Rituximab in Vasculitis

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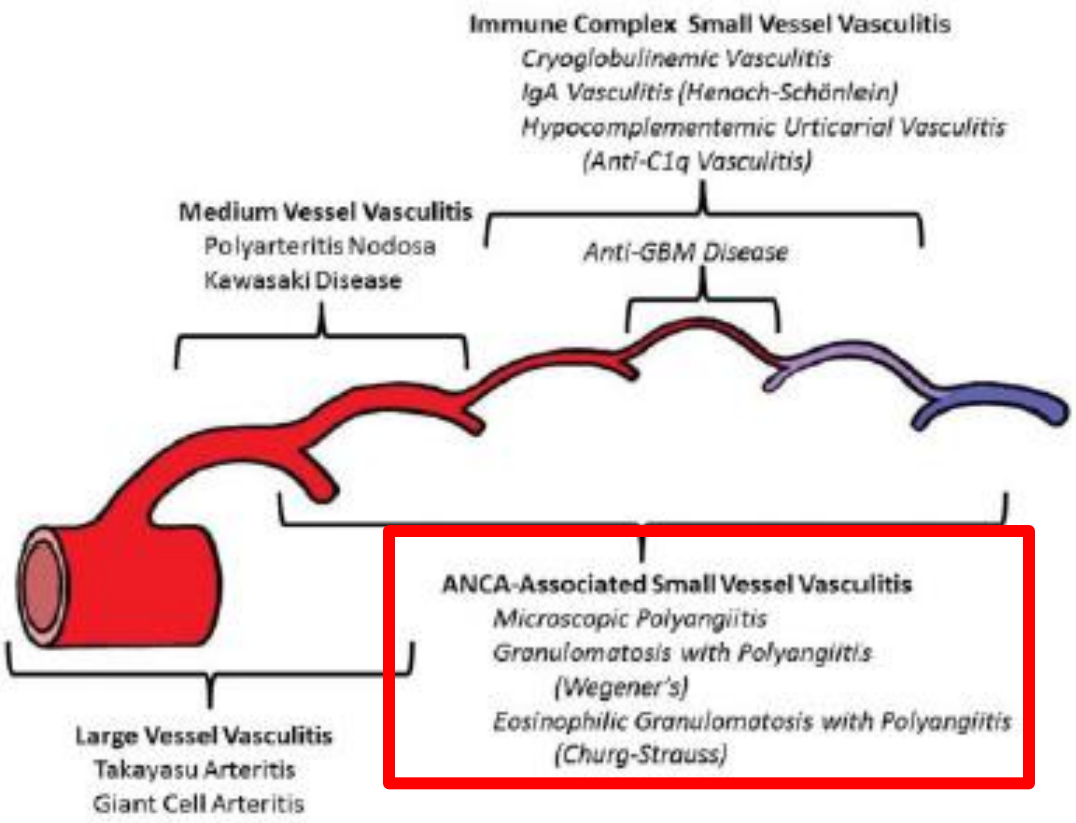
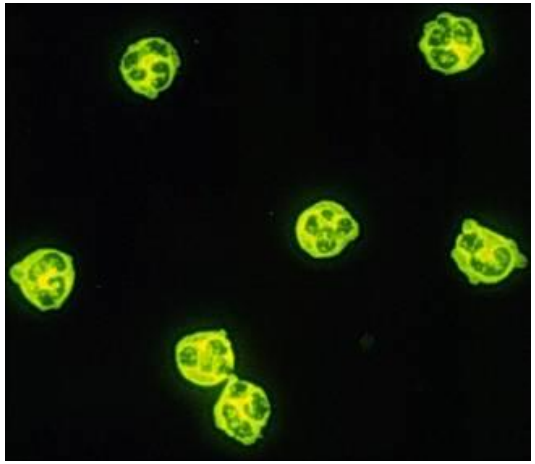
VASCULITIDES CLASSIFICATION



Chapel Hill, 2012

GPA & ANTI-NUCLEAR CYTOPLASMIC ANTIBODIES (ANCA)

- Main diagnostic criteria
- **> 90%** GPA are **ANCA+**
- Most cases are c-ANCA **anti-PR3+**
- 10% GPA are ANCA+ anti-MPO+

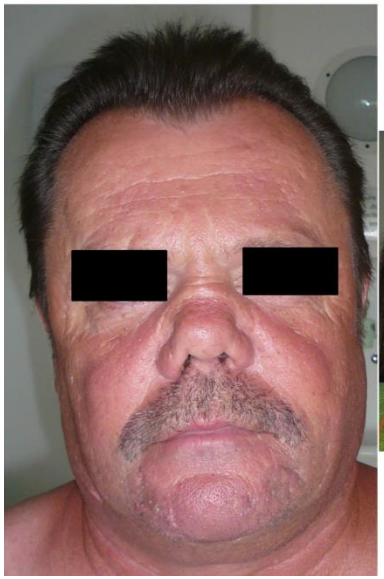


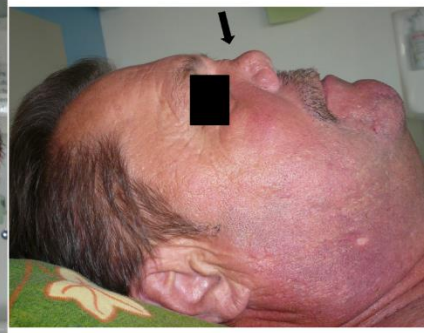
Systemic ANCA-vasculitis
Main Features

	GPA Wegener	MPA MPA	EGP Churg-Strauss
• **ANCA positivity**	95%	90%	70%
• **Relapse rates**	50%	30%	25%
• **Survival rates**	80%	50%	80%
• **First line Rx:**	steroids plus i.v. CYP, then AZA		
• **Second line Rx:**	oral CYP, MTX, AZA, IVIg, plasmapheresesis.		

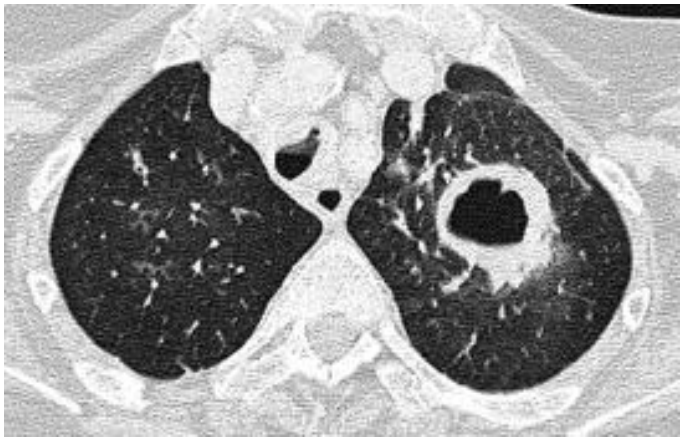
GPA: MAIN MANIFESTATIONS

E.N.T

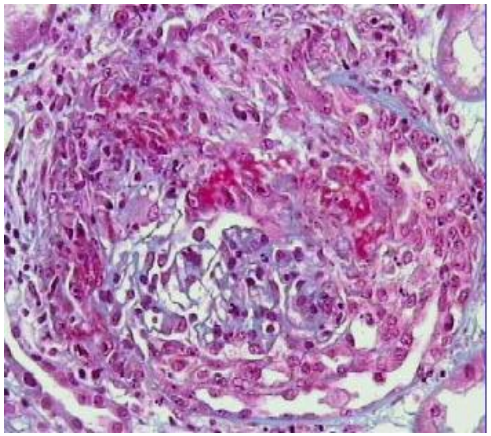


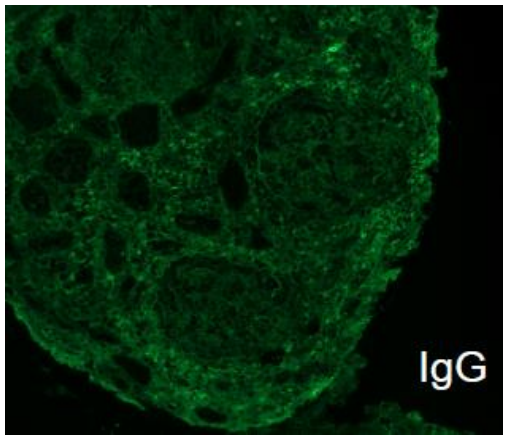


LUNGS



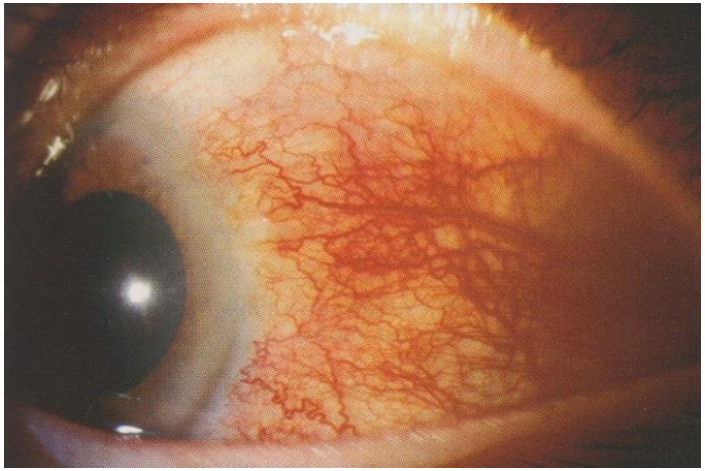
KIDNEYS



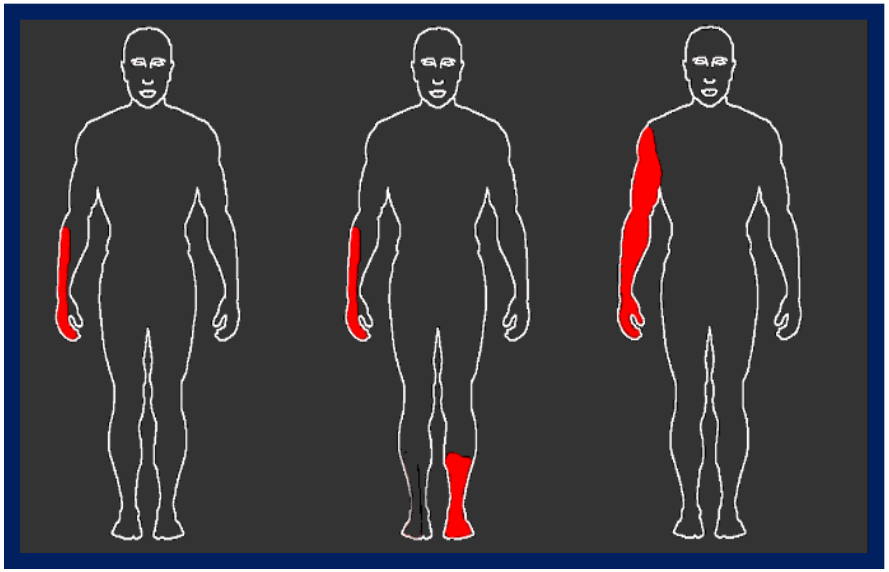


GPA: MAIN MANIFESTATIONS

SCLERITIS



NEUROPATHY



Treatment Strategy in ANCA-vasculitis

INDUCTION	MAINTENANCE
Steroids (1 mg/kg/d) ± *Bolus MP x 1-3 (15 mg/kg)* + CYC x 6-9 (600-700 mg/m^2) or RTX x 4 (375 mg/m^2/wk)	Steroids (18-24 months) + RTX 500 mg/6 months > AZA (2 mg/kg/d) or MTX (20-25 mg/wk)

Rituximab as induction treatment in ANCA-vasculitis

RAVE design - US trial

- 197 new (49%) or relapsing **GPA/MPA**

  creatinine < 4.0mg/dl, no lung hemorrhage
- Randomized, double-blind

  Rituximab 375mg/m^2/wk x 4 *versus* oral CYC
- **Primary end-point:**

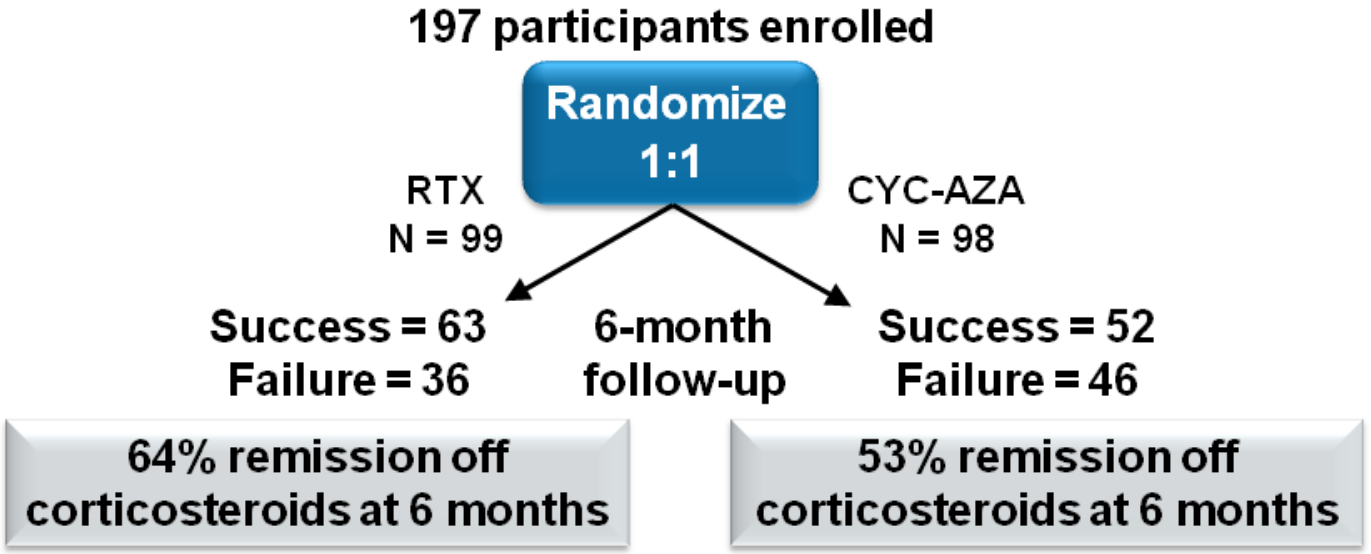
  remission and steroid withdrawal at 6 months

Stone J et al, *N Engl J Med* 2010

RAVE Design

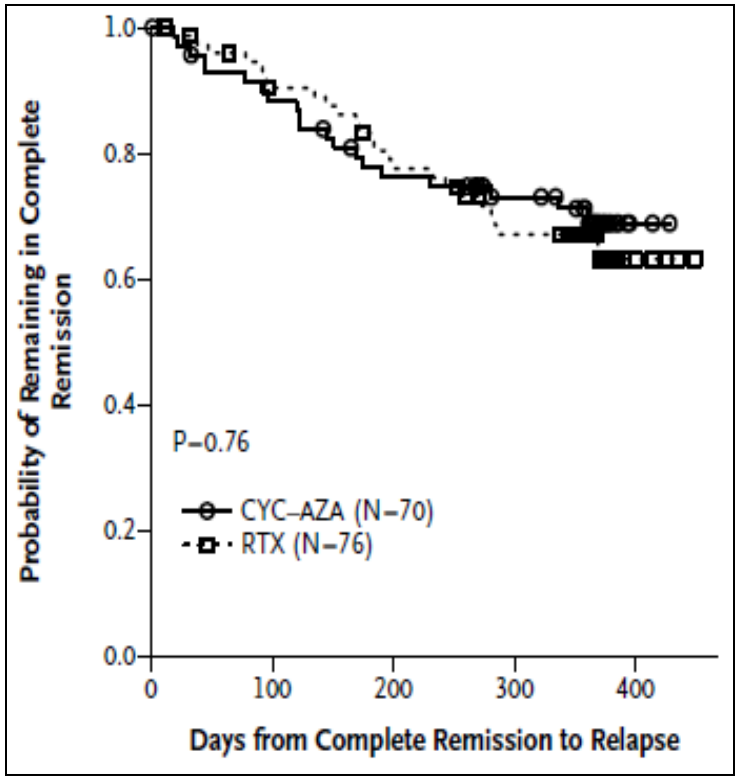
Success/complete remission:

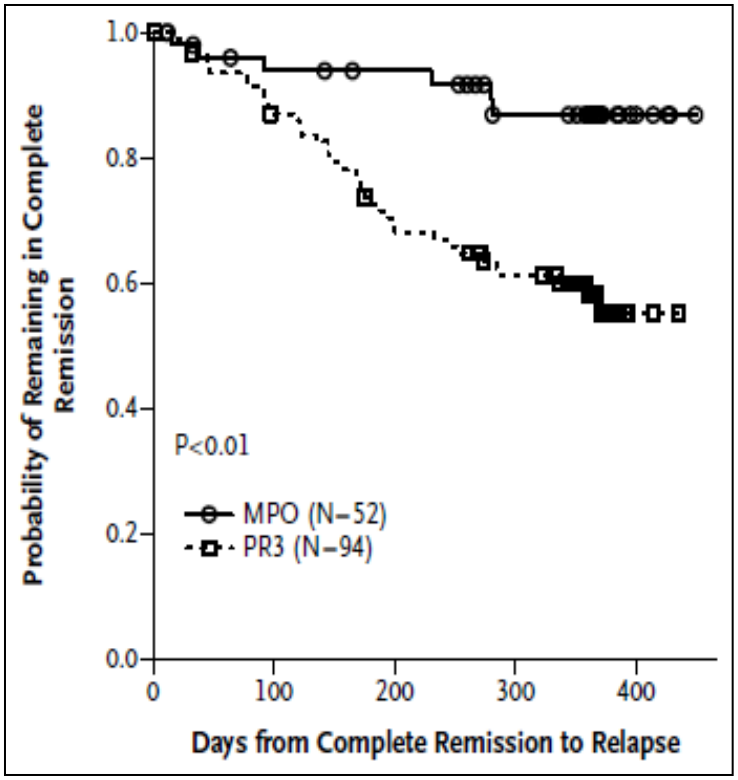
- BVAS/WG = 0
- Prednisone = 0
- No failure reason



Specks U, et al; for the RAVE study group. ANCA-Vasculitis Workshop 2011. Clinical & Experimental Immunology Special Issue: 15th International Vasculitis and ANCA Workshop. May 2011; Volume 164, Issue Supplement s1:1-154.

RAVE – Relapse rates according to type of ANCA





Specks U et al, N Engl J Med, 2013;369:417-27

RITUXVAS design = EUROPE TRIAL

  - **New** GPA/MPA **<u>with renal involvement</u>**
  - N=44
- Randomized, double-blind

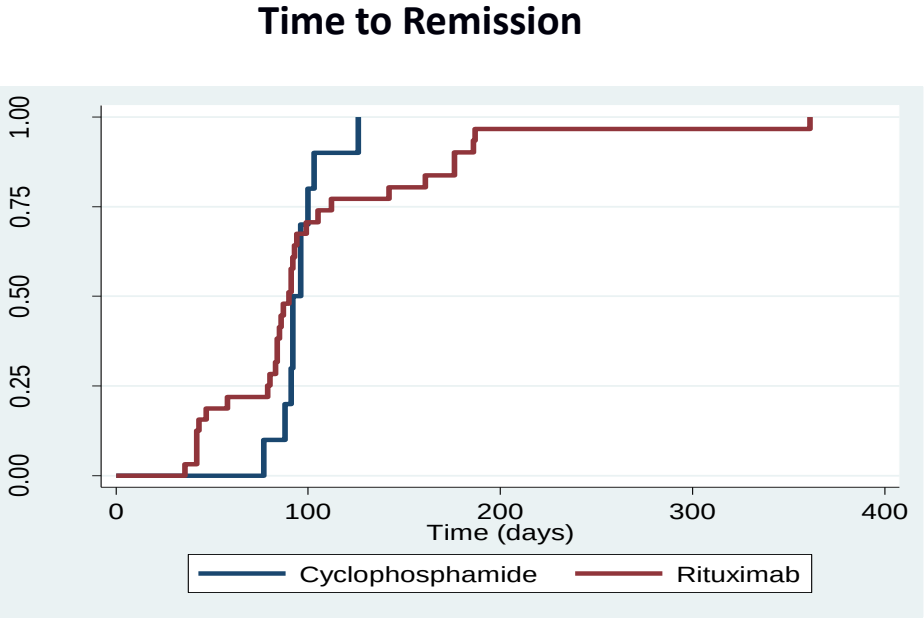
  Rituximab 375mg/m^2/wk x 4 *versus* oral CYC
- **Primary end-point:**

  remission and steroid withdrawal at **12 months**

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

RITUXVAS – Remission

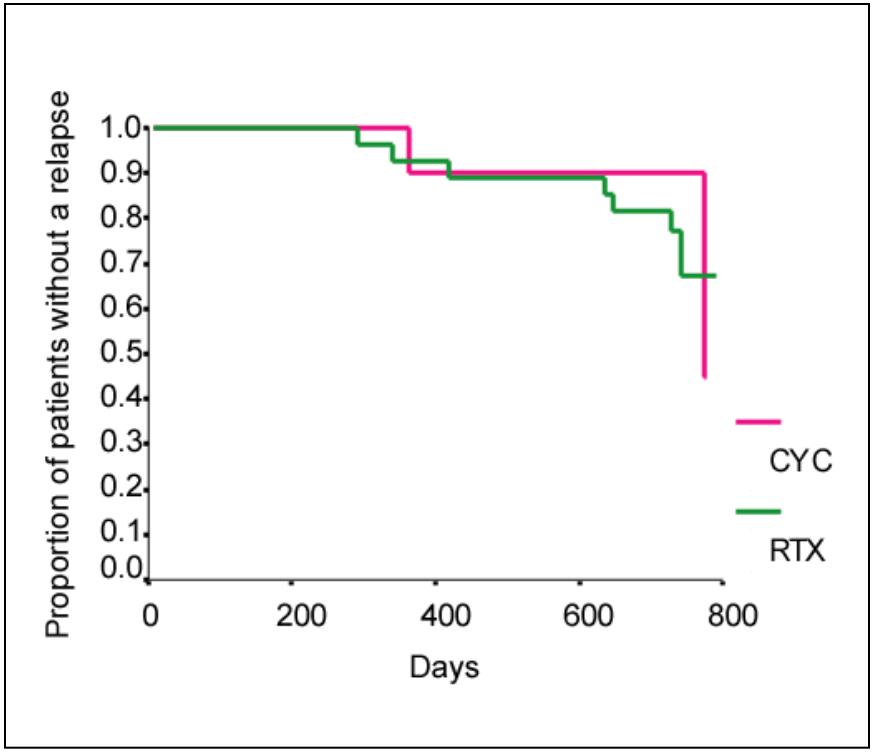
(BVAS = 0 for 6 months)



