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Redefining Second-Line Treatment Strategy, Sequencing, and Real-World Implementation in Relapsed/Refractory Multiple Myeloma: Insights From the 31st Annual Congress of the European Hematology Association

Moderator

Ajai Chari, MD
Professor of Medicine
Director, Multiple Myeloma Program
UCSF Helen Diller Family Comprehensive Cancer Center
University of California
San Francisco, California

Discussants

Peter M. Voorhees, MD
Professor of Medicine, Wake Forest University School of Medicine
Chief, Plasma Cell Disorders Division, Atrium Health / Levine Cancer Institute
Associate Director of Clinical Research, Atrium Health Wake Forest Baptist Comprehensive Cancer Center
Charlotte, North Carolina

Raymond Thertulien, MD, PhD
Community Hematologist/Oncologist
Novant Health Cancer Institute
Charlotte, North Carolina

Abstract: The management of relapsed/refractory (R/R) multiple myeloma (MM) continues to evolve with the introduction of novel therapies and the use of newer therapies in different treatment settings and combinations. Chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) and bispecific antibodies targeting BCMA and GPRC5D were initially introduced in the heavily pretreated R/R MM setting but have now demonstrated efficacy benefits in earlier lines of therapy. Encouraging results have recently been reported from 3 major phase 3 trials—MonumenTAL-3, MajesTEC-3, and MajesTEC-9—showing significant progression-free survival (PFS) as well as confirmed or preliminary overall survival (OS) improvements with bispecific-containing regimens over current standard-of-care triplets. Bispecific antibodies are associated with a risk of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) and on-target, off-tumor toxicities, including infections and hypogammaglobulinemia with BCMA-targeting agents and oral and skin-related toxicities with GPRC5D-targeting agents. Implementation of bispecific antibodies requires proactive monitoring and management by a knowledgeable and prepared interdisciplinary team. Treatment selection is individualized based on disease-related factors, treatment history, and patient-related factors and preferences. Adoption of bispecific antibodies in community-based oncology practices will be essential for maximizing the benefit of these therapies and ensuring they reach the patients in need.

Relapsed/Refractory Multiple Myeloma: Disease Overview and Treatment Landscape

Ajai Chari, MD

The management of relapsed/refractory (R/R) multiple myeloma (MM) continues to grow more complex with the availability of agents across 6 major therapeutic classes, including cereblon E3 ligase modulators (including immunomodulatory drugs [IMiDs] and cereblon E3 ligase modulators [CELMoDs]), proteasome inhibitors, immune therapies (a broad category including naked antibodies, antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor [CAR] T-cell therapy), chemotherapy, steroids, and an XPO inhibitor.[1] This treatment landscape and the rapid evolution of treatment approaches present challenges for selecting an optimal sequence and combination of active agents.

Recent clinical trials have demonstrated significant efficacy improvements with the use of novel approaches compared with newer triplet regimens in patients with R/R MM who have received at least 1 or 2 prior lines of therapy (LOT). These include CAR T-cell therapy with idecabtagene vicleucel (KarMMa-3) or ciltacabtagene autoleucel (CARTITUDE-4); belantamab mafodotin-based therapy (DREAMM-7, DREAMM-8); bispecific antibodies, including the B-cell maturation antigen (BCMA)-targeted teclistamab as monotherapy (MajesTEC-9) or with daratumumab (MajesTEC-3) and the GPRC5D-targeted talquetamab plus daratumumab with or without pomalidomide (MonumenTAL-3); and with incorporation of the CELMoD mezigdomide (SUCCESSOR-2).[2-12]

Notably, randomized trials have demonstrated more potent improvements in progression-free survival (PFS) with these new approaches despite effective triplet controls (vs doublet comparators of yesteryear) yielding impressive PFS themselves. Moreover, these PFS advantages are translating to improvements in overall survival (OS), as shown in the CARTITUDE-4, DREAMM-7, and MajesTEC-3 and MajesTEC-9 trials.[3,4,6-9]

These findings support a paradigm shift toward earlier use of novel therapies. Given the risk of patient attrition, it is no longer appropriate to "save" these therapies for later. For example, in MajesTEC-9, even though nearly 2/3 of patients in the control arm received salvage T-cell redirection therapies, the PFS benefit still translated into an OS benefit with early use of teclistamab.[8,9]

Aside from the concern for attrition, multiple clinical trials have also shown that newer agents are more effective when their use is shifted from the heavily pretreated towards the newly diagnosed setting. Emerging evidence indicates that T-cell fitness may be a contributing factor in the efficacy of newer therapies, as over the course of MM treatment T-cell populations become dysfunctional and less able to respond to immunotherapy.[13,14] Accordingly, although bispecific antibodies and CAR T-cell therapy were originally approved in the later-line settings, their use is increasingly being moved earlier, and they should be used as early as the second-line setting.[1]

The selection of a regimen in the second- and third-line settings is always guided by which agents have been used previously. The use of lenalidomide maintenance until progression, for example, has long limited the relevance of clinical trials which compare experimental regimens against a control regimen that includes lenalidomide-based therapy (eg, POLLUX).[15] Moreover, the CASTOR and ENDEAVOR trials demonstrated that resistance to lenalidomide was also associated with inferior outcomes even when neither the experimental nor control arms have an IMiD-containing regimen.[16,17] These issues are now also happening with anti-CD38 monoclonal antibodies daratumumab and isatuximab due to

