Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from TRANSFORM study

Berger, Stefan P; Sommerer, Claudia; Witzke, Oliver; Tedesco, Helio; Chadban, Steve; Mulgaonkar, Shamkant; Qazi, Yasir; de Fijter, Johan W; Oppenheimer, Federico; Cruzado, Josep M

Published in:
American Journal of Transplantation

DOI:
10.1111/ajt.15480

Take a deep dive into the business of transplantation!

Liver Transplant Financial Bootcamp

&

Kidney Transplant Financial Bootcamp

Co-located for 2019!

September 19–20, 2019

Loews Chicago O'Hare Hotel

Register at ASTS.org/bootcamps

ASTS
American Society of Transplant Surgeons®

Received: 26 December 2018 | Revised: 11 April 2019 | Accepted: 4 May 2019

DOI: 10.1111/ajt.15480

ORIGINAL ARTICLE

Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study

Stefan P. Berger[1] | Claudia Sommerer[2] | Oliver Witzke[3,4] | Helio Tedesco[5] | Steve Chadban[6] | Shamkant Mulgaonkar[7] | Yasir Qazi[8] | Johan W. de Fijter[9] | Federico Oppenheimer[10] | Josep M. Cruzado[11] | Yoshihiko Watarai[12] | Pablo Massari[13] | Christophe Legendre[14] | Franco Citterio[15] | Mitchell Henry[16] | Titte R. Srinivas[17] | Flavio Vincenti[18] | Maria Pilar Hernandez Gutierrez[19] | Ana Maria Marti[19] | Peter Bernhardt[19] | Julio Pascual[20] | on behalf of the TRANSFORM investigators

[1]Division of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[2]Department of Nephrology, Heidelberg University Hospital, Heidelberg, Germany

[3]Department of Infectious Diseases, University Hospital Essen, University Duisburg-Essen, Essen, Germany

[4]Department of Nephrology, University Hospital Essen, University Duisburg-Essen, Essen, Germany

[5]Nephrology Division, Hospital do Rim, Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil

[6]Department of Renal Medicine and Transplantation, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

[7]Renal and Pancreas Division, Saint Barnabas Medical Center, Livingston, New Jersey

[8]Division of Nephrology, Keck School of Medicine Renal Transplant Program, University of Southern California, Los Angeles, California

[9]LUMC Leids Universitair Medisch Centrum, Leiden, The Netherlands

[10]Department of Nephrology and Renal Transplantation, Renal Transplant Unit, Hospital Clinic of Barcelona, Barcelona, Spain

[11]Hospital Universitari De Bellvitge, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain

[12]Department of Transplant Surgery, Nagoya Daini Red Cross Hospital, Nagoya-City, Aichi, Japan

[13]Hospital Privado Centro Medico de Cordoba, Cordoba, Argentina

[14]Department of Kidney Transplantation, Adult Transplantation Service, Paris Descartes University and Necker Hospital, Paris, France

[15]Agostino Gemelli University Polyclinic Foundation, Catholic University of the Sacred Heart, Rome, Italy

[16]Department of Surgery, The Comprehensive Transplant Center, The Ohio State University, Wexner Medical Center, Columbus, Ohio

[17]Division of Nephrology, Medical University of South Carolina, Mount Pleasant, South Carolina

[18]Department of Surgery, Kidney Transplant Service, University of California, San Francisco, California

[19]Department of Research and Development, Novartis Pharma AG, Basel, Switzerland

[20]Department of Nephrology, Hospital del Mar, Barcelona, Spain

Abbreviations: ABMR, antibody-mediated acute rejection; AEs, adverse events; C_0, trough level; CI, confidence interval; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CsA, cyclosporine; D, donor; dnDSA, de novo donor-specific antibodies; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; EVR, everolimus; FAS, full analysis set; LD, living donor; M, number of evaluable patients; MDRD4, modification of diet in renal disease; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; R, recipient; RTxRs, renal transplant recipients; rCNI, reduced-exposure CNI; SAE, serious adverse event; SAF, safety analysis set; SCD, standard criteria donor; sCNI, standard-exposure CNI; SE, standard error; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection; UPCR, urine protein:creatinine ratio.

Stefan P. Berger and Claudia Sommerer are co-first authors.

Correspondence
Julio Pascual
Email: JPascualSantos@parcdesalutmar.cat

Funding information
Novartis Pharma AG

TRANSFORM (TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen) was a 24-month, prospective, open-label trial in 2037 de novo renal transplant recipients randomized (1:1) within 24 hours of transplantation to receive everolimus (EVR) with reduced-exposure calcineurin inhibitor (EVR + rCNI) or mycophenolate with standard-exposure CNI. Consistent with previously reported 12-month findings, noninferiority of the EVR + rCNI regimen for the primary endpoint of treated biopsy-proven acute rejection (tBPAR) or estimated glomerular filtration rate (eGFR) <50 mL/min per 1.73 m^2 was achieved at month 24 (47.9% vs 43.7%; difference = 4.2%; 95% confidence interval = −0.3, 8.7; P = .006). Mean eGFR was stable up to month 24 (52.6 vs 54.9 mL/min per 1.73 m^2) in both arms. The incidence of de novo donor-specific antibodies (dnDSA) was lower in the EVR + rCNI arm (12.3% vs 17.6%) among on-treatment patients. Although discontinuation rates due to adverse events were higher with EVR + rCNI (27.2% vs 15.0%), rates of cytomegalovirus (2.8% vs 13.5%) and BK virus (5.8% vs 10.3%) infections were lower. Cytomegalovirus infection rates were significantly lower with EVR + rCNI even in the D+/R− high-risk group (P < .0001). In conclusion, the EVR + rCNI regimen offers comparable efficacy and graft function with low tBPAR and dnDSA rates and significantly lower incidence of viral infections relative to standard-of-care up to 24 months. Clinicaltrials.gov number: NCT01950819.

KEYWORDS
clinical research/practice, immunosuppressant - mechanistic target of rapamycin (mTOR), immunosuppressant - mechanistic target of rapamycin: everolimus, immunosuppression/immune modulation, immunosuppressive regimens - minimization/withdrawal, kidney transplantation/nephrology, liver transplantation/hepatology

1 | INTRODUCTION

Calcineurin inhibitors (CNIs) remain the standard-of-care immunosuppressive therapy after kidney transplantation; however, their long-term use is associated with severe complications, such as chronic nephrotoxicity,[1-3] and infections[4] and de novo malignancies[5,6] remain a long-term risk of generalized immunosuppression. Viral infections are a significant cause of posttransplant morbidity and mortality.[7] Moreover, the presence of a cytomegalovirus (CMV) infection affects long-term renal allograft function specifically in patients at high risk of rejection.[8,9] Thus, immunosuppressive concepts in the field have progressed toward strategies facilitating de novo CNI reduction to provide better management of comorbidities in the long term while maintaining antirejection efficacy.[10-13]

In multiple randomized controlled trials, the mammalian target of rapamycin inhibitor (mTORi) everolimus (EVR) in combination with reduced-exposure CNI (cyclosporine [CsA] or tacrolimus [TAC]) was found to be noninferior to standard CNI regimens for antirejection efficacy, with comparable, if not better, allograft function up to 2 years after transplantation.[14-17] Additional benefits in terms of suppression of viral infections, especially CMV infections, have been reported with early EVR initiation.[18-22]

TRANSFORM (TRANSplant eFficacy and safety Outcomes with an eveRolimus-based regiMen; CRAD001A2433) is the largest trial to date in de novo renal transplant recipients (RTxRs) to evaluate the efficacy and safety of EVR with reduced-exposure CNI (EVR + rCNI) vs mycophenolic acid (MPA) with standard-exposure CNI (MPA + sCNI).[23] The study used a novel binary composite endpoint of treated biopsy-proven acute rejection (tBPAR) or suboptimal kidney function (estimated glomerular filtration rate [eGFR] <50 mL/min per 1.73 m^2) to simultaneously assess immunosuppressive efficacy and graft function preservation. This eGFR threshold represents moderate renal dysfunction and is associated with a significantly increased risk of subsequent death-censored graft loss.[24,25] The 1-year results from TRANSFORM demonstrated that de novo EVR + rCNI was noninferior to MPA + sCNI for the binary endpoint, with stable renal function, and comparable overall safety, but a significantly lower incidence of clinically important viral infections.[26,27] Efficacy, renal function, and safety outcomes, including infection risk, are reported here following completion of the 24-month study.

2 | MATERIALS AND METHODS

2.1 | Study design and population

TRANSFORM was a 24-month, prospective, randomized, open-label study in de novo RTxRs conducted at 186 centers across 42 countries.[26] The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization

Guidelines for Good Clinical Practice; all patients provided written informed consent. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee of the participating centers. The recruitment target was completed over 2 years. Eligible patients were randomized 1:1 within 24 hours of transplantation to either EVR + rCNI or MPA + sCNI. Stratification of patients and inclusion and exclusion criteria have been reported previously.[26]

2.2 | Study endpoints and assessments

Study endpoints, detailed assessments, sample size calculation, and rationale for the primary endpoint have been reported previously.[26] The primary endpoint, key secondary endpoints, and allograft function were assessed up to month 24. Safety objectives included the assessment of adverse events (AEs), serious AEs (SAEs), AEs leading to treatment discontinuation, CMV and BK virus (BKV) infections, proteinuria, and wound-healing events. CMV and BKV infections were recorded on the AE electronic case report form (e-CRF) and confirmed by polymerase chain reaction. Mean urine protein:creatinine ratio (UPCR) and UPCR categories were analyzed as part of central laboratory assessments in on-treatment patients at baseline, weeks 1 and 2, and months 1, 2, 4, 6, 12, 18, and 24. Incidence of donor-specific antibodies (DSA) by treatment and in relation to antibody-mediated acute rejection (ABMR) were separately assessed in a subset of safety analysis set (SAF) patients at baseline, month 12, and month 24.

2.3 | Immunosuppression

Immunosuppression regimens for the 2 treatment arms have been described previously.[26] Therapeutic drug monitoring was performed, and adherence to target trough levels (C_0) of both CNIs, EVR, and MPA was assessed up to month 24. Compliance for MPA was defined as the patient taking MPA, whereas compliance for CNI and EVR was defined as the imputed C_0 being within the protocol-defined range at any day.

