Néphropathies lupiques : quels traitements fondés sur des preuves ?

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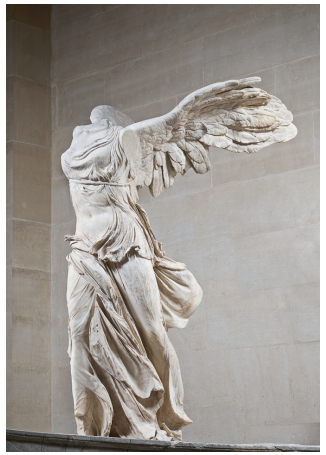
VICTOIRE



GROUPE COOPÉRATIF LUPUS RÉNAL

Méthode

NIVEAU 0

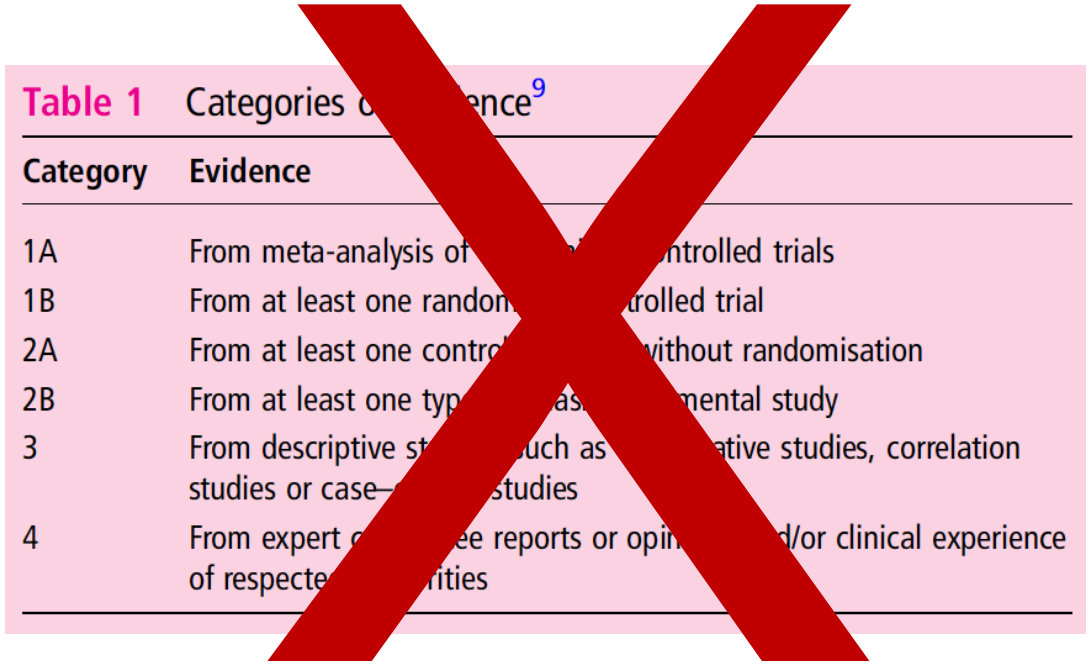


Table 1 Categories of evidence[9]

Category	Evidence
1A	From meta-analysis of controlled trials
1B	From at least one randomised controlled trial
2A	From at least one controlled study without randomisation
2B	From at least one type of quasi-experimental study
3	From descriptive studies such as comparative studies, correlation studies or case–control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

- **Niveau 1**: Etudes contrôlées phases II et III
- **Niveau 2**: Etude(s) contrôlée(s) phase II ou à puissance limitée
- **Niveau 3**: Post-hoc d'une étude contrôlée
- **Niveau 4**: Données prospectives non contrôlées
- **Niveau 5**: Données rétrospectives
- **Niveau 6**: Avis fondé sur l'expérience clinique

Traitement des GN prolifératives

Classes IIIA+/-C+/-V

Classes IVA+/-C+/-V

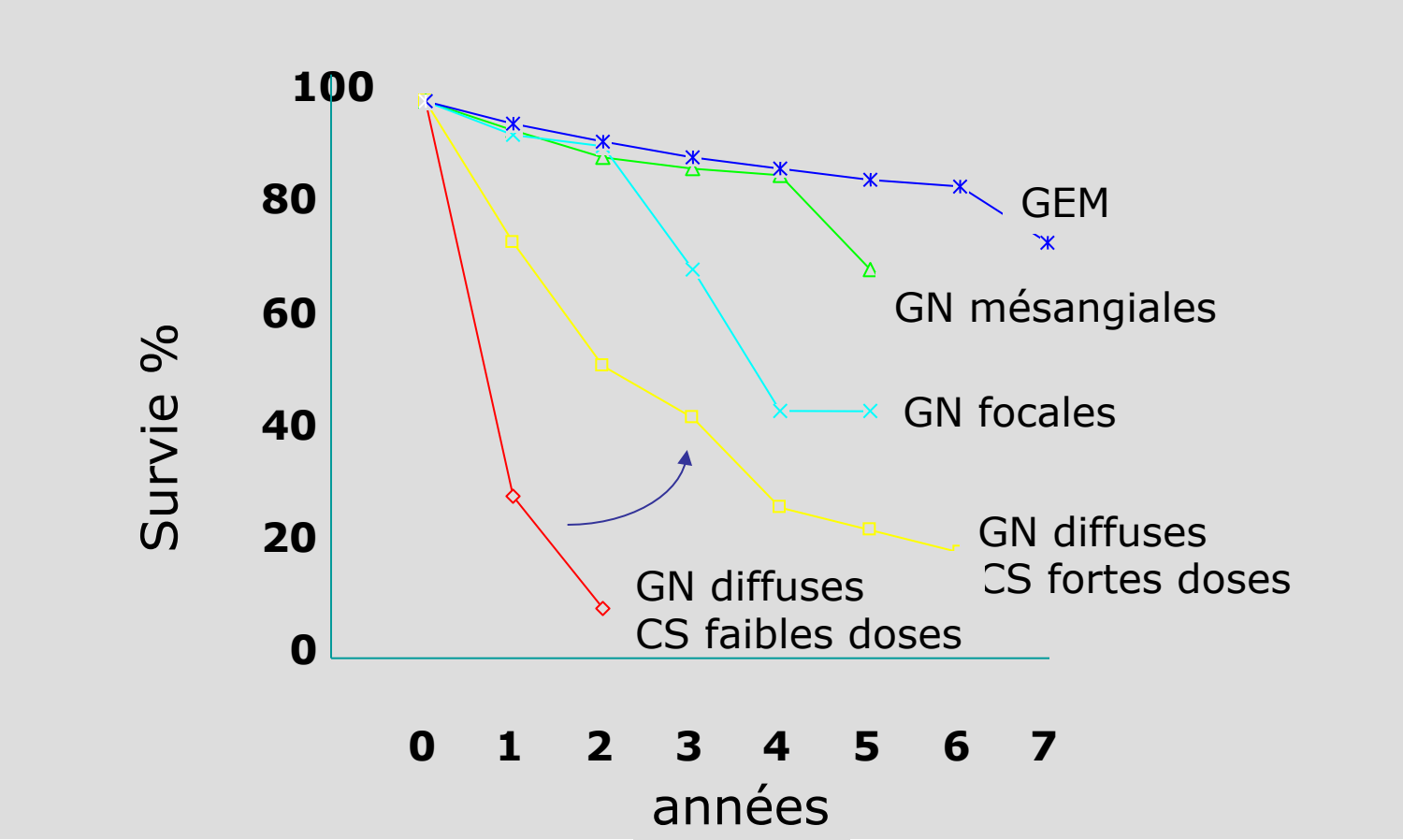
PAS LES CLASSES IIIC+/-V

PAS LES CLASSES IVC+/-V

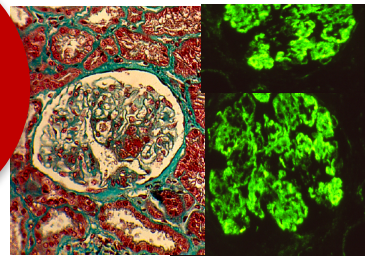
Histoire naturelle: Pronostic global

Pollak VE et al. Am. J. Kidney Dis. 2, suppl. 1:70, 1972

NIVEAU 5



NIVEAU 5



Diagnostic

P/C<0,5g/g
DFG stable ou
Normalisé
=
Remission

NIVEAU 3

+

Prévention des rechutes

NIVEAU 3

NIVEAU 2

Induction

Référence
=
stéroides + CYC IV

Entretien

Immunosuppresseur
+
Faible dose de stéroïdes

NIVEAU 2

NIVEAU 6

TRAITEMENT d’INDUCTION

=

traitement de la poussée

EVIDENCE FOR THE SUPERIORITY OF IMMUNOSUPPRESSIVE DRUGS AND PREDNISONE OVER PREDNISONE ALONE IN LUPUS NEPHRITIS

Results of a Pooled Analysis

DAVID T. FELSON, M.D., M.P.H., AND JENNIFER ANDERSON, PH.D.

