TREATMENT OF ANCA-ASSOCIATED VASCULITIS QUESTIONS AND CONCERNS

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French Vasculitis Study Group

Conflicts of interest

✓ Roche has provided rituximab for the MAINRITSAN trial, an academic trial sponsored by Paris Hospitals and granted by the Ministry of Health

✓ No personnal conflict of interest

The CS and immunosuppressants era

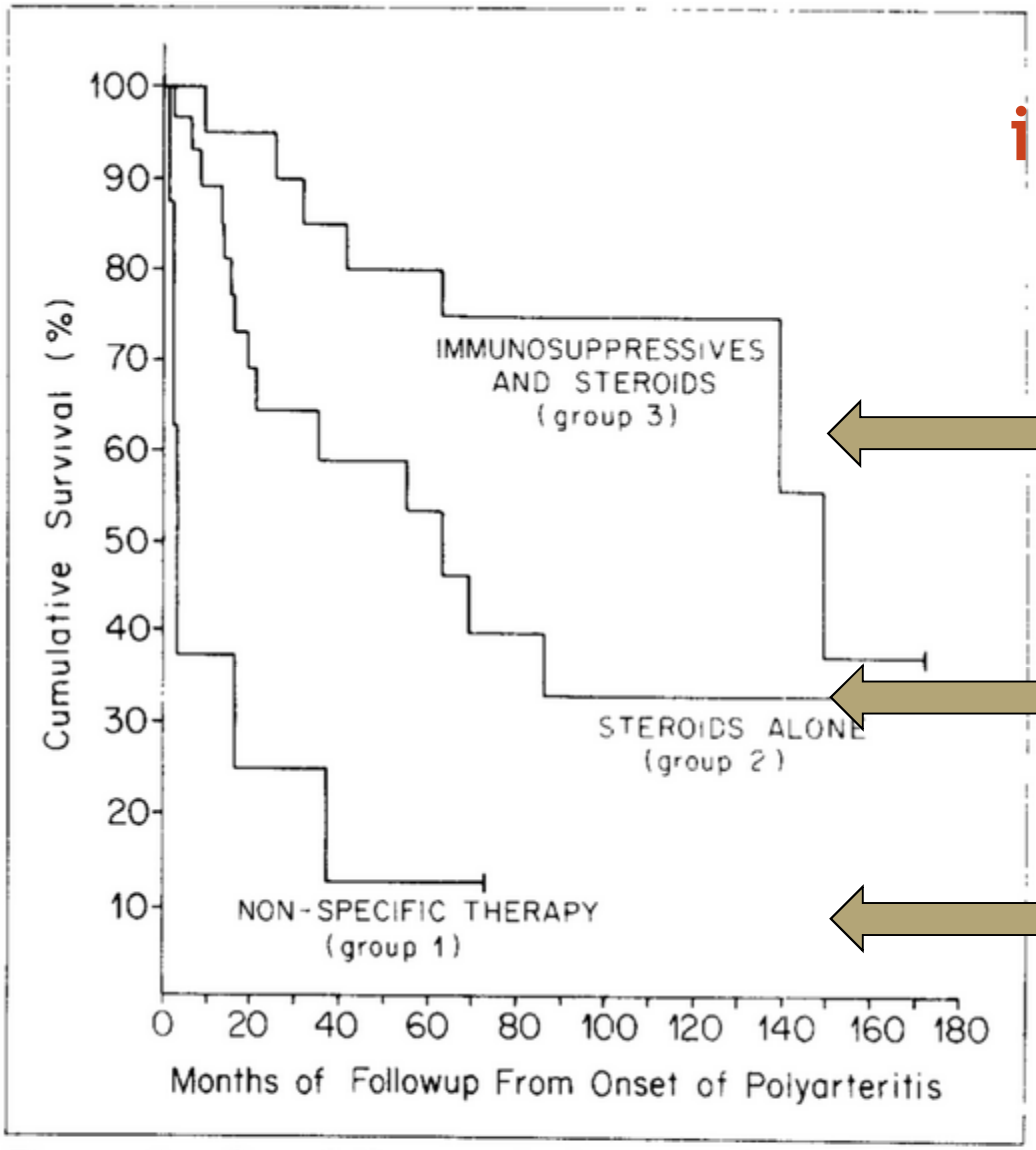


Figure 1. Cumulative survival curves in patients with polyarteritis nodosa receiving either (1) immunosuppressive agents and corticosteroids (group 3), (2) corticosteroids alone, (group 2) or (3) supportive therapy (group 1).

Cyclophosphamide

Corticosteroids

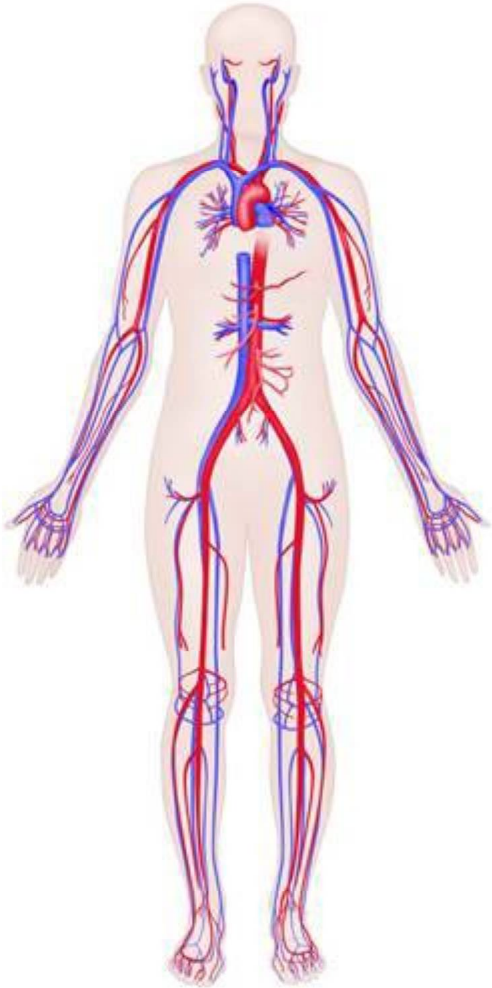
No treatment

Leib *et al*, *Am J Med* 1979;67:941

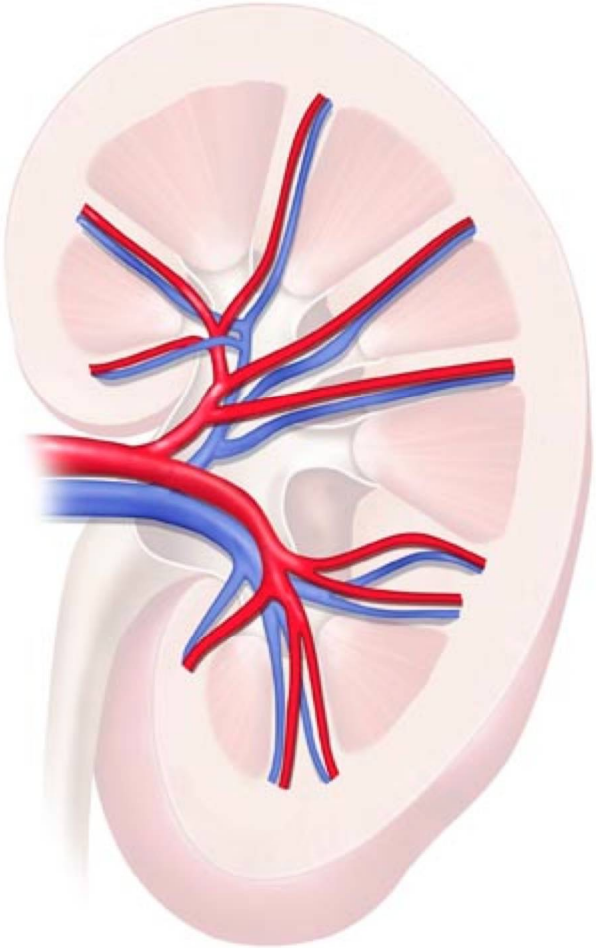
QUESTIONS TO ADDRESS

- ✓ Does classification play a role in treatment decision ?
- ✓ Induction treatment: immunosuppressants or biologics ? And what else ?
- ✓ Do patients need a maintenance treatment ?
- ✓ How long and how to treat in the long term ?

