Novel Approaches to the Treatment of Multiple Myeloma

Kathryn T. Maples, PharmD, Sara A. Scott, PharmD, and Sagar Lonial, MD
Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, Georgia

Abstract: The treatment landscape for multiple myeloma (MM) has evolved significantly over the last decade with the approval of novel therapies and combinations in the newly diagnosed and relapsed/refractory settings. There has also been a shift toward a risk-adapted approach to induction and maintenance regimens, with the goal of achieving better response rates for those with high-risk disease. The incorporation of anti-CD38 monoclonal antibodies into induction regimens has led to longer progression-free survival and higher rates of measurable residual disease negativity. In the relapsed setting, the emergence of B-cell maturation antigen–directed therapy, including antibody-drug conjugates, chimeric antigen receptor T-cell therapy, and more recently, bispecific antibodies, has produced deep and durable responses in heavily pretreated patients. This review article describes novel approaches to the treatment of MM in both the newly diagnosed and the relapsed/refractory setting.

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy in the United States.1 It is characterized by uncontrolled plasma cell proliferation, osteolytic bone lesions, and immunodeficiency.2 Despite significant advancements in the treatment landscape of MM over the last decade, this malignancy remains incurable, largely owing to the development of drug resistance, and the need for novel treatment regimens remains critical. This review article describes novel approaches to the treatment of MM in the newly diagnosed setting and for the relapsed/refractory patient.

Data Sources

Primary studies and review articles were identified through a literature search of PubMed and MEDLINE databases (January 1964 to January 2023). Key search terms included “multiple myeloma,” “daratumumab,” “B-cell maturation antigen,” and “bispecific antibody.” Data pending publication were accessed through the American Society of Clinical Oncology and the American Society of
Hematology. Additional resources included the National Comprehensive Cancer Network, product labeling, news releases, and ClinicalTrials.gov.

Treatement of Newly Diagnosed Multiple Myeloma

Treatment of newly diagnosed multiple myeloma (NDMM) should consist of sequential therapies comprising induction, consolidation, and maintenance. The therapies used in these 3 phases are selected according to patient fitness and transplant eligibility, and more recently, the patient’s cytogenetic risk.

Induction Therapy

Induction therapy consists of a regimen that includes at least 3 agents: a proteasome inhibitor, an immunomodulatory drug, and a corticosteroid. However, recent data from the CASSIOPEIA and GRIFFIN trials have suggested the addition of the anti-CD38 monoclonal antibody daratumumab (Darzalex, Janssen Biotech) to the regimen may be a preferred option for some patients.

CASSIOPEIA is an open-label, randomized phase 3 trial that evaluated the addition of daratumumab to the 3-drug regimen of bortezomib (Velcade, Millennium/Takeda Oncology), thalidomide, and dexamethasone (Daratumumab/VTd) in 1085 transplant-eligible patients with NDMM. At 100 days after consolidation with autologous stem cell transplant (ASCT), the stringent complete response (sCR) rate was 29% in the Daratumumab/VTd group vs 20% in the VTd group (odds ratio, 1.60; 95% CI, 1.21-2.13; P=0.0010). After consolidation, more patients receiving Daratumumab/VTd achieved a very good partial response (VGPR) or better compared with the VTd group (64% vs 30%; P<0.0001), sCR (67% vs 48%; P=0.0079), and CR or better (83% vs 60%; P=0.005). Additionally, longer progression-free survival (PFS) was observed in the Daratumumab/RVd group than in the RVd group, yielding a 55% reduction in the risk of death or disease progression (hazard ratio [HR], 0.45; 95% CI, 0.21-0.95). There was no difference seen between the groups in overall survival (OS; HR, 0.90; 95% CI, 0.31-2.56; P=0.8408).

The addition of daratumumab did not significantly affect safety in either trial, with the most common adverse events being peripheral neuropathy, constipation, peripheral edema, nausea, neutropenia, pyrexia, and thrombocytopenia. In both trials, daratumumab was associated with infusion-related reactions (IRRs), especially with the first dose. The incidence of IRRs can be mitigated slightly via the use of the subcutaneous formulation of daratumumab (daratumumab/hyaluronidase), which has lower rates of IRRs compared with the intravenous formulation, as reported in the COLUMBA trial.

Consideration of Cytogenetic Risk for Therapy

Cytogenetic risk is an established prognostic factor for newly diagnosed patients and is now being used as an additional consideration for treatment. High-risk cytogenetic abnormalities include t(4;14), t(14;16), del(17p), monosomy 17, 1q21 gain or amplification, MYC translocation, TP53 mutation, tetrasomies, and complex karyotype. This risk stratification approach has been recently studied in both the induction and maintenance setting for transplant-eligible and -ineligible patients.

