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Molecular Magic: Decoding the Unique Mechanism of CELMoDs

Announcer:
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Dr. Raje:
This is CME on ReachMD, and I am Dr. Noopur Raje. Today's discussion will focus on the mechanism of action of CELMoDs.

CELMoDs are the newest class of immunomodulatory drugs. They're even more potent than the existing immunomodulatory drugs, which include lenalidomide and pomalidomide. CELMoDs, which include iberdomide and mezigdomide, are immunomodulatory drugs which target a protein called cereblon. This protein belongs to the E3 ligase complex, and by targeting this protein, it actually causes apoptosis of your myeloma cells and it causes an inhibition in proliferation of those myeloma cells. It does this by impacting 2 transcription factors, Ikaros and Aiolos, and it's a really potent anti-myeloma agent.

We also have immune-related effects of these new CELMoDs, and that is, to me, one of the most exciting features. What it is known to do is, it is able to reverse T cell exhaustion in patients who have T cell dysfunction. It is also able to activate natural killer cell activity. And by doing so, it is able to augment some of the immune effects of the current treatments like CAR-T cells, like T cell engager treatments in the context of myeloma.

So really an exciting class of drugs right now. These are oral compounds, a lot more potent than both pomalidomide and lenalidomide. And because they are given orally, they're easy to combine with some of the backbone drugs that are available to us for myeloma. For example, we easily can combine these drugs with both proteasome inhibitors, like bortezomib and carfilzomib. We can also combine these drugs with agents such as the anti-CD38 monoclonal antibodies, such as daratumumab. They do differ from lenalidomide and pomalidomide. I will say that all the studies we've done to date with the CELMoDs are in patients who've had lenalidomide and pomalidomide, and the fact that they work in patients who are resistant to these drugs suggests how potent these immunomodulatory drugs are, or these new CELMoDs are.

The other thing which is really important is, as we've increased potency with this class of agents, we're seeing less in terms of toxicity. So certainly with both iberdomide as well as mezigdomide, we are seeing less in terms of GI toxicity, which we are quite familiar with, with lenalidomide. We're seeing less in terms of skin-related toxicity, such as skin rashes, very rare with both iberdomide and mezigdomide. And as of right now, we're studying them not just in the relapsed/refractory setting, but we've also brough them up front, and as we move them earlier in the course of the disease treatment paradigm, we are seeing very deep responses to the extent of MRD negative disease state, which is translating into very long durability of response with these drug classes.

Thank you for joining me today, and I hope this information was useful to you in your practice.

Announcer:
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