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Isatuximab in the Treatment of Multiple Myeloma: A Review and Comparison With Daratumumab

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Abstract

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of clonal plasma cells. Although advances in treatment have markedly improved survival outcomes for patients with MM, this disease is still considered incurable owing to its high incidence of relapse and refractoriness. Isatuximab is an anti-CD38 monoclonal antibody that can induce apoptosis in myeloma cells through a variety of mechanisms. Many clinical studies have demonstrated the efficacy and efficiency of isatuximab in both relapsed/refractory multiple myeloma (RRMM) and newly diagnosed multiple myeloma, leading to its approval for the treatment of adults with RRMM in combination therapies. In this review, the structure, mechanisms of action, pharmacokinetics, pharmacogenetics, and safety profile of isatuximab in MM are summarized. Additionally, isatuximab is compared with daratumumab in terms of mechanism and efficacy.

Keywords

isatuximab, monoclonal antibody, anti-CD38 antibody, relapsed/refractory, multiple myeloma, daratumumab

Abbreviations

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADPR, ADP ribose; AEs, adverse events; ATRA, all-*trans* retinoic acid; AUC, area under the plasma concentration-time curve; CDC, complement-dependent cytotoxicity; C_{max}, maximum predicted plasma concentration; Dara, daratumumab; Fc, fragment crystallizable; HRSMM, high-risk smoldering multiple myeloma; IgG, immunoglobulin G; IMiDs, immunomodulatory drugs; IRRs, infusion-related reactions; Isa, isatuximab; Kd, carfilzomib/dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; NAADP, nicotinic acid adenine dinucleotide phosphate; NCCN, National Comprehensive Cancer Network; ORR, overall response rate; Pd, pomalidomide/dexamethasone; PD-1, programmed cell death-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PIs, proteasome inhibitors; PR, partial response; QOL, quality of life; Rd, lenalidomide/dexamethasone; RRMM, relapsed/refractory multiple myeloma; VGPR, very good partial response; VMP, bortezomib/melphalan/prednisone; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone.

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Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of clonal plasma cells.[1] Over recent decades, the application of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) has extensively changed the natural process and improved the outcomes of the disease. However, the treatment of MM remains complex and challenging given the high incidence rate of disease relapse and patient resistance to treatment regimens.[2] There is a strong demand for novel treatment approaches, which has led to the development of many immunotherapy-based strategies over recent years.

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CD38, a cell-surface protein, functions as a receptor and can interact with CD31. It also has enzymatic activity related to the production of ADP ribose (ADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), which regulate intracellular calcium stores. Furthermore, the ADPR produced through CD38-mediated catalysis can be further metabolized to yield the immunosuppressive molecule adenosine.[3]

CD38 is highly expressed on normal plasma cells and malignant MM cells; however, its expression is low on myeloid and lymphoid cells, as well as in some non-hematopoietic tissues, making it an appealing target for novel MM-directed therapy.[4] Isatuximab, a CD38-targeting monoclonal antibody, has been approved by the United States Food and Drug Administration for the treatment of relapsed MM as a combination therapy with pomalidomide and dexamethasone (Isa-Pd) and carfilzomib and dexamethasone (Isa-Kd).[5]

This review summarizes the mechanisms of action, pharmacokinetics, pharmacogenetics, efficacy, and clinical safety of isatuximab in MM and compares isatuximab with daratumumab, the first anti-CD38 antibody developed, in terms of mechanism and efficacy. The mechanisms underlying resistance to CD38 monoclonal antibodies are also discussed.

Mechanisms of Action, Pharmacokinetics, and Pharmacogenetics

Mechanisms of Action

Isatuximab is an immunoglobulin G (IgG) 1 monoclonal antibody directed against a distinct epitope on CD38. Isatuximab mediates MM cell death through multiple mechanisms, including antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC), effects that are fragment crystallizable (Fc) region-dependent.[6] In the process of ADCC, which is the predominant mechanism underlying the effects of isatuximab, when Fcγ receptors on immune effector cells bind to the Fc region of the antibody, immune effector cells release toxic proteins, such as perforin and granzyme, leading to tumor cell lysis.[7]

Isatuximab can also directly induce MM cell death through caspase-dependent apoptosis and the lysosomal cell killing pathway without the need for cross-linking agents.[8,9] In addition, isatuximab can modulate the enzymatic activity of CD38 and enhance the natural killer cell- and T-cell-mediated immune response.[3,10]

