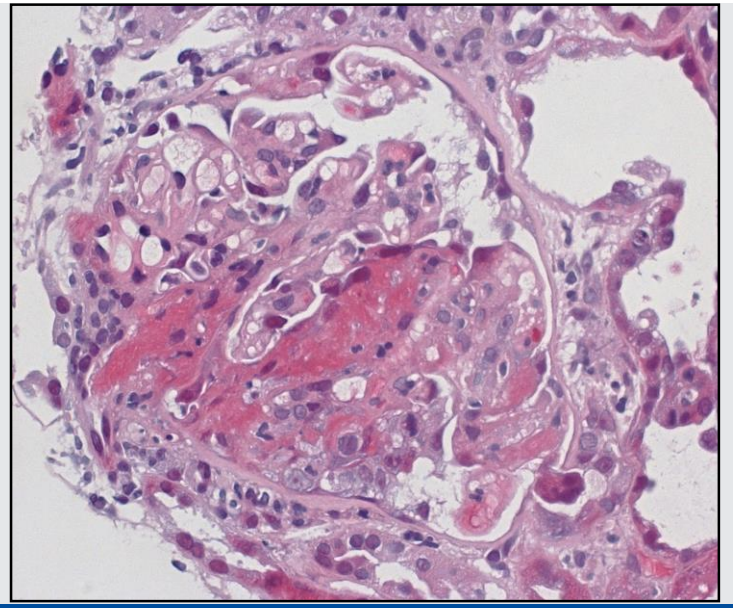


ANCA-Vaskulitis: Neue Leitlinien und Therapieoptionen

Adrian Schreiber

Medizinische Klinik mit Schwerpunkt Nephrologie und Internistische Intensivmedizin

Charité - Universitätsmedizin Berlin

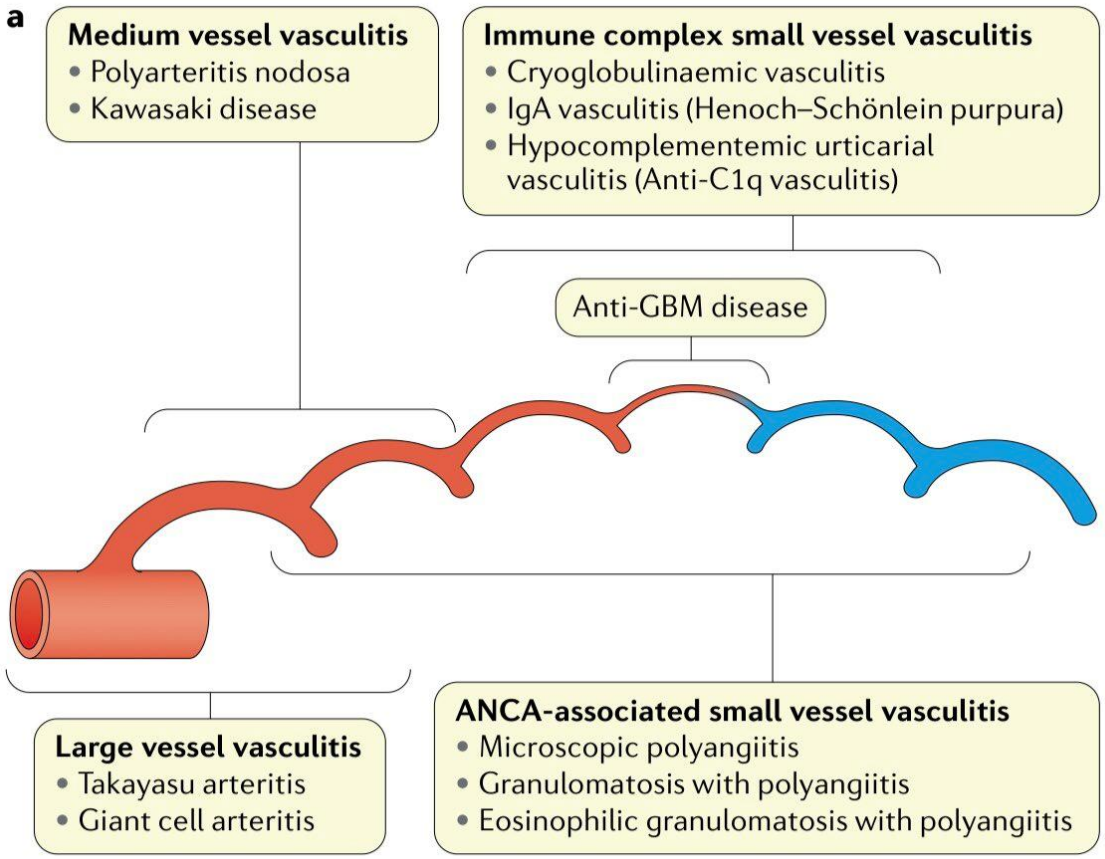
COI

Referenten-/Beraterhonorare/Forschungsunterstützung

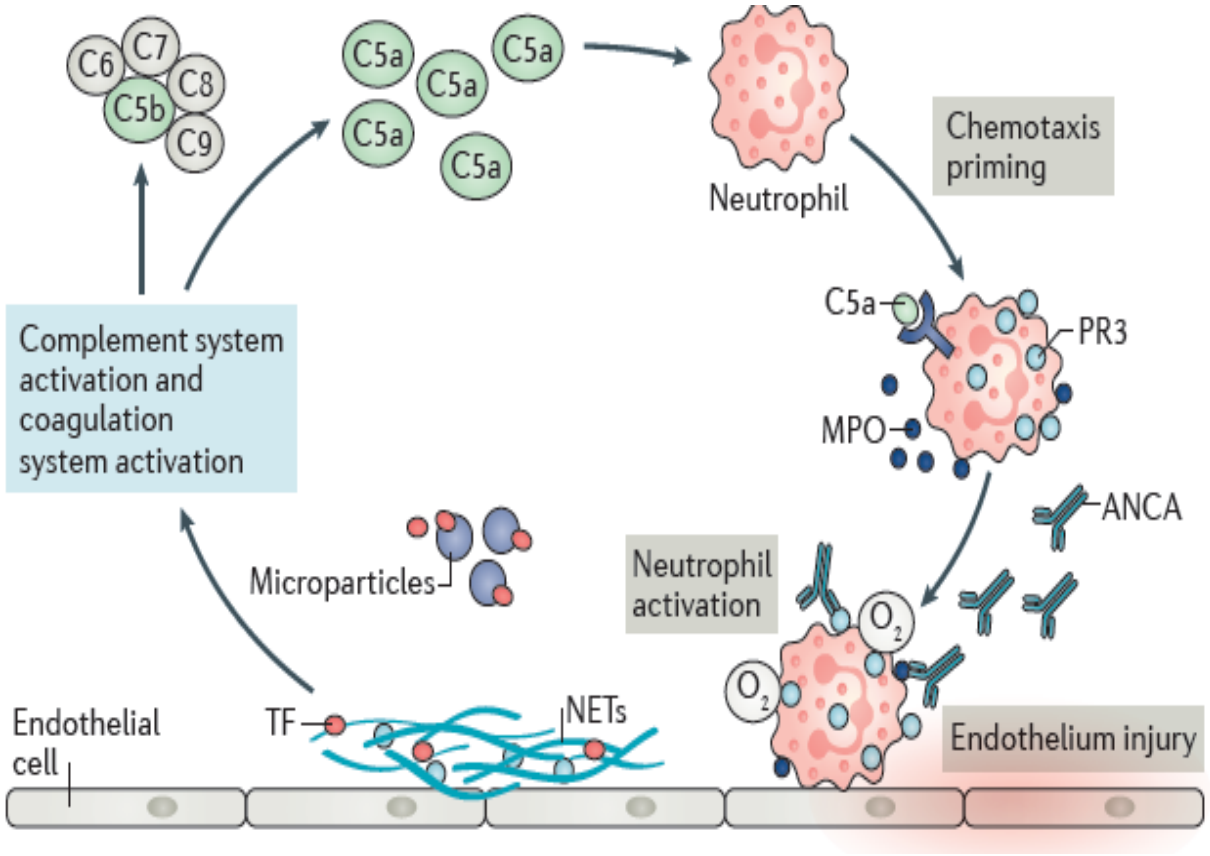
Vifor CSL, Novartis, Alexion, Hansa Biopharm, Otsuka, Stadapharm, AstraZeneca

PI in klinischen Studien bei AAV

Pathogenese AAV



Jennette *Arthr & Rheum* 2012



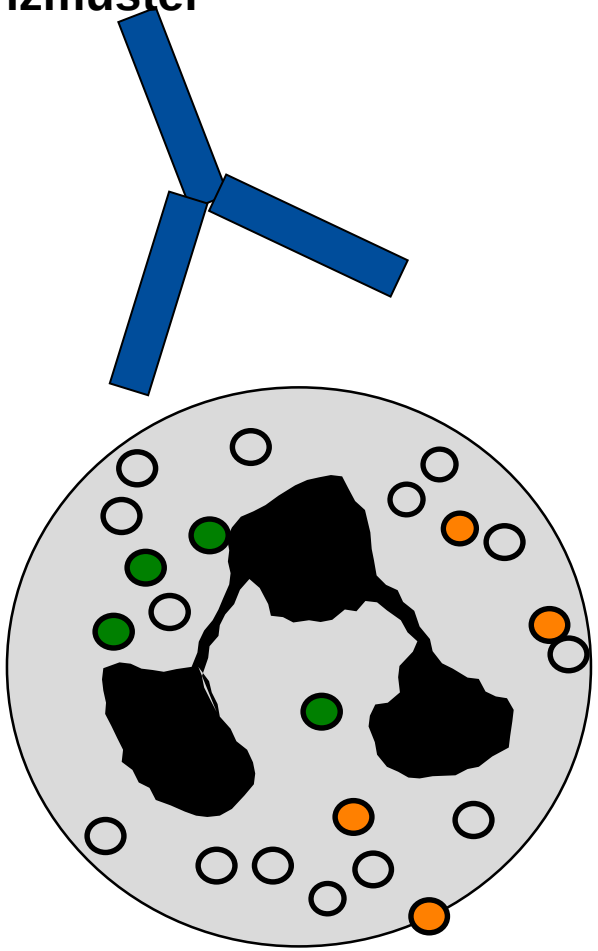
Chen, Jayne & Zhao *Nature Rev Nephrol* 2017

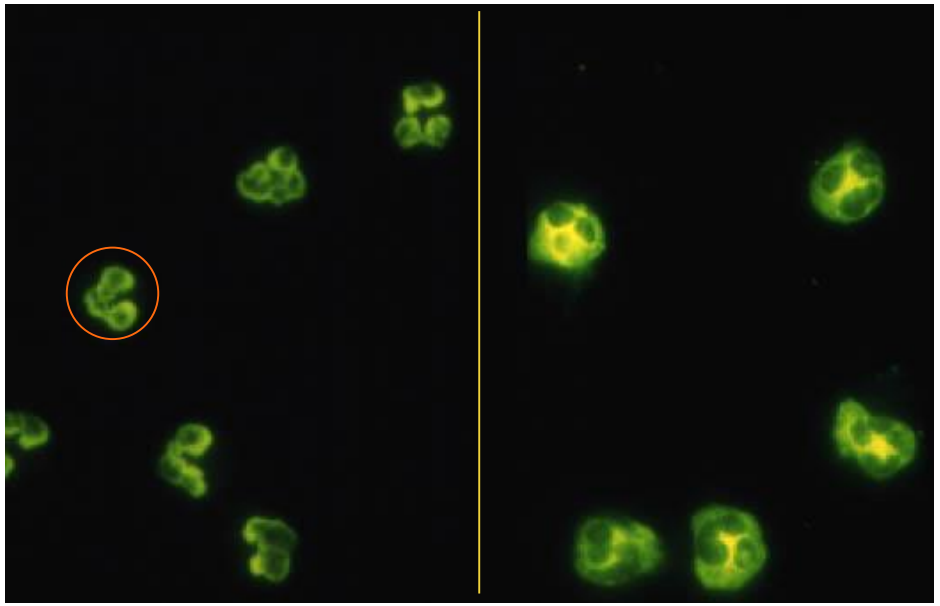
ANCA = Antineutrophile Cytoplasmatische Antikörper

pANCA vs. cANCA

„p“ = perinukleäres,
„c“ = cytoplasmatisches

Fluoreszenzmuster





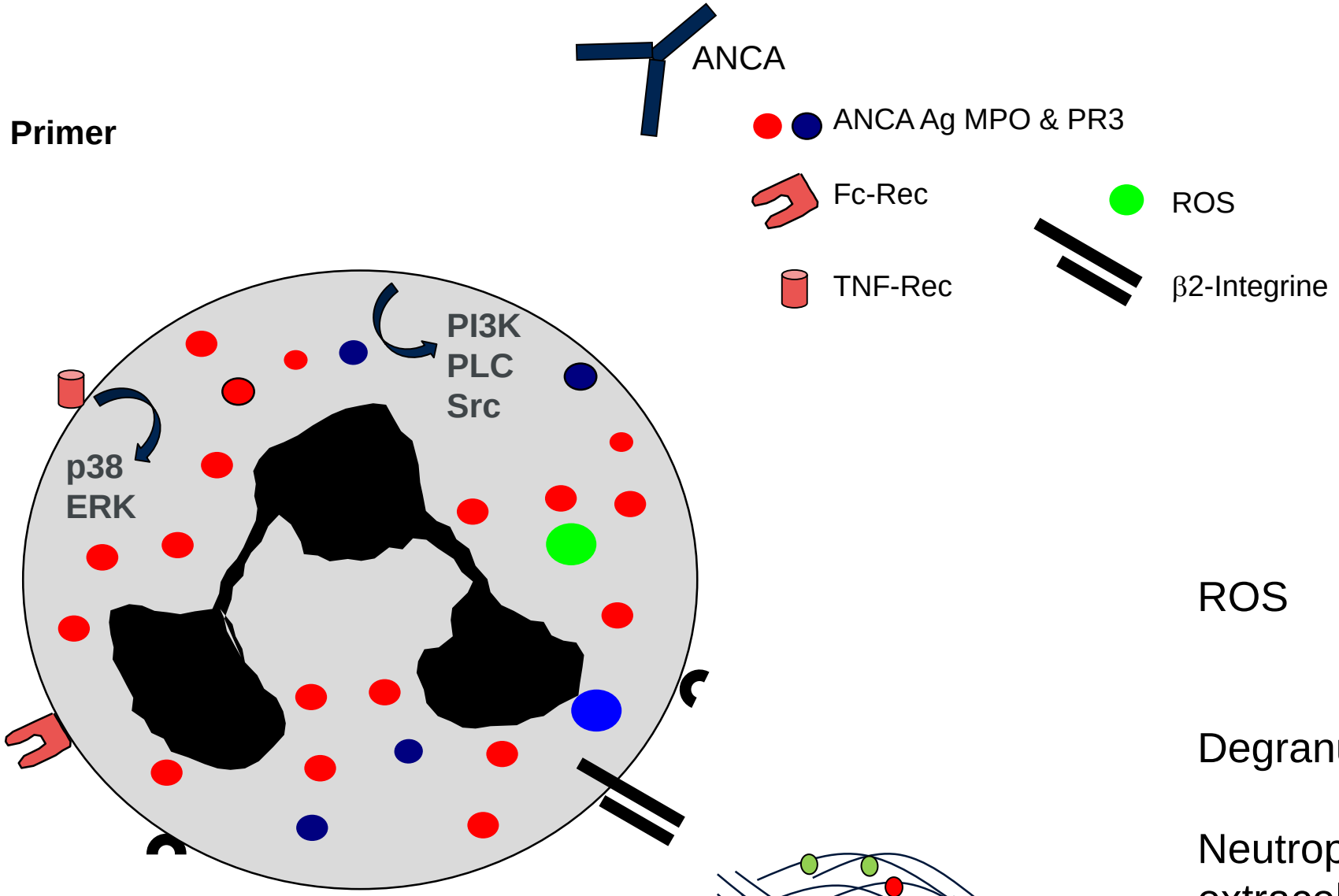
p-ANCA

MPO

c-ANCA

PR3

Primer

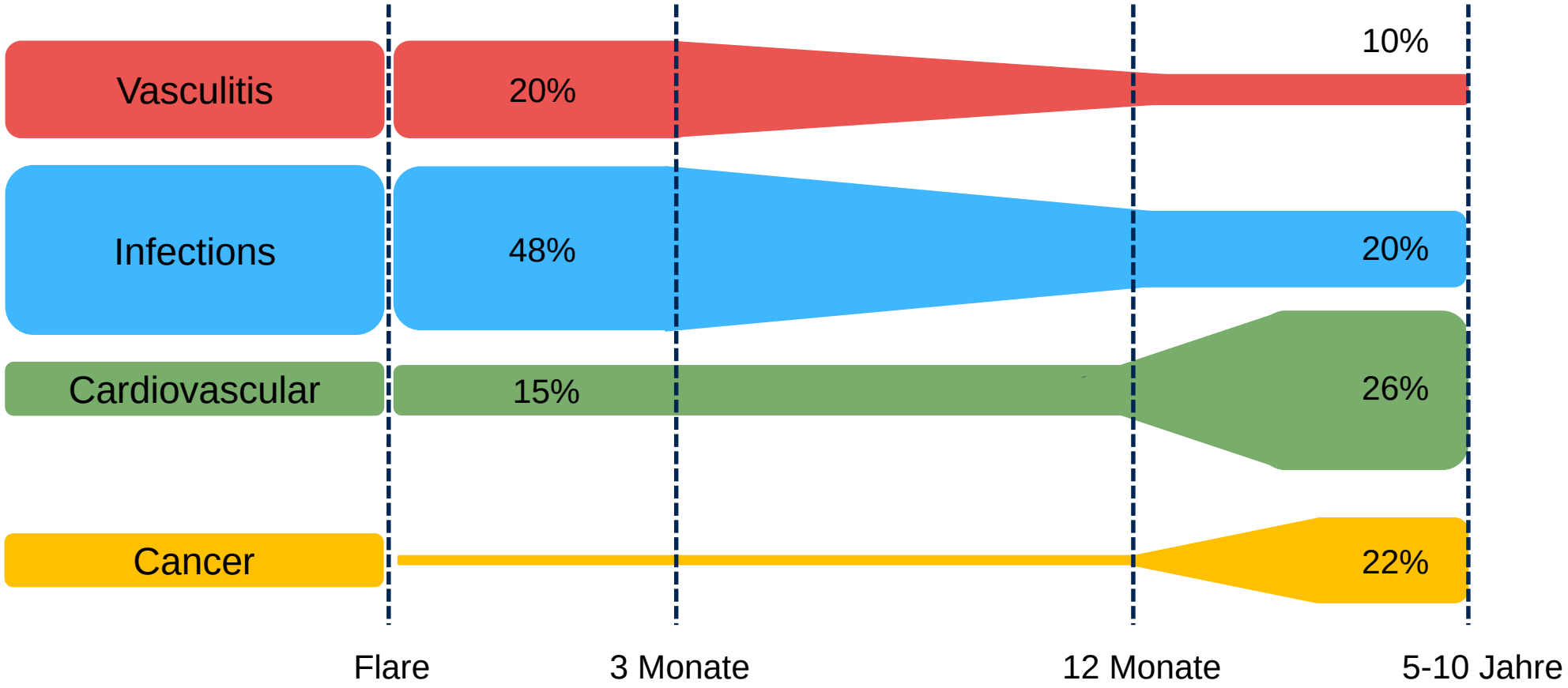


ROS

Degranulation

Neutrophil extracellular traps (NET)