2.4 | Analysis sets

The full analysis set (FAS) consisted of all randomized and transplanted patients; misrandomized patients and those randomized but not transplanted were excluded. The SAF consisted of all randomized patients who received ≥ 1 dose of study drug. For efficacy outcomes, an on-treatment observation was any assessment obtained on and after day 1 but no later than 2 days after

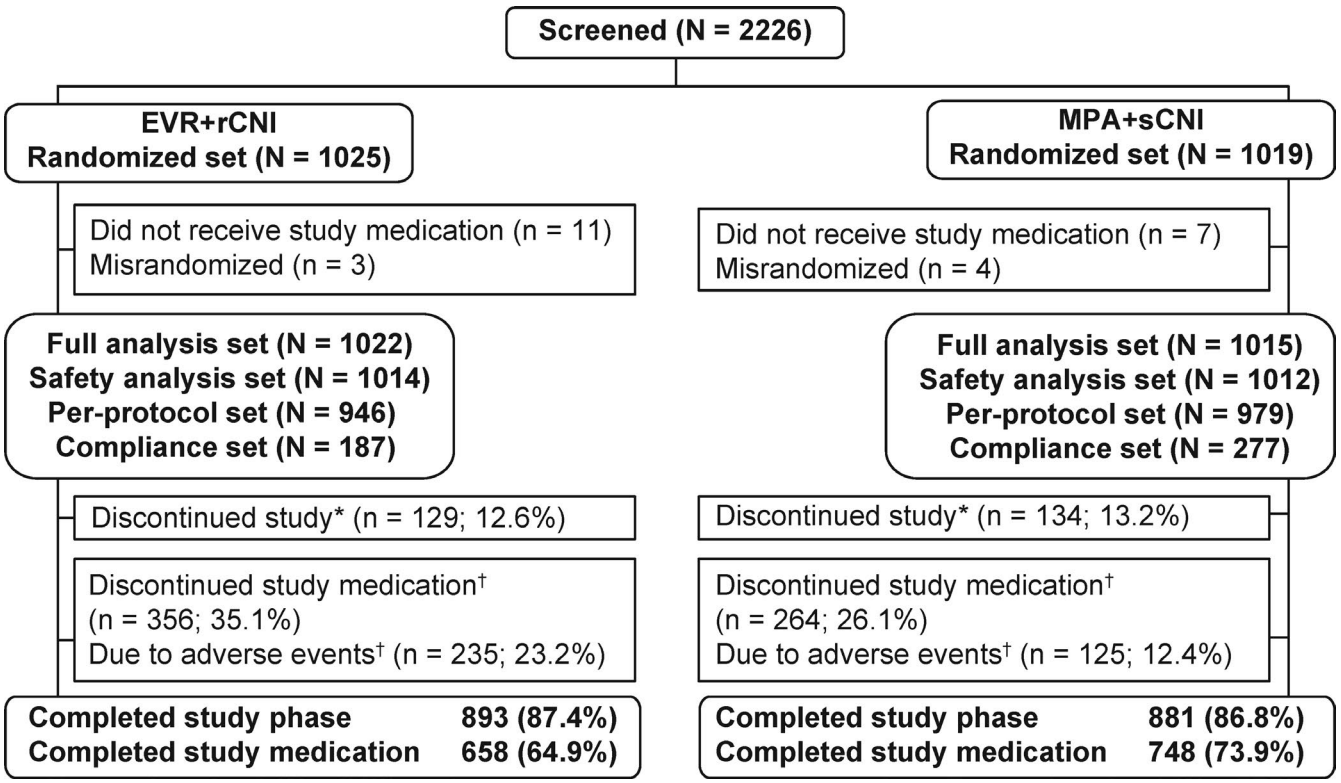


FIGURE 1 Patient disposition. Of 2226 screened patients, 2037 were randomized to the EVR + rCNI or MPA + sCNI arm. The reasons for study discontinuation (FAS) were subject decision (n = 54, EVR + rCNI vs n = 51, MPA + sCNI), graft loss (n = 35 vs n = 30), death (n = 29 vs n = 34), lost to follow-up (n = 9 vs n = 17), pregnancy (n = 0 vs n = 2), and technical problems (n = 2 vs 0). The reasons for discontinuation of study medication (SAF) were AEs (n = 235, EVR + rCNI vs n = 125, MPA + sCNI), subject decision (n = 29 vs n = 49), graft loss (n = 25 vs n = 22), death (n = 14 vs n = 16), lack of efficacy (n = 15 vs n = 5), lost to follow-up (n = 5 vs n = 10), and technical problems (n = 6 vs n = 5). *Based on the FAS; †Based on the SAF. AEs, adverse events; EVR, everolimus; FAS, full analysis set; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; SAF, safety analysis set; sCNI, standard-exposure calcineurin inhibitor

TABLE 1 Demographics and baseline characteristics (full analysis set)

Recipient characteristics	EVR + rCNI (N = 1022)	MPA + sCNI (N = 1015)
Age (y), mean (SD)	48.8 (14.12)	48.8 (14.52)
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)
Others	100 (9.8)	88 (8.7)
BMI (kg/m^2), mean (SD)	25.6 (4.24)	25.6 (4.25)
Diabetes mellitus at baseline, n (%)	279 (27.3)	270 (26.6)
Delayed graft function, n (%)	110 (10.8)	100 (9.9)
Induction, n (%)		
Basiliximab	849 (83.1)	844 (83.2)
rATG	171 (16.7)	171 (16.8)
Hemodialysis, n (%)	674 (65.9)	679 (66.9)
% PRA (most recent evaluation), mean (SD)[a]	2.7 (10.72)	2.7 (9.48)
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)
Loci B		
0	114 (11.2)	124 (12.2)
1	518 (50.7)	494 (48.7)
2	382 (37.4)	394 (38.8)
Loci DR		
0	240 (23.5)	193 (19.0)
1	495 (48.4)	557 (54.9)
2	279 (27.3)	262 (25.8)
Primary 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)
Donor characteristics	EVR + rCNI (N = 1022)	MPA + sCNI (N = 1015)
Age (y), mean (SD)[b]	48.4 (15.11)	48.2 (15.48)
Male, n (%)	493 (48.2)	508 (50.0)
Race, n (%)		
White	620 (60.7)	600 (59.1)
Asian	120 (11.7)	134 (13.2)
Black	23 (2.3)	22 (2.2)
Others[c]	259 (25.3)	259 (25.5)
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)
Standard criteria donor[d]	354 (70.0)	345 (68.3)
Expanded criteria donor[d]	152 (30.0)	160 (31.7)
Donation after circulatory death	5 (0.5)	3 (0.3)

Expanded criteria donor was defined as a brain-dead donor aged >60 years old *or* a donor aged >50 years with 2 of the following criteria: history of hypertension, terminal serum creatinine ≥ 1.5 mg/dL, or death resulting from cerebrovascular accident.
BMI, body mass index; D, donor; EVR, everolimus; HLA, human leukocyte antigen; IgA, immunoglobulin A; MPA, mycophenolic acid; PRA, panel reactive antibodies; R, recipient; rATG, rabbit antithymocyte globulin; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; SD, standard deviation.
[a]EVR + rCNI, n = 958 and MPA + sCNI, n = 954.
[b]EVR + rCNI, n = 1021 and MPA + sCNI, n = 1014.
[c]Others include Native American, Pacific Islander, unknown, other, and missing.
[d]Percentages are relative to the number of deceased heart-beating donors.

the discontinuation of randomized study medication. However, for safety outcomes, an on-treatment observation was any assessment obtained up to 7 days (inclusive) after discontinuation of study medication. The per-protocol set consisted of all patients in the FAS who completed the study without any major deviations from protocol procedures. The compliance set consisted of all patients in the FAS who were compliant for both CNIs, EVR, and MPA for at least 70% of days on study.

2.5 | Statistical analysis

All endpoints were compared using a confidence interval (CI) approach at months 12 and 24, and *P* values to test for no differences between treatment rates were computed. A noninferiority margin of 10% was set for the primary endpoint and the key secondary endpoint of tBPAR, graft loss, or death as described previously.[26] The event rates of various efficacy endpoints were estimated with the Kaplan-Meier product-limit formula. Differences between Kaplan-Meier plots corresponding to the 2 treatment arms were prepared after censoring event-free patients and tested pairwise using the log-rank test. Multiple imputation was used as the primary method for handling missing eGFR data. For incidence of eGFR < 50 mL/min per 1.73 m^2, a value for missing eGFR as a continuous variable was imputed and then dichotomized to derive the endpoint.[26]

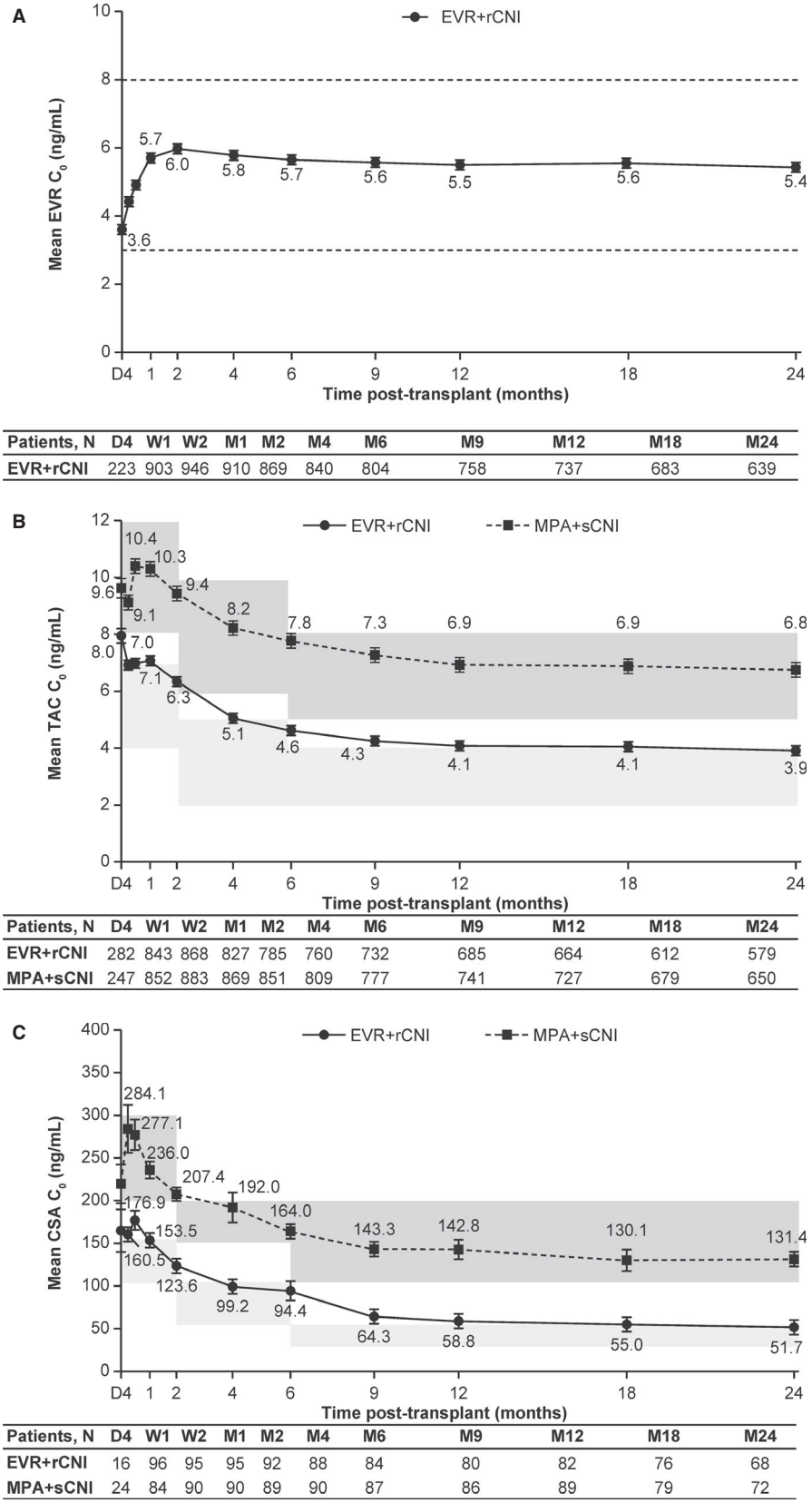


FIGURE 2 Exposure of everolimus, tacrolimus, and cyclosporine (SAF – on-treatment analysis). A, Mean EVR C_0 by visit window in the EVR + rCNI arm. The horizontal dashes indicate the protocol-defined target range of 3-8 ng/mL. B, Mean TAC C_0 by visit window and treatment. The shaded boxes indicate the protocol-defined TAC target C_0 ranges: EVR + rCNI arm: 4-7 ng/mL from RND to M2, 2-5 ng/mL from M3 to M6, and 2-4 ng/mL beyond M6; MPA + sCNI arm: 8-12 ng/mL from RND to M2, 6-10 ng/mL from M3 to M6, and 5-8 ng/mL beyond M6. C, Mean CsA C_0 by visit window and treatment. The shaded boxes indicate the protocol-defined CsA target C_0 ranges: EVR + rCNI arm: 100-150 ng/mL from RND to M2, 50-100 ng/mL from M3 to M6, and 25-50 ng/mL beyond M6; MPA + sCNI arm: 200-300 ng/mL from RND to M2, 150-200 ng/mL from M3 to M6, and 100-200 ng/mL beyond M6. Data are represented as mean ± SE. C_0, trough level; CsA, cyclosporine; D, day; EVR, everolimus; M, month; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; RND, randomization; sCNI, standard-exposure calcineurin inhibitor; SAF, safety analysis set; SE, standard error; TAC, tacrolimus; W, week

