CD38 as an immunotherapeutic target in multiple myeloma

CD38 As an Immunotherapeutic Target in Multiple Myeloma

Francesca Bonello[1*], Mattia D'Agostino[1*], Maria Moscvin[1], Chiara Cerrato[1], Mario Boccadoro[1], Francesca Gay[1]
*Both authors share the first authorship

[1]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy

Corresponding author: Francesca Gay, MD, PhD, Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy, Phone: +390116334301; Fax: +390116963737; E-mail: fgay@cittadellasalute.to.it
ORCID ID: https://orcid.org/0000-0002-8619-412X

Financial and competing interests disclosure
Mario Boccadoro has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, AbbVie, Bristol-Myers Squibb, research funding from Celgene, Janssen, Amgen, Bristol-Myers Squibb, Mundipharma, Novartis, and Sanofi. Francesca Gay has received honoraria from Takeda, Amgen, Celgene, Janssen, Bristol-Myers Squibb, and served on the advisory board for Takeda, Seattle Genetics, Celgene, and Roche. The remaining authors declare no financial and competing interests.

Funding
No funding was provided for this review article.

CD38 As an Immunotherapeutic Target in Multiple Myeloma

Review
References: 85
Tables: 2
Figures: 1

Abstract

Introduction: Multiple myeloma (MM) is a currently incurable hematologic tumor with heterogeneous clinical behavior and prognosis. During the last years, survival improved due to a better understanding of MM biology and the development of novel drugs, although it still remains unsatisfactory in many cases: new drugs and treatment strategies are needed. CD38 is uniformly expressed at high levels on MM cells and, to a lesser extent, on the surface of normal hematopoietic and non-hematopoietic cells, making this molecule an interesting target for immunotherapeutic approaches.

Areas covered: This review discusses the preclinical and clinical experience on different immunotherapeutic agents targeting CD38 in MM.

Expert commentary: Monoclonal antibodies (mAbs) targeting CD38 are currently changing the treatment scenario in MM, allowing physicians to reach unprecedented results, especially when anti-CD38 mAbs are used in combination with consolidated MM treatments. Other immunotherapies targeting CD38 – such as conjugated anti-CD38 mAbs, bispecific antibodies stimulating T cells to eliminate CD38+ MM cells, and CD38-specific chimeric antigen receptor (CAR) T cells – are interesting strategies, currently at earlier developmental stages.

Keywords
CD38, monoclonal antibodies, bispecific antibodies, drug conjugates, CAR T cells, multiple myeloma

Highlights

- CD38 surface antigen is highly expressed on myeloma plasma cells as well as on other immune system cells and is therefore a key target for immunotherapeutic agents.
- Mechanisms of action of anti-CD38 monoclonal antibodies (mAbs) include antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated phagocytosis (ADCP), as well as immunomodulatory effects on tumor microenvironment.
- Anti-CD38 action is enhanced by other compounds, such as immunomodulatory agents (IMiDs) and proteasome inhibitors, (PIs) in preclinical models.

- Daratumumab is the first anti-CD38 mAb showing high efficacy and favorable toxicity profile in clinical trials as monotherapy and in combinations with the currently approved standard regimens for myeloma treatment.
- Daratumumab main toxicity consists of infusion related reactions (IRRs), mainly involving the upper respiratory tract. Careful selection of patients and appropriate infusion premedication are the keys to avoid severe IRRs, which, however, are uncommon.
- Other anti-CD38 mAbs (isatuximab, MOR202 and TAK-079) are currently being evaluated in clinical trials. CD38 drug conjugates, bispecific antibodies and chimeric antigen receptor-T (CAR T) cells are also under investigation in multiple myeloma.

INTRODUCTION

Multiple Myeloma (MM) is a neoplastic hematologic disorder characterized by clonal proliferation of plasma cells in the bone marrow (BM) and, less frequently, by involvement of the peripheral blood and other extramedullary sites [1]. The clinical manifestations of the disease include signs of organ dysfunction, such as renal failure, anemia, bone lesions and hypercalcemia, along with an immunosuppressive microenvironment that leads to frequent infections.

The introduction of high-dose melphalan followed by autologous stem-cell transplantation in younger patients and the approval of novel agents such as proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) have substantially improved the life expectancy of myeloma patients [2]. Indeed, an increasing proportion of patients is achieving lasting remissions. However, the far majority of the patients will eventually experience relapse, with MM cells at relapse often refractory to the previously used drugs [3]. Altogether, this clearly demonstrates that novel therapies and therapeutic approaches for MM patients are still needed.

One of the most exciting advances for the treatment of MM has been the introduction of immunotherapeutic agents, including monoclonal antibodies (mAbs) and T cell-based therapies [4,5].

MAbs bind to specific antigens expressed on the surface of myeloma cells. The choice of the target antigen is a key issue affecting their efficacy and tolerability [6]. Target antigens exploitable for antibody-based immunotherapy should be highly expressed on cancerous cells and ideally not expressed on normal tissues. They should be involved in multiple processes initiating and promoting the oncogenesis of the disease. Depending on the antigen bound, mAbs involve several mechanisms of action that are unique to this drug class and differ from existing therapies for MM.

CD38 is a highly interesting target in MM, as virtually all MM cells express high levels of CD38 on their cell surface and many studies demonstrated that this molecule is engaged in immunosuppressive mechanisms happening in the myeloma-promoting microenvironment [7].

This review is aimed to analyze the current immunotherapeutic strategies exploiting the CD38 molecule to treat myeloma.

1. CD38 TISSUE DISTRIBUTION

CD38 (previously referred to as T10) was first identified in 1980 as a membrane-bound protein of 45 kDa [8]. It was described as a single-chain transmembrane type II glycoprotein encoded by a gene mapped on chromosome 4 (4p15) [9]. CD38 includes a long C-terminal extracellular

domain (258 amino acids, aa), a transmembrane segment (21 aa) and a short N-terminal cytoplasmic tail (21 aa).

Originally, scientific community considered CD38 to be a lymphocyte-specific protein; however, current results showed that it is expressed on lymphoid and myeloid cells as well as in many non-hematopoietic tissues [10].

CD38 expression in the immune system varies during lymphocyte development, activation and differentiation. Indeed, human CD38 is highly expressed on medullary thymocytes, downregulated in the majority of circulating mature T cells and up-regulated upon activation of T cells [10].

CD38 performs as a marker of ontogenesis in B lymphocytes: it is present at high levels in BM precursors, downregulated in resting normal B cells, and re-expressed in terminally differentiated plasma cells.

The molecule is highly expressed on normal plasma cells as well as on plasma cells derived from patients affected by MM. Indeed, >90% of the malignant plasma cells from patients with MM show surface expression of CD38 [11].

Regarding myeloid cells, circulating monocytes bear the molecule on their surface, while resident macrophages do not. Interestingly, recent reports have described an enzymatically active form of CD38 on osteoclast progenitors, exploiting an important function in the regulation of bone reabsorption [12].

CD38 is also expressed by cells of the innate immune system, including natural killer (NK) cells (approximately by 60% of them) and granulocytes (approximately 60% of monocytes, whereas it is absent from neutrophils) [13]. Red blood cells and platelets express CD38 at low levels as well.

Importantly, CD38 is expressed on immunosuppressive cells, such as T regulatory cells, B regulatory cells, and myeloid-derived suppressor cells. Accordingly, high CD38 expression may define a highly suppressive subset of T regulatory cells with reduced antitumor activity of the immune system [14].

Among solid tissues, the protein is expressed by epithelial cells in the prostate, beta-cells in the pancreas, Purkinje cells and neurofibrillary tangles in the brain, muscle cells (especially in the airway system), renal tubules, retinal gangliar cells and corneal cells in the eye [7].

The broad expression of CD38 may discourage the development of immunotherapies directed against this molecule; however, the analysis of CD38 expression levels across different cellular populations clearly shows that normal and malignant plasma cells express far the highest levels of CD38 followed by NK cells and other B and T cell subpopulations.

2. CD38 FUNCTIONS

CD38 regulates a wide range of physiological processes. CD38 dysfunction in murine models induces various defects, including impairment of insulin secretion, neutrophil chemotaxis, oxytocin release and development of diet-induced obesity [15]. CD38 is functionally pleiotropic, working as an ectoenzyme and as a receptor simultaneously. The identification of CD31 (also known as PECAM-1) as a non-substrate specific ligand was key in recognizing CD38 as a receptor [16]. Importantly, in vitro experiments showed that CD38/CD31 cross-talk is an important step in the regulation of cytoplasmic calcium fluxes and secretion of cytokines such as IL-6 and IL-10 [17]. Interestingly, this interaction probably regulates the migration of leukocytes and CD38 positive cancer cells through the endothelial cell wall. As described above, CD38 is structurally characterized by a very short cytoplasmic tail, suggesting an inability of this protein to act directly as a receptor. The precise mechanism of intracellular signal transduction is being investigated in different biological systems. In activated T lymphocytes, the formation of immunological synapses upon activation of CD38 suggested that CD38, in order to exert its biological function as a receptor, needs to be redirected to specialized phospholipid microdomains of the plasma membrane, in close proximity to professional receptors [18].