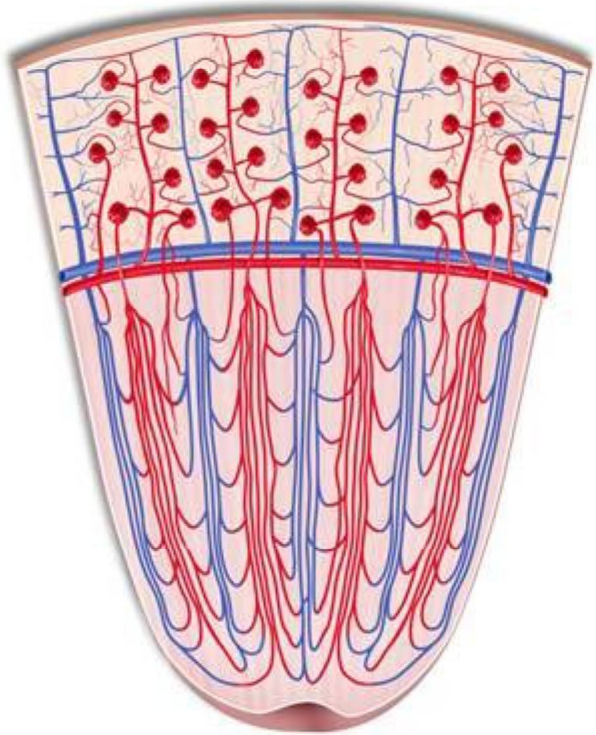
Large Vessels



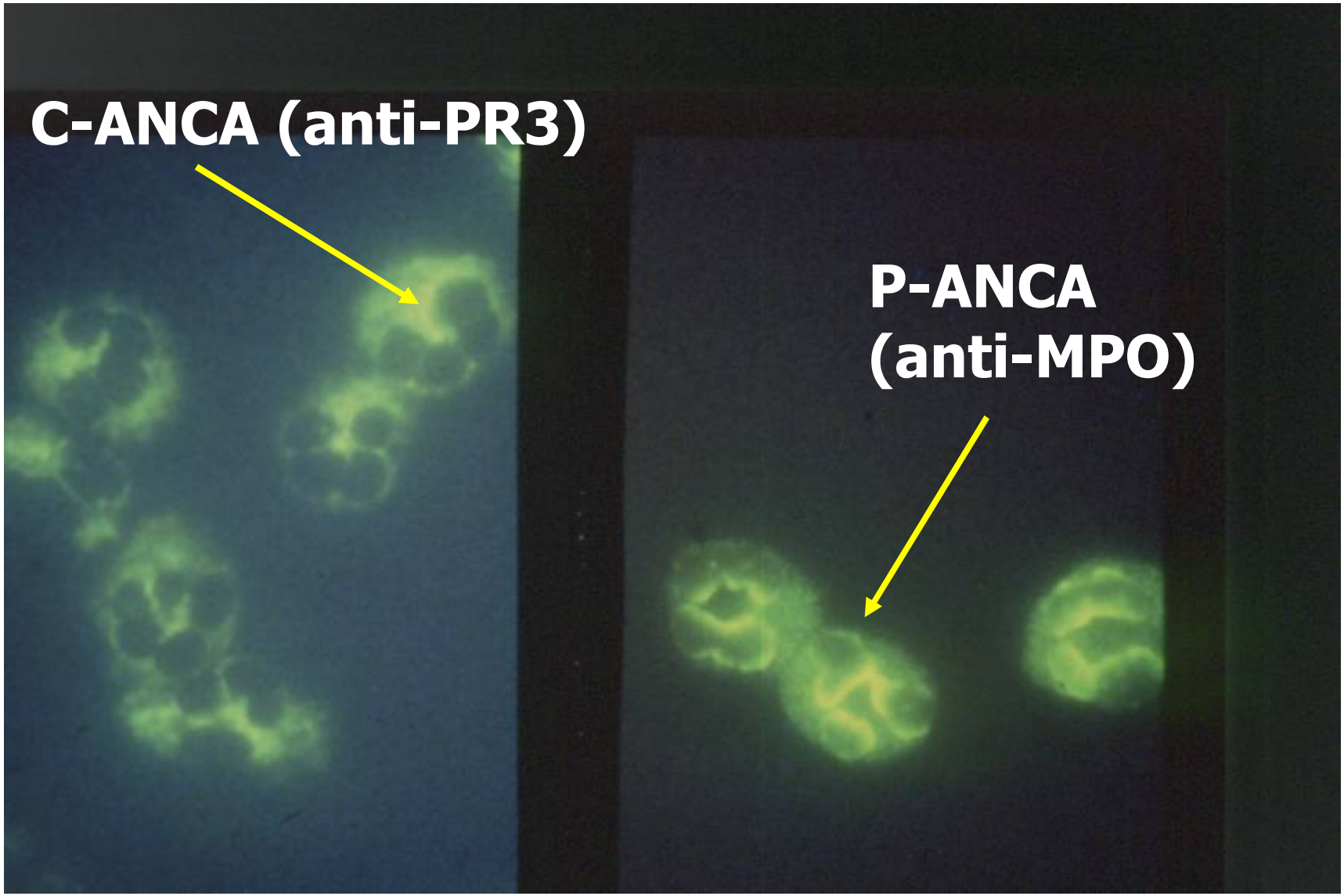
Medium Vessels



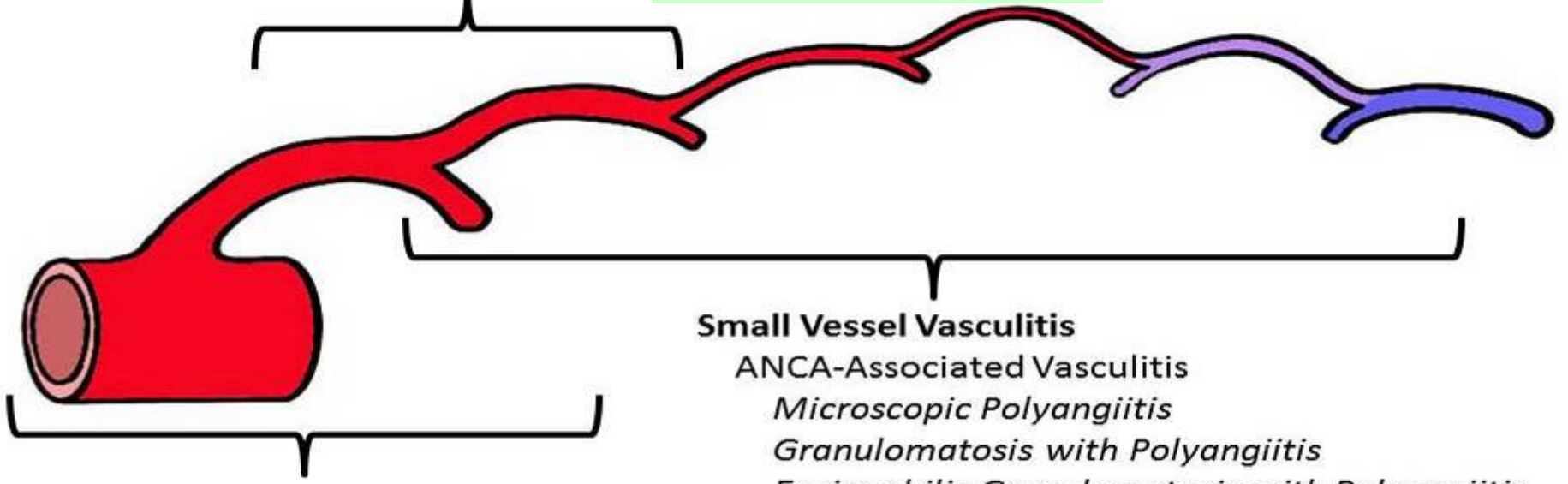
Small Vessels



ANCA



THE CHAPEL HILL NOMENCLATURE



Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

CS, CYC, HBV

immunoglobulins

Small Vessel Vasculitis
ANCA-Associated Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
Eosinophilic Granulomatosis with Polyangiitis
Immune Complex SVV
Anti-GBM Disease
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)

CS,CY,PE

HCV,PE, RTX

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

CS, MTX, Anti-TNF Anti-Il6?

No treatment

QUESTIONS TO ADDRESS

- ✓ Does classification play a role in therapeutic decision ?
- ✓ Induction treatment: immunosuppressants or biologics ? And what else ?
- ✓ Do patients need a maintenance treatment ?
- ✓ How long to treat ?
- ✓ Can we cure Vasculitides ?
- ✓ How to improve outcomes ?

SEVERITY

- ✓ **Five Factor Score**
  - ✓ Age > 65 y. old
  - ✓ Creatininemia > 150 μmol
  - ✓ GI involvement
  - ✓ Cardiac involvement

  - ✓ Absence of ENT manifestations (in GPA and EGPA only)

TREATMENT COMPRISES USUALLY TWO PERIODS

- **Induction- remission treatment**
  - Obtain a remission
  - Without or with few sequellaes
- **Maintenance treatment**
  - Prevent relapses

CONVENTIONAL TREATMENT FOR VASCULITIS

- ✓ Cyclophosphamide + steroids in systemic disease
- ✓ Methotrexate for non-renal GPA
- ✓ CS alone in some patients without poor-prognosis factors (FFS 0) (EGPA, MPA)
- ✓ Azathioprine or methotrexate for maintenance treatment

VASCULITIS WITHOUT POOR PROGNOSIS FACTOR

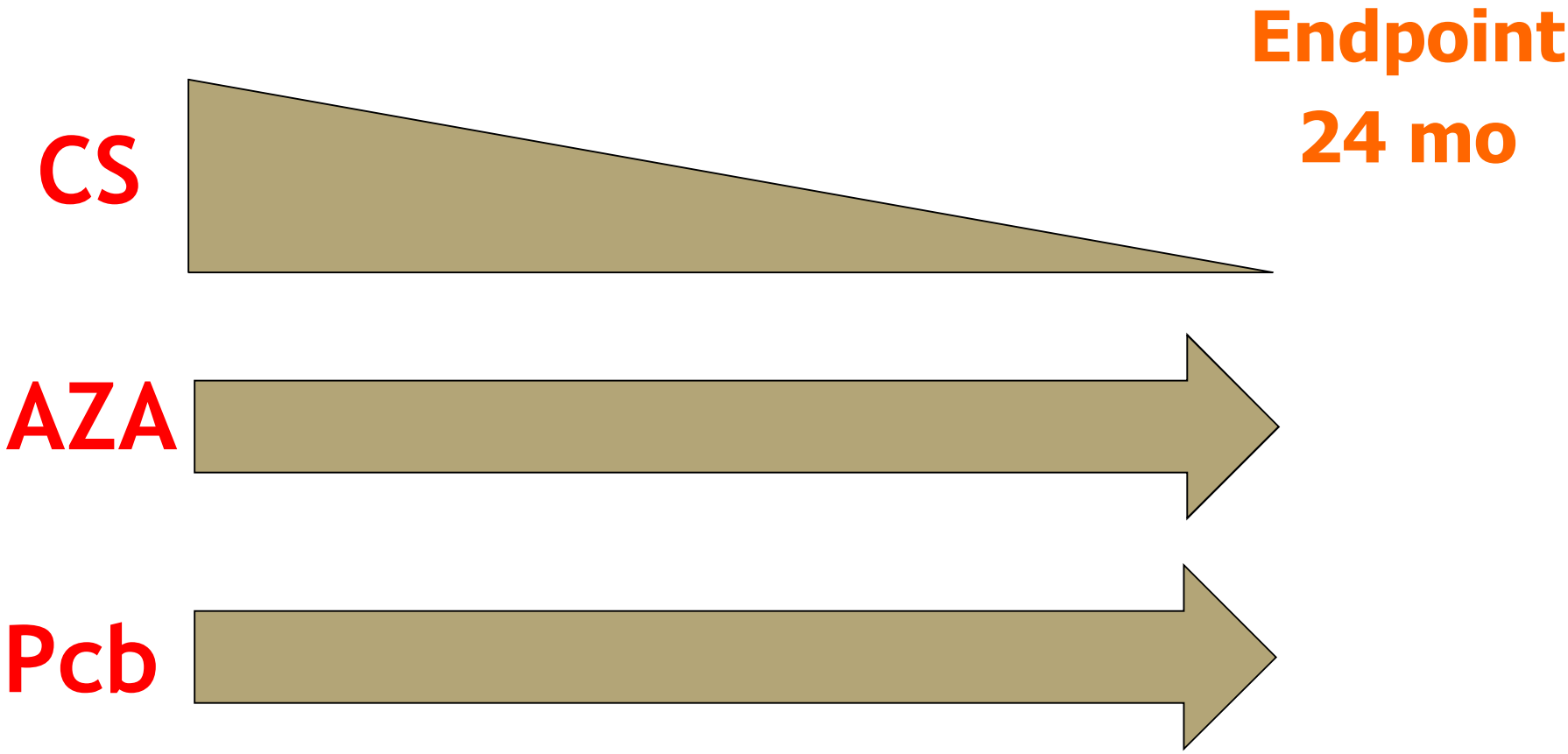
- ✓ CS alone
- ✓ Is azathioprine useful for steroid-sparing?

CS + AZA vs CS + placebo

In

EGPA, PAN and MPA without factors of poor prognosis

CHUSPAN 2

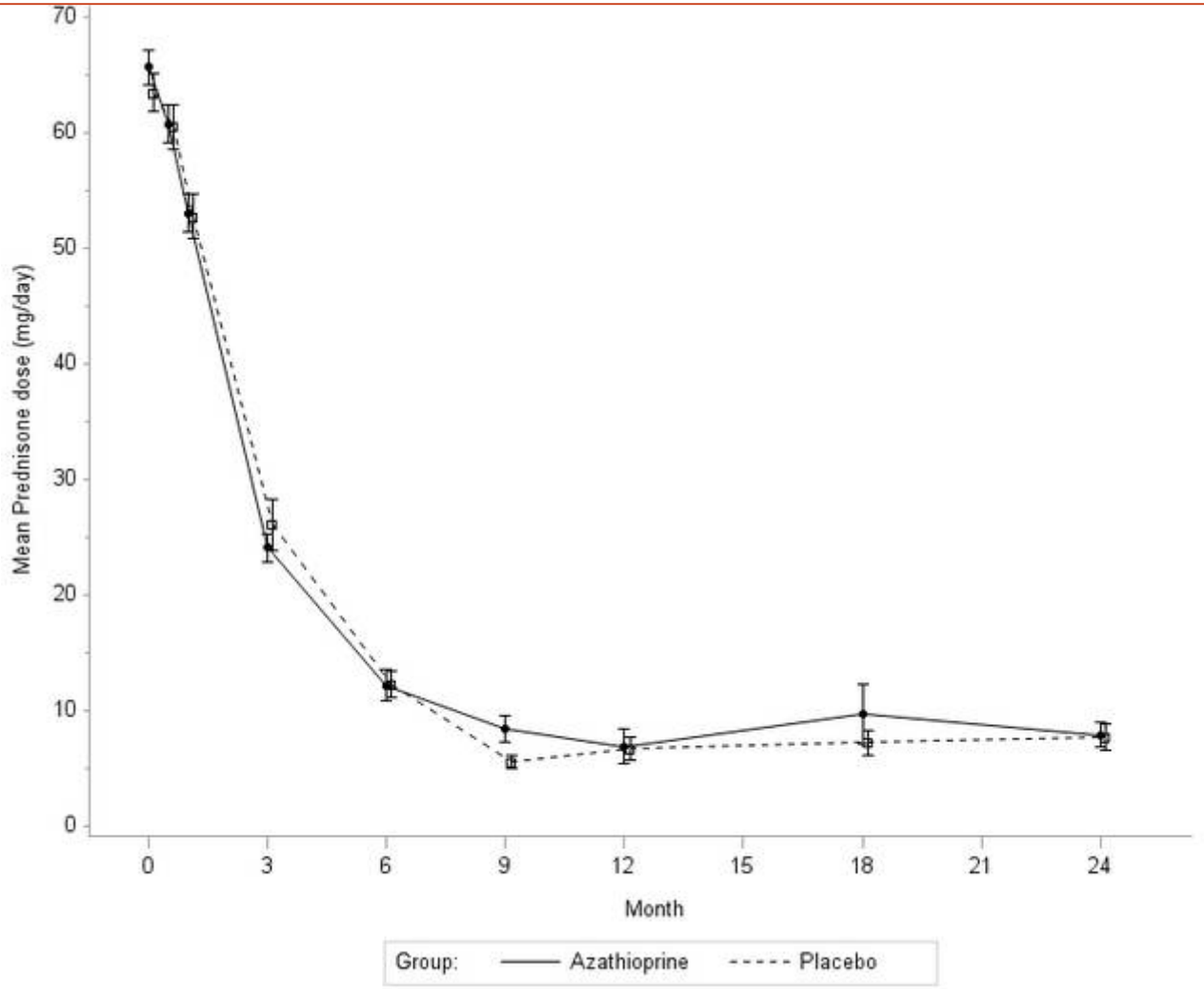


Multicenter, double-blind, randomized, controlled trial

12 months AZA/placebo treatment + 12 months FU

CHUSPAN 2

✓ Prednisone dose (mg)



CHUSPAN 2

- ✓ **95 randomized patients, 51 EGPA, 25 MPA, 19 PAN**

M 24	CS + AZA	CS + PLACEBO
Remission without relapse	52.2 %	51 %
Remission rate	95.6 %	87.8 %
Death	0	4.1 %

Remission and relapses are defined by the BVAS

EGPA treatment: CHUSPAN 2

- ✓ **95 randomized patients, including 51 EGPA**

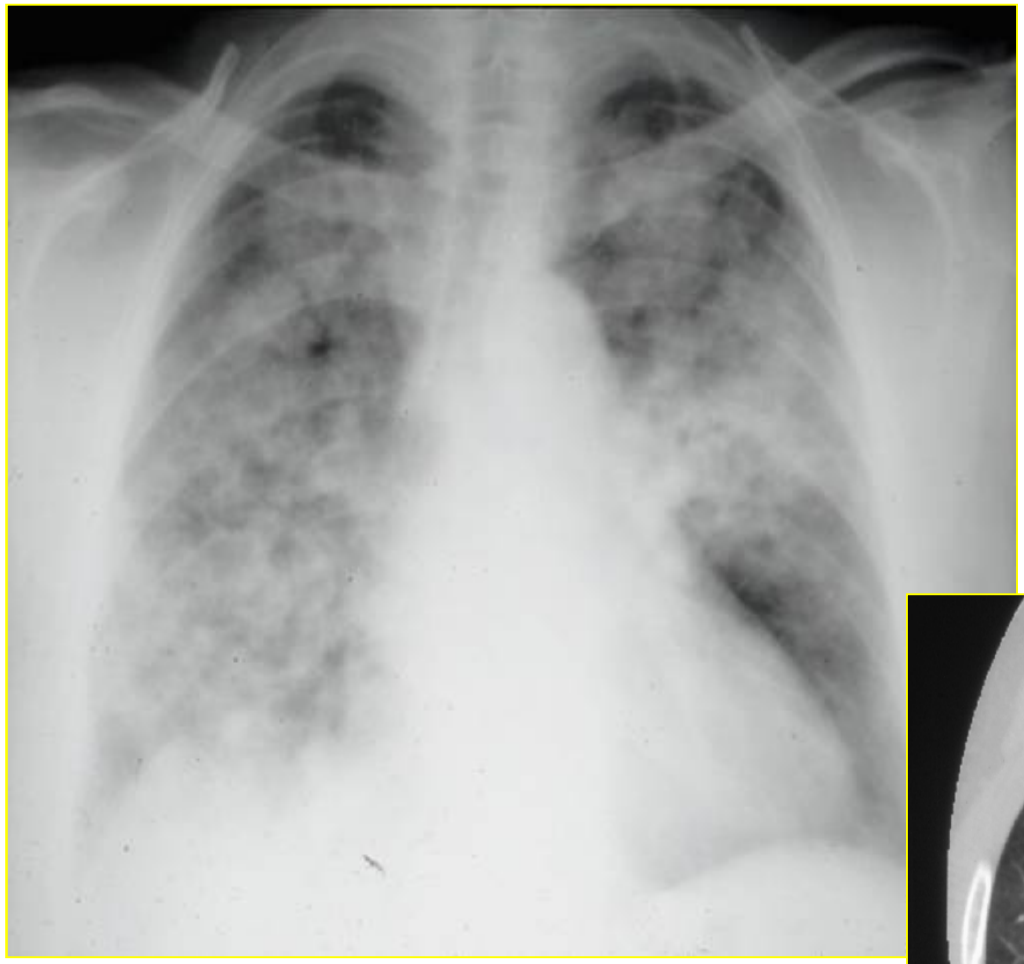
M 24 (EGPA group)	CS + AZA	CS + PLACEBO
Remission without relapse	53.9 %	52 %
Asthma + ENT flares	19.2 %	24 %

