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Management of metastatic colorectal cancer: consensus in the Gulf Cooperation Council countries

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***Abstract*:** Colorectal cancer (CRC) represents a major public health challenge globally, particularly in the Gulf Cooperation Council (GCC) countries, where it is identified as the second most prevalent form of cancer. Despite advancements in management strategies, tailored guidelines specific to the Gulf region are lacking. This paper presents consensus recommendations developed by a panel of experts from the GCC countries to address this gap. The guidelines cover epidemiology, screening, biomarkers, and treatment strategies for metastatic CRC. Treatment guidelines emphasize tailored approaches based on tumor characteristics, including sidedness and molecular profiles. Furthermore, the importance of maintenance therapy and emerging biomarkers are discussed. These guidelines aim to improve CRC management and outcomes in the Gulf region.

Keywords: clinical guidelines, colorectal cancer, Gulf Region, management

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Introduction

Colorectal cancer (CRC) is the third cancer worldwide in terms of incidence according to statistics by GLOBOCAN2022.[1] In the Gulf region, CRC is the second most common cancer with the highest incidence reported in Qatar and the lowest incidence reported in Oman.[2] CRC is becoming more common among young people in the Arab world due to the Arab population's adoption of the Western lifestyle.[3] This increase in incidence is linked to risk factors such as obesity, sedentary lifestyle, and dietary modifications, which are a consequence of socioeconomic shifts occurring in the area. Screening for CRC is linked to lower incidence and mortality rates globally, but due to cultural differences and lack of knowledge, screening participation is relatively low in the Arab region. Furthermore, most nations lack governmental screening programs.[4] Therefore, the increasing number of cases and the difference in socioeconomic capabilities of Arab countries warrant the development of metastatic CRC (mCRC) treatment guidelines that are tailored to economic capabilities as well as the therapeutic availabilities of the countries in the region.

Methods

Building upon the latest guidelines provided by "The first Middle East and North Africa expert consensus recommendations for the management of advanced colorectal cancer," which was published in 2022,[5] a new set of guidelines specific to the Gulf region was developed. This updated guideline incorporates the most recent advancements in management strategies and extends its coverage to include a broader spectrum of relevant areas.

To formulate these guidelines, a panel consisting of various specialists in the area of oncology assembled for a consensus meeting on September

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9, 2023. The meeting took place at Crowne Plaza in Riyadh, Kingdom of Saudi Arabia. During this session, the statements were thoroughly discussed and subjected to a voting process to ensure a comprehensive and collective approach to the guideline development process.

Panel composition

The panel comprised 16 oncologists from prominent medical centers in the Gulf region, representing Saudi Arabia, the United Arab Emirates, Kuwait, Qatar, and Oman. In addition, one international expert participated remotely via Zoom.

Statements

During the meeting, 80 statements were formulated and categorized into three main sections. The first section, titled "Epidemiology & screening in the Gulf Cooperation Council (GCC) Countries" included four statements. The second section focused on various biomarkers and contained 17 statements. The last section included the different treatment guidelines for a total of 59 statements (Table 1). Statements based on the latest published literature were formulated by a professor and were sent to voting via Survey Monkey (Supplemental Appendix) to all 16 experts prior to the meeting. During the meeting, statements that did not get agreements were discussed in addition to a new set of statements. After the meeting, the new set of statements was sent to experts for voting. Statements that got over 75% agreement were considered for inclusion in the consensus, while statements with less than 85% agreement were discussed again and voted upon.

The statements were drafted based on the latest guideline "The first Middle East and North Africa expert consensus recommendations for the management of advanced colorectal cancer."[5] most statements' evidence levels were added based on a literature review and according to an adapted version of the Infectious Diseases Society of America—US Public Health Service grading system (Table 2) and are given in the text between parenthesis.[6]

Discussion and voting process

The discussion and voting employed a modified Delphi method, with participants casting two types of votes: agree or disagree. Voting decisions were influenced by a review of the existing literature and an assessment of the feasibility and practical implications within the Gulf region. If fewer than 75% of the participants agreed on a statement, it was considered unmodified, indicating a lack of consensus.

Results

Epidemiology and screening in the GCC countries

1.a CRC screening must begin for men and women at the age of 45 in the general population (IV) ($A = 100\%$, $D = 0\%$)

1.b Screening for CRC can be done by fecal immunochemical test (FIT) or colonoscopy (I) ($A = 100\%$, $D = 0\%$)

1.c Lower screening rates in the GCC countries are associated with more advanced stages of CRC and lower survival (V) ($A = 100\%$, $D = 0\%$)

1.d CRC awareness campaigns in the GCC countries could help increase the screening rate and reduce the incidence of mCRC ($A = 100\%$, $D = 0\%$).

The latest update from the American Cancer Society advises starting CRC screening for the general population at age 45 rather than at 50. Correspondingly, the consensus within the Gulf region's panel suggests initiating screening no later than 45 in the general population, excluding those with a predisposing disease or a family history of CRC ($A = 100\%$).[7] The panel endorses both colonoscopy and FIT as viable screening methods ($A = 100\%$). The panel fully endorsed statements 1.c emphasizing the link between lower screening rates in the GCC countries and more advanced stages of CRC, resulting in lower survival rates (V) ($A = 100\%$). Concerning statement 1.d, the panel unanimously recognized that CRC awareness campaigns in the GCC countries could be crucial in improving screening rates and reducing the incidence of mCRC.

Biomarkers

Ras

2.a RAS testing should be carried out on all patients at the time of diagnosis of mCRC by next-generation sequencing (NGS) or PCR in accredited and experienced laboratories (I) ($A = 93.75\%$, $D = 6.25\%$)

2.b RAS testing can be performed on the primary CRCs and/or the metastasis (III) or

Table 1. Experts' consensus statements on the management of metastatic colorectal cancer.

No.	Statement	%
Epidemiology and screening in the GCC countries		
1	CRC screening must begin for men and women at the age of 45 in the general population (IV)	100
2	Screening for CRC can be done by FIT or colonoscopy (I)	100
3	Lower screening rates in the GCC countries are associated with more advanced stages of CRC and lower survival (V)	100
4	CRC awareness campaigns in the GCC countries could help increase the screening rate and reduce the incidence of mCRC	100
Biomarkers		
RAS		
5	RAS testing should be carried out on all patients at the time of diagnosis of mCRC by NGS or PCR in accredited and experienced laboratories (I)	93.75
6	RAS testing can be performed on the primary CRCs and/or the metastasis (III) or eventually on liquid biopsy when tissue biopsy cannot be done or is not available (II)	100
7	RAS analysis should include KRAS exons 2, 3, and 4 (codons 12, 13, 59, 61, 117, and 146) and NRAS exons 2, 3, and 4 (codons 12, 13, 59, 61, and 117) (V)	100
8	RAS mutational status is a negative predictive biomarker for treatment with anti-EGFR therapies (cetuximab or panitumumab; I); RAS mutational status is a negative predictive biomarker for treatment with anti-EGFR therapies (cetuximab or panitumumab) (I)	100
9	For patients with baseline RAS-wt mCRC who have initially responded to anti-EGFR therapy (CR, PR, or SD $\geqslant$4–6 months), testing of RAS mutational status is of clinical importance before rechallenging in third-line treatment (III)	100
BRAF and MSI		
10	BRAF testing (V600E only) should be carried out on all patients at the time of diagnosis of mCRC by PCR or by NGS panels in accredited and experienced laboratories (V)	100
11	BRAF V600E mutational status is a negative prognostic biomarker and a predictive biomarker for BRAF-targeted treatment (I)	100
12	Universal MMR or MSI testing is recommended in all patients newly diagnosed with mCRC (V)	100
13	MSI is evaluated by IHC, PCR, or a validated NGS panel in the first-line metastatic setting (V)	100
14	Detection of germline MSI in metastatic disease can assist the clinician in genetic counseling (II)	100
15	Tumor MSI testing has strong predictive value for the use of immune CPIs in the treatment of patients with mCRC (II)	100
Emerging biomarkers		
16	HER2 amplification is a predictive biomarker in previously treated mCRC (IV)	100
17	HER2 testing is performed by IHC and confirmed, if necessary (2+), by FISH (V)	100
18	Considering the availability of (T-DXd), HER2 testing may also be considered in tumors with KRAS/NRAS or BRAF mutation	100
19	HER2 amplification/overexpression may be predictive of resistance to anti-EGFR monoclonal antibodies (IV)	100
20	NTRK fusion detection is performed by IHC, FISH, DNA-based NGS, and RNA-based NGS (V)	100

