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What Is the Evidence Supporting HER2-Targeted TKI-Based Combination Regimens in Metastatic Colorectal Cancer?

Announcer:
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Dr. Cercek:
Hi, I'm Andrea Cercek. I'm a Medical Oncologist and the Section Head of the Colorectal Section at Memorial Sloan Kettering Cancer Center. And it's my pleasure to talk about the evidence supporting HER2-targeted TKI combination regimens in metastatic colorectal cancer.

So we learned very early that in colorectal cancer, we need combination therapies in order to be able to target HER2. So we can't just do a monoclonal antibody, we can't just do TKI, we need the combination of both drugs to get a response. And this was done in preclinical models and mouse models and has held throughout treatment so always we use dual targeting.

Heracles study was one of the first studies to look at HER2 targeting in metastatic colorectal cancer. So patients that had advanced disease, two lines of treatment or more, were HER2 positive, KRAS wild-type, and then had prior exposure to 5-FU oxaliplatin and irinotecan, as well as anti-EGFR monoclonal antibodies, all received lapatinib and trastuzumab. And they were treated until progression of disease, 32 patients were enrolled, and the primary endpoint was overall response rate. So this was more like a proof of concept, phase 2 study looking at the sensitivity of HER2 targeting in metastatic colorectal cancer.

So looking at the data in a little bit more detail as well as the long-term outcomes, in this study of, again, trastuzumab and lapatinib, the overall response rate was fantastic, 28%. One patient actually had a complete response 7 years out, so that patient is cured. And you know, when we think about treatment in the refractory setting that's not biomarker driven, with something like TAS-102 or regorafenib, both drugs are approved for benefit in survival, but there is no response rate at all.

And so this is clearly a very active target in metastatic colorectal cancer. The median PFS was 4.7 months and the median overall survival was 10 months, which is pretty impressive again in refractory disease.

The MOUNTAINEER study was a global open-label phase 2 trial. It actually started as a U.S. investigator-initiated study consisting just of a single cohort, and then was expanded to cohorts B and C. So patients with advanced disease, two or more lines of prior therapy, including fluoropyrimidine, irinotecan, oxaliplatin, and monoclonal antibodies that were HER2 amplified RAS wild-type, and had measurable disease were eligible. Cohort A consisted of tucatinib and trastuzumab. And then when the study was expanded, patients were randomized to either cohort B, which was again a combination of tucatinib and trastuzumab, or cohort C, which was just monotherapy with tucatinib. The endpoints of the study were looking at confirmed overall response rate in cohorts A and B that had the dual therapy. And then the secondary endpoints were looking at duration of response for cohorts A and B, including PFS, as well as overall survival. And then overall response rate in cohort C, which was just the monotherapy with tucatinib, assessed at 12 weeks, and

then also safety assessment.

So looking at our patient characteristics on the MOUNTAINEER study, the majority of the patients had left-sided tumors, which is known that HER2 amplified tumors tend to be more left-sided. A large majority of patients did have metastases present in the liver, as well as other sites including the lung. And response rates, this was to dual inhibitors tucatinib and trastuzumab. So in cohorts A and B, the overall response rate was 38%, which is a fantastic response if we think about other drugs that are approved in the setting in refractory disease that are approved for benefit in survival, such as TAS-102 and regorafenib, but there's no response rate at all, it just - they just have stability. And here, we saw a 38% overall response rate. And the duration of response was significant at a median of 12.4 months.

Then looking at the responses in a little bit more detail, I think waterfall plots are always so helpful because you just see the depth of these responses. Three patients had a clinical complete response. Many patients had a partial response. And there was significant reduction in tumor burden in patients, 65%. So really a large benefit here in terms of response rate.

And then looking at the PFS, the median PFS was 8.2 months. And then I think the real benefit here and the real striking finding is the median overall survival of 24.1 months, which we just don't see in refractory disease. So the patients who benefited, clearly have this durable long-term benefit of 2 years - median of 2 years.

And so in summary, looking at the landscape of monoclonal antibodies and TKIs in refractory HER2 amplified metastatic colorectal cancer, the Heracles study utilizing tucatinib and trastuzumab, a small number of patients response rate of 28%, median PFS of 4.7%. MyPathway pertuzumab and trastuzumab, 68 patients, 31% response rate, median PFS of 5.3 months. And then the MOUNTAINEER study, which we just discussed in detail, tucatinib and trastuzumab, larger number of patients, a 38% response rate, and a median PFS of 8.2 months.

All these studies together clearly tell us that HER2 is an important target in metastatic colorectal cancer, it absolutely should be checked. We have FDA approval now for tucatinib and trastuzumab. So for patients that are HER2 amplified RAS wild-type, it is absolutely a therapy that they should receive. And there are ongoing trials looking at other targeting of HER2 in addition to moving this therapy into the first-line setting with MOUNTAINEER-03. So it's really critical that we look at HER2, as one of our important biomarkers in metastatic colorectal cancer.

Thank you so much for your attention.

Announcer:
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