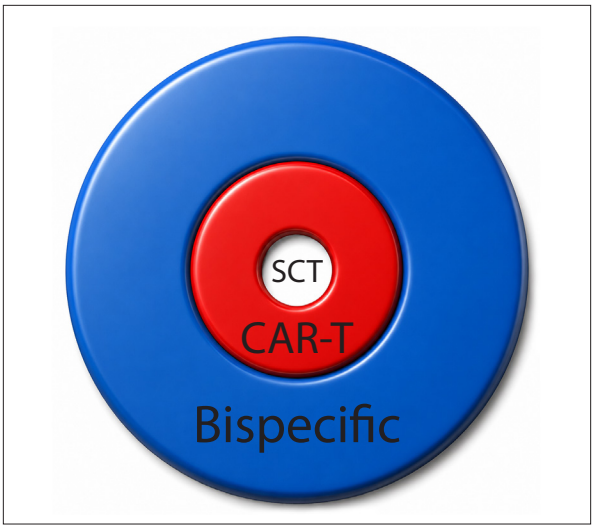

Figure 1. Eligibility[a] criteria have expanded with newer immunotherapies in multiple myeloma.
[a]Unlike SCT and CAR-T, there are no absolute medical contraindications (age/frailty, cardiac/pulmonary/renal/neurologic dysfunction, bulky disease) to bispecifics, except active infection.
CAR-T, chimeric antigen receptor T-cell therapy; SCT, stem cell transplant.
Courtesy of Ajai Chari, MD.

increased early use and concomitant earlier resistance to these agents.[1]

This raises questions about how to select second- and third-line therapy for patients who will increasingly already have resistance to both anti-CD38 and lenalidomide. In these patients with double-refractory disease, outcomes with standard triplets are poor, with median PFS of only 4 to 8 months.[3,4,7,13] Accordingly, it is especially important to use new therapies early in these patients.

The treatment of high-risk MM is another challenge, whether patients have high-risk cytogenetic abnormalities or are functionally high-risk based on the rapidity of progression after first-line therapy. However, recent data from the MajesTEC-3 trial indicate that teclistamab plus daratumumab is associated with significant improvements in PFS across genomic and functional high-risk subgroups.[6,7] It will be important to further refine risk definitions in the context of newer therapies.

Developing novel therapies and regimens is essential but not sufficient for improving outcomes for patients with MM. It is also necessary to ensure patients can access these newer therapies. Most patients with MM in the United States receive care in the community setting, and patients receiving care in community practices tend to be older with more comorbidities, which may limit their ability to access academic practices.[18] However, there are no absolute contraindications to current bispecific antibodies.[19-22] Eligibility for bispecific antibodies is broader than eligibility for CAR T-cell therapy, which is, in turn, broader than eligibility for autologous stem cell transplant (Figure 1).

Moreover, real-world data indicate that these agents can be safe and effective in older and frail patients with R/R MM.[23] Strategies including holding or delaying doses and employing supportive care measures can be used to improve tolerability in patients developing adverse events.[24] Given the demonstrated efficacy of bispecific antibodies, and their expanding use in MM and other malignancies, it is essential that we continue to make progress toward implementing bispecific antibodies in community practices.

Disclosures

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Redefining Second-Line Strategy After MonumenTAL-3, MajesTEC-3, and MajesTEC-9 (presented at the EHA 2026 Congress)

Peter M. Voorhees, MD

Recent randomized, phase 3 clinical trials have demonstrated a significant efficacy benefit with the use of bispecific antibody-containing regimens compared with standard of care in patients with R/R MM in early lines of relapse. These include the MonumenTAL-3 trial evaluating talquetamab plus daratumumab (with or without pomalidomide) after at least 1 line of therapy, the MajesTEC-3 trial of teclistamab plus daratumumab in patients with 1 to 3 prior lines of therapy, and the MajesTEC-9 trial evaluating teclistamab in patients with 1 to 3 prior lines of therapy, including anti-CD38.[1-6] Results of these trials are poised to help redefine the landscape of treatment for patients in early lines of myeloma relapse.

MonumenTAL-3: Design and Key Findings

The MonumenTAL-3 trial enrolled 864 patients with R/R MM who had received at least 1 prior line of therapy, including lenalidomide and a proteasome inhibitor, and randomly assigned them to 1 of 2 talquetamab-containing combination arms—talquetamab, daratumumab, and pomalidomide (Tal-DP), or talquetamab and daratumumab (Tal-D)—or the standard of care control arm, which was daratumumab, pomalidomide, and dexamethasone (DPd).[1,2]

The trial met its primary endpoint, demonstrating a significant improvement in PFS with Tal-DP and Tal-D compared with DPd, with a hazard ratio (HR) of 0.28 and 0.33, respectively (P<.0001 for both comparisons); 2-year PFS rates were 81.3% with Tal-PD, 77.6% with Tal-D, and 51.2% with DPd (Figure 2). Subgroup analyses showed consistent benefit with talquetamab-containing arms regardless of age, prior exposure to daratumumab, number of lines of prior therapy, and disease risk. Talquetamab-containing regimens were also associated with an improved depth of response, with MRD negativity (10^{-6}) rates of 48% with Tal-DP, 42% with Tal-D, and 10% with DPd, and a trend toward longer OS, with 2-year OS rates of 89.2%, 87.9%, and 79.1%, respectively.

In the safety analysis, rates of infection were lower with talquetamab than has been reported with the BCMA-targeting bispecific antibodies. Rates of grade 3 or higher infection were 38% with Tal-DP, 29% with Tal-D, and 42.4% with DPd.[1] In contrast, in the MajesTEC-3 trial, 54% of patients receiving teclistamab plus daratumumab arm had a grade 3 or higher infection.[3]

The rate of fatal infections was 0.7% with Tal-DP, 1.5% with Tal-D, and 1.8% with DPd. Talquetamab-containing regimens were associated with an increase in on-target toxicities that affect the skin, nails, and tongue, and the inferior olivary nucleus of the cerebellum. These result in rash-related events, dry skin, pruritus, and nail changes. However, few patients had to discontinue treatment due to side effects, and these were reversible. There was a high rate of dysgeusia, with many patients developing taste changes due to skin or oral side effects that in some instances led to weight loss. These were primarily grade 1/2 in severity and discontinuations due to oral

