Antibody Treatment in Multiple Myeloma

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Abstract: Antibody therapy, which has become a critical option in the treatment of multiple myeloma (MM), includes monoclonal antibodies, antibody-drug conjugates, and bispecific antibodies. Anti-CD38 and anti-SLAMF7 monoclonal antibodies were the first to enter the MM portfolio as treatment options for relapsed/refractory MM. More recently, daratumumab has become important in the treatment of newly diagnosed MM, and a subcutaneous formulation has been approved. BCMA-targeted antibody-drug conjugates and bispecific antibodies, which are the newest antibody therapies to be investigated, provide additional therapeutic options for patients with heavily pretreated MM. This article reviews how antibody therapy has influenced the treatment of MM, describes the unique adverse event profiles of each relevant drug class, and explains how to incorporate antibody therapy into practice.

Introduction

Significant advancements in the treatment of multiple myeloma (MM) have occurred over the last decade, with the US Food and Drug Administration (FDA) approving 9 new agents during this period. Of these 9 new antimyeloma drugs, 4 are antibody therapies, which have transformed the long-term outcomes and expectations of patients with myeloma.[1] Antibody therapy encompasses a wide variety of treatments, including monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), bispecific antibodies, and supportive care. In this article, we review how antibody therapy has altered the treatment landscape of MM, describe unique adverse events these agents have caused, and provide our institutional experience of using them in practice.

Sources of Data

Primary studies and review articles were identified through a literature search of the PubMed and MEDLINE databases (1964-August 2020). Key search terms included *multiple myeloma*, *monoclonal antibody*, *antibody-drug conjugate*, and *bispecific antibody*. Data pending

further publication were accessed through the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH). Additional resources included the National Comprehensive Cancer Network, product labeling, news releases, and ClinicalTrials.gov.

Anti-CD38 Monoclonal Antibodies

CD38 is a transmembrane glycoprotein expressed on lymphoid and myeloma cells; it acts as a receptor for the transduction of activation signals and serves as an ectoenzyme that catalyzes the production of nucleotides involved in calcium signaling.[2] CD38 is an excellent therapeutic target in myeloma because it is expressed with relatively high surface density on abnormal plasma cells, whereas expression is lower on normal myeloid and lymphoid cells.[3,4] Anti-CD38 antibodies induce cell death through multiple mechanisms that include the following: antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity, induction of apoptosis, and modulation of CD38 enzyme activity.[5-7]

Daratumumab (Darzalex, Janssen Biotech) is a first-in-class human immunoglobulin G1 kappa (IgG1κ) CD38-directed mAb that was approved for the treatment of MM on the basis of results of the phase 2 SIRIUS trial.[8] The initial FDA approval was for use as a single agent in the treatment of relapsed/refractory MM (RRMM) in patients with 3 or more prior lines of therapy. Since this first approval, daratumumab has been approved in combination with lenalidomide (Revlimid, Celgene)/dexamethasone (DaraRd)[9,10] and with bortezomib (Velcade, Millennium/Takeda Oncology)/dexamethasone (DaraVd)[11,12] in patients with at least 1 prior therapy; in combination with pomalidomide (Pomalyst, Celgene)/dexamethasone (DaraPd)[13] in patients with at least 2 prior therapies, including a proteasome inhibitor (PI) and lenalidomide; and in combination with carfilzomib (Kyprolis, Onyx)/dexamethasone (DaraKd)[14] in patients with at least 1 prior line of therapy (Table 1).

A single-center retrospective review reported an overall response rate (ORR) of 91.7% in patients treated with DaraPd who were daratumumab- and pomalidomide-naive. After a median follow-up of 41 months, the median progression-free survival (PFS) was not reached in this cohort of patients, which highlights the deep and durable responses achieved with DaraPd in first relapse.[15] Most recently, results from the APOLLO trial were presented in December 2020 as part of the 62nd ASH Annual Meeting and Exposition. This phase 3 trial randomly assigned 304 patients with RRRM and 1 or more prior lines of therapy, including lenalidomide and a PI, to DaraPd or Pd alone. After a median follow-up of 16.9