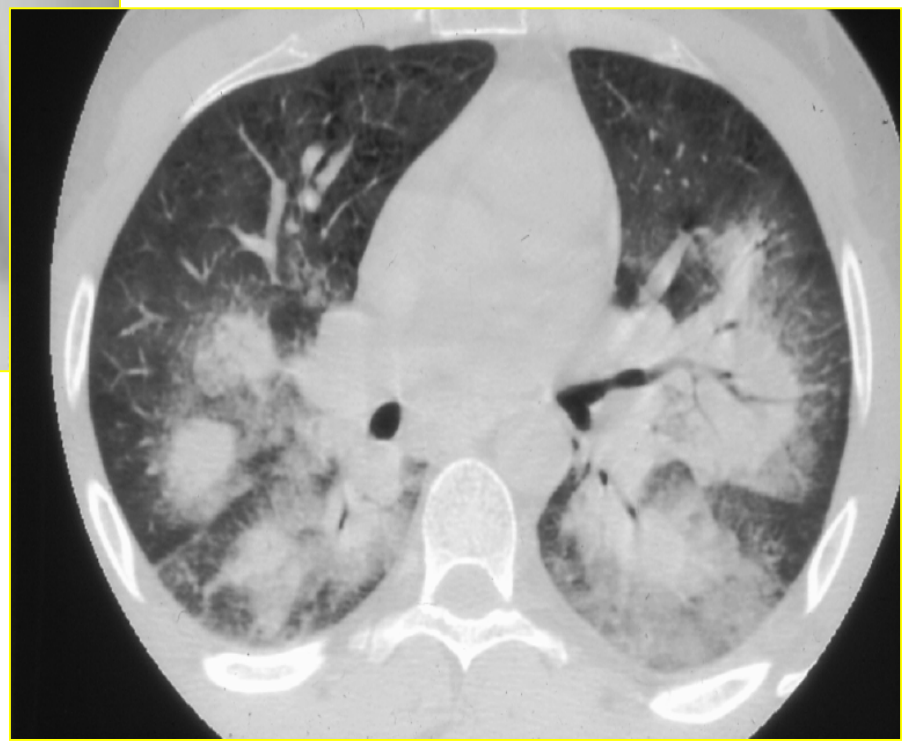
- ✓ Remission and relapses are defined by the BVAS

HOW TO TREAT VASCULITIDES

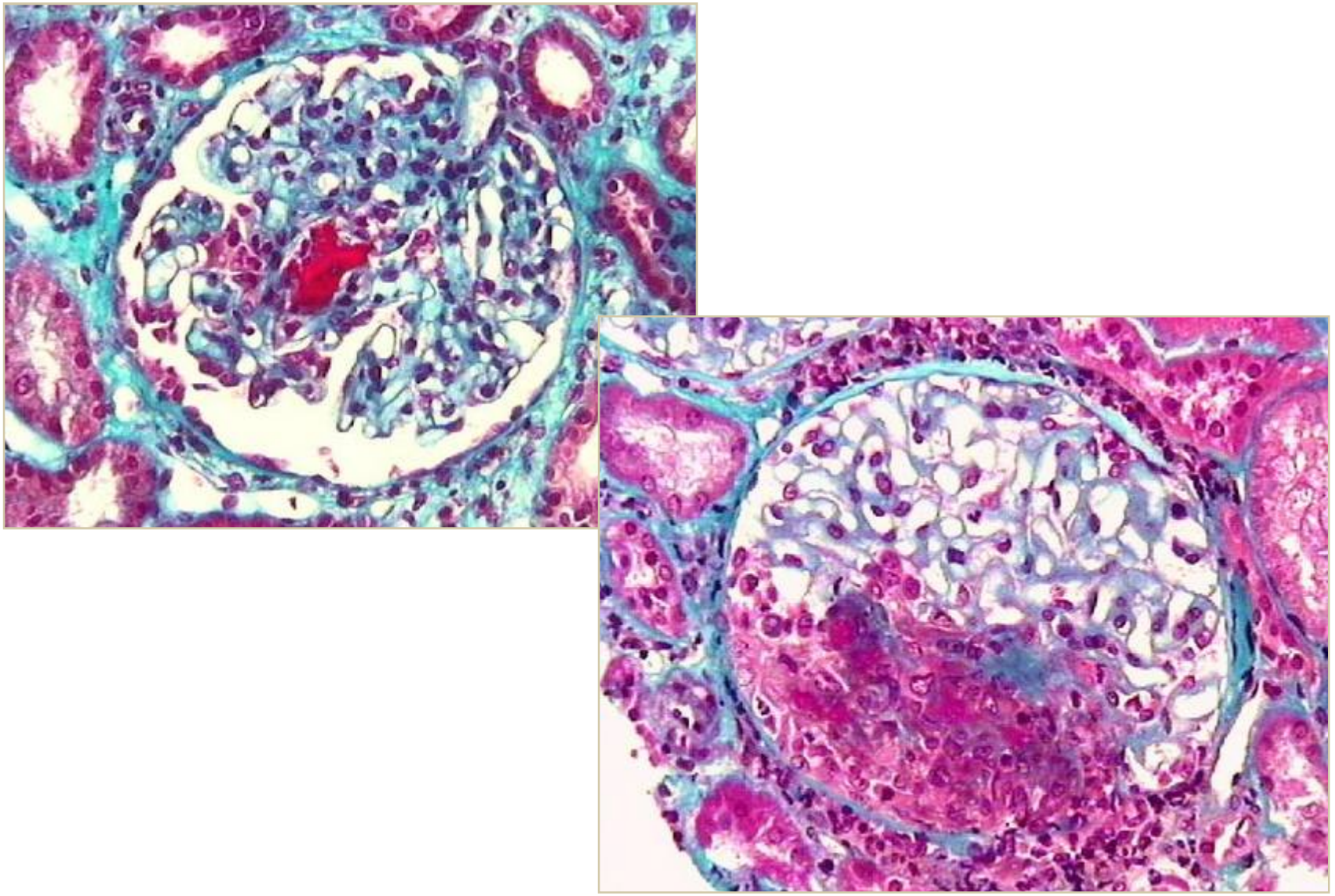
Pulse cyclophosphamide treatment

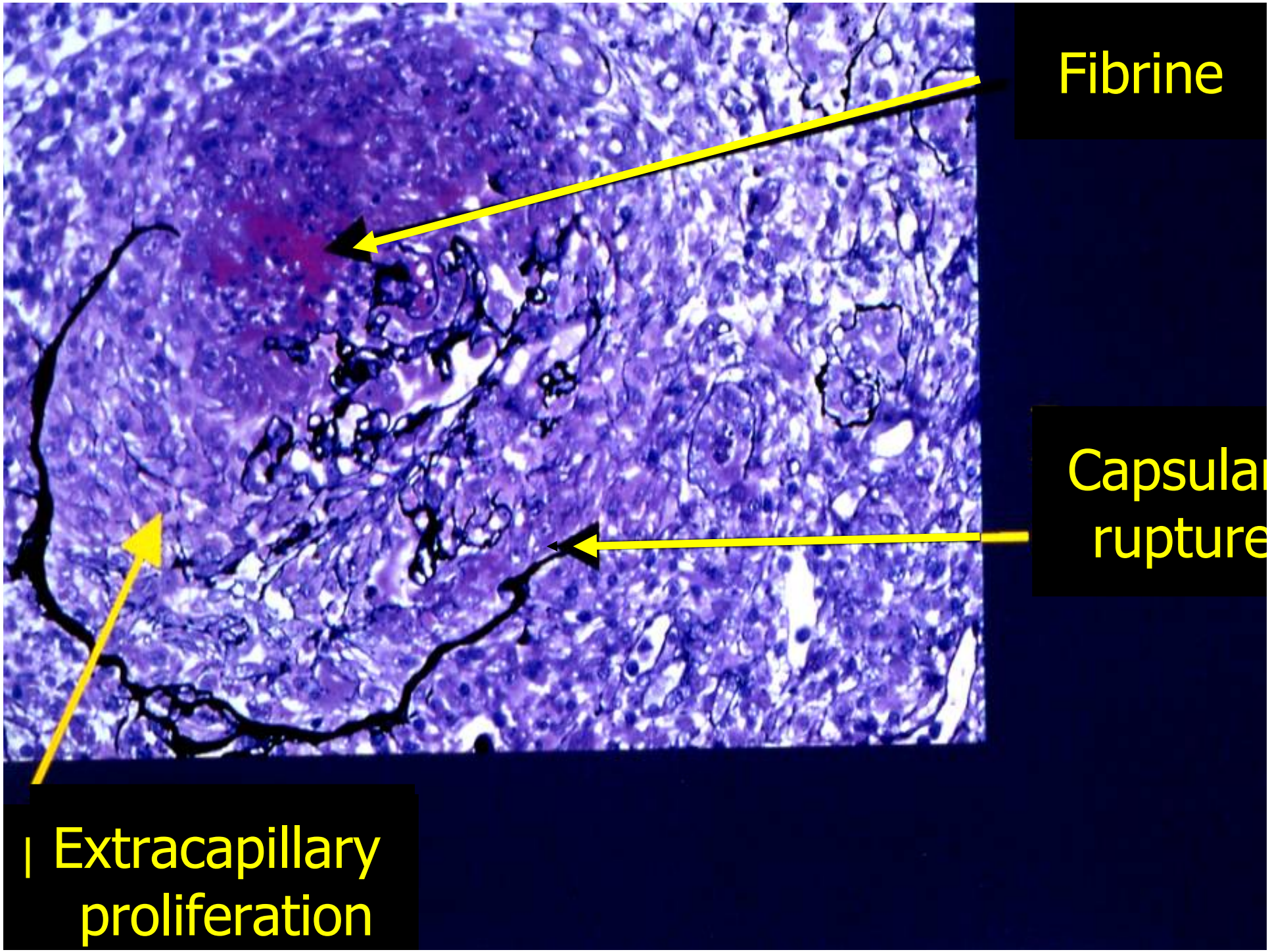
- **0.6 to 0.7gr/sq.m (or 15 mg/kg) D0, D15, D30**
  - then every 3 weeks until remission
  - 0.5 gr/sq.m in case of renal insufficiency or in patients > 65 yr.old





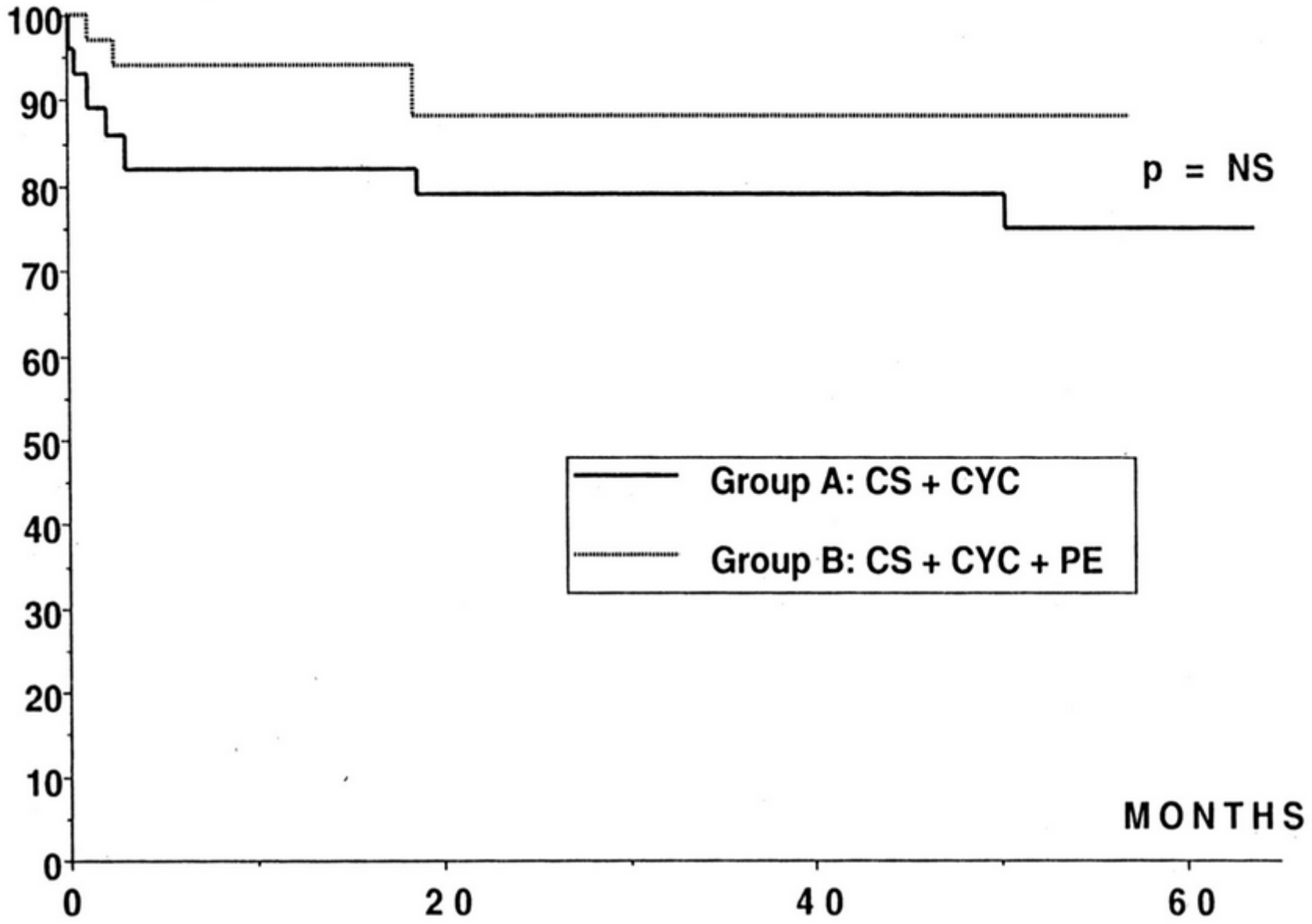
Rapid crescentic glomerulonephritis




Fibrine
Capsular rupture
Extracapillary proliferation

QUICK EFFECTIVENESS:

