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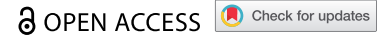
Anti CD38 monoclonal antibodies for multiple myeloma treatment

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ABSTRACT

CD38 is a transmembrane glycoprotein with ectoenzymatic activity and is highly and uniformly expressed on multiple myeloma (MM) cells. CD38 is expressed also at relatively low levels on normal lymphoid and myeloid cells, and in some tissues of non-hematopoietic origin. The specificity of this target has increased interest in new drugs and triggered the development of the CD38 monoclonal antibodies Daratumumab (fully human) and Isatuximab (chimeric). CD38 antibodies have pleiotropic mechanisms of action including Fc-dependent immune effector mechanisms, direct apoptotic activity, and immunomodulatory effects by the elimination of CD38+ immune-suppressor cells. Monoclonal antibody-based therapy has revolutionized MM therapy in the latest years increasing depth of response. This product review will focus on anti-CD38 monoclonal antibodies Daratumumab and Isatuximab efficacy, safety, pharmacokinetic and pharmacodynamic data from clinical trials.

Introduction

Multiple myeloma (MM) represents the second hematological cancer after non-Hodgkin's lymphomas.[1] While the disease is still defined incurable, in the past 20 y, MM patients have experienced great advances in progression-free survival (PFS) and overall survival (OS).[2–5] In fact, OS has increased from a median of 3–4 y to a median of 8–9 y.[5] The introduction of novel drugs changed completely the disease perspective. These drugs are: i) the immunomodulatory (IMIDs) thalidomide, lenalidomide, and pomalidomide; ii) the proteasome inhibitors (PIs) Bortezomib, Carfilzomib, Ixazomib; iii) the monoclonal antibodies (MoA) Daratumumab, Elotuzumab, Isatuximab, Belantamab. These drugs can be used alone or combined in triplet or quadruplet, leading to overwhelming responses that can reach 90% of the treated patients.[4] Also, particular aggressive conditions, such as extramedullary disease, can benefit from these associations.[6–8] Strategies such as consolidation therapy and maintenance after autologous stem cell transplantation (ASCT) further improved PFS and OS.[8,9] In particular, MoA directed toward CD38 have revolutionized the therapeutic landscape leading to high rates of complete remission and increasing depth of response.[10] The concept of minimal residual disease (MRD) has been introduced by the International Myeloma Working Group (IMWG) in the response evaluation.[11] Both multiparametric flow cytometry, Next-Generation Flow (NGF), and Next Generation Sequencing (NGS) can be utilized and detect MRD at 10^{-5} to 10^{-6} in the bone marrow aspirate. MRD negativity has become a surrogate for survival, and it is widely utilized in clinical trials, while it is still not mandatory in clinical practice.[12] The percentage of MRD negativity reached by anti CD38 MoA Daratumumab and Isatuximab has been unprecedented in multiple myeloma. This product review will focus on different aspects of these two drugs.

CD38 structure, expression, and function

The human CD38 antigen is a 46 kilodalton (kDa) type II transmembrane glycoprotein with a short N-terminal cytoplasmic tail and a long extracellular domain.[13] CD38 can be internalized and shed and[14] it also exists in a 39 kDa soluble form in biological fluids.[15] The gene encoding CD38 is on Chromosome 4. It is present in hematopoietic cells (its distribution seems to depend on the activation and differentiation of the cell) and can be expressed also in various tissues.[16] It is also expressed on regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells with a high surface expression associated with compromised immune surveillance for malignancies. CD38 is present in most of the circulating T- and B-cells are CD38-, and activated B- and T-cells, it is also present on monocytes, natural killer cells, dendritic cells, and plasma cells.[17] Progenitor stem cells can express CD38 but not immature stem cells,[18] it is present also on erythrocytes[19,20] and on platelets.[21] CD38 is a great target for MoA therapy in MM because MM plasma cells express higher levels of CD38 compared with normal cells. MM is not the only disease in which CD38 is expressed, it is also highly expressed in acute leukemia, chronic lymphocytic leukemia[22,23] and many types of lymphomas (mantle cell, follicular, diffuse large B-cell lymphoma).[24] Since immune suppressive cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) express CD38, they could be targeted by daratumumab.[25] Other tissues have a lower level of expression (eye, prostate, kidney, bone, pancreas, Purkinje cells, pituitary, smooth muscle cells).[26] CD38 functions as a receptor in signaling events, adhesion, and enzymatic activity,[27] in particular adhesion of CD38 is described in differentiating B-cells for interactions. Moreover, CD38 uses nicotinamide adenine dinucleotide

