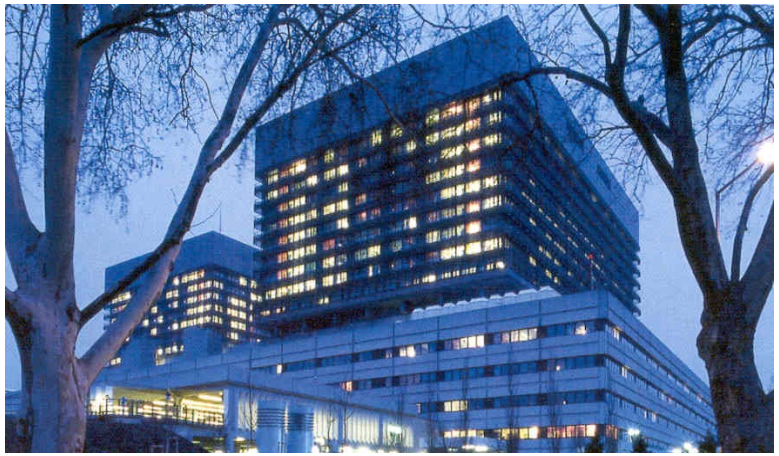
Durchbruch bei Antikörper-vermittelter Abstoßung



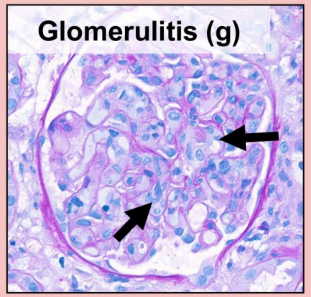
Georg Böhmig
Division of Nephrology and Dialysis
Department of Medicine III

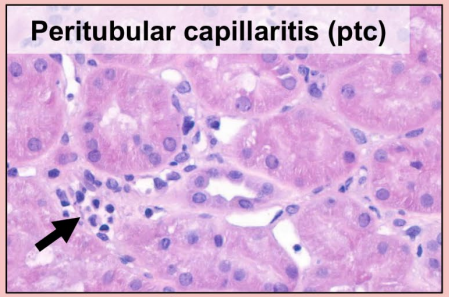
MEDICAL UNIVERSITY OF VIENNA

VIETAC
vienna transplant and complement laboratory

AMR/MVI (Banff 2022)

Active





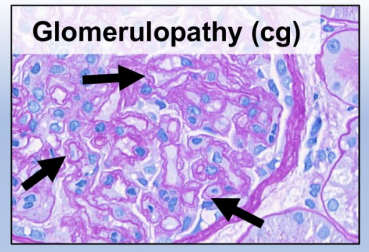
MVI (g+ptc)

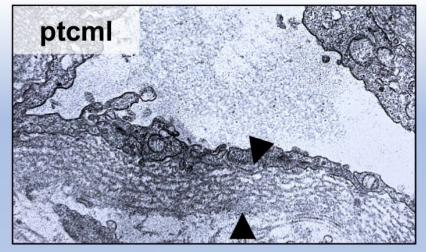
Active AMR:
MVI ≥ 2 AND **C4d ± DSA**
C4d WITH **MVI = 1** OR **v > 0** OR **TMA**

Probable active AMR:
DSA AND **MVI = 1** OR **v > 0** OR **TMA**

MVI, C4d negative, DSA negative:
MVI ≥ 2, BUT NO **C4d** OR **DSA**

Chronic active / inactive

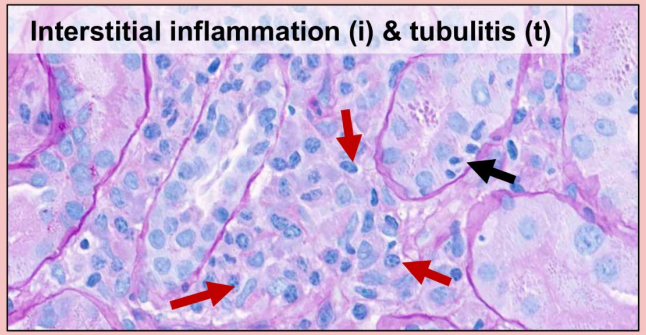




Chronic active AMR: **Active lesions*** AND **cg > 0** AND/OR **severe ptcml**

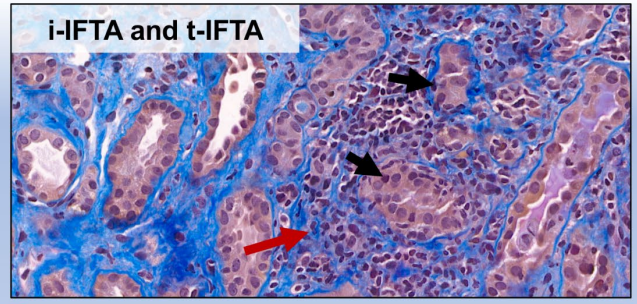
Chronic AMR: **cg > 0** AND/OR **severe ptcml** WITHOUT **active lesions****

TCMR (Banff 2019)



Borderline: **t ≥ 1** AND **i1** OR **t1 AND i ≥ 2**

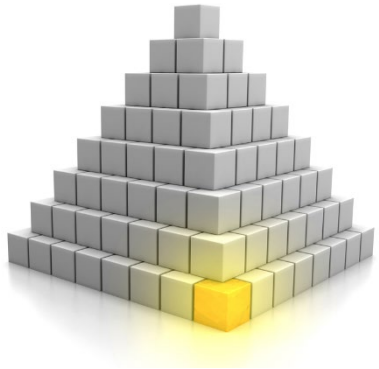
TCMR:
Grade IA: i ≥ 2 AND **t2**
Grade IB: i ≥ 2 AND **t3**
Grade IIA: v1 ± i AND/OR **t**
Grade IIB: v2 ± i AND/OR **t**
Grade III: v3 ± i AND/OR **t**



Chronic active TCMR:
Grade IA: (i-IFTA ≥ 2 AND **ti ≥ 2)** AND **(t2** OR **t-IFTA2)**
Grade IB: (i-IFTA ≥ 2 AND **ti ≥ 2)** AND **(t3** OR **t-IFTA3)**
Grade II: Neointima with mononuclear cells

Diebold et al., *Transplantation* 2024; in press

AMR – Cornerstones



► Frequent

AMR in ~3-12% of KTX recipients

► Clinical impact

Risk factor for graft loss
(e.g. DEKAF study: HR ~10-fold increased!)
Graft failure: ABMR=dominant cause

► High costs

Medicare & Medicaid, analysis 2006-2011:
4-fold increase in costs
plus ~35,000 $/patient/year over 2 years after diagnosis

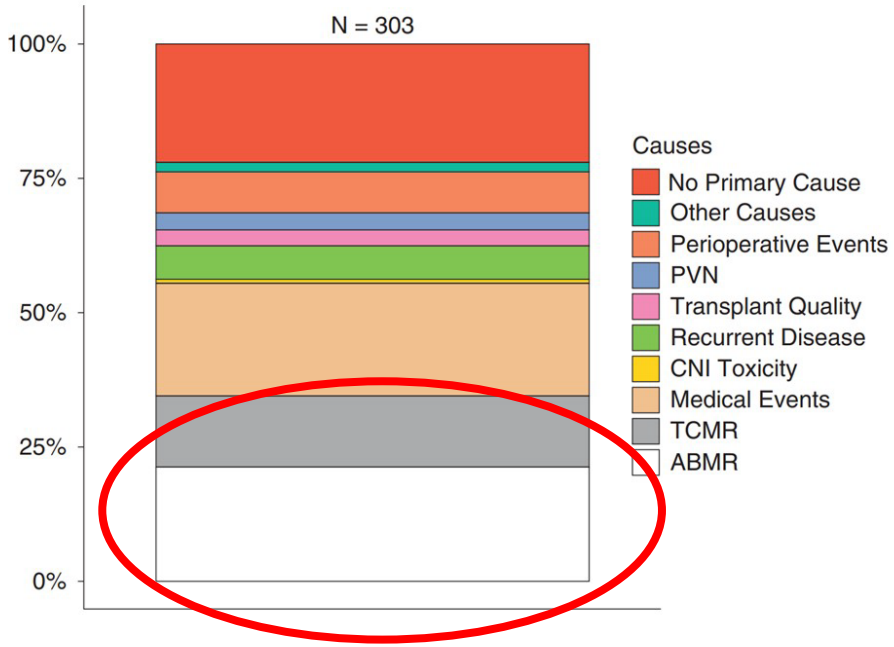
► Treatment?

Currently used treatments – low level of evidence

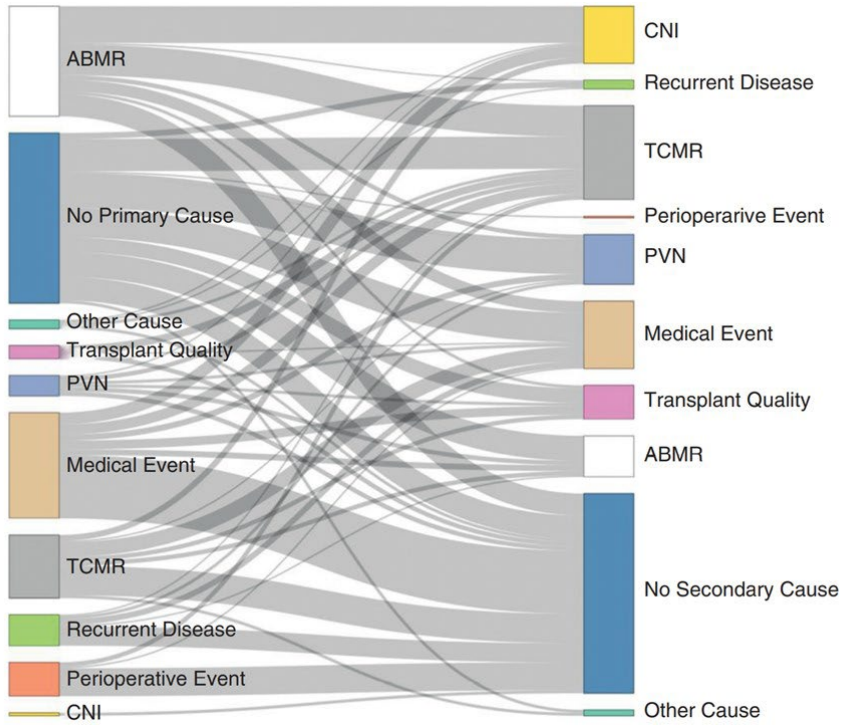
Hart et al., *Clin Transplant* 2021; 35(7):e14337; e14320
Sellares et al., *Am J Transplant* 2012 Feb;12(2):388
Mayrdorfer et al., *J Am Soc Nephrol* 2021; 32(6):1513
Hart et al., *J Med Econ* 2021; 24(1):1011
Schinstock et al., *Transplantation* 2020; 04(5):911

