Molecular biomarker testing for all patients with metastatic colorectal cancer (CRC) has become increasingly important because identifying targetable alterations can lead to meaningful clinical benefits. At a minimum, testing should include RAS, BRAF mutational status, microsatellite instability status, HER2 expression, NTRK, and RET mutations. For HER2-amplified cancer, the NCCN Guidelines offer multiple treatment options, including trastuzumab in combination with tucatinib or pertuzumab, and trastuzumab-deruxtecan. Combination trastuzumab + tucatinib has recently received approval by the FDA for refractory RAS wild-type, HER2-amplified CRC. The addition of bevacizumab to triluridine/tipiracil treatment has significantly prolonged median overall survival compared with triluridine/tipiracil alone, regardless of molecular subtypes. KRAS G12C–targeted therapies are on the horizon, with several agents in ongoing studies. Furthermore, bilevel blockade is important when addressing MAP kinase pathway alterations. Presented by Midhun Malla, MD, MS; Katrina S. Pedersen, MD, MS; and Aparna R. Parikh, MD, MS

ABSTRACT

Colorectal cancer (CRC) remains the third leading cancer incidence in the United States, with >150,000 patients diagnosed each year. There has been an increasing incidence in those aged <50 years, and CRC is expected to surpass breast cancer as the leading cause of cancer-related deaths by 2030 among those aged 20 to 49 years. As various molecular subsets emerge, multiple targeted therapies have been approved for specific alterations, including those with microsatellite unstable disease (4%–5% of metastatic CRC), BRAFV600E mutations (8%–10%), and HER2 amplification (3.3%–5%). Additionally, rare alterations in genes and transcripts such as NTRK, POLE, POLD, and RET have been identified. During the NCCN 2023 Annual Conference, Midhun Malla, MD, MS, Assistant Professor, West Virginia University Cancer Institute; Aparna R. Parikh, MD, MS, Assistant Professor, and Director, Global Cancer Care Program, Massachusetts General Hospital Cancer Center; and Katrina S. Pedersen, MD, MS, Associate Professor of Medicine, Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, discussed the importance of biomarker testing in patients with metastatic CRC and reviewed the results of recent clinical trials for the treatment of this disease.

Background

The timeline of CRC treatment has evolved significantly over the years, said Dr. Parikh, who noted that from the 1960s to 2004, chemotherapy was the primary treatment. In the early 2000s, biologics were introduced, along with a few additional chemotherapy drugs. Since that time, a number of targeted and immunotherapy agents have gained FDA drug approval, either specifically for CRC or on a tumor agnostic basis. In 2017, pembrolizumab demonstrated promising efficacy in microsatellite instability-high (MSI-H) solid tumors. Recently, breakthrough therapy designation and accelerated approval status have been granted by the FDA for KRAS G12C inhibitors, and tucatinib + trastuzumab combination, respectively, for HER2-amplified CRC.1

HER2 Testing and Treatment

According to Dr. Malla, HER2 testing in metastatic CRC is essential for identifying patients who may benefit from targeted therapies. The incidence of HER2 amplification is between 3.3% and 5% in metastatic CRC, and increases up to 10% in those with left-sided colon and rectal primaries with RAS/RAF wild-type disease. HER2 amplification is associated with complex signaling cascade downstream, leading to activation of MAP kinase, PI3K/mTOR, and STAT3 reactivation pathways. This process leads to cell growth, proliferation, tumor angiogenesis, and metastatic spread.2 HER2 amplification has also been shown to confer resistance to anti-EGFR inhibitors and is associated with inferior survival outcomes in patients with HER2-positive disease exposed to chemotherapy with cetuximab or panitumumab.

A retrospective study by Raghav et al3 demonstrated that patients with HER2-positive CRC treated with anti-EGFR inhibitors had significantly shorter median progression-free survival (PFS) compared with those with HER2-negative disease (2.8 vs 8.1 months). Dr. Malla believes this suggests that HER2 amplification is a negative
predictive biomarker of EGFR inhibitor response in metastatic CRC.

The MOUNTAINEER phase II study investigated the combination of trastuzumab + tucatinib in patients with HER2-positive, RAS wild-type metastatic CRC following disease progression on 5-fluorouracil, irinotecan, oxaliplatin, and vascular endothelial growth factor (VEGF) inhibitors where indicated. This study showed promising activity, said Dr. Malla, with objective response rates of 38% in the trastuzumab + tucatinib cohort. Median PFS and overall survival (OS) were approximately 8.2 and 24 months, respectively, for the second line and beyond. The safety profile of the combination therapy was manageable, with grade ≥3 adverse effects (AEs) occurring in approximately 40% of patients, and AEs leading to treatment discontinuation in 6%. The most common tucatinib-related AEs were diarrhea, fatigue, nausea, and dermatitis. The FDA granted accelerated approval for this combination in January 2023.

