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Sorting Through the Complexities of Managing Metastatic Colorectal Cancer: Strategies for Individualizing Treatment

Announcer Open:
Welcome to CME on Reach MD. This activity titled, Sorting Through the Complexities of Managing Metastatic Colorectal Cancer: Strategies for Individualizing Treatment, is provided by Partners for Advancing Clinical Education, PACE, and supported by an educational grant from Merck Sharp and Dohme, LLC and Seagen. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Ms. Sims:
Welcome back. We have a great topic coming up now for us and I'm happy to introduce our speaker, where the topic is, Sorting Through the Complexities of Managing Metastatic Colorectal Cancer: Strategies for Individualizing Treatment. And we're lucky today to have a wonderful speaker, Dr. Robert Lentz. He's Assistant Professor of Medicine at the Department of Medicine and the Division of Medical Oncology at the University of Colorado School of Medicine and Cancer Center in Aurora, Colorado, and welcome, Dr. Lentz.

Here are his disclosures.

And I'll just remind you all of our learning objectives for this session today. We'll try to - he will summarize current guideline recommendations for biomarker testing for patients with mCRC and identify novel treatment strategies appropriate for individuals with – based on patient and disease-related factors, and apply recommended steps to monitor for and manage treatment-related adverse events. We always start with a pretest. So, I'll have you get your polling skills ready.

Dr. Lentz:
Thanks, Terran. Good morning. Good afternoon, everybody. Great to be here today with you talking about metastatic colorectal cancer. So, as you probably know, this is a common and deadly disease. Colorectal cancer is the third most common cancer, as well as the third leading cause of cancer death in the United States. While you can see that new cases and deaths are overall decreasing in the figure in the left, the incidence and mortality are actually increasing in patients younger than the age of 50. And this is termed early onset colorectal cancer. The reasons for this are still being worked out. But it probably has to do with factors that include things like metabolic syndrome, physical inactivity, and the Western diet.

The 5-year survival for all stages of metastatic - of colorectal cancer has increased from 50 to 65% over the last several decades. But in the metastatic setting, 5-year survival remains poor at only about 14%. Because of the increasing incidence of early onset colorectal cancer, the USPSTF recently recommended lowering the age where colorectal cancer screening begins to 45 for patients without an increased risk based on family history. The recommended initial workup for colorectal cancer includes colonoscopy, bloodwork including the tumor marker CEA, a CT scan of the chest, abdomen, and pelvis, and a biopsy, which would often be via colonoscopy, but could also be of a metastatic site if there is suspicion of metastatic disease, as well as molecular biomarker testing, which we will explore in much more detail.

So, I'll turn it back to Terran for a case.

Ms. Sims:
Great. Here's our first case study. Kim, a 48-year-old, works full-time as an office manager and is married with two daughters younger than 12. Her family history reveals her father was diagnosed with colon cancer at age 63, and her paternal grandmother died of endometrial cancer at 52. She reported experiencing intermittent rectal bleeding for the past 3 months, and a recent chest x-ray revealed the presence of several lesions in her lungs. The assessment of Kim reveals a metastatic colorectal cancer characterized by primary

right-sided colon cancer with synchronous metastasis to the liver and lungs. She's not a candidate for surgery, and no other comorbidities are identified. She has a biopsy of the primary tumor, and liver metastasis shows no carcinoma and a high level of immune filtrate, molecular testing by NGS shows negative for KRAS, NRAS mutation, HER2 EBBR2 amplification, and NTRK fusion. She's positive for BRAF V600E mutation and MISH dMMR. She expressed concern regarding the potential impact of chemotherapy on her ability to continue working.

We'll start with a question about Kim. Which of these is the recommended initial treatment for Kim? And the best answer is D: Pembrolizumab. And we know that our speaker will help us out with this. And I'll turn it back over now to Dr. Lentz.

Dr. Lentz:
Thanks, Terran. Colorectal cancer in the metastatic setting is increasingly becoming a highly personalized treatment. In other words, because of all of these molecular tests that can be performed, and because of an increasing number of drugs that we have at our disposal to target these specific molecular alterations, it's very important to ensure that your patients are undergoing the appropriate molecular testing so that we can tailor the best treatments to the specific tumor that the patient has. And a lot of these mutations as well as drugs, probably sound like alphabet soup, a lot of abbreviations, a lot of complicated drug names. And so, the goal of much of our time today is to talk about these and hopefully make that more clear.

