17º CONGRESO SCT BCN BARCELONA 22-24 marzo 2023
SOCIETAT CATALANA DE TRASPLANTAMENT

Generalitat de Catalunya
Departament de Salut

PERIS 2016 2020

High acute rejection rates in absence of induction therapy and rapid steroid withdrawal in well-matched first living-donor kidney transplant recipients with preformed donor-reactive memory T cells

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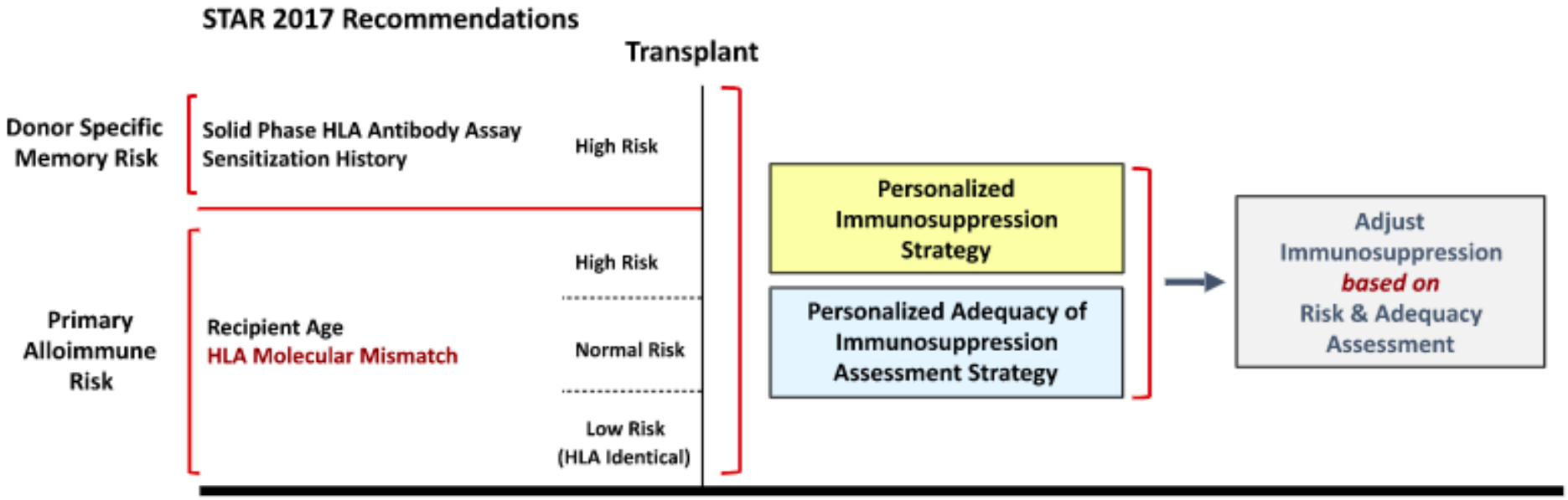
Background

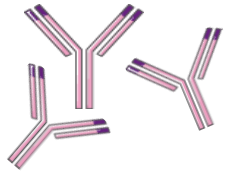
- Immunosuppression individualization in kidney transplantation is warranted to improve long-term outcomes balancing optimized control of alloimmunity and pharmacological side effects
- Risk stratification must include evaluation of both preformed alloimmune memory and risk of *de novo anti-donor* immune activation



