VASCULARITES PULMONAIRES

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SPIF, PARIS

21 Novembre 2015

Liens d'intérêt concernant cette présentation

- Aucun

Plan

- La nomenclature de Chapel Hill
- Granulomatoses avec polyangéite
- Granulomatose éosinophilique avec polyangéite
- ANCA et poumons
- Vascularites à cellules géantes

Plan

- La nomenclature de Chapel Hill
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XXIII.

Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht.

Von

Prof. A. Kussmaul und **R. Maier**

in Freiburg i. Br.

NOMS ET DESCRIPTIONS

1852	Rokitansky	Périartérite noueuse
1866	Küssmaul & Maier	Périartérite noueuse
1931	Wohlwill	Polyangéite microscopique
1936	Wegener	GPA (Wegener)
1951	Churg & Strauss	GEPA (Churg Strauss)
1967	Kawasaki	Kawasaki

ARTHRITIS & RHEUMATISM
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DOI 10.1002/art.37715

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and wileyonlinelibrary.com

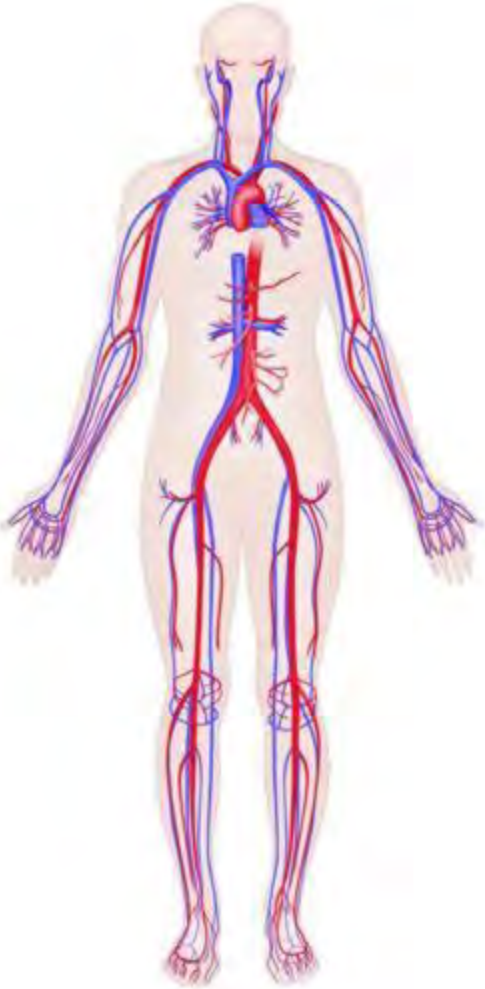
SPECIAL ARTICLE

2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides

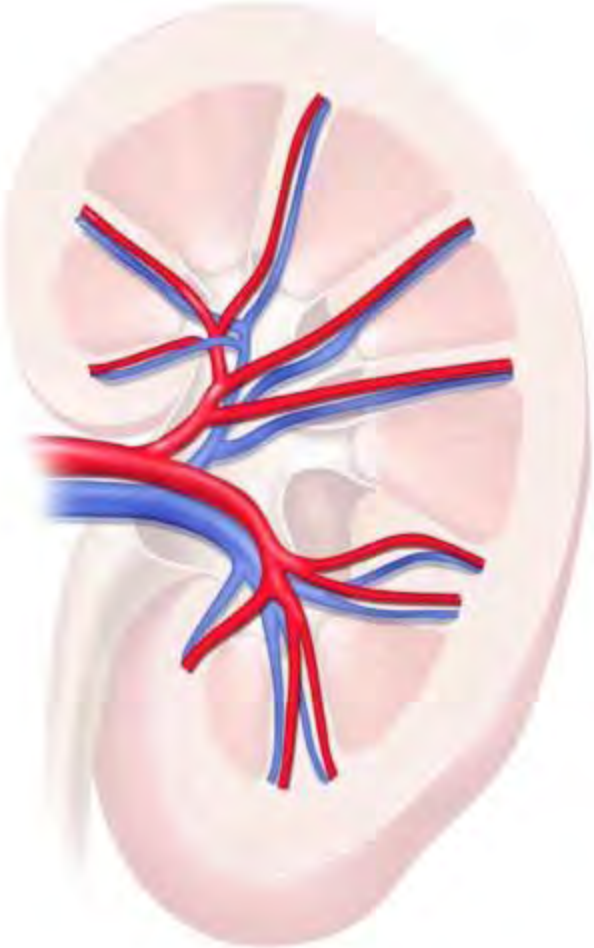
J. C. Jennette,[1] R. J. Falk,[1] P. A. Bacon,[2] N. Basu,[3] M. C. Cid,[4] F. Ferrario,[5] L. F. Flores-Suarez,[6] W. L. Gross,[7] L. Guillevin,[8] E. C. Hagen,[9] G. S. Hoffman,[10] D. R. Jayne,[11] C. G. M. Kallenberg,[12] P. Lamprecht,[13] C. A. Langford,[10] R. A. Luqmani,[14] A. D. Mahr,[15] E. L. Matteson,[16] P. A. Merkel,[17] S. Ozen,[18] C. D. Pusey,[19] N. Rasmussen,[20] A. J. Rees,[21] D. G. I. Scott,[22] U. Specks,[16] J. H. Stone,[23] K. Takahashi,[24] and R. A. Watts[25]

2nd Chapel Hill Consensus Conference 2012

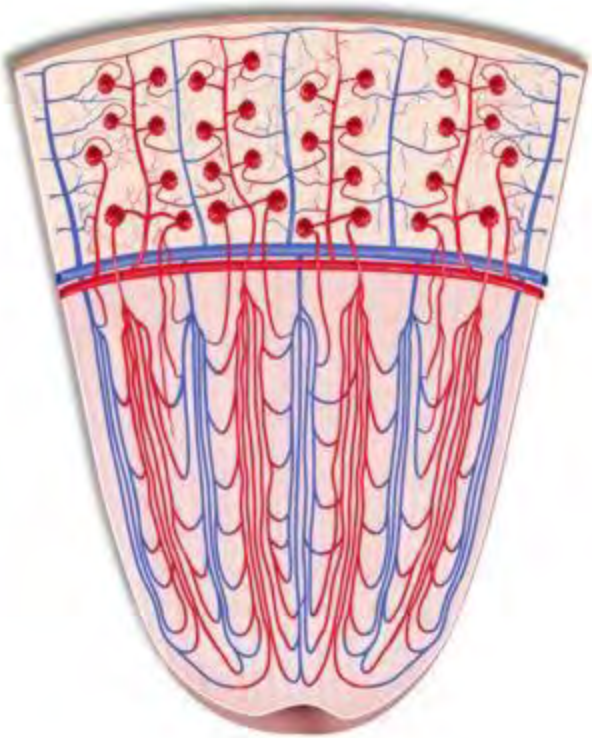
Large Vessels



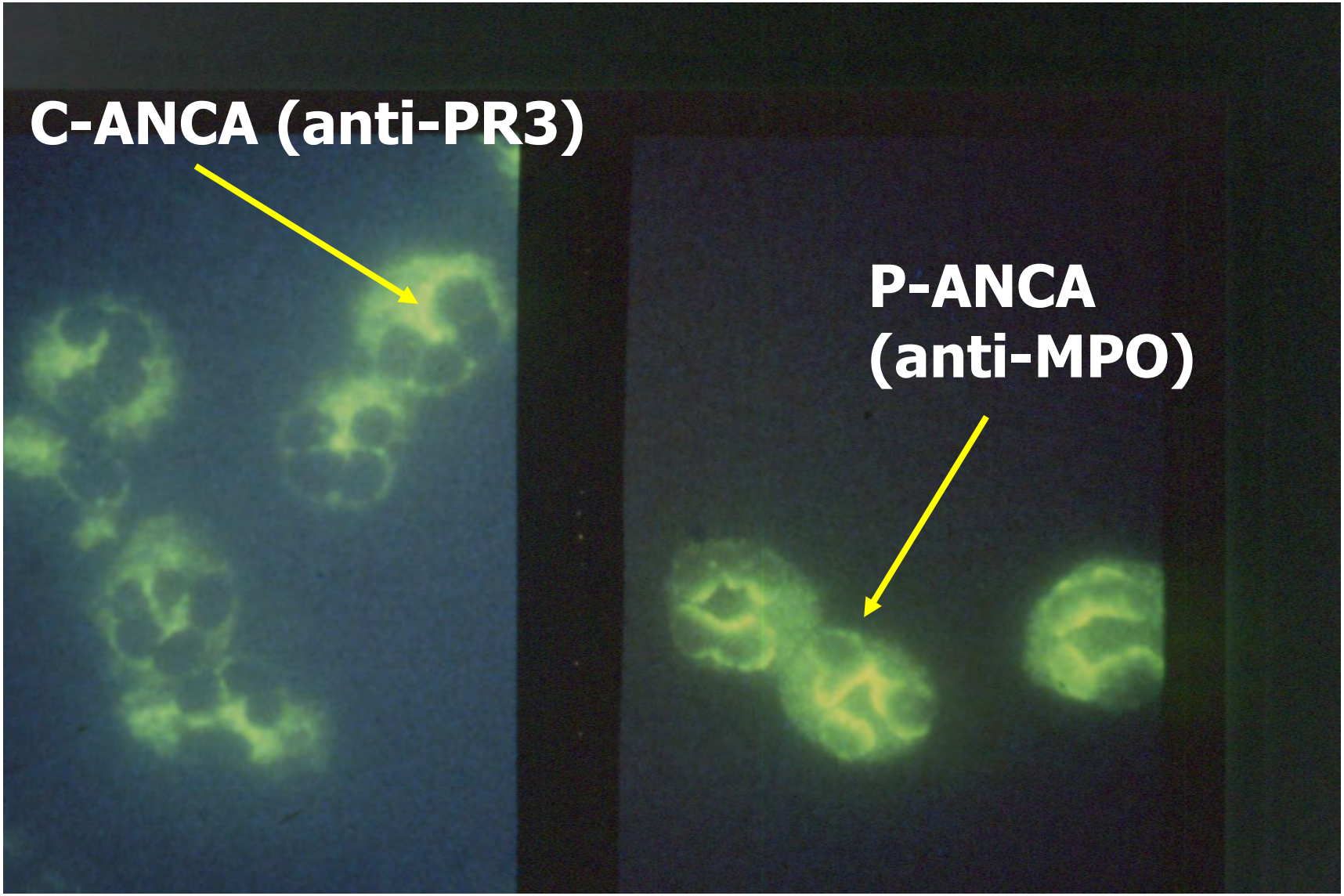
Medium Vessels



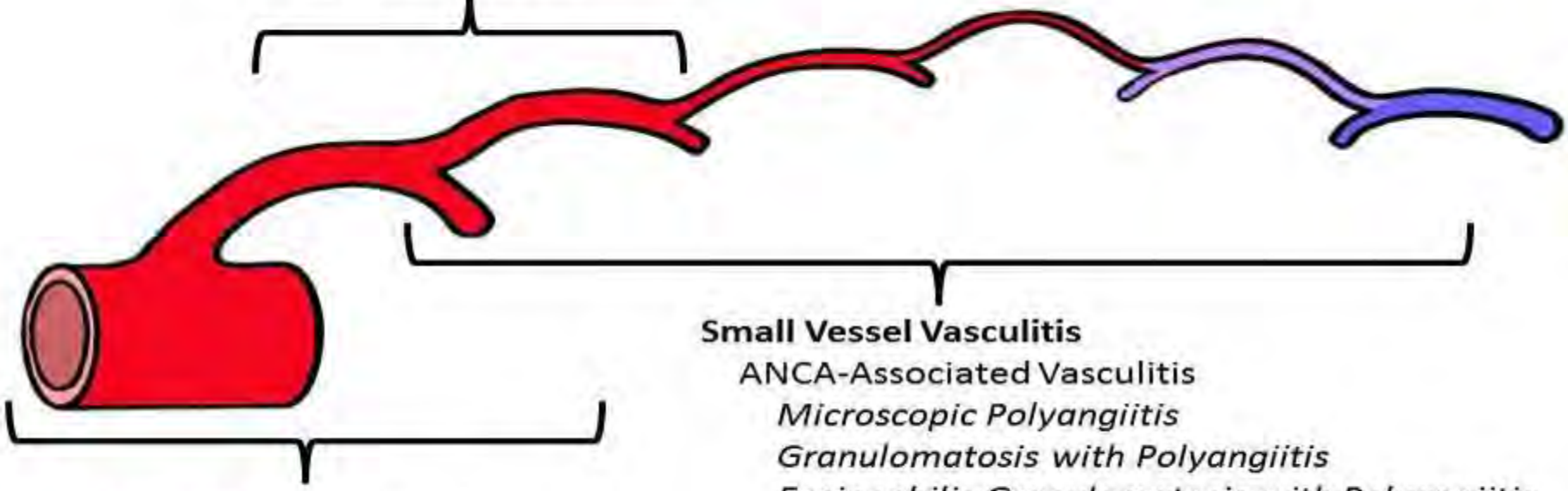
Small Vessels



ANCA



THE CHAPEL HILL NOMENCLATURE



Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

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)

Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

NOUVEAUX NOMS A CHAPEL HILL

- ✓ Granulomatose avec polyangéite (Wegener)
- ✓ Granulomatose avec polyangéite (Churg-Strauss)
- ✓ Vascularites avec anti-MBG (Goodpasture)

British cohort
1184 pts and 5844 controls
European replication cohort
1454 pts and 1666 controls

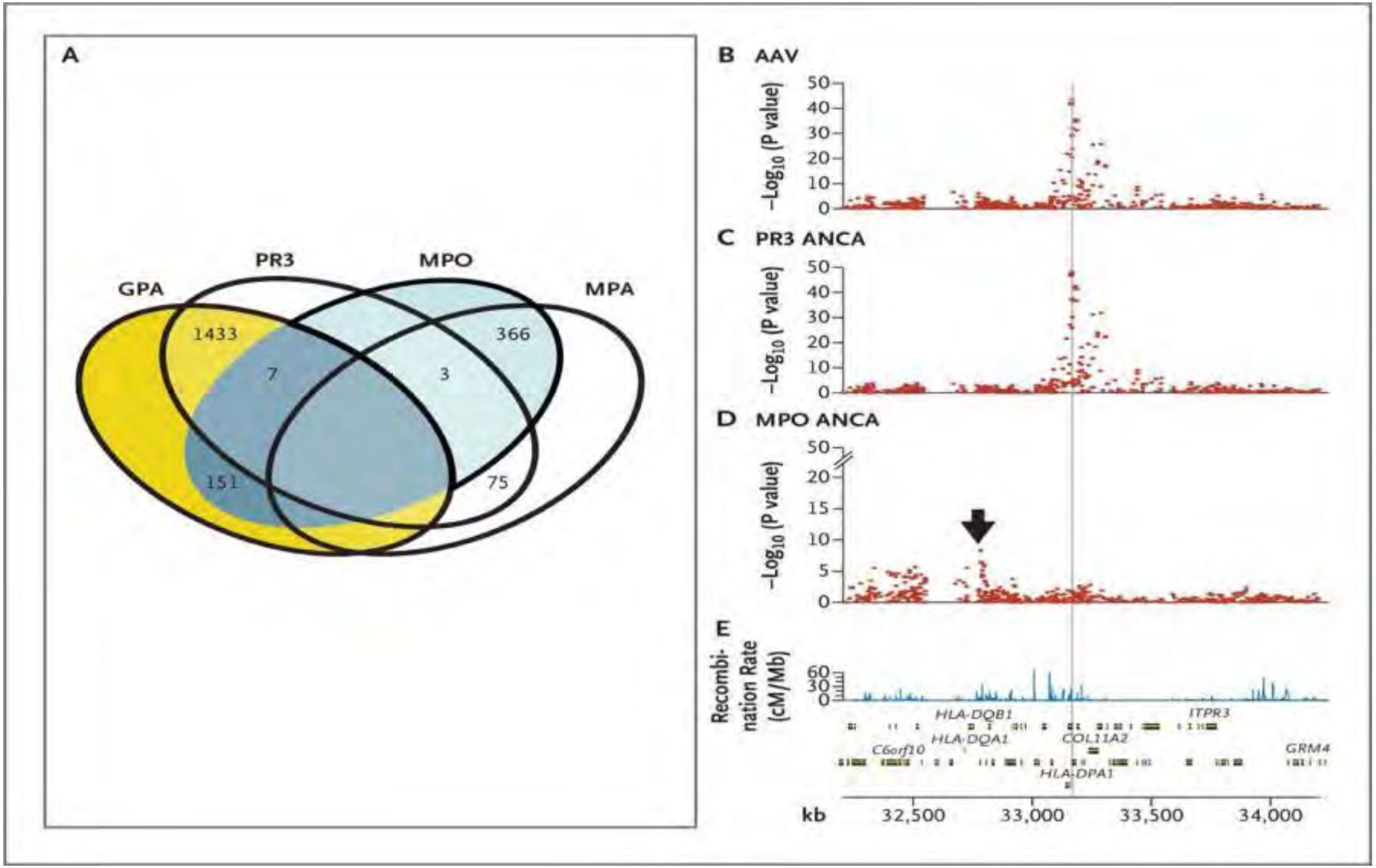
ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetically Distinct Subsets within ANCA-Associated Vasculitis

Paul A. Lyons, Ph.D., Tim F. Rayner, Ph.D., Sapna Trivedi, M.R.C.P., M.Phil., Julia U. Holle, M.D., Ph.D., Richard A. Watts, D.M., F.R.C.P., David R.W. Jayne, M.D., F.R.C.P., Bo Baslund, M.D., Ph.D., Paul Brenchley, Ph.D., Annette Bruchfeld, M.D., Ph.D., Afzal N. Chaudhry, Ph.D., F.R.C.P., Jan Willem Cohen Tervaert, M.D., Ph.D., Panos Deloukas, Ph.D., Conleth Feighery, M.D., Wolfgang L. Gross, M.D., Ph.D., Loic Guillevin, M.D., Iva Gunnarsson, M.D., Ph.D., Lorraine Harper M.R.C.P., Ph.D., Zdenka Hrušková, M.D., Mark A. Little, M.R.C.P.I., Ph.D., Davide Martorana, Ph.D., Thomas Neumann, M.D., Sophie Ohlsson, M.D., Ph.D., Sandosh Padmanabhan, M.D., Ph.D., Charles D. Pusey, D.Sc., F.Med.Sci., Alan D. Salama, F.R.C.P., Ph.D., Jan-Stephan F. Sanders, M.D., Ph.D., Caroline O. Savage, F.Med.Sci., Ph.D., Mårten Segelmark, M.D., Ph.D., Coen A. Stegeman, M.D., Ph.D., Vladimir Tesař, M.D., Ph.D., Augusto Vaglio, M.D., Ph.D., Stefan Wieczorek, M.D., Benjamin Wilde, M.D., Jochen Zwerina, M.D., Andrew J. Rees, M.B., F.Med.Sci., David G. Clayton, M.A., and Kenneth G.C. Smith, F.Med.Sci., Ph.D.

Lyons et al, NEJM 2012.



Lyons et al, NEJM 2012.

The NEW ENGLAND JOURNAL of MEDICINE

LES ANCA

ANCA et vascularites

- GPA = 80%
- GPA localisée = 50%
- PAM > 50%
- GEPA (Churg-Strauss): 30%
- PAN < 0 % (critères d'exclusion

LES PHENOTYPES DE LA GPA ET DE LA GEPA

VASCULARITES PULMONAIRES

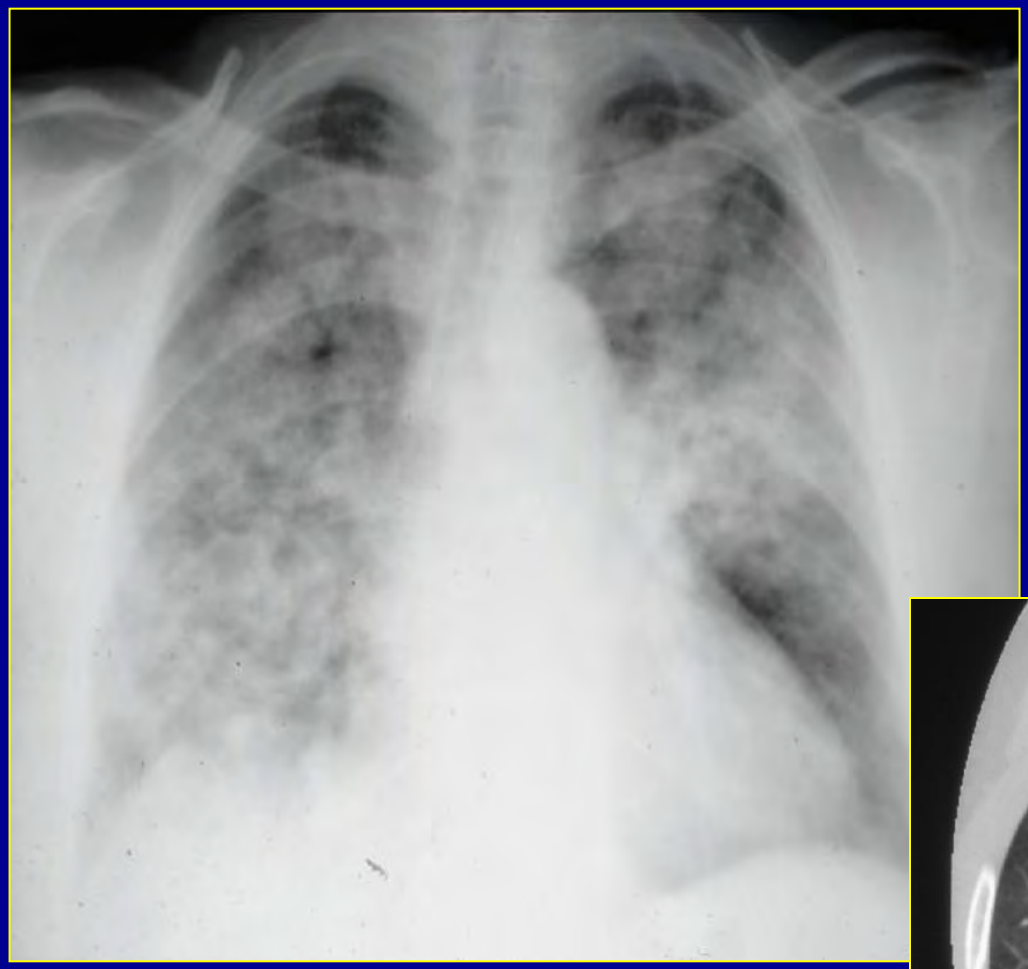
GRANULOMATOSE AVEC POLYANGEITE

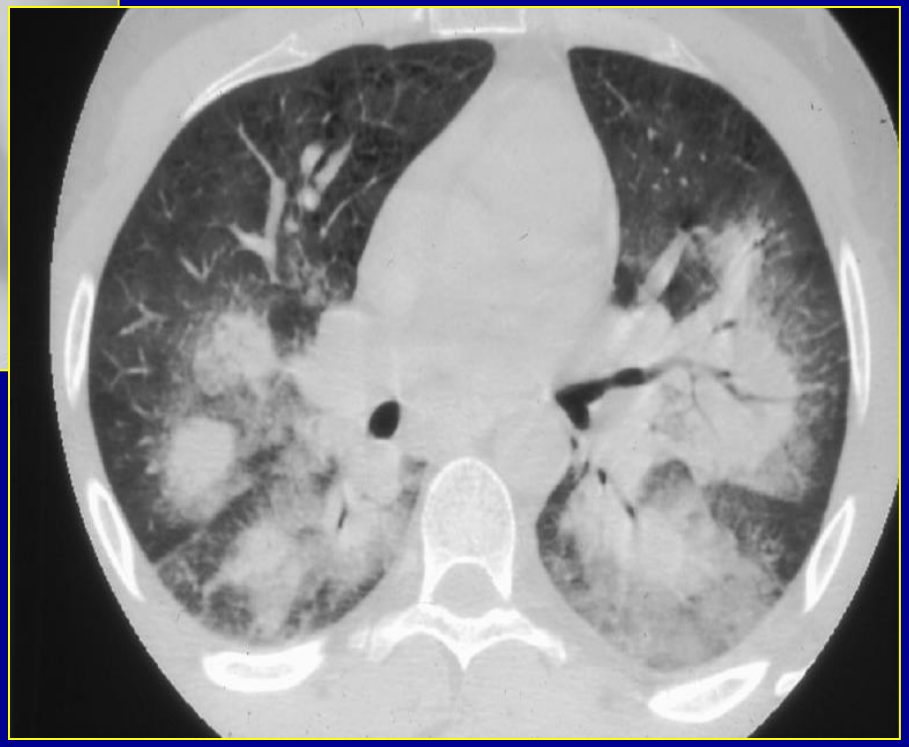
- Le poumon est atteint chez 80% des patients
- Nodules
  - uni- ou bilatéraux
  - unique ou multiple
  - la moitié sont excavés
- Hémorragie alvéolaire
  - parfois mineure
  - cercle souvent les nodules

