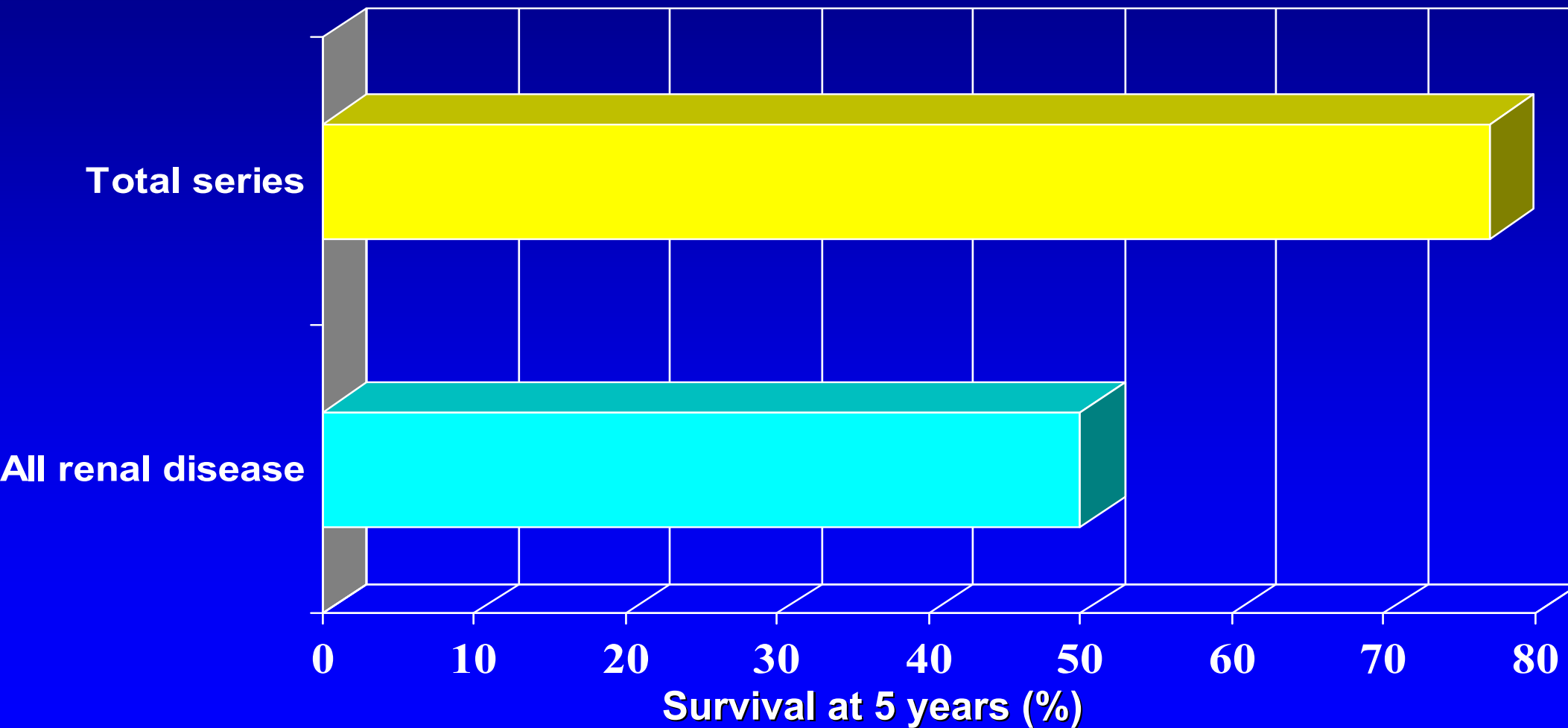


Medical Management of Lupus Nephritis, Current Therapies and Future Directions



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University of Miami, School of Medicine

Estimated 5-year patient survival for renal manifestations of SLE (1971)



Estes D, Christian CL. *Medicine* 1971;50:85-95.

Lupus Nephritis Classification ISN RPS 2004

Class I: Minimal mesangial: normal LM, deposits IF o EM

Class II: Mesangial proliferativa with mesangial deposits with/without minimal deposits subepithelial or subendothelial by IF o ME no visible by LM

Class III: Focal (<50 % glomeruli) proliferativa: A, A/C, C

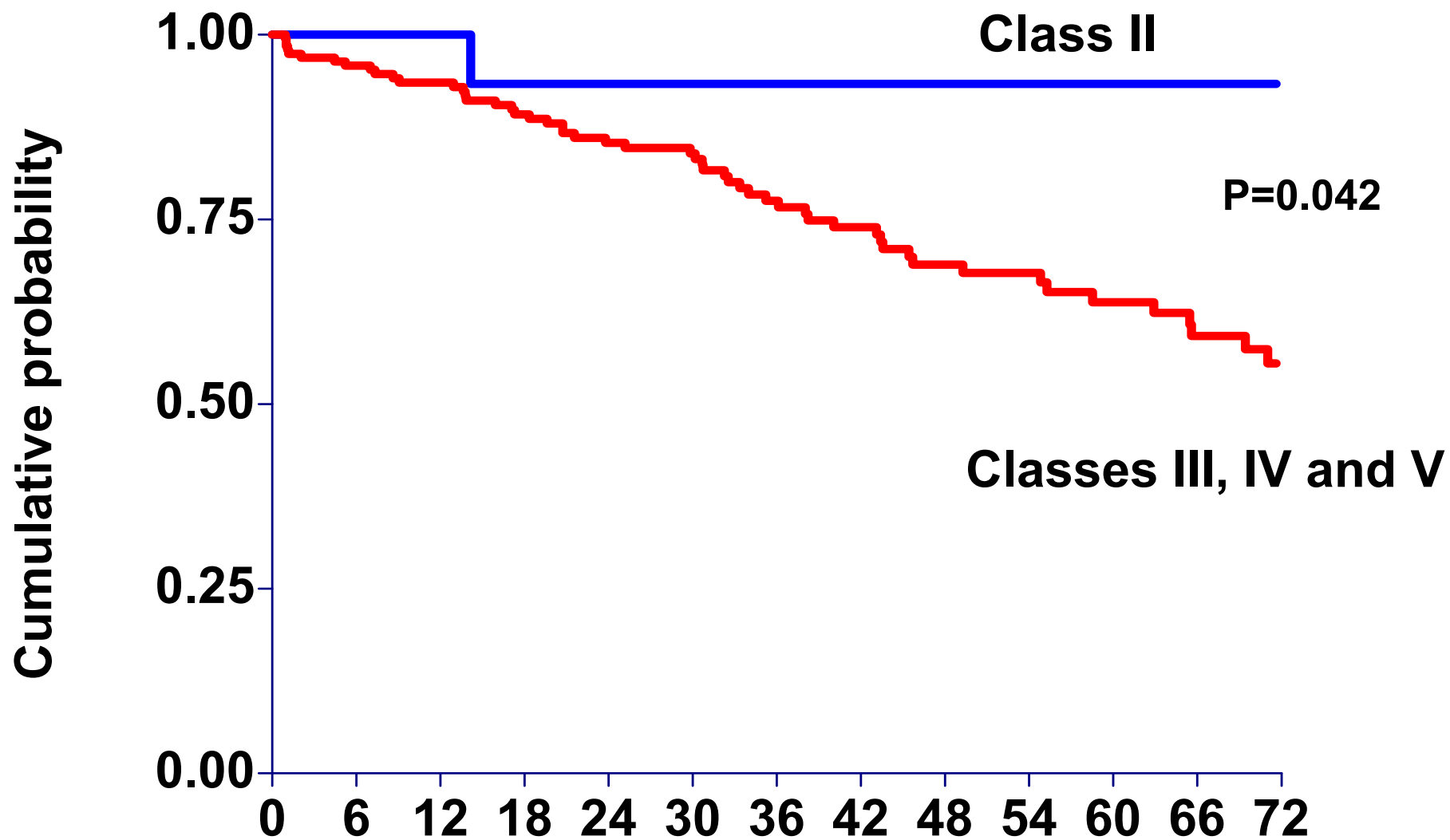
**Class IV: Diffuse proliferativa (proliferation intra y/o extracapilar with subendothelial deposits)
Subdivision: Segmental (IV-S) y global (IV-G)
A, A/C, C**

Class V: Membranosa: with/without classes III o IV

Class VI: Advanced sclerotic: > 90% glomeruli globally sclerotics

Survival of 213 lupus nephritis patients as a function of WHO classification

Free of doubling creatinine, ESRD or death



Contreras et al. Lupus 2005, 14: 890-95 t, months

Lupus Nephritis Indices of Activity and Chronicity

Activity *

- **Glomeruli**
 - Hypercellularity
 - Karyorrhexis or fibrinoid necrosis **
 - Cellular crescents **
 - Hyaline thrombi, wire loops
 - Leukocyte infiltration
- **Tubule/Interstitium**
 - Mononuclear cell infiltration

Chronicity *

- Glomerulosclerosis**
 - segmental
 - mesangial
 - global
- Fibrous crescent**
- Interstitial fibrosis**
- Tubule atrophy**

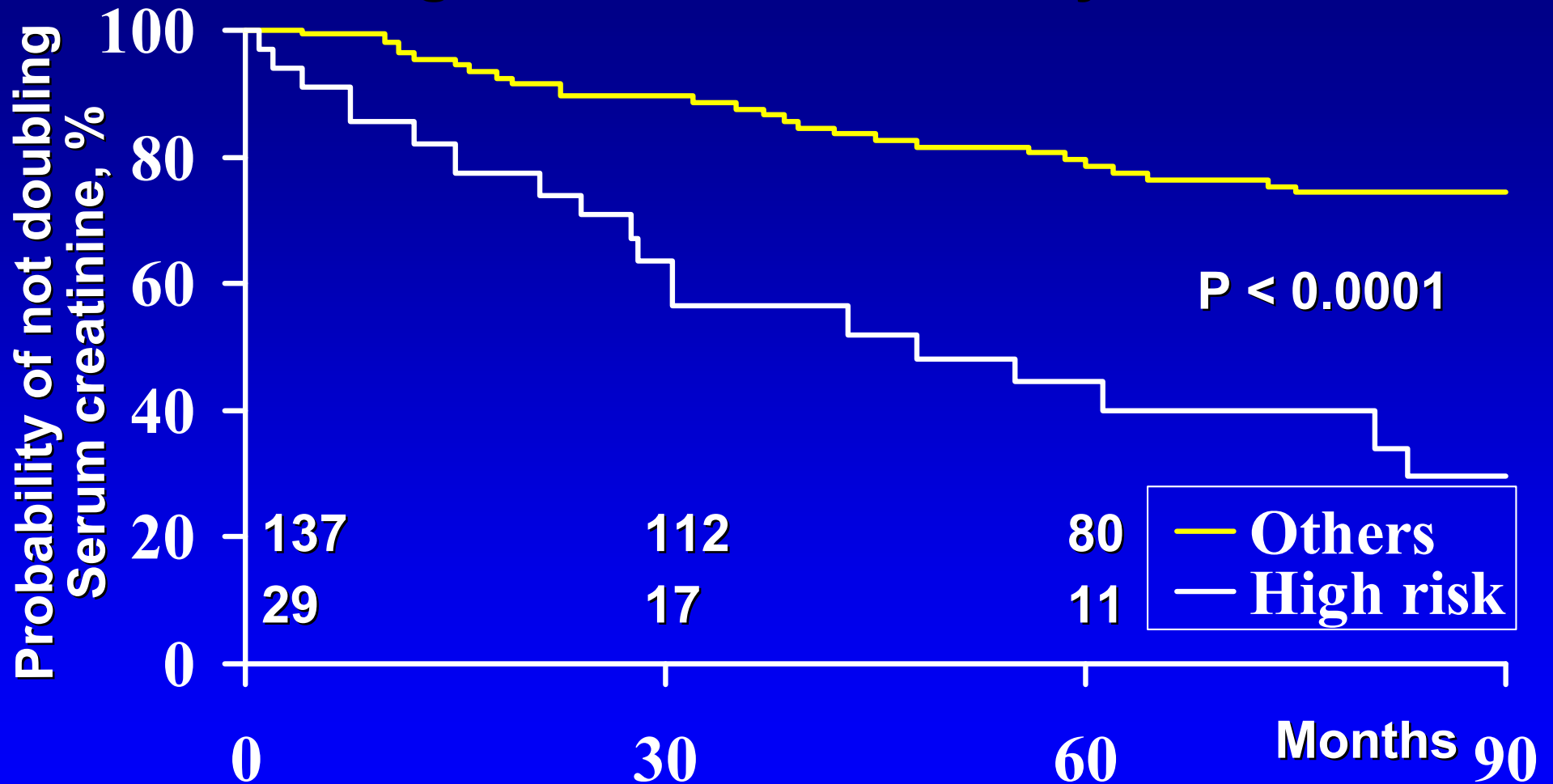
Vascular

- Noninflammatory necrotizing arteritis,**
- True vasculitis**
- Immune complex deposit**
- Thrombotic Microangiopathy**

*Score 0-3 for each item. **Multiply by 2 Activity Index

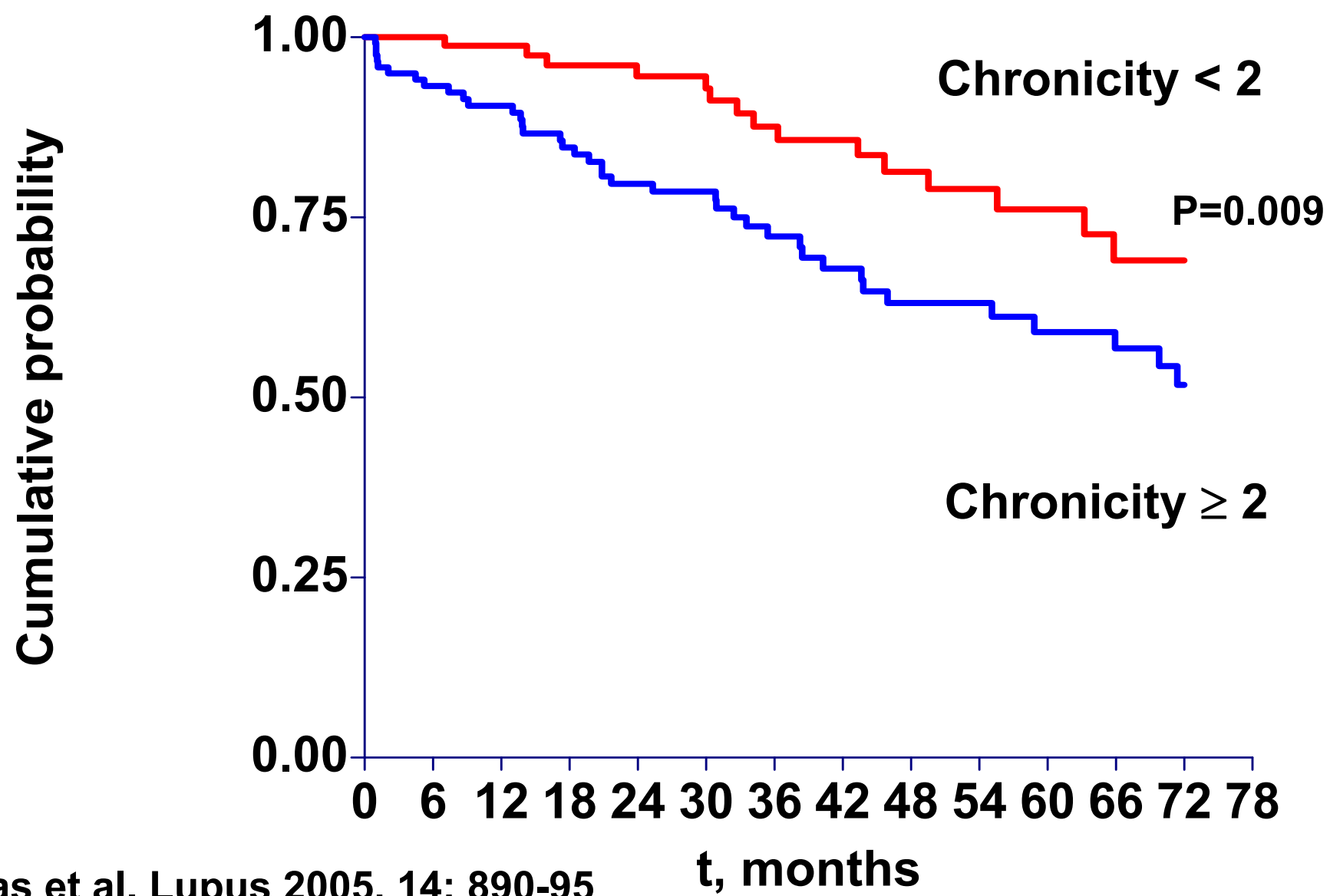
WHO classification: modified Pollak et al. J Lab Clin Med 1964; 63 (4)

Cumulative survival curves based on 166 lupus-nephritis patients demonstrating the probability of not reaching the renal insufficiency outcome



