AAV 2001-2021

Cyclophosphamide to Avacopan

Dr. John H. Stone
Massachusetts General Hospital
Harvard Medical School

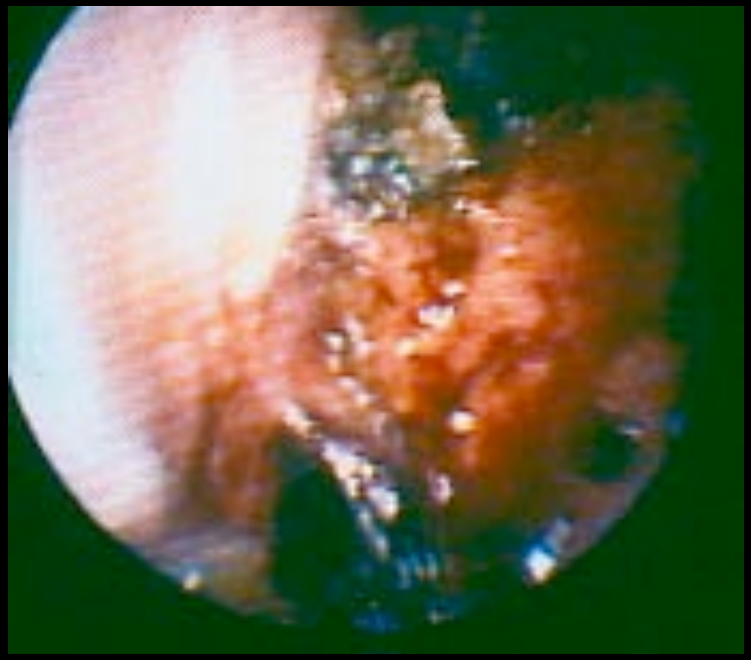
Disclosures

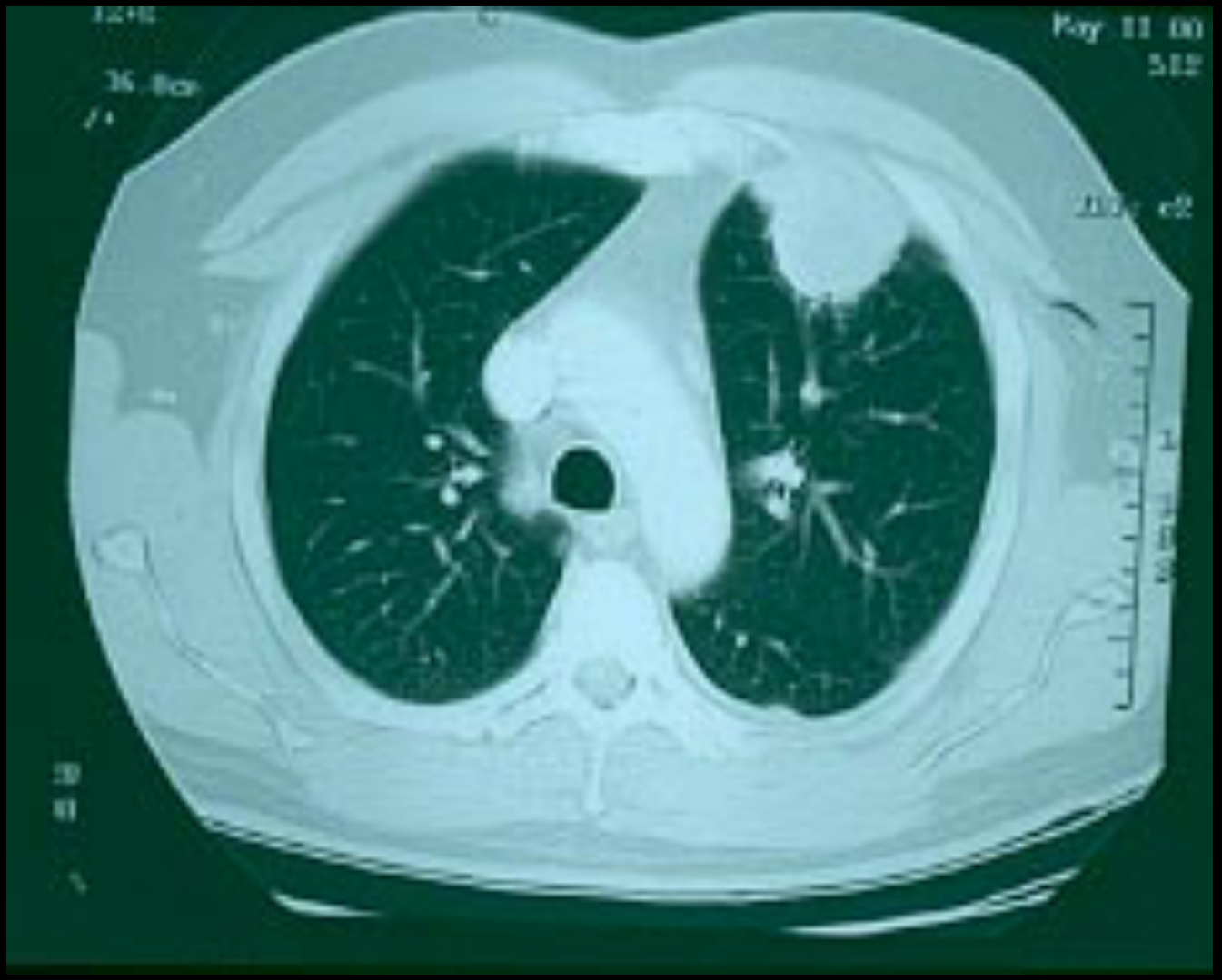
- Chemocentryx
- Roche/Genentech
- Sanofi
- Bristol-Myers Squib
- AstraZeneca
- Argenx
- AbbVie
- Q32BIO

