Evolving Management Strategies for *BRAF*-Mutant Metastatic Colorectal Cancer

Scott Kopetz, MD, PhD: Hello and welcome to this educational activity entitled *Involving Management Strategies for BRAF-Mutant Metastatic Colorectal Cancer*.

My name is Scott Kopetz. I'm a professor of GI Medical Oncology at MD Anderson Cancer, and I'm very pleased and honored to be joined by Dr. Rona Yaeger, who's an associate professor and the associate director of the Colorectal Cancer Center at Memorial Sloan Kettering Cancer Center in New York.

So, let's start with a bit of an overview of *BRAF* V600E mutation and its impact in colorectal cancer.

I think it's worth taking a step back and recognizing that colorectal cancer is composed of a diverse set of cancers that derive from different initial pathways, including the classical chromosomal instability pathway, and then other pathways that lead to microsatellite instability that are overlapping somewhat with the serrated or the methylated pathway.

It's this last pathway, the sessile serrated adenoma pathway, that is associated with very high rates of *BRAF* V600E mutation, and very interestingly strongly associated with methylation and epigenetic dysregulation. This can, on occasion, result in deficient mismatched repair through MLH1 methylation. But this is not a one-to-one overlap.

We know that this is a unique population with distinct clinical and pathologic features as well. There is a preponderance of this disease in the right side of the colon, although certainly we can see *BRAF* V600E mutations in other parts of the colon as well. There is a slight predominance toward older ages, more women than men, and it's associated with the biology I described previously. It's clinically very different as well with distinct metastatic spreads. These are patients who have a high rate of peritoneal and nodal metastases and do very poorly with standard of care therapy, where traditionally we're seeing much shorter progression-free survival across multiple lines of therapy.

When we look at the prognosis of V600E colorectal cancer stage by stage, there are large distinctions between wild-type and *BRAF* V600E mutation, and for stage II and III disease. We know this is a prognostic marker, both at early- and late-stage disease, which can have implications in recurrence.

These are data from patients who undergo disease profiling at academic centers. Highlighting some work, by Jon Loree, who looked at population estimates of patients who may not have presented to an oncologist, suggesting, in that setting, that *BRAF* mutation may be associated with substantially worse outcomes of median overall survival.

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Now, we know that *BRAF* V600E is associated with unique transcriptional subtypes as well. So, one of the classification systems that we use in the field is called consensus molecular subtypes (CMS), which use RNA profiling to help determine the different biologies of colorectal cancer. That has been separated into these four different groups.

BRAF-mutated tumors tend to have a much higher predominance of being in this CMS1 immune-activated subgroup that has this high degree of hypermethylation, as well as a higher rate of microsatellite instability. But intriguingly, even microsatellite-stable *BRAF* disease can present with this transcriptional profile.

In summary, we know that the *BRAF* V600E–mutated tumors are a unique subpopulation with respect to clinical outcomes, poor survival, poor responses to standard of care and systemic cytotoxic chemotherapy, unique pathologic characteristics, and mutation profiles. As mentioned, really strong epigenetic components are seen as well.

This unique biology for *BRAF* V600E colorectal cancer leads to a challenge in our clinical presentation and requires that we think about this as a distinct tumor entity.

So, with that, hopefully convinced you that this is something that we should be testing for. And when we look at our guidelines, the NCCN says that this should be part of our panel, both *NRAS*, *KRAS*, and *BRAF* should be done on all metastatic patients. And likewise, for ESMO and ESMO Asia. The global consensus is that *BRAF* testing should be done for all patients with metastatic disease.

One of the areas that has come up concerns the role of EGFR inhibitors and whether *BRAF* V600E is a negative predictor of outcome for EGFR inhibition, just like a *KRAS* or an *NRAS* mutation. Analyses demonstrate that in a *BRAF* and *RAS* wild-type population, we see a benefit in the meta-analysis of EGFR inhibitors. We're not able to demonstrate that degree of benefit from EGFR inhibition in those *RAS* wild-type but in *BRAF* V600–mutated tumors. So we think about this as a subset that does not benefit from EGFR inhibitors alone.