Since the publication of the CASSIOPEIA and GRIFFIN trials, further studies have evaluated patients with high-risk disease according to cytogenetics to optimize upfront therapy for this population. The randomized, open-label, phase 2 FORTE trial included 474 transplant-eligible patients with NDMM. Patients were randomized to receive carfilzomib (Kyprolis, Amgen), lenalidomide, and dexamethasone (KRd) followed by ASCT; KRd for 12 cycles without ASCT; or carfilzomib, cyclophosphamide, and dexamethasone (KCd) followed by ASCT. After the induction phase, all patients were rerandomized to maintenance with KR or lenalidomide monotherapy. Overall, 49% of the population had high-risk disease according to cytogenetics, defined by the investigators as del(17p), t(4;14), t(14;16), or amp(1q). Significantly more patients in the KRd group achieved a VGPR or better compared with the KCd-ASCT and KRd12 cohorts. This finding further translated into an improvement in 4-year PFS compared with both KCd plus ASCT (HR, 0.54; 95% CI, 0.38-0.78; P=0.0008) and KRd12 (HR, 0.61; 95% CI, 0.43-0.88; P=0.0084).
patients, though the presence of high-risk cytogenetics was associated with lower rates of MRD negativity ($10^{-5}$) and worse PFS than the absence of adverse cytogenetics. In the subgroup analysis, progression events or deaths in patients at high cytogenetic risk were lowest in the KRd-ASCT group. Patients with 2 or more high-risk cytogenetic abnormalities were less likely than those with fewer cytogenetic abnormalities to reach MRD negativity, had worse PFS, and benefited from ASCT. In the multicenter, single-arm, phase 2 MASTER trial, 123 patients received daratumumab in combination with carfilzomib, lenalidomide, and dexamethasone (Dara-KRd), followed by ASCT and then Dara-KRd maintenance. Of this population, 37% had 1 high-risk cytogenetic abnormality and 20% had 2 or more high-risk cytogenetic abnormalities. At a median follow-up of 25.1 months, MRD negativity ($<10^{-5}$) by next-generation sequencing was achieved in 80% of patients. For patients with 0, 1, and 2 or more high-risk cytogenetic abnormalities, MRD negativity was 78%, 82%, and 79%, respectively, suggesting that the 4-drug regimen of Dara-KRd may overcome the poor outcomes associated with high-risk cytogenetic abnormalities. However, the question about therapy discontinuation according to short intervals remains unknown.

The GMMG-CONCEPT study, an open-label, multicenter phase 2 trial, also supports the use of an intensified 4-drug regimen, including an anti-CD38 monoclonal antibody, to improve outcomes in patients with high-risk NDMM. This trial included patients with at least 1 high-risk feature, including del(17p), t(4;14), t(14;16), or more than 3 copies of 1q21. Patients received the anti-CD38 monoclonal antibody isatuximab (Sarcalix, Sanofi Genzyme) in combination with KRd (Isa-KRd). The interim analysis included the first 50 patients, all of whom had at least a PR, and 90% of patients had a VGPR or better. At a median follow up of 24.9 months, the median PFS was not reached, with a median 12-month PFS of 79.6% and a median 24-month PFS of 75.5%. MRD negativity ($10^{-5}$) was achieved in 20 of the 33 patients available for analysis.

### Consolidation Therapy With ASCT

Since the first positive trial displaying increased OS and event-free survival in patients with MM who received ASCT was published in 1996, high-dose chemotherapy followed by ASCT remains an essential part of myeloma therapy. The role of upfront vs delayed ASCT has been assessed in many clinical trials.

Most recently, the phase 3, randomized, open-label, phase 3 DETERMINATION trial confirmed the importance of upfront ASCT in eligible patients. This trial randomized 722 patients to triplet therapy with RVd plus ASCT or RVd alone. Both arms received lenalidomide maintenance. The primary endpoint of PFS was 67.5 vs 46.2 months, respectively (HR, 1.53; 95% CI, 1.23-1.91; $p<.0001$), supporting the use of upfront ASCT in eligible patients. However, no difference was seen in OS between

---

**Figure.** General principles that must be considered when selecting a treatment regimen for relapsed or refractory multiple myeloma. The multiple myeloma care team’s goal is to select the most effective and safe regimen while maintaining quality of life.