Vaskulitis - Mortalität



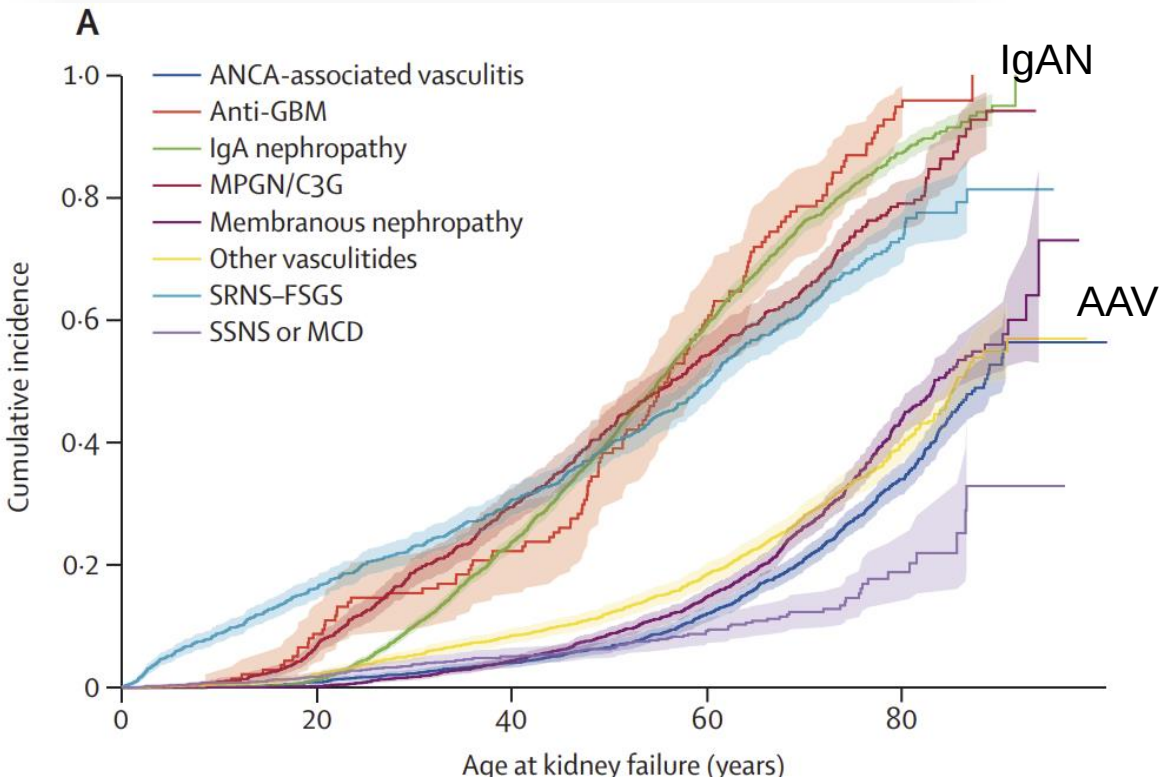
Retrospektive Datenanalyse, 535 Pat mit AAV aus verschiedenen EUVAS Studien

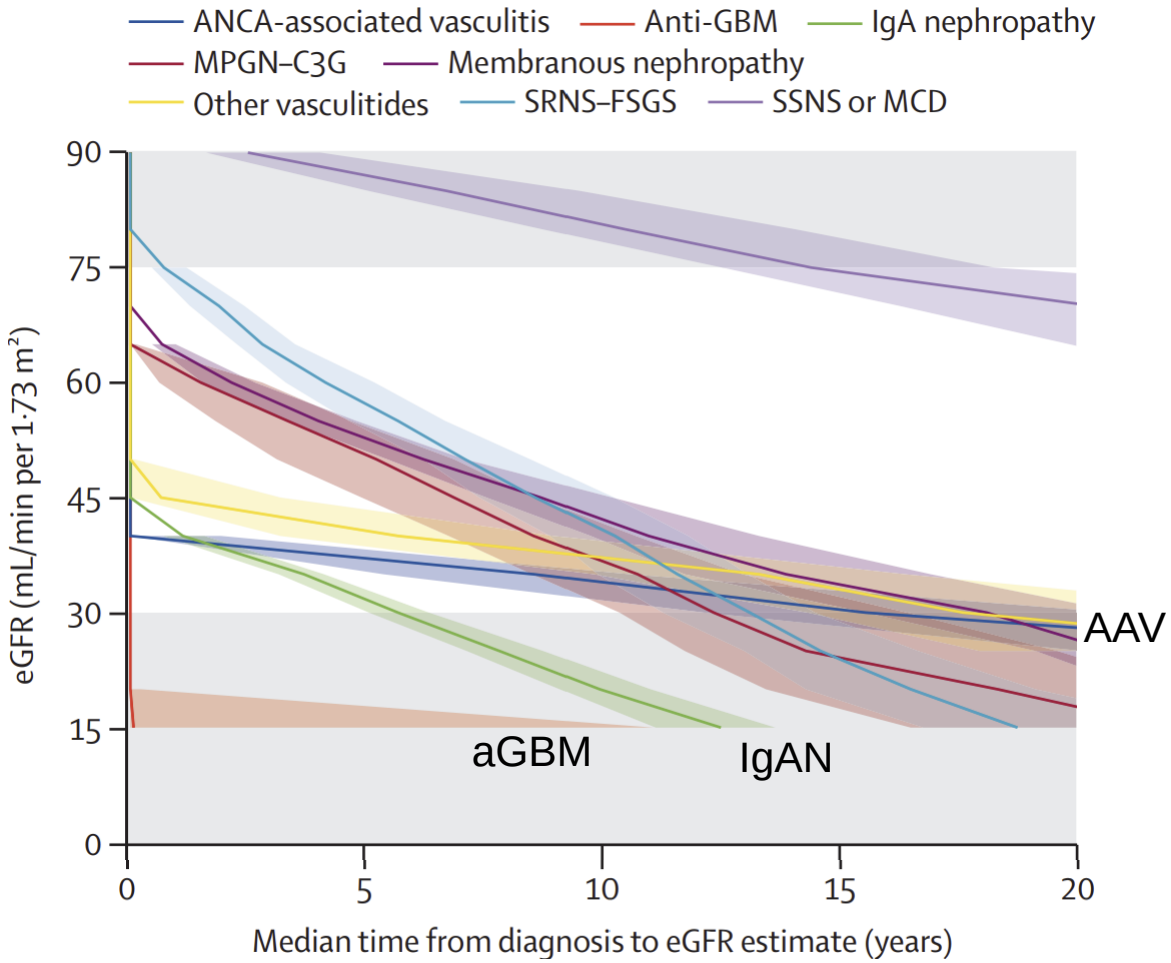
Adapted from Flossmann *Ann Rheum Dis*

Vaskulitis - Outcome

Effects of rare kidney diseases on kidney failure: a longitudinal analysis of the UK National Registry of Rare Kidney Diseases (RaDaR) cohort

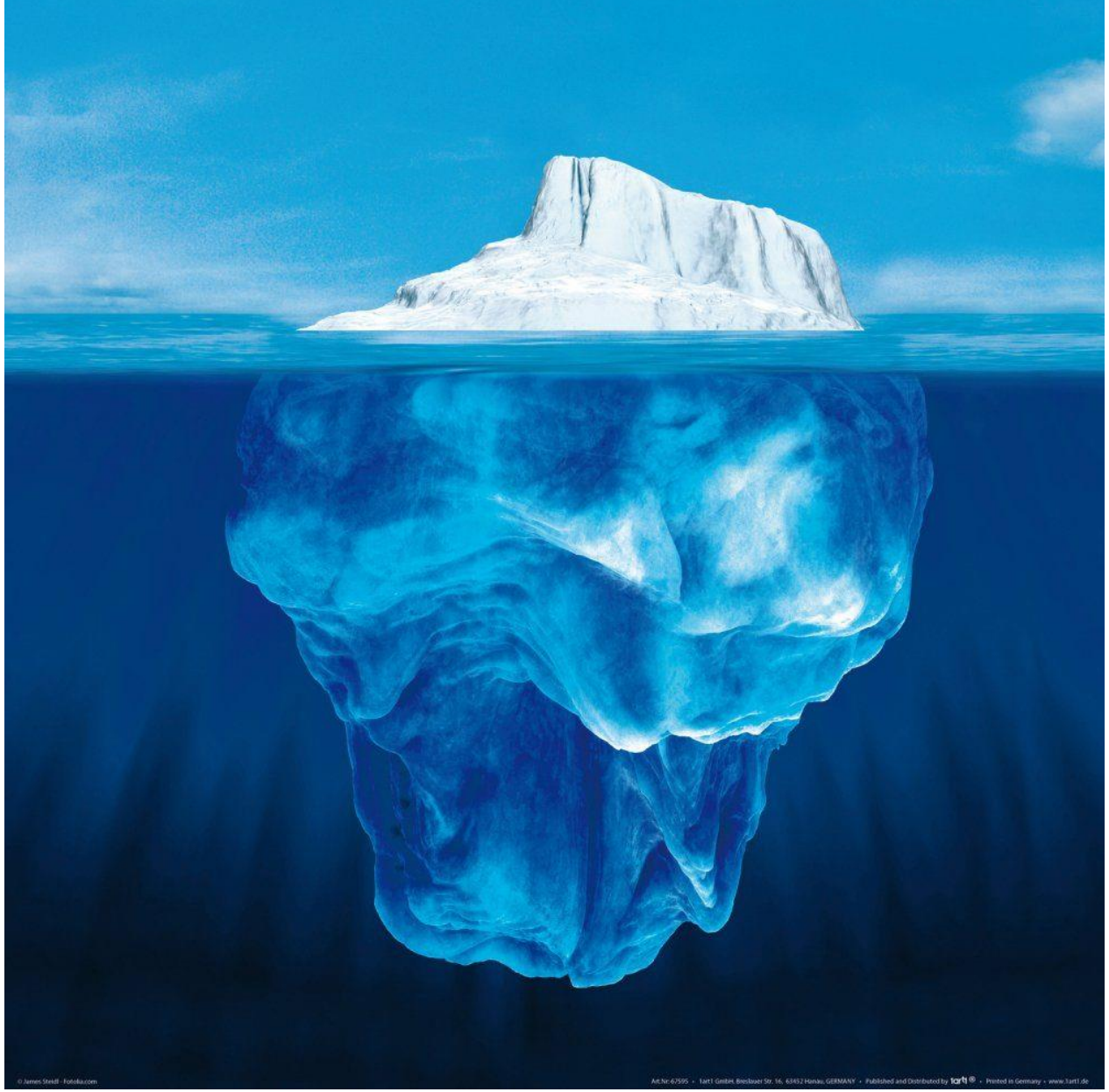
*Katie Wong, David Pitcher, Fiona Braddon, Lewis Downward, Retha Steenkamp, Nicholas Annear, Jonathan Barratt, Coralie Bingham, Constantina Chrysochou, Richard J Coward, David Game, Sian Griffin, Matt Hall, Sally Johnson, Durga Kanigicherla, Fiona Karet Frankl, David Kavanagh, Larissa Kerecuk, Eamonn R Maher, Shabbir Moochhala, Jenny Pinney, John A Sayer, Roslyn Simms, Smeeta Sinha, Shalabh Srivastava, Frederick W K Tam, Andrew Neil Turner, Stephen B Walsh, Aoife Waters, Patricia Wilson, Edwin Wong, Christopher Mark Taylor, Dorothea Nitsch, Moin Saleem, Detlef Bockenhauer, Kate Bramham, Daniel P Gale, for the RaDaR consortium**

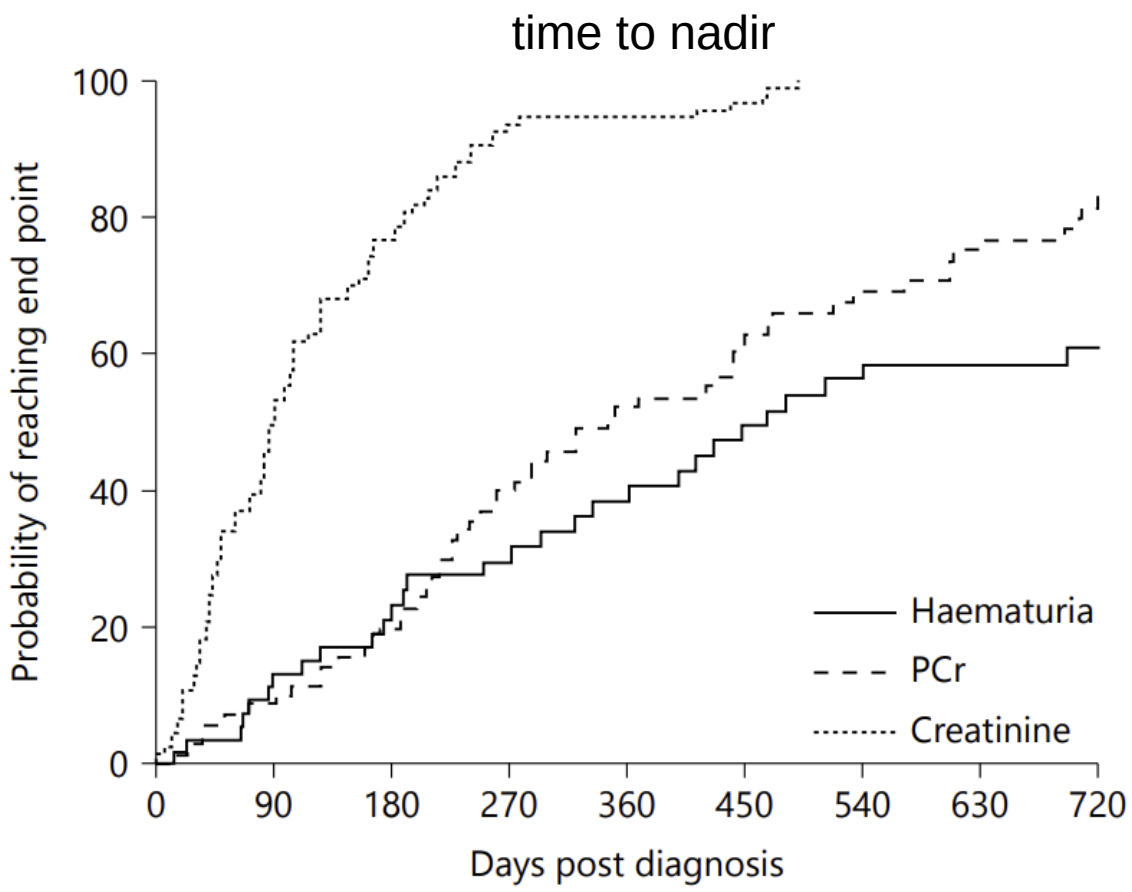




Zeit bis eGFR 30 mL/min:
10,5 Jahre bei AAV
4,0 Jahre bei IgAN

Wong *Lancet* 2024



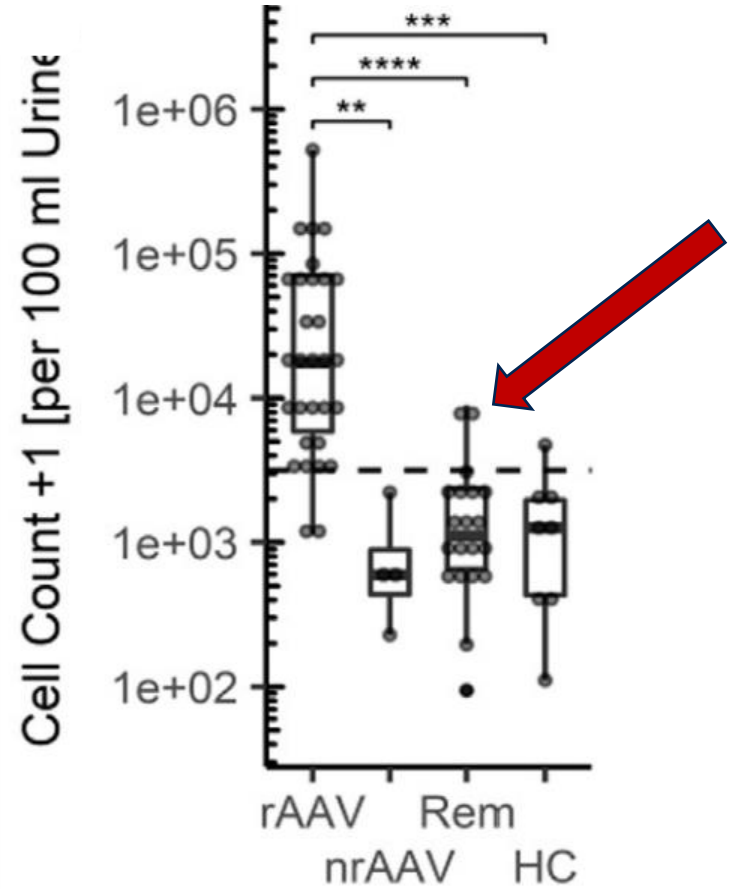


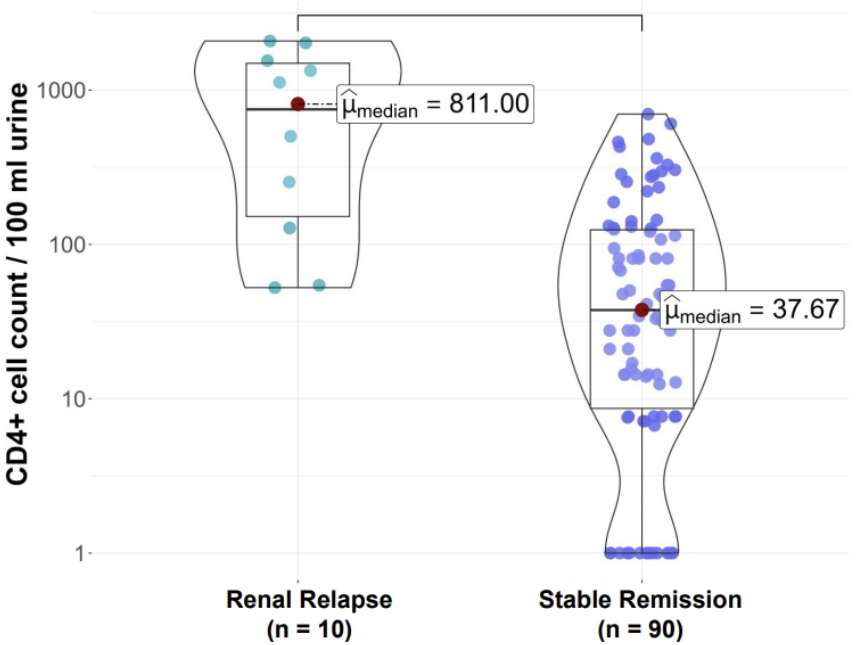
Oomatia *AJ Nephrol* 2015

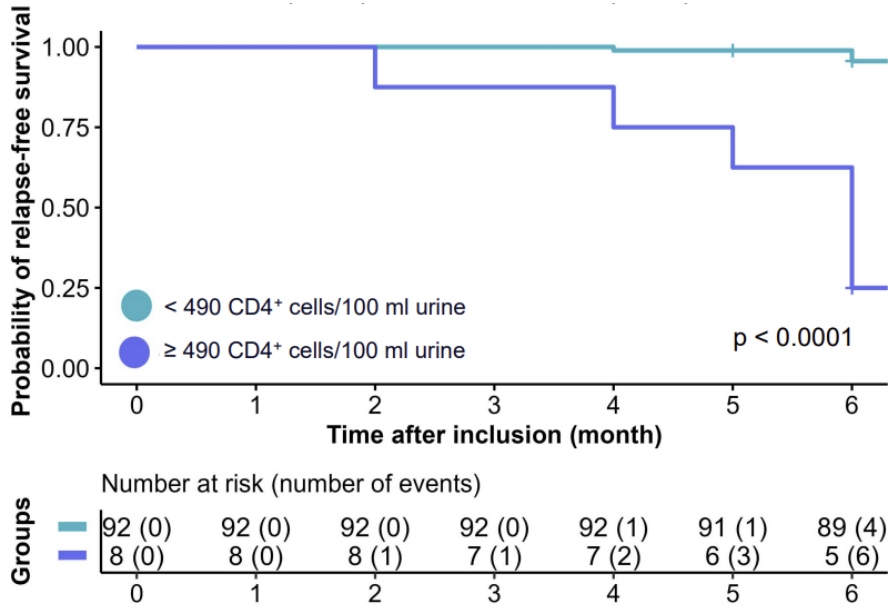
CLINICAL RESEARCH: GLOMERULAR AND TUBULOINTERSTITIAL DISEASES

Urinary CD4⁺ T Cells Predict Renal Relapse in ANCA-Associated Vasculitis

Prskalo, Luka[1]; Skopnik, Christopher M.[1]; Goerlich, Nina[1,2]; Freund, Paul[1]; Wagner, Leonie[1]; Grothgar, Emil[1]; Mirkheshti, Pouneh[1]; Klocke, Jan[1,2]; Sonnemann, Janis[1]; Metzke, Diana[1,2]; Schneider, Udo[3]; Hiepe, Falk[2,3]; Eckardt, Kai-Uwe[1]; Salama, Alan D.[4]; Bieringer, Markus[5]; Schreiber, Adrian[1]; Enghard, Philipp[1]







Prskalo *JASN* 2024

BVAS

Manifestation	Definition	Persistent	New / Worse
1. General	**Maximum scores**	**2**	**3**
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥38° C	Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5° C	2	2
Weight Loss ≥2 kg	Loss of dry body weight without dieting	2	2

2. Cutaneous	**Maximum scores**	**3**	**6**
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer	A disruption in the continuity of the skin	1	4
Gangrene	Extensive tissue necrosis	2	6
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2