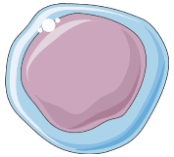
Wiebe C. et al. Am J Transpl. 2018

Background

Preformed alloimmune memory

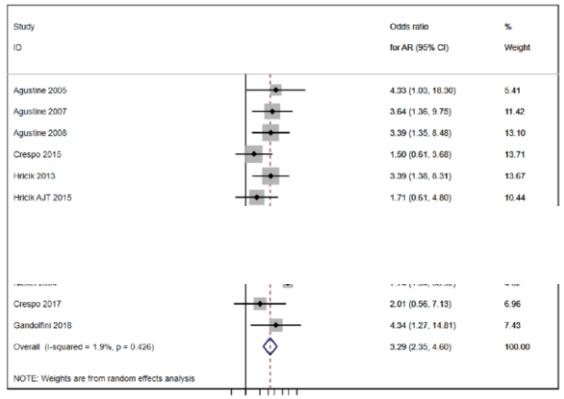


CIRCULATING DSA



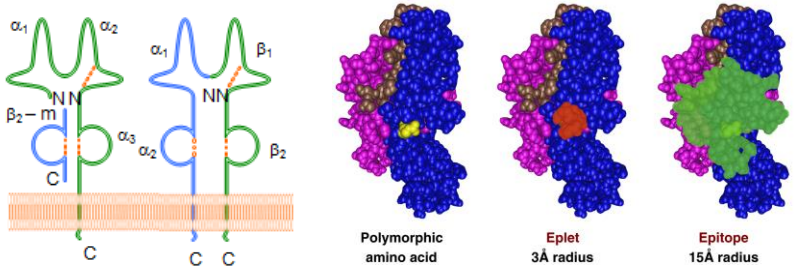
CIRCULATING DONOR-SP MEMORY T CELLS

Donor Specific IFNg T-cell ELISPOT

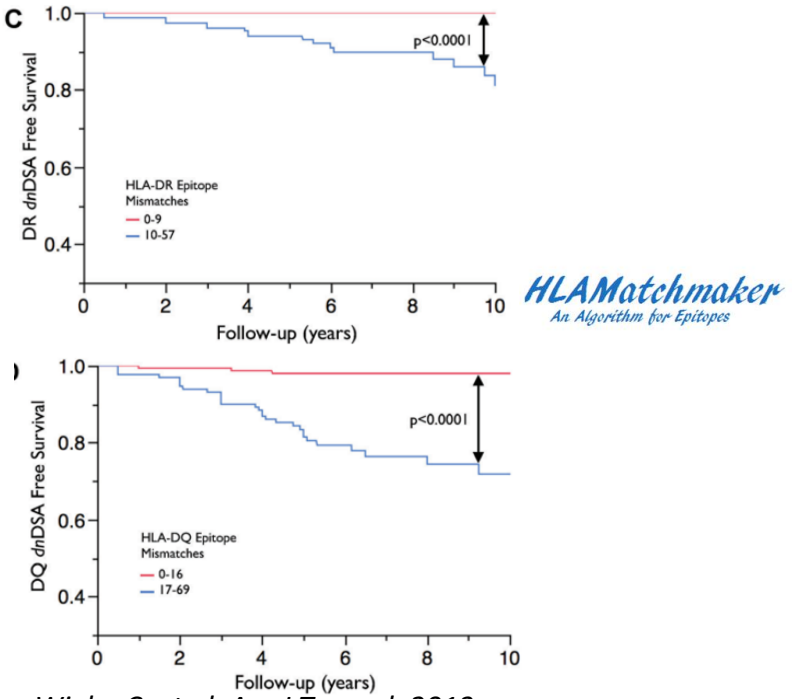


Montero N. et al. Tr Direct, 2019

de novo alloimmune activation



HLA MISMATCH



Wiebe C. et al. Am J Transpl. 2013

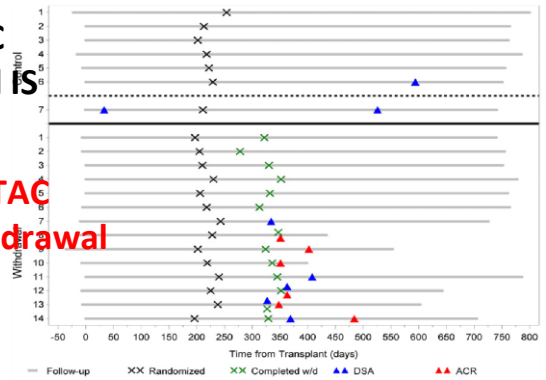
Background

Preformed T-cell alloimmune memory

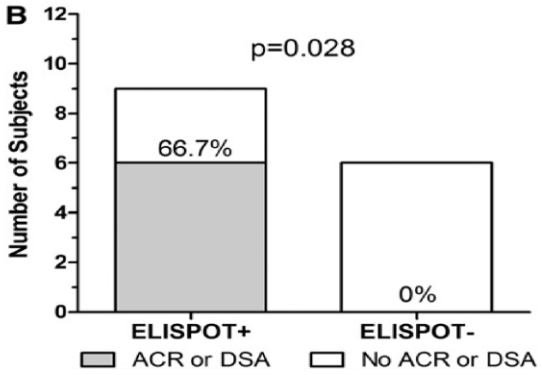
TAC WITHDRAWAL (CTOT-09)

TAC based IS

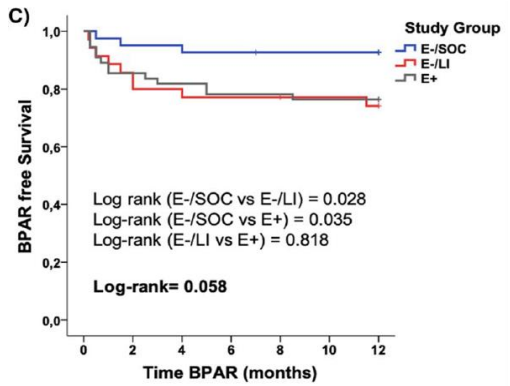
TAC withdrawal



Post hoc analysis



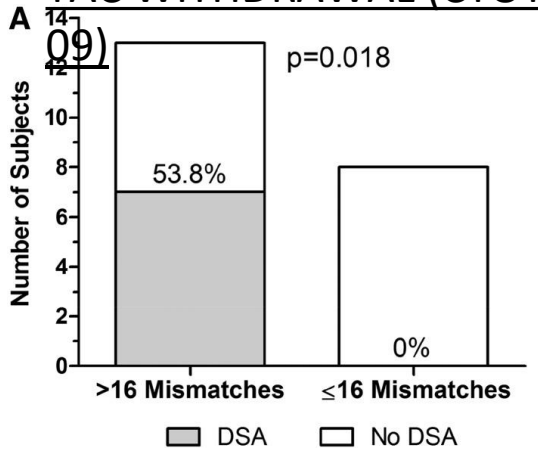
TAC MONOTHERAPY (CELLMIN)



de novo alloimmune activation

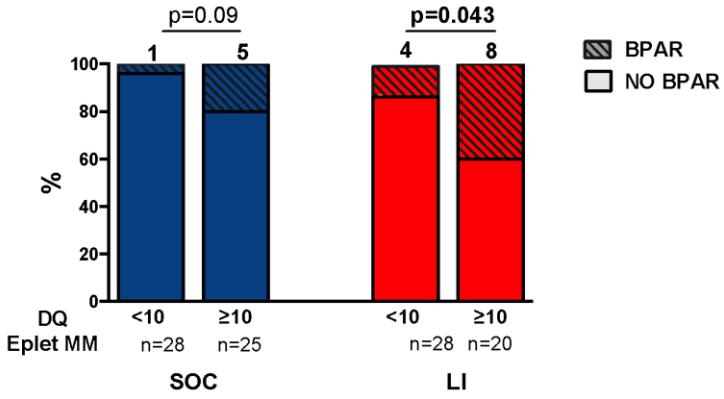
Post hoc analyses

TAC WITHDRAWAL (CTOT-09)



Hricik D.et al. Am. J Transplant, 2015

TAC MONOTHERAPY (CELLMIN)



Bestard O. et al. Am J Transplant. 2021

Hypothesis

Individualized immunosuppression based on baseline immune-risk stratification could improve allograft results controlling risk of rejection and dnDSA while avoiding unnecessary exposure to immunosuppression.