However, we know that it can be a target, in and of itself, and there are opportunities to treat this, as we will talk about in more detail, with targeted therapies. So, just acknowledging that while those are present in a minority of the population, it is one of our larger molecularly defined subsets of colorectal cancer, somewhere around 7% to 8%, perhaps as high as 10% in some series of patients with colorectal cancer.

This mutation is an activating oncogenic mutation; the tumor then activates cell signaling and cell cycle progression through the MAP kinase pathway. There have been efforts to use BRAF inhibitors in this setting, and single-agent BRAF can have activity across a number of different tumor types, including BRAF and MEK targeted therapy as well.

Inhibition in colorectal cancer is very different. One of the key features that we will touch on a little later is why colorectal cancer is different and how colorectal cancer adapts to that therapy and how we can deploy novel therapies.

I would like to bring in Dr. Yaeger to discuss some of these initial features about colorectal cancer, *BRAF* V600E biology.

Rona, thank you for joining me and for sharing your expertise. Can you explain some of the rationale about why we see such poor prognosis and poor outcomes in colorectal cancer for these patients and expand on your perspective of the need for treatment options?

Rona Yaeger, MD: Thank you for having me here. It's a pleasure to join you. I think it's a difficult question of what is underlying the biologic aggressive behavior of these tumors. I think we have a few insights, but we don't really know the real mechanism. *BRAF* V600E mutated colorectal cancers are like a different subset with a different behavior. And we can even see that they are often poorly differentiated. They, when localized, are more likely to have extensive nodal involvement. So, aggressive features that may be underlying some of this biology.

I think the behavior or the proclivity for certain metastatic sites may underly the short survival time. *BRAF* is associated with certain metastatic spreads, so peritoneal disease and ascites are commonly seen and difficult to treat. We also see affected distant nodes that we often don't see with other marker subsets, such as axillary nodes, supraclavicular nodes that we don't really think of as colorectal nodes. So there is probably something underlying that spread, and I don't think we know the biologic basis, but we have a clinical sense of different behavior that might underly the poor prognosis.

Kopetz: Okay. Well thank you, nicely summarized.

Can you discuss the clinical implications of *BRAF* mutation? So when you get that result back on a patient, what are your thoughts in terms of the clinical impact, and then how do you communicate that, if you do, to your patient?

Yaeger: Yeah, The outcomes with standard chemotherapy are disappointing. And luckily for us, we now are starting to have treatments that are matched to the mutation. So, I often tell patients, quite straightforwardly, that we think of *BRAF* as an aggressive feature, but it opens, for us, the treatment option that may give us the opportunity to do better. So I think it has implications for choice of treatment. And, as you showed also for EGFR inhibitors, selecting the appropriate regimen and the absence of activity to EGFR inhibitors alone is important as we think about what treatments we're going to use and whether we'd use combinations.

Kopetz: I think that balance of discussion with the patients about acknowledging its poor prognosis but then leaving them with the hope that we now have something tangible that we can target.

When do you do *BRAF* testing? Is it something that you do in early stage, stage II/III and how and when do you test BRAF in stage IV?

Yaeger: All patients with stage IV disease should have *BRAF* testing. It can be done as a polymerase chain reaction test because the V600E mutation is the clinically important alteration but often now is done with next-generation sequencing panels where we get a lot more information. In early-stage disease, it doesn't guide our treatment. But as we shift to using some of these next-generation panels, some of them are being brought in earlier for their information, such as microsatellite instability status. Sometimes we know *BRAF* status, as well, early on. But in patients who have metastatic disease, once we know they have metastatic disease, ideally before first-line treatment, they should be tested for the presence of a *BRAF* V600E mutation.

Kopetz: I think that's absolutely something we do in our standard practice. Everyone is getting that testing for stage IV. I will say for stage II/III, it's not completely clear that doing testing is beneficial yet, although we certainly hope that this can be incorporated in future adjuvant therapy, and it may be something in the future that we're more widely recommending. Current guidelines are not requiring *BRAF* testing for the earlier stage, as mentioned.

