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Molecular-Driven Treatment Advances in HER2+ Metastatic Colorectal Cancer

Announcer:
Welcome to CME on ReachMD. This activity, titled “Molecular-Driven Treatment Advances in HER2+ Metastatic Colorectal Cancer” is provided by Prova Education.

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Dr. Bekaii-Saab:
HER2 is amplified in 3% to 5% of colorectal cancer cases, and has emerged as an actionable target. Are you familiar with the most recent clinical data surrounding the treatment of HER2-expressing positive metastatic colorectal cancer?

This is CME on ReachMD, and I am Dr. Tanios Bekaii-Saab.

Dr. Hubbard:
And I’m Dr. Joleen Hubbard.

Dr. Bekaii-Saab:
Joleen, what can you tell us about molecular testing in the setting of metastatic colorectal cancer, and how does this relate to HER2-positive metastatic colorectal cancer?

Dr. Hubbard:
Thanks, Tony. ERBB2 is actually the proto-oncogene that leads to the upregulation and overexpression of the HER2 receptor. So there are several different ways that we can capture the overexpression of HER2 in colorectal cancer. The first and most common way would be by immunohistochemistry, which detects the upregulation of the HER2 receptor on the cancer cells. The second would be fluorescence in situ hybridization, known as FISH, that detects the overamplification of the gene within the cells, as well as next-generation sequencing panels that can detect the amplification of the ERBB2 gene. Overexpression of HER2 leads to downstream signaling of the MAPK pathway, which leads to cellular proliferation and metastatic potential, all of which we don’t want to happen in metastatic cancer.

I mentioned several ways that we can test for HER2. Typically, we want to do the testing on tissue, so the iXCI tissue or FISH testing on tissue or next-generation sequencing. There is some discrepancies between the expression in liquid biopsies and tissue biopsies, so for the time being we should really rely on tissue testing when possible.

Dr. Bekaii-Saab:
HER2, in addition to being a positive predictor to the activity of anti-HER2 therapies, it is also emerging as a negative predictor for the use of EGFR inhibitors. That’s important because when we think about most of the patients who actually overexpress HER2, those tend to be mostly on the left side and also tend to be RAS wild-type and even BRAF wild-type. So those are the patients that typically, when we see in clinic, end up being most likely to be prescribed EGFR inhibitors. And HER2-amplified tumors, we’ve shown that recently in a large analysis, do negatively predict for EGFR inhibitors. That emphasizes the importance of testing for HER2 early to decide on the

right patient for HER2 inhibitors, also to pick the patients who may not benefit from EGFR inhibitors.

Dr. Hubbard:
Tony, now that we have an understanding of the molecular testing for HER2-positive metastatic colorectal cancer, what are some factors to consider when we're selecting treatment for our patients, and how can we optimize their outcomes?

Dr. Bekaii-Saab:
Thanks, Joleen. Testing early makes the most sense. Specifically, patients that are highly likely to receive EGFR inhibitors, to decide early on who should be excluded from receiving these EGFR inhibitors, because what we found in that analysis is not only that patients may not benefit – and we know these agents come at a cost in toxicities – but also there may be a detriment. It also helps us with the planning for HER2-targeted therapies. And now that we have MOUNTAINEER-03, which is essentially looking at moving HER2-targeted strategies to first line, it becomes even more urgent to test early and be able to refer those patients to the clinical trial. It's very important to test early and to test consistently for all patients with metastatic colorectal cancer.

Thankfully, now we have also data that suggest, in addition to direct targeting, we have this group of agents, antibody-drug conjugates that seem to essentially work well not only in HER2-naïve patients, but also in the HER2-pretreated patients. So it allows us to plan across multiple lines of therapy for patients who may be found to be HER2 positive.

For those just tuning in, you're listening to CME on ReachMD. I am Dr. Tanios Bekaii-Saab, and here with me today is Dr. Joleen Hubbard. We are discussing molecularly driven treatment advances in HER2-positive metastatic colorectal cancer.

Dr. Hubbard:
And one of the things that we have seen with HER2-positive disease in breast cancer is a higher tendency for HER2-positive malignancies to metastasize to the brain. We'll see in a publication that's been published online from Chen, et al – it's a retrospective study looking at 99 patients with HER2-positive colorectal cancer, and they did find that these patients were 5 times more likely to have brain metastasis as opposed to patients with HER2-negative disease. Fortunately, we know that tucatinib has excellent activity in the brain based on the trials from the breast cancer population, so those that are at risk for brain metastasis with HER2-positive colorectal cancer will likely stand to benefit from the combination of tucatinib with trastuzumab, as well.

So, Tony, can you tell us a little bit about the recent FDA-approved combination of tucatinib plus trastuzumab for HER2-positive metastatic colorectal cancer?

Dr. Bekaii-Saab:
A lot of exciting data that keeps on coming and showing us the benefits of combining tucatinib with trastuzumab, which, as you mentioned, is now the first HER2-targeted therapy strategy in colorectal cancer to be approved, so that's an exciting time.

