Bispecific Antibodies in the Treatment of Multiple Myeloma

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KEYWORDS

• Multiple myeloma • Immunotherapy bispecific antibody • CAR T cell

KEY POINTS

- Bispecific antibodies (T-cell engaging antibodies) provide a new mode of action for anti-myeloma therapy by redirecting autologous T cells toward myeloma cells to mediate anti-tumor efficacy.
- Most of the bispecific antibodies in clinical development in myeloma are targeting B-cell maturation antigen, and other targets are GPRC5D, FCRH5, CD38, and CD19.
- Bispecific antibodies are currently approved in relapsed/refractory multiple myeloma (teclistamab already approved, elranatamab and talquetamab expected to be approved in a few weeks) in greater than third line of therapy can mediate overall response rate in greater than 60%, CR of 30% to 40% of patients, and a progression-free survival of around 1 year.

INTRODUCTION

Multiple myeloma (MM), the second most common hematologic malignancy in adult, is a plasma cell neoplasm characterized by bone lesions, kidney injury, anemia, and hypercalcemia.[1] The prognosis of MM patients has been dramatically improved over the last few decades by the introduction of various novel anti-MM agents including proteasome inhibitors, immunomodulatory drugs (IMiDs) and monoclonal antibodies (mAbs) and high-dose therapy with autologous stem cell transplant (ASCT). Results from recent randomized clinical trials showed a median overall survival (OS) of more than 8 years and a 4-year OS rate of more than 80% in patients who received induction with modern quadruple regimens followed by ASCT.[1–4] Even in the transplant ineligible elderly patients, the median OS was about 5 years.[1,5,6] However, MM is still considered an incurable disease, as most of the patients suffer from relapse and develop drug resistance over time[7] and the management of patients with relapsed/refractory (RR) MM remains challenging. More recently, T-cell-based immunotherapies, for example,

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chimeric antigen receptor (CAR)-modified T-cells and bispecific antibodies (bsAbs), have been developed to fight against MM using the patient's own immune system.[8] To date, several CAR T-cell and bsAb products have been investigated within clinical trials and have shown promising efficacy in RRMM patients.[9,10] In the 2020s, the US Food and Drug Administration (FDA) approved the first B-cell maturation antigen (BCMA)-directed CAR T-cell therapies idecabtagene vicleucel (ide-cel or bb2121) and ciltacabtagene autoleucel (cilta-cel), and the first BCMAxCD3 bsAb teclistamab.[11–13] Moreover, CAR T-cell and bsAb products are being evaluated in earlier lines of treatment and/or as frontline therapy in newly diagnosed (ND) MM patients.[10,14] The development of CAR T-cell and bsAb are leading to a paradigm shift in the treatment of RRMM and will greatly further improve the outcome of MM patients. Unlike autologous CAR T-cell therapy, which requires ex vivo manufacturing process, bsAb presents an off-the-shelf product that is readily available and can be administered directly to the patients.[7,15] Ultimately, bsAbs are integrated into the standard of care of MM patients currently in late line but increasingly in clinical trials also in earlier lines of therapy. In this review, the authors provide an overview of potential drug targets, mechanisms of action, efficacy and safety data from recent clinical trials, resistance mechanisms, and future directions of bsAb therapies in MM.

POTENTIAL BISPECIFIC ANTIBODY TARGETS AND MECHANISMS OF ACTION

In brief, bsAb is a T-cell-based therapy that bridges the MM cells and the patients' T-cells in vivo.[16] Therefore, first, bsAbs recruit and activate T cells, for example, by binding to the T-cell co-receptor CD3.[17] Second, similar to mAbs, bsAbs recognize specifically an antigen target, which ideally is uniquely expressed on MM cells and absent on other tissue to avoid on-target off-tumor toxicity. In this way, an immune synapse is built between the MM cells and the patients' own T cells, leading to T-cell (mainly CD8+ T cells) activation and proliferation, which induce MM cell lysis by release of granzymes, perforins, and different cytokines such as interleukin (IL)-6, IL-2, inferon-gamma (INF-γ), IL-5, and monocyte chemoattractant protein-1 (MCP-1).[7,18–21] Currently, the most commonly used bsAbs in MM include bispecific T-cell engagers (BiTE, Amgen, Thousand Oaks, CA) and DuoBody (Genmab A/S, Copenhagen, Denmark).[18,22] BiTE is a molecule containing two single-chain variable fragments linked with each other, whereas DuoBody consists of two different antigen-binding fragments and a functional constant region fragment (Fc), which can extend the half-life time of the molecule.[23,24] So far, several MM-specific immune targets for bsAb have been investigated in preclinical and/or clinical setting, for example, BCMA, G-protein-coupled receptor family C group 5 member D (GPRC5D), Fc receptor-homolog 5 (FcRH5), CD38, CD138, CD19, and signaling lymphocytic activation molecule family-7 (SLAMF7).[25] Herein, the authors summarize the mechanisms of action and the preclinical development of bsAbs targeting the above-mentioned antigens.

