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# Safety of Everolimus With Reduced Calcineurin Inhibitor Exposure in De Novo Kidney Transplants: An Analysis From the Randomized TRANSFORM Study

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Abbreviations

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| BKV | BK virus |
| BPAR | biopsy-proven acute rejection |
| CI | confidence interval |
| CMV | cytomegalovirus |
| CNI | calcineurin inhibitor |
| CsA | cyclosporine |
| DSA | donor-specific antibodies |
| EBV | Epstein-Barr virus |
| EC-MPS | enteric-coated mycophenolate sodium |
| GFR | glomerular filtration rate |
| HCV | hepatitis C virus |
| IRT | interactive response technology |
| MMF | mycophenolate mofetil |
| MPA | mycophenolic acid |
| mTOR | mammalian target of rapamycin |
| PRA | panel reactive antibodies |
| RR | risk ratio |
| SMQ | Standardised MedDRA Query |
| TRANSFORM | Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen |
| WHO | World Health Organization |

Abstract

*Background*: The safety profiles of standard therapy versus everolimus with reduced-exposure calcineurin inhibitor (CNI) therapy using contemporary protocols in de novo kidney transplant recipients have not been compared in detail.

*Methods*: TRANSFORM was a randomized, international trial in which de novo kidney transplant patients were randomized to everolimus with reduced-exposure CNI (N=1014) or mycophenolic acid (MPA) with standard-exposure CNI (N=1012), both with induction and corticosteroids.

*Results*: Within the safety population (everolimus 1014, MPA 1012), adverse events with a suspected relation to study drug occurred in 62.9% versus 59.2% of patients given everolimus or MPA, respectively (p=0.085). Hyperlipidemia, interstitial lung disease, peripheral edema, proteinuria, stomatitis/mouth ulceration, thrombocytopenia and wound healing complications were more frequent with everolimus, while diarrhea, nausea, vomiting, leukopenia, tremor and insomnia were more frequent in the MPA group. The incidence of viral infections (17.2% versus 29.2%; p<0.001), CMV infections (8.1% versus 20.1%; p<0.001), CMV syndrome (13.6% versus 23.0%, p=0.044) and BKV infections (4.3% versus 8.0%, p<0.001) were less frequent with everolimus. CMV infection was less common with everolimus versus MPA after adjusting for prophylaxis therapy in the D+/R- subgroup (p<0.001). Study drug was discontinued more frequently due to rejection or impaired healing with everolimus, and more often due to BKV infection or BKV nephropathy with MPA.

*Conclusion*. De novo everolimus with reduced-exposure CNI yielded a comparable incidence, though a distinctly different pattern, of adverse events versus current standard-of-care. Both regimens are safe and effective, yet their distinct profiles may enable tailoring for individual kidney transplant recipients.

## Introduction

Inhibitors of mammalian target of rapamycin (mTOR) block growth-factor-mediated cell proliferation, suppressing T-cell activation and exerting a potent immunosuppression effect in recipients of an organ transplant.[1] The mTOR signalling pathway, however, also regulates a variety of other cellular functions involved in metabolism, apoptosis and growth[2] and it is therefore unsurprising that, in common with other classes of immunosuppressive therapy, mTOR inhibitors are associated with a number of potential adverse events. Meta-analyses of randomized controlled trials investigating the mTOR inhibitors everolimus[3-5] and sirolimus[6] have reported higher rates of events such as dyslipidemia, proteinuria, peripheral edema, anemia and stomatitis/mouth ulceration, with lower rates of infection (specifically cytomegalovirus [CMV] infection) compared to controls. However, these analyses included all trials performed since mTOR inhibitors first became available, incorporating a wide range of regimens and dosing protocols, and their findings may be of limited relevance to today's practice. In the earliest studies, a large loading dose of the first mTOR inhibitor, sirolimus, was given and target blood concentrations were high by current standards (e.g. 30 ng/mL), resulting in a high rate of adverse events.[7,8] Lower sirolimus doses were better tolerated[7-9] but were inadequate to prevent rejection when given de novo without concomitant calcineurin inhibitor (CNI) therapy.[9] Everolimus combined with reduced-exposure CNI therapy from the time of kidney transplantation, or shortly thereafter, avoids the need for high mTOR inhibition dosing and has been shown to maintain immunosuppressive efficacy compared to conventional CNI-based regimens.[10,11] Understanding the safety implications of this approach, however, has been hampered by the fact that even the most recent randomized trials of de novo everolimus with reduced-exposure CNI have usually employed cyclosporine (CsA),[10,11] while tacrolimus is now the most widely used CNI in this setting. Where concomitant tacrolimus has been given, everolimus exposure has not been optimal.[12]

TRANSFORM (Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen) was a randomized, international trial which compared everolimus with reduced-exposure CNI versus mycophenolic acid (MPA) with standard-exposure CNI in 2,037 de novo kidney transplant patients.[13] The majority of patients (~90%) received tacrolimus. Results showed the everolimus-based regimen to be non-inferior to standard therapy for the primary endpoint, a combination of treated biopsy-proven acute rejection (BPAR) or estimated glomerular filtration rate (GFR) <50 mL/min/1.73m$^2$ at one year post-transplant.[13] Here, we examine the one-year safety outcomes of the study, focusing on adverse events of interest.

## Methods

### *Study design and conduct*

TRANSFORM was a randomized, open-label, two-arm study performed at 186 centers in 42 countries worldwide (NCT01950819).[13] The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at participating centers and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

### *Patients*

The study enrolled de novo kidney transplant patients aged ≥18 years who had received a graft from a living or deceased heart-beating donor. Exclusion criteria included multiorgan transplantation, cold ischemia time >30 hours, high risk of rejection (based on local practice for assessment of anti-donor reactivity e.g. high panel reactive antibodies [PRA] or presence of pre-existing donor-specific antibodies [DSA]), recipient or donor positive for hepatitis C virus (HCV), and body mass index >35 kg/m$^2$. (See Table S1 [SDC, http://links.lww.com/TP/B683] for full inclusion and exclusion criteria).

*Study treatment*

Patients were randomized in a 1:1 ratio via a computer-generated randomization list, stratified within treatment groups by donor type (living, deceased standard criteria or deceased expanded criteria) and by CNI (CsA or tacrolimus). The decision whether to use CsA or tacrolimus was made according to center practice, but the study protocol specified that no more than 20% of subjects were to receive CsA. Investigators were notified of the randomization group by telephone-based interactive response technology (IRT).

All patients received induction therapy with basiliximab (20 mg on days 0 and 4) or rabbit antithymocyte globulin (1.5 mg/kg/day, total dose ≤6 mg/kg), with the choice of agent made according to center practice.