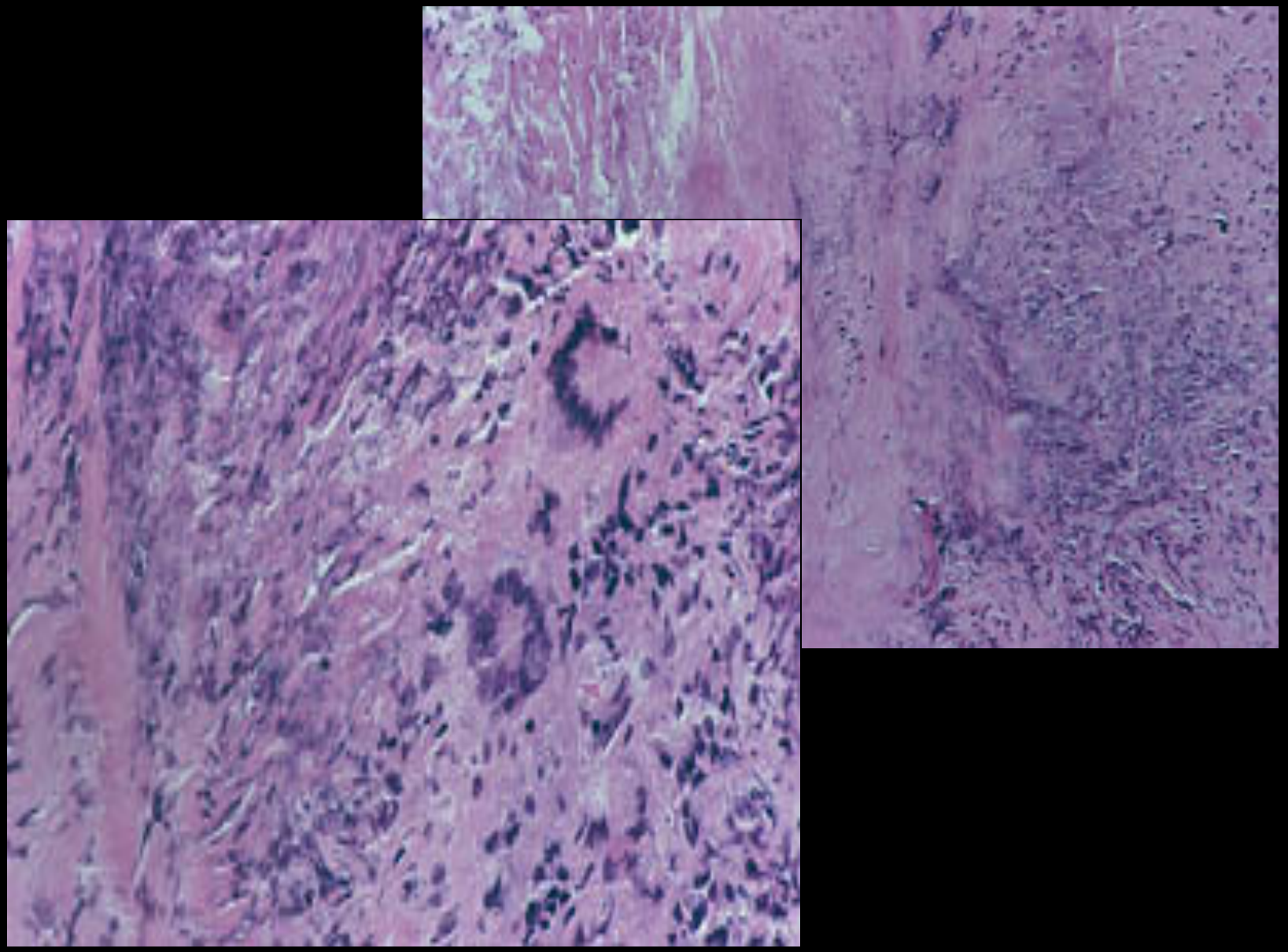
A Patient:
Mr. S

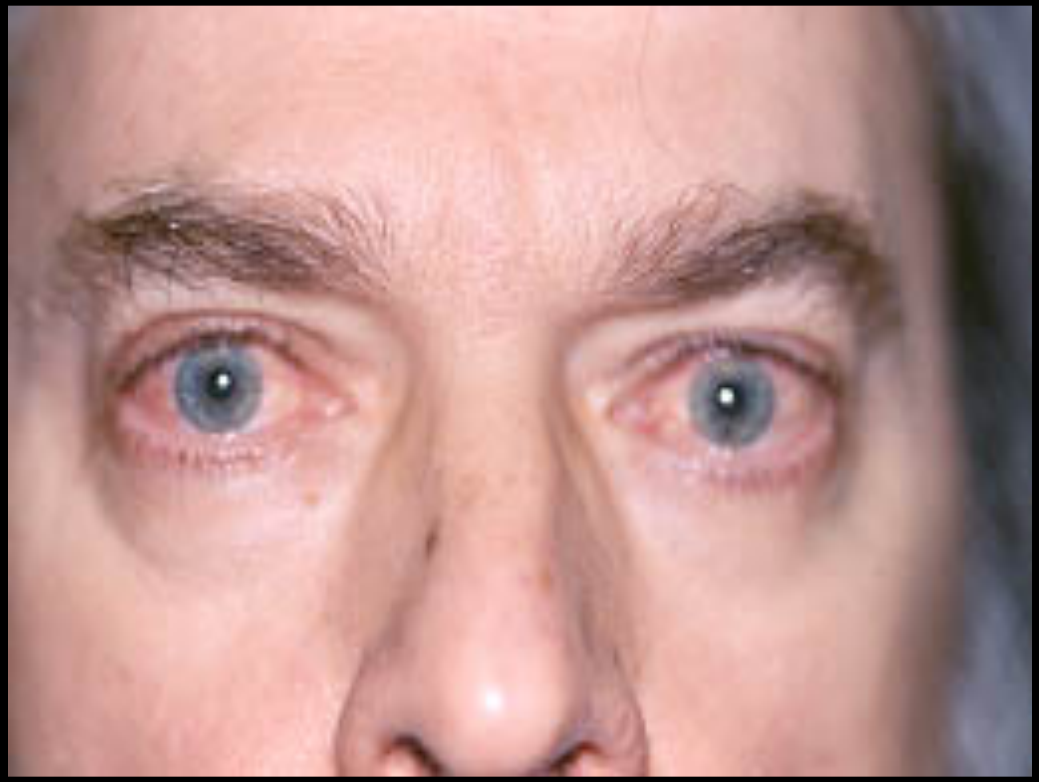
Holiday Party

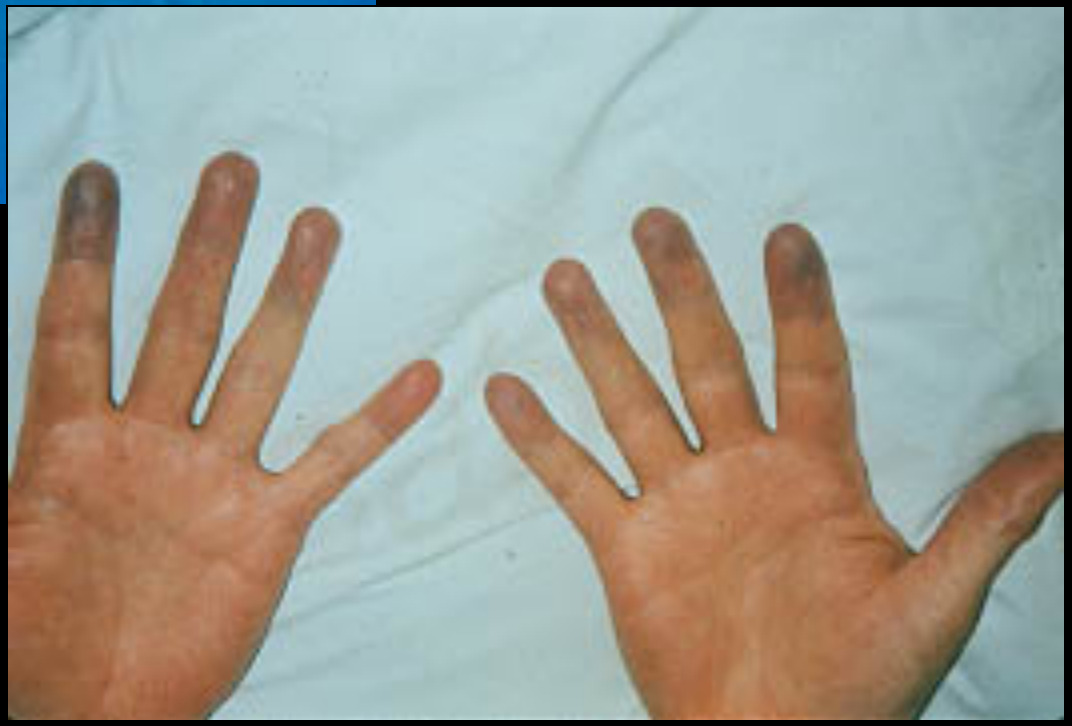
December, 2001

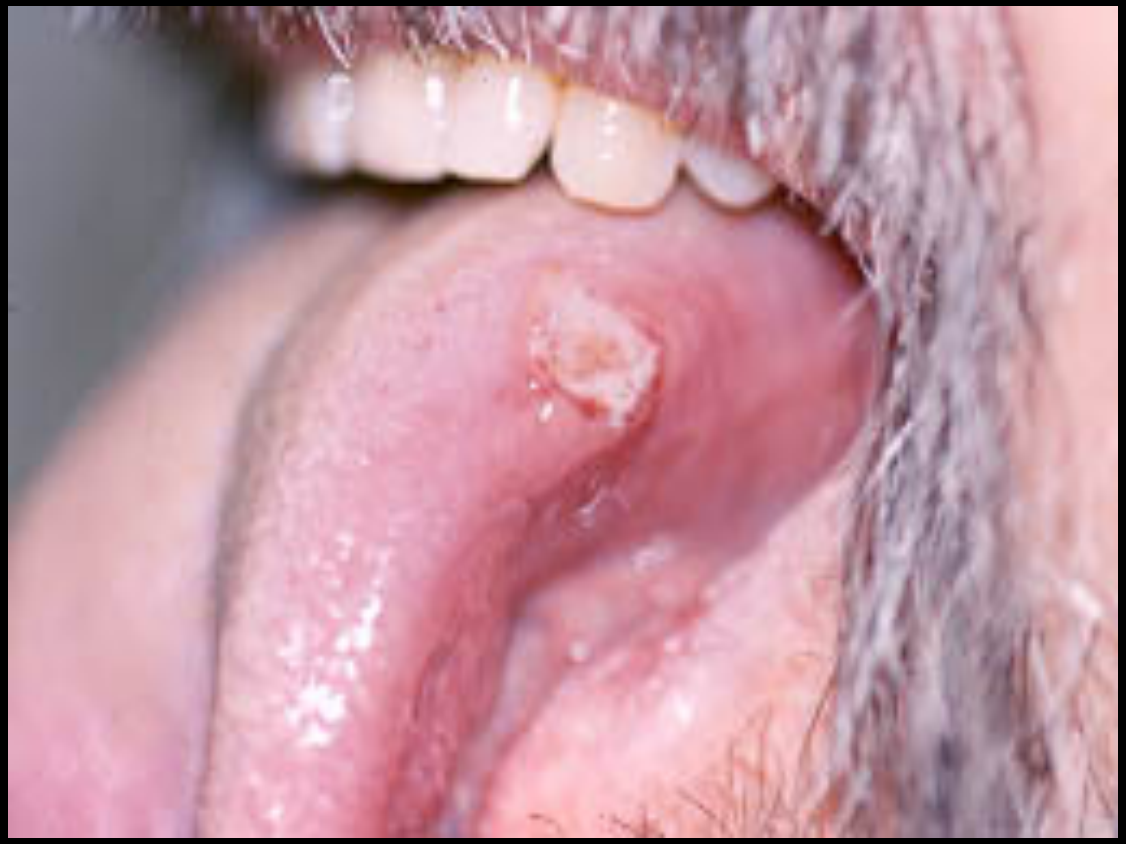


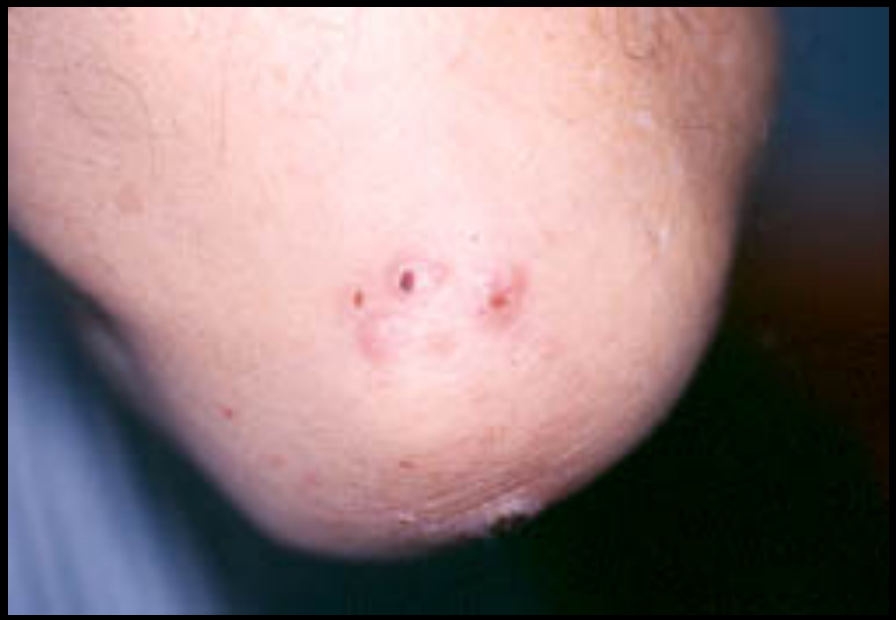






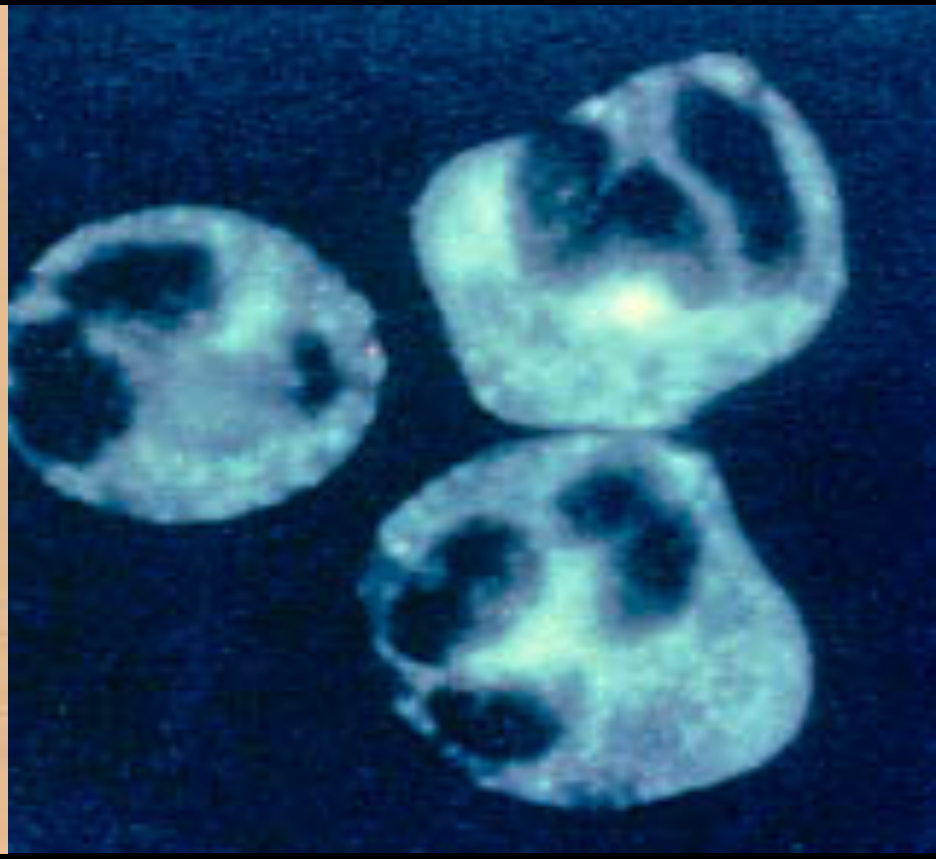






Urinalysis: 3+ proteinuria, 40-50 RBCs/hpf

Serum Cr 1.3 mg/dL



PR3-ANCA 194 (nl < 20)

Cyclophosphamide:

Daily or Intermittent?

“CYCLOPS”

I.V. CYC regimen:
Q 2 weeks

Cyclophosphamide:

Daily or Intermittent?

Titratable

Serum creatinine and BUN

Date	Creatinine (mg/dL)	BUN (mg/dL)
Feb 13th	1.3	19

Admitted

Serum creatinine and BUN

Date	Creatinine (mg/dL)	BUN (mg/dL)
Feb 13th	1.3	19
Admitted Feb 15th	1.4	22

Serum creatinine and BUN

Date	Creatinine (mg/dL)	BUN (mg/dL)
Feb 13th	1.3	19
Admitted Feb 15th	1.4	22
Feb 20th	2.7	55

Serum creatinine and BUN

	Date	Creatinine (mg/dL)	BUN (mg/dL)
Admitted	Feb 13th	1.3	19
	Feb 15th	1.4	22
	Feb 20th	2.7	55
	Feb 25th	5.1	81

Serum creatinine and BUN

