ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs for Relapsed or Refractory Multiple Myeloma

Benjamin Derman, MD
Assistant Professor of Medicine
Interim Director, Multiple Myeloma Program
UChicago Medicine
Chicago, Illinois

H&O What are the most recent drug approvals for relapsed or refractory myeloma?

BD We have seen an influx of immunotherapies for relapsed or refractory myeloma over the past 5 years. First, we saw the introduction of 2 chimeric antigen receptor (CAR) T-cell therapies, in which genetically engineering a patient's endogenous T cells to recognize and attack myeloma cells essentially turns them into "heat-seeking missiles." Both of the currently approved CAR T-cell therapies for myeloma target B-cell maturation antigen (BCMA): idecabtagene vicleucel (ide-cel; Abecma, Bristol Myers Squibb/2seventy bio), approved in 2021, and ciltacabtagene autoleucel (cilta-cel; Carvykti, Janssen Oncology/Legend Biotech), approved in 2022. BCMA remains an excellent target for myeloma therapies because it is ubiquitously expressed in plasma cells, with relatively limited off-tumor toxicity.

Ide-cel was initially approved for use in patients who had undergone at least 4 lines of therapy. It later received expanded approval for use in patients who had undergone at least 2 prior lines on the basis of the phase 3 KarMMa-3 trial, which showed a median progression-free survival (PFS) of 13.3 months with ide-cel vs 4.4 months with standard-of-care therapy at a median follow-up of 15.9 months.[1] Similarly, cilta-cel first received approval for use in patients with heavily pretreated myeloma but is now approved for use in patients with a single prior line of therapy whose disease is refractory to lenalidomide.

We have also seen the introduction of 4 bispecific antibodies for use in patients with relapsed/refractory disease who have received at least 4 prior lines of therapy. Bispecific antibodies bind both T cells and myeloma cells, bringing them together physically and activating T-cell–mediated killing of myeloma cells. Three of these agents target BCMA: teclistamab (Tecvayli, Janssen Biotech), which was approved in 2022; elranatamab (Elrexfio, Pfizer), which was approved in 2023; and linvoseltamab (Lynozyfic, Regeneron), which was approved in 2025. Talquetamab (Talvey, Janssen Biotech), which targets G protein-coupled receptor class C group 5 member D (GPRC5D), received approval in 2023.

Another option is belantamab mafodotin (Blenrep, GSK), which was reapproved in October 2025 for use in combination with bortezomib and dexamethasone (Vd) for relapsed/refractory myeloma after at least 2 prior therapies. Belantamab mafodotin is another agent that targets BCMA, but it is an antibody-drug conjugate (ADC) and does not rely on T-cell engagement. Belantamab mafodotin was withdrawn from the market in 2022 but was returned on the basis of results of the phase 3 DREAMM-7 trial, which found significant improvements in PFS and overall survival (OS) in a comparison of belantamab plus Vd with daratumumab (Darzalex, Janssen Biotech) plus Vd.[2]

H&O How has the sequencing of therapy changed with the introduction of new agents?

BD How to sequence these newer therapies is one of the biggest unresolved questions in myeloma right now. As a field, we still do not have a definitive answer. We now have 3 ways to target BCMA, for example: CAR T-cell therapy, bispecifics, and ADCs. The key question is whether the order matters. And if it does, which approach should come first? Because both CAR T-cell therapy and

bispecific antibodies rely on functional T cells, we also have a practical concern that we can use strategies that redirect T cells only so many times in the same patient.

For this reason, we came together as the International Myeloma Working Group to publish guidelines regarding the use of T-cell–engaging bispecific antibodies[3] and the sequencing of immunotherapy for myeloma.[4] One important issue we considered is access. Off-the-shelf therapies such as bispecific antibodies and ADCs are available in both academic and community settings, whereas CAR T-cell therapy is still limited to specialized centers. So it is easy for those of us at referral centers to say CAR T-cell therapy should come first if we believe that, but the real-world picture is more complicated.

> Looking ahead, we may be routinely using next-generation sequencing to assess for mutations or other alterations in BCMA or GPRC5D that could help guide subsequent therapy choices.

Up until the end of 2025, CAR T-cell therapy trials produced some of the longest PFS outcomes in relapsed/refractory myeloma, and we also know that CAR T-cell therapy tends to be less effective after prior exposure to bispecific antibodies or ADCs. It can still work in that setting, but response durations are much shorter. The reverse is also true; if a patient receives CAR T-cell therapy first and then later receives a BCMA-directed bispecific antibody, the bispecific often does not perform as well as it would in a BCMA-naive patient. The exception is switching of targets. Talquetamab adds an important nuance to this discussion because it targets GPRC5D rather than BCMA. In post hoc and real-world analyses, talquetamab has shown meaningful activity even after prior BCMA-directed CAR T-cell therapy, which makes it a valuable option for relapse after this therapy. At the same time, talquetamab has been studied as a bridging strategy before BCMA CAR T-cell therapy, with data suggesting it can provide disease control and help patients reach CAR T-cell infusion successfully. However, talquetamab appears to be less effective after prior BCMA bispecific antibody exposure. In practical terms, this finding reinforces the broader principle that we can effectively redirect T cells only so many times as disease evolves.