Objective

To determine the effect of individualizing the immunosuppressive therapy in LDKT patients based on baseline immune-risk stratification according to two biomarkers (donor Specific IFNg **T-cell ELISPOT** assay and donor/recipient **HLA class II Eplet Mismatch**), in a **composite end-point** (loss of renal function, incidence of acute rejection and development of dnDSA) at **2 years** of follow-up as compared to patients who are managed according to standard of care immunosuppression.

Methods

Multicentric, randomized trial to evaluate the efficacy of baseline Immune-risk stratification based on selective Biomarkers (HLA class II Eplet mismatching and donor-specific IFN-γ ELISPOT) to optimize Immunosuppressive therapy in Living-kidney transplant patients (**BIOIMMUN**)

Nº EudraCT 2017-002293-39

Generalitat de Catalunya
Departament de Salut

PERIS 2016 2020

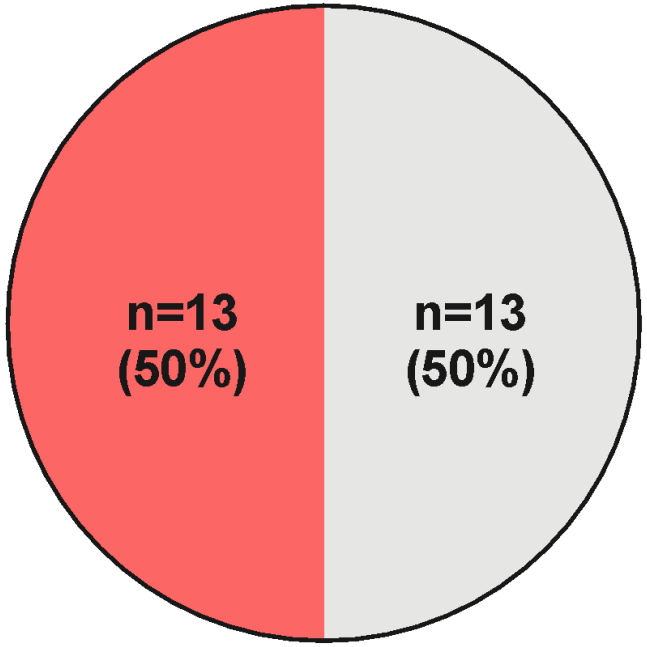
Living-donor Kidney transplant patients
N=164

Randomization 1:1
(stratification for donor age > 55a)