ISS, International Staging System.
the 2 groups. ASCT remains a category 1 recommendation in the National Comprehensive Cancer Network (NCCN) guidelines, and upfront ASCT is preferred.  

**Maintenance Therapy**

Maintenance therapy is used to maintain a response for as long as possible after ASCT. The questions of which medications to use and for what duration remain controversial, particularly in patients with high-risk MM. A retrospective study including 45 patients with high-risk features, defined as del(17p), del(1p), t(4;14), t(14;16), or plasma cell leukemia, looked at intensifying maintenance therapy. After upfront ASCT, patients received RVd for 3 years, followed by lenalidomide monotherapy. The median PFS was 32 months, and the 3-year OS rate was 93%. An additional study examined long-term follow-up of 1000 patients who received RVd induction followed by risk-adapted maintenance therapy. The median PFS was 65 months (95% CI, 58.7-71.3) for the entire cohort, 40.3 months (95% CI, 33.5-47.0) for high-risk patients, and 76.5 months (95% CI, 66.9-86.2) for standard-risk patients. The median OS was 126.6 months in the overall cohort, 78.2 months in high-risk patients, and not yet reached in standard-risk patients.

More recent trials have explored alternative maintenance strategies. The 886 patients in the CASSIOPEIA trial who achieved a PR or better after consolidation were rerandomized to maintenance therapy with either daratumumab every 8 weeks or observation for 2 years. PFS appeared to be significantly better in the daratumumab group than in the observation group (HR, 0.53; 95% CI, 0.42-0.68; P < .0001). However, when Dara-VTd plus daratumumab maintenance was compared with Dara-VTd plus observation maintenance, no significant difference was seen (HR, 1.02; 95% CI, 0.71-1.47; P = .9133). In contrast, the GRIFFIN trial showed that the addition of daratumumab in the induction and maintenance settings improved 4-year PFS compared with RVd followed by lenalidomide alone in 87.2% vs 70%, respectively; HR, 0.45; 95% CI, 0.21-0.95; P = .0324). Intensification of maintenance therapy may also improve depth and duration of response in patients at high risk by cytogenetics. In the FORTE trial, all patients were randomized to either KR or lenalidomide alone for maintenance therapy. The 3-year PFS was significantly longer with the combination maintenance regimen than with lenalidomide alone, at 75% vs 65%, respectively (HR, 0.64; 95% CI, 0.44-0.94; P = .023). Similarly to induction, 3-year PFS was 82% with KR maintenance vs 72% with lenalidomide alone (HR, 0.59; 95% CI, 0.36-0.95; P = .030). This advantage was maintained in the subgroup of high-risk patients.

Though these trials have found a significant PFS benefit with maintenance therapy, no clinical trials have displayed an OS benefit with maintenance therapy.

**Clinical Application**

Many institutions are developing guidelines for initial therapy that consider both transplant eligibility and cytogenetic risk for all phases of therapy. Although there is likely some variation in the regimens selected, quadruplet regimens are becoming the standard for transplant-eligible patients. Additionally, we have seen the incorporation of risk-stratified recommendations in the NCCN guidelines for maintenance therapy. At this time, lenalidomide maintenance retains the category 1 recommendation; however, dual maintenance with bortezomib/lenalidomide or carfilzomib/lenalidomide is now recommended for high-risk MM. Continuous maintenance therapy until disease progression or unacceptable tolerability remains the standard for now, and MRD testing is not currently being used outside of clinical trials.

**Treatment of Relapsed/Refractory Multiple Myeloma**

Currently, there is no universally accepted standard for the optimal regimen or sequencing of regimens in the treatment of relapsed or refractory multiple myeloma (RRMM). The Figure highlights some general principles that influence treatment, such as patient-specific features (eg, performance status, comorbidities), disease morbidity (eg, rate of progression, renal impairment), risk assessment, treatment history, and patient lifestyle. Additionally, we can split the recommendations into 2 categories: early relapse vs late relapse.

**Early Relapse**

Early relapse refers to relapse in patients who have received 1 to 3 prior lines of therapy. For patients experiencing their first relapse (meaning that they are receiving second-line therapy), anti-CD38 triplet regimens have shown deep and durable responses compared with common doublet regimens, with tolerable additional adverse effects. These factors make anti-CD38 triplet regimens the most favored approach in this setting. Daratumumab and isatuximab are monoclonal antibodies (mAbs) targeting the CD38 glycoprotein that is highly expressed on MM cells. They have been studied in combination with proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs). Building on the success of the CASTOR and POLLUX trials, daratumumab and isatuximab have been combined with second-generation PIs and IMiDs in recent years in the APOLLO, CANDOR, ICARIA, and IKEMA randomized phase 3
trials, which are summarized in Table 1. Although we have seen the emergence of anti-CD38 mAb therapy in the frontline setting, these regimens remain a critical component of the management of RRMM and are an option for those who received an upfront anti-CD38 agent, as long as the progression did not occur on daratumumab or isatuximab maintenance therapy. The choice between these regimens should be based on patient-specific factors, such as the timing of relapse, disease cytogenetics, and patient preference/lifestyle.

