



IMPACT OF DESENSITIZATION THERAPY WITH ISATUXIMAB IN HIGHLY SENSITIZED PATIENTS WAITLISTED FOR KIDNEY TRANSPLANTATION

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BACKGROUND

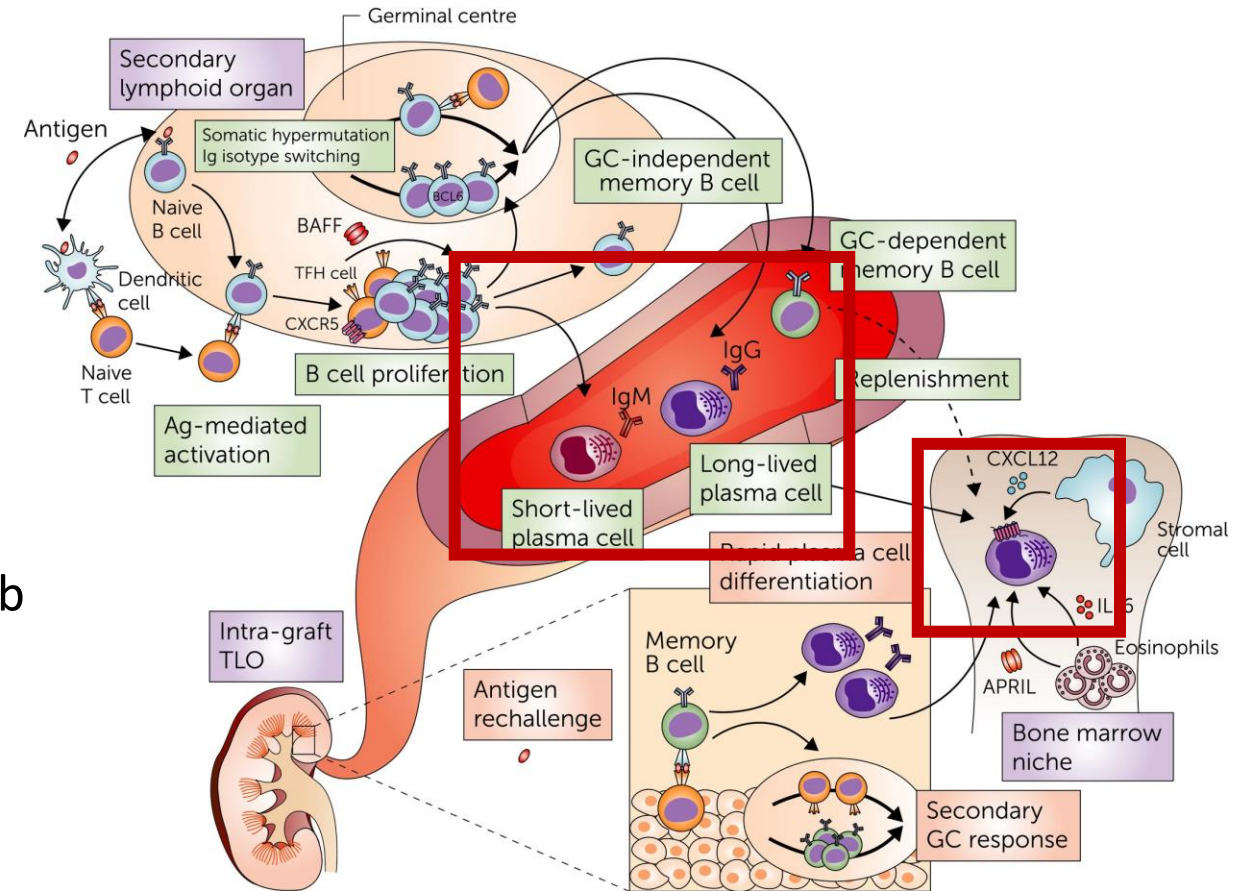
- Sensitization against HLA antigens is one of the main barriers to access kidney transplantation, leading to longer waitlist time and ABMR.

Circulating
HLA-sp mBCs

Bone marrow
HLA-sp LLPCs

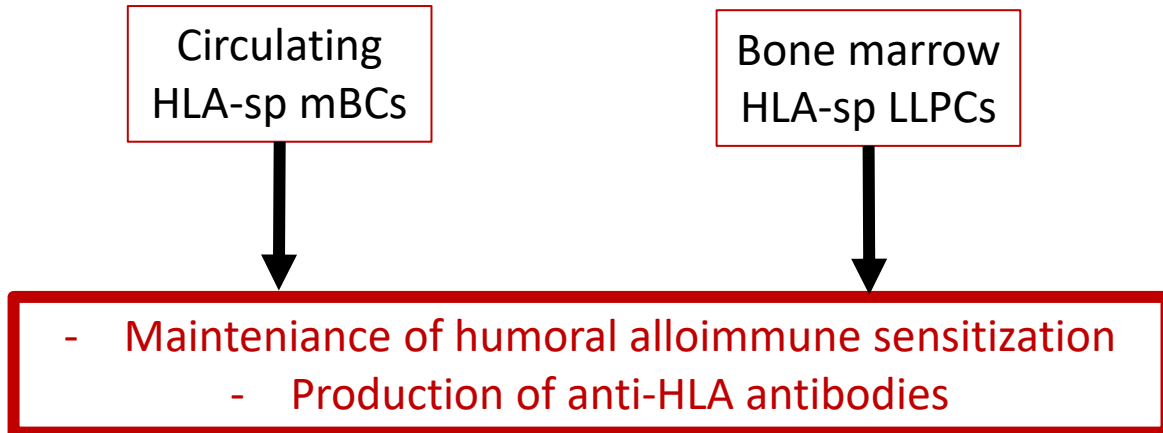
- Maintenance of humoral alloimmune sensitization
- Production of anti-HLA antibodies

- New therapeutic approaches targeting Ab producing cells are arising.