In the everolimus group, the everolimus dose was adjusted to target a trough concentration ($C_0$) of 3–8 ng/mL throughout the study. The tacrolimus target $C_0$ range in the everolimus group was 4–7 ng/mL during months 0–2, 2–5 ng/mL during months 3–6 and 2–4 ng/mL thereafter; corresponding target ranges for CsA were 100–150 ng/mL, 50–100 ng/mL and 25–50 ng/mL, respectively. In the MPA group, MPA was given as enteric-coated mycophenolate sodium (EC-MPS; 1.44 g/day) or mycophenolate mofetil (MMF; 2.0 g/day), which could be reduced after week 2 to EC-MPS 1.08 g/day or MMF 1.5 g/day in patients receiving tacrolimus but not those given CsA. The tacrolimus dose was adjusted to target $C_0$ concentrations of 8–12 ng/mL during months 0–2, 6–10 ng/mL during months 3–6, and 5–8 ng/mL thereafter; corresponding target ranges for CsA were 200–300 ng/mL, 150–200 ng/mL and 100–200 ng/mL, respectively.

Trough concentrations of everolimus, tacrolimus and CsA were recorded locally at all post-baseline study visits i.e. day 4, weeks 1, 2 and 4, and months 2, 6, 9 and 12 post-transplant.

Corticosteroid therapy was mandatory for all patients, administered according to local practice but with a minimum dose of prednisolone 5 mg/day or equivalent.

CMV pre-emptive therapy and/or prophylaxis was recommended for all cases in which the donor was CMV seropositive and the recipient was CMV seronegative, and was to be considered for all CMV-seropositive recipients. Where used, CMV prophylaxis was to be given for ≥3 months post-transplant. Prophylactic treatment with intravenous ganciclovir or oral valganciclovir was recommended, administered according to local practice. CMV prophylaxis was also recommended following antibody treatment of acute rejection episodes. *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia prophylaxis was to be given for ≥6 months to all patients.

*Adverse event reporting*

All adverse events and infections were reported via standard data collection applying Standardised MedDRA Query (SMQ) definitions. The following adverse events were considered to be of particular interest since they are recognized side effects of mTOR inhibitors, MPA formulations or CNI agents: anemia, hyperlipidemia, thrombocytopenia, new-onset diabetes mellitus (defined according to World Health Organization [WHO] criteria), interstitial lung disease, major cardiovascular events (defined as ischemic heart disease and cardiac failure), malignancy, proteinuria, stomatitis/mouth ulceration, peripheral edema, wound healing events/ complications, pleural effusion, gastrointestinal ulcer, diarrhea, nausea, vomiting, leukopenia, tremor and insomnia.

Infection rates are based on infections reported as adverse events, by type of infection and micro-organism. Additionally, data were collected specifically on CMV and BK virus (BKV) infections on separate clinical report forms. Serology assessment of recipients and donors at baseline included CMV and Epstein-Barr virus (EBV) status. The incidence of CMV infection reported as an adverse event (with either positive PCR or pp65 testing, or positive for anti-CMV IgM), was a pre-defined endpoint. *Post hoc*, the incidence of CMV infection was analyzed according to whether CMV prophylaxis was given or not, and according to donor/recipient serology. CMV syndrome and CMV disease with organ involvement were

defined by the investigator. The incidence of BKV infection was also a pre-specified endpoint, defined as any level of BKV viruria or viremia (based on screening or clinically indicated testing) with no specified minimum thresholds for viral load, BKV viruria or viremia (clinically indicated testing), or biopsy-confirmed BK nephropathy. Data on CMV and BKV events were captured on a specific clinical report form. Viral loads were not recorded and no threshold was applied for positive viruria or viremia.

*Statistical analysis of safety events*

All safety analyses were based on the safety population, comprising all patients who were randomized and received at least one dose of study drug. The relationship between the incidence of adverse events of interest and treatment groups was assessed using risk ratio (RR) values and the corresponding 95% confidence interval (CI), compared between groups by the Chi squared test or the Fisher's exact test, depending upon the size of the groups. Kaplan-Meier estimates of time to events (CMV or BKV infection) were compared between groups using the log rank test. In a post hoc analysis, the correlation between the number of wound healing events in each patient and everolimus exposure, defined as mean everolimus concentration from (i) day 4 to week 4, (ii) baseline to month 2 or (iii) baseline to month 12, was assessed using Spearman's rank order correlation. Correlation analyses excluded patients who were no longer receiving everolimus at week 4, month 2 or month 12, respectively. The level of statistical significance was defined at $p<0.05$ for two-tailed tests. Analyses were performed using SAS statistical software, Version 9.4 (or higher) for Unix.

**Results**

*Patient population and outcomes*

The intent-to-treat population comprised 2037 patients. Eleven patients did not receive study medication. Thus, the safety population comprised 2026 patients (everolimus 1014, MPA 1012), of whom 1843 completed the month 12 study visit (everolimus 921, MPA 922) (Figure 1). The treatment groups were well-matched at baseline (Table 1).

By month 12, 16 and 27 patients in the everolimus and MPA groups, respectively, had died (98.4% and 97.2% survival [p=0.091]) and among the survivors, 32 and 25 patients had lost their graft (96.8% and 97.5% death-censored graft survival [p=0.377]) (Kaplan-Meier estimates). Graft loss was caused by rejection in four patients in the everolimus group (1 hyperacute, 1 acute T-cell mediated, 2 acute antibody-mediated) and five patients in the MPA group (1 hyperacute, 3 acute T-cell, 1 chronic antibody-mediated). The rate of treated treated BPAR was 11.5% in the everolimus group and 8.8% in the MPA group (difference 2.7%, 95% CI [–1.2%, 6.5%]) (Kaplan-Meier estimates based on the intention-to-treat population).

*Immunosuppression*

The majority of patients (83.1%, 1692/2037) received basiliximab induction; 16.9% (342/2037) received rabbit antithymocyte globulin. At month 12, 72.7% (737/1014) of patients in the everolimus group and 81.2% (822/1012) patients in the MPA group remained on study drug (p<0.001).

The mean (SD) everolimus trough concentration during the 12-month study was 5.3 (1.3) ng/mL. Virtually all patients (939/1014, 92.6%) had a mean concentration within target range (i.e. 3–8 ng/mL); only 21 patients (2.1%) had a mean concentration above 8 ng/mL over the 12-month study. From baseline to month 2, the mean (SD) concentration was 4.9 (1.8) ng/mL, and 81.6% (827/1014) were within target range. Most patients in the everolimus group (913/1014; 90.0%) and the MPA group were receiving tacrolimus (916/1012; 90.5%) at study entry; the remainder received CsA. At the various study visits up to month 12, the proportion of patients with tacrolimus trough concentration above target ranged from 25% to 44% in the everolimus group and from 11% to 27% in the MPA group, while the proportion of patients with CsA concentration above target ranged from 17% to 61% in the everolimus group and from 7% to 32% in the MPA group.

