ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Antibody-mediated rejection is a leading cause of kidney-transplant failure. The targeting of CD38 to inhibit graft injury caused by alloantibodies and natural killer (NK) cells may be a therapeutic option.

METHODS

In this phase 2, double-blind, randomized, placebo-controlled trial, we assigned patients with antibody-mediated rejection that had occurred at least 180 days after transplantation to receive nine infusions of the CD38 monoclonal antibody felzartamab (at a dose of 16 mg per kilogram of body weight) or placebo for 6 months, followed by a 6-month observation period. The primary outcome was the safety and side-effect profile of felzartamab. Key secondary outcomes were renal-biopsy results at 24 and 52 weeks, donor-specific antibody levels, peripheral NK-cell counts, and donor-derived cell-free DNA levels.

RESULTS

A total of 22 patients underwent randomization (11 to receive felzartamab and 11 to receive placebo). The median time from transplantation until trial inclusion was 9 years. Mild or moderate infusion reactions occurred in 8 patients in the felzartamab group. Serious adverse events occurred in 1 patient in the felzartamab group and in 4 patients in the placebo group; graft loss occurred in 1 patient in the placebo group. At week 24, resolution of morphologic antibody-mediated rejection was more frequent with felzartamab (in 9 of 11 patients [82%]) than with placebo (in 2 of 10 patients [20%]), for a difference of 62 percentage points (95% confidence interval [CI], 19 to 100) and a risk ratio of 0.23 (95% confidence interval [CI], 0.06 to 0.83). The median microvascular inflammation score was lower in the felzartamab group than in the placebo group (0 vs. 2.5), for a mean difference of –1.95 (95% CI, –2.97 to –0.92). Also lower was a molecular score reflecting the probability of antibody-mediated rejection (0.17 vs. 0.77) and the level of donor-derived cell-free DNA (0.31% vs. 0.82%). At week 52, the recurrence of antibody-mediated rejection was reported in 3 of 9 patients who had a response to felzartamab, with an increase in molecular activity and biomarker levels toward baseline levels.

CONCLUSIONS

Felzartamab had acceptable safety and side-effect profiles in patients with antibody-mediated rejection. (Funded by MorphoSys and Human Immunology Biosciences; ClinicalTrials.gov number, NCT05021484; and EUDRACT number, 2021-000545-40.)

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CME

Antibody-mediated rejection is a leading cause of kidney allograft failure.[1-3] The diagnosis of such organ rejection is based on serologic, morphologic, and molecular criteria, as outlined in the Banff classification.[4] No therapies have been approved for the treatment of antibody-mediated rejection.[5] To date, efficacy has not been shown in clinical trials of the CD20 antibody rituximab, the proteasome inhibitor bortezomib, or complement inhibitors.[6-9] A recent phase 3 trial evaluating an interleukin-6 antibody, clazakizumab, was prematurely terminated because of a lack of efficacy,[10,11] despite earlier studies that showed encouraging results.[12,13] Thus, there is an unmet therapeutic need for the treatment of antibody-mediated rejection.[14]

CD38 is a transmembrane glycoprotein that is expressed by immune and hematopoietic cells, particularly plasma cells and natural killer (NK) cells.[15] Depletion of malignant plasma cells with CD38 monoclonal antibodies has been approved for the treatment of multiple myeloma.[16-18] CD38 has emerged as a promising therapeutic target in antibody-mediated rejection, given the potential for its use as a target for the depletion of the plasma cells that produce donor-specific antibodies and NK cells, which are presumed to be critical for microvascular inflammation.[19-21] Clinical evidence from anecdotal reports has suggested that the targeting of CD38 could prevent or reverse antibody-mediated rejection.[22-25]

Felzartamab is an investigational, fully human IgG1 monoclonal CD38 antibody that depletes target cells through antibody-dependent cellular cytotoxicity and phagocytosis.[26,27] We conducted a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety, side-effect profile, and preliminary efficacy of felzartamab in the treatment of antibody-mediated rejection that has occurred at least 180 days after kidney transplantation.

Methods

Trial Design and Oversight

We conducted the trial at the Medical University of Vienna and at Charité Universitätsmedizin Berlin (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial patients were followed for 52 weeks. Details regarding the trial design are provided in the Supplementary Appendix and have been published previously.[28]

The trial protocol (available at NEJM.org) was approved by the local ethics committee at each trial site and by federal regulatory agencies. The trial was externally monitored and adhered to the principles of Good Clinical Practice, Good Laboratory Practice, the Declaration of Helsinki, and the Declaration of Istanbul. The trial was financed by MorphoSys and Human Immunology Biosciences through an unrestricted grant awarded to the sponsor, Medical University of Vienna. Representatives of the sponsor designed the trial, gathered the data, and confirmed the accuracy of the reporting. The first three authors and the last two authors wrote the first draft of the manuscript and made the decision to submit it for publication. All the authors contributed to the writing of the manuscript and signed data confidentiality agreements. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

A Quick Take is available at NEJM.org

Patients

Adult patients (>18 years of age) were eligible to participate in the trial if they had biopsy-diagnosed antibody-mediated rejection of a functioning kidney allograft at least 180 days after transplantation, an estimated glomerular filtration rate (eGFR) of at least 20 ml per minute per 1.73 m^2 of body-surface area, and the presence of donor-specific antibody. All the patients provided written informed consent. Details regarding the inclusion and exclusion criteria and the Banff classification for kidney rejection[4] are provided in the Supplementary Appendix (including Table S1).