1st KT
No DSA
cPRA<75%

Results: interim safety analysis

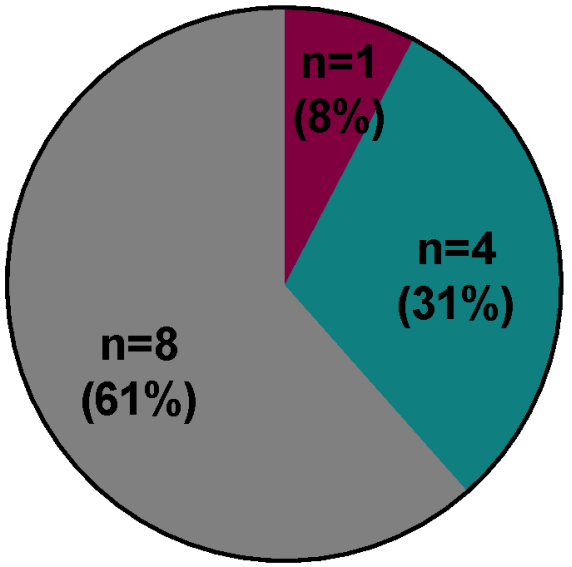
ALL COHORT



n = 26

A
B

GROUP A

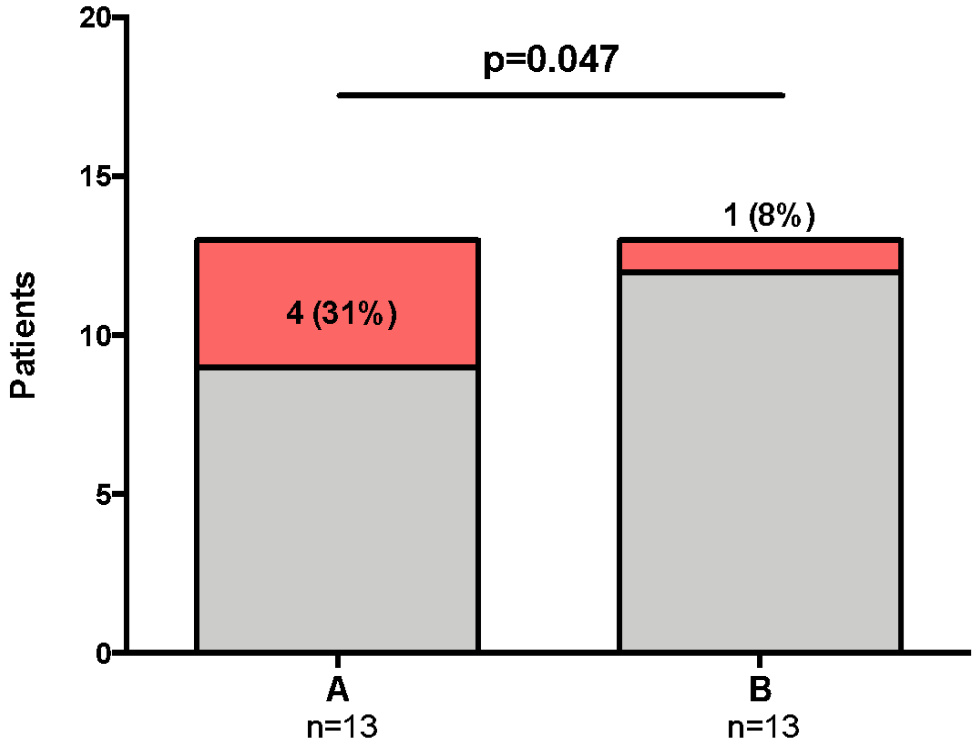


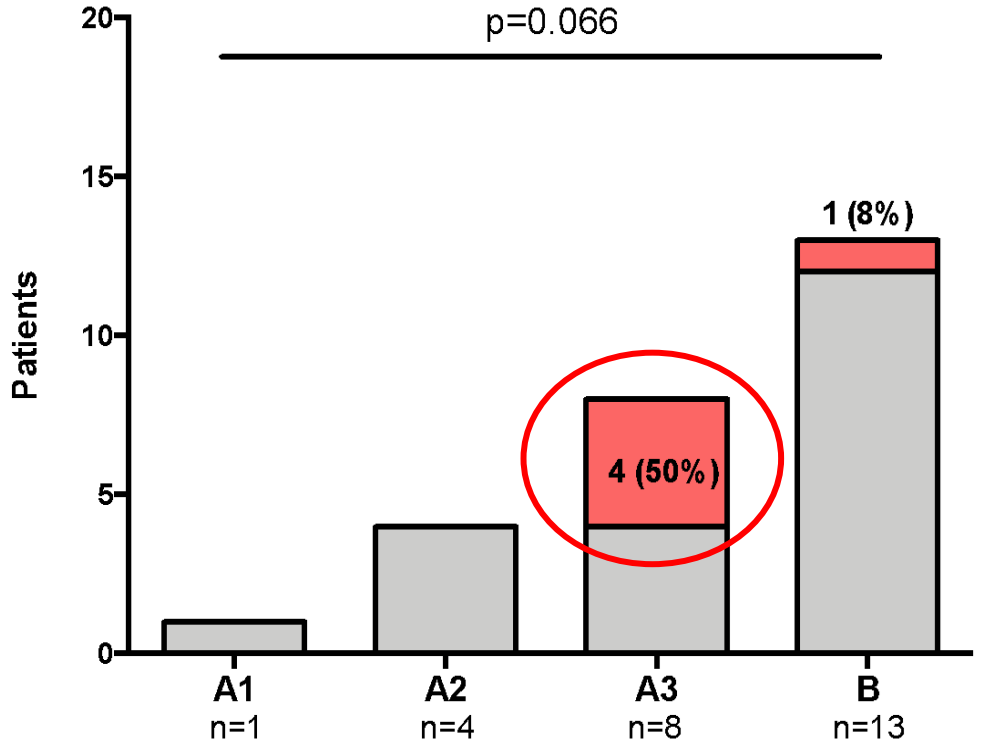
POS IFN-γ ELISPOT (A1)
NEG IFN-γ ELISPOT / HIGH Eplet MM (A2)
NEG IFN-γ ELISPOT / LOW Eplet MM (A3)

Results

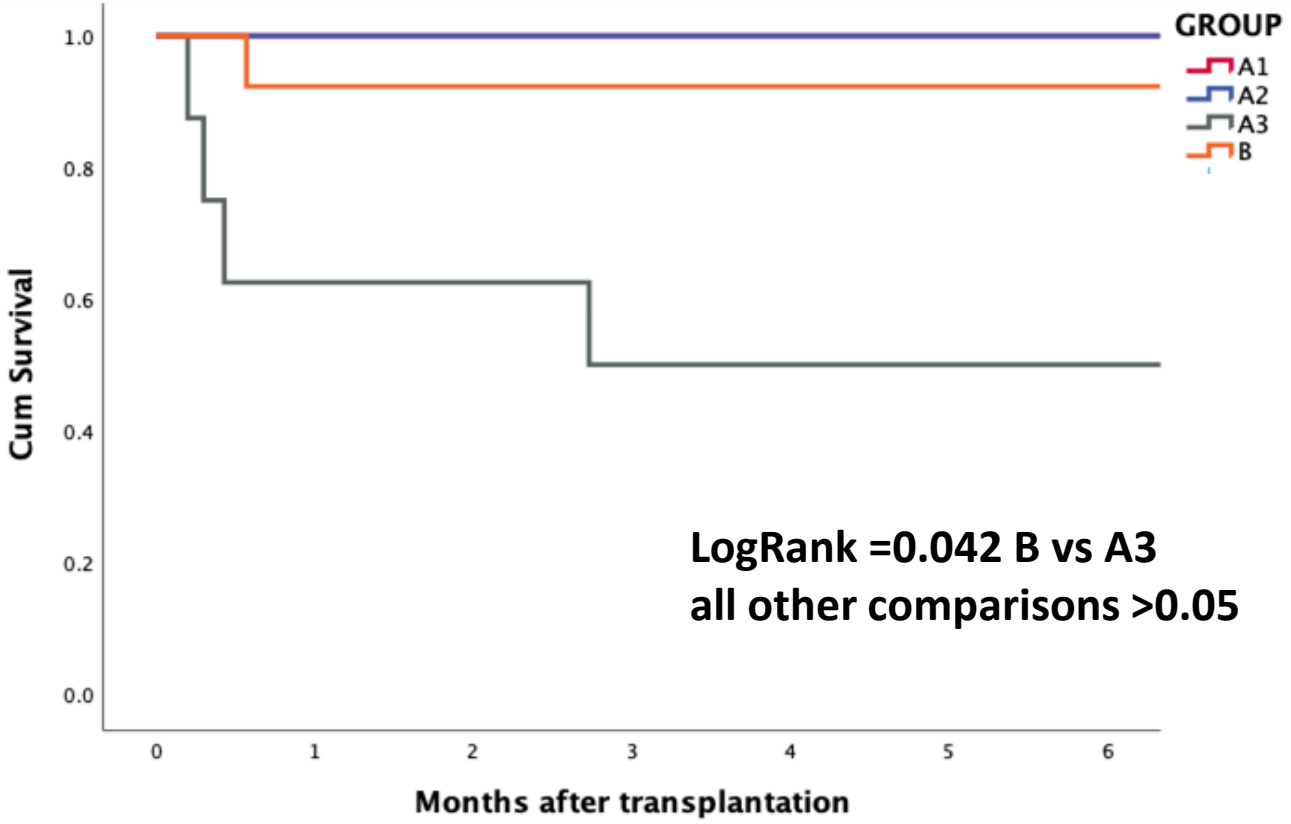
Exceeding BPAR rates in group A:

- *Group A 4/13 (31%) vs group B 1/13 (8%)*
- *Group A3: 4/8 (50%)*





Results



LogRank =0.042 B vs A3
all other comparisons >0.05

Banff 2019:

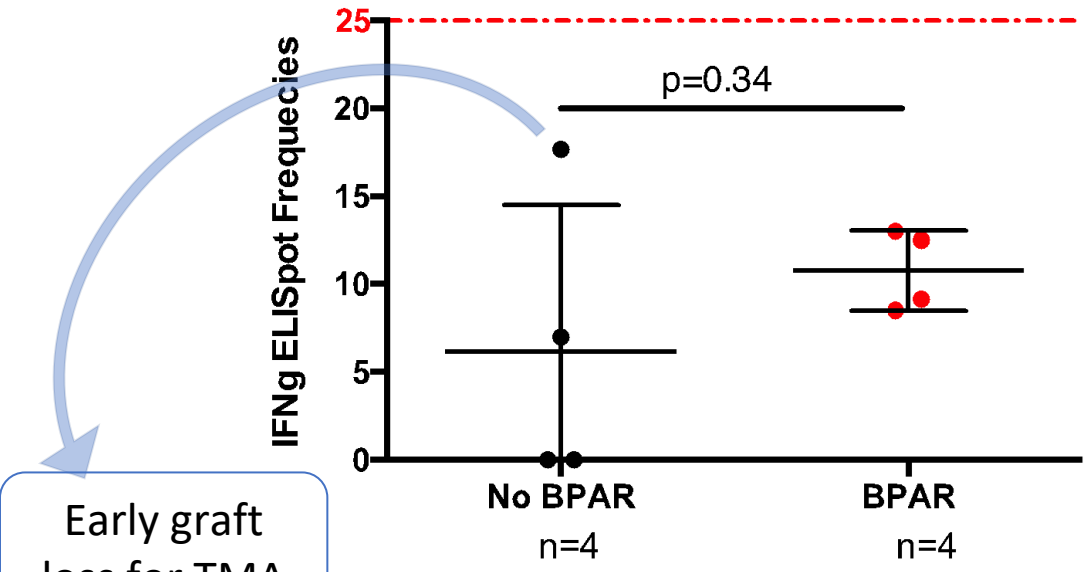
- Group A3: 2 IA, 2 IIA
- Group B: 1 IA

Mean time to BPAR: 25±32days

SAFETY AMENDMENT

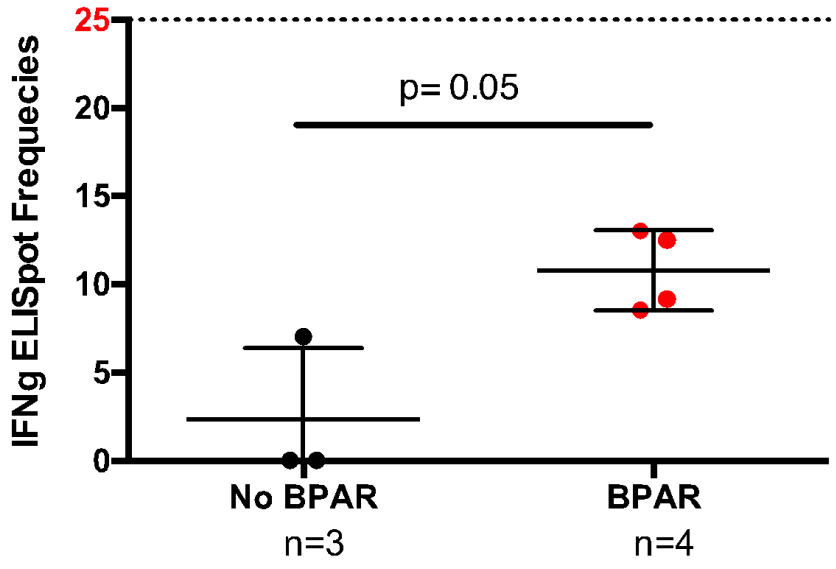
Biomarker post-hoc analysis: pretransplant IFNg ELISPOT

