CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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The Role of *HER2* Amplification Testing in Metastatic Colorectal Cancer

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H&O How common is human epidermal growth factor receptor 2 (*HER2*) amplification in metastatic colorectal cancer (mCRC)?

KR *HER2* amplification is found in approximately 3% to 4% of all cases of mCRC. Most of these amplifications, however, are found in *RAS*/*BRAF* wild-type patients—so the chance of finding *HER2* amplification is less than 2% in *RAS/BRAF* mutant patients vs approximately 6% to 8% in *RAS/BRAF* wild-type patients.

H&O Which patients with mCRC should be tested for *HER2* amplification status?

KR Most of our data regarding the clinical utility of *HER2* amplification relate to *RAS/BRAF* wild-type mCRC. Even though *HER2* amplification can be found in *RAS/BRAF* mutant patients, we do not yet know the clinical significance of this or how to target it effectively.

H&O How can *HER2* amplification status affect treatment decisions?

KR Finding *HER2* amplification has 2 major implications in *RAS/BRAF* wild-type mCRC. First, the current standard of care in *RAS/BRAF* wild-type mCRC is treatment with anti–epidermal growth factor receptor (EGFR) antibodies, such as cetuximab (Erbitux, Lilly) and panitumumab (Vectibix, Amgen). Preclinical as well as retrospective clinical data have shown that the presence of these amplifications reduces the clinical benefit of anti-EGFR agents.

Second, finding *HER2* amplification opens the possibility of using HER2-blocking agents. When we identify patients with *HER2* amplification, we should enroll them in clinical trials of HER2-blocking agents in lieu of treatment with anti-EGFR therapy whenever possible.

> We believe that *HER2* amplification is truly predictive of benefit with anti-EGFR agents.

H&O What are some of the studies that have looked at targeted treatments in *HER2* amplified mCRC?

KR Two major studies have looked at this, HERACLES-A (Dual-Targeted Therapy With Trastuzumab and Lapatinib in Treatment-Refractory, KRAS Codon 12/13 Wild-Type, HER2-Positive Metastatic Colorectal Cancer) and MyPathway (A Study Evaluating Herceptin/Pertuzumab Treatment Targeted Against HER2

Overexpressed/Amplified Advanced CRC). Both of these studies looked at dual blockade to target HER2—trastuzumab (Herceptin, Genentech) plus lapatinib (Tykerb, Novartis) in HERACLES-A and trastuzumab plus pertuzumab (Perjeta, Genentech) in MyPathway. Although both these studies were single-arm, they showed that dual anti-HER2 therapy had a response rate of approximately 30% to 35% and a progression-free survival of approximately 4 1/2 to 5 months. These are very promising early studies that need validation in larger clinical trials.

H&O What are the studies that looked at the relationship between *HER2* amplification status and response to anti-EGFR agents?

KR Multiple preclinical and clinical studies have looked at this relationship. The HERACLES-A study also reported on prior treatment with anti-EGFR agents in 15 patients with mCRC who were enrolled, and no objective responses to these agents were seen in these patients with *HER2* amplification.

Our group conducted a study using 2 different cohorts of patients with mCRC that we presented at the 2016 American Society of Clinical Oncology annual meeting. We found that median progression-free survival with anti-EGFR agents in mCRC was less than 3 months in patients with *HER2* amplification, compared with more than 8 months in patients without *HER2* amplification. Among patients who received a non–anti-EGFR agent, progression-free survival was similar in both the groups. We therefore believe that *HER2* amplification is truly predictive of benefit with anti-EGFR agents.

H&O Does *HER2* amplification have prognostic implications for patients with mCRC?

KR Although the data regarding this are limited and conflicting, most studies have not shown *HER2* amplification to be a prognostic factor in metastatic colorectal cancer. Our group and Jeong and colleagues showed that although median progression-free survival on anti-EGFR therapy was significantly lower in patients with *HER2* amplification than in those without, overall survival was not significantly different between the groups (although the patient numbers are limited).