Randomization and Treatment

Patients were assigned in a 1:1 ratio to receive felzartamab or placebo by permuted-block randomization stratified according to trial site and category of antibody-mediated rejection. Over a 20-week period, patients received nine intravenous infusions of felzartamab at a dose of 16 mg per kilogram of body weight (in 250 ml of 0.9% saline over a period of 30 to 90 minutes) or matching placebo (0.9% saline). The nine infusions were administered once per week for 4 weeks, followed by once per month for 5 months. An observational period extended through week 52.

Details regarding randomization, the administration of felzartamab and placebo, and immunosuppression are provided in the Supplementary Appendix.

OUTCOMES

Outcomes were assessed at 17 trial visits throughout the 52-week period. A full list of outcomes and details regarding biobanking, biopsy evaluation, and laboratory methods are provided in the Supplementary Appendix.

The primary outcome was the safety and side-effect profile of felzartamab. Key safety assessments were vital signs and laboratory safety; viral testing for severe acute respiratory syndrome coronavirus 2, cytomegalovirus, herpes simplex, herpes zoster, and polyomavirus viremia; and for-cause allograft biopsies. Adverse events were classified according to the definitions used in the *Medical Dictionary for Regulatory Activities*, version 26.0, and were graded by the investigators. Key prespecified safety outcomes were the number and per-patient incidence of serious adverse events, infusion-related reactions, and infections or infestations.

Key secondary efficacy outcomes were the resolution of antibody-mediated rejection (defined as chronic [inactive] rejection or no rejection after treatment); the level of microvascular inflammation (glomerulitis plus the peritubular capillaritis score), and the resolution of microvascular inflammation to a score of 0, as compared with a score of 1 to 6; a molecular classifier score of antibody-mediated rejection[29]; the change in the immunodominant mean fluorescence intensity of donor-specific antibody; the NK-cell count in peripheral blood; the level of donor-derived cell-free DNA (reported as either the percentage of total cell-free DNA in plasma or the absolute count); the viral load of torque teno virus (TTV), a nonpathogenic commensal virus that was used as a marker of functional immunity; and the eGFR slope.

STATISTICAL ANALYSIS

This was an exploratory trial with a primary safety objective. Consequently, no formal type I error or power considerations were applied when planning for enrollment. Analyses were performed according to the intention-to-treat principle and included all the patients who had undergone randomization; there was no imputation of missing data. Categorical variables were summarized according to absolute and relative frequencies. We used Wald's method to estimate risk ratios and their confidence intervals. Continuous data were summarized with the calculation of medians and interquartile ranges.

Between-group comparisons were summarized according to mean differences, with confidence intervals estimated from a t-distribution that assumed unequal variance between the groups. We estimated eGFR trajectories using a linear mixed model, with eGFR measured every 4 weeks as a dependent variable, with fixed effects for time and treatment (and their interaction) and patient-specific random effects for intercept and slope. Fisher unadjusted P values are provided for the prespecified safety outcomes. The widths of the confidence intervals have not been adjusted for multiplicity and are not intended for hypothesis testing.

RESULTS

PATIENTS

From October 2021 through March 2023, a total of 22 kidney-transplant recipients with antibody-mediated rejection were randomly assigned to receive felzartamab or placebo (Fig. S2). Pharmacokinetic data for felzartamab are shown in Figure S3. The trial treatment was completed by 21 of the patients after 1 patient in the placebo group had graft loss caused by rejection at week 14. After completion of the last scheduled patient visit, the database was locked and unblinded on March 7, 2024.

The median time until trial inclusion was 9 years (interquartile range, 5 to 18) after transplantation. Baseline characteristics were generally well balanced between the two groups, except that the median age was older in the placebo group and the median eGFR was higher in the felzartamab group (Table 1).

Overall, 7 of 22 patients (32%) had active antibody-mediated rejection, and 15 of 22 patients (68%) had chronic active antibody-mediated rejection. The presence of human leukocyte antigen (HLA) class II donor-specific antibody was observed in 13 of 22 patients (59%), and a mean fluorescence intensity of donor-specific antibody of more than 10,000 was observed in 8 of 22 patients (36%). The median eGFR was 37 ml per minute per 1.73 m^2 (interquartile range, 33 to 64). The median ratio of spot urine protein to creati-

Table 1. Characteristics of the Patients at Transplantation and Trial Entry.*

Characteristic	Felzartamab (N = 11)	Placebo (N = 11)	Total (N = 22)
At transplantation			
Female sex — no. (%)	4 (36)	7 (64)	11 (50)
Median age (IQR) — yr	33 (26–42)	46 (37–54)	39 (32–53)
Race — no. (%)†			
White	9 (82)	11 (100)	20 (91)
Asian	2 (18)	0	2 (9)
Living donor — no. (%)	4 (36)	2 (18)	6 (27)
Median donor age (IQR) — yr	47 (30–51)	37 (28–52)	43 (27–52)
Previous kidney transplantation — no. (%)	3 (27)	4 (36)	7 (32)
Median HLA (A, B, DR) mismatch level (IQR)	3 (2–4)	3 (2–3)	3 (2–3)
Median cold ischemia time (IQR) — hr	11 (3–14)	14 (10–20)	12 (4–16)
Complement-dependent cytotoxicity — no. (%)			
Panel reactivity of ≥10%	2 (18)	2 (18)	4 (18)
Missing data	1 (9)	2 (18)	3 (14)
Preformed anti-HLA donor-specific antibody — no. (%)			
Patients‡	4 (36)	4 (36)	8 (36)
Missing data	4 (36)	4 (36)	8 (36)
At trial entry			
Median recipient age (IQR) — yr	42 (35–50)	56 (49–64)	50 (39–59)
Median time after transplantation (IQR) — yr	9 (6–14)	10 (6–19)	9 (5–18)
Median eGFR (IQR) — ml/min/1.73 m^2	60 (35–69)	36 (31–43)	37 (33–64)
Median protein:creatinine ratio (IQR)§	690 (232–1248)	1338 (187–1614)	993 (178–1510)
Immunosuppression — no. (%)			
Three drugs	9 (82)	9 (82)	18 (82)
Tacrolimus-based drug	10 (91)	8 (73)	18 (82)
Type of antibody-mediated rejection — no. (%)¶			
Active	4 (36)	3 (27)	7 (32)
Chronic active	7 (64)	8 (73)	15 (68)
Additional borderline lesion	1 (9)	2 (18)	3 (14)
Feature of donor-specific antibody			
HLA class I only — no. (%)	4 (36)	3 (27)	7 (32)
HLA class II only — no. (%)	6 (55)	7 (64)	13 (59)
HLA class I and II — no. (%)	1 (9)	1 (9)	2 (9)
Anti-DQ — no. (%)	6 (55)	5 (45)	11 (50)
>10,000 mean fluorescence intensity of peak level — no. (%)	5 (45)	3 (27)	8 (36)
Median no. of antibodies (IQR)	1 (1–2)	1 (1–2)	1 (1–3)