ITT



Early graft loss for TMA

PP

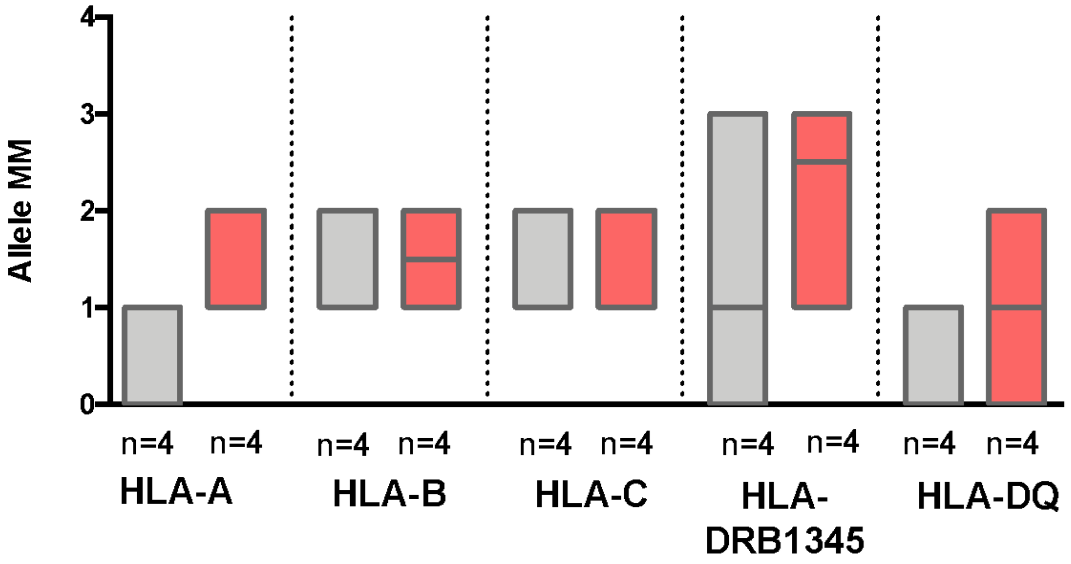


All rejecting patients displayed low but detectable frequencies of IFNg producing donor-specific T cells