NIVEAU 2

METHODS

We confined our evaluation to clinical trials that met the following criteria: (1) patients had systemic lupus erythematosus and clinical or biopsy evidence of lupus nephritis (in most studies patients fulfilled the American Rheumatism Association's criteria[16] for the disease; (2) patients were assigned to treatment randomly or consecutively after enrollment in the study; (3) the concurrent control group in each study received prednisone alone; and (4) the experimental group received immunosuppressive agents along with prednisone. The immunosuppressive drug could be cyclophosphamide, azathioprine, or both. A MEDLINE search and a review of the literature showed that eight published studies fulfilled these criteria.[5-12]

Felson & Anderson, NEJM 1984

NIVEAU

2

EVIDENCE FOR THE SUPERIORITY OF IMMUNOSUPPRESSIVE DRUGS AND PREDNISONE OVER PREDNISONE ALONE IN LUPUS NEPHRITIS

Results of a Pooled Analysis

DAVID T. FELSON, M.D., M.P.H., AND JENNIFER ANDERSON, PH.D.

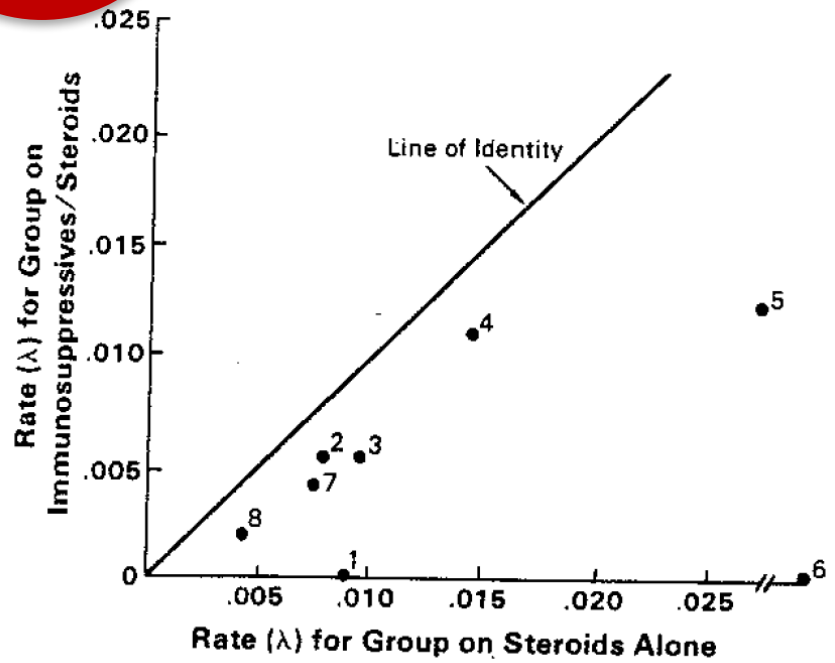


Figure 1. Rate of Renal Deterioration in Patients Treated with Steroids Alone and in Those Treated with a Combination of Immunosuppressive Drugs and Steroids.
Each point represents a study.

X2 creatinine or 25% ClCreat decrease or ESRD

	No. of Patients		Outcome Rate (λ)		
	Steroids alone	Combined therapy	Steroids alone	Combined therapy	P value
All studies	113	137			
Renal deterioration	37	27	0.0096	0.0048	0.006
ESRD	24	16	0.0058	0.0028	0.023
Nephritis-related death	19	12	0.0049	0.0022	0.024
All deaths	32	29	0.0083	0.0052	0.066

λ = % outcome/ month

Felson & Anderson, NEJM 1984

NIVEAU

2

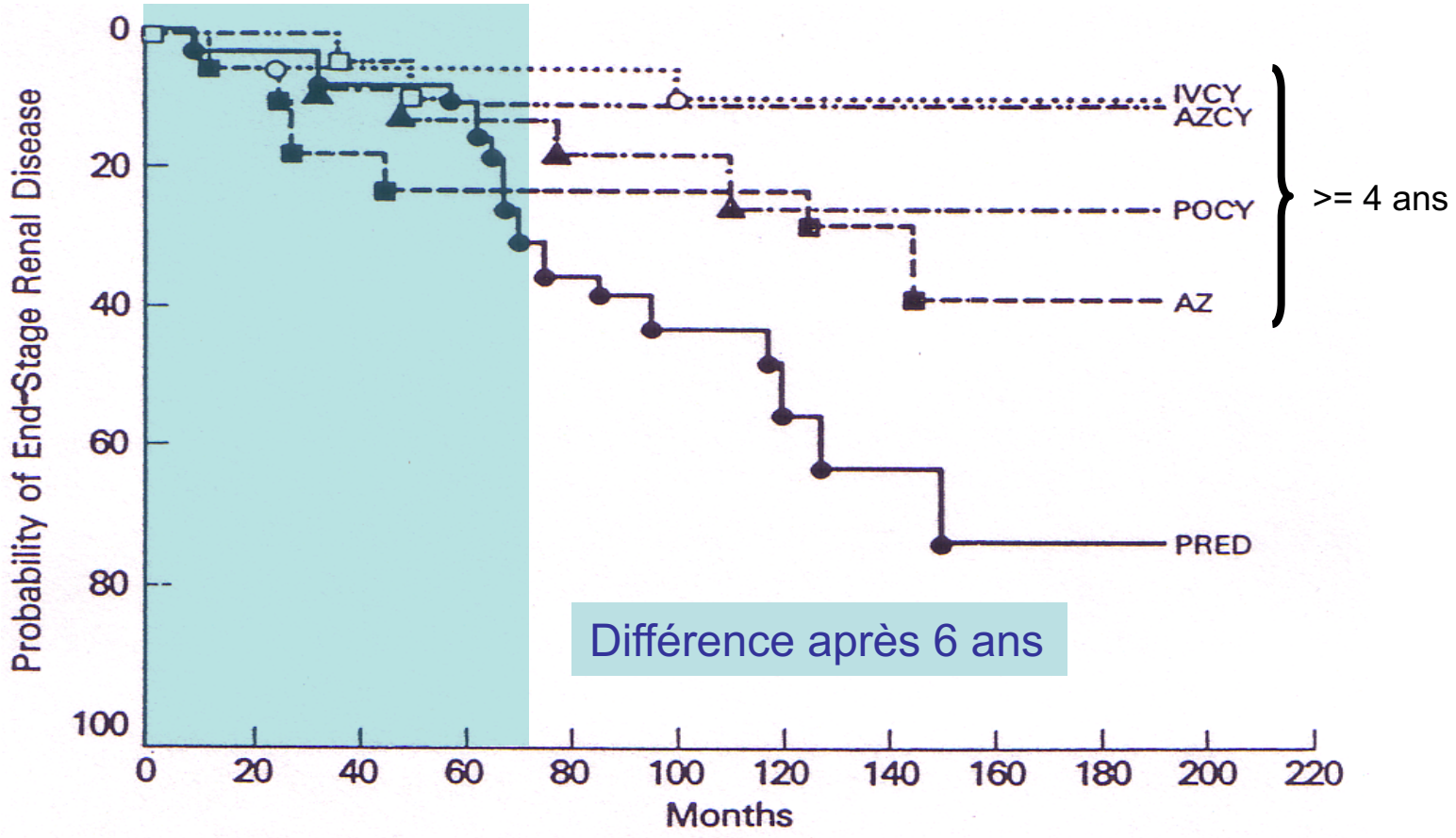
Donadio *NEJM* 1978
Austin *NEJM* 1986
Boumpas Lancet 1992

