#### **Review Article**

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# Indian consensus statement on the management of metastatic colorectal cancer

Ashok K. Vaid<sup>1\*</sup>, Prabrajya N. Mohapatra<sup>2</sup>, Chirag Desai<sup>3</sup>

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#### \*Correspondence: Dr. Ashok K. Vaid,

E-mail: akvaid@yahoo.com

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#### **ABSTRACT**

In India, the annual incidence rates for colon cancer are 4.4 (males) and 3.9 (females) per 100,000. A common guideline for the management of metastatic colorectal cancer (mCRC) in the Indian subcontinent is lacking. Four virtual advisory board meetings consisting of a panel of 31 experts were conducted to discuss and arrive at a consensus on the treatment patterns and clinical evidence on the management of mCRC in Indian patients. The consensus covered the entirety of treatment patterns suited for the Indian subcontinent and its alignment with Pan-Asian adapted European Society for Medical Oncology guidelines. Recommendations were provided for choosing the first- and second-line agents for treatment. Types of, recommendations for, and management using salvage therapy and immunotherapy as well as management of adverse effects were discussed. Thus, the mCRC consensus is expected to serve as effective and readily available guidance for practicing oncologists across India.

Keywords: Salvage therapy, Treatment patterns, Colorectal cancer

#### **INTRODUCTION**

Colorectal cancer (CRC) remains an alarming health problem worldwide. In 2008, an estimated 1.2 million people were affected globally. Both men and women tend to be equally affected although there are significant regional disparities, with the disease being more prevalent in Western countries and less prevalent in Asia and Africa. Early detection using screening techniques, introduction of clinical practice standards for systematizing cancer care, greater patient awareness, and most importantly, better treatment modalities have all contributed to a reduction in CRC mortality over the last decade. There are several international consensus recommendations for the management of CRC, but none that are particular to India. Four advisory board meetings involving 29 oncologists

from across India were conducted to discuss published oncology trials and guidelines and arrive at a consensus on the management of mCRC in the Indian setting, highlighting the importance of maximum tumor shrinkage, and suppression of further tumor spread and growth. The experts also discussed the rationale and preferences in choosing the drugs for first, second, and maintenance therapy of mCRC.

#### **COLORECTAL CANCER - EPIDEMIOLOGY**

CRC is the third and second most common cancer in men (10.0%) and women (9.4%), respectively. Colon cancer ranks eighth and ninth among men and women, respectively. The annual incidence rates for colon cancer in India are 4.4 (males) and 3.9 (females) per 100,000.

<sup>&</sup>lt;sup>1</sup>Department of Medical and Haemato-Oncology, Medanta Cancer Institute, Gurugram, Haryana, India

<sup>&</sup>lt;sup>2</sup>Department of Medical Oncology, Apollo Gleneagles Hospital, Kankurgachi, Kolkata, West Bengal, India

<sup>&</sup>lt;sup>3</sup>Department of Oncology and Hemato-Oncology, Hemato-Oncology Clinic, Vedanta Institute of Medical Sciences, Ahmedabad, Gujarat, India

A significant number of patients initially present with metastatic disease. About 25% of the patients present with de novo mCRC.<sup>2</sup> CRC can be diagnosed using colonoscopy, biopsy, ultrasound, computed tomography (CT) scan, positron emission tomography (PET), or PET-CT.<sup>3</sup>

#### Risk factors

Age

CRC risk increases with age. For colon cancer, the average age at the time of diagnosis is 68 years for men and 72 years for women, while it is 63 years for rectal cancer in both men and women.<sup>4</sup>

#### Family history of CRC

Members of families with certain uncommon inherited conditions also have a higher risk of CRC and other types of cancer including familial adenomatous polyposis (FAP); attenuated familial adenomatous polyposis (AFAP), a subtype of FAP; Gardner syndrome, a subtype of FAP; and juvenile polyposis syndrome.<sup>4</sup>

