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Optimizing Treatment and Patient Selection in BRAF V600E-Mutated Metastatic Colorectal Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Optimizing Treatment and Patient Selection in BRAF V600E-Mutated Metastatic Colorectal Cancer” is provided by AGILE.

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Dr. Kopetz:
BRAF V600E-mutated metastatic colorectal cancer is a very aggressive subset of colorectal cancer, and the standard of care options have been very limited. More strategies are on the horizon, but how will these emerging strategies really be utilized in our daily clinical practice?

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

Dr. Taieb:
And I am Dr. Julien Taieb.

Dr. Kopetz:
So we have lots to discuss today, so let’s get started. Dr. Taieb, can you first give us a brief overview of the genomic biomarkers associated with colorectal cancer?

Dr. Taieb:
Yeah, thanks for this question, Dr. Kopetz. I think that, clearly, today we cannot talk anymore about one colorectal cancer. We have different colorectal cancers with different molecular profiles. What is really mandatory today – this may evolve in the forthcoming years – is really to have from the beginning, before starting the first line, at least 3 types of markers: MSI status for immunotherapy selection eventually and despite the problem of the genetic Lynch syndrome or others; the BRAF mutation, V600E especially, because here, again, what will happen, we will discuss that specific treatment option for our patients; and the RAS compound that is divided in NRAS and KRAS, which we need the full RAS profile from the beginning.

Dr. Kopetz:
Yeah, and this is such an important point that you make, that this testing is something that should be done early because really understanding the landscape of patients really gives the best understanding of the treatments that we should be providing across the treatment continuum. So I think, really, this idea of testing early in patients, upon the diagnosis of metastatic disease, is really an important point in clinical practice.

Dr. Taieb:
Absolutely. And, Dr. Kopetz, with this overview in mind, how does the pathophysiology of tumor genetics provide us with target treatment? Let’s think specifically about targets for patients with BRAF V600E-mutant metastatic colorectal cancer.

Dr. Kopetz:
Certainly. We know that BRAF V600E is a critical oncogene, and this mutation results in constitutive activation of the BRAF protein and results in MAP kinase pathway signaling. The biology of this tumor really shows exquisite sensitivity to the MAP kinase pathway, meaning these are tumors that are very dependent on MAP kinase pathway signaling for their cell survival and proliferation. The challenge is really how do we optimally inhibit this, and how do we really adapt to the ways that the tumor can rewire in response to inhibition of single nodes. And that's really been the advances that's been made in this field, is understanding how to both target the V600E mutation, but also target the tumor adaptations that occur afterwards, most commonly now with the combination of an EGFR inhibitor.

Dr. Taieb:
Yeah, this is a very critical point because we know that as compared to others, BRAF V600E-mutant tumors, colorectal cancer, do not respond well to the only BRAF inhibitor. And another point that is important, I think, for the audience is to remember that V600E is the mutation that we call BRAF mutant. The others, BRAF mutation, do exist. They are much more rare – less than 10% of all BRAF mutations – and currently, they are not so certainly of poor prognosis, as compared to the BRAF V600E, and we don't have any specific therapeutic option for these patients.

Dr. Kopetz:
For those just tuning in, you're listening to CME on ReachMD. I'm Scott Kopetz, and here with me today is Dr. Julien Taieb, and we're discussing how to apply emerging treatment regimens to clinical practice for BRAF V600E-mutated metastatic colorectal cancer.

Good point. So, let's start with our first case. This was a patient initially diagnosed with localized, left-sided colon cancer. No distant metastasis, so surgery was done – left-handed colectomy with staging of a T3 N1b microsatellite stable tumor. Mutation testing was done. RAS was wild-type, but a BRAF V600E mutation was detected. So after treating with 12 cycles of FOLFOX, the evaluation showed a new iliac lymph node and 2 lung nodules.

Dr. Taieb, can you take us through what you would consider for first-line treatment for a patient like this with a BRAF V600E-mutant metastatic colorectal cancer?

Dr. Taieb:
So I think this case is quite interesting because we are here on the patient that is relapsing after adjuvant FOLFOX. So generally, the idea was, I would say, since 5 to 6 years, that as BRAF were super-aggressive disease, giving an aggressive treatment makes a lot of sense, and we are really motivated to give a triplet chemotherapy, generally with bevacizumab in these patients. Because the disease is severe, we want very intensive first line. However, we also know from the TRIBE trial that when someone has received FOLFOX, maybe the triplet, chemotherapy first-line with bev, is not as good as in the other and does not reach the advantage that we are looking for with this aggressive first line. And it can be debated here to start, for example, with a FOLFIRI bevacizumab only, also depending of course on your patient condition and biological examination, because you know that not all patients are eligible for this triplet regimen.

The second question is that you know that BRAF mutants are exclusive from RAS mutation, so when you are BRAF mutant, you are RAS wild-type. And here, we may also discuss the role of cetuximab first line with a doublet chemotherapy, for example, or even a triplet as it has been demonstrated in small subgroups, analyzed in some studies like VOLFI study. And it's a real question. And the German trial, phase 2 trial, randomized, will compare this triplet chemo with bev or with cetuximab.

