

Considerations for next therapy after anti-CD38 monoclonal antibodies used as first line

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In the current treatment paradigm, the use of anti-CD38 monoclonal antibodies (mAbs) in frontline has notably increased, for both transplant-ineligible and transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) patients. As a result, patients with multiple myeloma (MM) are frequently exposed to or develop resistance to anti-CD38 mAb therapy during the initial stages of treatment. Here, we review second-line (first relapse) and some third-line (second relapse) therapies for patients with MM with disease progression after exposure to anti-CD38 mAb-based therapy. We discuss therapies including B-cell maturation antigen (BCMA)-targeted and non-BCMA-targeted therapeutic options in the setting of prior anti-CD38 mAb exposure/refractoriness.

LEARNING OBJECTIVES

- Discuss non-B-cell maturation antigen (BCMA)-directed multiple myeloma (MM) treatment options in first and second relapse after anti-CD38 monoclonal antibody (mAb) exposure
- Review the use of BCMA-directed MM therapies in first and second relapse after anti-CD38 mAb exposure
- Review management of MM in second relapse after anti-CD38 mAb exposure

CLINICAL CASE

A 63-year-old African American man was diagnosed with multiple myeloma (MM) 3 years ago. At the time of diagnosis, he had immunoglobulin G (IgG) κ , stage II disease per the Revised International Staging System. Additionally, bone marrow pathology revealed standard-risk features, including t(11;14) and monosomy 13. Positron emission tomography/computed tomography showed no fluorodeoxyglucose (FDG) avid osseous lesions. He was treated with daratumumab (Dara), lenalidomide (Len), bortezomib (Bortez), and dexamethasone (Dex) (DRVd) for 4 cycles. He then underwent stem cell harvest, followed by another 4 cycles of DRVd consolidation. Given his standard-risk disease and achievement of stringent complete remission after the first 4 cycles of induction therapy, he opted to forego autologous stem cell transplantation (ASCT). He received maintenance therapy with Dara-Len for 2 years and then Len single-agent maintenance onward. The following year, he developed relapsed disease with a new paraspinal L5 plasmacytoma and symptomatic bilateral rib lytic lesions. M spike was 1.8 g/dL, repeat bone marrow biopsy showed 40% plasma cell involvement, and

fluorescence in situ hybridization analysis detected an additional finding of 3 copies of duplication 1q.

Use of anti-CD38 mAbs in frontline treatment of NDMM

The integration of anti-CD38 monoclonal antibodies (mAbs) in the frontline treatment of newly diagnosed multiple myeloma (NDMM) has become a standard-of-care (SoC) approach based on various clinical trials. The pivotal MAIA trial, which encompassed a cohort of patients with transplant-ineligible (TI) NDMM treated with Dara in the frontline setting laid the foundation for this approach. Data published in 2022 showed a 44% reduction in risk of death or progressive disease and sustained measurable residual disease (MRD) negativity (using next-generation sequencing at 10^{-5}),¹ with nearly 15% of patients with TI NDMM maintaining MRD negativity at or beyond 6 months and ~11% at or beyond 12 months, which translated to favorable progression-free survival (PFS) outcomes.¹ The tolerability and safety of Dara-Len-Dex in the MAIA regimen proved to be reassuringly comparable to those of Len-Bortez-Dex,^{2,3} leading to a surge in the utilization

of anti-CD38 mAb therapy as a primary treatment option for patients with TI NDMM.

In the United States, there is an increasing trend in the utilization of quadruplet mAb-based therapy as frontline treatment for patients with transplant-eligible (TE) NDMM based on the phase 2 GRIFFIN trial. Results published in 2022 showed an impressive MRD-negative rate of 64% in the Dara cohort compared to 30% in the non-Dara arm ($P < .0001$), with 44% of patients sustaining MRD negativity at or beyond 12 months,⁴ as well as superior PFS and MRD negativity and deepening of complete remission rates over time in the Dara-containing arm. No additional safety concerns and no notable differences in ability to proceed with ASCT were observed in the Dara-quadruplet group compared to the triplet group.⁴ The PERSEUS phase 3 clinical trial evaluation of this quadruplet regimen in patients with NDMM with PFS as the primary end point is ongoing.⁵

In Europe, the phase 3 randomized CASSIOPEIA trial assessed Dara in combination with Bortez, thalidomide, and dex (D-VTd) vs VTd induction in patients with TE NDMM. The first randomization was 1:1 to quadruplet versus triplet therapy, and the second randomization allowed patients with partial or better response to receive maintenance with Dara vs observation only. The D-VTd group had clinically superior complete remission (CR) of 39% vs 26% in the VTd group, with MRD-negative rates of 64% and 44% ($P < .0001$), respectively.⁶ At a median follow-up of 35.4 months after the second randomization, median PFS for the Dara cohort was not reached, whereas it was 46.7 months for the VTd cohort.⁶

