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Chemotherapy

Management of Metastatic Colorectal Cancer (mCRC): Real-World Recommendations

Purvish M. Parikh[1] Ankur Bahl[2] Gopal Sharma[3] Raja Pramanik[4] Jyoti Wadhwa[5] Peush Bajpai[6] Sunny Jandyal[7] A. P. Dubey[8] Aditya Sarin[9] Subash Chandra Dadhich[10] Avinash P. Saklani[11] Ashok Kumar[12] Abhijit Chandra[13] Saumitra Rawat[14] C. Selvasekar[15] Shyam Aggarwal[16]

[1] Department of Clinical Hematology, Sri Ram Cancer Center, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India
[2] Department of Medical Oncology, Fortis Hospital, Gurugram, Haryana, India
[3] Department of Medical Oncology, Max Healthcare Hospital, New Delhi, India
[4] Department of Medical Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[5] Department of Medical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[6] Department of Medical Oncology, Manipal Hospital, New Delhi, India
[7] Department of Medical Oncology, Action Cancer Hospital, New Delhi, India
[8] Department of Medical Oncology, Delhi Heart and Lung Institute, New Delhi, India
[9] Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, India
[10] Department of Laparoscopic Surgery, Arogya Hospital, Vizag, Andhra Pradesh, India
[11] Department of Surgical Gastroenterology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[12] Department of Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGI), Lucknow, Uttar Pradesh, India
[13] Department of Surgical Gastroenterology, King George Medical University, Lucknow, Uttar Pradesh, India
[14] Department of Surgical Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India
[15] Clinical Services and Specialist Surgery, The Christie NHS Foundation Trust, Manchester, United Kingdom
[16] Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, India

Address for correspondence Purvish M. Parikh, MD, DNB, FICP, PHD, ECMO, CPI, Department of Clinical Hematology, Sri Ram Cancer Center, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur 302022, Rajasthan, India (e-mail: purvish1@gmail.com).

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Abstract

Purvish M. Parikh

Introduction Metastatic CRC is considered as a heterogenous disease. Its management is therefore complex and dynamic. In order the give a ready reference to community oncologists, we developed this real world recommendations.

Methods A group of experts with academic background and real world experience in mCRC got together. We reviewed the current literature and the insights gained from our real world experience. Based on the same we put together these recommendations.

Recommendations (Results) Molecular testing should be done wherever possible. Most of these patients will be treated with a palliative approach. Doublet chemotherapy is a long-standing standard of care. Triplet therapy may be offered where a more aggressive approach is indicated. Combination with anti -vascular endothelial growth factor antibodies and/or anti EGFR antibodies is also considered standard. In the first-line setting, pembrolizumab can be used for patients with mCRC and microsatellite instability-high or deficient mismatch repair tumours; Left and right sided tumours are

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distinct entities. Combination of chemotherapy and targeted therapy is used as per individual patient and tumour characteristics.
Oligometastatic disease can be approached with potentially curative intent. Cytoreductive surgery plus chemotherapy can be offered to selected patients with peritoneal only metastases. Stereotactic body radiation therapy can be used as local therapy for patients with oligometastatic liver only disease who cannot be taken up for surgery. New strategies include induction-maintenance chemotherapy and perioperative chemotherapy. All drugs/ regimen included as standard of care in the first line can also be used in subsequent lines. Specific targetable driver mutation tumours can be treated accordingly with their complementary biological therapy.
Conclusion Multidisciplinary team management and shared decision making are possible when patient and caregivers choose to become active participants.

Keywords
- aggressive cancer
- overall survival
- personalized oncology
- systemic therapy

Introduction

Metastatic colorectal cancer (mCRC) is not considered a curable disease and hence continues to be a significant health care problem. Till a few years ago, its 5-year relative overall survival (OS) was less than 15%.[1,2] Also, about a third of all patients with CRC will have metastatic disease, either at initial presentation or during follow-up.[3,4] In addition, its incidence of CRC is increasing among younger population—often called young onset CRC.[5] In the early days, standard first-line therapy was 5-fluorouracil (5-FU) and leucovorin combination that yielded a response in approximately 20% of patients and the median survival of mCRC remained 12 months. Advent of oxaliplatin and irinotecan and its addition to 5-FU and leucovorin doubled the OS to nearly 2 years. Fortunately, novel combinations and targeted therapies have improved outcome, especially for specific molecular subtypes. Important subgroups of patients that need specific strategies include right-/left-sided primary tumors, completely resectable oligometastatic and liver-limited disease as well as older patients.[6–9] As a result, we are able to personalize therapy that, in the last 15 years, has led to improvement in OS as well as quality of life (QoL) of patients with mCRC. This is thanks to the availability of novel agents, like bevacizumab, cetuximab, S1, ziv-aflibercept, ramucirumab, and panitumumab.[10,11]