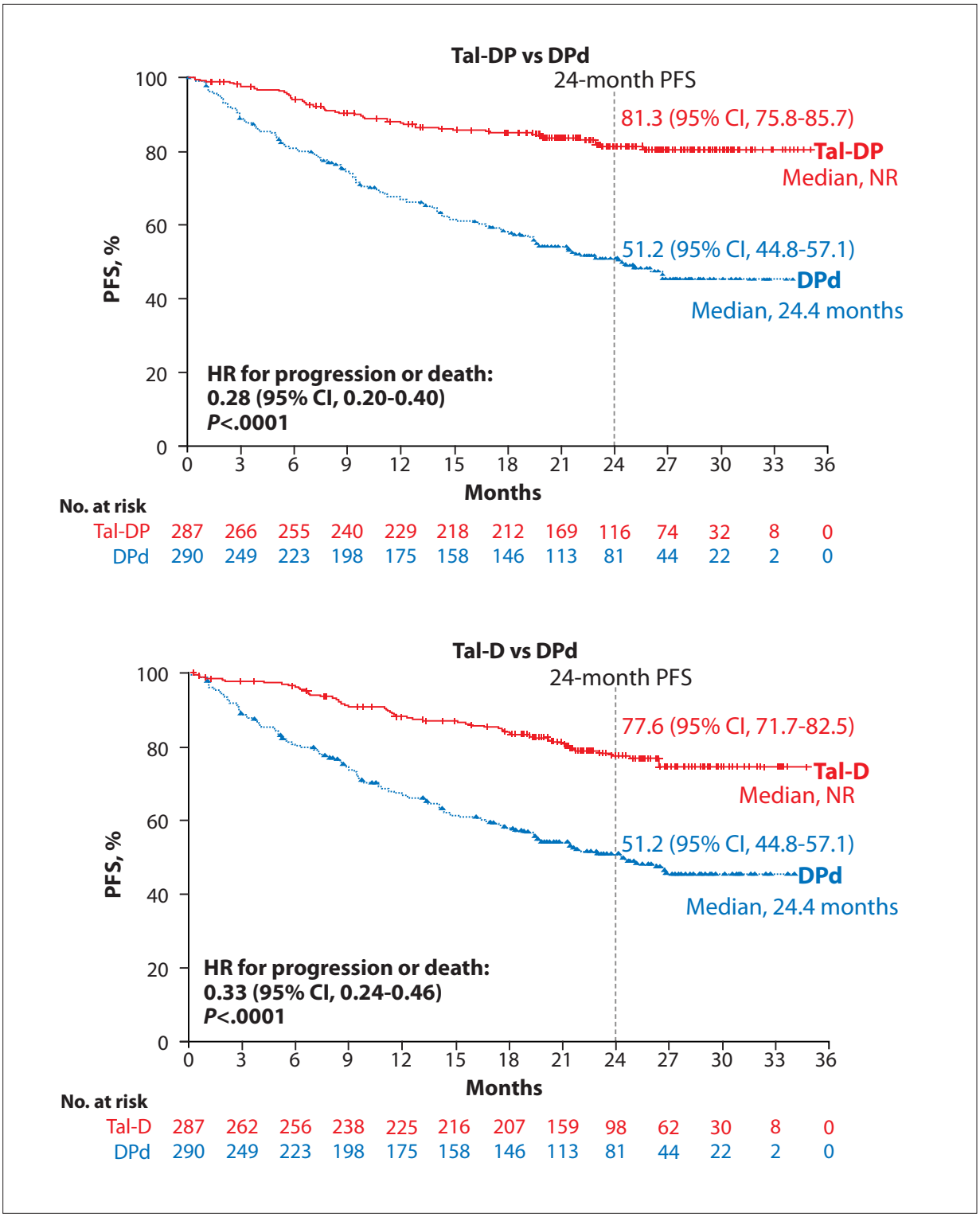

Figure 2. PFS outcomes with talquetamab-containing regimens vs standard of care in MonumenTAL-3.
DPd, daratumumab, pomalidomide, and dexamethasone; HR, hazard ratio; NR, not reached; PFS, progression-free survival; Tal-D, talquetamab and daratumumab; Tal-DP, talquetamab, daratumumab, and pomalidomide.
Adapted from: Voorhees PM et al. Presented at: European Hematology Association (EHA) 2026 Congress; June 11-14, 2026; Stockholm, Sweden.[1]

