



**HAL**  
open science

# HLA Desensitization in Solid Organ Transplantation: Anti-CD38 to Across the Immunological Barriers

Nizar Joher, Marie Matignon, Philippe Grimbert

► **To cite this version:**

Nizar Joher, Marie Matignon, Philippe Grimbert. HLA Desensitization in Solid Organ Transplantation: Anti-CD38 to Across the Immunological Barriers. *Frontiers in Immunology*, 2021, 12, pp.688301. 10.3389/fimmu.2021.688301 . hal-03759648

**HAL Id: hal-03759648**

**<https://hal.u-pec.fr/hal-03759648>**

Submitted on 24 Aug 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

3     **Nizar JOHER<sup>1,2</sup>, Marie MATIGNON<sup>1,2</sup>, Philippe Grimbert<sup>1,2\*</sup>**

4     <sup>1</sup>Assistance Publique-Hôpitaux de Paris AP-HP, Hôpital Universitaire Henri Mondor, Service de  
5     Néphrologie et Transplantation, Fédération Hospitalo-Universitaire «Innovative therapy for immune  
6     disorders», Créteil, France

7     <sup>2</sup> Université Paris Est Créteil UPEC, Institut National de la Santé et de la Recherche Médicale  
8     INSERM U955, Institut Mondor de Recherche Biomédicale IMRB, Équipe 21, Créteil, France

9     **\* Correspondence:**

10    Corresponding Author: Pr Philippe GRIMBERT, Département de Néphrologie et Transplantation,  
11    Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris APH-HP, 51 Avenue du Maréchal de  
12    Latre de Tassigny 94010 Créteil, France. E-mail: [philippe.grimbert@aphp.fr](mailto:philippe.grimbert@aphp.fr)

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<sup>+</sup> 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<sup>+</sup> and CD8<sup>+</sup> 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<sup>+</sup>  
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**

169

### 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<sup>+</sup> hematopoietic cells and CD38 antibodies induce a profound depletion of  
194 CD38<sup>+</sup> 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**

