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What Is the Importance of Cereblon to the Mechanism of Action of Immunomodulatory Drugs and CELMoDs® in MM?

Announcer:
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Dr. Patel:
Hello, my name is Krina Patel. I'm from UT MD Anderson Cancer Center in Houston, Texas. This presentation is on the importance of cereblon to the mechanism of action of immunomodulatory drugs and other CELMoDs in multiple myeloma. So on this next slide, you will see a figure from a review paper by Holstein, et al. in JCO 2018 that depicts the cereblon pathway used by IMiDs and CELMoDs for their anti-myeloma effects. So immunomodulatory drugs or IMiDs and cereblon E3 ligase modulation drugs, CELMoDs, bind cereblon and induce the ubiquitination of specific substrates. And then cereblon, along with three other proteins, form the CUL4-RING E3 ligase complex, which has E3 ubiquitin ligase activity. And all IMiDs and CELMoDs bind the Ikaros family of zinc finger proteins, one is Ikaros and the other is Aiolos.

On the next slide, you'll see the structures for both LEN and POM on the left and IBER and mezigdomide or CC-92480 on the right. LEN and POM in general are smaller molecules compared to IBER. And basically when LEN and POM were initially evaluated clinically and then approved for treatment for a multiple myeloma, we didn't have a specific mechanism of action. We knew that these drugs worked in different pathways for both anti-myeloma effects as well as in the immune microenvironment. But once we figured out the cereblon pathway in a few studies in 2010, as well as in 2014, that are really well-described in that review from the last slide, then we were able to actually find more efficient molecules known as IBER and CC-92480 that can then utilize that cereblon pathway for anti-myeloma effects.

So you'll see iberdomide and some of the preclinical data and IBER basically has enhanced affinity for binding to cereblon compared to LEN and POM. It basically leads to rapid protein degradation and increase depth of protein degradation, and it can do this at lower concentrations than what's needed with LEN or POM, which then, of course, leads to increased efficacy in preclinical studies. And so in the middle, you can see that the EC50 for LEN, POM, and IBER are very different. And basically, the Ikaros and Aiolos are much better degraded with IBER even at lower doses. So then in preclinical models, basically IBER shows that it coops cereblon to enable enhanced degradation of the target proteins. It's 20 times higher affinity than LEN or POM and 20-fold more efficient than LEN or POM in degrading those substrates.

Basically, you can see some pre-clinical studies with iberdomide inhibiting proliferation in POM-resistant cell lines. So the picture on the left basically shows two different cell lines, one that is not POM-resistant and then the second line, the KMS12BM with the a is the POM-resistant cell line in the top. You can see what happens when you put one micromolar of POM in the non-resistant cell line. You see the degradation of the Aiolos. However, in the POM-resistant in the right side, you see that POM isn't able to degrade Aiolos. And then in the IBER, which is underneath, you actually can see the difference. It does the same for the POM-resistant versus the non-POM-resistant cell line. And so on the right side, you see all the different cell lines that have different amounts of cereblon expression in blue

and IBER at 0.1 micromolar levels is able to actually still knock down all of those different cell lines with different levels of cereblon expression, so even cell lines that have low levels of cereblon expression. It leads to proliferation inhibition. So in general, POM-resistant cell lines usually have lower cereblon levels. Some can also have mutations in the cereblon gene, which is what we think some of the mechanisms of resistance is in patients. And so our CELMoDs can potentially overcome that through this mechanism. And then finally, you see that IBER and mezigdomide actually do synergize with other anti-myeloma agents just like we've seen with LEN and POM. On the left, you see IBER induces deeper cell killing in combination with PIs versus POM. And on the right side, you can see that CC-92480 has increased induction of apoptosis in combination compared with POM combinations.

And so finally, for our take home points, all IMiDs and CELMoDs bind the Ikaros family of zinc finger proteins. Iberdomide has a higher affinity than both lenalidomide and POM for cereblon and therefore potently degrades both Aiolos and Ikaros more than LEN and POM. CC-92480 has a unique and rapid degradation profile stemming from the enhanced efficiency to drive the formation of a protein-protein interaction between Ikaros, Aiolos, and cereblon, and then both iberdomide and mezigdomide induce cytotoxic effects in a cereblon-dependent fashion that leads ultimately to the induction of apoptosis, even in the context of low or mutated cereblon protein. Thank you for your attention.

Announcer:
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