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Current Guideline Recommendations for Biomarker-Based Second-Line Treatment of mCRC

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Dr. Parikh:
Hi, and welcome to CME on ReachMD. I'm Dr. Aparna Parikh. I'm a GI oncologist at the Mass General Cancer Center, and today I'm going to discuss the current NCCN Guidelines recommendations for biomarker-based second-line treatment of metastatic colorectal cancer.

So today in terms of biomarkers, it's certainly been a tremendously exciting time in terms of biomarker development for patients with metastatic colorectal cancer. The pie used to be sliced very thinly. We're into just two big pieces, and I think prior to the last several years where we used to think about patients that were KRAS mutated with no really KRAS-targeted options available. And then, non-KRAS- mutated patients. This, initially, biomarker breakdown allowed us to select patients, along with sidedness, who were eligible for anti-eGFR therapy, noting that patients that were KRAS mutant did not benefit from anti-eGFR therapy.

But over the last several years, we have seen that pie getting sliced in smaller and smaller pieces, and it's really exciting to see the advent of new targeted therapies beyond just microsatellite instability for patients with metastatic colorectal cancer.

So what I wanted to do is just go over some of these alterations and kind of comment on the prevalence of them and then we can go over some of the therapies in each of these, noting that per NCCN Guidelines, biomarker testing is actually entirely standard of care now. And I would make the argument that no patient should be starting even first-line therapy, without biomarker testing. Again, very reasonable to order the biomarker testing and start some therapy that is more general, such as chemotherapy, and then waiting for your kind of targeted or biologics subsequently as you get that biomarker testing that will later come in.

So in terms of the biomarker-directed options, there's several now. And those options include the BRAF V600E alteration, with the advent of, now, encorafenib and siltuximab or panitumumab, with kind of, again, now, data that has supported the approval of that in the second line from the BEACON study. Any day now, we're expected to see the first-line data of that same combination, encorafenib plus anti-eGFR therapy with chemotherapy, in the first-line setting. That's the BREAKWATER study. And this theme will keep coming up over and over again as we see the development of targeted therapies in later lines of therapies. Many studies that are now looking at how you move this up into earlier lines of therapy. So that's BRAF V600E. And BRAF V600E is a small kind of patient population, around 8% to 10%, but again, very relevant for the right patients.

The next biomarker that is becoming increasingly relevant in colorectal cancer is HER2.

So the largest two studies to date come and the data to date comes from two studies. So the first study was the MOUNTAINEER study, and the MOUNTAINEER study was looking at tucatinib plus trastuzumab in HER2-amplified patients who were found to be RAS wild-type. And this is important as I differentiate the two mechanisms of the two HER2 therapies. And so, again, this is a targeted therapy

and looked at the combination of tucatnib and trastuzumab in the patients that were HER2 positive by local testing, including IHC, ISH, and NGS testing. And the definition of HER2 positivity is either 3+ on IHC or patients who have a HER2 score of 2+ would then be reflexed to FISH testing and would be FISH positive based on the HER2/CEP17 ratio of over 2 and more than 50% of cells.

NGS is another methodology for testing HER2. In the MOUNTAINEER study, we saw nearly a 40% response rate for these patients with a median PFS of 8.2 months and a median OS of 24 months. MOUNTAINEER is now being looked at in earlier lines of therapy in combination with chemotherapy in the first-line setting, and so we're going to see more and more data of looking at these targeted therapies in earlier lines of therapies.

One of the other HER2-directed options came from specifically the DESTINY-CRC02 study. And this was a randomized phase 2 study looking at patients that were HER2 amplified. Unlike MOUNTAINEER allowed for patients to be RAS mutant as well, albeit a smaller portion of patients, and again in this study, patients actually had to have centrally confirmed HER2 testing and had to be, per the study, IHC 3+ or IHC 2+ or ISH positive. As we know that, unlike other ADCs for HER2 and colorectal cancer, we did not see efficacy in the HER2-low patients. This study also demonstrated around a 40% response rate for these patients. And notably, in DESTINY-CRC02, these patients were allowed to have prior HER2-directed therapy. In terms of the FDA approval and the NCCN Guidelines, currently the FDA-approved tumor-agnostic indication for trastuzumab deruxtecan was only in the IHC 3+ patient population.

So the way I think about sequencing these is, for a patient that is RAS/RAF wild-type and HER2 amplified with no prior HER2-directed therapy, trastuzumab and tucatinib is my therapy of choice. And then for patients who happen to have a RAS mutation, as well as had prior exposure to HER2-directed therapy, would use trastuzumab deruxtecan. And again, this is because of different mechanisms with the ADCs and HER2 to deliver the chemotherapy payload into the tumor, whereas the trastuzumab/tucatinib is actually a targeted therapy option, targeting the kind of HER2 pathway.

So then, moving on to there are other options, as well. KRAS G12C, again, a small portion of patients with colorectal cancer have a G12C alteration, and we have in the NCCN Guidelines the approval as well as an approval breakthrough of G12C-targeted therapy plus anti-eGFR therapy. And the NCCN Guidelines allow for the use of sotorasib or adagrasib with cetuximab or panitumumab.

But we are seeing similarly for G12C, and I forgot to mention this for HER2, trials looking at this in earlier lines of therapy. So the MOUTAINEER-3 study for HER2 is being looked at with chemotherapy with trastuzumab and tucatinib in the first-line setting and then G12C with the KRYSTAL study, one of the KRYSTAL studies, that is now looking at second line versus chemotherapy, as well. So we'll see this trend more and more in terms of moving these targeted therapies up.

And finally, you do see rare fusions in colorectal cancer, TRK, RET, exceedingly rare, 1% of patients. I think in 10 years or so, I've kind of maybe seen one of each. But several options with different TRK inhibitors, entrectinib, larotrectinib, repotrectinib, for the TRK-fused patients, and then selpercatinib for the RET-fused patients.

Announcer:
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