Causes of Graft Loss

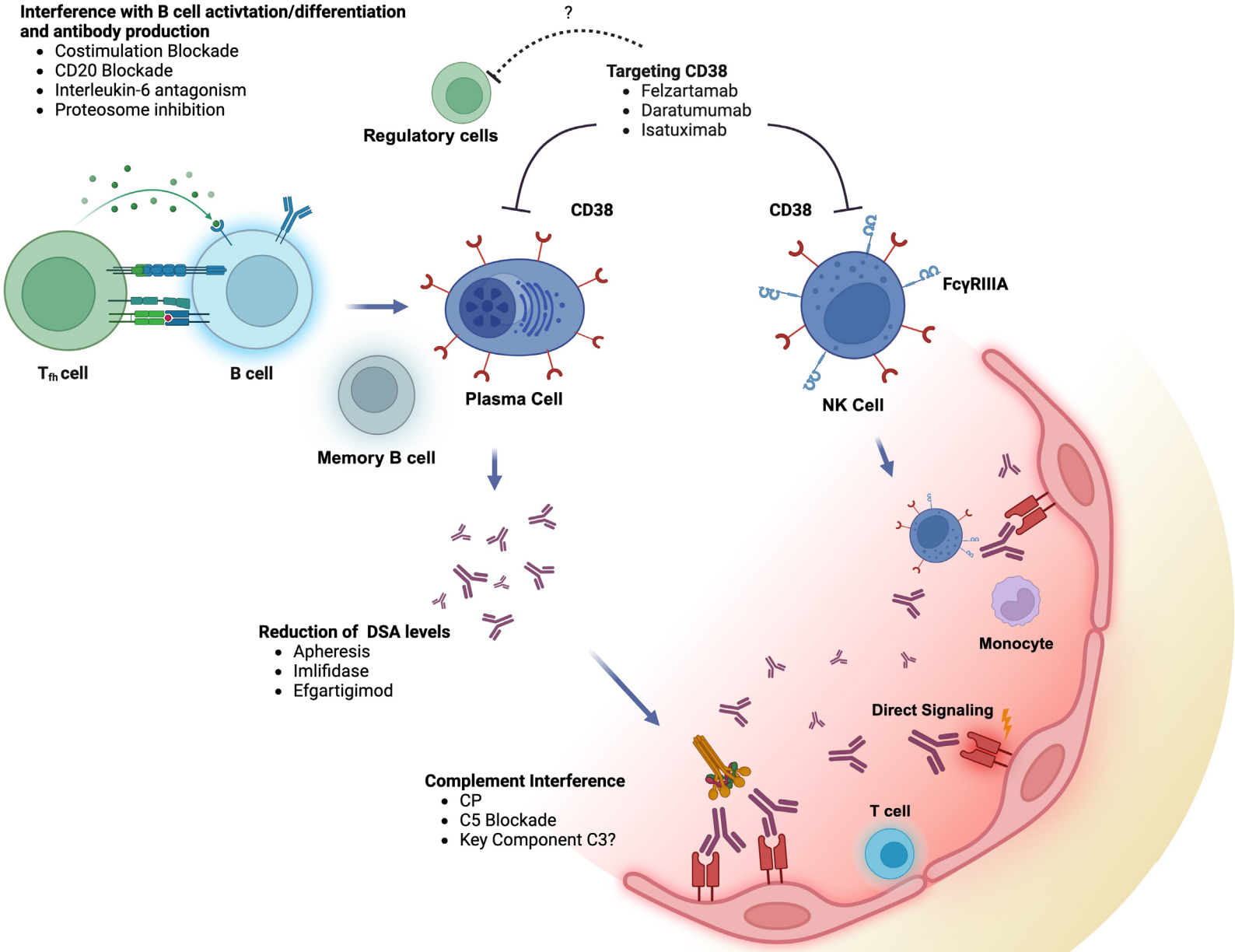
Primary causes



Primary/secondary



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



Diebold et al., *Transplantation* 2024; in press

AMR – „Standard-of-Care“ Therapy

2019 Expert Consensus - Transplantion Society Working Group

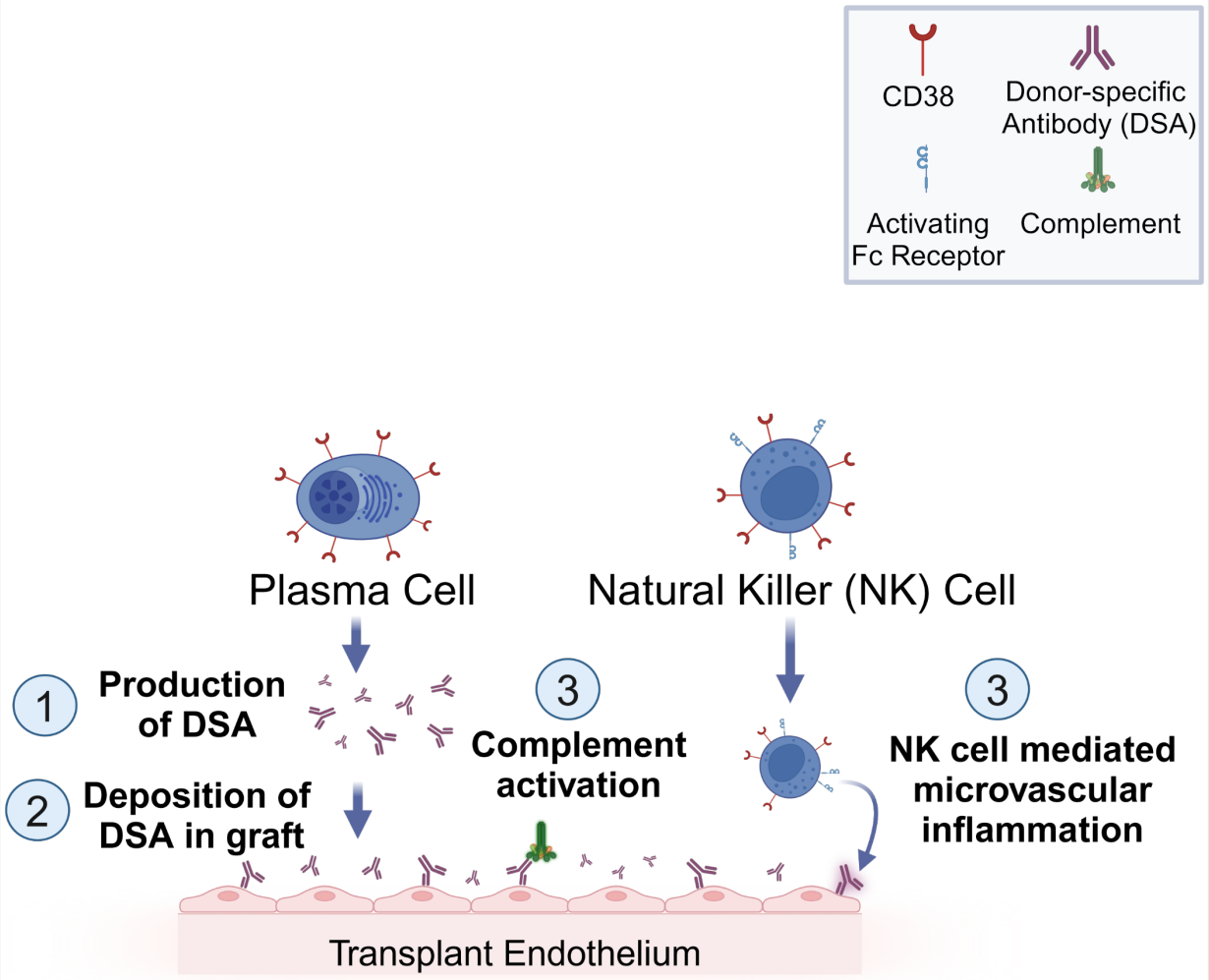
Timing	DSA	Histology (Banff 2017)	Standard of care[a]	Consider adjunctive therapies
Early[a] Acute (<30 days posttransplant)	Preexisting DSA (or nonimmunologically naive)	Active AMR	Plasmapheresis (daily or alternative day × 6 based on DSA titer) (1C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C) Corticosteroids (E0)	Complement inhibitors (2B) Rituximab 375 mg/m^2 (2B) Splenectomy (3C)
Late (>30 days posttransplant)	Preexisting DSA	Active AMR	Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b] IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C) Corticosteroids (E0)	Rituximab 375 mg/m^2 (2B)
		Chronic AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C)	IVIG (3C)
	De novo DSA	Active AMR	Optimize baseline immunosuppression (eg, add steroids if on a steroid-free regimen) (1C) Evaluate and manage nonadherence	Plasmapheresis and IVIG (3C) Rituximab (3C)
		Chronic AMR		IVIG (3C)

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

AMR – Phase II-IV Trials

Primary target	Compound	MOA	Trial phase	Trial acronym	Identifier	Author, year
DSA	**Imlifidase**	IgG cleavage	II (finished)	-	NCT03897205	Halleck, 2024
Plasma cells	**Bortezomib**	Proteasome inhibition	II (finished) II (finished) II (recruiting)	**BORTEJECT** **TRIBUTE** -	NCT01873157 NCT02201576 NCT03737136	Eskandary, 2018 - -
PC/NK cells	**Felzartamab**	CD38 binding	II (finished)	-	NCT05021484	Mayer, 2024
B cells	**Rituximab**	B cell depletion	III (finished) II (prematurely terminated) IV (prematurely terminated) III (active, not recruiting)	**RITUX-ERAH** **TRITON** **RituxiCAN-C4** **TAR:GET-1**	NCT01066689 2010-023746-67 NCT00476164 NCT03994783	Sautenet, 2016 Moreso, 2018 Shiu, 2020 -
	Fostamatinib	SYK inhibition	II (recruiting)	**FOSTAMR**	NCT03991780	-
IL-6/IL-6R	**Clazakizumab**	IL-6 binding	II (finished) III (prematurely terminated)	- **IMAGINE**	NCT03444103 NCT03744910	Doberer, 2021 -
	Tocilizumab	IL-6R blockade	III (recruiting)	**INTERCEPT**	NCT04561986	-
Complement	**C1-INH**	CP/AP/LP blockade	II (finished) III (prematurely terminated) III (prematurely terminated)	- - -	NCT01147302 NCT02547220 NCT03221842	Montgomery, 2016 - -
	BIVV0020	C1s inhibition	II (recruiting)	-	NCT05156710	-
	Eculizumab	C5 blockade	III (finished) II (prematurely terminated)	- -	NCT01327573 NCT01895127	Kulkarni, 2017 -

CD38 Antibody Felzartamab in Late AMR



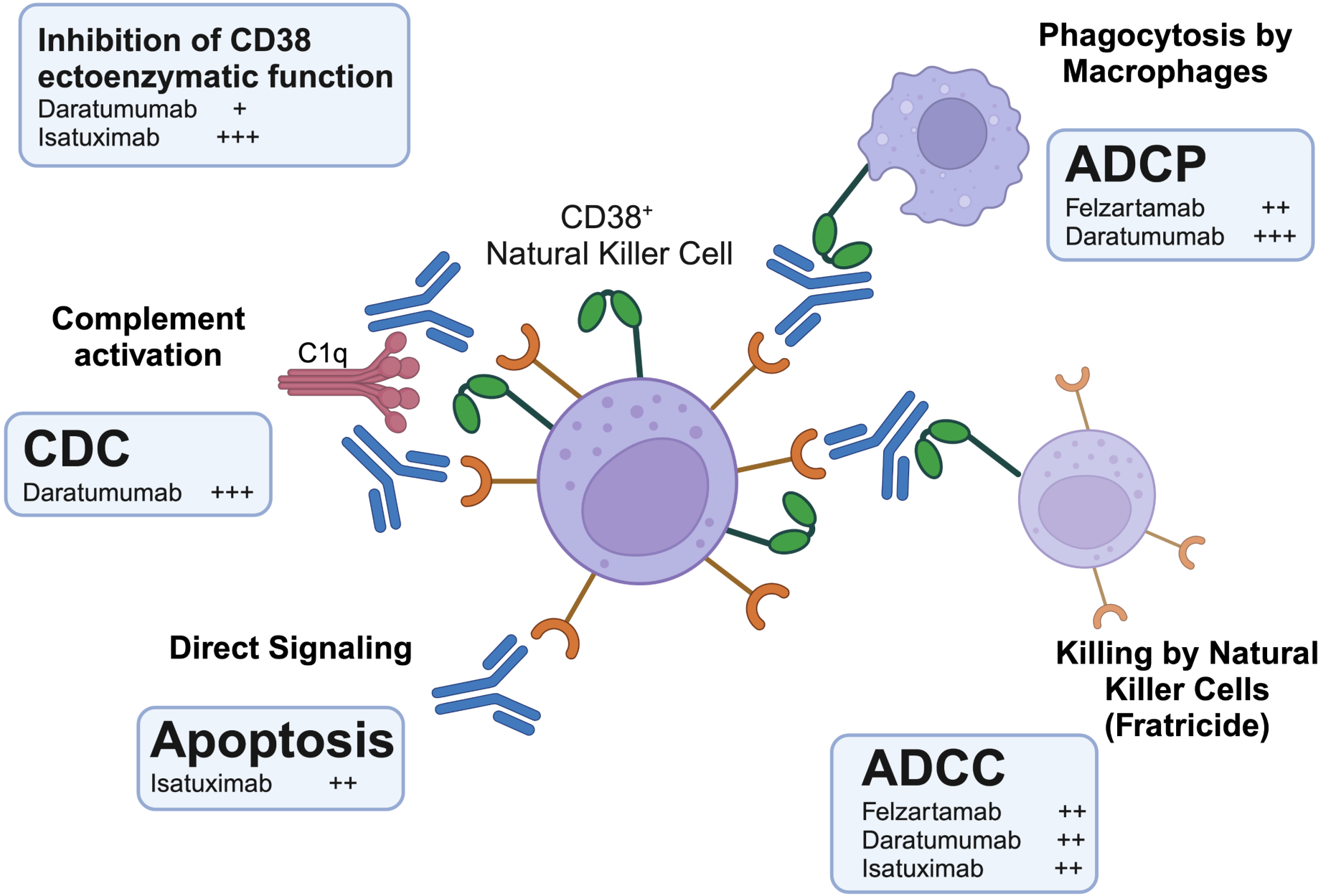
CD38

- Multifunctional receptor and enzyme
- Expressed on various types of immune cells:
  - ✓ highest expression on plasma cells
  - ✓ expression on subsets of:
    NK cells, T cells, B cells, and myeloid cells

