

Longitudinal assessment of alloreactive memory T and B cells in the EUTRAIN kidney transplant cohort

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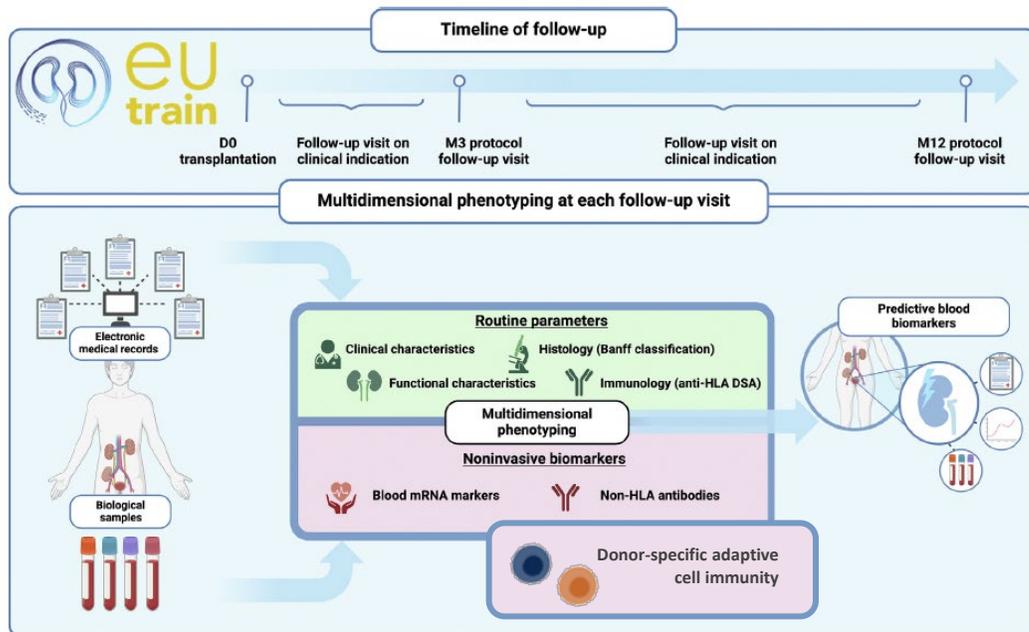
The European TRAnsplantation and INnovation consortium for risk stratification in kidney transplant patients

Transforming Kidney Transplantation Monitoring & Risk Stratification

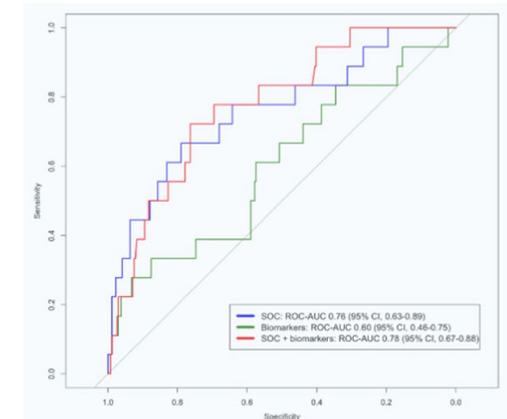
- **Limitations of current monitoring:** Relies on **nonspecific markers** (sCreat, proteinuria) and **histopathology**, lacking precision and predictive value.
- **EUTRAIN's solution:** EU-TRACER prediction system that integrates **immunological biomarkers, multi-omics, tissue injury assessment, epidemiology, and clinical data** for improved risk stratification.



EU-TRAIN multimodal biomarker study



No added value of mRNA biomarkers and non-HLA antibodies to detect allograft rejection beyond SOC



Goutadier V et al. Kidney Int. 2024

Integrating donor-specific cell-based functional assays with other biomarkers and multidimensional risk stratification models to improve detection of rejection risk and enhance personalized transplant management

HYPOTHESIS AND OBJECTIVES

Within the multicenter EUTRAIN project, the study of **Donor-specific T-Cell (DST) and Donor (HLA)-sp memory B cells (mBC)** aims at describing the role of functional cellular immunity in relation to the development of **allograft rejection**