(Continued)

Table 1. (Continued)

No.	Statement	%
21	NTRK fusion testing should be limited to tumors with KRAS-wt, NRAS-wt, and BRAF-wt, and preferably in dMMR/MSI-H previously treated mCRC (IV)	100
Treatment		
22	The sidedness of CRC is an important prognostic and predictive marker for the treatment of mCRC (IV)	100
23	According to a simplified classification, right-sided tumors are tumors located between the cecum and the splenic flexure	100
24	Systemic therapy (including targeted agents such as anti-EGFR or antiangiogenic) is not indicated in patients with upfront resectable metastases during perioperative therapy (II)	93.75
25	Complete cytoreductive surgery can be considered in experienced centers for patients with limited peritoneal metastases, liver, and pulmonary lesions (V)	93.75
RAS-wt		
26	In unresectable right-sided metastatic cancer, bevacizumab in combination with chemotherapy must be preferably used in the first-line setting because anti-EGFR agents do not show a clear improvement in PFS and OS in this setting (III)	100
27	In left-sided tumors, anti-EGFR agents and chemotherapy are the standard of care in the first-line setting	87.5
28	Anti-EGFR agents should preferably be used in combination with FOLFOX (folinic acid, 5-FU, and oxaliplatin) or FOLFIRI (folinic acid, 5-FU, and irinotecan) rather than capecitabine-based or bolus 5-FU-based regimens (I)	100
29	Biweekly cetuximab is as efficient and well-tolerated as weekly cetuximab and thus has to be preferred to improve patient and health resource constraints (I)	100
30	Maintenance is possible with anti-EGFR agents and 5-FU after induction in RAS-wt mCRC (II)	100
31	The combination of cetuximab with irinotecan is more active than cetuximab alone in irinotecan-refractory patients (II)	100
32	In RAS-wt left-sided mCRC, rechallenging with anti-EGFR agents in third-line treatment and beyond is a good option, ideally based on a tumor biopsy or liquid biopsy result reconfirming the RAS-wt status (III)	100
BRAF mutation		
33	FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin)/FOLFOX in combination with bevacizumab is the best option for mCRC with BRAF mutation in the first-line setting (II)	87.5
34	BRAFV600E-mutated mCRC previously treated with chemotherapy, with or without antiangiogenic agents, should be treated with encorafenib and cetuximab (I)	100
35	Tumors with mutated BRAF and MSI-H should be treated with first-line immunotherapy (II)	93.75
MSI		
36	MSI/MMR status should be determined before any treatment for early and mCRC by IHC, PCR, or a validated NGS panel (V)	87.5
37	Single-agent immunotherapy (pembrolizumab) is a registered treatment option for first-line treatment of MSI-H upfront nonresectable mCRC (I)	100
38	Combination immunotherapy (nivolumab plus ipilimumab) is also a valid treatment option for first-line treatment of MSI-H upfront nonresectable mCRC (III)	100
39	Pembrolizumab, nivolumab, or a combination of nivolumab and ipilimumab are recommended as a subsequent-line therapy in patients with MSI-H tumors that are naïve to immune CPIs (I)	100

(Continued)

Table 1. (Continued)

No.	Statement	%
RAS mutation		
40	mCRC with RAS mutation should not be treated with anti-EGFR therapies (I)	100
41	mCRC patients receiving FOLFOX plus bevacizumab should be considered for maintenance therapy after 16–24 weeks of induction optimally with fluoropyrimidine plus bevacizumab (I)	100
42	mCRC patients who received bevacizumab in first-line therapy should be considered for continued antiangiogenic treatment (bevacizumab, aflibercept, ramucirumab) after progression (I)	100
Beyond second-line mCRC options		
43	Having passed initial treatment with fluoropyrimidines combined with oxaliplatin and/or irinotecan (plus targeted therapy) patients should be offered the option of third-line treatment (I)	100
44	The objective of mCRC treatment in the third-line setting is to increase survival while maintaining the quality of life of patients	100
45	When establishing a therapeutic sequence beyond 2L setting mCRC, an option must be used that increases survival with good tolerance and ideally allows the patient to continue to be treated thereafter	100
46	Trifluridine/tipiracil ± bevacizumab is effective and safe in the third-line setting of mCRC treatment (after the use of oxaliplatin-, irinotecan-based therapy, and biological therapies) and is supported by a high level of evidence (I)	100
47	Regorafenib is effective in patients with mCRC in the third-line setting and beyond. The tolerability of this agent is a matter of concern (I)	100
48	Fruquintinib, an oral VEGFR inhibitor, offers efficacy and safety in later lines of mCRC patients with prior exposure to trifluridine/tipiracil and/or regorafenib (I)	100
49	Based on clinical experience in RAS/BRAF-wt mCRC, retreatment (rechallenge) with anti-EGFR agents is an option to be assessed for patients who have PFS ⩾ 4–6 months to anti-EGFR in 1L, an anti-EGFR-free treatment interval of at least 4 months and remain wild-type according to tumor biopsy or liquid biopsy (II)	100
50	Anti-HER2 agents (trastuzumab-tucatinib, trastuzumab plus lapatinib, pertuzumab/T-DXd, or T-DXd) are treatment options in previously treated amplified/overexpressed HER2 mCRC	93.75
51	Pre-treated patients may be offered extended molecular testing by NGS to identify druggable alterations of the tumor genome	100
KRAS G12C mutation		
52	The optimal first-line treatment in KRAS G12C mutation is doublet + bevacizumab OR FOLFOXIRI + Bev	100
53	Optimal second-line treatment in KRAS G12c mutation (those who are treated with FOLFOX first line) (c) Doublet + Bev (d) Other options (i) Sotorasib + panitumumab (ii) Adagrasib + cetuximab (iii) Trifluridine/tipiracil + bevacizumab	100
54	Optimal third-line treatment in KRAS G12c mutation (c) Trifluridine/tipiracil + bevacizumab (iv) PFS benefits both RAS-mutant and RAS-wt patients (v) Similar OS RAS-wt and RAS-mutant patients (d) Other options (vi) Regorafenib	100

(Continued)

Table 1. (Continued)

