

The Management of Relapsed and Refractory Multiple Myeloma

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ABSTRACT

The treatment of patients with relapsed and refractory multiple myeloma has become increasingly complex due to the rising number of available therapies. Patients are also increasingly exposed to, and refractory to, multiple classes of therapy at the time of progression. Patients who are at an early point in their myeloma disease course are likely to have several effective options, but choices and prognosis are limited for relapsing patients who are more heavily pretreated, particularly if they are at least triple-class refractory. When selecting the next line of therapy, it remains essential to consider patient comorbidities and frailty as well as treatment history and disease risk. Fortunately, the myeloma treatment landscape continues to evolve with the development of therapies directed toward new biologic targets, such as B-cell maturation antigen. These new agents, including bispecific T-cell engagers and chimeric antigen receptor T-cell therapy, have shown unprecedented efficacy in late-line myeloma and will be increasingly used at earlier time points. Novel combinations of currently approved treatments, including quadruplets and salvage transplantation, also remain important options for consideration.

PERSPECTIVE

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Introduction

Multiple myeloma (MM) is a plasma cell malignancy that remains incurable, but survival is increasing due to ongoing development of new therapies. The median survival of a patient with newly diagnosed MM is estimated to be between 5 and 8 years.¹ Historically, the treatment of newly diagnosed MM has focused on fitness for autologous transplant, with recent changes due to the use of monoclonal antibodies, quadruplets, and intensified consolidation and maintenance to try to increase depth and duration of response and overcome high-risk disease features. The ever-expanding landscape of antimyeloma therapies provides more options for the next line of treatment at the time of disease relapse. It can be challenging for clinicians to integrate the results of clinical trials that have differing eligibility criteria from their patient's clinical situation to choose the “best” next line of therapy upon myeloma progression. This article will provide an overview of the current approach to treating patients with relapsed and relapsed/refractory multiple myeloma (RRMM), with a focus on practical decision-making and emerging therapeutic options.

Definition of Relapsed Myeloma

Relapsed myeloma is defined as disease progression after response to initial treatment.² The current standard definition for progressive myeloma was last updated by the International Myeloma Working Group (IMWG) in 2016.³ Changes in laboratory parameters, imaging findings, or new clinical features can be utilized as criteria for progressive disease (**Table 1**).³ IMWG guidelines state that, ideally, the documentation of progression involves consecutive discrete measurements of a parameter; they also suggest that serum free light chains be utilized only if serum and urinary monoclonal protein are unmeasurable. In practice, a patient who relapses with a new clinical feature, such as hypercalcemia or renal insufficiency, should be treated

urgently. Patients with low-risk MM, with low-level biochemical recurrence—ie, less than the IMWG bar—can often wait some time before new treatment begins. RRMM implies that a patient meets the definition of progression either during therapy or within 60 days of their last treatment.

Molecular Testing

Newly diagnosed MM has been clinically subclassified on the basis of recurrent cytogenetic abnormalities, some with prognostic implications.^{4,5} Ultimately, the revised international staging system (R-ISS) incorporated deletion 17p, t(4;14), and t(14;16) as the relevant

genetic markers for high-risk myeloma.⁶ Additional abnormalities that convey poorer prognosis include t(14;20) and gain (≥3 copies)/amplification (≥4 copies) 1q.⁷ Gene expression profiling can identify additional high-risk signatures, but it is not widely available.⁸ Analysis of next-generation sequencing (NGS) of whole genome data from a data repository determined that patients with newly diagnosed MM with either biallelic inactivation of *TP53* or amplification of *CKS1B* in the setting of ISS3 disease had an extremely poor prognosis, with a median overall survival (OS) of 20.7 months. While this specific finding was coined “double-hit” myeloma,⁹ this

terminology can be generalized. Co-presence of the other high-risk genetic features, including gain of 1q concurrent with t(4;14), t(14;16), or del(17p),¹⁰ also has an additive deleterious prognostic effect.¹¹ Although some mutations appear to be “founder” events, patients can acquire new mutations, including deletions of p53 or gain of 1q, at relapse.¹²⁻¹⁴ Furthermore, due to technical issues, important mutations with treatment implications, such as t(11;14), are sometimes missed, particularly if fluorescence in situ hybridization (FISH) testing is not performed on sorted plasma cells. Therefore, we recommend repeating FISH analysis at the time of relapse.

Minimal residual disease (MRD) testing in MM can be performed on bone marrow aspirate to assess for depth of disease response at an increased sensitivity.^{3,15} As data regarding the importance of sustained MRD after initial treatment continue to grow, there is emerging evidence that attainment of MRD negativity following treatment for relapse appears to be important as well. Attainment of MRD negativity was associated with prolonged progression-free survival (PFS) and OS in patients with RRMM in a meta-analysis; MRD negativity may overcome high cytogenetic risk.¹⁶ Achievement of sustained MRD negativity,¹⁷ and the combination of MRD negativity with complete response,¹⁸ are both associated with prolonged PFS in patients with RRMM. Loss of MRD negativity is associated with an increased risk of disease progression.^{19,20} The optimal management of patients who have lost MRD negativity but have not yet met criteria for progression is unknown, and the role of preemptive therapy is being evaluated in clinical trials.^{21,22}

Stratification for Treatment Selection

Both disease-related and patient-related factors must be considered when deciding on an approach to treatment at

TABLE 1. International Myeloma Working Group (IMWG) Criteria for Myeloma Disease Progression³

IMWG criteria for progressive multiple myeloma

Increase of 25% from lowest measured response value in:

- Serum M protein, absolute increase ≥0.5 g/dL
 - Absolute increase ≥1 g/dL if minimum M protein ≥5 g/dL
- Urine M protein, absolute increase ≥200 mg/day
- Difference between involved and uninvolved free light chains, absolute increase ≥10 g/dL
 - Light chain criteria can only be used if no measurable serum or urine M protein
- Bone marrow plasma cell percentage regardless of baseline status, absolute increase ≥10 %
 - Bone marrow criteria can only be used if no measurable light chains or serum or urine M protein

