

Oncology Treatment Pathways[®]

Diagnostic Testing & Personalized Medicine

Novel Targeted Immunotherapies in Multiple Myeloma, With a Focus on Bispecific Antibodies

Epidemiology, Diagnosis, and Staging of Multiple Myeloma

Multiple myeloma (MM) is a hematopoietic malignancy anticipated to be associated with approximately 34,470 new diagnoses and 12,640 deaths in the United States in 2022.¹ However, the number of cases may be increasing in many parts of the world, particularly among men, individuals aged over 50 years, and those who reside in high-income countries.^{2,3}

MM diagnosis traditionally has necessitated existence of end-organ damage defined by “CRAB” criteria (ie, calcium levels, renal insufficiency, anemia, and the presence of bone lesions).^{2,4} More recently, the International Myeloma Working Group (IMWG) updated its diagnostic criteria to additionally include SLiM, defined as 1 or more of the following features: at least 60% clonal plasma cells in the bone marrow, involved/uninvolved free light chain ratio of at least 100, or MRI results showing more than 1 focal bone marrow

lesion.⁴ Because both tumor and patient characteristics can impact clinical outcomes, staging systems integrate these characteristics to effectively categorize the disease. The International Staging System (ISS) uses laboratory measures, such as serum β -2 microglobulin and serum albumin levels. The Revised-ISS (R-ISS) expands on measures to include prognostic cytogenetic features, such as the presence of such high-risk abnormalities as the t(4;14) or t(14;16) chromosomal translocations or the loss of parts of the short arm of chromosome 17 (ie, del[17p]).^{2,4}

MM is characterized by abnormally elevated levels of monoclonal antibodies (mAbs).^{4,5} The exact cause of the disease remains unknown, although some research suggests that genetic abnormalities in oncogenes related to external factors may play a role.⁵ During the monoclonal gammopathy of undetermined significance (MGUS) premalignant stage, the appearance of a cytogenetic

abnormality can lead to growth of abnormal asymptomatic premalignant clonal plasma cells and mAb production. Following the appearance of an additional cytogenetic abnormality, cells can continue to asymptotically proliferate during smoldering MM before progression to overt MM.^{5,6}

Although there remains no definitive cure for MM, the development of new therapies over the past several years has led to better outcomes and prolonged survival.⁶⁻⁹ Novel and emerging immunotherapies contribute to these improved outcomes.

Novel Immunotherapies in NDMM

Treatment for newly-diagnosed MM (NDMM) depends on whether patients are candidates for high-dose therapy and transplant.⁴ Newly-diagnosed patients who are eligible for autologous stem cell transplant generally have sufficient hepatic, renal, cardiac, and pulmonary function.⁴ Transplant candidates

typically receive induction therapy to reduce tumor burden before undergoing stem cell mobilization, harvesting, and, finally, the autologous stem cell transplant.²

The mAbs are frequently used in the NDMM landscape in both transplant-eligible and -ineligible patients. Quadruple therapy consisting of the CD38-targeting mAb daratumumab in combination with lenalidomide, bortezomib, and dexamethasone is a recommended regimen for transplant-ineligible patients in the National Comprehensive Cancer Network (NCCN) guidelines.⁴ Daratumumab given in combination with either bortezomib, thalidomide, and dexamethasone; carfilzomib, lenalidomide, and dexamethasone; or cyclophosphamide, bortezomib, and dexamethasone are also listed as therapies there are useful in certain circumstances.⁴ Daratumumab monotherapy is additionally included as a recommended regimen for maintenance therapy after transplantation.⁴

Daratumumab can also be used in NDMM patients who are not eligible for transplant; it is recommended in combination with lenalidomide and dexamethasone as a preferred regimen in the NCCN guidelines for transplant-ineligible patients.⁴ Quadruplet regimens (including daratumumab in combination with bortezomib, melphalan, and prednisone or in combination with cyclophosphamide, bortezomib, and dexamethasone) are also listed as recommended regimens.⁴