No.	Statement	%
55	Optimal fourth-line treatment in KRAS G12c mutation (b) Fruquintinib	100
BRAF-V600E mutation		
56	Optimal first-line treatment for BRAF V600E mutation is (e) FOLFOX plus bevacizumab (recommended treatment) (i) FOLFOXIRI + bevacizumab is not better than FOLFOX + bevacizumab (f) Other options (i) Binimetinib + encorafenib + cetuximab (ii) FOLFOX + encorafenib + cetuximab (g) EGFR inhibitors plus chemotherapy should be avoided (h) About 30% BRAF mutation in MSI-H tumors. CPI should be applied first line in BRAF-mut MSI-H mCRC. (i) Pembrolizumab, nivolumab, or nivolumab/ipilimumab is also effective in BRAF mutation (ii) ORR, PFS, and OS superior with immune CPIs compared to chemotherapy	93.33
57	Optimal second-line treatment in BRAF V600E mutation (b) Encorafenib + cetuximab	100
58	Optimal third-line treatment in BRAV V600E mutation (c) No data from the SUNLIGHT Study (d) No data from the FRESCO-2 Study	100
59	*BRAF*-V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely	93.33
60	Prognostic role: Evidence does not support a prognostic role of HER2 overexpression.	92.86
61	Testing: If the tumor is already known to have a KRAS/NRAS or BRAF mutation, HER2 testing is not indicated	92.86
62	Resistance to anti-EGFR agents: HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.	92.86
HER2 amplification/overexpression		
63	HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in RAS/BRAF-wt tumors (reported at 5%–14%)	100
64	Optimal first-line treatment in HER2+ patients (c) Standard first-line treatment (i) But potentially avoid cetuximab since HER2 amplification may be associated with resistance to anti-EGFR agents No evidence regarding first-line use of HER-directed agents	100
65	Optimal second-line treatment in HER2+ patients if KRAS-wt (only phase-II data) (d) Trastuzumab + lapatinib (e) Trastuzumab + pertuzumab (f) Trastuzumab + tucatinib	100
66	Optimal second-line treatment in HER2+ patients independent of RAS status (b) T-DXd (ii) IHC3+/wild type: ORR = 68.3% (iii) IHC3+/mutant: ORR = 9.8% (iv) IHC2+/wild type: ORR = 14.6% (v) IHC2+/mutant: ORR = 7.3% (vi) PFS overall 5.8 months; OS overall 13.4 months (at the dose of 5.4 mg/kg q 3w)	100

(Continued)

Table 1. (Continued)

No.	Statement	%
MSI-H/dMMR		
67	Frequency: 3.5%–5.0%	93.33
68	Optimal first-line treatment in MSI-H/dMMR (a) Pembrolizumab monotherapy (b) Nivolumab/ipilimumab	93.33
69	Optimal second-line treatment in MSI-H/dMMR (a) Nivolumab/ipilimumab (if not pretreated with CPI)	93.33
70	Optimal third-line treatment in MSI-H/dMMR (a) Pembrolizumab	93.33
NTRK fusions		
71	Frequency: 0.2%–1%	100
72	NTRK fusions were more prevalent in cancers that were wild type for KRAS, NRAS, and BRAF	100
73	A majority (77%) of the CRCs harboring NTRK fusions were also dMMR	100
74	Larotrectinib and entrectinib are effective	100
Liver-limited disease		
75	Optimal first-line treatment in RAS/BRAF-wt and left-sided tumors with initially unresectable CRLM (c) Doublet + panitumumab = doublet plus bevacizumab (d) Doublet + cetuximab = triplet + cetuximab	92.86
76	Optimal first-line treatment in RAS/BRAF-mutated and/or right-sided tumors with initially unresectable CRLM (b) FOLFOXIRI + bevacizumab more effective than doublet + Bev	92.86
Maintenance therapy		
77	Doublet chemotherapy with FOLFIRI can be applied until the progression of the disease. However, oxaliplatin-based combination chemotherapy is associated with toxic side effects (neurotoxicity) that preclude prolonged treatment. To reduce toxicity and to ensure continuation of treatment, oxaliplatin-free maintenance therapies allowing the continued use of fluoropyrimidine (in combination with a biological) have been established.	100
78	If induction therapy with an oxaliplatin/fluoropyrimidine-based regimen has been started in combination with bevacizumab, maintenance therapy using a fluoropyrimidine plus bevacizumab is recommended.	100
79	If oxaliplatin-based chemotherapy has been started in combination with anti-EGFR agents (cetuximab or panitumumab), de-escalation to maintenance therapy with a fluoropyrimidine plus an anti-EGFR agent is advised.	100
80	Once the disease progressess during maintenance therapy, consideration should be given to reintroducing the initially successful induction chemotherapy, especially if progression occurs after 3 months of starting maintenance therapy. However, if progression occurs within the first 3 months, the patient should be switched to second-line therapy.	100

CPI, checkpoint inhibitor; CR, complete response; CRC, colorectal cancer; CRLM, colorectal liver metastases; dMMR, MMR-deficient; FISH, fluorescence in situ hybridization; FIT, fecal immunochemical test; 5-FU, 5-fluorouracil; GCC, Gulf Cooperation Council; IHC, immunohistochemistry; mCRC, metastatic CRC; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, MSI-high; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response;SD, stable disease; T-DXd, trastuzumab deruxtecan; wt, wild-type; VEGFR, vascular endothelial growth factor receptor.

Table 2. Levels of evidence.

	Evidence – Based Medicine
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with suspicion of bias (low methodological quality) or meta-analyses of such trials or trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies of case–control studies
V	Studies without control group, case reports, expert opinions

eventually on liquid biopsy when tissue biopsy cannot be done or is not available (II) ($A = 100\%$, $D = 0\%$)

2.c RAS analysis should include KRAS exons 2, 3, and 4 (codons 12, 13, 59, 61, 117, and 146) and NRAS exons 2, 3, and 4 (codons 12, 13, 59, 61, and 117) (V) ($A = 100\%$, $D = 0\%$)

2.d RAS mutational status is a negative predictive biomarker for treatment with anti-EGFR therapies (cetuximab or panitumumab; I) ($A = 100\%$, $D = 0\%$)

2.e In patients with baseline RAS wild-type (wt) mCRC that have initially responded to anti-EGFR therapy (CR, PR, or SD ⩾4–6 months), testing of RAS mutational status is of clinical importance before rechallenging in third-line treatment (III) ($A = 100\%$, $D = 0\%$).

The panel aligns with the consensus of other expert groups, including the European Society for Medical Oncology and the Pan-Asian panel of experts, on the significance of RAS mutations as predictive biomarkers.[8–10] The panel specifically agrees that RAS mutational status is a negative predictive biomarker for anti-EGFR therapies, with unanimous support ($A = 100\%$). They recommend performing RAS testing at the time of mCRC diagnosis using NGS or PCR in accredited laboratories, a recommendation that also received substantial backing ($A = 93.75\%$). The consensus includes the option of conducting RAS testing on primary CRCs, metastases, or, if needed, via liquid biopsy ($A = 100\%$). There is unanimous agreement on performing this test when a tissue biopsy is not feasible or accessible. Statement 2.c, emphasizing the inclusion of KRAS and NRAS analysis of specific exons, garnered significant agreement from the panel ($A = 100\%$). The panel also identifies RAS mutational status as a critical determinant in guiding treatment with anti-EGFR therapies (cetuximab or panitumumab) ($A = 100\%$). For patients with baseline RAS-wt mCRC who have responded to anti-EGFR therapy, the panel considers it essential to test RAS mutational status prior to reinitiating third-line treatment ($A = 100\%$).

