
# Humorale Abstoßung abgeschafft??

## Nephropathologische und molekulare Ergebnisse von Felzartamab

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# Disclosures

I have received research funds and/or honoraria from:

Aicuris, Alexion, Astellas, AstraZeneca, Biohope, Carealytics, CareDx, Chiesi, CSL Behring, DTB GmbH, Eledon, HiBio, MSD, Natera, Neovii, Oncocyte, Oska, Otsuka, Paladin, Pfizer, Pirche, Sanofi, smart care solutions, Stada, Takeda, Veloxis, Vifor and Xenothera

# Antibody-Mediated Kidney Tx Rejection (AMR)

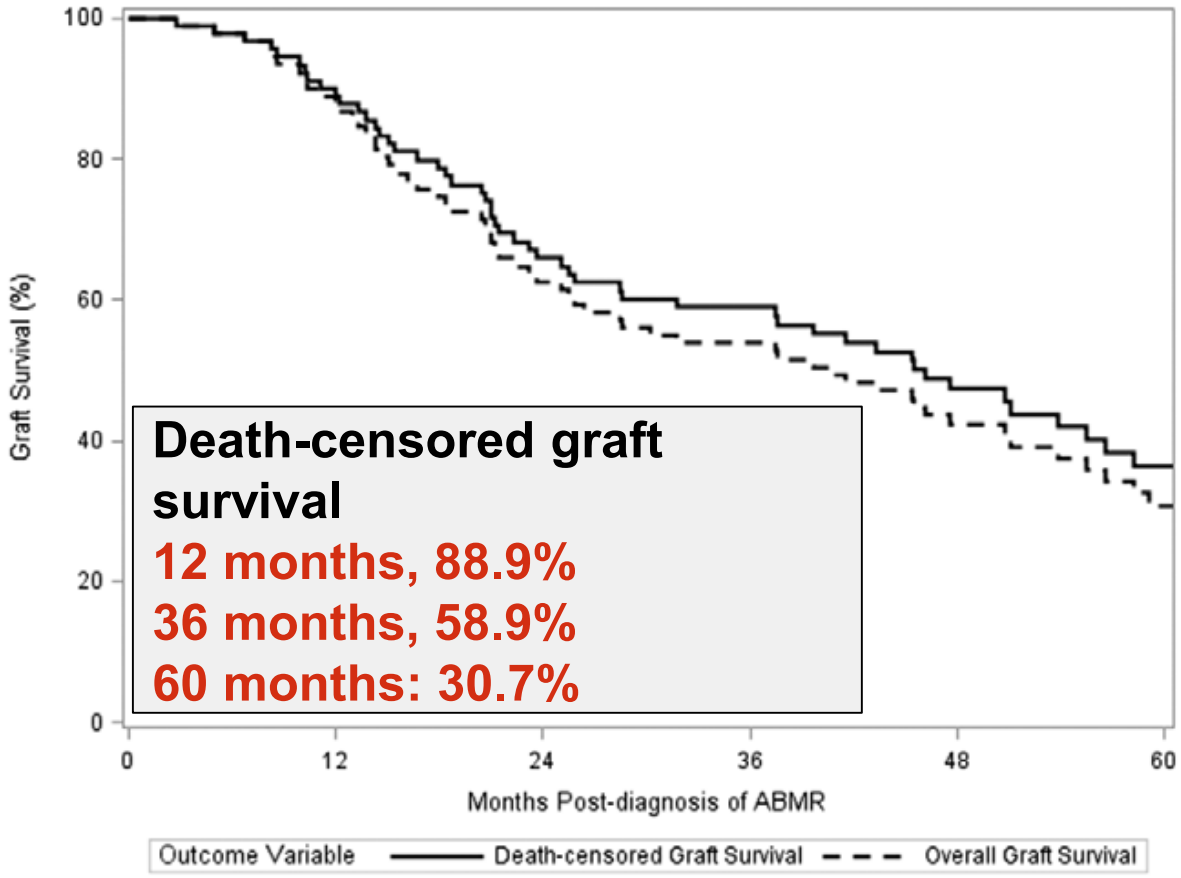
- Diagnosis according to Banff classification[1]
- ≈6% incidence of AMR at 5 years[2]
- Long-term outcomes after diagnosis are poor[3,4]
- Late AMR is the leading cause of late graft loss[3]
- 4 x higher costs[6]
- Risk factors[2,4,5]:

  mismatched donor, TCMR

  underimmunosuppression,

  **non adherence….**

**Late active AMR & Allograft survival[2]**





1) Naesens M et al, AJT 2022
2) Hart A, Singh D et al Clin Transplant 2021
3) Mayrdorfer et al., JASN 2021
4) Irish et al., Transplantation. 2021
5) Hart A. Schladt DP
6) Hart A, ZaunD et al J Med Economics 2021

# Meta-Analysis on evidence for treatment of ABMR in 2018 just n=21 controlled trials!!

**TABLE 1.** Therapeutic agents used against DSAs in the treatment of antibody-mediated rejection and the evidence supporting their role

| Therapy | Action | Evidence supporting the treatment[a] |
|---|---|---|
| Plasmapheresis (PP)[b] | Decrease the titer and block the effect of DSA | Low, benefit not consistently demonstrated |
| Immunoadsorption (column) | Decrease the titer of DSA | Low, seems beneficial |
| IVIG | Decrease the titer and block the effect of DSA | Very low |
| Bortezomib | Decrease production of DSA | Very low |
| Corticosteroids | Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells | Very low |
| Anti-thymocyte preparations | Reduce production of DSA by decreasing Helper T cells, suppression of T cells | Very low |
| Eculizumab | Block complement activation resulting from DSA activation | Very low |
| Mycophenolate | Block the effect and decrease production of DSA, suppression of T cells | Very low |
| Rituximab | Decrease production of DSA | Very low |
| Cyclophosphamide | Decrease production of DSA | Very low |

**Summary: low quality and (very) low evidence**

Wan S. et al. Transplantation 2018; 102(4): 557–568. doi: 10.1097/TP.0000000000002049.
Roberts DM et al., Transplantation 2012; 94(8): 775–83. doi: 10.1097/TP.0b013e31825d1587.

