <5%. Long-term follow-up indicated no differences in malignancy rates between the treatment groups. There was no apparent difference in time to B-cell repletion between the OCR dose groups.

Conclusions: In placebo-controlled clinical trials of RA, OCR500+MTX was associated with a higher risk of serious infections compared with placebo +MTX. The safety profile of OCR 200+MTX was comparable with placebo+MTX.

- Higher risk of severe infection !!!

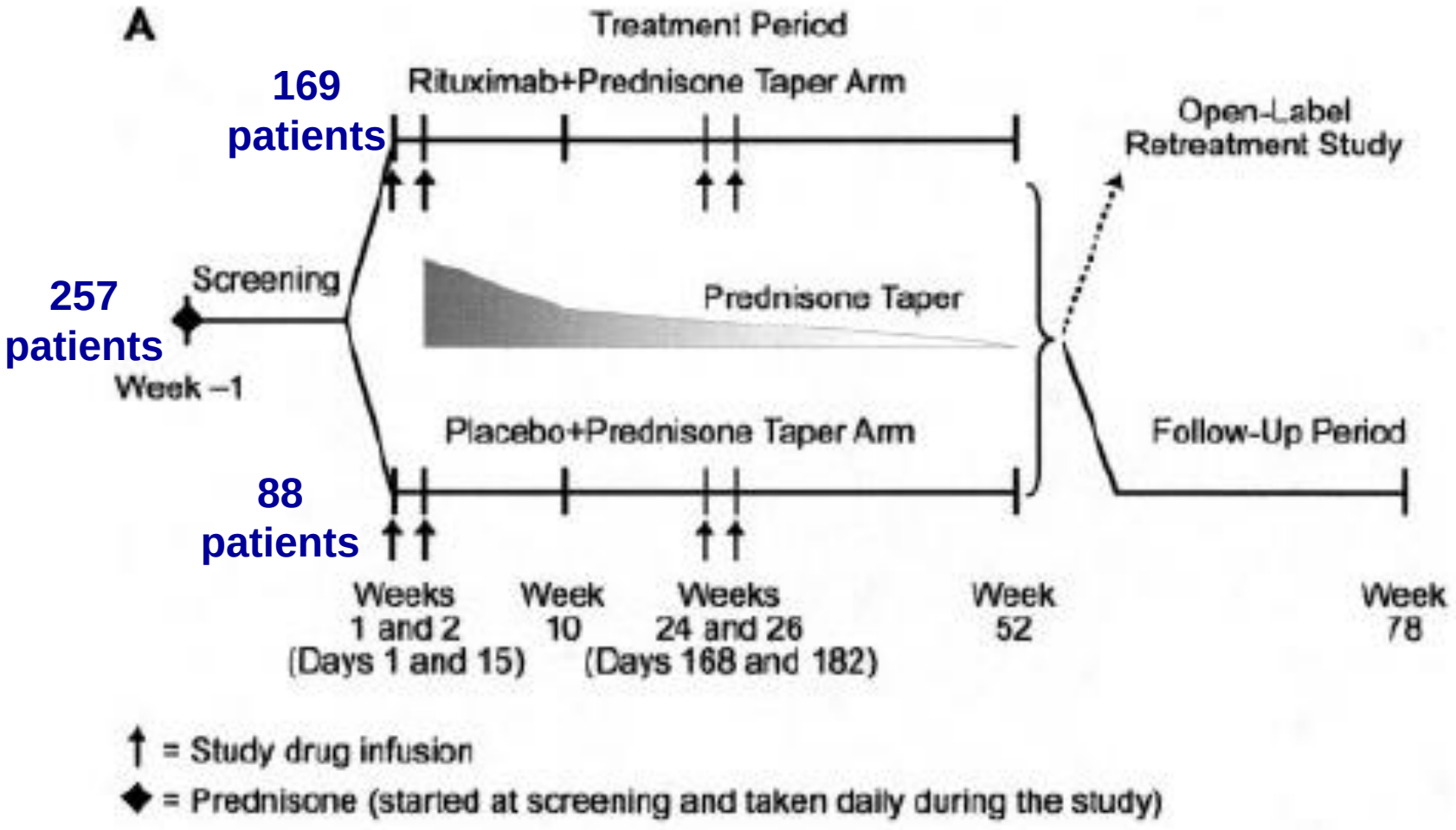
Potential B-cell-targeted therapies for lupus nephritis.



•Jul 2012 Nature Reviews Nephrol

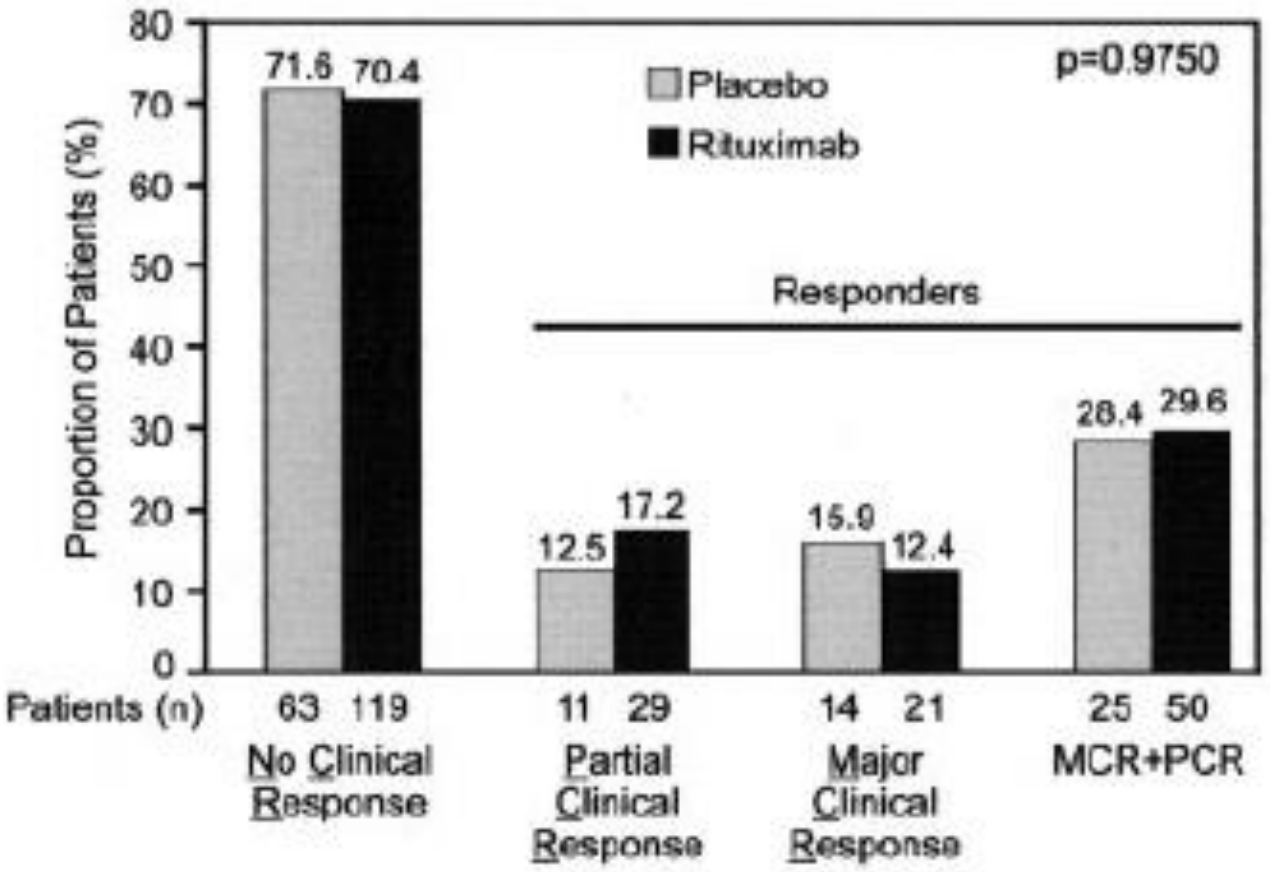
EXPLORER (I)

Efficacy of rituximab in moderately to severely active SLE



Merrill JT Arthritis Rheum 2010

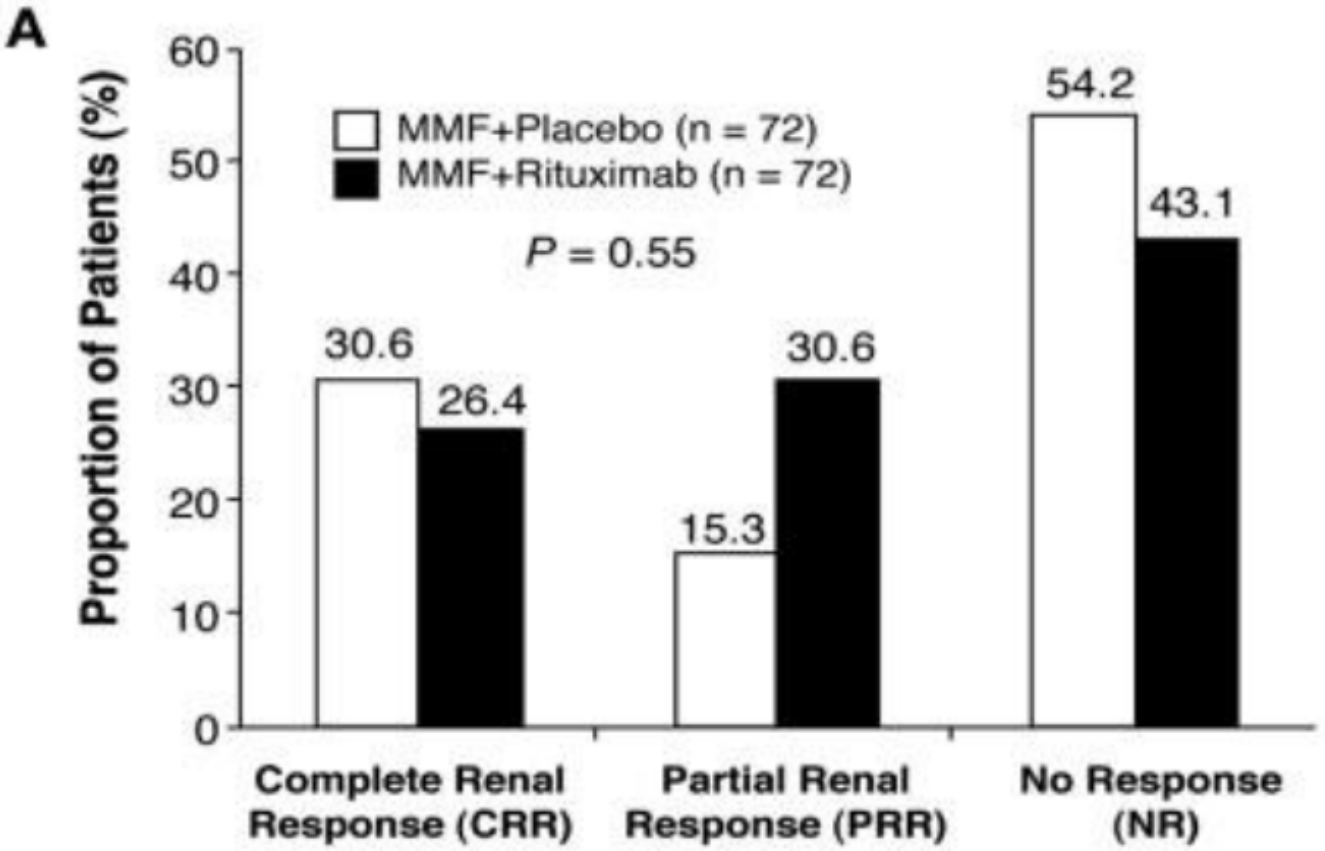
Proportion of patients experiencing a major clinical response (MCR), a partial clinical response (PCR), and no clinical response (NCR) at 52 weeks