270

271

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

279

280 **References**

- 281 1. OPTN: Organ Procurement and Transplantation Network - OPTN [Internet]. [cited 2021 Mar  
282 14]. Available from: <https://optn.transplant.hrsa.gov/>
- 283 2. Agence de la biomédecine [Internet]. [cited 2021 Mar 14]. Available from:  
284 <https://www.agence-biomedecine.fr/>
- 285 3. Loupy A, Lefaucheur C. Antibody-Mediated Rejection of Solid-Organ Allografts. *N Engl J*  
286 *Med* [Internet]. 2018 Sep 19 [cited 2021 Mar 14]; Available from:  
287 <https://www.nejm.org/doi/10.1056/NEJMra1802677>
- 288 4. Valenzuela NM, Reed EF. Antibody-mediated rejection across solid organ transplants:  
289 manifestations, mechanisms, and therapies. *J Clin Invest*. 2017 Jun 30;127(7):2492–504.
- 290 5. The XIIIth Banff Conference on Allograft Pathology: The Banff 2015 Heart Meeting Report:  
291 Improving Antibody-Mediated Rejection Diagnostics: Strengths, Unmet Needs, and Future  
292 Directions - PubMed [Internet]. [cited 2021 Mar 14]. Available from:  
293 <https://pubmed.ncbi.nlm.nih.gov/27862968/>
- 294 6. Schinstock CA, Askar M, Bagnasco SM, Batal I, Bow L, Budde K, et al. A 2020 Banff  
295 Antibody-mediated Injury Working Group examination of international practices for diagnosing  
296 antibody-mediated rejection in kidney transplantation - a cohort study. *Transpl Int Off J Eur Soc*  
297 *Organ Transplant*. 2021 Mar;34(3):488–98.
- 298 7. Roux A, Levine DJ, Zeevi A, Hachem R, Halloran K, Halloran PF, et al. Banff Lung Report:  
299 Current knowledge and future research perspectives for diagnosis and treatment of pulmonary  
300 antibody-mediated rejection (AMR). *Am J Transplant Off J Am Soc Transplant Am Soc Transpl*  
301 *Surg*. 2019 Jan;19(1):21–31.
- 302 8. Drachenberg CB, Torrealba JR, Nankivell BJ, Rangel EB, Bajema IM, Kim DU, et al.  
303 Guidelines for the diagnosis of antibody-mediated rejection in pancreas allografts—updated Banff  
304 grading schema. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2011  
305 Sep;11(9):1792–802.
- 306 9. Demetris AJ, Bellamy C, Hübscher SG, O’Leary J, Randhawa PS, Feng S, et al. 2016  
307 Comprehensive Update of the Banff Working Group on Liver Allograft Pathology: Introduction of  
308 Antibody-Mediated Rejection. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*.  
309 2016 Oct;16(10):2816–35.
- 310 10. Loupy A, Haas M, Roufousse C, Naesens M, Adam B, Afrouzian M, et al. The Banff 2019  
311 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell- and antibody-mediated  
312 rejection. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2020 Sep;20(9):2318–31.
- 313 11. Zhang R. Donor-Specific Antibodies in Kidney Transplant Recipients. *Clin J Am Soc*  
314 *Nephrol CJASN*. 2018 Jan 6;13(1):182–92.
- 315 12. Butler CL, Valenzuela NM, Thomas KA, Reed EF. Not All Antibodies Are Created Equal:  
316 Factors That Influence Antibody Mediated Rejection. *J Immunol Res*. 2017;2017:7903471.
- 317 13. Lefaucheur C, Viglietti D, Mangiola M, Loupy A, Zeevi A. From Humoral Theory to  
318 Performant Risk Stratification in Kidney Transplantation. *J Immunol Res*. 2017;2017:5201098.
- 319 14. Lefaucheur C, Viglietti D, Bentelejewski C, Duong van Huyen J-P, Vernerey D, Aubert O, et  
320 al. IgG Donor-Specific Anti-Human HLA Antibody Subclasses and Kidney Allograft Antibody-  
321 Mediated Injury. *J Am Soc Nephrol JASN*. 2016 Jan;27(1):293–304.
- 322 15. Loupy A, Lefaucheur C, Vernerey D, Prugger C, Duong van Huyen J-P, Mooney N, et al.  
323 Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med*. 2013 Sep  
324 26;369(13):1215–26.
- 325 16. Montgomery RA, Tatapudi VS, Leffell MS, Zachary AA. HLA in transplantation. *Nat Rev*  
326 *Nephrol*. 2018 Sep;14(9):558–70.
- 327 17. Tinckam KJ, Keshavjee S, Chaparro C, Barth D, Azad S, Binnie M, et al. Survival in  
328 sensitized lung transplant recipients with perioperative desensitization. *Am J Transplant Off J Am*