* eGFR denotes estimated glomerular filtration rate, HLA human leukocyte antigen, and IQR interquartile range.
† Race was reported by the patients.
‡ Data regarding donor-specific antibody before transplantation were available for 14 recipients. Solid-phase HLA antibody screening after patients had been placed on the waiting list was implemented at the Vienna transplantation unit in July 2009.
§ In this calculation, protein was measured in milligrams and creatinine in grams.
¶ Antibody-mediated rejection was graded according to the 2019 Banff Classification of Allograft Pathology. No patients had additional T-cell–mediated rejection.

Table 2. Adverse Events.*

Event	Felzartamab (N=11)		Placebo (N=11)	
	no. of patients (%)	*no. of events*	*no. of patients (%)*	*no. of events*
Any adverse event — no. (%)	11 (100)	119	11 (100)	81
Mild	11 (100)	61	9 (82)	37
Moderate	11 (100)	55	11 (100)	42
Severe	2 (18)	3	1 (9)	2
Treatment-related — no. (%)†	10 (91)	27	7 (64)	11
Infusion-related reaction — no. (%)‡	8 (73)	8	0	0
Serious event	1 (9)	2	4 (36)	7
Covid-19 pneumonia	0	0	2 (18)	2
Urinary tract infection	0	0	2 (18)	2
Hyponatremia	0	0	1 (9)	1
RSV infection	0	0	1 (9)	1
Clostridium difficile diarrhea	0	0	1 (9)	1
Acute kidney injury	1 (9)	1	0	0
Viral keratoconjunctivitis	1 (9)	1	0	0

* Covid-19 denotes coronavirus disease 2019, and RSV respiratory syncytial virus.
† The determination that an adverse event was related to felzartamab or placebo was made by the investigators.
‡ Infusion-related reaction was a predefined adverse event of special interest. In the felzartamab group, such events were classified as mild (in 2 patients) or moderate (in 6 patients).

nine was 993 (interquartile range, 178 to 1510), with urinary protein measured in milligrams and creatinine measured in grams. Molecular analysis revealed fully developed antibody-mediated rejection in most patients (Table S2). Triple immunosuppression was being administered to 18 of 22 patients (82%) (Fig. S4 and Table S3).

SAFETY

Adverse events were reported in all the patients and were predominantly mild or moderate in severity (Table 2 and Table S4). A greater incidence of adverse events was reported in the felzartamab group than in the placebo group (119 vs. 81 events), as were adverse events that were deemed by the trial investigators to be related to felzartamab or placebo (27 vs. 11 events). No patients discontinued treatment because of adverse events, and there were no fatal adverse events. The frequency of serious adverse events, which were primarily infection-related, was lower in the felzartamab group than in the placebo group (in 1 patient [9%] vs. 4 patients [36%]).

During the first infusion, mild or moderate infusion-related reactions were reported in 8 patients (73%) in the felzartamab group and in no patients in the placebo group (P=0.001) (Tables S4 and S5). The most frequent adverse events were infections, which occurred in 17 of 22 patients (77%) and were more frequent in the felzartamab group than in the placebo group (in 10 patients [91%] vs. 7 patients [64%]; P=0.31). The frequency of nasopharyngitis was greater in the felzartamab group than in the placebo group (in 9 patients [82%] vs. 3 patients [27%]; P=0.03), as was the frequency of coronavirus disease 2019 (in 7 patients [64%] vs. 3 patients [27%]; P=0.20) (Table S6). Cytomegalovirus viremia was reported in 1 patient in the felzartamab group. Laboratory analyses did not reveal meaningful changes in safety laboratory measures (Table S7 and Fig. S5).

BIOPSY RESULTS

Biopsy procedures were performed at 24 weeks and 52 weeks in 11 patients in the felzartamab group and in 10 patients in the placebo group. A patient in the placebo group who had graft loss at week 14 was not included in the analysis.

In this patient, biopsy that had been performed shortly before graft loss showed persistent chronic active antibody-mediated rejection.

At week 24, resolution of antibody-mediated rejection — which included either chronic (inactive) rejection or no rejection — had occurred in 9 of 11 patients (82%) in the felzartamab group and in 2 of 10 patients (20%) in the placebo group, for a between-group difference of 62 percentage points (95% confidence interval [CI], 19 to 100) and a risk ratio of 0.23 (95% CI, 0.06 to 0.83) (Fig. 1 and Fig. S6). The effect of felzartamab on rejection activity was characterized by a reduction in the microvascular inflammation score, with a median score of 0 (interquartile range, 0 to 1) in the felzartamab group and 2.5 (interquartile range, 2 to 3) in the placebo group at week 24, for a mean between-group difference of −1.95 (95% CI, −2.97 to −0.92) (Fig. 1B). A score of 0 was reported in 7 of 11 patients (64%) with felzartamab and in 1 of 10 patients (10%) with placebo, for a between-group difference of 54 percentage points (95% CI, 11 to 98) and a risk ratio of 0.40 (95% CI, 0.18 to 0.91).