Another notable European quadruplet phase 3 trial (ALCYONE) evaluated Dara, Bortez, melphalan, and prednisone (D-VMP) vs VMP in TI NDMM, focusing on PFS. In the final analysis at a 40.1-month median follow-up, both PFS and overall survival (OS) were significantly better in the D-VMP cohort, with hazard ratios of 0.60 ($P = .0003$; 95% confidence interval [CI], 0.46-0.80) and 0.42 ($P < .0001$; 95% CI, 0.34-0.51), respectively.⁷ Additionally, the overall response rate (ORR), CR or better, and MRD negativity rates in the D-VMP-treated patients were all significantly superior to those in the VMP arm. The infectious adverse events (AEs) were notably more increased in the Dara cohort.⁷

Finally, the GMMG-HD7 trial, a phase 3 trial, successfully achieved its primary end point in just 18 weeks, with the isatuximab (Isa)-RVd quadruplet regime attaining >50% MRD negativity in the quadruplet group pre-ASCT. The post-ASCT results from this trial will possibly be practice informing, given the planned double-randomization study design before and after ASCT.⁸

What would best be used for second-line therapy for this patient?

There are several factors to consider when choosing the next best regimen for a patient with MM with relapsed disease. These can be categorized as follows: (1) prior regimen received, (2) disease risk stratification, and (3) patient conditions (Table 1). In this clinical case, the patient experienced disease progression in less than 4 years with prior Dara exposure and prolonged Len therapy with progression on Len. It is important to factor in his prior

Table 1. Factors to consider when selecting the next line of therapy in patients with relapsed MM

Prior MM directed therapies (induction/first line)	MM disease risk stratification	Patient conditions
Triplet vs quadruplet therapy <ul style="list-style-type: none"> • Triplet <ul style="list-style-type: none"> ◦ DRd vs RVd • Quadruplet <ul style="list-style-type: none"> ◦ D-RVd* ◦ Clinical trial 	High risk vs standard risk <ul style="list-style-type: none"> • Cytogenetics <ul style="list-style-type: none"> ◦ Hypoploidy ◦ Hyperploidy • Fluorescence in situ hybridization <ul style="list-style-type: none"> ◦ Del 17p, t(4;14), t(14;16), t(14;20), gain 1q, loss 1p • Next-generation sequencing • Genomic expression profiling 	Renal disease <ul style="list-style-type: none"> • Cast nephropathy • Nonmalignant etiology • Severity • Medication toxicity
Alkylator* <ul style="list-style-type: none"> • Bendamustine • Cyclophosphamide • Anthracycline • Doxorubicin • Doxil 	Time to relapse <ul style="list-style-type: none"> • Early (<12 mo vs <24 mo) • Late (>48 mo) • Slow (asymptomatic/biochemical) • Rapid (symptomatic) 	Neuropathy <ul style="list-style-type: none"> • MM related • Nonmalignant etiology
Proteasome inhibitor <ul style="list-style-type: none"> • Bortezomib • Carfilzomib • Ixazomib 	Extramedullary disease <ul style="list-style-type: none"> • Plasmacytomas <ul style="list-style-type: none"> ◦ Visceral ◦ Skin • Central nervous system disease 	Bone lesions (symptomatic vs asymptomatic)
ASCT <ul style="list-style-type: none"> • Transplant ineligible • Transplant eligible 	Peripheral blood plasma cells <ul style="list-style-type: none"> • <5% • >5% • >20% 	Steroid (tolerant vs intolerant)
Institutional/resources <ul style="list-style-type: none"> • Advanced cancer care center • Community medical center 		Non-MM-related health conditions <ul style="list-style-type: none"> • Cardiovascular • Renal disease

*Based on the GRIFFIN trial, a phase 2 trial; the phase 3 (PERSEUS) trial needed to support FDA approval of the quadruplet regimen is ongoing.

*Some patient cases require induction triplet inclusive of traditional chemotherapeutic agent, for various reasons, such as renal insufficiency.

exposure to Dara and prolonged Len exposure when determining the best next course of therapy.