# Recommended Treatment for Antibody-mediated Rejection After Kidney

**…no conclusive evidence to support any specific therapy…**

**…..clinical trials…are urgently needed…**

| Timing | DSA | (Banff 2017) | Standard of care[a] | 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]<br>IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (1C)<br>Corticosteroids (EO) | Complement inhibitors (2B)<br>Rituximab 375 mg/m$^2$ (2B)<br>Splenectomy (3C) |
| Late (>30 days posttransplant) | Preexisting DSA | Active AMR | Plasmapheresis (daily or alternative day × 4–6 based on DSA titer) (2C)[b]<br>IVIG 100 mg/kg after each plasmapheresis treatment or IVIG 2 g/kg at end of plasmapheresis treatments (2C)<br>Corticosteroids (EO) | 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)<br>Evaluate and manage nonadherence | Plasmapheresis and IVIG (3C)<br>Rituximab (3C) |

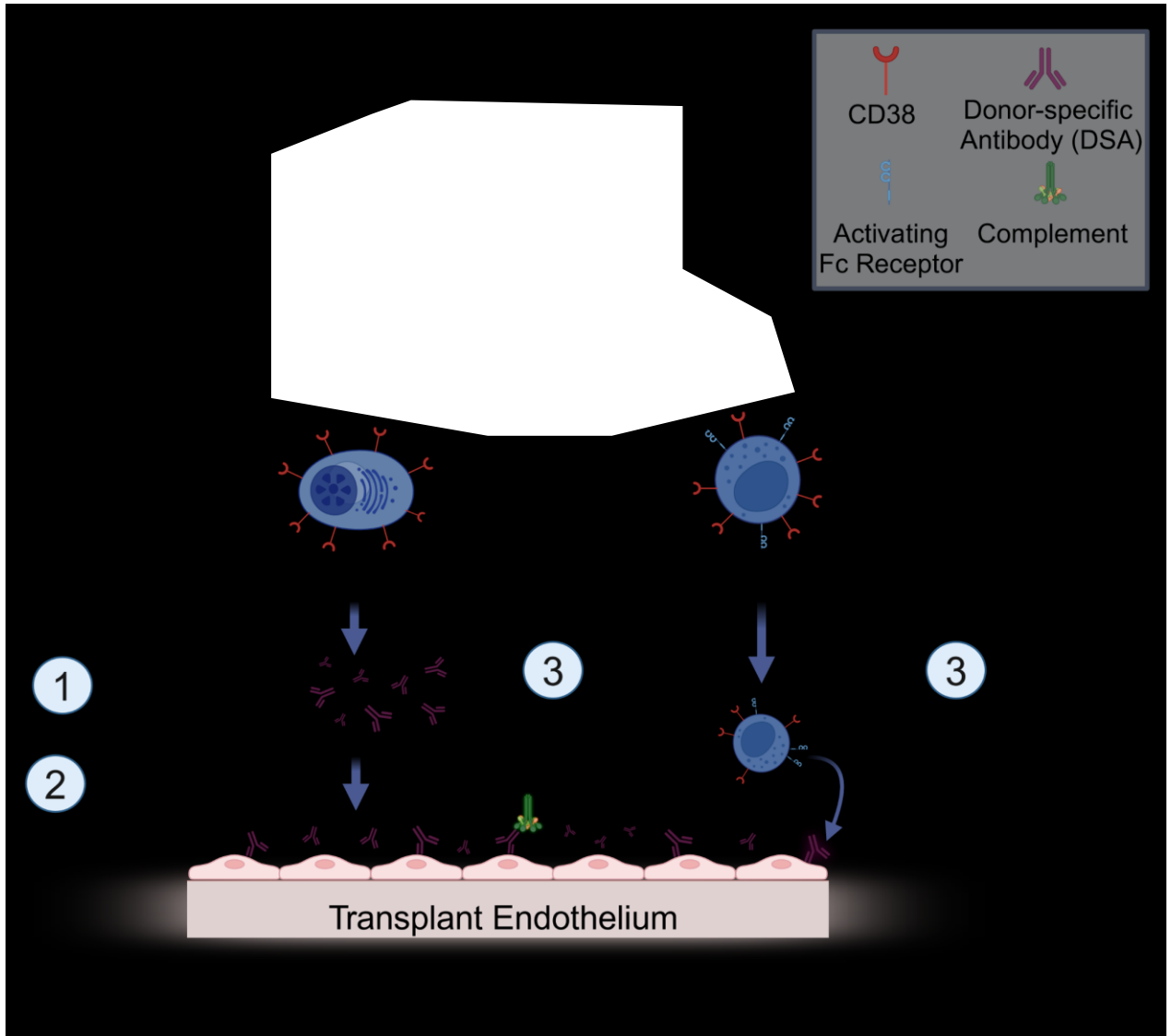
AMR, antibody-mediated rejection; DSA, donor-specific antibody; EO, expert opinion; IVIG, intravenous immune globulins; KDIGO, Kidney Disease: Improving Global Outcomes.

**…an unmet need for treatment of AMR**

Wolters Kluwer TRANSPLANTATION

Schinstock C. A. et al.,Transplantation 104(5): 911–922, May 2020; doi: 10.1097/TP.0000000000003095.