BRAF and microsatellite instability

3.a BRAF testing (V600E only) should be carried out on all patients at the time of diagnosis of mCRC by PCR or by NGS panels in accredited and experienced laboratories (V) ($A = 100\%$, $D = 0\%$)

3.b BRAF V600E mutational status is a negative prognostic biomarker and a predictive biomarker for BRAF-targeted treatment (I) ($A = 100\%$, $D = 0\%$)

3.c Universal mismatch repair (MMR) or microsatellite instability (MSI) testing is recommended in all patients newly diagnosed with mCRC (V) ($A = 100\%$, $D = 0\%$)

3.d MSI is evaluated by immunohistochemistry (IHC), PCR, or a validated NGS panel in the first-line metastatic setting (V) ($A = 100\%$, $D = 0\%$)

3.e Detection of germline MSI in metastatic disease can assist the clinician in genetic counseling (II) ($A = 100\%$, $D = 0\%$)

3.f Tumor MSI testing has strong predictive value for the use of immune checkpoint inhibitors (CPIs) in the treatment of patients with mCRC (II) ($A = 100\%$, $D = 0\%$).

Emphasizing the importance of testing for BRAF mutations, especially V600E, in mCRC patients at diagnosis using PCR or NGS panels in accredited laboratories (V) ($A = 100\%$), the panel is in agreement with recommendations from the European Society for Medical Oncology and

Pan-Asian experts. Emphasizing the pivotal role of baseline testing in cancer management, the NCCN also advocates conducting this testing through PCR or NGS panels, supplementing it with other pertinent biomarkers for effective mCRC management.[11] The experts also agree that BRAF V600E mutational status acts as both a negative prognostic marker and a positive predictive biomarker for BRAF-targeted treatments (I) ($A = 100\%$). While BRAF mutations are relatively rare in CRC, occurring in about 2.5%, their prevalence increases in mCRC, with BRAFV600E mutations found in approximately 8%–12% of cases. Studies such as CAIRO, CAIRO2, COIN, and FOCUS have highlighted its significance as an independent negative prognostic factor in mCRC.[12–16] With emerging BRAF-targeted therapies like encorafenib plus cetuximab,[17] BRAF now plays a pivotal role as a major predictive biomarker in mCRC. MSI is identified in approximately 4%–5% of mCRC cases.[18] The experts recommend universal testing for MMR or MSI in all newly diagnosed mCRC patients ($A = 100\%$). This testing is valuable for genetic counseling ($A = 100\%$). The panel concurs on using IHC, PCR, or NGS panels for MMR or MSI testing ($A = 100\%$). MSI serves as a predictive factor, playing a crucial role in determining the use of immune CPIs for mCRC patients ($A = 100\%$). Evidence from the KEYNOTE-177 trial highlights the efficacy of pembrolizumab in improving progression-free survival (PFS), improving overall survival (OS), and reducing treatment-related adverse events for patients with MSI-high (MSI-H)/MMR-deficient (dMMR) mCRC as a first-line therapy compared to chemotherapy.[19,20]

Emerging biomarkers

- 4.a HER2 amplification is a predictive biomarker in previously treated mCRC (IV) ($A = 100\%$, $D = 0\%$)
- 4.b HER2 testing is performed by IHC and confirmed, if necessary (2+), by fluorescence in situ hybridization (FISH); (V) ($A = 100\%$, $D = 0\%$)
- 4.c Considering the availability of (trastuzumab deruxtecan (T-DXd)), HER2 testing may also be considered in tumors with KRAS/NRAS or BRAF mutation ($A = 100\%$, $D = 0\%$)
- 4.d HER2 amplification/overexpression may be predictive of resistance to anti-EGFR monoclonal antibodies (IV) ($A = 100\%$, $D = 0\%$)
- 4.e NTRK fusion detection is performed by IHC, FISH, DNA-based NGS, and RNA-based NGS (V) ($A = 100\%$, $D = 0\%$)
- 4.f NTRK fusion testing should be limited to tumors with KRAS-wt, NRAS-wt, and BRAF-wt, and preferably in dMMR/MSI-H previously treated mCRC (IV) ($A = 100\%$, $D = 0\%$).

HER2, a key oncogenic driver and therapeutic target in breast and gastric cancers, is increasingly recognized as an important biomarker in mCRC ($A = 100\%$). The prevalence of HER2 amplification in mCRC varies, with studies indicating expression levels between 2% and 9.5%.[21] Notably, HER2 amplification is more prevalent in RAS-wt and BRAF-wt mCRC cases.[21] The panel supports HER2 testing through IHC and, if necessary (2+), confirmation by FISH ($A = 100\%$). In their discussions, the panel highlighted that testing for HER2 amplification or overexpression is predictive of resistance to anti-EGFR monoclonal antibodies ($A = 100\%$). RAS mutation predicts resistance to agents directed against HER2. However, due to a different mode of action, the antibody-derived drug conjugate T-DXd is also active in RAS mutant tumors.

NTRK fusions are exceedingly rare in mCRC, constituting only 0.35% in a cohort of 2314 CRC patients, primarily occurring in those with RAS-wt and BRAF-wt.[22] As a result, the panel recommends limiting NTRK fusion testing to tumors that are RAS-wt and BRAF-wt, ideally in dMMR/MSI-H tumors ($A = 100\%$). The recommended testing methods include IHC, FISH, DNA-based NGS, and RNA-based NGS ($A = 100\%$).

Treatment

- 5.a The sidedness of the primary tumor is an important prognostic and predictive marker for the treatment of mCRC (IV) ($A = 100\%$, $D = 0\%$)
- 5.b According to a simplified classification, right-sided primary tumors are tumors located between the cecum and the splenic flexure ($A = 100\%$, $D = 0\%$)
- 5.c Systemic therapy (including targeted agents such as anti-EGFR or antiangiogenic) is not indicated in patients with upfront resectable metastases during perioperative therapy (II) ($A = 93.75\%$, $D = 6.25\%$)

5.d Complete cytoreductive surgery can be considered in experienced centers for patients with limited peritoneal metastases, liver, and pulmonary lesions (V) ($A = 93.75\%$, $D = 6.25\%$).

The intricate association between primary tumor sidedness and CRC stands out as a pivotal prognostic and predictive factor for managing mCRC (IV) ($A = 100\%$). This linkage derives from the divergent embryological origins of the right and left colon.[23] The panel defines the right colon as extending from the cecum to the splenic flexure ($A = 100\%$). They also state that systemic therapy, including anti-EGFR or antiangiogenic agents, is generally not indicated for patients with initial resectable metastases during perioperative therapy (II) ($A = 93.75\%$). For cases involving limited peritoneal metastases along with liver and pulmonary lesions, the experts recommend considering the possibility of complete cytoreductive surgery at specialized centers (V) ($A = 93.75\%$).