Regardless of stage, all patients with colorectal cancer should have testing for microsatellite instability, abbreviated MSI, and/or mismatch repair, abbreviated MMR. If a patient is microsatellite instability high or deficient in the mismatch repair proteins, that is a biomarker of response to standard of care immune checkpoint inhibitors, targeting the PD-1 and/or CTLA-4 axes, for example, pembrolizumab, as we saw in this case. MSI and MMR are both looking at a similar phenotype in the tumor. MSI testing is performed via PCR, and mismatch repair testing is performed via immunohistochemistry. And there's a very high correlation between the two. And so typically, we only need to perform testing for one or the other.

And then everything else that is on this slide are recommended tests for patients who have metastatic disease. This includes RAS mutations, KRAS, NRAS. And if there is a KRAS or NRAS mutation, this confers that EGFR inhibitor therapy is unlikely to be effective. A BRAF V600E mutation confers eligibility for a BRAF inhibitor, encorafenib, in combination with an EGFR inhibitor, cetuximab or panitumumab. NTRK fusions are rare in colorectal cancer, but they actually occur more commonly in patients who have deficient mismatch repair tumors and confer eligibility for NTRK inhibitors, larotrectinib, for example. HER2 amplification is present in several percent of patients with metastatic CRC and confers eligibility for anti-HER2 therapy, and fortunately, there are now four different combinations that we have at our disposal in this setting.

Importantly, anti-HER2-directed therapies are only likely to be effective if the patient is wild-type for RAS and BRAF. If a RET fusion is detected, the patient could be treated with standard of care, selpercatinib.

And so, in the metastatic setting, it's recommended to do all of this testing via large panel-based next generation sequencing, preferably on a tumor biopsy. But if this is not possible, a liquid blood-based biopsy can be performed.

I'll also point out that specifically for HER2, we usually detect an amplification on next generation sequencing because IHC or FISH are not commonly performed in colorectal cancer, contrary to something like breast cancer, so it's important to make sure that the patient did actually have NGS that included evaluation for a HER2 amplification, and if not, then IHC or FISH should be ordered.

This slide shows the frequency of many of these molecular alterations in metastatic colorectal cancer. BRAF V600E occurs in about 7.5%, HER2 amplification in about 3%, NTRK fusions are very rare.

I mentioned the importance of immune therapy in patients who are MSI high but unfortunately, this only occurs in 5% of tumors. In other words, 95% of patients with metastatic CRC do not derive benefit from standard of care immune checkpoint inhibitors. About 40% of patients with metastatic CRC have a KRAS mutation. There are two drugs, sotorasib and adagrasib, which we will touch on later, that can be used in patients that specifically have a KRAS G12C mutation. This is a minority of patients among the KRAS mutations. And so, if a patient does not have a G12C mutation, those two drugs cannot be used because they are ineffective.

So, to summarize this section, universal MSI and/or MMR testing is recommended for patients with colorectal cancer of all stages. And I mentioned that MMR is detected via immunohistochemistry and MSI is detected via next generation sequencing. All patients with metastatic disease should undergo broad panel-based testing for the mutations and alterations listed on the slide, among others. And tumor tissue biopsy is preferred, but if there's insufficient tumor tissue, a liquid blood-based biopsy is acceptable. The first learning objective here is to perform MSI and/or MMR testing on all patients diagnosed with colorectal cancer. And if a patient is MSI high and/or deficient MMR, this confers for benefit of standard of care immune checkpoint inhibitors, such as pembrolizumab in the metastatic setting.

I'll turn it back over to Terran.

Ms. Sims:
Great. So, here's a question for us now. Which of the following is the significance of dMMR MSIH in selecting therapy for metastatic colorectal cancer? So, the best answer is D: Indication for immune checkpoint inhibitors. And it looks like 75% of you all got that right, so we definitely learned something in that section of the presentation. Thank you, Dr. Lentz. And I'll turn it back over to you.

