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Diagnosis and Treatment of Metastatic Colorectal Cancer
A Review

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IMPORTANCE Colorectal cancer (CRC) is the third most common cause of cancer mortality worldwide with more than 1.85 million cases and 850 000 deaths annually. Of new colorectal cancer diagnoses, 20% of patients have metastatic disease at presentation and another 25% who present with localized disease will later develop metastases.

OBSERVATIONS Colorectal cancer is the third most common cause of cancer mortality for men and women in the United States, with 53 200 deaths projected in 2020. Among people diagnosed with metastatic colorectal cancer, approximately 70% to 75% of patients survive beyond 1 year, 30% to 35% beyond 3 years, and fewer than 20% beyond 5 years from diagnosis. The primary treatment for unresectable metastatic CRC is systemic therapy (cytotoxic chemotherapy, biologic therapy such as antibodies to cellular growth factors, immunotherapy, and their combinations.) Clinical trials completed in the past 5 years have demonstrated that tailoring treatment to the molecular and pathologic features of the tumor improves overall survival. Genomic profiling to detect somatic variants is important because it identifies the treatments that may be effective. For the 50% of patients with metastatic CRC with *KRAS/NRAS/BRAF* wild-type tumors, cetuximab and panitumumab (monoclonal antibodies to the epithelial growth factor receptor [EGFR]), in combination with chemotherapy, can extend median survival by 2 to 4 months compared with chemotherapy alone. However, for the 35% to 40% of patients with *KRAS* or *NRAS* sequence variations (formerly termed *mutations*), effective targeted therapies are not yet available. For the 5% to 10% with *BRAF V600E* sequence variations, targeted combination therapy with BRAF and EGFR inhibitors extended overall survival to 9.3 months, compared to 5.9 months for those receiving standard chemotherapy. For the 5% with microsatellite instability (the presence of numerous insertions or deletions at repetitive DNA units) or mismatch repair deficiency, immunotherapy may be used in the first or subsequent line and has improved treatment outcomes with a median overall survival of 31.4 months in previously treated patients.

CONCLUSIONS AND RELEVANCE Advances in molecular profiling of metastatic CRC facilitate the ability to direct treatments to the biologic features of the tumor for specific patient subsets. Although cures remain uncommon, more patients can anticipate extended survival. Genomic profiling allows treatment selection so that more patients derive benefit and fewer are exposed to toxicity from ineffective therapies.

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Colorectal cancer (CRC) is the third most common cause of cancer-related death in the United States, and in 2020, an estimated 147 950 new cases and 53 200 deaths were projected.[1] Among people diagnosed with colon cancer, 20% have metastatic CRC,[2] and 40% present with recurrence after previously treated localized disease.[3] The prognosis of metastatic CRC is poor, with a 5-year survival rate of less than 20%.[2] New treatment strategies that use pathologic and molecular tumor testing to select therapy have the potential to improve prognosis. This review summarizes current evidence regarding diagnosis and systemic treatment for patients with unresectable metastatic CRC.

Methods

PubMed and Cochrane databases were searched from January 1, 2014, to June 1, 2020, using a Cochrane Highly Sensitive Search Strategy to identify randomized clinical trials (RCTs), meta-analyses, and systematic reviews, using established Medical Subject Headings for CRC diagnosis and treatment. References of identified articles were reviewed. RCTs, meta-analyses, and practice guidelines were prioritized. US Food and Drug Administration (FDA) documents in the public domain and labels for all antineoplastic drugs indicated for treatment of metastatic CRC were

retrieved from the agency's website and reviewed. A total of 222 phase 3 RCTs, 111 meta-analyses, 97 systematic reviews, and 4 practice guidelines were evaluated for this review.

Clinical Presentation

Patients with CRC typically present with rectal bleeding, microcytic anemia, altered bowel habits, and chronic abdominal pain.[2] Median age at onset is 67 years. Although only 12% of patients are younger than age 50, the US incidence of CRC presenting before age 50 has increased approximately 2% per year since the 1990s, and 17 930 cases and 3640 deaths were projected among patients younger than age 50 years in 2020.[1] Reasons for the increase in CRC in patients younger than age 50 remain poorly understood. Obesity, sedentary lifestyle, and diets high in processed food may contribute.[4,5]

Metastatic CRC may consist of tumors identified at a distant site following a previously treated localized CRC (nonmetastatic or stage I-III) or may present de novo at stage IV, defined as metastatic disease or cancer that has spread outside the original colorectal mass. The most common sites of metastasis include lymph nodes, liver, lung, and peritoneum.[6] Among people presenting with CRC, the likelihood of developing metastases is less than 10% for stage I (lymph node–negative with tumor extending up to the muscularis propria); 10% to 20% for stage II (lymph node–negative with tumor extending through the muscularis propria or into other structures); and 25% to 50% for stage III (lymph node–positive) CRC.[7] Complete surgical resection with negative pathologic margins and adjuvant chemotherapy for stage III cancer decreases recurrence and risk of subsequent distant metastases to 20% to 30% of patients.

Approximately half of CRCs arise in the right side or proximal colon, which is embryologically derived from the midgut. These tumors typically present with fatigue, anemia, and abdominal pain or cramping. Left-sided tumors (ie, those in the distal colon and rectum) are derived from the embryologic hindgut and typically present with altered bowel habits such as constipation, narrow caliber stool, or rectal bleeding.[8,9] Immediate bowel surgery to resect the primary tumor is rarely necessary for patients with metastatic CRC. For patients with symptomatic bowel obstruction or major bleeding, palliative surgical options include resection, bypass ostomy, or endorectal stent placement to alleviate symptoms and facilitate initiation of chemotherapy.

Principles of Diagnosis

Pathologic confirmation of CRC is required before chemotherapy. Adenocarcinoma is the most common histology. Melanoma, lymphoma, neuroendocrine, and squamous cell tumors can arise in the bowel and require distinct treatment. Typically, colonoscopy-guided biopsy confirms the primary cancer, and biopsy of the liver, lung, or lymph node confirms metastases. For patients with previously diagnosed stage I to III CRC presenting with intrabdominal lymphadenopathy or liver lesions, biopsy is unnecessary if the patient is too frail for treatment or if the diagnosis is clear and molecular profiling is available from the primary tumor.

Diagnostic staging should include contrast-enhanced computed tomography imaging of the chest, abdomen and pelvis. Magnetic resonance imaging and positron-emission tomography may help distinguish metastases from benign lesions when computed tomography alone is unclear. Bone and central nervous system metastases are rare, and bone scans and brain imaging are unnecessary in asymptomatic patients. Serum levels of carcinoembryonic antigen (CEA) and cancer antigen 19-9 (CA19-9) protein tumor markers can help monitor treatment response but cannot confirm the presence or absence of CRC.

Molecular Profiling

To identify tumor subtypes for which targeted therapy may be available, all metastatic CRC tumors should undergo molecular profiling (**Box**). All CRC tumors should be tested for either mismatch repair deficiency (MMR-D) via immunohistochemistry or microsatellite instability-high (MSI-H) via polymerase chain reaction to screen for Lynch syndrome.[10] Lynch syndrome is the most common hereditary colorectal predisposition syndrome that is caused by an inherited alteration in one of 5 genes (*MLH1* [OMIM,120436], *MSH2* [OMIM, 609309], *MSH6* [OMIM, 600678], *PMS2* [OMIM, 600259] and *EPCAM* [OMIM, 185535]). The general population prevalence of Lynch syndrome is approximately 0.3%,[11] with approximately 3% of all CRC occurring among patients with Lynch syndrome.[12] Patients with Lynch syndrome have increased risk of colorectal, endometrial, ovarian, gastric, urinary tract, and many other cancer types. Microsatellite instability occurs when tumors accumulate numerous insertions or deletions at sites of repetitive DNA units called microsatellites. Normally, errors in base-pair matching during DNA replication are corrected, but a faulty mismatch repair process may result in the accumulation of insertions or deletions that predispose to malignant tumors. Five percent of metastatic CRC tumors are MMR-D or MSI-H, either due to Lynch syndrome or sporadic mutations, and may respond to immunotherapy. In addition to MMR-D and microsatellite instability, metastatic CRC tumors are also tested for mutations in *KRAS* (OMIM, 190070), *NRAS* (OMIM, 164790) and *BRAF* (OMIM, 164757).[10,13] However, next-generation sequencing is increasingly performed with multigene panels. Most insurers cover multigene panel tests for metastatic CRC, and there is potential benefit to identifying sequence variations (formerly termed *mutations*; [such as *ERBB2* {OMIM, 164870}] amplifications or *NTRK* gene fusions) and other genetic targets for investigational agents that exist in fewer than 2% of patients with metastatic CRC. Current research focuses on identifying new tumor biomarkers for treatment. Somatic tumor profiles can help match patients with clinical trials and identify the most common molecular targets for new drug development.