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(NAD)+ as a substrate for cyclase activity, hydrolase activity, and ectoenzymatic activity.[22–32] Through interactions, CD38 may play a part in regulating leukocytes' cellular motility, adhesion, and modification of the extracellular matrix.

Daratumumab

Daratumumab (Dara) is a human immunoglobulin G1 kappa (IgG1κ) MoA from Janssen that binds to CD38 (first-in-class). Dara is used for MM treatment and is also being developed for lymphomas, leukemias therapy, and systemic AL amyloidosis. Dara can be given by intravenous (IV) infusion or subcutaneously (SC) 5 min compared with 7 h for an IV first infusion, even though short infusion times have been reported.[33,34] SC administration can lower the rate of infusion-related reactions (IRRs) as well to reduce health care professional time spent. Dara IV received marketing authorization in November 2015 in the US and is now approved in over 90 countries worldwide for MM treatment. Dara SC is currently approved in the US and EU and is either approved or under review in several other countries worldwide. An indication for use of Dara SC for the treatment of AL amyloidosis is also approved or under review in many countries.

Mechanisms of action

Dara can have different mechanisms of action: complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and direct cytotoxicity by induction of apoptosis by Fc gamma receptor-mediated.[35,36] Dara can eliminate highly immunosuppressive subsets of CD38+ Tregs, CD38+ MDSCs, and CD38+ regulatory B-cells (B-regs).[25] The main mechanisms of action of anti-CD38 antibodies are described in Figure 1.

Pharmacokinetics

The pharmacology and mechanism of action of daratumumab were assessed by extensive experiments. The pharmacology experiments focused on inhibition of CD38 enzymatic activity, ADCP, CDC, and ADCC, apoptosis, and reactivity with normal human tissues. Dara reduced tumor growth in mouse xenograft models. When Dara was combined with lenalidomide or bortezomib in MM in-vitro studies, plasma cell killing was demonstrated.[37] Pomalidomide or lenalidomide can also increase the activity of anti-CD38 antibodies including Dara by upregulation of CD38.[38]

Dara's half-life estimated following the first 16 mg/kg dose was 9 d. Based on population PK analysis, the mean half-life associated with nonspecific linear elimination was approximately 18 d. In participants with MM, Dara SC exposure showed non-inferiority in a monotherapy study using 1,800 mg (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as compared to 16 mg/kg Dara IV for the same dosing schedule.

Efficacy

Table 1 shows the main Dara efficacy studies as monotherapy and combination therapy.[39–53] Dara IV clinical benefit was demonstrated in a phase 1 study of Dara monotherapy in relapsed/refractory MM patients (Study GEN501) and confirmed in a phase 2 study (Study MMY2002). Data from phase 3 studies showed Dara IV efficacy when used in combination with chemoimmunotherapy in participants with relapsed/refractory MM (RRMM) (in combination with lenalidomide and dexamethasone [Rd] [Study MMY3003], bortezomib-dexamethasone [Vd] [Study MMY3004]), pomalidomide and dexamethasone [DPd cohort of Study MMY1001], carfilzomib and dexamethasone [20160275 CANDOR study and DKd cohort of MMY1001], Dara, carfilzomib, lenalidomide, and dexamethasone [DKRd cohort of study
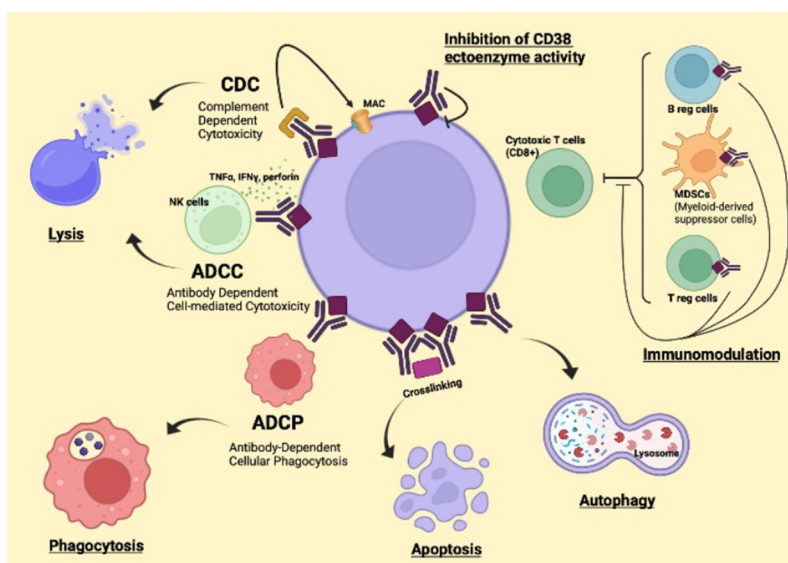

