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ORIGINAL ARTICLE

Everolimus-facilitated calcineurin inhibitor reduction in Asian de novo kidney transplant recipients: 2-year results from the subgroup analysis of the TRANSFORM study

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Abstract

Objective: We analyzed the efficacy and safety of an everolimus with reduced-exposure calcineurin inhibitor (EVR+rCNI) versus mycophenolic acid with standard-exposure CNI (MPA+sCNI) regimen in Asian patients from the TRANSFORM study.

Methods: In this 24-month, open-label study, de novo kidney transplant recipients (KTxRs) were randomized (1:1) to receive EVR+rCNI or MPA+sCNI, along with induction therapy and corticosteroids.

Results: Of the 2037 patients randomized in the TRANSFORM study, 293 were Asian (EVR+rCNI, $N = 136$; MPA+sCNI, $N = 157$). At month 24, EVR+rCNI was noninferior to MPA+sCNI for the binary endpoint of estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2 or treated biopsy-proven acute rejection (27.0% vs. 29.2%, $P = .011$ for a noninferiority margin of 10%). Graft loss and death were

reported for one patient each in both arms. Mean eGFR was higher in EVR+rCNI versus MPA+sCNI (72.2 vs. 66.3 ml/min/1.73 m^2, $P = .0414$) even after adjusting for donor type and donor age (64.3 vs. 59.3 ml/min/1.73 m^2, $P = .0582$). Overall incidence of adverse events was comparable. BK virus (4.4% vs. 12.1%) and cytomegalovirus (4.4% vs. 13.4%) infections were significantly lower in the EVR+rCNI arm.

Conclusion: This subgroup analysis in Asian de novo KTxRs demonstrated that the EVR+rCNI versus MPA+sCNI regimen provides comparable antirejection efficacy, better renal function, and reduced viral infections (NCT01950819).

KEYWORDS
everolimus, kidney transplant, reduced calcineurin inhibitor, reduced cyclosporine, reduced tacrolimus

1 | INTRODUCTION

The incidence of end-stage renal disease is increasing among Asians across the world.[1,2] According to the National Health and Nutrition Examination Survey (NHANES) 2011–2014 data from 5907 participants in the United States, the prevalence of end-stage renal disease is 1.5 times higher in Asians than in Caucasians.[3] Kidney transplantation is the treatment of choice for patients with end-stage renal disease. In Asia, there is an extreme shortage of deceased donor organs for transplantation with ~95% of the organ source being living donation.[4] Given the gap in organ availability and the ever-increasing need, the focus of the immunosuppressive regimens following successful kidney transplantation is to prevent graft rejection without impacting allograft function. Calcineurin inhibitors (CNIs; tacrolimus [TAC] and cyclosporine [CsA]) remain the standard-of-care immunosuppressive therapy following kidney transplantation.[5] However, the long-term use of CNIs is associated with chronic nephrotoxicity, infections, and de novo malignancies, which are common causes of mortality and morbidity following kidney transplantation.[6–11] Further, optimizing CNI-associated nephrotoxicity is critical, as kidney function during the first year posttransplant is a well-established predictor of long-term graft survival.[12–14] Therefore, immunosuppressive strategies are needed that facilitate de novo CNI reduction with a goal of improving long-term patient and graft outcomes while maintaining the current low acute rejection (AR) rates.

Everolimus (EVR), a mammalian target of rapamycin inhibitor, acts through mechanisms complementary to CNIs, thereby allowing a reduction of CNI exposure.[15] Additionally, EVR is associated with beneficial effects on cardiovascular stability, decreased incidence of neoplasms, and reduced infections.[16–22] In the pivotal A2309 study, a phase 3b, multicenter, 24-month, open-label study of 833 de novo deceased or living donor kidney transplant recipients (KTxRs), the use of EVR was associated with a greater than 60% reduction in CsA exposure with comparable efficacy and renal function to a mycophenolic acid plus standard-exposure CsA (MPA+sCsA) regimen over the 2-year period.[23,24] Similarly, in the US92 study, a 12-month, randomized, multicenter trial involving 613 de novo KTxRs from either deceased or unrelated living donors—EVR in combination with reduced-exposure TAC had comparable efficacy and safety to a mycophenolate mofetil (MMF) plus standard-exposure TAC regimen.[25] The effect of EVR in combination with reduced-exposure CsA (EVR+rCsA) was evaluated in 122 (120 living donors and 2 deceased donors) Japanese de novo KTxRs (A1202 study). In this study, EVR facilitated a ~52% reduction in CsA exposure at month 12 with noninferior efficacy and numerically better renal function versus an MMF+sCsA regimen up to month 24.[26]

Advancing renal TRANSplant eFficacy and safety Outcomes with an eveRoliMus-based regimen (TRANSFORM; NCT01950819) was a 24-month, randomized, open-label study that evaluated the efficacy and safety of EVR with a reduced-exposure CNI (EVR+rCNI) versus MPA with a standard-exposure CNI (MPA+sCNI) in 2037 deceased or living donor de novo KTxRs.[27–29] The 12- and 24-month results from the TRANSFORM study demonstrated that the de novo EVR+rCNI regimen was noninferior to MPA+sCNI for the binary endpoint assessing both the immunosuppressive efficacy and preservation of graft function.[28,29] Further, the EVR+rCNI regimen was associated with low rates of treated biopsy-proven acute rejection (tBPAR) and de novo donor-specific antibodies (*dn*DSA), a significantly lower incidence of viral infections, and comparable overall safety to the MPA+sCNI regimen. In the TRANSFORM study, ~15% of the total randomized patients were Asian. Given the paucity of literature on the use of the EVR+rCNI regimen in Asian de novo KTxRs from a randomized controlled setting, a pre-specified subgroup analysis from the TRANSFORM study, despite the limited population, was considered to be beneficial in understanding the efficacy and safety profile of the regimen in this cohort. Here, we report the 24-month data from Asian patients who participated in the TRANSFORM study.

2 | METHODS

2.1 | Study design and conduct

TRANSFORM was a 24-month, multicenter, randomized, open-label, two-arm study in de novo KTxRs. The study recruited patients across 186 centers in 42 countries worldwide. Methods for the TRANSFORM study, including inclusion/exclusion criteria, the

immunosuppression regimen, and patient stratification have been described in detail previously.[27–29] Briefly, eligible patients were randomized in a 1:1 ratio within 24 h after transplantation to receive either the EVR+rCNI or MPA+sCNI regimen. Induction therapy with basiliximab or rabbit antithymocyte globulin was mandatory for all patients. In addition, corticosteroids were mandatory for all patients through month 24, administered according to local practice but with a minimum daily dose of 5 mg of prednisone or equivalent.

In the EVR+rCNI arm, the TAC dose was adjusted to target trough 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 contrast, the TAC dose in the MPA+sCNI arm was adjusted to a target trough 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. MPA was given as enteric-coated mycophenolate sodium (1.44 g/d) or MMF (2.0 g/d), which could be reduced after week 2 to enteric-coated mycophenolate sodium 1.08 g/d or MMF 1.5 g/d in patients receiving TAC but not those given CsA.