3. Mucous Membranes / eyes	**Maximum scores**	**3**	**6**
Mouth ulcers / granulomata	Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers	Ulcers on the genitalia or perineum	1	1
Adnexal inflammation	Salivary or lacrimal gland inflammation.	2	4
Significant proptosis	>2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis	Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis	Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1
Blurred vision	Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss*	Acute loss of vision	*	6
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage)	Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate (exclude hard exudates) / retinal haemorrhage	2	6

4. ENT	**Maximum scores**	**3**	**6**
Bloody nasal discharge / crusts / ulcers / granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis	Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss	Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6

5. Chest	**Maximum scores**	**3**	**6**
Wheeze	Wheeze on clinical examination	1	2
Nodules or cavities*	New lesions detected on imaging	*	3
Pleural effusion / pleurisy	Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate	Detected on chest X-ray or CT scan	2	4
Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure	The need for artificial ventilation	4	6

6. Cardiovascular	**Maximum scores**	**3**	**6**
Loss of pulses	Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease	Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis	Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina.	2	4
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure	Heart failure by history or clinical examination	3	6

7. Abdominal	**Maximum scores**	**4**	**9**
Peritonitis	Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea	Of recent onset	3	9
Ischaemic abdominal pain	Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6

8. Renal	**Maximum scores**	**6**	**12**
Hypertension	Diastolic >95 mm Hg	1	4
Proteinuria	>1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria	'Moderate' on urinalysis or ≥10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 µmol/L	At first assessment only	2	4
Serum creatinine 250-499 µmol/L		3	6
Serum creatinine ≥500 µmol/L		4	8
>30% rise in creatinine or >25% fall in creatinine clearance *	Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	*	6

9. Nervous system	**Maximum scores**	**6**	**9**
Headache	Unaccustomed & persistent headache	1	1
Meningitis	Clinical evidence of meningism	1	3
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke	Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion	Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy	Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy	Objective sensory deficit in a non-dermatomal distribution	3	6
Mononeuritis multiplex	Single or multiple specific motor nerve palsies	3	9

Moran *JASN* 202

VDI

VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***usually have a VDI score of zero,*** unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse since the onset of vasculitis

	No	Yes
1. Musculoskeletal		
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertention		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericaritis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name
Trial Number
Date
Centre

	No	Yes
7. Peripheral vascular disease		
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

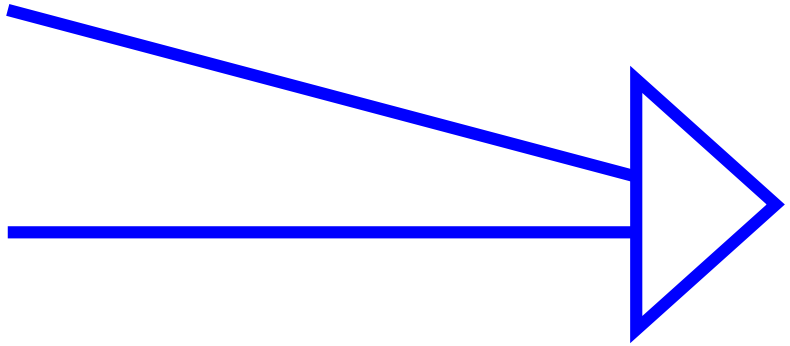
Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

AAV-PRO

Organ-Specific Symptoms	Systemic Symptoms	Treatment Side Effects
Social and Emotional Impact	Concerns about the Future	Physical function

Therapie der schweren ANCA Vasculitis/NCGN

Induktion



Steroid

+/-

Avacopan

Rituximab (anti-CD20)

Oder

Cyclophosphamid

ggfs. zusätzlich

Plasmaaustausch

Erhaltung

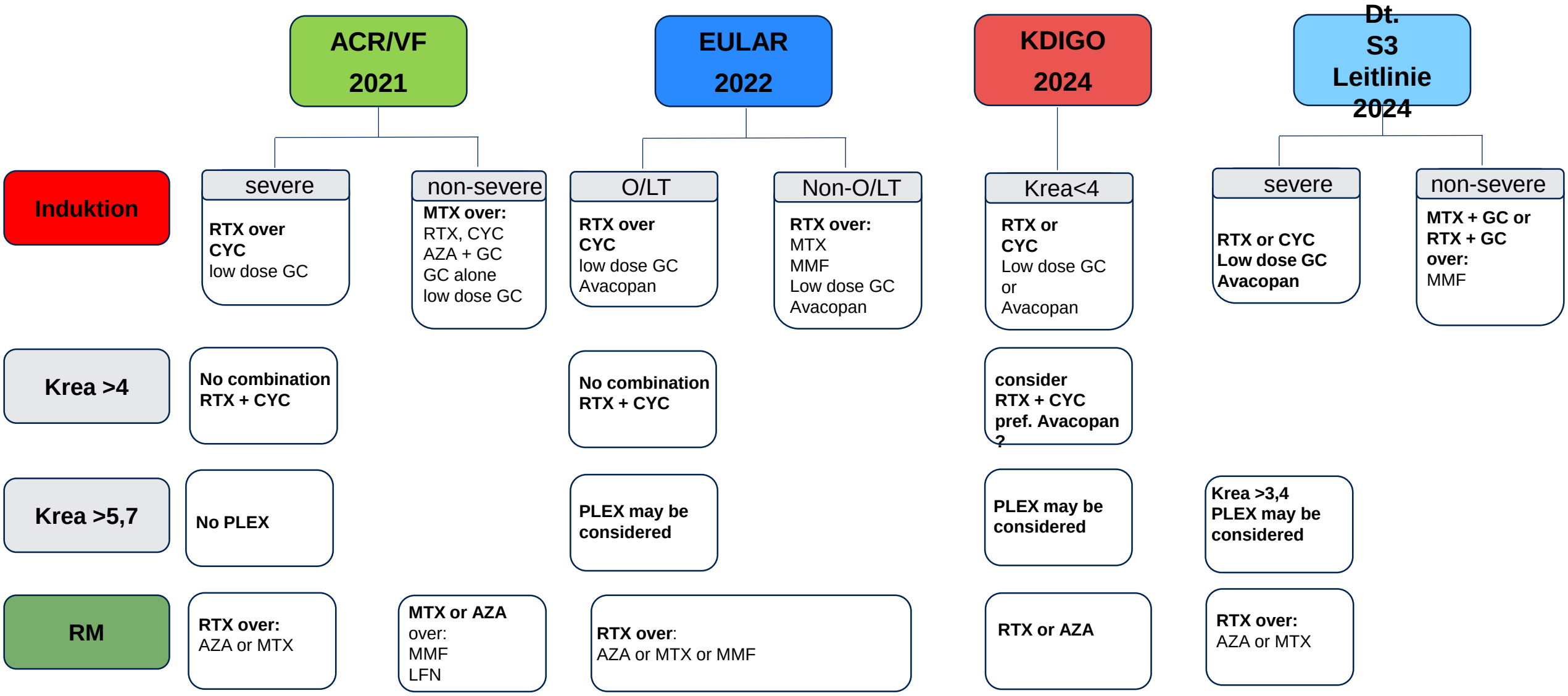
Rituximab

Azathioprin

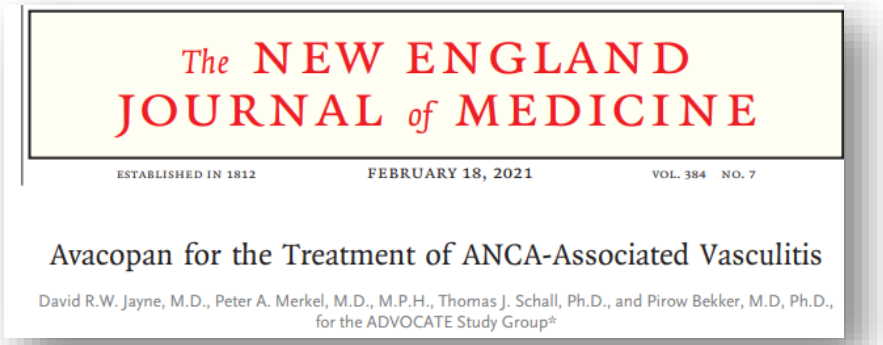
MTX

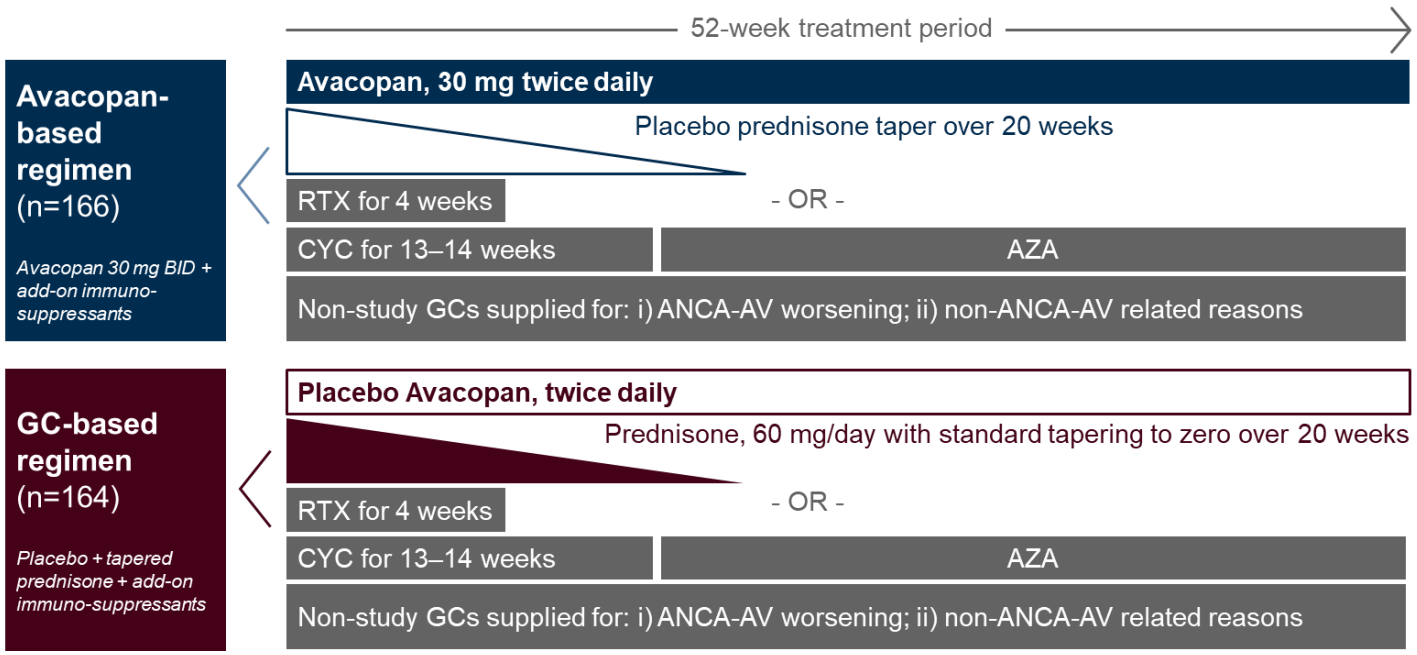
MMF

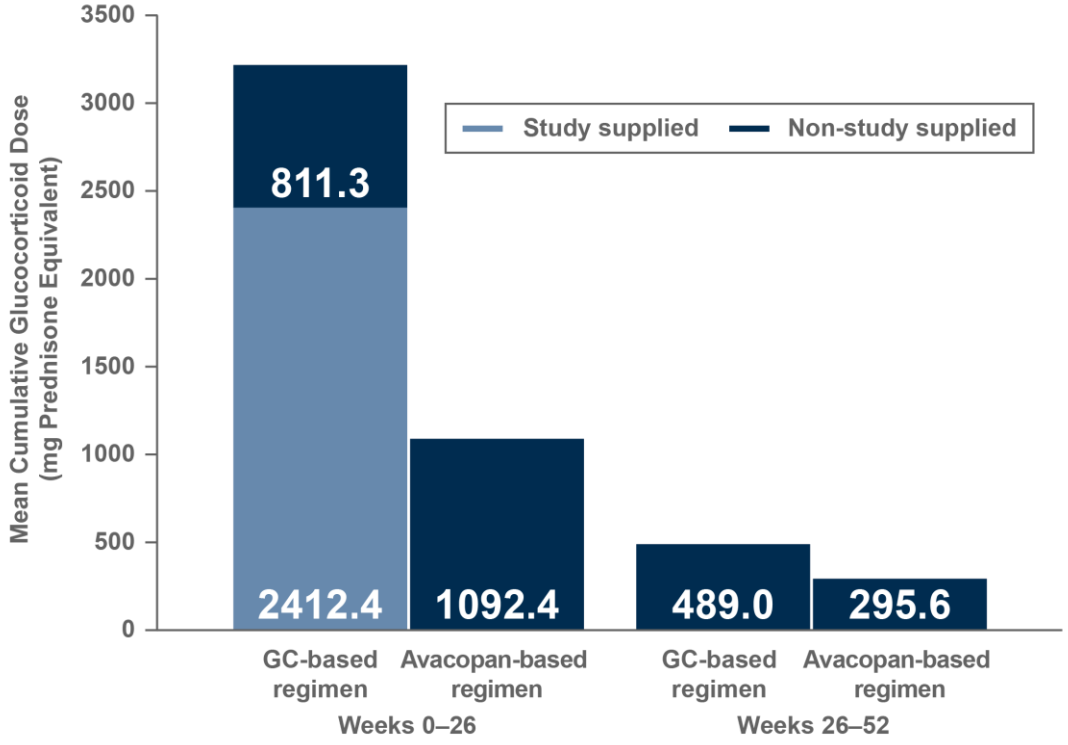
Guidelines


ACR/VF 2021
EULAR 2022
KDIGO 2024
Dt. S3 Leitlinie 2024
Induktion
severe
RTX over
CYC
low dose GC
non-severe
MTX over:
RTX, CYC
AZA + GC
GC alone
low dose GC
O/LT
RTX over
CYC
low dose GC
Avacopan
Non-O/LT
RTX over:
MTX
MMF
Low dose GC
Avacopan
Krea<4
RTX or
CYC
Low dose GC
or
Avacopan
severe
RTX or CYC
Low dose GC
Avacopan
non-severe
MTX + GC or
RTX + GC
over:
MMF
Krea >4
No combination
RTX + CYC
No combination
RTX + CYC
consider
RTX + CYC
pref. Avacopan
?
Krea >5,7
No PLEX
PLEX may be
considered
PLEX may be
considered
Krea >3,4
PLEX may be
considered
RM
RTX over:
AZA or MTX
MTX or AZA
over:
MMF
LFN
RTX over:
AZA or MTX or MMF
RTX or AZA
RTX over:
AZA or MTX

ADVOCATE Trial – Avacopan (C5aR-Hemmer)

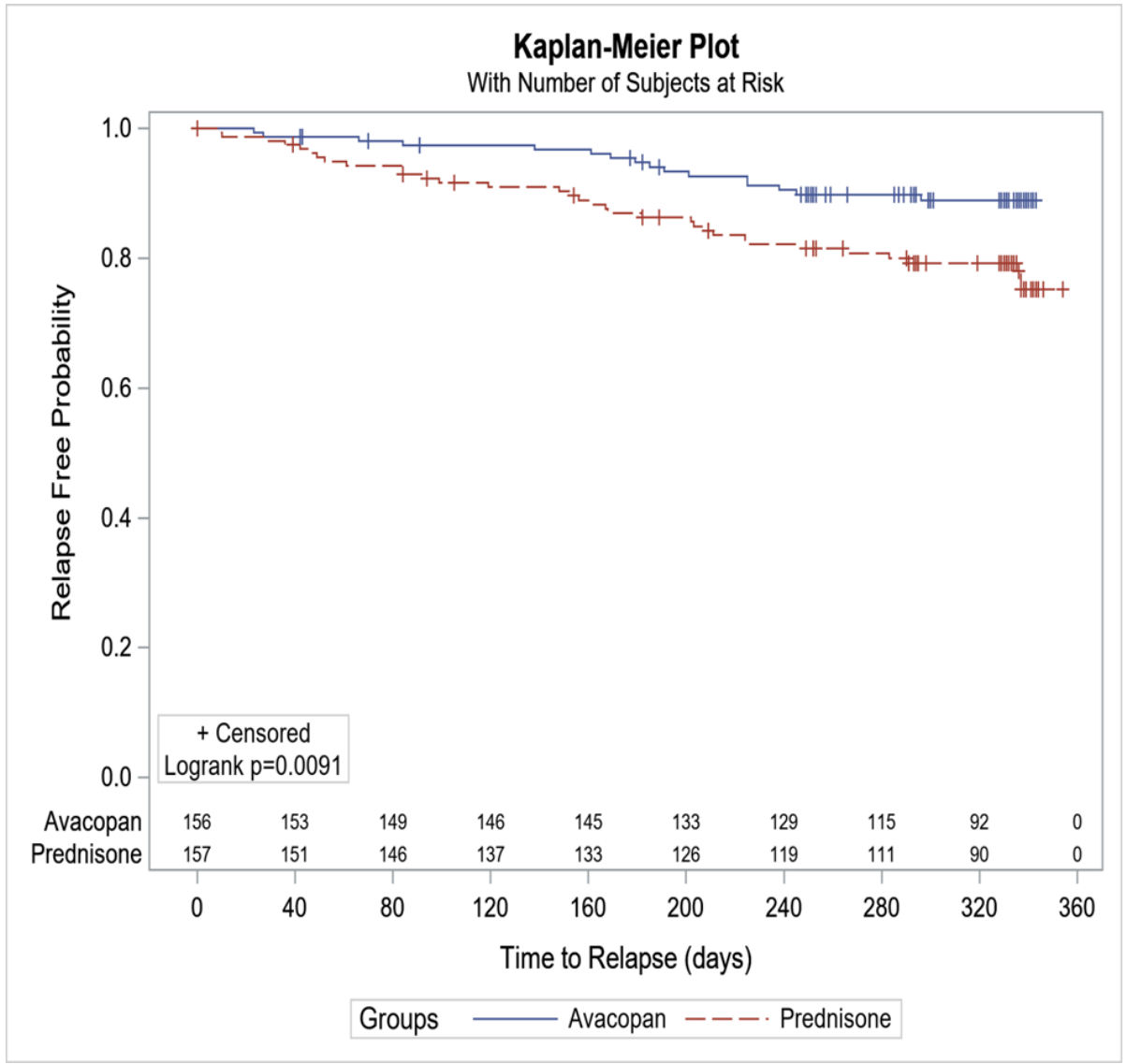




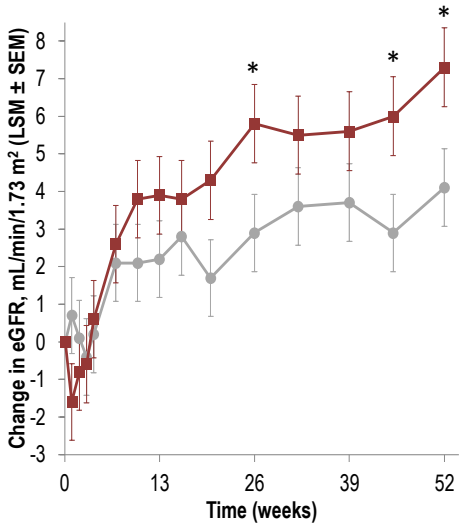


Jayne et al. *NEJM* 2021

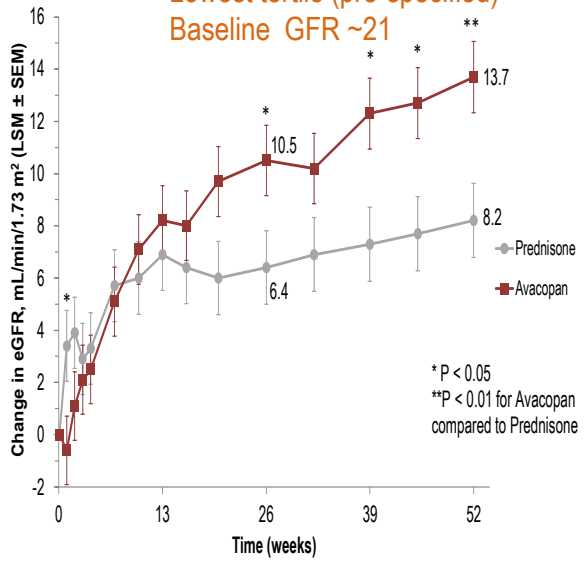
ADVOCATE Trial – Avacopan (C5aR-Hemmer)



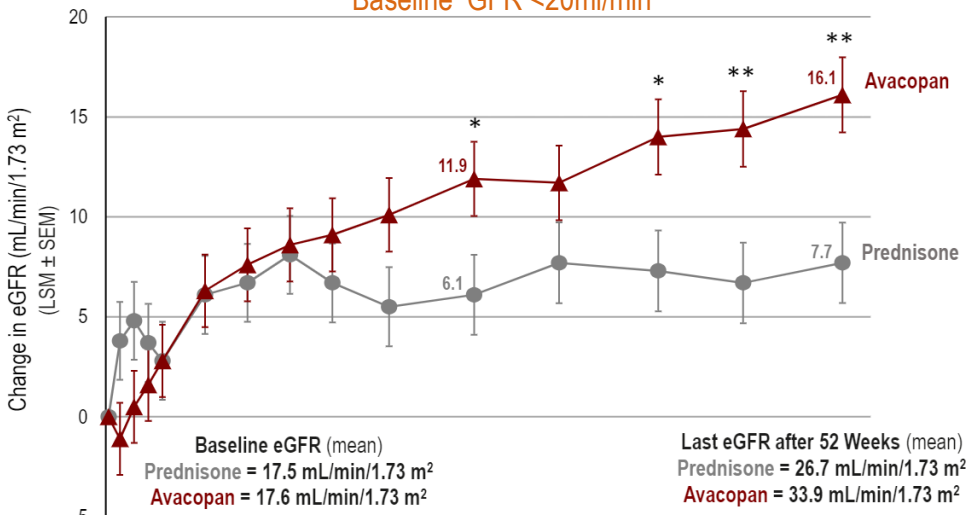
Baseline GFR ~45



Lowest tertile (pre-specified)
Baseline GFR ~21



Baseline GFR <20ml/min



Jayne et al. *NEJM* 2021

ADVOCATE Trial – Avacopan (C5aR-Hemmer)

	Avacopan group	Prednisone group	All patients
Week 26			
6 domains	1 (1%)	1 (1%)	2 (1%)
5 domains	4 (3%)	4 (3%)	8 (3%)
4 domains	14 (9%)	17 (11%)	31 (10%)
3 domains	23 (15%)	41 (27%)	64 (21%)
2 domains	56 (36%)	44 (29%)	100 (33%)
1 domain	43 (28%)	32 (21%)	75 (24%)
0 domains	13 (8%)	14 (9%)	27 (9%)
Total	154 (100%)	153 (100%)	307 (100%)

A patient was considered to have involvement of a specific domain if there was either an increase or a decrease in the domain score at the timepoint of interest.