# 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)

# Felzartamab Trial Scheme and Study Flow

Mayer K et al
NEJM 2024

Screening
N=31

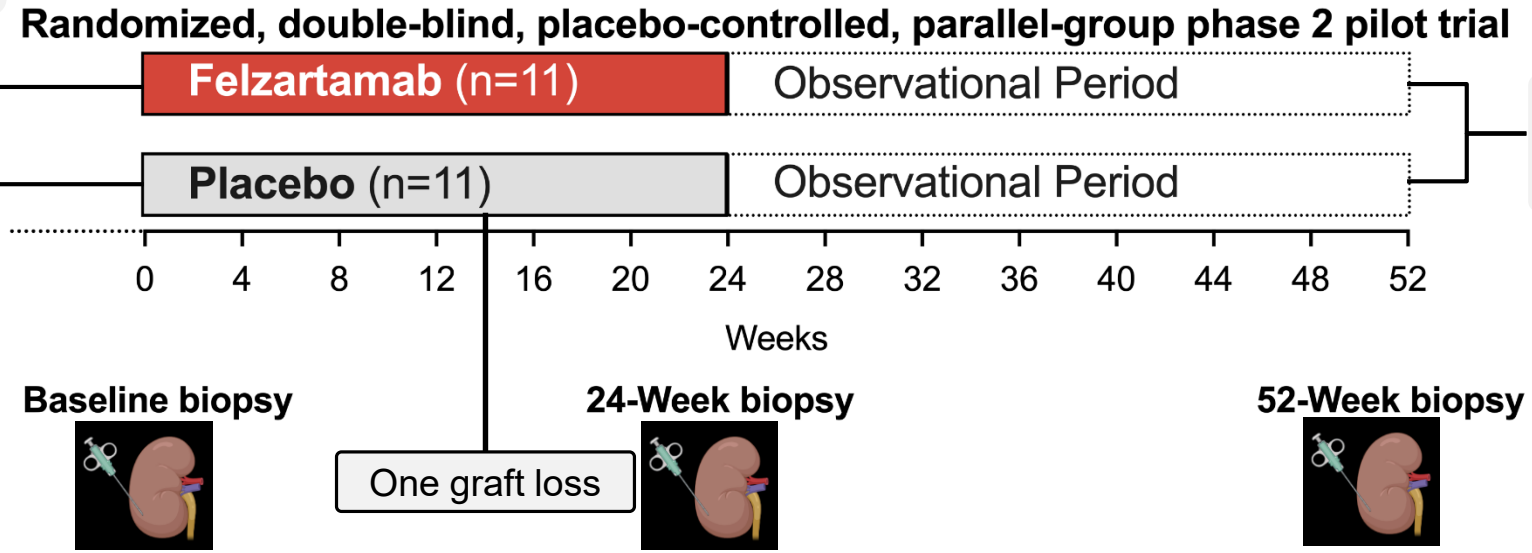
**N=22**
1:1
randomized

**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

AMR, Antibody-mediated rejection; DSA, Donor-specific antibody; dd-cfDNA, Donor-derived cell-free DNA; eGFR, estimated glomerular filtration rate

# Key Patient Characteristics at Baseline

Mayer K et al
NEJM 2024

| | Placebo (N=11) | Felzartamab (N=11) | Total (N=22) |
|---|---|---|---|
| **Female sex** – no. (%) | 7 (63.6) | 4 (36.4) | 11 (50.0) |
| **Median recipient age** (IQR) – yr | 56 (49–64) | 42 (35–50) | 50 (39–59) |
| **Preformed anti-HLA DSA** – no. (%)† | 4 (36.4) | 4 (36.4) | 8 (36.4) |
| **Median time after Tx** (IQR) – yr | 10 (6–19) | 9 (6–14) | 9 (5–18) |
| **Median eGFR** (IQR) – mL/min/1.73 $m^2$ | 36 (31–43) | 60 (35–69) | 37 (33–64) |
| **Median protein/crea ratio** (IQR) – mg/g | 1338 (187–1614) | 690 (232–1248) | 993 (178–1510) |
| **Triple immunosuppression** – no. (%) | 9 (81.8) | 9 (81.8) | 18 (81.8) |
| **Tacrolimus-based** – no. (%) | 8 (72.7) | 10 (90.9) | 18 (81.8) |
| **Banff 2019 AMR phenotypes** – no. (%) | | | |
| **Active AMR** | 3 (27.3) | 4 (36.4) | 7 (31.8) |
| **Chronic active AMR** | 8 (72.7) | 7 (63.6) | 15 (68.2) |
| **DSA characteristics** | | | |
| **Anti-DQ DSA** – no. (%) | 5 (45.5) | 6 (54.5) | 11 (50.0) |
| **Peak MFI of DSA >10,000** – no. (%) | 3 (27.3) | 5 (45.5) | 8 (36.4) |

† Pre-transplant DSA data were available for 14 recipients

# Primary Outcome: Safety of Felzartamab

Mayer K et al
NEJM 2024

| | 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 |

***P=0.001***

**Eight infusion-related reactions: mild to moderate severity**

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

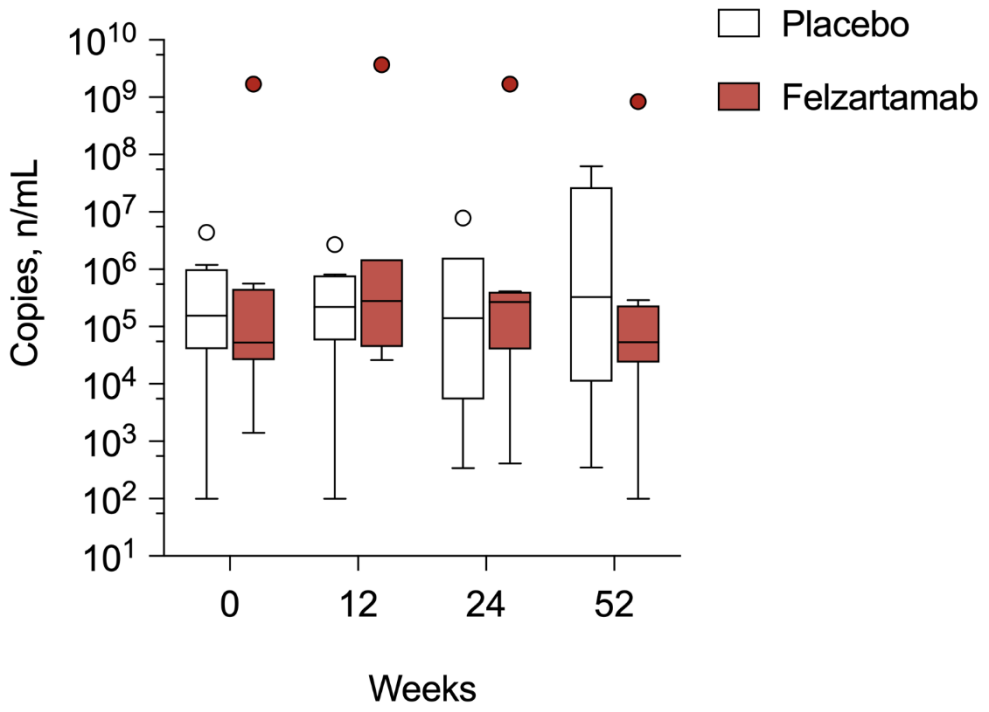
AE, Adverse event; RSV, Respiratory syncytial virus; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event; TRAE, Treatment-related adverse event

