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Everolimus with Reduced Calcineurin Inhibitor Exposure in Renal Transplantation

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ABSTRACT

Background Everolimus permits reduced calcineurin inhibitor (CNI) exposure, but the efficacy and safety outcomes of this treatment after kidney transplant require confirmation.

Methods In a multicenter noninferiority trial, we randomized 2037 *de novo* kidney transplant recipients to receive, in combination with induction therapy and corticosteroids, everolimus with reduced-exposure CNI (everolimus arm) or mycophenolic acid (MPA) with standard-exposure CNI (MPA arm). The primary end point was treated biopsy-proven acute rejection or eGFR < 50 ml/min per 1.73 m² at post-transplant month 12 using a 10% noninferiority margin.

Results In the intent-to-treat population (everolimus *n*=1022, MPA *n*=1015), the primary end point incidence was 48.2% (493) with everolimus and 45.1% (457) with MPA (difference 3.2%; 95% confidence interval, -1.3% to 7.6%). Similar between-treatment differences in incidence were observed in the subgroups of patients who received tacrolimus or cyclosporine. Treated biopsy-proven acute rejection, graft loss, or death at post-transplant month 12 occurred in 14.9% and 12.5% of patients treated with everolimus and MPA, respectively (difference 2.3%; 95% confidence interval, -1.7% to 6.4%). *De novo* donor-specific antibody incidence at 12 months and antibody-mediated rejection rate did not differ between arms. Cytomegalovirus (3.6% versus 13.3%) and BK virus infections (4.3% versus 8.0%) were less frequent in the everolimus arm than in the MPA arm. Overall, 23.0% and 11.9% of patients treated with everolimus and MPA, respectively, discontinued the study drug because of adverse events.

Conclusions In kidney transplant recipients at mild-to-moderate immunologic risk, everolimus was non-inferior to MPA for a binary composite end point assessing immunosuppressive efficacy and preservation of graft function.

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Despite improvements in early kidney graft survival, long-term results remain unsatisfactory with one in four patients returning to dialysis within 5 years post-transplant.¹ Several studies have implicated chronic antibody-mediated rejection as the most common cause of late graft failure, particularly in patients who are nonadherent, including the ongoing Long-Term Deterioration of Kidney Allograft

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Function (DeKAF) study.^{2,3} However, in a recently published study by Stegall *et al.* on the basis of a large cohort of patients who underwent prospective kidney biopsies over 10 years, the most frequently noted pathologies were arterial hyalinosis and glomerulosclerosis⁴—injuries associated with exposure to calcineurin inhibitors (CNIs) as well as with antibody-mediated rejection.⁵ Transplant glomerulopathy was present in only 12% of patients. Thus, even in the absence of rejection, the graft is vulnerable to chronic insults which can lead to deteriorating kidney function. The most notable of such insults is the dose-dependent nephrotoxicity associated with long-term CNI therapy.⁶ Kidney function during the first year post-transplant is a well established predictor of long-term graft survival^{7–10} and the importance of preserving good graft function, in addition to avoiding rejection, is now recognized.^{11,12}

The use of mammalian target of rapamycin (mTOR) inhibitors with low tacrolimus levels may mitigate the chronic injury reported by Stegall *et al.*⁴ Additional potential long-term benefits of mTOR inhibitors described in experimental models and reported in clinical trials include suppression of cytomegalovirus (CMV) replication,¹³ protection from intimal hyperplasia¹⁴ and atherosclerosis,^{15,16} and antiangiogenic^{17,18} and antiproliferative¹⁹ actions that may induce an antioncogenic action although clinical evidence for an effect on post-transplant malignancy remains mixed.^{20–23} The initial enthusiasm for mTOR inhibitors after sirolimus was approved for *de novo* use in kidney transplantation, however, has waned and use of mTOR inhibitors has become less common. In part, this was because of complications associated with early high-exposure mTOR inhibitor regimens given *de novo*^{24,25} or in maintenance patients with deteriorating graft function,²⁶ and reduced efficacy of CNI-free regimens on the basis of mTOR inhibition.^{27,28}

The protocol of the Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen (TRANSFORM) trial incorporates lessons learned after almost two decades of mTOR inhibition in kidney transplantation. TRANSFORM was designed to test the hypothesis that everolimus with reduced-exposure CNI is noninferior to current standard of care, mycophenolic acid (MPA) and standard-exposure CNI, both with induction therapy and maintenance corticosteroids, in preventing acute rejection and preserving graft function. Results at 1 year, including the novel primary composite end point of treated biopsy-proven acute rejection (tBPAR) or suboptimal kidney function (eGFR < 50 ml/min per 1.73m²), are reported here.

METHODS

Study Design and Oversight

TRANSFORM was a randomized, open-label, two-arm study. Patients were recruited at 186 centers in 42 countries worldwide.

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

Significance Statement

The use of mammalian target of rapamycin inhibitors has been recognized as a potential immunosuppressive strategy to reduce exposure to calcineurin inhibitors (CNI), but there has been no consensus on the optimum protocol for safety and efficacy. This large international trial of >2000 *de novo* transplant patients used a novel binary end point that assessed both immunosuppressive efficacy and graft function. The study found that at 1 year, an everolimus-based regimen with reduced CNI exposure was noninferior to the current standard of mycophenolic acid with standard CNI exposure. Cytomegalovirus and BK virus infections were significantly reduced under everolimus. These results provide evidence that a *de novo* regimen of everolimus with low-exposure tacrolimus maintains immunosuppression and preserves graft function, while reducing viral infections, offering an alternative to conventional CNI-mycophenolate protocols.

Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patients

De novo kidney transplant patients aged ≥ 18 years who had received a graft from a living or deceased heart-beating donor were eligible. Patients who had undergone a previous kidney transplant could be enrolled if the first graft had not been lost due to immunologic reasons. Exclusion criteria included multiorgan transplantation, HLA-identical living-related donation, cold ischemia time >30 hours, high risk of rejection (on the basis of local practice for assessment of anti-donor reactivity, *e.g.*, high panel reactive antibodies or presence of preexisting donor-specific antibodies [DSA]), recipient or donor positive for hepatitis C virus, and body mass index >35 kg/m². Full inclusion and exclusion criteria are shown in Supplemental Table 1. Recruitment was planned to ensure that the population included $\geq 50\%$ living-donor recipients and $\leq 20\%$ patients receiving cyclosporine (CsA).