#### Evolution of therapeutic landscape

Despite advanced chemotherapy and targeted therapy, the 5-year survival rate in mCRC is 20% or less. For patients with liver metastases, those who are eligible for surgical resection, an increase in the 5-year survival rates reaching up to 50% has been observed. Following surgical resection, however, most of the patients will ultimately develop recurrent disease, for which many will require further treatment with systemic therapy. Since 2000s, primary systemic therapy for unresectable mCRC has been fluorouracil-based chemotherapy in combination with oxaliplatin/irinotecan, yielding an overall survival (OS) of 24 months. The addition of molecules which target either vascular endothelial growth factor (VEGF) or the epidermal growth factor receptor (EGFR) to combination chemotherapy in RAS wild-type disease has further improved patient outcomes, reaching up to 30 months.<sup>5,6</sup>

### CHALLENGES CONTRIBUTING TO POOR PROGNOSIS

#### Rectal cancer in young Indians

Rectal cancer in the young is a major problem in India with unclear etiology, warranting further investigation.<sup>7</sup>

#### Lymph node yield in CRC

Colorectal surgeons and dedicated pathologists must resect/report a minimum of 12 lymph nodes in CRC treatment to ensure surgical quality as well as optimal pathology that can in turn enable accurate disease staging and facilitate planning of adjuvant treatment.<sup>7</sup>

#### Specialization in CRC surgery

With the advent of stapling devices, surgery has evolved remarkably. A good quality total mesorectal resection (TME) with a double-stapled low rectal anastomosis is now the standard of care.<sup>7</sup>

#### Minimal access CRC surgery

Laparoscopic surgery is better than conventional surgery. Favorable evidence of abdominoperineal resections is increasing, and earlier stages of low rectal cancer can be treated with laparoscopic low anterior resection.<sup>7</sup>

# Aim of therapy - maximum tumor shrinkage and suppression of further tumor spread

Systemic therapy for mCRC has patient-specific and disease-specific predictive markers. Tumor burden is the key factor in opting curative or palliative therapy. Curative therapy aims complete remission to prevent recurrence, encompassing adjuvant chemotherapy following surgery. Palliative therapy refers to any chemotherapy administration that is not curative. Systemic therapy for mCRC includes chemotherapy with a biologic. 8

#### Patient characteristics

Geriatric CRC patients less frequently treated with preoperative radiotherapy were more likely to undergo abdominoperineal resections and to die during hospitalization. Unmarried patients have a significantly higher mortality risk than married patients due to diagnostic delay. Not only do less-educated patients have to significantly undergo preoperative radiotherapy but they also have a higher risk of undergoing abdominoperineal resection and to die after colorectal surgery.<sup>10</sup>

# PRIOR ADJUVANT TREATMENT BEFORE STARTING THERAPY

Adjuvant therapy decreases recurrence risk by approximately one-third. It improves disease-free survival (DFS) and OS.<sup>11</sup> Neoadjuvant treatment assesses initial tumor response and toxicity profile of the same regimen that might be considered for additional systemic therapy given in the adjuvant setting. Preoperative therapy has shown significant downstaging with improved resectability and better progression-free survival (PFS) and OS in gastrointestinal cancers.<sup>12</sup>

#### **TUMOR CHARACTERISTICS**

Well-differentiated polypoid adenocarcinomas with pronounced inflammation were seen frequently in patients without metastases, indicating a benign behavior of tumors with favorable prognosis. The macroscopic appearance of the tumor is related to prognosis. No association was found between tumor size and differentiation or degree of inflammation. A significant association is seen between tumor size and Dukes' staging. Among patients with well-differentiated Dukes' B tumors and pronounced inflammation, recurrence development is not seen. Patients with superficial polypoid lesions have been shown to be good candidates for local treatment.<sup>13</sup>

#### Biomarker testing and its implication on choosing firstline therapy

CRC management includes the detection of KRAS, v-Raf murine sarcoma viral oncogene homolog B (BRAF), neuroblastoma RAS viral oncogene homolog (NRAS), and PIK3CA gene mutations and administration of targeted adjuvant therapy with anti-EGFR antibodies. CRC patients can benefit from microsatellite instability (MSI) tests and the detection of loss of heterozygosity of chromosome 18q that can be helpful in guiding therapeutic decisions with regard to administration of 5-FU (Table 1).<sup>14</sup>

