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BRAF-Mutant Metastatic Colorectal Cancer: Characteristics & Challenges

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Announcer:
Welcome to ReachMD. This medical industry feature, titled "*BRAF*-Mutant Metastatic Colorectal Cancer: Characteristics & Challenges" is sponsored by Pfizer.

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Here's your host, Dr Jennifer Caudle.

Dr Caudle:
Welcome to our program. Today we're going to be talking about *BRAF*-mutant metastatic colorectal cancer, or CRC.

I'm your host, Dr Jennifer Caudle, and joining me today is Dr Dustin Deming. Welcome, Dr Deming!

Dr Deming:
Thank you so much, Dr Caudle. I'm thrilled to be here today.

Dr Caudle:
So let's start with an overview, because the estimated SEER data for 2020 indicate that CRC is the fourth most common cancer in the United States.

And despite improvements in screening, early detection, and treatment—which have contributed to an overall reduction in annual deaths from CRC—CRC is second only to lung cancer as a cause of cancer mortality.

It's estimated that there will be approximately 150,000 new cases of CRC by the end of 2020, and almost 33,000 will be metastatic.

Now, we know that chemotherapy regimens with or without biologics have helped to extend overall survival for many patients with metastatic CRC. But as you well know, Dr Deming, these regimens have limited efficacy for a subset of patients with metastatic CRC, including those patients with *BRAF* mutations.

Can you elaborate on this subset of patients?

Dr Deming:
Yes. We know that up to 15% of patients with metastatic CRC harbor the *BRAF* V600E mutation, which is the most frequently occurring *BRAF* mutation.

BRAF mutations have been shown to have negative prognostic value in metastatic colorectal cancer. That is, the presence of *BRAF* mutations in this subset of patients is an indicator of the potential for worse clinical outcomes.

For example, in a molecular subgroup analysis of a large Phase 3 study comparing first-line treatment with triplet chemotherapy plus a biologic to doublet chemotherapy plus the same biologic, patients with *BRAF*-mutant metastatic colorectal cancer experienced approximately 6 to 8 months of progression-free survival, or PFS. This PFS was approximately half that of those who were *BRAF* wild-

type. Ultimately, patients in this study who had *BRAF*-mutant metastatic CRC also had greatly reduced median overall survival, compared to patients who were *BRAF* wild-type.

Patients with *BRAF* V600E–mutant metastatic CRC have also been shown to have high rates of attrition after first- and second-line treatment. In one population cohort study of close to 1900 patients with metastatic CRC, about 11% of patients found to have a *BRAF* V600E mutation received third-line treatment.

Dr Caudle:
Has it been your observation that *BRAF*-mutant CRC is a distinct molecular subtype of CRC?

Dr Deming:
Yes, we do know that *BRAF* mutations activate the mitogen-activated protein kinase pathway, or MAP kinase pathway, downstream from EGFR.

The MAP kinase pathway—or the RAS/RAF/MEK/ERK signaling cascade—drives cell proliferation, differentiation, and survival.

BRAF V600E mutations activate BRAF kinase activity, which in turn leads to phosphorylation and activation of the MEK1 and MEK2 kinases and sustained cell proliferation and survival.

Dr Caudle:
Now let's talk about the phenotypic characteristics associated with *BRAF* V600E–metastatic CRC.

You know, one major caveat here is that all patients with metastatic CRC should be tested for a *BRAF* mutation at diagnosis, not just those with the phenotypic characteristics that we're about to discuss.

With that in mind, Dr Deming, can you tell us about some of the phenotypic characteristics associated with *BRAF*-mutated metastatic CRC?

Dr Deming:
Although *BRAF* wild-type tumors can be found throughout the colon and rectum, *BRAF*-mutated tumors are often found in the proximal colon, which we refer to as right-sided disease.

Actually, about 1 in 3 patients with *BRAF*-mutant metastatic CRC has a tumor located on the left side of the colon. Therefore, it is important to note that patients with left-sided disease should still be tested for the presence of a *BRAF* mutation, and the same treatment guidelines should be followed.

BRAF-mutant tumors are also more likely to be stage T4, with multiple metastatic sites that have invaded an adjacent organ or penetrated the visceral peritoneum and have a serrated, mucinous histology. Typically, these tumors are also poorly differentiated.

Dr Caudle:
Switching gears, can you speak to some of the recent research into the pattern of metastatic spread in patients with *BRAF*-mutated metastatic CRC as well?

Dr Deming:
Sure. One retrospective analysis of more than 500 patients with metastatic colorectal cancer who had known *BRAF* mutation status investigated patterns of metastatic spread. The authors observed that compared to *BRAF* wild-type metastatic CRC, metastatic spread in *BRAF*-mutant metastatic colorectal cancer was more likely to be via peritoneal disease or lymph-node metastasis and less likely to spread to the lungs.

Dr Caudle:
And I understand that the aggressive nature of *BRAF*-mutant metastatic CRC means that fewer patients are eligible for surgical resection.

Dr Deming:
Unfortunately, that's true as well. In the retrospective study that I just mentioned, patients with *BRAF*-mutant metastatic CRC were significantly less likely to undergo metastasectomy compared to patients with *BRAF* wild-type disease.

And, a separate retrospective case series found that when patients with *BRAF*-mutant metastatic CRC do undergo metastasectomy, they have shorter survival compared with patients who had *BRAF* wild-type tumors.

Dr Caudle:
Those are great insights, Dr Deming. Let's shift gears briefly to the subject of microsatellite instability, or MSI, in the context of

metastatic CRC. What should we know about this?

Dr Deming:
Sure. MSI occurs in approximately 5% of patients with metastatic CRC. We also know there is some overlap between MSI and *BRAF* mutations, and that about 30% of *BRAF*-mutant CRCs are also MSI.

However, many patients with *BRAF* mutations are actually microsatellite stable, or MSS. For example, one retrospective analysis found that 71% of patients with *BRAF*-mutant metastatic CRC were MSS, while 29% were MSI. And in a meta-analysis of 26 studies, patients with *BRAF*-mutant/MSS metastatic CRC had shorter overall survival than those with *BRAF* wild-type/MSS disease.

There is, of course, considerable research being directed at the treatment of *BRAF*-mutant metastatic CRC.

And the bottom line here is that it's important to test for *BRAF* mutations in patients with metastatic colorectal cancer and that we know a patient's mutation status before starting treatment.

Dr Caudle:
And that's a topic definitely worthy of its own discussion, but unfortunately we are out of time for today.

You know, I'd really like to thank my guest, Dr Dustin Deming, for joining me to focus on *BRAF*-mutant metastatic CRC. Dr Deming, it was great speaking with you today.

Dr Deming:
Thank you so much for having me. I hope our discussion today gave some background into the characteristics of *BRAF*-mutant metastatic colorectal cancer and the challenges we face when treating these patients.

Dr Caudle:
For ReachMD, I'm your host, Dr Jennifer Caudle, and stay tuned for the next episode in our series, where we'll discuss in greater detail the role of pathologists and the biomarker report in the treatment of metastatic CRC.

Announcer:
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