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Real-world evidence regarding cancer, mortality, and graft failure risk with *de novo* belatacept use among kidney transplant recipients in the United States

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Abstract

Belatacept is a selective T-cell co-stimulation blocker used in maintenance immunosuppression for kidney transplant recipients (KTRs), but evidence on cancer risk and other outcomes is limited. This retrospective cohort study used linked US transplant and cancer registry data on KTRs treated with belatacept (N=1514) or tacrolimus (N=7570) as initial maintenance therapy. We used multivariable Cox regression models to compare incidence of invasive cancer, cutaneous squamous cell carcinoma (cSCC), posttransplant lymphoproliferative disorder (PTLD), death, and graft failure/retransplantation (GF/RT) between belatacept and tacrolimus users. Overall, cancer incidence was 10.1 and 12.6 per 1000 person-years in belatacept and tacrolimus users, respectively. We did not find increased risk with belatacept for cancer overall (adjusted hazard ratio [HR] 0.83, 95% confidence interval [95%CI] 0.53–1.30), individual cancer types, or cSCC. Belatacept was associated with increased risk of death (adjusted HR 1.22, 95%CI 1.04–1.43).

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Declaration of interests

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but lower risk of GF/RT more than four years after transplantation (0.54, 0.35–0.83). PTLN risk was increased among EBV-seropositive KTRs (adjusted HR 1.96, 95%CI 1.03–3.73). This study provides reassurance that belatacept does not increase cancer risk among KTRs, and there was a long-term protective association for GF/RT. However, we found evidence suggesting a potential increased risk of PTLN and death with belatacept use.

Keywords

kidney transplantation; belatacept; cancer; mortality; Epstein-Barr virus; squamous cell carcinoma; posttransplant lymphoproliferative disorders

1. Introduction

Kidney transplantation is a lifesaving therapy for patients with end-stage kidney disease, but kidney transplant recipients (KTRs) can suffer from substantial morbidity due to prolonged use of immunosuppressive medications. The goal of immunosuppression therapy is to reduce rejection and thereby prolong graft survival.¹ The therapeutic regimen attempts to balance keeping rejection rates low while minimizing the impact of over-immunosuppression and drug toxicities.¹ However, complications of long-term immunosuppressive therapy including infections, cardiovascular disease, and cancer, are major issues.

Cancer is a common complication and major cause of death in transplant recipients.^{2,3} KTRs have a 28% higher risk of any type of cancer compared to the general population.⁴ Specifically, KTRs have an elevated risk of kidney cancer, non-Hodgkin lymphoma, and melanoma,⁴ resulting in large part from decreased immune surveillance due to maintenance immunosuppression, effects of oncogenic viruses, and, for kidney cancer, the presence of native end-stage kidneys.

The most common maintenance immunosuppression for KTRs is based on the use of a calcineurin inhibitor (CNI), antiproliferative agents, and glucocorticoids. Although CNI-based therapy improves early graft survival, the nephrotoxic effect of CNIs result in chronic graft damage.⁵ Belatacept, a T-lymphocyte co-stimulation blocker, inhibits T-cell activation by preventing CD28 binding to B7 proteins on antigen presenting cells. In this way, belatacept is intended to replace CNIs and prevent rejection while avoiding CNI-associated toxicities.⁶

Belatacept was approved in 2011 for use in KTRs to prevent organ rejection. In clinical practice, belatacept is preferred over CNIs or mammalian target of rapamycin (mTOR) inhibitors for KTRs who have experienced or are at risk of toxicity from those agents, such as nephrotoxicity, recurrent infections, or neurological side effects. This preference extends to recipients who are at relatively low risk of rejection, such as older individuals, those well-matched by human leukocyte antigen, and recipients of living donor transplants. Although the efficacy of belatacept, including lower nephrotoxicity compared with cyclosporine (a CNI), is established,⁷ the overall benefits and risks compared to tacrolimus, the CNI in predominant use today and the cornerstone of KTR maintenance therapy, are less studied.⁸

In particular, uncertainty exists regarding the long-term effect of belatacept use on cancer incidence among KTRs.⁸ All medications that induce immunosuppression can lead to loss of immune control of oncogenic viral infections (e.g., Epstein–Barr virus [EBV]). Several randomized controlled trials reported higher incidence of serious viral infections, including cytomegalovirus and EBV, among belatacept users compared with CNI users.^{9,10} EBV-naïve solid organ recipients face a higher risk of developing posttransplant lymphoproliferative disorder (PTLD) compared to those who are latently infected and EBV-seropositive at the time of transplantation, owing to an inadequate immune response to primary EBV infection after transplantation.¹¹ Belatacept is associated with increased risk of PTLD in KTRs who are EBV-seronegative at the time of transplantation.⁹ This association led to a black box warning that belatacept is contraindicated in KTRs who are EBV-seronegative or whose EBV serostatus is unknown before transplantation.⁶

Another important safety consideration is the mechanism by which belatacept downregulates T-cell activation. T-cells in tumors can express CTLA-4, which binds to B7 proteins on antigen presenting cells, suppressing T-cell activation and facilitating evasion of the immune system by the cancer. Blocking CTLA-4 promotes antitumor immunity. For example, ipilimumab, a monoclonal antibody that blocks CTLA-4, improves survival for several cancers, including metastatic melanoma.¹² Thus, the use of belatacept in KTRs to downregulate T-cell activation resembles the pathway tumors exploit to evade immune surveillance. Prior studies of belatacept provided limited data for an assessment of cancer outcomes beyond PTLD.^{7,9,13–17}

To address these gaps in knowledge, we compared cancer risk between KTRs treated with belatacept or tacrolimus in a large population sample in the US. We also examined the association of belatacept use with other key posttransplant outcomes, namely, patient and graft survival.

2. Materials and methods

2.1 Study design and data sources

This retrospective cohort study included KTRs identified from the National Cancer Institute's Transplant Cancer Match (TCM) Study, a linkage between the US solid organ transplant registry (Scientific Registry of Transplant Recipients, SRTR) and 34 US state and regional cancer registries.¹⁸ The SRTR data system includes data on all transplant recipients, candidates, and donors in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services oversees the activities of the OPTN and SRTR contractors. The study was not considered human subjects research by the National Institutes of Health and was approved, as necessary, by the institutional review boards at participating cancer registries.

We included KTRs without a simultaneous or previous transplant of another organ. Eligible KTRs had to have received their kidney transplant between June 16, 2011, and December 31 2019, as belatacept was approved for clinical use on June 15, 2011.⁶ Our analysis of invasive cancer incidence used the linked cancer registry data and so was restricted to KTRs living

in a TCM cancer registry region (herein “TCM cohort”). Of 135,175 KTRs transplanted in the study period, 74,946 (55.4%) resided in participating TCM cancer registry regions. We further restricted the TCM cohort to KTRs without a cancer diagnosis prior to transplant, as recorded in the cancer registries (Figure 1).

