

IMMUNOLOGICAL AND HISTOLOGICAL REVERSAL OF REFRACTORY ABMR WITH DARATUMUMAB IN KIDNEY TRANSPLANT PATIENTS.

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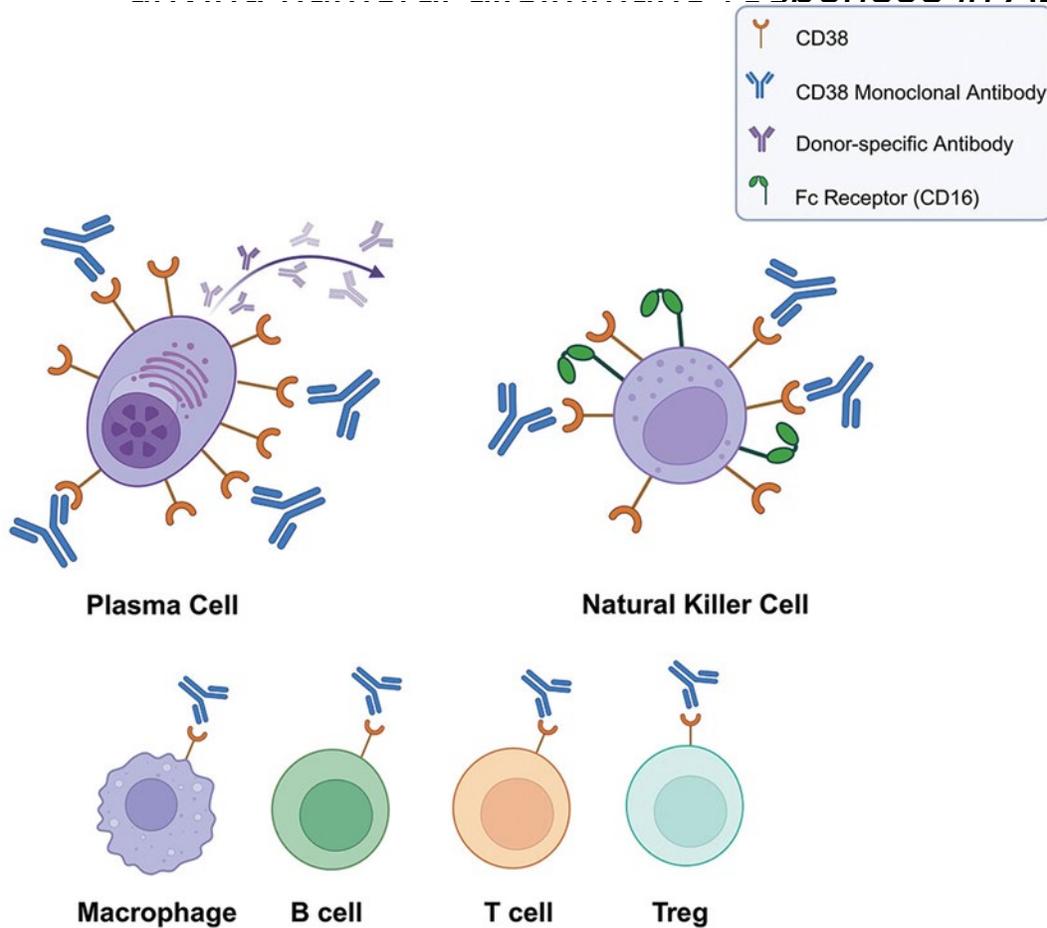
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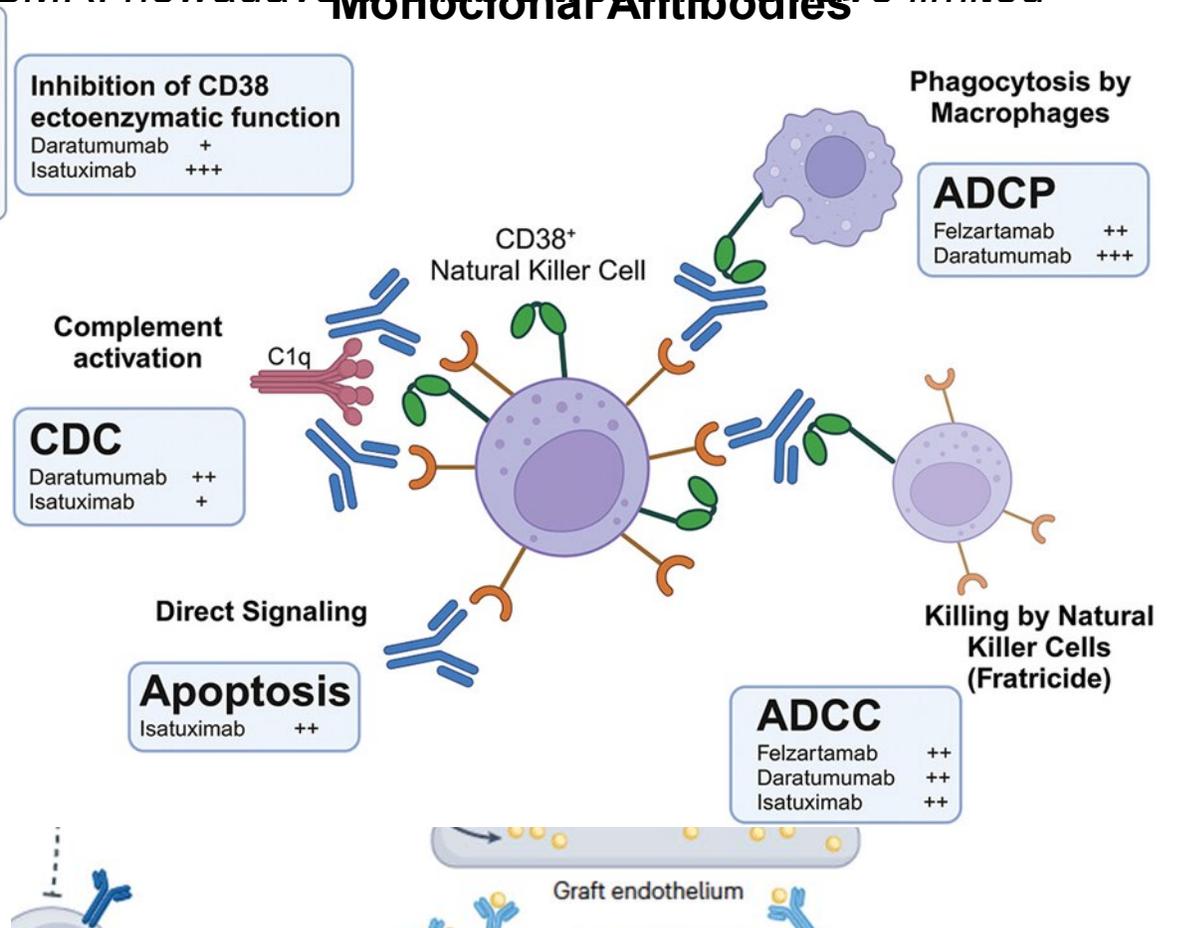
BACKGROUND