months, the median PFS was 12.4 months with DPd vs 6.9 months with Pd.[16] The combination to gain approval most recently is DaraKd, which was studied in the phase 3 CANDOR trial in patients who had received 1 to 3 prior lines of therapy. After a median follow-up of 16.9 months for the DaraKd group and 16.3 months for the Kd group, the median PFS was not reached for DaraKd vs 15.8 months for Kd (hazard ratio [HR], 0.63; 95% CI, 0.46-0.85; P=.0014).[14,17] Combination therapy is preferred over single-agent therapy for RRMM and can be selected according to patient-specific disease factors and tolerability. Because disease progresses on lenalidomide maintenance in the majority of patients, our practice is to utilize DaraPd in first relapse. DaraKd is a suitable option for patients whose disease is refractory to or who cannot tolerate bortezomib, whose disease is refractory to lenalidomide, or who have a contraindication to another immunomodulatory drug (IMiD).

With the success of daratumumab for RRMM, studies of the agent were begun for newly diagnosed MM (NDMM), and it is currently FDA-approved in combination with Rd (DaraRd),[18] with bortezomib/thalidomide/dexamethasone (DaraVTD),[19] and with bortezomib/melphalan/prednisone (DaraVMP)[20] (Table 1). The randomized, phase 3 CASSIOPEIA trial investigated DaraVTD vs VTD in transplant-eligible patients with newly diagnosed disease. At day 100 after autologous stem cell transplant (ASCT), a stringent complete response (sCR) was achieved in 29% of the DaraVTD group vs 20% of the VTD group (P=.0010), and the rates of minimal residual disease (MRD) negativity (10^{-5}) were 64% and 44%, respectively (P<.0001).[19] The addition of daratumumab to the standard induction regimen in the United States, which consists of lenalidomide/bortezomib/dexamethasone (RVD), was investigated in the phase 2, randomized, open-label GRIFFIN study, which compared DaraRVD with RVD in transplant-eligible patients with newly diagnosed disease. The sCR rate at the end of post-ASCT consolidation was 42.4% with DaraRVD compared with 32.0% with RVD (odds ratio [OR], 1.57; 95% CI, 0.87-2.82; 1-sided P=.068). After a median follow-up of 22.1 months, sCR rates improved to 62.6% with DaraRVD and 45.4% with RVD, suggesting that responses continue to deepen over time. MRD negativity (10^{-5}) rates were also improved with DaraRVD vs RVD, at 51.0% vs 20.4%, respectively (P<.0001).[21] In both CASSIOPEIA and GRIFFIN, the addition of daratumumab did not affect the ability to collect stem cells before ASCT. Notably, cyclophosphamide mobilization was utilized in CASSIOPEIA, whereas filgrastim alone was used in GRIFFIN for the initial attempt.[19,21] On the basis of the improved response rates obtained by incorporating daratumumab in the induction setting, it has become our

