Table 1. Summary of randomized controlled trials of everolimus in liver transplantation

References	Study design	Study population	Treatment groups	Key results	
				Efficacy	Renal function
De Simone et al, 2012 Saliba et al, 2013 (H2304)	24-month prospective, randomized, multicenter, open-label study	De novo liver transplant recipients	EVR + reduced TAC (N=245): EVR C0 3–8 ng/mL and TAC C0 3–5 ng/mL TAC control (N=243): TAC C0 8–12 ng/mL until month 4 and C0 6–10 ng/mL thereafter TAC-withdrawal (N=231): EVR C0 6–12 ng/mL with CNI elimination at month 4	Comparable composite efficacy failure rate at month 12* and month 24 between EVR + reduced TAC and TAC control	Superior renal function assessed by eGFR in EVR + reduced TAC group compared with TAC control
Fischer et al, 2015	36-month prospective, randomized, multicenter, open-label study	De novo liver transplant recipients	EVR + reduced TAC (N=245): EVR C0 3–8 ng/mL and TAC C0 3–5 ng/mL TAC control (N=243): TAC C0 8–12 ng/mL until month 4 and C0 6–10 ng/mL thereafter TAC-withdrawal (N=231): EVR C0 6–12 ng/mL with CNI elimination at month 4	The composite efficacy failure endpoint (tBPAR, graft loss or death) occurred in 11.5% of EVR+Reduced TAC patients versus 14.6% TAC Controls from randomization to month 36 (difference, -3.2%; 95% confidence interval, -10.5% to 4.2%; P = 0.334). Treated BPAR occurred in 4.8% versus 9.2% of patients (P = 0.076).	From randomization to month 36, mean (SD) estimated glomerular filtration rate decreased by 7.0 (31.3) mL/min per 1.73 m2 in the EVR+Reduced TAC group, and 15.5 (22.7) mL/min per 1.73 m2 in the TAC Control group (P = 0.005).
Sterneck et al, 2014	24-month, prospective, randomized, multicenter, open-label study	De novo liver transplant recipients	Liver transplant patients were randomized at 4 weeks to start everolimus and discontinue CNI, or continue their current CNI-based regimen.	Biopsy-proven acute rejection, graft loss and death were similar between groups. Adverse events led to study drug discontinuation in five CNI-free patients and five CNI	The adjusted mean eGFR benefit from randomization to month 35 was 10.1 mL/min (95% confidence interval [CI] −1.3, 21.5 mL/min, p = 0.082) in favor of CNI-free versus CNI using Cockcroft-Gault,

				patients (12.2% vs. 12.5%, p = 1.000) during the extension phase.	9.4 mL/min/1.73 m2 (95% CI −0.4, 18.9, p = 0.053) with Modification of Diet in Renal Disease (four-variable) and 9.5 mL/min/1.73 m2 (95% CI −1.1, 17.9, p = 0.028) using Nankivell.
Sterneck et al, 2016	60-month, prospective, randomized, multicenter, open-label study	De novo liver transplant recipients	Liver transplant patients were randomized at 4 weeks to start everolimus and discontinue CNI, or continue their current CNI-based regimen.	At M59 post-randomization, the adjusted mean eGFR was significantly higher in the EVR group, with a benefit of 12.4 mL/min using Cockcroft-Gault (95% CI: 1.2; 23.6; p = 0.0301). Also, there was a significant benefit for adjusted and unadjusted eGFR using the four-variable Modification of Diet in Renal Disease (MDRD4) or Nankivell formula.	During the extension period, treatment failure rates were similar. SAEs occurred in 26 (63.4%) and 28 (70.0%) of the patients in EVR and CNI groups, respectively.
Fischer et al, 2012 (PROTECT)	12-month prospective, randomized, multicenter, open-label study	De novo liver transplant recipients	EVR (N=101): EVR C0 5–12 ng/mL (C0 8–12 ng/mL with CsA) Control (N=102): CNI-based regimen	Similar incidence of graft loss and rejection episodes	No significant difference in mean calculated GFR (Cockcroft-Gault) at 11 months postrandomization* Significant improvement in GFR using Modification of Diet in Renal Disease in favor of EVR at month 11
Masetti et al, 2010	12-month, prospective, randomized, single-center, open-label study	De novo liver transplant recipients	Early CNI withdrawal followed by EVR monotherapy (N=52): C0 6–10 ng/mL until day 30, 8–12 ng/mL until the end of month 6 and 6–10 ng/mL thereafter Standard CsA (N=26): C0 225±25 ng/mL until day 30, then 200±25 ng/mL	Similar incidence of acute rejection	Significant improvement in renal function (eGFR, Modification of Diet in Renal Disease 4) at Month 12 in the EVR group versus CsA group*

			until the end of month 6 and 150±25 ng/mL thereafter		
Levy et al, 2006 (B158 study)	12-month randomized, double-blind, placebo-controlled study (with 24-month open-label extension)	De novo liver transplant recipients	EVR 1 mg/day + CsA (N=28) EVR 2 mg/day + CsA (N=30) EVR 4 mg/day + CsA (N=31) Placebo + CsA (N=30)	Similar incidence of composite efficacy failure between groups and lower rate of treated acute rejections in the EVR group versus placebo	Stable serum creatinine and creatinine clearance from month 1 onward

Notes:

*Indicates primary endpoint. Composite efficacy failure = treated biopsy-proven acute rejection, graft loss, or death.

Abbreviations: EVR, everolimus; TAC, tacrolimus; C0, trough level; CNI, calcineurin inhibitor; eGFR, estimated glomerular filtration rate; PROTECT, Prevention of Transplant Atherosclerosis With Everolimus and Anti-cytomegalovirus Therapy; CsA, cyclosporine.