#### Preferred first-line management in patients with RASmutated and RAS-WT microsatellite-stable mCRC

Biologicals (targeted agents) are indicated as first treatment for most patients unless contraindicated. The Cetuximab Combined with Irinotecan in First-Line Therapy for mCRC (CRYSTAL) study demonstrated that the addition of cetuximab to a combined first-line chemotherapy regimen of irinotecan, infusional fluorouracil, and leucovorin (FOLFIRI) significantly reduced the risk of progression of mCRC compared with chemotherapy alone (hazards ratio [HR]=0.85; p=0.048).<sup>15</sup>

Cutsem et al randomly assigned patients to receive FOLFIRI with or without cetuximab. The ascertainment rate of patients analyzed for tumor KRAS status was increased from 45%-89%, with mutations detected in 37% of the tumors. The addition of cetuximab to FOLFIRI in patients with KRAS wild-type disease resulted in significant improvements in OS (median, 23.5 vs. 20.0 months; HR=0.796; p=0.0093), PFS (median, 9.9 vs. 8.4 months; HR=0.696; p=0.0012), and response rate (57.3% vs. 39.7%; odds ratio=2.069; p<0.001) compared with FOLFIRI alone.<sup>15</sup>

The updated analysis indicated that cetuximab and FOLFIRI combination significantly improved OS as first-line treatment in patients with mCRC compared with patients receiving FOLFIRI alone.<sup>15</sup>

When used, the VEGF antibody bevacizumab should be administered in combination with cytotoxic doublets FOLFOX/CAPOX/FOLFIRI/S1 plus oxaliplatin (SOX)/S1 plus irinotecan, cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction is the goal; fluoropyrimidine monotherapy should be given to patients unable to tolerate aggressive treatment. <sup>16</sup>

EGFR antibodies should be used in combination with FOLFOX/FOLFIRI, and Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies.<sup>16</sup>

#### Factors affecting choice of second-line treatment

Second-line treatment options for patients with mCRC should be based on the type of line setting or on previous adjuvant treatment in some patients (Table 2). Usually, most mCRC patients who have received a FOLFOX/XELOX or FOLFIRI/XELIRI as first-line treatment will have the other regimen as second-line treatment.<sup>17</sup>

### Pan-Asian adapted ESMO guidelines for second-line treatment

Bevacizumab-naïve patients should be considered for treatment with an antiangiogenic (bevacizumab/aflibercept) as second-line treatment. Aflibercept should be restricted to a combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen. Patients receiving bevacizumab as first-line therapy should be considered for treatment with aflibercept or ramucirumab (in combination with FOLFIRI) when treated as first-line therapy with oxaliplatin or EGFR antibodies in combination with FOLFIRI/irinotecan for patients with RAS wt (BRAF wt) disease. Relative benefit of EGFR antibodies is similar as maintenance therapy as compared with second-line therapy. <sup>16</sup>

Table 1: Examples of biomarkers for colorectal cancer diagnosis, progression, prognosis, and treatment.

Biomarker	Importance	nce Prognostic factor	
<b>BRAF</b> mutations	Specific phenotype and metastasis; resistance to anti- EGFR mAb	Yes	Yes, potentially
KRAS mutations	Heterogeneity of CRC; resistance to anti-EGFR mAb	Yes, potentially	Yes
MSI	Resistance to 5-FU Yes		
APC mutations	Poorer overall survival	Yes	Yes
Micro-RNA	Early detection of CRC, prognostic stratification, and therapy-response prediction		Yes
PIK3CA mutations	Poor prognosis and particular clinico-pathological characteristics; resistance to anti-EGFR mAb		
Loss of PTEN	High tendency to develop metastasis; Resistance to anti-EGFR mAb	-	Yes potentially

CRC: colorectal cancer; EGFR: epidermal growth factor receptor; MSI: microsatellite instability.

