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1 **HLA Desensitization in Solid Organ Transplantation: Anti-CD38 to Across the**
2 **Immunological Barriers**

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13 **Keywords: Anti-CD38, Daratumumab, HLA Desensitization, Humoral Response, Solid Organ**
14 **Transplantation**

15 **Abstract**

16 The presence of anti-human leucocyte antigen (HLA) antibodies in the potential solid organ
17 transplant recipient's blood is one of the main barriers to access to a transplantation. The HLA
18 sensitization is associated with longer waitlist time, antibody mediated rejection and transplant lost
19 leading to increased recipient's morbidity and mortality. However, solid organ transplantation across
20 the HLA immunological barriers have been reported in recipients who were highly sensitized to HLA
21 using desensitization protocols. These desensitization regimens are focused on the reduction of
22 circulating HLA antibodies. Despite those strategies improve rates of transplantation, it remains
23 several limitations including persistent high rejection rate and worse long-term outcomes when
24 compare with non-sensitized recipient population. Currently, interest is growing in the development
25 of new desensitization approaches which, beyond targeting antibodies, would be based on the
26 modulation of alloimmune pathways. Plasma cells appears as an interesting target given their critical
27 role in antibody production. In the last decade, CD38-targeting immunotherapies, such as
28 daratumumab, have been recognized as a key component in the treatment of myeloma by inducing an
29 important plasma cell depletion. This review focuses on an emerging concept based on targeting
30 CD38 to desensitize in the field of transplantation.

31 Introduction

32 HLA sensitization and antibody-mediated rejection

33 Solid organ transplantation (SOT) has become the best therapeutic option for end-stage organ
34 disease but faces two major issues: the limited transplant supply and the poor long-term transplants
35 outcome which have not improved over the past 30 years (1–3). This observation is related to the
36 occurrence of antibody-mediated rejection (ABMR) which remains the death-censored leading cause
37 of transplant loss across all solid organ transplants (3,4). ABMR is defined on the association of
38 histologic lesions (microvascular inflammation), histologic evidence of alloantibodies – endothelium
39 interaction (c4d staining) and circulating donor-specific antibodies mostly directed against human
40 leucocyte antigens (HLA) (3–10). Following blood transfusion, pregnancy or previous graft failure,
41 candidates for organ transplantation can become sensitized against HLA and produce circulating anti-
42 HLA antibodies (11,12). In particular, pending on their properties donor-specific anti-HLA
43 antibodies (DSA), are responsible for ABMR leading to allograft dysfunction and graft loss (13–
44 18). Currently, immunomonitoring of the transplant candidate’s is routinely performed in order to
45 stratify the immunological risk by determining the presence and specificity of anti-HLA antibodies
46 and potential DSA (11,16). The highly sensitized patients have longer waitlist times with significant
47 adverse effect on both quality and quantity of life (1,2). Several strategies are applied to limit the
48 time on the waiting list of highly immunized patients such as prioritization in transplant’s access,
49 promotion of transplantation from living-donor allografts, development of kidney paired donation
50 and desensitization.

51 52 Desensitization and solid organ transplantation’s outcome

53 Current desensitization strategies have been developed in kidney transplantation and extended
54 to other solid organ transplantation (17–21). The goal of desensitization regimens in presensitized
55 transplant candidates is twofold including the reduction of anti-HLA level to allow transplantation
56 and the improvement of transplantation outcome through the prevention of ABMR (22). A stepwise
57 approach is commonly used to desensitize including, (i) either high-dose intravenous
58 immunoglobulin (IVIG) or low dose IVIG in association with plasmapheresis to remove antibodies
59 and, (ii) anti-CD20 targeting agent, such as rituximab, to prevent rebound antibodies development
60 by B cell depletion (23–27). Regarding the kidney transplantation field, despite the desensitizing
61 effect, the subsequent transplantation is associated with higher rate of rejection and higher rate of
62 hospital readmission after transplantation (28–30). However, long term outcomes for patient and
63 graft survival have been reported to be similar to that of non-sensitized patients (31). Furthermore,
64 the benefit of desensitization compared to remaining on the transplant waiting list has been evaluated
65 only in few large studies and their results remain controversial (32,33). Montgomery *et al.* and
66 Orandi *et al.* reported a survival benefit at five years after kidney transplantation in 211 and 1025
67 desensitized patients respectively compared to patients remaining on the waiting list (34,35).
68 Interestingly, in a study performed on 213 desensitized recipients of living donor transplants,
69 Manook *et al.* showed that desensitization was not associated with a survival benefit compared to
70 matched sensitized control patients who were waitlisted (36). On the other hand, keeping patients a
71 long time on dialysis represent a considerable financial burden while decreasing the quality and
72 length of life for affected patients (32,33). Thus, it appear as necessary to develop novel therapeutic
73 approaches in order to prevent ABMR and improve long-term survival of transplanted organs in
74 highly immunized recipient.

