

Help Us Solve
The Cruel Mystery

LUPUSTM

FOUNDATION OF AMERICA
GEORGIA CHAPTER



Lupus and Your Kidneys

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Kidney Inflammation and Abnormal Function as a Result of Lupus (Lupus Nephritis)

- Types of lupus nephritis
- Current treatment options
 - Latest clinical study results
 - Newer therapies
- Predicting treatment response

Major Types of Lupus Nephritis

- Lupus nephritis is grouped into 6 major types or classes (Class I-VI)
 - Class I and II Mesangial
 - Class III Focal
 - Class IV Diffuse
 - Class V Membranous
 - Class VI Advanced sclerotic
- The higher the Class number, the more advanced the disease
- Injuries to the kidney (lesions) are also labeled as “active” or “chronic”
 - Active lesions can be treated, chronic lesions cannot
- Advanced kidney disease is also known as end-stage renal disease

How does my doctor determine if I have lupus nephritis and what type of lupus nephritis I have?

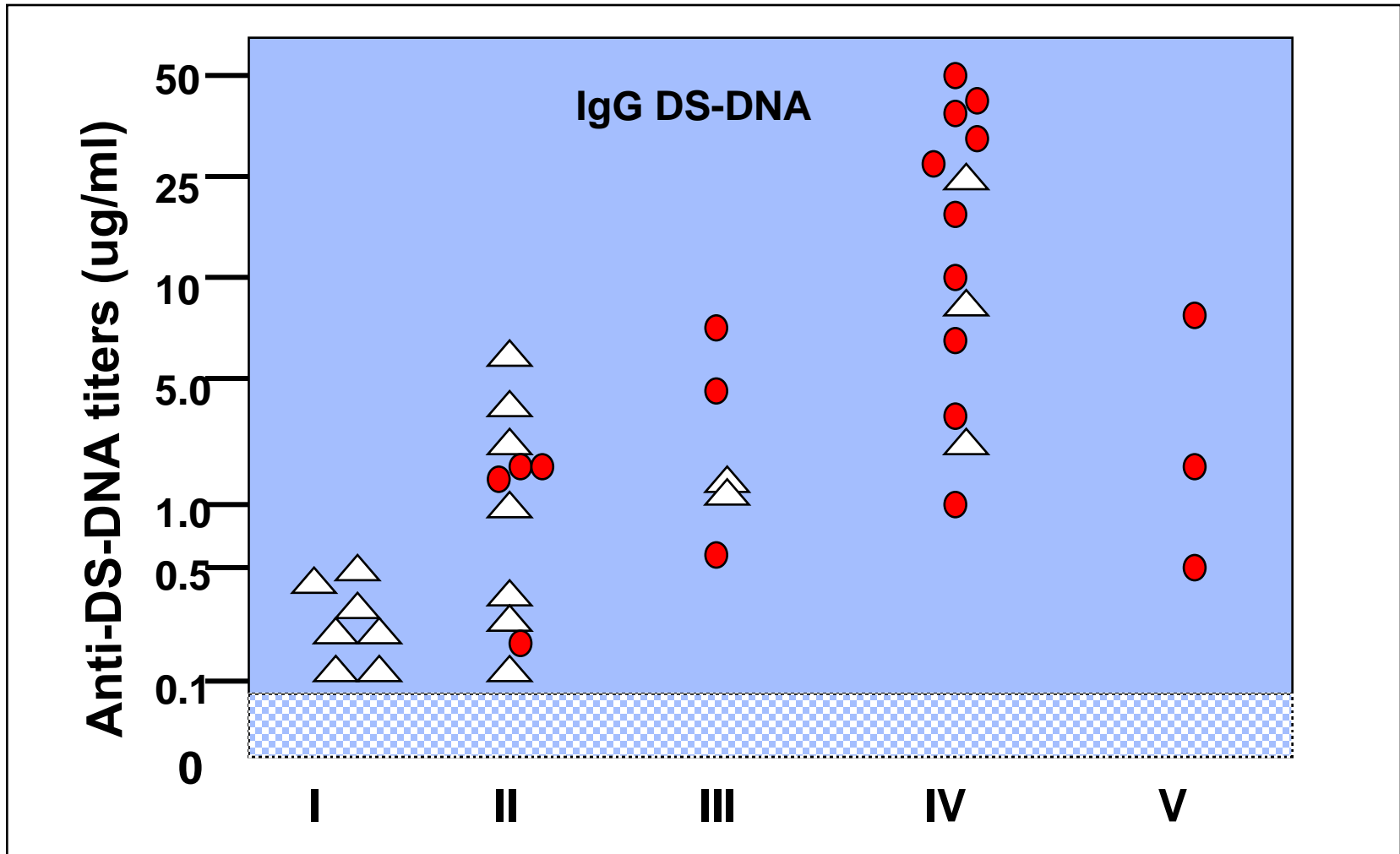
Tests to Determine Class of Lupus Nephritis

- Blood tests provide clues
- Elevation in serum creatinine or BUN levels
- Greater the amount of anti-dsDNA
- Lower the amount of complement
- More protein appears in urine

These changes alert the physician to be more aggressive with diagnosis and treatment

- Tissue sample (kidney biopsy)
 - amount of inflammation
(potentially reversible, treatable)
 - amount of scarring
(irreversible)

