Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417-27. DOI: 10.1056/NEJMoa1213277

(PDF updated August 2, 2013.)

SUPPLEMENTARY APPENDIX

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Immune Tolerance Network TrialShare System

The data and figures of this report are accessible through the ITN TrialShare system (itntrialshare.org). The reader can view and filter the underlying data to generate figures and analysis results in addition to those presented in this report.

Logging in for the first time:

Click the "Create An Account" button on the itntrialshare.org home page. An email will be sent to activate your account and set up your password. This takes no more than 2-3 minutes.

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- When you log on to **itntrialshare.org** you will see the ITN TrialShare Home page. Click on the study links on the Welcome and Study Catalog tabs to navigate to a specific study.

- In addition, navigate to any study section by clicking the appropriate links available in the navigator tree on the right.

- One can download the study protocol and view study datasets in the Study Navigator on the Overview tab.

- Analysis datasets and reports are available on the Data & Reports tab of a study.

- See individual participant level data views on the Participants tab of a study. Some fields have been masked in order to protect personal identifying information.

- For more information, refer to the guides and video tutorials available on the Home page "Getting Started" tab.

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Supplementary Methods

Definition of Severe Disease

The designation "severe" ANCA-associated vasculitis applied in this trial is defined as disease activity that threatens the function of the affected organ and has the potential to induce irreversible organ damage or to threaten the patient's life unless effective therapy is implemented promptly. Such disease manifestations include scleritis, peripheral or central nervous system involvement, alveolar hemorrhage, gastrointestinal involvement and glomerulonephritis.

This definition of severe disease formed the basis for the validated vasculitis disease activity assessment instrument BVAS/WG that was used in the Wegener's Granulomatosis Etanercept Trial as well as this trial.[1,2,3] This definition of severe disease applied equally to patients with a new diagnosis or relapsing disease at baseline as well as to relapses occurring during the trial.[3]

At inception of the trial patients with one or more of these disease manifestations were considered to have severe disease that warrants treatment with the combination of glucocorticoids and cyclophosphamide as the standard of care.[2]

Patients fulfilling this definition of severe disease have been referred to by a variety of different terms including "generalized"[4], "generalized organ-threatening"[5] or simply "organ-threatening"[6] by other investigators, who all agreed at the time our trial began that such patients should receive glucocorticoids in combination with cyclophosphamide for remission induction.

The definition of severe ANCA-associated vasculitis applied in this trial needs to be distinguished from the term "severe renal disease" which is applied by some investigators for patients with serum creatinine >5.6 mg/dl.[5,6]

1. Stone JH, et al. Arthritis Rheum 2001;44:912-20.
2. TheWGETResearchGroup. N Engl J Med 2005;352:351-61.
3. Stone JH, et al. N Engl J Med 2010;363:221-32.
4. Jayne D, et al. N Engl J Med 2003;349:36-44.
5. Lapraik C,et al. Rheumatology 2007;46:1615-6.
6. Menahem S, et al. Nephrology 2008; 13:S24-S36.

Schematic of Trial Design

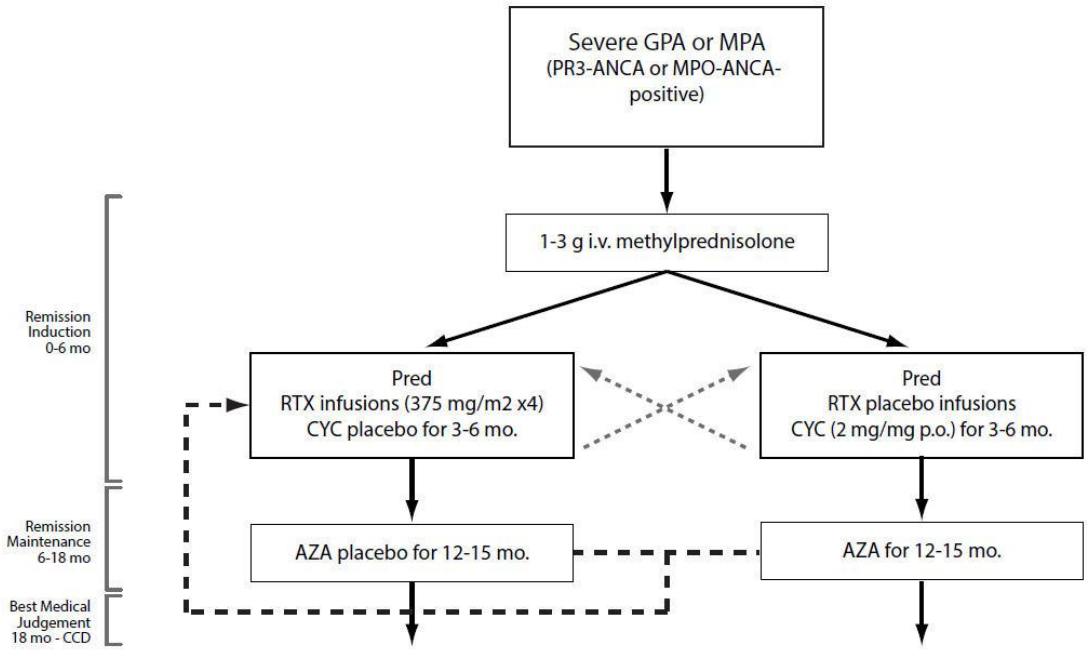


Figure S1 Diagram of the trial design

The experimental treatment phase consisted of a 6 months remission induction phase followed by a 12 months remission maintenance phase. Patients who remained on the originally assigned treatment through month 18 were subsequently treated according to best medical judgment and followed for safety until the common close-out date (CCD). The CCD was the date the last enrolled patient completed 18 months of study therapy. The primary endpoint was at 6 months.

Patients who experienced a severe flare between month 1 and month 6 were eligible for blinded cross-over to the opposite treatment arm. Patients who experienced a severe flare between months 6 and 18 were eligible for treatment with the rituximab remission induction regimen applied in an open-label fashion.

Patients who experienced a limited disease relapse were treated with an increased dose of prednisone determined by the investigator followed by the protocol-prescribed prednisone dose taper. These patients remained in the originally assigned treatment group unless their disease progressed to a severe relapse, or they developed another reason to discontinue the protocol-prescribed treatment and were switched to treatment according to best medical judgment.

Patients who achieved remission and did not have a severe relapse remained on the originally assigned treatment through 18 months. Consequently, patients assigned to rituximab received no other immunosuppressive treatment after achieving complete remission, unless they developed a relapse.

Depending on the timing of the severe disease flare, patients who suffered such relapses could be exposed to the following sequence of remission induction therapies: rituximab, followed by cyclophosphamide, cyclophosphamide followed by rituximab, rituximab followed by rituximab, cyclophosphamide/azathioprine followed by rituximab.

Treatment of Disease Relapses

Patients who experienced severe relapses during the first 6 months were eligible for blinded crossover to the opposite treatment arm and received the other full remission induction regimen[3,8]. Patients who experienced severe relapses between months 6 and 18 were eligible for re-induction with open-label rituximab and glucocorticoids. Limited relapses were treated with prednisone[3,8].

Potential Reasons for Primary Outcome Failure at Month 6, 12 and 18.

Complete remission is defined as having achieved a BVAS/WG = 0 and having discontinued prednisone regardless of being on or off maintenance azathioprine or azathioprine-placebo at 6, 12, and 18 months.

The percentage of participants in complete remission at 12 and 18 months after randomization was analyzed within the intention-to-treat sample. Participants were classified as **treatment failures** for each specific time point of analysis (6, 12 or 18 months) if any of the following conditions were met prior to the time point of interest:

- Participants were classified as an Early Treatment Failure at or before month 1.
- Participants had experienced a severe disease relapse.
- Participants had experienced a limited disease relapse.
- Participants crossed over to the other treatment arm.
- Participants received treatment with open-label rituximab and glucocorticoids for a severe disease relapse.
- Participants were treated with an increased prednisone dose for a limited disease relapse.
- Participants were removed from protocol-prescribed study therapy and treated according to best medical judgment.
- Participant died.

Disease relapses were defined as a BVAS/WG increase $\geq$1 after achieving a BVAS/WG of 0. A relapse was defined as severe if at least one major BVAS/WG item was scored.