The dynamics of Banff lesion scores through week 52 are shown in Figure S7. Changes in the morphologic characteristics of allografts were accompanied by a substantially lower molecular score reflecting the probability of antibody-mediated rejection in the felzartamab group than in the placebo group. At 24 weeks, the median score was 0.17 (interquartile range, 0.09 to 0.51) in the felzartamab group and 0.77 (interquartile range, 0.37 to 0.86) in the placebo group, for a mean difference of −0.39 (95% CI, −0.64 to −0.14) Fig. 1C. Patients in the felzartamab group also had lower scores for any type of rejection and pathogenesis-based transcript sets reflecting the NK-cell burden, gamma interferon effects, cytotoxic T cells, and transcripts selective for donor-specific antibody (Figs. S8 and S9). At 24 weeks, subclinical T-cell–mediated rejection that was graded as Banff type IA developed in a patient in the felzartamab group (Table S8). Three months later, biopsy revealed spontaneous resolution of tubulointerstitial infiltrates. Consistent values for a molecular score of less than 0.2 for T-cell–mediated rejection were observed in biopsy samples in the felzartamab group. Morphologic and molecular scores that indicate chronic transplant injury were unaffected by treatment.

Biopsies at week 52 (6 months after completion of treatment) indicated recurrence of rejection in 3 of the 9 patients in the felzartamab group who had a response to treatment. Median scores for microvascular inflammation remained lower in the felzartamab group than in the placebo group (1 [interquartile range, 0 to 2] vs. 2 [interquartile range, 2 to 3.5]), for a mean difference between groups of −1.58 (95% CI, −2.70 to −0.45). Among the patients who received felzartamab, 6 still had either chronic (inactive) or no rejection (Fig. 1). However, molecular scores related to rejection and NK-cell burden increased toward baseline levels.

BLOOD BIOMARKERS

At 24 weeks, the median CD16^{bright} NK-cell count in peripheral blood was lower in the felzartamab group than in the placebo group (16 cells per microliter [interquartile range, 8 to 41] vs. 54 cells per microliter [interquartile range, 38 to 170]), for a mean difference of −87 cells per microliter (95% CI, −177 to 4) (Fig. 2). At 12 weeks, the median fraction of donor-derived cell-free DNA was 0.33% (interquartile range, 0.25 to 0.40) in the felzartamab group and 0.95% (interquartile range, 0.37 to 1.63) in the placebo group, for a mean difference of −0.75 percentage points; 95% CI, −1.41 to −0.09); at week 24, the median fraction of donor-derived cell-free DNA was 0.31% (interquartile range, 0.21 to 0.49) in the felzartamab group and 0.82% (interquartile range, 0.34 to 2.90) in the placebo group, for a mean between-group difference of −0.58 percentage points (95% CI, −1.90 to 0.73), with increases toward baseline levels by week 52 (Fig. 2 and Fig. S10). There was evidence of modestly lower values for the mean fluorescence intensity of the peak donor-specific antibody, total IgG, and IgM with felzartamab treatment (Fig. S11). As reflected by the TTV viral load, the level of overall immunosuppression did not increase in either trial group (Fig. 2); the numbers of T cells, B cells, and CD138+ antibody-secreting cells in peripheral blood remained unaffected (Fig. S12).

CLINICAL OUTCOMES

At 1 year, survival was 100% in the two trial groups. One graft loss in the placebo group had occurred because of persistent chronic active antibody-mediated rejection. The 1-year eGFR slope

