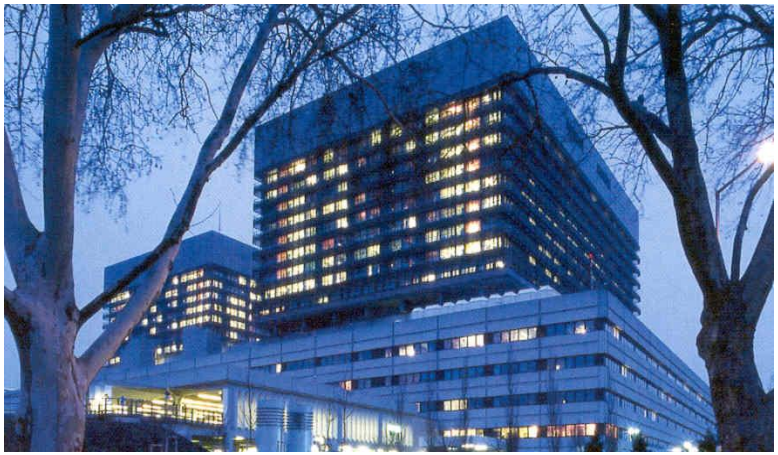
Neue Therapieoptionen der Antikörper-vermittelten Abstoßung



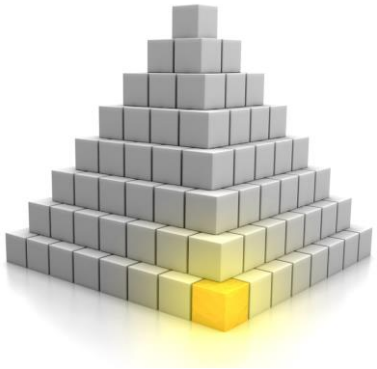
Georg Böhmig
Abteilung für Nephrologie und Dialyse
Univ. Klinik für Innere Medizin III

MEDICAL UNIVERSITY OF VIENNA

46. Nephrologisches Seminar
Heidelberg
18. März 2022

VIETAC
vienna transplant and complement laboratory

ABMR - Cornerstones



► Häufig

ABMR bei ~3-12% aller NTX Patienten

► Relevant

Risikofaktor für Tx-Verlust
(DEKAF-Studie: HR ~10-fach erhöht!)
Organverlust: ABMR=dominante Ursache

► Teuer

Medicare & Medicaid, Analyse 2006-2011:
Insgesamt 4-fach erhöhte Kosten
Plus ~35,000 $/Patient/Jahr über 2 Jahre nach Diagnose

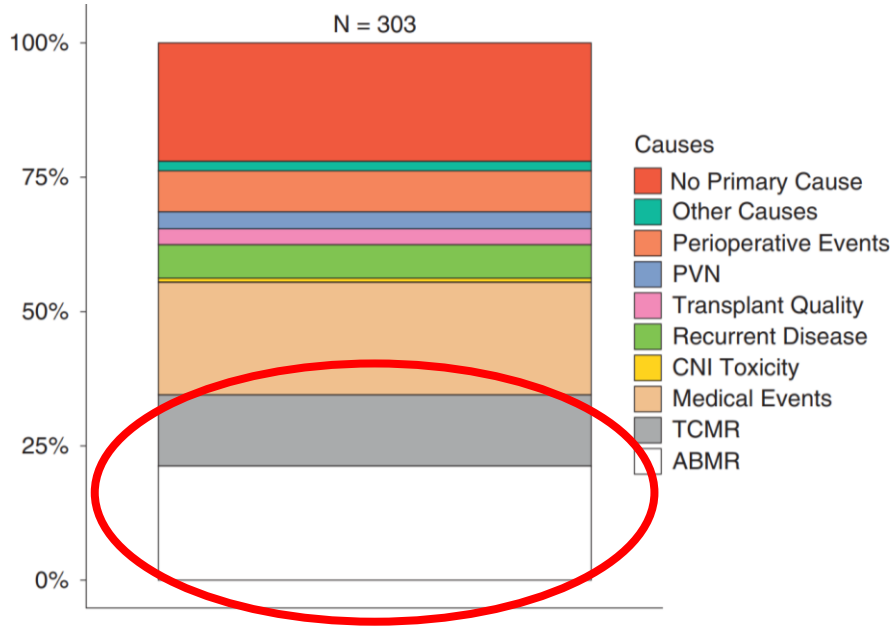
► Therapie?

Niedrige Evidenzlage, nur Off-label Use

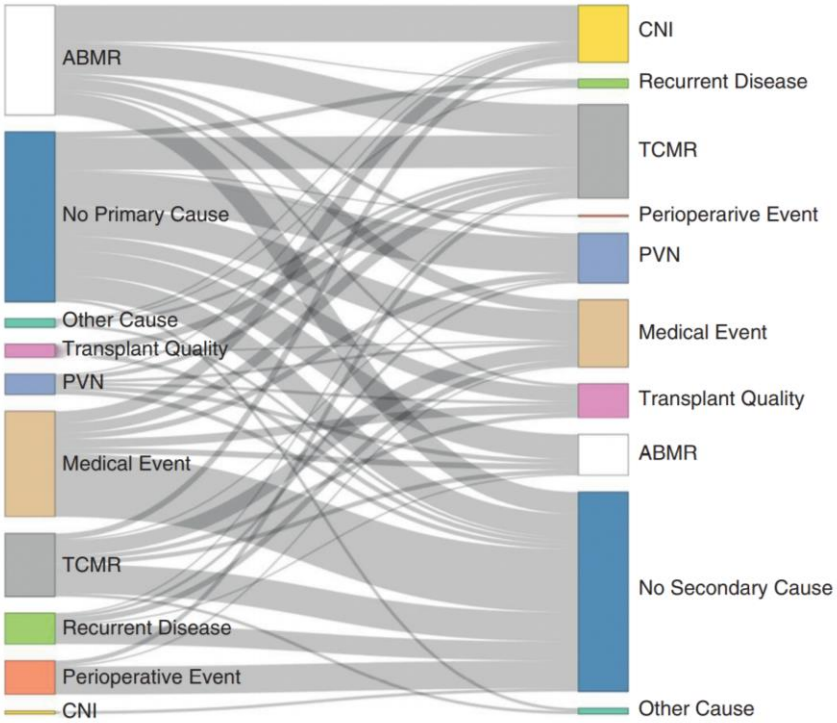
Hart et al., *Clin Transplant* 2021; 35(7):e14337; e14320
Sellares et al., *Am J Transplant* 2012 Feb;12(2):388
Mayrdorfer et al., *J Am Soc Nephrol* 2021; 32(6):1513
Hart et al., *J Med Econ* 2021; 24(1):1011
Schinstock et al., *Transplantation* 2020; 04(5):911