In cases where the patient does not exhibit refractoriness to Dara, the APOLLO and CANDOR trials provide appropriate second-line options. The APOLLO trial evaluated 304 patients randomized to receive Dara-pomalidomide-Dex (DPd; $n = 151$) vs Pd ($n = 153$) post-first relapse (1 to 3 prior lines of therapy). Most patients (79.6%) were Len refractory, with almost half (48%) being proteasome inhibitor (PI) refractory and 42.4% being both PI and Len refractory. After a median follow-up of 39.6 months, DPd had a median OS of 34.4 months (95% CI, 23.7-40.3) vs 23.7 months for Pd (95% CI, 19.6-29.4). Almost 10% of the DPd cohort was exposed to prior anti-CD38 mAb therapy.⁹ The CANDOR trial compared Dara-carfilzomib-Dex (DKd) vs Kd after 1 to 3 prior lines of therapy and primarily assessed PFS. Final analysis showed that at a median follow-up of 50 months, the DKd group demonstrated a median PFS of 28.4 months, whereas the Kd group had a PFS of 15.2 months, with MRD negativity rates of 28% in the DKd group and 9% in the Kd group.¹⁰ The use of carfilzomib instead of Bortez in the CANDOR trial is supported by several trials, including the pivotal phase 3 ENDEAVOR trial, which compared carfilzomib-Dex (Kd) to Bortez-Dex (Vd) in patients with relapsed or refractory MM (RRMM). The trial showed a median PFS of 18.7 months with Kd vs 9.4 months with Vd (hazard ratio = 0.53; 95% CI, 0.44-0.65; $P < .0001$). Updated interim analysis also showed improved OS for the carfilzomib group compared to the Bortez cohort.¹¹

Isatuximab (Isa) is another mAb that targets CD38 plasma cell surface antigen but differs from Dara in epitope binding.¹² This difference may translate to distinct treatment outcomes when either agent is used. An *in vitro* study suggested that Isa exhibits a higher potency than Dara in inhibiting CD38 enzymatic activity¹³; despite this, a phase 2 study evaluating the use of Isa in patients with Dara-refractory MM (within 6 months of Dara exposure) yielded disappointing results.¹⁴ In the same study, minimal responses were observed in patients with ≥ 6 months from the last Dara dose treated with Isa. This distinction highlights the importance of considering the timing of prior Dara exposure when treatment strategies involving another anti-CD38 mAb are planned.

Notably, isatuximab is approved by the Food and Drug Administration (FDA) in the United States for use in combination with carfilzomib and Dex (IsaKd) in patients with RRMM after 1 to 3 prior lines of therapy, based on the IKEMA study.¹⁵ The final analysis, after a median follow-up of 44 months, showed a median PFS of 35.7 months with IsaKd (95% CI, 25.8-44.0) vs 19.2 months for Kd (95% CI, 15.8-25.0), translating to a 42% risk reduction of death or MM disease progression for the Isa-containing regimen.¹⁶

For the patient in this clinical case, retaining Bortez as a component of his second-line therapy is a reasonable consideration. This decision is grounded in the facts that his prior exposure to Bortez was limited to just 8 cycles and his last encounter with this drug was over 12 months ago.

The BOSTON regimen, which combines selinexor (Seli) with Bortez and Dex (SvD), is a viable non-B-cell maturation antigen (BCMA) second-line treatment option for this patient. Seli is an oral selective inhibitor of nuclear export medication that binds and inhibits XP01, resulting in myeloma cell destruction. Seli has shown efficacy in Len-resistant and mAb-exposed patients

with RRMM. The BOSTON trial had a median PFS for SvD of ~14 months compared to ~9.5 months for Vd ($P = .0075$).^{17,18} Another key trial (STORM) that investigated Seli in patients with RRMM showed favorable efficacy and tolerability in combination with pomalidomide and Dex (SPD).¹⁹⁻²¹ Experience with Seli use has shown the importance of anticipatory management of potential gastrointestinal and electrolyte adverse effects, often well mitigated with acceptable safety and tolerance, especially in the combination regimens with doses of Seli below 80 mg weekly. For many patients, especially in the community oncology setting, the BOSTON regimen may be an ideal option to salvage patients in second relapse and/or bridge patients to clinical trial opportunities or next therapeutic care such as immune cellular therapy or ASCT for those eligible. The triplet regimens from the OPTIMISM (PVd) and CASTOR (DVd) trials are potential Bortez-based second-line therapies.

Two other potential second-line non-BCMA therapeutic options to consider are carfilzomib, pomalidomide, and Dex (KPd), and carfilzomib, cyclophosphamide (Cy), and Dex (KCyd), as supported by findings from the EMN011/HOVON114 and MCRN-003/MYX.1 phase 2 trials.²² The caveat is that those trials were smaller phase 2 institutional studies with no phase 3 data support, although the trials' results are compelling.

It is worth noting that the TOURMALINE-MM1²³ and ELO-QUENT²⁴ studies, which evaluated ixazomib (Ixa) with Len-Dex (IxaRd) and elotuzumab (Elo) with Len-Dex (EloPd), respectively, in patients after 1-3 prior lines of therapy, would not be suitable next-line options in this case. This is because the patients enrolled in these studies were not exposed to Dara.

