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Guideline-recommended second-line treatment following an immune checkpoint inhibitor in renal cell carcinoma

Announcer:
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Dr. Duran:
Hello, this is CME on ReachMD, and I'm Dr. Ignacio Duran.

Dr. Xu:
And I'm Dr. Vincent Xu.

Dr. Duran:
Dr. Xu, what are the guideline-based treatment options for the second-line treatment of renal cell cancer following an immune checkpoint inhibitor? Could you tell us?

Dr. Xu:
That's a great question and this is a field that's moving so quickly, and we have several recent trials that have changed our practice here. The first takeaway that I think we need to remember is that two large, randomized trials have shown us that we should not challenge with further checkpoint inhibitors in patients who have recently had progression on an immune checkpoint inhibitor.

This has been shown by two trials. The first was CONTACT-03, which, after prior immunotherapy treated patients with cabozantinib with or without atezolizumab. This trial was completely negative. No progression-free survival or overall survival benefit. Only added toxicity from the atezolizumab.

The second trial recently released from ESMO is TiNivo-2, which treated patients after prior immunotherapy with either tivozanib alone or tivozanib + nivolumab. Again, no progression-free survival benefit, no overall survival benefit, and no role for adding PD-1 after prior checkpoint inhibitors.

So, indeed, for most patients who have progression on an immunotherapy-based regimen, the second and third-line treatments should focus on TKIs. And we have some really great TKI options in this setting. We know that cabozantinib based on modern trials has a 30 to 40% objective response rate after prior immunotherapy. We saw this in the CaboPoint trial and we saw this in the cabozantinib monotherapy arm of CONTACT-03. So, really great TKI, multi-targeted. Also gets to MET, for example, in addition to VEGF, and can have nice responses after IO TKI.

Another regimen is lenvatinib, which can be combined with everolimus. We know from Study 205 that the combination of lenvatinib and everolimus has about a 43% objective response rate in the refractory setting. An advantage of the lenvatinib + everolimus is it's probably the best opportunity for most patients to get an mTOR inhibitor, which otherwise has a very low response rate on its own.

More recently, we have data from tivozanib, not just from the TiNivo-2 study, but from TIVO-3. And we know from these trials that tivozanib also can have activity after prior TKI and after prior immunotherapy with the response rate in the 20% range.

Finally, we have the latest kid on the block, which is HIF2-alpha inhibition, and belzutifan was recently approved in the US based on LITESPARK-005 where it was superior to single-agent everolimus and is a great option for patients given its excellent tolerability and lack of overlapping side effects compared to TKI's.

Dr. Duran, how does this affect our current NCCN guidelines?

Dr. Duran:
Well, thank you, Dr. Xu. You did such a wonderful review that it's going to be difficult to add much to this. But I think the guidelines are quite useful in these contexts where we may need two or a few ideas. And probably how to approach the amount of many of these patients, I think mentally we should first need to consider histology as a key determinant and of course, what was the previous treatment received. And this is how the guidelines also guide us through the different treatment options.

So, let's start by the easiest scenario. Metastatic clear cell RCC and our patient received previously any form of immunotherapy in first-line. Well, you summarized very well, I will repeat very briefly. We got enough evidence not to promote the sequential use of IO-based combos. And I think you summarized the data very well, and the guidelines offer you the option of switching to an alternative mechanism of action and this is going to be around inhibiting angiogenesis mostly. And you summarized the data around cabo, tivo, those different drugs. So, I think that's very well-summarized.

But let's go to another clinical scenario. What if my patient did not receive any IO-based treatment in first-line, and now presents with progression? I think the guidelines suggest that these patients can be approached with several different options and those options include, IO as a single-agent as nivolumab, and this is based on the randomized phase 3 study of CheckMate-025. Or also, the other option is cabozantinib, based on METEOR phase three study, showing benefit in overall survival for this compound compared with everolimus. But I think the guidelines here are quite inclusive, and offering patients a broader option by proposing also, TKI IO combos in this context, I think could be a reasonable approach, mostly because we may be missing some efficacy that that we may infer from the combinations. But it's also true that we need to discuss with our patients the lack of high level evidence in this particular setting as we mentioned.

And then, we move to the complicated scenario. The non-clear cell, the message is the data generally is scarce in this context. Multiple tumor types are put together under the same umbrella in these studies, and despite advances in the treatment of clear-cell RCC, the improvement in non-clear cell is actually limited. High quality studies are missing and therefore, we try to be very inclusive in the guidelines. And as you can see, there are options to utilize cabozantinib, which is probably the drug that has more evidence, mostly in the papillary context. But as you were very well mentioned before, we could use also lenvatinib/pembro or cabo/nivo, or even there is a mention for erlotinib/bevacizumab for patients with fumarate hydratase deficiency.

So, summarizing,RCC is becoming a busier space. I think we need to have rational thinking when we're sequencing therapies. We've got enough data in the clear-cell kidney cancer setting. The data in the non-clear cell is a little bit more limited, but I think these guidelines really help us to put the focus on the right treatment.

Dr. Xu:
Thank you, Dr. Duran, for an excellent discussion, and thank you for listening.

Announcer:
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