- 329 Soc Transplant Am Soc Transpl Surg. 2015 Feb;15(2):417–26.
- 330 18. Plazak ME, Gale SE, Reed BN, Hammad S, Ton V-K, Kaczorowski DJ, et al. Clinical  
331 Outcomes of Perioperative Desensitization in Heart Transplant Recipients. *Transplant Direct*. 2021  
332 Feb;7(2):e658.
- 333 19. Bourassa-Blanchette S, Patel V, Knoll GA, Hutton B, Fergusson N, Bennett A, et al. Clinical  
334 outcomes of polyvalent immunoglobulin use in solid organ transplant recipients: A systematic review  
335 and meta-analysis - Part II: Non-kidney transplant. *Clin Transplant*. 2019 Jul;33(7):e13625.
- 336 20. Shah KS, Patel J. Desensitization in heart transplant recipients: Who, when, and how. *Clin  
337 Transplant*. 2019 Aug;33(8):e13639.
- 338 21. Matsumoto CS, Rosen-Bronson S. Donor-specific antibody and sensitized patients in  
339 intestinal transplantation. *Curr Opin Organ Transplant*. 2021 Apr 1;26(2):245–9.
- 340 22. Schinstock CA, Smith BH, Montgomery RA, Jordan SC, Bentall AJ, Mai M, et al. Managing  
341 highly sensitized renal transplant candidates in the era of kidney paired donation and the new kidney  
342 allocation system: Is there still a role for desensitization? *Clin Transplant*. 2019 Dec;33(12):e13751.
- 343 23. Vo AA, Choi J, Cisneros K, Reinsmoen N, Haas M, Ge S, et al. Benefits of rituximab  
344 combined with intravenous immunoglobulin for desensitization in kidney transplant recipients.  
345 *Transplantation*. 2014 Aug 15;98(3):312–9.
- 346 24. Vo AA, Peng A, Toyoda M, Kahwaji J, Cao K, Lai C-H, et al. Use of intravenous immune  
347 globulin and rituximab for desensitization of highly HLA-sensitized patients awaiting kidney  
348 transplantation. *Transplantation*. 2010 May 15;89(9):1095–102.
- 349 25. Vo AA, Lukovsky M, Toyoda M, Wang J, Reinsmoen NL, Lai C-H, et al. Rituximab and  
350 intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med*. 2008 Jul  
351 17;359(3):242–51.
- 352 26. Loupy A, Suberbielle-Boissel C, Zuber J, Anglicheau D, Timsit M-O, Martinez F, et al.  
353 Combined posttransplant prophylactic IVIg/anti-CD 20/plasmapheresis in kidney recipients with  
354 preformed donor-specific antibodies: a pilot study. *Transplantation*. 2010 Jun 15;89(11):1403–10.
- 355 27. Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical Aspects of Intravenous Immunoglobulin  
356 Use in Solid Organ Transplant Recipients. *Am J Transplant*. 2011;11(2):196–202.
- 357 28. Amrouche L, Aubert O, Suberbielle C, Rabant M, Van Huyen J-PD, Martinez F, et al. Long-  
358 term Outcomes of Kidney Transplantation in Patients With High Levels of Preformed DSA: The  
359 Necker High-Risk Transplant Program. *Transplantation*. 2017 Oct;101(10):2440–8.
- 360 29. Orandi BJ, Luo X, King EA, Garonzik-Wang JM, Bae S, Montgomery RA, et al. Hospital  
361 readmissions following HLA-incompatible live donor kidney transplantation: A multi-center study.  
362 *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2018 Mar;18(3):650–8.
- 363 30. Motter JD, Jackson KR, Long JJ, Waldram MM, Orandi BJ, Montgomery RA, et al. Delayed  
364 graft function and acute rejection following HLA-incompatible living donor kidney transplantation.  
365 *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2020 Dec 28;
- 366 31. Kahwaji J, Jordan SC, Najjar R, Wongsaroj P, Choi J, Peng A, et al. Six-year outcomes in  
367 broadly HLA-sensitized living donor transplant recipients desensitized with intravenous  
368 immunoglobulin and rituximab. *Transpl Int Off J Eur Soc Organ Transplant*. 2016 Dec;29(12):1276–  
369 85.
- 370 32. Süsal C, Opelz G. Transplantation: Desensitization and survival in kidney transplant  
371 recipients. *Nat Rev Nephrol*. 2017 Apr;13(4):196–8.
- 372 33. Heidt S, Claas FHJ. Transplantation in highly sensitized patients: challenges and  
373 recommendations. *Expert Rev Clin Immunol*. 2018 Aug 3;14(8):673–9.
- 374 34. Montgomery RA, Lonze BE, King KE, Kraus ES, Kucirka LM, Locke JE, et al.  
375 Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med*. 2011 Jul  
376 28;365(4):318–26.
- 377 35. Orandi BJ, Luo X, Massie AB, Garonzik-Wang JM, Lonze BE, Ahmed R, et al. Survival

378 Benefit with Kidney Transplants from HLA-Incompatible Live Donors. *N Engl J Med*. 2016 Mar  
379 10;374(10):940–50.

380 36. Manook M, Koeser L, Ahmed Z, Robb M, Johnson R, Shaw O, et al. Post-listing survival for  
381 highly sensitised patients on the UK kidney transplant waiting list: a matched cohort analysis. *Lancet*  
382 *Lond Engl*. 2017 18;389(10070):727–34.

383 37. Jordan SC, Ammerman N, Choi J, Huang E, Peng A, Sethi S, et al. The role of novel  
384 therapeutic approaches for prevention of allosensitization and antibody-mediated rejection. *Am J*  
385 *Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2020 Jun;20 Suppl 4:42–56.