The mAbs elotuzumab and isatuximab are not currently approved for use in NDMM, but the efficacy of these agents is currently being investigated in this treatment setting.¹⁰ Similarly, other immunotherapeutic options are also being explored in the

NDMM setting, including antibody-drug conjugates (ADCs) and chimeric antigen receptor (CAR) T-cell therapies.^{1,10,11}

Novel immunotherapies in Relapsed/Refractory MM

The advent of new therapies for MM has substantially improved the clinical outcomes of patients.^{7-9,12,13} Unfortunately, almost all patients with MM inevitably suffer a relapse.^{8,12} Patients with relapsed/refractory MM (RRMM) are characterized as either being nonresponsive while on salvage therapy or having myeloma that recurs within 60 days of treatment after previously achieving at least a minimal response.¹⁴ RRMM patients are frequently resistant to many available treatments, which adds to the challenges associated with treatment selection.^{15,16}

Fortunately, the treatment landscape is rapidly changing. New and emerging therapies, including immunotherapies discussed in this report, may hold potential for patients with difficult-to-treat RRMM.¹⁶

Monoclonal Antibodies

The mAbs remain a commonly used and effective treatment option in the RRMM setting. Current guideline-recommended therapies target either the transmembrane glycoprotein CD38 (daratumumab and isatuximab) or the glycoprotein SLAMF7 (elotuzumab).^{4,10}

The CD38 transmembrane glycoprotein is an attractive therapeutic target, since it is expressed at high levels in MM cells while having lower expression on myeloid cells, lymphoid cells, and nonhematopoietic tissue.¹⁷ However, anti-CD38 mAbs may still target a high number of activated lymphocytes and CD34-positive hematopoietic

progenitor cells.¹⁸ Daratumumab is an anti-CD38 antibody frequently used in the treatment of MM, including RRMM, with a multimodal mechanism of action that induces complement-dependent cytotoxicity, kills cells through antibody-dependent cellular cytotoxicity (ADCC), and involves Fc-mediated antibody-dependent cellular phagocytosis (ADCP).^{4,17}

Although the monoclonal antibody isatuximab exhibits a mechanism of action similar to that of daratumumab, it targets a separate epitope of CD38; unlike other CD38-targeting antibodies, it may be able to induce apoptosis directly.¹⁹ Daratumumab has an approved subcutaneous (SC) formulation with comparable efficacy that may offer a preferable route for some patients.^{4,20} An SC formulation of isatuximab is also in development.^{19,21}

The glycoprotein SLAMF7 also plays a role in immune regulation; it is similarly expressed on the MM cell surface, representing another attractive therapeutic target.¹⁰ Elotuzumab binds the target to increase natural killer (NK) cell activity and likely acts through ADCC and ADCP.¹⁰

Triplet regimens with mAbs are generally preferred in patients with RRMM at first relapse, although there is a lack of trials directly comparing the multitude of different combinations.¹¹ The mAb daratumumab is commonly combined with bortezomib and dexamethasone or lenalidomide and dexamethasone.⁴ The NCCN guidelines further break down RRMM therapies according to whether patients have become refractory to either bortezomib or lenalidomide to help facilitate treatment decisions.⁴ Carfilzomib and dexamethasone in combination with daratumumab

or isatuximab is recommended in patients who have disease that is refractory to either lenalidomide or bortezomib.⁴ All 3 mAbs are used in combination with pomalidomide and dexamethasone: daratumumab is recommended in this combination after 1 prior therapy containing lenalidomide and a proteasome inhibitor; isatuximab or elotuzumab is recommended in this combination after 2 prior therapies.⁴ The NCCN additionally recommends use of daratumumab as a monotherapy, in combination with selinexor and dexamethasone, or as part of a potent quadruple agent combination with cyclophosphamide, bortezomib, and dexamethasone.⁴

Antibody-drug Conjugates

ADCs consist of a cytotoxic drug (“payload”) bound to an mAb via a cleavable or noncleavable linker that remains stable in circulation. Upon target cell binding, the ADC is internalized via endocytosis, after which lysosomal degradation ensues, leading to cleavage of the chemical linker, release of the cytotoxic payload, and subsequent induction of tumor cell apoptosis.¹⁰ Similar to mAbs and other immunotherapies, ADCs often exhibit a multimodal mechanism of action.¹¹