Merrill JT Arthritis Rheum 2010

Lunar 2012

Rituximab



Arthitis and Rheum, 2012,64:1215-1226

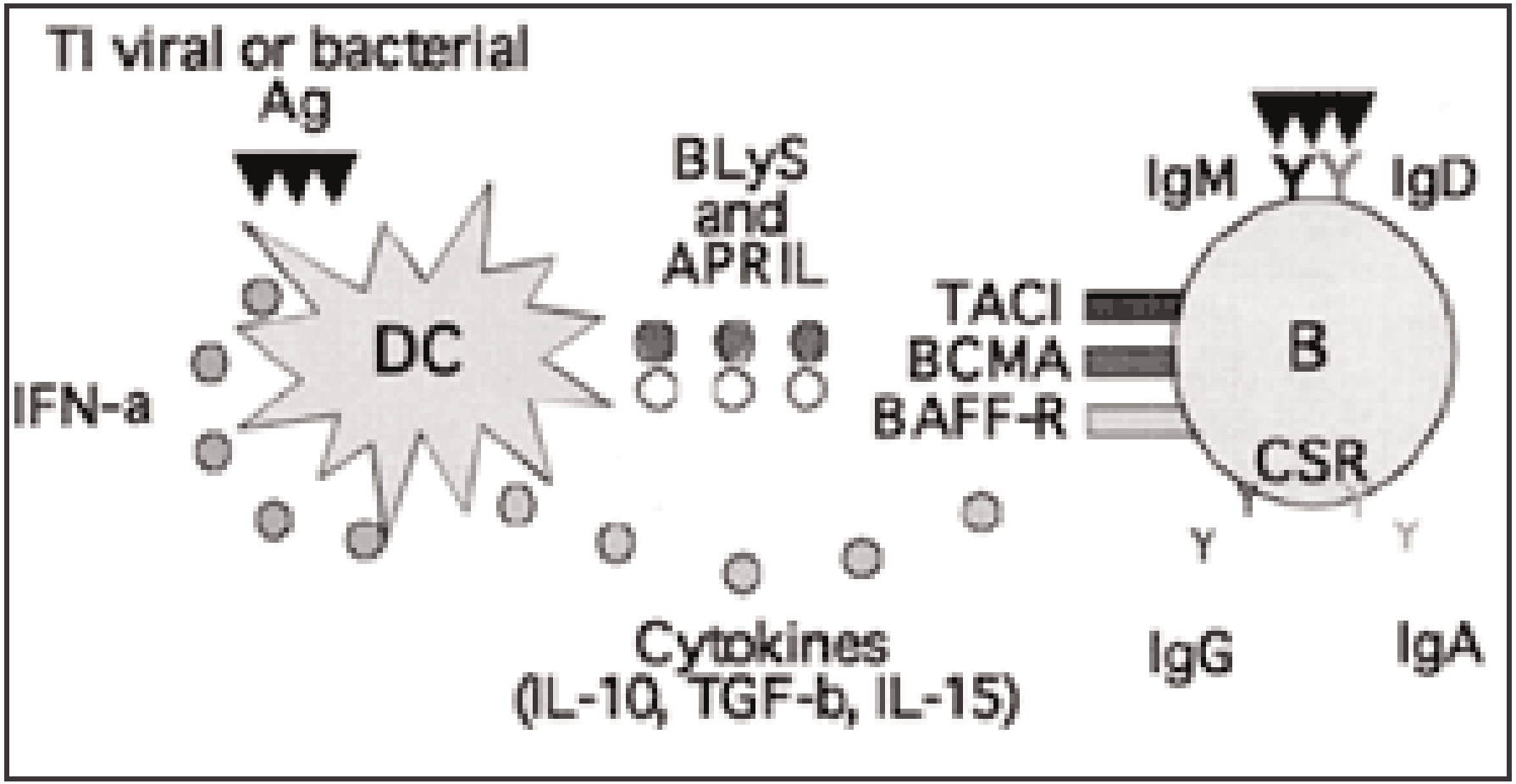
B-cell-depletion therapy in SLE--what are the current prospects for its acceptance?

Favas C, Isenberg DA.

Nat Rev Rheumatol. 2009 Dec;5(12):711-6.

- The failure of rituximab, a monoclonal antibody that induces B-cell depletion, to meet its primary and secondary end points in trials of nonrenal SLE (EXPLORER) and renal (LUNAR) lupus nephritis has been disappointing given the success reported in many open-label studies. Concluding that B-cell-depletion therapy is not effective in SLE seems rather extreme.
- Further analysis of the as-yet unpublished results and their comparison with data from published studies might provide insight into whether B-cell depletion will eventually be accepted as a useful approach for the treatment of SLE.

B lymphocyte stimulator (BLyS)



Litinskiy et al. Nat Immunol. 2002; 3:822-9

Belimumab

- BLISS 52
  - Randomised, double-blind, placebo-controlled
  - 867 patients
  - Moderate degree of SLE activity
    - Only seropositive patients
    - Exclusion of renal and CNS lupus
  - Limitated background therapy
    - more strictly controlled and time limited
  - SOC -1mg/kg– 10mg/kg – D1/D14/D28/W4
  - Multicentre – Worldwild
  - Response W52
  - Outcome measurement
    - composite endpoint, SLE responder index (SRI)

Benlysta (belimumab): anti-BAFF in SLE

- Seropositive SLE patients (ie, antinuclear antibody positive and/or anti-DNA positive) without active nephritis or active central nervous system disease were enrolled in two phase II/III studies (BLISS-52 and BLISS-76) and treated with placebo, 1 mg/kg of anti-BAFF, or 10 mg/kg of anti-BAFF.
- Primary endpoint: SRI (SLE Responder Index),
- Both studies showed superiority of the 10 mg/kg dose to placebo at 12 months (56.7% of patients have shown improvement when treated with a 10 mg/kg dose of belimumab in addition to standard treatment as opposed to 43.6% improvement under standard treatment and placebo).
- Benlysta (belimumab): agreement US FDA (july 2011).

Wallace DJ *et al. Arthritis Care Res (Hoboken)* 2009 ; **62** : 580 – 1 .
Petri M *et al*. *Arthritis Rheum* 2010;**62**:S190 (abstract).

Only three drugs were FDA-approved for the treatment of SLE:

Prednisone

Aspirin

Hydroxychloroquine

Belimumab efficacy is 'mild' but market potential still great: anticipating us approval of the first lupus drug since 1957.

Weintraub B. BioDrugs. 2011 Jun 1;25(3):203-5.

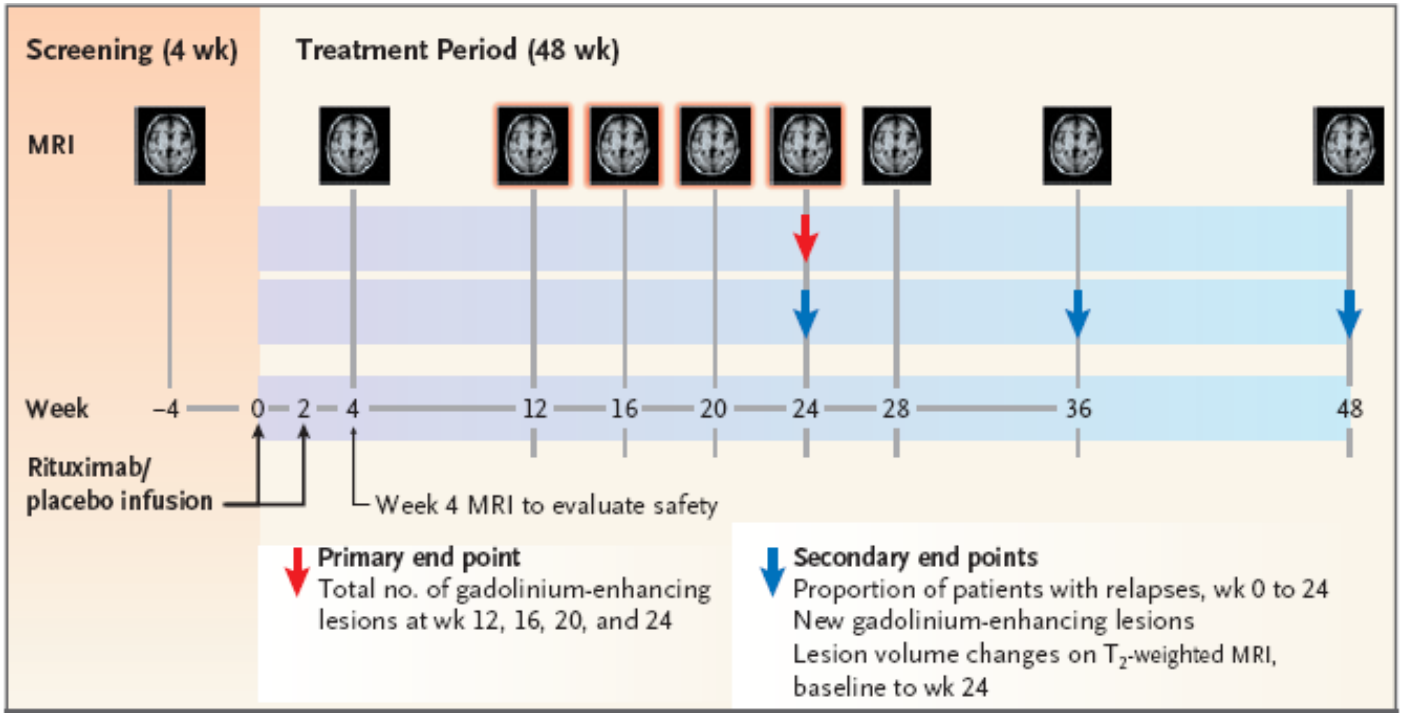
Sclérose en plaques

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

B-Cell Depletion with Rituximab in Relapsing–Remitting Multiple Sclerosis

Stephen L. Hauser, M.D., Emmanuelle Waubant, M.D., Ph.D., Douglas L. Arnold, M.D., Timothy Vollmer, M.D., Jack Antel, M.D., Robert J. Fox, M.D., Amit Bar-Or, M.D., Michael Panzara, M.D., Neena Sarkar, Ph.D., Sunil Agarwal, M.D., Annette Langer-Gould, M.D., Ph.D., and Craig H. Smith, M.D., for the HERMES Trial Group*



Rituximab for relapsing-remitting multiple sclerosis

- One trial involving 104 adult RRMS patients This trial evaluated rituximab as monotherapy versus placebo, with a single course of 1000 mg intravenous rituximab (on day 1 and day 15).
- Patients receiving rituximab had a significant reduction in total number of gadolinium-enhancing lesions at week 24 (mean number 0.5 versus 5.5; relative reduction 91%) and in annualised rate of relapse at week 24 (0.37 versus 0.84) but not at week 48 (0.37 versus 0.72).
- There is not sufficient evidence to support the use of rituximab as a disease-modifying therapy for RRMS because only one RCT was included.
- The potential benefits of rituximab for treating RRMS need to be evaluated in large-scale studies that are of high quality along with long-term safety

He D et al. Cochrane 2013

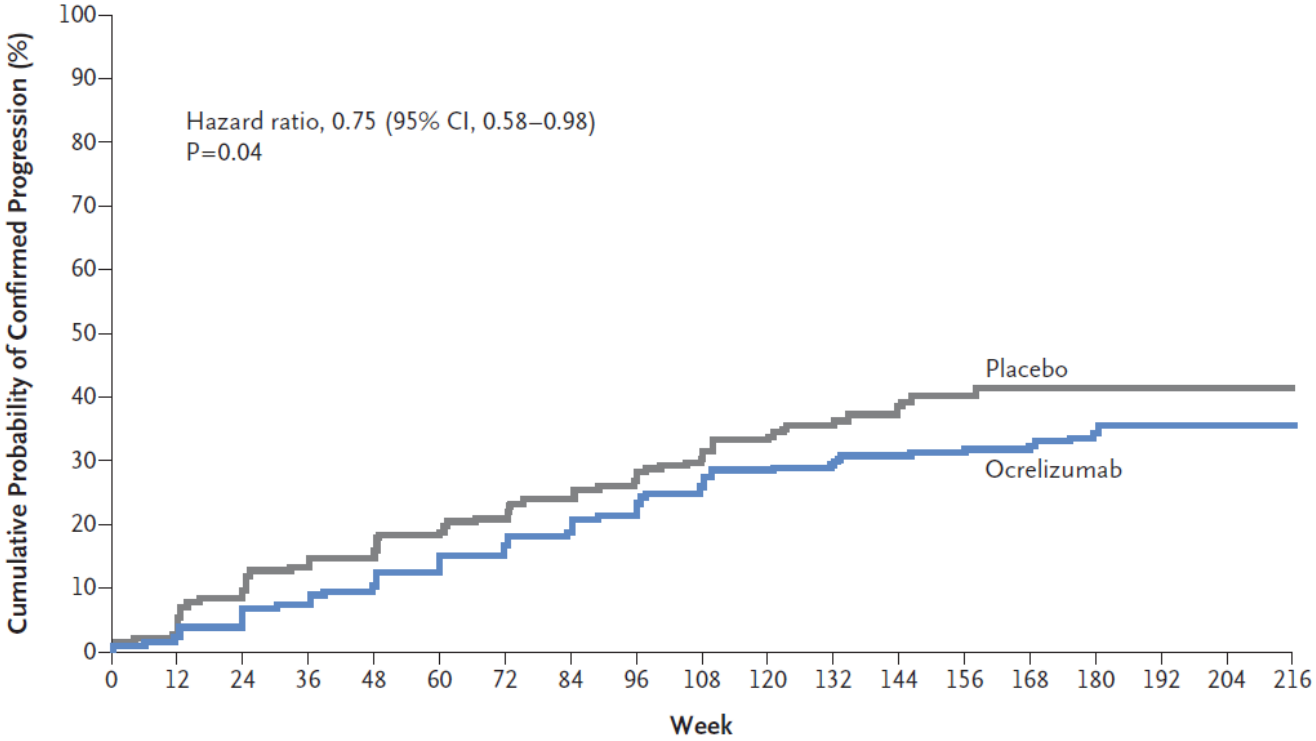
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 19, 2017 VOL. 376 NO. 3