Lack of correlation of Anti-DNA Antibody Levels and Severity of Lupus Nephritis



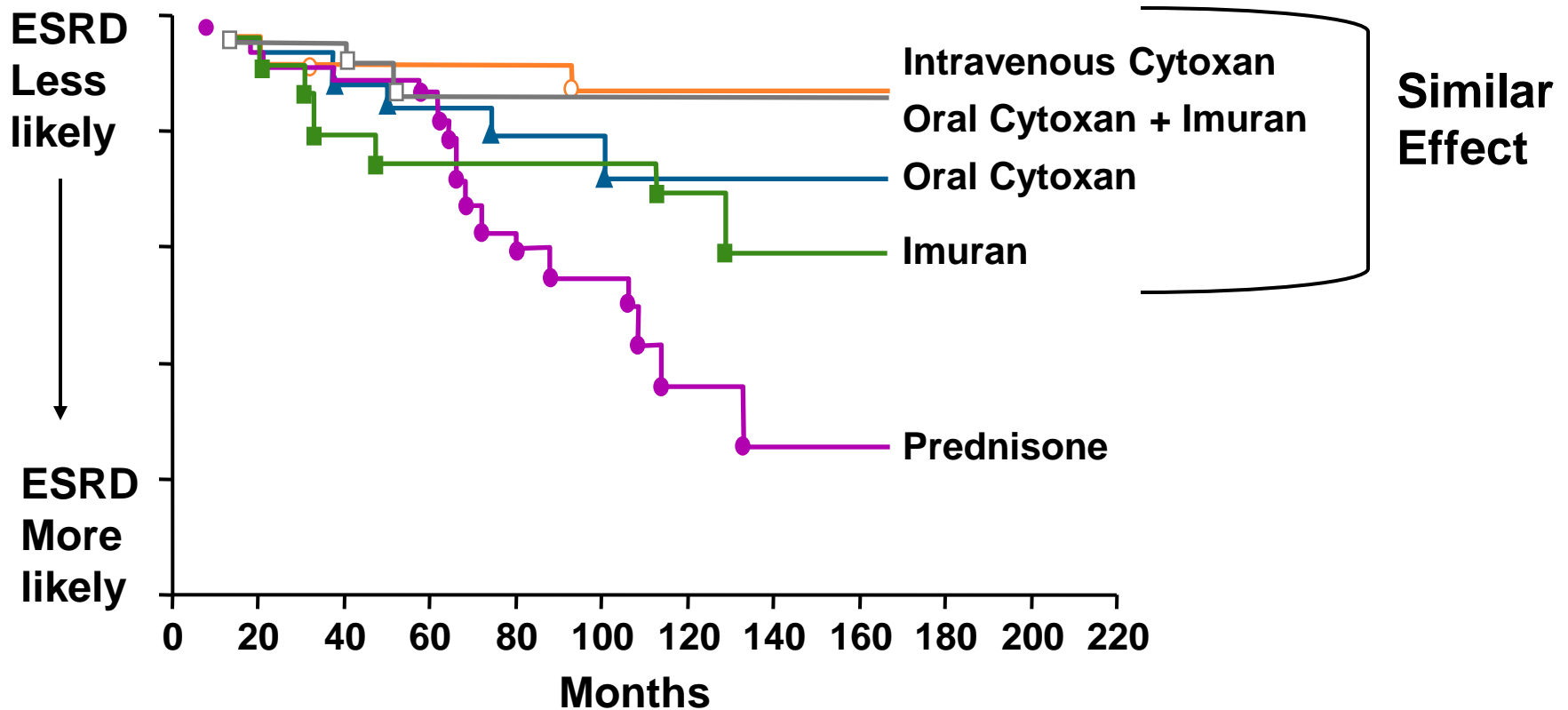
Treatment for Lupus Nephritis

Treatment - Lupus Nephritis Options

- Steroids
 - Methylprednisolone (IV) or prednisone (oral)
 - May be given at intervals (pulsed)
 - Dose typically reduced over time
- Cytoxan (cyclophosphamide)
 - Intravenous (IV) or oral
- Imuran (azathioprine)
- CellCept (mycophenolate mofetil MMF)
- Other immunosuppressive medication
- Clinical Trials

