The Role of MMF in Lupus Nephritis : Is there any place left for cyclophosphamide?

GERALD APPEL, MD

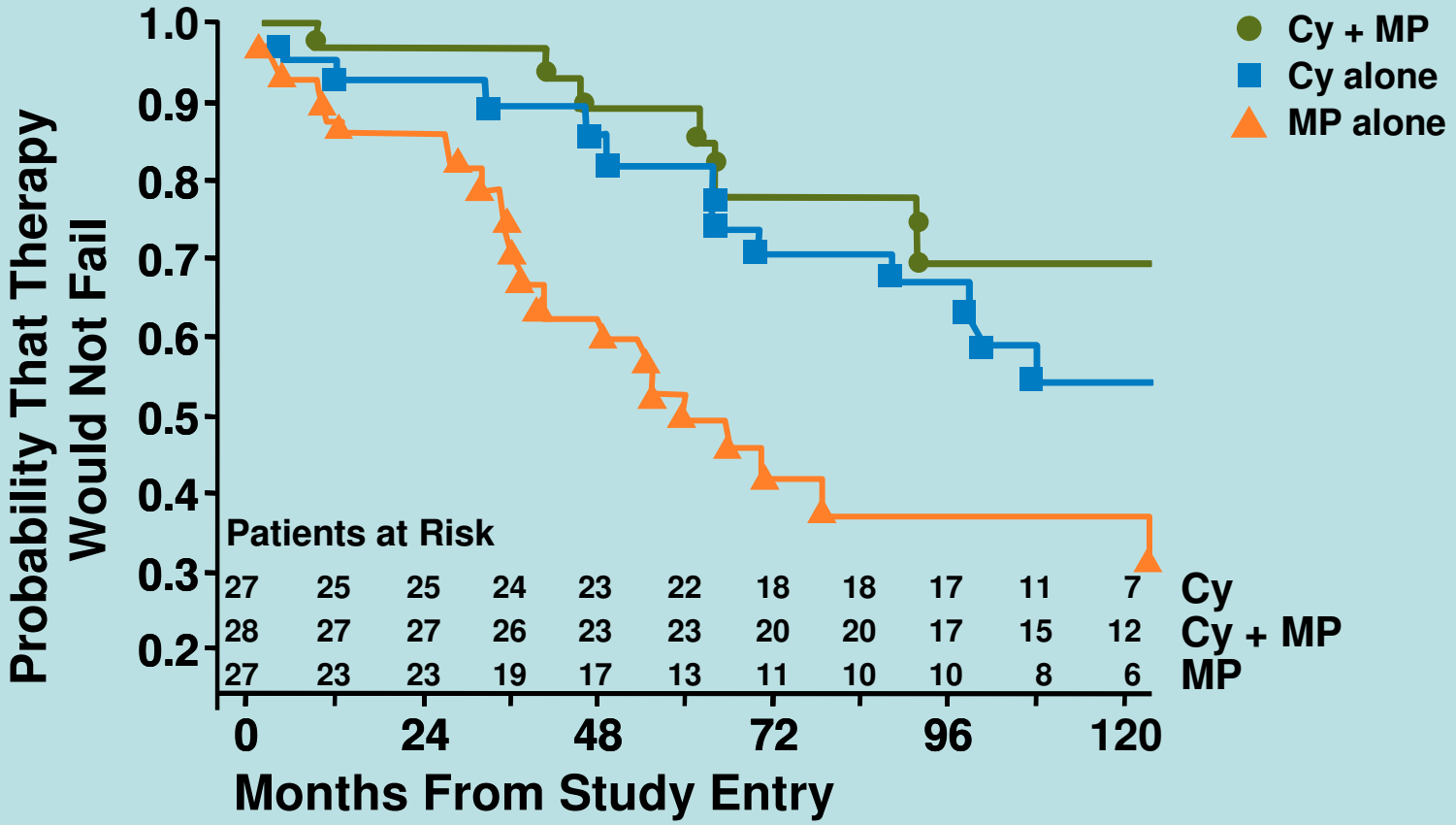
Professor of Clinical Medicine
Columbia University –College of Physicians and Surgeons
NY-Presbyterian Hospital
New York, New York

Questions to be Answered

- **Why did we need alternate therapy to cyclophosphamide ? Efficacy? Toxicity?**
- **Did mycophenolate mofetil prove equally effective to cyclophosphamide?**
- **Did mycophenolate mofetil have fewer side effects?**
- **Does MMF work in severe DPLN?**
- **What is the role of MMF vs cyclophosphamide used in EuroLupus like regimens?**

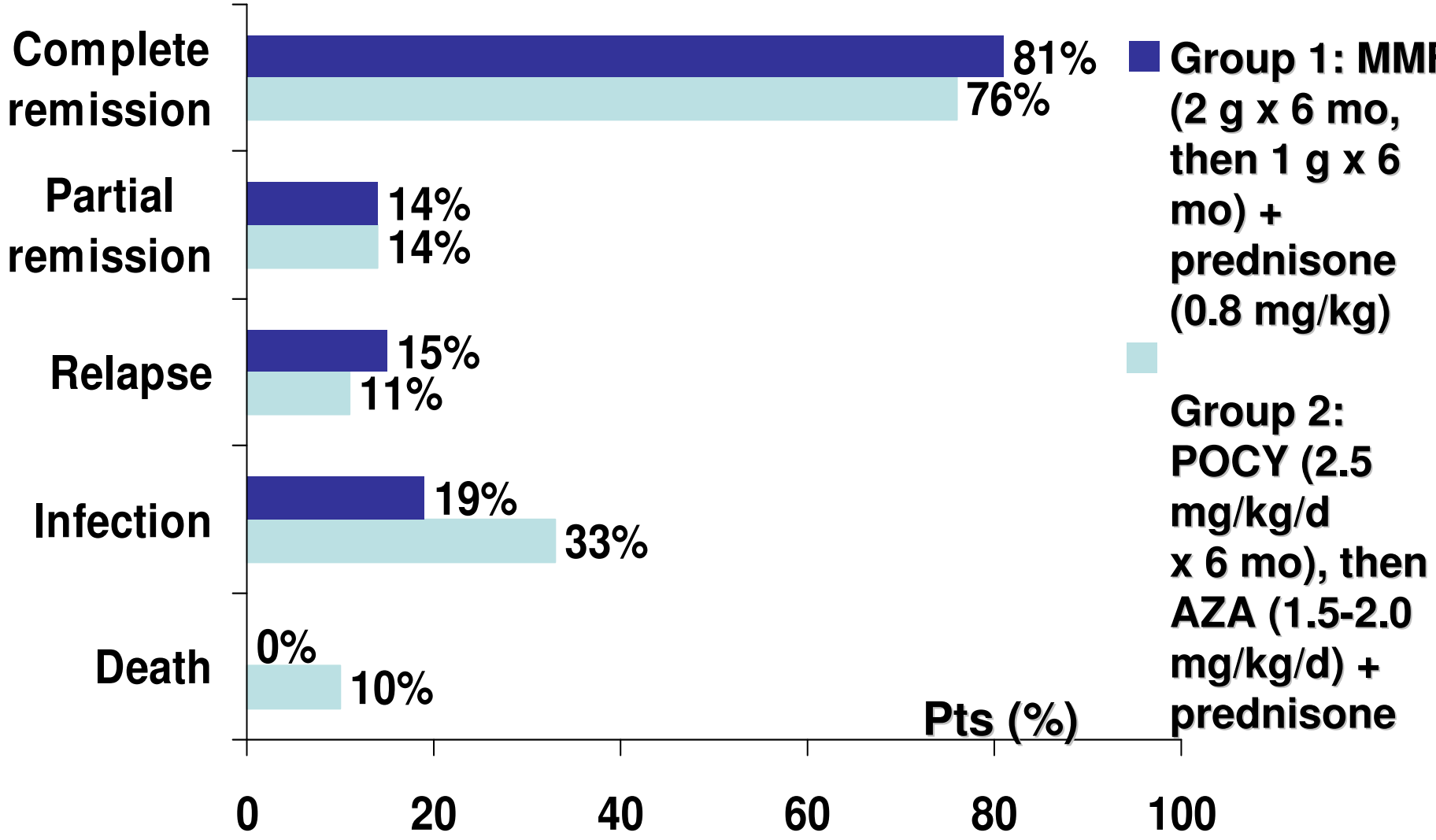
Kaplan-Meier Analysis of Failure of Therapy

Illei GG, et al. Ann Intern Med. 2 001



Event	Cy Therapy (n = 21)	Combination Therapy (n = 20)
	n/n	n/n
Hypertension	10/20	10/20
Ischemic heart disease	1/19	4/19
Hyperlipidemia	7/20	8/19
Valvular heart disease	9/19	7/21
Avascular necrosis	6/21	6/20
Osteoporosis	4/18	3/19
Premature menopause	9/16	10/18
Major infections	7/21	9/20
Herpes zoster infection	6/21	5/20

Efficacy of MMF vs sequential POCY-AZA in 42 patients with DPLN



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

Sequential Therapy for Proliferative LN IV Cy Induction – IV Cy vs. AZA vs. MMF Maintenance