Statistical Analyses

All comparisons of subjects achieving a binary outcome, remaining on original treatment, or experiencing a flare or adverse event use a Chi-squared test or a Fisher's exact test. Wald confidence limits of 95% are calculated for differences between treatment arms in primary and other outcomes at all time points.

Participant-months are the total participant time in the study through the time of interest, prior to the censoring date. Rates of flares between treatment groups were compared by a Poisson regression model, adjusting for clinical study site and ANCA type, with the natural log of participant months used as an offset. Rates of adverse events, including pneumonia events, between treatment groups use a similar Poisson regression model, except without adjusting for clinical study site.

Time-to-event comparisons are performed using a log-rank test. Descriptive statistics are generated for analyses of time to event for only those experiencing an event, with comparisons being done by the Wilcoxon rank-sum test. Cumulative BVAS/WG scores employ worst observation carried forward, with a reported measure of the natural log of the area under curve (AUC) + 1. Other continuous measure comparisons (cumulative glucocorticoid dose, Vasculitis Damage Index scores, and SF-36 scores) use the Wilcoxon rank-sum test.

Estimates of creatinine clearance (eCrCl) were calculated using the Cockcroft-Gault method. Comparisons between treatment arms in eCrCl values and change over time were performed using a random coefficients mixed model, with random effects of intercept and time since randomization. The model was adjusted for dichotomous baseline variables such as severe renal failure, new versus relapsing disease, ANCA type (MPO versus PR3), and AAV diagnosis (MPA versus GPA). All eCrCl values up to and including the date of censoring were used in the model.

Censoring

For all time-to-event analyses, subjects are considered censored on the day of the earliest occurrence of any of the following events that may have occurred prior to the event analyzed:

- Blinded cross-over to alternate treatment

- Given a course of rituximab in an open-labeled fashion
- Put on treatment according to best medical judgment (BMJ)
- Reaching the 18 month visit
- Termination or withdrawal from the study

The only exception is for time-to-relapse analyses. For this, disease relapses that occurred within 10 days after a subject was moved to BMJ are included as events, and subjects without relapse up to that time are censored at the date of BMJ plus 10 days, unless they are censored for another reason before that time.

Timing of Relapses

For the analyses of time to first relapse after achieving remission (BVAS/WG = 0) or complete remission (BVAS/WG = 0 and prednisone dose = 0 mg), the date of the relapse is assumed to be the first date of a prednisone dose increase over the previous 21 days prior to the recorded relapse date. If there was no increase of prednisone dose before the date of the recorded relapse, then the relapse date is the date of the recorded relapse.

Imputations

Imputations were made for the following specific situations:

- In a small number of subjects the termination visit coincided with the timing of a scheduled 18 month study visit, and data were only recorded on the termination visit forms. In such cases, the data from the termination visit were used in substitute of missing 18 month data.
- In cases where a missing prednisone dose was the only reason for failure of the primary outcome at 12 and 18 months, the following imputation was made for the analysis of the primary outcome at 12 and 18 months: the prednisone dose was imputed as 0 if the preceding dose prior to the missing value was 0, the subject was a primary endpoint success at 6 months, and neither a relapse nor an increase in BVAS/WG score had been recorded at any time prior to the respective time-point of analysis.

- For eCrCl calculations by the Cockcroft-Gault method, weight values that differed by more than 50 from the baseline value after conversion of the recorded units to kg were converted back to the original value. This algorithm was implemented to correct erroneous weight unit recordings.

Supplementary Results

Table S1. Additional Efficacy Outcome Measures.

Efficacy outcome measure	***Rituximab*** ***N = 99***	***Cyclophosphamide/ azathioprine*** ***N = 98***	***P-value***
*Time to complete remission (days, mean (SD))**	183 (43.3)	204 (65.7)	0.09
Time to remission and < 10 mg/d prednisone (days, mean (SD))†	138 (54.6)	139 (45.1)	0.57
Time to remission (days, mean (SD))†	71 (51.1)	62 (49.8)	0.07
Severe relapses (Cumulative relapses, patients)			
Before 6 months	5, 4	10, 10	0.09
Before 12 months	14, 13	19, 17	0.41
Before 18 months	22, 20	23, 21	0.83
Limited relapses (Cumulative relapses, patients)			
Before 6 months	13, 11	14, 14	0.50
Before 12 months	28, 23	23, 21	0.76
Before 18 months	37, 27	30, 24	0.66
Rate of Severe Relapses (per participant-month)			
Before 6 months	0.009	0.019	0.19
Before 12 months	0.014	0.020	0.30
Before 18 months	0.016	0.017	0.78
Rate of Limited Relapses (per participant month)			
Before 6 months	0.024	0.026	0.83
Before 12 months	0.028	0.024	0.57
Before 18 months	0.027	0.023	0.49
Time from achieving complete remission to first relapse (days, mean (SD))	176 (91.2)	142 (99.2)	0.16
Time from achieving remission and < 10 mg Pred to first relapse (days, mean (SD))	195 (100.2)	150 (116.5)	0.06
Time from achieving remission to first relapse (days, mean (SD))	219 (122.7)	198 (114.0)	0.52

Table S1. Additional Efficacy Outcome Measures (continued).

Efficacy outcome measure	***Rituximab*** ***N = 99***	***Cyclophosphamide/ azathioprine*** ***N = 98***	***P-value***
Mean (SD); median (IQR) of BVAS/WG scores of relapses between month 6 and 18 in patients who achieved complete remission	3.3 (2.15); 2.5 (2.0, 4.5)	3.9 (2.6); 4.0 (2.0, 4.5)	0.39
Mean (SD) cumulative BVAS/WG area under the curve/month ‡			
Before 6 months	0.87 (0.534)	0.86 (0.534)	0.77
Before 12 months	0.80 (0.651)	0.83 (0.677)	0.96
Before 18 months	0.86 (0.740)	0.88 (0.763)	>0.99
Cumulative glucocorticoid dose between baseline and (mean, mg (SD))			
6 months	3974 (1073)	4358 (1828)	0.11
12 months	4215 (1406)	4729 (2178)	0.05
18 months	4607 (1809)	5058 (3139)	0.30
Vasculitis Damage Index			
Mean (SD) at12 months	2.2 (1.98)	2.2 (2.03)	0.57
Mean (SD) at18 months	2.3 (2.18)	2.3 (2.08)	0.80
Mean (SD) change from baseline to 18 months	1.3 (1.59)	1.3 (1.43)	ND
SF-36			
Mean (SD) physical component summary at 18 month	46.0 (9.97)	47.2 (9.51)	0.45
Mean (SD) change of physical component summary from baseline	9.3 (10.69)	9.3 (11.45)	ND
Mean (SD) mental component summary at 18 month	53.0 (9.70)	53.6 (8.71)	0.85
Mean (SD) change of mental component summary from baseline	11.6 (12.23)	9.0 (11.18)	ND

* Complete remission is defined as BVAS/WG = 0 and prednisone dose = 0 mg/d;

† Remission is defined as BVAS/WG = 0

‡ Natural log of the area under the curve + 1

Time to Relapse Analyses by Clinical Subsets

Figure S2A. Time to first relapse after achieving complete remission by diagnosis.
https://www.itntrialshare.org/RAVE18mos/SuppFig2.html