386 38. Leibler C, Thiolat A, Elsner RA, El Karoui K, Samson C, Grimbert P. Costimulatory  
387 blockade molecules and B-cell-mediated immune response: current knowledge and perspectives.  
388 *Kidney Int*. 2019 Apr;95(4):774–86.

389 39. Tangye SG, Ma CS, Brink R, Deenick EK. The good, the bad and the ugly - TFH cells in  
390 human health and disease. *Nat Rev Immunol*. 2013 Jun;13(6):412–26.

391 40. Nutt SL, Hodgkin PD, Tarlinton DM, Corcoran LM. The generation of antibody-secreting  
392 plasma cells. *Nat Rev Immunol*. 2015 Mar;15(3):160–71.

393 41. Kwun J, Knechtle S. Experimental modeling of desensitization: What have we learned about  
394 preventing AMR? *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2020 Jun;20  
395 Suppl 4:2–11.

396 42. Brynjolfsson SF, Persson Berg L, Olsen Ekerhult T, Rimkute I, Wick M-J, Mårtensson I-L, et  
397 al. Long-Lived Plasma Cells in Mice and Men. *Front Immunol*. 2018;9:2673.

398 43. Jordan SC, Ammerman N, Choi J, Kumar S, Huang E, Toyoda M, et al. Interleukin-6: An  
399 Important Mediator of Allograft Injury. *Transplantation*. 2020 Dec;104(12):2497–506.

400 44. Choi J, Aubert O, Vo A, Loupy A, Haas M, Puliyananda D, et al. Assessment of Tocilizumab  
401 (Anti-Interleukin-6 Receptor Monoclonal) as a Potential Treatment for Chronic Antibody-Mediated  
402 Rejection and Transplant Glomerulopathy in HLA-Sensitized Renal Allograft Recipients. *Am J*  
403 *Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2017 Sep;17(9):2381–9.

404 45. Clazakizumab as an Agent to Reduce Donor Specific HLA Antibodies and Improve  
405 Outcomes in Patients with Chronic & Active Antibody-Mediated Rejection Post-Kidney  
406 Transplantation [Internet]. ATC Abstracts. [cited 2021 Mar 21]. Available from:  
407 [https://atcmeetingabstracts.com/abstract/clazakizumab-as-an-agent-to-reduce-donor-specific-hla-](https://atcmeetingabstracts.com/abstract/clazakizumab-as-an-agent-to-reduce-donor-specific-hla-antibodies-and-improve-outcomes-in-patients-with-chronic-active-antibody-mediated-rejection-post-kidney-transplantation/)  
408 [antibodies-and-improve-outcomes-in-patients-with-chronic-active-antibody-mediated-rejection-post-](https://atcmeetingabstracts.com/abstract/clazakizumab-as-an-agent-to-reduce-donor-specific-hla-antibodies-and-improve-outcomes-in-patients-with-chronic-active-antibody-mediated-rejection-post-kidney-transplantation/)  
409 [kidney-transplantation/](https://atcmeetingabstracts.com/abstract/clazakizumab-as-an-agent-to-reduce-donor-specific-hla-antibodies-and-improve-outcomes-in-patients-with-chronic-active-antibody-mediated-rejection-post-kidney-transplantation/)

410 46. MD SJ. A Phase I/II Trial to Evaluate the Safety and Tolerability of Clazakizumab (Anti-IL-6  
411 Monoclonal) to Eliminate Donor Specific HLA Antibodies (DSAs) and Improve Transplant Rates in  
412 Highly-HLA Sensitized Patients Awaiting Renal Transplant [Internet]. *clinicaltrials.gov*; 2020 Oct  
413 [cited 2021 Mar 18]. Report No.: NCT03380962. Available from:  
414 <https://clinicaltrials.gov/ct2/show/NCT03380962>

415 47. Woodle ES, Shields AR, Ejaz NS, Sadaka B, Girnita A, Walsh RC, et al. Prospective Iterative  
416 Trial of Proteasome Inhibitor-Based Desensitization. *Am J Transplant*. 2015;15(1):101–18.