The study protocol was approved by the independent ethics committee or the institutional review board of each participating center. The study was conducted in accordance with the recommendations of the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

2.2 | Study objectives

The primary objective of the TRANSFORM study was to evaluate the effect of EVR+rCNI versus MPA+sCNI on the binary composite of tBPAR or estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2 (4-Modification of Diet in Renal Disease [MDRD4]) at month 12 posttransplant. The key secondary objective was the composite efficacy failure rate of tBPAR, graft loss, or death. In addition, a donor-specific antibody (DSA) analysis was carried out in a subset of patients at participating centers. The efficacy and safety analyses were further explored up to month 24. Both the 12-month primary and the 24-month secondary results have been reported separately.[28,29] The focus of this subgroup analysis was to evaluate the efficacy and safety of the EVR+rCNI regimen in comparison to the MPA+sCNI regimen in Asian patients participating in the TRANSFORM study. Further, a multivariate analysis was conducted to identify the clinical factors affecting the renal function in the EVR+rCNI and MPA+sCNI arms.

2.3 | Statistical analysis

All efficacy analyses are based on the full analysis set, which consisted of all randomized and transplanted patients. For the incidence of eGFR < 50 ml/min/1.73 m^2 or to build the binary endpoint, a value for missing eGFR as a continuous variable was computed using a multiple imputation approach and then dichotomized to derive the endpoint.[29] The event rate for the composite efficacy failure of tBPAR, graft loss, or death was estimated using a Kaplan–Meier product-limit formula and the standard error was derived based on Greenwood's formula. A non-inferiority of EVR+rCNI versus MPA+sCNI for the binary endpoints was evaluated using a 10% non-inferiority margin. All efficacy endpoints were compared using a confidence interval (CI) approach. For the renal function analyses, on-treatment population was used without imputation. The on-treatment set consisted of patients with any assessment obtained on and after day 1, but no later than 7 days after the discontinuation of randomized study medication. A univariate analysis was conducted using CNI type, donor age, sex, body mass index, end-stage renal disease, donor type, delayed graft function, AR within 12 months, infections within 12 months, and proteinuria within the first 12 months as potential variables to identify their impact on renal function. A t-test was applied to continuous variables and a chi-square test to categorical variables to detect differences between patients with eGFR < 50 or ≥50 ml/min/1.73 m^2 at month 24. Variables with $P < .10$ in univariate analyses were included in a regression logistic model. Odds ratios and the 95% CIs were computed for factors related with eGFR < 50 ml/min/1.73 m^2 at month 24. The safety analyses are based on the safety set, consisting of all patients who received at least one dose of the study drug. Relative risk ratios (95% CIs) were calculated to compare adverse events (AEs) between the treatment arms. AEs were captured as reported by investigators using electronic case report forms (eCRF), and infections were captured using an additional eCRF. The level of statistical significance was set at $P < .05$ for two-tailed tests. Analyses were performed using SAS statistical software version 9.4 or higher.

3 | RESULTS

3.1 | Patient population

Of the 2037 patients randomized in the TRANSFORM study, 293 were Asian and were included in this analysis (Australia, $n = 13$; Belgium, $n = 1$; Brazil, $n = 1$; Germany, $n = 2$; Spain, $n = 4$; France, $n = 1$; India, $n = 38$; Italy, $n = 1$; Japan, $n = 34$; South Korea, $n = 53$; Malaysia, $n = 5$; Netherlands, $n = 1$; Philippines, $n = 29$; Saudi Arabia, $n = 20$; Singapore, $n = 5$; Sweden, $n = 1$; Thailand, $n = 27$; Taiwan, $n = 23$; United States, $n = 34$). A total of 136 patients were randomized to the EVR+rCNI arm and 157 patients to the MPA+sCNI arm (**Figure 1**). Of these, 91.2% ($n = 124$) and 92.4% ($n = 145$) of patients completed the 24-month study in the EVR+rCNI and MPA+sCNI arms, respectively. Study drug discontinuation was more frequent in the EVR+rCNI arm versus the MPA+sCNI arm (23.5% vs. 17.2%); AEs were the most frequent reason for study drug discontinuation in both study arms (16.2% vs. 11.5%, respectively).

Recipient and donor baseline characteristics were comparable between the treatment arms (**Table 1**). Around 84% of patients received allografts from Asian donors and living donor kidney transplantation was performed for ~85% of patients.

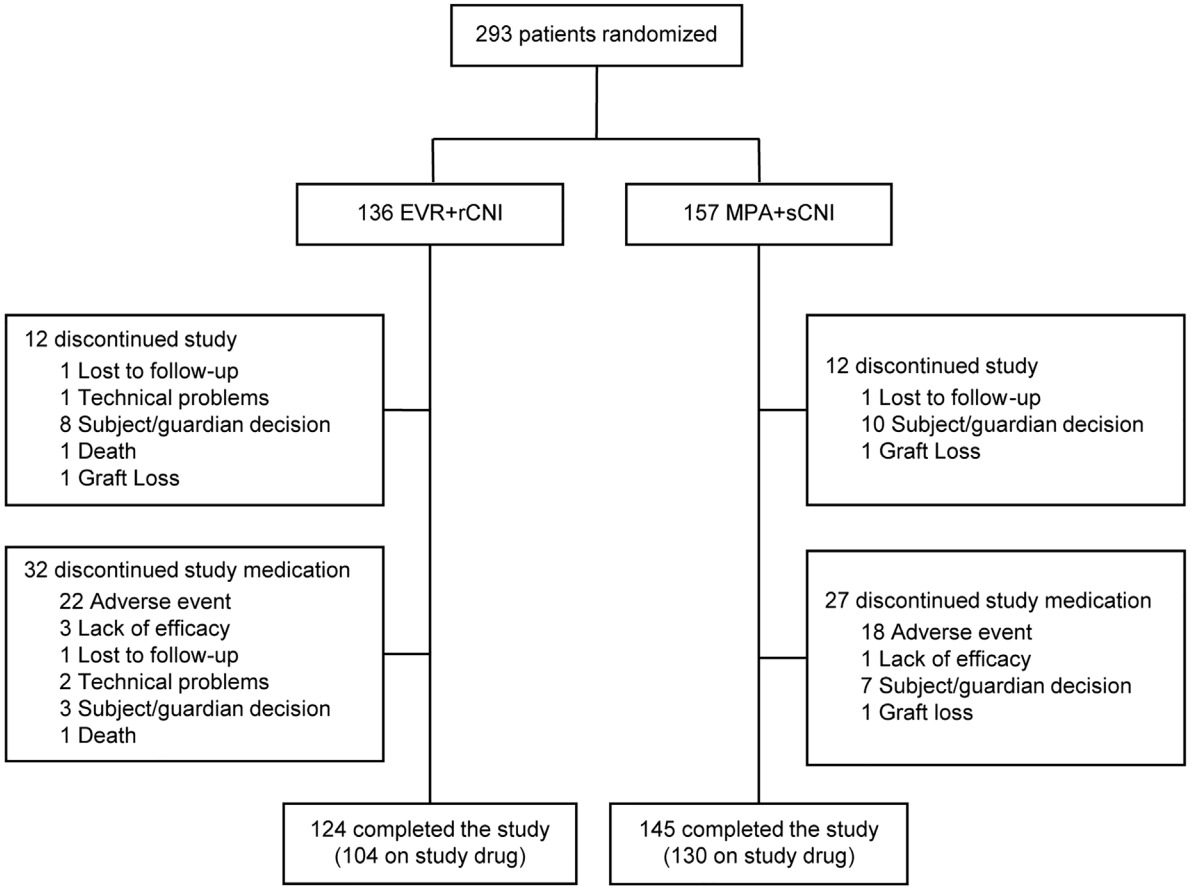


FIGURE 1 Patient disposition.
Abbreviations: EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitors; sCNI, standard-exposure CNI