Relative risk ratios (95% CI) were calculated to compare AEs between treatments. CMV event rates between treatments were compared by a χ^2 test, and a Cochran-Mantel-Haenszel test was applied to check for independence of CMV event rates and treatment arms adjusted for CMV prophylaxis therapy. The level of statistical significance was defined at $P < .05$ for 2-tailed tests. Analyses were

TABLE 2 Efficacy endpoints at months 12 and 24 (full analysis set)

	Month 12				Month 24			
	EVR + rCNI	MPA + sCNI	Difference (95% CI)	*P* value	EVR + rCNI	MPA + sCNI	Difference (95% CI)	*P* value
Full analysis set, n (%)	**N = 1022**	**N = 1015**			**N = 1022**	**N = 1015**		
Primary endpoint[a]	489 (47.9)	456 (44.9)	3.0 (−1.4, 7.3)	.187	489 (47.9)	443 (43.7)	4.2 (−0.3, 8.7)	.067
tBPAR, graft loss, or death	146 (14.4)	131 (13.0)	1.4 (−1.6, 4.4)	.353	169 (18.0)	147 (17.3)	0.8 (−4.6, 6.1)	.782
tBPAR	107 (10.8)	91 (9.2)	1.6 (−1.1, 4.2)	.243	118 (12.8)	98 (12.1)	0.7 (−4.4, 5.8)	.794
tBPAR excluding grade IA rejections	66 (6.6)	53 (5.4)	1.3 (−0.8, 3.3)	.241	74 (8.3)	55 (5.8)	2.5 (−0.1, 5.2)	.062
Borderline lesions	43 (4.3)	37 (3.8)	0.6 (−1.2, 2.3)	.517	46 (4.7)	38 (3.9)	0.8 (−1.0, 2.6)	.404
AR	147 (14.8)	133 (13.4)	1.4 (−1.7, 4.4)	.384	167 (17.8)	144 (18.7)	−0.9 (−7.5, 5.7)	.793
aAMR	73 (7.4)	61 (6.1)	1.2 (−1.0, 3.4)	.284	84 (8.9)	69 (11.2)	−2.4 (−8.6, 3.9)	.460
cAMR	9 (0.9)	14 (1.4)	−0.5 (−1.5, 0.4)	.280	13 (1.6)	18 (1.9)	−0.2 (−1.6, 1.1)	.731
tAR	129 (12.9)	117 (11.8)	1.1 (−1.8, 4.0)	.438	145 (15.5)	126 (16.8)	−1.2 (−7.7, 5.2)	.704
BPAR	114 (11.5)	95 (9.6)	1.9 (−0.8, 4.6)	.175	127 (13.7)	104 (12.8)	0.9 (−4.3, 6.1)	.726
Graft loss	33 (3.3)	28 (2.8)	0.5 (−1.0, 2.0)	.542	37 (3.7)	32 (3.2)	0.5 (−1.1, 2.1)	.572
Death	20 (2.0)	28 (2.8)	−0.8 (−2.2, 0.5)	.234	32 (3.7)	36 (4.2)	−0.5 (−2.7, 1.6)	.634
eGFR < 50 mL/min per 1.73 m^2[a]	456 (44.6)	424 (41.8)	2.9 (−1.5, 7.2)	.201	474 (46.4)	423 (41.6)	4.7 (0.2, 9.2)	.040
On-treatment analysis, n (%)	**N = 764**	**N = 846**			**N = 721**	**N = 810**		
Primary endpoint[a]	296 (38.7)	329 (38.9)	−0.2 (−4.9, 4.6)	.952	256 (35.5)	290 (35.8)	−0.3 (−5.1, 4.5)	.904
tBPAR, graft loss, or death	97 (12.7)	107 (12.6)	0.0 (−3.2, 3.3)	.977	111 (17.3)	115 (17.3)	0.0 (−6.7, 6.7)	.998
tBPAR	59 (7.9)	70 (8.4)	−0.5 (−3.2, 2.2)	.696	61 (10.1)	69 (11.2)	−1.2 (−7.5, 5.2)	.716
tBPAR excluding grade IA rejections	37 (4.9)	40 (4.8)	0.1 (−2.0, 2.2)	.919	40 (7.1)	38 (4.8)	2.3 (−1.0, 5.5)	.168
Borderline lesions	26 (3.5)	31 (3.7)	−0.3 (−2.1, 1.6)	.779	27 (3.8)	26 (3.3)	0.5 (−1.3, 2.4)	.568
AR	83 (11.1)	97 (11.6)	−0.6 (−3.7, 2.6)	.723	88 (13.9)	97 (17.1)	−3.2 (−11.2, 4.8)	.432
aAMR	31 (4.1)	40 (4.8)	−0.7 (−2.7, 1.4)	.518	33 (5.2)	42 (10.1)	−5.0 (−12.3, 2.4)	.184
cAMR	5 (0.7)	11 (1.3)	−0.7 (−1.6, 0.3)	.179	8 (1.6)	12 (1.5)	0.1 (−1.6, 1.8)	.892
tAR	72 (9.6)	89 (10.7)	−1.1 (−4.0, 1.0)	.480	75 (12.0)	87 (15.7)	−3.7 (−11.5, 4.2)	.358
BPAR	64 (8.5)	72 (8.6)	−0.1 (−2.9, 2.6)	.933	67 (10.9)	73 (11.8)	−0.9 (−7.4, 5.6)	.780
Graft loss	32 (4.2)	26 (3.1)	1.1 (−0.7, 3.0)	.236	36 (5.1)	30 (3.8)	1.3 (−0.8, 3.4)	.222
Death	20 (2.7)	27 (3.2)	−0.6 (−2.2, 1.1)	.498	32 (5.2)	35 (5.1)	0.1 (−2.8, 3.0)	.938
eGFR < 50 mL/min per 1.73 m^2[a]	265 (34.7)	291 (34.4)	0.3 (−4.4, 4.9)	.903	222 (30.8)	247 (30.5)	0.3 (−4.3, 4.9)	.900

aAMR, acute antibody-mediated rejection; AR, acute rejection; BPAR, biopsy-proven acute rejection; cAMR, chronic antibody-mediated rejection; CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tAR, treated AR; tBPAR, treated BPAR.

[a]Represents raw incidence rates; all remaining values are Kaplan-Meier incidence rates; *P* value for no difference ([EVR + rCNI] − [MPA + sCNI] = 0).

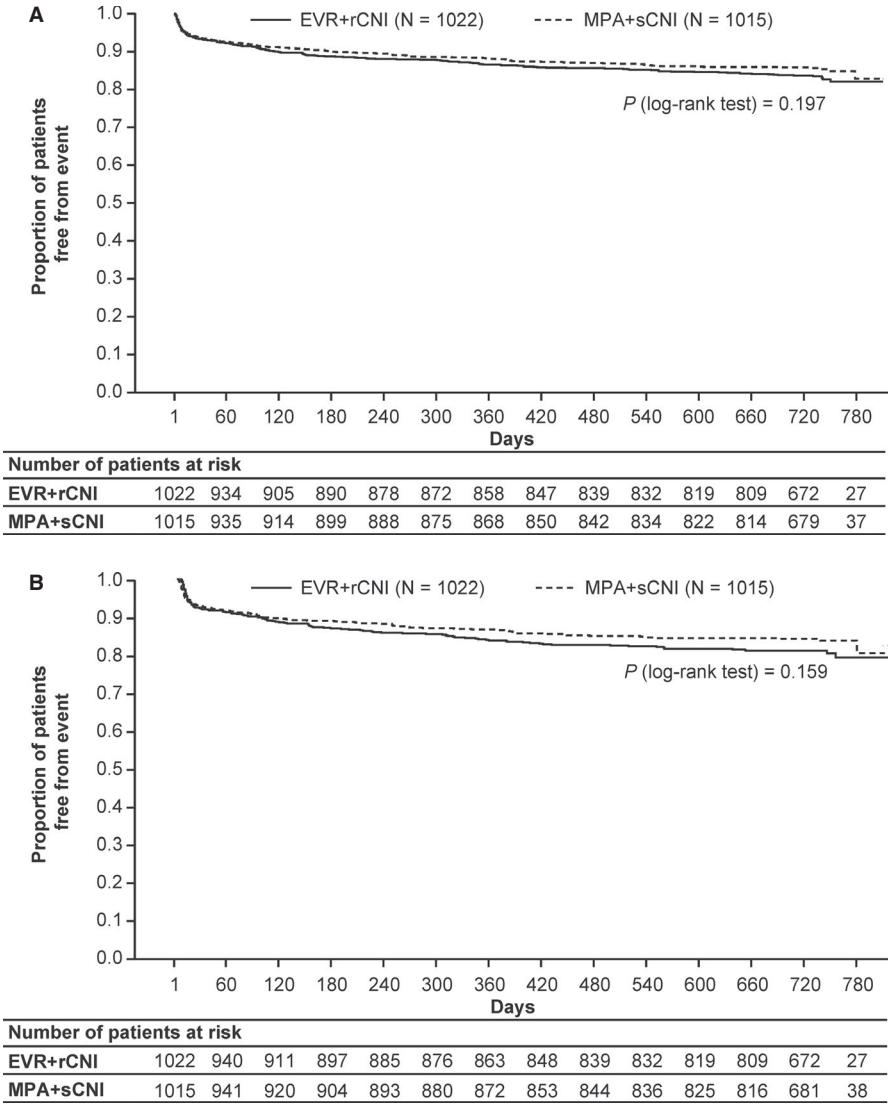


FIGURE 3 Kaplan-Meier plot for the proportion of patients free from (A) the composite efficacy failure endpoint of tBPAR, graft loss or death, and (B) tBPAR (FAS – 24-month analysis). *P* values were determined by log-rank test. EVR, everolimus; FAS, full analysis set; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor; tBPAR, treated biopsy-proven acute rejection

performed using SAS® statistical software (SAS Institute Inc., Cary, NC), version 9.4 (or higher) for Unix.