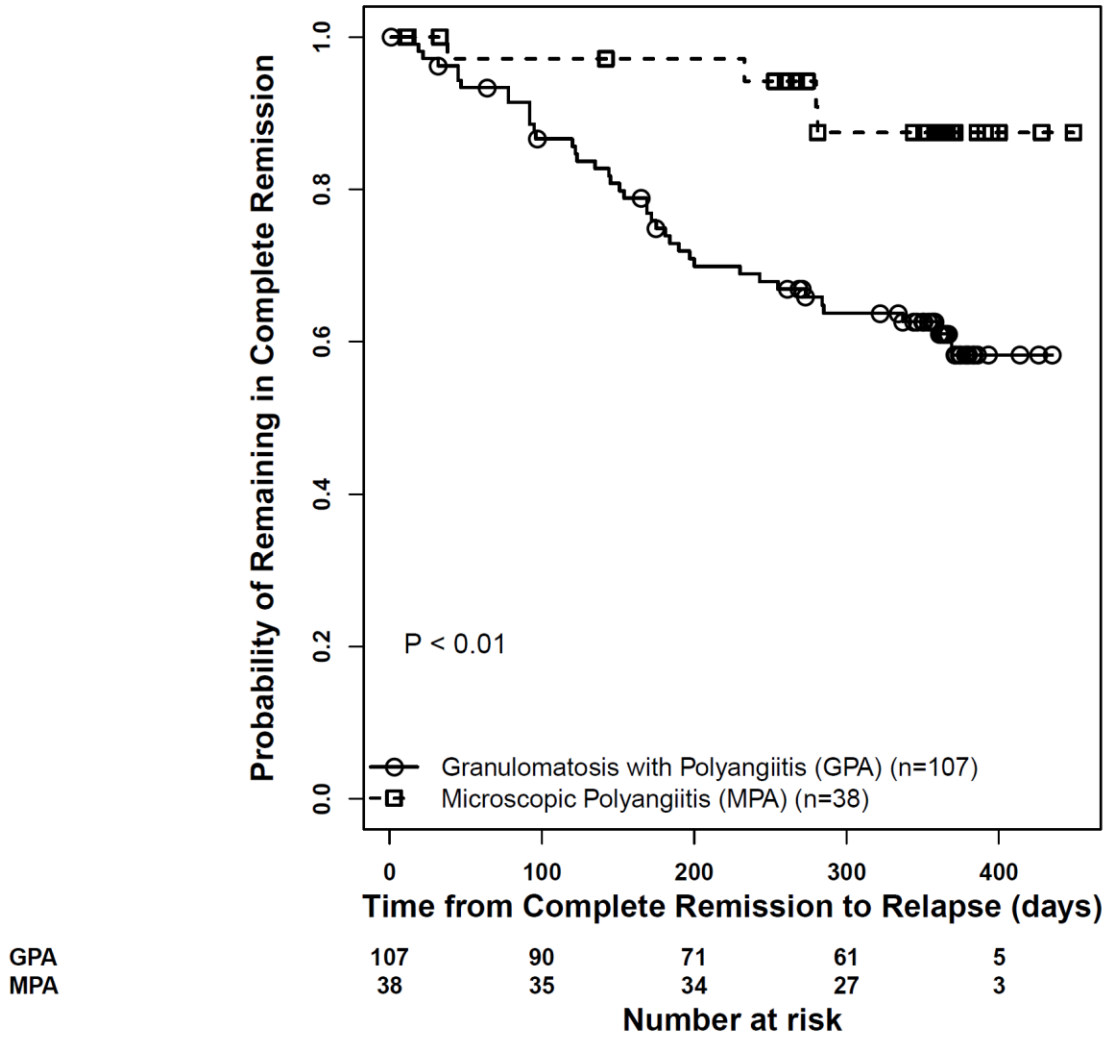
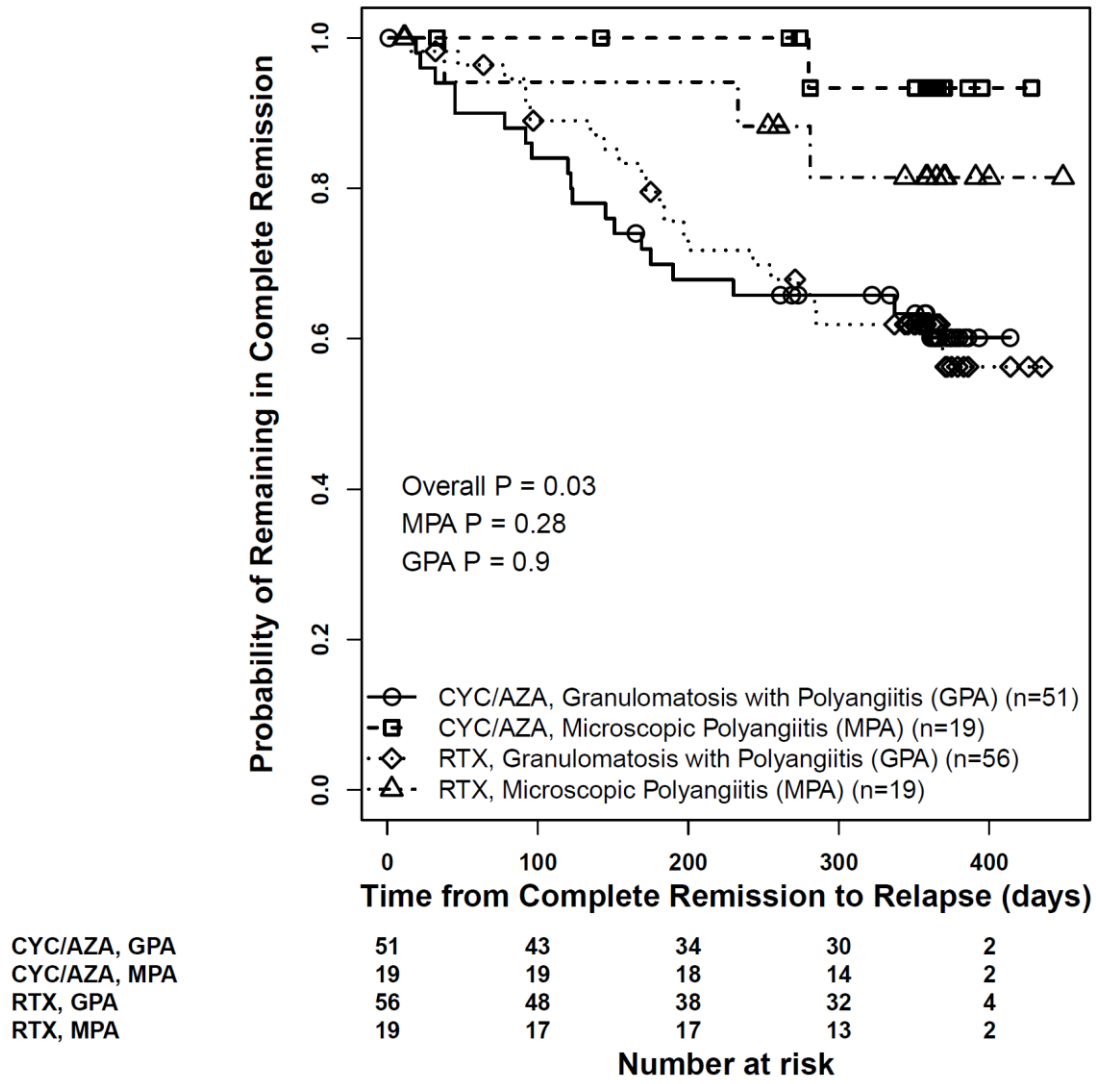


Figure S2B. Time to first relapse after achieving complete remission by diagnosis for each treatment group. https://www.itntrialshare.org/RAVE18mos/SuppFig2.html



The overall P value is for the comparison of the four patient groups displayed, whereas the subsequent P-values are for the comparison of the two treatment groups within the defined patient subgroups of MPA and GPA, respectively.

Figure S3A. Time to first relapse after achieving complete remission by New Diagnosis versus Relapsing Disease at baseline. https://www.itntrialshare.org/RAVE18mos/SFig3.html