BCMA, also known as CD269 or tumor necrosis factor receptor superfamily 17 (TNFRSF17), is highly expressed in malignant plasma cells with low expression level in healthy human tissues.[26] BCMA is a type III transmembrane glycoprotein, which binds to B-cell-activating factor and a proliferation-inducing ligand. In turn, BCMA can regulate B-cell proliferation and differentiation into plasma cells, and in MM cells, BCMA represents an important pro-survival factor by activating various antiapoptotic pathways including nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB), mitogen-activated protein kinase, and protein kinase B (AKT).[27–31] Therefore, the BCMA has been selected as an ideal drug target for MM therapy. In cell lines and/or animal models, the BCMAxCD3 bsAbs BI 836909 and JNJ-64007957 (teclistamab)

could lead to selective lysis of BCMA+ MM cells.[32,33] Currently, BCMA is the most commonly used immune target for CAR T cells and bsAb in MM patients.

GPRC5D is a transmembrane receptor expressed in the hair follicle and in the bone marrow from MM patients. Although the function of GPRC5D has not yet been determined, it has been found that overexpression of GPRC5D is associated with poor prognosis in patients with MM.[34–38] GPRC5D is considered as a drug target for anti-MM immunotherapy.[39] JNJ-64407564 (talquetamab), a GPRC5DxCD3 bsAb, could induce cell death of GPRC5D+ MM cells in vitro, in patient samples ex vivo and in mouse models.[40] Currently, GPRC5D-targeted bsAbs are investigated in clinical trials.

FcRH5 (also known as FcRL5, IFGP5, BXMAS1, CD307, or IRTA2) is a surface molecule predominantly expressed on B cells and malignant plasma cells, with the function of FcRH5 remaining not fully understood.[41–43] Moreover, MM cells displayed higher FcRH5 expression level compared with healthy plasma cells, and especially MM cell lines with 1q21 copy number abnormalities showed increased FcRH5 expression, as the FcRH5 gene is located on the human chromosome 1 band 1q23.1.[19,41,42,44] The FcRH5xCD3 bsAb BFCR4350 A (cevostamab) showed effective T-cell activation, cytokine release, and MM cell death in vitro and in vivo.[19] At present, cevostamab is further developed within clinical trials.

CD38, a type II transmembrane glycoprotein, is involved in cell adhesion and signaling and acts as an ectoenzyme for intracellular calcium mobilization.[45] CD38 is overexpressed on plasma cells and considered a drug target for treatment of MM, and CD38-targeted mAbs daratumumab and isatuximab have been approved by the US FDA for the treatment of MM in different combinations.[46–48] In a recent study, AMG424, a CD38xCD3 bsAb, could kill CD38+ MM cells and induce T-cell proliferation, with attenuated cytokine release in vitro and in vivo,[49] but the further clinical development of the drug was terminated.

CD138 (also known as syndecan-1) is a transmembrane heparin sulfate proteoglycan highly expressed on MM cells and can support the cell adhesion and survival of MM cells.[50,51] In cell lines, CD138xCD3 bsAbs h-STL002 and m-STL002 showed cytotoxicity against CD138+ MM cells by T-cell activation, highlighting that CD138 might be a potential drug target of bsAb for the treatment of MM.[52]

CD19 is widely expressed in B-cell lineage, but only a low proportion of MM cells were CD19+ as demonstrated by studies using flow cytometry.[53,54] However, a recent study using single molecule-sensitive direct stochastic optical reconstruction microscopy showed that MM cells with ultra-low CD19 expression (<100 molecules per cell) could also be eliminated by anti-CD19 CAR T cells, suggesting that CD19 could be a potential target for MM immunotherapies.[55] Thus, blinatumomab, the approved bsAb for B-cell precursor acute lymphoblastic leukemia (B-ALL), might also be a candidate drug for the treatment of CD19+ MM.[56–59]

SLAMF7 (also known as CS1 or CD319) is a member of the SLAMF, which is highly expressed in plasma cells and almost absent in other healthy tissues.[60] SLAMF7 can support the interaction between MM cells and bone marrow stromal cells and can promote MM cell survival by activating ERK1/2, STAT3, and AKT pathways.[61–63] SLAMF7-targeted mAb elotuzumab has been approved by the US FDA for the treatment of RRMM.[64,65] A preclinical study has evaluated a bsAb targeting SLAMF7 and NKG2D, which is widely expressed on cytotoxic immune cells including NK cells, CD8+ T cells, $\gamma\delta$ T cells, and NKT cells; in MM cell lines and mouse models, this SLAMF7xNKG2D bsAb facilitated immune synapse between SLAMF7+ MM cells and NKG2D+ immune effector cells, leading to activation of the most cells and MM cell lysis.[66]

Taken together, several bsAbs targeting different antigens have been developed for the treatment of MM in preclinical studies. However, most of the above-mentioned bsAbs for MM should be further tested in the clinical routine, especially the bsAbs targeting "non-BCMA" antigens. At the time of writing, clinical data are only available for bsAbs targeting BCMA, GPRC5D, FcRH5, and CD38.

SELECTED CLINICAL DATA OF BISPECIFIC ANTIBODIES IN RELAPSED/REFRACTORY MULTIPLE MYELOMA

At present, several bsAbs have been approved for the treatment of RRMM, and as previously mentioned, BCMA represents the most commonly used bsAb target in RRMM. Here, the authors provide a brief summary of selected clinical data of bsAb in RRMM (**Table 1**).