75 76 Desensitization regimens targeting plasma cells

77 The available therapeutic tools to manage the humoral response appears modestly successful
78 in the context of SOT and alloimmunity. Indeed, antibody rebound due to plasma cells (PC), which

79 do not express CD20, limit the efficacy of the most commonly used strategy combining IGIV,
80 plasmapheresis and B cell depletion by anti-CD20 depleting agent. Targeting PC with new
81 pharmacological tool from autoimmunity and cancer research could allow a better management of the
82 humoral response in desensitization protocols (37). In the germinal center, after the enhancement of
83 alloantigen responses by T follicular helper (Tfh), activated B cells develop into memory-B cells,
84 progress to plasmablasts and ultimately to antibody-producing PC (38,39). These PC are the long-
85 lived mediators of lasting humoral immunity and persist in medullary niche where they can secrete
86 high-affinity complement-activating DSAs (38,40). Several emerging strategies aim to deplete PCs
87 compartment in order to prevent ABMR (37,41). First, Interleukin 6 (IL-6) is a cytokine promoting
88 Tfh and enhancing the progression of B cells to high-affinity antibodies producing PC (42).
89 Tocilizumab, a first-in-class humanized monoclonal antibody (mAb) with specificity for IL-6R,
90 reduce inflammation within the allograft during ABMR in heart and kidney transplantation (43) and
91 induce circulating DSA reduction (44). Clazakizumab is a humanized IgG1 mAb with specificity for
92 IL6 which can also induce circulating DSA reduction (45). Both Tocilizumab and Clazakizumab are
93 pharmacological agents with major interest in the development of desensitization strategies targeting
94 PC (37,46). On another hand, proteasome inhibitors represent one of the most promising solution to
95 deplete PC in the setting of desensitization, targeting more selectively PCs population. Bortezomib
96 and carfilzomib have been evaluated in desensitization trials, lacking control group, leading to
97 controversial results (47,48). Both induce significant PCs depletion whereas DSA level did not
98 significantly decrease or rebound occurred rapidly. In fact, targeting PC may lead to rapid germinal
99 center activation by deleting the negative feedback usually provided by PC and rebound humoral
100 immunity and compensation (49). Therefore, dual targeting approach (combining PCs depletion with
101 proteasome inhibitors and costimulation blockade) may silence the germinal center and prevent
102 humoral compensation. This strategy has been recently evaluated using carfilzomib and belatacept as
103 desensitization in highly sensitized non-human primate model with a reduction of bone marrow PC,
104 DSA levels reduction, and prolongation of allograft survival. Most animals experienced ABMR with
105 humoral-response rebound, suggesting desensitization must be maintained after transplantation using
106 ongoing suppression of the B cell response (50,51). An emerging therapy to induce DSA reduction
107 and to prevent rebound DSA development is the use of antiplasma cell therapies such as anti-CD38,
108 anti-CD19 or bispecific anti-CD3 / anti-BCMA (B cell maturation antigen). In this review, we
109 propose to focus on anti-CD38 as a desensitization regimen in SOT.