SRTR data include information on KTRs’ demographic characteristics, transplanted organ, and immunosuppressive regimen at transplant. The SRTR also includes follow-up information provided by transplant centers on outcomes not recorded by the linked cancer registries, including cutaneous squamous cell carcinoma (cSCC), PTLTD, death, treatment for acute rejection, and graft failure/retransplantation (GF/RT). For analyses of these outcomes, which did not rely on cancer registry data, we included all eligible KTRs in the SRTR, not restricting to those in the 34 TCM registry regions (i.e., “SRTR cohort”; Figure 1).

2.2. Exposure and outcome measures

The exposure of interest was the use of belatacept as a maintenance immunosuppressive medication at the time of initial hospital discharge following transplantation. For comparison, we included KTRs who used tacrolimus (the most commonly used CNI during the study period) as a maintenance immunosuppressive medication at the time of discharge after transplantation. KTRs who were prescribed belatacept and tacrolimus concomitantly were excluded from the analysis. We also excluded KTRs prescribed cyclosporine or an mTOR inhibitor at baseline because they were rarely used during this period. KTRs using other maintenance immunosuppressive medications including mycophenolate, azathioprine, or corticosteroids, remained in the analysis.

Outcomes included incidence of invasive cancer overall and for specific sites. These analyses were based on the first such incident cancer recorded in the TCM cohort. We grouped cancers with fewer than 25 cases in the TCM cohort into similar sites if applicable or categorized them under “miscellaneous.” In addition, we analyzed cSCC, PTLTD, death from any cause, and GF/RT as outcomes using the SRTR cohort (Figure 1). For deaths that occurred on or before December 31, 2019, underlying cause of death (COD) was assigned using linked data from the National Death Index (NDI).²

2.3. Statistical analysis

Since there were notable differences between belatacept and tacrolimus users on multiple characteristics (see Results), we used a propensity score (PS) to match belatacept users to a group of tacrolimus users. The PS was derived from a logistic regression model for the probability of receiving belatacept based on the following baseline characteristics: age at transplantation (<30, 30–39, 40–49, 50–59, 60+ years); sex; race/ethnicity (non-Hispanic White, non-Hispanic Black/Hispanic/other); education (high school or less, college or above); transplantation calendar period (2011–2013, 2014–2016, 2017–2019); expanded donor criteria (yes/no); presence of diabetes mellitus (yes/no); body mass index (BMI) (underweight/normal [BMI ≤24.9], overweight/obese [BMI ≥25.0]); induction immunosuppression with a polyclonal antibody (yes/no), an IL2 antagonist (yes/no), or corticosteroids (yes/no); and maintenance therapy with corticosteroids (yes/no). Tacrolimus users were matched using a 5:1 selection ratio, and sampled without replacement, using a

“greedy” matching algorithm with a caliper width of 0.2 times the pooled common standard deviation of the logits of the PS values.^{19,20}

We evaluated the effectiveness of PS matching by assessing variable balance before and after matching (Supplementary Table 1), examining the overall distribution of the PS and the standardized difference for individual dichotomous variables (Supplementary Table 2, Supplementary Figure 1). To assess PS model fit, we randomly split the dataset in half, used each half to predict treatment probabilities in the other, and combined the data to assess model calibration. We calculated the expected frequency of belatacept treatment by summing all cross-predicted probabilities and comparing that to the observed frequency. We also conducted a Hosmer and Lemeshow goodness-of-fit test. We also measured the area under the receiver operating characteristic curve (AUC) in the cross-predicted dataset.

Our primary analyses were restricted to belatacept users and the PS-matched tacrolimus users. We describe the baseline characteristics of these individuals at the time of transplantation. We followed KTRs starting from transplantation. For analyses of invasive cancers, cSCC, and PTLT, we censored follow-up at the earliest of death, GF/RT, loss to follow-up by the SRTR, or (for invasive cancers) end of cancer registry coverage. For GF/RT, we considered death and loss to follow-up by the SRTR as censoring events, and for death we censored at GF/RT or loss to follow-up by the SRTR.

We present Kaplan-Meier curves showing the probability of invasive cancer, death, and GF/RT as a function of time since transplantation. We used Cox proportional hazards regression models to compare the incidence of events in belatacept and tacrolimus users. Hazard ratios (HRs) were adjusted for age at transplantation, sex, race/ethnicity, transplantation year, and EBV serostatus at transplantation. For individual cancer types with fewer than 10 events, we present frequencies but did not perform a formal analysis.

Log-negative-log curves were generated to visually assess the proportionality assumption in the Cox models. For GF/RT, we divided the follow-up time at the median and calculated separate HRs for the first 4 years following transplant and subsequently, because proportionality was violated. In addition, we conducted analyses of GF/RT, death, and PTLT stratified by the baseline EBV serostatus of the recipients. We also calculated cause-specific mortality rates in belatacept and tacrolimus users and measured associations of each cause of death with belatacept use, censoring the analysis after December 31, 2019 (end date of NDI data on CODs).

We conducted three sensitivity analysis. First, we estimated the HRs for belatacept use based on the entire unmatched tacrolimus group instead of just the PS-matched group. Second, to accommodate the correlation in outcomes arising from individuals receiving a transplant in the same center, we fit frailty models that included transplant center as a random effect. Third, to account for the individual matching that arose from the PS matching, we ran Cox models with the matched group included as a stratum variable, which allows for a separate baseline hazard for each matched set.

We used SAS (version 9.4; SAS Institute, Inc.) for all analyses. We considered statistical significance at $p < 0.05$ (two-sided) for all analyses except for separate cancer sites

and cause-specific mortality, where a Bonferroni correction was applied for multiple comparisons (p-value threshold: 0.005).

3. Results

A total of 135,175 individuals received a kidney-only transplant in the US between January 16, 2011, and December 31, 2019. Of these, 126,678 were included in the study, including 1,514 who used belatacept and 125,164 who used tacrolimus as part of their baseline maintenance immunosuppressive regimen (SRTR cohort, Figure 1). Among these, 65,280 resided in an area covered by a TCM cancer registry and did not have a pretransplant cancer (TCM cohort: 815 on belatacept and 64,465 on tacrolimus). Finally, 7,570 tacrolimus users were PS-matched with belatacept users in the SRTR cohort, and 4,057 tacrolimus users were PS-matched to belatacept users in the TCM cohort. The PS-matched group of tacrolimus users was more similar to the belatacept users than the overall group of tacrolimus (Supplementary Table 1). Our PS models were well calibrated as the sum of cross-predicted probabilities was very close to the observed frequency (data not shown) and Hosmer and Lemeshow goodness-of-fit tests were nonsignificant (TCM cohort $p=0.32$; SRTR cohort $p=0.49$). The AUC was 0.70 for the TCM cohort and 0.67 for the SRTR cohort, showing good discrimination of the PS model.