3 | RESULTS

3.1 | Patient population

Of 2226 screened patients, 2037 were transplanted and randomized to either EVR + rCNI (N = 1022) or MPA + sCNI (N = 1015). Of these, 87.4% and 86.8% of patients completed the 24-month study in the EVR + rCNI and MPA + sCNI arms, respectively (Figure 1). Discontinuation of study medication occurred more frequently in the EVR + rCNI vs MPA + sCNI arm (35.1% vs 26.1% of patients). AEs were the main reason for drug discontinuation in both of the arms (23.2%, EVR + rCNI vs 12.4%, MPA + sCNI). Most discontinuations from study drug occurred within the first 6 months of randomization (219/356 [61.5%], EVR + rCNI vs 148/264 [56.1%], MPA + sCNI); only 16.3% (58/356) in the EVR + rCNI arm and 17.8% (47/264) in the MPA + sCNI arm occurred after 12 months. The proportion of compliant patients was low in both arms but higher for MPA + sCNI (187/1022 [18.3%], EVR + rCNI vs 277/1015 [27.3%], MPA + sCNI). Recipient and donor baseline characteristics were balanced between arms (Table 1). Approximately 10% of patients in both arms experienced delayed graft function (10.8%, EVR + rCNI vs 9.9%, MPA + sCNI).

3.2 | Immunosuppression

In the EVR + rCNI arm, mean EVR C_0 was within target range starting from Day 4 until month 24 (Figure 2A). More than 80% of on-treatment patients were within range from month 2 onwards (Figure S1A). Among TAC-receiving patients, the mean TAC C_0 was above or near the upper limit of target range in the EVR + rCNI arm from months 2 to 24, whereas it was within range in the MPA + sCNI arm throughout the study (Figure 2B). Adherence to TAC C_0 was poorer in the EVR + rCNI vs MPA + sCNI arm throughout the study: between months 2 and 24, 24.2%-43.8% of patients were above the target range in the EVR + rCNI arm, whereas 13.1%-37.8% of

TABLE 3 Efficacy endpoints at month 24 by CNI subgroups (full analysis set)

	TAC-receiving patients				CsA-receiving patients			
n (%)	EVR + rCNI N = 915	MPA + sCNI N = 917	Difference (95% CI)	*P* value	EVR + rCNI N = 100	MPA + sCNI N = 95	Difference (95% CI)	*P* value
Primary endpoint[a]	429 (46.9)	391 (42.6)	4.3 (−0.4, 9.1)	.071	54 (54.0)	50 (52.6)	1.5 (−12.8, 15.7)	.842
tBPAR, graft loss, or death	148 (17.8)	126 (16.8)	1.0 (−4.8, 6.8)	.733	19 (19.2)	18 (19.1)	0.0 (−11.1, 11.2)	.994
tBPAR	102 (12.4)	83 (11.7)	0.7 (−4.7, 6.2)	.790	15 (15.5)	15 (16.0)	−0.5 (−10.9, 9.9)	.929
Graft loss	31 (3.5)	25 (2.8)	0.7 (−1.0, 2.3)	.429	5 (5.0)	5 (5.3)	−0.3 (−6.5, 5.9)	.922
Death	29 (3.8)	33 (4.3)	−0.5 (−2.8, 1.7)	.642	3 (3.2)	2 (2.2)	1.0 (−3.7, 5.7)	.684
eGFR < 50 mL/min per 1.73 m^2[a]	415 (45.4)	374 (40.8)	4.6 (−0.1, 9.4)	.055	53 (53.0)	47 (49.5)	4.2 (−10.1, 18.5)	.566

P value for no difference ([EVR + rCNI] − [MPA + sCNI] = 0).

CI, confidence interval; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure CNI; sCNI, standard-exposure CNI; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection

[a]Represents raw incidence rates; all remaining values are Kaplan-Meier incidence rates.

patients were below the target range in the MPA + sCNI arm (Figure S1B). Similar patterns were observed among CsA-receiving patients (Figures 2C). At month 24, only 60.1% of TAC-receiving and 44.1% of CsA-receiving patients in the EVR + rCNI arm were within the target range (Figures S1B,C). The mean MPA doses in the MPA + sCNI arm and mean body-weight-adjusted corticosteroid doses in both arms are shown in Table S1.

3.3 | Efficacy outcomes

Noninferiority of the EVR + rCNI to MPA + sCNI regimen could be confirmed for the primary endpoint of tBPAR or eGFR < 50 mL/min per 1.73 m^2 at months 12 and 24 (Table 2). The month 24 incidence of the primary endpoint was 47.9% for EVR + rCNI and 43.7% for MPA + sCNI arms, respectively (difference = 4.2% 95% CI: −0.3, 8.7; *P* = .006 for noninferiority; *P* = .067 for difference). The event rates for composite efficacy failure (tBPAR, graft loss, or death) at month 24 were also consistent with month 12; the EVR + rCNI regimen was noninferior (*P* < .001) and not significantly different (*P* = .782) from the MPA + sCNI regimen (Table 2). At month 24, no significant between-arm difference in the incidence of tBPAR (12.8%, EVR + rCNI vs 12.1%, MPA + sCNI; *P* = .794) was noted; however, there was a small difference in the percentage of recipients with an eGFR < 50 mL/min per 1.73 m^2 (46.4% vs 41.6%; *P* = .040). Figure 3 shows Kaplan-Meier plots for the proportion of patients free from the composite efficacy failure endpoint and tBPAR up to month 24. Between months 12 and 24, newly occurring tBPAR (1.3% vs 0.9%), graft loss (0.4% in both arms), and death (1.3% vs 0.8%) events were very low and comparable between the 2 arms. When endpoints were assessed in the on-treatment population, the between-arm differences in incidence of primary endpoint, composite efficacy failure, tBPAR, graft loss, and death were comparable at months 12 and 24 (*P* > .05).

Efficacy endpoints were also evaluated by type of CNI used and donor category. Among TAC- and CsA-receiving patients, between-arm differences were not significant for any of the efficacy parameters, but incidences of primary endpoint and eGFR <50 mL/min per 1.73 m^2 were slightly lower in TAC-receiving patients compared with CsA-receiving patients (Table 3). When efficacy endpoints were evaluated by donor categories (living [LD], standard criteria deceased [SCD], and expanded criteria deceased [ECD]), between-arm differences were largely comparable (Table 4). However, the incidences of primary endpoint and eGFR <50 mL/min per 1.73 m^2 were significantly higher in the EVR + rCNI vs MPA + sCNI arm among recipients of SCDs.

Furthermore, the incidence of overall and de novo (dn) DSA was estimated at month 24 in the overall and on-treatment populations. In total, 475 patients in the EVR + rCNI arm and 477 patients in the MPA + sCNI arm consented to participate in the DSA substudy. Among evaluable patients at month 24, the incidence of baseline DSA in the overall population was comparable (11.0% vs 12.8%; *P* = .9138) and that in the on-treatment population was lower (6.4% vs 14.4%) with the EVR + rCNI regimen (*P* = .0444; Table 5). Interestingly, dnDSA incidence with EVR + rCNI was higher in the overall population (47/210 [22.4%] vs 39/220 [17.7%]; *P* = .5047), but lower in the on-treatment patients (7/57 [12.3%] vs 13/74 [17.6%]; *P* = .6801). To evaluate the effect of TAC reduction on risk of dnDSA, we measured mean TAC C_0 in patients with dnDSA (Figure S2). Mean TAC C_0 in these patients was above target range in the EVR + rCNI arm up to month 24 and comparable to that in the MPA + sCNI arm at month 24 (5.7 ng/mL, EVR + rCNI vs 6.5 ng/mL, MPA + sCNI; *P* = .3324).

3.4 | Renal function

Renal function was stable from months 1 to 24 in the FAS (Figure 4A). In the FAS, month 24 eGFR (modification of diet in renal disease

TABLE 4 Efficacy endpoints at month 24 by donor category (full analysis set)

	LD				SCD				ECD			
n (%)	EVR + rCNI N = 511	MPA + sCNI N = 507	Difference (95% CI)	*P* value	EVR + rCNI N = 354	MPA + sCNI N = 345	Difference (95% CI)	*P* value	EVR + rCNI N = 152	MPA + sCNI N = 160	Difference (95% CI)	*P* value
Primary endpoint[a]	196 (38.4)	176 (34.7)	3.6 (−2.4, 9.7)	.242	171 (48.3)	136 (39.4)	8.9 (1.3, 16.5)	.022	120 (78.9)	130 (81.3)	−2.5 (−12.0, 6.9)	.597
tBPAR, graft loss, or death	56 (11.7)	64 (13.1)	−1.4 (−5.8, 3.0)	.524	72 (24.0)	52 (20.3)	3.7 (−8.8, 16.1)	.566	40 (27.0)	31 (23.2)	3.8 (−8.1, 15.6)	.534
tBPAR	48 (9.6)	52 (10.9)	−1.3 (−5.2, 2.6)	.507	49 (17.8)	34 (15.5)	2.3 (−10.6, 15.1)	.728	20 (14.1)	12 (7.8)	6.3 (−0.9, 13.5)	.086
Graft loss	9 (1.8)	9 (1.8)	0.0 (−1.7, 1.6)	.973	16 (4.7)	10 (3.0)	1.7 (−1.2, 4.6)	.255	12 (8.2)	13 (8.5)	−0.3 (−6.5, 6.0)	.936
Death	5 (1.6)	11 (2.2)	−0.6 (−2.8, 1.5)	.569	17 (5.3)	13 (3.9)	1.4 (−1.9, 4.7)	.396	10 (7.2)	12 (11.8)	−4.7 (−14.7, 5.4)	.361
eGFR <50 mL/min per 1.73 m^2[a]	185 (36.2)	161 (31.8)	4.5 (−1.4, 10.5)	.138	165 (46.6)	131 (38.0)	8.7 (1.1, 16.3)	.025	121 (79.6)	129 (80.6)	−0.8 (−10.4, 8.7)	.865

P value for no difference ([EVR + rCNI] − [MPA + sCNI] = 0).

CI, confidence interval; eGFR, estimated glomerular filtration rate; ECD, expanded criteria donor; EVR, everolimus; LD, living donor; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; SCD, standard criteria donor; sCNI, standard-exposure calcineurin inhibitor; tBPAR, treated biopsy-proven acute rejection.

[a]Represents raw incidence rates; all remaining values are Kaplan-Meier incidence rates.

[MDRD4]) was 52.6 vs 54.9 mL/min per 1.73 m^2 in the EVR + rCNI vs MPA + sCNI arm, respectively (*P* = .028). eGFR was also stable and without any clinically relevant between-arm differences in on-treatment patients (Figure 4B) and in a subset of patients who achieved TAC target C_0 (Figure 4C). No clinically relevant differences were observed in month 24 eGFR between arms by CNI (Figure 4D-E) and donor (Figure 4F-H) subcategories. Nevertheless, eGFR at month 24 was 4-5 mL/min per 1.73 m^2 higher in TAC- vs CsA-receiving patients in both treatment arms. eGFR in both arms at month 24 was above or near the clinically significant level of 60 mL/min per 1.73 m^2 for the LD and SCD subgroups, but below 45 mL/min per 1.73 m^2-for the ECD subgroups.