As an alternative to obtaining a pathologic specimen, which requires invasive biopsy, peripheral blood may be screened for circulating tumor DNA (ctDNA), consisting of tumor-specific sequence variations released from apoptotic or necrotic tumor cells circulating in blood.[14] Testing of ctDNA remains investigational but is an active area of ongoing research. One meta-analysis of 21 studies involving 1812 patients with nonmetastatic

and metastatic CRC showed that ctDNA evaluation for *KRAS* sequence variations had sensitivity of 67% and specificity of 96%.[15]

Germline sequence variations are present in up to 10% of patients with metastatic CRC.[16] Patients with MSI-H and MMR-D tumors, age younger than 50 years, or suggestive family history should undergo genetic testing. Germline testing does not affect chemotherapy options but helps determine family members' risk.

Therapy and Prognosis

Metastatic CRC may be limited to a few metastatic foci, typically in the liver or lung, that a surgeon can remove entirely. Metastatic CRC is termed *resectable* when the primary tumor and all metastases are amenable to complete surgical removal. However, in these patients, nodal infiltration and occult micrometastatic dissemination is common. Resection of metastatic CRC achieves long-term cure for less than 20% of metastatic CRC patients. When metastatic CRC may be resectable, surgical and medical oncologists should collaborate to formulate treatment plans. Radiation oncologists should be involved if the primary tumor is in the rectum.[17]

Systemic chemotherapy is the primary treatment for metastatic CRC. Drugs with FDA-approved indications for metastatic CRC are listed in **Table 1**. Metastatic CRC remains incurable for most patients. Based on population-based data from the National Cancer Institute, 5-year survival for metastatic CRC is 14% (Box).[2] Estimates of survival today are based on trials that began 4 to 6 years ago and do not reflect recent advances. Although cure for metastatic CRC is rare, recent large clinical trials that included patients healthy enough to receive chemotherapy have shown that intensive treatment with multiple systemic therapies can help patients survive for 2 to 3 years.

Survival depends on the molecular subtype, which informs prognosis by identifying both a tumor's natural history as well as therapies that are and are not likely to be effective. For the 50% of patients with *KRAS/NRAS/BRAF* wild-type metastatic CRC, median survival with treatment is approximately 30 months (**Figure**),[18,19] with survival rates of 80% at 1 year, 40% at 3 years and 20% at 5 years after start of first-line chemotherapy.[19] Median survival was 19 months for trial participants with right-sided primary tumors and 34 months for left-sided primary tumors,[20] which may be related to the distinct genomic patterns between right- and left-sided CRCs. In an analysis of tumors from 1319 patients at a single institution, right-sided tumors were more than twice as likely to have MSI-H and more commonly have *KRAS* sequence variations (42.5% vs 18.9%; $P = .001$) and *BRAF* sequence variations (26.6% vs 3.2%; $P < .001$) compared with left-sided tumors.[21] A pooled analysis of 5 RCTs involving 1239 patients found median overall survival was 21.0 months for patients with *KRAS* sequence variations and 11.7 months for those with *BRAF* sequence variations[22] (although the trials did not include *BRAF*-directed therapy [combination *BRAF* and monoclonal antibodies that inhibit EGFR, which have a median overall survival of approximately 9 months for this subset of metastatic CRC with historically poor prognosis]).[23,44] Patients with MSI-H and MMR-D tumors have a better prognosis than patients with microsatellite stable or MMR-proficient tumors because they respond to immunotherapy agents.[24]

Other factors influencing metastatic CRC prognosis include previous receipt of adjuvant chemotherapy, time between adjuvant therapy and development of metastases (shorter is associated with worse prognosis), comorbid conditions, and frailty. Without treatment, survival with metastatic CRC is typically 6 to 12 months. Patients with a life expectancy of less than 6 months, due to other comorbid illness, rarely derive benefit from systemic chemotherapy. For frail patients who cannot tolerate or do not want intensive therapies, single-agent fluorouracil or capecitabine may extend survival to 12 to 18 months, with only modest toxicity. Multiagent chemotherapy is necessary to attain survival beyond 18 months.

Box. Commonly Asked Questions About Metastatic CRC

When Is Immunotherapy an Appropriate Therapy for Metastatic CRC?

Five percent of metastatic CRCs have MSI-H or MMR-D tumors. In patients with MSI-H or MMR-D tumors, immunotherapy extends survival significantly more than traditional chemotherapy. However, CRC without this molecular profile does not respond to immunotherapy.

What Is the Prognosis for Metastatic CRC?

Population-based data from the National Cancer Institute indicate that the 5-year survival rate for metastatic CRC is 14%. Recent large clinical trials that included patients who were healthy enough to receive chemotherapy reported that median survival is 2 to 3 years. Survival depends on the molecular subtype of the tumor, as well as a patient's comorbid illnesses and level of fitness. Patients with *KRAS/NRAS* wild-type tumors respond to monoclonal antibodies that inhibit the epithelial growth factor receptor (cetuximab and panitumumab) and have better prognosis than patients with sequence variations in these genes who do not respond to these therapies.

Can Metastatic CRC Be Cured?

In approximately 10% to 20% of patients, metastatic CRC can be treated with surgery and chemotherapy, and cures can sometimes be achieved. This typically occurs when there are a small number of metastases confined to a single organ, such as the liver or lung. All patients with CRC who have limited metastatic disease should be evaluated by a multidisciplinary team of specialists that includes surgeons.

Should Patients With Metastatic CRC Have Molecular Tumor Profiling?

Molecular tumor profiling consists of pathologic testing of tumor tissue to assess for MSI-H or MMR-D and for sequential variants in *KRAS*, *NRAS*, and *BRAF* genes. This testing is valuable for all patients with metastatic CRC who are willing and able to receive chemotherapy because it provides information about the optimal treatment. For many patients, molecular tumor profiling can be completed on the primary CRC even if it was resected years before metastatic recurrence. In patients for whom tumor tissue is unavailable, a new biopsy may be required. Molecular tumor profiling is covered by most insurance companies.

Abbreviations: CRC, colorectal cancer; MMR-D, mismatch repair-deficient (or deficiency in some contexts); MSI-H, microsatellite instability-high.

Table 1. FDA-Approved Drugs for the Treatment of Metastatic Colorectal Cancer

Drug name[a]	Year of FDA approval	Mechanism of action	Typical use	Selected common adverse effects (% grades 1-4)[b]	Selected potentially severe adverse effects (% grades 3-4)[b]
Leucovorin	1952	Folic acid analog; interrupts DNA synthesis	In combination with fluorouracil	Not reported	Not reported
Fluorouracil	1962	Pyrimidine analog; interrupts DNA synthesis	In combination with leucovorin	Anemia (79), diarrhea (61), mucositis (62), nausea (51), neutropenia (46)	Coronary vasospasm (<8), diarrhea (10), mucositis (14), neutropenia (8)
Irinotecan	1996	Topoisomerase I inhibitor; interrupts the breaking and rejoining of DNA strands during replication	Used as a single agent or in combination	Anemia (97), alopecia (60), diarrhea (83), nausea (82), neutropenia (96)	Anemia (7), diarrhea (31), nausea (16), neutropenia (31)
Capecitabine, oral	1998	Pyrimidine analog; interrupts DNA synthesis	Used as a single agent or in combination (oral fluorouracil)	Anemia (80), diarrhea (55), hand/foot syndrome (54), nausea (43), neutropenia (13)	Coronary vasospasm (<8), diarrhea (10), mucositis (14), neutropenia (8), hand/foot syndrome (17)
Oxaliplatin	2002	Alkylating agent; causes DNA breaks	Used only in combination, not as a single agent	Anemia (64), diarrhea (46), nausea (64), peripheral neuropathy (76), thrombocytopenia (30)	Hypersensitivity reaction (<1), neuropathy (7), neutropenia (<10)
Cetuximab	2004	Recombinant chimeric monoclonal antibody to *EGFR*; interrupts or stops cell growth	Used only for *KRAS/NRAS* wild-type tumors	Acneiform rash (90), constipation (54), diarrhea (42), headache (38), hypomagnesemia (55), nausea (64)	Hypersensitivity reaction (2), hypomagnesemia (6-17), rash (16)
Bevacizumab[c]	2004	Humanized monoclonal antibody to VEGF; interrupts growth of blood vessels	In combination with fluorouracil/leucovorin, oxaliplatin, irinotecan	Delayed wound healing (4), diarrhea (21), hypertension (34)	Gastrointestinal perforation (2), hemorrhage (4), hypertension (5), proteinuria (1), thromboses (5)
Panitumumab	2006	Humanized monoclonal antibody to *EGFR*; interrupts or slows down cell growth	Used only for *KRAS/NRAS* wild-type tumors	Diarrhea (21), hypomagnesemia (38), nausea (23), skin toxicity (90), acneiform (57)	Hypersensitivity reaction (1), hypomagnesemia (2), skin toxicity (16)
Regorafenib, oral	2012	Multikinase inhibitor; inhibits cell growth and interrupts growth of blood vessels	Used as a single agent	Diarrhea (43), hand/foot syndrome (53), hemorrhage (18), hypophosphatemia (57), hypertension (30), pain (59)	Cardiac ischemia (1), hand/foot syndrome (17), hemorrhage (3), hepatotoxicity (0.3)
Ziv-aflibercept	2012	Recombinant fusion protein that functions as a decoy receptor to bind VEGF-A, VEGF-B, and placental growth factor; interrupts growth of blood vessels	In combination with FOLFIRI[d]	Diarrhea (69), hypertension (41), proteinuria (62)	Diarrhea (19), gastrointestinal perforation (0.8), hemorrhage(3), proteinuria (8)
Ramucirumab	2015	Recombinant humanized monoclonal antibody to VEGF-R2; interrupts growth of blood vessels	In combination with FOLFIRI[d]	Diarrhea (14), hypertension, (16) proteinuria (15)	Arterial thromboses (2), gastrointestinal perforation (0.7), hemorrhage (4), hypertension (8)
Trifluridine and tipiracil (TAS-102), oral	2015	Nucleic acid analogue/ thymidine phosphorylase inhibitor; interrupts DNA synthesis	Used as a single agent	Anemia (77), diarrhea (32), nausea (48), leukopenia (77), neutropenia (67)	Anemia (18), leukopenia (21), neutropenia (38)
Pembrolizumab	2017, 2020	Humanized monoclonal antibody against PD-1 receptor; activates T-cell–mediated immune response	Used only for MSI-H/MMR-D tumors; approved in the first or subsequent line of therapy	Arthralgia (16), nausea (16), diarrhea (13), pruritus (13), hypothyroidism (10)	Colitis (2), hepatitis (2), pancreatitis (3), pneumonitis (2)
Nivolumab	2017	Humanized monoclonal antibody against PD-1 receptor; activates T-cell–mediated immune response	Used only for MSI-H/MMR-D tumors	Diarrhea (21), hypothyroidism (10), pruritus (14), rash (13)	Colitis (1), hepatitis (1), pancreatitis (8)
Ipilimumab	2018	Humanized monoclonal antibody against CTLA-4; activates T-cell–mediated immune response	Used only for MSI-H/MMR-D tumors in combination with nivolumab	Diarrhea (32), pruritus (31), rash (29)	Pneumonitis (<1), colitis (7), hepatitis (4)
Encorafenib, oral	2020	*BRAF* inhibitor; interrupts or slows down cell growth	Used only for *BRAF V600E*–variant tumors in combination with cetuximab	Anemia (34), arthralgia (26), nausea (34), rash (26)	Anemia (4), cutaneous malignancies (1), hemorrhage (2)

