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Reprint of "Immunomodulatory effects of CD38-targeting antibodies"☆

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ABSTRACT

The fist in class CD38-targeting antibody, daratumumab, is currently approved as single agent and in combination with standards of care for the treatment of relapsed and refractory multiple myeloma. Based on the high activity and favorable toxicity profile of daratumumab, other CD38 antibodies, such as isatuximab, MOR202, and TAK-079, are being evaluated in MM and other malignancies. The CD38-targeting antibodies have classic Fc-dependent immune effector mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). These mechanisms of action are dependent on CD38 expression on the tumor cells. There is increasing evidence that CD38 antibodies also improve host-anti-tumor immune response by eliminating CD38-positive immune suppressor cells, including regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells. Indeed, daratumumab treatment results in a marked increase in T cell numbers and activity. CD38-targeting antibodies probably also reduce adenosine production in the bone marrow microenvironment, which may contribute to improved T cell activity. Preclinical and clinical studies have demonstrated that CD38-targeting antibodies have synergistic activity with several other anti-cancer drugs, including various agents with immune stimulating activity, such as lenalidomide and pomalidomide, as well as PD1/PD-L1 inhibitors.

1. Introduction

In 1980 CD38 was identified in by Drs. E.L Reinherz, S. Schlossman and at that time named T10 [1,2]. CD38 is highly and uniformly expressed on MM cells, and at relatively low levels on normal lymphoid and myeloid cells, but also in some tissues of non-hematopoietic origin such as prostate, smooth muscle, and eye [3–7]. CD38 is a type 2 transmembrane protein and functions as an adhesion molecule [8]. Furthermore, CD38 also has ectoenzymatic activity and is involved in the generation of nucleotide metabolites, which play a role in the regulation of intracellular calcium stores [8,9].

Based on the high CD38 expression on MM cells, it was identified as a potential therapeutic target. Daratumumab (fully human; Janssen Pharmaceuticals) is the first in class therapeutic CD38 antibody and currently approved for various indications for the treatment of MM patients. Based on the high activity and good tolerability of CD38 antibodies, several other CD38-targeting antibodies are in clinical development. This includes the chimeric antibody isatuximab (Sanofi), MOR202 (fully human; Morphosys), and TAK-079 (fully human, Takeda). In this review, we will discuss the mechanisms of action of these CD38 antibodies with a strong focus on immune-mediated modes of action, which can be divided into classic immune effector mechanisms and novel immunomodulatory activities. Since these novel immunomodulatory effects of CD38 antibodies are (largely) independent of CD38 expression on tumor cells, CD38 antibodies alone or in combination may also be active in CD38-negative tumors.

2. Classic Fc-dependent immune effector mechanisms

Daratumumab and other CD38 antibodies can bind with their Fc tail to Fc gamma receptors, (FcγRs) which are present on immune effector cells [10]. This interaction leads to activation of these immune cells and subsequent killing of MM cells via antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP). The Fc tail of several CD38 antibodies can also bind to C1q, which is the first component of the complement pathway [11].

2.1. ADCC

ADCC is mainly mediated by FcγR-expressing NK cells [12]. Following the binding of FcγRs to the Fc region of the CD38 antibody, NK cells release cytotoxic molecules such as granzymes and perforins,

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which will subsequently kill the target cells.

Daratumumab-mediated ADCC is very effective against both MM cell lines and primary MM cells [13,14]. However, ADCC-mediated killing of primary MM cells is very heterogeneous among different patient's samples, which is partly explained by differences in target expression levels [14]. Furthermore, daratumumab-mediated ADCC is also dependent on the ratio between NK cells and MM cells (effector: target ratio) in samples [14]. Importantly, there is no difference in the extent of ADCC between samples obtained from extensively pretreated patients and newly diagnosed, untreated, patients [14].

Immunomodulatory drugs (IMiDs) increase NK cell numbers and activity, and thereby synergize with daratumumab in ADCC assays with MM cell lines or primary MM cells [12,15]. Even in the setting of IMiD-refractory MM cells, IMiDs synergize with daratumumab [12]. This indicates that immune effector cells from IMiD-refractory MM patients can still be modulated by lenalidomide or pomalidomide.

NK cells have high CD38 expression, which may explain the rapid and marked NK cell depletion in patients treated with daratumumab [16]. This NK cell depletion may reduce the relative contribution of ADCC to kill MM cells. However, the extent of NK cell reduction was not associated with the efficacy or safety profile of daratumumab monotherapy [16].