# Overall Immunosuppressive Burden

Mayer K et al
NEJM 2024

**No overall increases in infection-related AEs/SAEs**

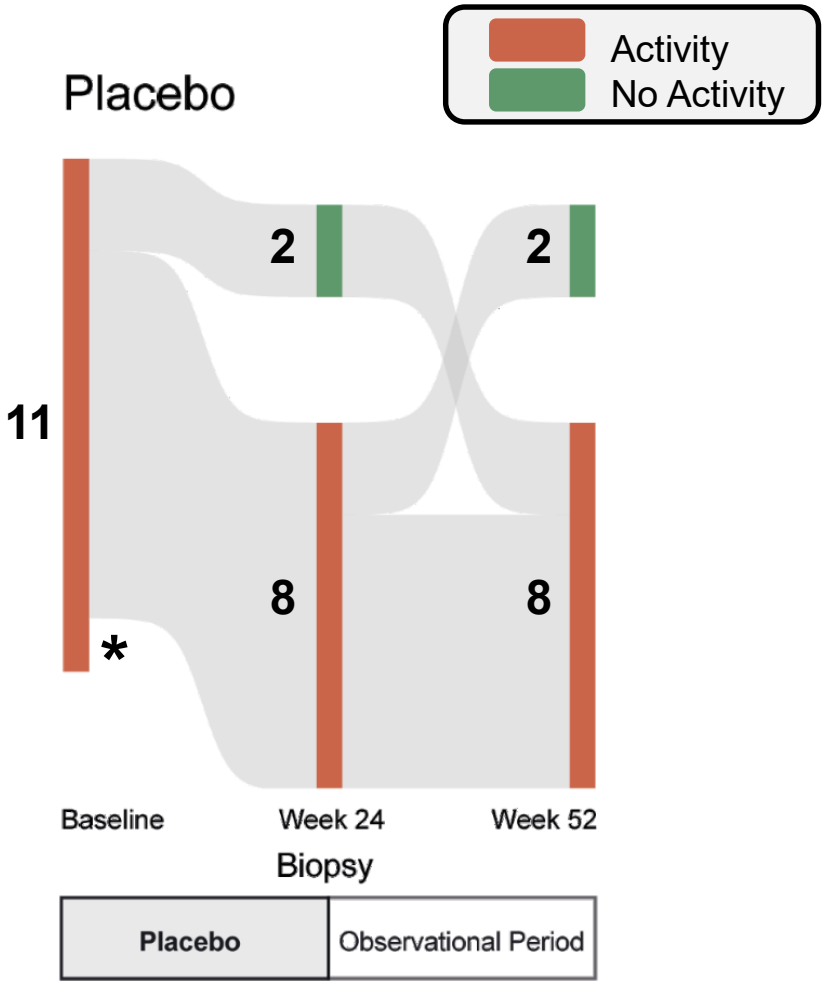
**Torque Teno Virus (TTV) Load**

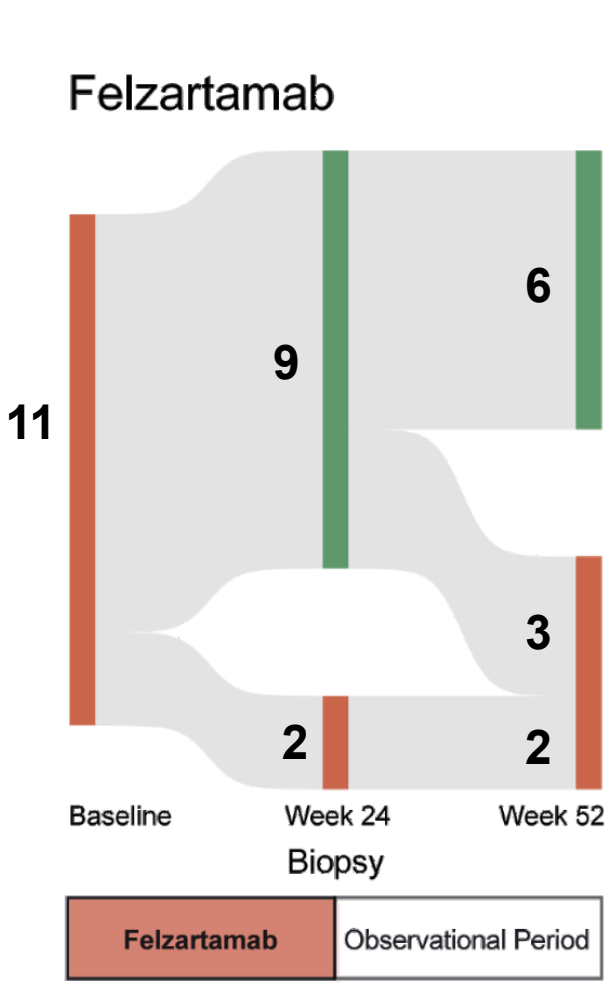



TTV is a non-pathogenic commensal virus and a marker of functional immunity

# Reduction in AMR Activity

Mayer K et al
NEJM 2024




**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%)

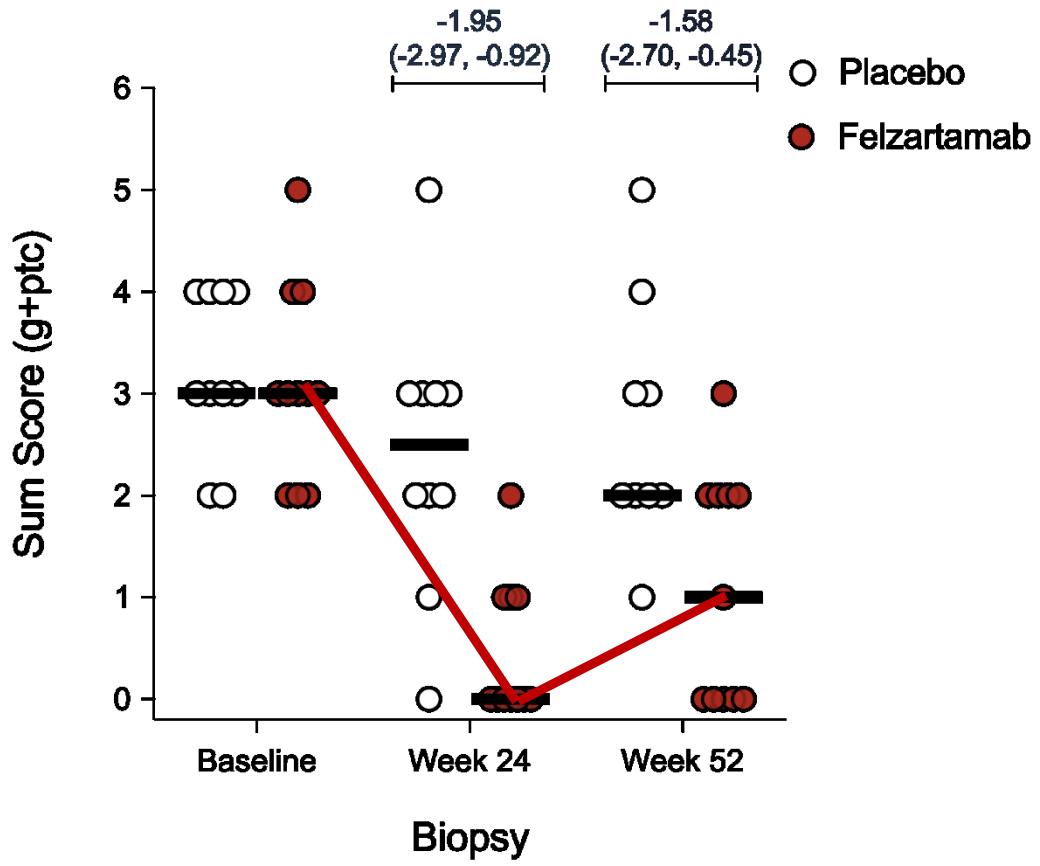
*One patient in the placebo group lost their graft prior to Week 24 due to ongoing chronic active AMR

