Belatacept and Long-Term Outcomes in Kidney Transplantation

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ABSTRACT

BACKGROUND
In previous analyses of BENEFIT, a phase 3 study, belatacept-based immunosuppression, as compared with cyclosporine-based immunosuppression, was associated with similar patient and graft survival and significantly improved renal function in kidney-transplant recipients. Here we present the final results from this study.

METHODS
We randomly assigned kidney-transplant recipients to a more-intensive belatacept regimen, a less-intensive belatacept regimen, or a cyclosporine regimen. Efficacy and safety outcomes for all patients who underwent randomization and transplantation were analyzed at year 7 (month 84).

RESULTS
A total of 666 participants were randomly assigned to a study group and underwent transplantation. Of the 660 patients who were treated, 153 of the 219 patients treated with the more-intensive belatacept regimen, 163 of the 226 treated with the less-intensive belatacept regimen, and 131 of the 215 treated with the cyclosporine regimen were followed for the full 84-month period; all available data were used in the analysis. A 43% reduction in the risk of death or graft loss was observed for both the more-intensive and the less-intensive belatacept regimens as compared with the cyclosporine regimen (hazard ratio with the more-intensive regimen, 0.57; 95% confidence interval [CI], 0.35 to 0.95; P = 0.02; hazard ratio with the less-intensive regimen, 0.57; 95% CI, 0.35 to 0.94; P = 0.02), with equal contributions from the lower rates of death and graft loss. The mean estimated glomerular filtration rate (eGFR) increased over the 7-year period with both belatacept regimens but declined with the cyclosporine regimen. The cumulative frequencies of serious adverse events at month 84 were similar across treatment groups.

CONCLUSIONS
Seven years after transplantation, patient and graft survival and the mean eGFR were significantly higher with belatacept (both the more-intensive regimen and the less-intensive regimen) than with cyclosporine. (Funded by Bristol-Myers Squibb; ClinicalTrials.gov number, NCT00256750.)
The use of prolonged maintenance immunosuppressive therapy after kidney transplantation has improved the short-term outcomes, but the effect on long-term allograft survival is not known. Prospective, phase 3, randomized studies examining the outcomes of immunosuppressive regimens beyond 5 years or showing a survival advantage of newer immunosuppressive regimens over that afforded by regimens containing the calcineurin inhibitor cyclosporine are lacking. Belatacept is a selective costimulation blocker that has been developed to improve long-term outcomes in kidney-transplant recipients by providing effective immunosuppression without the toxic effects of calcineurin inhibitors.

Current standard-of-care immunosuppressive regimens combine calcineurin inhibitors with antiproliferative drugs, with or without maintenance glucocorticoids. Calcineurin inhibitor–based regimens, however, may not adequately preserve allograft function, leading to deteriorating kidney function, which is a risk factor for death from cardiovascular causes in kidney-transplant recipients. The development of donor-specific antibodies has also been associated with negative post-transplantation outcomes, including an increased risk of antibody-mediated rejection and graft failure. The lack of improvement in long-term patient and graft survival is multifactorial, but cardiovascular disease, calcineurin inhibitor–associated nephotoxicity, emergence of donor-specific antibodies, and nonadherence to treatment are major contributors.

Belatacept, a fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through costimulation blockade. Belatacept was approved by the U.S. Food and Drug Administration and the European Medicines Agency in 2011, on the basis, in part, of 3-year data from two phase 3 studies: the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) and BENEFIT–Extended Criteria Donors (BENEFIT-EXT). A less-intensive belatacept regimen is approved for use only in patients who are positive for Epstein–Barr virus (EBV), given the increased risk of post-transplantation lymphoproliferative disorder, predominantly involving the central nervous system, in EBV-seronegative patients. Patients in the belatacept trial were not prospectively stratified according to EBV status when the study started, since no safety signal was identified on the basis of EBV-negative serostatus. The decision to restrict belatacept for use only in EBV-positive patients was based on the findings of the phase 3 trials. The present report summarizes the final efficacy and safety results up to 7 years (84 months) after transplantation in the intention-to-treat population of BENEFIT.

