Outcomes at 7 years post-transplant in black vs nonblack kidney transplant recipients administered belatacept or cyclosporine in BENEFIT and BENEFIT-EXT

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Abstract
Clinical outcomes are generally worse for black vs nonblack renal allograft recipients. In BENEFIT and BENEFIT-EXT, recipients were randomized to belatacept more intense-based, belatacept less intense-based, or cyclosporine-based immunosuppression. At year 7, belatacept was associated with superior graft survival vs cyclosporine in BENEFIT (recipients of living or standard criteria deceased donor kidneys); belatacept was associated with similar graft survival vs cyclosporine in BENEFIT-EXT (recipients of extended criteria donor kidneys). In both studies, renal function was superior for belatacept-treated vs cyclosporine-treated patients. Seven-year outcomes were examined by race post hoc in each study. The effect of race and treatment on time to death or graft loss was compared using Cox regression. The interaction between treatment and race was also considered. Glomerular filtration rate (GFR) was estimated from months 1 to 84 using a repeated-measures model. In total, 8.3% (55/666) and 13.1% (71/543) of patients in BENEFIT and BENEFIT-EXT,
1 INTRODUCTION

Black renal allograft recipients administered calcineurin inhibitor-based or mammalian target of rapamycin (mTOR) inhibitor-based immunosuppression have poorer outcomes than nonblacks. Registry data show acute rejection (AR) rates at 1 year post-transplant to be significantly higher in black vs nonblack patients.1,2,12 Graft loss rates at 5 years post-transplant are also higher3,4—independent of living or deceased donor kidney status.5

Racial disparities in kidney transplant outcomes have been attributed to immunologic, pharmacokinetic, and socioeconomic factors.5 In vitro testing performed prior to transplantation has shown black patients to display more intense, nonspecific immunoreactivity than whites.6 Black individuals also exhibit increased expression of co-stimulatory molecules and/or cytokines.7,8 These immunologic properties may negatively impact graft survival.6-8 The pharmacokinetics of several immunosuppressives vary by race. The bioavailability of calcineurin and mTOR inhibitors is lower in blacks vs whites,1,9-11 and mycophenolate mofetil is cleared more rapidly in black vs white renal allograft recipients.12,13 Thus, the higher rates of graft failure among black kidney transplant recipients may result from inadequate immunosuppression. The role of socioeconomic factors is controversial,5,14 as it may be confounded by racial differences in income, healthcare access, and insurance coverage. For example, black and white Canadian renal allograft recipients have similar graft survival rates.15 Such data, which contrast with those from US renal transplant populations,3,4,16 may be due to Canadians having access to free health care, including the cost of transplantation and post-transplantation follow-up.15 However, in a US retrospective analysis, a graft survival disadvantage persisted among black renal allograft recipients, independent of whether they had received universal health care from the Department of Veterans Affairs.17

The available data on racial disparities in kidney transplant recipients derive from patients treated with calcineurin or mTOR inhibitors. The calcineurin inhibitors are potentially nephrotoxic, which may contribute to graft dysfunction and loss.18-22 The mTOR inhibitors are not directly nephrotoxic, but sirolimus and everolimus are poorly tolerated, and both may be associated with worsening allograft function (increased proteinuria) in kidney transplant recipients with pre-existing renal parenchymal damage.23-25 Moreover, everolimus carries a black box warning related to an increased risk of renal allograft thrombosis.26 While there is a need to optimize immunosuppressive regimens in all kidney transplant recipients, this is particularly acute for black patients, given their predisposition to poorer post-transplant outcomes.

Belatacept is a selective T-cell co-stimulation blocker indicated for preventing organ rejection in adult kidney transplant recipients.27 Belatacept was approved in the US and Europe in 2011 based, in part, on data from 2 randomized phase 3 trials comparing belatacept more intense (MI)-based, belatacept less intense (LI)-based, and cyclosporine-based immunosuppression in de novo kidney transplant recipients. The Belatacept Evaluation of Nephroprotection and Efficacy as First-Line Immunosuppression Trial (BENEFIT) and BENEFIT-Extended Criteria Donors (BENEFIT-EXT) had similar designs, except that patients in BENEFIT were transplanted with a living or standard criteria deceased donor kidney,28 while patients in BENEFIT-EXT received an extended criteria donor kidney.29 In intention to treat analyses performed at 7 years post-transplant, belatacept was associated with superior graft survival vs cyclosporine in BENEFIT20 and similar graft survival vs cyclosporine in BENEFIT-EXT.31 In both studies, renal function was superior in belatacept-treated vs cyclosporine-treated patients.30,31 In the present post hoc analysis, outcomes at 7 years post-transplant were compared in black vs nonblack patients participating in BENEFIT and BENEFIT-EXT.