Pharmacokinetics and Pharmacogenetics

At the recommended dose and schedule (10 mg/kg weekly for 4 weeks and every 2 weeks thereafter), it takes an average of approximately 8 weeks for isatuximab to reach steady-state. The predicted maximum plasma concentration (C_{max}) of isatuximab at steady-state is 351 μg/mL and its area under the plasma concentration-time curve (AUC) is 72 600 μg·h/mL (51.7%). The mean predicted total distribution volume is 8.13 L. The time to near-complete (≥99%) elimination after the last dose is approximately 2 months.[11]

Pharmacokinetic modeling in the preliminary stage of drug development demonstrated that isatuximab exhibits both linear and nonlinear elimination, with linear clearance accounting for 90% of the total clearance. Isatuximab is cleared through protein catabolic pathways. Patients secreting IgG M-protein demonstrate an almost two-fold higher isatuximab clearance rate compared with those secreting non-IgG M-protein.[12]

Isatuximab has no pharmacokinetic interaction with other anti-MM agents such as pomalidomide, lenalidomide, and dexamethasone.[13,14] Clinical findings, along with exposure-response analyses and a pharmacokinetic/pharmacodynamics modeling framework, have supported the 20 mg/kg dose for isatuximab monotherapy and the 10 mg/kg dose for combination therapy.[13,15,16]

Isatuximab in Relapsed/Refractory Multiple Myeloma (RRMM) (Table 1)

Isatuximab Monotherapy

The first single-agent isatuximab study was conducted on 84 patients with RRMM who had received a median of 5 (range: 1-13) lines of therapy with an IMiD and a PI. This phase I trial demonstrated that isatuximab monotherapy was well tolerated at doses of up to 20 mg/kg. At doses of ≥10 mg/kg, Isatuximab displayed notable clinical activity with an overall response rate (ORR) of 23.8% and median progression-free survival (PFS) of 3.7 months. Approximately 51% of the patients experienced infusion-related reactions (IRRs), with most being of grade 1 or 2 severity.[13]

Table 1. Pivotal Clinical Studies of Isatuximab in RRMM.

Study group	Isa monotherapy	Isa-Pd versus Pd (ICARIA-MM)	Isa-Rd	Isa-Kd versus Kd (IKEMA)
Median prior lines	5	3	5	2
Median ORR (%)	24.3	60.4 versus 35.3	56	87 versus 83
Median PFS (months)	3.6	11.53 versus 6.47	8.5	NR versus 19.2
Median OS (months)	18.6	At 12 months: 72% versus 63%	NR	
Reference	[17]	[18]	[19]	[20]

Abbreviations: ORR, overall response rate; PFS, progression-free survival; OS, overall survival; RRMM, relapsed/refractory multiple myeloma; Isa, isatuximab; Pd, pomalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; Kd, carfilzomib/dexamethasone; NR, not reached.

In a dose-finding study for isatuximab in RRMM, 97 patients were assigned to 4 different treatment schedules, as follows: 3 mg/kg Q2W, 10 mg/kg Q2W (2 cycles)/Q4W, 10 mg/kg Q2W, and 20 mg/kg QW (1 cycle)/Q2W. The ORR was 24.3% in groups receiving isatuximab at doses of ≥10 mg/kg and was even higher among patients over the age of 70 than in younger patients (46.2% vs 19.7%). There were also notable differences in ORRs (40.9% vs 17.3%) between patients with and those without high-risk cytogenetic markers.[17] In stage 2 of this study, the activity of isatuximab (20 mg/kg QW/Q2W) as a single agent or in combination with dexamethasone (Isa-dex) was assessed. The Isa-dex group achieved a markedly higher ORR (43.6%) than the Isa group (23.9%). The most common adverse events (AEs) of ≥grade 3 were a decrease in the lymphocyte count (Isa 27.5% vs Isa-dex 48.1%) and anemia (Isa 22.9% vs Isa-dex 14.8%). This study showed that dexamethasone, a "backbone treatment" of various regimens,[21,22] could improve clinical activity when combined with isatuximab, with no unexpected safety issues being detected.[23]