Randomization and Study Treatment

Patients were randomized in a 1:1 ratio within 24 hours after transplantation. A randomization sequence, stratified within treatment groups by donor type (living, deceased standard criteria, or deceased expanded criteria) and by the type of CNI (CsA or tacrolimus), was generated by a computer program and implemented by telephone-based interactive response technology.

All patients received induction therapy with basiliximab (20 mg \times 2 doses, on days 0 and 4) or rabbit anti-thymocyte globulin (rATG, 1.5 mg/kg per day, total dose ≤ 6 mg/kg).

In the everolimus group, the starting dose of everolimus was 1.5 mg twice a day or 0.75 mg twice a day, respectively, in patients receiving concomitant tacrolimus or CsA. The dose was subsequently adjusted to target an everolimus trough concentration (C_0) of 3–8 ng/ml throughout the study. The tacrolimus dose was adjusted to target C_0 concentrations of 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, 50–100, and 25–50 ng/ml, respectively.

In the MPA group, MPA was given as enteric-coated mycophenolate sodium (1.44 g/d) or mycophenolate mofetil (2.0 g/d), which could be reduced after week 2 to enteric-coated mycophenolate sodium 1.08 g/d or mycophenolate mofetil 1.5 g/d 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, 150–200, and 100–200 ng/ml, respectively.

Blood concentrations of everolimus, tacrolimus, and CsA were determined locally.

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

CMV prophylaxis (given for at least 3 months post-transplant) was recommended for all donor positive/recipient negative (D+/R–) patients. *Pneumocystis jirovecii* (*Pneumocystis carinii*) pneumonia prophylaxis was given for at least 6 months to all patients.

Study End Points

The primary end point was a binary composite of tBPAR or eGFR < 50 ml/min per 1.73 m² (Modification of Diet in Renal Disease [MDRD]²⁹) at 12 months post-transplant. eGFR was calculated at each study visit (baseline; day 1; weeks 1, 2, 4; months 2, 4, 6, 9, and 12) on the basis of assays at a central laboratory. tBPAR was defined as receipt of antirejection treatment and local histologic diagnosis of acute rejection according to Banff 2009 criteria.³⁰ A threshold of 50 ml/min per 1.73 m² was selected because it represents a moderate level of renal dysfunction³¹ and is associated with a significantly increased risk for subsequent death-censored graft loss.^{9,10} The key secondary end point was a composite efficacy failure end point of tBPAR, graft loss, or death at 12 months post-transplant.¹² A full list of other secondary and exploratory end points is shown in Supplemental Table 2.

Statistical Analyses

On the basis of results from the A2309 study,³² it was assumed that the event rate in each arm would be 50%. A sample size of 1020 patients in each treatment arm (2040 in total) with a one-sided α error of 0.025 was estimated to provide at least 95% power to demonstrate noninferiority for the primary end point at month 12 in the overall study population, and in the tacrolimus-treated subpopulation with an assumption that approximately 80% of patients would be randomized to tacrolimus. A noninferiority margin of 10% was used in this study because it was used previously (A2309³²) and accepted by health authorities.

Event rates were compared between groups using a hierarchical testing strategy: (1) noninferiority of everolimus versus MPA for the primary end point using a 10% noninferiority

margin; (2) noninferiority of everolimus versus MPA for the key secondary end point with a 10% noninferiority margin; and (3) superiority of everolimus versus MPA on the basis of the primary end point. The fixed hypothesis testing procedure would not inflate overall type I error rate. Therefore, each hypothesis was tested at the one-sided 0.025 significance level and no multiplicity adjustment was needed. Supportive analyses for the primary end point included an analysis on the basis of the per protocol population.

Details of other statistical methods, and the populations for analysis, are shown in Supplemental Table 3. Analyses were performed using SAS statistical software, Version 9.4 (or higher) for Unix.

RESULTS

Patients

Between December of 2013 and January of 2016, 2226 patients were screened, of whom 2037 were transplanted and randomized and comprised the intent-to-treat population (Figure 1). The month 12 study visit was completed by 90.5% (925 of 1022) and 90.8% (922 of 1015) of patients in the everolimus and MPA groups, respectively, with 72.1% (737 of 1022) and 81.0% (822 of 1015) of patients still on study medication. The per protocol population (*i.e.*, patients with no major protocol violations) included 1925 patients (everolimus 946, MPA 979).

Recipient and donor characteristics were comparable between treatment groups (Table 1).

Study Medication

The majority of patients (83.1%, 1692 of 2037) received basiliximab induction (Table 1).

By weeks 1 and 2, respectively, 70.4% and 83.9% of patients randomized to everolimus had an everolimus trough concentration ≥ 3 ng/ml. Mean everolimus trough concentration was within target range in the everolimus group throughout the 12-month study phase (tacrolimus-treated patients 4.4–5.9 ng/ml; CsA-treated patients 5.0–6.1 ng/ml). At study entry, 913 patients (90.0%) and 100 patients (9.9%) in the everolimus group were receiving tacrolimus and CsA, respectively, compared with 916 patients (90.6%) and 95 (9.4%) in the MPA group. Mean tacrolimus trough concentration remained near or above the upper limit of the target range in the everolimus arm with 25%–44% of patients above the upper limit at any study visit, but it was within range in the MPA arm (Supplemental Figure 1). The mean CsA trough concentration was near or above the target range in both groups from month 2 onwards, with 17%–61% and 7%–32% of patients in the everolimus and MPA groups above the upper limit at any study visit, respectively (Supplemental Figure 1).