The characteristics of KTRs in the TCM and SRTR cohorts included in our primary analyses are presented in Table 1. The median age at transplantation was 57 years in belatacept users and 56 years in tacrolimus users. Most participants were male, and the most frequent racial/ethnic group was non-Hispanic White. Forty-one percent of the transplants among belatacept users occurred between 2014 and 2016. Among belatacept users, 8.5% in the TCM cohort and 6.0% in the SRTR cohort were EBV-seronegative at transplantation. Fifty-four percent of belatacept users received induction therapy with polyclonal antibodies, and 46% received IL2 antagonists. More than 98% of KTRs in both groups received mycophenolate as part of their baseline maintenance immunosuppression. The proportion of KTRs treated for acute rejection in the first 18 months posttransplant was higher in belatacept compared to tacrolimus users (SRTR cohort: 14.5% [N=220] vs. 6.4% [N=499], $p<0.001$).

Among KTRs in the TCM cohort, the median duration of follow-up was 2.3 years for belatacept users and 2.5 years for tacrolimus users. The overall incidence of cancer was 10.1 and 12.6 per 1,000 person-years for belatacept users and tacrolimus users, respectively. An estimated 3.6% of KTRs in both groups were diagnosed with cancer within 3 years after transplantation; these proportions increased to 4.7% in belatacept users and 6.4% in tacrolimus users 5 years after transplantation (Figure 2A, Supplementary Table 3). All cancers in the belatacept group occurred within 6 years posttransplant (Figure 2A, Supplementary Table 3). Among specific cancer outcomes, colorectal cancer was the most common in belatacept users followed by stomach cancer and non-Hodgkin lymphoma (Table 2). Prostate cancer and non-Hodgkin lymphoma were the most common in tacrolimus users (Table 2). We did not find a significant difference in overall cancer risk associated with belatacept use (adjusted HR 0.83, 95% confidence interval [CI] 0.53–1.30) (Table 2, Figure 2A). No association was observed between belatacept and risk for specific cancer types, although the number of events in these analyses was small (Table 2).

In the SRTR cohort, the median duration of follow-up was 4.0 years for both groups. An estimated 8.3% of belatacept users and 6.2% of tacrolimus users died within 3 years after transplantation; these proportions increased to 13.9% and 11.3%, respectively, at 5 years, and 19.1% and 17.9%, respectively, at 7 years (Figure 2B, Supplementary Table 3). Mortality rates were higher in belatacept users (31.0 vs. 25.9 per 1,000 person-years; adjusted HR 1.22, 95%CI 1.04–1.43; Table 2). The risk of death associated with belatacept was 20% increased among EBV-seropositive KTRs (adjusted HR 1.20, 95%CI 1.01–1.41; Table 3) and nearly two-fold increased among EBV-seronegative KTRs (1.98, 1.12–3.50; Table 3). Of the 1,024 deaths in the SRTR cohort, 743 (73.6%) occurred through December 31, 2019 (Table 4) and had a COD available. Belatacept was not associated with any specific COD (Table 4).

GF/RT rates were similar in both groups (19.6 vs. 20.6 per 1,000 person-years; adjusted HR 0.95, 95%CI 0.79–1.16). This association exhibited non-proportionality, i.e., belatacept was not associated with GF/RT in the first four years posttransplant (adjusted HR 1.16, 95%CI 0.93–1.44) but was associated with reduced risk after four years posttransplant (adjusted HR 0.54, 95%CI 0.35–0.83; *p* for interaction 0.002). This time-dependency of the association between belatacept and GF/RT is shown graphically in Figure 2C, where the curves diverge after 6 years posttransplant. The association between belatacept and GF/RT was similar among EBV-seropositive KTRs (Table 3, Supplementary Figure 2).

PTLD risk was 62% higher with belatacept use (adjusted HR 1.62, 95%CI 0.89–2.95; Table 2). In our analysis stratified by recipients' EBV serostatus (Table 3), belatacept was associated with increased PTLT risk among KTRs who were EBV-seropositive at transplantation (adjusted HR 1.96, 95%CI 1.03–3.73) (Table 3). There were no PTLT events among EBV-seronegative KTRs, so the association could not be assessed in that group.

In our sensitivity analysis using the unmatched group of all tacrolimus users, we found similar associations with belatacept use for cancer overall, death, GF/RT, PTLT and cSCC (Supplementary Tables 4 and 5). However, in the unmatched analysis stratified by EBV serostatus, the associations between belatacept and mortality were no longer significant (EBV-seropositive KTRs: adjusted HR 1.14, 95%CI 0.98–1.33; EBV-seronegative KTRs: 1.50, 0.91–2.47; Supplementary Table 3). The additional sensitivity analyses that incorporated transplant center effects or individual matching produced similar results to the main analysis (Supplementary Table 6).

4. Discussion

In this large study based on real-world evidence, KTRs who used belatacept as part of their initial maintenance immunosuppressive regimen did not experience an overall increased risk of cancer, but belatacept was associated with an increased risk of PTLT in EBV-seropositive KTRs compared to those who used tacrolimus. Of concern, belatacept use was also associated with an increased risk of death. In addition, we demonstrated a long-term nephroprotective effect of belatacept compared with tacrolimus, specifically, we showed a decreased risk of GF/RT among KTRs who received belatacept.

Our study provides reassurance that belatacept does not increase the risk of invasive cancer. A few randomized trials have reported null associations between belatacept use and cancer outcomes,^{7,9,13} but the trials were too small to precisely estimate an effect. Our study had a much larger number of KTRs, leading to a more precise estimate for cancer overall, despite the low number of site-specific cancer events and the relatively short median follow-up duration. We also found that belatacept was not associated with risk of cSCC. In contrast, a recent small retrospective study found that, among KTRs with an initial diagnosis of cSCC, switching to belatacept from a CNI reduced the risk of developing a new cSCC.²¹

A new and notable finding in our study is the observed association between belatacept use and an increased risk of death. The five-year estimated mortality among belatacept users in our study is higher than that reported in the BENEFIT trial⁷ but comparable to that reported in BENEFIT-EXT among KTRs with extended criteria donors.⁹ These two randomized trials did not report a difference in mortality between KTRs treated with belatacept or cyclosporine. The difference in results between the trials and our study may be attributed to the fact that the trials recruited only carefully screened participants, whereas our study utilized real-world data on a much larger population of KTRs. Additionally, BENEFIT and BENEFIT-EXT compared belatacept with cyclosporine, while our study compared it with tacrolimus, the current standard-of-care immunosuppressant agent.