**Table 2: Factors affecting choice of second-line treatment.** 

Factors	Recommendations	
Patients with mCRC that have progressed with an oxaliplatin-plus-fluoropyrimidine (5-FU or capecitabine) regimen without any biologics in the first-line setting	Chemotherapy (FOLFIRI or irinotecan monotherapy), either alone or with one of the biologics	
Patients whose disease progressed after an irinotecan- plus–fluoropyrimidine (5-FU or capecitabine) regimen without any biologics in the first-line setting	Chemotherapy (FOLFOX or XELOX) alone or with one of the biologics is recommended	
mCRC patients whose disease progressed with maintenance therapy (fluoropyrimidine plus bevacizumab or an anti-EGFR antibody) after the first-line setting	Traditional paradigm of first line <i>vs.</i> second line treatment may not apply well to the choice of optimal systemic therapy	
If there are no significant residual toxicities from induction chemotherapy	Resumption of the same first-line induction chemotherapy is commonly suggested until further tumor progression, and the same algorithm discussed earlier will be recommended at the time of tumor progression on the resumed induction chemotherapy	

EGFR, epidermal growth factor receptor; FOLFIRI, first-line chemotherapy regimen of irinotecan, infusional fluorouracil, and leucovorin; FOLFOX, folinic acid/5-FU/oxaliplatin; mCRC, metastastic colorectal cancer; XELOX, chemotherapy regimen consisting of capecitabine combined with oxaliplatin.

#### REFRACTORY RAS-WT MCRC

#### Trifluridine/tipiracil (TAS-102)

The phase III "RECOURSE" trial (n=800) compared TAS-102 with placebo for mCRC patients who had received prior chemotherapy plus anti-VEGF therapy and/or anti-EGFR monoclonal antibodies for RAS WT mCRC. Median OS was 7.1 versus 5.3 months (HR 0.68; 95% confidence interval [CI] 0.58-0.81; p<0.001) and small improvement in median PFS was seen (2.0 vs. 1.7 months; HR 0.48; 95% CI, 0.41 to 0.57, p<0.001]. A subsequent phase II study (n = 93) reached the primary endpoint of improved median PFS for the combination compared to TAS-102 alone (4.6 vs. 2.6 months; HR 0.45; 95% CI, 0.29–0.72; p=0.0015); median OS was also improved (9.4 vs. 6.7 months; HR 0.55; 95% CI 0.32-0.94; p=0.028). Ramucirumab combined with TAS-102 in the "REMETY" phase I study reported a 58.3% disease control rate (DCR) at 8 weeks. Oxaliplatin and TAS-102 in a phase II trial showed a DCR of 67% at 8 weeks and no dose-limiting toxicities. Despite supportive preclinical data, a phase I/II trial of TAS-102 and panitumumab in 56 patients with RAS WT mCRC (with no prior anti-EGFR or regorafenib) reported a 33.3% PFS rate at 6 months, which was below the prespecified threshold for activity.<sup>18</sup>

#### Regorafenib

Based on the results of the phase III "CORRECT" trial (n=760) comparing regorafenib to placebo, the primary endpoint was met with improved median OS (6.4 vs. 5.0 months; HR 0.77; 95% CI 0.64–0.94; p=0.0052) and slightly improved PFS (1.9 vs. 1.7 months, HR 0.49; p<0.0001]. Adverse effects with regorafenib 160 mg/day for 21 days of a 28-day cycle was high. Over 50% of the patients had grade 3 or higher toxicity; dose modification was done in over 70% of the patients.

The "ReDOS" phase II trial was performed to address the side effects of starting 80 mg daily and titrating up by 40 mg per week to 160 mg. More patients-initiated cycle 3 of treatment compared to standard dosing. However, progression occurred prior to cycle 3 in 47% of the patients on the modified schedule arm versus 37% with standard dosing. The OS and PFS were not statistically significantly different.<sup>18</sup>

#### ASPECCT trial

Price et al randomized 999 chemotherapy-refractory patients with mCRC whose Eastern Cooperative Oncology Group (ECOG) performance status was 2 or less and who had wild-type KRAS exon 2 tumors to receive either panitumumab (6 mg/kg once every 2 weeks) or cetuximab (initial dose 400 mg/m²; 250 mg/m² once a week thereafter). OS was similar in both groups (HR 0.97, 95% CI 0.84–1.11). Panitumumab was estimated to retain 105.7% (95% CI 81.9–129.5) of the effect of cetuximab on OS. The results showed that panitumumab was non-inferior to cetuximab and that these agents provided similar OS benefit in this heavily pretreated patient population, with more than 50% of participants having OS longer than 10 months. Both agents had expected toxicity profiles.<sup>19</sup>