BCMAxCD3 Bispecific Antibodies

AMG420, a BCMAxCD3 bsAb, is the first-in-class bsAbs developed for MM. In a phase 1 study (NCT02514239), a total of 42 RRMM patients received AMG420 at 0.2 to 800 μg/d as a continuous infusion due to its short half-life time. The overall response rate (ORR) was 31% and 70% in the entire cohort and at the maximum tolerated dose of 400 μg/d, respectively. Adverse events (AEs) $\geq$ grade 3 included infection (19%), peripheral polyneuropathy (5%), edema (2%), and cytokine release syndrome (CRS) (2%). Serious AEs were seen in 48% patients (n = 20), including infections (n = 14) and polyneuropathy (n = 2). There was no grade $\geq$ 3 neurotoxicity observed.[67] The drug was not further developed for it required application as a continuous infusion.

AMG701 is a BCMAxCD3 bsAb with an extended half-life time of 112 hours, which enables weekly dosing of this product. In a phase 1 study (NCT03287908), 75 RRMM patients were treated with AMG701 at 3 to 12 mg weekly as intravenous infusions until disease progression, showing an ORR of 36% in the entire group and 83% at the dose of 9 mg weekly. The median response duration was 3.8 months with a maximum duration of 23 months. Four patients with negative minimal residual disease (MRD) showed sustained MRD negativity at the last observations up to 20 months later. The most common hematological AEs included anemia (43%), neutropenia (23%), and thrombocytopenia (20%). The most common non-hematological AEs were CRS (61%), diarrhea (31%), fatigue (25%), and fever (25%). Serious AEs were observed in 29 (39%) patients, including infections (n = 13), CRS (n = 7), and asymptomatic pancreatic enzyme rise (n = 2). Reversible treatment-related neurotoxicity was seen in six patients (all grade 1–2).[68] Further clinical development of this drug was stopped by the sponsor.

Teclistamab (JNJ-64007957) is a humanized BCMAxCD3 bsAb. In the phase 1/2 MajesTEC-1 study (NCT03145181 and NCT04557098), teclistamab was given to RRMM patients with $\geq$ 3 prior treatment lines. A total of 165 patients received a subcutaneous injection of teclistamab weekly at a dose of 1.5 mg/kg after step-up doses of 0.06 mg/kg and 0.3 mg/kg. The ORR was 63.0%, including 65 patients (39.4%) with complete response (CR) or better, and 44 patients (26.7%) reached MRD negativity. Common AEs included infections (76.4%; $\geq$ grade 3: 44.8%), CRS (72.1%; $\geq$ grade 3: 0.6%), neutropenia (70.9%; $\geq$ grade 3: 64.2%), anemia (52.1%; $\geq$ grade 3: 37.0%), and thrombocytopenia (40.0%; $\geq$ grade 3: 21.2%). Neurotoxic events were seen in 24 (14.5%) patients, with 5 (3.0%) patients suffering from immune effector cell-associated neurotoxicity syndrome (ICANS) (all grade 1 or 2). After a median follow-up of 14.1 months, the median progression-free survival (PFS) was 11.3 months (95% CI, 8.8–17.1).[69] Moreover, in the phase 1b MajesTEC-2 study (NCT04722146),

Table 1
Selected clinical data of bispecific antibody therapy for relapsed/refractory multiple myeloma

ClinicalTrials.gov Identifier	Bispecific Antibody	Targets	Study Phase	Estimated Enrollment	Status as of July 2023	Response Rates	AEs ≥ Grade 3
NCT02514239	AMG420	BCMA/CD3	1	43 patients	Completed	42 patients were treated. ORR: 31% (13/42); at MTD of 400 μg/d: 70% (7/10) including 50% (5/10) MRD-negative CR	Infection 19%; PNP 5%; edema 2%; CRS 2%
NCT03836053	AMG420	BCMA/CD3	1/2	23 patients	Completed	N/A	N/A
NCT03269136 Magnetismm-1	Elranatamab (PF-06863135)	BCMA/CD3	1	101 patients	Active, not recruiting	58 patients were treated. ORR in part 1: 70% (14/20) including CR/sCR of 30% (6/20); ORR at the RP2D: 83% (5/6)	No CRS ≥ grade 3 Lymphopenia 64%; neutropenia 60%: anemia 38%; thrombocytopenia 31%
NCT04649359 MagnetisMM-3	Elranatamab (PF-06863135)	BCMA/CD3	2	187 patients	Active, not recruiting	123 patients were treated. ORR 61.0%. In patients with 2–3 prior lines of therapy (n = 26): ORR 73.1%	Most common AEs ≥ grade 3 were hematologic. Non-hematologic AEs ≥ grade 3: COVID-pneumonia (10.6%), hypokalemia (9.8%), pneumonia (7.3%), sepsis (6.5%), hypertension (6.5%), ALT increased (5.7%), and SARS-COV-2 test positive (5.7%)