Dr. Lentz:
Okay, thanks so much. So, tumor sidedness is another prognostic factor, and this refers to right versus left side of the colon, with right-sided disease being the ascending colon and transverse colon up to the splenic flexure, and a left-sided tumor being at or distal to the splenic flexure.

For reasons that are not entirely understood, right-sided tumors confer a worse prognosis and are more commonly associated with Lynch syndrome. So MSI high, Lynch syndrome being the hereditary form of MSI high and are also more likely to have KRAS or BRAF mutations. Also for reasons that we don't understand, the EGFR inhibitors, cetuximab and panitumumab, do not appear to work in patients with a right-sided tumor. On the contrary, a left-sided cancer is associated with a more favorable prognosis, and the EGFR inhibitors can be used as long as the patient is wild-type for RAS.

There are many considerations to select the optimal treatment in your patients with metastatic CRC as including factors such as clinical status, like prior treatments, comorbidities, performance status, and age; tumor characteristics, such as the tumor burden, resectability, and sidedness as we just mentioned; the molecular characteristics as we have discussed in detail; as well as patient-centered factors, like preferences for aggressiveness of therapy, or side effect profile, or psychosocial factor.

To summarize this section, consider tumor characteristics, prior treatments, responses, and the patient's current status and goals when selecting therapy for metastatic CRC.

We are fortunate to have many treatments at our disposal for metastatic CRC. And many of the drugs on this slide have contributed to the improvement in overall survival as I showed you at the beginning of our session. And so, the top table here depicts the initial recommended therapy for patients with metastatic CRC who have not previously received treatment who are appropriate for intensive therapy.

And so, I'll go left to right in this table. In most patients, we use a two-drug – two chemotherapy-drug cytotoxic backbone, most commonly FOLFOX but this could also be CAPOX or FOLFIRI; all of them are equivalent in terms of efficacy. And patients who are often young and/or healthier and/or desire to be more aggressive, a triple cytotoxic regimen such as FOLFIRINOX or FOLFOXIRI can be used. Both of these regimens, FOLFIRINOX and FOLFOXIRI, use the same chemotherapy drugs, 5-FU, irinotecan, and oxaliplatin but the doses are different. And in the U.S., FOLFIRINOX is preferred. It has a lower dose of 5-FU, which American patients tolerate better.

And then we typically add a biologic agent to the chemotherapy backbone, either an EGFR inhibitor or the VEGF inhibitor, bevacizumab. As a reminder, patients are eligible for an EGFR inhibitor if they have left-sided disease, and also a RAS/RAF wild-type. So, in that situation, I would recommend adding cetuximab or panitumumab to the chemotherapy backbone. If they're not eligible for an EGFR inhibitor, I would add bevacizumab as long as there are no contraindications, for example, recent thrombosis, uncontrolled hypertension, or bleeding problems.

What I just described is the initial treatment in patients with microsatellite stable disease, again the 95% of patients who will have MSS disease. If a patient has microsatellite instability high cancer, the immune checkpoint inhibitors, as I'll show you on the subsequent slides, have really revolutionized the treatment of this cancer, improving outcomes compared to chemotherapy, most commonly either with pembrolizumab or nivolumab, with or without ipilimumab. Pembrolizumab and nivolumab are both anti-PD-1 agents, and ipilimumab is an anti-CTLA-4 agent. So, if a patient has untreated MSI high colorectal cancer, the initial treatment recommendation is an immune checkpoint inhibitor, as we saw in the case that we examined thus far.

The bottom table shows recommended therapy in patients who are not appropriate for intensive therapy due to age or comorbidities, for example. And in this case, we would typically use a single chemotherapy drug, 5-FU or capecitabine, with or without a biologic agent. So, bevacizumab or an EGFR inhibitor could be appropriate here as well, based on the same factors, mutational status and tumor sidedness. The EGFR inhibitors also have single-agent activity, as shown in the middle of the bottom table. So that's also an option. And if a patient has HER2-positive disease, HER2 inhibitors, as we'll look at more momentarily, are also an option in the untreated setting. The immune checkpoint inhibitors are similarly well tolerated in patients who are not appropriate for, quote unquote, intensive chemotherapy if they are MSI high or deficient MMR, just like patients who have better functional status to begin with.