High risk = histology showed crescents and moderate to severe interstitial fibrosis. Austin HA, et al. Nephrol Dial Transplant 1995;10:1620

Survival of 213 Lupus Nephritis Patients as a Function of chronicity index Free of doubling creatinine, ESRD or death

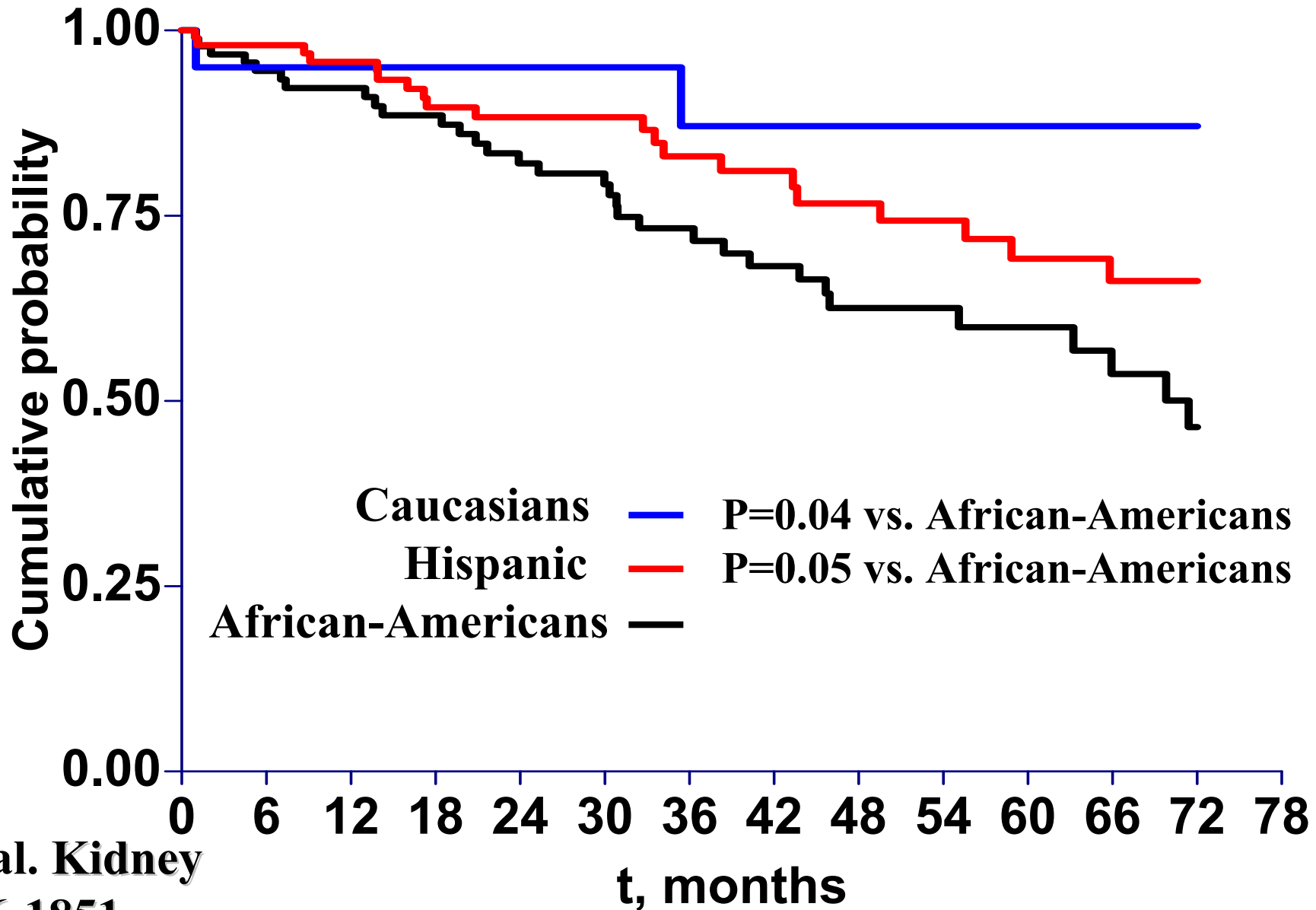


Other Factors (than histological parameters) Associated with Increased Risk of Chronic Renal Failure

- **African-American**
- **Hispanic**
- **Male gender**
- **Age < 24 years**
- **Hypertension**
- **High creatinine**
- **Nephrotic range proteinuria**
- **Anemia**
- **Anticardiolipins**
- **Lack of remission**
- **Relapse**

**Outcomes
in African
Americans
and
Hispanics
with lupus
nephritis**

Survival: Free of doubling creatinine, ESRD or death



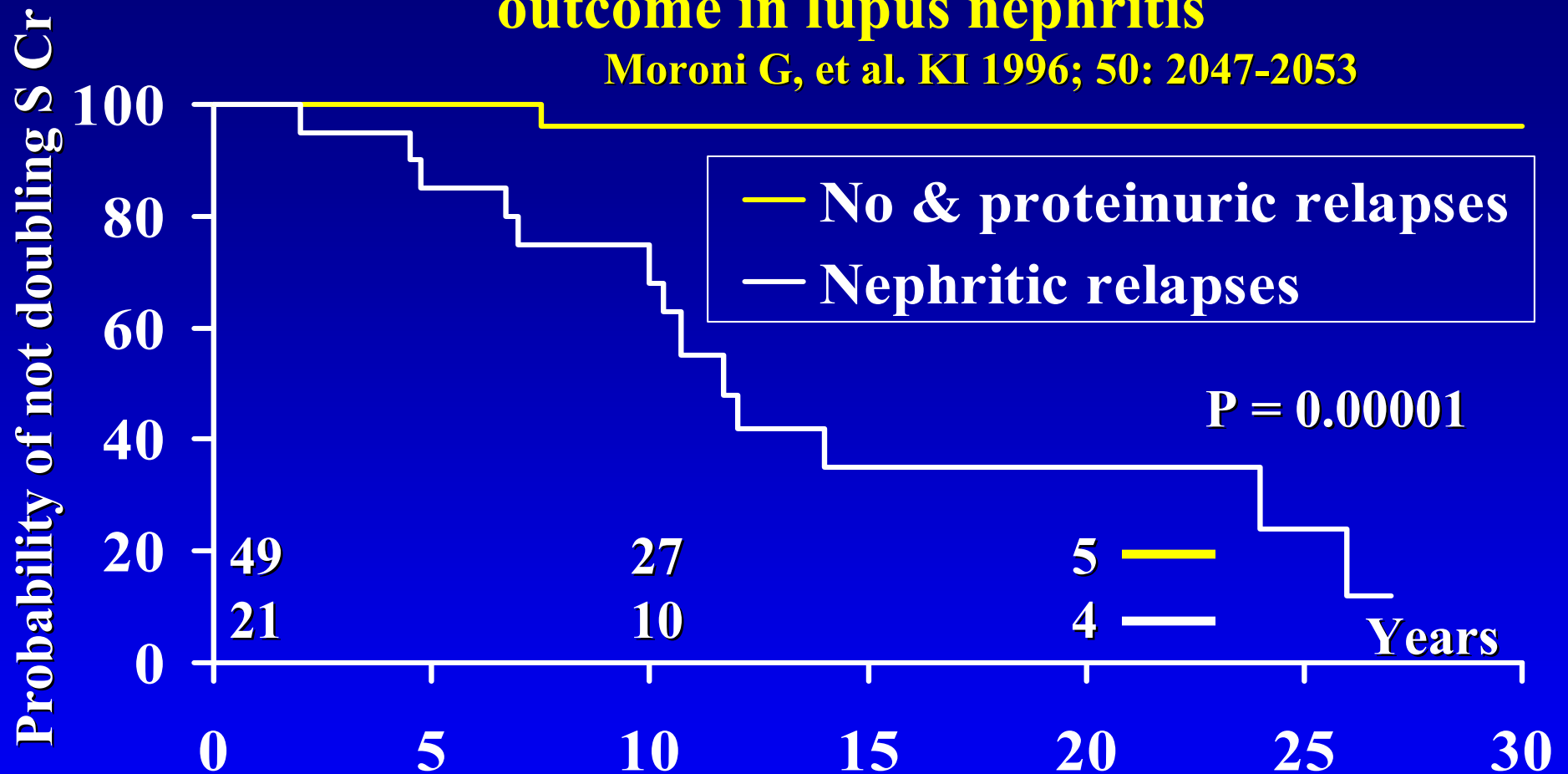
Remission Predicts Long-term Outcome in Severe Lupus Nephritis

- 86 patients in trial of high dose prednisone and oral CTX +/- plasmapheresis
- Clinical remission (serum creatinine ≤ 1.4 mg/dL and proteinuria ≤ 0.33 g/day) in 37 patients (43%)

	At 5 years	At 10 years
Patient survival		
Remission	95%	95%
No remission	69%	60%
Renal survival		
Remission	94%	94%
No remission	45%	31%

“Nephritic relapses” are predictors of bad long-term outcome in lupus nephritis

Moroni G, et al. KI 1996; 50: 2047-2053



Nephritic relapse: \uparrow S Cr of $\geq 30\%$, active sediment and \uparrow proteinuria.
By multivariate analysis, male gender ($p=0.015$) & HTN ($p=0.004$) were independent predictors of nephritic relapses

Evolving Therapeutic Strategies for Lupus Nephritis

Cyclophosphamide (CY)

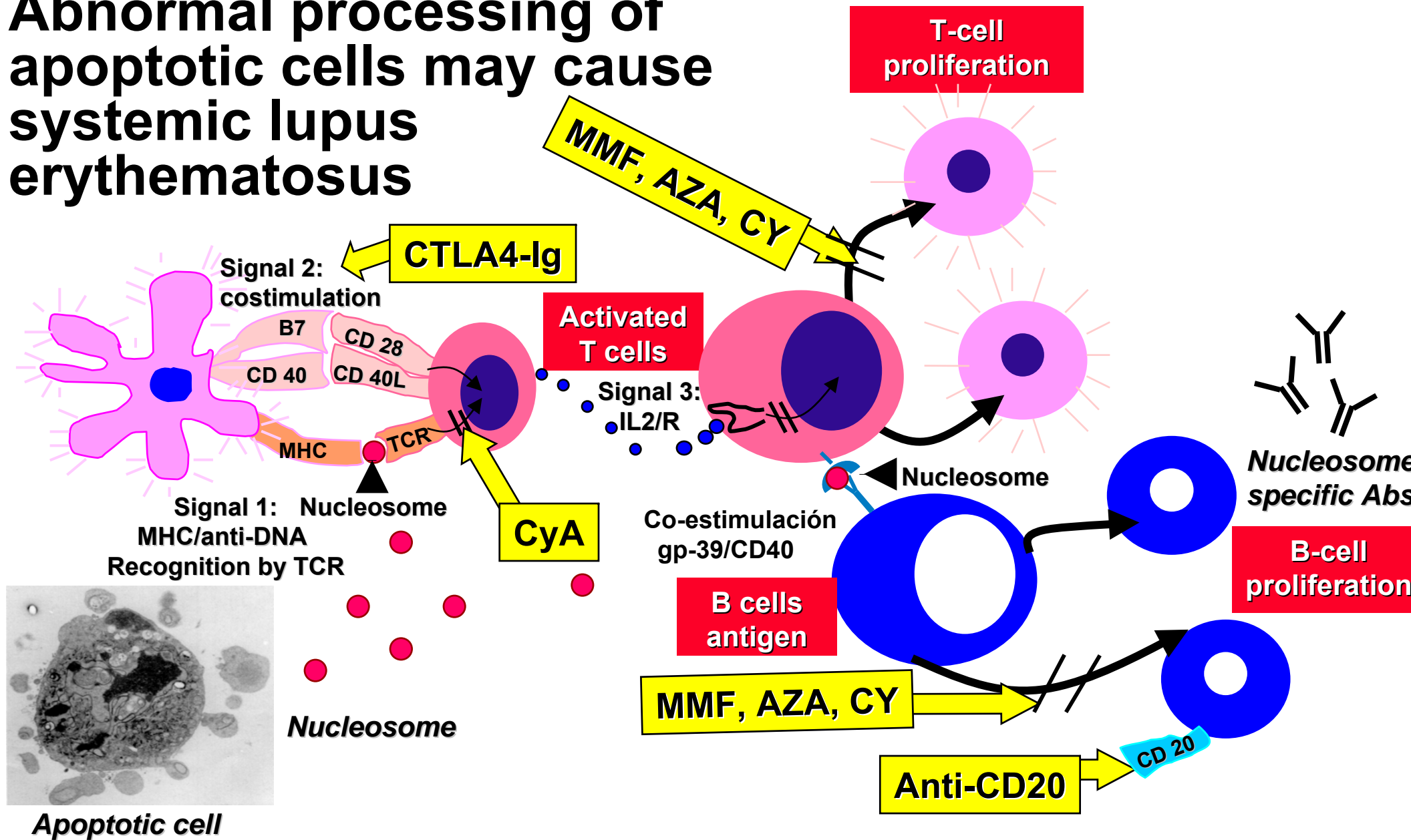
Azathioprine (AZA)

Mycophenolate Mofetil (MMF)

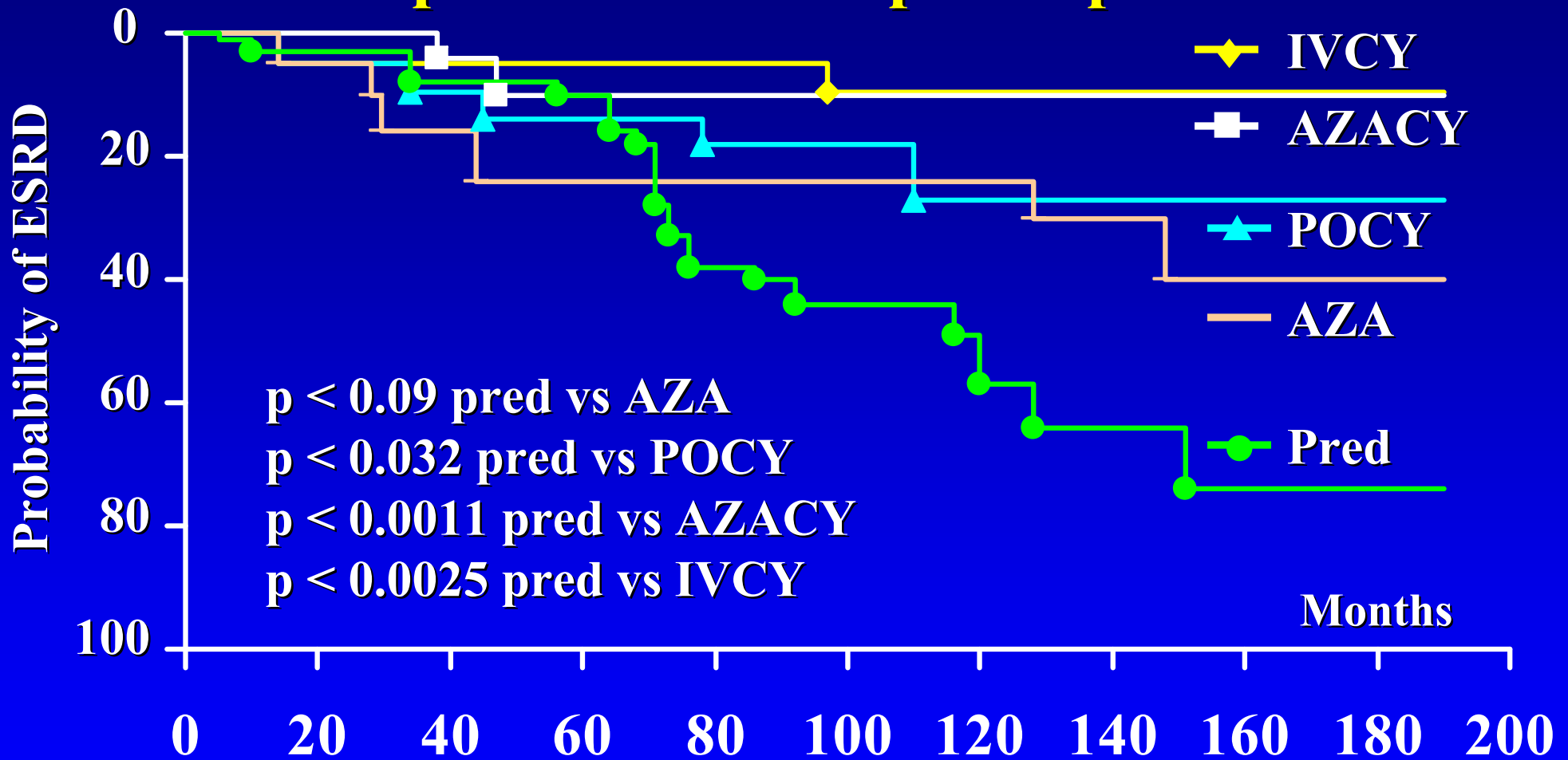
Cyclosporine (CyA)