CD38 Expression on Immune Cells

a



Possible Mechanism of Action of CD38 Monoclonal Antibodies

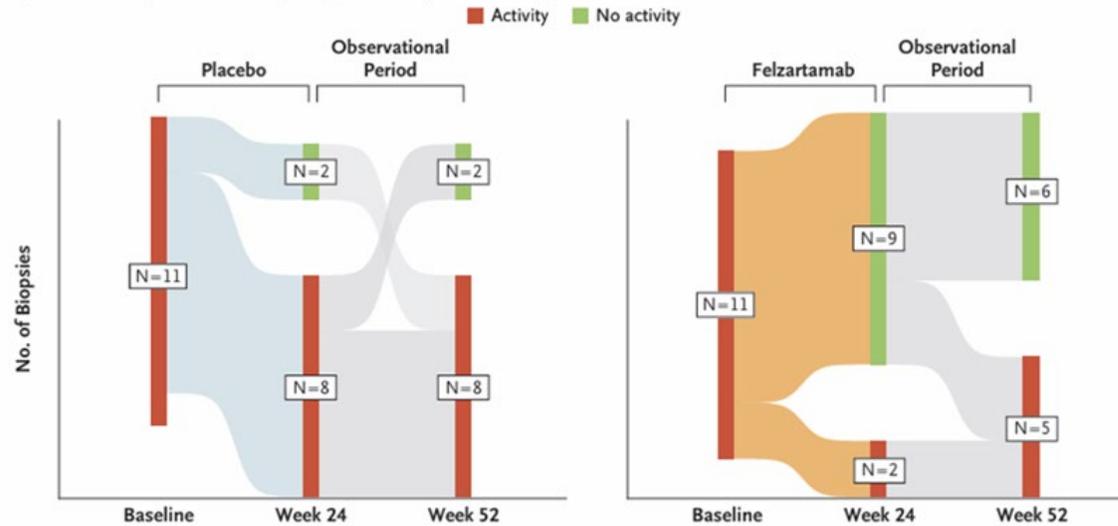


All three available drugs targeting CD38: Daratumumab, Isatuximab and Felzartamab, despite its mechanistic differences, have proved to effectively deplete CD38+ cells through both Fc-Dependent and Independent mechanisms