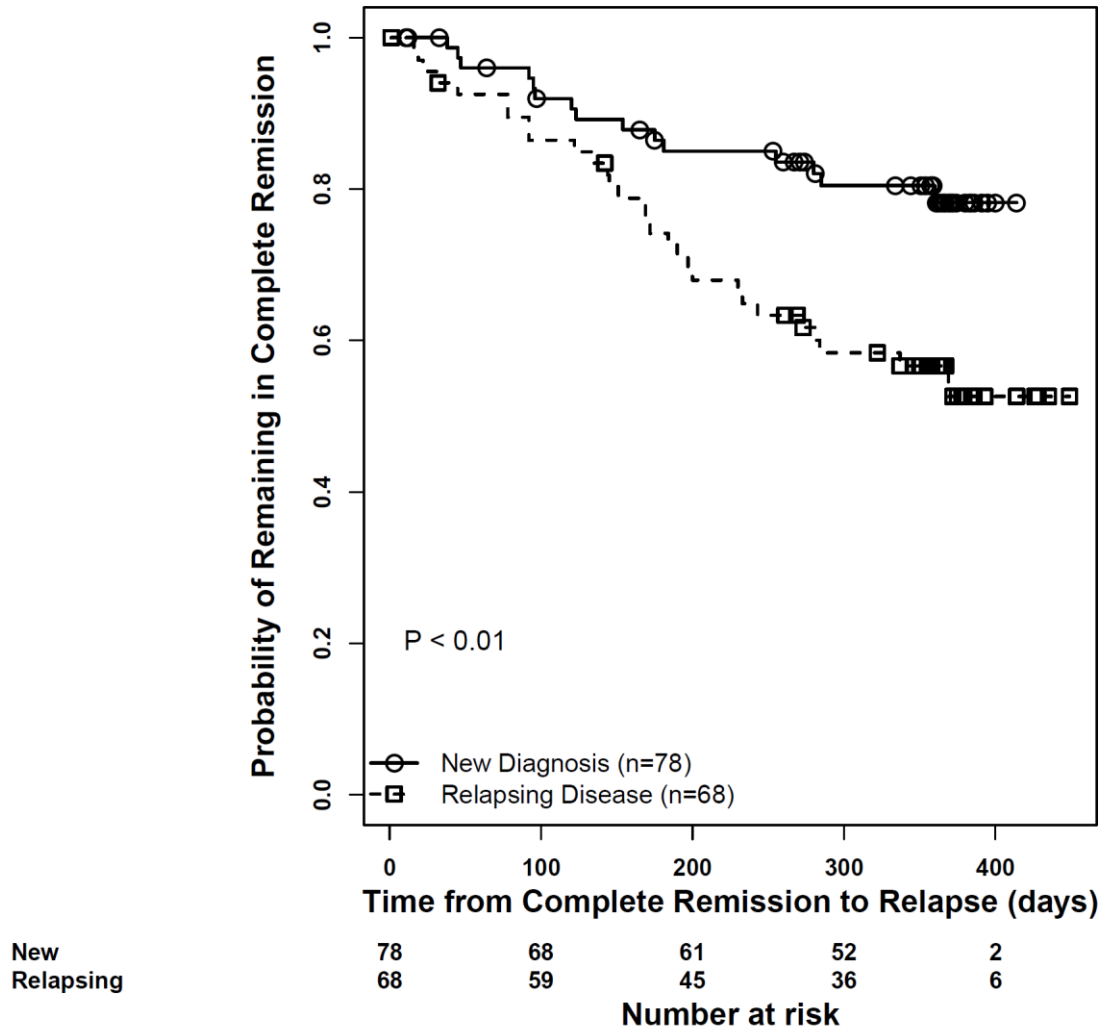
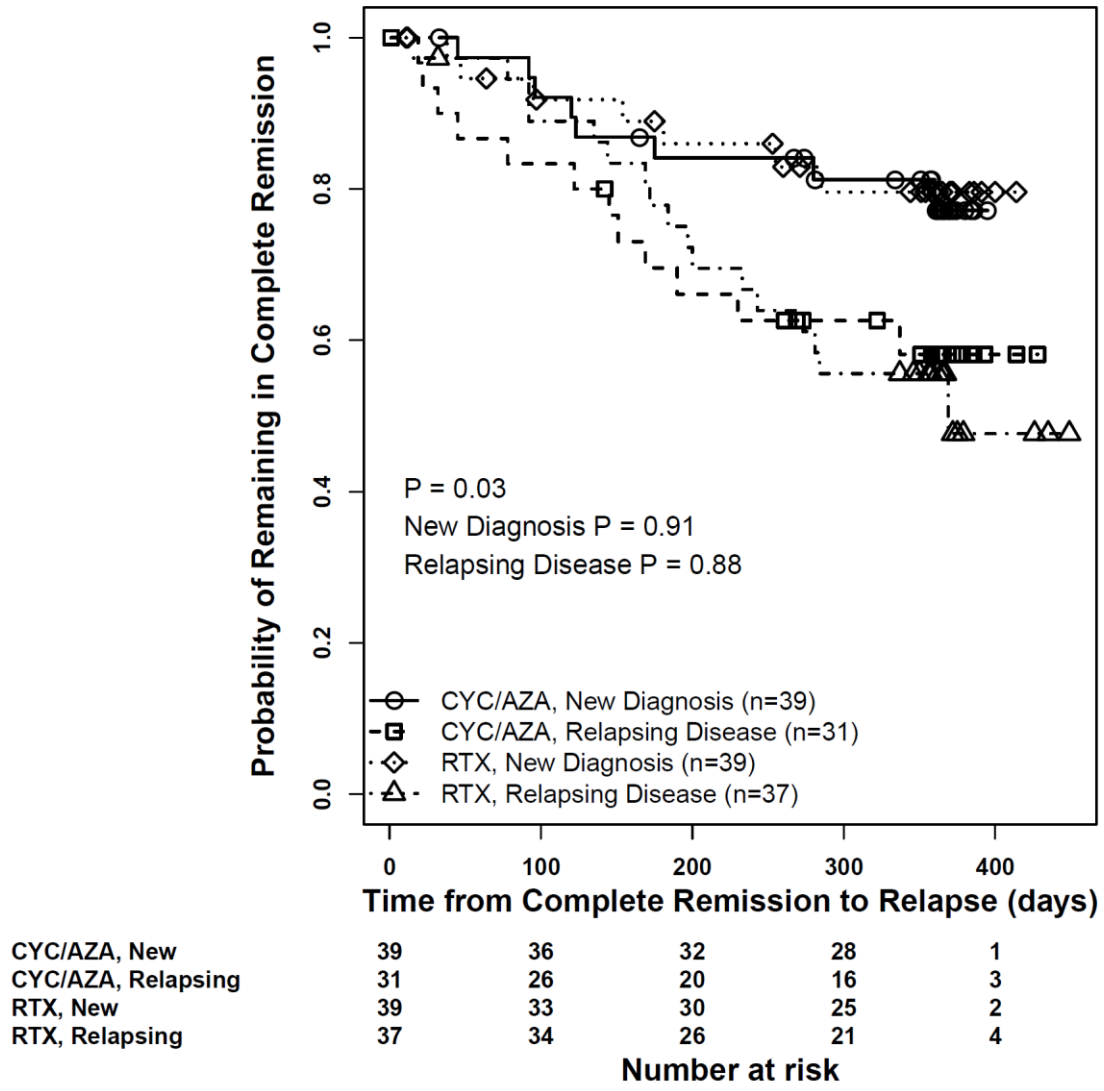


Figure S3B. Time to first relapse after achieving complete remission by New Diagnosis versus Relapsing Disease at baseline for each treatment group.

https://www.itntrialshare.org/RAVE18mos/SFig3.html



The overall P value is for the comparison of the four patient groups displayed, whereas the subsequent P-values are for the comparison of the two treatment groups within the defined patient subgroups of New Diagnosis and Relapsing Disease at baseline, respectively.

Figure S4A. Time to first disease relapse after achieving complete remission by Major Renal Disease versus No Major Renal Disease at baseline.