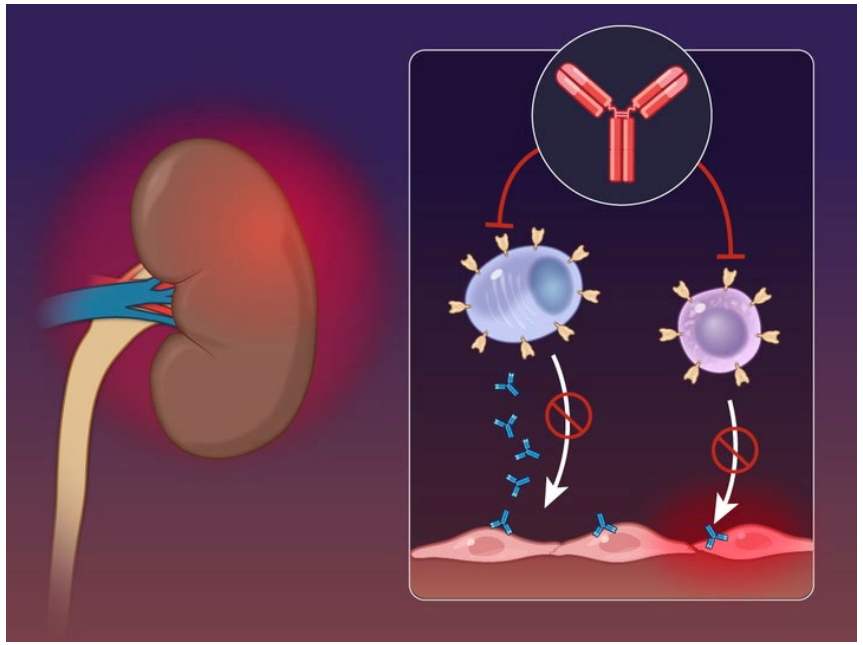
Felzartamab

- Human IgG1λ CD38 antibody
- Primary mode of action:
  - ✓Lysis of target cells via antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis[1]
  - ✓but not complement-dependent cytotoxicity[1]

[1] Boxhammer et al. Blood 2015; 126: 3015 (abstract)


Inhibition of CD38 ectoenzymatic function
Daratumumab +
Isatuximab +++
Phagocytosis by Macrophages
ADCP
Felzartamab ++
Daratumumab +++
CD38+ Natural Killer Cell
Complement activation
C1q
CDC
Daratumumab +++
Direct Signaling
Apoptosis
Isatuximab ++
Killing by Natural Killer Cells (Fratricide)
ADCC
Felzartamab ++
Daratumumab ++
Isatuximab ++

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

K.A. Mayer, E. Schrezenmeier, M. Diebold, P.F. Halloran, M. Schatzl, S. Schranz, S. Haindl, S. Kasbohm, A. Kainz, F. Eskandary, K. Doberer, U.D. Patel, J.S. Dudani, H. Regele, N. Kozakowski, J. Kläger, R. Boxhammer, K. Amann, E. Puchhammer-Stöckl, H. Vietzen, J. Beck, E. Schütz, A. Akifova, C. Firbas, H.N. Gilbert, B. Osmanodja, F. Halleck, B. Jilma, K. Budde, and G.A. Böhmig

Mayer et al., N Engl J Med, 2024; 391(2):122-132

Trial Scheme and Study Flow

Screening
N=31

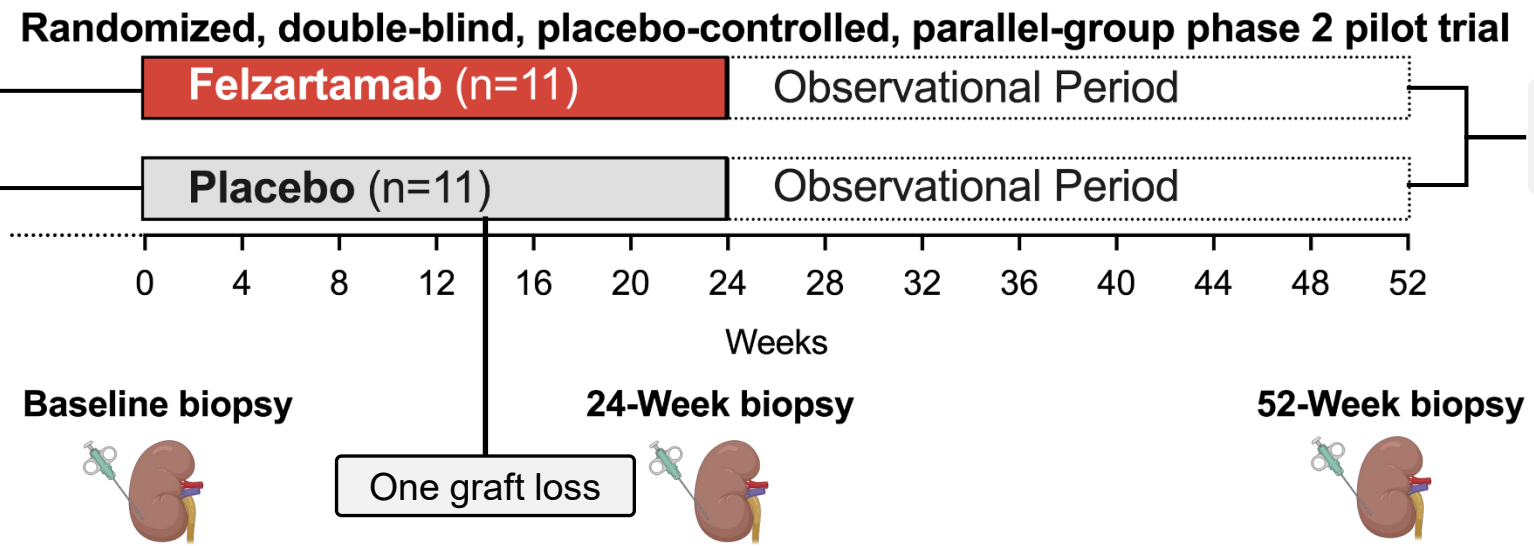
N=22
1:1 randomized

Sites:
Vienna
Berlin

Key inclusion criteria
- DSA+ active or chronic active AMR
- eGFR >20 mL/min/1.73m^2
- ≥180 days post-transplant

Primary outcome
- Safety and tolerability

Key secondary outcomes
- AMR activity
- DSA characteristics
- NK and plasma cell counts
- dd-cfDNA
- eGFR slope



22 were included in the intention-to-treat analysis

Primary Outcome: Safety of Felzartamab

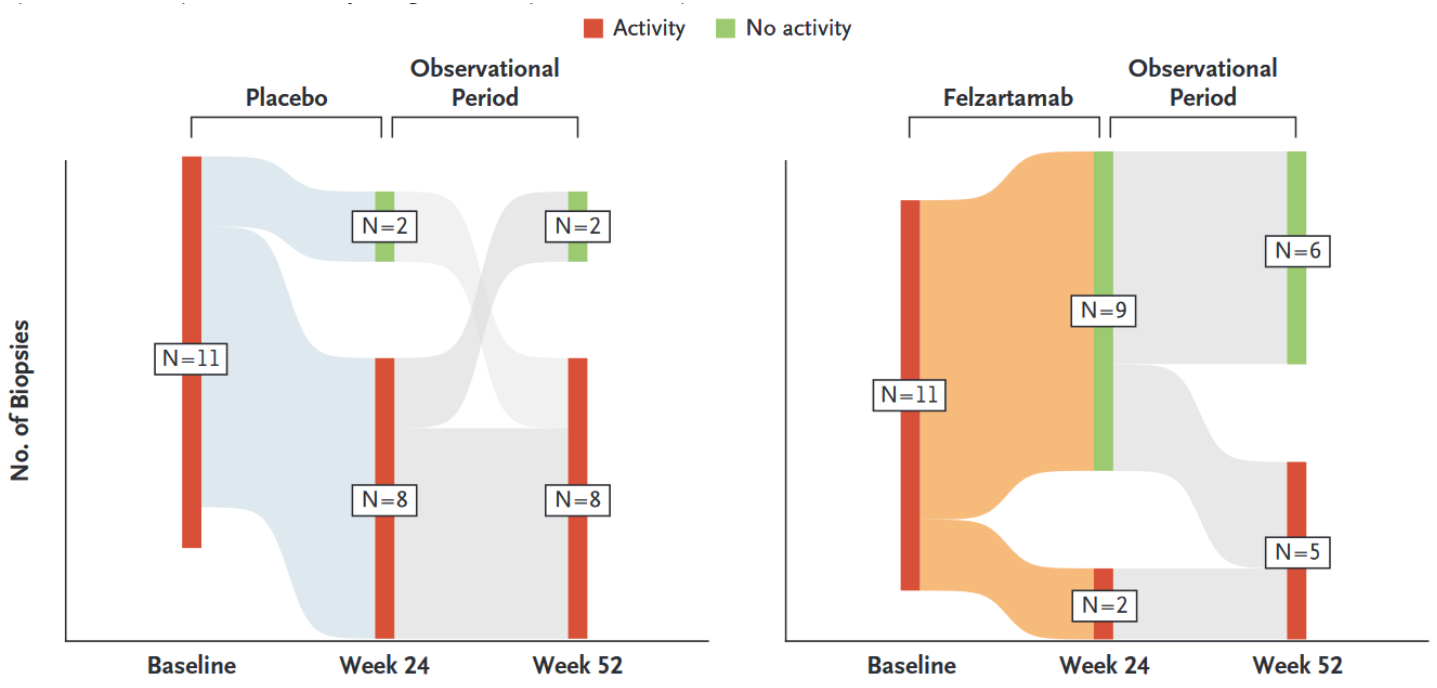
	Placebo (N=11)		Felzartamab (N=11)	
	Patients with AE – no. (%)	Number of AE	Patients with AE – no. (%)	Number of AE
Patients with a TEAE – no. (%)	11 (100)	81	11 (100)	119
Mild	9 (81.8)	37	11 (100)	61
Moderate	11 (100)	42	11 (100)	55
Severe	1 (9.1)	2	2 (18.2)	3
Patients with a TRAE – no. (%)	7 (63.6)	11	10 (90.9)	27
Infusion-related reaction	0 (0)	0	8 (72.7)	8

P=0.001

Eight infusion-related reactions: mild to moderate severity

- **Limited to first dose**
- **Symptomatic treatment and reduced infusion rate**
- **No treatment discontinuations**

Reduction in AMR Activity



Resolution of AMR activity at Week 24:

Felzartamab: 9/11 patients (81.8%)

Placebo: 2/10 patients (20.0%)

Difference: 61.8%
(95% CI: 18.6%, 100%)

Relative Risk (RR): 0.23
(95% CI: 0.06, 0.83)

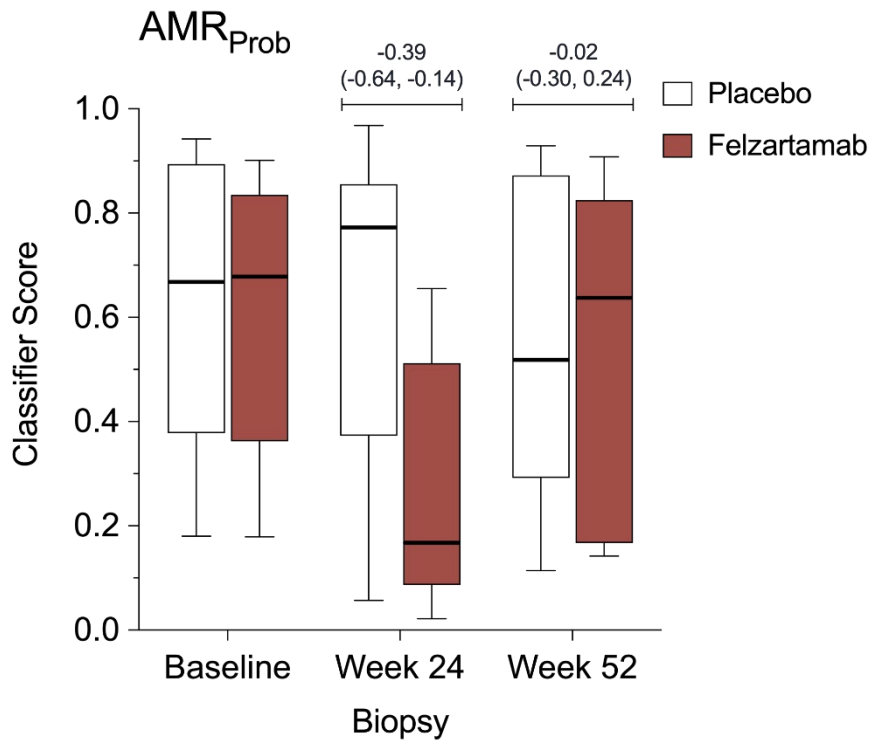
Recurrence of AMR activity at Week 52:

3/9 of Felzartamab-treated patients (33%)

*One patient in the placebo group lost their graft prior to Week 24 due to ongoing chronic active AMR

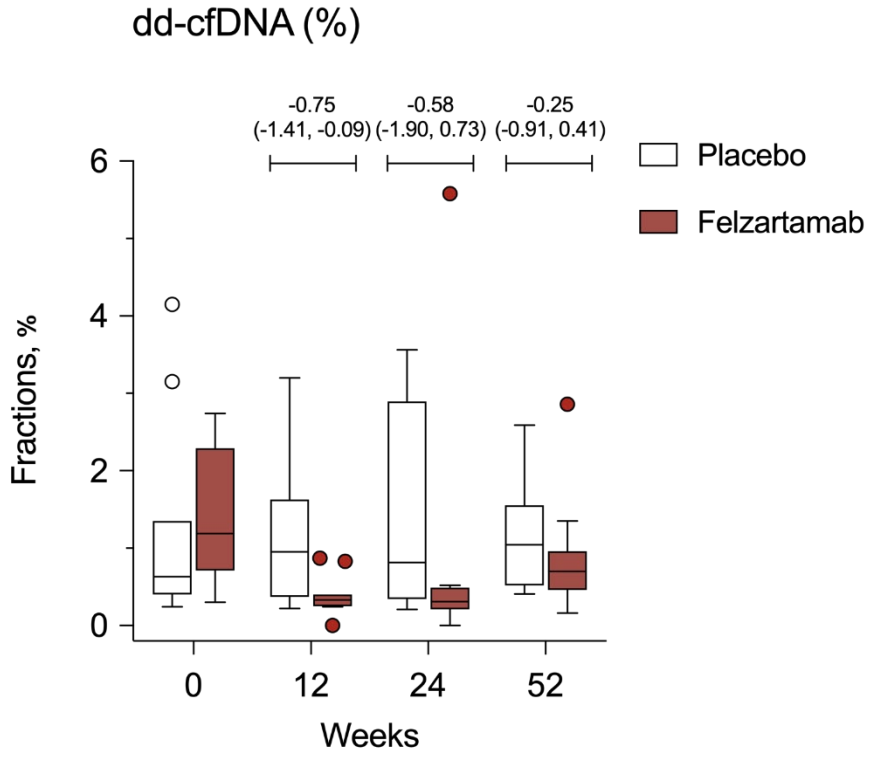
Reduction in Molecular AMR and Injury

MMDx® Molecular AMR classifier (AMR_{Prob})



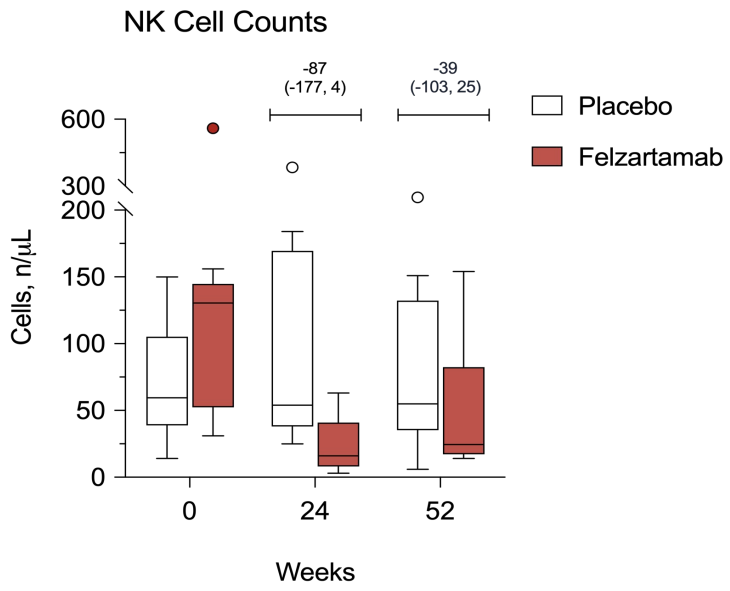
No molecular features of TCMR

Injury biomarker

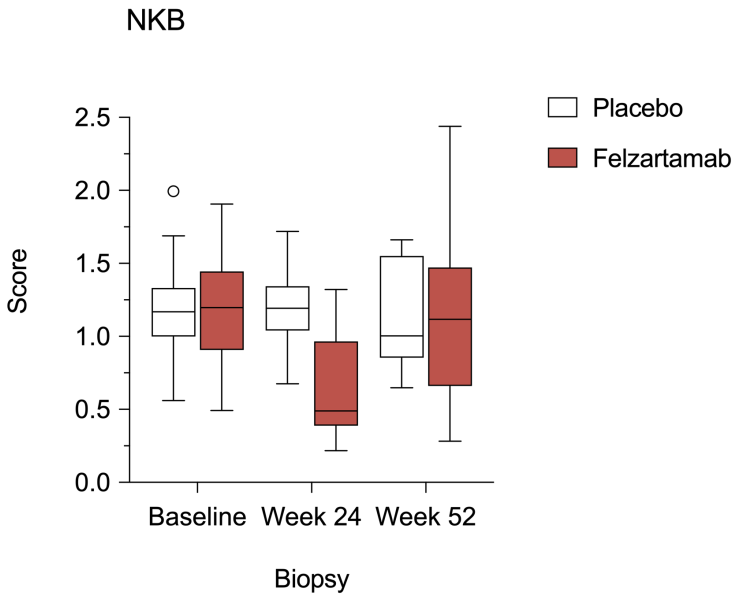


Effect on NK cells and DSA

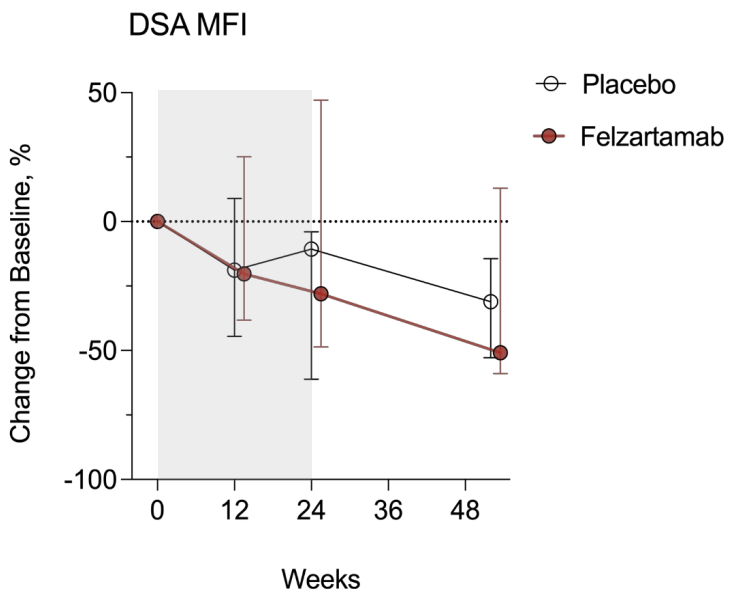
Peripheral NK Cell Counts



MMDx® Molecular NK Cell Burden



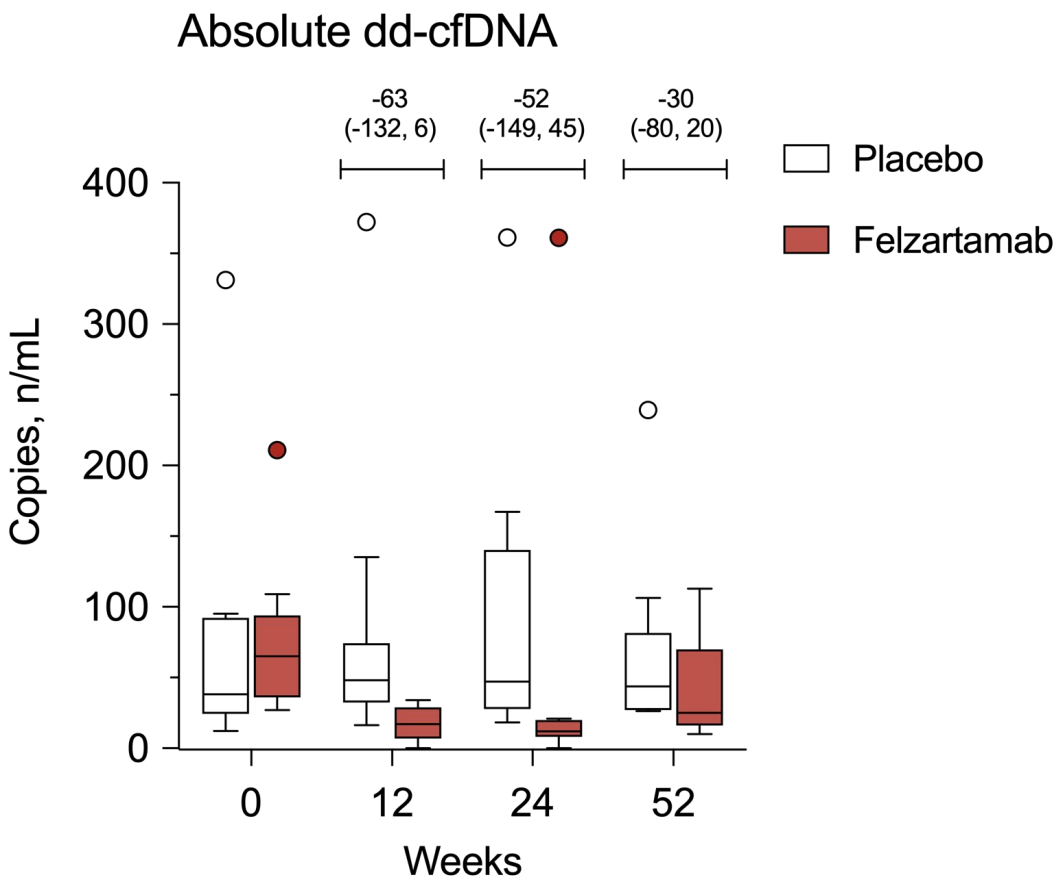
Immunodominant DSA levels



Rapid normalization of dd-cfDNA levels

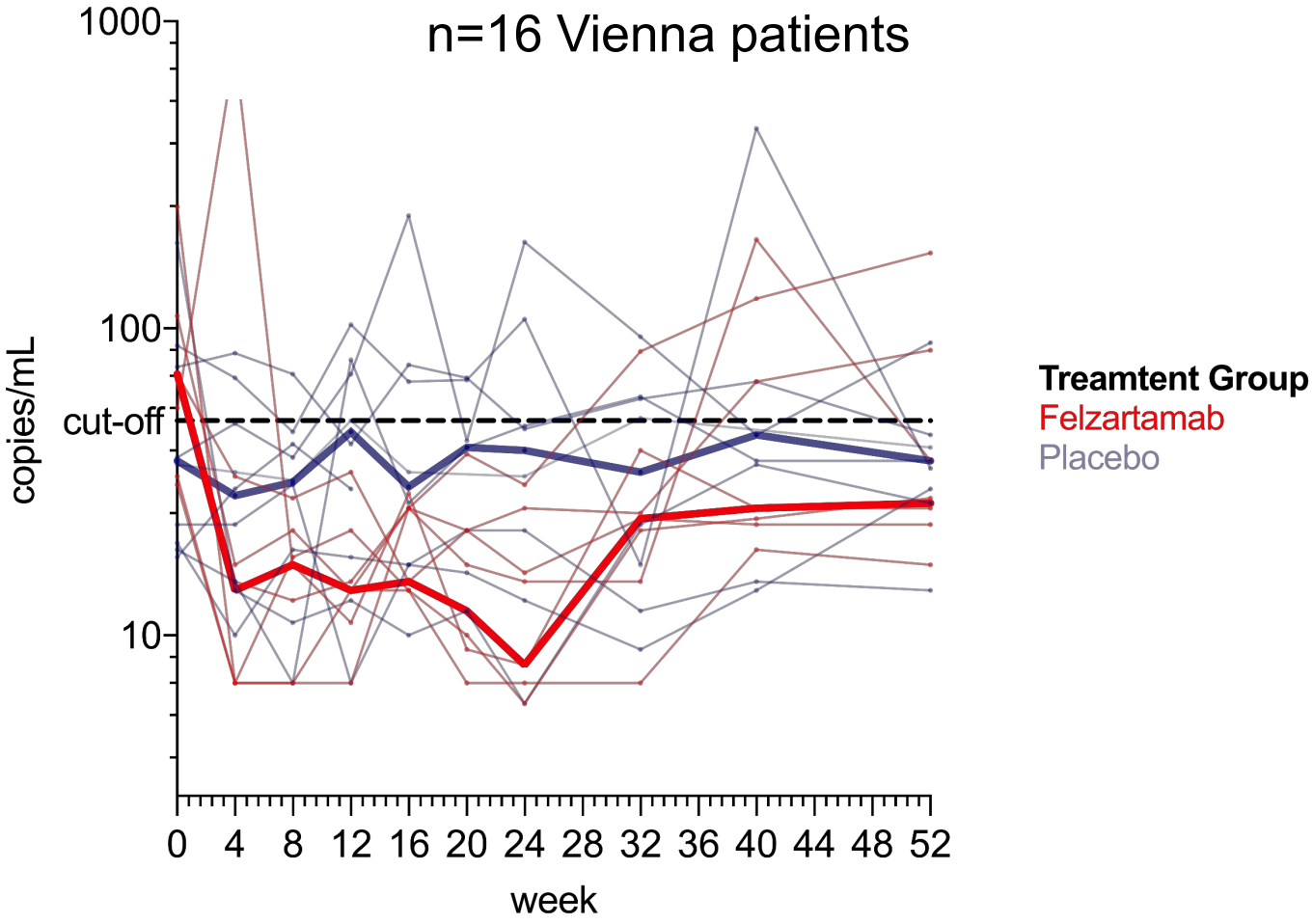
Injury biomarker: dd-cfDNA

n=22 patients



Additional timepoints:

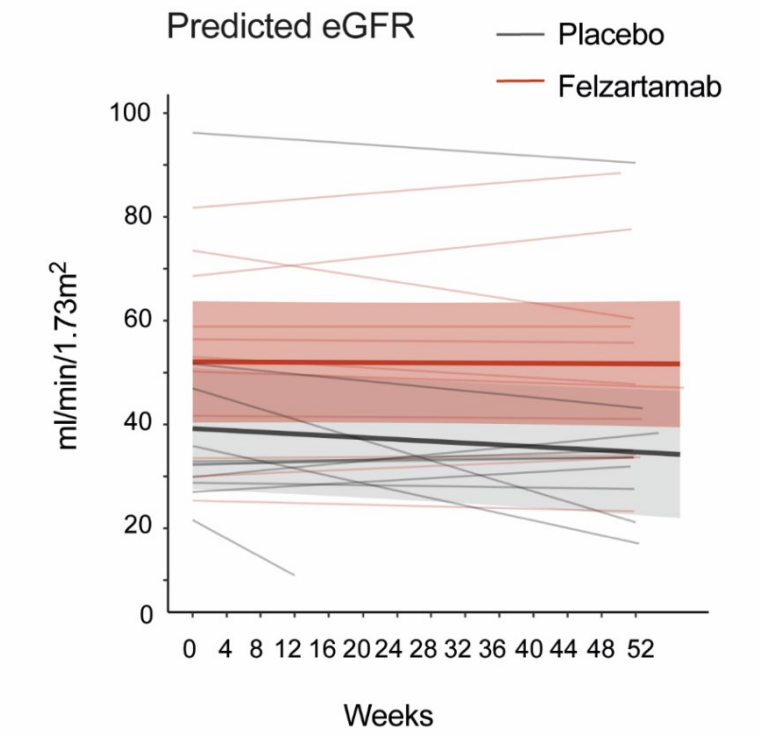
n=16 Vienna patients



Schatzl et al., *in preparation*

Kidney Function and Proteinuria

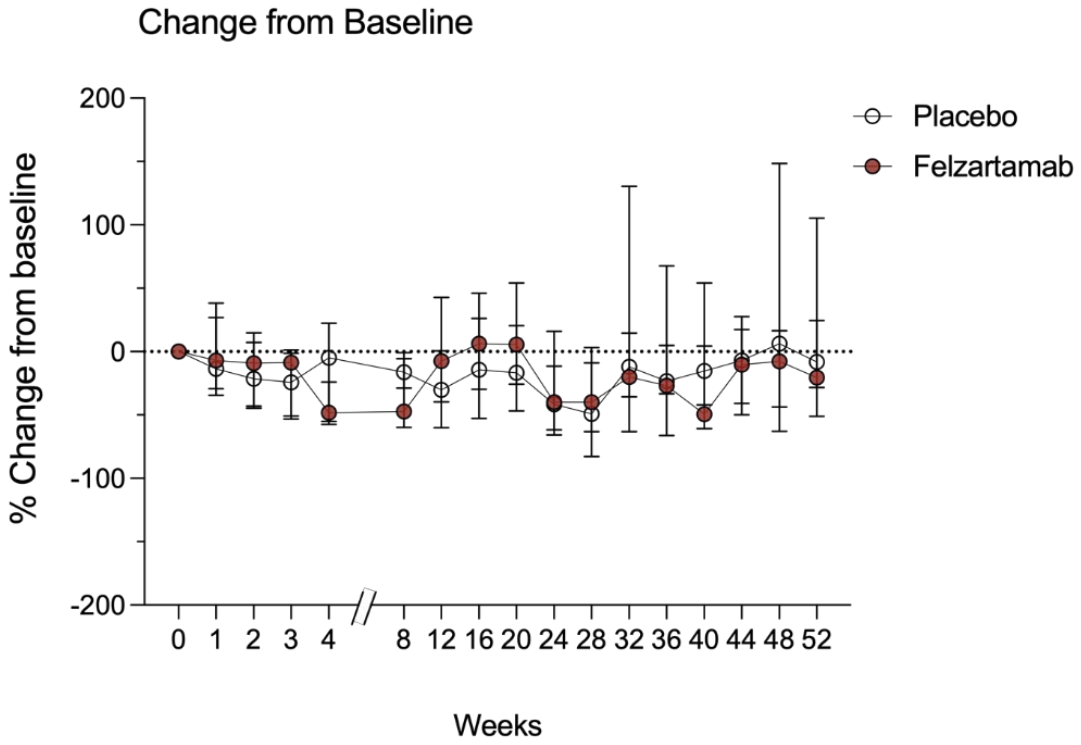
eGFR slope



Felzartamab: −0.39 mL/min/1.73 m² per year
(95% CI: −5.47, 4.69)

Placebo: −4.53 mL/min/1.73 m² per year
(95% CI: −9.83, 0.77)

Urinary Protein-Creatinine Ratio



No difference between groups

Mayer et al., N Engl J Med, 2024; 391(2):122-132

Felzartamab Treatment Effect: iBox Score

Lombardi et al., *in revision*

iBox

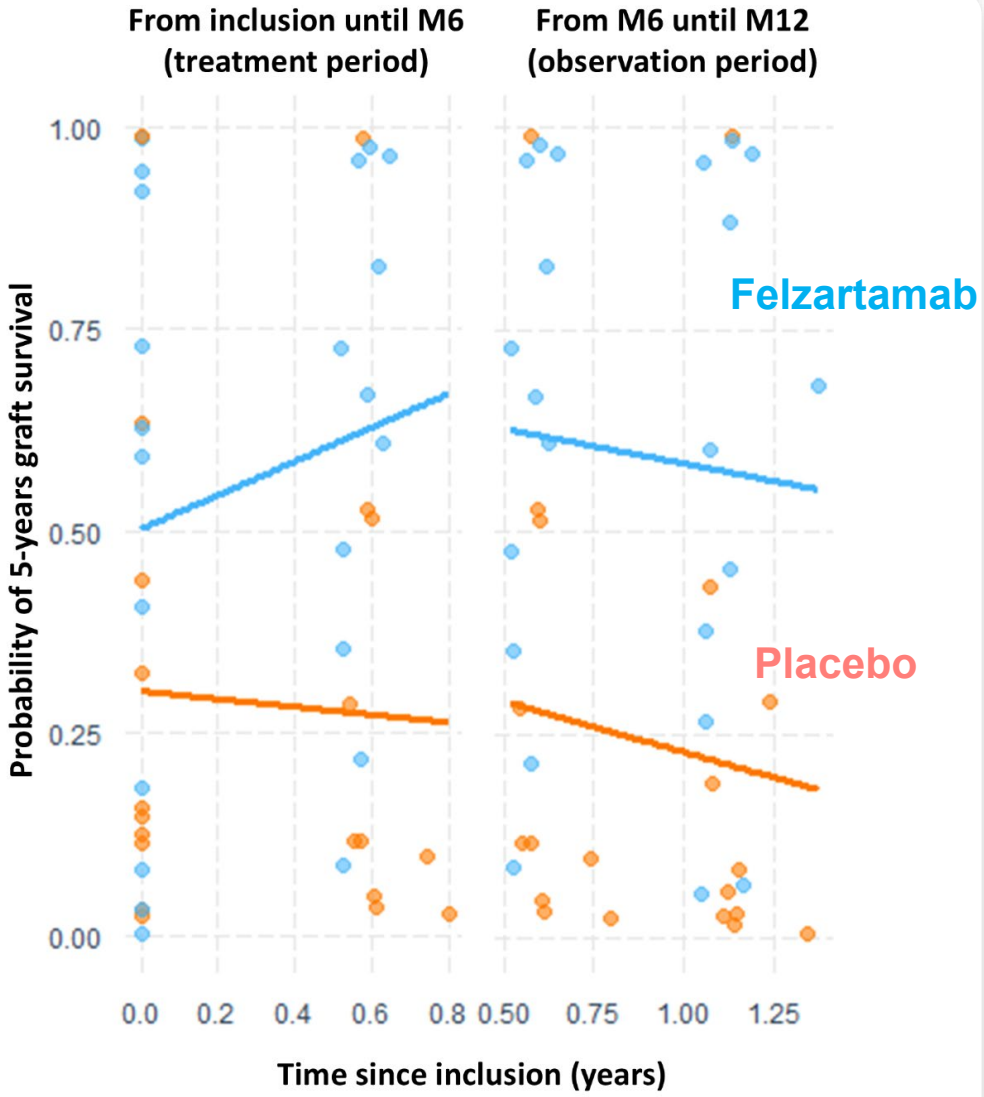
Algorithm for predicting the risk of kidney transplant loss[1]:

Time after transplantation
eGFR (ml/min/1.73 m²)
Proteinuria (mg/g)
Anti-HLA DSA MFI
Histology: *g, ptc, i, t cg*

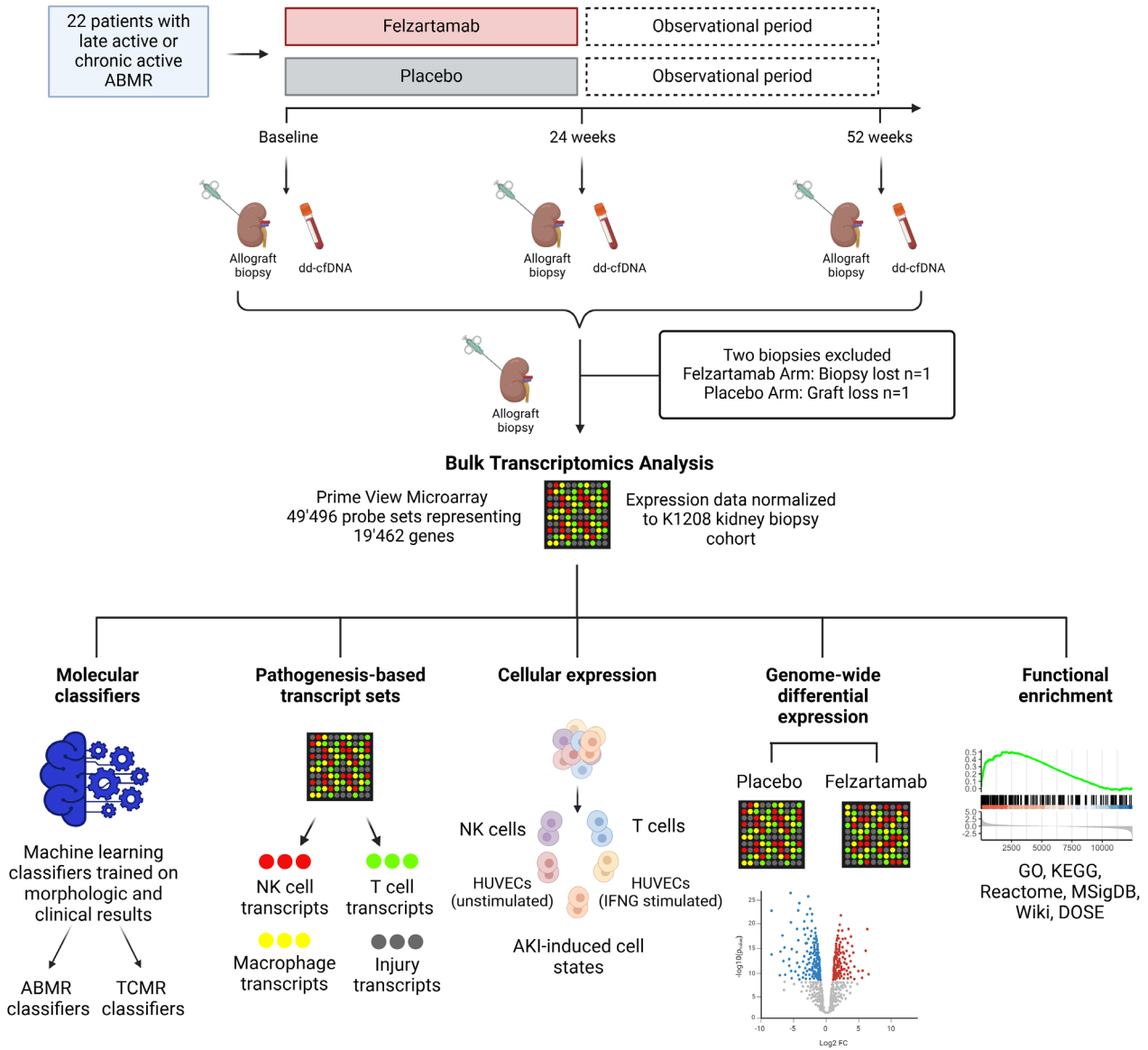
→ **Probability of 5-year graft survival:**