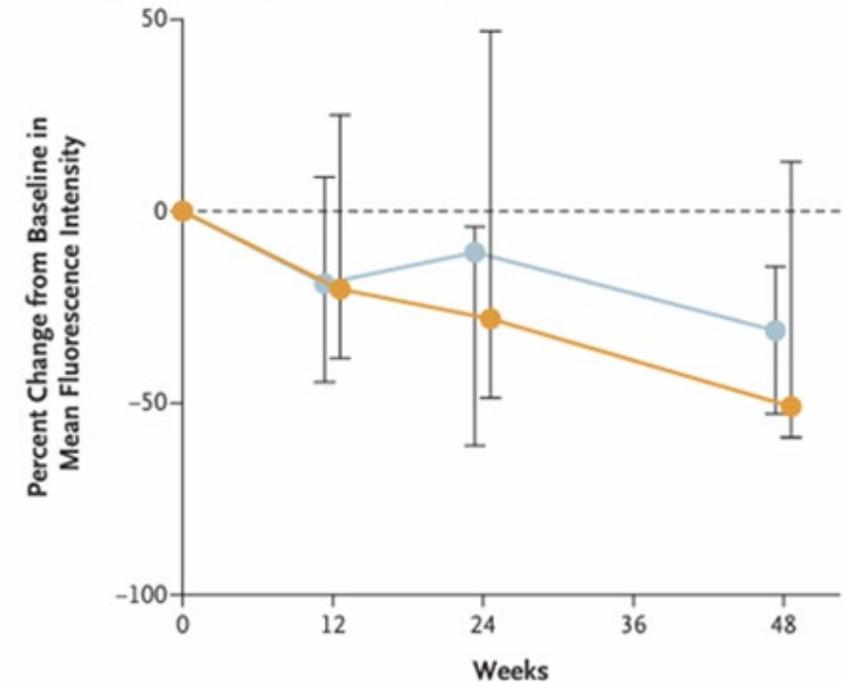
A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection

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A Sankey Plots of the Dynamics of Morphologic Antibody-Mediated Rejection



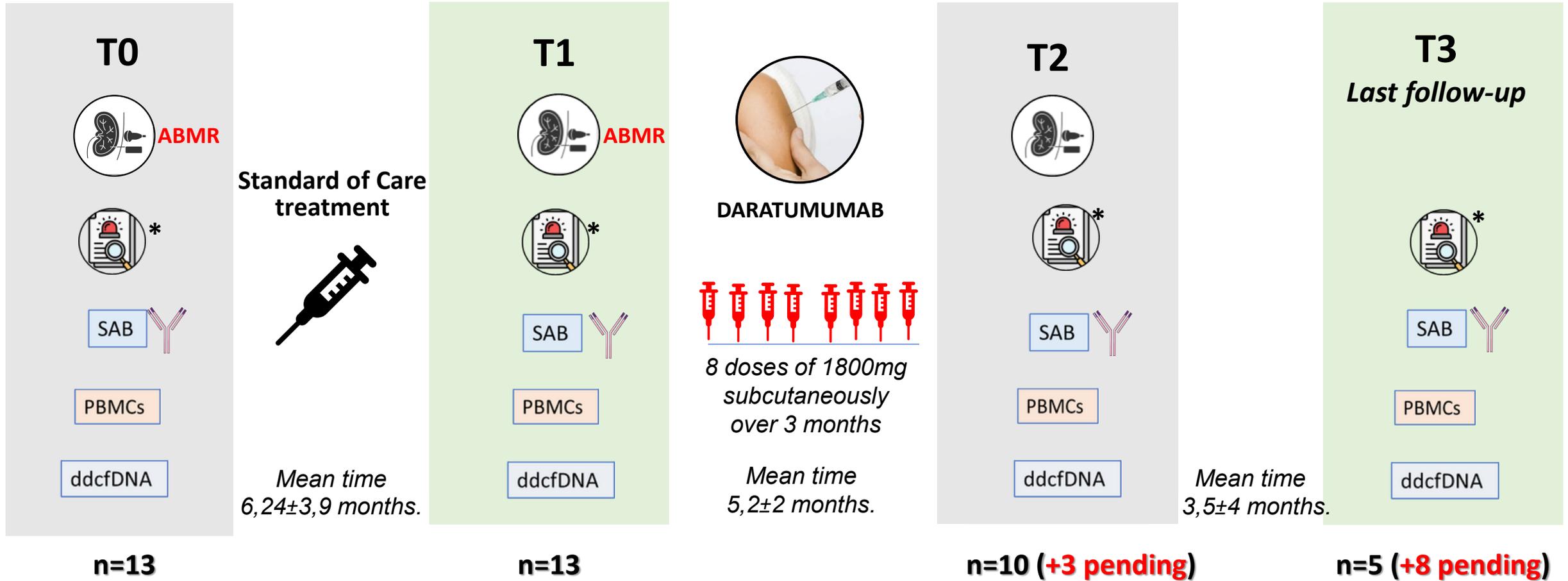
A Change in Donor-Specific Antibody Level



