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Advances in the Care of Patients with MSI-H/dMMR or HER2+ Colorectal Cancers

Announcer:
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Dr. Parikh:
Welcome to Chapter 1 of this series. Today we're going to be talking about biomarkers for metastatic colorectal cancer [CRC] patients. We know that 12%-15% of all patients with metastatic colorectal cancer are found to be microsatellite unstable or have deficiency in MMR proteins. We know in the stage 4 setting, the lack of MMR proteins is actually a poor prognostic biomarker whereas in earlier-stage disease, MSI-high patients actually do quite well. We are also learning about HER2 amplifications as an important biomarker in metastatic CRC. The prognostic value of HER2 is more debatable than MSI-high patients. Nonetheless, these biomarkers are really important for our patients with metastatic colorectal cancer. So today we're going to start to think about how we can actually use these current biomarkers to best optimize outcomes for our patients with these alterations.

This is CME on ReachMD, and I'm Dr. Aparna Parikh from the MGH Cancer Center, and today, here with me are Dr. Dustin Deming and Dr. Scott Kopetz.

Dr. Deming:
Hello. Thanks for having me.

Dr. Kopetz:
Likewise. Delighted to be here. Thanks.

Dr. Parikh:
All right, let's get started. So, Dr. Deming, I would love for you to set the stage for us for this chapterized course. And it would be great if you could tell us how we could identify the right treatments for the right patients with MSI-high metastatic CRC particularly based on the current NCCN guidelines.

Dr. Deming:
Thank you. So it's really important to now understand that colorectal cancer is just not one disease, and as soon as someone is diagnosed with colorectal cancer, it's really important for us to understand their microsatellite instability high – or MSI-high – or mismatch repair status, because those patients who have MSI-high cancers or are mismatch repair deficient, those cancers are much more likely to be Lynch syndrome-related cancers, so they have a hereditary predisposition to cancer. In addition, this is now changing the way in which we treat patients, with these patients being candidates for immunotherapy options.

There's multiple ways in which this testing can be done. This can be done commonly looking at immunohistochemistry for mismatch repair proteins. Additionally, there are well-validated, PCR [polymerase chain reaction]-based tests that report out microsatellite

instability, and now what's happening quite commonly is that physicians are getting next-gen sequencing [NGS] panels done, which can provide this information in multiple different ways. This includes the microsatellite status in addition to being able to identify actually mutant changes in some of the mismatch repair genes, and then also can get a sense of the tumor mutation burden, which can be helpful in identifying patients with microsatellite instability. All of these tests have pros and cons, and actually I recommend in general that more than 1 of these assays are actually performed for these patients, because there – especially patients with advanced disease, because there are such important clinical implications for the finding of MSI-high status or mismatch repair deficient status. So in general, in my practice I actually get mismatch-repair immunohistochemistry performed in addition to a NGS panel. That NGS panel can also give us a lot of additional information that we need to treat these patients, including KRAS, NRAS, BRAF and HER2 status, among others.

Dr. Parikh:
That's great. Thanks so much for that great overview.

Dr. Kopetz, in your mind, what are some of the best practices for testing for MSI-high disease? So we've talked a lot so far about IHC [immunohistochemistry], NGS, as well as PCR, but is there anything else that you'd like to discuss to really think about testing?

Dr. Kopetz:
Yeah, I think the key methods, just to reiterate, is that it's really every patient that should be tested. And this is not just metastatic disease, but any stage of disease. So the current guidelines really suggest that this should be deployed as the first – one of the first tests that we do when a patient's diagnosed with cancer.

This is different from what many of us were taught in training, where we were taught the Amsterdam or Bethesda criterias to try to identify patients where mismatch-repair testing was appropriate. And those are no longer relevant in our clinical practice. We should really be testing everyone.

Now the type of test, as Dr. Deming mentioned, is probably less critical. In our practice we're using immunohistochemistry just because of its speed and ease of getting this information back, but I agree that complementary testing certainly is reasonable.

The other question that comes up is should you be testing again later in disease, or should you test the metastatic site if initial testing was done on the primary tumor? And our experience has been that, really, these are highly concordant, that if you have testing done on a patient at one sample, one point in time, that's usually sufficient. I think as Dr. Deming mentioned, if there is a very high suspicion that there's a strong family history, it's still worth referring patients over for genetic testing, even in the absence of a of an MSI-high finding, and sometimes repeat testing with other methodologies is warranted.