*Adverse events*

The incidence of adverse events and serious adverse events was similar between treatment groups overall (Table 2) and within geographical regions (Table S2, SDC, http://links.lww.com/TP/B683). Among the adverse events of interest, hyperlipidemia, interstitial lung disease, peripheral edema, proteinuria, stomatitis/mouth ulceration, thrombocytopenia, and wound healing events (including lymphoceles) were more frequent in the everolimus group than the MPA group (Table 2). The increased rate of hyperlipidemia in the everolimus group was observed despite more frequent use of statin therapy (everolimus 56.8%, MPA 43.6%; p<0.001). On the other hand, diarrhea, nausea, vomiting, leukopenia, tremor and insomnia were significantly more frequent in the MPA group (Table 2). The incidence of anemia (everolimus 22.4%, MPA 23.0%; p=0.732) and use of epoetin therapy (everolimus 30.9%, MPA 29.2%; p=0.401) were similar between groups. New-onset diabetes (everolimus 13.2%, MPA 12.1%) and use of insulin therapy (everolimus 37.4%, MPA 37.5%; p=0.976) were also comparable. Gastrointestinal ulcers, major cardiovascular events, malignancy and pleural effusion occurred at comparable rates in both groups (Table 2). The incidence of thrombotic events in the everolimus versus MPA groups was 1.3% versus 0.5% (p=0.059) for thrombotic microangiopathy, 3.2% versus 2.4% (p=0.282) for deep vein thrombosis, 1.6% versus 0.5% (p=0.016) for pulmonary embolism, 0.2% versus 0.0% (p=0.157) for graft thrombosis and 0.4% versus 0.2% (p=0.415) for hemolytic uremic syndrome.

At month 12, the median urine protein-creatinine ratio was 100 mg/g in both treatment groups; proteinuria in the nephrotic range (≥3,000 mg/g) was present in 3.1% (30/953) of everolimus-treated patients and in 1.4% (13/940) of MPA-treated patients (p=0.051).

*Infections*

The overall rate of infections was lower in the everolimus group (52.0% versus 59.8%; p<0.001). This difference arose largely from a substantially lower rate of viral infections (17.2% versus 29.2%; p<0.001) (Table 3).

The incidence of CMV infections reported as adverse events was lower under everolimus therapy than MPA (3.6% versus 13.3%; p<0.001) (Table 3), a finding confirmed on Kaplan-Meier analysis (log rank test p<0.001) (Figure 2a). The mean (SD) time to first CMV infection was 115 (106) days and 121 (93) days in the everolimus and MPA groups, respectively (p=0.728). Based on data from the specific CMV clinical report form, CMV infections were significantly less frequent in everolimus-treated patients (8.1% versus 20.1% in the MPA group, p<0.001), with more than a three-fold reduction in infections among high-risk (D+/R-) patients (Table 3). CMV syndrome was reported in 15 everolimus patients and 50 MPA patients (13.6% versus 23.0%, p=0.044), with CMV disease (i.e. histological evidence for organ involvement) in one and six patients, respectively. Among patients for whom CMV serology was known at baseline, the incidence of CMV infection was 7.4% (39/528) with everolimus versus 14.6% with MPA (76/522) in the subgroup of patients given CMV prophylaxis and 8.8% (43/486) versus 25.9% (127/490) in those without prophylaxis. For high risk D+/R- patients, the incidence was 15.7% (20/127) with everolimus versus 34.3% (35/102) with MPA in those given prophylaxis, and 20.8% (5/24) versus 38.9% (14/36) in those without prophylaxis. The rate of CMV infection was significantly lower with everolimus versus MPA after adjusting for prophylaxis therapy overall and in the D+/R- and D+/R+ subgroups (both p<0.001) (Table 4).

BKV infections reported as adverse events were less frequent with everolimus than MPA (4.3% versus 8.0%, p<0.001), a finding confirmed on Kaplan-Meier analysis (log rank test p=0.001) (Figure 2b). The mean (SD) time to first BKV infection was 142 (93) days and 134 (106) days in the everolimus and MPA groups, respectively (p=0.677). Based on data from

the specific BKV clinical report form, significantly fewer patients on everolimus were reported to have either BKV viruria or viremia, or BKV viremia (both p<0.001) (Table 3). Significantly fewer patients in the everolimus group were reported to have BKV viruria or viremia based on screening or clinically indicated testing (p<0.001 overall; p<0.001 for viremia only) or based solely on clinically indicated testing (p=0.010) (Table 3).

*Wound healing complications*

Wound healing complications occurred in 19.8% of everolimus-treated patients and 16.2% of MPA-treated patients (p=0.034). Lymphocele, wound dehiscence and impaired healing (as defined by the investigator during adverse event reporting) occurred more frequently under everolimus (Table 5). Impaired healing was associated with a significantly higher rate of study discontinuation in the everolimus group compared to the MPA group (Table 6). When the association between wound healing complications and mean everolimus concentration was examined during the periods from (i) day 4 to week 4 (ii) day 4 to month 2 and (iii) day 4 to month 12, no significant associations were found during any of these periods for fluid collections, wound complications or wound pain, or for the specific events of lymphocele, wound dehiscence and impaired healing (Table S3, SDC, http://links.lww.com/TP/B683).

*Discontinuations, dose adjustments and temporary interruptions of study drugs*

Discontinuation of study medication (>21 days) due to adverse events was more frequent under everolimus (23.0% versus 11.9% with MPA, p<0.001) (Table 6), accounting for 77.3% (214/277) of discontinuations in the everolimus group versus 60.5% (115/190) of discontinuations in the MPA group (p<0.001). Kaplan-Meier analysis confirmed this finding (log rank p<0.001) (Figure 3). Proteinuria and acute kidney injury only led to discontinuation of everolimus. Transplant rejection led to discontinuation of the everolimus-based regimen in 15 patients (1.5%).[13] BKV infection and biopsy-confirmed BKV nephropathy were more frequent causes of study drug discontinuation in the MPA arm than the everolimus group (Table 6).

In contrast, dose adjustments or temporary interruptions (≤21 days) due to adverse events were more frequent in the MPA group (25.4% with everolimus versus 48.2% with MPA, p<0.001), with neutropenia and tremor showing marked differences between groups (Table 6).

**Discussion**

The safety profile of everolimus and reduced-exposure CNI in this large randomized trial of de novo kidney transplant patients was consistent with expectations. In particular, the anticipated increases in hyperlipidemia, proteinuria and stomatitis/mouth ulceration under mTOR inhibition compared to a standard regimen of MPA with CNI were evident. Equally, the typical adverse events of diarrhea, nausea, vomiting, leukopenia, tremor and insomnia were, as expected, more frequent in the MPA group. The trial confirmed that the risk of CMV infection is significantly less frequent under everolimus, both overall and in the high-risk D+/R- subgroup with or without CMV prophylaxis. BKV infections were also significantly less common in the everolimus-treated cohort.