	Avacopan group	Prednisone group	p value*
CWS			
BMI at week 13	1·1 (5·1)	3·8 (8·1)	0·0006
BMI at week 26	1·9 (6·3)	3·8 (8·2)	0·018
Glucose tolerance at week 13	0·2 (2·5)	2·9 (9·6)	0·0006
Glucose tolerance at week 26	2·9 (9·2)	3·4 (10·1)	0·64
Blood pressure at week 13	8·9 (13·2)	8·6 (12·3)	0·84
Blood pressure at week 26	13·8 (15·8)	13·8 (14·4)	0·99
Lipid metabolism at week 13	5·7 (5·7)	7·6 (6·7)	0·0052
Lipid metabolism at week 26	8·1 (6·7)	10·6 (7·5)	0·0021
Glucocorticoid myopathy at week 13	0·3 (1·6)	1·1 (6·7)	0·15
Glucocorticoid myopathy at week 26	0·4 (1·9)	1·9 (9·9)	0·059
Skin toxicity at week 13	0·8 (2·3)	1·9 (4·8)	0·0078
Skin toxicity at week 26	1·2 (3·4)	2·2 (4·7)	0·023
Neuropsychiatric effects at week 13	3·0 (12·7)	3·7 (13·2)	0·61
Neuropsychiatric effects at week 26	2·9 (11·7)	5·3 (15·7)	0·12
Infection at week 13	6·8 (22·7)	8·0 (24·6)	0·64
Infection at week 26	8·7 (25·3)	15·6 (38·6)	0·066

- Avacopan wirksamer in der Induktion einer anhaltenden Remission
- durch Avacopan schnellere GFR-Besserung, vor allem bei niedrigerer GFR
- unter Avacopan weniger Glucocorticoid-NW

Patel et al. *LancRheum* 2023

KI REPORTS
KIReports.org

Avacopan in Anti-Neutrophil Cytoplasmic Autoantibodies–Associated Vasculitis in a Real-World Setting

Jonas Zimmermann[1,2,7], Janis Sonnemann[1,2,7], Wolfram J. Jabs[3,7], Ulf Schönermarck[4], Volker Vielhauer[4], Markus Bieringer[5], Udo Schneider[6], Ralph Kettritz[1,2] and Adrian Schreiber[1,2]

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Received 1 March 2024; revised 6 June 2024; accepted 2 July 2024

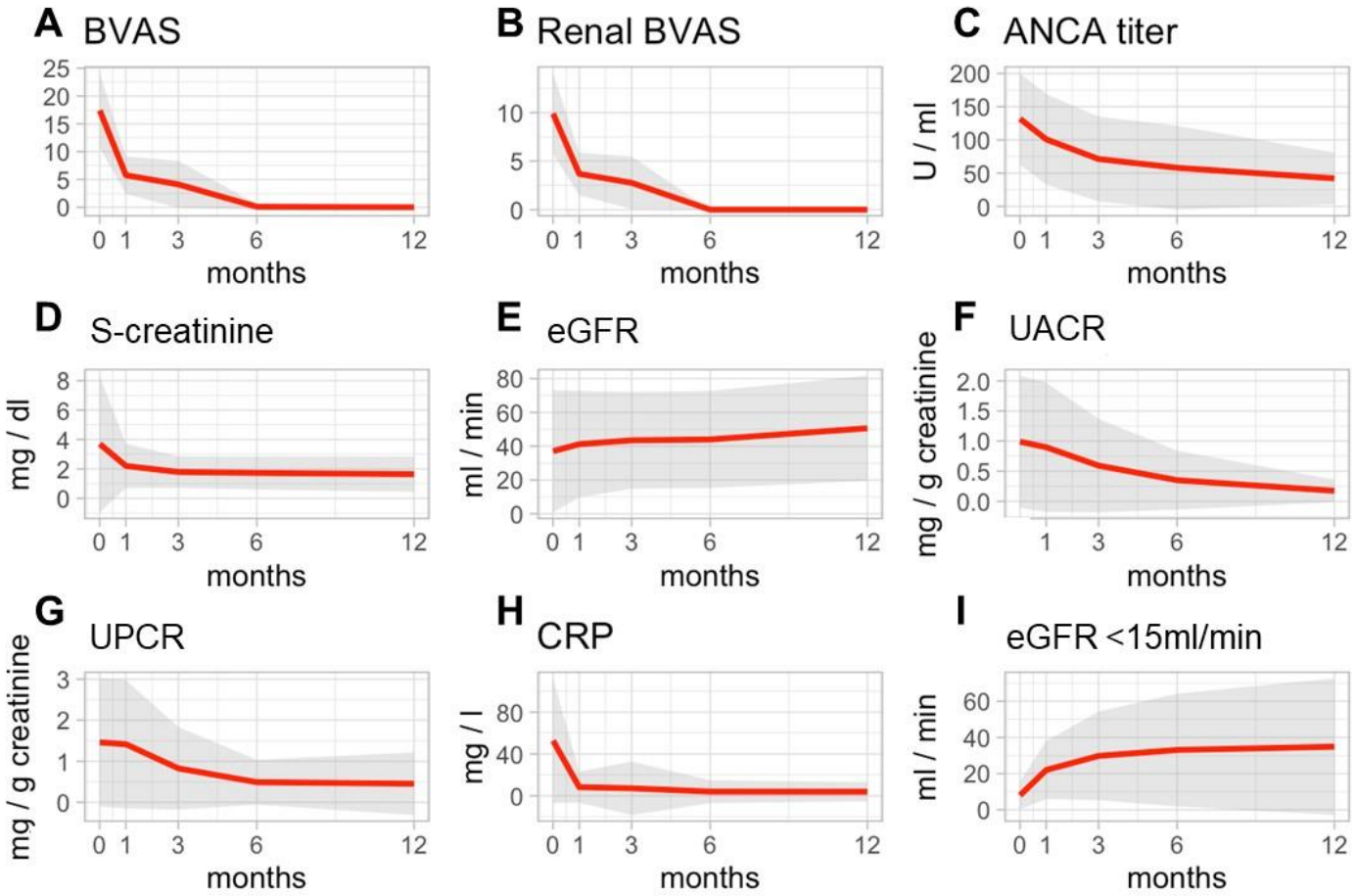
Kidney Int Rep (2024) ■, ■–■; https://doi.org/10.1016/j.ekir.2024.07.007

Jonas Zimmermann| 29. September 2024 | 11:40Uhr | ECC Raum II

Vaskulitis – Avacopan Real world Evidence

Table 1: Patient and clinical characteristics and treatment

Characteristic	
Sex – No. (%)	
Female	18/39 (46)
Male	21/39 (54)
Age – years (mean; IQR)	64 (51, 72)
Diagnosis/Antibody – No. (%)	
GPA / PR3-ANCA	22/39 (56)
MPA / MPO-ANCA	15/39 (38)
MPA+anti-GBM-disease / MPO+anti-GBM	2/39 (5)
Newly diagnosed/Relapse – No. (%)	
Newly diagnosed	20/39 (51)
Relapsed	19/39 (49)
BVAS (at time of diagnosis) – mean	17

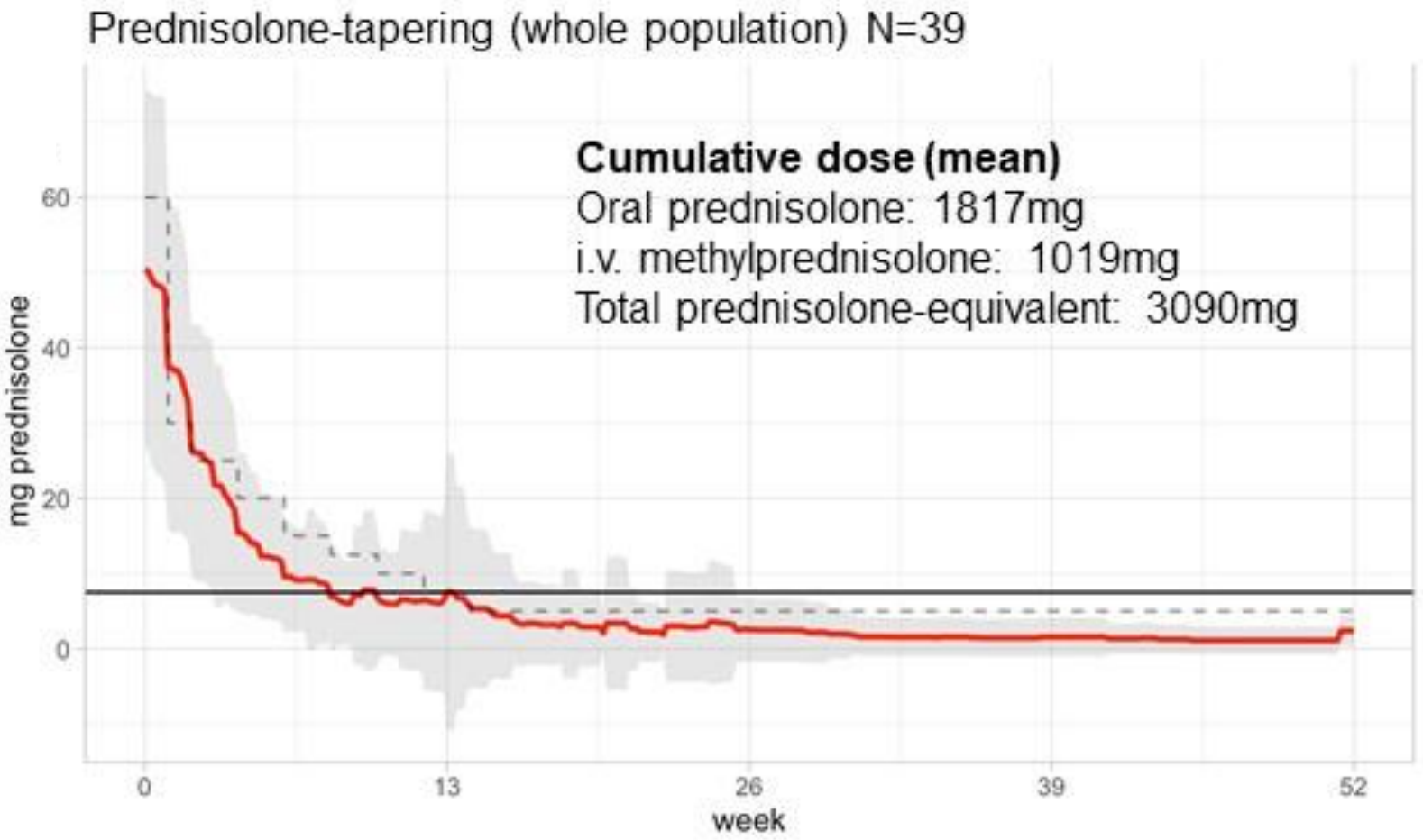


15 Pat (38%) eGFR <15ml/min, 7 Pat (18%) Dialyse

in Pat mit eGFR <15ml/min: eGFR 8 -> 35ml/min

Zimmermann, .. Schreiber *Klrep* 2024

Vaskulitis – Avacopan Real world Evidence



ADVOCATE:
1676mg + 654mg during the screening = 2330mg

Zimmermann, .. Schreiber *KIrep* 2024

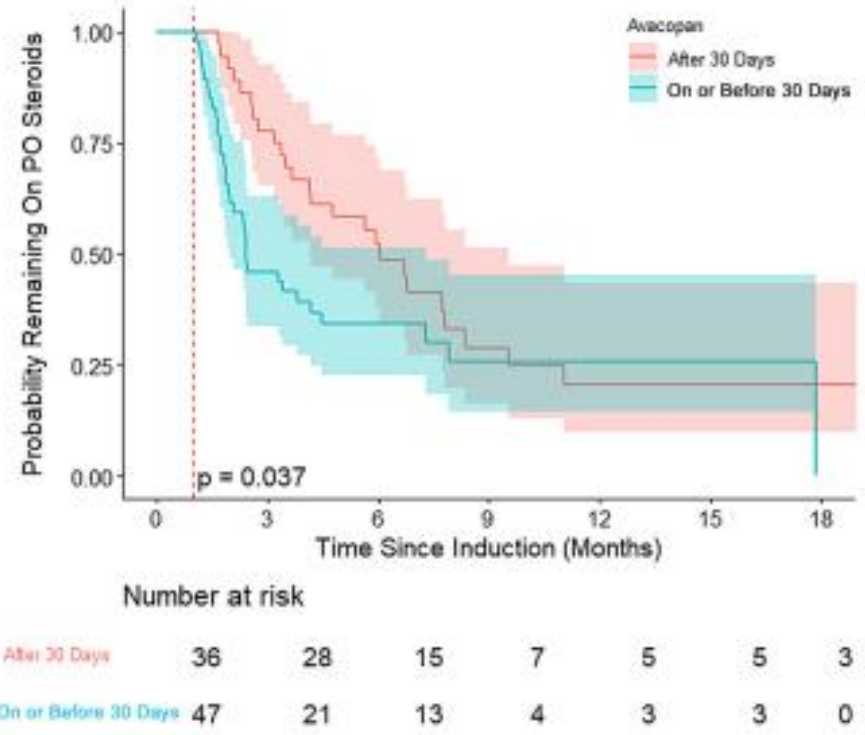
Vaskulitis – Avacopan Real world Evidence

Table 3. Primary and secondary outcomes

Primary outcome	
Clinical remission at wk 26	61/68 (90%)
Clinical remission at wk 52	32/38 (84%)
Secondary outcomes	
Change in eGFR (baseline to wk 26 ($n = 48$)	+12.2 (25.4)
Change in eGFR (baseline to wk 52) ($n = 22$)	+19.8 (23.1)
Duration of hematuria, wk	14.4 (9.1–20.6)
Resolution of hematuria	42 (68%)
Proteinuria at wk 26, mg/g Cr	454 (154–1163)
Proteinuria at wk 52, mg/g Cr	290 (143–742)
Proteinuria, nadir, mg/g Cr	397 (150–896)
Time to nadir proteinuria, wk	15.4 (8.6–29.2)
Clinical relapse	3 (3%)
Infections requiring hospitalization	12 (13%)
Dialysis dependence[a]	6 (9%)
Death	4 (4%)

Table 4. Predictors of clinical remission at 26 weeks

Predictors	OR (95% CI)
Age (per/yr)	1.04 (0.99–1.11)
Early avacopan initiation	1.79 (0.37–9.8)
PLEX	0.20 (0.04–1.17)
Pulse methylprednisolone (per 100 mg)	1.01 (0.95–1.07)
RTX therapy (no CYC)	0.64 (0.11–3.11)
Combination therapy (RTX + low-dose CYC)	2.42 (0.48–17.8)
CYC therapy (no RTX)	N/A

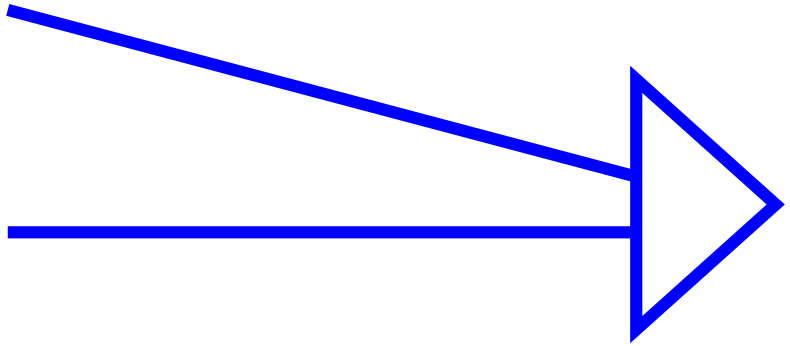


Avacopan was stopped in 20% (n=18) prior to 52 weeks due to adverse events:
Transaminitis (n=4)
gastrointestinalrelated side effects (n=3)
worsening kidney function, worsening proteinuria
increase prednisone for ongoing sinus disease, COVID19, fingertip necrosis, chest pain, shortness of breath, neuropathy, new malignancy diagnosis, pruritus, and financial cost burden

Zonosi *Klrep* 2024

Therapie der schweren ANCA Vasculitis/NCGN

Induktion



Steroid

+/-

Avacopan

Rituximab (anti-CD20)