3.2 | Immunosuppression

The majority of patients in both treatment arms received basiliximab induction (84.6% in the EVR+rCNI arm and 86.6% in the MPA+sCNI arm). The mean EVR trough concentration was within the target range of 3–8 ng/ml throughout the duration of the study (**Figure 2A**). At most time points, more patients in the EVR+rCNI arm were above the target range for TAC (23.8%–41.8%) and CsA (9.5%–68.2%) trough concentrations compared with those in the MPA+sCNI arm (TAC: 4.5%–27.8%; CsA: 4.8%–22.7%) (**Figure 2B** and **2C**).

3.3 | Efficacy

At month 24, the EVR+rCNI arm was noninferior to the MPA+sCNI arm for the binary endpoint of eGFR < 50 ml/min/1.73 m^2 or tBPAR (27.0% vs. 29.2%; difference −2.2; 95% CI: −12.7 to 8.3; $P = .011$ for a noninferiority margin of 10%) (**Table 2**). The incidence of tBPAR was numerically lower in the EVR+rCNI arm versus the MPA+sCNI arm (8.2% vs. 15.7%, $P = .068$), although statistical significance was not met. The incidence of eGFR < 50 ml/min/1.73 m^2 was comparable between the treatment arms (25.4% [EVR+rCNI] vs. 22.2% [MPA+sCNI], $P = .539$). A subanalysis by CNI type showed a comparable incidence of the binary endpoint in patients treated with either TAC or CsA in both of the treatment arms (**Table 2**).

The Kaplan–Meier event rate for composite efficacy failure (tBPAR, graft loss, or death) was noninferior and numerically lower in the EVR+rCNI arm versus the MPA+sCNI arm at month 24 (9.0% vs. 16.9%; difference −7.9, 95% CI: −16.1 to .4; $P < .001$ for a noninferiority margin of 10%). The composite efficacy failure rate was mostly driven by tBPAR for both of the arms. One graft loss and one death were reported in both of the treatment arms, respectively. The Kaplan–Meier incidence rate of composite efficacy failure was comparable in the patients treated with CsA in both of the treatment arms (16.0% vs. 9.1%, $P = .470$) but was significantly lower in patients treated with TAC in the EVR+rCNI arm versus the MPA+sCNI arm (7.4% vs. 18.1%, $P = .019$). All other efficacy endpoints were comparable between the treatment arms (**Table 2**). More than half of the ARs (9/17) in the EVR+rCNI arm and a majority (20/28) of ARs in the MPA+sCNI arm were reported within the first 6 months posttransplant. It is important to note that steroids were used for all of the ARs reported in this subanalysis.

TABLE 1 Demographics and baseline characteristics (full analysis set)

Parameters	EVR+rCNI (*N* = 136)	MPA+sCNI (*N* = 157)
Recipient		
Age (years), mean (SD)	44.3 (13.60)	42.4 (12.24)
Male, *n* (%)	85 (62.5)	114 (72.6)
BMI (kg/m^2), mean (SD)	23.7 (4.59)	23.4 (3.99)
Diabetes at baseline, *n* (%)	42 (30.9)	45 (28.7)
Delayed graft function, *n* (%)	10 (7.4)	6 (3.8)
Induction, *n* (%)		
Basiliximab	115 (84.6)	136 (86.6)
rATG	21 (15.4)	21 (13.4)
End-stage disease leading to transplantation, *n* (%)		
Glomerular disease	24 (17.6)	24 (15.3)
Hypertension/nephrosclerosis	11 (8.1)	25 (15.9)
Diabetes mellitus	24 (17.6)	21 (13.4)
Interstitial nephritis	5 (3.7)	3 (1.9)
IgA nephropathy	20 (14.7)	33 (21.0)
Other[a]	52 (38.2)	51 (32.5)
Current dialysis, *n* (%)		
Hemodialysis	92 (67.6)	105 (66.9)
Peritoneal dialysis	24 (17.6)	28 (17.8)
None	20 (14.7)	24 (15.3)
Number of HLA mismatching, *n* (%)		
Loci A		
0	34 (25.0)	31 (19.7)
1	71 (52.2)	86 (54.8)
2	24 (17.6)	37 (23.6)
Missing	7 (5.1)	3 (1.9)
Loci B		
0	14 (10.3)	21 (13.4)
1	75 (55.1)	77 (49.0)
2	40 (29.4)	56 (35.7)
Missing	7 (5.1)	3 (1.9)
Loci DR		
0	25 (18.4)	28 (17.8)
1	63 (46.3)	84 (53.5)
2	41 (30.1)	42 (26.8)
Missing	7 (5.1)	3 (1.9)
Cold ischemia time (hours), mean (SD)	3.8 (5.80)	4.2 (6.36)
PRA % (most recent evaluation), mean (SD)	5.1 (15.57)	4.0 (12.50)
PRA % (peak evaluation), mean (SD)	7.0 (19.21)	4.4 (12.89)
Donor		
Age (years), mean (SD)	42.8 (14.16)	42.7 (14.34)
Female, *n* (%)	73 (53.7)	78 (49.7)
Race, *n* (%)		
Asian	117 (86.0)	129 (82.2)

(Continues)

TABLE 1 (Continued)

Parameters	EVR+rCNI (*N* = 136)	MPA+sCNI (*N* = 157)
Caucasian	14 (10.3)	19 (12.1)
Others[b]	5 (3.7)	9 (5.7)
Ethnicity, *n* (%)		
East Asian	52 (38.2)	60 (38.2)
Southeast Asian	27 (19.9)	39 (24.8)
South Asian	22 (16.2)	21 (13.4)
West Asian	8 (5.9)	6 (3.8)
Other[c]	27 (19.9)	31 (19.7)
Donor category, *n* (%)		
Living related	78 (57.4)	93 (59.2)
Living unrelated	39 (28.7)	38 (24.2)
Deceased heart beating	18 (13.2)	26 (16.6)
Standard criteria donor[d]	13 (72.2)	23 (88.5)
Expanded criteria donor[d]	5 (27.8)	3 (11.5)
Deceased non-heart beating	1 (.7)	0 (.0)

Abbreviations: BMI, body mass index; EVR, everolimus; HLA, human leukocyte antigen; MPA, mycophenolic acid; PRA, panel reactive antibodies; rATG, rabbit antithymocyte globulin; rCNI, reduced-exposure calcineurin inhibitors; sCNI, standard-exposure CNI; SD, standard deviation.
[a]Includes pyelonephritis, polycystic disease, drug-induced toxicity, vasculitis, obstructive disorder/reflux, renal hypoplasia/dysplasia, unknown, and other.
[b]Includes Native American, black, unknown, other, and missing.
[c]Includes not reported, Hispanic or Latino, mixed ethnicity, unknown, other, and missing.
[d]The percentage is relative to the number of deceased heart beating donors.