110 **CD38-Targeting strategies**

111

112 CD38 and CD38-targeting antibodies

113 The protein CD38 is a type II transmembrane glycoprotein known as a multifunctional
114 molecule. CD38 play dual roles as receptors and ectoenzymes (52). The CD38/CD31 interactions are
115 crucial to leukocyte adhesion and transmigration through the endothelium (53). CD38 is also an
116 enzyme that catalyzes several reactions leading to the regulation of cytoplasmic calcium fluxes and a
117 wide range of others physiological functions such as cellular metabolism (52). CD38, found
118 throughout the immune system especially natural killer and PC, is highly expressed in multiple
119 myeloma cells (54). Altogether, this has triggered the development of several CD38 antibodies to
120 treat multiple myeloma (54–56). Daratumumab (DARZALEX®, Janssen), fully human IgG1-kappa,
121 was the first CD38 antibody that was recognized as an emerging therapy against myeloma in the last
122 decade (57). Daratumumab have multiple effects including Fc-dependent immune-effector
123 mechanisms and direct effects. The Fc-dependent immune-effector mechanisms include antibody-
124 dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-
125 dependent cytotoxicity (54,55). Direct effects include induction of apoptosis, as well as inhibition of
126 CD38 ectoenzyme function, which may lead to disruption of the PCs niche. Those Fc-dependent
127 effects and direct effects are associated with deep and sustained CD38⁺ cells depletion, mostly PC
128 and NK cells (54,55,58). The ability of daratumumab to efficacy deplete PCs compartment permit to
129 use it as an new agent in therapeutic armamentarium for multiple myeloma (56). Large clinical trials
130 have demonstrated significant improvements in the outcome of patients with relapsed multiple
131 myeloma with use of daratumumab and it has been recently approved in front-line regimens (56–60).
132 Isatuximab (SARCLISA®, Sanofi) is a chimeric IgG1-kappa which has stronger direct effects than
133 daratumumab but lower ability to induce Fc-dependent immune-effector mechanisms, while it
134 remains unknown whether these functional differences observed between different CD38 antibodies
135 affect their therapeutic utility (55,61). Many other strategies targeting CD38 are under development
136 and a selection is listed in Table 1. The CD38-targeting antibodies generally represent a safe
137 treatment. Indeed, the most reported toxicity is infusion related reactions which remain successfully
138 controlled by premedication and infusion rate management with low frequency of recurrence during
139 subsequent injections (62). A higher rate of viral infections in patients treated with daratumumab has
140 been reported in some studies leading to a recommended administration of valaciclovir during the
141 administration of anti-CD38 antibodies (62).

142

143 Immunomodulatory effects of CD38-targeting antibodies

144 CD38-targeting antibodies have immunomodulatory effects such as improving the host-anti-
145 tumor immune response (63). Krejcik *et al.* showed that daratumumab monotherapy against myeloma
146 was associated with both CD4⁺ and CD8⁺ T cell expansion(64). This increase in T-helper cells and
147 cytotoxic T-cell was associated with functional modification including elevated antiviral and
148 alloreactive functional responses, and significantly greater increases in T-cell clonality as measured
149 by T-cell receptor sequencing (63,64). These modifications are associated with depletion of CD38⁺
150 immunosuppressive cells including regulatory T cells, regulatory B cells, and myeloid-derived
151 suppressor cells. It is well known that such regulatory cells inhibit the host-anti-tumor immune
152 response in the context of several malignancies including multiple myeloma (65–67). Altogether, this
153 immunomodulatory activity of CD38 antibodies may be essential to their therapeutic efficacy.
154 Indeed, it has been highlighted in clinical trials showing that expansion of effector T-cells and
155 eradication of immune suppressors cells by daratumumab used against refractory and newly
156 diagnosed multiple myeloma was correlated to a marked improvement in response and progression-
157 free survival (57,59,63,67). It might be hypothesized that these immunomodulatory abilities have
158 important implication for sustained control of the tumor and further deepening of response (63). As a

159 result of these pleiotropic immune modulation, CD38 antibodies also enhance anti-tumor activity of
160 others anti-cancer drugs with several studies highlighting that CD38-targeting antibodies have strong
161 synergistic activity, such as combination to lenalidomide as well as to PD1/PD-L1 inhibitors (56,68).
162 Besides effect on immune cells, CD38 antibodies may also modulate immunometabolic pathway.
163 Indeed, CD38-targeting agent's exposure could lead to lower adenosine level in tumoral
164 microenvironment, which is known as immunosuppressive metabolite (69,70). All these properties
165 enhancing the anti-tumoral response are of major interest in the field of oncology while it could be
166 problematic in immunosuppressive strategies such as autoimmune diseases treatment or
167 desensitization and SOT's context.