Prevention of Advanced Renal Disease

Combination Therapy is Superior

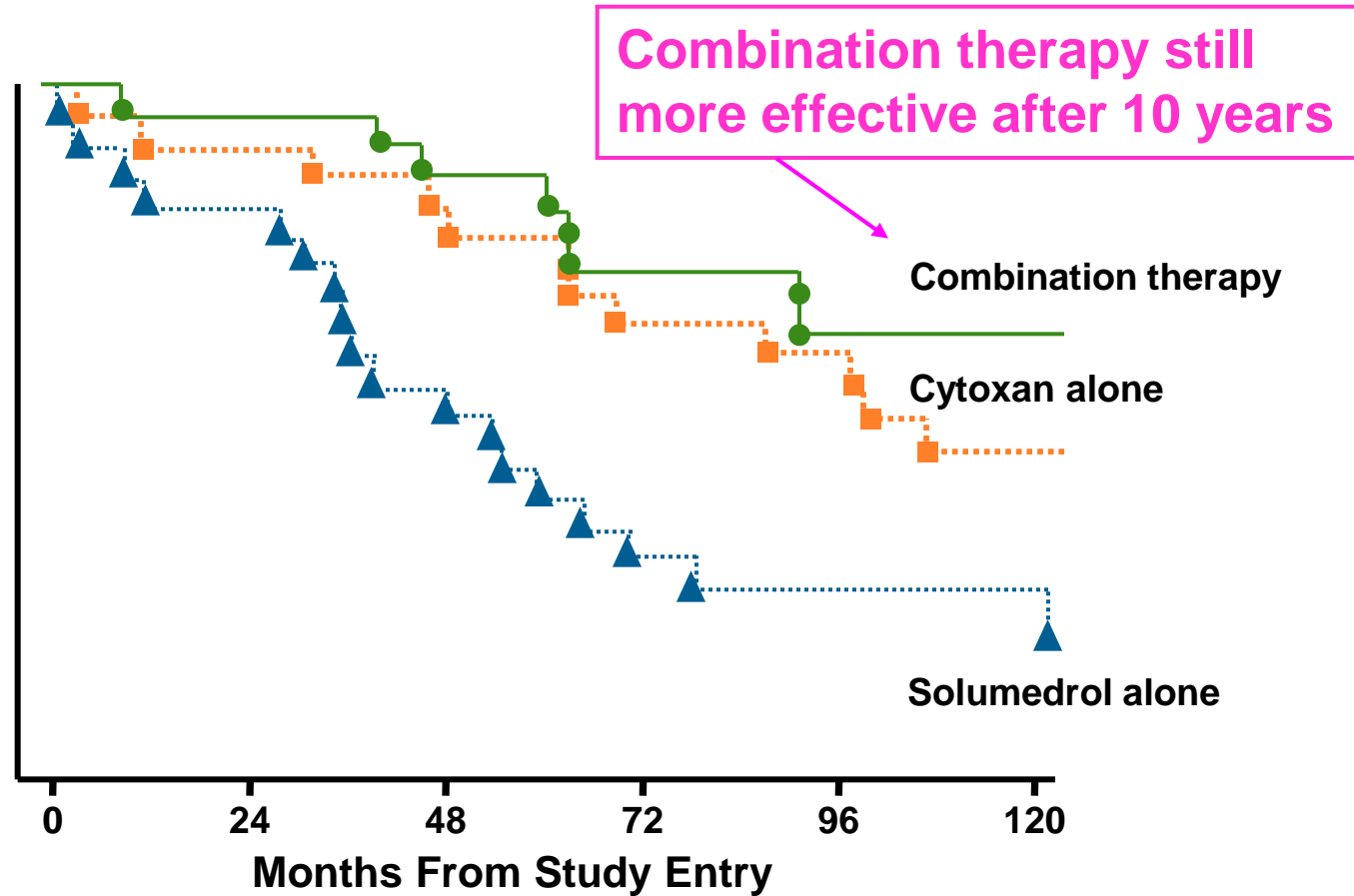


Long-term Follow-up

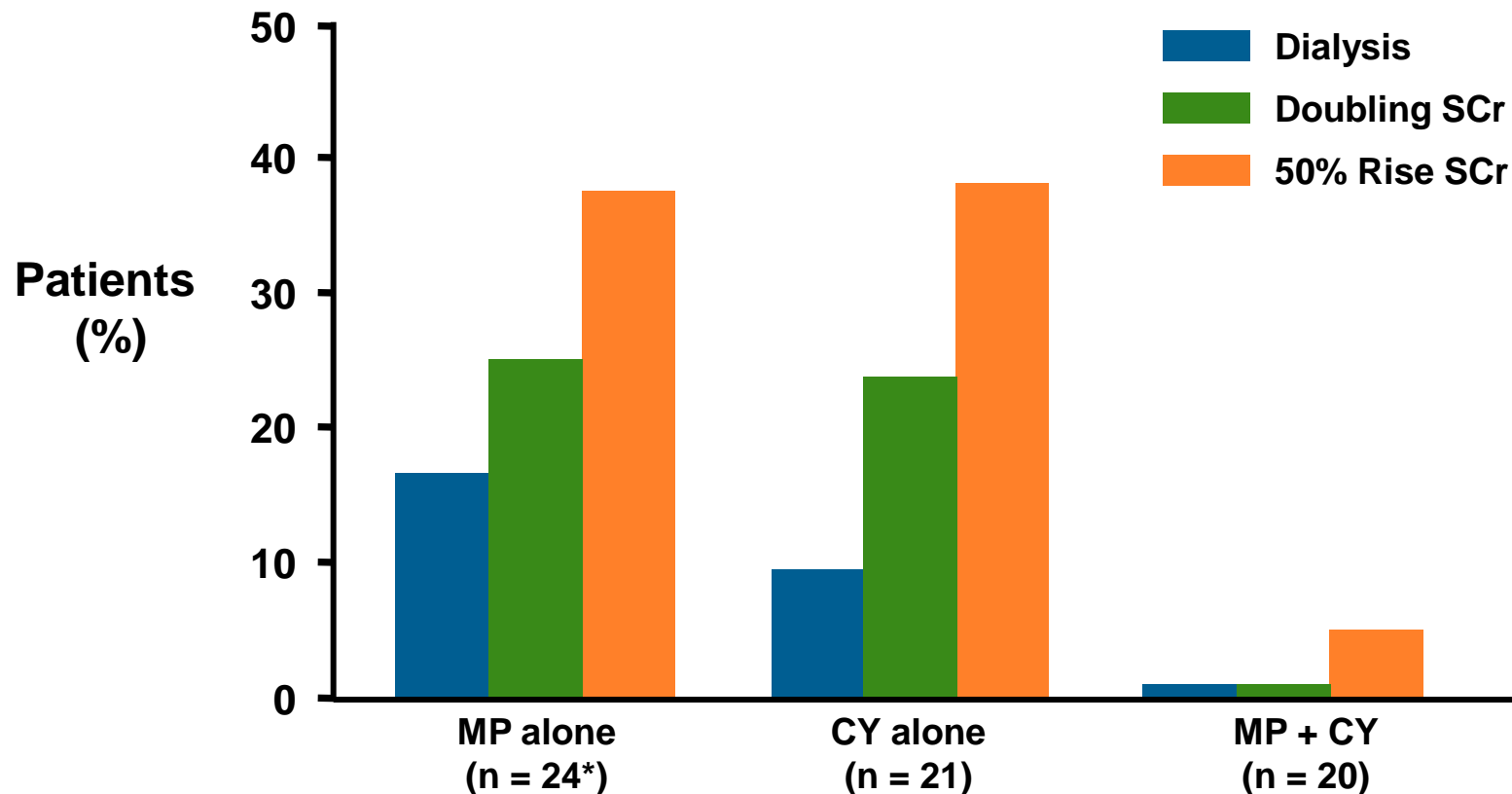
Likely that therapy would succeed



Likely that therapy would fail



Long-term Follow-up of Protocol Completers in WHO Class IV LN

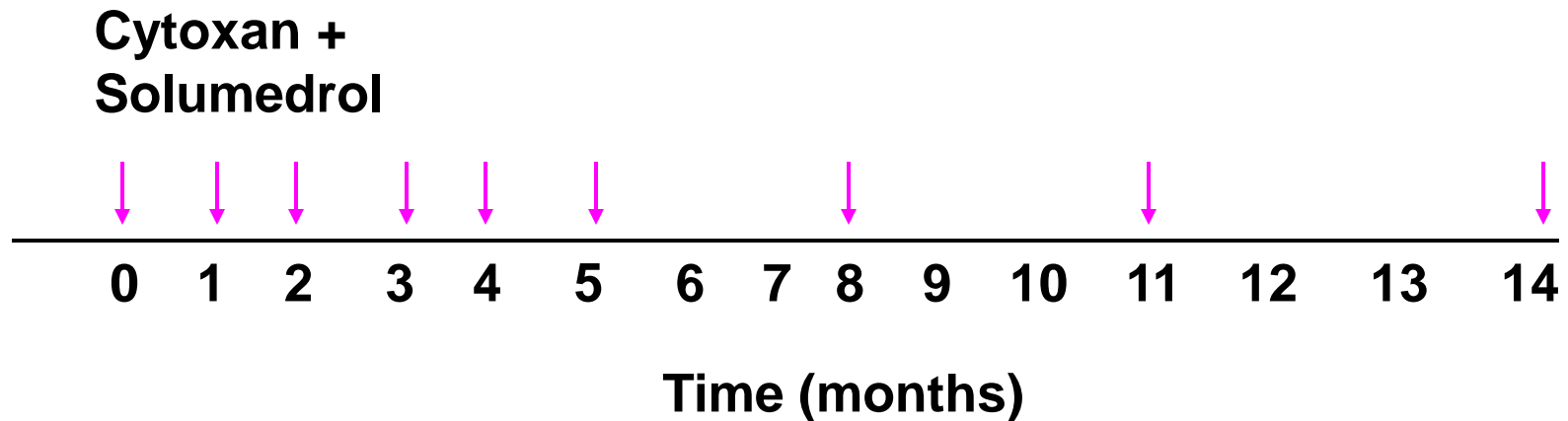


*14 of 24 patients received CY after study completion

Illei GG, et al. *Ann Intern Med.* 2001;135:248-257.