Biomarker post-hoc analysis: donor/recipient HLA allele MM

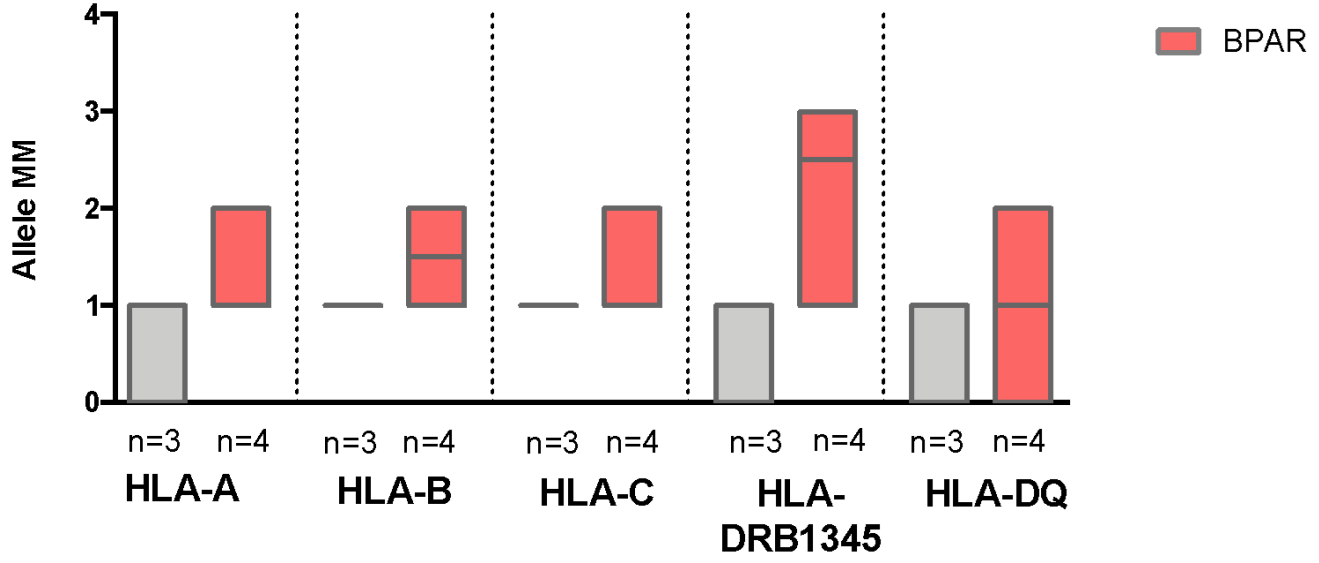
ITT

* All p >0.005



PP

* All p >0.005

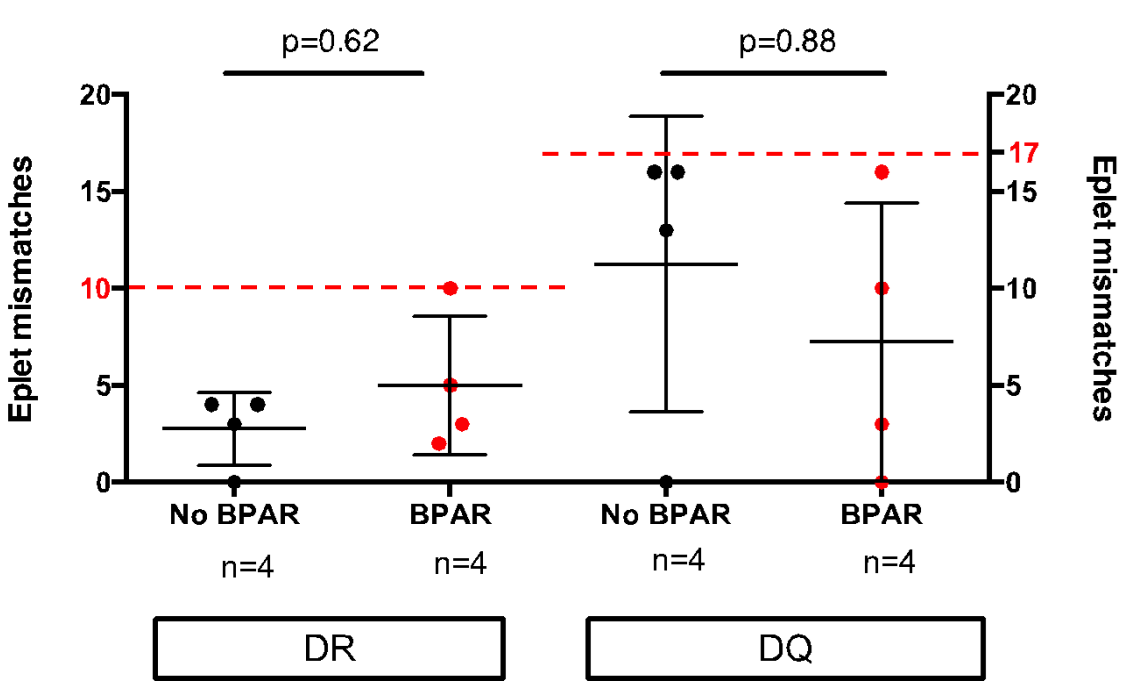


No statistical difference in class I/II HLA allele mismatches between rejecting patients and non-rejectors.

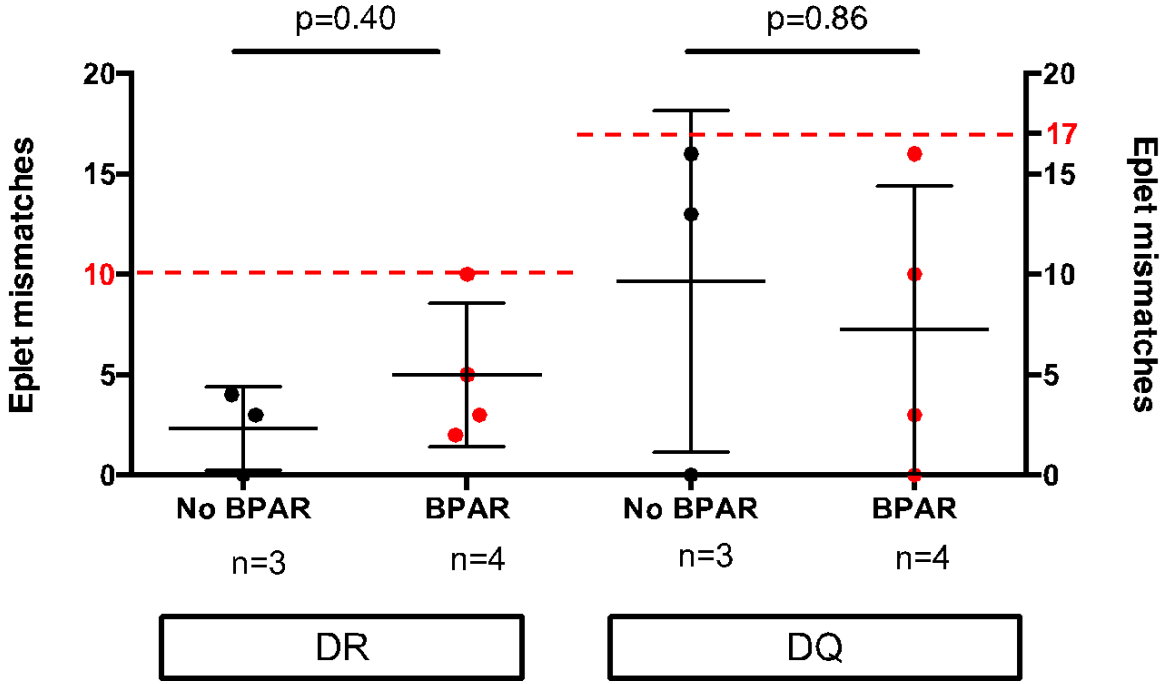
Biomarker reanalysis: Class II donor/recipient HLA Eplet MM

HLAMatchmaker
An Algorithm for Epitopes

ITT



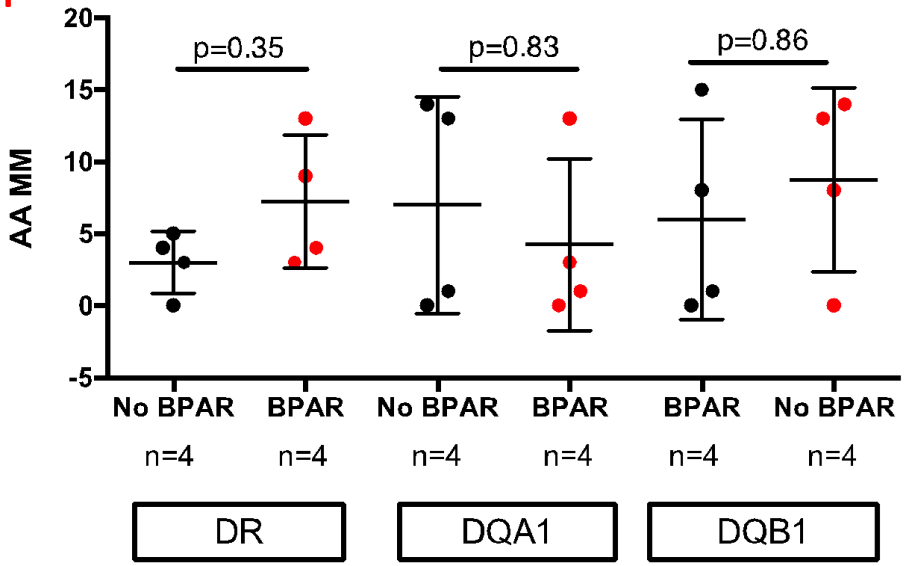
PP



- *No statistical difference in class I/II Eplet MM load between rejecting patients and non-rejectors.*
- *No difference in Single Molecule DR/DQ Eplet MM risk score (Wiebe at al, 2019)*
- *No difference with the latest versions of HLAMatchmaker software (V4.0 and V3.1)*