- Slope: Baseline to Month 6 = treatment effect
- Slope: Month 6 to Month 12 = off treatment

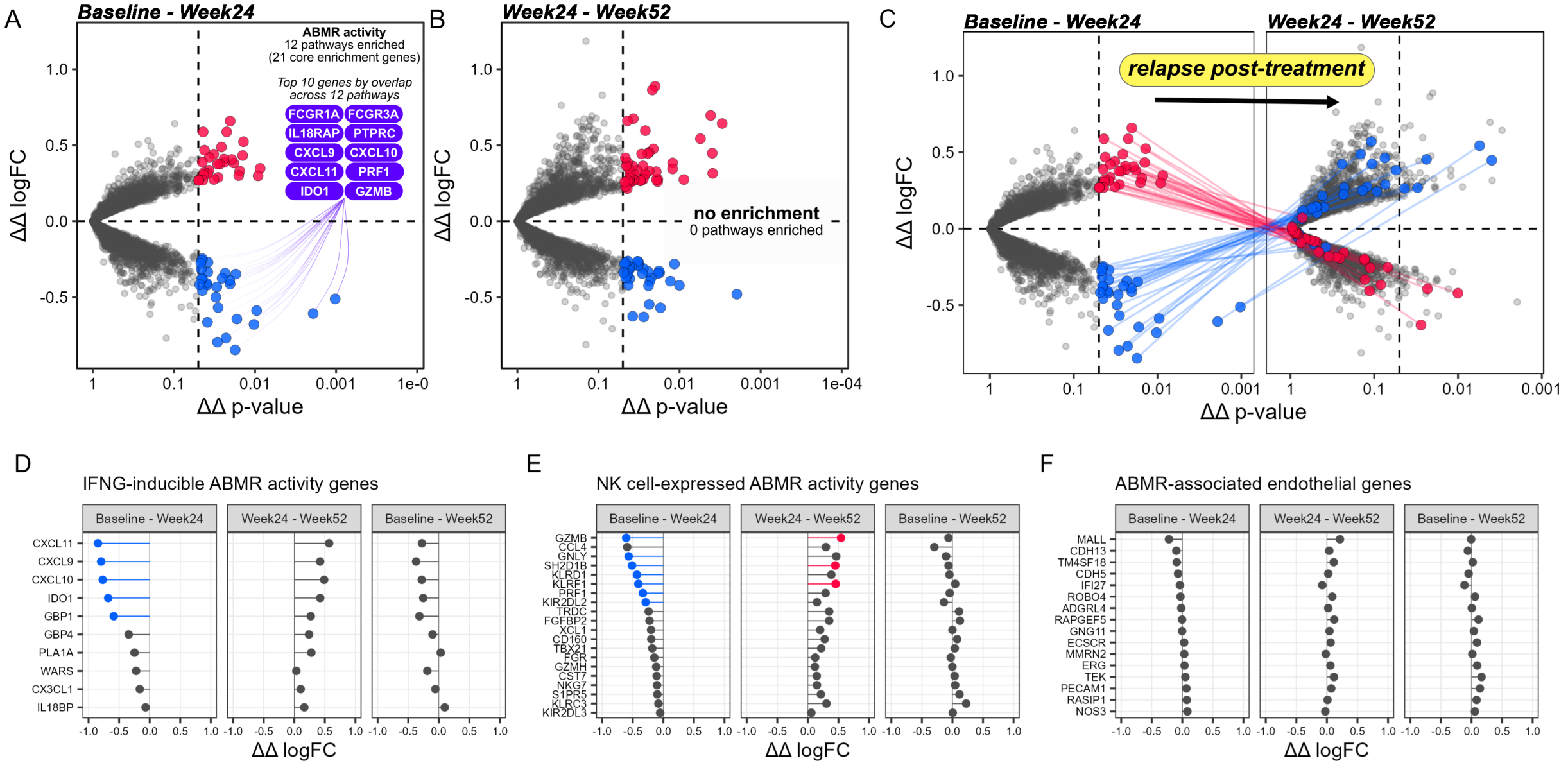
[1]Loupy at et al., *BMJ 2019*



Felzartamab - Transcriptomics



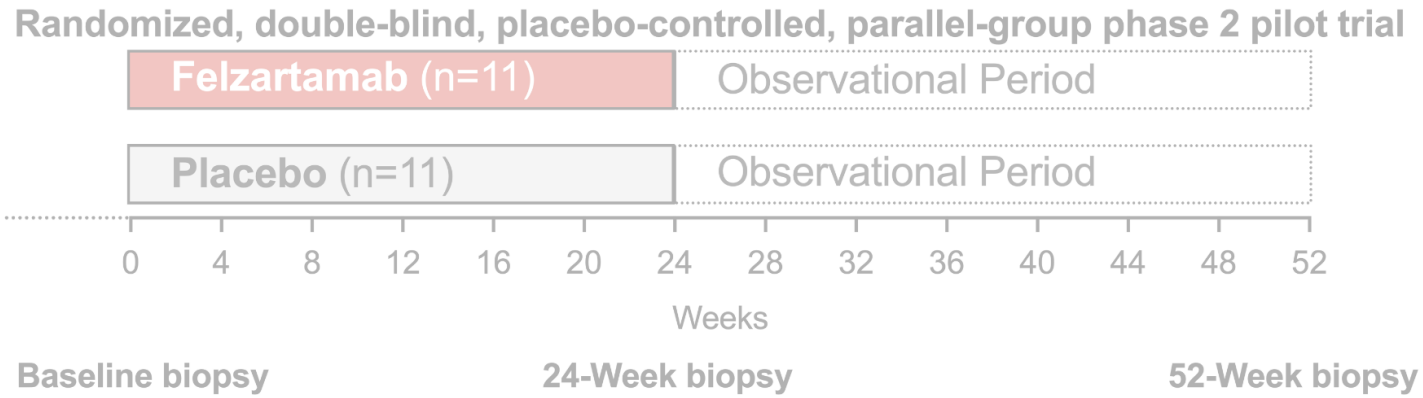
Diebold et al., Nature Med, accepted



Diebold et al., Nature Med, accepted

Trial Extension

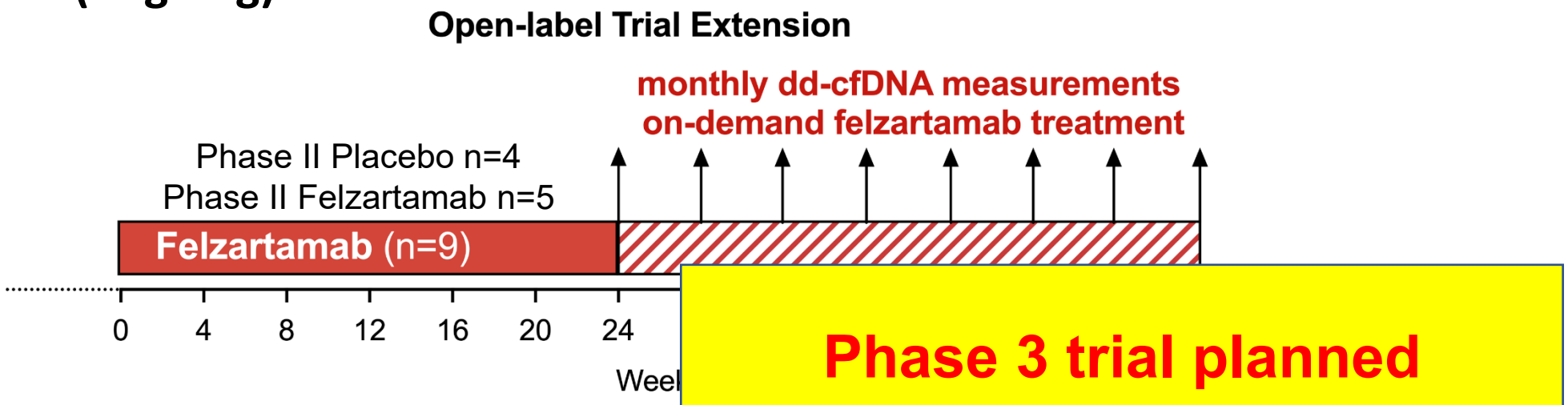
Original Trial



AMR activity after phase 2
Placebo n=8
Felzartamab n=5

Phase 2 Trial Extension (ongoing)

