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THERAPY IN PRACTICE

Practical Considerations for the Use of Daratumumab, a Novel CD38 Monoclonal Antibody, in Myeloma

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Abstract Monoclonal antibodies (mAbs) are a recent addition to multiple myeloma (MM) therapies and a number of mAbs directed at myeloma cell surface molecules are in development. Daratumumab is a CD38 mAb that has demonstrated substantial activity and good tolerability in four phase I, phase I/II and phase II studies as monotherapy, as well as in combination with current standard treatments in MM. The positive results obtained in the relapsed/refractory setting in patients with advanced-stage disease and in a small number of patients with newly diagnosed disease provide the rationale for the investigation of the agent in a number of ongoing phase III trials. mAbs are generally better tolerated than conventional chemotherapy; however, their use requires other special considerations. Such factors include those common to all mAbs, namely infusion-related reactions, but also factors that are observed with mAbs used in myeloma, such as interference with response assessment, or factors that are related to CD38 mAbs such as daratumumab, for instance blood typing interference. Our review provides an overview of the results from the daratumumab clinical trials conducted to date, as well as practical management considerations for the use of daratumumab based on our experience with the agent.

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Key Points

Monoclonal antibodies (mAbs) present a new development in the treatment of multiple myeloma.

Daratumumab is a fully human mAb directed at CD38 that has shown significant clinical activity and good tolerability as monotherapy and in combination with current standard therapies in patients with relapsed/refractory multiple myeloma, which was approved by the US FDA in November 2015.

mAb therapy, in myeloma as in other diseases, is associated with specific management considerations. Practical recommendations regarding these, as well as the administration and scheduling of daratumumab, are provided in this review.

Extensive clinical development of daratumumab is currently ongoing, which will help define the place for the agent in the treatment of multiple myeloma.

1 Introduction

Immunotherapy, aimed at engaging the immune system in the fight against malignant cells, is an attractive concept in cancer treatment. A number of different strategies can be distinguished, such as mAbs, chimeric antigen receptor (CAR) T cells, checkpoint inhibition and vaccination. mAbs are a widely used treatment modality in hematology, with rituximab being the most prominent example. The agent was approved for the treatment of lymphoma in 1997 by the US FDA and in 1998 by the European Medicines Agency (EMA) [1], and is now considered a standard therapy in lymphoma that has had a major impact on survival [2]. A large body of experience has been accumulated regarding the appropriate management of patients receiving rituximab.

In multiple myeloma (MM), the introduction of proteasome inhibitors (PIs) (e.g. bortezomib and carfilzomib) and immunomodulatory drugs (IMiDs; e.g. lenalidomide and pomalidomide) heralded a major change in the management of the disease. These agents form the backbone of current treatment strategies and have led to significant improvements in patient survival [3]. However, for patients who are refractory to these agents, the prognosis remains poor, with a median overall survival (OS) of only 9 months [3, 4]. Novel strategies are therefore needed and immunotherapy, particularly the mAbs, presents an exciting new approach. mAbs combine a high specificity for antigens on the surface of the neoplastic cell or in the microenvironment and the capability to engage immune cells.

In MM, the search for mAbs to target the tumor cell has been elusive until the recent past; however, a large number of mAbs are currently under investigation. Among them, elotuzumab, a humanized immunoglobulin (Ig) G1 kappa mAb that targets the signaling lymphocytic activation molecule-F7 (SLAMF7, also known as CS1), has advanced furthest in clinical testing. Recently, CD38 has been identified as an attractive target for mAb therapy in myeloma, and three CD38 mAbs are currently being investigated in clinical trials—the chimeric IgG1 kappa mAb isatuximab (SAR650984) and two human mAbs, daratumumab (IgG1 kappa) and MOR202 (IgG1 lambda). Daratumumab is the CD38 mAb for which the clinical development has progressed furthest and is the focus of our review. It has shown highly promising results in preclinical and clinical studies. It was granted breakthrough status by the FDA in 2013 [5] and was approved by the FDA in November 2015 for the treatment of patients who have received three or more prior lines of therapy, including a PI and an immunomodulatory agent, or who are double refractory to a PI and an immunomodulatory agent [6]. Daratumumab is currently undergoing regulatory review by the EMA [7].

Our aim was to provide a summary of the daratumumab clinical trials conducted in multiple myeloma to date on the one hand, and to outline management considerations on the other hand, with the addition of practical recommendations based on our experience with the agent.

2 Target and Mode of Action of Daratumumab

CD38 is a transmembrane glycoprotein that combines adhesion, receptor and enzymatic functions [8–12]. As an ectoenzyme, it exerts its catalytic function on the external surface of the cell membrane. It catalyzes the conversion of nicotinamide adenine dinucleotide (NAD) + to adenosine diphosphate ribose (ADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), and is thus involved in the mobilization of calcium, a key factor in signaling pathways of cell growth, survival and differentiation [8, 10]. CD38 is normally expressed by precursor and activated B and T cells, as well as myeloid cells, natural killer (NK) cells, erythrocytes, platelets and plasma cells [10]. In leukocytes, it functions as a plasma membrane signaling receptor and acts as a co-receptor on B cells, where it modulates B cell receptor signals [13]. It is also involved in the chemotaxis of neutrophils and monocytes [14, 15], and mediates the production of cytokines by effector cells, the proliferation of T lymphocytes, and the protection of mature B lymphocytes and dendritic cells from apoptosis [16]. CD38 is not expressed by pluripotent hematopoietic

precursor cells, which may be important for bone marrow recovery, in particular, when CD38 mAbs are used in combination with myelotoxic drugs [17, 18].

While the expression on normal lymphoid and myeloid cells is relatively low, CD38 is highly and uniformly expressed on myeloma cells [10, 11, 19, 20]. Through the production of adenosine, CD38 is thought to play an important role in the survival of the myeloma cell in the bone marrow environment [12, 21]. The high expression on myeloma cells combined with important enzymatic and signaling functions make CD38 an attractive target for immunotherapy [10, 21].