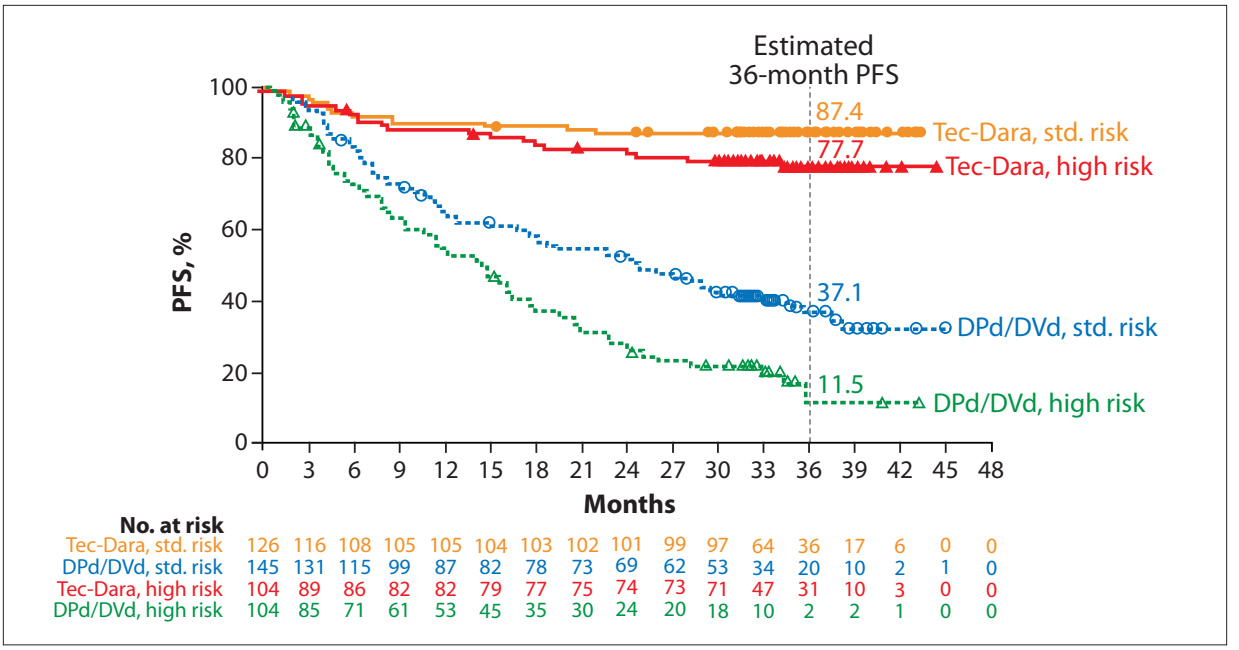

Figure 3. PFS outcomes with teclistamab plus daratumumab vs standard of care based on cytogenetic[a] and functional risk status in the MajesTEC-3 trial.

ASCT, autologous stem cell transplantation; DPd/DVd, daratumumab with pomalidomide and dexamethasone/daratumumab with bortezomib and dexamethasone; FISH, fluorescence in situ hybridization; HR, hazard ratio; PFS, progression-free survival; std., standard; Tec-Dara, teclistamab in combination with daratumumab.

[a]Cytogenetic risk was centrally assessed by FISH. Functional high-risk status included only those patients with 1 prior line of therapy and disease progression ≤18 months after receiving ASCT or starting initial therapy.

Adapted from: Banerjee R et al. Presented at: European Hematology Association (EHA) 2026 Congress; June 11-14, 2026; Stockholm, Sweden.[4]

toxicity or weight changes were uncommon. Finally, an on-target toxicity that has gained substantial attention is ataxia and balance disorders, which were observed in 12.4% to 14.5% of patients receiving talquetamab-containing regimens, though only 2%-3% were grade 3. This will be important to monitor closely moving forward.

MajesTEC-3: Design and Key Findings

The MajesTEC-3 trial compared teclistamab plus daratumumab (tec-dara) against DPd or daratumumab, bortezomib, and dexamethasone (DVd) in 587 patients with MM with 1 to 3 prior lines of therapy.[3,4] After a median follow-up of 34.5 months, tec-dara was associated with a significant improvement in PFS over standard of care, with estimated 36-month PFS rates of 83.4% and 29.7%, respectively (HR, 0.17; *P*<.001) (Figure 3). MRD negativity rates (10^{-5}) were 58.4% and 17.1%, respectively. Rates of serious AEs were 70.7% and 62.4%, respectively; fatal AEs occurred in 7.1% and 5.9% of patients, respectively; and grade 3/4 infections occurred in 54.1% and 43.4% of patients, respectively.

MajesTEC-9: Design and Key Findings

The MajesTEC-9 trial enrolled patients with R/R MM who had received 1 to 3 prior lines of therapy and required that patients had previously received an anti-CD38 antibody, either daratumumab or isatuximab.[5,6] Approximately 85% of patients were refractory to prior anti-CD38. Patients were randomly assigned to single-agent teclistamab or a standard of care control regimen consisting of pomalidomide, bortezomib, and dexamethasone (PVd) or carfilzomib and dexamethasone (Kd). The absence of daratumumab in the control arm reflects this different population.

The trial met its primary endpoint, demonstrating a significant PFS improvement with teclistamab vs PVd or Kd, with estimated 18-month PFS rates of 69.8% and 26.9%, respectively (HR, 0.29; *P*<.001; Figure 4). Subgroup analyses also showed a consistent PFS benefit across key groups. MRD negativity rates (10^{-5}) were also higher with teclistamab vs standard of care, at 86.4% vs 45.5%, as was OS, with estimated 18-month OS rates of 79.2% and 68.6%, respectively (HR, 0.60; *P*=.002).

BCMA-targeted agents such as teclistamab are associated with an increased risk of infection. In MajesTEC-9, teclistamab was associated with a grade 3/4 infection rate of 41.6%, compared with 29% with