On imaging:

- Discovery of new lesions
- Increase of ≥50% in sum of products of maximal perpendicular diameters of more than 1 lesion
- Increase of ≥50% in the longest diameter of previous lesion that was >1 cm on short axis measurement
- Increase of ≥50% in circulating plasma cells (minimum of 200 cells/μL) if there are no other measures of disease

IMWG criteria for clinical progression of multiple myeloma

Detection of new or increasing end-organ dysfunction (such as CRAB: calcium elevation, renal insufficiency, anemia, bone abnormalities) related to underlying myeloma

- Hypercalcemia (>11 mg/dL)
- Rise in serum creatinine by ≥2 mg/dL
- Decrease in hemoglobin by ≥2 g/dL not related to another cause
- New bone lesions or soft tissue plasmacytomas
- Increase in size of bone lesion or plasmacytoma by ≥50% and ≥1 cm as measured by sum of products of maximal perpendicular diameter
- Hyperviscosity due to paraprotein

PERSPECTIVE BY

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Emerging Strategies to Manage Relapsed and/or Refractory Multiple Myeloma

Multiple myeloma (MM) remains a malignancy that is largely incurable but highly treatable. The prognosis for patients with MM has improved substantially over the past 2 decades with the introduction of therapeutics that have improved patient quality of life and prolonged overall survival (OS). However, nearly all patients with MM ultimately relapse, including those who have experienced a complete response to initial therapy.^{1,2} Clinicians are challenged to determine how to treat relapsed and/or refractory MM (RRMM) by integrating previously administered therapies, patient comorbidities, potential treatment-related adverse events, putative benefit of emerging agents, financial toxicity, and patient wishes. In the current issue, Gahvari and Callander provide a comprehensive overview of the current approach to treating patients with RRMM with a focus on practical decision-making and the role of emerging therapeutic options.

At diagnosis, the genetic, epigenetic, metabolic, and cellular architecture of MM is complex and heterogeneous across patients. Somatic mutations, chromosomal translocations, deletions, and epigenetic modifications within each patient are evident and drive clonal evolution. Clonal diversity continuously evolves throughout the treatment continuum, and patients harbor multiple subclones.³ Disease progression leads to the emergence of drug resistance and eventually to relapsed/refractory disease.⁴ Relapsed and progressive MM acquires additional mutations and genetic alterations that render the disease more resistant, leading to progressively shorter durations of remission or response to each salvage therapy. The heterogeneity of myeloma cells within each patient highlights the need to simultaneously target multiple pathways.

Selection of an optimal strategy at relapse is more complicated because at least 10 classes of drugs have been FDA approved for MM, including alkylators, steroids, proteasome inhibitors, histone deacetylase inhibitors, nuclear export inhibitors, immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), peptide-drug conjugates, chimeric antigen receptor (CAR) T cells, and bispecific T-cell engagers (BiTEs). With the exception of CAR T cells and BiTEs, these antimyeloma drugs have been combined in doublet, triplet, or quadruplet regimens and have been delivered, when appropriate, antecedent to autologous stem cell transplantation (ASCT).²

As Gahvari and Callander point out, there is currently no consensus treatment for patients with RRMM. While multiple regimens have been approved, none have been evaluated head to head, and individual registry trials have enrolled different patient populations with dissimilar treatment histories. Collectively, these studies demonstrate the benefit of a triplet over doublet regimen at relapse. Based upon results from the phase 3 POLLUX study (NCT02076009), the addition of daratumumab to lenalidomide and dexamethasone significantly lengthened progression-free survival (PFS) among patients with RRMM.⁵ For patients with newly diagnosed MM who were ineligible for ASCT, the risk of disease progression or death was significantly lower among those who received daratumumab, lenalidomide and dexamethasone than among those who received lenalidomide and dexamethasone alone.⁶ While daratumumab/lenalidomide/dexamethasone demonstrated superior OS, the study utilized an IMiD-naïve patient population. Regimens that combined mAbs—*isatuximab/carfilzomib/dexamethasone*, and *daratumumab/carfilzomib/*

the time of myeloma progression. An important consideration is the potential harm to the patient from myeloma-related morbidity if a response is not achieved or is not durable. Patients with high-risk

disease, or who are heavily pretreated, are at risk for early relapse and transient responses to systemic therapy, and they should be considered for clinical trials, novel agents, and cellular therapy, or the

standard-of-care options with the highest probability of effectiveness. However, disease risk needs to be weighed against patient comorbidities, frailty, and patient preferences and goals.

dexamethasone—also demonstrated improved PFS in early-line relapsed disease. These regimens merit consideration in lenalidomide-refractory and mAb-naïve patients. There are also limited data on the ideal or recommended sequence of mAbs in the RRMM setting. Isatuximab can directly induce apoptosis in myeloma cells, whereas daratumumab cannot induce cell death without being combined with cross-linking agents. Isatuximab also modulates CD38 enzymatic activity more effectively than daratumumab and may benefit daratumumab-refractory patients, whereas elotuzumab may have reduced efficacy following daratumumab-based therapy.

Patients who are actively relapsing after exposure to multiple lines of therapy (ie, late-line relapse) are likely to be at least triple-class refractory and penta-class exposed. Hence, historically, the likelihood of a response to the next line of therapy is low, regardless of the agent. Bendamustine, as monotherapy or combined with proteasome inhibitors or IMiDs, can elicit responses. Selinexor-based therapy has some benefit. Intensive regimens including PACE (cisplatin, doxorubicin, cyclophosphamide, and etoposide) or hyperfractionated cyclophosphamide-based regimens (with or without bortezomib or daratumumab) can serve as a temporizing bridge to the next line of therapy for aggressive relapses.