N = 59 93% F 33 yo 46% AA

WHO III = 12 WHO IV = 46 Vb = 1

AI > 8 / 24 CI 1.9 - 3.6

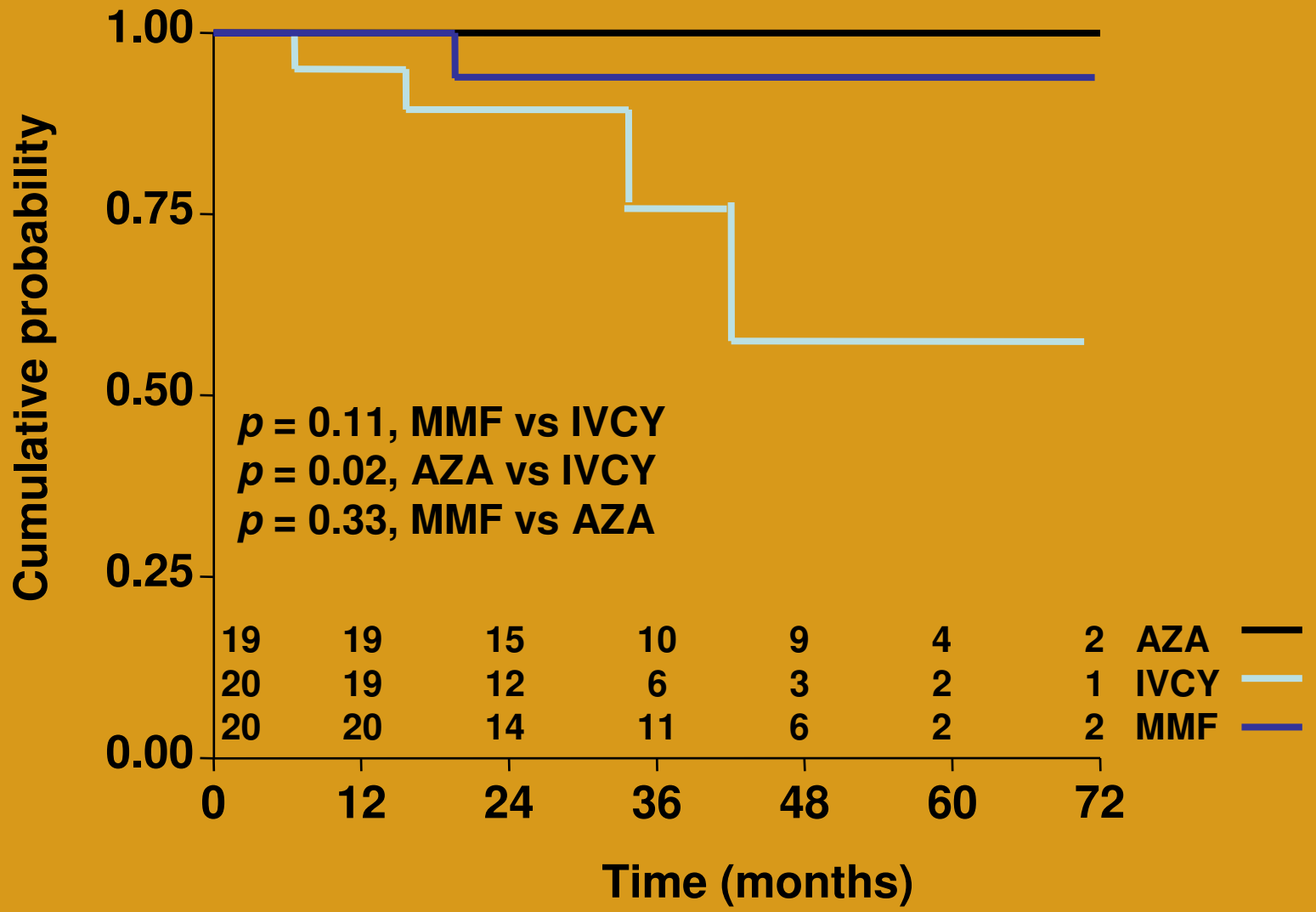
HBP > 95% Active Serology

Neph Synd 64% Palb 2.7 g/dl Up/Ucr > 5

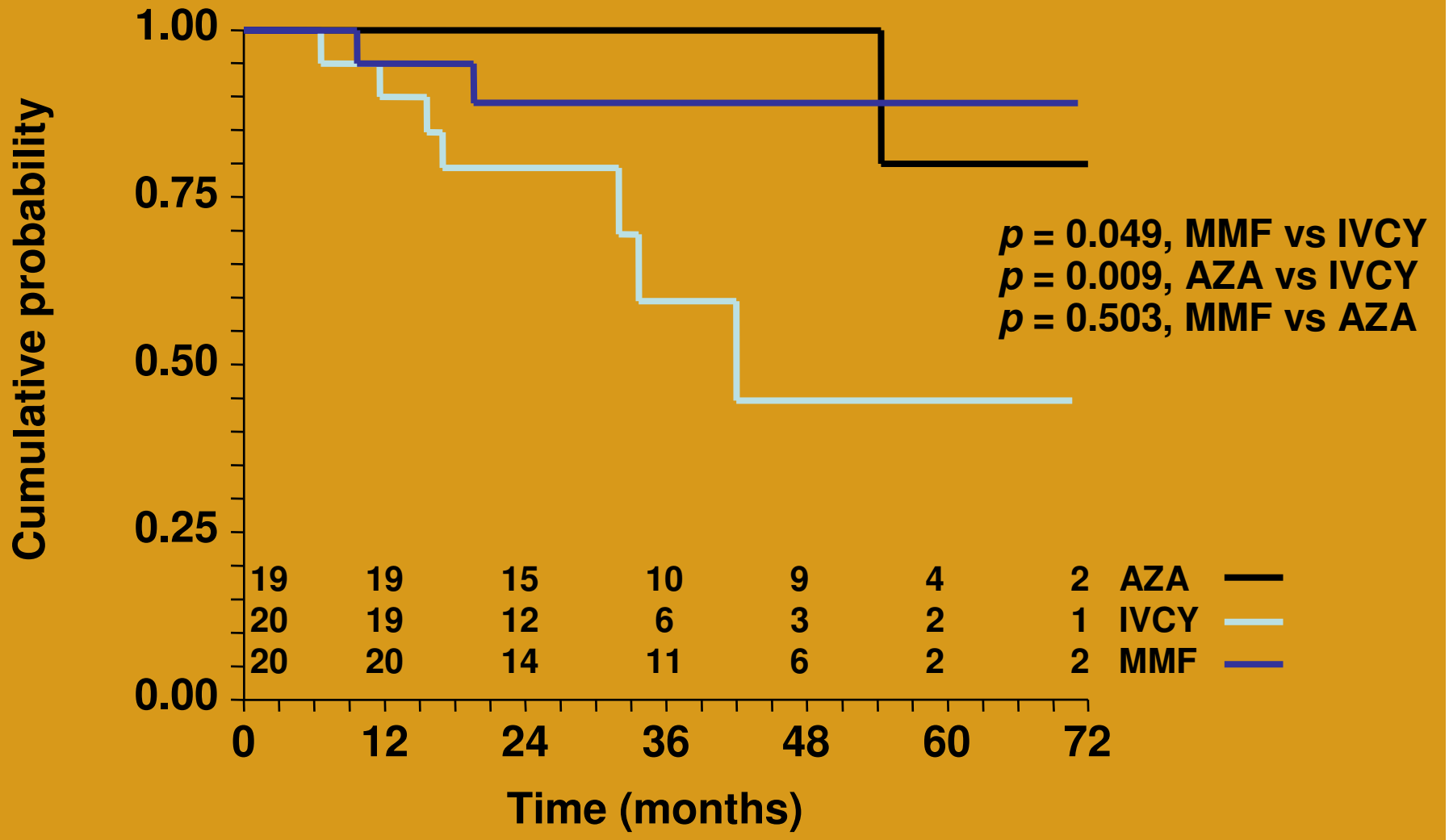
Pcreat 1.6 g/dl

U. Miami G. Contreras et al. NEJM 2004

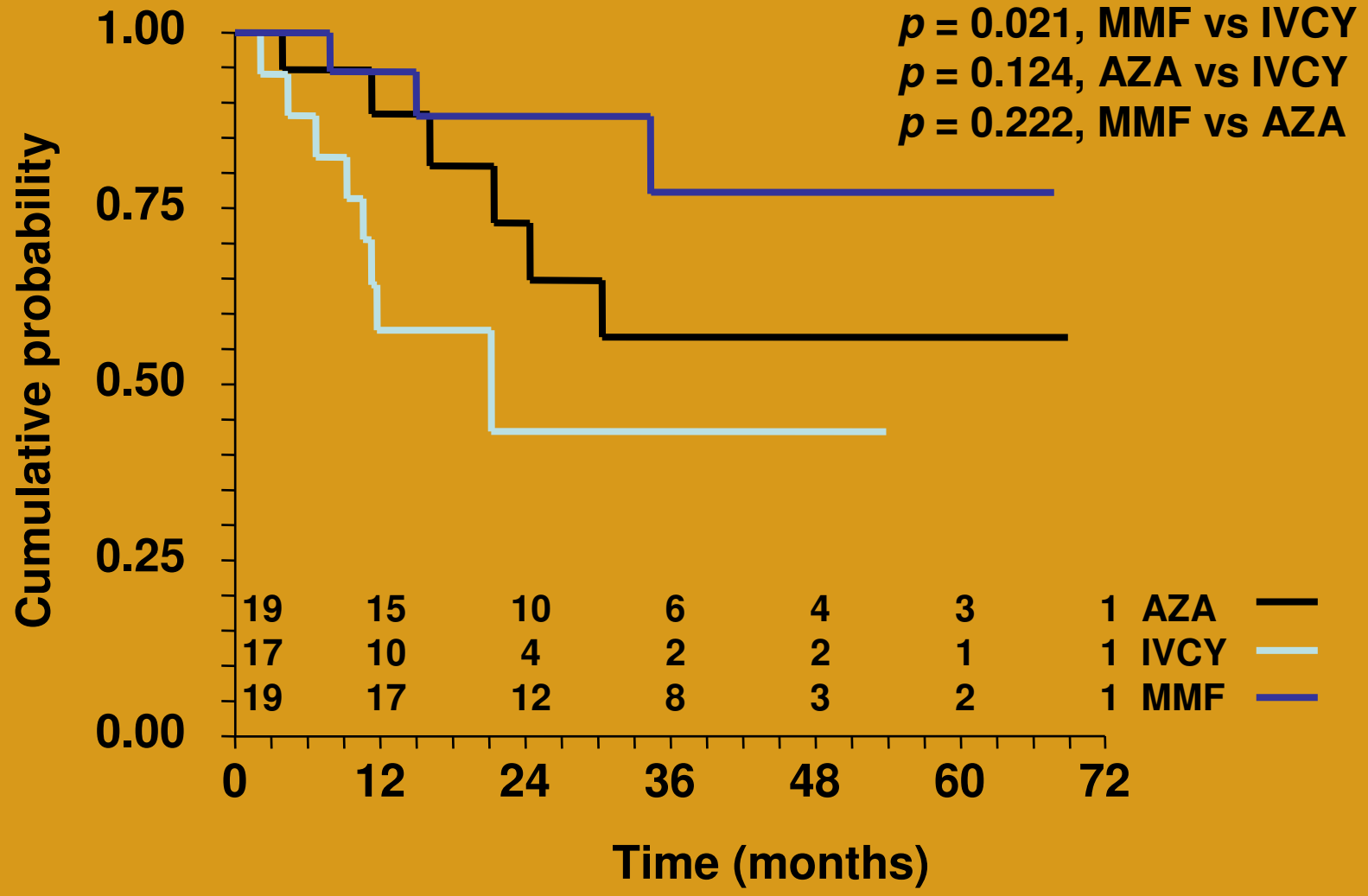
Patient survival



Free of clinical event (death or CRF)



Relapse during maintenance phase – Free of Relapse



Sequential LN Rx: IV CY vs AZA vs MMF Maintenance Therapy

Side Effects of Therapy

	Hospital Days Per Patient Year	Amenorrhea (%)	Infection (%)	Major (%)
IV CY	13	32	68	12
AZA	1*	7*	28*	3
MMF	1*	6*	21*	3

Contreras G, et al. NEJM 2004

Multicenter Trial of MMF vs IVCyc for Induction Therapy of Severe LN

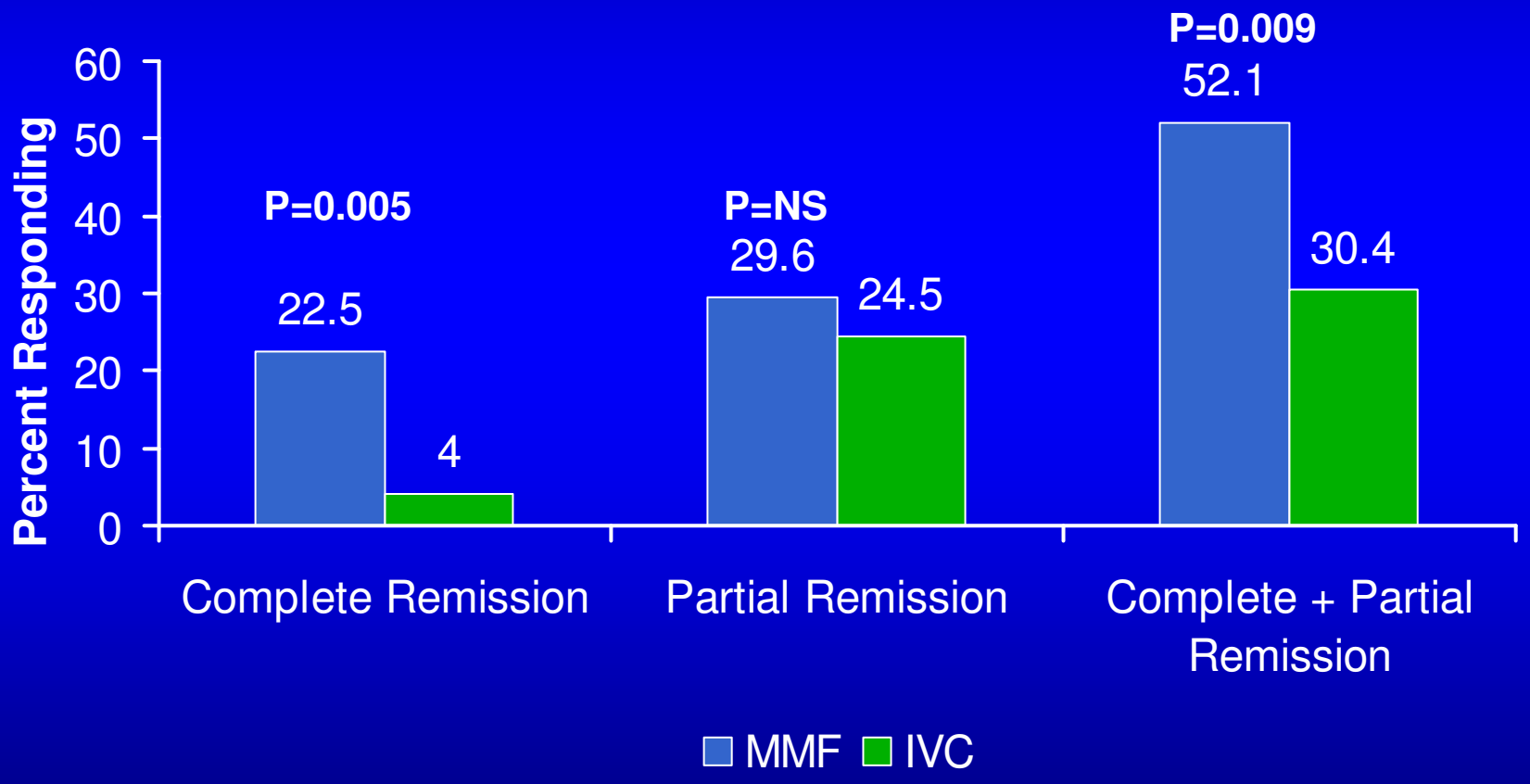
- Multicenter, randomized, nonblinded trial of induction RX of 140 patients with severe active LN
- Designed as equivalence trial
- Hypothesis: MMF has equivalent efficacy with superior tolerability profile vs. Intravenous cyclophosphamide
-