VASCULARITES PULMONAIRES

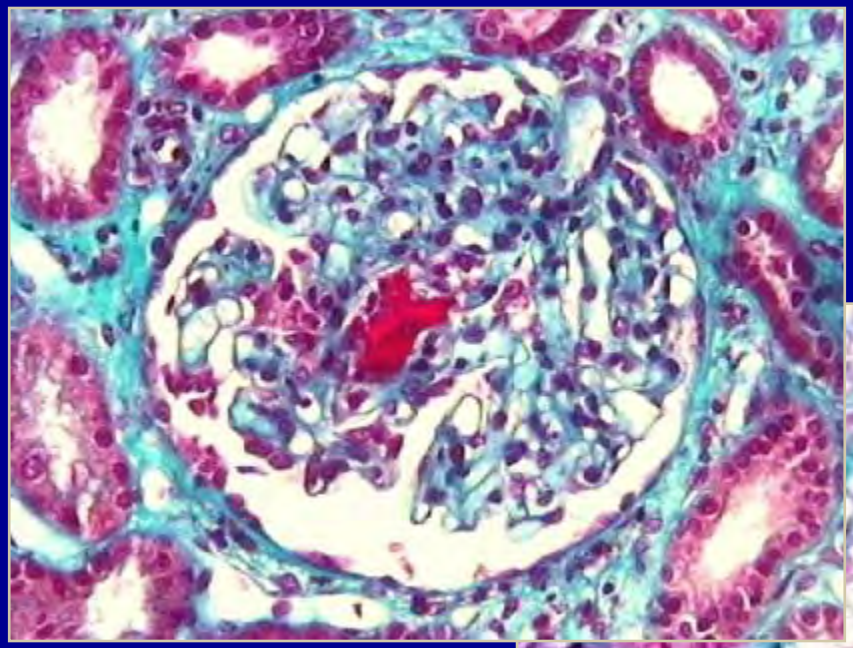
- L'hémorragie alvéolaire n'est pas un élément de mauvais pronostic des vascularites, même si elle peut être sévère, voire mortelle

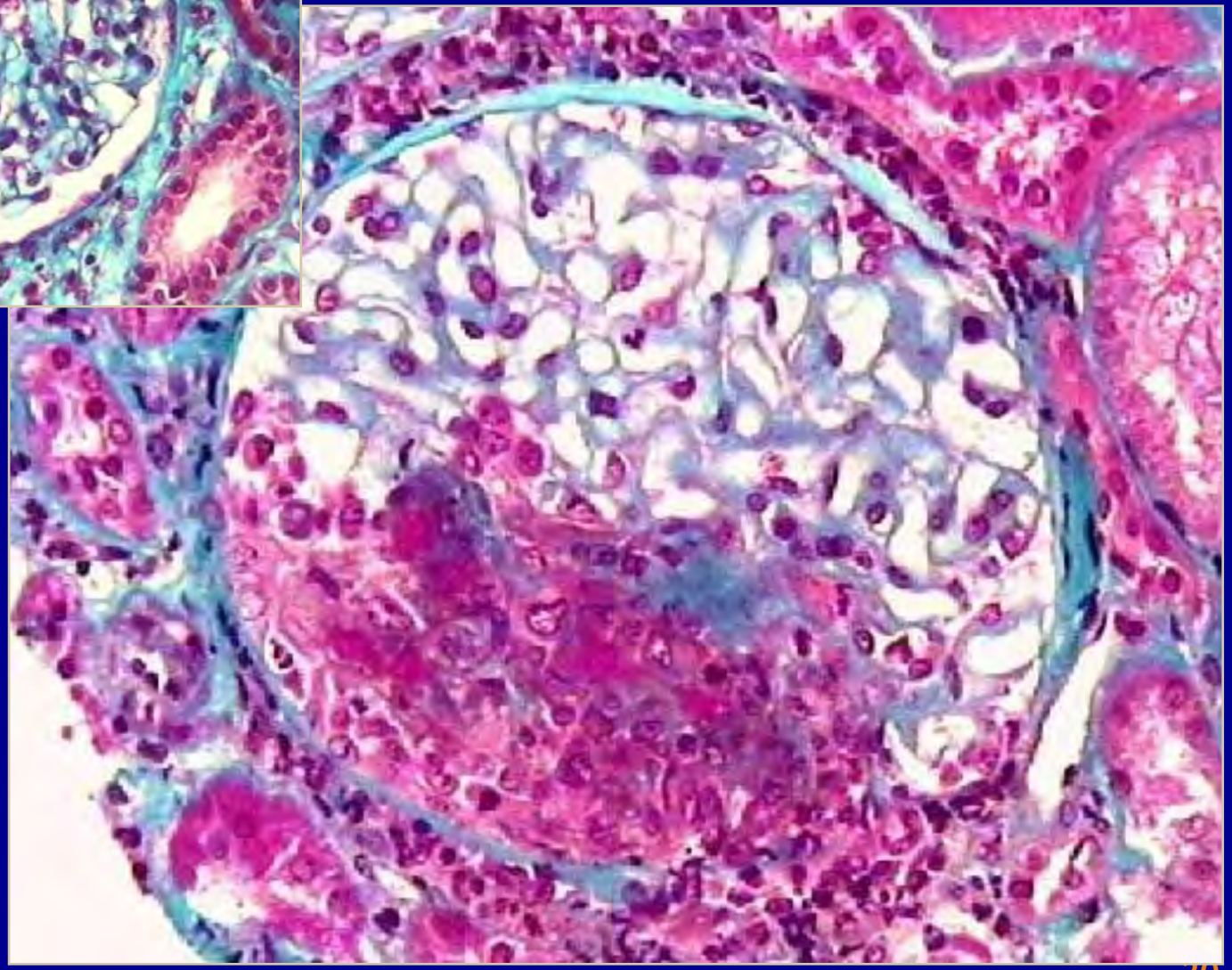
- La raison est que les formes graves d'hémorragie alvéolaire sont généralement associées à une atteinte rénale, qui est l'élément majeur du pronostic