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis

X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, J. de Seze, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, K.W. Rammohan, K. Selmaj, A. Traboulsee, A. Sauter, D. Masterman, P. Fontoura, S. Belachew, H. Garren, N. Mairon, P. Chin, and J.S. Wolinsky, for the ORATORIO Clinical Investigators*

B 24-Wk Confirmed Disability Progression



No. at Risk

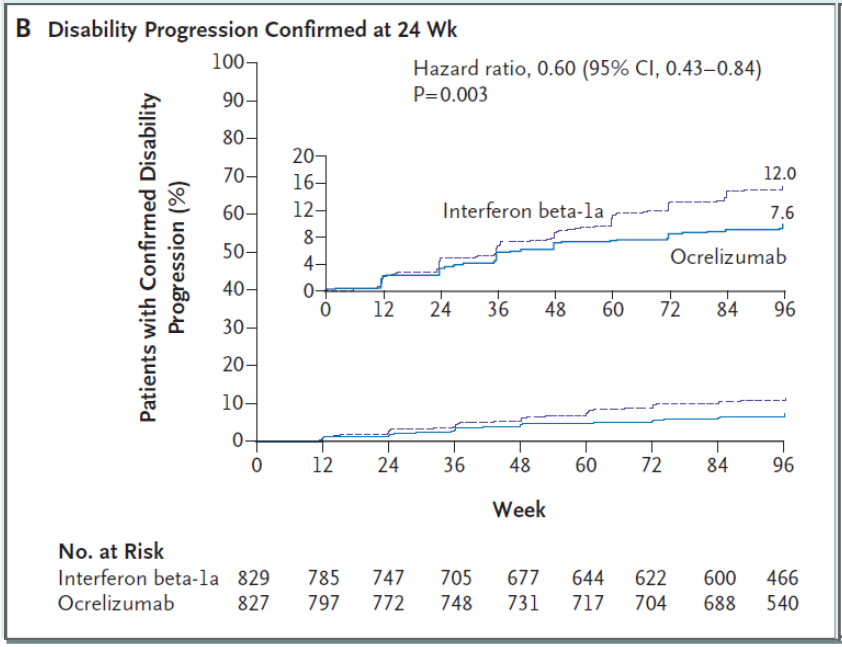
Placebo	244	234	214	202	193	183	176	166	157	148	139	125	89	70	50	33	22	7	2
Ocrelizumab	487	465	454	437	421	397	384	367	349	330	313	290	217	177	144	87	50	21	7

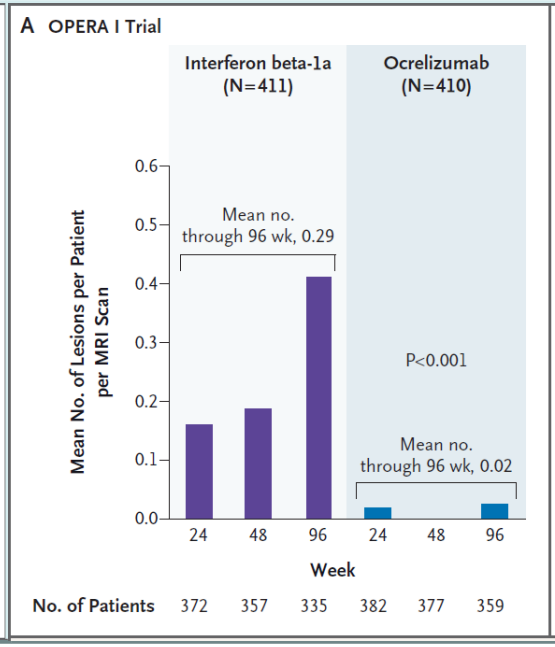
The NEW ENGLAND JOURNAL of MEDICINE

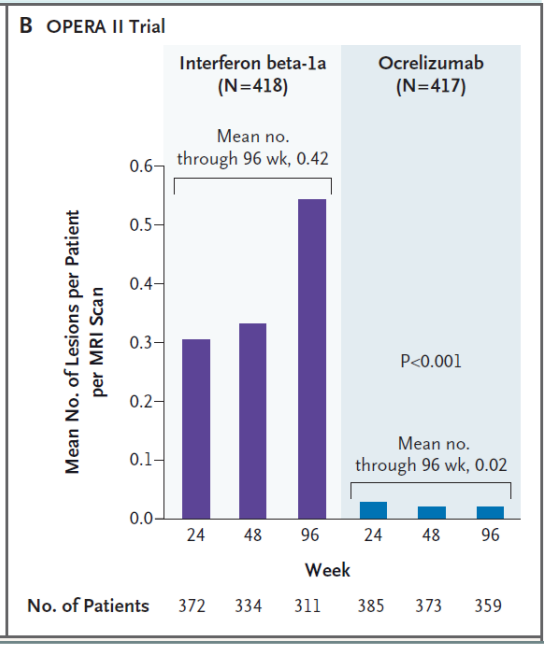
ORIGINAL ARTICLE

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis

S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.-P. Hartung, B. Hemmer, F. Lublin, X. Montalban, K.W. Rammohan, K. Selmaj, A. Traboulsee, J.S. Wolinsky, D.L. Arnold, G. Klingelschmitt, D. Masterman, P. Fontoura, S. Belachew, P. Chin, N. Mairon, H. Garren, and L. Kappos, for the OPERA I and OPERA II Clinical Investigators*







Among patients with relapsing multiple sclerosis, ocrelizumab was associated with lower rates of disease activity and progression than interferon beta-1a over a period of 96 weeks. Larger and longer studies of the safety of ocrelizumab are required.

Ocrelizumab in multiple sclerosis

- Roche's OCREVUS (ocrelizumab) approved in the European Union for relapsing forms of multiple sclerosis and primary progressive multiple sclerosis
- First and only approved disease-modifying medicine for people in the European Union (EU) with early primary progressive multiple sclerosis (PPMS)
- An important new treatment option for people with active relapsing forms of MS (RMS) that significantly suppressed three major markers of disease activity and disability progression compared with Rebif (interferon beta-1a)
- A favourable benefit-risk profile demonstrated in three large Phase III studies with a diverse patient population, including those early in the disease
- OCREVUS is administered by intravenous infusion every six months, with no routine testing between dosing

Natalizumab in multiple sclerosis

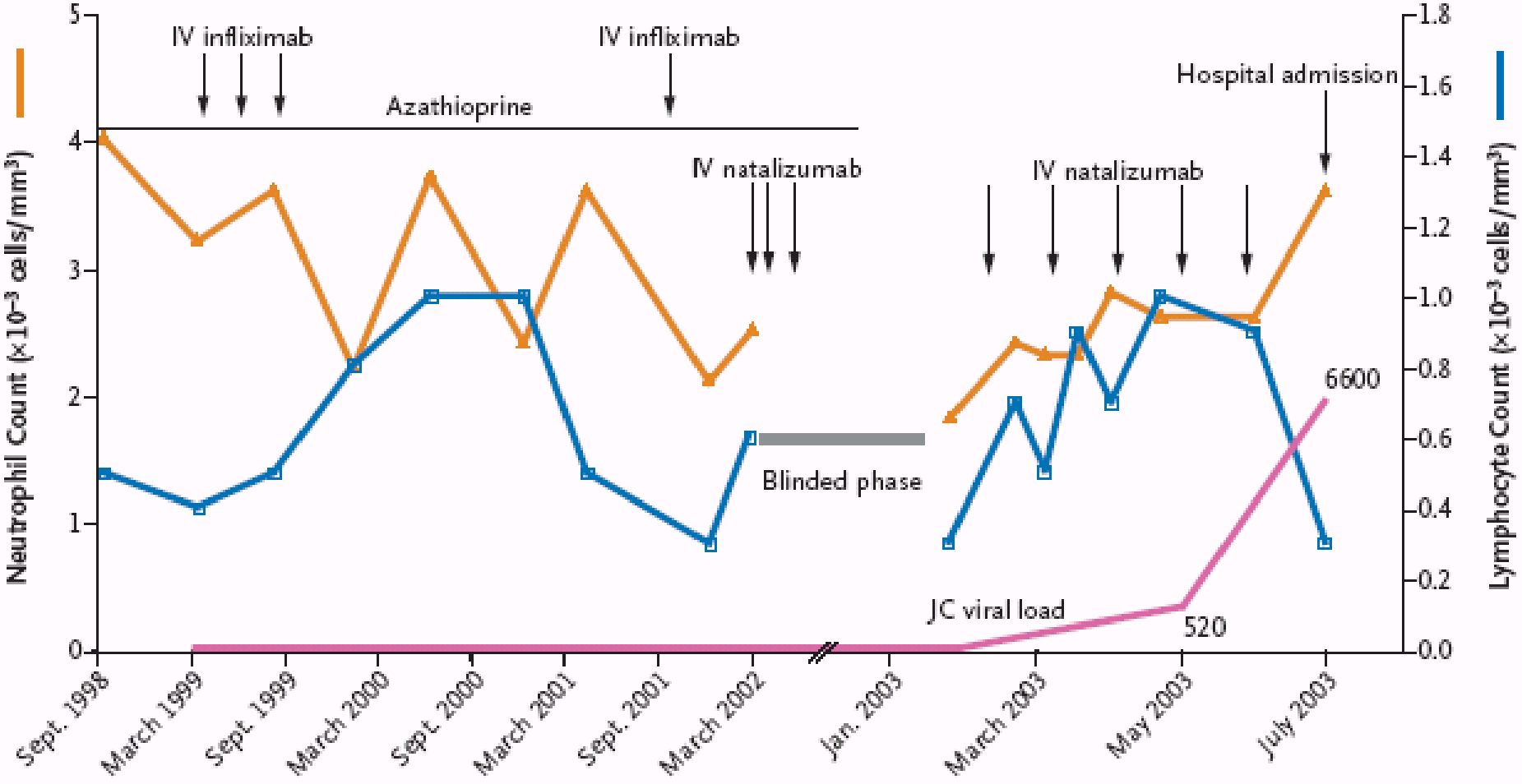
Table 3. Relapses during and after Treatment.

Relapses	Placebo	3 mg of Natalizumab/kg	6 mg of Natalizumab/kg	P Value	
				Placebo vs. 3 mg of Natalizumab	Placebo vs. 6 mg of Natalizumab
During treatment					
Total no. of patients	71	68	74		
Total no. of relapses	36	18	15		
No. of objective relapses	18	3	8		
No. of patients with a relapse	27	13	14	0.02	0.02
No. of patients with an objective relapse	15	3	8	0.004	0.11
No. of patients requiring corticosteroid treatment	22	5	7	<0.001	0.002
After treatment					
Total no. of patients	69	67	67		
Total no. of relapses	24	24	26		
No. of objective relapses	11	10	4		
No. of patients with a relapse	24	21	23	0.72	1.00
No. of patients with an objective relapse	11	8	4	0.62	0.16