Additional options for early-relapse disease include venetoclax (Venclexta, AbbVie/Genentech) combined with dexamethasone for MM patients with t(11;14), combination regimens based on selinexor (Xpovio, Karyopharm) or elotuzumab (Empliciti, Bristol Myers Squibb), and other PI-IMiD combinations. Specifically, venetoclax and selinexor are agents with novel mechanisms of action, which make them an attractive therapy option to treat patients with MM that has become refractory to some traditional agents. Combinations with these agents are finding a more predominant role in the early-relapse setting.

Venetoclax is a selective B-cell lymphoma/leukemia 2 (BCL2) inhibitor that induces cell death in MM cells that have the 11;14 translocation. Although initial results of the phase 3 BELLINI trial were concerning owing to the higher incidence of death noted in the venetoclax arm, it is important to note that only 13% of the patients in this study had t(11;14). In a subgroup analysis of patients with t(11;14), both PFS and OS favored the venetoclax arm. These updated data, in addition to prior phase 1/2 studies, support the use of venetoclax in combination with dexamethasone for RRMM with t(11;14). The dose of venetoclax for MM ranges from 400 to 800 mg daily; no ramp-up is needed because tumor lysis syndrome is rare with this agent. Ongoing studies with venetoclax in various combinations will help further delineate the role of this agent for RRMM.

Selinexor is a first-in-class oral agent that reversibly inhibits exportin 1 (XPO1), which blocks the nuclear export of tumor suppressor proteins, growth regulators, and messenger RNA of oncogenic proteins. Selinexor was first approved in combination with bortezomib and dexamethasone for patients with 1 to 3 prior lines of therapy, as long as the progression did not occur on daratumumab, carfilzomib, and pomalidomide and dexamethasone; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; Vd, bortezomib and dexamethasone; VGPR, very good partial response.

### Table 1. Major Studies Evaluating Efficacy of Daratumumab and Isatuximab Combinations in RRMM

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Patient population</th>
<th>Prior lines of therapy, median (range)</th>
<th>Prior IMiD, %</th>
<th>Prior PI, %</th>
<th>High risk, %</th>
<th>Median PFS, mo</th>
<th>ORR, %</th>
<th>≥VGPR, %</th>
<th>MRD neg, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASTOR</td>
<td>DaraVd vs Vd</td>
<td>RRMM</td>
<td>2 (1-9)</td>
<td>71.3 vs 80.2</td>
<td>67.3 vs 69.6</td>
<td>26.3 vs 27.4</td>
<td>16.7 vs 7.1</td>
<td>85 vs 63</td>
<td>63 vs 29</td>
<td>14 vs 2</td>
</tr>
<tr>
<td>POLLUX</td>
<td>DaraRd vs Rd</td>
<td>RRMM</td>
<td>1 (1-11)</td>
<td>55.2 vs 55.1</td>
<td>85.7 vs 85.5</td>
<td>17.4 vs 24.7</td>
<td>44.5 vs 17.5</td>
<td>92.9 vs 76.4</td>
<td>80.4 vs 49.3</td>
<td>30.4 vs 5.3</td>
</tr>
<tr>
<td>APOLLO</td>
<td>Dara (SC)-Pd vs Pd</td>
<td>RRMM</td>
<td>2 (1-5)</td>
<td>79 vs 80</td>
<td>100 vs 100</td>
<td>38 vs 32</td>
<td>12.4 vs 6.9</td>
<td>69 vs 46</td>
<td>51 vs 20</td>
<td>9 vs 2</td>
</tr>
<tr>
<td>CANDOR</td>
<td>DaraKd vs Kd</td>
<td>RRMM</td>
<td>2 (1-2)</td>
<td>66 vs 71</td>
<td>93 vs 90</td>
<td>15 vs 17</td>
<td>NR vs 15.8</td>
<td>84 vs 75</td>
<td>69 vs 49</td>
<td>18 vs 4</td>
</tr>
<tr>
<td>ICARIA-MM</td>
<td>IsaPd vs Pd</td>
<td>RRMM</td>
<td>3 (2-4)</td>
<td>100 vs 100</td>
<td>100 vs 100</td>
<td>16 vs 24</td>
<td>11.5 vs 6.5</td>
<td>60 vs 35</td>
<td>32 vs 9</td>
<td>5 vs 0</td>
</tr>
<tr>
<td>IKEMA</td>
<td>IsaKd vs Kd</td>
<td>RRMM</td>
<td>2 (1-2)</td>
<td>76 vs 81</td>
<td>93 vs 85</td>
<td>23 vs 25</td>
<td>NR vs 19.15</td>
<td>87 vs 83</td>
<td>73 vs 56</td>
<td>29.6 vs 13.0</td>
</tr>
</tbody>
</table>