Figure 1. Mechanism of action of anti-CD38.

◆CD38; ⅄ anti-CD38 (Daratumumab or Isatuximab); CDC, Complement Dependent Cytotoxicity; ADCC, Antibody Dependent Cell-mediated Cytotoxicity; ADCP, Antibody-Dependent Cellular Phagocytosis.

Table 1. Selected trials of daratumumab in multiple myeloma.

Clinical Trial	Phase	Setting	Treatment	ORR (%)	CR (%)	MRD neg (%)
NCT 00574288 (GEN501)	1/2	RRMM	Monotherapy, dose-escalation	36	4,7	NA
NCT 02316106 (SMM2001 - CENTAURUS)	2	SMM (intermediate-R, high-R)	Monotherapy	56,1 (intense arm) 53,7 (intermediate arm) 37,5 (short arm)	5,0 10,0 0,0	NA
NCT 01985126 (MMY2002 – SIRIUS)	2	RRMM	Monotherapy	29,2	2,8	NA
GEN501 + SIRIUS	1/2	RRMM	Monotherapy	31,1	4,7	NA
NCT 01615029 (GEN503)	1/2	RRMM	Dara-Rd, dose escalation	81	25,0	34,4
NCT 03158688 (CANDOR)	3	RRMM	Dara-Kd vs Kd	84,3 vs 74,7	29,0 vs 10,0	14 vs 3
NCT 02874742 (MMY2004 – GRIFFIN)	2	NDMM eligible for HDT or ASCT	Dara-RVd vs RVd	99 vs 91,8	80 vs 61	51 vs 20
NCT 03357952 (MMY2036)	multiphase	RRMM	Anti PD1-Dara	44,4	NA	NA
NCT 02076009 (MMY3003 – POLLUX)	3	RRMM	Dara-Rd vs Rd	92,9 vs 76,4	43,1 vs 19,2	22,4 vs 4,6
NCT 02136134 (MMY 3004 – CASTOR)	3	RRMM	Dara-Vd vs Vd	85 vs 63 92 vs 74 (1 prior line treatment)	30 vs 10 43 vs 15	14 vs 2 20 vs 3
NCT 02541383 (MMY3006 – CASSIOPEIA)	3	NDMM eligible for ASCT	Dara-VTd vs VTd	92,6 vs 89,9	39 vs 26	64 vs 44
NCT02195479 (MMY3007 - ALCYONE)	3	NDMM ineligible for HDT and ASCT	Dara-VMP vs VMP	90,9 vs 73,9	42,6 vs 24,4	22,3 vs 6,2
NCT 02252172 (MMY3008 – MAIA)	3	NDMM ineligible for HDT and ASCT	Dara-Rd vs Rd	92,9 vs 81.3	47,6 vs 24,9	24,2 vs 7,3
NCT 03412565 (MMY2040 – PLEIADES)	2	NDMM	Dara sc VMP vs Dara sc VRd vs Dara sc Rd	89,6 97,0 93,8	47,8 16,5 38,5	16,4 n.a 15,4
NCT 03180736 (MMY3013 – APOLLO)	3	RRMM	Dara sc Pd vs Pd	68,9 vs 46,4	25 vs 4	9 vs 2