417 48. Tremblay S, Driscoll JJ, Rike-Shields A, Hildeman DA, Alloway RR, Girnita AL, et al. A  
418 prospective, iterative, adaptive trial of carfilzomib-based desensitization. *Am J Transplant Off J Am*  
419 *Soc Transplant Am Soc Transpl Surg*. 2020 Feb;20(2):411–21.

420 49. Kwun J, Burghuber C, Manook M, Iwakoshi N, Gibby A, Hong JJ, et al. Humoral  
421 Compensation after Bortezomib Treatment of Allosensitized Recipients. *J Am Soc Nephrol JASN*.  
422 2017 Jul;28(7):1991–6.

423 50. Ezekian B, Schroder PM, Mulvihill MS, Barbas A, Collins B, Freischlag K, et al.  
424 Pretransplant Desensitization with Costimulation Blockade and Proteasome Inhibitor Reduces DSA  
425 and Delays Antibody-Mediated Rejection in Highly Sensitized Nonhuman Primate Kidney  
426 Transplant Recipients. *J Am Soc Nephrol JASN*. 2019 Dec;30(12):2399–411.

- 427 51. Schroder PM, Schmitz R, Fitch ZW, Ezekian B, Yoon J, Choi AY, et al. Preoperative  
428 carfilzomib and lulizumab based desensitization prolongs graft survival in a sensitized non-human  
429 primate model. *Kidney Int.* 2021 Jan;99(1):161–72.
- 430 52. Quarona V, Zaccarello G, Chillemi A, Brunetti E, Singh VK, Ferrero E, et al. CD38 and  
431 CD157: A long journey from activation markers to multifunctional molecules. *Cytometry B Clin*  
432 *Cytom.* 2013;84B(4):207–17.
- 433 53. Dianzani U, Malavasi F. Lymphocyte adhesion to endothelium. *Crit Rev Immunol.*  
434 1995;15(2):167–200.
- 435 54. van de Donk NWCJ, Usmani SZ. CD38 Antibodies in Multiple Myeloma: Mechanisms of  
436 Action and Modes of Resistance. *Front Immunol.* 2018;9:2134.
- 437 55. van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma:  
438 back to the future. *Blood.* 2018 Jan 4;131(1):13–29.
- 439 56. van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. *Lancet Lond Engl.* 2021 Jan  
440 30;397(10272):410–27.
- 441 57. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38  
442 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med.* 2015 Sep 24;373(13):1207–  
443 19.
- 444 58. Casneuf T, Xu XS, Adams HC, Axel AE, Chiu C, Khan I, et al. Effects of daratumumab on  
445 natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma.  
446 *Blood Adv.* 2017 Oct 24;1(23):2105–14.
- 447 59. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al.  
448 Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med.* 2016 Oct  
449 6;375(14):1319–31.
- 450 60. Touzeau C, Moreau P. Daratumumab for the treatment of multiple myeloma. *Expert Opin*  
451 *Biol Ther.* 2017;17(7):887–93.
- 452 61. Lammerts van Bueren J, Jakobs D, Kaldenhoven N, Roza M, Hiddingh S, Meesters J, et al.  
453 Direct in Vitro Comparison of Daratumumab with Surrogate Analogs of CD38 Antibodies  
454 MOR03087, SAR650984 and Ab79. *Blood.* 2014 Dec 6;124(21):3474–3474.
- 455 62. Radocha J, van de Donk NWCJ, Weisel K. Monoclonal Antibodies and Antibody Drug  
456 Conjugates in Multiple Myeloma. *Cancers.* 2021 Mar 29;13(7).
- 457 63. van de Donk NWCJ. Immunomodulatory effects of CD38-targeting antibodies. *Immunol*  
458 *Lett.* 2018 Jul;199:16–22.
- 459 64. Krejcik J, Casneuf T, Nijhof IS, Verbist B, Bald J, Plesner T, et al. Daratumumab depletes  
460 CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple  
461 myeloma. *Blood.* 2016 Jul 21;128(3):384–94.
- 462 65. Zhang L, Tai Y-T, Ho M, Xing L, Chauhan D, Gang A, et al. Regulatory B cell-myeloma cell  
463 interaction confers immunosuppression and promotes their survival in the bone marrow milieu.  
464 *Blood Cancer J.* 2017 Mar 24;7(3):e547.
- 465 66. Dwivedi S, Rendón-Huerta EP, Ortiz-Navarrete V, Montaña LF. CD38 and Regulation of the  
466 Immune Response Cells in Cancer. *J Oncol.* 2021;2021:6630295.
- 467 67. Adams HC, Stevenaert F, Krejcik J, Van der Borgh K, Smets T, Bald J, et al. High-  
468 Parameter Mass Cytometry Evaluation of Relapsed/Refractory Multiple Myeloma Patients Treated  
469 with Daratumumab Demonstrates Immune Modulation as a Novel Mechanism of Action. *Cytom Part*  
470 *J Int Soc Anal Cytol.* 2019 Mar;95(3):279–89.
- 471 68. Chen L, Diao L, Yang Y, Yi X, Rodriguez BL, Li Y, et al. CD38-Mediated  
472 Immunosuppression as a Mechanism of Tumor Cell Escape from PD-1/PD-L1 Blockade. *Cancer*  
473 *Discov.* 2018 Sep;8(9):1156–75.
- 474 69. Vijayan D, Young A, Teng MWL, Smyth MJ. Targeting immunosuppressive adenosine in  
475 cancer. *Nat Rev Cancer.* 2017 Dec;17(12):709–24.