To summarize, this is the PARADIGM study, which was presented at ASCO last year, and actually just published about a week ago, which asked the question: In untreated patients who have left-sided RAS wild-type disease, is the addition of an EGFR inhibitor, panitumumab or bevacizumab, superior when added to standard FOLFOX chemotherapy? And what you see here is that panitumumab rather than bevacizumab improved survival by about 3.5 months, with a very high response rate of 80%. And so, if a patient is eligible, I would recommend the addition of an EGFR inhibitor to chemotherapy rather than bevacizumab in the first line.

I will turn to looking at data for MSI high tumors treated with immune therapy. So, this is KEYNOTE-177, which was presented first in 2021 and really revolutionized the treatment of MSI high colorectal cancer, and led to a paradigm shift in treating these patients with first-line chemotherapy to what the current standard of care is, treating them with a first-line immune checkpoint inhibitor. So, what you see here is pembrolizumab versus chemotherapy in MSI high untreated patients in the metastatic setting. Pembrolizumab is in green, chemotherapy is in blue. On the left, you see a doubling of progression-free survival with pembrolizumab versus chemotherapy, 16 versus 8 months. On the right, overall survival trends towards improvement with pembrolizumab versus chemotherapy. But it's not statistically significant, likely due to an approximately 60% crossover rate from patients initially treated with chemotherapy to immune therapy after that, which of course narrows that difference. So, this is oftentimes the immune therapy drug that is recommended in the first-line setting for patients with MSI high CRC. Importantly pembrolizumab versus chemotherapy not only improved progression-free survival, but also improved quality of life. And patients treated with pembro had fewer severe adverse events compared to those with chemotherapy. So, this is usually well tolerated, again, even in patients who are older and/or with more comorbidities.

Another option in patients with MSI high disease is nivolumab with or without ipilimumab. And so, this is the CheckMate 142 trial. This was not a randomized trial. This was a phase 2 study that enrolled patients with MSI high CRC to either first-line nivolumab plus ipilimumab in blue, or second-line nivolumab in orange alone, or nivolumab plus ipilimumab in green. And what I'll highlight is the first-line data. So, we're looking at the blue curve here, nivolumab plus ipi, and you see an objective response rate of 69% with this combination, 2-year PFS of 75%, 2-year overall survival of 79%. Nivolumab plus ipilimumab has not been directly compared to pembrolizumab. And so, we don't know details on that direct comparison. We do know that in cross-trial comparisons, which of course have their limitations, objective response rate is higher, 69% with ipi/nivo, versus about 45% with pembrolizumab. And so again, if a patient is younger, healthier, desires a higher response rate, you may opt for ipi/nivo rather than pembro. But the trade-off there is that there are more side effects likely with ipi/nivo compared with pembro, and that is often in the form of colitis.

So, this slide summarizes what we have discussed so far, showing immune checkpoint inhibitor options in metastatic CRC. Dostarlimab is another anti-PD-1 immune checkpoint inhibitor that does have approval for previously treated patients, MSI high patients. It is not as commonly used, but it is an option as well.

So, to summarize this section, be aware of the recommended treatment settings and associated molecular markers for use of immune checkpoint inhibitors in metastatic CRC. I'd also like to add here that, as you probably know, MSI high and/or deficient MMR can occur in either an inherited setting, so Lynch syndrome, or an acquired setting where there is a mutation in the tumor that generates or leads to that MSI high phenotype. And the most common route of a somatic or acquired MSI high phenotype is by way of a BRAF V600E mutation, because that BRAF mutation actually leads to methylation of one of the mismatch repair proteins, which suppresses its expression, creating that deficient mismatch repair phenotype. And so, if you see a patient that is MSI high plus a BRAF mutation, like we see in the case of Kim, that is essentially never Lynch syndrome, that is an acquired pattern. And these patients can be treated first with an immune checkpoint inhibitor, and then in the second line they could actually be treated with BRAF-targeted therapy, encorafenib plus cetuximab.

I'll turn it back to Terran for the case.