168 **CD38 antibodies in solid organ transplantation**

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170 CD38 antibodies in non tumoral context

171 In the last decade, several strategies to handle with autoimmune or alloimmune pathologic
172 situations include CD38 antibodies (71–73). Indeed, long-lived plasma cells, which produce
173 pathogenic antibodies, are unresponsive to standard immunosuppression. Besides PC depletion and
174 immunomodulatory effect, CD38 expression on PCs from patients with autoimmune condition (74)
175 and reduction of auto-antibodies in patients exposed to daratumumab (75) support the evaluation of
176 daratumumab in patients with autoantibody-dependent disorders and, in extension, to alloimmune
177 situation such as SOT. Available evidence about CD38 antibodies efficacy in these situations are
178 mostly cases reports of daratumumab use against immune cytopenia. Daratumumab were used to
179 treat warm autoimmune hemolytic anemia post-hematopoietic stem cell transplant (76), refractory
180 cold agglutinin disease (77), Evans syndrome (78) and pure red cell aplasia (79) with improvement in
181 the majority of cases. Regarding other autoimmune disease, the administration of daratumumab in
182 two patients with refractory lupus was recently described exhibiting clinical responses associated
183 with significant depletion of long-lived plasma cells and modulation of effector T-cell responses
184 (80). As regard as autoimmune encephalitis, targeting CD38 was achieved with daratumumab in one
185 case of life-threatening anti-NMDA receptor encephalitis and in one case of refractory anti-CASPR2
186 encephalitis with improvements of neurological sequelae (81,82). In the last case, severe septicemia
187 leading to patient death highlight an unmet need of rigorous clinical investigation to determine the
188 efficacy and tolerance of CD38-targeting agent in autoimmune disease.

189

190 CD38 antibodies and ABMR treatment

191 In antibody-mediated non-neoplastic diseases, alloimmune situation such as SOT represent a
192 field where targeting CD38 is promising. As alloantibody-producing PC express CD38 at a higher
193 level than other CD38⁺ hematopoietic cells and CD38 antibodies induce a profound depletion of
194 CD38⁺ PC, CD38 appears as a rational target to handle with harmful alloantibodies such as DSA
195 (83,84). Currently, only few studies have been published regarding the use of CD38 antibodies for
196 desensitization in patients awaiting transplantation or for treatment of ABMR. Concerning treatment
197 of ABMR, the first report was in a patient with refractory early active ABMR caused by anti-A
198 isohemagglutinins after kidney transplantation from his ABO-incompatible sister (85). Based on the
199 efficacy of daratumumab in the treatment of pure red cell aplasia following ABO-incompatible
200 hematopoietic stem cell (79) and non-response of several therapies; daratumumab were tested as a
201 rescue solution leading to a significant decrease of the pathogenic isohemagglutinins and resolution
202 of tissue damage in the kidney biopsy. Kwun and colleagues also published a case report of
203 daratumumab as a therapeutic strategy for refractory heart and kidney rejection in a patient who
204 received heart and kidney transplants due to systemic lupus (72). Both transplant biopsy showed T
205 cell-mediated rejection, ABMR and diffuse PC infiltration associated to the presence of several
206 DSA. To face refractory cardiogenic shock and acute kidney failure dependent to dialysis, a
207 compassionate use of daratumumab lead to the resolution of both allograft function, improvement in
208 acute kidney lesions with decreased PCs infiltrate and dramatic decline for the majority of DSA. A
209 recurrent acute PC-rich rejection on kidney biopsy and significant ascension of DSA were
210 successfully managed with daratumumab. Recently, two others cases were reported: one refractory
211 ABMR after a heart transplant successfully treated with daratumumab and one chronic active ABMR
212 in a kidney allograft recipient diagnosed with myeloma exposed to daratumumab (73,86). In the last
213 one, the exhaustive immuno-monitoring showed that the main mode of action seems to be based on
214 PC depletion, with profound PCs reduction in the bone marrow and peripheral blood and the
215 abrogation of in vitro alloantibody production by PC enriched from bone marrow aspirates, leading
216 to significant reduction in DSA levels (73). Another observation is that daratumumab led to depletion