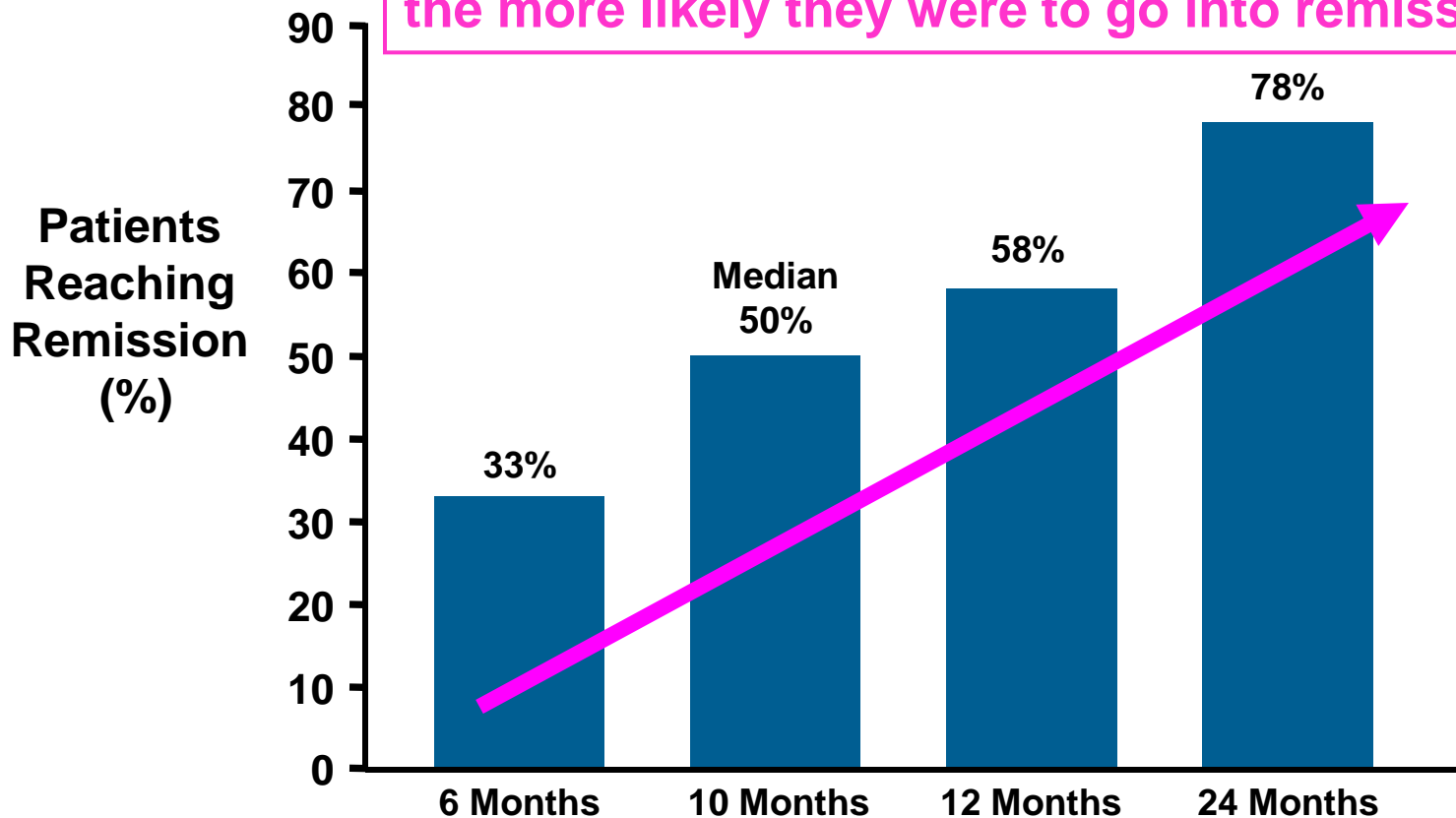
Standard Treatment 2001/2002

- Pulse of IV Cytoxan with a pulse of Solumedrol every month for 6 months then again every third month thereafter