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ClinicalTrials.gov Identifier	Bispecific Antibody	Targets	Study Phase	Estimated Enrollment	Status as of July 2023	Response Rates	AEs ≥ Grade 3
NCT03145181 MajesTEC-1	Teclistamab (JNJ-64007957)	BCMA/CD3	1	282 patients	Recruiting	165 patients were treated. ORR: 63.0%, including 39.4% (n = 65) CR or better and 26.7% (n = 44) MRD-negative patients	CRS 0.6%, neutropenia 64.2%, anemia 37.0%, thrombocytopenia 21.2%, infections 44.8%
NCT04722146 MajesTEC-2	Teclistamab (JNJ-64007957)	BCMA/CD3	1b	140 patients	Active, not recruiting	32 patients received tec-dara-len. ORR was 13/13 evaluable patients at 0.72 mg/kg and 13/16 evaluable patients at 1.5 mg/kg	No CRS ≥ grade 3, neutropenia 68.8%, fatigue 6.3%, insomnia 3.1%, pyrexia 6.3%, febrile neutropenia 12.5%, infections 28.1%
NCT05243797 MajesTEC-4	Teclistamab (JNJ-64007957)	BCMA/CD3	3	1530 patients	Recruiting	N/A	N/A
NCT05552222 MajesTEC-7	Teclistamab (JNJ-64007957)	BCMA/CD3	3	1060 patients	Recruiting	N/A	N/A
NCT03933735	TNB-383B	BCMA/CD3	1	220 patients	Active, not recruiting	124 patients were treated. ORR: 57% including 29% CR or better	No CRS ≥ grade 3, neutropenia 67%, anemia 17% in 40 mg cohort; CRS 2%, neutropenia 35%, anemia 12%, and thrombocytopenia 12% in 60 mg cohort

NCT03486067	Alnuctamab (ALNUC, CC-93269)	BCMA/CD3	1	220 patients	Recruiting	70 patients were treated with IV ALNUC with ORR 39%; 47 patients were treated with SC ALNUC with ORR: 51% with 17% ≥ CR	No CRS ≥ grade 3, neutropenia 30%, and anemia 17%
NCT03287908	AMG701	BCMA/CD3	1	174 patients	Active, not recruiting	75 patients were treated with ORR 36% including 4 sCR stringent CRs, 1 MRD-negative CR, 6 VGPRs, and 6 PRs	CRS 7%, serious AEs 39% including four deaths
NCT03761108	REGN-5458	BCMA/CD3	1/2	309 patients	Active, not recruiting	252 patients were treated. ORR at 200 mg dose levels was 64%; at doses 50 mg was 50%	At 200 mg: CRS 37%, fatigue 32%, and anemia 28% At 50 mg: CRS 53%, fatigue 33%, and anemia 40% ICANS ≥ grade 3: 2% (n = 2) at 200 mg and 1% (n = 1) at 50 mg
NCT04083534	REGN-5459	BCMA/CD3	1/2	43 patients	Active, not recruiting	N/A	N/A
NCT04108195 TRIMM-2	Teclistamab (JNJ-64007957)	BCMA/CD3	1b	294 patients	Active, not recruiting	33 patients were treated with tec + dara. Partial response or better: in cohort dara + tec 1500 μg/kg (n = 13/17); in cohort dara + tec 3000 μg/kg (n = 4/4); in cohort dara + tec 300 μg/kg (n = 1/2)	66.7% of patients had grade 3/4 AEs. Neutropenia 36.4%; thrombocytopenia 33.3%, anemia 24.2%, diarrhea 3.0%
	Talquetamab (JNJ-64407564)	GPRC5D/CD3	1b	294 patients	Active, not recruiting	N/A	N/A

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ClinicalTrials.gov Identifier	Bispecific Antibody	Targets	Study Phase	Estimated Enrollment	Status as of July 2023	Response Rates	AEs ≥ Grade 3
NCT03399799 MonumenTAL-1	Talquetamab (JNJ-64407564)	GPRC5D/CD3	1	320 patients	Recruiting	95 patients were treated with SC talquetamab. ORR was 70% at 405 μg/kg weekly dose and the ORR was 71% at 800 μg/kg biweekly dose	At the 405 μg/kg weekly dose: CRS ≥ grade 3 (n = 1), neutropenia 60%, skin-related AEs 13%, infections ≥ grade 3 (n = 1); at the 800 μg/kg biweekly dose no CRS ≥ grade 3, neutropenia 35%, skin-related AEs: 13%; infections ≥ grade 3 (n = 1)
NCT04557150	RG6234 (RO7425781, forimtamig)	GPRC5D/CD3	1	480 patients	Recruiting	ORR: 68%, including 50% ≥VGPR	CRS: 85.4% (grade 3: 2.4%) Neurologic toxicity (headache and confusion): 7.3% Skin-related AEs: 66% Dysgeusia: 36.6%
NCT03309111	ISB1342	CD38/CD3	1	245 patients	Recruiting	24 patients received ISB1342. ORR N/A	Infusion-related reactions 17%, delirium (n = 1)
NCT03445663	AMG424	CD38/CD3	1	27 patients	Terminated	N/A	N/A
NCT03275103	Cevostamab (BFCR4350 A)	FcRH5/CD3	1	420 patients	Recruiting	160 patients had been enrolled. ORR was 54.5% at 160 mg dose level; ORR was 36.7% at 90 mg dose level	CRS 1.3%, ICANS 1.4%, infections 18.8%, neurologic/psychiatric 3.8%, anemia 21.9%, and diarrhea 0.6%
NCT03173430	Blinatumomab	CD19/CD3	1	6 patients	Terminated	N/A	N/A

Abbreviations: AE, adverse event; ALT, alanine transaminase; BCMA, B-cell maturation antigen; CR, complete remission; CRS, cytokine release syndrome; CD3, CD3 (cluster of differentiation 3) is a protein complex and T cell co-receptor; ICANS, immune effector cell-associated neurotoxicity syndrome; MRD, minimal residual disease; N/A, not available; ORR, overall response rate; RP2D, recommended phase 2 dose; sCR, stringent complete remission; VGPR, very good partial remission.