	RTX	CYC
Sustained remission	25/33 **(76%)**	9/11 **(82%)**
No sustained remission	2 incomplete response 6 deaths	1 incomplete response 1 death

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

RITUXVAS - Relapse



	RTX N=33	CYC N=11
Relapse	**7 (21%)**	**2 (18%)**
Major	1 (3%)	2 (18%)
Minor	6 (18%)	0 (0%)

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

RITUXVAS
Safety and secondary objectives

	Rituximab (n=33)	CYC (n=11)
Deaths (all causes)	6 (18%)	2 (18%)
Treatment failure (including deaths)	8 (24%)	2 (18%)
Delay to remission (days)	85	92
Patients at 5mg/d prednisone at M9	96 %	89 %
GFR at M12 (ml/mn/1,73m2)	39	27
ANCA negative at M12	100 %	80 %

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

Treatment of Systemic ANCA Vasculitis Summary

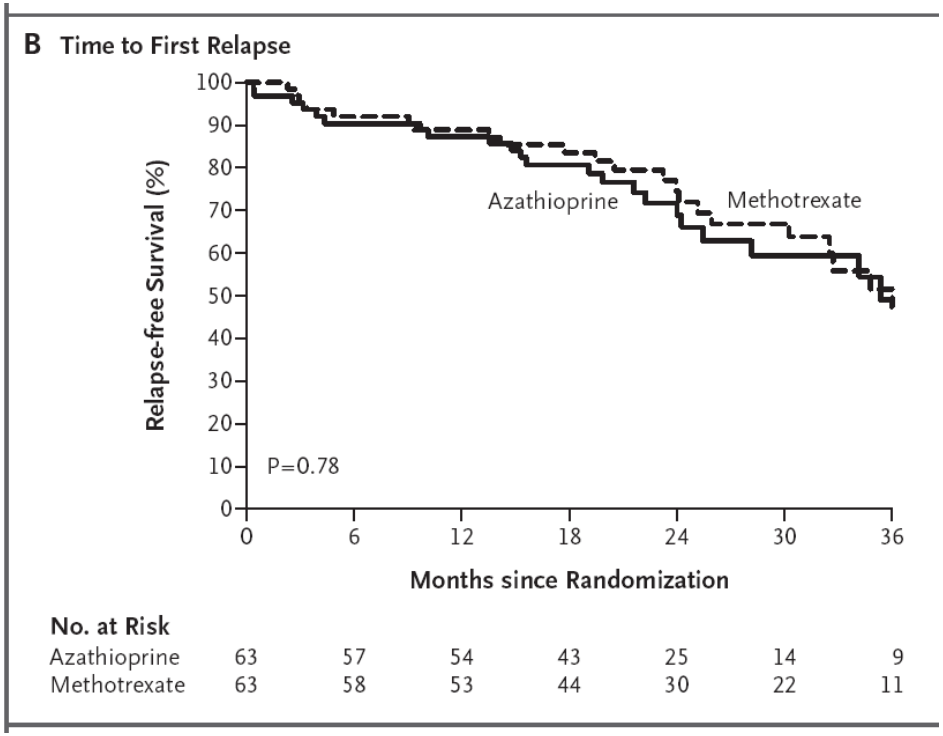
- **Induction of remission:**
  - **RTX :**
    - non inferior to CYC for induction in GPA and MPA
    - women in age of childbearing
  - **CYC might be better used if :**
    - EGP, anti-GBM, IAH, renal insufficiency (creatinin >350 µmol/l)
    - Granulomatous manifestations with lifethreatening or functionnal risk

Rituximab as maintenance treatment in ANCA-vasculitis

Treatment Strategy in ANCA-vasculitis

INDUCTION	MAINTENANCE
Steroids (1 mg/kg/d) ± *Bolus MP x 1-3 (15 mg/kg)* + CYC x 6-9 (600-700 mg/m^2) or RTX x 4 (375 mg/m^2/wk)	Steroids (18-24 months) + RTX 500 mg/6 months > AZA (2 mg/kg/d) or MTX (20-25 mg/wk)

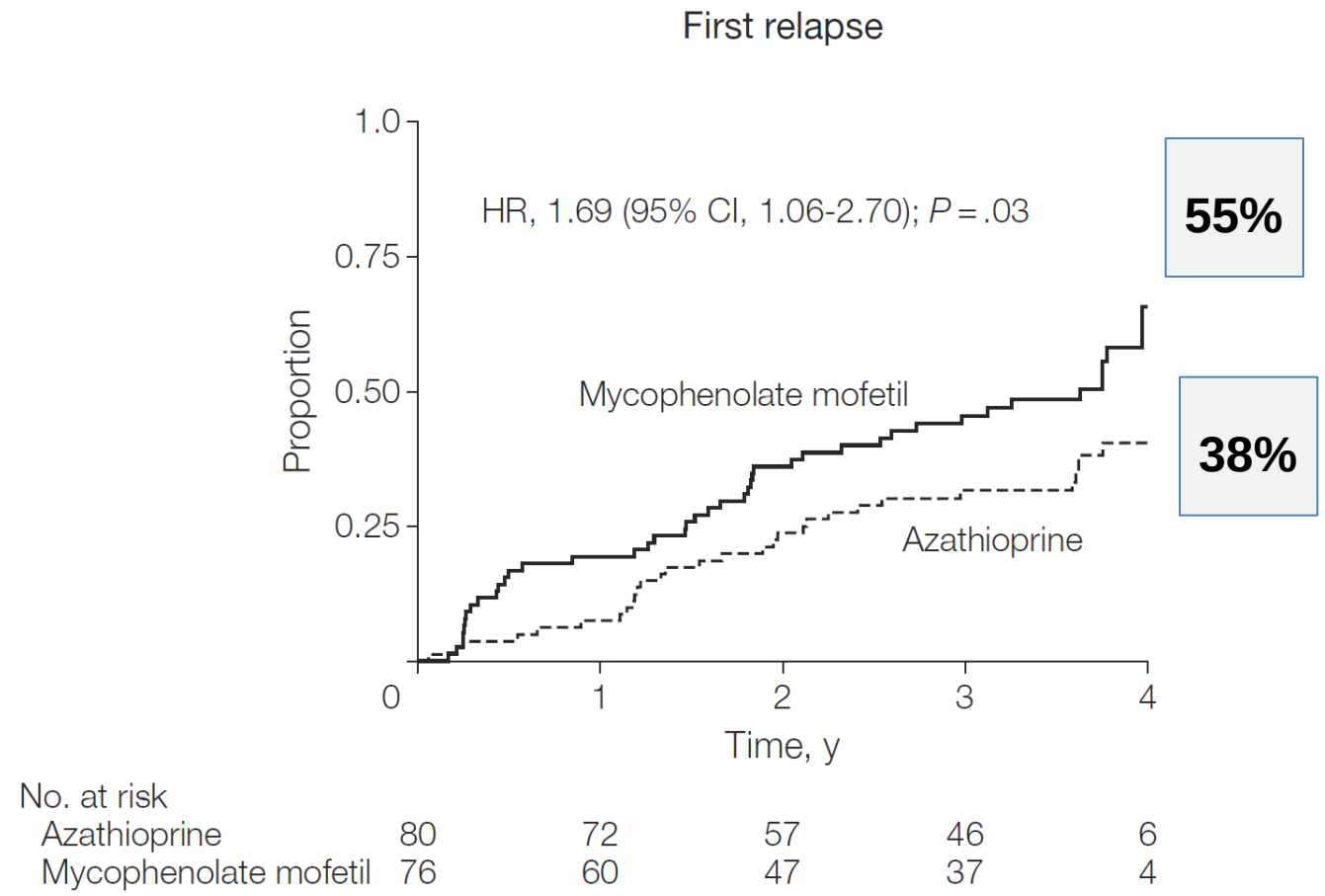
AZA or MTX are not different for maintenance treatment in ANCA-vasculitis



- AZA 2 mg/kg/d vs. MTX 0.3 mg/kg/d (max 25)
- After remission with prednisolone & cyclophosphamide orally or IV , 6 months

Pagnoux C. N Engl J Med 2008;359:2790

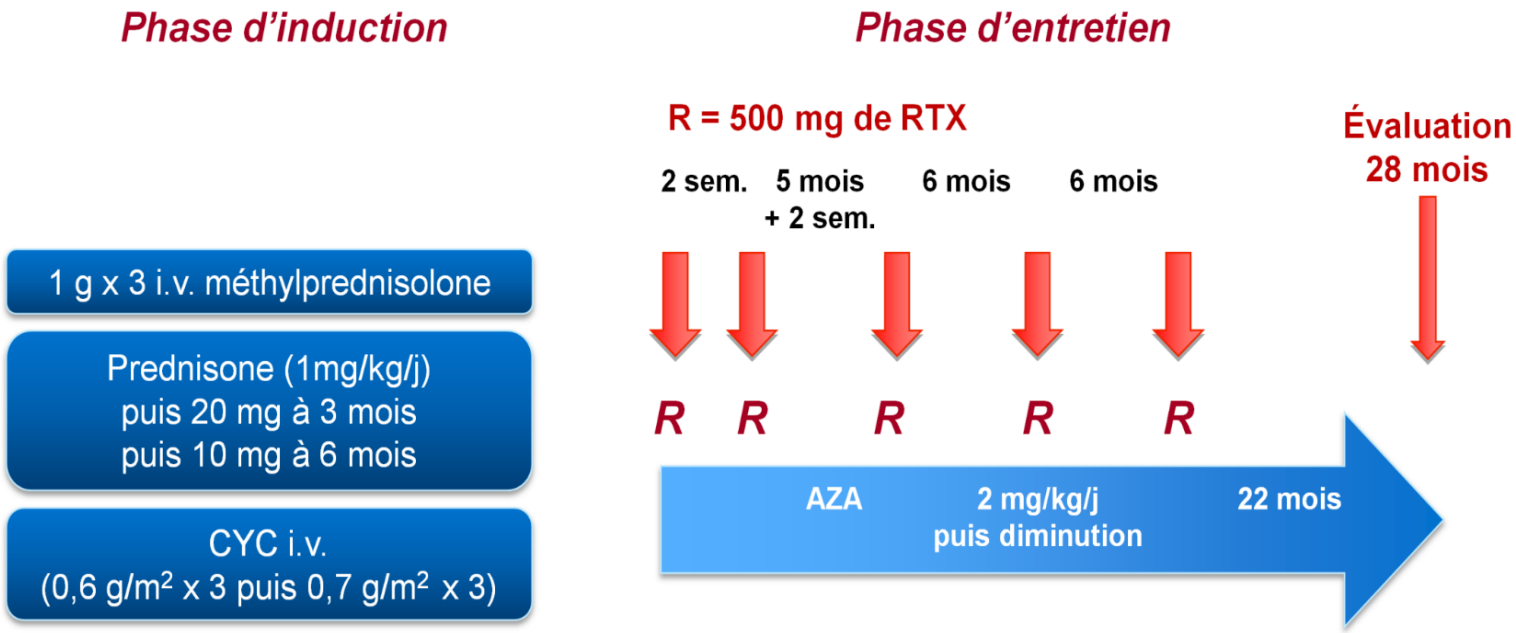
AZA is superior to MMF for maintenance treatment in ANCA-vasculitis



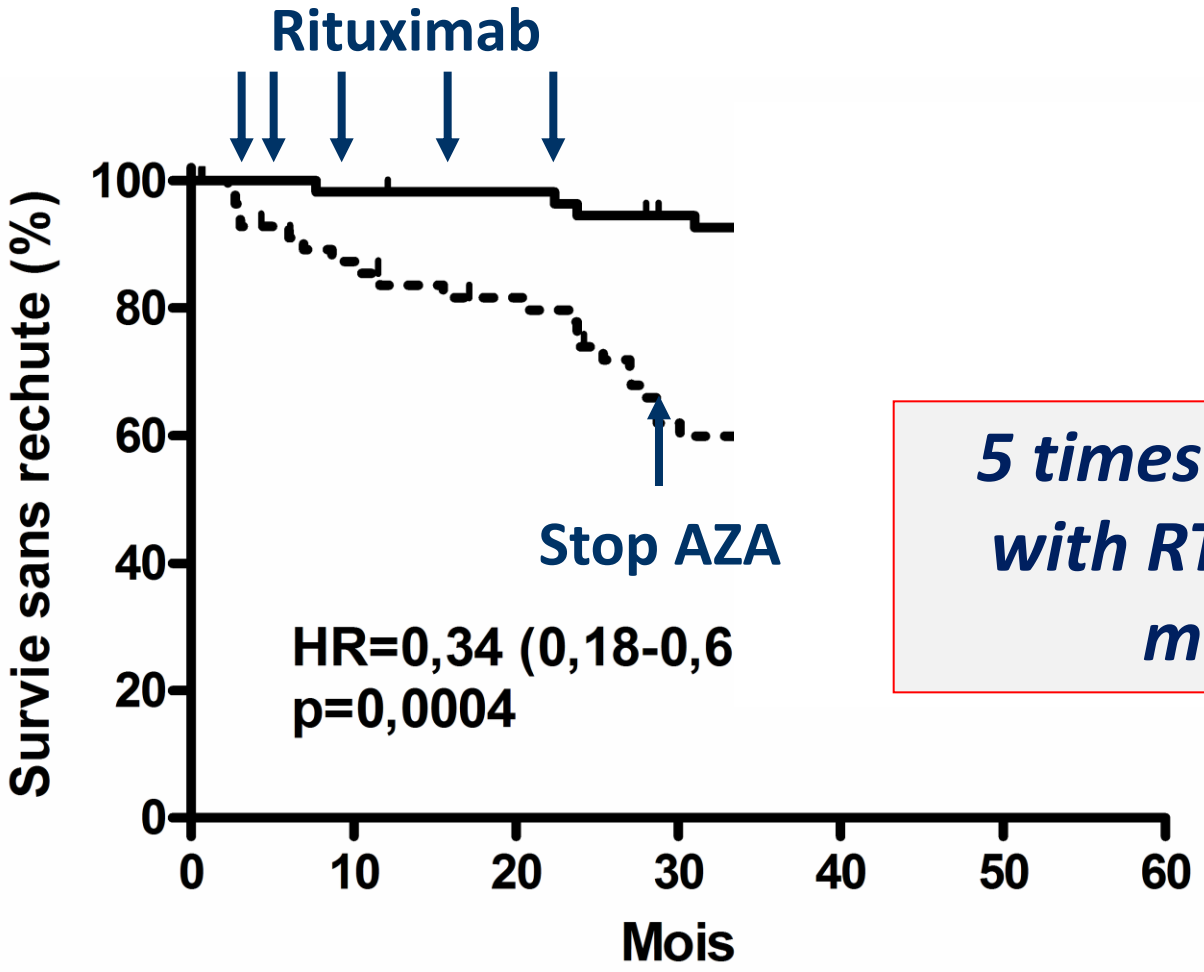
- *AZA 2 mg/kg/d vs. MMF 2 gr/d*
- *After remission with prednisolone & cyclophosphamide orally or IV , 6 months*
- *Objective: stopping IS at month 42*

Hiemstra TF. JAMA. 2010;304:2381-8

Maintenance of remission using Rituximab for systemic ANCA-associated vasculitis - *MAINRITSAN Trial*



Maintenance of remission using Rituximab for systemic ANCA-associated vasculitis - *MAINRITSAN Trial*



5 times less relapses with RTX vs. AZA at month 28

Guillevin, N Engl J Med, 2014

Predictive Factors of Relapse in ANCA Vasculitis

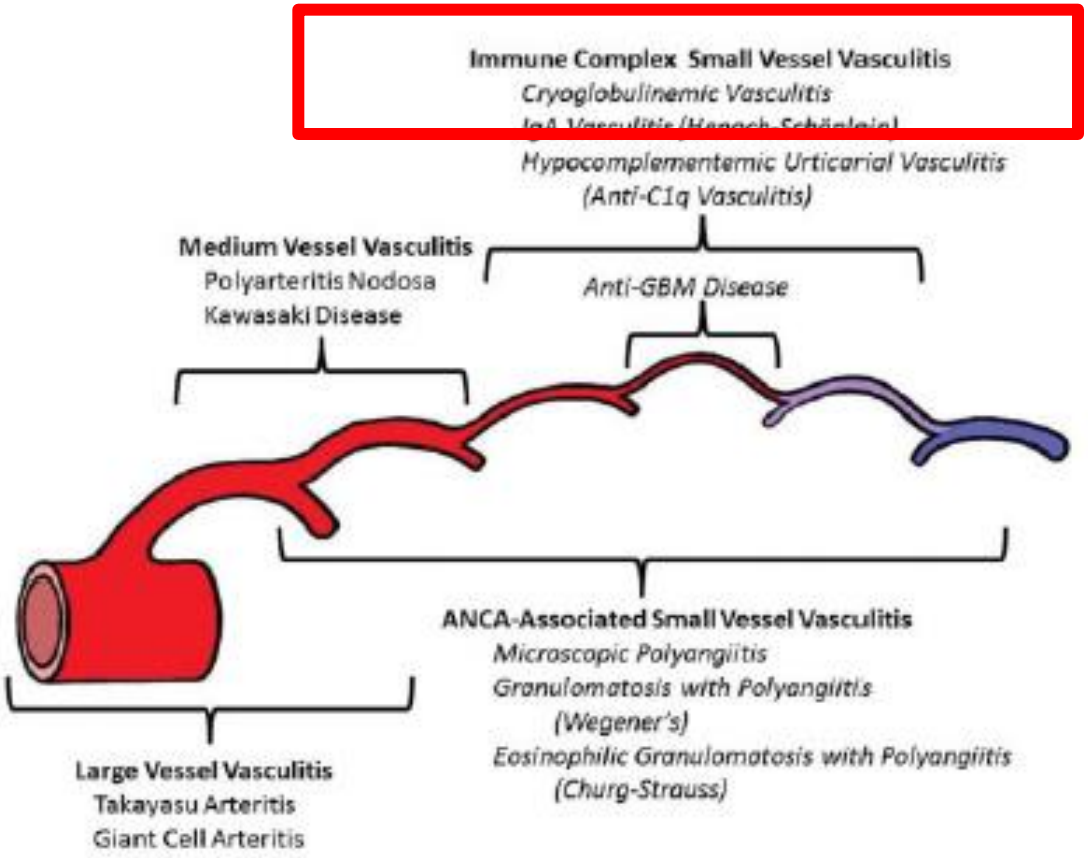
	Univariate		*Multivariate*	
	HR (IC 95%)	P	HR (IC 95%)	P
Age	1 (0,97-1,04)	0,81	-	-
Male gender	1,48 (0,47-4,64)	0,5	-	-
GPA	5,39 (0,70-41,5)	0,11	-	-
ANCA anti-PR3	6,29 (0,82-48,2)	0,08	12,5 (1,47-106)	0,02
ANCA anti-MPO	0,29 (0,04-2,20)	0,23		
ANCA positive at month12	4,45 (1,60-12,36)	<0,01	7,79 (2,51-24,2)	<0,01
GFR < 60 ml/min	0,43 (0,14-1,36)	0,15	-	-

Terrier B, SNFMI 2014

Treatment of Systemic ANCA Vasculitis Summary

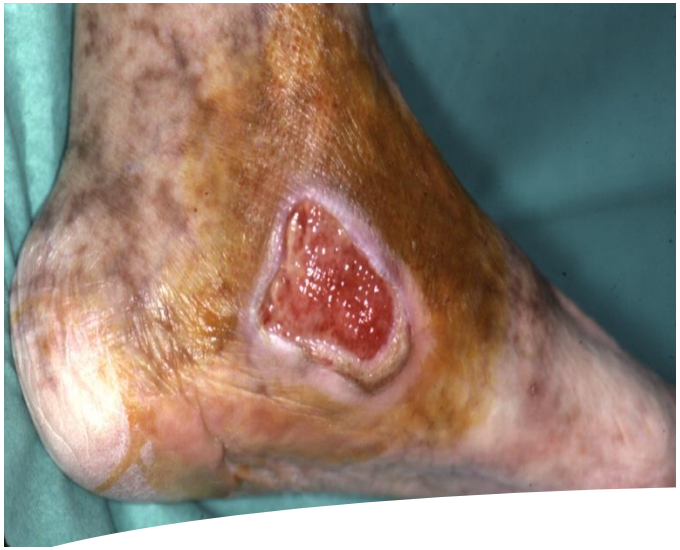
- **Induction of remission:**
  - **RTX:**
    - non inferior to CYC for induction in GPA and MPA
    - women age of childbearing
  - **CYC better used if:**
    - EGP, anti-GBM, IAH, renal insufficiency (creatinin >350 µmol/l)
    - Granulomatous manifestations with lifethreatening or functionnal risk
- **Maintenance of remission :**
  - **Rituximab** superior to AZA or MTX
  - MMF less effective