Various factors could contribute to the higher mortality among belatacept users, including the type, doses, and timing of other immunosuppressive agents.²² Another critical factor may be the rate of acute rejection. In the BENEFIT trial, acute rejection was more common in the belatacept group compared to the cyclosporine group.¹⁰ Similarly, in our study, treatment for acute rejection was more than twice as common in the first 18 months posttransplant among belatacept users than tacrolimus users. Such treatment, which involves, intensification of the immunosuppressive regimen, could have increased the risk of severe infection. However, our cause-specific mortality analysis did not identify any specific COD attributable to belatacept use. Given the different levels of statistical significance between our PS-matched analysis and the sensitivity analysis based on all tacrolimus users, we cannot exclude chance as an explanation for the apparent increase in mortality.

A novel finding in our study is the observed association between belatacept use and increased PTLT risk among EBV-seropositive KTRs. EBV plays a key role in the development of a large fraction of PTLT tumors.²³ Immunosuppressive agents decrease T-cell immune surveillance, resulting in EBV-induced proliferation of B-cells.^{23,24} Our results suggest that belatacept has a greater effect than tacrolimus in causing loss of immune control of EBV, even in the setting of infection that is already established at the time of transplantation.

PTLT risk is greatest in individuals who are EBV-seronegative at the time of transplantation, among whom primary EBV infection after transplantation can lead to uncontrolled viral replication. BENEFIT-EXT reported an increased risk of PTLT in EBV-seronegative KTRs,²⁵ which resulted in a black box warning to avoid belatacept use in this subgroup of patients. As a result, very few EBV-seronegative KTRs were prescribed belatacept in the US after approval of the medication. Given the small number of EBV-seronegative KTRs

and absence of PTLT events in this group, we were unable to assess the association between belatacept use and PTLT risk among EBV-seronegative KTRs.

Our study supports a long-term beneficial effect of belatacept on graft survival, which may be attributable to its less nephrotoxic nature.²⁶ In the BENEFIT trial of KTRs receiving kidneys from standard criteria donors, a less intensive belatacept regimen reduced the risk of graft loss by 43% compared with a cyclosporine-based regimen.⁷ Among KTRs who received kidneys from extended criteria donors in BENEFIT-EXT, belatacept was associated with improved long-term kidney function in comparison with cyclosporine, although the association with graft loss was not significant.^{7,9} We observed a protective association between belatacept and GF/RT after 4–6 years posttransplant, consistent with the long-term nephrotoxic effects of CNIs leading eventually to graft failure.⁴

Our study has several important strengths. We utilized data from a large population-based sample of belatacept users, which allowed us to assess associations of belatacept with several important outcomes in a real-world setting. We compared belatacept with tacrolimus, which is now the most commonly used immunosuppressive medication in kidney transplantation. Finally, we were able to incorporate data from 34 population-based cancer registries (covering 55.4% of the US KTR population during this period) to assess the incidence of invasive cancers.

This study also has several limitations. First, exposure to belatacept and tacrolimus was determined from the baseline maintenance immunosuppressive regimen, i.e., at the time of initial hospital discharge following transplantation. Thus, our findings may be generalizable only to KTRs who receive belatacept as a baseline maintenance immunosuppressant medication. KTRs in our study might later have been converted to or from belatacept or another regimen, but we could not assess that. To the extent this conversion occurred, it most likely would have biased our results towards the null. Second, since this study is not a randomized trial, there might be differences between belatacept and tacrolimus users that contributed to their risk of the outcomes that we evaluated. We attempted to mitigate this issue through PS matching. Nonetheless, residual confounding by unmeasured factors could have affected the results.

A third limitation is that, due to the relatively recent introduction of belatacept, our study could only estimate the short-term association with cancer, while cancer incidence typically increases with longer follow-up after transplantation.²⁷ For other outcomes, our study included a much larger number of belatacept users at risk in each time period compared to prior studies.^{7,9} PTLT can occur early (within 2 years following transplantation) or later.²⁸ In BENEFIT, all PTLT cases occurred within the first 2 years posttransplant. In our study, 10 of the 14 PTLT cases among belatacept users and 23 of the 47 cases among tacrolimus users occurred within 2 years, but we also had a substantial number of KTRs followed beyond this period. Fourth, due to the black box warning, only a small number of EBV-seronegative transplant recipients received belatacept, so we were limited in assessing this group. Finally, we excluded KTRs who concurrently received tacrolimus, cyclosporine, or mTOR inhibitors, to allow a straightforward comparison of belatacept with tacrolimus.

Our results therefore do not apply directly to KTRs receiving belatacept in combination with certain other medications.

In conclusion, our study indicates that belatacept presents a similar overall cancer risk profile for KTRs, compared to a tacrolimus-based immunosuppressive regimen. We found that belatacept was associated with a long-term beneficial effect in reducing the incidence of GF/RT compared to tacrolimus. Of concern, however, we observed an increased risk of PTLT associated with belatacept use among EBV-seropositive KTRs, suggesting that this medication causes marked loss of EBV control even among individuals who have been infected with the virus before transplantation. Finally, the new finding in our study was the higher mortality in KTRs treated with belatacept, pointing to the need for further investigation to characterize adverse events in KTRs treated with belatacept.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The Transplant Cancer Match Study principal investigator is the custodian for the data. Agreements between the National Cancer Institute, the Health Resources and Services Administration, and participating registries do not allow the investigators to share the data with outside researchers. Interested collaborators can use the study data at the National Cancer Institute under supervision by the principal investigator or can participate in analyses through review of tabulated data. Investigators who are interested in accessing SRTR data may apply at <https://www.srtr.org>.