Okay. The final question is when you have a patient who has a *BRAF* V600E mutation, before you start to think about targeted therapies, as we will get into in the next section, how do you think about deploying standard-of-care chemotherapies? Do you tend to bias more toward the FOLFOXIRI triplet cytotoxic for initial treatment of patients, or are you treating them differently in any way with that initial regimen?

Yaeger: So I think it's not truly settled what is the best first-line regimen. I tend to use doublet treatment, and I tend to save the other agent for a later line, often third line after

targeted therapy. As you alluded to, there are some data, because this is an aggressive subset that triplet therapy with a FOLFOXIRI combination regimen may help improve outcomes. And in patients who are fit and able to tolerate it, it is worth considering. I often don't have the *BRAF* status at the time I start treatment. At my center it takes time to get the sequencing results. So often we start, and if I see someone is on a doublet and they have a so-so response, I may add that third chemotherapeutic agent and get some more activity that way. Also, I will see their tolerance at that point, so I feel comfortable adding that third agent if I see that they're able to tolerate it.

Kopetz: I think that summarizes our experience as well. There was some older evidence suggesting that perhaps *BRAF* patients had a preferential benefit with the triplet compared to the doublet based on very small numbers of patients. And it turns out in subsequent studies that really has not been validated. So we think there could be benefit from a triplet cytotoxic with *BRAF*, just like there could other more aggressive subsets of colorectal potentially as well. But it may not be unique to the *BRAF* mutations.

We'll now turn and talk a little bit more about some of the combination treatment approaches in patients who have had prior treatment for *BRAF* V600E mutation-positive metastatic colorectal cancer.

BRAF inhibitors alone do not provide as much benefit compared to other tumor types, including melanoma. This is some of the original work just showing very different levels of activity despite having a very similar mutation profile, identical treatment. That led to a whirlwind of work to try to understand the reasons why *BRAF* V600E tumors are avoiding cell death.

A nice summary of a large body of work by Rene Bernards, Ryan Corcoran, and others have demonstrated this concept of adaptive resistance. The idea here is that homeostatic regulation is critical in biologic systems, including cancer cells. This is especially true in colorectal and especially true of growth pathways such as the MAP kinase. The recognition is that inhibition of a single node in a pathway results in a compensation in the signaling to restore homeostasis. So specifically, activation after the mutation in *BRAF*.

With inhibition of BRAF, you get a transient inhibition in the MAP kinase signaling pathway, but that releases these feedback mechanisms. And these feedback mechanisms then can release upstream inhibition of a number of things, including signaling through the EGFR pathway. And this signaling then can come down, signal around the inhibited *BRAF* V600E and restore pathway activation.

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A key finding was that even though the *BRAF* tumors are not sensitive to an EGFR inhibitor alone, the key finding is that when you inhibit BRAF, you now uncover, through this adaptive resistance, a dependency on EGFR. And then when you inhibit EGFR, you can get pathway inhibition.

There's a large body of work of a number of early-stage studies that led up to this, but the end result was the recent BEACON trial, which is a study of patients with second- or third-line *BRAF* V600E metastatic colorectal cancer without prior treatment with an EGFR inhibitor now treated with either a control arm of chemotherapy and an EGFR or doublet of BRAF and EGFR, encorafenib and cetuximab. Or interestingly a triplet arm, where there is a MEK inhibitor included as well, based on some early single-arm data suggesting that the MEK inhibitors may improve outcome. Co-primary outcomes were overall survival and objective response rate.

The bottom line is that there was, indeed, improvement in overall survival with a doublet of 9.3 months versus a control of 5.9 months that was statistically significant and met its primary endpoint.

The response rates were higher then as well. And response rates of 2% in the control and 20% in the doublet with waterfall plots there. Intriguingly, however, the addition of the MEK inhibitor, although it did increase the response rate, did not improve overall survival or progression-free survival, so that was not recommended to proceed forward. So the FDA has now approved encorafenib in combination with cetuximab for second- or third-line colorectal cancer with a *BRAF* V600E mutation.