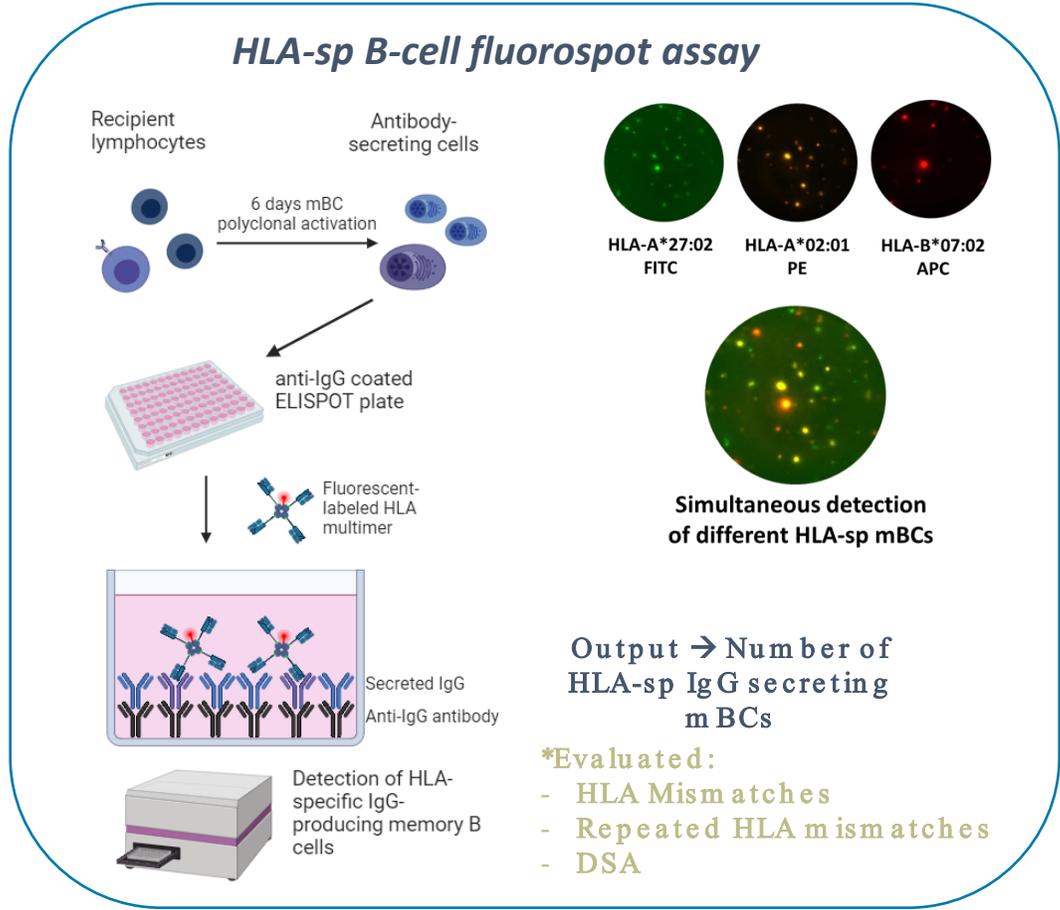
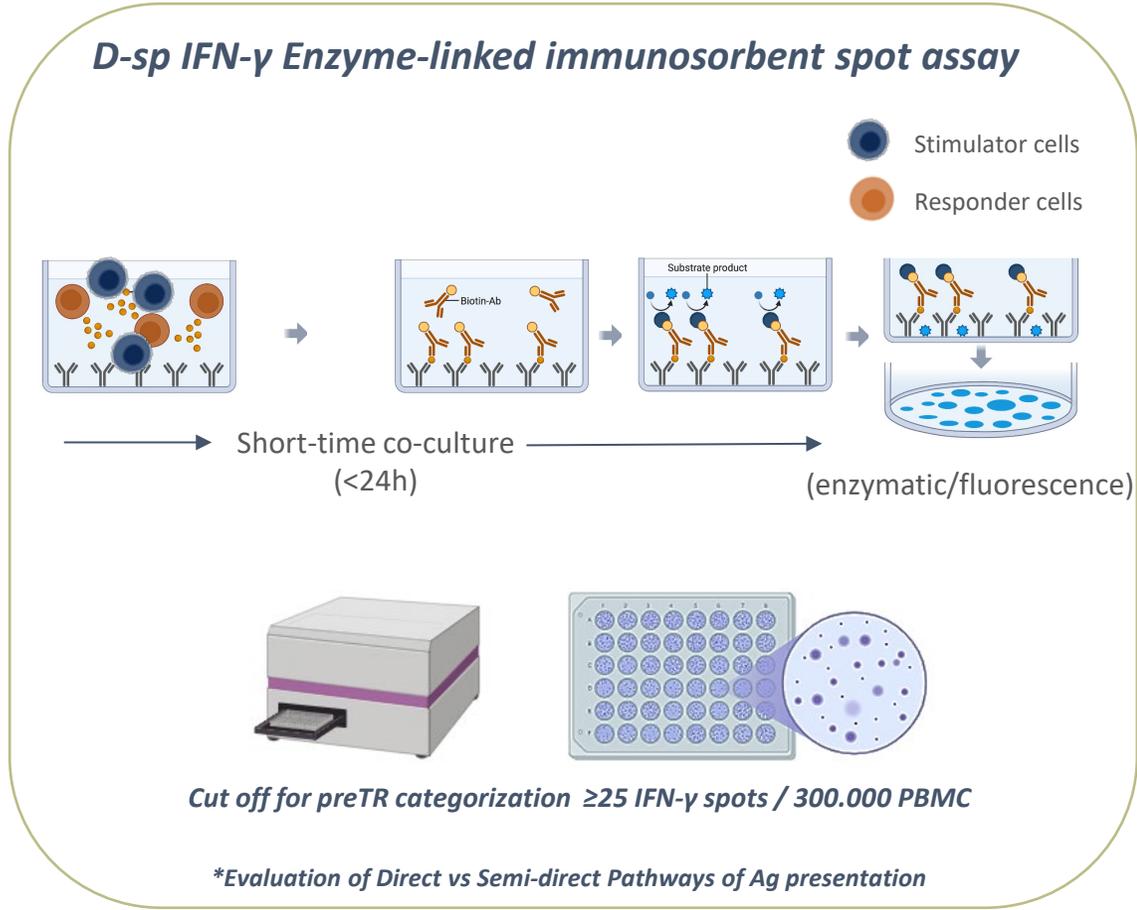
OBJECTIVES:

1. Describe the dynamics of DST and d-sp mBC responses in a multicenter cohort at different timepoints of kidney transplantation.
2. Assess the association between DST and mBC and the advent of BPAR when measured pre-transplantation and at the time of protocol or for-cause biopsies, further evaluating their role in risk stratification.

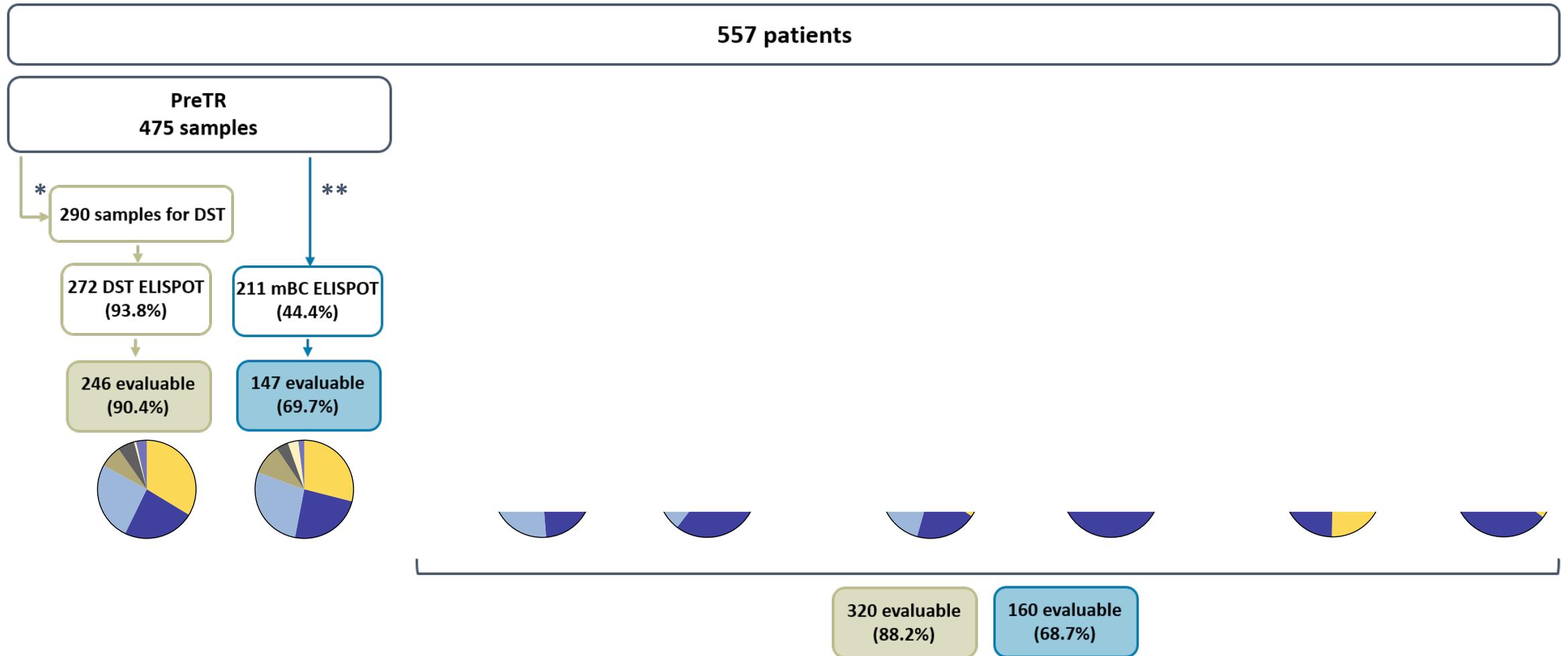


STUDY DESIGN AND METHODS:

Study of Pre-transplant and Post-transplant DST and d-sp mBC in the EUTRAIN cohort of Kidney Transplant Patients



STUDY DESIGN AND METHODS:



■ Saint Louis
 ■ Necker
 ■ HVH Barcelona
 ■ Nantes
 ■ Geneva
 ■ Bicetre
 ■ Charite/Virchow

International multi center validation study

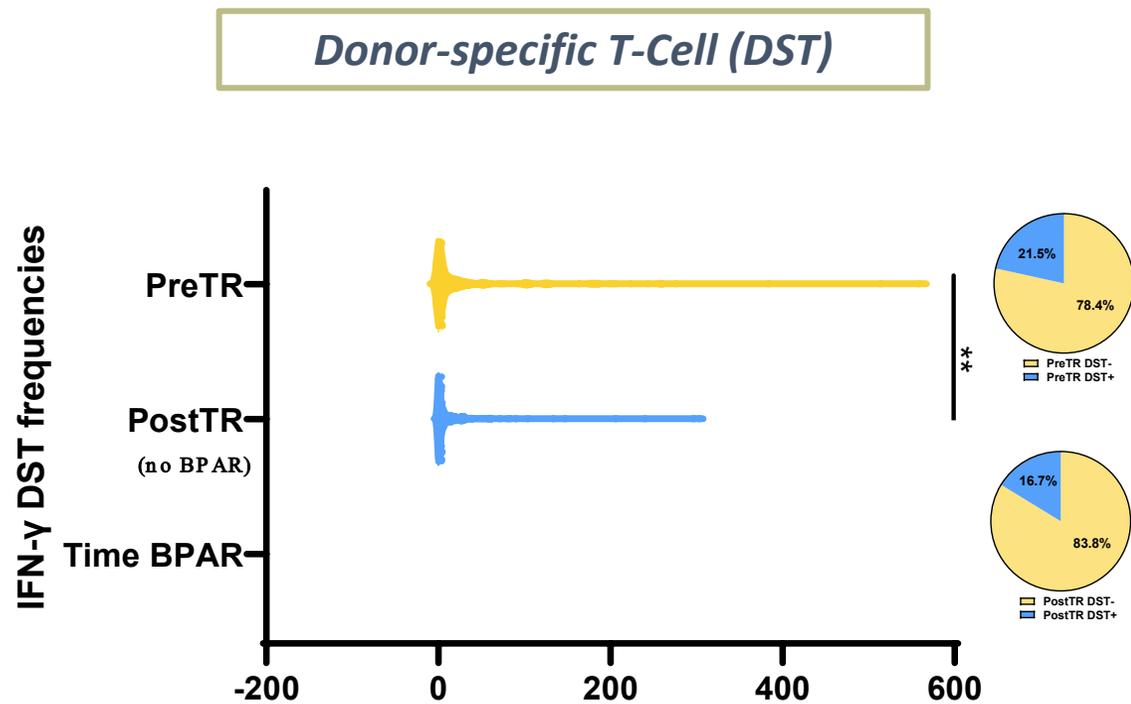
*Donor sample availability
 **Not technically applicable (low cell viability; no HLA specificities available)

Clinical and demographics variables of the study

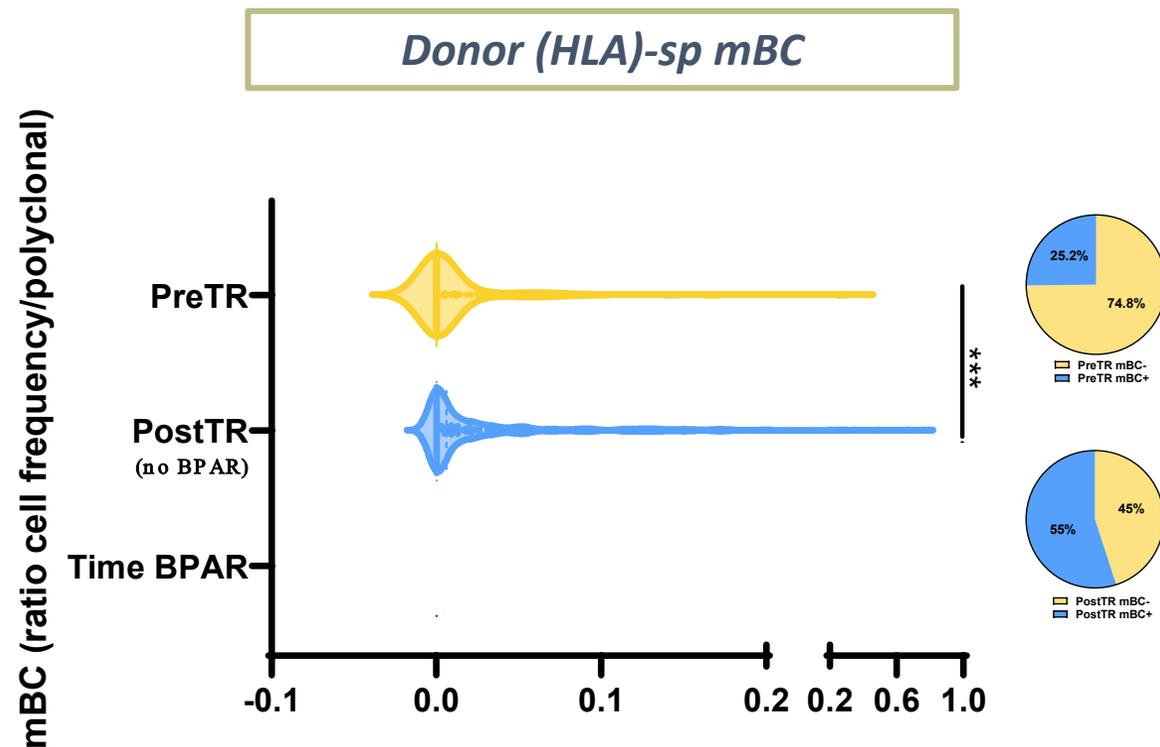
Demographics	EUTRAIN cohort (n=557)	PreTR DST subcohort (n=246)	p value (all vs DST)	PreTR mBC subcohort (n=147)	p value (all vs mBC)
Age (years)	54.28±14.50	53.41±14.73	0.563	53.88±15.19	0.833
Time HD (months)	3.96±4.44	3.58±3.50	0.714	4.14±4.09	0.359
Gender (female)	163 (35.8)	87 (35.5)	0.934	58 (39.7)	0.395
Time Cold Ischemia (minutes)	745.45±480.46	773.10±496.55	0.553	767.18±468.42	0.531
DGF (yes, %)	124 (26.1)	71 (30.0)	0.270	38 (26.8)	0.866
D0 DSA (yes, %)	117 (23.0)	36 (22.9)	0.988	19 (19.8)	0.492
D0 DSA (MFI)	577.62±2279.93	541.15±1643.00	0.288	627.24±2288.11	0.883
PreTR DST (positive)	-	53 (21.5)	na	-	
PreTR DST (frequencies)	-	30.46±72.82	na	-	
PreTR mBC (positive)	-	-		37 (25.2)	na
PreTR mBC (ratio HLA-sp/polyclonal)	-	-		0.017±0.056	na
BPAR events (yes, %)	57 (12.3)	26 (12.0)	0.895	23 (17.6)	0.123
TCMR	35 (7.6)	17 (7.8)	0.906	15 (11.5)	0.159
ABMR	20 (4.3)	8 (3.7)	0.695	8 (6.1)	0.397
Mixed	2 (0.4)	1 (0.5)	0.959	0 (0)	0.451
rATG (yes, %)	265 (54.6)	145 (60.2)	0.157	83 (59.3)	0.330
CNI (yes, %)	522 (97.8)	219 (97.3)	0.729	132 (97.1)	0.636