	Date	Creatinine (mg/dL)	BUN (mg/dL)
Admitted	Feb 13th	1.3	19
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Serum creatinine and BUN

	Date	Creatinine (mg/dL)	BUN (mg/dL)
Admitted	Feb 13th	1.3	19
	Feb 15th	1.4	22
	Feb 20th	2.7	55
	Feb 25th	5.1	81
Admitted	Mar 4th	7.4	101

Serum creatinine and BUN

	Date	Creatinine (mg/dL)	BUN (mg/dL)
	Feb 13th	1.3	19
Admitted	Feb 15th	1.4	22
	Feb 20th	2.7	55
	Feb 25th	5.1	81
Admitted	Mar 4th	7.4	101
	Mar 6th	8.1	115

Serum creatinine and BUN

	Date	Creatinine (mg/dL)	BUN (mg/dL)
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	Feb 20th	2.7	55
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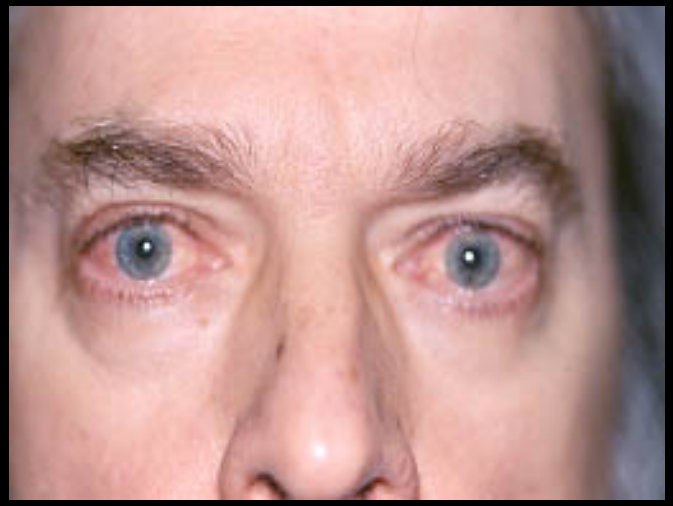
Admitted	Mar 4th	7.4	101
	Mar 6th	8.1	115

What next?…



Serum creatinine = 8.1 mg/dL

Options:

Door A: More steroids?
Door B: Increase cyclophosphamide?
Door C: Kidney biopsy?
Door D: Plasma exchange?

What About Plasma Exchange?

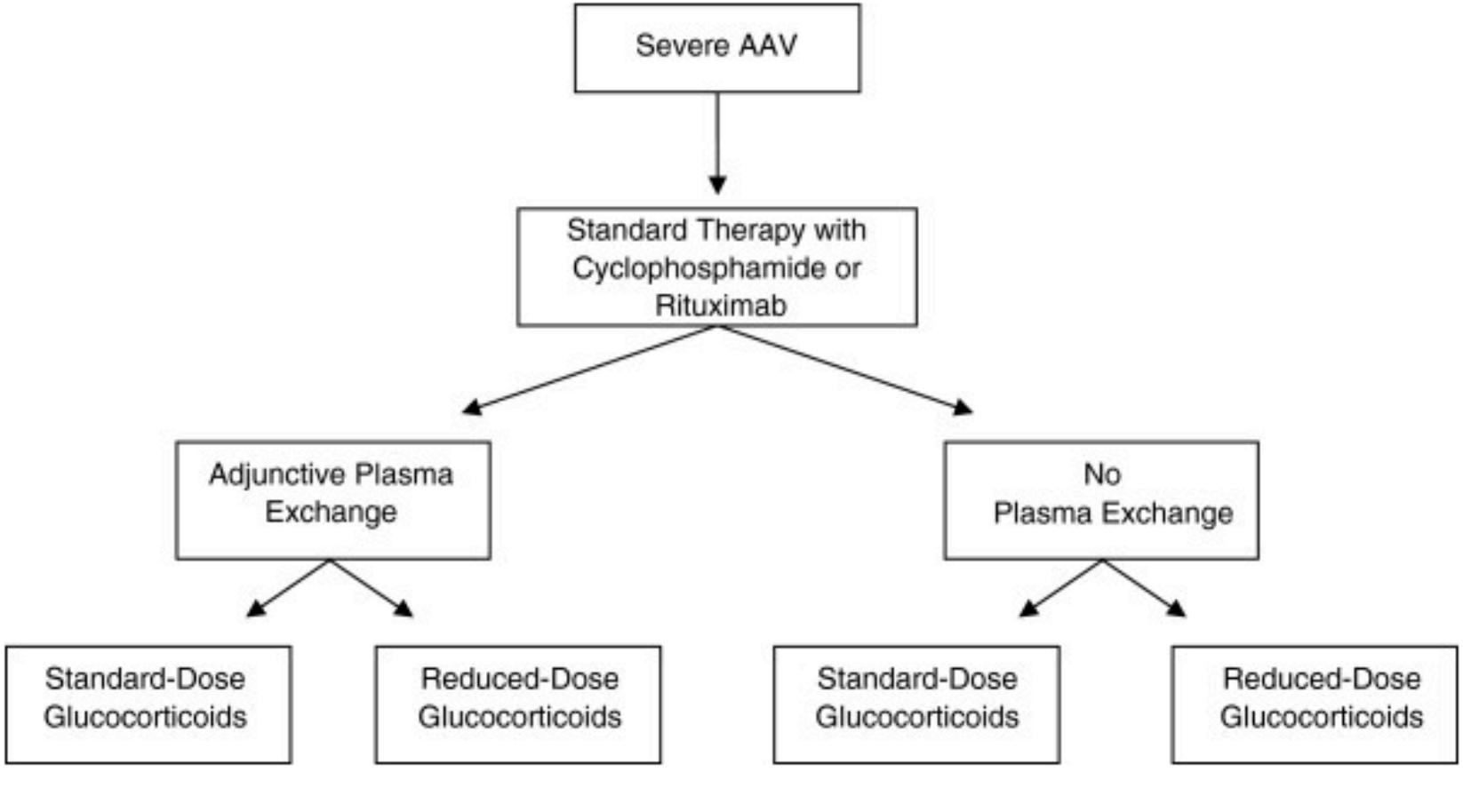
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