Some of the adverse events include diarrhea, abdominal pain, nausea, vomiting, intestinal obstruction, and changes in hemoglobin, creatinine, bilirubin, and creatine kinase. We see that the doublet is very well tolerated and overall lower rates of grade 3 and above adverse events compared to control. The MEK inhibitor did add toxicity, but again did not add meaningfully to the overall survival and is no longer recommended in standard of care.

Now some specific toxicities of interest. We see a number of dermatologic changes, including keratoacanthomas. So these are things that should be monitored and watched, and we do occasionally require dermatologic intervention for treatment of these.

Other side effects we can see include myalgia/arthralgias. These can be treated conservatively. Occasionally if severe, dose interruptions or even low-dose steroids for a short duration. We see, on occasion, renal dysfunction, and a number of

manifestations that can occur. And the recommendation is to monitor that, maintaining adequate fluid intake, as well as just being cognizant of this potential.

There is not any improvement with the addition of the MEK inhibitor. There were some subgroup analyses that looked at patients with more involved disease, higher organ involvement, higher CEA, more inflammatory disease state, as measured by the C-reactive protein may respond better with the addition of the MEK inhibitor. But all of those remain exploratory at this point.

While we recognized that MEK inhibition wasn't the solution to improve the outcome of BRAF and EGFR, there are efforts to focus on earlier administration that may result in better outcomes. And this is being manifested in earlier trials, as we'll have a chance to chat a little bit about. There are first-line studies ongoing, as well as discussions about and studies in the adjuvant setting that are of interest to try to explore as well. I think recognition that there is more needed to understand signaling at the time of progression as well.

We have multiple different resistance mechanisms that have been identified, including *RAS* mutations, EGFR pathway activations, *MEK* mutations, amplifications of various key pathways. And this all results in MAP kinase pathway reactivation. So it's really intriguing that we have not come across a mechanism of resistance that has not, in some way, led to MAP kinase pathway reactivation. I think about this and describe it to my patients as a convergent evolution. It's multiple different ways that the tumors evolved all do the same thing. Just as we see convergent evolution in biology, where we have a very similar phenotype and feature of certain animals, even though they evolve in different ways. So this is a key feature. As Dr. Yaeger mentioned earlier, we talk to patients and say this gives us something to target.

I think just acknowledging that there are a number of different combinations being explored in patients taking encorafenib and cetuximab who have disease progression, including looking at pan-RAF inhibitors, SHP2 inhibitors, and a number of ERK inhibitor studies then as well. So I think a lot of hope that we'll be able to explore other options in the future and explore other combinations that may extend the benefit of the BRAF and EGFR combination.

Rona, one of the things that we also see is the use of panitumumab in combination with encorafenib. What are your thoughts about that, and do you see that as an equivalent option to cetuximab?

Yaeger: So the FDA approval was for encorafenib and cetuximab, but the NCCN Guidelines include both cetuximab and panitumumab. There are good data that they really are very similar. They've been compared head-to-head in terms of efficacy. So, I think that in terms of efficacy, they have similar efficacy in the setting. Cetuximab has a higher rate of an allergic reaction while the panitumumab may have more dermatologic toxicity. I think that different places may have preference for which EGFR antibody is used. We have no reason to think that one will work better in this setting. So I think the use of either is appropriate.

Like you, since we were involved with encorafenib and cetuximab, I usually have the preference for that regimen. But I think it's reasonable, and it isn't listed in the NCCN Guidelines. Cetuximab is listed with an every-2-week schedule, which also makes the regimen simpler.

Kopetz: We'll stop now and present some virtual cases.

Yaeger: Thank you, Scott, for all the information and for the great overview. I brought two cases of mine that I thought were interesting and probably would be interesting to discuss together.

The first patient presented when she was 68 years old with no medical history, active, feeling well, who was up to date with all of her health maintenance and was found to be anemic and diagnosed with a deep venous thrombosis (DVT). And she was up to date with colonoscopies; her previous one was 2 years earlier. Because of the new anemia and DVT, she was referred for a repeat colonoscopy, which showed a mass in the ascending colon. It wasn't completely obstructing the colon, but the mass was biopsied and found to be an infiltrating moderately differentiated adenocarcinoma.