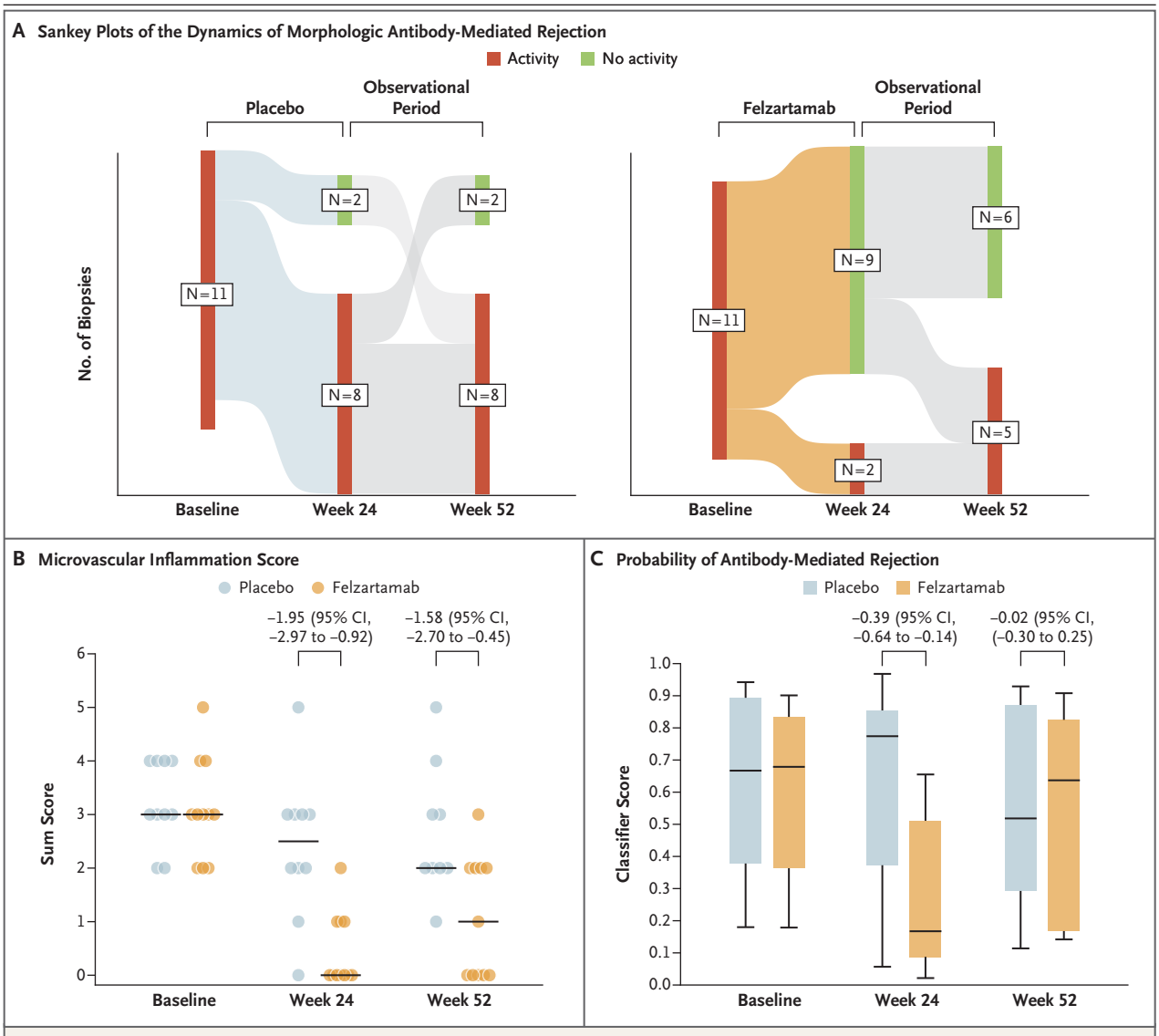

Figure 1. Antibody-Mediated Rejection.

Panel A shows Sankey plots of the dynamics of morphologic antibody-mediated rejection (active or chronic active) as compared with no activity (chronic inactive or no rejection) in the felzartamab and placebo groups across biopsy samples obtained at baseline, week 24, and week 52. Vertical stacks represent biopsy time points and include the numbers of biopsies that were performed. The arrows (gray or colored bands) indicate the movement of biopsy results between groups from baseline to week 52; the width of the arrows is proportional to the number of cases. Panel B shows the microvascular inflammation score (a sum score of glomerulitis and peritubular capillaritis) in biopsy samples according to the Banff classification at baseline, week 24, and week 52. The horizontal lines indicate medians. At 24 weeks, 7 of 11 patients who had received felzartamab had a microvascular inflammation score of 0 as compared with 1 of 10 patients in the placebo group. At 52 weeks, 4 of 11 patients in the felzartamab group maintained a microvascular inflammation score of 0 as compared with 0 of 10 in the placebo group. Panel C shows a molecular score reflecting the probability of antibody-mediated rejection in biopsy samples obtained at baseline, week 24, and week 52. The horizontal line in each box represent the median, the tops and bottoms of the boxes represent the upper and lower limits of the interquartile range, and the I bars represent 1.5 times the interquartile range. One patient in the placebo group had allograft loss after 14 weeks, so biopsy samples at week 24 and week 52 were not available. In addition, microvascular inflammation was not calculated for one patient at baseline and for another at week 52 in the placebo group (no grading of peritubular capillaritis because of interstitial infiltrates). Week 24 molecular data were missing for one patient in the felzartamab group. Mean differences and 95% confidence intervals between the felzartamab and placebo groups are provided for biopsy results obtained at weeks 24 and 52.

was −0.39 ml per minute per 1.73 m^2 (95% CI, −5.47 to 4.69) in the felzartamab group and −4.53 ml per minute per 1.73 m^2 (95% CI, −9.83 to 0.77) in the placebo group (difference, 4.14 ml per minute per 1.73 m^2; 95% CI, −3.20 to 11.48) (Fig. S13). In the two groups, the ratio of spot urinary protein to creatinine did not change over time (Fig. S14). Table S9 shows the representativeness of the findings in the predominantly White European trial patients with respect to the occurrence of antibody-mediated rejection worldwide.

DISCUSSION

In this prospective, randomized, placebo-controlled trial that enrolled adult kidney-transplant recipients with late active or chronic active antibody-mediated rejection, felzartamab had an acceptable safety profile and showed potential therapeutic benefit. The incidence of mild or moderate adverse events, including first-dose infusion-related reactions, was greater with felzartamab than with placebo. However, there was no evidence indicating that treatment with felzartamab increased the incidence of serious adverse events, and no patients discontinued treatment because of an adverse event.

Previous trials that have evaluated various treatments to combat antibody-mediated rejection have not shown meaningful morphologic or molecular changes.[6-9,13] Our trial shows greater resolution of antibody-mediated rejection with felzartamab than with placebo (82% vs. 20%) at week 24, along with decreases in microvascular inflammation and rejection-related transcript scores. Moreover, plasma levels of donor-derived cell-free DNA, which are used to diagnose graft injury,[30] were lower at weeks 12 and 24 in the felzartamab group, which indicates the clinical relevance of these results. Although this trial was not powered for clinical outcomes, the results suggest a potential stabilization of the eGFR slope, which is a surrogate for long-term allograft survival.[31] Of note, the effect of felzartamab was not durable after treatment discontinuation, as shown by the rejection features that had recurred by week 52, suggesting that continuing treatment would be required for long-term prevention of rejection-related graft loss.