PLASMA EXCHANGES



Guillevin, Arthritis Rheum 1995; 38: 1683

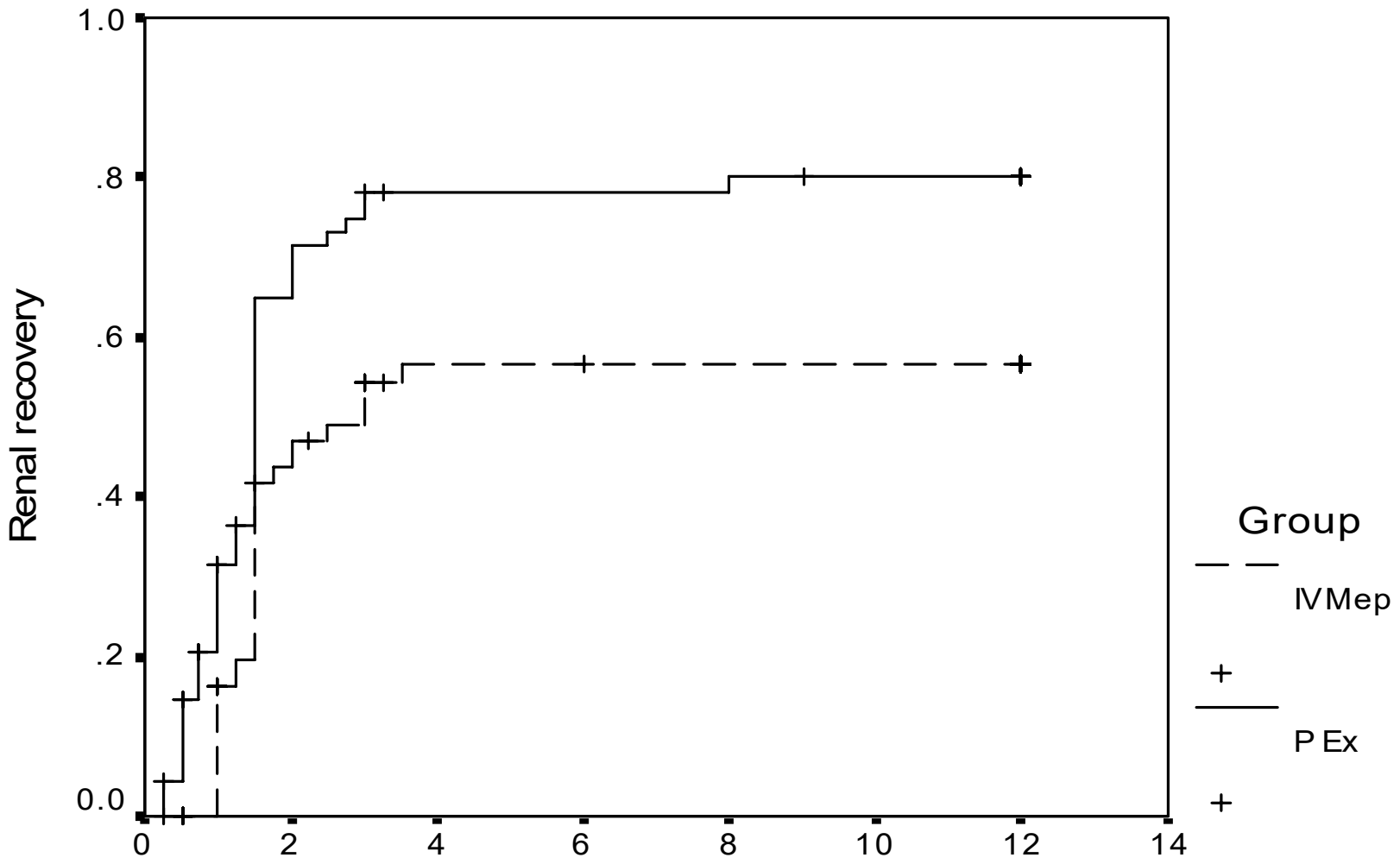
PLASMA EXCHANGES IN SEVERE AAV

Plasma exchanges MEPEX

- ✓ Comparison of pulses MPS to PE in ANCA+ vasculitis with creatininemia > 500 μmol/L
- ✓ 150 patients

Jayne D et al, JASN 2008

PLASMA EXCHANGES IN SEVERE AAV



Renal recovery

Jayne, JASN 2007, 18: 2180-7

R I T U X I M A B

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

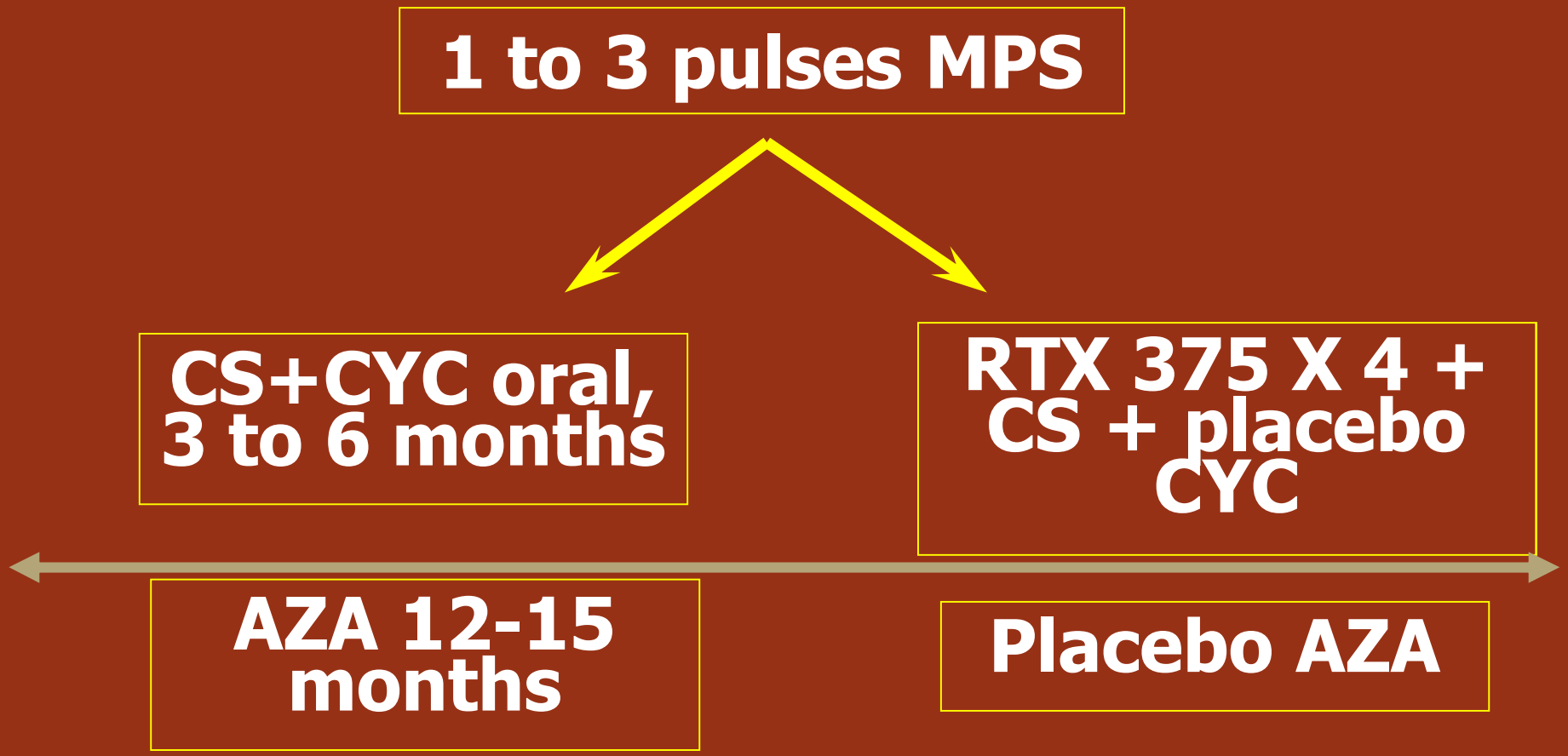
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, R.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. [illegible]

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

RAVE



CROSS OVER IF NEEDED

Stone N Engl J Med 2010, **363(3): 221-232.**

RAVE: RESULTS

- **Primary endpoint (BVAS=0, stop CS at 6 months) reached by:**
  - 63 of the 99 patients in the rituximab group 64%
  - 52 of 98 in the control group 53%
  - The treatment difference of 11% between the groups met the criterion for non inferiority (P<0.001)

Stone N Engl J Med, 2010, **363(3): 221-232.**

RAVE: RESULTS

- **Secondary endpoint (BVAS 0, < 10 mg CS, at 6 months) reached by:**
  - 70 patients treated with rituximab 71%
  - 61 patients in the control group 62%

Stone N Engl J Med, 2010, **363(3): 221-232**

RAVE: RESULTS

- **Adverse events:**
  - No significant differences between the treatment groups
- **Events leading to discontinuation of treatment:**
  - 14 patients in the rituximab group 14%
  - 17 in the control group 17%

Stone N Engl J Med, 2010, **363(3): 221-232**

QUESTIONS TO ADDRESS

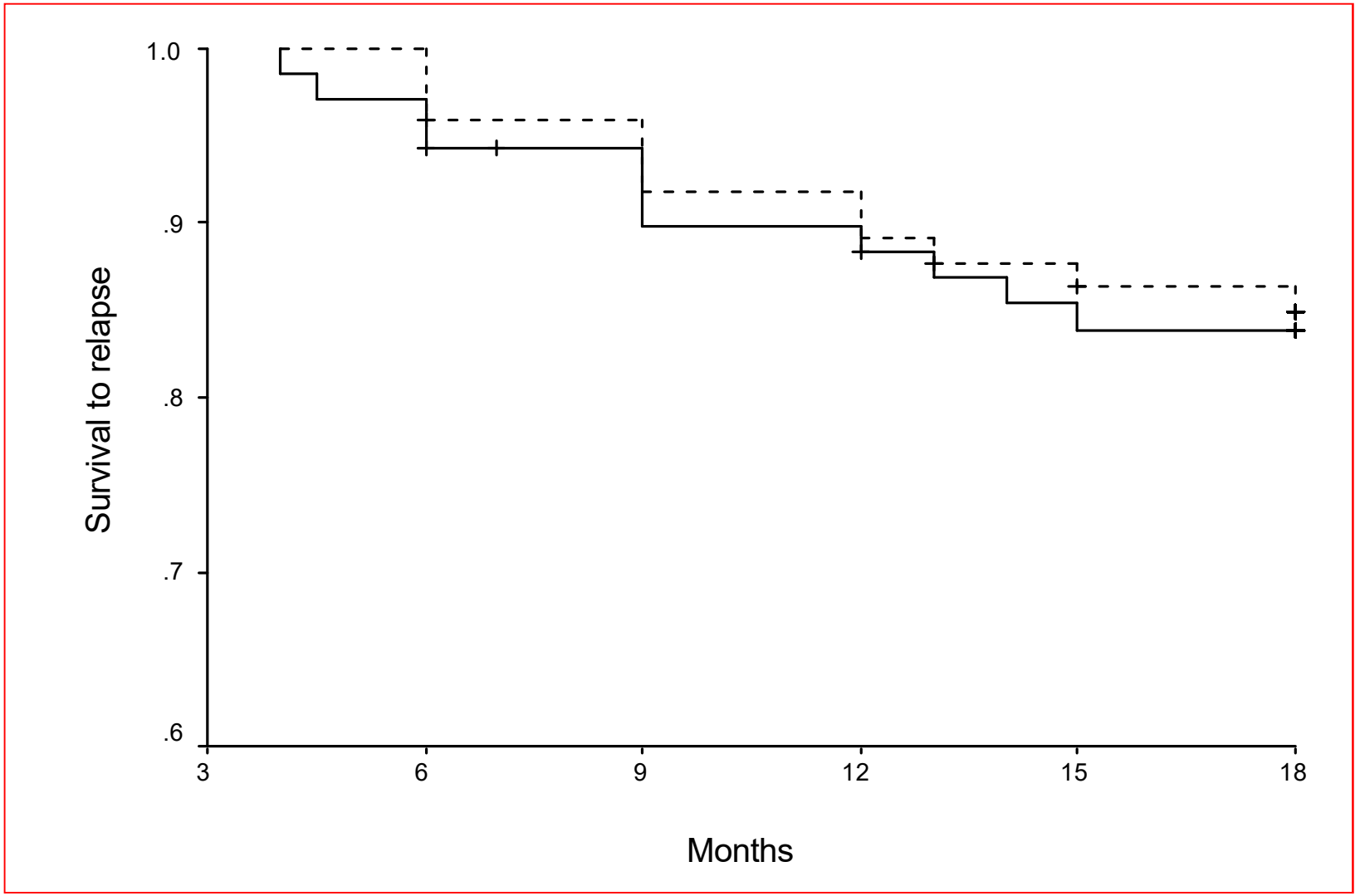
- ✓ Does classification play a role in therapeutic decision ?
- ✓ Induction treatment: immunosuppressants or biologics ? And what else ?
- ✓ **Do patients need a maintenance treatment ?**
- ✓ How long to treat ?