#### Maintenance treatment

Maintenance chemotherapy following initial treatment is beneficial for patients with mCRC than continuing a full induction regimen until disease progression.<sup>20</sup> Table 3 summarizes the Pan-Asian adapted ESMO guidelines for maintenance treatment.<sup>16</sup>

Patient response is the primary factor in determining maintenance therapy. If the patient has good response with the initial therapy, maintenance therapy could be commenced. Patients not responding to induction chemotherapy may not be good candidates for maintenance therapy. The current standard is based on the regimen used in CAIRO3 maintenance treatment trial.<sup>21</sup>

#### CAIRO3

Previously untreated 558 mCRC patients with stable disease or better after 6 cycles of capecitabine, oxaliplatin, and bevacizumab (CAPOX-B) were randomized between observation (arm A) or maintenance treatment with capecitabine 625 mg/m<sup>2</sup> bid daily continuously and bevacizumab 7.5 mg/kg iv q3 weeks (arm B). Upon first progression (PFS1), CAPOX-B was reintroduced in 61%

in arm A and 47% in arm B. There was a significant benefit for maintenance treatment in terms of PFS1, time to second progression (TT2PD), and second progression (PFS2) with a median of 8.5 versus 11.7 months, respectively (HR 0.67; p<0.0001). Subgroup analysis showed a significant interaction for treatment in patients with synchronous metastases with resected primary tumor (n = 180: median OS was 18.0 for A versus 25.0 months for B [p<0.0001]) and for patients with complete/partial response to induction treatment before randomization (n = 366), with median OS of 18.8 months (A) and 24.1 months (B; p<0.0001).<sup>22</sup> The study findings were positive for maintenance therapy, with a doubling of PFS from 4.1 to 8.5 months.<sup>21</sup>

Table 3: Pan Asia ESMO guidelines for maintenance treatment.

Factors	Guidelines			
Patients receiving fluoropyrimidine and oxaliplatin plus	Should be considered for maintenance therapy after			
bevacizumab therapy as induction therapy	16–24 weeks. (fluoropyrimidine + bevacizumab)			
Patients receiving FOLFIRI	Continue on induction therapy—at a minimum— for as long as tumor shrinkage continues and the treatment is tolerable			
For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab	A fluoropyrimidine plus bevacizumab is considered as maintenance therapy			
Individualization of treatment approaches based on discussion with the patient is essential.  Initial induction therapy or a second-line therapy has to be reintroduced at radiological or first signs of symptomatic progression. In case of second-line therapy, re-introduction of the initial induction treatment is included in treatment strategy.				

FOLFIRI, first-line chemotherapy regimen of irinotecan, infusional fluorouracil, and leucovorin; FOLFOXIRI, 5-FU, leucovorin, oxaliplatin and irinotecan; mCRC, metastastic colorectal cancer.

#### RATIONALE FOR SIDEDNESS ANALYSIS

The location of the primary tumor, in terms of right- or left-sided origin, has been investigated for its role in helping to prognosticate and predict outcomes.<sup>23</sup>

# BIOLOGIC AND CLINICAL DIFFERENCES BY SIDE

Right-sided tumors have worse outcomes than left-sided (distal) ones. The reasons could be:

#### Origin

While right side of the colon originates from the midgut, the left originates from the hindgut.

#### Signaling pathways

The serrated pathway is more prevalent in the right side; BRAF mutations develop, and CpG island hypermethylation occurs. Mutations in KRAS, TP53, and APC typically occur in left-sided tumors.

#### Clinical characteristics

Patients with right-sided tumors tend to be older and females, with tumors having BRAF, PIK3CA, and KRAS

mutations and tumors classified as microsatellite instability—high (MSI-H). Prognosis is worse for these patients with mCRC. Patients with left-sided tumors are usually younger, have KRAS and NRAS wild-type disease, and demonstrate amplification in EGFR and human epidermal growth factor receptor 2 as well as high EGFR ligand expression. Prognosis for these patients is better than for those with right-sided tumors.