Next to its receptor function, CD38 was recently described as part of the leukocyte ectonucleotidases family, characterized by two main substrates: nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP+). CD38 converts NAD+ to ADP ribose (ADPR) directly (hydrolase activity) or through formation and degradation of cyclic ADP ribose to ADPR (cyclase activity). Furthermore, in acidic conditions, CD38 catalyzes the generation of nicotinic acid-adenine dinucleotide phosphate (NAADP) from NADP+. Overall, the final result of these catalytic reactions is the generation of potent intracellular Ca2+ mobilizing compounds (cADPR, ADPR and NAADP) followed by activation of signaling pathways that control various biological processes, such as lymphocyte proliferation [19]. Interestingly, recent studies suggest a pivotal role for CD38 involved in the production of adenosine, which has immunosuppressive effects [20]. Thus, this enzyme is suggested to function as an “immunological switch” capable of converting a pro-inflammatory extracellular environment into an adenosine-rich, anti-inflammatory niche, suppressing anti-tumor immunity and promoting tumor progression.

3. CD38 AS A TARGET FOR IMMUNOTHERAPY

The high and constant expression of CD38 on malignant plasma cells has prompted the development of targeted immunotherapies. However, the mechanism of action of anti-CD38 agents does not rely only on CD38 expression on tumor cells. The immune functions activated by mAbs are paradigmatic, comprising both fragment crystallizable (Fc)-dependent effector mechanisms relying on CD38 expression in tumor cells (i.e. antibody-dependent cell-mediated cytotoxicity, ADCC; antibody-dependent cell-mediated phagocytosis, ADCP; complement-

dependent cytotoxicity, CDC) and immunomodulatory effects relying on CD38 expression in suppressive cells in the tumor microenvironment [21–23].

ADCC and ADCP are activated through the binding of Fc γ receptors expressed by immune effector cells to the Fc tail of anti-CD38 mAbs.

The main effector cells mediating ADCC are NK cells that upon activation release cytotoxic molecules (granzymes, perforins) that lead to the elimination of mAbs-coated cells. As discussed above, CD38 is expressed by NK cells and a marked depletion in this cell population following anti-CD38 mAbs infusion can be detected [24]. Although the extent of NK cells depletion does not correlate with a decreased clinical efficacy [24], the infusion of ex vivo–expanded $CD38^{-/low}$ autologous NK cells that are not depleted by anti-CD38 mAbs is currently being evaluated in the preclinical setting to understand if it may further increase the efficacy of anti-CD38 induced ADCC [25].

In ADCP, MM cells opsonized by mAbs are eliminated by phagocytosis and the main immune cell population fulfilling this task are the macrophages. CD47 expressed by cancer cells could impair this mechanism inhibiting phagocytosis, thus anti-CD47 mAbs can potentiate ADCP. Indeed, in preclinical models, there is evidence of synergism of anti-CD47 mAbs and anti-CD38 mAbs in inducing ADCP [26]. Moreover, low-dose cyclophosphamide enhances Fc-γ receptors expression on macrophages and lowers CD47 expression on cancer cells, boosting mAbs-induced ADCP and providing a biologic rationale for combination therapy [27].

CDC is activated through the binding of complement component 1q (C1q) to the Fc tail of anti-CD38 mAbs. This interaction leads to the production of anaphylatoxins recruiting other immune cells, to the C3b deposition on MM cells favoring ADCP, and to the membrane attack complex formation directly lysing MM cell [28]. The expression of complement inhibitory molecules such as CD55 and CD59 on MM cells could be one of the mechanisms involved in acquired resistance to anti-CD38 mAbs [29].

Patients' treatment with anti-CD38 mAbs rapidly induces a reduction in CD38 expression on malignant plasma cells, independently from clinical response. Thus, the mechanisms inducing and maintaining clinical response in patients cannot rely only on ADCC, ADCP and CDC, which require CD38 expression. Indeed, after anti-CD38 therapy, there is a clear expansion in the T cell population with an increased T cell clonality whose specificity is unknown; the entity of this expansion correlates with clinical response [14].

Starting from this observation, many immunomodulatory mechanisms of anti-CD38 therapies have been described so far, all of them alleviating immunosuppression, which is a hallmark of MM microenvironment. As an example, , CD38 is expressed on immunosuppressive cells such as T regulatory cells, myeloid-derived suppressor cells, and B regulatory cells whose elimination boosts T-cytotoxic cell function [14].

The immune stimulatory activity of anti-CD38 mAbs may explain the strong preclinical and clinical synergistic effect of their association with IMiDs such as lenalidomide and pomalidomide. Indeed, one of the most prominent mechanisms of action of IMiDs is the enhancement of NK and T cells immune function [30]. Similarly, the efficacy of anti-CD38 mAbs plus PIs has also been shown in preclinical models, even though its mechanism is currently less clear [30].

The high expression of CD38 on myeloma cells could also be utilized to selectively direct immunotoxins against tumor cells. Indeed, cytotoxic compounds can be conjugated to anti-CD38 monoclonal antibodies in order to preferentially hit the cells with a higher CD38 surface expression [31,32].

Redirecting the host immune system against tumor cells is the rationale for CD38 bispecific antibodies. These antibodies are designed to activate and connect T cells with myeloma cells expressing CD38 as surface antigen in order to redirect T cell-dependent cellular cytotoxicity [33,34].

CD38 is not only a target for mAbs, but also for adoptive cell therapy. T cells engineered to express a chimeric antigen receptor (CAR) that incorporates both an extracellular CD38-recognition domain and an intracellular T-cell signaling domain can specifically recognize and kill CD38+ cells [35]. Differently from T cells engineered to express a specific T cell receptor, chimeric antigen receptor (CAR) T cells are not HLA-restricted; therefore, any patient expressing any HLA type can be treated with CAR-T.

The main mechanisms of action of immunotherapeutic agents targeting CD38 are summarized in *Figure 1*.

4. CD38 MONOCLONAL ANTIBODIES

Major clinical trials with anti-CD38 monoclonal antibodies are summarized in *Table 1*.

Ongoing phase III clinical trials involving anti-CD38 monoclonal antibodies are summarized in *Table 2*.

Daratumumab

Daratumumab is an anti-CD38 fully human monoclonal antibody. Its main mechanisms of action were previously described. In an in-vitro comparison between anti-CD38 antibodies (daratumumab, SAR650894, MOR202 and TAK79), daratumumab showed the highest efficacy in inducing CDC at low concentration [36]. ADCC was equally induced by all the anti-CD38 mAbs. ADCP was more potently induced by daratumumab and TAK-079 compared to MOR202.

On the basis of the encouraging preclinical results daratumumab was initially tested as monotherapy in the GEN501 phase 1/2 trial. 32 relapsed/refractory multiple myeloma (RRMM) patients were enrolled in the dose-escalation phase and divided in 10 cohorts receiving daratumumab from 0.005 mg/kg to 24 mg/kg. No maximum tolerated dose (MTD) was found. In the phase II expansion study, 72 patients received daratumumab at the dose of 8 mg/kg or 16 mg/kg with different schedules. All patients had received at least 2 previous lines of therapy (median 4 lines) and were mostly refractory to bortezomib and/or lenalidomide (63% of pts refractory to both drugs). Overall response rate (ORR) was 10% in the 8 mg/kg cohort and 36% in the 16 mg/kg cohort and median progression free survival (PFS) was 2.4 months and 5.6 months respectively. Daratumumab proved to be well tolerated, with the main toxicity consisting of infusion-related reactions (IRRs) occurring in 71% of patients, mainly limited to the first administration and of grade 1-2 [37]. In the phase II SIRIUS trial, 106 heavily pretreated patients (median prior lines 5), all refractory to both a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), were enrolled. They received daratumumab as single agent at the dose of 16 mg/kg. ORR was 29%, median PFS was 3.7 months and median overall survival (OS) was 17.5 months. Side effects were easily manageable and did not lead to treatment discontinuation. IRRs occurred in 42% of patients, and only 5% were of grade 3 [38]. Usmani et al. conducted a pooled analysis of the two studies mentioned above including patients who had received daratumumab at 16 mg/kg (n 148). The ORR was 31%, with 4.7% of patients achieving a complete response (CR). After a median follow up of 21 months, median PFS and OS were 4 months and 20 months respectively [39]. On the basis of the results of these two pivotal studies, in 2015 the Food & Drug Administration (FDA) approved daratumumab monotherapy for RRMM patients who had received at least three prior lines including a PI and an IMiD or who are double refractory to a PI and an IMID [40]. Daratumumab monotherapy was also approved by the European Medical Agency (EMA) for RRMM patients previously treated with a PI and an IMiD who had progressed under their last therapy [41].

In the earliest clinical trials, it had been noticed that daratumumab interfered with blood compatibility tests. The drug causes false positives in the antibodies screens, since it binds to the CD38 present on reagent red cells [42]. This may lead to delays in red blood cells (RBC) transfusions in myeloma patients. Several strategies have been developed to solve this problem. One of the most efficient is to treat CD38+ reagent red cells with dithiothreitol (DTT), which denatures CD38 surface antigen and eliminates daratumumab interference [43]. Other solutions include the neutralization of free daratumumab in plasma and the use of cord blood cells (CD38-) [44]. Moreover, performing cross-matching tests before starting daratumumab further increases the safety of the transfusion process. In the clinical practice, patients should be supplied with a transfusion card indicating their blood type (ABO, Rh and indirect antiglobulin test [IAT]) and stating that they are being treated with an anti-CD38 agent. The card should specify information about the IAT interference, which may last up to 6 months after the last infusion [45].