3.4 | Renal function

The renal function, as measured by eGFR (MDRD4) remained significantly higher with the EVR+rCNI versus MPA+sCNI regimen throughout the 24-month study, except at months 12 and 18 (**Figure 3**). At month 24, the difference between the mean eGFR with the EVR+rCNI and MPA+sCNI arm reached 5.9 ml/min/1.73 m^2 (72.2 vs. 66.3 ml/min/1.73 m^2, $P = .0414$). After adjusting by donor type and donor age, no significant differences were observed in the overall population (56.5 vs. 57.2 ml/min/1.73 m^2, $P = .4311$) whereas, numerically better eGFR was seen with EVR+rCNI arm versus MPA+sCNI arm in Asian patients (64.3 vs. 59.3 ml/min/1.73 m^2, $P = .0582$).

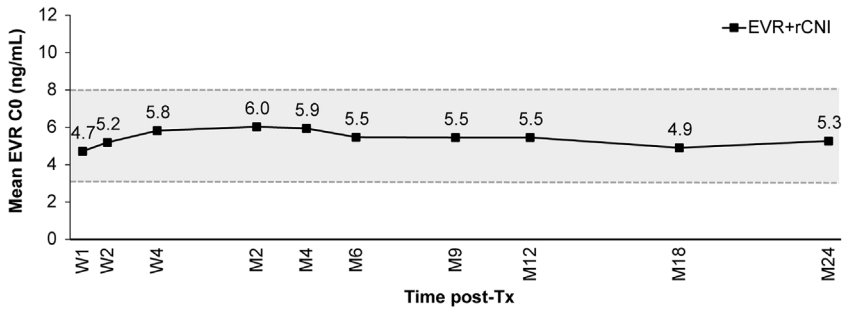
At month 24, the mean (standard deviation) urinary protein/creatinine ratio was 380.8 (1038.0) mg/g in the EVR+rCNI arm versus 203.7 (457.2) mg/g in the MPA+sCNI arm ($P = .0896$). The majority of patients in both treatment arms (83.2% in the EVR+rCNI arm and 92.0% in the MPA+sCNI arm) had a urinary protein/creatinine ratio of 30 to < 500 mg/g ($P = .1144$). Incidence of moderate/nephrotic range proteinuria (≥500 mg/g) was numerically lower in patients receiving concomitant ACEi/ARB therapy compared with those without, in both the treatment groups (11.8% vs. 22.0% in the EVR+rCNI arm, 4.5% vs. 10.1% in MPA+sCNI arm). There were no statistically significant differences in proteinuria between either treatment groups for patients taking or not taking ACEi/ARB therapy ($P = .3071$ and $P = .0847$, respectively).

The univariate regression analysis revealed that donor age ($P < .001$), donor sex ($P = .008$), donor type ($P < .001$), delayed graft function ($P = .033$), AR within the first 12 months ($P < .001$), and proteinuria (<1000 or ≥1000 mg/d) within the first 12 months ($P = .001$) were associated with the eGFR outcomes at month 24 (**Table 3**). The multivariate logistic regression analysis also showed that donor age ($P < .001$), deceased donor type ($P < .001$), AR within the first 12 months posttransplant ($P < .001$), and proteinuria > 1000 mg/d within the first 12 months posttransplant ($P = .002$) were significantly associated with poor eGFR outcomes (**Figure 4**).

3.5 | DSA

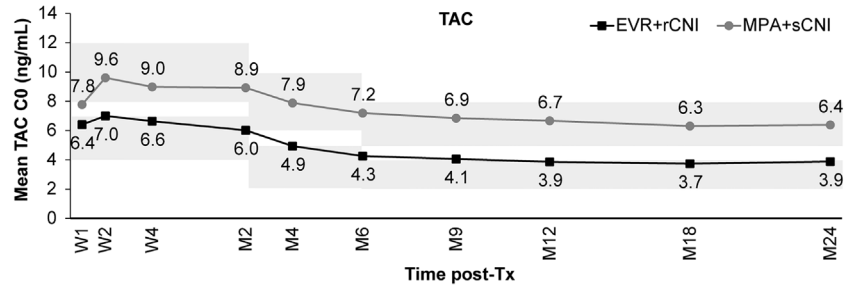
The incidence of DSA at baseline and month 24 and *dn*DSA at month 24 was estimated in the safety set and in the on-treatment population of the safety set. A total of 104 patients of Asian origin (51 in the EVR+rCNI arm and 53 in the MPA+sCNI arm) consented to participate in a DSA substudy (**Table 4**). Among the patients with evaluable data, the incidence of DSA at baseline and month 24 was comparable between the treatment arms. Similarly, the incidence of *dn*DSA at month 24 was comparable between the treatment arms in both the safety set (12.5% vs. 17.9%, $P = .9057$) and in the on-treatment population (.0% vs. 16.7%, $P = .3894$).

(A)



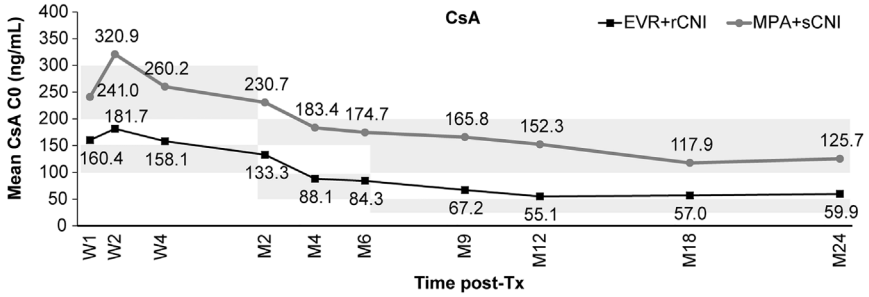
Time post-Tx	W1	W2	W4	M2	M4	M6	M9	M12	M18	M24
Number of patients										
EVR+rCNI	128	132	126	123	124	121	117	116	111	101

(B)



Time post-Tx	W1	W2	W4	M2	M4	M6	M9	M12	M18	M24
Number of patients										
EVR+rCNI	106	106	107	103	103	101	98	96	87	83
MPA+sCNI	131	130	130	131	124	118	117	119	116	107
% patients										
EVR+rCNI										
Above target	31.1	39.6	24.3	24.3	41.7	23.8	41.8	32.3	39.1	32.5
Within target	47.2	45.3	64.5	58.3	56.3	73.3	55.1	63.5	58.6	67.5
Below target	21.7	15.1	11.2	17.5	1.9	3.0	3.1	4.2	2.3	-
MPA+sCNI										
Above target	9.2	17.7	9.2	4.5	8.8	10.2	23.9	19.3	12.0	15.9
Within target	33.6	46.9	50.8	47.7	68.8	56.8	65.0	65.5	63.2	62.6
Below target	57.3	35.4	40.0	47.7	22.4	33.1	11.1	15.1	24.8	21.5