Combinations With IMiDs

Mikhael et al reported the results of their phase 1b study on Isa-Pd combination therapy. This study included 45 patients who had been heavily pretreated with a median of 3 (range: 1-10) therapy lines; 82% of the patients were refractory to lenalidomide and 84% to PIs. The patients were randomized to isatuximab dosing regimens of 5, 10, or 20 mg/kg QW/Q2W. Pomalidomide and dexamethasone were administered at the standard treatment dosage. After a median follow-up of 9.2 months, the ORR was 62.2%, twice as high as that for pomalidomide/dexamethasone (Pd) alone (28%-31%).[24–26] Attal et al found similar results in a phase 3 study, with improved ORR and median PFS being reported in the Isa-Pd cohort compared with the Pd group (ORR: 60.4% vs 35.3%, PFS: 11.53 months vs 6.47 months). Moreover, responses were achieved faster in the Isa-Pd cohort. The median time to first response better than partial remission was 35 days versus 58 days in the Pd-only group.[18] In addition, for patients experiencing renal impairment, the Isa-Pd regimen also yielded longer PFS than Pd treatment alone (9.5 months vs 3.7 months).[27] Extended PFS was also observed in patients above 75 years of age and those with high-risk cytogenetics.[28,29]

Martin et al assessed the isatuximab plus lenalidomide and dexamethasone regimen and reported an ORR of 48% among patients who had received more than 3 pretreatment lines and an ORR of 52% among those refractory to lenalidomide. In addition, the isatuximab 10 mg/kg QW/Q2W regimen achieved a longer PFS (9.7 months) than the 10 mg/kg Q2W regimen (5.7 months). Treatment-emergent AEs of grade ≥3 were pneumonia, fatigue, lung infection, febrile neutropenia, anaphylactic reaction, and hypokalemia.[19]

Combination With Carfilzomib

Trials of Isa-Kd also showed promising outcomes. The IKEMA study enrolled 302 patients with RRMM who were randomly assigned to the Isa-Kd arm or the carfilzomib/dexamethasone (Kd) arm at a 3:2 ratio. The Isa-Kd arm showed better outcomes, achieving an ORR of 87% and PFS not reached at 20.7 months of follow-up compared with 83% and 19.2 months, respectively, for the Kd arm.[20] Notably, 41.4% of the Isa-Kd population reached minimal residual disease (MRD) negativity with very good partial response (VGPR) or better, compared with only 22.9% in the Kd cohort.[30] Better PFS and disease response was also demonstrated even among patients with renal impairment. More patients in the Isa-Kd group showed reversal of renal impairment and durable renal responses relative to the Kd group.[31]

Isatuximab in Newly Diagnosed MM

Based on the results obtained with isatuximab in RRMM, many clinical trials have also been conducted to evaluate the activity of isatuximab in newly diagnosed MM (NDMM). Significant results have been reported in trials incorporating isatuximab in conventional standard triplet therapy of bortezomib/lenalidomide/dexamethasone (VRD) or bortezomib/cyclophosphamide/dexamethasone (VCD) in transplant-ineligible NDMM patients.[13,32] The ORR was 100% and 93.3% for these 2 regimens, respectively. The most frequent toxicities included constipation, IRRs, diarrhea, and peripheral sensory neuropathy.[33]

A recent interim analysis of the GMMG-CONCEPT trial reported the best response of the first 50 high-risk MM patients that received induction therapy with isatuximab/carfilzomib/lenalidomide/dexamethasone (Isa-KRd). In total, 45 out of the 50 patients showed a VGPR or better and 20 of 31 evaluable patients reached MRD negativity. The median 24-month PFS was 75.5%.[34]

Despite these promising results, more clinical studies are required to demonstrate the efficacy of isatuximab in patients with NDMM irrespective of eligibility for transplantation.

Isatuximab in High-Risk Smoldering Multiple Myeloma

High-risk smoldering multiple myeloma (HRSMM) is considered an asymptomatic cancer with a high risk of progression to MM after 5 years of diagnosis.[35] A multicenter, phase 2 trial studied isatuximab treatment in 24 HRSMM patients and demonstrated potential clinical activity, with an ORR of 62.5% and a clinical benefit rate of 79% being achieved. Additionally, isatuximab treatment improved the quality of life (QOL) scores of patients and decreased their anxiety regarding progression to MM.[36]

Toxicity Profiles

Preclinical and clinical studies have shown that isatuximab is safe, with IRRs being the most commonly reported nonhematologic adverse reactions. Most AEs were moderate and occurred during the first infusion.[13,19] IRRs mostly included symptoms

such as nasal congestion, dry cough, rhinitis, sore throat, and dyspnea.[34] To prevent IRRs, patients received standard prophylactic medications, including diphenhydramine, methylprednisolone, ranitidine, and acetaminophen, 15 to 30 min before infusion.[37,38] Fatigue, upper respiratory tract infections, dyspnea, pneumonia, and urinary tract infections were also frequently observed in isatuximab combination therapy,[20,24] which was in agreement with the toxicity profile of the individual drugs.