Oncologists are quickly realizing that the modern patient's needs and demands are growing.[12,13] Easy access to up-to-date information on real-time basis and the use of online resources, especially GPT 4.0 (and similar artificial intelligence tools), means that patients feel that they know more than their doctors.[14] It is sometimes impossible to convince the patient and their families that information is not the same as insight, that believing more in Dr. Google is usually to their detriment, and that the experience of the oncologist is best to personalize and navigate the patient through the mCRC management journey.

Most western literature and guidelines assume that all patient will be able to undergo appropriate molecular testing for the classification of patients into corresponding molecular subgroups (with their prognostic and predictive implications).[15] In reality, this is not even possible in the best of developed nations. For instance, Western European data shows that next-generation sequencing (limited or extensive panel) or tests to document tumor mutational burden availability in routine practice is extremely heterogeneous.[16]

If available, such tests can make a big difference to that small fraction of patients. For instance, mCRC patients include approximately 4 to 5% that have deficient mismatch repair disease (dMMR)/microsatellite instability-high (MSI-H) tumors, a group where immunotherapy is considered standard of care and improves OS significantly.[17,18] Other tumor markers of importance include *KRAS*, *NRAS*, *BRAF*, and *HER2*.[19–22]

Patients with left-sided tumors showing *RAS* wild-type (wt) can be routinely given anti-epidermal growth factor receptor (EGFR) agents in combination with chemotherapy (CT).[23] This strategy has improved their OS from 12 months (two decades ago) to 40 months, a more than threefold benefit. Similarly, patients having *BRAF* V600E–mutant mCRC can be given CT-free regimen, containing encorafenib plus cetuximab.[24]

A pragmatic approach is therefore necessary. This includes involvement of palliative, supportive care, psychologic, and nutritional services as and when required. For this to succeed, all stake holders (patients, oncologists, caregivers, allied health care professionals) must come together to discuss objectives and expectations of the patients and their family.[25]

Therefore, when managing a patient with mCRC, the first is to ascertain whether their disease is potentially curable by surgical resection of metastases or not. If yes, an aggressive approach is warranted, including the use of neoadjuvant/ perioperative systemic therapy. If not, the main goals will be to focus on extension of the duration of quality life.

Management of Patients with mCRC (►Table 1)

First-Line Therapy

When Patient Cannot Undergo Molecular Testing

Standard of care is a doublet CT. Options include FOLFOX (folinic acid, FU, and oxaliplatin); FOLFIRI (folinic acid, FU, and irinotecan); CAPOX (capecitabine and oxaliplatin); and SOX (S1 and oxaliplatin).[9,26–29] They work best if the patient's tumor is microsatellite stable (MSS) and/or