Abbreviations: *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; *EGFR*, epithelial growth factor receptor; FDA, Food and Drug Administration; MMR-D, mismatch repair-deficient; MSI-H, microsatellite instability-high; PD-1, programmed cell death-1; VEGF, vascular endothelial growth factor.

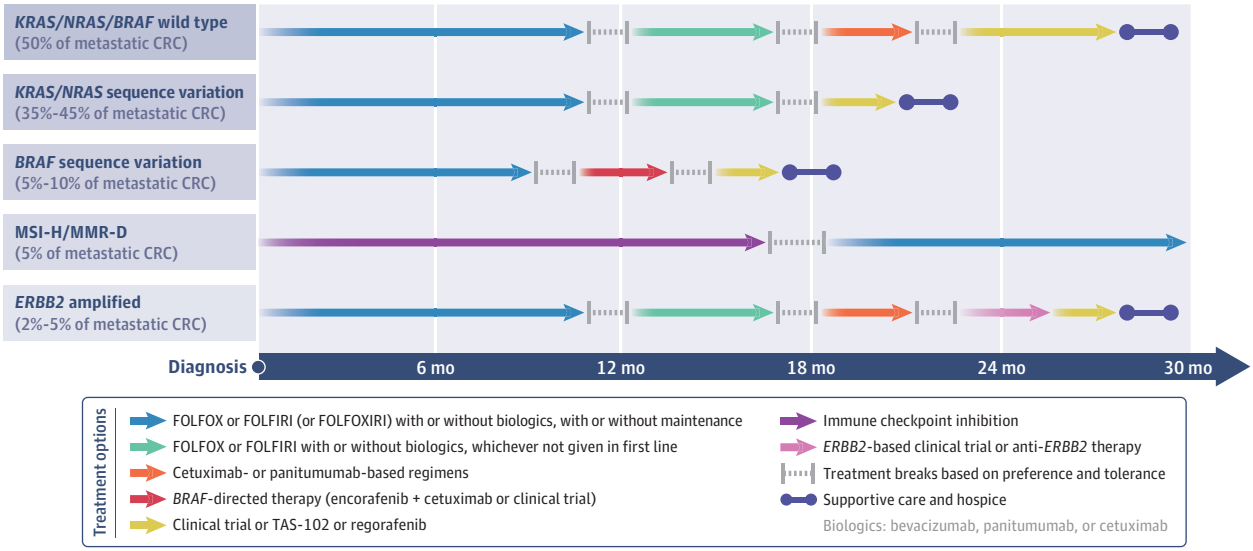
[a] Drugs are administered intravenously except where noted.

[b] Rates of common adverse effects were obtained from review of US FDA labels (preferentially describing results in metastatic CRC patients with monotherapy), US FDA new drug application medical review, and clinical trial reports, and include symptoms of any severity (low to high indicated by grades 1-4). Severe adverse effects include rates of grade 3 and 4 toxicity only. These rates vary based on drug regimen and combination and are approximations that do not reflect variation in dosing, use of supportive care medications, and synchronous use of multiple chemotherapy drugs. Notably, toxicities listed on these labels are derived entirely from clinician-filtered assessments. More contemporary trials collect patients' direct reports of toxicity burden. *Selected* indicates that the columns of adverse effects do not encompass all adverse effects.

[c] The US FDA has also approved biosimilars to bevacizumab (first in 2017).

[d] FOLFIRI indicates a fluorouracil/leucovorin and irinotecan regimen.

Figure. Prototypical Treatment Trajectories for Patients With Unresectable Metastatic Colorectal Cancer According to Molecular Subtype



The timelines indicate median survival times for prototypical patients who are healthy enough for intensive treatment. However, trajectories vary greatly within groups, and there are several alternatives concordant with practice guidelines. Patients' preferences, other conditions, and tolerance of treatment influence these trajectories. The duration of treatment breaks is longer for patients with stable disease and shorter for those who have disease progression. Investigational treatments are not shown but should be considered at each decision point given that available therapies do not achieve cure. The FOLFOX regimen indicates intravenous fluorouracil/leucovorin and oxaliplatin; FOLFIRI regimen, fluorouracil/leucovorin and irinotecan; and FOLFOXIRI regimen, fluorouracil/leucovorin, oxaliplatin, and irinotecan. CRC indicates colorectal cancer; MSI-H, microsatellite instability-high; MMR-D, mismatch repair-deficient.

Oncologists should help patients make informed decisions, based on each patient's goals, symptoms, and occupational, financial, and mental health concerns, in coordination with professionals from surgery, nursing, palliative care, social work, and primary care. In the setting of incurable malignancy, patients should also receive information about clinical trials as part of therapeutic options at each therapeutic decision point.

Systemic Therapy

First-line Therapy for Metastatic CRC

Fluoropyrimidines (either intravenous fluorouracil or oral capecitabine) have been first-line conventional chemotherapy for metastatic CRC for more than 50 years and are pyrimidine antagonists or antimetabolites that interfere with DNA synthesis. Fluorouracil is given in combination with leucovorin, a folic acid derivative that potentiates the cytotoxic inhibitory effects of fluorouracil. Oral capecitabine formulations were not associated with better or worse overall survival compared with intravenous fluorouracil therapy. For example, a meta-analysis of 8 RCTs involving 4363 patients compared the FOLFOX regimen (intravenous fluorouracil, leucovorin, and oxaliplatin) with CAPOX (oral capecitabine and oxaliplatin) and reported no associated differences in overall survival (odds ratio [OR], 1.04; $P = .56$).[25] A meta-analysis of 6 RCTs involving 1220 patients compared FOLFIRI (fluorouracil, leucovorin and irinotecan) and CAPIRI (capecitabine and irinotecan) and showed no association of either therapy with improved overall survival (pooled difference in median overall survival, 0.82 months; $P = .8$).[26] S-1 is a combination agent for treating metastatic CRC outside the United States that combines the fluorouracil prodrug tegafur with compounds that block its degradation and mitigate its toxic effects on the gastrointestinal tract. This review highlights fluorouracil/leucovorin and capecitabine, which are therapies typically used in North America.