217 of NK cells infiltrating the allograft and circulating NK cells, which is major interest knowing the
218 potential role of NK cells in microvasculature inflammation through engagement of their Fc gamma
219 receptor IIIA with endothelium-bound DSA (87). Interestingly, while follow up biopsy showed
220 resolution of humoral activity, it was observed tubulointerstitial inflammation which prompted
221 steroid treatment. The author highlighted that the molecular signature of this infiltrate was not similar
222 to signature of T-cell mediated rejection leading to question the trigger of this infiltrate not associated
223 with graft dysfunction. Indeed, daratumumab may trigger T-cell alloresponse, even if circulating
224 regulatory T cells were not reduced in the patient's blood which is not necessarily correlated to the
225 modification of immune cell populations at a tissue level. Moreover, the authors recently reported
226 long term data of this case without evidence of ABMR rebound after daratumumab discontinuation
227 (88). Although it is difficult to decipher the role of a rescue with daratumumab added to a complex
228 antirejection therapy, a drug that specifically deplete PC with a favorable safety profile could
229 represent a step forward in the field.

230

231 CD38 antibodies and desensitization

232 The ability of CD38 to desensitize has been evaluated in both preclinical and clinical contexts
233 and published in the same study (72). The preclinical study was based on the use of daratumumab in
234 a non-human primate model which has the most biological similarity to humans for solid organ
235 transplant biology (41,89). The authors paired donors and recipients for maximal HLA mismatching
236 and practiced, for allosensitization, two serial skin grafts before transplantation with a kidney from
237 paired skin graft donor (72). Daratumumab and plerixafor (anti- CXCR4), known to induce
238 mobilization of PC from bone marrow to peripheral blood, were given as desensitization therapy with
239 an initiation 8-12 weeks after sensitization and 8 weeks before kidney transplantation. Animals
240 received for induction anti-CD4 and anti-CD8 antibodies and for maintenance immunosuppression
241 tacrolimus, mycophenolate mofetil and a methylprednisolone taper. This desensitization regimen
242 reduced significantly preformed DSA, with more than 50% reduction compared with the pretreatment
243 time point, and prolonged graft survival with a depletion of PC without altering the germinal center
244 response since the Tfh population was not eliminated (72). However, desensitized monkeys showed
245 delayed ABMR associated to DSA rebound and T cell-mediated rejection perhaps due to immune
246 deviation. Indeed, the authors observed a reduction of regulatory B and T cells after desensitization
247 with rapid emergence of activated T cells after kidney transplantation. This observation could be
248 related to immunomodulatory effects of daratumumab but CXCR4 inhibition, due to plerixafor, is
249 also known to limit regulatory compartment and to promote effector cells with a potential role in
250 these cell- mediated rejection (90). Thus, in transplant recipients following desensitization with
251 daratumumab, it would be interesting to elaborate new strategies than current immunosuppressive
252 regimens in order to manage these DSA rebounds and the risk of T cell-mediated rejection.
253 Concerning the clinical setting, the authors used daratumumab in a heart transplant candidate
254 remaining highly sensitized after multiple courses of plasmapheresis, high-dose IVIG, and rituximab.
255 It was observed a significant and persistent decrease of allosensitization allowing a heart
256 transplantation six months after daratumumab infusion (72). Currently, based on these promising
257 results, daratumumab are under investigation for desensitization in patients awaiting solid-organ
258 transplantation in two clinical trial, one ruled by the nephrology department of Henri Mondor
259 Hospital (Créteil, France) and another one directed by Stanford University (ClinicalTrials.gov,
260 NCT04204980 and NCT04088903 (91,92)). Regarding the trial in kidney transplantation, sensitized
261 patients with calculated panel reactive antibodies (cPRA) > 95% awaiting on the French National
262 kidney allograft waiting-list for at least three years are eligible for the study and are randomly
263 assigned to one of the two steps : (step 1) dose-escalation with 4 mg/kg of daratumumab weekly for
264 four weeks, then with 8 mg/kg weekly for four weeks and then 16 mg/kg weekly for four weeks;
265 (step 2) expansion cohort with eight weekly doses of 16 mg/kg. The primary outcomes are defined

266 as: adverse events, intra-patient variation of cPRA and anti-HLA levels. Several other outcomes are
267 also of interest such as percentage of patients engrafted, and intra-patient variation of ABO antibody
268 titers (91).

269 **Conclusion**

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Therapeutic improvement is required for both prevention and treatment of humoral alloresponse in solid organ transplantation. CD38 antibodies are a promising solution to profoundly deplete high affinity anti-HLA producing plasma cells. Preclinical and clinical experimental results suggests that daratumumab is a potentially therapeutic strategy to reduce DSA production and prevent and/or treat antibody-mediated rejection. However, CD38-targeting agent induce immune deviation which could be deleterious for solid organ transplants enhancing cellular-mediated rejection. Clinical studies are now needed to clarify the indications and efficacy of these promising therapeutic strategies.