Dr. Parikh:
Yeah, those are all such great points, and can't echo those sentiments enough. I think we have the reflex testing now on every new CRC diagnosis. There's a lot of real-world data sets that have shown that there's still undertesting despite incredibly efficacious therapeutic options for these patients, so just echoing Dr. Deming's and Kopetz's comments on universal testing for this as indeed the best practice.

So with that, thank you, and now we'll move to Chapter 2. And in Chapter 2 we're going to talk about setting patient expectations in the treatment of MSI CRC, now that we've talked about testing. So stay tuned for this next chapter.

Dr. Parikh:
Welcome back to Chapter 2. We were just discussing how to identify the right treatment for the right patient with biomarker testing for microsatellite instability. And now we're going to start to talk about setting expectations about how we treat our patients that are MSI-high.

So, Dr. Kopetz, in the last couple of years, we have seen a tremendous amount of data, both in colon cancer or rectal cancer, neoadjuvant, metastatic, adjuvant – really blossoming of data in this space in terms of clinical trials for MSI patients. But in metastatic CRC, what are some of your standout data – or what is the standout data from you in terms of clinical trials for MSI patients in the metastatic disease?

Dr. Kopetz:
So for patients with MSI-high colorectal cancer, immunotherapy can be game changers. We have now many years of data that suggest in patients with second- and third-line or beyond metastatic colorectal cancer, immunotherapy with pembrolizumab, nivolumab or nivolumab and ipilimumab, can all provide very profound responses that can be durable. When we look at the 1-, 2-year progression-free survival [PFS] curves, now supplemented with more than 5 years of follow-up, it's fair to say that a subset of these patients can be cured with this immunotherapy. We also now have data demonstrating the survival advantage of treatment initiation in first-line therapy with pembrolizumab, where that is now considered the standard of care for patients with metastatic disease. There is emerging data for

patients with localized therapy that immunotherapy in the neoadjuvant setting for either colon or rectal cancer, here the NICHE-2 study or the Rectal Cancer Study from Memorial Sloane-Kettering that was reported, can demonstrate very high response rates and suggests that we may be able to avoid surgery in a subset of these patients.

Dr. Parikh:
Yeah, and I think the biology of localized disease versus metastatic disease and the different responses is fascinating. And before I turn the questions back to Dr. Deming to talk about toxicity, I think one important comment on toxicity is the CTLA-4, PD-1 combinations. Dr. Kopetz, I would love for you to just comment for a minute on how you're thinking about using the doublet. Are you ever considering it in first line, or are you doing it at progression to try to salvage or recapture responses to immunotherapy? And then we'll talk about some of the challenges with toxicity that we see, particularly with the doublets.

Dr. Kopetz:
Yeah, let's say that, you know, with the doses of CTLA-4 that were utilized, there is slightly higher toxicities, but still manageable. In my practice, I tend to turn to the doublet more commonly than the single PD-1 inhibitor. But this is based on limited cross-trial, cross-cohort comparison, really suggesting a higher plateau in that PFS curve. Randomized studies really ask the question about whether there's a difference between PD-1 or PD-1 and CTLA-4 ongoing, and that's really going to provide us with more definitive information on our strategy that we should be utilizing.

Dr. Parikh:
Totally agree. And Dr. Kopetz just talked a little bit, Dr. Deming, about some of the toxicities, particularly with doublet versus monotherapy. Could you chat a little bit about some of these immune-related AEs [adverse events] that we're seeing commonly and how they're best managed, entirely recognizing this could be a chapter in and of itself?

Dr. Deming:
So, correct. The immune adverse events can be a major problem for patients undergoing therapy with the immune checkpoint inhibitors. Thankfully, we have learned, unfortunately the hard way, but thankfully we've learned that we can dose many of these inhibitors at a much lower dose than what we were initially using, and so the immune-related adverse events were much more significant at the much higher doses, especially of drugs like ipilimumab when we were using much higher doses. Now using the more common lower-dose treatment strategies, those immune-related adverse events have become much less common and also much less significant. And so now with combination anti-PD-1, anti-CTLA-4 therapy, we're seeing up to 20% of patients having immune-related adverse events of a significant nature. The immune-related adverse events can be of all different degrees. Commonly, we're seeing things like pruritus, rash, fatigue. These can be often managed with simple interventions. Sometimes a dose delay is helpful. Sometimes for things like a mild rash, we're using topical steroids. As the adverse events become more significant with things like diarrhea from immune-related colitis or immune hepatitis, we're thinking about more significant interventions such as steroids. The key with almost all of these immune-related adverse events is catching them early. So the earlier we realize that the immune system is doing things we don't want it to do and the earlier we intervene, especially with systemic steroids, the better the patients will do. There are, however, still instances where patients develop quite severe endocrinopathies or in rare instances we can see the immune system affecting the lungs or heart, et cetera, and sometimes steroids aren't enough, and we need to turn to drugs like infliximab to further suppress the immune system.