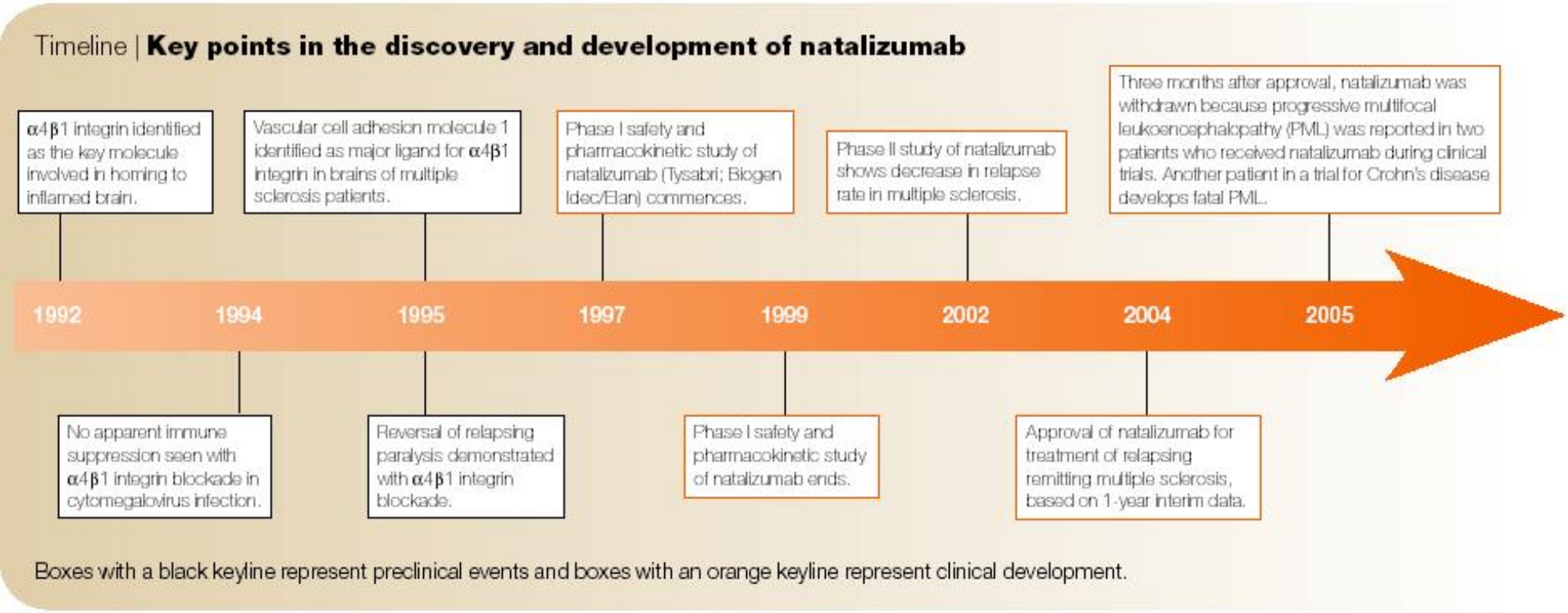
Miller DH, NEJM, 2003

Progressive Multifocal Leukoencephalopathy after Natalizumab Therapy for Crohn's Disease

Gert Van Assche, M.D., Ph.D., Marc Van Ranst, M.D., Ph.D.,
Raf Sciot, M.D., Ph.D., Bénédicte Dubois, M.D., Ph.D.,
Séverine Vermeire, M.D., Ph.D., Maja Noman, M.D.,
Jannick Verbeeck, M.Sc., Karel Geboes, M.D., Ph.D.,
Wim Robberecht, M.D., Ph.D., and Paul Rutgeerts, M.D., Ph.D.



Natalizumab



Natalizumab was approved in 2004 by the FDA. It was subsequently withdrawn from the market by its manufacturer after it was linked with three cases of the rare neurological condition progressive multifocal leukoencephalopathy (PML) when administered in combination with interferon beta-1a.
The drug was returned to the US market in 2006 under a special program.
By January 2010, 31 cases of PML were attributed to natalizumab. The FDA did not withdraw the drug from the market because its clinical benefits outweigh the risks involved. In the European Union, it has been approved for human use only for the treatment of multiple sclerosis and only then as a monotherapy

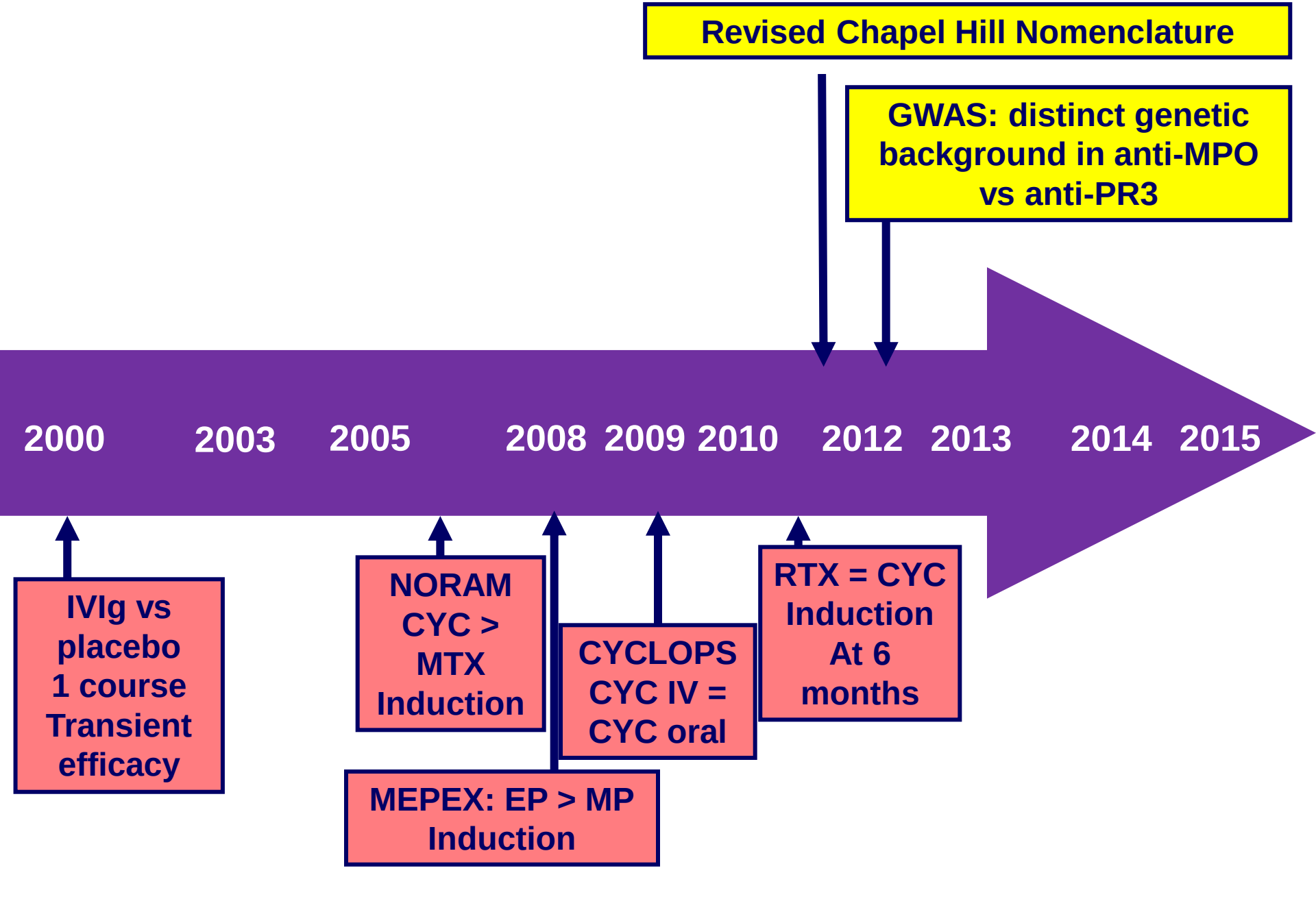
Vascularites ANCA positives

Therapeutic strategy in ANCA-associated vasculitides

State of the art in 2000

- **Induction**
  - ✓ Glucocorticoids
  - ✓ Cyclophosphamide (IV, oral)
- **Maintenance**
  - ✓ Cyclophosphamide
  - ✓ Azathioprine

Therapeutic strategy in AAV: 2000 - 2017



RAVE

197 patients

1 à 3 pulse methylprednisolone

Prednisone + CYC oral, 3 à 6 months + placebo Rituximab	Rituximab 375 X 4 + prednisone + placebo CYC
Azathioprine 12-15 mois	Placebo

Stone JH et al. N Engl J Med 2010; 363: 221-32

RITUXVAS

44 patients

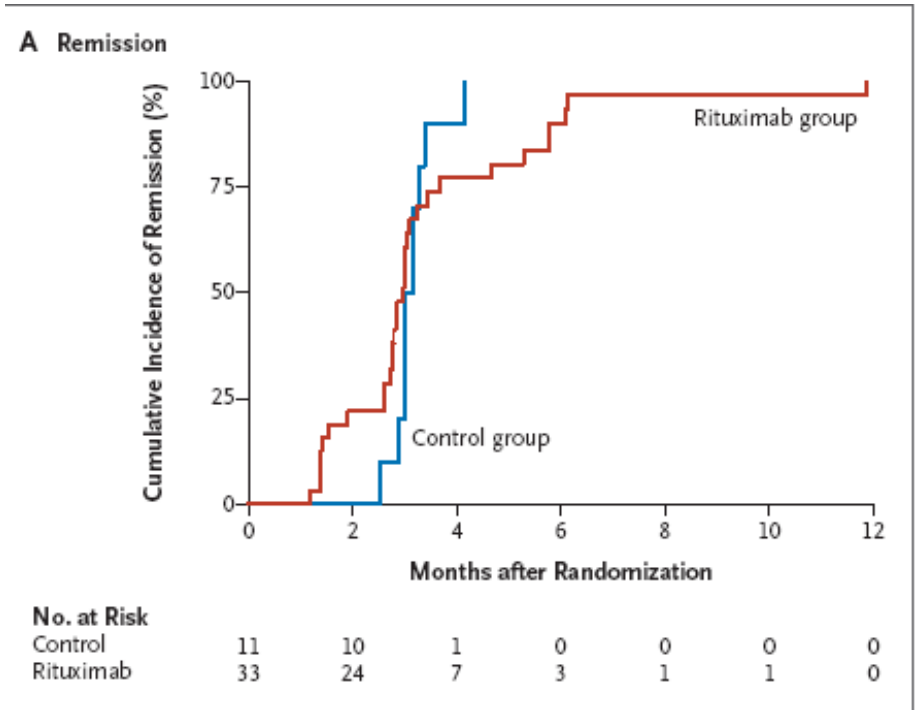
11 patients

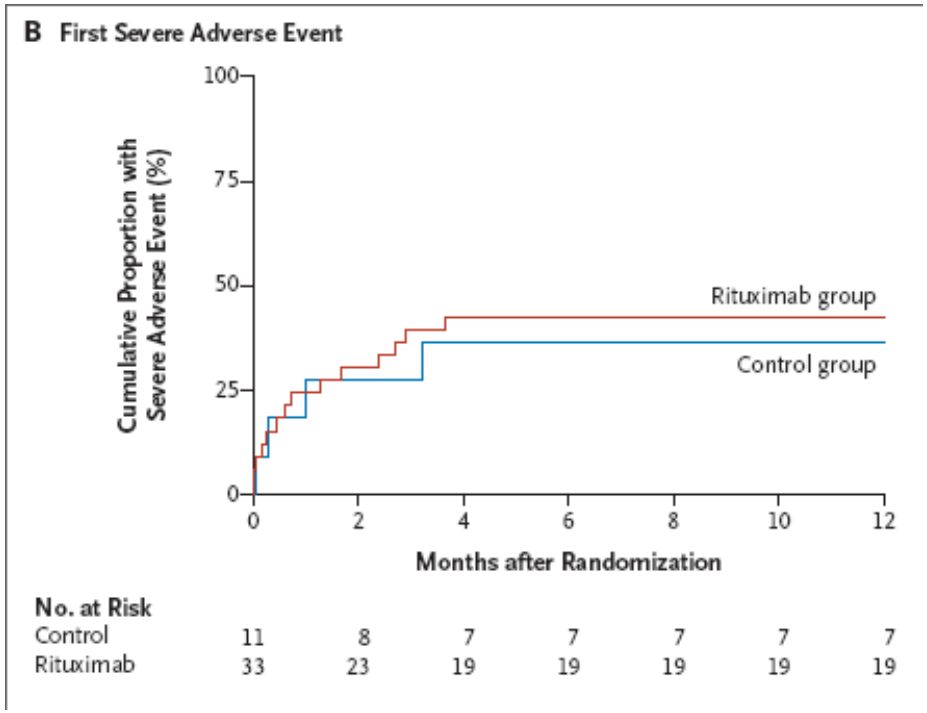
33 patients

Prednisone + CYC IV, 3 à 6 months	Rituximab 375 x 4 prednisone 2 bolus CYC
Azathioprine	Nothing