Ginzler E. … Appel G N Eng J Med Nov. 2005

Baseline Patient Characteristics

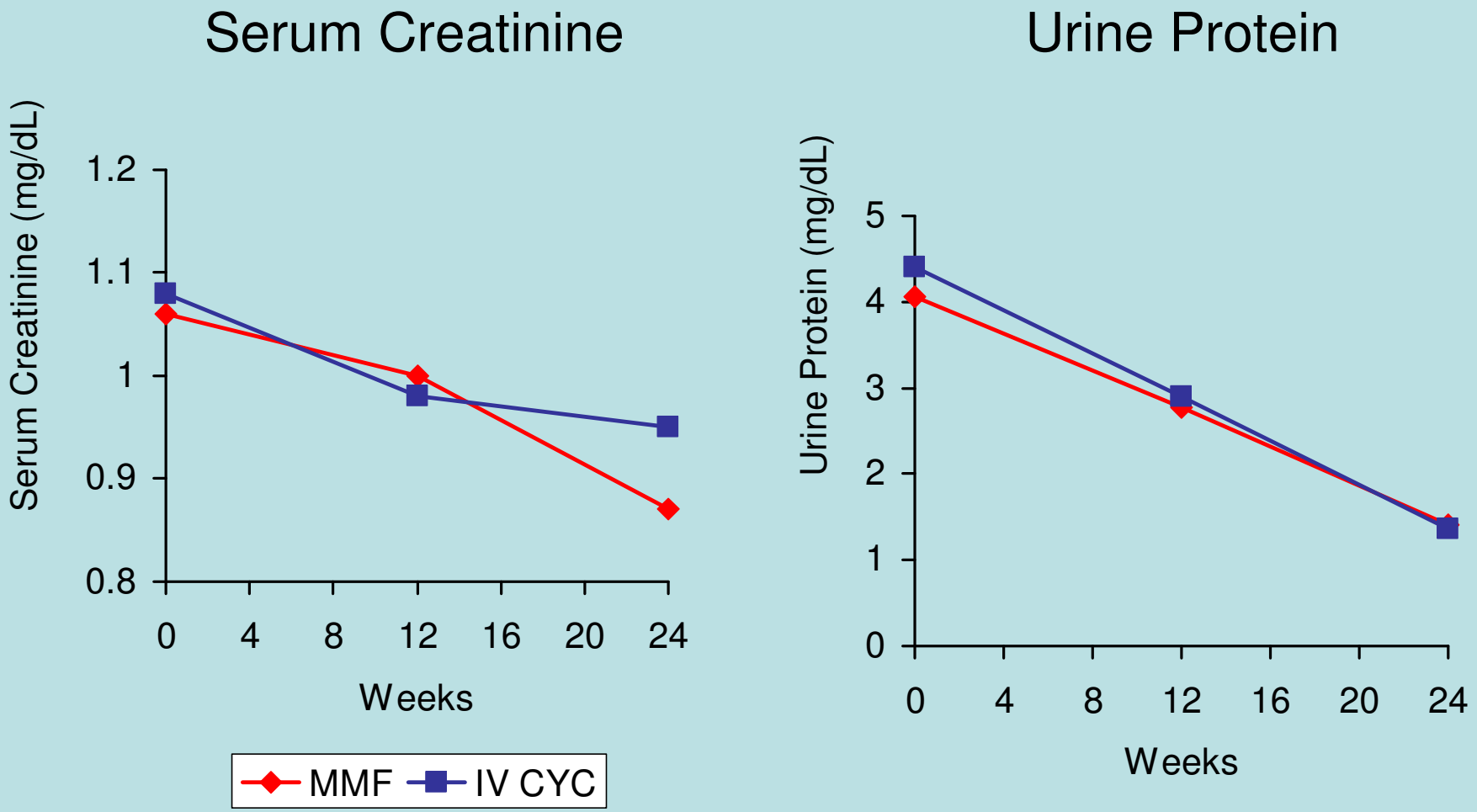
	MMF (n=71)	IVC (n=69)
Age (yrs)	32.5 ± 10.0	31.0 ± 9.0
Female	61 (86%)	65 (94%)
Black	43 (61%)	36 (52%)
Duration of SLE, mo.	43.72 ± 66.88	58.70 ± 80.64
Screatinine, mg/dL	1.06 ± 0.52	1.08 ± 0.49
Urine protein, g/24 hr	4.06 ± 3.14	4.41 ± 3.51
Urine sediment		
RBC/hpf	24.1 ± 50.3	33.2 ± 115.5
WBC/hpf	12.6 ± 23.5	10.3 ± 17.3
Salbumin, g/L	2.81 ± 0.95	2.69 ± 0.56

Remission Rates: MMF vs. IVC
Intent to treat analysis



Ginzler E. … Appel G N Eng J Med Nov. 2005

Change in Serum Creatinine and Urine Protein Excretion



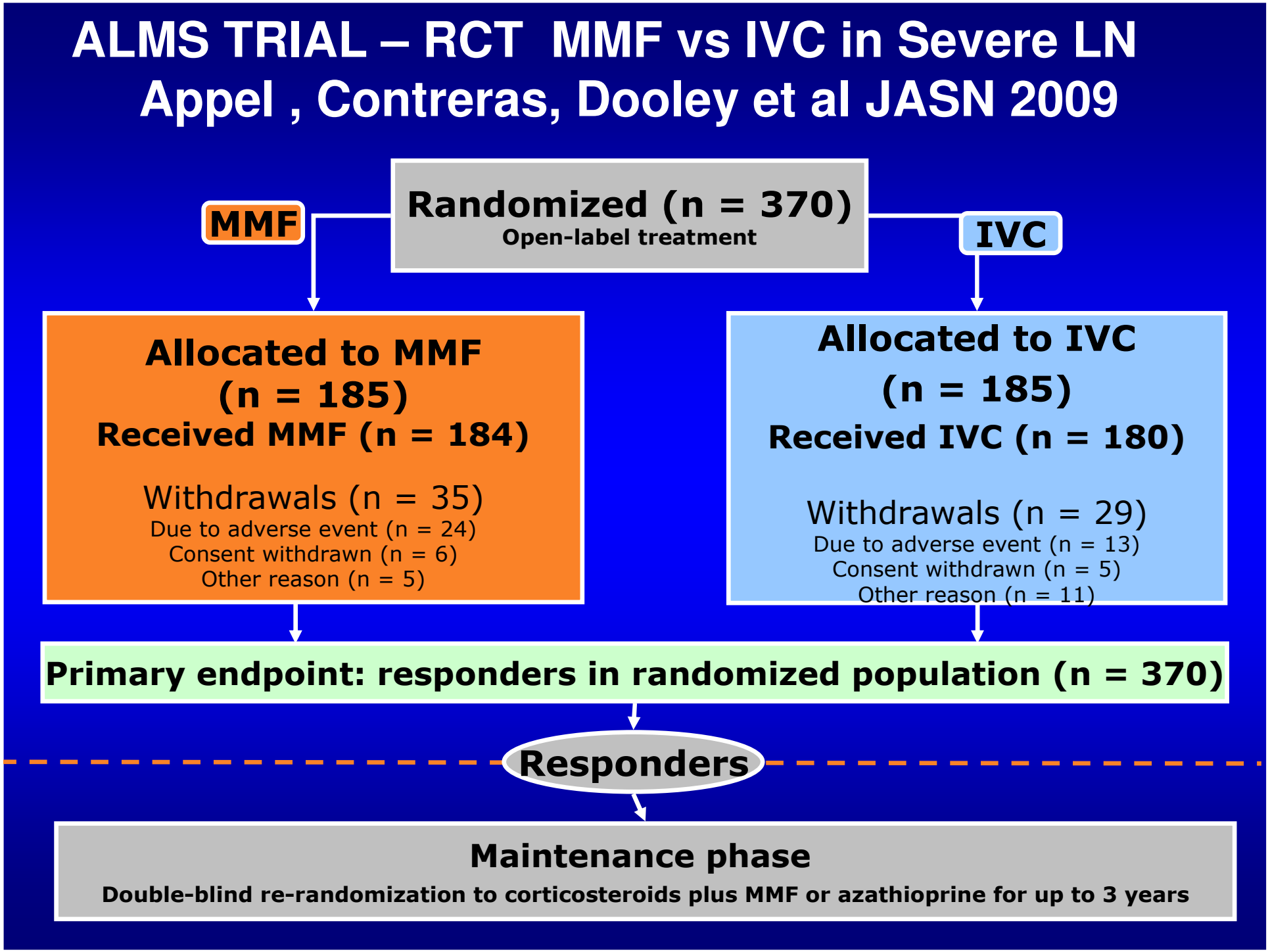
NEJM 11/05 Study – Last Outcomes

	MMF	IVC
• Renal Flare	8	8
• Renal Failure	4	7
• Death	4	8

- All p = NS at Mean follow-up 36 and 37 months

Ginzler E. … Appel G N Eng J Med Nov. 2005

ALMS TRIAL – RCT MMF vs IVC in Severe LN
Appel , Contreras, Dooley et al JASN 2009



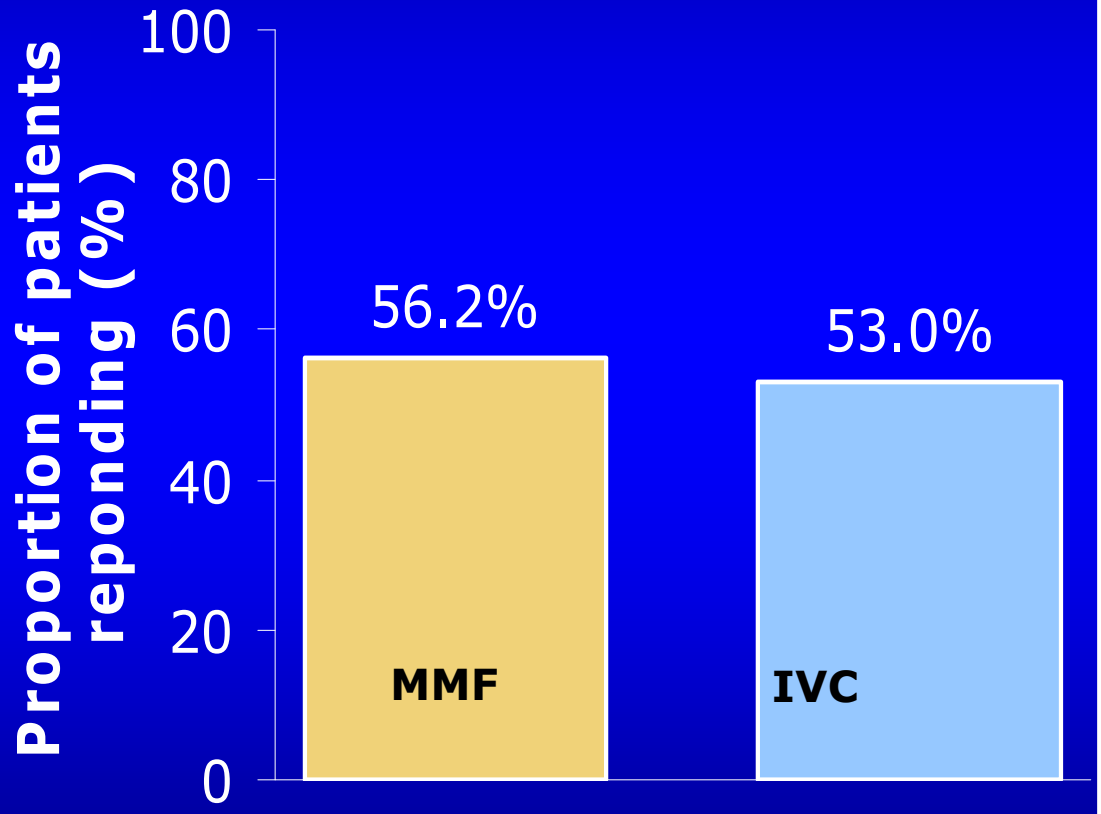
ALMS TRIAL Primary Endpoint: Responders at Month 6

Response judged by blinded Clinical Endpoint Committee:

Decrease in proteinuria to <3g if baseline nephrotic (≥3g/d) , or by ≥50% in patients ith subnephrotic (<3g/d) proteinuria

and

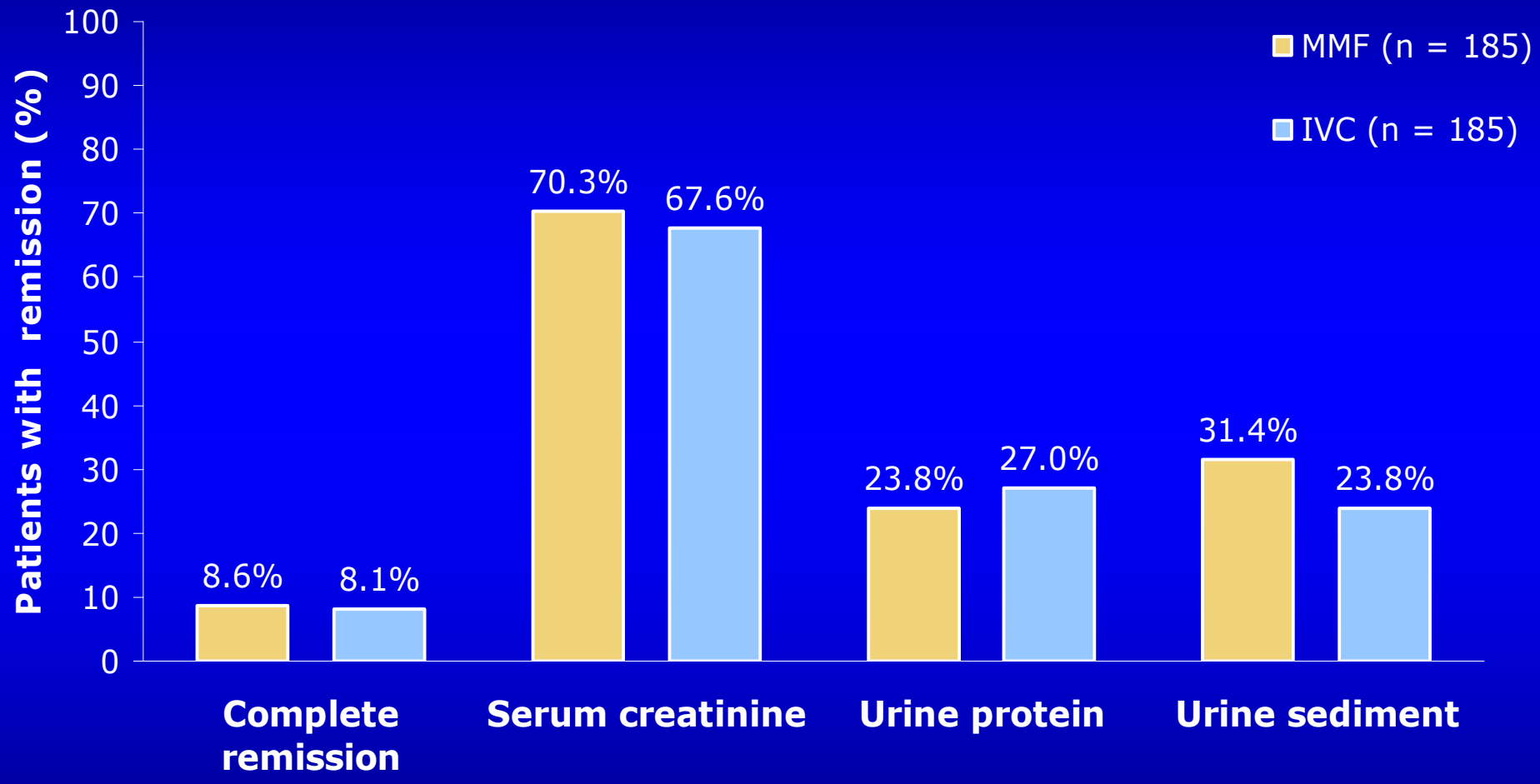
Stabilization of serum creatinine level (24-week level ± 25% of baseline), or improvement



MMF was not superior to IVC (p = 0.575)

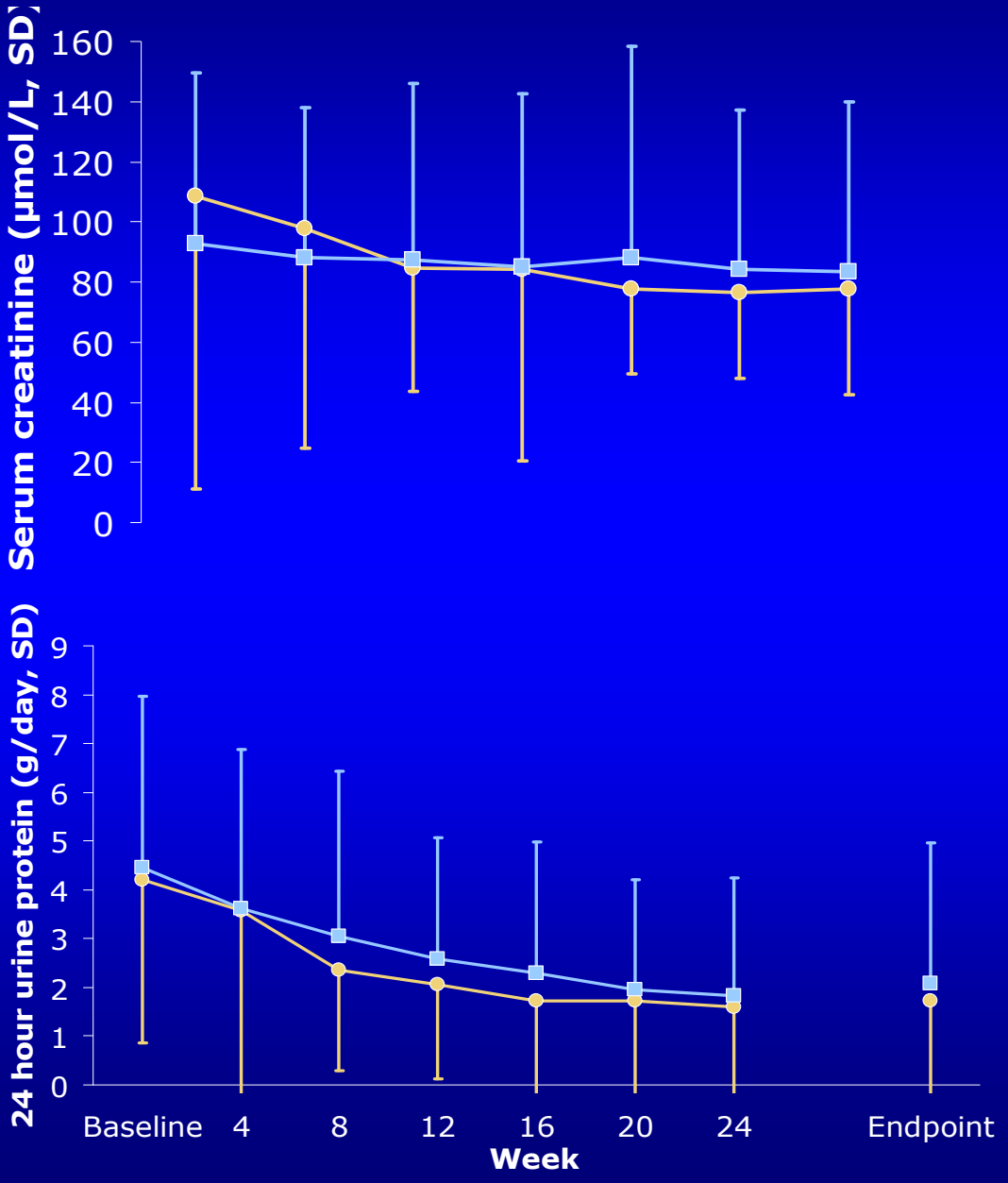
Appel , Contreras, Dooley et al JASN 2009

Remission Rates by Renal Criteria



No significant differences between groups in complete remission or by individual criteria

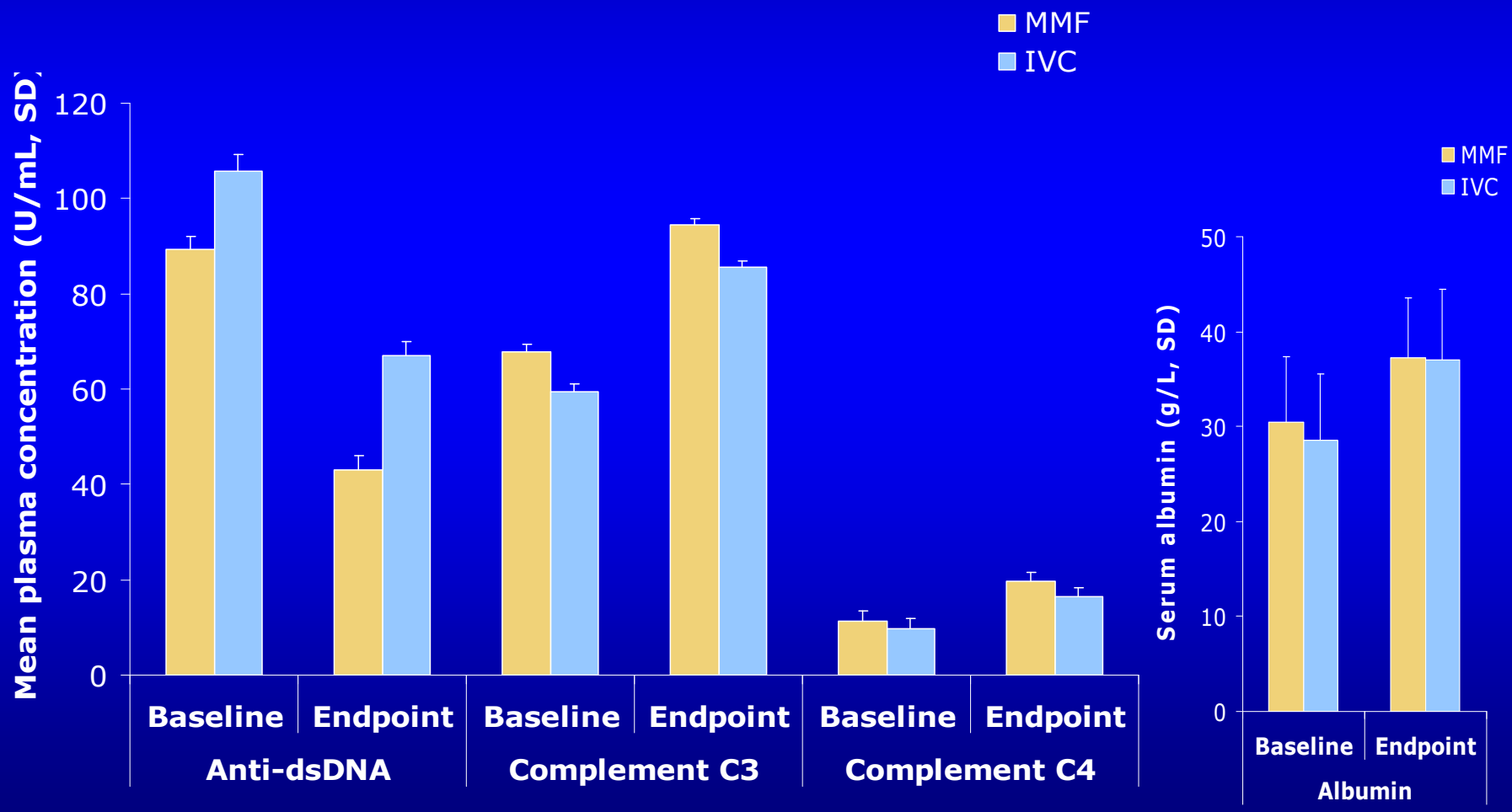
ALMS Trial - Renal Variables



Serum creatinine and urine protein levels improved in both the MMF and IVC groups

ALMS - Key Non-Renal Variables

Appel , Contreras, Dooley et al JASN 2009



ALMS Trial - Adverse Events (AEs) Occurring in ≥10% of Patients

MMF (n = 184)	
AE	**n (%)**
Diarrhea	**52 (28)**
Headache	**38 (20)**
Peripheral edema	**35 (19)**
Arthralgia	**29 (15)**
Nausea	27 (14)
Hypertension	26 (14)
Nasopharyngitis	25 (13)
Vomiting	25 (13)
Cough	24 (13)
Anemia	23 (12)
Alopecia	20 (10)
Deaths	**9(4.9)**

IVC (n = 180)	
AE	**n (%)**
Nausea	**82 (45)**
Vomiting	**68 (37)**
Alopecia	**64 (35)**
Headache	**47 (26)**
Arthralgia	43 (23)
Leukopenia	38 (21)
Pyrexia	30 (16)
Edema, peripheral	30 (16)
Nasopharyngitis	29 (16)
URI	28 (15)
Hypertension	25 (13)
Diarrhea	23 (12)
Deaths	**5(3)**

ALMS Trial - Summary

- Study did not show that MMF was superior to IVC
- Overall response rates similar with MMF and IVC in all renal and non-renal parameters
- Adverse Events for MMF and IVC were broadly similar over 24 weeks, and consistent with previous reports
- Ongoing maintenance phase compares MMF with azathioprine for up to 3 years

Appel , Contreras, Dooley et al JASN 2009

MMF in LN with Poor Renal Function: Analysis of the ALMS Data

- ***Background:*** **Controversy whether MMF is superior or equal to IV cyclophosphamide in LN with severe renal dysfunction.**
- ***Methods*****: Post Hoc analysis of pts with a baseline GFR < 30 ml/min in the ALMS controlled trial of MMF vs IV Cyclophosphamide.**
- ***Analysis*****: Change in renal function, proteinuria, overall response and adverse events.**

Walsh M, Solomons N, Jayne D, for the ALMS group JASN 19: 780A, 2008.