Ms. Sims:
Great. Thank you. So, here's Kim. You prescribed pembrolizumab and tell her that she can receive a treatment infusion either 200 mg every 3 weeks, or 400 every 6 weeks. You both think less frequent visits to the infusion center would be helpful and she begins treatment with 400 mg every 6 weeks. After two cycles of pembrolizumab, a follow-up CT scan reveals a partial response. However, Kim reports 3 or 4 bowel movements daily, more than she used to, and she has no pain or bloating. Testing ruled out infection and you determine that she has grade 1 colitis related to her treatment.

So, here's a test. What would be your recommendation for management of Kim’s grade 1 immune-related colitis? And the best answer is: Continue pembrolizumab and consider supportive loperamide, and we'll push on and let Dr. Lentz talk to us about that. Dr. Lentz?

Dr. Lentz:
Thank you. Immune-related colitis is very common, as looks like most of you are familiar with. The immune-related adverse events related to immune therapy are unpredictable, and in both what organ they affect and also timing. So, how I describe this to my patients is that immune-related adverse events occur in response to the immune therapy, when there's activation of the body's immune system.

And instead of killing tumor cells, it turns on, so to speak, the body's own organs. And so, this is really autoimmune disease due to treatment, which can affect any organ system in the body, as you see in the figure on the right here. We don't have any way to predict currently who will develop immune-related adverse events and how severe they will be, and what organs they will affect.

And interestingly, these immune-related adverse events can occur at any time during immune therapy, and sometimes even years after starting, and sometimes even after the immune checkpoint inhibitor is no longer being given. The most common onset is 2 to 3 months after starting, and the most common organ systems affected would be thyroid, hypothyroidism, colon, so colitis, and skin, most commonly with a low-grade maculopapular rash. Most commonly, these are mild, grade 1, and can be managed with pills or creams. But in approximately 10 to 20% of patients treated with immune therapy, they can be severe or life-threatening.

And, of course, patients need to be educated that the side effect profile of immune checkpoint inhibitors is often very different than with chemotherapy. And so, if they start experiencing any new symptoms on an immune checkpoint inhibitor, they should reach out to clinic because these are much easier to manage if recognized earlier rather than later. If immune-related adverse events are suspected, a complete workup including lab tests is necessary to rule out other often more common causes as well.

So, this is an example of recommended management of immune-related colitis as we saw in this case. So, grade 1 colitis or diarrhea is an increase of less than 4 stools per day from baseline or a mild increase in ostomy output. In this case, it's important to rule out infection, most commonly C. diff, continue the immune checkpoint inhibitor, and treat symptomatically with drugs like loperamide and fluids. If the diarrhea is more severe, so an increase of 4 to 6, or sometimes that's 10 to 15 stools per day, it's important to hold the immune checkpoint inhibitor and treat with steroids, usually starting with prednisone or prednisone equivalent of 1 mg/kg daily, followed by a slow taper over 4 to 6 weeks, as well as involvement of gastroenterology, often a flex sig or colonoscopy is done to help evaluate the severity of the disease microscopically.

If patients are not improving on steroids a quick escalation, of just a couple days later of biologic therapy, is necessary. This is often with infliximab or vedolizumab, or sometimes an increase in the steroid dose. And so, as severity increases, it becomes more likely that permanent discontinuation of the immune checkpoint inhibitor would be necessary.

I'll also mention here that there are great references for how to manage not only colitis, but all of the immune-related adverse events and references on the slide here, a publication from JCO. This platform, I believe, also has different recommended guidelines for immune-related adverse events.

So back to the case for Kim.

Ms. Sims:
Great. Thank you. So following initiation of loperamide and supportive care with fluid management and hydration, the symptoms of colitis resolved. Kim continued pembrolizumab throughout. At 18 months following initial administration on pembrolizumab, Kim experiences disease progression. And because her tumor is positive for BRAF V600E, Kim receives encorafenib and cetuximab as her next line of therapy. She responds to treatment and tolerates it well and she remains progression free at 3 months on follow-up.

This is our other case, James. James is 74 years old and has been diagnosed with metastatic CRC with metastases to the lungs and liver, and left-sided sigmoid colon adenocarcinoma. He has molecular testing with NGS including MSS, RAS wild-type BRAF WT ER BT2 [28:22] and amplification. The treatment history is achieved CR on the first line FOLFOX plus bevacizumab. He presents today with progressive disease on PET/CT imaging, and his ECOG performance status is 1. Which of these is a recommended option for James' next therapy? And the best answer is D: Trastuzumab plus tucatinib, and I'll put it back over to Dr. Lentz.