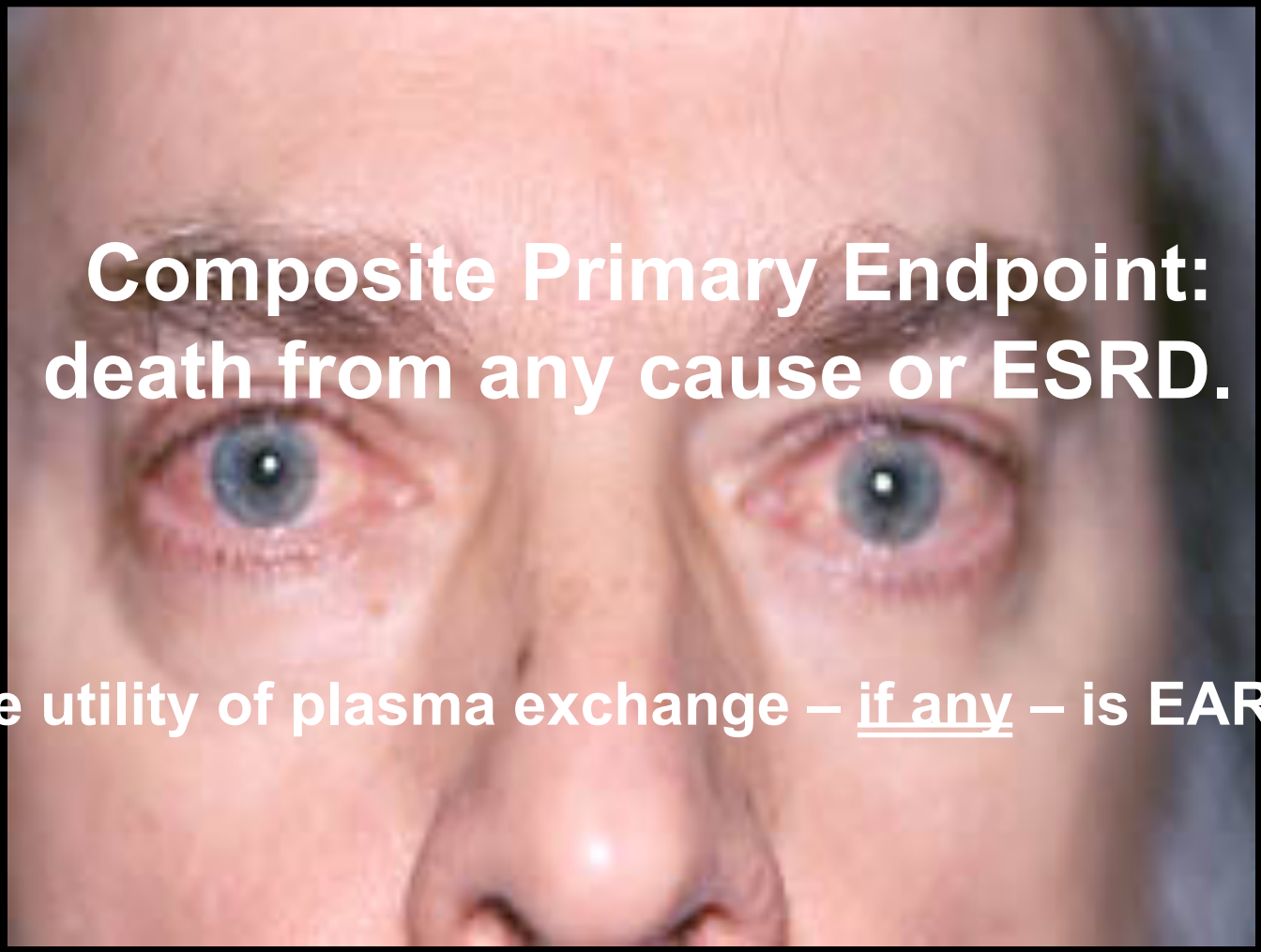
Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

Would Plasma Exchange Have Altered Mr. S' Outcome?

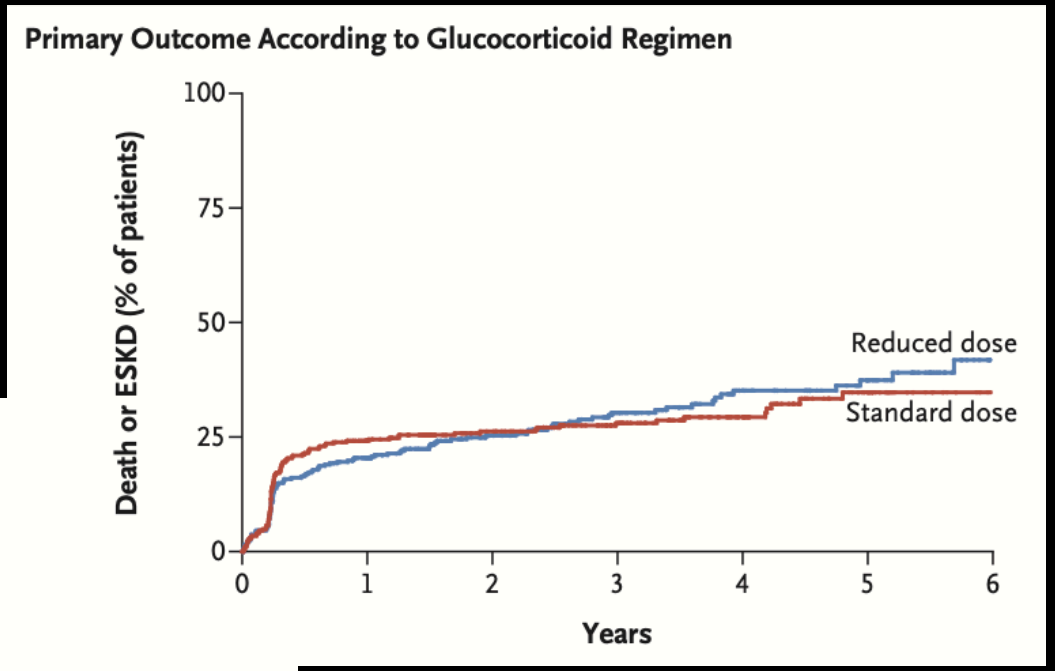


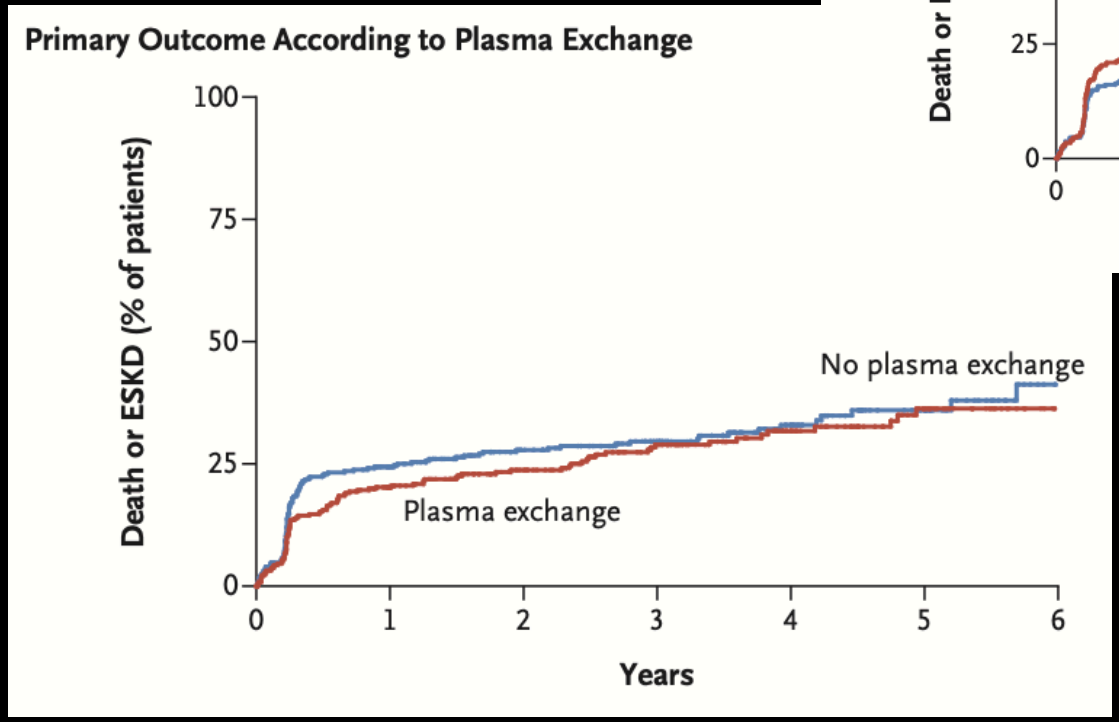
PEXIVAS: Doomed to Fail



The utility of plasma exchange – <u>if any</u> – is EARLY

Primary Outcome





Secondary Outcomes

Secondary Outcome	Plasma Exchange vs. No Plasma Exchange	Reduced-Dose vs. Standard-Dose Glucocorticoid Regimen
	effect size (95% CI)	
Death from any cause	0.87 (0.58–1.29)	0.78 (0.53–1.17)
End-stage kidney disease	0.81 (0.57–1.13)	0.96 (0.68–1.34)
Sustained remission	1.01 (0.89–1.15)	1.04 (0.92–1.19)
Serious adverse events	1.21 (0.96–1.52)	0.95 (0.75–1.20)
Serious infections at 1 year	1.16 (0.87–1.56)	0.69 (0.52–0.93)

Other Problems with PEXIVAS

- Underlying Premise
- Steroid regimen
- Does it convince anyone?

Conclusions:

1. Plasma exchange does not reduce the incidence of death or ESKD.

2. A faster glucocorticoid taper was noninferior to a standard-dose regimen with respect to death or ESKD.

Editorial

“Without baseline biopsy data, the proportion of patients who had kidney dysfunction caused by active inflammation, which may respond to immunomodulatory therapy, as compared with chronic sclerosis, which would not respond to this therapy, is unknown….”