Abnormal processing of apoptotic cells may cause systemic lupus erythematosus



Long term preservation of renal function in 111 patients with Lupus Nephritis



Steinberg AD and Steinberg SC. NIH. Arthritis Rheum 1991;34(8):945-950

Therapy of lupus Nephritis

Complication	Treatment Group				
	% of the patients at risk				
	Pred	AZA	POCY	AZACY	IVCY
Major infection	25	11	17	14	10
Herpes zoster *	7	11	33	32	25
Hemorrhagic ♠	0	0	17	14	0
Cystitis					
Cancer	0	11	17	0	0
Premature ovarian ♥	8	18	71	53	45
Mortality	11	11	11	14	15

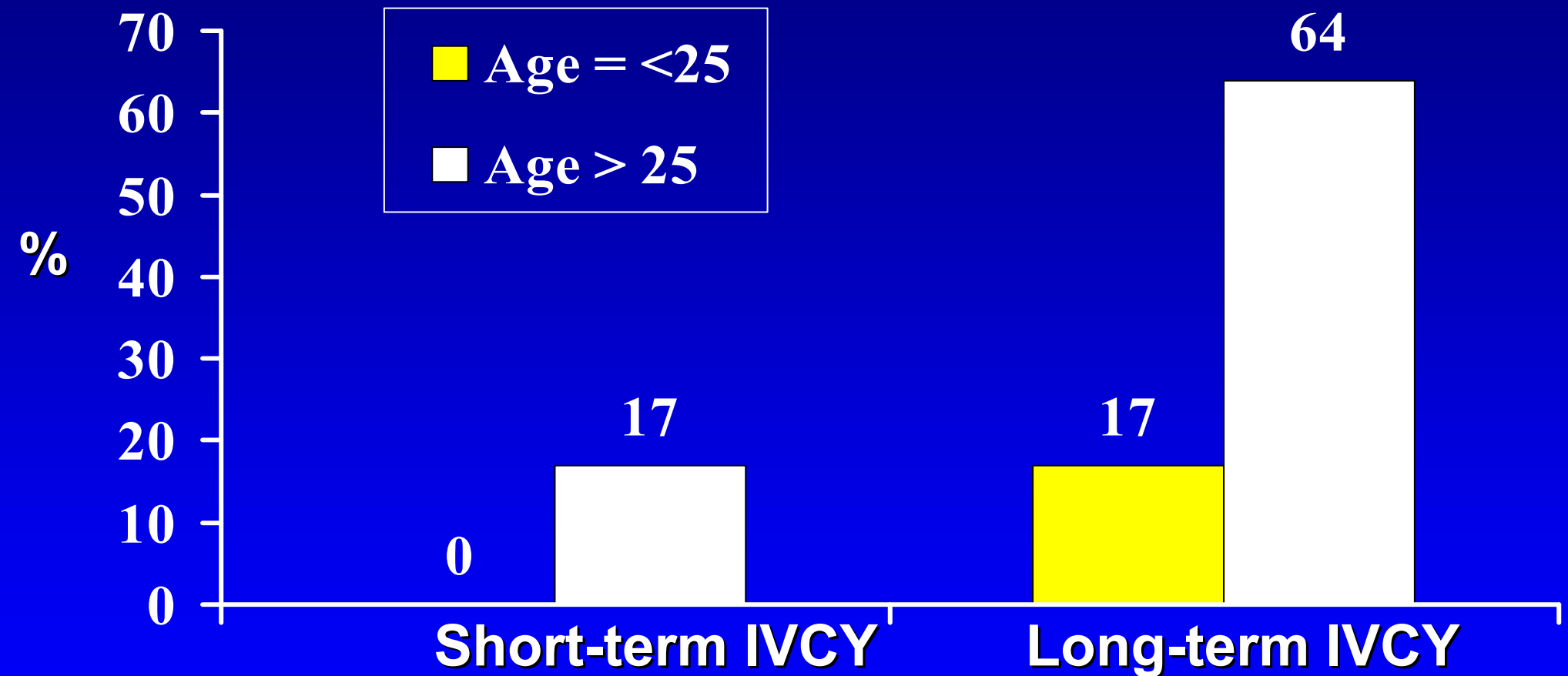
* p<.05 groups 1 and 2 vs 3, 4 and 5

♠ p<.01 groups 1, 2 and 5 vs 3 and 4

♥ p<0.01 groups 1 and 2 vs 3, 4 and 5

NIH. N Engl J Med 1986;314:614-619

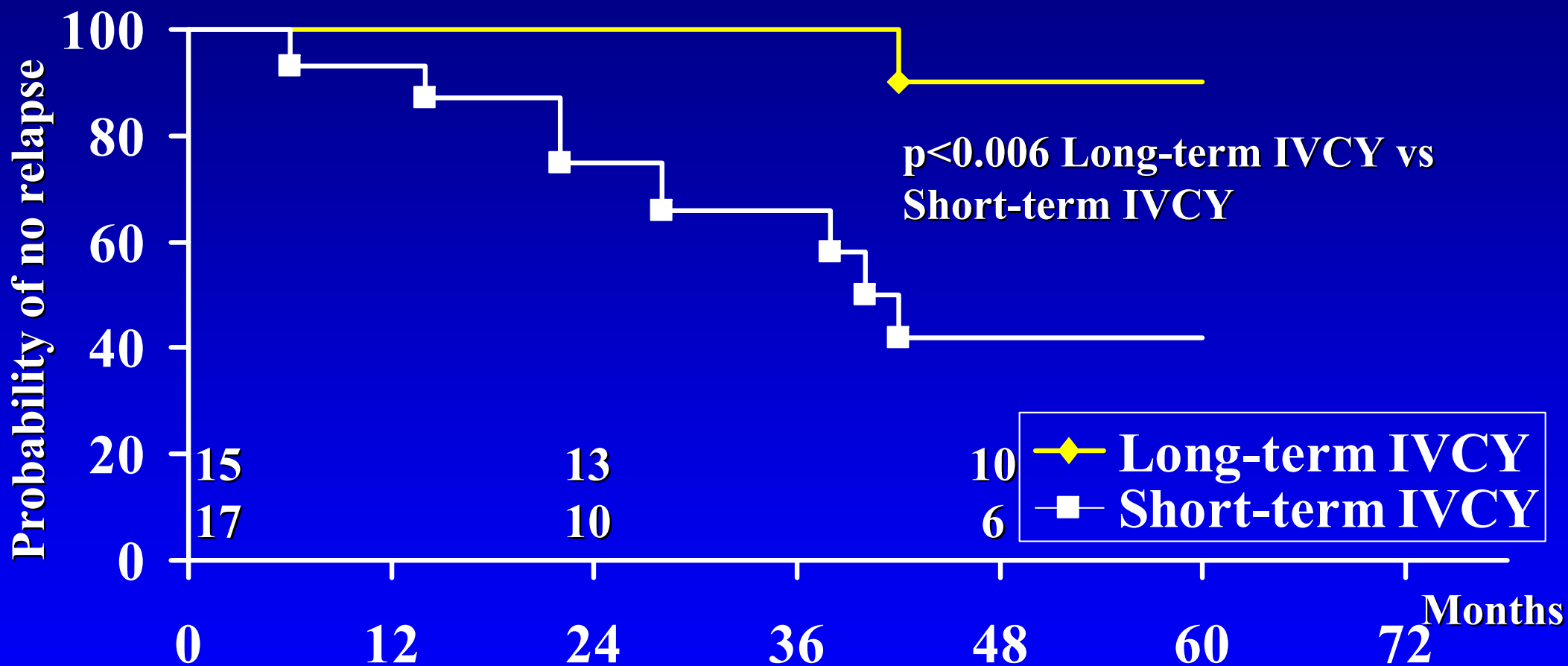
Rate of sustained amenorrhea in patients treated with IVCY according to duration of therapy and age



$p = 0.04$ short-term vs. long-term IVCY.

Boumpas DT. et al. Ann Inter Med 1993; 119: 366-369.

Controlled trial: two regimens of pulse IVCY in patients with severe lupus nephritis



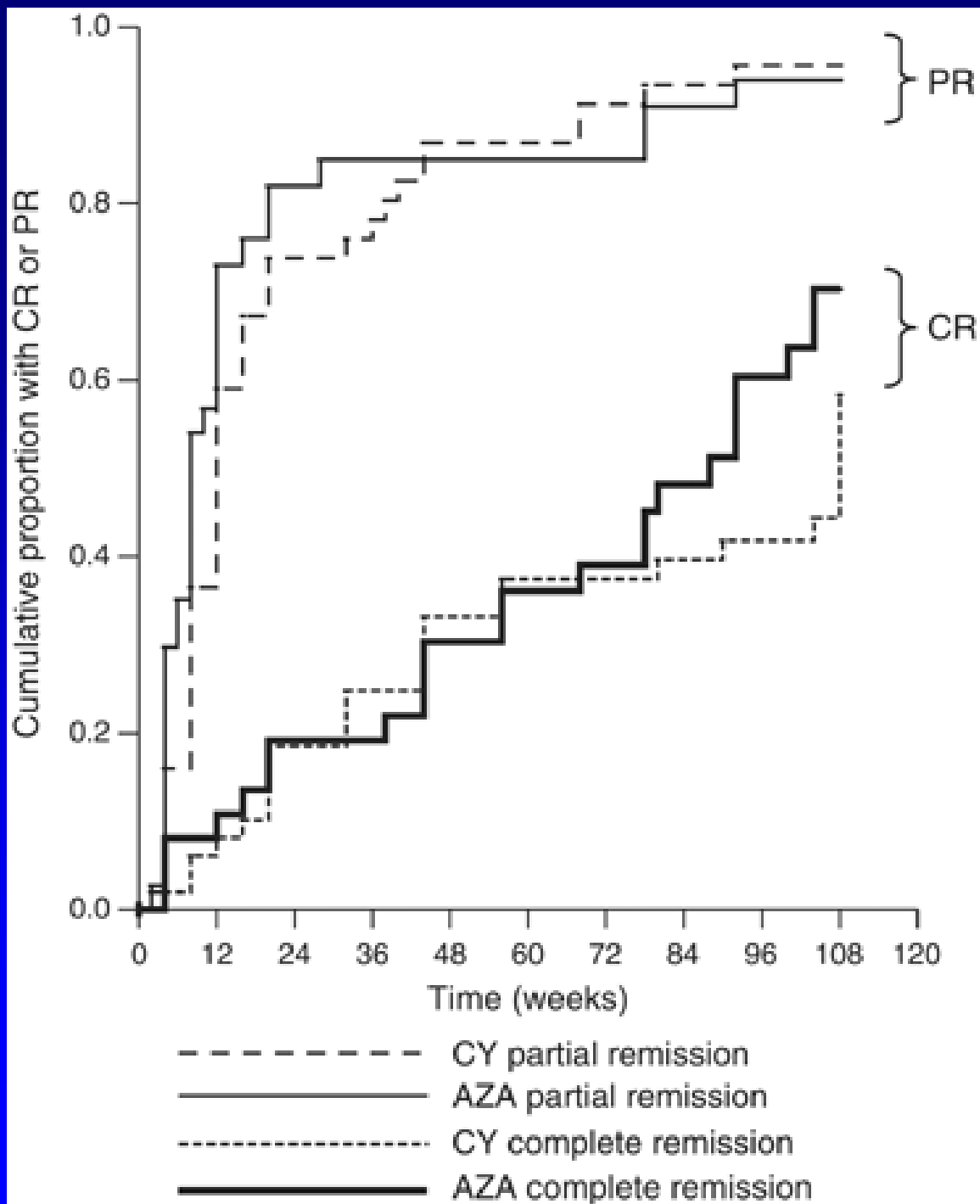
Long-IVCY= monthly x 6 then quarterly x 2 ys; Short-IVCY= monthly x 6.

Boumpas DT, et al. NIH. Lancet 1992;340: 741-45

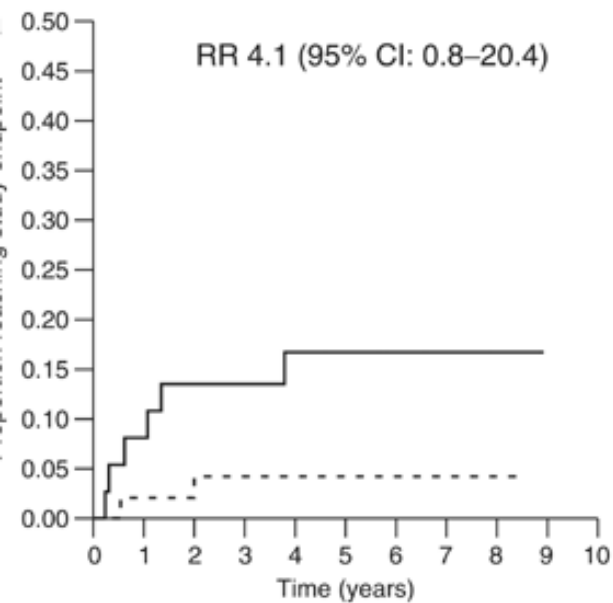
Azathioprine/methylprednisolone, n=37 (MP 1 g IV x 3 days baseline, 2 and 6 weeks with AZA 2 mg/kg/day) versus cyclophosphamide, n=50 (IVCY 0.75 g/m² q mon x 6 then q3mon) in proliferative lupus nephritis. A randomized controlled trial.

- **Patient histological characteristics (N = 87)**
 - WHO Class III and Vc = 9% Mean Activity Index: 9/24
 - WHO Class IV and Vd = 91% Mean Chronicity Index: 2-3/12
- **Demographics: Mean age 31, 75% Caucasians, 82% female,**
- **Mean BP 140/80 mmHg**
- **53% nephrotic, mean urine 24 hr protein 3.75 g**
- **Mean Cr: 1.25 mg/dL**

C Grootsholten et al for the Dutch Working Party on Systemic Lupus Erythematosus. KI (2006) 70, 732–742.

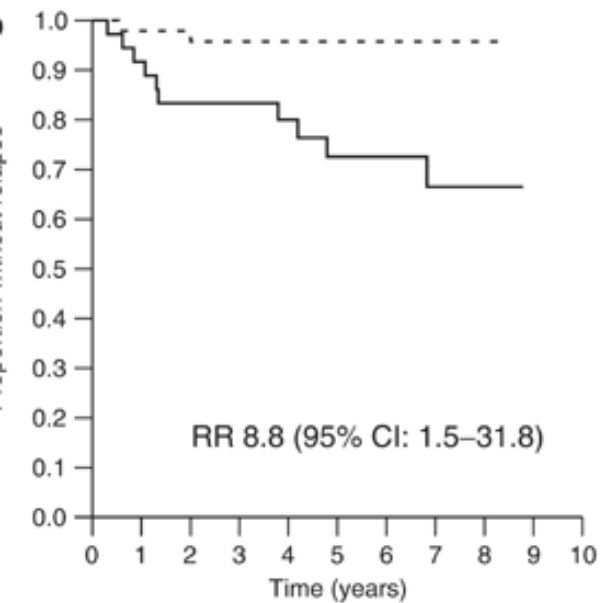


Cumulative incidence of first complete or partial remission. Cumulative incidence of first complete or partial remission in the first 2 years of follow-up. PR, partial remission; CR, complete remission; CY, group treated with intravenous cyclophosphamide; and oral prednisone, AZA, group treated with i.v.MP, azathioprine, and oral prednisone.



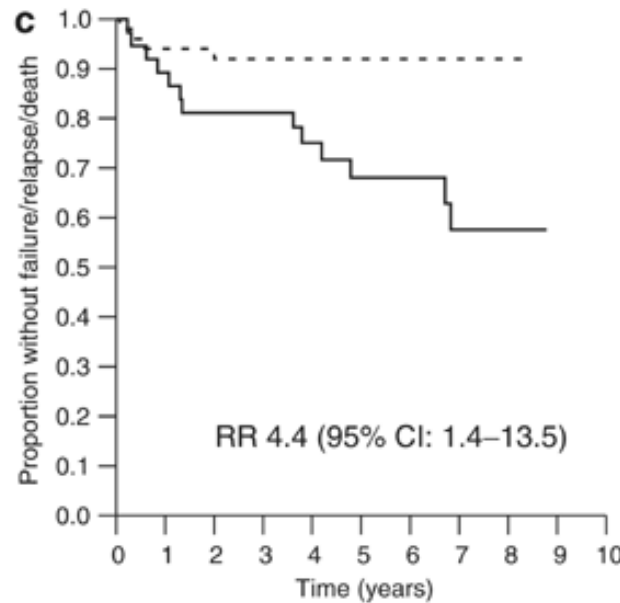
Patients at risk

CY	50	46	46	45	35	29	19	9	3	0
AZA	37	34	31	31	25	21	16	13	10	0



Patients at risk

CY	50	46	46	45	35	29	19	9	3	0
AZA	37	33	29	29	23	19	14	11	8	0



Patients at risk

CY	50	46	46	45	35	29	19	9	3	0
AZA	37	33	29	29	23	19	14	11	8	0

Kaplan–Meier estimates. Kaplan–Meier curves showing (a) proportion of patients reaching the end point of the study, unsustained doubling of serum creatinine, (b) proportion of patients free of relapse, and (c) proportion of patients free of treatment failure, relapse, or death. RR and 95% CI are given. CY=group treated with intravenous cyclophosphamide and oral prednisone, AZA=group treated with i.v.MP, azathioprine, and oral prednisone. KI

Azathioprine/methylprednisolone, n=37 (MP 1 g IV x 3 days baseline, 2 and 6 weeks with AZA 2 mg/kg/day) versus cyclophosphamide, n=50 (IVCY 0.75 g/m² q mon x 6 then q3mon) in proliferative lupus nephritis. A randomized controlled trial.