2 METHODS

2.1 Study designs

The designs of BENEFIT (ClinicalTrials.gov identifier: NCT00256750) and BENEFIT-EXT (ClinicalTrials.gov identifier: NCT00114777) have been published.28,29 Briefly, BENEFIT and BENEFIT-EXT were 3-year, international, multicenter, randomized, partially blinded, active-controlled, parallel-group, phase 3 studies of de novo adult kidney transplant recipients. Patients in BENEFIT received a living or standard criteria deceased donor kidney,28 while patients in BENEFIT-EXT received an extended criteria donor kidney.29 Extended criteria donor kidneys were protocol defined as those from donors aged ≥60 years; those from donors aged 50-59 years with ≥2 other risk factors (death due to cerebrovascular accident, history of hypertension, or terminal serum creatinine level >1.5 mg/dL); those with an
anticipated cold ischemia time ≥24 hours; and those from nonheart-beating donors (donation after cardiac death).29

Patients were randomized (1:1:1) to receive maintenance immunosuppression with a belatacept MI-based, belatacept LI-based, or cyclosporine-based regimen. All patients received basiliximab induction, mycophenolate mofetil, and corticosteroids.28,29 If approved by the treating physician, patients were allowed to continue study treatment beyond 3 years with additional written informed consent and continuation of the immunosuppressive regimen to which they had been randomized.32,33 For the present analysis, patients in each study were categorized as black or nonblack; race was self-identified.

Both studies were conducted in accordance with the principles outlined in the Declaration of Helsinki. The institutional review boards/ethics committees at participating sites approved the study protocols, and all patients provided written informed consent.

2.2 | Outcomes and statistics

Efficacy and safety from randomization to month 84 (year 7) were examined post hoc in black and nonblack patients and analyzed separately for BENEFIT and BENEFIT-EXT. Analyses were performed on all evaluable patients, assessed per the intention to treat principle at 84 months post-transplant. The evaluable population was composed of patients who were alive and observable at 84 months postrandomization or who had died or experienced graft loss by month 84.

For the examination of time to death or graft loss, patients were stratified into 1 of 6 subgroups based on race and treatment assignment. Data are summarized using Kaplan–Meier curves and event rates. Hazard ratios and 95% confidence intervals (CIs) at month 84 were calculated from 2 models of Cox regression. In the first model, race and treatment were regarded as independent variables. In the second model, the interaction between treatment and race was considered; cyclosporine-treated nonblack patients served as the reference population, with no adjustment for multiplicity.

The Kaplan–Meier method was used to assess a combined end point comprising time to first occurrence of death, graft loss, or estimated glomerular filtration rate (GFR) <30 mL/min/1.73 m² in BENEFIT. This end point was also explored in BENEFIT-EXT, but the estimated GFR threshold was lowered to <20 mL/min/1.73 m² because renal function was generally lower in recipients of extended criteria donor kidneys. GFR was estimated via the 6-variable Modification of Diet in Renal Disease equation.34

AR was defined as central biopsy-proven rejection that was either clinically suspected for protocol-defined reasons or clinically suspected for other reasons and treated. AR incidence from randomization to month 84 was summarized using Kaplan–Meier cumulative events rates and curves.

Estimated mean GFR and corresponding CIs were determined from months 1-84 using a repeated-measures model with an unstructured covariance matrix. This model takes into account between-subject variability and the intrasubject correlation between estimated GFR measurements across all time points, and assumes that missing data are missing at random. The model included treatment, time, and a time × treatment interaction; no further adjustment was made for other potentially confounding covariates. Time was regarded as a categorical variable (intervals of 3 months up to month 36 and intervals of 6 months thereafter). A slope-based model without imputation was used to determine whether there was a difference between each of the belatacept slopes and the cyclosporine slope, assuming linearity of the estimated GFR values between months 1 and 84. The difference between slopes was tested using contrasts. Time was regarded as a continuous variable, treatment as a fixed effect, and intercept and time as random effects; no further adjustment was made for other potentially confounding covariates. Sensitivity analyses were performed in which GFR values that were missing due to death or graft loss were imputed as zero; the same models were used as for the analyses without imputation.

Adverse events were mapped to terms from the Medical Dictionary for Regulatory Activities version 17.0 and expressed

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**FIGURE 1** Patient numbers by race and treatment allocation in (A) BENEFIT and (B) BENEFIT-EXT. MI, more intense; LI, less intense

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as incidence rates adjusted per 100 person-years of treatment exposure.

3 | RESULTS

3.1 | BENEFIT: Patients

In total, 8.3% (55/666) of patients in BENEFIT were black (Figure 1A). Compared with nonblacks, a greater percentage of blacks were from North America and had diabetes or hypertensive nephrosclerosis as the reported cause of end-stage renal disease (Table 1). Table S1 summarizes the duration of follow-up by race in each treatment arm.

