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Why CELMoDs Matter in Myeloma

Announcer:
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Dr. Lonial:
This is CME on ReachMD, and I'm Dr. Sagar Lonial, and I'm going to discuss a little bit about why CELMoDs matter in multiple myeloma.

So CELMoDs are a new class of agents, and the 2 soon-to-be-available CELMoDs are iberdomide and mezigdomide. And what we know about them is that, while similar to their predecessors in the IMiD category of lenalidomide, pomalidomide, and thalidomide, they bind cereblon, their impacts are a lot more broader than what we see with those previous compounds in the IMiD category.

Why we're so excited about CELMoDs in the context of multiple myeloma is that both iberdomide and mezigdomide have a much more potent binding affinity for cereblon, and that allows us to potentially overcome previous resistance to the IMiD category of agents. And so they are just simply more effective in and of their own in terms of targeting cereblon, particularly in myeloma cells.

What's also interesting, however, is that their ability to activate immune function, particularly T cells and NK cells, has been engineered to be far greater than what we see with Lenalidomide, or pomalidomide or thalidomide. And so where I think that's really exciting is, you can potentially take an exhausted T cell subset or compartment and wake that T cell subset back up, make them active, and allow them to be great partners with other potential immune drugs, or in and of themselves. And so when I think about the current revolution in therapy for multiple myeloma, I think about agents like the bispecifics, the antibody-drug conjugates, the CAR-T cells, the monoclonal antibodies, and that the CELMoD category is particularly well suited to really make each of those therapies significantly better, and even better than what we saw with the previous IMiD category because of their specific focus on activating T cells, NK cells, and other potential immune targets that make these therapies more effective.

Now, we have seen very good examples in early-phase drug development either of iberdomide and mezigdomide alone or in combination with agents such as proteasome inhibitors like bortezomib or carfilzomib or potentially in combination with agents such as daratumumab, that they can potentially overcome drug resistance.And this really occurs through mechanisms, again, related to potency for binding and binding affinity for cereblon that allows these new CELMoD categories to more effectively bind the target and potentially kill myeloma cells directly.

Additionally, while the previous IMiD category, really, its greatest effect was to slow down cell growth, it didn't have nearly the cytotoxic effect that the CELMoD categories, particularly iberdomide and mezigdomide, have at killing myeloma cells. So previously you would slow down cell division. You might prevent cells from really continuing to grow, but they were more cytostatic as opposed to the CELMoD category which is cytotoxic. And that really lends itself, again, to great partnership with drugs, like the proteasome inhibitors, where you get immunogenic cell death. And then on top of that, you're waking up and activating T cells and directly killing myeloma cells

as well.

So I think that this is really an exciting new development in the area of management of both relapsed and refractory myeloma as a single agent, as well as potentially partnering with other immune and nonimmune-mediated drugs in the context of relapsed myeloma.

And from your perspective, I think it would be really nice to have more weapons in our armamentarium, particularly weapons that can help overcome drug resistance to classes of agents that patients may have been previously exposed to, such as lenalidomide or pomalidomide. And what I'm particularly excited about is actually moving drugs like iberdomide and mezigdomide to earlier lines of therapy, perhaps even avoiding the use of agents like lenalidomide and pomalidomide because the adverse event profile for iberdomide and mezigdomide is significantly better. These are better-tolerated drugs, they're more potent, they're better immune activators, and, ultimately, they're better partners for many of our immune therapy drugs.

So I think this has been a great bite-size discussion. Our time is up. Thank you so much for listening.

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