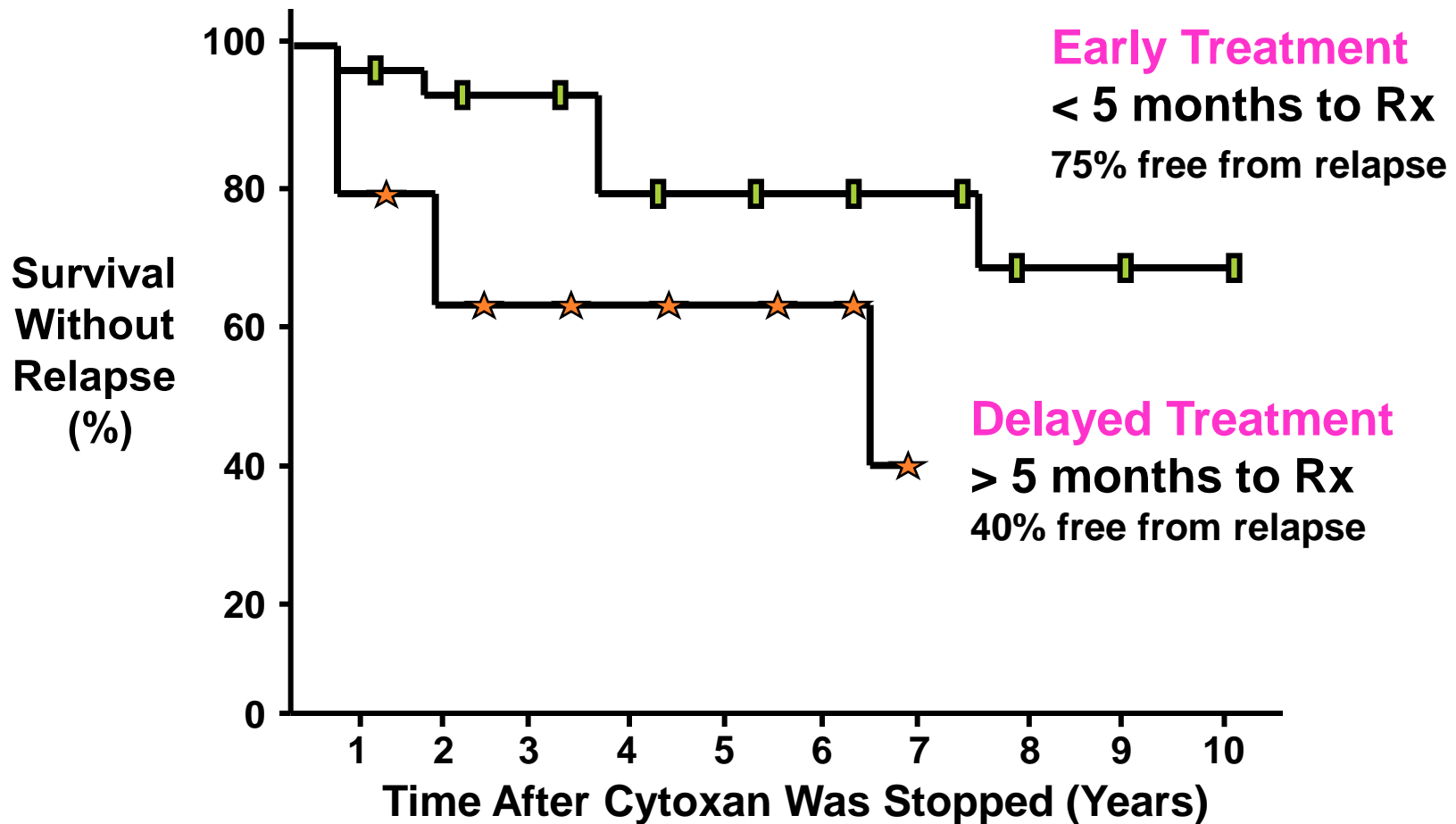


Long-term Cytoxan Therapy Improves Remission Rates

In one study, the longer patients were on Cytoxan the more likely they were to go into remission



Starting Cytoxan Early Reduces Relapse Rates



Event	Cytosan (n = 21)	Combination Therapy (n = 20)
	n/n	n/n
High blood pressure	10/20	10/20
Heart disease limiting blood flow to heart	1/19	4/19
Elevated fat in blood (hyperlipidemia)	7/20	8/19
Heart disease affecting flaps that regulate blood flow through the heart	9/19	7/21
Tissue death resulting from lack of blood supply	6/21	6/20
Bone fragility (osteoporosis)	4/18	3/19
Premature menopause	9/16	10/18
Major infections	7/21	9/20
Herpes zoster infection	6/21	5/20

What are the factors that determine who will respond well to drug therapy for lupus nephritis?

“Predicting” Results

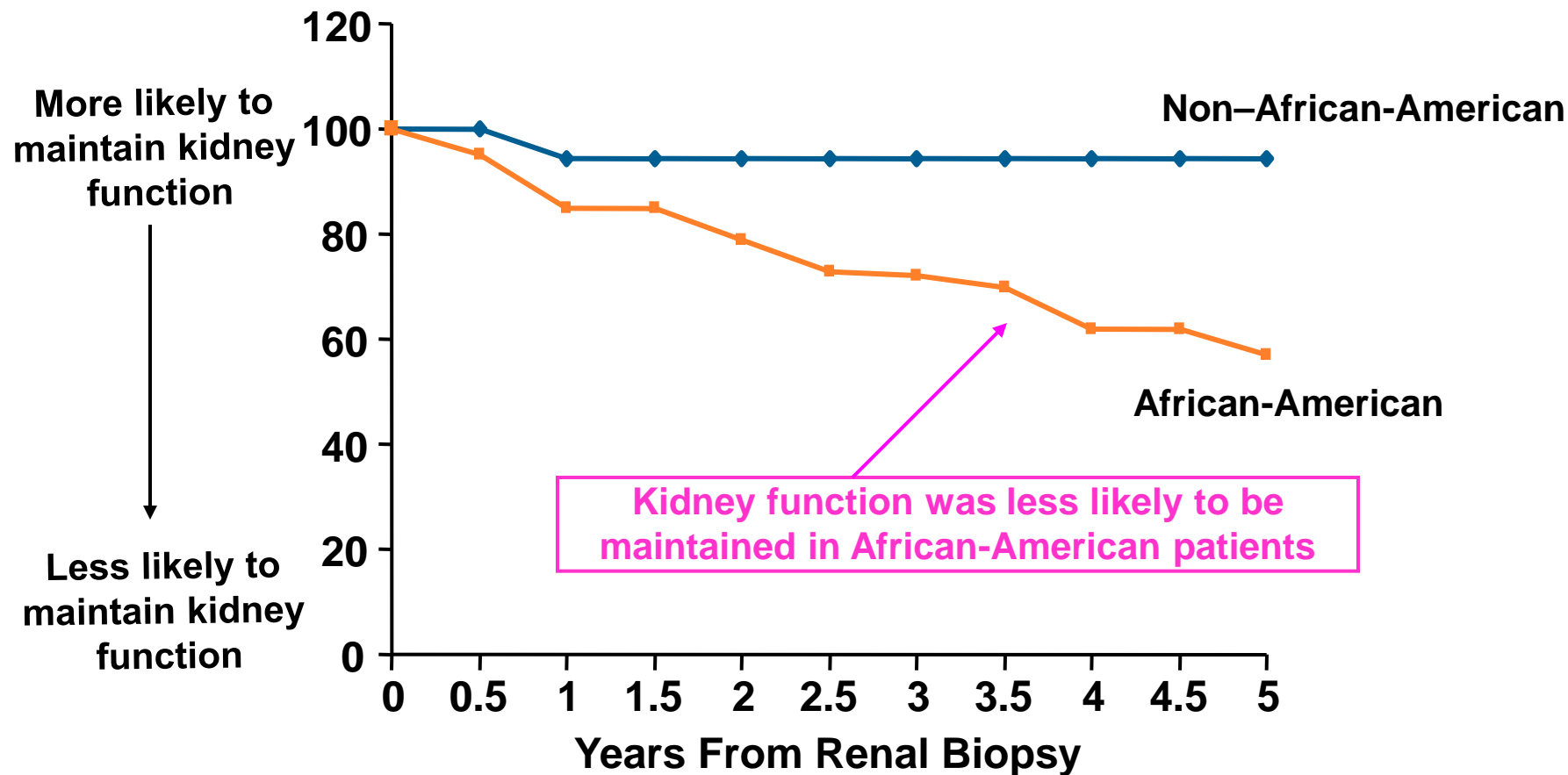
- Some groups of patients respond better to therapy than others
- Risk factors for progression to renal disease and renal failure
 - Higher initial blood values of creatinine
 - Mild anemia
 - African-American
 - Severe “activity” and “chronicity”
(kidney biopsy)