RAS wild-type

6.a In unresectable mCRC with right-sided primary tumors, bevacizumab in combination with chemotherapy must be preferably used in the first-line setting because anti-EGFR agents do not show a clear improvement in PFS and OS in this setting (III) ($A = 100\%$, $D = 0\%$)

6.b In unresectable mCRC with left-sided primary tumors, anti-EGFR agents plus chemotherapy are the standard of care in the first-line setting ($A = 87.5\%$, $D = 12.5\%$)

6.c Anti-EGFR agents should preferably be used in combination with FOLFOX (folinic acid, 5-fluorouracil (5-FU), and oxaliplatin) or FOLFIRI (folinic acid, 5-FU, and irinotecan) rather than capecitabine-based or bolus 5-FU-based regimens (I) ($A = 100\%$, $D = 0\%$)

6.d Biweekly cetuximab is as efficient and well-tolerated as weekly cetuximab and thus has to be preferred to improve patient and health resource constraints (I) ($A = 100\%$, $D = 0\%$)

6.e Maintenance is possible with anti-EGFR agents plus 5-FU after induction in RAS-wt mCRC (II) ($A = 100\%$, $D = 0\%$)

6.f The combination of cetuximab with irinotecan is more active than cetuximab alone in irinotecan-refractory patients (II) ($A = 100\%$, $D = 0\%$)

6.g In RAS-wt left-sided mCRC, rechallenging with anti-EGFR agents in third-line treatment and beyond is a good option, ideally based on a tumor biopsy or liquid biopsy result reconfirming the RAS-wt status (III) ($A = 100\%$, $D = 0\%$).

For unresectable mCRC with right-sided primary tumors, the expert panel recommends using bevacizumab in combination with chemotherapy as the first-line treatment. This recommendation is based on the finding that anti-EGFR agents do not demonstrate a significant benefit in PFS or OS in this scenario (III) ($A = 100\%$). For RAS-wt left-sided tumors, the panel supports the use of anti-EGFR agents in conjunction with chemotherapy as the standard first-line approach ($A = 87.5\%$). All experts align with statement 6.c, as supported by the COIN trial, which negates the benefit of combining a capecitabine-based regimen with anti-EGFR therapies.[15] Regarding cetuximab administration frequency, the entire panel agrees that a biweekly regimen is as effective and well-tolerated as the weekly schedule, and it is preferred for reducing patient and healthcare resource burdens ($A = 100\%$). This perspective is substantiated by recent studies demonstrating comparable effectiveness between weekly and biweekly cetuximab, influencing the US FDA's approval of biweekly cetuximab for RAS-wt mCRC treatment.[24–26] Considering maintenance therapy and options for RAS-wt mCRC after induction, the panel suggests the viability of anti-EGFR agents combined with 5-FU, with support from recent trials. Moreover, in irinotecan-refractory patients, the experts concur with the efficacy of combining cetuximab with irinotecan, emphasizing its superiority over cetuximab alone (II) ($A = 100\%$). For RAS-wt mCRC with left-sided primaries that have responded to first-line anti-EGFR therapy, the panel recommends considering rechallenge with anti-EGFR agents in third or subsequent lines of treatment, provided RAS-wt status is confirmed through tumor or liquid biopsy (III) ($A = 100\%$). The CRICKET trial supports this strategy, revealing an overall response rate of 21% and a disease control rate of 54% with a liquid biopsy-driven rechallenge approach.[27]

BRAF mutation

7.a FOLFIRINOX (folinic acid, 5-FU, irinotecan, and oxaliplatin)/FOLFOX in combination with bevacizumab is the

best option for mCRC with BRAF mutation in the first-line setting (II) ($A = 87.5\%$, $D = 12.5\%$)

7.b BRAFV600E-mutated mCRC progressing on first-line chemotherapy, with or without antiangiogenic agents, should be treated with encorafenib and cetuximab (I) ($A = 100\%$, $D = 0\%$)

7.c Tumors with mutated BRAF and MSI-H should be treated with first-line immunotherapy (II) ($A = 93.75\%$, $D = 6.25\%$).

For mCRC with a BRAF mutation in the first-line setting, the expert panel recommends FOLFOX or FOLFOXIRI combined with bevacizumab as the optimal treatment choice (II) ($A = 87.5\%$). Data from the TRIBE trial, which compared FOLFIRI plus bevacizumab with FOLFOXIRI plus bevacizumab, show a median OS of 29.8 months for FOLFOXIRI plus bevacizumab, indicating a superior outcome compared to the 25.8 months median OS with FOLFIRI plus bevacizumab. While exploratory subgroup analysis in the TRIBE study suggests an OS benefit for triplet versus doublet therapy in 28 BRAF-mutant CRC patients, recent meta-analysis findings do not consistently confirm this advantage.[28] Lastly, in agreement with statement 7.d, the panel acknowledges the efficacy of first-line immunotherapy for tumors with mutated BRAF and MSI-H, as demonstrated in the KEYNOTE-177 trial (II) ($A = 93.75\%$). In this trial, pembrolizumab demonstrated significant benefits for patients with BRAFV600E mutation and MSI-H disease, highlighting the relevance of immunotherapy in this context.[20]

Microsatellite instability

8.a MSI/MMR status should be determined before any treatment for early and mCRC by IHC, PCR, or a validated NGS panel (V) ($A = 87.5\%$, $D = 12.5\%$)

8.b Single-agent immunotherapy (pembrolizumab) is a registered treatment option for first-line treatment of MSI-H upfront nonresectable mCRC (I) ($A = 100\%$, $D = 0\%$)

8.c Combination immunotherapy (nivolumab plus ipilimumab) is also a valid treatment option for first-line treatment of MSI-H upfront nonresectable mCRC (III) ($A = 100\%$, $D = 0\%$)

8.d Pembrolizumab, nivolumab, or the combination of nivolumab and ipilimumab are recommended as a subsequent-line therapy in patients with MSI-H tumors that are naïve to immune CPIs (I) ($A = 100\%$, $D = 0\%$).

The expert panel engaged in extensive discussions and reached a consensus on the critical importance of determining MSI/MMR status before initiating any treatment for both early and mCRC. They emphasized the need for accurate diagnostic methods, including IHC, PCR, or a validated NGS panel, to confirm the MSI/MMR status ($A = 87.5\%$). In light of the pivotal KEYNOTE-177 trial, which showcased the significant benefit of pembrolizumab monotherapy for treatment-naïve MSI-H mCRC,[20] the panel acknowledged the strong evidence supporting single-agent immunotherapy with pembrolizumab as a registered and recommended first-line treatment option ($A = 100\%$). Moreover, the CheckMate 8HW trial results were thoroughly discussed,[29] providing Level I evidence demonstrating a significant PFS benefit for nivolumab in combination with low-dose ipilimumab as first-line treatment for MSI-H nonresectable mCRC.[30] The panel, after careful consideration, reached a unanimous consensus in recommending this combination immunotherapy as a valid and effective treatment option ($A = 100\%$). The experts thoroughly reviewed options for subsequent-line therapy in patients with MSI-H tumors who have not previously received immune CPIs. Drawing insights from trials such as KEYNOTE-164,[31] the panel recommended pembrolizumab, nivolumab, or the combination of nivolumab and ipilimumab as suitable and effective treatment options for therapy-refractory MSI-H mCRC tumors ($A = 100\%$). These recommendations were backed by strong clinical evidence from the trials, highlighting the importance of making informed, evidence-based decisions in the management of MSI-H CRC.

RAS mutation

9.a mCRC with RAS mutation should not be treated with anti-EGFR therapies (I) ($A = 100\%$, $D = 0\%$)

9.b mCRC patients receiving FOLFOX plus bevacizumab should be considered for maintenance therapy after 16–24 weeks of induction optimally with fluoropyrimidine plus bevacizumab (I) ($A = 100\%$, $D = 0\%$)

9.c mCRC patients who received bevacizumab in first-line therapy should be considered for continued antiangiogenic treatment (bevacizumab, aflibercept, ramucirumab) after progression (I) ($A = 100\%$, $D = 0\%$).