Oder

Cyclophosphamid

ggfs. zusätzlich

Plasmaaustausch

Erhaltung

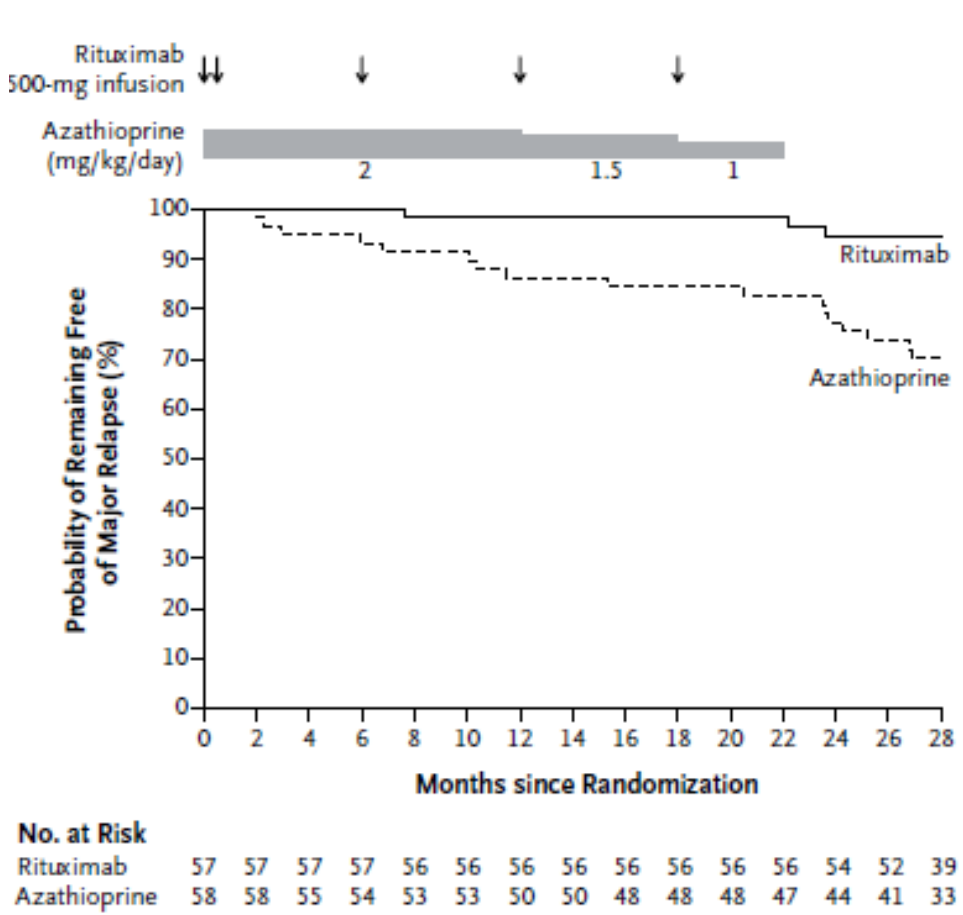
Rituximab

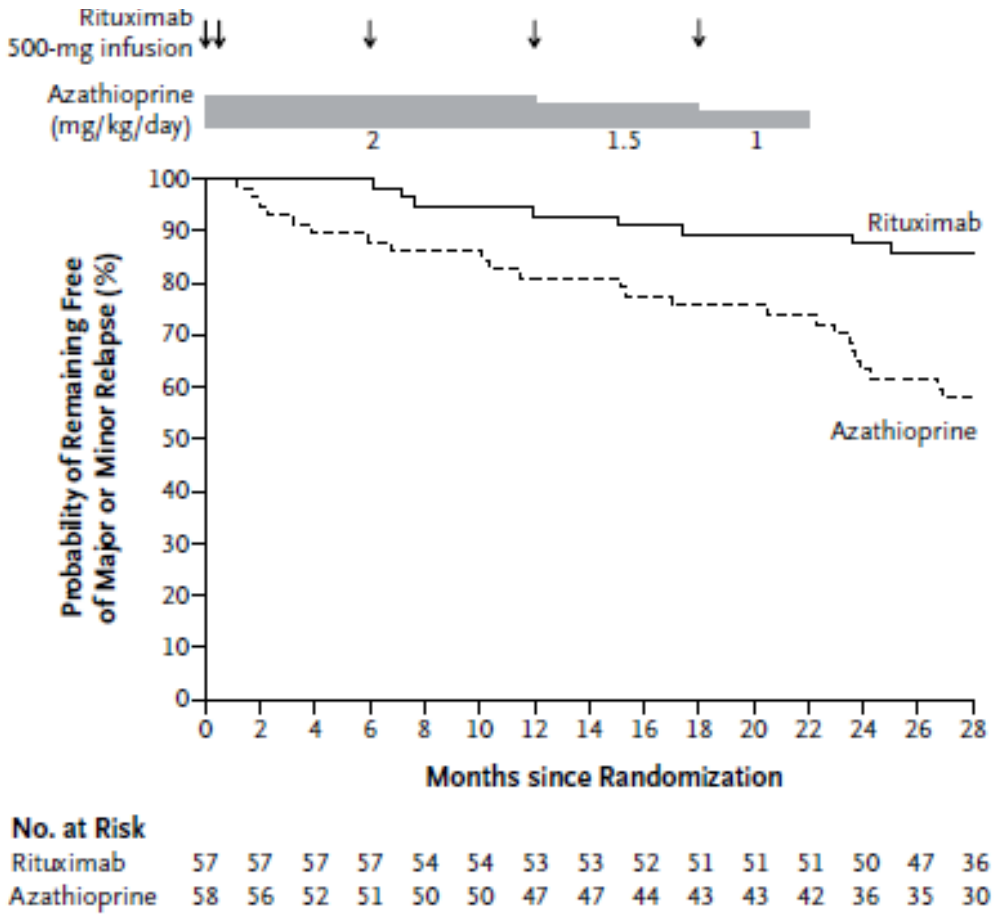
Azathioprin

MTX

MMF

Remission – Therapie Mainritsan 1





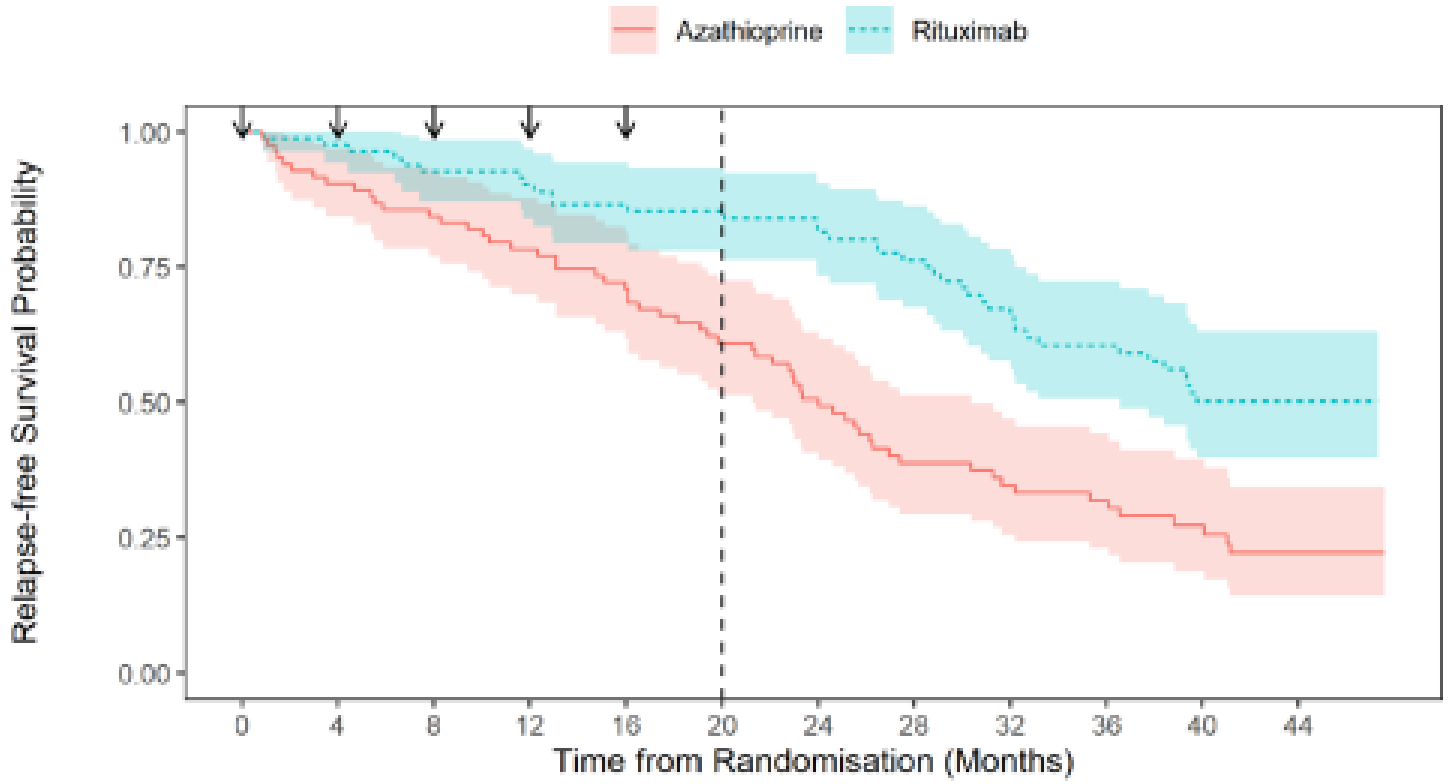
RTX Azathioprin überlegen

Guillevin *NEJM* 2014

Remission – Therapie RITAZAREM

Relapsierende AAV

1g RTX alle 4 Monate (bis Monat 20) versus Azathioprin 2mg/kg bis Monat 24 (abgesetzt Monat 27)



Smith *ARD* 2023

Remission – Therapie Mainritsan 2

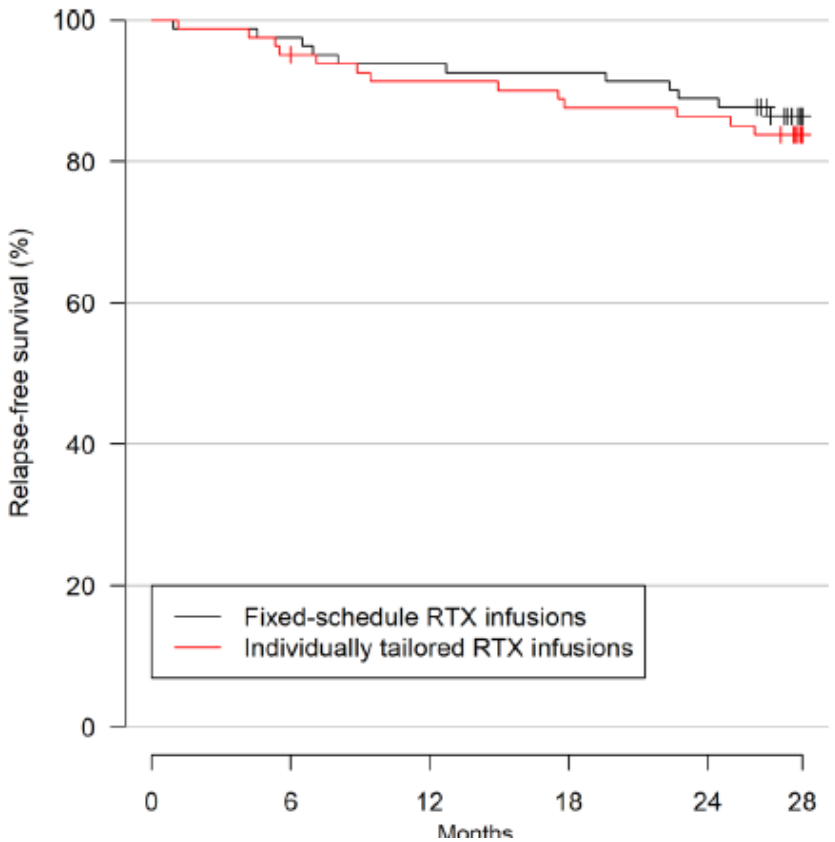


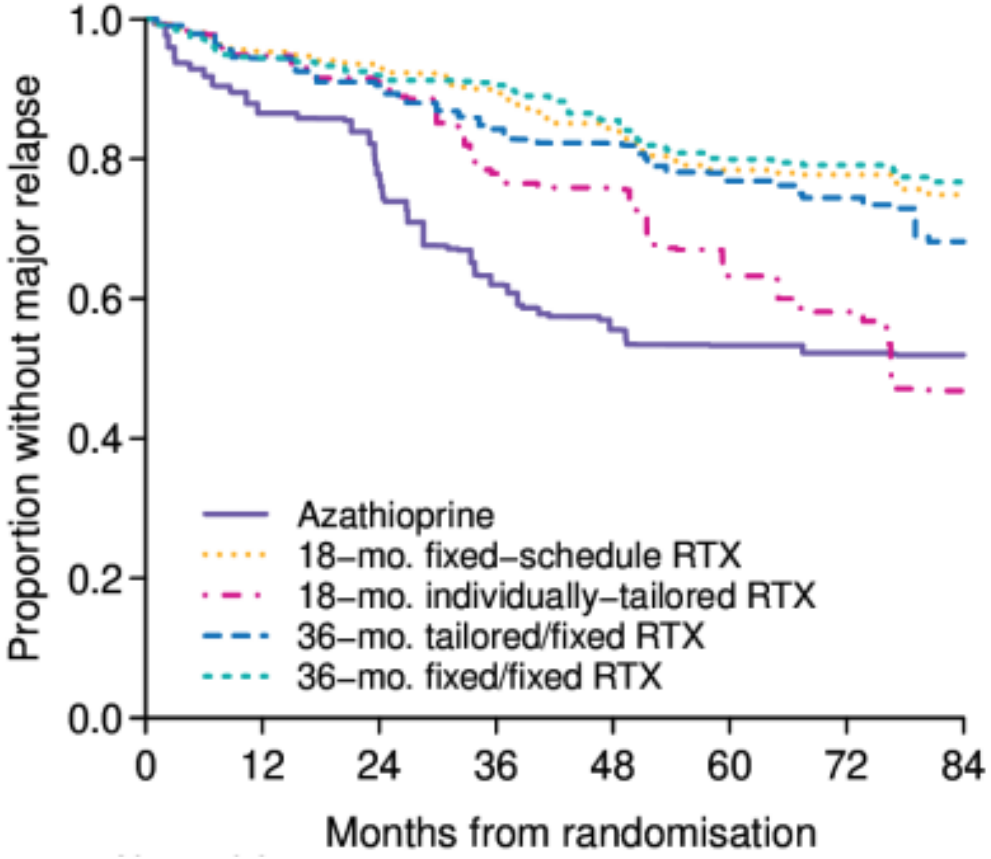
Table 2 ANCA evolution and B-cell detection patterns throughout follow-up for patients with ≥1 relapses or none

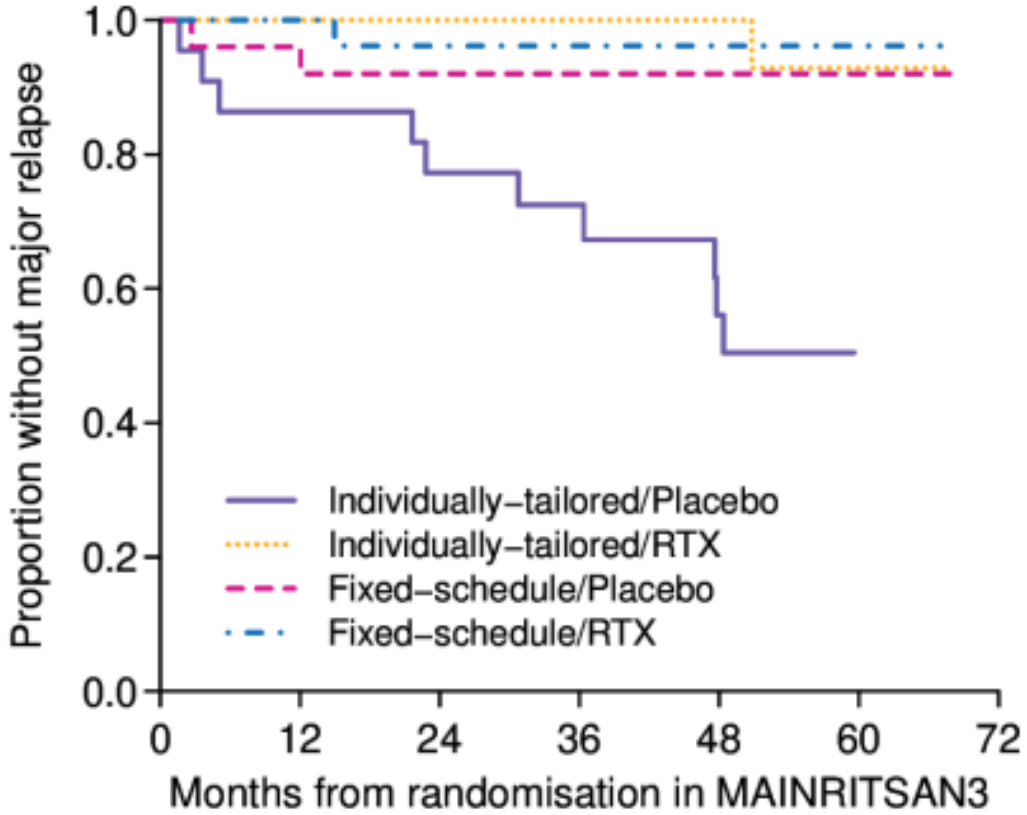
Parameter profile	Patients with ≥1 relapse(s) (n=22)*	Patients with No relapse (n=139)
ANCA evolution (%)		
Always negative	7 (31.8)	33 (23.7)
Negative at inclusion and became positive	3 (13.6)	14 (10.1)
Positive at inclusion and became negative	2 (9.1)	51 (36.7)
Positive at inclusion and titres rose	1 (4.5)	10 (7.2)
Positive at inclusion and remained stable	9 (40.9)	29 (20.9)
Circulating CD19+ B cell evolution (%)		
Always negative	11 (50)	8 (5.8)
Detected at least once	11 (50)	131 (94.2)
ANCA and circulating CD19+ B cell evolutions (%)		
ANCA-negative and no circulating B cells detected	4 (18.2)	5 (3.6)
Other	18 (81.8)	134 (96.4)

1.5-fache Reduktion an Rituximabinfusionen
17,3% (tailored) vs. 9,9% Relapse (p=0,22), major relapses auch häufiger (7,4 vs 3,7%)
Kein Benefit in Infekt. Komplikationen (19,8 vs 11,1%)

Charles *ARD* 2018

Remission – Therapie RTX wie lange?





Azathioprin unterlegen

RTX tailored schlechter

RTX länger als 18 Monate ohne sicheren zusätzlichen Benefit wenn initial fixed Regimen

Delestre *ARD* 2023

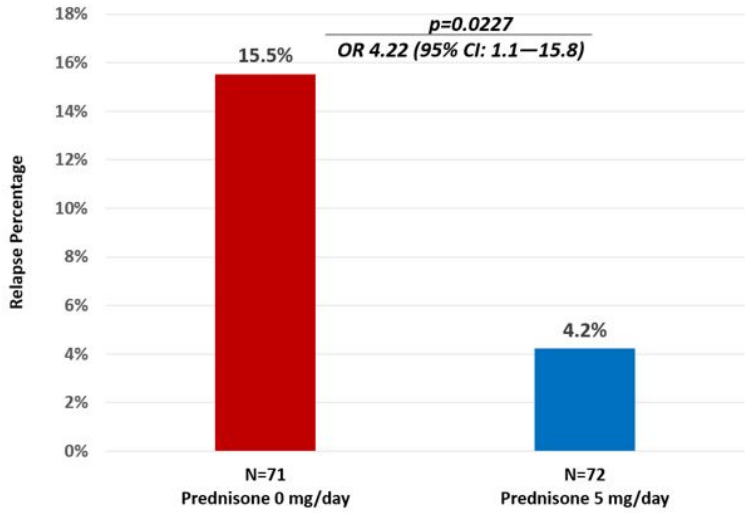
Remission – Steroide TAPIR study

GPA Pat in Remission, Induktionstehrapie innerhalb 12 Monate
Prednisolon 5-20mg/d
-> randomisiert in 5mg vs 0mg
1st EP: relapse rate

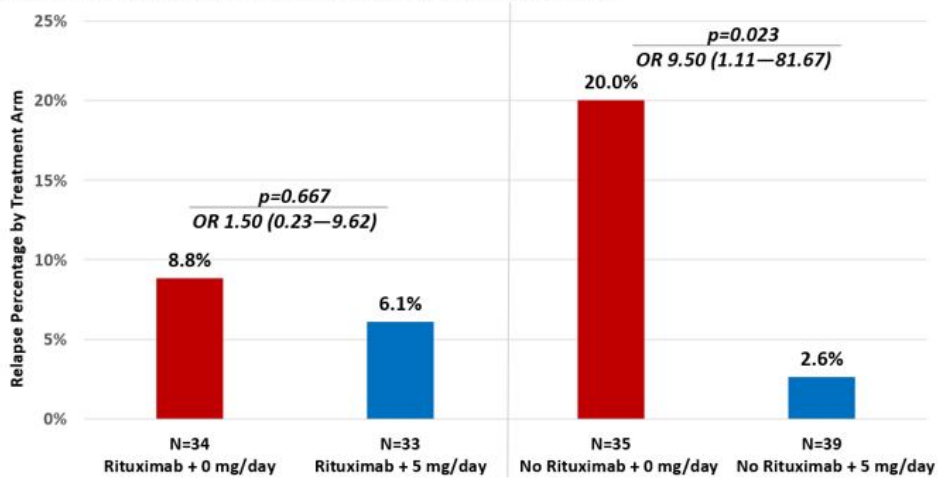
Table 1. Baseline characteristics of the study population

	0 mg (N=71)	5 mg (N=72)	p-value
Age at randomization years, Median (IQR)	58.5 (49.4-66.8)	57.44 (44.1-64.4)	0.2425
Sex N (%)			
Female	29 (41%)	39 (54%)	0.1107
Male	42 (59%)	33 (46%)	
Race N (%)			
American Indian/Alaska Native	1 (1.4)	1 (1.4)	0.1590
Asian	7 (9.9)	3 (4.2)	
Black or African American	0 (0.0)	1 (1.4)	
Unknown or Not Reported	0 (0.0)	4 (5.5)	
White	63 (88.7)	63 (87.5)	
Disease duration years, Median (IQR)	0.90 (0.63-7.74)	0.87 (0.64-3.50)	0.3870
Disease Status N (%)			
New disease	41 (58)	40 (56)	0.7915
Relapsing disease	30 (42)	32 (44)	
ANCA N (%)			
PR3-ANCA	53 (83)	60 (88)	0.3251
MPO-ANCA	5 (8)	7 (10)	
Both PR3 & MPO	1 (1)	0 (0)	
ANCA Negative/Unknown	5 (8)	1 (2)	
Treatment N (%)			
Rituximab	34 (49%)	33 (46%)	0.6824
Methotrexate	14 (20%)	11 (15%)	0.4360
Azathioprine	13 (19%)	24 (33%)	0.0505
Mycophenolate	2 (3%)	0 (0)	0.2377

A. Proportion of patients with disease relapse by Month 6



B. Rate of disease relapse at Month 6 stratified by use of rituximab



Unter kompletter Seroidreduktion mehr Minor relaps
Dieses bei RTX-basierter Therapie nicht signifikant

Merkel *ACR* 2024

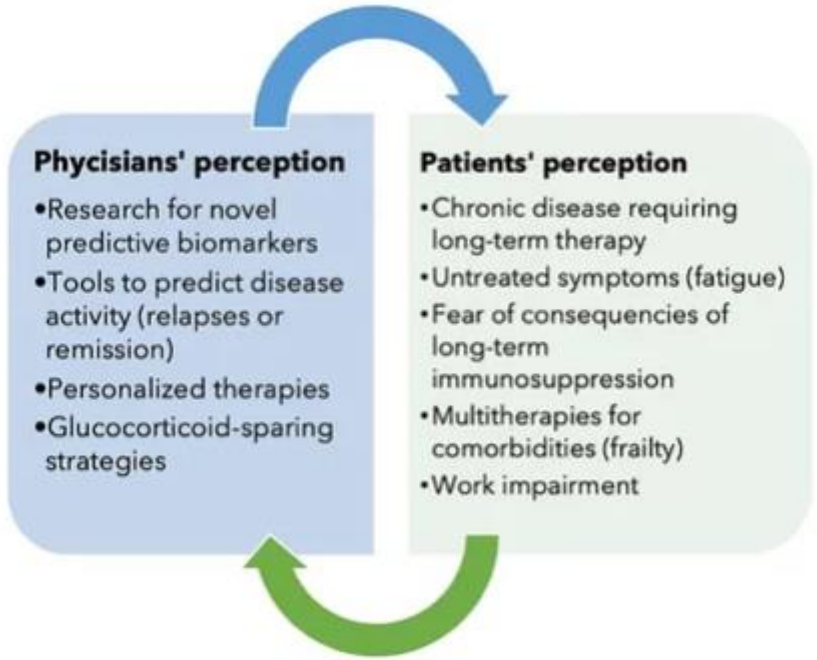
Outcome – was ist entscheidend?

