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[www.reachmd.com](http://www.reachmd.com)

[info@reachmd.com](mailto:info@reachmd.com)

(866) 423-7849

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### Real-World Ready: Practical Tips for Community Oncologists

#### Announcer:

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#### Dr. Richter:

Hello, this is CME on ReachMD, and I'm Dr. Joshua Richter. Here with me today is my esteemed colleague Dr. Sagar Lonial.

CELMoDs are an interesting therapy that's currently under investigation for myeloma. Sagar, what can you tell us about these agents?

#### Dr. Lonial:

Thank you, Josh. So CELMoDs are a new category of agents that are distinct from their previous category of immunomodulatory agents, drugs such as lenalidomide or pomalidomide or thalidomide, that bind cereblon and really have very different properties and binding affinity than the CELMoD category of agents.

The CELMoD category of agents are iberdomide and mezigdomide, and what we know about these 2 agents in specific is that they're able to bind cereblon. But in addition to that, they more potently not only bind cereblon and myeloma but actually bind cereblon and T cells and NK cells, allowing us to take exhausted phenotype T cells and potentially make them active and functional again and, at the same time, increase the number and activation state of NK cells as well. And what this potentially allows us to do is have great partnership with other immune targets in myeloma, including unconjugated antibodies, bispecific antibodies, antibody-drug conjugates, and even potentially be a great adjunct before CAR-T cell collection or even after CAR-T cell therapy.

And what we know about this category not only is that they're more potent at binding cereblon, but they actually are more potent and able to overcome drug resistance, particularly resistance to agents such as lenalidomide or pomalidomide. And what's really, I think, exciting is that when you bring them earlier in the disease course and begin to look at combinations, say, of iber with dara or iber with bortezomib, that we're beginning to see MRD negative rates that exceed what we've seen in previous combinations of len with bortezomib or len with an anti-CD38 antibody.

So together, I think the implications for clinical practice are, A, better tolerated, B, more potent, C, able to partner really well with immune-activating agents and really give us the opportunity, in my mind, not just to save for later, but potentially supplant the previous category of immunomodulatory agents.

#### Dr. Richter:

I think this is absolutely exciting and I think one of the key things that you pointed out is the combinability of these agents. And one thing that I would love to hear your thoughts on, and that you already really alluded to this, is that I think the initial approvals are going to be in combination with some of our standard therapies, like bortezomib, daratumumab, and carfilzomib. But given the nature of the mode of action of these therapies and their implications on T cells and NK cells, they become a really great combination for some of our T cell redirection, either along with bispecific antibodies or as an adjunct, maybe post CAR-T. And because they're oral, it allows patients not

to have to travel back and forth to treatment centers more frequently.

So just wondering your thoughts on any particular combinations that you think may not be part of the initial approval but maybe coming down the line.

**Dr. Lonial:**

No, I think that's a great point, and we're already beginning to see some of that preliminary data combining, for example, the BCMA-directed bispecific elranatamab with iberdomide, to really try and enhance the efficacy and reduce T cell exhaustion. We know that that's a potential resistance mechanism for the bispecific class of drugs.

We've also seen trials that have used either iber or mezi following CAR-T cell therapy, allowing us, potentially, to keep the CAR-T cell persistence better than what we would see in the absence of any maintenance therapy. And I think while there may be a very small fraction of patients that get away with 5-year durations of remission, that is not the majority of patients who are getting CAR-T cells. Certainly in my practice, and you're nodding your head, which makes me think it's the same in your practice as well. And so doing things that can augment T cell persistence, such as the CELMoDs, really do represent important potential activities and opportunities for us down the road.

**Dr. Richter:**

Absolutely. And I think much in the same way with autotransplant, how we partnered with our community colleagues that if they're getting the initial CAR-T or even the step-up with bispecific at the academic center, utilizing CELMoDs in either long-term maintenance combination with bispecifics or post CAR-T can really work together with our community colleagues to provide this type of therapy for everyone.

And ultimately, I'd like to say thank you, Sagar, for this great discussion. And we'd like to thank the audience for joining us today.

**Announcer:**

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