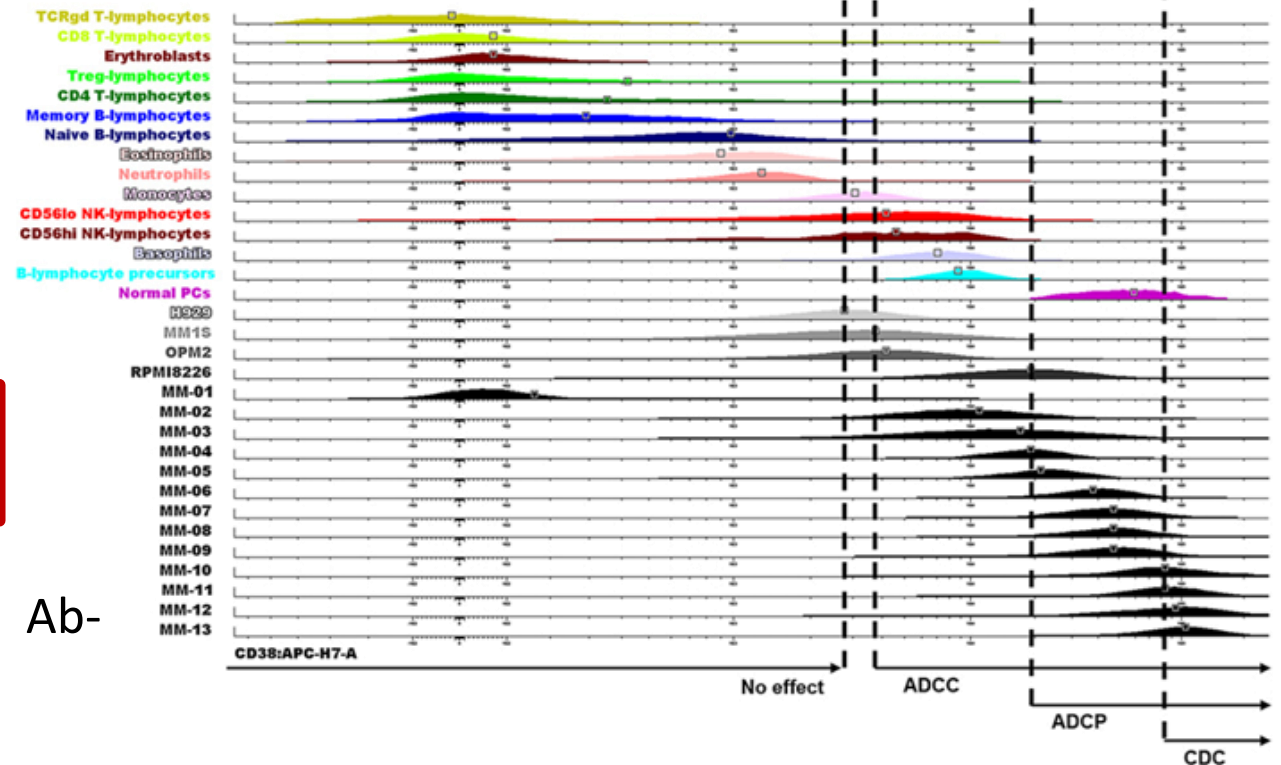


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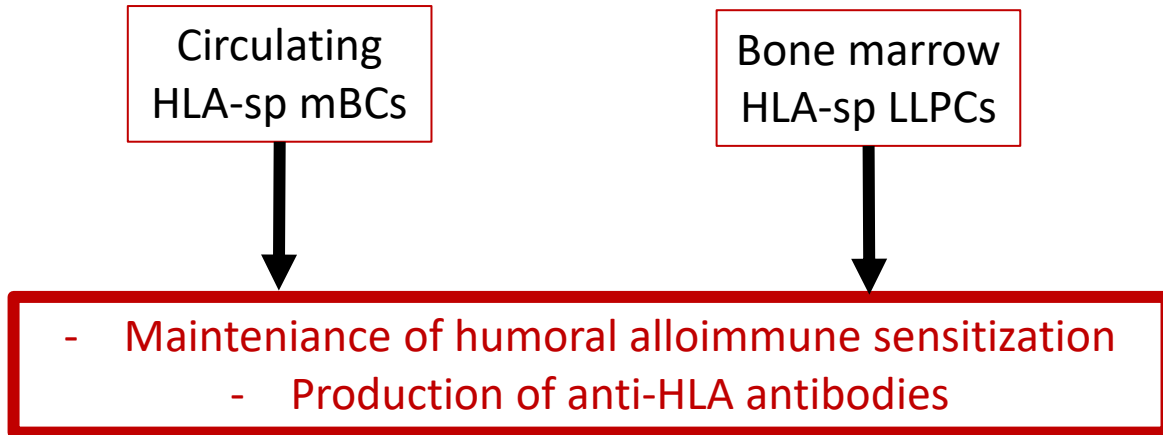


- New therapeutic approaches targeting Ab-producing cells are arising
- Anti-CD38 monoclonal antibody Isatuximab has been shown to target plasma cells in multiple myeloma patients

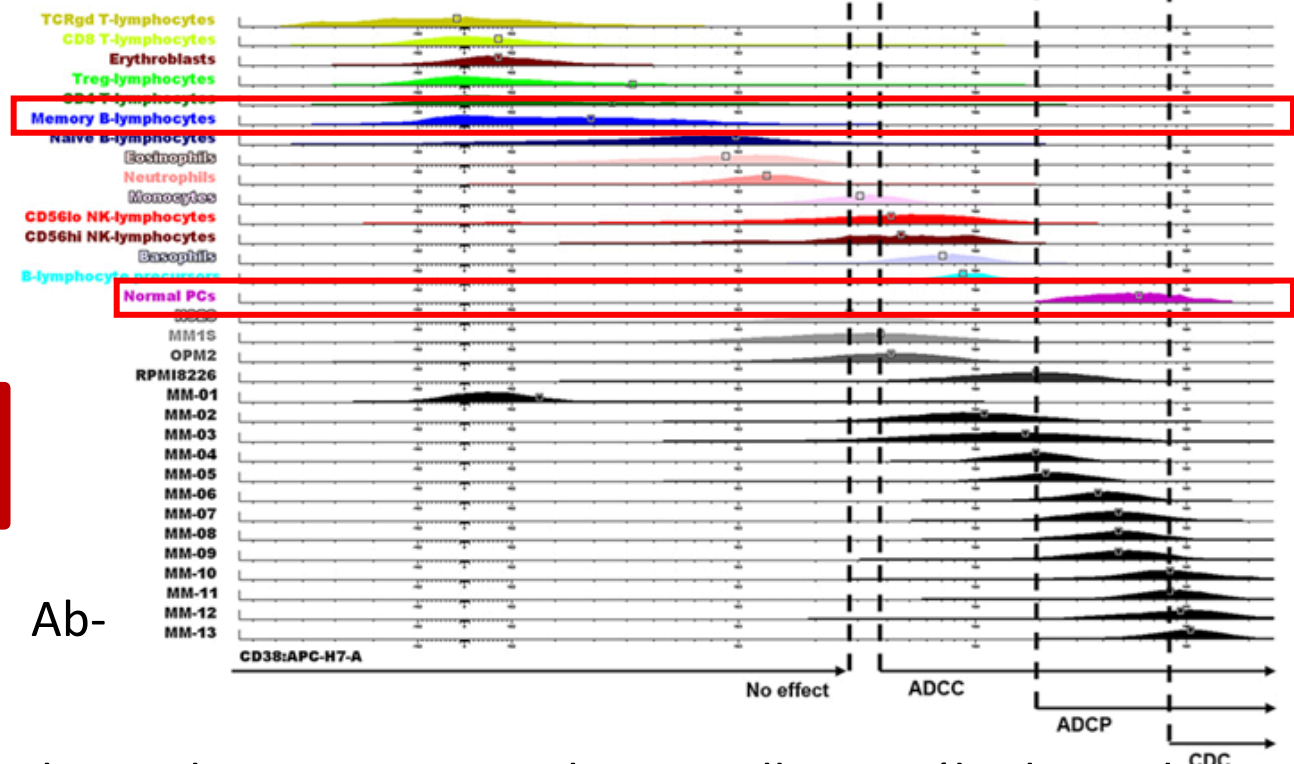


BACKGROUND

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- New therapeutic approaches targeting Ab-producing cells are arising
- Anti-CD38 monoclonal antibody Isatuximab has been shown to target plasma cells in multiple myeloma patients
- Targeting plasma cells through an anti-CD38 monoclonal antibody (mab) in SOT may reduce titers of anti-HLA antibodies.