The scarcity of trials that have integrated the first salvage regimen into the assessment of frontline therapies to define optimal treatment sequencing in homogeneous or similar patient populations is also problematic. The management of RRMM is made even more complex with the advent of quadruplet therapy for transplant-eligible patients. The phase 2 GRIFFIN trial (NCT02874742) highlighted deeper and more sustained responses with upfront daratumumab plus lenalidomide, bortezomib, and dexamethasone than with lenalidomide, bortezomib, and dexamethasone alone.⁷ Earlier exposure to daratumumab will significantly affect the approach to second-line therapy.

Gahvari and Callander highlight exciting cellular and immunotherapeutics that constitute the next frontier for the management of RRMM. Real-world experience with FDA-approved regimens in specific populations should further guide therapy beyond subgroup analysis of registry trials. For example, the management of patients with primary refractory MM vs those being treated for relapsed MM after

a treatment-free interval is of particular importance and may mandate a more cellular immunologic approach compared with current approaches. Also, integrating high-risk cytogenetics (eg, 1q gain) into treatment decisions has not been uniformly applied in trials or real-world practice. Two B-cell maturation antigen (BCMA)-directed CAR T-cell agents, idecabtagene vicleucel and ciltacabtagene autoleucel, have shown efficacy in patients previously challenged with 3 lines or more of therapy.^{8,9} Teclistamab is a BiTE that targets CD3-positive T cells and BCMA-positive myeloma cells and is now FDA approved for patients who have received 3 prior lines of therapy.¹⁰ GC012F is an autologous BCMA-CD19 dual-targeting CAR T-cell therapy. In a phase 1 single-arm study, deep and durable responses as well as a favorable safety profile were reported with GC012F in patients with heavily pretreated RRMM. Based on these results, the safety and feasibility of GC012F were tested frontline for patients with newly diagnosed with MM who are high risk and transplant eligible.¹¹ Again, a favorable safety profile and high efficacy, with a 100% objective response rate and 100% minimal residual disease negativity, were reported.

Broader adoption of cellular therapies within the global immuno-oncology market requires careful consideration of costs, and unique toxicities, product quality standardization, and overcoming barriers to minimize production delays. It requires solving health care-related cost-to-value, coverage restrictions, and reimbursement issues. Finally, the broad administration of cellular therapies and the expansion of precision medicine approaches to treat MM will impact patient distribution to community oncologists, academic health centers, and specialized clinical centers that are designed to streamline CAR T-cell production, distribution, and administration. The past 2 decades have seen significant progress in MM, but the future therapeutic landscape may be even more promising, as more effective agents that overcome RRMM are developed and are better tolerated. ■

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For references visit
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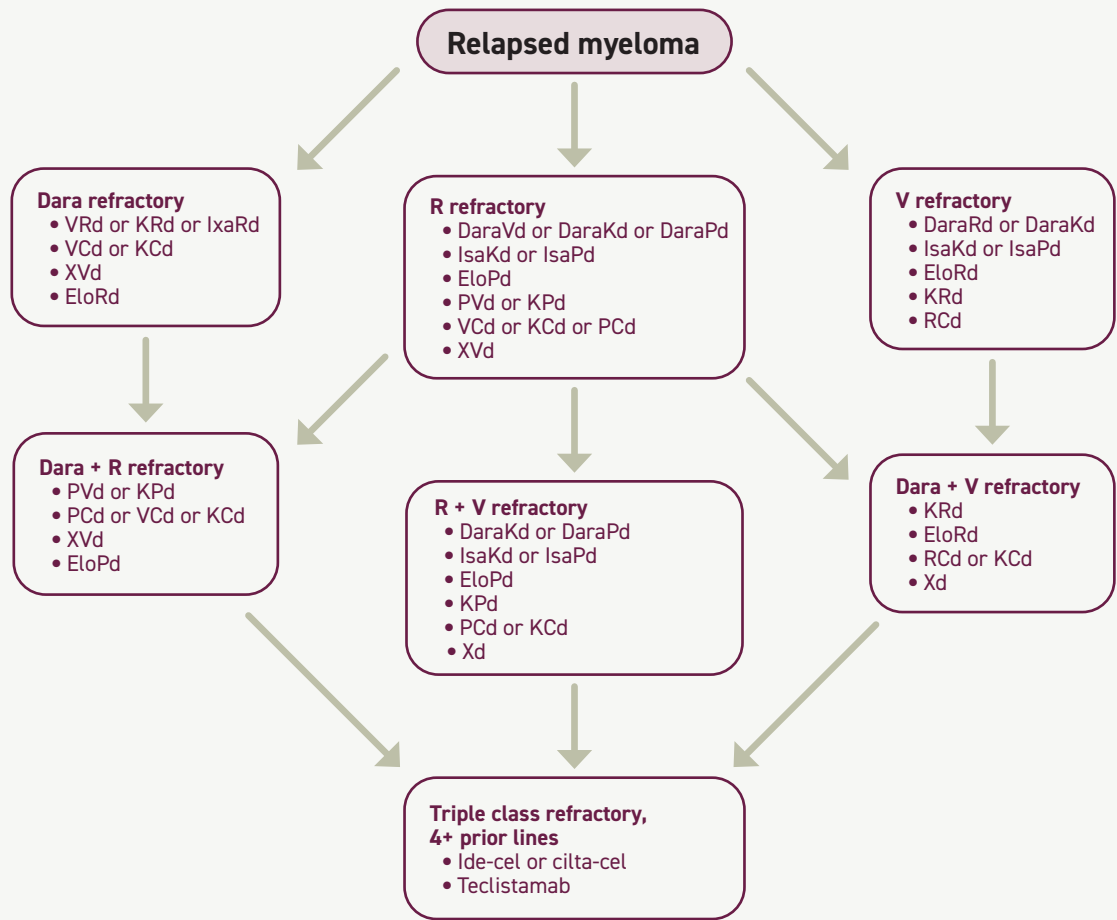
High-risk Disease Features

