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Clarifying the Value of Anti-EGFR Therapy in Metastatic Colorectal Cancer

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[CHAPTER 1]

Dr. Kopetz:
With a median survival of less than 3 years, patients who are diagnosed with metastatic colorectal cancer have an uphill climb ahead of them. Studies have shown that both mutational status and tumor sidedness impact survival and disease progression. For patients with BRAF V600E-mutated metastatic colorectal cancer who have already undergone aggressive first-line treatment, the prognosis is dismal, with a median survival of about 1 year. Despite advances in therapeutic treatment options, there is still a high unmet need for updated, practice-changing clinical evidence that would ultimately improve outcomes for patients with metastatic colorectal cancer, especially for those with right-sided tumors and BRAF mutations.

This CME on ReachMD, and I'm Dr. Scott Kopetz.

Dr. Smyth:
And I'm Dr. Elizabeth Smyth.

Dr. Elez:
And I'm Dr. Elena Elez.

Dr. Kopetz:
Let's get started with our first chapter. Dr. Smyth, can you give us a brief overview of the global impact of metastatic colorectal cancer and the importance of molecular testing?

Dr. Smyth:
So let's first of all split this into colorectal incidence and mortality. Colorectal cancer is the third most common cancer diagnosed globally. About 1.8 million patients are diagnosed with colorectal cancer every year. This is about 10% of all cancers diagnosed. Colorectal cancer is on the increase. We can anticipate cases that are diagnosed will increase by around 30% by 2030. Currently, colorectal cancer is more common in countries which are highly developed, like the US and Europe, but the incidence rate has stabilized or might even be decreasing in those countries, whereas we are seeing a rapid increase in colorectal cancer incidence in lower income countries, probably due to adoption of a more Western diet and lifestyle. The prognosis of colorectal cancer is very dependent on the stage at which it is diagnosed. This could be up to 90% for stage 1 and 2 colorectal cancer, but it's only 14% for patients with metastatic or stage 4 colon cancer. Unfortunately, this represents a large number of patients globally, and by 2030 there

could be more than 1.1 million deaths from colon cancer every year.

Dr. Kopetz:
So we now have a strong foundation for our upcoming discussion, and we'll bring Chapter 1 to a close. In Chapter 2, we'll be talking about molecular testing. Stay tuned.

[CHAPTER 2]

Dr. Kopetz:
Welcome back. In our last chapter, we looked at the impact of metastatic colorectal cancer on patients around the world. Now, in Chapter 2, we'll focus on molecular testing.

With a multitude of different testing modalities available, along with a handful of targetable biomarkers in metastatic colorectal cancer, this landscape can be challenging to navigate. Dr. Elez, can you walk us through the different actionable biomarkers in metastatic colorectal cancer and how you go about testing for them?

Dr. Elez:
Absolutely. Now we cannot take any decision in advanced colorectal cancer without testing some crucial biomarkers that have an importance in the underlying biological disease of these particular patients. So it is mandatory to test exomes 2, 3 and 4 of both KRAS and NRAS. The importance here is to select an anti-EGFR treatment combined with chemotherapy for the frontline setting, and this is particularly important for those patients who have a left-sided colorectal cancer. Also, since 2016, we are testing exome 15 of BRAF at the beginning because of the bad prognosis effect of this particular biomarker. But we also know that patients whose tumor has a BRAF V600E mutation do not obtain benefit of adding anti-EGFR treatment to the chemo backbone. So this is particularly important, but I would also say that testing the microsatellite instability is particularly relevant to consider those patients for immunotherapy in case the tumors are MSI-high. We surely have now evidence about the potential role of HER2. It is true that we don't have trials in the frontline setting assessing the combination of targeted treatment with chemotherapy for these particular patients, but we know that we have several compounds related to this particular biomarker with impressive efficacy in second and third line.

Also, for some selected patients, I would say those patients who have an MSI-high tumor without mutations, in either KRAS, NRAS and BRAF, and without a Lynch syndrome – these patients may have an enrichment of NTRK fusions. I mean, in this particular case, it's important to offer them a targeted treatment, if it is available. An important thing, also, to discuss is the accessibility to perform these tests. The preferred scenario would be to perform an NGS [next-generation sequencing] panel in order to assess for all these particular molecular aberrations, and for example, in the refractory setting and in a research environment, we can consider other platforms of testing to then more genes but also fusions. But it is important to be testing all of our patients, particularly in the frontline.

So it is not an exclusion to offer surgery for these patients, but it needs to be discussed in a molecular tumor board. Sometimes, the first physician that meets the patient, for example, could be the surgeon in certain cases. It would be interesting to offer a systemic treatment prior to offering any other type of surgical approach. So it's particularly important to discuss these patients in multidisciplinary tumor boards.

Dr. Kopetz:
Thank you, Dr. Elez, for a nice summary, and I fully agree that mutation testing for KRAS, NRAS, BRAF is critical. MSI testing should be done in all patients, and also HER2 and potentially fusion testing, as you mentioned, in selected patients. I think also recognizing how to interpret these different mutations, especially BRAF as we'll get to, where V600E mutations can be actionable, unlike other alterations that may be found.

So this wraps up Chapter 2. In Chapter 3, we'll focus on therapy selection for the specific BRAF V600E mutation. Stay tuned.

[CHAPTER 3]

Dr. Kopetz:
Welcome back. In the previous chapter, we discussed molecular testing and biomarkers in metastatic colorectal cancer. Now, in Chapter 3, we're going to dive into treatment selection. Selecting the right therapy for the right patient at the right time is key to improving patient outcomes in metastatic colorectal cancer.

Dr. Smyth, how would you go about selecting the appropriate therapeutic treatment regimen in patients diagnosed with BRAF V600E-mutated metastatic colorectal cancer?