Since daratumumab showed enhanced activity in combination with IMiDs and PIs in preclinical models, it was subsequently investigated in clinical trials in association with the backbone regimens for RRMM. In the phase III POLLUX trial, 569 RRMM patients were randomized to receive standard lenalidomide-dexamethasone (Rd) treatment or Rd plus daratumumab. Patients had received a median of 1 previous line of therapy and 44% of patients had received both a PI and an IMiD. The ORR was higher in the triplet arm (93% vs 76%) and responses were significantly deeper (CR or better 43% vs 19%) [46]. Minimal residual disease (MRD) negativity was reached in 25% vs 6% of patients (threshold 10^{-5}) [47]. The rate of 1-year PFS was 83% in the daratumumab group versus 60% in the control group (hazard ratio [HR] for progression or death 0.37). A PFS benefit was seen also in high-risk cytogenetic patients [48]. Data on OS were immature at the time of the analysis, although recently a PFS2 advantage has been reported [49]. The addition of daratumumab to Rd did not increase significantly the toxicity profile of the regimen. IRRs occurred in 48% of patients, mainly limited to the first infusion, and limited to grade 1-2 [46]. Daratumumab in combination with bortezomib and dexamethasone (Vd) was compared to standard Vd in the phase III CASTOR trial. 498 patients who had received at least one prior therapy (median 2) were enrolled. 48% of patients had received both a PI and an IMiD in previous treatments. The daratumumab-Vd arm had a higher ORR (83% vs 63%), with 19% vs 9% rates of CR or better. MRD negativity was reached in 12% vs 2% of patients (threshold 10^{-5}) [50]. A PFS benefit was also observed, with a 1-year PFS of 61% vs 27% (HR for progression of death 0.39). Long-term follow-up is ongoing, and recently a PFS2 advantage has also been reported [49]. A slightly higher rate of grade ≥3 adverse events was observed in the triplet arm (76% vs 62%), especially in terms of hematologic toxicity. Particularly, thrombocytopenia rate was significantly higher in the daratumumab-Vd arm (grade ≥3 45% vs 33%). Patients aged ≥65 years old or with ISS III were at increased risk of developing thrombocytopenia [51]. Treatment discontinuation rates due to adverse events were similar in the two arms. IRRs occurred in 45% of patients [52]. The triplet regimens of daratumumab with Vd or Rd have been approved by FDA and EMA as standard treatment for RRMM patients who had received at least one previous therapy.

Daratumumab is also under evaluation when associated to pomalidomide and dexamethasone (Pd). In a phase II trial, the triplet daratumumab-Pd was administered to 103 RRMM patients who had received at least 2 prior therapies (median 4) including lenalidomide and bortezomib [53]. In this heavily pretreated population, ORR was 66% with a 22% rate of CR or better. MRD negativity was reached by 7% of patients (threshold 10^{-5}). Median PFS and OS were 9.9 months and 25.1 months respectively). The main grade ≥3 toxicities were hematological (particularly neutropenia 77%). Non-hematological toxicities were similar to those observed with Pd alone in previous trials. IRRs occurred in 50% of patients [53]. Although cross-trial comparisons should be interpreted with caution, the triplet daratumumab-Pd showed a higher efficacy compared to Pd alone in the MM-003 trial (ORR 31%, median PFS 3.8 months, median OS 12.7 months) [54]. APOLLO is an ongoing phase III trial that will provide a direct comparison

between daratumumab-Pd and Pd. The triplet is approved by FDA for RRMM patients who have received at least two prior therapies including a PI and lenalidomide. Other daratumumab-based regimens are currently under investigation in RRMM patients. Daratumumab was associated with carfilzomib and dexamethasone (KD) in a phase Ib trial on 85 RRMM patients. Preliminary results showed an ORR of 84% and a 1-year PFS of 74% [55]. The safety profile appeared to be similar to those of individual therapies. CANDOR (NCT03158688) is an ongoing phase III trial comparing the triplet daratumumab-KD to KD. Another ongoing study is investigating daratumumab in association with the oral PI ixazomib (NCT03439293).

In consideration of its high efficacy and favorable safety profile, daratumumab is currently being evaluated in newly diagnosed multiple myeloma (NDMM) patients. In the phase III ALCYONE trial, the combination of daratumumab with melphalan-bortezomib-prednisone (VMP) was compared to VMP, which represents one of the standards of care for NDMM transplant-ineligible patients. Seven hundred and six patients were enrolled, with a median age of 71 years old. The ORR was 91% in the quadruplet arm vs 74% in the VMP arm. Responses were deeper in the daratumumab-VMP arm (≥CR 43% vs 24%) and MRD negativity was reached in 22% versus 6% of patients (threshold 10^{-5}). At the time of the analysis, 1-year PFS was 87% versus 76% (HR for progression or death 0.5). The PFS benefit was also consistent in patients ≥75 years old and in high-risk patients according to International Staging System (ISS) or cytogenetic profile [56]. Follow-up for long-term survival is ongoing. Grade ≥3 adverse events were similar in the two groups, except from infections (23% in the daratumumab-VMP arm vs 15% in the VMP arm) that, however, did not translate into a higher rate of discontinuation [57]. Therefore, daratumumab-VMP proved to be a safe and effective option in the transplant-ineligible setting, also including very elderly patients. Daratumumab is currently under evaluation in combination with Rd in NDMM patients in a randomized phase III trial (NCT02252172) whose first results are expected in 2019. In the transplant-eligible setting, the Cassiopeia trial is comparing daratumumab plus bortezomib-thalidomide-dexamethasone (VTD) to the standard VTD as induction and consolidation strategy (NCT02541383). Daratumumab with lenalidomide-bortezomib-dexamethasone (RVd) is currently being compared to RVd as induction and consolidation strategy in a phase II trial on NDMM patients receiving autologous stem-cell transplant (ASCT) [58]. The Perseus phase III study, comparing daratumumab with RVd vs RVd in NDMM patients, is also underway (NCT03710603). A preliminary phase Ib study is evaluating daratumumab with carfilzomib-lenalidomide-dexamethasone in NDMM regardless of transplant eligibility. Of the 22 patients enrolled so far, the ORR was 100% with a 57% rate of CR or better. The safety profile seemed favorable [59].

In the trials described above, daratumumab proved to be well tolerated, with the main toxicity consisting in IRRs (occurring in 42%-71% of patients in clinical trials). IRRs are generally mild and limited to first administration. Treatment discontinuation due to IRRs is uncommon. Main symptoms involve the respiratory tract, with throat irritation, cough and dyspnea. As

mentioned above, the respiratory pattern of daratumumab-induced IRRs can be partially explained by CD38 expression by airway muscle cells. Besides standard premedication of mAbs administration with steroids, antihistamines and antipyretics, the addition of a leukotriene receptor antagonist (montelukast) showed to be beneficial in preventing severe respiratory IRRs and it is therefore recommended in clinical practice. Delayed IRRs can be prevented by oral corticosteroid therapy for the two days following daratumumab infusion. Patients with severe pulmonary comorbidities, such as obstructive disease, are particularly at risk of developing severe respiratory IRRs and the risk-benefit balance of daratumumab therapy should be evaluated [45].

Isatuximab

Isatuximab (SAR 650984) is an anti-CD38 IgG-k chimeric monoclonal antibody. As previously described, it showed significant activity against myeloma cells in in vitro and in vivo xenograft models. SAR shows a strong direct proapoptotic activity independent from Fc cross-linking [60]. So far, it is the only anti-CD38 antibody holding this feature. This property is remarkably interesting since it allows SAR to kill tumor cells without the host immune effector mechanisms, which are often suppressed in the bone marrow micro-environment of myeloma patients [61,62]. Similarly to daratumumab, SAR holds an immunomodulatory effect acting on CD38 positive regulatory T cells.

Isatuximab was initially tested as single agent in a phase I/II trial in a heavily pretreated RRMM population (median prior lines 5). During the dose escalation phase, no MTD was found up to the dose of 20 mg/kg and the ORR was 32%. Based on this, a second dose-finding phase was added to further investigate safety and efficacy. Isatuximab appeared to be well tolerated with only 10% of patients having experienced grade ≥3 drug-related adverse events. The IRR rate was 50% (3% of grade 3-4). Efficacy data were immature at the time of first analysis [63]. Preclinical models showed that isatuximab tumoricidal activity is enhanced by lenalidomide and pomalidomide [61]. Therefore, isatuximab was tested in combination with standard Rd in a phase I dose escalation study. RRMM patients had received a median of 5 previous line of therapy and 83% were refractory to lenalidomide. As in the previous trial, no MTD was found up to 20 mg/kg. The ORR was 56% and responses were also achieved in lenalidomide-refractory patients (ORR 52%). Median PFS was 8.5 months. The triplet appeared to be well tolerated, with the main adverse events being IRRs (56%) [64]. Isatuximab was also tested in combination with Pd in a phase Ib trial, showing a 56% ORR and a favorable safety profile [65]. The currently ongoing phase III ICARIA trial (NCT02990338) is comparing the triplet isatuximab-Pd to standard Pd treatment in RRMM patients who had received at least 2 previous therapies, including lenalidomide and a PI [66]. Other phase III ongoing trials are evaluating the combination of isatuximab with KD in RRMM patients (NCT03275285) and with VRD in NDMM patients (NCT03319667).

Other anti-CD38 monoclonal antibodies

MOR202 is a fully human anti-CD38 monoclonal antibody. Preclinical studies showed that the antibody acts mainly by inducing ADCC and ADCP [67]. Differently from daratumumab and isatuximab, MOR202 does not seem to induce CDC, which is assumed to be the main mechanism leading to IRRs [68,69]. Therefore, a lower rate of IRRs is expected in clinical trials. MOR202 is currently being evaluated in a phase Ib/II clinical trial on RRMM patients. The drug is administered as single agent and in combination with lenalidomide or pomalidomide. No MTD has been found up to the dose of 16 mg/kg. The drug seems to be well tolerated with mainly hematological toxicities. As expected, the rate of IRRs was low (7%, mainly limited to the first administration and all grade ≤2). At the time of analysis, the global ORR was 45%, with 3 CR in the MOR202-IMiDs cohorts [70].