“Predicting” Results (Cont’ d)

- Tissue extractions (biopsies) are important predictors of outcome
- Follow up biopsy in individuals that do not respond is important for future treatment

If the biopsy after 6 months of treatment still shows that the disease is progressing, you may be placed on a different therapy

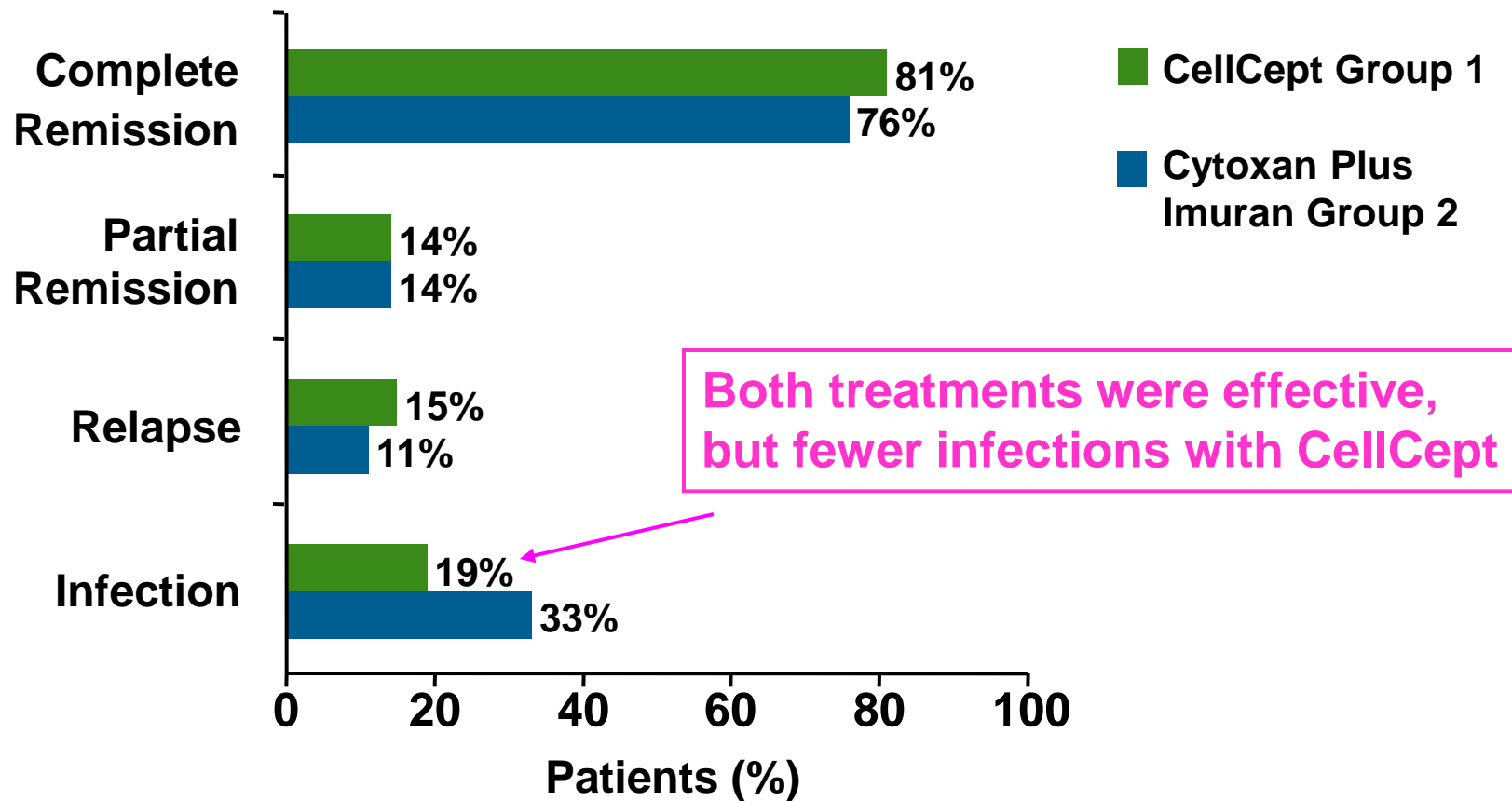
Worse Outcomes in African-Americans