(C)



Time post-Tx	W1	W2	W4	M2	M4	M6	M9	M12	M18	M24
Number of patients										
EVR+rCNI	24	23	23	23	21	21	22	22	21	19
MPA+sCNI	21	22	21	22	23	24	23	23	17	16
% patients										
EVR+rCNI										
Above target	45.8	47.8	30.4	30.4	23.8	9.5	68.2	45.5	52.4	63.2
Within target	20.8	47.8	47.8	21.7	71.4	71.4	27.3	50.0	47.6	36.8
Below target	33.3	4.3	21.7	47.8	4.8	19.0	4.5	4.5	-	-
MPA+sCNI										
Above target	19.0	22.7	4.8	9.1	21.7	12.5	17.4	21.7	-	-
Within target	57.1	45.5	57.1	40.9	52.2	58.3	73.9	65.2	76.5	81.3
Below target	23.8	31.8	38.1	50.0	26.1	29.2	8.7	13.0	23.5	18.8

FIGURE 2 Trough concentrations of (A) everolimus (B) tacrolimus, and (C) cyclosporine (safety analysis set).
Abbreviations: C_0, trough level; CsA, cyclosporine; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitors; sCNI, standard-exposure CNI; TAC, tacrolimus; Tx, transplant; W, week. Shaded area represents target trough levels

TABLE 2 Efficacy outcomes at month 24 (full analysis set)

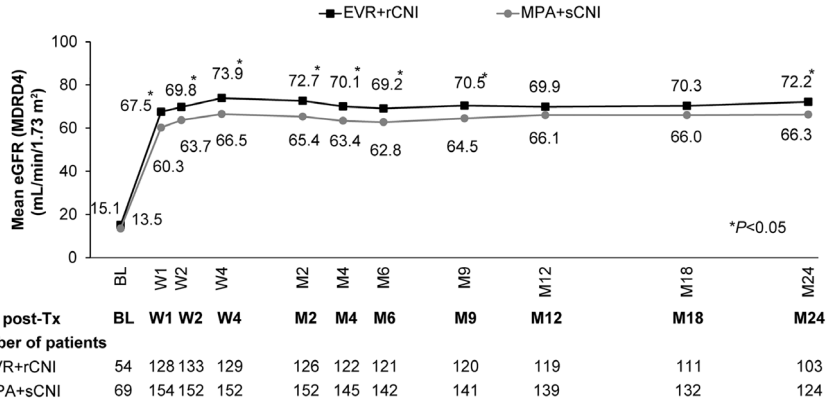
Endpoint, *n*(%)	EVR+rCNI(*N* = 136)	MPA+sCNI(*N* = 157)	Difference(95%CI)	*P*-value*
tBPAR or eGFR < 50 ml/min/1.73 m²[a]	37(27.0)	46(29.2)	−2.2 (−12.7,8.3)	.679
Tacrolimus[b]	30/111(26.7)	40/135(29.6)	−2.8 (−14.3, 8.7)	
Cyclosporine[b]	7/25(28.3)	6/22(27.3)	1.0(−24.7,26.7)	.939
tBPAR, graft loss, or death	12 (9.0)	24 (16.9)	−7.9 (−16.1, .4)	.062
Tacrolimus[b]	8/111 (7.4)	22/135 (18.1)	−10.7 (−19.7, −1.8)	.019
Cyclosporine[b]	4/25 (16.0)	2/22 (9.1)	6.9 (−11.8, 25.6)	.470
tBPAR	11(8.2)	22(15.7)	−7.5 (−15.5,.6)	.068
Graft loss	1 (.8)	1 (.6)	.2 (−1.8, 2.2)	.860
Death	1(.8)	1(.7)	.1(−1.9,2.1)	.928
Graft loss or death	2 (1.6)	2 (1.3)	.3 (−2.5, 3.1)	.850
BPAR	13(9.6)	24(17.0)	−7.3 (−15.7,1.1)	.087
tBPAR excluding grade IA rejections	9 (6.7)	12 (9.2)	−2.5 (−9.6, 4.5)	.484
tBPAR,graft loss,death,or losstofollowup	18(13.3)	33(22.2)	−9.0 (−18.1,.2)	.054
BPAR, graft loss, or death	14 (10.4)	26 (18.2)	−7.7 (−16.3, .9)	.078
Acuterejection	17(12.9)	28(19.6)	−6.7 (−15.9,2.4)	.149
Acuterejectionwithinfirst 6months	9(6.6)	20(12.7)	−6.2 (−12.9,.5)	.071
Acuterejectionafter first 6months	8(5.9)	8(5.1)	−1.1 (−8.5,6.4)	.779
Acuterejectionandsteroidsused	17(12.5)	28(17.8)	−6.7 (−15.9,2.4)	.149
Acuterejectionandsteroidsnot used	0	0	–	–
Acuteantibody-mediatedrejection	11(8.4)	18(13.2)	−4.7 (−12.7,3.2)	.242
Chronic active antibody-mediated rejection	1 (.8)	3 (2.0)	−1.2 (−3.9, 1.5)	.374
Treatedacuterejection	14(10.7)	25(17.6)	−6.9 (−15.6,1.7)	.117
eGFR < 50 ml/min/1.73 m²[a]	35 (25.4)	35 (22.2)	3.1 (−6.9, 13.2)	.539

Abbreviations: BPAR, biopsy-proven acute rejection; CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; MPA, mycophenolic acid; *N*, number of patients in subgroup; rCNI, reduced-exposure calcineurin inhibitors; *n*, number of patients with event; sCNI, standard-exposure calcineurin inhibitors; tBPAR, treated BPAR.

[a] Endpoints compared using raw incidence rates, other endpoints are compared using Kaplan–Meier incidence rates.

[b] Data presented as n/N (%).

*P-value to test for no difference ([EVR+rCNI] − [MPA+sCNI] = 0.



