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**Improving HER2 Biomarker Testing in Metastatic Colorectal Cancer**

**HER2** (also known as ERBB2) amplification or overexpression occurs in a relatively small proportion of metastatic colorectal cancer (mCRC) cases; nevertheless, early identification of patients with this alteration, ideally through next-generation sequencing (NGS) testing, can help with selection of appropriate therapy and referral to clinical trials involving emerging HER2-targeted therapies for mCRC. This article discusses the clinical burden of mCRC, recommendations for and barriers to uptake of molecular testing, clinical and economic benefits of early NGS testing, and clinical trial data on HER-targeted approaches for mCRC. It is based on recent Insights interviews with Ryan Haumschild, PharmD, MS, MBA; Kristen Ciombor, MD; and Kanwal Raghav, MBBS, MD.

**Clinical Burden of mCRC**

**Trends**

The incidence rates of colorectal cancer (CRC) decreased among adults 55 years of age and older from the mid-1980s to 2013; however, they increased by 2.4% per year among adults 20 to 29 years old and 1.0% per year among adults 30 to 39 years old. Additionally, from the mid-1990s to 2013, the CRC incidence increased in adults aged 40 to 49 years (1.3%/year) and those aged 50 to 54 years (0.5%/year). The increased incidence observed among younger patients prompted the United States Preventive Services Task Force to add a screening colonoscopy recommendation for average-risk individuals.

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Thus, although progress has been made in biomarker testing for CRC who may benefit from lifestyle intervention, early detection, and treatment for residents of the CRC-related incidence and mortality. Additionally, the CRC-related mortality rate is 30% to 40% higher among residents of poor counties compared with those living in affluent counties, highlighting the need for increased education on strategies for prevention, early detection, and treatment for residents of impoverished areas, said Haumschild. Assistance with transportation to infusions and follow-up appointments, strategies to deliver therapies to patients with adherence challenges, and referrals to a social worker to address societal difficulties may also help to identify patients at increased risk for CRC who may benefit from lifestyle intervention or early screening.

**Social Determinants of Health**

Haumschild said that social determinants of health—place of residence, education, socioeconomic status, and social support and network—play a role in the stage at which the patient is diagnosed and the survival outcome, noting that ways to address barriers to care are important for improving outcomes. The southern and midwestern regions of the United States have the highest incidence of CRC; Haumschild pointed out that this partially may be due to their large population of Black individuals, who have a higher CRC-related incidence and mortality. Additionally, the CRC-related mortality rate is 30% to 40% higher among residents of poor counties compared with those living in affluent counties, highlighting the need for increased education on strategies for prevention, early detection, and treatment for residents of impoverished areas, said Haumschild. Assistance with transportation to infusions and follow-up appointments, strategies to deliver therapies to patients with adherence challenges, and referrals to a social worker to address societal difficulties may also help to identify patients at increased risk for CRC who may benefit from lifestyle intervention or early screening.

**Molecular Testing for mCRC**

Although most molecular testing is performed in the metastatic setting, microsatellite instability (MSI) and mismatch repair (MMR) testing is recommended by guidelines for all patients with newly diagnosed CRC of any stage, because information on the hereditary or genetic component of the cancer may help to predict prognosis and response to certain therapies, said Ciombor. Molecular testing used to be performed after exhausting standard-of-care options; currently, Ciombor performs molecular tests on all patients with metastatic disease upon diagnosis, because the results can affect the choice of therapy. “We used to think [molecular testing] was important only when patients had sort of run out of good treatment options that were standard of care,” said Ciombor. “Now we know that it really can impact lines of therapy, even in the first-line setting.”

Ciombor also noted that the molecular profile of mCRC can change over time, and retesting after progression may help to identify potentially beneficial therapies. For example, patients with RAS/RAF wild type (WT) mCRC often are treated with EGFR inhibitors; they eventually may develop resistance via development of a RAS mutation or clone that may disappear after the EGFR inhibitor is discontinued. “We can monitor the emergence and the decay of this clone, which can also lead to the potential for us to recycle that line of therapy once the mutant clone decays enough that patients can be reclassified to that,” said Ciombor.

