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Panel: CELMoDs® – A Novel Advance or Another IMiD?

Announcer:
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Dr. Lonial:
Hello, I'm Doctor Sagar Lonial from the Emory University School of Medicine in Atlanta, Georgia and I'm joined by my two colleagues, Dr. Krina Patel from the MD Anderson Cancer Center in Houston, Texas, and Dr. Maria V. Mateos from Salamanca, Spain. And we're going to talk about some of the unique aspects that these new CELMoD classes, both iberdomide and mezigdomide, formerly known as CC-92480, in terms of what they bring to the table, as a new anti-myeloma therapy and their uniqueness here. So Dr. Mateos, you want to get us started off really talking a little bit about some of what you see these two drugs really bring to the table at this time?

Dr. Mateos:
Well, definitely iberdomide together with the CC-480 are different drugs in comparison with the theoral lenalidomide and pomalidomide. And not only because, well, the mechanism of action, I would say that it is a complimentary. It is, well, a more potent immunomodulatory affect in comparison with the lenalidomide and pomalidomide, but also because they have a demonstrated that to be effective in refractory myeloma patients to both the lenalidomide and pomalidomide. But, in addition to this aspects related with the efficacy and the mechanism of action, I would like also to remark the safety profile because definitely iberdomide and CC-480 are more potent than lenalidomide and pomalidomide, but the safety profile is quite important. They have been in principle evaluated in a heavily treated the myeloma patients. And when we evaluate the number of patients who required those reduction of iberdomide or CC-480, because of side effects, the number of patients is quite reduced. And when we evaluate in more detail, a methodological toxicity like neutropenia, we can see how grade three, four neutropenia is not observed in more than approximately one third of patients treated with these new CELMoDs. And in addition, the proportion of patients developing neutropenia or other severe infections is quite reduced.

But if we remember when we use lenalidomide and pomalidomide, some patients sometimes disclaimer, because of asthenia and fatigue. We know how the mode of administration of these new CELMoDs and this is related with the chemical is to and the isomer form result in the fact that these adverse events that definitely impact in the quality of life of the patients like asthenia and fatigue are really very frequently reported in patients treated with iberdomide and CC-480. So from my point of view, we put together the efficacy together with the safety profile. I think that they deserve as it is being done, evaluated in heavily pretreated myeloma patients but also in other lines of therapy as well as in combination with other partners.

Dr. Lonial:
And thank you, Dr. Mateos. And Dr. Patel, you know, I think the question that always comes up is the binding target is the same. What's really different? And I think there are some differences that you want to highlight a little bit.

Dr. Patel:
Yeah. I think, you know IMiDs, historically, have been fantastic to use as maintenance or, you know, kind of adding, synergizing with other immune therapies like monoclonal antibodies. And I think what's really exciting for the CELMoDs is we actually see this activation

of T cells and NK cells to a completely different degree. There's more cytokines that are produced, that are more activating cytokines. Like IL15 IL2. So you're actually seeing much more CD8 T cells that are more activated and there's actually less exhaustion because usually, we'll see these T cells get really exhausted really fast but they've actually seen less exhaustion. Same thing with the NK cells. You actually see this increase in NK cell function. And to be able to use that with all of these new immune therapies coming through, I'm just really excited to see how together that can actually improve the anti myeloma effect but also potentially how we improve the micro environment to a much better... The T-cells and NK cells will hopefully be able to surveillance better. I mean, these are again, abstract thoughts but this is the stuff I get to get really excited about. So I think the toxicity piece is so big, that for our patients, that to have less toxicity but then to have improved efficacy even translationally in, you know, the other cells which those are supposed to help us with all the other therapies we have with myeloma I think is pretty phenomenal.

Dr. Lonial:
Yeah, no, no. I think one of the things that has struck me in the presentations on the early data with Iber in particular, I think we're just a little bit behind that in the data with Mezzy right now, but certainly in Iber is when you look at grade three, grade four adverse events that are non-heme, there's a lot of zeros there. And we know with drugs like Pom and Lan, that is rarely the case. There are patients who get significant adverse events, associated with both of those drugs, but they seem to be much lower frequency and much lower grade that I think really does allow patients to stay on longer. And I think, you know, all of us have anecdotes of great outcomes with patients. My favorite was on the phase one study when we were at the maximum tolerated dose, the patient, I saw them at cycle four or something like that. And they said to me, "I thought you told me, this wasn't a placebo controlled trial." And I said, "It's not." And the patient said, "But I don't feel like you're giving me anything." You know, that's... We almost never hear that with the certainly that is something we can see more and hear more frequently with the CELMoD class as well. I think, you know, the other point that Dr. Mateos raised, as well, is the idea about efficacy in the triple class refractory patient population. Do you guys just want to one of you or both of you touch briefly on what a challenge that continues to be, you know, Dr. Mateos, you mentioned people are getting three drugs as part of induction therapy. The triple class refractory group is not just more but it's moving earlier than we saw before. Really necessitating this shift.

Dr. Mateos:
Yeah, sure. This is true. And we had the opportunity to see how iberdomide in combination with the dexamethasone work quite well in this population. And in addition, as I previously pointed out, even in the population already exposed to the BCMA targeted therapy and definitely this population is going to be in front of us earlier on in the near future. So I think that there is a clear role for iberdomide that may be in combination with, again, inhibitors for anti CD38 to monoclonal antibodies because majority of the patients will be exposed as part of the first line of therapy. Maybe the second line can be BCMA targeted therapy and why not to utilize as third line, iberdomide and CC-480. But for me, this is applicable to the near future because if we envision a bit more the future, definitely iberdomide because of the safety profile will the survey to be utilized as part of the first line of therapy and maybe CC-480 in the relapse refractory setting because it's true that the incidence of neutropenia is a bit higher in comparison with iberdomide.

Dr. Lonial:
Yeah. Dr. Patel, you want to add anything?

Dr. Patel:
No, I completely agree that, you know, for us, we usually we're using four drugs up front. And so by third line, I'm sort of saying, okay, which is the best next therapy I can give. And how can I minimize toxicity? So we are using a lot of the medications we already have earlier and I think that's the big need. But then as Dr. Mateos said, bringing this to potentially even take over the place of the IMiDs, if they really are so much better, I'm excited about.

Dr. Lonial:
Yeah, no, I think this has been a great discussion. And clearly there are a number of different areas that represent unique areas as we've talked about in this as well as significant remaining unmet medical needs in our field. And I think both of these new CELMoDs really do help address some of those issues going forward. So thank you again for your time, for this great discussion, and we look forward to the data in the future.

Announcer:
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