Abbreviations

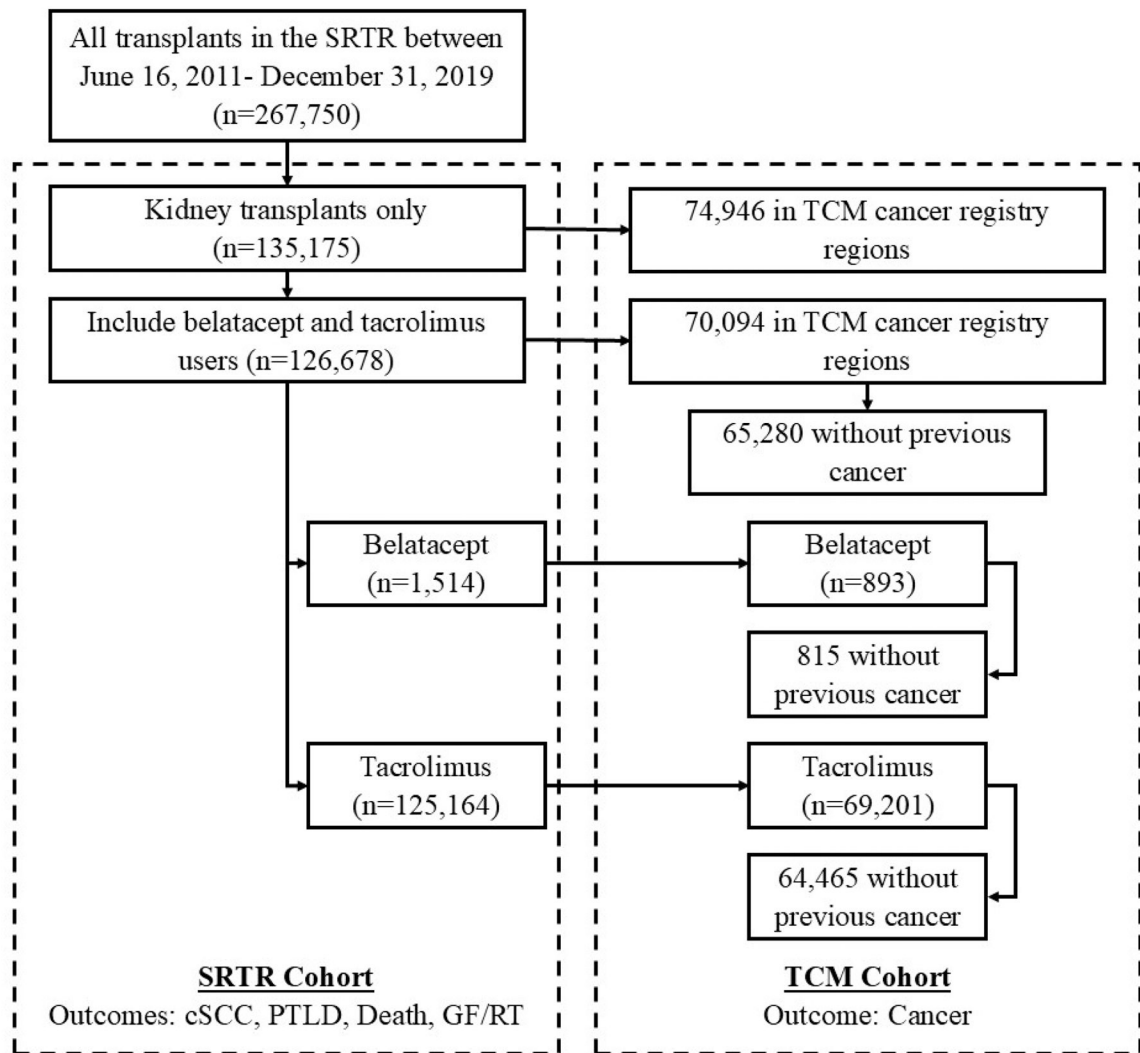
BMI	body mass index
CI	confidence interval
CNI	calcineurin inhibitor
cSCC	cutaneous squamous cell carcinoma
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
EBV	Epstein–Barr virus
GF/RT	graft failure/retransplantation
HR	hazard ratio
KTR	kidney transplant recipients
mTOR	mammalian target of rapamycin
NDI	National Death Index
PS	propensity score
PTLD	posttransplant lymphoproliferative disorder
SRTR	Scientific Registry of Transplant Recipients
TCM	Transplant Cancer Match.

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Abbreviation: cSCC cutaneous squamous cell carcinoma, GF/RT graft failure/retransplantation, PTLTD posttransplant lymphoproliferative disorders, SRTR Scientific Registry of Transplant Recipients; TCM Transplant Cancer Match

Figure 1:

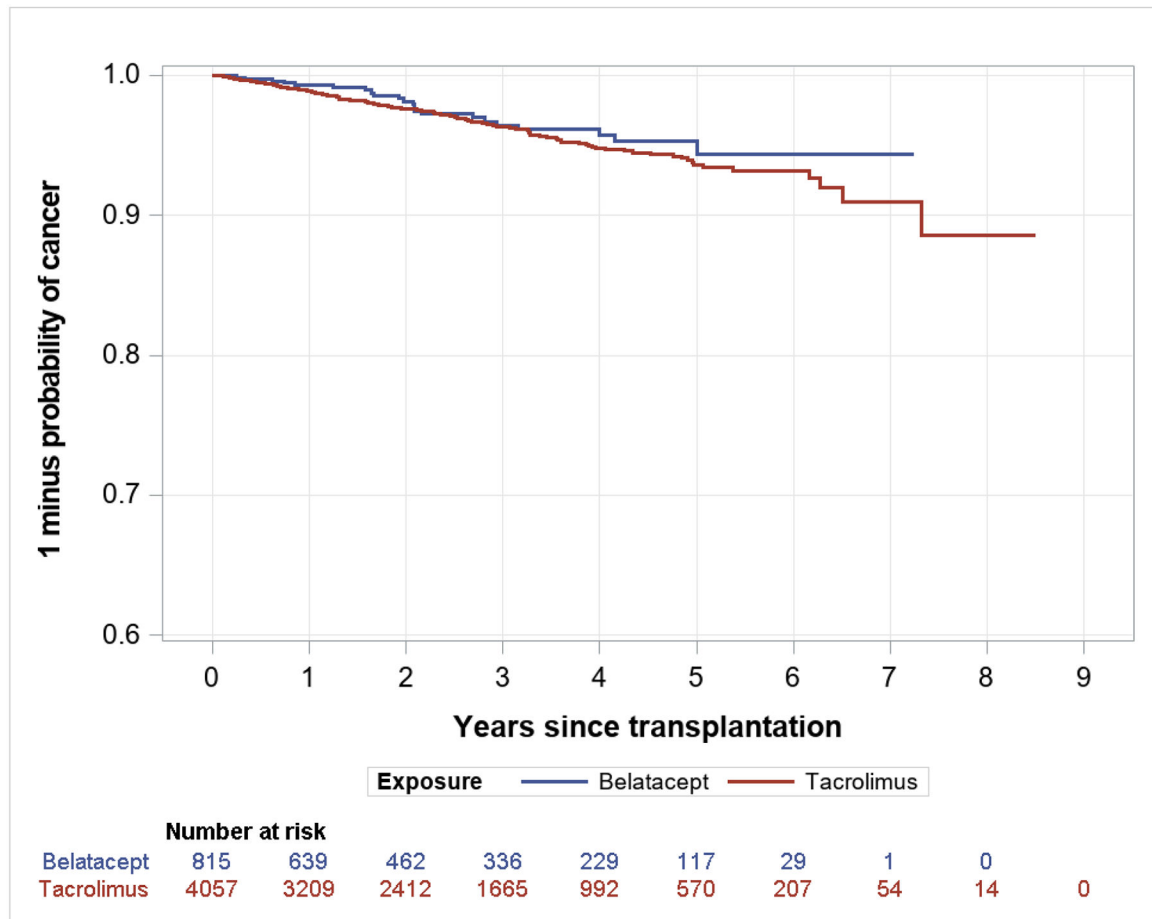
Study flow chart showing cohort selection