In designing this trial, our primary hypothesis was that felzartamab could interfere with alloantibody-producing plasma cells, consistent with the effects of anti-CD38 treatment in multiple myeloma[16-18] and aberrant plasma cells in autoantibody-mediated diseases.[32-34] Preliminary studies have shown that treatment with daratumumab may decrease levels of donor-specific antibody.[22-24] In a single-group trial involving sensitized transplantation candidates, treatment with the CD38 antibody isatuximab led to a significant — albeit moderate — reduction in anti-HLA antibody levels, plasmablasts, and plasma cells.[35] In our trial, treatment with felzartamab resulted in only modest decreases in the total IgG and the mean fluorescence intensity of donor-specific antibody. Hence, modulation in the production of donor-specific antibodies may not solely explain the observed clinical benefit.

The observed depletion of circulating $CD16^{bright}$ NK cells, which are known to be more cytotoxic than other NK-cell subpopulations and to mediate antibody-dependent cellular cytotoxicity, and the reduction in NK-cell–associated gene transcripts in the week 24 biopsy samples are noteworthy and are consistent with observations from studies investigating CD38 antibodies for the treatment of myeloma and for use in transplantation.[23,35,36] It has been suggested that depletion of these cells is the result of NK-cell fratricide triggered by antibody-dependent cellular cytotoxicity.[37] Because NK cells are important effector cells in antibody-mediated rejection,[19-21] the depletion of NK cells expressing Fc gamma receptor IIIA in our trial may be a critical, albeit not necessarily exclusive, mechanism of action. By targeting NK cells, felzartamab could potentially be effective in cases of rejection that are negative for donor-specific antibody, in which NK cells may become activated by missing self-recognition.[4] The recovery of NK-cell counts and levels of donor-derived cell-free DNA after the end of felzartamab treatment paralleled the rejection observed in the week 52 biopsy samples. It is possible that combined monitoring of peripheral-blood NK cells and donor-derived cell-free DNA could be useful in guiding the treatment of antibody-mediated rejection without repeated biopsies.

Although there is concern about the risk of infection with NK-cell depletion, it is important to note that treatment with felzartamab did not

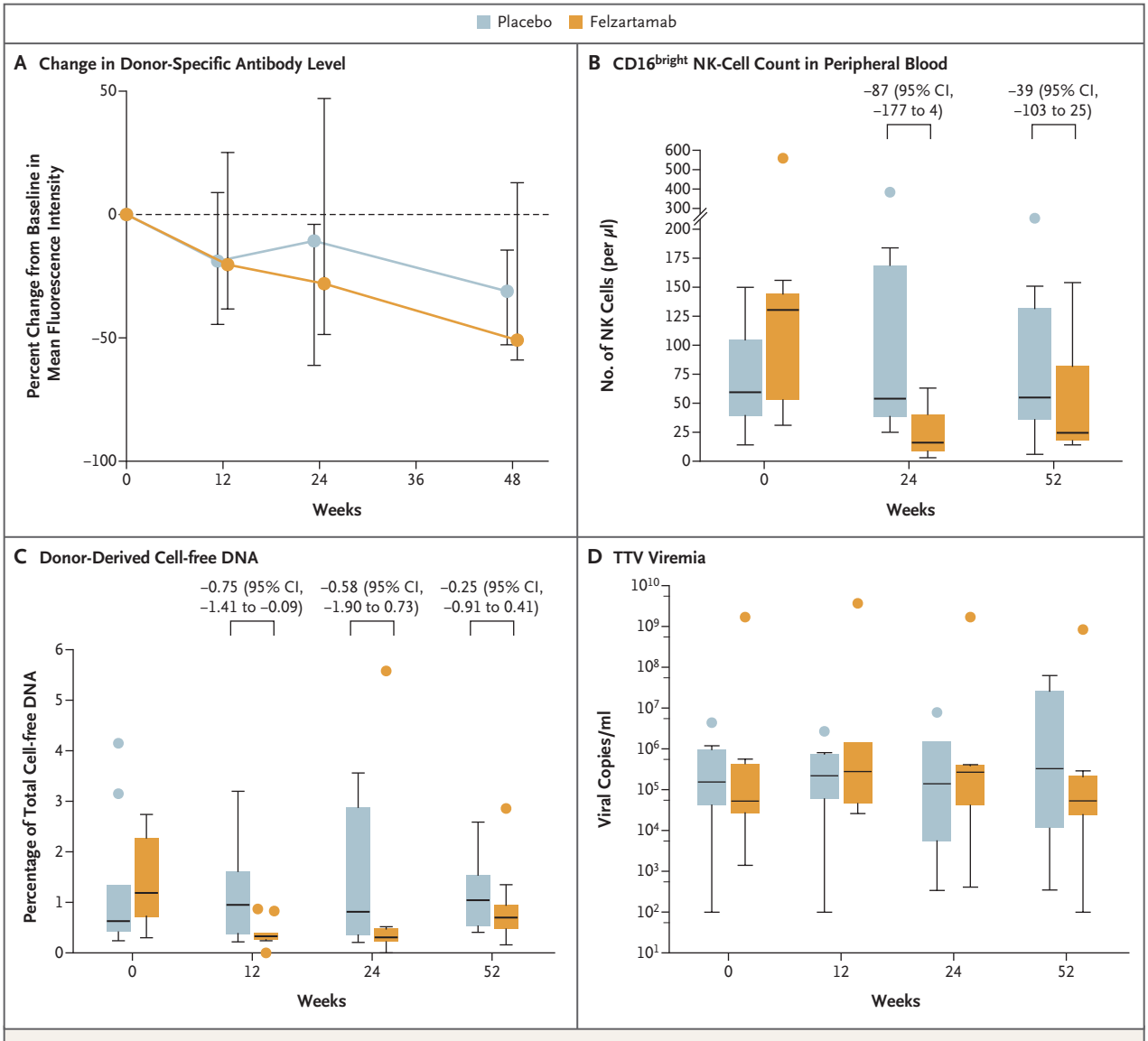

Figure 2. Biomarkers in Peripheral Blood.