Table 1 Approach to a patient with mCRC

1.	All patients with mCRC should first be categorized as to whether a potentially curative approach is possible or not
2.	If a potentially curative approach is possible
a.	In case of isolated metastatic or oligometastatic disease, discuss with colleagues to consider for surgical resection. Ideally this should be in a multidisciplinary tumor board, where available
b.	For patients with clearly resectable mCRC, surgery should be the first choice. Any form of systemic therapy in such patients has not been proven to improve OS as yet. However, perioperative CT offers a significant DFS advantage
c.	Patients with borderline resectable disease can be considered for conversion therapy with multiagent neoadjuvant chemotherapy—which could also be in the form of perioperative or adjuvant chemotherapy. No targeted therapy has been shown to be of substantial benefit in these patients. We do not recommend adding anti-VEGF or anti-EGFR agents to chemotherapy for such patients (immunotherapy and dMMR are exceptions, see below)
d.	After short duration systemic therapy, if patients continue to have resectable oligometastatic disease (SR, PR, CR), synchronous resection followed by completion of 6 months of perioperative systemic therapy is recommended
e.	One way to select patient for upfront surgery would be to use the clinicopathological risk scores (e.g., Fong score)
	(i) Low-risk patient directly taken up for upfront surgery
	(ii) High-risk patients to be given perioperative CT
f.	There is scope to use ctDNA monitoring in selected patients receiving perioperative CT
g.	Liver-directed therapies like radiofrequency ablation (RFA) or microwave ablation have shown similar results as compared with surgery in carefully selected patients (collision trial). Other liver-directed therapies (like intrahepatic chemotherapy or radioembolization) are not considered as part of standard treatment currently and may be used only if surgery is not possible
h.	Carefully selected patients with peritoneal-only CRC are candidates for cytoreductive surgery. Addition of HIPEC is currently not standard of care. Oxaliplatin is not to be used as the chemotherapy agent while using HIPEC. No phase 3 randomized clinical trial has shown OS benefit using this approach
3.	For those where a potentially curative approach is not possible
A	First line:
(i)	When molecular testing is not possible
	First-line systemic therapy can be doublet or triplet
	(a) Doublet chemotherapy include FOLFOX, FOLFIRI, CAPOX, or SOX
	(b) Triplet chemotherapy includes FOLFOXIRI and FOLFIRINOX. While RR and DFS are better as compared with doublet CT, there is no strong evidence for improved OS
	(c) If oxaliplatin- or irinotecan-containing regimens cannot be used, 5-FU, capecitabine, or S1 can be combined with a biological agent (like bevacizumab) as an alternate standard of care
	(d) Adding a biologic agent to first-line chemotherapy is appropriate, especially for aggressive tumors
	(e) Toxicity is a significant challenge when anti-VEGF (like bevacizumab) is added to triplet chemotherapy
	(f) Anti-EGFR therapy must be added to left-sided tumors (unless contraindicated) and probably avoided in right-sided tumors (only when RAS wt is confirmed)
	(g) Induction-maintenance approaches with a limited number of oxaliplatin-containing treatment cycles upfront and maintenance therapy with a fluoropyrimidine and biological combination can be considered standard of care
	(h) In case of disease progresses while on maintenance therapy, oxaliplatin reintroduction may still provide benefit
(ii)	For those where molecular testing is possible
	(a) Tumors should undergo testing for
	(i) extended RAS mutations
	(ii) MMR/MSI status
	(iii) HER2 overexpression or amplification
	(iv) BRAF, especially for V600E status

(*Continued*)

Table 1 (*Continued*) Approach to a patient with mCRC

	(v) If feasible, a wider panel may be used
	(b) Treatment guided by specific molecular testing results
	(i) Patients with BRAF V600E–mutated tumors should be considered for second-line and beyond treatment with the doublet regimen of encorafenib and anti-EGFR antibody. Dabrafenib and trametinib are other option, since they have received tissue agnostic approval
	(ii) Patients with HER2-amplified cancers should be evaluated for trials with agents directed against HER2, including newer antibody-drug conjugates
	(iii) Patients with MSI-H/dMMR tumors can be treated with
	(1) single-agent pembrolizumab
	(2) combination of nivolumab/ipilimumab
	(3) Either of the above may be preferred over standard multiagent chemotherapy in eligible patients (KEYNOTE-177 trial and CheckMate 8HW)
B.	Second line:
(i)	Any standard of care drug/regimen not used in the first line should be considered when patient needs second-line therapy
(ii)	Continuing anti-VEGF therapy is possible in select patients beyond first-line progression (data from bevacizumab)
(iii)	Sequential exposure to all appropriate agents can lead to longest possible survival
(iv)	Addition of appropriate local therapy can be considered for patients with progressive disease at a single site
C.	Third line and beyond (disease refractory to other approved agents):
(i)	Consider regorafenib, fruquintinib, or trifluridine/tipiracil with or without anti-VEGF (like bevacizumab)
(ii)	Choice and sequence of these agents shall be based on patient preferences and the need to avoid specific adverse events
D.	At all time, patients should be considered for:
(i)	Participation in clinical trials
(ii)	Best supportive care

Abbreviations: CR, complete response; CT, chemotherapy; ctDNA, circulating tumor deoxyribonucleic acid; DFS, disease-free survival; dMMR, deficient mismatch repair disease; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; HIPEC, hyperthermic intraperitoneal chemotherapy; mCRC, metastatic colorectal cancer; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, microsatellite instability-high; OS, overall survival; PR, partial response; RR, response rate; SR, spontaneous regression; VEGF, vascular endothelial growth factor; wt, wild-type.

proficient mismatch repair (pMMR). The choice between these options is primarily based on the expected adverse effect profile.