ANCA+ VASCULITIDES

CYCAZAREM

- Comparison of 3 to 6 mo. oral CYC + CS then azathioprine or oral CYC for 12 mo.+ 10 mg/d CS. After 12 mo all the patients were treated with azathioprine
- 150 patients followed for 18 mo.

D Jayne for the EUVAS group. New Engl J Med July 2003, 349: 36-44



Randomized trial of cyclophosphamide versus azathioprine as remission maintenance therapy for ANCA-associated vasculitis
D Jayne for the EUVAS group. New Engl J Med July 2003, 349: 36-44

WEGENT

Pagnoux C, et al, NEJM 2008, 359: 2790

Systemic Wegener's granulomatosis:

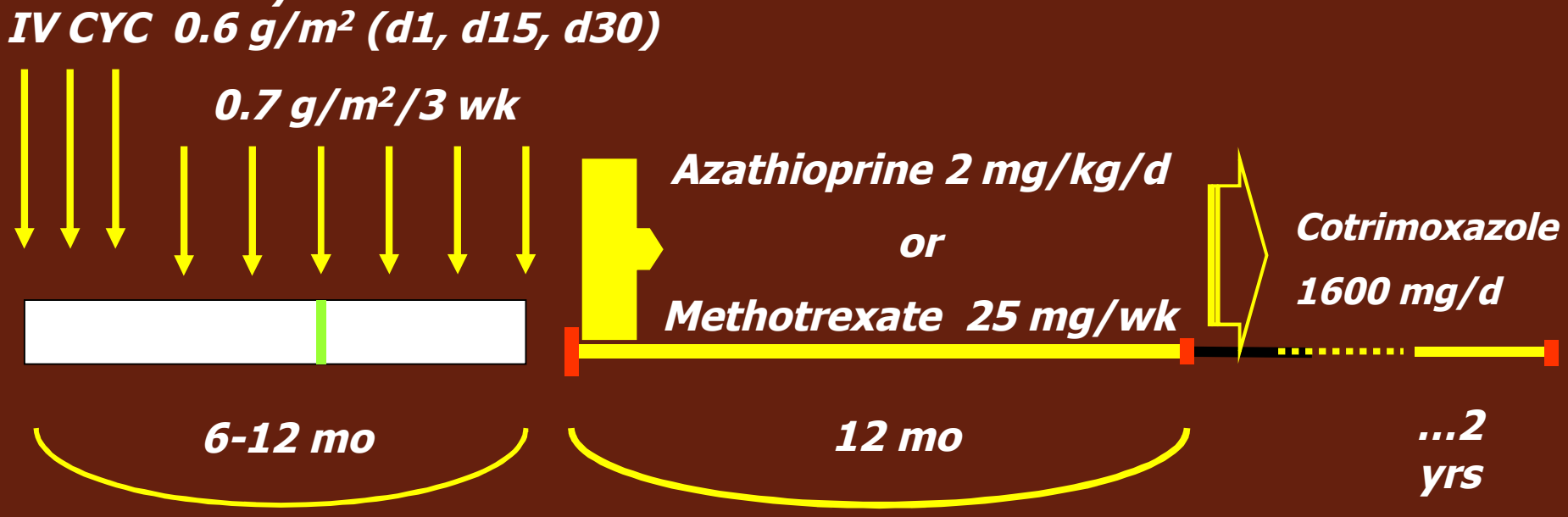
≥ 2 organs involved

or kidney involvement

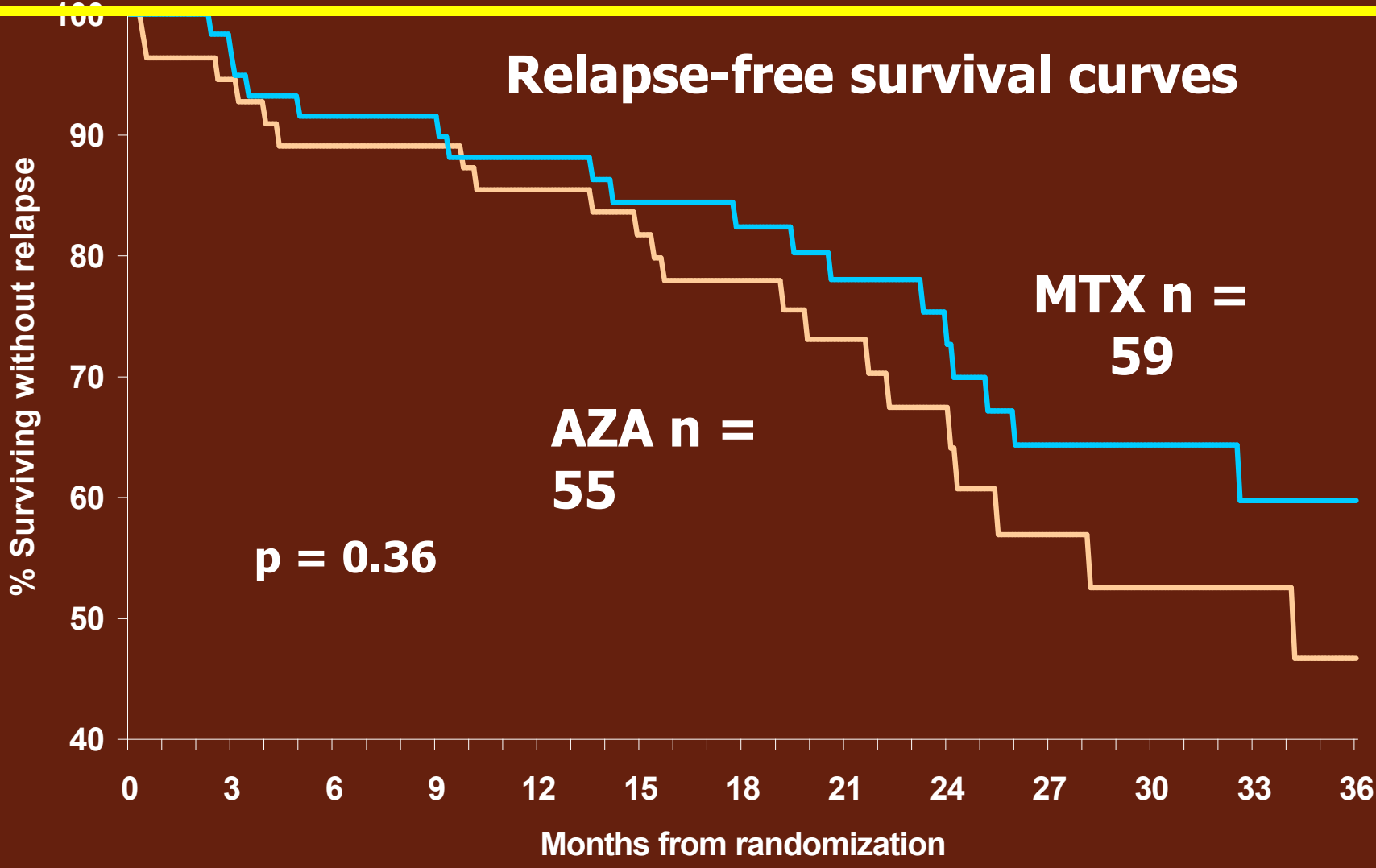
or 1 organ involved + general symptoms (fever, weight loss…)

Microscopic polyangiitis:

with FFS ≥ 1



WEGENT Pagnoux C, et al, NEJM 2008



Relapse-free survival at 18 mo: AZA 77.9% [66.9–89.0]; MTX 82.4% [72.4–92.3]

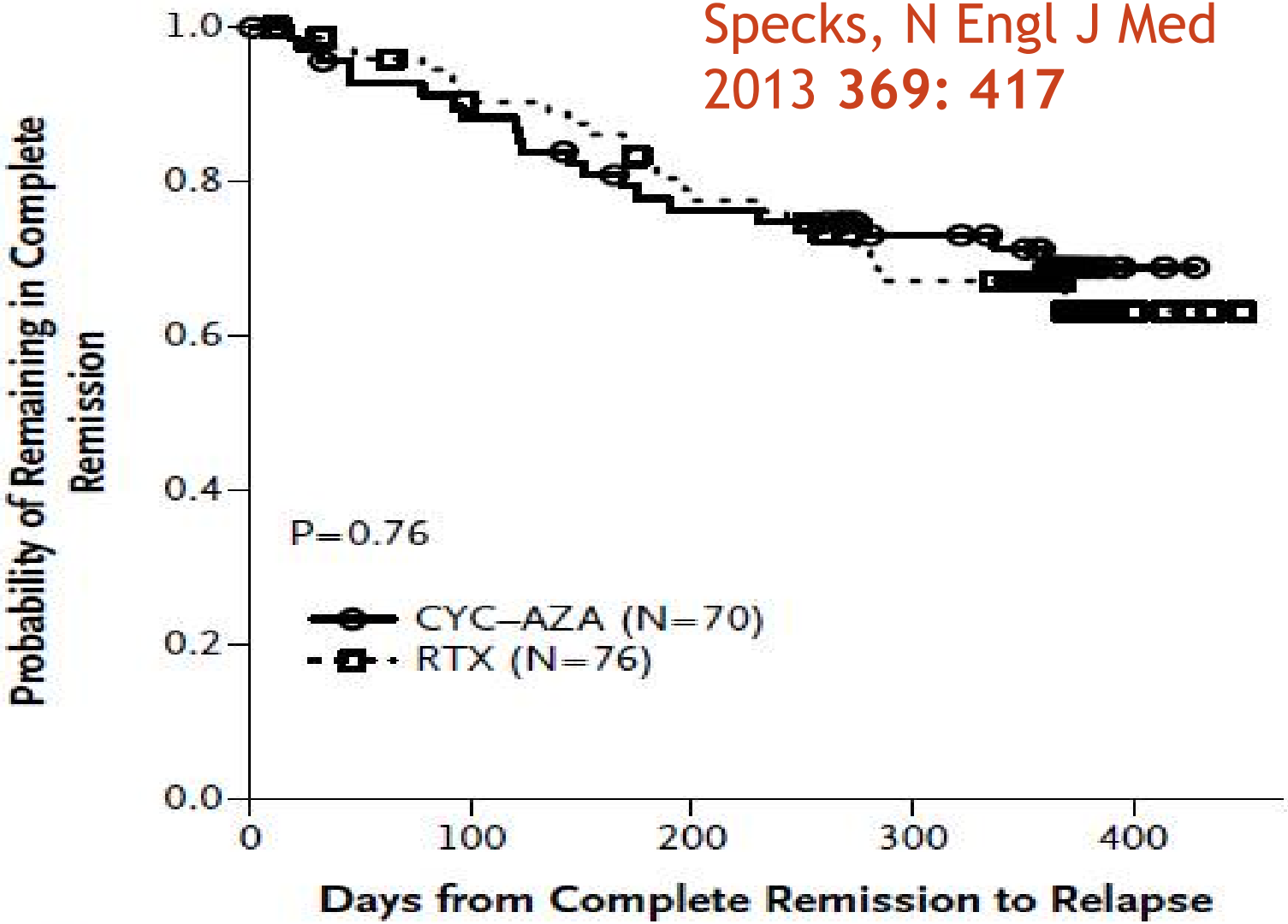
Relapse-free survival at 24 mo: AZA 67.5% [53.9–81.0]; MTX 72.6% [60.0–85.2]

R I T U X I M A B

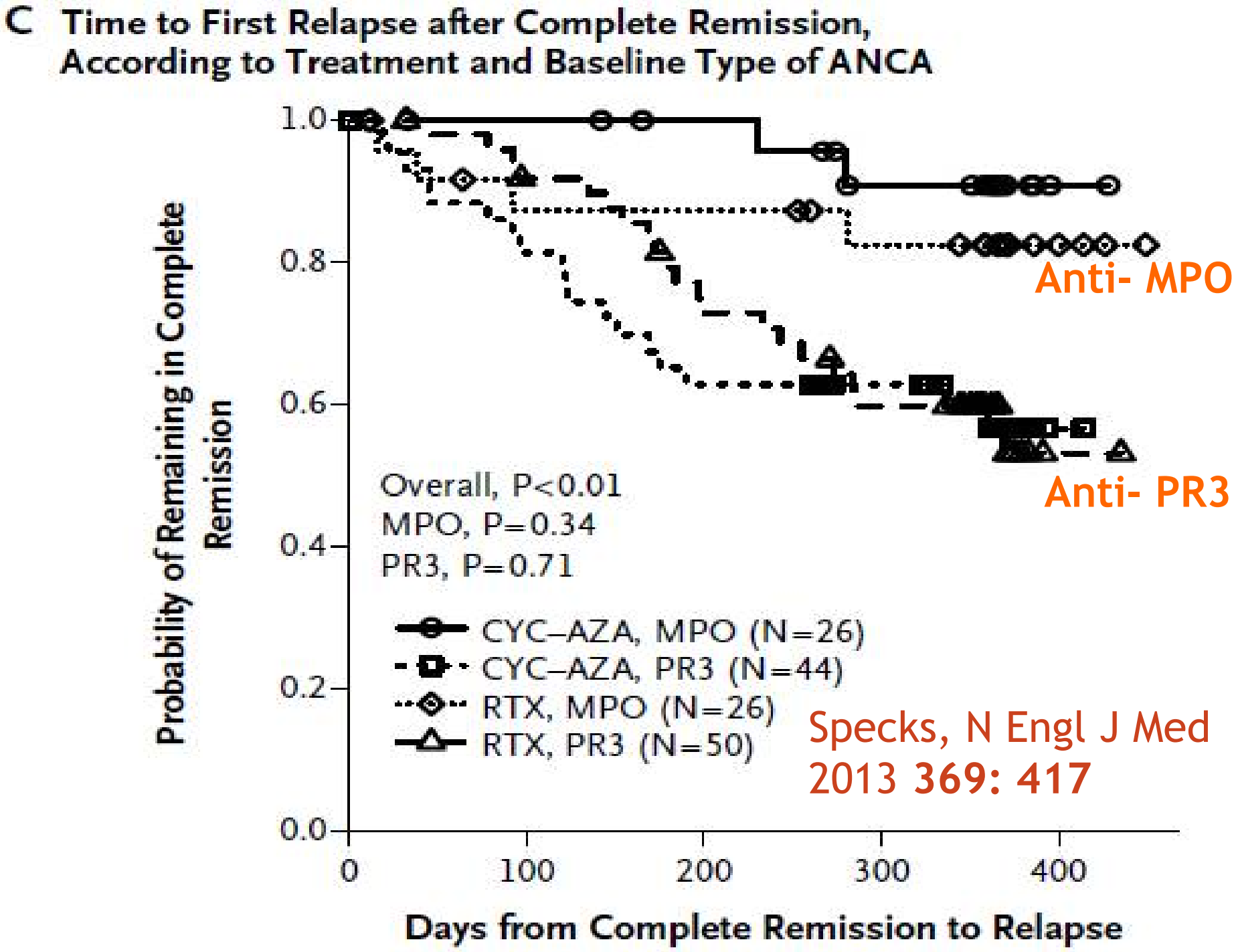
No maintenance treatment ?