Shown is the percent change in the mean fluorescence intensity of donor-specific antibody in the two trial groups (Panel A); line plots show medians, and I bars indicate interquartile ranges. Also shown are box plots of peripheral-blood CD16^{bright} NK-cell counts (Panel B), the fraction of donor-derived cell-free DNA (Panel C), and the number of copies of torque teno virus (TTV) (Panel D). In Panels B through D, the horizontal line in each box represents the median, the tops and bottoms of boxes represent the upper and lower limits of the interquartile range, and the I bars represent 1.5 times the interquartile range; outliers are indicated by circles. One patient in the placebo group had allograft loss after 14 weeks, so week 24 and 52 biomarker results were unavailable. Levels of donor-specific antibody were undetectable at day 0 in three patients (two in the felzartamab group and one in the placebo group) despite detectable levels of donor-specific antibody at screening, and no TTV DNA was detected in four patients (one in the felzartamab group and three in the placebo group); no data were imputed in these analyses. For NK-cell counts and donor-derived cell-free DNA, mean differences and 95% confidence intervals between the felzartamab and placebo groups are provided for selected time points.

result in the complete ablation of NK cells. Casneuf and colleagues[36] found no association between the level of NK-cell depletion and the incidence of infection-related adverse events after anti-CD38 treatment in patients with multiple myeloma, a finding that could be attributed to residual NK-cell activity. Similarly, we did not observe substantial increases in the frequency or

severity of infection-related complications. In addition, there were no increases in TTV viral load, a marker that is presumed to reflect overall immunosuppression.[38,39]

Experimental data have suggested that the CD38 antibody daratumumab could promote T-cell–mediated rejection through depletion of regulatory cells,[22] a hypothesis that was supported by clinical case reports suggesting the occasional occurrence of features of this form of rejection.[23,40] One patient in the felzartamab group had complete resolution of microvascular inflammation accompanied by subclinical tubulointerstitial infiltrates that spontaneously resolved a few weeks later — a result that could reflect a dysregulated alloresponse with potential implications for long-term outcome. However, none of the felzartamab-treated patients had molecular T-cell–mediated rejection. These observations potentially differentiate felzartamab from other CD38 antibodies and could be explained by intrinsic differences in the mode of action, including the capacity to lyse cells through complement-dependent cytotoxicity, or by differences in the target epitope that have an effect on activity in the CD38 enzyme ectodomain.[17]

Inherent limitations of our trial include the small sample size and short duration, which may have precluded the detection of subtle outcome differences and changes in clinical factors, such as kidney function. Although other demographic characteristics suggest that this cohort was representative of patients with late antibody-mediated rejection, the results from a predominantly White European population may not be generalizable to transplant populations in other regions, including North America. Nevertheless, our trial identified a remarkable — and thus far unusual — effect size of felzartamab treatment on morphologic features, gene expression, and release of donor-derived cell-free DNA. The results of this trial suggest that felzartamab may have the potential to effectively and safely reverse ongoing antibody-mediated rejection, which underscores the potential of felzartamab as a therapeutic option warranting further investigation in the context of late or even early rejection after organ transplantation.

The present pilot trial showed that felzartamab met its primary outcome of apparent safety and an acceptable side-effect profile.

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APPENDIX

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REFERENCES

1. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. N Engl J Med 2018;379:1150-60.
2. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant 2012;12:388-99.
3. Mayrdorfer M, Liefeldt L, Wu K, et al. Exploring the complexity of death-censored kidney allograft failure. J Am Soc Nephrol 2021;32:1513-26.
4. Naesens M, Roufosse C, Haas M, et al. The Banff 2022 Kidney Meeting report: reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics. Am J Transplant 2024;24:338-49.
5. Mayer KA, Budde K, Jilma B, Doberer K, Böhmig GA. Emerging drugs for antibody-mediated rejection after kidney trans-