**Methods**

**Study Design and Oversight**

The trial design has been published previously. The original study was a 3-year, international, randomized, single-blind, parallel-group study with an active control. The participants were adults who received a kidney transplant from a living or deceased donor, with deceased donors meeting standard-criteria donor status on the basis of age and other benchmarks. Patients were randomly assigned (in a 1:1:1 ratio) to a more-intensive belatacept-based regimen, a less-intensive belatacept-based regimen, or a cyclosporine-based regimen for primary immunosuppression. All patients received basiliximab induction, mycophenolate mofetil, and glucocorticoids. Patients were eligible to continue with the assigned therapy beyond 36 months if they provided written informed consent and if they received the approval of their physician. After 36 months, patients were required to continue the assigned regimen to remain in the study.

The study was conducted in accordance with the Declaration of Helsinki. The ethics committee at each site approved the study protocol. All patients provided written informed consent.

The sponsor, Bristol-Myers Squibb, designed the study and gathered and analyzed the data in collaboration with the study investigators. All the authors vouch for the accuracy and completeness of the data and analyses, and the first author vouches for the fidelity of the study to the protocol. A medical writer at CodonMedical, an Ashfield company, who was paid by the sponsor, wrote the first draft of the manuscript under the direction of the authors. No contractual arrangements were in effect to allow the sponsor to have sole control of the data or to withhold publication of the data.
OUTCOME MEASURES
The primary objective at month 12 was an assessment of the composite end point of patient and graft survival, renal function, and the incidence of acute rejection in each belatacept regimen as compared with the cyclosporine regimen. For the present analysis, outcomes were evaluated from randomization to month 84 (year 7). The contributions of the individual components — patient survival and graft survival — of the composite end point of patient and graft survival were also determined. Renal function was assessed on the basis of the estimated glomerular filtration rate (eGFR), which was calculated with the use of the six-variable Modification of Diet in Renal Disease equation. Safety outcomes were expressed as incidence rates per 100 person-years of exposure to the assigned treatment. The development of donor-specific antibodies was determined centrally by means of solid-phase flow cytometry (FLowPRA, One Lambda); the HLA class specificity of detected antibodies was assessed with the use of the LABScreen single-antigen-bead–based assay (One Lambda).

STATISTICAL ANALYSIS
In this prospective analysis, we used a log-rank test to assess the time to death or graft loss with each belatacept regimen as compared with the cyclosporine regimen. Kaplan–Meier survival curves and event rates are presented. Hazard ratios and 95% confidence intervals for death or graft loss for the first 60 months and for the first 84 months were derived with the use of Cox regression; for the calculation of hazard ratios, data were censored at month 60 and month 84, respectively. Time to death and time to graft loss, with censoring of data for patients who died, were assessed as sensitivity analyses in order to determine the contribution of each component to the composite end point; both statistical methods were used, without adjustment for multiple comparisons. In the analyses of the time to death or graft loss, censoring rules were as follows: first, if a date of death but no date of graft loss was reported for a patient, the time to the event was defined as the time from transplantation to the date of death; second, if a graft-loss date but not a date of death was reported for a patient, the time to the event was defined as the time from transplantation to the date of graft loss; third, if both a graft-loss date and a date of death were reported for a patient, the time to the event was defined as the time from transplantation to the date of graft loss; and fourth, if no date of death or graft-loss date was reported, the data were censored at the reported date of the last follow-up assessment. For patients treated for up to 7 years, the last follow-up assessment was at 7 years. For patients who discontinued treatment before 7 years and were not followed thereafter, censoring occurred on the date of the last available follow-up assessment.

The mean eGFR and corresponding confidence intervals were determined from month 1 to month 84 with the use of a repeated-measures model with an unstructured covariance matrix, which takes into account between-patient variability and the intrapatient correlation of eGFR measurements across all time points. This model assumed that missing data were missing completely at random and included treatment, time, and a time-by-treatment interaction; no adjustment was made for other potentially confounding covariates. Time was expressed as a categorical variable (in intervals of 3 months up to month 36 and intervals of 6 months thereafter). A sensitivity analysis was performed in which eGFR values that were missing because of death or graft loss were imputed as zero. The model that was used for the primary analysis was also used for this sensitivity analysis but with a Toeplitz covariance matrix, which best fit the data because the unstructured covariance matrix was not converging.

