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Breaking New Ground in mCRC: Exploring Novel Targets in mCRC

Announcer:
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Dr. Kopetz:
Hi. This is CME on ReachMD, and I'm Dr. Scott Kopetz. Here with me today is Dr. Cathy Eng.

Dr. Eng, let's talk about some of the emerging treatment advances in metastatic colorectal cancer. What novel therapies and targets are you excited about?

Dr. Eng:
I think the one thing that I wanted to touch upon in this short segment is really the data from STELLAR-303, which is a phase 3 trial. The reason I bring it up, as Dr. Kopetz is aware, we haven't had a lot of home runs with the use of immune checkpoint inhibition or immunotherapy in the setting of metastatic colorectal cancer.

So this STELLAR-303 was a large phase 3 trial, international trial, specifically in refractory and metastatic colorectal cancer patients. Zanzalintinib is a novel small-molecule tyrosine kinase inhibitor involving MET, vascular endothelial growth factor, as well as other kinases, including AXL and MET.

It had some very promising earlier activity based upon a phase 2 trial, and as a result, it moved on to phase 3. There's been various formulations of this drug that have been conducted, but now we have this new agent. It's 100 mg daily, and it was investigated in combination with atezolizumab, so immune check inhibitor, versus basically the control arm, which was regorafenib at a standard dose of 160 mg daily.

And the primary endpoint here was overall survival. And basically, Dr. Saeed was able to demonstrate that this trial, which did include patients with liver metastasis—I know there's a lot of discussion about whether or not immunotherapy should be provided to patients with liver metastasis just based upon other studies that have been conducted. Smaller studies have demonstrated some benefit for non-liver metastasis. But regardless, the primary endpoint was overall survival, and they were able to demonstrate an improvement in overall survival, a difference of 1.5 months, so 10.9-month median overall survival versus 9.4 months, and the hazard ratio was 0.8.

Now, there is some interesting data to suggest that—although it's rather early—to suggest there may be some increased benefit in non-liver metastasis, and that was a difference of a little bit of about 3 months. So we look forward to more data there.

The one thing I think that's important to mention that we cannot avoid is that there were some increased toxicities associated with this regimen versus regorafenib

Many of us do not provide regorafenib at a full dose of 160. There was some associated diarrhea, hypertension, fatigue, nausea, reduced appetite.

But I think with any new agent, you may need to adjust the dose a little bit according to the patient. And obviously, this provides another new option for patients. So I look forward to seeing what the plans are for this combination for our refractory metastatic colorectal cancer patient population.

Dr. Kopetz:
Completely agree. A lot of enthusiasm for that and opportunities to learn more as we get more data. An area that was of interest and excitement on my side is the development of the ADCs to CEACAM5 and seeing some activity there.

CEACAM5 is expressed on colorectal cancer pretty broadly, so there are certainly opportunities to use that to target therapies with the antibody-drug conjugate and using a topoisomerase inhibitor, which we know will work in colorectal cancer.

The data that has been presented earlier this year, for example, with precemtabart tocentecan—precem-TCT, as it's also called—showing some activity response rates around 30%, PFS of 6.9 months in all irinotecan-pretreated patients. Now that was immature data and waiting for confirmation of a lot of those responses, and we'll get more data on that as well.

But I think really showing the promise of ADCs, and I think we're seeing that as well as that C-MET ADC really showing benefit and opportunities there. So stay tuned in this space. I think antibody-drug conjugates are coming to colorectal cancer, and we just have to figure out how to position those and identify the right targets for them.

Dr. Eng:
Fully agree.

Dr. Kopetz:
So this concludes our discussion of novel targeted therapies and a lot of exciting areas in colorectal cancer. And thanks for tuning in.

Announcer:
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