https://www.itntrialshare.org/RAVE18mos/SFig4.html

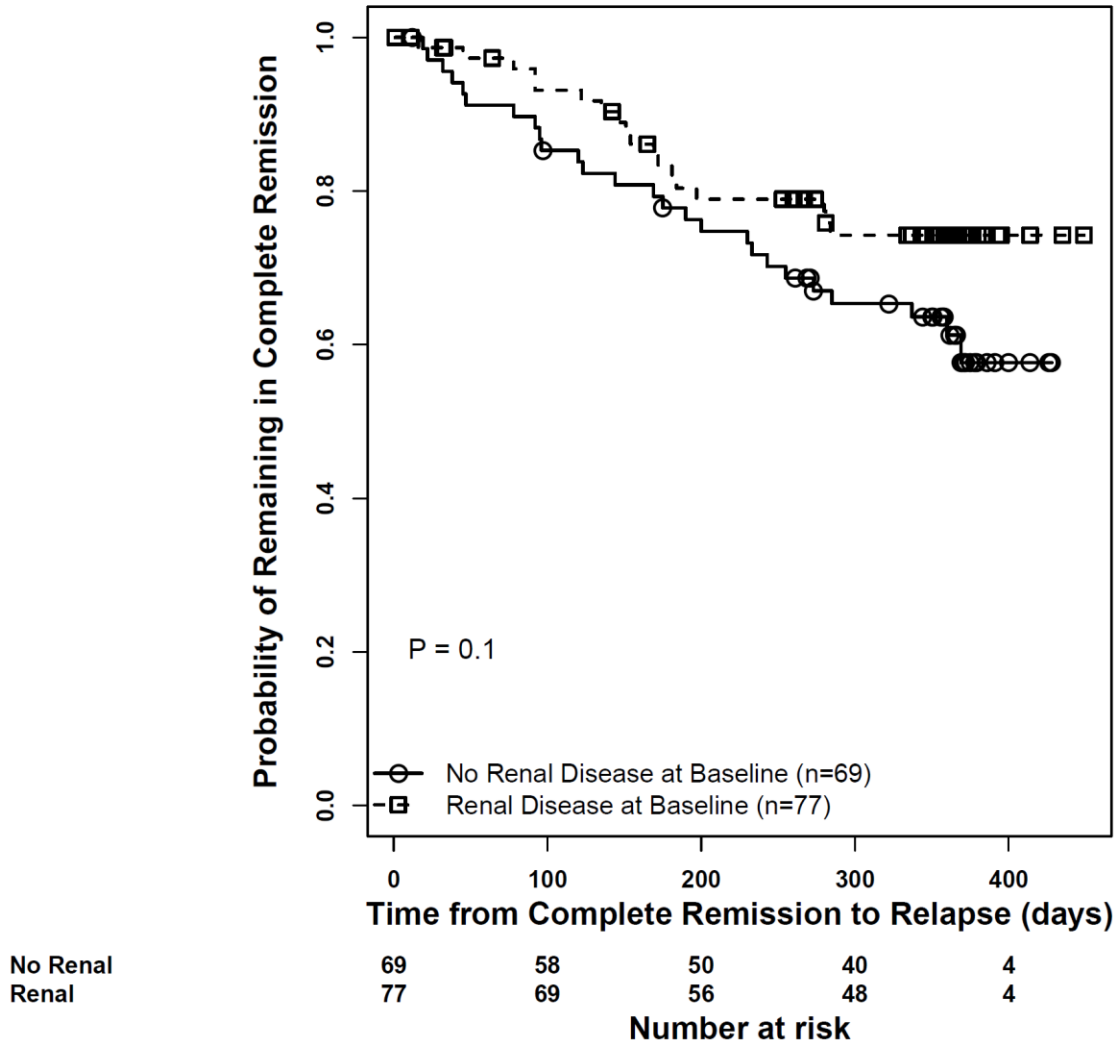
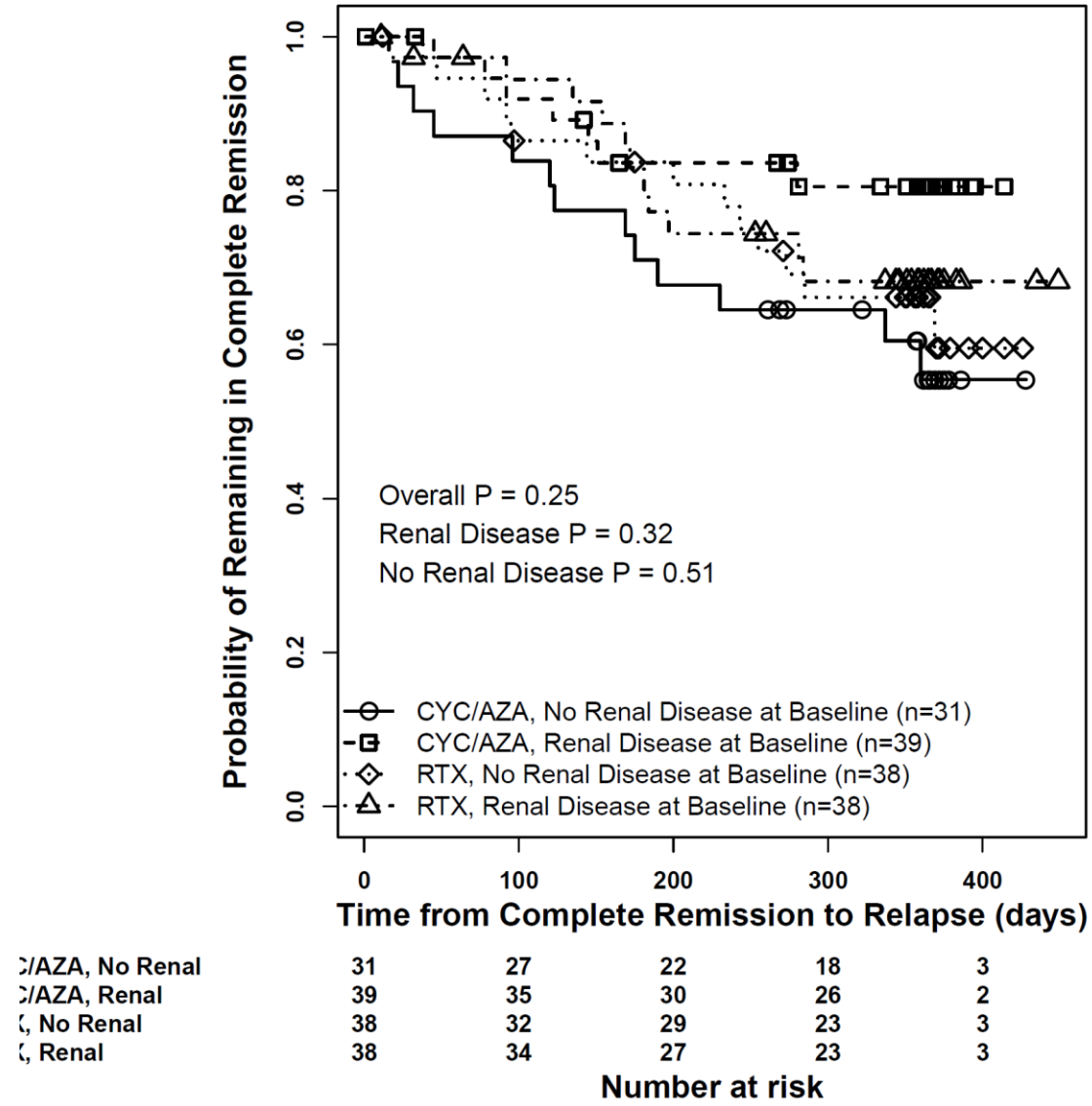


Figure S4B. Time to first disease relapse after achieving complete remission by Major Renal Disease versus No Major Renal Disease at baseline for each treatment group.

https://www.itntrialshare.org/RAVE18mos/SFig4.html



The overall P value is for the comparison of the four patient groups displayed, whereas the subsequent P-values are for the comparison of the two treatment groups within the defined patient subgroups of Major Renal Disease and No Major Renal Disease at baseline, respectively.

Figure S5. Time to first disease relapse after achieving complete remission for PR3-ANCA positive patients with GPA and Relapsing Disease at baseline versus all others.
https://www.itntrialshare.org/RAVE18mos/SFig5.html