Combined everolimus/CNI regimens avoid the high mTOR inhibitor concentrations required in CNI-free regimens, improving tolerability. In the randomized HERAKLES study, patients given everolimus (3–8 ng/mL, as here) combined with CNI discontinued everolimus less frequently than patients given higher-exposure everolimus (5–10 ng/mL) without CNI.[11] It has been suggested that when everolimus trough concentration is maintained in the range 3–8 ng/mL, most adverse events can be managed successfully without the need to discontinue the drug.[14,15] For example, hyperlipidemia is exacerbated by mTOR inhibitors,[15] but levels of total cholesterol are typically towards the upper end of normal[10,11] and can often be managed by statin therapy.[16] It is also possible that investigators were more likely to respond to clinical events by discontinuing everolimus than discontinuing MPA/CNI. The overall rates of adverse events, serious adverse events and events with suspected relation to study drug were comparable between groups, but everolimus-based treatment was discontinued twice as

frequently as the control regimen. Transplant rejection, for example, occurred in 100 everolimus patients and 83 MPA patients,[13] but led to everolimus discontinuation in 15 patients but MPA/CNI discontinuation in only one patient. Acute kidney injury prompted everolimus withdrawal in seven patients, but no patient in the MPA group, despite similar rates of occurrence (7% versus 6%). In this study, as elsewhere,[10] dose reductions or interruptions were twice as frequent in the control arm. This may partly reflect the fact that MPA dosing is not concentration-controlled, which could necessitate more dose alterations, but also indicates a disinclination to stop CNI entirely.

An important safety advantage for everolimus was the lower rate of viral infections, specifically CMV and BKV infections. The reduction in CMV infections under everolimus was highly convincing and, importantly, was consistently observed in the subgroup of patients who received CMV prophylaxis, and in the high-risk D+/R- patients; CMV syndrome was also less frequent. This was as expected based on previous experience[10,17,18] and, given the known association between CMV infection and long-term survival,[19] is highly relevant. Data relating to an effect on BKV infection have so far been inconclusive.[18] Non-interventional studies have suggested a lower rate of BKV viremia under everolimus with low-exposure CNI versus standard CNI therapy,[20] and case reports have described reduced viral load or BKV clearance after switching to everolimus.[21,22] To our knowledge, however, this is the first randomized trial to show a significant reduction in BKV infection rates with everolimus and reduced CNI therapy.

Wound healing complications are a potential safety concern with mTOR inhibitor therapy due to their potential to inhibit fibrosis, a key component of the healing process.[23] Randomized[10,24] and observational[25] studies of everolimus with low-exposure CsA have described similar[24,25] or slightly higher[10] rates of wound-related events than with standard CNI regimens. In the current trial, there was again a slightly higher rate of wound healing complications in the everolimus arm (19.8% versus 16.2%). Recently, Shihab et al

investigated the association between everolimus and adverse events based on data from the A2309 study, in which de novo kidney transplant patients were randomized to everolimus targeting a trough concentration of 3–8 ng/mL or 6–12 ng/mL, both with reduced-exposure CsA, or to MPA with standard CsA.[26] Over this range of everolimus concentrations, the authors demonstrated higher rates of wound healing events with mean everolimus concentration >8 ng/mL, but detected no differences when everolimus was in the range 3–6 versus 6–8 ng/mL, i.e. there was no relationship between wound healing events and exposure within the recommended range of 3-8 ng/mL. In the current study, patients virtually all had a mean everolimus level within the range 3–8 ng/mL, and there was again no positive association between the risk of wound healing complications and everolimus trough concentration, either over the short- or long-term. (It should be noted that obesity is a well-documented risk factor for poor healing after transplantation,[27-29] and highly obese patients (>35 kg/m$^2$) were excluded from the study so these results do not necessarily apply to such individuals.)

There was a higher incidence of pulmonary embolism under everolimus, and a trend to more thrombotic microangiopathy, compared to the MPA group. Although thrombotic events in organ transplant recipients are multifactorial in origin and may occur under both CNI or mTOR inhibitor therapy,[30,31] there is evidence that mTOR inhibition is associated with a procoagulant state,[32] which could compound endothelial injury caused by CNIs[33,34] and predispose to thrombomicroangiopathy. Although thrombotic complications were uncommon in both groups in this study, this data warrants capture of such events as a pre-specified endpoint in future studies.

This analysis benefitted from the large study population of TRANSFORM. More patients in the everolimus group discontinued study drug prematurely, a potential source of bias in favor of everolimus, but since adverse events were the dominant reason for discontinuation the risk of bias is limited. It is possible that the more frequent dose reductions or interruptions in the

MPA group in response to adverse events lowered the risk for subsequent adverse events, but this cannot be confirmed. The mean tacrolimus trough concentration was above target in a somewhat higher proportion of everolimus-treated patients than MPA-treated patients at month 12, which may also have influenced adverse event rates. As with all standard adverse event reporting, the definition of events was at the investigators' discretion. This subjective methodology meant, for example, that wound healing events were potentially subject to between-center differences in the severity required to qualify for an 'adverse event' and in categorization of the events. Equally, there were no protocol-specified thresholds for laboratory-defined events such as anemia. While these are limitations, variations in centers' definitions should not have affected comparative findings since they applied equally to both treatment arms. We are also aware that inclusion of maintenance steroid therapy within both regimens may limit generalizabilty of these findings to centers that routinely seek to avoid steroids. Lastly, although TRANSFORM was the largest randomized trial conducted to date in de novo kidney transplant patients, the size and duration of the study does not permit a meaningful assessment of the risk for rare events such as malignancy. The cytostatic effects of mTOR inhibitors have prompted interest in a possible role in preventing post-transplant malignancy,[35] with analyses showing a benefit for the secondary prevention of squamous cell carcinoma,[35] and for prevention of non-melanoma skin cancer and other cancers,[36,37] but this cannot be evaluated here. Other longer-term complications, such as the occurrence of major cardiovascular events, will be analyzed at the two-year study visit. Mortality rates at the two-year visit will also be of interest, in view of the non-significant trend to lower mortality in the everolimus cohort versus the MPA-treated group at one year (p=0.091). Commentators have previously stressed the need for additional mortality data from well-designed longer-term transplant studies assessing mTOR inhibitor therapy.[38]

In conclusion, this large randomized trial in de novo kidney transplant patients confirms the efficacy[13] and the balanced safety profile of everolimus, targeting a concentration in the range 3–8 ng/mL, given in conjunction with reduced-exposure CNI. The study showed excellent graft and patient survival rates (all ≥97%) in both treatment arms at 12 months post-transplant. Although restricted to the first year post-transplant, the current results help to provide guidance when considering use of this regimen in de novo recipients. Where pre-transplant comorbidity includes problematic dyslipidemia, thrombocytopenia or factors that predispose to delayed wound healing such as obesity and diabetes, everolimus with reduced CNI is a less favorable option. Where patients are at high risk for leukopenia, gastrointestinal complications or for CMV or BKV infection, however, de novo therapy with everolimus and reduced-exposure CNI offers a potential benefit.