ABMR = dominante Verlustursache

Primäre Verlustursachen

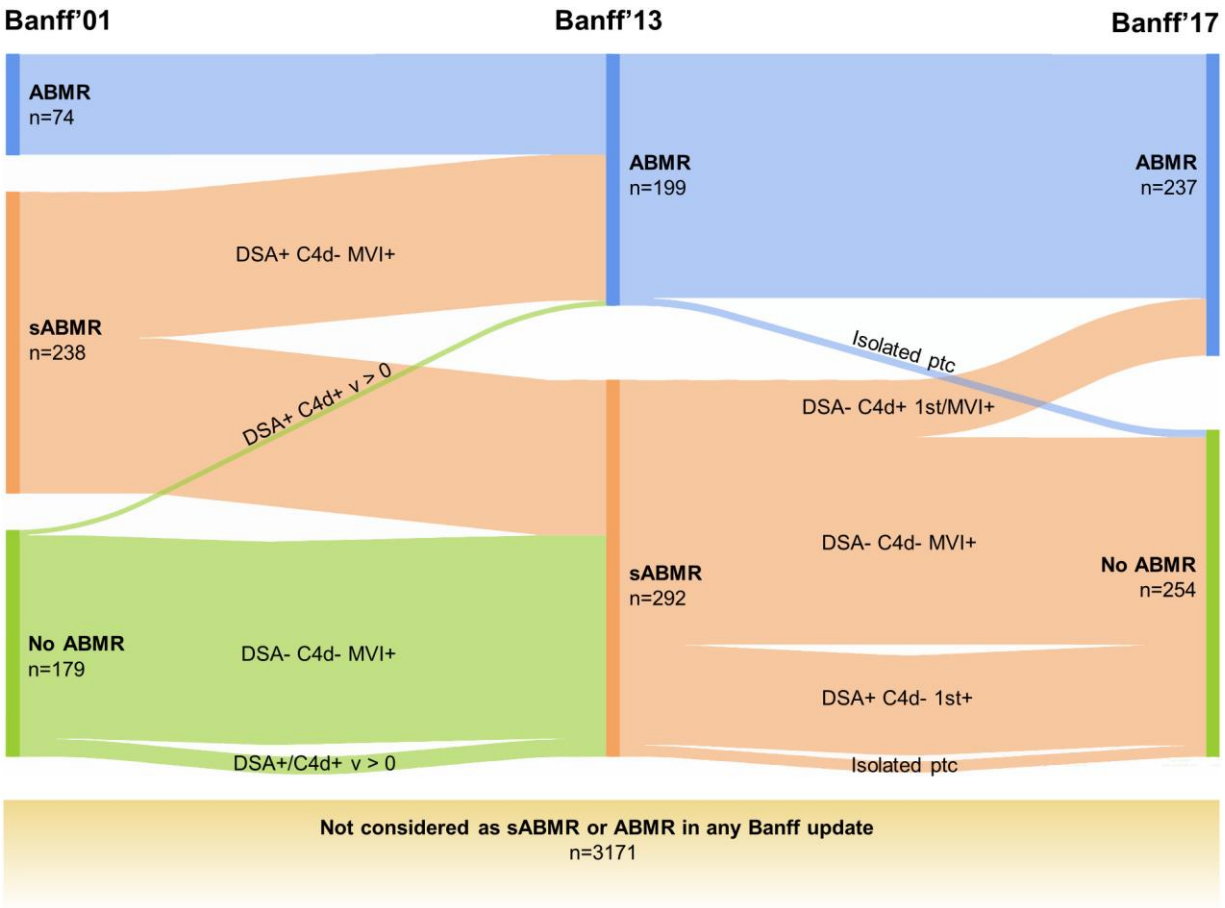


Prim./sek. Verlustursachen



Mayrdorfer et al., *J Am Soc Nephrol* 2021: 32:1513

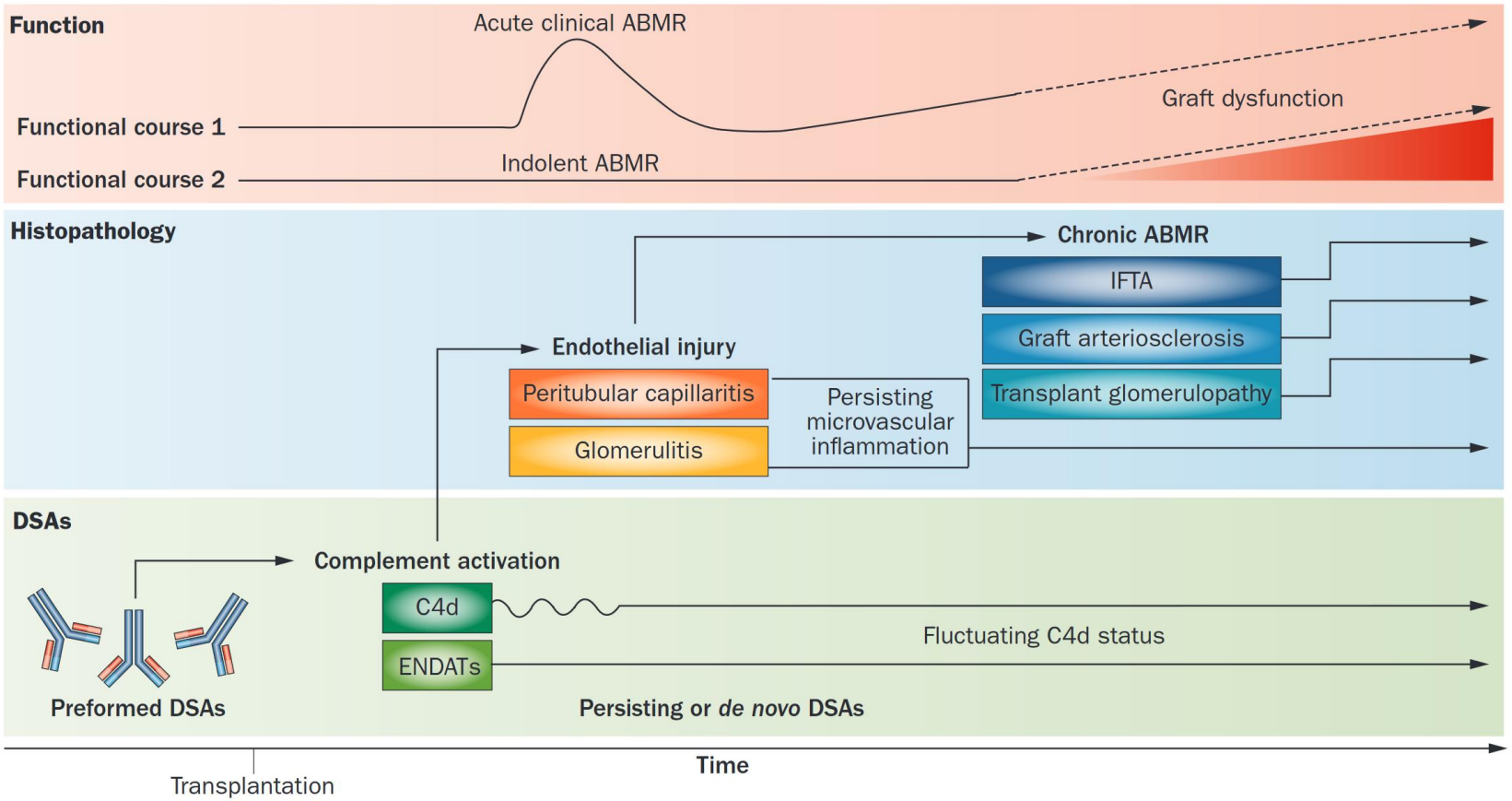
ABMR – Diagnostische Unsicherheiten



Callemeyn et al., *Am J Transplant* 2021 Jul;21(7):2413

ABMR – Pathophysiologie

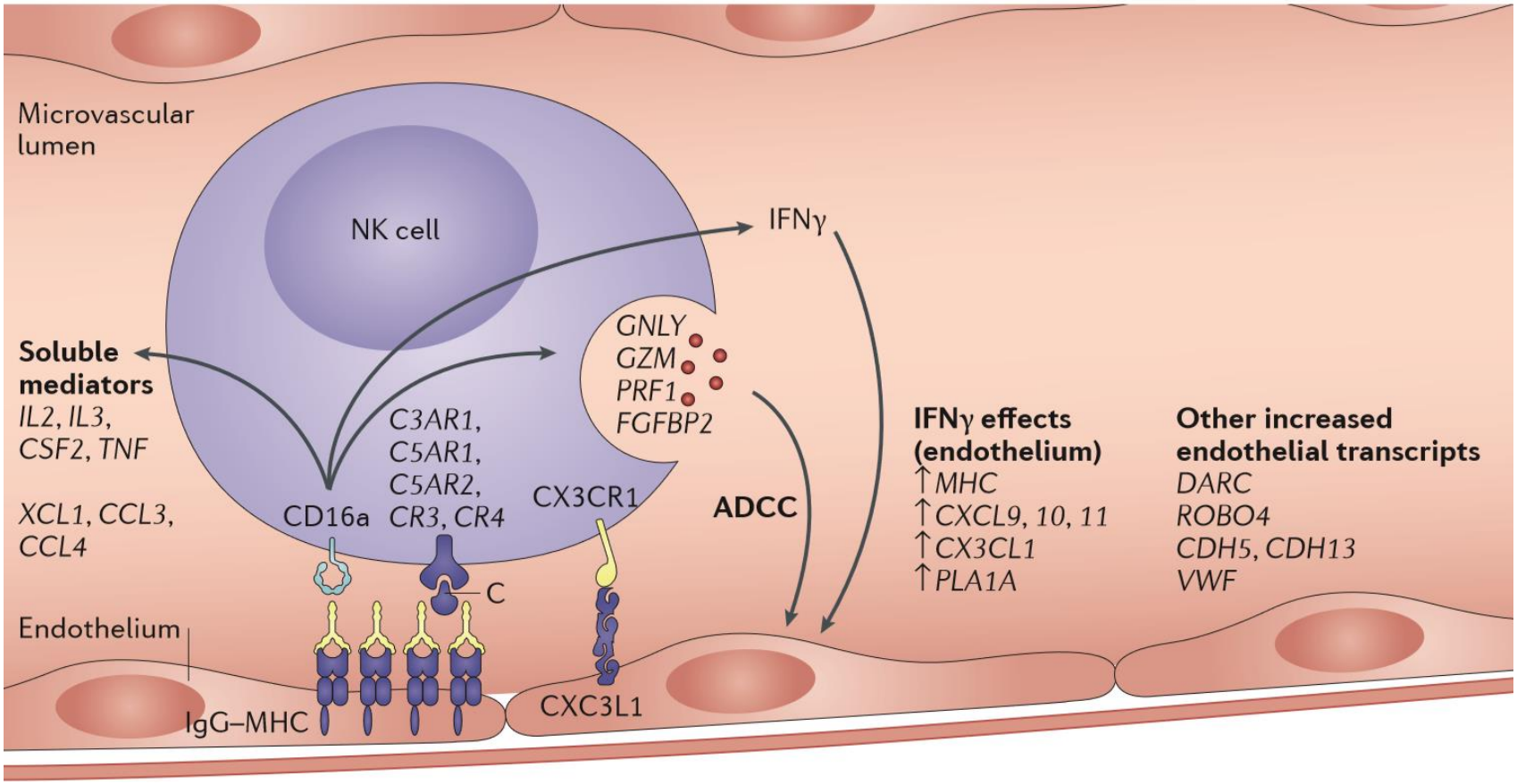
Konventionelles Konzept



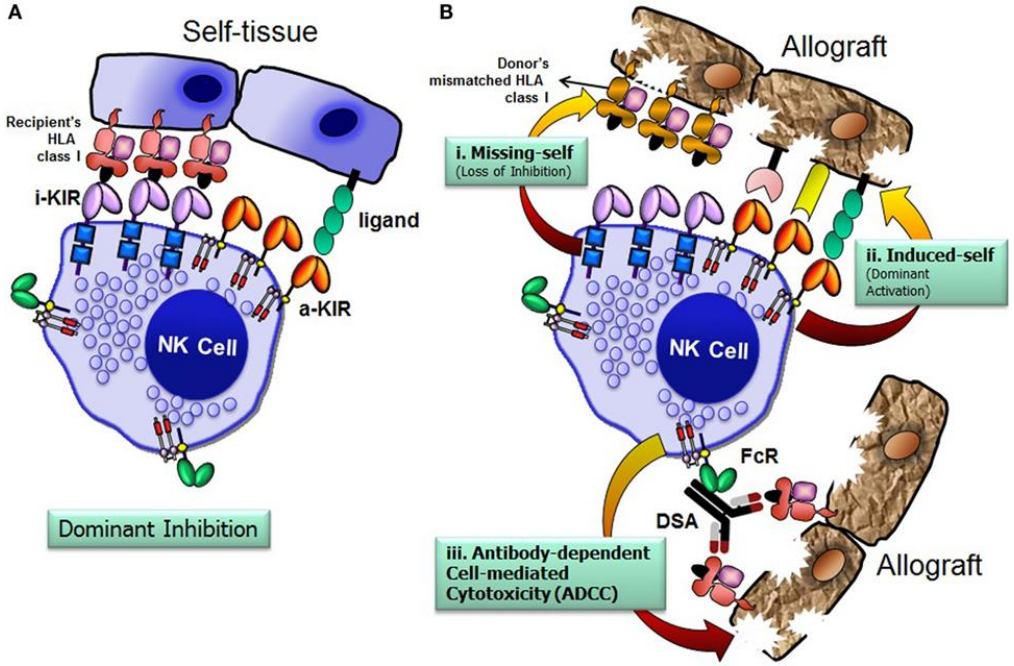
Loupy et al., *Nat Rev Nephrol* 2012; 8(6): 348

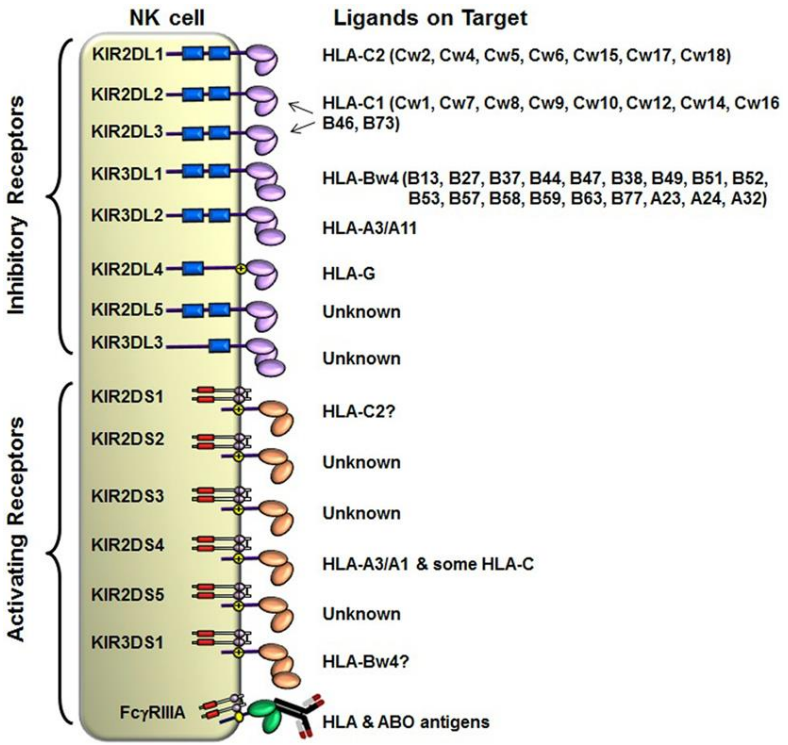
ABMR – Pathophysiologie

Transcript-Analysen ► Zentrale Rolle der NK Zellen



Halloran et al., *Nat Rev Nephrol*, 2016:1212, 534–548

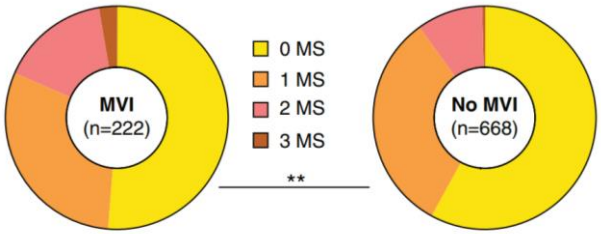


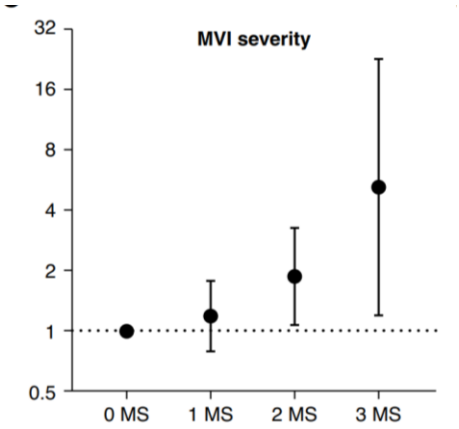


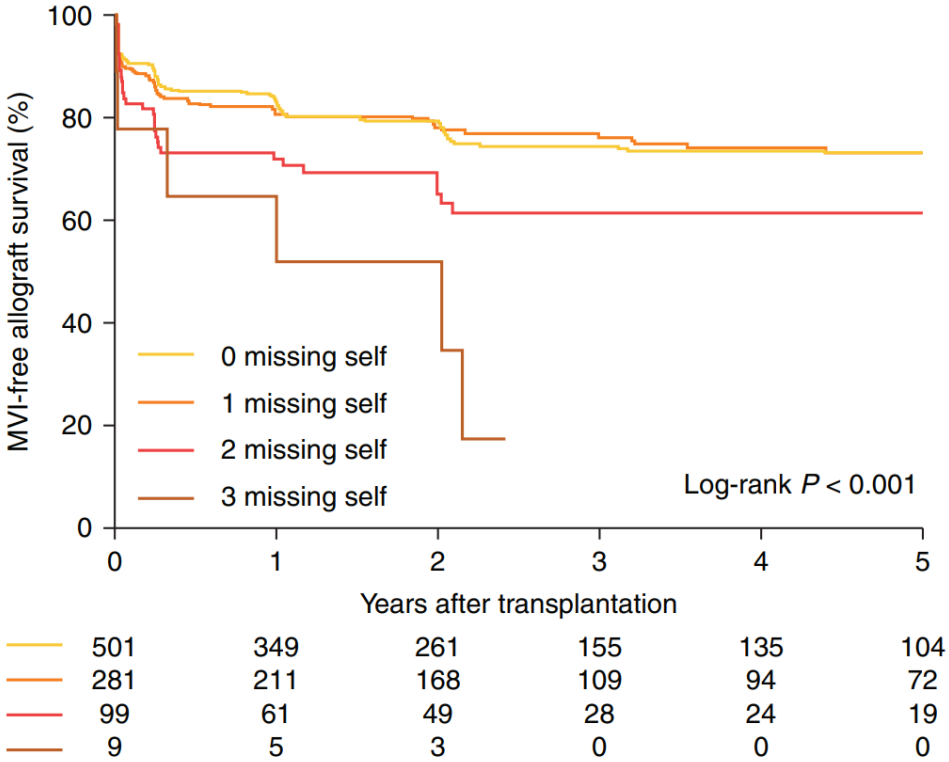
Rajalingam, *Front Immunol* 2020; 7:585

Missing self?

Monozentrische Kohortenstudie (Leuven) 924 Tx, 2004-2013
Serielle Protokollbiopsien







Callemeyn et al., J Am Soc Nephrol 2021: 32:2070

ABMR – „Standard-of-Care“ Therapie

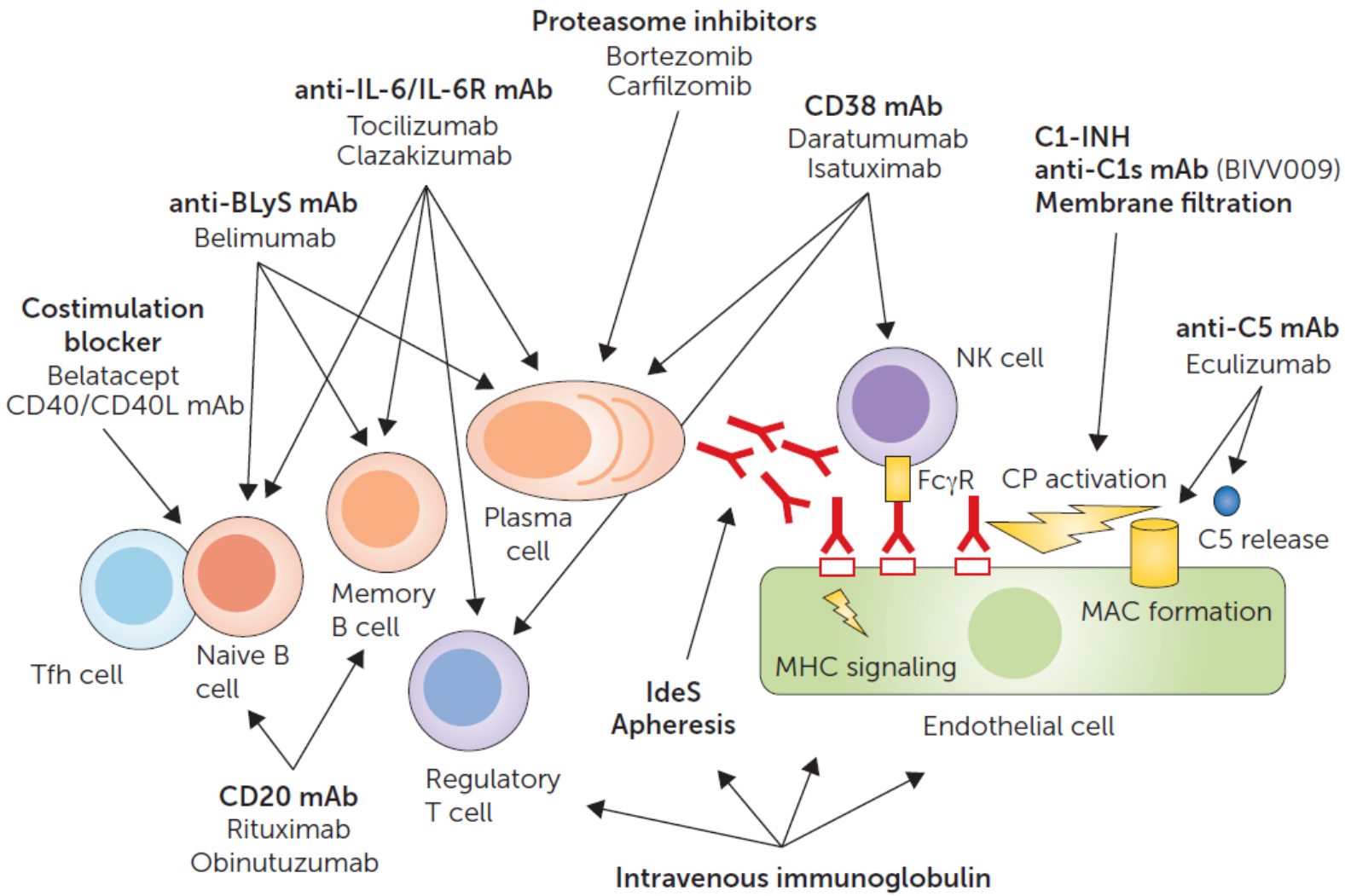
2019 Expert Consensus - Transplantion Society Working Group

Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologi-cally naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 bas DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheres or IVIG 2 g/kg at end of plasmaphere s (1C) Corticosteroids (EO)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	Preexisting DSA	Active AMR	Plasmapheresis (daily or alter 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after pheresis treatment or IVIG 2 g/kg at apheresis treatments (2C) Corticosteroid	Rituximab 375 mg/m^2 (2B)
		Chronic AMR	Optimize unosuppression (eg, add steroids if on e regimen) (1C)	IVIG (3C)
	De novo DSA	Active AMR	O ine immunosuppression (eg, add steroids if oid-free regimen) (1C) Eval e and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
		Chronic AMR		IVIG (3C)

Niedriges Evidenz-Level

Schinstock et al., *Transplantation* 2020; 04(5):911

ABMR – Potenzielle Therapieansätze



Böhmig, Eskandary, Doberer & Halloran, *Transpl Int* 2019; 32: 775

ABMR - Aktuelle „Studienlandschaft“

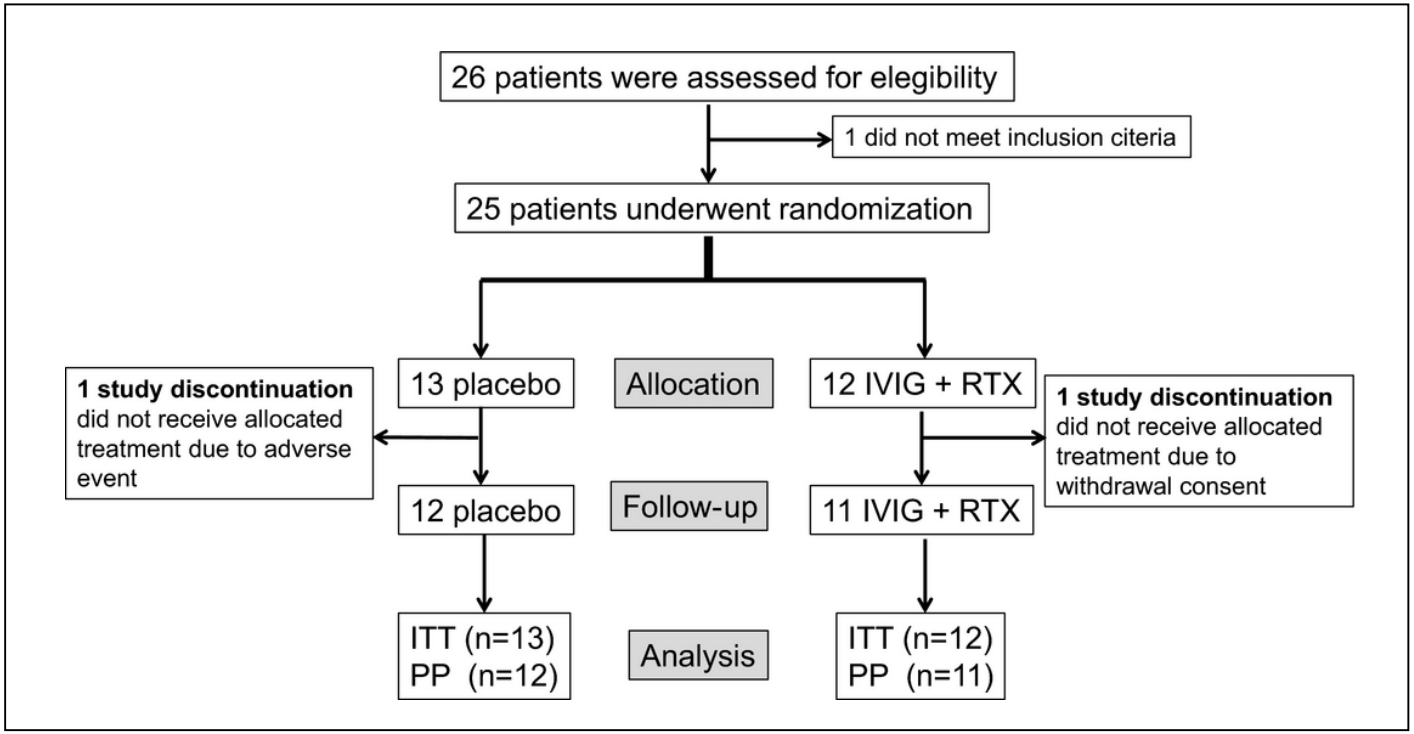
Target	Therapie	Wirkmechanismus	Phase (Akronym)	Studienstatus	ClinicalTrials.gov	Erstautor (Jahr)
DSA	Imlifidase	IgG Inaktivierung	II	aktiv	NCT03897205	-
Plasmazellen	Bortezomib	Proteasom-Inh.	II (BORTEJECT)	finalisiert	NCT01873157	Eskandary, 2018
			II (TRIBUTE)	finalisiert	NCT02201576	unpubliziert
			II	aktiv	NCT03737136	-
	Felzartamab	CD38++ Depletion	II	aktiv	NCT05021484	-
B Zellen	Rituximab	CD20+ Depletion	III (RITUX-ERAH)	finalisiert		Sautnet, 2016
			II (TRITON)	vorzeitig beendet		Moreso, 2018
			IV (RituxiCAN)	vorzeitig beendet		Shiu, 2020
			III (TAR:GET-1)	aktiv		-
	Fostamatinib	SYK Inhibition	II (FOSTAMR)	aktiv	NCT03991780	-
IL-6/IL-6R	Clazakizumab	IL-6 Blockade	II	finalisiert	NCT03444103	Doberer 2021
			III (IMAGINE)	aktiv	NCT03744910	-
	Tocilizumab	IL-6R Blockade	III (INTERCEPT)	aktiv	NCT04561986	-
Complement	C1 INH	CP/AP/LP Blockade	II	finalisiert	NCT01147302	Montgomery 2016
			III	vorzeitig beendet	NCT02547220	
			III	vorzeitig beendet	NCT03221842	
	BIVV0020	CP Blockade	II	aktiv	NCT05156710	-
	Eculizumab	C5 Blockade	II	finalisiert	NCT01327573	Kulkarni, 2017
			II	vorzeitig beendet	NCT01895127	-