Fluoropyrimidine monotherapy is generally well tolerated and typically used to treat frail or elderly patients. However, for reasonably healthy patients, first-line therapy consists of either oxaliplatin-based regimens (FOLFOX or CAPOX) or irinotecan-based regimens (FOLFIRI or CAPIRI). These regimens may be administered with or without additional targeted therapy. Comparisons of FOLFOX and FOLFIRI for first-line treatment of metastatic CRC demonstrated similar overall survival (eg, an RCT found a median overall survival of 31.4 months with FOLFOX used in combination with bevacizumab vs 30.1 months for FOLFIRI used in combination with bevacizumab (hazard ratio [HR], 0.99 [95% CI, 0.79-1.25]).[27] Oxaliplatin causes more sensory neuropathy, and irinotecan causes more diarrhea and alopecia. Most patients eventually receive both regimens by transitioning from one to the other when metastatic CRC grows despite treatment or when dose-limiting toxicity requires switching therapies. Patients who received adjuvant FOLFOX for stage III cancer may respond to reintroduction of FOLFOX for metastatic CRC. However, for patients with recurrence within 12 months of adjuvant FOLFOX or with persistent neuropathy, FOLFIRI is preferred. Treatments for metastatic CRC and the major toxicities associated with the treatments are shown in **Table 2**. Recent RCTs for metastatic CRC treatment are shown in **Table 3**. Patients should typically undergo restaging every 2 to 3 months with computed tomography scans of the chest, abdomen, and pelvis. Patients with tumor regression

Table 2. Chemotherapy Regimens Used for Treatment of Metastatic Colorectal Cancer

Regimen name and component drugs[a]	Dosing schedule	First-line use	Selected dose-limiting toxicities/adverse effects[b]	Additional comments
Oxaliplatin-containing regimens				
FOLFOX (fluorouracil, leucovorin, and oxaliplatin)	Every 2 weeks, half-day infusion in clinic with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	Yes	Pancytopenia, neuropathy, hypersensitivity	The most commonly used adjuvant regimen
CAPOX (capecitabine and oxaliplatin)[c]	Every 3 weeks with infusion in clinic and oral capecitabine for 2 weeks, 1 week off	Yes	Pancytopenia, diarrhea, hand/foot -syndrome, neuropathy, hypersensitivity	A common adjuvant regimen; substitutes oral capecitabine for intravenous fluorouracil
FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan)	Every 2 weeks, half day infusion in clinic with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, neuropathy, hypersensitivity	Intensive regimen used for patients who are fit or possible candidates for surgical resection of limited metastatic disease or both
FOLFOX plus cetuximab or panitumumab	Every 2 weeks, half day infusion in clinic, with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, hand/foot-syndrome, hypomagnesemia, hypersensitivity reactions. neuropathy, skin toxicity	For tumors that are *KRAS/NRAS/BRAF* wild type; ineffective for tumors with sequence variations in these genes
IROX (irinotecan and oxaliplatin)	Every 3 weeks, half day infusion in clinic	Rare	Diarrhea, neuropathy	Nonstandard regimen but useful for patients intolerant of fluorouracil due to severe dihydropyrimidine dehydrogenase deficiency or coronary vasospasm
Irinotecan-containing regimens (other than those including oxaliplatin)				
Irinotecan	Frequency dependent on dosing schema	No	Diarrhea	Severe diarrhea and neutropenia may occur in patients with *UGT1A* (NCBI 7361) polymorphism
FOLFIRI (fluorouracil, leucovorin, and irinotecan)	Every 2 weeks, half day infusion in clinic, with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea	Not used in adjuvant regimens; dosing schedule is identical to FOLFOX
CAPIRI (capecitabine and irinotecan)[c]	Every 3 weeks with infusion in clinic and oral capecitabine for 2 weeks, 1 week off	Yes	Pancytopenia, diarrhea, hand/foot-syndrome	Substitutes oral capecitabine for intravenous fluorouracil
Irinotecan plus cetuximab or panitumumab	Either weekly or every 2 weeks by infusion	No	Diarrhea, hypomagnesemia, infusion reaction, skin toxicity	*KRAS/NRAS/BRAF* wild type
FOLFIRI plus cetuximab or panitumumab	Every 2 weeks, half day infusion in clinic with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	Yes	Pancytopenia, diarrhea, hypomagnesemia, infusion reaction, skin toxicity	*KRAS/NRAS/BRAF* wild type
Fluorouracil-containing regimens (other than combinations with oxaliplatin and irinotecan)				
Fluorouracil and leucovorin	Bolus and continuous infusion regimens	Yes	Pancytopenia, mucositis	Single-agent regimen; often optimal for frail patients with major comorbidities
Capecitabine	Oral regimen given for 3 of every 4 weeks	Yes	Pancytopenia, hand/foot syndrome	May be preferred if no plans to intensify treatment
VEGF-containing regimens				
Bevacizumab plus FOLFOX, CAPOX, FOLFIRI, CAPIRI, FOLFOXIRI, fluourouracil and leucovorin, or capecitabine	Infusion time depends on specific chemotherapy given	Yes	Hypertension, bowel perforation, poor wound healing, proteinuria, thrombosis	All molecular subtypes
FOLFIRI plus ramucirumab	Every 2 weeks, half day infusion in clinic with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	No	Pancytopenia, diarrhea, hypertension, poor wound healing, proteinuria	All molecular subtypes
FOLFIRI plus zif-aflibercept	Every 2 weeks, half day infusion in clinic with infusional fluorouracil delivered continuously via pump for 2 days as outpatient	No	Pancytopenia, diarrhea	All molecular subtypes
EGFR antibody monotherapy				
Cetuximab	Either weekly or every 2 weeks by infusion	No	Infusion reaction, hypomagnesemia, skin toxicity	*KRAS/NRAS* wild type
Panitumumab	Every 2 weeks by infusion	No	Infusion reaction, hypomagnesemia, skin toxicity	*KRAS/NRAS* wild type

(continued)

Table 2. Chemotherapy Regimens Used for Treatment of Metastatic Colorectal Cancer (continued)

Regimen name and component drugs[a]	Dosing schedule	First-line use	Selected dose-limiting toxicities/adverse effects[b]	Additional comments
Immunotherapy regimens for metastatic CRCs with MSI-H/MMR-D				
Pembrolizumab	Every 3 or 6 weeks by infusion	Yes	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only
Nivolumab	Every 2 weeks by infusion	No	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only
Nivolumab plus ipilimumab	Every 2 weeks by infusion	No	Fatigue, colitis, dermatitis, hepatitis, pneumonitis, thyroiditis	MSI-H/MMR-D only
Combination regimens for metastatic CRCs that express *BRAF V600E* sequence variation and are RAS wild type				
Encorafenib plus cetuximab	Either weekly or every 2 weeks infusion with continuous oral regimen	No	Diarrhea, pancytopenia, skin toxicity	*BRAF V600E* variant
Other regimens for refractory metastatic CRC				
Regorafenib	Oral regimen given for 3 of 4 weeks	No	Hand/foot syndrome, hypophosphatemia, hepatotoxicity	All molecular subtypes
Trifluridine plus tipiracil (TAS-102)	Oral regimen days 1-5 and 8-12 every 4 weeks	No	Pancytopenia, nausea	All molecular subtypes
Trastuzumab plus pertuzumab or lapatinib or tucatinib[d]	Every 3 weeks or weekly infusion with continuous oral regimen	No	Diarrhea, hypokalemia, cardiotoxicity	*ERBB2* amplified

Abbreviations: CRC, colorectal cancer; FDA, Food and Drug Administration; MMR-D, mismatch repair-deficient; MSI-H, microsatellite instability-high.

[a] The component drugs are listed at the first mention of each regimen in this table.

[b] *Selected* indicates that the column does not encompass all adverse effects.

[c] CAPOX is also known as XELOX, and CAPIRI is also known as XELIRI, based the proprietary formulation of capeditabine (Xeloda).

[d] These agents are US FDA approved for treatment of *ERBB2* breast cancer and the US FDA labels have not been updated to include their use in metastatic CRC. There are no randomized clinical trials that support their efficacy in metastatic CRC, but response rates in patients with *ERBB2*-amplified tumors refractory to other treatments have led practice guidelines to endorse these therapies. For the rare patient with *ERBB2*-amplified metastatic CRC, physicians may administer these drugs off label.

continue therapy, those with disease progression switch to next-line treatment, and those with stable disease continue treatment if it has been well tolerated. Important considerations in treatment are listed in **Table 4** and the Box.

The VEGF inhibitor bevacizumab may be administered with either irinotecan or oxaliplatin containing chemotherapy in first-line metastatic CRC. A systematic review and meta-analysis of 7 RCTs involving 2040 patients found that combination therapy (bevacizumab plus FOLFOX or FOLFIRI) was associated with improved progression-free survival (time since starting therapy when the cancer is not growing; [HR, 0.79; $P < .001$]) but not overall survival (HR, 0.92; $P = .18$).[50] Bevacizumab should not be administered to patients who have undergone recent surgery because it is associated with delayed wound healing and increased risk rates of bowel perforation (0.3%-3%), arterial thrombosis (5%) and bleeding (0.4%-7%).[51,52] In 2017, the FDA approved the first bevacizumab biosimilar, or highly similar biologic drug, that had similar efficacy and safety to bevacizumab and is less expensive.