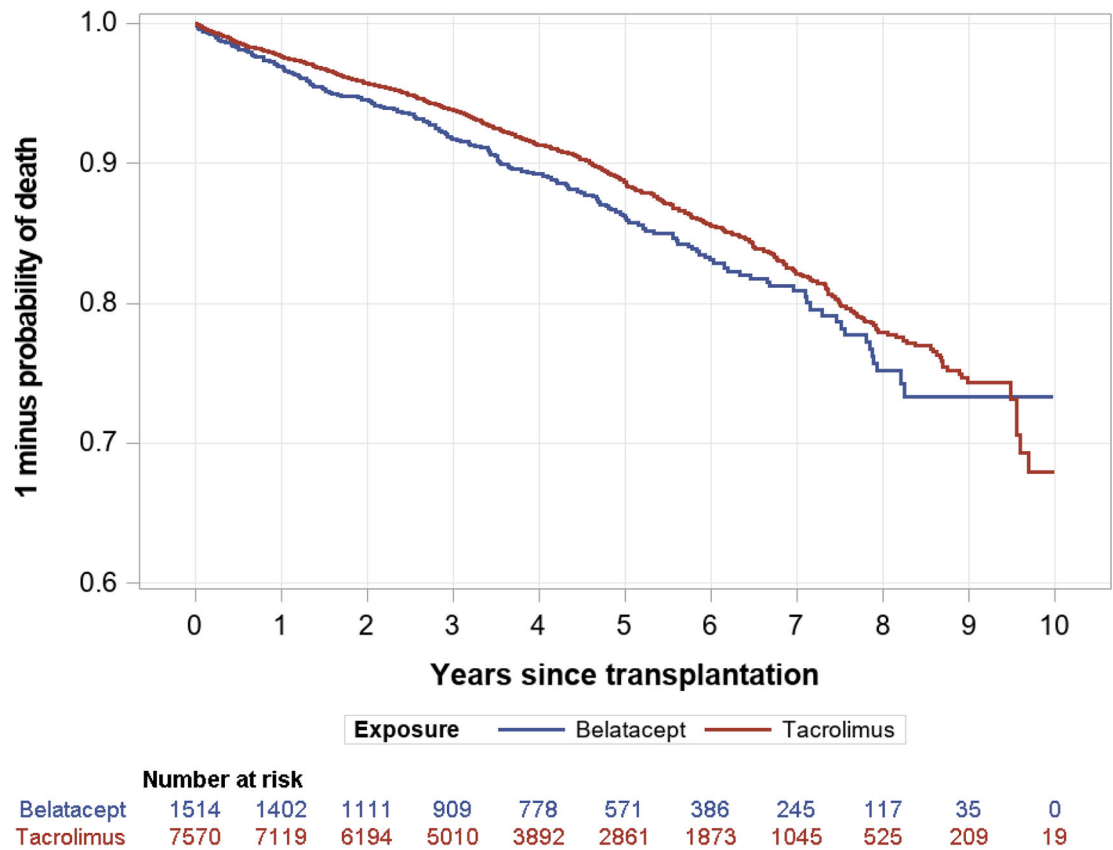
Abbreviations: cSCC cutaneous squamous cell carcinoma, GF/RT graft

failure/retransplantation, KTR kidney transplant recipients, PTLTD posttransplant

lymphoproliferative disorders, SRTR Scientific Registry of Transplant Recipients, TCM

Transplant Cancer Match.





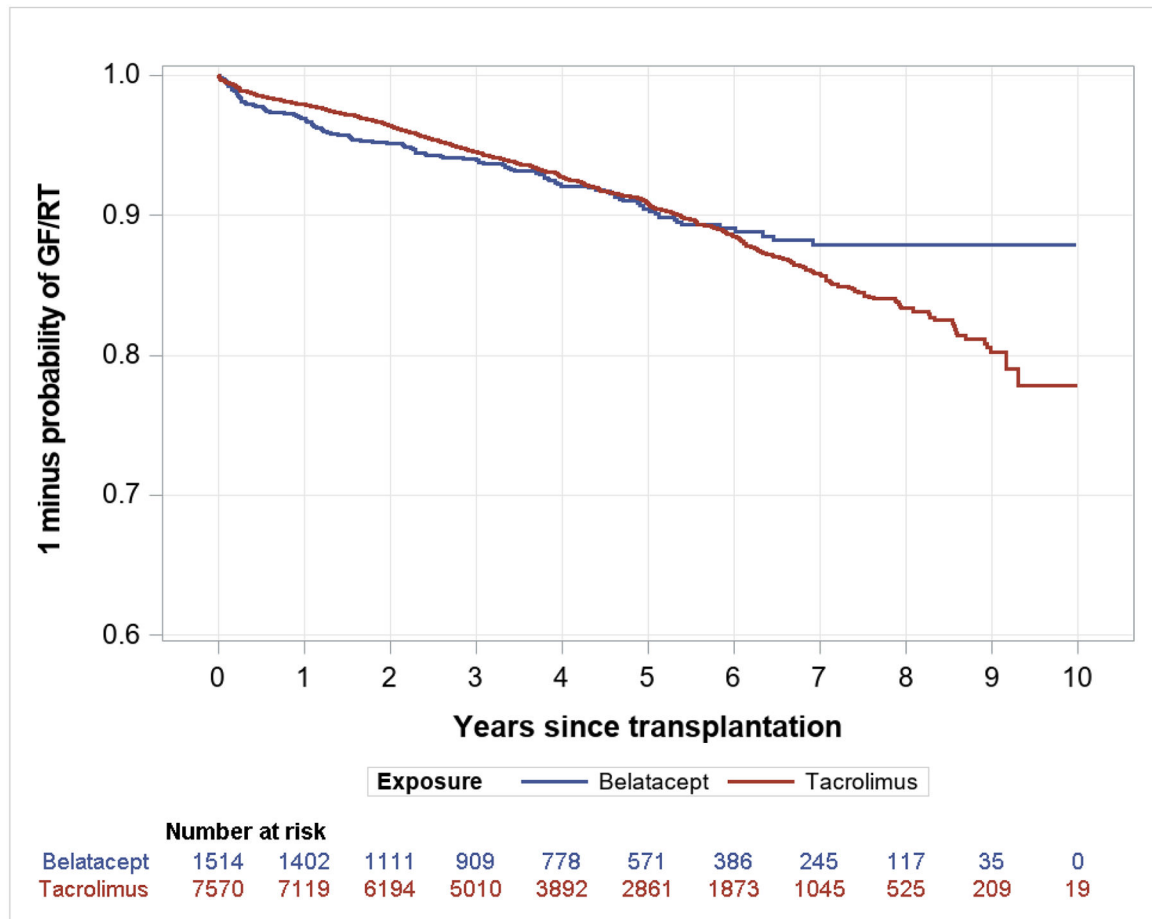


Figure 2:
Kaplan-Meier curves for any cancer, death or graft failure/retransplantation
In panel A, death and graft failure/retransplantation were considered censoring events for cancer. In panels B and C, graft failure/retransplantation and death were considered censoring events for death and graft failure/retransplantation, respectively.