Rituximab/IVIG

TRITON – RCT, Phase 2
(Spanien, 6 Transplantationszentren)

Therapie
- ► **IVIG (4 x 0.5 g/kg)**
- ► **Rituximab (1 x 375 mg/m²)**

Inklusion
- ► **DSA+ Tx-Glomerulopathie**
- ► **GFR >20 ml/min/1.73 m²**

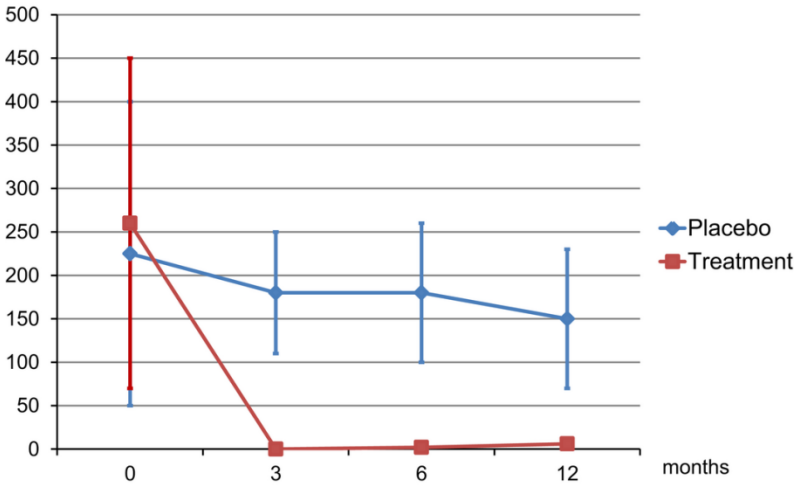


Ursprünglich geplante Fallzahl: n=25/Gruppe
Aber: begrenztes Budget & verzögerte Rekrutierung

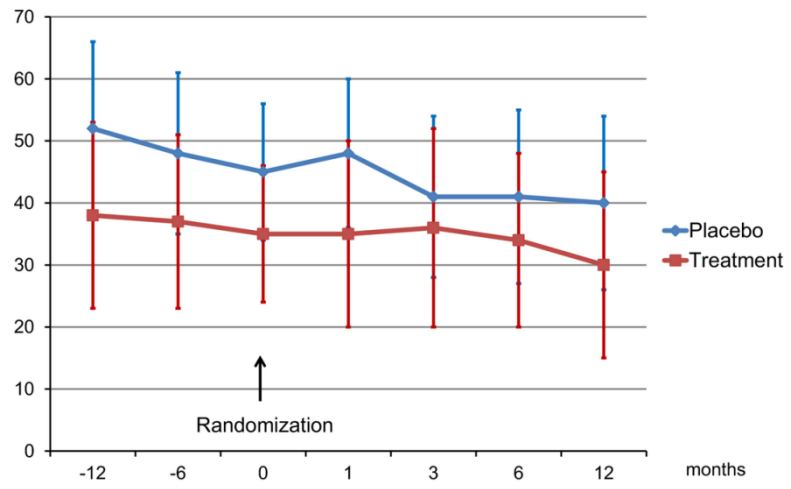
Moreso et al., *Am J Transplant* 2018, 18: 927

Rituximab/IVIG

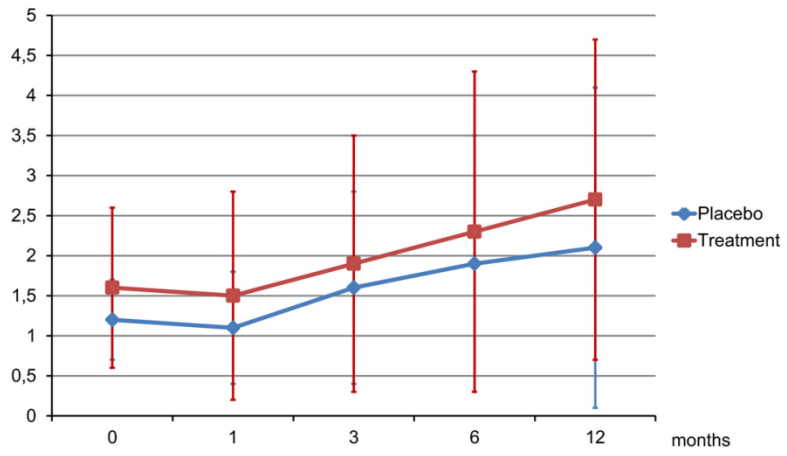
CD20+ Zellen/mm³



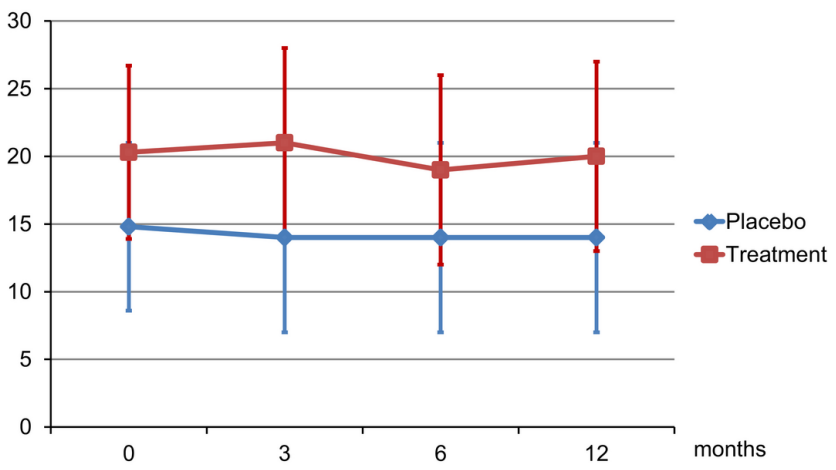
eGFR (ml/min/1.73 m²)



Proteinurie (g/day)



Immundominanter DSA (MFI x 1000)



Moreso et al., *Am J Transplant* 2018, 18: 927

Proteasom-Inhibition (Bortezomib)

BORTEJECT – RCT, Phase 2
(Wien, monozentrisch)

44 NTX Empfänger
Inklusionskriterien:
DSA+ und ABMR Morphologie
≥6 Monate nach Tx
eGFR ≥20mL/min/1.73 m^2

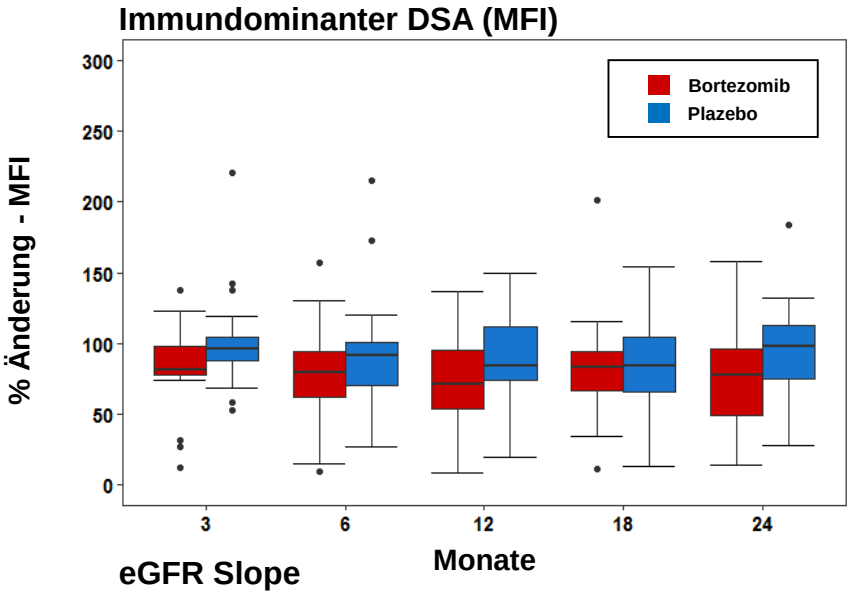
Bortezomib
(2 Zyklen)
21 Patienten

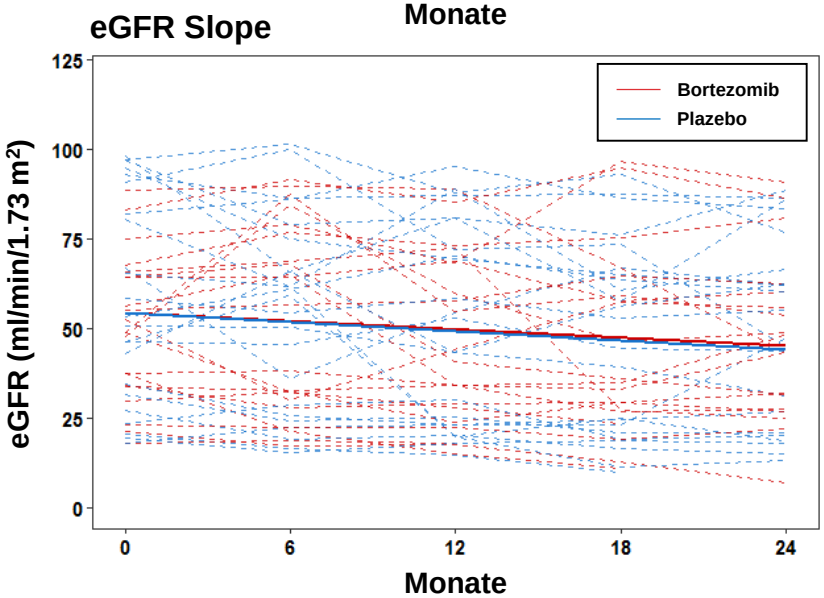
Plazebo
(2 Zyklen)
23 Patienten

24 Monate Follow-up

Primärer Endpunkt
eGFR Slope

Sekundäre Endpunkte
mGFR, DSA, 24-Mo-Bx, Tx-Überleben



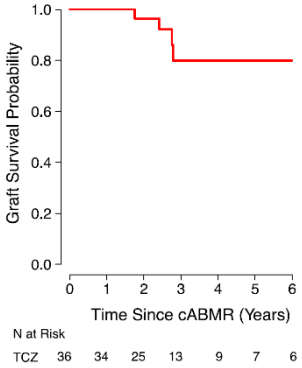


Eskandary et al., *J Am Soc Nephrol* 2018; 29:591

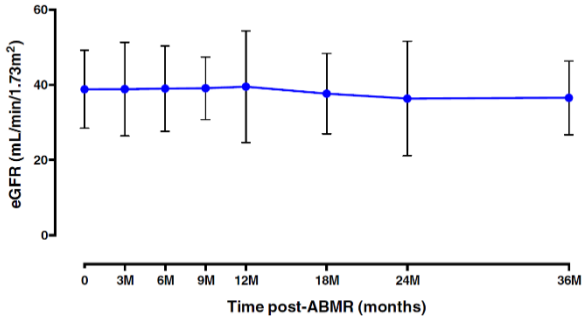
IL-6R Blockade (Tozilizumab)

Unkontrollierte Fallserie (36 NTX-Empfänger)

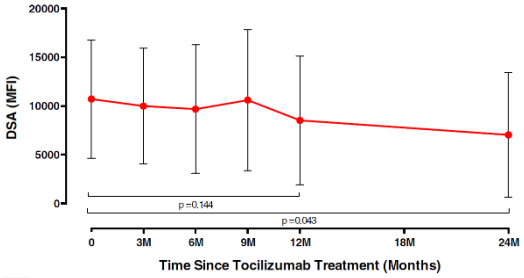
Transplantatüberleben



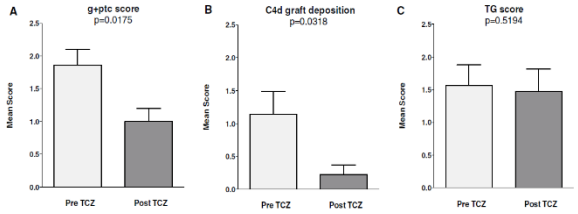
eGFR (erwachsene Patienten)



DSA-MFI



Biopsieresultate (Patienten-Subgruppe)



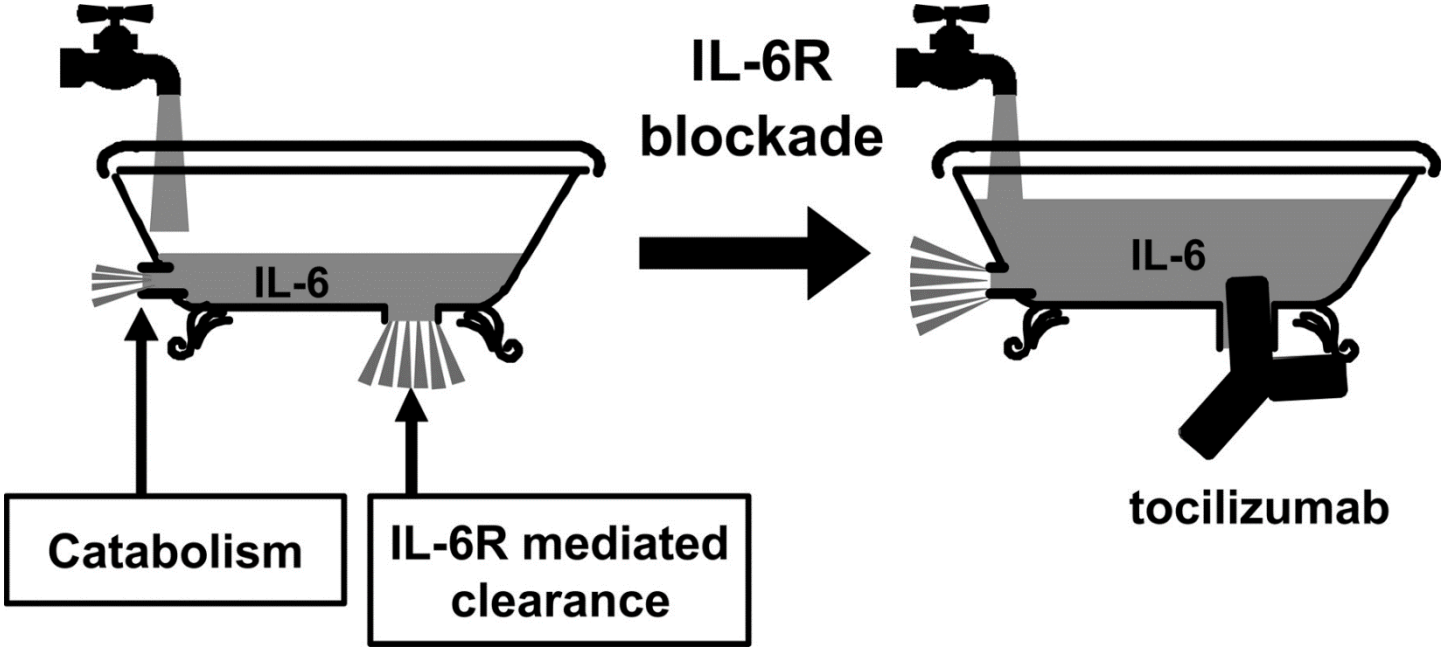
Choi et al., *Am J Transplant* 2017; 17:2381

IL-6R Blockade (Tozilizumab)

Weitere Fallserien und Studien

Erstautor (Jahr)	N=	Kontrollgruppe	Abstoßung	Therapie	Vorherige Th.	Results
Lavacca (2021)	15	keine	cABMR	Tocilizumab	keine (First Line)	Stabilisierung
Sharma (2021)	1	keine	cABMR (DSA-)	Tocilizumab	RTX/IVIG	Stabilisierung
Massat (2021)	9	historisch (n=37)	cABMR	Tocilizumab +initial DFFP	DFFP/IVIG/RTX	Kein Effekt
NCT04561986 (multicenter)	50	Placebo (1:1)	cABMR	Tocilizumab vs. Plazebo		Keine Daten (eGFR Verlauf)

Akkumulation von IL-6 unter IL-6R Blockade?