Adverse events	AZA	IVCY
All infections per 100 pts-ys*	37	18
Herpes Zoster	12	3
Premature ovarian failure, N	2 **	2
Cancer, N	1	-
Deaths, N	3	2

*** P <0.05, ** received also IVCY**

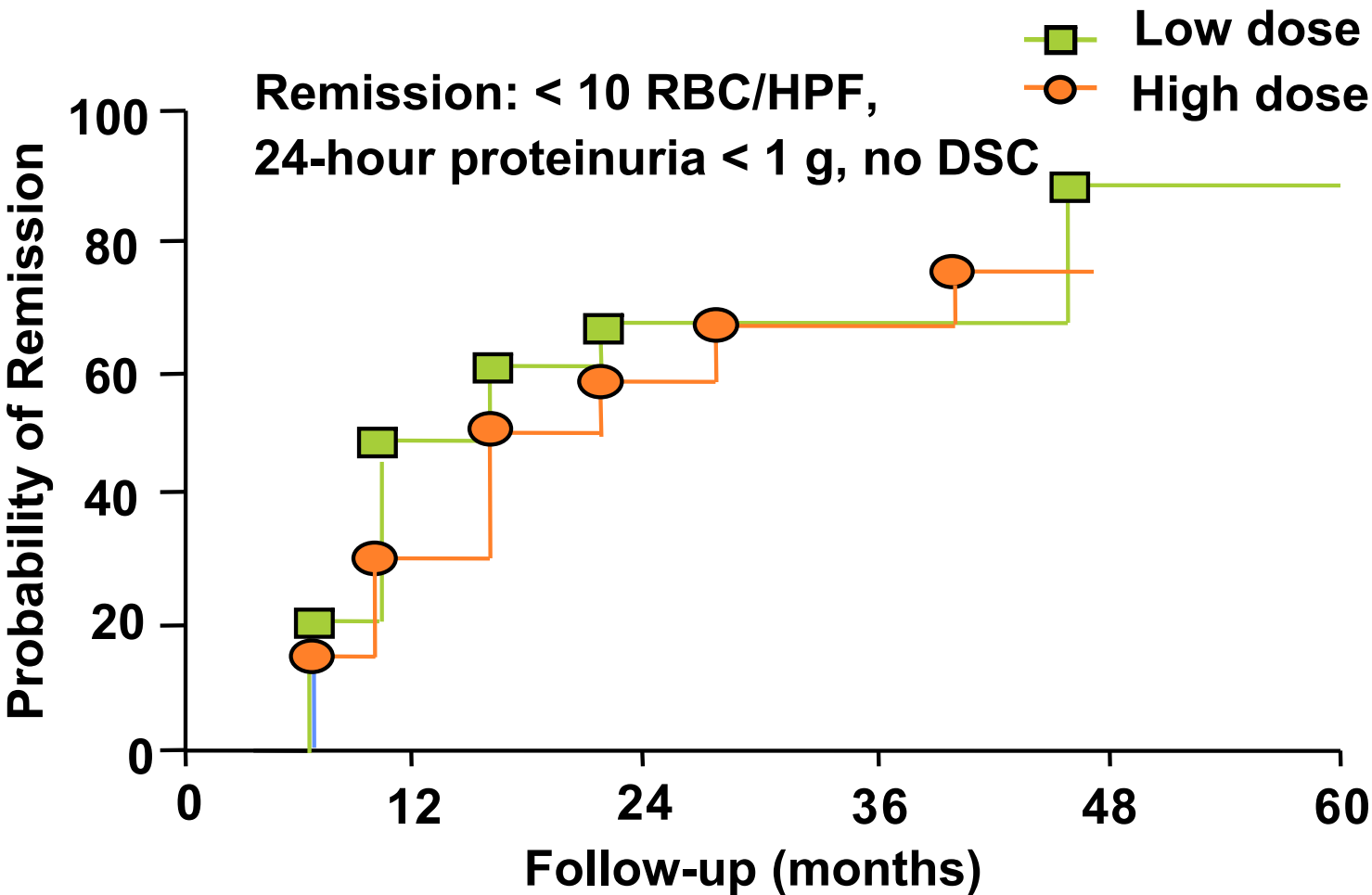
Induction Clinical Trials:

- 1. Houssiau F, et al, Arthritis Rheum 2002; 8: 2121-31.**
- 2. Chan TM et al. New Engl J Med 2000; 343: 1156-62. (Chan TM, et al, JASN April 2005).**
- 3. Weixin Hu, et al. Chin Med J 2002; 115: 705-9**
- 4. Lin YK, et al: J Clin Derm31: 636 –638, 2002**
- 5. Flores-Suarez LF, Villa AR. JASN 15: PO257, 2004**
- 6. Ong LM, et al. Nephrol 10: 504 –510, 2005.**
- 7. Ginzler EM, et al. NEJM 24, Nov 2005**
- 8. Aspreva lupus management study (ALMS). JASN May 2009**

European Lupus Nephritis Trial (ELNT): Sequential regimens of IVCY (low-dose vs. high-dose) induction followed by AZA maintenance with corticosteroids

- **Patient histological characteristics (N = 90)**
 - **WHO Class III n = 21 Activity Index: 10/24**
 - **WHO Class IV n = 62 Chronicity Index: 1/12**
 - **WHO Class Vc+b n = 7**
- **Demographics: Mean age 31, 84% Caucasians,
9% Africans, 7% Asians, 93% female**
- **47% hypertensive**
- **24-hs urine protein 3.04 g**
- **Cr: 1.15 mg/dL**

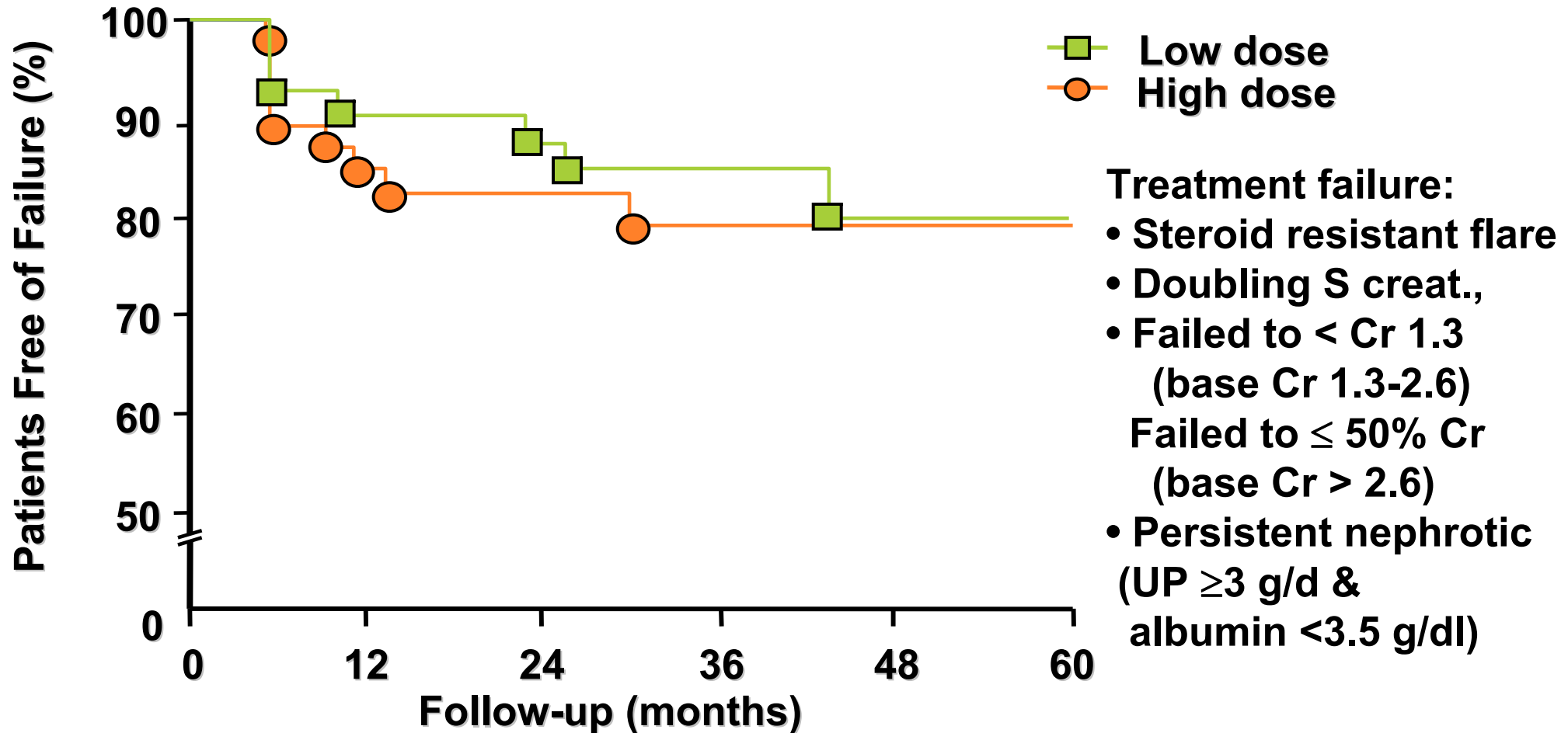
ELNT: Remission



90 pts=WHO III, IV,
Vc+d
Methylprednisolone IV
0.75 g x3
LD = Low-dose IVCY:
0.5 g q2 weeks for 6
pulses followed by
AZA maintenance +
corticosteroids
HD = High-dose IVCY
0.5 g/m² monthly x 6
followed by 2 pulses
q3 months then AZA
maintenance +
corticosteroids

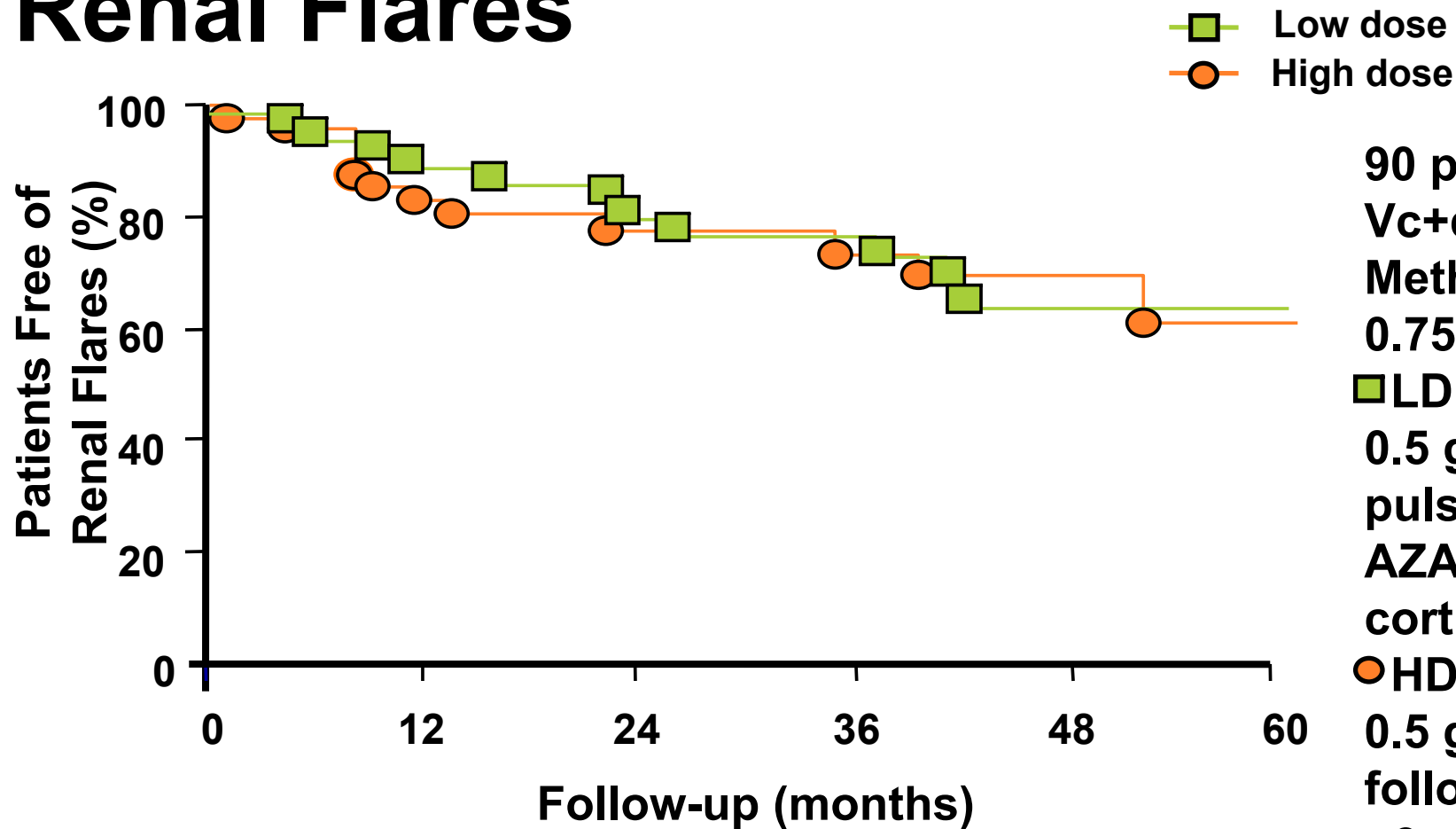
Houssiau FA, et al. Arthritis Rheum. 2002;46:2121-2131.

European Lupus Nephritis Trial: Primary Outcome of Treatment Failure



Houssiau FA, et al. Arthritis Rheum. 2002;46:2121-2131.

European Lupus Nephritis Trial: Renal Flares



90 pts=WHO III, IV,
Vc+d

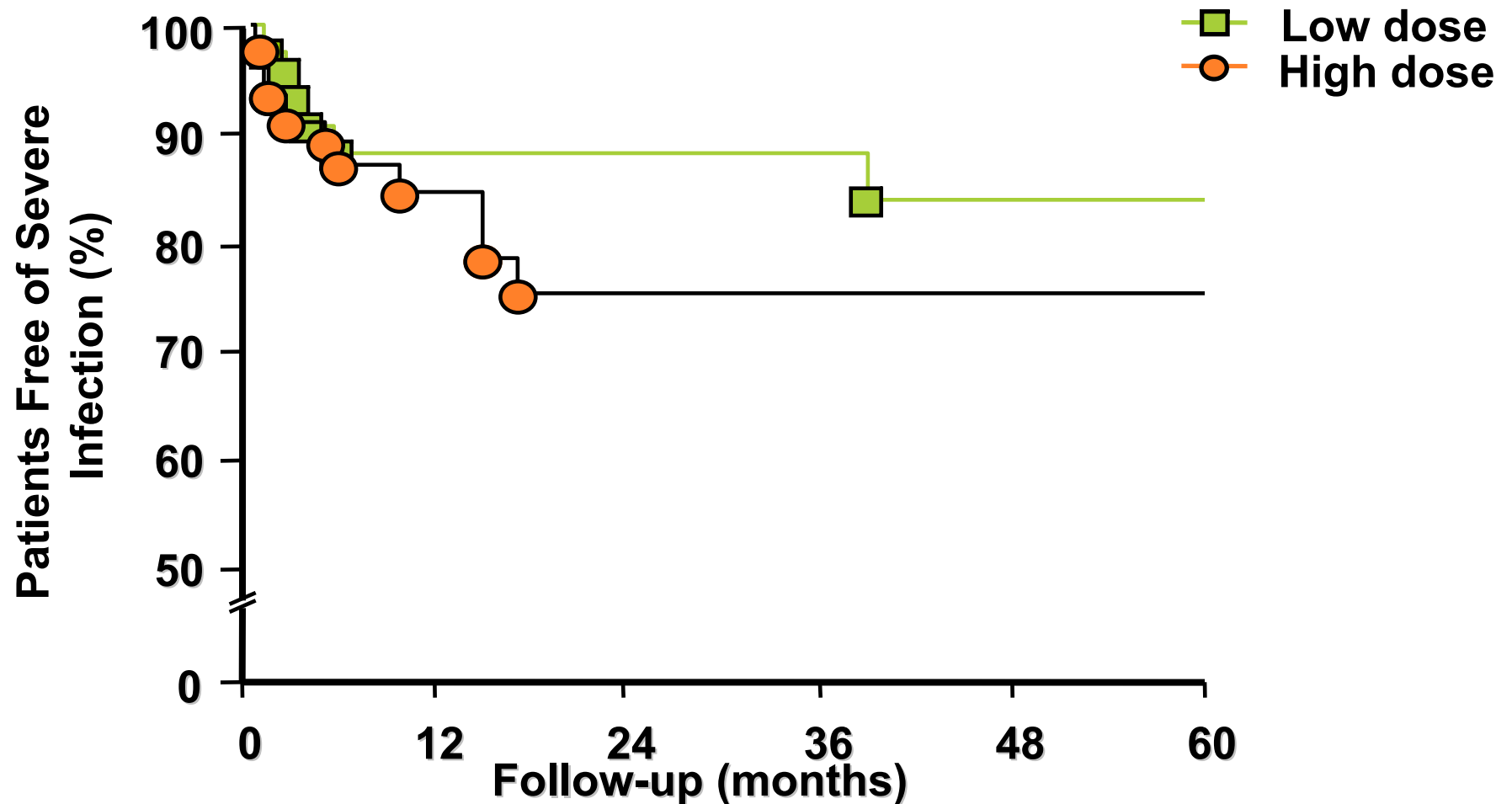
Methylprednisolone IV
0.75 g x3

■ LD = Low-dose IVCY:
0.5 g q2 weeks for 6
pulses followed by
AZA maintenance +
corticosteroids

● HD = High-dose IVCY
0.5 g/m² monthly x 6
followed by 2 pulses
q3 months then AZA
maintenance +
corticosteroids

Houssiau FA, et al. *Arthritis Rheum.* 2002;46:2121-2131.