Association of the AAV-PRO questionnaire with established outcome measures in AAV

Annika Maunz[1], Johann Jacoby[2], Joerg Henes [3], Joanna C. Robson [4], Bernhard Hellmich [1], Christian Löffler [1,5,*]

Table 4. Correlation analyses of AAV-PRO domains with BDI, SF-36, BVAS and VDI

		OSSs (*r*)	SSS (*r*)	TSE (*r*)	SEI (*r*)	CAF (*r*)	PF (*r*)
BDI	t1	0.380**	0.454**	0.519**	0.760**	0.615**	0.319**
	t2	0.509**	0.550**	0.659**	0.779**	0.746**	0.423**
SF-36/PF	t1	–0.267**	–0.557**	–0.337**	–0.491**	–0.418**	–0.844**
	t2	–0.487**	–0.671**	–0.441**	–0.622**	–0.575**	–0.839**
SF-36/RFP	t1	–0.364**	–0.603**	–0.429**	–0.636**	–0.547**	–0.619**
	t2	–0.522**	–0.663**	–0.494**	–0.744**	–0.661**	–0.702**
SF-36/RPE	t1	–0.300**	–0.420**	–0.406**	–0.593**	–0.475**	–0.370**
	t2	–0.482**	–0.501**	–0.482**	–0.664**	–0.585**	–0.481**
SF-36/E&F	t1	–0.387**	–0.658**	–0.465**	–0.683**	–0.588**	–0.619**
	t2	–0.554**	–0.731**	–0.594**	–0.807**	–0.733**	–0.726**
SF-36/EWB	t1	–0.377**	–0.579**	–0.525**	–0.787**	–0.706**	–0.530**
	t2	–0.491**	–0.595**	–0.569**	–0.776**	–0.751**	–0.612**
SF-36/SocF	t1	–0.274**	–0.524**	–0.309**	–0.533**	–0.448**	–0.468**
	t2	–0.470**	–0.552**	–0.554**	–0.598**	–0.572**	–0.519**
SF-36/Pain	t1	–0.376**	–0.654**	–0.396**	–0.474**	–0.391**	–0.540**
	t2	–0.443**	–0.723**	–0.519**	–0.625**	–0.561**	–0.645**
SF-36/GH	t1	–0.419**	–0.633**	–0.423**	–0.641**	–0.569**	–0.632**
	t2	–0.494**	–0.600**	–0.518**	–0.650**	–0.602**	–0.649**
BVAS	t1	0.116 x	0.184*	0.145 x	0.151 x	0.079 x	0.288**
	t2	0.154 x	0.100 x	0.224*	0.319**	0.339**	0.256*
VDI	t1	0.107 x	0.031 x	0.053 x	0.036 x	0.108 x	0.005 x
	t2	0.254*	0.150 x	0.092 x	0.152 x	0.201*	0.169*



Maunz *Rheum* 2024

Vaskulitis-spez PRO korrelieren nur eingeschränkt mit etablierten Vaskulitis-Parametern (BVAS, VDI)

Quartuccio *Frontiers Imm 2023*

Therapierefraktärität-Induktionstherapie

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Stone NEJM 2010

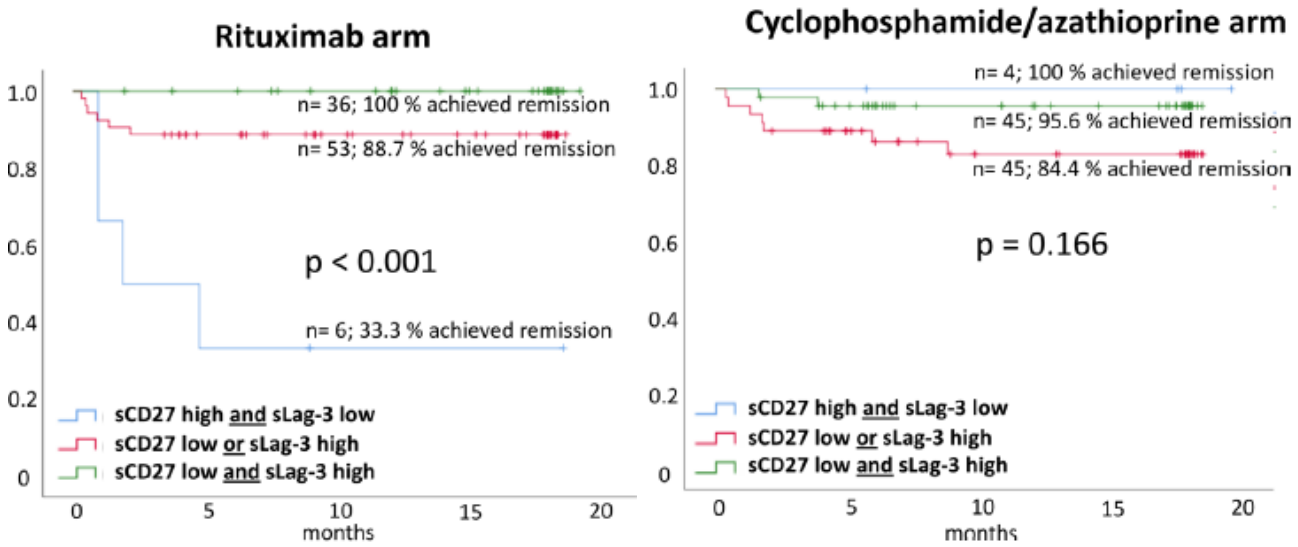
Efficacy Measure	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Difference	P Value
	number (percent)		*percentage points (95% CI)*	
Complete remission				
6 mo	63 (64)	52 (53)	11 (–3 to 24)	0.13
12 mo	47 (47)	38 (39)	9 (–5 to 22)	0.22
18 mo	39 (39)	32 (33)	7 (–7 to 20)	0.32
Remission and <10 mg/day of prednisone				
6 mo	70 (71)	60 (61)	10 (–4 to 23)	0.16
12 mo	59 (60)	60 (61)	–2 (–15 to 12)	0.82
18 mo	54 (55)	52 (53)	2 (–12 to 15)	0.84
Complete remission at any time†	76 (77)	70 (71)		0.15

TRANSLATIONAL SCIENCE

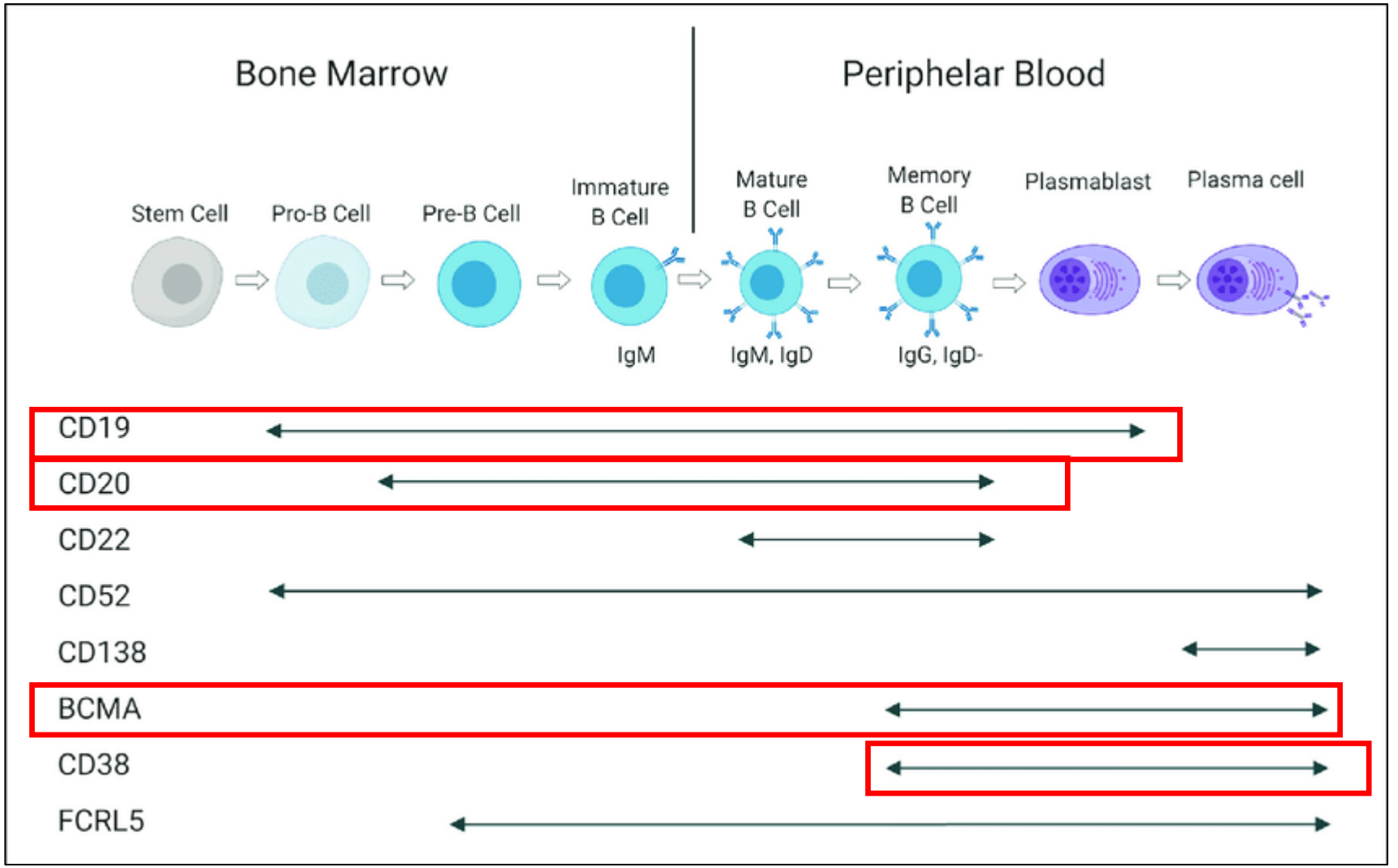
Association of baseline soluble immune checkpoints with the risk of relapse in PR3-ANCA vasculitis following induction of remission

Gabriele Gamerith,[1] Finn Mildner,[1] Peter A Merkel,[2] Kristina Harris,[3] Laura Cooney,[3] Noha Lim,[3] Robert Spiera ,[4] Philip Seo,[5] Carol A Langford,[6] Gary S Hoffman,[6] E William St Clair,[7] Fernando C Fervenza,[8] Paul Monach,[9] Steven R Ytterberg,[10] Duvuru Geetha ,[11] Arno Amann,[1] Dominik Wolf,[1] Ulrich Specks,[12] John H Stone ,[13] Andreas Kronbichler [14]

Gamerith AnnRheumDis 2022



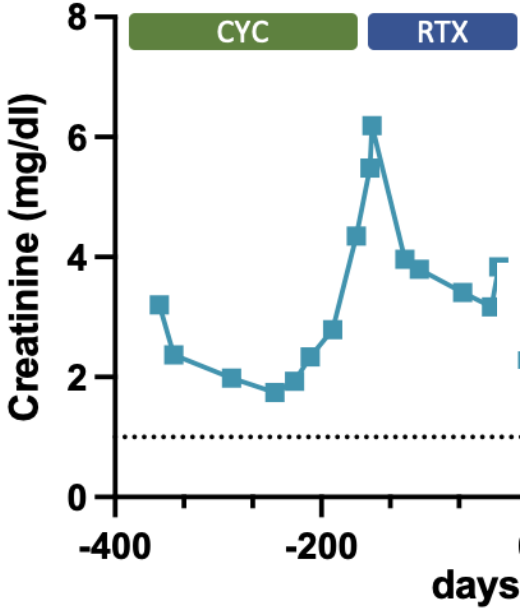
Surface antigens

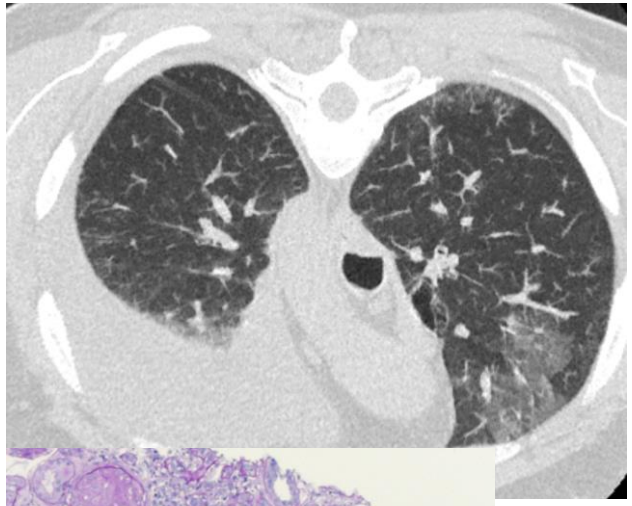


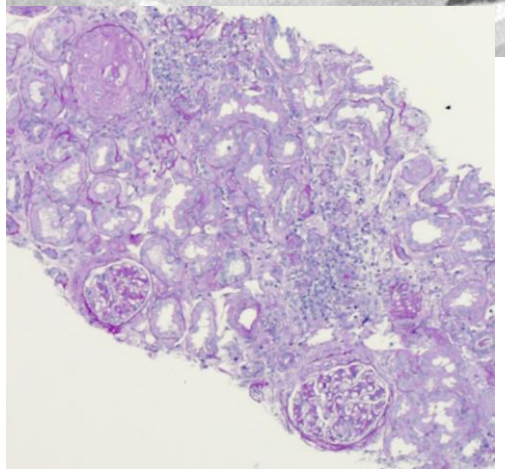
Lejeune M. et al., Front Immunol 2020

Novel treatment approaches: Daratumumab

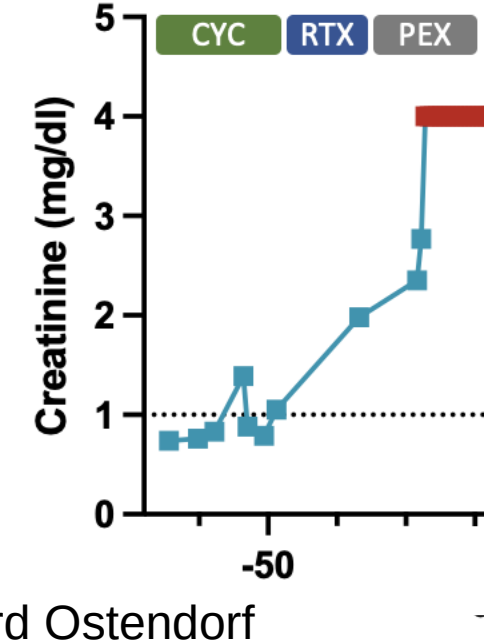
Patient 1: 57j, male
MPO-ANCA+ MPA
active kidney disease
active pulmonary disease

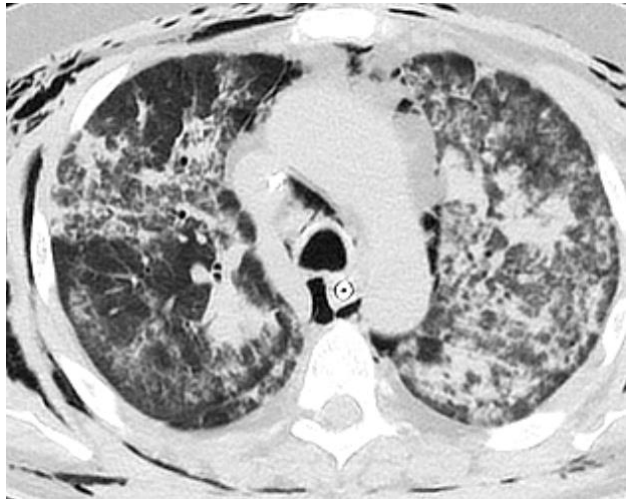






Patient 2: 41j, male
PR3-ANCA+ GPA
dialysis-dependent AKI,
ARDS with vvECMO,
Cardial manifestation (aortic stenosis)