When tumors of the right colon metastasize, usually the outcomes could be worse.<sup>24</sup>

The FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with mCRC (FIRE-3) trial was a randomized phase III trial comparing FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment in patients with KRAS wt mCRC.<sup>25</sup>

Post hoc statistical modelling showed a significant interaction between primary tumor location and treatment for OS, but not for overall response rate (ORR) or PFS upon multivariable analysis of the FIRE-3 RAS wt population. This analysis also showed that primary tumor location and BRAF mutational status were prognostic factors for both PFS and OS, sex was a prognostic factor for PFS but not OS, and treatment was associated with OS but not PFS. In FIRE-3, FOLFIRI plus cetuximab had

higher treatment effects in left-sided versus right-sided tumors. These observations underscore that mCRC is a heterogeneous disease.<sup>25</sup>

#### **SALVAGE THERAPY**

Regorafenib as salvage therapy has shown to improve OS in patients with mCRC. In a study of 20 patients with mCRC, 8 patients receiving 160 mg regorafenib/day were unable to continue with the initial dose of 160 mg due to grade 3 adverse events. A reduced dose of 120 mg regorafenib was assessed with dose modification in 12 patients (120 mg group). The optimal response of patients receiving 160 mg and 120 mg doses was 0.0% and 8.3% (1/12), respectively. In the 160 mg group, 3 patients exhibited stable disease (SD). Among the 120 mg group patients, 1 exhibited partial response (PR) with SD. The median PFS was 77 days and median OS was 204 days for the 120 mg group. In the 160 mg group, incidence of adverse effects was 25% (3/8) for hand-foot skin reaction (HFSR), 12.5% (1/8) for small intestinal hemorrhage, and 12.5% (1/8) for anemia and thrombocytopenia. Incidence of adverse effects in the 120 mg group was 8.3% (1/12) of grade >3 hypertension Thus, the 120 mg group experienced lower treatment-related toxicity compared with the 160 mg group. Therefore, an initial dose modification of 120 mg regorafenib is recommended as an alternative strategy for the treatment of mCRC in the salvage setting.<sup>26</sup>

#### **IMMUNOTHERAPY**

Immunotherapy is designed to amplify patient immune response to cancer cells by targeting checkpoint molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and PD ligand 1 (PD-L1) proteins that inhibit immune response via feedback mechanisms. Currently, pembrolizumab, nivolumab, and a combination of nivolumab and ipilimumab were approved by the Food and Drug Administration (FDA) to treat high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) mCRC cases progressing after treatment with fluoropyrimidine, oxaliplatin, and irinotecan (Table 4).<sup>27</sup>

Table 4: Selected clinical trials of the FDA-approved ICI for the treatment of MSI-H/dMMR patients.

Drug	Study	Phase	Target	Dose	ORR
Pembrolizumab	KEYNOTE 164	II	PD-1	200 mg/3 weeks	33%
Nivolumab	CheckMate 142	II	PD-1	3 mg/kg every 2 weeks	31.1%
Nivolumab + Ipilimumab	CheckMate 142	II	PD-1 and CTLA-4	First 4 doses: Nivolumab 3 mg/kg, Ipilimumab 1 mg/kg on the same day every 3 weeks. Then: nivolumab 3 mg/kg every 2 weeks	55%

CTLA-4, cytotoxic T-lymphocyte—associated antigen 4; dMMR, deficient mismatch repair; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitors; MSI-H: microsatellite instability high; ORR, objective response rate; PD1: programmed cell death protein 1.