Biomarker post hoc analysis: other algorithms of D/R HLA molecular MM

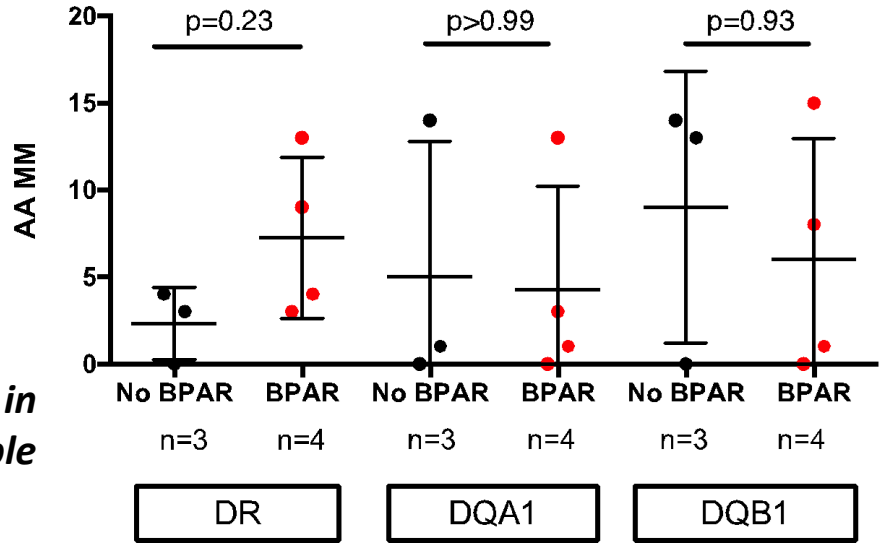
ITT

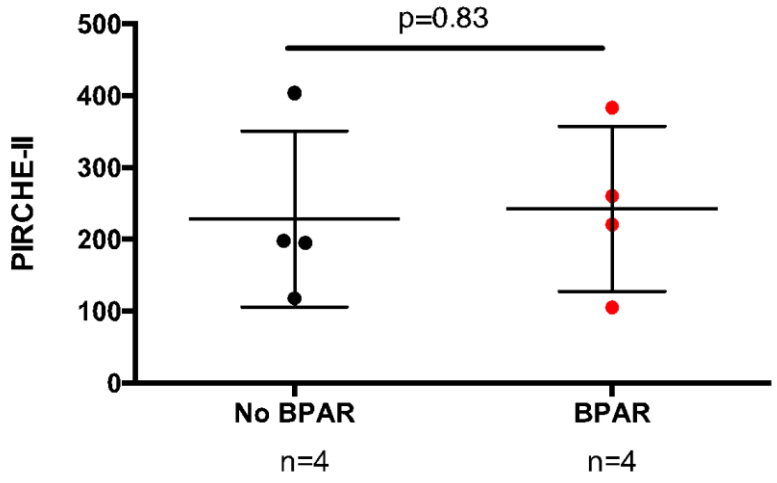


HLA-EMMA
Epitope Mismatch Algorithm

**** No difference in soluble accessible AA MM***

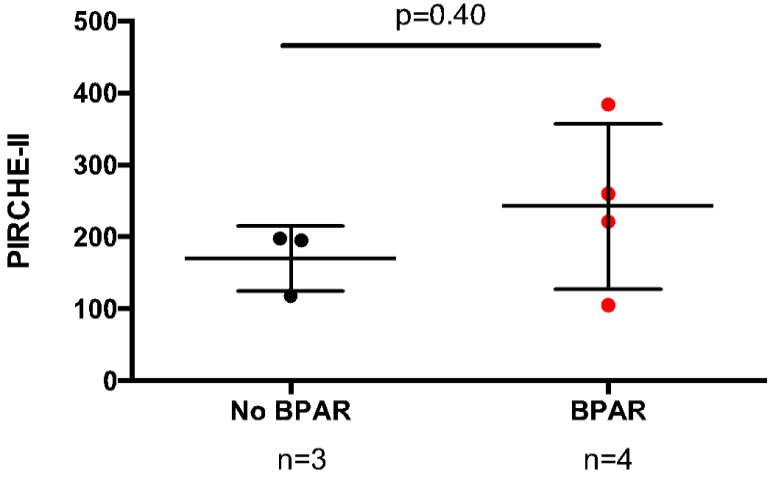
PP





PIRCHE

**** No difference in any presented peptide per locus***



Conclusions

- While in retrospective studies pretransplant donor Sp T-cell ELISPOT freq. <25/300,000 PBMCs have high NPV for acute rejection, in this study patients with low but detectable donor-reactive T cell frequencies displayed an excessive risk of early TCMR under minimized IS (No induction/early steroid w/w).

- No difference in allelic nor molecular HLA mismatches was observed between rejectors and non rejectors, supporting the hypothesis of a memory response.

- After these observation the trial was amended. Currently, A3 group receives a 3-mo steroid course after transplantation. No further rejection episodes have been observed. **The trial is ongoing.**

Rapid steroid withdrawal in absence of induction therapy in a TAC/MMF based immunosuppressive regimen should be highly discouraged in presence of low but detectable preformed donor-reactive memory T-cells, despite good D/R HLA allele/molecular matching.

Moltes gracies!

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