She underwent a CT scan of the chest, abdomen, and pelvis, which showed circumferential wall thickening of the cecum and the ascending colon had associated luminal narrowing and associated lymphadenopathy in the area. She developed some pain while getting set up for surgery and was admitted and went directly to surgery. However, before the surgery, a repeat scan showed a possible subcapsular hepatic lesion. So at surgery, she underwent a right hemicolectomy and was found to have a T4N2 cancer of the cecum. The tumor was moderately differentiated and MMR proficient.

I brought this case up because I thought it was interesting. It had a few features that I found striking. First of all, it seemed like things happened very fast in this patient who had been up to date, and even though she had a colonoscopy, it seemed like this tumor developed quickly. I think was quite advanced for someone who was really quite up to

date. And also, I think it echoes what you had mentioned about patients being a little older with right-sided tumors. We see an age shift for *BRAF*.

I met her after surgery, and she came to me with a story. She had had a really tough time with surgery. She lost a lot of weight and had a wound VAC in place and was recovering when I met her. I told her we should evaluate what was seen in the CT scan and ordered a liver MRI, which unfortunately showed a lesion in the right hepatic lobe with two small satellite lesions. So, I decided—but I want your thoughts—because she, at that point, had minimal liver disease, to think about starting systemic therapy.

So my first question is, I'm meeting this person who just had surgery, had a tough time but comes with what appears to be limited disease. And we set her up for mutation testing but we had to think about how to time everything.

Kopetz: It's a great case and highlights a lot of things that we see in a real practice. It would be great to have all that molecular information at the time that the patient was right in front of you, but that's not our practice. It takes some time to get that and to really have the picture become clear. So I completely agree that patients that present like this, especially when we have patients that have really high nodal involvement like that, even if it's an isolated, resectable disease in the liver, there is always kind of an inclination to start systemic chemotherapy and assess the biology. I think someone who had a tough time with surgery is not ready to turn around and repeat anything surgical there. So, I certainly agree that starting some first-line therapy would be my practice as well.

Yaeger: The first question would be do you test your patients with newly diagnosed metastatic colorectal cancer for *BRAF* mutation?

Kopetz: It's something that we do on all of our patients. I think we are trying to get tissue testing when available. I think sometimes, for the reasons you mentioned, when we need to make some treatment decisions sooner, we are now starting to incorporate some circulating tumor DNA into our standard practice for patients with untreated metastatic disease that can help. That can give us a much faster turnaround time on the results, so that can be useful. But we don't get as much information as we get out of the tissue testing, so there is a bit of a trade-off there. But I think the answer is we can try to get that test back as fast as we can.

Yaeger: So, this patient started first-line treatment with FOLFOX. She improved her performance status as we went through treatment and recovered from surgery. And we ended up doing five cycles and then getting our first scan. Over that time, we got the results from the tissue testing from the colon resection that showed the *BRAF* V600E mutation. But when we got that first scan, unfortunately, it showed progression.

So, then we're left to choose what to do next second line.

Kopetz: That's such a common situation that we see when we see a lot of these patients that have this *BRAF* V600E mutation will have progression on first-line therapy, which is something we don't normally see. Normally we at least get some disease debility, if not regression, on those first scans. So it can be one of our first reflections of just how aggressive the biology is. Again, as a general rule of thumb, we wouldn't necessarily exclude surgery for patients who have a *BRAF* V600E, but we would hold them to the exact same standards that we would for others. You have to have disease under control. It has to be a reasonably good biology to proceed forward with that.

There are a lot of discussions of 'well should we just, as a blanket statement, say no one with a V600E mutation should go to liver surgery.' And I say no, I wouldn't go that far, but we still need to pay attention to the biology, right. I think this is a good example of biology that's just not favorable, at the moment, and trying to think about how we can treat her systemically. I think in this setting now the cytotoxic chemotherapy has not worked, we're now in second line. We can really follow the biology and treat with targeted therapy. So, this is a patient that I would then offer encorafenib and cetuximab at this point.