HYPOTHESIS AND OBJECTIVES

Desensitization with anti-CD38 monoclonal antibody may deplete HLA-sp plasma cells and reduce titers of anti-HLA antibodies in highly sensitized kidney transplant patients



- Study the mechanistic effect of anti-CD38 in bone marrow and peripheral blood humoral immune cell populations.
- Track functional circulating IgG-secreting HLA-sp mBCs during and after desensitization treatment.
- Assess HLA-sp IgG-secreting plasma cells in the bone marrow before and after therapy.

METHODOLOGY

Anti-CD38 mAb Isatuximab multinational clinical trial (NCT04294459)

- 18-70 years old patients
- Active kidney transplant waitlist candidates
- Highly sensitized (cPRA >80%)

All enrolled patients
N=23

PBMCs
N=16

Bone marrow
N=3



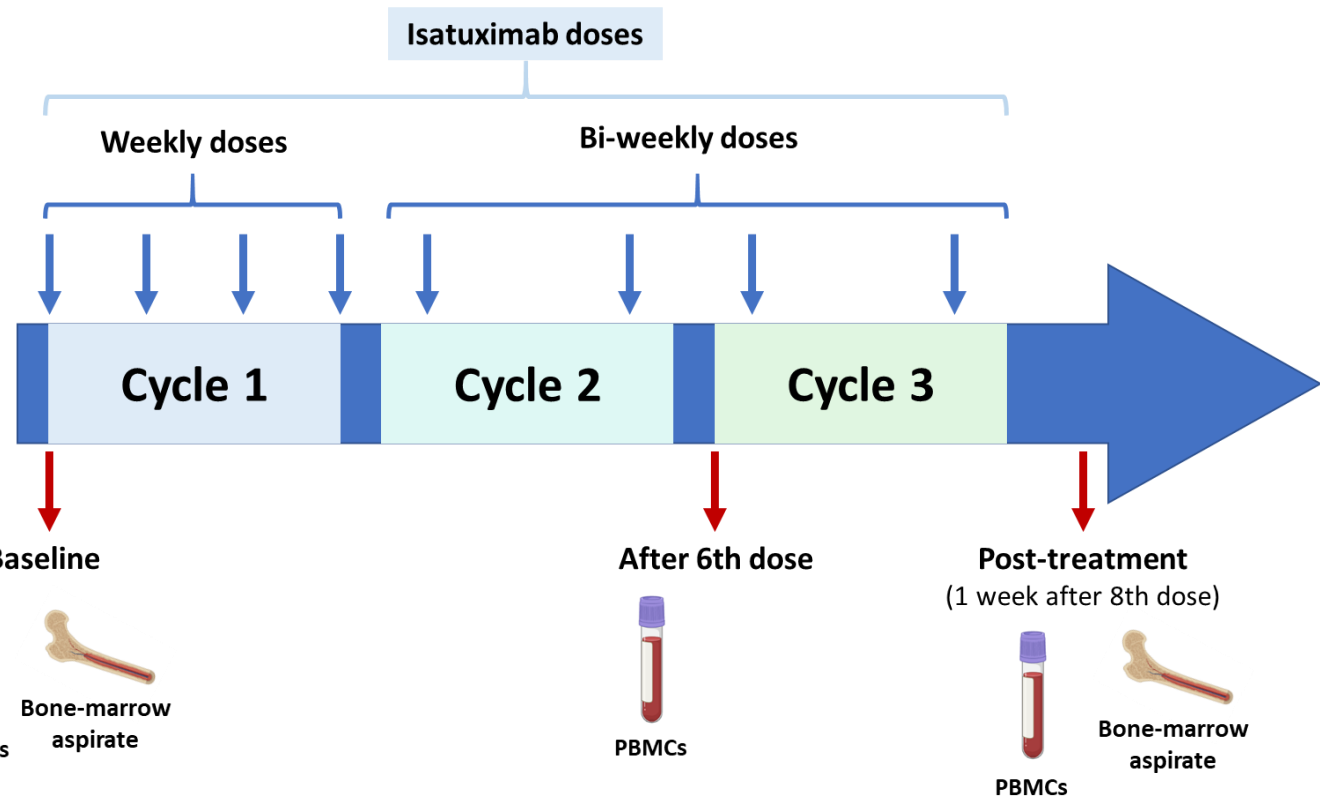
Memory B cells expansion

High dimensional spectral cytometry



Functional assessment of HLA-sp LLPCs

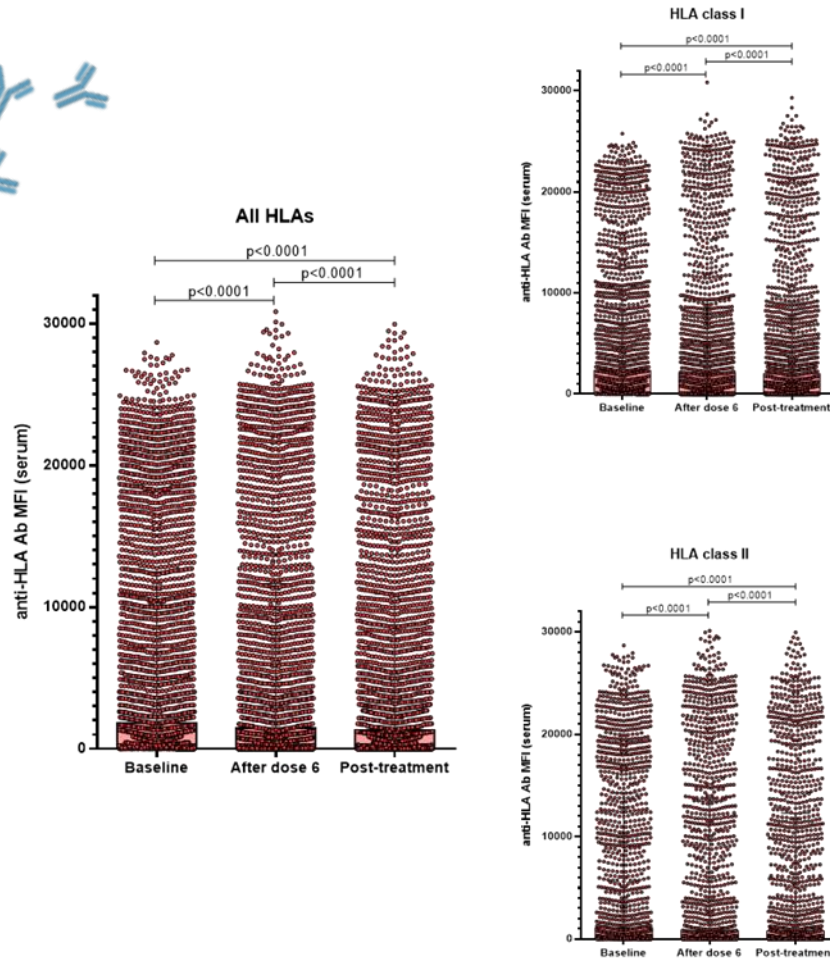
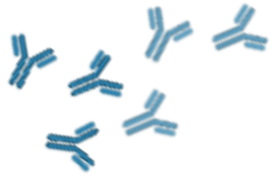
1. HLA-sp B cell Fluorospot assay.