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Scott Kopetz and here with me today are Dr. Elizabeth Smyth and Dr. Elena Elez. We're discussing the value of targeted treatment in the management of patients with metastatic colorectal cancer.

Dr. Smyth:
So in the first-line setting, at the moment, our treatment of choice for BRAF-mutant colon cancer is a chemotherapy doublet or triplet plus or minus an antiangiogenic drug. But in the second-line setting, we have a new standard of care specifically targeted at the V600E mutation.

To successfully treat BRAF-mutant colorectal cancer, we need to target both BRAF and the EGFR pathway. The BEACON trial established the combination of encorafenib and cetuximab as a new standard of care for patients with V600E-mutant colorectal cancer who have been treated with previous chemotherapy. In the BEACON trial, encorafenib and cetuximab and a triple regimen of encorafenib, cetuximab, and binimetinib – a MEK inhibitor – improved survival compared to control. However, binimetinib did not add further benefit compared to the doublet treatment, so doublet treatment with encorafenib and cetuximab is preferred. We can expect a response rate of around 20%, a PFS [progression-free survival] of around 4.5 months, and a median survival of about 9 months for encorafenib and cetuximab regimen.

The next question is can we bring BRAF-directed therapy into the first line. The first data that we have seen presented in this sphere is from the ANCHOR trial. This was a phase 2, nonrandomized trial in just under 100 patients with treatment-naïve, BRAF V600E-mutant colorectal cancer. Treatment was the triplet of anchoratinib – encorafenib, binimetinib, and cetuximab. What we saw was response rates of around 48%, a median PFS of just under 6 months, an immediate overall survival of just over 17 months, which is better than expected for a BRAF-mutant population.

The question then is can we go one better if we use BRAF inhibition with chemotherapy? And that's what the BREAKWATER trial is doing. This is a large, global, phase 3 randomized trial which has just presented a safety run-in of encorafenib and cetuximab plus either FOLFOX or FOLFIRI chemotherapy, which are our standard first-line regimens in colorectal cancer. It was really important to understand whether encorafenib impacted on the metabolism of irinotecan via UGT1A1 and CYP3A4 enzymes, because this happens in vitro. So just over 50 patients were enrolled in the safety run-in, and no new safety signals were noted, which is reassuring. The most important takeaway from BREAKWATER is that, as expected, encorafenib did not affect the metabolism of oxaliplatin, but the area under the curve of irinotecan and SN-38, which is the active metabolite of irinotecan, were significantly reduced by encorafenib. These results mean that FOLFOX will be the choice moving forward to combine with cetuximab and encorafenib in the phase 3 randomized trial, and hopefully we'll see a positive result for patients with BRAF V600E mutations in years to come.

Dr. Kopetz:
Thank you, Dr. Smyth, for a nice summary and really the hope that as we move from later lines therapy, as seen in the BEACON, into earlier lines, we'll be able to improve the efficacy of the targeted therapy potentially combined with cytotoxic chemotherapy. And as you alluded, how we put this together and the appropriate regimens really require some attention and thought, but we're encouraged by the safety data seen so far in the field.

With all this new information, providers are still challenged with how to effectively integrate information into daily practice. Dr. Elez, can you talk about the challenges clinicians encounter in the clinic?

Dr. Elez:
It's important to stress that the BEACON trial is a first phase 3 randomized clinical trial specific for BRAF V600E population, with more than 300 patients included in the trial, and it is on a strong evidence about the role of this combination – encorafenib, cetuximab – in the second- and in the third-line setting. It has represented a change in the treatment of metastatic colorectal cancer, as we are treating patients of a poor prognosis and at risk of rapid progression with a targeted therapy alone. The advantage of this particular combination is that these patients do respond fast, and with that important difference of response, and must be a part of the continuum of care for this particular population. So my recommendation would be to refer this treatment in the second-line setting.

It is also important to think about the coexistence of the BRAF V600E mutation and the MSI-high condition in these patients. We know that the reasoning for the efficacy of pembrolizumab in the frontline setting compared with the standard of care – but this would be a situation in which in the second-line setting we could also offer a combination of encorafenib/cetuximab, so for this – particularly for these patients, the chemo would be the option in the refractory setting, and that's awesome considering the evolution of the new treatment in metastatic colorectal cancer.

Dr. Kopetz:
That's great. Before we wrap up, Dr. Smyth, Dr. Elez, can you both provide us your key takeaways from today?

Dr. Smyth:
I think that we're moving from an era where we felt very pessimistic about patients who had BRAF-mutant colorectal cancer. Historically, they had a poor prognosis, but now we have an effective, targeted therapy for them, which has shown benefit in terms of improving

overall survival first line, and it now has the possibility of moving into first-line treatments. So for me, it's about performing the NGS so we can have the best discussion around prognosis and prediction and using the right treatments at the right stage. So for me, this is encorafenib and cetuximab in second line.

Dr. Elez:
It's crucial to understand the molecular profile of each tumor type, particularly in the case of metastatic colorectal cancer. We cannot lose the opportunity to treat our patients with a particular molecular aberration, like BRAF V600E mutation, with targeted agents that have demonstrated clear, improved outcomes in this patient population. So the sooner we have this information, the better for our patients, as we can plan the treatment and strategy from the first line to the refractory setting.

Dr. Kopetz:
Unfortunately, that's all the time we have for today. I want to thank our audience for listening and for both Dr. Elizabeth Smyth and Dr. Elena Elez for joining me and sharing all of their valuable insights. It was great to speak to you both today.

Dr. Smyth:
Thanks for the invitation, Dr. Kopetz. It was lovely to speak with you, too.

Dr. Elez:
Thank you so much. Thank you for your attention and a pleasure to share these minutes with you.

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