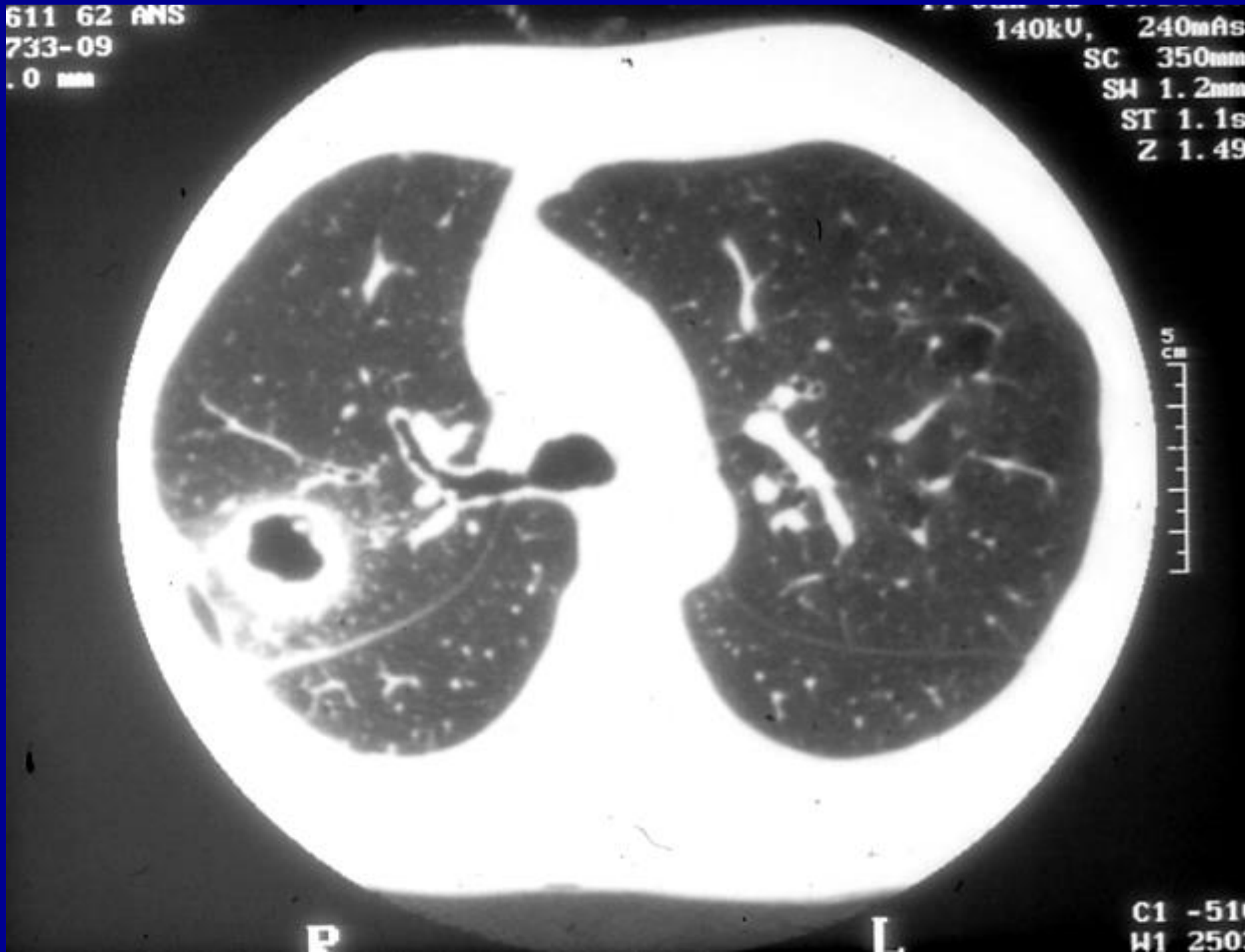


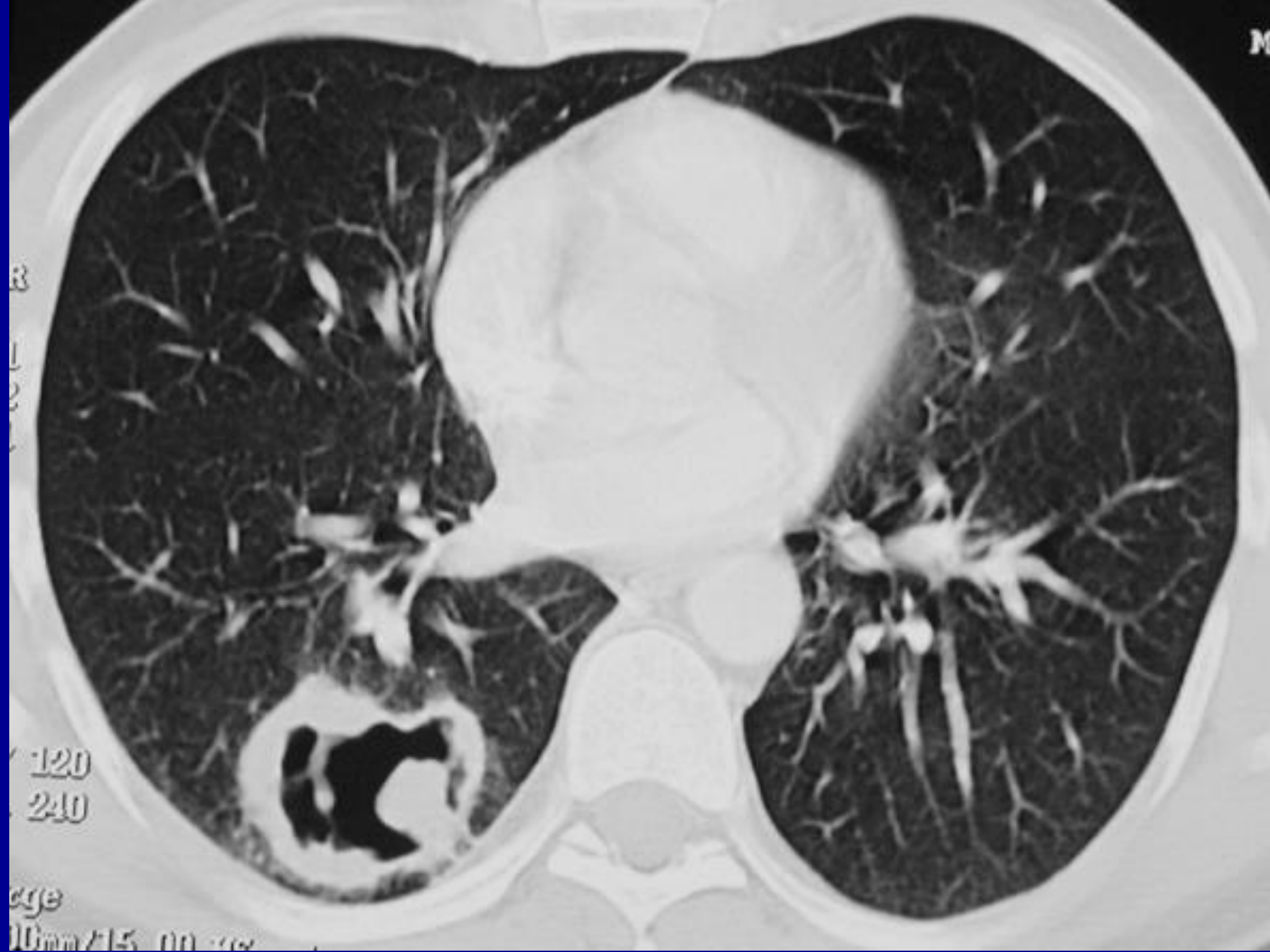


Glomérulonéphrite extracapillaire






611 62 ANS
733-09
.0 mm
140kV, 240mAs
SC 350mm
SH 1.2mm
ST 1.1s
Z 1.49
5 cm
R
L
C1 -51
W1 250



CLASSIFICATION DE L'ACR

Masi et al, 1990 Arthritis Rheum

- Asthme
- Eosinophilie
- Antécédent d'allergie
- Infiltrats pulmonaires
- Sinusite
- Eosinophilie extravasculaire

4 à 6 critères permettent de classer

PHENOTYPES DE LA GEPA

Sablé-Fourtassou R, Cohen P, Mahr A, Pagnoux C, Mouthon L, Jayne D, ... Guillevin L. Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 2005;143(9):632-8.

Sinico RA, Di Toma L, Maggiore U, Bottero P, Radice A, Tosoni C, et al. Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 2005;52(9):2926-35.

PHENOTYPES DE LA GEPA

ANCA+	p <	odd ratio
Reins	0.0005	19.6

ANCA neg.	p <	odd ratio
Coeur	0.0002	12

PNEUMONIE INTERSTITIELLE ASSOCIÉE AUX ANCA

PNEUMONIE INTERSTITIELLE

- Fibrose pulmonaire
- ANCA +, anti-MPO
- avec ou sans vascularite
- Rare en Europe
- Serait plus fréquent au Japon

MALADIES PULMONAIRES ASSOCIÉES AUX ANCA

- Fibrose pulmonaire
- Vascularites pulmonaires
- Bronchectasies (C Tcherakian)

ANCA et POUMONS

- ✓ L'œuf ou la poule?
  - ✓ observations de fibroses débutant avant l'apparition des ANCA
  - ✓ ANCA avec ou sans vascularites?

2015

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

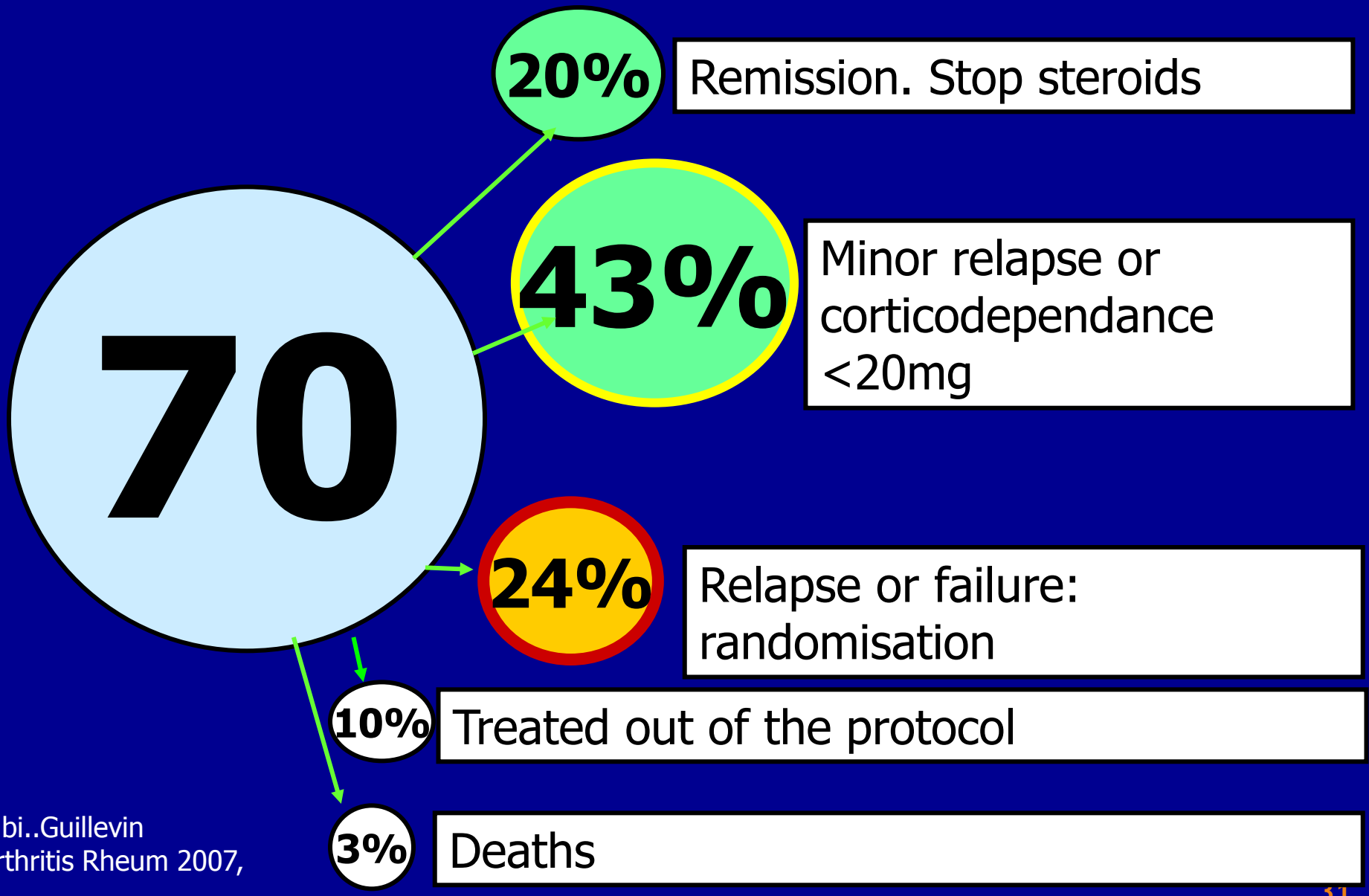
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management

Matthieu Groh [a], Christian Pagnoux [b], Chiara Baldini [c], Elisabeth Bel [d], Paolo Bottero [e], Vincent Cottin [f], Klaus Dalhoff [g], Bertrand Dunogué [a], Wolfgang Gross [g], Julia Holle [g], Marc Humbert [h], David Jayne [i], J. Charles Jennette [j], Romain Lazor [k], Alfred Mahr [l], Peter A. Merkel [m], Luc Mouthon [a], Renato Alberto Sinico [n], Ulrich Specks [o], Augusto Vaglio [p], Michael E. Wechsler [q], Jean-François Cordier [f], Loïc Guillevin [a,*]

Eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome): where are we now?

Matthieu Groh[1], Christian Pagnoux[2] and Loïc Guillevin[1]

TRAITEMENT CS. FFS = 0



Ribi..Guillevin
Arthritis Rheum 2007,

Journal of Autoimmunity 43 (2013) 60–69

Contents lists available at SciVerse ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Long-term outcomes of 118 patients with eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) enrolled in two prospective trials

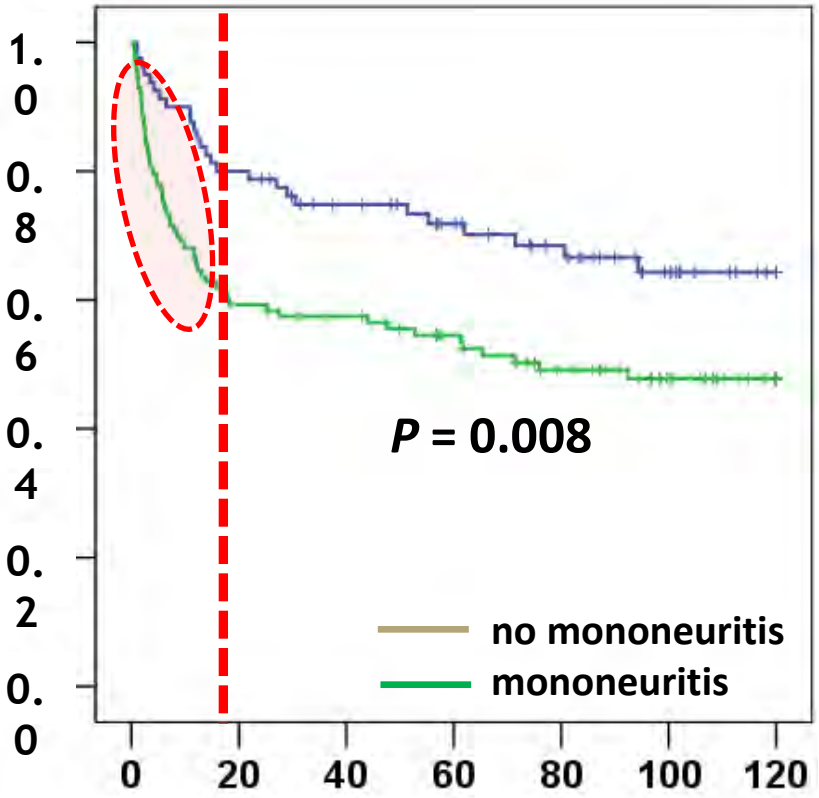
Maxime Samson [a,b], Xavier Puéchal [a], Hervé Devilliers [c], Camillo Ribi [a,d], Pascal Cohen [a], Marc Stern [e], Christian Pagnoux [a], Luc Mouthon [a], Loïc Guillevin [a,*] for the French Vasculitis Study Group

Last Visit

- **Mean follow-up:** 97.6 ± 39.6 months
- **Among the 165/193 survivors:**
  - **57% on CS:** 8 ± 0.6 mg/day
  - **17% on IS:**
    - AZA: 61%
    - MTX: 18%
    - MMF: 11%