The mean (SD) MPA dose in the MPA group at month 12 was 1110 (398) mg/d. The median (range) corticosteroid dose at month 12 was 0.09 (0.0–16.0) mg/kg per day and 0.09

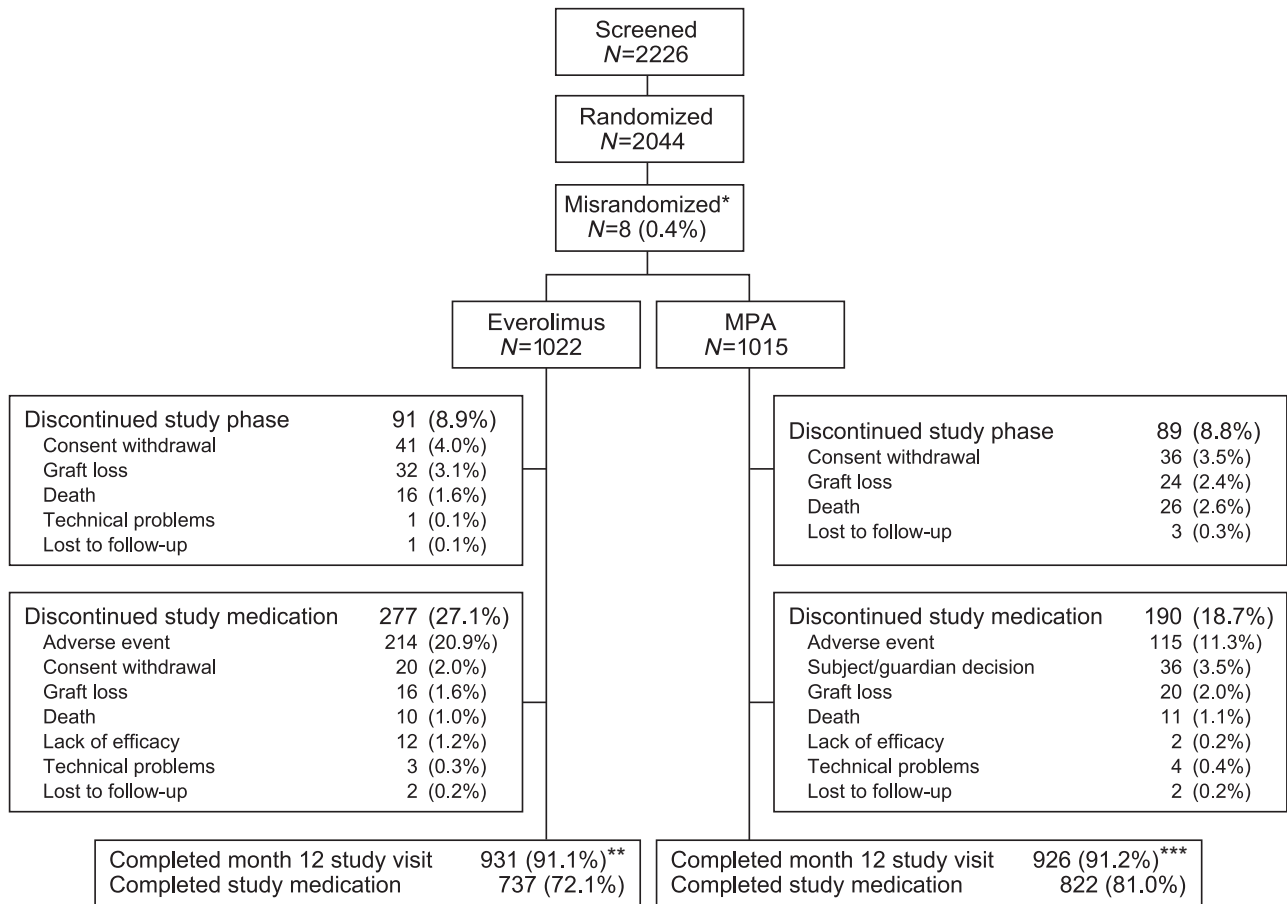


Figure 1. In total, 2037 patient were transplanted and randomized and comprised the intention-to-treat (ITT) population. The month 12 study visit was completed by more than 90% of patients in both treatment groups. *One misrandomized patient received study medication and was included in the ITT population. **Six of these patients completed their month 12 visit after day 450. ***Four of these patients completed their month 12 visit after day 450.

(0.0–25.4) mg/kg per day in the everolimus and MPA groups, respectively. Doses of MPA and steroids during the study are presented in Supplemental Table 4.

Efficacy

Binary Composite End Point

The everolimus group was noninferior to the MPA group for the primary end point (tBPAR or eGFR < 50 ml/min per 1.73 m² [MDRD4] at month 12 post-transplant). The incidence was 48.2% (493 of 1022) with everolimus versus 45.1% (457 of 1015) with MPA, a difference of 3.2% with 95% confidence interval (95% CI) –1.3% to 7.6%, where the upper limit of the 95% CI was below the noninferiority margin of 10%. Similar results were shown for the per protocol population, in which the incidence of the primary end point was 47.3% (448 of 946) with everolimus versus 44.0% (431 of 979) with MPA (difference 3.3%; 95% CI, –1.2% to 7.8%).

When analyzed in the subgroup of patients treated with tacrolimus, the primary end point occurred in 47.8% and 44.7% of patients in the everolimus and MPA groups, respec-

tively (Table 2). For the smaller subgroup treated with CsA, the incidence was 51.5% and 47.3%, respectively (Table 2). Rates of the primary end point were somewhat higher in patients treated with basiliximab induction (everolimus 49.2%, MPA 46.9%) than those given rATG induction (everolimus 42.7%, MPA 36.2%) (Table 2).

Other Efficacy End Points

The Kaplan–Meier estimate of the key secondary end point of tBPAR, graft loss, or death at month 12 post-transplant, was 14.9% versus 12.5% in the everolimus versus MPA groups, respectively; difference 2.3%, with 95% CI, –1.7% to 6.4%, supporting the noninferiority of everolimus to MPA (Figure 2). The Kaplan–Meier estimate of tBPAR was 11.5% in everolimus patients (100 of 1022) and 8.8% in MPA patients (83 of 1015) (difference 2.7%; 95% CI, –1.2% to 6.5%).