A slope-based model without imputation of missing values was also used to determine whether there was a difference between the slope for each belatacept regimen and the slope for cyclosporine, assuming the linearity of the eGFR values between months 1 and 84. The difference between slopes was tested with the use of a contrast statement within the SAS model (SAS software, version 9.2; SAS Institute). Time was regarded as a continuous variable, treatment as a fixed effect, and the intercept and time as random effects; no adjustment was made for other potentially confounding covariates. A sensitivity analysis was performed in which eGFR values that were missing because of death or graft loss were imputed as zero; the model used for the slope analysis without imputation was also used for this analysis.
RESULTS

STUDY PARTICIPANTS

Participants were randomly assigned to a treatment group between January 13, 2006, and June 14, 2007. Of the 666 patients who underwent randomization and transplantation, 660 patients were treated; 153 of the 219 patients treated with the more-intensive belatacept regimen, 163 of the 226 treated with the less-intensive belatacept regimen, and 131 of the 215 treated with cyclosporine were followed for the full 84-month period (Fig. 1), and all available data were analyzed. The median duration of follow-up for each treatment group was 84.0 months (range: more-intensive belatacept, 0.2 to 84.0 months; less-intensive belatacept, 0.03 to 84.0 months; and cyclosporine, 0.07 to 84.0 months) (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Data on adherence to medication were collected up to month 36 and are summarized in Table S1 in the Supplementary Appendix.

EFFICACY

On the basis of Kaplan–Meier estimates, rates of death or graft loss with more-intensive belatacept, less-intensive belatacept, and cyclosporine were 7.8%, 8.0%, and 11.4%, respectively, at month 36; 10.2%, 9.2%, and 20.2%, respectively, at month 60; and 12.7%, 12.8%, and 21.7%, respectively, at month 84 (Table S2 in the Supplementary Appendix). At month 60, the hazard ratio for the comparison of more-intensive belatacept with cyclosporine was 0.53 (95% CI, 0.27 to 1.05; P=0.049), and the hazard ratio for the comparison of less-intensive belatacept with cyclosporine was 0.47 (95% CI, 0.23 to 0.94; P=0.02). At month 84, the respective hazard ratios were 0.62 (95% CI, 0.33 to 1.14; P=0.11) and 0.55 (95% CI, 0.30 to 1.04; P=0.06) (Fig. 2B). Causes of death are summarized in Table S4 in the Supplementary Appendix.

Kaplan–Meier estimates for rates of graft loss among patients receiving more-intensive belatacept, those receiving less-intensive belatacept, and those receiving cyclosporine, with censoring of data for death, were 4.7%, 4.1%, and 4.6%, respectively, at month 36; 4.7%, 4.1%, and 9.8% at month 60; and 4.7%, 5.4%, and 9.8% at month 84 (Table S5 in the Supplementary Appendix). At month 60, the hazard ratio for the comparison of more-intensive belatacept with cyclosporine was 0.49 (95% CI, 0.22 to 1.09; P=0.07). At month 84, the respective hazard ratios were 0.56 (95% CI, 0.25 to 1.21; P=0.12) and the hazard ratio for the comparison of less-intensive belatacept with cyclosporine was 0.49 (95% CI, 0.22 to 1.09; P=0.07). At month 84, the Kaplan–Meier cumulative rates of biopsy-proven acute rejection were 24.4%, 18.3%, and 11.4% with more-intensive belatacept, less-intensive belatacept, and cyclosporine, respectively.

ESTIMATED GLOMERULAR FILTRATION RATE

The mean eGFR increased during the first 7 years with both belatacept-based regimens but declined with the cyclosporine-based regimen (Fig. 3). At months 12, 36, 60, and 84, the mean eGFR values were 67.0, 68.9, 70.2, and 70.4 ml per minute per 1.73 m² of body-surface area, respectively, with more-intensive belatacept and 66.0, 68.9, 70.3, and 72.1 ml per minute per 1.73 m² with less-intensive belatacept. The corresponding values for cyclosporine were 52.5, 48.6, 46.8, and 44.9 ml per minute per 1.73 m². The estimated differences in the eGFR significantly favored each belatacept regimen over cyclosporine (P<0.001 for the overall treatment effect of each belatacept regimen).