2.2. ADCP

Activation of FcγRs on the surface of macrophages by antibody-opsonized tumor cells induces phagocytosis, resulting in internalization and degradation of the target cells. ADCP is an efficient killing mechanism of daratumumab, whereby individual macrophages rapidly and sequentially engulf multiple MM cells [17]. ADCP is partly dependent on the ratio of monocytes to MM cells [14].

Phagocytosis is regulated by the CD47/SIRPα pathway. CD47 expressed on the tumor binds to SIRPα on macrophages, which results in inhibition of phagocytosis [18]. CD47-blocking antibodies enhance induction of ADCP of cancer cells upon treatment with therapeutically used antibodies including rituximab [19]. Two different groups recently showed that neutralization of CD47, also augments macrophage-mediated phagocytosis induced by CD38 antibodies [20,21].

In addition, low doses of cyclophosphamide improve daratumumab-mediated ADCP of MM cells, which is probably mediated by increased FcγR expression on macrophages as well as reduced levels of CD47 on tumor cells [22,23].

2.3. CDC

Daratumumab bound to the MM cell surface activates complement via the classical pathway with as first step the binding of C1q to the Fc portion of daratumumab. This leads to C1q activation, which eventually results in formation of membrane attack complexes, which generate pores in the MM cell surface leading to lysis of the cells [13,24]. Furthermore, in this process also anaphylatoxins are produced which can recruit immune cells to the tumor. In addition, deposition of C3b on the MM cell surface stimulates phagocytosis and cytotoxic killing.

The CD38 antibodies differ in their ability to induce CDC. Daratumumab was selected from a set of CD38 antibodies, based on its high efficacy to induce CDC-mediated lysis of tumor cells [13]. Indeed, daratumumab is the most potent CDC inducer of all currently available CD38 antibodies, while MOR202 has weak CDC activity [25]. Differences in extent of complement activation, may explain differences in the frequency of infusion-related reactions among the CD38 antibodies. Indeed, MOR202 treatment is associated with a relatively low rate of infusion reactions, when compared to daratumumab or isatuximab [26].

Daratumumab-mediated CDC against primary MM cells is variable among different patient's samples, but (similar to ADCC) there is no difference in the extent of CDC between samples from newly diagnosed patients or extensively pretreated patients [14]. This indicates that mechanisms of resistance to CD38 antibodies are different from those leading to resistance to alkylating drugs, IMiD, or proteasome inhibitors. Heterogeneity in daratumumab-mediated CDC is partly explained by differences in expression of the target protein CD38 [14]. MM cells with high levels of CD38 are more effectively killed by daratumumab, when compared to cells with low CD38 expression.

Cells also express membrane-bound complement regulators to prevent uncontrolled amplification and activation of complement. This includes the complement-inhibitory proteins (CIPs) CD46, CD55 and CD59 [11]. Differences in baseline expression levels of these proteins do not explain the variation in complement-mediated lysis of MM cells [27]. However, we found that upregulation of CD55 and CD59 on the MM cell surface occurs at the time development of progressive disease during daratumumab treatment [27]. In some patients, we also observed the presence of different cell populations with different expression of CD55 or CD59. After the initiation of daratumumab treatment, the subpopulation with highest CIP expression was relatively more resistant and responsible for the relapse [27].

3. Immunomodulatory effects

As described in the previous section, the Fc-dependent immune effector mechanisms and direct effects of CD38 antibodies, require CD38 expression on the tumor cell surface in order to kill MM cells. However, we recently described that daratumumab treatment induces a rapid and uniform CD38 reduction on MM cells [27,28]. Directly after the first daratumumab infusion, there is an approximately 90% reduction in CD38 expression levels on the MM cell surface [28]. This is the consequence of selection of tumor cells with relatively low CD38 levels, and maybe more important the result of trogocytosis [28]. In the process of trogocytosis, there is transfer of CD38-daratumumab complexes from the tumor cell to immune effector cells such as neutrophils and monocytes [28,29]. In addition, daratumumab induces the redistribution of CD38 molecules and formation of distinct polar aggregates, which can be subsequently released as microvesicles [30]. Importantly, these microvesicles not only contain CD38 and daratumumab, but also other molecules are transferred from the MM cell surface to these vesicles [30,31]. The effects of these microvesicles within and outside the bone marrow microenvironment are currently unknown.