The discussion shifted dramatically in December 2025, when initial results from the phase 3 MajesTEC-3 trial were published.[5] This study showed that a combination of daratumumab and hyaluronidase (Darzalex Faspro, Janssen Biotech) plus the bispecific antibody teclistamab improved PFS and OS in relapsed/refractory myeloma vs standard-of-care triplet therapy, which consisted of either daratumumab plus pomalidomide (Pomalyst, Celgene) and dexamethasone or daratumumab plus bortezomib and dexamethasone. We had already expected the investigational regimen to improve response rates and durability, but the magnitude of the benefit was striking. At 3 years, more than 80% of patients were alive without progression, the strongest PFS result we have seen in a phase 3 trial in relapsed/refractory myeloma. It forces us to reconsider where CAR T-cell therapy fits in the treatment sequence and raises a practical question: if we move bispecific antibodies earlier into second- or third-line settings, can we achieve outcomes comparable with those of CAR T-cell therapy for some patients?

In practice, this question is now a central discussion at first relapse. Do we use a more conventional regimen that may be easier to deliver but is likely to be less effective, or do we move earlier to an immune-based approach such as CAR T-cell therapy or a bispecific antibody? Most of us increasingly favor the latter approach, but the right choice depends on a nuanced discussion with the patient, including disease biology, treatment goals, access, logistics, and toxicity considerations.

H&O In what circumstances would you recommend CAR T-cell therapy earlier in relapsed/refractory disease?

BD I tend to favor earlier CAR T-cell therapy for patients with high-risk disease. Patient preference is also a major factor. One of the key advantages of CAR T-cell therapy is the potential for a treatment-free interval because patients do not need ongoing treatment after the initial infusion. By contrast, bispecifics are generally continued over time because we still do not know when it is safe to stop treatment. In MajesTEC-3, patients stayed on the therapy indefinitely. Patients still need a lot of supportive care after CAR T-cell therapy, including the use of intravenous immunoglobulin (IVIG) to protect against infections. But from a quality-of-life perspective, patients who get well have a lot of freedom and can go 3, 4, or even 5 years or longer without needing to change their treatment. If patients can go 5 years without evidence of disease, we

start to wonder whether we might be able to consider their disease cured.

Unfortunately, CAR T-cell therapy can be associated with significant toxicity. Serious and sometimes fatal infections can occur, and in some cases severe complications may develop, such as enterocolitis or even parkinsonism-like neurologic toxicity, that may not be reversible. Inflammatory toxicities can also occur, including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and immune effector cell–associated hemophagocytic lymphohistiocytosis–like syndrome. So I view CAR T-cell therapy as a high-risk, high-reward approach, and as we gain more experience, we are learning how to reduce the risk side to improve outcomes further. For the right patient, particularly someone with high-risk disease features who is motivated by the possibility of a durable response and time off therapy, CAR T-cell therapy can be a very attractive option.

H&O In what circumstances would you recommend a bispecific agent before CAR T-cell therapy?

BD A major advantage of bispecific antibodies is access—that is, they are readily available and can be started quickly. They do not carry some of the rare but serious toxicities we worry about with CAR T-cell therapy, such as severe enterocolitis and parkinsonism. Bispecifics do carry an even higher risk of infections than what we see with CAR T-cell therapy. That said, outcomes improved in MajesTEC-3 when IVIG use and antimicrobial prophylaxis were reinforced, which highlights how important supportive care is with these agents. Talquetamab has a distinct toxicity profile that is also important to discuss with patients. It can cause significant nail changes, skin toxicity including peeling or sloughing early in treatment, and dysgeusia that can be quite impactful, leading to reduced oral intake and meaningful weight loss.

Bispecifics are not approved for use as second-, third-, or even fourth-line treatment, but any expansion of earlier-line approvals would immediately change the treatment landscape and shift how we sequence these therapies in routine practice.