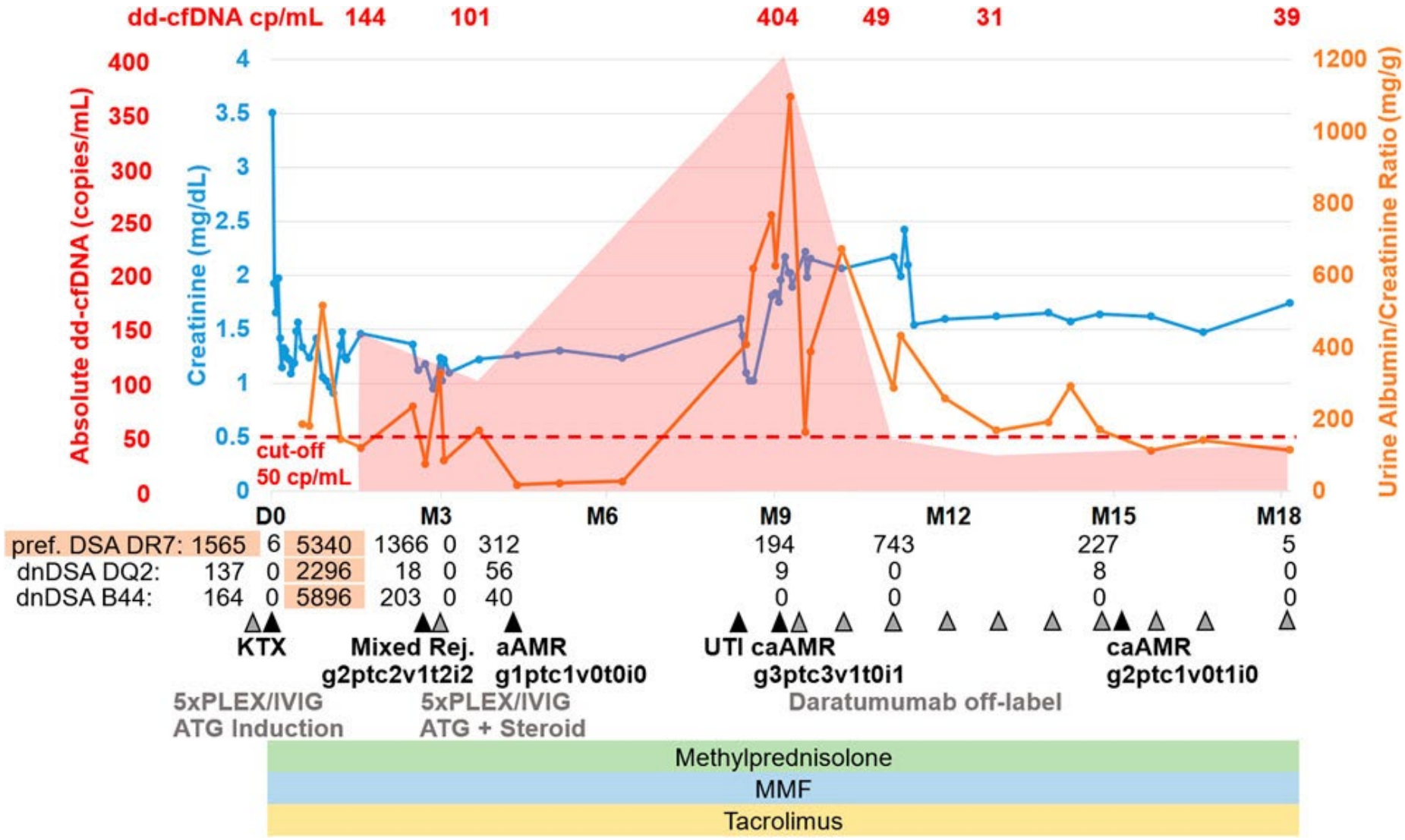
AMR activity after phase 2



Targeting CD38 in AMR – Case reports/series

Author, year	Treatment schedule	Patients	Patients, Results
Kwun et al., 2019	Daratumumab (IV) + Eculizumab 8 infusions; 12 infusions after AMR recurrence	N=1	• Late, DSA+ AMR after combined KTK+HTX • AMR resolution (prolongation of therapy after AMR recurrence) • DSA-MFI reduction
Spica et al., 2019	Daratumumab (IV) 6 infusions	N=1	• Early AMR (7 days) after ABOi Tx • AMR resolution • ABO Ab reduction
Doberer et al., 2021	Daratumumab (IV) 9 months	N=1	• Late, DSA+ AMR • Resolution of AMR activity (morphology/MMDx) • Depletion of PC and NK cells • DSA-MFI reduction • Sublinical BL lesion (t3; no molecular TCMR)
Süsal et al., 2023	Daratumumab (SC) + BG-specific IA 4 doses	N=1	• Early, DSA+/ABO Ab+ AMR (5 days after ABO+HLAi Tx) • AMR resolution • ABO and HLA Ab reduction
Zhu et al., 2023	Daratumumab (IV) / + PP/IVIG >1 year	N=2	• Late AMR • Decrease in AMR activity (morphology) • DSA-MFI reduction • TCMR (+AMR recurrence) in one patient
Lemal et al., 2024	Daratumumab (IV) Single dose	N=3	• Active AMR • AMR resolution • DSA-MFI decline to negative; FCXM conversion
Vicklicky et al., 2024	Daratumumab (SC) 6 months	N=1	• Early, DSA+ AMR • AMR resolution (morphology/MMDx) • DSA-MFI decline to negative • dd-cfDNA reduction
Osmanodja et al., 2024	Daratumumab (IV) 9 months	N=2	• Early/late DSA+ AMR • Resolution of AMR acivity • Depletion of NK cells • DSA-MFI reduction • dd-cfDNA reduction

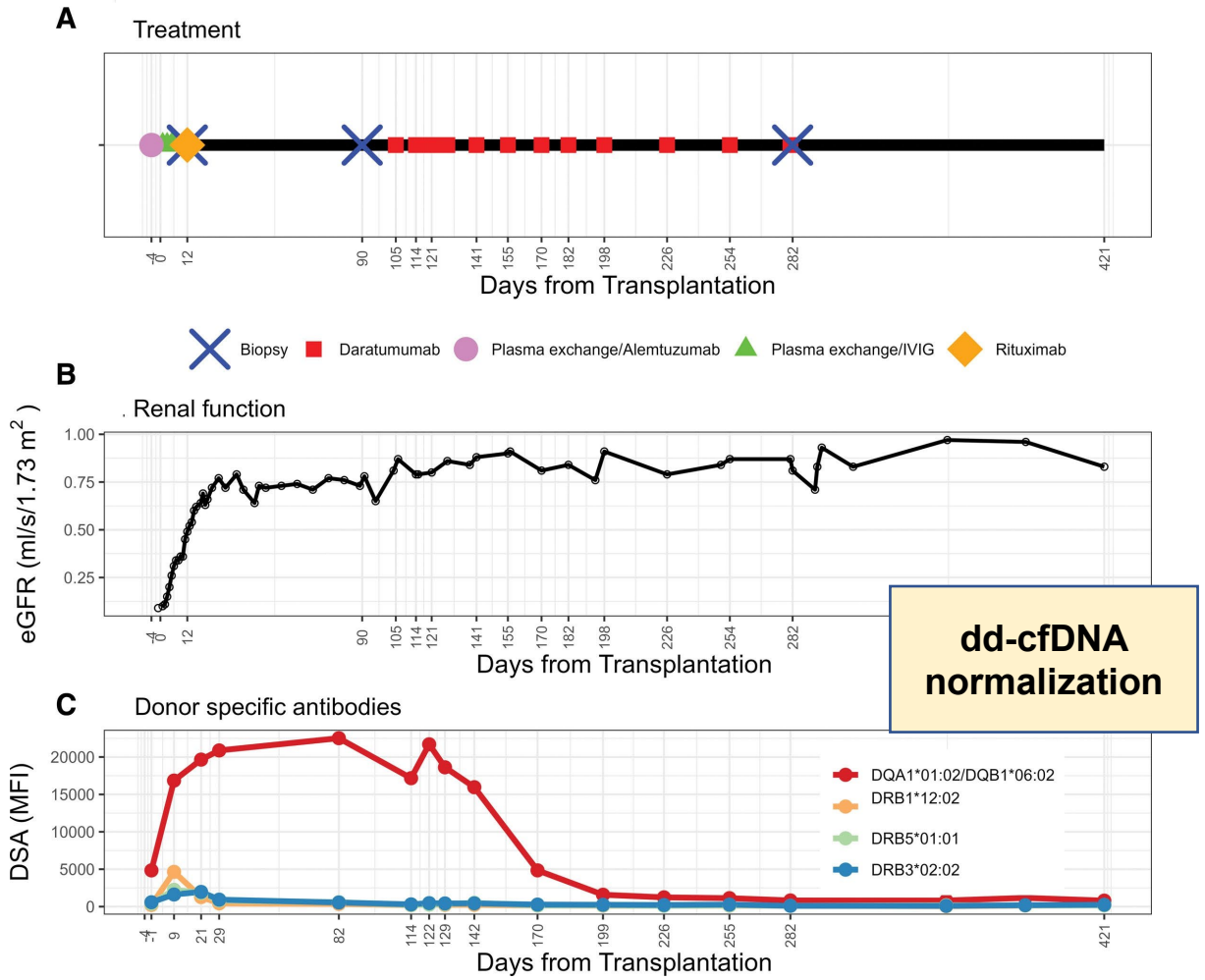
Targeting CD38 in refractory AMR after desensitization – Leipzig/Berlin Case 1



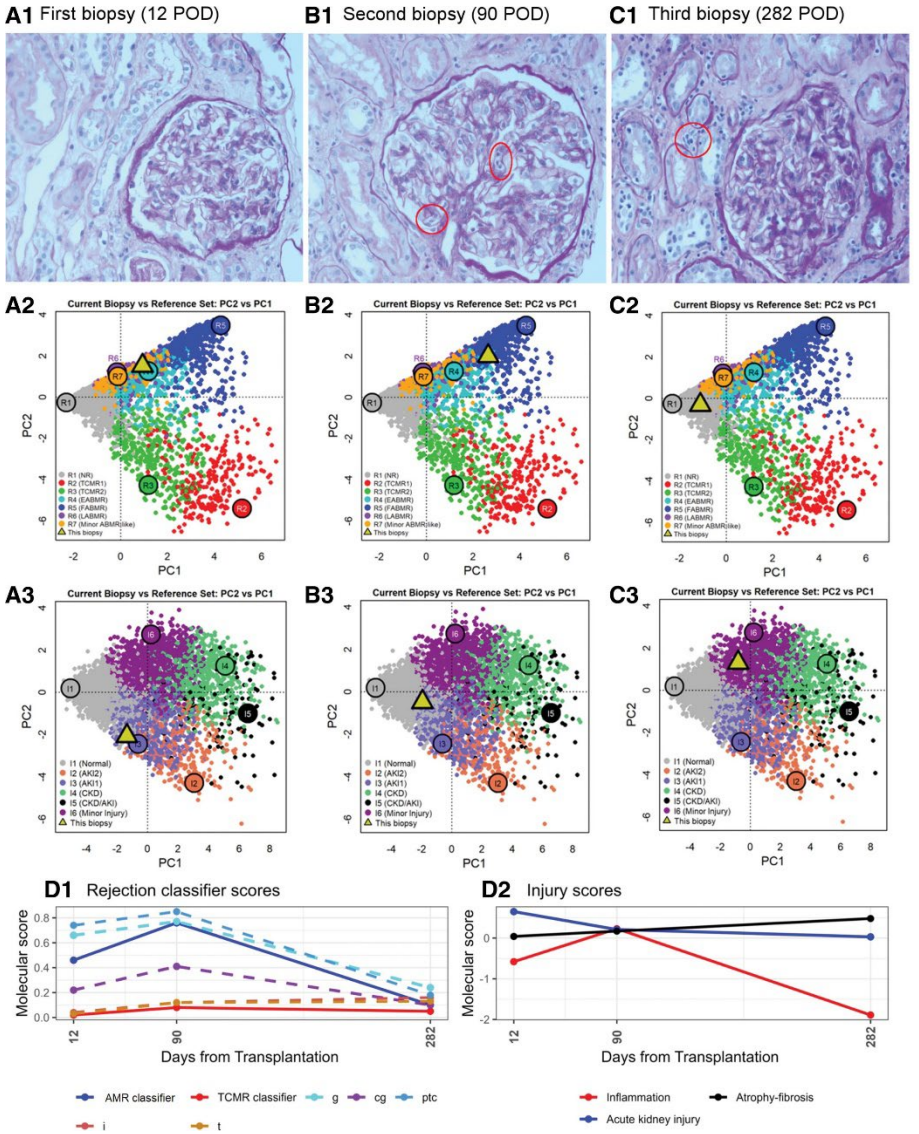
Osmanodja et al, Transplant Int 2024, in press

Targeting CD38 in refractory AMR after desensitization – Prague Case

- **4th KTX, 91% cPRA + HLA class II DSA (MFI 4200)**
- **Desensitization with PP+IVIG (+RTX)/alemtuzumab**