Following binding to CD38, daratumumab is understood to exert its cytotoxic effects through a number of mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cell-mediated phagocytosis (ADCP), as well as the direct induction of apoptosis upon secondary crosslinking [22–24]. In vitro, daratumumab was found to be the most active CDC-activating mAb of the CD38 mAbs currently undergoing investigation [25]. In addition, the modulation of cellular enzymatic activities associated with calcium mobilization and signaling is thought to contribute to the cytotoxic effect [26]. Moreover, an immunomodulatory effect of daratumumab was recently described following an analysis of patient samples from two clinical trials in which patients with advanced-stage disease received daratumumab [27]. Following daratumumab treatment, increased adaptive immune responses were observed, evidenced by T-cell increases alongside increases in CD8+:CD4+ ratios, antiviral responses, anti-allotypic responses and T-cell clonality. Interestingly, subpopulations of regulatory T cells, B cells and monocytes were identified that expressed high levels of CD38 and were found to be highly immunosuppressive and sensitive to treatment with daratumumab. These results suggest that daratumumab may have an important immunomodulatory role by eliminating cells that suppress the immune system in myeloma and potentially releasing an antimyeloma response, as reflected by the emergence of spikes of clonal T cells and improved anti-allotypic responses.

3 Antimyeloma Activity of Daratumumab

3.1 Preclinical Activity

Daratumumab demonstrated potent in vitro activity against myeloma cells isolated from patients and myeloma cell lines [22, 23]. Of note, in preclinical studies, synergy in inducing ADCC between lenalidomide or bortezomib and daratumumab was shown [28, 29]. In addition, the benefit of combining daratumumab and lenalidomide could also be shown in lenalidomide/bortezomib-resistant multiple myeloma cell lines and even in primary multiple myeloma cells from bone marrow mononuclear cells derived from lenalidomide- and/or bortezomib-refractory patients [30].

3.2 Clinical Activity: Daratumumab Monotherapy

To date, the results of four clinical studies with daratumumab have been published or presented at congresses (Table 1). In the first-in-human study of daratumumab (GEN501), designed as a phase I/II trial, patients with relapsed/refractory MM who had received two or more prior lines of therapy and who were ineligible for autologous stem cell transplantation were treated with daratumumab single agent administered in a dose-escalation scheme [31]. In the first part of the study, involving 32 patients, the dose of daratumumab, administered intravenously once weekly, was increased gradually, with three patients treated at each dose level from 0.005 to 24 mg/kg without observation of a dose-limiting toxicity. Among 12 patients who received daratumumab 4–24 mg/kg, a partial response (PR) was seen in four patients and a minimal response (MR) was seen in three patients. Overall, daratumumab showed a favorable tolerability profile. Serious adverse events (AEs) occurred in 37 % of patients and included pyrexia, infections (9 % each), bronchospasm (6 %), anemia, thrombocytopenia, atrial fibrillation, abdominal pain, and hepatobiliary disorders (3 % each). Infusion-related reactions (IRRs) were observed in 63 % of patients, of which 6 % were grade 3 or 4 (bronchospasm and hypersensitivity, 3 % each).

In part 2 of the study, two dosing cohorts were selected (8 mg/kg and 16 mg/kg) and 30 and 42 patients, who had received a median of four prior therapies, were treated, respectively [31]. The overall response rate (ORR) was 36 % in the 16 mg/kg cohort [two patients complete response (CR), two patients very good PR (VGPR), and 11 patients PR], and 10 % in the 8 mg/kg group (three patients PR). The median time to response was 0.9 months in the 16 mg/kg group. The median duration of response was longer in the 16 mg/kg group (not reached for the 16 mg/kg group and 6.9 months for the 8 mg/kg group). The median progression-free survival (PFS) was 5.6 months in the 16 mg/kg group and 2.4 months in the 8 mg/kg group, while the 1-year OS was 77 % in both groups. Most AEs were grade 1 or 2, with the most common, defined as occurring in at least 25 % of patients, being fatigue, allergic rhinitis, and pyrexia. Overall, grade 3 or 4 AEs were seen in 26 % of patients in the 16 mg/kg group and 53 % of patients in the 8 mg/kg group. Grade 3 or 4 events that occurred in two or more patients were pneumonia (five patients), thrombocytopenia (four patients), and

Table 1 Overview of results of daratumumab trials

Trial details		Results	
		Efficacy	Infusion-related reactions
Lokhorst et al. [31] Phase I/II: daratumumab monotherapy	Part 1: dose escalation ($n = 32$) Part 2: expansion study ($n = 72$) Relapsed/refractory MM Median 4 prior lines	Part 1: 4 PR, 3 MR in 12 patients who received daratumumab 4–24 mg/kg Part 2: 16 mg/kg group: ORR 36 %, DOR not reached, PFS 5.6 months; 8 mg/kg group: ORR 10 %, DOR 6.9 months, PFS 2.4 months	Part 1: 63 % (all grades), 6 % (grade 3/4) Part 2: 71 % (all grades), 1 patient with grade 3 reaction
Lonial et al. [32] Phase II: daratumumab monotherapy	$n = 106$ Relapsed/refractory MM Median 5 prior lines	ORR 29 %, DOR 7.4 months, PFS 3.7 months, 1-year survival rate 64.8 % At subsequent cutoff: median OS 17.5 months	42 % (all grades), 5 % (grade 3)
Usmani et al. [33] Combined efficacy analysis of monotherapy studies	$n = 148$ Relapsed/refractory MM Median 5 prior lines	ORR 31 %, ≥VGPR 13 % Median PFS: not estimable Median OS: 19.9 months	48 % (46 % during first infusion, 4 % during second infusion, and 3 % during subsequent infusions)
Plesner et al. [35, 36] Phase I/II: daratumumab + Len + Dex	Part 1: dose escalation ($n = 13$) Part 2: expansion cohort ($n = 32$) Relapsed/refractory MM Median 2 prior lines	Part 1: ORR 100 % Part 2: ORR 81 %, ≥VGPR 63 %, CR 9 %, sCR 25 % 18-month PFS 72 %, 18-month OS 90 %	56 % (grade 2 or lower in the majority of cases, 2 patients with grade 3 IRRs), no grade 4
Mateos et al. [37] Phase Ib: daratumumab + backbone agents	Newly diagnosed MM ($n = 25$): VD, VMP, VTD Relapsed/refractory MM ($n = 24$) Median 4 prior lines: Pom–Dex	Newly diagnosed: ORR 100 % Relapsed disease: 54.5 %	49 %, generally grade 1 or 2 (three grade 3, no grade 4)
Chari et al. [39] Daratumumab + Pom–Dex	Relapsed/refractory MM ($n = 98$) Median 4 prior lines	ORR 71 %, sCR 5 %, CR 3 %, VGPR 33 % ORR in double-refractory disease: 67 % 6-month PFS: 66 %	52 patients, mainly grade 2 or lower, 6 patients with grade 3 2 patients discontinued due to IRR