The case described here, use of ASCT in second-line treatment is possible, given the patient completed stem cell harvest and deferred frontline transplantation. Both the phase 3 IFM 2009 and DETERMINATION trials, which evaluated ASCT in frontline vs later in relapse, indicate that ASCT remains important for select MM patients.^{25,26} The IFM 2009 trial included 700 patients randomly assigned to ASCT early after 3 cycles of RvD with consolidation of 2 RvD cycles, compared to RvD for 8 cycles. Len maintenance was for 1 year. The primary end point was PFS, and at a median follow-up of 93 months, the median PFS was 47.3 months vs 35 months for the ASCT group vs the RvD-alone group, respectively (hazard ratio = 0.70; 95% CI, 0.95-0.83). The MRD negativity rates were superior in the ASCT group (29.8%) vs RvD alone (20%; $P = .01$). Of the patients who relapsed, 68.4% proceeded to second-line therapy (ASCT, $n = 217$; RvD alone, $n = 262$); 22.6% received a second ASCT and 76.7% of the RvD-alone group received ASCT post-first relapse. The median PFS showed no statistical difference between the groups, and the median OS was 62.2% and 60.2% in the ASCT and RvD-alone groups, respectively.^{12,25}

The DETERMINATION trial evaluated patients with NDMM who received RvD induction with ASCT up front ($n = 365$) vs no frontline ASCT ($n = 357$), with both groups receiving Len maintenance until disease relapse. PFS was the primary end point of the trial. The median follow-up was 76.0 months, with a median PFS of 67.5 months vs 46.2 months, respectively. The OS at 5 years was 80.7% and 79.2%, respectively.²⁶

These studies suggested that whether ASCT is performed up front or delayed, the overall survival benefit does not seem to be significantly different. It is important to note that both DETERMINATION and IFM 2009 were preplanned for PFS as the

primary end point. Additionally, only ~35% of the patients in the DETERMINATION trial received ASCT at the time of first relapse, which may have impacted the OS outcome.^{25,26} Consequently, the timing of ASCT frontline vs post first relapse remains controversial, with the data suggesting that ASCT is a reasonable option for second-line treatment if not performed previously.

CLINICAL CASE (continued)

The patient is fully cognizant of the reoccurring nature of his myeloma disease and is concerned about treatment options in the event of a second relapse.

What would best be used for third-line therapy for this patient?

Depending on the choice of second-line therapy, third-line treatment options may include options as discussed above (Table 2). The choice of third-line therapy may also depend on the nature of the relapse, whether it is rapidly progressive or indolent. Treatment options in this scenario can encompass combination chemotherapy such as Dex, Cy, etoposide, and cisplatin (DCEP) or Bortez, Dex, cisplatin, doxorubicin, Cy, and etoposide (VD-PACE), as well as BCMA-targeted therapies such as chimeric antigen receptor T-cell (CAR-T) therapies. Some examples of sequencing therapies from NDMM through second RRMM are listed below:

1. DRVd (TE) → ASCT → DR → first relapse → PVd, SVd, or clinical trial → second relapse → clinical trial, BCMA-targeted therapy (CAR-T or bispecific [eg, teclistamab]), or non-BCMA-targeted therapy (eg, talquetamab)
2. DRd (TI) → R → first relapse → DPd, DVd, KRd, or clinical trial → second relapse → clinical trial, SVd, PVd, BCMA-targeted therapy (CAR-T or bispecific [eg, teclistamab]), or non-BCMA-targeted therapy (eg, talquetamab)
3. RVd (TI or TE) → R → first relapse → ASCT (TE), PVd, DPd, SVd, DVd, or clinical trial → second relapse → clinical trial, BCMA-targeted therapy (CAR-T or bispecific [eg, teclistamab]), or non-BCMA-targeted therapy (eg, talquetamab).

CLINICAL CASE (continued)

The patient is interested in newer therapies and asks about BCMA-targeted treatment options in first and second relapse. He is aware of the market withdrawal of belantamab mafodotin (belamaf) in 2022 and has many questions about this treatment.

What is belamaf and how does it work? Why was it withdrawn? What other BCMA-directed second-line therapeutic options exist for patients with MM after anti-CD38 resistance?

Belamaf is an antibody-drug conjugate that targets BCMA found on the surface of the malignant plasma cells in MM. Belamaf is

Table 2. Current US FDA-approved triplet regimens for management of RRMM in the second line