A Time to First Relapse after Complete Remission, According to Treatment

Specks, N Engl J Med 2013 **369: 417**



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


C Time to First Relapse after Complete Remission, According to Treatment and Baseline Type of ANCA
Probability of Remaining in Complete Remission
1.0
0.8
0.6
0.4
0.2
0.0
0
100
200
300
400
Days from Complete Remission to Relapse
Overall, P<0.01
MPO, P=0.34
PR3, P=0.71
CYC–AZA, MPO (N=26)
CYC–AZA, PR3 (N=44)
RTX, MPO (N=26)
RTX, PR3 (N=50)
Anti- MPO
Anti- PR3
Specks, N Engl J Med 2013 369: 417

M A IN R IT S A N

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

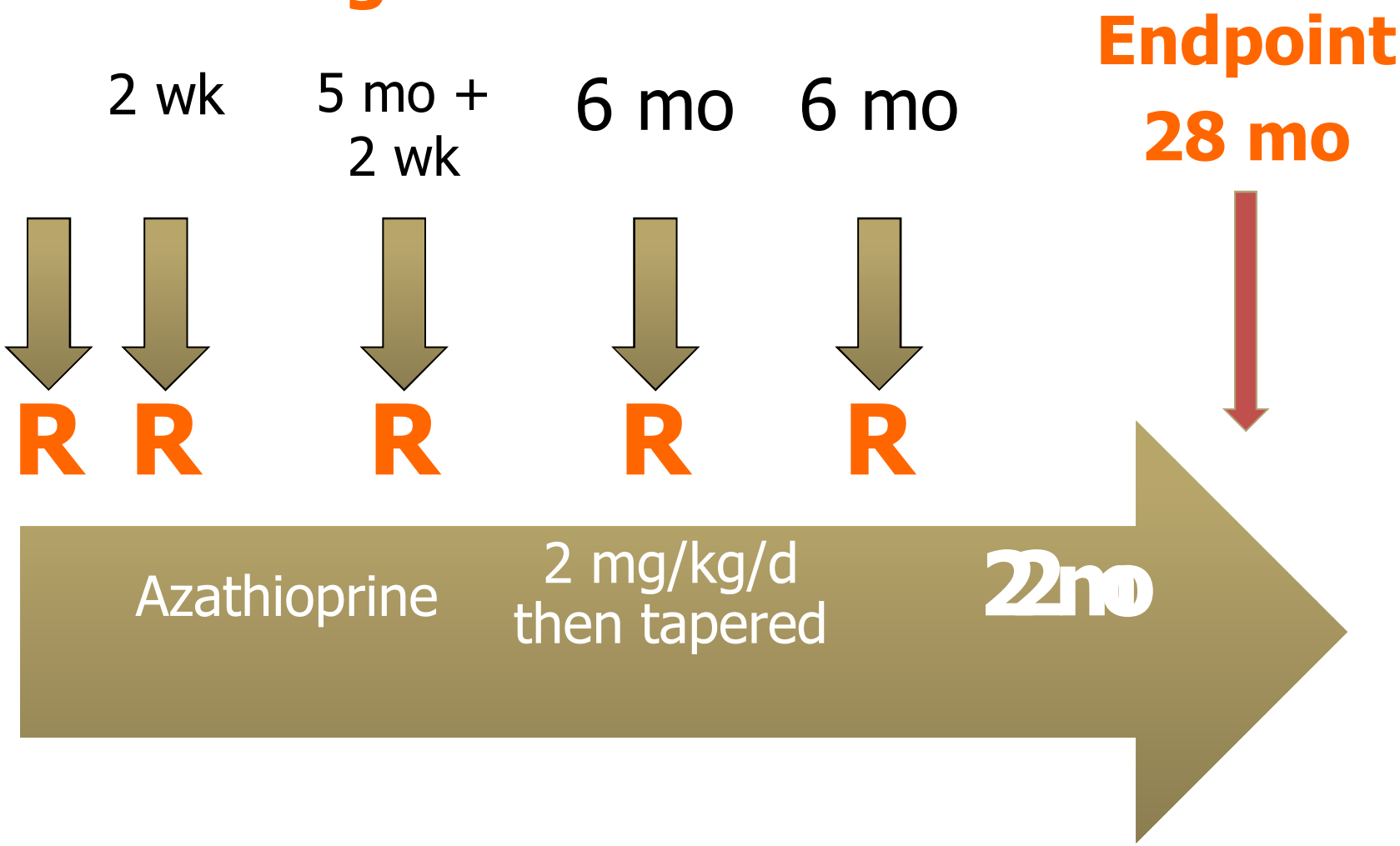
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

Guillevin, NEJM 2014; 37: 1771-80

Maintenance treatment

R = 500 mg of rituximab



Guillevin, NEJM 2014; 37: 1771-80

Azathioprine group drop outs *

27/58 (46.5%)

- ✓ 17 major relapses (**28.8%**)
- ✓ 5 for severe adverse events (**8.5%**)
- ✓ 5 stopped treatment for other reasons, mainly personal (**8.5%**)

* Several causes for the same patient

Guillevin, NEJM 2014; 37: 1771-80

Rituximab group drop outs *

6/58 (10.3%)

- ✓ 3 major relapses (**5.2%**)
- ✓ 3 stopped treatment for other reasons, personal for 1

* Several causes for the same patient

Guillevin, NEJM 2014; 37: 1771-80

ANCA

%	DIAGNOSIS	REMISSION (obtained with CYC)	M 28
AZATHIOPRINE	93.2	69.6	60.8
RITUXIMAB	94.7	53.7	24.4

The same proportion of anti-PR3 and anti-MPO was observed at M28

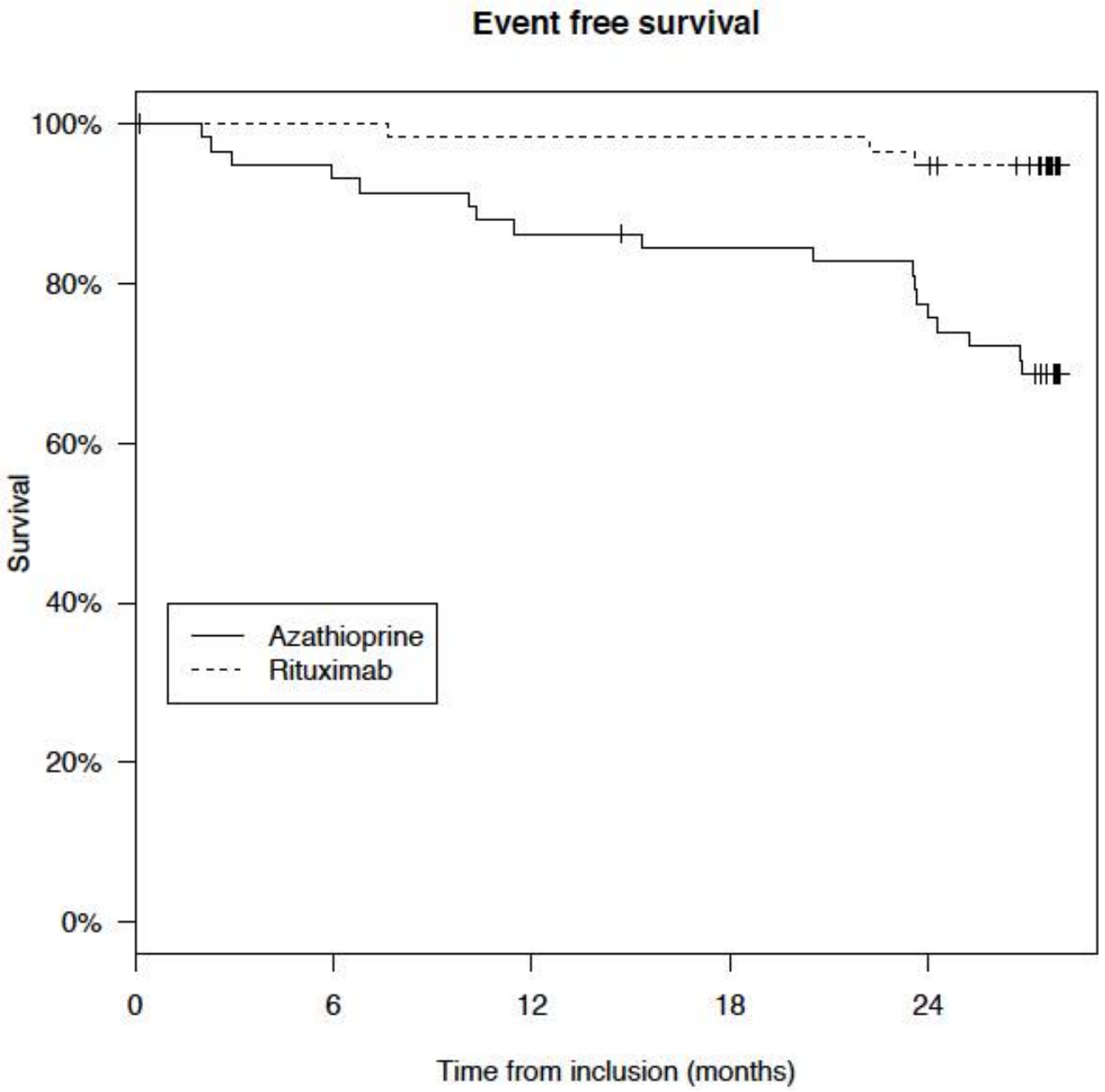
Guillevin, NEJM 2014; 37: 1771-80

Deaths during follow-up (28 months)

2/115 (1.7%)

- Azathioprine: 2 (**3.5%**)
  - ✓ Septicemia 5 months after inclusion, at the time of relapse and treatment intensification
  - ✓ Death 24 months after inclusion, of pancreatic cancer
- ✓ Rituximab: 0 (**0%**)

Guillevin, NEJM 2014; 37: 1771-80


Event free survival
100%
80%
60%
40%
20%
0%
Survival
Azathioprine
Rituximab
0
6
12
18
24
Time from inclusion (months)

P = 0.002

QUESTIONS TO ADDRESS

- ✓ Does classification play a role in therapeutic decision ?
- ✓ Induction treatment: immunosuppressants or biologics ? And what else ?
- ✓ Do patients need a maintenance treatment ?
- ✓ **How long and how to treat in the long term ?**

A treatment adapted to surrogate markers?