Comparable clinical and demographics variables between the global EUTRAIN cohort and the evaluated sub-cohorts for preTR DST and preTR mBC

Donor-specific T-Cell (DST) & Donor (HLA)-sp mBC Immune memory. Differences between time points of assessment



*Reduction on DST responses after Kidney TX
DST inflation at the time of BPAR*

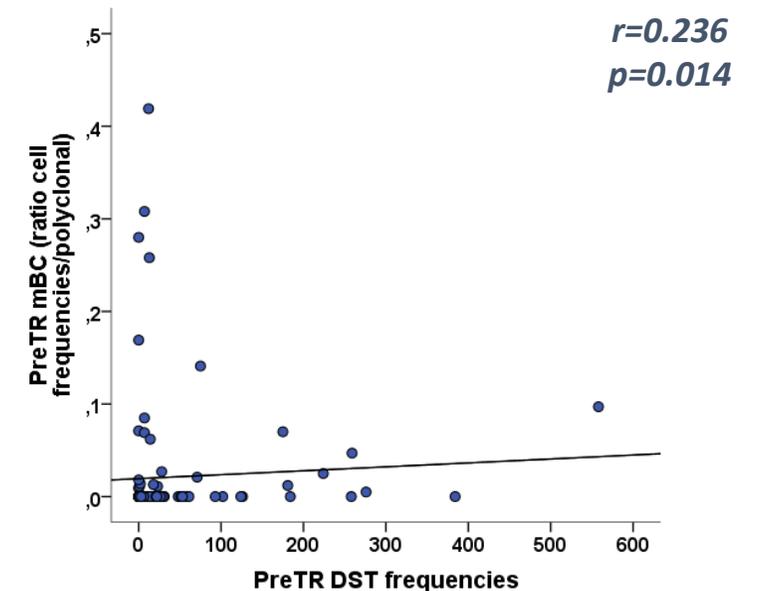


*Increased mBC frequencies PostTR
and at the time of BPAR*

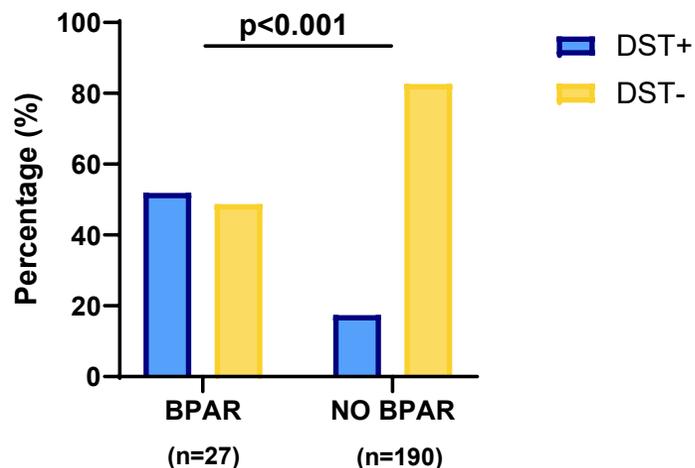
Clinical & Demographic variables associated with PreTR DST and mBC

	PreTR DST			PreTR mBC		
	DST+ (n=53)	DST- (n=193)	p value	mBC+ (n=37)	mBC- (n=110)	p value
Age (years ±SD)	54.90±13.03	53.01±15.16	0.453	53.64±13.22	53.96±15.85	0.837
Gender (Female)	14 (26.9)	73 (37.8)	0.145	46 (42.2)	12 (32.4)	0.294
Time HD (years ±SD)	3.68±4.04	3.56±3.36	0.718	4.41±4.63	4.05±3.93	0.704
HLA MM (number ±SD)						
- Class I HLA	4.76±1.48	4.35±1.62	0.280	4.57±1.45	4.38±1.59	0.767
- Class II HLA	3.76±1.81	3.06±1.52	0.062	3.14±1.74	2.91±1.51	0.674
PreTR immunization (yes)	13 (29.5)	68 (41.0)	0.167	13 (40.6)	38 (39.6)	0.442
- Transfusions (yes)	7 (16.3)	33 (20.8)	0.514	6 (20.0)	19 (20.0)	1.000
- Pregnancies (yes)	11 (26.8)	35 (23.2)	0.627	8 (26.7)	26 (29.2)	0.789
- Transplants (yes)	2 (4.5)	25 (14.9)	0.067	8 (25.0)	12 (12.2)	0.073
PreTR DSA (yes)	7 (18.4)	29 (24.4)	0.145	7 (33.3)	12 (16.0)	0.078
MFI DSA (index MFI)	803.06±2700.40	458.58±1129.47	0.639	1624.95±4352.74	329.42±897.92	0.053