Table 1. Daratumumab-Based Regimens for the Treatment of Myeloma

Study Name	Combination Therapy	Median Follow-up, mo	Median PFS, mo	ORR	≥VGPR	SAEs (Grades 3/4)
Relapsed/refractory MM						
SIRIUS[8]	Daratumumab (n=106)	9.3	3.7	31%	12%	Anemia (24%), thrombocytopenia (19%), neutropenia (12%), fatigue (3%)
POLLUX[9,10]	DaraRd (n=286) vs Rd (n=283)	44.3	44.5 vs 17.5	92.9% vs 76.4%	75.8% vs 44.2%	Neutropenia (51.9% vs 37.0%), anemia (12.4% vs 19.6%), thrombocytopenia (12.7% vs 13.5%), diarrhea (5.3% vs 3.2%), pneumonia (7.8% vs 8.2%)
CASTOR[11,12]	DaraVd (n=251) vs Vd (n=247)	40.0	16.7 vs 7.1	82.9% vs 63.2%	59.2% vs 29.1%	Thrombocytopenia (45.3% vs 32.9%), anemia (14.4% vs 16.0%), neutropenia (12.8% vs 4.2%), neuropathy (4.5% vs 6.8%), pneumonia (8.2% vs 9.7%)
Phase 1b[13]	DaraPd (n=103)	13.1	8.8	60%	42%	Neutropenia (77%), anemia (28%), thrombocytopenia (19%), fatigue (12%), dyspnea (8%), back pain (6%)
APOLLO[16]	DaraPd (n=151) vs Pd (n=153)	16.9	12.4 vs 6.9	–	51.0% vs 19.6%	Neutropenia (68% vs 51%), leukopenia (17% vs 5%), lymphopenia (12% vs 3%), febrile neutropenia (9% vs 3%), pneumonia (13% vs 7%)
CANDOR[14,17]	DaraKd (n=312) vs Kd (n=154)	17	NR vs 15.8	84% vs 75%	–	Serious AEs (56.2% vs 45.8%), grade ≥3 cardiac failure (3.9% vs 8.5%)
Newly diagnosed MM						
MAIA[18]	DaraRd (n=368) vs Rd (n=369)	28	NR vs 31.9	92.9% vs 81.3%	79.3% vs 53.1%	Neutropenia (50% vs 35.3%), anemia (11.8% vs 19.7%), infections (32.1% vs 23.3%), pneumonia (13.7% vs 7.9%)
CASSIOPEIA[19]	DaraVTD (n=543) vs VTD (n=542)	Cutoff June 19, 2018	NR vs NR	92.6% vs 89.9%	83% vs 78%	Neutropenia (28% vs 15%), lymphopenia (17% vs 10%), stomatitis (13% vs 16%), thrombocytopenia (11% vs 7%), neuropathy (9% vs 9%)
ALCYONE[20]	DaraVMP (n=350) vs VMP (n=356)	40.1	36.4 vs 19.3	90.9% vs 73.9%	73% vs 50%	Neutropenia (39.9% vs 38.7%), thrombocytopenia (34.4% vs 37.6%), infections (23.1% vs 14.7%), anemia (15.9% vs 19.8%), pneumonia (11.3% vs 4%)
GRIFFIN[21]	DaraRVD (n=104) vs RVD (n=103)	22.1	NR vs NR	99.0% vs 92.9%	96.0% vs 79.5%	Neutropenia (41.1% vs 24.6%), lymphopenia (23.2% vs 21.6%), thrombocytopenia (16.2% vs 8.8%), anemia (9.1% vs 5.9%), fatigue (6.1% vs 5.9%)

DaraKd, daratumumab, carfilzomib, and dexamethasone; DaraPd, daratumumab, pomalidomide, and dexamethasone; DaraRd, daratumumab, lenalidomide, and dexamethasone; DaraRVD, daratumumab, lenalidomide, bortezomib, and dexamethasone; DaraVd, daratumumab, bortezomib, and dexamethasone; DaraVMP, daratumumab, bortezomib, melphalan, and prednisone; DaraVTD, daratumumab, bortezomib, thalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; mo, months; NR, not reached; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; RVD, lenalidomide, bortezomib, and dexamethasone; SAE, significant adverse event; Vd, bortezomib and dexamethasone; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VTD, bortezomib, thalidomide, and dexamethasone.

practice to utilize a quadruplet-based regimen for patients with standard-risk NDMM.

Monoclonal antibodies may require lengthy infusions, and infusion-related reactions are a common adverse event.[22,23] Daratumumab formulated with hyaluronidase-fihj (Darzalex Faspro, Janssen) was recently approved by the FDA in various combinations for the treatment of both NDMM and RRMM. The randomized, phase 3 COLUMBA trial compared this subcutaneous formulation of daratumumab (SC Dara; n=263) with standard intravenous daratumumab (IV Dara; n=259) in patients with RRMM who had received at least 3 prior lines of therapy. SC Dara was administered as a flat dose of 1800 mg over a 3- to 5-minute subcutaneous push weekly for cycles 1 to 2, then every 2 weeks for cycles 3 to 6, then monthly for cycles 7 and beyond. IV Dara was administered intravenously at the standard 16-mg/kg dose at the same frequency. At a median follow-up of 7.5 months, the ORR was 41% with SC Dara vs 37% with IV Dara. The maximum trough concentration was 593 μg/mL with SC Dara vs 522 μg/mL with IV Dara, and the rates of all-grade infusion-related reactions were 13% vs 34%, respectively.[24] With this approval, it is likely that all daratumumab-based regimens will be switched to the SC Dara formulation, with patient preference and unique clinical scenarios being the few outliers to continue IV Dara. Our institution has chosen to implement a 3.5-hour observation period after cycle 1, day 1 with SC Dara on the basis of median time to infusion-related reaction in the COLUMBA trial. No observation period was implemented for subsequent doses or for patients being switched from IV Dara.