VASCULITIDES CLASSIFICATION

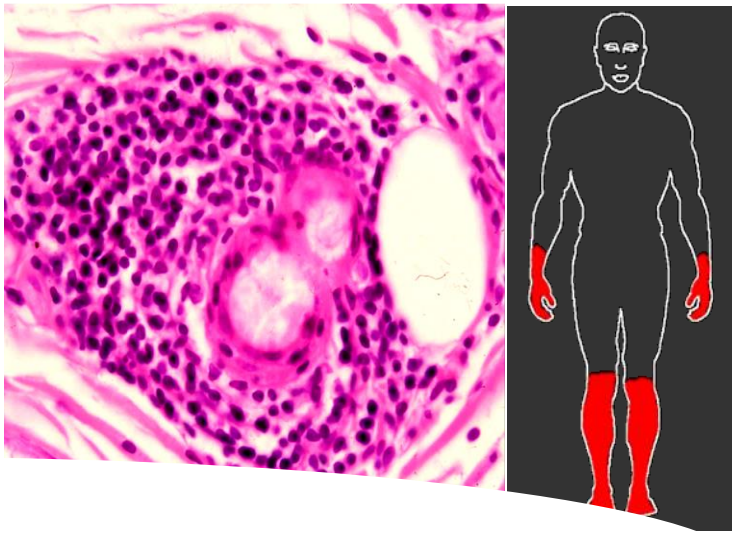


Chapel Hill, 2012

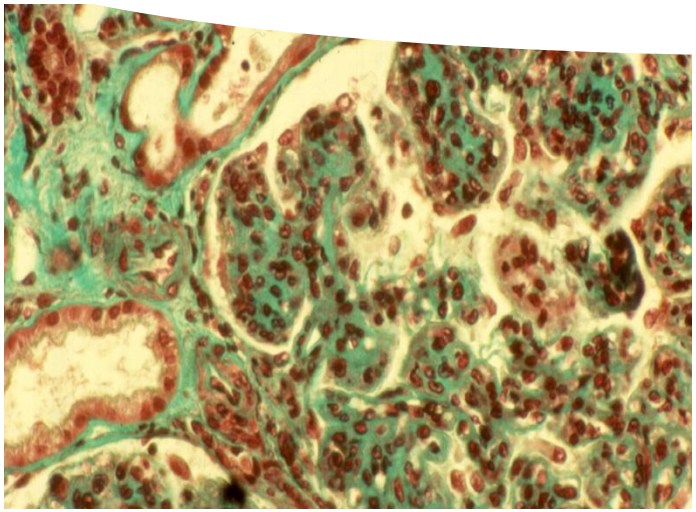
Skin Purpura



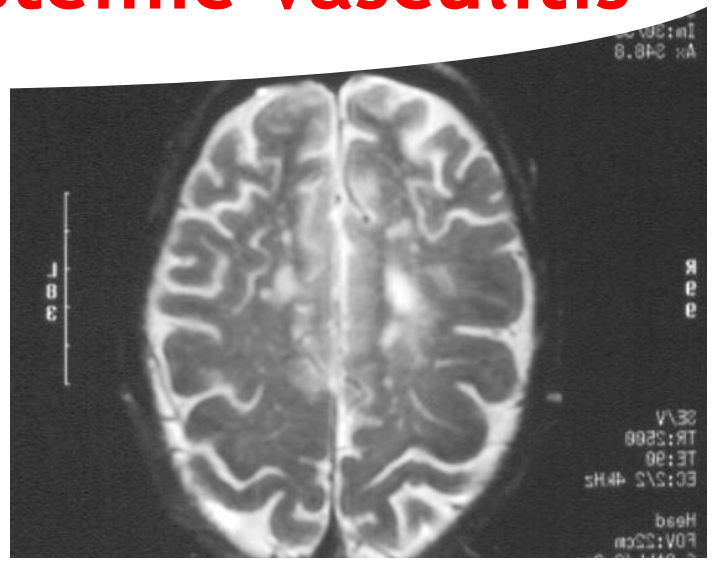
Neuropathy



Cryoglobulinemia-Systemic Vasculitis



Membrano-proliferative Glomerulonephritis



CNS Vasculitis

Features of Mixed Cryoglobulinemia Vasculitis

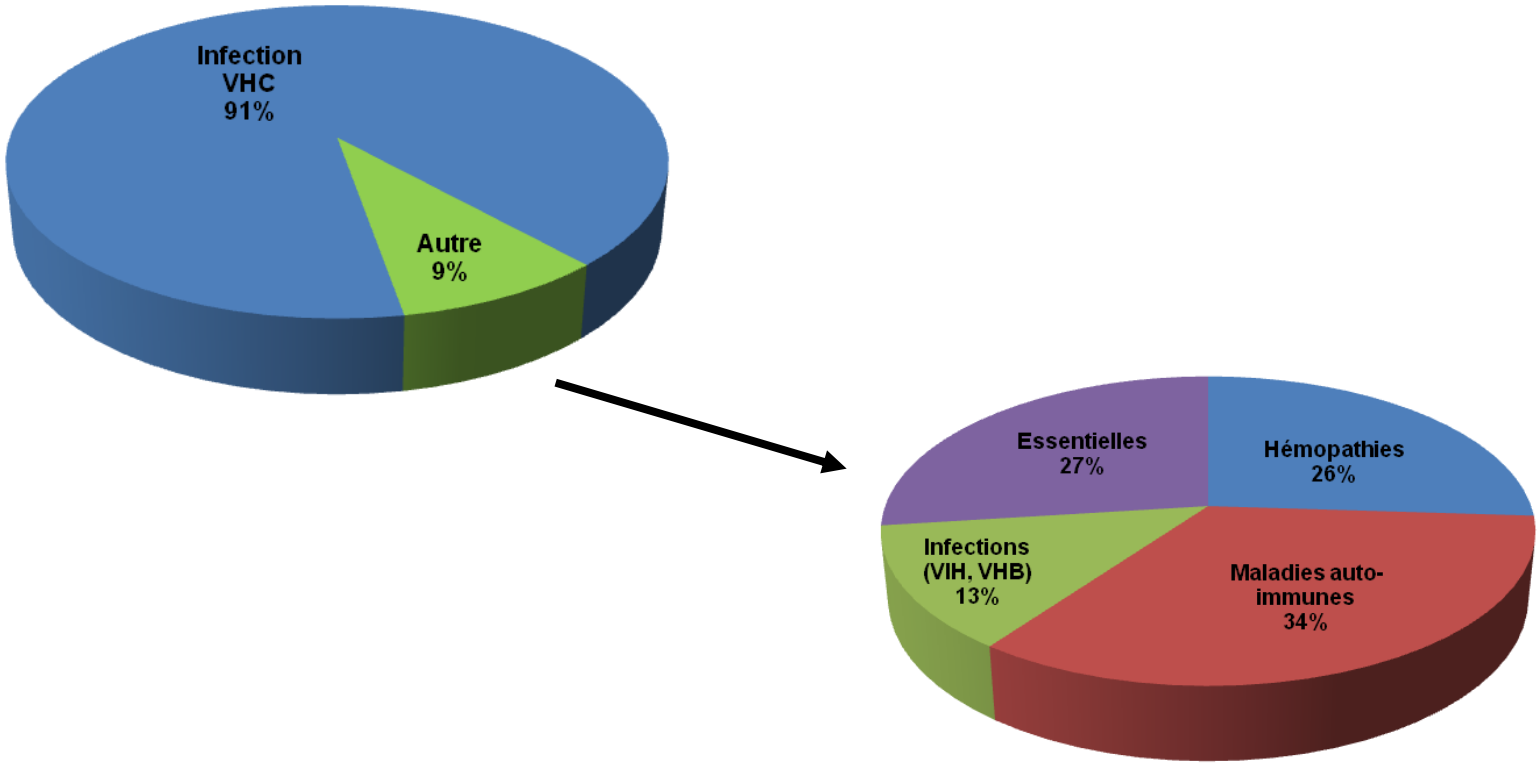
Age at disease onset (yrs)	54 ± 13 (29-72)
Female/Male ratio	3
Purpura	98%
Weakness	98%
Arthralgias	91%
Arthritis (non-erosive)	8%
Raynaud's phenomenon	32%
Sicca syndrome	51%
Peripheral neuropathy	81%
Renal involvement	31%
B-cell non-Hodgkin's lymphoma	**11%**
Hepatocellular carcinoma	**3%**

RR=34

n=250 patients

Ferri C, Mascia MT, Saadoun D, Cacoub P. 2009

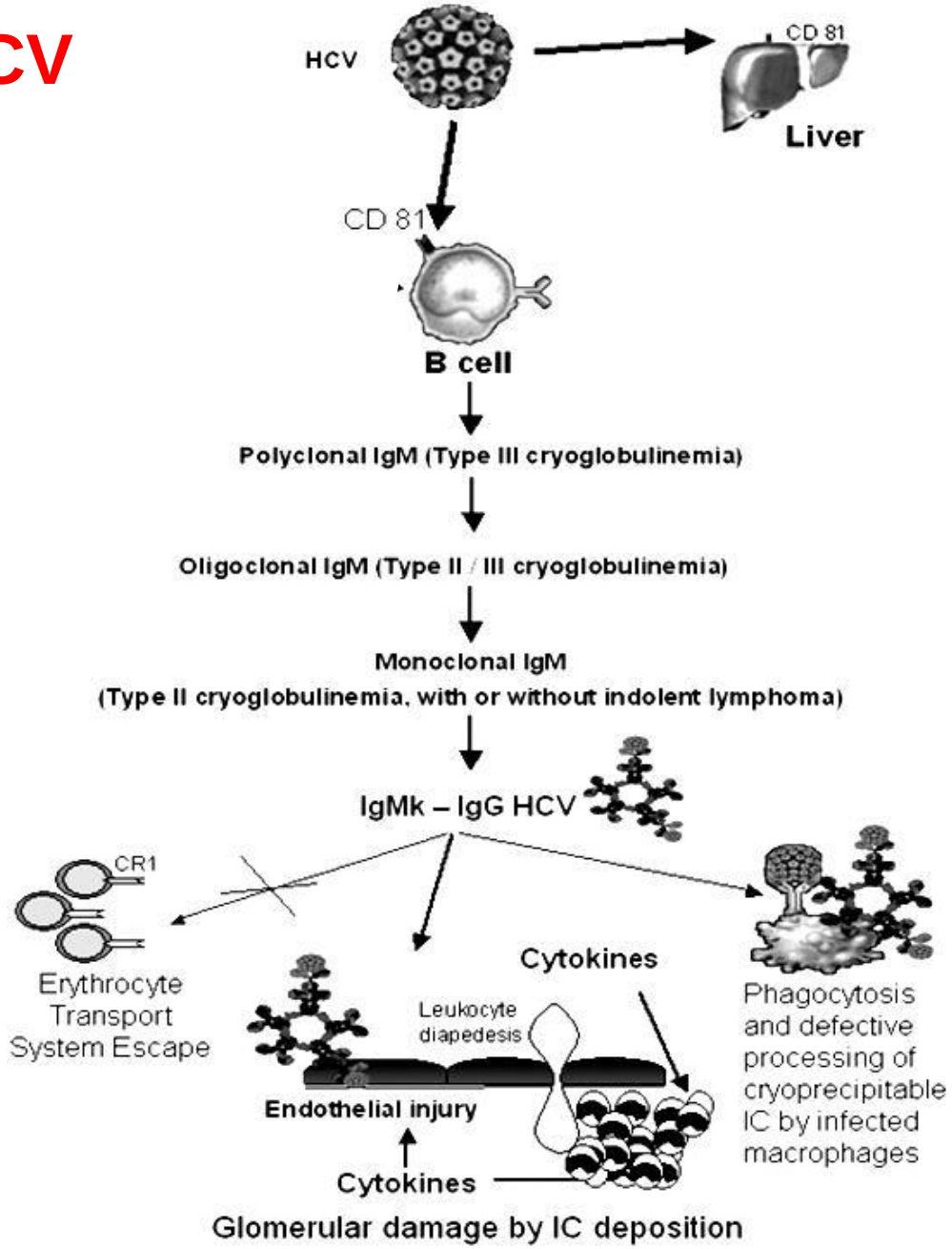
Mixed Cryoglobulinemia and Related Diseases: Hepatitis C virus first !



N = 1,434 patients

Saadoun, Arch Intern Med, 2006

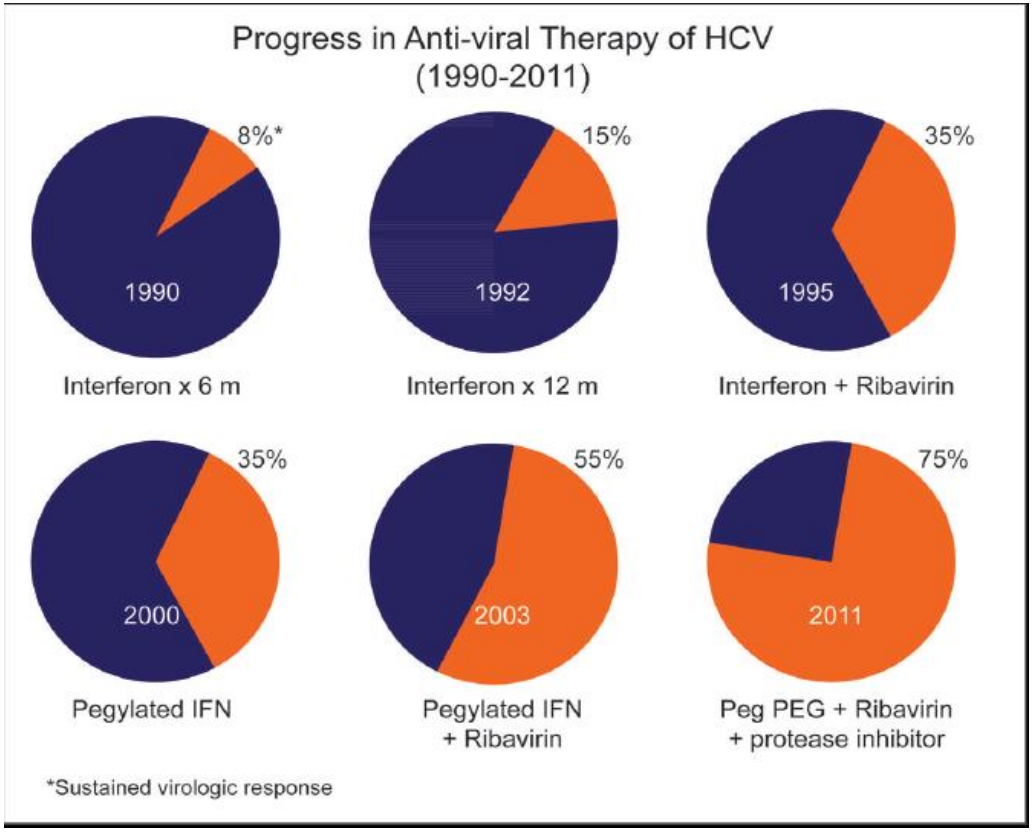
Mechanisms of HCV Cryoglobulinemia Vasculitis



Roccatello, D. et al. Nephrol. Dial. Transplant. 2004

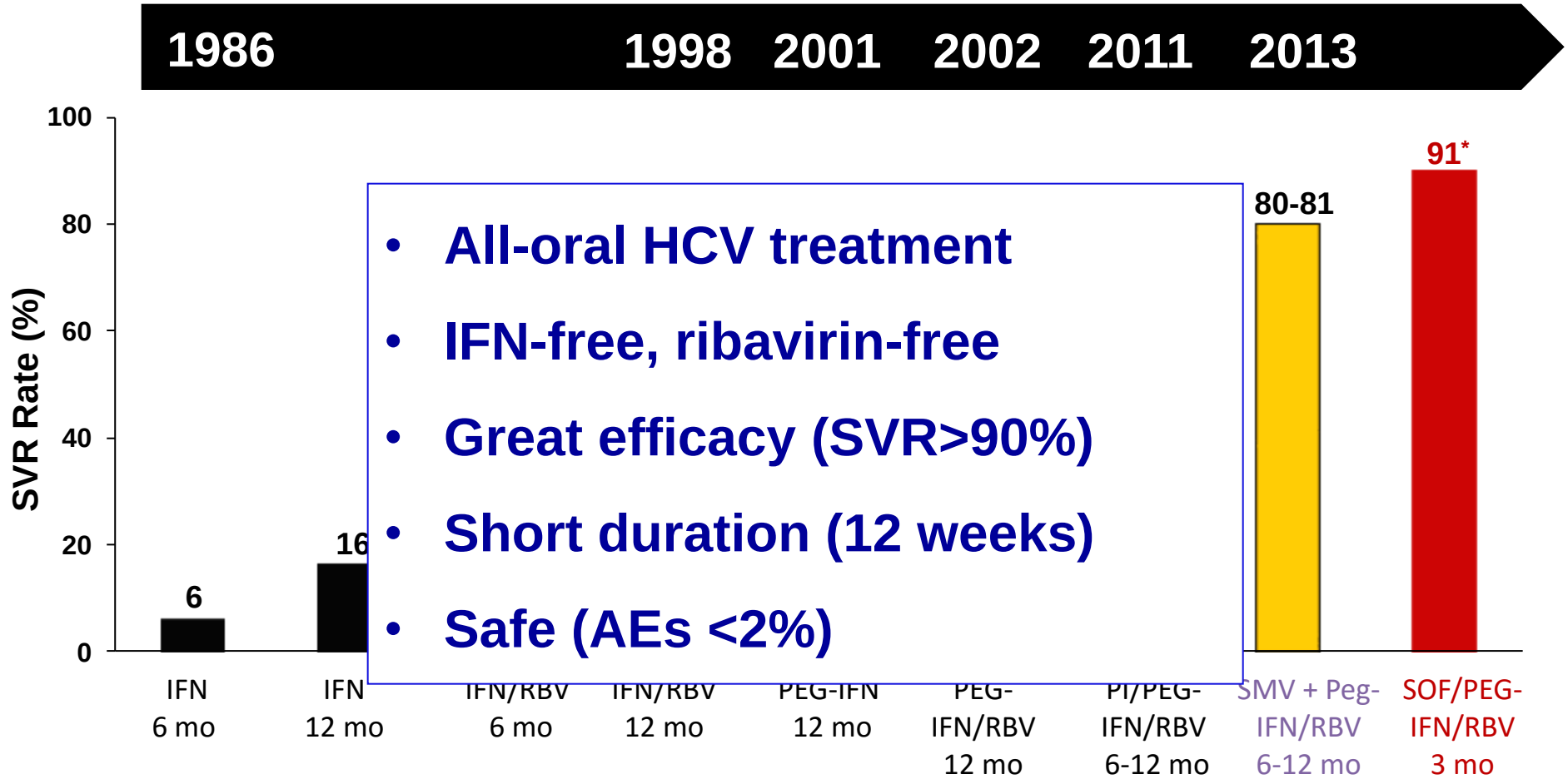
Virological Response Correlates with Clinical Remission in HCV-Cryoglobulinemia Vasculitis

- Non virological response
- Sustained virological response



Zuckerman, J Rheumatol 2000. Naarendorp, J Rheumatol 2001. Cacoub, Arthritis Rheum 2002, Zaja F, Blood 2003. Sansonno D, Blood 2003 , Cacoub, Arthritis Rheum 2005, Saadoun, Arthritis Rheum 2007; Saadoun, D et al , Ann Rheum Dis 2014

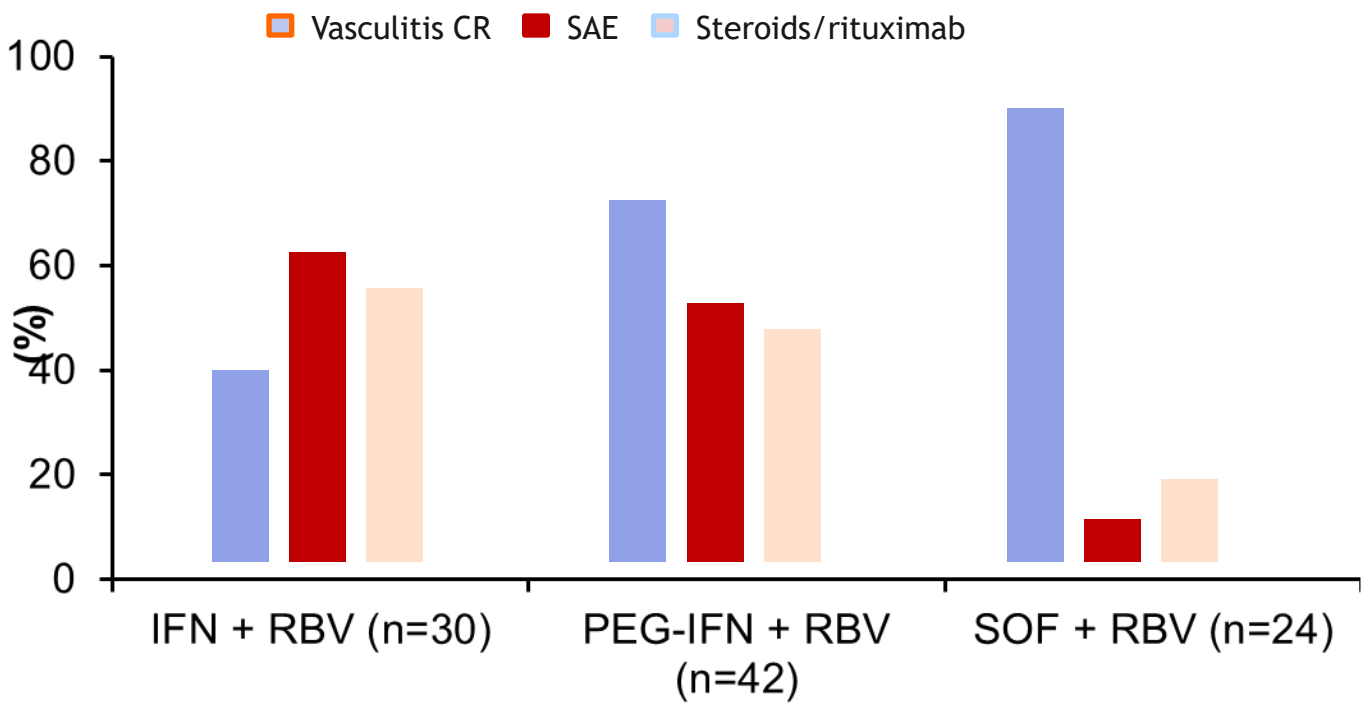
Sustained Virological Response Rates in Patients With HCV



*SVR12 rate of 90% among GT 1 patients in the Phase 3 NEUTRINO trial (12 weeks of SOF+PEG-IFN+RBV)