European Lupus Nephritis Trial: Severe Infections



Houssiau FA, et al. Arthritis Rheum. 2002;46:2121-2131.

Adverse events in the European Lupus Nephritis Trial:

Adverse events	Low Dose- IVCY-AZA	High dose IVCY-AZA
Leukopenia, N (%) *	5 (11)	5 (11)
Bone marrow aplasia, N (%)	-	1
Menopause, N (%)	2 (5)	2 (4)
AZA induced hepatitis, N (%)	3 (7)	-

* WBC < 4000 per cubic μ L occurred in 2 pts in each group during the induction phase.

Houssiau FA, et al. Arthritis Rheum. 2002;46:2121-2131.

Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis

Study design: randomized clinical trial

Methods: 42 Asian patients with WHO class IV were randomized to:

- 1) oral MMF + steroids x 12 months, or**
- 2) sequential oral cyclophosphamide (OCY) + steroid x 6 months then CY was replaced by azathioprine x 6 months**

Patient characteristics

Histological: Activity Index: 9/24

Chronicity Index: 3.2/12

Mean age 37.5

93% female,

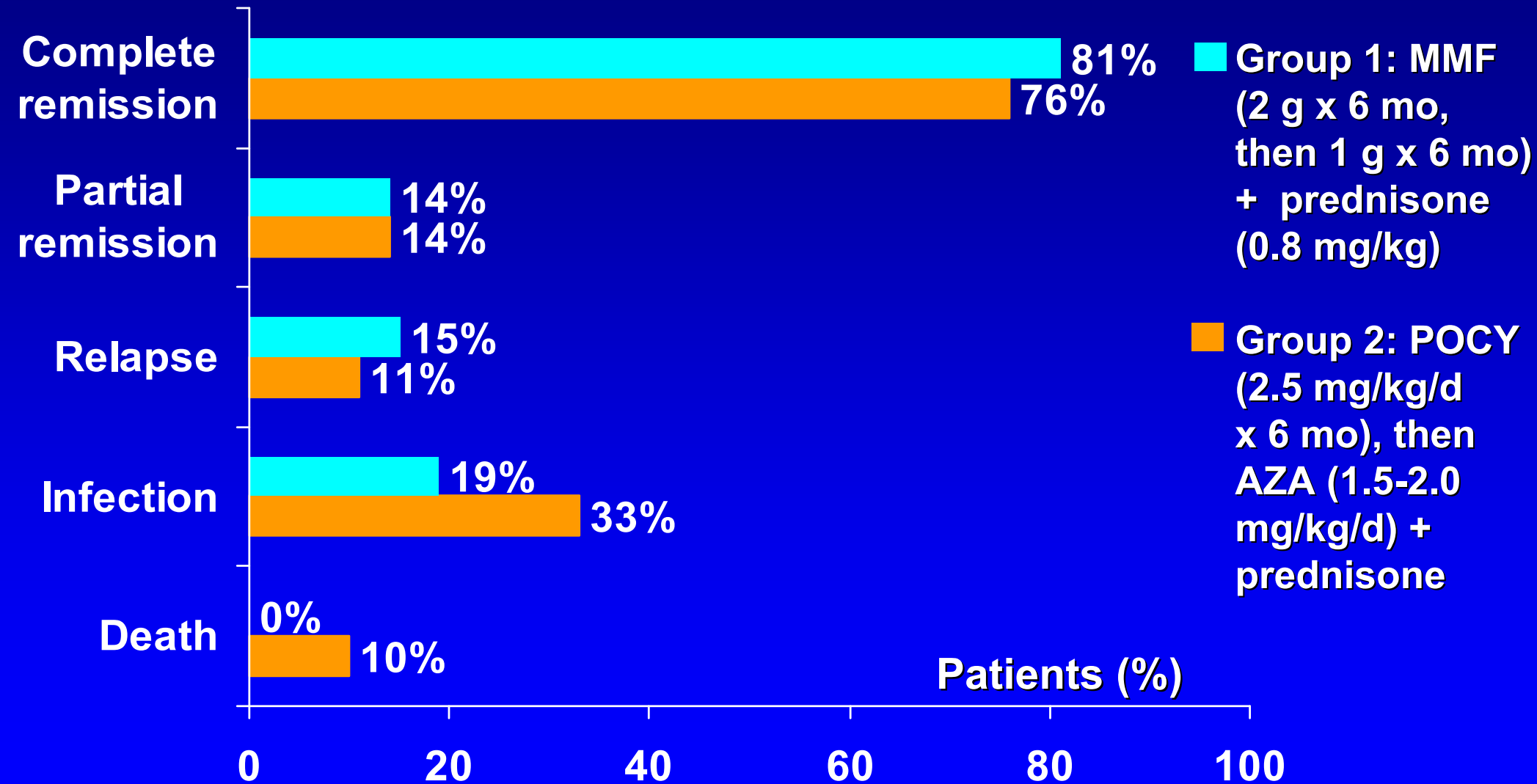
24-hs urine protein 5.8 to 3.7 g/day

Cr: 1.2 mg/dL

Duration: 12 months

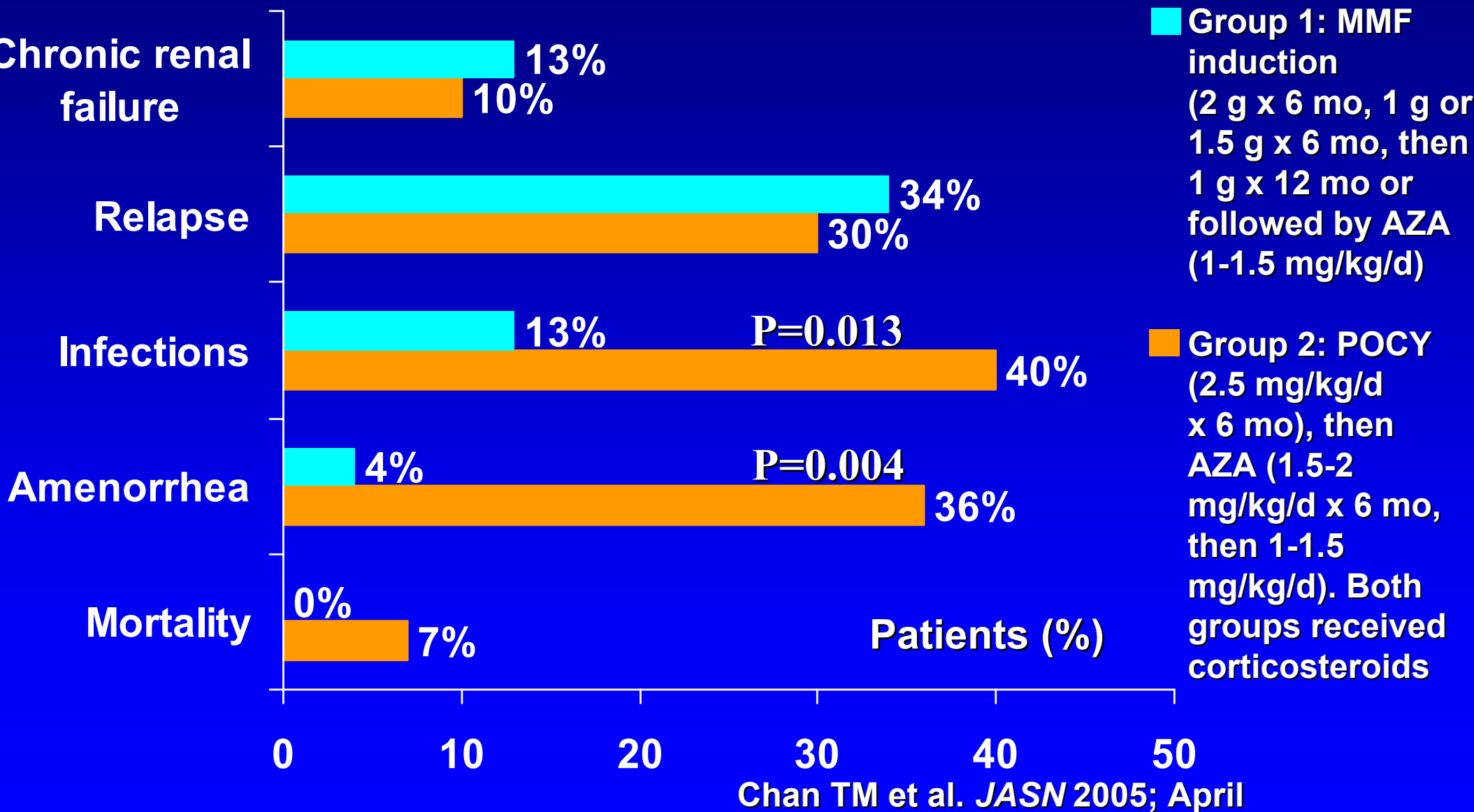
NEJM 2000;343:1156-62

Efficacy of MMF vs sequential POCY-AZA in 42 patients with diffuse proliferative lupus nephritis



Chan TM et al. *New Engl J Med* 2000; 343:1156-62.

Long-Term Study of Mycophenolate Mofetil as Continuous Induction and Maintenance (n=32) Treatment for Diffuse Proliferative Lupus Nephritis compared to Sequential POCY-AZA (n=30)



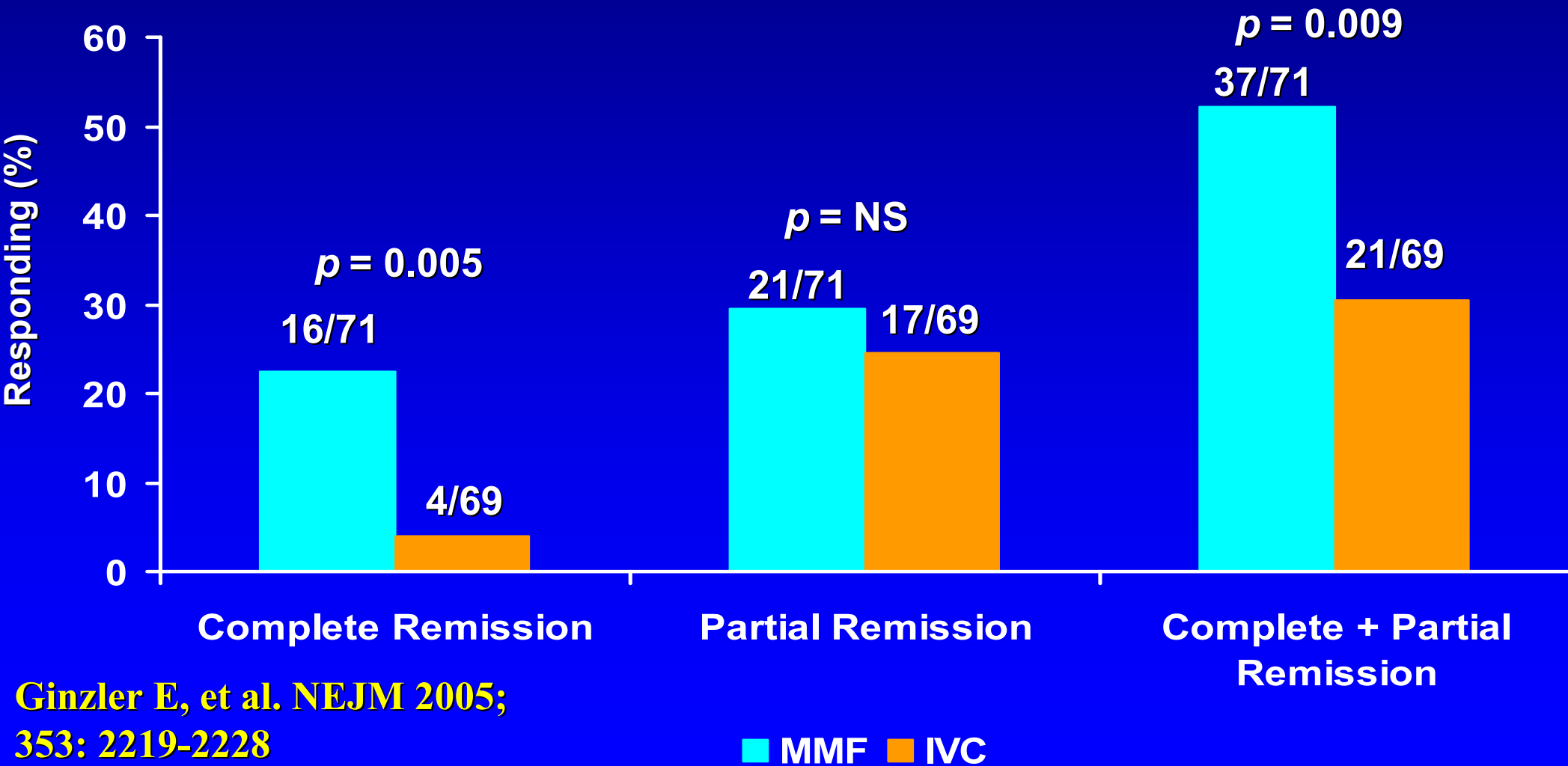
Six months induction: MMF (n=71) vs. intravenous cyclophosphamide (IVCY) (n=69) in severe lupus nephritis, FDA sponsored trial:

- **Demographics: Mean age 32,**
- **79 (56 %) African Americans**
- **90 % female**
- **Patient WHO histological characteristics**
 - Class IV, n = 76**
 - Class III, n = 22**
 - Class V, n = 27**
 - Class V + III or IV, n = 15**
- **Mean 24-hs urine protein 4.1 – 4.4 g per day**
- **Mean serum creatinine: 1.1 mg/dL**

Ginzler E, et al. NEJM 2005; 353: 2219-2228

Complete remission: at 24 weeks, return of serum creatinine, proteinuria, and urine sediment to normal