At month 24, the differences between EVR + rCNI and MPA + sCNI arms for proportion of patients with eGFR (MDRD4) categories <30 (9.1% vs 7.9%), 30-<45 (21.5% vs 21.0%), 45-<60 (30.8% vs 30.4%), and ≥60 mL/min per 1.73 m^2 (38.6% vs 40.8%) were small and without any consistent trends. Most patients had UPCR of 30-<500 mg/g at month 24 (85.7%, EVR + rCNI vs 90.9%, MPA + sCNI), with mean values of 290.24 (EVR + rCNI) and 233.01 mg/g (MPA + sCNI; *P* = .0614).

3.5 | Safety outcomes

Up to month 24, 32 (3.2%) patients died in the EVR + rCNI arm, and 35 (3.5%) patients died in the MPA + sCNI arm. Cardiac arrest was the most frequent cause of death (6, EVR + rCNI and 4, MPA + sCNI). Gastrointestinal disorders were the reason for death in 1 and 4 patients in the EVR + rCNI and MPA + sCNI arms, respectively.

The incidences of overall AEs and SAEs were similar between arms (Table 6). Most AEs occurred in the first 12 months, and none of the AEs had an incidence of ≥10% in either arm from months 12 to 24. While study drug discontinuation rates were comparable from months 12 to 24 (3.8% vs 2.9%), the rate of dose adjustment due to AEs was significantly lower in the EVR + rCNI arm (8.9%, EVR + rCNI vs 11.9%, MPA + sCNI; risk ratio [95% CI]: 0.75 [0.58, 0.97]). At month 24, proteinuria events reported as AEs (14.1% vs 7.0%) and those leading to drug discontinuation (2.6% vs 0.0%) were higher in the EVR + rCNI arm. The frequency of aphthous ulcers was slightly higher in the EVR + rCNI arm (3.0% vs 0.6%). Occurrence of benign or malignant neoplasms was generally low and comparable between arms (7.2% vs 9.0%), with similar frequencies of basal (1.8% vs 1.1%) and squamous (0.9% vs 1.1%) cell nonmelanoma skin carcinomas. Incidence of posttransplant diabetes mellitus was similar in both of the arms (19.6% vs 18.6%).

Incidence of overall infections was significantly lower in the EVR + rCNI vs MPA + sCNI arm (57.6% vs 65.6%; *P* < .001) up to month 24. In particular, viral infections, including CMV (4.3% vs 15.6%; *P* < .001) and BKV (4.5% vs 8.6%; *P* < .001), were markedly lower in the EVR + rCNI arm. The incidences of both CMV infection and syndrome were lower with EVR + rCNI at month 24 (Table 7). Moreover, the lower incidence of CMV events with EVR + rCNI was irrespective of baseline serology and prophylaxis status (Table 8).

TABLE 5 Incidence of DSA up to month 24 (safety analysis set)

	Overall population			On-treatment patients		
	EVR + rCNI, N = 475	MPA + sCNI, N = 477	*P* value[a]	EVR + rCNI, N = 475	MPA + sCNI, N = 477	*P* value[a]
DSA at baseline	M = 264	M = 296		M = 78	M = 111	
Overall, n (%)	29 (11.0)	38 (12.8)	.9138	5 (6.4)	16 (14.4)	.0444
Anti-class I, n (%)	10 (3.8)	12 (4.1)		0 (0)	7 (6.3)	
Anti-class II, n (%)	9 (3.4)	12 (4.1)		4 (5.1)	3 (2.7)	
Anti-class I + anti-class II, n (%)	10 (3.8)	14 (4.7)		1 (1.3)	6 (5.4)	
DSA at month 24	M = 445	M = 438		M = 376	M = 397	
Overall, n (%)	117 (26.3)	103 (23.5)	.7122	83 (22.1)	87 (21.9)	.9965
Anti-class I, n (%)	34 (7.6)	34 (7.8)		29 (7.7)	29 (7.3)	
Anti-class II, n (%)	44 (9.9)	38 (8.7)		32 (8.5)	34 (8.6)	
Anti-class I + anti-class II, n (%)	39 (8.8)	31 (7.1)		22 (5.9)	24 (6.0)	
De novo DSA at month 24	M = 210	M = 220		M = 57	M = 74	
Overall, n (%)	47 (22.4)	39 (17.7)	.5047	7 (12.3)	13 (17.6)	.6801
Anti-class I, n (%)	12 (5.7)	13 (5.9)		3 (5.3)	3 (4.1)	
Anti-class II, n (%)	22 (10.5)	18 (8.2)		3 (5.3)	7 (9.5)	
Anti-class I + anti-class II, n (%)	13 (6.2)	8 (3.6)		1 (1.8)	3 (4.1)	

DSA, donor-specific antibodies; EVR, everolimus; M, no. of evaluable patients; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
[a]χ^2 test.

4 | DISCUSSION

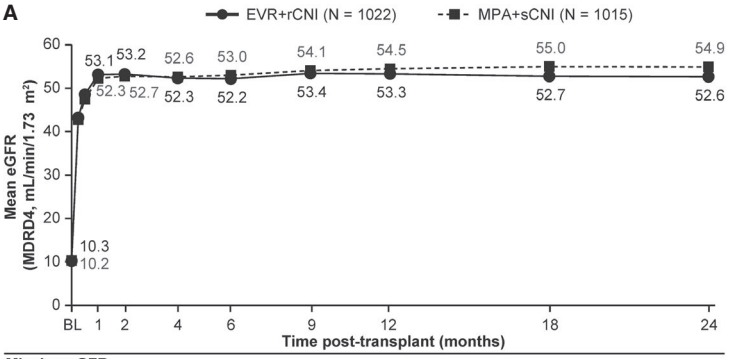
Two-year follow-up results from this study, the largest in de novo RTxRs, validate that an immunosuppression regimen combining EVR (C_0: 3-8 ng/mL) with reduced-exposure CNI is a suitable and viable alternative to standard-of-care therapy comprising MPA with standard-exposure CNI in that it maintains antirejection efficacy and facilitates the preservation of renal function via reduced CNI exposure, while providing additional benefits of significantly lower opportunistic viral infections, such as CMV and BKV, and low rates of dnDSA and overall mortality.

The noninferiority of EVR + rCNI to MPA + sCNI regimen for the primary endpoint was maintained up to 2 years posttransplantation.[26] In comparison to the A2309 study, which combined EVR with reduced-exposure CsA, the TRANSFORM study with <10% of CsA-receiving patients achieved lower overall efficacy failure and tBPAR rates at month 24 for the EVR (3-8 ng/mL) + rCNI regimen.[15] Efficacy failure rates with EVR + rCNI at month 24 in TRANSFORM were even lower than those at month 12 in US92, indicating that the early attainment of EVR target C_0 with a higher starting dose in TRANSFORM facilitated long-term benefit in immunosuppressive efficacy.[17,26] Consistent with the FAS population, between-arm differences in antirejection efficacy were not statistically significant among on-treatment patients.

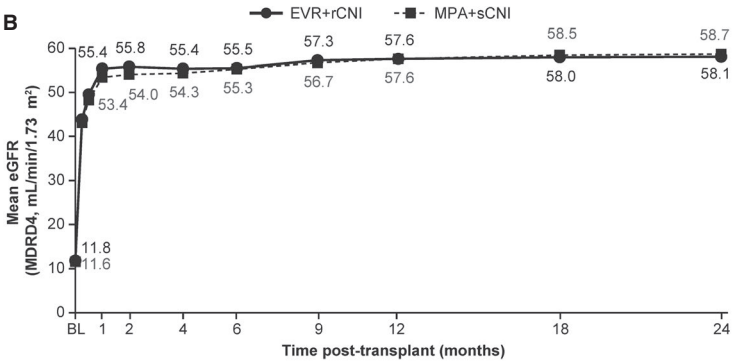
Conflicting reports exist in the literature about the association of mTORi with development of dnDSA[28,29]; while early or late conversion from CNI to EVR was associated with higher risk of dnDSA, EVR as a maintenance therapy with low-dose CNI does not increase the risk.[29-31] However, prospective studies evaluating the association between de *novo* EVR use and the development of dnDSA are scarce.[32] Our results corroborate that de novo EVR with reduced-exposure CNI is not associated with a higher incidence of dnDSA compared to standard-of-care up to 2 years posttransplantation. Despite a low number of evaluable patients at month 24, we believe that occurrence of dnDSA with the EVR + rCNI regimen does not translate into a high risk of acute and chronic ABMR and acute rejections as evident from the low and comparable incidence of these events between the 2 treatment arms.

Recent studies indicate an association between TAC reduction and dnDSA development. A TAC C_0 of <8 ng/mL significantly increased dnDSA risk in the first year after kidney or kidney/pancreas transplantation, and the risk increased with decreasing TAC C_0.[33] In a separate study, recipients with high human leukocyte antigen class II eplet mismatch scores were prone to develop dnDSA at TAC levels of <5 ng/mL.[34] In the TRANSFORM study, incidence of dnDSA was comparable in both of the treatment arms among on-treatment patients. However, the mean TAC C_0 was well above the target range (2-4 ng/mL) in the EVR + rCNI arm (5.7 ng/mL); thus, the effect of TAC reduction to <5 ng/mL on incidence of dnDSA could not be evaluated in TRANSFORM.

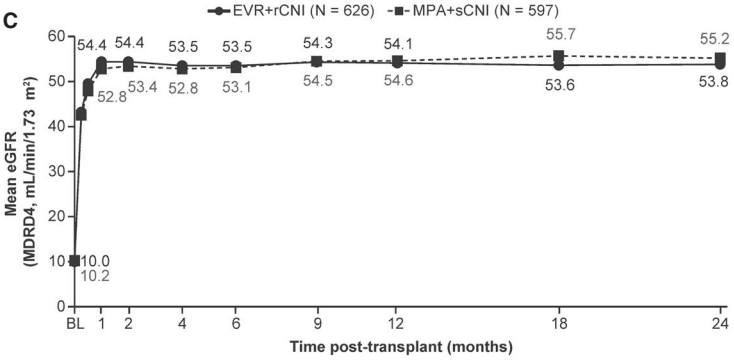
In keeping with 1-year results, renal function was stable and comparable in both treatment arms up to 2 years.[26] Although the month

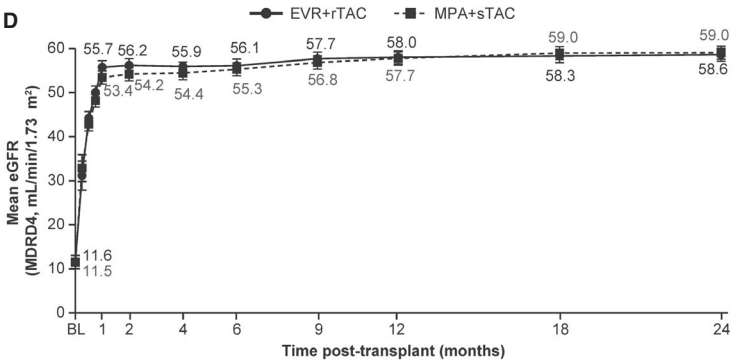


Missing eGFR values, n (%)	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	68 (6.7)	62 (6.1)	34 (3.3)	59 (5.8)	88 (8.6)	108 (10.6)	55 (5.4)	73 (7.1)	67 (6.6)	126 (12.3)	137 (13.4)
MPA+sCNI	56 (5.5)	52 (5.1)	36 (3.5)	38 (3.7)	42 (4.1)	68 (6.7)	62 (6.1)	76 (7.5)	76 (7.5)	130 (12.8)	135 (13.3)



Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	448	945	963	917	878	848	816	768	742	680	640
MPA+sCNI	498	952	966	956	937	900	865	832	816	739	719

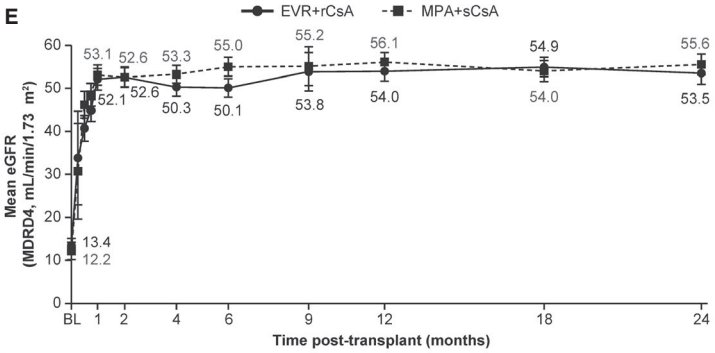




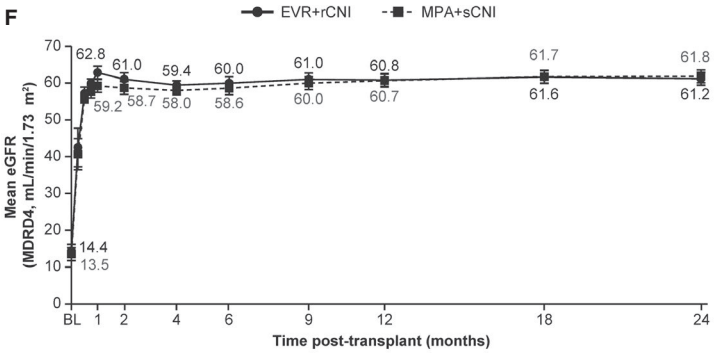
Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rTAC	404	853	867	825	788	762	732	689	665	609	573
MPA+sTAC	451	865	876	866	849	813	782	752	735	664	645

FIGURE 4 A, Mean eGFR (MDRD4) by visit window and treatment in the FAS with multiple imputation for missing eGFR. Imputation for missing eGFR values was performed by assigning a value of 0 for missings due to graft loss or using a multiple imputation method. Table indicates the number and percentage of missing eGFR values by treatment arm and visit. B, Mean eGFR (MDRD4) by visit window and treatment in the on-treatment population without multiple imputation for missing eGFR. C, Mean eGFR (MDRD4) by visit window and treatment in the FAS excluding patients with TAC above the target range in the EVR + rCNI arm and those with TAC below the target range in MPA + sCNI arm with multiple imputation for missing eGFR. Mean eGFR (MDRD4) in the on-treatment CNI subgroups (D) TAC and (E) CsA and the on-treatment donor subgroups (F) LD, (G) SCD, and (H) ECD by visit window and treatment. Data are represented as mean ± SE. BL, baseline; eGFR, estimated glomerular filtration rate; ECD, expanded criteria donor; EVR, everolimus; FAS, full analysis set; LD, living donor; M, month; MDRD, modification of diet in renal disease; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; SCD, standard-criteria donor; sCNI, standard-exposure calcineurin inhibitor; SE, standard error; TAC, tacrolimus; W, week

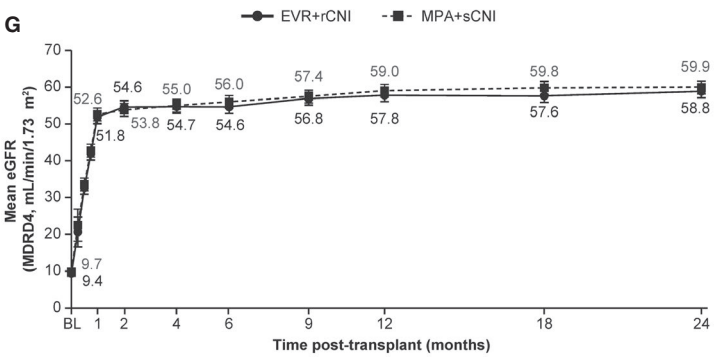
FIGURE 4 (Continued)



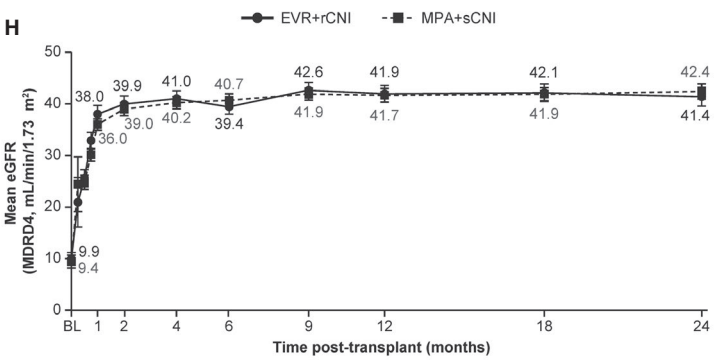
Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCsA	44	92	96	92	90	86	84	79	77	71	67
MPA+sCsA	47	87	90	90	88	87	83	80	81	75	74



Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	209	473	479	462	453	445	429	409	400	366	347
MPA+sCNI	246	474	484	483	475	463	449	431	427	394	381



Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	171	329	337	319	299	288	281	262	255	233	217
MPA+sCNI	187	321	330	324	320	303	297	289	280	246	245



Patients, N	BL	W1	W2	M1	M2	M4	M6	M9	M12	M18	M24
EVR+rCNI	66	139	142	132	123	112	104	96	86	80	75
MPA+sCNI	63	155	149	146	140	131	117	110	107	97	91

TABLE 6 Adverse events and infections at month 24 (safety analysis set)

	Month 24			Month 12 to Month 24		
Preferred term, n (%)	EVR + rCNI (N = 1014)	MPA + sCNI (N = 1012)	Risk ratio (95% CI)	EVR + rCNI (N = 1014)	MPA + sCNI (N = 1012)	Risk ratio (95% CI)
Any AE/infection	1000 (98.6)	992 (98.0)	1.01 (0.99, 1.02)	552 (54.4)	588 (58.1)	0.94 (0.87, 1.01)
Nonfatal AE/infection	628 (61.9)	621 (61.4)	1.01 (0.94, 1.08)	180 (17.8)	188 (18.6)	0.96 (0.79, 1.15)
AEs/infection leading to study drug discontinuation	276 (27.2)	152 (15.0)	1.81 (1.52, 2.16)	39 (3.8)	29 (2.9)	1.34 (0.84, 2.15)
AEs leading to dose adjustment/interruption	496 (48.9)	612 (60.5)	0.81 (0.75, 0.88)	90 (8.9)	120 (11.9)	0.75 (0.58, 0.97)
AE (≥10% in any treatment arm) up to month 24						
Blood and lymphatic system disorders	444 (43.8)	502 (49.6)	0.88 (0.80, 0.97)	54 (5.3)	61 (6.0)	0.88 (0.62, 1.26)
Anemia	238 (23.5)	242 (23.9)	0.98 (0.84, 1.15)	17 (1.7)	22 (2.2)	0.77 (0.41, 1.44)
Leukopenia	**96 (9.5)**	**201 (19.9)**	**0.48 (0.38, 0.60)**	**2 (0.2)**	**15 (1.5)**	**0.13 (0.03, 0.58)**
Gastrointestinal disorders	656 (64.7)	689 (68.1)	0.95 (0.89, 1.01)	165 (16.3)	151 (14.9)	1.09 (0.89, 1.34)
Abdominal pain	99 (9.8)	115 (11.4)	0.86 (0.67, 1.11)	17 (1.7)	24 (2.4)	0.71 (0.38, 1.31)
Constipation	246 (24.3)	243 (24.0)	1.01 (0.87, 1.18)	9 (0.9)	12 (1.2)	0.75 (0.32, 1.77)
Diarrhea	257 (25.3)	349 (34.5)	0.73 (0.64, 0.84)	68 (6.7)	66 (6.5)	1.03 (0.74, 1.43)
Nausea	191 (18.8)	229 (22.6)	0.83 (0.70, 0.99)	20 (2.0)	20 (2.0)	1.00 (0.54, 1.84)
Vomiting	122 (12.0)	151 (14.9)	0.81 (0.65, 1.01)	18 (1.8)	17 (1.7)	1.06 (0.55, 2.04)
General disorders and administration site conditions	552 (54.4)	469 (46.3)	1.17 (1.08, 1.28)	127 (12.5)	96 (9.5)	1.32 (1.03, 1.70)
Peripheral edema	**350 (34.5)**	**245 (24.2)**	**1.43 (1.24, 1.64)**	**66 (6.5)**	**39 (3.9)**	**1.69 (1.15, 2.49)**
Pyrexia	139 (13.7)	158 (15.6)	0.88 (0.71, 1.08)	27 (2.7)	27 (2.7)	1.00 (0.59, 1.69)
Infections and infestations	**698 (68.8)**	**768 (75.9)**	**0.91 (0.86, 0.96)**	**264 (26.0)**	**317 (31.3)**	**0.83 (0.72, 0.95)**
BKV infection	**59 (5.8)**	**104 (10.3)**	**0.57 (0.42, 0.77)**	8 (0.8)	14 (1.4)	0.57 (0.24, 1.35)
CMV infection	**28 (2.8)**	**137 (13.5)**	**0.20 (0.14, 0.30)**	**2 (0.2)**	**13 (1.3)**	**0.15 (0.03, 0.68)**
Nasopharyngitis	110 (10.8)	118 (11.7)	0.93 (0.73, 1.19)	37 (3.6)	42 (4.2)	0.88 (0.57, 1.36)
Upper respiratory tract infection	85 (8.4)	104 (10.3)	0.82 (0.62, 1.07)	39 (3.8)	33 (3.3)	1.18 (0.75, 1.86)
Urinary tract infection	259 (25.5)	287 (28.4)	0.90 (0.78, 1.04)	58 (5.7)	78 (7.7)	0.74 (0.53, 1.03)
Investigations	463 (45.7)	439 (43.4)	1.05 (0.96, 1.16)	92 (9.1)	94 (9.3)	0.98 (0.74, 1.28)
Increased blood creatinine	175 (17.3)	159 (15.7)	1.10 (0.90, 1.34)	28 (2.8)	29 (2.9)	0.96 (0.58, 1.61)
Metabolism and nutrition disorders	752 (74.2)	725 (71.6)	1.04 (0.98, 1.09)	137 (13.5)	147 (14.5)	0.93 (0.75, 1.15)
Diabetes mellitus	139 (13.7)	127 (12.5)	1.09 (0.87, 1.37)	13 (1.3)	10 (1.0)	1.30 (0.57, 2.95)
Hypercholesterolemia	103 (10.2)	61 (6.0)	1.69 (1.24, 2.28)	11 (1.1)	10 (1.0)	1.10 (0.47, 2.57)
Hyperglycemia	143 (14.1)	148 (14.6)	0.96 (0.78, 1.19)	12 (1.2)	9 (0.9)	1.33 (0.56, 3.14)
Hyperkalemia	170 (16.8)	186 (18.4)	0.91 (0.76, 1.10)	9 (0.9)	13 (1.3)	0.69 (0.30, 1.61)
Hyperlipidemia	**136 (13.4)**	**75 (7.4)**	**1.81 (1.38, 2.37)**	15 (1.5)	19 (1.9)	0.79 (0.40, 1.54)
Hypocalcemia	110 (10.8)	99 (9.8)	1.11 (0.86, 1.43)	9 (0.9)	3 (0.3)	2.99 (0.81, 11.03)
Hypokalemia	150 (14.8)	87 (8.6)	1.72 (1.34, 2.21)	11 (1.1)	8 (0.8)	1.37 (0.55, 3.40)
Hypomagnesemia	134 (13.2)	169 (16.7)	0.79 (0.64, 0.98)	7 (0.7)	13 (1.3)	0.54 (0.22, 1.34)
Hypophosphatemia	190 (18.7)	168 (16.6)	1.13 (0.93, 1.36)	7 (0.7)	6 (0.6)	1.16 (0.39, 3.45)
Metabolic acidosis	77 (7.6)	101 (10.0)	0.76 (0.57, 1.01)	7 (0.7)	10 (1.0)	0.70 (0.27, 1.83)
Nervous system disorders	311 (30.7)	344 (34.0)	0.90 (0.80, 1.02)	61 (6.0)	67 (6.6)	0.91 (0.65, 1.27)
Headache	136 (13.4)	116 (11.5)	1.17 (0.93, 1.48)	28 (2.8)	24 (2.4)	1.16 (0.68, 1.99)
Tremor	**102 (10.1)**	**145 (14.3)**	**0.70 (0.55, 0.89)**	**4 (0.4)**	**14 (1.4)**	**0.29 (0.09, 0.86)**