Traitement de référence
=
stéroïdes + CYC IV

CYC IV + Stéroïdes = « NIH »

NIVEAU

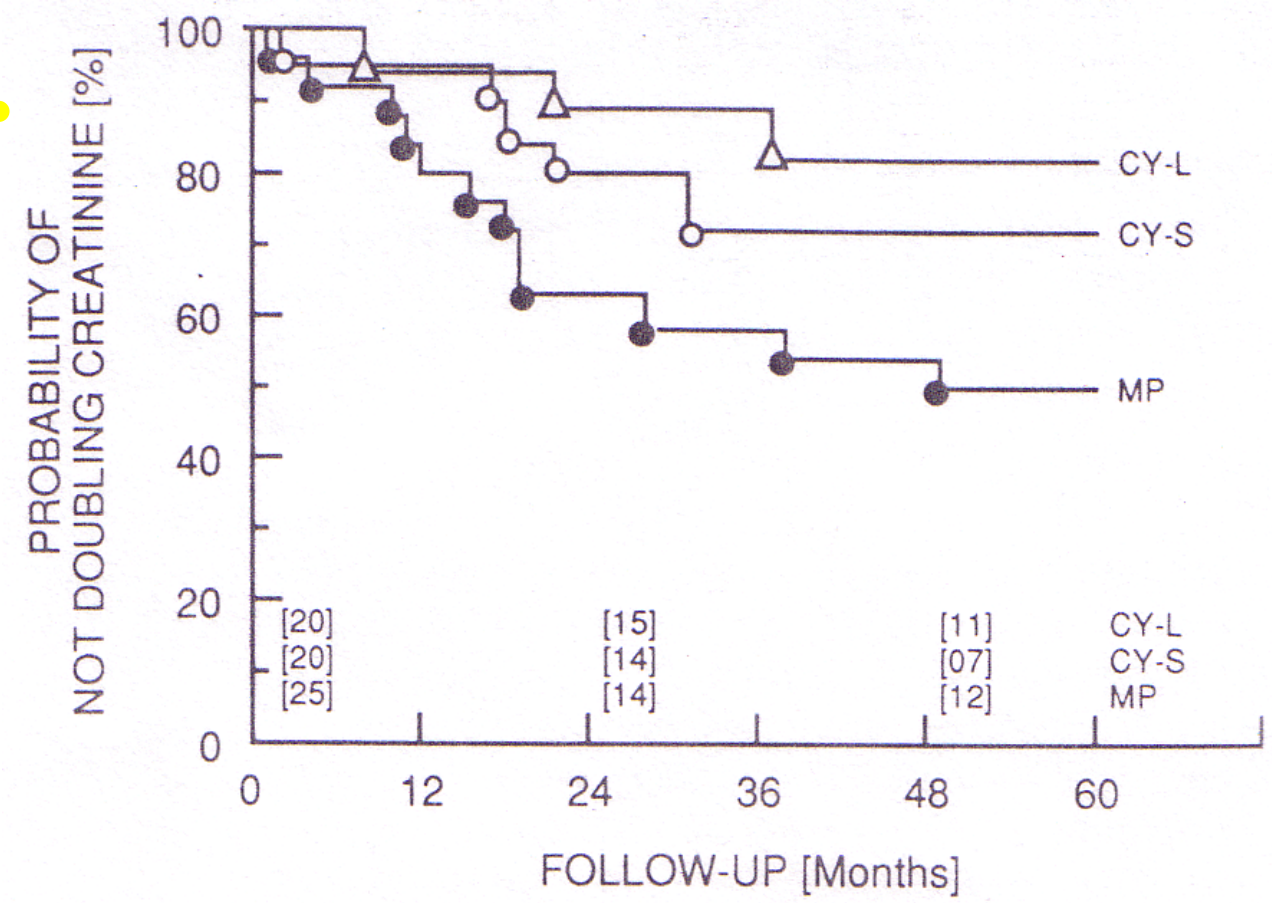
2?