Fam-Trastuzumab-Deruxtecan-nxki (T-DXd)

Dr. Malla discussed the use of the antibody–drug conjugate fam-trastuzumab deruxtecan (T-DXd) and its evaluation in the DESTINY-CRC01 Study. This open-label, multicenter phase II study assessed patients with unresectable or metastatic CRC who had any level of positive HER2 expression and had RAS/RAF wild-type disease; it also allowed patients who had received prior anti-HER2 therapy. Patients were divided into 3 cohorts based on HER2 immunohistochemistry and fluorescence in situ hybridization (FISH) results.

Key findings from the study include significant improvement in the confirmed objective response rate, the primary endpoint of the study, to 45% in the HER2 3+ or 2+ (FISH-positive) cohorts. No responses were observed in the 2+ (FISH-negative) and 1+ cohorts. Lastly, 8 of the 78 total patients enrolled experienced interstitial lung disease/pneumonitis, with 3 cases resulting in death (grade 5). Median time to onset was 61.0 days (range, 9–165 days), and corticosteroids were used for management.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer have been updated to include these regimens for patients with proficient mismatch repair (pMMR) who have experienced disease progression on oxaliplatin- or irinotecan-based regimens and have HER2-amplified disease (Figure 1). Dr. Malla also emphasized the importance of considering HER2-targeted clinical trials and the need for confirmatory phase III data to support phase II findings.

Refractory Metastatic CRC: New Standard of Care?

In the nontargeted refractory metastatic CRC space, the combination of triluridine/tipiracil + bevacizumab has emerged as a potential new standard of care based on findings from the SUNLIGHT study. This open-label, randomized phase III trial enrolled patients with refractory metastatic CRC who had experienced disease progression or were intolerant to prior FOLFOX (leucovorin/fluorouracil/oxaliplatin)/FOLFIRI (leucovorin/fluorouracil/irinotecan)-based regimens. The study compared triluridine/tipiracil + bevacizumab with triluridine/tipiracil alone, with OS as the primary endpoint.

Findings from the SUNLIGHT study were presented at the 2023 ASCO Gastrointestinal Cancers Symposium. Key findings include: (1) median OS was significantly prolonged to 10.8 months with triluridine/tipiracil + bevacizumab compared with 7.5 months with triluridine/tipiracil alone (hazard ratio [HR], 0.61; 95% CI, 0.49–0.77); (2) benefits were observed across all subsets, with a particular focus on European and rest-of-the-world populations, as North American representation was very limited; (3) PFS was significantly improved: 5.6 versus 2.4 months (HR, 0.44; 95% CI, 0.36–0.54); and (4) the safety profile was manageable, with neutropenia, nausea, and anemia being comparable or slightly higher in terms of any-grade side effects.

“The SUNLIGHT study demonstrated the potential benefit of triluridine/tipiracil + bevacizumab in refractory metastatic CRC in a randomized trial,” said Dr. Malla. “Although the safety profile is manageable, further investigation is needed to address optimal dosing, scheduling, and survival outcomes in Western populations.”

Neoadjuvant Chemotherapy: MSI-H Colon Cancer

As Dr. Pedersen reported, the recently released NCCN Guidelines for Colon Cancer have undergone significant restructuring due to the findings from several studies. These studies have provided valuable insights into neoadjuvant treatment options and their effects on patient outcomes dependent on tumor microsatellite status.

The FOxTROT trial, which included >1,000 patients with both pMMR and deficient MMR (dMMR) (analogous to microsatellite-stable and MSI-H tumors, respectively), compared the standard approach of up-front hemicolectomy followed by up to 6 months of adjuvant oxaliplatin-based doublet chemotherapy to a neoadjuvant arm. The neoadjuvant arm involved administering oxaliplatin and fluorouracil or capecitabine for 6 weeks, followed by surgery, and then up to a perioperative total of 3 versus 6 months of adjuvant therapy. This trial revealed that patients with dMMR or MSI-H disease were less likely to have a meaningful response to neoadjuvant chemotherapy compared with patients with pMMR. However, it is important to note this did not increase their likelihood of recurrence later, added Dr. Pedersen.

The recent NICHE and NICHE-2 studies focused specifically on patients with clinical stage II or III disease, which presents challenges in terms of accurate clinical
staging and appropriate patient selection in colon cancer, said Dr. Pedersen. These studies involved administering a single neoadjuvant treatment of ipilimumab with nivolumab, followed 2 weeks later by a single dose of nivolumab, followed by resection 2 weeks after the second dose of immunotherapy. Despite the brief neoadjuvant treatment period, the primary endpoint of improved rates of major pathologic response were overwhelmingly positive (95%). Of note, no treatment-related AEs led to delays in the perioperative treatment is recommended for patients with dMMR/MSI-H disease without contraindications to immunotherapy, immune checkpoint inhibitors, and separated based on dMMR or MSI-H disease versus other settings and metastatic frontline settings, up to 6 months of perioperative treatment is recommended for patients with resectable metastatic CRC.

“This remarkable result is particularly striking, considering some of these patients are already 5 years out from therapy,” said Dr. Pedersen. “The disease-free survival data are still pending, but the impressive responses observed after just 2 doses of immunotherapy suggest a significant impact on the treatment of colon cancer.” This is reflected by the recently released major updates to the NCCN Guidelines for Colon Cancer, Version 1.2023, giving separate treatment pathways for early-stage CRC based on MSI status.