### TABLE 1 Baseline characteristics by race and treatment

|                | BENEFIT | BENEFIT-EXT |
|----------------|---------|-------------|
|                | Belatacept MI | Belatacept LI | Cyclosporine | Belatacept MI | Belatacept LI | Cyclosporine |
| Mean age (SD), y | 45.5 (14.0) | 47.3 (9.9) | 48.2 (16.0) | 55.2 (12.5) | 50.1 (13.2) | 54.4 (11.4) |
| Black          | 43.4 (14.6) | 42.1 (13.7) | 43.1 (14.1) | 57.0 (12.6) | 57.0 (12.1) | 55.8 (12.4) |
| Nonblack       | 10/15 (66.7) | 14/23 (60.9) | 10/17 (58.8) | 16/25 (64.0) | 19/24 (79.2) | 13/22 (59.1) |
| Male, n/N (%)  | 141/204 (69.1) | 132/203 (65.0) | 155/204 (76.0) | 103/159 (64.8) | 110/151 (72.8) | 103/162 (63.6) |
| Region, n/N (%)|         |             |            |             |             |             |
| North America  | 9/15 (60.0) | 14/23 (60.9) | 11/17 (64.7) | 15/25 (60.0) | 15/24 (62.5) | 16/22 (72.7) |
| Nonblack       | 90/204 (44.1) | 82/203 (40.4) | 87/204 (42.6) | 35/159 (22.0) | 26/151 (17.2) | 30/162 (18.5) |
| South America  | 4/15 (26.7) | 7/23 (30.4) | 3/17 (17.6) | 7/25 (28.0) | 7/24 (29.2) | 5/22 (22.7) |
| Nonblack       | 31/204 (15.2) | 29/203 (14.3) | 30/204 (14.7) | 38/159 (23.9) | 40/151 (26.5) | 45/162 (27.8) |
| Europe         | 2/15 (13.3) | 2/23 (8.7) | 2/17 (11.8) | 3/25 (12.0) | 2/24 (8.3) | 1/22 (4.5) |
| Nonblack       | 49/204 (24.0) | 58/203 (28.6) | 52/204 (25.5) | 85/159 (53.5) | 83/151 (55.0) | 87/162 (53.7) |
| Rest of world  | 0 | 0 | 1/17 (5.9) | 0 | 0 | 0 |
| Nonblack       | 34/204 (16.7) | 34/203 (16.7) | 35/204 (17.2) | 1/159 (0.6) | 2/151 (1.3) | 0 |
| Pretransplant dialysis, n/N (%) | 13/15 (86.7) | 21/23 (91.3) | 14/17 (82.4) | 25/25 (100.0) | 23/24 (95.8) | 22/22 (100.0) |
| Nonblack       | 164/204 (80.4) | 171/203 (84.2) | 172/204 (84.3) | 147/159 (92.5) | 142/151 (94.0) | 148/162 (91.4) |
| Pretransplant diabetes, n/N (%) | 3/15 (20.0) | 9/23 (39.1) | 6/17 (35.3) | 8/25 (32.0) | 5/24 (20.8) | 10/22 (45.5) |
| Nonblack       | 35/204 (17.2) | 24/203 (11.8) | 31/204 (15.2) | 30/159 (18.9) | 23/151 (15.2) | 43/162 (26.5) |
| Categorized PRA, n/n (%) | 0 <20% | 17/17 (100.0) | 24/25 (96.0) | 22/24 (91.7) | 20/22 (90.9) |
| Nonblack       | 180/204 (88.2) | 172/203 (84.7) | 181/204 (88.7) | 153/159 (96.2) | 143/151 (94.7) | 148/162 (91.4) |
| ≥20%           | 3/15 (20.0) | 9/23 (39.1) | 6/17 (35.3) | 8/25 (32.0) | 5/24 (20.8) | 10/22 (45.5) |
| Nonblack       | 35/204 (17.2) | 24/203 (11.8) | 31/204 (15.2) | 30/159 (18.9) | 23/151 (15.2) | 43/162 (26.5) |
| Pretransplant diabetes, n/N (%) | 11/15 (73.3) | 19/23 (82.6) | 17/17 (100.0) | 24/25 (96.0) | 22/24 (91.7) | 20/22 (90.9) |
| Nonblack       | 180/204 (88.2) | 172/203 (84.7) | 181/204 (88.7) | 153/159 (96.2) | 143/151 (94.7) | 148/162 (91.4) |

MI, more intense; LI, less intense; PRA, panel reactive antibody.

<sup>a</sup>PRA data missing for the remaining patients.