(Continues)

TABLE 6 (Continued)

Preferred term, n (%)	Month 24			Month 12 to Month 24		
	EVR + rCNI (N = 1014)	MPA + sCNI (N = 1012)	Risk ratio (95% CI)	EVR + rCNI (N = 1014)	MPA + sCNI (N = 1012)	Risk ratio (95% CI)
Psychiatric disorders	207 (20.4)	246 (24.3)	0.84 (0.71, 0.99)	18 (1.8)	26 (2.6)	0.69 (0.38, 1.25)
Insomnia	100 (9.9)	138 (13.6)	0.72 (0.57, 0.92)	8 (0.8)	9 (0.9)	0.89 (0.34, 2.29)
Renal and urinary disorders	497 (49.0)	487 (48.1)	1.02 (0.93, 1.11)	96 (9.5)	92 (9.1)	1.04 (0.79, 1.37)
Hematuria	110 (10.8)	114 (11.3)	0.96 (0.75, 1.23)	19 (1.9)	14 (1.4)	1.35 (0.68, 2.69)
Proteinuria	**143 (14.1)**	**71 (7.0)**	**2.01 (1.53, 2.64)**	23 (2.3)	17 (1.7)	1.35 (0.73, 2.51)
Respiratory, thoracic, and mediastinal disorders	302 (29.8)	306 (30.2)	0.99 (0.86, 1.13)	77 (7.6)	73 (7.2)	1.05 (0.77, 1.43)
Cough	86 (8.5)	104 (10.3)	0.83 (0.63, 1.08)	19 (1.9)	24 (2.4)	0.79 (0.44, 1.43)
Vascular disorders	426 (42.0)	397 (39.2)	1.07 (0.96, 1.19)	69 (6.8)	67 (6.6)	1.03 (0.74, 1.42)
Hypertension	241 (23.8)	233 (23.0)	1.03 (0.88, 1.21)	27 (2.7)	34 (3.4)	0.79 (0.48, 1.30)

AEs, adverse events; BKV, BK virus; CI, confidence interval; CMV, cytomegalovirus; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.
Bold values represent statistically significant between-arm differences based on relative risk.

24 eGFR was lower in patients receiving EVR + rCNI (−2.3 mL/min per 1.73 m^2), the difference was not clinically relevant. In general, >40% of patients in both treatment arms had eGFR <50 mL/min per 1.73 m^2 at months 12 and 24. Mean eGFR in the EVR + rCNI arm at month 24 in TRANSFORM (52.6 mL/min per 1.73 m^2) was comparable to that observed at 2 years in the A2309 study (52.2 mL/min per 1.73 m^2).[15] The absence of renal function benefit with the EVR + rCNI regimen could be partly explained by the fact that a large proportion of patients did not attain the recommended CNI target range in the EVR + rCNI arm. Poor adherence to protocol-defined CNI target ranges could be attributed to the widely different local center practices in using EVR-based immunosuppression in combination with reduced-dose TAC or CsA. Results from the SYMPHONY trial indicated that adhering to lower predefined drug levels is challenging in the clinical setting.[12,13] TRANSFORM was the first study to aim for a TAC C_0 of 2-5 ng/mL for months 3-6 and 2-4 ng/mL beyond month 6 in combination with EVR, which were lower than those used in earlier studies such as US92.[17] The CsA C_0 in TRANSFORM in the early posttransplant period were also lower than those in the A2309 study.[14] These stringent recommendations for CNI C_0 reduction in TRANSFORM could have led to poorer CNI adherence and suboptimal renal function benefit. In this context, exposure-response analyses from the A2309 and US92 studies showed that among patients with EVR C_0 of 3-8 ng/mL, renal dysfunction (low [<30 mL/min per 1.73 m^2] or decreased eGFR) was highest with month 24 CsA C_0 ≥100 ng/mL and month 12 TAC C_0 ≥5 ng/mL, respectively.[20,35] Given the limitation with adherence to protocol-defined CNI levels, we suggest that recommendations for CNI adherence in clinical practice should be based on actual drug concentrations instead of protocol-defined levels.

The occurrence of most AEs at month 24 was consistent with the known safety profiles of EVR, MPA, and CNIs.[12-17] Given the high immunosuppression load in the early posttransplant period, AEs were more frequent in the first 12 months in both arms. In line with the month 12 findings, the incidence of AEs leading to study drug discontinuation was higher in the EVR + rCNI arm, whereas the incidence of AEs leading to dose adjustment was higher in the MPA + sCNI arm.[26] A similar trend toward higher discontinuation due to AEs with the EVR + rCNI regimen was observed in the A2309 study at month 24.[15] This trend indicates a general tendency toward discontinuing EVR or switching to standard CNI more readily than adjusting EVR dose to manage related AEs.[32]

Consistent with previous studies, the EVR + rCNI regimen offered significant protection from viral infections up to 24 months,[14,15,17-20,22,26,36] thereby confirming the antiviral effect of EVR even in the presence of TAC levels above target range. Of interest, the CMV incidence was also significantly lower with EVR + rCNI in high-risk (D+/R−) patients. In a recent study in D+/R− patients, EVR + rTAC (3-5 ng/mL) did not significantly reduce the CMV infection rate, but delayed infection onset and showed a trend toward lower recurrence vs MPA + TAC (5-10 ng/mL) or azathioprine + TAC (5-10 ng/mL).[36] The very high TAC C_0 of 5-15 ng/mL in addition to potent induction therapy with rabbit antithymocyte globulin and steroids in all 3 groups during the first 3 months could have undermined the benefit of EVR in this study.

Because of its latency in the kidney, BKV commonly affects RTxRs and can manifest with various renal complications such as interstitial nephritis, gradual renal dysfunction, and BK-associated nephropathy.[7] TAC-based immunosuppressive regimen is associated with a high risk of BKV incidence, replication, and/or associated nephropathy.[37-39] Conflicting reports exist in the literature regarding the role of EVR in preventing BKV infections, with some studies showing no or only slight benefit of EVR.[21,40] In this regard, it is interesting that the benefit of significantly lower incidence of BKV infections in the EVR + rCNI vs MPA + sCNI arm was maintained up to 2 years in TRANSFORM. Whether this effect was a result of lower TAC exposure or a direct effect of EVR on viral replication needs further investigation.

In daily practice, not all patients can be initiated or maintained on the standard-of-care regimen. TRANSFORM, as the largest study in de

TABLE 7 BKV- and CMV-related information at month 24 (safety analysis set)

	EVR + rCNI (1014), n (%)	MPA + sCNI (N = 1012), n (%)
BKV-related information		
Any BKV infection	103 (10.2)	154 (15.2)
BKV infection with a urinary or serological sign	102 (10.1)	154 (15.2)
Clinical- or laboratory-indicated BKV infection	47 (4.6)	72 (7.1)
BKV infection with organ involvement (histological evidence)	17 (1.7)	25 (2.5)
CMV-related information		
Clinical signs of CMV infection assessed	53 (5.2)	132 (13.0)
CMV syndrome	18 (1.8)	59 (5.8)
Histological signs for CMV	2 (0.2)	8 (0.8)
Histological organ examination		
Colon	3 (0.3)	4 (0.4)
Kidney	2 (0.2)	7 (0.7)
Liver	0 (0.0)	0 (0.0)
Lung	0 (0.0)	0 (0.0)
Other	2 (0.2)	4 (0.4)

BKV, BK virus; CMV, cytomegalovirus; EVR, everolimus; MPA, mycophenolic acid; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.

TABLE 8 CMV events at month 24 by baseline serology and prophylaxis status (safety analysis set)

	EVR + rCNI, N = 1014, n/M (%)	MPA + sCNI, N = 1012, n/M (%)	*P* value
CMV serology status at baseline			(1)
Total	88/1014 (8.7)	225/1012 (22.2)	<.0001
D+/R+	39/509 (7.7)	128/518 (24.7)	<.0001
D+/R−	30/151 (19.9)	60/139 (43.2)	<.0001
D−/R+	11/142 (7.7)	19/147 (12.9)	.1490
D−/R−	3/168 (1.8)	8/168 (4.8)	.1253
With prophylaxis			(2)
Total	44/530 (8.3)	92/520 (17.7)	<.001
D+/R+	13/242 (5.4)	33/257 (12.8)	.004
D+/R−	24/128 (18.8)	45/103 (43.7)	<.001
D−/R+	4/71 (5.6)	8/79 (10.1)	.312
D−/R−	2/67 (3.0)	5/64 (7.8)	.219
Without prophylaxis			(2)
Total	44/484 (9.1)	133/492 (27.0)	<.001
D+/R+	26/267 (9.7)	95/261 (36.4)	<.001
D+/R−	6/23 (26.1)	15/36 (41.7)	.222
D−/R+	7/71 (9.9)	11/68 (16.2)	.267
D−/R−	1/101 (1.0)	3/104 (2.9)	.327

(1) *P* value for χ^2 test. (2) *P* value for Cochran-Mantel-Haenszel test.
CMV, cytomegalovirus; D, donor; EVR, everolimus; M, number of evaluable patients; MPA, mycophenolic acid; R, recipient; rCNI, reduced-exposure calcineurin inhibitor; sCNI, standard-exposure calcineurin inhibitor.

novo RTxRs to date, captured real-world evidence from 186 centers worldwide with widely differing experience levels in using EVR-based immunosuppression and unequivocally established the noninferiority of the EVR + rCNI regimen to the current standard-of-care. The study findings provided guidance on de novo use of EVR depending on initial transplant characteristics within the broad range of eligibility criteria,

and regardless of donor type, induction agent, and CNI combination. Nevertheless, exclusion of patients with high immunological risk and inclusion of only ≈4% of black patients limit the generalizability of the results. Furthermore, poor adherence to protocol-defined CNI C_0 yielding an overall compliance of ≈20% and absence of follow-up beyond 2 years are key limitations of the study. Given the open-label design, introduction of investigator bias during the reporting of AEs and discontinuation of study drugs cannot be excluded. The suboptimal adherence to CNI target levels is a major limitation of our study, and conclusions concerning the study endpoints including renal function and rejection risk only apply to the drug exposure that was actually achieved.