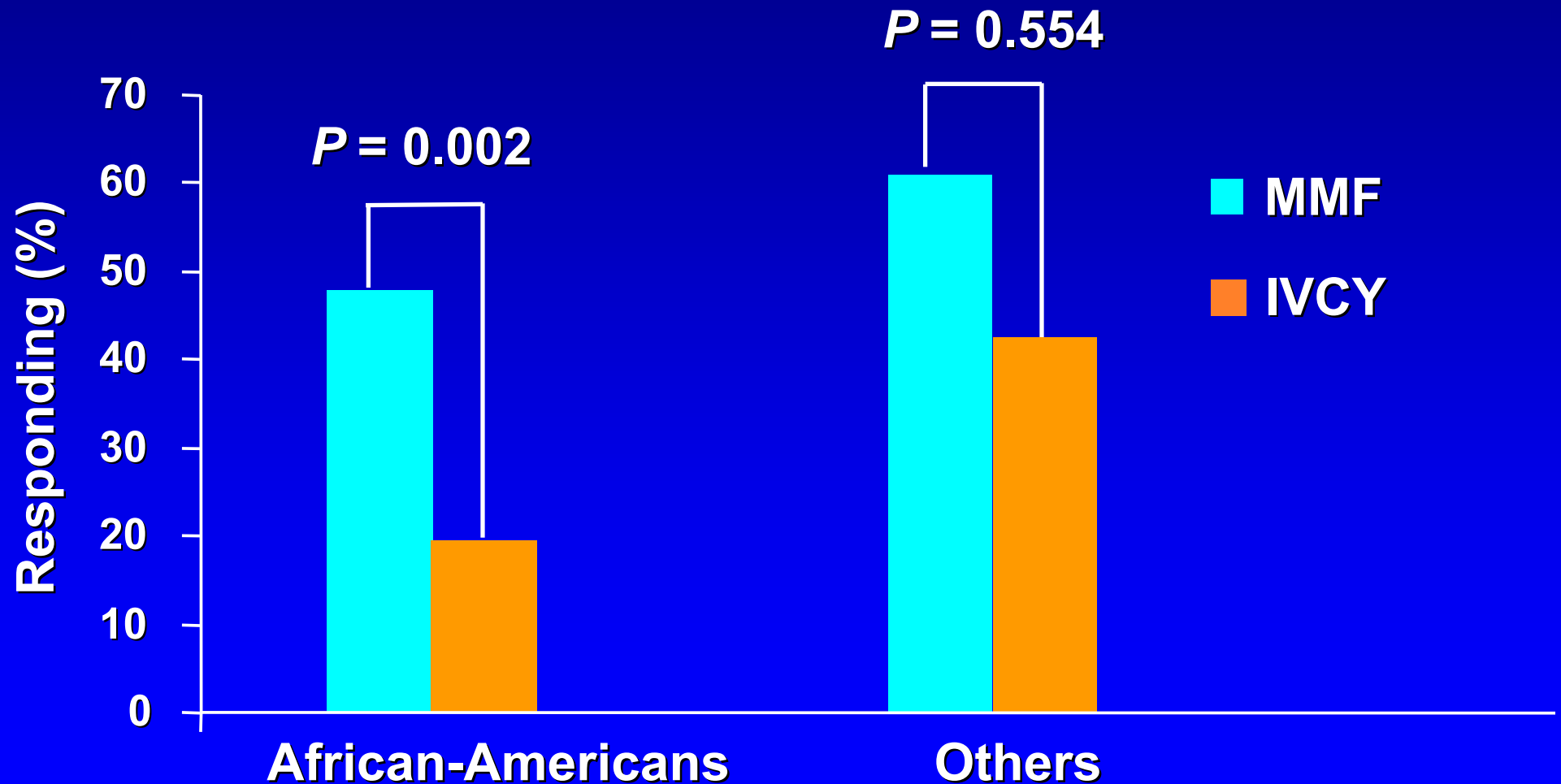
Partial remission: $\geq 50\%$ improvement in all abnormal renal parameters without worsening of any



**Ginzler E, et al. NEJM 2005;
353: 2219-2228**

MMF vs IVCY Complete + Partial Remission: African-Americans vs. Others

Intent-to-Treat analysis



Six months induction: MMF vs. intravenous cyclophosphamide (IVCY) in severe lupus nephritis, FDA sponsored trial:

Adverse events	MMF (n = 83)	IVCY (n = 75)
Severe infections	1	6
Necrotizing fasciitis	0	1
Gram-negative sepsis	0	1
Pneumonia, lung abscess	1	4
Lymphopenia (< 800/mL ³)	18	28
Neutropenia (< 1000/mL ³)	1	1
UGI (nausea, vomiting, etc)	23	25
Diarrhea	15	2
Amenorrhea	0	2
Severe rash	1	0
Alopecia	0	8
Deaths during treatment	0	3 *

* 1 patient died after declining therapy.

Ginzler E, et al.
NEJM 2005; 353:
2219-2228

Aspreva Lupus Management Study (ALMS): Induction-Phase Results

- **Between 27 July 2005 and 6 October 2006, 370 patients with SLE and active nephritis were enrolled at 88 centers in 20 countries in North America, Latin America, Asia, Australia, and Europe.**
- **Mycophenolate Mofetil (n = 185) Compared with Intravenous Cyclophosphamide (n =185)**
- **Demographics: Mean age 30 (range 12 to 75)**
- **Race: 147 Caucasian, 123 Asian, 100 Non-Caucasian/Non-Asian (from whom 46 were of African Ancestry and 54 of others mixed race)**
- **Ethnicity: 239 Non Hispanics, 131 Hispanics**
- **Female = 313**
- **Patient histological characteristics (N = 370)**
 - ISP Class IV = 225 Class V = 60**
 - Class III = 35 Class V + IV =27**
 - Class V + III = 23**
 - Active = 258**
 - Active and Chronic = 122**
- **24-hs urine protein 4.1 g and Serum Cr: 1.1 mg/dL **JASN 2009; 20: 1103-1112****

Treatment Compliance

Oral corticosteroids twice daily

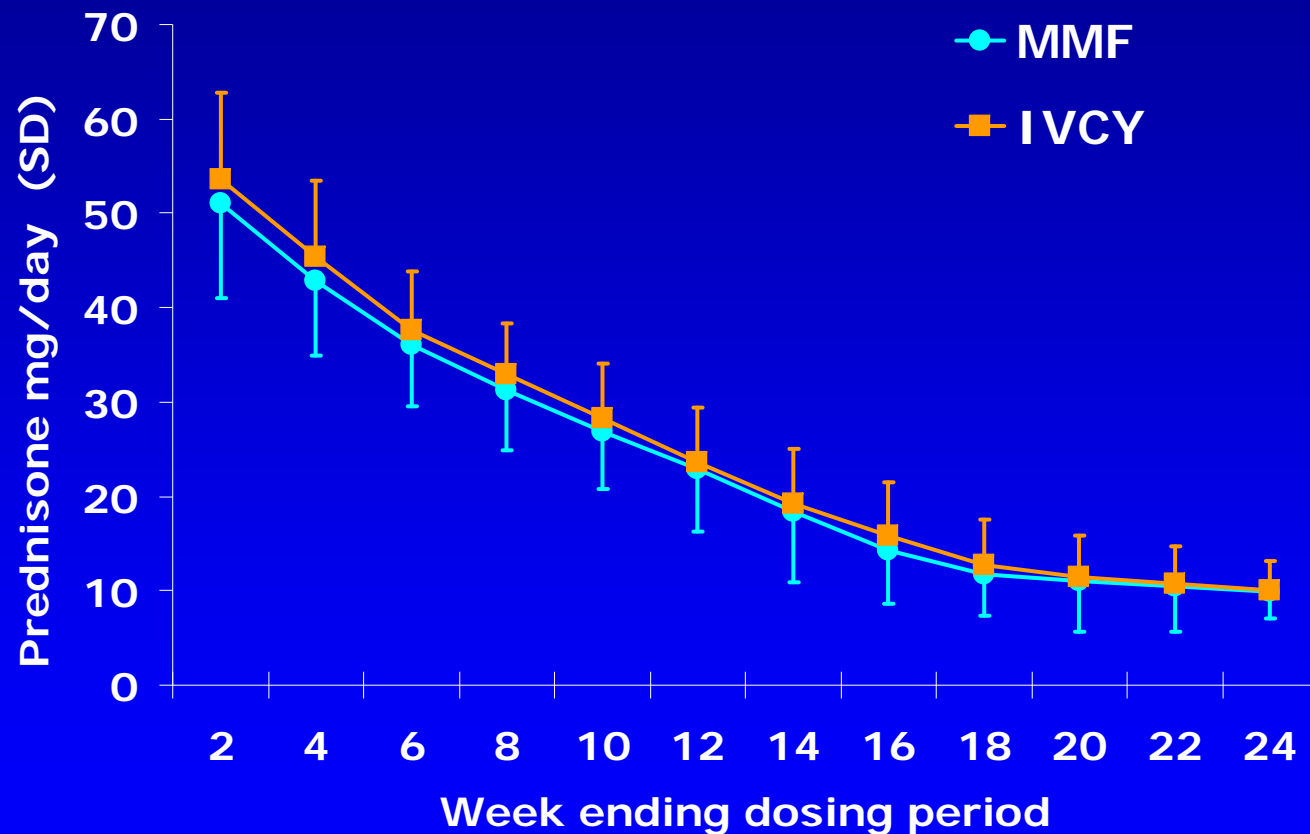
Oral MMF twice daily

Mean (SD):
2.5 (0.58) (g/day)

IVCY in monthly pulses

Mean dose per infusion:
0.78 g/m²

Mean (SD) number
infusions: 5.6 (1.1)



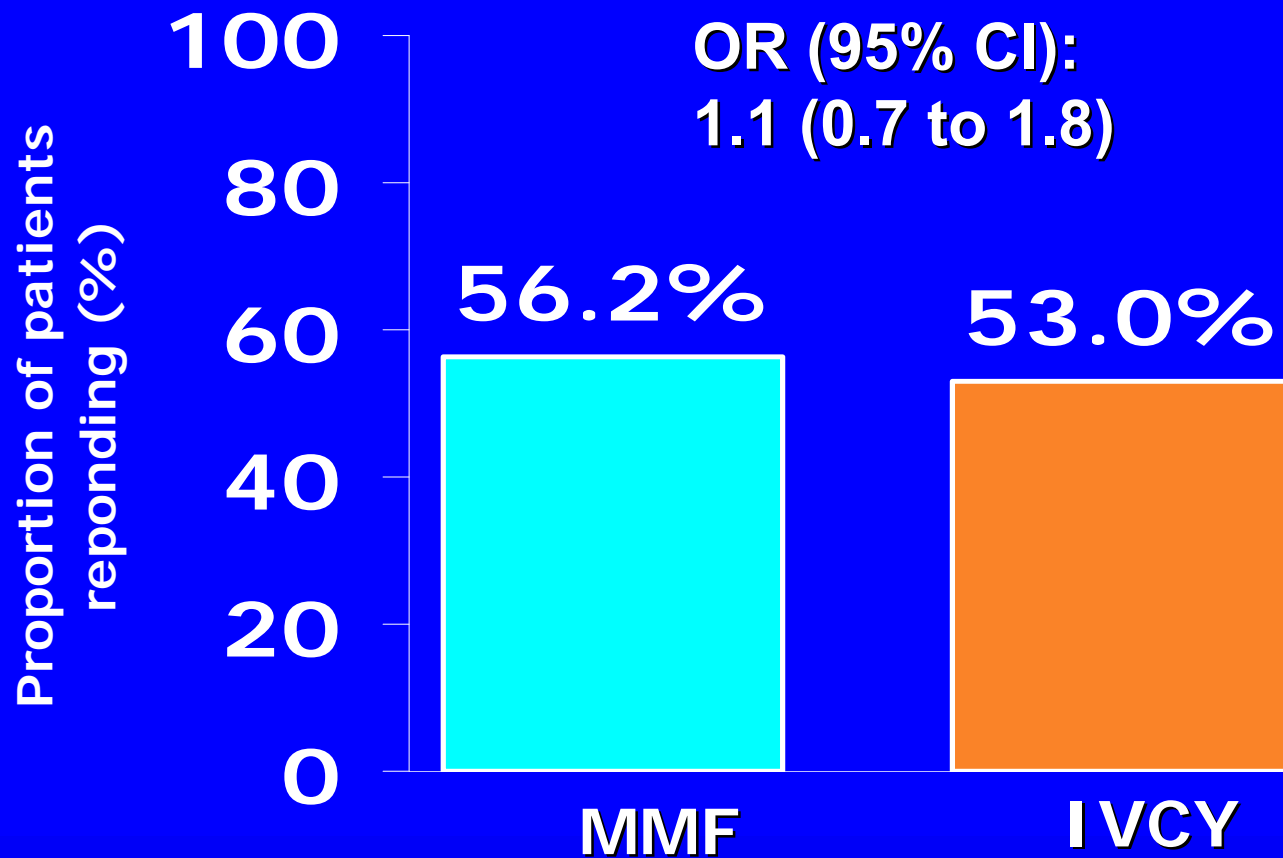
JASN 2009; 20: 1103-1112

Primary Endpoint: Responders at 6 Months

Response was judged by a blinded Clinical Endpoint Committee, by the criteria:

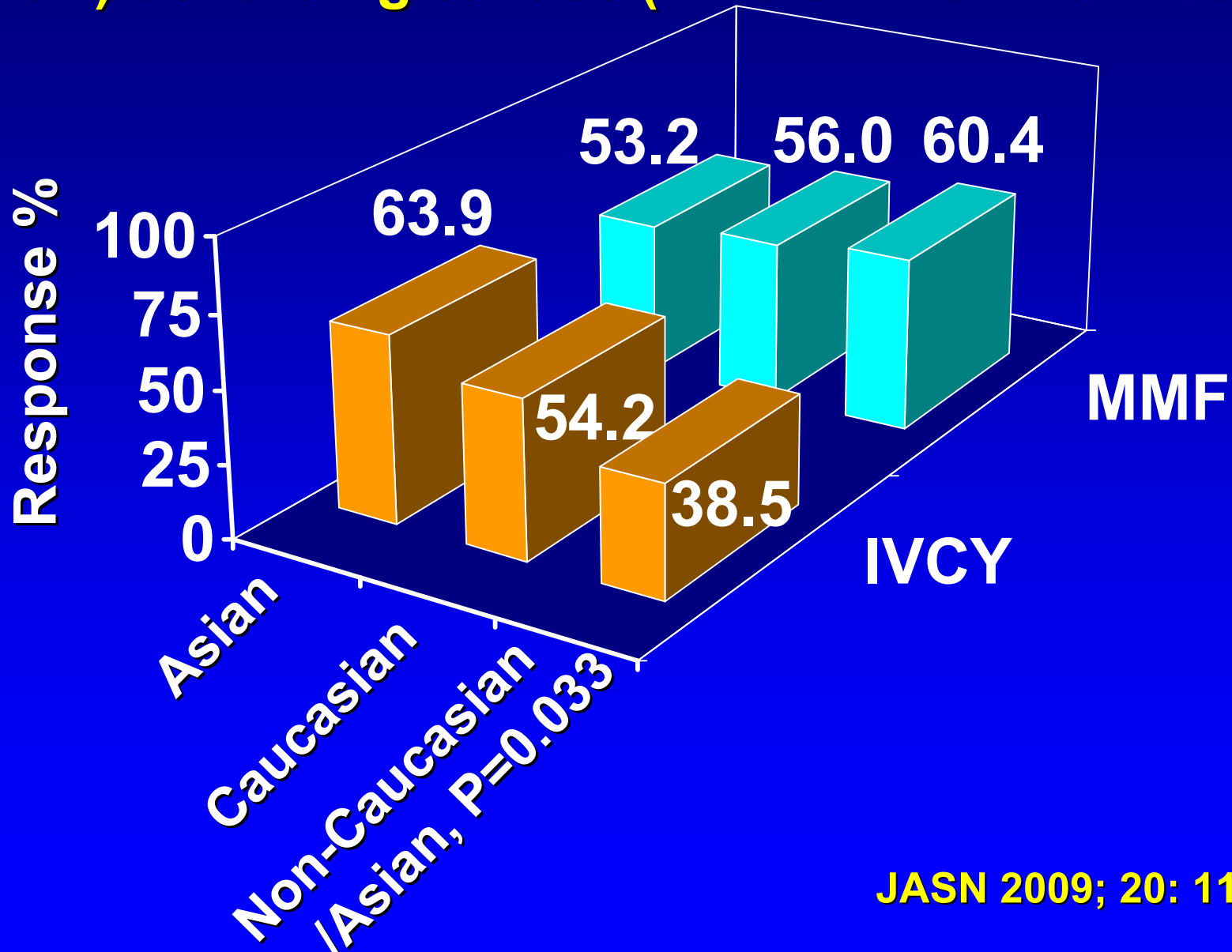
Decrease in Uprot/Ucreat to <3 in patients with baseline nephrotic (≥ 3), or by $\geq 50\%$ in patients subnephrotic (<3) proteinuria and stabilization of serum creatinine level (24-week level $\pm 25\%$ of baseline) or improvement