Dara, daratumumab; IMiD, immunomodulatory drug; Isa, isatuximab; Kd, carfilzomib and dexamethasone; mo, months; MRD neg, measurable residual disease negative; NR, not reached; ORR, overall response rate; Pd, pomalidomide and dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; Rd, lenalidomide and dexamethasone; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous; Vd, bortezomib and dexamethasone; VGPR, very good partial response.
dosing strategy has proven to be more tolerable than the original twice-weekly dosing strategy. In the phase 2 STORM trial, all-grade nausea and decreased appetite occurred in 72% and 56% of patients, respectively. It is recommended to use a dual antiemetic approach for selinexor-based regimens, consisting of a long-acting agent (eg, olanzapine or rolapitant) and a breakthrough agent (eg, ondansetron or prochlorperazine).

Late Relapse
Late relapse refers to relapse in patients who have received 4 or more prior lines of therapy. Historically, RRMM patients had poor outcomes when they reached the late-relapse phase of the disease. The MAMMOTH study previously evaluated outcomes in 275 MM patients who were refractory to anti-CD38 mAbs, and reported a median OS of 8.6 months (95% CI, 7.6-9.9) from the time of refractoriness to anti-CD38 mAbs. Response rates to subsequent lines of therapy were low and there was a need for novel therapeutic options.

B-cell maturation antigen (BCMA) is a type III transmembrane glycoprotein with cysteine-rich extracellular domains that lacks a signal peptide. BCMA is undetectable on naïve B cells, hematopoietic stem cells, and normal nonhematologic tissues, suggesting that BCMA is not required for overall B-cell homeostasis, but is critical to the survival of long-lived plasma cells. With the discovery of BCMA as an ideal target for the treatment of patients with MM, BCMA-targeted antibody-drug conjugates (ADCs), chimeric antigen receptor (CAR) T-cell therapies, and bispecific antibodies have come to the market that have produced deep and durable responses in heavily pretreated patients.

Antibody-Drug Conjugates
Belantamab mafodotin-blmf (Blenrep, GSK) was the first-in-class ADC to receive accelerated approval by the US Food and Drug Administration (FDA) for the treatment of RRMM after 4 prior therapies. Belantamab mafodotin is an afucosylated, humanized immunoglobulin G1 (IgG1) monoclonal antibody that is covalently linked to the microtubule inhibitor MMAF via a protease-resistant maleimidocaproyl linker. Belantamab mafodotin binds directly to BCMA on the MM cell membrane. After it is internalized, MMAF is released via proteolytic cleavage, which induces cell cycle arrest at the growth 2 mitosis (G2-M) phase followed by MM cell apoptosis. The accelerated approval was obtained from the phase 2, multicenter DREAMM-2 trial, in which patients received belantamab mafodotin at 2.5 or 3.4 mg/kg intravenously once every 3 weeks until disease progression or unacceptable toxicity. The overall response rate (ORR) was 31% in the 2.5 mg/kg cohort and 34% in the 3.4 mg/kg cohort. Keratopathy