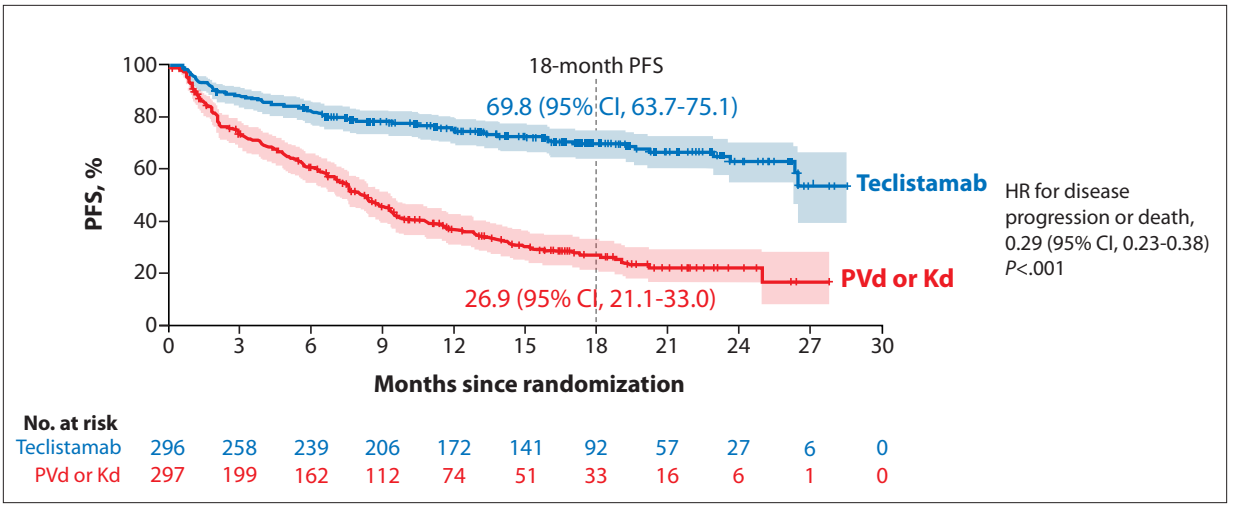

Figure 4. PFS outcomes with teclistamab vs PVd or Kd in MajesTEC-9.
HR, hazard ratio; Kd, carfilzomib and dexamethasone; PFS, progression-free survival; PVd, pomalidomide, bortezomib, and dexamethasone.
Adapted from: Touzeau C et al. *N Engl J Med.* 2026;395(5):440-453.[3]

standard of care. The incidence of fatal infections was 5.5% and 2.8%, respectively.

Implications for Selecting Therapy in R/R MM

In summary, the MonumenTAL-3, MajesTEC-3, and MajesTEC-9 trials reported remarkable outcomes with the use of bispecific antibody-based regimens in patients with R/R MM. In the future, additional follow-up from all these trials may reveal a clear choice for second-line therapy. However, with the available evidence, these trials cannot be compared, as they included different patient populations. As a result, treatment selection is guided by patient preference and the adverse event profile.

All else being equal, a BCMA-targeted strategy first, followed by a GPRC5D-targeted strategy later, makes the most sense for most patients. However, there are patient subgroups in which using a talquetamab-based approach first may be preferable. This includes patients with a history of recurrent high-grade infections requiring hospitalization and patients with severe pulmonary disease, as most high-grade infections occurring with BCMA bispecific antibodies are respiratory in nature.

In terms of later sequencing, a talquetamab-based strategy may also be preferable in a patient with relapse after BCMA CAR T-cell therapy. Although the data available are limited, and are taken from a heavily pretreated population, talquetamab does appear to be more effective than a BCMA bispecific antibody following relapse after BCMA CAR T-cell therapy.[7,8] Therefore, with the data currently available, I would recommend a talquetamab-based approach for a patient with relapse after BCMA CAR T-cell therapy, particularly for patients with an unexpected early relapse.

Disclosures

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Real-World Adoption of Bispecific Antibodies in the Community and Outpatient Settings: Insights From OPTec and OPTal (presented at the ASCO Annual Meeting 2026)

Raymond Thertulien, MD, PhD

Adoption of bispecific antibodies in the community requires that clinics be prepared and equipped to safely deliver these therapies. Bispecific antibodies are associated with risks of cytokine release syndrome (CRS) and neurotoxicity including immune effector cell–associated neurotoxicity syndrome (ICANS) in addition to other longer-term toxicities. In the MajesTEC-1 study of teclistamab and the MonumenTAL-1 study of talquetamab, approximately 72% and 76% of patients, respectively, developed CRS.[1,2] These events primarily occurred during step-up dosing. As a result, the prescribing information for both teclistamab and talquetamab require patients to be hospitalized for 48 hours following each step-up dose to allow for close monitoring and management of CRS and neurologic toxicity.[3,4]

However, in a cohort study of MonumenTAL-1, prophylactic use of the interleukin 6 (IL-6) blocking agent tocilizumab prior to the first talquetamab step-up dose, and daily dexamethasone after each step-up dose and the cycle 1 day 1 dose, was associated with a reduction in the CRS incidence to 23%, all grade 1.[5] Moreover, in a real-world analysis of 119 patients with MM, a single dose of tocilizumab before the first dose of a bispecific antibody (teclistamab, elranatamab, linvoseltamab, or talquetamab) reduced the overall rate of CRS to 0% to 13% (primarily grade 1) without compromising efficacy.[6] This prophylactic measure could allow for outpatient administration of bispecific antibodies for patients with MM.

At the 2026 American Society of Clinical Oncology Annual Meeting, results were presented from the nonrandomized multicenter, prospective, phase 2 OPTec/OPTal trial evaluating outpatient administration of teclistamab and talquetamab with prophylactic use of tocilizumab before step-up dosing.[7] The community-based trial opened in August 2023 and enrolled 52 patients with R/R MM. Patients received teclistamab (n=45) or talquetamab (n=7) in the outpatient setting using the US Food and Drug Administration–approved step-up dosing schedule, with a single dose of prophylactic tocilizumab 8 mg/kg administered before the first step-up dose. Specific recommendations were employed, including home monitoring and use of intravenous immunoglobulin (IVIG) for immunoglobulin G levels less than 400 mg/dL. Specific restrictions related to caregiver requirements and travel distance were also implemented.

The overall incidence of CRS in the teclistamab arm was 8.9%, with 6 CRS events occurring in 4 of 45 patients, all grade 1 in severity. The overall incidence of CRS in the talquetamab arm was 28.5%, with 4 CRS events occurring in 2 of 7 patients, including 3 grade 1 events and 1 grade 2 event (Table 1). No ICANS events were reported.

The most common grade 3 or higher adverse events were neutropenia (n=13), sepsis (n=4), and anemia (n=4). There was 1 grade 5 fatal sepsis event in a patient receiving teclistamab. No hypogammaglobulinemia or IVIG was reported. Infections occurred in 51.1% of patients receiving teclistamab (17.8% grade ≥3) and 71.4% of patients receiving talquetamab (28.6% grade ≥3).

Use of prophylactic tocilizumab did not appear to affect the efficacy of teclistamab or talquetamab in these analyses. In the teclistamab arm, the overall response rate (ORR) was 68.9%, with 51.1% of patients attaining a very good partial response (VGPR) or better and 24.4% attaining a stringent complete response (sCR) or complete response (CR). In the talquetamab arm, the ORR was 71.4%, with 71.4% of patients attaining a VGPR or better and 28.6% attaining an sCR or CR.