IL-6 Rebound?

Nishimoto et al., *Blood* 2008; 112:3959

Vorteil einer direkten Neutralisation von IL-6?

Clazakizumab

(früher ALD518)

Humanisierter mAb gegen IL-6

IgG1 Subklasse

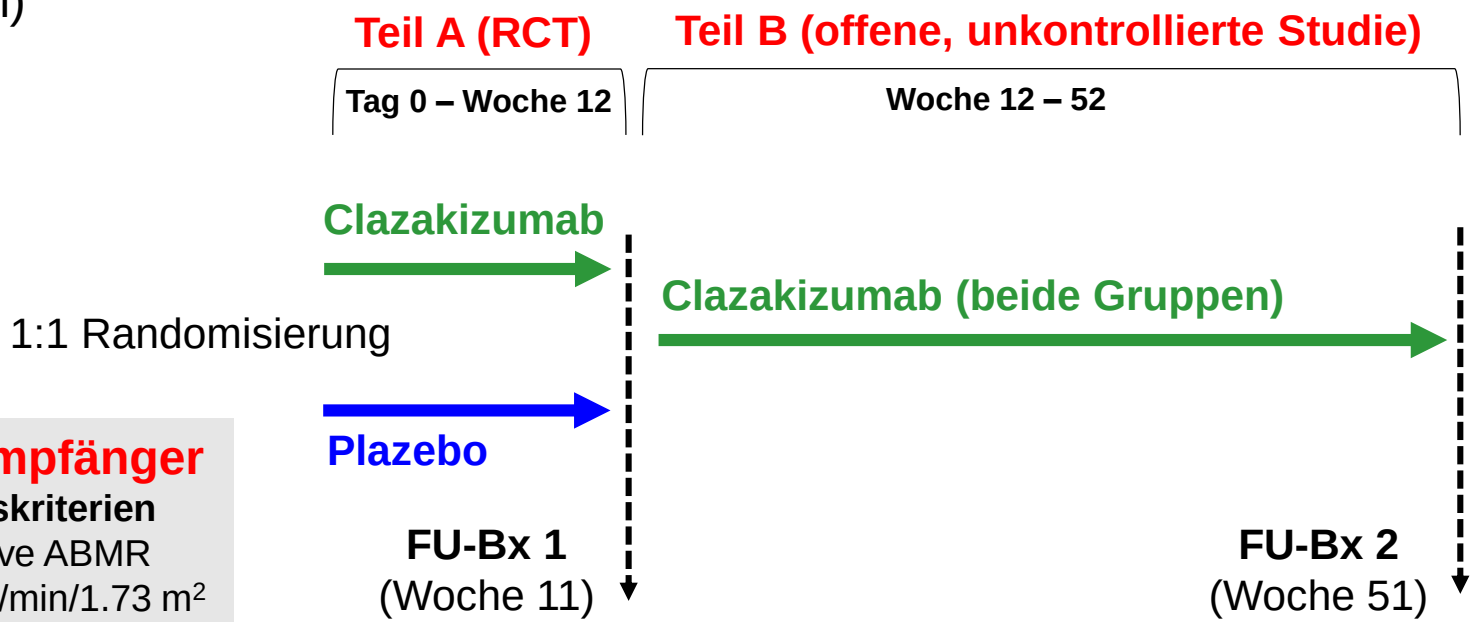
Subkutane Anwendung (25 mg/Injektion)

Halbwertszeit: ~30 Tage

‚Best-in-class' IL-6 Antagonist

IL-6 Neutralisation (Clazakizumab)

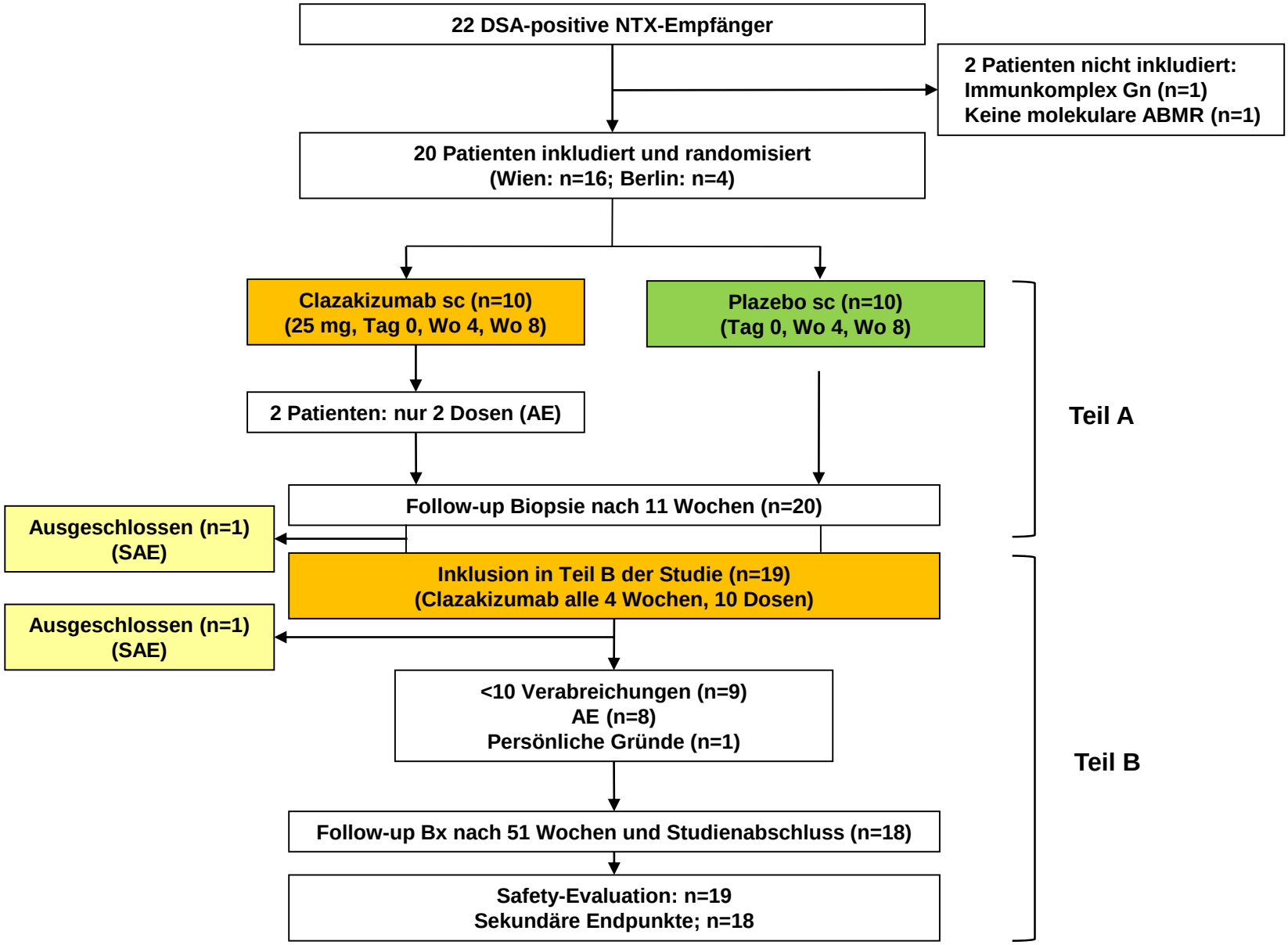
RCT, Phase 2 Studie
(Wien, Berlin)



20 NTX Empfänger
Inklusionskriterien
Späte aktive ABMR
eGFR >30 ml/min/1.73 m^2
≥365 Tage post-NTX

Primärer Endpunkt
Sicherheit
Sekundäre Endpunkte
PK/PD, DSA Charakteristika, FU-Bx Resultate, Leukozyten-Subpopulationen, Marker für Inflammation und Endothelaktivierung/schaden, TTV Load, Pantoprazol PK

Doberer et al, *J Am Soc Nephrol*, 2021; 32:708

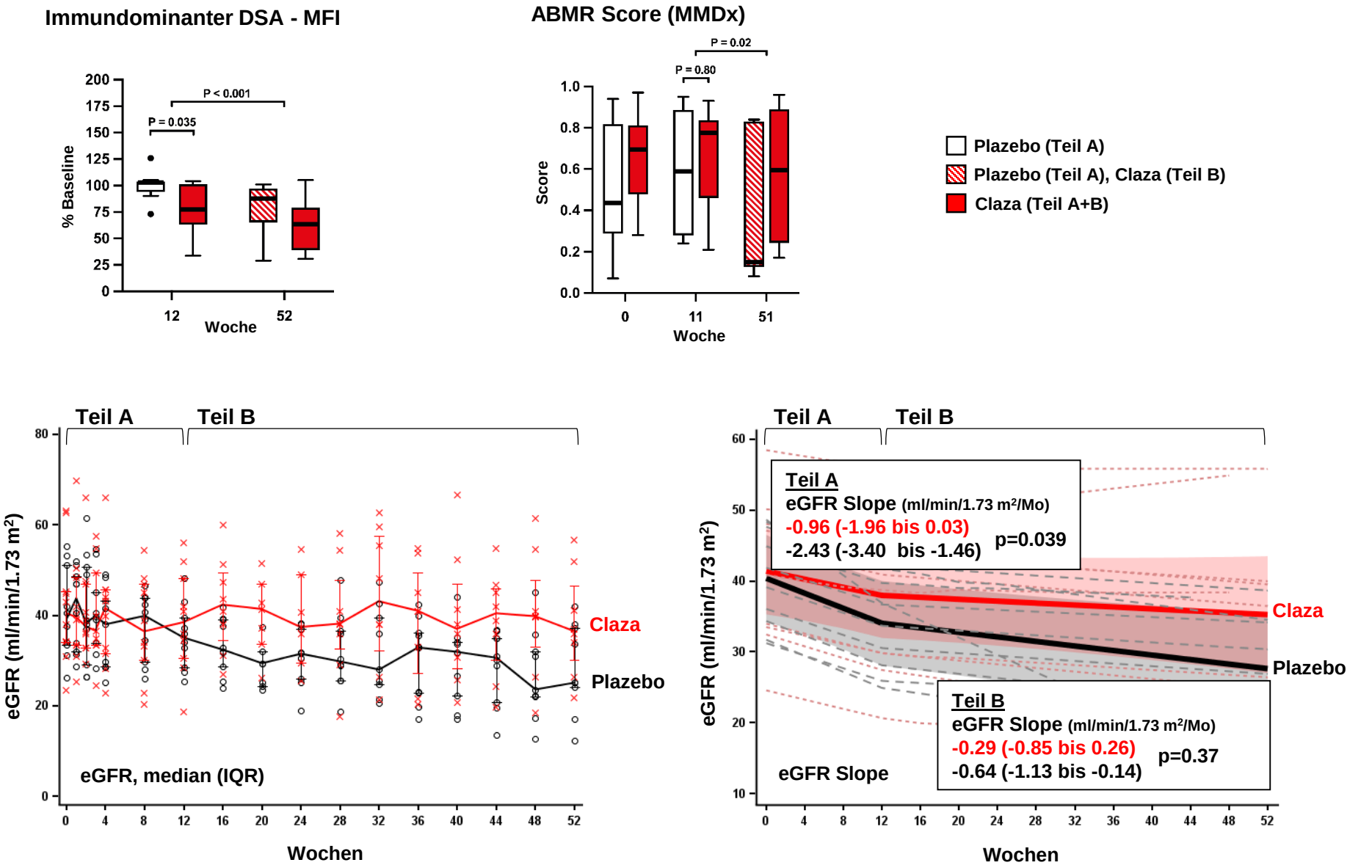

22 DSA-positive NTX-Empfänger
2 Patienten nicht inkludiert:
Immunkomplex Gn (n=1)
Keine molekulare ABMR (n=1)
20 Patienten inkludiert und randomisiert
(Wien: n=16; Berlin: n=4)
Clazakizumab sc (n=10)
(25 mg, Tag 0, Wo 4, Wo 8)
Plazebo sc (n=10)
(Tag 0, Wo 4, Wo 8)
2 Patienten: nur 2 Dosen (AE)
Teil A
Follow-up Biopsie nach 11 Wochen (n=20)
Ausgeschlossen (n=1)
(SAE)
Inklusion in Teil B der Studie (n=19)
(Clazakizumab alle 4 Wochen, 10 Dosen)
Ausgeschlossen (n=1)
(SAE)
<10 Verabreichungen (n=9)
AE (n=8)
Persönliche Gründe (n=1)
Teil B
Follow-up Bx nach 51 Wochen und Studienabschluss (n=18)
Safety-Evaluation: n=19
Sekundäre Endpunkte; n=18

Schwerwiegende unerwünschte Ereignisse (SAE)

SAEs, n (%)	Teil A Clazakizumab (n=10)	Teil A Plazebo (n=10)	Teil B Clazakizumab (n=19)
Infektionen	0	0	5 (26.3)
Pneumonie	0	0	2 (10.5)
Pyelonephritis	0	0	1 (5.3)
Ovarialabszess	0	0	1 (5.3)
Aseptische Meningitis (Coxsackie-Virus)	0	0	1 (5.3)
Gastrointestinale AEs	1 (10)	0	1 (5.3)
Divertikulitis	1 (10) Withdrawal	0	1 (5.3) Withdrawal
Andere	0	1 (10)	0
Fieber/Leukopenie	0	1 (10)	0
Pleuraerguss	1 (10)	0	1 (5.3)
Pleurodese	0	0	1 (5.3)
Permanente Thoraxdrainage	0	0	1 (5.3)
Akutes Nierenversagen	1 (10)	0	0

DSMB-Entscheidung/Amendment-Ethikkommission:

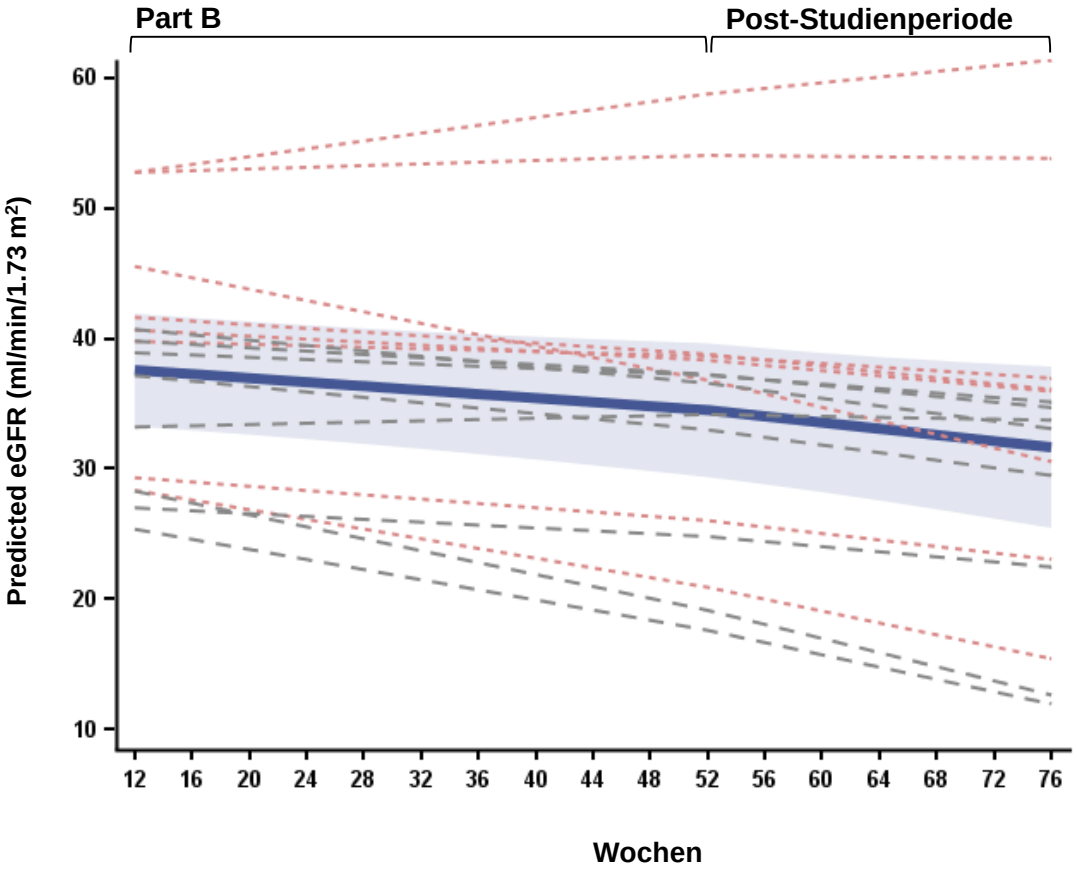
►Reduktion der Dosis ad 12.5 mg bei Nachweis einer Divertikulose (2 aktive Patienten)

