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How the 2025 IMWG Guidelines are Reshaping Sequencing in R/R Multiple Myeloma

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol-Myers Squibb. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss the 2025 International Myeloma Working Group, or IMWG, guidelines on sequencing T-cell-redirecting therapies in relapsed and refractory multiple myeloma is Dr. Mansi Shah. She's an Associate Professor and the Clinical Director of Multiple Myeloma at Rutgers Cancer Institute.

Dr. Shah, thank you so much for being here today.

Dr. Shah:
Thank you so much for having me. I'm so excited to be talking about T-cell-directed therapies and their sequencing in the options for multiple myeloma.

Dr. Caudle:
Well, I am as well. So why don't we just dive right in? The IMWG guidelines outline a new sequencing framework based on disease stage, immune function, and therapeutic goals. Can you walk us through how these three factors guide treatment sequencing in relapsed or refractory multiple myeloma?

Dr. Shah:
Sure. What I like about the new IMWG sequencing guidelines is that it forces us to take a step back and think strategically about where a patient is in their disease course and what their immune system can tolerate. Is there an early relapse where we might have time for CAR T planning, or is this a late penta-refractory relapse where we need fast disease control and more emergent therapy?

Then, we look at immune reserve because these immunotherapies depend on functional T cells. Low counts, recent intensive therapy, especially cytotoxic therapy, and prior T-cell engagement all influence what's going to work next—particularly the last line of therapy that the patient has received.

And finally, what's our goal right now—deep remission, long-term disease control, or bridging someone safely to destination CAR T? And the guidelines really shift us towards thoughtful, patient-centered sequencing rather than just moving through the drugs one by one as they were approved.

Dr. Caudle:
Thank you for that. And to build on that, the IMWG specifically recommends prioritizing CAR T-cell therapy in eligible patients with triple-class or penta-refractory disease while using bispecific antibodies earlier or even as bridging strategies. So how might this guidance change how we think about real-world sequencing?

Dr. Shah:
I think the guideline is very clear that for truly triple class or penta-refractory patients who are fit and eligible, CAR T is still a preferred option because it gives you the deepest, most durable remissions. But in the real world, timing and access are everything. So, there's this brain-to-vein—we think about CAR T, and by the time we actually accomplish it, there's a delay. And a lot can happen to a patient in those time periods. So that's where bispecifics have really changed how we practice. They're off the shelf, they're fast, and now we're just using them as late light salvage or as a bridge.

I do want to highlight the MAJESTIC-3 trial, which was just talked about at ASH, which looked at teclistamab plus daratumumab and showed an 83 percent reduction in the risk of progression or death versus standard daratumumab-based triplet regimens, which are typically what we use currently as the standard of care. And these are patients who have received one to three prior lines of therapy, and there's a very clear separation in progression-free survival as well as overall survival at about three years follow-up now. This is the kind of result that can really move a bispecific combination into the second-line standard of care, especially as a steroid-sparing therapy. It's outpatient and on a familiar schedule that most patients have already experienced.

So when you put the IMWG sequencing framework next to the data like MAJESTIC-3, I think the message is we have to be much more intentional. We can't just say “CAR T someday.” We need to think about when we can get to “destination CAR T.” We need to refer earlier for cell collection but also recognize that some patients may appropriately get a bispecific-based combination in the second-line in the near future and then need a different target or modality later.

The sequencing conversation is no longer CAR T versus bispecifics; it's how we thoughtfully integrate both in the right sequence based on access, the disease tempo, and, of course, the patient in front of us.

Dr. Caudle:
And the guidelines also address differences in relapse timing. For example, we might manage patients who relapse within 12 months of frontline therapy differently than those with later or more functional relapses. How does this distinction impact your approach to treatment planning, particularly when it comes to sequencing immune-based therapies?

Dr. Shah:
So relapse timing really influences how I quickly need to move toward a cellular therapy strategy. So if a patient relapses early, especially within that first 12 to 18 months after induction therapy and consolidation with transplant, I assume that there's aggressive disease biology. And my instinct is to plan for CAR T rather quickly versus cycling through multiple lines of therapy or relying on other agents first, especially given that the bispecifics in the current state are not approved for second- or third-line therapy, and they're only available in those settings via clinical trials. So, for these functionally high-risk patients, these are the patients that I want to collect, and they should be referred as quickly as they are recognized because we don't want them to miss that window of opportunity to receive cell therapy.

On the other hand, for patients who relapse later and have more of a later relapse, I have a little more room to think about the prior therapies and their disease kinetics as well as comorbidities and individual patient characteristics, but the intention is still the same. I want them to get to CAR T—maybe not immediately in that moment, but that's the direction I'm planning towards. And that's why I call it “destination CAR T.”

And I just want to add that what we used to call “functional high risk” is evolving. In the era of quad induction, which most of us in the US are using, and potentially doublet maintenance, which many of us are using, patients are doing well for very long periods of time. So the traditional 12-to-18-month cutoff, which was defining “functionally high risk” in the triplet era, may no longer be the right definition. And the definition of “functional high risk” probably needs to shift towards a time that's later because outcomes upfront are so much better now.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Mansi Shah about the 2025 IMWG guidelines on treatment sequencing in relapsed and refractory multiple myeloma.

Now, Dr. Shah, in addition to CAR T and bispecifics, the guidelines also position antibody-drug conjugates as options later in the sequence. So where do you see antibody-drug conjugates fitting into treatment plans, especially when patients are ineligible for or progressing on T-cell therapies?