These findings indicate that a single dose of prophylactic tocilizumab before the first step-up dose of teclistamab or talquetamab reduces the incidence of CRS without adversely affecting efficacy or safety. An ongoing cohort of the study is evaluating the effect of prophylactic oral dexamethasone on the incidence of CRS in patients receiving teclistamab.[7]

Although the incidence of CRS is reduced with the use of prophylactic treatment, CRS still occurs in a proportion of patients. Accordingly, adoption of bispecific antibodies in the community will require the development of protocols that can be readily executed in the community and education of community providers on how to execute these protocols.

The International Myeloma Working Group (IMWG) has developed consensus guidelines for the management

Table 1. Overview of CRS Events in the OPTec/OPTal Studies and Their Management

CRS	Teclistamab (n=45)	Talquetamab (n=7)
Events, n	6 events in 4 patients (8.9%)	4 events in 2 patients (28.5%)
Grade	Grade 1: 6	Grade 1: 3 Grade 2: 1
Timing	• 2 occurred on days 2-3, between SUD1 (day 1) and SUD2 (day 4) • 2 occurred on days 5-7, between SUD2 (day 4) and full dose (day 8) • 1 occurred during C1 • 1 occurred during C2	• 1 occurred on days 5-7, between SUD2 (day 4) and SUD3 (day 8) • 3 occurred on days 16-56, after the first full dose
Management	• No patients were admitted; all were managed with dexamethasone (dose range, 8-20 mg)	• Grade 1: 1 patient developed 3 events (days 34, 41, 53) and was admitted for all events (SAE); received dexamethasone (8 mg) and/or antibiotics • Grade 2: 1 patient was hospitalized (SAE); received dexamethasone (10 mg), fluid hydration, and tocilizumab. Resolved within 3 days. Talquetamab was held for 1 week post-CRS resolution. SUD2 was repeated 7 days after resolution and no further CRS was reported.

C, cycle; CRS, cytokine release syndrome; SAE, serious adverse event; SUD, step-up dose.

of adverse events following administration of bispecific antibodies in the outpatient setting.[8] According to these guidelines, tocilizumab is recommended for grade 1 CRS and early intervention is encouraged. However, at our institution, we administer a small dose of dexamethasone for patients with grade 1 CRS. The IMWG guidelines state that grade 1 CRS can initially be managed with supportive measures, with early tocilizumab encouraged for patients with persistent grade 1 CRS (>24 hours), to prevent the progression of CRS to grade 2 or 3. I hope that once our community oncologists gain experience with bispecific antibodies, they will be able to use tocilizumab more judiciously, given the cost associated with the use of this agent.

CRS is a predictable toxicity that typically occurs during a narrow window, the step-up period. In contrast, bispecific antibodies are also associated with other toxicities that can occur over a longer term, including neurotoxicity and more frequent adverse events such as infection and hypogammaglobulinemia with BCMA-targeted agents and epithelial toxicities with GPRC5D-targeted agents.[9] Infection can present a particular challenge, as it can develop throughout the treatment period, including 6 to 12 months after starting therapy.

Effective implementation of bispecific antibodies in the community will require that clinicians are aware of the timing of onset of different toxicities and recommendations for their management. For example, if a patient develops a fever 1 to 2 months after starting a BCMA-targeted bispecific antibody, the physician must be aware that this could be an atypical infection and initiate an appropriate workup rather than assuming the patient has CRS and should receive steroids. Again, this will require a workflow of how to approach the management of patients receiving bispecific antibodies over the course of treatment.

Disclosures

Dr Thertulien serves on speaker bureaus and advisory boards of and as consultant for Johnson & Johnson, Sanofi, Bristol Myers Squibb, and GlaxoSmithKline.

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Practical Approach to Second-Line Treatment Strategy, Sequencing, and Real-World Implementation in Relapsed/Refractory Multiple Myeloma: Q&A

Ajai Chari, MD; Peter M. Voorhees, MD; and Raymond Thertulien, MD, PhD

H&O How should clinicians think about sequencing CAR T-cell therapy, BCMA-directed bispecific antibodies, and GPRC5D-directed therapies in R/R MM?

AC The first consideration is CAR T-cell therapy eligibility, based on disease burden/rate of disease progression, comorbidities, and the patient's ability to tolerate treatment-related toxicities. For eligible patients, treatment selection should be based on shared decision-making. Importantly, when CAR T-cell therapy is being considered, bispecific antibody therapy should generally be avoided before apheresis (in the so-called holding period), as prior bispecific exposure may adversely affect the CAR T-cell product and subsequent outcomes. Early coordination between community oncologists and a CAR T-cell center is therefore essential to facilitate appropriate sequencing. For patients who are not candidates for CAR T-cell therapy, bispecific antibodies provide an effective alternative without the logistical requirements of apheresis and manufacturing.

RT Treatment selection should be guided by an expert at a center offering both CAR T-cell therapy and bispecific antibodies, with shared decision-making based on patient factors and disease tempo. Rapidly progressive disease may preclude waiting for CAR T-cell manufacturing currently, although bridging therapy can be used to control disease during the vein-to-vein interval.

When BCMA-directed CAR T-cell therapy is planned, antigen switching is preferred; a GPRC5D-directed bispecific antibody can provide bridging therapy after apheresis while preserving BCMA-directed CAR T-cell therapy. Similarly, when CAR T-cell therapy is being deferred but remains a future option, a non-BCMA bispecific antibody may be preferred. Because prior bispecific antibody exposure may impair subsequent CAR T-cell efficacy, unnecessary BCMA-directed therapy before CAR T-cell therapy should be avoided. If CAR T-cell therapy is not a future option, the choice of bispecific antibody target can be based on other patient- and disease-specific considerations.