Table 2. BCMA-Targeted CAR T-Cell Products

<table>
<thead>
<tr>
<th>Name</th>
<th>BCMA scFv</th>
<th>Costimulatory</th>
<th>Transduction</th>
<th>Extra safety domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ide-cel</td>
<td>Murine</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>Cilta-cel</td>
<td>Bi-epitope</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>CAR-BCMA</td>
<td>Murine</td>
<td>CD28</td>
<td>γ-Retrovirus</td>
<td>No</td>
</tr>
<tr>
<td>CAR T-BCMA</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>Bb21217</td>
<td>Murine</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>Yes, PI3K inhibitor</td>
</tr>
<tr>
<td>CT053</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>P-BCA-101</td>
<td>Fully human</td>
<td>anti-BCMA centrin</td>
<td>4-1BB</td>
<td>PiggyBac DNA modification system</td>
</tr>
<tr>
<td>CT03A</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>JCARH125</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
<tr>
<td>MCARH171</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>γ-Retrovirus</td>
<td>Yes, tEGFR</td>
</tr>
<tr>
<td>FCARH143</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>Lentivirus</td>
<td>Yes, tEGFR</td>
</tr>
<tr>
<td>BCMA CAR-T</td>
<td>Fully human</td>
<td>4-1BB</td>
<td>γ-Retrovirus</td>
<td>Yes, tEGFR</td>
</tr>
<tr>
<td>KITE-585</td>
<td>Fully human</td>
<td>CD28</td>
<td>Lentivirus</td>
<td>No</td>
</tr>
</tbody>
</table>

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, cilta-celagen autoleucel; ide-cel, idecataegene vicleucel; PI3K, phospho-inositol 3-kinase; scFv, single-chain variable fragment; tEGFR, truncated human EGFR.
was the most common adverse event, occurring in 71% of those in the 2.5 mg/kg cohort and 77% of those in the 3.4 mg/kg cohort, leading to the Risk Evaluation and Mitigation Strategy (REMS) program associated with this agent. Based upon these results, the FDA approved dosing was 2.5 mg/kg and the median duration of response at this dose was 12.5 months.39,40

Belantamab mafodotin was a novel treatment option for RRMM patients; however, the drug was withdrawn from the market in November 2022 when the confirmatory phase 3 trial failed to meet its primary endpoint. The phase 3 DREAMM-3 study randomized patients with RRMM after 2 or more prior lines of therapy to receive either belantamab mafodotin or pomalidomide and dexamethasone (pom-dex). The primary endpoint was PFS. After a median follow-up of 11.5 months for belantamab mafodotin and 10.8 months for pom-dex, the median PFS was 11.2 months vs 7 months, respectively (HR, 1.03).41 Patients who responded to belantamab mafodotin were allowed to continue on the drug through a compassionate use program, which is currently the only access to this therapy outside of a clinical trial. Belantamab mafodotin is under investigation in a variety of different combinations for both early-relapse and late-relapse disease, and we anticipate results from these ongoing trials to determine the future role of this therapy in the management of MM patients.

Additional BCMA-directed ADCs remain under investigation as well. HDP-101 is a fully humanized, novel BCMA antibody conjugated to amanitin via a non-cleavable maleimidocaproyl linker. Amanitin differs from microtubule inhibitors in that it inhibits the transcription process by binding to eukaryotic RNA polymerase I, irrespective of the proliferation status of the target cells.42 In preclinical evaluation, HDP-101 showed cytotoxic to BCMA-positive MM cell lines, regardless of the BCMA expression level.43 A first-in-phase, phase 1/2a trial with HDP-101 is currently planned (NCT04879043).

BCMA-targeted ADC products hold promise for “off-the-shelf” therapy for the management of MM; however, further investigation is needed to determine the ideal combination and sequencing. It is worth noting that ADCs require ongoing infusions because the drug is cleared by malignant cells via receptor-mediated endocytosis. In addition, the bystander effect of the payload component may limit utilization.44 Novel cytotoxic payloads and ADC structure alterations are currently under investigation to improve efficacy and safety.45

**CAR T-Cell Therapy**

CAR T-cell therapy genetically modifies autologous T cells with a transgene that encodes a CAR to identify and eliminate cells expressing a tumor-associated antigen. Anti-BCMA CAR T cells will bind to the BCMA-expressing cells, which then transmits a signal to promote T-cell expansion and activation, eliminate target cells, and cause the CAR T cells to persist.36,45 There are currently more than 10 BCMA-targeted CAR T-cell products being investigated in clinical trials (Table 2). Although these CAR T-cell constructs have similarities, there are differences in the costimulatory domains, the species used to generate the anti-BCMA single-chain variable fragment (scFv), method of transduction (ie, lentiviral vs y-retroviral vectors), and the presence of additional safety domains. The most common toxicities associated with CAR T-cell therapy are cytokine release syndrome (CRS) and neurotoxicity, and these products have a REMS program associated with them.46 Unlike the ADCs that target BCMA, CAR T-cell therapy is not an “off-the-shelf” product and requires a manufacturing period of approximately 4 weeks, during which patients may require bridging therapy. Therefore, CAR T-cell therapy can be challenging to use in patients experiencing rapid disease progression.