Triplet CT FOLFIRINOX (folinic acid, FU, oxaliplatin, and irinotecan) can also be used in the first line for subgroup of patients meeting the above criteria and whose preferred choice is an aggressive approach (e.g., right-sided tumors, BRAF V600E mutated).[26] In the TRIBE trial, FOLFOXIRI plus bevacizumab were compared with either FOLFIRI and bevacizumab alone.[30] The triplet combination improved OS. The TRIPLETE study compared FOLFOX versus FOLFOXIRI in combination with panitumumab for patients with advanced RAS and BRAF wt mCRC (88% left sided), which also showed benefit.[26] This survival benefit comes with the cost of higher grade 3 or 4 toxicities, which would adversely affect QoL. Neither bevacizumab nor cetuximab should be given along with triplet CT.

When using 5-FU, it is now standard to use either infusional route or replace with oral fluoropyrimidine-based regimen. Both are better than bolus 5-FU–based regimen, especially in combination with irinotecan

Neither oxaliplatin nor bevacizumab should be used as single agents.[31]

All patients should be considered for addition of anti-vascular endothelial growth factor (VEGF) drugs (like bevacizumab) in addition to CT (doublet), especially for right-sided tumors. Addition of bevacizumab improves response rate (RR) and OS. The main adverse effects of anti-VEGF like bevacizumab are hypertension, bleeding, gastrointestinal perforations, poor wound healing, and thrombotic events (both arterial and venous).[32] Bevacizumab can only be used with extreme caution, in patients with past arterial thrombotic event, recent surgery, and obstructive primary tumors.

When Patients Undergo Molecular Testing

Tumors should undergo testing for extended RAS and BRAF mutations, MMR/MSI status, HER2 overexpression or amplification, and programmed death-ligand expression. Circulating tumor deoxyribonucleic acid (DNA) can also be done where possible.

Anti-EGFR drug should be added to doublet CT as first-line therapy to patients with left-sided tumors, when their

molecular tests show they have MSS or pMMR *RAS* wt mCRC. When using anti-EGFR antibodies, tests should confirm that the tumor is wt for KRAS exons 2, 3, and 4 and NRAS exons 2, 3, and 4. This is called the extended RAS panel.[33–38] This is because such mutations in RAS are found in more than 50% of cases. They are responsible for active downstream signaling that bypasses the blockage of EGFR receptors. The CRYSTAL trial demonstrated that combination of FOLFIRI with cetuximab was superior to FOLFIRI alone (better RR, progression-free survival [PFS], and OS).[39] The PRIME trial using FOLFOX confirmed the benefit of using the anti-EGFR approach—this time with panitumumab. These agents are therefore now standard of care for the first-line treatment of extended RAS wt tumors.

The main adverse effects of anti-EGFR agents are acneiform skin rash, diarrhea, hypomagnesemia, and hypersensitivity reactions. Prophylactic treatment with oral doxycycline and topical corticosteroids can reduce skin toxicity in the majority of patients, based on the results of the STEPP trial.[40]

Anti-VEGF and anti-EGFR agents should not be given at the same time because of their antagonistic effect. The FIRE-3 trial suggests that FOLFIRI plus cetuximab gives better OS than FOLFIRI plus bevacizumab.[41] Updated results taking into consideration additional mutations in KRAS and NRAS demonstrated an even larger OS benefit.

Pembrolizumab is now part of the standard of care for first-line management of patients when molecular studies show they have MSI-H and/or dMMR. KEYNOTE-177 compared pembrolizumab to CT.[42] PFS was better with pembrolizumab, with approximately 10% of patients achieving complete response. It is interesting to see the benefit even when crossover to the pembrolizumab was permitted at disease progression for patients on the CT arm (which did occur in 60% of patients). No wonder OS difference did not reach statistical significance (hazard ratio, 0.74; 95% confidence interval, 0.53–1.03; p IS 0.0359 (P = 0.0359)).[17]

Another alternative is the combination of nivolumab and ipilumab,[43] but it is usually not preferred over single-agent pembrolizumab.

Left- and right-sided colonic cancers are two distinct cancer types. Left-sided CRC tumors are those that are located between the splenic flexure and the rectum. They usually present with wt BRAF and KRAS point mutations (codons 12, 13, and 61), copy-number alterations, and other structural genomic aberrations such as chromosomal instability and loss of heterozygosity. Right-sided CRC tumors are found between the cecum and the hepatic flexure. They usually have BRAF V600E point mutations, wt for KRAS, diploid copy number, MSI, DNA hypermutation, and DNA hypermethylation. Median survival of patients with right- versus left-sided tumors was 31.4 versus 24.2 months, respectively ($p \leq 0.01$).[44] These differences could be based on embryological and microbial factors. The right (proximal)-sided colon is derived from the embryonic midgut whereas the rest of the colon (distal transverse colon to rectum region) originates from the embryonic hindgut. Trials indicate cetuximab having an OS advantage for left-sided tumors and bevacizumab for right-sided tumors.[44] The PARADIGM trial also confirmed the advantage of panitumumab as compared with bevacizumab. Data for patients with transverse colon cancers (between hepatic and splenic flexure) is currently absent.[45]