The slope-based analysis of the change from month 1 to month 84 showed that patients randomly assigned to the more-intensive belatacept regimen had a gain in the mean eGFR of 1.30 ml
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per minute per 1.73 m² per year (95% CI, 0.83 to 1.77) and those assigned to the less-intensive regimen had a gain of 1.39 ml per minute per 1.73 m² per year (95% CI, 0.93 to 1.84). Over the same period, patients randomly assigned to cyclosporine had a decline in the mean eGFR (−1.04 ml per minute per 1.73 m² per year; 95% CI, −1.53 to −0.54). The eGFR slopes diverged significantly between belatacept and cyclosporine over time. The treatment-by-time interaction effect derived from the mixed-effects model significantly favored each belatacept regimen over cyclosporine (P<0.001).

Figure 1. Number of Patients Who Were Enrolled, Underwent Randomization, and Completed the Study.
Patients who could be evaluated were those who were followed for at least 84 months or who had died or had graft loss by month 84. LI denotes less intensive, LTE long-term extension, and MI more intensive.
Belatacept MI vs. cyclosporine: hazard ratio for death or graft loss, 0.57 (95% CI, 0.35–0.95); P=0.02
Belatacept LI vs. cyclosporine: hazard ratio for death or graft loss, 0.57 (95% CI, 0.35–0.94); P=0.02
Belatacept MI vs. cyclosporine: hazard ratio for death, 0.62 (95% CI, 0.33–1.14); P=0.11
Belatacept LI vs. cyclosporine: hazard ratio for death, 0.55 (95% CI, 0.30–1.04); P=0.06
Belatacept MI vs. cyclosporine: hazard ratio for death-censored graft loss, 0.56 (95% CI, 0.25–1.21); P=0.12
Belatacept LI vs. cyclosporine: hazard ratio for death-censored graft loss, 0.59 (95% CI, 0.28–1.25); P=0.15
For the analysis in which eGFR values that were missing because of death or graft loss were imputed as zero, the mean eGFR values at months 12, 36, 60, and 84 were 64.3, 64.8, 63.9, and 62.0 ml per minute per 1.73 m², respectively, with the more-intensive belatacept regimen and 63.8, 65.2, 65.2, and 63.3 ml per minute per 1.73 m² with the less-intensive regimen. The corresponding values for cyclosporine were 49.8, 44.3, 39.1, and 36.6 ml per minute per 1.73 m².

With imputation of missing values, differences in the eGFR remained significantly in favor of belatacept (P<0.001 for the overall treatment effect of each belatacept regimen vs. cyclosporine).

Results of the slope-based analysis with imputation showed a slight increase in the mean eGFR from month 1 to month 84 for patients randomly assigned to the more-intensive belatacept regimen (0.20 ml per minute per 1.73 m² per year; 95% CI, −0.38 to 0.78) and those assigned to the less-intensive regimen (0.38 ml per minute per 1.73 m² per year; 95% CI, −0.18 to 0.95), whereas patients randomly assigned to cyclosporine had a decline in the mean eGFR (−1.92 ml per minute per 1.73 m² per year; 95% CI, −2.51 to −1.32). With imputation of missing values, the treatment-by-time interaction effect remained significantly in favor of each belatacept regimen (P<0.001).

**SAFETY**

At month 84, the cumulative frequencies of serious adverse events for the more-intensive and less-intensive belatacept regimens and for cyclosporine were 49.8, 44.3, 39.1, and 36.6 ml per minute per 1.73 m². With imputation of missing values, differences in the eGFR remained significantly in favor of belatacept (P<0.001 for the overall treatment effect of each belatacept regimen vs. cyclosporine).

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cases of post-transplantation lymphoproliferative disorder occurred in the first 24 months. Among patients known to be EBV-positive before transplantation, 1 case of lymphoproliferative disorder, occurring between 12 and 24 months after transplantation, was reported in the group assigned to the more-intensive belatacept regimen (incidence rate, 0.1 cases per 100 person-years); 2 cases, occurring during the first 12 months after transplantation, were reported in the group assigned to the less-intensive belatacept regimen (incidence rate, 0.2 cases per 100 person-years); and 1 case, occurring between 60 and 72 months after transplantation, was reported in the cyclosporine group (incidence rate, 0.1 cases per 100 person-years).