Isatuximab-irfc (Sarclisa, Sanofi Genzyme), the newest CD38 mAb, binds to a different epitope on the human cell surface antigen CD38. It has received FDA approval for the treatment of RRMM in combination with pomalidomide and dexamethasone (IsaPd) in patients with at least 2 prior therapies, including lenalidomide and a PI. IsaPd was compared with Pd in patients with RRMM in the randomized, phase 3 ICARIA-MM study. After a median follow-up of 11.6 months, median PFS was 11.5 months with IsaPd vs 6.5 months with Pd alone (HR, 0.593; 95% CI, 0.44-0.81; P=.001) (Table 2).[25] Isatuximab is dosed intravenously at 10 mg/kg weekly for cycle 1, then every other week for cycles 2 and beyond. Because the ICARIA-MM trial excluded patients with prior exposure to a CD38 mAb, it is currently unknown if isatuximab can be used in patients after daratumumab or vice versa. Additionally, the phase 3 IKEMA trial randomly assigned patients with RRMM and 1 to 3 prior lines of therapy to isatuximab plus carfilzomib/dexamethasone (IsaKd; n=179) vs Kd alone (n=123). The carfilzomib was dosed twice weekly for 3 of 4 weeks, and isatuximab

was dosed once weekly for 4 weeks, then every 2 weeks thereafter. An interim analysis recently illustrated that after a median follow-up of 20.7 months, the median PFS was not reached for IsaKd vs 19.15 months for Kd (HR, 0.531; 95% CI, 0.318-0.889; 1-sided P=.0007).[26] As in the CANDOR population previously discussed, IsaKd could be considered for patients with MM refractory to bortezomib and lenalidomide who are in first relapse, with the twice-weekly dosing frequency of carfilzomib a possible limitation for some patients. Isatuximab monotherapy has been investigated as monotherapy,[27] in combination with dexamethasone (IsaD),[27] and in combination with lenalidomide and dexamethasone (IsaRd)[28] in phase 1 and 2 studies (Table 2). Owing to the continued every-other-week dosing and the approval of SC Dara, our current approach is still to use DaraPd in first relapse.

Anti-CD38 mAbs have become a backbone in the treatment of newly diagnosed and relapsed MM; combination therapies have produced deep and durable responses without adding a significant adverse effect burden. Modified anti-CD38 mAbs, such as TAK-573, an anti-CD38 mAb attenuated with interferon alfa (IFN-α), and TAK-079, a laboratory-generated, high-affinity antibody, are also currently undergoing investigation for RRMM.[29,30] Hepatitis B reactivation can occur during anti-CD38 therapy, so hepatitis B serologies should be checked before it is started, and proper prophylaxis should be initiated if indicated. Anti-CD38 mAbs also can interfere with serologic testing, so a type and screen must be drawn before administration.[1]

Anti-SLAMF7 Monoclonal Antibody

Elotuzumab (Empliciti, Bristol Myers Squibb) is an immunostimulatory antibody that directly targets SLAM family member 7 (SLAMF7), also known as cell-surface glycoprotein CD2 subset 1 (CS1). Because the glycoprotein CS1 is found in abundance on myeloma cells and is expressed at low levels on most immune cells, including natural killer (NK) cells, the selective destruction of myeloma cells is possible with minimal effects on healthy tissues.[31] Elotuzumab has a dual mechanism of action that includes the direct activation of NK cells and antibody-dependent cytotoxicity via the CD16 pathway. In addition to its immune properties, elotuzumab prevents the adhesion of myeloma cells to bone marrow stromal cells.[32]

Elotuzumab is an ineffective treatment for myeloma when used as a single agent, but durable treatment responses have been achieved when it is paired with an IMiD. Currently, elotuzumab is approved for the treatment of relapsed myeloma when paired with lenalidomide or pomalidomide and dexamethasone (Table 2).