Austin *NEJM* 1986 & Steinberg *Arth Rheum* 1991

Référence = CYC IV + Stéroïdes

NIVEAU 2



Prednisone PO et

CY-L
Bolus/mois – 6mois
et /3mois – 2 ans

CY-S
Bolus/mois – 6mois

MP
Bolus/mois – 6mois

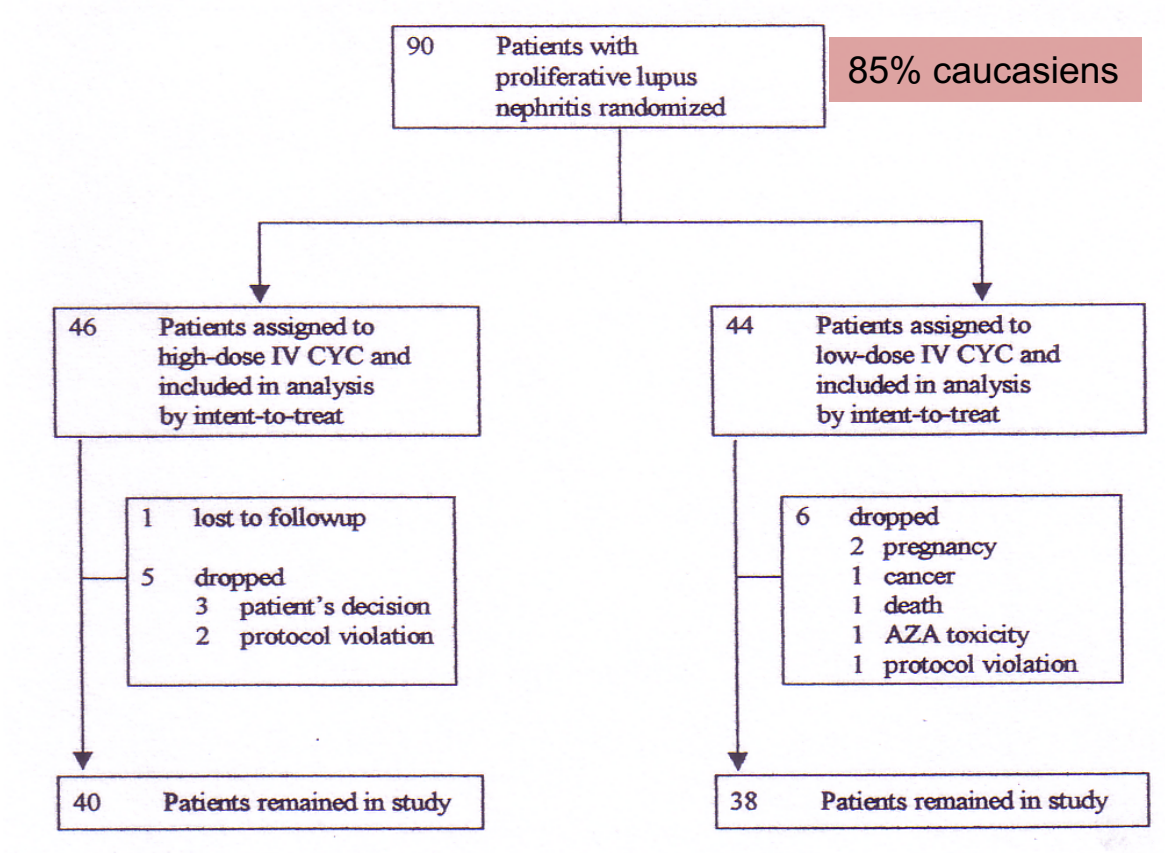
Boumpas *Lancet* 1992; 340:741

réduction du CYC pendant l’induction

EUROLUPUS

NIVEAU 2

CYC = 500 mg – 750 mg/m^2
CYC/mois – 6mois
CYC/3mois 6 mois
=
8.5 g



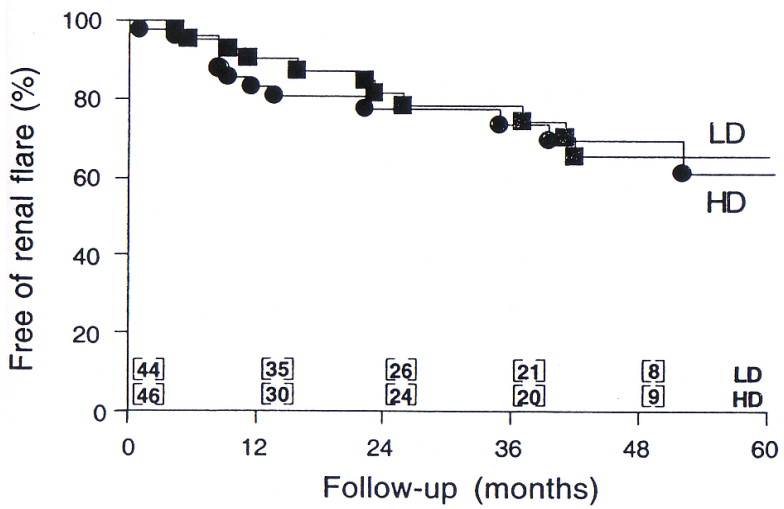
500 mg CYC/2s
3mois
= 3 g

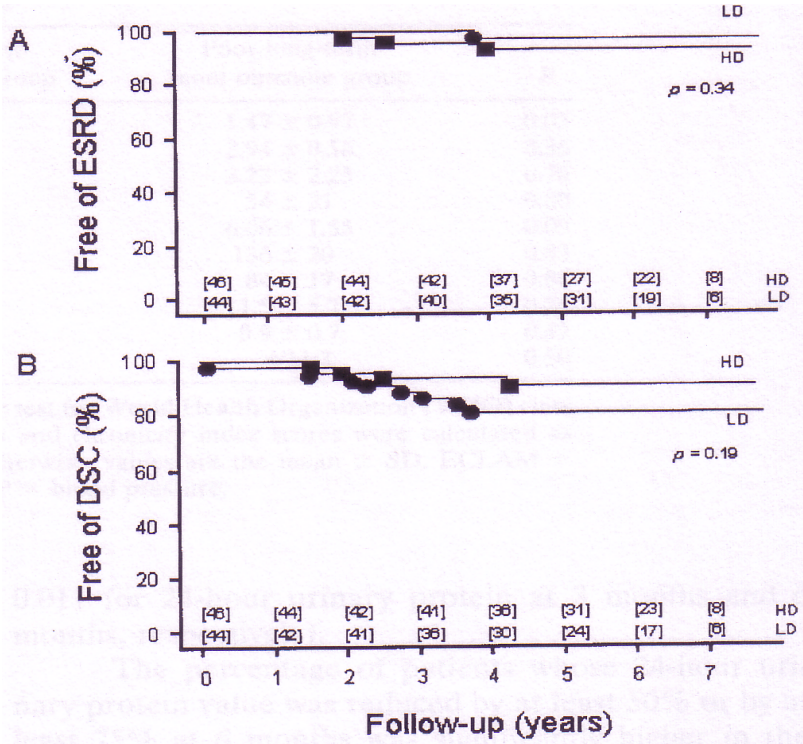
Entretien = AZA – 2 ans

Houssiau FA *Arth Rheum* 2002; 46 : 2121 et 2004; 12: 3934

EUROLUPUS

NIVEAU 2



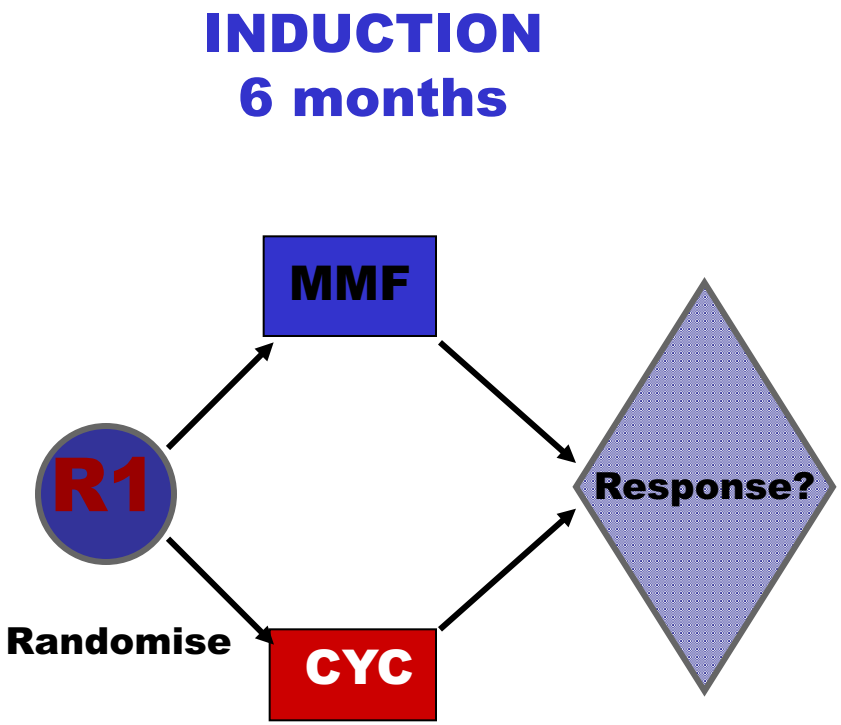


Suppression du CYC pendant l'induction

MMF

Aspreva Lupus Management Study: **négative**

NIVEAU 3



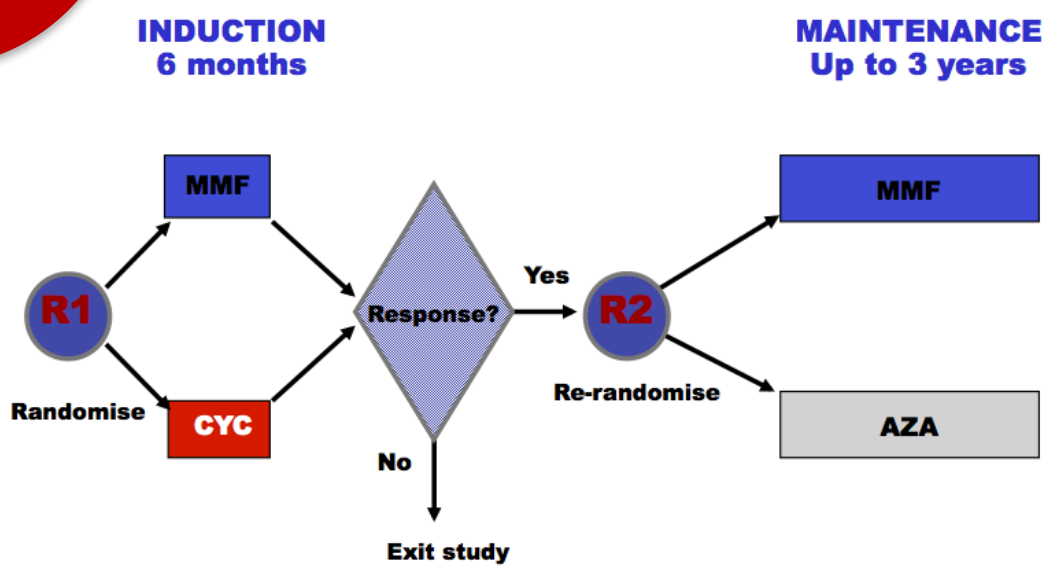
370 patients	MMF	CYC
Réponse	56.2%	53%
Arrêt pour intolérance	24	13
Arrêt pour infection	12	4
Décès	9	5