CD38 reduction occurs rapidly in all patients, including those with durable remissions or with increasing depth of response [28]. Also the incidence of complete response and minimal-residual disease negativity increases over time when patients are treated with daratumumab in combination with lenalidomide-dexamethasone or bortezomib-dexamethasone, even when partner drugs are stopped [32–35]. Altogether, this indicates that daratumumab must also have activity that is independent of CD38 on the MM cell surface. In the following section, we will discuss the CD38 antibody-induced mitigation of tumor-induced immune suppression, which is mediated by depletion of immune suppressor cells and possibly reduced adenosine production in the MM bone marrow microenvironment.

3.1. Effect on immune suppressor cells

3.1.1. Daratumumab eliminates immune suppressor cells in MM patients

Immune dysfunction in MM is, in part, mediated by regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Regulatory B cells (Bregs) also contribute to an immunosuppressive microenvironment via production of IL-10 [36]. Importantly, Bregs also abrogate NK cell-mediated ADCC against MM cells [36]. Since CD38 is present on these immunosuppressive cells, we evaluated the effect of daratumumab on these immune suppressor cells. Daratumumab as single agent significantly reduced the frequency of regulatory B cells [37]. Furthermore, daratumumab also eliminated the subset of CD38-positive regulatory T cells (approximately 10% of total Treg

population), while the Tregs without CD38 expression were not affected [37]. Importantly, the subpopulation of CD38-positive Tregs is more potent in suppressing T cell proliferation, when compared to CD38-negative Tregs [37]. MDSCs were also effectively killed by daratumumab in CDC and ADCC assays [37].

The immunomodulatory effects of daratumumab were also studied in the POLLUX study. In this study MM patients, who had received at least one prior line of therapy, were treated with lenalidomide-dexamethasone with or without daratumumab. Lenalidomide is an immunomodulatory agent, which has direct anti-MM effects, but also eliminates MM cells via stimulation of the immune system [38]. Addition of daratumumab to lenalidomide-dexamethasone resulted in a marked improvement in response, minimal residual disease-negativity rate, and progression-free survival [35]. Consistent with observations from daratumumab monotherapy, Tregs are also reduced following treatment with daratumumab in combination with lenalidomide-dexamethasone (DRd), but not with lenalidomide-dexamethasone (Rd) alone [39].

3.1.2. Daratumumab induces T cell expansion in MM patients

Daratumumab monotherapy treatment results in a marked increase in both CD4+ and CD8+ T cells, probably as a consequence of the reduction of immune suppressor cells [37]. This increase in T cells was observed both in blood samples and in bone marrow. The median maximum increase in T cell counts was higher in patients who responded to daratumumab, when compared to non-responders [37].

In the POLLUX study, the proportion of T cells increased preferentially in deep responders (complete response or better) who received DRd, when compared to Rd [39].

3.1.3. Effect of daratumumab on T cell activation and functionality in MM patients

The expanded T cells were characterized in patients treated with daratumumab monotherapy or with DRd.

Specific T cell populations were altered by single agent daratumumab, including a decrease in naïve T cells, and concomitant increase in effector memory CD8+ T cells [37]. Furthermore, daratumumab treatment led to increased T cell clonality which was positively correlated with the increase in CD8+ T cells [37]. The reactivity of these T cell clones is currently unknown and focus of active investigations. Interestingly, patients who achieved partial response or better with daratumumab monotherapy had significantly improved functional T cell responses to viral and allo-antigens as measured by IFN-γ production, when compared with baseline [37].

In the POLLUX study, mass-cytometry by time-of-flight (CyTOF) analysis showed that daratumumab treatment induced a shift in composition of the T cells towards granzyme B-positive and HLA-DR-positive CD8+ T cells [39]. DRd also led to a higher proportion of effector and effector memory cells, when compared to Rd alone [39]. Furthermore, only in the daratumumab-containing arm an increase in T cell clonality was observed, which was associated with expansion of CD8+ T cells [39,40].

Similar immunomodulatory effects were also observed in another study with daratumumab plus lenalidomide or pomalidomide by using single-cell RNA sequencing [41]. This study also demonstrated that M1 macrophages predominate in the bone marrow of sensitive patients, while refractory patients had predominantly M2 macrophages in the bone marrow microenvironment [41]. These observations suggest that a M1 macrophage signature represents a potential biomarker of response to daratumumab plus IMiD treatment [41].