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540

541 **Tables**

542

543 **Table 1. Selection of therapeutical regimens targeting CD38**

544

Anti-CD38 strategies	Nature and mechanism	Statut	NCT number
Daratumumab <i>Janssen</i>	Fully human IgG1-kappa anti-CD38 mAb	Approved	X
Isatuximab <i>Sanofi</i>	Chimeric IgG1-kappa anti-CD38 mAb	Approved	X
Felzartamab - MOR202 <i>MorphoSys AG</i>	Fully human IgG1-lambda anti-CD38 mAb	Ongoing in auto-immune field	NCT04733040 NCT04145440
Mezagitamab - TAK-079 <i>Takeda</i>	Fully human IgG1-lambda anti-CD38 mAb	Ongoing in hemato-oncology	NCT03439280
CID-103 <i>CASI Pharmaceuticals</i>	Fully human IgG1 anti-CD38 mAb	Ongoing in hemato-oncology	NCT04758767
ISB 1342 <i>Glennmark Phamaceuticals</i>	CD3xCD38 bispecific antibody to redirect cytotoxic potential of T cells to CD38 ⁺ cells	Ongoing in hemato-oncology	NCT03309111
TAK-169 <i>Takeda</i>	Antibody drugs conjugates: anti-CD38 Ab fragment combined to a Shiga-like toxin (payload: ribosome inactivation)	Ongoing in hemato-oncology	NCT04017130
TAK-573 <i>Takeda</i>	Antibody drugs conjugates: humanized IgG4 anti-CD38 mAb combined to interferon α (payload: anti-proliferative effects)	Ongoing in hemato-oncology	NCT03215030
²¹¹At-OKT10-B10 <i>Fred Hutchinson Cancer Research Center</i>	Antibody drugs conjugates: anti-CD38 mAb combined to radioactive Astatine ²¹¹ At (payload: radiation)	Ongoing in hemato-oncology	NCT04579523 NCT04466475
STI-6129 <i>Sorrento Therapeutics</i>	Antibody drugs conjugates: anti-CD38 mAb combined to Duostatin5 (payload: tubulin inhibition)	Ongoing in hemato-oncology	NCT04316442
KP1237 <i>Kleo Pharmaceuticals</i>	Endogenous-antibodies recruiting molecule targeting CD38 in order to enhance antibody-dependant destruction mechanism	Ongoing in hemato-oncology	NCT04634435
Anti-CD38 CAR-T Cells <i>Sorrento Therapeutics</i>	Imunne cell therapy based on autologous T cells modified into anti-C38 CAR-T cells	Ongoing in hemato-oncology	NCT03464916

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546

547 **Table 2. CD38 antibody use in solid organ transplantation**

548

549 *ABMR: antibody mediated rejection, ATG: anti-human thymocytes globulins, DSA: donor specific*

550 *antibodies, IVIG: intravenous immunoglobulins, MMF: mycophenolate mofetil, NHP: non-human*

551 *primate, PC: plasma cells, Ref. : reference, TCMR: T cell mediated rejection, Tx: transplantation*