The awareness of molecular profiling for mCRC is increasing among oncologists and patients, yet Ciombor commented that most patients are not fully educated on how it can affect treatment choice. Therefore, discussions with patients about different testing platforms and results interpretation is important when they begin treatment and attend subsequent visits. She added that rapid turnaround of these tests also is important, because the choice of first-line therapy should be based on the underlying genomic alterations. Guidelines recommend testing for universal MMR and MSI for all patients newly diagnosed with CRC and tumor genotyping for KRAS, NRAS, BRAF, and HER2 for all patients with mCRC. Genotyping can be performed either individually or as part of an NGS panel; however, according to the guidelines, NGS panels have the advantage of being able to detect rare and actionable alterations, such as NTRK fusions. Although HER2 is included on many NGS panels, it can also be detected using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). Haumschild added that testing for tumor mutational burden and NTRK fusions also may be considered. Guidelines note that NTRK fusions have been identified only in tumors that are pan-WT for KRAS, NRAS, and BRAF, and they are more common in tumors with MMR-deficiency/MSI-high status.

“That’s really one of the exciting things about metastatic colorectal cancers. We’re finding more...
[key biomarker] targets as we continue to do more research,” said Haumschild. Ciombor noted that because NGS has a high number of actionable genes of interest and greater testing efficiency, she uses it in most patients instead of piecemeal testing of each gene. The commercial NGS panel that she uses at Vanderbilt-Ingram Cancer Center includes clinically actionable mutations as well as targets that may be important in the future or that are being studied in clinical trials (eg, PIK3CA).

The inclusion of targets that are not yet clinically actionable allows clinicians to revisit a patient’s NGS data if the targets become actionable.

Haumschild added that biomarker testing can help providers streamline their approach to treatment decisions, and adherence to guideline-recommended biomarker testing may help improve patient outcomes in general and reduce exposure to expensive therapies likely to be ineffective for the patient’s molecular subtype.

However, a retrospective review of data from electronic medical records of patients diagnosed with metastatic colon cancer between 2013 and 2017 showed that only 40% of patients received biomarker testing that aligned with current guidelines. Patients were more likely to receive biomarker testing if they were treated at an academic center (44% vs 29% in a community setting; P < .001), presented with de novo metastatic disease (42% vs 24% with progression from an earlier stage; P < .001), were diagnosed before the age of 65 years (44% vs 35% diagnosed at age ≥ 65 years; P < .001), and were women (44% vs 36% among men; P < .001). Of patients given the anti-EGFR therapies cetuximab or panitumumab, 28% had received testing for RAS and BRAF that aligned with current guidelines. The tumors of 7% of those given cetuximab or panitumumab were positive for KRAS or NRAS mutations; they should not have been given anti-EGFR therapy because of the risk for adverse events (AEs).

Haumschild added that screening for actionable mutations before initiating treatment can also reduce exposure to, and costs associated with, therapies that are unlikely to benefit the patient, which may reduce overall costs for payers even when considering additional costs of NGS testing. In their retrospective review of medical record data from 1497 patients with pathologically confirmed metastatic colon cancer, Gutierrez et al concluded that 4.6% of the patients were incompletely genotyped and were given inappropriate therapy. Assuming a cost of $6500 for comprehensive NGS testing and $6000 weekly for treatment with cetuximab, 250 mg/m², they estimated that the associated annual expenditures for this inappropriate therapy would have covered the costs of NGS testing for all 1497 patients.

“At the end of the day, the patients [who] need it the most are getting the therapy, and we don’t have to expose patients to unnecessary therapies if they’re not going to see that positive benefit,” said Haumschild. “There’s a huge opportunity for us to improve adherence. As discussed in this study, [we must] stay adherent to these guideline-recommended biomarkers and make sure we’re screening patients before treatment [to reduce] exposure of expensive medications to all patients but really [leverage] those unique therapies for those [who] need them the most. That’s ultimately what we’re trying to do as health care providers. And I know our payers and health care provider teams really would appreciate that.”