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**Figure 1.** Patient disposition (safety population).

**Figure 2.** Kaplan-Meier plots of time to first event for (A) CMV infection and (B) BKV infection, according to treatment group (safety population).

**Figure 3.** Kaplan-Meier plot of time to discontinuation of study medication according to treatment group (safety population).

**Table 1.** Baseline Characteristics (Safety Population).

| | Everolimus (N = 1014) | MPA (N = 1012) |
|---|---|---|
| Age, years, mean (SD) | 49.4 (14.09) | 49.3 (14.49) |
| Male, n (%) | 707 ( 69.7) | 705 ( 69.7) |
| Race, n (%) | | |
| White | 743 (72.7) | 735 (72.4) |
| Asian | 136 (13.3) | 157 (15.5) |
| Black | 43 (4.2) | 35 (3.4) |
| Other | 100 (9.8) | 88 (8.7) |
| End-stage renal disease leading to transplant, n (%) | | |
| Glomerular disease | 157 (15.4) | 176 (17.3) |
| Polycystic disease | 147 (14.4) | 149 (14.7) |
| Diabetes mellitus | 128 (12.5) | 131 (12.9) |
| Hypertension/nephrosclerosis | 124 (12.1) | 125 (12.3) |
| IgA nephropathy | 88 (8.6) | 103 (10.1) |
| Other | 377 (36.9) | 331 (32.6) |
| Missing | 1 (0.1) | 0 (0.0) |
| Hemodialysis, n (%) | 674 (65.9) | 679 (66.9) |
| Body mass index (kg/m$^2$), mean (SD) | 25.6 (4.25) | 25.6 (4.25) |
| Diabetes, n (%) | 278 ( 27.4) | 268 ( 26.5) |
| Hypertension, n (%)[a] | 859 ( 84.7) | 879 ( 86.9) |
| Anemia, n (%)[a] | 300 ( 29.6) | 318 ( 31.4) |
| Cardiac disorders, n (%)[a,b] | 326 (32.1) | 331 (32.7) |
| Donor category, n (%) | | |
| Living related | 299 ( 29.5) | 313 ( 30.9) |
| Living unrelated | 207 ( 20.4) | 192 ( 19.0) |
| Deceased heart-beating | 503 ( 49.6) | 504 ( 49.8) |
| Standard criteria donor[c] | 352 ( 70.0) | 345 ( 68.5) |
| Expanded criteria donor[c] | 151 ( 30.0) | 159 ( 31.5) |
| Deceased non-heart-beating | 5 ( 0.5) | 3 ( 0.3) |
| CMV serology, n (%) | | |
| D+/R+ | 510 (50.3) | 520 (51.4) |
| D+/R- | 151 (14.9) | 138 (13.6) |
| D-/R+ | 141 (13.9) | 147 (14.5) |
| D-/R- | 169 (16.7) | 168 (16.6) |
| Unknown/missing | 43 (4.2) | 39 (0.9) |

CMV, cytomegalovirus; MPA, mycophenolic acid; SD, standard deviation.
[a]As defined by the investigator.
[b]According to MedDRA categories.
[c]The denominator is the number of deceased heart-beating donors.

**Table 2**. Adverse Events[a] According to Treatment Group (Safety Population).

| | Everolimus (N = 1014) | MPA (N = 1012) | Risk Ratio (95% CI) | *P*-Value |
|---|---|---|---|---|
| Any adverse event | 993 (97.9) | 984 (97.2) | 1.01 (0.99, 1.02) | 0.308 |
| Any serious adverse event | 557 (54.9) | 568 (56.1) | 0.98 (0.91, 1.06) | 0.588 |
| Any adverse event with suspected relation to study drug | 638 (62.9) | 599 (59.2) | 1.06 (0.99, 1.14) | 0.085 |
| Adverse events of interest | | | | |
| Anemia | 227 (22.4) | 233 (23.0) | 0.97 (0.83, 1.14) | 0.732 |
| Leukopenia | 94 (9.3) | 192 (19.0) | 0.49 (0.39, 0.62) | <0.001 |
| Thrombocytopenia | 75 (7.4) | 38 (3.8) | 1.97 (1.35, 2.88) | <0.001 |
| Diarrhea | 219 (21.6) | 316 (31.2) | 0.69 (0.70, 0.80) | <0.001 |
| Gastrointestinal ulcer | 7 (0.7) | 12 (1.2) | 0.58 (0.23, 1.47) | 0.247 |
| Nausea | 177 (17.5) | 214 (21.1) | 0.83 (0.69, 0.99) | 0.036 |
| Stomatitis and mouth ulceration | 78 (7.7) | 21 (2.1) | 3.71 (2.31, 5.95) | <0.001 |
| Vomiting | 110 (10.8) | 141 (13.9) | 0.78 (0.62, 0.98) | 0.035 |
| Peripheral edema | 373 (36.8) | 262 (25.9) | 1.42 (1.25, 1.62) | <0.001 |
| Hyperlipidemia | 350 (34.5) | 188 (18.6) | 1.86 (1.59, 2.17) | <0.001 |
| Tremor | 98 (9.7) | 137 (13.5) | 0.71 (0.56, 0.91) | 0.007 |
| Insomnia | 91 (9.0) | 130 (12.8) | 0.70 (0.54, 0.90) | 0.005 |
| Proteinuria | 128 (12.6) | 57 (5.6) | 2.24 (1.66, 3.02) | <0.001 |
| Interstitial lung disease | 11 (1.1) | 3 (0.3) | 3.66 (1.02, 13.08) | 0.032 |
| Pleural effusion | 11 (1.1) | 11 (1.1) | 1.00 (0.43, 2.29) | 0.996 |
| Major cardiovascular events[b] | 56 (5.5) | 74 (7.3) | 0.76 (0.54, 1.06) | 0.100 |
| Malignancy | 26 (2.6) | 24 (2.4) | 1.08 (0.63, 1.87) | 0.780 |
| New-onset diabetes mellitus[c] | 134 (13.2) | 122 (12.1) | 1.10 (0.87, 1.38) | 0.432 |
| Wound healing events/complications | 201 (19.8) | 164 (16.2) | 1.22 (1.01, 1.47) | 0.034 |

CI, confidence interval; MPA, mycophenolic acid

[a]As reported by the investigator.
[b]Defined as ischemic heart disease and cardiac failure.
[c]Defined according to WHO criteria.