Although myeloma risk stratification is traditionally performed at the time of diagnosis, the R-ISS classification has been shown to continue to convey

prognostic information if recalculated in patients at the time of relapse.²³ In addition to R-ISS status, high-risk genetic features, and lactate dehydrogenase levels,²⁴ other findings

associated with poorer prognosis at relapse include the presence of extramedullary disease,²⁵ circulating plasma cells and plasma cell leukemia,²⁶ and renal insufficiency.²⁷

FIGURE. Relapsed Myeloma Treatment Algorithm



Relapsed myeloma considerations

- At any relapse: Evaluate for clinical trial.
- Elderly or frail: Consider starting with dose reduction or doublet and utilizing monoclonal antibody.
- Autologous stem cell transplant: Consider if no previous transplant or if time to progression is after first transplant at least 3 years.
- Aggressive relapse: If not refractory, consider K, Isa or Dara, immunomodulator.
- If t(11;14), then venetoclax.

C, cyclophosphamide; cilta-cel, ciltacabtagene autoleucel; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; ide-cel, idecabtagene vicleucel; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib (Kyprolis); P, pomalidomide; R, lenalidomide (Revlimid); V, bortezomib (Velcade); X, selinexor (Xpovio).

An additional risk factor is rapid time to progression after previous therapy. Early relapse after induction therapy or transplant is ominous and portends a poor prognosis even when receiving modern antimyeloma therapy; this phenomenon can occur even in the

absence of high-risk cytogenetics.²⁸ Relapse within 12 months of initial therapy has been associated with a median OS ranging between 21 months and 26 months in data from 2 different studies, compared with median OS of 91 months or longer for patients with later relapses.^{29,30}

Effect of Previous Treatment History

Relapsed myeloma is characterized by a progressively shorter duration of response with each subsequent line of therapy.³¹ However, as triplet combinations and maintenance therapy have become more common in

myeloma care, patients are more likely to be exposed or refractory to the main classes of antimyeloma treatment at the time of progression. Newer terminology to describe such patients includes (1) triple-class exposed or refractory, meaning exposed or refractory to an immunomodulator (IMiD), proteasome inhibitor (PI), and anti-CD38 monoclonal antibody, and (2) penta-class exposed or refractory, meaning exposed or refractory to 2 IMiDs, 2 PIs, and an anti-CD38 antibody.³² The prognosis of such patients is dismal: In a multicenter retrospective analysis, triple-class refractory patients experienced a median PFS and OS of 2.8 months and 10.3 months respectively, while penta-class refractory patients experienced a median PFS and OS of 2.5 months and 6.9 months, respectively.³³

Elderly and Frail Patients

Frailty can be defined as an age-associated decline in multiple physiologic systems leading to increased vulnerability in the setting of stressors.³⁴ The optimal treatment of frail patients with relapsed myeloma can be challenging, and a balance needs to be struck between dose intensity and toxicity. Frail patients with myeloma are at increased risk for treatment-related adverse events causing premature treatment discontinuation and poorer survival.³⁵ Randomized prospective studies enrolling elderly, frail, and/or transplant-ineligible patients have focused on the newly diagnosed only. Although scoring systems have been developed to help clinicians assess frailty and guide treatment decisions, frailty scores have been validated only for survival outcomes in patients newly diagnosed with MM and not in those with relapsed disease.³⁶⁻³⁹

In recent clinical trials of RRMM, elderly and/or frail patients have benefited when newer therapies are added to established backbones. Separate subgroup analyses of trials comparing carfilzomib-, pomalidomide-,

daratumumab-, and isatuximab-based triplets with doublets suggest a preserved efficacy and survival advantage.⁴⁰⁻⁴³ However, it is possible that older patients enrolled in these trials are not particularly representative of the general elderly RRMM population, who would be less likely to meet the rigorous entry criteria for such trials.

Frail patients may lose the opportunity to benefit from the most effective therapies if those therapies are not offered early: A real-world study found an attrition rate of more than 40% at every instance of disease progression throughout the entire MM course of transplant-ineligible patients.⁴⁴ When in doubt regarding a patient's frailty, it may be preferable to start treatment at a lower dose or doublet and escalate if tolerated or there are improvements in functional status.⁴⁵

Therapy Selection

Regimens for relapsed myeloma can be classified on the basis of their approval: for early-line relapse (1-3 prior lines of therapy) or late-line relapse (4 or more prior lines of therapy). Unsurprisingly, published clinical trial data that are used to guide treatment decisions are not applicable to all real-world situations.⁴⁶ If available, clinical trial opportunities should be pursued for all patients.

Early-Line Relapse

Most patients will have previously received induction therapy with a triplet combination containing steroids and 2 of the following: a PI, IMiD, or anti-CD38 antibody. However, some patients are now receiving antibody-based quadruplets in the front line. Patients presenting with renal failure at the time of their myeloma diagnosis may have received a cyclophosphamide-based regimen. Some patients may have received up-front autologous transplant, and many will have received maintenance therapy regardless of whether they underwent transplant.⁴⁷

The main principles of choosing a new regimen are to (1) utilize at least one therapeutic class not used in induction, (2) avoid agents to which a patient is not sensitive or is refractory, and (3) account for toxicities caused by previous treatment. Therapies that were previously effective and have not been utilized recently, to which the patient is not refractory, can be retried.⁴⁸ An algorithmic approach to selecting therapy is shown in the **Figure**.