552

553

ABMR Treatment								
Ref.	Transplant	Sensitization	IS strategy	Immune event	Treatment	AntiCD38 use	Evolution	Observation
72	Heart + Kidney	Immunized: Preformed DSA	- Induction: ATG -Maintenance: + Tacrolimus + MMF + Steroid	- <i>Delay post-Tx:</i> 17 months - <i>Clinical findings:</i> Cardiogenic shock and acute kidney injury requiring dialysis - <i>Anti-HLA:</i> de novo DSA and one preformed DSA - <i>Histology:</i> TCMR and ABMR with PC-predominant infiltration in both transplants	Steroid pulses + ATG + Plasmapheresis + IVIG + Rituximab + Eculizumab	Daratumumab: - 16 mg/kg - 8 weekly infusions	- <i>Clinical:</i> Heart allograft function returned to baseline + no more need of dialysis - <i>Anti-HLA:</i> Dramatic decline of MFI for majority of DSA at 3 months - <i>Histology:</i> Significant improvement in acute lesions and the PC infiltrate significantly decreased	-20 weeks after: recurrent acute PC-rich rejection on kidney biopsy -Significant reascension of the MFI of two class 2 DSAs -New series of Daratumumab infusions with kidney allograft function improvement
73	Kidney	Immunized: Preformed DSA	- Induction: ? -Maintenance: + Tacrolimus + MMF + Steroid	- <i>Delay post-Tx:</i> 13 years - <i>Clinical findings:</i> Progressive graft dysfunction and proteinuria in the context of newly diagnosed myeloma - <i>Anti-HLA:</i> 1 DSA - <i>Histology:</i> chronic active ABMR	None other treatment	Daratumumab: - 16 mg/kg - 8 weekly infusions + 8 fortnightly infusions + 1 monthly infusion thereafter for 9 months	- <i>Clinical:</i> Stabilization of renal function and proteinuria - <i>Anti-HLA:</i> DSA levels became undetectable after 14 weeks - <i>Histology:</i> Abrogation of microvascular inflammation with a decrease of intra-graft NK cells densities	-3 months after: subclinical borderline rejection - High-grade tubulitis and mild interstitial infiltrates which were dominated by T-cells -Improvement with high-dose intravenous steroid.
85	Kidney	Immunized: ABOi (Anti-A)	- Induction: + Basiliximab + Rituximab -Maintenance: + Tacrolimus + MMF + Steroid	- <i>Delay post-Tx:</i> 30 days - <i>Clinical findings:</i> acute kidney failure - <i>Antibodies:</i> rise in Anti-A titers - <i>Histology:</i> ABMR	Steroid pulses + ATG + Immunoabsorption + Eculizumab	Daratumumab: - 16 mg/kg - 6 weekly infusions	- <i>Clinical:</i> Recovering of kidney function at baseline - <i>Anti-A:</i> Reduction in Anti-A titers leading to discontinuation of immunoabsorption - <i>Histology:</i> No lesion	
86	Heart	Immunized: History ABMR Preformed DSA	- Induction: ? -Maintenance: + Tacrolimus + MMF + Steroid	- <i>Delay post-Tx:</i> 13 years - <i>Clinical findings:</i> congestive heart failure - <i>Anti-HLA:</i> increase of DSA titers - <i>Histology:</i> ABMR	Steroid pulses + Immunoabsorption	Daratumumab: - 16 mg/kg - 8 weekly infusions + 8 fortnightly infusions + 1 monthly infusion thereafter for 9 months	- <i>Clinical:</i> Renal and cardiac improvement in 4 weeks - <i>Anti-HLA:</i> DSA titers are only slightly reduced - <i>Histology:</i> No lesions	
Desensitization								
Ref.	Status	Transplantation	AntiCD38 use	Other treatment	Efficacy	AE	IS strategy	Observation
72	Preclinical: NHP	Kidney	Daratumumab: -16 mg/kg -4 weekly infusions (8 weeks before Tx)	Plerixafor (anti- CXCR4): -0.24 mg/kg -same frequency	Significant reduction of DSA levels and prolonged graft survival	None	Induction: anti-CD4 + anti-CD8 Maintenance: Tacrolimus + MMF + Steroid	-Delayed ABMR -DSA rebound -TCMR -Reduction of Breg and Treg -Emergence of activated T cells after kidney transplantation in the desensitization group
72	Clinical	Heart	Daratumumab: -16 mg/kg -8 weekly infusions	Plasmapheresis + high-dose IVIG + Rituximab	Significant and persistent reduction of DSA levels and heart transplant access at 6 months	None	NA	Died from surgical complication

554

555 **Figures**

556

557 **Figure 1. Immune effects of anti-CD38 antibody in the context of solid organ transplantation.**

558

559 *ABMR: antibody mediated rejection, Breg: regulatory B cell, DSA: donor specific antibodies, PC:*
560 *plasma cell, TCMR: T cell mediated rejection, Treg: regulatory T cell.*

561

562 **1 Conflict of Interest**

563 The authors declare that the review was conducted in the absence of any commercial or financial
564 relationships that could be construed as a potential conflict of interest.

565 **2 Author Contributions**

566 NJ, MM and PG designed the review, collected and interpreted data from literature, and wrote the
567 manuscript.

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