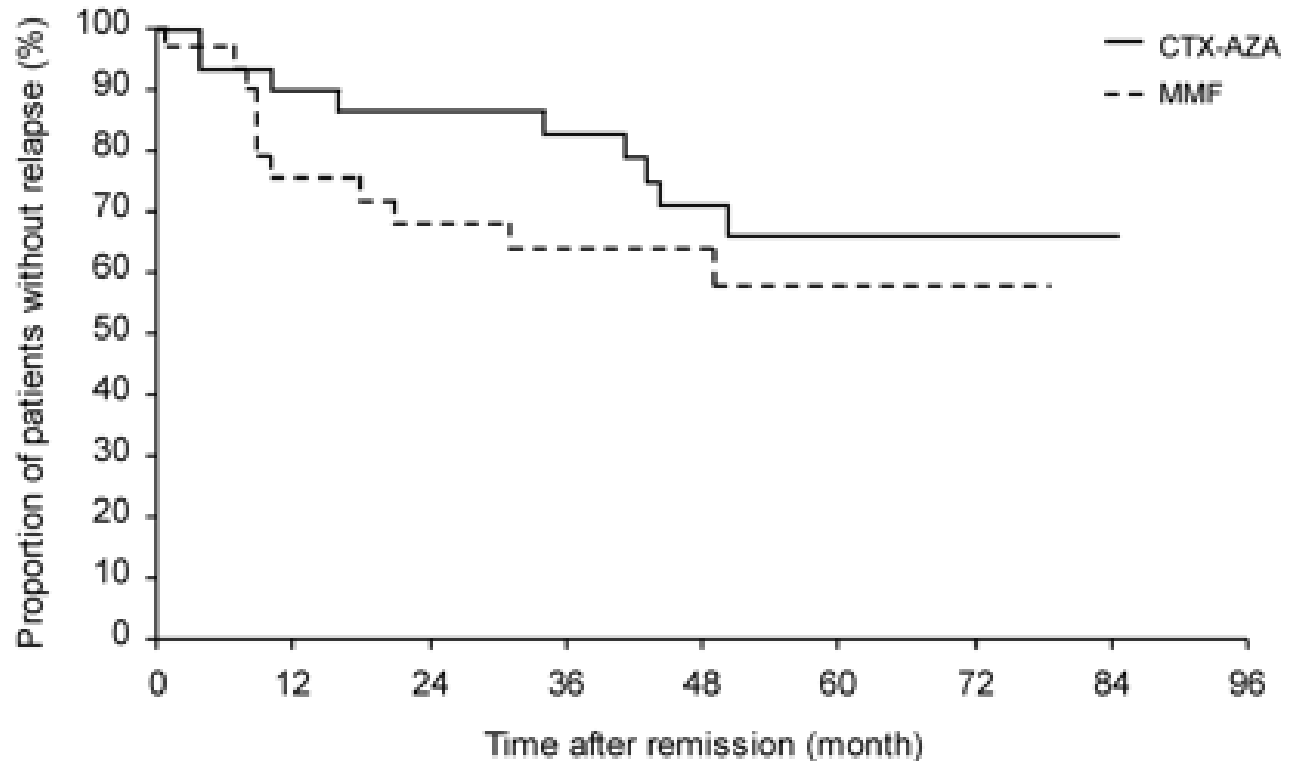
What about alternative approaches to induction?

Do we always need to treat with Cytosoxan?

CellCept vs Oral Cytoxan Plus Imuran (Cont' d)



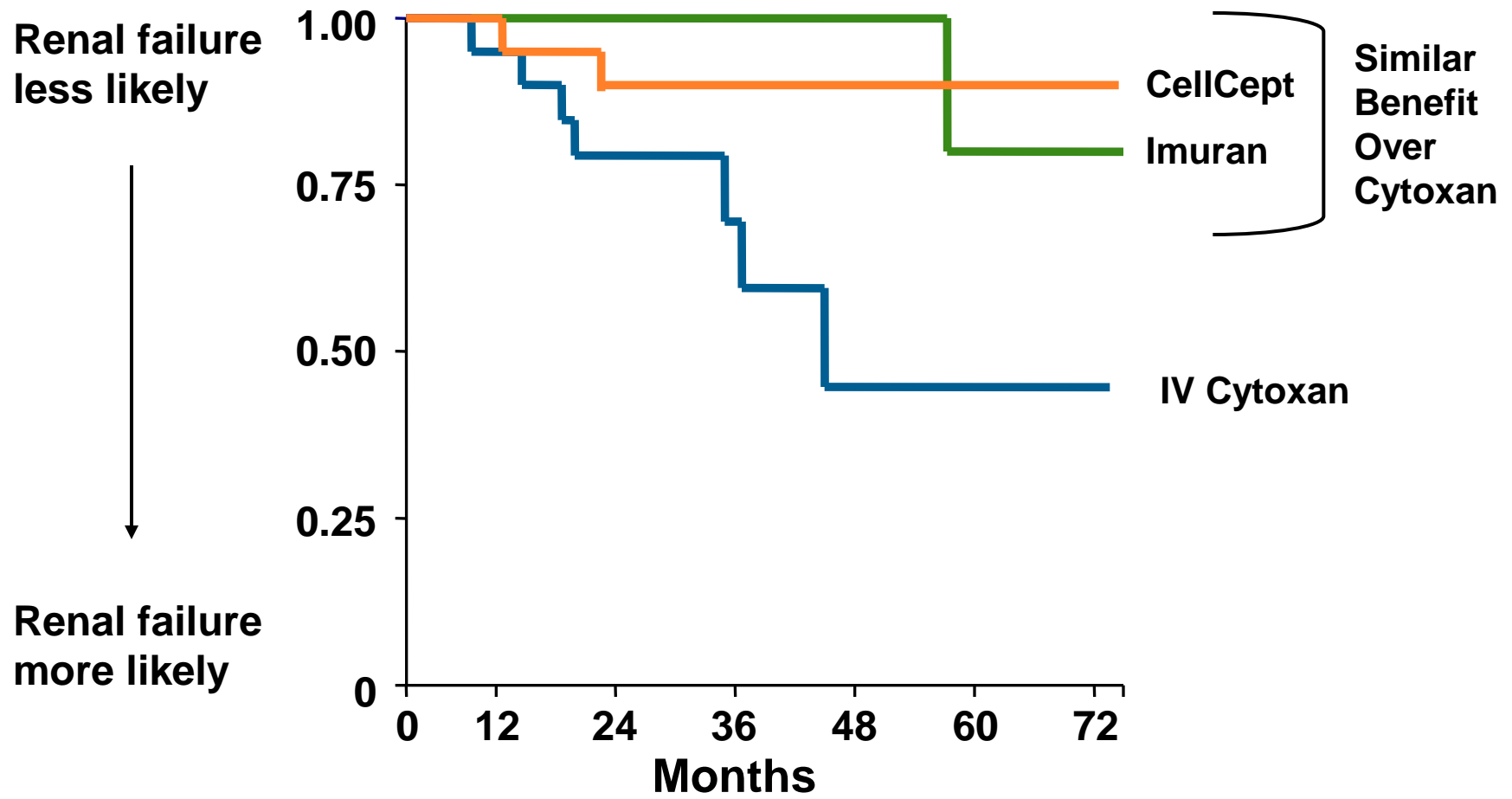
Relapse-free Survival After Achieving Remission in Patients with DPLN



Number of patients	30	27	24	22	15	9	4	CTX-AZA
	32	20	18	14	11	7	4	MMF

Induction and Maintenance Therapy for Lupus Nephritis?