In terms of hematological laboratory abnormalities, the most common grade ≥3 AEs of the isatuximab regimen were neutropenia, lymphopenia, leukopenia, thrombocytopenia, and anemia.[17,19,20,24] Most were manageable with dose modifications and the use of granulocyte colony-stimulating factors.[24]

Comparison with Daratumumab

Daratumumab was the first CD38-targeting monoclonal antibody developed and was approved for MM treatment in 2015. The efficacy of daratumumab monotherapy and the combination with IMiDs or PIs in both RRMM and NDMM have been demonstrated in a series of clinical trials (Table 2).

Daratumumab in RRMM

Daratumumab monotherapy in RRMM yielded an ORR of 29.2% and PFS of 3.7 months.[39] Concerning combination regimens, according to the result of the open-label, phase 3 POLLUX trial, the ORR and median PFS were notably enhanced by the addition of daratumumab to lenalidomide and dexamethasone (Dara-Rd) when compared with those of the Rd group (ORR 92.9% vs 76.4% and PFS 44.5 months vs 17.5 months, respectively). Benefits were also observed among patients aged >75 years and among those with a high cytogenetic risk.[41] The APOLLO study investigated the efficacy of Pd with (Dara-Pd) or without daratumumab among a total of 304 patients who had received pretreatment with at least one therapy. After a median duration of 16.9 months, 51% of the Dara-Pd cohort reached VGPR or better, which was comparable to that of the control group (17.2%).[40]

The CASTOR trial recruited 498 patients with RRMM. Prolonged PFS and increased MRD negativity were found in the group receiving triple therapy consisting of daratumumab, bortezomib, and dexamethasone compared with the group receiving bortezomib and dexamethasone alone (median PFS, 16.7 months vs 7.1 months; MRD negativity, 14% vs 2%).[42] The CANDOR study demonstrated that the risk of disease progression or death was markedly lower in patients receiving daratumumab plus Kd than in those receiving Kd only (median PFS: not reached and 15.8 months, respectively).[43]

Daratumumab in NDMM

Daratumumab has also been studied in patients with NDMM who are ineligible for stem cell transplantation. The phase 3 MAIA study reported that the Dara-Rd regimen significantly prolonged overall survival and PFS.[44] Similar conclusions were reached in the ALCYONE trial, which enrolled 706 transplantation-ineligible patients with NDMM to compare the activity of daratumumab, bortezomib, melphalan, and prednisone (Dara-VMP) with that of VMP alone. The ORR was 90.9% versus 73.9% and the median PFS was 36.9 months versus 19.3 months, respectively.[45]

Daratumumab has also demonstrated high clinical efficacy among patients eligible for transplantation. In the phase 3, open-label, randomized CASSIOPOEIA trial, 1085 patients were assigned to 2 groups, namely, a bortezomib, thalidomide, and dexamethasone (VTd) group or a daratumumab combined with VTd (Dara-VTd) group. All the patients received 4 pre-transplant induction cycles and 2 post-transplant consolidation cycles. One hundred days after transplantation, daratumumab had improved the MRD negativity rate by 20% (64% for Dara-VTd vs 44% for VTd).[46]

The GRIFFIN trial, another phase 3 trial for transplant-eligible patients, assessed the activity of a combination of daratumumab with the conventional triple regimen bortezomib, lenalidomide, and dexamethasone (Dara-VRd). After a median follow-up of 22.1 months, an increase in MRD negativity was found in the Dara-VRd arm (51%, compared with 20.4% in the VRd arm).[47]

Furthermore, incorporating daratumumab into MM therapy is considered to prolong PFS even among high-risk patients with chromosome abnormalities, including del(17p), t(4;14), and t(14;16).[48,49]