Time post-Tx	BL	W1	W2	W4	M2	M4	M6	M9	M12	M18	M24
Number of patients											
EVR+rCNI	54	128	133	129	126	122	121	120	119	111	103
MPA+sCNI	69	154	152	152	152	145	142	141	139	132	124

FIGURE 3 Estimated GFR during the study (on-treatment analysis).
Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate; EVR, everolimus; M, month; MDRD4, 4-Modification of Diet in Renal Disease; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitors; sCNI, standard-exposure CNI; Tx, transplant; W, week

TABLE 3 Univariate analysis for patients with eGFR below or above 50 ml/min/1.73 m^2 at month 24

Variables		eGFR < 50 ml/min/1.73 m^2 ($N = 65$)	eGFR ≥ 50 ml/min/1.73 m^2 ($N = 228$)	*P*-value*
Treatment	EVR+rCNI, *n* (%)	32 (49.2)	104 (45.6)	.606
	MPA+sCNI, *n* (%)	33 (50.8)	124 (54.4)	
CNI type	Cyclosporine, *n* (%)	10 (15.4)	37 (16.2)	.870
	Tacrolimus, *n* (%)	55 (84.6)	191 (83.8)	
Age, mean (SD)		45.9 (13.70)	42.5 (12.59)	.061
Donor age, mean (SD)		52.2 (13.36)	40 (13.30)	<.001
Sex	Female, *n* (%)	16 (24.6)	78 (34.2)	.144
	Male, *n* (%)	49 (75.4)	150 (65.8)	
Donor sex	Female, *n* (%)	43 (66.2)	108 (47.4)	.008
	Male, *n* (%)	22 (33.8)	119 (52.2)	
BMI	<30, *n* (%)	59 (90.8)	203 (89.0)	.688
	≥30, *n* (%)	6 (9.2)	25 (11.0)	
End-stage renal disease	Glomerular disease, *n* (%)	7 (10.8)	41 (18.0)	.332
	Diabetes mellitus, *n* (%)	12 (18.5)	33 (14.5)	
	All other diseases, *n* (%)	46 (70.8)	154 (67.5)	
Donor type	Living donor, *n* (%)	48 (73.8)	200 (87.7)	<.001
	Standard criteria deceased donor, *n* (%)	10 (15.4)	26 (11.4)	
	Expanded criteria deceased donor, *n* (%)	7 (10.8)	1 (.4)	
Delayed graft function	Yes, *n* (%)	7 (10.8)	9 (3.9)	.033
	No, *n* (%)	58 (89.2)	219 (96.1)	
AR within first 12 M	Yes, *n* (%)	21 (32.3)	24 (10.5)	<.001
	No, *n* (%)	44 (67.7)	204 (89.5)	
Infection within first 12 M	Yes, *n* (%)	20 (30.8)	65 (28.5)	.723
	No, *n* (%)	45 (69.2)	163 (71.5)	
Proteinuria within first 12 M (mg/d)[a]	<1000, *n* (%)	54 (83.1)	220 (96.5)	.001
	≥1000, *n* (%)	9 (13.8)	8 (3.5)	

Abbreviations: AR, acute rejection; BMI, body mass index; CI, confidence interval; d, day; eGFR, estimated glomerular filtration rate; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitors; sCNI, standard-exposure CNI; SD, standard deviation.
[a]For eGFR < 50 ml/min/1.73 m^2, proteinuria data was available for 63 patients.
**P*-value for a t-test or chi-square test for continuous or categorical variables, respectively.

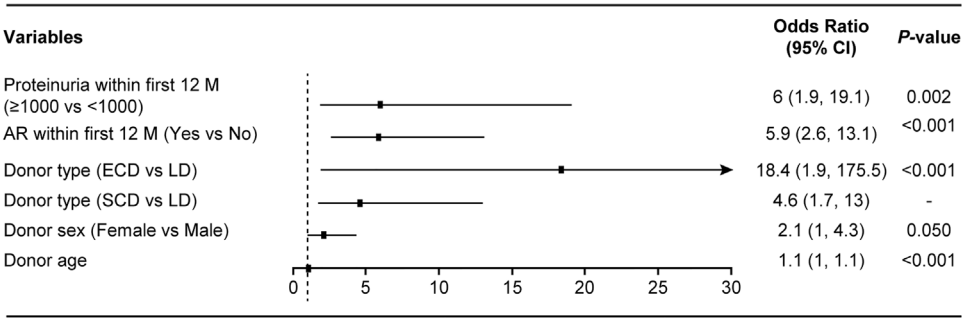


FIGURE 4 Multivariate analysis for patients with eGFR below or above 50 ml/min/1.73 m^2 at month 24.
Abbreviations: AR, acute rejection; ECD, expanded criterial donor; eGFR, estimated glomerular filtration rate; LD, living donor; M, month; SCD, standard criteria donor

TABLE 4 Incidence of DSA up to month 24

	Safety analysis set			On-treatment analysis		
	EVR+rCNI	MPA+sCNI	*P*-value[a]	EVR+rCNI	MPA+sCNI	*P*-value[a]
n (%)	*N* = 51	*N* = 53		*N* = 51	*N* = 53	
DSA at baseline	M = 42	M = 38		M = 7	M = 14	
Overall	8 (19.1)	9 (23.7)	.912	0 (.0)	5 (35.7)	.193
Anti-class I	3 (7.1)	3 (7.9)		0 (.0)	2 (14.3)	
Anti-class II	1 (2.4)	2 (5.3)		0 (.0)	0 (.0)	
Anti-class I + anti-class II	4 (9.5)	4 (10.5)		0 (.0)	3 (21.4)	
DSA at month 24	M = 49	M = 50		M = 41	M = 45	
Overall	13 (26.5)	16 (32.0)	.624	10 (24.4)	14 (31.1)	.433
Anti-class I	5 (10.2)	5 (10.0)		4 (9.8)	4 (8.9)	
Anti-class II	3 (6.1)	7 (14.0)		2 (4.9)	7 (15.6)	
Anti-class I + anti-class II	5 (10.2)	4 (8.0)		4 (9.8)	3 (6.7)	
De novo DSA at month 24	M = 32	M = 28		M = 4	M = 6	
Overall	4 (12.5)	5 (17.9)	.906	0 (.0)	1 (16.7)	.389
Anti-class I	2 (6.3)	2 (7.1)		0 (.0)	0 (.0)	
Anti-class II	1 (3.1)	2 (7.1)		0 (.0)	0 (.0)	
Anti-class I + anti-class II	1 (3.1)	1 (3.6)		0 (.0)	1 (16.7)	

Abbreviations: DSA, donor-specific antibodies; EVR, everolimus; M, no. of evaluable patients; MPA, mycophenolic acid; *N*, no. of patients with signed informed consent; *n*, number of patients with response; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
[a]Chi-square or Fisher test.

3.6 | Safety

At month 24, the EVR+rCNI and MPA+sCNI arms had a comparable incidence of AEs (97.8% vs. 98.1%), serious AEs (50.7% vs. 50.3%), and AEs leading to study drug discontinuation (15.4% vs. 12.7%) (**Table 5**). One patient died in the EVR+rCNI arm due to cardio respiratory arrest, and one patient in the MPA+sCNI arm died due to fungal sepsis.