Yaeger: I thought the same, and I also gave encorafenib and cetuximab second line. She did well with treatment and tolerated it well. After 3 months of treatment, imaging showed some modest decrease in the liver lesions, which remained overall still a relatively low volume. And she was seen by our liver surgeons who thought that the disease was resectable. She underwent resection of her liver metastases. Actually, after surgery, not knowing what to do, we ended up doing 3 more months of encorafenib and cetuximab to do 6 months. She didn't get so much FOLFOX to do a 6-month perioperative treatment. And she did well, and we watched her. But unfortunately, 8 months after surgery, liver recurrence occurred, speaking to the tough biology of this disease.

Kopetz: We also see a lot of nodal recurrence as well. So, even these patients who can clear the liver, sometimes you'll see these retroperitoneal nodes appear very commonly. But I think at the same time, it's worth acknowledging that for our liver resection patients, our goals of success aren't always about curing the patient. We'd love to do

that if we can, but I think we can say, at the same time, there's for this patent probably absolutely value in having those 8 months off of treatment and having the opportunity to, perhaps, recover a bit from her treatment and be in a better shape to take whatever treatments are coming next.

Yaeger: I chose another case with a patient who had some side effects with treatment for us to discuss the management of side effects with targeted therapy. This is another patient in my practice. This is a 42-year-old woman with metastatic *BRAF* V600E colon cancer. She initially presented with stage III disease but recurred quickly. Imaging soon after adjuvant therapy showed evidence of recurrence. She had received adjuvant FOLFOX treatment very close to when she was found to have recurrent disease. She received second-line treatment with encorafenib and panitumumab. She struggled with toxicity with the treatment.

She's young and active, and developed some dry skin, mild acneiform rash on her face but erythematous nodules on her arms and legs that were painful, and arthralgia with her upper shoulders and elbows that limited her. So my first question would be, thinking about the causes of these side effects and then how to manage them.

Kopetz: I think what you described is, of course, a very common pattern. The dry skin, acneiform rash can be attributed to the EGFR predominantly, but also there can be some components of that with the single-agent BRAF alone. It's interesting that anecdotally and, perhaps, looking at some of the non-randomized data out there would suggest that the combination of BRAF and an EGFR inhibitor may actually result in lower rates of acneiform rash in given patients. But again, for a given patient, the question is how to manage that, right. I think we would typically manage that in a way very similar to what we'd do for an EGFR inhibitor alone and trying to provide guidance regarding topical steroids for that as well.

As mentioned, the arthralgias and probably the erythematous nodules as well tend to be more of the *BRAF* type of pattern. And those, again the fault is to give the topical steroids, it's the dermatologist's first choice for many of these types of rashes, although, I must say I have not seen that erythematous nodularity respond quite as well to steroids as some of the acneiform based ones. Arthralgias we will typically try to treat conservatively with nonsteroidal anti-inflammatory drugs. As a first step, trying to do that avoiding treatment breaks, if needed, but there are some patients who do have to occasionally take treatment breaks and get the arthralgias back under control, but those tend to be fairly rare.

Yaeger: We sent her to the dermatologist to give us some guidance as well. The dermatologist thought that the nodular area, like you said, was likely related to encorafenib and that she was having toxicity from both agents. The arthralgias, as you mentioned, are related to the encorafenib, and the thought was since that was causing a big impact on her activity level, that our goal would be to try to manage it as best we can. So we ended up giving a low-dose steroid, which gave some relief. But we didn't want to continue that. And in this person who had progressed quickly after adjuvant therapy, we wanted to push the treatment, and we just started it. So, at the time it was before we were able to get binimetinib, and we added in binimetinib. The reason we did that because, exactly as you mentioned, that the EGFR antibody and the RAF inhibitor can have opposing effects.