Excitingly, because of how common it has been that immune therapies are being utilized, there are now great resources for medical oncologists using these agents. The NCCN has developed immune-related adverse event guidelines that are very useful and also just recently published from immune-related adverse events – a patient guideline that is a patient-friendly version of these guidelines that can be very helpful for the patients to understand what to look out for and how to manage – at least the basics of how to manage some of these immune-related adverse events.

Dr. Parikh:
So early recognition, multidisciplinary management and there's best practices for checking baseline labs, for example, to understand where patients are starting from as they're starting to sort out these AEs. But I think something that the GI oncology field is increasingly becoming adept to – you know, well behind some of our melanoma and lung colleagues, but we stand on and greatly appreciate their guidance and being the trailblazers for us in this space.

So with that, we'll wrap up Chapter 2, and we're now going to move to HER2-positive metastatic CRC, so stay tuned for this next chapter.

Dr. Parikh:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Aparna Parikh, and here with me today are Drs. Dustin Deming and Dr. Scott Kopetz, and we've been discussing advances in the care of patients with metastatic microsatellite high colorectal cancer, as well as HER2-amplified colorectal cancer.

Welcome back to Chapter 3. After discussing some recent data and adverse events in terms of immunotherapy and microsatellite instability, we're going to shift gears now to some targeted therapies, and particularly emerging treatments in the HER2 CRC space, which is really exciting. And again, we've seen some exciting data over the last couple of years that is really moving the needle for how we start to think about this important biomarker.

So, Dr. Deming, can you comment on some of the ongoing but also completed trials now in HER2 disease?

Dr. Deming:
Sure, so there's been a lot of really exciting work done now, specifically looking at this HER2-amplified population. So there is only about, 3%-5% of patients in the metastatic setting that have HER2 amplification, but when it is amplified, especially in the absence of a concomitant KRAS mutation, patients can respond extremely well to HER2-targeted therapies. One of the first studies that really showed significant benefit to targeting HER2 was the MyPathway study, that looked at the combination of trastuzumab and pertuzumab, specifically for HER2-mutated colorectal cancer, and saw that this therapy was very well tolerated, and approximately 30%-40% of patients had partial response to this therapy. Additionally, the DESTINY-CRC01 study has demonstrated that trastuzumab deruxtecan also has activity in this setting.

Now this therapy is a little bit different than a PR [progesterone receptor]-targeted combination like trastuzumab/pertuzumab in that this antibody-drug conjugate [ADC] does have more significant side effects, as this is a real chemotherapy, in addition to it being targeted to HER2-amplified cancers and does have the risk of interstitial lung disease, which can be fatal, though thankfully quite uncommon. More recently, we're now seeing data coming out of the MOUNTAINEER Phase 2 clinical trial, which has now shown significant activity for the combination of tucatinib plus trastuzumab for patients with HER2-amplified metastatic colorectal cancer. This study showed a similar response rate with this combination to that seen in the MyPathway study, but excitingly in this study, we do see significant prolonging of a progression-free survival, out to 8 months with this combination. This wasn't a randomized study, wasn't compared directly to trastuzumab/pertuzumab, so we don't know about the potential benefit of these 2 regimens versus each other, but both are now very reasonable options for patients with metastatic HER2-amplified colorectal cancer.

Additionally, there are ongoing studies including the MOUNTAINEER-03 study, which is looking at the combination of tucatinib and trastuzumab, specifically for patients in the first-line setting, in combination with FOLFOX chemotherapy versus standard of care treatment. And also, excitingly, there is a SWOG study, 1613, that is looking at comparing standard of care cetuximab and irinotecan for these patients versus trastuzumab/pertuzumab. This will be a really important study as we figure out where in the lines of therapy we should place HER2-directed therapies.

Dr. Parikh:
Yeah, it's great to have so many options, and I think one other comment is we tend to see more HER2 amplifications, more in rectal cancers too than colon cancers, although the testing is the same for both, and in the NCCN guidelines, we also had the option previously for Herceptin, lapatinib, and I think the important thing that will boost with the antibodies and small molecules is that Herceptin alone really didn't have single-agent activity. So it's great now that we have these options plus an ADC to start to think about how to sequence care for these patients.