3.1.4. Immunomodulatory activity of daratumumab in other cancers

Similarly, in chronic lymphocytic leukemia (CLL), daratumumab not only has direct immune-mediated activity (ADCC, CDC, and ADCP) [42,43], but also decreases Treg-mediated immunosuppression leading to a potentiation of CD8+ T cell-induced killing of CLL cells [43]. Furthermore, CD38-targeting antibodies have also been shown to deplete CD38-positive MDSCs in solid tumor models and this resulted in a decreased tumor growth rate in tumor-bearing mice [44].

3.1.5. Immunomodulatory effects of other CD38 antibodies

To the best of our knowledge, it is currently unknown whether MOR202 and TAK-079 have similar immunomodulatory effects, when compared to daratumumab. At this moment there is only limited information available for isatuximab regarding immunomodulatory activity. Furthermore, existing data is predominantly derived from preclinical models, while daratumumab-mediated immunomodulatory effects have been studied in both preclinical and clinical studies.

Isatuximab decreases the frequency of CD38-positive Tregs by induction of apoptosis and inhibition of proliferation [45]. Isatuximab also reduces production of immune inhibitory cytokines such as TGF-β and IL-10 and blocks Treg trafficking. Altogether, this explains that isatuximab enhances NK- and CD8+ T cell-mediated immune responses against MM cells [45].

It has recently been shown that osteoclasts protect MM cells against T cell-mediated cytotoxicity, which is in part mediated by PD-L1 and IDO [46]. Interestingly, isatuximab restores T cell responses by inhibiting the expression of immune-checkpoint molecules on osteoclasts [46].

Finally, isatuximab treatment led to the development of T cell responses against the therapeutic target CD38, as well as to other tumor-associated antigens. These adaptive immune responses were observed in 2 patients with relapsed/refractory MM, who achieved a complete response, but not in 2 patients without response to isatuximab monotherapy [47].

3.1.6. Open questions

In conclusion, daratumumab reduces immune suppression in the bone marrow microenvironment by eradicating CD38-positive immune suppressor cells, which allows helper and cytotoxic T cell to expand. It is expected that the increase in T cell frequency and activity, leads to a better host-anti-tumor immune response. These immunomodulatory effects are also observed when daratumumab is combined with lenalidomide-dexamethasone [39]. Combinations of daratumumab with alkylating agents (such as cyclophosphamide) or proteasome inhibitors (such as bortezomib or carfilzomib) also have marked anti-MM activity, but at this moment it is unknown to what extent these immunomodulatory effects are impaired by adding potentially immunosuppressive anti-MM agents to daratumumab.

3.2. Effect of CD38 antibodies on adenosine and NAD+ levels

As ectoenzyme CD38 is involved in the generation of molecules that regulate calcium signaling. In addition, CD38 is involved in the production of extracellular adenosine from NAD^+, provided CD38 is operating in the presence of other ectoenzymes such as the ectonucleotide pyrophosphatase/phosphodiesterase CD203a and 5′-nucleotidase CD73 [48]. Specifically, CD38 hydrolyzes NAD^+ to adenosine diphosphate ribose (ADPR), which is converted to AMP by CD203a. AMP is finally dephosphorylated by CD73 to adenosine [49]. This pathway is active in several malignancies including gliomas, melanomas, and prostate cancer, as well as in MM [49]. Indeed, adenosine levels were significantly higher in the bone marrow microenvironment of MM patients, when compared to patients with monoclonal gammopathy of undetermined significance (MGUS) or smoldering MM [50]. Also patients with international staging system (ISS) stage 3 disease had higher adenosine concentrations in the bone marrow microenvironment, when compared to patients with ISS stage 1 or 2 [50].

Adenosine binds to P1 purinergic receptors and hampers immune cell infiltration and activation [49]. The immunosuppressive effects of adenosine primarily impair the activity of NK cells and CD8+ T cells [49]. Furthermore, adenosine promotes the generation and infiltration

of immune suppressive cells such as Tregs and MDSCs [49].

Therefore, inhibition of the adenosinergic ectoenzyme function by CD38-targeting antibodies may lead to lower adenosine levels in the bone marrow microenvironment [25]. In addition, daratumumab-mediated reduction of CD38 cell surface expression on tumor cells and non-malignant cells in the bone marrow microenvironment may also contribute to diminished production of adenosine [28], resulting in a better host-anti-tumor immune response. However, the exact consequences of inhibition of CD38 ectoenzyme activity by the different CD38 antibodies remain to be further documented.