Within the subgroup of patients given tacrolimus, the incidence of tBPAR was 10.0% and 8.3% in the everolimus and MPA groups, respectively; for the CsA-treated subgroup the incidences were 26.1% and 14.0% (Table 2). Low rates of

Table 1. Characteristics at baseline (intention-to-treat population)

Characteristic	Everolimus (n=1022)	MPA (n=1015)
Mean age (SD), yr	49.3 (14.1)	49.3 (14.5)
Male, n (%)	710 (69.5)	707 (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)
Mean BMI (SD), kg/m ²	25.6 (4.2)	25.6 (4.3) ^a
ESRD 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)
Diabetes at baseline, n (%)	279 (27.3)	269 (26.5)
Hemodialysis, n (%)	674 (65.9)	679 (66.9)
Mean PRA (SD) (most recent evaluation)	2.7 (10.7)	2.7 (9.5)
HLA mismatching, n (%)		
Loci A		
0	178 (17.4)	172 (16.9)
1	550 (53.8)	545 (53.7)
2	286 (28.0)	295 (29.1)
Missing	8 (0.8)	3 (0.3)
Loci B		
0	114 (11.2)	124 (12.2)
1	518 (50.7)	494 (48.7)
2	382 (37.4)	394 (38.8)
Missing	8 (0.8)	3 (0.3)
Loci DR		
0	240 (23.5)	193 (19.0)
1	495 (48.4)	557 (54.9)
2	279 (27.3)	262 (25.8)
Missing	8 (0.8)	3 (0.3)
Mean cold ischemia time (SD), h	8.4 (7.8)	8.4 (7.8)
Delayed graft function, n (%)	79 (7.7)	72 (7.1)
Induction, n (%)		
Basiliximab	849 (83.1)	843 (83.1)
rATG	171 (16.7)	171 (16.8)
Missing	2 (0.2)	1 (0.1)
Donor		
Mean age (SD), yr	48.4 (15.18)	48.2 (15.48)
Male, n (%)	493 (48.2)	508 (50.0)
Race, n (%)		
White	620 (60.7)	599 (59.0)
Asian	120 (11.7)	134 (13.2)
Other	282 (27.6)	279 (27.5)
Donor category, n (%)		
Living related	302 (29.5)	315 (31.0)
Living unrelated	209 (20.5)	192 (18.9)
Deceased heart-beating	506 (49.5)	505 (49.8)
Deceased non-heart-beating	5 (0.5)	3 (0.3)
Donor criteria, n (%) ^a		
Standard criteria deceased donor	354 (70.0)	345 (68.3)
Expanded criteria deceased donor	152 (30.0)	160 (31.7)

tBPAR were observed in the subgroup given rATG induction (everolimus 6.8%, MPA 4.2%) (Table 2).

Graft loss occurred in 32 patients in the everolimus group and in 25 patients in the MPA group (Kaplan–Meier estimates 3.2% versus 2.6%). The most common cause of graft loss in both groups was infarction/thrombosis with no identified technical cause (ten everolimus, nine MPA). Rejection led to graft loss in four everolimus patients (one hyperacute, one acute T cell-mediated, two acute antibody-mediated) and five MPA patients (one hyperacute, three acute T cell, one chronic antibody-mediated). There were 16 and 27 deaths, respectively (Kaplan–Meier estimates 1.6% and 2.8%, $P=0.08$), most frequently due to cardiac arrest (everolimus $n=2$, MPA $n=3$), myocardial infarction ($n=2$ in each group), and sepsis ($n=3$ and $n=2$). No other cause of death occurred in more than one patient.

All other efficacy end points at month 12 occurred at a similar rate between groups (Figure 3).

Renal Function

Using multiple imputation for missing values, mean (SD) eGFR at 12 months was 53.0 (0.7) and 54.4 (0.7) ml/min per 1.73 m² in the everolimus and MPA groups, respectively. Renal function was stable from week 4 through to month 12: mean (SD) change was 0.0 (0.5) ml/min per 1.73 m² versus 2.3 (0.5) ml/min per 1.73 m² for the everolimus and MPA groups, respectively (Supplemental Figure 2). The predicted slope (SEM) of change in eGFR (ml/min per 1.73 m²) over time, calculated using a mixed effect model, was 0.0007 (0.0015) in the everolimus group versus 0.0074 (0.0015) in the MPA group. This was significantly different between groups ($P=0.001$) but is unlikely to be clinically relevant.

DSA and Antibody-Mediated Rejection

The presence of DSA was assessed using local assays and according to locally determined thresholds in a subset of subjects at participating centers. In total, 476 and 477 patients participated in this substudy from the everolimus and MPA groups,

Table 1. Continued

Characteristic	Everolimus (n=1022)	MPA (n=1015)
CMV serology, n/N (%)		
D+/R-	153 of 978 (15.6)	139 of 976 (14.2)
D+/R+	514 of 978 (52.6)	522 of 976 (53.5)
D-/R+	141 of 978 (14.4)	147 of 976 (15.1)
D-/R-	170 of 978 (17.4)	168 of 976 (17.2)

BMI, body mass index; IgA, immunoglobulin A; PRA, panel reactive antibodies; HLA, human leukocyte antigen; D, donor; R, recipient.

^aDenominator is the number of deceased heart-beating donors.

respectively. Rates of DSA at baseline and month 12 were similar between groups, as were the incidence and type of *de novo* DSA at month 12 (Table 3).

Acute antibody-mediated rejection occurred at a similar rate in both groups (7.8% versus 5.8%; difference 2.0%; 95% CI, -1.5% to 5.5%) (Figure 3).

Safety

Adverse Events

The incidences of adverse events and serious adverse events were similar between treatment groups (Table 4). Rates of new-onset diabetes mellitus, major cardiovascular events, and malignancies were comparable. Hyperlipidemia, interstitial lung disease, peripheral edema, proteinuria, stomatitis/mouth ulceration, thrombocytopenia, thrombotic/thromboembolic events, wound healing events/complications, hypokalemia, and proteinuria were more frequent in the everolimus group than the MPA group (Table 4). Diarrhea, nausea, vomiting, tremor, leukopenia, and insomnia were more frequent in the MPA group (Table 4).

Discontinuation of study drug due to adverse events was more frequent in the everolimus group (23.0% versus 11.9% in the MPA group; risk ratio [RR], 1.94; 95% CI, 1.58 to 2.37). Graft rejection, proteinuria, and impaired healing were more frequent causes of discontinuation in the everolimus group, whereas polyomavirus-associated nephropathy and BK virus infection were more frequent causes in the MPA group (Supplemental Table 5). Conversely, adverse events leading to dose adjustment

or temporary interruption were less frequent with everolimus versus MPA (25.4% versus 48.2%; RR, 0.53; 95% CI, 0.47 to 0.60).