TAK-079 is a new anti-CD38 monoclonal antibody that has not been tested in clinical trials so far. Preclinical studies showed promising activity against plasma cells. Indeed, TAK-079 and daratumumab induce similar amounts of ADCC and ADCP [36]. TAK-079 is under evaluation not only in multiple myeloma, but also for the treatment of autoimmune diseases such as systemic lupus erythematosus [71].

Anti-CD38 immunotoxins and bispecific antibodies

The clinical success of naked mAbs targeting CD38 prompted the preclinical development of conjugated and bispecific antibodies. Different immunotoxins and radioimmunotherapeutic agents conjugated to anti-CD38 mAbs were tested and demonstrated efficacy in preclinical models [72].

In particular, Goldmacher and colleagues reported the development of an immunotoxin composed of an anti-CD38 antibody HB7 conjugated to a chemically modified ricin molecule. They showed that the conjugated antibody was capable of effectively killing CD38-positive human myeloma and lymphoma cell lines. Importantly, low levels of toxicity for normal progenitor cells of granulocyte/macrophage or erythroid lineages were observed [73].

Later, Bolognesi *et al.* showed the results of a different immunotoxin consisting of an anti-CD38 mAb IB4 coupled to saporin-S6, a type 1 ribosome-inactivating protein. This immunotoxin was capable of exerting strong and specific cytotoxic effects on selected CD38-positive lymphoma cell lines [74]. A note of caution for *in vivo* applications of these immunotoxins comes from the notion that the molecule is expressed by a subset of progenitor hematopoietic cells as well as almost all immune cells. Thus, further studies about the potential toxic effects on the immune system compartment are necessary.

As indicated by clinical investigations, plasma cells are very sensitive to radiation therapy, as demonstrated by the success of conventional radiotherapy as a curative approach in isolated plasmacytomas or as pain control in extramedullary disease localizations in RRMM patients. Besides, anti-CD38 mAbs can be used as a way to selectively deliver radionuclides to tumor cells. Green and colleagues used a 2-step pre-targeted radioummunotherapy with ^{90}Yttrium anti-CD38 mAbs adopting the streptavidin-biotin method to optimize the delivery of therapeutic radiations [75]. In the first step, an antibody-streptavidin (Ab-SA) construct is infused localizing to tumor sites; then a small molecular weight radioactive molecule (radio-DOTA-biotin) is administered as a second step. The small second-step molecule tightly binds to the Ab-SA while the unbound molecules are excreted in the urine. This mechanism maximizes the delivery of radiations to the tumor, limiting non-specific radiation to normal tissues. The construction of bispecific anti-CD38 / anti-^{90}Y-DOTA is a further optimization step that has been tested in myeloma mice models [76]. Of note, all the treated mice obtained complete remissions from MM, with low levels of radioactivity delivery in normal tissues, making this approach an interesting candidate for clinical translation.

However, the wider therapeutic use of bispecific antibodies is to engage T cells to the tumor site stimulating them to kill target cells; this approach has been clinically validated by the results obtained with blinatumumab (an anti-CD19/anti-CD3 bispecific mAb) in acute lymphoblastic leukemia [77]. GBR 1342 is a bispecific antibody targeting CD3 and CD38 that, in preclinical studies, efficaciously redirected T cells cytotoxicity towards myeloma cells both in vitro and in mice xenograft models [78]. Based on these preclinical results, a first-in-human study is currently ongoing (NCT03309111): here GBR 1342 is given as monotherapy in highly pretreated patients.

Another interesting anti-CD38/anti-CD3 bispecific mAb has been developed and preclinically tested by Chu and colleagues [79]. Differently from other bispecific products, they produced a mAb that maintains a full Fc domain modified to abolish the binding of Fc-γ receptors, in order to reduce non-selective T cell activation. However, the presence of Fc maintains a long serum half-life that is a limitation for other bispecific mAbs therapies, often requiring continuous pump infusion. This type of mAbs produced in vitro elimination of human myeloma cell lines and their infusion into humanized mice and in monkeys was able to effectively recruit T cells to kill CD38+ cells as well.

Other approaches using small molecules are currently under research; for instance, nanobodies and nanoparticles are used instead of mAbs in order to deliver immunotoxins [80] or to increase the delivered dose of standard treatments such as bortezomib without increasing side effects [81].

Anti-CD38 CAR T cells

The introduction of CAR T cell therapy in oncologic hematology is changing the treatment paradigm of many diseases such as acute lymphoblastic leukemia and lymphoma, producing impressive response rates in highly refractory patients [82]. Two important advantages of CAR T cells over mAbs are their higher potential to induce strong anti-tumor reactions upon infusion and their putative capability to persist in vivo exerting durable anti-tumor memory T cell surveillance. However, the strong cytotoxic effect of CAR T cells makes the choice of the target antigen a more sensitive issue than in mAbs therapy because of the higher risk of on-target off-tumor toxicity. As discussed above, although CD38 is mainly and highly expressed by malignant plasma cells, it is also broadly expressed in many other cell types, thus posing concerns about the use of anti-CD38 CAR T cells in the myeloma setting. To improve the safety of anti-CD38 CAR T cells, Drent and colleagues have recently described a new strategy (based on a light chain exchange technology) that increases the affinity of CD38 CAR T cells for myeloma cells, sparing other CD38+ healthy hematopoietic cells [83].

A preclinical evaluation of T cells equipped with an anti-CD38 CAR construct coupled with intracellular 4-1BB costimulatory domain was performed by the Dutch group of Drent and colleagues [35]. These cells are capable to proliferate, produce inflammatory mediators and lyse MM cell lines and MM cells harvested from therapy-resistant patients. Their activity correlates with CD38 expression levels. As expected, besides CD38+ MM cells, CD38+ normal hematopoietic cells were lysed as well. However, CD34+CD38- progenitor cells were not harmed. In order to improve the safety and make a clinical translation feasible, approaches to control adoptively transferred CAR T cells are warranted and may include: the implementation of the CAR construct with a suicide gene that works as a safety switch that can be triggered on demand; the reversible control of the expression of CAR at the cell surface of infused T cells; and the optimization of CAR affinity in order to selectively kill target cells. Indeed, in a recent publication, the same Dutch research group tested the feasibility and activity of a doxycycline-inducible Tet-on CD38-CAR design using an affinity-optimized anti-CD38 CAR T cell [84]. With this approach, researchers can control CAR expression using different doses of doxycycline to induce different levels of CAR expression at the cell surface. In this approach, CAR-mediated target lysis is doxycycline dose-dependent and, importantly, the removal of doxycycline leads to a gradual elimination of off-tumor lysis. This aspect couples with an affinity optimization of anti-CD38 CAR T cells that makes them already able to discern between $CD38^{high}$ MM cells and $CD38^{int}$ hematopoietic cells. These two mechanisms maximize safety, making this approach potentially interesting for clinical translation.

Another anti-CD38 CAR-T cell approach with interesting preclinical data came from Sorrento Therapeutics [85]. The antigen recognition domain of the anti-CD38 CAR was based on a fully human anti-CD38 mAb. These cells demonstrated activation, proliferation and cytokines production upon antigen engagement, efficient in-vitro killing of MM cells, and complete eradication of MM in xenograft MM mice models with no activity in cells expressing normal or

low CD38 levels. These results prompted the evaluation of this construct in a first-in-human study that is currently ongoing (NCT03464916).

5. CONCLUSIONS

The spectrum of possible treatment strategies in the setting of MM is rapidly widening, thanks to new combinations of drugs, with different mechanisms of action, that have recently been investigated and developed. Novel agents targeting specific molecules and pathways are included in these new options, and anti-CD38 mAbs are particularly promising. One of their most important mechanisms of action consists in the Fc-dependent immune effector functions (ADCC, ADCP and CDC). Fc-dependent immune effector mechanism is probably more effective in the early phase of mAb treatment, since the CD38 protein is rapidly depleted on the MM cell surface after initiation of treatment. Anti-CD38 mAbs also eliminate CD38 positive immune suppressor cells, improving the host anti-tumor immune response. Furthermore, the reduction of immune suppressor cells leads to an increase of CD4+ and CD8+ T cells. Finally, they provide direct induction of apoptosis and modulation on the bone marrow micro-environment. Due to their pleiotropic mechanism of action, anti-CD38 mAbs have significant activity as single agents. They guarantee high levels of tolerability, thanks to an optimal toxicity profile. For these two reasons, they are also optimal partners for combination strategies with other anti-MM agents, both immunomodulatory agents or proteasome inhibitors and alkylating agents.

6. EXPERT OPINION

Daratumumab is approved by the FDA and the EMA as single agent and also in combination with Rd and Vd as standard treatment for RRMM patients who had received at least one previous therapy. The use of mAbs seems to be more effective in the early phases of the disease, when the immune system is less compromised. Indeed, daratumumab is currently under evaluation in the newly diagnosed setting. The recently published data from the ALCYONE trial can potentially lead to the approval of a new standard of care in elderly patients. The trial showed an increased rate of infections in the DARA-VMP arm compared with VMP, which, however, did not lead to an increased discontinuation rate compared to the control arm. Given the potential ability of melphalan to damage NK and T cells, even at low dose, it would be interesting to see which will be the efficacy andsafety profile of the combination of daratumumab with immunomodulatory agents alone (such as Rd), which is currently under investigation. Ongoing trials investigating the role of daratumumab in combination with the standard of care for NDMM patients will clarify whether 3 or 4 drug regimens including mAbs plus IMiDs and/or PIs will change the treatment landscape over the next few years, both for transplant-eligible and -ineligible patients. It is likely that the number of patients treated with daratumumab will increase in the near future. As a consequence, a more rapid administration

of therapy will become of crucial importance. The PAVO study demonstrated that a fixed dose of 1800 mg daratumumab in a subcutaneous formulation can be administered in a few minutes, with similar efficacy compared with the iv formulation but with a lower rate of infusion-related reactions.