The expert panel engaged in comprehensive discussions and reached a unanimous consensus on crucial treatment strategies for mCRC, addressing different aspects of therapeutic decision-making. The panel agreed with the recommendation that mCRC patients with RAS mutations should not be treated with anti-EGFR therapies, emphasizing the importance of avoiding such treatments in this specific population ($A = 100\%$). The experts deliberated on the optimal duration of induction therapy for mCRC patients receiving FOLFOX plus bevacizumab and concluded that maintenance therapy should be considered after 16–24 weeks of induction, preferably with a fluoropyrimidine plus bevacizumab regimen ($A = 100\%$). The panel stressed the significance of evidence from a meta-analysis, which demonstrated no added benefit of continuing the induction regimen until progression, advocating for a maintenance strategy with fluoropyrimidine with bevacizumab as the preferred option.[32] For RAS-mutant mCRC patients who received bevacizumab as first-line treatment, the panel recommended considering antiangiogenic agents (bevacizumab, aflibercept, or ramucirumab) following disease progression ($A = 100\%$). The experts acknowledged the findings from the ML18147 study, a phase III trial, which supported the effectiveness of continuing bevacizumab in the second line for mCRC patients progressing on a first-line regimen containing bevacizumab.[33] In addition, insights from another phase III trial reinforced the recommendation, indicating that continuation or reintroduction of bevacizumab as a second- or subsequent-line therapy beyond progression on bevacizumab is associated with better survival.[34] The panel, through these discussions, highlighted the importance of personalized and evidence-based approaches in determining the most appropriate treatment strategies for mCRC patients in different clinical scenarios.

Beyond second-line mCRC options

10.a Having passed initial treatment with fluoropyrimidines combined with oxaliplatin and/or irinotecan (plus targeted therapy), patients should be offered the option of third-line treatment (I) ($A = 100\%$, $D = 0\%$)

10.b The objective of mCRC treatment in the third-line setting is to increase survival while maintaining the quality of life of patients ($A = 100\%$, $D = 0\%$)

10.c When establishing a therapeutic sequence beyond 2L setting mCRC, an option must be used that increases survival with good tolerance and ideally allows the patient to continue to be treated thereafter ($A = 100\%$, $D = 0\%$)

10.d Trifluridine/tipiracil ± bevacizumab is effective and safe in the third-line setting of mCRC treatment (after the use of oxaliplatin-, irinotecan-based therapy, and biological therapies) and is supported by a high level of evidence (I) ($A = 100\%$, $D = 0\%$)

10.e Regorafenib is effective in patients with mCRC in the third-line setting and beyond. Tolerability of this agent is a matter of concern (I) ($A = 100\%$, $D = 0\%$)

10.f Fruquintinib, an oral VEGFR inhibitor, offers efficacy and safety in later lines of mCRC patients with prior exposure to trifluridine/tipiracil and/or regorafenib (I) ($A = 100\%$, $D = 0\%$)

10.g Based on clinical experience in RAS/BRAF-wt mCRC, retreatment (rechallenge) with anti-EGFR agents is an option to be assessed for patients who have PFS ⩾ 4–6 months to anti-EGFR in 1L, an anti-EGFR-free treatment interval of at least 4 months and remain wild type according to tumor biopsy or liquid biopsy (II) ($A = 100\%$, $D = 0\%$)

10.h Anti-HER2 agents (trastuzumab-tucatinib, trastuzumab plus lapatinib, pertuzumab/T-DXd, or T-DXd) are treatment options in previously treated amplified/overexpressed HER2 mCRC ($A = 93.75\%$, $D = 6.25\%$)

10.i Pre-treated patients may be offered extended molecular testing by NGS to identify druggable alterations of the tumor genome ($A = 100\%$, $D = 0\%$).

The consensus statements regarding the third-line treatment options for mCRC demonstrate unanimous agreement among the expert panel. Participants strongly supported the proposition that patients who have completed initial

treatment with fluoropyrimidines, oxaliplatin, and/or irinotecan, along with targeted therapy, should be offered the option of third-line treatment ($A = 100\%$). Moreover, the overarching objective of third-line mCRC treatment was collectively acknowledged as aiming to increase survival while preserving patients' quality of life, garnering unanimous agreement ($A = 100\%$). The importance of selecting therapeutic sequences beyond the second line was underscored, emphasizing the need for options that enhance survival with good tolerance and the potential for continued treatment ($A = 100\%$). Consensus also emerged on specific treatment modalities in the third-line setting, with high levels of support for the effectiveness and safety of trifluridine/tipiracil ± bevacizumab ($A = 100\%$) and regorafenib (100%). In addition, fruquintinib, an oral VEGFR inhibitor, was deemed efficacious and safe in later lines of treatment ($A = 100\%$). The expert panel emphasized the importance of considering retreatment with anti-EGFR agents for RAS/BRAF-wt mCRC patients meeting specific criteria ($A = 100\%$). Furthermore, anti-HER2 agents were identified as viable treatment options for previously treated amplified/overexpressed HER2 mCRC ($A = 93.75\%$). Finally, the majority supported the notion that pre-treated patients may benefit from extended molecular testing via NGS to identify druggable alterations in the tumor genome ($A = 100\%$). This comprehensive consensus reflects the collective expertise and agreement within the panel, providing valuable insights into the evolving landscape of mCRC management.

KRAS G12C mutation

- 11.a Optimal first-line treatment in KRAS G12C mutation is doublet + bevacizumab or FOLFOXIRI + bevacizumab ($A = 100\%$, $D = 0\%$)
- 11.b Optimal second-line treatment in KRAS G12c mutation (those who are treated with FOLFOX first line) ($A = 100\%$, $D = 0\%$)
  - (a) Doublet + bevacizumab
  - (b) Other options
    - (i) Sotorasib + panitumumab
    - (ii) Adagrasib + cetuximab
    - (iii) Trifluridine/tipiracil + bevacizumab
- 11.c Optimal third-line treatment in KRAS G12c mutation ($A = 100\%$, $D = 0\%$)
  - (a) Trifluridine/tipiracil + bevaciz umab
    - (iv) PFS benefits both RAS-mutant and RAS-wt patients
    - (v) Similar OS RAS-wt and RAS-mutant patients
  - (b) Other options
    - (vi) Regorafenib
- 11.d Optimal fourth-line treatment in KRAS G12c mutation ($A = 100\%$, $D = 0\%$)
  - (a) Fruquintinib
    - (i) PFS and OS benefit both RAS-mutant and RAS-wt patients.

The expert consensus strongly supports specific treatment strategies for patients with KRAS G12C mutation at various lines of therapy. For the optimal first-line treatment in this subgroup, the panel recommends doublet + bevacizumab or FOLFOXIRI + bevacizumab, as indicated by the TRIBE and CAIRO5 trials[28,35] ($A = 100\%$). In the second-line setting for those initially treated with FOLFOX, the unanimous agreement favors the use of doublet + bevacizumab. Alternatively, the panel acknowledges several options, including sotorasib + panitumumab, adagrasib + cetuximab, and trifluridine/tipiracil + bevacizumab, as supported by studies such as CodeBreak 300,[36] KRYSTAL-1,[37] and SUNLIGHT,[38] respectively ($A = 100\%$). Moving to the third-line treatment, the consensus points to trifluridine/tipiracil + bevacizumab, supported by SUNLIGHT, showcasing PFS benefits in both RAS-mutant and RAS-wt patients and similar OS outcomes between these groups.[39,40] In addition, regorafenib is recognized as an alternative option ($A = 100\%$). For the fourth-line treatment, the panel unanimously recommends fruquintinib, citing data from the FRESCO-2 study, which demonstrates PFS and OS benefits in both RAS-mutant and RAS-wt patients[40] ($A = 100\%$).