Incidences of AEs such as mouth ulceration (14.7% vs. 4.5%) and stomatitis (5.9% vs. .6%) were significantly higher in the EVR+rCNI arm, while BK virus infection (5.1% vs. 15.3%), hypomagnesemia (5.1% vs. 12.7%), leukopenia (.7% vs. 14.6%), cytomegalovirus (CMV) infection (2.2% vs. 9.6%), and tremor (1.5% vs. 9.6%) were significantly higher in the MPA+sCNI arm. Among AEs of interest, the incidences of diabetes mellitus (DM) (14.0% vs. 14.6%), hyperlipidemia (17.6% vs. 12.7%), and peripheral edema (12.5% vs. 12.1%) were comparable between the treatment arms. Overall, posttransplant DM was reported in 24 (25.5%) patients in the EVR+rCNI arm and 22 (19.6%) in the MPA+sCNI arm; 12 patients in each arm were receiving concomitant DM medication (including insulin, metformin, glimepiride, and gliclazide). Benign, malignant, and unspecified (including cysts and polyps) neoplasms were reported in 1.5% of patients

TABLE 5 Safety outcomes at month 24 (safety analysis set)

Preferred term, *n* (%)	EVR+rCNI (*N* = 136)	MPA+sCNI (*N* = 157)	Risk ratio (95% CI)
Any AE/infection	133 (97.8)	154 (98.1)	1.00 (.96, 1.03)
At least one serious AE/infections	69 (50.7)	79 (50.3)	1.01 (.80, 1.27)
AE/infection leading to study drug discontinuation	21 (15.4)	20 (12.7)	1.21 (.69, 2.14)
AEs ≥ 10% in any treatment group[a]			
Anemia	14 (10.3)	21 (13.4)	.77 (.41, 1.45)
BK virus infection	7 (5.1)	24 (15.3)	.34 (.15, .76)
Increased blood creatinine	20 (14.7)	24 (15.3)	.96 (.56, 1.66)
Constipation	26 (19.1)	28 (17.8)	1.07 (.66, 1.74)
Cough	16 (11.8)	12 (7.6)	1.54 (.75, 3.14)
Diabetes mellitus	19 (14.0)	23 (14.6)	.95 (.54, 1.67)
Diarrhea	21 (15.4)	33 (21.0)	.73 (.45, 1.21)
Headache	14 (10.3)	9 (5.7)	1.80 (.80, 4.02)
Hyperglycemia	15 (11.0)	21 (13.4)	.82 (.44, 1.54)
Hyperkalemia	8 (5.9)	17 (10.8)	.54 (.24, 1.22)
Hyperlipidemia	24 (17.6)	20 (12.7)	1.39 (.80, 2.39)
Hypertension	26 (19.1)	22 (14.0)	1.36 (.81, 2.29)
Hypocalcemia	16 (11.8)	13 (8.3)	1.42 (.71, 2.85)
Hypomagnesemia	7 (5.1)	20 (12.7)	.40 (.18, .93)
Hypophosphatemia	15 (11.0)	21 (13.4)	.82 (.44, 1.54)
Insomnia	14 (10.3)	15 (9.6)	1.08 (.54, 2.15)
Leukopenia	1 (.7)	23 (14.6)	.05 (.01, .37)
Mouth ulceration	20 (14.7)	7 (4.5)	3.30 (1.44, 7.56)
Nasopharyngitis	17 (12.5)	22 (14.0)	.89 (.49, 1.61)
Nausea	9 (6.6)	21 (13.4)	.49 (.23, 1.04)
Edema peripheral	17 (12.5)	19 (12.1)	1.03 (.56, 1.91)
Pyrexia	21 (15.4)	23 (14.6)	1.05 (.61, 1.82)
Upper respiratory tract infection	17 (12.5)	25 (15.9)	.79 (.44, 1.39)
Urinary tract infection	22 (16.2)	24 (15.3)	1.06 (.62, 1.80)
Death	1 (.7)	1 (.6)	1.15 (.07, 18.28)
Cardio-respiratory arrest	1 (.7)	0 (.0)	–
Fungal sepsis	0 (.0)	1 (.6)	–
Any infection[b,c]	52 (38.2)	88 (56.1)	.68 (.53, .88)
Bacterial	25 (18.4)	29 (18.5)	1.00 (.61, 1.61)
E. Coli	10 (7.4)	12 (7.6)	.96 (.43, 2.16)
Viral	23 (16.9)	62 (39.5)	.43 (.28, .65)
BK Virus	6 (4.4)	19 (12.1)	.36 (.15, .89)
Cytomegalovirus	6 (4.4)	21 (13.4)	.33 (.14, .79)
Unknown	4 (2.9)	13 (8.3)	.36 (.12, 1.06)
Unknown	17 (12.5)	22 (14.0)	.89 (.49, 1.61)

Abbreviations: AE, adverse events; CI, confidence interval; eCRF, electronic case report form; EVR, everolimus; rCNI, reduced-exposure calcineurin inhibitors; MPA, mycophenolic acid; sCNI, standard-exposure calcineurin inhibitors.

[a]Reported by investigator in the AE eCRF.

[b]Infections ≥ 5% in any treatment group are shown.

[c]Reported in the infections eCRF.

in the EVR+rCNI arm and in 3.8% of patients in the MPA+sCNI arm.

The overall incidence of any infection (38.2% vs. 56.1%), and viral infections (16.9% vs. 39.5%) in particular, was significantly lower in the EVR+rCNI arm than in the MPA+sCNI arm. Further, the incidence of BK virus (4.4% vs. 12.1%) and CMV (4.4% vs. 13.4%) infection was significantly lower in the EVR+rCNI arm versus the MPA+sCNI arm (**Table 5**).

4 | DISCUSSION

The 24-month results from this subgroup analysis of the TRANSFORM study demonstrate the noninferiority of the EVR+rCNI to MPA+sCNI regimen for the binary endpoint of eGFR < 50 ml/min/1.73 m^2 or tBPAR in Asian de novo KTxRs. In the Asian cohort, the EVR+rCNI regimen provided additional benefits in terms of significantly better renal function with comparable efficacy and safety.

In terms of baseline characteristics, cold ischemia time was lower in the Asian subset compared with the overall population (4.0 vs. 8.4 h, respectively).[28] This may be reflective of a large number of living donor kidney transplantation in the Asian cohort.[30] The living donor kidney transplant was performed in 84.6% of patients in the Asian subset compared to 50.0% of patients in the overall study.[29] Further, the Asian subset had younger recipients and donors compared to the overall study population. The mean recipient age in the Asian subset was 43.3 years compared to 48.8 years in the overall population.[29] Similarly, the mean age of the donor was 42.7 years in the Asian subset versus 48.3 years in the overall population.[28,29]

In line with the overall results, the EVR+rCNI regimen was found to be noninferior to the MPA+sCNI regimen for the binary endpoint of eGFR < 50 ml/min/1.73 m^2 or tBPAR (27.0% vs. 29.2%) at month 24.[28,29] Interestingly, the incidence of the binary endpoint in the Asian subset was lower for both treatment arms compared to the overall population (47.9% in the EVR+rCNI arm vs. 43.7% in the MPA+sCNI arm).[29] The incidence of composite efficacy failure (tBPAR, graft loss, or death), and tBPAR in particular, was lower with the EVR+rCNI regimen compared with MPA+sCNI, although the difference was not statistically significant. Interestingly, the efficacy of the EVR+rCNI regimen was more pronounced in the Asian cohort compared to the overall results (9.0% vs. 18.0% for composite efficacy failure and 8.2% vs. 12.8% for tBPAR, respectively).[29] Further, graft loss and death was reported for one patient each in both arms. The high graft and patient survival seen in this cohort is in line with the A1202 study, which evaluated the efficacy and safety of the EVR+rCsA regimen in comparison to the MMF+sCsA regimen in Japanese de novo KTxRs.[25,31]

The BPAR rate of the EVR+rCNI group was 9.6% versus 17.0% in the MPA+sCNI group; this is in contrast to the results in the overall TRANSFORM study (11.5% in the EVR+rCNI group vs. 9.6% in the MPA+sCNI group).[29] This could be because of the younger patients and donors, a higher proportion of living donors, lower cold ischemia time, fewer patients with previous renal transplantations, and a lower percentage of panel reactive antibodies in Asian patients as opposed to the overall population. We tried to evaluate whether this increased incidence of rejections in the MPA+sCNI arm was associated with post-transplant CMV infections. Of note, only one patient in the EVR group had a viral infection 2 months after transplantation and experienced an AR episode at 4 months after transplantation whereas nine patients in the MPA+sCNI arm experienced an AR after a CMV infection.