JASN 2009; 20: 1103-1112

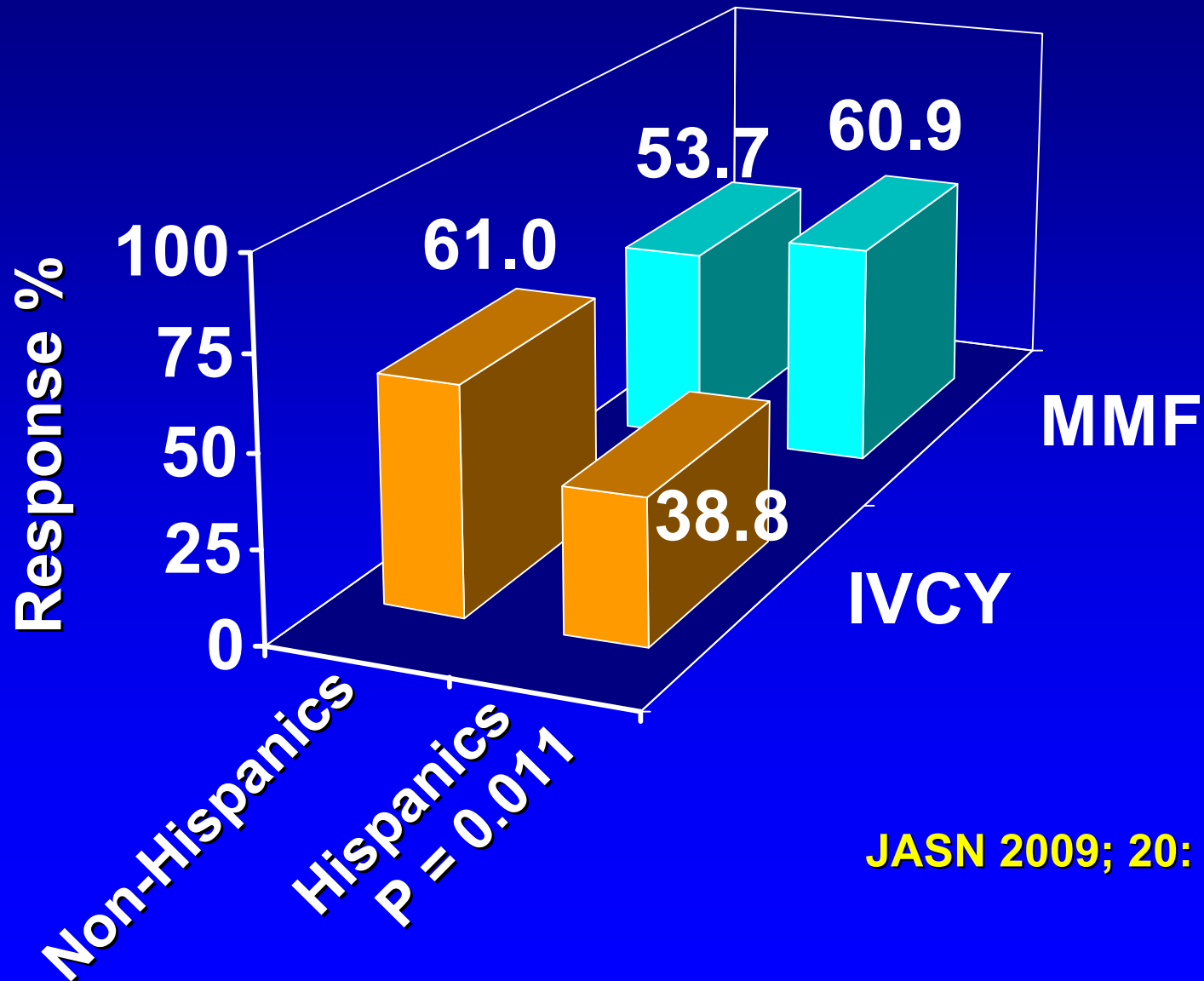


MMF was not superior to IVCP
($p = 0.575$)

Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to race (P= 0.047 for interaction)

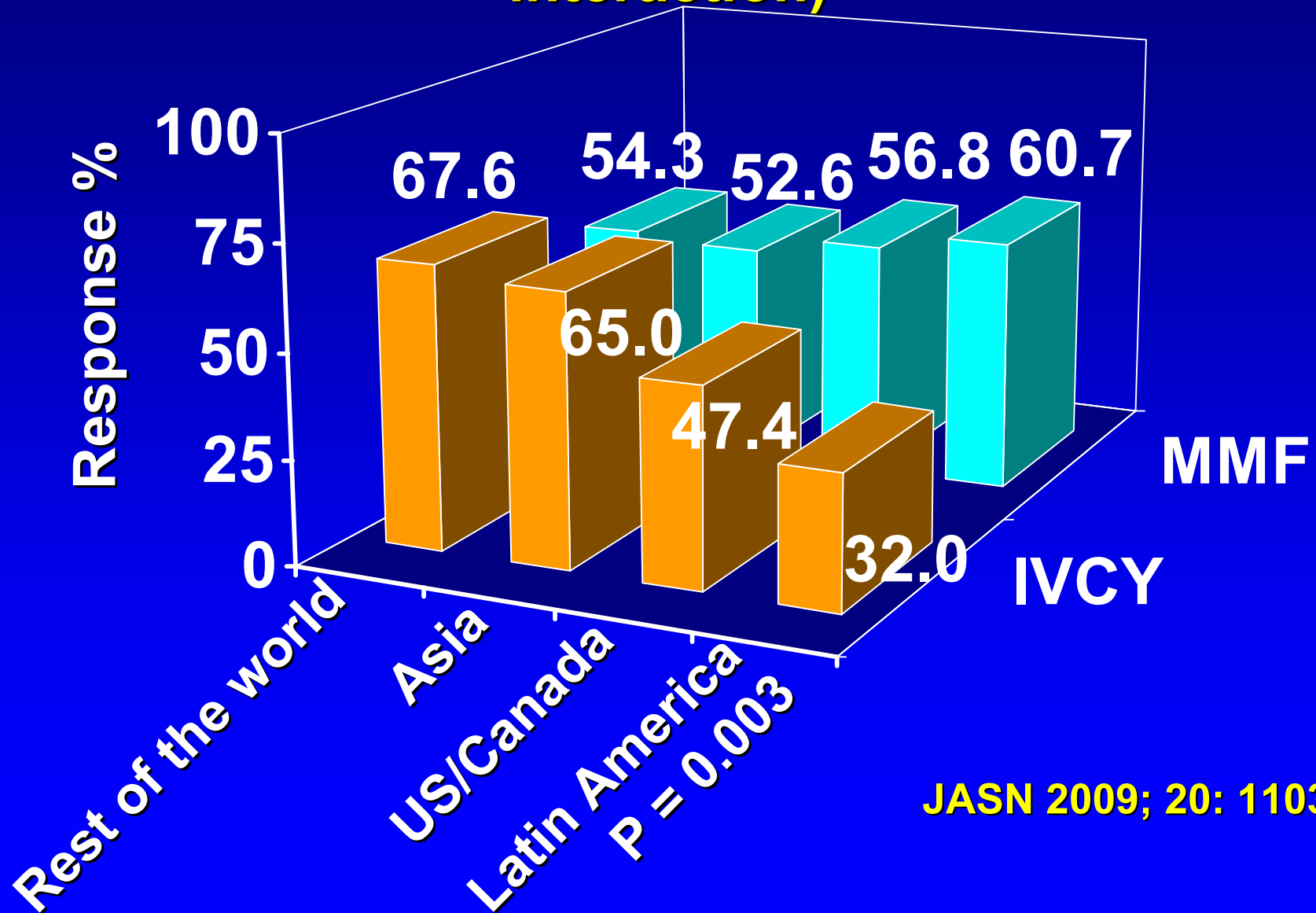


Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to Hispanic Ethnicity



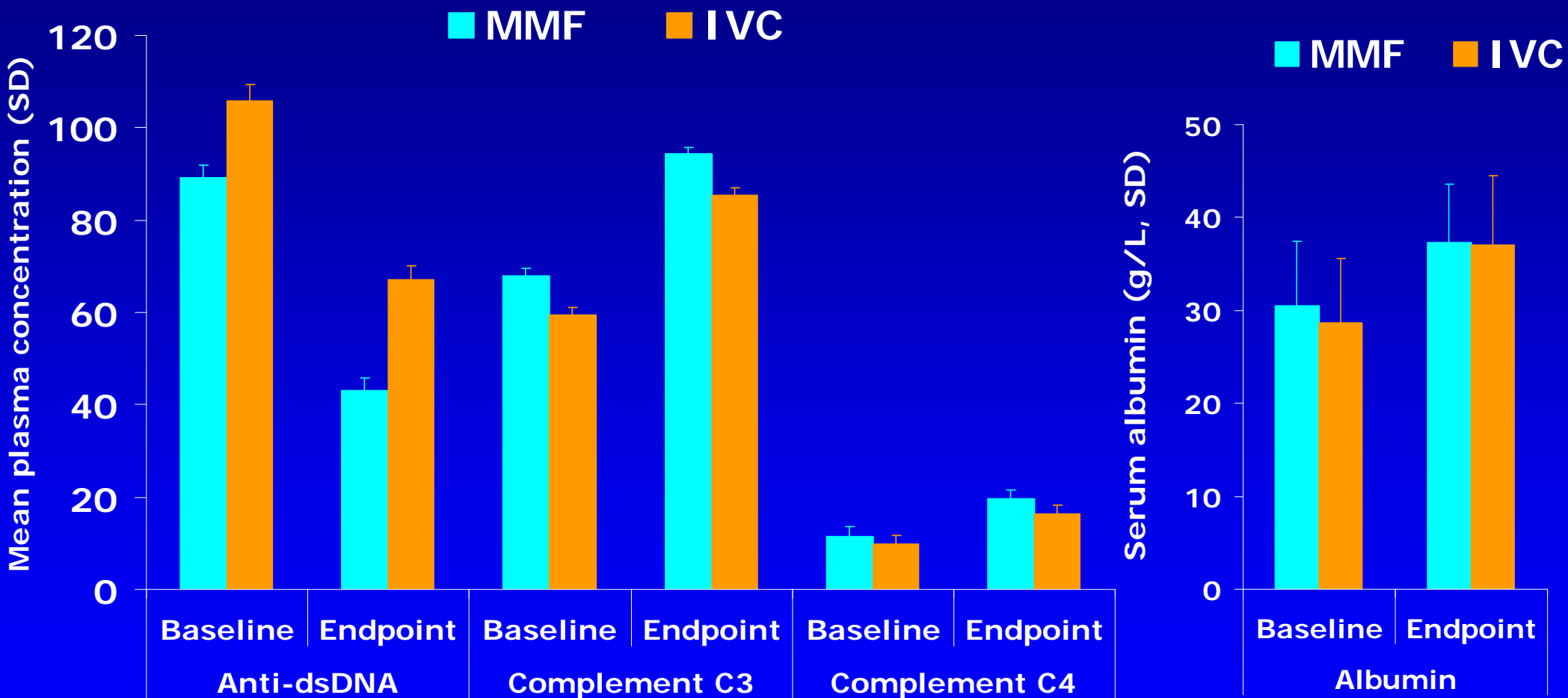
JASN 2009; 20: 1103-1112

Response to induction of patients with lupus nephritis: Mycophenolate mofetil (MMF) versus cyclophosphamide (IVCY) according to Geographic area (P=0.069 for interaction)

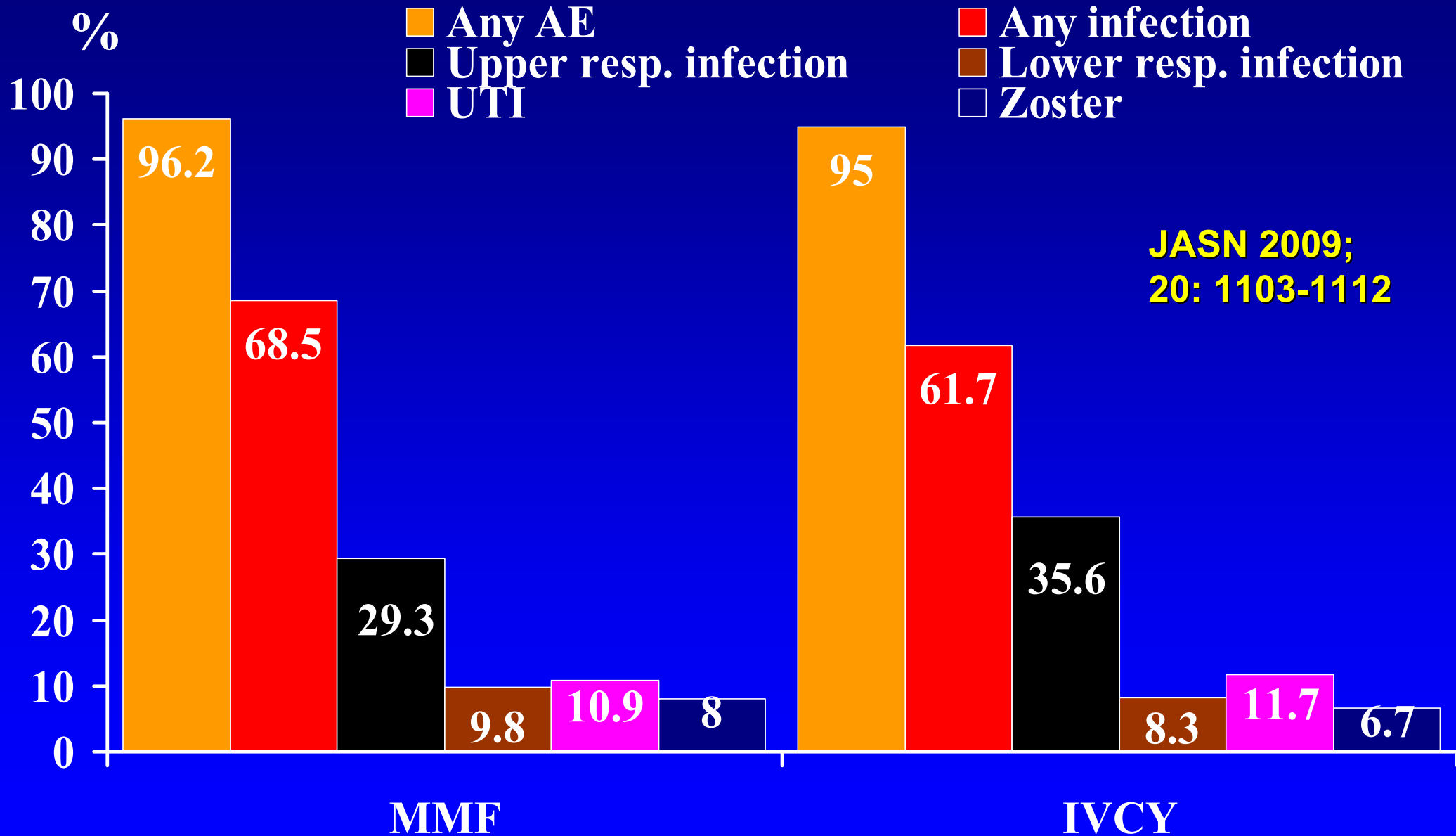


JASN 2009; 20: 1103-1112

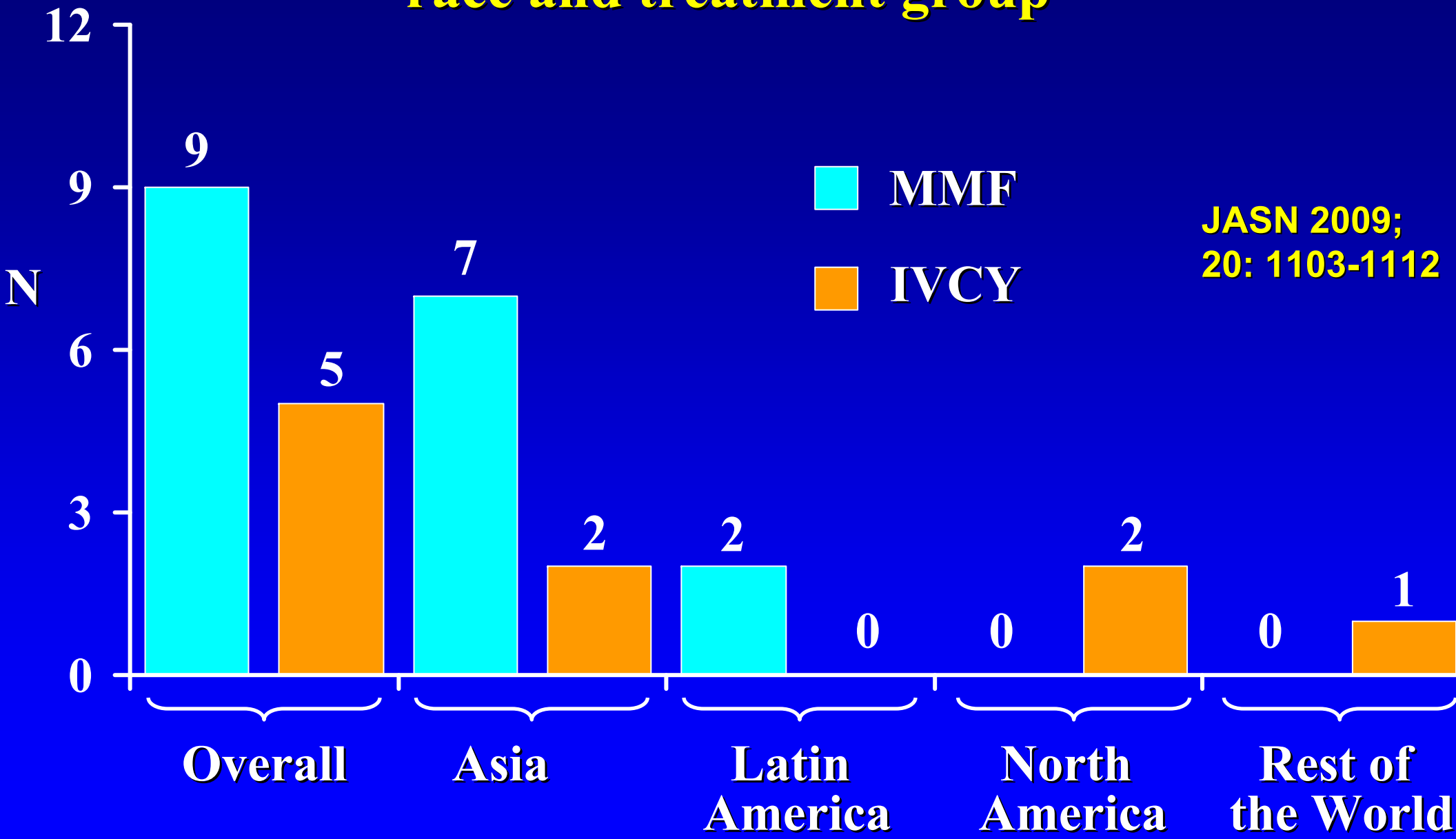
Key Non-Renal Variables



Percentage of patients reporting adverse events by treatment group



Number of deaths during induction of lupus nephritis by race and treatment group



The role of MMF Maintenance in Clinical Trials:

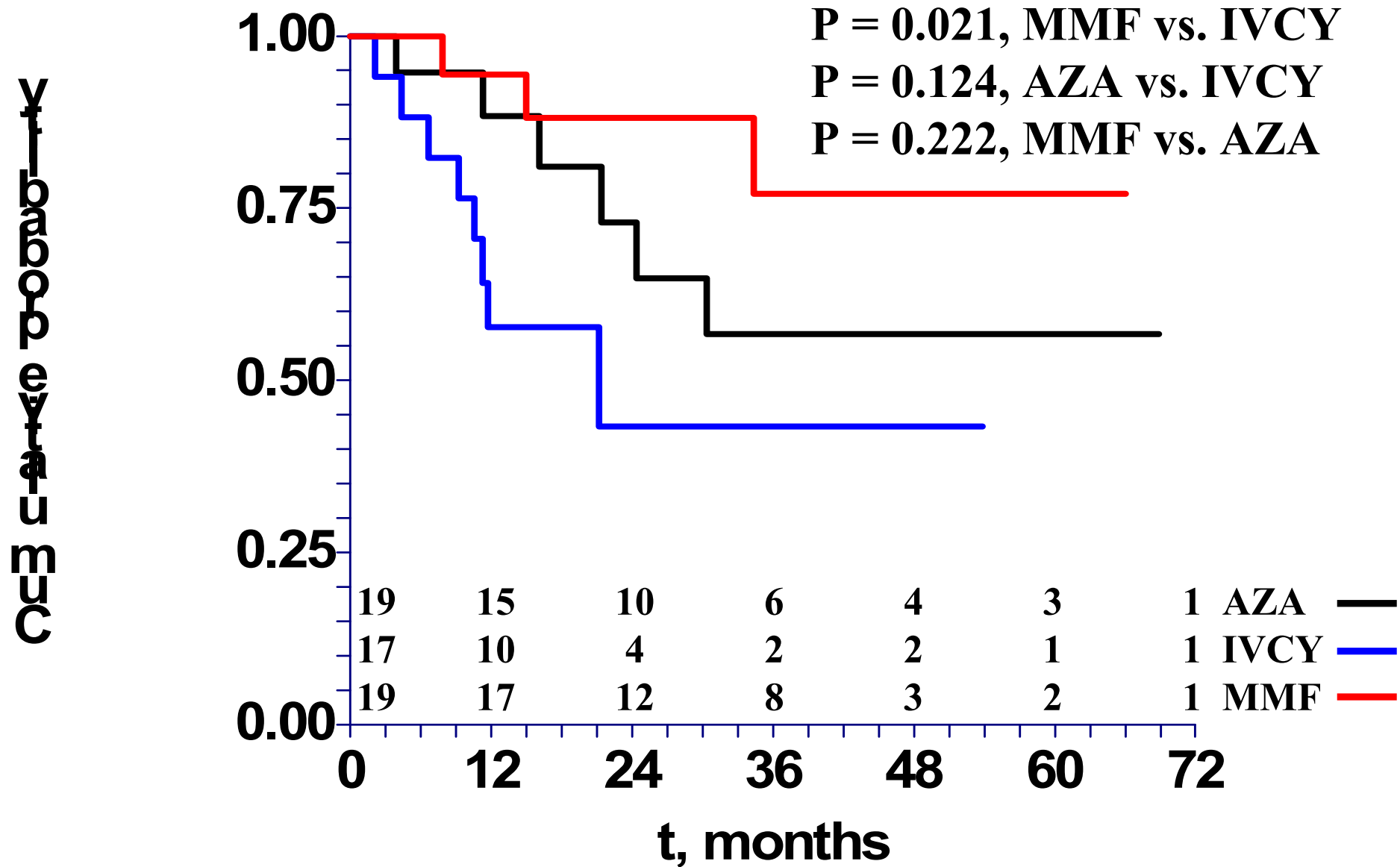
- 1. Contreras G, et al. NEJM March 2004.**
- 2. ALMS (Aspreva Lupus Management Study)**
- 3. MAINTAIN from Euro-Lupus group**

Maintenance Therapy for severe LN: quarterly IVCY vs. AZA vs. MMF after short-term IVCY induction in sequential regimens

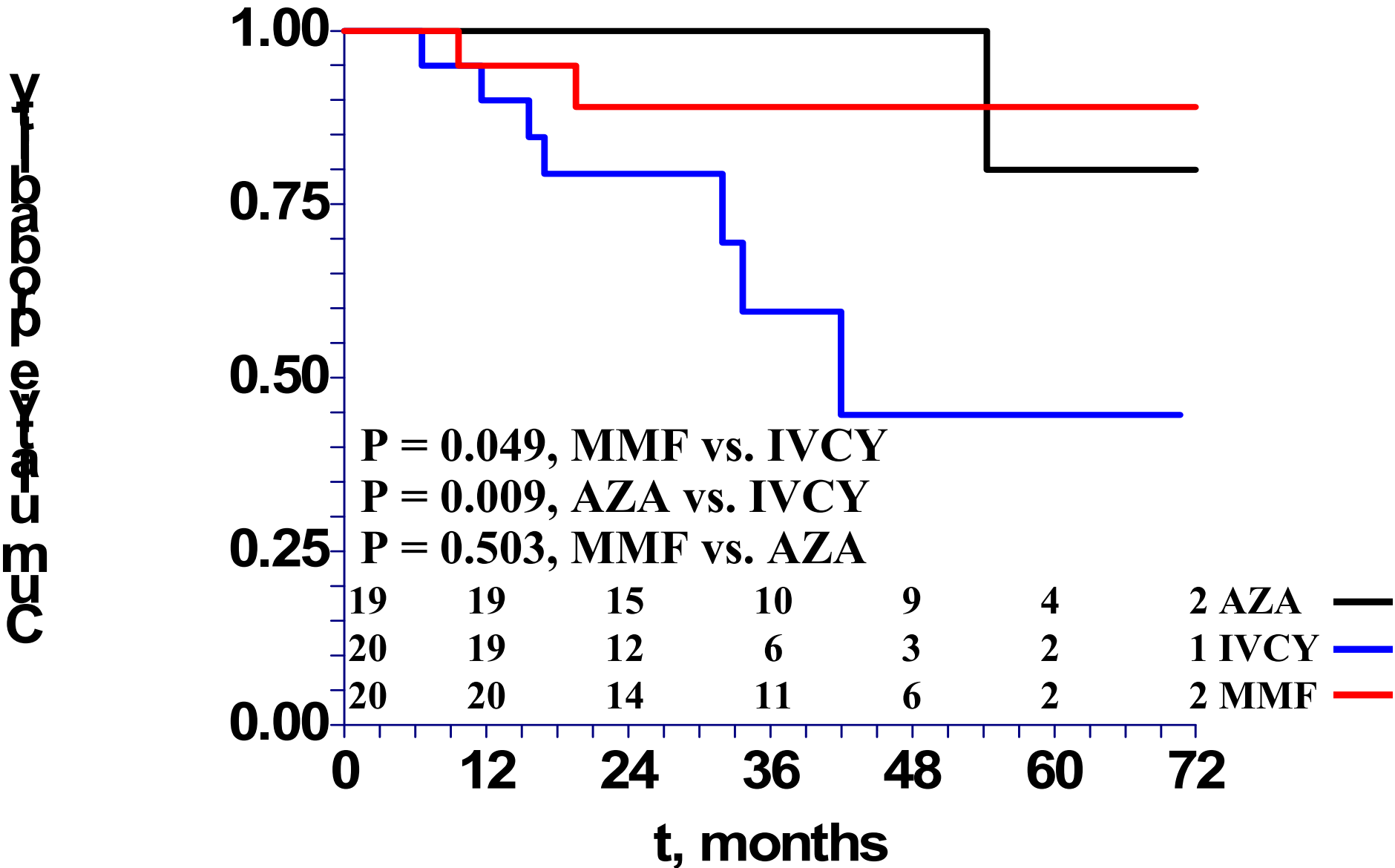
- **Patient histological characteristics (N = 59)**
 - WHO Class III n = 12 Activity Index: 8/24
 - WHO Class IV n = 46 Chronicity Index: 1.9-3.6/12
 - WHO Class Vb n = 1
- **Demographics: Mean age 33, 46% African-American, 49% Hispanics, 5% Caucasians, 93% female,**
- **95% hypertensive**
- **64% nephrotic, urine protein/Cr: > 5.0, Alb: 2.7**
- **Cr: 1.6 mg/dL,**

Contreras G, et al. NEJM. March 2004

Results (V): Free of relapse



Results (IV): Free of clinical event (death or CRF)



Maintenance therapies: IVCY vs AZA vs MMF

Hospitalizations and Side Effects of Therapy

	Hospital days per pt-yr *	Amenorrhea * %	Infections 100 pt-ys Total θ	Major Ω
IVCY	10	32	77	25
AZA	1	8	29	2
MMF	1	6	32	2

AZA or MMF vs. IVCY: * $p \leq 0.03$; $\theta p < 0.01$; $\Omega p \leq 0.02$.

Major infections: pneumonia, sepsis, meningitis.

Doses of immunosuppressant received during maintenance therapy

Visit range	AZA mg/kg/d	IVCY mg/m ²	MMF mg/d, median (95%CI)
0-6	1.2 ± 0.4	542 ± 70	1500 (1500-2000)
6-12	1.0 ± 0.5	565 ± 62	1500 (1500-2000)
12-18	1.1 ± 0.6	562 ± 106	1250 (1000-1500)
18-24	0.8 ± 0.6	530 ± 119	1000 (500-1500)
24-30	1.1 ± 0.5	644 ± 4	1000 (500-1250)
30-36	1.1 ± 0.6	541 ± 36	500 (250-500)

MMF dose = median and 95% CI. Data reported as mean ± SD.

A randomized pilot trial comparing cyclosporine (CyA) vs. azathioprine (AZA) for maintenance therapy in diffuse lupus nephritis over four years

- **Patient Histological characteristics (N = 69)**
 - WHO class IV: 60
 - WHO class Vc or Vd: 9
 - Activity Index: 7/24
 - Chronicity Index: 2.5-2.8
- **Demographics: Mean age 32, predominantly Caucasians, 90% female**
- **Mean Creatinine 0.9 mg/dL, Urine protein: 2.4 g/24 hr**

Treatment protocol

- Induction phase
 - Methylprednisolone 0.5-1.0 g IV daily x 3 followed by prednisone 0.5–1.0 mg/kg/day x 2 months
 - Oral cyclophosphamide 1-2 mg/kg/day x 3 months
- Central Randomization stratified only by center
- Maintenance phase (\approx 2 years)
 - CyA (neoral®) 4 mg/kg/day titrated to keep trough blood level 75 – 200 ng/mL, creatinine $<$ 30%+ of baseline, and aiming for proteinuria $<$ 1 g/day
 - AZA 1.5 - 2 mg/kg/d titrated to keep WBC $>$ 4000/mm³
 - During maintenance, patients received $<$ 0.5 mg/kg/d prednisone

Primary outcome: overall incidence of SLE relapse over 2 years

	CyA, N=36	AZA, N=33
Nephritic relapse, N	1	1
Proteinuric relapse, N	4	6
Extra-renal relapse, N	2	1
Overall, N	7	8
Overall SLE relapses per 100 pts-ys	10.6	13.4
Overall exposure pts-ys	65.9	59.8

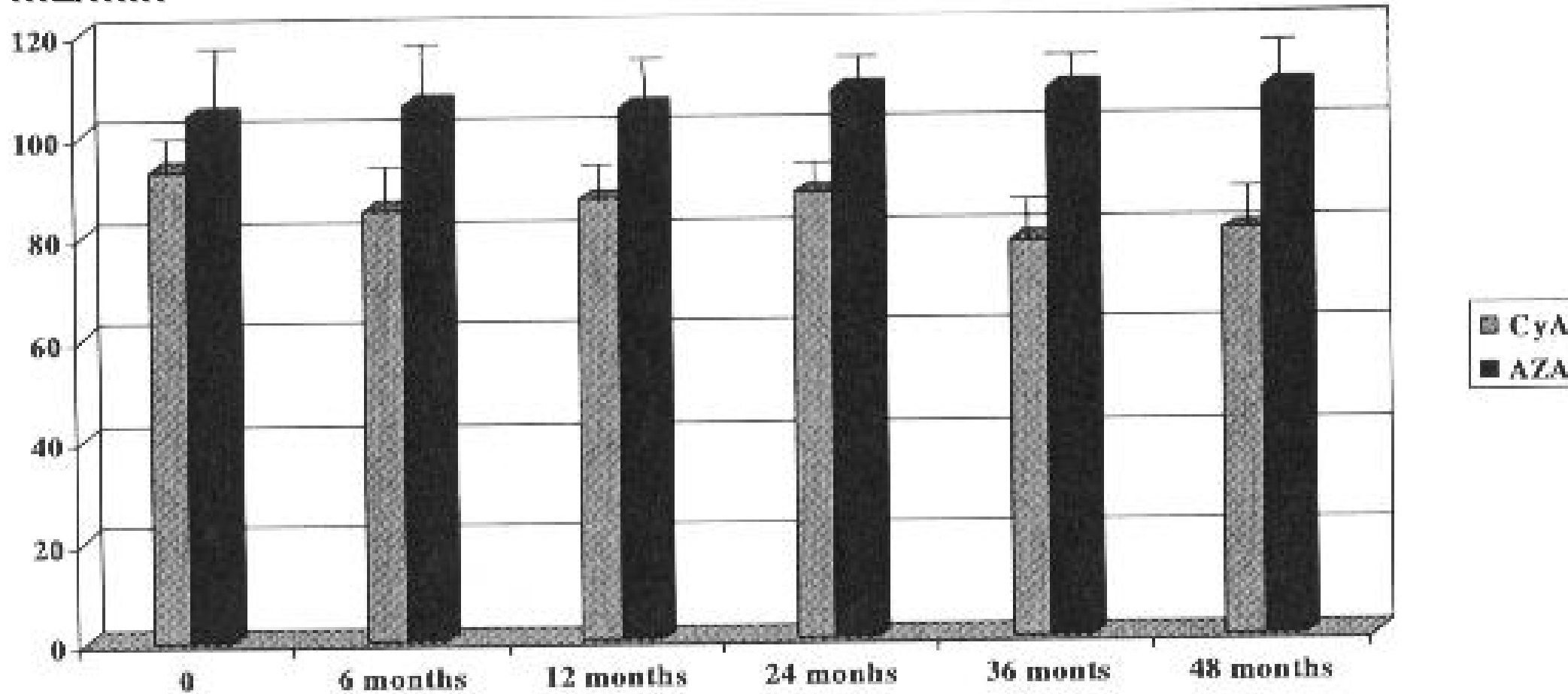
Nephritis relapse: \uparrow creatinine $\geq 30\%$ of baseline accompanied \uparrow proteinuria and/or active urine sediment (≥ 5 RBC x HPF).

Proteinuric relapse: \uparrow proteinuria of at least 2g/day (if prior level ≤ 3.5) or doubling proteinuria.

Moroni G, et al. CJASN. In press

A randomized pilot trial comparing cyclosporine (CyA) vs. azathioprine (AZA) for maintenance therapy in diffuse lupus nephritis over four years

CrCl
mL/min



Adverse events	CyA, incidence events per 100 pts-ys	AZA, incidence events per 100 pts-ys
Leukopenia	6.1	16.7
Infections	10.6	23.4
Anemia	7.6	8.4
Hypertension	10.6	8.4
HTN crisis	1.5	0
↑ Cholesterol	3	6.7
Diabetes	0	1.7
Hyperkalemia	1.5	0
Gum hyperplasia	3	0
Hypertrichosis	3	0
Arhtralgias	21.2	5
GI disorders	16.7	5

Questions:

Induction:

What do we start with? CY or MMF?

Is MMF efficacious as prolong induction-maintenance therapy in Caucasian, African-American and Hispanic populations?

Should we switch to maintenance therapy when achieving complete or partial remission?

Are there adjuvant therapies that consolidate complete remission?

Questions:

Maintenance:

Is Mycophenolate Mofetil superior to Azathioprine or Calcineurin Inhibitors?

Should we continue exposing patients to long-term Cyclophosphamide?

Can we stop maintenance therapy after 3 years?