The EGFR inhibitors (cetuximab and panitumumab) are only effective for patients with *KRAS/NRAS* wild-type metastatic CRC[28] and are generally interchangeable. They extend survival by less than 2 months when used alone. Typically, they are combined with other chemotherapy regimens. In an RCT comparing FOLFOX plus panitumumab to FOLFOX alone, there was a survival benefit in the *KRAS* wild-type population (median overall survival, 23.8 months with FOLFOX plus panitumumab vs 19.4 months with FOLFOX alone [HR, 0.83; $P = .03$]), but not in patients with variant *KRAS* (median overall survival, 15.5 months with FOLFOX plus panitumumab vs 19.2 months for FOLFOX alone [HR, 1.16; $P = .16$]).[28]

RCTs have directly compared combination first-line chemotherapy with either an EGFR inhibitor (cetuximab or panitumumab) or VEGF inhibitor (bevacizumab) for first-line *KRAS* wild-type metastatic CRC.[19,29,53] The CALGB/SWOG 80405 study randomized 1137 *KRAS* wild-type metastatic CRC patients to receive FOLFOX or FOLFIRI, according to investigator preference, with the addition of either cetuximab or bevacizumab. There were no significant differences in median overall survival (30.0 months for cetuximab vs 29.0 months for bevacizumab; HR, 0.88 95% CI, 0.77-1.01]) or the secondary end point of progression-free survival (median, 10.5 months vs 10.6 months; HR, 0.95 [95% CI, 0.84-1.08]).[19] In addition to RAS status, the primary tumor location in the right or left colon (including the rectum) is associated with response to EGFR inhibition.[54,55] Practice guidelines recommend that first-line EGFR inhibitors be used with chemotherapy only for *KRAS/NRAS* wild-type, left-sided metastatic CRC.[10]

The triplet regimen FOLFOXIRI (fluorouracil, oxaliplatin, irinotecan) was investigated for treatment of nonfrail patients with poor

Table 3. Recent Clinical Trials for the Treatment of Metastatic Colorectal Cancer[a]

Source[b]	Years recruited	Intervention group, No.	Comparison Group, No.	Median overall survival (95% CI), mo		Difference in overall survival, median, mo	Selected grade 3 or 4 toxicity, % (% intervention group vs % comparison group)[c]	Comments
				Intervention group	Comparison group			
First-line systemic treatment for previously untreated metastatic CRC								
PRIME,[28] 2014[d]	2006-2008	FOLFOX plus panitumumab *KRAS* wild type, N = 325 *KRAS* variant, N = 221	FOLFOX *KRAS* wild type, N = 331 *KRAS* variant, N = 219	*KRAS* wild type, 23.8 (20.0-27.7) *KRAS* variant, 15.5 (13.1-17.6)	*KRAS* wild type, 19.4 (17.4-22.6) *KRAS* variant, 19.2 (16.2-21.5)	*KRAS* wild type, 4.4 HR, 0.83 (95% CI, 0.7-0.98); *P* = .03 *KRAS* variant, −3.7 HR, 1.16 (95% CI, 0.94-1.41); *P* = .16	*KRAS* wild type Skin toxicity (37 vs 2), diarrhea (18 vs 9), hypomagnesemia (7 vs <1) *KRAS* variant Neutropenia (37 vs 48), skin toxicity (31 vs 1), diarrhea (20 vs 10), hypomagnesemia (6 vs <1)	Benefit only in *KRAS* wild type; decreased overall survival in *KRAS* variant (non-significant)
FIRE3,[29] 2014	2007-2012	FOLFIRI plus cetuximab, N = 297	FOLFIRI plus bevacizumab, N = 295	28.7 (24.0-36.6)	25.0 (22.7-27.6)	3.7; HR, 0.77 (95% CI, 0.62-0.96); *P* = .02	Hematologic toxicity (25 vs 21), skin reaction (26 vs 2), diarrhea (11 vs 14)	All *RAS* wild type (exon 2 codon 12/13)
TRIBE,[18] 2015[d]	2008-2011	FOLFOXIRI plus bevacizumab, N = 252	FOLFIRI plus bevacizumab, N = 256	29.8 (26.0-34.3)	25.8 (22.5-29.1)	4; HR, 0.8 (95% CI, 0.65-0.98); *P* = .03	Neutropenia (50 vs 21), diarrhea (19 vs 11), peripheral neuropathy (5 vs 0)	Treatment effect was not different across subtypes (*RAS*/*BRAF* wild type, *RAS* variant, *BRAF* variant) *P* for interaction, 0.52
WJOG4407G,[27] 2016	2008-2012	FOLFIRI plus bevacizumab, N = 197	FOLFOX plus bevacizumab, N = 198	31.4 (27.6-36.4)	30.1 (26.8-35.5)	1.3; HR, 0.99 (95% CI, 0.79-1.25); *P* = .73 for superiority	Leukopenia (11 vs 5), neutropenia (46 vs 35), peripheral neuropathy (0 vs 22), venous thromboembolism (6 vs 2)	
CALGB/SWOG 80405,[19] 2017	2005-2012	FOLFOX or FOLFIRI plus cetuximab, N = 578	FOLFOX or FOLFIRI plus bevacizumab, N = 559	30.0	29.0	1.0; HR, 0.88 (95% CI, 0.77-1.01); *P* = .08	Hematologic toxicity (31 vs 30), diarrhea (11 vs 9), sensory neuropathy (13 vs 14)	All *KRAS* wild type
TAILOR,[30] 2018	2010-2016	FOLFOX plus cetuximab, N = 193	FOLFOX, N = 200	20.7 (15.9-22.1)	17.8 (14.9-19.6)	2.9; HR, 0.76 (95% CI, 0.61-0.96); *P* = .02	Neutropenia (62 vs 43), leukopenia (27 vs 21), skin reaction (26 vs 0)	All *RAS* wild type (*KRAS*/*NRAS*, exons 2-4)
TRIBE2,[31] 2020	2015-2017	FOLFOXIRI plus bevacizumab, followed by reintroduction at progression, N = 339	FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab after progression, N = 340	27.4 (23.7-30.0)	22.5 (20.7-24.8)	4.9; HR, 0.82 (95% CI, 0.68-0.98); *P* = .03	Diarrhea (17 vs 5), neutropenia (50 vs 21), arterial hypertension (7 vs 10)	FOLFOXIRI plus bevacizumab also with improved time to second progression

(continued)

Table 3. Recent Clinical Trials for the Treatment of Metastatic Colorectal Cancer[a] (continued)

Source[b]	Years recruited	Intervention group, No.	Comparison Group, No.	Median overall survival (95% CI), mo		Difference in overall survival, median, mo	Selected grade 3 or 4 toxicity, % (% intervention group vs % comparison group)[c]	Comments
				Intervention group	Comparison group			
KEYNOTE-177,[32] 2020	2016-2018	Pembrolizumab, N = 153	Investigator's choice: FOLFOX, FOLFOX plus bevacizumab, FOLFOX plus cetuximab, FOLFIRI, FOLFIRI plus bevacizumab, or FOLFIRI plus cetuximab, N = 154	Not reported	Not reported	Not reported	Overall (22 vs 66)	MSI-H/MMR-D CRC progression-free survival: (16.5 mos vs 8.2 mos; HR (95% CI) 0.60 (0.45-0.8); *P* < .01
Phase 3 trials of maintenance therapy for metastatic CRC (2014-2019)								
CAIRO3,[33] 2017 CAIRO3,[34] 2015	2007-2012	Maintenance capecitabine plus bevacizumab, N = 279	Observation, N = 279	21.6 (19.5-23.7)	18.2 (16.1-20.3)	3.4; HR, 0.86 (95% CI, 0.71-1.03); *P* = .10	Hypertension (24 vs 18), hand-foot skin reaction (23 vs 0), sensory neuropathy (10 vs 5)	Induction with CAPOX plus bevacizumab Benefit of maintenance therapy greatest in RAS/BRAF wild type and BRAFV600E subsets (post hoc analysis)
PRODIGE9,[35] 2018	2010-2013	Maintenance bevacizumab, N = 247	Observation, N = 247	21.7	22	−0.3; HR, 1.07 (95% CI, 0.88-1.29); *P* = .50	During chemotherapy-free interval, cardiovascular (9 vs 2), gastrointestinal (4 vs 4), hematologic (0.8 vs 0.8)	Induction with FOLFIRI plus bevacizumab Bevacizumab monotherapy did not improve chemotherapy-free interval, progression-free survival, or overall survival
Second-line systemic treatment for metastatic CRC (2014-2015)								
AXEPT,[36] 2018	2013-2015	Capecitabine plus irinotecan with or without bevacizumab, N = 326	FOLFIRI, with or without bevacizumab, N = 324	16.8 (15.3-19.1)	15.4 (13.0-17.7)	1.4; HR, 0.85 (95% CI, 0.71-1.02); *P* for inferiority = <.001	Diarrhea (7 vs 3), neutropenia (17 vs 43), hand-foot skin reaction, (2 vs <1)	
ASPECCT,[37] 2016 ASPECCT,[38] 2014	2010-2012	Panitumumab, N = 499	Cetuximab, N = 500	10.2 (9.4-11.4)	9.9 (9.0-10.8)	0.3; HR, 0.94 (95% CI, 0.82-1.07); *P* for inferiority = .002	Rash (5 vs 3.6), hypomagnesemia (7 vs 2.8), diarrhea (2 vs 1.8)	*KRAS* wild type (exon 2) patients with increased skin toxicity had improved overall survival