3.2 | BENEFIT: Efficacy

In the black subgroup, 60.0% (9/15) of belatacept MI-treated, 73.9% (17/23) of belatacept LI-treated, and 64.7% (11/17) of cyclosporine-treated patients were assessed for death or graft loss at 84 months post-transplant. The corresponding values in the nonblack subgroup were 70.6% (144/204), 71.9% (146/203), and 58.8% (120/204), respectively. Nonblack patients randomized to cyclosporine had the greatest risk of death or graft loss. In the black subgroup, Kaplan-Meier estimated rates of death or graft loss at month 84 were 0% for belatacept MI, 13.0% for belatacept LI, and 13.7% for cyclosporine. The corresponding values in the nonblack subgroup were 13.6%.
12.8%, and 22.5%, respectively. The hazard ratio for the comparison of each belatacept regimen with cyclosporine was 0.57 (95% CI 0.35-0.94). There was no effect of race on time to death or graft loss: the hazard ratio for the comparison of blacks vs nonblacks was 0.62 (95% CI 0.25-1.53). No interactive effect between treatment and race was observed (Figure 2A).

In the black subgroup, Kaplan–Meier estimated rates of time to first occurrence of death, graft loss, or estimated GFR <30 mL/min/1.73 m² at month 84 were 0% for belatacept MI, 17.6% for belatacept LI, and 42.5% for cyclosporine. The corresponding values in the nonblack subgroup were 16.7%, 18.1%, and 35.5%, respectively. Black patients randomized to cyclosporine-based immunosuppression were at the greatest risk of meeting this combined end point (Figure S1).

At month 84, the Kaplan–Meier cumulative event rate of AR was numerically higher for belatacept-based vs cyclosporine-based immunosuppression, but was generally similar between black and nonblack patients within each treatment arm (Figure 3A). Among black patients, the Kaplan–Meier cumulative event rate of AR was 27.3% for belatacept MI, 22.0% for belatacept LI, and 12.9% for cyclosporine. Among nonblack patients, these values were 24.2%, 17.9%, and 11.2%, respectively. Of those black patients who experienced AR, 75.0% (3/4) of belatacept MI-treated, 60.0% (3/5) of belatacept LI-treated, and 50.0% (1/2) of cyclosporine-treated patients had grade II AR (Table S2). The corresponding values in nonblack patients were 75.5% (37/49), 68.6% (24/35), and 42.9% (9/21), respectively. Table S3 summarizes AR episodes by treatment for AR. Of those patients (irrespective of race) who experienced AR, the Kaplan–Meier estimated rates of death or graft loss at month 84 were 15.1% for belatacept MI, 25.0% for belatacept LI, and 28.6% for cyclosporine. The hazard ratio for the comparison of belatacept MI with cyclosporine was 0.93 (95% CI 0.28-3.08); the hazard ratio for the comparison of belatacept LI with cyclosporine was 1.63 (95% CI 0.51-5.19).
3.3 | BENEFIT: Renal function

In both racial subgroups, estimated mean GFR increased over 7 years for belatacept-based immunosuppression, but declined for cyclosporine-based treatment (Figure 4). For all treatment arms, estimated mean GFR was comparable in blacks and nonblacks over time. However, estimated differences in GFR significantly favored each belatacept-based regimen vs cyclosporine-based treatment.
in both racial subgroups (each $P < .0001$ for overall treatment effect).

For the slope-based analysis of the estimated change in GFR over months 1-84, belatacept-treated black and nonblack patients experienced mean gains, while all cyclosporine-treated patients—irrespective of race—experienced mean declines. Black patients randomized to belatacept MI or LI experienced estimated mean GFR gains of $+0.20$ (95% CI $−1.52$ to $1.92$) and $+2.98$ (95% CI $1.62-4.34$) mL/min/1.73 m$^2$ per year, respectively, while cyclosporine-treated black patients had an estimated mean decline equivalent to $−1.72$ (95% CI $−3.33$ to $−0.11$) mL/min/1.73 m$^2$ per year. Compared with cyclosporine, the interaction of the treatment vs time effect deriving from the repeated-measures model significantly favored belatacept LI ($P < .0001$); the comparison of cyclosporine with belatacept MI was not significant ($P = .11$). For nonblack patients, the estimated mean gain in GFR was $+1.38$ (95% CI $0.90-1.87$) mL/min/1.73 m$^2$ per year for those randomized to belatacept MI and $+1.22$ (95% CI $0.74-1.70$) mL/min/1.73 m$^2$ per year for those randomized to belatacept LI. Nonblack patients administered cyclosporine-based immunosuppression had an estimated mean GFR decline of $−0.97$ (95% CI $−1.49$ to $−0.45$) mL/min/1.73 m$^2$ per year. Relative to cyclosporine, the slope estimates in the nonblack subgroup differed for belatacept MI ($P < .0001$) and LI ($P < .0001$). Sensitivity analyses in which GFR values that were missing due to patient death or graft loss were imputed as zero yielded similar results (Figure S2).