MMY1001]), and in participants with newly diagnosed MM who were ineligible for high-dose therapy (in combination with bortezomib-melphalan-prednisone [VMP] [Study MMY3007]) and Rd [Study MMY3008], or eligible for autologous stem cell transplant (in combination with bortezomib, thalidomide, and dexamethasone [VTd] [MMY3006]). The clinical benefit of Dara SC has been demonstrated as monotherapy (MMY3012) and in participants with relapsed/refractory MM (in combination with Rd and DKd [MMY2040] and Pd [MMY3013]) as well as in participants with newly diagnosed MM (in combination with VMP and bortezomib, lenalidomide, and dexamethasone [VRd] [MMY2040]). The clinical benefit of Dara IV and SC monotherapy and combination therapy has also been demonstrated in AL amyloidosis (AMY3001) and high-risk SMM (SMM2001-CENTAURUS).

Safety

Among the 156 MM patients treated with 16 mg/kg Dara as monotherapy in studies MMY2002, GEN501, MMY1002, the most frequently reported adverse events (TEAE) were fatigue (40%), nausea, anemia (28% each), back pain (26%), cough (24%), neutropenia (23%), pyrexia (22%), upper respiratory tract infection (22%), and thrombocytopenia (21%). Grade 3 or 4 TEAE were reported in 57% of participants treated with 16 mg/kg. Among the 156 participants, 41.7% experienced grade 3 and 15.4% grade 4 events. In the GEN503 and MMY3003, a total of 318 participants have been treated with Dara in combination with Rd (DRd) as the primary analysis. A total of 281 MM patients in Study MMY3003 received Rd alone. The most frequently reported TEAE reported in participants receiving DRd treatment were neutropenia (66%) and diarrhea (57%). Also upper respiratory tract infection (40%), anemia, fatigue (38% each), cough (36%), nasopharyngitis (33%), muscle spasms (32%), constipation (31%), thrombocytopenia (30%), nausea (29%), pyrexia, insomnia (26% each). Grade 3/4 TEAE was reported in 90% of patients who received DRd treatment. The most frequently reported were neutropenia (58%), anemia (17%), and thrombocytopenia (15%). TEAE leading to discontinuation were reported for 13% of participants in the DRd treatment group (pneumonia, 5 participants, 2%), septic shock, anemia, thrombocytopenia, and hypercalcemia (2 participants, 1% each).

A total of 226 (95.4%) MM patients in the Vd group and 240 (98.8%) participants in the DVd group had at least 1 or more TEAE (at least 10%). The most common TEAE included diarrhea, anemia, thrombocytopenia, peripheral sensory neuropathy, and upper respiratory tract infection. A total of 461 participants were treated in the CANDOR study. The safety profiles observed in the DKd (N = 308) and Kd (N = 153) arms were generally consistent with the known profiles of the study treatments administered. The most frequently reported (20% of participants in either treatment group) adverse events included thrombocytopenia (37.3%, 29.4%), anemia (32.8%, 31.4%), diarrhea (31.5%, 14.4%), hypertension (30.5%, 27.5%), upper respiratory tract infection (29.2%, 22.9%), fatigue (24.4%, 18.3%), and dyspnea (19.8%, 22.2%).

In the CASSIOPEIA study, the most common (at least 10%) Grade 3 or 4 TEAE during induction/ASCT/consolidation phase were neutropenia and stomatitis in both groups. The overall incidence of serious TEAE was similar for both groups (D-VTd: 46.8%; VTd: 47.4%). The most common (≥3%) TEAE reported were neutropenia (D-VTd: 3.9%; VTd: 1.5%),

pneumonia (D-VTd: 3.5%; VTd: 1.7%), pyrexia (D-VTd: 2.8%; VTd: 4.3%), and pulmonary embolism (D-VTd: 1.5%; VTd: 3.7%). IRRs were presented with Dara IV. In particular, the majority of IRRs occurred at the first infusion and were Grade 1 to 2, and 4% of patients had an IRR at more than one infusion.[54] Severe reactions have occurred, including dyspnea, hypoxia, bronchospasm, hypertension, laryngeal edema, pulmonary edema, vomiting, nausea, nasal congestion, cough, and chills. Less common symptoms were allergic rhinitis and pyrexia. Fatal IRRs were not reported. Pre-medication of patients with antihistamines, antipyretics, and corticosteroids can reduce IRRs before treatment with Dara.