Isatuximab is another anti-CD38 monoclonal antibody. After the encouraging results obtained in phase I and II trials, it is now being investigated in phase III studies in comparison with the standard of care in NDMM and RRMM patients. MOR202 and TAK-079 are newer anti-CD38 mAbs under clinical development. Particularly, MOR202 is expected to have an even better safety profile in terms of IRRs than the other anti-CD38 monoclonal antibodies, since it induces less CDC, which is thought to be the main effector of IRRs; the mechanism of action, involving mainly ADCC, might question the opportunity to test this drug with alkylating agents, or rather only in combination with IMIDs. A great challenge for the future will be identifying the most effective drug combinations involving different anti-CD38 mAbs and, in the context of a still incurable disease, the most effective therapy sequencing. Particularly, it should be investigated whether agents used in previous lines may impair the efficacy of anti-CD38 mAbs used in subsequent lines as well as the role of anti-CD38 monoclonal antibody re treatment.

Another challenge for future research will be the identification of biomarkers of response able to provide the best clinical setting for the use of mAbs, in order to improve and personalize treatment. Since CD38 is highly expressed in the early stage of plasma-cell clonal evolution, anti-CD38 agents are currently being investigated in smoldering MM to evaluate whether they can prevent or delay the progression to symptomatic MM. Besides, it has been noted that RRMM cells might downregulate or even lose the expression of CD38 on their surfaces, particularly in the most aggressive extramedullary forms. For this very reason, assessment of CD38 expression before starting therapy with an anti-CD38 monoclonal antibody can be considered, even if the plasma cells expressed CD38 at the time of first diagnosis. Research on biomarkers able to predict the efficacy of anti-CD38 therapy is currently ongoing. Likely, anti-CD38 antibodies could also be used for the treatment of other CD38-positive malignancies. Likewise, due to their immunomodulatory activity, anti-CD38 antibodies could conceivably be of value in CD38-negative cancers, in combination with other molecules with different mechanisms of action. Results of ongoing first-in-human trials will clarify if the use of anti-CD38 conjugated immunotoxins, bispecific antibodies and CAR-T will represent options for MM patients. Future research should be directed to understand which patients could benefit more from each specific therapeutic approach.

Financial and competing interests disclosure

MB has received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, AbbVie, Bristol-Myers Squibb, research funding from Celgene, Janssen, Amgen, Bristol-Myers Squibb, Mundipharma, Novartis, and Sanofi. FG has received honoraria from Takeda, Amgen, Celgene,

Janssen, Bristol-Myers Squibb, and served on the advisory board for Takeda, Seattle Genetics, Celgene, and Roche. The remaining authors declare no financial and competing interests.

Funding
No funding was provided for this review article.

Bibliography

[*The annotated bibliography is below*].

[1] Palumbo A, Anderson K. Multiple myeloma. N. Engl. J. Med. [Internet]. 2011 [cited 2017 Jul 11];364:1046–1060. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMra1011442.

[2] American Cancer Society. About Multiple Myeloma [Internet]. [cited 2018 Sep 4]. Available from: https://www.cancer.org/cancer/multiple-myeloma/about.html.

[3] Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia [Internet]. 2014 [cited 2017 Sep 6];28:1122–1128. Available from: http://www.nature.com/doifinder/10.1038/leu.2013.313.

[4] D'Agostino M, Boccadoro M, Smith EL. Novel Immunotherapies for Multiple Myeloma. Curr. Hematol. Malig. Rep. [Internet]. 2017 [cited 2018 Sep 4];12:344–357. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28819882.

[5] Gay F, D'Agostino M, Giaccone L, et al. Immuno-oncologic Approaches: CAR-T Cells and Checkpoint Inhibitors. Clin. Lymphoma Myeloma Leuk. [Internet]. 2017 [cited 2018 Sep 4];17:471–478. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28689001.

[6] D'Agostino M, Gazzera G, Cetani G, et al. Clinical and Pharmacologic Features of Monoclonal Antibodies and Checkpoint Blockade Therapy in Multiple Myeloma. Curr. Med. Chem. [Internet]. 2018 [cited 2018 Sep 4];25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29756564.

[7] van de Donk NWCJ, Richardson PG, Malavasi F. CD38 antibodies in multiple myeloma: back to the future. Blood [Internet]. 2018 [cited 2017 Dec 14];131:13–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29118010.

[8] Reinherz EL, Kung PC, Goldstein G, et al. Discrete stages of human intrathymic differentiation: analysis of normal thymocytes and leukemic lymphoblasts of T-cell lineage. Proc. Natl. Acad. Sci. U. S. A. [Internet]. 1980 [cited 2018 May 9];77:1588–1592. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6966400.

[9] Nakagawara K, Mori M, Takasawa S, et al. Assignment of CD38, the gene encoding human leukocyte antigen CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase), to chromosome 4p15. Cytogenet. Genome Res. [Internet]. 1995 [cited 2018 Sep 4];69:38–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7835083.

[10] Deaglio S, Mehta K, Malavasi F. Human CD38: a (r)evolutionary story of enzymes and receptors. Leuk. Res. [Internet]. 2001 [cited 2017 Dec 14];25:1–12. Available from: http://www.sciencedirect.com/science/article/pii/S014521260000093X.

[11] Leo R, Boeker M, Peest D, et al. Multiparameter analyses of normal and malignant human plasma cells: CD38++, CD56+, CD54+, cIg+ is the common phenotype of myeloma cells. Ann. Hematol. [Internet]. 1992 [cited 2018 Sep 4];64:132–139. Available from: http://link.springer.com/10.1007/BF01697400.

[12] Costa F, Toscani D, Chillemi A, et al. Expression of CD38 in myeloma bone niche: A rational basis for the use of anti-CD38 immunotherapy to inhibit osteoclast formation. Oncotarget [Internet]. 2017 [cited 2018 Sep 4];8:56598–56611. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28915615.

[13] Atanackovic D, Steinbach M, Radhakrishnan SV, et al. Immunotherapies targeting CD38 in Multiple Myeloma. Oncoimmunology [Internet]. 2016 [cited 2018 Sep 4];5:e1217374. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27999737.

[14] Krejcik J, Casneuf T, Nijhof IS, et al. Daratumumab depletes CD38+ immune regulatory cells, promotes T-cell expansion, and skews T-cell repertoire in multiple myeloma. Blood [Internet]. 2016 [cited 2018 Sep 4];128:384–394. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27222480.
[15] Malavasi F, Deaglio S, Funaro A, et al. Evolution and Function of the ADP Ribosyl Cyclase/CD38 Gene Family in Physiology and Pathology. Physiol. Rev. [Internet]. 2008 [cited 2018 Sep 4];88:841–886. Available from: http://www.physiology.org/doi/10.1152/physrev.00035.2007.
[16] Deaglio S, Morra M, Mallone R, et al. Human CD38 (ADP-ribosyl cyclase) is a counter-receptor of CD31, an Ig superfamily member. J. Immunol. [Internet]. 1998 [cited 2018 Sep 4];160:395–402. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9551996.
[17] Lande R, Urbani F, Di Carlo B, et al. CD38 ligation plays a direct role in the induction of IL-1beta, IL-6, and IL-10 secretion in resting human monocytes. Cell. Immunol. [Internet]. 2002 [cited 2018 Oct 29];220:30–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12718937.
[18] Munoz P, Mittelbrunn M, de la Fuente H, et al. Antigen-induced clustering of surface CD38 and recruitment of intracellular CD38 to the immunologic synapse. Blood [Internet]. 2008 [cited 2018 Sep 4];111:3653–3664. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18212246.
[19] Guse AH, da Silva CP, Berg I, et al. Regulation of calcium signalling in T lymphocytes by the second messenger cyclic ADP-ribose. Nature [Internet]. 1999 [cited 2018 Sep 4];398:70–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10078531.
[20] Allard B, Beavis PA, Darcy PK, et al. Immunosuppressive activities of adenosine in cancer. Curr. Opin. Pharmacol. [Internet]. 2016 [cited 2018 Sep 4];29:7–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27209048.
[21] de Weers M, Tai Y-T, van der Veer MS, et al. Daratumumab, a Novel Therapeutic Human CD38 Monoclonal Antibody, Induces Killing of Multiple Myeloma and Other Hematological Tumors. J. Immunol. [Internet]. 2011 [cited 2018 Oct 29];186:1840–1848. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21187443.
[22] Overdijk MB, Verploegen S, Bögels M, et al. Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. MAbs [Internet]. 2015 [cited 2018 Oct 29];7:311–320. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25760767.
[23] Krejcik J, Frerichs KA, Nijhof IS, et al. Monocytes and Granulocytes Reduce CD38 Expression Levels on Myeloma Cells in Patients Treated with Daratumumab. Clin. Cancer Res. [Internet]. 2017 [cited 2018 Oct 29];23:7498–7511. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29025767.
[24] Casneuf T, Xu XS, Adams HC, et al. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma. Blood Adv. [Internet]. 2017 [cited 2018 Sep 4];1:2105–2114. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29296857.
[25] Wang Y, Zhang Y, Hughes T, et al. Fratricide of NK Cells in Daratumumab Therapy for Multiple Myeloma Overcome by Ex Vivo-Expanded Autologous NK Cells. Clin. Cancer Res. [Internet]. 2018 [cited 2018 Sep 4];24:4006–4017. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29666301.
[26] van Bommel PE, He Y, Schepel I, et al. CD20-selective inhibition of CD47-SIRPα “don’t eat me” signaling with a bispecific antibody-derivative enhances the anticancer activity of daratumumab, alemtuzumab and obinutuzumab. Oncoimmunology [Internet]. 2018 [cited 2018 Sep 4];7:e1386361. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29308308.
[27] Naicker S, Rigalou A, McEllistrim C, et al. Patient Data Supports the Rationale of Low Dose Cyclophosphamide to Potentiate the Anti-Myeloma Activity of Daratumumab through Augmentation of Macrophage-Induced ADCP. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #121 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/121?sso-checked=true.
[28] van de Donk NWCJ, Moreau P, Plesner T, et al. Clinical efficacy and management of monoclonal antibodies targeting CD38 and SLAMF7 in multiple myeloma. Blood [Internet]. 2016 [cited 2018 Sep 4];127:681–695. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26631114.