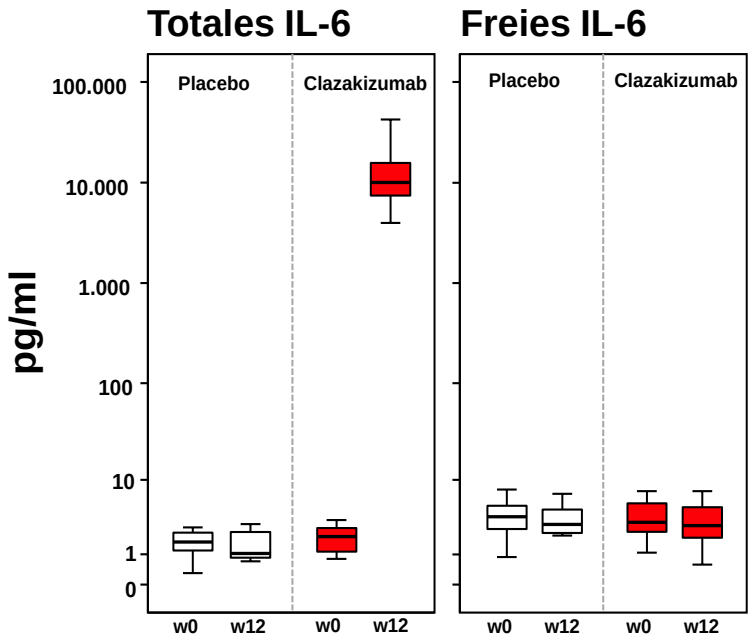


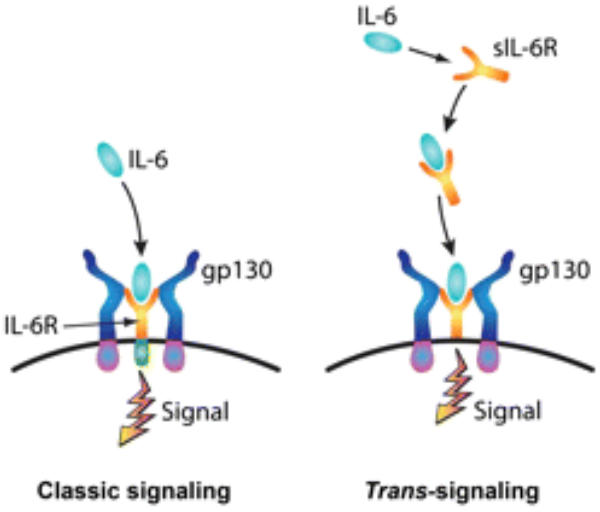
Doberer et al, *J Am Soc Nephrol*, 2021; 32:708

Rebound nach Clazakizumab?

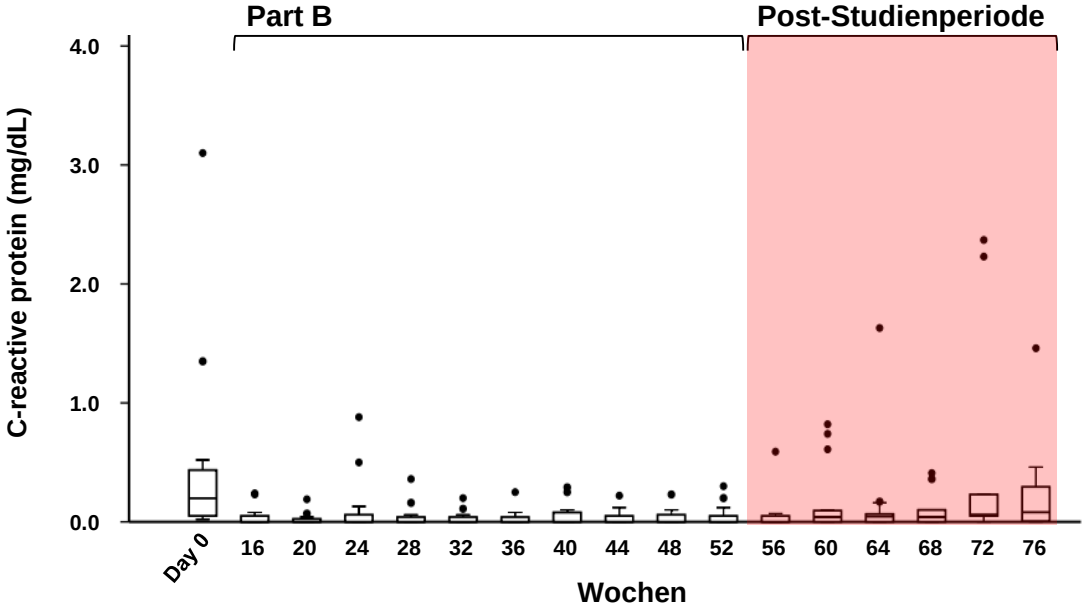
eGFR slope





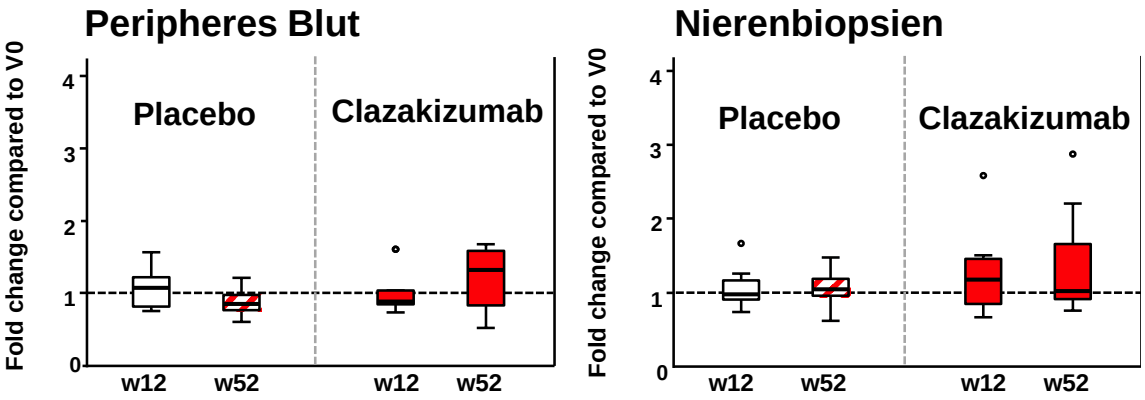


Lee et al., J Immunol, 2011, 186: 3226

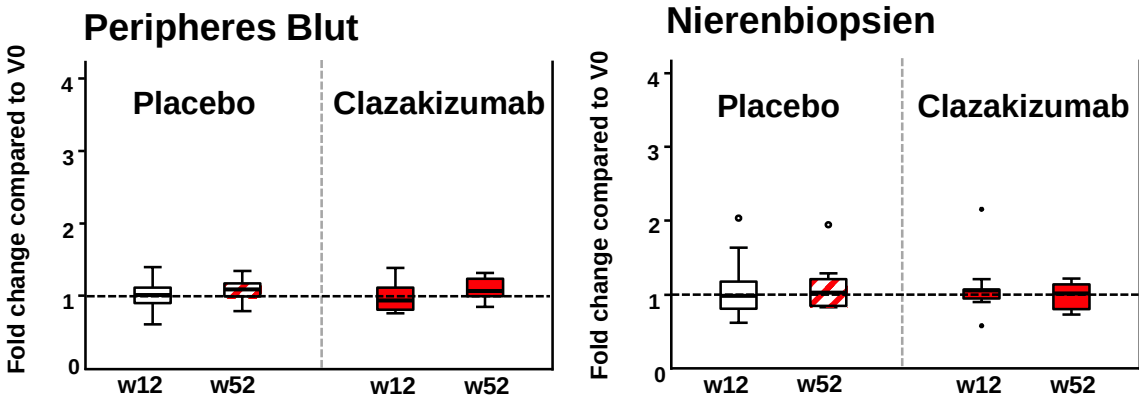


Borski et al, *unpublizierte Daten*

IL-6 Rezeptor (RNA)



gp130 (RNA)



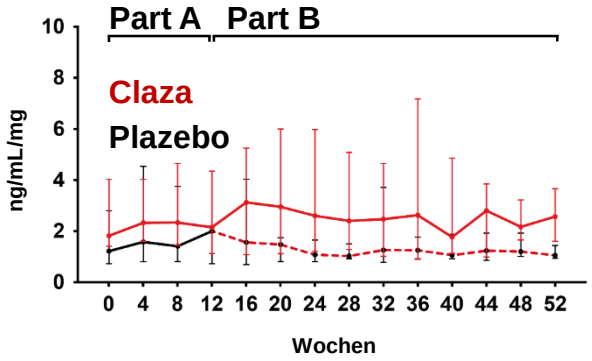
Borski et al, *unpublizierte Daten*

Kein Effekt auf Pantoprazol-Metabolismus (CYP2C19/CYP3A4)

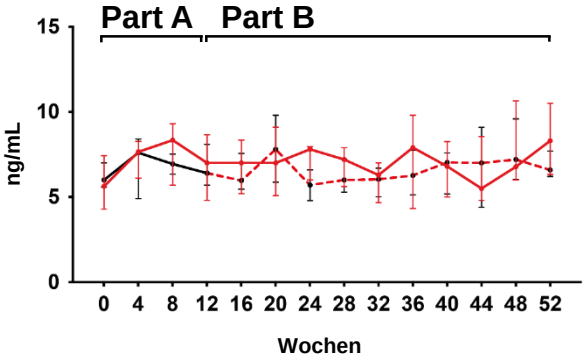
PK parameters†	Total (n = 20)	Clazakizumab (n = 10)	Placebo (n = 10)
Day 0			
$T_{1/2}$ (h)	1.08 (0.86–1.72)	1.55 (0.98–3.09)	0.94 (0.76–1.33)
C_{max} (µg/ml)	1.49 (1.10–2.59)	1.66 (1.07–3.45)	1.37 (1.08–2.44)
$AUC_{0\text{-last}}$ (µg/ml*h)	2.88 (1.82–4.02)	3.67 (1.76–9.18)	2.71 (1.70–3.32)
$AUC_{0\text{-inf}}$ (µg/ml*h)	3.16 (2.21–7.84)	4.21 (2.11–13.01)	3.14 (2.31–3.94)
Week 12			
$T_{1/2}$ (h)	1.08 (0.97–1.9)	1.90 (0.98–3.86)	1.0 (0.84–1.19)
C_{max} (µg/ml)	1.45 (1.09–2.83)	1.66 (0.98–3.02)	1.38 (1.26–2.0)
$AUC_{0\text{-last}}$ (µg/ml*h)	2.70 (1.75–5.41)	3.45 (1.62–11.39)	2.05 (1.74–3.92)
$AUC_{0\text{-inf}}$ (µg/ml*h)	3.66 (2.03–7.52)	6.67 (2.47–20.65)	2.33 (1.91–4.43)
Week 52			
$T_{1/2}$ (h)	1.03 (0.89–2.10)	2.10 (1.41–2.98)	0.89 (0.80–1.00)
C_{max} (µg/ml)	1.97 (0.99–2.89)	2.75 (1.49–3.82)	1.57 (0.93–2.32)
$AUC_{0\text{-last}}$ (µg/ml*h)	3.82 (1.78–7.10)	6.87 (2.79–12.98)	2.37 (1.72–4.17)
$AUC_{0\text{-inf}}$ (µg/ml*h)	4.22 (1.99–8.18)	8.09 (2.92–20.60)	2.75 (1.84–4.66)

► Kein Effekt auf CNI-Metabolismus

C_0/D Ratio (Tacrolimus)



C_0 Spiegel (Tacrolimus)

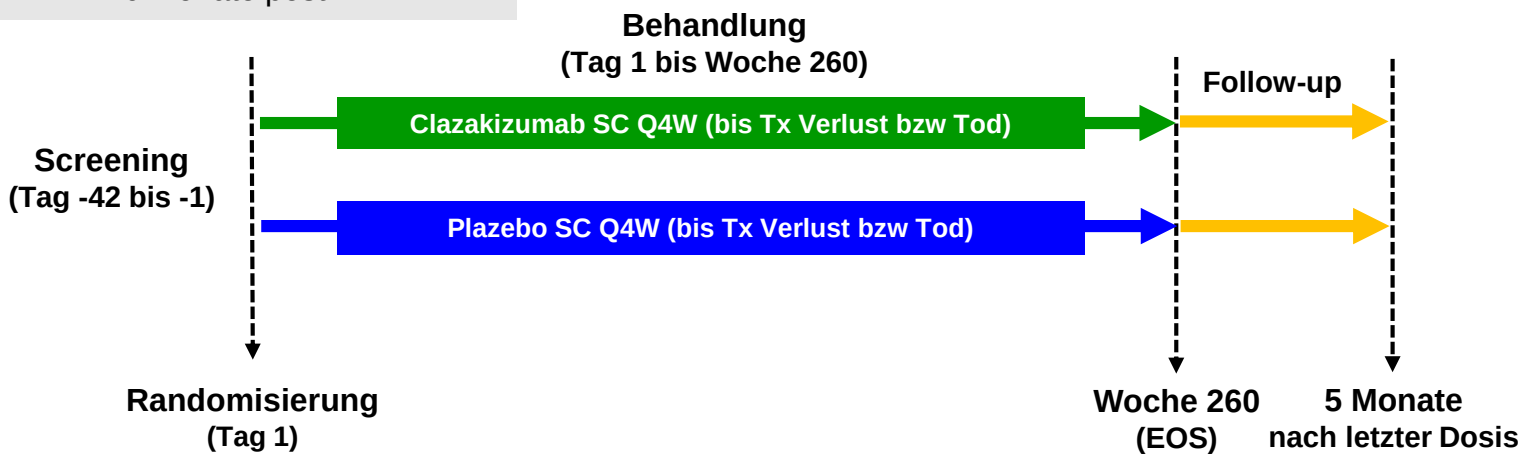


Mühlbacher et al, *Transplant Int* 2021; 34(8):1542

IMAGINE Studie (Clazakizumab)

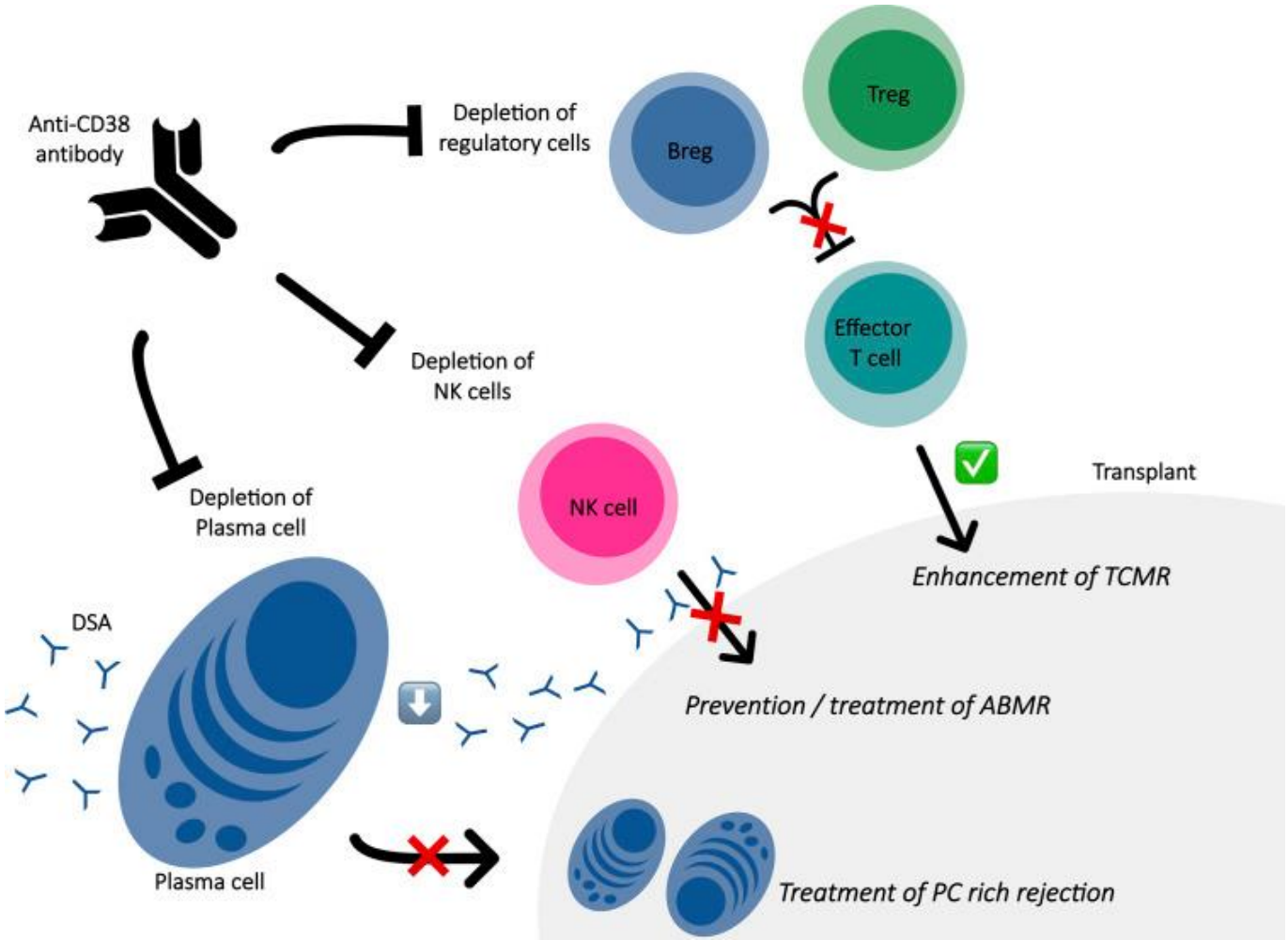
Laufende Phase 3 Studie; RCT
(>80 Zentren in Nordamerika, Europa und Australien)

350 NTX-Empfänger
Inklusionskriterien
cABMR (Banff 2015)
DSA-Positivität
eGFR 25-65 ml/min/1.73 m^2
>6 Monate post-NTX



Primärer Endpunkt (kombiniert):
- Dialysewiederbeginn
- Tx-Nephrektomie
- Retransplantation
- eGFR <15 mL/min/1.73 m^2
- Tod

CD38 - Target in der Organtransplantation?