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02

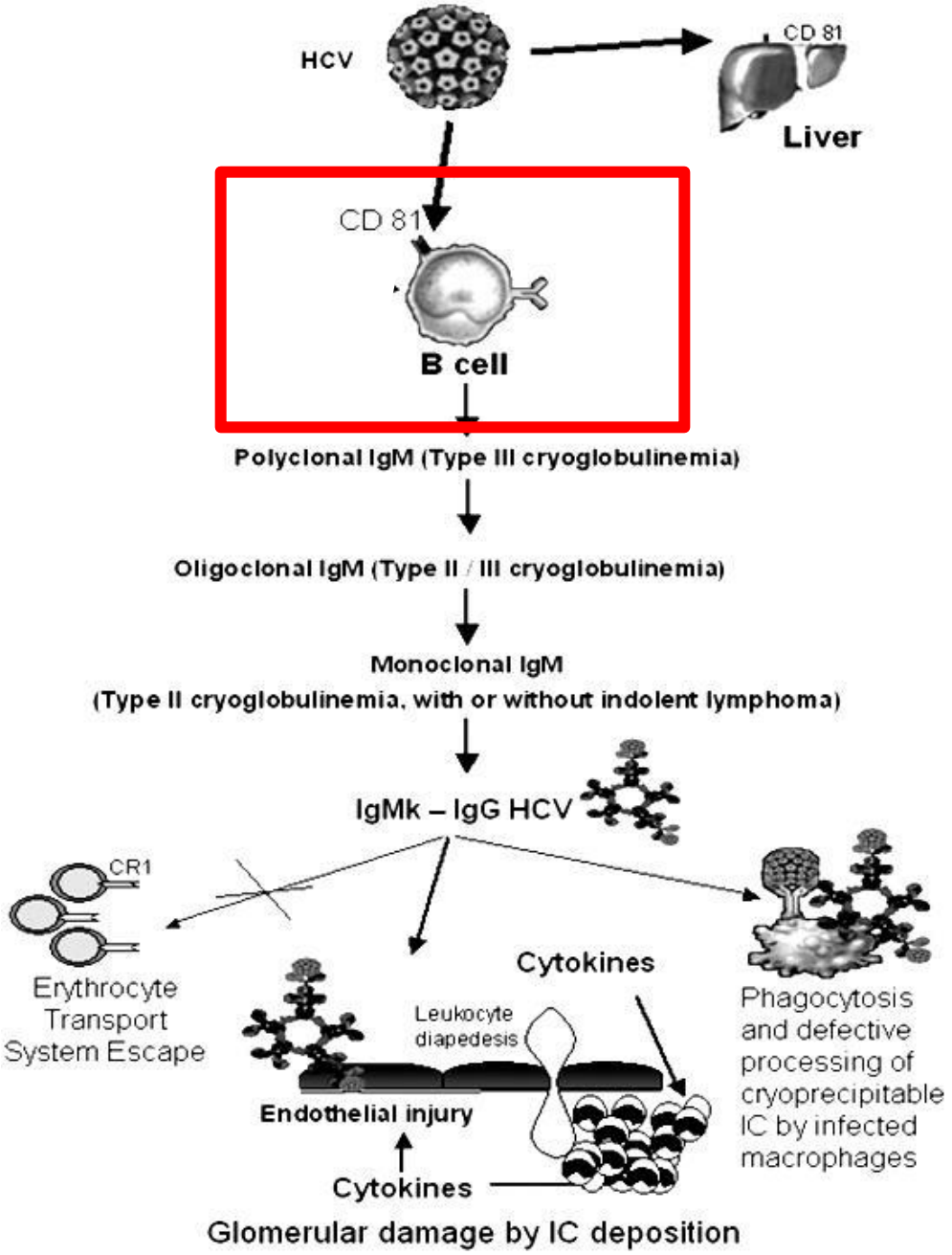
Increased antiviral efficacy is associated with less need for immunosuppressants



CR: complete remission; SAE: serious adverse event;

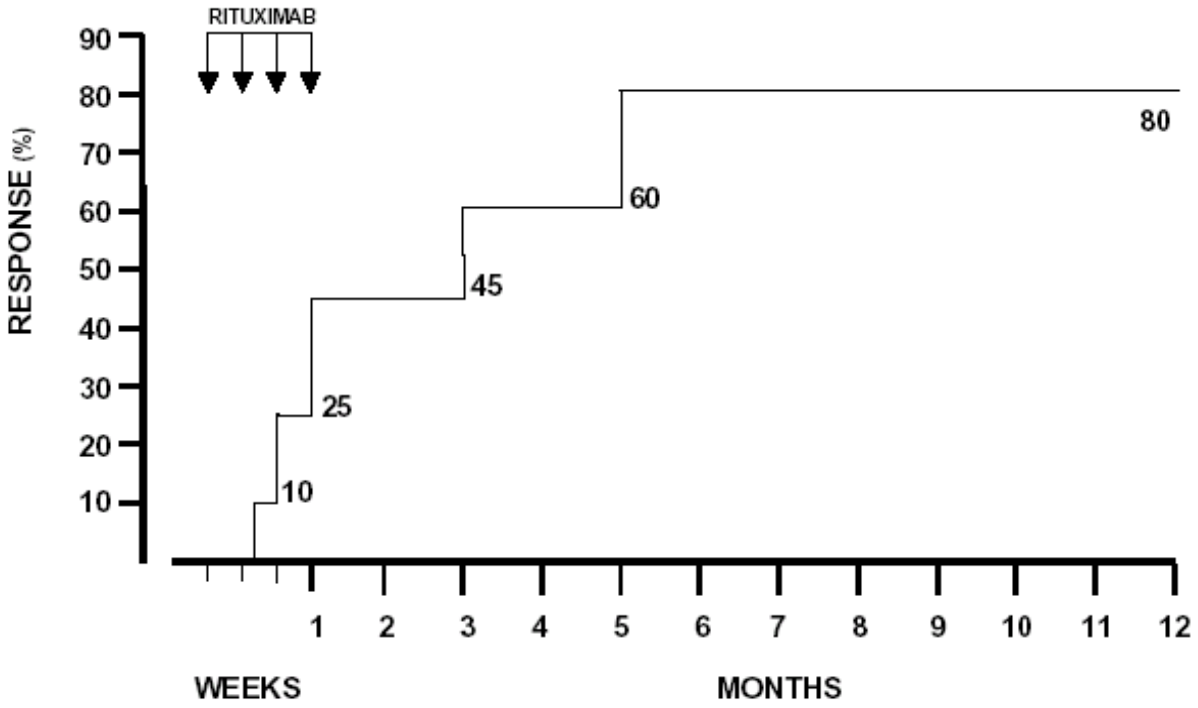
Cacoub P, Saadoun D, unpublished data

Rationale for Rituximab Treatment in Cryoglobulinemic Vasculitis



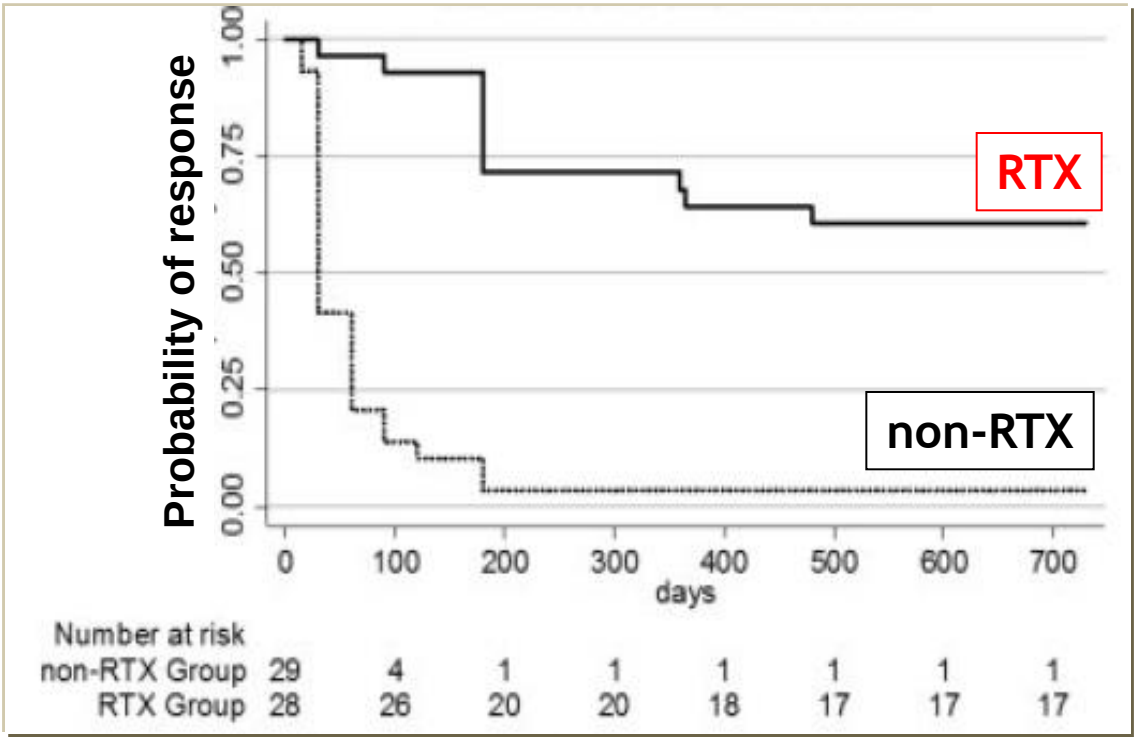
Roccatello, D. et al. Nephrol. Dial. Transplant. 2004

Treatment of Mixed Cryoglobulinemia Resistant to Interferon Alpha with Rituximab



Sansonno D et al, Zaja F et al, Blood 2003

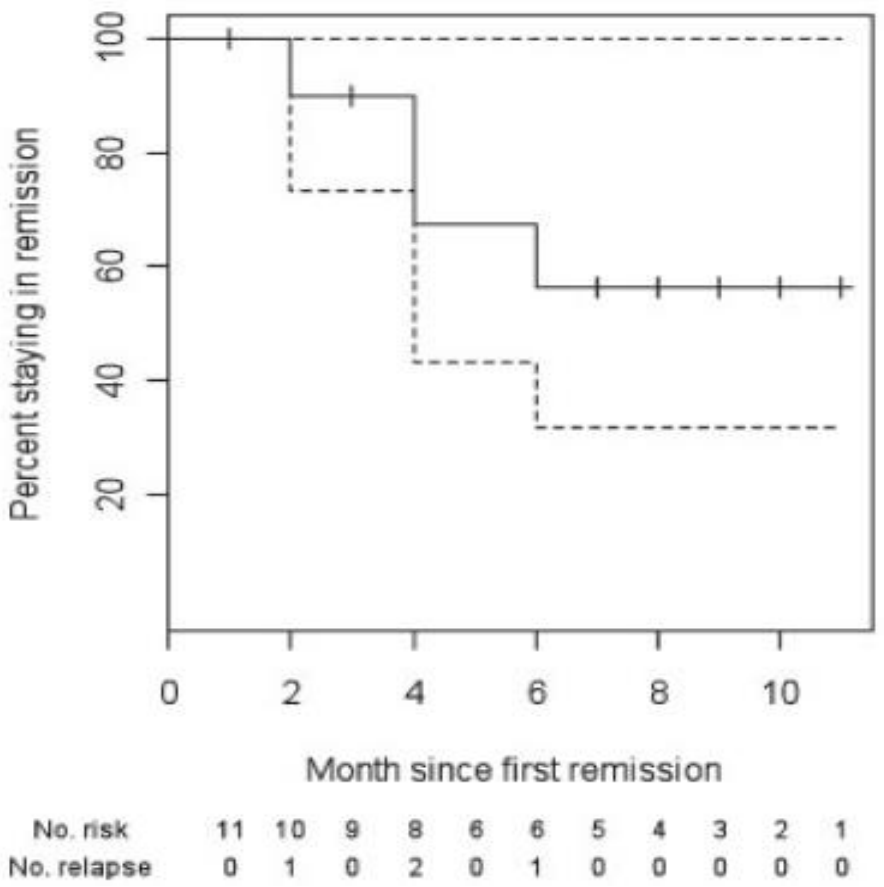
Rituximab (RTX) is Superior to Immunosuppressants for Severe HCV-Cryoglobulinemic Vasculitis



Non RTX group included conventional treatment i.e., glucocorticosteroids, azathioprine or cyclophosphamide, or plasmapheresis.

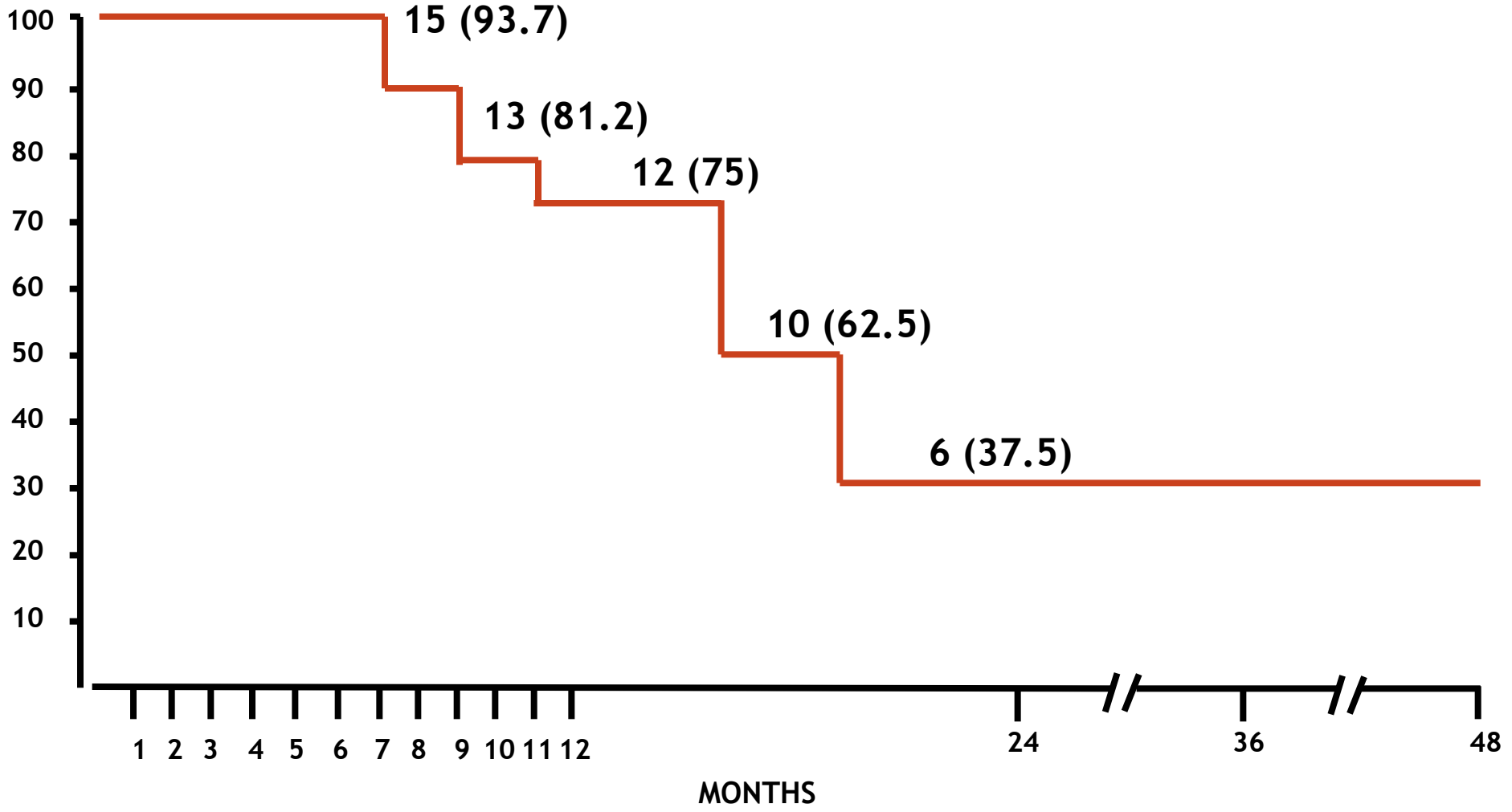
De Vita S, Arthritis Rheum 2012

Rituximab vs. Placebo in HCV-MC Vasculitis: Poor Response Maintenance



Sneller MC, Arthritis Rheum 2012

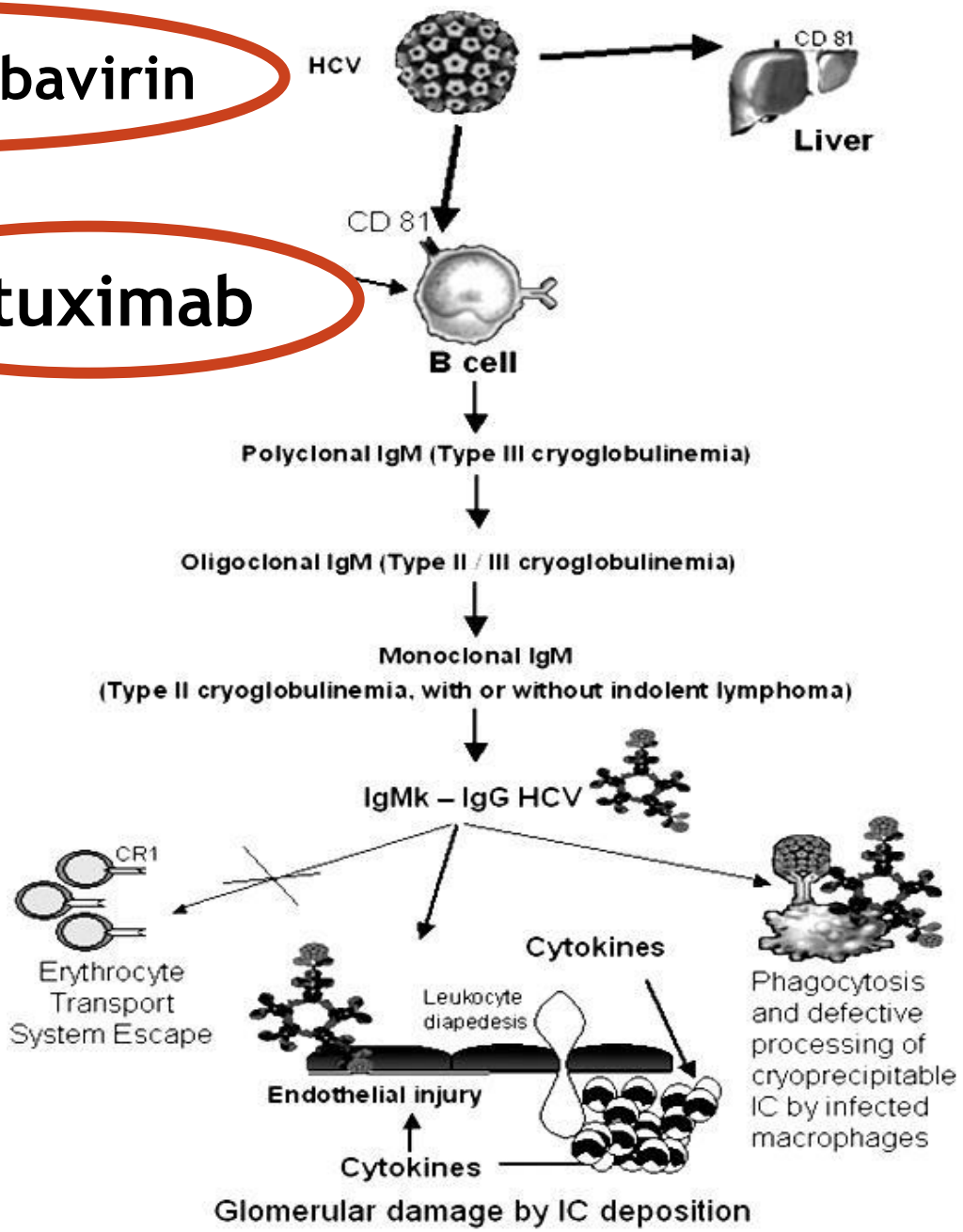
Poor Response Maintenance after Discontinuation of Rituximab for Cryoglobulinemia Vasculitis



Sansonno D et al, 2007

PegIFN plus Ribavirin

Rituximab



Rituximab plus Peg-interferon-α/ribavirin compared with Peg-interferon-α/ribavirin in hepatitis C–related mixed cryoglobulinemia

David Saadoun,[1,2] Mathieu Resche Rigon,[3] Damien Sene,[1] Benjamin Terrier,[1,2] Alexandre Karras,[4] Laurent Perard,[5] Yoland Shoindre,[1] Brigitte Coppéré,[5] François Blanc,[6] Lucile Musset,[7] Jean-Charles Piette,[1] Michele Rosenzwajg,[2] and Patrice Cacoub[1,2]

BLOOD, 22 JULY 2010 • VOLUME 116, NUMBER 3

PegIFNα-ribavirin vs. RTX plus PegIFNα-ribavirin in HCV-Mixed Cryoglobulinemia

Parameters	All n=93	PegIFNα-ribavirin n=55	RTX-PegIFNα-ribavirin n=38	*P*
Time clinical response, months	**6.8 ± 4.7**	**8.4 ± 4.7**	**5.4 ± 4.0**	0.004
Clinical response				
CR	**68 (73.1)**	**40 (72.7)**	**28 (73.7)**	**0.98**
PR	22 (23.6)	13 (23.6)	9 (23.7)	
NR	3 (3.2)	2 (3.6)	1 (2.6)	
Relapse	17 (18.3)	10 (18.1)	7 (18.4)	

Saadoun D et al, Blood 2010

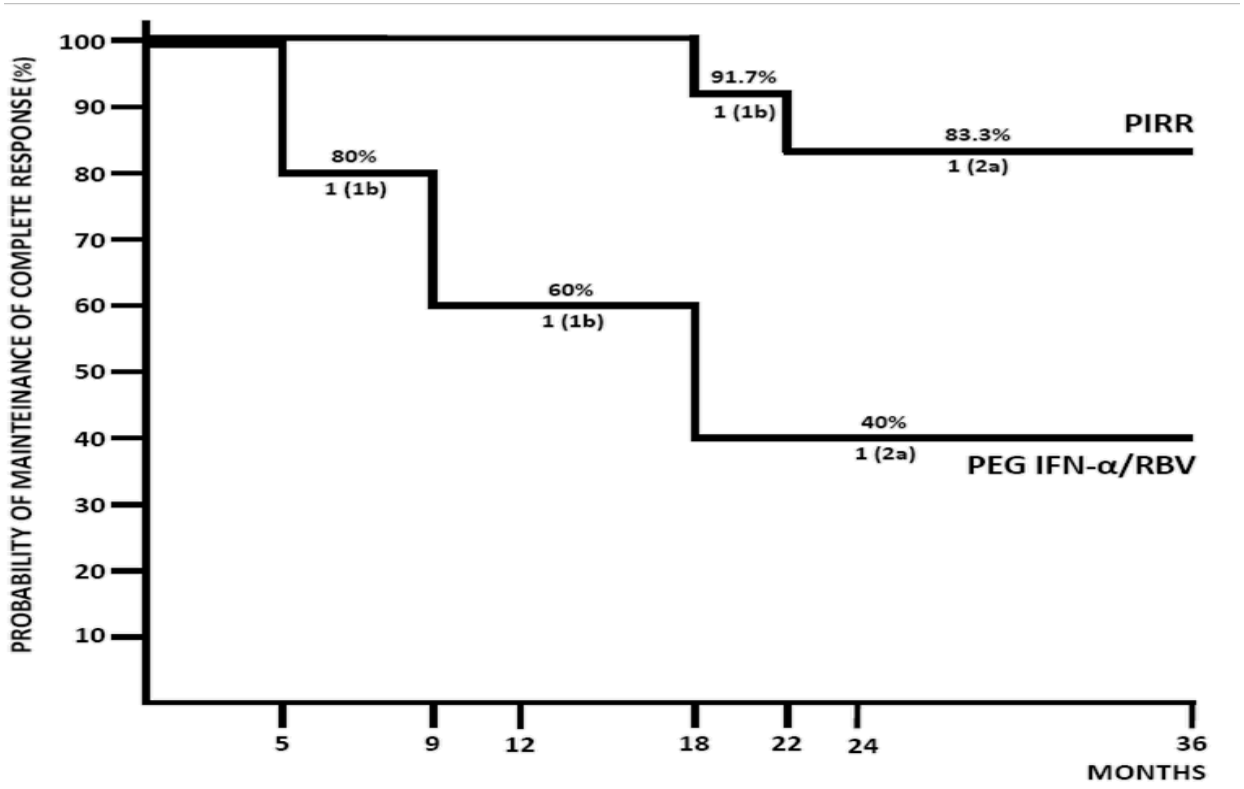
Better Course of Kidney Parameters in HCV-Mixed Cryoglobulinemia who Received Rituximab