CR complete response, *Dex* dexamethasone, *DOR* duration of response, *IRR* infusion-related reaction, *Len* lenalidomide, *MR* minor response, *MM* multiple myeloma, *ORR* overall response rate, *OS* overall survival, *PR* partial response, *PFS* progression-free survival, *POM* pomalidomide, *sCR* stringent complete response, *VGPR* very good partial response, *VD* bortezomib and dexamethasone, *VMP* bortezomib melphalan prednisone, *VTD* bortezomib thalidomide dexamethasone

neutropenia, leukopenia, anemia, and hyperglycemia (two patients each). IRRs were seen in 71 % of patients and were grade 1 and 2, except for one patient with a grade 3 reaction. The majority of IRRs occurred during the first infusion. Of note, there were no discontinuations due to IRRs. In this trial, different infusion rates in both the 8 and 16 mg/kg groups were investigated and a higher infusion rate was found to be associated with a higher incidence of IRRs, pointing to the role of the infusion rate in the management of IRRs. This trial was the first to demonstrate the substantial activity and good tolerability of daratumumab monotherapy in patients with advanced disease and limited further treatment options, and paved the way for additional trials investigating this drug.

Lonial et al. recently published the results of a second daratumumab monotherapy study involving a larger number of patients ($n = 106$) [MMY2002, SIRIUS trial] [32]. Patients had substantially advanced disease, were heavily pretreated, and had highly refractory disease. The median time since the initial diagnosis of myeloma was 4.8 years and the patients had received a median of five prior lines of therapy. Eighty percent had undergone autologous stem cell transplantation previously and 95 % had disease refractory to a PI and an IMiD. In addition, 63 % of patients were refractory to pomalidomide, 48 % were refractory to carfilzomib, 66 % were refractory to three of four therapies (bortezomib, lenalidomide, carfilzomib, pomalidomide) and 31 % were refractory to all four agents.

Initially, a small number of patients were randomized 1:1 to receive daratumumab either 8 mg/kg every 4 weeks (18 patients) or 16 mg/kg every week for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter (16 patients). Following a response evaluation, the 16 mg/kg dose was established as the recommended dose for further study and an additional 90 patients were enrolled at this level. Considering all patients dosed at 16 mg/kg ($n = 106$), the ORR was 29.2 % (3 stringent CRs [sCRs], 10 VGPRs, 18 PRs), with a median time to response of 1 month and a median duration of response of 7.4 months. Of note, responses were seen across the different subgroups investigated, e.g. age ≥75 years, more than three prior lines of therapy, and refractory to PIs and IMiDs. With a median follow-up of 9.3 months, the median PFS was 3.7 months and the 1-year survival rate was 64.8 %. At a subsequent cutoff, the median OS was 17.5 months. Serious treatment-emergent AEs were noted in 30 % of patients and grade 3/4 AEs were noted in 23 % of patients. There were no discontinuations due to AEs. The most frequent AEs of any grade were fatigue (40 %) and anemia (33 %). IRRs, which occurred in 42 % of patients, did so predominantly during the first infusion, were usually grade 1 or 2 (5 % grade 3, no grade 4), and were manageable. Only 6 % of patients had an infusion-related reaction beyond the first infusion. The most common IRRs included nasal congestion (12 %), throat irritation (7 %), cough, dyspnea, chills and vomiting (6 % each). Of note, no patients discontinued treatment due to IRRs. The investigators concluded that the impressive efficacy results combined with the good tolerability make daratumumab a new standard of care in this setting.

A combined efficacy analysis of the two monotherapy studies (GEN501, SIRIUS) was conducted, which included only patients who had received daratumumab 16 mg/kg, which is the recommended dose [33]. Patients ($n = 148$) had received a median of five prior lines of therapy, 86 % were refractory to both a PI and an IMiD and, notably, 39 and 55 % were refractory to carfilzomib or pomalidomide, respectively. In this combined analysis, the ORR was 31 %, with a VGPR rate of 13 % or better. Of note, two patients had CR and three patients had an sCR. The median duration of response was 7.6 months and, at a median follow-up of 14.8 months, 50 % of responders were progression-free at 12 months. The median PFS was not estimable for responders (≥PR), but was 3.2 months for those achieving MR or stable disease (SD) and 0.9 months for those with progressive disease (PD). For the overall group, the median OS was 19.9 months, with a 1-year OS rate of 69 %. For responders (≥PR), the median OS was not estimable, but was 17.5 months for those achieving MR or SD and 3.7 months for those with PD. The AE profile was consistent with those of the individual studies. The most frequent grade 3 or higher AEs were anemia (18 %), thrombocytopenia (14 %), and neutropenia (10 %). Forty-eight percent of patients had IRRs; 46 % occurred during the first infusion, 4 % during the second infusion, and 3 % during subsequent infusions. These results further illustrate the remarkable single-agent activity of daratumumab in patients with very advanced-stage disease who are refractory to current treatment options, including PIs and IMiDs, and who typically only survive for 8–9 months at this stage of the disease [4, 34].