Infections

Infections occurred less frequently in the everolimus group (52.0% versus 59.8% in the MPA group; RR, 0.87; 95% CI, 0.80 to 0.94), a difference accounted for by fewer viral infections (17.2% versus 29.2%; RR, 0.59; 95% CI, 0.50 to 0.69) (Table 4). CMV infection was less frequent in the everolimus group (3.6% versus 13.3% in the MPA group; RR, 0.27; 95% CI, 0.19 to 0.38), with clinical signs of CMV infection, CMV syndrome, and histologic signs of CMV in 3.9% (40 of 1014), 1.5% (15 of 1014), and 0.1% (1 of 1014) of everolimus patients, respectively, and in 11.2% (113 of 1012), 4.9% (50 of 1012), and 0.6% (6 of 1012) of patients in the MPA group.

BK virus infection (viruria or viremia) occurred in 4.3% and 8.0% of everolimus and MPA patients, respectively (RR, 0.54; 95% CI, 0.38 to 0.77), with histologic evidence for organ involvement in 1.2% (12 of 1014) and 2.1% (21 of 1012).

Table 2. Efficacy end points at month 12 (intention-to-treat population)

End Point	Everolimus n/N (%)	MPA n/N (%)	Difference (Everolimus – CNI)	95% CI
tBPAR or eGFR<50 ml/min per 1.73 m ²				
All patients	493 of 1022 (48.2)	457 of 1015 (45.1)	3.2	-1.3 to 7.6
Tacrolimus-treated patients	437 of 914 (47.8)	410 of 917 (44.7)	3.1	-1.6 to 7.7
CsA-treated patients	51 of 100 (51.1)	45 of 95 (47.3)	3.9	-10.3 to 18.0
Basiliximab-treated patients	418 of 849 (49.2)	395 of 843 (46.9)	2.3	-2.5 to 7.2
rATG-treated patients	73 of 171 (42.7)	62 of 171 (36.2)	6.5	-4.2 to 17.1
tBPAR, graft loss, or death ^a				
All patients	137 of 1022 (14.9)	122 of 1015 (12.5)	2.3	-1.7 to 6.4
Tacrolimus-treated patients	120 of 914 (13.3)	104 of 917 (11.9)	1.4	-1.7 to 4.6
CsA-treated patients	16 of 100 (29.2)	15 of 95 (15.9)	13.3	-13.7 to 40.3
Basiliximab-treated patients	115 of 849 (15.4)	107 of 843 (13.3)	2.1	-2.7 to 6.8
rATG-treated patients	21 of 171 (12.6)	15 of 171 (9.0)	3.6	-3.0 to 10.2
tBPAR ^a				
All patients	100 of 1022 (11.5)	83 of 1015 (8.8)	2.7	-1.2 to 6.5
Tacrolimus-treated patients	88 of 914 (10.0)	70 of 917 (8.3)	1.7	-1.1 to 4.5
CsA-treated patients	12 of 100 (26.1)	13 of 95 (14.0)	12.1	-15.8 to 40.0
Basiliximab-treated patients	89 of 849 (12.5)	76 of 843 (9.8)	2.7	-1.9 to 7.3
rATG-treated patients	11 of 171 (6.8)	7 of 171 (4.2)	2.6	-2.3 to 7.6

^aKaplan–Meier estimate of incidence rate was used.

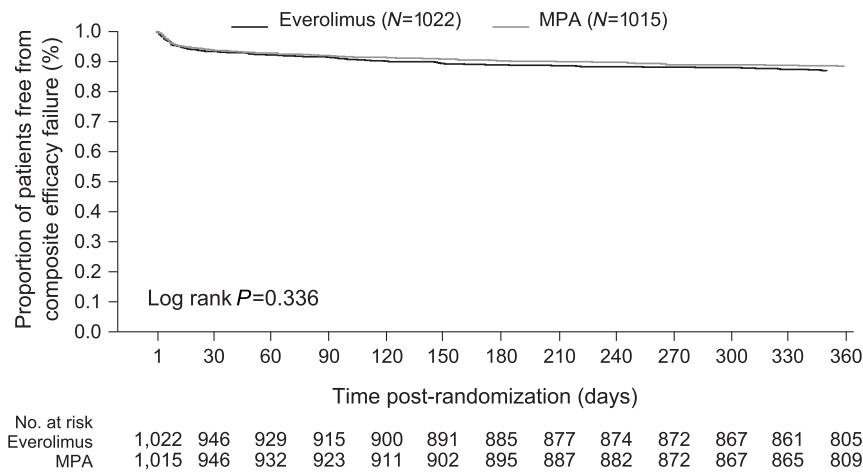


Figure 2. The Kaplan-Meier estimate of the key secondary endpoint of tBPAR, graft loss or death at month 12 post-transplant was 14.9% versus 12.5% in the everolimus versus MPA groups, respectively; difference 2.3% with 95% CI [-1.7% to 6.4%], supporting the non-inferiority of everolimus to MPA (ITT population). ITT, intention-to-treat.

Infections reported as serious adverse events occurred in 26.8% (272 of 1014) and 30.1% (305 of 1012) of patients in the everolimus and MPA groups, respectively (RR, 0.89; 95% CI, 0.78 to 1.02).

Laboratory Results

The mean urine protein-to-creatinine ratio was higher in the everolimus group up to week 4, but similar from month 2

onwards (Supplemental Figure 3). Proteinuria in the nephrotic range (≥ 3000 mg/g) was present in 3.1% (30 of 953) of patients and 1.4% (13 of 940) of patients in the everolimus and MPA groups, respectively, at month 12 or end of treatment visit (Supplemental Table 6).

Total cholesterol, LDL-cholesterol, and triglycerides were higher in the everolimus group versus the MPA group; the LDL/HDL-cholesterol level was comparable (Supplemental Table 5). Lipid-lowering medication was used by 59.3% (601 of 1014) and 45.9% (465 of 1012) of patients, respectively. One or more clinically abnormal liver function values, among patients with normal liver function tests at baseline, were detected in 19.5% of everolimus patients (84 of 435) and 22.0% (117 of 484) of MPA patients.