BRAF-V600E mutation

- 12.a Optimal first-line treatment in BRAF V600E mutation is ($A = 93.33\%$, $D = 6.67\%$)
  - (a) FOLFOX plus bevacizumab (recommended treatment)
    - (i) FOLFOXIRI + bevacizumab is not better than FOLFOX + bevacizumab

(b) Other options
  (i) Binimetinib + encorafenib + cetuximab
  (ii) FOLFOX + encorafenib + cetuximab
(c) EGFR inhibitors plus chemotherapy should be avoided
(d) About 30% BRAF mutation in MSI-H tumors
(e) CPI should be applied first line in BRAF-mut MSI-H mCRC
  (i) Pembrolizumab, nivolumab, or nivolumab/ipilimumab are also effective in BRAF mutation
  (ii) ORR, PFS, and OS superior with immune CPIs compared to chemotherapy

12.b Optimal second-line treatment in BRAF V600E mutation ($A = 100\%$, $D = 0\%$)
(a) Encorafenib + cetuximab

12.c Optimal third-line treatment in BRAV V600E mutation ($A = 100\%$, $D = 0\%$)
(a) No data from the SUNLIGHT Study
(b) No data from the FRESCO-2 Study.

The consensus recommendations for the management of BRAF V600E mutation in mCRC highlight evidence-based approaches for different treatment lines. In the first-line setting, the majority consensus leans toward FOLFOX plus bevacizumab, supported by a meta-analysis conducted by Cremolini et al.[41] Importantly, the panel emphasizes that FOLFOXIRI + bevacizumab does not confer superior benefits over FOLFOX + bevacizumab. Alternative options include Binimetinib + encorafenib + cetuximab[42] and FOLFOX + encorafenib + cetuximab.[43] The consensus discourages the use of anti-GFR inhibitors plus chemotherapy and underscores that approximately 30% of BRAF mutations occur in MSI-H tumors, warranting the application of immune CPIs as a first-line treatment in BRAF-mut MSI-H mCRC. Key studies such as KEYNOTE 177 and CheckMate 142 provide robust evidence for the effectiveness of pembrolizumab, nivolumab, or nivolumab/ipilimumab, with superior objective response rates, PFS, and OS compared to chemotherapy[20,44] ($A = 93.33\%$). Moving to the second line, the unanimous agreement supports encorafenib + cetuximab ($A = 100\%$). However, the optimal third-line treatment lacks data from both the SUNLIGHT Study[45] and the FRESCO-2 Study ($A = 100\%$).

13.a *BRAF*-V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely ($A = 93.33\%$, $D = 6.67\%$)

13.b Prognostic role: Evidence does not support a prognostic role of HER2 overexpression

13.c Testing: If the tumor is already known to have a KRAS/NRAS or BRAF mutation, HER2 testing is not indicated

13.d Resistance to anti-EGFR agents: HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.

The panel reached a consensus indicating a reduced likelihood of response to panitumumab or cetuximab, whether used alone or combined with cytotoxic chemotherapy, in the presence of the BRAF-V600E mutation ($A = 93.33\%$). This insight informs a more nuanced understanding of treatment responses tailored to the molecular profile of CRC. In addition, the panel delves into the prognostic role of HER2 overexpression and notes that the available evidence does not support a prognostic significance. Regarding testing protocols, the consensus is that HER2 testing is not necessary if the tumor already has a known KRAS/NRAS or BRAF mutation, thereby simplifying the diagnostic process. In addition, the panel emphasizes the potential predictive role of HER2 amplification or overexpression in contributing to resistance against anti-EGFR agents. This nuanced perspective on molecular markers provides clinicians with valuable guidance in navigating the intricacies of treatment decisions, further individualizing therapeutic approaches for patients with CRC, particularly those with the BRAF-V600E mutation.[46]

HER2 amplification/overexpression

14.a HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in RAS/BRAF-wt tumors (reported at 5%–14%) ($A = 100\%$, $D = 0\%$)

14.b Optimal first-line treatment in HER2+ patients
(a) Standard first-line treatment
  (i) But potentially avoid cetuximab since HER2

amplification may be associated with resistance to anti-EGFR agents
(b) No evidence regarding first-line use of HER-directed agents

14.c Optimal second-line treatment in HER2+ patients if KRAS-wt (only phase-II data)
(a) Trastuzumab + lapatinib
(b) Trastuzumab + pertuzumab
(c) Trastuzumab + tucatinib

14.d Optimal second-line treatment in HER2+ patients independent of RAS status
(a) T-DXd
(i) IHC3+/wild type: ORR = 68.3%
(ii) IHC3+/mutant: ORR = 9.8%
(iii) IHC2+/wild type: ORR = 14.6%
(iv) IHC2+/mutant: ORR = 7.3%
(v) PFS overall 5.8 months; OS overall 13.4 months (at the dose of 5.4 mg/kg q 3w).

The consensus among the panel recognizes the rarity of HER2 amplification/overexpression in CRC, occurring in approximately 3% overall, with a higher prevalence in RAS/BRAF-wt tumors, reported at 5%–14% ($A = 100\%$). The discussion on optimal first-line treatment for HER2+ patients requires cautious considerations. While standard first-line treatment is recommended, there is a suggestion to potentially avoid cetuximab, as HER2 amplification may be linked to resistance to anti-EGFR agents.[47,48] Importantly, there is currently no evidence regarding the first-line use of HER-directed agents. Moving to the second-line treatment, the panel delineates strategies based on KRAS status. For KRAS-wt patients, trastuzumab + lapatinib, trastuzumab + pertuzumab, and trastuzumab + tucatinib are presented as options, supported by phase-II data from the HERACLES,[49] MyPathway,[50] and Mountaineer trials,[51] respectively. Furthermore, irrespective of RAS status, T-DXd emerges as a promising option for second-line treatment, as demonstrated in the Destiny-CRC02 trial,[52] showcasing notable objective response rates and encouraging PFS and OS outcomes across different subgroups. These nuanced recommendations underscore the need for personalized treatment approaches in HER2+ CRC patients, considering both molecular characteristics and available clinical evidence.

MSI-high/MMR-deficient

15.a Frequency: 3.5%–5.0% ($A = 93.33\%$, $D = 6.67\%$)

15.b Optimal first-line treatment in MSI-H/dMMR
(a) Pembrolizumab monotherapy
(b) Nivolumab/ipilimumab

15.c Optimal second-line treatment in MSI-H/dMMR
(a) Nivolumab/ipilimumab (if not pretreated with CPI)

15.d Optimal third-line treatment in MSI-H/dMMR
(a) Pembrolizumab.