Ideal targets are highly expressed in malignant cells with low expression in healthy cells to limit treatment toxicity.¹⁰ BCMA represents an attractive target for the development of ADCs, bispecific antibodies, and other immunotherapies, since it is primarily expressed in plasma blasts and mature plasmacytes.¹⁰

There have been some ocular safety concerns associated with current and emerging ADCs attributable to linkers and other design components, although these ad-

verse events (AEs) typically appear to be mild and reversible.²² Overall, the otherwise acceptable safety profiles, the ability to use the treatments as a monotherapy, and the off-the-shelf availability of these agents may make them an attractive option for older patients.¹¹

The ADC belantamab mafodotin is a first-in-class humanized immunoglobulin G 1 mAb directed towards BCMA that is conjugated to the cytotoxic payload monomethyl auristatin F (MMAF) via a noncleavable linker.¹⁰ The NCCN guidelines list the therapy as an approved option for treatment of RRMM patients who have had at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a protease inhibitor, and an immunomodulatory agent.⁴ The novel immunotherapy is also being investigated in combination therapy with a variety of other agents.¹⁰

Other ADCs also in development for use in the RRMM setting include the novel agent MEDI2228. Similar to belantamab mafodotin, MEDI2228 also targets BCMA, but it uses a pyrrolobenzodiazepine payload as opposed to MMAF. Initial phase 1/2 research results suggest encouraging efficacy, reporting an overall response rate (ORR) of 61% with acceptable toxicity; however, reversible photophobia was observed in 60% of patients.¹¹

Bispecific Antibodies

Bispecific antibodies are an emerging class of immunotherapeutics designed to target and bind malignant plasma cells as well as cytotoxic NK T cells. Simultaneous binding of both targets generates an immunologic coupling, resulting in the activation of NK T cells and subsequent destruction of cancerous plasma

cells.^{5,23} Due to this dual mechanism of action, these agents are often referred to as bispecific T-cell engagers. Although this class of immunotherapeutics is still emerging, it holds considerable promise as an off-the-shelf option that could provide deep responses with a manageable safety profile. A selection of the leading emerging bispecific antibodies and their various malignant targets can be seen in the **Table**.²³⁻⁵⁰ Research surrounding each of these therapies is continuing to evolve.

BCMA-Targeting Bispecific Antibodies

The transmembrane glycoprotein BCMA is important for B-cell survival, and it interacts with its natural ligands BAFFR and APRIL, which have roles in B-cell activation and proliferation. BCMA activation results in the activation of prosurvival pathways, and associated overexpression in MM cells correlates with increased cell proliferation. Because BCMA expression is considerably elevated in patients with MM compared with healthy patients, it represents an attractive target in the development of novel immunotherapeutics.^{5,10} Consequently, a number of emerging bispecific antibodies are designed to target BCMA (**Table**).²³⁻⁵⁰

JNJ64007957 (teclistamab)

JNJ64007957, also known as teclistamab, is another BCMA-targeting bispecific antibody currently under investigation in several clinical trials for use in various MM treatment settings (**Table**).²³⁻⁵⁰ Results from phase 1 of the MajesTEC-1 study (NCT03145181), which aimed to identify the recommended phase 2 dose (RP2D), demonstrated early promising efficacy, with 65% of patients achieving a partial response

(PR) or better.^{35,36} The dose-expansion, phase 2 portion of the trial (NCT04557098) examined the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of teclistamab in 165 patients with triple class-exposed RRMM.^{37,38} Updated results with a data cutoff of September 7, 2021, and Novem-

ber 9, 2021, showed responses in 64% (95% CI, 56%-72%) of patients, of whom 30% achieved a complete response (CR).⁵¹ Median duration of response (DOR) was not reached; the 12-month DOR rate was 66% (95% CI, 49%-79%). Cytokine release syndrome (CRS) was observed in 72% of patients and

was generally low grade (grade, ≤ 2) and reversible.⁵¹ Infections occurred in 63% of patients, including grade 3 or 4 infections in 35% of patients. Immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 3% of patients; all instances were low grade (grade, ≤ 2).⁵¹ The researchers con-

Table.