Joher et al., *Front Immunol,* 2021; 12:688301

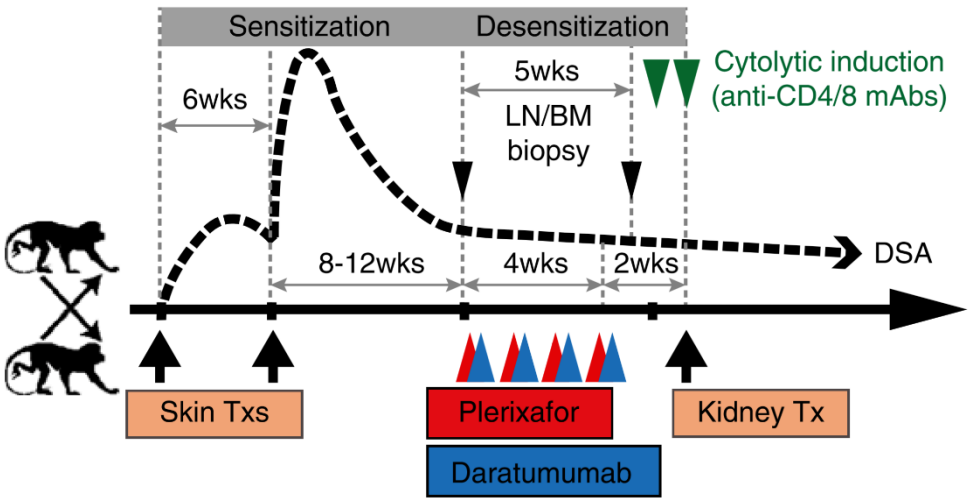
CD38 als therapeutisches Target - Konzepte

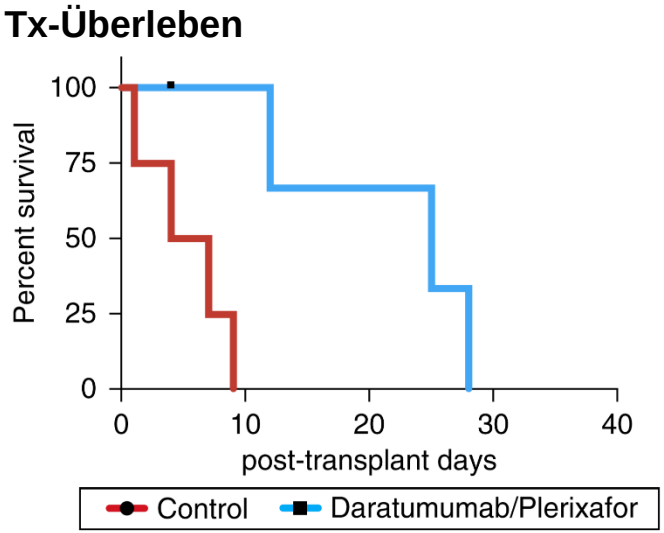
TABLE 1 | Selection of therapeutical regimens targeting CD38.

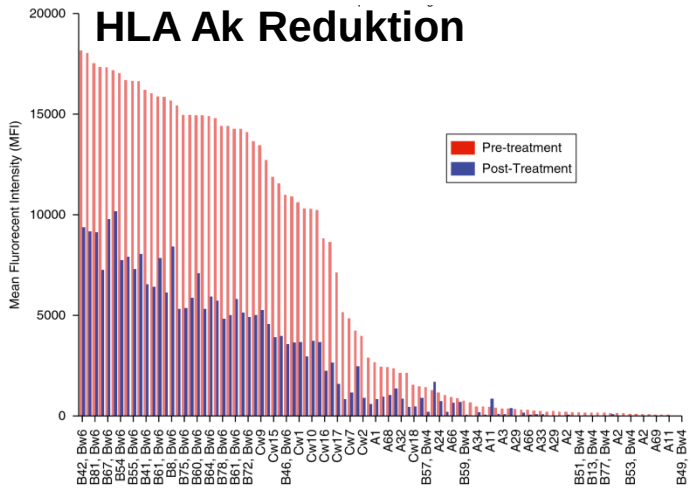
Anti-CD38 strategies	Nature and mechanism	Statut	NCT number
Daratumumab *Janssen*	Fully human IgG1-kappa anti-CD38 mAb	Approved	X
Isatuximab *Sanofi*	Chimeric IgG1-kappa anti-CD38 mAb	Approved	X
Felzartamab - MOR202 *MorphoSys AG*	Fully human IgG1-lambda anti-CD38 mAb	Ongoing in auto-immune field	NCT04733040 NCT04145440
Mezagitamab - TAK-079 *Takeda*	Fully human IgG1-lambda anti-CD38 mAb	Ongoing in hemato-oncology	NCT03439280
CID-103 *CASI Pharmaceuticals*	Fully human IgG1 anti-CD38 mAb	Ongoing in hemato-oncology	NCT04758767
ISB 1342 *Glennmark Phamaceuticals*	CD3xCD38 bispecific antibody to redirect cytotoxic potential of T cells to $CD38^{+}$ cells	Ongoing in hemato-oncology	NCT03309111
TAK-169 *Takeda*	Antibody drugs conjugates: anti-CD38 Ab fragment combined to a Shiga-like toxin (payload: ribosome inactivation)	Ongoing in hemato-oncology	NCT04017130
TAK-573 *Takeda*	Antibody drugs conjugates: humanized IgG4 anti-CD38 mAb combined to interferon α (payload: anti-proliferative effects)	Ongoing in hemato-oncology	NCT03215030
^{211}At-OKT10-B10 *Fred Hutchinson Cancer Research Center*	Antibody drugs conjugates: anti-CD38 mAb combined to radioactive Astatine ^{211}At (payload: radiation)	Ongoing in hemato-oncology	NCT04579523 NCT04466475
STI-6129 *Sorrento Therapeutics*	Antibody drugs conjugates: anti-CD38 mAb combined to Duostatin5 (payload: tubulin inhibition)	Ongoing in hemato-oncology	NCT04316442
KP1237 *Kleo Pharmaceuticals*	Endogenous-antibodies recruiting molecule targeting CD38 in order to enhance antibody-dependent destruction mechanism	Ongoing in hemato-oncology	NCT04634435
Anti-CD38 CAR-T Cells *Sorrento Therapeutics*	Imunne cell therapy based on autologous T cells modified into anti-C38 CAR-T cells	Ongoing in hemato-oncology	NCT03464916

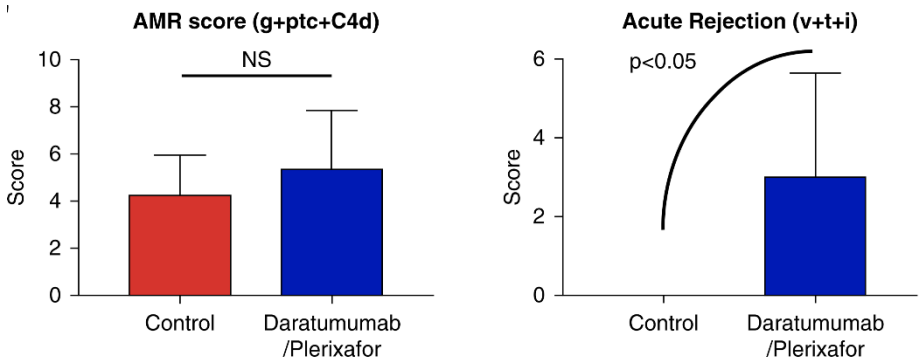
Joher et al., *Front Immunol,* 2021; 12:688301

CD38 Ak Daratumumab – Tiermodell









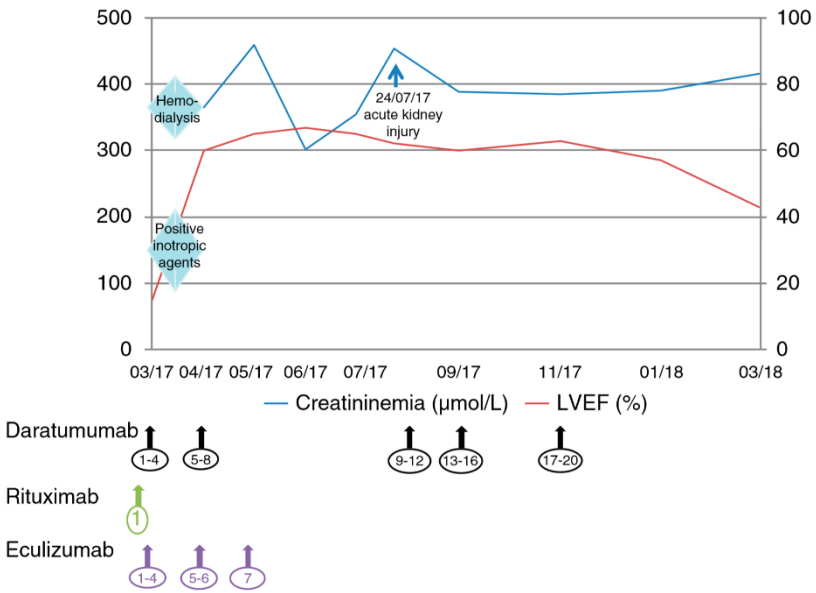
►Plasmablasten-Reduktion

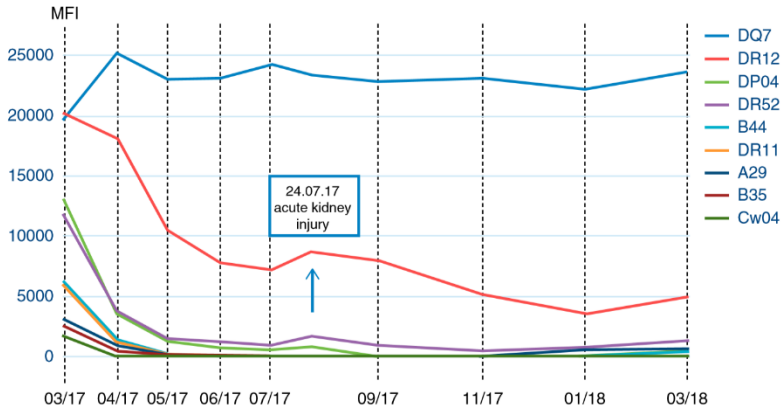
►Reduktion regulatorischer B-Zellen

Kwun et al., *J Am Soc Nephrol* 2019; 30(7):1206

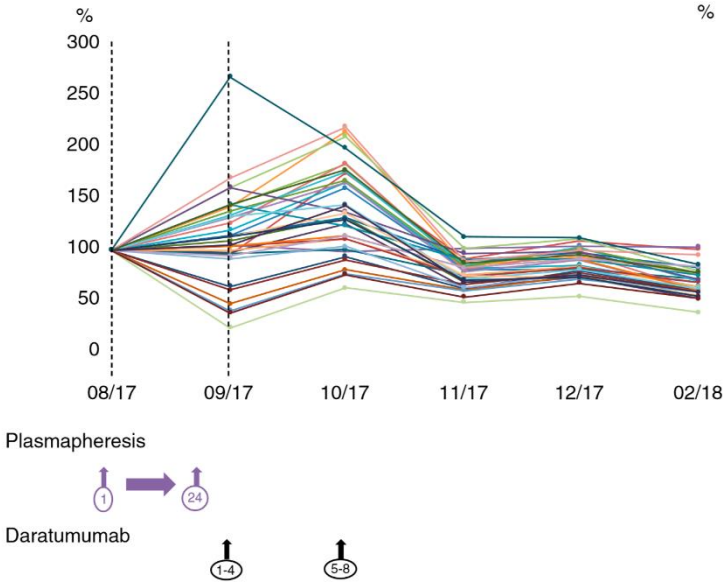
CD38 Antibody Daratumumab – Fallberichte

ABMR nach Herz/Nieren-Tx





Desensibilisierung eines HTX Kandidaten



PP/IVIG/Rituximab: kein Effekt

Daratumumab:

- ► **cPRA 98% ► 62%**
- ► **Erfolgreiche Tx**

Kwun et al., *J Am Soc Nephrol* 2019; 30(7):1206

Fallbericht -Wien

NTX-Empfänger, 49a, männlich

IK-Glomerulonephritis

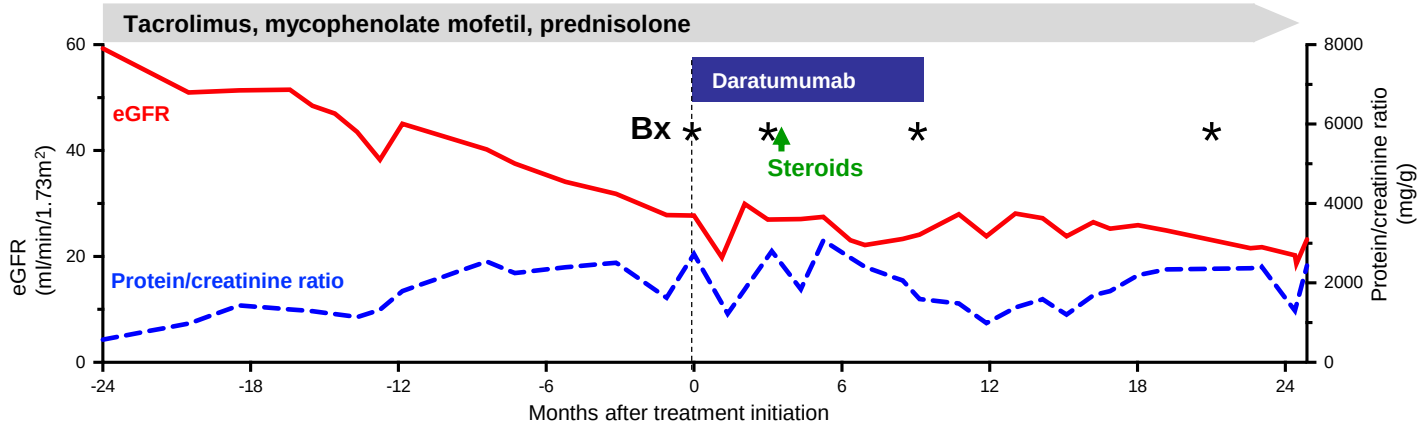
März 2005
2. NTX
HLA Mismatch: 2-1-1
CDC-PRA: 4%

Juni 2018
***De novo* DSA (anti-DQ6)**
Chronische ABMR & Myelom

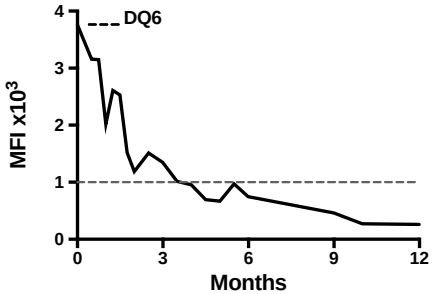
► CD38 mAk Daratumumab
(zwei Fliegen mit einem Streich?)