### 3.4 | BENEFIT: Safety

Other than any-grade fungal infections, which were reported more frequently among black vs nonblack cyclosporine-treated patients (16.34 vs 7.00 cases per 100 person-years of exposure, respectively), no notable differences in safety were seen between racial subgroups in any treatment arm (Table S4). No black patient developed post-transplant lymphoproliferative disorder (PTLD) by month 84. Seven nonblack patients had PTLD by month 84 (belatacept MI, $n = 3$; belatacept LI, $n = 2$; cyclosporine, $n = 2$).

### 3.5 | BENEFIT-EXT: Patients

In total, 13.1% (71/543) of patients in BENEFIT-EXT were black (Figure 1B). Compared with nonblacks, a greater percentage of blacks were from North America and had hypertensive nephrosclerosis as the reported cause of end-stage renal disease (Table 1).

### 3.6 | BENEFIT-EXT: Efficacy

In the black subgroup, 56.0% (14/25) of belatacept MI-treated, 66.7% (16/24) of belatacept LI-treated, and 68.2% (15/22) of cyclosporine-treated patients were assessed for death or graft loss at 84 months post-transplant. The corresponding values in the nonblack subgroup were 71.7% (114/159), 80.8% (122/151), and 57.4% (93/162), respectively. Black patients randomized to cyclosporine had the greatest risk of death or graft loss. In the black subgroup, Kaplan–Meier estimated rates of death or graft loss at month 84 were 27.0% for belatacept MI, 34.6% for belatacept LI, and 54.9% for cyclosporine. The corresponding values in the nonblack subgroup were 34.1%, 34.8%, and 32.9%, respectively. The hazard ratio for the comparison of belatacept MI with cyclosporine was 0.91 (95% CI $0.62-1.33$), and the hazard ratio for the comparison of belatacept LI with cyclosporine was 0.92 (95% CI $0.63-1.35$). No effect of race on time to death or graft loss was observed (black vs nonblack: hazard ratio, 1.16; 95% CI $0.75-1.81$). There was also no significant interaction between treatment and race on time to death or graft loss (Figure 2B).

In the black subgroup, Kaplan–Meier estimated rates of time to first occurrence of death, graft loss, or estimated GFR $<20$ mL/min/1.73 m$^2$ at month 84 were 27.0% for belatacept MI, 34.6% for belatacept LI, and 59.7% for cyclosporine. The corresponding values in the nonblack subgroup were 38.7%, 37.2%, and 43.3%, respectively. As observed in BENEFIT, black patients randomized to cyclosporine-based immunosuppression were at the greatest risk of achieving this combined end point (Figure S3).

At month 84, the Kaplan–Meier cumulative event rate of AR was numerically higher for cyclosporine-treated vs belatacept-treated black patients; in the nonblack cohort, the Kaplan–Meier cumulative event rate of AR was greater for belatacept-based vs cyclosporine-based immunosuppression (Figure 3B). Among black patients, the Kaplan–Meier cumulative event rate of AR was 20.2% for belatacept MI, 18.5% for belatacept LI, and 33.2% for cyclosporine. Among nonblack patients, these values were 21.3%, 19.7%, and 15.3%, respectively. The absolute percentage of grade II AR events was numerically higher in belatacept MI-treated (100.0% [5/5]) and belatacept LI-treated (75.0% [3/4]) black patients vs cyclosporine-treated black patients (66.7% [4/6]) (Table S2). The corresponding values in nonblack patients were 76.7% (23/30), 80.0% (24/30), and 82.6% (19/23), respectively. Of those patients (irrespective of race) who experienced AR, the Kaplan–Meier estimated rates of death or graft loss at month 84 were 33.9% for belatacept MI, 36.5% for belatacept LI, and 55.2% for cyclosporine. The hazard ratio for the comparison of belatacept MI with cyclosporine was 0.48 (95% CI $0.20-1.17$); the hazard ratio for the comparison of belatacept LI with cyclosporine was 0.57 (95% CI $0.25-1.31$).