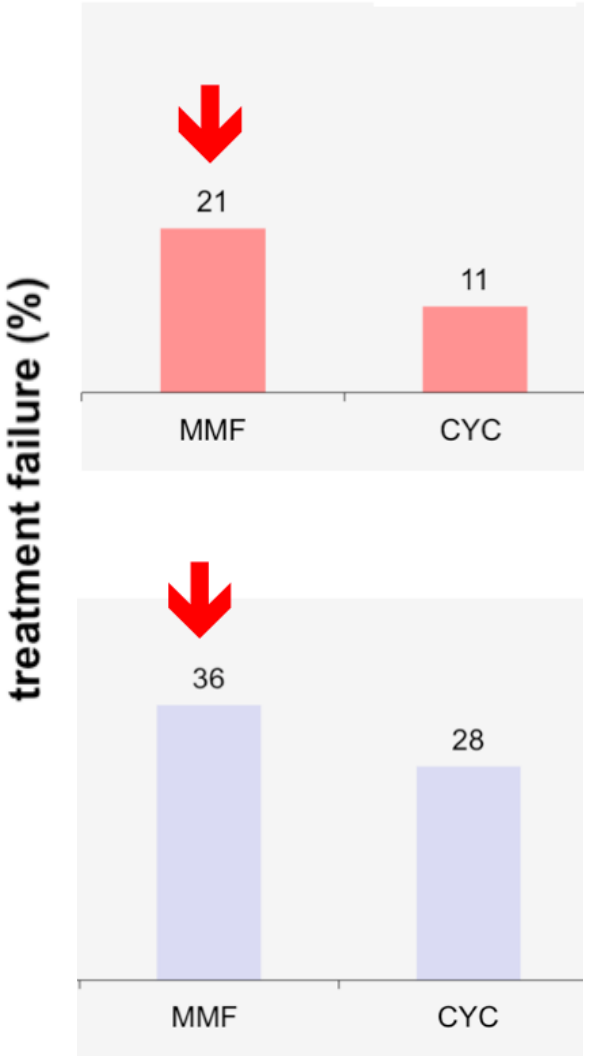
Appel G JASN 2009, 20: 1103-

ALMS II = 227 patients

induits par CYC ou MMF re-randomisés AZA vs MMF en entretien

NIVEAU 3-5





Jayne/ Appel ASN2010
Rovin cJASN 2013

+ anti-CD20
en induction ?

LUNAR trial did not meet its primary endpoint

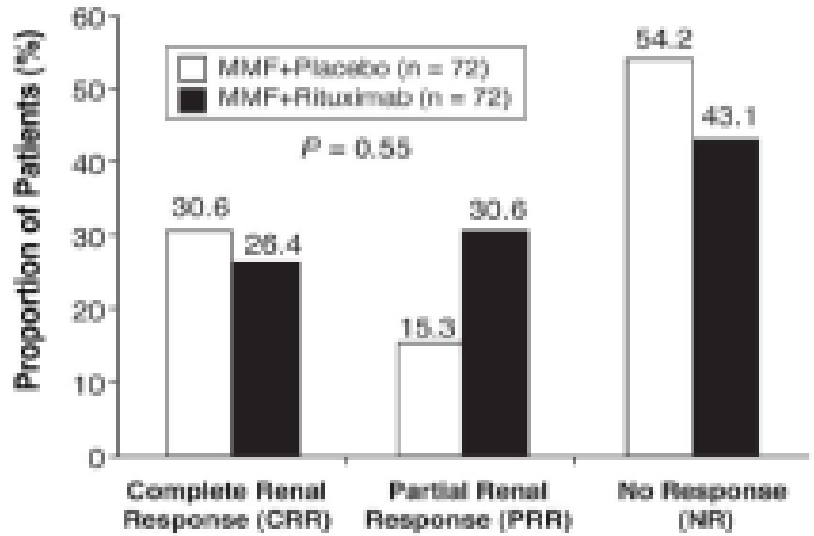
144 pts
class IIIA and IVA
Prot/UCreat >1

standard treatment
MMF + prednisone

+

N=72 **rituximab 1g**
J1, 15, 168, 182

placebo N=72



1 year
% complete or partial remission?

Rovin Arthritis & Rheum 2012

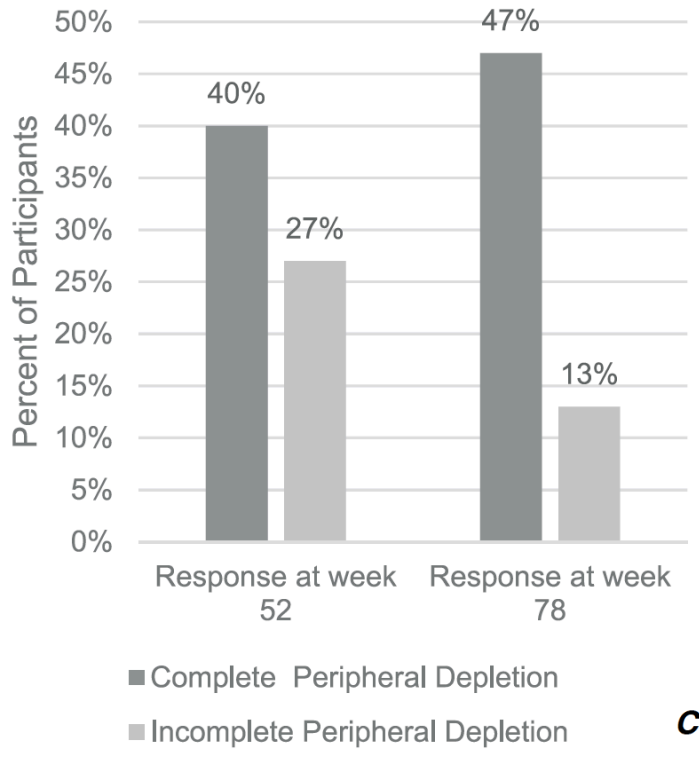
Peripheral Blood B Cell Depletion after Rituximab and Complete Response in Lupus Nephritis

Liliana Michelle Gomez Mendez,[1] Matthew D. Cascino,[2] Jay Garg,[2] Tamiko R. Katsumoto,[2] Paul Brakeman,[1] Maria Dall'Era,[1] Richard John Looney,[3] Brad Rovin,[4] Leonard Dragone,[2] and Paul Brunetta[2]

Definition of B Cell Depletion	Patients Who Achieved Depletion by Week 52, *n* (% of Total)	Patients Who Achieved Depletion by Week 78, *n* (% of Total)	Maximum Time to Achievement of Depletion in Days
CD19<20 cells/μl	68 (100)	68 (100)	86
CD19<5 cells/μl	68 (100)	68 (100)	182
CD19=0 cells/μl	53 (78)	53 (78)	365

LUNAR, the Lupus Nephritis Assessment with Rituximab study.

NIVEAU 3



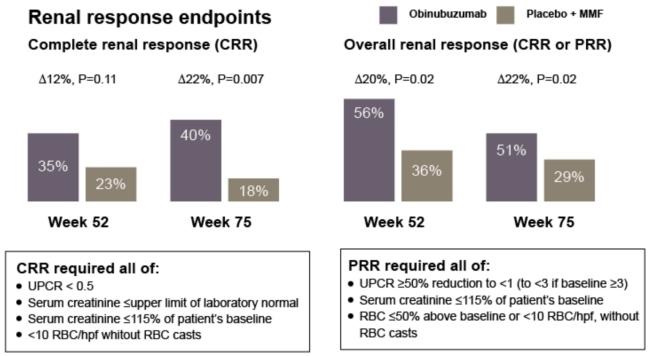
***CJASN ePress*. Published on August 8, 2018 as doi: 10.2215/CJN.01070118**

NIVEAU 2

NOBILITY

GENENTECH'S GAZYVA (OBINUTUZUMAB) DELIVERS POSITIVE TOPLINE RESULTS FOR PHASE II LUPUS NEPHRITIS STUDY

- *NOBILITY showed that Gazyva helped more patients achieve a complete renal response when added to standard of care*
- *The Phase II study met both primary and key secondary endpoints*
- *There are currently no FDA-approved therapies for lupus nephritis*



SOUTH SAN FRANCISCO, Calif. — JUNE 10, 2019 — Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced positive topline results for NOBILITY, a Phase II clinical trial investigating the safety and efficacy of Gazyva® (obinutuzumab) for adults with proliferative lupus nephritis. The study met its primary endpoint, showing Gazyva, in combination with standard of care (mycophenolate mofetil or mycophenolic acid and corticosteroids), demonstrated enhanced efficacy compared to placebo plus standard of care alone in achieving complete renal response at one year. In addition, Gazyva met key secondary endpoints showing improved overall renal responses (complete and partial renal response) and serologic markers of disease activity as compared to placebo.