teclistamab was given in combination with other anti-MM agents such as daratumumab and lenalidomide. In this study, 32 patients received weekly teclistamab with step-up dosing of 0.72 or 1.5 mg/kg together with daratumumab 1800 mg and lenalidomide 25 mg (tec-dara-len). The most common AE was CRS (81.3%, all grade 1/2), and no ICANS was reported. The ORR was 100% (13/13) at 0.72 mg/kg and 81% (13/16) at 1.5 mg/kg in evaluable patients. Infections were reported in 24 (75.0%) patients, including upper respiratory infection (21.9%, $n = 7$), COVID-19 (21.9%, $n = 7$), and pneumonia (21.9%, $n = 7$).[70] In the phase 1b TRIMM-2 trial (NCT04108195), 33 RRMM patients with a median of five prior lines therapies were treated with teclistamab in combination with daratumumab (tec + dara). Mechanistically, it was observed that daratumumab could reduce CD38+ immunosuppressive regulatory T and B cells, increasing the T-cell clonality and functional response.[71,72] Of note, the ORR was 78% (18/23) in evaluable patients in the TRIMM-2 trial. The most common AE was CRS (54.5%, all grade 1/2) and no ICANS was reported. Other frequent AEs included neutropenia (36.4%; all grade 3/4), thrombocytopenia (36.4%; $\geq$ grade 3: 33.3%), anemia (36.4%; $\geq$ grade 3: 24.2%), diarrhea (36.4%; $\geq$ grade 3: 3.0%), nausea (30.3%; all grade 1/2), pyrexia (30.3%; all grade 1/2), and infections (51.5%; $\geq$ grade 3: 24.2%). Median duration of response (DOR) was not reached, and a data update is being excepted with a longer follow-up.[73] Currently, teclistamab is being investigated in the first line in ND MM. For instance, the phase 3 MajesTEC-4 study (NCT05243797) will compare the combination "tec-len" (teclistamab, lenalidomide) versus lenalidomide alone as maintenance therapy after ASCT in NDMM. Results from this trial will provide new insights into maintenance regimens that could improve response and prolong survival duration for NDMM.[74] In addition, the phase 3 MajesTEC-7 study (NCT05552222) will investigate the combination of "Tec-DR" (teclistamab, daratumumab, lenalidomide) versus DRd (daratumumab, lenalidomide, and dexamethasone) in NDMM which is not eligible or intended for ASCT. This trial may provide insights into a possible new first-line treatment with improved efficacy in transplant ineligible NDMM.[75] In 2022, teclistamab was approved by the European Medicines Agency for adult RRMM patients, who have received ≥ 3 prior lines of therapy, and in the United States, teclistamab received the FDA approval for the treatment of RRMM with ≥ 4 prior lines of therapy.[13] Currently, the phase 2 DSMM-XX trial (NCT05695508) is evaluating teclistamab in combination with DRd with or without bortezomib as induction therapy followed by ASCT and teclistamab in combination with daratumumab and lenalidomide as posttransplant maintenance in NDMM.

Elranatamab (PF-06863135) is another BCMAxCD3 bsAb evaluated in the phase 1 MagnetisMM-1 trial (NCT03269136). A total of 58 RRMM patients received subcutaneous elranatamab as monotherapy ($n = 50$) or in combination with lenalidomide ($n = 4$) or pomalidomide ($n = 4$). CRS were reported in 48 (83%) patients (all $\leq$ grade 2). Hematological AEs included lymphopenia ($n = 37$, 64%; 12% grade 3, 52% grade 4), neutropenia ($n = 37$, 64%; 31% grade 3, 29% Grade 4), anemia ($n = 32$, 55%; 38% grade 3), injection site reaction ($n = 31$, 53%; all $\leq$ grade 2), and thrombocytopenia ($n = 30$, 52%; 14% grade 3, 17% grade 4). Among the 20 patients who received efficacious dosing (215–1000 μg/kg), the ORR was 70% (14/20) with $\geq$ CR rate of 30% (6/20). At the recommended phase 2 dose of 1000 μg/kg, the ORR was 83%.[76] In the phase 2 study MagnetisMM-3 (NCT04649359), elranatamab was administrated as single agent in patients with RRMM.[77] A total of 123 patients were included, and the ORR was 61.0%. In patients who received two to three prior lines of therapy ($n = 26$), the ORR was 73.1%, including 19.2% sCR, 26.9% CR, and 23.1% very good partial remission (VGPR). The most common $\geq$ grade 3 AEs were hematologic, and COVID-pneumonia showed the most common non-hematologic AE.[78]

Alnuctamab (also referred to as BMS-986349 or CC-93269), a humanized immunoglobulin G (IgG1) BCMAxCD3 bsAb with an asymmetric 2-arm, is characterized by bivalent binding to BCMA and monovalently binding to CD3ε in a 2 + 1 format.[79] In the most recent update of the first-in-human phase 1 study CC-93269-MM-001 (NCT03486067), 70 patients received alnuctamab intravenously and 39% of them achieved an objective response. The median DOR was 146.1 weeks in patients who reached a response with intravenous alnuctamab therapy. In addition, 47 patients were treated with CC-93269 subcutaneously in dose escalation (10 mg: $n = 6$; 15 mg: $n = 4$; 30 mg: $n = 6$; and 60 mg: $n = 3$) as well as in dose expansion (10 mg: $n = 19$; 30 mg: $n = 9$). The most common AE was CRS (53%) and all CRS events were $\leq$ grade 2. Grade 1 ICANS was reported in one patient. Subcutaneous CC-93269 exhibited an improved safety profile compared with intravenous application. This study is currently ongoing.[80]