#### Pembrolizumab

Pembrolizumab is used to treat unresectable or metastatic MSI-H or dMMR solid tumors not responding to other forms of treatment. FDA approval was based on a study that included 149 patients with MSI-H or dMMR cancer, 90 of which had CRC. Pembrolizumab displayed an ORR of 39.6% (95% CI: 31.7, 47.9).<sup>27</sup>

#### Nivolumab and ipilimumab

Ipilimumab is a CTLA-4 inhibitor that was approved for the treatment of MSI-H or dMMR CRC based on the results of the same study that led to the approval of nivolumab monotherapy. In the checkmate 142 trial, 82 dMMR or MSI-H patients were treated with a combination of ipilimumab and nivolumab, followed by nivolumab monotherapy and had an ORR of 46% (95% CI: 35,58). Nivolumab and ipilimumab disables two different checkpoints that both downregulate immune response, resulting in better clinical response. Ipilimumab has a half-life of approximately 15 days and displays linear clearance

that is steady over time, unlike nivolumab and pembrolizumab.<sup>27</sup>

#### Phase III KEYNOTE-177 study

The study findings demonstrated that front-line therapy with the immune checkpoint inhibitor pembrolizumab doubled PFS versus standard of care chemotherapy in patients with MSI-H or dMMR mCRC. At 12- and 24-months follow-up, PFS was 55.3% and 48.3% with pembrolizumab versus 37.3% and 18.6% with chemotherapy, respectively. The ORR was also better with pembrolizumab, with 43.8% patients showing a reduction in tumor size compared with 33.1% patients on chemotherapy.<sup>28</sup>

#### MANAGEMENT OF ADVERSE EFFECTS

It is important to remember that therapeutic goals typically change according to the line of therapy being administered.<sup>29</sup>

#### Regorafenib and hand-foot skin reaction

In hand-foot skin reaction (HFSR) associated with regorafenib, prodromal phase of dysesthesia is seen, which develops into bilateral painful asymmetric erythema and callus-like hyperkeratosis. HFSR management includes risk reduction and HFSR symptom alleviation; the skin should be kept well hydrated with urea-based cream, calluses should be regularly removed, and pain medication used as needed. Alternative dosing of regorafenib (80 mg/day dose with weekly dose escalation up to the standard 160 mg/day dose) suggests that a reduced starting dose can result in fewer subjective complaints about adverse effects such as HFSR.<sup>29</sup>

#### Bevacizumab

Bleeding, hypertension, and proteinuria were closely monitored in the pivotal phase III trial of bevacizumab, AVF2107, which was conducted in treatment-naive mCRC patients.<sup>30</sup>

Following are suggestions based on the findings: Bevacizumab should not be initiated in uncontrolled hypertensive patients, blood pressure should be measured at least every 2-3 weeks in bevacizumab-treated patients, the antihypertensive regimen selection should be left to the treating physician, bevacizumab-treated patients should be monitored for proteinuria by urine protein-creatinine ratio (which also avoids the inaccuracies with dipstick urine assays), and the inconvenience of 24-hour collections, and bevacizumab therapy should be interrupted in patients with proteinuria levels  $\geq 2$  g/day and should be permanently discontinued in hypertensive crisis/nephrotic syndrome.<sup>30</sup>

## OPTIMIZATION OF MEDICATION ADHERENCE: EDUCATION

Physician-patient communication promotes patient satisfaction with medical care and fosters higher adherence levels. Treatment-related adverse effects can affect willingness, adherence, and quality of life. Unchecked adverse effects can impact physical and mental functions. Thus, effective communication regarding potential adverse effects and subsequent management strategies remains essential for patients with mCRC.<sup>29</sup>

#### Factors affecting adherence

Non-adherence increases patients' risk profile and can compromise outcomes, which is why it should be closely monitored.<sup>29</sup>

Patient- and treatment-related factors affecting adherence are: patient-related-general condition and socioeconomic, psychosocial, or financial considerations. Treatmentrelated-patient monitoring and management of symptoms and side effects; patient education on drug-drug or drugfood interactions.<sup>29</sup>

Effective communication between health care provider and patient before treatment initiation and during treatment is necessary. Patients should be encouraged to speak with health care providers during the treatment journey.<sup>29</sup>

#### Educational intervention

Healthcare providers can educate patients to promote medication adherence by explaining medicine intake, by counselling patients on nonadherence, and by discussing about the health and associated treatments.<sup>31</sup>

#### **CONCLUSION**

In conclusion, the review provides guidance on the rationale in selecting chemotherapeutic agents as first-line, second-line, salvage, refectory, and maintenance therapy, adverse events and their management, and optimization of medication adherence to improve prescription adherence and in turn treatment outcome.

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