	PegIFNα-ribavirin n=10	*p*	RTX-PegIFNα-ribavirin n=21	*p*
Kidney inv. CR	**4 (40)**		**17 (80.9)**	**0.04**
Creatininemia (µmol/l)				
Baseline	150 ± 30		**217 ± 47**	
EOF	169 ± 44	0.28	**136 ± 27**	0.03
GFR (ml/min)				
Baseline	58 ± 7		**42 ± 5**	
EOF	59 ± 9	0.41	**57 ± 4**	0.01
Daily Proteinuria (gr/d)				
Baseline	3.1 ± 0.9		**3 ± 1**	
EOF	1.2 ± 0.5	0.046	**0.4 ± 0.1**	<0.001

Saadoun D et al, Blood 2010

RTX/Peg-IFNα-Ribavirin vs. Peg-IFNα-Ribavirin in HCV Systemic Vasculitis

Maintenance of Complete Response

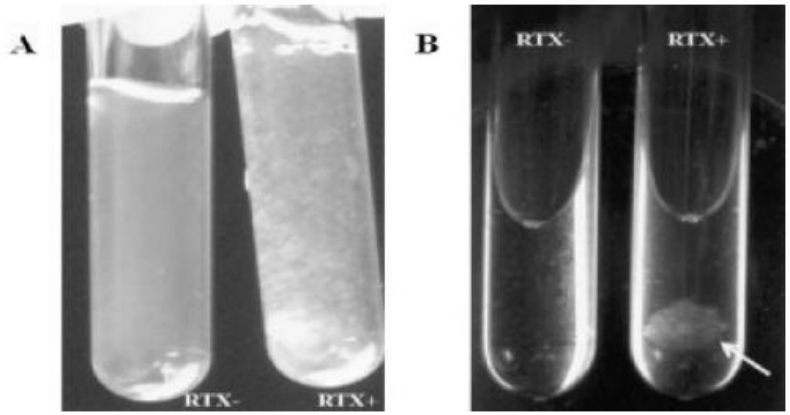


Dammacco F et al, Blood 2010

ARTHRITIS & RHEUMATISM
Vol. 60, No. ●, Month 2009, pp 000–000
DOI 10.1002/art.●

Rituximab May Complex With IgMκ Mixed Cryoglobulin and Induce Severe Systemic Reactions in Patients With Hepatitis C Virus–Induced Vasculitis

Damien Sène, Pascale Ghillani-Dalbin, Zahir Amoura, Lucile Musset, and Patrice Cacoub



Risk Factors of Cryoglobulinemia Vasculitis Worsening with Rituximab

	Patients with vasculitis flare (n=7)	Patients without vasculitis flare (n=43)	
Gender, male n (%)	5 (71%)	21 (49%)	
Age, median [min; max]	75.0 (54.0 to 78.0)	56.0 (49.0 to 67.0)	0.15
Type II cryoglobulin	7 (100%)	34 (81%)	0.58
IgM Kappa	7 (100%)	29 (88%)	1
Cryoglobulin level at diagnosis (g/l), median (IQT)	**2.1 (1.7-2.5)**	**0.4 (0.2-0.8)**	**0.0004**
Etiology of cryoglobulinemic			
Idiopathic	1 (14%)	4 (9%)	0.55
Lymphoproliferation associated to HCV	**4 (57%)**	**5 (12%)**	**0.015**
Autoimmune disease	1 (14%)	6 (14%)	1
HCV	6 (86%)	31 (72%)	0.66
Cirrhosis	3 (43%)	6 (14%)	0.38

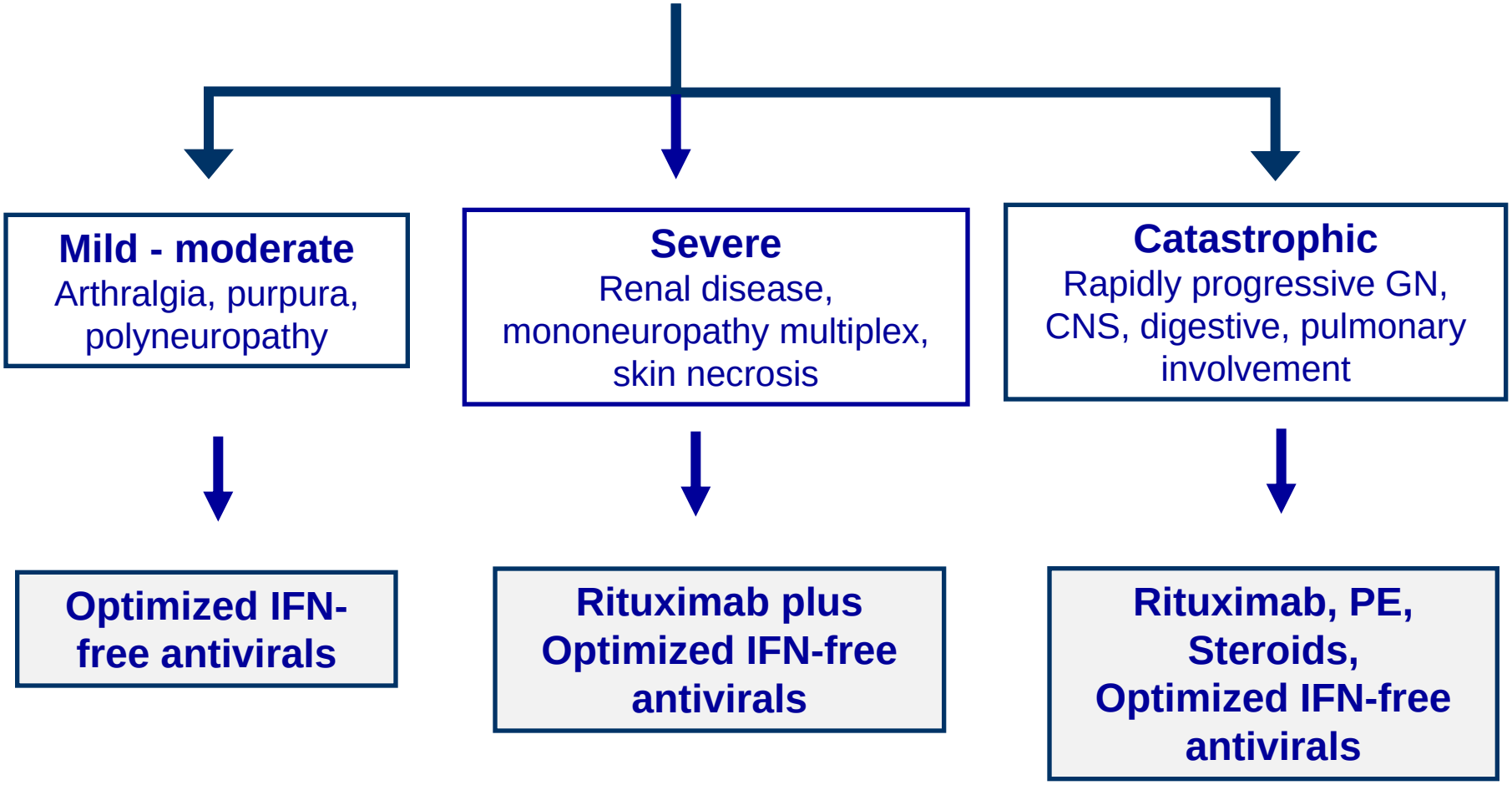
Desbois AC et al, 2016

Risk Factors of Cryoglobulinemia Vasculitis Worsening with Rituximab

	Patients with flare (n=8)	Patients without flare (n=60)	
Fever, n (%)	1 (12%)	4 (7%)	0.48
Kidney involvement, n (%)	**7 (88%)**	**14 (23%)**	**0.0008**
Skin, n(%)	7 (88%)	36 (60%)	0.24
Nerve, n (%)	6 (75%)	29 (48%)	0.26
GUT, n (%)	2 (25%)	3 (5%)	0.10
Heart, n (%)	0 (0%)	2 (3%)	1
Cryoglobulin level (g/l), mean	1.4	0.4	0.10
Creatinin (µmol/l),	96.5 [58.0 to 375.0]	71.0 [30.0 to 256.0]	0.22
Gammaglobulin (g/l),	**2.9 [2.3-13.8]**	**10.1 [3.3-40.0]**	**0.005**
C4 (g/l),	**0.02**	**0.05**	**0.023**
Plasmapheresis, n (%)	1 (12%)	8 (14%)	1
Corticoids, n (%)	3 (38%)	21 (35%)	1
Rituximab 1g x2	1 (12.5%)	5 (8.3%)	
Rituximab 375mg/m2 x 4	7 (87.5%)	55 (91.7%)	

Desbois AC et al, 2016

HCV Cryoglobulinemia Vasculitis Therapeutic Strategies



- If failure or contra-indication to HCV treatment, Rituximab may be used alone. HCV: hepatitis C virus; GN: glomerulonephritis; CNS: central nervous system

Cacoub P et al, Ann Rheum Dis 2013

Gracias

- **D. Saadoun, Paris**
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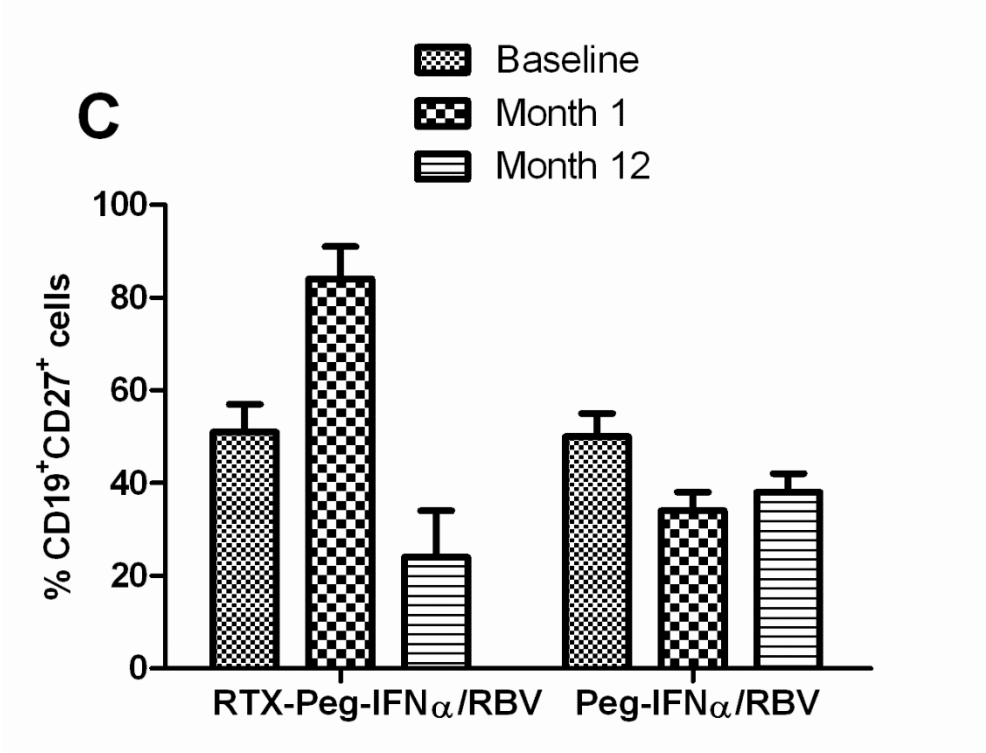
- GERMIVIC members

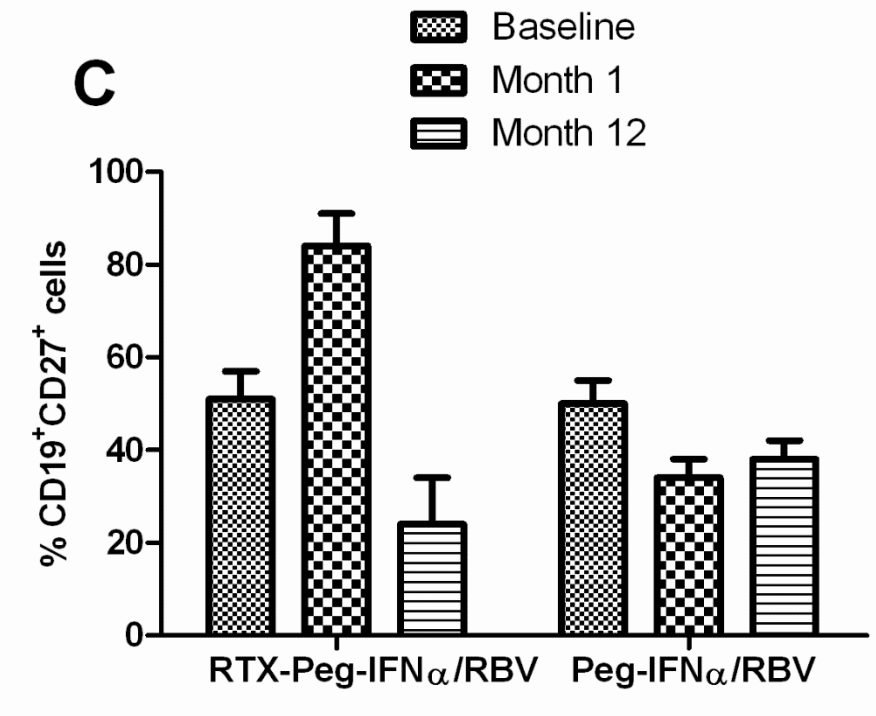
Antiviral therapy alone decreases the memory B cells

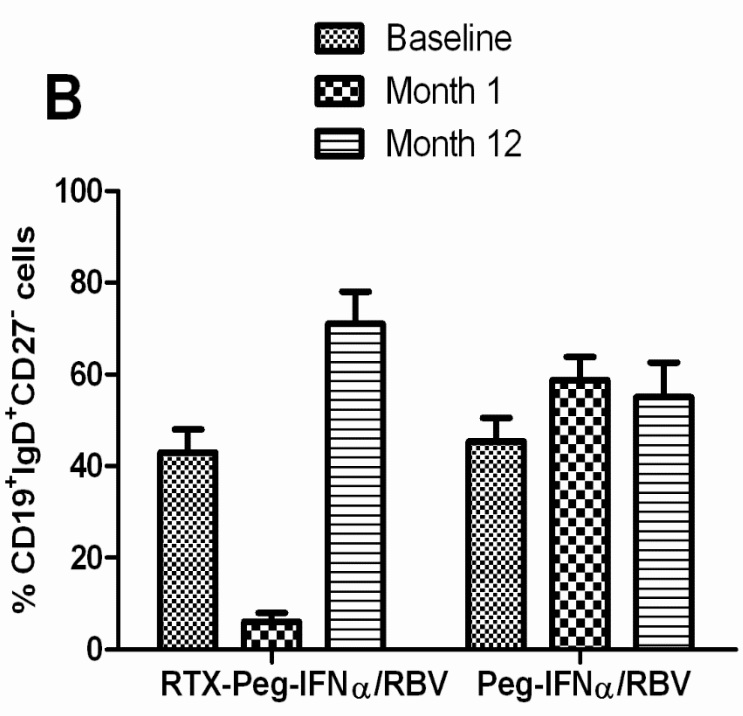


Saadoun D et al, Blood 2010

Antiviral therapy alone decreases the memory B cells

Antiviral therapy plus Rituximab decrease naive B-cells





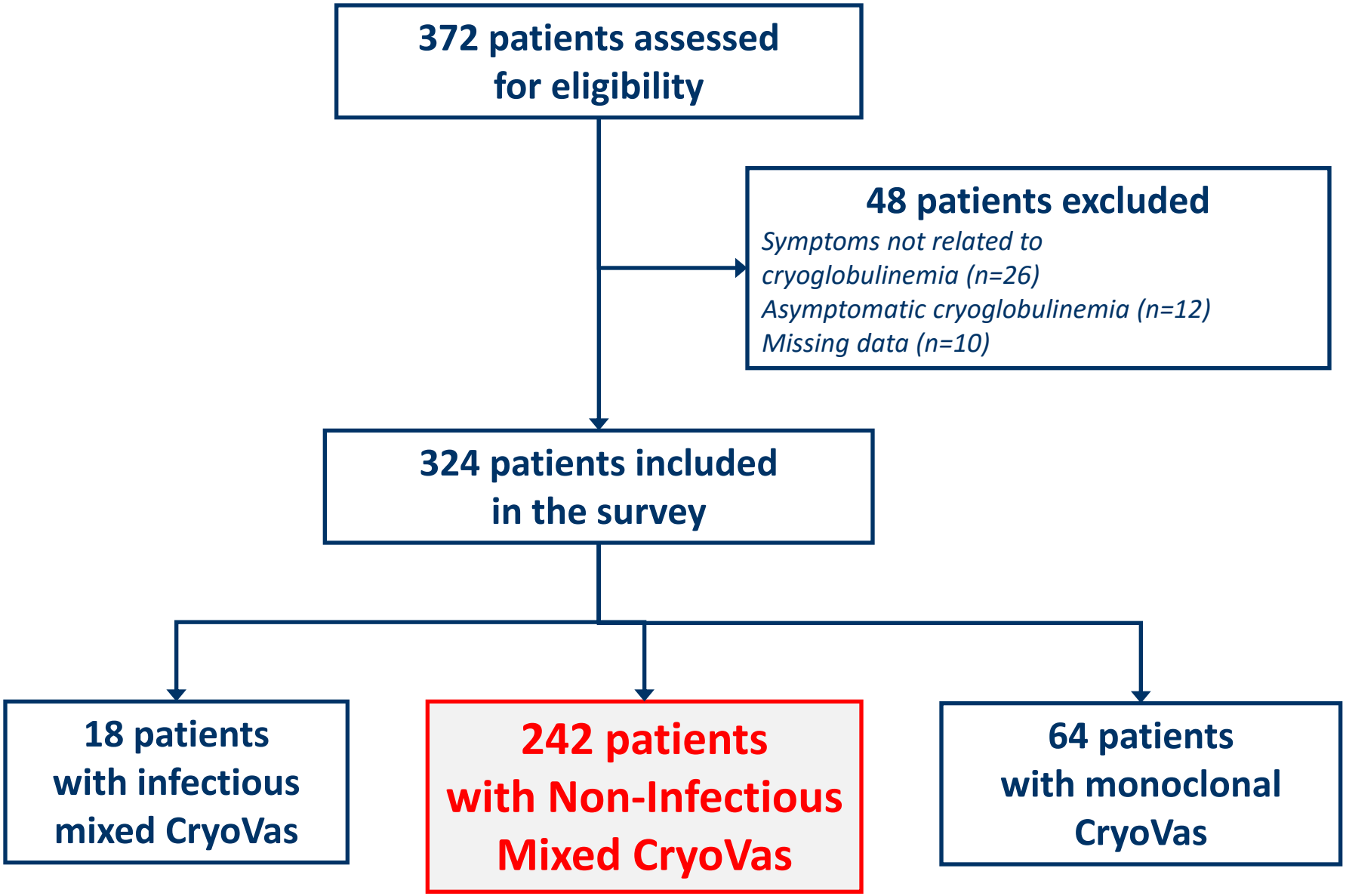
Saadoun D et al, Blood 2010

blood

2012 119: 5996-6004
Prepublished online April 3, 2012;
doi:10.1182/blood-2011-12-396028

Management of noninfectious mixed cryoglobulinemia vasculitis: data from 242 cases included in the CryoVas survey

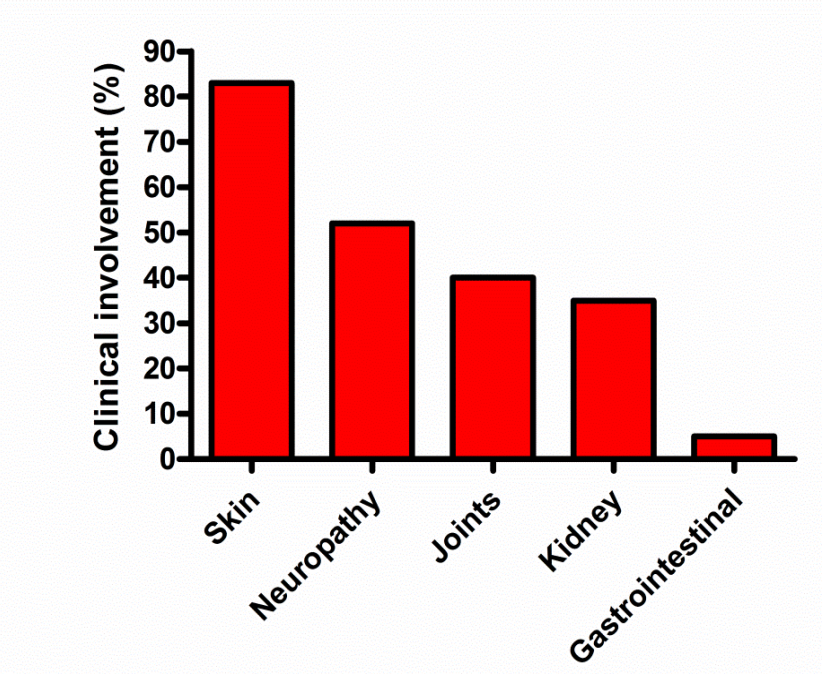
Benjamin Terrier, Evguenia Krastinova, Isabelle Marie, David Launay, Adeline Lacraz, Pauline Belenotti, Luc de Saint-Martin, Thomas Quemeneur, Antoine Huart, Fabrice Bonnet, Guillaume Le Guenno, Jean-Emmanuel Kahn, Olivier Hinschberger, Patricia Rullier, Elisabeth Diot, Estibaliz Lazaro, Frank Bridoux, Thierry Zénone, Fabrice Carrat, Olivier Hermine, Jean-Marc Léger, Xavier Mariette, Patricia Senet, Emmanuelle Plaisier and Patrice Cacoub