REGN5458 (linvoseltamab) is a BCMAxCD3 bsAb been investigated in RRMM within the phase 1/2 LINKER-MM1 trial (NCT03761108). A total of 252 RRMM patients were enrolled and treated with linvoseltamab at 50 or 200 mg dose. The ORR was 64% in the 200-mg dose cohort ($n = 58$) and 50% at 50 mg ($n = 104$). The most common AEs at 200 mg were CRS 37%, fatigue 32%, and anemia 28% and at 50 mg were CRS 53%, fatigue 33%, and anemia 40%. ICANS $\geq$ grade 3 occurred in 2% patients ($n = 2$) in the 200-mg cohort and in 1% patients ($n = 1$) at 50 mg.[81]

TNB-383B (ABBV-383), a BCMAxCD3 bsAb with two BCMA binding domains, was evaluated in a phase 1 study (NCT03933735). In this study, 124 RRMM patients ($\geq$3 prior lines of therapy) received ABBV-383 intravenously in a dose escalation cohort (0.025–120 mg, $n = 73$) and a dose expansion cohort (60 mg, $n = 51$). The ORR was 57% of all evaluable patients ($n = 122$) including 29% of patients with CR or better. At the dose $\geq$ 40 mg, the ORR was 68%. The most common hematological AEs $\geq$ grade 3 were neutropenia (34%) and anemia (16%). The most common nonhematological AEs included CRS (57%) and fatigue (30%), and $\geq$ grade 3 CRS was observed in three (2%) patients.[82]

GPRC5DxCD3 Bispecific Antibodies

Talquetamab (JNJ-64407564) is the first bsAb-targeting GPRC5DxCD3 bsAb in MM.[83] In the phase 1 MonumenTAL-1 trial (NCT03399799), 232 patients with RRMM received subcutaneous talquetamab. Of note, patients previously treated with BCMA-directed therapies were eligible in this study. Overall, 30 and 44 patients received the recommended phase 2 doses of 405 μg/kg weekly and 800 μg/kg biweekly, respectively, and the ORR was similar in both patient cohorts (405 μg/kg weekly: 70%; 800 μg/kg biweekly: 64%). Likewise, the CRS rates were comparable in the both groups with 77% at 405 μg/kg weekly and 80% at 800 μg/kg biweekly. Of note, skin-related AEs (all grade 1/2) were found in a significant proportion of patients (405 μg/kg weekly: 67% including 57% nail disorders; 800 μg/kg biweekly: 70% including 27% nail disorders). Moreover, dysgeusia represented a frequent and relevant AE that might lead to weight loss in this study (405 μg/kg weekly: 63%; 800 μg/kg biweekly: 57%).[84,85] Currently, based on these results, a biologics license application has been submitted to the FDA for talquetamab for the treatment of RRMM. Further studies investigating talquetamab either as monotherapy (NCT04634552) or in combination with other anti-MM agents [eg, RedirecTT-1 (NCT04586426), MonumenTAL-2 (NCT05050097), MonumenTAL-3 (NCT05455320), TRIMM-2 (NCT04108195), and TRIMM-3 (NCT05338775)] are underway. Most recently, Cohen and Morillo[86] reported the first results from the RedirecTT-1 study (NCT04586426) with the combination teclistamab and talquetamab in RRMM. A total of 63 patients with RRMM pretreated with a median of five (range 1–11) therapy lines were enrolled in this trial, with the majority of the patients being penta-refractory

(40/63, 63%). Extramedullary disease (EMD) was observed in 43% (27/63) of the patients. The most common treatment-emergent AEs included CRS (81%; grade 3: 3%), neutropenia (76%; grade 3/4: 75%), and anemia (60%; grade 3/4: 43%), and one patient presented with ICANS. The ORR was 84% (52/62) and 73% (19/26) in the entire group and in patients with EMD, respectively. At the recommended phase 2 dose, the ORR was 92% (12/13) among all evaluable patients.[87]

RG6234 (also referred to as RO7425781 or forimtamig) is another GPRC5DxCD3 bsAb characterized by increased half-life with a silent Fc-region. In a phase 1 trial (NCT04557150), 41 RRMM patients received RG6234 at a dosing level of 0.006 to 10 mg. CRS occurred in 85.4% (grade 3: 2.4%, all others grade 1/2) of the patients and CNS toxicity (headache and confusion) was observed in 3 (7.3%) patients. Skin-related AEs and dysgeusia were observed in 66% and 36.6% of patients, respectively. The ORR was 68% among the 34 patients with evaluable response data, including 50% with VGPR or better.[88]

Importantly, compared with BCMAxCD3 bsAbs, GPRC5D-targeting bsAbs induces a much lower B-cell depletion and, subsequently, lower grade of hypogammaglobulinemia and infectious complications.[89,90]