IRRs with Dara SC were less present. In clinical trials, approximately 9% (74/832) of patients experienced IRRs and occurred following the first injection (all Grade 1–2). IRRs occurring with subsequent injections were seen in <1% of patients. The median time to onset of IRRs following Dara was 3 h (range 15–83 h). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in <1% of patients. Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, chills, vomiting, nausea, cough, pruritis, allergic rhinitis, pyrexia, and chest pain. Severe reactions have occurred: bronchospasm, dyspnea, hypoxia, hypertension.

Isatuximab

Isatuximab is a chimeric humanized IgG1 monoclonal antibody from Sanofi that binds to a specific epitope on the human cell surface antigen CD38. Isatuximab is approved for the treatment of RRMM, and it can be given by intravenous infusion.

Mechanisms of action

Isatuximab mechanisms of action are Fc dependent and Fc independent. The Fc-dependent mechanisms induced by Isatuximab include ADCC, ADCP, and CDC.[55] ADCC is the dominant mechanism and it is mediated by activating Fcγ receptors on the surface of natural killer cells binding to the Fc regions of the antibodies.[56] While ADCC was seen with both CD38 high and low expression in MM cells, ADCP was seen only with CD38 high expression in MM cells, and CDC was seen in less than half of patient samples. Also, the programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) pathway and MM cell-secreted transforming growth factor-beta (TGF-β) are tumor cell-related features that could suppress CD38-mediated ADCC. Isatuximab can directly activate NK cells and promote NK cell-mediated cytotoxicity via cross-linking of CD38 and CD16. Finally, Isatuximab-induced CDC was observed in cell lines with high CD38 receptor density (>250,000 molecules/cell) and limited expression of inhibitory complement regulatory proteins (CD46, CD55, and CD59; <50,000 molecules/cell).[57] In terms of Fc-independent activities, Isatuximab induces direct cytotoxicity against MM cells in vitro via caspase-dependent apoptosis and lysosome-mediated non-apoptotic cell killing.[58] Isatuximab has also demonstrated immunomodulatory effects in vitro that may contribute indirectly to the control of tumor growth in MM.

Some of the demonstrated effects are MM cell lysis by NK cells direct activation or by CD8+ cells and suppression of CD38+ regulatory T cells. Isatuximab can mitigate the immunosuppressive tumor microenvironment by reducing inhibition of NK and CD8+ cells.[55,56,59]

Pharmacokinetics

Isatuximab demonstrates non-linear pharmacokinetics with target-mediated drug disposition due to its binding to the CD38 receptor. After intravenous (IV) administration of Isatuximab at the approved dosage (10 mg/kg weekly for 4 weeks and then every 2 weeks), the median time to reach a steady-state is 8 weeks. Linear clearance of the drug decreases over time by 50% to a steady-state value of 9.55 mL/h (.229 L/d). The terminal half-life of Isatuximab is 28 d. At a steady state, ≥99% elimination of the drug from plasma was predicted to occur ≈2 months after the last dose. Based on a population pharmacokinetic analysis, the renal or hepatic impairment does not have a clinically meaningful effect on the pharmacokinetics of Isatuximab and does not require any dose adjustment.[60,61]