Data from recent randomized phase 3 trials, all of which highlight approved combinations for early-line relapse, are shown in **Table 2**.⁴⁹⁻⁶⁹ These regimens all demonstrate the benefit of utilizing a triplet over a doublet at relapse if tolerated. It is hard to directly compare the listed triplet regimens because none were evaluated head to head and the trials all enrolled at least somewhat different patient populations with different previous treatment histories. Daratumumab/lenalidomide (Revlimid)/dexamethasone (DaraRd), daratumumab/bortezomib (Velcade)/dexamethasone (DaraVd), carfilzomib (Kyprolis)/lenalidomide/dexamethasone (KRd), elotuzumab/lenalidomide/dexamethasone (EloRd), and isatuximab/pomalidomide/dexamethasone (IsaPd) all showed a benefit in median OS as compared with their control arms.^{51,54,59,61,63} The other trials do not yet have mature OS data for reporting purposes, except for the comparison of lenalidomide/dexamethasone (Rd) with ixazomib/Rd, which showed a PFS but not an OS benefit to adding ixazomib, possibly due to differences in treatment received between the 2 arms after progression.⁶⁹ While DaraRd demonstrates the best OS outcome numerically, the study involved a patient population that was almost completely IMiD unexposed, emphasizing why many expert panels recommend utilizing IMiD-based combinations in patients sensitive to them. It should also be noted

that bortezomib in DaraVd was stopped after 8 cycles to minimize toxicity. Regimens combining monoclonal antibodies with carfilzomib—namely, isatuximab/carfilzomib/dexamethasone (IsaKd) and daratumumab/carfilzomib/dexamethasone (DaraKd)—demonstrated the second- and third-longest reported PFS, respectively, among patients with myeloma with early-line relapse, although OS data have yet to be reported for either combination. These 2 regimens merit strong consideration in patients who are lenalidomide refractory and have not yet been treated with a monoclonal antibody.

In general, if a patient has not been

previously exposed or demonstrated resistance to a monoclonal antibody, they should receive one as part of their next line of therapy. However, there are limited data on the next best choice of regimen if a patient has previously received a monoclonal antibody. There are also limited data on the ideal sequencing of monoclonal antibodies. Isatuximab may have modest clinical benefit in daratumumab-refractory patients,⁷⁰ while elotuzumab-based regimens may display reduced efficacy when administered after daratumumab-based therapy.⁷¹ Many experts recommend not re-treating

with an anti-CD38 antibody, unless the patient is more than 6 months from the last dose and was not refractory.

Another area of uncertainty is selection of therapy for patients with high-risk disease, as not all trials incorporate the same definition of high-risk cytogenetics, use the same threshold for cytogenetic positivity, or utilize R-ISS staging. Many trials are also missing cytogenetic data on significant numbers of patients; for example, in the trial comparing carfilzomib/dexamethasone (Kd) with DaraKd, cytogenetic data were not available for more than 50% of enrolled patients. With the

TABLE 2. Data From Recent Randomized Phase 3 Trials of Early-Line Relapsed Myeloma⁴⁶⁻⁶⁹

Trial	Total pts ^a	Median (range) prior lines of treatment ^{a,b}	Prior treatments	ORR	Median PFS (mo)	Median OS (mo)
POLLUX: DaraRd vs Rd ⁴⁹⁻⁵¹	569	1 (1-11)	Refract IMiD: 7.4% Refract PI: 21.8%	92.9% vs 76.4%	44.5 vs 17.5	67.6 vs 51.8
CASTOR: DaraVd vs Vd ⁵²⁻⁵⁴	498	2 (1-10)	Refract R: 28.3% Prior PI: 68.5%	84.6% vs 63.2%	16.7 vs 7.1	49.6 vs 38.5
CANDOR: DaraKd vs Kd ^{55,56}	466	2 (1-3)	Refract R: 33.0% Refract V: 29.0%	84.3% vs 72.7%	28.6 vs 15.2	NR
APOLLO: DaraPd vs Pd ⁵⁷	304	2 (1-5)	Refract R: 79.3% Refract PI: 48.0%	68.9% vs 46.4%	12.4 vs 6.9	NR
ASPIRE: KRd vs Rd ^{58,59}	792	2 (1-3)	Refract IMiD: 21.8% Nonresp PI: 14.9%	87.1% vs 66.7%	26.1 vs 16.6	48.3 vs 40.4
ELOQUENT-2: EloRd vs Rd ^{60,61}	646	2 (1-4)	Refract T: 9.9% Refract V: 21.8%	78.5% vs 65.5%	19.4 vs 14.9	48.3 vs 39.6
ICARIA-MM: IsaPd vs Pd ^{62,63}	307	3 (2-4)	Refract R: 92.5% Refract PI: 75.9%	63.0% vs 33.3%	11.5 vs 6.5	24.6 vs 17.7
IKEMA: IsaKd vs Kd ^{64,65}	302	2 (1-3)	Refract R: 32.8% Refract PI: 33.1%	86.6% vs 82.9%	35.7 vs 19.2	NR
OPTIMISSM: PVd vs Pd ⁶⁶	559	2 (1-4)	Refract R: 69.9% Refract PI: 13.2%	82.2% vs 50.0%	11.2 vs 7.1	NR
BOSTON: XVd vs Vd ⁶⁷	402	2 (1-3)	Prior R: 38.3% Prior V: 69.4%	76.4% vs 62.3%	13.93 vs 9.46	NR
TOURMALINE-MM1: lXRd vs Rd ^{68,69}	722	1 (1-3)	Refract T: 12.5% Refract PI: 1.7% Prior V: 69.0%	78.3% vs 71.5%	20.6 vs 14.7	53.6 vs 51.6

^aCombined between experimental and control groups.