MMF in LN with Poor Renal Function: Analysis of the ALMS Data

29 Pts (18 MMF, 11 IVC).

Baseline: MMF vs IVC similar in age, proteinuria (5.1 and 4.6 g/day), chronicity on bx, and GFR (21 vs 24 ml/min).

No difference in composite outcome of response to proteinuria and Scr;

GFR increased 20 ml/min more with MMF ;

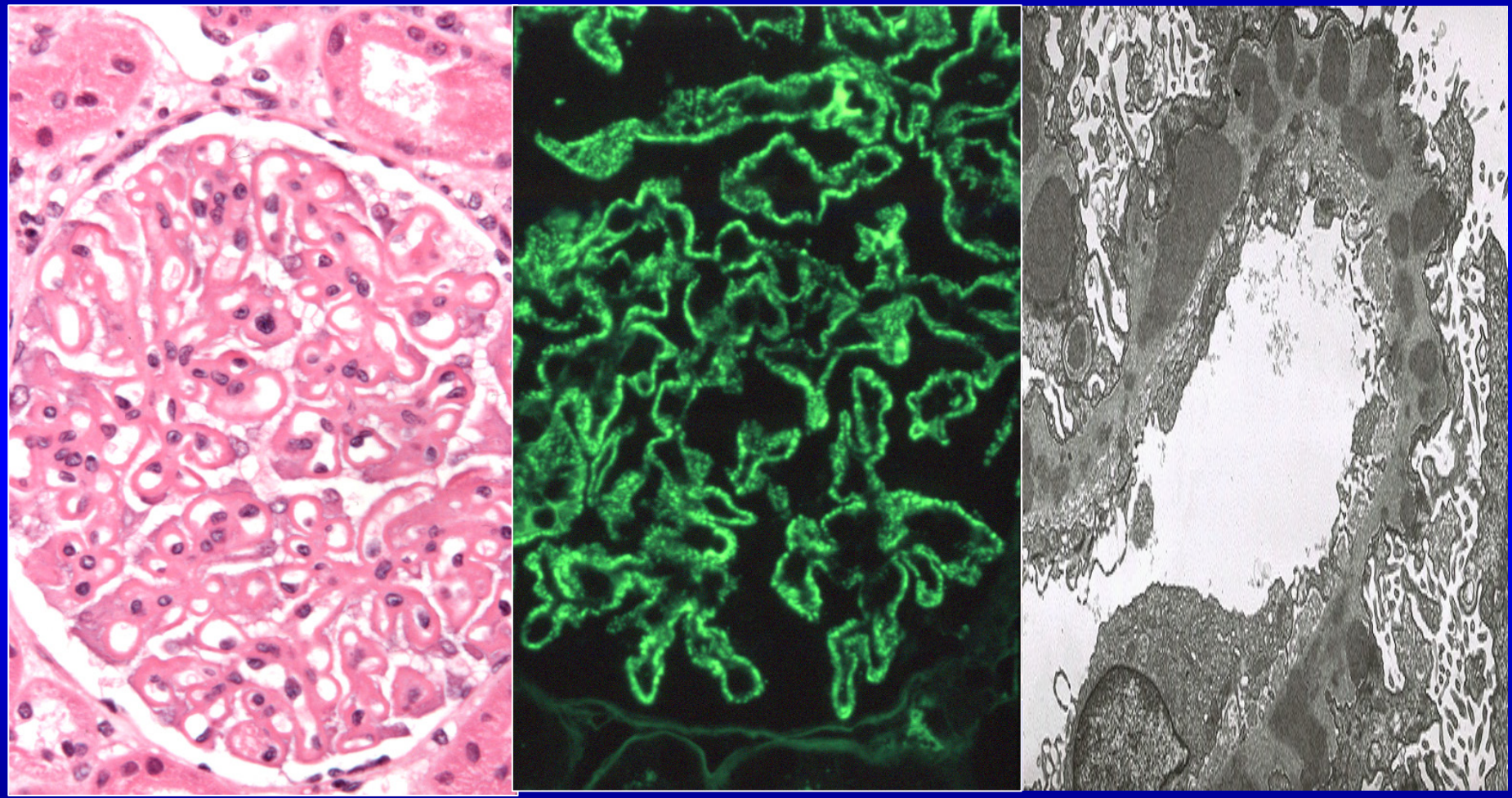
Proteinuria decreased (0.8g/d) more with MMF.

25% of both groups had treatment limiting adverse events.

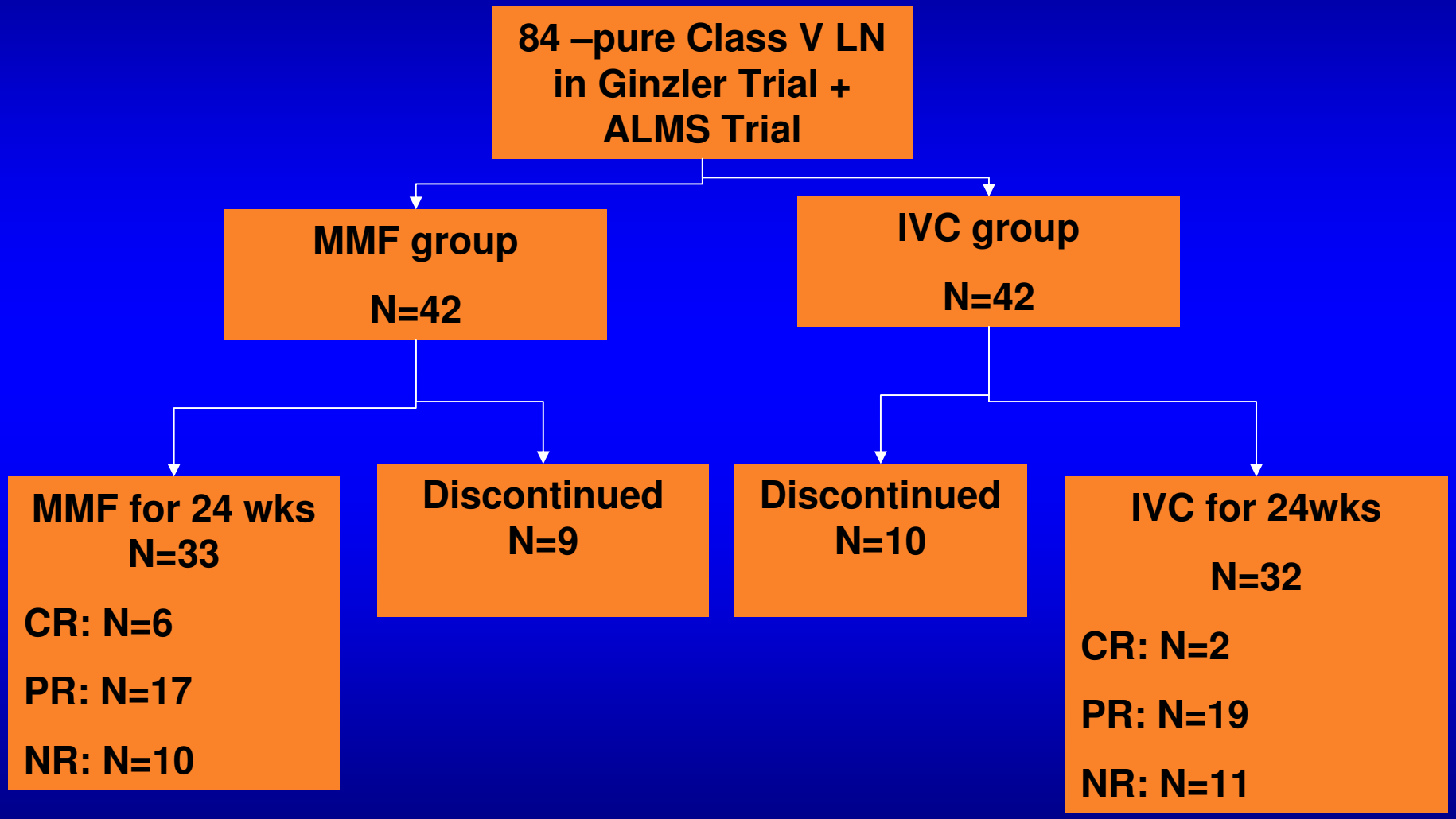
Conclusion: No evidence that IVC is more effective than MMF in pts with severe LN.

Walsh M, Solomons N, Jayne D, for the ALMS group JASN 19: 780A, 2008.