The agent idecabtagene vicleucel (Abecma, Bristol Myers Squibb/2seventy Bio), also known as ide-cel or bb2121, is the first BCMA-targeted CAR T-cell therapy to be approved by the FDA for the treatment of RRMM after 4 prior lines of therapy.47 Ide-cel modifies autologous T cells with a lentiviral vector encoding a second-generation CAR, which includes a murine anti-BCMA scFv, a CD137 (4-1BB) costimulatory motif, and a CD3-zeta signaling domain.48 The approval of ide-cel was based on the phase 2 KarMMa trial in RRMM patients after 3 or more prior lines of therapy. A total of 128 patients received ide-cel, with 84% being triple-refractory and 26% being penta-refractory; the median number of prior lines of therapy was 6.49 After a median follow-up of 15.4 months, the ORR was 73%, the median PFS was 8.8 months, and the median duration of response was 10.7 months in all treated patients. Responses were observed in all subgroups, including those with extramedullary disease (ORR, 70%) and those with Revised International Staging System (R-ISS) stage III disease (ORR, 48%), both of which are difficult to treat. The most common adverse events were cytopenias (all grade, 97%) and CRS (all grade, 84%). Notably, only 5 patients (4%) had grade 3 CRS, 1 patient had grade 4 CRS, and 1 patient had grade 5 CRS.50 The confirmatory phase 3 KarMMa-3 trial, which was an international, open-label study, randomized 386 myeloma patients with 2 to 4 prior lines of therapy (including an IMiD, PI, and daratumumab) in a 2:1 ratio to receive either ide-cel or 1 of 5 standard-of-care regimens. At a median follow-up of 18.6 months, the median PFS was 13.3 months with ide-cel vs 4.4 months with standard of care (HR for disease progression
The median number of prior lines of therapy was 6. Ple-cell refractory, and 33% had high-risk cytogenetics. In a population of 157 patients, 77.7% of patients were triple-class refractory, and 84% were exposed to a penta drug. Patients had a median of 6 prior lines of therapy. After a median follow-up of 24 months, the ORR was 97.9%, and 82.5% achieved an sCR. Notably, responses deepened over time, and neither the median duration of response nor the median PFS were reached. Grade 3 or greater CRS and neurotoxicity rates were 4% and 9%, respectively. As previously mentioned, several other BCMA-directed CAR T-cell products are currently in development in addition to allogeneic and non-BCMA targeted CAR T cells. Ide-cel and ciltacabtagene autoleucel, also known as cilt-cel, LCAR-B38M or JN-4528 (Carvykti, Janssen Oncology/Legend Biotech), is a dual epitope-binding CAR T-cell construct directed against two distinct BCMA epitopes and was the second BCMA-targeted CAR T-cell product to receive FDA approval. The bi-epitope target improves the binding avidity and is unique to LCAR-B38M. CARTITUDE-1 was a single-arm, phase 1b/2 study in RRMM patients after 3 or more prior lines of therapy. A total of 97 patients received cilt-cel, of whom 99% were refractory to anti-CD38 therapy and 84% were exposed to a penta drug. Patients had a median of 6 prior lines of therapy. After a median follow-up of 24 months, the ORR was 97.9%, and 82.5% achieved an sCR. Notably, responses deepened over time, and neither the median duration of response nor the median PFS were reached. Grade 3 or greater CRS and neurotoxicity rates were 4% and 9%, respectively.

As previously mentioned, several other BCMA-directed CAR T-cell products are currently in development in addition to allogeneic and non-BCMA targeted CAR T cells. Ide-cel and cilt-cel are also being investigated in earlier lines of therapy. The precise role, combination, and sequencing of CAR T cells in relation to traditional MM therapy has yet to be fully determined, and ongoing trials will play a role in shaping this. It is important to highlight that ide-cel and cilt-cel offer a potential “one-and-done” treatment option for RRMM patients, which can be an attractive option for those who have been on continuous therapy for many years.