Among EBV-negative patients, 2 cases of lymphoproliferative disorder, 1 occurring during the first 12 months after transplantation and 1 occurring between 12 and 24 months after transplantation, were reported in the group assigned to the more-intensive belatacept regimen (incidence rate, 1.6 cases per 100 person-years), and 1 case, occurring during the first 12 months after transplantation, was reported in the cyclosporine group (incidence rate, 0.6 cases per 100 person-years). Post-transplantation lymphoproliferative disorder did not occur in any of the EBV-negative patients who were randomly assigned to the less-intensive belatacept regimen.

### Table 1. Cumulative Incidence Rates of Selected Adverse Events.*

| Event                                              | More-Intensive Belatacept (N = 219) | Less-Intensive Belatacept (N = 226) | Cyclosporine (N = 221) |
|----------------------------------------------------|------------------------------------|-------------------------------------|------------------------|
| no. of events/100 person-yr                        |                                    |                                     |                        |
| Serious infections                                 | 10.6                               | 10.7                                | 13.3                   |
| Urinary tract infection                            | 1.9                                | 2.0                                 | 3.1                    |
| Cytomegalovirus infection                          | 1.4                                | 1.1                                 | 0.8                    |
| Pneumonia                                          | 0.7                                | 1.1                                 | 1.4                    |
| Pyelonephritis                                     | 0.7                                | 0.7                                 | 0.9                    |
| Sepsis                                             | 0.8                                | 0.5                                 | 0.8                    |
| Gastroenteritis                                    | 0.7                                | 0.3                                 | 0.7                    |
| Acute pyelonephritis                               | 0.5                                | 0.3                                 | 0.2                    |
| Upper respiratory tract infection                  | 0.1                                | 0.2                                 | 0.5                    |
| Serious gastrointestinal disorders                  | 3.9                                | 2.2                                 | 3.8                    |
| Serious general disorders and administration-site conditions | 2.5                        | 2.3                                 | 2.7                    |
| Serious cardiac disorders                          | 2.0                                | 1.4                                 | 2.2                    |
| Serious vascular disorders                         | 1.8                                | 1.5                                 | 2.9                    |
| Serious blood and lymphatic system disorders        | 1.6                                | 1.0                                 | 1.6                    |
| Serious hepatobiliary disorders                    | 0.5                                | 0.3                                 | 0.7                    |
| Serious endocrine disorders                        | 0.2                                | 0.3                                 | 0.5                    |
| Cancer of any grade                                | 2.1                                | 1.8                                 | 2.6                    |

* Only events occurring at an adjusted rate of 2% or more of patients in any treatment group are reported. Event rates have been adjusted for the duration of treatment exposure (expressed in person-years). For serious infections and cancer of any grade, treatment exposure was calculated from the randomization date to the date of the event, the date of the last follow-up assessment, or month 84, whichever was earliest. For all other events, treatment exposure was calculated from the randomization date to the date of the event, the date of the last dose of study medication plus 56 days, or month 84, whichever was earliest. Infections are classified according to the preferred terms in the Medical Dictionary for Regulatory Activities.

### DONOR-SPECIFIC ANTIBODIES

The absolute proportion of patients in whom donor-specific antibodies developed by year 7 is shown in Figure S1 in the Supplementary Appendix according to treatment group. The Kaplan–Meier cumulative rates for the development of donor-specific antibodies at months 36, 60, and
The corresponding values for cyclosporine were 8.7%, 16.2%, and 17.8%. The Kaplan–Meier cumulative rate for the development of donor-specific antibodies was significantly lower with each belatacept regimen than with cyclosporine (P<0.001). Information on specific antibody classes is provided in Figure S1 in the Supplementary Appendix.

**Discussion**

In the present study, patients randomly assigned to either a more-intensive or a less-intensive belatacept regimen had a 43% reduction in the risk of death or graft loss at 7 years, as compared with patients randomly assigned to cyclosporine. The treatment effect was similar for each component of the composite end point (time to death and time to graft loss). The reduction in the risk of death at 7 years was 38% with the more-intensive belatacept regimen and 45% with the less-intensive regimen as compared with cyclosporine. The corresponding values for the reduction in the risk of graft loss, with censoring of data for patients who died, were 44% and 41%. The difference in patient and graft survival between belatacept-based and cyclosporine-based immunosuppression was both statistically and clinically significant.