FcRH5xCD3 Bispecific Antibodies

Cevostamab (BFCR4350 A) is an FcRH5xCD3 bsAb.[19] In the updated analysis of the phase 1 GO39775 trial (NCT03275103), 160 RRMM patients received intravenous cevostamab Q3W. Cevostamab was administered for a fixed duration of 17 cycles or until progression/unacceptable toxicity. CRS occurred in 128 (80.0%) patients (grade 3: 1.3%, all others grade 1/2), and CRS-associated ICANS was reported in 21 (13.1%) patients. Anemia and neutropenia were found in 51 (31.9%; $\geq$ grade 3: 21.9%) and 24 (15.0%%; $\geq$ grade 3: 13.8%) patients, respectively. In the 158 patients with evaluable efficacy data, response was observed at the 20- to 198-mg target dose levels, and higher target dose was associated with increased efficacy. The ORR was 54.5% and 36.7% at the 160 and 90 mg target dosing, respectively. Among the 16 patients who completed the 17 cycles, 8 of them showed a sustained response of $\geq$ 6 months after completion of therapy.[91–93]

CD38xCD3 Bispecific Antibodies

ISB1342 is the first humanized CD38xCD3 bsAb for MM. A phase 1 trial of ISB1342 in RRMM patients is still ongoing (NCT03309111). In the initial analysis, ISB1342 was given in 24 RRMM patients as infusion once weekly in 6 dose-escalation groups (range: 0.2/0.3–1.0/4.0 mg/kg). The most common AEs were infusion-related reactions (42%; grade 3: 16.7%), anemia (21%; grade 3: 4.2%), CRS (17%), thrombocytopenia (17%), diarrhea (13%), and lymphopenia (8.4%, all $\geq$ grade 3). Efficacy analysis is still pending.[94]

CD19xCD3 Bispecific Antibody

Blinatumomab is a humanized CD19xCD3 bsAb mainly used in the treatment of non-Hodgkin's lymphoma and ALL.[95] Blinatumomab was investigated in a pilot study (NCT03173430) in combination with salvage ASCT in RRMM. This study was terminated in 2020 due to slow accrual.

POTENTIAL RESISTANCE MECHANISMS

Although the results of recent clinical trials have demonstrated promising efficacy of bsAbs in RRMM, there are still patients who do not respond to the therapy or suffer

from relapse in the course of the disease. However, the resistance mechanism of bsAbs in RRMM is poorly understood and has yet to be further explored. So far, the following factors have been reported to be associated with bsAb resistance in RRMM: loss of antigen, T-cell exhaustion, lack of recruitment or priming of T-cells, and immunosuppressive bone marrow microenvironment.[96]

The stable presence of the target antigens is a prerequisite for a successful bsAb therapy.[26] To date, the loss of antigen has already been reported to be a tumor intrinsic resistance mechanism in CAR T-cell and bsAb therapy for different hematologic malignancies. Homozygous BCMA loss was reported as a tumor intrinsic resistance mechanism in MM patients treated with BCMA-directed CAR T-cell therapy.[97,98] In bsAbs, CD20 negative relapse was found in B-cell non-Hodgkin lymphoma patients treated with CD20xCD3 bsAb REGN1979.[99,100] In MM patients treated with BCMAxCD3 and GPRC5DxCD3 bsAbs, the underlying mechanism of antigen loss has been further elucidated using genomic diagnostics such as whole genome sequencing and single-cell RNA sequencing. The expression level of target antigen was an important determinant of response in GPRC5DxCD3 bsAb therapy JNJ-7564, and bone marrow samples with higher GPRC5D expression showed superior MM cell lysis compared with those with lower GPRC5D expression.[101] More recently, Truger and colleagues[102] found biallelic BCMA gene deletion in a patient who received BCMAxCD3 bsAb AMG420, and this patient did not respond to anti-BCMA antibody drug conjugate belantamab mafodotin. Similarly, Lee and colleagues[103] reported a patient with biallelic BCMA gene deletion at the time point of disease progression after BCMAxCD3 bsAb therapy, and clonal biallelic GPRC5D loss following GPRC5DxCD3 bsAb was detected in another patient with preexisting monoallelic GPRC5D loss in 79.2% of the cells before bsAb therapy. Moreover, monoallelic BCMA loss coupled with de novo BCMA extracellular domain point mutation c.81 G greater than C [p.(R27P)] was identified as resistance mechanism in a patient progressing after BCMAxCD3 bsAb.[104] These findings suggested that irreversible complete antigen (eg, BCMA and GPRC5D) loss caused by deletion and/or mutation of the gene encoding for the target antigen may appear after bsAb therapy in MM patients, possibly due to the high selection pressure by bsAb that may lead to expansion of a preexisting small subclone without target antigen expression before bsAb treatment.[26] Importantly, in the study of Truger and colleagues, monoallelic BCMA and GPRC5D deletions were detected in 8% and 15% of MM patients being T-cell immunotherapy naïve, respectively, and these patients may have an increased risk to develop biallelic BCMA and GPRC5D loss after T-cell-based immunotherapies such as CAR T-cells or bsAb. However, gain of FcRH5 and SLAMF7 genes (both located in chromosome 1q) were significantly enriched in RRMM compared with NDMM, suggesting a low risk of FcRH5 and SLAMF7 loss in the course of the disease.[26,102] Taken together, irreversible complete antigen loss resulted by deletion and/or mutation represents a potential resistance mechanism to bsAb therapy in MM, and the selection of a drug targeting the "most suitable" antigen by genetic/genomic analysis is a crucial step for a successful treatment.