TIME TO 1ST ADDITIONAL TREATMENT

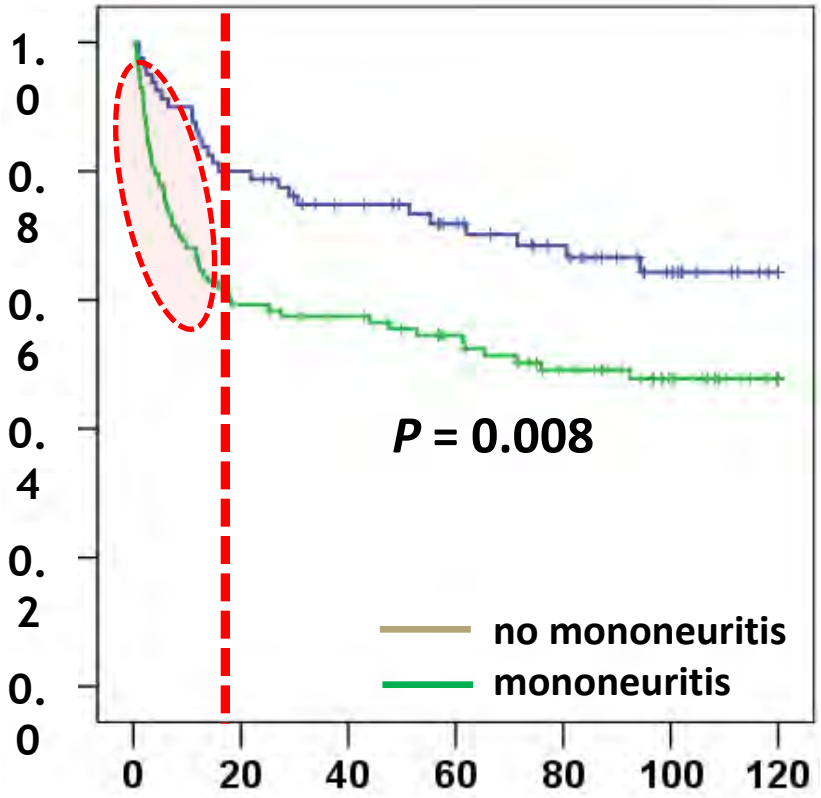
Mononeuritis multiplex



18 months

TIME TO 1ST ADDITIONAL TREATMENT

Mononeuritis multiplex



18 months

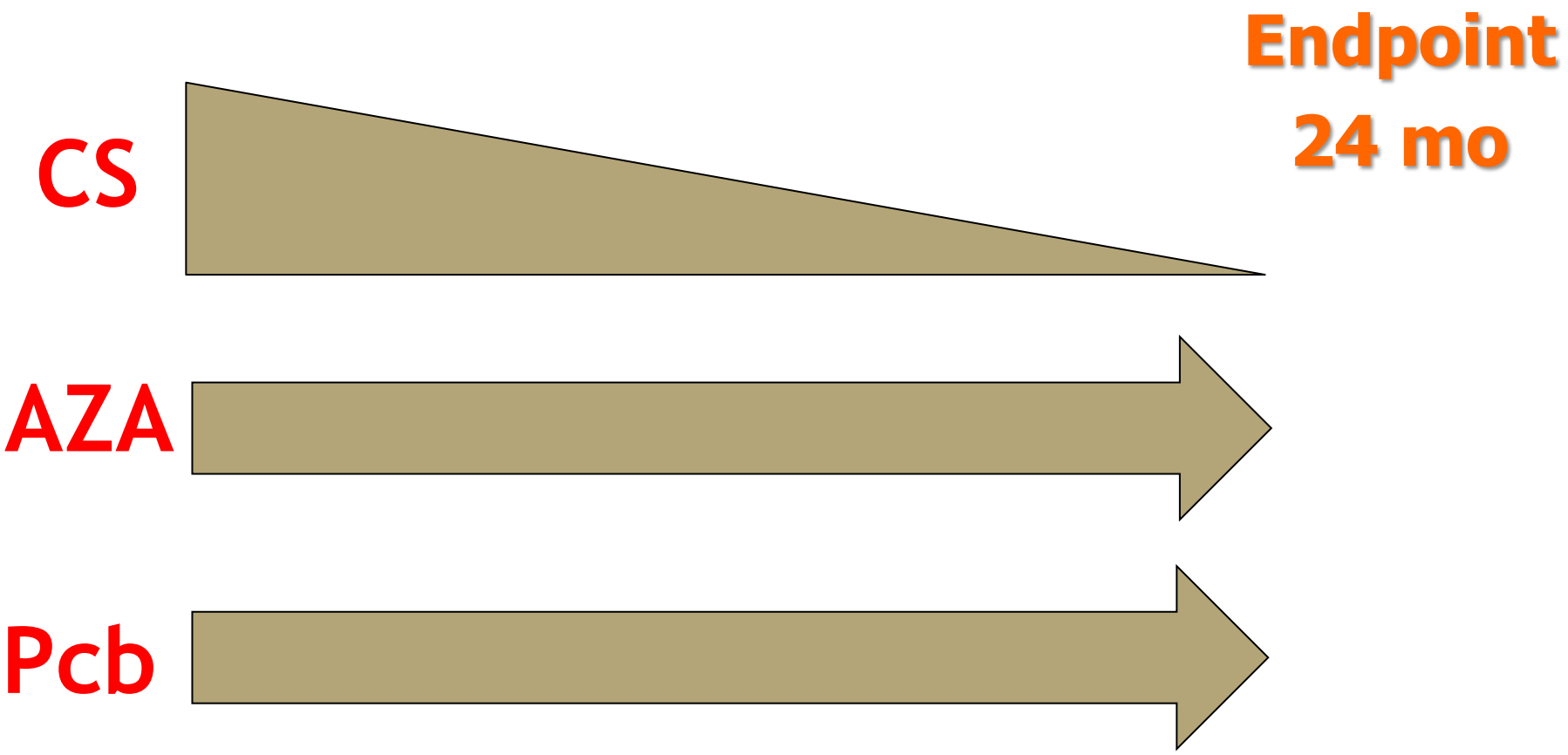
45 patients:

- **23 failures** on CS
  22 relapses (12 severe)
- FFS = 0 (n=42)
  FFS = 1 (n=3)
  FFS = 2 (n=1)
- Mononeuritis progression (n=28/45)
- **Non-neurological symptoms (n=37/45)**

EGPA treatment

- **FFS 0** = CS only
- **FFS > 0** = CS + IS
- **But**
  - FFS 0 patients treated with CS alone relapse more frequently even if mortality did not increase
  - Other drugs have not been evaluated

CHUSPAN 2



Multicenter, double-blind, randomized, controlled trial

12 months AZA/placebo treatment + 12 months FU

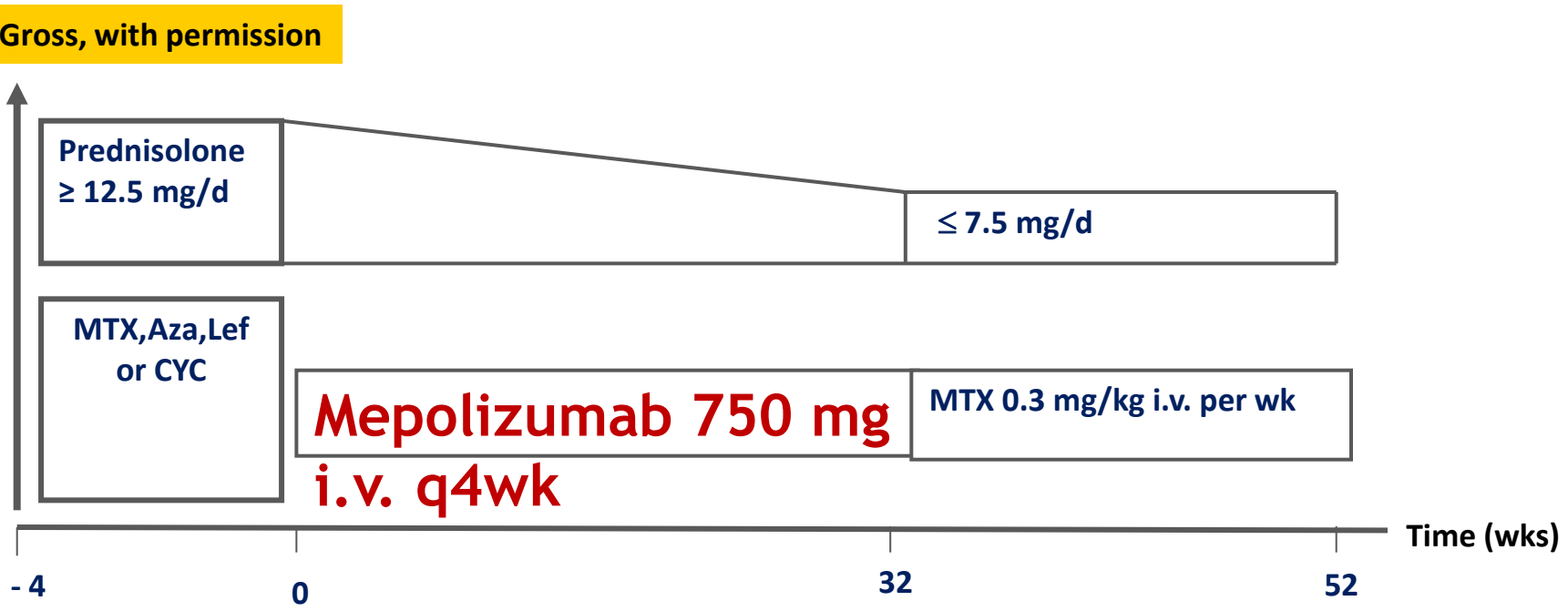
EGPA treatment: CHUSPAN 2

✓ **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

MEPOCHUSS: OPEN-LABEL PHASE II TRIAL OF MEPOLIZUMAB (ANTI-IL5) IN ACTIVE, RELAPSING OR REFRACTORY EGPA (CSS)



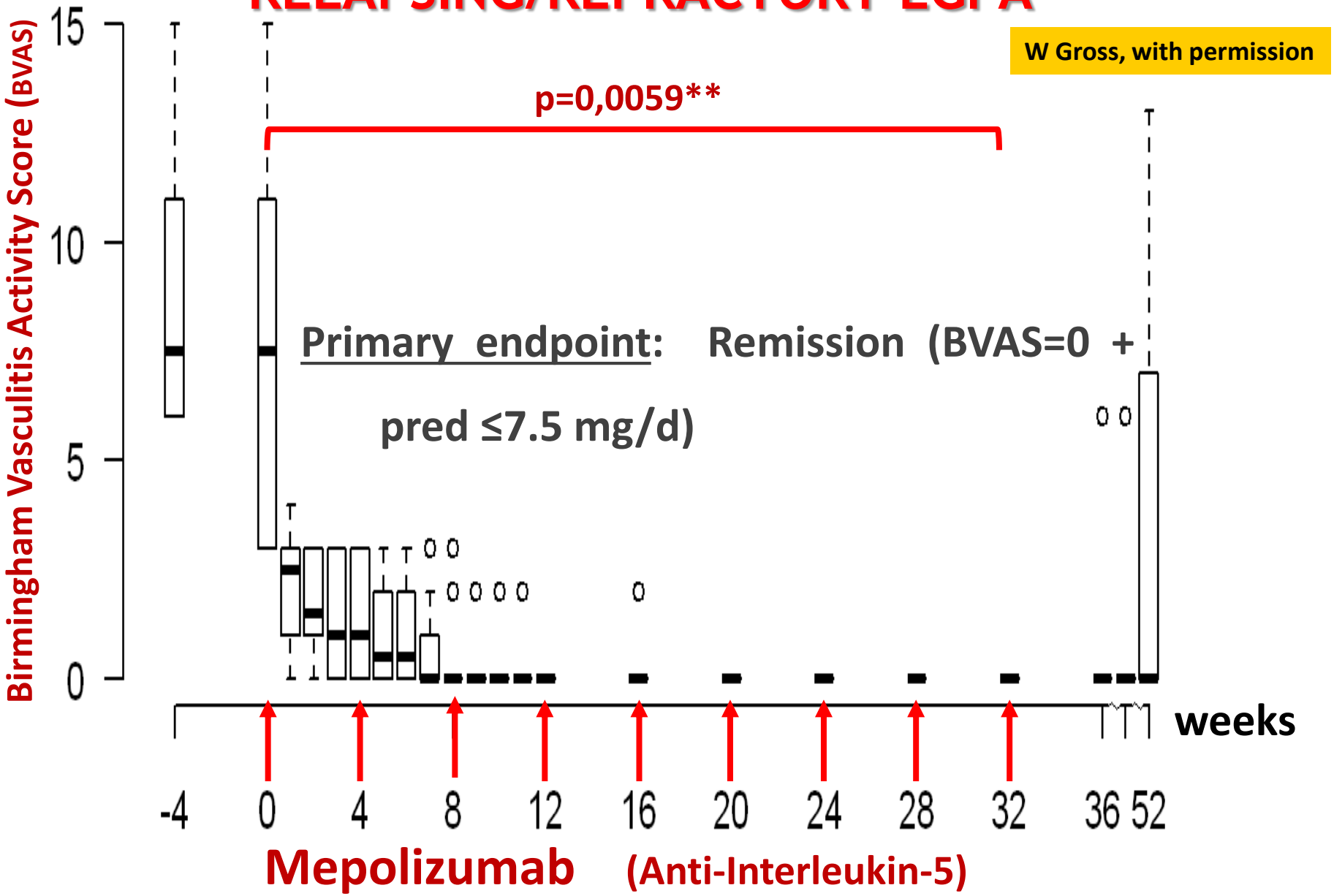
disease activity at start of Mepo:

- Heart: perimyocarditis (4)
- PNS: mononeuritis/polyneuropathy (4)
- Gi: eosinophilic colitis (1)
- ENT: sinusitis/otitis media (4)
- A: arthralgia/arthritis (3)

6/10 pts. perimyocarditis/ mononeuritis

Moosig F et al., Ann Intern Med 2011

MEPOLIZUMAB (ANTI-IL5) IN ACTIVE, RELAPSING/REFRACTORY EGPA



Moosig F et al., Ann Intern Med 2011

TRAITEMENT D'ENTRETIEN

The NEW ENGLAND JOURNAL of MEDICINE

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

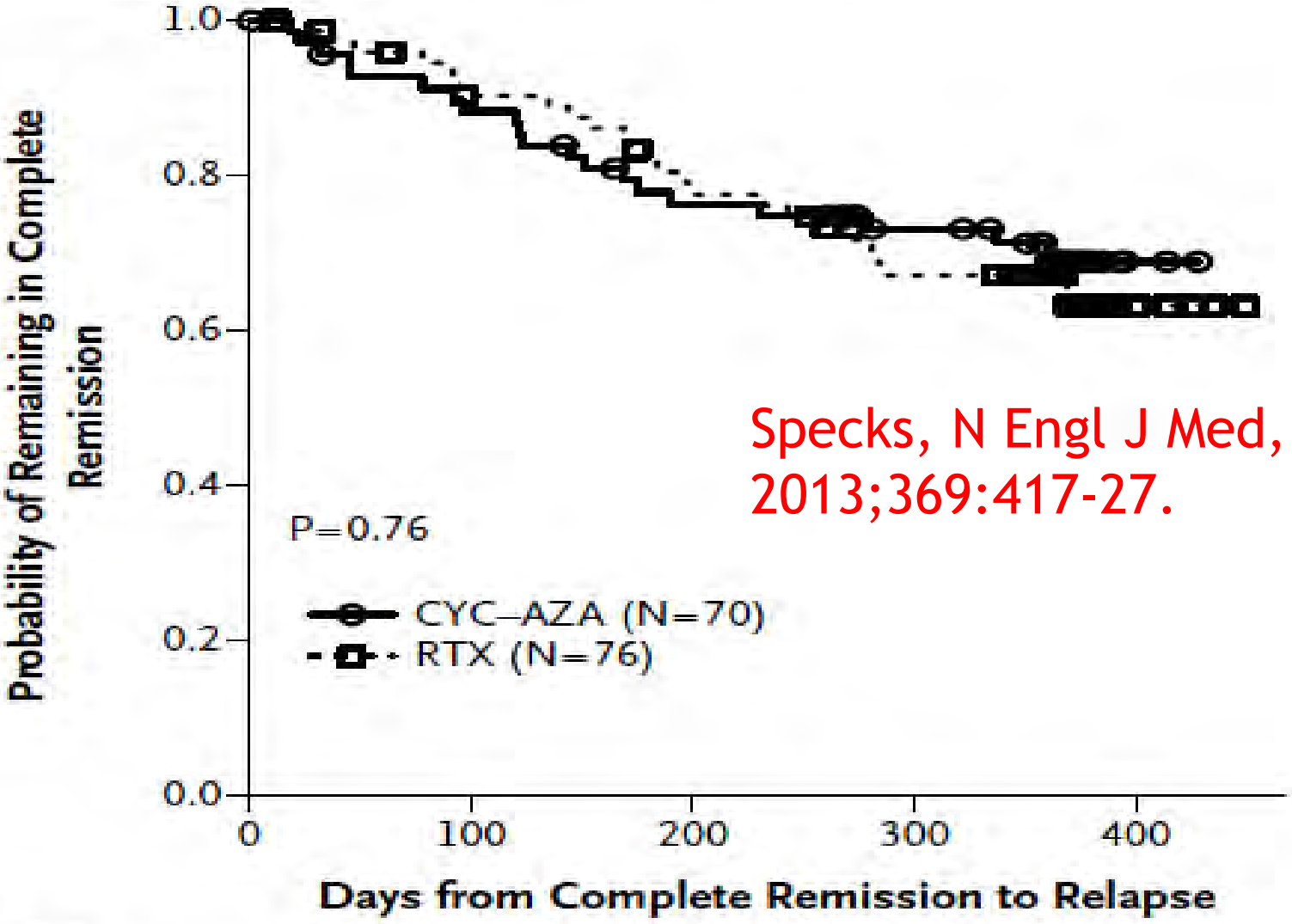
Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

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. J

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*

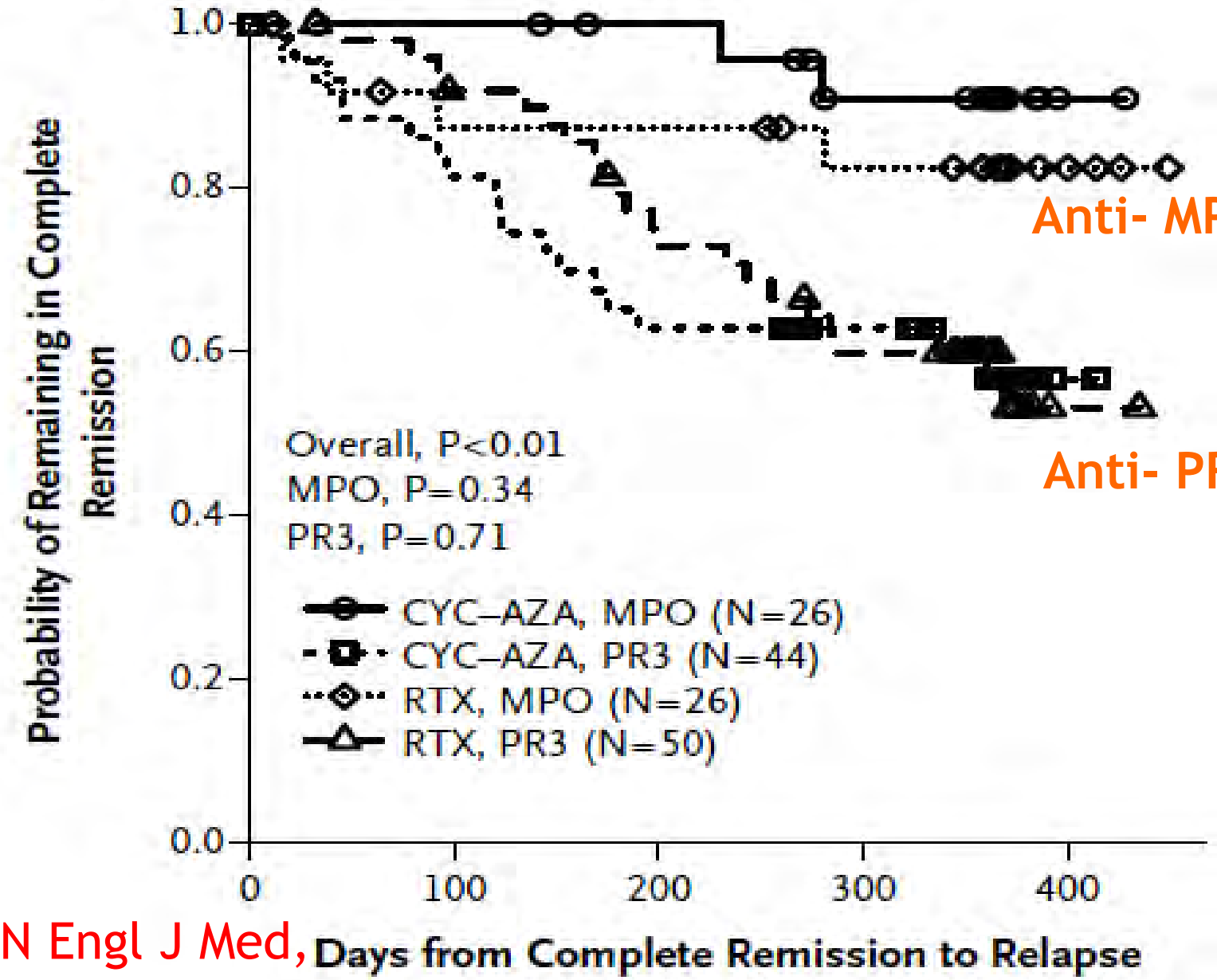
A Time to First Relapse after Complete Remission, According to Treatment



Specks, N Engl J Med, 2013;369:417-27.

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

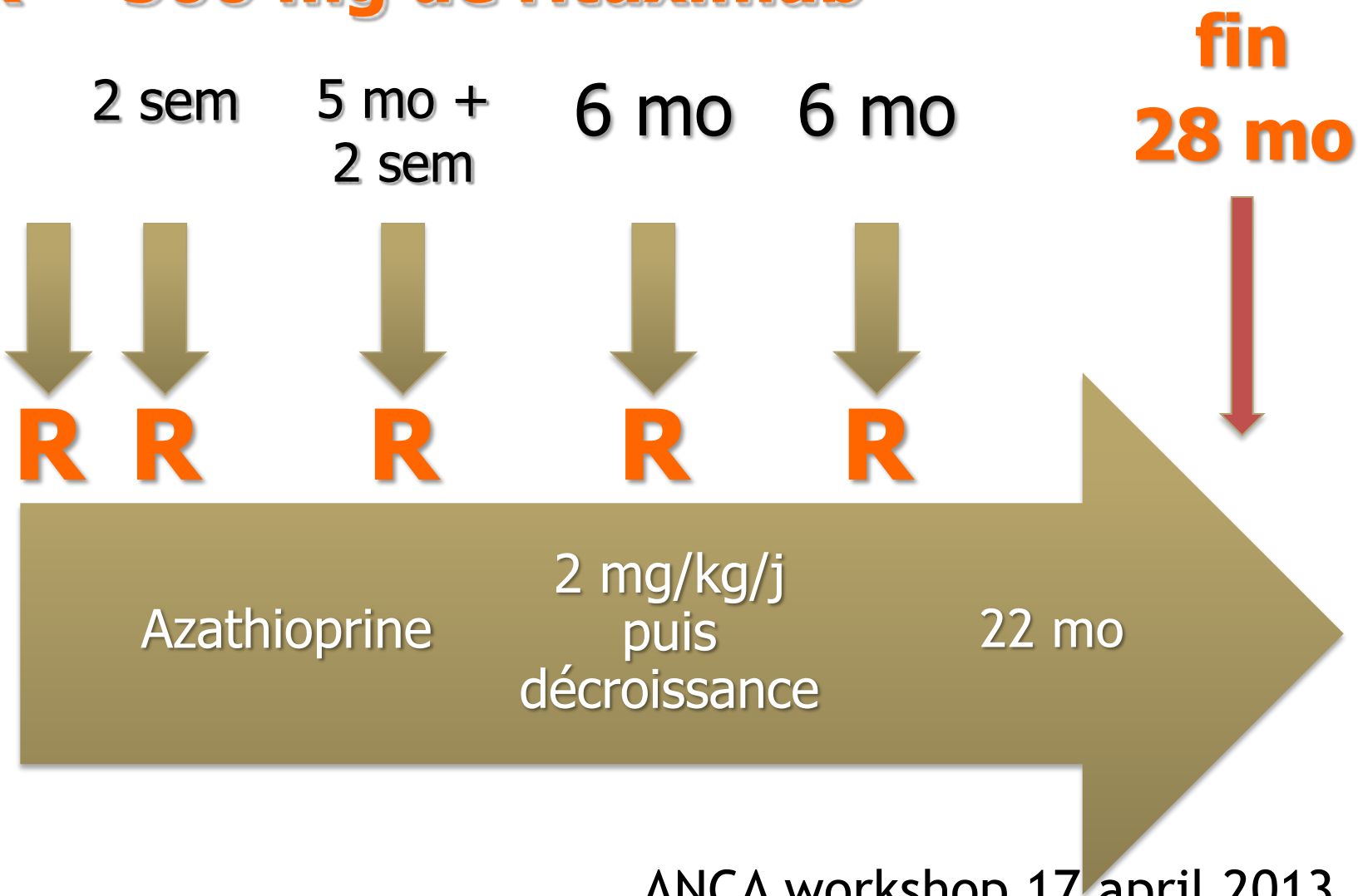


Specks, N Engl J Med, 2013;369:417-27.