### 3.7 | BENEFIT-EXT: Renal function

In both racial subgroups, estimated mean GFR increased over 7 years for belatacept-based immunosuppression, but declined for cyclosporine-based treatment (Figure 5). For all treatment arms, estimated mean GFR was similar for blacks and nonblacks over time. The estimated differences in GFR significantly favored belatacept-based vs cyclosporine-based immunosuppression in the black ($P = .0005$ for overall treatment effect) and nonblack cohorts ($P < .0001$ for overall treatment effect).
For the slope-based analysis of renal function, black patients randomized to belatacept MI or LI experienced estimated mean GFR gains of +2.13 (95% CI 0.36–3.89) and +1.22 (95% CI −0.49 to 2.92) mL/min/1.73 m² per year, respectively, while cyclosporine-treated black patients had an estimated mean decline of −1.00 (95% CI −3.06 to 1.07) mL/min/1.73 m² per year. The interaction of the treatment vs. time effect deriving from the repeated-measures model significantly favored belatacept MI vs. cyclosporine (P = .0242); the comparison of cyclosporine with belatacept LI was not significant (P = .10). Irrespective of treatment, all nonblack patients experienced estimated mean gains in GFR; the estimated mean gain in GFR for belatacept MI-treated nonblack patients was +1.34 (95% CI 0.82–1.87) mL/min/1.73 m² per year. The corresponding values in belatacept LI-treated and cyclosporine-treated nonblack patients were +1.54 (95% CI 1.03–2.05) and +0.10 (95% CI −0.44 to 0.63) mL/min/1.73 m² per year, respectively. Relative to cyclosporine, the slope estimates in nonblack patients differed for belatacept MI (P = .0012) and LI (P = .0001). Sensitivity analyses in which GFR values that were missing due to patient death or graft loss were imputed as zero yielded similar trends, but statistical significance was lost (Figure S4).

### 3.8 BENEFIT-EXT: Safety

Other than serious infections, which were reported more frequently among black vs nonblack cyclosporine-treated patients (30.86 vs 19.23 cases per 100 person-years of exposure, respectively), no notable differences in safety were seen between racial subgroups in any treatment arm (Table S4). By month 84, PTLD was reported in 1 Epstein-Barr

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**FIGURE 4** Estimated mean GFR from mo 1–84, as determined via repeated-measures modeling in (A) black and (B) nonblack patients participating in BENEFIT. GFR, glomerular filtration rate; MI, more intense; LI, less intense; CsA, cyclosporine.
virus negative black patient randomized to belatacept LI and 8 nonblack patients (belatacept MI, n = 2; belatacept LI, n = 5; cyclosporine, n = 1).

4 DISCUSSION

While calcineurin inhibitor-treated black kidney transplant recipients typically have poorer outcomes than calcineurin inhibitor-treated nonblacks, the results from these post hoc analyses of BENEFIT and BENEFIT-EXT show that efficacy and safety are similar in belatacept-treated black and nonblack patients. In BENEFIT, Kaplan–Meier estimated rates of death or graft loss at month 84 ranged from 0% to 13.0% in belatacept-treated black patients and 12.8%-13.6% in belatacept-treated nonblack patients. Notably, these rates are consistent with those reported in the overall intention to treat populations (12.7%-12.8%). In contrast to published data, the Kaplan–Meier estimated rate of death or graft loss at month 84 was numerically lower in cyclosporine-treated black vs nonblack patients (13.7% vs 22.5%, respectively); however, this finding may reflect the small number of blacks enrolled in BENEFIT (n = 55).

Kaplan–Meier estimated rates of death or graft loss at month 84 in BENEFIT-EXT were similar in belatacept-treated blacks (34.1%-34.8%) and nonblacks (33.4%-34.7%). In keeping with previously reported rates, the Kaplan–Meier estimated rate of death or graft loss at month 84 was numerically greater for cyclosporine-treated black vs nonblack patients (54.9% vs 32.9%, respectively).
In BENEFIT, AR occurred more frequently—irrespective of race—in kidney transplant recipients administered belatacept versus cyclosporine, with greater proportions of belatacept-treated (60.0%-75.5%) than cyclosporine-treated (42.9%-50.0%) patients having grade II AR by month 84. These results mirror those observed at 12 months post-transplant, and most AR episodes in belatacept-treated patients occur within the first 6 months post-transplant. In BENEFIT, the occurrence of AR did not appear to be influenced by race, as Kaplan–Meier cumulative event rates for AR at month 84 were similar in blacks and nonblacks administered belatacept MI (27.3% vs 24.2%, respectively), belatacept LI (22.0% vs 17.9%), or cyclosporine (12.9% vs 11.2%).

In contrast to BENEFIT, cyclosporine-treated black patients participating in BENEFIT-EXT were at the greatest risk of AR (Kaplan–Meier cumulative event rate at month 84, 33.2%). This was unexpected and is likely a consequence of the small number of blacks enrolled in BENEFIT-EXT (n = 71). Similarly, in BENEFIT-EXT, Kaplan–Meier cumulative event rates for AR at month 84 were comparable in blacks (18.5%-20.2%) and nonblacks (19.7%-21.3%) administered belatacept. In terms of AR severity, a numerically greater proportion of belatacept-treated (75.0%-100.0%) vs cyclosporine-treated (66.7%) black patients experienced grade II AR. However, rates of grade II AR were similar across treatment arms in the nonblack subgroup (76.7%-82.6%). No black patient in BENEFIT or BENEFIT-EXT experienced grade III AR; 4 nonblack BENEFIT participants (belatacept MI, n = 3; belatacept LI, n = 1) and 1 nonblack BENEFIT-EXT participant randomized to belatacept MI had grade III AR.