Probability of Freedom From Death or Chronic Renal Failure



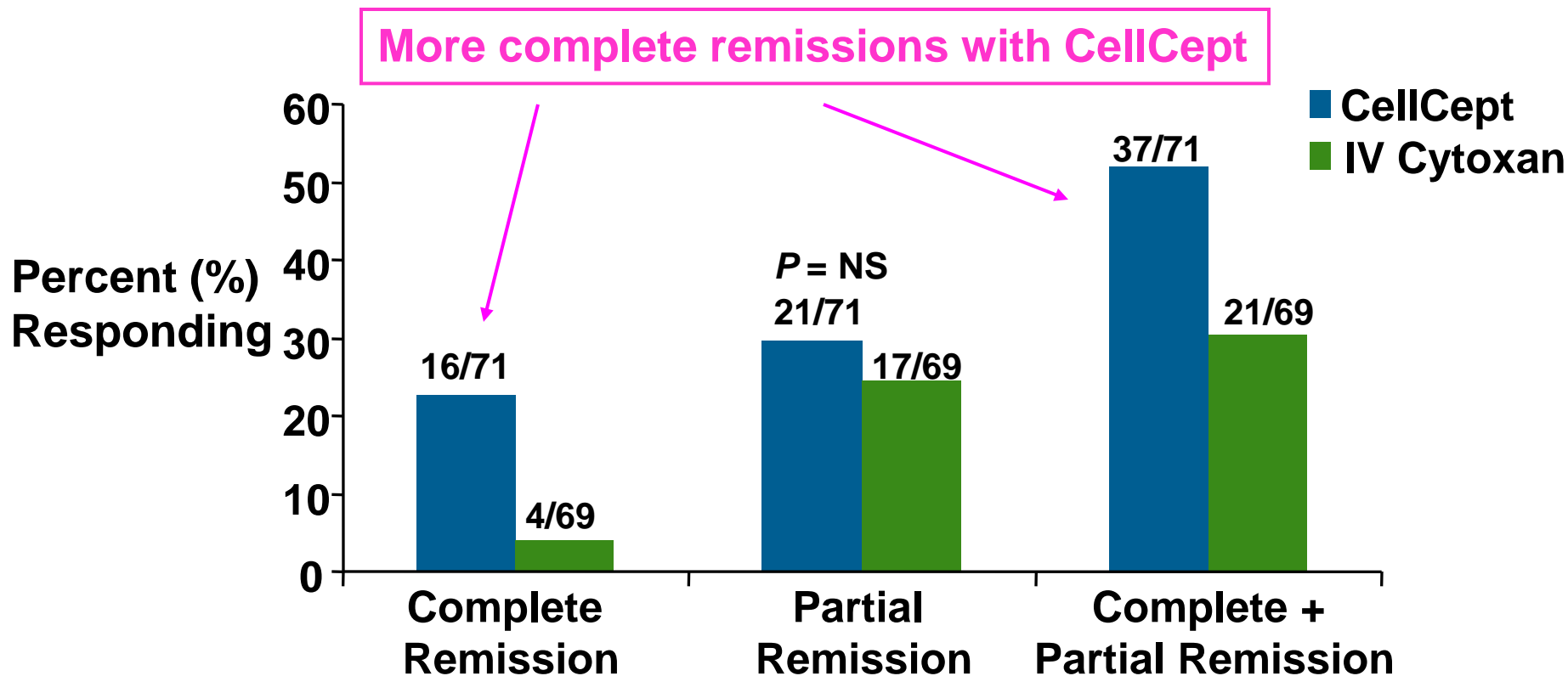
Side Effects of Therapy

	Hospital Days Per Patient Year	Loss of Menstruation (%)	Infection (%)	Major (%)
IV Cytosan	13	32	68	12
Imuran	1*	7.5*	28*	3
CellCept	1*	6.1*	21*	3

Oral CellCept vs IV Cytoxan

- Patients randomly assigned to groups
- Multiple centers involved
- Mostly female African-American patients with Class III or IV lupus nephritis
- Treatment groups
 - Oral CellCept
 - IV Cytoxan
- Measured remissions and partial remissions

CellCept vs Cytosxan Remission Rates



Similar results when African-American patients analyzed separately

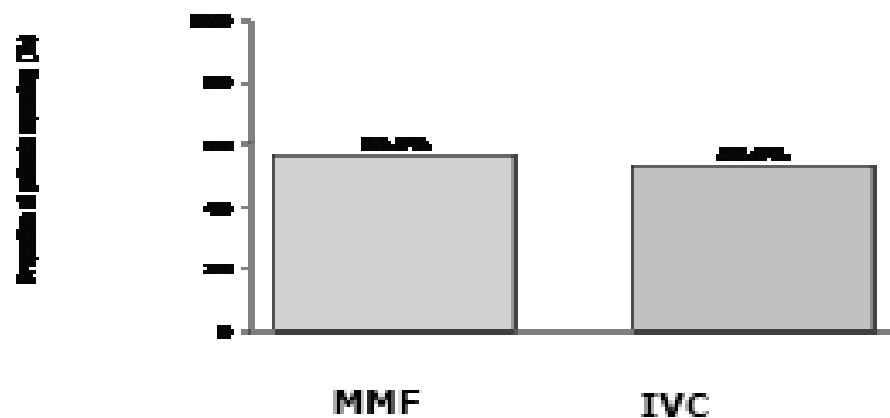
ALMS Trial - Primary Endpoint: Responders at Month 6

Response judged by
blinded Clinical Endpoint
Committee:

Decrease in proteinuria
to <3g if baseline
nephrotic ($\geq 3\text{g/d}$),
or by $\geq 50\%$ in patients with
subnephrotic (<3g/d)
proteinuria

and

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



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

Novel Approaches - Lupus Nephritis

- Directed antibody therapy
 - Anti-CD20
 - Anti-BLyS
 - Anti-CD40
 - Anti-C5
 - Anti-IL10
 - Anti-IFN- γ

Biomarkers

Take Home Messages

- Early diagnosis and therapy are important
- Combination therapy with steroids and immunosuppressive agents (e.g. cytoxan, MMF, immuran) improves results (e.g. better survival and fewer side effects)
- Outlook for African-Americans is better than ever
- New treatments are being developed and tested, and many look promising