60 pts/arm

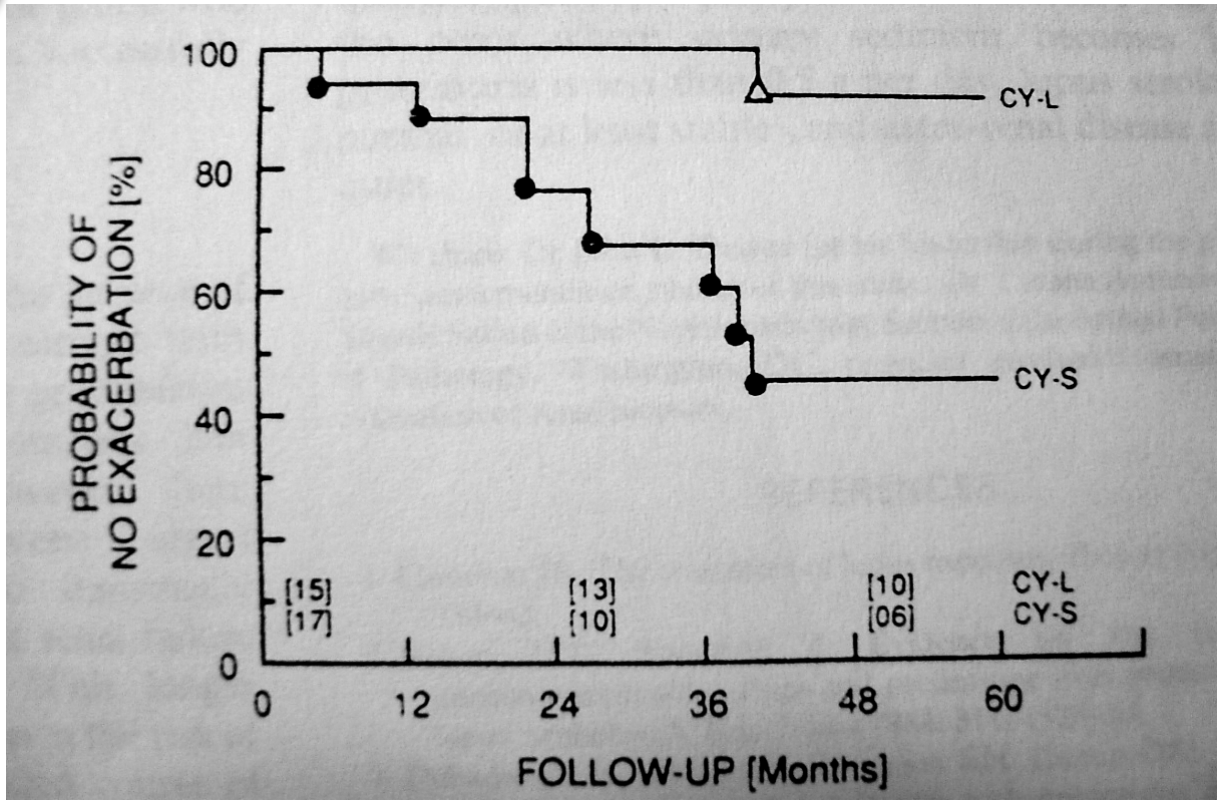
ASN 2019
ACR 2019

TRAITEMENT d’ENTRETIEN

1ère démonstration de l'intérêt d'un traitement d'entretien

NIVEAU 2-3

Réduction risque de rechute avec CY-L



Prednisone PO et

CY-L
Bolus/mois – 6mois
et /3mois – 2 ans

CY-S
Bolus/mois – 6mois

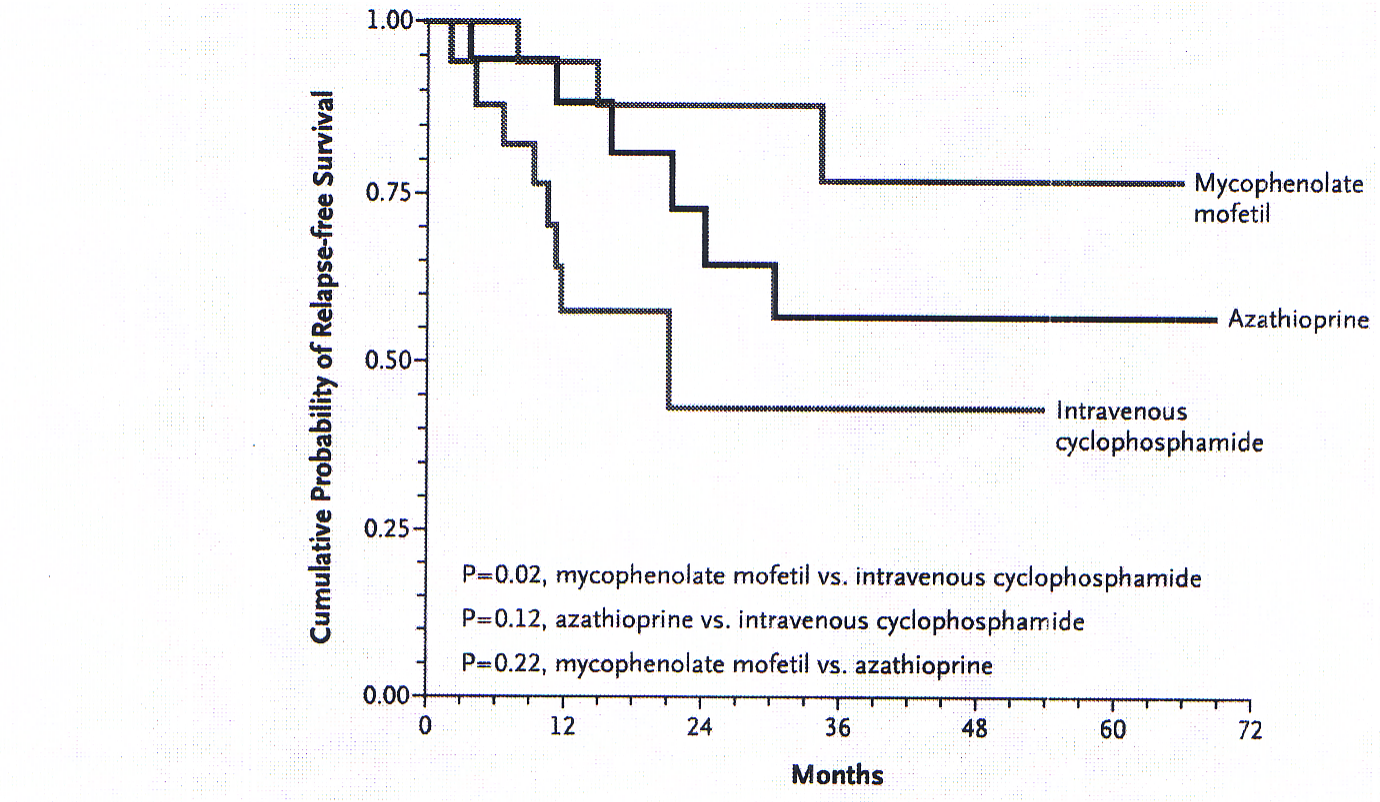