Regimen (study)	Survival outcomes, PFS (mo) and OS (mo)	Median lines of therapy (range)	Included anti-CD38 mAb-exposed/refractory patients	Included Len-refractory patients
DPd (APOLLO)	Median OS 34.4 (95% CI, 23.7–40.3) DPd vs 23.7 (95% CI, 19.6–29.4) Pd	2 (1–5)	No	Yes
KRd (ASPIRE)	Median PFS 26.1 (95% CI, 23.3–30.5) KRd vs 16.6 (95% CI, 15–20.6; $P < .001$) Rd Median OS 48.3 (95% CI, 42.4–52.8) KRd vs 40.4 (95% CI, 33.6–44.4; $P = .0045$) Rd	2 (1–3)	No	No
SVd (BOSTON)	Median PFS 13.9 SVd vs 9.46 Vd ($P = .0075$)	2 (1–3)	Yes	Yes
DKd (CANDOR)	Median PFS 28.4 DKd vs 15.2 Kd	2 (1–5)	No	Yes
DVd (CASTOR)	Median PFS 16.7 DVd vs 7.1 Vd ($P < .0001$)	2 (1–9)	No	Yes
EloRd (ELOQUENT-2)	Median PFS 19.4 EloRd vs 14.9 Rd ($P = .014$) Median OS 43.7 EloRd vs 39.6 Rd ($P = 0.025$)	2 (1–4)	No	No
IsaKd (IKEMA)	Median PFS 35.7 (95% CI, 25.8–44.0) IsaKd vs 19.2 (95% CI, 15.8–25.0) Kd	2 (1–4)	No	Yes
PVd (OPTIMISM)	Median PFS 11.2 (95% CI, 9.66–13.73) PVd vs 7.1 (95% CI, 5.88–8.48; $P < .0001$) Vd	2 (1–2)	No	Yes
DRd (POLLUX)	Median PFS 44.5 (95% CI, 34.1–NE) DRd vs 17.5 (95% CI, 13.9–20.8; $P < .0001$) Rd 65% vs 57% OS	1 (1–11)	No	Yes
IxaRd (TOURMALINE-MM1)	Median PFS 19.4 IxaRd vs 14.9 Rd ($P = 0.0014$) Median OS 43.7 IxaRd vs 39.6 Rd ($P = 0.025$)	Range: 1–3	No	No

Doublet FDA-approved options are not included in this table. KCyD (MYX.1/MCRN-00) and KPd (EMN011/H0114) are not included although they are strongly supported by smaller phase 2 studies.

NE, not evaluable.

conjugated to monomethyl auristatin-F (MMAF), a microtubule inhibitor that binds to tubulin and impedes microtubule assembly, resulting in cell cycle arrest and apoptosis.²⁷ An additional effect of belamaf is the activation of MM cell death through the antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis.^{28,29} Belamaf gained conditional accelerated FDA approval in August 2020 based on the phase 2 DREAMM-2 trial.³⁰ The safety and efficacy data were favorable, except for keratopathy, an unusual adverse effect seen only in antibody drug conjugate MM therapy.^{30,31} The FDA approval for belamaf was later withdrawn in November 2022, when the phase 3 DREAMM-3 trial failed to meet the conditional requirement, falling short of its primary PFS end point with a hazard ratio of 1.03 (95% CI, 0.72-1.47).³² Of note, belamaf remains approved for use in Europe.³³

The ALGONQUIN, DREAMM-12, and DREAMM-15 trials are currently evaluating the management of keratopathy, focusing on both efficacy and mitigation of toxicity. Preliminary findings indicate that when belamaf was combined with pomalidomide and Dex at different doses, the ORR increased from 82% to 95%.^{25,26} The belamaf dose of 1.92 mg/kg every 4 weeks in the combination with pomalidomide and Dex has had significant efficacy with reduced keratopathy adverse effects. Further results from the ALGONQUIN, DREAMM-12, and DREAMM-15 trials are forthcoming.

Other BCMA-targeted therapies have shown significant clinical benefit in patients with MM with triple refractory disease (refractory to PIs, immunomodulatory drugs [IMiDs], and anti-CD38 mAbs). The current US FDA-approved BCMA-targeted therapies are the CAR-T therapies idecabtagene vicleucel (ide-cel)³⁴ and ciltacabtagene autoleucel (cilta-cel),³⁵ plus the bispecific antibody teclistamab.³⁶ These newer therapies are currently approved for use in the late refractory and relapsed setting, beyond fourth-line MM therapy. Due to their promising results in treating advanced RRMM, ongoing clinical trials are now assessing the efficacy of these BCMA therapies in the first and second relapse as well (Table 3).

The CARTITUDE-4 trial, a phase 3 randomized study, has shown impressive early results of chimeric antigen receptor T-cell therapy in patients with RRMM who had received 1 to 3 prior lines of therapy, including PIs and IMiDs, and with disease unresponsive to Len. The trial compared cilta-cel to the SoC regimens pomalidomide, Bortez, and Dex (PvD) and Dara, pomalidomide, and Dex (DPd). The primary end point of the study was evaluation of PFS in the intent-to-treat population. At a median follow-up of 16 months, the median PFS was not reached in the cilta-cel-treated patients, while it was 11.8 months in the SoC cohort. This translates to an impressive 74% reduction in the risk of disease progression or death in the cilta-cel cohort (hazard ratio, 0.26; 95% CI, 0.18-0.38; $P < .0001$). ORR was 85% vs 67%

Table 3. Clinical trials assessing the efficacy of BCMA-targeted therapies in earlier lines of therapy