In bsAb therapies, the patients' own T cells are activated after establishing an immune synapse between MM and T cells, leading to cytokine release and tumor elimination. Therefore, the functionality of the patient's T cells may be an important factor that correlates with the therapy outcome. Leblay and colleagues[105] reported that MM patients responding to CAR T cells or bsAb therapy displayed a higher CD4/CD8 ratio and higher proportions of memory like T cells (T memory stem cells [Tscm] and central memory T cells) in comparison to patients resistant to T-cell-based immunotherapies. Moreover, these resistant patients likewise showed increased numbers/percentages of terminally exhausted T cells and senescent cells with upregulated

expression of certain T-cell checkpoint molecules such as LAG3, TIGIT, and PD1. In addition, decreased anti-MM effect of JNJ-7564, a GPRC5DxCD3 bsAb, was found in elderly patients (>67 years) with low T-cell counts and thus low effector/target ratios (E:T), and in patients with high frequency of PD1+ T cells, MHC class II cell surface receptor (HLA-DR)+ activated T cells or immunosuppressive regulatory T cells as well as bone marrow stromal cells.[101] Recently, Neri and colleagues reported that CD8+ T cells were preferentially expanded by bsAb, and CD8+ naïve and memory T cells were enriched in responders to BCMAxCD3 bsAb therapy, while increased numbers/percentages of exhausted T cells, for example, granzyme K (GZMK)+ CD8+ T cells were found in resistant patients. In general, the current application schedule of bsAbs, mainly weekly or biweekly until progression, is probably not the ideal mode of application, leading to T-cell exhaustion with reduced antitumor efficacy and a considerable risk of severe infections. In RR B-ALL patients, 28-day continuous blinatumomab infusion resulted in reduced T-cell function. In an in vitro model with the CD19xCD3 bsAb AMG562, treatment-free intervals led to strong functional reinvigoration of T cells and transcriptional reprogramming. Importantly, treatment-free intervals improved T-cell expansion and tumor control in vivo.[106] In RRMM treated with teclistamab, patients showed sustained response after the switch from weekly to a less frequent biweekly dosing schedule, with a median DOR of 20.5 (range 1–23) months since switch.[107] Altogether, a fixed duration of administration of bsAbs and treatment-free intervals may significantly reduce infectious complications without interfering with antitumor efficacy.

Furthermore, the expression of major histocompatibility complex (MHC) class I on MM cells could support the cell–cell interaction between CD8+ T cells and MM cells, leading to amplified T-cell response and may be epitope spreading and thus priming/induction of a neo-antigen-specific T-cell response. On the other hand, the loss of MHC receptor molecules was described as a bsAb-induced adaption, which might result in immune escape and resistance to bsAbs.[108,109]

Combination therapy is a strategy to enhance the efficacy of bsAbs in RRMM by modulating the immune microenvironment. For instance, IMiD and BCMAxCD3 bsAb AMG701 acted synergistically and could overcome the immunosuppressive microenvironment associated with the presence of bone marrow stromal cells and osteoclasts that contribute to MM cell proliferation and drug resistance. Moreover, IMiD enhanced AMG701 efficacy by inducing T-cell differentiation to memory phenotypes, reducing immunosuppressive regulatory T cells and increasing CD8/CD4 ratios and percentages of Tscm.[110] Similarly, in vivo, BCMAxCD3 bsAb demonstrated only limited anti-MM effect in mice with high tumor burden, and concurrent administration of pomalidomide could increase T-cell response even in IMiD resistant cases, but induced T-cell exhaustion and, in turn, resulted in rapid progression thereafter. In contrast, by the addition of cyclophosphamide, T-cell exhaustion could be lessened, and durable remission was induced by reducing tumor burden as well as depleting regulatory T cells in vivo.[111] On the other hand, the triple combination with anti-PD1 checkpoint inhibitor in addition to bsAb and IMiD showed sustained activation and expansion of non-exhausted effector T cell at tumor sites probably by IL-2 production.[112]

SUMMARY AND OUTLOOK

The treatment of MM is evolving dramatically. Novel immunotherapies, that is, CAR T cells and bsAb, are leading to a paradigm shift of the MM treatment. When compared with CAR T-cell therapies, bsAb tends to show lower grade toxicity, which is limited to the first few weeks of administration. Thus, bsAb can be administrated in

outpatient setting after the first doses with hospitalization. On the other hand, the ORR, CR rates, and PFS of bsAb therapies are lower and shorter when compared with most of the CAR T-cell products.[113] In brief, although bsAb therapies have shown promising efficacy and acceptable safety profile, these novel agents are still in their "infancy" with multiple unaddressed issues. For instance, the mechanisms of toxicities, including CRS, ICANS, and prolonged cytopenia following bsAb therapies, remain poorly understood. Moreover, most of the MM patients treated with bsAbs suffer from relapse in the course of the disease, and the multiple resistance mechanisms have to be addressed to further improve their efficacy. BsAb containing combination regimens have been described in in vitro and in vivo models and are currently entering clinical trials.

CLINICS CARE POINTS

- Severe cytokine release syndrome and neurotoxicity are observed only in a minority of patients receiving bispecific antibodies, but cytopenias and especially severe infections (up to 40% of treated patients) are frequently observed.
- Modifications of the current treatment schedules, for example, combination regimens and fixed therapy duration or longer treatment-free intervals, are currently tested in clinical trials to improve efficacy and reduce infectious complications
- Bispecific antibodies are increasingly used in earlier lines of therapy (as induction or consolidation or maintenance) as well as in combination regimens to further increase the anti-myeloma efficacy

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