Doberer et al., *Transplantation*, 2021; 105:451

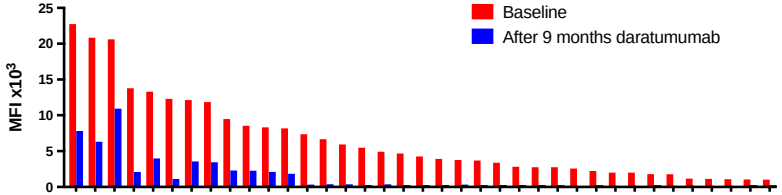
Klinischer Verlauf



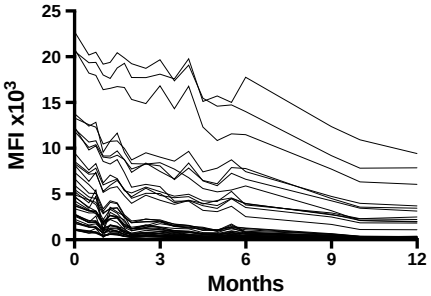
DSA



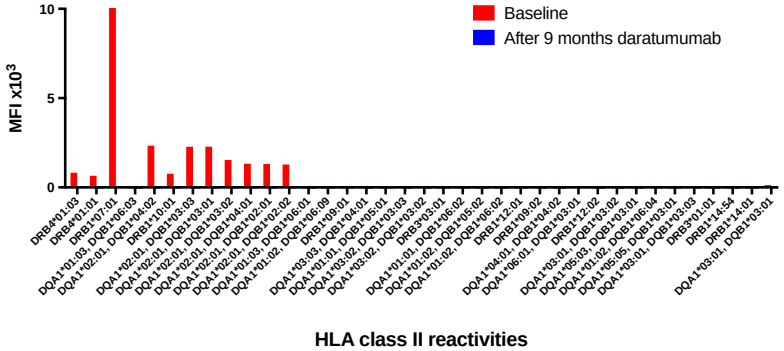
Patientenserum



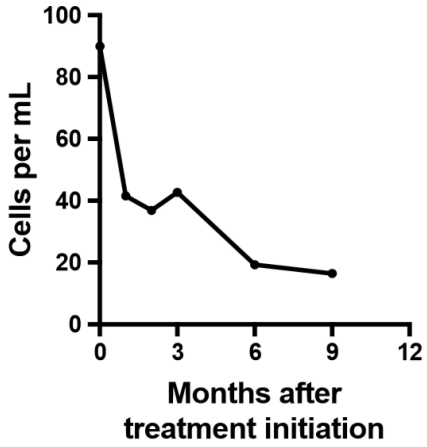
Non-DSA



Knochenmark – Plasmazellen/Überstand

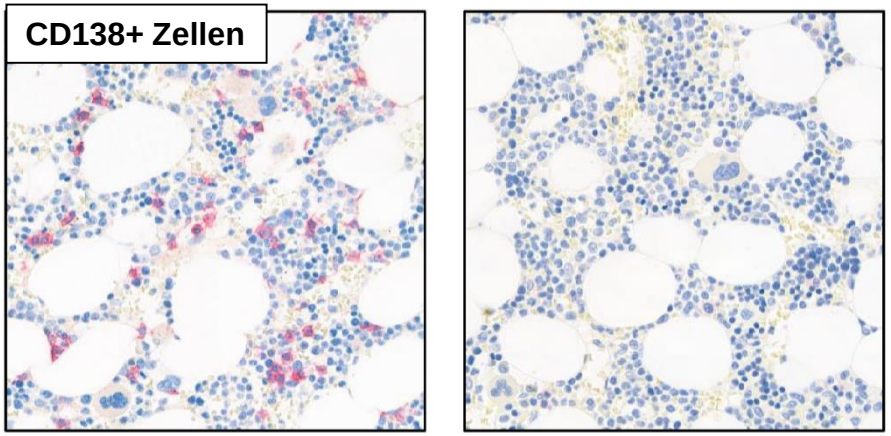


CD138+ PC (peripheres Blut)

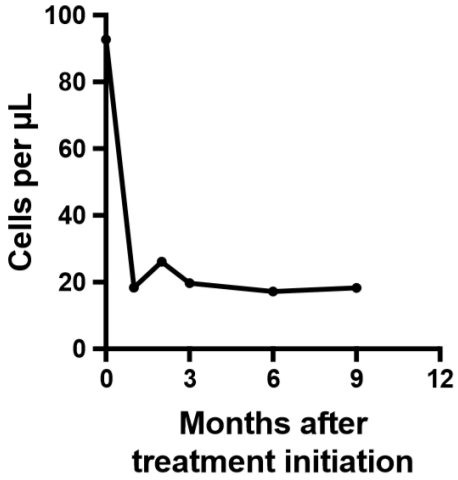


KM Bx (Index)

KM Bx (9 Monate)



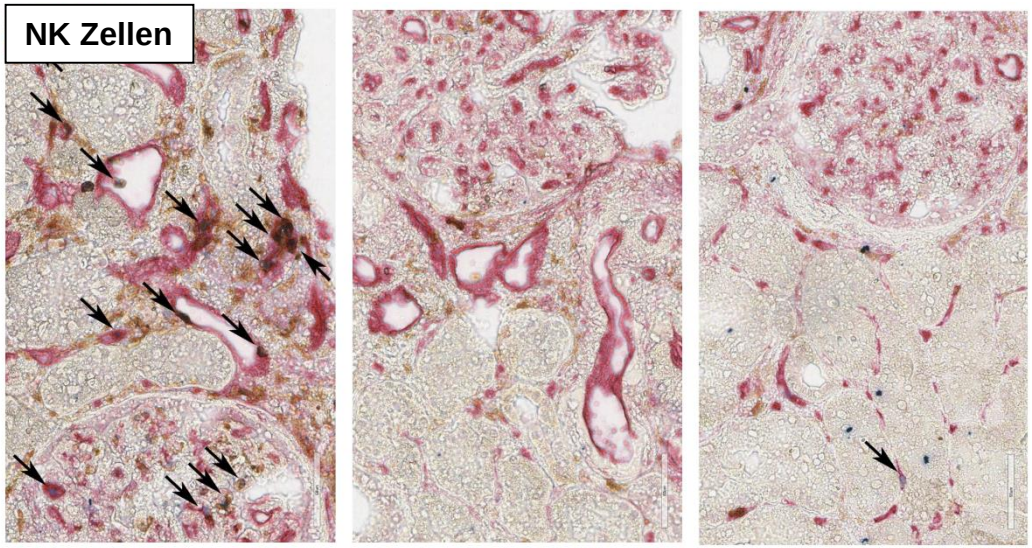
NK Zellen (peripheres Blut)



Index Bx

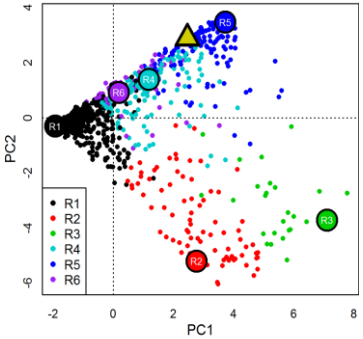
3-Mo-Bx

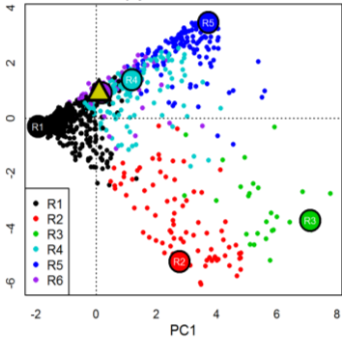
9-Mo-Bx

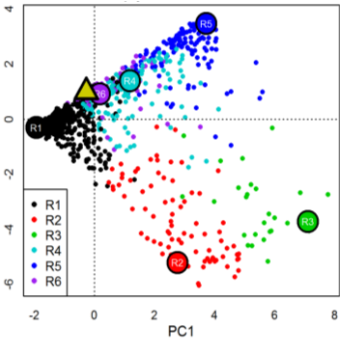


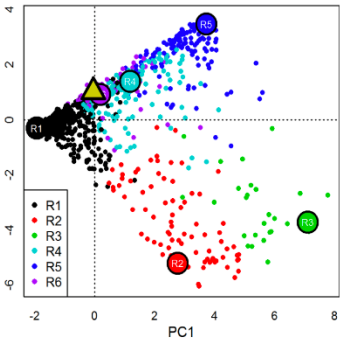
Index Bx	3-Mo Bx	9-month Bx	21-month Bx

MMDx







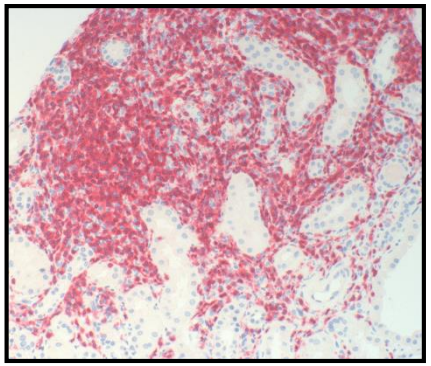


Fully developed ABMR (AMR score: 0.79)	Late stage ABMR (AMR score: 0.09)	Late stage ABMR (AMR score: 0.06)	Late stage ABMR (AMR score: 0.14)

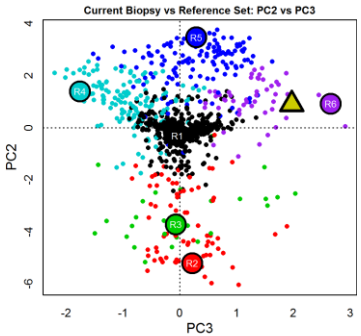
Banff 17

Chronic active AMR	TG + Borderline (i1/t3)	TG	TG
g+ptc sum score: 3	g+ptc sum score: 0	g+ptc sum score: 1	g+ptc sum score: 0
cg score: 3	cg score: 3	cg score: 3	cg score: 3

CD3+ infiltrates



TCMR Score: 0.00



Doberer et al., *Transplantation*, 2021; 105:451

CD38 Antikörper Felzartamab

(MOR202; MOR03087)

Rekombinant
IgG1
voll-humanisiert
ADCC/ADCP (kein CDC)

<u>Klinische Studien:</u>
Multiples Myelom (Phase 1/2a/abgeschlossen, Phase 3/aktiv)
Membranöse GN (Phase 2/aktiv)
Transplantation (bislang keine Studie)

Noch für keine Indikation zugelassen (FDA, EMA)

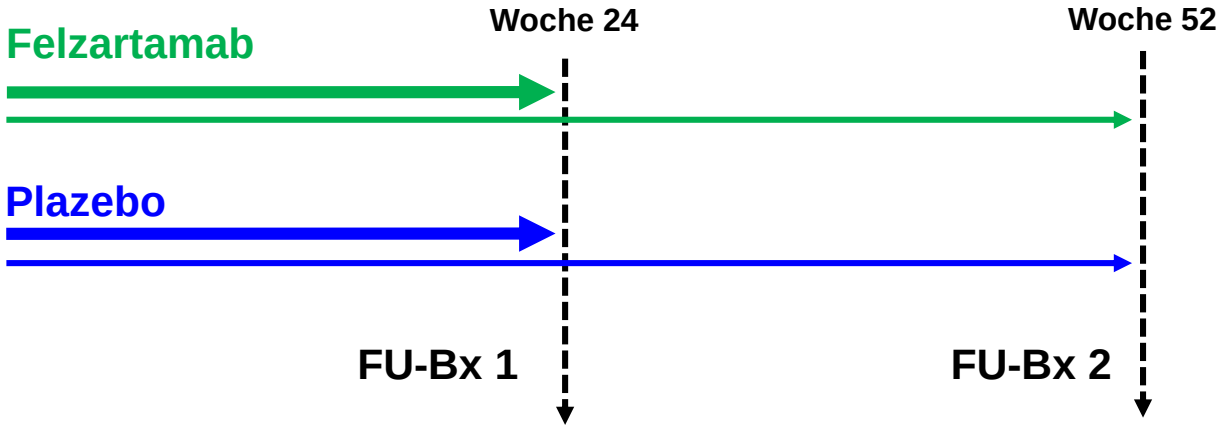
Vergleichsweise geringeres Risiko für Infusionsreaktionen

Sehr geringes Immunisierungsrisiko (ADA)

Felzartamab bei später ABMR

Laufender RCT; Phase 2
Wien, Berlin, Grenoble

2 Interimanalysen
(nach Inklusion von 10 bzw. 20 Patienten)



1:1 Randomisierung

20 NTX Empfänger
Inklusionskriterien:
Späte aktive ABMR
eGFR >20 ml/min/1.73 m^2
≥180 Tage post-NTX

Primärer EP
Sicherheit
Sekundäre EPs
DSA Charakteristika, FU-Bx Resultate, Leukozyten-Subpopulationen, Marker für Inflammation und Endothelaktivierung/schaden, TTV Load
eGFR Slope, Proteinurie, iBOX

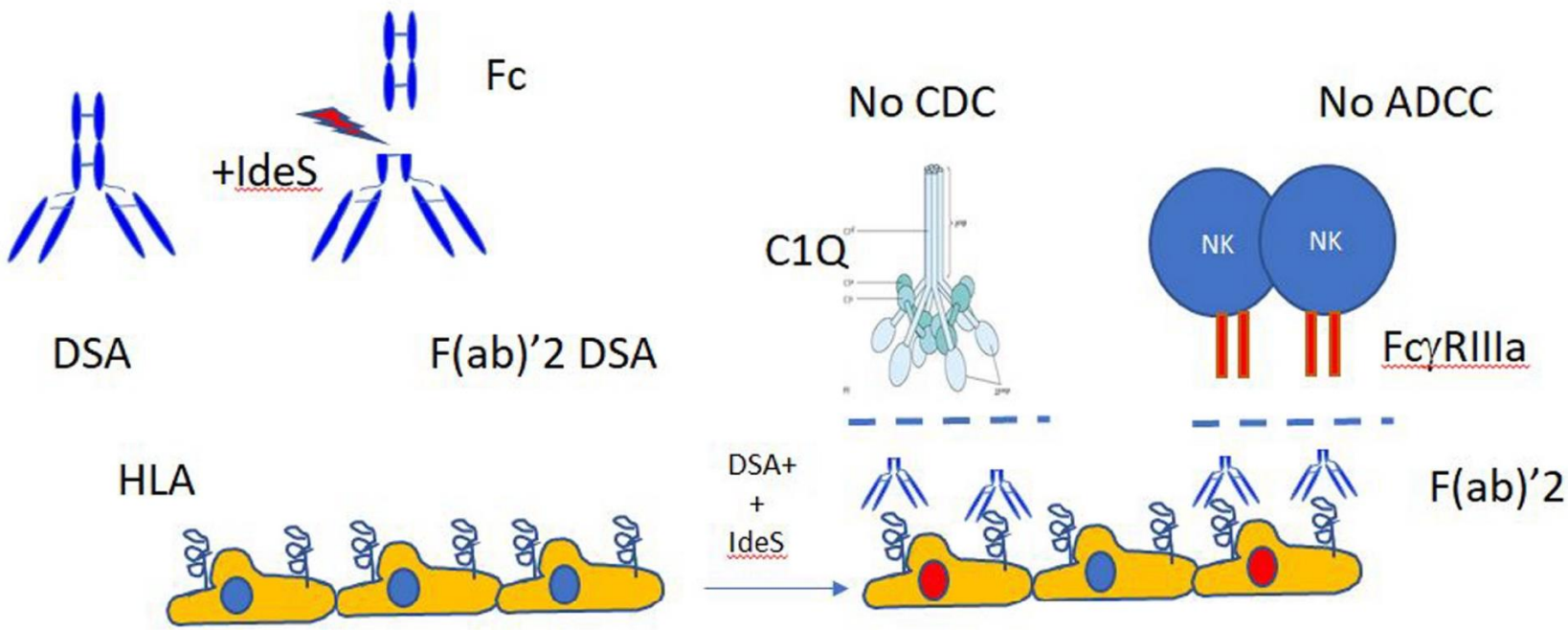
Status – 18. März 2022
6 Patienten inkludiert

ClinicalTrials.gov Identifier: NCT05021484

Imlifidase/IdeS

„Immunoglobulin G degrading enzyme of *Streptococcus pyogenes*“

- ► **Blockiert Fc-abhängige Effektormechanismen**
- ► **F(ab’)2 binden weiter an Epitope**



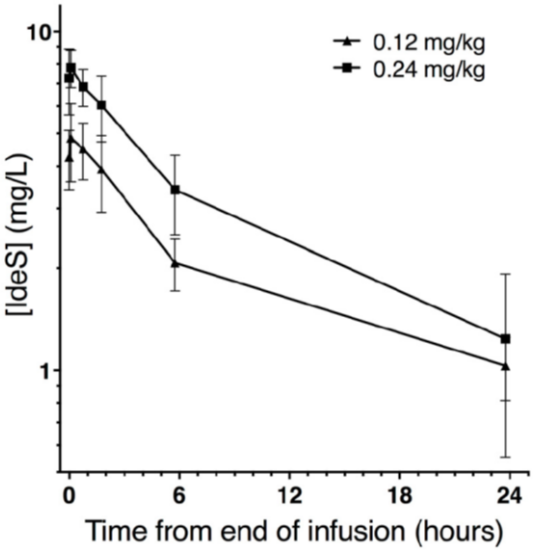
Ge et al., Transplantation 2020; 104(8):1574
Huang et al. Am J Transplant 2022; 22(3):691