- Participants: **11 patients** Felzartamab VS **11 patients** placebo
- ➔ *acceptable safety and side-effect profiles, decrease on ABMR histology with Felzartamab as compared to placebo*

MATERIALS AND METHODS

Phase Ia/II , prospective Single Center interventional pilot study n=13



*Clinical follow-up for side effects monitoring and renal function

MATERIALS AND METHODS: BASELINE CHARACTERISTICS

CARACTERÍSTIC	N 13
Male, sex n (%)	8 (62)
Median recipient age (yr)	40 (22-59)
Type of donor:	
LRD. n (%)	2 (15)
BDD. n (%) / DCA. n (%)	4 (29) / 7 (50)
Previous kidney transplantation, n (%)	8 (69)
Median cPRA at transplantation	76 ± 41
Preformed anti-HLA donor-specific antibody, n (%)	8 (61)
Positive crossmatch at transplantation, n (%)	5 (43)
Immunosuppression induction treatment:	
Thymoglobulin, n (%) / Basiliximab, n (%)	10 (77) / 3 (23)
Immunosuppression: Maintenance treatment, n (%)	
Steroids + mycophenolic acid + Tacrolimus	(13) 100
Initial rejection treatment	
IVIG+Plasma exchang/IA, n (%)	10 (77)
Rituximab, n (%)	8 (62)
Eculizumab, n (%)	4 (31)
Esterease inhibidor C1, n (%)	1 (8)
Median time after kidney transplantation, (months)	38 ± 46,4

100% ABMR circulating DSA+

T0
(before conventional therapy)



ai	0,72 ±0,9
at	0,91±0,83
av	0,18±0,4
ag	1,55±0,93
ptc	1,91±0,7
C4d	5 positive (45%)
IFTA (ci+ct)	2,09±1,1
cg	1 positive (9%)

T1
(before-daratumumab)



ai	0,4 ±0,5
at	0,8±0,63
av	0±0
ag	1,8±0,78
ptc	2±4,7
C4d	3 positive (30%)
IFTA (ci+ct)	2,5±0,84
cg	4 positive (40%)

T0

SAB 

MFI	11102 ±7345
Class I n(%)	4 (26)
Class II n(%)	11 (73)
DR	3 (20)
DQ	9 (60)
DP	1 (7)
Preformed/de novo	10(67)/ 5(33)

T1

SAB 

MFI	8628 ± 6780
Class I n(%)	5 (26)
Class II n(%)	14 (74)
DR	3 (16)
DQ	10 (53)
DP	1 (5)
Preformed/de novo	12(63)/ 7(37)

RESULTS

ADVERSE EVENTS

INFUSION

- * 1 CASE OF LOCAL ERITEMA

DURING
TREATMENT

- * 2 CASES OF PNEUMONIA
- * 1 CASE OF PYELONEPHRITIS
- * 1 CASE OF SEPTIC SHOCK

SEVERE
ADVERSE
EVENTS

- * THERE WERE NO DEATHS
- * NO LOSS OF GRAFT DURING FOLLOW-UP

Follow-up with a mean of 6,8±5,1 months

RESULTS

EVOLUTION OF RENAL FUNCTION

Both:
Clinical n=5
Subclinical n=5

No statistically significant change in graft function and proteinuria over follow-up neither in clinical nor subclinical rejections