Although daratumumab also kills tumor cells both *via* ADCC, ADCP, and CDC and by reducing the immunosuppressive activity of regulatory T and B cells, the underlying mechanisms differ slightly from those of isatuximab in several aspects. First, the 2 agents target distinct CD38 epitopes.[50] Secondly, isatuximab can directly induce apoptosis in myeloma cells,[8,9] whereas daratumumab cannot induce cell death without being combined with cross-linking agents.[51] Furthermore, isatuximab modulates CD38 enzymatic activity more effectively than daratumumab.[9]

The results of studies assessing isatuximab therapy were comparable to those for daratumumab. The ORRs for the Isa-Pd and Dara-Pd regimens were 60.4% to 62.6% and 60.66%, respectively,[18,24,52] while those for the Isa-Kd and Dara-Kd regimens were 87% and 84%, respectively.[20,43] However, the 2 drugs have not been studied in the same setting. Moreover, the infusion time for isatuximab at the 10 mg/kg dose was approximately 3 h,[24] which was shorter than the 3.9 h or longer reported for daratumumab.[43] On the other hand, while daratumumab can be administered subcutaneously, isatuximab-based regimens rely on intravenous formulations, which limits their application. A phase 1b study is currently ongoing to evaluate a subcutaneous formulation of Isa-Pd (ClinicalTrials.gov ID: NCT04045795).

It remains uncertain whether isatuximab can be an alternative to daratumumab in MM therapy. A phase 1b study of Isa-Pd administered by fixed-volume infusion enrolled 7

Table 2. Pivotal Clinical Studies of Daratumumab in RRMM and NDMM.

Study group	Number of patients	Median ORR (%)	Median PFS (months)	Median OS	Reference
RRMM					
Dara monotherapy (SIRIUS)	148	29.2	3.7	1-year OS: 65%	39
Dara-Pd versus Pd (APOLLO)	151 versus 153		12.4 versus 6.9		40
Dara-Rd versus Rd (POLLUX)	286 versus 283	92.9 versus 76.4	44.5 versus 17.5	NR (at 42 months: 65% vs 57%)	41
Dara-Vd versus Vd (CASTOR)	251 versus 247	83.0 versus 63.0	16.7 versus 7.1	NR (at 3 years: 61% vs 51%)	42
Dara-Kd versus Kd (CANDOR)	312 versus 154	84.3 versus 74.7	NR versus 15.8	NR	43
NDMM					
Dara-Rd versus Rd (MAIA)	368 versus 369	92.9 versus 81.3	NR versus 33.8	NR	44
Dara-VMP versus VMP (ALCYONE)	350 versus 356	90.9 versus 73.9	36.9 versus 19.3	NR	45
Dara-VTd versus VTd (CASSIOPOEIA)	543 versus 542	92.6 versus 89.9	NR (at 8 months : 93% vs 85%)	NR	46
Dara-VRd versus VRd (GRIFFIN)	104 versus 103	99.0 versus 81.8	NR (at 24 months: 95.8% vs 89.8%)	NR (at 24 months: 95.8% vs 93.4%)	47

Abbreviations: RRMM, relapsed/refractory multiple myeloma; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; PFS, progression-free survival; OS, overall survival; Dara, daratumumab; Pd, pomalidomide/dexamethasone; Rd, lenalidomide/dexamethasone; NR, not reached; Kd, carfilzomib/dexamethasone; Vd, bortezomib/dexamethasone; VMP, bortezomib/melphalan/prednisone; VTd, bortezomib/thalidomide/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.

daratumumab-refractory patients with RRMM. Of the 6 participants for whom the response could be evaluated, 3 experienced a minimal response (MR) or better.[53] Another small case series consisting of 9 patients also demonstrated encouraging results for Isa-Pd after daratumumab therapy, with 7 patients showing a MR or better.[54] Mikhael et al reported the effect of single-agent isatuximab in patients who developed daratumumab resistance. One of 32 patients achieved a MR and 17 had stable disease as best overall response.[55] A descriptive analysis reported the outcomes of the Isa-Pd regimen in 5 relapsed patients who had previously received daratumumab therapies. One achieved a partial response (PR), 2 achieved a minor response-stable disease, and 2 achieved progressive disease as best response.[56] Isatuximab-based regimens have shown poor activity in patients refractory to daratumumab, which may be due to their partly overlapping mode of action. The results of several trials assessing isatuximab in patients exposed or refractory to daratumumab have been reported; however, their conclusions are limited owing to the small sample sizes and the possibility of patient selection bias.