**Table 3.** Infections at Month 12 According to Treatment Group (Safety Population).

| | Everolimus (N = 1014) | MPA (N = 1012) | Risk Ratio (95% CI) | *P*-Value |
|---|---|---|---|---|
| Reported as adverse events, n (%)[a] | | | | |
| *Any infection* | | | | |
| Bacterial infection | *527 (52.0)* | *605 (59.8)* | *0.87 (0.80, 0.94)* | *<0.001* |
| Any fungal infection | 353 (34.8) | 381 (37.6) | 0.92 (0.82, 1.04) | 0.184 |
| Viral infection | 69 (6.8) | 46 (4.5) | 1.50 (1.04, 2.15) | 0.028 |
| CMV | 174 (17.2) | 296 (29.2) | 0.59 (0.50, 0.69) | <0.001 |
| BKV | 36 (3.6) | 135 (13.3) | 0.27 (0.19, 0.38) | <0.001 |
| | 44 (4.3) | 81 (8.0) | 0.54 (0.38, 0.77) | <0.001 |
| CMV infection n/M (%)[b] | | | | |
| *Any CMV infection* | *82 (8.1)* | *203 (20.1)* | *0.40 (0.32, 0.51)* | *<0.001* |
| D+/R+ at baseline | 39/510 (7.6) | 121/520 (23.3) | 0.33 (0.23, 0.46) | <0.001 |
| D+/R- at baseline | 25/151 (16.6) | 49/138 (35.5) | 0.47 (0.31, 0.71) | <0.001 |
| D-/R+ at baseline | 9/141 (6.4) | 18/147 (12.2) | 0.52 (0.24, 1.12) | 0.088 |
| D-/R- at baseline | 5/169 (3.0) | 5/168 (3.0) | 0.99 (0.29, 3.37) | 0.992 |
| Unknown or missing | 4/43 (9.3) | 10/39 (25.6) | 0.36 (0.12, 1.06) | 0.050 |
| CMV syndrome, n/M (%)[c] | 15/110 (13.6) | 50/217 (23.0) | 0.59 (0.35, 1.00) | 0.044 |
| CMV disease, n/M (%)[d] | 1/71 (1.4) | 6/123 (4.9) | 0.29 (0.04, 2.35) | 0.212 |
| BKV infection, n (%)[b] | | | | |
| BKV viruria or viremia (screening or clinically indicated testing) | 77 (7.6) | 126 (12.5) | 0.61 (0.47, 0.80) | <0.001 |
| BKV viremia (screening or clinically indicated testing) | 58 (5.7) | 104 (10.3) | 0.55 (0.40, 0.75) | <0.001 |
| BKV viruria or viremia (clinically indicated testing) | 34 (3.4) | 58 (5.7) | 0.59 (0.39, 0.89) | 0.010 |
| Biopsy-confirmed BKV nephropathy | 12 (1.2) | 21 (2.1) | 0.57 (0.28, 1.15) | 0.113 |

BKV, BK virus; CI, confidence interval; CMV, cytomegalovirus; M, total number of patients assessed; MPA, mycophenolic acid; N, total number of patients; n, number of patients with event within each category.

[a]As reported by the investigator as adverse events, by type of infection and micro-organism.

[b]Reported on specific CMV/BKV clinical report forms.

[c]Denominator is the number of patients with clinical signs of CMV infection.

[d]Denominator is the number of patients undergoing biopsy.

**Table 4.** Cytomegalovirus (CMV) Infection by Donor/Recipient Serology Status at Baseline in Patients With or Without Prophylactic Therapy, According to Treatment Group (Safety Population).

| | Any CMV Infection, n/M (%)[a] | | *P*-Value[a] |
|---|---|---|---|
| | Everolimus (N = 1,014) | MPA (N = 1,012) | |
| All patients, n/M (%)[b] | | | <0.001 |
| Prophylaxis | 39/528 (7.4) | 76/522 (14.6) | |
| No prophylaxis | 43/486 (8.8) | 127/490 (25.9) | |
| D+/R+ | | | <0.001 |
| Prophylaxis | 13/240 (5.4) | 30/260 (11.5) | |
| No prophylaxis | 26/270 (9.6) | 91/260 (35.0) | |
| D+/R- | | | <0.001 |
| Prophylaxis | 20/127 (15.7) | 35/102 (34.3) | |
| No prophylaxis | 5/24 (20.8) | 14/36 (38.9) | |
| D-/R+ | | | 0.079 |
| Prophylaxis | 3/72 (4.2) | 7/79 (8.9) | |
| No prophylaxis | 6/69 (8.7) | 11/68 (16.2) | |
| D-/R- | | | 0.984 |
| Prophylaxis | 3/68 (4.4) | 2/65 (3.1) | |
| No prophylaxis | 2/101 (2.0) | 3/103 (2.9) | |
| Unknown or missing | | | 0.069 |
| Prophylaxis | 1/21 (0.0) | 2/16 (12.5) | |
| No prophylaxis | 4/22 (18.2) | 8/23 (34.8) | |

CMV infection was defined as CMV viruria or CMV, CMV syndrome or CMV organ involvement. CMV prophylaxis was defined as the use of antiviral drugs started within 14 days of transplantation and taken consecutively for 30 days or more.

CMV, cytomegalovirus; M, total number of patients assessed; MPA, mycophenolic acid; N, total number of patients; n, number of patients with event within each category.

[a]Reported on CMV/BKV clinical report forms.
[b]Cochran-Mantel-Haenszel test to check for independence of CMV event rates and treatment arms adjusted for CMV prophylaxis therapy.

**Table 5.** Wound-Related Events Reported as Adverse Events in ≥2% Patients in Either Treatment Group by Month 12 (Safety Population).

| | Treatment Group | | | |
|---|---|---|---|---|
| | Everolimus (N = 1,014) | MPA (N = 1,012) | Risk Ratio (95% CI) | *P*-Value |
| Fluid collections | | | | |
| Lymphocele | 74 (7.3) | 52 (5.1) | 1.42 (1.01, 2.00) | 0.044 |
| Perinephric collection | 30 (3.0) | 25 (2.5) | 1.20 (0.71, 2.02) | 0.499 |
| Post-procedural hematoma | 24 (2.4) | 20 (2.0) | 1.20 (0.67, 2.15) | 0.547 |
| Seroma | 23 (2.3) | 19 (1.9) | 1.21 (0.66, 2.20) | 0.537 |
| Total | 139 (13.7) | 108 (10.7) | 1.28 (1.01, 1.63) | 0.037 |
| Wound complications | | | | |
| Wound dehiscence | 39 (3.8) | 18 (1.8) | 2.16 (1.25, 3.75) | 0.005 |
| Impaired healing | 35 (3.5) | 8 (0.8) | 4.37 (2.04, 9.37) | <0.001 |
| Wound complication | 33 (3.3) | 41 (4.1) | 0.80 (0.51, 1.26) | 0.339 |
| Total | 96 (9.5) | 62 (6.1) | 1.54 (1.14, 2.10) | 0.005 |
| Wound pain | | | | |
| Procedural pain | 96 (9.5) | 104 (10.3) | 0.92 (0.71, 1.20) | 0.542 |
| Incision site pain | 50 (4.9) | 59 (5.8) | 0.85 (0.59, 1.22) | 0.370 |
| Total | 144 (14.2) | 154 (15.2) | 0.93 (0.76, 1.15) | 0.519 |

Patients could have more than one event within each category.