Trials of Leading Emerging BCMA × CD3-targeting Bispecific Antibodies in RRMM²³⁻⁵⁰

Agent (generic name)	Targets	NCT number/Clinical trial	Trial phase	Treatment setting
AMG701	BCMA × CD3	NCT03287908	Phase 1/2	Monotherapy or in combination with pomalidomide +/- dexamethasone
CC-93269	BCMA × CD3	NCT03486067	Phase 1	Monotherapy
PF-06863135 (elranatamab)	BCMA × CD3	NCT04649359/ MagnetisMM-3	Phase 2	Monotherapy
		NCT03269136/MagnetisMM-1	Phase 1	Monotherapy and in combination with immunomodulatory agents
REGN5458	BCMA × CD3	NCT03761108	Phase 1/2	Monotherapy
JNJ-64007957 (teclistamab)	BCMA × CD3	NCT03145181/MajesTEC-1	Phase 1	Intravenous and subcutaneous monotherapy
		NCT04557098	Phase 2	
		NCT04108195/TRIMM-2	Phase 1	Daratumumab + talquetamab or teclistamab + daratumumab ± pomalidomide
		NCT05083169/MajesTEC-3	Phase 3	Daratumumab + teclistamab compared with daratumumab + pomalidomide and dexamethasone or daratumumab + bortezomib and dexamethasone
		NCT04586426 RedirecTT-1	Phase 1	Combination therapy of teclistamab with talquetamab ± daratumumab
ABBV-383 (TNB-383B)	BCMA × CD3	NCT03933735	Phase 1/2	Monotherapy
JNJ-64407564 (talquetamab)	GPCR5D × CD3	NCT03399799 MonumentAL-1	Phase 1	Monotherapy
		NCT04634552 TALMMY1001-Pt3	Phase 2	
		NCT04108195 TRIMM-2	Phase 1	Daratumumab + talquetamab and teclistamab and daratumumab ± pomalidomide
		NCT04586426 RedirecTT-1	Phase 1	Combination therapy of teclistamab with talquetamab ± daratumumab
BFCR4350A (cevastamab)	FcRH5 × CD3	NCT03275103	Phase 1	Monotherapy

NCT, National Clinical Trial; RRMM, relapsed/refractory multiple myeloma.

cluded that 9-month follow-up data with teclistamab reaffirmed a high rate of deep and durable responses with no new safety signals.⁵¹

The phase 3 MajesTEC-3 trial (NCT05083169) is examining the safety and efficacy of teclistamab in combination with daratumumab vs daratumumab plus pomalidomide and dexamethasone or daratumumab plus bortezomib and dexamethasone in patients with RRMM.^{41,42} The trial began in October 2021, and it is currently recruiting patients.⁴²

AMG701

AMG701 dually targets BCMA on MM cells and CD3 on T cells.²⁴ AMG701 currently is being explored in an RRMM setting as a monotherapy or in combination with pomalidomide with or without dexamethasone.²⁵ Results from the first in human study (NCT03287908) with ongoing dose escalation of AMG701 found that 16 of 45 patients (36%) had a therapeutic response at doses of 3 to 12 mg. The observed response rate was 83% (5 of 6 patients, including 3 PRs and 2 very good PRs [VGPRs]) in patients who had earlier dose escalation with 9 mg.²⁶ CRS was the most common nonhematologic AE, occurring in 61% of patients; however, the majority of these were low grade, and the 5 reported grade 3 events were all reversible with corticosteroids and tocilizumab.²⁶ The authors concluded that the bispecific treatment had encouraging efficacy and a manageable safety profile, supporting additional investigation of AMG701 that is ongoing.^{25,26} Research evaluating AMG701 in preclinical models demonstrate that lenalidomide and pomalidomide may work synergistically to enhance T-cell modulation, suggesting a potential role for using AMG701 in combination therapy

with these agents.⁵²

CC-93269

CC-93269 is another BCMA-directed bispecific antibody currently being studied in an RRMM setting.²⁷ Initial results, as of October 2019, for an ongoing, phase 1, dose-finding study (NCT03486067) of CC-93269 reported an ORR in 13 of 30 patients (43%) enrolled, with an ORR of 89% in patients receiving 10 mg (n = 9).^{27,28} Researchers concluded that these results support a manageable safety profile with encouraging efficacy for CC-93269, and the study is continuing to enroll patients for participation in the dose-escalation phase.^{27,28}

