



## **King's Research Portal**

DOI: 10.1016/S0140-6736(20)30167-7

Document Version Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):

Sawitzki, B., Harden, P., Reinke, P., Moreau, A., Hutchinson, J. A., Game, D. S., Tang, Q., Guinan, E., Battaglia, M., Burlingham, W. J., Roberts, I., Streitz, M., Josien, R., Böger, C. A., Scotta, C., Markmann, J. F., Hester, J., Juerchott, K., Braudeau, C., ... Geissler, E. K. (2020). Regulatory cell therapy in kidney transplantation (The ONE Study): a harmonised design and analysis of seven non-randomised, single-arm, phase 1/2A trials. *The Lancet*, *395*(10237), 1627-1639. https://doi.org/10.1016/S0140-6736(20)30167-7

## Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

## General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
You may not further distribute the material or use it for any profit-making activity or commercial gain
You may freely distribute the URL identifying the publication in the Research Portal

## Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.



**Fig. 1:** ONE Study design and patient disposition for the multicenter RGT and six monocenter CTG trials. RGT = Reference Group Trial; CTG = Cell Therapy Group trials; Mreg: regulatory macrophages; ATDC: autologous tolerogenic dendritic cells; pTreg-1 / pTreg-2: polyclonal regulatory T cells; darTreg-sBC: donor-alloantigen reactive Treg; darTreg-CSB: costimulatory blockade generated Treg.



<b>B.</b> Severity of 1st BCAR episode	RGT (N=8)	CTG (N=6)
Central pathological diagnosis		•
Acute TCMR IA	1 (12.5 %)	1 (16.7 %)
Acute TCMR IIA	3 (37.5 %)	2 (33.3 %)
Acute TCMR IB	1 (12.5 %)	1 (16.7 %)
Acute TCMR IIB	0 (0.0 %)	2 (33.3 %)
Borderline changes	3 (37.5 %)	0 (0.0%)
ABMR diagnosed locally?		
Yes	1 (12.5 %)	2 (33.3 %)
No	7 (87.5 %)	4 (66.7 %)
Response to treatment		
Glucocorticoid-responsive	4 (50.0 %)	3 (50.0 %)
Responsive to depleting antibody treatment	3 (37.5 %)	3 (50.0 %)
Not applicable*	1 (12.5 %)	0 (0.0 %)



**Fig. 2:** *Primary endpoint (BCAR) data.* 2A). Kaplan-Meier estimates of the cumulative BCAR-free survival probability in the RGT (N=66) and CTG (N=38) intention-to-treat analysis sets (87.7 % vs. 84.2 % at 60 weeks). Censored patients marked with ticks. 2B). Severity of first BCAR episode by central pathological diagnosis and response to treatment. \* Patient treated with low-dose oral steroids and by not tapering immunosuppression. 2C). Kaplan-Meier estimates of the cumulative BCAR-free survival probability in the RGT (N=47) and CTG (N=32) per-protocol analysis sets (82.8 % vs. 81.3 % at 60 weeks). Censored patients marked with ticks.

RGT = Reference Group Trial; CTG = Cell Therapy Group trials; BCAR = biopsyconfirmed acute rejection; TCMR = T cell-mediated rejection; ABMR = antibodymediated rejection.







35





**Fig. 3:** *ONE Study safety data (normalized).* 3A) Incidence rate of treatment-emergent SAEs by MedDRA primary SOC. 3B) Incidence rate of treatment-emergent infections (all AEs) by study site. 3C) Incidence proportion of treatment-emergent infections (all AEs) over time. 3D) Incidence rate of treatment-emergent infections (all AEs) by MedDRA HLGT. 3E) Incidence rate of treatment-emergent viral infections (all AEs) by MedDRA HLT.

All adverse events coded using MedDRA version 20.1. Treatment-emergent (S)AEs are events with onset date equal to or after first dose of any study drug. All events coded to the MedDRA PT: "Transplant rejection" are excluded, since rejection was measured as the primary efficacy endpoint. RGT = Reference Group Trial; CTG = Cell Therapy Group trials; SOC = System Organ Class; HLGT = High Level Group Term; HLT = High Level Term; PSY = Patient study years; NEC = Not elsewhere classified.



**Fig. 4:** *Leukocyte subset alterations in ESRD patients and time-dependent changes after kidney transplantation.* A) Principal component analysis revealing the differences in leukocyte subset between whole blood samples from end stage renal renal disease (ESRD, n= 70) and healthy controls (HC, n= 98). B) Box-and-whiskers plots of absolute numbers from leukocyte subpopulations with highest influence at the PCA shown in A. C) Time-dependent changes from visit 1 prior to transplantation (V01) to visit 10 at 60 weeks post-transplant (V10) of monocyte, B cell, CD4<sup>+</sup> and CD8<sup>+</sup> T cell subset composition (stacked bars of mean proportions) in whole blood samples of RGT patients (n=59). Statistical analysis by Kruskal-Wallis-Test. \* p<0.05, \*\* p<0.01





**Fig. 5:** *Differences in post-transplant changes between RGT and CTG patients.* A) Differences in post-transplant changes in regulatory T cells. Box and whisker plots of absolute numbers and proportions of CD4<sup>+</sup>CD25<sup>high</sup>CD127<sup>low</sup> Tregs as well as % CD4<sup>+</sup> T cells with demethylated TSDR in whole blood samples collected pre-transplant (V01) and at the end of the observation period (15 months post-transplant, V10) from RGT (n=59) and CTG patients (n=38) measured as described in material and methods. B) Differences in post-transplant changes in CD8<sup>+</sup> T cell subpopulations. Box and whisker plots of absolute numbers of CD8<sup>+</sup>CD28<sup>+</sup>, CD8<sup>+</sup>CD45RA<sup>+</sup>CCR7<sup>-</sup> T<sub>EMRA</sub> and CD8<sup>+</sup>CD57<sup>+</sup> chronically activated cells in whole blood samples collected pre-transplant (V01) and at the end of the observation period (15 months post-transplant, V10) from RGT (n=59) and CTG patients (n=38). C) Differences in post-transplant changes in marginal zone-like B cells and dendritic cell subpopulation. Box and whisker plots of absolute numbers and proportions of marginal zone-like B cells, CD16<sup>+</sup> mDCs and pDCs in whole blood samples collected pre-transplant (V01) and at the end of the observation period (15 months post-transplant, V10) from RGT (n=59) and CTG patients (n=59) and CTG patients (n=38). Statistical analysis by by Wilcoxon matched-pairs signed rank and Dunn's multiple comparison test. \* p<0.05, \*\* p<0.01, \*\*\*\* p<0.001