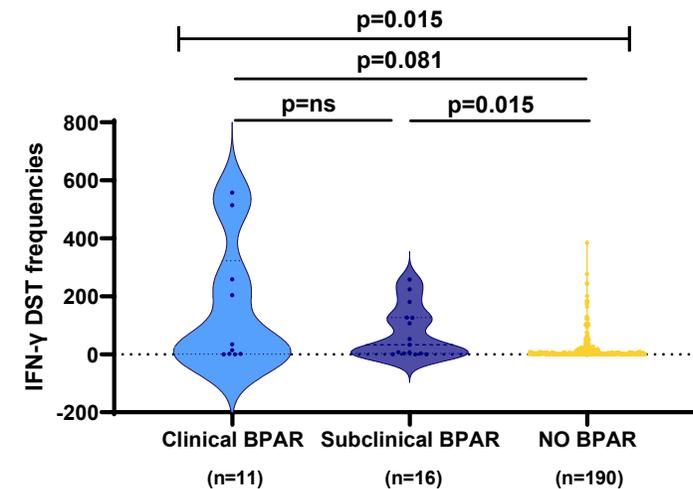
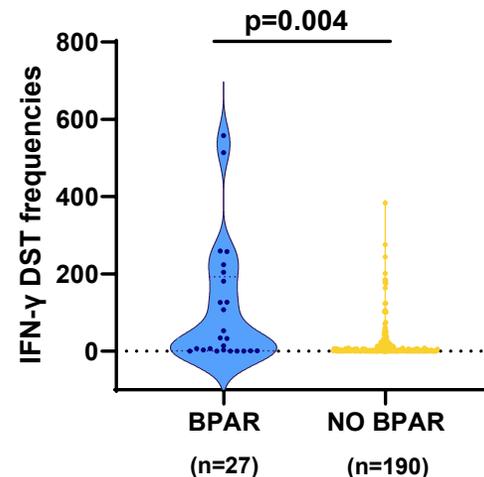
PreTR DST and mBC were not associated to major clinical factors, although d(HLA)sp mBC+ associated with DSA and DSA MFI index



PreTR DST and incidence of BPAR

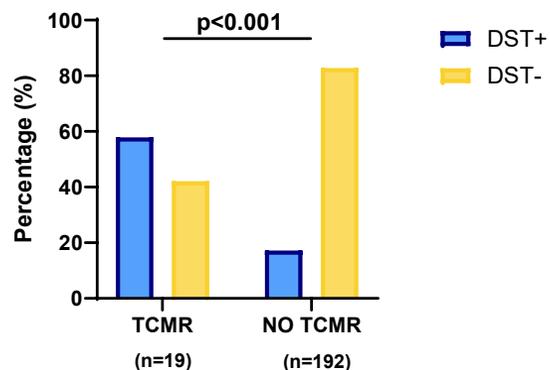


NPV 91.8%; PPV 28.3%; St 48.1%; Sp 82.6%

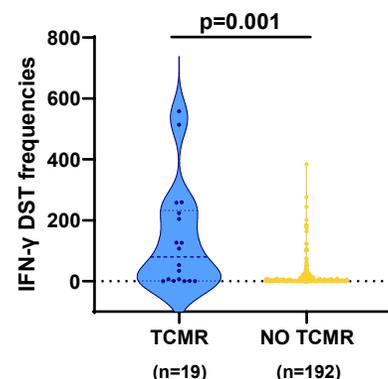


Significantly higher PreTR DST frequencies and High-risk DST categories (DST+) in patients developing BPAR

T cell mediated rejection

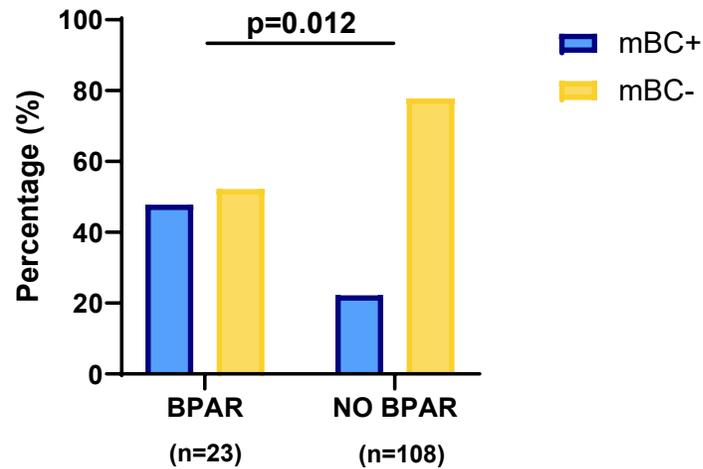


NPV 95.2%; PPV 25.0%; St 57.9%; Sp 82.8%

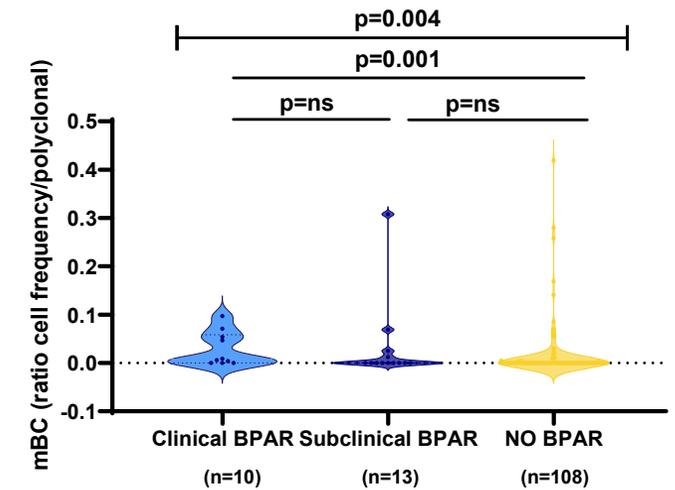
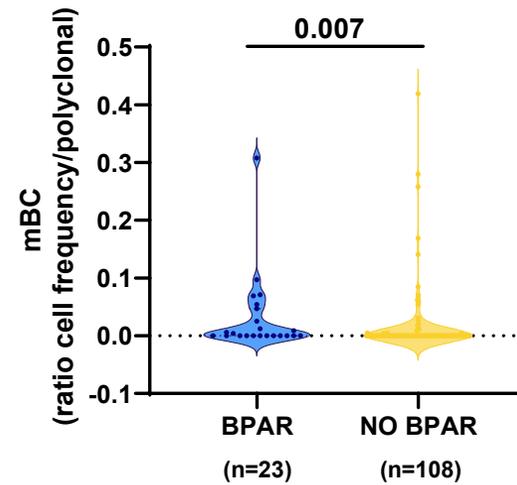