**First-Line Immune Checkpoint Inhibitors for MSI-H Metastatic CRC**

Dr. Pedersen discussed adjuvant therapy for resected oligometastatic disease, highlighting the lack of strong randomized trial data for resected stage IV CRC. As noted previously, the NCCN Guidelines have been restructured and separated based on dMMR or MSI-H disease versus recommendations for patients with microsatellite-stable tumors. Based on extrapolated data from stage II and III adjuvant settings and metastatic frontline settings, up to 6 months of perioperative treatment is recommended for patients with resectable metastatic CRC.

In patients with MSI-H disease without contraindications to immunotherapy, immune checkpoint inhibitors (anti–PD-1, anti–CTLA-4) can be considered. This recommendation is mainly based on the frontline use of immune checkpoint inhibitors for unresectable CRC, with KEYNOTE-177 and CheckMate 142 being the 2 major studies informing clinical decision-making.

KEYNOTE-177 was a randomized phase III trial comparing pembrolizumab for up to 2 years versus investigator’s choice of chemotherapy in 307 patients with newly
diagnosed, unresectable stage IV colon or rectal cancer. The results showed a benefit from PD-1 inhibition for patients with MSI-H disease.\(^\text{10}\) CheckMate 142 was a nonrandomized, multicohort trial with one cohort receiving nivolumab in the frontline, a second-line cohort, and a frontline cohort of ipilimumab + nivolumab.\(^\text{10}\) Outcomes for pembrolizumab and nivolumab were nearly identical across the trials. However, adding CTLA-4 inhibition with ipilimumab improved the response rate, PFS, and OS,\(^\text{11}\) although this is not based on randomized phase III data.

**Circulating Tumor DNA in Stage IV Resected CRC**

Dr. Pedersen discussed the prognostic value of circulating tumor DNA (ctDNA) in stage II and III resected CRC and its potential role in stage IV oligometastatic CRC with liver disease (CRC-LM). A study by Tie et al\(^\text{12}\) aimed to understand the dynamics of ctDNA in terms of positive/negative status and its implications on patient outcomes. The study enrolled 54 patients into 2 cohorts: one with up-front surgery and ctDNA testing over time, and the second with up-front chemotherapy, followed by surgery and ctDNA testing across the perioperative and surveillance periods.

Key findings from the Tie et al\(^\text{12}\) study demonstrated that, of the total study population, 24% with oligometastatic CRC with liver metastases were ctDNA-positive after surgery. Patients who were ctDNA-positive had an 83% recurrence risk over the next 3 years, whereas those who were ctDNA-negative had a 31% risk of recurrence. Lastly, patients who remained ctDNA-positive after receiving surgery or adjuvant chemotherapy had a 100% likelihood of cancer metastasis, whereas those who converted to ctDNA negativity after adjuvant treatment had a 33% likelihood of recurrence.

Dr. Pedersen suggested that ctDNA testing may potentially play a role in guiding treatment decisions for patients with stage IV oligometastatic liver disease, particularly in less straightforward cases. However, this currently remains an unofficial clinical practice because there is no predictive therapeutic benefit associated with ctDNA at this point.

**Miscellaneous Metastatic Treatment Updates**

Furthermore, Dr. Pedersen discussed the progress in targeting **KRAS** mutations in cancer, specifically focusing on the **KRAS** G12C mutation. Although only a small percentage of CRCs have the G12C mutation, targeted therapies such as sotorasib and adagrasib have shown activity in clinical trials.\(^\text{13}\) Adagrasib, in particular, has received breakthrough therapy designation by the FDA based on a phase I/II trial published in *The New England Journal of Medicine*.\(^\text{14}\) The trial investigated adagrasib as monotherapy and in combination with cetuximab, with the latter showing enhanced likelihood of benefit, as expected from the CRC trial experience that MAPK pathway targeting requires 2-level blockade at the EGFR receptor to prevent escape loop signaling and rapid drug resistance.

**NTRK** fusions, although rare in CRC (with a prevalence of <1%), are reportedly more common in right-sided tumors, elderly females, and patients with nodal metastasis, and confer a poor prognosis. Tumor-agnostic FDA-approved treatments for **NTRK** fusion–positive tumors include larotrectinib and entrectinib, which have demonstrated effectiveness.

Finally, **RET** fusions were briefly discussed because, although uncommon in CRC, they can be targeted by the FDA-approved treatment selpercatinib for any **RET** fusion–positive solid tumor type. Dr. Pedersen emphasized the importance of comprehensive DNA and RNA testing, including assessing for fusions, to identify suitable targeted therapies for patients.

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**Correspondence:** Midhun Malla, MD, MS, West Virginia University, 1 Medical Center Drive, Morgantown, WV 26508. Email: midhun.malla@hsc.wvu.edu; Katrina S. Pedersen, MD, MS, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8056, St. Louis, MO 63110. Email: kpedersen@wustl.edu; and Aparna R. Parikh, MD, MS, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Boston, MA 02114. Email: aparna.parikh@mgh.harvard.edu

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