Recent findings show that CD38 (as a NADase) also controls immunotherapeutic anti-tumor T cell response via the regulation of NAD + levels and Sirt1/Foxo1 activity [51]. In addition, CD38 loss compromises the suppressive activity of Tregs and MDSCs, and induced more IFN-γ secretion in NK cells [51,52]. Interestingly, antibody-mediated targeting of CD38 on T cells increased NAD+ levels and improved their anti-tumor potential in a melanoma mouse model [51].

4. Other effects of CD38 antibodies

CD38 have potent classic and novel immune-mediated activities, but also other effects. These non-immune-mediated activities will be briefly discussed in the following section.

4.1. Direct induction of apoptosis

Isatuximab was selected from a large panel of CD38 antibodies based on its ability to induce apoptosis in tumor cells in the absence of any cross-linking agent [53]. Indeed, isatuximab directly induces MM cell death by binding to CD38 on the cell surface. The direct induction of cell death by isatuximab is mediated via the classical caspase-dependent apoptotic pathway and the lysosomal-associated cell death pathway [54]. Lysosome-mediated non-apoptotic cell death triggered by isatuximab is characterized by lysosomal enlargement, lysosomal membrane permeabilization and cathepsin hydrolase release [54]. These isatuximab-induced direct anti-MM activities can be enhanced by pomalidomide and lenalidomide [54].

In contrast, daratumumab does not directly induce apoptosis after binding to CD38, but needs FcγR-mediated crosslinking [55]. Similarly, MOR202 does not have direct apoptosis-inducing activity.

4.2. Effect on osteoclasts

In the MM bone marrow microenvironment, there is an increased formation and activity of osteoclasts leading to enhanced bone resorption [56]. This together with reduced osteoblastogenesis leads to the formation of lytic bone lesions, which are present in the majority of MM patients. In addition, osteoclasts also produce several cytokines, which support MM cell survival and proliferation.

CD38 is expressed by early osteoclast progenitors, but not by mature osteoclasts or osteoblasts [57]. Indeed, daratumumab is capable of inhibiting osteoclastogenesis by targeting early osteoclast progenitors [57]. ATRA treatment increased the effects of daratumumab on osteoclast formation. The inhibitory effect of daratumumab on osteoclast formation was only observed in the presence of other immune effector cells, which may explain that isatuximab has no effect on osteoclastogenesis from isolated CD14-positive cells [46].

5. CD38-targeting antibodies combined with other immunomodulatory agents

Since CD38 antibodies have pleiotropic mechanisms of action, these agents are attractive as combination partner with other standards of care. Indeed, marked clinical synergy between CD38 antibodies and proteasome inhibitors or alkylating agents has been demonstrated in newly diagnosed and relapsed/refractory MM [22,34,58,59]. In addition, given the immunomodulatory effects of CD38 antibodies, several combinations with other anti-MM agents with immune stimulatory properties have been or are currently being explored in MM.

5.1. IMiDs

IMiDs, such as lenalidomide and pomalidomide, have direct anti-MM effects, which are mediated by binding of IMiDs to Cereblon, which promotes ubiquitination and subsequent proteasomal degradation of the substrate proteins Aiolos and Ikaros, leading to growth inhibition and apoptosis [38]. In addition, IMiDs also have indirect anti-tumor effects by inhibiting angiogenesis and reducing MM cell adhesion, as well as immune stimulatory activity including enhancing NK cell activity and CD4+ and CD8+ T cell costimulation [38,60]. Several preclinical studies, which showed synergy between CD38 antibodies and IMiDs, formed the preclinical rationale for the clinical evaluation of these combinations [12,61].

The randomized phase 3 POLLUX study showed that DRd induced a higher overall response rate including a higher frequency of complete response and minimal residual disease-negativity, when compared to Rd alone in patients with at least one prior line of therapy [35]. This resulted in a superior progression-free survival in patients treated with DRd compared to Rd. Importantly, achieving MRD-negativity was associated with a superior outcome, when compared to MRD-positive patients [32]. The most common adverse events related to daratumumab were infusion-related reaction, which mainly occurred during the first infusion. There was also a higher rate of neutropenia, fatigue, diarrhea, and infections in the DRd arm, when compared to Rd, which may be related, at least in part, to longer treatment exposure in the daratumumab arm [35]. Similarly, Rd in combination with isatuximab or MOR202 leads to marked anti-MM activity with a favorable toxicity profile [26,62].