Table 2. Combination Therapy With Elotuzumab- and Isatuximab-Based Therapies for Myeloma

Study Name	Combination Therapy	Median Follow-up, mo	Median PFS, mo	ORR	≥VGPR	SAEs (Grades 3/4)
ICARIA-MM[25]	IsaPd (n=154) vs Pd (n=153)	11.6	11.5 vs 6.5	60% vs 35%	32% vs 9%	Infusion reactions (38% vs 0%), upper respiratory tract infections (28% vs 17%), diarrhea (26% vs 20%)
IKEMA[26]	IsaKd (n=179) vs Kd (n=123)	20.7	NR vs 19.15	86.6% vs 82.9%	72.6% vs 56.1%	Respiratory infections (32.2% vs 23.8%), cardiac failure (4.0% vs 4.1%), thrombocytopenia (29.9% vs 23.8%), neutropenia (19.2% vs 7.4%)
Phase 2[27]	Isatuximab vs IsaD	–	4.8 vs 7.9	26% vs 44%	–	–
Phase 1b: isatuximab, lenalidomide, and dexamethasone[28]	IsaRd (N=57)	9	8.5	51%	36.5%	Neutropenia (60%), leukopenia (53%), thrombocytopenia (38%), anemia (25%), pneumonia (9%), fatigue (7%)
ELOQUENT-2[33,34]	EloRd (n=321) vs Rd (n=325)	48	19.4 vs 14.9	79% vs 66%	35% vs 29%	Lymphocytopenia (77% vs 49%), anemia (19% vs 21%), thrombocytopenia (19% vs 20%), neutropenia (34% vs 44%), fatigue (8% vs 8%), diarrhea (5% vs 4%), back pain (5% vs 4%)
ELOQUENT-3[35]	EloPd (n=60) vs Pd (n=57)	9.1	10.3 vs 4.7	53% vs 26%	20% vs 9%	Anemia (10% vs 20%), neutropenia (13% vs 27%), thrombocytopenia (8% vs 5%), infections (13% vs 22%), cardiac disorders (7% vs 4%), hyperglycemia (8% vs 7%), dyspnea (3% vs 2%)

EloPd, elotuzumab, pomalidomide, and dexamethasone; EloRd, elotuzumab, lenalidomide, and dexamethasone; IsaD, isatuximab and dexamethasone; IsaKd, isatuximab, carfilzomib, and dexamethasone; IsaPd, isatuximab, pomalidomide, and dexamethasone; IsaRd, isatuximab, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; mo, months; NR, not reached; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; Rd, lenalidomide and dexamethasone; SAEs, significant adverse events; VGPR, very good partial response

The approvals for these 2 treatment regimens were based on data from the ELOQUENT-2 and ELOQUENT-3 clinical trials. The randomized, phase 3 ELOQUENT-2 trial evaluated the safety and efficacy of elotuzumab plus lenalidomide and dexamethasone (EloRd) vs that of lenalidomide and dexamethasone (Rd) alone. The median PFS in patients receiving EloRd was 19.4 months, which was 5.5 months longer than that of patients receiving Rd (14.9 months).[33] Furthermore, treatment with EloRd reduced the risk for disease progression or death by 30%, and both the safety and efficacy of this regimen were sustained over an extended follow-up period of 5 years.[34]

The results from the phase 2, randomized, open-label ELOQUENT-3 trial indicated that elotuzumab in combination with pomalidomide and dexamethasone (EloPd) improves PFS in patients with disease refractory to lenalidomide and a PI. In this study, EloPd extended patients' time to disease progression by 46%, and the ORR with EloPd was increased vs the ORR with pomalidomide and dexamethasone (Pd) alone (53% vs 26%, respectively). Results also showed that EloPd doubled the median PFS compared with Pd alone, at 10.25 vs 4.67 months, respectively.[35] It is worth noting that the improved PFS was demonstrated across all subgroups, including patients with high-risk disease, making EloPd an attractive regimen for our patients with relapsed myeloma.