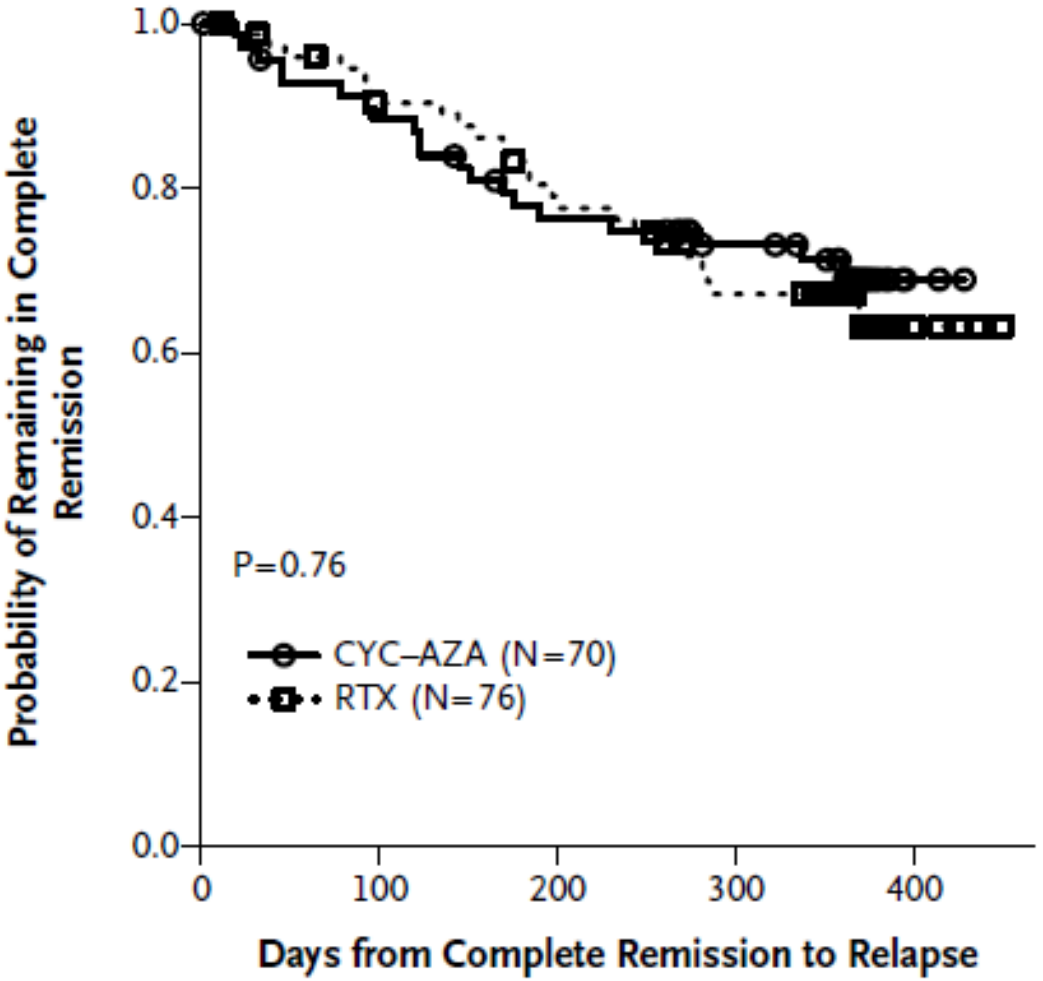
Jones RB et al. N Engl J Med 2010; 363: 211-20

RITUXVAS: Cumulative Incidence of Remission and Cumulative Proportion of Patients with a Severe Adverse Event.





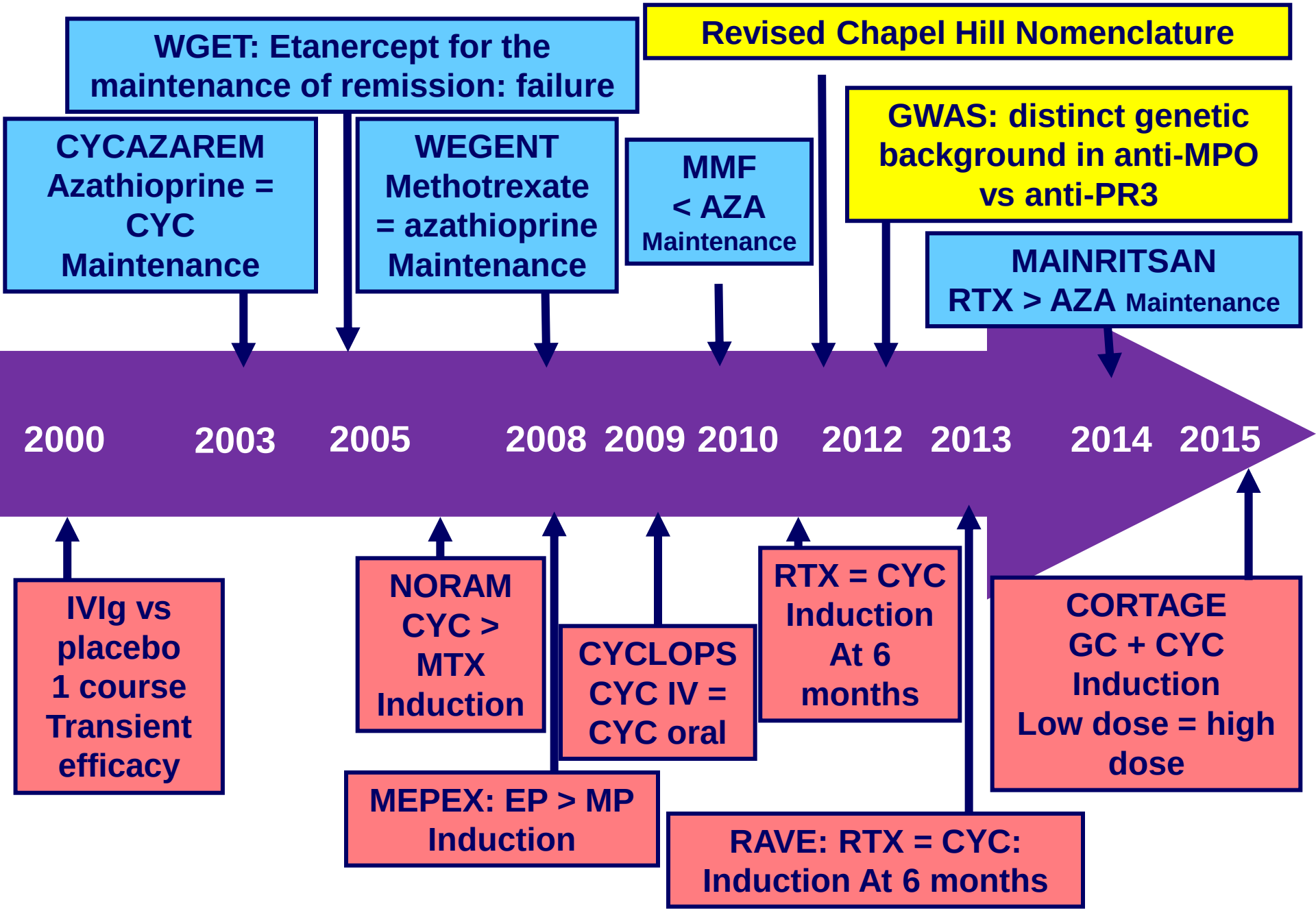
RAVE: Time to first relapse after complete remission according to treatment