(continued)

Table 3. Recent Clinical Trials for the Treatment of Metastatic Colorectal Cancer[a] (continued)

Source[b]	Years recruited	Intervention group, No.	Comparison Group, No.	Median overall survival (95% CI), mo		Difference in overall survival, median, mo	Selected grade 3 or 4 toxicity, % (% intervention group vs % comparison group)[c]	Comments
				Intervention group	Comparison group			
20050181,[39] 2014[d]	2006-2008	FOLFIRI plus panitumumab *KRAS* wild type, N = 303 *KRAS* variant, N = 238	FOLFIRI KRAS wild type, N = 294 KRAS variant, N = 248	*KRAS* wild type, 14.5 (13.0-16.1) *KRAS* variant, 11.8 (10.4-13.3)	*KRAS* wild type, 12.5 (11.2-14.2) *KRAS* variant, 11.1 (10.3-12.4)	*KRAS* wild type, 2 HR, 0.92 (95% CI, 0.78-1.10); *P* = .37 *KRAS* variant, 0.7 HR, 0.93 (95% CI, 0.77-1.13); *P* = .48	*KRAS* wild type Skin toxicity (37 vs 2), neutropenia (20 vs 23), diarrhea (14 vs 9), hypomagnesemia (3 vs <1) *KRAS* variant Skin toxicity (32 vs 1), neutropenia (14 vs 17), diarrhea (14 vs 11), hypomagnesemia (5 vs 0)	Progression-free survival and overall survival were longer for worst-grade skin toxicity (2-4 vs 0-1 or FOLFIRI)
RAISE,[40] 2015	2010-2013	FOLFIRI plus ramucirumab, N = 536	FOLFIRI plus placebo, N = 536	13.3 (12.4-14.5)	11.7 (10.8-12.7)	1.6; HR, 0.84 (95% CI, 0.73-0.98); log-rank *P* = .02	Neutropenia (38 vs 23), hypertension (11 vs 3), diarrhea (11 vs 10)	
Third- or later-line systemic treatment for metastatic CRC (2013-2020)								
CORRECT,[41] 2013	2010-2011	Regorafenib, N = 505	Placebo, N = 255	6.4 (3.6-11.8)	5.0 (2.8-10.4)	1.4; HR, 0.77 (95% CI, 0.64-0.94); *P* = .005	Hand-foot skin reaction (17 vs <1), diarrhea (7 vs 1), hypertension (7 vs 1)	
RECOURSE,[42] 2015	2012-2013	TAS-102, N = 534	Placebo, N = 266	7.1 (6.5-7.8)	5.3 (4.6-6.0)	1.8; HR, 0.68 (95% CI, 0.58-0.81); *P* < .001	Neutropenia (38 vs 0), leukopenia (21 vs 0), diarrhea (3 vs <1)	
ImBlaze37,[43] 2019	2016-2017	Atezolizumab plus cobimetinib, N = 183	Atezolizumab, N = 90 Regorafenib, N = 90	Atezolizumab plus cobimetinib, 8.87 (7-10.61)	Atezolizumab, 7.10 (6.05-10.05) Regorafenib, 8.51 (6.41-10.71)	Atezolizumab plus cobimetinib vs regorafenib HR, 1.00 (95% CI, 0.73-1.38); *P* = .99 Atezolizumab vs regorafenib HR, 1.19 (95% CI, 0.83-1.71); *P* = .34	Diarrhea (11 vs 1 vs 6), anemia (6 vs 0 vs 3), increased CPK (7 vs 0 vs 1)	>96% Of each group had microsatellite stability
BEACON CRC,[23] 2019 BEACON CRC,[44] 2021	2017-2019	Encorafenib and binimetinib plus cetuximab, N = 224 Encorafenib plus cetuximab, N = 220	FOLFIRI plus cetuximab or irinotecan plus cetuximab, N = 221	Encorafenib and binimetinib plus cetuximab, 9.3 (8.2-10.8) Encorafenib plus cetuximab, 9.3 (8.0-11.3)	FOLFIRI plus cetuximab or irinotecan plus cetuximab, 5.9 (5.1-7.1)	Encorafenib and binimetinib plus cetuximab vs control HR, 0.60 (95% CI, 0.47-0.75) Encorafenib plus cetuximab vs control HR, 0.61 (95% CI, 0.48-0.77)	Diarrhea (10.8 vs 2.8 vs 10.4), acneiform dermatitis (2.7 vs 0.5 vs 2.6), nausea (4.5 vs 0.5 vs 1.6), hemoglobin decrease (23.4 vs 5.6 vs 5.2)	*BRAF V600E* variant CRC, overall survival was similar for encorafenib and binimetinib plus cetuximab vs encorafenib plus cetuximab (HR, 0.95 [95% CI, 0.74-1.21])

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Table 3. Recent Clinical Trials for the Treatment of Metastatic Colorectal Cancer[a] (continued)

Source[b]	Years recruited	Intervention group, No.	Comparison Group, No.	Median overall survival (95% CI), mo		Difference in overall survival, median, mo	Selected grade 3 or 4 toxicity, % (% intervention group vs % comparison group)[c]	Comments
				Intervention group	Comparison group			
NCT01876511,[24] 2015[e]	2013-2015	Pembrolizumab, N = 11 MSI-H/MMR-D CRC, N = 11 Microsatellite stable/MMR proficient CRC, N = 21	NA	MSI-H/MMR-D, not reached Microsatellite stable/MMR proficient, 5.0	NA	NA	All patients combined, diarrhea (6), pancreatitis (6)	Phase 2, MSI-H/MMR-D CRC (trial cohorts also included a cohort of MSI-H/MMR-D non-CRCs (n=7) and MMR-proficient CRC
CheckMate142,[45] 2017[e]	2014-2016	Nivolumab, N = 74	NA	Not reached	NA	NA	Elevated lipase (8), elevated amylase (3)	Phase 2, MSI-H/MMR-D CRC
CheckMate142,[46] 2018[e]	2015-2016	Nivolumab plus ipilimumab, N = 119	NA	Not reached	NA	NA	Elevated aspartate taminotransferase/ alanine aminotransferase (11), elevated lipase (4), anemia (3), colitis (3)	Phase 2, MSI-H/MMR-D CRC
KEYNOTE-164,[47] 2020[e]	2015-2017	Pembrolizumab ≥2 prior lines, N = 61 Pembrolizumab ≥1 prior line, N = 63	NA	≥2 Prior lines, 31.4 (21.4-not reached) ≥1 Prior line, not reached (19.2-not reached)	NA	NA	≥2 Lines, arthralgia (2), pancreatitis (3), pneumonitis (2) ≥1 Line, pneumonitis (2)	Phase 2, MSI-H/MMR-D CRC
HERACLES,[48] 2016[d]	2012-2015	Trastuzumab plus lapatinib, N = 27	NA	Not reported	NA	NA	Skin rash (4), increased bilirubin (4)	Phase 2, *KRAS* wild type (exon 2, codons 12 and 13), *ERBB2* amplified metastatic CRC
MyPathway,[49] 2019[e]	2014-2017	Trastuzumab plus pertuzumab, N = 57	NA	Not reported	NA	NA	Hypokalemia (5), abdominal pain (5)	Phase 2a, *ERBB2* amplified metastatic CRC

Abbreviations: CRC, colorectal cancer; CPK, creatinine phosphokinase; HR, hazard ratio; MMR-D, mismatch repair-deficient; MMR-P, mismatch repair-proficient; MSI-H, microsatellite instability-high; NA, not applicable.

[a] Combination regimens comprise the following drugs: FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), and FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan).

[b] When available, data from updated reports were used rather than results from the original article.

[c] Indicates percent in the intervention group vs percent in the comparison group unless otherwise indicated. *Selected* indicates that the column does not encompass all adverse effects.

[d] For 3 studies, the reference for the initial publication was not included in the reference list of this article: PRIME (2010), TRIBE (2014 [source for toxicity data]), and 20050181 (2010).

[e] Included trials are phase 3 except for phase 2 studies with important consequences for management (NCT01876511, CheckMate142, KEYNOTE-164, HERACLES, and MyPathway).