Phase 1 Studie - IgG Inaktivierung und Rebound

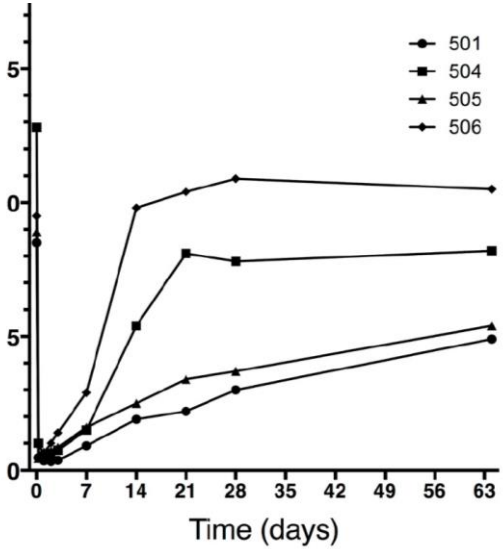
First-in-man, randomisiert, geblindet
‚Single ascending dose'
20 gesunde Probanden

keine SAEs

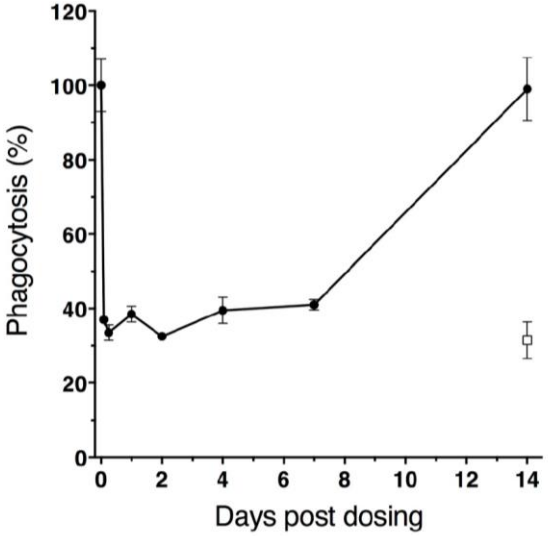
Pharmakokinetik



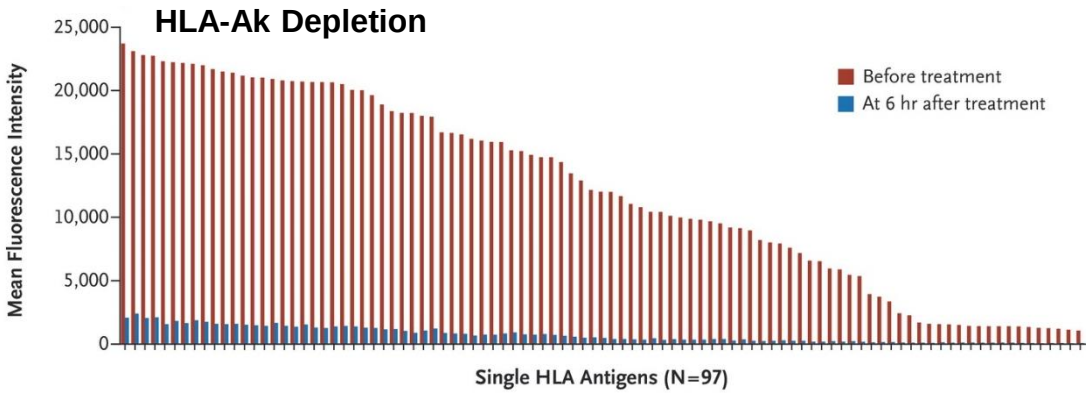
IgG Elimination (0.24 mg/kg)



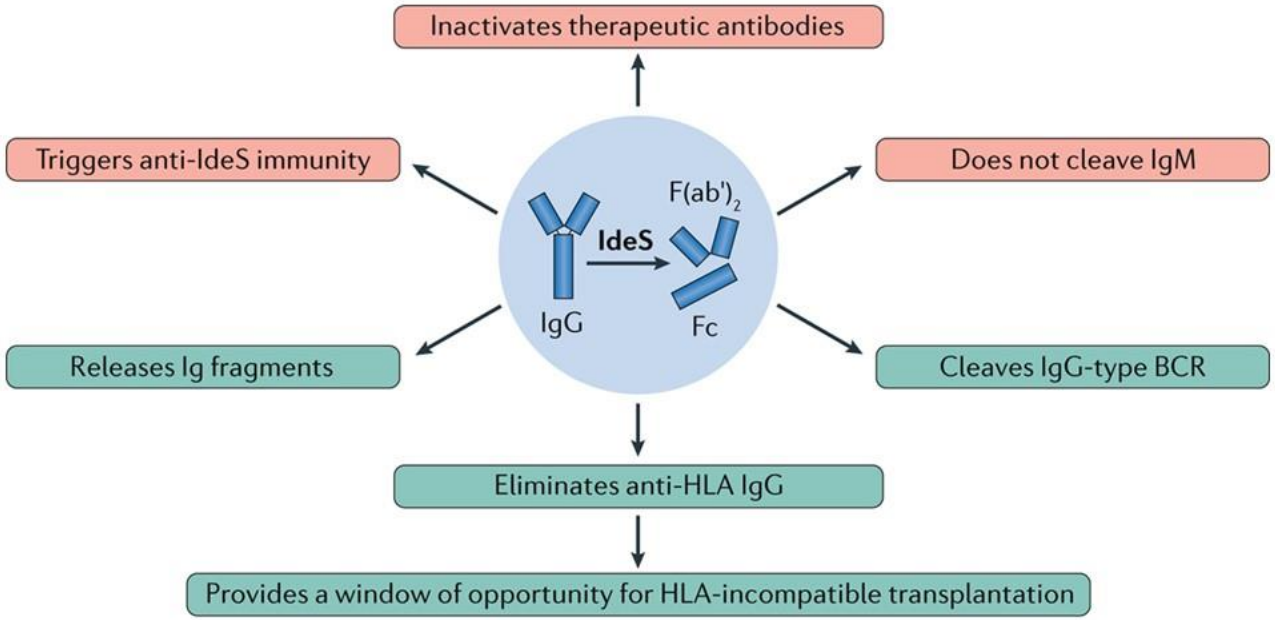
IgG-abhängige Phagozytose



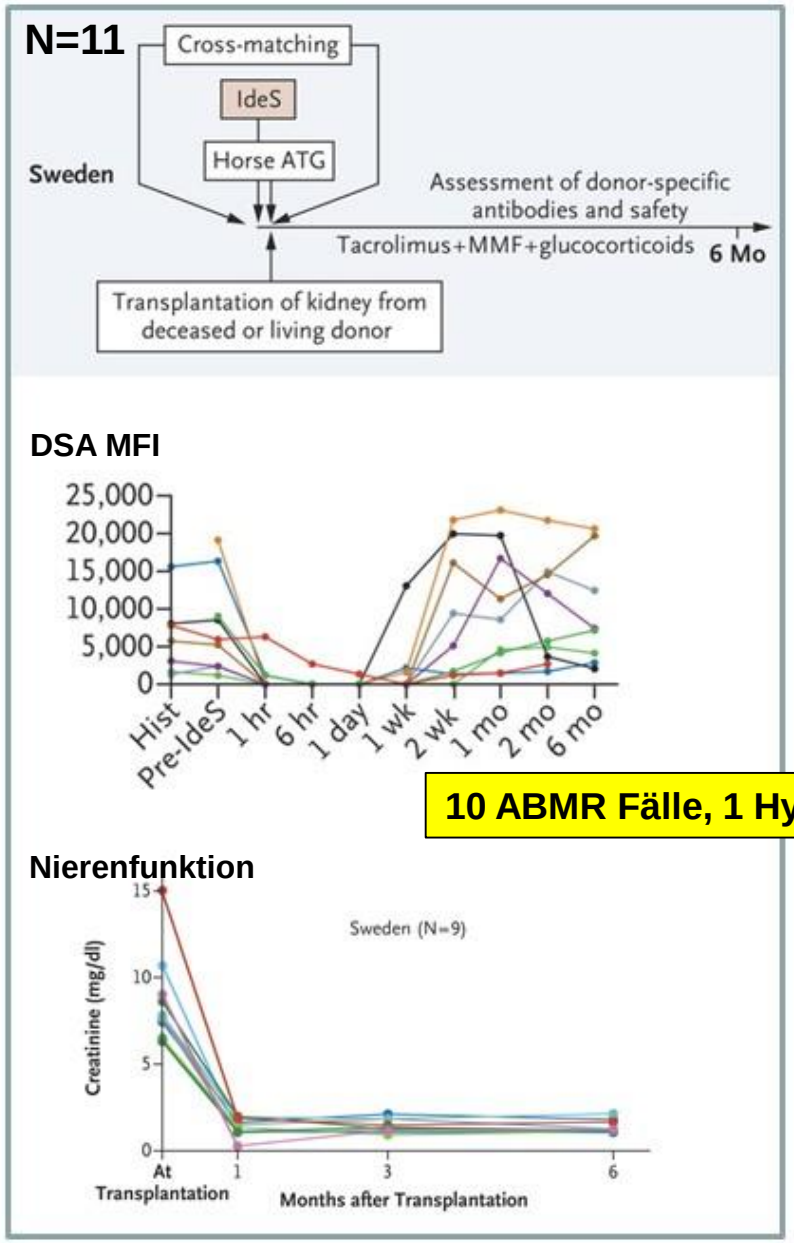
Winstedt et al, *PLoSOne* 2015; 10: e0132011

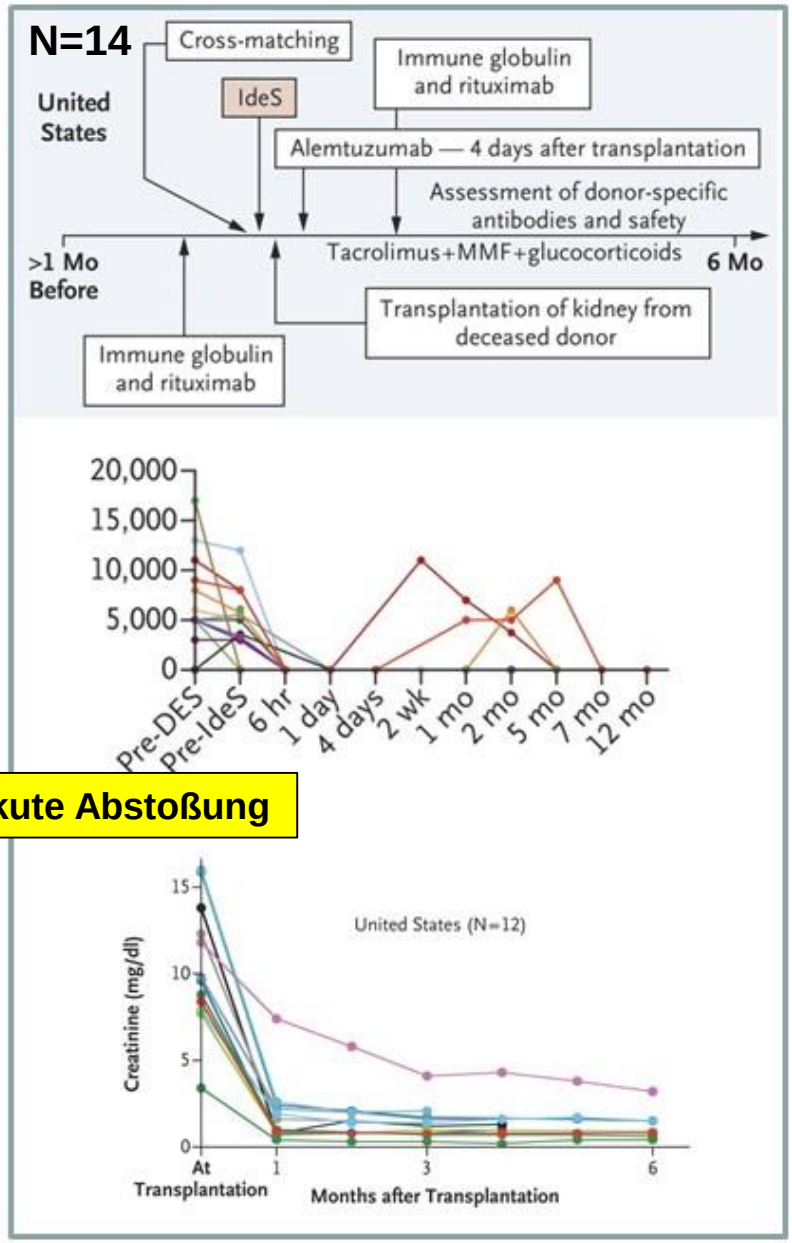


Jordan et al. *N Engl J Med* 2017;377:442



Böhmig & Rostaing, *Nat Rev Nephrol*, 2017



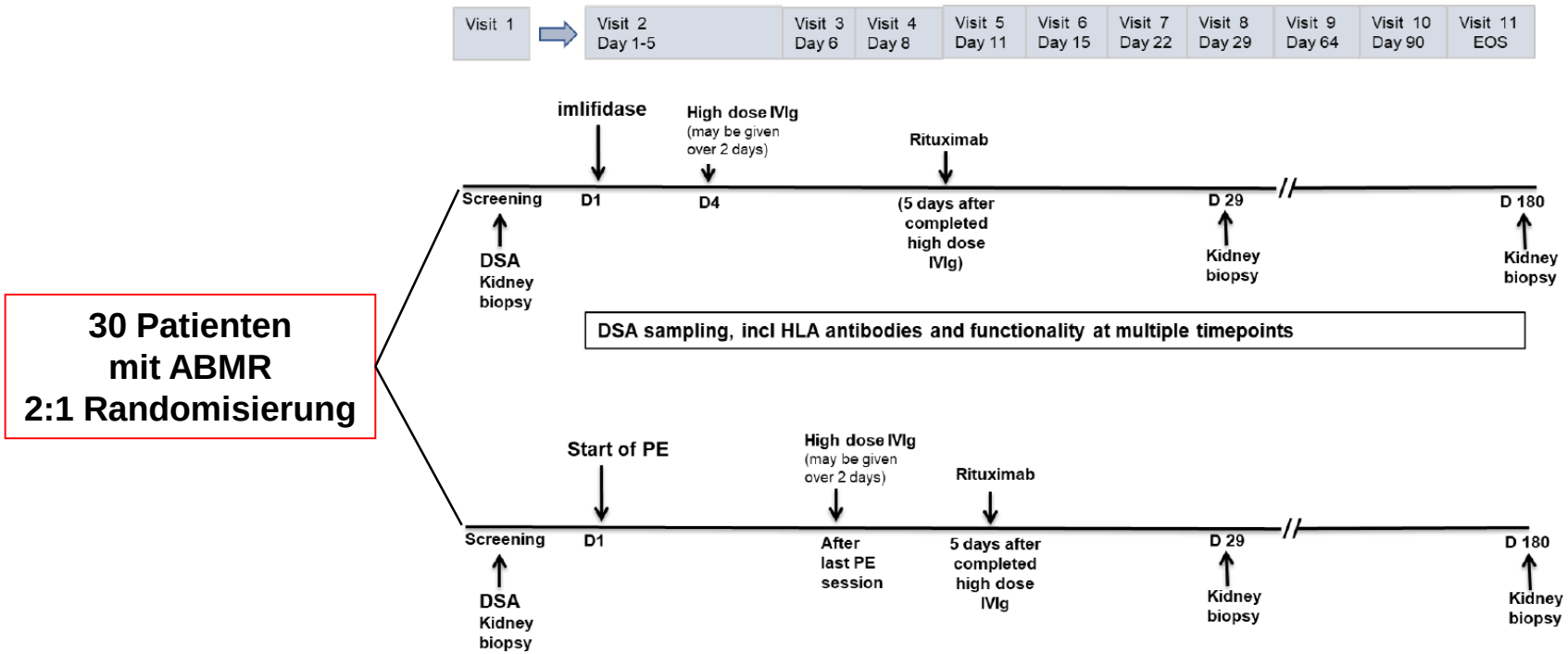


10 ABMR Fälle, 1 Hyperakute Abstoßung

Jordan et al., *N Engl J Med* 2017; 377(5):442

Imlifidase bei aktiver oder chronisch aktiver ABMR

Laufender RCT; Phase 2 (5-10 Zentren)



ClinicalTrials.gov Identifier: NCT03897205

Zusammenfassung

- **ABMR geht mit ungünstigem Transplantatüberleben einher**

- **Für die häufige späte ABMR gibt es derzeit keine Evidenz-basierte Therapie (Rezente ‚negative' RCTs: BORTEJECT, TRITON)**

- **Aktuell sind mehrere interessante Konzepte in klinischer Evaluation: IL-6 Antagonismus; CD38 Ak; IdeS**

- **Für einen breiten Einsatz solcher Therapien ist die Evidenz aktuell jedoch zu niedrig (Fallberichte, Fallserien, wenige kleine prospektive Studien)**

- **Neue Konzepte müssen systematisch in größeren Studien evaluiert werden (z.B. IMAGINE Studie)**

- **Das Design solcher Studien erfordert die Definition valider Surrogat-Endpunkte (eGFR Slope, iBOX etc.?)**