Haumschild added that payer implementation of requirements for certain genomic tests before providing access to a medication would help to reduce testing variability among health care providers and medication use across different practice settings, which, in turn, would provide more effective treatments for patients and reduce costs for payers. Genomic testing is being incorporated as part of clinical pathways in several cancer types (eg, lung cancer) and could be a valuable addition to clinical pathways for mCRC, added Haumschild. Additionally, building optimal therapeutic sequences into clinical pathways or order sets in integrated delivery networks can help educate providers about the optimal sequencing of therapies for mCRC.

“As a payer, I want to make sure I’m approving therapies if they’re high cost or, for unique patient populations, that they’re sequenced appropriately,” said Haumschild. “There’s nothing worse than treating a patient early on with a therapy, and then [the patient does not have] the opportunity [to try] subsequent therapies that would push out their progression-free survival (PFS) or give them the best overall response rate possible.”

HER2 AMPLIFICATION/OVEREXPRESSION IN mCRC

HER2 amplification or overexpression occurs in a relatively small proportion (2%-6%) of mCRCs, with a higher prevalence seen in patients with left-sided tumors and RAS WT disease. Despite its relatively low prevalence, HER2 amplification is important to recognize in mCRC, because multiple HER2-targeted therapies in clinical development have shown promising results, said Ciombor. She ensures that all her patients, and particularly those with RAS WT disease, receive testing for HER2. To maximize efficiency, she also recommends HER2 testing in the same NGS panel that contains other markers (eg, RAS) instead of RAS testing followed by HER2 testing if the tissue is found to be RAS WT; the latter is more time-consuming and requires more tumor tissue. However, she noted that HER2 IHC with FISH for confirmation is adequate if the provider does not have access to NGS. “What we previously considered rare is now very actionable, and [it] can really affect patients,” said Ciombor.

However, Ciombor noted that many barriers exist that limit access to HER2 biomarker testing, including lack of knowledge among providers about what to test for, lack of insurance coverage for NGS testing, and inadequate provider awareness about available HER2 therapies for mCRC. She added that access to optimal molecular testing is an essential component to optimizing treatment for patients with mCRC, and inclusion of testing for seemingly rare targets (eg, HER2) is essential. “Patients [with mCRC] who can’t get good molecular testing are really at a disadvantage when it comes to their treatment,” said Ciombor. “It’s important to really make sure that you have all the actionable alterations covered in terms of testing so that you can truly personalize the patient’s care by [considering the results of] their molecular testing.
and other factors, such as their comorbidities, goals, and preferences. Molecular testing is certainly 1 piece of the pie in terms of how I consider what is the best treatment for our patient.”

**SELECTION OF PATIENTS FOR HER2 TESTING IN mCRC**

When identifying candidates for HER2 testing, Raghav and his colleagues look for patients with mCRC harboring RAS and BRAF WT in the clinical setting and expand this to include those with RAS-mutant disease in the research setting. Although guidelines state that HER2-directed therapy is only indicated in HER2-amplified disease that is RAS and BRAF WT, Raghav said that his team also tests for levels of HER2 expression and mutations in the research setting.

Raghav added including NGS as part of the quality metrics when assessing performance is necessary to optimize use and increase uptake of NGS. Collecting biomarker information through NGS testing, he said, may help with development of population subsets that can be included in current and future clinical trials of targeted agents.

Haumschild noted that providers increasingly are ordering NGS tests and that payers are encouraging the use of these tests to ensure appropriate prescription of medications, but the panel of targets needs to be clinically appropriate to be covered. He said that payers are likely to cover an NGS panel if it includes biomarkers that apply to approximately 80% of the mCRC population and show the ability to guide treatment choice and therefore improve patient care.

“Typically, if it checks those boxes, we’re going to be most likely approving those next-generation sequencing and encouraging those prior to treatment decisions so we know the most appropriate therapeutic selections are occurring,” he said.