Results from the 7-year analysis of the present study contrast with those from the 7-year analysis of BENEFIT-EXT, in which recipients of kidneys obtained from deceased donors meeting expanded-criteria status (i.e., older age and more coexisting conditions than standard-criteria donors) were also randomly assigned to receive treatment with the more-intensive belatacept regimen, the less-intensive regimen, or cyclosporine. An analysis of the study data of BENEFIT-EXT at 7 years after transplantation showed that the rates of death and graft loss with the belatacept-based regimens were similar to the rates with the cyclosporine-based regimen. The participants in BENEFIT had several advantages over the participants in BENEFIT-EXT. In addition to receiving healthier kidneys (i.e., kidneys from living donors or kidneys obtained from standard-criteria deceased donors), the BENEFIT participants were younger overall (mean age, 43.2 years vs. 56.2 years), as were their donors (mean age, 40.2 years vs. 43.2 years); also, the transplant recipients in the present study had fewer coexisting conditions. These covariates may have contributed to the different outcomes of the two studies. Notably, a post hoc analysis of BENEFIT-EXT data showed a 41% reduction in the risk of death, graft loss, or a mean eGFR that was less than 30 ml per minute per 1.73 m² 7 years after transplantation among patients randomly assigned to the more-intensive or less-intensive belatacept regimen as compared with those assigned to cyclosporine (Fig. S2 in the Supplementary Appendix). We believe this finding is important because an eGFR value of less than 30 ml per minute per 1.73 m² is equivalent to stage 4 or higher chronic kidney disease, a point at which it is apparent that some patients (if they have further progression) will need maintenance dialysis.

In this phase 3 randomized trial, the clinically and statistically significant improvements in renal function that were observed with belatacept as compared with cyclosporine at earlier time points were sustained at 7 years. Rates of acute rejection were similar to those in previous reports, with few cases occurring after 36 months (no case of acute rejection with more-intensive belatacept, one case with less-intensive belatacept, and two cases with cyclosporine). The long-term safety profile of belatacept was consistent with that described previously. Most cases of post-transplantation lymphoprolierative disorder occurred during the first 24 months, a finding that is consistent with the findings in kidney-transplant recipients treated with calcineurin inhibitor–based immunosuppressive regimens.

The development of donor-specific antibodies can lead to allograft failure. Donor-specific antibodies are estimated to develop in 11% of patients during the year after kidney transplantation and in 20% of patients by 5 years after transplantation. In our study, the cumulative event rates for the development of donor-specific antibodies at year 7 were significantly lower with both belatacept-based regimens than with the cyclosporine-based regimen, a finding that supports earlier analyses of the data from this trial. Class 1 donor-specific antibodies typically develop within 6 months after transplantation and are associated with a better prognosis than
class II antibodies.30 The frequency of class II donor-specific antibodies in our study was lower with both belatacept regimens than with cyclosporine. This finding is consistent with the effect of costimulation blockade in experimental transplantation.31

One limitation of our trial was that we did not compare belatacept with tacrolimus, the current standard-of-care calcineurin inhibitor. However, patient and graft survival outcomes with contemporary tacrolimus-based regimens are similar to those observed with cyclosporine-based regimens.5,12-34

Another limitation is that data for patients who did not have an event were censored at the last follow-up assessment, which was earlier than year 7 for patients who discontinued the study. However, in each treatment group, patient retention was high, with a prolonged median duration of follow-up. Adherence to the study medication (not a primary focus of the study) was not directly assessed beyond month 36. We expected that adherence would differ for the two types of study medication, since cyclosporine was administered orally by the patient at home and belatacept was administered intravenously under the supervision of a health care provider.

We assessed efficacy and safety outcomes in kidney-transplant recipients who were treated with maintenance immunosuppression beyond 5 years; other studies of immunosuppressive regimens have reported outcomes up to 5 years after kidney transplantation.35-39 In our study, the risk of death or graft loss at year 7 was significantly lower for belatacept-treated patients than for cyclosporine-treated patients; this result was made more notable by the fact that the survival benefit emerged as early as 5 years after transplantation.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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