Boumpas *Lancet* 1992; 340:741

Suppression du CYC en entretien

NIVEAU

2

Entretien

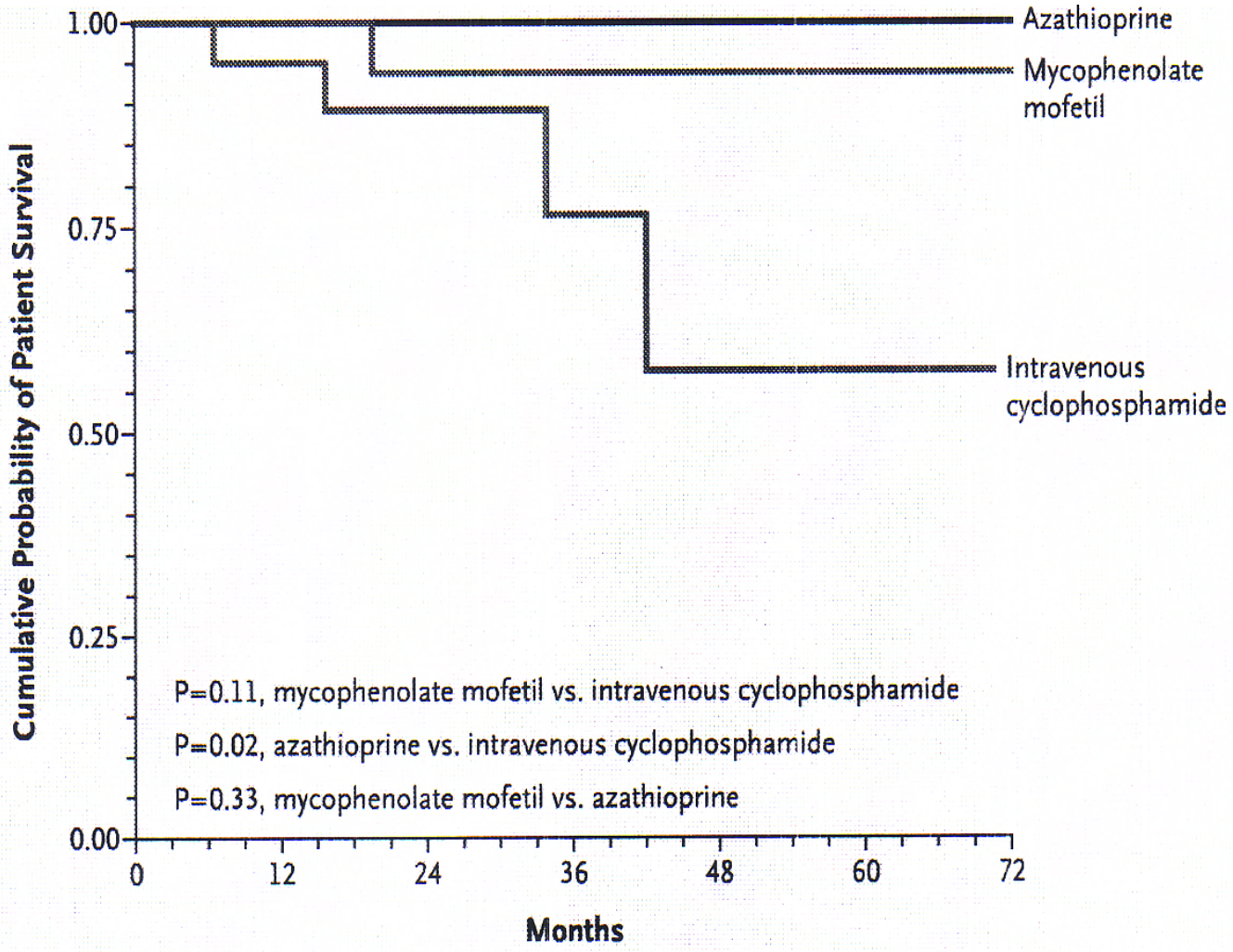


No. at Risk							
Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1

Contreras *NEJMed* 2004; 350: 971

NIVEAU

2



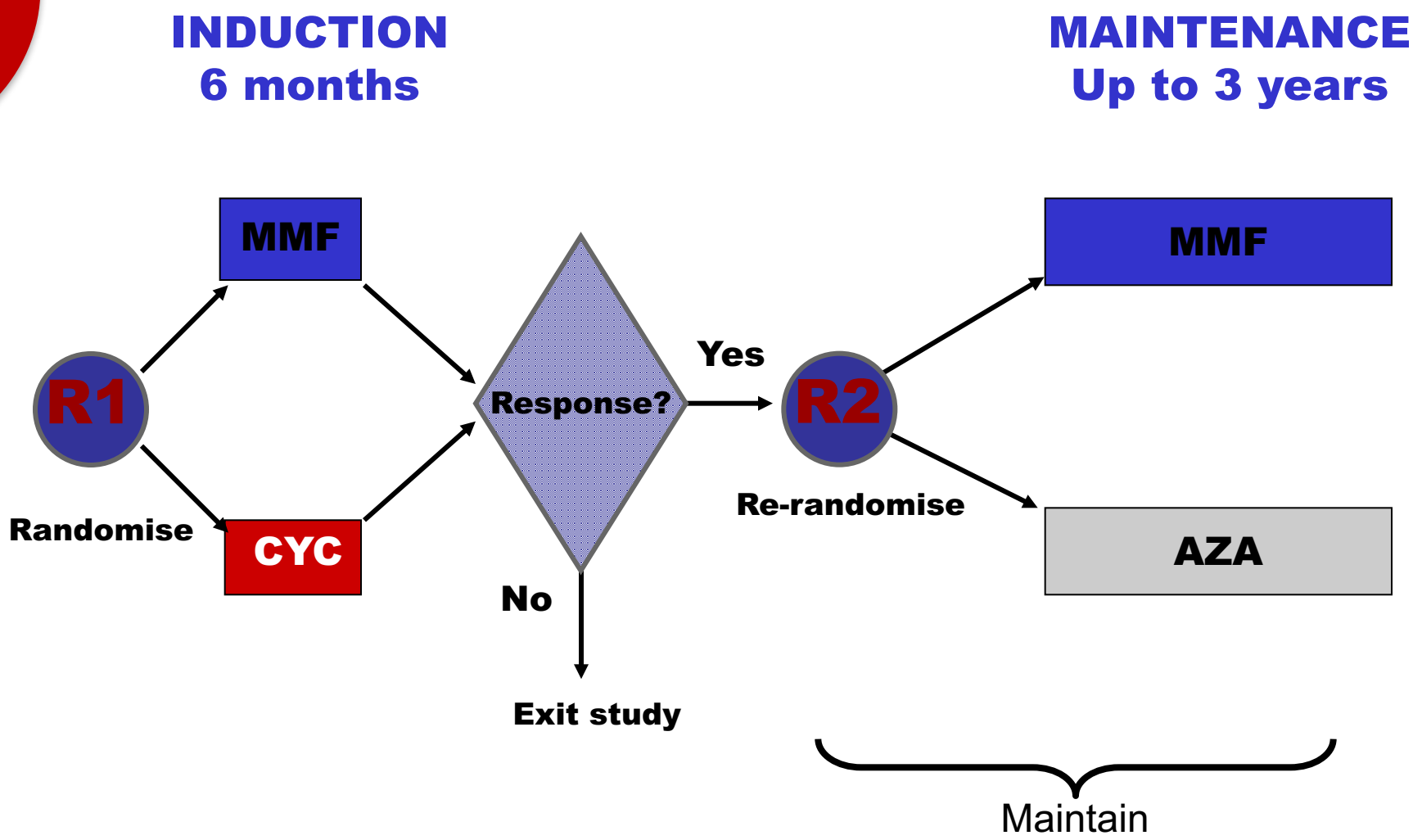
No. at Risk							
Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