Since it seemed that she was okay overall with the effect of the EGFR inhibitor, that adding maybe another agent to counter the effect of encorafenib might give us some support for the encorafenib-related toxicity that seemed to be limiting her. And so the idea is that perhaps the joints and perhaps there's some hyperproliferation of the skin due to activation of a pathway from encorafenib in the normal tissues. So we gave binimetinib, and with doing that, we were able to stop the steroids and get her to continue. And, exactly like you said, we did the supportive measures that we could to help with the acneiform rash. We had topical steroids, we had her limit sun exposure, and sometimes these side effects get better with some time. So we got binimetinib onboard, and a few weeks passed, and we reached a balance that we were able to continue treatment without actually having to reduce the other agents or delay.

Kopetz: That's fascinating, really interesting. I'm glad you found a good solution for her. I need to think about how we can use the biology to not only understand how to best address efficacy, but also the side effects. I think those are really fascinating bodies of research on these type of side effects. Great case, thank you.

So we'll end with a few viewpoints. I think that what we know is that there is a lot of work in this area. I think I highlighted some of the combinations being explored in the resistance to BRAF and EGFR, and we await some of those results. And I think there's even other strategies coming beyond that.

We're also aware of the phase 2 ANCHOR data that has looked at the triplet—again this was before the BEACON readout when the study was designed—but showing that there are higher response rates in first-line settings. The earlier that the targeted therapies are administered at least a trend toward improved outcome.

And that's set the stage then for the ongoing BREAKWATER trial, which is now asking the question do we even get better outcomes when we're administering these targeted

therapies in first-line treatment. So, this is a large study that both Dr. Yaeger and I have the privilege of being involved in. Over 800 patients to be enrolled. Patients are getting randomized among control chemotherapy; a provider's choice of FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI with or without bevacizumab; and a treatment arm of encorafenib and cetuximab alone, a targeted therapy only chemo-free arm; or the combination of encorafenib, cetuximab and either FOLFOX or FOLFIRI. The primary endpoint is progression-free survival, and again this is a study that's actively ongoing.

There are a number of other efforts being initiated, and we talked a little bit about some of the excitement around the hope about moving this into the adjuvant setting. There are studies looking at combinations with immunotherapy based on some of that transcriptomic associations and preclinical and early clinical data, as talked about before. I think the encouraging thing is this is a subset of patients for whom there is a lot of ongoing effort and research, and we certainly hope that we'll be able to build on the encorafenib and cetuximab backbone and our improved understanding of the biology in the future.

In conclusion, *BRAF* V600E–mutated metastatic colorectal cancer has a poor prognosis and now novel therapeutic options. Hopefully we've convinced you that *BRAF* testing should be done as part of a standard of care and should be done early in the treatment course. As Dr. Yaeger and I mentioned, we test this at the diagnosis of metastatic disease. Combination strategies to treat *BRAF* V600E in second or third line are now FDA approved, with encorafenib and cetuximab now FDA approved. And as discussed, encorafenib and panitumumab on the NCCN Guidelines. You should be aware of the side effects that can come with that, but these are ones that could be readily managed with conservative measures, as discussed.

We're excited by the future direction of the field, both first-line studies that are being initiated, adjuvant studies that are in late development, and the hope that we'll be able to have novel combinations to build upon encorafenib and cetuximab for metastatic patients.

So with that, thank you for your interest in this presentation and discussion. Thank you.

References

Ahronian LG, Sennott Em, Van Allen EM, et al. Clinical acquired resistance to BRAF inhibitor combinations in *BRAF*-mutant colorectal cancer through MAPK pathway alterations. *Cancer Discov*. 2015;5(4):1-10.

Benson AB, Venook AP, Al-Hawary MM, et al. NCCN Clinical Practice Guidelines in Oncology. Colon Cancer. v3.2021. ©2021 National Comprehensive Cancer Network, Inc. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.

Chu JE, Johnson B, Morris VK, et al. Population-based screening for *BRAF* V600E in metastatic colorectal cancer (mCRC) to reveal true prognosis. *J Clin Oncol*. 2019;37(15):3579.

Clarke CN, Kopetz ES. *BRAF* mutant colorectal cancer as a distinct subset of colorectal cancer: clinical characteristics, clinical behavior, and response to targeted therapies. *J Gastrointest Oncol.* 2015;6(6):660-667.