Dr. Kopetz, how will emerging evidence, whether it's the first line or starting to think about sequencing, you know, how does this make you think about where HER2 fits in, in the landscape of treatment for metastatic colorectal cancer?

Dr. Kopetz:
I think it's great to have these options, and now this is a space, a population that's clearly well defined. You know, we do think about these populations slightly differently. Right now, most of the HER2-targeting therapies being done in kind of second line or beyond – although as mentioned, there's a first-line randomized study that is going to be looking at the role of tucatinib and trastuzumab in first line.

It's important to recognize that the targeted therapies have their best data in patients that have a RAS wild-type tumor. Although KRAS is not seen as frequently in the HER2-amplified population, it certainly is still seen. But we think that those patients may not do quite as well with the targeted therapies. In contrast, the ADCs, by it's mechanism of action, really is active, we think, in both populations, although again, clinical data is still emerging. I do incorporate the RAS status to try to pick best treatments for our patients, and really, at this point the utilization is kind of in that second- or third-line setting.

Dr. Parikh:
Yeah, and, you know, one thing maybe we can just comment on before we wrap up this section. So I think Takeaway A, again, is that testing is important, and the same way we talked about MSI-high testing as being universal, HER2 should absolutely be tested in all patients with metastatic disease.

Anyway, that was a great Chapter 3, and we're going to move on to Chapter 4 now. And in Chapter 4, we're going to talk about regional considerations for the testing and treatment of MSI-high disease. So stay tuned for Chapter 4.

Dr. Parikh:
Welcome back. Now that we've discussed the future of HER2-amplified CRC, we're going to go back and talk about regional considerations in the testing and treatment of MSI-high disease.

Dr. Kopetz, you're obviously a US-based oncologist, but would love to pick your brain a little bit and hear your thoughts on your understanding and impressions of the MSI-high testing outside of the US, and are there any global guidelines that may vary or, you know, perhaps under testing or over testing – I guess there is no such thing as over testing, but just to start to think about global context for MSI-high testing outside of the US.

Dr. Kopetz:
That is a key message that we hope we can leave this chapter with, is that, you know, MSI testing should be done universally. When we think about global guidelines, we acknowledge that there's a deviation in what's available and treatments and therapeutics that vary very widely throughout the world. Fortunately, there's a fair bit of consensus around what we should be doing as far as biomarker testing. Current guidelines really are recommending MSI-high testing for patients. And this is clear because of the association with the hereditary syndrome and screening for that, but also the opportunity, where available, to treat the patients with PD-1-based therapy. We do see, however, that there's variable uptake. And part of this is access to testing and awareness, but there is variable uptake despite the fact that there's a near-universal recommendation to broadly MSI test.

Dr. Parikh:
Dr. Deming, can you tell us a little bit about recent approvals outside of the US for immunotherapy?

Dr. Deming:
So pembrolizumab has now received approval in the EU for metastatic colorectal cancer that's MSI-high or mismatch repair deficient. So much like is also FDA-approved here in the US, this approval, I think, is a great advance for patients. The key that's – and we're all talking about is making sure that the testing is done.

So to be able to use these therapies in the first-line setting, where we really want to use them for these patients, we have to have that testing done up front and before the treatment is started. For colorectal cancer, it's often pretty easy to see a patient, get that diagnosis of metastatic colon cancer, and want to start FOLFOX or FOLFIRI, but really, we're doing these patients with MSI-high cancers a disservice by not giving them immunotherapies in the first-line setting. And it's quite impressive, actually, how poorly these patients can do with standard chemotherapy. This is not only seen in the metastatic setting, but in the neoadjuvant setting as well. Really important for these patients to have testing done early and get started on therapies in that first-line setting.

Dr. Parikh:
All great points, and the take-home message that I hope you're hearing over and over again is testing for MSI-high disease. Testing is only useful if you have the therapies to go with the test, and exposure to immunotherapy is really a game changer for these patients. And so test for these biomarkers, like MSI-high disease. Especially exciting to hear about the EU approval, so hopefully more patients across the globe will have access to checkpoint inhibitors for this patient segment.

But unfortunately, that's all the time we have today, so I really wanted to thank our audience for listening in today, and thanks to my good friends and colleagues, Dr. Deming and Dr. Kopetz, for joining me and sharing their always valuable insights. It's great speaking with you today, as always.

Dr. Deming:
Thanks so much. Enjoyed it.

Dr. Kopetz:
Thank you. My pleasure.

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