Trial	No. of prior lines of therapy	Median PFS, mo (median follow up)	ORR, n (%); CR, n(%); MRD, n(%)	Hazard ratio (95% CI)
Cilta-cel trials				
CARTITUDE-2 ³⁹	1-3	N/A	18 (88.9); 18 (27.8); 9 (100)	N/A
CARTITUDE-4 ³⁷	1-3	Not reached (15.9 mo)	176 (85); 152 (73); 126 (61)	0.26 (0.18-0.38) ($P < .0001$)
CARTITUDE-5 ⁴⁰	0 (NDMM, TI)	N/A (recruiting)	N/A	N/A
CARTITUDE-6 [NCT05257083]	0 (NDMM, TE)	N/A (recruiting)	N/A	N/A
Ide-cel trials				
KarMMa-2 ⁴¹	1-3	N/A (recruiting)	37 (83.8); 37 (45.9); 13 (85)	N/A
KarMMa-3 ³⁸	2-4	13.3 (18.6)	181 (71); 98 (39); 50 (20)	0.49 (0.38-0.65) ($P < .001$)
KarMMa-4 ⁴²	0 (NDMM, high-risk)	N/A	N/A	N/A
KarMMa-7 ⁴³	1-3	N/A	N/A	N/A
Elranatamab trials				
MagnetisMM-1 ⁴⁴	2-15		55 (64); 35 (31); N/A	
MagnetisMM-3 ⁴⁵			123 (61); 123 (35); 29 (89.7)	
MagnetisMM-4 ⁴⁶	≥3	N/A	N/A	N/A
MagnetisMM-5 ⁴⁷	>1	N/A	N/A	N/A
Teclistamab trial				
MajesTEC-3 ⁴⁸	1-3	N/A (recruiting)	N/A	N/A
Talquetamab trials				
TRIMM-2 ⁴⁹	>3	N/A	50 (78); 50 (16); N/A	N/A
RedirecTT-1 ⁵⁰	On/after lines of therapy	20.9 (13.4)	93 (86.6); 93 (22); N/A	N/A

N/A, not applicable.

($P < .0001$), and MRD negativity was 61% vs 16% ($P < .0001$) in favor of cilta-cel. These favorable results may lead to use of cilta-cel as second-line therapy after first relapse for patients with RRMM.³⁷

Similarly, the international KARMMA-3 trial evaluated ide-cel vs SoC (5 regimens) in patients with RRMM after receiving 2 to 4 prior lines of therapy. The primary end point was PFS, which at a median follow-up of 18.6 months was 13.3 months for ide-cel vs 4.4 months in the SoC, translating to a risk reduction of disease progression or death of 61% for ide-cel (95% CI, 0.38-0.65; $P < .001$). The ORR was 71% vs 42% ($P < .001$), and complete remission rate was 39% vs 5%, favoring ide-cel. There were no unexpected adverse toxicities, and cytokine release syndrome (CRS) and neurotoxicity (NT) rates were similar to other ide-cel trial rates, with the majority being grade 1 (88% CRS; 15% NT) and few grade 3 or above (5% CRS; 3% NT).³⁸

Bispecific antibodies are also being assessed in earlier lines of therapy in RRMM; some examples include the MajesTEC trial series evaluating teclistamab in combination with Len and Dara. Other BCMA-targeted bispecifics also being evaluated in combination with Len and Dara include elranatamab in the Magne-tisMM trials (Table 3).

Discussion

The treatment landscape for patients with RRMM is rapidly changing, with use of anti-CD38 mAb-based therapy now routinely administered as SoC for both TE and TI patients with NDMM. This change has impacted the next line of therapy offered post-first relapse. In relapsed disease, it is important to consider the prior therapeutic regimen received; the depth and duration of prior treatment response; disease cytogenetic status (high-risk vs standard risk); use of frontline ASCT; refractoriness of disease to Pls, IMiDs, and/or anti-CD38 mAbs; and patient tolerability and fitness when choosing the next therapeutic regimen after anti-CD38 mAb exposure in the front line. Moving anti-CD38 mAbs to NDMM has resulted in newer therapies with novel mechanisms of action, such as BCMA-targeted therapies being moved earlier in the treatment paradigm. These include cellular therapies, such as ide-cel and cilta-cel CAR-T therapies and bispecific antibodies (teclistamab) that have been approved by the FDA within the last 2 years; current clinical trials are addressing evaluation of CAR-T therapies and bispecific antibodies in the early post-first relapse setting, potentially moving us closer to a cure for the disease. The toxicity profile of these therapies, namely, CRS, neurotoxicity, and cytopenias, along with its impact on the T-cell immune milieu of treated patients with MM, remains to be a concern, requiring close monitoring and specialized training.