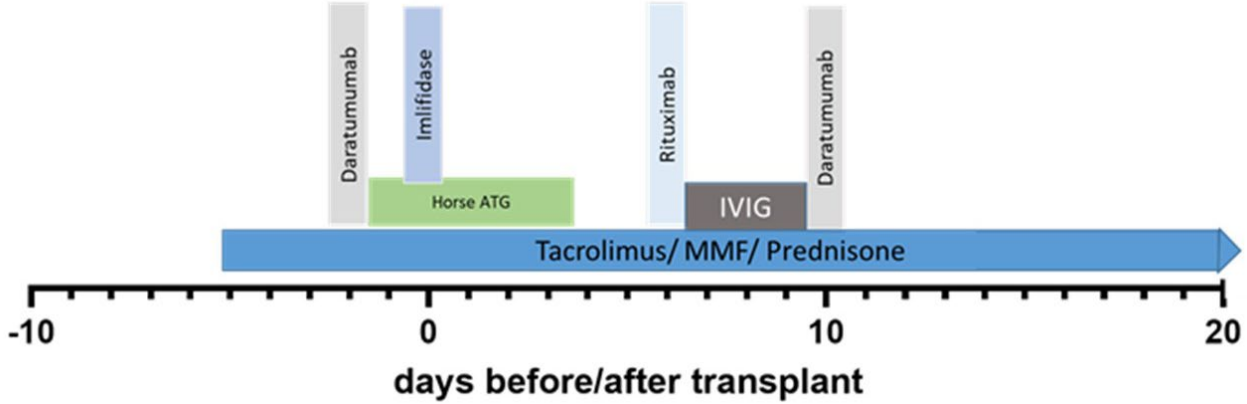
dd-cfDNA normalization

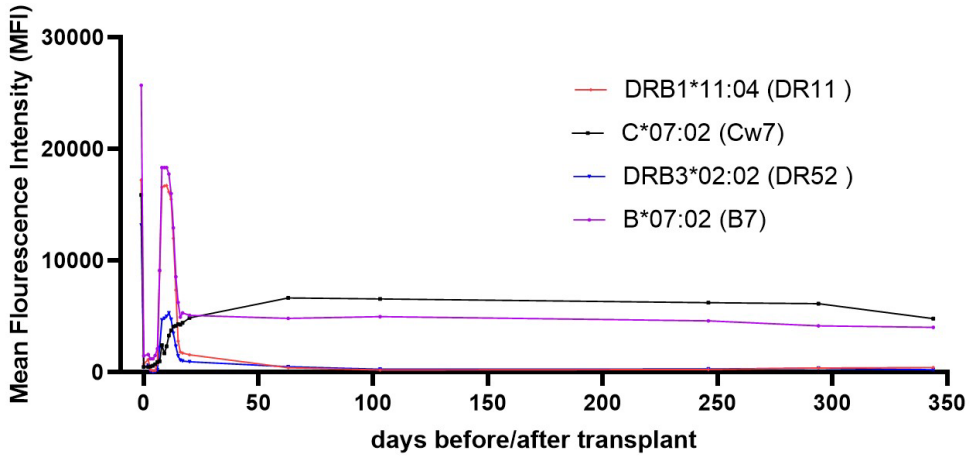


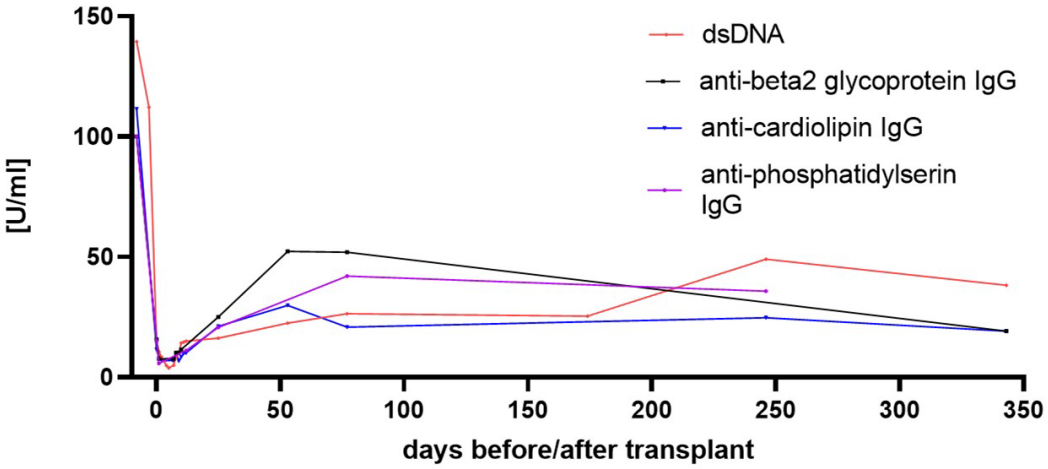
Viklicky et al, Transplant Direct 2024; 10(8):p e1685

Combined desensitization with imlifidase plus daratumumab?

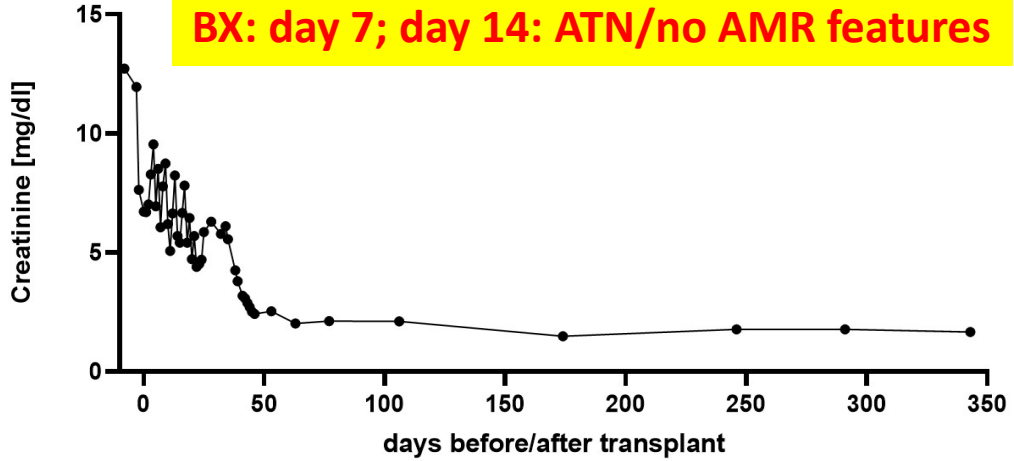
- 35-year-old female patient with SLE and antiphospholipid syndrome
- Previous graft loss due to renal vein thrombosis)
- ABO/HLAi LD-TX; positive T- and B-cell CDC-XM







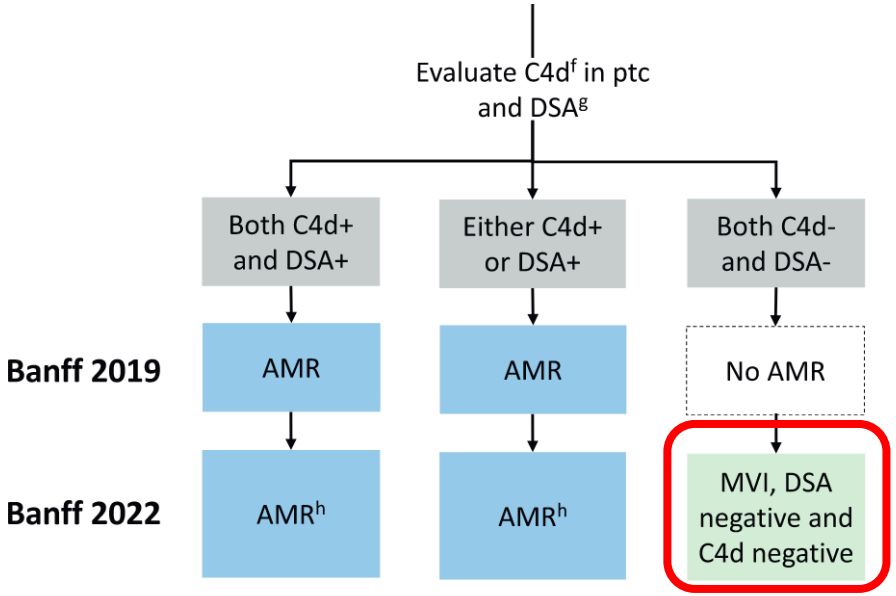
BX: day 7; day 14: ATN/no AMR features



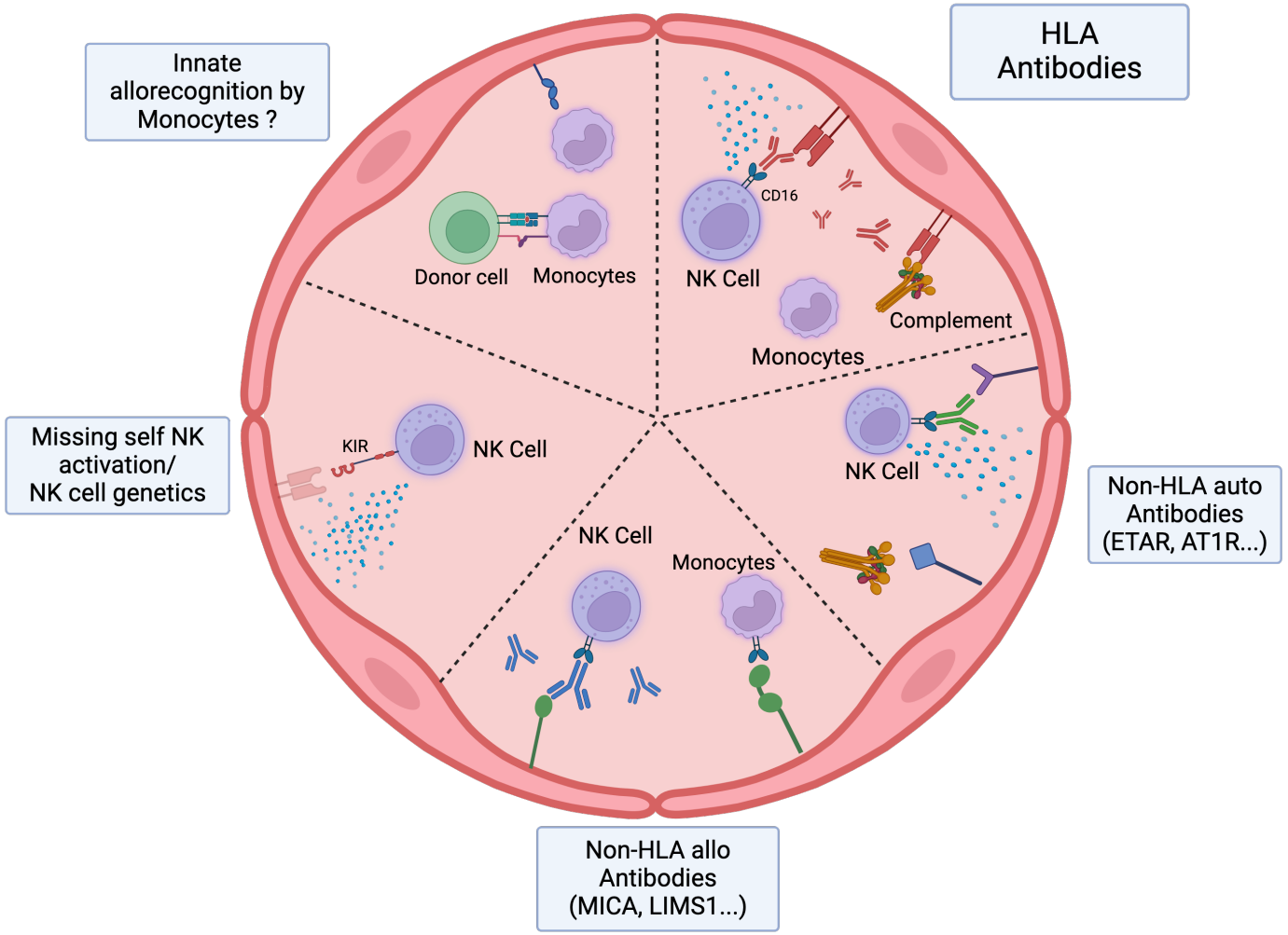
Schrezenmeier et al, Transfus Med Hemother 2024; 51(3):158-163

Pathogenesis of MVI? (DSA+ vs DSA- MVI?)

40-50% MVI cases without HLA-DSA



Naesens et al, Am J Transplant 2024; 24:338



HLA DSA-negative MVI(+v) in three 2024 Vienna Cases – Response to CD38 mAb

Variables	Case 1 (2024)	Case 2 (2024)	Case 3 (2024)
Tx Type; Date	DD Tx; February 2024	DCD Tx; April 2024	ABOi LD Tx; June 2026
Tx Number	Second Tx	First Tx	First Tx
Timing	Early	Early (after 2 months)	Early (Index Bx after 3 days)
Immunosuppression	IL-2R/Tac/MMF/Pred	IL-2R/Tac/MMF/Pred	IAS/IL-2R/Tac/MMF/Pred
Graft function	DGF	SCr 1.3 mg/dL; PCR 1000 mg/g	Dialysis dependency
HLA-DSA	none	none	none
Other	none	none	Anti-B 1:8 (no increase)
MVI	g+ptc score = 6	g+ptc score = 4	g+ptc score = 4
C4d staining	negative	Positive (score = 3)	Positive (score = 3)
Intimal arteritis	v score = 2	v score = 1	v score = 1
TCMR/BL	No tubulo-interstitial rejection	No tubulo-interstitial rejection	No tubulo-interstitial rejection
MMDx	Index Bx: no MMDx	Index Bx: no MMDx	Index Bx: ABMR score 0.43; under PP increase to 0.82
Treatment	Immunoadsorption Daratumumab (3 mo)	Immunoadsorption Daratumumab (3 mo)	Steroids; Plasmapheresis Daratumumab (3 mo)
Response	▼▼ histologic/molecular AMR	▼▼ histologic/molecular AMR	▼▼ histologic/molecular AMR

Unpublished data

Summary & Conclusions

ABMR is associated with adverse graft survival

NK cell play a critical role as effector cells (and treatment target?)

There may be a contribution of DSA-dependent/-independent activation

Several systematic trials have revealed negative results (RCTs: BORTEJECT, TRITON, IMAGINE)

New concepts should be tested in well designed RCTs (e.g. IMAGINE)

Surrogate endpoints that accurately predict graft failure need to be defined

Targeting CD38 is a promising concept (Felzartamab Ph2 trial)

Department of Medicine III
Matthias Diebold
Konstantin Doberer
Farsad Eskandary
Susanne Haindl
Katharina Mayer
Martina Schatzl
Georg A. Böhmig

Department of Pathology
Heinz Regele
Nicolas Kozakowski
Johannes Kläger

Institute of Virology
Hannes Vietzen
Elisabeth Puchhammer-Stöckl

Department of Clinical Pharmacology
Bernd Jilma
Sabine Schranz

Eva Schrezenmeier
Aylin Akifova
Klemens Budde

University of Alberta

Patrick Gauthier
Jeff Reeve
Phil Halloran

University of Basel

Matthias Diebold

Uptal Patel
Donna Flecher
Houston Gilbert