Efficacy

Main Isatuximab trials are described in Table 2. Isatuximab has been first-in human evaluated in a phase I multicenter, open-label, dose-escalation study as single-agent in RRMM.[62] The study enrolled 84 patients. Isatuximab was administered intravenously every 2 weeks (Q2W) or QW, in 2-week cycles. The primary objective was to determine the maximum tolerated dose (MTD), and secondary objectives were evaluation of safety/tolerability, pharmacokinetics/pharmacodynamics, and preliminary efficacy. The MTD was not reached; no cumulative adverse reactions were noted. In patients receiving Isatuximab ≥10 mg/kg, the overall response rate (ORR) was 23.8%. In high-risk patients, the ORR was 16.7%. The median (range) duration of response at doses ≥10 mg/kg was 25 (range 8–30) weeks among high-risk patients versus 36 (range 6–85) weeks for other patients. A subsequent phase I-b trial (NCT02283775) evaluated Isatuximab plus pomalidomide and dexamethasone in patients with RRMM. Patients enrolled had received ≥2 prior MM therapies, including lenalidomide and a proteasome inhibitor (PI). They received Isatuximab at 5, 10, or 20 mg/kg (weekly for 4 weeks, followed by every 2 weeks), pomalidomide 4 mg (days 1–21), and dexamethasone 40 mg (weekly) in 28-dy cycles until progression/intolerable toxicity. The primary objective was to determine the safety and recommended dose of Isatuximab with this combination, 45 patients were enrolled. Most of the patients were refractory to their prior regimen (91%), with 82% lenalidomide-refractory and 84% PI-refractory. ORR was 62%; median duration of response (DOR) was 18.7 months; median PFS was 17.6 months. Based on this trial, the dose of 10 mg/kg weekly/every 2 weeks Isatuximab was selected for future studies.[63] To confirm these data and reduce the infusion duration, we designed another phase I-b trial (NCT02283775) to evaluate the efficacy and safety of a fixed-volume infusion of Isatuximab plus pomalidomide and dexamethasone (Pd) in RRMM, who had received ≥2 prior lines of therapy. This trial was composed of two parts: part A was an Isatuximab dose-escalation study, while in the part B, Isatuximab

Table 2. Selected trials of isatuximab in multiple myeloma.

Clinical Trial	Phase	Setting	Treatment	ORR (%)	CR (%)	MRD neg (%)
*First -in human isatuxiamb	1	RRMM	Monotherapy, dose-escalation	18,2 (1–5 mg/kg) 23,8 (≥10 mg/kg)	0 1,6	NA
NCT 02283775 (PomdeSAR)	1 B	RRMM	Isa-Pd	62,2	4,4	NA
NCT 02332850	1 B	RRMM	Isa-Kd	66	3,4	NA
NCT 01749969	1 B	RRMM	Isa-Rd	56	3,8	NA
NCT 02990338 (ICARIA—MM)	3	RRMM	Isa-Pd vs Pd	60 vs 35	5 vs 2	5 vs 0
NCT 03275285 (IKEMA)	3	RRMM	Isa-Kd vs Kd	87 vs 83	40 vs 28	30 vs 13

(10 mg/kg) was administered as a fixed infusion volume of 250 mL with standard doses of Pd. The primary endpoint for Part B was the incidence of Grade (Gr) ≥3 infusion reactions (IRs) during the first six Isatuximab infusions.[64] Forty-seven patients were enrolled. The median duration of exposure was 36.9 weeks. The ORR in all subjects on Part B was 53.2% and 62.2% in Part A, with similar VGPR and CR rates (23.4% and 4.3% in Part B versus 22.2% and 2.2% in Part A, respectively).[64] In another phase Ib study, Isatuximab was combined with Carfilzomib (K) and dexamethasone in 33 RRMM.[65] Patients were previously treated with a median of three lines. With a median follow-up of 26.7 months, the ORR was 70%. The median PFS was 10.1 months.[65] Isatuximab was combined with lenalidomide and dexamethasone in another phase I b study. The trial enrolled 57 RRMM patients. Isatuximab-lenalidomide-dexamethasone was generally well tolerated, and the MTD was not reached. In the efficacy evaluable population (52/57), the ORR was 56%. Overall median PFS was 8.5 months.[66] Isatuximab showed efficacy and tolerability as a monotherapy and combination therapy in Phase I/II studies in RRMM. The Phase III ICARIA-MM study (NCT02990338) was a randomized, multicentre, open-label trial, which evaluated Isatuximab in combination with pomalidomide and low-dose dexamethasone (IsaPd) versus Pd alone in RRMM. Eligible participants were RRMM that had received at least two previous lines of treatment, including lenalidomide and a PI. A total of 307 patients were randomly assigned to treatment: 154 to IsaPd and 153 to Pd treatment. At a median follow-up of 11.6 months, the median PFS was 11.5 months in the IsaPd group versus 6.5 months in the Pd group, p = .001.[67]