PreTR DST associates with higher incidence of TCMR, but not ABMR

PreTR d(HLA)sp mBC and incidence of BPAR

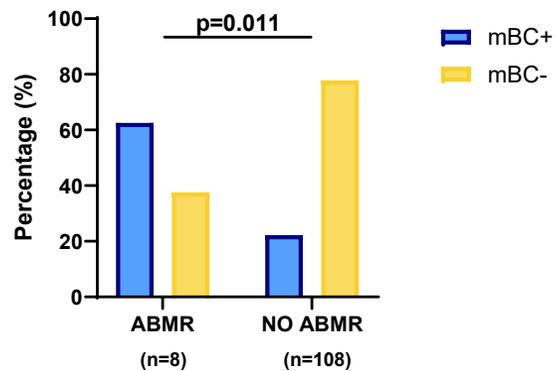


NPV 87.5%; PPV 31.34%; St 47.8%; Sp 77.8%

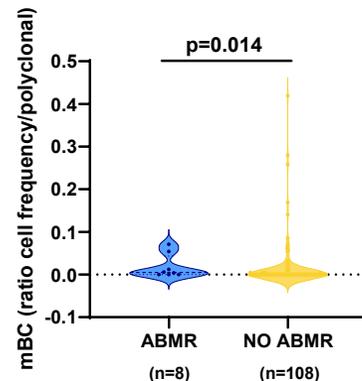


Significantly higher preTR d(HLA)sp mBC frequencies and High-risk mBC categories (mBC+) in patients developing BPAR, especially in clinical BPAR

Antibody mediated rejection



NPV 96.6%; PPV 17.2%; St 62.5%; Sp 77.8%

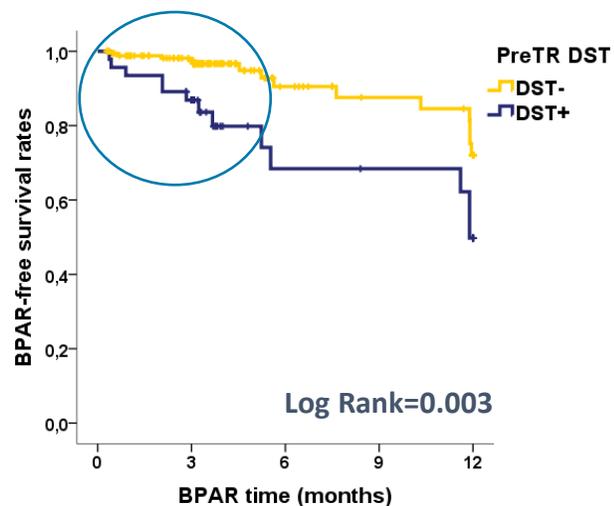


PreTR d(HLA)-sp mBC associates with higher incidence of ABMR, but not with TCMR

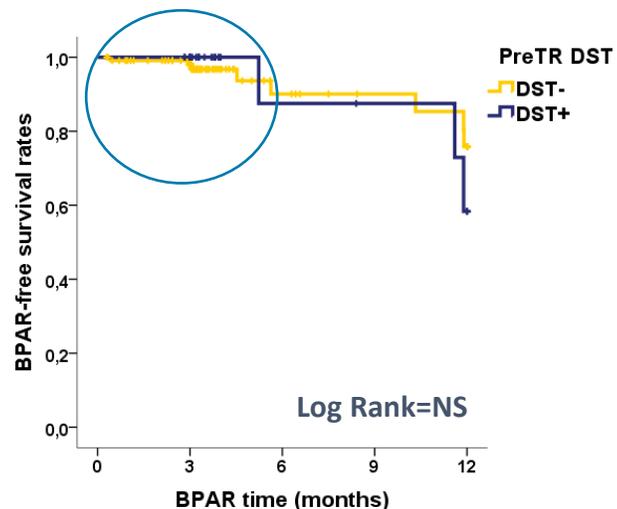
PreTR DST and mBC and cumulative BPAR rates

DST

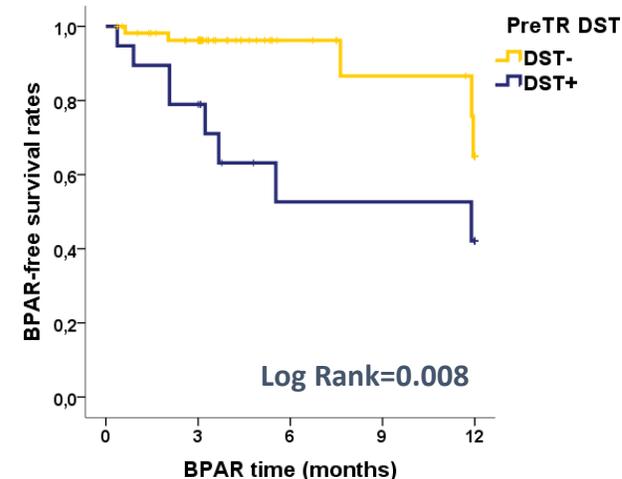
Biopsy-proven rejection



Use of rATG



No rATG



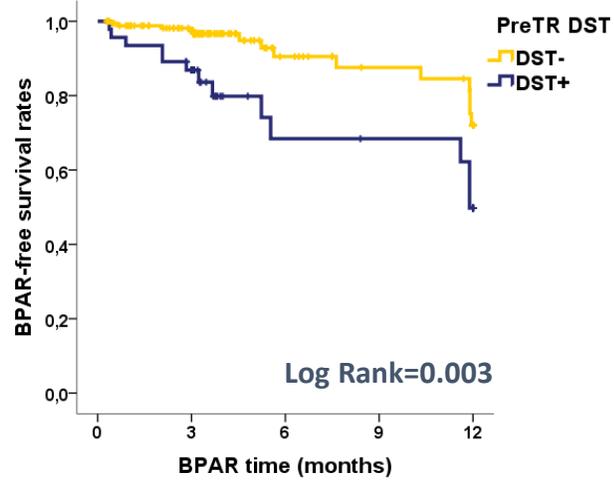
Higher cumulative rejection rates in preTR DST+

Induction with T cell depleting agents reduces the incidence of BPAR rates in preTR DST+

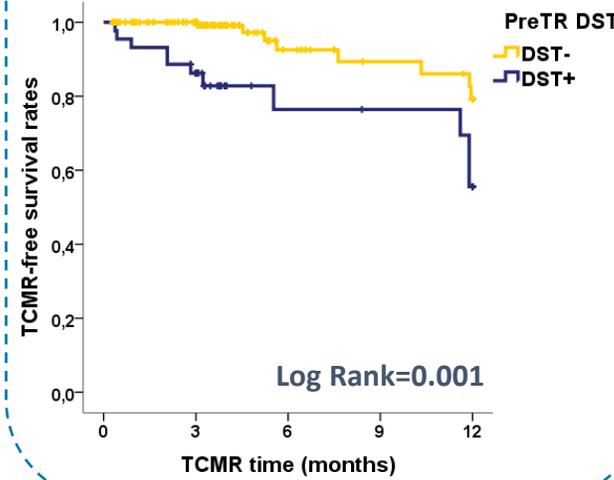
PreTR DST and mBC and cumulative BPAR rates