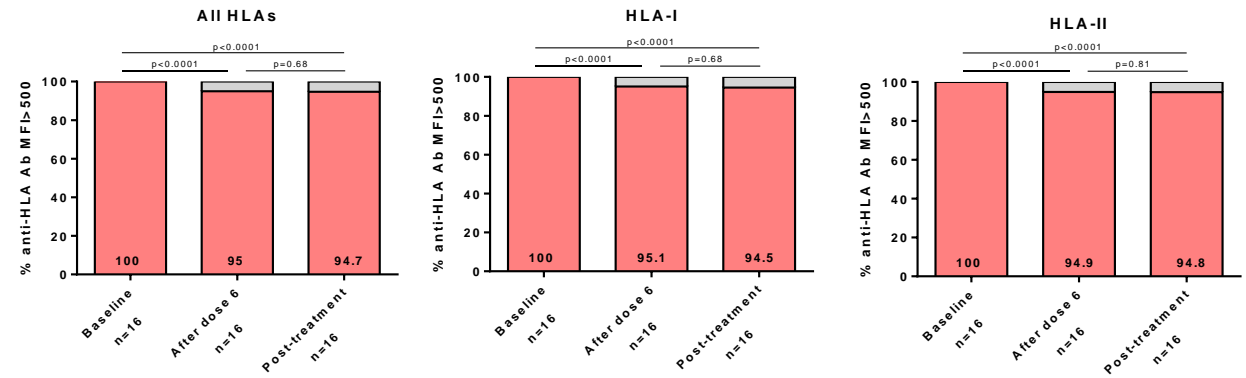
Functional assessment of HLA-sp mBCs

1. Analysis of mBCs culture supernatants with SAB.
2. HLA-sp B cell Fluorospot assay.

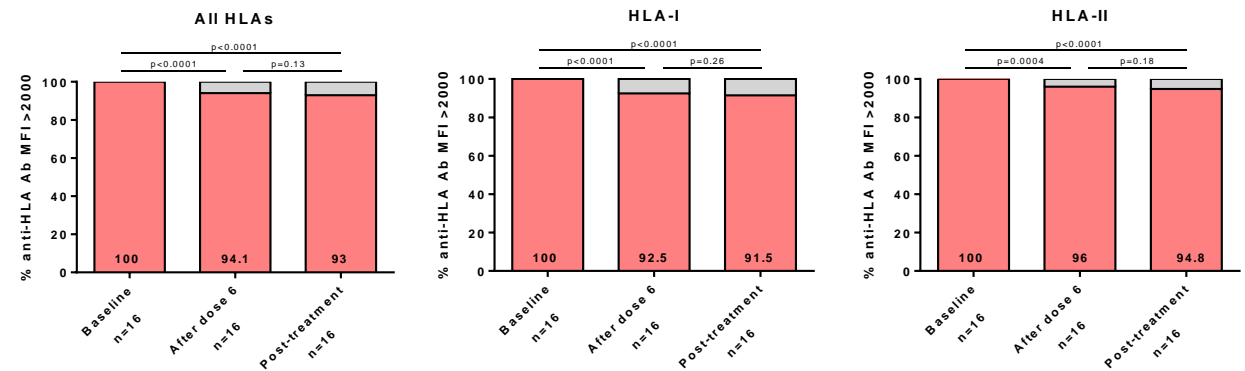
RESULTS: serological compartment



% MFI < 500 anti-HLA circulating Ab in serum



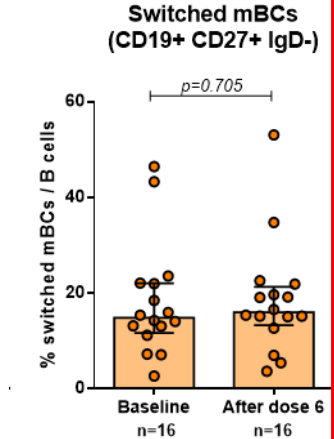
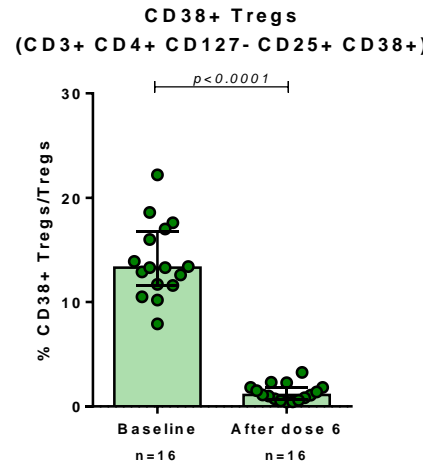
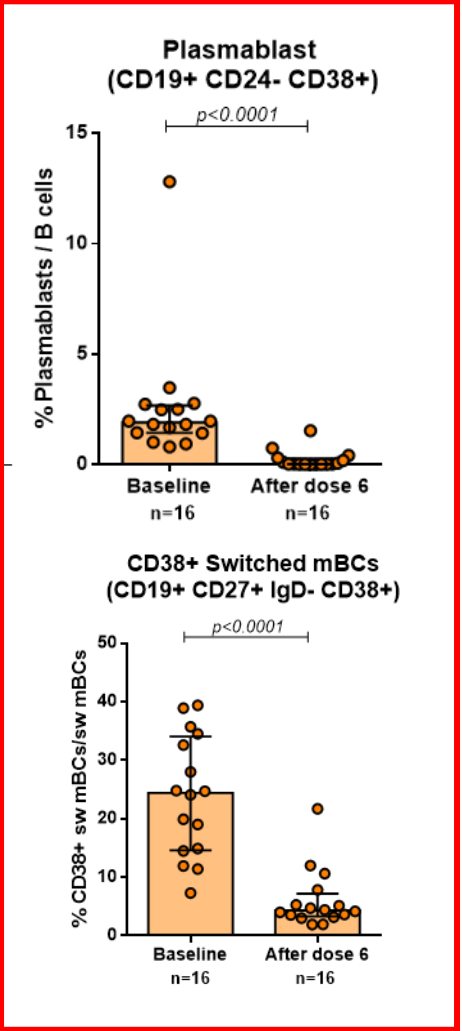
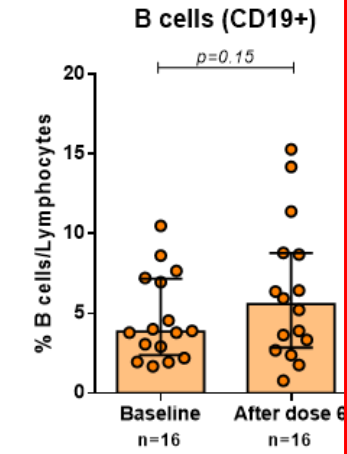
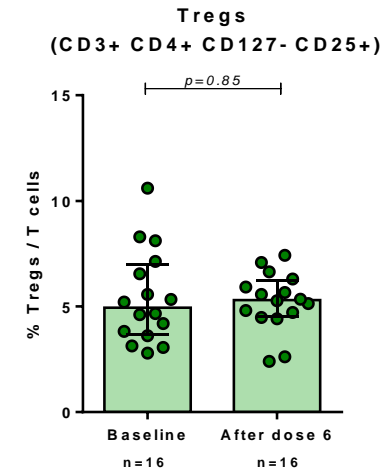
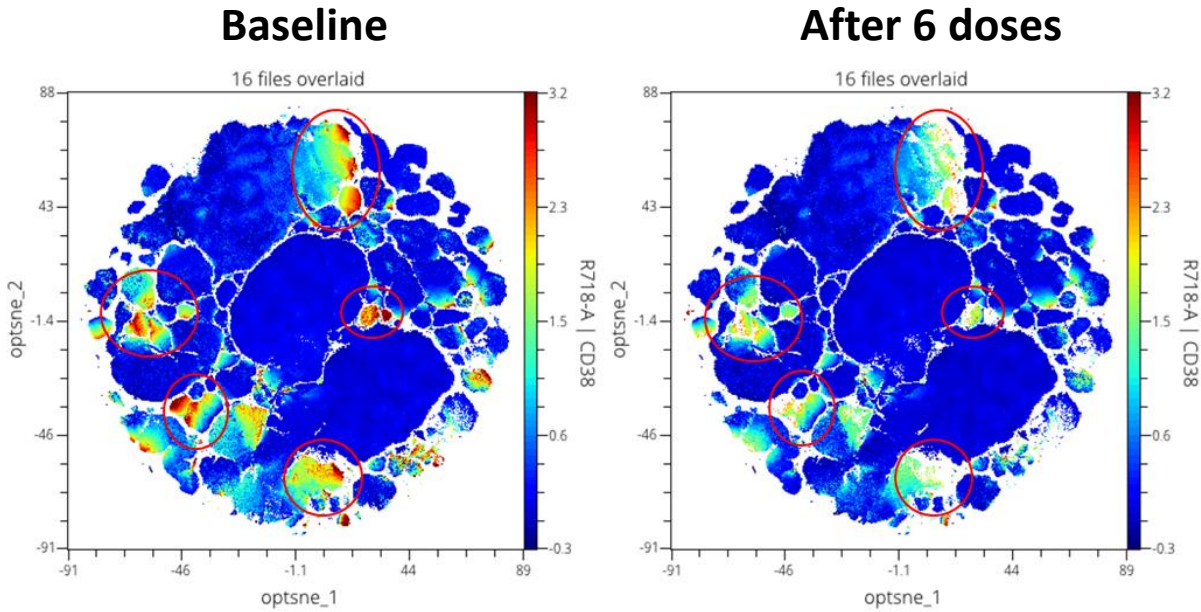
% MFI < 2000 anti-HLA circulating Ab in serum