In the overall results, the on-treatment eGFR at month 24 was comparable between the EVR+rCNI and MPA+sCNI regimens (58.1 vs. 58.7 ml/min/1.73 m^2; $P = .5701$).[29] In the Asian cohort, the eGFR at month 24 was significantly higher with the EVR+rCNI regimen (72.2 vs. 66.3 ml/min/1.73 m^2; $P = .0414$). The univariate analysis showed that younger donor age was associated with significantly better renal function in both arms; in the MPA+sCNI arm, the use of TAC versus CsA and a living donor versus a deceased donor were associated with significantly better renal function than in the EVR+rCNI arm. The multivariate analysis showed that increasing donor age, deceased donor type, AR within the first 12 months posttransplant, and proteinuria > 1000 mg/d within the first 12 months posttransplant were significantly associated with poor eGFR outcomes. It is important to note that eGFR was comparatively higher in the Asian cohort in both arms versus the overall population, a finding that merits further prospective studies with longer follow-up data.

Information on the development of DSA with EVR therapy is limited to conversion studies in the transplant setting. However, data from these studies evaluating conversion from CNI to EVR therapy are conflicting.[32–36] Ten-year results from a single-center analysis of the A1202 study by Narumi et al. reported DSA data from 24 patients who underwent living donor kidney transplantation and received EVR+rCsA ($n = 13$) or MMF+sCsA ($n = 11$) within 24 h of transplantation. The accumulative class II DSA development at 10 years was 15.4% in patients receiving EVR+rCsA and 18.3% in patients receiving MMF+sCsA. There was no significant difference for the anti-human leukocyte antigen antibody and DSA-free survival between the two groups.[37] Interestingly, a prospective, randomized controlled clinical trial has rarely evaluated the development of DSA with de novo use of an EVR-based CNI-reduction regimen in KTxRs. In our study, the incidence of DSA and *dnDSA* was comparable between the EVR+rCNI and MPA+sCNI arms based on the available data at month 24. In addition, the incidences of acute and chronic antibody-mediated rejections were overall low and comparable between the treatment groups. Given the limited number of patients with evaluable DSA data at month 24, these results preclude any firm conclusions, and further data in a larger patient cohort with a longer follow-up duration would be needed to validate these findings.

Infections are the second largest cause of death with a functioning graft in KTxRs.[11] Among infections, opportunistic viral infections such as CMV and BK virus are the most common causes of morbidity and mortality in the kidney transplant setting. In a pooled analysis of three randomized clinical trials in de novo KTxRs, the EVR+rCsA versus MPA+sCsA regimen was associated with a significantly lower rate of CMV infection/disease, even in patients who received CMV prophylaxis.[21] In the A2309 trial, EVR+rCsA was associated with a significantly lower incidence of CMV infection and of BK virus infection

compared with MPA+sCsA at month 24.[24] In our study, the incidence of CMV and BK virus infection was significantly lower in the EVR+rCNI arm than in the MPA+sCNI arm. These results are in line with those seen in the earlier studies.[21,24]

A similar pattern toward higher discontinuation due to AEs with the EVR + rCNI regimen was observed in the overall study at month 24.[29] This pattern indicates a general tendency toward discontinuing EVR or switching to standard CNI more readily than adjusting EVR dose for the management of associated AEs. Overall, the safety of the EVR regimen in Asian patients was in line with the known safety profile, and no new or unexpected safety signals were identified.[38]

Besides the open-label design, the main limitation of this subanalysis of the TRANSFORM study was the suboptimal adherence to the target CNI levels in the EVR+rCNI arm and lack of long-term follow-up. Another limitation of the study was the patients were recruited from different geographies around the world with different genetic profiles and phenotypes. There could be a possibility of patients qualifying as multi-racial. It is also important to note that this subanalysis was not adequately powered to confirm the posttransplant outcomes. Nevertheless, this analysis provides supportive evidence of the efficacy and safety of the EVR+rCNI regimen in Asian de novo KTxRs.

In conclusion, the 24-month results from the subgroup analysis of the TRANSFORM study demonstrate that the EVR+rCNI versus MPA+sCNI regimen in Asian de novo KTxRs provides comparable antirejection efficacy and high and comparable patient and graft survival, with no new or unexpected safety concerns identified. Given the clinical benefits in terms of significantly better renal function, low *dn*DSA rates, and significantly reduced viral infections seen in this cohort, the EVR+rCNI regimen may represent a valid alternative treatment option to the standard-of-care regimen of MPA+sCNI in Asian de novo KTxRs.

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CONFLICT OF INTEREST

Yoshihiko Watarai has received consulting honoraria and travel grants from Novartis, Astellas, and Chugai Pharma. Romina Danguilan has received speaker's honoraria from Novartis, Astellas, MSD, Sanofi, Macropharma, and Pharmalink. Concesa Casasola, Shen-Shin Chang, Prajej Ruangkanchanasetr, Terence Kee, Hin Seng Wong, Takashi Kenmochi, Angel Joaquin Amante, Kuo-Hsiung Shu, Atiporn Ingsathit, Duck Jong Han, and Myoung Soo Kim have no conflict of interest. Peter Bernhardt and Maria Pilar Hernandez-Gutierrez are employees of Novartis.

AUTHOR CONTRIBUTIONS

Yoshihiko Watarai, Romina Danguilan, Concesa Casasola, Shen-Shin Chang, Prajej Ruangkanchanasetr, Terence Kee, Hin Seng Wong, Takashi Kenmochi, Angel Joaquin Amante, Kuo-Hsiung Shu, Atiporn Ingsathit, Duck Jong Han, and Myoung Soo Kim were study investigators and were responsible for the study design/conduct, data interpretation, drafting/revising, and approval of the final manuscript. Peter Bernhardt and Maria Pilar Hernandez-Gutierrez were responsible for the study design and protocol writing, and were involved in data acquisition and analysis, and drafting/revising and approval of the final manuscript.

DATA AVAILABILITY STATEMENT

Anonymized patient-level data from clinical trials may be shared by Novartis in a consortium called ClinicalStudyDataRequest.com (CSDR) in accordance with Novartis' policy for sharing clinical trial data (https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Novartis.aspx).

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