CI, confidence interval; MPA, mycophenolic acid.

**Table 6.** Adverse Events Leading to Study Drug Discontinuation in ≥0.5% of Patients in Either Group, or to Dose Adjustment or Temporary Interruption in ≥1.0% of Patients in Either Group (Safety Population).

| n (%) | Everolimus (N = 1,014) | MPA (N = 1,012) | Risk ratio risk (95% CI) |
|---|---|---|---|
| Adverse events leading to study drug discontinuation (>21 days) in ≥0.5% of patients in either group, n (%)[a] | | | |
| *Any adverse event* | *233 (23.0)* | *120 (11.9)* | *1.94 (1.58. 2.37)* |
| Leukopenia | 4 (0.4) | 9 (0.9) | 0.44 (0.14, 1.44) |
| Diarrhea | 0 (0.0) | 6 (0.6) | - |
| Impaired healing | 12 (1.2) | 1 (0.1) | 11.98 (1.56, 91.93) |
| Peripheral edema | 14 (1.4) | 0 (0.0) | - |
| BK virus infection | 3 (0.3) | 12 (1.2) | 0.25 (0.07, 0.88) |
| Transplant rejection | 15 (1.5) | 1 (0.1) | 14.97 (1.98, 113.10) |
| CMV infection | 1 (0.1) | 5 (0.5) | 0.20 (0.02, 1.71) |
| Polyomavirus-associated nephropathy | 5 (0.5) | 14 (1.4) | 0.36 (0.13, 0.99) |
| Graft loss | 8 (0.8) | 9 (0.9) | 0.89 (0.34, 2.29) |
| Acute kidney injury | 7 (0.7) | 0 (0.0) | - |
| Proteinuria | 22 (2.2) | 0 (0.0) | - |
| Renal impairment | 5 (0.5) | 2 (0.2) | 2.50 (0.49, 12.83) |
| Lymphocele | 5 (0.5) | 0 (0.0) | - |
| Adverse events leading to dose adjustment or temporary interruption (≤21 days) in ≥1.0% of patients in either group, n (%)[a] | | | |
| Any adverse event | *258 (25.4)* | *488 (48.2)* | *0.53 (0.47, 0.60)* |
| Anemia | 11 (1.1) | 5 (0.5) | 2.20 (0.77, 6.30) |
| Neutropenia | 1 (0.1) | 23 (2.3) | 0.04 (0.01, 0.32) |
| Thrombocytopenia | 15 (1.5) | 6 (0.6) | 2.50 (0.97, 6.40) |
| Abdominal pain | 0 (0.0) | 12 (1.2) | 0.00 |
| Pyrexia | 7 (0.7) | 12 (1.2) | 0.58 (0.23, 1.47) |
| Transplant rejection | 4 (0.4) | 6 (0.6) | 0.67 (0.19, 2.35) |
| CMV viremia | 3 (0.3) | 10 (1.0) | 0.30 (0.08, 1.08) |
| Urinary tract infection | 22 (2.2) | 25 (2.5) | 0.88 (0.50, 1.55) |
| Complications of transplanted kidney | 6 (0.6) | 10 (1.0) | 0.60 (0.22, 1.64) |
| Increased blood creatinine | 16 (1.6) | 25 (2.5) | 0.64 (0.34, 1.19) |

| | | | |
|---|---|---|---|
| Toxicity to various agents | 3 (0.3) | 21 (2.1) | 0.14 (0.04, 0.48) |
| Tremor | 6 (0.6) | 35 (3.5) | 0.17 (0.07, 0.41) |

CI, confidence interval; CMV, cytomegalovirus; MPA, mycophenolic acid.

[a]As reported by the investigator.