H&O Have the recent data regarding *HER2* amplification status and mCRC affected the way you treat your patients?

KR Yes, definitely. We check *HER2* amplification status in all patients with *RAS*/*BRAF* wild-type mCRC. If patients are positive for *HER2* amplification, we explain the limited possibility of benefit from anti-EGFR agents and make sure they understand the toxicities associated with these drugs. Most of the patients at MD Anderson who have mCRC and *HER2* amplification receive anti-HER2 therapies as part of a clinical trial.

H&O What are some of the other studies that are looking at *HER2* amplification status and CRC?

KR Multiple studies, both randomized clinical trials and nonrandomized studies, are looking at HER2 inhibition in relevant patients with mCRC.

S1613 (Trastuzumab and Pertuzumab or Cetuximab and Irinotecan Hydrochloride in Treating Patients With Locally Advanced or Metastatic HER2/Neu Amplified Colorectal Cancer That Cannot Be Removed by Surgery; NCT03365882) is a randomized clinical trial that is being conducted through the National Cancer Institute's National Clinical Trials Network. This study, which encompasses more than 600 centers across the United States, is randomly assigning patients with locally advanced or metastatic *HER2* amplified CRC who have not received an anti-EGFR agent to either trastuzumab/pertuzumab or the current standard of care, which is the anti-EGFR agent cetuximab plus the chemotherapy agent irinotecan, with crossover to the HER2 therapy arm for the latter.

> I think that all patients with metastatic colorectal cancer should get the benefit of knowing their *HER2* amplification status.

One of the single-arm studies is MOUNTAINEER (Tucatinib and Trastuzumab in Treating Patients With HER2+ Metastatic Colorectal Cancer; NCT03043313), which is a phase 2 trial looking at a combination of the anti-HER2 agents tucatinib and trastuzumab. In addition, a phase 2 open-label study (DS-8201a in Human Epidermal Growth Factor Receptor 2-Expressing Colorectal Cancer; NCT03384940) is looking at the experimental antibody-drug conjugate DS-8201a, which is designed to deliver cytotoxic chemotherapy in a targeted fashion to cells that contain the HER2 antigen. Finally, a phase 1 study is looking at the use

of the experimental bispecific HER2 antibody ZW25 in a variety of HER2-expressing cancers, including CRC (NCT02892123).

H&O What should be the next steps in research?

KR We already have quite a few studies that are validating the role of HER2 inhibition in relevant patients with mCRC. When these and the S1613 randomized study are completed, we will know more about the value of HER2 inhibition in mCRC and when we can avoid the use of anti-EGFR agents that add toxicity without being helpful.

After that, the next step will be to figure out which specific anti-HER2 agents work best, and in which patients. We will have to identify biomarkers to help us know which of the patients with *HER2* amplification are most likely to respond to a particular anti-HER2 strategy. For example, our early data show that patients with high gene copy numbers are more likely to respond to dual anti-HER2 inhibition. Biomarkers such as these and other co-occurring molecular alterations may also be instrumental in distinguishing between patients who are likely to respond to a particular anti-HER2 strategy and those who will do better with a different anti-HER2 approach. We also want to identify biomarkers that will let us know when patients are developing resistance to these agents, so we can change our approach. For example, we may wish to use combination therapies that target other resistance pathways.

H&O Do you have any further advice for clinicians regarding HER2 testing in CRC?

KR I strongly recommend that clinicians test *HER2* amplification status in patients with mCRC, at least in those who are *RAS*/*BRAF* wild-type. *HER2* amplification can be tested by any of the next-generation sequencing panels that clinicians might be using. Even when people do not have access to next-generation sequencing panels, *HER2* amplification testing can be done very simply by immunohistochemistry. Immunohistochemistry is an inexpensive test that is readily available in all pathology laboratories because it is done routinely in breast and gastric cancer. I think that all patients with mCRC should get the benefit of knowing their *HER2* amplification status so that they can make an informed decision regarding clinical trials and treatment with anti-EGFR antibodies.

Disclosure

Dr Raghav has no disclosures to report.

Suggested Readings

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