MAINRITSAN

Traitement d'entretien

R = 500 mg de rituximab



Résultats

Azathioprine : sorties*

27/58 (46.5%)

- ✓ 17 rechutes majeures (**28.8%**)
- ✓ 5 pour EI graves (**8.5%**)
- ✓ 5 arrêts pour d'autres raisons, généralement personnelles (**8.5%**)

* Plusieurs causes chez le même malade

Rituximab *

6/58 (10.3%)

- ✓ 3 rechutes majeures (**5.2%**)
- ✓ 3 arrêts de traitement pour d'autres raisons, personnelle dans un cas

* Plusieurs causes chez le même malade

ANCA

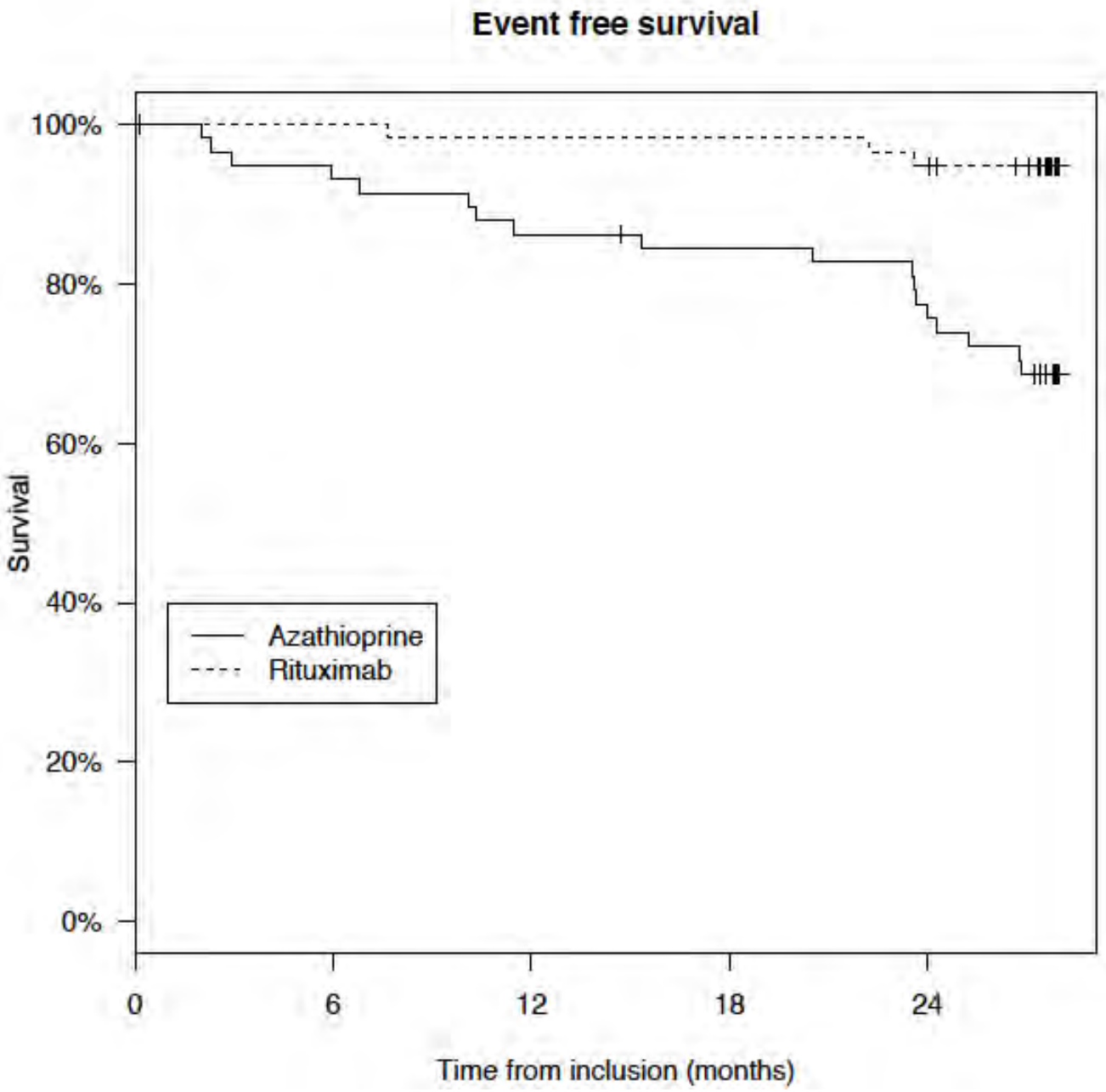
%	DIAGNOSTIC	REMISSION (SOUS CYC)	M 28
AZATHIOPRINE	93.2	69.6	60.8
RITUXIMAB	94.7	53.7	24.4

Même proportion d'anti-PR3 et d'anti-MPO à M28

Décès à 28 mois

2/115

- Azathioprine: 2 (**3.3%**)
  - ✓ Septicémie 5 mois après inclusion, au moment d'une rechute avec intensification thérapeutique
  - ✓ Décès 24 mois après inclusion, de cancer du pancréas
- ✓ Rituximab: 0 (**0%**)

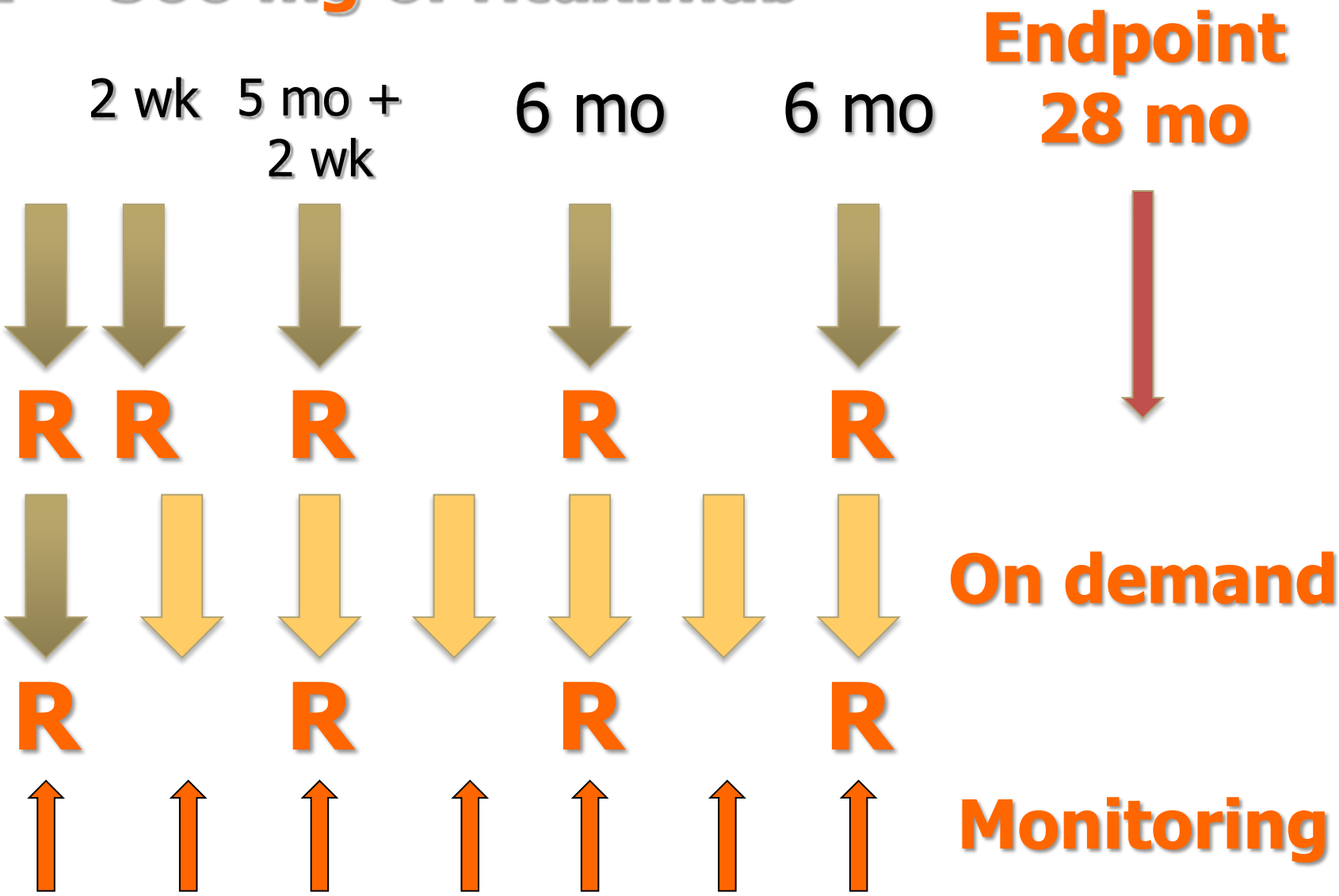

Event free survival
100%
80%
60%
40%
20%
0%
Survival
Azathioprine
Rituximab
0
6
12
18
24
Time from inclusion (months)