CI, Confidence interval

# Reduction in Microvascular Inflammation

Mayer K et al
NEJM 2024

## Microvascular Inflammation (MVI)




**MVI score at Week 24:** median (IQR)

**Felzartamab:** 0 (0−1)

**Placebo:** 2.5 (2−3)

**Mean difference between groups: −1.95**
(95% CI: −2.97, −0.92)

**MVI score of 0 at Week 24:**

**Felzartamab:** 7/11 (63.6%)

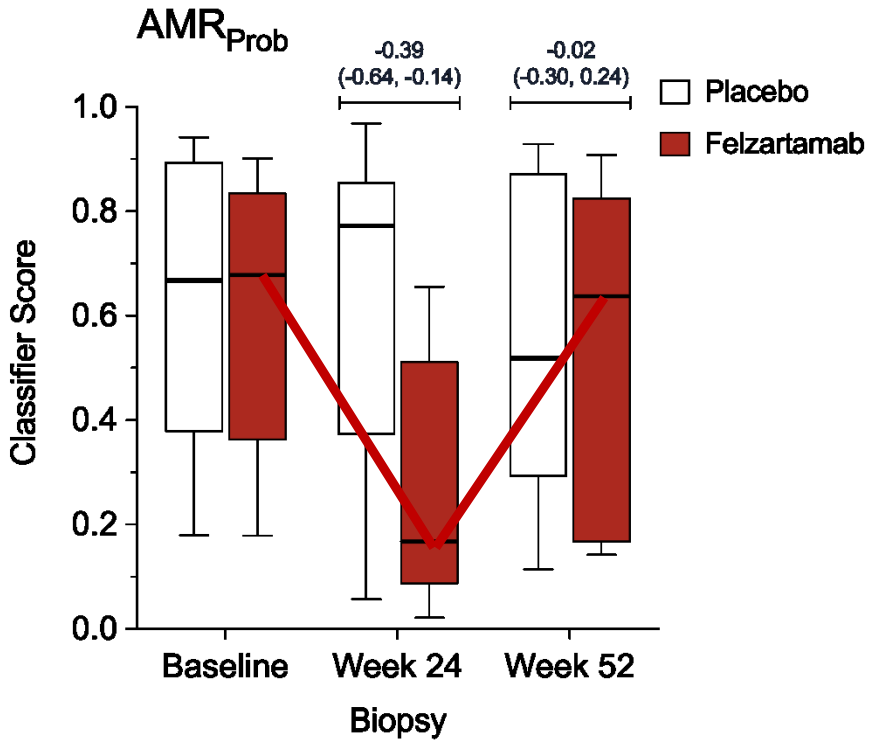
**Placebo:** 1/10 (10%)