3.3 Clinical Activity: Daratumumab in Combination with Current Standard Regimens

Daratumumab has also been investigated in combination with current standard regimens. In a phase I/II study involving 45 patients with relapsed and refractory MM following a median of two prior therapies, daratumumab was combined with lenalidomide and dexamethasone [35, 36]. Daratumumab was dose-escalated from 2 to 16 mg/kg in part 1 of the study ($n = 13$), and then administered at 16 mg/kg in the expansion cohort ($n = 32$). Lenalidomide was administered at 25 mg on days 1–21, and dexamethasone was administered at 40 mg weekly. With a mean duration of follow-up of 12.9 months for part 1, the overall best response was 100 % (31 % CR, 46 % VGPR, 23 % PR) [35]. In the most recent update of part 2 of the study, data for 32 patients who had received a median of two prior lines were presented with a median follow-up of 15.6 months. In this group, the ORR was 81 %, including 19 % PR, 28 % VGPR, 9 % CR, and 25 % sCR (63 % VGPR or better). The clinical benefit rate (≥MR) was 88 %, and 91 % of patients were progression-free at 12 months. Responses were found to deepen over time, with a time to first response of 1 month and a time to best response of 5.1 months. The 18-month PFS and OS rates were 72 and 90 %, respectively. The most frequent treatment-emergent AEs were neutropenia (84 %), cough (50 %), diarrhea (44 %) and muscle spasms (44 %), and the most frequent grade 3 or higher AEs were neutropenia (78 %), thrombocytopenia (13 %) and anemia (13 %). Sixteen patients had serious AEs, eight of which were due to infection. IRRs were noted in 18 patients [56 %; cough (25 %), allergic rhinitis, nausea, vomiting (9 % each), dyspnea, nasal congestion (6 % each)]; these were grade 2 or lower in the majority of patients. In all patients who experienced an IRR, this occurred during the first infusion, with three patients having IRRs in the second or subsequent infusions. In two patients, grade 3 IRRs were noted (laryngeal edema and hypertension), but no grade 4 IRRs were reported [36].

An accelerated infusion program, which was investigated in the trial, was found to be tolerable, but was

Table 2 Ongoing clinical development of daratumumab [67]

Name of study	Treatment	Disease stage	Phase
MAIA (MMY3008) NCT02252172	Daratumumab + Len/Dex vs. Len/Dex	Newly diagnosed, not eligible for transplantation	III
ALCYONE (MMY3007) NCT02195479	Daratumumab + VMP vs. VMP	Newly diagnosed, not eligible for transplantation	III
CASSIOPEIA (MMY3006) NCT02541383	Daratumumab + VTD vs. VTD	Newly diagnosed, eligible for transplantation	III
POLLUX (MMY3003) NCT02076009	Daratumumab + Len/Dex vs. Len/Dex	Relapsed or refractory	III
CASTOR (MMY3004) NCT02136134	Daratumumab + bortezomib/Dex vs. bortezomib/Dex	Relapsed or refractory	III
NCT02519452 Evaluation of subcutaneous daratumumab	Daratumumab + recombinant Human hyaluronidase	Relapsed or refractory	I
CENTAURUS (SMM2001) NCT02316106	Daratumumab monotherapy	High-risk smoldering MM	II

Len lenalidomide, *Dex* dexamethasone, *MM* multiple myeloma, *VMP* bortezomib melphalan prednisone, *VTD* bortezomib thalidomide dexamethasone

associated with a higher incidence of grade 1/2 AEs and will require further investigation [35]. Based on the positive results of this phase I/II trial, the combination of daratumumab, lenalidomide and dexamethasone is being investigated in a randomized phase III trial in the relapsed/refractory setting (POLLUX; http://www.clinicaltrials.gov) (Table 2). Furthermore, a phase III trial has also been initiated in the front-line setting to assess the combination, prospectively, in newly diagnosed patients who are not eligible for transplantation (MAIA) (http://www.clinicaltrials.gov).

To date, one further daratumumab combination study has been presented. In this phase Ib trial, Mateos et al. treated 25 patients with newly diagnosed MM with daratumumab plus bortezomib and dexamethasone (VD), bortezomib, melphalan and prednisone (VMP) or bortezomib, thalidomide and dexamethasone (VTD), while 24 patients with relapsed/refractory MM were treated with the combination of pomalidomide–dexamethasone (Pom–Dex) plus daratumumab [37]. Among the patients with relapsed/refractory MM, the median number of prior therapies was four, all patients had received prior treatment with PIs, IMiDs and steroids, and 92 % were refractory to their last line of treatment. The ORR in 35 evaluable patients was 100 % in the newly diagnosed group and 54.5 % in those with relapsed or relapsed and refractory disease. The combinations were well tolerated and the addition of daratumumab did not result in significant additional toxicity other than IRRs, which occurred in 24 patients (49 %). The IRRs were generally grade 1 or 2 (three grade 3 and no grade 4) and the majority occurred on the first day of the first cycle. Across all patients, grade 3 AEs occurred in 22 (45 %) patients, with the most frequent being neutropenia (25 %), thrombocytopenia (10 %), anemia (8 %), and pneumonia (6 %). Furthermore, daratumumab was not found to have a negative impact on stem cell mobilization [38].

Recently updated results of the Pom–Dex plus daratumumab arm including 98 patients with a median of four prior therapies, 67 % of whom were refractory to both a PI and an IMiD, confirmed the previous results [39]. The ORR was 71 %, including 5 % sCR, 4 % CR, 33 % VGPR, and 28 % PR. The ORR in patients with double-refractory disease was 67 %. At a median follow-up time of 4.2 months, 47 of 53 responders (89 %) had not progressed, and the 6-month PFS rate was 66 %. The most frequent grade 3 or higher AEs were neutropenia ($n = 60$), anemia ($n = 25$), leukopenia ($n = 20$), and thrombocytopenia ($n = 15$). Serious AEs occurred in 42 % of patients. Overall, the rate of grade 3 or higher AEs was similar to that observed with Pom–Dex alone, and no new safety signals were observed with daratumumab + Pom–Dex. IRRs occurred in 52 patients and were predominately grade 2 or lower. Six patients had grade 3 IRRs and two patients discontinued because of an IRR. The IRRs occurred in 53, 1, and 0 % of patients during the first, second, and subsequent infusions, respectively.