DST

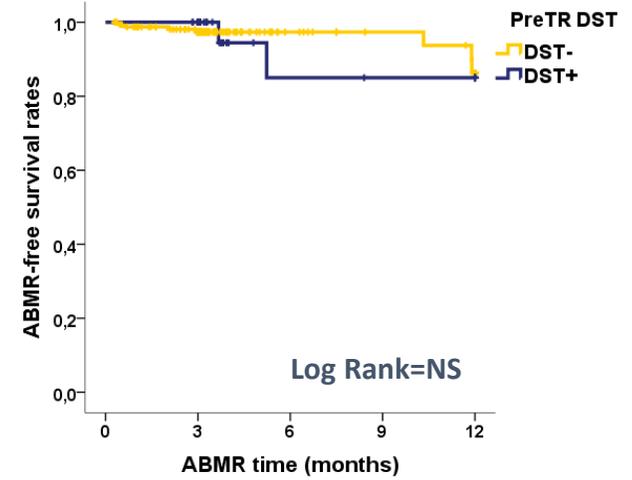
Biopsy-proven rejection



T cell mediated rejection

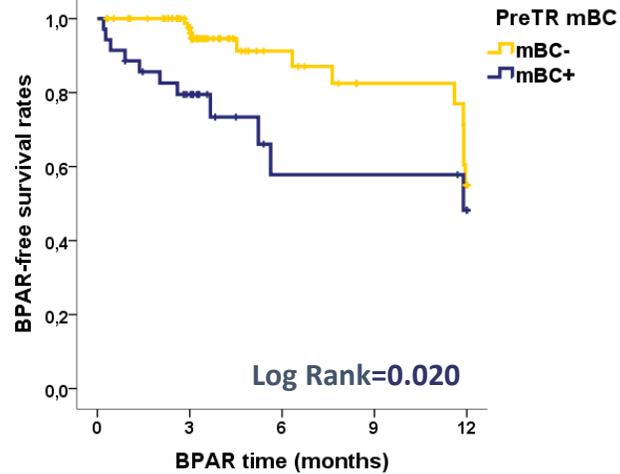


Antibody mediated rejection

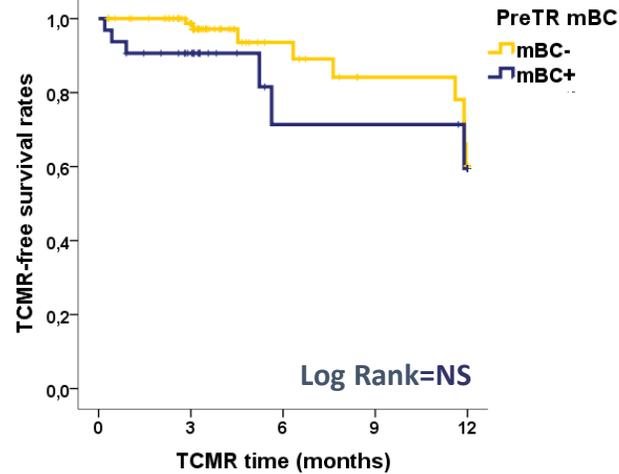


mBC

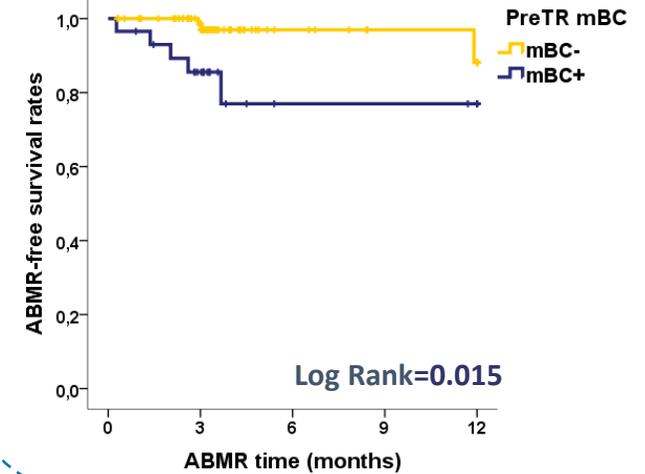
Biopsy-proven rejection



T cell mediated rejection



Antibody mediated rejection



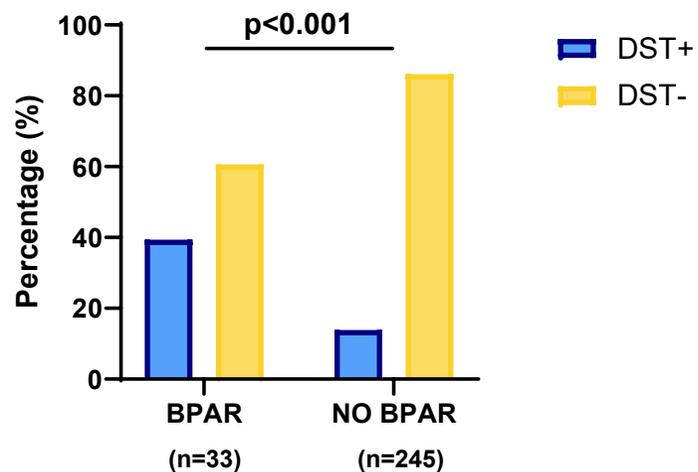
Independent predictors of BPAR

Clinically relevant variables (Recipient age; Time on dialysis; Cold ischemia time; DGF; rATG induction; CNI treatment; mTORi treatment and Belatacept treatment) and PreTR mBC ratio, not significant in the univariate analysis are not depicted in the multivariate model

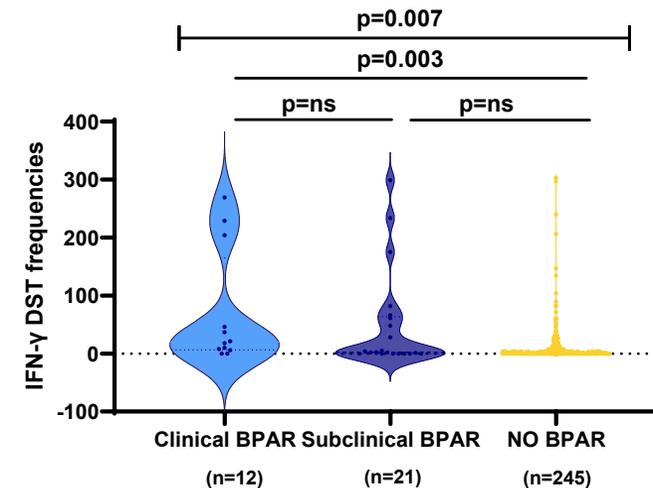
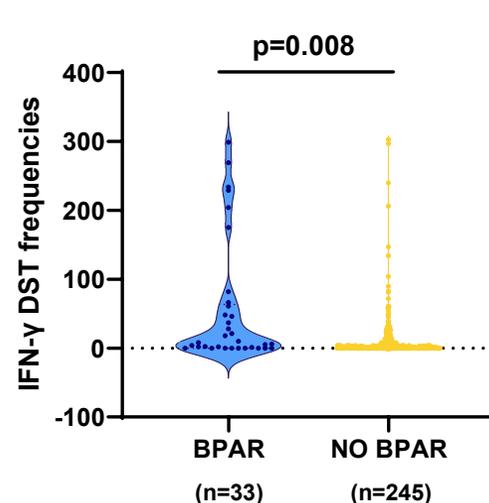
BPAR yes/no	Univariate			Multivariate		
	HR	CI 95%	p value	HR	CI 95%	p value
PreTR DSA (MFI index)	1.000	1.000-1.000	0.028	1.000	1.000-1.001	0.046
PreTR DST (frequencies)	1.009	1.005-1.014	<0.001	1.010	1.004-1.016	0.001
PreTR DST&mBC (frequencies)	214.596	4.535-10155.306	0.006	639.812	3.158-129642.850	0.017