^bEstimated.

d, dexamethasone; dara, daratumumab; elo, elotuzumab; IMiD, immunomodulator; isa, isatuximab; ix, ixazomib; K, carfilzomib (Kyprolis); mo, months; nonresp, nonresponder to; NR, not reached; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; PI, proteasome inhibitor; pt, patient; R, lenalidomide (Revlimid); refract, refractory to; T, thalidomide; V, bortezomib (Velcade); X, selinexor (Xpovio).

TABLE 3. Antimyeloma Regimens From Smaller Studies⁷⁵⁻⁸¹

Trial	Total pts	Median (range) prior lines	Prior treatment	ORR	Median PFS (mo)
Ven-d ⁷⁵	31	5 (2-12)	Refract IMiD: 87.1% Refract PI: 87.1% Refract Dara: 87.1%	48.4%	10.8 ^c
ELOQUENT-3: EloPd vs Pd ^{76,77}	117 ^a	3 (2-8) ^{a,b}	Refract R: 87.2% ^a Refract PI: 80.3% ^a	53.3% vs 26.3%	10.3 vs 4.7
KPd ⁷⁸	47	2 (1-3)	Refract R: 100% Refract V: 44.7%	61.7%	10.3
PCd vs Pd ⁷⁹	70 ^a	4 (2-12) ^{a,b}	Refract R: 100% ^a Refract V: 74.3% ^a Refract K: 41.4% ^a	64.7% vs 38.9%	9.5 vs 4.4
KCd ⁸⁰	75	2 (1-3)	Prior IMiD: 81.3% Prior PI: 86.7%	85.3%	17.0
VCd vs RCd ⁸¹	155 ^a	1 ^{a,b}	Prior IMiD: 51.6% ^a Prior T: 42.6% ^a Prior V: 51.0% ^a	64.5% vs 79.7%	16.3 vs 18.6

^aCombined between experimental and control groups.

^bEstimated.

^cReported as TTP and not PFS.

C, cyclophosphamide; d, dexamethasone; Elo, elotuzumab; IMiD, immunomodulator; K, carfilzomib (Kyprolis); mo, months; ORR, overall response rate; P, pomalidomide; PFS, progression-free survival; PI, proteasome inhibitor; pt, patient; R, lenalidomide (Revlimid); refract, refractory to; TTP, time to progression; V, bortezomib (Velcade); ven, venetoclax; X, selinexor (Xpovio).

increasing recognition of the negative prognostic implications of gain 1q, more trials are incorporating this into their classification of high-risk cytogenetics. One post hoc subgroup analysis suggested that isatuximab may be able to overcome the negative impact of isolated gain 1q.⁷² Other subgroup analyses have suggested that selinexor may be efficacious in patients with 17p deletions as well as in those with RAS-mutated myeloma; neither analysis was statistically powered.^{73,74} While these findings are intriguing, they will need to be confirmed prospectively before they can be used to guide treatment decisions.

Other Regimens

Table 3 lists examples of other effective antimyeloma regimens that have not been studied in large or randomized trials.⁷⁵⁻⁸¹ Some have been studied at later relapse but can be effective earlier as well. Of note, venetoclax is highly active

in myeloma with t(11;14), and venetoclax-based therapy should be strongly considered in this subset of patients. Although venetoclax with bortezomib and dexamethasone was associated with increased mortality among unselected patients with RRMM, it was recognized that the subset of patients with t(11;14) experienced improved outcomes.⁸² These findings were later confirmed in a phase 1/2 trial of venetoclax and dexamethasone.⁷⁵

The carfilzomib/pomalidomide/dexamethasone (KPd) regimen is efficacious in relapsed myeloma,^{78,83,84} as are pomalidomide/cyclophosphamide/prednisone⁸⁵ or dexamethasone (PCd)⁸⁶⁻⁸⁸ and carfilzomib/cyclophosphamide/dexamethasone (KCd),^{80,89} but none have been analyzed in randomized controlled studies. Although frequently utilized in the first-line, bortezomib or lenalidomide can be used in relapsed disease, although they have rarely been

compared prospectively. One phase 3 trial did compare fixed-duration bortezomib/cyclophosphamide/dexamethasone (VCd) with lenalidomide/cyclophosphamide + dexamethasone (RCd) in patients at first relapse; RCd had higher response rates but similar PFS.⁸¹ Of the trials listed in **Table 2**, the only combination with a demonstrated OS benefit is elotuzumab pomalidomide/dexamethasone, which led to a median OS of 29.8 months compared with 17.4 months with pomalidomide/dexamethasone (Pd) alone.

Salvage Transplantation

For all patients who are candidates for autologous transplant and have not received this frontline therapy, transplant is recommended as second-line therapy based on data from multiple studies showing similar OS comparing delayed transplant with frontline transplant.⁹⁰⁻⁹² While a new course

TABLE 4. Published Phase 2 Trial Results of BCMA-Directed Therapies

Trial	Total pts	Median (range) prior lines	Prior treatment	ORR	Median PFS (mo)
DREAMM-2 Belantamab mafodotin ^{112,113}	97	7 (3-21)	TCR: 100%	32.0%	2.8
KarMMa Ide-cel ¹¹⁷	128	6 (3-16)	TCR: 84.4% PCR: 25.8%	73.4%	8.8
CARTITUDE-1 Cilta-cel ^{118,121}	97	6 (4-8)	TCR: 87.6% PCR: 42.3%	97.9%	NR; 54.9% at 27 mo
MajestEC-1 Teclistamab ¹²⁴	165	5 (2-14)	TCR: 77.6% PCR: 30.3%	63.0%	11.3

BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucl; dara, daratumumab; ide-cel, idecabtagene vicleucl; K, carfilzomib (Kyprolis); mo, months; NR, not reached; ORR, overall response rate; P, pomalidomide; PCR, penta-class refractory; PFS, progression-free survival; pt, patients; R, lenalidomide (Revlimid); TCR, triple-class refractory; V, bortezomib (Velcade).