Editorial

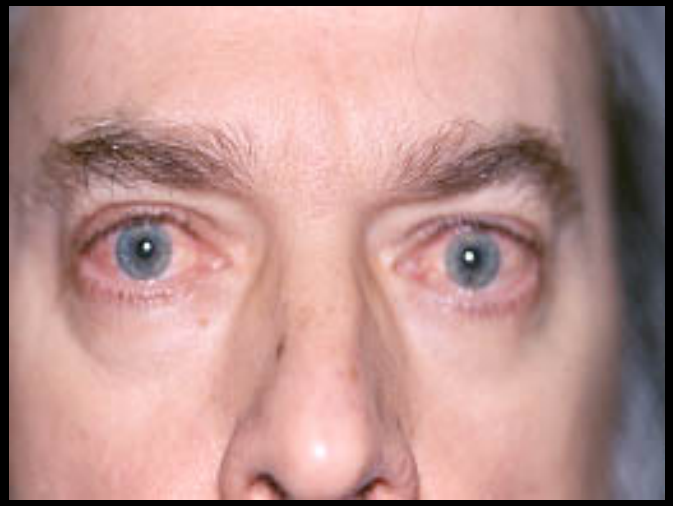
"Without baseline biopsy data, the proportion of patients who had kidney dysfunction caused by active inflammation, which may respond to immunomodulatory therapy, as compared with chronic sclerosis, which would not respond to this therapy, is unknown. A subgroup of patients with aggressive kidney disease with minimal scarring may benefit from plasma exchange."

Editorial (cont.):

“In our judgment, until a study specifically designed to evaluate efficacy in patients with pulmonary hemorrhage has been performed,

Editorial (cont.):

"In our judgment, until a study specifically designed to evaluate efficacy in patients with pulmonary hemorrhage has been performed, plasma exchange should remain part of the induction regimen for patients with ANCA-induced pulmonary hemorrhage."



Serum creatinine = 8.1 mg/dL

Options:

Door A: More steroids?
Door B: Increase cyclophosphamide?
Door C: Kidney biopsy?
Door D: Plasma exchange?

CYC lowered as
renal function worsened:

125 mg/day $\rightarrow\rightarrow$ 50 mg/day

Date	Creatinine (mg/dL)	BUN (mg/dL)
Mar 18th, ‘02	4.7	74
Mar 25th, ‘02	3.2	54
May 10th, ‘02	1.9	20
June 10th, ‘02	1.8	20

Date	Creatinine (mg/dL)	BUN (mg/dL)
Mar 18th, '02	4.7	74
Mar 25th, '02	3.2	54
May 10th, '02	1.9	20
June 10th, '02	1.8	20

→ Azathioprine 100 mg/day

2007	1.9	ANCA negative


• Recurrence
• Renal failure
• Transplant
• CMV retinitis
• Blind

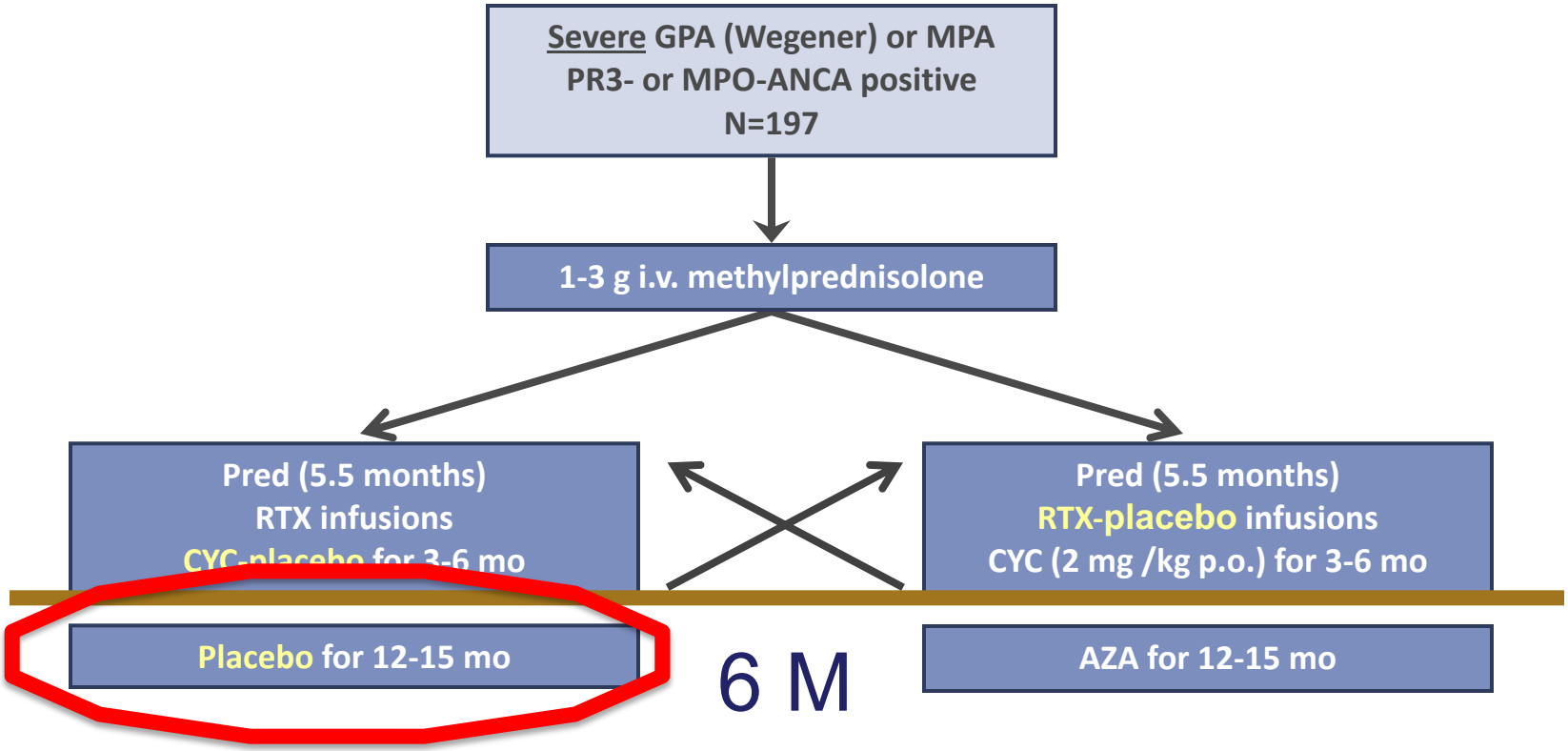
WHAT CAUSED THIS?

- Transplant regimen?
- Azathioprine?
- Cyclophosphamide?
- Rituximab?
- **Glucorticoids?**

The RAVE Trial

- Challenged CYC head to head
- Stopped prednisone completely in < 6 months
- Blinded trial

RAVE Trial Design



RAVE Primary Endpoint (6 mos)

BVAS/WG = 0 *and* Prednisone = 0 mg

CYC (N=98)
53%

Only 53% of CYC-treated patients achieved the primary outcome?

Why?

The trial was blinded

Prednisone stopped entirely

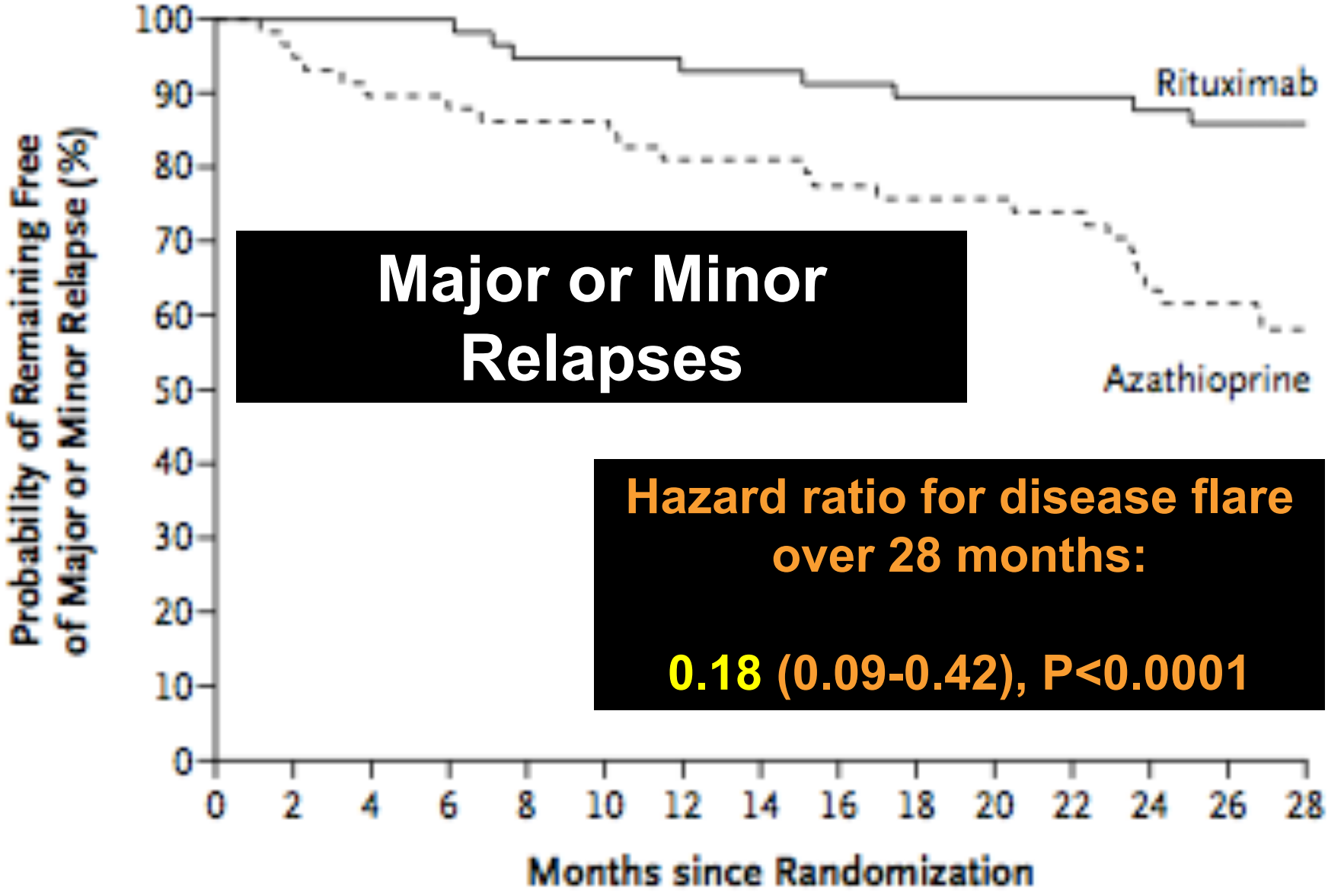
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

A positive superiority trial against an active comparator.