The consensus within the panel acknowledges the frequency of MSI-H/dMMR CRC at 3.5%–5.0% ($A = 93.33\%$). The discussion centers on the optimal treatment strategies at different lines of therapy for this molecular subtype. For first-line treatment, the unanimous agreement supports pembrolizumab monotherapy and nivolumab/ipilimumab, aligning with the established efficacy of immune checkpoint inhibition in MSI-H/dMMR tumors. As a second-line option, the consensus recommends nivolumab/ipilimumab, especially for patients who have not previously received CPIs. This recommendation is based on evidence supporting the efficacy of this combination in individuals who are naïve to immune CPIs. In the third-line setting, the panel observes a lack of specific evidence to determine the optimal treatment approach, underscoring the need for additional research and clinical trials to guide the best treatment strategies beyond the initial lines of therapy. The consensus provides a clear and evidence-based approach for the management of MSI-H/dMMR CRC, emphasizing the importance of immunotherapy in the first and second lines additionally in the third line with pembrolizumab considering the data of keynote-164.[31]

NTRK fusions

16.a Frequency: 0.2%–1% ($A = 100\%$, $D = 0\%$)

16.b NTRK fusions were more prevalent to cancers that were wild type for KRAS, NRAS, and BRAF

16.c A majority (77%) of the CRCs harboring NTRK fusions were also dMMR

16.d Larotrectinib and entrectinib are effective.

The panel discussion revolves around the infrequent occurrence of NTRK fusions in CRC, with a frequency ranging from 0.2% to 1% ($A = 100\%$). Remarkably, the consensus notes that NTRK fusions are predominantly found in cancers that are wild type for KRAS, NRAS, and BRAF, emphasizing the importance of evaluating the molecular landscape comprehensively for accurate diagnosis and treatment decisions. Furthermore, the consensus highlights an intriguing association, with a majority (77%) of CRCs harboring NTRK fusions also exhibiting MMR deficiency, suggesting potential connections between these distinct molecular aberrations. The panel uniformly recognizes the efficacy of larotrectinib and entrectinib, providing targeted therapeutic options for patients with NTRK fusions. These recommendations, supported by emerging evidence, underscore the significance of identifying and addressing NTRK fusions in CRC, contributing to the evolving landscape of precision medicine in oncology.

Liver-limited disease

17.a Optimal first-line treatment in RAS/BRAF-wt and left-sided tumors with initially unresectable colorectal liver metastases (CRLM) ($A = 92.86\%$, $D = 7.14\%$)
- (a) Doublet + panitumumab = doublet plus bevacizumab
- (b) Doublet + cetuximab = triplet + cetuximab

17.b Optimal first-line treatment in RAS/BRAF-mutated and/or right-sided tumors with initially unresectable CRLM ($A = 92.31\%$, $D = 7.69\%$)
- (a) FOLFOXIRI + bevacizumab more effective than doublet + bevacizumab.

The panel's discussion on the optimal first-line treatment for initially unresectable CRLM in the context of RAS/BRAF-wt and left-sided tumors centers on two distinct approaches, both supported by CAIRO5.[35] The consensus endorses the use of either doublet + panitumumab or doublet + bevacizumab, recognizing their comparable efficacy in this specific patient subset. In addition, the panel introduces an alternative for left-sided tumors, proposing doublet + cetuximab or triplet + cetuximab based on findings from the TRICE study, offering clinicians valuable options for tailoring treatment strategies.[53] Turning to RAS/BRAF-mutated and/or right-sided tumors with initially unresectable CRLM, the consensus leans toward FOLFOXIRI + bevacizumab as the preferred regimen, emphasizing its superior effectiveness compared to doublet + bevacizumab, as evidenced by CAIRO5[35] ($A = 92.86\%$). These recommendations underscore the importance of considering tumor molecular characteristics and site in tailoring first-line treatment strategies for unresectable CRLM, offering clinicians evidence-based guidance for optimized patient care.

Maintenance therapy

18.a Doublet chemotherapy with FOLFIRI can be applied until the progression of the disease. However, oxaliplatin-based combination chemotherapy is associated with toxic side effects (neurotoxicity) that preclude prolonged treatment. To reduce toxicity and to ensure continuation of treatment, oxaliplatin-free maintenance therapies allowing the continued use of a fluoropyrimidine (in combination with a biological) have been established ($A = 100\%$, $D = 0\%$).

18.b If induction therapy with an oxaliplatin/fluoropyrimidine-based regimen has been started in combination with bevacizumab, maintenance therapy using a fluoropyrimidine plus bevacizumab is recommended ($A = 100\%$, $D = 0\%$).

18.c If oxaliplatin-based chemotherapy has been started in combination with anti-EGFR agents (cetuximab or panitumumab), de-escalation to maintenance therapy with a fluoropyrimidine plus an anti-EGFR agent is advised ($A = 100\%$, $D = 0\%$).

18.d Once progression of the disease occurs during maintenance therapy, consideration should be given to reintroducing the initially successful induction chemotherapy, especially if progression occurs after 3 months of starting maintenance therapy. However, if progression occurs within the first 3 months, the patient should be switched to second-line therapy ($A = 100\%$, $D = 0\%$).

The panel discussion addresses the nuanced approach to maintenance therapy in CRC, acknowledging the challenges posed by oxaliplatin-based combination chemotherapy. The consensus

recognizes that while doublet chemotherapy with FOLFIRI can be sustained until disease progression, oxaliplatin-based regimens like FOLFOX[54] and CAPOX[55] often lead to neurotoxic side effects, necessitating a shift to oxaliplatin-free maintenance therapies. These maintenance strategies, involving a fluoropyrimidine in combination with a biological agent, are implemented to reduce toxicity and ensure the continuity of treatment. The panel underscores specific recommendations for maintenance therapy based on the initial induction regimen. For those starting with an oxaliplatin/fluoropyrimidine-based regimen in combination with bevacizumab, maintenance therapy utilizing a fluoropyrimidine plus bevacizumab is advised, as supported by studies such as Simkens et al.[56] and Hegewisch-Becker et al.[57] In cases where oxaliplatin-based chemotherapy is initiated with anti-EGFR agents, the consensus recommends de-escalation to maintenance therapy with a fluoropyrimidine plus an anti-EGFR agent, drawing on evidence from studies like Pietrantonio et al.[58] and OncLive.[59] Furthermore, the panel suggests a thoughtful approach to disease progression during maintenance therapy, advocating for the consideration of reintroducing the initially successful induction chemotherapy. These nuanced recommendations provide clinicians with valuable guidance for tailoring maintenance therapy in CRC, optimizing treatment outcomes while mitigating potential toxicities ($A = 100\%$).

Conclusion

In conclusion, this paper presents comprehensive guidelines for the management of CRC in the Gulf region, developed through consensus among experts from GCC countries. These guidelines cover essential topics such as epidemiology, screening, biomarkers, and treatment strategies, providing tailored recommendations to enhance outcomes for patients with mCRC. By incorporating the latest evidence-based practices and considering regional factors, these guidelines aim to standardize and optimize CRC care in the Gulf region, ultimately reducing the burden of this disease. Further research and implementation efforts are warranted to ensure the widespread adoption and effectiveness of these guidelines in clinical practice.

Disclaimer

These guidelines build upon the previously published guidelines titled "The first Middle East and North Africa expert consensus recommendations for the management of advanced colorectal cancer," to provide an updated version of the guidelines specific to the Gulf region. As these guidelines are standard across the region, certain statements are unavoidably identical and cannot be altered without compromising their accuracy and integrity, and thus a degree of overlap can be found between the text and tables of the two papers. The publisher of the original guidelines granted permission to the authors to adapt and reproduce sections of the text and tables for use in these newly created guidelines.

Declarations

Ethics approval and consent to participate

The manuscript reflects the opinions of the participating oncologists from different GCC countries, based on uptodate knowledge. There is no patient involvement or direct therapeutic interventions.

Consent for publication

Not applicable.

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