No. at Risk					
CYC–AZA	70	61	51	43	3
RTX	76	65	55	45	5

Specks U et al. NEJM 2013

Therapeutic strategy in AAV: 2000 - 2017



MAINRITSAN trial

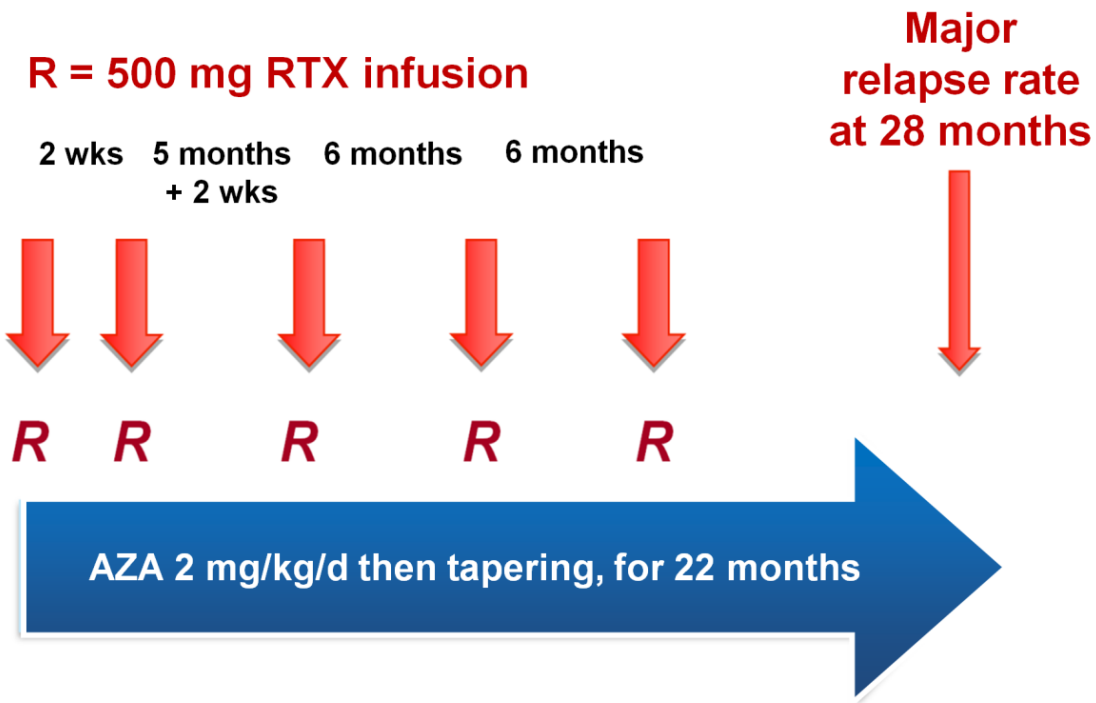
Induction therapy

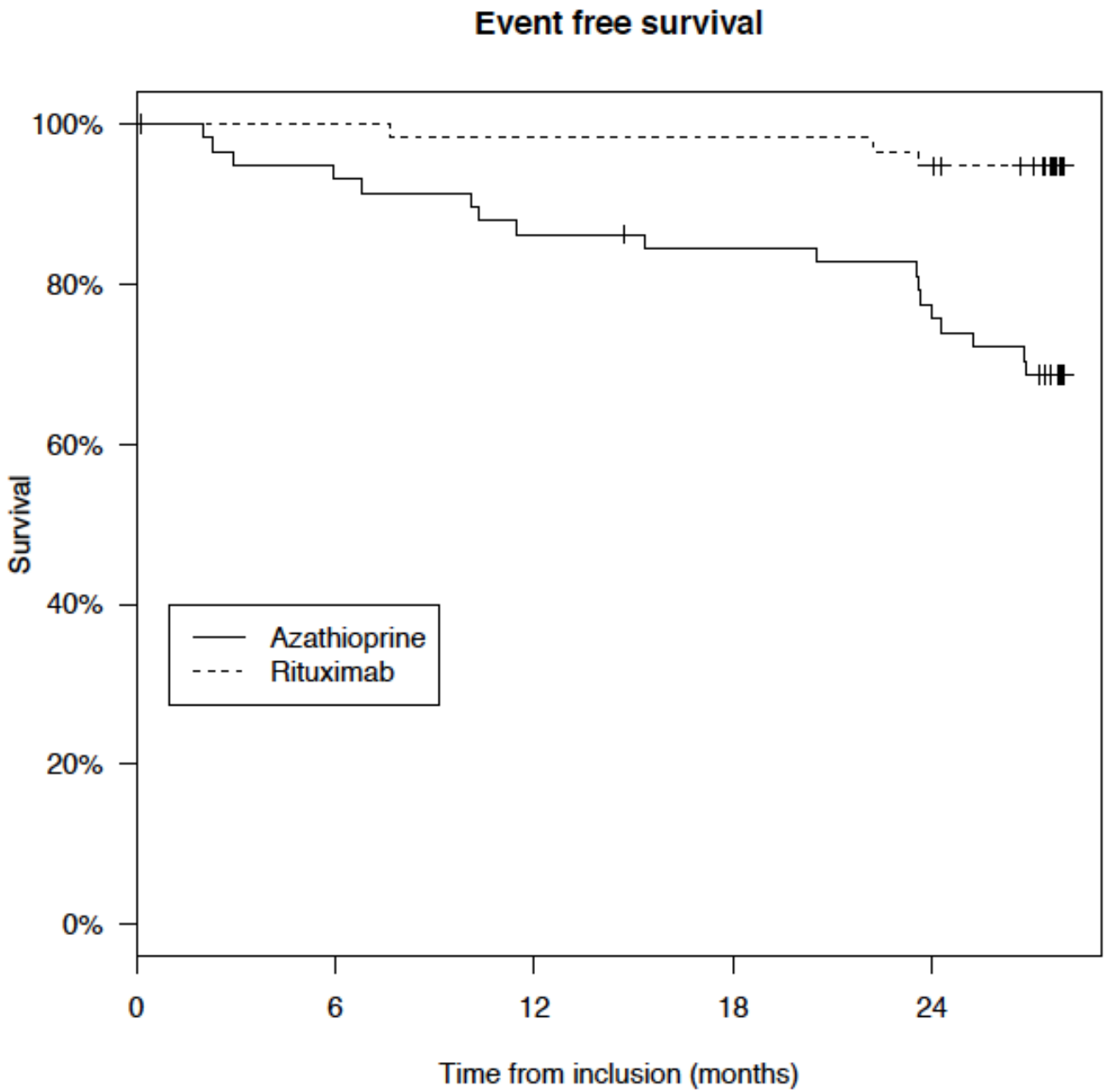
1 g x 3 i.v. methylprednisolone

Prednisone (1 mg/kg/day)
then 20 mg/d at 3 months
then 10 mg/d at 6 months

CYC i.v.
0.6 g/m2 x 3 then 0.7 g/m2 x 3

Maintenance therapy



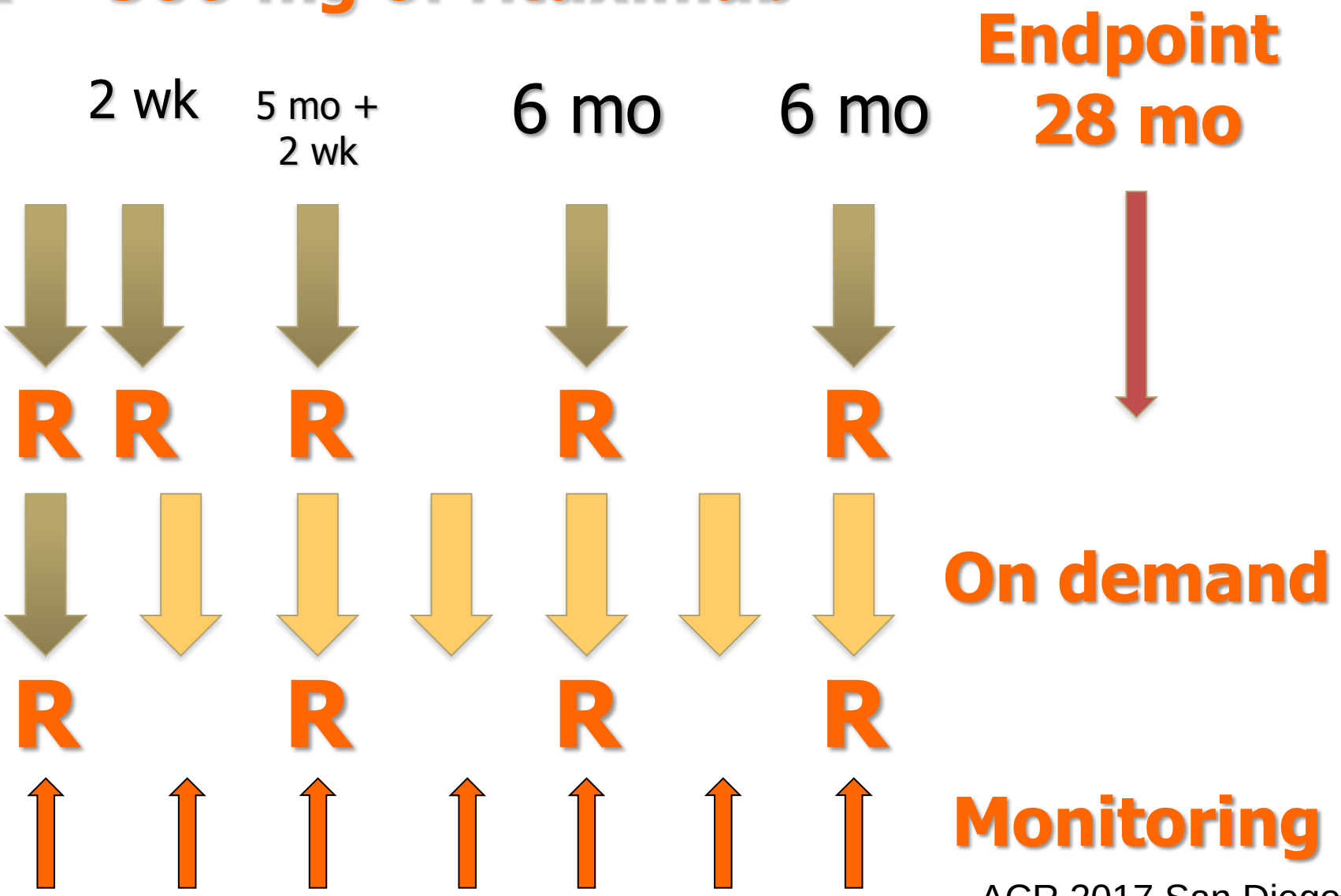


P = 0.002

Guillevin, NEJM 2014; 37: 1771-80

Maintenance treatment

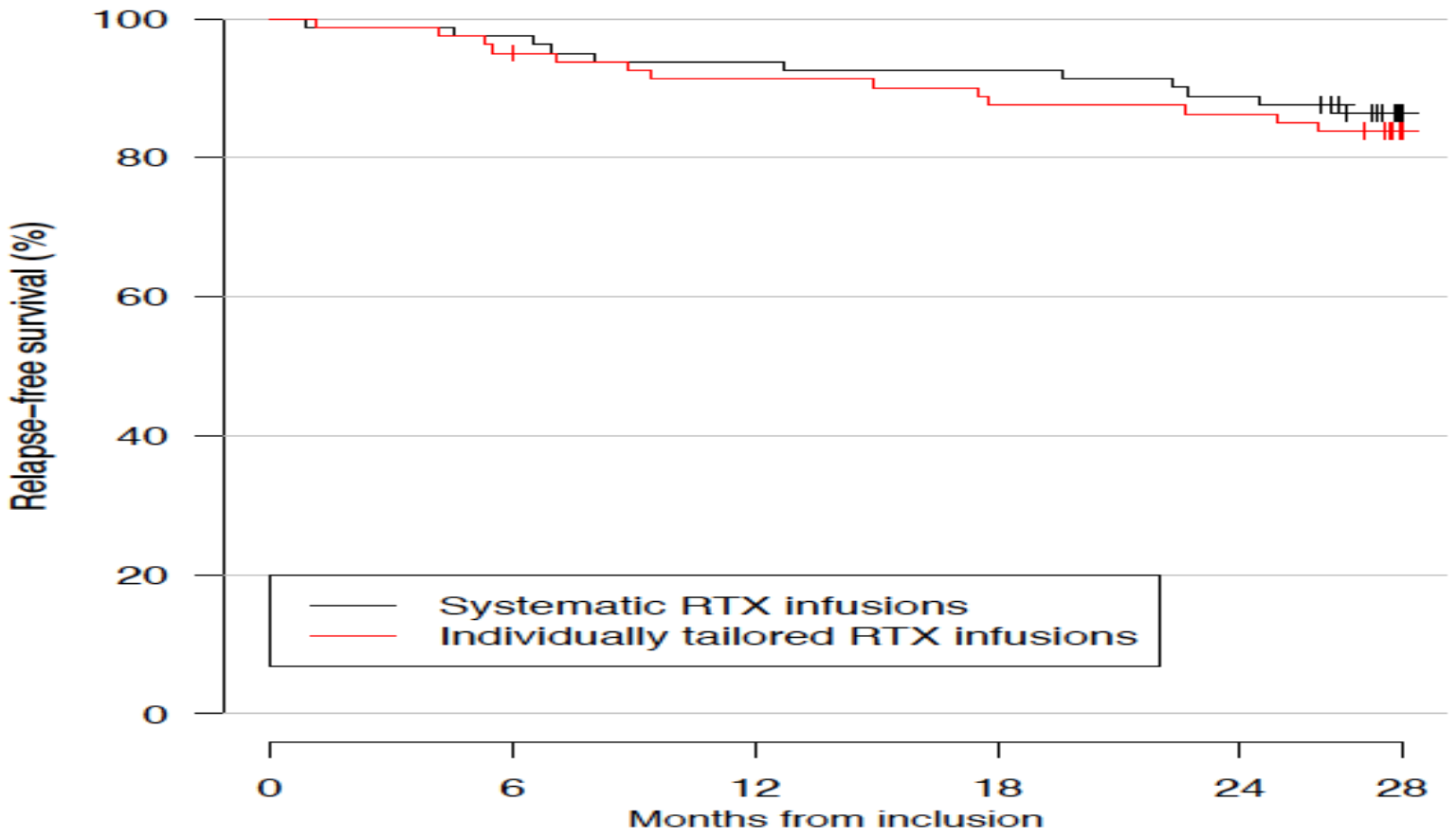
R = 500 mg of rituximab



MAINRITSAN 2

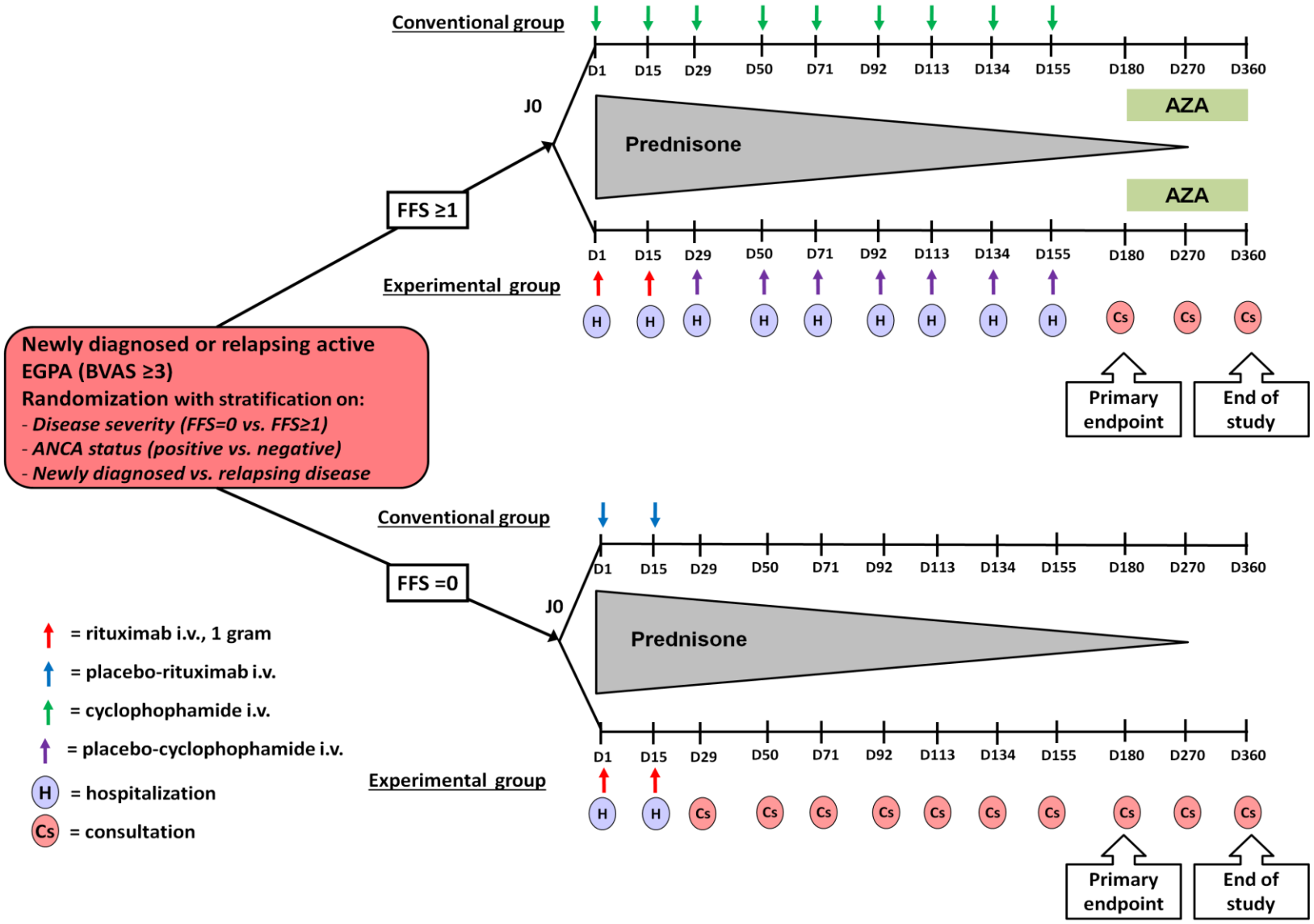
Parameter	Fixed dose	On demand
RTX infusions, n	**5**	**3**
Relapses	**17%**	**10%**
Major relapses	**7.4%**	**3.7%**