Taken together, daratumumab presents an exciting new addition to the existing treatment options for myeloma. It has demonstrated impressive activity in patients with advanced disease and limited remaining options. In addition, the tolerability of the agent is remarkable, making it a

Table 3 Infusion rates for daratumumab administration [31]

	Dilution volume (ml)	Initial infusion rate (first hour) (ml/h)	Increments of infusion rate	Maximum infusion rate (ml/h)
First infusion	1000	50	50 ml/h every hour	200
Second infusion[a]	500	50	50 ml/h every hour	200
Subsequent infusions[b]	500	100	50 ml/h every hour	200

[a] Escalate only if there were no grade 1 (mild) or higher infusion reactions during the first 3 h of the first infusion

[b] Escalate only if there were no grade 1 (mild) or higher infusion reactions during a final infusion rate of ≥100 ml/h in the first two infusions

suitable option across the patient spectrum. A number of phase III trials in the relapsed/refractory setting, as well as the upfront setting, are ongoing, the results of which are eagerly awaited (Table 2).

4 Optimal Dose and Schedule

4.1 Optimal Daratumumab Dose and Schedule

Based on the available clinical evidence, the optimal dose of daratumumab single agent is 16 mg/kg as an intravenous infusion administered weekly during the first 8 weeks, every 2 weeks for the following 16 weeks and monthly thereafter. This was the optimal dose defined in the GEN501 and SIRIUS trials [31, 32]. The optimal duration of treatment is as yet unknown and, in the currently ongoing trials, daratumumab is being administered until disease progression or unacceptable toxicity, but, to date, no sign of long-term toxicity has been observed with daratumumab.

4.2 Daratumumab Infusion

The infusion solution is prepared as a 1000 mL (first dose only) or 500 mL dilution of daratumumab in sterile, pyrogen free 0.9 % NaCl on the day of the planned infusion [31, 40]. Daratumumab is administered as an intravenous infusion through a well-functioning intravenous catheter using an infusion set with a flow regulator to control the infusion rate. The drug must be filtered using an inline filter (0.2 μM) during the infusion.

4.3 Daratumumab Administration and Infusion Rate

Daratumumab is administered as an intravenous infusion, with each patient's dose calculated based on the patient's weight rounded to the nearest kilogram. The first infusion of daratumumab (dilution volume 1000 ml) should be administered at an initial rate of 50 ml/h in the first hour, with subsequent increases at the rate of 50 ml/h every hour up to a maximum infusion rate of 200 ml/h possible (Table 3) [31]. The same should be undertaken for the second infusion (dilution volume 500 ml). For subsequent infusions (dilution volume 500 ml), the initial rate for the first hour can be 100 ml/h. Increases in the infusion rate of 50 ml/h every hour up to a maximum infusion rate of 200 ml/h are possible. Importantly, increases in infusion rates should only be carried out if the prior infusion was well tolerated. Of note, any increase in infusion rate can lead to the occurrence of IRRs. Therefore, careful monitoring of the patient is needed to detect IRRs as early as possible. If IRRS are observed, the infusion should be paused promptly, symptoms should be treated accordingly, and the infusion can be resumed at a lower rate when the symptoms have abated.

4.3.1 Practical Recommendations Based on our Experience

If no infusion reactions occur during the first two infusions, the infusion time can be reduced to 3.5 h, but not less, by the third infusion.

Table 4 Management considerations concerning monoclonal antibody use in hematology in general, and myeloma in particular

			CD38 monoclonal antibodies		
	Rituximab	Elotuzumab	Daratumumab	Isatuximab	MOR202
Infusion-related reactions	×	×	×	×	×
Interference with response assessment	×	×	×	×	×
Interference with blood typing			×	×	×

5 Managing Daratumumab Therapy in Myeloma

There are special management considerations concerning the use of therapeutic mAbs in hematology in general and MM in particular (Table 4), which we outline in the following sections.

5.1 Blood Typing in Patients Receiving CD38 mAb Therapy

A frequent problem in laboratory medicine is the interference of endogenous and exogenous substances with assays for clinical analytes. Major endogenous compounds that can interfere with laboratory results are hemoglobin, bilirubin, lipids, and paraproteins [41]. For example, paraproteins can result in precipitation or chemical or immunological interference from specific or non-specific binding of a particular analyte [42]. The main exogenous sources of interference are therapies administered to the patient [41]. For many drugs, interference with laboratory tests are unknown and are discovered by chance when unexpected laboratory results are found that do not conform with the patient's condition [43]. The increasing use of diagnostic and therapeutic mAbs has highlighted the possible interference of these agents with routine laboratory tests. In a review on the interference of mAbs with laboratory diagnostic procedures, Ostrov and Amsterdam explain that interference, apart from being categorized into endogenous or exogenous, can be due to direct or indirect mechanisms [44]. While direct interference occurs when the mAb itself appears as the analyte in the assay, indirect interference develops when antibodies interact with reagents or with the analyte target, thus altering test performance. They describe that, particularly in immunoassays, which rely on the precise binding of mAb assay reagents with other complex biologic antigen/analyte reagents, exogenous indirect interference may occur. For example, in transplant patients, concerns have been raised that mAbs may interfere with human leukocyte antigen (HLA) typing [44].

When daratumumab was investigated in the phase I and II studies described above, an interference with routine laboratory tests used in blood transfusion medicine was found. In patients who were receiving daratumumab, the indirect antiglobulin test (IAT; Coombs test), which is used for the detection of irregular blood group antibodies, was found to be false positive [43, 45]. This was found to be not daratumumab-specific but rather a class effect of CD38 mAbs [43]. Importantly, daratumumab does not interfere with ABO/RhD typing [45]. Daratumumab, bound to red blood cells (RBCs), only masks the detection of antibodies to minor antigens in the patient's serum.

