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What Are the Clinical Features of HER2 Amplified Colorectal Cancers?

Announcer:
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Dr. Cercek:
Hi, my name is Andrea Cercek. I'm a Medical Oncologist and Section Head Colorectal Cancer at Memorial Sloan Kettering Cancer Center. And I'm excited today to discuss the clinical features of HER2 amplified colorectal cancers.

So HER2 as a target in colorectal cancer, it's a receptor tyrosine kinase which is encoded by ERBB2, it has no soluble ligand that we know of, and it heterodimerizes with other ligand-bound HER2 family members. And when HER2 heterodimerizes with HER3, that heterodimer is a potent driver of PI3 kinase signaling. And there are multiple therapies that target HER2 and the HER2 heterodimers. And once they dimerize, they basically turn on and lead to cell growth differentiation and cell survival in cancer cells.

So when we look at HER2 across multiple tumor types, you can see that it's altered in many tumor types. Of course, the breast and gastric are most common and most known and sort of most developed in terms of targeting, but obviously is seen in colon as well. And we have HER2 amplification, overexpression, and then HER2 mutation. And all of those can lead to tumorigenesis. But what we're going to specifically talk about today is HER2 gene amplification as a target.

So HER2 amplification in colorectal cancer. It's about 4%. This is in the metastatic setting. And we believe it's similar in early-stage disease as well. And it's actually enriched in the RAS/RAF wild-type tumors where it ends up being about 10% of all-comers. But it's an important part of the biomarker pie, if you will, in colorectal cancer.

So what do we know about it in terms of clinical characteristics? Many of these tumors most typically are left sided, not exclusively, but the large majority are in the sigmoid or the rectum. There's homogeneous expression of HER2 in colorectal cancer. It's actually not mutually exclusive with RAS or BRAF mutations, which is important to keep in mind, particularly when we think about treatment and targeted treatment with combination of monoclonal antibodies and TKIs. Because the tumors need to be RAS wild-type. So it's always important to check for HER2 amplification as well as RAS mutation in particular. And it is more commonly associated with lung and brain metastases. And I'll show that data in a little bit. And, you know, I have a question mark here for whether or not it's resistant to anti-EGFR antibodies. But we do see this over and over in preclinical models as well as in retrospective analyses of patients that had HER2 amplified RAS wild-type tumors that received anti-EGFR therapy that benefit, which is significantly less than what we're seeing in patients that have RAS wild-type tumors that are left sided and not HER2 amplified.

And this is just some other data to show you. So this was a nice retrospective analysis, looking at patients that received anti-EGFR therapy in the metastatic setting, standard of care, left-sided tumors. And you can clearly see by the graph that the patients that had the HER2 amplified tumors that received the same anti-EGFR therapy did significantly worse in terms of PFS, progression-free survival. So really suggesting that we shouldn't treat this population that's HER2 amplified RAS wild-type with anti-EGFR therapy but rather focus on HER2 targeting.

So looking at the clinical characteristics of HER2 tumors in a little bit more detail, and this was nice work done by the Italian group led by Dr. Sartore-Bianchi. Again just to show you more likely to occur in the rectum, more likely to metastasize to the lungs, and actually more likely to involve multiple metastatic sites. So just something to keep in mind when seeing these patients. Of course, you know, I can't stress enough the importance of next generation sequencing in all-comers with metastatic colorectal cancer, looking at that pie, looking at potential biomarkers, but particularly for HER2 amplified RAS wild-type patients in terms of treatment options, as we now have FDA approval in third-line for HER2 amplified RAS wild-type tumors with tucatinib and trastuzumab, something to keep in mind when seeing these patients if you meet them later on in therapy and they'd have not yet had next generation sequencing or specifically HER2 amplification.

Thank you.

Announcer:
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