MAINRITSAN 2



ACR 2017 San Diego

REOVAS (EGPA)


Conventional group
D1 D15 D29 D50 D71 D92 D113 D134 D155 D180 D270 D360
J0
Prednisone
AZA
AZA
FFS ≥1
D1 D15 D29 D50 D71 D92 D113 D134 D155 D180 D270 D360
Experimental group
H H H H H H H H H Cs Cs Cs
Primary endpoint
End of study
Newly diagnosed or relapsing active EGPA (BVAS ≥3)
Randomization with stratification on:
- Disease severity (FFS=0 vs. FFS≥1)
- ANCA status (positive vs. negative)
- Newly diagnosed vs. relapsing disease
Conventional group
D1 D15 D29 D50 D71 D92 D113 D134 D155 D180 D270 D360
FFS =0
J0
Prednisone
D1 D15 D29 D50 D71 D92 D113 D134 D155 D180 D270 D360
Experimental group
H H Cs Cs Cs Cs Cs Cs Cs Cs Cs Cs
Primary endpoint
End of study
= rituximab i.v., 1 gram
= placebo-rituximab i.v.
= cyclophophamide i.v.
= placebo-cyclophophamide i.v.
H = hospitalization
Cs = consultation

Therapeutic strategy in ANCA-associated vasculitides
State of the art in 2017

- **Induction**
  - ✓ Glucocorticoids
  - ✓ Cyclophosphamide (IV, ~~oral~~)/Rituximab
  - ✓ Plasma exchanges
- **Maintenance**
  - ✓ ~~Cyclophosphamide~~
  - ✓ Azathioprine
  - ✓ Methotrexate
  - ✓ Rituximab

- **Avoid adverse events / prophylaxis of infections/ Vaccination**

Efficacy

Fcγ receptor type IIIA polymorphism influences treatment outcomes in patients with rheumatoid arthritis treated with rituximab

Objective To assess the association between a single nucleotide polymorphism in the gene of *FCGR3A* and the response to treatment with rituximab (RTX) in rheumatoid arthritis (RA).

Methods SMART. Among the 224 patients included, 111 could be genotyped and were included in an ancillary study of SMART.

Results Among the 111 patients, 90 (81%) were responders of whom 30 (27%) were good responders. V allele carriage was significantly associated with a higher response rate (91% of responders vs 70%, OR 4.6 (95% CI 1.5 to 13.6), p=0.006).

In multivariate analysis, V allele carriage was independently associated with response to RTX (OR 3.8 (95% CI 1.2 to 11.7), p=0.023).

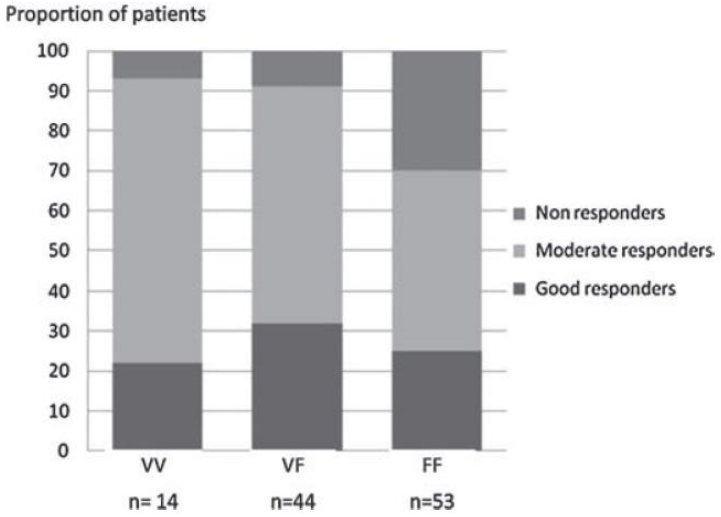


Figure 1 EULAR response rate according to FCGR3A genotype distribution. V, valine; F, phenylalanine.

Conclusion **The 158V/F polymorphism of *FCGR3A* seems to influence the response to RTX in patients with RA after failure, intolerance or contraindication to TNF blockers.**

Ruyssen-Witrand A et al. Ann Rheum Dis 2012

Quelle tolérance?

Prémédication

1. **Méthylprednisolone** 100 mg
2. **Polaramine** 1 Amp. *IVD.*
3. **Perfalgan** 1 gr. en perfusion de 10 mn

Rave: adverse events at 18 months

Table 2. Adverse Events through 18 Months.*

Variable	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Total (N=197)	P Value
Total no. of participant-months	1371.5	1331.9	2703.4	
Adverse events				
Total no. of events	1399	1420	2819	
Participants with ≥1 event — no. (%)	98 (99)	98 (100)	196 (99)	>0.99
Events/participant-mo	1.02	1.07	1.04	0.24
Serious adverse events				
Total no. of events	59	63	122	
Participants with ≥1 event — no. (%)	42 (42)	37 (38)	79 (40)	0.50
Events/participant-mo	0.04	0.05	0.05	0.63
Deaths — no. (%)†	2 (2)	2 (2)	4 (2)	
Participants with ≥1 episode of leukopenia of grade 2 or higher — no. (%)	5 (5)	23 (23)	28 (14)	<0.001
Participants with ≥1 episode of infection of grade 3 or higher — no. (%)	12 (12)	11 (11)	23 (12)	>0.99
Pneumonia-related adverse events				
Total no. of events	4	11	15	
Participants with ≥1 episode of pneumonia — no. (%)	3 (3)	11 (11)	14 (7)	0.03
Pneumonia-related adverse events/participant-mo	0.0029	0.0083	0.0055	0.08

Specks U et al. NEJM 2013

The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease

Characteristics and treatments of patients receiving rituximab

Baseline Characteristics (N = 177)	
Age (years) at first rituximab	47 (13–82)
Male sex	54 (31%)
Diagnosis	100 (56%)
Primary Systemic Vasculitis	75 (42%)
Granulomatosis with polyangiitis (Wegener's)	15 (8%)
Microscopic Polyangiitis	10 (6%)
Churg Strauss Syndrome	43 (24%)
Systemic lupus erythematosus	3 (2%)
Behcet's disease	3 (2%)
Henoch Schonlein Purpura	28 (16%)
Other[#]	
Prior disease duration (months)	52 (0–396)
Prior cyclophosphamide (N = 176)	121 (69%)
Cumulative cyclophosphamide (g) (N = 171)	8 (0–163)
Prior therapies (N = 176)	
Mycophenolate Mofetil	123 (70%)
Azathioprine	107 (61%)
Methotrexate	46 (26%)
Intravenous immunoglobulin	40 (23%)
Hydroxychloroquine	29 (16%)
Anti-tumor necrosis factors agents	26 (15%)
Plasma exchange	26 (15%)
Alemtuzumab	20 (11%)
Other IS/IM[$]	63 (36%)
Number of prior IS/IM agents (excluding steroids) (N = 176)	3 (0–14)

Marco et al. BMC Musculoskeletal Disorders 2014, 15:178

The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease

Frequency and severity of low immunoglobulin levels

	IgG				IgM	IgA
	< 6 g/L	Mild 5-5.9 g/L	Moderate 3-4.9 g/L	Severe < 3 g/L	<0.4 g/L	<0.8 g/L
Baseline hypogammaglobulinaemia	18 (13%)	6 (5%)	9 (6%)	3 (2%)	14 (10%)	14 (10%)
Hypogammaglobulinaemia	61 (34%)	18 (10%)	36 (20%)	7 (4%)	90 (51%)	40 (23%)

Baseline hypogammaglobulinaemia (N = 136): total number and proportion in parentheses of patients with low immunoglobulin levels at time of first rituximab. Hypogammaglobulinaemia (N = 177): total number and proportion in parentheses of patients with low immunoglobulin levels following rituximab for at least three consecutive months at some point during follow-up.

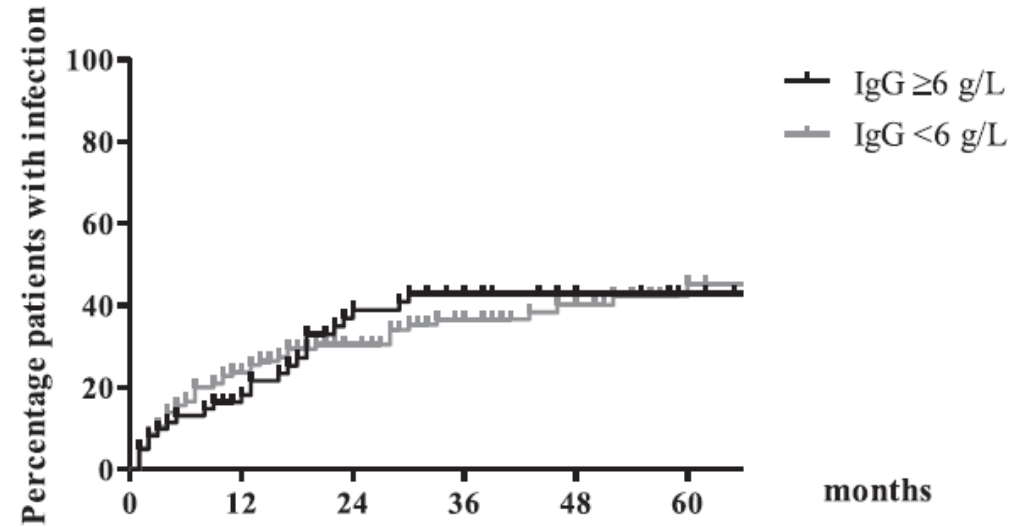


Figure 2 Time to first severe infection following first rituximab. Time to first severe infection according to IgG levels. The time to first severe infection was not different when patients with IgG levels ≥6 g/L (N = 116) and IgG levels <6 g/L (N = 61) (p = 0.953) were compared.

Conclusion

- Prior CYC exposure and GC but not cumulative RTX dose was associated with increased incidence of hypogammaglobulinaemia.
- Severe infections were common but were not associated with Ig levels. Repeat dose RTX appears safe with judicious monitoring.

Marco et al. BMC Musculoskeletal Disorders 2014, 15:178

Rituximab: hepatitis B flare

- Hépatite B chronique active
- Risque de réactivation évolutive sous rituximab (+ polychimiothérapie)
- Une dizaine de cas d'évolution fatale décrits dans la littérature
- Traitement préventif par lamivudine recommandé

Hernandez JA et al, Hematologica 2003; Westhoff Th, Blood 2003
Tsutsumi Y, Leukemia lymphoma 2004; Law JK, Leukemia lymphoma 2005
Niscola P, Leukemia 2005; Sarrechia C, J Infect Chemother. 2005
Arlet JB, Neuromuscular disorders 2006 (en révision)

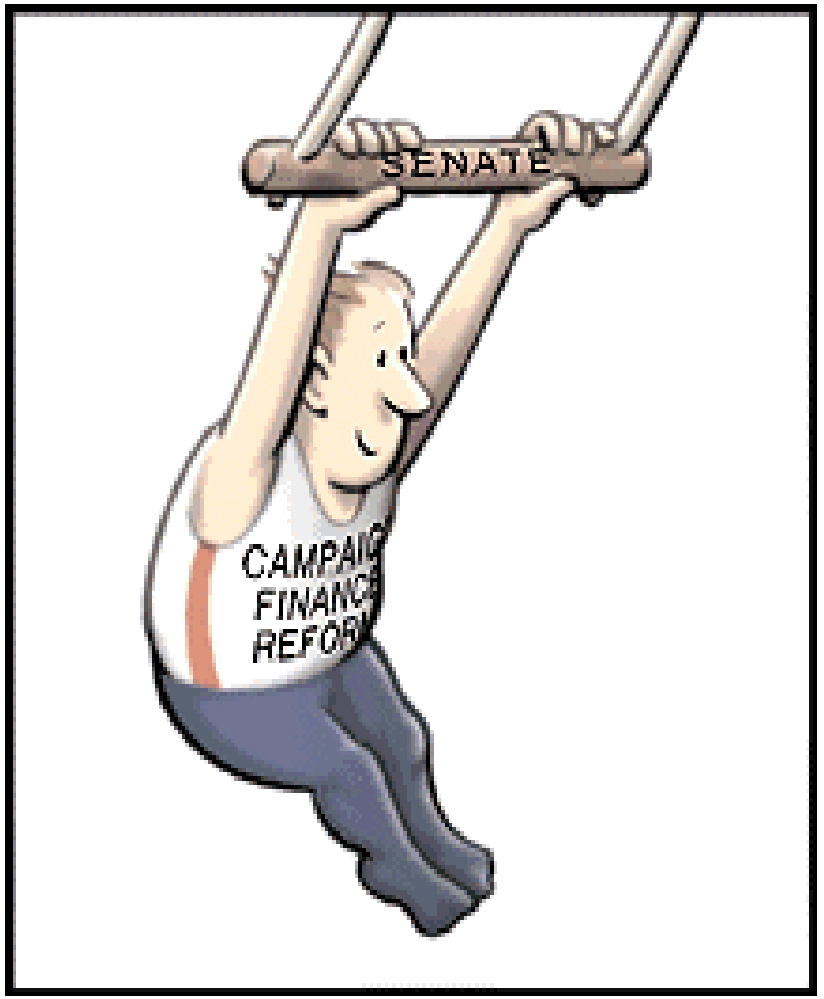
P jiroveci et rituximab

- **Etude retrospective des infections à P jiroveci associées à un traitement par rituximab entre 1998 et 2011.**
- **30 patients.**
- **Pathologie de fond: hémopathies malignes dans 90% des cas. Corticothérapie 73% des patients, en association à différentes chimiothérapies.**
- **3 patients (10%): sans traitement chimiothérapique associé ou exposition aux corticoides**
- **88% défaillance respiratoire, 53% hospitalisés en soins intensifs**
- **Décès: 30%.**
- **Prophylaxie de la PcP justifiée chez les patients à risqué**