➡ Isatuximab decrease significantly levels of circulating anti-HLA Abs

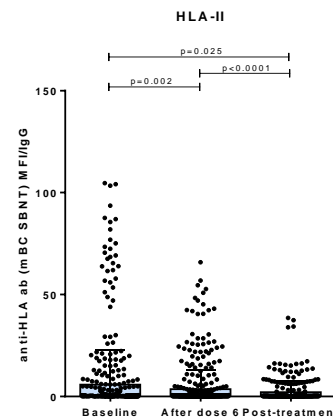
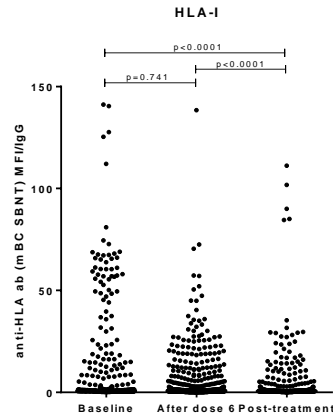
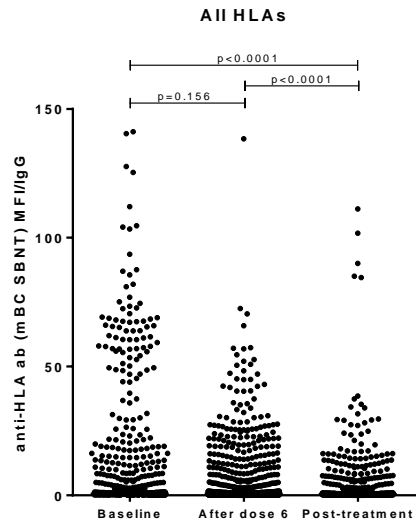
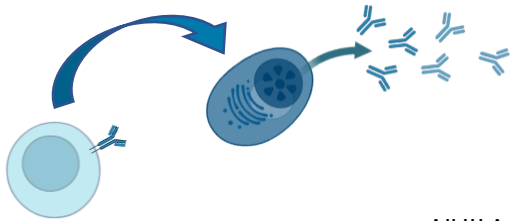
➡ 5.3% of anti-HLA Abs positive at baseline become negative after treatment.

RESULTS: Changes in circulating PBMCs

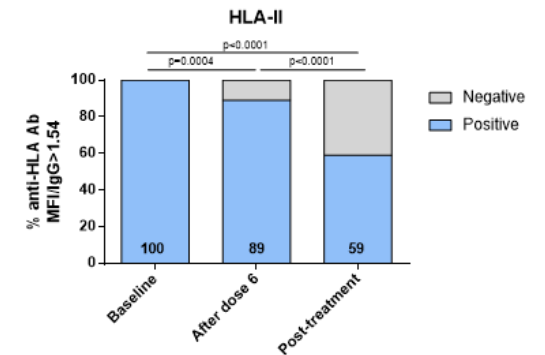
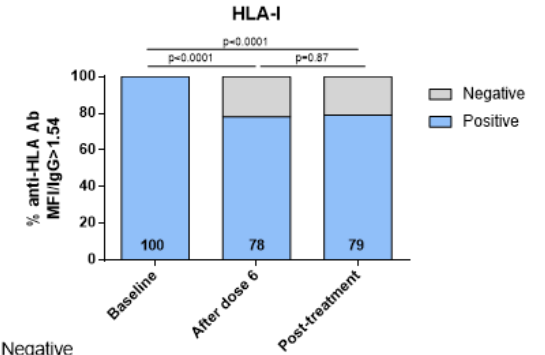
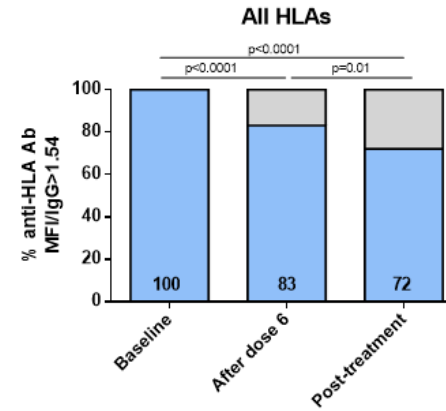