Lupus Nephritis Class V

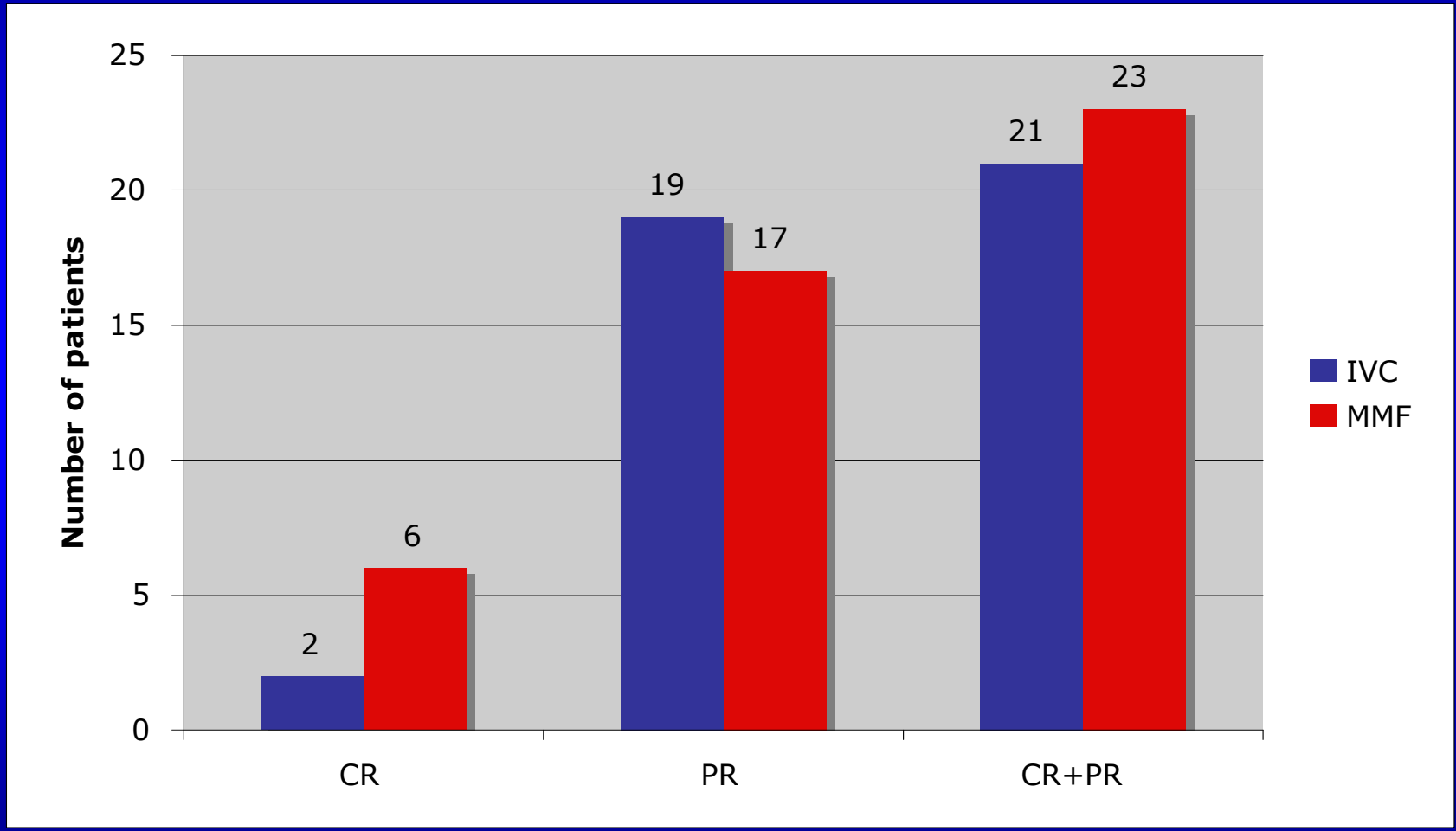


Lupus Membranous Nephropathy: *IVC vs. MMF*



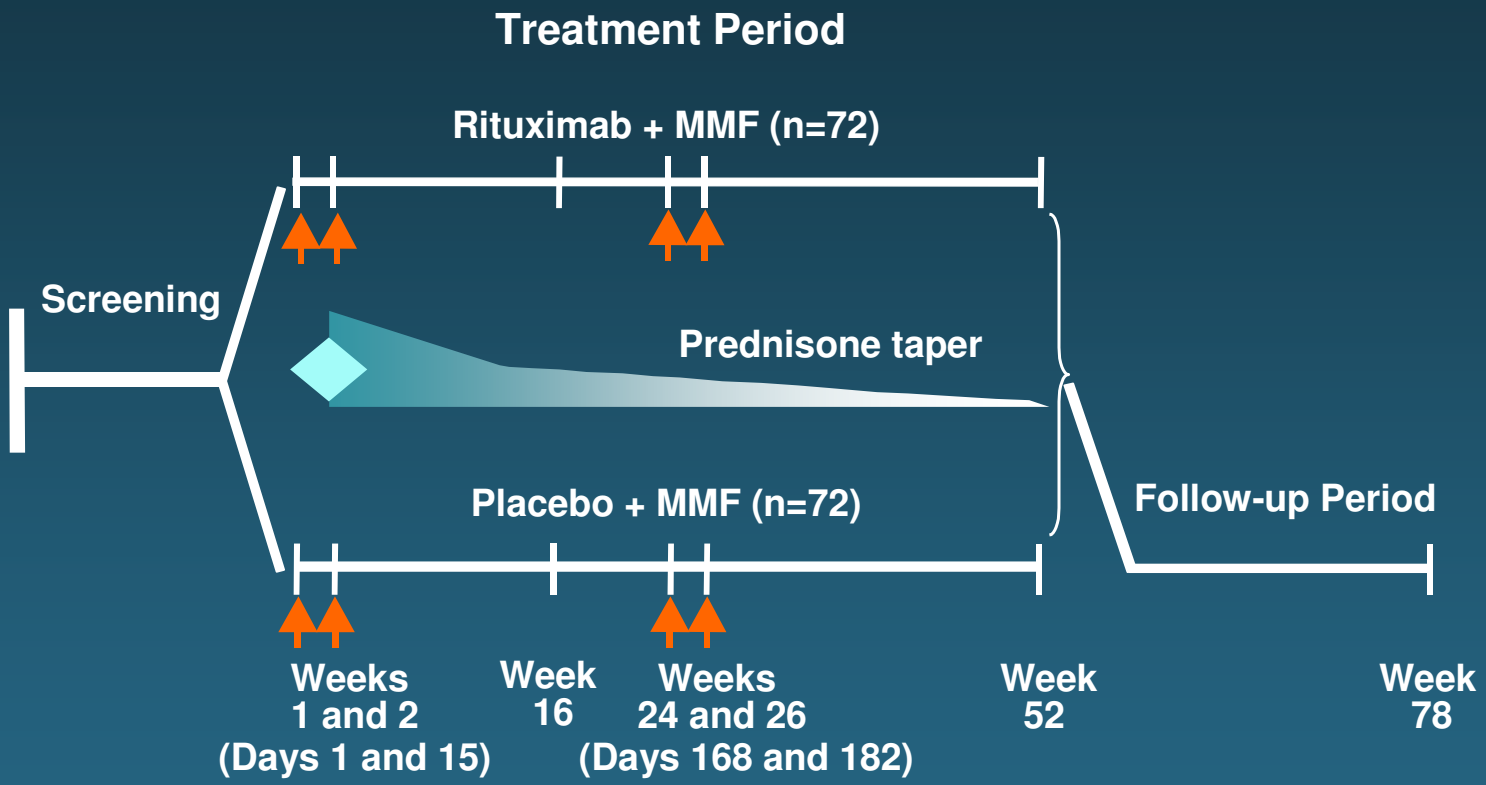
Radhakrishnan J, Moutzouris D, Ginzler G, and Appel G J
Kidney Int. 77:152-160, 2009.

Absolute partial and Complete Remission Rates Membranous LN



Radhakrishnan J, Moutzouris D, Ginzler E, and Appel G
Kidney Int 77:152-160, 2009.

LUNAR Study Design

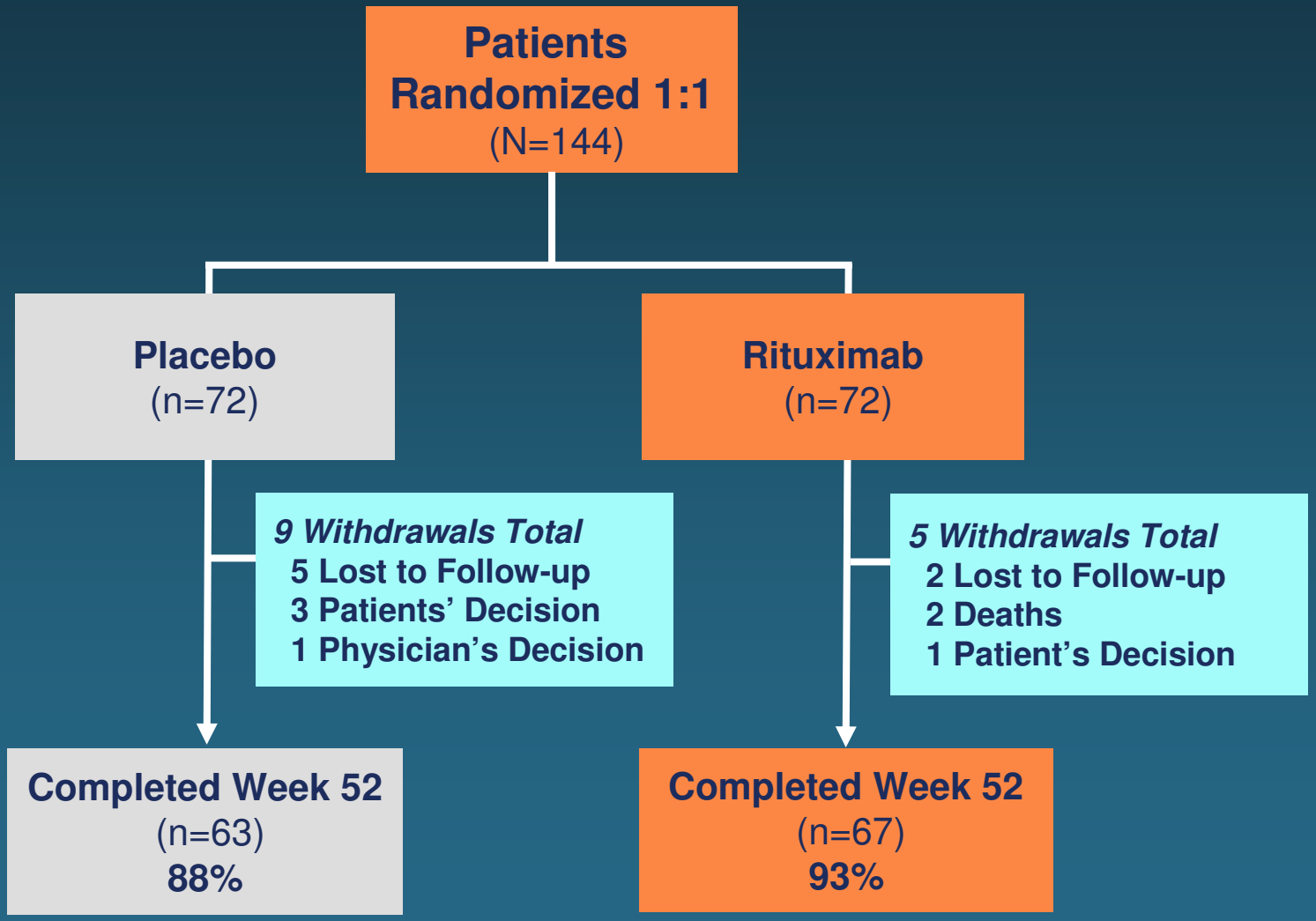


= Study drug infusion.

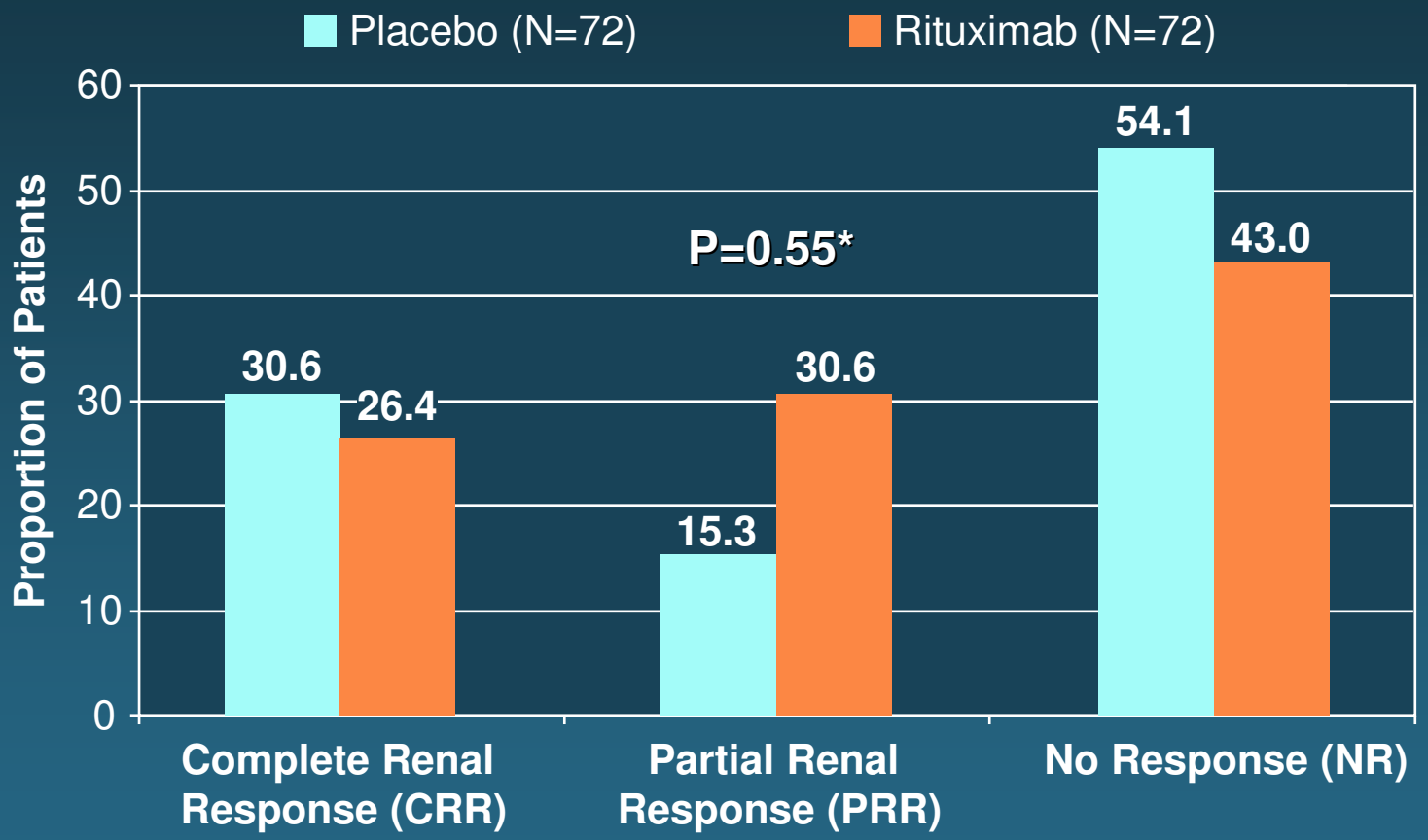
= Corticosteroids:

- 1000 mg IV methlyprednisolone given at days 1 and then days 2, 3, or 4
- Oral prednisone initiated at 0.75 mg/kg/day after IV steroids and then tapered to 10 mg/day by day 112