PF-06863135 (elranatamab)

PF-06863135, also known as elranatamab, is a BCMA-directed bispecific antibody under investigation in a number of clinical trials for its use in different MM settings. The ongoing, open-label, multicenter, nonrandomized, phase 2 MagnetisMM-3 study (NCT04649359) is examining elranatamab monotherapy in patients with disease that was refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 anti-CD38 mAb.^{29,30} Patients were split into 2 cohorts (cohort A, patients naïve to BCMA-directed treatments; cohort B, patients with previous exposure to BCMA-directed ADCs or CAR T-cell therapy). As of December 31, 2021, initial safety results including 60 patients in cohort A who had received at least 1 dose reported the therapy to be well-tolerated at a 76-mg weekly dose regimen, with a 2-step-up priming dose regimen given during week 1. No AEs of CRS of grade 3 or more or ICANS were reported.³⁰

Meanwhile, the MagnetisMM-1 study (NCT03269136) is exam-

ining elranatamab given alone or given with immunomodulatory therapies in an RRMM setting.^{31,32} As of November 2021, updated results including 55 patients who received monotherapy with elranatamab reported an ORR of 64% (95% CI, 50%-75%), with 31% of patients achieving a CR or better.³² Although 67% of patients experienced CRS, all events were of grade 2 or less.³² The authors concluded that elranatamab therapy produced durable molecular and clinical responses with a manageable safety profile.³²

REGN5458

The BCMA-targeting bispecific antibody REGN5458 is being evaluated in an ongoing phase 1/2 trial (NCT03761108) in patients with RRMM with disease that was double- or triple-refractory or who were intolerant to prior systemic therapy lines.^{33,34} As of September 2021, results were reported for 73 patients who had received REGN5458 monotherapy.³⁴ Fatigue (45.2%), CRS (38.4%), pyrexia (35.6%), and nausea (32.9%) were the most common treatment-related AEs, with all observed CRS and neurotoxicity events reported as low grade (grade, ≤ 2) events.³⁴ Study investigators concluded that REGN5458 provided patients early, deep, and durable responses with a manageable safety profile.³⁴

ABBV-383

ABBV-383 (formerly known as TNB-383B) is another BCMA-targeting bispecific antibody being studied in patients with RRMM.^{44,45} As of early January 2022, interim results from a phase 1 study (NCT03933735), which included a total of 124 enrolled patients (dose escalation, n = 73; dose

expansion, n = 51) reported an ORR of 57% (122 efficacy-evaluable patients), with 43% defined as having a VGPR or better.⁴⁵ Among the 49 evaluable patients in the 60-mg dose expansion cohort, the reported ORR was 59%, with 39% defined as a VGPR or better.⁴⁵

Overall, the most common non-hematologic treatment-emergent AEs included CRS (57%), fatigue (30%), nausea (29%), and diarrhea (27%).⁴⁵ In the 60-mg dose expansion cohort, 73% of patients experienced CRS, although only 1 event was reported as being at least grade 3.⁴⁵ The most common hematologic AEs in the overall population included neutropenia (37%) and anemia (29%), with similar rates observed across both dose-expansion cohorts.⁴⁵ Investigation of ABBV-383 is ongoing, with dosing variations aiming to determine an optimal regimen still being explored.⁴⁵

GPRC5D-Targeting Bispecific Antibodies

GPRC5D is a G protein-coupled receptor with a function that is not well understood. However, the receptor is highly expressed in malignant bone marrow plasma cells and is associated with poor prognosis in patients with MM. Consequently, there has been new interest in GPRC5D as a therapeutic target in MM.²³