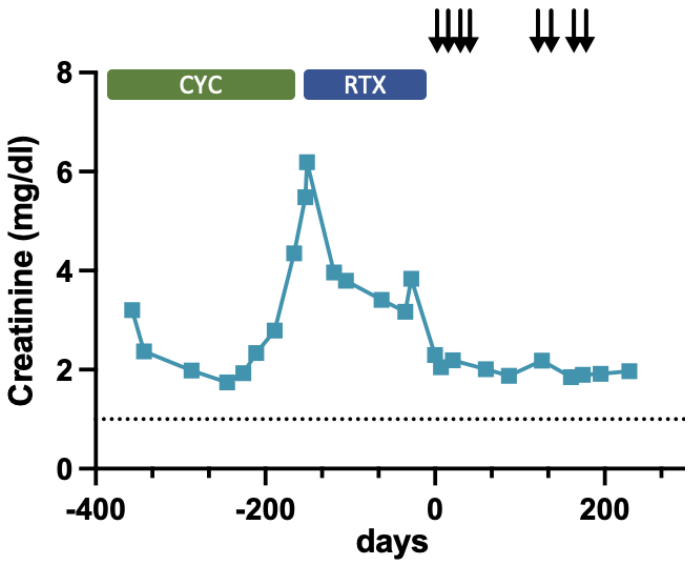


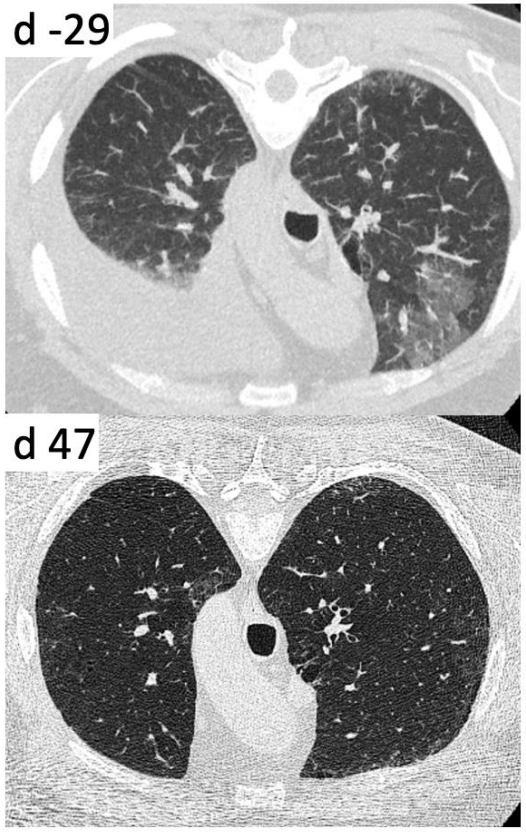
Lennard Ostendorf

Ostendorf, …, Schreiber RMD open 2023

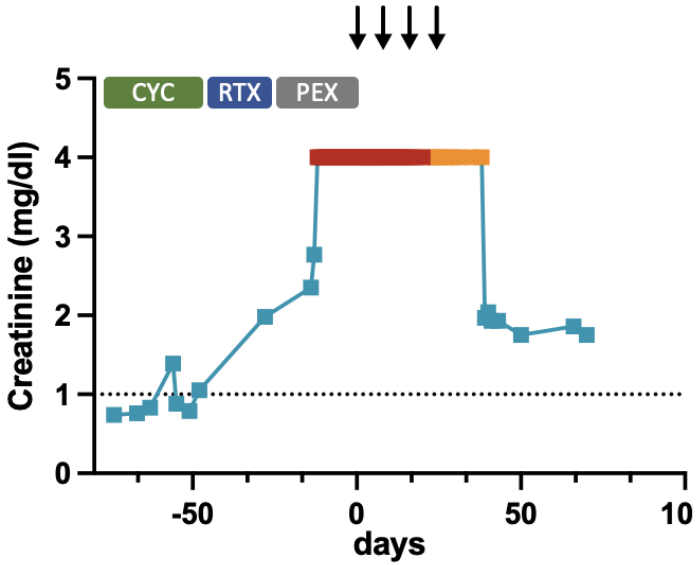
Novel treatment approaches: Daratumumab

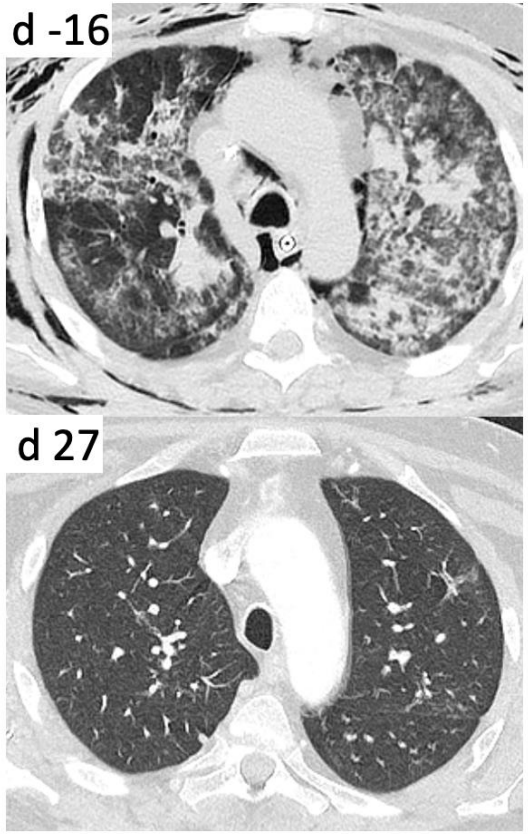
Patient 1





Patient 2





Ostendorf, …, Schreiber RMD open 2023

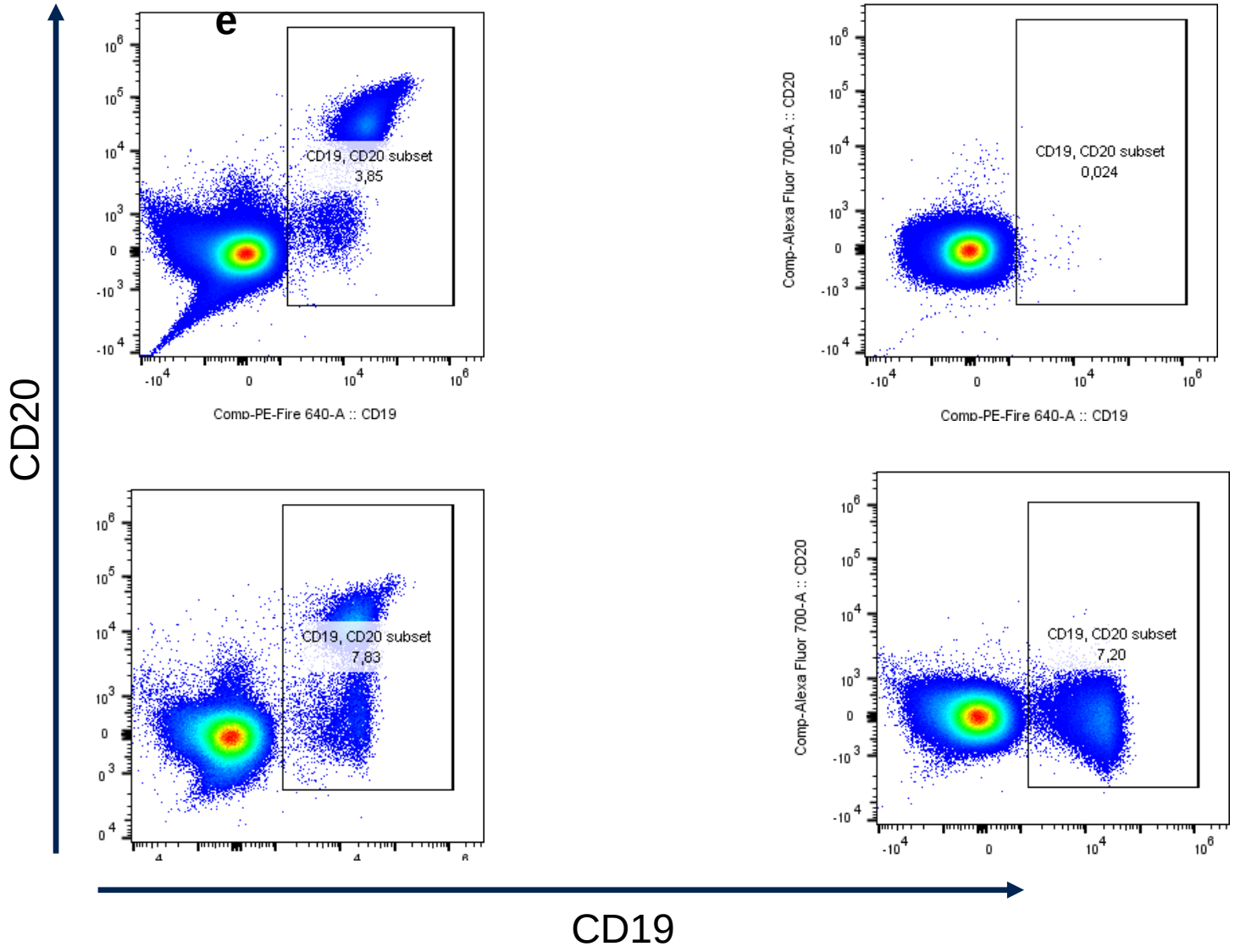
Insufficient depletion of tissue antibody-producing cells

Kontrolle

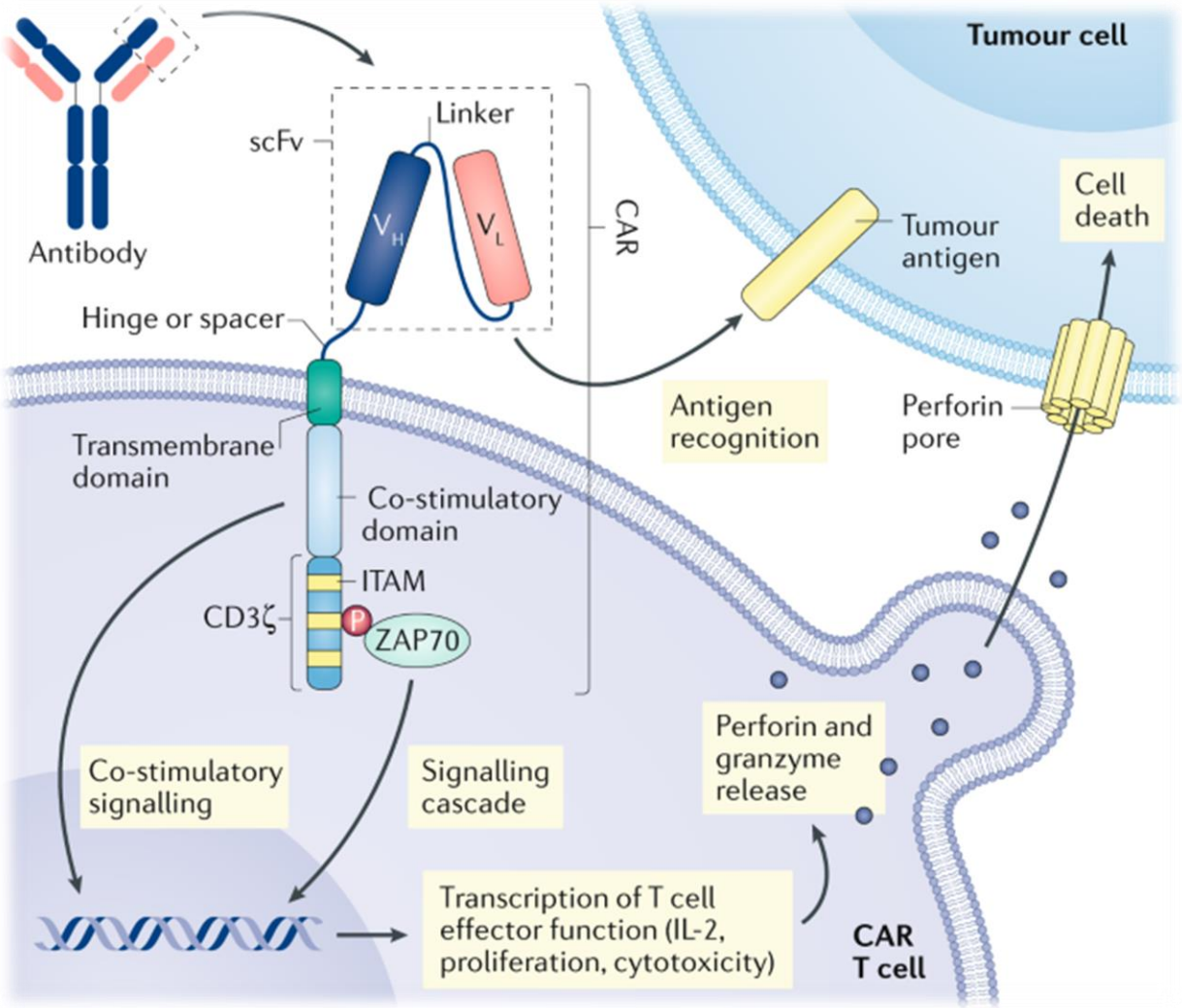
RTX Behandlung

blood

Bone-marrow

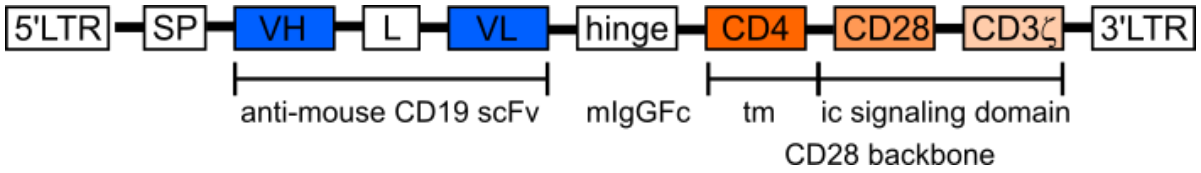


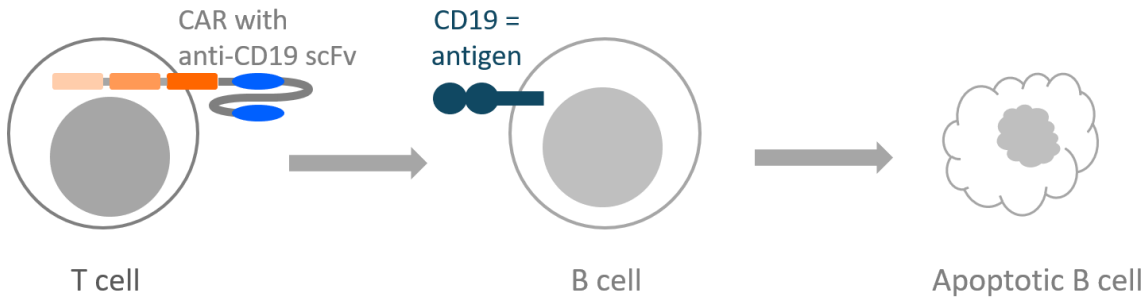
Cellular therapies as a new option for improved depletion of B cells



June C. et al.,Science 2018

Chimeric antigen receptor (CAR) T cells



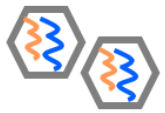


Höpken lab

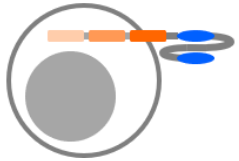
WT

Isolate T cells of spleen and lymph nodes

Activate T cells to proliferate in vitro



Transduce T cells retrovirally



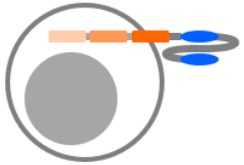
Harvest T cells for injection

Schreiber lab

MPO$^{-/-}$

Immunize MPO$^{-/-}$ mice with MPO

Irradiate to deplete endogenous leukocytes

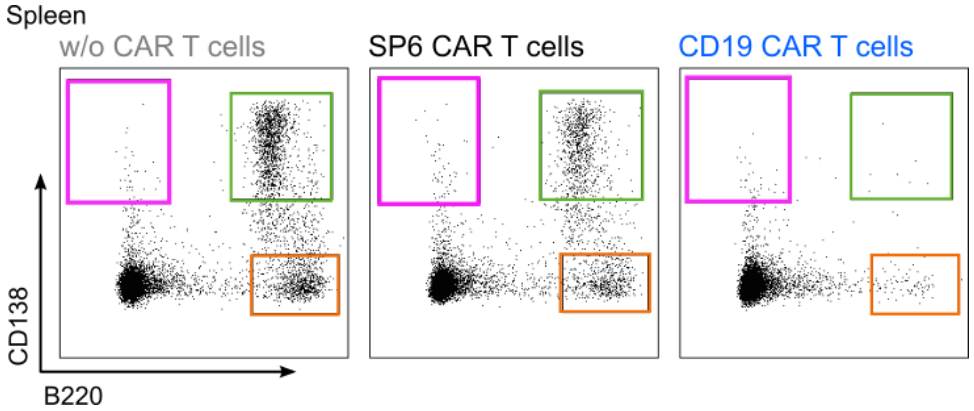


Inject CAR T and WT bone marrow cells

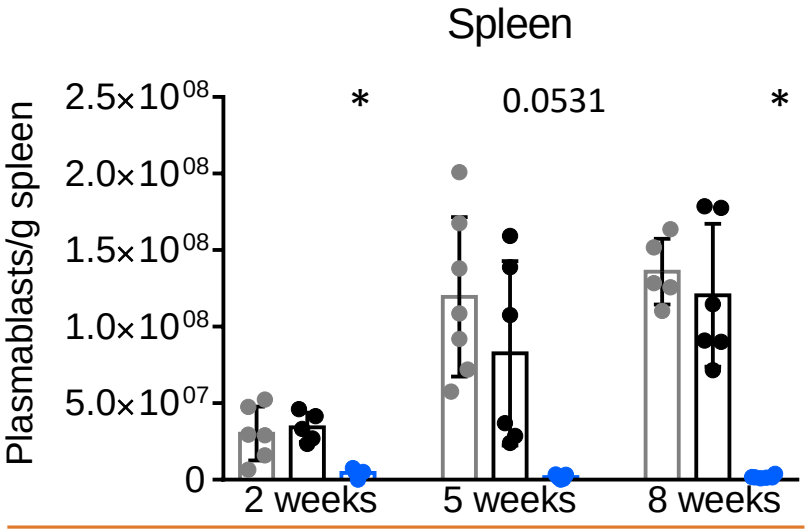
Analyse disease course

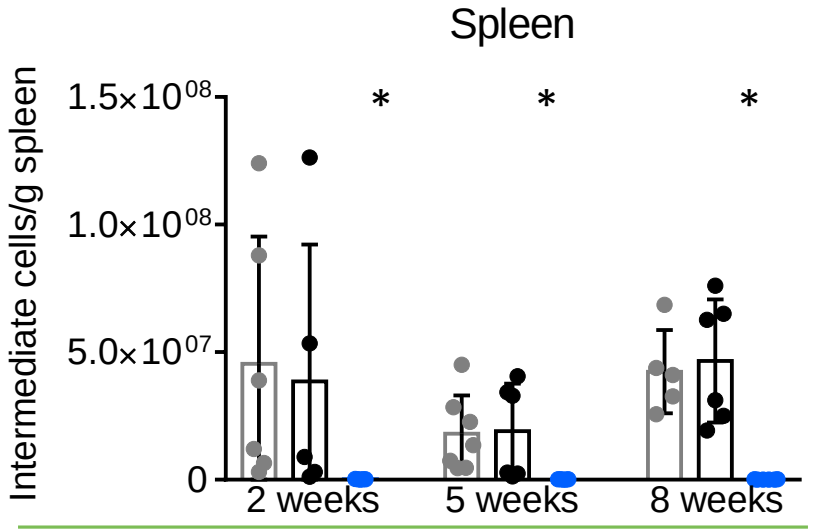
Lodka,…, Schreiber ARD 2024

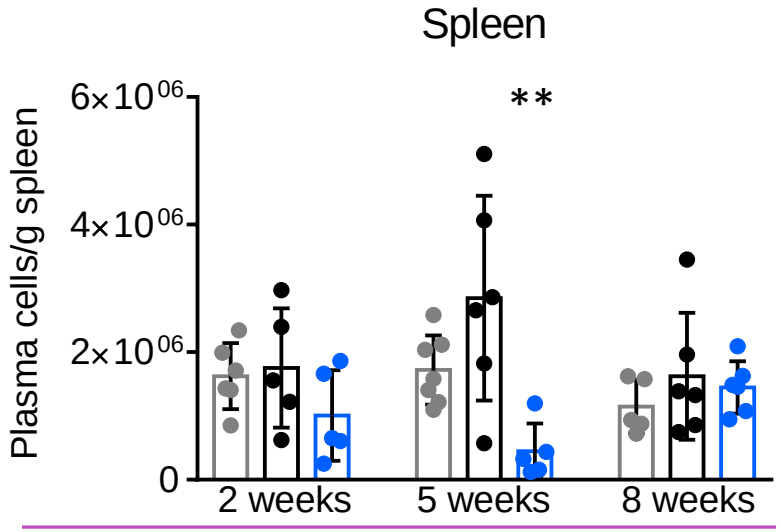
Plasmablasts & intermediate plasma cells decreased after CD19 CAR T-treatment