Dr. Lentz:
Thanks, Terran. In patients who progress on first-line therapy, we still have many drugs at our disposal that have been shown to improve outcomes, including survival. However, as you can see in the figure on the right, fewer patients receive subsequent lines of therapy compared to initial chemotherapy or targeted therapy as appropriate, usually because of things like worsening symptom burden and declining performance status. So, it's really important again here to consider patient-related factors when selecting later lines of therapy. This slide summarizes the preferred subsequent therapy, again based on the molecular profile, so I can't emphasize enough how important the molecular profile is.

I'll go left to right in this table. So, in patients who are RAS BRAF wild-type who are naïve to an EGFR inhibitor, but are able to receive it because their tumor is on the left side, we would recommend an alternate cytotoxic chemotherapy. So, if they got FOLFOX initially, we'd recommend FOLFIRI or irinotecan alone in the second line plus an EGFR inhibitor. If a patient has a BRAF V600E mutation, we would recommend the BRAF inhibitor, encorafenib, plus an EGFR inhibitor in the second line. If patient is MSI high and did not receive immune checkpoint inhibitor in the first-line setting, immune checkpoint inhibitor therapy should be used in the second-line setting with the same options as we looked at previously.

If a patient is HER2-positive, so they have the HER2 amplification or HER2 overexpression, there are four potential treatment options, a trastuzumab plus lapatinib, trastuzumab plus pertuzumab, or trastuzumab plus tucatinib. The fourth option is the antibody drug conjugate, trastuzumab deruxtecan, and we have a whole slide dedicated to this later on. In the rare instance where you detect an NTRK fusion, the NTRK inhibitors, entrectinib or larotrectinib, can be used.

Finally, if a patient is not eligible for any of these targeted therapies, so they received chemotherapy plus bevacizumab in the first line, it would be recommended to switch types of chemotherapy, so FOLFOX to FOLFIRI, for example, and continue the bevacizumab in the second-line setting even beyond progression, because that has been shown to improve outcomes.

This slide shows the BEACON study, which led to the approval of encorafenib and cetuximab for BRAF mutated CRC in the second-line or beyond setting. And so, we'll start on the right here, in orange shows overall survival for patients treated with encorafenib and cetuximab, versus second-line chemotherapy, which was irinotecan based plus cetuximab. There was an improvement in survival with a hazard ratio of 0.6 with the BRAF inhibitor combination. So, this is what is recommended.

Initially, which sometimes leads to confusion, the triple combination of encorafenib plus cetuximab plus the MEK inhibitor, binimetinib, was actually approved by the FDA about 2 years ago. But in longer follow-up, it was realized that the addition of binimetinib to the double combination did not improve outcomes and increased toxicity. So again, encorafenib plus an EGFR inhibitor in the second-line setting for a patient who has a BRAF V600E mutation.

This slide summarizes the HER2 targeted therapies. So trastuzumab and pertuzumab are both monoclonal antibodies directed at HER2. You're probably familiar with these potentially from the breast cancer or gastric cancer space. Lapatinib and tucatinib are both tyrosine kinase inhibitors, so pills. And trastuzumab deruxtecan is an antibody drug conjugate. This includes two components. The first is an antibody, trastuzumab directed at HER2. The second is actually a cytotoxic payload, that's the deruxtecan. And so, when this compound binds to the tumor cell, it gets taken up inside the tumor cell, the cytotoxic payload is released, hopefully with the goal of killing the tumor cells. These combinations have not been compared head to head, so we don't have that data. But we do have promising response rates and survival reported for all of these in their individual studies, as you can see on the right.

The most promising combinations so far comes from the MOUNTAINEER study with tucatinib plus trastuzumab, the third entry in this table, with a response rate of 38% in previously treated patients, and a median overall survival of 24 months. So, while we don't know exactly which one of these is best, I will often start with trastuzumab and tucatinib for a patient who has not received a prior HER2-directed therapy. It's also important to note that the addition of trastuzumab or pertuzumab alone to standard chemotherapy is ineffective. So, we would not add trastuzumab to FOLFOX or FOLFIRI, for example.