Talquetamab (JNJ-64407564) is a first-in-class, GPRC53-targeting, bispecific antibody that is currently being investigated in several clinical trials (**Table**).²³⁻⁵⁰ The phase 1 MonumentAL-1 trial (NCT03399799) is examining monotherapy with talquetamab in an RRMM setting.^{46,47} The primary objectives for part 1 of the trial were to examine safety, preliminary efficacy, pharmaco-

kinetics, and pharmacodynamics of talquetamab and to determine RP2D, of which 2 were identified: 405 µg/kg SC once weekly (n = 30) and 800 µg/kg SC every 2 weeks (n = 44).⁴⁶ Part 2 of the trial is currently assessing the safety and tolerability of these 2 RP2Ds, using step-up dosing to minimize CRS.⁴⁶ As of January 2022, updated results showed an ORR of 70% in the 30 response-evaluable patients in the 405-µg/kg group and of 64% in the 44 response-evaluable patients in the 800-µg/kg group.⁴⁶ AEs were generally low grade (grade, ≤ 2), with CRS and cytopenia being among the most frequently observed.⁴⁶ CRS occurred most frequently during step-up dosing, whereas cytopenias occurred during step up and cycle 1 and 2 doses; however, these were generally reversible and resolved within 1 week.⁴⁶ Overall, the pharmacokinetic and pharmacodynamic profiles were similar between the 2 doses, and further investigation in phase 2 and 3 studies remain ongoing.⁴⁶⁻⁴⁸

The ongoing phase 1 TRIMM-2 study (NCT04108195) is examining the anti-CD38 mAb daratumumab in combination with teclistamab or talquetamab with or without pomalidomide.^{39,40} As of January 2022, updated results included 37 eligible patients from the daratumumab plus teclistamab cohort, with a reported ORR of 78% (VGPR, 73%).⁴⁰ CRS (6.1%) was the most frequently observed AE; all events were reported as low grade (grade, ≤ 2). Investigators believed that efficacy results may suggest a potential role for the use of this combination therapy in heavily pretreated patients with RRMM.⁴⁰

The ongoing phase 1b RedirectT-1 study (NCT04586426)

is exploring teclistamab given with the GPCR5D-targeting talquetamab with or without daratumumab in patients with RRMM.⁴³ Recruitment for the trial is ongoing; it will include a 2-part study design (dose escalation and dose expansion).

FcRH5-Targeting Bispecific Antibodies

FcRH5 is a member of the immunoglobulin superfamily. It likely has a role in isotype expression and proliferation during antigen-primed B-cell development. As with other therapeutic targets discussed, it is highly expressed on malignant MM cells compared with healthy cells.²³

A clinical trial (NCT03275103) examined monotherapy with the FcRH5-targeting bispecific antibody cevostamab in patients with RRMM who were no longer appropriate candidates for other established therapies.⁵⁰ In all, 160 patients were enrolled as of a May 2021 data cutoff.⁵⁰ Of these, 158 patients were efficacy (dose-dependent)-evaluable. ORR was assessed in 2 dose-expansion cohorts, with 24 of 44 patients (54.5%) responding at the 160-mg dose level and 22 of 60 patients (36.7%) responding at the 90-mg dose level.⁵⁰ CRS (80%) was the most common AE; however, events were generally low grade (grade 1, 42.5%; grade 2, 36.3%; grade 3, 1.3%), as has been seen with other bispecific antibodies.⁵⁰ Compared with single-step dosing, the double step-dosing approach appeared to correlate with a better safety profile.⁵⁰ The trial remains ongoing, and investigators currently are recruiting with an estimated goal of 390 participants.⁴⁹

CAR T-Cell Therapies

CAR T-cell therapy is a category

of adoptive cellular therapy that uses T cells engineered to express a chimeric receptor directed towards a tumor epitope.^{53,54} Following infusion, the CAR T cells travel to the site of the tumor to target and destroy malignant cells. This leads to CAR T-cell proliferation, release of tumor antigens, and enhancement of a wider immune response.⁵³