Although Raghav noted that data are sparse on the comparison of HER2 amplification testing in the academic versus community setting, he said that NGS and expanded NGS panels tend to be used more frequently and earlier in the course of management in academic practices. Raghav added that when more than 4 or 5 actionable molecular markers need to be measured, testing all the markers simultaneously in an NGS panel is more cost- and time-efficient than is performing separate tests for each marker; however, not all the payer systems have recognized NGS panels as standard of care.

“Hopefully, we can bridge that divide completely, and [then] HER2 testing, including NGS, becomes the standard of care for all patients across the academic as well as the community settings,” he said.

**CLINICAL TRIALS OF HER2-TARGETED THERAPIES IN mCRC**

Because single-agent HER2 therapy has not been shown to be effective in mCRC, said Raghav, clinical trials of HER2-targeted therapies generally focus on dual HER2 inhibition (use of 2 HER2-targeted agents) or HER2 antibody-drug conjugates (a humanized HER2 monoclonal antibody linked to a cytotoxic topoisomerase I inhibitor payload [eg, trastuzumab deruxtecan]).

The results of the phase 2 HERACLES trial (NCT03225937) showed that treatment with trastuzumab (an HER2-directed monoclonal antibody) plus lapatinib (a small molecule tyrosine kinase inhibitor [TKI] targeting HER2) led to an objective response in 10 of 31 patients (31%; 95% CI, 16%-49%) with highly refractory, HER2-positive (HER2+) mCRC who previously received a median of 5 lines of therapy; stable disease was noted in an additional 13 patients (42%; 95% CI, 26%-69%). Six of 27 patients (22%) experienced grade 3 toxicities, including fatigue (n = 4), skin rash (n = 1), and elevated bilirubin (n = 1). In the MyPathway trial (NCT02091141), results among 57 patients with HER2-amplified mCRC who were included in the analysis showed that trastuzumab plus pertuzumab (an HER2-targeted monoclonal antibody) led to an objective response in 18 patients (32%; 95% CI, 20%-35%); the median duration of treatment was 2.1 months. The most common all-grade treatment-emergent AEs (TEAEs) were diarrhea (33%), fatigue (32%), and nausea (30%), and the most common grade 3 to 4 TEAEs were hypokalemia and abdominal pain (5% each).

The single-arm, phase 2 MOUNTAINEER trial (NCT03043313) evaluated trastuzumab with tucatinib, a small molecule HER2-targeted TKI, in patients with previously treated HER2-positive mCRC. During the European Society for Medical Oncology World Congress on Gastrointestinal Cancer 2022, results were presented from 84 patients assigned to receive tucatinib and trastuzumab. The analysis showed a confirmed objective response rate (ORR) of 38.1% (95% CI, 27.7%-49.3%), a median duration of response of 12.4 months (95% CI, 8.5 months to 20.5 months), a median PFS of 8.2 months (95% CI, 4.2 months to 10.3 months), and a median OS of 24.1 months (95% CI, 20.3 months to 36.7 months). Among patients assigned to receive tucatinib and trastuzumab (n = 86), the most common (incidence ≥ 20%) TEAEs were diarrhea (grade 1 or 2: 60.5%, grade 3: 3.5%), fatigue (grade 1 or 2: 41.9%, grade 3: 2.3%), nausea (grade 1 or 2: 34.9%), and infusion-related reaction (grade 1 or 2: 20.9%). Hypertension was the most common grade 3 or worse AE (grade 3: 7%).