RESULTS

EVOLUTION OF GRAFT HISTOLOGY

MVI

c4d

ai

at

cg

IFTA

Microvascular inflammation was significantly decreased in follow-up kidney biopsies after Daratumumab treatment

No difference in transplant glomerulopathy, tendency toward higher IFTA score at follow-up

RESULTS

EVOLUTION OF DSAs MFI

CLASS I n=5

CLASS II n=14

Anti-DR and DP n=4

Anti-DQ n=10

*Overall, DSA MFI decreased after Daratumumab treatment.
A rebound after end of treatment was observed especially in High MFI, antiDQ DSAs*

RESULTS

EVOLUTION OF GRAFT FUNCTION AND HISTOLOGY ACCORDING TO DSA EVOLUTION

eGFR

Proteinuria mg/g

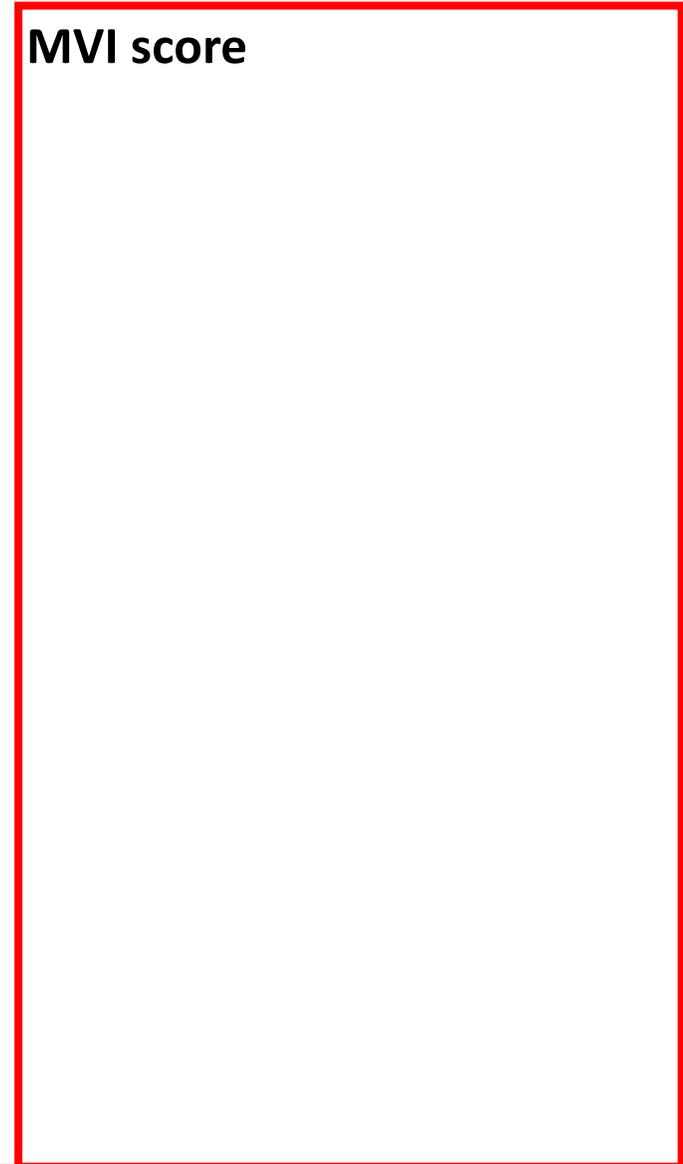
MVI score

DSA responders

n=6

DSA
non- responders

n=4



CONCLUSIONS:

- Daratumumab rescue therapy for refractory ABMR cases, shows an optimal safety profile with mild adverse events and good tolerability.
- All patients displayed a significant decrease of MVI lesions, which translated into the stabilization of kidney graft function.
- Daratumumab induced a significant, albeit transient reduction on circulating DSAs MFI, especially class I and anti-DR HLA antibodies.
- Improvement on MVI lesions was also observed in patients without changes on DSA levels, suggesting a direct effect on cellular infiltrates beyond plasma cell-induced DSAs.
- Mechanistic studies on cellular responses are ongoing to decipher patient profiles best responsive to this treatment.
- Maintenance therapy after ABMR rescue therapy with CD38-targeting therapies remains a main challenge to be investigated.



THANKS SO MUCH FOR YOUR
ATTENTION