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Why Test for HER2 in Metastatic Colorectal Cancer: From Negative Predictive Biomarker to Emerging Oncotarget

Announcer:
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Dr. Strickler:
Hi, I'm John Strickler, Associate Professor of Medicine at Duke University Medical Center in Durham, North Carolina. Today, I'm going to present on why we should test for HER2 in metastatic colorectal cancer. Its role from a negative predictive biomarker to an emerging oncotarget.

Historically, EGFR, otherwise known as HER1, has been the most relevant target in the development and growth of colon cancer. And EGFR has several roles in the development and growth of colon cancers from adhesion, angiogenesis, cell proliferation, cell survival, invasion, and metastasis. What we've learned over many years is that there are various genomic alterations that can drive resistance to EGFR inhibitors. These include classically KRAS and NRAS mutations, but have also been found to be other alterations like EGFR ectodomain mutations. And the topic of this talk today, ERBB2, otherwise known as HER2 amplification.

A number of investigators have explored ERBB2, or HER2 amplification, as a driver of acquired resistance to anti-EGFR therapies. This is a series that we conducted at Duke University several years ago, in which we examined a cohort of 69 patients who had progressed on prior anti-EGFR therapies and found that ERBB2 amplification, or HER2 amplification, was enriched in these patients, suggesting that this may be an important driver in this patient subset.

Looking more globally at ERBB2 amplification in colon cancer, overall, this is a fairly rare alteration. It occurs in 2 to 3% of patients, depending on the dataset. But what we found is that it is enriched in certain groups of patients, particularly those patients who have either KRAS exon 2 wild-type disease or have KRAS, NRAS, and BRAF wild-type disease. In the KRAS exon 2 wild-type patient population, the Heracles investigators found a rate of 5% and then in single institution retrospective series, the rate approached 12 to 13% in this enriched group of patients with RAS and BRAF wild-type disease.

Now, ERBB2 and ERBB3 genomic alterations can occur in all types of different forms. The most common form we are discussing today is ERBB2 amplification, which is otherwise known as a copy number gain. But there are other alterations that we've seen published in the literature including ERBB2 mutations, ERBB3 mutations. And, in general, the most actionable alteration is ERBB2 amplification in colon cancer, which predicts pathway dependence and oncogene addiction.

When we look at HER2 or ERBB2 testing, this is something that's increasingly seen as something that we should order at the time of original – of diagnosis of metastatic disease. There are a number of ways we can test for ERBB2 amplification. Most commonly in the United States tissue NGS panels are used, and this will also detect ERBB2 mutations which are not actionable in metastatic colon cancer. But there are other assays which are also well validated. IHC and FISH is the more traditional way to test for HER2 overexpression or amplification. And these assays have been validated for breast cancer and gastric cancer. And when they are used

for colon cancer, either approach will work to detect HER2 overexpression or amplification. So there's not a standardized colon assay in the United States. Or at least it's not clinically validated in the United States at this point, but those other assays could be used.

Now one of the key findings about HER2 amplified metastatic colorectal cancer is that it can drive resistance to anti-EGFR therapies. In work based out of Italy, they looked at several hundred patient-derived xenograft models of patients and found that in those mouse models that were HER2 amplified, there was a primary resistance to anti-EGFR therapy, suggesting that we would not want to give a patient who has an ERBB2 amplified or HER2 amplified cancer an anti-EGFR therapy. That's been followed up by a number of retrospective studies, and this is shown here as a meta-analysis looking at a number of these anti-EGF – at the studies looking at the impact of HER2 amplification on response to anti-EGFR therapies. Here in this meta-analysis, patients who received anti-EGFR therapies and had HER2 positive disease did demonstrably worse if they received an anti-EGFR therapy, so this suggests primary resistance to an anti-EGFR therapy addition. In addition, in this meta-analysis, it was found that patients who had HER2 positive disease were half as likely to respond to an anti-EGFR therapy.

Thank you for watching this activity.

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