The treatment landscape for RRMM includes various triplet-based regimens, and sometimes quadruplet-based regimens. When selecting patients for an elotuzumab-based therapy, we have to consider their prior lines of treatment. The rate of EloRd use in RRMM is often low because the majority of patients will have

had disease progression on maintenance lenalidomide. Therefore, the ideal population in which EloRd treatment can be considered consists of patients with disease progression who have not previously received maintenance therapy. Secondly, one could consider adding elotuzumab and dexamethasone to lenalidomide if the relapse is indolent, although no data are currently available to support this approach. At first relapse, EloPd is a treatment option based on clinical guidance; however, our current approach is to use DaraPd because of clinical trial data showing rapid, deep, and durable treatment responses with this combination.[23]

Elotuzumab was also investigated in a randomized phase 2 study that compared induction with elotuzumab/RVD (EloRVD) vs RVD alone for patients with high-risk NDMM; however, this trial failed to show an improvement in PFS and overall survival (OS) with the addition of an mAb. After a median follow-up of 53 months, the median PFS was 31 months with EloRVD vs 34 months with RVD (P=.449). Similarly, median OS was 68 months with EloRVD vs not reached with RVD (P=.239).[36] Further research is needed to evaluate the efficacy of elotuzumab in combination with other agents.

B-Cell Maturation Antigen Target

B-cell maturation antigen (BCMA), a receptor found ubiquitously on myeloma cells but rarely expressed on healthy naive and memory B cells, is required for the survival of malignant plasma cells.[37] Thus, BCMA is a highly selective and favorable target for immune-based therapy. Further, BCMA on MM cells is associated with an immunosuppressive bone marrow microenvironment, and increased levels of soluble BCMA (sBCMA) are associated with disease progression and worse outcomes.[38]

Anti-BCMA Monoclonal Antibody-Drug Conjugate: Balantamab Mafodotin

Belantamab mafodotin (Blenrep, GlaxoSmithKline) is an anti-BCMA monoclonal ADC that was recently approved for the treatment of patients with RRMM who have received at least 4 prior therapies, including a CD38 monoclonal antibody, a PI, and an IMiD. The antibody component of belantamab mafodotin binds to BCMA and is then internalized by myeloma cells; then, release of a microtubule-disrupting agent called monomethyl auristatin F (MMAF) leads to destruction of the myeloma cells via cellular apoptosis, cell cycle arrest, and antibody-dependent cell-mediated cytotoxicity.[39]

DREAMM-1 was a first-in-human, open-label study of belantamab mafodotin (formerly GSK2857916) that assessed its safety and pharmacokinetics in patients with RRMM and provided preliminary clinical data. The study included a dose escalation and an expansion phase; in the latter, the recommended phase 2 dosing of 3.4 mg/kg was used. Interim analyses revealed an ORR of 60% and a PFS of 7.9 months. Corneal toxicity and thrombocytopenia were the most commonly reported adverse events. After 14 months of follow-up, the ORR was sustained at 60% but the PFS was extended to 12 months, and a very good partial response (VGPR) or better was achieved in 54% of patients.[40] In addition, no new safety events were identified during the extended follow-up period. Overall, the results showed that GSK2857916 could achieve both deep and durable treatment responses in a heavily pretreated patient population.

The successes of the DREAMM-1 study subsequently led to the pivotal DREAMM-2 study. This was an open-label, randomized trial examining 2 doses of belantamab mafodotin: 3.4 mg/kg vs 2.5 mg/kg given intravenously once every 3 weeks. Compared with the patients enrolled in DREAMM-1, those enrolled in DREAMM-2 had overall more aggressive disease and poorer performance status, and they had received a greater number of prior of lines of therapy. Efficacy results in the lower-dose cohort were similar to those in the higher-dose cohort; ORRs were 31% vs 34%, respectively. The most common grade 3 or higher adverse events were keratopathy (27%), thrombocytopenia (20%), and anemia (20%).[41] The safety and tolerability of belantamab mafodotin in this study were consistent with previously reported data; however, the safety profile in the 2.5-mg/kg cohort was more favorable, including a smaller overall incidence of serious adverse events, thrombocytopenia, neutropenia, and adverse events leading to dose delay or dose reductions. The 2.5-mg/kg dose is now the FDA-approved dosing strategy. Keratopathy refers to microcyst-like epithelial changes observed during an eye examination; it can present with or without symptoms such as blurry vision or dry eyes. A Risk Evaluation and Mitigation Strategy (REMS) program was established along with the approval of this medication to ensure completion of an ophthalmic examination before every dose; therefore, close collaboration between oncologists and ophthalmologists is needed.[42]