CI, Confidence interval

# Reduction in Molecular AMR and Injury

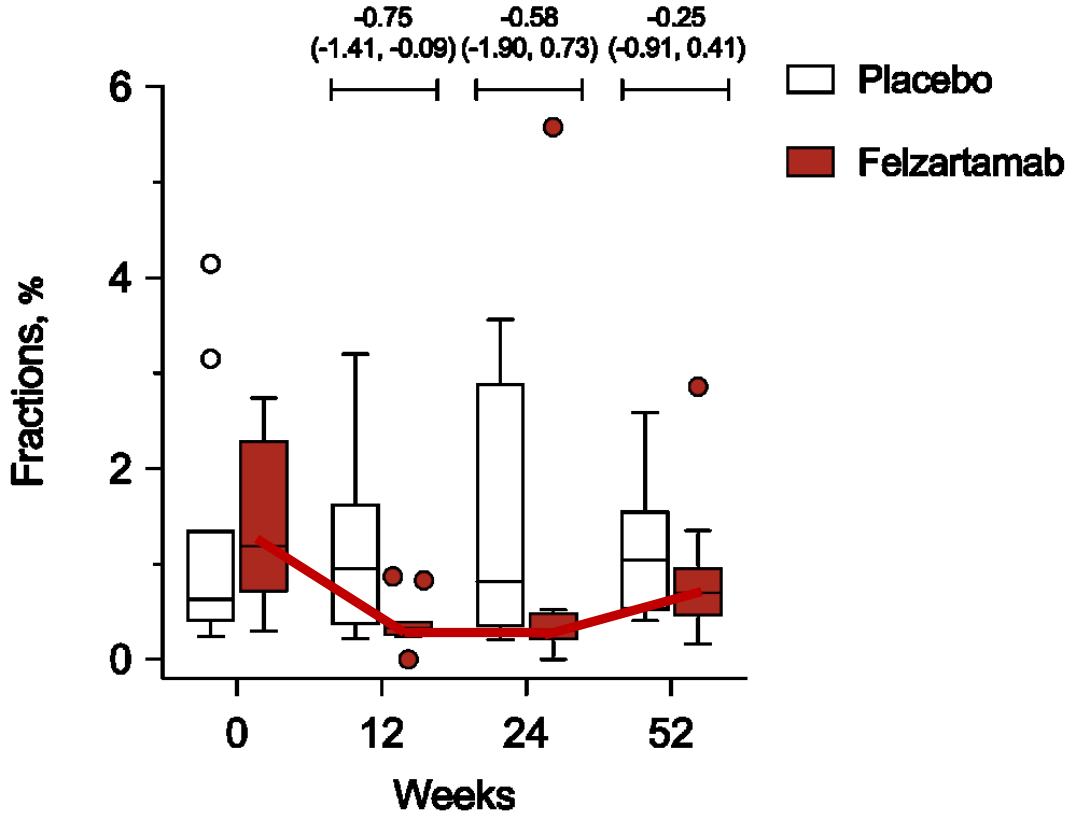
Mayer K et al
NEJM 2024

## MMDx® Molecular AMR classifier ($AMR_{Prob}$)




**No molecular features of TCMR**

## Injury biomarker
## Dd-cfDNA (%)



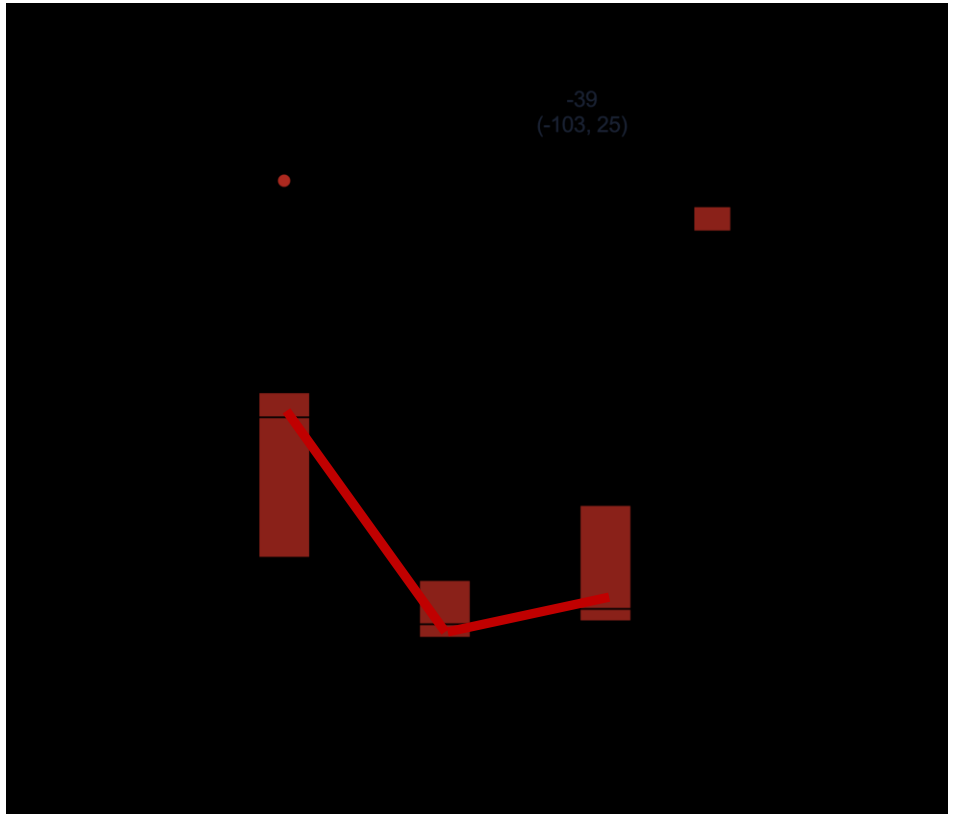

MMDx, The Molecular Microscope® Diagnostic System; TCMR, T cell-mediated rejection