Patient Disposition



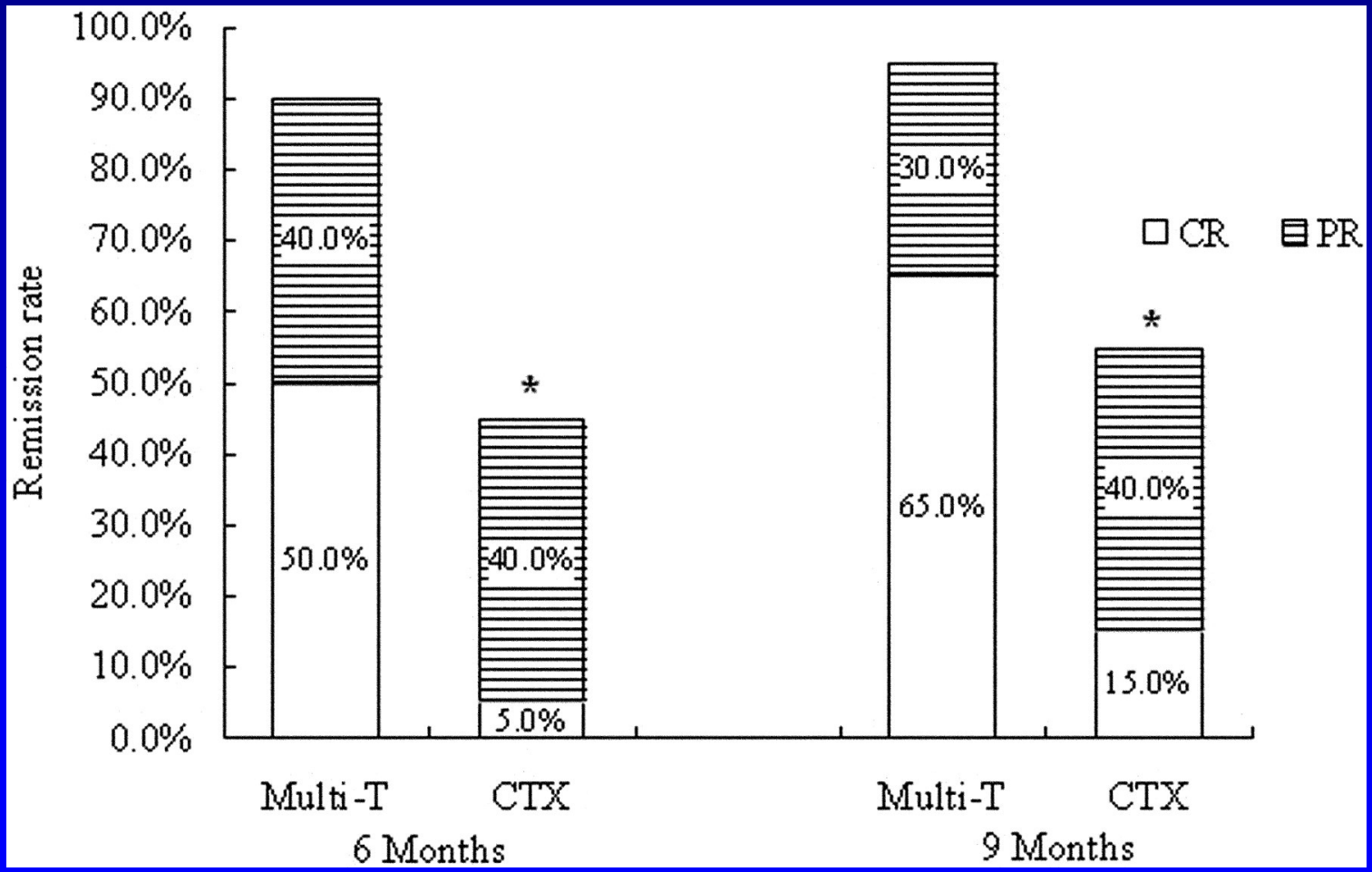
Primary Endpoint: Renal Response at Week 52



Furie R et al ACR 2009

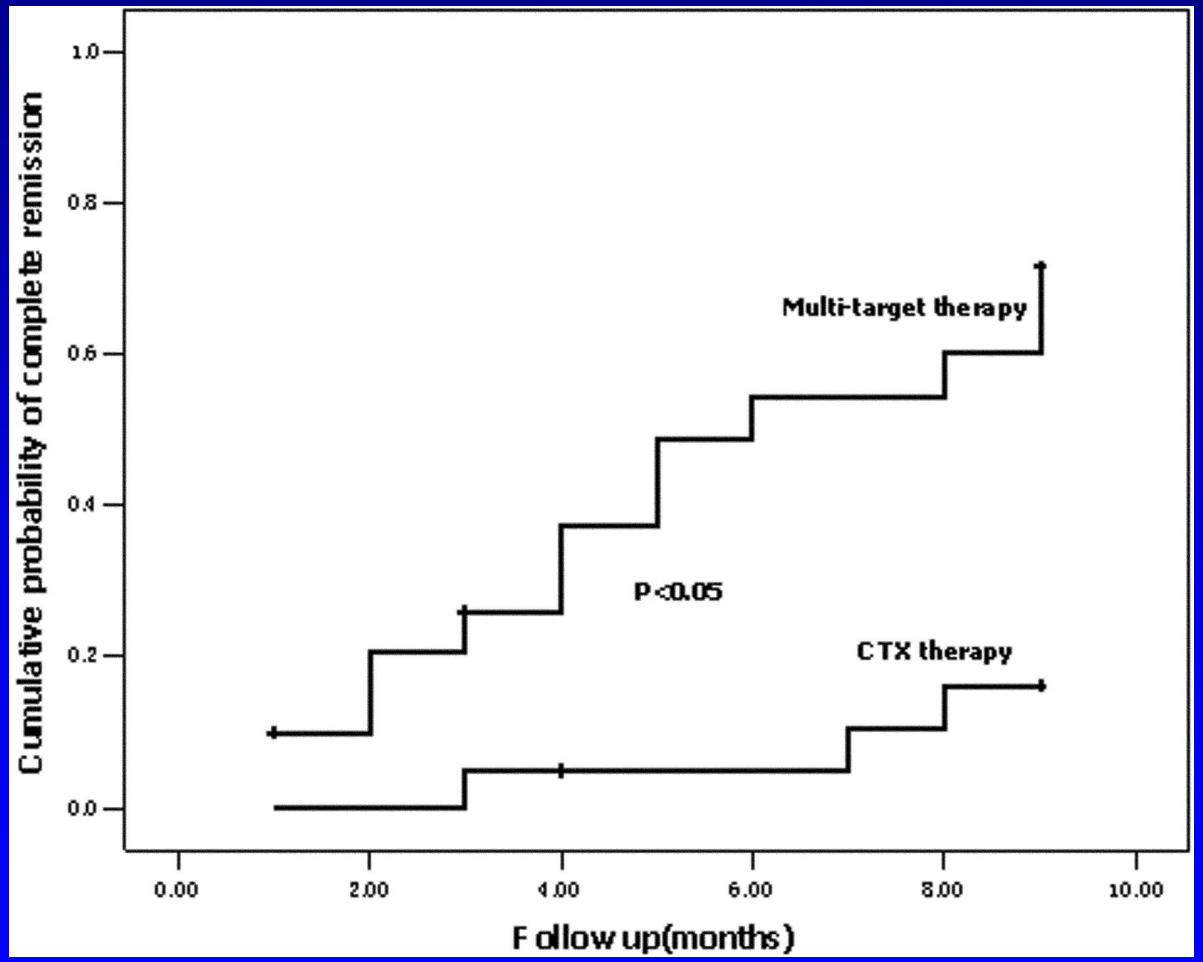
Mean MMF dose: Placebo: 2.4±0.62 g; Rituximab: 2.7±0.41 g

Remission rates in the multitarget therapy and IVCY groups after 6 and 9 months (intention-to-treat)



Bao, H. et al. J Am Soc Nephrol 2008;19:2001-2010

Probability of achieving complete remission for patients treated with multitarget therapy or IVCY



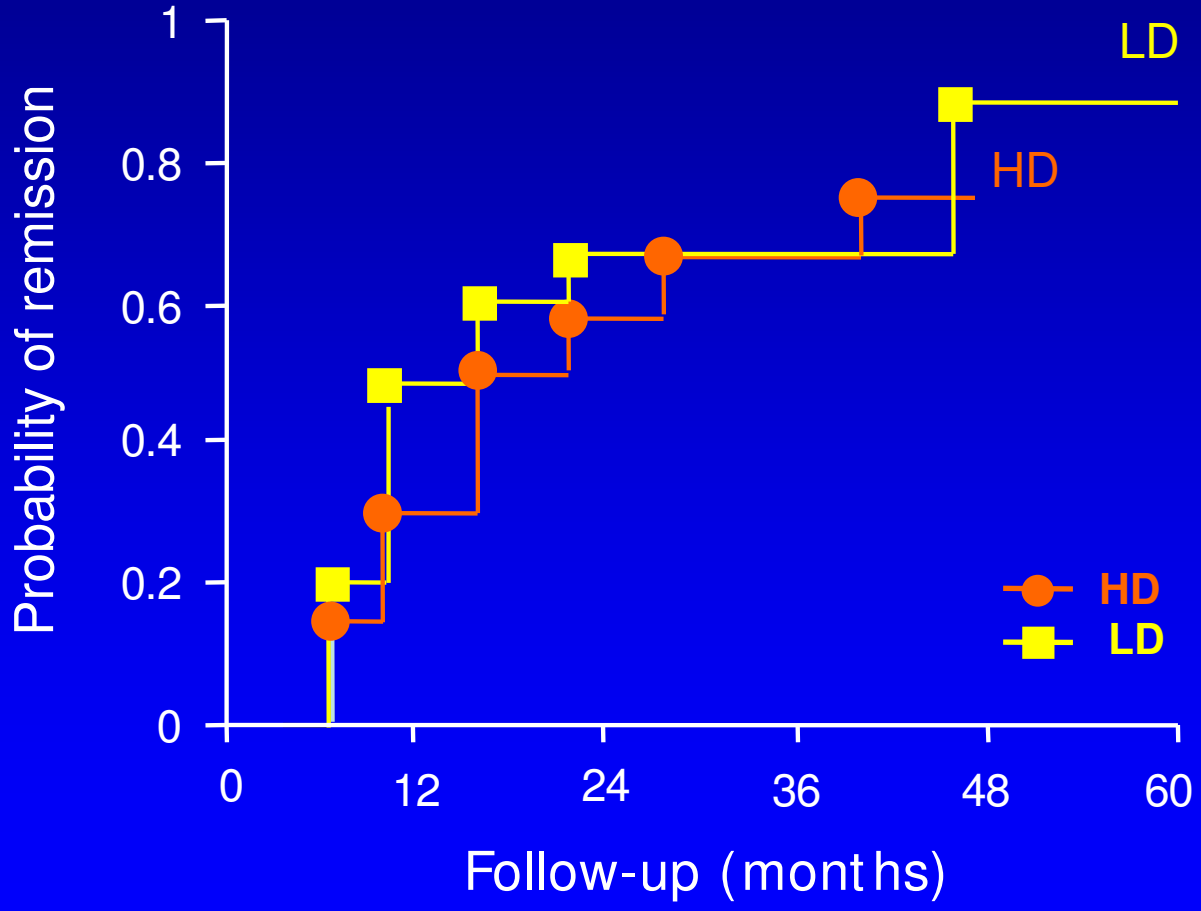
Bao, H. et al. J Am Soc Nephrol 2008;19:2001-2010

The Euro-Lupus Nephritis Trial

- Multicenter prospecitive trial of 90 LN pts with Proliferative LN (WHO III,IV,Vc-d)
- High dose IVCYT (6 mo IVP + 2 quarterly pulses) vs Low dose IV CYT (IVP q 2 wks x 6 followed by AZA)
- Follow 41 months