The investigators conclude that the addition of Isatuximab to Pd significantly improves PFS in patients with RRMM, with acceptable toxicity in heavily pre-treated and frail patients.[68] In a subgroup analysis of the ICARIA study, efficacy was determined in patients with renal impairment (RI; estimated glomerular filtration rate <60 mL/min/1.73 m^2). Isatuximab and pomalidomide were given with the same schedule. Median PFS for patients with RI was 9.5 months with IsaPd and 3.7 months with Pd. The ORR with and without RI was higher with IsaPd (56% and 68%) than Pd (25% and 43%). A complete renal response rate of 71.9% was observed with IsaPd and 38.1% with Pd. Isatuximab pharmacokinetics were comparable between the subgroups, suggesting no need for dose adjustment in patients with RI.[68]

The IKEMA phase III trial (NCT03275285) evaluated the combination of Isatuximab, Carfilzomib, and Dexamethasone (IsaKd) Vs Carfilzomib dexamethasone (Kd) in RRMM. The primary endpoint was the PFS. A total of 302 patients have been randomized. Patients in the Isatuximab group received Isatuximab 10 mg/kg IV (days 1, 8, 15, and 22 in the first 28-day cycle; days 1 and 15 in subsequent cycles). In both groups, Carfilzomib was administered IV at 20 mg/m^2 on days 1 and 2 of cycle 1; 56 mg/m^2 on days 8, 9, 15, and 16 of cycle 1; and then 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 of subsequent cycles. The median number of previous lines of therapy was 2, and data were similar between groups and 45% of patients were refractory to immunomodulatory drugs. After a median follow-up of 2 y, the ORR was 87% in the experimental arm and 83% in the control group, without statistically significant difference. Even there was not a difference in ORR, the responses were better in IsaKd group, VGPR or better was reported in 73% of patients versus 56% in the control group (p = .0011). CR occurred in 40% versus 28% of patients. The MRD negativity rate was more than double in the IsaKd group than in the control group: 30% versus 13% p = .0004. Progression-free survival 2 and OS were not mature. Median time to first response in responders was similar in both groups: 32 d (IQR 30–40) in the IsaKd and 33 d (30–58) in the control group. Duration of response and time to next treatment was longer in the Isatuximab group than in the control group.

At a median follow-up of 20.7 months, the addition of Isatuximab to Kd showed a significant improvement in PFS with an HR of .53 (99% CI .32–.89, p = .0007). At 2 y, the estimated PFS was 68·9% (95% CI 60.7–75.8) in the IsaKd group versus 45.7% (35.2–55.6) in the control group.[69]

Safety

Isatuximab in monotherapy and combination with other drugs was generally well tolerated. The most frequent adverse events were IRRs that occurred in 51% of enrolled patients. IRRs were mostly grade 1/2, occurred predominantly during Cycle 1, and led to treatment discontinuation in two patients.[62] After the introduction of mandatory prophylactic treatment, 36/73 patients (49.3%) experienced IRRs. The IRRs mostly resolved in 1 d, either spontaneously or with few medications. The most common symptoms (≥5%) reported during IRRs were chills, dyspnea, nausea, headache, chest discomfort, and pyrexia, all of which were grade 1/2 in intensity. Except for IRRs, the most common (>10%) TEAE of any grade, were fatigue, nausea, upper respiratory tract infection, and cough. Among hematological toxicity, the most frequent grade 3/4 TEAEs were lymphopenia, anemia, thrombocytopenia, and neutropenia, the incidence, and severity of these events did not appear to be dose-dependent.[62] These data were confirmed with the safety