Corcoran RB, Atreya CE, Falchook GS, et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in *BRAF* V600-mutant colorectal cancer. *J Clin Oncol*. 2015;33(34):4023-4031.

Falchook GS, Millward M, Hong D, et al. BRAF inhibitor dabrafenib in patients with metastatic *BRAF*-mutant thyroid cancer. *Thyroid* 2015;25(1):71-77.

Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated *BRAF* in metastatic melanoma. *N Engl J Med*. 2010;363:809-819.

Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21(11):1350-1356.

Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations. *N Engl J Med*. 2015;373:726-736.

Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E–mutated colorectal cancer. *N Engl J Med*. 2019;381:1632-1643.

Kopetz S, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E metastatic colorectal cancer: updated survival results from a randomized, three-arm, phase III study versus choice of either irinotecan or FOLFIRI plus cetuximab (BEACON CRC). *J Clin Oncol*. 2020;38(15):4001.

Kopetz S, Desai J, Chan E, et al. Phase II pilot study of vemurafenib in patients with metastatic *BRAF*-mutated colorectal cancer. *J Clin Oncol*. 2015;33(34):4032-4038.

Kopetz S, Grothey A, Yaeger R, et al. BREAKWATER: randomized phase 3 study of encorafenib (enco) + cetuximab (cetux) ± chemotherapy for first-line (1L) treatment (tx) of *BRAF* V600E-mutant (BRAFV600E) metastatic colorectal cancer (mCRC). *J Clin Oncol.* 2021;39(15):TPS3619.

McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in *BRAF*(V600E) and *BRAF*(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014;15(3):323-332.

Misale S, Bozic I, Tong J, et al. Vertical suppression of the EGFR pathway prevents onset of resistance in colorectal cancers. *Nat Comm*. 2015;6:8305.

Morris V, Overman MJ, Jiang ZQ, et al. Progression-free survival remains poor over sequential lines of systemic therapy in patients with *BRAF*-mutated colorectal cancer. *Clin Colorectal Cancer* 2014;13(3):164-171.

Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced *BRAF*(V600)-mutated melanoma: a phase 1b study. *Lancet Oncol*. 2014;15:954-965.

Rowland A, Dias MM, Wiese MD, et al. Meta-analysis of *BRAF* mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for *RAS* wild-type metastatic colorectal cancer. *Br J Cancer* 2015;112(12):1888-1194.

Roth AD, Tejpar S, Delorenzi M, et al. Prognostic role of *KRAS* and *BRAF* in stage II and III resected colon cancer: results of the translational study on the PETACC-3, EORTC 40993, SAKK 60-00 trial. *J Clin Oncol*. 2010;28:466-474.

Sinicrope FA, Shi Q, Smyrk TC, et al. Molecular markers identify subtypes of stage III colon cancer associated with patient outcomes. *Gastroenterology* 2015;148:88-99.

Sinicrope FA, Shi Q, Allegra CJ, et al. Association of DNA mismatch repair and mutations in *BRAF* and *KRAS* with survival after recurrence in stage III colon cancers: a secondary analysis of 2 randomized clinical trials. *JAMA Oncol*. 2017;3(4):472-480.

Sanowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the *BRAF* V600E mutation in microsatellite-stable colon cancers. *Cancer Res*. 2005;65:6063-6069.

Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated *BRAF* V600E–mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. *J Clin Oncol.* 2021;39(4):273-284.

Tiacci E, Park JH, De Carolis L, et al. Targeting mutant *BRAF* in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. 2015;373:1733-1747.

Tie J, Gibbs P, Lipton L, et al. Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the *BRAF*V600E mutation. *Int J Cancer* 2011;128(9):2075-2084.

Tran B, Kopetz S, Tie J, et al. Impact of *BRAF* mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer* 2011;117:4623-4632.

Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422.

Van Cutsem E, Tabernero J, Taieb J, et al. ANCHOR CRC: results from a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated *BRAF* V600E–mutant metastatic colorectal cancer. *Ann Oncol*. 2021;32(3):S222.

Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. *Ann Oncol*. 2018;29(1):44-70.