Consistent with previous analyses of BENEFIT and BENEFIT-EXT, belatacept-treated patients had significantly better renal function than cyclosporine-treated patients; this was observed in both racial subgroups. However, the results from these post hoc analyses should be interpreted with caution because the overall number of black patients was small. Moreover, of the 126 renal allograft recipients of African origin enrolled to BENEFIT and BENEFIT-EXT, most (63.5%, n = 80) were recruited from North America, with smaller proportions recruited from South America (26.2%, n = 33) and the European Union (9.5%, n = 12). Despite their shared ancestral origins, it is possible that these 3 patient subsets differed not only in terms of living in disparate geographic regions, but also in terms of underlying immunologic risk. Thus, conclusions drawn from the overall dataset may not be applicable to patients in all regions (or even outside the confines of the clinical trial setting where adherence is likely higher than in clinical practice), but they do suggest that efficacy and safety in belatacept-treated patients are not influenced by race. The similarity in outcomes in the black and nonblack subgroups is supported by population pharmacokinetic analyses, which found race to have minimal clinical impact on belatacept pharmacokinetics.

To conclude, we found belatacept-treated black patients to be at similar risk of death or graft loss and AR as belatacept-treated nonblack patients. In both racial subgroups, renal function improved over 7 years for belatacept-based treatment but declined for cyclosporine-based immunosuppression. Estimated mean GFR was generally similar in blacks and nonblacks administered belatacept, and no new belatacept safety signals emerged when stratifying patients by race.

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AUTHORS’ CONTRIBUTIONS
S.F., F.V., A.D., V.D.G., L.R., J.M.P., and C.P.L designed the studies. S.F., F.V., A.D., M.A., B.B., V.D.G., L.M., K.R., L.R., C.Z., J.M.P., and C.P.L collected the data. S.F., F.V., A.D., M.A., B.B., V.D.G., L.M., K.R., L.R., C.Z., U.M.-K., M.P., L.Y., J.M.P., and C.P.L analyzed and interpreted the data. M.P performed safety monitoring. All authors contributed to the drafting of this article or made critically important revisions and provided final approval to submit this manuscript for publication.

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REFERENCES
1. Narayanan M, Panekwycz O, El-Ghoroury M, et al. Outcomes in African American kidney transplant patients receiving tacrolimus and mycophenolic acid immunosuppression. Transplantation. 2013;95:566-572.
2. Gralla J, Le CN, Cooper JE, Wiseman AC. The risk of acute rejection and the influence of induction agents in lower-risk African American kidney transplant recipients receiving modern immunosuppression. Clin Transplant. 2014;28:292-298.
3. Purnell TS, Luo X, Kucirka LM, et al. Reduced racial disparity in kidney transplant outcomes in the United States from 1990 to 2012. J Am Soc Nephrol. 2016;27:2511-2518.
4. Hart A, Smith JM, Skeans MA, et al. Kidney. Am J Transplant. 2016;16(Suppl 2):11-46.
5. Gordon EJ, Ladner DP, Caicedo JC, Franklin J. Disparities in kidney transplant outcomes: a review. Semin Nephrol. 2010;30:81-89.
6. Kerman RH, Kimball PM, Van Buren CT, Lewis RM, Kahan BD. Possible contribution of pretransplant immune responder status to renal allograft survival differences of black versus white recipients. Transplantation. 1991;51:338-342.

7. Hutchings A, Guay-Woodford L, Thomas JM, et al. Association of cytokine single nucleotide polymorphisms with B7 costimulatory molecules in kidney allograft recipients. Pediatr Transplant. 2002;6:69-77.

8. Suthanthiran M, Khanna A, Cukran D, et al. Transforming growth factor-beta1 hyperexpression in African American end-stage renal disease patients. Kidney Int. 1998;53:639-644.

9. Lindholm A, Welsh M, Alton C, Kahan BD. Demographic factors influencing cyclosporine pharmacokinetic parameters in patients with uremia: racial differences in bioavailability. Clin Pharmacol Ther. 1992;52:359-371.

10. First MR, Schroeder TJ, Monaco AP, Simpson MA, Curtis JJ, Armenti VT. Cyclosporine bioavailability: dosing implications and impact on clinical outcomes in select transplantation subpopulations. Clin Transplant. 1996;10(1 Pt 1):55-59.