Contreras NEJMed 2004; 350: 971

NIVEAU

1-2

Aspreva Lupus Management Study



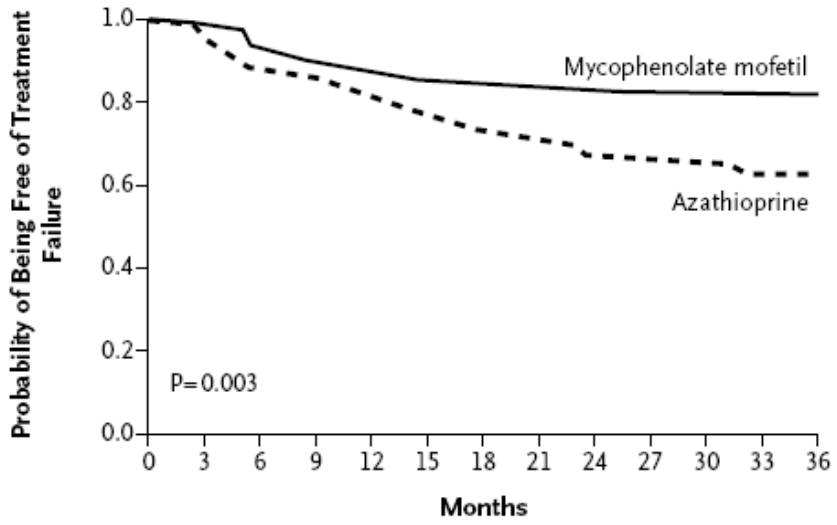
NIVEAU

1-2

Mycophenolate versus Azathioprine as Maintenance Therapy for Lupus Nephritis

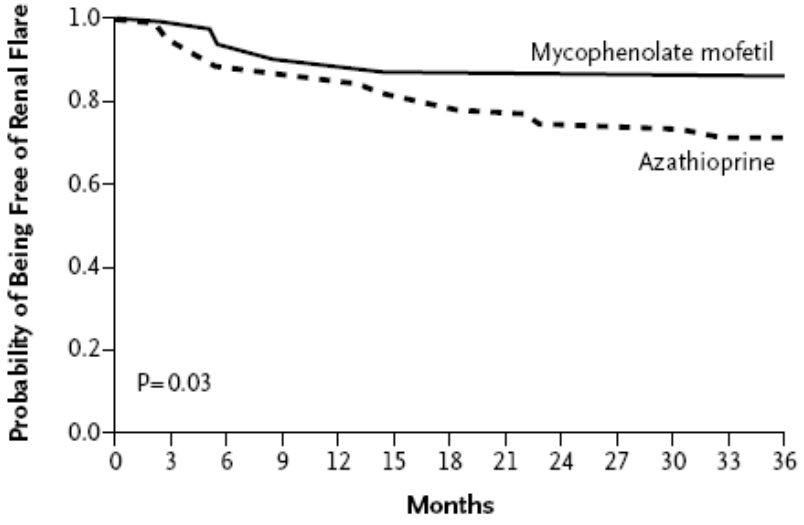
Mary Anne Dooley, M.D., M.P.H., David Jayne, M.D., Ellen M. Ginzler, M.D., M.P.H., David Isenberg, M.D., Nancy J. Olsen, M.D., David Wofsy, M.D., Frank Eitner, M.D., Gerald B. Appel, M.D., Gabriel Contreras, M.D., M.P.H., Laura Lisk, B.Sc., and Neil Solomons, M.D., for the ALMS Group*

A



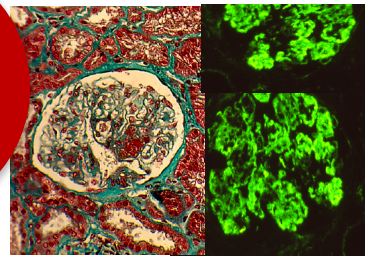
No. at Risk												
Mycophenolate mofetil	116	109	101	92	88	87	82	79	78	75	74	72
Azathioprine	111	101	88	81	77	70	64	61	58	56	52	51

B



No. at Risk												
Mycophenolate mofetil	116	109	102	92	89	88	82	80	78	75	74	73
Azathioprine	111	101	89	82	77	71	65	62	60	58	56	54

NIVEAU 5



Diagnostic

NIVEAU 3

P/C<0,5g/g
DFG stable ou
Normalisé
=
Remission

+

NIVEAU 3

Prévention des rechutes

NIVEAU 2

Induction

Réference
=
stéroides + CYC IV

Entretien

Immunosuppresseur
+
Faible dose de stéroïdes

NIVEAU 2

NIVEAU 6

Résumé = NIVEAU 6

	Induction	Entretien	Ne pas oublier
NIVEAU 2 — 1ère ligne	« Eurolupus »	NIVEAU 1-2 — MMF > Aza (Durée? ↓ Malvar KI2019 Essai WIN-lupus) GROUPE COOPÉRATIF LUPUS RÉNAL	ACE Hydroxychloroquine Prophylaxie antiinfectieuse
NIVEAU 6 — En cas de sévérité	« NIH » ????		
NIVEAU 3 — Si CYC non souhaité	MMF as ALMS		
NIVEAU 6 — 2e ligne	Switch from CYC to MMF or MMF to CYC		
? — Place?	obinutuzumab NIVEAU 2		

PERSPECTIVES

NIVEAU 4

RITUXILUP

EXTENDED REPORT

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,[1] Damien Ashby,[1] Ruth J Pepper,[1] H Terence Cook,[1,2] Jeremy B Levy,[1] Megan Griffith,[1] Tom D Cairns,[1] Liz Lightstone[1,2,3]

50 consecutive patients enrolled

ORIGINAL RESEARCH

Annals of Internal Medicine

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized Trial

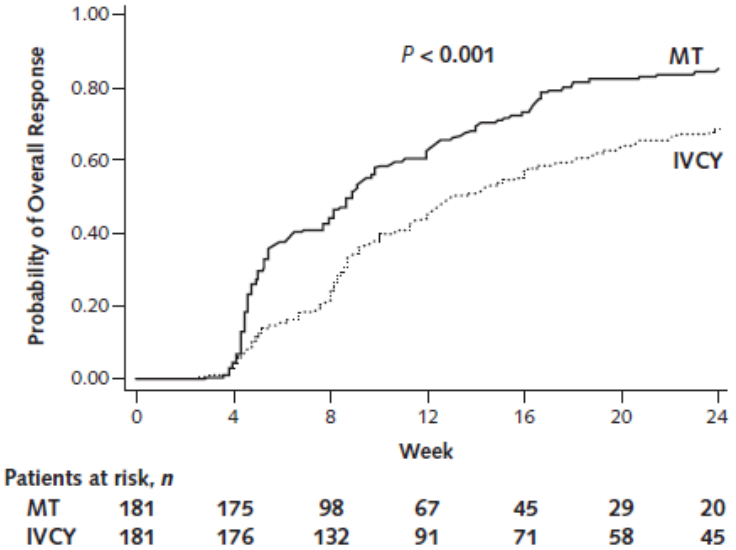
Zhihong Liu, MD; Haitao Zhang, MD; Zhangsuo Liu, MD; Changying Xing, PhD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Hongli Lin, MD; Fuyou Liu, MD; Yongcheng He, MD; Yani He, MD; Lining Miao, MD; Nan Chen, MD; Ying Li, MD; Yong Gu, MD; Wei Shi, MD; Weixin Hu, MD; Zhengzhao Liu, MD; Hao Bao, MD; Caihong Zeng, PhD; and Minlin Zhou, MD

NIVEAU ?

Tac 2mg twice daily
MMF 500 twice daily
High dose steroids

« NIH-short »

Characteristic	Multitarget (n = 181)	Intravenous Cyclophosphamide (n = 181)
Women, *n* (%)	168 (92.8)	161 (89.0)
Age at enrollment, *y*	30.3 (23.3, 38.6)	33.6 (24.2, 41.5)
Duration of LN, *mo*	2 (1, 12)	3 (1, 13)
First onset of LN, *n (%)*	102 (56.4)	87 (48.1)
Pathologic classification, *n* (%)†		
Class III	10 (5.5)	9 (5.0)
Class IV	74 (40.9)	76 (42.0)
Class V	32 (17.7)	37 (20.4)
Class III+V	19 (10.5)	7 (3.9)
Class IV+V	46 (25.4)	52 (28.7)



MT = multitarget; IVCY = intravenous cyclophosphamide.

Ann Intern Med. 2015;162:18-26.

MERCI