dd-cfDNA, Donor-derived cell-free DNA

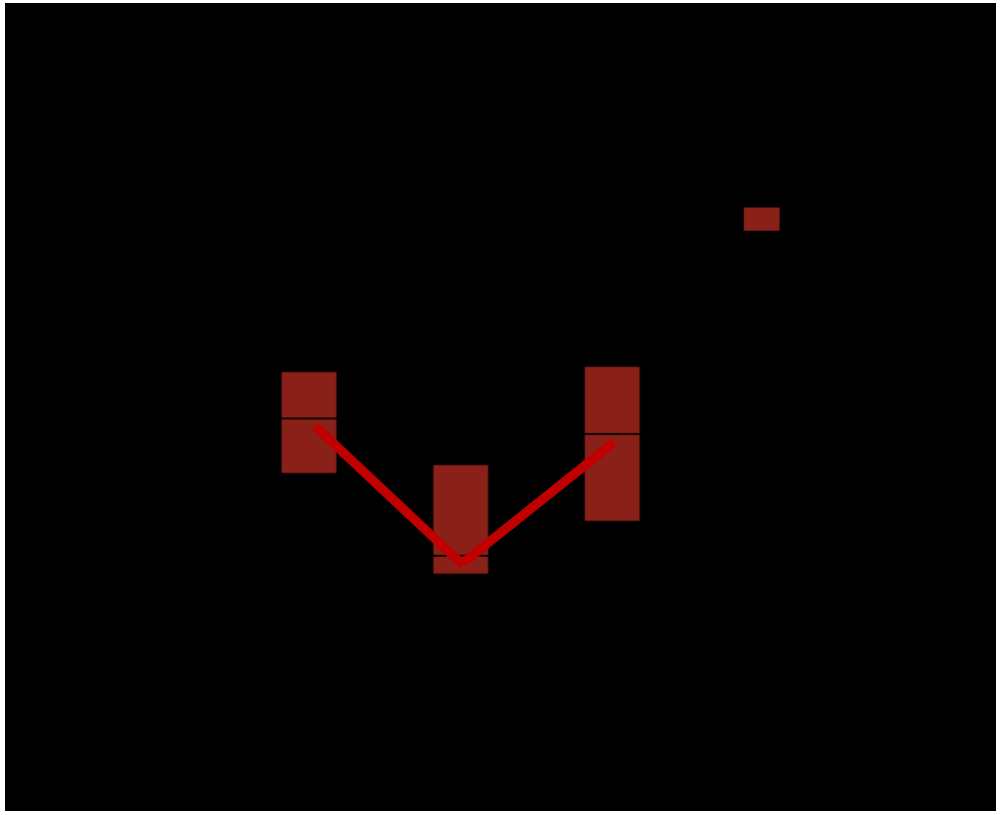
# Reduction in NK Cell Count and Burden

Mayer K et al
NEJM 2024

## Peripheral NK Cell Counts




## MMDx® Molecular NK Cell Burden (NKB)

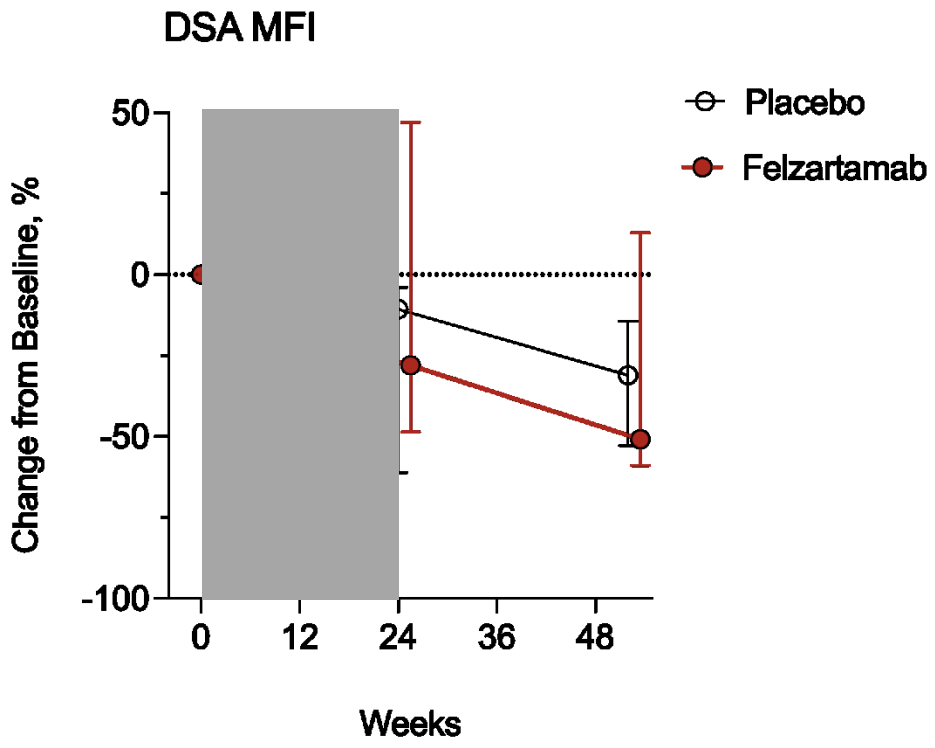


MMDx, The Molecular Microscope® Diagnostic System

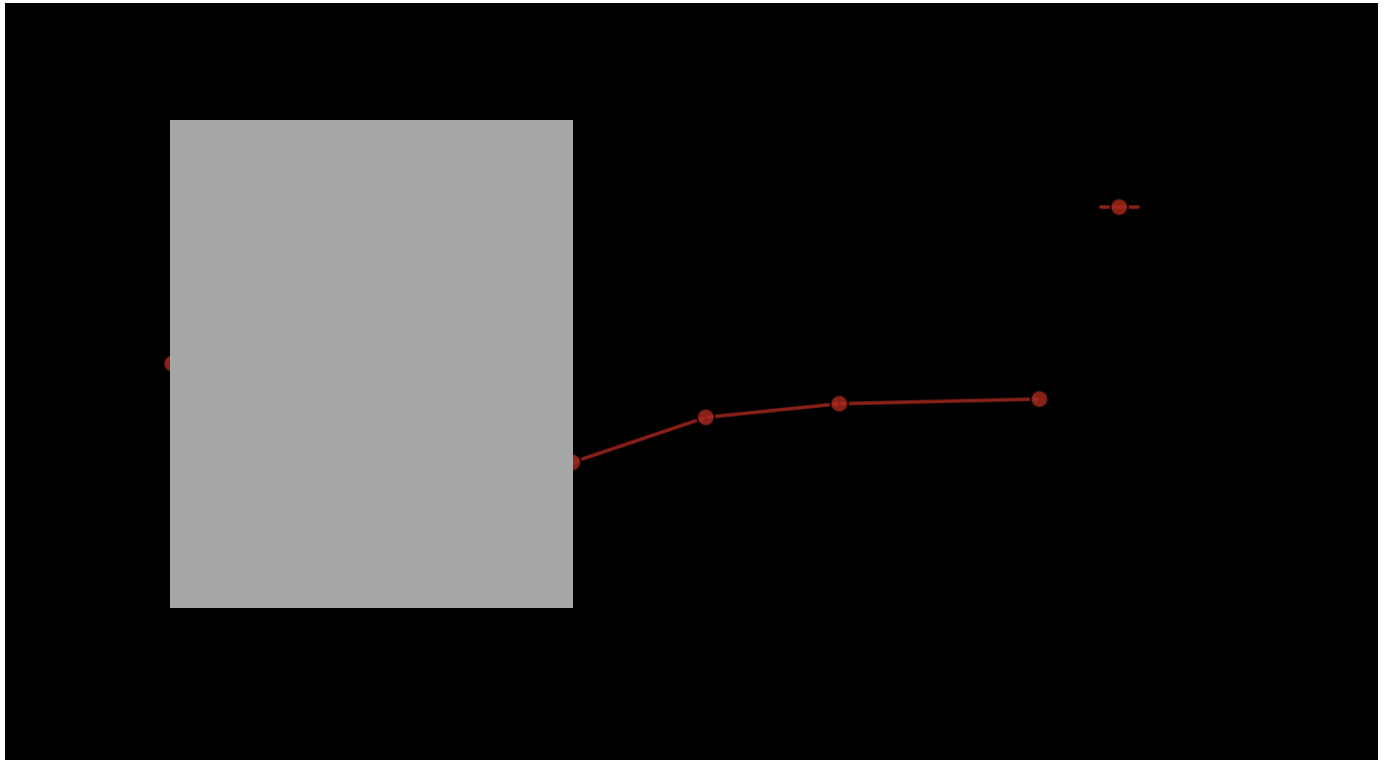
# Levels of Donor-specific Antibodies (DSA)