11. Kovarik JM, Hsu CH, McMahon L, Berthier S, Rordorf C. Population pharmacokinetics of everolimus in de novo renal transplant patients: impact of ethnicity and comedication. Clin Pharmacol Ther. 2001;70:247-254.

12. Tornatore KM, Sudachda P, Dole K, et al. Mycophenolic acid pharmacokinetics during maintenance immunosuppression in African American and Caucasian renal transplant recipients. J Clin Pharmacol. 2001;51:1213-1222.

13. Tornatore KM, Sudachda P, Attwood K, et al. Race and drug formulation influence on mycophenolic acid pharmacokinetics in stable renal transplant recipients. J Clin Pharmacol. 2013;53:285-293.

14. Goldberg-Rumyantsev AS, Koford JK, Baird BC, et al. Role of socioeconomic status in kidney transplant outcome. Clin J Am Soc Nephrol. 2006;1:313-322.

15. Yeates K, Wiebe N, Gill J, et al. Similar outcomes among black and white renal allograft recipients. J Am Soc Nephrol. 2009;20:172-179.

16. Isaacs RB, Nock SL, Spencer CE, et al. Racial disparities in renal transplant outcomes. Am J Kidney Dis. 1999;34:706-712.

17. Chakrera HA, O’Hare AM, Johansen KL, et al. Influence of race on kidney transplant outcomes within and outside the Department of Veterans Affairs. J Am Soc Nephrol. 2005;16:269-277.

18. Klintmalm G, Bohman SO, Sundelin B, Wilczek H. Interstitial fibrosis in renal allografts after 12 to 46 months of cyclosporin treatment: beneficial effect of low doses in early post-transplantation period. Lancet. 1984;2:950-954.

19. Palestine AG, Austin HA 3rd, Balow JE, et al. Renal histopathologic alterations in patients treated with cyclosporine for uveitis. N Engl J Med. 1986;314:1293-1298.

20. Randhawa PS, Shapiro R, Jordan ML, Starzl TE, Demetris AJ. The histopathological changes associated with allograft rejection and drug toxicity in renal transplant recipients maintained on FK506. Clinical significance and comparison with cyclosporine. Am J Surg Pathol. 1993;17:60-68.

21. Starzl TE, Fung J, Jordan M, et al. Kidney transplantation under FK506. JAMA. 1990;264:63-67.

22. Nankivell BJ, Borrows RJ, Fung CL, O’Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349:2326-2333.

23. Büchler M, Caillard S, Barbier S, et al. Sirolimus versus cyclosporine in kidney recipients receiving thymoglobulin, mycophenolate mofetil and a 6-month course of steroids. Am J Transplant. 2007;7:2522-2531.

24. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT trial. Transplantation. 2009;87:233-242.

25. Wiseman AC, McCague K, Kim Y, Geissler F, Cooper M. The effect of everolimus versus mycophenolate upon proteinuria following kidney transplant and relationship to graft outcomes. Am J Transplant. 2013;13:442-449.

26. Novartis Pharma Stein AG. Everolimus (ZORTRESS) prescribing information. Stein, Switzerland: Novartis Pharma Stein AG; 2015.

27. Bristol-Myers Squibb. Belatacept (NULOJIX) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2014.

28. Vincenti F, Charpentier B, Vanrenterghem Y, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10:535-546.

29. Durrbach A, Pestana JM, Pearson T, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010;10:547-557.

30. Vincenti F, Rostaing L, Grinyó J, et al. Belatacept and long-term outcomes in kidney transplant. N Engl J Med. 2016;374:333-343.

31. Durrbach A, Pestana JM, Florman S, et al. Long-term outcomes in belatacept-treated vs. cyclosporine-treated recipients of extended criteria donor kidneys: final results from BENEFIT-EXT, a phase III randomized study. Am J Transplant. 2016;16:3192-3201.

32. Rostaing L, Vincenti F, Grinyó J, et al. Long-term belatacept exposure maintains efficacy and safety at 5 years: results from the long-term extension of the BENEFIT study. Am J Transplant. 2013;13:2875-2883.

33. Charpentier B, Medina PJ, Del CRM, et al. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. Am J Transplant. 2013;13:2884-2891.

34. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-470.

35. Kasiske BL, Nefly TJ 3rd, Riggio RR, et al. The effect of race on access and outcome in transplantation. N Engl J Med. 1991;324:302-307.

36. Vincenti F, Larsen CP, Alberu J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant. 2012:210-217.

37. Pestana JO, Grinyo J, Vanrenterghem Y, et al. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. Am J Transplant. 2012:630-639.

38. Zhou Z, Shen J, Hong Y, Kaul S, Pfister M, Roy A. Time-varying belatacept exposure and its relationship to efficacy/safety responses in kidney-transplant recipients. Clin Pharmacol Ther. 2012;92:251-257.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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