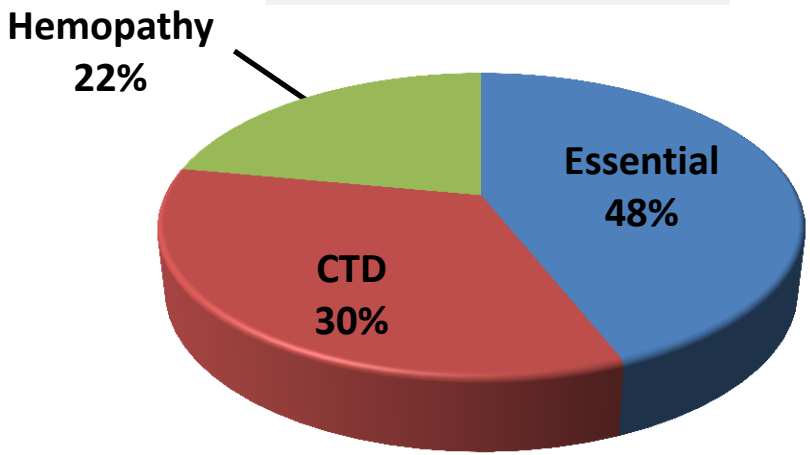
Terrier B et al. Blood 2012

Baseline Characteristics of Non-Infectious Mixed Cryoglobulinemia

62.6 ± 14.5 years
Females : 69%



Etiologic factors



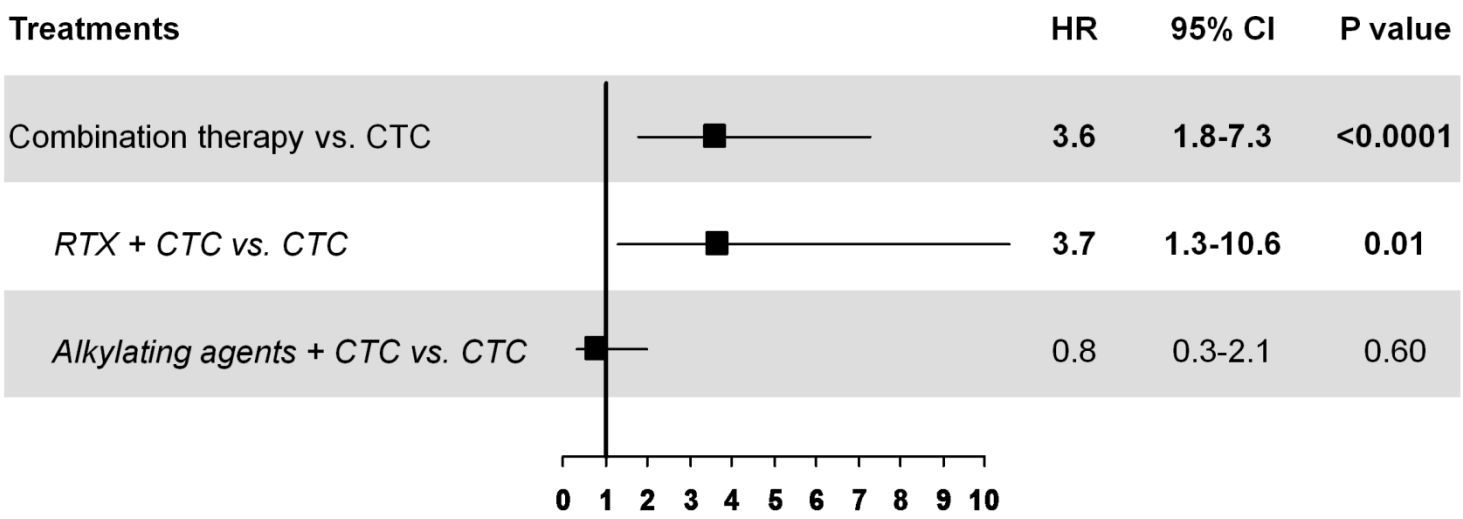
Terrier B et al. Blood 2012

Therapeutic Regimens Used in Non-Infectious Mixed CryoVas

	n=209
Lines of treatment, n (%)	1.8 ± 1.2
Corticosteroids	209 (100%)
Rituximab	104 (50%)
Alkylating agents	97 (46%)
Plasmapheresis	43 (21%)
Azathioprine/MMF	31 (15%)

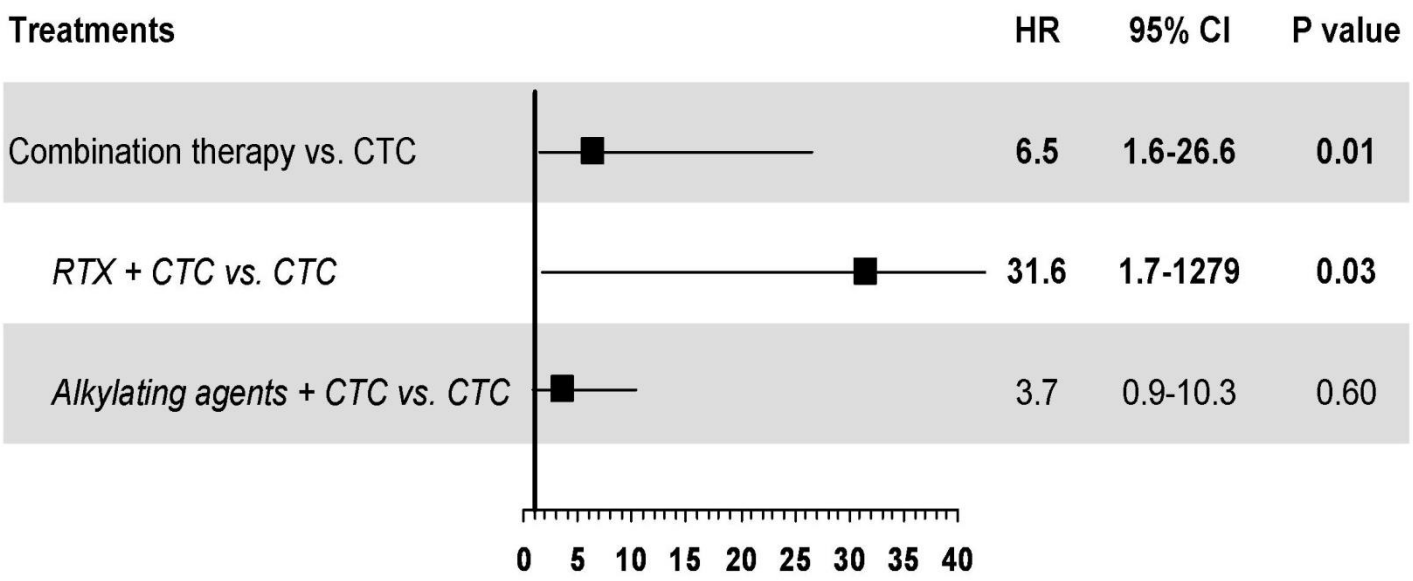
Terrier B et al. Blood 2012

Therapeutic Strategies Associated with a Complete Clinical Response in Non-Infectious Mixed Cryoglobulinemia



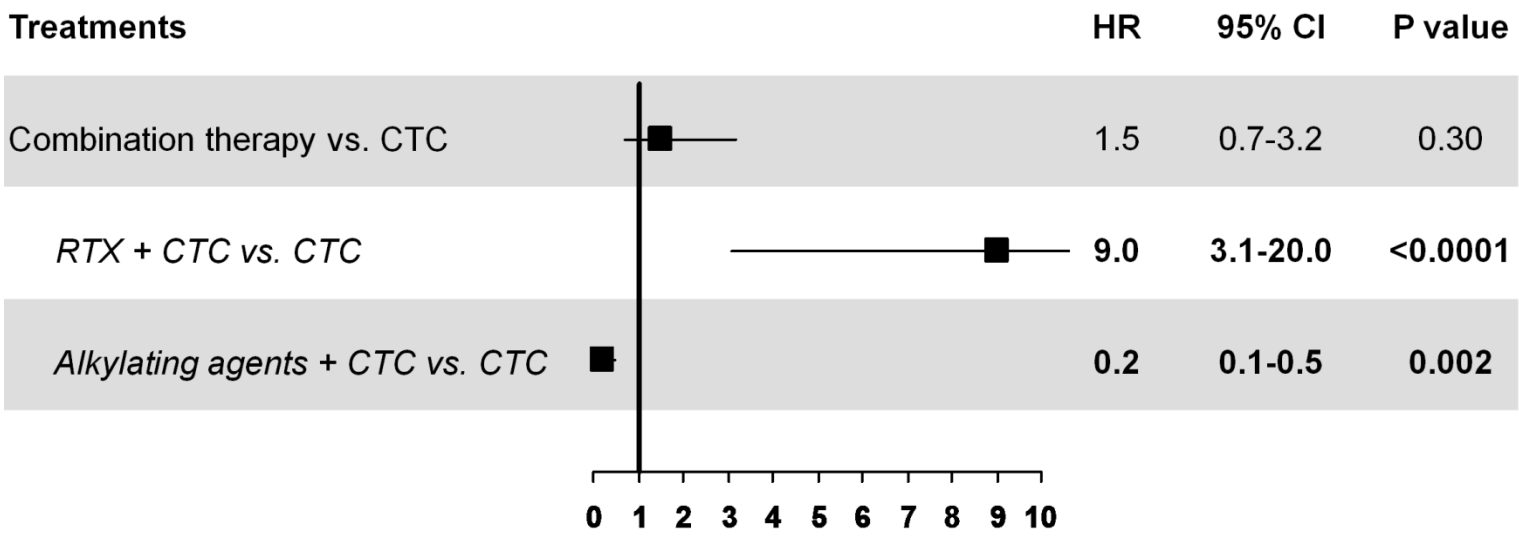
Terrier B et al. Blood 2012

Greater Efficacy of Rituximab plus Steroids on Renal Response in Non-Infectious Mixed Cryoglobulinemia



Terrier B et al. Blood 2012

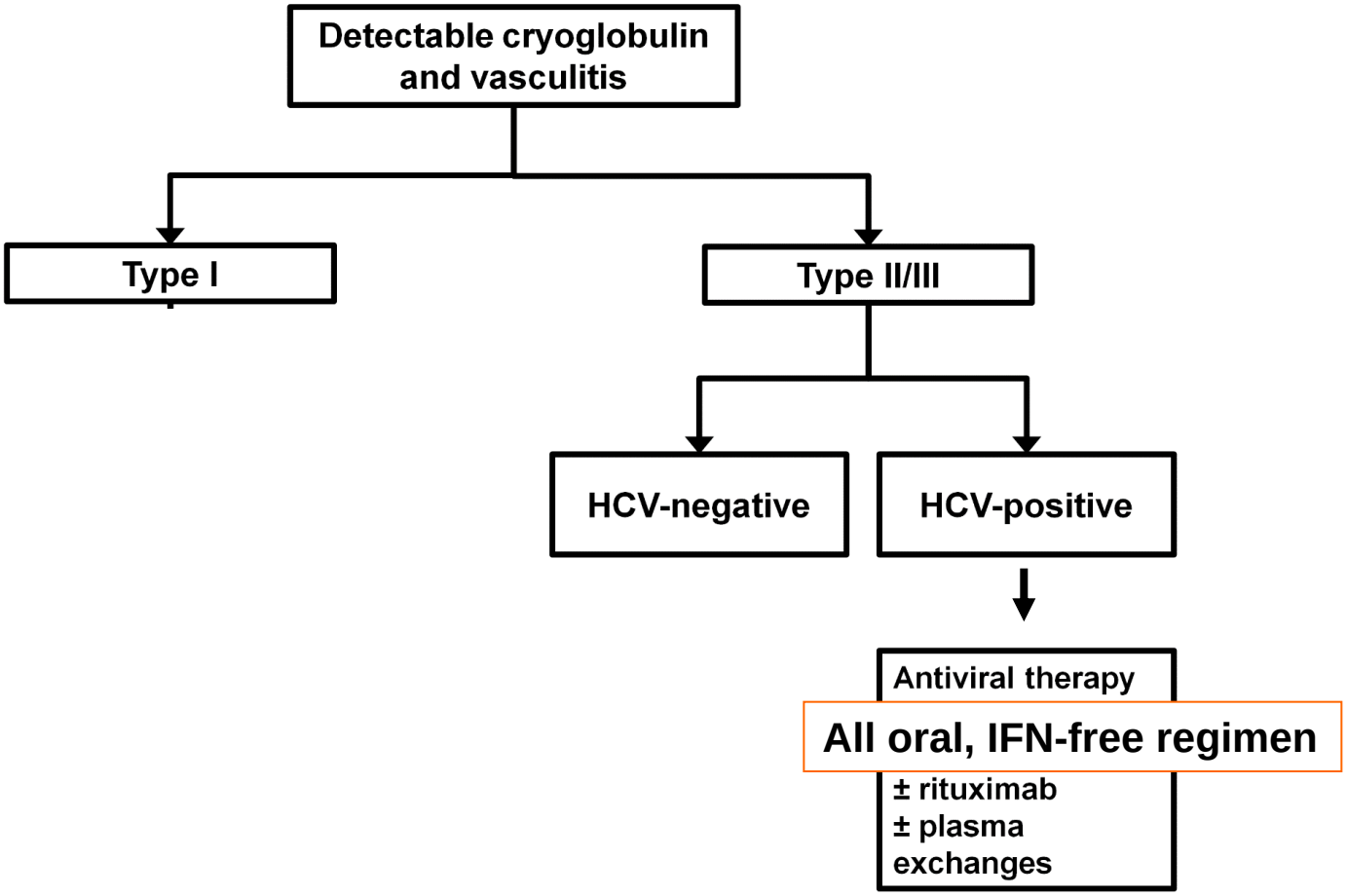
Increased Risk of Severe Infections Using Rituximab plus Steroids in Non-Infectious Mixed Cryoglobulinemia



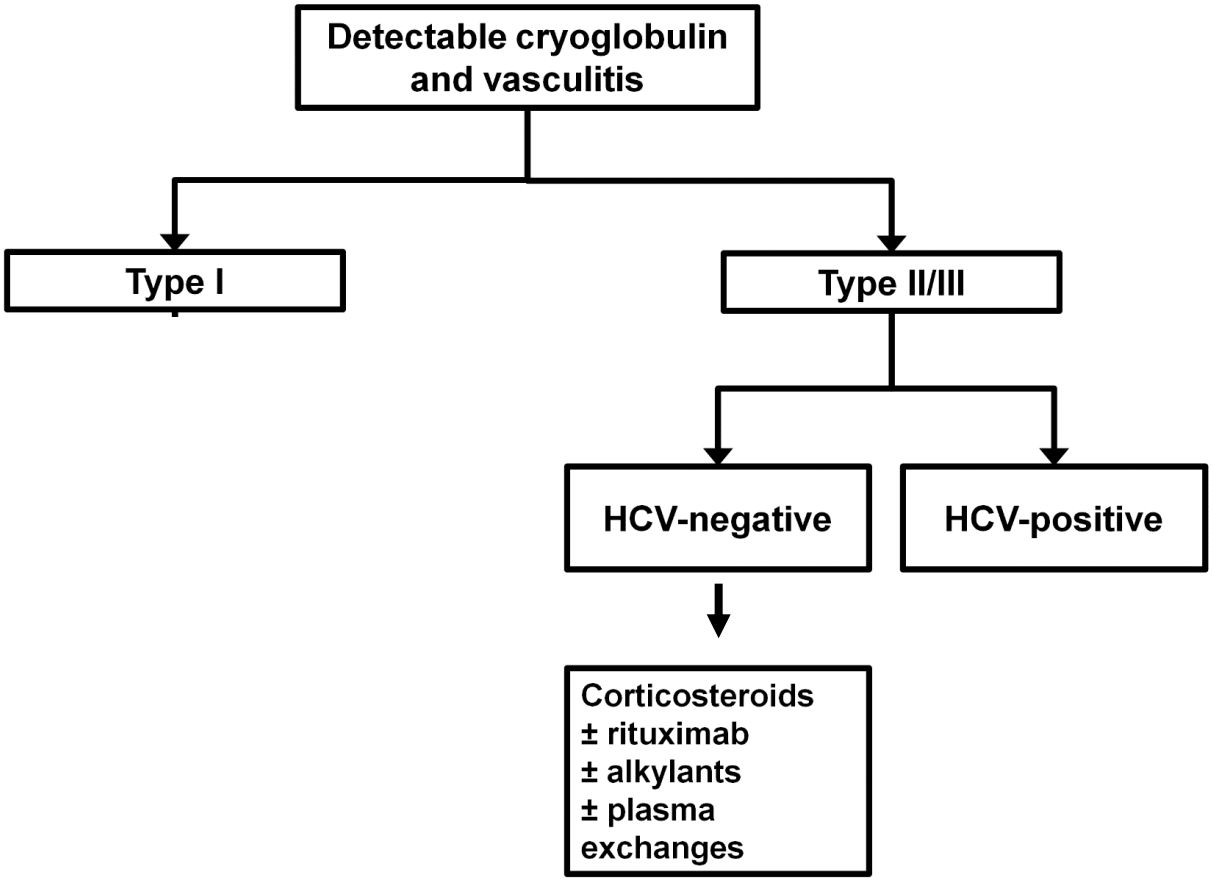
- **Prednisone > 50 mg/d was associated with serious infections (71% vs. 39%, P=0.008)**

Terrier B et al. Blood 2012

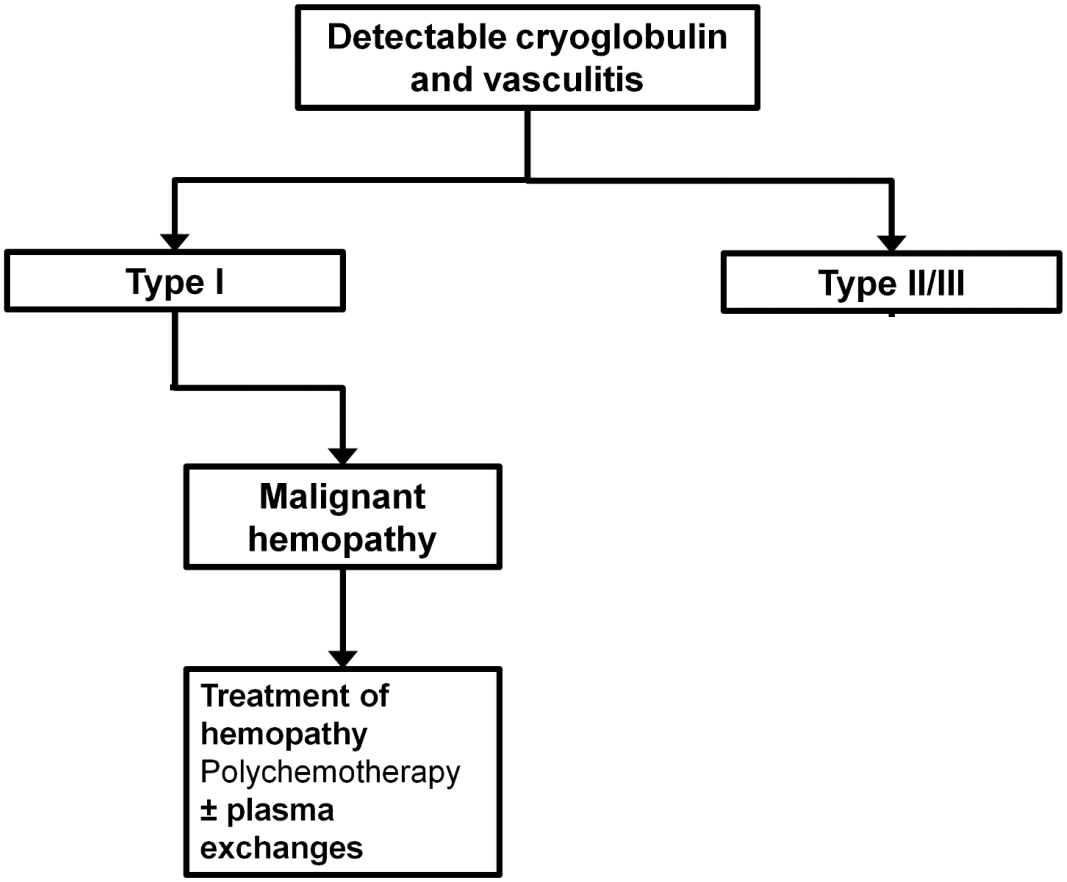
Management According to the Type of Cryoglobulin and HCV Status