Pomalidomide is a next-generation IMiD with more potent immune stimulatory activity in preclinical studies, when compared to lenalidomide [60]. Daratumumab combined with pomalidomide and dexamethasone induced rapid, deep, and durable responses in heavily pretreated MM patients (median of 4 prior lines of therapy) in a phase 1b study [63]. Added toxicity due to daratumumab mainly consisted of infusion-related reactions. Based on the promising results from this study, the randomized phase 3 APOLLO study is currently enrolling relapsed and/or refractory MM patients to evaluate pomalidomide-dexamethasone with or without daratumumab. Isatuximab and MOR202 have also shown to be active when combined with pomalidomide-dexamethasone [26,64]. A phase 3 trial evaluating pomalidomide-dexamethasone with or without isatuxumab is ongoing (ICARIA trial).

Interestingly, in patients progressing on daratumumab, the addition of lenalidomide or pomalidomide induced clinical responses, while at the same time these patients were refractory to the IMiD drug when it was given in a prior line of therapy [65]. Similarly, in another study 33% of daratumumab and pomalidomide-refractory patients responded when they received the combination of daratumumab plus pomalidomide-dexamethasone [66]. Altogether, these case series demonstrate the clinical synergy between CD38-targeting antibodies and IMiDs, even in patients refractory to both classes of drugs.

5.2. PD1 and PD-L1 blocking agents

In the bone marrow microenvironment PD-L1 is expressed on MM cells and MDSCs, while PD1 is expressed on T cells and NK cells [67]. Activity of NK cells and T cells is impaired by binding of PD1 to PD-L1, leading to an impaired host-anti-tumor immune response. PD1/PD-L1 blocking antibodies have no single agent activity in extensively pretreated MM patients [68], but these antibodies have marked activity in other malignancies including Hodgkin's lymphoma, melanoma, and lung cancer [69–71].

Mechanisms of resistance towards anti-PD1/PD-L1 agents include defects in the tumor antigen presentation pathway, depletion of neoantigen repertoire, insufficient diversity and abundance of T cells, insensitivity of tumor cells to T cell effector molecules, recruitment of immune suppressive cells, and compensatory upregulation of alternative checkpoint molecules [72]. Interestingly, it was recently demonstrated that CD38 was upregulated after anti-PD-L1 antibody treatment in a lung cancer mouse model, which was associated with inhibition of CD8+ T cell function [73]. Altogether, these data suggest that increased CD38 expression is a new mechanism of resistance to PD1/PD-L1 blocking therapy. Indeed, there was marked synergy when a CD38-targeting antibody was added to anti-PD-L1 antibody treatment in a lung cancer mouse model [73].

Based on these data, several studies are currently ongoing to evaluate the combination of daratumumab or isatuximab with a PD1/PD-L1 blocker in relapsed/refractory MM patients. This combination of CD38 and PD-1/PD-L1 antibodies may also be effective in CD38-negative tumors, since the CD38-antibody-mediated depletion of immune suppressor cells, may synergize with the inhibition of the PD1/PD-L1 pathway. Indeed, daratumumab plus nivolumab is evaluated in a wide variety of malignancies, irrespective of CD38 expression levels on the tumor [10].

5.3. Other combinations

Combinations of CD38 antibodies with other immunotherapeutic agents are currently investigated in preclinical models. This includes combinations with CAR T cells and other inhibitors of immune checkpoints.

6. Conclusion

CD38 antibodies have Fc-dependent immune effector mechanisms such as CDC, ADCC, and ADCP, which are dependent on CD38 expression levels on the tumor cells. In addition, CD38-targeting antibodies also improve the host-anti-tumor immune response by depleting CD38-positive immune suppressor cells such as Tregs, Bregs, and MDSCs (Fig. 1). Reduced adenosine production in the local tumor microenvironment and increased NAD+ levels in T cells, may also contribute to mitigation of tumor-induced immunosuppression (Fig. 1). Since CD38 protein is rapidly reduced on the MM cell surface and NK cells are rapidly depleted after initiation of daratumumab treatment, we expect that Fc-dependent immune effector mechanisms are most important in reducing tumor burden during the early phase of daratumumab therapy, while the novel immunomodulatory activities are important for sustained control of the tumor and further deepening of response (Fig. 2).