Dr. Shah:
I really think of antibody-drug conjugates as useful in a very select group of patients. In my mind, they're not replacing CAR T or bispecifics, but they do fill that later-line space, especially for patients who have good cytotoxic tolerance but may not have the immune fitness for another round of T-cell engagement.

And this comes up a lot in the real world. If someone's had prolonged BCMA bispecific therapy, there may be significant immune dysfunction, and they may be dealing with recurrent infections. They also are at increased risk, and many experience hypogammaglobulin anemia. So it's not always safe or practical to keep pushing that T-cell axis. So that's often where, in those patients who've had recurrent infections, are hospitalized, and have very low infection reserve, as I like to call it, I might be thinking about ADCs.

So, practically, I consider them once I feel like the patient has either exhausted or we can't safely deliver further T-cell-directed strategies. It's another important tool we have in our toolbox, and it does broaden our options when T-cell pathway isn't the right one in that moment.

Dr. Caudle:
Shifting to eligibility criteria, the IMWG emphasizes factors like functional status, immune reserve, and prior antigen exposure. Given that, what factors do you consider most critical when deciding if a patient is a strong candidate for CAR T or a bispecific?

Dr. Shah:
In practice, most patients I'm evaluating for CAR T haven't been exposed to BCMA yet. And this also is important because of the way the therapies available have been approved. So BCMA CAR T is approved for second line and beyond, whereas BCMA-targeted bispecifics are approved for fifth line in the current setting. And so, as we're thinking about what to use when, I think of all patients as eligible for BCMA CAR T unless there are factors that would make CAR T unfeasible at that moment.

When someone has been exposed to BCMA CAR T, the first thing I look at is disease kinetics. How quickly is the disease relapsing? How is the disease behaving? And do I have time to get them through collection and bridging therapy so that we can administer CAR T?

Next, I think about prior therapies and whether the patient has any remaining options that will actually hold or bridge the patient long enough to reach CAR T. Adequate bridging, as we're learning with more and more data that's available, is so critical. And if I don't think I can safely bridge the patient, that changes the plan more than anything else.

Then, it also becomes a question of logistics. Can this person reliably follow up? Do they have adequate support? Do we have the capacity to administer CAR T safely? And do they have adequate support and understanding to get through the monitoring period, especially initially, but also enough support to possibly undergo or be evaluated for the late toxicities that can occur with CAR T? So these issues often determine feasibility more than disease biology does.

And finally, functional status and organ function are the last things that I will weigh in. Many patients are sometimes debilitated because of active disease, and my goal is to reverse that with effective therapy rather than exclude them upfront because of their functional status. And like I said, I actually think of everyone as CAR T eligible until proven otherwise, and so I try not to disqualify patients prematurely based on frailty that might improve once the disease is under control.

Dr. Caudle:
And if we focus on one more recommendation, the guidelines support the use of sequential T-cell-redirecting therapies—for example, switching from a BCMA-directed agent to one targeting GPRC5D. Can you share your thoughts on this kind of sequencing and when you would make that switch?

Dr. Shah:
Yes, and that's one of the most practical takeaways that we are seeing from this guideline. We're learning that switching targets matters.

So if a patient progresses after BCMA-targeted therapy, I'm generally not recycling BCMA-targeted therapy immediately. I'm thinking about switching the antigen and moving to GPRC5D or another non-overlapping target. And that's consistent with the guidance and what we're seeing clinically, where responses are deeper and more durable when we change the antigen rather than change the drug that might also target this previous antigen, such as BCMA.

The timing is another nuanced criteria. So if someone had a long response to their BCMA approach—say more than a year after BCMA CAR T—there may be room to reconsider a BCMA-targeted approach like a bispecific agent later. But shorter responses to CAR T, an aggressive progression, or clear antigen escape push me much more firmly towards a GPRC5D-targeted option.

Biologically, it makes sense to switch targets, and clinically, we're seeing that sequencing across targets preserves options. And again, I'm always thinking a step ahead. If I use a GPRC5D-targeted agent now, am I positioning the patient to be still eligible for a BCMA-targeted therapy later or for a clinical trial? So these are some of the things that I think about for sequencing of BCME- and GPRC5D-targeted therapeutics.

Dr. Caudle:
Excellent. And as we wrap up, Dr. Shah, what's one takeaway from these guidelines that you want listeners to keep in mind when caring for patients with relapsed and refractory multiple myeloma?

Dr. Shah:
If there's any takeaway, it's this: don't wait to refer the patients. Early referral for CAR T, even potentially before a patient is relapsing, is really where we can change outcomes and improve accessibility to these therapies. We finally have therapies that can deliver deep,

durable responses, and I think the guidelines reinforce that we should be using our strongest options earlier rather than saving them for the very end.

Planning for CAR T ahead of time rather than reacting to worsening disease can make all the difference. That timing piece is becoming just as important as the therapy itself in this day and age.

Dr. Caudle:
That's a great takeaway for us to think on as we come to the end of today's program. And I'd like to thank my guest, Dr. Mansi Shah, for walking us through the 2025 IMWG guidelines on sequencing T-cell-redirecting therapies and potential impacts on clinical practice.

Dr. Shah, it was great having you on the program.

Dr. Shah:
Thank you so much for having me here today.

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