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A Molecular Deep Dive Into *BRAF*-Mutant Colorectal Cancer

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ANNOUNCER INTRO:

Welcome to ReachMD. This medical industry feature, titled "A Molecular Deep Dive Into *BRAF*-Mutant Colorectal Cancer," is sponsored by Pfizer. This program is intended for healthcare providers.

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Here's your host, Dr Charles Turck.

The participants have been paid by Pfizer for their time.

Dr Turck:

BRAF-mutated CRC tumors represent a distinct biological entity, and considerable research has been focused on learning more about this aggressive subtype with generally poor prognosis. Today, we'll be examining the pathways and mechanisms of *BRAF*-mutant colorectal cancer, or CRC, including the various distinctions that have been observed even within *BRAF*-mutant CRC.

This is ReachMD, and I'm Dr Charles Turck. Joining me is oncologist Dr Andrea Cercek. Great to have you on the program, Dr Cercek.

Dr Cercek:

Thank you so much, Dr Turck.

Dr Turck:

Glad to speak with you. So, to start, we know that up to 15% of patients with metastatic CRC harbor a *BRAF* mutation, so let's take a bit to get grounded in the basic science of *BRAF*-mutant metastatic CRC, starting with the molecular pathway involved.

Dr Cercek:

Certainly. At the molecular level, BRAF is a component of the mitogen-activated protein-kinase pathway. Typically referred to as the MAP-kinase pathway, it is 1 of 2 key signaling pathways in CRC located downstream from the epidermal growth factor receptor, or EGFR. The other pathway is the PI3K/AKT pathway. These pathways activate cellular proliferation, differentiation, and growth.

Within the MAP-kinase pathway, BRAF is a serine/threonine protein kinase that belongs to the family of RAF kinases. Activated RAF proteins phosphorylate and activate MEK1 and MEK2. MEK1 and 2, in turn, phosphorylate and activate ERK. Finally, ERK phosphorylates transcription factors and other key cellular activities in the cell nucleus, ultimately leading to cell growth and division.

A *BRAF* mutation drives persistent MAP-kinase signaling, resulting in uncontrolled cell proliferation and tumor growth.

Dr Turck:

So, for patients with metastatic CRC and a *BRAF* mutation, is that mutation thought to be the primary oncogenic event?

Dr Cercek:

It appears that way. Preclinical research in animal models has suggested that the role of *BRAF* mutations can play in colorectal tumorigenesis as a driver of persistent MAP-kinase signaling that results in uncontrolled cellular proliferation and tumor growth.

For example, one study introduced a *BRAF* mutation into the intestinal cells of adult mice. This resulted in DNA methylation defects that accumulated slowly over time—similar to how the serrated neoplasia pathway functions in humans.

The authors observed that the accumulation of multiple gene-specific DNA methylation events was driven by extended oncogenic *BRAF* signaling, leading to rapidly proliferating tissue.

This was present even in tissue where the only morphological change was stable hyperplasia and was thought unlikely to be secondary to other genetic changes associated with progression to malignancy.

So, *BRAF* mutations in the MAP-kinase pathway resulted first in extensive hyperplasia, evolving over time into murine serrated adenomas.

Dr Turck:

So, let's expand on that. Can you tell us more about the research out there that suggests there are distinctions even among *BRAF* mutations?

Dr Cercek:

Absolutely. More than 30 *BRAF* mutations have been found, and 3 different classes of *BRAF* mutations have been identified.

Class 1 includes *BRAF* V600E mutations. To be specific, a V600E mutation represents a single amino acid substitution at codon 600 of exon 15 in chromosome 7, leading to the replacement of valine for glutamic acid. In fact, the majority of *BRAF* mutations identified are *BRAF* V600E mutations, which are RAS-independent.

Non-V600E *BRAF* mutations can be further divided into Class 2 and Class 3, based on the manner of oncogenic signaling involved. Class 2 *BRAF* mutations are RAS-independent like Class 1 mutations, whereas Class 3 mutations are RAS-dependent.

Dr Turck:

What are the clinical implications of each class?

Dr Cercek:

BRAF-mutant CRCs differ by class in their phenotypic presentations.

Patients with Class 1 *BRAF*-mutant CRCs—that is, those with *BRAF* V600E mutation—are more likely to be female, be older than age 60, and have right-sided disease. Many present with advanced disease, having poorly differentiated tumors displaying mucinous histology. They also have an increased incidence of peritoneal and distant lymph node involvement, and decreased likelihood of liver-limited disease. The phenotype associated with Class 2 is similar to Class 1.