Probability of Remaining Free of Major or Minor Relapse (%)
100
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28
Months since Randomization
Rituximab
Azathioprine
Major or Minor Relapses
Hazard ratio for disease flare over 28 months:
0.18 (0.09-0.42), P<0.0001

But we really do have another problem…

42% of the patients in RAVE were primary outcome failures

ARTHRITIS & RHEUMATISM
Vol. 65, No. 9, September 2013, pp 2441–2449
DOI 10.1002/art.38044

Clinical Outcomes of Remission Induction Therapy for Severe Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

E. M. Miloslavsky,[1] U. Specks,[2] P. A. Merkel,[3] P. Seo,[4] R. Spiera,[5] C. A. Langford,[6] G. S. Hoffman,[6] C. G. M. Kallenberg,[7] E. W. St.Clair,[8] N. K. Tchao,[9] L. Viviano,[10] L. Ding,[10] L. P. Sejismundo,[4] K. Mieras,[2] D. Iklé,[11] B. Jepson,[11] M. Mueller,[12] P. Brunetta,[13] N. B. Allen,[8] F. C. Fervenza,[2] D. Geetha,[4] K. Keogh,[2] E. Y. Kissin,[14] P. A. Monach,[14] T. Peikert,[2] C. Stegeman,[7] S. R. Ytterberg,[2] and J. H. Stone,[1] for the Rituximab in ANCA-Associated Vasculitis–Immune Tolerance Network Research Group

Six-Month Outcomes

RTX	Outcome	CYC/AZA
7	Uncontrolled Disease	3
3	Severe Flare	9
11	Limited Flare	14
5	Adverse Event	10
9	BVAS/WG > 0 or still on prednisone	11
1	Other	2
1	Death	2

47 of 197 patients (24%) failed within the first six months because of active disease.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

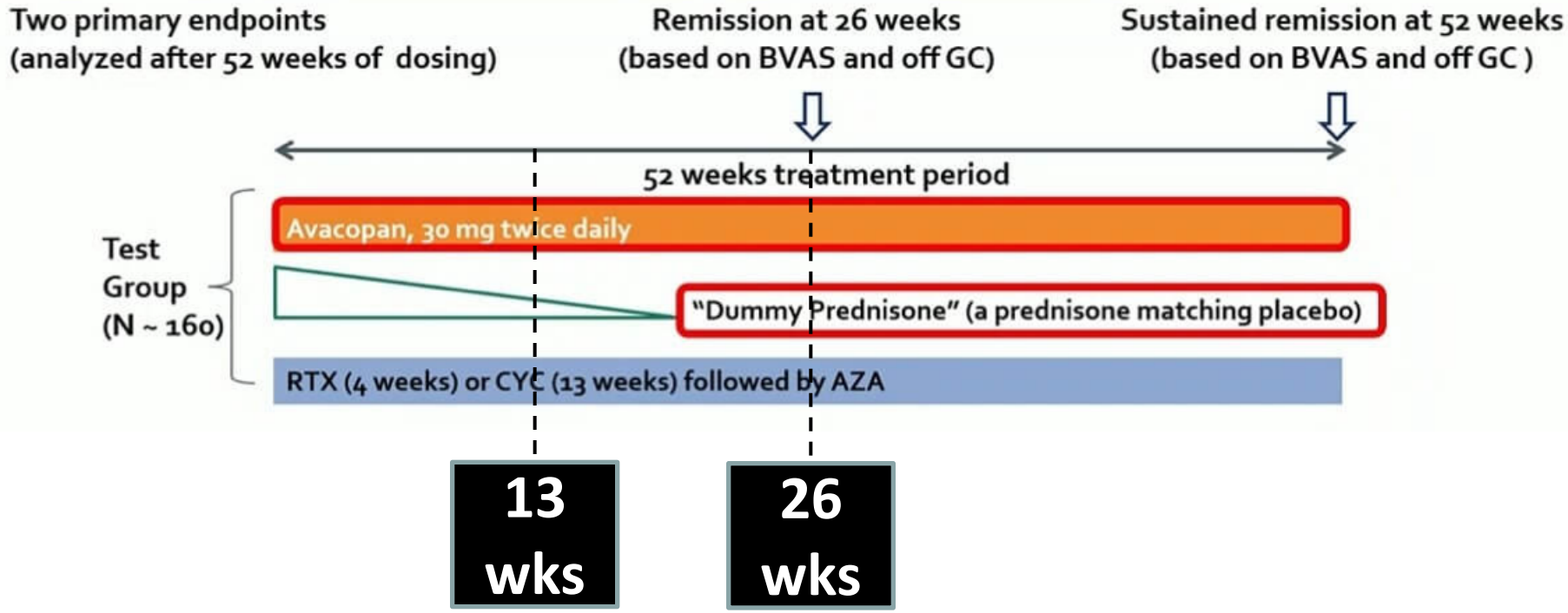
Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*

Avacopan:
First-in-class complement inhibitor

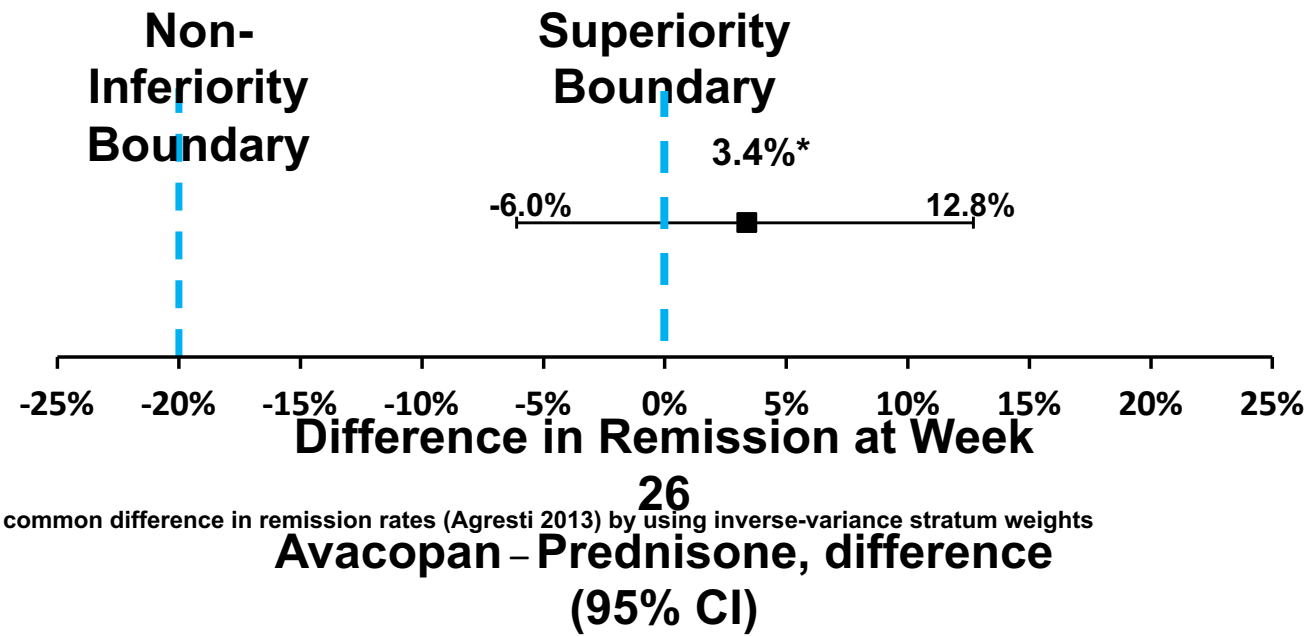
Reduction in steroid morbidity:
Glucocorticoid Toxicity Index (GTI)

ADVOCATE Trial Design



Primary Endpoint: Avacopan Non-Inferior to Prednisone in Week 26 Clinical Remission

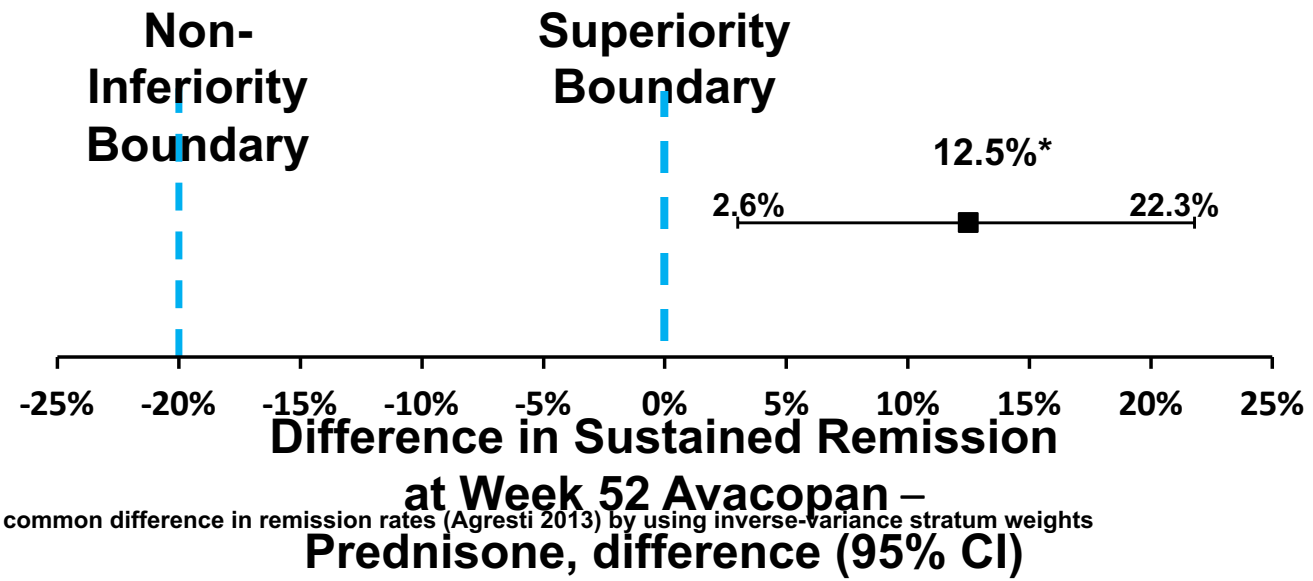
	Patients Achieving Clinical Remission n (%)	Non-Inferiority p-value	Superiority p-value
Avacopan (N=166)	120 (72.3%)	< 0.0001	0.2387
Prednisone (N=164)	115 (70.1%)		