The MAINRITSAN 2 study

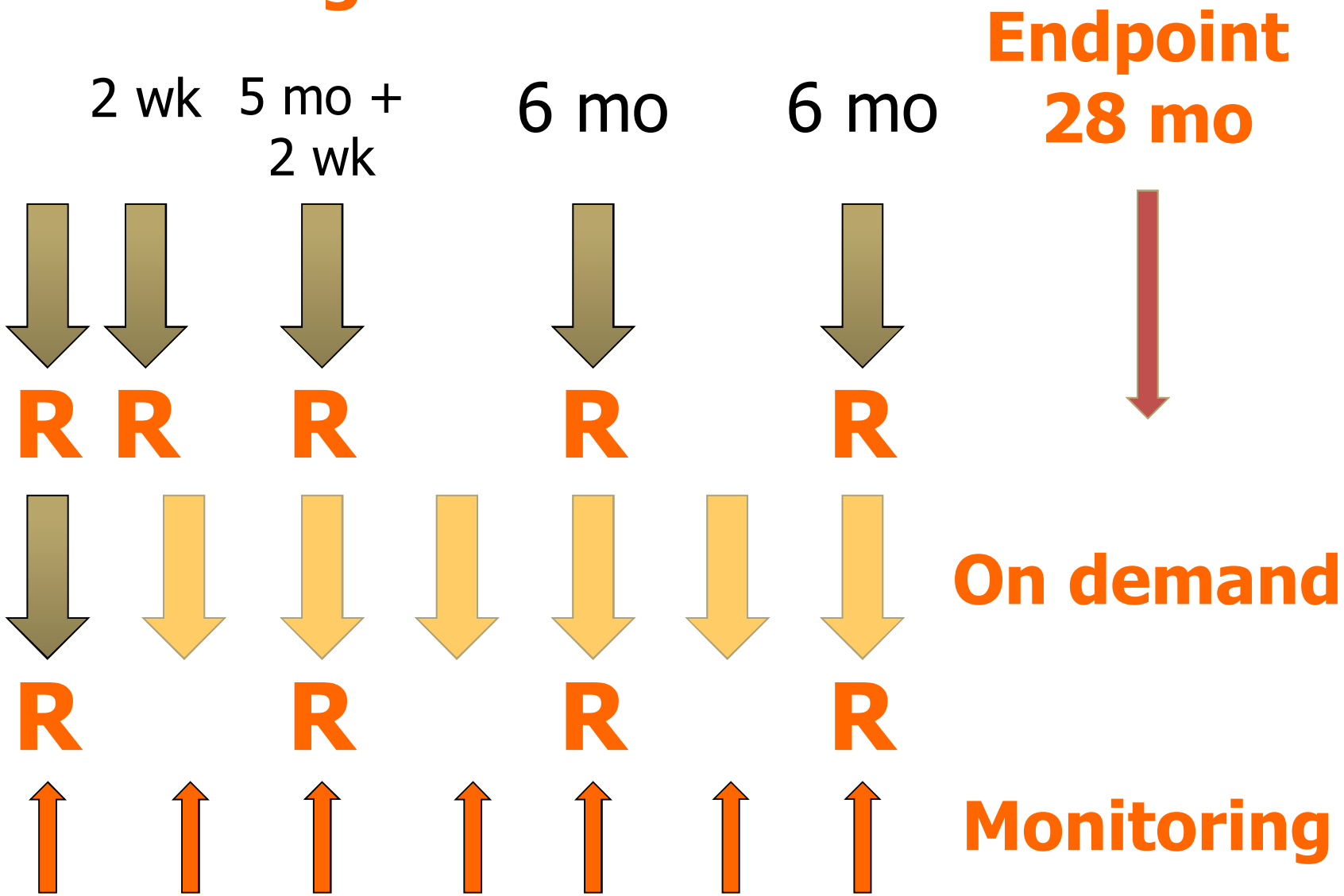
✓Objectives

- ✓To determine whether treatment adapted to ANCA status and CD19 is as effective as a fixed administration schedule

- ✓Safety in each arm
- ✓Inclusions 162 within 11 months (completed)

Maintenance treatment

R = 500 mg of rituximab

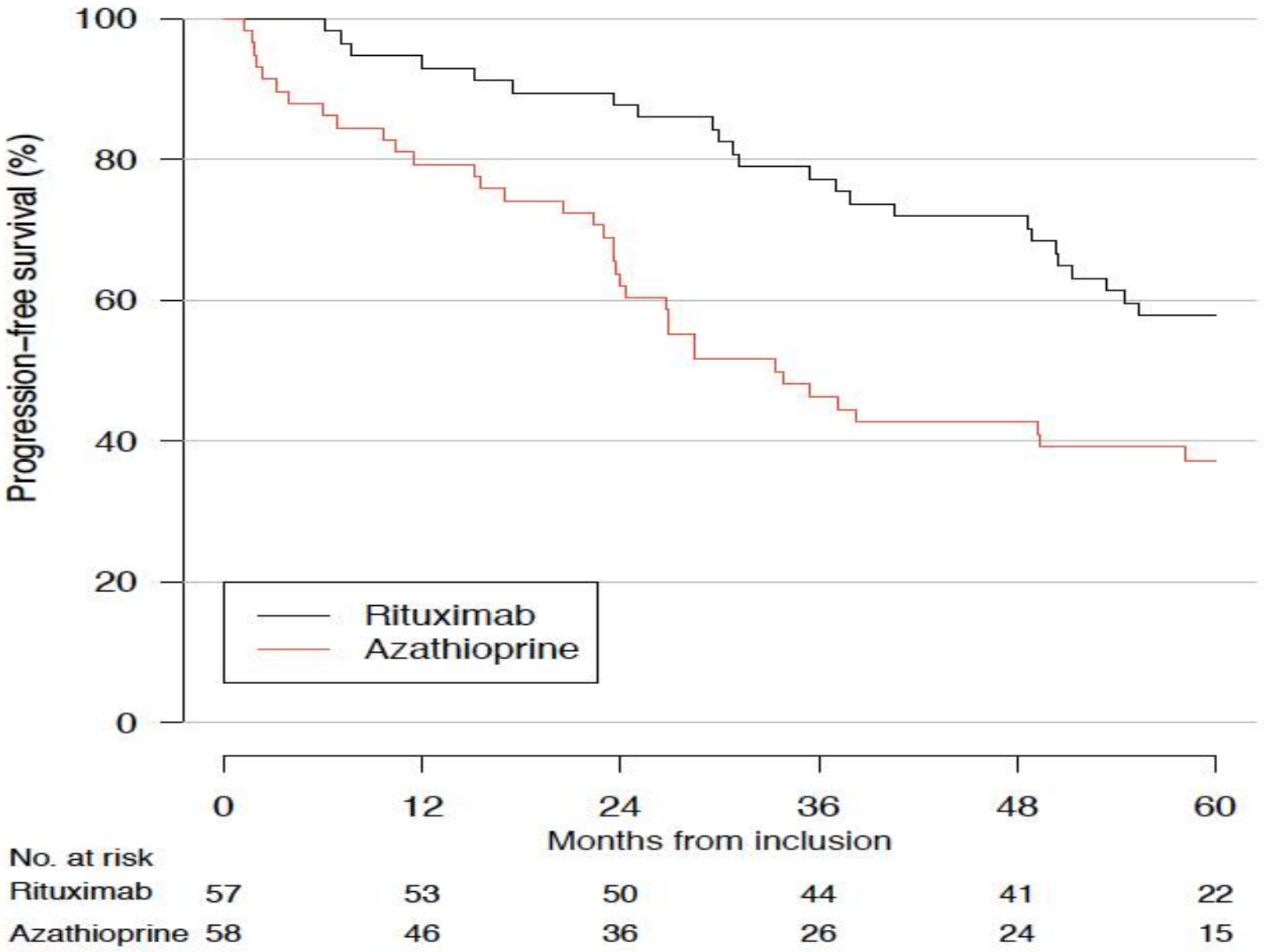


✓Results

- ✓ Safe treatment
- ✓ Effective in both groups
- ✓ Less rituximab infusions in the arm “on demand” (**3 vs 5** *ie* **1.5 gr vs 2.5 gr**)
- ✓ Slightly more relapses in the “on demand” arm (not significant)
- ✓ No predictive value of the ANCA titer and/or CD 19

