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A Pathologist's Perspective: The Role of Biomarker Testing in Metastatic Colorectal Cancer

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ANNOUNCER OPENING:

Welcome to ReachMD. This medical industry feature, titled "A Pathologist's Perspective: The Role of Biomarker Testing in Metastatic Colorectal Cancer," is sponsored by Pfizer.

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Here's your host, Dr Jennifer Caudle.

Dr Caudle:

Welcome to our program. Today, we'll be discussing the role of the biomarker report in the treatment of metastatic colorectal cancer, or metastatic CRC.

I'm your host, Dr Jennifer Caudle, and joining me today is Dr Fernando Uriel Garcia. He will bring us the pathologist's perspective on this important tool in the clinical management of metastatic CRC, which helps to determine prognosis and appropriate treatment options. Welcome, Dr Garcia.

Dr Garcia:

Thank you so much, Dr Caudle. It's good to be here today.

Dr Caudle:

As I'm sure our audience would agree, the biomarker report is playing an increasingly critical role in the diagnosis and selection of treatments for metastatic CRC, which is truly a heterogeneous disease.

You know, in current practice, the pathology and biomarker reports provide histologic and molecular information that may help determine prognosis and appropriate treatment options for patients with metastatic CRC.

Testing also lets us know if the patient has Lynch syndrome, which is the most common inherited colon cancer syndrome, and that allows us to counsel patients and family members about the need to start CRC screening early and more frequently.

Dr Garcia:

Across the board, in oncology and pathology, there is certainly a growing understanding of the various molecular mechanisms involved in CRC tumorigenesis. This has also helped with the development of therapies and ability to determine who may be appropriate to receive them.

Various reputable pathology and oncology organizations have jointly published standards for biomarker testing in CRC. The underlying objective was to inform the treatment decisions.

The latest version of these guidelines was published in 2017. These guidelines are aligned with the current guidelines for biomarker

testing from the National Comprehensive Cancer Network®, or NCCN®, which also provides recommendations for appropriate therapies.

Dr Caudle:

The biomarker report can now provide insight on prognosis and possible treatment options for metastatic CRC, such as targeted therapy for patients with certain mutation statuses.

You know, more than 10 years ago, studies first showed that patients with certain *RAS* mutations were less likely to benefit from EGFR inhibitors. Today, the labels for EGFR inhibitors specify that they are not indicated for the treatment of patients with *RAS*-mutant metastatic CRC.

Today, the biomarker report identifies a number of mutations that help determine appropriate treatment options for patients with metastatic CRC.

Dr Garcia:

Biomarker testing for patients with metastatic colorectal cancer should be done as soon as possible to inform prognosis and therapeutic decision making.

To determine eligibility for therapy, the joint molecular testing guidelines recommend *RAS* mutational testing for all patients with metastatic CRC, specifying a number of *KRAS*- and *NRAS*-activating mutations that should be assessed.

The joint guidelines also stipulate testing for *BRAF* V600E mutational status in patients with metastatic CRC for prognostic stratification. However, we are now aware that the presence of *BRAF* mutation has treatment implications as well.

Another recommendation from the joint guidelines is that all patients with CRC be tested for the presence of deficient mismatch repair, or dMMR, to identify patients at risk for Lynch syndrome and for prognostic stratification. In patients with dMMR tumors that display a loss of *MLH1* expression, *BRAF* V600E mutation analysis is also needed to evaluate the risk of Lynch syndrome.

In addition, we now routinely test for microsatellite instability, or MSI, which the joint guidelines acknowledge as an emerging biomarker to help predict response to immunotherapy.

Dr Caudle:

The latest NCCN Guidelines® also recommend *RAS* and *BRAF* testing in all patients with metastatic CRC. The NCCN Guidelines® also specify the need to test for HER2 amplification in those patients with metastatic CRC who are *KRAS, NRAS*, and *BRAF* wild-type.

Some molecular abnormalities, such as *RAS* and *BRAF* mutations, are generally mutually exclusive.