CHEST 2013; 144(1):258–265

Conclusions

- **Large number of biologics available, new generations coming up**
- **Rituximab: revolution in the treatment of rheumatoid arthritis and ANCA associated vasculitis**
- **Cost-benefit studies are necessary**
- **Improve efficacy: increase immunosuppression ?? Combine ?**
- **From the use of biologics we learn from the pathophysiology of autoimmune diseases**
- **New treatments: new risks (infections)**



French Vasculitis Study Group

CMR
CENTRE MALADIES RARES
VASCULARITES | SCLÉRODERMIES
GOUGEROT-SJÖGREN | LUPUS

Hôpital Cochin
Paris

www.vascularites.org

Luc.mouthon@cch.aphp.fr

Referral Center for
Rare Systemic and
Autoimmune Diseases

PTI

Situation temporairement acceptable

RITUXIMAB

Purpura thrombopénique idiopathique sévère (plaquettes < 30 000/ mm3) en cas de :

- **contre-indication ou échec ou rechute aux corticoïdes et/ ou aux immunoglobulines IV**

et

- **contre-indication ou échec à la splénectomie.**

Traitement par rituximab (Mabthera) au cours du purpura thrombopénique immunologique

Étude	Nombre de patients	Effet bénéfique	RC	RP	RM
Stasi *et al.* [33]	25	13 (52 %)	5	5	3
Braendstrup *et al.* [94]	35	17 (44 %)	7	6	4
Godeau *et al.* [35]	60	24 (40 %)	18*	6	
Medeot *et al.* [36]	26	18 (69 %)	14	4	
Zaja** *et al.* [37]	28	21 (75 %)	12	9	

(RC : réponses complètes ; RM : réponses mineures ; RP : réponses partielles).

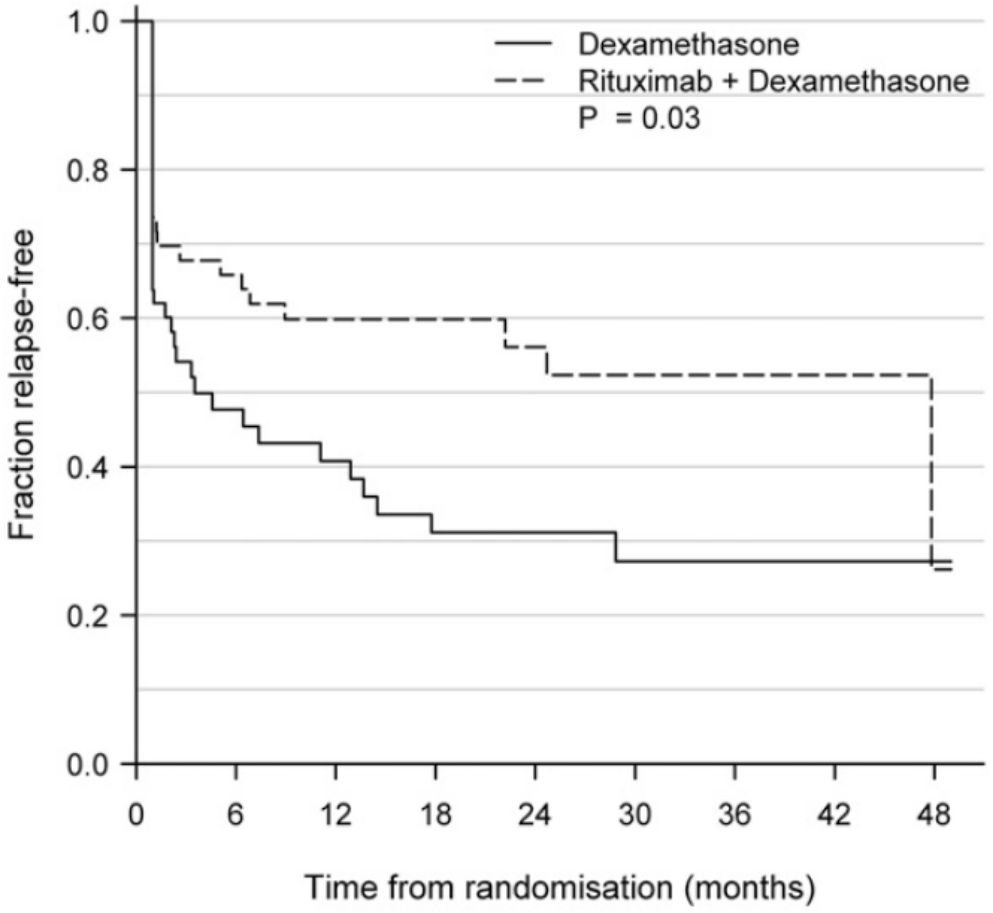
* plaquettes >150 G/L.

** rituximab à 100 mg par semaine pendant 4 semaines.

Apilot randomized trial of adjuvant rituximab or placebo for nonsplenectomized patients with immune thrombocytopenia Arnold DM Blood 2012

- **Pilot randomized trial to determine the feasibility of recruitment, protocol adherence, and blinding of a larger trial of rituximab versus placebo; and to evaluate the potential efficacy of adjuvant rituximab in ITP.**
- **Nonsplenectomized adults with newly diagnosed or relapsed ITP who were receiving standard ITP therapy for a platelet count below 30 109/L were randomly allocated to receive 4 weekly infusions of 375 mg/m2 rituximab or saline placebo. Sixty patients were recruited.**
- **After 6 months: no difference between rituximab and placebo groups for the composite outcome of any platelet count below 50 109/L, significant bleeding or rescue treatment once standard treatment was stopped (21/32 [65.6%] vs 21/26 [80.8%]; relative risk 0.81, 95% confidence intervals, 0.59%-1.11%).**
- **Timely accrual poses a challenge to the conduct of a large randomized trial of rituximab for presplenectomy ITP. No difference in the frequency**
- **of the composite outcome was observed in this pilot trial (*Blood*. 2012;119(6):1356-1362)**

Rituximab and dexamethasone vs dexamethasone monotherapy in newly diagnosed patients with primary immune thrombocytopenia



No. at risk									
DXM	58	22	17	12	9	7	3	3	1
RTX+DXM	53	34	28	22	15	11	7	3	1

Gudbrandsdottir Blood. 2013;121(11):1976-1981

Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients

- **Multicenter registry of 248 adult patients with ITP treated with rituximab.**
- **In total, 173 patients received 4 infusions of 375 mg/m2 and 72 received 2 fixed 1-g infusions 2 weeks apart. The choice of the rituximab regimen was based on the physician's preference.**
- **Overall, 38 patients showed minor intolerance. Seven showed infection (n 5 11 cases).**
- **Three patients died of infection 12 to 14 months after rituximab infusions, but the role of rituximab was questionable.**
- **152 patients (61%) showed an overall initial response (platelet count ‡30 3 109/L and ‡2 baseline value). At a median follow-up of 24 months, 96 patients (39%) showed a lasting response.**
- **On multivariate analysis, the probability of sustained response at 1 year was significantly associated with ITP duration <1 year (P5.02) and previous transient complete response to corticosteroids (P 5.05).**
- **With its benefit/risk ratio, rituximab used off-label may remain a valid option for treating persistent or chronic ITP in adults.**

Khellaf M et al. Blood. 2014;124(22):3228-3236

Anémie hémolytique autoimmune

A phase III randomized trial comparing glucocorticoid monotherapy versus glucocorticoid and rituximab in patients with autoimmune haemolytic anaemia

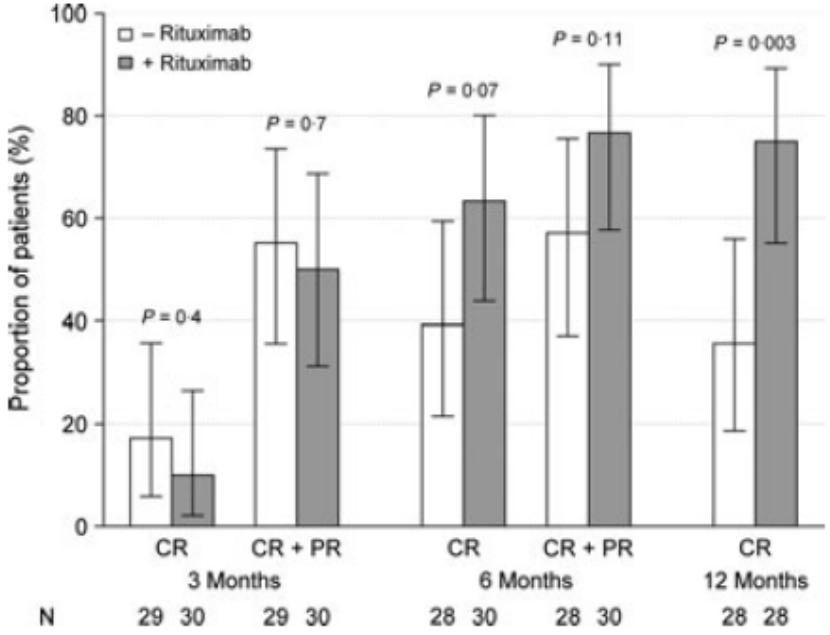


Fig 2. Proportions of patients with newly diagnosed warm-antibody reactive autoimmune haemolytic anaemia that showed any response (CR + PR) or a complete response (CR) at 3, 6 and 12 months after initiating treatment with rituximab and prednisolone combined ($N = 32$) or prednisolone alone ($N = 32$). CR, complete response; PR, partial response.

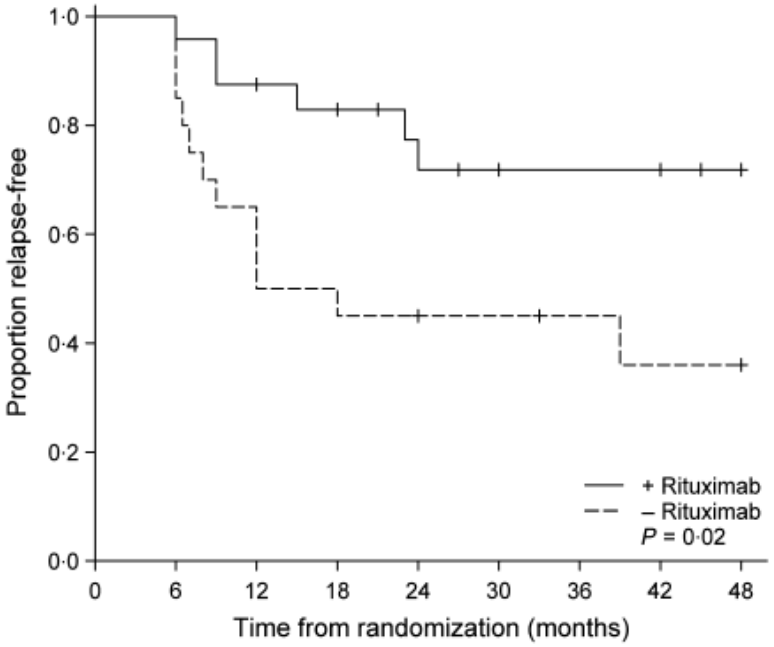


Fig 3. Relapse-free survival in patients with newly diagnosed warm-antibody reactive autoimmune haemolytic anaemia randomized to receive rituximab and prednisolone combined or prednisolone alone as first-line therapy.

Using rituximab and prednisolone combined rather than prednisolone alone as first-line treatment in WAIHA increases both the rate and the duration of the response

Birgens et al. BJH 2013