The corneal adverse reactions associated with belantamab mafodotin are a known class effect of ADCs that contain a microtubule inhibitor payload, but they do not appear to be permanent sequelae. The proposed mechanism of toxicity is related to the nonspecific uptake of belantamab mafodotin into the basal corneal epithelial cells, which leads to release of the payload Cys-mcMMAF and apoptosis.[43,44] This toxicity should be evaluated by an eye care professional, who should assess both the corneal examination findings and changes in best-corrected visual acuity (BCVA).[42] The ocular adverse events and corneal findings associated with belantamab mafodotin have been

previously described.[45,46] Notably, in the DREAMM-2 study, only 1 patient (1%) in the 2.5-mg/kg cohort (n=95) had to discontinue therapy permanently owing to keratopathy. More commonly, keratopathy led to dose reductions (23%) or dose delays (47%). The dose delays secondary to keratopathy started at week 4 and the dose reductions started at week 13 for patients in the 2.5-mg/kg cohort, with a median time to re-initiation of treatment of 83 days (range, 28-146).[41] Patients should be instructed to apply 1 to 2 drops of preservative-free artificial tears in each eye at least 4 times daily starting with the first infusion and to avoid contact lenses. Corticosteroid eye drops are no longer being recommended because they did not demonstrate benefit in DREAMM-2. Dose reductions and dose delay recommendations are provided per the Keratopathy and Visual Acuity (KVA) scale found on the belantamab mafodotin prescribing information. These strategies are the primary management recommendations for ocular toxicity.[42] The approval of belantamab mafodotin as monotherapy in the treatment of RRMM is revolutionary because we have limited treatment options other than chemotherapy and clinical trials for this patient population with highly refractory disease. The question now becomes, what clinical benefit can be achieved by combining belantamab mafodotin with other agents, and will doing that in turn alter its line in therapy? Several clinical trials seeking to answer this question are ongoing.

BCMA Bispecific Antibodies

Bispecific antibodies (BiAbs) are the latest mAbs to enter the MM treatment landscape. BiAbs engage both CD3+ T cells and a tumor-associated antigen (eg, CD19, CD33, or BCMA), which ultimately results in cancer cell death and T-cell proliferation.[47] Although not yet approved for the treatment of MM, BCMA BiAbs are emerging as promising therapeutic options in early clinical studies.

AMG420 was the first anti-BCMA bispecific T-cell engager (BiTE) to demonstrate activity in MM. Like other first-generation BiTEs, AMG420 has a short half-life, so that the administration of an extended, continuous infusion is required. The first-in-human, phase 1 study evaluated various doses of AMG420, which was administered according to a 4-weeks-on, 2-weeks-off schedule for up to 10 planned cycles, or until disease progression or intolerability (Table 3).[48] AMG420 was used to treat 42 patients with a median of 5 prior lines of therapy. The median exposure was 1 cycle (range, 1-10 cycles); however, responders received a median of 7 cycles (range, 1-10 cycles), and the median duration of response was 8.4 months. The ORR was 31% (95% CI, 17.6-47.1) across all doses and was 70% (95% CI, 34.8-93.3) at the 400-μg/d dose, which was determined to be the maximum tolerated dose (MTD). Grade 2 to 4 cytokine

Table 3. Bispecific Antibodies

Agent	Current Stage of Development
BCMA/CD3 Target	
AMG420[48]	Phase 1b (NCT03836053)
AMG701[49]	Phase 1/2 (NCT03287908)
CC-93269[50]	Phase 1 (NCT03486067)
REGN5458[51]	Phase 1/2 (NCT03761108)
REGN54[59]	Phase 1/2 (NCT04083534)
Teclistamab[52]	Phase 1 (NCT0314518) Phase 2 (NCT04557098)
PF-06801591	Phase 1 (NCT03269136)
TNB-383B	Phase 1 (NCT03933735)
CD38/CD3	
ISB 1342	Phase 1/2 (NCT03309111)
FcRL5/CD3	
BFCR4350A	Phase 1 (NCT03275103)
GPRC5D/CD3	
Talquetamab	Phase 1/2 (NCT04634552)