- 476 70. Chatterjee S, Daenthanasamak A, Chakraborty P, Wyatt MW, Dhar P, Selvam SP, et al.  
477 CD38-NAD+Axis Regulates Immunotherapeutic Anti-Tumor T Cell Response. *Cell Metab.* 2018 Jan  
478 9;27(1):85-100.e8.
- 479 71. Zaninoni A, Giannotta JA, Galli A, Artuso R, Bianchi P, Malcovati L, et al. The  
480 Immunomodulatory Effect and Clinical Efficacy of Daratumumab in a Patient With Cold Agglutinin  
481 Disease. *Front Immunol.* 2021;12:649441.
- 482 72. Kwun J, Matignon M, Manook M, Guendouz S, Audard V, Kheav D, et al. Daratumumab in  
483 Sensitized Kidney Transplantation: Potentials and Limitations of Experimental and Clinical Use. *J*  
484 *Am Soc Nephrol JASN.* 2019 Jul;30(7):1206–19.
- 485 73. Doberer K, Kläger J, Gualdoni GA, Mayer KA, Eskandary F, Farkash EA, et al. CD38  
486 Antibody Daratumumab for the Treatment of Chronic Active Antibody-mediated Kidney Allograft  
487 Rejection. *Transplantation.* 2021 Feb 1;105(2):451–7.
- 488 74. Cole S, Walsh A, Yin X, Wechalekar MD, Smith MD, Proudman SM, et al. Integrative  
489 analysis reveals CD38 as a therapeutic target for plasma cell-rich pre-disease and established  
490 rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Res Ther.* 2018 May 2;20(1):85.
- 491 75. Frerichs KA, Verkleij CPM, Bosman PWC, Zweegman S, Otten H, van de Donk NWCJ.  
492 CD38-targeted therapy with daratumumab reduces autoantibody levels in multiple myeloma patients.  
493 *J Transl Autoimmun.* 2019 Dec;2:100022.
- 494 76. Tolbert VP, Goldsby R, Huang J, Shimano K, Melton A, Willert J, et al. Daratumumab Is  
495 Effective in the Treatment of Refractory Post-Transplant Autoimmune Hemolytic Anemia: A  
496 Pediatric Case Report. *Blood.* 2016 Dec 2;128(22):4819–4819.
- 497 77. Tomkins O, Berentsen S, Arulogun S, Sekhar M, D'Sa S. Daratumumab for disabling cold  
498 agglutinin disease refractory to B-cell directed therapy. *Am J Hematol.* 2020 Jul 11;
- 499 78. Blennerhassett R, Sudini L, Gottlieb D, Bhattacharyya A. Post-allogeneic transplant Evans  
500 syndrome successfully treated with daratumumab. *Br J Haematol.* 2019 Oct;187(2):e48–51.
- 501 79. Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for Delayed Red-Cell  
502 Engraftment after Allogeneic Transplantation. *N Engl J Med.* 2018 08;379(19):1846–50.
- 503 80. Ostendorf L, Burns M, Durek P, Heinz GA, Heinrich F, Garantziotis P, et al. Targeting CD38  
504 with Daratumumab in Refractory Systemic Lupus Erythematosus. *N Engl J Med.* 2020 Sep  
505 17;383(12):1149–55.
- 506 81. Ratuszny D, Skripuletz T, Wegner F, Groß M, Falk C, Jacobs R, et al. Case Report:  
507 Daratumumab in a Patient With Severe Refractory Anti-NMDA Receptor Encephalitis. *Front Neurol.*  
508 2020;11:602102.
- 509 82. Scheibe F, Ostendorf L, Reincke SM, Prüss H, von Brünneck A-C, Köhnlein M, et al.  
510 Daratumumab treatment for therapy-refractory anti-CASPR2 encephalitis. *J Neurol.* 2020  
511 Feb;267(2):317–23.
- 512 83. Martin TG, Corzo K, Chiron M, Velde H van de, Abbadessa G, Campana F, et al.  
513 Therapeutic Opportunities with Pharmacological Inhibition of CD38 with Isatuximab. *Cells.* 2019  
514 Nov 26;8(12).
- 515 84. Flores-Montero J, de Tute R, Paiva B, Perez JJ, Böttcher S, Wind H, et al. Immunophenotype  
516 of normal vs. myeloma plasma cells: Toward antibody panel specifications for MRD detection in  
517 multiple myeloma. *Cytometry B Clin Cytom.* 2016 Jan;90(1):61–72.
- 518 85. Spica D, Junker T, Dickenmann M, Schaub S, Steiger J, Rüfli T, et al. Daratumumab for  
519 Treatment of Antibody-Mediated Rejection after ABO-Incompatible Kidney Transplantation. *Case*  
520 *Rep Nephrol Dial.* 2019 Dec;9(3):149–57.
- 521 86. Aguilera Agudo C, Gómez Bueno M, Krsnik Castillo I. Daratumumab for Antibody-  
522 mediated Rejection in Heart Transplant-A Novel Therapy: Successful Treatment of Antibody-  
523 mediated Rejection. *Transplantation.* 2021 Mar 1;105(3):e30–1.
- 524 87. Parkes MD, Halloran PF, Hidalgo LG. Evidence for CD16a-Mediated NK Cell Stimulation in