**Figure 1.**

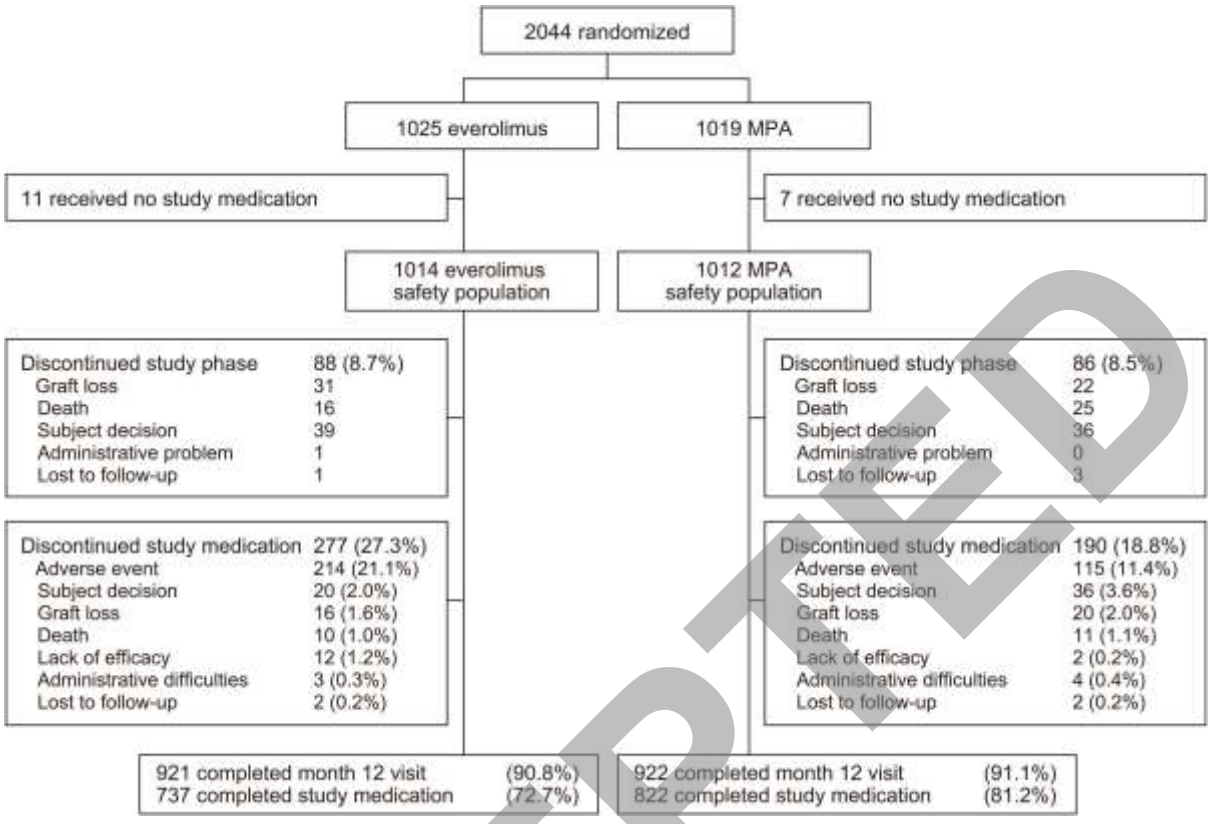

**Figure 2A.**

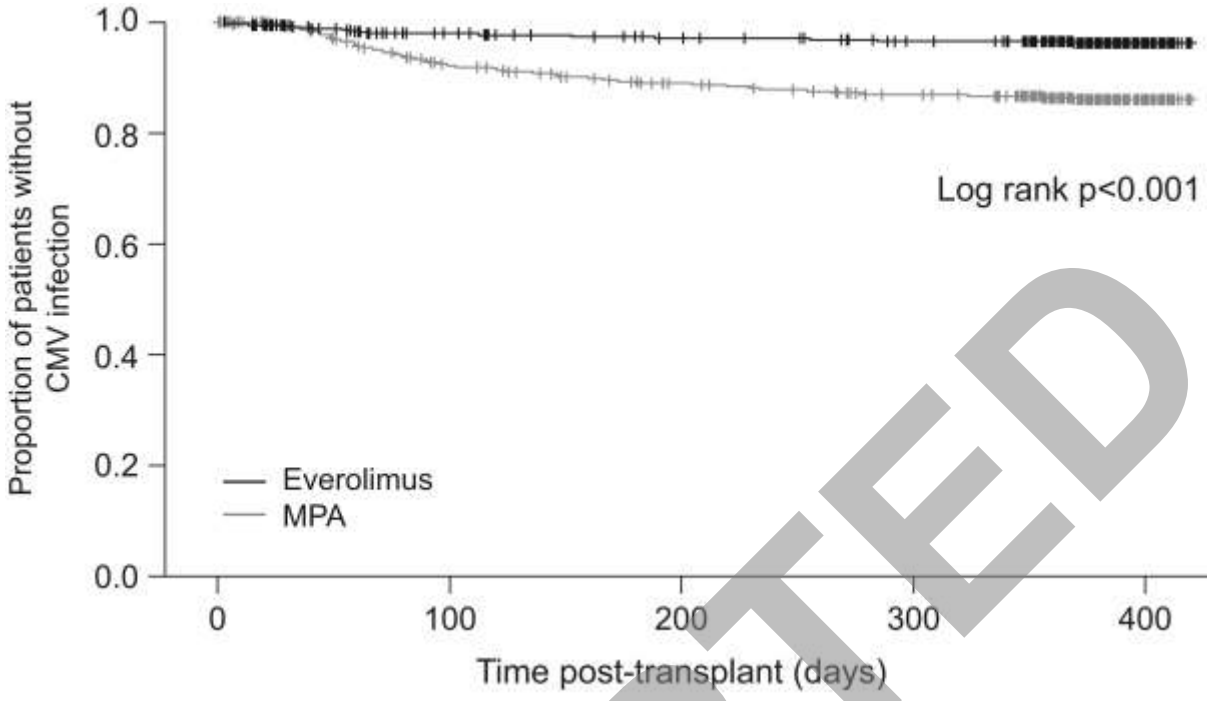

**Figure 2B.**

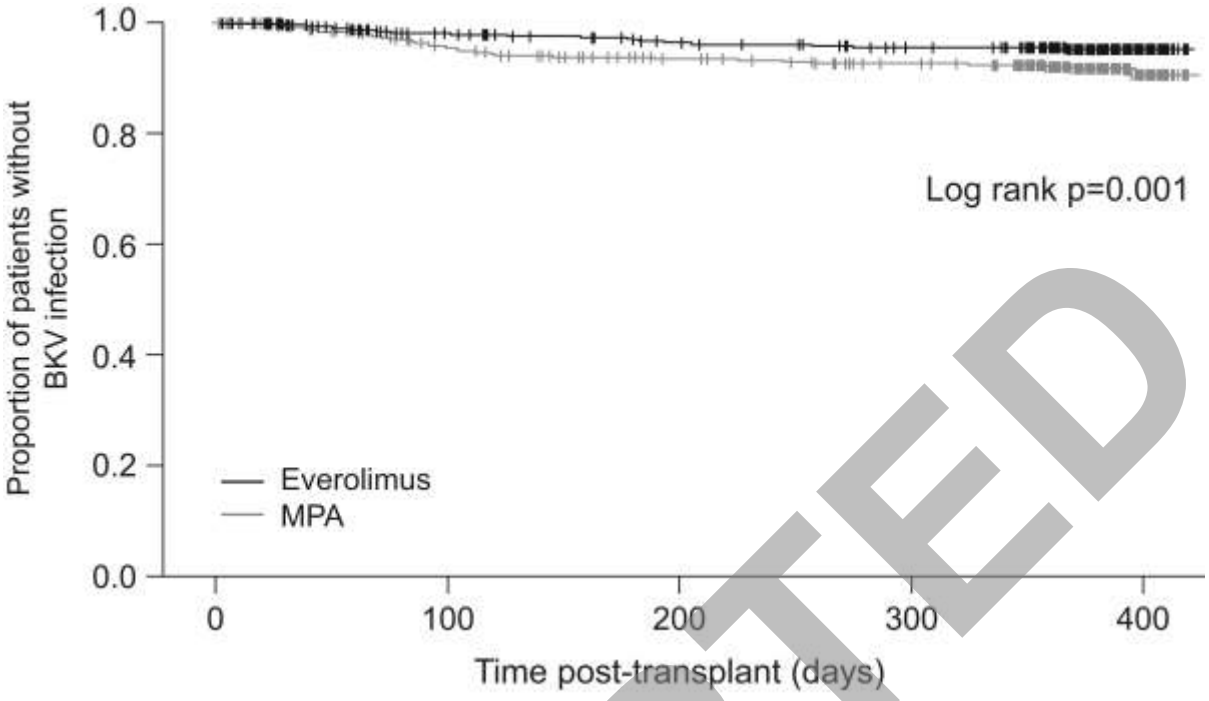

**Figure 3.**