Balancing Efficacy and Renal Function Preservation after Kidney Transplantation with Everolimus and Reduced Calcineurin Inhibitors for Better Graft Outcomes: Design of the TRANSFORM Study

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Background

- Acute rejection and poor graft function are the two well-defined, modifiable risk factors for allograft failure at one year post kidney transplantation (KTx)[1]
- Chronic allograft vasculopathy, cardiovascular (CV) disease and malignancies are leading causes of mortality and the rate of renal graft function decline after the first year post-transplant is a significant predictor of all-cause mortality in KTx[2,3]
- Calcineurin inhibitor (CNI)-based immunosuppression offers good short-term efficacy but has been shown to be a major contributor of renal dysfunction after KTx[4]
- Previous studies have shown that everolimus (EVR) facilitated-CNI exposure reduction in kidney transplant recipients (KTxR) starting on EVR within the first month after KTx can lead to improved renal function in the long term[5, 6]
- Here, we present the design of TRANSFORM (**TRANS**plant e**F**ficacy and safety **O**utcomes with an eve**R**olimus-based regi**M**en), an ongoing large phase IV study to evaluate the efficacy and safety of two immunosuppressive regimens [EVR-facilitated reduced (r) CNI exposure versus mycophenolic acid (MPA) plus standard (s) CNI exposure] in adult de novo KTx recipients

Study Objectives

Primary objective

- To evaluate the effect of EVR with reduced exposure to CNI vs. MPA with standard exposure to CNI on the composite of treated biopsy-proven acute rejection (tBPAR) rate or proportion of KTxR with estimated glomerular filtration rate (eGFR) <50 mL/min/1.73m² (eGFR calculated by modified diet for renal diseases-4 [MDRD-4] formula) at Month 12 post-transplantation

Key secondary objectives

- To evaluate composite efficacy failure (tBPAR, graft loss, or death) at Month 12 post-transplantation
- To evaluate the binary composite endpoint of tBPAR or eGFR < 50 mL/min/1.73m² (MDRD4 formula) at Month 12 among compliant subjects

Other secondary objectives included (evaluated by treatment group)

- The incidence of composite endpoint of tBPAR or eGFR <50 mL/min/1.73m² (MDRD-4 formula) at Month 24
- The incidence of composite endpoint of tBPAR, graft loss, eGFR <50 mL/min/1.73m² or death at Months 12 and 24
- Renal allograft function measured by eGFR at Months 12 and 24
- The evolution of renal function over time by eGFR slope analysis
- The incidence of adverse events (AEs) including any AEs leading to study regimen discontinuation and serious AEs
- The incidence of CMV and BKV infections, new onset diabetes mellitus and chronic kidney disease with associated proteinuria
- The incidence of major cardiovascular (CV) events and malignancies

Exploratory objectives (in subsets of patients)

- Explore the incidence of donor-specific antibodies (DSA) by treatment group, and in relation to acute rejection
- Assess the development of chronic allograft nephropathy/interstitial fibrosis and tubular atrophy (CAN/IFTA) by renal protocol biopsy

Methods

Study design

- TRANSFORM **(NCT01950819)** is a 24M, multi-centre, open-label, randomised, two-arm study in adult *de novo* KTxR with an observational follow-up extending to five years post-Tx
- Patients fulfilling the eligibility criteria will be randomised to EVR+rCNI or MPA+sCNI arm (1:1) with basiliximab or antithymocyte globulin induction and steroids **(Figure 1)**.
- Randomisation strata include donor type (living donors, deceased standard criteria donors, or deceased expanded criteria donors) and CNI usage (cyclosporine [CsA] or tacrolimus [TAC])

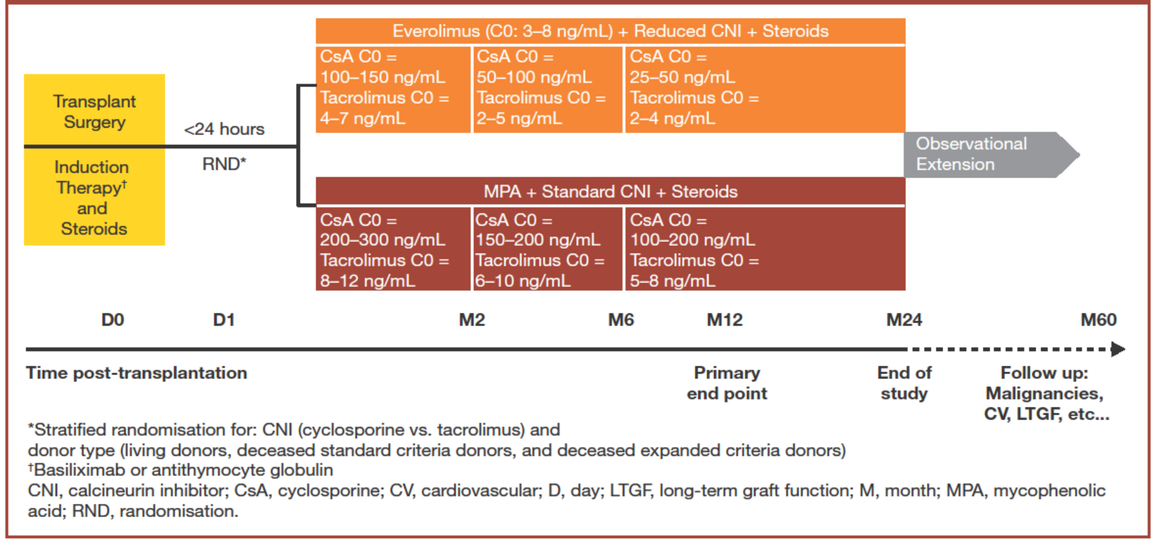
Treatment period

- Patients will be randomised into two study arms within 24 h post-transplant for a treatment period of 24 months
- Patients completing 24 months of treatment will be able to participate in a 36-months observational extension study, with outcomes analysed up to 5 years post-Tx which will include patient and graft survival, eGFR and incidence of CV disease, malignancies, and infection