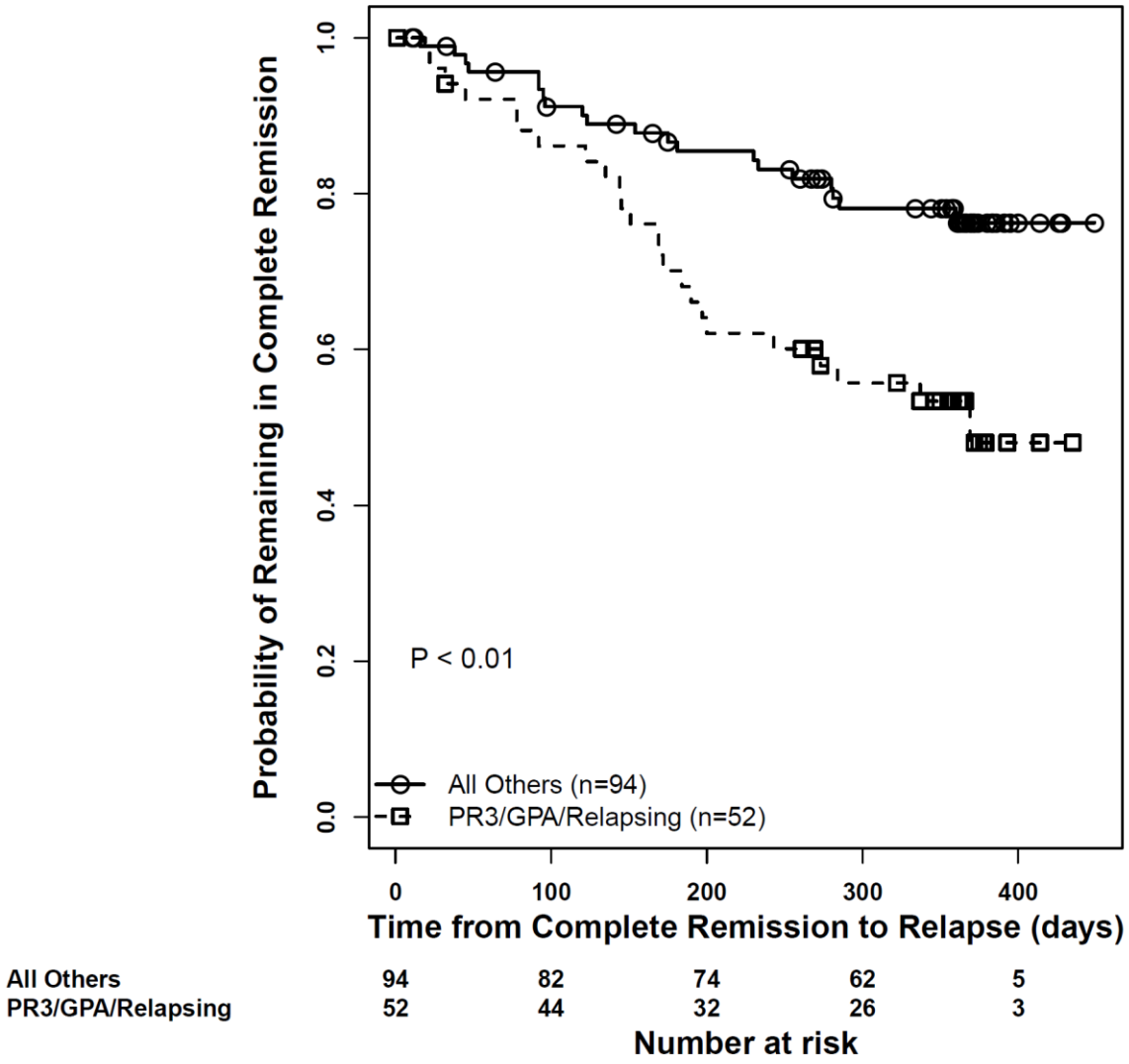


Figure S6A. Time to first disease relapse after achieving complete remission for PR3-ANCA positive patients with GPA and Relapsing Disease at baseline versus New Diagnosis of MPO-ANCA positive patients with MPA. https://www.itntrialshare.org/RAVE18mos/SFig6.html

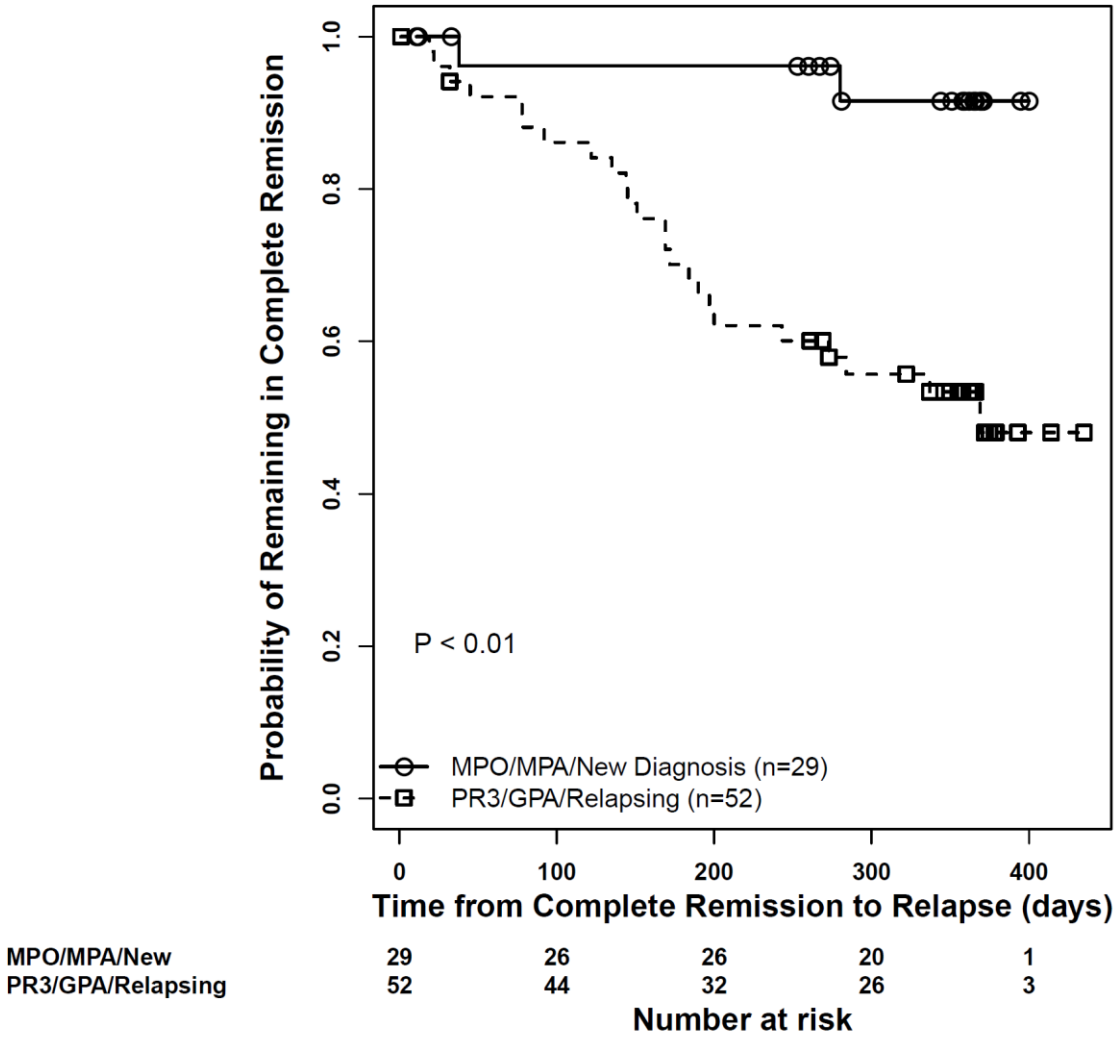
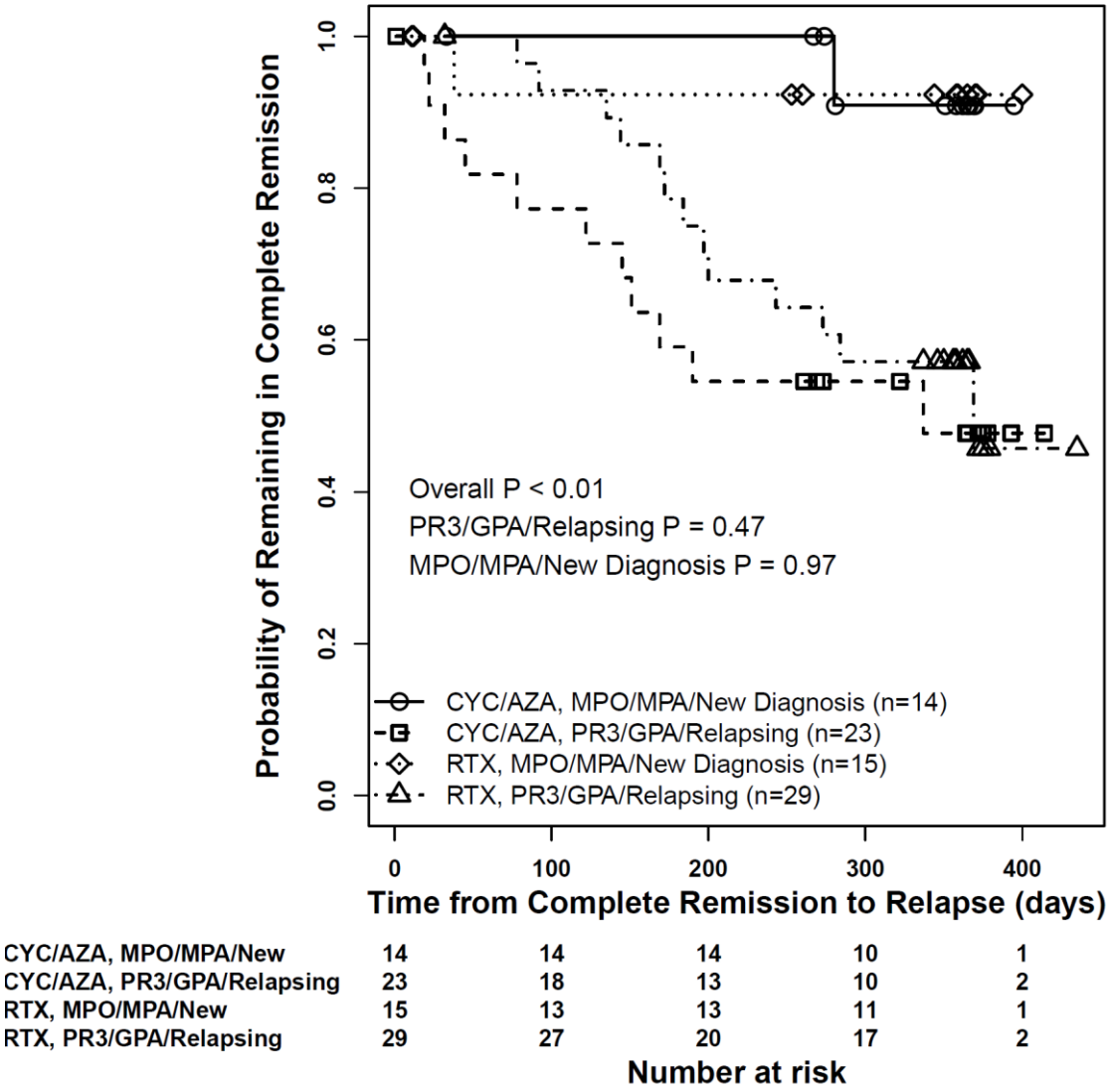