Conclusions and Future Directions

Isatuximab-based therapies have demonstrated effectiveness and a manageable safety profile in the treatment of MM. The enhancement of anti-MM activity resulting from the addition of IMiDs to CD38 monoclonal antibodies may be due to the increased effect exerted by ADCP and ADCC, as well as CD38 upregulation, on regulatory T cells.[6] Pomalidomide has been shown to enhance isatuximab-mediated ADCP and ADCC *in vitro*.[50] Meanwhile, PIs show substantial efficacy in combination with isatuximab, likely due to their multiple effects on MM cells and the tumor microenvironment.[50]

However, different from Dara-VMP and Dara-Rd, which have been recommended by the National Comprehensive Cancer Network (NCCN) for patients with NDMM who are not eligible for transplantation, there is currently a lack of results on the application of isatuximab in NDMM. Several trials evaluating isatuximab combination therapies in NDMM are currently underway.[57] Additionally, the IONA-MM trial (ClinicalTrials.gov ID: NCT04458831) is ongoing to confirm the efficacy and safety of isatuximab-based therapies in a real-world setting.

Although therapeutic strategies that incorporate CD38 antibodies have demonstrated efficacy in MM and have been tolerated by patients, primary resistance and acquired resistance have both been reported. Several studies have investigated the mechanisms of resistance and potential strategies to overcome it, as shown in Table 3. One of the associated mechanisms may be related to reduced CD38 expression, resulting in an impairment of classic Fc-mediated cytotoxic activities.[10] Thus, the addition of other drugs, such as all-*trans* retinoic acid (ATRA) and the histone deacetylase inhibitor ricolinostat, which increase the expression of CD38, may be a potential approach for reversing resistance.[58,59] In patients on daratumumab monotherapy who achieve PR or better before progression, the addition of ATRA and the reintensification of daratumumab resulted in significantly prolonged disease control (median PFS 9.9 months vs 17.7months).[60] Isatuximab-mediated ADCC was also enhanced through the use of ATRA in MM cell lines.[9] However, in the most recent study, Frerichs et al found that

Table 3. Potential Strategies to Overcome Resistance.

Potential strategies to overcome resistance	Mechanisms	References
IMiDs	Enhanced ADCC, ADCP, direct effects, and immunomodulatory activity of CD38 antibodies	6
ATRA	Enhanced ADCC and CDC and downregulation of CD55 and CD59 expression levels	58
Administration of *ex vivo*-expanded NK cells	Enhanced ADCC	62
YM-155	Downregulation of survivin expression	63
PD-1/PD-L1 inhibitors	Enhanced immunomodulatory activity	64
Anti-CD47 monoclonal antibodies	Downregulation of CD47 expression	65

Abbreviations: IMiDs, immunomodulatory drugs; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; NK, natural killer.

the increased efficacy associated with the addition of ATRA was limited and temporary due to the transient nature of the upregulation of CD38 expression.[61]

Increased expression levels of complement inhibitors (CD55 and CD59) also contribute to the resistance to anti-CD38 antibodies.[9,66] The CDC-resistant MOLP-8 cell line expresses high levels of CD59, and inhibition of CD59 lead to cell lysis by isatuximab-mediated CDC.[9]

Bone marrow stromal cells also protect myeloma cells against CD38 antibody-mediated ADCC through the upregulation of antiapoptotic molecules such as survivin.[10] This effect could be partially reversed by the downregulation of survivin expression using the small-molecule inhibitor YM-155.[63]

Other mechanisms of resistance include the upregulation of CD47 and several alternative immune checkpoints as well as the reduction of NK cell numbers.[65,67,68] Studies have shown that using *ex vivo*-expanded CD38-knockout NK cells can enhance daratumumab-mediated ADCC activity.[62] The combined targeting of the CD38 and programmed cell death-1 (PD-1) or programmed death ligand-1 (PD-L1) pathways also contributes to improving the efficacy of anti-CD38 antibodies. PD-1 blockade markedly enhanced daratumumab-mediated cytotoxicity *in vivo* in murine CD38+ tumor models.[64]

In conclusion, isatuximab monotherapy and combination regimens provide additional treatment options in MM; however, more studies are needed to assess their potential for application in this disease.

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