P = 0.002

MAINRITSAN 2

Maintenance treatment

R = 500 mg of rituximab



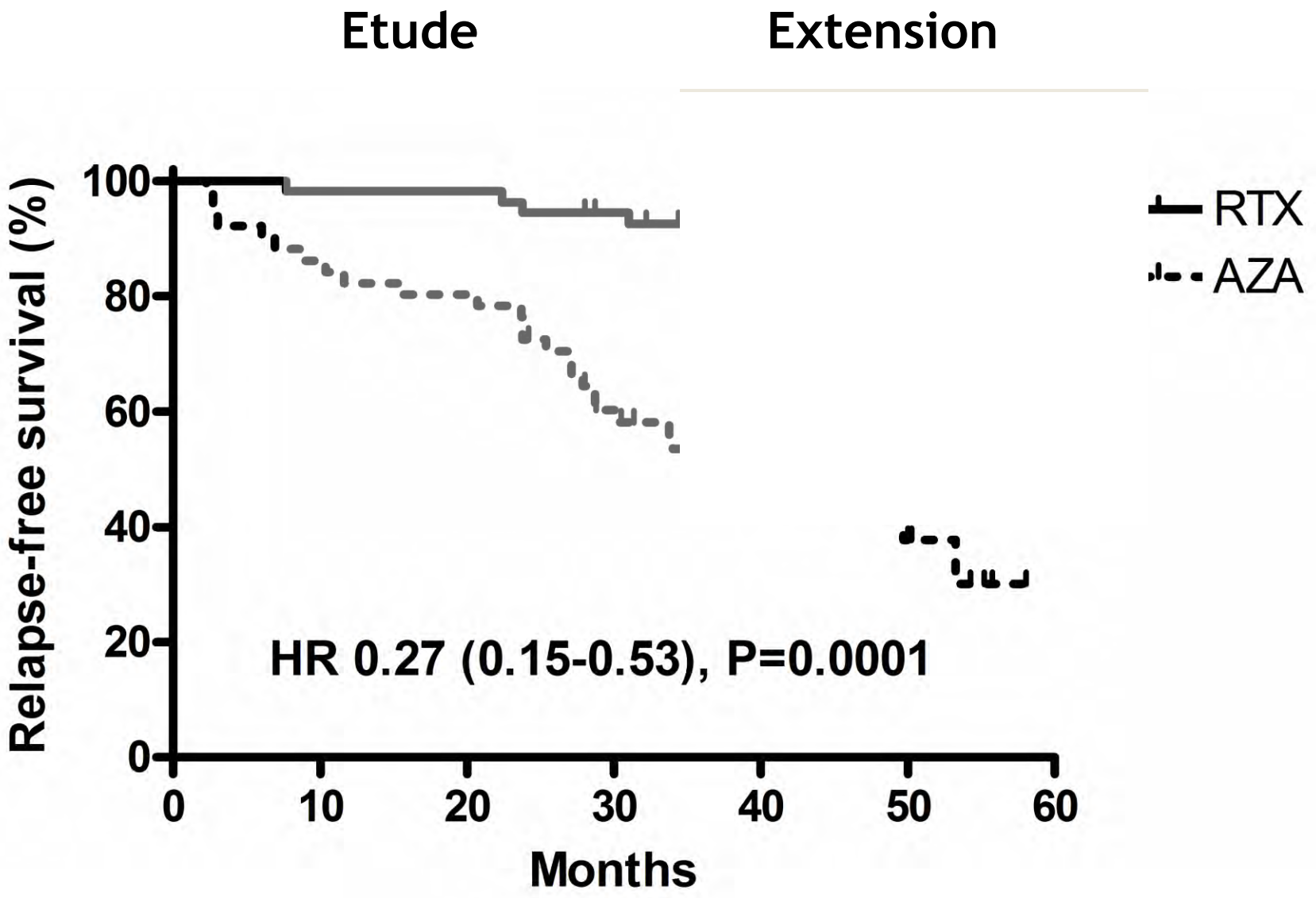
Suivi à long terme de MAINRITSAN 1

MAINRITSAN extension

- ✓ Suivi moyen: 43.6 mois (IQR, 38.0-49.5 months)

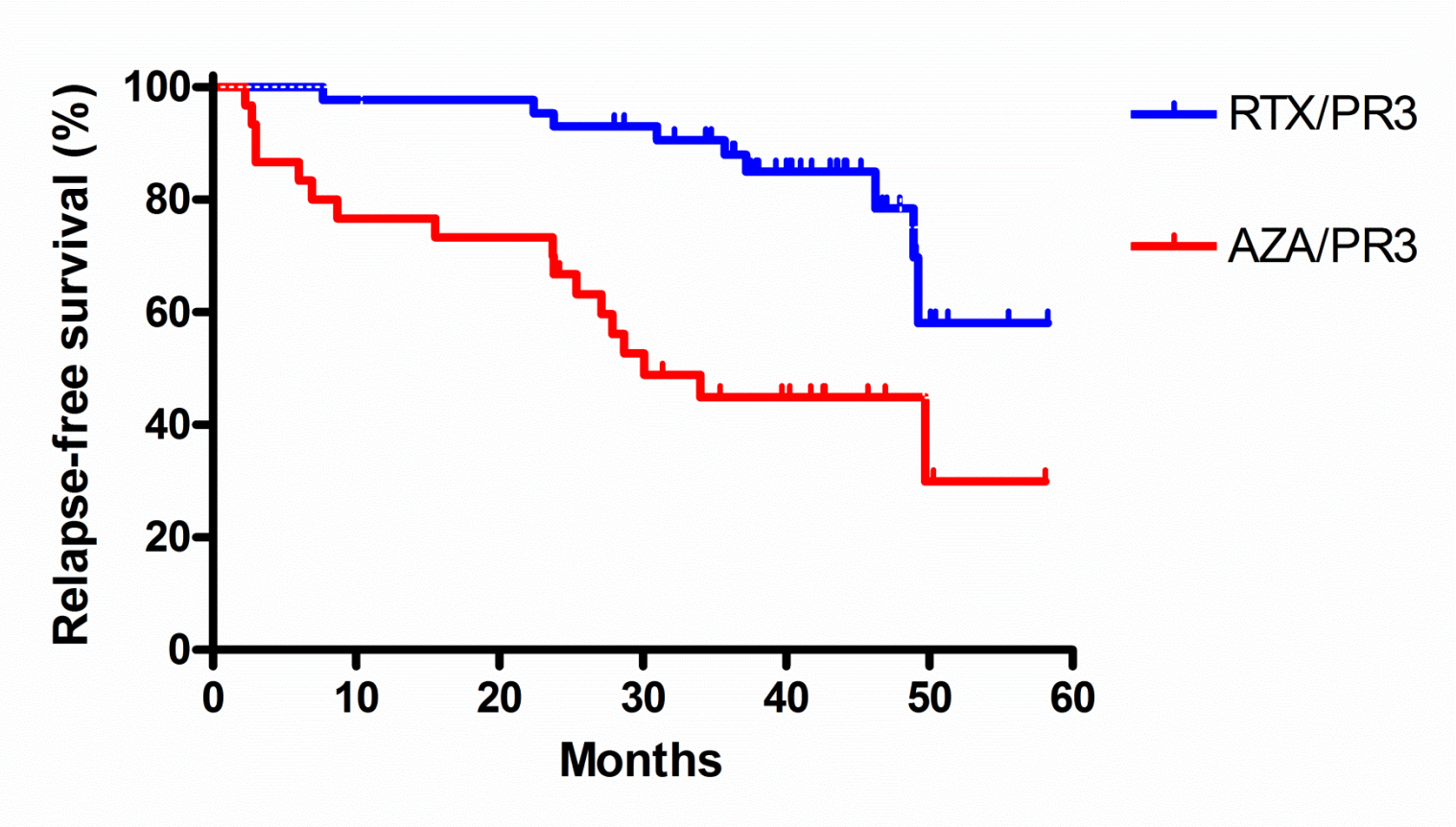
- ✓ Rechutes majeures
  - ✓10/55 (18.2%) sous RTX
  - ✓28/51 (54.9%) sous AZA

MAINRITSAN extension



MAINRITSAN extension – Results

Relapse-free survival according to ANCA specificity



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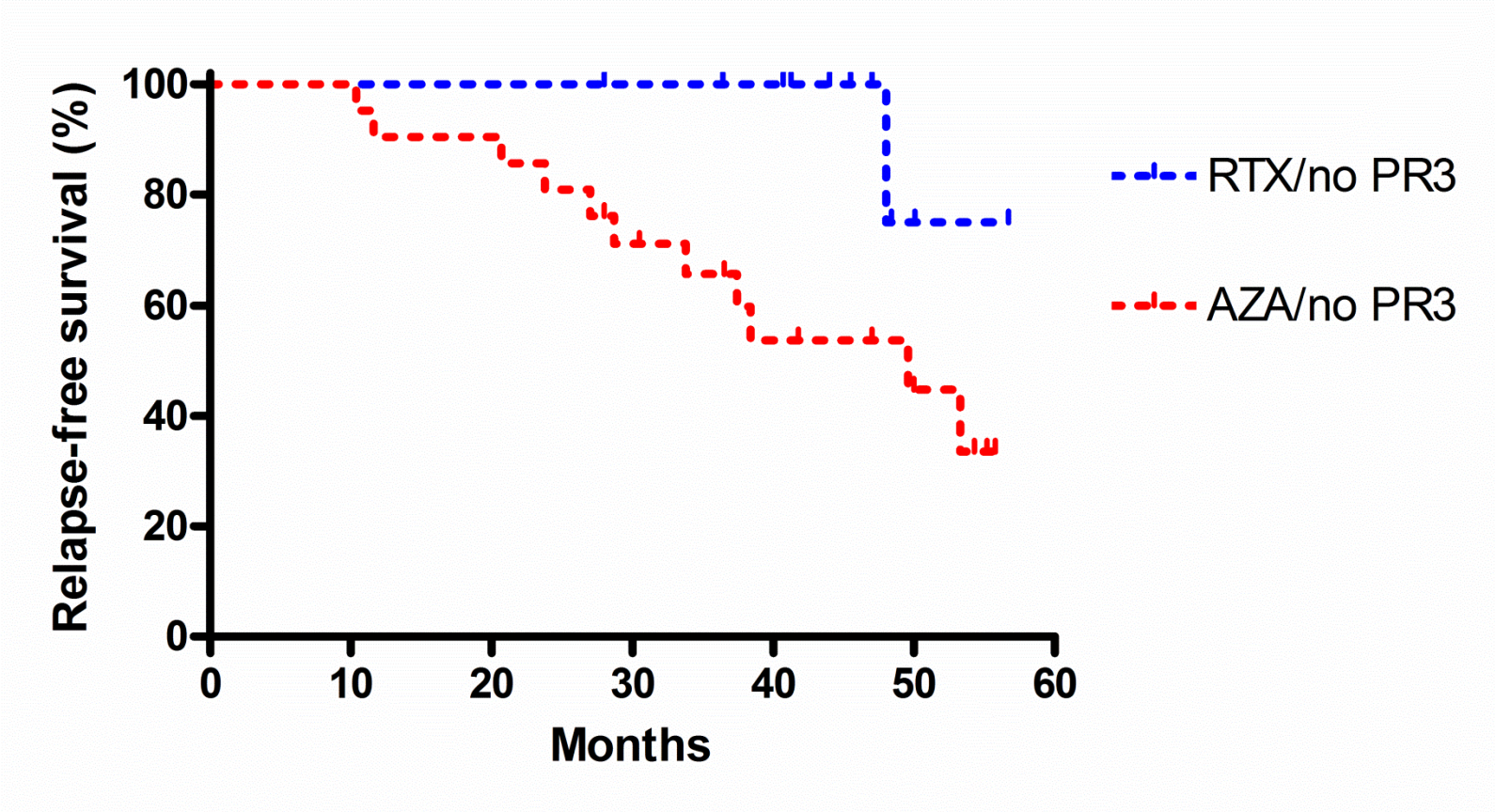

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Rituximab: Recommendations of the French Vasculitis Study Group (FVSG) for induction and maintenance treatments of adult, antineutrophil cytoplasm antibody-associated necrotizing vasculitides

Pierre Charles[1,2], Boris Bienvenu[3], Bernard Bonnotte[4], Pierre Gobert[5], Pascal Godmer[6], Éric Hachulla[7], Mohamed Hamidou[8], Jean-Robert Harlé[9], Alexandre Karras[10], Jean-Christophe Lega[11], Alain Le Quellec[12], Alfred D. Mahr[13], Luc Mouthon[1], Thomas Papo[14], Xavier Puéchal[1], Gregory Pugnet[15], Maxime Samson[4], Jean Sibilia[16], Benjamin Terrier[1], Frederick Vandergheynst[17], Loïc Guillevin[1], for the FVSG[1]

Recommendations

- 1. Cyclophosphamide and rituximab both effectively induce AAV remission but the FVSG recommends rituximab in the following situations (expert consensus):
  - Patients who have already relapsed
  - After IV CYC failure
  - Young patients with fertility concerns
  - Patients who have already received >10 grams of CYC

Recommendations

- 7. Prophylaxis against infections is recommended
  - Cotrimoxazole for PJP
  - Anti-TB drugs if needed
  - Vaccination is highly recommended (pneumonia, influenza) as soon as possible before treatment
  - IVIg SHOULD NOT be prescribed systematically for infection prophyllaxy
  - For hypogammaglobulinemic patients, IVIg prescription should follow the recommendations established for secondary immune-deficiency management

French Vasculitis Study Group

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