Figure S6B. Time to first disease relapse after achieving complete remission for PR3-ANCA positive patients with GPA and a severe relapse at baseline versus newly diagnosed MPO-ANCA positive patients with MPA for each treatment group.

https://www.itntrialshare.org/RAVE18mos/SFig6.html



Number at risk					
CYC/AZA, MPO/MPA/New	14	14	14	10	1
CYC/AZA, PR3/GPA/Relapsing	23	18	13	10	2
RTX, MPO/MPA/New	15	13	13	11	1
RTX, PR3/GPA/Relapsing	29	27	20	17	2

The overall P value is for the comparison of the four patient groups displayed, whereas the subsequent P-values are for the comparison of the two treatment groups within the defined patient subgroups of PR3-ANCA positive relapsing GPA and new diagnosis of MPO-ANCA positive MPA at baseline, respectively.

Effect of Treatment on B- and T-Cell Counts

Ninety-four (96%) of 98[*] rituximab-treated patients had achieved blood B-cell depletion at 1 month, and all at 4 months. Only 7 (8%) of the 86[†] cyclophosphamide/azathioprine-treated patients had achieved blood B-cell depletion at 1 month, but 73 (85%) by 9 months (**Figure S7A**).

Most rituximab-treated patients fully reconstituted their B-cells between 9 and 12 months. Of the 61 rituximab-treated patients who remained on their originally-assigned treatment by month 18, 43 (70%) had reconstituted, 13 (21%) had re-detectable B-cells, and only 4 (7%) remained depleted[‡] (**Figure S7A**). In contrast, B-cell counts remained low in the majority of patients treated with cyclophosphamide/azathioprine: only 7 (11%) of the 63 patients remaining in this treatment arm at 18 months had their B-cells reconstituted by that time. Twenty-seven (43%) had re-detectable B-cells, and 18 (29%) remained depleted. The remainder (n=11, 17%) never depleted their counts (**Figure S7A**).

T-lymphocyte counts increased from baseline in the rituximab-treated subjects, reaching a plateau by 6 months, and remained at that level throughout 18 months (**Figure S7B**). In contrast, in the cyclophosphamide/azathioprine arm, T-lymphocyte counts decreased from baseline, reached a nadir at 2-4 months, and subsequently increased coinciding with transition to azathioprine (**Figure S7B**).

[*] One-month B-cell data were unavailable for 1 rituximab-treated patient.
[†] Twelve cyclophosphamide-treated patients were excluded from this analysis because they had been crossed over or treated by best medical judgment before 6 months.
[‡] One additional patient had no detectable B-cells at months 12, but no subsequent B-cell determinations.

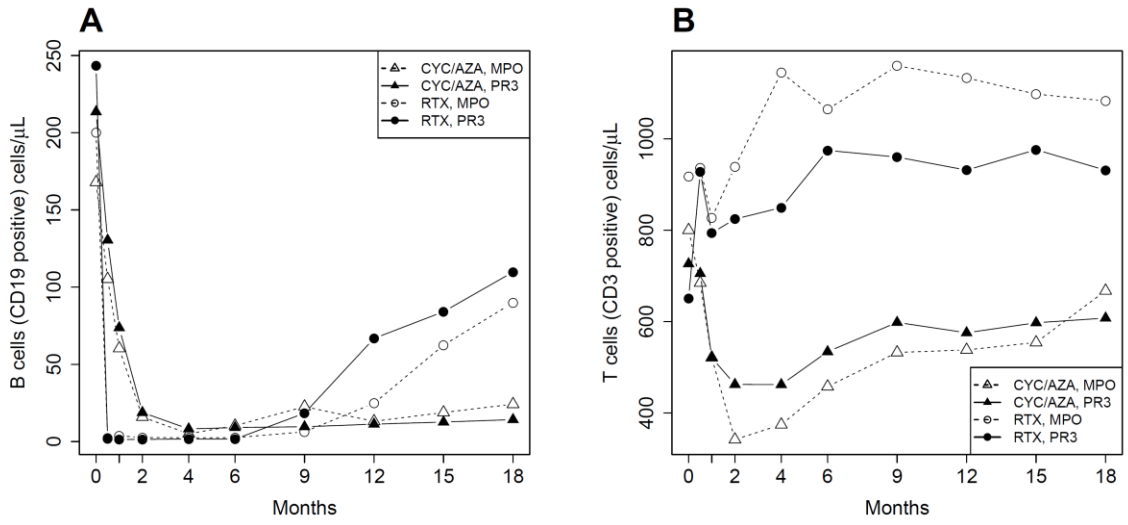


Figure S7. Peripheral Blood B- and T-lymphocyte Counts in the Rituximab and Cyclophosphamide/azathioprine Treatment Groups.

(https://www.itntrialshare.org/RAVE18mos/SFig7.html)

Panel A shows the mean peripheral-blood B-cell counts in the rituximab (RTX) and cyclophosphamide/azathioprine (CYC/AZA) groups according to antineutrophil cytoplasmic antibody (ANCA) type. The counts in most patients who received rituximab decreased to less than 10 CD19+ cells per cubic millimeter after two infusions and remained at that level until 6 months. B-cell counts decreased more slowly in the cyclophosphamide/azathioprine group than in the rituximab group and remained detectable, at low levels. MPO denotes ANCA directed against myeloperoxidase, and PR3 ANCA directed against proteinase 3. Panel B shows the mean peripheral-blood CD3+ T-cell counts in the rituximab and cyclophosphamide/azathioprine groups according to antineutrophil cytoplasmic antibody (ANCA) type. An initial increase in T-cell counts from baseline was observed in the rituximab group, which was maintained throughout the observation period. In contrast, cyclophosphamide induced a significant reduction in T-cell counts from baseline with partial recovery of T-cell counts after treatment was switched from cyclophosphamide to azathioprine.

Relationship of blood B-cell counts and relapses.