525 Antibody-Mediated Kidney Transplant Rejection. *Transplantation*. 2017 Apr;101(4):e102–11.  
526 88. Mayer KA, Doberer K, Eskandary F, Halloran PF, Böhmig GA. New concepts in chronic  
527 antibody-mediated kidney allograft rejection: prevention and treatment. *Curr Opin Organ Transplant*.  
528 2021 Feb 1;26(1):97–105.  
529 89. Kirk AD. Crossing the bridge: large animal models in translational transplantation research.  
530 *Immunol Rev*. 2003 Dec;196:176–96.  
531 90. Mollica Poeta V, Massara M, Capucetti A, Bonocchi R. Chemokines and Chemokine  
532 Receptors: New Targets for Cancer Immunotherapy. *Front Immunol*. 2019;10:379.  
533 91. Assistance Publique - Hôpitaux de Paris. Desensitization in Kidney Allograft Recipients  
534 Before Transplantation Using Daratumumab [Internet]. [clinicaltrials.gov](https://clinicaltrials.gov); 2020 May [cited 2021 Mar  
535 23]. Report No.: NCT04204980. Available from: <https://clinicaltrials.gov/ct2/show/NCT04204980>  
536 92. Witteles R. A Phase 1 Study of Daratumumab for Reduction of Circulating Antibodies in  
537 Patients With High Allosensitization Awaiting Heart Transplantation [Internet]. [clinicaltrials.gov](https://clinicaltrials.gov);  
538 2020 Oct [cited 2021 Mar 23]. Report No.: NCT04088903. Available from:  
539 <https://clinicaltrials.gov/ct2/show/NCT04088903>  
540

541 **Tables**

542

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

544

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

545

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 + Immunoadsorption + 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 immunoadsorption - <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 + Immunoadsorption	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.

568 **3 Funding**

569 None.