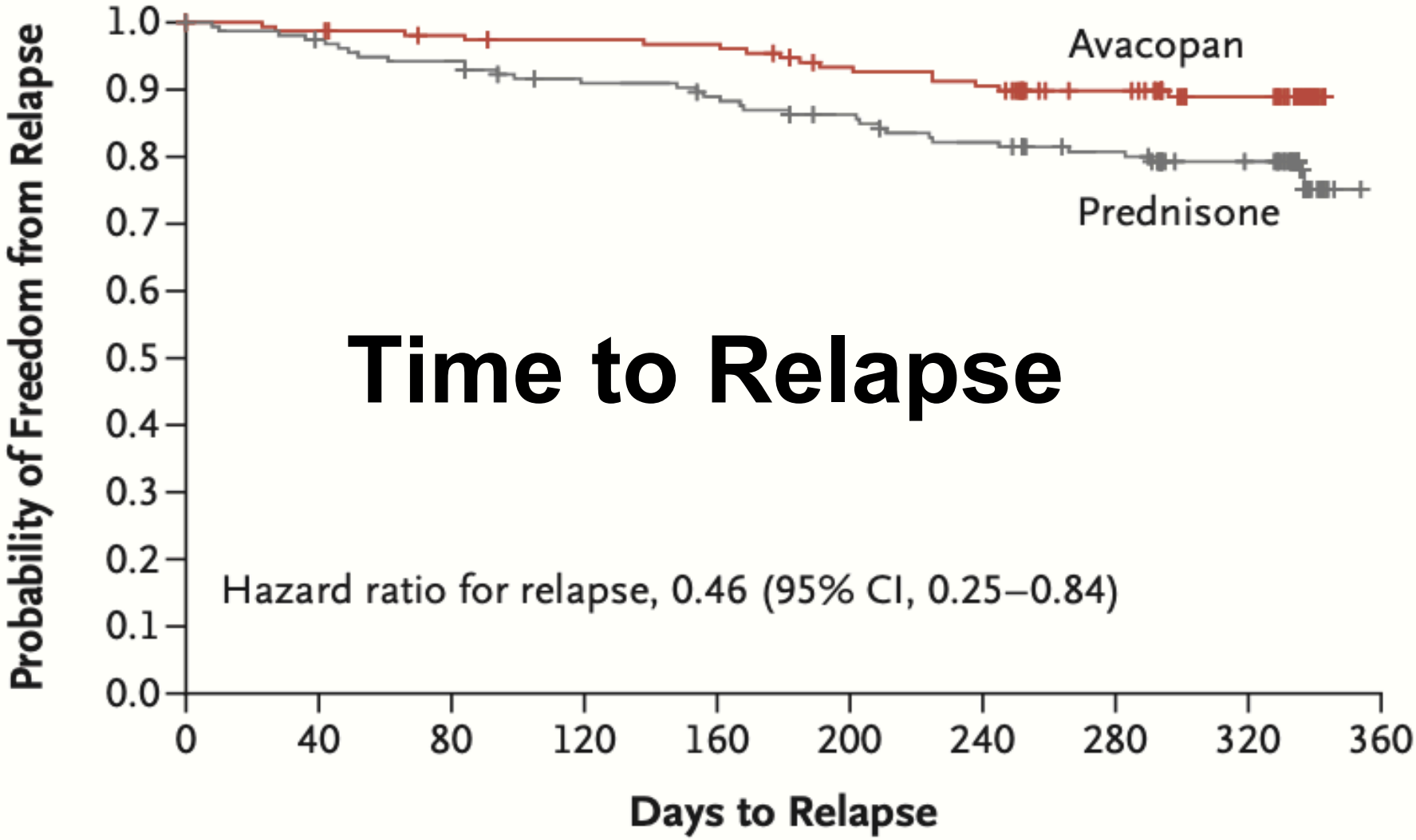
*Summary score estimate of common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights

Primary Endpoint: Avacopan Superior to Prednisone in Week 52 Sustained Remission

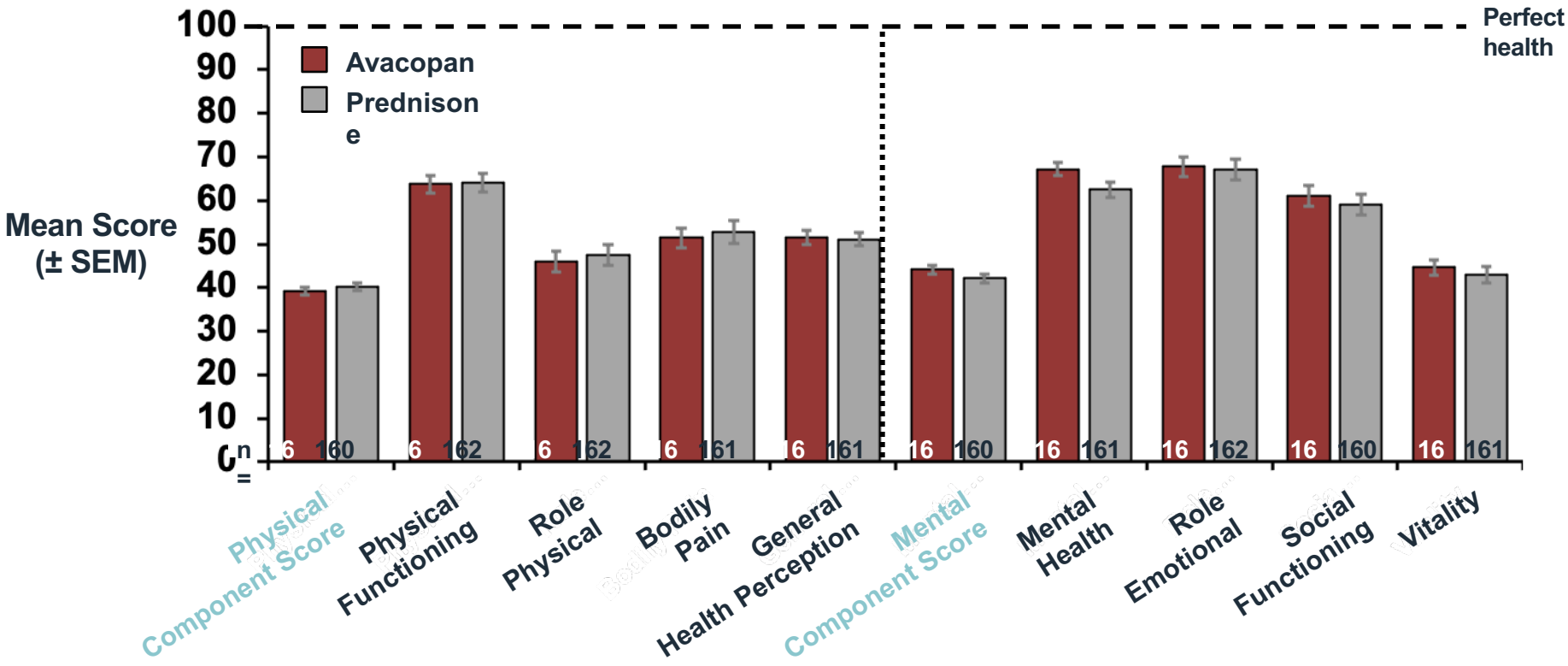
	Patients Achieving Sustained Remission n (%)	Non-Inferiority p-value	Superiority p-value
Avacopan (N=166)	109 (65.7%)	< 0.0001	0.0066
Prednisone (N=164)	90 (54.9%)		