PreTR DSA MFI, DST and DST&d(HLA)-sp mBC are independent correlates of BPAR

PostTR DST and incidence of BPAR

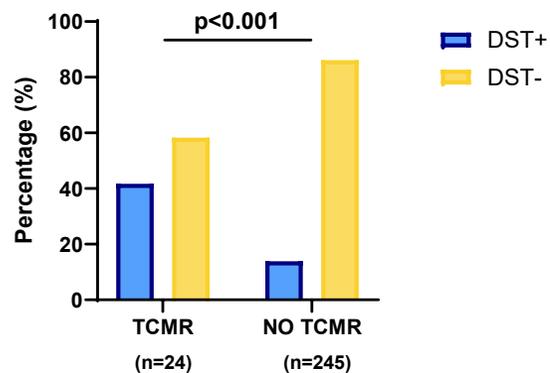


NPV 91.3%; PPV 27.7%; St 39.4%; Sp 86.1%

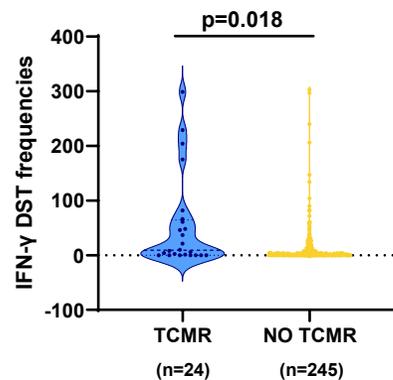


Significantly higher PostTR DST frequencies and High-risk DST categories (DST+) in patients with ongoing BPAR

T cell mediated rejection

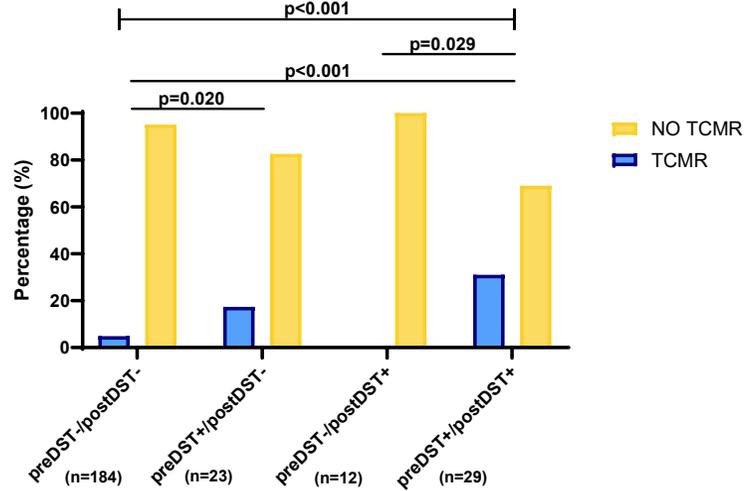
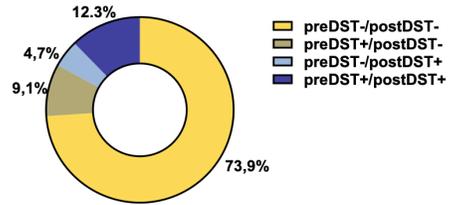


NPV 93.8%; PPV 22.7%; St 41.7%; Sp 86.1%

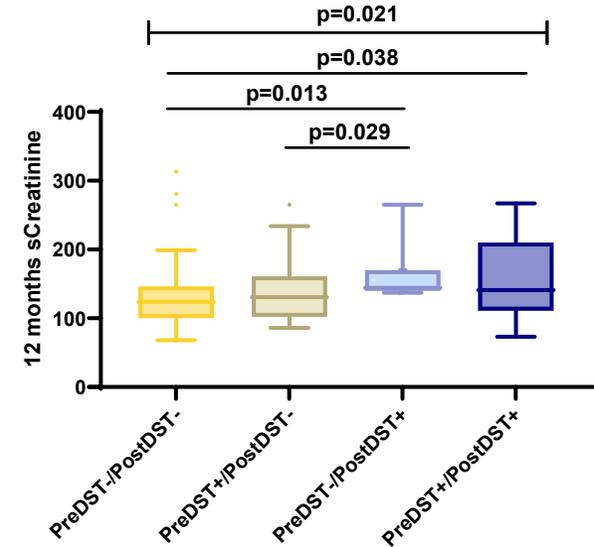


PostTR DST associates with ongoing TCMR, but not ABMR

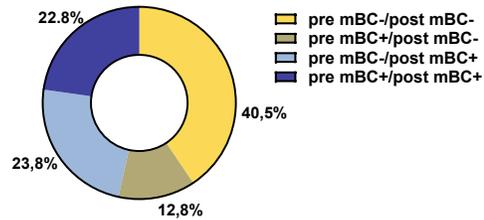
Monitoring DST and mBC overtime and allograft outcomes



PostTR DST+ associates with ongoing BPAR (TCMR), particularly in those patients with persistent DST+



PostTR DST+ associates with worse allograft function at 12months



Persistent mBC+ associate with ABMR rejection

SUMMARY

- A significant inhibition of PreTR DST is observed after TR, whereas an inflation in mBc frequencies occurs, suggesting a suboptimal germinal center control with current (T-cell targeting) IS.
- High frequencies of PreTR DST and mBc associate with higher BPAR rates, TCMR and ABMR, respectively. T-cell depletion abrogates the deleterious effect of preformed DST on post-TR TCMR.
- PostTR, high DST frequencies associates with ongoing BPAR, primarily TCMR, especially in patients with preformed DST. These patients display the worst kidney graft function at 12 months. Persistent mBC+ associate with ABMR.
- This blinded, prospective, observational multicenter study, underscores the role of adaptive T and B-cell immune memory favoring kidney allograft rejection and paves the way for future clinical trials aiming at personalizing immunosuppressive therapies

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