of systemic therapy is often administered prior to salvage transplant, in retrospective studies the use of reinduction has not been associated with improved duration of response or OS after transplant.^{93,94} Lack of response to reinduction may predict for poorer outcomes⁹⁴ and this knowledge may be helpful for planning therapy after transplant. However, even patients with chemorefractory disease can still derive benefit from salvage first transplant.⁹⁵

Patients relapsing after an autologous transplant can sometimes benefit from a salvage second transplant, although prospective randomized data are limited. One UK study showed that second transplant was associated with superior OS compared with oral cyclophosphamide, but it did not utilize novel therapies as a comparator.⁹⁶ Data from a German study that enrolled patients relapsing after 1 to 3 prior lines showed no differences between Rd followed by second transplant vs Rd alone: Median PFS was similar at 20.7 months vs 18.8 months. However, 29% of patients assigned to second transplant did not receive it, potentially confounding results.⁹⁷ Retrospective analyses have indicated that a second transplant is more likely to

benefit patients with treatment-sensitive disease and those who had a remission that lasted at least 36 months after first transplant^{98,99}; it even can be efficacious in patients refractory to daratumumab.¹⁰⁰ It is important to develop a plan for the next therapy after recovery from second transplant to forestall disease relapse; for example, a Center for International Blood and Marrow Transplant Research analysis showed that maintenance therapy post second transplant was associated with significantly prolonged PFS and OS.¹⁰¹

For select patients, salvage allogeneic transplant can be considered, although its use may be declining given the continued new therapeutic options for myeloma. Longitudinal analyses of patients with newly diagnosed disease,^{102,103} as well as of those with RR disease,¹⁰⁴ who receive allogeneic transplant show that a subset of patients experience long-term disease control. The first results of a prospective study of allogeneic transplant in high-risk MM, including relapsed disease, were recently published and demonstrated an estimated 24-month PFS of 52% and nonrelapse mortality of 11.7%.¹⁰⁵ While transplant-related morbidity and mortality remain a concern,

allogeneic transplant should be considered for young and fit patients while their myeloma is still chemosensitive, given the expectation that all other treatment options will eventually be exhausted. Patients considering this option should be treated at transplant centers with experience in this clinical setting, ideally as part of a clinical trial.

Late-Line Relapse

Patients exposed to multiple lines of therapy who relapse are likely to be triple-class refractory and penta-class exposed. In this setting, the likelihood of a response to the next line of therapy historically has been low irrespective of the specific agent, although the response rate may be higher with carfilzomib- or alkylator-based therapy.³²

Bendamustine has been studied as monotherapy as well as in combination with PIs and IMiDs and can be a useful option.¹⁰⁶ If not previously used, selinexor-based therapy was associated with an increased chance of benefit vs retrying classes of agents previously used.¹⁰⁷ For aggressive disease relapses, high-dose cytotoxic chemotherapy¹⁰⁸⁻¹¹⁰ can be employed to obtain temporary disease control as a bridge to the next line of therapy. In addition to pursuing clinical trial options, B-cell maturation antigen (BCMA)-directed therapy should be strongly considered if not already used, and will be discussed further in the next section.

Emerging and Novel Therapies

BCMA, a member of *TNFRSF17*, is highly expressed on MM cells, promotes MM cell survival and proliferation, and is minimally expressed elsewhere.¹¹¹ The first commercially available therapy targeting BCMA was belantamab mafodotin, an antibody-drug conjugate composed of a BCMA antibody linked to a microtubule-disrupting drug. As a single agent, belantamab mafodotin showed activity in a very heavily pre-

TABLE 5. Select Ongoing Trials of Newer Antimyeloma Therapies in RRMM

Trial	Trial identifier	Trial design	Patient population
KarMMa-2 Ide-cel	NCT03601078	Phase 2, multiple cohorts, including newly diagnosed and relapsed MM	For relapsed MM: TCE and at least 3 prior lines or 1 prior line with early relapse
KarMMa-3 Ide-cel vs SOC (DaraPd, DaraVd, IxaRd, Kd, or EloPd)	NCT03651128	Randomized phase 3	TCE and 2-4 prior lines
CARTITUDE-2 Cilta-cel	NCT04133636	Phase 2, multiple cohorts, including newly diagnosed and relapsed MM	For relapsed MM: 1-3 prior lines including PI and R or 1 line including PI and IMiD with early progression or TCE and prior BCMA-directed therapy
CARTITUDE-4 Cilta-cel vs PVd or DaraPd	NCT04181827	Randomized phase 3, 2 arms	Refract R, 1-3 prior lines
MajesTEC-3 Teclistimab/Dara vs DaraVd or DaraPd	NCT05083169	Randomized phase 3, 2 arms	1-3 prior lines including PI and R, if only 1 prior line must be R refractory
MagnetisMM-3 Elranatamab	NCT04649359	Phase 2, 2 cohorts	TCR, cohorts stratified by exposure to prior BCMA-directed therapy
MagnetisMM-5 Elranatamab vs Elranatamab/Dara vs DaraPd	NCT05020236	Randomized phase 3, 3 arms	At least 1 prior line including PI and R
MonumenTAL-1 Talquetamab	NCT04634552	Phase 1/2, 3 cohorts	At least 3 prior lines; cohorts stratified by prior T-cell redirection therapy exposure
EXCALIBER-RRMM IberDara-d vs DaraVd	NCT04975997	Randomized phase 3, multiple iber dose levels	1-2 prior lines of therapy
CAMMA 1 Cevostamab Cevostamab-Pd Cevostamab-Dara-d	NCT04910568	Phase 1b, multiple cohorts	At least 1 or at least 2 prior lines depending on cohort

BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucl; d, dexamethasone; Dara, daratumumab; Elo, elotuzumab; iber, iberdomide; ide-cel, idecabtagene vicleucl; Ixa, ixazomib; K, carfilzomib (Kyprolis); MM, multiple myeloma; P, pomalidomide; PI, proteasome inhibitor; R, lenalidomide (Revlimid); RRMM, relapsed/refractory MM; SOC, standard of care; TCE, triple-class exposed; TCR, triple-class refractory; V, bortezomib (Velcade).

treated population of patients with RRMM, with a median duration of response of 11.0 months, some deepening of response observed over time, and a median OS of 13.7 months. In patients who achieved at least a partial response, the median OS was not reached, with 88% alive at 1 year. The unique treatment-related toxicity is keratopathy, experienced by 72% of patients at any grade, with a grade 3/4 rate of 46%.^{112,113} While numerous clinical trials are currently evaluating belantamab mafodotin

in combination with other agents,^{114,115} belantamab mafodotin was pulled from the US market in November 2022 due to failure of belantamab monotherapy to show significant improvement in PFS compared with Pd in a phase 3 randomized trial involving patients with RRMM.¹¹⁶

The next commercially approved BCMA-directed therapies were both chimeric antigen receptor (CAR) T-cell products: idecabtagene vicleucl (ide-cel) in March 2021¹¹⁷ followed by

ciltacabtagene autoleucl (cilta-cel) in February 2022¹¹⁸. Both ide-cel and cilta-cel demonstrated unprecedented outcomes compared with non-BCMA-directed therapies for such heavily pretreated patients^{119,120} and demonstrated low rates of grade 3/4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), although 6% of patients receiving cilta-cel suffered treatment-related parkinsonism.¹²¹ An indirect comparison between the 2

CART-cell products suggests that cilta-cel has higher efficacy.¹²² Availability for commercial ide-cel and cilta-cel remains very constrained, and most centers are not yet able to provide this therapy to the majority of eligible patients. Downsides to CAR T-cell therapy include the time delay required for manufacturing, during which time patients can experience disease progression and morbidity.¹²³ Furthermore, it remains to be seen whether real-world outcomes with ide-cel and cilta-cel match those reported in clinical trials. The authors' experience has been that patients with rapidly progressive MM do not experience meaningful or durable responses to ide-cel.

The first bispecific T-cell engager to treat myeloma, teclistamab, was granted accelerated approval in late 2022. Findings from a phase 2 study of teclistamab, which targets CD3 and BCMA, showed favorable outcomes compared with the other available BCMA-directed therapies, including an overall response rate of 63% and median duration of response of 18.4 months, with minimal rates of grade 3/4 CRS or ICANS.¹²⁴ Teclistamab, ide-cel, and cilta-cel are all approved for patients with RRMM who have been at least triple-class exposed with at least 4 prior lines of therapy.

Optimal selection and sequencing of BCMA-directed therapy remain to be determined, although BCMA-directed bispecific T-cell engagers have been shown to be efficacious in patients relapsing after a BCMA-directed CART product.¹²⁵ Patients who urgently need a response should be preferentially considered for teclistamab given the time delay from leukapheresis to manufacturing to receipt of a CART product, as well as current supply constraints. One potential advantage of ide-cel and cilta-cel is that they are a single treatment;

patients will experience a treatment-free interval afterward.

Table 4 lists the reported pivotal trials for the aforementioned BCMA-directed therapies,^{112,113,117,118,124} while **Table 5** lists ongoing clinical trials involving these and other novel agents, specifically evaluating their utility in earlier lines of therapy and in combination with other agents. Iberdomide is a modulator of cereblon with increased potency compared with lenalidomide and pomalidomide.¹²⁶ Talquetamab is a bispecific T-cell engager targeting CD3 and GPRC5D; the latter is a transmembrane protein with high expression in myeloma cells.¹²⁷ GPRC5D is also being evaluated as a target for CAR T.^{128,129} Cevostamab is a bispecific T-cell engager targeting CD3 and FCRL5, which is a membrane protein restricted to B cells that has increased expression on MM cells.^{130,131}

Another area of active interest is quadruplet therapy, particularly in patients with early-line relapse or high-risk disease before they have become multiclass refractory. Ongoing combinations under evaluation include elotuzumab with IsaPd (NCT04835129), elotuzumab with KPd, selinexor with DaraVd, daratumumab with KPd, and daratumumab with ixazomib and Pd.¹³²⁻¹³⁵ Also, a series of selinexor-based combinations are under investigation as part of the multiarm phase 1b/2 STOMP trial (NCT02343042).¹³⁶⁻¹³⁸

Conclusions

The treatment of RRMM continues to evolve with the approval of new classes of therapy. Even so, certain principles stay constant, and it remains important to assess all patients on the basis of their disease risk as well as their fitness and comorbidities. The variety of approved anti-MM regimens means that patients with early-line relapses will have several

effective regimens to choose among, although the lack of direct comparisons among regimens makes it hard to definitively rank regimens in terms of superiority. Frail patients can still benefit from triplet regimens, while patients with high-risk MM, including double-hit myeloma, continue to benefit less than standard-risk patients from the currently available regimens. Increased use of MRD-based end points to assess response and dynamically reassess risk, as well as the approval of quadruplets for relapsed disease, are likely, pending results of ongoing trials.

The management of late-stage RRMM remains challenging, as any response to therapy tends to be transient. BCMA-directed therapy has shown great promise, with some patients experiencing durable responses. As CAR T products remain very supply-limited, bispecific T-cell engagers and other off-the-shelf immunotherapy products will likely be increasingly employed. Current clinical trials are clarifying the optimal sequencing of these agents in the context of other anti-MM treatments, but it will not be surprising if therapies directed toward BCMA and other novel targets will be deployed at earlier time points and in combination with current standard-of-care agents. These advances indicate that the survival for patients with RRMM will continue to improve with time. ■

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 For references visit
cancernetwork.com/4.23_MM