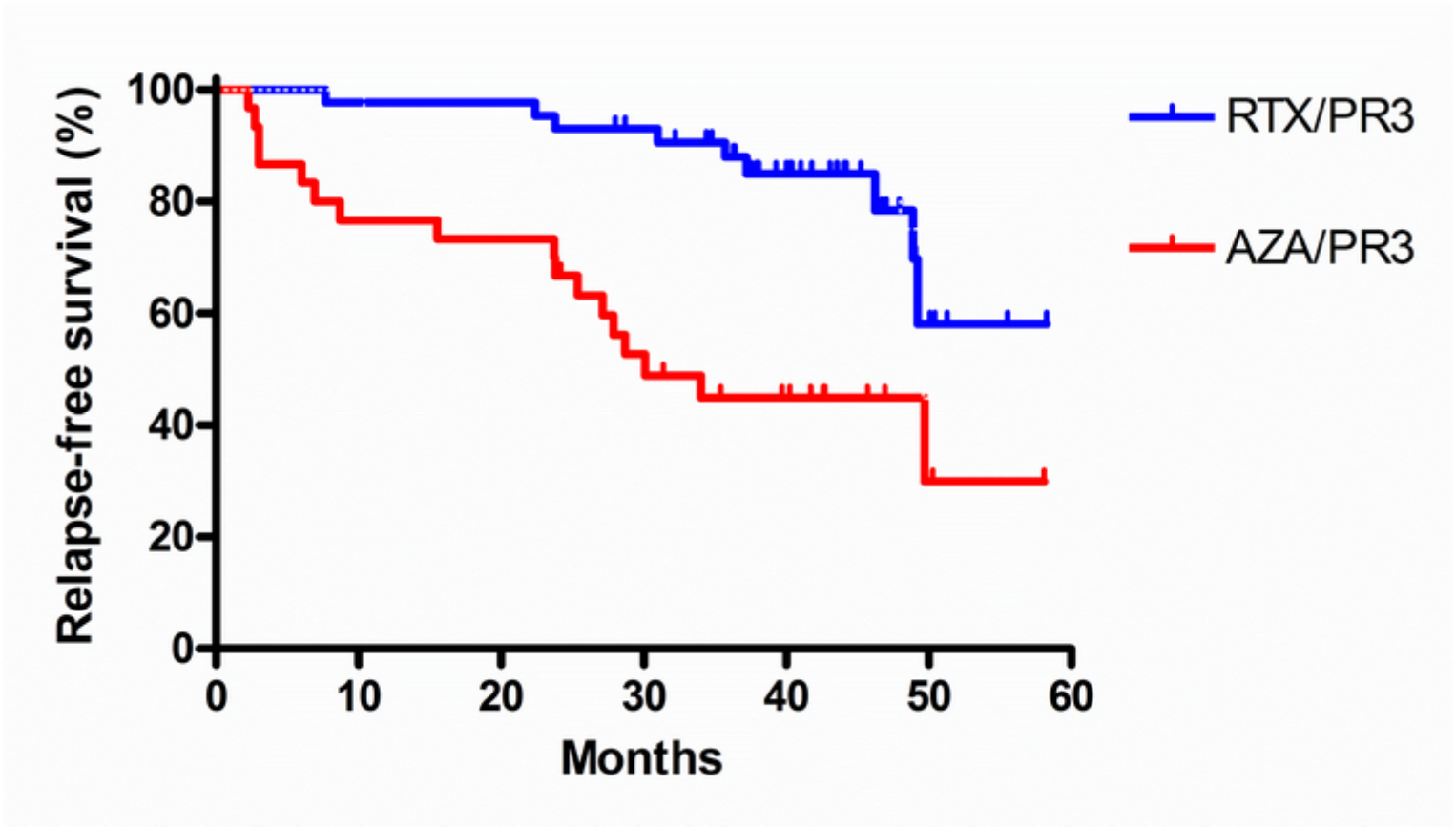
Long term follow up of MAINRITSAN 1

MAINRITSAN. Follow up at 60 months



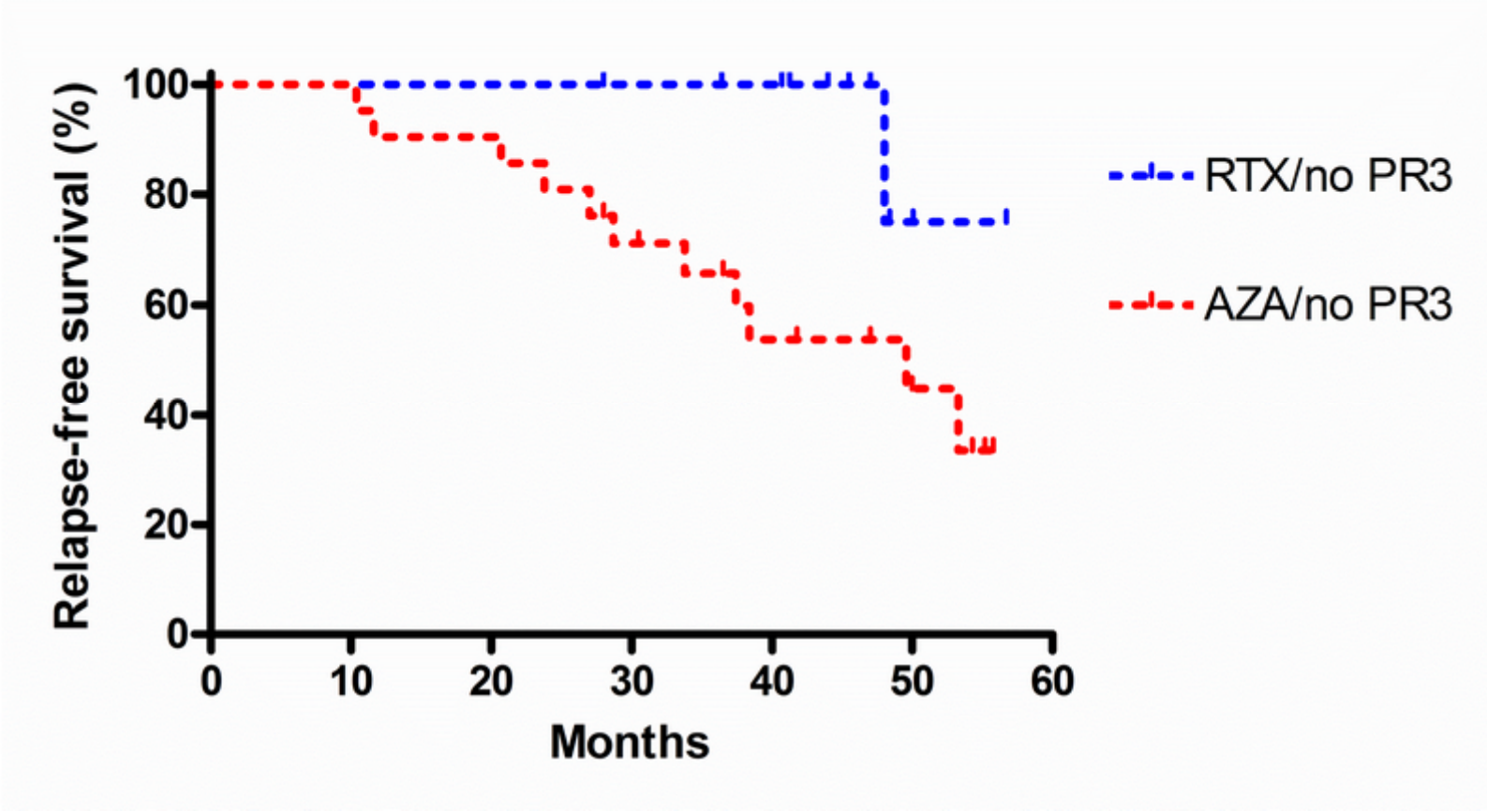
MAINRITSAN
Long term follow up

Relapse-free survival according to ANCA specificity

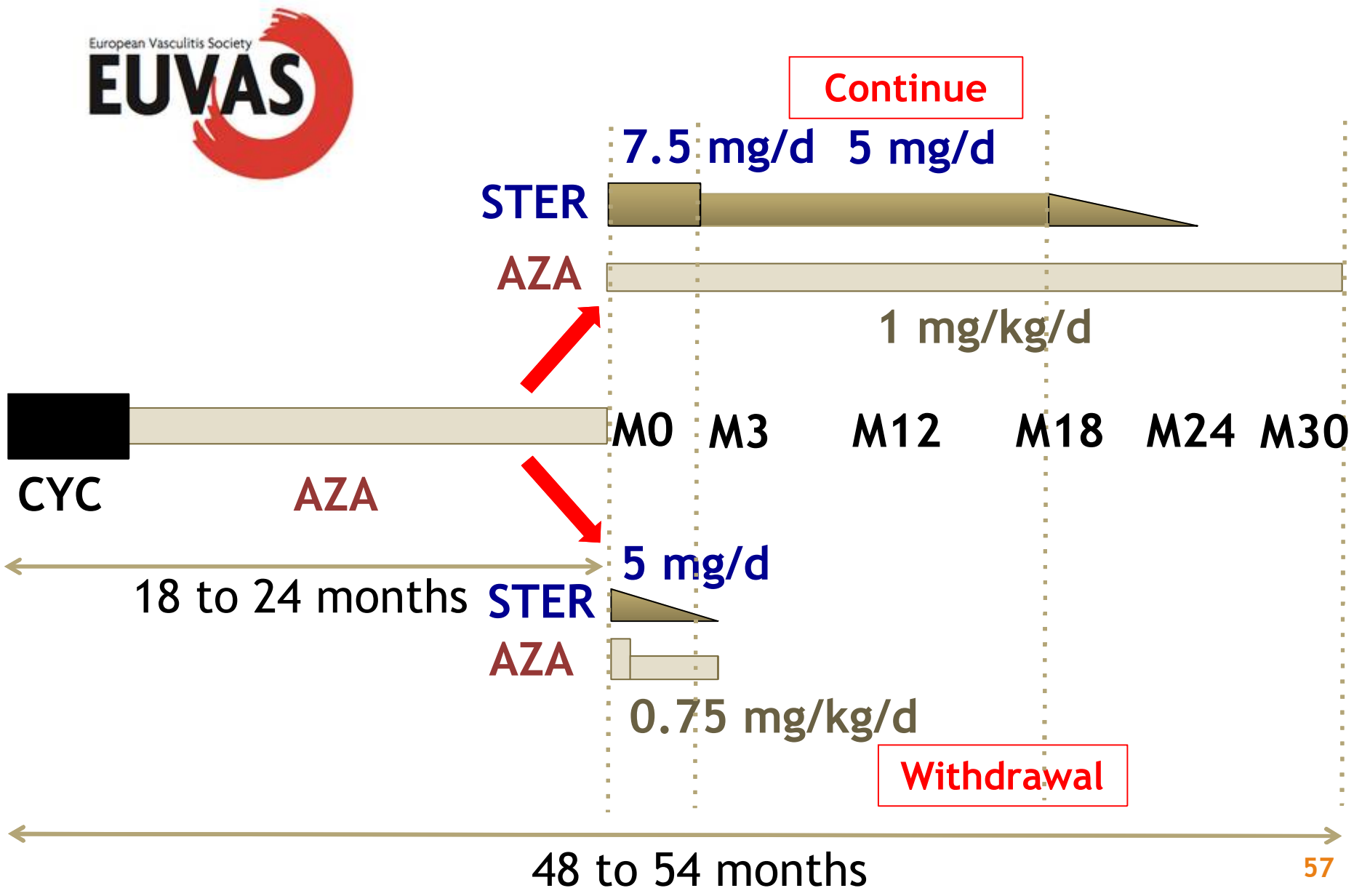


MAINRITSAN
Long term follow up

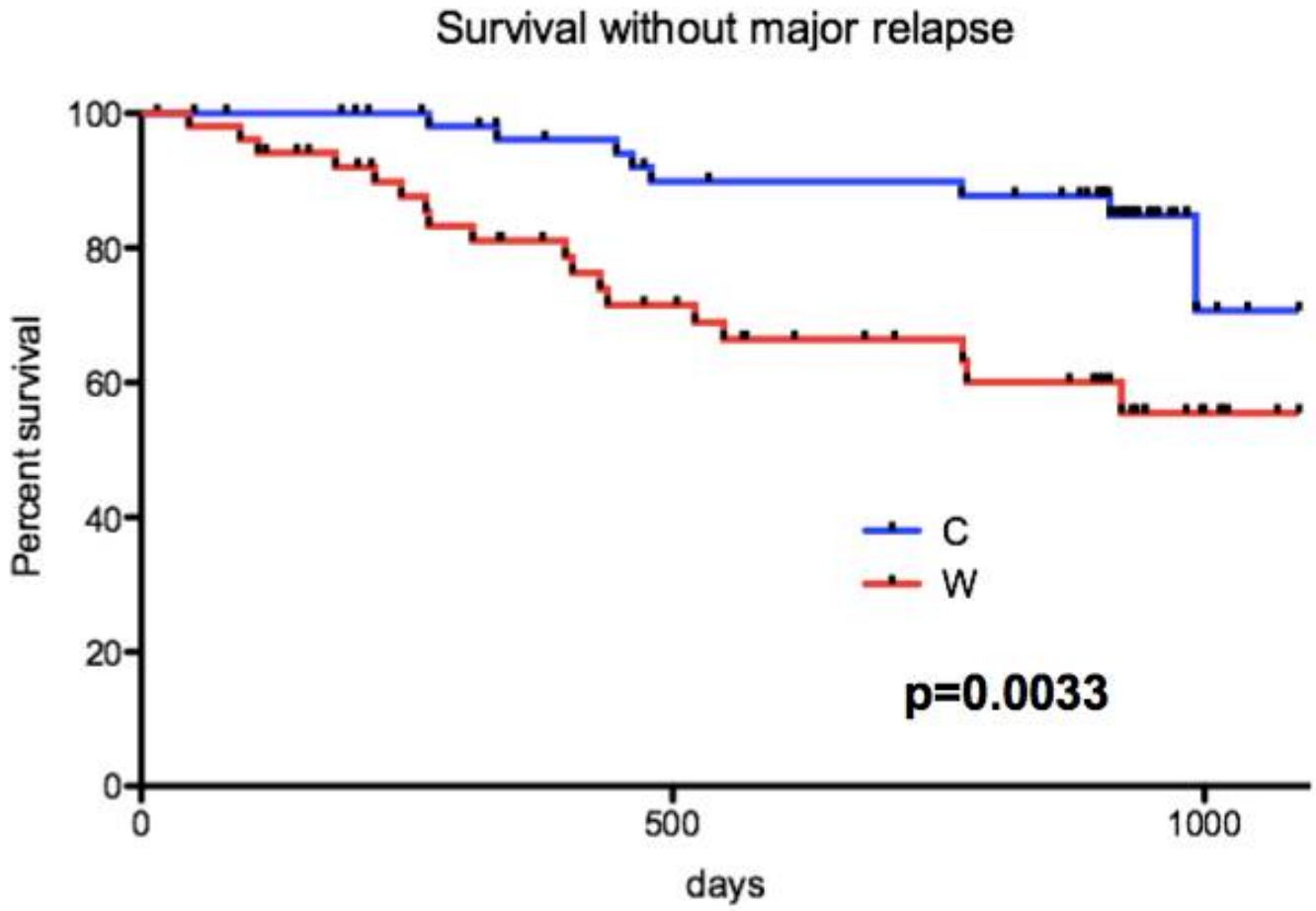
Relapse-free survival according to ANCA specificity



REMAIN : Immunosuppressive regimen



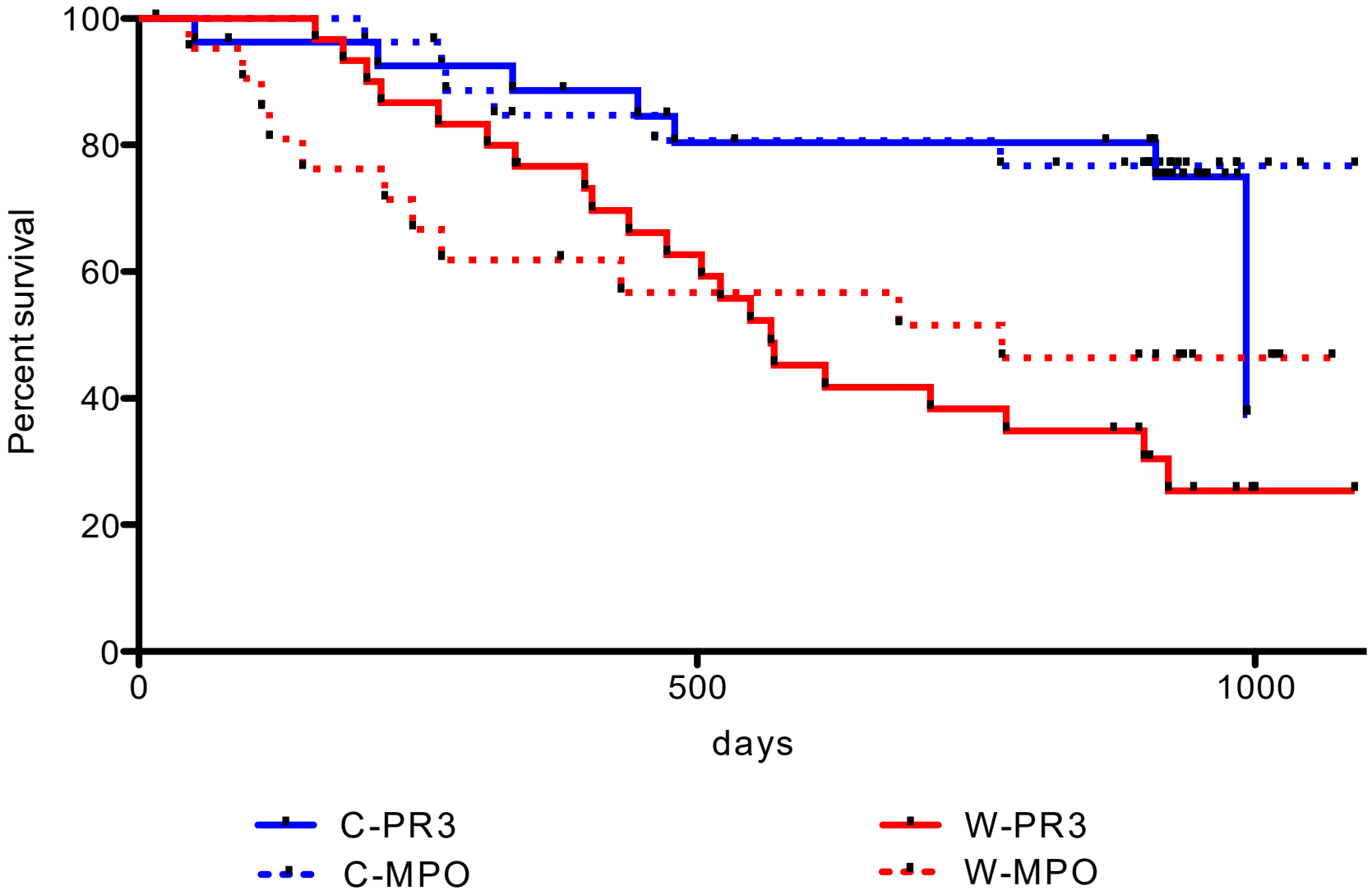
Results : primary end-point



subjects at risk							
	C	59	56	48	43	42	17
	W	51	45	34	25	20	9

Predictors of relapse

Survival without relapse / ANCA type

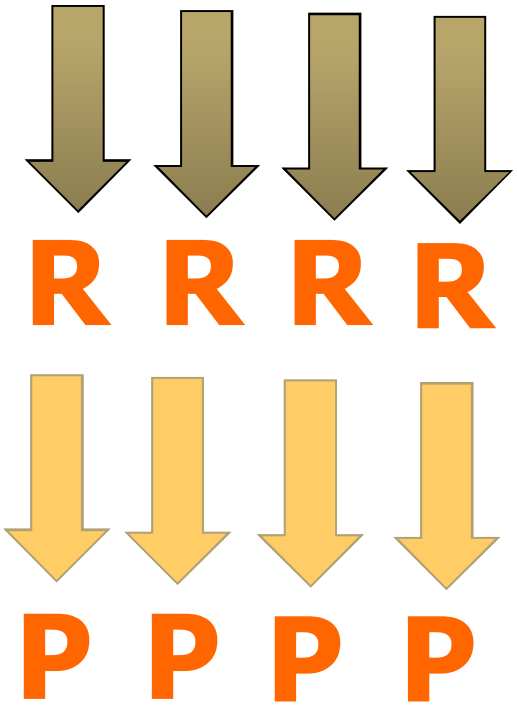


MAINRITSAN 3

R = 500 mg of rituximab

18 months

Endpoint
28 mo



Patients in remission at 28 months of the MAINRITSAN 2 study

Conclusions

- ✓ Treatment of AAV is rapidly improving, mainly because of a better use of steroids and cytotoxic drugs.
- ✓ Rituximab is the competitor of cyclophosphamide for induction of remission.
- ✓ Other biotherapies have a more limited place.
- ✓ New drugs are evaluated: mepolizumab (EGPA), abatacept, anti-chemokines (ANCA-vasculitides)

Conclusions

- ✓ To maintain remission, a treatment is needed.
- ✓ Rituximab is the most effective drug to maintain remission.
- ✓ The “general care” takes a major place in patient’s management.
- ✓ Some markers emerge to predict relapses and, may be, the group of patients who will never relapse.

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