PMV I would add that that risk of BCMA loss or mutation is lower in patients with relapse after a BCMA CAR T-cell therapy than it is for patients who receive a BCMA bispecific antibody until progression. Accordingly, for a patient who is a candidate for CAR T-cell therapy, and understands its toxicities, CAR T-cell therapy followed by a subsequent bispecific antibody appears to be the best strategy. If we are choosing between BCMA and GPRC5D bispecific antibodies, the choice is driven by patient characteristics. It may be preferable to start with talquetamab in patients with a clinical course characterized by high-grade infection or severe pulmonary disease, and to start with a BCMA-based strategy in patients without those comorbidities, given their more limited range of on-target, off-tumor side effects.

H&O Are there other factors that drive treatment selection in early lines of relapse?

AC The more resistant a patient is, the earlier newer therapies should be considered, including bispecific antibodies and CAR T-cell therapy. It is particularly important to move to these in patients refractory to both anti-CD38 and lenalidomide. Other factors that warrant escalation of intensity, rather than going with the usual approaches, are functional high-risk disease, genomic high-risk disease, and extramedullary disease.

RT The tempo of the relapse is key. Additionally, in my practice, anyone with primary refractory or functional high-risk disease goes to CAR T-cell therapy with some kind of bridging therapy to prevent the disease from exploding out of control.

H&O How do the results of MonumenTAL-3 and MajesTEC-9 collectively influence second-line treatment decision-making in R/R MM?

PMV MonumenTAL-3 expands talquetamab-based therapy into earlier relapse, providing a potential option for patients with recurrent high-grade infections or significant pulmonary comorbidity. Also, after cilta-cel

in first relapse, talquetamab could be considered in the third-line setting.

MajesTEC-9 is particularly relevant as more patients develop anti-CD38–refractory disease by first relapse after frontline anti-CD38–based therapy. We have patients receiving daratumumab plus lenalidomide and dexamethasone or isatuximab plus lenalidomide and dexamethasone until disease progression, or a quadruplet regimen including an anti-CD38 followed by anti-CD38 plus lenalidomide until progression. Although MajesTEC-3 demonstrated impressive efficacy with teclistamab plus daratumumab, the incremental benefit of adding an anti-CD38 antibody in anti-CD38–refractory disease remains uncertain. MajesTEC-9 therefore supports consideration of single-agent teclistamab at first relapse in this population.

AC Although outcomes from MonumenTAL-3 and MajesTEC-9 cannot be directly compared because of differences in anti-CD38–refractory status, MajesTEC-3 and MonumenTAL-3 provide a useful comparison of bispecific antibody plus daratumumab in non-daratumumab–refractory populations. A key distinction is the safety profile. BCMA-directed therapies such as teclistamab are associated with more infections. Although MajesTEC-3 demonstrated remarkable PFS (HR, 0.17), OS crossover occurred, likely influenced by the COVID-19 pandemic and the absence of routine IVIG use at the time, highlighting the potential infectious risks of BCMA targeting.

In contrast, MonumenTAL-3 did not show an OS crossover, and grade 3/4 infections were lower with talquetamab plus daratumumab (29%) than with DPd (42.4%) which importantly is not event-adjusted for the 70% longer time to progression or death in the talquetamab-daratumumab arm. This distinct infection profile may reflect preservation of humoral immunity and is an important consideration when selecting a GPRC5D-directed regimen. The trade-off is talquetamab's characteristic toxicity profile, including oral toxicity and taste changes that can contribute to weight loss, as well as rash and nail changes. These toxicities should not be minimized. Weight loss, particularly in older patients receiving multiple antihypertensive medications, can contribute to orthostasis/dizziness/ataxia; however, close monitoring for the rare but important AE of cerebellar dysfunction is important.

An additional advantage is that talquetamab toxicities generally do not overlap with those of other myeloma therapies, potentially facilitating combination strategies. Whether talquetamab plus daratumumab and pomalidomide offers a meaningful advantage over talquetamab plus daratumumab remains uncertain; although MRD negativity was numerically higher with the triplet (52.3% vs 46.3%), longer follow-up is needed. Ultimately, the rapid onset of response with these agents allows a flexible, response-adapted approach: starting with one agent and adding therapy sequentially if the response is inadequate, potentially enabling more individualized or fixed-duration treatment strategies.

H&O How should the DPd comparator data and the hazard ratios reported in MonumenTAL-3 be interpreted?

RT The HR for PFS of 0.28 with Tal-DP vs DPd and 0.33 with Tal-D vs DPd in MonumenTAL-3 showed a significant improvement with the talquetamab-based regimens compared with an already effective triplet regimen. These results substantially exceeded what we achieve with triplet regimens commonly used in community oncology practice.

H&O What role does patient input and counselling play in the second-line setting?

AC Treatment selection should be based on shared decision-making. Key questions for the patient are: How important is a treatment-free interval? How willing are they to take the rare but not zero risks of CAR T-cell therapy such as neurologic toxicity, secondary cancer, and colitis, which affect quality of life and survival? Distance from the infusion center is another factor when considering the need for weekly or biweekly visits.

RT I usually advocate that patients be referred to a center where CAR T-cell therapy and bispecific antibodies are offered so they can be informed about all the options available to them, the requirements for each, and their efficacy and potential toxicities. Although geographic location could be a factor, if patients can more easily access a clinic offering a bispecific antibody, this may be preferable.

PMV These are extraordinarily complex discussions, and patient input is critical. I set aside more time for these discussions than I did historically, as decision-making is far more complicated today. The counseling process may require more than one visit with the first visit focusing on discussions about CAR T-cell therapy vs bispecific antibody, and the second on addressing which bispecific antibody regimen is the best approach and finalizing a plan. We provide patients with resources and reputable online sources to do additional homework between these visits.

H&O What other factors influence the choice between BCMA-directed and GPRC5D-directed bispecific strategies in R/R MM?