Each CAR T-cell therapy targets specific biological markers on the surface of tumor cells.⁵⁴ These therapies are newest to the immunotherapy treatment landscape for MM. The 2 currently approved CAR T-cell therapies for MM target BMCA.^{23,54} On March 26, 2021, the BCMA-targeting idecabtagene vicleucel (ide-cel) became the first FDA-approved CAR T-cell therapy for the treatment of adult patients with RRMM.⁵⁵ More recently, ciltacabtagene autoleucel (cilta-cel), another BCMA-directed CAR T-cell therapy, received FDA approval in February 2022.⁵⁶ Clinical trials for both therapies showed promising efficacy with comparable ORRs. The phase 2 KarMMA study (NCT03361748) evaluating the use of ide-cel in patients with RRMM showed an ORR of 73% (95% CI, 66%–81%) at a median follow-up of 13.3 months (range, 0.2–21.2 months).⁵⁷ Results from the CARTITUDE-1 study (NCT03548207), which evaluated cilta-cel in patients with RRMM, reported an ORR of 97% (95% CI, 91.2%–99.4%), with a CR noted among 67% of patients at a median follow-up of 12.4 months (range, 10.6–15.2 months).⁵⁸ Notably, these clinical trials examined slightly different populations, with a greater number of patients with extramedullary disease (39%) or high-risk cytogenetic features (35%) receiving ide-cel in the

KarMMA trial versus cilta-cel in the CARTITUDE-1 trial (13% and 24%), respectively.^{57,58}

In terms of safety outcomes, 92 of 97 patients (95%) receiving cilta-cel experienced CRS; however, events were generally of a lower grade, with grade 3 CRS observed in 3 patients (3%) and grade 4 and 5 events occurring in 1 patient (1%) each.⁵⁸ Meanwhile, a total of 107 patients (84%) who received ide-cel experienced a CRS event. The majority of these were reported as grade 1 or 2 events, but 5 patients (4%) experienced grade 3 CRS, and grade 4 and 5 events were observed in 1 patient (< 1%) each.⁵⁷ Researchers in both studies concluded that the overall safety profiles for these treatments were comparable with those of other CAR T-cell therapies.^{57–59}

Both cilta-cel and ide-cel are currently recommended by the NCCN guidelines for treatment of RRMM in patients who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.⁴

Despite the efficacy demonstrated with CAR T-cell therapies in RRMM, there are some logistical disadvantages unique to these immunotherapies. CAR T cells are derived from cells collected from patients and that are engineered and expanded in the laboratory before being infused back into patients.^{53,54} Consequently, CAR T-cell treatment requires the use of designated centers along with the collection of white blood cells (leukapheresis), bridging, lympho-depleting chemotherapy, infusion, and extended monitoring.⁶⁰ Moreover, care is compounded by a lengthy manufacturing time (28

days), a demand for treatment that outstrips availability, disparities related to care access, and overall cost (\$419,500–\$465,000 per infusion) of the treatment.⁶⁰

Future Perspectives: How Will Bispecific Antibodies Impact the Treatment Landscape?

Continued evolution of the MM treatment landscape is expected, and bispecific antibodies are anticipated to further shift future treatment options.²³ In addition to the emerging bispecific options discussed here, a number of other bispecific and trispecific antibodies are currently being investigated in preclinical stages.²³ However, it remains unclear how all of these emerging options will integrate into current therapeutic options and overall therapy sequencing in MM patients.²³ Given their efficacy and promise, bispecific therapies may also play a role in earlier lines of therapy to provide patients an early and deep response for maximum clinical benefit.²³ Furthermore, CRS and neurotoxicity remain an ongoing issue with use of bispecific antibodies, and further investigation is needed to understand which patients are at greatest risk for these AEs and how these may best be mitigated.²³ Because bispecific antibodies and CAR T-cell therapies offer treatment options associated with high response rates and deep responses, further research directly comparing these therapies will be of particular interest to help determine how to best integrate these and other emerging treatment options into the current therapeutic landscape.²³ ■

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