Table 4. Principles of Managing Patients With Metastatic Colorectal Cancer

Clinical characteristic of patient with metastatic CRC	Action to consider
Initial evaluation and choice of treatment intent and modality	
Poor functional status, including life expectancy <6 mo	Recommend palliative care without systemic therapy
	Manage bowel obstruction or bleeding with stent or palliative radiation
Symptomatic bowel obstruction or significant bleeding	Surgical management with diverting ostomy can provide significant palliation even for frail patients who choose not to receive systemic therapy
Significant comorbidity, frailty, or both but life expectancy ≥6 mo	Single-agent fluorouracil or capecitabine palliates symptoms and extends life expectancy
	Systemic therapy can be intensified or discontinued based on tolerance
Limited metastatic disease that could be completely resected (resectable metastases)	Multidisciplinary team management with oncology and appropriate surgical specialists (colorectal, thoracic, hepatobiliary); alternatives include initial surgery or several months of neoadjuvant chemotherapy before resection
	Clarify that the majority of patients will have recurrence despite intensive treatment
Metastatic disease that is unresectable and previously resected or adequately controlled primary tumor (unresectable metastases)	Initiate systemic chemotherapy (such as FOLFOX [fluorouracil, leucovorin, and oxaliplatin] or FOLFIRI [fluorouracil, leucovorin, and irinotecan] regimens) or immunotherapy in MSI-H/MMR-D cancers
	Clarify that systemic treatment rarely achieves cure and that while it is typical to survive 2 to 3 years with intensive treatment, there is wide variation in treatment response based on tumor biology and other factors
	Address patient's goals and preferences with respect to continuing to work, and connecting with supports to address financial, caregiving, and mental health strain
	Obtain molecular tumor profiling to inform treatment selection
Factors that influence choice of initial systemic treatment and management	
Rectal primary tumor	Include radiation oncology in multidisciplinary decision making
	Radiation is rarely required as initial therapy when metastases are present and may induce myelosuppression which impairs future tolerance of systemic treatment
Elevated serum level of carcinoembryonic antigen	Tracking carcinoembryonic antigen levels monthly can provide an indication of tumor burden
	Large increases in carcinoembryonic antigen levels should prompt reimaging for progression
Right-sided primary tumor	Avoid unnecessary resection of the primary tumor; obstruction is rare
	Avoid use of first-line cetuximab and panitumumab given low response rates
Prior adjuvant chemotherapy	If metastases develop within 6 months of adjuvant single-agent fluorouracil, intensification to multiagent regimens such as FOLFOX or FOLFIRI is necessary
	If metastases develop within 6 months of adjuvant FOLFOX, use FOLFIRI
Unknown *KRAS*, *NRAS*, *BRAF* and/or microsatellite instability	Obtain molecular tumor profiling using a multigene panel, which includes these genomic features or ask pathology to evaluate these features
Anticipated need for surgery	Avoid VEGF inhibitors for 6 to 8 weeks before and after major surgery
Significant peripheral neuropathy from comorbid illness such as diabetes or adjuvant oxaliplatin	Avoid or delay use of oxaliplatin to prevent worsening peripheral neuropathy
	Vigilance with close monitoring is required with dose reduction or discontinuation before neuropathy limits function
Hyperbilirubinemia	Avoid or delay use of irinotecan, which is metabolized in the liver
Poor tolerance of adjuvant chemotherapy	Carefully review chemotherapy history and tailor treatment for metastatic disease based on prior tolerance, adverse effects, and reason for discontinuation
Tumor factors that influence treatment modification or choice of systemic treatment and management	
Somatic variant in the *KRAS* or *NRAS* genes	Avoid use of cetuximab or panitumumab as these agents are not effective for patients with these molecular features
Somatic variant in the *BRAF* gene	Recognize poor prognosis, prioritize clinical trials
	Use second-line therapy with encorafenib plus cetuximab
Somatic variant in the *ERBB2* gene	Drugs that block the *ERBB2* receptor like trastuzumab may work but prioritize clinical trials over their off-label use
Microsatellite instability-high	Prioritize immunotherapy containing regimens
Clinical factors that influence treatment modification or choice of systemic treatment and management	
Fluorouracil-associated coronary vasospasm	Comanage with cardiology. Infusional fluorouracil is more likely to lead to vasospasm and should be avoided. Consider vasodilators and inpatient management
History of febrile neutropenia	Consider white blood cell growth factor support after review of prior treatment
Severe pancytopenia; mucositis after fluorouracil treatment	Evaluate for dihydropyrimidine dehydrogenase deficiency and reduce the dose based on results. Consider IROX (irinotecan and oxaliplatin) regimen in cases of homozygous dihydropyrimidine dehydrogenase deficiency
Severe diarrhea following irinotecan-containing regimens	Reduce dose based on symptoms and intensify antidiarrheal medications
	Consider testing for *UGT1A1* polymorphisms and reduce dose based on results
Frailty after second-line treatment (third line if *KRAS*/*NRAS* wild type)	Consider palliative and supportive care over use of later-line systemic treatments with marginal survival advantage and substantial toxicity

(continued)

Table 4. Principles of Managing Patients With Metastatic Colorectal Cancer (continued)

Clinical characteristic of patient with metastatic CRC	Action to consider
Other factors to consider	
Life expectancy ≥6 mos	Consider clinical trial options at each decision point
CRC diagnosis at <50 y of age or family history of CRC	Provide genetic counseling and testing to inform risk mitigation for family members
Any unresectable metastatic CRC diagnosis	Patients should understand the incurable nature of unresectable metastatic CRC and should receive support to ensure choices reflect personal goals and priorities

Abbreviations: CRC, colorectal cancer; VEGF, vascular endothelial growth factor.

prognosis metastatic CRC (right-sided tumors, *BRAF V600E* variants, large tumor volume) and whose tumor may become resectable if a substantial response is achieved.[56] In the phase 3 TRIBE study, FOLFOXIRI plus bevacizumab improved overall survival compared with FOLFIRI plus bevacizumab (29.8 months vs 25.8 months; HR, 0.8 [95% CI, 0.65-0.98]) but was associated with neutropenia (50% vs 20.5%), diarrhea (18.8% vs 10.6%), stomatitis (8.8% vs 4.3%) and peripheral neuropathy (5.2% vs 0%). Patients with frailty, comorbidity, or impaired functional status poorly tolerated this therapy.[18,57,58]

Clinicians may order dihydropyrimidine dehydrogenase genotyping before administering regimens that include fluorouracil or capecitabine. Three percent of people have an autosomal-recessive inherited deficiency of the enzyme required for catabolism of these agents.[59] For partial dihydropyrimidine dehydrogenase deficiency, fluorouracil and capecitabine dose reduction is necessary.[60] For total deficiency, these drugs should be avoided, and the IROX regimen (irinotecan and oxaliplatin) can be substituted as an alternative first-line regimen.[61] The IROX regimen is also useful for treating patients who experience severe coronary vasospasm from fluorouracil, another uncommon but potentially life-threatening treatment complication.

For MSI-H/MMR-D metastatic CRC, the immune checkpoint inhibitor pembrolizumab was FDA approved in June 2020 for first-line therapy, based on results of the phase 3 KEYNOTE-177 trial, which randomized 307 patients with untreated MSI-H/MMR-D metastatic CRC to first-line pembrolizumab (an immune checkpoint inhibitor) or investigators' choice of standard chemotherapy (FOLFOX or FOLFIRI with or without bevacizumab or cetuximab). The trial demonstrated a doubling of progression-free survival with pembrolizumab (median progression-free survival, 16.5 months vs 8.2 months [HR, 0.6; $P = .002$]) with decreased overall toxicity (22% vs 66%).[32] Survival data are difficult to interpret because patients who progressed in the chemotherapy group were able to crossover to receive pembrolizumab.

Maintenance Chemotherapy vs Treatment Holidays for Stable Metastatic CRC

Most metastatic CRC patients respond to first-line therapy with either FOLFOX or FOLFIRI for several months but then have stable disease. Continuation of FOLFOX therapy is eventually limited by peripheral neuropathy. Continuing FOLFIRI therapy becomes difficult because it causes fatigue, chronic diarrhea, or both adverse events in more than 80% of patients.[62] When patients become intolerant of these combination regimens, maintenance treatment with fluorouracil plus leucovorin may be continued with or without biologics such as bevacizumab, cetuximab, or panitumumab. Alternatively, therapy can be discontinued temporarily until tumor progression occurs on diagnostic imaging or clinical symptoms progress.

Second- and Third-line Therapy for Metastatic CRC

When metastatic CRC progresses, selecting a second-line regimen requires consideration of prior chemotherapy exposure, timing of progression after first-line therapy, molecular testing results, tolerance of previous chemotherapy, and patient preferences. Patients with *BRAF V600E* or MSI-H/MMR-D tumors should receive targeted therapy or participate in clinical trials. For other patients, second-line therapy may be the cytotoxic regimen not administered previously.

For *KRAS/NRAS* wild-type metastatic CRC, cetuximab or panitumumab may be used as monotherapy or combined with FOLFOX, FOLFIRI, or irinotecan. These treatments are largely interchangeable.[37,38]

No RCTs have directly compared bevacizumab with the 2 other VEGF therapies, zif-aflibercept and ramucirumab, which are FDA-approved for second-line treatment combined with FOLFIRI. Each VEGF drug improves overall survival by 1 to 2 months compared with placebo.[40,63-67]

After progression on FOLFOX and FOLFIRI, patients with *KRAS/NRAS/BRAF* wild-type tumors who have not received an EGFR inhibitor should receive one combined with irinotecan for third-line therapy. However, patients with *KRAS/NRAS* mutant tumors are considered to have refractory disease after progression on second-line treatment.