However, Class 3 *BRAF*-mutant CRCs typically present with an entirely different phenotype. They occur more often in male patients of younger age and those with *BRAF* V600E mutations. They are more likely to present with left-sided disease, with the majority being node-negative and having non-mucinous histology. They usually display an absence of peritoneal metastases.

Dr Turck:

And are the phenotypic differences matched by differences in clinical outcomes?

Dr Cercek:

Yes, they are. Patients with Class 1 and Class 2 *BRAF*-mutant metastatic colorectal cancer generally have worse median progression-free survival and overall survival than those with Class 3 *BRAF*-mutant metastatic CRC.

One retrospective study compared 117 patients with *BRAF*-mutated metastatic colorectal cancer who had been categorized as having Class 1, Class 2, or Class 3 *BRAF* mutations. Outcomes in these patients were compared to each other and to patients with *BRAF* wild-type metastatic CRC. For patients with Class 1 and Class 2 *BRAF* mutations, median progression-free survival with first-line treatment

was 7.3 and 7.0 months, respectively. However, for patients with Class 3 *BRAF* mutations, median progression-free survival was 13.8 months, which was actually longer than it was for patients with *BRAF* wild-type disease, who had a median progression-free survival of 10.1 months.

Median overall survival was 21 to 23.4 months for patients with Class 1 and 2 *BRAF* mutations, 44.5 months for those with Class 3 *BRAF* mutations, and 42.2 months for those with *BRAF* wild-type disease.

Dr Turck:

With that in mind, are there prognostic implications associated with each distinct class of *BRAF* mutation?

Dr Cercek:

There are, but there are even further distinctions within *BRAF* V600E mutations. As already noted, *BRAF* V600E mutations are by far the most frequently occurring in CRC; however, further analyses of gene expression in *BRAF*-mutant CRC have determined that there are 2 main transcriptional subsets of *BRAF* V600E–mutant CRC tumors: namely, BM1, or *BRAF*-mutant 1, and BM2, or *BRAF*-mutant 2.

These subtypes appear to be independent of MSI status, gender, and sidedness.

Furthermore, these transcriptional subtypes also display different signaling patterns at the molecular level. Based on an analysis of gene expression data from 218 patients with colorectal cancer, BM1 CRC tumors were more *KRAS*-enriched compared to BM2 tumors, as well as when compared to *KRAS*-mutant CRCs. BM1 tumors also display an overall stronger immune profile, with activation of various interleukin pathways.

On the other hand, KRAS signaling in BM2 tumors was similar to *BRAF* and *KRAS* double wild-type tumors. BM2 CRC tumors were associated with activation of cell-cycle checkpoint genes and deregulation of the cell cycle.

BM2 occurs in more than twice as many patients as BM1. These transcriptional subtypes may also have prognostic relevance, given that BM1 tumors have shown a trend toward poorer survival than BM2 tumors.

For the medical oncologist, these transcriptional subtypes may someday offer insight into the likelihood of response to different treatment strategies. For example, one cell line study found that BM1 CRC tumors tended to be more responsive to BRAF inhibition than BM2 tumors, while BM2 tumors tended to be more responsive to cyclin-dependent kinase 1, or CDK1, inhibition.

It has been suggested that, in future clinical trials, it may be useful to stratify patients with *BRAF* V600E mutations by transcriptional subtypes.

Dr. Turck:

Dr Cercek, before we close today, let's look at how BRAF inhibition alone has not proven to be an effective strategy in *BRAF*-mutant metastatic CRC. Could you share some thoughts about the proposed mechanisms of resistance?

Dr Cercek:

Certainly. Exclusively targeting *BRAF* V600E can cause EGFR-adaptive feedback. It turns out that inhibition of BRAF transiently blocks MAP-kinase signaling, but in turn leads to a loss of ERK-dependent negative feedback.

There are other molecular alterations in the MAP-kinase pathway that could lead to resistance. These include *RAS* alterations, *KRAS* mutations or amplification, *BRAF* amplification, and *MEK1* mutations. There are still other mechanisms of resistance that may affect the PI3K pathway, including PDGFRβ overexpression, amplification of hepatocyte growth factor, and IGF1R activation.

However, to sum up these complex molecular processes, what we know is that inhibiting BRAF V600E alone provides an escape strategy to bypass the blockade. This has led to extensive research exploring other therapeutic strategies.

Dr Turck:

Well, I know the entire oncology community looks forward to the fruits of that labor, which will hopefully result in more options to treat patients with *BRAF*-mutant metastatic CRC.

Dr Cercek:

Thanks, Dr Turck. Appreciate you having me here today.

Dr Turck:

For ReachMD, I'm Dr Charles Turck. Thanks for joining us today.

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