Recently, our group, which included you, John Strickler, myself, and others, presented the primary analysis of MOUNTAINEER which is a phase 2 study of tucatinib and trastuzumab for HER2-positive metastatic colorectal cancer. This study started with Cohort A, which was an investigator-initiated trial, and given the signals that were seen early on for refractory patients, this became an industry-sponsored study, with tucatinib/trastuzumab in Cohort B similar to Cohort A, and then Cohort C was asking the question of contribution of tucatinib as single agent. This study reached its primary endpoint of response, and the response rate was 38%. This was centrally confirmed.

Most interesting is not just that there were a lot of responders, but the durability of responses was more than a year, which is one of the highest reported in this disease with this targeted strategy. We see that in clinic, in those patients that we treated on this study, some of them are 4 to 5 years and continue to be on treatment – just pretty amazing as such. The good news is this is a very well-tolerated regimen, and most patients did not require any dose modifications. There's also an interesting aspect when we look at the median PFS [progression-free survival], about 8 months, when we look at the median overall survival, 24 months. The tucatinib single-agent arm did not have a meaningful response rate. Those patients who actually did not achieve a response, which is pretty much the majority who went on C, on tucatinib alone, were allowed to cross over to tucatinib plus trastuzumab, and the response rate did go up to 17%. Now still, not significant compared to tucatinib/trastuzumab from the get-go, which tells us you hit biology early, you have your best effect. Dr. Wu, our colleague from Mayo Clinic in Phoenix, also presented data on the quality of life, and show that patients who received tucatinib and trastuzumab maintained their quality of life. And that's important, especially when we're seeing those patients going for many years on the combination.

This is approved now in the refractory setting. It's important for us to continue exploring the role of this combination in earlier lines of therapy. We truly believe that you hit biology early, your effect will be most meaningful. And in this sense, there is a study called MOUNTAINEER-03 which is looking at first-line treatment of HER2-amplified patients with metastatic colorectal cancer. This is a phase 3 study that randomizes patients to FOLFOX plus tucatinib plus trastuzumab versus FOLFOX plus biologic of choice. This is ongoing,

it's a worldwide study, and then hopefully will confirm the activity of tucatinib and trastuzumab and continue to consolidate the role of tucatinib and trastuzumab in patients with HER2-positive metastatic colorectal cancer.

Joleen, can you provide some perspective on ongoing trials and some results that were presented recently and where these drugs, in your viewpoint, may fit into clinical practice now with tucatinib and trastuzumab being approved?

Dr. Hubbard:
Yeah, so we have another exciting agent called trastuzumab deruxtecan which has been FDA-approved for use in metastatic HER2-positive breast cancer. And we saw from the DESTINY-CRC study that this trastuzumab deruxtecan does have activity in patients with HER2-overexpressing metastatic colorectal cancer, and what is interesting is it even had activity in patients who had already received HER2-directed therapy. So ongoing studies will help us determine where trastuzumab deruxtecan will actually fit in metastatic HER2-positive colorectal cancer, but if I had to guess, I would suspect it would be approved for use after prior HER2-directed therapy, since it did appear to have activity in those patients. Another combination that was tested was trastuzumab plus lapatinib. And unfortunately, we did not see the degree of activity that was expected from this combination, but the study that did look at this, they have ongoing molecular analyses to identify is there a particular subset of HER2-positive patients that would respond to this regimen more than others? So more to come on that population. And then the other combination would be trastuzumab plus pertuzumab, and that was tested in the MyPathway study.

Now if you look at cross-trial comparison, it appeared that the trastuzumab plus tucatinib from the MOUNTAINEER study had improved response rates and disease control than the trastuzumab/pertuzumab combination from MyPathway. However, the MyPathway patients were more heavily pretreated, so it's not a fair comparison between the 2 regimens. So it will be interesting to see how the combination of trastuzumab and pertuzumab, if that will play a role in metastatic colorectal cancer in the future. I believe it may be another option for patients. But we'll see if that combination is ever tested head-to-head with trastuzumab and tucatinib; would be an interesting study.

Dr. Bekaii-Saab:
Well, this has certainly been a fascinating conversation, but before we wrap up, Joleen, what is your one take-home message for our audience?

Dr. Hubbard:
So we need to be doing the molecular analysis at first diagnosis of metastatic disease. That way, we can look for HER2 overexpression, and we can identify patients for first-line clinical trials, but also identify other mutations that make it so patients would not respond to HER2-directed treatment, such as BRAF or KRAS.

Tony, what would be your final thoughts?

Dr. Bekaii-Saab:
With the recent approval of tucatinib and trastuzumab in HER2-positive metastatic colorectal cancer, this becomes our preferred treatment option for patients with HER2-positive metastatic colorectal cancer.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening and thank you, Dr. Hubbard, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Hubbard:
It's a pleasure speaking with you as well, Tony. Thank you very much.

Announcer:
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