Key inclusion criteria

- Male or female patients aged ≥18 years old and randomised within 24 h of transplant surgery
- Recipient of a kidney with a cold ischemia time <30 hours
- Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal allograft from a deceased heart beating donor, or from a living unrelated, or living related non-human leukocyte antigen (HLA) identical donor, or from an expanded criteria donor (ECD) ECD was defined as:
  - Brain-dead donor >60 years old or
  - Donor age >50 years old with two of the following criteria:
    - History of hypertension
    - Terminal serum creatinine ≥1.5 mg/dL
    - Death resulting from cerebrovascular accident

Figure 1. Study design



*Stratified randomisation for: CNI (cyclosporine vs. tacrolimus) and donor type (living donors, deceased standard criteria donors, and deceased expanded criteria donors)
†Basiliximab or antithymocyte globulin
CNI, calcineurin inhibitor; CsA, cyclosporine; CV, cardiovascular; D, day; LTGF, long-term graft function; M, month; MPA, mycophenolic acid; RND, randomisation.

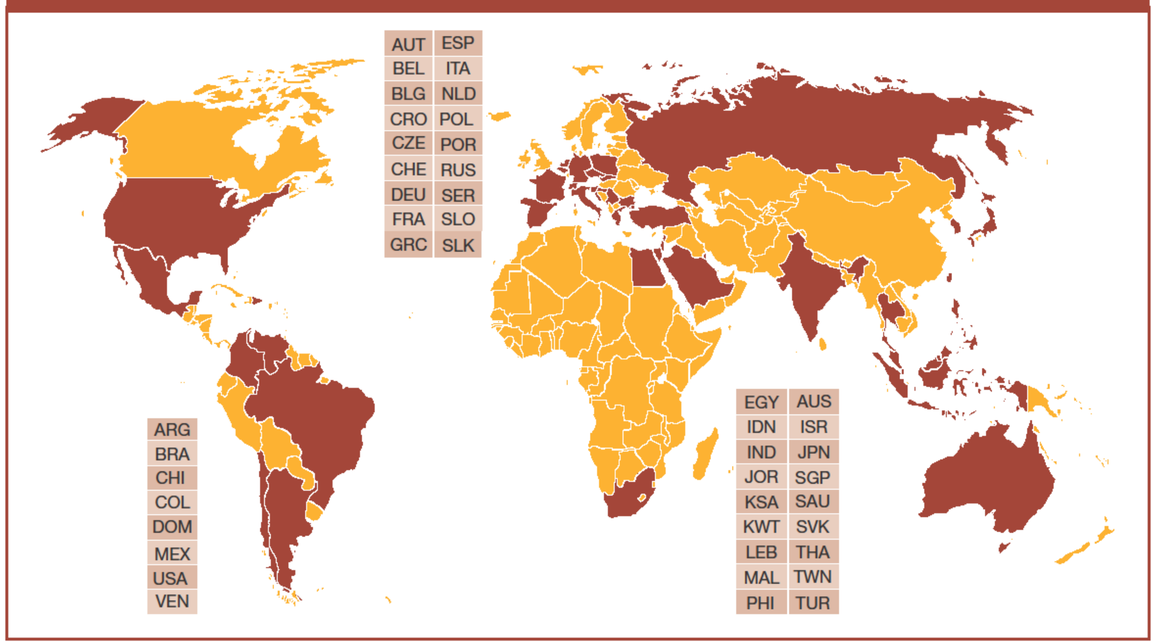
Key exclusion criteria

- Multi-organ transplant recipient
- Patients who are unable to tolerate oral medication at the time of randomisation
- Usage of other investigational drugs within 30 days or five drug half-lives of enrolment, except for dialysis related drugs
- ABO incompatible allograft or complement-dependent lymphocytotoxic (CDC) cross-match positive transplant
- High immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity [e.g. high panel reactive antibodies (PRA) and/or the presence of pre-existing donor specific antigen (DSA)]

Study Status

- Approximately 2040 patients are expected to be enrolled by the end of 2015 across 44 countries comprising > 200 study sites (**Figure 2**).
- Enrolment of the first patient was reported on 03 December 2013 and recruitment of the last patient is expected by December 2015
- Since study start in December 2013, >110 patients were screened and > 100 patients were randomised in this study across 11 countries (13 sites).

Figure 2. Participating countries



Summary

- TRANSFORM is the largest study hitherto designed to evaluate immunosuppressive regimens in *de novo* KTxR.
- The TRANSFORM trial, for the first time, combines the measurement of anti-rejection efficacy with the measure of graft function (eGFR) in a single, clinically relevant composite primary endpoint.
- The TRANSFORM trial will generate data to evaluate the effect of EVR with reduced exposure to CNI on allograft recipients from different donor types as well as outcome data for treatment with this regimen up to 5 years.

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N) Renal Transplantation. N1) Transplantation basic science and immune-tolerance of allogenic and xenogenic transplants.
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