As we know, oxaliplatin-based first-line therapy can lead to cumulative neurotoxicity. This led to the concept of continuous versus intermittent (stop and go) oxaliplatin therapy. First point is that complete discontinuation of therapy is likely to be detrimental and not recommended.[46,47] The induction-maintenance approach consists of a limited number of oxaliplatin-containing treatment cycles upfront followed by maintenance therapy with a fluoropyrimidine and targeted agent combination. This has become one of the standards of care for mCRC today. The CAIRO3 study showed the benefit of fluoropyrimidine and bevacizumab combination.[48] Similarly, there is survival benefit with the combination of fluoropyrimidine and anti-EGFR monoclonal antibody as well. Maintenance fluoropyrimidine plus panitumumab is not recommended—data from the VALENTINO study.[49]

In summary, the induction-maintenance regimen should have a limited duration of induction with oxaliplatin-based therapy followed by prolonged maintenance with fluoropyrimidine and monoclonal antibody combination. Such an approach has the benefit of minimizing toxicity. It is important to remember that oxaliplatin can be reintroduced at the time of progression and should provide a reasonable response, based on the OPTIMOX1 trial.[50]

Patients should receive all active cytotoxic drugs in the course of their therapy to optimize outcome (sequencing them as appropriate for individual patients).[51]

Second-Line Therapy

A significant number of CRC tumors become resistant or refractory to therapy, even if the initial response was good. Such patients are candidates for second-line systemic therapy.

Any drug or regimen not used in the first line can be used in the second line of treatment for mCRC.

The ML18147 trial proved that continuing bevacizumab beyond progression improves OS.[52] The rationale is that a prolonged inhibition of the VEGF proangiogenic pathway is required to maximize the treatment benefit. This was seen in all subgroups. PFS was also with bevacizumab.

Other anti-VEGF drugs with benefit include ziv-aflibercept (VEGF receptor [VEGFR] decoy fusion protein) and ramucirumab (human monoclonal antibody against VEGFR).[53,54]

Single-agent bevacizumab is not beneficial either as maintenance or as second-line therapy.

Encorafenib plus cetuximab can also be offered to patients with previously treated *BRAF* V600E–mutant mCRC that has progressed after at least one previous line of therapy.[55]

Third-Line Therapy and Beyond

After two lines of treatment, the reintroduction of CT and rechallenge with previously used targeted agents are not effective.

Regorafenib provides modest OS benefit.[56] Its significant toxicities include hand-foot syndrome, fatigue, diarrhea, and hypertension.

The SUNLIGHT trial in third-line treatment of mCRC documented that trifluridine and tipiracil (TAS-102) also improves OS similarly and received U.S. Food and Drug Administration (FDA) approval in 2015. Neutropenia is the most important side effect.[21]

Fruquintinib (oral tyrosine kinase selective inhibitor of VEGFR-1, -2, and -3) studied in the FRESCO trial showed improvement in the primary endpoint of OS.[57] The follow-up FRESCO-2 trial confirmed the results and led to U.S. FDA approval in November 2023.[57]

Special Circumstances

Patients Factors: Older Patients

The AVEX phase 3 trial showed that the combination of capecitabine and bevacizumab is safe and improves PFS in the geriatric group. SOX trial similarly showed efficacy and safety in older patients.[58]

Tumor Location

Oligometastatic CRC

When a patient of mCRC has a potentially resectable metastatic disease (e.g., hepatic resection), the average 5-year survival rate is approximately 30%. When preoperative CT is used to downsize the cancer, OS of patients (subset who undergo successful neoadjuvant therapy followed by R0 resection of metastases) approaches the survival of patients with initially resectable metastases.[59,60] The benefit is much lower if there are multiple lesions, interval between the diagnosis of the primary tumor and recurrence is short, and initial presentation is with stage 3 disease.[59–62] Data shows that patients receiving perioperative CT have better PFS as compared with those undergoing cytoreductive surgery (CRS) alone. But OS might not be different. If the patient was previously on bevacizumab, its use should be discontinued approximately 6 to 8 weeks before the planned surgery. The most common site of such metastasis is liver and lung.