Table 1:

Baseline characteristics of kidney transplant recipients using belatacept and propensity score matched tacrolimus users in the TCM and SRTR cohorts.

Variables	TCM		SRTR	
	Belatacept	Tacrolimus	Belatacept	Tacrolimus
		Matched		Matched
Total participants, n	815	4057	1514	7570
Age at transplantation in years, median (IQR)	57 (45–64)	56 (44–64)	57 (46–65)	57 (45–65)
Age category, n (%)				
<30 Years	53 (6.5)	281 (6.9)	88 (5.8)	426 (5.6)
30–39 Years	90 (11.0)	497 (12.3)	142 (9.4)	734 (9.7)
40–49 Years	122 (15.0)	616 (15.2)	244 (16.1)	1293 (17.1)
50–59 Years	220 (27.0)	1069 (26.4)	390 (25.8)	1905 (25.2)
60–69 Years	243 (29.8)	1220 (30.1)	464 (30.7)	2275 (30.1)
≥70 Years	87 (10.7)	374 (9.2)	186 (12.3)	937 (12.4)
Sex, n (%)				
Female	276 (33.9)	1354 (33.4)	508 (33.6)	2504 (33.1)
Male	539 (66.1)	2703 (66.6)	1006 (66.4)	5066 (66.9)
Race/ethnicity, n (%)				
White, non-Hispanic	411 (50.4)	2299 (56.7)	814 (53.8)	4252 (56.2)
Black/Hispanic/Other	404 (49.6)	1758 (43.3)	700 (46.2)	3318 (43.8)
Educational status, n (%)				
≤High School/unknown	370 (45.4)	1700 (41.9)	654 (43.2)	3073 (40.6)
College or above	445 (54.6)	2357 (58.1)	860 (56.8)	4497 (59.4)
Calendar year of transplantation category, n (%)				
2011–2013	230 (28.2)	1223 (30.2)	311 (20.5)	1626 (21.5)
2014–2016	424 (52.0)	2246 (55.4)	621 (41.0)	3337 (44.1)
2017–2019	161 (19.8)	588 (14.5)	582 (38.4)	2607 (34.4)
Living donor, n (%)	261 (32.0)	1237 (30.5)	469 (31.0)	2283 (30.2)
Expanded donor, n (%)	157 (19.3)	793 (19.6)	296 (19.6)	1407 (18.6)
First transplant, n (%)	807 (99.0)	4025 (99.2)	1502 (99.2)	7487 (98.9)
Total years on dialysis, median (IQR)	2.6 (0.8–4.9)	2.8 (0.8–5.3)	2.5 (0.7–4.6)	2.9 (0.8–5.3)
Cytomegalovirus serology status, n(%)				
Positive/missing/unknown	533 (65.4)	2522 (62.2)	949 (62.7)	4609 (60.9)
Negative	282 (34.6)	1535 (37.8)	565 (37.3)	2961 (39.1)
EBV serology status, n (%)				
Positive/missing/unknown	746 (91.5)	3634 (89.6)	1423 (94.0)	6829 (90.2)
Negative	69 (8.5)	423 (10.4)	91 (6.0)	741 (9.8)
Hepatitis B virus infection, n (%)				
Uninfected/unknown	735 (90.2)	3680 (90.7)	1379 (91.1)	6949 (91.8)

Variables	TCM		SRTR	
	Belatacept	Tacrolimus	Belatacept	Tacrolimus
		Matched		Matched
Active/Resolved	80 (9.8)	377 (9.3)	135 (8.9)	621 (8.2)
Hepatitis C virus infection, n (%)				
Negative/unknown	801 (98.3)	3914 (96.5)	1476 (97.5)	7311 (96.6)
Positive	14 (1.7)	143 (3.5)	38 (2.5)	259 (3.4)
Diabetes mellitus, n (%)	326 (40.0)	1628 (40.1)	585 (38.6)	2858 (37.8)
BMI, median (IQR)	28.3 (24.9–32.6)	28.6 (25.2–32.4)	28.6 (24.8–32.7)	28.3 (24.9–32.3)
BMI category, n (%)				
Underweight/Normal	216 (26.5)	976 (24.1)	410 (27.1)	2066 (27.3)
Overweight/Obese	599 (73.5)	3081 (75.9)	1104 (72.9)	5504 (72.7)
Induction therapy, n (%)				
Polyclonal antibodies	442 (54.2)	2024 (49.9)	820 (54.2)	4031 (53.3)
IL2 antagonists	377 (46.3)	1827 (45.0)	549 (36.3)	2642 (34.9)
Alemtuzumab	99 (12.2)	435 (10.7)	243 (16.1)	1091 (14.4)
Rituximab	5 (0.6)	92 (2.3)	6 (0.4)	126 (1.7)
Corticosteroids	705 (86.5)	3513 (86.6)	1271 (84.0)	6339 (83.7)
Other maintenance therapy, n (%)				
Mycophenolate mofetil	799 (98.0)	4010 (98.8)	1475 (97.4)	7458 (98.5)
Azathioprine	1 (0.1)	11 (0.3)	4 (0.3)	25 (0.3)
Corticosteroids	614 (75.3)	2972 (73.3)	1109 (73.3)	5527 (73.0)
Number of HLA mismatches, n (%)				
0–3	241 (29.6)	1225 (30.2)	416 (27.5)	2249 (29.7)
4–6	574 (70.4)	2832 (69.8)	1098 (72.5)	5321 (70.3)

Abbreviations: BMI body mass index, HLA human leucocyte antigen, IQR interquartile range, PS propensity score, SRTR Scientific Registry of Transplant Recipients; TCM Transplant Cancer Match.