plantation: a focus on phase II & III trials. Expert Opin Emerg Drugs 2022;27:151-67.
6. Moreso F, Crespo M, Ruiz JC, et al. Treatment of chronic antibody mediated rejection with intravenous immunoglobulins and rituximab: a multicenter, prospective, randomized, double-blind clinical trial. Am J Transplant 2018;18:927-35.
7. Eskandary F, Regele H, Baumann L, et al. A randomized trial of bortezomib in late antibody-mediated kidney transplant rejection. J Am Soc Nephrol 2018;29:591-605.
8. Kulkarni S, Kirkiles-Smith NC, Deng YH, et al. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. Am J Transplant 2017;17:682-91.
9. Eskandary F, Jilma B, Mühlbacher J, et al. Anti-C1s monoclonal antibody BIVV009 in late antibody-mediated kidney allograft rejection — results from a first-in-patient phase 1 trial. Am J Transplant 2018;18:916-26.
10. Nickerson PW, Böhmig GA, Chadban S, et al. Clazakizumab for the treatment of chronic active antibody-mediated rejection (AMR) in kidney transplant recipients: phase 3 IMAGINE study rationale and design. Trials 2022;23:1042.
11. Heeger PS, Haro MC, Jordan S. Translating B cell immunology to the treatment of antibody-mediated allograft rejection. Nat Rev Nephrol 2024;20:218-32.
12. Choi J, Aubert O, Vo A, et al. Assessment of tocilizumab (anti-interleukin-6 receptor monoclonal) as a potential treatment for chronic antibody-mediated rejection and transplant glomerulopathy in HLA-sensitized renal allograft recipients. Am J Transplant 2017;17:2381-9.
13. Doberer K, Duerr M, Halloran PF, et al. A randomized clinical trial of anti-IL-6 antibody clazakizumab in late antibody-mediated kidney transplant rejection. J Am Soc Nephrol 2021;32:708-22.
14. Schinstock CA, Mannon RB, Budde K, et al. Recommended treatment for antibody-mediated rejection after kidney transplantation: the 2019 Expert Consensus from the Transplantation Society Working Group. Transplantation 2020;104:911-22.
15. Horenstein AL, Faini AC, Morandi F, et al. The circular life of human CD38: from basic science to clinics and back. Molecules 2020;25:4844.
16. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. N Engl J Med 2018;378:518-28.
17. Raab MS, Engelhardt M, Blank A, et al. MOR202, a novel anti-CD38 monoclonal antibody, in patients with relapsed or refractory multiple myeloma: a first-in-human, multicentre, phase 1-2a trial. Lancet Haematol 2020;7(5):e381-e394.
18. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2024;390:301-13.
19. Hidalgo LG, Sis B, Sellares J, et al. NK cell transcripts and NK cells in kidney biopsies from patients with donor-specific antibodies: evidence for NK cell involvement in antibody-mediated rejection. Am J Transplant 2010;10:1812-22.
20. Diebold M, Vietzen H, Heinzel A, et al. Natural killer cell functional genetics and donor-specific antibody-triggered microvascular inflammation. Am J Transplant 2024;24:743-54.
21. Lamarthée B, Callemeyn J, Van Herck Y, et al. Transcriptional and spatial profiling of the kidney allograft unravels a central role for FcγRIII+ innate immune cells in rejection. Nat Commun 2023;14:4359.
22. Kwun J, Matignon M, Manook M, et al. Daratumumab in sensitized kidney transplantation: potentials and limitations of experimental and clinical use. J Am Soc Nephrol 2019;30:1206-19.
23. Doberer K, Kläger J, Gualdoni GA, et al. CD38 antibody daratumumab for the treatment of chronic active antibody-mediated kidney allograft rejection. Transplantation 2021;105:451-7.
24. de Nattes T, Kaveri R, Farce F, et al. Daratumumab for antibody-mediated rejection: is it time to target the real culprit? Am J Transplant 2023;23:1990-4.
25. Süsal CC, Kraft L, Ender A, et al. Blood group-specific apheresis in combination with daratumumab as a rescue therapy of acute antibody-mediated rejection in a case of ABO- and human leukocyte antigen-incompatible kidney transplantation. SAGE Open Med Case Rep 2023;11:2050313X231211050.
26. Endell J, Boxhammer R, Wurzenberger C, Ness D, Steidl S. The activity of MOR202, a fully human anti-CD38 antibody, is complemented by ADCP and is synergistically enhanced by lenalidomide in vitro and in vivo. Blood 2012;120:4018. abstract.
27. Boxhammer R, Weirather J, Steidl S, Endell J. MOR202, a human anti-CD38 monoclonal antibody, mediates potent tumoricidal activity in vivo and shows synergistic efficacy in combination with different antineoplastic compounds. Blood 2015;126:3015. abstract.
28. Mayer KA, Budde K, Halloran PF, et al. Safety, tolerability, and efficacy of monoclonal CD38 antibody felzartamab in late antibody-mediated renal allograft rejection: study protocol for a phase 2 trial. Trials 2022;23:270.
29. Halloran PF, Madill-Thomsen KS, Reeve J. The molecular phenotype of kidney transplants: insights from the MMDx Project. Transplantation 2024;108:45-71.
30. Oellerich M, Sherwood K, Keown P, et al. Liquid biopsies: donor-derived cell-free DNA for the detection of kidney allograft injury. Nat Rev Nephrol 2021;17:591-603.
31. Irish W, Nickerson P, Astor BC, et al. Change in estimated GFR and risk of allograft failure in patients diagnosed with late active antibody-mediated rejection following kidney transplantation. Transplantation 2021;105:648-59.
32. Cole S, Walsh A, Yin X, et al. Integrative analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther 2018;20:85.
33. Ostendorf L, Burns M, Durek P, et al. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. N Engl J Med 2020;383:1149-55.
34. Holzer M-T, Ruffer N, Huber TB, Kötter I, Ostendorf L, Krusche M. Daratumumab for autoimmune diseases: a systematic review. RMD Open 2023;9(4):e003604.
35. Vincenti F, Bestard O, Brar A, et al. Isatuximab monotherapy for desensitization in highly sensitized patients awaiting kidney transplant. J Am Soc Nephrol 2024;35:347-60.
36. Casneuf T, Xu XS, Adams HC III, et al. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. Blood Adv 2017;1:2105-14.
37. Wang Y, Zhang Y, Hughes T, et al. Fratricide of NK cells in daratumumab therapy for multiple myeloma overcome by *ex vivo*-expanded autologous NK cells. Clin Cancer Res 2018;24:4006-17.
38. Doberer K, Schiemann M, Strassl R, et al. Torque teno virus for risk stratification of graft rejection and infection in kidney transplant recipients — a prospective observational trial. Am J Transplant 2020;20:2081-90.
39. De Vlaminck I, Khush KK, Strehl C, et al. Temporal response of the human virome to immunosuppression and antiviral therapy. Cell 2013;155:1178-87.
40. Scalzo RE, Sanoff SL, Rege AS, et al. Daratumumab use prior to kidney transplant and T cell-mediated rejection: a case report. Am J Kidney Dis 2023;81:616-20.