There are some unique side effects with these drugs of course, one of them is heart failure, as you may be familiar with from the breast cancer space, and so it's recommended to follow these patients at baseline with an echocardiogram as well as periodically during treatment. Interstitial lung disease is a very important toxicity as we saw in one of the case questions so far with trastuzumab deruxtecan, and occurred in 9% of patients, and actually was fatal in several patients. So, if a patient has new pulmonary symptoms, it's very important to hold trastuzumab deruxtecan and evaluate for suspected interstitial lung disease as shown in the algorithm here. This would include high-resolution CT, pulmonary consult, and excluding infections. If there is a grade 1 ILD, which is actually asymptomatic with just imaging findings, you need to hold trastuzumab deruxtecan until it fully resolves and treat with steroids with a taper. If there is grade 2 or worse interstitial lung disease, as we saw in this patient, and that is any symptoms related to ILD with imaging findings, the drug needs to be permanently discontinued. Steroids are used, usually prednisone at 1 mg/kg daily, followed by a taper over at least 1 month.

This slide is mostly for your reference. It details additional treatment options for the rare alterations that you may encounter. So again, a RET fusion can be treated with selpercatinib, and an NTRK fusion can be treated with entrectinib or larotrectinib.

Ms. Sims:
Alright. So, which of these is the recommended second-line option for patients with BRAF V600E mutated mCRC? And so, the best answer is B: Encorafenib plus cetuximab. Thank you. And the rationale is here on the screen. Dr. Lentz, did you want to comment on that?

Dr. Lentz:
Yeah, it looks like the next most common answer was trastuzumab/pertuzumab, which is an option for HER2 amplification or overexpression. So, I think the easiest way to remember that encorafenib is for BRAF mutation is the RAF in the name. It's a bit of word soup with all these complicated names, but encoraf is for BRAF.

Ms. Sims:

Great. And here's another question: What is the most appropriate next step with trastuzumab deruxtecan if grade 2 interstitial lung disease is suspected? So, the best answer here is to permanently discontinue the drug, start steroid, and obtain a pulmonary consult. And I think Dr. Lentz has really emphasized that for us here today. Thank you. That's wonderful. Dr. Lentz, I'll turn it back over to you.

Dr. Lentz:
So, in the third-line and beyond setting, there are two additional options, regorafenib and trifluridine/tipiracil with or without bevacizumab. While these are options, they don't work well. Unfortunately, response rates are only several percent, and they improve survival by not more than several months compared to best supportive care. So regorafenib is a pill and it can cause side effects such as hand-foot syndrome, diarrhea, hypertension. And in order to reduce the severity of side effects upon initiation, it's recommended to start at 80 mg daily and increase weekly by 40 mg up to the recommended final dose of 160 mg per day. This is based on the ReDOS study as listed on the slide. And this has been shown to reduce side effects without compromising efficacy. Trifluridine/tipiracil on the right is also a pill which can be combined with bevacizumab, as I'll show you on the next slide. Common adverse events with this include neutropenia, anemia, and GI upset.

This is the SUNLIGHT study, which was just presented at GI ASCO this year, where the investigators looked at the addition of bevacizumab to trifluridine/tipiracil alone. And so, in blue is trifluridine/tipiracil plus bevacizumab, and in green is trifluridine/tipiracil alone. You can see that the addition of bev improves overall survival on the left, as well as progression-free survival on the right. Objective response rate with this combination is still only 6%. And so, usually in the third-line and beyond setting we prefer clinical trials if they're available.

I mentioned that therapy for KRAS G12C mutant cancer is really evolving. Unfortunately, only 3 to 4% of patients with metastatic CRC have a KRAS G12C mutation. If they do, adagrasib or sotorasib can both be used. These are approved by the FDA for patients with lung cancer and a KRAS G12C mutation, and they can be used off label here. The best data so far comes from the combination of adagrasib, the KRAS G12C inhibitor, plus the EGFR inhibitor, cetuximab, with a response rate of 46%, as you can see in the table on the right. There are ongoing studies of both sotorasib and adagrasib in combination with EGFR inhibitors in bigger trials, and clinical trials are further evaluating drugs that can target all KRAS mutations, not just G12C. So, I would use adagrasib or sotorasib in combination, preferably with an EGFR inhibitor, if a patient is in the third-line or beyond setting, potentially, you could talk about it with your patient for the second line as well. We just don't have all of that data yet.