Liver Disease-Directed Therapy

Liver-directed therapy can be divided into surgical and nonsurgical interventions. Besides CRS, they include stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA), radioembolization, internal/external beam radiation, and hepatic artery CT administration.[63,64]

Of all the options, SBRT may be considered first following systemic therapy for patients with oligometastatic CRC who cannot be offered surgical resection. Irrespective of the choice of liver-directed non-CRS modality, it should be clear that it will have little, if any, effect on the OS of the patient.[65,66]

Combinations of surgical resection and RFA, as well as external beam radiation, continue to be studied in few specialty centers.

Systemic therapy can be combined with surgery if the mCRC patient has a reasonable chance of ultimately undergoing potentially curative resection of their liver metastases. This is especially true if the liver metastases are large or are many in number. Such perioperative CT should be limited to 6 months of total duration (counting both preoperative and postoperative administration) based on the EORTC 40983 data.[67]

Value of biologic agents (like EGFR and VEGF inhibitors) is unclear for patients with potentially resectable liver metastases.

Peritoneal-Only Metastasis

CRS plus systemic CT (±hyperthermic intraperitoneal CT [HIPEC]) may be considered for selected patients with isolated colorectal peritoneal metastases. PRODIGE 7 study indicates significant PFS benefit, indicating the hope of cure in a selected subgroup.[68] PRODIGE-7-ACCORD-15 trial showed no difference in OS between the two groups, suggesting that the additional value of HIPEC to CRS was not proven. Perhaps this was because the CT selected (for HIPEC or for systemic therapy) was incorrect in the trial. If HIPEC is added, the CT agent should not be oxaliplatin.[69] In general, this approach is possible for those patients who are candidates for complete CRS irrespective of any previous therapy received by them (provided they have no extraperitoneal metastases).

Tumor Characteristics

BRAF-Mutated Tumors

The median survival of patients with BRAF-mutated stage IV CRC is only 12 to 14 months.[36]

A meta-analysis of 44 studies showed that there is no benefit in using EGFR inhibitors without combining with a BRAF inhibitor in these patients.[70]

The BEACON study used cetuximab and encorafenib (BRAF inhibitor) with or without the MEK inhibitor binimetinib and was well tolerated compared with irinotecan (with or without 5-FU) and cetuximab.[71] Updated trial report also showed better median OS for triplet as well as doublet over control. Three-drug combination of irinotecan, cetuximab, and vemurafenib (BRAF V600E inhibitor) also showed PFS benefit. Current National Comprehensive Cancer Network guidelines and FDA approval recommend the doublet regimen in second-line and beyond treatment for patients with BRAF V600E–mutated mCRC.[72]

Non-V600E mutations in the BRAF region (atypical BRAF mutations) are seen in 2 to 3% of all patients with CRC. They can be divided into class II (RAS-independent; intermediate to high kinase activity) and class III (RAS-dependent; low kinase activity). Studies indicate their OS may be better than those with BRAF V600E–mutated or BRAF wt tumors.[41] These patients will not benefit much from anti-EGFR antibodies.[73]

HER2 Overexpression/Amplification

HER2 overexpression is seen in approximately 5% of mCRC, more in left-sided tumors. The HERACLES trial used

trastuzumab and lapatinib that resulted in 30% objective response rate (ORR) in patients who had received more than four lines of therapy.[74] Similar findings of 30% ORR was also seen in the MyPathways trial using trastuzumab and pertuzumab.[75] The U.S. FDA granted accelerated approval of tucatinib in combination with trastuzumab for RAS wt/HER2-amplified unresectable CRC or mCRC that has progressed after fluoropyrimidine-, oxaliplatin-, and irinotecan-based CT. Since grade 3 and 4 treatment-emergent adverse events were seen in half the patients (49.4%), the reduced dose of 5.4 mg/kg dose is preferable over the 6.4 mg/kg dose. It is projected that this will result in similar efficacy and less toxicity.

KRAS G12C–Mutated Tumors

KRAS G12C mutations are seen in 3 to 4% of CRCs. Such patients have a worse outcome as compared with those with other KRAS mutations. The KRYSTAL study used adagrasib alone or in combination with panitumumab.[76] Both the ORR and response duration are higher with the combination. Sotorasib, another KRAS G12C inhibitor, when used in combination with cetuximab in the CODEBREAK101 trial, showed better results than sotorasib alone, with a RR of 30%.[77]

Conflict of Interest

None declared.

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