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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Data Dive: Clinical Evidence Behind CELMoDs

Announcer:
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Dr. Lonial:
This is CME on ReachMD, and I'm Dr. Sagar Lonial. Today, I'm going to review the clinical evidence supporting the use of CELMoDs for the treatment of multiple myeloma.

Just to refresh your memory, the CELMoDs are a new category of more potent cereblon-binding agents known as iberdomide and mezigdomide, or iber and mezi for short. What we know about these class of agents is that they're highly effective and more potent at binding cereblon and have different downstream targets than the previous class of immunomodulatory agents that include agents such as lenalidomide, pomalidomide, and thalidomide. And while, certainly, these drugs do bind cereblon in myeloma cells, and unlike, again, the IMiD class are cytotoxic to myeloma cells, unlike the previous category, which is cytostatic to myeloma cells, that same target, cereblon, is present in NK cells and T cells and allows us to make those treatments even more effective.

And so not only do you directly kill myeloma cells, you activate immune cells like T cells and exhausted T cells, and NK cells, making partnership with immune therapies far more effective.

Let's start off with iberdomide. What we've seen with iber is response rates of between 28% and 33% in combination with dexamethasone in the context of 5 to 6 prior lines of therapy. And that was evaluated in a couple of cohorts for combinations and really represents single-agent or combination activity in partnership with dexamethasone.

When we look at combinations of iber, particularly with daratumumab in the relapsed and refractory setting, we're seeing responses well over 50%, and that is among a cohort of patients that are both pomalidomide and lenalidomide resistant, and many of those patients are daratumumab resistant as well. So we see that synergy between the CELMoD category and the anti-CD38 antibodies coming out front and center in the context of late lines of therapy.

What we've also seen is nice combinability with agents such as bortezomib and carfilzomib with very high overall response rates, again, reflecting the synergy that we've seen between cereblon-binding agents, as well as the proteasome inhibitors.

What we're seeing data on more recently now is the newly diagnosed cohorts where iberdomide is being combined with bortezomib with or without the anti-CD38 antibody daratumumab. And what we're seeing in those combinations in the newly diagnosed cohort is not only very high overall response rate in excess of 80% to 90%, but we're also seeing MRD negativity rates higher than what we saw in previous trials, such as the MAIA trial, using lenalidomide in combination with daratumumab, where the MRD negative rate was only half of what we're seeing when we combine iberdomide with daratumumab as well.

So these are really exciting new trials and really exciting developments, suggesting that combinations of standard myeloma agents with iberdomide have the potential to not only overcome drug resistance but to actually drive patients to deeper levels of MRD negativity,

deeper than what we saw with the previous immunomodulatory class of agents.

Now, the second drug in this category is mezigdomide, or mezi. And we saw very early promising response rates of mezi plus dexamethasone in relapsed and refractory myeloma, with response rates in excess of 50%.And when we combine mezi with carfilzomib, as well as combine mezi with bortezomib, we're seeing similarly higher rates of overall response rate than we saw with previous combinations of either len or palm, with bortezomib or carfilzomib. And this to me, again, really signals not only the tolerability of the CELMoD category of agents but also the ability to achieve deep and durable responses, because these drugs are far more potent than the previous category of immunomodulatory agents.

And so I think, in aggregate, the combination data of iber as well as mezi with other commonly used agents, such as proteasome inhibitors and anti-CD38 antibodies, really lends itself nicely to future combinations allowing us to, we hope, achieve deep and durable responses and potentially even MRD negativity at higher rates than we've seen before.

Well, that's been a great bite-sized moment. Thank you very much for your attention and I'll see you in the next module.

Announcer:
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