So, to summarize this section, individualizing later line therapy in refractory metastatic CRC, novel tumor agnostic treatments offer benefit for patients with certain mutations, RET, NTRK, KRAS G12C. There are two pills that are approved in the third-line and beyond setting, regorafenib and trifluridine/tipiracil, the latter of which is ideally combined with bevacizumab. Unfortunately, these are minimally effective, but they are options if patients don't have access to clinical trials. The side effects vary, of course, between these interventions, and the same patient and disease-related factors should be considered when selecting therapy in this setting. And again, to emphasize this point, educate patients on clinical trial options and refer for clinical trials where appropriate. We need better treatment options in refractory CRC. To summarize further, choose the later line therapies based on patient factors and adverse event profiles of therapy. Finally, to improve adherence to oral therapy in later lines, it's important to have a strategy in the clinic or the group to help patients really understand the importance of adhering to these drugs, and also reporting side effects frequently because they may not be seen in clinic as often. And oftentimes, digital tools such as patient portals may help patients report side effects and also get in touch with the office sooner rather than later. Educate patients and their caregivers about the importance of adherence to oral therapies and optimizing treatment outcomes.

And finally, this is the last summary slide before a few questions, is the action plan. To summarize our talk today, perform MSI and/or MMR testing on all patients regardless of stage who are diagnosed with colorectal cancer. Consider tumor characteristics, prior treatments, responses, and the patient's current status and goals when selecting therapy. Be aware of the recommended treatment settings and associated molecular markers for use of immune checkpoint inhibitors. Choose later line treatments based on patient factors and adverse event profiles of therapy. And as we just discussed, educate patients and their caregivers about the importance of adherence to oral therapies and optimizing treatment outcomes.

I'll turn it back to Terran for a few post-test questions.

Ms. Sims:
Great. We do have a couple of questions, Dr. Lentz, so I'll move on to those. Here's a question from Prima, which says: Is it true that right-sided tumors are more common in older patients and left-sided more common in younger?

Dr. Lentz:
Yeah, it's a good question. Rectal cancers, as I mentioned that early onset colorectal cancer is increasing in frequency. And many of these cancers are rectal cancers, which are included in left-sided - in the left side of the colon classification. So yes, we are seeing more

left-sided disease in younger patients because of the rectal cancer, compared with right-sided disease which may arise in older patients. The only caveat there is that MSI high tumors which can occur in young people can also be right-sided more frequently than left-sided. But that is not a very high proportion of colorectal patients overall.

Ms. Sims:
Great. And one more question, Dawn says: Is there a time situation where you would repeat molecular testing?

Dr. Lentz:
Usually not. The molecular profile of colorectal cancer minimally changes over time, so I would not rebiopsy on progression in order to understand a new molecular profile of the cancer. This is commonly done, I believe in lung cancer, looking for resistance mutations.

The one area where this is evolving is with the use of EGFR inhibitors. And so, one evolving strategy is actually to repeat a liquid biopsy, a blood-based ctDNA assay, to look for KRAS, NRAS, BRAF, or other mutations which may confer resistance or susceptibility to an EGFR inhibitor. So, if a patient is RAS/RAF wild-type, they get an EGFR inhibitor in the first line, you'll often find if you do ctDNA after that, that they've developed a resistance mutation, which makes sense. But then if they go on to a subsequent line of therapy that does not include an EGFR inhibitor, oftentimes you'll see that resistance mutation has resolved. So, you may actually be able to reinitiate the use of an EGFR inhibitor after prior progression, if supported by the molecular profile.

Ms. Sims:
Great. Thank you so much. And Dr. Lentz, I want to thank you for a wonderful presentation. You certainly helped me make sense of the need for molecular testing, but also how to sort that out in terms of treatment options and side effect profiles. Thank you again.

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