Raghav noted that there are insufficient data to demonstrate a clear superiority of 1 dual HER2-targeted regimen over another and that some of the differences among the trials may be due to differences in patient selection. For example, the HERACLES trial defined HER2 positivity using IHC and FISH testing, whereas the MyPathway trial defined HER2 positivity as a positive HER2 finding using any test combination or NGS panel conducted in Clinical Laboratory Improvement Amendments (CLIA)-validated laboratories. Although he described the AEs of HER2-targeted therapy as generally manageable, Raghav said that he checks heart function before starting therapy and frequently over the course of treatment to ensure the agents are not causing long-term damage; a grade 3 decrease in left ventricular ejection fraction was noted in 2 patients (6%) who received trastuzumab and lapatinib in the HERACLES-A trial (NCT03225937).
“The bottom line is that dual anti-HER2 inhibition works very well in patients who [have] treatment-refractory metastatic colorectal cancer and have HER2 overexpression or amplification,” said Raghav. “They are also very well-tolerated treatments overall compared [with] other options that you have in colorectal cancer.”

Treatment with trastuzumab deruxtecan showed promise in the phase 2 DESTINY-CRC01 trial (NCT03384940), which studied its efficacy and safety in patients with HER2-expressing mCRC. An analysis of data from 53 patients in cohort A (HER2 IHC, 3+ or 2+; ISH positivity) showed an ORR of 45.3% (95% CI, 31.6%-59.6%) after a median follow-up of 27.1 weeks. The most common grade 3 or worse TEAEs were decreased neutrophil count (22%) and anemia (14%), and 6% of patients had adjudicated interstitial lung disease or pneumonitis (including 2 cases of grade 5 effects).

The study authors noted that interstitial lung disease and pneumonitis require close monitoring and intervention; however, trastuzumab deruxtecan provides a promising and durable option in patients who are heavily pretreated, including those who previously received HER2-targeted therapies. Raghav emphasized the importance of keeping a high clinical suspicion for interstitial lung disease during treatment with trastuzumab deruxtecan.

**HER2- AND EGFR-TARGETED THERAPIES**

Knowing a patient’s HER2 status may provide a more targeted option for HER2-amplified mCRC than the conventional FOLFOX6 (oxaliplatin, folinic acid [leucovorin], and fluorouracil) or FOLFIRI (folinic acid [leucovorin], fluorouracil, and irinotecan) options, which yield short PFS (particularly in the second-line setting) and 3 or 4 AEs in over 50% of patients when used in the first-line setting. Additionally, said Raghav, data showing that HER2+ mCRC is less likely to respond to anti-EGFR therapy further support testing for HER2 status before starting treatment, both to avoid unnecessary exposure to EGFR inhibitors and to provide an opportunity to enroll in clinical trials of HER2-targeted therapy. Results of a retrospective, longitudinal cohort study of patients with mCRC showed that of patients with RAS WT tumors treated with EGFR-targeted monoclonal antibodies, those with HER2 amplification or overexpression were 50% less likely to have a response than were those with HER2-negative disease (odds ratio, 0.52; 95% CI, 0.27-0.98; P = .044); further, they tended to have a shorter median PFS (5.7 months [95% CI, 4.9-6.0 months] vs 7 months [95% CI, 6.0-8.0 months], respectively; hazard ratio, 1.35 [95% CI, 0.96-1.89]; P = .087).

“I find that doing that testing in terms of looking for sure that we can sequence the best therapies appropriately for the patients,” said Ciombor.

**FUTURE DIRECTIONS FOR HER2 TESTING**

Raghav noted that the testing for HER2 status and uptake of HER2-targeted therapy for mCRC is improving. However, he commented, oncologists may need time to increase their awareness about low-prevalence targets such as HER2, because they may not see many patients with this molecular aberration. Raghav said that accessibility to HER2 testing should be adequate, because HER2 IHC is widely available; however, he added, FDA approval of HER2-targeted therapies for mCRC is the next major hurdle to improving therapeutic options for affected patients with tumors that harbor this molecular aberration.

“HER2 is a small, but an important, biomarker that should be looked for in all patients with metastatic colorectal cancer because of the immense therapeutic impact that it can create on the life of these patients,” said Raghav. “I would urge all oncologists to try to identify these patients as early as possible in their treatment continuum, not only because it has a tremendous therapeutic impact in the life of these patients because of available therapies, but also because we need to identify these patients so we can further research and help all patients with this subset.”

**REFERENCES**