In de novo RTxRs with low-to-moderate immunological risk, the EVR + rCNI regimen is a valid alternative to the standard-of-care regimen comprising MPA + sCNI, providing comparable antirejection efficacy, stable renal function, and low rates of mortality and dnDSA, with an advantage of significantly reduced viral infections, up to 2 years posttransplantation.

ACKNOWLEDGMENTS

The authors thank Prachiti Narvekar, Novartis Healthcare Pvt. Ltd., for medical writing support and editorial assistance. The TRANSFORM study was funded by Novartis Pharma AG, Basel, Switzerland.

AUTHOR CONTRIBUTIONS

J.P., H.T., S.C., F.O., C.S., 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., Y.Q., J.W.d.F., J.M.C., and P.M. recruited patients and collected data. M-P.H-G undertook the statistical analyses. A-M.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.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*: S.P.B. is a member of advisory boards for Astellas, Chiësi, and Novartis (all payments made to institution) and has received travel support from Chiësi and Astellas. C.S. has received institutional research grants from Novartis, Chiësi, and Astellas. O.W. has received research funds and/or honoraria from Amgen, Alexion, Astellas, Basilea, Biotest, Bristol-Myers Squibb, Correvio, Chiësi, Gilead, Hexal, Janssen, Dr. F. Köhler Chemie, MSD, Novartis, Roche, Pfizer, Sanofi, and TEVA. 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.C. has received institutional research funding, travel support or consulting honoraria from Novartis, Astellas and Alexion. S.M. has received research grants from Novartis and Astellas. Y.Q. has received speaker's honoraria from Alexion, Mallinckrodt, and Relypssa. J.W.deF. has received research grants from Astellas, BMS, and Novartis. F.O. has received speaker fees and travel support from Novartis. J.M.C. has received honoraria from Sandoz and Novartis and travel grants from Chiesi. Y.W. has received speaker fees and travel support from Novartis. P.M. has received research honoraria from Novartis Argentina and Squibb Bristol Myers Argentina. C.L. has received travel grants from Astellas, Novartis, Chiesi, Genzyme, and CSL Behring and speaker fees from Astellas, Novartis, Genzyme, and Alexion. F.C. has received consulting honoraria and travel grants from Novartis and Astellas. M.H. has received consulting honoraria from Novartis. T.R.S. has received study grants and speakers' honoraria from Novartis. F.V. has received research grants from Novartis, Astellas, Genentech, Bristol Myers Squibb, Angion Pharmaceuticals, Merck, and Pfizer. M-P.H-G., A-M.M., and P.B. are employees of Novartis. J.P. has received consulting honoraria from Novartis and Chiesi, travel grants from Novartis and Chiesi, and his institution has received research grants from Novartis, Astellas, Chiesi, and Amgen.

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).

ORCID

Helio Tedesco https://orcid.org/0000-0002-9896-323X
Christophe Legendre https://orcid.org/0000-0002-1743-2948
Flavio Vincenti https://orcid.org/0000-0002-6701-4680

REFERENCES

1. Chapman JR. Chronic calcineurin inhibitor nephrotoxicity-lest we forget. *Am J Transplant*. 2011;11(4):693-697.
2. Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. *Am J Nephrol*. 2013;37(6):602-612.
3. Sprangers B, Nair V, Launay-Vacher V, et al. Risk factors associated with post-kidney transplant malignancies: an article from the Cancer-Kidney International Network. *Clin Kidney J*. 2018;11(3):315-329.
4. Singh N. Infectious complications in organ transplant recipients with the use of calcineurin-inhibitor agent-based immunosuppressive regimens. *Curr Opin Infect Dis*. 2005;18(4):342-345.
5. Hojo M, Morimoto T, Maluccio M, et al. Cyclosporine induces cancer progression by a cell-autonomous mechanism. *Nature*. 1999;397(6719):530-534.
6. Maluccio M, Sharma V, Lagman M, et al. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. *Transplantation*. 2003;76(3):597-602.
7. Weikert BC, Blumberg EA. Viral infection after renal transplantation: surveillance and management. *Clin J Am Soc Nephrol*. 2008;3(Suppl 2):S76-S86.
8. Erdbruegger U, Scheffner I, Mengel M, et al. Impact of CMV infection on acute rejection and long-term renal allograft function: a

systematic analysis in patients with protocol biopsies and indicated biopsies. *Nephrol Dial Transplant*. 2012;27(1):435-443.
9. Sagedal S, Hartmann A, Nordal KP, et al. Impact of early cytomegalovirus infection and disease on long-term recipient and kidney graft survival. *Kidney Int*. 2004;66(1):329-337.
10. Jouve T, Noble J, Rostaing L, et al. Tailoring tacrolimus therapy in kidney transplantation. *Expert Rev Clin Pharmacol*. 2018;11(6):581-588.
11. Witzke O, Sommerer C, Arns W. Everolimus immunosuppression in kidney transplantation: what is the optimal strategy? *Transplant Rev (Orlando)*. 2016;30(1):3-12.
12. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med*. 2007;357(25):2562-2575.
13. Ekberg H, Bernasconi C, Tedesco-Silva H, et al. Calcineurin inhibitor minimization in the Symphony study: observational results 3 years after transplantation. *Am J Transplant*. 2009;9(8):1876-1885.
14. Tedesco Silva Jr H, Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant*. 2010;10(6):1401-1413.
15. Cibrik D, Silva HT Jr, Vathsala A, et al. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. *Transplantation*. 2013;95(7):933-942.
16. Langer RM, Hene R, Vitko S, et al. Everolimus plus early tacrolimus minimization: a phase III, randomized, open-label, multicentre trial in renal transplantation. *Transpl Int*. 2012;25(5):592-602.
17. Qazi Y, Shaffer D, Kaplan B, et al. Efficacy and safety of everolimus plus low-dose tacrolimus versus mycophenolate mofetil plus standard-dose tacrolimus in de novo renal transplant recipients: 12-month data. *Am J Transplant*. 2017;17(5):1358-1369.
18. Nashan B, Gaston R, Emery V, et al. Review of cytomegalovirus infection findings with mammalian target of rapamycin inhibitor-based immunosuppressive therapy in de novo renal transplant recipients. *Transplantation*. 2012;93(11):1075-1085.
19. Brennan DC, Legendre C, Patel D, et al. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: pooled analysis of three clinical trials. *Am J Transplant*. 2011;11(11):2453-2462.
20. Shihab F, Qazi Y, Mulgaonkar S, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving low doses of tacrolimus. *Am J Transplant*. 2017;17(9):2363-2371.
21. Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV infections in renal transplant recipients receiving an mTOR inhibitor-based regimen versus a CNI-based regimen: a systematic review and meta-analysis of randomized, controlled trials. *Clin J Am Soc Nephrol*. 2017;12(8):1321-1336.
22. Devresse A, Leruez-Ville M, Scemla A, et al. Reduction in late onset cytomegalovirus primary disease after discontinuation of antiviral prophylaxis in kidney transplant recipients treated with de novo everolimus. *Transpl Infect Dis*. 2018;20(2):e12846.
23. Pascual J, Srinivas T, Chadban S, et al. TRANSFORM: a novel study design to evaluate the effect of everolimus on long-term outcomes after kidney transplantation. *Open Access J Clin Trials*. 2014;6:45-54.
24. Kasiske BL, Israni AK, Snyder JJ, et al.; Patient Outcomes in Renal Transplantation I. The relationship between kidney function and long-term graft survival after kidney transplant. *Am J Kidney Dis*. 2011;57(3):466-475.
25. Srinivas TR, Oppenheimer F. Identifying endpoints to predict the influence of immunosuppression on long-term kidney graft survival. *Clin Transplant*. 2015;29(7):644-653.
26. Pascual J, Berger SP, Witzke O, et al. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. *J Am Soc Nephrol*. 2018;29(7):1979-1991.
27. Tedesco-Silva H, Pascual J, Viklicky O, et al. Safety of everolimus with reduced calcineurin inhibitor exposure in de novo kidney transplants: an analysis from the randomized TRANSFORM study. *Transplantation*. 2019; https://doi.org/10.1097/tp.0000000000002626 [Epub ahead of print].
28. O'Leary JG, Samaniego M, Barrio MC, et al. The influence of immunosuppressive agents on the risk of de novo donor-specific HLA antibody production in solid organ transplant recipients. *Transplantation*. 2016;100(1):39-53.
29. Perbos E, Juinier E, Guidicelli G, et al. Evolution of donor-specific antibodies (DSA) and incidence of de novo DSA in solid organ transplant recipients after switch to everolimus alone or associated with low dose of calcineurin inhibitors. *Clin Transplant*. 2014;28(9):1054-1060.
30. Budde K, Zeier M, Witzke O, et al. Everolimus with cyclosporine withdrawal or low-exposure cyclosporine in kidney transplantation from Month 3: a multicentre, randomized trial. *Nephrol Dial Transplant*. 2017;32(6):1060-1070.
31. Liefeldt L, Brakemeier S, Glander P, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. *Am J Transplant*. 2012;12(5):1192-1198.
32. Pascual J, Diekmann F, Fernandez-Rivera C, et al. Recommendations for the use of everolimus in de novo kidney transplantation: false beliefs, myths and realities. *Nefrologia*. 2017;37(3):253-266.
33. Davis S, Gralla J, Klem P, et al. Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation. *Am J Transplant*. 2018;18(4):907-915.
34. Wiebe C, Rush DN, Nevins TE, et al. Class II eplet mismatch modulates tacrolimus trough levels required to prevent donor-specific antibody development. *J Am Soc Nephrol*. 2017;28(11):3353-3362.
35. Shihab FS, Cibrik D, Chan L, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. *Clin Transplant*. 2013;27(2):217-226.
36. Cristelli MP, Esmeraldo RM, Pinto CM, et al. The influence of mTOR inhibitors on the incidence of CMV infection in high-risk donor positive-recipient negative (D+/R−) kidney transplant recipients. *Transpl Infect Dis*. 2018;20(4):e12907.
37. Suwelack B, Malyar V, Koch M, et al. The influence of immunosuppressive agents on BK virus risk following kidney transplantation, and implications for choice of regimen. *Transplant Rev (Orlando)*. 2012;26(3):201-211.
38. Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant*. 2005;5(3):582-594.
39. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med*. 2002;347(7):488-496.
40. van Doesum WB, Gard L, Bemelman FJ, et al. Incidence and outcome of BK polyomavirus infection in a multicenter randomized controlled trial with renal transplant patients receiving cyclosporine-, mycophenolate sodium-, or everolimus-based low-dose immunosuppressive therapy. *Transpl Infect Dis*. 2017;19(3):e12687.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Berger SP, Sommerer C, Witzke O, et al. Two-year outcomes in de novo renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from the TRANSFORM study. *Am J Transplant*. 2019;00:1-17. https://doi.org/10.1111/ajt.15480