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Off-label drug use

Monique Hartley-Brown: nothing to disclose.
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References

- San-Miguel J, Avet-Loiseau H, Paiva B, et al. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. *Blood*. 2022;139(4):492-501.
- Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J*. 2020;10(5):53.
- Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519-527.
- Chari A, Kaufman JL, Laubach JP, et al. Daratumumab plus lenalidomide, bortezomib, and dexamethasone (D-RVd) in transplant-eligible newly diagnosed multiple myeloma (NDMM) patients (Pts): final analysis of griffin among clinically relevant subgroups. *Blood*. 2022;140(suppl 1):7278-7281.
- Sonneveld P, Broijl A, Gay F, et al. Bortezomib, lenalidomide, and dexamethasone (VRd)±daratumumab (DARA) in patients (pts) with transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): a multicenter, randomized, phase III study (PERSEUS). *J Clin Oncol*. 2019;37(15 suppl):TPS8055.
- Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(10):1378-1390.
- Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132-141.
- Goldschmidt H, Mai EK, Bertsch U, et al; German-Speaking Myeloma Multicenter Group (GMMG) HD7 investigators. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. *Lancet Haematol*. 2022;9(11):e810-e821.
- Dimopoulos MA, Terpos E, Boccadoro M, et al. Subcutaneous daratumumab plus pomalidomide and dexamethasone (D-Pd) versus pomalidomide and dexamethasone (Pd) alone in patients with relapsed or refractory multiple myeloma (RRMM): overall survival results from the phase 3 Apollo study [abstract]. *Blood*. 2022;140(suppl 1):7272-7274.
- Usmani SZ, Quach H, Mateos M-V, et al. Final analysis of carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone in the CANDOR study. *Blood Adv*. 2023;7(14):3739-3748.
- Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2017;18(10):1327-1337.
- Leleu X, Martin T, Weisel K, et al. Anti-CD38 antibody therapy for patients with relapsed/refractory multiple myeloma: differential mechanisms of action and recent clinical trial outcomes. *Ann Hematol*. 2022;101(10):2123-2137.
- Lammerts van Bueren J, Jakobs D, Kaldenhoven N, et al. Direct in vitro comparison of daratumumab with surrogate analogs of CD38 antibodies MOR03087, SAR650984 and Ab79. *Blood*. 2014;124(21):3474.
- Mikhael J, Belhadj-Merzoug K, Hulin C, et al. A phase 2 study of isatuximab monotherapy in patients with multiple myeloma who are refractory to daratumumab. *Blood Cancer J*. 2021;11(5):89.
- Moreau P, Dimopoulos M-A, Mikhael J, et al; IKEMA study group. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. *Lancet*. 2021;397(10292):2361-2371.
- Martin T, Dimopoulos M-A, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in patients with relapsed multiple myeloma: updated results from IKEMA, a randomized phase 3 study. *Blood Cancer J*. 2023;13(1):72.
- Dolph M, Tremblay G, Leong H. Cost effectiveness of triplet selinexor-bortezomib-dexamethasone (XVd) in previously treated multiple myeloma (MM) based on results from the phase III BOSTON trial. *Pharmacoeconomics*. 2021;39(11):1309-1325.

18. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. *Lancet*. 2020;396(10262):1563-1573.
19. Podar K, Shah J, Chari A, Richardson PG, Jagannath S. Selinexor for the treatment of multiple myeloma. *Expert Opin Pharmacother*. 2020;21(4):399-408.
20. Vogl DT, Dingli D, Cornell RF, et al. Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti-CD38 Ab refractory multiple myeloma (MM): STORM Study. *Blood*. 2016;128(22):e526-e531.
21. Nooka AK, Costa LJ, Gasparetto CJ, et al. Guidance for use and dosing of selinexor in multiple myeloma in 2021: consensus from international myeloma foundation expert roundtable. *Clin Lymphoma Myeloma Leuk*. 2022;22(7):e526-e531.
22. Sonneveld P, Zweegman S, Cavo M, et al. Carfilzomib, pomalidomide and dexamethasone (KPD) in patients with first progression of multiple myeloma refractory to bortezomib and lenalidomide. Final report of the EMN011/HOVON114 trial [abstract]. *Blood*. 2021;138(suppl 1):1664.
23. Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;374(17):1621-1634.
24. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med*. 2015;373(7):621-631.
25. Perrot A, Lauwers-Cances V, Cazaubiel T, et al. Early versus late autologous stem cell transplant in newly diagnosed multiple myeloma: long-term follow-up analysis of the IFM 2009 trial. *Blood*. 2020;136(suppl 1):39.
26. Richardson PG, Jacobus SJ, Weller EA, et al; DETERMINATION Investigators. Triplet therapy, transplantation, and maintenance until progression in myeloma. *N Engl J Med*. 2022;387(2):132-147.
27. Markham A. Belantamab mafodotin: first approval. *Drugs*. 2020;80(15):1607-1613.
28. Eastman S, Shelton C, Gupta I, Krueger J, Blackwell C, Bojczuk PM. Synergistic activity of belantamab mafodotin (anti-BCMA immuno-conjugate) with PF-03084014 (gamma-secretase inhibitor) in Bcma-expressing cancer cell lines. *Blood*. 2019;134(suppl 1):4401.
29. Montes de Oca R, Alavi AS, Vitali N, et al. Belantamab mafodotin (GSK2857916) drives immunogenic cell death and immune-mediated anti-tumor responses in vivo. *Mol Cancer Ther*. 2021;20(10):1941-1955.
30. Lonial S, Lee HC, Badros A, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. *Cancer*. 2021;127(22):4198-4212.
31. Wahab A, Rafee A, Mushtaq K, et al. Ocular toxicity of belantamab mafodotin, an oncological perspective of management in relapsed and refractory multiple myeloma. *Front Oncol*. 2021;11:678634.
32. GSK provides update on DREAMM-3 phase III trial for Blenrep in relapsed/refractory multiple myeloma. News release. GlaxoSmithKline; 2022.
33. BLENREP (belantamab mafodotin): EU summary of product characteristics. European Medicines Agency (EMA).
34. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384(8):705-716.
35. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398(10297):314-324.
36. Kang C. Teclistamab: first approval. *Drugs*. 2022;82(16):1613-1619.
37. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N Engl J Med*. 2023;389(4):335-347.
38. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N Engl J Med*. 2023;388(11):1002-1014.
39. Simmons GL, Castaneda Puglianini O. T-cell-based cellular immunotherapy of multiple myeloma: current developments. *Cancers (Basel)*. 2022;14(17).
40. Dytfeld D, Dhakal B, Agha M, et al. Bortezomib, lenalidomide and dexamethasone (VRd) followed by ciltacabtagene autoleucel versus Vrd followed by lenalidomide and dexamethasone (Rd) maintenance in patients with newly diagnosed multiple myeloma not intended for transplant: a randomized, phase 3 study (CARTITUDE-5) [abstract]. *Blood*. 2021;138(suppl 1):1835.
41. Usmani S, Patel K, Hari P, et al. KarMMa-2 cohort 2a: efficacy and safety of idecabtagene vicleucel in clinical high-risk multiple myeloma patients with early relapse after frontline autologous stem cell transplantation [abstract]. *Blood*. 2022;140(suppl 1):875-877.
42. Usmani SZ, Berdeja JG, Truppel-Hartmann A, et al. KarMMa-4: idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T-cell therapy, in high-risk newly diagnosed multiple myeloma [abstract]. *Blood*. 2020;136(suppl 1):18-19.
43. Raje NS, Berdeja JG, Rodriguez-Otero P, et al. KarMMa-7, a phase 1/2, dose-finding and dose-expansion study of combination therapies with idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy for relapsed/refractory multiple myeloma (RRMM) [abstract]. *Blood*. 2021;138(suppl 1):4830.
44. Sebag M, Raje NS, Bahlis NJ, et al. Elranatamab (PF-06863135), a B-cell maturation antigen (BCMA) targeted CD3-engaging bispecific molecule, for patients with relapsed or refractory multiple myeloma: results from MagnetisMM-1 [abstract]. *Blood*. 2021;138(suppl 1):895.
45. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. *Nat Med*. 2023;29(9):2259-2267.
46. Landgren O, Kazandjian D, O'Connell A, Finn G, Raje N. MagnetisMM-4: an open label, phase 1B/2 umbrella study of elranatamab in combination with other anti-cancer treatments for patients with multiple myeloma [abstract]. *Blood*. 2022;140(suppl 1):10172-10173.
47. Grosicki S, Crafoord J, Koh Y, et al. MagnetisMM-5: an open-label, multicenter, randomized phase 3 study of elranatamab as monotherapy and in combination with daratumumab in patients with relapsed/refractory multiple myeloma. *J Clin Oncol*. 2022;40(16 suppl):tps8074.
48. Mateos MV, Bahlis NJ, Costa LJ, et al. MajesTEC-3: randomized, phase 3 study of teclistamab plus daratumumab versus investigator's choice of daratumumab, pomalidomide, and dexamethasone or daratumumab, bortezomib, and dexamethasone in patients with relapsed/refractory multiple myeloma. *J Clin Oncol*. 2022;40(16 suppl):TPS8072.
49. Dholaria BR, Weisel K, Mateos M-V, et al. Talquetamab (tal) + daratumumab (dara) in patients (pts) with relapsed/refractory multiple myeloma (RRMM): updated TRIMM-2 results [abstract]. *J Clin Oncol*. 2023;41(16 suppl):8003.
50. Cohen YC, Morillo D, Gatt ME, et al. First results from the RedirecTT-1 study with teclistamab (tec) + talquetamab (tal) simultaneously targeting BCMA and GPRC5D in patients (pts) with relapsed/refractory multiple myeloma (RRMM) [abstract]. *J Clin Oncol*. 2023;41(16 suppl):8002.

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