The agglutination that is caused by CD38 mAbs in vitro and which leads to the false-positive results in the IAT can be explained by the expression of CD38 on erythrocytes, which has previously been described [8, 11, 46, 47]. Indeed, in vitro, the binding of daratumumab to RBCs could be shown [45] and results remain positive for up to 5 months [43]. In vivo, the administration of daratumumab was shown to be associated with a clinically not significant decrease in hemoglobin of approximately 1.6 g/dL and a compensatory increase in reticulocytes; however, daratumumab did not lead to anemia [43]. The small decrease in hemoglobin is not considered to be due to complement-mediated lysis, but rather a result of Fc-receptor-mediated clearance of daratumumab-loaded RBCs in the spleen. Only a small number of patients required transfusions, which were due to the underlying disease and not a result of the binding of daratumumab to CD38 on erythrocytes. In these patients, no major transfusion-related events were observed [43, 45]. In addition, an analysis of the frequency of RBC transfusions and any transfusion-related AEs in the SIRIUS trial, in which 124 patients with very advanced disease were treated with daratumumab monotherapy, showed that there were no transfusion-related reactions in the 47 patients who required transfusions [48].

Importantly, strategies to overcome the interference of CD38 mAbs with IATs have been developed, including the denaturation of cell surface CD38 by the reducing agent dithiothreitol (DTT) and the addition of an excess of soluble CD38 or neutralizing anti-idiotype antibodies. Using these methods, irregular antibody screening and identification could be restored [43, 45].

The interference of CD38 mAbs presents an in vitro clinical laboratory challenge. In order to conduct reliable blood compatibility testing, immunohematology laboratories/transfusion medicine departments will need to be informed when a patient is receiving CD38 mAbs so that strategies can be chosen. Furthermore, it has been suggested that patients undergoing CD38 mAb therapy carry a blood transfusion card to indicate the specific therapy they are receiving [43]. One option to avoid delays in providing compatible RBC transfusions is to obtain an RBC phenotype prior to initiating daratumumab therapy, and providing phenotypically matched blood thereafter [48].

5.1.1 Practical Recommendations Based on our Experience

Daratumumab does not interfere with ABO/RhD typing; however, immunohematology laboratories/transfusion medicine departments need to be informed if patients are receiving CD38 mAbs so that the reliable strategies outlined above to overcome the interference of CD38 mAbs

with IATs can be implemented. We support the suggestion by Oostendorp et al. of a patient wallet card [43]. Such a card should specify the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab, along with information on the IAT interference for healthcare providers/transfusion medicine departments. Patients should carry this card throughout the treatment period and for at least 6 months after the treatment ends.

The possible methods for immunohematology laboratories/transfusion medicine departments to provide safe RBCs for transfusion to patients receiving daratumumab include (1) providing ABO/RhD compatible, phenotypically or genotypically matched units, and (2) providing ABO/RhD compatible, K-negative units after ruling out or identifying allo-antibodies using DTT-treated reagent RBCs.

Uncrossmatched, ABO/RhD compatible RBC units should be administered if a transfusion is needed as an emergency, as per local transfusion medicine department practice.

5.2 Assessment of Response for Patients Receiving Daratumumab

According to the International Myeloma Working Group (IMWG) criteria, the absence of M protein on serum protein electrophoresis (SPE) and serum immunofixation electrophoresis (IFE) are requirements for a CR.

An interference with SPE has been described for several therapeutic agents, for example antibiotics and radio-opaque agents [49]. In addition, therapeutic mAbs, including chimeric human-mouse immunoglobulins (rituximab, siltuximab, infliximab, cetuximab), humanized mAbs (trastuzumab, bevacizumab, adalimumab), as well as human mAbs (ofatumumab) have been shown to lead to false-positive results on SPE [50, 51]. mAbs, as immunoglobulins, can appear on SPE and IFE, thereby preventing a distinction between therapeutic antibody and a patient's clonal immunoglobulin, and making the validation of a CR unfeasible. It has been described that therapeutic mAbs become undetectable in patients approximately 3 months after the cessation of therapy [50].

Approximately 50 % of patients with MM produce an IgG kappa M protein, and daratumumab, an IgG1 kappa mAb, has been detected on SPE and IFE assays [52]. The concentration of daratumumab used clinically is equivalent to approximately 1 g/L and thus, for an M spike of less than 2 g/L, a distinction between daratumumab and remaining M protein is not possible, obscuring the assessment of CR and, in some patients, depending on the level of the M protein at the start of therapy, VGPRs. Similarly, for elotuzumab, which is also an IgG1 mAb, an interference of the antibody with the assessment of CR and sCR has been suggested [53]. The same is expected for the other CD38 antibodies, SAR650984 (isatuximab) and MOR202.

Therefore, a specific assay is needed to discriminate between mAb and M protein. Such an assay has been developed and validated for daratumumab [54]. It involves the addition of an anti-idiotype mAb to patient samples, which binds daratumumab. As a result, the migration of daratumumab on IFE is shifted, enabling the confirmation of CR. Further work is needed to implement the assay in routine clinical practice.

5.2.1 Practical Recommendations Based on our Experience

Consider that persisting M component may be due to the therapeutic mAb and presents a false-positive result that does not indicate recurrence or resistance to treatment. In some patients, it may be possible to identify two M spikes at different locations by carefully examining the SPE and IFE, which help to monitor the disease response, and a patient can qualify for CR if it is evident that the M spike present in the SPE or immunofixation results from the mAb interference [55]. If the patient is receiving daratumumab therapy, a specific assay has been devised to distinguish M protein and therapeutic antibody.

5.3 Infusion-Related Reactions of Monoclonal Antibody Therapy

Virtually all systemic chemotherapeutic agents can be associated with IRRs, and symptoms can vary in severity from mild to life-threatening. Patients may experience chills, fever, nausea, asthenia, headache, skin rash, or pruritus. In addition, bronchospasm, hypotension, urticaria and angioedema may also occur. Of the cytotoxic agents used in cancer therapy, taxanes and platinum agents are among those most frequently associated with infusion reactions [56, 57]. Of the agents used in myeloma, hypersensitivity reactions have been described for melphalan, pegylated liposomal doxorubicin, and carfilzomib [58–61].