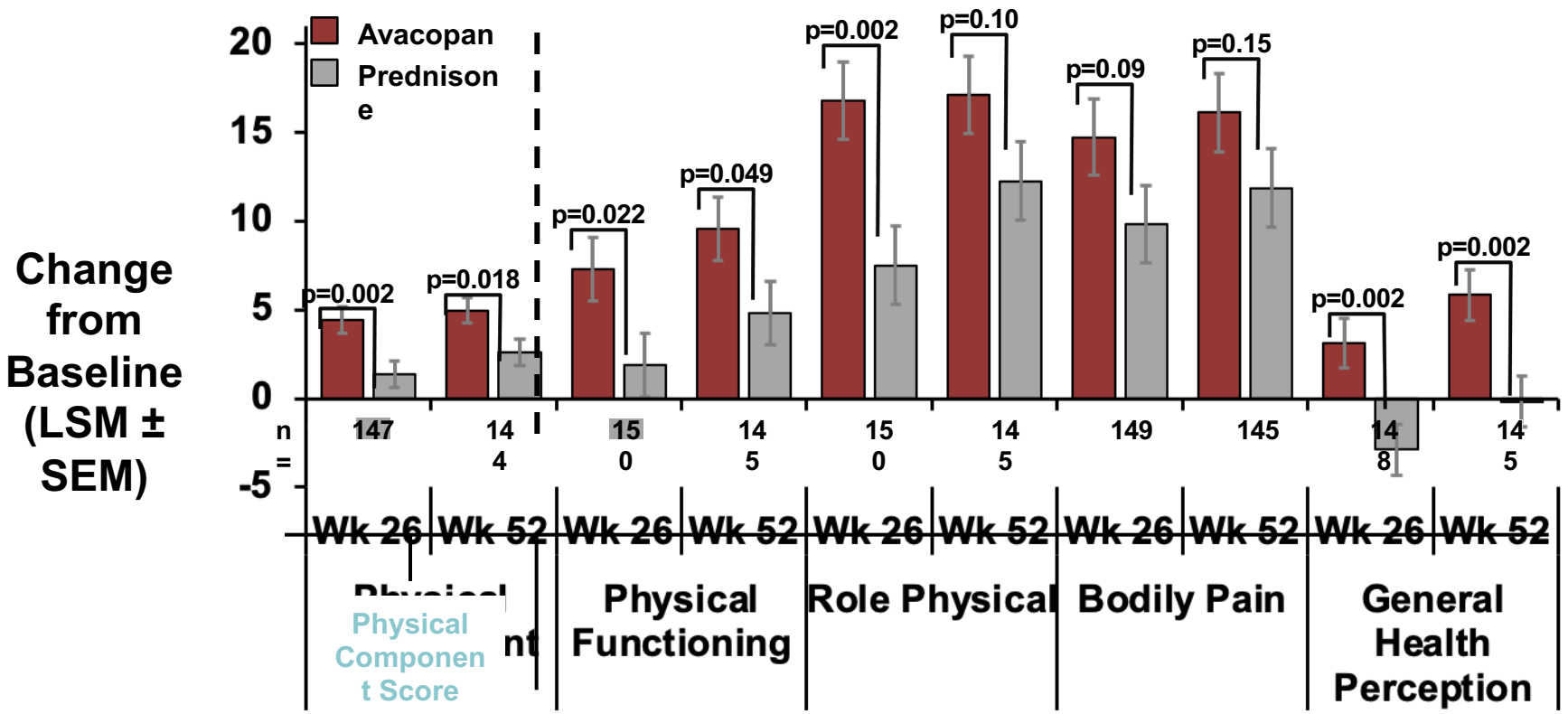
*Summary score estimate of common difference in remission rates (Agresti 2013) by using inverse-variance stratum weights


Probability of Freedom from Relapse
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Avacopan
Prednisone
Time to Relapse
Hazard ratio for relapse, 0.46 (95% CI, 0.25–0.84)
0
40
80
120
160
200
240
280
320
360
Days to Relapse

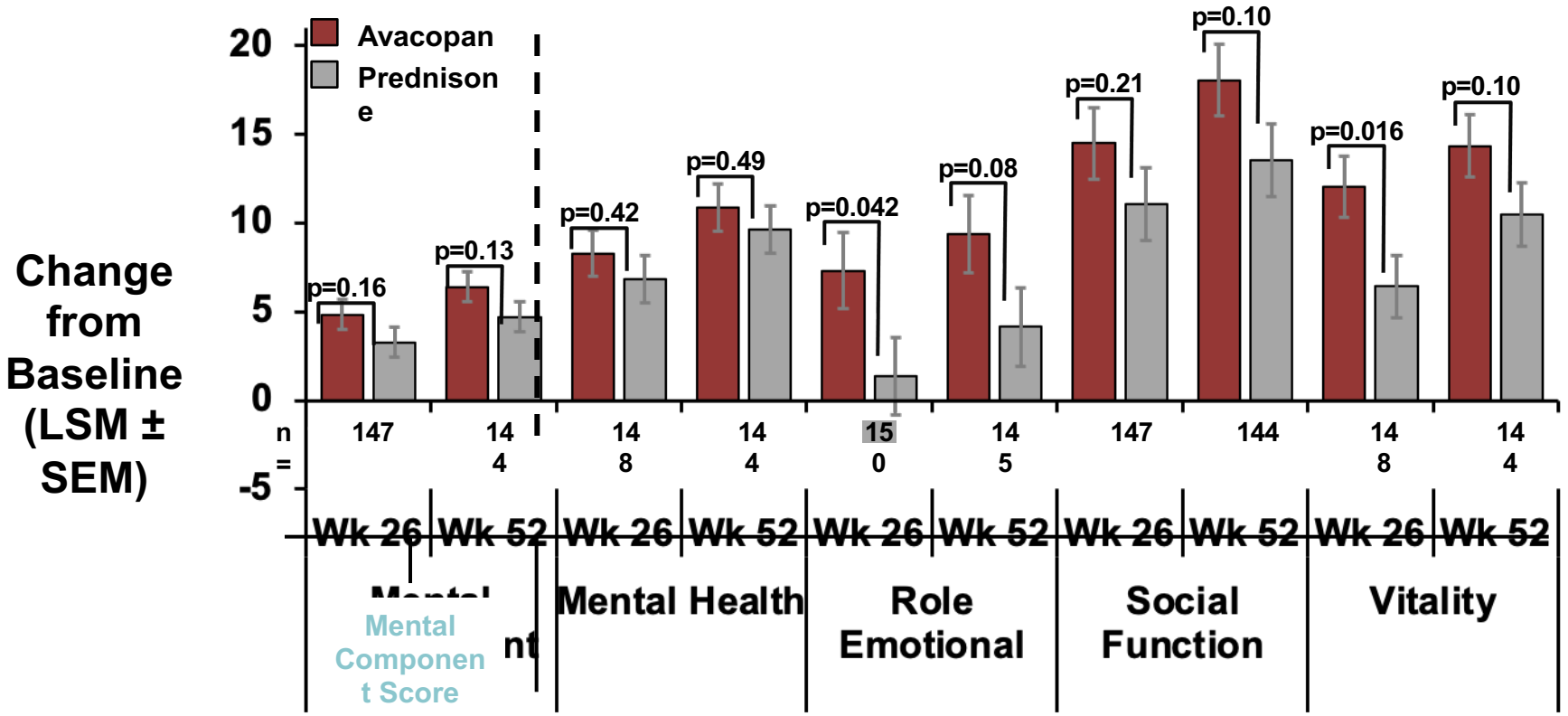
Impaired QOL at Baseline Measured by SF-36



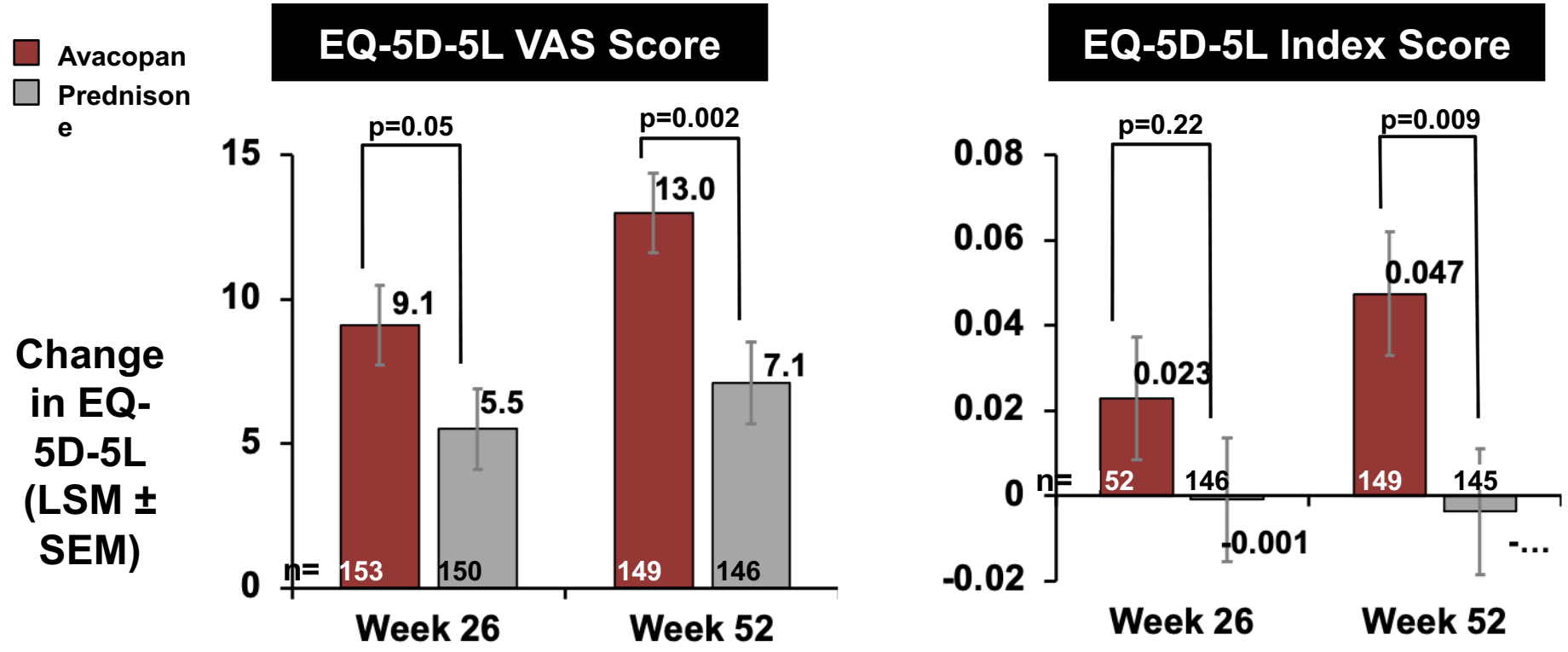
Avacopan Improved Health-Related QoL: SF-36 Physical Component Domains



SF-36 Mental Component Domains



Significant Improvement in EQ-5D-5L at Week 52 with Avacopan Compared to Prednisone



VAS = visual analogue scale (0-100)

Treating Mr. S: 2021

- **Rituximab + avacopan**
  - Minimal prednisone
  - No cyclophosphamide
  - Consider additional RTX at four months
- **Follow closely**
  - Re-induce if disease returns
- **Maintenance?**

Thank you!