Dr Garcia:

Another example of mutations that are typically mutually exclusive occurs in testing for Lynch syndrome, which is seen in 2%-4% of patients with CRC. Usually, but not always, a *BRAF* V600E mutation–positive result and the absence of *MLH1* expression precludes Lynch syndrome.

Although a mutation might be less common in the general population of patients with metastatic colorectal cancer, there are some molecular findings that may co-occur.

For example, *BRAF* V600E mutations, a known predictor for poor prognosis, are found in up to 15% of all patients with metastatic CRC. About 30% of patients with *BRAF*-mutant metastatic colorectal cancer are also MSI-high.

Dr Caudle:

With this growing list of molecular markers, oncologists have started to move away from ordering individual testing and have moved towards requesting next-generation sequencing, or NGS, panels that can cover the full array of biomarker testing.

Dr Garcia:

That's right. An NGS cancer panel gives us the ability to test for all these molecular markers. When a tumor biopsy is not possible, liquid biopsy potentially offers a noninvasive means to test patients for a wide range of actionable mutations.

However, there are a variety of valid techniques still used in pathology laboratories. We can certainly test for *KRAS*, *NRAS*, and *BRAF* mutations individually with tissue from either the primary tumor or the metastasis, using such techniques as immunohistochemistry or polymerase chain reaction, commonly referred to as IHC and PCR, respectively.

HER2 testing may be done with either IHC or fluorescence in situ hybridization, commonly referred to as FISH testing. MMR testing may be done via IHC, while MSI testing may be done via a PCR test. HER2 amplification is present in between 5%-14% of patients with *RAS*/*BRAF* wild-type tumors. *NTRK* fusions are extremely rare in colorectal cancer, occurring in less than 1% of patients and limited to those with *KRAS*, *NRAS*, and *BRAF* wild-type status. *NTRK* fusion testing can also be done by IHC or FISH. However, an IHC test can produce false positive for *NTRK* fusions and requires confirmation with RNA next-generation sequencing.

What's critical, regardless of the molecular diagnostic tool employed, is that all testing is conducted according to the appropriate laboratory practices.

We can test our patients for the mutations that we have been discussing, because they each may have such an important implication for the patients who might be appropriate for a targeted therapy, and in other cases, for those who should not receive a particular treatment.

Dr Caudle:

Let's review the current implications of biomarker testing results on selecting patients with metastatic CRC for treatment with a targeted therapy.

Patients with *KRAS* or *NRAS* wild-type disease or those with *BRAF* V600E–mutant metastatic CRC may be eligible for treatment with a monoclonal antibody or a kinase inhibitor.

Patients with dMMR or MSI-H metastatic CRC may be eligible for immunotherapy regimen as initial or later-line therapy.

And although HER2 amplification does not seem to have the same prognostic value in CRC that it does in breast cancer, HER2 inhibitors are under investigation as treatment for patients with metastatic CRC whose tumors overexpress HER2. Patients may be eligible for clinical trials.

Lastly, *NTRK* fusions may indicate treatment with a TRK inhibitor.

Of course, all of these patients remain eligible for various chemotherapy regimens, depending on their individual clinical variables.

Dr Garcia:

In summary, appropriate cancer treatment relies upon molecular diagnostics. And it is more important than ever that oncologists and pathologists work in partnership to stay constantly aware of the latest developments.

Dr Caudle:

The pathologist is a critical member of the multidisciplinary team at every stage of cancer treatment. And having all this molecular information about patients' tumors has greatly contributed to patient care.

Before we close today, I'd like to thank Dr Garcia for joining me and sharing his expertise on molecular testing for biomarkers in metastatic CRC.

Dr Garcia:

Thank you so much for having me. I've enjoyed our conversation.

Dr Caudle:

I have as well, and for ReachMD, I'm your host Dr Jennifer Caudle. Stay tuned for the next episode in our series, which will discuss *BRAF* mutations as oncogenic drivers for CRC tumorigenesis, as well as heterogeneity among *BRAF* mutations.

ANNOUNCER CLOSE:

This program was sponsored by Pfizer. If you missed any part of this discussion, visit reachmd.com/industryfeature. This is ReachMD. Be part of the knowledge.