BRAF V600E-Variant Metastatic CRC

BRAF V600E variants activate the MEK/ERK pathway, which increases cell proliferation and inhibits apoptosis or cell death. *BRAF* variants exist in multiple cancer types but are found in only 5% to 10% of metastatic CRC and confer poor prognosis.[68] *BRAF V600E* metastatic CRC is more common in women, older patients, those with right-side, poorly differentiated tumors, and those with sessile serrated polyp precursors.[69] This metastatic CRC subset has a higher rate of microsatellite instability and epigenetic modifications such as hypermethylation.[70]

The phase 3 BEACON CRC trial randomized 665 patients with *BRAF V600E* metastatic CRC who had progressed through at least 1 previous regimen to combination encorafenib (BRAF inhibitor), binimetinib (MEK inhibitor), and cetuximab (EGFR inhibitor), or encorafenib plus cetuximab, or the control group of the investigator's choice of cetuximab with irinotecan or FOLFIRI.[23,44] Patients who received combination encorafenib, binimetinib and cetuximab and those who received encorafenib plus cetuximab had median overall survival of 9.3 months, compared with 5.9 months for the control group. Adverse effects were less common in the encorafenib plus cetuximab group (57.4%) compared with the encorafenib, binimetinib, and cetuximab (65.8%) group, and the control group (64.2%). The most common severe adverse effects included fatigue (4%), hemoglobin decrease (6%), and anemia (4%). Severe acneiform dermatitis was present in 2.7% of encorafenib, binimetinib and cetuximab patients, 0.5% of encorafenib and cetuximab patients, and 2.6% of controls.[44] Some degree of acneiform dermatitis occurred in 29% of patients.[23,44] Based on this trial, the FDA in 2020 approved combination encorafenib and cetuximab for *BRAF V600E*-variant metastatic CRC after progression through first-line therapy. It is unknown whether including encorafenib and cetuximab in first-line treatment provides even greater survival gain.

MSI-H or MMR-D Metastatic CRC

MSI-H/MMR-D metastatic CRC tumors are generally less responsive to conventional cytotoxic chemotherapy.[71] Before immunotherapy was available, median overall survival for MSI-H/MMR-D metastatic CRC ranged from 10.1 to 17.3 months (depending on *BRAF* variant status).[72] Immunotherapy has improved outcomes for these patients. MSI-H/MMR-D tumors have deficiencies in MMR resulting in DNA replication errors, frameshift mutations, and production of abnormal proteins or neoantigens that are immune system targets.[73]

Three immunotherapy regimens were approved in the past 5 years for second- or third-line treatment of MSI-H/MMR-D metastatic CRC: (1) pembrolizumab; (2) nivolumab; and (3) combination nivolumab plus ipilimumab.[24,45-47,74] In the phase 2 KEYNOTE-164 trial, 124 patients with MSI-H/MMR-D metastatic CRC received pembrolizumab for up to 2 years.[47] For those who received at least 2 prior therapies, the median overall survival was 31.4 months (95% CI, 21.4 months-not reached) at 31 months of follow-up. In the phase 2 CheckMate 142 study, one cohort received nivolumab (a monoclonal antibody against PD-1) monotherapy; after 12 months of follow-up, the overall survival rate was 73%.[45] In the cohort combining nivolumab pus ipilimumab (a monoclonal antibody against cytotoxic T-lymphocyte antigen 4 [CTLA4]), the overall survival rate at 12 months was 85%.[46] The study did not compare nivolumab with nivolumab plus ipilimumab directly, although absolute overall survival rates were higher for combination therapy. Severe toxicity for the combination, including liver injury, elevated lipase, and colitis, occurred in 32% of patients, compared with 20% for in patients who received nivolumab alone.[45,46] It is unknown whether combination immunotherapy regimens provide benefit beyond single-agent immunotherapy. However, it is clear that for MSI-H/MMR-D metastatic CRC, sustained responses of greater than 1 year can be achieved. Immune checkpoint inhibition is associated with toxicities related to inhibiting the immune system's normal protections from immune overactivation. The unchecked immune system can mistakenly target a patient's normal organs in addition to the cancer, which results in dermatitis, thyroiditis, colitis, pneumonitis, and hepatitis,[75] but these adverse effects can often be treated.

Microsatellite Stable or MMR-Proficient Metastatic CRC

Immunotherapy has improved outcomes for patients with MSI-H/MMR-D metastatic CRC but has not been effective in microsatellite stable/MMR-proficient tumors, which comprise 95% of metastatic CRC.[43,74] While preclinical studies supported combining immune checkpoint blockade with other drugs or biologics that modulate the tumor microenvironment to overcome resistance of microsatellite stable/MMR-proficient metastatic CRC to immunotherapy,[76] this strategy has not been effective in any phase 3 clinical trials. For example, the IMblaze370 study, which combined atezolizumab (an immune checkpoint inhibitor and monoclonal antibody against programmed cell death-ligand 1) with cobimetinib (a MEK inhibitor), showed no improvement in overall survival compared with regorafenib.[43] Laboratory investigations are needed to better understand mechanisms of resistance and the role of the tumor microenvironment and gut microbiome.[77,78] There is no approved or recommended immunotherapy regimen or combination therapy for microsatellite stable/MMR-proficient metastatic CRC.

ERBB2-Amplified Metastatic CRC

The human epidermal growth factor receptor (*ERBB2* [formerly *HER2*]) is a receptor tyrosine kinase involved in cell growth and differentiation.[79] *ERBB2* amplification contributes to growth of multiple cancer types. FDA-approved therapies exist for *ERBB2*-amplified breast and gastric cancers. Small single-group phase 2 studies have investigated dual *ERBB2* blockade in metastatic CRC by combining trastuzumab (a monoclonal antibody targeting the *ERBB2* receptor) with other *ERBB2*-targeting agents, including pertuzumab (a monoclonal antibody to the dimerization domain of ERBB2) and lapatinib (a tyrosine kinase inhibitor against *EGFR1* and *ERBB2*). Initial results showed that 20% to 30% of pretreated *ERBB2*-amplified patients objectively improved (or had decreased tumor size) with these regimens.[48,49] These 2 single-group trials included small numbers of patients (84 in total), and further studies are needed to define optimal therapy for these patients. Patients with *ERBB2*-amplified metastatic CRC should be considered for targeted therapy, preferably in a clinical trial.

Treatment-Refractory Metastatic CRC

Patients with metastatic CRC who experience disease progression despite treatment with FOLFOX, FOLFIRI, and biologic or targeted therapies have refractory disease. There are no approved therapies that improve survival by 3 or more months for these

patients. Management includes palliative care, clinical trial participation, or either of 2 oral FDA-approved chemotherapy drugs (regorafenib [approved in 2012] or trifluridine and tipiracil [TAS-102; approved in 2017]).

In the CORRECT trial, regorafenib, a small-molecule multikinase inhibitor that disrupts tumor blood flow and cancer growth, demonstrated a median overall survival improvement of 1.4 months compared with placebo (6.4 vs 5.0 months; HR, 0.77 [95% CI, 0.65-0.94]; $P = .005$).[41] Regorafenib caused significant hand-foot syndrome (17%) and gradual dose-escalation is often necessary to assess tolerance before initiating full-dose treatment.[80] In the RECOURSE trial, TAS-102 improved median overall survival by 1.8 months compared with placebo (7.1 vs 5.3 months; HR, 0.68 [95% CI, 0.58-0.81]; $P < .001$) Severe neutropenia (38% with TAS-102 and 0% with placebo) was the most severe important toxicity.[42] Because expected survival gains from regorafenib and TAS-102 are small, most oncologists advise investigational trials for patients with refractory metastatic CRC before treatment with these drugs.

While overall prognosis for metastatic CRC remains poor, with fewer than 20% of patients surviving beyond 5 years, advances in the diagnosis and treatment of unresectable metastatic CRC have enabled personalized care based on the tumor's molecular profile with improved outcomes for some subtypes. Since 2014, targeted biologic therapies and immune checkpoint inhibition have changed the approach to management of uncommon molecularly defined subsets of metastatic CRC, although further research is required to optimize the sequencing of treatments and combat mechanisms of resistance. Research priorities include developing approaches to treat *KRAS/NRAS*–variant tumors and overcome the resistance of most metastatic CRC to immunotherapy. Care delivery priorities include ensuring that all patients have access to an oncology team that can coordinate care, facilitate informed management decisions, and provide support necessary to maximize the effectiveness and tolerability of metastatic CRC treatment.

Limitations

This review has several limitations. First, drugs discussed in this review were approved by the FDA and available in the United States but may not be available in other countries. Second, outcomes and prognostic estimates were derived from trials conducted primarily in North America and Europe, where patients typically have access to high-quality supportive care necessary to administer them safely. Results may not apply to patients outside of North America and Europe. Third, clinical trial results may not be generalizable to people who are typically older and less healthy than RCT participants. Fourth, results of clinical trials reported in 2020 were typically initiated 5-years earlier, and prognostic estimates may not reflect recent therapeutic advances.

Conclusions

Advances in molecular profiling of metastatic CRC enable directing treatments to the biologic features of the tumor for specific patient subsets. Although cures remain uncommon, more patients can anticipate extended survival. Genomic profiling allows treatment selection so that more patients derive benefit and fewer are exposed to toxicity from ineffective therapies.

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