As a result of these pleiotropic mechanisms of action, CD38 antibodies have high single agent activity and strong synergy with other anti-cancer agents in MM patients. At the same time, these drugs are also well tolerated with infusion reactions as most frequent adverse event. In MM, CD38 antibodies are currently incorporated in the treatment of both relapsed/refractory and newly diagnosed patients. In addition, CD38 antibodies are evaluated in other CD38-positive malignancies such as acute myeloid leukemia [74], T-cell acute lymphoblastic leukemia [75], amyloid light-chain amyloidosis [76–78], and NK/T cell lymphomas [79,80]. Based on their potent immunomodulatory activities, we expect that CD38 antibodies will also be of value in CD38-negative cancers, probably in combination with other types of immunotherapies [10].

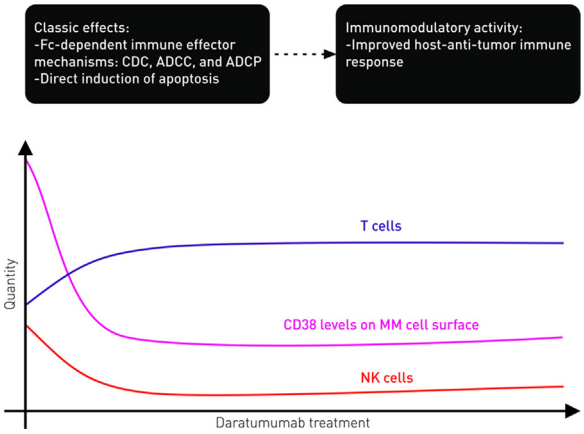

Fig. 2. Daratumumab rapidly eliminates MM cells via classic Fc-dependent immune effector mechanisms, which is followed by an improved host-anti-tumor immune response.
Since CD38 protein is rapidly reduced on the MM cell surface and NK cell numbers are also rapidly decreased after initiation of daratumumab treatment, we expect that CD38-dependent and Fc-dependent immune effector mechanisms (antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)) are most important in reducing tumor burden during the early phase of daratumumab therapy. Following CD38 reduction on the MM cell surface and NK cell depletion, the novel immunomodulatory activities of daratumumab are important for sustained control of the tumor and further deepening of response. Shown is the effect of daratumumab on NK cell and T cell numbers, as well as on CD38 expression on MM cells.

Authorship

NvdD performed literature searches and prepared the manuscript.

Conflict of interest

N.W.C.J.v.d.D. has received research support from Janssen Pharmaceuticals, AMGEN, Celgene, Novartis, and BMS, and serves in advisory boards for Janssen Pharmaceuticals, AMGEN, Celgene, BMS, Novartis, Takeda, Bayer, and Servier.

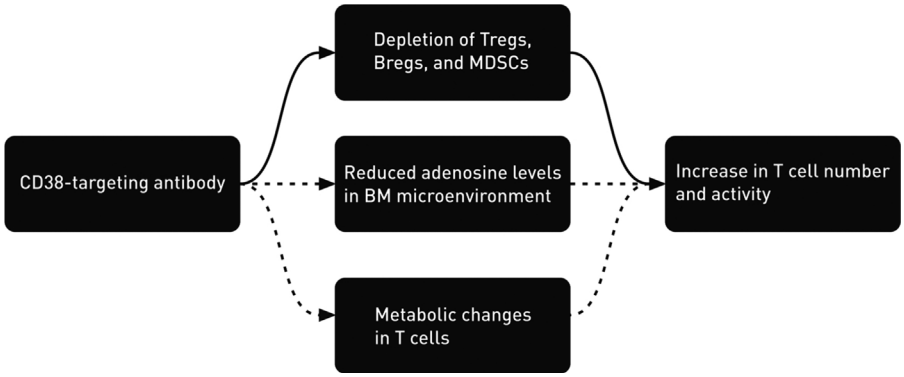

Fig. 1. CD38 antibodies improve T cell numbers and function.
CD38-antibodies increase T cell numbers and T cell activity by depletion of immune suppressor cells including Tregs, Bregs, and MDSCs. Reduced production of adenosine in the bone marrow microenvironment and increased levels of NAD+ in T cells may also contribute to improved T cell function, but this requires further investigations.
Of note, modes of action of daratumumab are extensively studied, while additional studies are required for isatuximab, TAK-079, and MOR202.

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