[29] Nijhof IS, Casneuf T, van Velzen J, et al. CD38 expression and complement inhibitors affect response and resistance to daratumumab therapy in myeloma. Blood [Internet]. 2016 [cited 2018 Sep 4];128:959–970. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27307294.
[30] van de Donk NWCJ. Immunomodulatory effects of CD38-targeting antibodies. Immunol. Lett. [Internet]. 2018 [cited 2018 Sep 4];199:16–22. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0165247818301470.
[31] Teicher BA, Chari RVJ. Antibody Conjugate Therapeutics: Challenges and Potential. Clin. Cancer Res. [Internet]. 2011 [cited 2018 Sep 4];17:6389–6397. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22003066.
[32] Sherbenou DW, Behrens CR, Su Y, et al. The development of potential antibody-based therapies for myeloma. Blood Rev. [Internet]. 2015 [cited 2018 Sep 4];29:81–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25294123.
[33] de Zafra C, Balazs M, Fajardo F, et al. Preclinical Characterization of AMG 424, a Novel Humanized T Cell-Recruiting Bispecific Anti-CD3/CD38 Antibody. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #500 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/500?sso-checked=true.
[34] Zou J, Chen D, Zong Y, et al. Immunotherapy based on bispecific T-cell engager with hIgG1 Fc sequence as a new therapeutic strategy in multiple myeloma. Cancer Sci. [Internet]. 2015 [cited 2018 Sep 4];106:512–521. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25664501.
[35] Drent E, Groen RWJ, Noort WA, et al. Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. Haematologica [Internet]. 2016 [cited 2018 Sep 4];101:616–625. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26858358.
[36] Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in Vitro Comparison of Daratumumab with Surrogate Analogs of CD38 Antibodies MOR03087, SAR650984 and Ab79. Blood [Internet]. 2014 [cited 2018 Sep 4];124:Abstract #3474 [ASH 2014 56th Meeting]. Available from: http://www.bloodjournal.org/content/124/21/3474?sso-checked=true.
[37] Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N. Engl. J. Med. [Internet]. 2015 [cited 2017 Oct 27];373:1207–1219. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1506348.
[38] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet [Internet]. 2016 [cited 2018 May 9];387:1551–1560. Available from: https://www.sciencedirect.com/science/article/pii/S0140673615011204.
[39] Usmani SZ, Weiss BM, Plesner T, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood [Internet]. 2016 [cited 2017 Oct 27];128:37–44. Available from: http://www.bloodjournal.org/content/128/1/37?sso-checked=true.
[40] McKeage K. Daratumumab: First Global Approval. Drugs [Internet]. 2016 [cited 2018 Sep 4];76:275–281. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26729183.
[41] Tzogani K, Penninga E, Schougaard Christiansen ML, et al. EMA Review of Daratumumab for the Treatment of Adult Patients with Multiple Myeloma. Oncologist. 2018;23:594–602.
[42] Murphy MF, Dumont LJ, Greinacher A, et al. Interference of New Drugs with Compatibility Testing for Blood Transfusion. N. Engl. J. Med. [Internet]. 2016 [cited 2018 Sep 4];375:295–296. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27468082.
[43] Chapuy CI, Nicholson RT, Aguad MD, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion [Internet]. 2015 [cited 2018 Sep 4];55:1545–1554. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25764134.
[44] Bub CB, Reis IN Dos, Aravechia MG, et al. Transfusion management for patients taking an anti-CD38 monoclonal antibody. Rev. Bras. Hematol. Hemoter. [Internet]. 2018 [cited 2018 Sep 4];40:25–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29519368.
[45] Moreau P, van de Donk NWCJ, Miguel JS, et al. Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma. Drugs [Internet]. 2016 [cited 2018 Sep 4];76:853–867. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27113582.
[46] Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for

Multiple Myeloma. N. Engl. J. Med. [Internet]. 2016 [cited 2017 Oct 26];375:1319–1331. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1607751.
[47] San-Miguel J, Dimopoulos MA, Usmani S, et al. Depth of Response and MRD with Daratumumab Plus Lenalidomide and Dexamethasone (DRd) vs Lenalidomide and Dexamethasone (Rd) in RRMM: POLLUX. Clin. Lymphoma Myeloma Leuk. [Internet]. 2017 [cited 2018 Sep 5];17:e17–e18. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2152265017303191.
[48] Usmani SZ, Dimopoulos MA, Belch A, et al. Efficacy of Daratumumab, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma Patients with 1 to 3 Prior Lines of Therapy: Updated Analysis of Pollux. Blood [Internet]. 2016 [cited 2018 Sep 5];128:Abstract #1151 [ASH 2016 58th Meeting]. Available from: http://www.bloodjournal.org/content/128/22/1151?sso-checked=true.
[49] Dimopoulos MA, White DJ, Benboubker L, et al. Daratumumab, Lenalidomide, and Dexamethasone (DRd) Versus Lenalidomide and Dexamethasone (Rd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of Pollux. Blood [Internet]. 2017 [cited 2018 Oct 30];130:Abstract #739 [ASH 2017 59th Annual Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/739.
[50] Spencer A, Hungria VTM, Mateos M-V, et al. Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of Castor. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #Abstract #3145 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/3145?utm_source=TrendMD&utm_medium=cpc&utm_campaign=Blood_TrendMD_0.
[51] Bhatnagar V, Gormley NJ, Luo L, et al. FDA Approval Summary: Daratumumab for Treatment of Multiple Myeloma After One Prior Therapy. Oncologist [Internet]. 2017 [cited 2018 Sep 4];22:1347–1353. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28904172.
[52] Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N. Engl. J. Med. [Internet]. 2016 [cited 2017 Oct 26];375:754–766. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1606038.
[53] Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Blood [Internet]. 2017 [cited 2017 Dec 18];130:974–981. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28637662.
[54] San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet. Oncol. 2013;14:1055–1066.
[55] Lonial S, San-Miguel JF, Martínez-Lopez J, et al. Daratumumab in Combination with Carfilzomib and Dexamethasone in Patients (pts) with Relapsed Multiple Myeloma (MMY1001): An Open-Label, Phase 1b Study. Blood [Internet]. 2017 [cited 2018 Sep 5];130:Abstract #1869 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/1869?sso-checked=true.
[56] San-Miguel J, Iida S, Blade J, et al. Daratumumab plus Bortezomib-Melphalan-Prednisone (VMP) in Elderly (≥75 Years of Age) Patients with Newly Diagnosed Multiple Myeloma Ineligible for Transplantation (ALCYONE). HemaSpehere [Internet]. 2018;2:5 [Abstract #S107-EHA 2018 23rd Congress]. Available from: https://learningcenter.ehaweb.org/eha/2018/stockholm/214502/jesus.san-miguel.daratumumab.plus.bortezomib-melphalan-prednisone.28vmp29.in.html.
[57] Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N. Engl. J. Med. [Internet]. 2017 [cited 2017 Dec 18];[Ahead of print-NEJMoa1714678]. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1714678.
[58] Voorhees PM, Costa LJ, Reeves B, et al. Interim Safety Analysis of a Phase 2 Randomized Study of Daratumumab (Dara), Lenalidomide (R), Bortezomib (V), and Dexamethasone (d; Dara-Rvd) Vs. Rvd in Patients (Pts) with Newly Diagnosed Multiple Myeloma (MM) Eligible for High-Dose Therapy (HDT) and Au. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #1879 [ASH 2017 59th Meeting]. Available from:

http://www.bloodjournal.org/content/130/Suppl_1/1879.
[59] Chari A, Usmani SZ, Krishnan A, et al. Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients with Newly Diagnosed Multiple Myeloma (MMY1001): Updated Results from an Open-Label, Phase 1b Study. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #3110 [ASH 2017 59th Meeing]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/3110/tab-e-letters?sso-checked=true.
[60] Deckert J, Wetzel M-C, Bartle LM, et al. SAR650984, A Novel Humanized CD38-Targeting Antibody, Demonstrates Potent Antitumor Activity in Models of Multiple Myeloma and Other CD38+ Hematologic Malignancies. Clin. Cancer Res. [Internet]. 2014 [cited 2018 Sep 4];20:4574–4583. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24987056.
[61] Jiang H, Acharya C, An G, et al. SAR650984 directly induces multiple myeloma cell death via lysosomal-associated and apoptotic pathways, which is further enhanced by pomalidomide. Leukemia [Internet]. 2016 [cited 2018 Sep 4];30:399–408. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26338273.
[62] D'Agostino M, Salvini M, Palumbo A, et al. Novel investigational drugs active as single agents in multiple myeloma. Expert Opin. Investig. Drugs [Internet]. 2017 [cited 2017 Dec 14];26:699–711. Available from: https://www.tandfonline.com/doi/full/10.1080/13543784.2017.1324571.
[63] Martin T, Richter J, Vij R, et al. A Dose Finding Phase II Trial of Isatuximab (SAR650984, Anti-CD38 mAb) As a Single Agent in Relapsed/Refractory Multiple Myeloma. Blood [Internet]. 2015 [cited 2018 Sep 4];126:Abstract #509 [ASH 2015 57th Meeting]. Available from: http://www.bloodjournal.org/content/126/23/509?sso-checked=true.
[64] Martin T, Baz R, Benson DM, et al. A Phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma. Blood [Internet]. 2017 [cited 2018 Sep 4];129:blood-2016-09-740787. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28483761.
[65] Richardson PG, Mikhael J, Usmani SZ, et al. Updated Results from a Phase Ib Study of Isatux-imab Plus Pomalidomide (Pom) and Dexame-thasone (dex) in Relapsed/Refractory Multiple Myeloma (RRMM). Blood [Internet]. 2017 [cited 2018 Sep 4];130:1887 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/1887/tab-article-info?sso-checked=true.
[66] Richardson PG, Attal M, Campana F, et al. Isatuximab plus pomalidomide/dexamethasone versus pomalidomide/dexamethasone in relapsed/refractory multiple myeloma: ICARIA Phase III study design. Futur. Oncol. [Internet]. 2018 [cited 2018 Sep 4];14:1035–1047. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29268619.
[67] Endell J, Boxhammer R, Wurzenberger C, et al. The Activity of MOR202, a Fully Human Anti-CD38 Antibody, Is Complemented by ADCP and Is Synergistically Enhanced by Lenalidomide in Vitro and in Vivo. Blood [Internet]. 2012 [cited 2018 Sep 4];120:Abstract #4018 [ASH 2012 54th Meeting]. Available from: http://www.bloodjournal.org/content/120/21/4018.
[68] Raab MS, Goldschmidt H, Agis H, et al. A phase I/IIa study of the human anti-CD38 antibody MOR202 (MOR03087) in relapsed or refractory multiple myeloma (rrMM). Am. Soc. Clin. Oncol. [ASCO] Annu. Meet. [Internet]. 2015 [cited 2017 Dec 14]. p. Abstract 8574. Available from: http://www.myelomabeacon.com/docs/asco2015/8574.pdf.
[69] Tawara T, Hasegawa K, Sugiura Y, et al. Complement activation plays a key role in antibody-induced infusion toxicity in monkeys and rats. J. Immunol. [Internet]. 2008 [cited 2018 Feb 6];180:2294–2298. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18250438.
[70] Raab M, Chatterjee M, Goldschmidt H, et al. MOR202 with Low-Dose Dexamethasone (Dex) or Pomalidomide/Dex or Lenalidomide/Dex in Relapsed or Refractory Multiple Myeloma (RRMM): A Phase I/IIa, Multicenter, Dose-Escalation Study. HemaSphere [Internet]. 2018;2:373 (Abstract #S848, EHA 2018 23rd Congress]. Available from: https://learningcenter.ehaweb.org/eha/2018/stockholm/214462/marc.raab.mor202.with.low-dose.dexamethasone.28dex29.or.pomalidomide.dex.or.html.
[71] Wang X, Dahl M, Nguyen D, et al. The Anti-CD38 Monoclonal Antibody TAK-079 Depletes Antibody Secreting Cells from Normal and SLE Patients - ACR Meeting Abstracts. ACR/ARHP

Annu. Meet. [Internet]. 2016 [cited 2018 Sep 4]. p. Abstract #1085. Available from: https://acrabstracts.org/abstract/the-anti-cd38-monoclonal-antibody-tak-079-depletes-antibody-secreting-cells-from-normal-and-sle-patients/.
[72] Atanackovic D, Steinbach M, Radhakrishnan SV, et al. Immunotherapies targeting CD38 in Multiple Myeloma. Oncoimmunology [Internet]. 2016 [cited 2018 Sep 4];5:e1217374. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27999737.
[73] Goldmacher VS, Bourret LA, Levine BA, et al. Anti-CD38-blocked ricin: an immunotoxin for the treatment of multiple myeloma. Blood [Internet]. 1994 [cited 2018 Oct 29];84:3017–3025. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7524764.
[74] Bolognesi A, Polito L, Farini V, et al. CD38 as a target of IB4 mAb carrying saporin-S6: design of an immunotoxin for ex vivo depletion of hematological CD38+ neoplasia. J. Biol. Regul. Homeost. Agents [Internet]. 2005 [cited 2018 Oct 29];19:145–152. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16602630.
[75] Green DJ, Orgun NN, Jones JC, et al. A Preclinical Model of CD38-Pretargeted Radioimmunotherapy for Plasma Cell Malignancies. Cancer Res. [Internet]. 2014 [cited 2018 Sep 4];74:1179–1189. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24371230.
[76] Green DJ, O'Steen S, Lin Y, et al. CD38-bispecific antibody pretargeted radioimmunotherapy for multiple myeloma and other B-cell malignancies. Blood [Internet]. 2018 [cited 2018 Sep 4];131:611–620. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29158362.
[77] Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. N. Engl. J. Med. [Internet]. 2017 [cited 2018 Sep 4];376:836–847. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1609783.
[78] Richter JR, Landgren CO, Kauh JS, et al. Phase 1, multicenter, open-label study of single-agent bispecific antibody t-cell engager GBR 1342 in relapsed/refractory multiple myeloma. J. Clin. Oncol. [Internet]. 2018;36:Abstract #TPS3132 [ASCO 2018 Annual Meeting]. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.TPS3132.
[79] Chu SY, Miranda Y, Phung S, et al. Immunotherapy with Long-Lived Anti-CD38 × Anti-CD3 Bispecific Antibodies Stimulates Potent T Cell-Mediated Killing of Human Myeloma Cell Lines and CD38+ Cells in Monkeys: A Potential Therapy for Multiple Myeloma. Blood [Internet]. 2014 [cited 2018 Sep 4];124:Abstract #4727 [ASH 2014 56th Meeting]. Available from: http://www.bloodjournal.org/content/124/21/4727?sso-checked=true.
[80] Li T, Qi S, Unger M, et al. Immuno-targeting the multifunctional CD38 using nanobody. Sci. Rep. [Internet]. 2016 [cited 2018 Sep 4];6:27055. Available from: http://www.nature.com/articles/srep27055.
[81] de la Puente P, Luderer MJ, Federico C, et al. Enhancing proteasome-inhibitory activity and specificity of bortezomib by CD38 targeted nanoparticles in multiple myeloma. J. Control. Release [Internet]. 2018 [cited 2018 Sep 4];270:158–176. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29196043.
[82] June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N. Engl. J. Med. [Internet]. 2018 [cited 2018 Sep 4];379:64–73. Available from: http://www.nejm.org/doi/10.1056/NEJMra1706169.
[83] Drent E, Themeli M, Poels R, et al. A Rational Strategy for Reducing On-Target Off-Tumor Effects of CD38-Chimeric Antigen Receptors by Affinity Optimization. Mol. Ther. [Internet]. 2017 [cited 2018 Oct 29];25:1946–1958. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28506593.
[84] Drent E, Poels R, Mulders MJ, et al. Feasibility of controlling CD38-CAR T cell activity with a Tet-on inducible CAR design. Shiku H, editor. PLoS One [Internet]. 2018 [cited 2018 Sep 4];13:e0197349. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29847570.
[85] Sorrento Therapeutics Inc. Sorrento's TNK Therapeutics Provides Progress Update for its Anti-CD38 and CD123 CAR-T Programs for Treatment of Hematological Malignancies [Internet]. CISION PR Newswire. 2016 [cited 2018 Sep 4]. Available from: https://www.prnewswire.com/news-releases/sorrentos-tnk-therapeutics-provides-progress-update-for-its-anti-cd38-and-cd123-car-t-programs-for-treatment-of-hematological-malignancies-300371312.html.

Annotated Bibliography

[35] Drent E, Groen RWJ, Noort WA, et al. Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. Haematologica [Internet]. 2016 [cited 2018 Sep 4];101:616–625. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26858358.

[35]* Preclinical evaluation of the potential role of CD38 chimeric antigen receptor T cells in multiple myeloma.

[38] Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet [Internet]. 2016 [cited 2018 May 9];387:1551–1560. Available from: https://www.sciencedirect.com/science/article/pii/S0140673615011204.

[38]* Phase II trial proving the efficacy of daratumumab monotherapy in heavily pretreated RRMM patients.

[46] Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N. Engl. J. Med. [Internet]. 2016 [cited 2017 Oct 26];375:1319–1331. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1607751.

[46] A large phase III trial leading to the approval of daratumumab-Rd in RRMM patients.**

[50] Spencer A, Hungria VTM, Mateos M-V, et al. Daratumumab, Bortezomib, and Dexamethasone (DVd) Versus Bortezomib and Dexamethasone (Vd) in Relapsed or Refractory Multiple Myeloma (RRMM): Updated Efficacy and Safety Analysis of Castor. Blood [Internet]. 2017 [cited 2018 Sep 4];130:Abstract #Abstract #3145 [ASH 2017 59th Meeting]. Available from: http://www.bloodjournal.org/content/130/Suppl_1/3145?utm_source=TrendMD&utm_medium=cpc&utm_campaign=Blood_TrendMD_0.

[50] A large phase III trial leading to the approval of daratumumab-Vd in RRMM patients.**

[57] Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N. Engl. J. Med. [Internet]. 2017 [cited 2017 Dec 18];[Ahead of print-NEJMoa1714678]. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1714678.

[57]* A large phase III trial potentially changing the treatment landscape for NDMM transplant-ineligible patients.