BCMA, B-cell maturation antigen.

release syndrome (CRS) was observed in 3 patients who received higher doses, and the 2 non–treatment-related deaths that occurred were from pulmonary aspergillosis and fulminant hepatic failure secondary to adenovirus. An ongoing phase 1b study is investigating intermittent dosing (NCT03836053). AMG701, another anti-BCMA BiTE, differs from AMG420 in that it has an extended half-life owing to delayed renal clearance resulting from an additional Fc fragment, which allows once-weekly dosing.[49] The first-in-human, phase 1 study with AMG701 is currently ongoing (NCT03287908).

Interim results from the first-in-human study with CC-93269, a different anti-BCMA/CD3 BiAb, were presented at the 2019 ASH Annual Meeting. CC-93269 was administered to 30 patients with a median of 5 prior lines of therapy (range, 3-13) in various dose escalations. The ORR was found to be 43.3%, with an sCR/CR rate of 16.7%. Notably, in the 9 patients treated with the 10-mg dose, the ORR was 88.9%, with an sCR/CR rate of 44.4%. One or more grade 3 or 4 treatment-related adverse events were reported in 73.3% of patients; most of the grade 3 or higher adverse events were neutropenia (43.4%), anemia (36.7%), and thrombocytopenia (16.7%). CRS developed in 23 patients (76.7%); most cases occurred after the initial dose and were grade 1 or 2 (73.3%). Only one CRS event of grade 3 or higher was reported.[50] These interim results are promising, and enrollment continues to determine the recommended phase 2 dose.

Preliminary results from the first-in-human, phase 1/2 study with REGN5458, another anti-BCMA/CD3 BiAb, were also presented at the 2019 ASH Annual Meeting. REGN5458 was investigated at doses of 3 and 6 mg in a weekly, as well as an every-2-week, dosing strategy in 7 patients with a median of 7 prior lines of therapy. Responses were observed in 4 of the 7 patients (57%), and 2 of the patients in the 6-mg group were MRD-negative. CRS was noted in 3 patients, in no case grade 3 or higher.[51] Enrollment in this study is currently ongoing (NCT03761108).

Lastly, initial results from the ongoing first-in-human study of teclistamab (JNJ-64007957) were presented at the 2020 ASCO Virtual Scientific Program. Teclistamab, an anti-BCMA/CD3 BiAb, was given intravenously at doses ranging from 0.3 to 270 μg/kg to 66 patients with RRMM, who had a median of 6 prior therapies (range, 2-14). A response occurred in 20 of 52 patients (38%) who received a dose equal to or greater than 38.4 μg/kg, and 7 of the 9 patients (78%) who received the highest dose responded. The notable all-grade adverse events were CRS (56%), neutropenia (26%), anemia (23%), and neurotoxicity (8%). All of the CRS events were grade 1 or 2 and typically occurred with the first dose.[52] The phase 2 study is not yet recruiting but will evaluate the recommended phase 2 dose, to be administered subcutaneously (NCT04557098).

The development of BiAb therapy is ongoing, with several other products under investigation (Table 3), as described in a previous review.[53] These additional antibodies include other BCMA/CD3 BiAbs, a CD38/CD3 BiAb, an FcRL5/CD3 BiAb, and a GPRC5D/CD3 BiAb; drugs with the same target vary slightly in design and administration. If these BiAbs are approved by the FDA, additional off-the-shelf products with novel mechanisms of action will be available for patients with RRMM.

Conclusion

Antibody therapy has become a critical component in the treatment of MM during the last decade. The mAbs were initially introduced in the treatment of RRMM, and they are now being investigated and utilized in the frontline setting. With the success of the naked antibodies, such as daratumumab, isatuximab, and elotuzumab, conjugated antibodies and BiAbs are beginning to enter the landscape and are needed to overcome resistance to and relapse after prior therapies. Belantamab mafodotin is now FDA-approved and offers a novel therapeutic option for heavily pretreated patients, and the role of BiAb therapy continues to be investigated. Antibody therapy options for the treatment of MM continue to evolve and are achieving responses that are both deeper and more durable.

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