Belantamab mafodotin is also relevant in this discussion of sequencing because it offers a BCMA-targeted option that does not redirect T cells. In the United States, the combination of belantamab mafodotin plus Vd is approved for patients with relapsed/refractory myeloma after at least 2 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent. By contrast, belantamab mafodotin plus pomalidomide/dexamethasone (Bela-Pd) is not currently approved by the US Food and Drug Administration (FDA). That said, Bela-Pd can still be an appealing regimen conceptually in selected patients because the visit schedule may be more favorable than it is in some other immune-based approaches, particularly when treatment logistics and quality of life are major considerations.

A concern with belantamab mafodotin is ocular toxicity, particularly keratopathy, and consequently vision changes. As a result, patients need to see an eye doctor before each dose to rule out keratopathy or significant changes in their vision. Patients are required to use preservative-free lubricant eye drops while on this medication. In some cases, we can address side effects by decreasing the dose or frequency of the drugs.

Looking ahead, we may be using next-generation sequencing routinely to assess for mutations or other alterations in BCMA or GPRC5D that could help guide subsequent choices of therapy.

H&O Are we seeing deeper, more durable responses with the latest drug combinations?

BD This is an important question because we are moving past just looking at the response rate. Now, we want to look at how long the response is, and how deep. Historically, we focused on achieving a complete response in myeloma, in which the blood and bone marrow do not show evidence of myeloma by conventional methods. Increasingly, however, the goal is measurable residual disease (MRD) negativity, which provides a much more sensitive assessment of disease burden. The FDA has also signaled growing acceptance of MRD as an endpoint, including MRD-based data, to support accelerated approval in certain settings. That acceptance has increased awareness across the field that MRD status is a highly important prognostic marker. We do not know whether the FDA guidance will extend to MRD data for bispecific antibodies or CAR T-cell therapy, however.

H&O Which subpopulations of patients with myeloma have the greatest unmet need?

BD The biggest unmet need is in patients with ultra–high-risk features. This can apply to patients with multiple high-risk chromosomal abnormalities, extramedullary disease, plasma cell leukemia, or central nervous system myeloma. All the exciting therapies we have just discussed do not work nearly as well in these populations.

H&O What do you see changing in myeloma treatment over the next few years?

BD Over the next 5 to 10 years, we hope to learn how

best to combine these agents in the frontline to make them as efficacious as they can be. As with most cancers, our first shot at treating myeloma is typically going to be our best one. That is why we want to maximize what we are doing up front without hurting patients, which involves targeting BCMA in the frontline, most likely via CAR T-cell therapy or bispecific antibodies. Multiple studies are ongoing looking at various combinations in the frontline. And so the question ultimately is going to be centered around what is the least amount of drug we can get away with and still get an excellent response. The answer will probably be less for the standard-risk patients and more for the high-risk patients.

I am also looking forward to learning more about the best way to deliver CAR T-cell therapy. We got an early glimpse of the future at the most recent ASH Annual Meeting, in a presentation on in vivo CAR T-cell therapy.[6] Instead of using the standard process of administering lymphodepleting chemotherapy, collecting a patient's T cells, sending them for manufacturing, and reinfusing them weeks later, this strategy uses an off-the-shelf lentiviral vector to generate CAR T cells directly in the patient. In that very small early cohort, all 4 patients achieved MRD negativity by month 1. These are very preliminary data, but they are extremely exciting and may point to a more scalable way to deliver CAR T-cell therapy in the future.

Disclosures

Dr Derman has consulted for Johnson & Johnson, Sanofi, Pfizer, Canopy Care, COTA Healthcare, Legend Biotech USA, and Siemens; has served as a clinical trial reviewer for BMS; and has received research funding from GSK and Amgen.

References

1. 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.
2. Hungria V, Robak P, Hus M, et al; DREAMM-7 study investigators. Belantamab mafodotin plus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (DREAMM-7): updated overall survival analysis from a global, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2025;26(8):1067-1080.
3. Rodriguez-Otero P, Usmani S, Cohen AD, et al; International Myeloma Working Group. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. *Lancet Oncol*. 2024;25(5):e205-e216.
4. Costa LJ, Banerjee R, Mian H, et al. International myeloma working group immunotherapy committee recommendation on sequencing immunotherapy for treatment of multiple myeloma. *Leukemia*. 2025;39(3):543-554.
5. Costa LJ, Bahlis NJ, Perrot A, et al; MajesTEC-3 Trial Investigators. Teclistamab plus daratumumab in relapsed or refractory multiple myeloma. *N Engl J Med*. 2026;394(8):739-752.
6. Harrison S, Ho PJ, Lim S-L, et al. Minimal residual disease (MRD)-negative outcomes following a novel, in vivo gene therapy generating anti–B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cells in patients with relapsed and refractory multiple myeloma (RRMM): preliminary results from inMMyCAR, the first-in-human phase 1 study of KLN-1010 [ASH abstract LBA-1]. *Blood*. 2025;164(2)(suppl).