The IRRs seen with mAbs are generally mild and only a small fraction of patients develop severe reactions [60, 62]. The highest risk of a reaction is during the first or second exposure to the mAb, with the risk declining with subsequent infusions [60, 62, 63]. With rituximab, approximately 77 % of patients experience IRRs during the first infusion, however only 10 % of these are severe (grade 3/4) [60]. The following infusion reactions have been described with rituximab: urticaria, hypotension, angioedema, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular

fibrillation, or cardiogenic shock [57]. The majority of rituximab IRRs occur during the first infusion and decline substantially during subsequent infusions (30 % with the fourth infusion; 14 % with the eighth infusion) [60]. In clinical practice, the application of premedication, which typically consists of corticosteroids and antihistamines, is routine to reduce the risk of IRRs occurring. Close monitoring of patients is required and in the case of IRRs, an interruption of the infusion and symptom management is essential. Upon resolution of the symptoms, a restart of the infusion at 50 % of the infusion rate can be considered [57, 60].

With daratumumab, IRRs were seen in 42–71 % of patients, and occurred mostly during the first infusion [31, 32, 64]. IRRs were grade 1/2 in almost all cases, and discontinuations due to IRRs were rare. With daratumumab monotherapy, no discontinuations and no grade 4 IRRs have been seen [31, 32]. Daratumumab IRRs are characterized by nasal congestion, throat irritation, cough, dyspnoea, chills, and vomiting [31, 32]. The occurrence of IRRs can be influenced by the infusion rate, as suggested by an analysis of different infusion regimens [31]. In order to prevent the occurrence of IRRs with daratumumab, the following premedication regimen is recommended approximately 1 h prior to every daratumumab infusion: intravenous corticosteroid (methylprednisolone 100 mg or an equivalent long-acting corticosteroid for the first two infusions, and 60 mg thereafter [in the absence of IRRs in the first two infusions]), oral antipyretics (paracetamol 650–1000 mg) plus an oral or intravenous antihistamine (diphenhydramide 25–50 mg or equivalent). In our experience, the leukotriene receptor antagonist montelukast (10 mg) can be beneficial as an optional premedication. The doses of steroids used as premedication are substantially lower than the therapeutic doses typically used, such that the antimyeloma activity observed in the daratumumab single-agent studies can be attributed to daratumumab alone [64].

If IRRs occur despite the implementation of such a regimen, it is crucial to stop the daratumumab infusion immediately, even if only mild symptoms are detectable. The infusion should be halted until symptoms have resolved and the appropriate symptom management should be instigated. The administration of an antihistamine can be considered, which may shorten the time to the restart of the infusion and may also result in faster resolution of the symptoms. The restart of daratumumab infusions at a lower infusion rate following the resolution of symptoms is feasible [64]. Table 5 outlines recommendations for the management of IRRs [64].

Table 5 Recommendations for the management of infusion-related reactions [64]

IRR	Action
Grade 1 or 2	The infusion should be paused and can be restarted when the patient's condition is stable
	When restarting, the infusion rate should be half of that used before the interruption
	The infusion rate can subsequently be increased
Grade 2 or higher event of laryngeal edema	The patient must be withdrawn from treatment[a]
Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 h from onset	
Grade 3 or higher	The infusion must be stopped and the patient must be observed carefully until resolution of the IRR
	If the IRR remains at grade 3 or 4 after 2 h, the patient must be withdrawn from treatment
	If the IRR decreases to grade 1 or 2 within 2 h, the infusion may be restarted. Upon restart, the infusion rate should be half that employed before the interruption. Subsequently, the infusion rate may be increased
	If the IRR returns to grade 3 or 4 after restart of the infusion, the procedure described above may be repeated
	If the IRR increases to grade 3 or 4 for a third time, the patient must be withdrawn from treatment

IRR infusion-related reaction

[a] According to the published information, patients with grade 2 or higher laryngeal edema should be withdrawn. However, based on our experience, consideration may also be given to admitting patients with grade 2 or higher laryngeal edema, which occurred after the first infusion, to hospital to administer the second dose, using premedication with corticosteroids and antihistamines, and under careful observation

The application of oral corticosteroids on the first and second day after all infusions (methylprednisolone, 20 mg; or equivalent in accordance with local standards) is useful to prevent the occurrence of delayed IRRs.

Special care should be taken in patients with a history of obstructive pulmonary disease for whom medications, including short- and long-acting bronchodilators and inhaled corticosteroids, can be considered. In addition, these at-risk patients may be hospitalized for monitoring for up to 2 nights after an infusion. Physicians may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in case a bronchospasm occurs after patients are released from the hospital. The postmedication may be discontinued after the first four infusions if the patient has not experienced any major IRRs.

5.3.1 Practical Recommendations Based on our Experience

A premedication regimen administered approximately 1 h prior to every daratumumab infusion should be used to reduce the risk of IRRs occurring. The premedication should consist of an intravenous corticosteroid (methylprednisolone 100 mg or an equivalent long-acting corticosteroid), an oral antipyretic (paracetamol 650–1000 mg) plus an oral or intravenous antihistamine (diphenhydramide 25–50 mg or equivalent). For the daratumumab infusion, the use of an infusion set with a flow regulator is recommended to control the infusion rate. As IRRs mainly occur during the first infusion, it is important to be alert in order to detect early mild symptoms that mostly affect the upper respiratory tract. Prompt action is essential in case of IRRs, even if symptoms are only mild; the daratumumab infusion should be stopped immediately. The use of an antihistamine may shorten the period of treatment interruption and may lead to a faster resolution of symptoms. The infusion can be restarted at a lower rate once symptoms have resolved (Table 5). Dose modification of daratumumab is not recommended, but dose delay is the primary method for the management of side effects.

Patients with known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 s (FEV_1) <50 % of predicted normal, or with moderate or severe persistent asthma within the past 2 years, should not receive daratumumab. In fact, FEV_1 testing should be performed for patients in whom COPD is suspected, and they must be excluded if FEV_1 is <50 % of the predicted value.