profile shown in phase III trials, ICARIA and IKEMA. The incidence of TEAEs was similar in the ICARIA study, both for patients enrolled in the experimental arm and the control group (respectively 99% vs 98%).[67] Incidence of TEAEs was consistent with the data from IKEMA, where the incidence of any grade TEAEs in the IsaKd arm was 97% while in Kd was 96%.[69] The two Isatuximab-based triplets showed similar side effects, the most frequent non-hematological TEAEs of any grade in the Isatuximab combination therapy recipients included IRRs, respiratory infections (upper respiratory tract infection, pneumonia, and bronchitis), and dyspnea.[67,69] Most of the Isatuximab recipients enrolled in ICARIA and IKEMA study experienced IRRs, they mainly occurred in the first infusion of the first cycle, with a manageable profile, most of them were grade 1–2 and resolved in the same infusion day. Anaphylactic reactions occurred in <1% of the patients. IRRs led to the discontinuation of Isatuximab in <1% of patients in IKEMA,[69] similar to the ICARIA study. Other significant non-hematological TEAEs were upper respiratory tract infections, 36% in the IKEMA trail and 28% in the ICARIA, most of them were grade 1–2, only 3–4% were TEAEs of grade 3–4.[67,69] In both phase III trials, a minimal increased risk of pneumonia was observed in the Isatuximab group compared to the control group. About 20% of patients enrolled in Isatuximab group in the ICARIA study developed pneumonia vs 17% in the control group, similar data were seen in the IKEMA study (29% versus 23%).[67,69] In the IKEMA study, an increased rate of hypertension was observed in both groups, 37% in the experimental arm and 31% in the control group. Hematological AEs in the IKEMA were in the Isatuximab group: anemia in 99% of patients (grade 3 or more 22%), neutropenia in 55% (19% grade 3–4), thrombocytopenia 94% (30% grade 3–4), data were almost similar in the control group.[69] In the ICARIA study, the main difference in hematological toxicities was the incidence in both groups of neutropenia, reported in 96% of patients in Isatuximab group and 93% in the control group, 85% and 70% were grade 3–4, respectively.[67]

New anti CD38 monoclonal antibodies

MOR202 is a human IgG1λ CD38 antibody derived from a phage library (MorphoSys AG, Planegg, Germany) and has demonstrated high efficacy in-vitro and in-vivo in preclinical studies.[70,71] MOR202 has anti-myeloma activity via ADCC and ADCP but does not have CDC. In a recent multicenter phase 1–2 study,[71] In this study, 91 refractory/relapsed MM patients with a median of 3 previous lines of therapy were treated (35 with MOR202 monotherapy, 56 with combinations with dexamethasone (N = 18), with pomalidomide and dexamethasone (N = 21), with lenalidomide and dexamethasone (N = 17)). Different treatment schedules were used for MOR202 given IV at doses between .001 mg/kg and 16 mg/kg in a 3 + 3 design. The recommended dose was 16 mg/kg in 30-min infusions. IRRs were more present in MOR202 monotherapy without steroids (14/35, 40%) than in combination therapy (4/56, 7%).

The more common TEAE were lymphopenia grade 3 or higher in 35/91 (38%) patients and neutropenia in 30 (33%). Serious adverse events (SAE, defined as events requiring hospitalization or life-threatening, including events resulting in death)

occurred in 51/91 (56%) patients (7 in the group as monotherapy, 4 in the group combined with dexamethasone, 13 in the group combined with pomalidomide dexamethasone, 17 in the lenalidomide dexamethasone). SAE were mostly due to IRRs (hypersensitivity, tachycardia, pyrexia, 18/91, 20%) and pneumonia (4/91,4%). Regarding efficacy, in the monotherapy or dexamethasone group, 9/35 (26%) had stable disease, while an ORR was seen in 26/56 (46%) in the combination group (4 CR, 5 VGPR, 12 PR, 5 SD). The median duration of response was 16.7 months.

TAK-079 is a fully human, non-agonistic, IgG1 from Takeda, a cell-depleting monoclonal antibody that binds human CD38 with high affinity. It has been reported to act with ADCC, ADCP, and CDC. Recent data on TAK-079 showed an ORR of 33% at the dose of 600 mg sc in relapsed/refractory MM patients with a median of 4 prior lines of therapy. TAK −079 seems to have the advantage of the sc route of administration and a promising safety profile (no IRRs, no significant hematologic toxicity).[72]

Conclusion

Anti-CD38 monoclonal antibodies represent the first immunotherapeutic approach in multiple myeloma. These new drugs have increased the therapeutic choice for clinicians. The safety profile is good, and efficacy is unprecedented when these drugs are combined with other agents such as proteasome inhibitors and immunomodulatory drugs. Future perspectives should focus on patient selection and timing of therapy, together with the understanding of mechanisms of resistance with the intent to prolong efficacy and survival.

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