DISCUSSION

The primary end point of this study, uniquely, combined the efficacy end point of graft rejection (tBPAR) with an assessment of graft function (eGFR < 50 ml/min per 1.73 m²). This novel approach was considered more indicative of potential long-term graft and patient survival than a conventional end point comprising only efficacy parameters such as

	Everolimus n (KM%)		MPA n (KM%)	Difference [95% CI]	P value
eGFR <50 ml/min per 1.73 m² or tBPAR^{††}	493 (48.2)		457 (45.1)	3.2 [-1.3 to 7.6]	0.160
tBPAR, graft loss, or death [†]	137 (14.9)		122 (12.5)	2.3 [-1.7 to 6.4]	0.252
eGFR <50 ml/min per 1.73 m ^{2†}	463 (45.4)		428 (42.2)	3.2 [-1.3 to 7.6]	0.161
tBPAR, graft loss, death or loss to follow up	169 (17.8)		157 (15.8)	2.0 [-2.2 to 6.1]	0.355
eGFR <50 ml/min per 1.73 m ² , tBPAR, graft loss or death [†]	497 (48.7)		468 (46.1)	2.6 [-1.8 to 7.0]	0.247
Graft loss or death	48 (4.8)		52 (5.3)	-0.5 [-2.4 to 1.4]	0.612
Graft loss	32 (3.2)		25 (2.6)	0.6 [-0.8 to 2.1]	0.398
Death	16 (1.6)		27 (2.8)	-1.2 [-2.4 to 0.1]	0.081
tBPAR	100 (11.5)		83 (8.8)	2.7 [-1.2 to 6.5]	0.176
BPAR	105 (12.0)		87 (9.2)	2.8 [-1.1 to 6.6]	0.163
tAR	124 (12.5)		110 (11.7)	0.8 [-2.1 to 3.8]	0.578
AR	136 (13.8)		127 (13.4)	0.4 [-2.7 to 3.5]	0.808
AMR	64 (7.8)		57 (5.8)	2.0 [-1.5 to 5.5]	0.257
tBPAR excluding grade IA rejections	67 (8.1)		49 (5.1)	3.0 [-0.5 to 6.5]	0.094

Figure 3. All efficacy endpoints at month 12 occurred at a similar rate in the everolimus and MPA groups (ITT population). Difference was defined as everolimus – MPA. 95% CI and P values test for no difference. The primary end point is shown in bold text. *P=0.001 for non-inferiority; [†]P<0.001 for noninferiority; ^{††}compared using raw incidence rates (other end points are compared using Kaplan–Meier incidence rates). AMR, antibody-mediated rejection; AR, acute rejection; ITT, intention-to-treat; KM, Kaplan-Meier; tAR, treated acute rejection.

Table 3. DSA

Variable	Everolimus (n=476)	MPA (n=477)
DSA at baseline		
Yes	29 of 263 (11.0)	37 of 292 (12.7)
Anti-class I	11 of 263 (4.2)	11 of 292 (3.8)
Anti-class II	9 of 263 (3.4)	12 of 292 (4.1)
Both anti-class I and anti-class II	10 of 263 (3.8)	14 of 292 (4.8)
No	234 of 263 (89.0)	255 of 292 (87.3)
Missing	213	185
DSA at month 12		
Yes	51 of 374 (13.6)	47 of 339 (13.9)
Anti-class I	12 of 374 (3.2)	16 of 339 (4.7)
Anti-class II	24 of 374 (6.4)	24 of 339 (7.1)
Both anti-class I and anti-class II	15 of 374 (4.0)	7 of 339 (2.1)
No	323 of 374 (86.4)	292 of 339 (86.1)
Missing	102	138
<i>de novo</i> DSA at month 12 ^a		
Yes	19 of 187 (10.2)	25 of 184 (13.6)
Anti-class I	5 of 187 (2.7)	8 of 184 (4.3)
Anti-class II	10 of 187 (5.3)	14 of 184 (7.6)
Both anti-class I and anti-class II	4 of 187 (2.1)	3 of 184 (1.6)
No	168 of 187 (89.8)	159 of 184 (86.4)

^aIn patients without DSA at baseline in whom DSA were assessed at month 12.

biopsy-proven acute rejection (BPAR), graft loss, or death, or only eGFR. In this large international population of *de novo* kidney transplant patients, everolimus was noninferior to MPA for this composite primary end point. Similar between-treatment differences in incidences were observed in the subgroups of patients who received either tacrolimus or CsA. Both regimens achieved good and comparable immunosuppressive efficacy with a low rate of tBPAR. The two treatment groups were also associated with similarly well preserved graft function during the first post-transplant year. Rates of CMV and BK virus infection were lower with everolimus.

Combination therapy with tacrolimus and MPA has become the standard of care after kidney transplantation, partly on the basis of findings from the landmark SYMPHONY trial.³³ SYMPHONY showed higher eGFR and a lower incidence of BPAR with MPA+tacrolimus versus MPA+CsA or versus a CNI-free regimen combining MPA and the mTOR inhibitor sirolimus.³³ Since then, an increased rate of acute rejection using sirolimus in a CNI-free regimen from time of transplant has been confirmed elsewhere.³⁴ In contrast, everolimus with reduced CsA from time of transplant does not increase the risk for BPAR.³² In the CsA-treated subgroup of this trial, the Kaplan–Meier estimate of tBPAR, graft loss, or death was high for everolimus-treated patients (29.2%), due to the last occurrence of a tBPAR event, which influenced the Kaplan–Meier estimate. The raw incidence rates of tBPAR, graft loss, or death were similar with everolimus/CsA (16.0%) or MPA/CsA (15.9%). Similar results were observed in the incidence of tBPAR (Table 2). Inclusion of reduced-exposure tacrolimus in the investigational arm of this study ensured

equivalent efficacy, on the basis of tBPAR, to the MPA group. Previously, the US92 study also randomized *de novo* kidney transplant patients to everolimus with reduced tacrolimus or to MPA with standard-exposure tacrolimus, but in that trial the starting dose of everolimus was only 0.75 mg twice a day compared with 1.5 mg twice a day for tacrolimus-treated patients in this trial, giving rise to inadequate early everolimus exposure and a higher rate of tBPAR versus standard therapy.³⁵ At weeks 1 and 2, the proportion of patients with everolimus trough concentration above the minimum target level (3 ng/ml) was only 64.2% and 66.5% in the US92 study compared with 70.4% and 83.9% in this trial. Here, the comparable rates of *de novo* DSA in the two treatment arms also point to equivalent immunosuppressive potency with the everolimus plus reduced CNI regimen versus MPA plus standard CNI regimen. Although between-study comparisons must always be approached cautiously, the 1-year incidence of tBPAR in the subgroup treated with everolimus and tacrolimus (10.0%) in our trial is comparable with the reported rate of BPAR excluding borderline values in the tacrolimus arm of the SYMPHONY study (12.3%).³³