AC BCMA- and GPRC5D-directed therapies have distinct toxicity profiles, with BCMA-targeted agents associated with greater infection risk and GPRC5D-targeted agents with more oral and skin toxicities. In patients with recurrent respiratory infections or underlying COPD/bronchiectasis, a GPRC5D-directed therapy may be preferred, whereas patients for whom taste is particularly important may favor a BCMA-directed approach. Weight loss with talquetamab appears greatest among patients with obesity, while normal-weight patients lose less and underweight patients may gain weight; however, a patient's baseline weight alone is not an evidence-based basis for target antigen selection. Importantly, after prior BCMA-directed therapy, switching targets is preferred, as subsequent BCMA-directed therapies have substantially shorter PFS.

PMV I would add that there is also a higher rate of grade 3/4 neutropenia with the BCMA bispecifics, though this is usually manageable.

H&O Which specific patients would you consider for talquetamab in second-line?

RT Second-line talquetamab, as in MonumenTAL-3, could be considered for specific patient populations and treatment scenarios, including if the patient could not withstand the infection risk of BCMA-targeted agents but they could tolerate toxicities such as the epithelial side effects associated with talquetamab. Treatment history is also a consideration. MonumenTAL-3 did not include daratumumab-refractory patients; therefore, a patient who had previously received and is refractory to daratumumab would not be appropriate for this type of regimen based on the evidence.

AC A history of recurrent respiratory infections or underlying pulmonary disease are the main populations in which I would consider talquetamab in second-line. Anti-CD38 exposure/refractoriness is also an important consideration: teclistamab plus daratumumab is most applicable in anti-CD38–naive or minimally exposed patients, whereas its benefit after progression on anti-CD38 therapy is less clear, particularly given the potential for increased infection risk. This concern is less pronounced with talquetamab because of its distinct safety profile, making anti-CD38 combination therapy a potentially reasonable option even after prior anti-CD38 exposure. The differential infectious risks can be seen when looking at the outcomes of CD38-refractory patients in recently published TRIMM2 studies of each of these two doublet regimens.

H&O How do you maximize efficacy when patients rarely stay on therapy until progression?

PMV I believe that patients should not stay on bispecific antibody therapy until disease progression. Emerging evidence suggests that patients who have responded well to a bispecific antibody and then discontinue because of side effects or personal preference maintain responses for an extended period. Specialists also believe that the risk of antigen escape will drop when bispecific antibodies are not used until disease progression. The question "how long is enough" is being evaluated.

RT In clinical practice, we often discontinue therapy before progression because of various reasons, including the achievement of deep and sustained responses, toxicity, cost, and inconvenience. Against this backdrop, how should we optimize the frequency and dosing of these agents? Depth of response is an important parameter. If a patient attains sustained MRD negativity for more than 1 to 2 years, discontinuation of treatment could be considered. In patients with functional high-risk disease or extramedullary disease, this is not advisable. Patients with standard-risk disease with sustained MRD negativity do not need treatment for perpetuity.

H&O What operational changes are needed to deliver talquetamab safely in outpatient settings?

PMV Outpatient step-up dosing requires robust monitoring, particularly between clinic visits. Institutional approaches vary, but prophylactic tocilizumab can reduce CRS risk and facilitate safer outpatient administration.

We need to build on the OPTec/OPTal trial to give community oncologists the opportunity to develop protocols for outpatient administration and toxicity management, enabling patients to receive these effective therapies closer to home. We have done this successfully at our institution.

Clinicians should remain vigilant for delayed toxicities, particularly infections and hypogammaglobulinemia with BCMA bispecifics, with IVIG used routinely for these patients. Talquetamab-associated toxicities likewise require familiarity and proactive management, much as clinicians have learned to manage other class-specific toxicities such as EGFR inhibitor–associated rash.

AC Prophylactic tocilizumab can reduce the risk of grade 1 (and also grade 2, though more variably) CRS and facilitate step-up dosing. Administering step-up doses on days 1, 3, 5, and 7 extends tocilizumab coverage across more doses. Because CRS risk persists, particularly with high disease burden, patients should have dexamethasone and acetaminophen readily available for management. As tocilizumab is a monoclonal antibody, additional doses may provide limited benefit unless significant time has elapsed since the initial prophylactic dose.

RT Successful outpatient step-up dosing requires education of patients, treating providers, and the broader health care team, including after-hours and emergency department staff. Bispecific-associated CRS is generally low grade and manageable with tocilizumab, allowing most patients to be treated safely as outpatients. However, inpatient monitoring may be appropriate for frail patients, those with limited caregiver support, or those with high disease burden and greater CRS risk.

H&O What are the biggest barriers to talquetamab adoption and how do we overcome them?

AC The primary barrier to talquetamab use is limited familiarity, which can be addressed through education of patients, caregivers, and the multidisciplinary care team. Patients should be counseled to expect oral, skin, and nail toxicities, which are generally reversible and manageable and can even be biomarkers of response. Discontinuation due to adverse events has been relatively uncommon, particularly when rapid myeloma responses are so common. Skin toxicities usually occur early and can be managed with emollients and topical steroids, while nail changes are largely cosmetic. Oral toxicities are more challenging but often improve by 3 months without dose modification, according to recent data from the TALISMAN study. Maintenance of caloric intake is essential. Multidisciplinary collaboration remains essential for effective toxicity management.

PMV Provider education on the expected time course and management of adverse events is essential, particularly during the first 3 to 6 months of talquetamab therapy. Early nutrition consultation can help patients manage taste changes; keeping nails short and using oral rinses may also help mitigate nail and oral toxicities. Infection prophylaxis is important with all bispecifics, including antiviral and *Pneumocystis jirovecii* pneumonia prophylaxis, with IVIG considered based on immunoglobulin G levels, particularly when daratumumab is combined with talquetamab. Grade 1 cerebellar toxicity warrants individualized risk–benefit assessment, whereas grade ≥2 events should prompt treatment discontinuation.