➔ **Isatuximab depleted circulating plasmablast and reduced significantly CD38+ mBCs**

RESULTS: repertoire of anti-HLA Abs in circulating mBCs



% Negative HLAs in mBCs



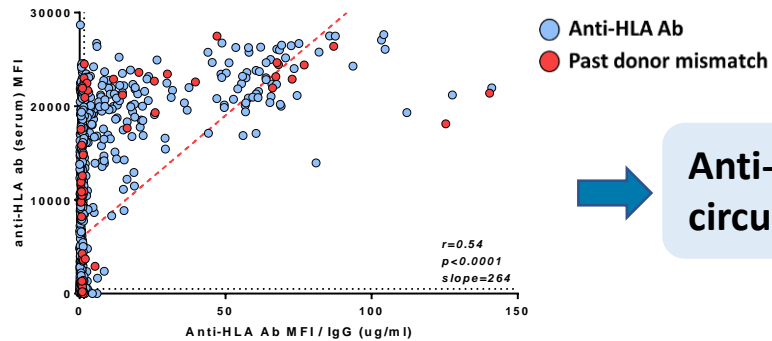
Significant decrease in levels of anti-HLA Abs secreted by HLA-sp mBCs



28% of anti-HLA Abs from mBCs become negative after desensitization

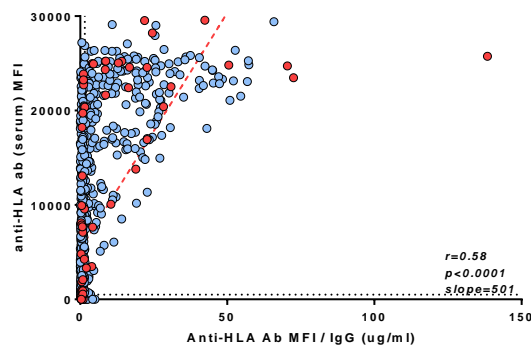
RESULTS: HLA-sp mBCs against past donors HLAs

Baseline

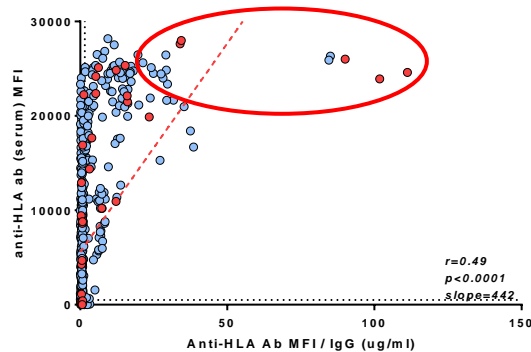


Anti-HLA Abs repertoire from mBCs correlates moderately with circulating anti-HLA Abs in serum