w/o CAR T cells
SP6 CAR T cells
CD19 CAR T cells

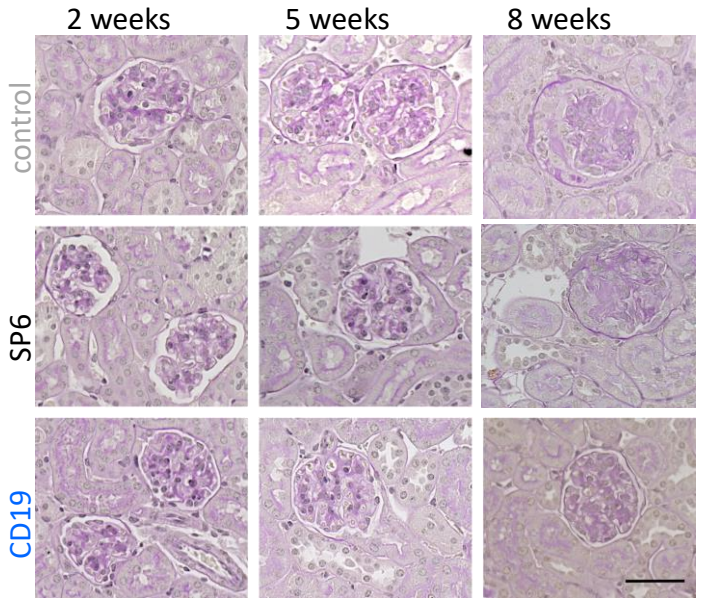


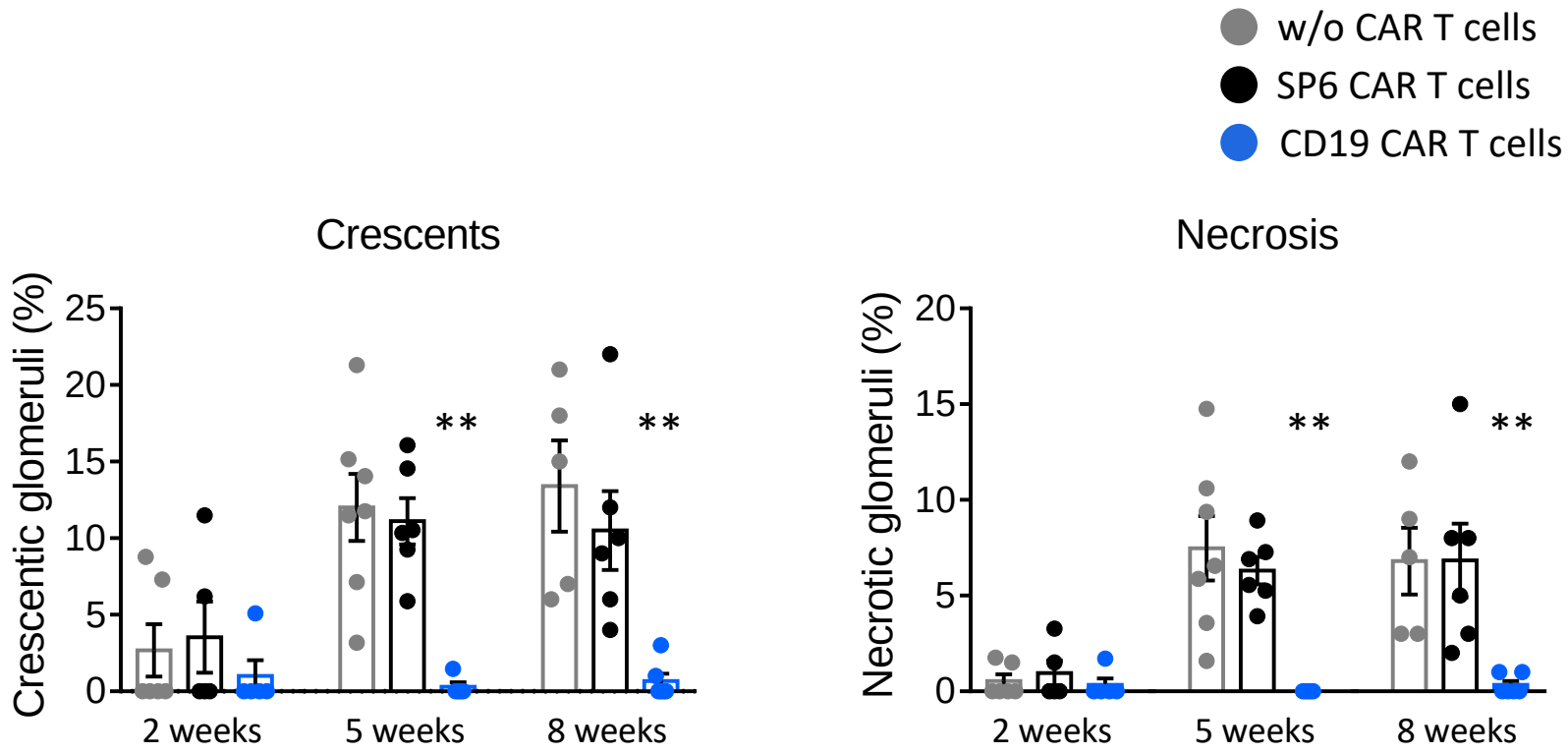




Lodka,…, Schreiber ARD 2024

Histopathological changes strongly decreased in CD19 CAR T-treated mice





Lodka,…, Schreiber ARD 2024

CD19 CAR-T in human AAV

PR3-ANCA-positive granulomatosis with polyangiitis (GPA) with kidney, lung, joint, ENT, eye, and skin involvement, ED 12/1994 (Hamburg)

- 52 yrs, male
- Medical history:

→1995-2001 Endoxan (po) and Prednisolon (po)

→ 03/06 Relapse with skin, joint, and ENT involvement

→ 3x Endoxan i.v. (Berlin Buch)
o cumulative Cyclophosphamide: 150 g !!

→Azathioprin 5-11/06 -> Intolerance

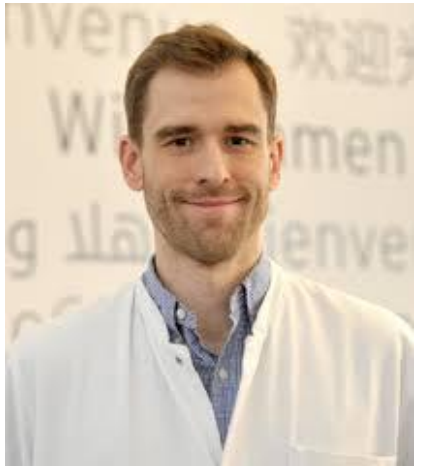
→MMF 11/06-08/09 -> Arthralgias

→MTX 25 mg/Woche s.c. 08/09-12/14

→ 12/2014 Relapse with skin vasculitis

→RTX 4x 375mg/m2 12/14 &1/2015

→RTX 04/15, 05/15, 11/15



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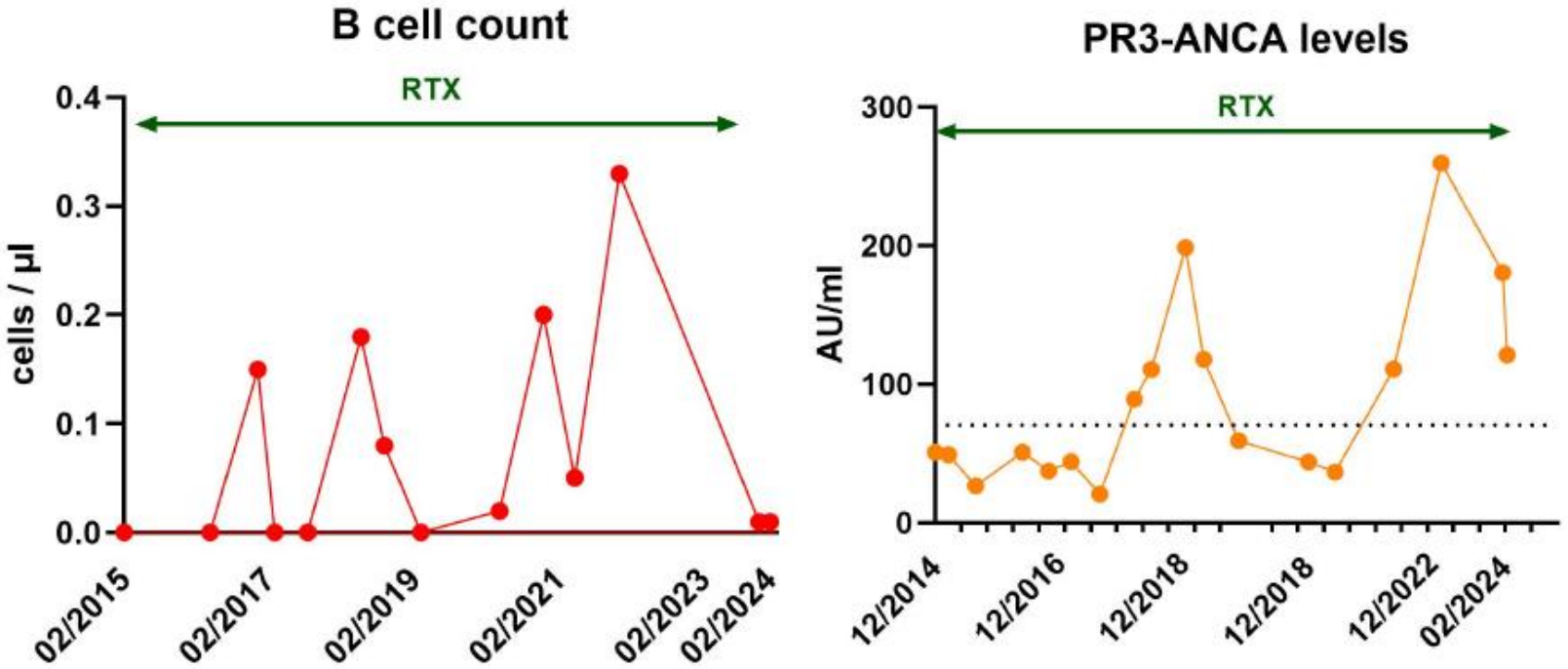
PR3-ANCA-positive granulomatosis with polyangiitis (GPA)

- Relapse 8/16 Skin vasculitis and arthralgias
- RTX 1g 8/16
- 12/16 additional MTX -> Intolerance (Nausea, headaches)
- 3/17 RTX, additional Azathioprin
- 6/17 persistent biopsy-proven leukocytoclastic cutaneous vasculitis with necrosis
- MMF 2g/d
- 11/17-2/19 Pause of therapy because of Therapy fatigue
- 02/2019 Majorrelapse Lung
- 3/19 Rituximab 4x 375mg/m2
- 10/19: Rituximab 500mg
- 4/20: Rituximab 500mg
- 12/20: Rituximab 500mg
- 5/22: Rituximab 500mg
- 11/23 Minor Relapse with rising ANCA, Arthralgias, erythrozyturia
- 11/23 Rituximab 1000mg

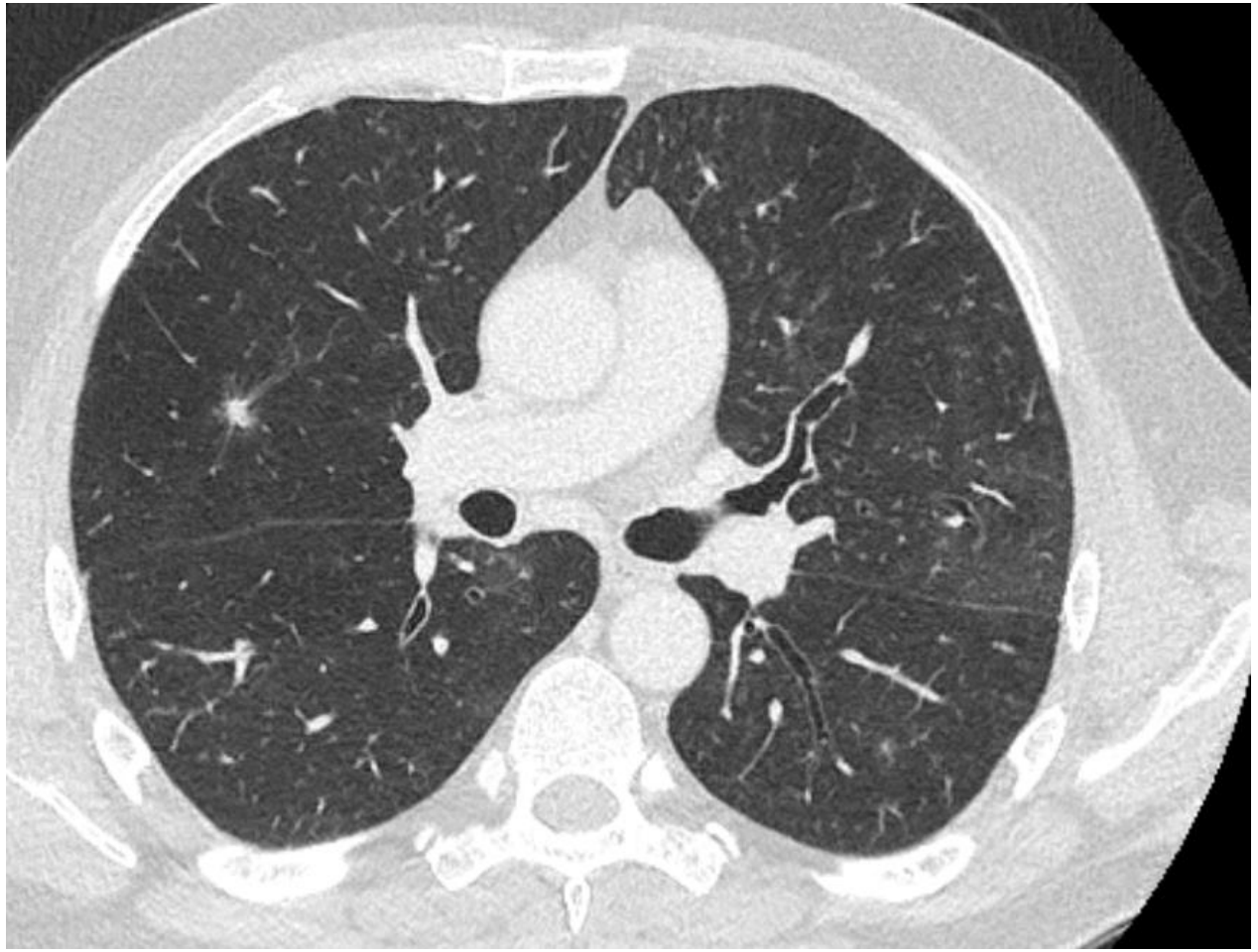
PR3-ANCA-positive granulomatosis with polyangiitis (GPA)

Positive PR3-ANCA and incomplete B cell depletion despite continuous treatment with Rituximab



PR3-ANCA-positive granulomatosis with polyangiitis (GPA)

New lung granuloma formation, dyspnea and B-symptomatology despite treatment with rituximab

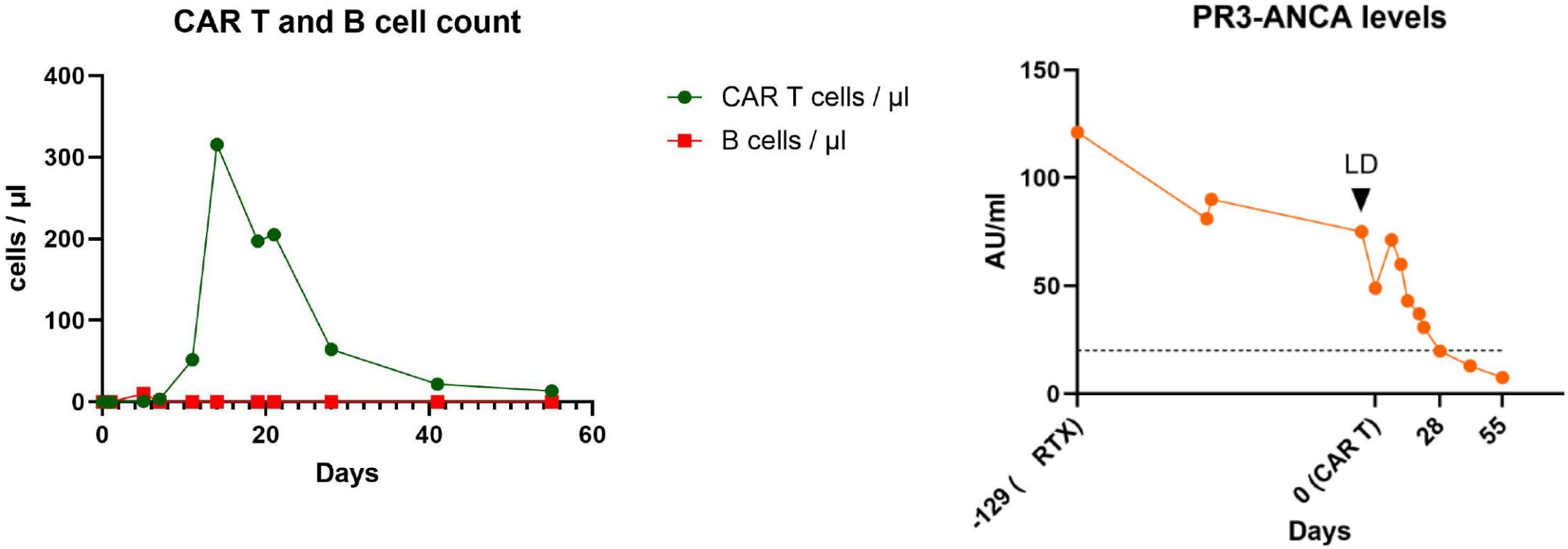


2 small new granulomas in the right lower lobe

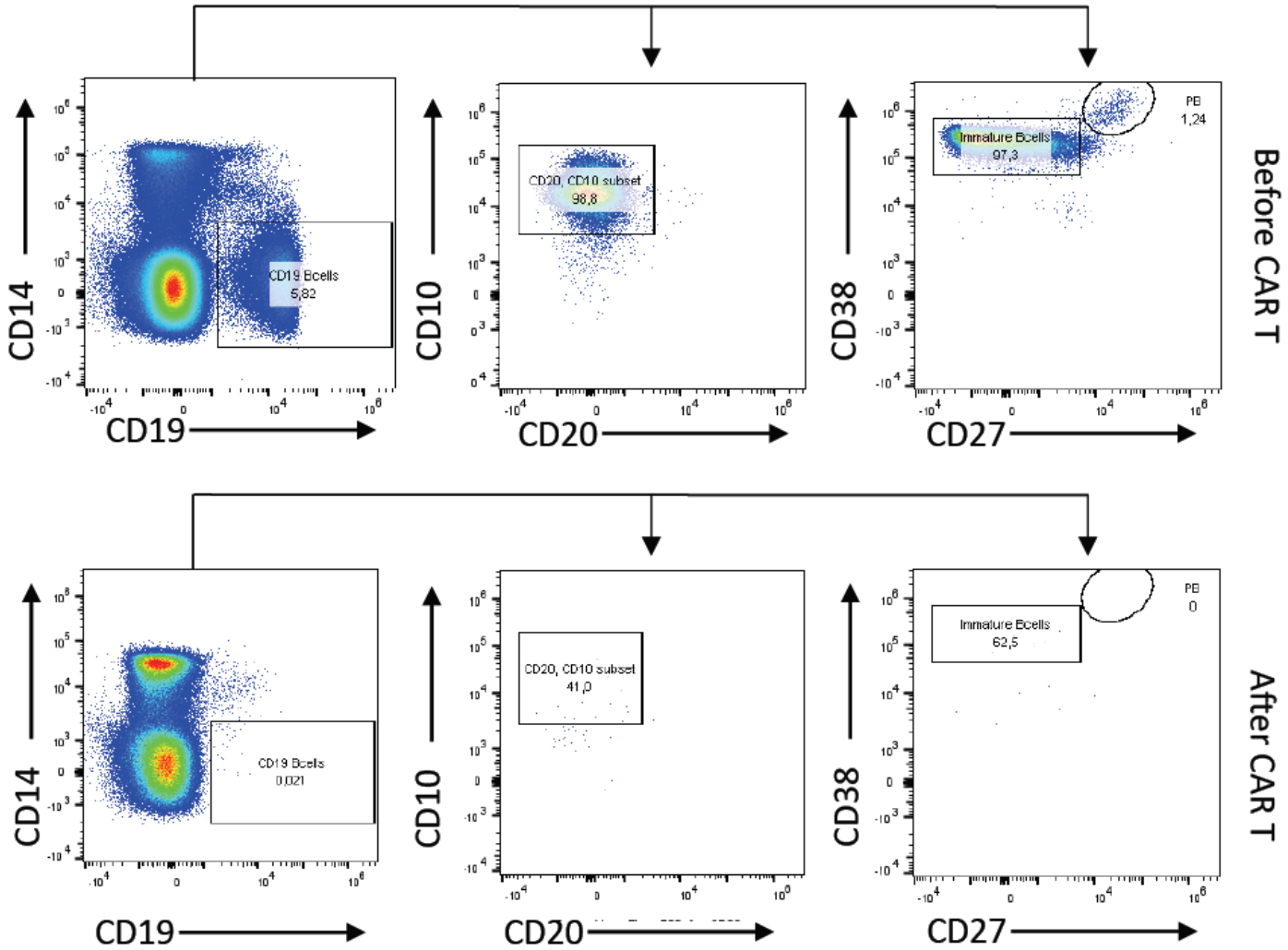
CAR T cell therapy

Date infusion	20.06.2024
Cell count	1.0 x 10^8 / 10^6 CAR-positive viable T-Zellen
Karnofsky-Index before therapy	100%
ECOG Score before therapy	0
Lymphodepletion	Cyclophosphamid Fludarabin
Cytokine Release Syndrome (CRS)	Grad I
Neurotoxicity (ICANS)	No ICAN
CAR-T-induzierte Zytopenie	NCI Grad 0
Antiinfektive Prophylaxe	Aciclovir / Cotrimoxazol

CAR T cells, B cells and PR3-ANCA in the peripheral blood after CAR T cell therapy



CD19+ B cells in the bone marrow are diminished post-treatment



- ANCA Vaskulitis verbunden mit erhöhter Morbidität und Mortalität
- Avacopan als Therapieoption in der Induktionstherapie
- CAR-T als aufkommende Therapieoption

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