Table 2:

Outcomes associated with belatacept use in kidney transplant recipients

Outcome	Belatacept	Tacrolimus	Belatacept vs. tacrolimus		
	Incidence per 1,000 py (N)	Incidence per 1,000 py (N)	Unadjusted HR (95%CI)	p	Adjusted HR* (95%CI)
TCM Cohort					
Overall invasive cancer	10.1 (22)	12.6 (139)	0.81 (0.52–1.27)	0.362	0.83 (0.53–1.30)
Specific invasive cancer sites					
Oral cavity/oropharynx	0	0.7 (8)	--		--
Stomach	1.4 (3)	0			
Colorectum	1.8 (4)	0.4 (4)	--		--
Pancreas	0.5 (1)	0.4 (4)	--		--
Lung	0.9 (2)	1.4 (16)	0.65 (0.15–2.85)	0.571	0.70 (0.16–3.08)
Melanoma	0.5 (1)	0.4 (4)	--		--
Breast (female only)	0	2.1 (8)	--		--
Prostate (male only)	0	2.4 (17)	--		--
Bladder	0.5 (1)	0.4 (4)	--		--
Kidney	0.5 (1)	1.9 (21)	0.24 (0.03–1.80)	0.156	0.24 (0.03–1.77)
Thyroid	0.5 (1)	0.2 (2)	--		--
Non-Hodgkin lymphoma	1.4 (3)	2.3 (25)	0.62 (0.19–2.07)	0.440	0.75 (0.22–2.50)
Myeloma	0	0.2 (2)	--		--
Miscellaneous	2.3 (5)	2.2 (24)	1.05 (0.40–2.74)	0.925	1.06 (0.40–2.77)
SRTR Cohort					
Death	31.0 (191)	25.9 (833)	1.18 (1.01–1.38)	0.037	1.22 (1.04–1.43)
GF/RT	19.6 (121)	20.6 (661)	0.95 (0.78–1.15)	0.586	0.95 (0.79–1.16)
PTLD	2.3 (14)	1.5 (47)	1.55 (0.85–2.82)	0.150	1.62 (0.89–2.95)
cSCC	6.6 (40)	7.5 (235)	0.89 (0.64–1.24)	0.486	0.92 (0.65–1.28)

Abbreviations: CI confidence interval, cSCC cutaneous squamous cell carcinoma, GF/RT graft failure/retransplantation, HR hazard ratio, PTLT posttransplant lymphoproliferative disorders, py person-years.

--No inferential analysis was performed when the total number of events was < 10.

Bolded results indicate statistical significance (p<0.005 for invasive cancers, p<0.05 for other outcomes).

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* Adjusted for age (3 categories: <40, 40–59, and 60+ years), sex (male, female), race (non-Hispanic White, Black/Hispanic/Other), transplant year (3 categories: 2011–2013, 2014–2016, 2017–2019), and Epstein-Barr virus serostatus (negative, positive/missing/unknown).

Table 3:

Associations of belatacept with risk of PTLD, death, and graft failure/retransplantation among kidney transplant recipients, stratified by recipient EBV serostatus at transplantation

Outcome	Belatacept	Tacrolimus	Belatacept vs. tacrolimus		
	Incidence per 1,000 py (N)	Incidence per 1,000 py (N)	Unadjusted HR (95%CI)	Adjusted HR* (95%CI)	p
EBV-seropositive at transplantation					
Death	30.4 (174)	26.3 (702)	1.14 (0.96–1.34)	1.20 (1.01–1.41)	0.035
GE/RT	19.4 (111)	19.5 (521)	0.98 (0.80–1.21)	0.98 (0.80–1.20)	0.848
PTLD	2.3 (13)	1.2 (32)	1.91 (1.00–3.65)	1.96 (1.03–3.73)	0.042
cSCC	6.6 (37)	8.0 (209)	0.83 (0.58–1.17)	0.84 (0.59–1.19)	0.334
EBV-seronegative at transplantation					
Death	42.9 (16)	21.9 (72)	2.09 (1.21–3.56)	1.98 (1.12–3.50)	0.019
GE/RT	24.1 (9)	25.8 (85)	0.95 (0.48–1.89)	1.06 (0.52–2.17)	0.871
PTLD	0	3.1 (10)	--	--	
cSCC	2.7 (1)	5.9 (19)	0.48 (0.06–3.58)	0.65 (0.09–4.96)	0.676

Abbreviations: EBV Epstein-Barr virus, GF/RT graft failure/retransplantation, HR hazard ratio, PTLTD posttransplant lymphoproliferative disorders, py person-years. Individuals with unknown or missing EBV serostatus were excluded from the analysis. Bolded results indicate statistical significance ($p < 0.05$).

--Model did not converge due to small sample size.

* Adjusted for age (3 categories: <40, 40–59, and 60+ years), sex (male, female), race (non-Hispanic White, Black/Hispanic/Other), and transplant year (3 categories: 2011–2013, 2014–2016, 2017–2019).

Table 4:

Associations of belatacept use with cause-specific mortality

Cause of death*	Belatacept	Tacrolimus	Belatacept vs. tacrolimus			
	Mortality per 1000 py (N)	Mortality per 1000 py (N)	Unadjusted HR (95%CI)	p	Adjusted** HR (95%CI)	p
Heart diseases	5.1 (25)	4.1 (108)	1.22 (0.79–1.88)	0.372	1.25 (0.81–1.94)	0.314
Neoplasms	3.3 (16)	3.9 (104)	0.81 (0.48–1.37)	0.431	0.83 (0.49–1.40)	0.481
Cerebrovascular diseases	--	0.9 (23)	1.60 (0.69–3.74)	0.274	1.72 (0.73–4.01)	0.214
Diabetes mellitus	3.0 (15)	3.2 (85)	0.94 (0.54–1.63)	0.827	0.97 (0.56–1.65)	0.902
Kidney diseases	3.9 (19)	2.8 (73)	1.40 (0.85–2.32)	0.190	1.43 (0.86–2.37)	0.167
Influenza and pneumonia	--	0.8 (20)	1.87 (0.79–4.42)	0.155	1.84 (0.78–4.37)	0.165
Other infections	--	1.8 (47)	0.57 (0.23–1.42)	0.225	0.57 (0.23–1.43)	0.229
All other causes	5.9 (29)	5.0 (133)	1.16 (0.78–1.74)	0.465	1.19 (0.79–1.78)	0.402

Bolded results indicate statistical significance ($p < 0.05$).

Abbreviations: HR hazard ratio, py person-years.

* Data on cause of death were obtained from a linkage to the National Death Index. Analyses were censored after December 31, 2019. Some cells based on small numbers of deaths are suppressed according to the data use agreement.

** Adjusted for age (3 categories: <40, 40–59, and 60+ years), sex (male, female), race (non-Hispanic White, Black/Hispanic/other), transplant year (3 categories: 2011–2013, 2014–2016, 2017–2019), and EBV serostatus (negative, positive/missing/unknown).