Although B-cells were profoundly reduced in both treatment arms, this parameter alone did not predict the risk of relapse for individual patients. Patients who had achieved complete remission with rituximab were at low risk for relapse as long as B-cells were depleted. Only 3 (12.5% of all relapses) limited relapses occurred while B-cells were undetectable. All 21 of the other relapses in this group (87.5%), including all severe relapses, occurred after B-cells became re-detectable. Nevertheless, two-thirds of the rituximab-treated patients reconstituted their B-cells without relapsing before the 18-month time-point. In comparison, the relationship between relapse risk and B-cells in the cyclophosphamide/azathioprine arm was less clear. Six (30%) patients had relapses (2 were severe) in the absence of B-cells, and 11 (55%) when B-cells were re-detectable. Three patients with relapses (15%) had never depleted their B-cells.

Relationship of ANCA-Titers and Relapse

Methods and Definitions

Serum samples were collected and frozen at each study visit. Serial measurements of PR3-ANCA and MPO-ANCA were conducted post-hoc by direct ELISA under standardized conditions. All serial samples from each individual patient were evaluated in the same assay run and in the same assay plate. All serum samples had undergone the same number of freeze-thaw cycles (two). ANCA titers ≥ 20 units were deemed positive. An ANCA titer rise was defined as an increase greater or equal to twice the value of the nadir or ≥40 if the patient had turned ANCA negative. Conversely, a decrease was defined as a 50% reduction in ANCA titer.

Table S2. Relationship of Relapses with ANCA-titers

	Severe Relapse*	**Limited Relapse***	**No Relapse**
Rituximab group			
ANCA negative	1	4	14
ANCA-titer persistently positive but unchanged or decreasing	1	2	12
ANCA-titer increase	7	9	26
Total	**9**	**15**	**52**
Cyclophophamide/azathioprine group			
ANCA negative	1	1	19
ANCA-titer persistently positive but unchanged or decreasing	1	3	13
ANCA-titer increase	8	6	**18**
Total	**10**	**10**	**50**

***first relapse after achieving complete remission

Adverse Events

Table S3. Adverse Events Through Common Close Out, Intention-to-treat Analysis.

Variable	Rituximab Group (n = 99)	Cyclophosphamide/ Azathioprine Group (n = 98)	Total	P
Sum of participant-months	3589.9	3296.1	6886.0	
Total adverse events	1947	1838	3785	
Number of participants with at least one adverse event (%)	99 (100%)	98 (100%)	197 (100%)	NA
Rate of adverse events*	0.54	0.56	0.55	0.38
Total serious adverse events	122	100	222	
Number of participants with at least one serious adverse event (%)	60 (60.6%)	47 (48.0%)	107 (54.3%)	0.08
Rate of Serious Adverse Events*	0.03	0.03	0.03	0.43
Deaths all causes (%)	2 (2.0)	2 (2.0)	4 (2.0)	
Total non-disease related serious adverse events	77	60	137	
Number of participants with at least one non-disease related serious adverse event (%)	45 (45.5%)	33 (33.7%)	78 (39.6%)	0.09
Rate of non-disease related serious adverse events*	0.02	0.02	0.02	0.38

* Rate = events per participant-month

Immunoglobulins

Table S4. Immunoglobulin G concentrations at baseline, 6, and 18 months for patients remaining on the originally assigned treatment.

	RTX	**CYC/AZA**	***P-value***
IgG (mg/dl) at baseline*	N=80	N=72	
Mean (SD)	927 (290)	987 (402)	0.36
Median (min,max)	898 (393, 2123)	946 (322, 2598)	
IgG (mg/dl) at 6 months			
Mean (SD)	649 (284)	671 (296)	0.44
Median (min,max)	607 (89, 2314)	661 (139,2081)	
Change from baseline to 6 months			
Mean (SD)	-278 (325)	-316 (345)	0.81
Median (min,max)	-246 (-1198,1447)	-251 (-1648, 196)	
IgG (mg/dl) at baseline†	N=59	N=55	
Mean (SD)	975 (281)	934 (354)	0.50
Median (min,max)	924 (581,2123)	902 (322,2598)	
IgG (mg/dl) at 18 months			
Mean (SD)	766 (265)	808 (363)	0.50
Median (min,max)	737 (239,1415)	770 (134,2703)	
Change from baseline to 18 months			
Mean (SD)	-210 (299)	-126 (282)	0.13
Median (min,max)	-185 (-1175,426)	-121 (-760,420)	

*****Patients with matching baseline and 6 months samples

†Patients with matching baseline and 18 months samples

Deaths in RAVE

Two patients originally assigned to rituximab and two patients originally assigned to cyclophosphamide/azathioprine died between enrollment and the common close out date.

Patient 1 was a 65 year-old man with an 18 months history of GPA who had a severe disease relapse at baseline (ear, nose and throat involvement, glomerulonephritis and alveolar hemorrhage), was PR3-ANCA positive, and was randomized to rituximab. He received rituximab on day 1, 7 and 14, was deemed an early treatment failure because of progression to respiratory and renal failure. He was moved to treatment according to best medical judgement on day 16. He received cyclophosphamide from day 16-36. Cyclophosphamide was discontinued on day 36 because of pancytopenia. The patient subsequently developed a severe *Escherichia faecalis* infection of his dialysis catheter, respiratory tract infection, and sepsis with *Enterococcus* and *Escherichia coli*, and died of multi-organ failure attributed to AAV on day 64. The death was deemed unrelated to study drug by the investigator. Because the onset of the multi-organ failure listed as the serious adverse event leading to the death precedes the patient's switch to treatment according to best medical judgment, this death is included in Table 2 of the manuscript, even though the death occurred 50 days after the censoring date.

Patient 2 was a 68 year-old woman with severe chronic obstructive lung disease (COPD), who was newly diagnosed with severe MPA (glomerulonephritis), MPO-ANCA positive, at baseline. She was randomized to cyclophosphamide/azathioprine. The patient's vasculitis activity responded well to treatment, but she developed an exacerbation of her COPD requiring treatment with 60 mg of prednisone daily for 3 weeks. At the 4 month study visit (day 112), the patient was deemed in remission, and cyclophosphamide was switched to azathioprine. The patient was switched from cyclophosphamide to azathioprine on day 112. The patient then developed pseudomonas pneumonia, bacteremia and sepsis with multi-organ system failure and death on day 123. The death was deemed as possibly related to study drug by the investigator.

Patient 3 was an 81 year-old man who was newly diagnosed with severe MPA (glomerulonephritis), MPO-ANCA positive, at baseline and was randomized to cyclophosphamide/azathioprine. On study day 21, the patient presented with symptoms of dyspnea, fever, cough and rigors. A chest roentgenogram showed bilateral lower lobe infiltrates. Bronchoalveolar lavage revealed alveolar hemorrhage and was positive for *Pneumocystis*

jerovecii (the patient had been non-compliant with prescribed pneumocystis pneumonia prophylaxis). The study medication (cyclophosphamide) was interrupted. The patient progressed to respiratory failure requiring mechanical ventilation. Echocardiogram revealed a diffuse wall motion abnormalities consistent with cardiomyopathy or coronary artery disease, severe dysfunction with left ventricular ejection fraction of 25%. He was also diagnosed with non-ST-segment elevation myocardial infarction. He subsequently developed *Staphylococcus aureus* and *Escherichia coli* sepsis and died of septic shock on day 55. The death was deemed as possibly related to study drug by the investigator

Patient 4 was a 78 year-old woman with MPO-ANCA positive MPA who entered the trial with a severe disease relapse at baseline. She was randomized to rituximab and achieved complete remission, met the primary outcomes at months 6 and 12 and remained in complete remission until the 15 months study visit. At 16 months after enrollment the patient experienced a severe disease flare (glomerulonephritis and alveolar hemorrhage). Remission induction therapy with open-label rituximab was initiated. There was no immediate response and the patient was moved to best medical judgment. The patient received plasma exchange and one dose of intravenous cyclophosphamide. The patient died from respiratory failure attributed to uncontrolled disease activity 7 weeks after initiation of therapy for the severe flare. There was no evidence of systemic or pulmonary infection. The death was deemed unrelated to study medication. Because the severe disease flare leading to the death precedes the patient's switch to treatment according to best medical judgment, this death is included in Table 2 of the manuscript, even though the death occurred 54 days after the censoring date.

Malignancies in RAVE

In our report of the primary endpoint results of the RAVE trial, we had provided a detailed listing and analysis of all malignancies that had occurred in RAVE at that time of the report (beyond the primary endpoint of 6 months). No additional malignancies were observed between the time of that report and the common close-out date of the trial.

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