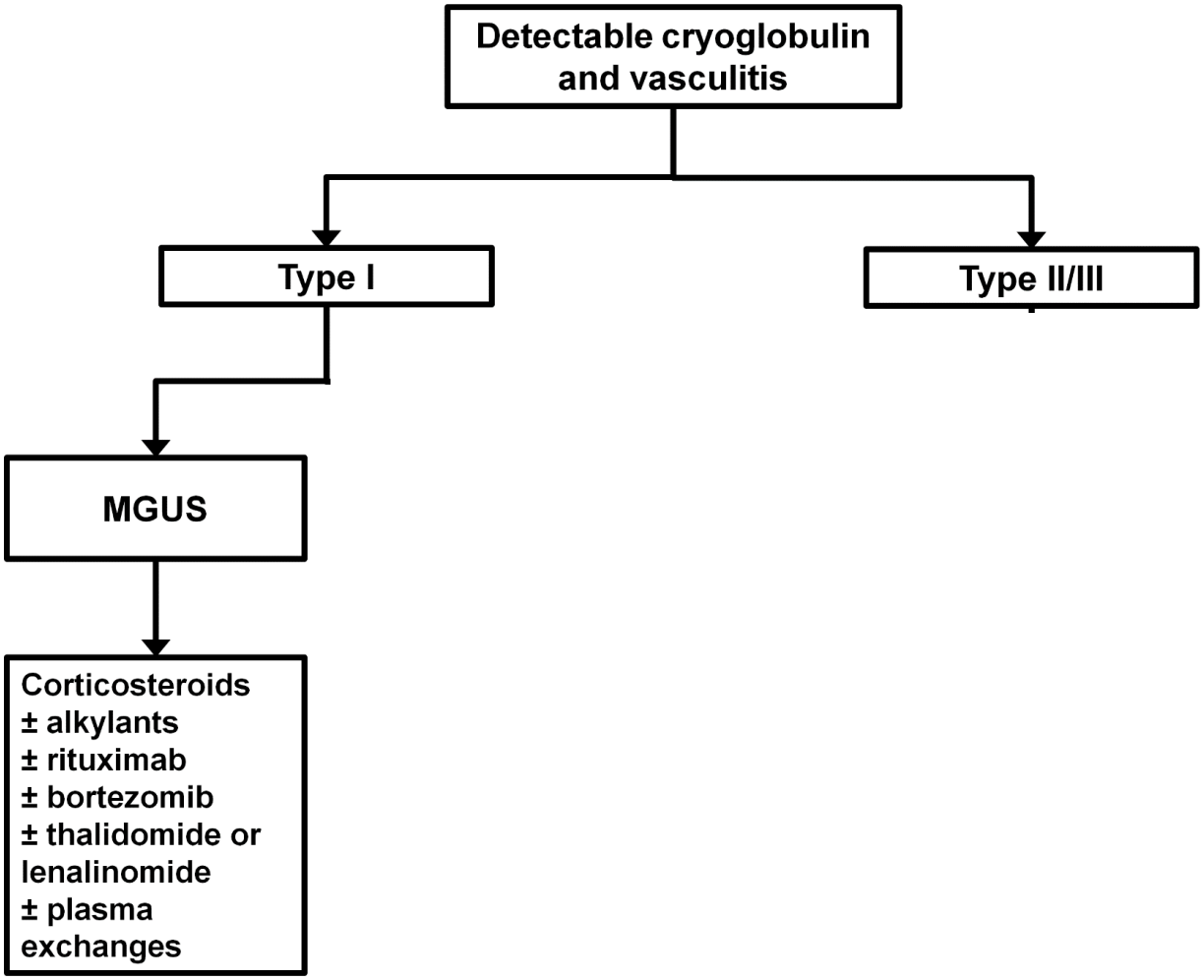
ManagManagement According to the Type of Cryoglobulin and HCV Status



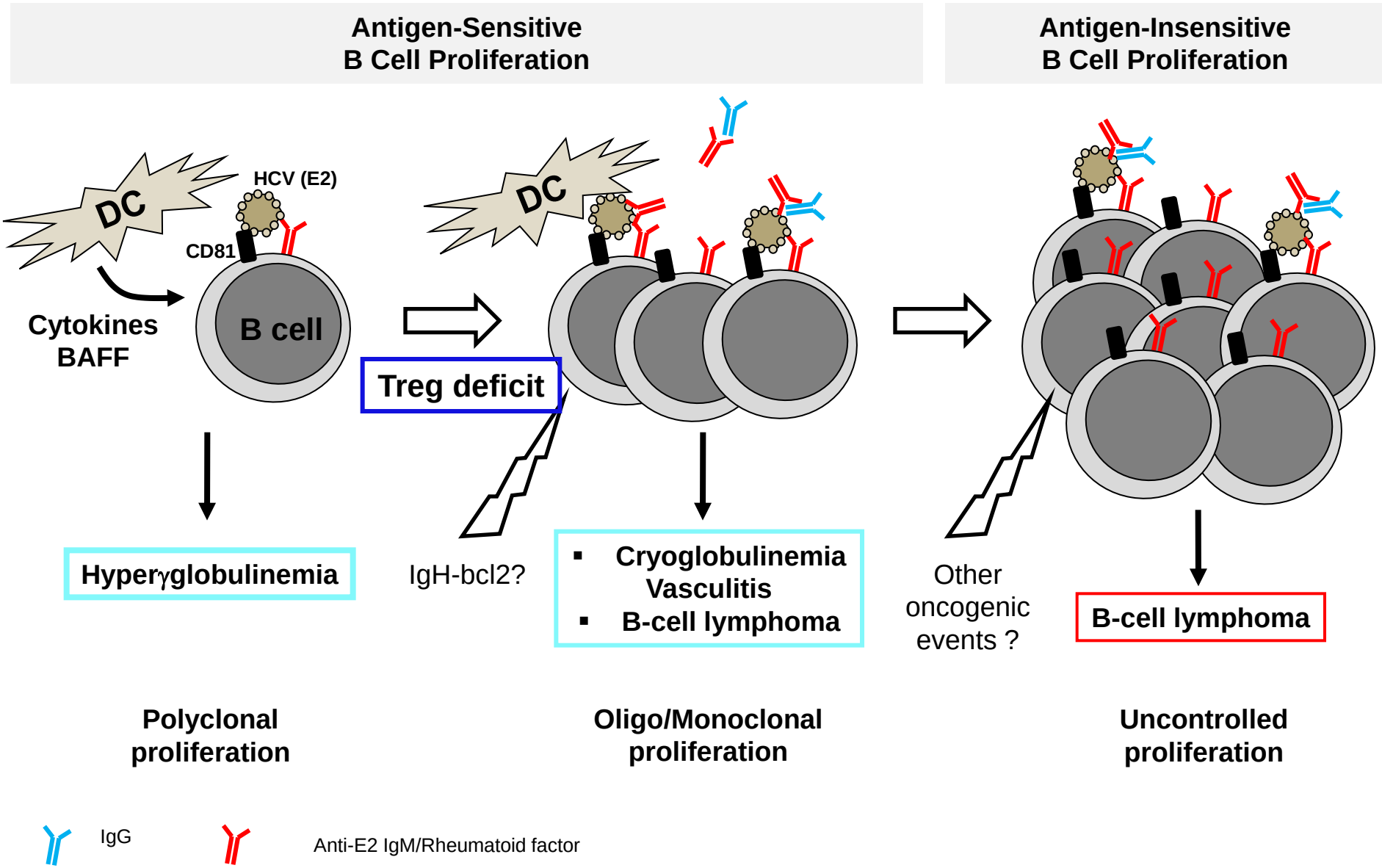
Management According to the Type of Cryoglobulin and HCV Status



Management According to the Type of Cryoglobulin and HCV Status



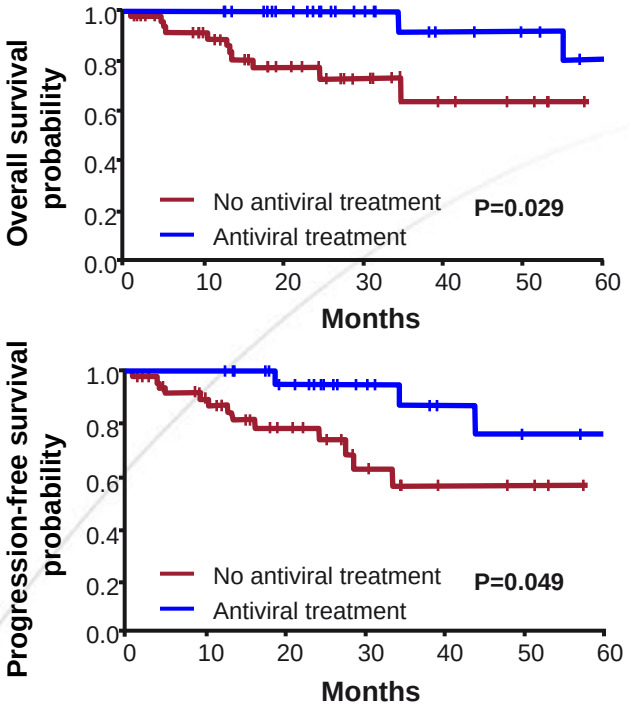
HCV Induced Lymphoproliferative Disorders: from Cryoglobulinemia to B-Cell Lymphoma



SVR is associated with improvements in HCV-related B-cell lymphoma

- n=116
- DLBCL, 39%; MZL, 39%; other, 22%
- HCV therapy in 70 patients
- PEG-IFN + RBV (+ PI in six patients)
- SVR 43/70 (61%)

- **SVR correlated with haematological response in MZL (P<0.001)**



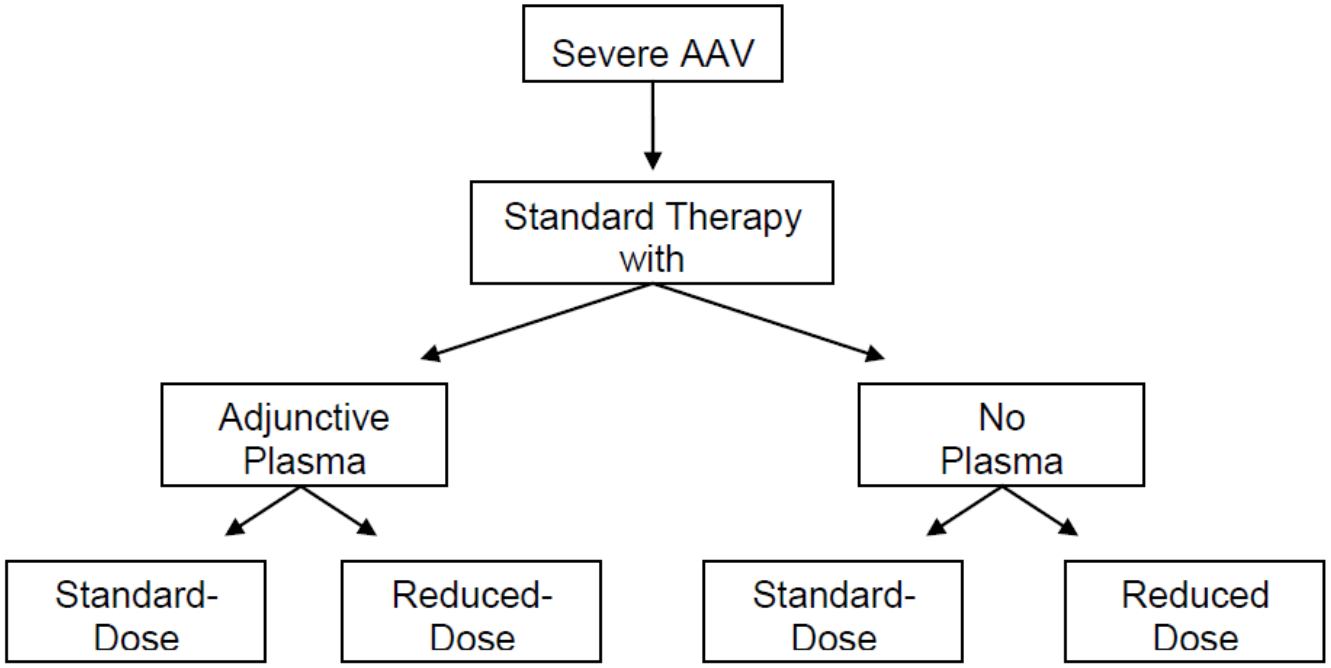
DLBCL: diffuse large B-cell lymphoma;
MZL: marginal zone lymphoma

Michot JM, et al. Am J Hematol 2015;90:197–203

Unsolved Issues in the Treatment of ANCA Vasculitis

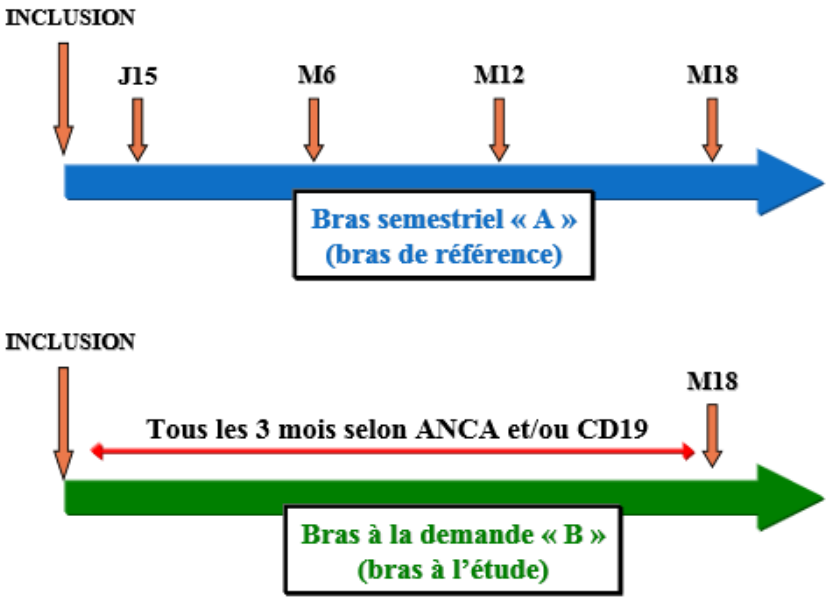
PEXIVAS Trial

- **700 patients**
- **GFR < *50 ml/min***
- ***IAH***



Essai MAINRITSAN2
Modalités d'administration du rituximab

- ✓ 160 patients
- ✓ Critère de jugement principal : survie sans rechute
- ✓ Bras :
  - ✓ RTX semestriel
  - ✓ RTX selon les paramètres biologiques

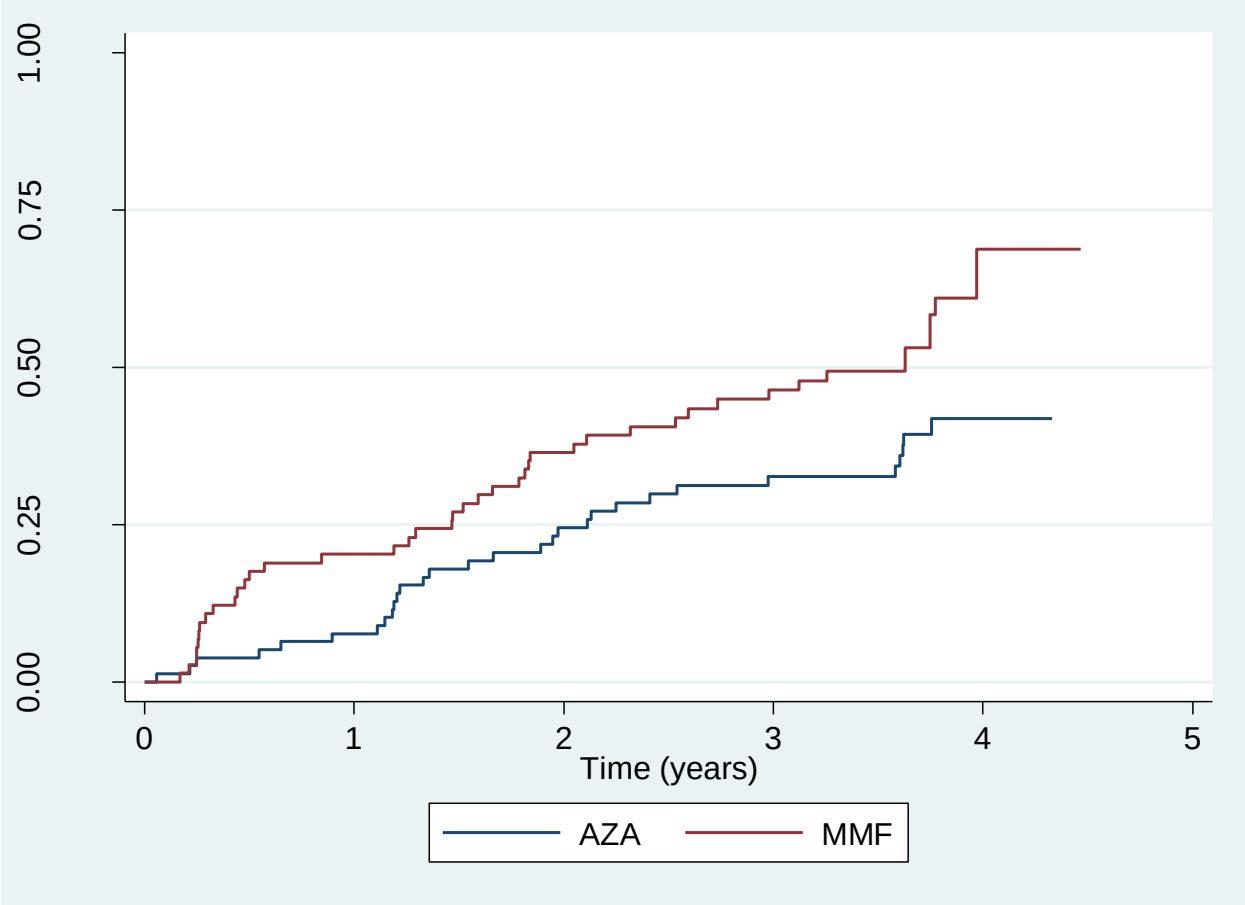


Essai RITAZAREM

Rituximab in Maintenance of Vasculitis

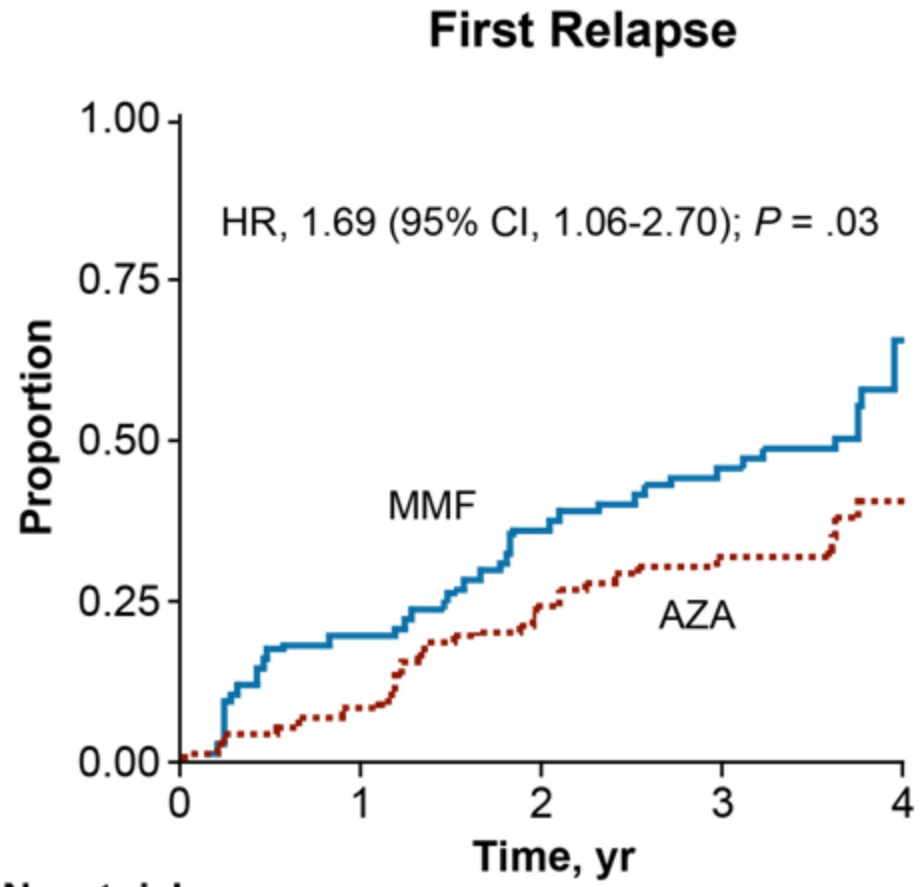
- ✓ 190 patients
- ✓ Critère de jugement principal : survie sans rechute
- ✓ Bras :
  - ✓ RTX : 1 g à M4, M8, M12, M16, M20
  - ✓ AZA : 2 mg/kg/j de M4 à M27
- ✓ Induction des patients par RTX
- ✓ Taux d'infections sévères ?