Mayer K et al
NEJM 2024

## Immunodominant DSA levels



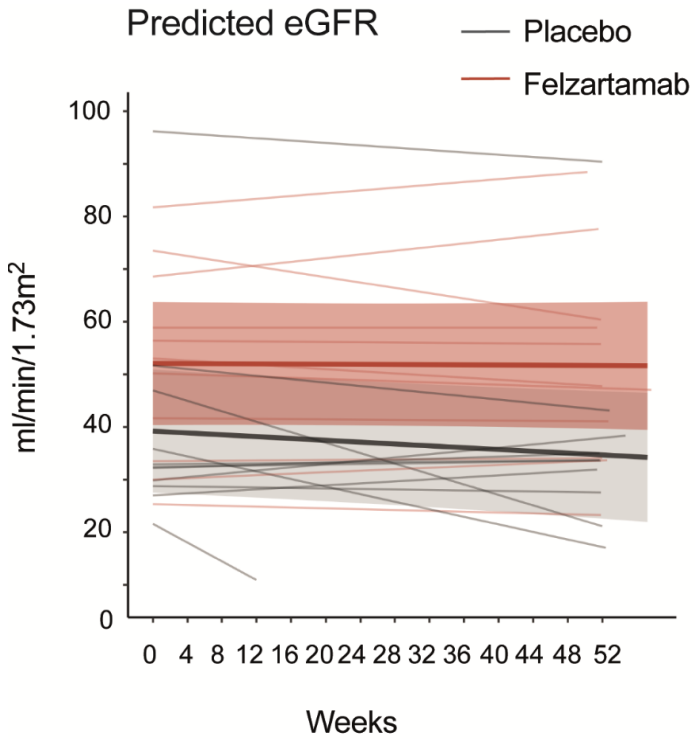

## Immunoglobulin G level



# Kidney Function and Proteinuria

Mayer K et al
NEJM 2024

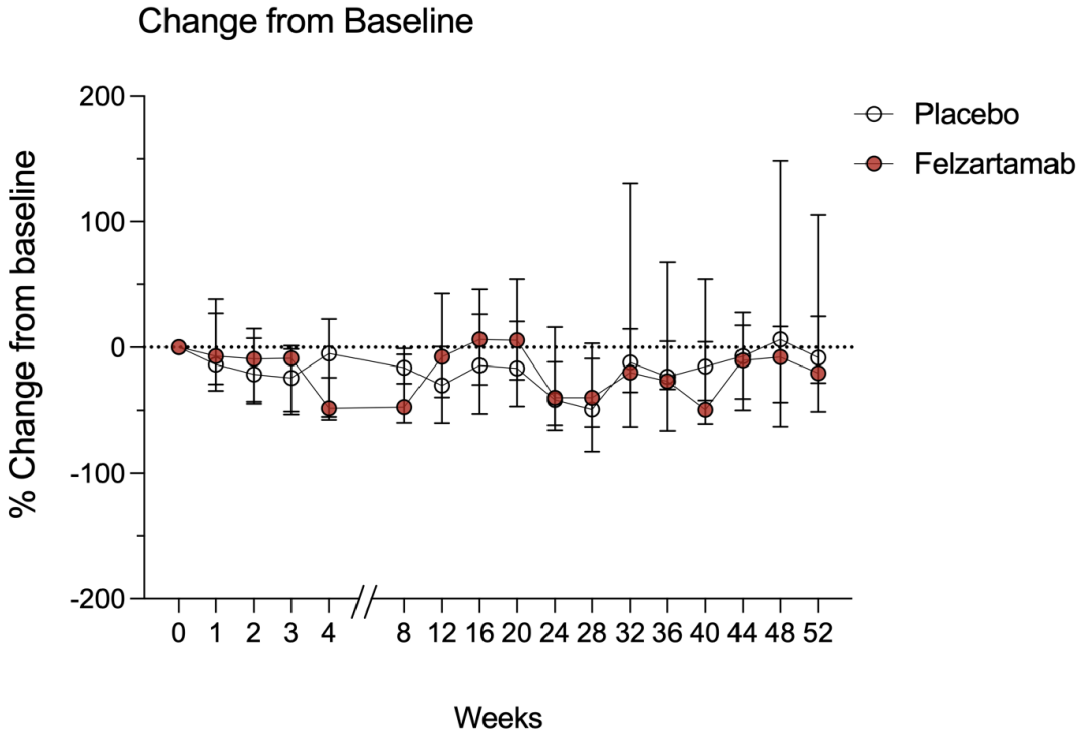
## eGFR slope




**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

eGFR, estimated glomerular filtration rate; CI, Confidence interval

# Felzartamab Treatment Effect: iBox Score

Lombardi et al., *AJT 2025*

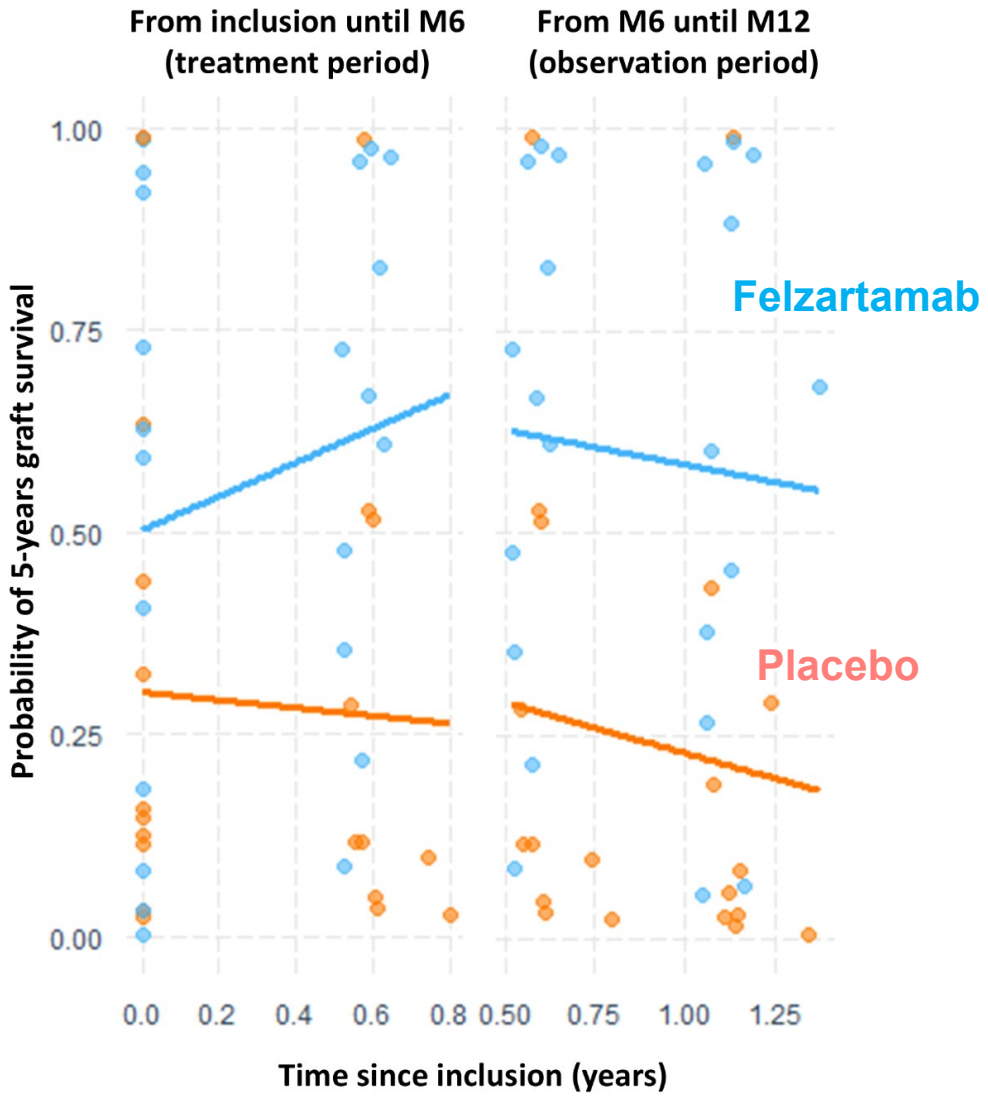
**iBox**

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*

# Conclusion treatment of AMR

- Low or very low evidence
- Many small retrospective studies with different combination therapies using different definitions in different populations
- Only a few small prospective randomized trials with limitations
- aCD38 therapy is the first treatment to show histological and molecular resolution with normalisation of injury marker cfDNA via NK effector cell depletion, but no effect on antibody levels

We need more evidence from larger prospective randomized trials:
Felzartamab phase III trial has started in Q1/2025


# Thank you for your attention

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