The validity of the DSA data is limited by the fact that DSA were assessed locally, with consequent variations between assays and definitions, and DSA sampling was incomplete with information on DQ antibodies missing. However, the similarity in rates of antibody-mediated rejection between treatment groups is a robust observation.

The finding that there was no increased risk for *de novo* DSA or antibody-mediated rejection in patients randomized to everolimus with reduced CNI contrasts with data suggesting that *de novo* DSA may be more frequent in patients given everolimus in a CNI-free regimen.³⁶

Renal function, assessed by eGFR, was stable in the everolimus group over the course of the study and was virtually identical to the MPA group. Other randomized studies of everolimus with reduced-exposure CNI have also observed comparable renal function versus standard therapy with up to 2 years' follow-up.^{32,35,37} Exposure to tacrolimus or CsA was near or above target range during the study, with up to 44% of tacrolimus-treated patients having a trough concentration above target at any one point, such that the between-group difference in exposure was less than planned. A *post hoc* analysis of results from the large randomized A2309 trial recently showed that higher tacrolimus concentrations are associated with a significantly increased risk for low eGFR and decreased eGFR at month 12 after kidney transplantation in everolimus-treated individuals.³⁸ In that analysis, tacrolimus trough concentrations above 4 ng/ml were associated with inferior renal outcomes, with a further increase in risk above 6 ng/ml. Here, the reduction in CNI exposure in the everolimus/reduced tacrolimus group versus controls in this study (4.1 ng/ml

Table 4. Adverse events (safety population)

Adverse Event	Everolimus (n=1014)	MPA (n=1012)	RR (Everolimus versus MPA) (95% CI)
Any adverse event, n (%)	993 (97.9)	984 (97.2)	1.01 (0.99 to 1.02)
Any serious adverse event, n (%)	557 (54.9)	568 (56.1)	0.98 (0.91 to 1.06)
Any adverse event leading to study drug discontinuation, n (%)	233 (23.0)	120 (11.9)	1.94 (1.58 to 2.37)
Adverse events occurring more frequently in the everolimus group, n (%) ^a			
Hyperlipidemia	340 (33.5)	188 (18.6)	1.86 (1.59 to 2.17)
Interstitial lung disease	11 (1.1)	3 (0.3)	3.66 (1.02 to 13.08)
Peripheral edema	373 (36.8)	262 (25.9)	1.42 (1.25 to 1.62)
Stomatitis and mouth ulceration	78 (7.7)	21 (2.1)	3.71 (2.31 to 5.95)
Thrombocytopenia	82 (8.1)	40 (4.0)	2.05 (1.42 to 2.96)
Thrombotic and thromboembolic events	119 (11.7)	84 (8.3)	1.41 (1.08 to 1.84)
Wound healing events/complications	201 (19.8)	164 (16.2)	1.22 (1.01 to 1.47)
Hypokalemia	144 (14.2)	82 (8.1)	1.75 (1.36 to 2.27)
Proteinuria	128 (12.6)	57 (5.6)	2.24 (1.66 to 30.2)
Adverse events occurring more frequently in the MPA group, n (%) ^a			
Diarrhea	219 (21.6)	316 (31.2)	0.69 (0.60 to 0.80)
Nausea	177 (17.5)	214 (21.1)	0.83 (0.69 to 0.99)
Vomiting	110 (10.8)	141 (13.9)	0.78 (0.62 to 0.98)
Tremor	98 (9.7)	137 (13.5)	0.71 (0.56 to 0.91)
Leukopenia	94 (9.3)	192 (19.0)	0.49 (0.39 to 0.62)
Insomnia	91 (9.0)	130 (12.8)	0.70 (0.54 to 0.90)
Infections, n (%)			
Any infection	527 (52.0)	605 (59.8)	0.87 (0.80 to 0.94)
Any serious infection	272 (26.8)	305 (30.1)	0.89 (0.78 to 1.02)
Any viral infection	174 (17.2)	296 (29.2)	0.59 (0.50 to 0.69)
CMV infection	36 (3.6)	135 (13.3)	0.27 (0.19 to 0.38)
BK virus infection	44 (4.3)	81 (8.0)	0.54 (0.38 to 0.77)
Any bacterial infection	353 (34.8)	381 (37.6)	0.92 (0.82 to 1.04)
Any fungal infection	69 (6.8)	46 (4.5)	1.50 (1.04 to 2.15)

^aEvents captured by standard adverse event reporting, or prespecified events of interest, which occurred in $\geq 10\%$ of patients in either group and for which the 95% CI of the RR did not include 1.0 (excluding prespecified events of interest).

versus 6.9 ng/ml for tacrolimus trough concentration at month 12) was not found to confer a renal benefit, consistent with experience from the **A** twelve-month, multicenter, open-label, randomized Study of the Safety, tolerability and Efficacy of Certican™ with IL-2 receptor antagonist, corticosteroids and two different exposure levels of Tacrolimus in *de novo* renal transplant recipients (ASSET) study.³⁹ Unexpectedly, there was a small increase in eGFR in the control arm during the course of the study, which has not been observed with MPA plus conventional CNI regimens in recent studies.^{16,33,40,41} Mean eGFR at month 12 was 53–54 ml/min per 1.73 m² in both treatment arms, similar to that seen in the MPA+tacrolimus group of the SYMPHONY study (54 ml/min per 1.73 m² by MDRD formula). Given that 30% of the deceased-donor recipients received a graft from expanded criteria donor recipients in this trial compared with only 18% in the MPA+tacrolimus arm of SYMPHONY, a sustained eGFR > 50 ml/min per 1.73 m² can be regarded as satisfactory.

