Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/what-do-the-mechanistic-differences-between-imid-and-celmod-based-therapies-mean-for-clinical-practice/14328/

Released: 08/30/2022
Valid until: 08/30/2023
Time needed to complete: 1h 25m

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

What Do the Mechanistic Differences Between IMiD and CELMoD® -Based Therapies Mean for Clinical Practice?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Lonial:
Hello. My name is Sagar Lonial, and I'm from Emory University School of Medicine. And this presentation is on, What Do Mechanistic Differences Between IMiD and CELMoD Based Therapies Mean for Clinical Practice? As we begin to think about the novel CELMoDs or Cereblon E3 Ligase Modulators in development, there really are two that are quite separate and different from the previous IMiD class of agents. The previous classes included agents like Thalidomide, Lenalidomide, and Pomalidomide that structurally are somewhat similar, but actually quite distinct from the new CELMoD category of agents. And the two that are best known in the new CELMoD category of agents are Iberdomide, formerly known as CC-220, or Mezigdomide, formerly known as CC-92480. And, what we know about these two agents is that they were developed intentionally to enhance the impact on immune function, as well as more potent binding affinity for Cereblon, the known target for this entire class of agents.

So, let's start off with Iberdomide, or the novel CELMoD agent CC-220. What we can see from this figure is significant improvements in terms of binding and downstream regulation. Ikarose and Aiolos with Iberdomide compared to Pomalidomide and Lenalidomide. And this increases the rate of protein degradation, and the depth of protein degradation. And, certainly, is able to help overcome drug resistance, particularly when binding affinity or access to the binding pocket, becomes a significant issue. And for this reason, we see significant enhancement in degradation when Iberdomide is used over Lenalidomide and Pomalidomide. And that potency is reflected in the current table.

When we look at another CELMoD agent, Mezigdomide or CC-92480, you'll also see that different from what we see with Pomalidomide and Lenalidomide, the potency in Aiolos degradation efficiency is far greater. And in fact, unlike LEN and POM, Mezigdomide also appears to have Cytotoxic effects. So it doesn't just impair cell growth, it actually impairs cell survival. And again, this in part is engineered, specifically, to be able to help have these mechanisms of action. So, what we know about both Iberdomide and Mezigdomide is that they have potent effects on T-cell Activation and NK Cell Proliferation. And as you can see on the next slide, this is clearly available, both with CD8 T cell upregulation and downregulation of some of the suppressive markers. And we also see upregulation of NK Cells, and downregulation of some of the suppressive NK Cell markers on cells. And this is actually from actual translational data from patients, as well.

So when we look at real differences between these classes, between the IMiDs and the CELMoDs, it's clear that the binding affinity is quite different. That the CELMoD agents are far more potent and more tightly bound to Cereblon, the intracellular target. The impact on downstream targets are actually quite different. And in fact, this may be part of why the immune-enhancing effects are so much greater with the CELMoDs than with IMiD class. And additionally, the PK may be quite different. And we see this with Mezigdomide or 480 specifically, where there is actually a lot more extramedullary availability of the drug, suggesting that this drug may be more potent in

extramedullary disease than any other Cereblon binding agents we have in Myeloma. And this certainly has been born out in clinical trial data, as well. And finally, the impact on immune cells may be far more potent, and this really leads to a significant improvement in overall benefit in terms of immune activation in partnership with Monoclonal Antibodies with bispecifics and potentially with T-cells, as well. Either as a way to improve the Luciferase product, or to improve longevity after T-cell infusion, in general. So, thank you again for your attention, and look forward to further discussions with you in the future. Thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.