And the last question I would like to raise is, is the first line, and especially in a patient that relapsed after adjuvant FOLFOX, a good setting to give targeted agent – BRAF-targeted agent – in this patient? And here, we don't have a lot of data first line. I think that in some of the level of the registration, we may be able in some countries to use the combo encorafenib and cetuximab, but we have the ANCHOR trial that tested encorafenib plus binimetinib, a MEK inhibitor, plus cetuximab in first line in approximately 90 patients with metastatic BRAF V600E-mutant colorectal cancer. This trial will be finally reported at ASCO this year, but it has been already reported for the intermittent incidence of the first part of the trial – the 41st patient at ESMO-GI last year. And what we are seeing is that the response rate is quite impressive, around 50%. It was, I think, 50% exactly on the first analysis. PFS [progression-free survival] were more or less similar to what has been reported in second line – a bit disappointing. And we are waiting for the OS [overall survival] result at ASCO this year.

So we can see that the landscape is moving and that we cannot really be sure of what will be the first-line standard treatment for BRAF mutant in the future. And of course, the idea would be to combine the chemotherapy and the RAF-targeted agent. And we will have these end scores in a few years from now, because it's the BREAKWATER study combining chemotherapy and encorafenib and cetuximab up front. Of course, this trial is starting now. It is recruiting, but we will have to wait for a few years to have the final results.

Dr. Kopetz:

Yeah, and it's really well summarized and really reflects the fact that the landscape is continuing to change. And I think there is certainly a lot of interest and good rationale for why one should be combining targeted and chemotherapy here. I think, you know, recognizing that the chemotherapy can improve the duration of disease control, the hope is, but really trying to optimize the response with the combination. And I think taking advantage of the strengths of both the modalities, I think, is really the direction we need to go. But then again, that's why we do the study, and we certainly look forward to the BREAKWATER results to follow.

Dr. Taieb:
Thank you, Dr. Kopetz. So now can we focus on a second case? It's a woman of 62 years old, with metastatic BRAF V600E-mutant colon cancer. She has been treated previously with FOLFIRINOX bev – the triplet chemotherapy plus bev. She has a right-sided colon primary tumor that is in place, and she is progressing. So what would be your attitude and treatment possibilities for this patient today?

Dr. Kopetz:
Yeah, so this a population that aligns exactly with the BEACON study. So really taking patients who have had 1 or 2 prior lines of therapy, of systemic chemotherapy, and asking the question in the BEACON study, compared to control of a FOLFIRI, irinotecan with cetuximab. The study looked at a combination of encorafenib and cetuximab or the triplet of encorafenib, binimetinib, and cetuximab. And the study met its primary endpoint of demonstrating the advantage of and survival of the triplet as well as the doublet compared to control. Now, the study, I think, to many of our surprise, really demonstrated very strong activity in response with the doublet of the encorafenib and cetuximab, but no clear benefit with the addition of binimetinib. What we saw was that the response rates were higher – approximately 20% versus 27% in the second and third line, but that there was no improvement in the progression-free survival or overall survival in this population. So this has left us with a new standard of care of encorafenib and cetuximab – the doublet – which really has demonstrated activity and survival benefit in this population.

So that is the treatment that this patient received. Went on to have a response to treatment and was able to stay on therapy for about 6 months. The toxicities of the regimen are fairly well tolerated. The skin toxicities that we typically would see with an EGFR inhibitor actually appear to be somewhat mitigated with the addition of a BRAF inhibitor. Very interesting biology related to the feedback in the skin and modulation of that toxicity. But other side effects can include some of the fatigue, some mild nausea, there can be some arthralgias that can come with the BRAF inhibitor as well.

But the next steps, really, in this field are trying to understand how do we increase the duration of disease control? So even though, as Julien mentioned, in the ANCHOR study and others, we can get response rates as high as 50% depending on where we deploy these targeted therapies, what we know is that the tumor can adapt. And the tumor can find mechanisms to reactivate that MAP kinase signaling, remembering these are tumors that are exquisitely addicted to this pathway, and they find alternate mechanisms to reactivation. So there is a number of areas ongoing for future research, really looking at how do we come back at the time of progression and now try to intercept some of this restored MAP kinase signaling? And there's a number of studies looking at ERK inhibitors, SHIP2 inhibitors CDK4/6 inhibitors in combination that are ongoing.

Well, this has certainly been a fascinating conversation, but before we wrap up, Julien, can you share your one take-home message with the audience?

Dr. Taieb:
Yes, of course, Scott. I think that the main take-home message is to test our patients up front to have the full molecular profile and to be able to identify these BRAF V600E, but also the other biomarker-defined subgroups, to have specific therapeutic approaches. We have seen that for BRAF V600E, there is a lot of new options, and that we have something to build on for the future treatment strategy in these patients, but first you need to test.

Dr. Kopetz:
Absolutely, couldn't agree with that more. And I would add, as you mentioned, that this is an area that is constantly evolving, and we have new regimens coming – combinations and new approaches – so certainly encourage, where possible, getting patients into clinical trials, because this is really the only way that we're going to be able to make progress in this population and improve outcomes for our patients.

So unfortunately, that's all the time we have today, but I really want to thank our audience for listening, and thank you, Julien, for joining me and sharing all your valuable insights. It was great speaking with you today.

Dr. Taieb:
Thank you.

Announcer:
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