In terms of safety, everolimus targeting a trough concentration of 3–8 ng/ml avoided the increased rates of lymphocele seen previously,³³ although wound healing complications were slightly more frequent overall. Other adverse events often associated with mTOR inhibitor therapy, including proteinuria and

dyslipidemia, rarely led to everolimus discontinuation. The risk of proteinuria is higher under mTOR inhibition in patients receiving kidney transplants.⁴² This effect is a dose-dependent effect when everolimus is used *de novo*⁴³ and may be related to podocyte injury⁴⁴ and inhibition of vascular endothelial growth factor signaling.⁴⁵ Discontinuation of study drug due to adverse events was twice as frequent in the everolimus group versus controls, possibly partly due to the high number of participating centers ($n=189$), many of which were unfamiliar with use of everolimus-based protocols. Conversely, dose changes or temporary interruptions were twice as frequent in the MPA group, raising the possibility that in this open-label study some case investigators may have been more reluctant to discontinue the conventional regimen than to switch patients from the everolimus protocol to standard therapy.

CMV infection occurred in fewer than a third as many patients under everolimus compared with MPA. Although steroid doses were higher in the MPA group, and MPA dosing was relatively high, this observation is consistent with previous experience in kidney transplantation.¹³ A minimum of 6 months' CMV prophylaxis with valganciclovir, instead of the minimum of 3 months recommended here, has been shown to be advantageous⁴⁶ and may be particularly relevant for patients receiving non-mTOR inhibitor regimens. BK virus

infections were also less frequent with everolimus, a point of potential interest. There has been mixed evidence in published studies for an effect of mTOR inhibition on the risk of BK infection after kidney transplantation.⁴⁷ Some initial studies have suggested that BK viral load may be reduced after initiation of everolimus therapy after onset of infection.^{48,49}

TRANSFORM is one of the first trials to apply a novel combined end point which incorporates both acute rejection and graft function at 1 year, an approach recognized as helpful for improving long-term survival.^{11,12} The study benefited from the largest population of *de novo* kidney transplant patients included in a randomized trial to date. It involved 186 centers, with widely differing degrees of experience in using everolimus-based immunosuppression, which may have contributed to the variable adherence to CNI exposure targets in patients treated with everolimus. Local determinations of tacrolimus concentrations, with known discordance of results between assay types,⁵⁰ may also have contributed. CsA concentrations were relatively high and above target range in a relatively high proportion of patients. The resulting narrowing of the planned difference in exposure between treatment groups is a limitation of the trial.

Additionally, graft biopsy specimens were read locally at each center, and although graded according to Banff 2009 criteria³⁰ this inevitably introduces center-specific variation. It should also be noted that the study specifically excluded patients at high risk for rejection and included only approximately 4% of black patients, so the findings should not be extrapolated to individuals at high immunologic risk. Furthermore, follow-up to month 12 post-transplant does not encompass the long-term effects of the treatment regimens on renal function or parameters such as development of DSA or antibody-mediated rejection.

In conclusion, in this large population of *de novo* kidney transplant patients at mild-to-moderate immunologic risk, a regimen of everolimus with reduced tacrolimus from the time of transplant was noninferior to MPA plus conventional CNI for a binary end point assessing both immunosuppressive efficacy and preservation of graft function. Renal function remained stable in both groups during the first year post-transplant despite a high proportion of expanded criteria donor recipients, and rates of tBPAR were low in patients given tacrolimus with either everolimus or MPA. A significant reduction in the incidence of clinically important viral infections was observed with everolimus. Patients are now being followed to 2 years post-transplant.

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J.P., H.T., S.C., F.O., C.S., R.O., Y.W., C.L., F.C., M.H., T.R.S., and F.V. comprised the scientific steering committee and designed the

study with input from the sponsor, Novartis Pharma AG. All of the scientific steering committee members, S.P.B., O.W., S.M., and Y.Q. recruited patients and collected data. W.-L.L. undertook the statistical analyses. A.M. and P.B. provided medical input. All authors had access to the study data, assessed the analyses, critically reviewed the manuscript, and approved the final version for publication.

DISCLOSURES

J.P. has received consulting honoraria from Novartis and travel grants from Novartis and Chiesi, and his institution has received research grants from Novartis, Astellas, Chiesi, and Amgen. S.P.B. has received consulting honoraria and travel grants from Novartis, Astellas, and Chiesi. His institution has received research grants from Astellas and Novartis. O.W. has received research funds and/or honoraria from Alexion, Astellas, Bristol-Myers Squibb, Chiesi, Janssen-Cilag, MSD, Novartis, Pfizer, Roche, and Shire. H.T. has received consulting honoraria and travel grants from Novartis, Pfizer, BMS, and Roche, and his institution has received research grants from Novartis, Pfizer, BMS, Roche, Veloxis, and Teraclone. S.M. has received research grants from Novartis and Astellas. Y.Q. has received speaker's honoraria from Alexion, Mallenckrodt, and Relypsa. S.C. has received research funding, travel support, or consulting honoraria from Novartis, Astellas, and Alexion. F.O. has received consulting honoraria and travel grants from Novartis, Astellas, Pfizer, BMS, and Roche, and his institution has received research grants from Novartis and Astellas. C.S.'s institution has received research grants from Novartis and Astellas. R.O. has received speaker's honoraria from Novartis. Y.W. has received speaker's honoraria from Novartis, Astellas, Chugai, and Roche, and travel grants from Roche. C.L. has received speaker's honoraria from Alexion and Novartis, and travel grants from Alexion, Novartis, and Amgen. F.C. has received consulting honoraria and travel grants from Novartis, Astellas, Pfizer, and Bristol Myers Squibb. M.H. has received consulting honoraria from Novartis. T.R.S. has received consulting honoraria from Novartis, and grants from Astellas, Bristol Myers Squibb, and Novartis. W.-L.L., A.M., and P.B. are employees of Novartis. F.V. has received research grants from Novartis, Astellas, Genentech, Alexion, and Bristol Myers.

APPENDIX 1

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