After 6th doses

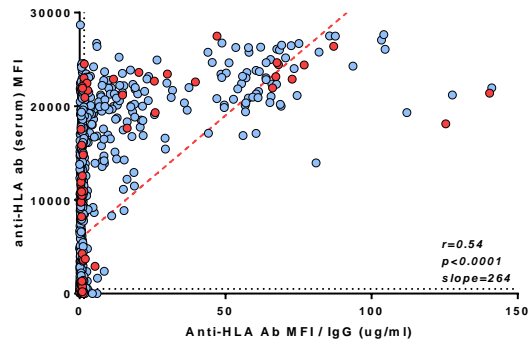


Post-treatment

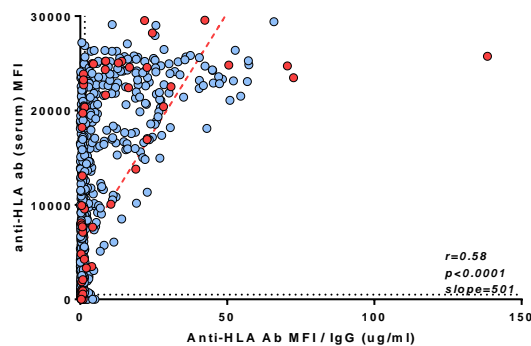


RESULTS: HLA-sp mBCs against past donors HLAs

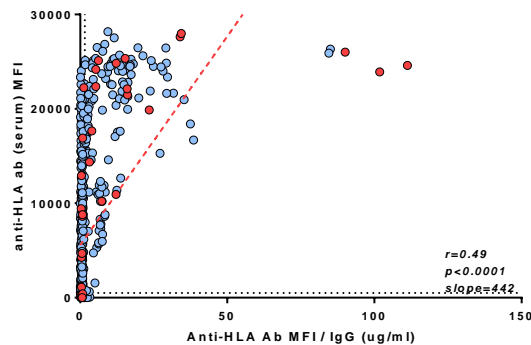
Baseline



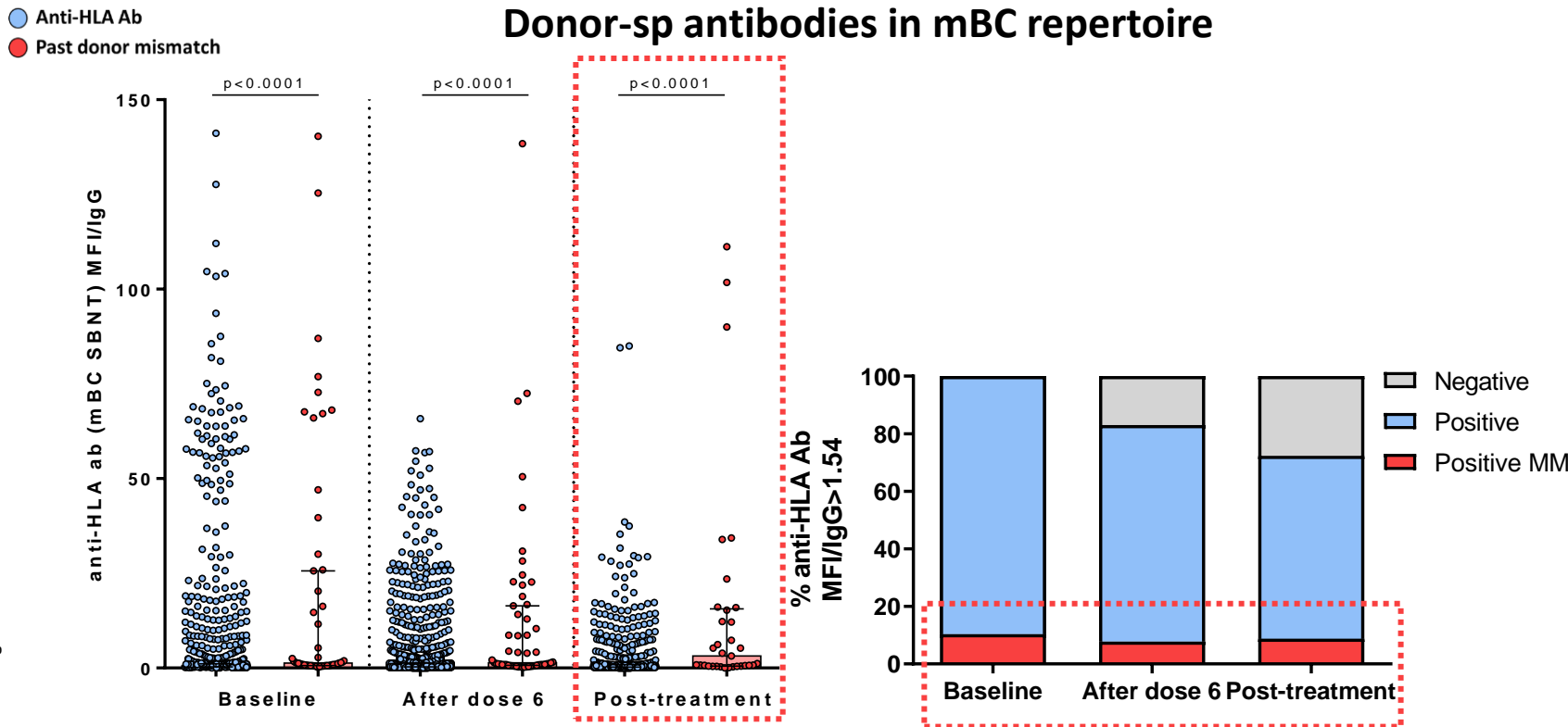
After 6th doses



Post-treatment



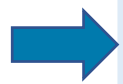
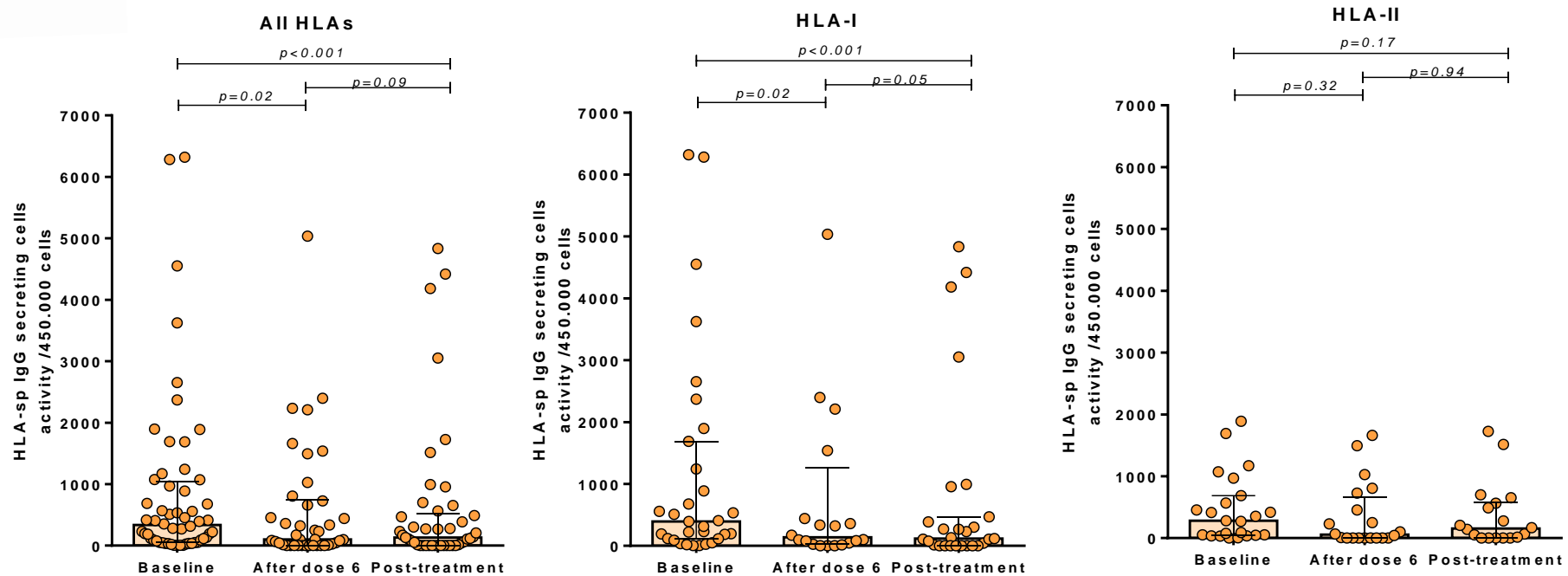
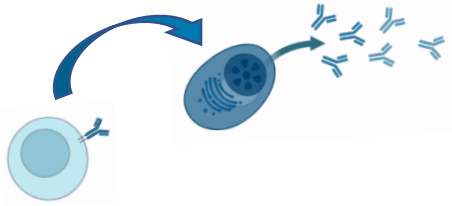
Donor-sp antibodies in mBC repertoire



Donor-specific anti-HLA Abs in mBCs are higher than non-donor-sp Abs, specially after treatment

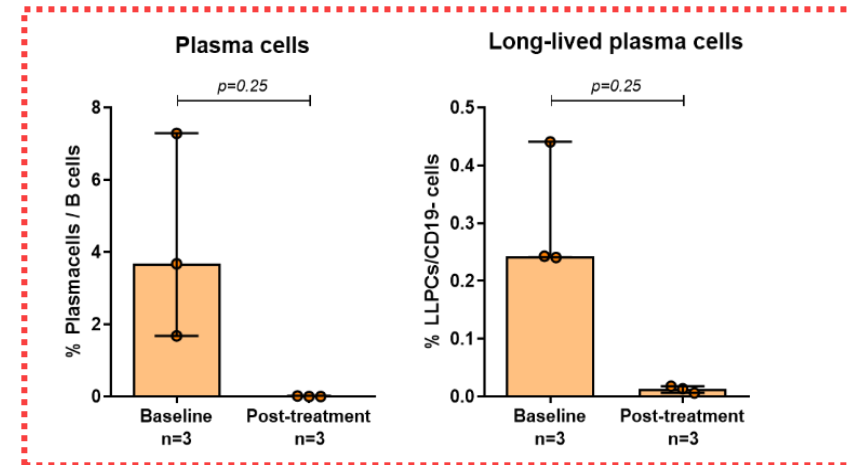
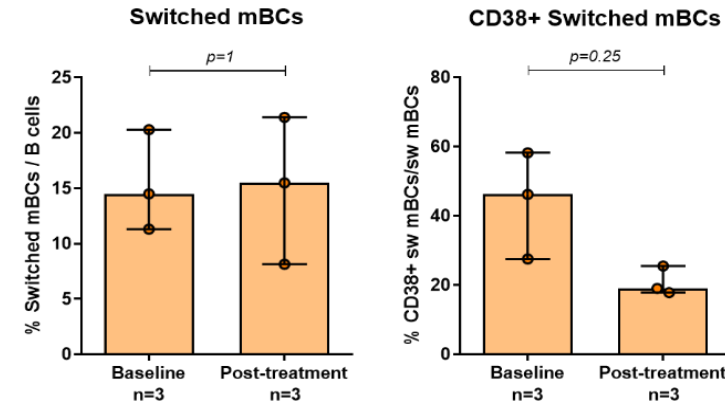
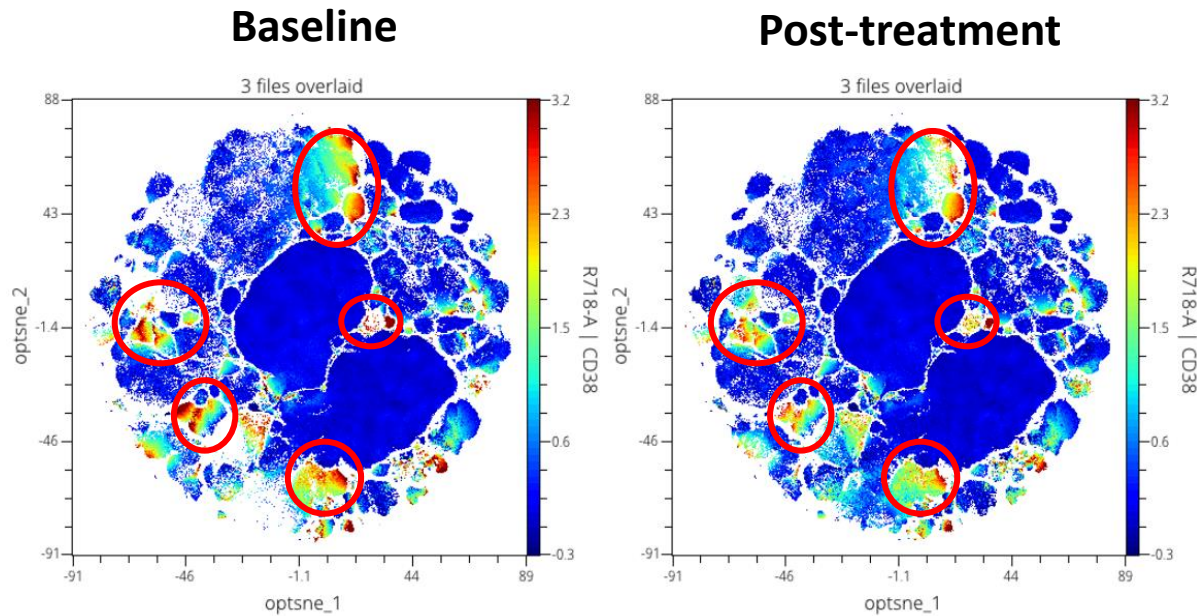
Majority of depleted anti-HLA Abs from mBCs are not specific from a past donor