Houssiau et al. Arthritis & Rheumatisms 46: 2121-2131, 2002

Euro Lupus Trial - Remission

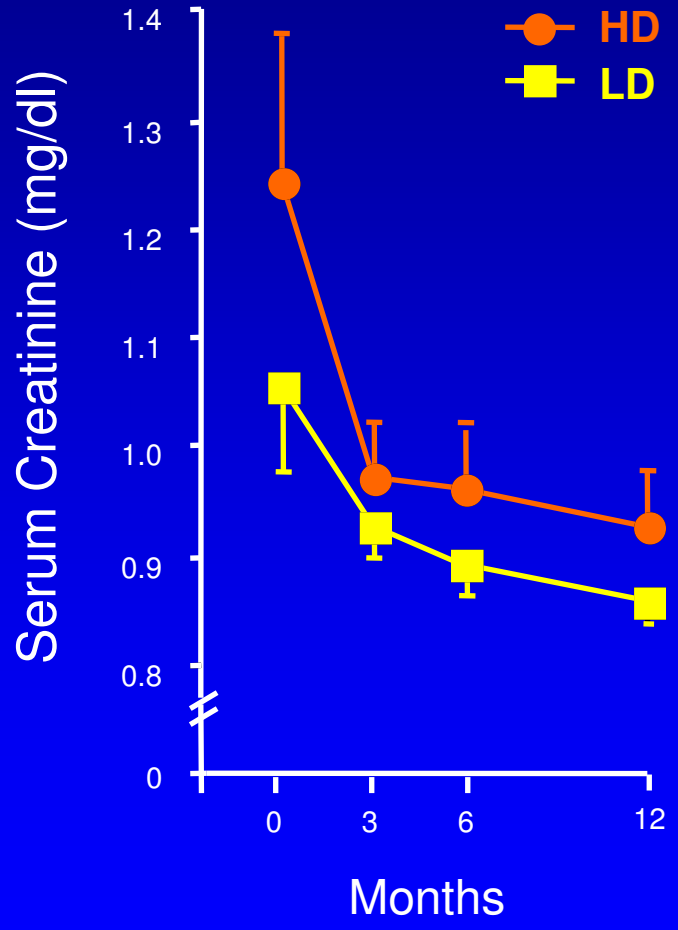


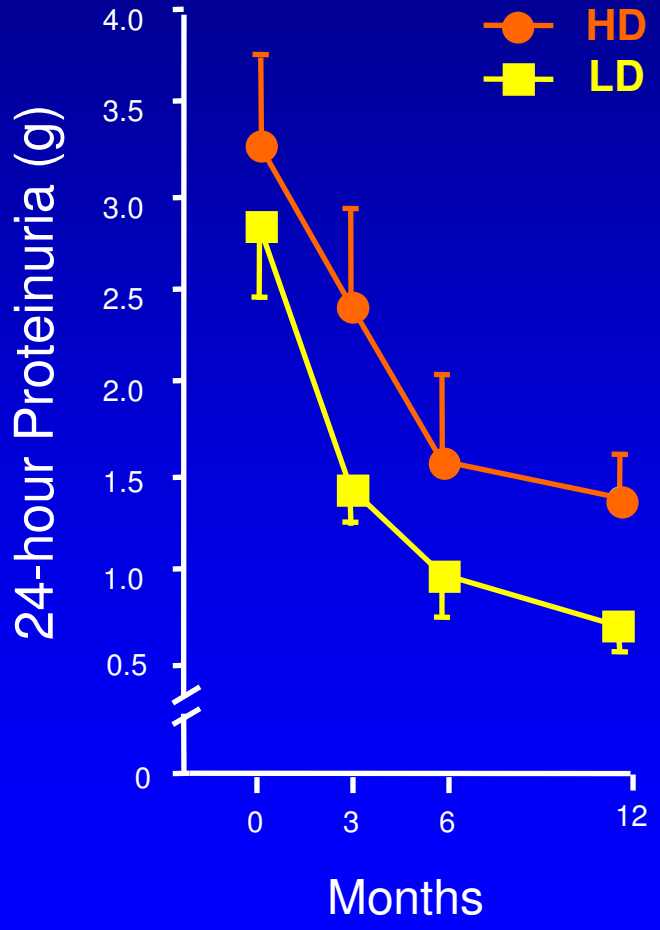
Remission: < 10 RBC/hpf, 24-h proteinuria < 1g, no DSC

UCL

Houssiau *et al.*, Arthritis Rheum, 2002

Euro Lupus Trial Renal Findings



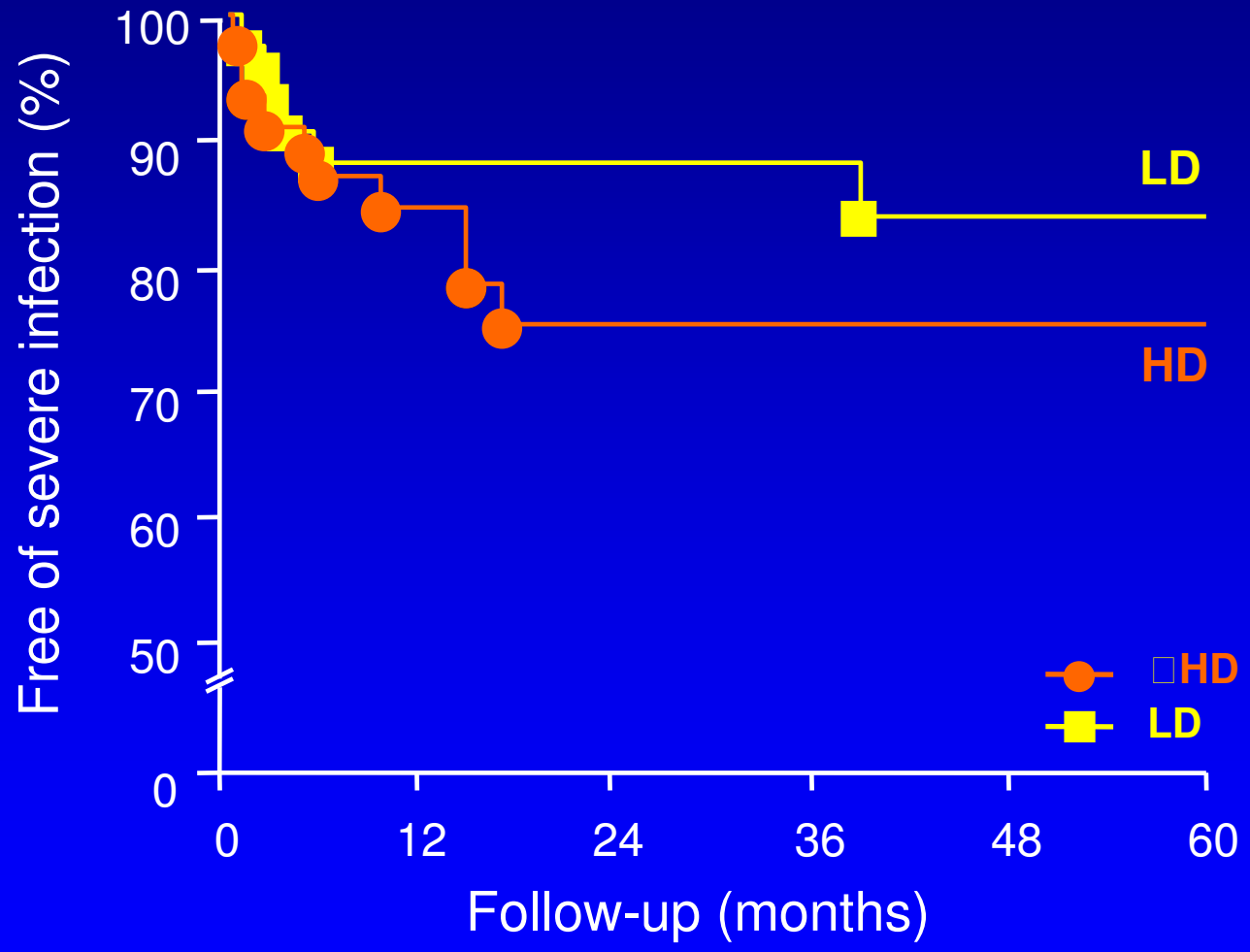


UCL

p < 0.005 for « repeated measures » analyses (ANOVA)
p > 0.05 for « between groups » comparisons

Houssiau *et al.*, Arthritis Rheum, 2002

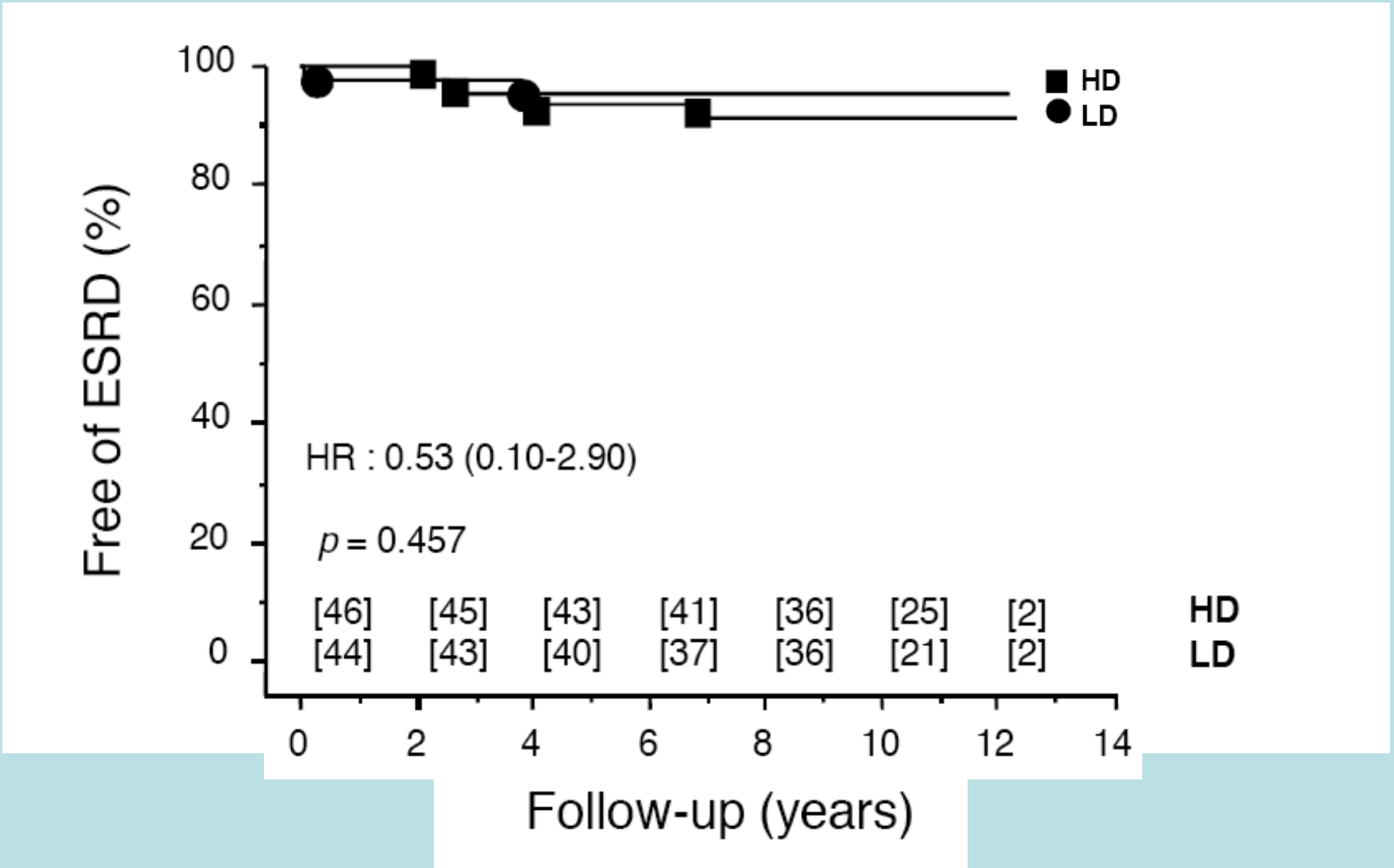
Euro Lupus Trial - Severe infection



UCL

Houssiau *et al.*, Arthritis Rheum, 2002

ELNT - 10 year FU - ESRD



Houssiau FA *et al*. *Ann Rheum Dis* 2009,

ELNT - 10 year FU

	All	High-dose IVCY	Low-dose IVCY
Current serum creatinine (mg/dl)	1.0 ± 0.5	1.0 ± 0.4	1.0 ± 0.6
Current 24h-proteinuria (g)	0.6 ± 1.2	0.6 ± 1.3	0.5 ± 1.0
Ongoing GC therapy (% of patients)	73	71	75
Ongoing IS therapy (% of patients)	56	59	53
Ongoing BP lowering therapy (% of patients)	68	68	67
Additional IS drugs ever received** (n)	0.7 ± 0.9	0.7 ± 0.9	0.7 ± 0.9
Ever received MMF (% of patients)	30	30	29
Cumulative IVCY dose (g)	7.6 ± 2.5	9.5 ± 2.5	5.5 ± 4.8***

Houssiau FA *et al. Ann Rheum Dis* 2009, Jan 20 (Epub ahead of print)

ELNT - 10 year FU - Conclusions

- Euro-Lupus Regimen achieves good clinical results in the very long-term

Limitations:

Death and ESRD rates are low
Mainly Caucasians
Only moderately severe LN
Long-term IS (GC and other IS)
Referral centers

Houssiau FA *et al*. *Ann Rheum Dis* 2009,

ALMS Maintenance Trial

- All 277 patients in ALMS trial who received induction therapy with either IV cyclophosphamide or MMF and went into remission were randomized again after 26 weeks to either oral MMF or oral AZA.
- MMF 1 g BID vs Azathioprine 2 mg/kg for up to 3 yrs follow.
- Endpoint - renal failure, ESRD, doubling creatinine, lack of renal remission.
- RESULTS AVAILABLE THIS WEEK!!!!!!

Conclusion

- MMF may be used as induction or maintenance therapy for both proliferative and membranous lupus nephritis.
- MMF is as effective as cyclophosphamide for severe lupus nephritis.
- MMF is at least as low in toxicity as cyclophosphamide. It is NOT without toxicity.
- There still is some role for cyclophosphamide, but with the EuroLupus regimen not the older NIH regimen.