6 Other Practical Recommendations

6.1 Herpes Zoster Prophylaxis

Patients with multiple myeloma have a significantly increased risk of developing viral infections, including herpes zoster (varicella zoster virus reactivation) compared with healthy controls [65]. For patients receiving daratumumab, it is recommended that herpes zoster prophylaxis be initiated within 1 week of starting daratumumab, and to continue for 3 months following treatment [40].

6.2 Fever

Following the administration of daratumumab, patients are not expected to develop fever; however, they should be advised to contact their treating physician should fever occur.

6.3 Liver Function

No dosage adjustments of daratumumab are necessary for patients with mild hepatic impairment based on a population pharmacokinetic analysis [40]. No data were available for moderate or severe hepatic impairment.

6.4 Patients with Lung Disease

In the clinical trials conducted to date, patients with lung disease were excluded because of the expression of CD38 on endothelial cells; however, it can be speculated that with careful monitoring it may be possible to treat these patients with daratumumab. Further data are needed to provide firm recommendations.

6.5 Daratumumab in Special Populations

Daratumumab single agent seems to be effective in the following special patient populations, although the low number of patients precludes strong recommendations.

6.5.1 Renal Failure

Daratumumab is not metabolized by the kidney, therefore renal failure is not a contraindication for treatment with this agent. Twelve patients with moderate renal failure (creatinine clearance ≥30 and <60 ml/min) were included in the GEN501 trial, 33 % of whom responded to treatment with daratumumab single agent [31]. In the SIRIUS trial, 42 patients had a creatinine clearance of 30–60 ml/min,

and the ORR in these patients was 26.2 % [32]. The number of patients with severe renal impairment was too low in the two studies to make any statement.

6.5.2 Advanced Age

In the GEN501 study, daratumumab was administered to 16 patients aged 65–74 years, 56 % of whom responded [31], while none of the four patients who were 75 years or older responded. In the SIRIUS trial, 36 patients were aged between 65 and <75 years, while 12 patients were 75 years or older, respectively. The ORR in these subgroups of patients was 25 and 33.3 %, respectively, indicating that the efficacy of daratumumab is comparable in young or elderly MM patients [32].

6.5.3 Extramedullary Disease

Fourteen patients included in the SIRIUS trial had extramedullary disease, 21.4 % of whom achieved at least PR, indicating that daratumumab single agent might be effective in patients with disease involvement outside the bone marrow [32].

6.6 Retreatment with Daratumumab

Early results indicate that retreatment with daratumumab after previous treatment with this agent may be feasible. Alici et al. reported the results for two patients with triple-refractory disease (IMiDs, PIs, cytostatic drugs) who achieved a response to initial daratumumab therapy but relapsed after treatment [66]. They rechallenged with daratumumab and observed a PR in both patients. Although these results will need to be confirmed in larger patient groups, they suggest that retreatment with daratumumab is feasible and effective.

7 Future Directions

Daratumumab is currently being investigated in a number of trials (Table 2) [67]. In the relapsed/refractory setting, two large, international, phase III trials investigating daratumumab in combination with current standard treatments have been initiated. In the CASTOR trial, the combination of daratumumab, bortezomib, and dexamethasone is being compared with bortezomib/dexamethasone alone. Approximately 480 participants will be randomly assigned to receive either daratumumab plus bortezomib/dexamethasone or bortezomib/dexamethasone alone. The second large, international trial in the relapsed/refractory setting is the POLLUX trial, in which daratumumab is being added to lenalidomide/dexamethasone and compared with lenalidomie/dexamethasone alone. It is planned to enrol approximately 570 patients. In both trials, the primary outcome measure is PFS.

Large, international, phase III trials are also ongoing in the frontline setting; two trials have been initiated in the non-transplant setting. In the ALCYONE trial, in which it is planned to enrol approximately 700 patients, daratumumab is being added to VMP and compared with VMP alone. In both arms, nine cycles of therapy are initially administered. In the daratumumab arm, this is followed by continuous daratumumab until PD, unacceptable toxicity, or study end. In the MAIA study, daratumumab is combined with lenalidomide/dexamethasone and compared with lenalidomide/dexamethasone alone. In both arms, treatment will be administered until PD or unacceptable toxicity, and approximately 730 patients will be enrolled. PFS is the primary outcome measure in both trials.

The Intergroupe Francophone du Myelome (IFM) and the Dutch/Belgium Haemato-Oncology Foundation for Adults in the Netherlands (HOVON) are cooperating in a trial to investigate daratumumab in the transplant setting (CASSIOPEIA). Patients will be randomized to receive either VTD or VTD + daratumumab as induction and consolidation. Following a second randomization step, patients will either receive daratumumab maintenance therapy or will only be observed. Over 1000 patients will be included in the trial and the primary outcome measures are sCR after consolidation therapy and PFS after maintenance therapy.

There are also ongoing trials to investigate daratumumab in smoldering myeloma and other hematological malignancies, as well as a subcutaneous formulation of the agent.

This expansive clinical development illustrates that daratumumab is expected to have a significant impact on the treatment of multiple myeloma across the different treatment lines and patient spectra, and the trials outlined above will help to define the optimal place for daratumumab in the treatment of myeloma.

8 Conclusions

CD38 mAbs represent an exciting recent addition to the therapeutic armamentarium in multiple myeloma. It is hoped that their incorporation into current treatment strategies will enable a more effective and targeted approach with improved outcomes. Results from daratumumab clinical trials conducted to date have been overwhelmingly positive, demonstrating the substantial efficacy and good tolerability of the agent. There are a number of particular considerations regarding the administration and management of daratumumab and the CD38 mAbs in

general in the treatment of myeloma. We have outlined some of these in the present article with the aim of providing our recommendations and learnings from the clinical trials for their management so that the incorporation of these agents into routine practice is as straightforward as possible to enable our patients to benefit from this highly effective new strategy.

Compliance with Ethical Standards

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