RESULTS: Functional assessment of HLA-sp mBCs at a single cell level through HLA-sp fluorospot assay



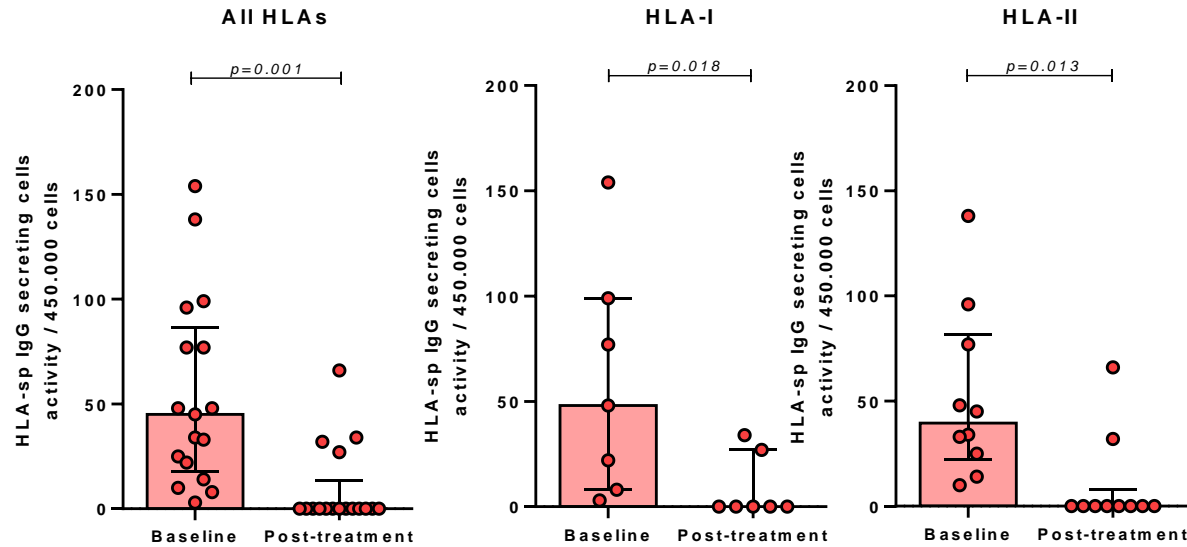
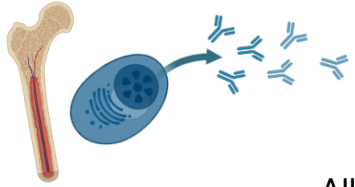
Isatuximab reduces circulating IgG-secreting and functionally active HLA-sp mBCs, being more effective against class I HLAs than class II

RESULTS: Depletion of bone marrow CD38+ plasma cells and LLPCs

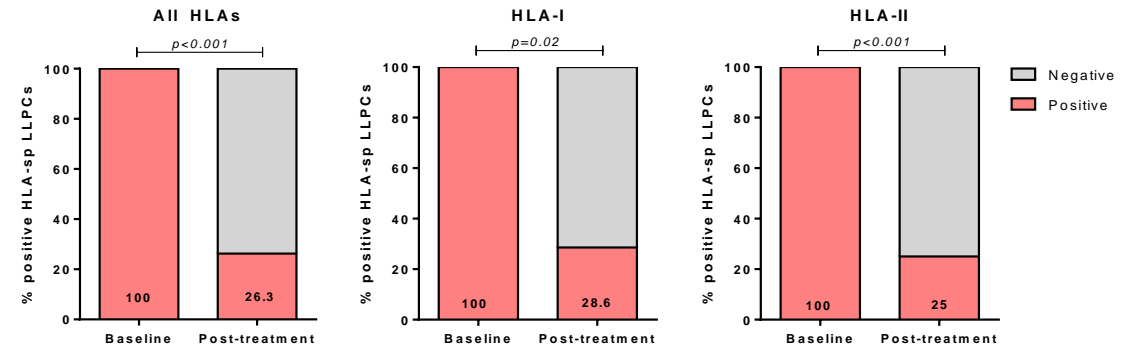


Bone-marrow plasma cells and long-lived plasma cells were drastically reduced after desensitization with isatuximab

RESULTS: Depletion of bone marrow HLA-sp plasma cells



% Negative HLAs in bone marrow plasma cells



➔ Isatuximab reduces significantly functional IgG-secreting HLA-sp plasma cells in the bone marrow

➔ 74% of HLA-sp plasma cells detected at baseline were depleted after treatment

Conclusions

- Desensitization with Isatuximab lowers levels of anti-HLA circulating antibodies.
- Targeting HLA-sp plasma cells through CD38 successfully depleted plasma cells in the bone marrow, both phenotypically and functionally.
- Besides plasma cells, Isatuximab may reduce circulating HLA-sp mBCs and its production of anti-HLA Abs.
- **Isatuximab is able to reduce the burden of sensitization in highly immunized patients**

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