Figure title and legend

Figure 1. Mechanism of action of immunotherapeutic agents targeting CD38

Abbreviations. T reg: T regulatory cells; MDSC: myeloid-derived suppressor cells; B reg: B regulatory cells; TCR: T-cell receptor; FcγR: fragment crystallizable γ receptor; MHC: major histocompatibility complex; CAR: chimeric antigen receptor; C1q: complement component 1q; ADCP: antibody-dependent cell-mediated phagocytosis; ADCC: antibody-dependent cell-mediated cytotoxicity; C DC: complement-dependent cytotoxicity.

Table 1. Main clinical trials involving daratumumab and isatuximab

STUDY	N	PREVIOUS LINES N (median)	BORT REFR. N (%)	LEN REFR. N (%)	MEDIAN AGE (years)	REGIMEN	OR R	EFFICACY	G ≥3 HEMATOLOGICAL TOXICITY	G ≥3 NON-HEMATOLOGICAL TOXICITY (reported in ≥5% patients)
DARATUMUMAB										
SIRIUS [38]	106	≥3 (median 5)	95 (90%)	93 (88%)	64	Dara	29%	PFS 3.7 m OS 17.5 m	Neutropenia 12% Thrombocytophenia 19% Anemia 24%	IRRs 5%
POLLUX [46–48]	569	≥1 (median 1)	124 (22%) refr. to PI	0	65	Dara-Rd vs Rd	93% vs 76%	PFS NR vs 18.4 m OS na	Neutropenia 52% vs 37% Thrombocytophenia 13% vs 14% Anemia 12% vs 20%	IRRs 5% Pneumonia 8% vs 8% Dhiarrea 5% vs 3% Fatigue 6% vs 3%
CASTOR [50]	498	≥1 (median 2)	0	163 (33%) refr. to IMiD	64	Dara-Vd vs Vd	83% vs 63%	PFS NR vs 7.2 m OS na	Neutropenia 13% vs 4% Thrombocytophenia 45% vs 33% Anemia 14% vs 16%	IRRs 9% PNP 5% vs 7% Pneumonia 8% vs 10% Hypertension 7% vs 1%
NCT01998971 [53]	103	≥2 (median 4)	73 (71%)	91 (89%)	64	Dara-Pd	66%	PFS 9.9 m OS 25.1 m	Neutropenia 77% Thrombocytophenia 19% Anemia 28%	IRRs 4% Fatigue 12% Pneumonia 10% Febrile neutropenia 8%
ALCYONE [57]	706	no	-	-	71	Dara-VMP vs VMP	91% vs 74%	PFS NR vs 18.1 m OS na	Neutropenia 40% vs 39% Thrombocytopenia 34% vs 38% Anemia 16% vs 20%	IRRs 5% Infections 23% vs 15%
ISATUXIMAB										
NCT01749969 [64]	57	≥2 (median 5)	35 (65%)	47 (82%)	61	Isa-Rd	56%	PFS 8.5 m OS na	Neutropenia 60% Thrombocytophenia 38% Anemia 25%	IRRs 9% Pneumonia 9% Febrile neutropenia 5% Fatigue 7%
NCT02283775 [65]	36	≥2 (median 4)	26 (72%) refr. to PI	25 (69%) refr. to IMiD	66	Isa-Pd	56%	na	Neutropenia 83%	IRRs 3%

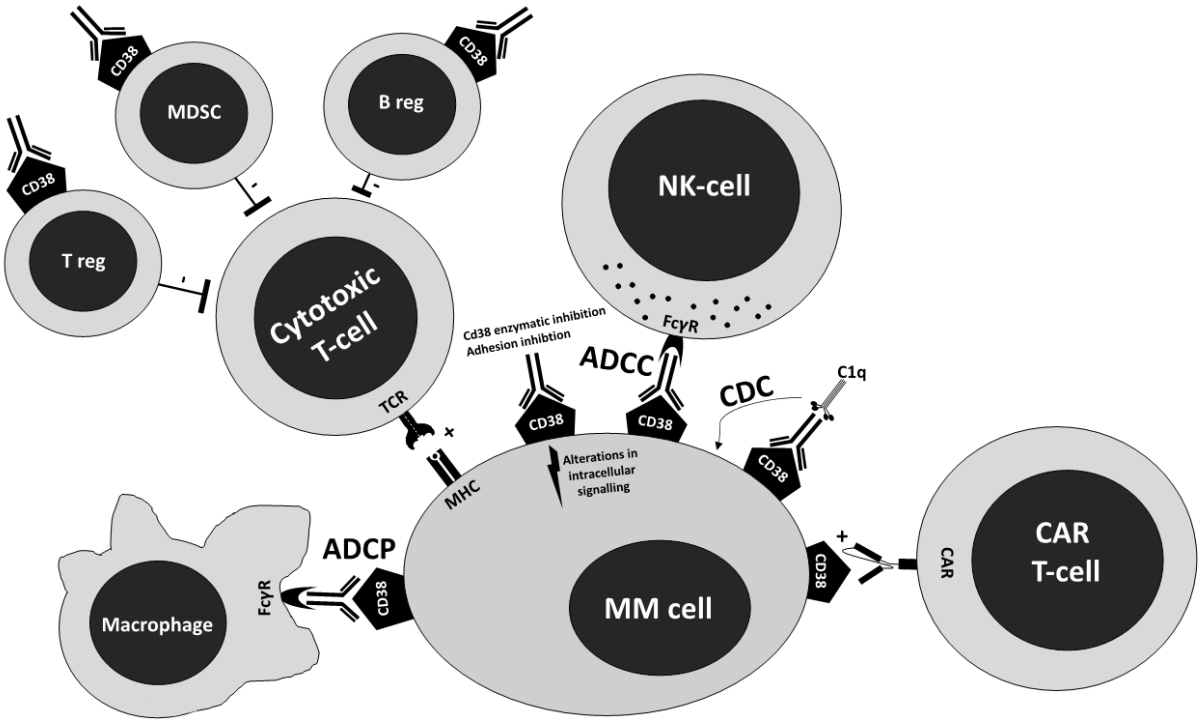
Abbreviations. NCT: ClinicalTrials.gov identifier; Bort: bortezomib; Len: lenalidomide; ORR: overall response rate; IRRs: infusion related reactions; Rd: lenalidomide-dexamethasone; Vd: bortezomib, dexamethasone; Pd: pomalidomide, dexamethasone; PFS: progression-free survival; OS: overall survival; NR: not reached; PNP: peripheral neuropathy; PI: proteasome inhibitor; IMiD: immunomodulatory drug; refr.: refractory.

Table 2. Ongoing phase III trials involving daratumumab and isatuximab in multiple myeloma patients

	Setting	Arm A - Part 1	Experimental: Arm B - Part 1	Arm A - Part 2	Arm B - Part 2
DARATUMUMAB					
NCT02541383	NDMM	Bortezomib-thalidomide-dexamethasone **(VTD)**	Bortezomib-thalidomide-dexamethasone (VTD) plus daratumumab **(Dara-VTD)**	Observation	Daratumumab every 8 weeks for 2 years
NCT03217812 (Asia Pacific Region)	NDMM	Bortezomib-melphalan-prednisone **(VMP)**	Bortezomib-melphalan- prednisone plus daratumumab **(Dara-VMP)**		
NCT03710603	NDMM	Bortezomib-lenalidomide-dexamethasone (**VRD**)	Daratumumab SC-bortezomib-lenalidomide-dexamethasone (**Dara-VRD**)		
NCT03180736	RRMM	Pomalidomide-dexamethasone **(Poma-dex)**	Pomalidomide-dexamethasone plus daratumumab **(Dara-Poma-dex)**		
NCT03277105	RRMM	Daratumumab IV	Daratumumab SC		
NCT03234972 (Chinese participants)	RRMM	Bortezomib-dexamethasone **(Vd)**	Bortezomib-dexamethasone plus daratumumab **(Dara-Vd)**		
NCT03301220	SMM	Active Monitoring	Daratumumab SC		
ISATUXIMAB					
NCT03617731	NDMM	Bortezomib-lenalidomide - dexamethasone **(VRd)**	bortezomib-lenalidomide - dexamethasone plus isatuximab **(Isa-VRd)**	Lenalidomide for three years or until progression	Lenalidomide plus isatuximab for three years or until progression
NCT03319667	NDMM, not eligible for transplant	Bortezomib-lenalidomide - dexamethasone **(VRd)**	Bortezomib-lenalidomide - dexamethasone plus isatuximab **(Isa-VRd)**	Lenalidomide plus IV or oral dexamethasone	Lenalidomide plus IV or oral dexamethasone plus isatuximab
NCT03275285	RRMM	Carfilzomib - dexamethasone **(Kd)**	Carfilzomib – dexamethasone plus isatuximab **(Isa-Kd)**		
NCT02990338	RRMM	Pomalidomide – dexamethasone **(Poma-dex)**	Pomalidomide-dexamethasone plus isatuximab **(Isa-Poma-dex)**		

Abbreviations. NCT: ClinicalTrials.gov identifier; MM: multiple myeloma; NDMM: newly diagnosed MM; RRMM: relapsed/refractory MM; SMM: smoldering MM; V: bortezomib; R: lenalidomide; D: dexamethasone; T: thalidomide; P: pomalidomide; M: melphalan; K: carfilzomib; Dara, daratumumab; Isa, isatuximab; SC: subcutaneous; IV: intravenous.

Figure 1


CD38
MDSC
B reg
T reg
Cytotoxic T-cell
TCR
MHC
NK-cell
FcγR
Cd38 enzymatic inhibition
Adhesion inhibtion
ADCC
CDC
C1q
Alterations in intracellular signalling
ADCP
Macrophage
MM cell
CAR
CAR T-cell