**Bispecific Antibodies**

Bispecific antibodies (BiAbs) engage both CD3+ T cells and a tumor-associated antigen (eg, CD19, CD33, or BCMA), which leads to cancer cell death and T-cell proliferation. CRS is a common adverse event with BiAbs, whereas neurotoxicity is much less common than with CAR T-cell therapy. Teclistamab (Tecvayli, Janssen Biotech), also known as JNJ-64007957, is a first-in-class BCMA/CD3 T-cell–redirecting bispecific IgG4 antibody that received FDA approval in 2022 for RRMM after 4 or more prior lines of therapy. This recent approval was according to results from the phase 1/2 MajesTEC-1 study. In the overall population of 157 patients, 77.7% of patients were triple-class refractory, and 33% had high-risk cytogenetics. The median number of prior lines of therapy was 6. The ORR was 63%, with 58.8% of patients achieving a VGPR or better, and the median duration of response was 18.4 months. The median PFS was 11.3 months, and the median OS was also 11.3 months. The most common adverse events were neutropenia (all grade, 70.9%; grades 3-4, 64.2%) and CRS (all grade, 72.1%; grades 3-4, 6.0%). The median time to onset of CRS was 2 days (range, 1-6) and the median duration of CRS was 2 days (range, 1-9). Infections occurred in 76.4% of patients, and hypogammaglobulinemia occurred in 74.5% of patients. Patients on teclistamab should be monitored closely for neutropenia, infections, and hypogammaglobulinemia, and proper prophylaxis again infections and intravenous immunoglobulin should also be initiated when appropriate. Additionally, there is a REMS program associated with teclistamab owing to CRS and neurotoxicity. This REMS program states that patients are to be monitored for 48 hours following the 2 step-up doses as well as the first full treatment dose before starting the once-weekly 1.5 mg/kg dosing. Although this is an “off-the-shelf” product with the ease of subcutaneous administration, there are logistical applications that must be considered before starting a patient on teclistamab, including inpatient vs outpatient administration of the step-up doses.

The development of BiAb therapy, which includes different administration techniques and dosing frequencies, is an ongoing process and has been described in previous reviews. There are several other BCMA-targeting BiAbs (including elranatamab and REGN5458), as well other targets including GPRC5D (eg, talquetamab), and FcRH5 (eg, cevostamab), that are currently under investigation and will offer additional treatment options for patients with RRMM. Of note, BiAbs do require functioning T cells to be most efficacious, which should be considered when discussing the ideal sequencing of BCMA-targeted products.

**Future Directions**

The treatment landscape of MM is continuously evolving. In addition to the novel therapies that have already been reviewed, we also have next-generation IMiDs, including iberdomide (CC-220) and mezigdomide (CC-92480), which have shown activity in pomalidomide-resistant disease. Iberdomide and mezigdomide are oral agents that are structurally similar to currently available IMiDs; however, these novel cereblon modulators bind to cereblon with a higher affinity than lenalidomide or pomalidomide do. Mutation-driven therapy is also emerging, allowing for customized treatment plans according to a patient’s specific disease mutations. Vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and dabrafenib (Tafinlar, Novartis) as monotherapy are being investigated in MM...
patients who have a \textit{BRAF} mutation.\textsuperscript{59} There are also ongoing trials combining a \textit{BRAF} inhibitor with a MEK inhibitor (eg, dabrafenib with trametinib [Mekinist, Novartis] or encorafenib [Braftovi, Pfizer] with binitemelinib [Mektovi, Pfizer]) in attempts to subvert potential escape mechanisms and development of resistance.\textsuperscript{60} These combinations offer an all-oral drug therapy option with novel mechanisms of action and are an intriguing option for personalized medicine.

Conclusion

MM remains an incurable malignancy, so the purpose of new treatment regimens in both the newly diagnosed and the relapsed setting is to achieve deeper and more durable responses. The addition of anti-CD38 mAbs to the frontline setting has led to higher rates of sCR as well as MRD negativity, and is becoming a widely accepted standard for transplant-eligible patients. We are also starting to use a risk-stratified approach to induction and maintenance regimen selection.

In the relapsed setting, there is no single universally accepted standard approach, with patient- and disease-specific factors influencing treatment selection. Anti-CD38 combination regimens are the most commonly used triplet approach in first relapse, and we have seen improvement in late relapse outcomes with the utilization of CAR T-cell therapy and BiAbs. Ongoing investigations seek to provide further clarification on proper sequencing and combination of all our available therapies to treat MM, and we will continue to see the treatment paradigm shift and grow.

Disclosures

Dr Maple has served as consultant for GlaxoSmithKline, Janssen, Karyopharm, Pfizer, and Sanoft-Aventis. Dr Scott has no relevant financial disclosures. Dr Lonial has received research funding from Bristol Myers Squibb, Celgene, and Takeda, and has been a consultant for AbbVie, Amgen, Bristol Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Janssen, Novartis, Pfizer, and Takeda.

References

23. Xpovio (selinexor) [prescribing information]. Newton, MA: Karyopharm; 2022.