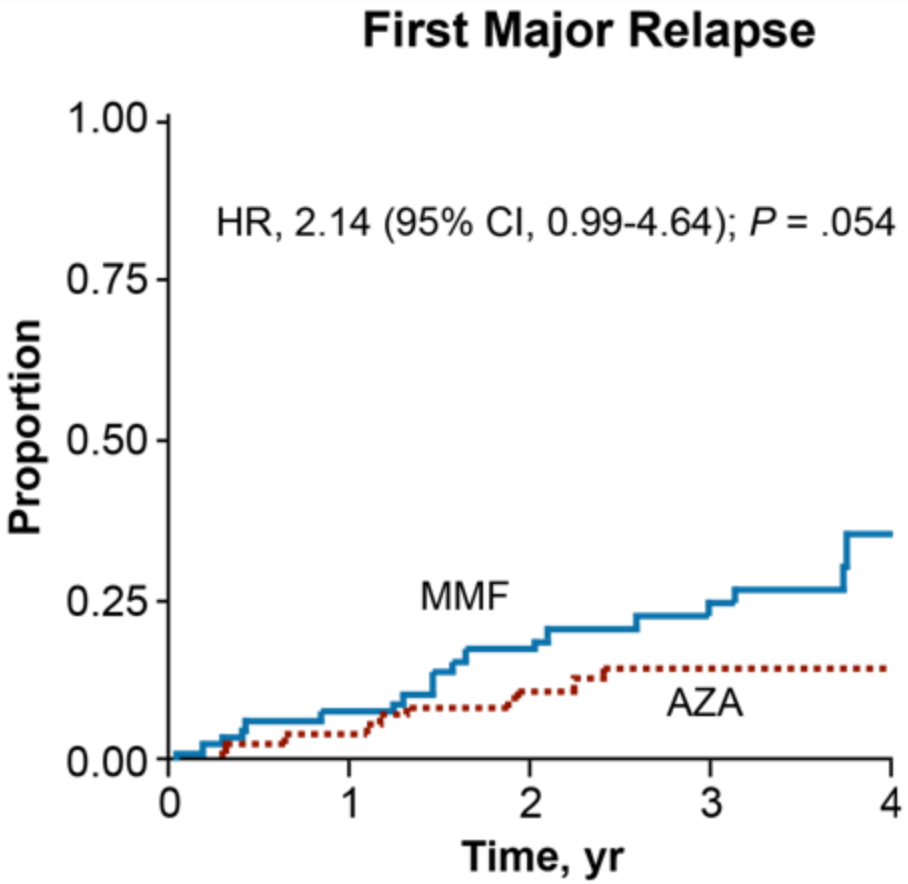
Cumulative Incidence of Relapse in ANCA Vasculitis with AZA vs. MMF (IMPROVE trial)



Hiemstra TF et al, JAMA 2010

IMPROVE: Time to Relapse





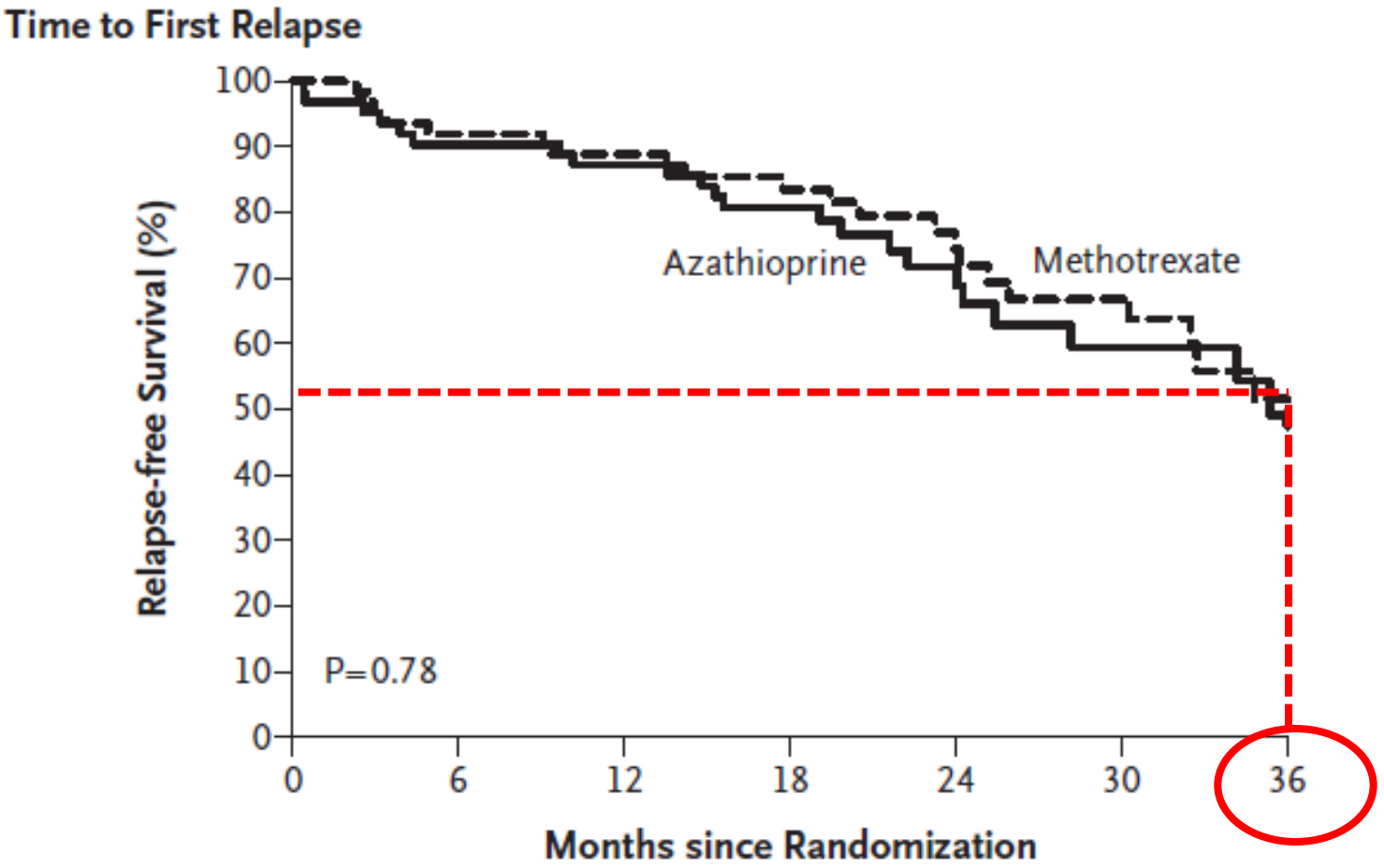
No. at risk

AZA	80	72	57	46	6
MMF	76	60	47	37	4

	80	72	57	46	6
	76	60	47	37	4

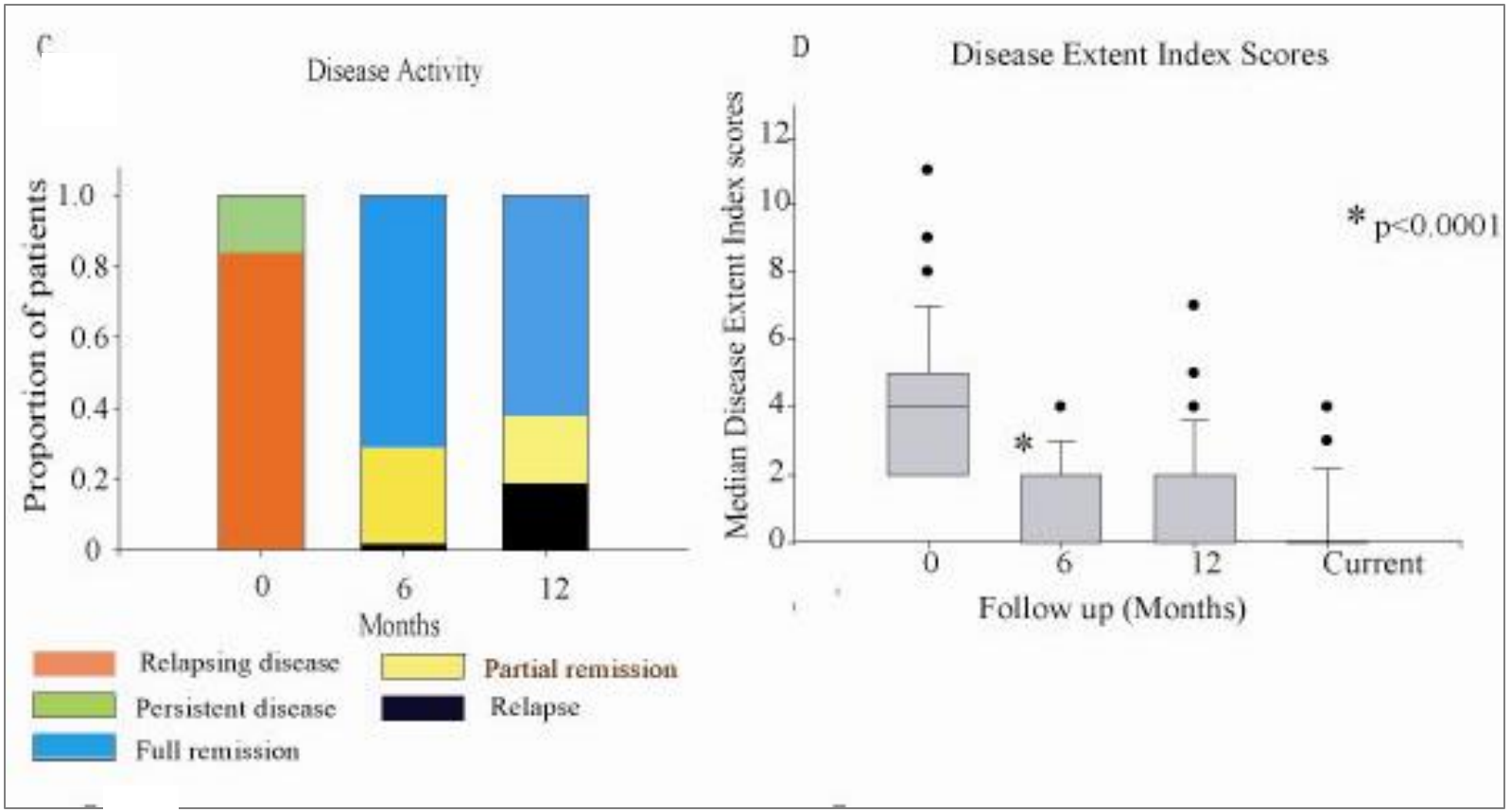
Hiemstra TF, et al. *JAMA*. 2010;304:2381.

Cumulative Incidence of Relapse in ANCA Vasculitis with AZA vs. Methotrexate

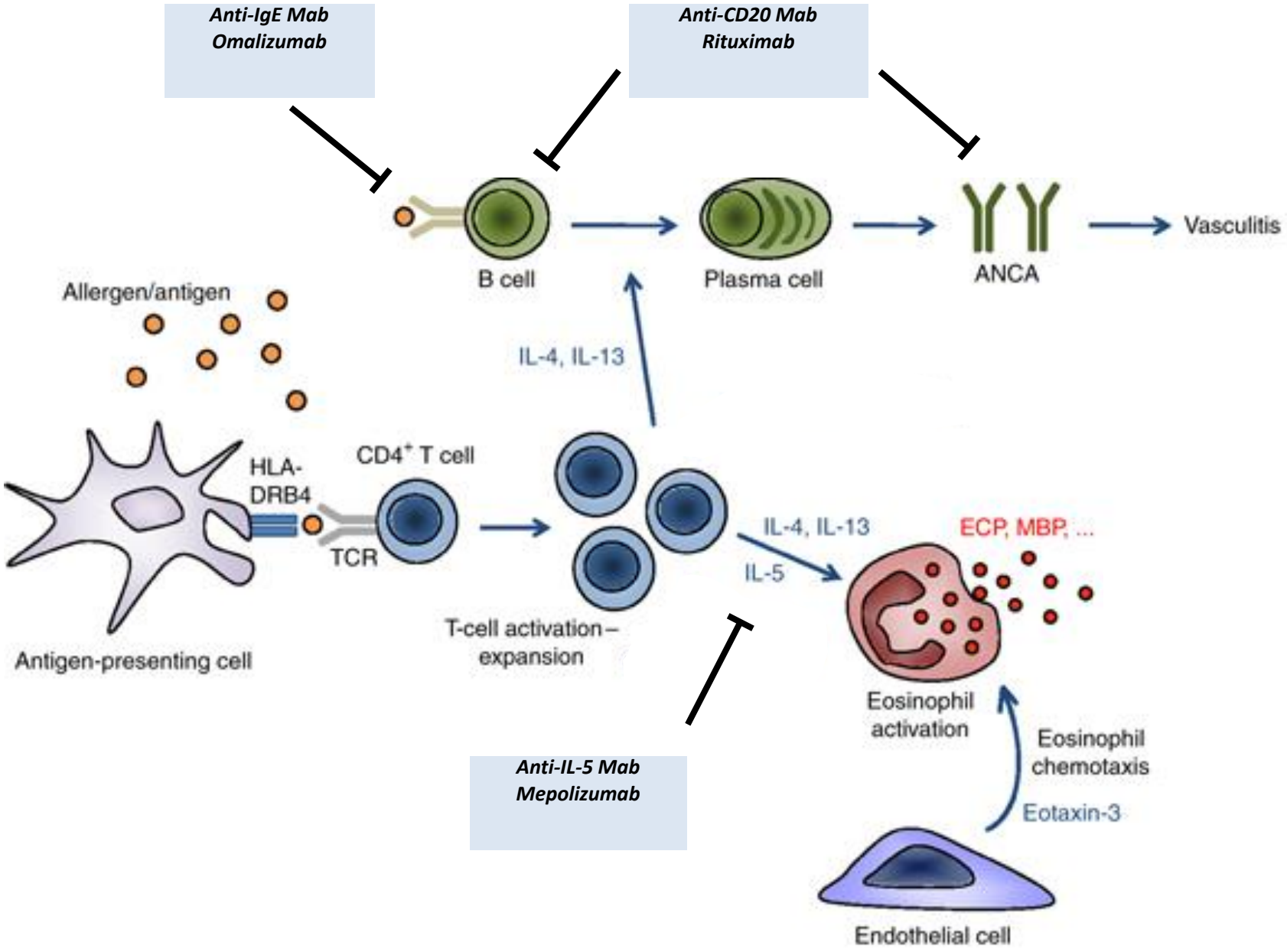


Pagnoux C, NEJM, 2008

Rituximab for refractory vasculitis (n = 63)



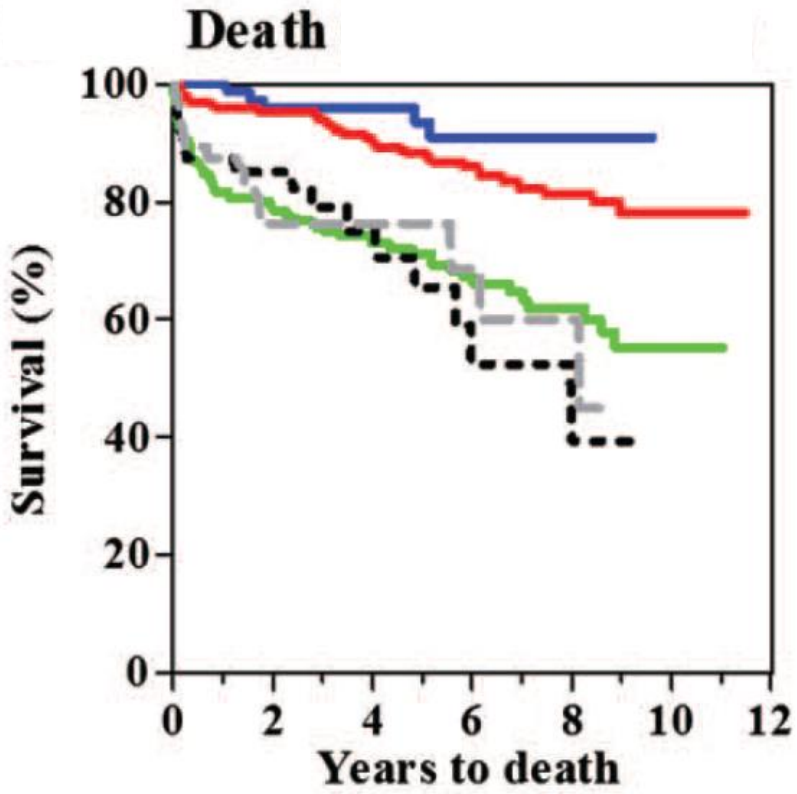
Jones, *Arthritis Rheum* 2009



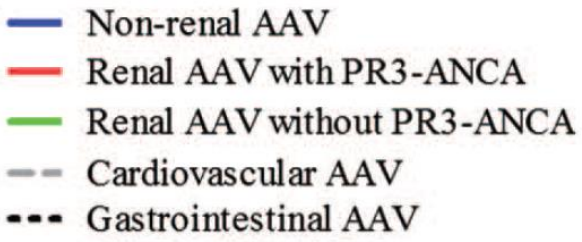
Adapted from Vaglio, Kidney Int, 2009

Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis

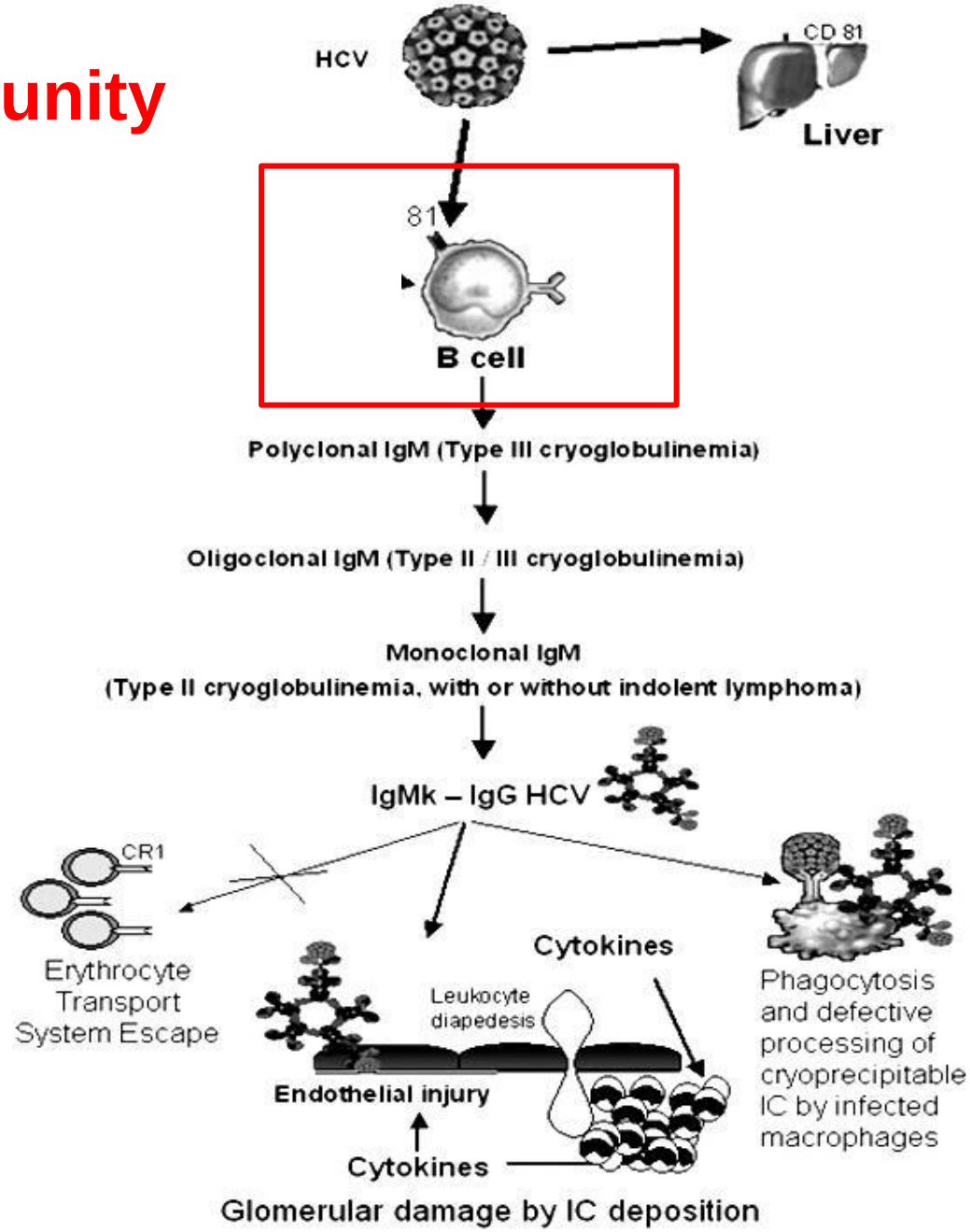
Mahr A et al, Ann Rheum Dis, 2013;72:1003-10



Variable	Risk of death HR (95% CI)	p Value
Non-renal AAV	1 (reference)	
Renal AAV with PR3-ANCA	2.07 (0.81 to 5.27)	0.13
Renal AAV without PR3-ANCA	5.87 (2.36 to 14.57)	<0.0005
CV AAV	6.41 (2.33 to 17.67)	<0.0005
GI AAV	6.74 (2.45 to 18.55)	<0.0005

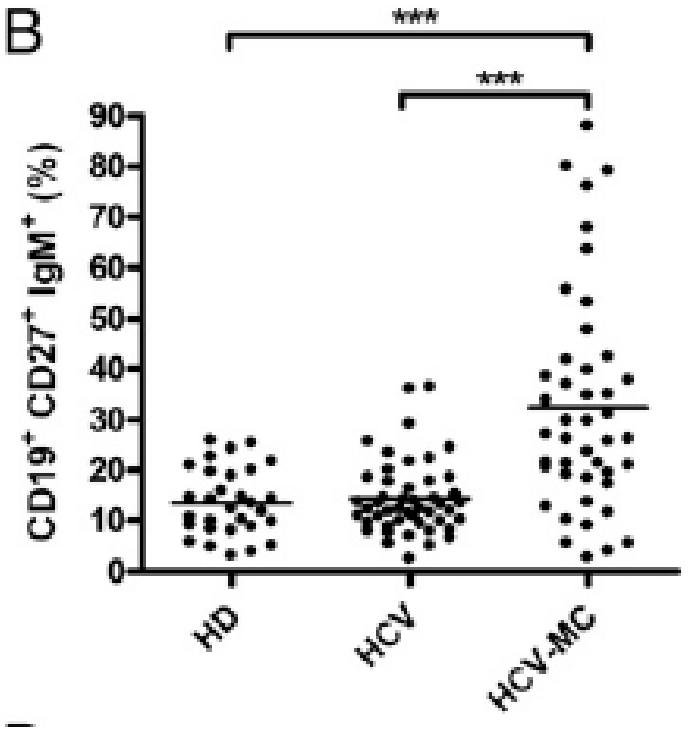


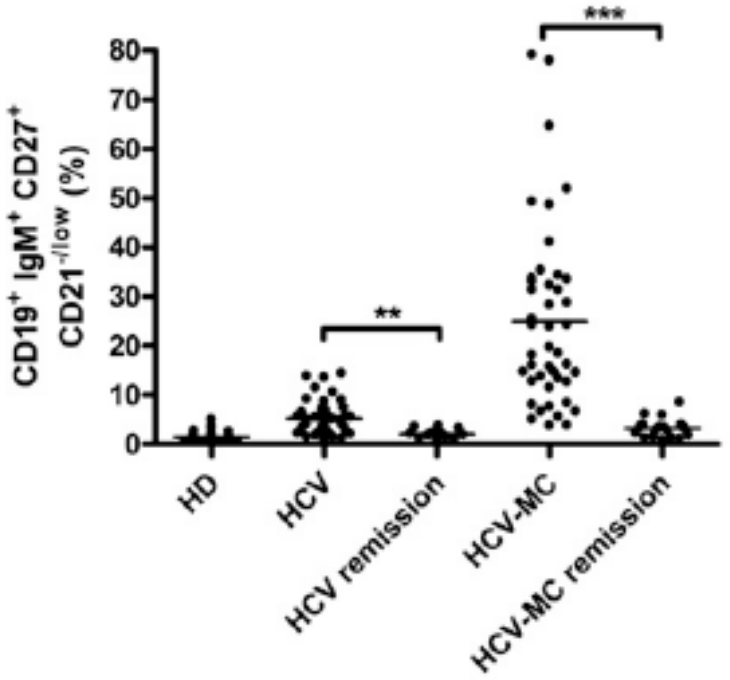
A Role for B Cell Immunity in HCV-Vasculitis



Roccatello, D. et al. Nephrol. Dial. Transplant. 2004

$CD21^{-/low}$ $CD27^{+}$ IgM^{+} B Lymphocytes Expand in HCV-Mixed Cryoglobulinemic Patients





Terrier B et al. J Immunol, 2011

HCV-Related Lymphoproliferative Disorders: from Cryoglobulinemia to B-NHL