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SPECIAL ARTICLE

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INCIDENCE AND EPIDEMIOLOGY

Information on the incidence and epidemiology of colorectal cancer (CRC) is provided in Supplementary Material Section 1, available at https://doi.org/10.1016/j.annonc.2026.03.005.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Details regarding the diagnosis, pathology and molecular biology of metastatic CRC (mCRC) are provided in Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2026.03.005.

Recommendations

- In the case of clinical or radiological suspicion of mCRC, histological diagnosis of colorectal adenocarcinoma or related metastases should always be confirmed before administration of anticancer therapy [IV, A].
- A biopsy should generally be carried out ≤2 weeks from the first consultation [IV, B]. Ideally, ≥80% of histopathological diagnoses for cases of suspected CRC should generally be reported within 7 days of biopsy [IV, B].
- All available specimens should be reviewed by a pathologist to select the most appropriate sample for downstream molecular characterisation [V, A].
- Enrichment of tumour cell content (>20%) by macro- or micro-dissection is recommended before DNA extraction [IV, A].
- Molecular testing on the primary tumour or metastatic sites is recommended in all patients at the time of mCRC diagnosis [I, A]. Results of molecular tests should be reported in ≤14 days [I, A].
- Circulating tumour DNA (ctDNA) assays are recommended when rapid results are clinically important or when tissue biopsies are not possible or appropriate [III, A].
- Testing for mutations in exons 2, 3 and 4 of *KRAS* and *NRAS* is recommended to identify patients who may benefit from treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) [III, A; ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) score: not applicable]. Reporting the specific mutation is mandatory [I, A].
- Testing for $BRAF^{V600E}$ mutations can be recommended for prognostic assessment [I, B] and is recommended

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to identify patients who may benefit from V-Raf murine sarcoma viral oncogene homologue B (BRAF)-targeted therapy [I, A; ESCAT score: I-A].
- ctDNA assessment for *RAS, BRAF* and preferably also *EGFR* can be recommended before anti-EGFR rechallenge [II, B].
- Testing to detect mismatch repair-deficient (dMMR) and microsatellite instability-high (MSI-H) status is recommended to identify patients who may benefit from immune checkpoint inhibitor (ICI) therapy [I, A; ESCAT score: I-A] and can be recommended to inform genetic counselling for Lynch syndrome [II, B].
- Testing for human epidermal growth factor receptor 2 (HER2) overexpression and/or *HER2* amplification is recommended to identify patients who may benefit from anti-HER2 targeted agents [III, A; ESCAT score: II-B].
- When multigene tumour next-generation sequencing is available and applicable, testing for *POLE* or *POLD1* mutations (ESCAT score: II-B) and genomic aberrations, for which targeted therapies are approved in tumour-agnostic indications (e.g. *NTRK* fusions, *RET* fusions; ESCAT score: I-C), may be considered [III, C].
- Testing for dihydropyrimidine dehydrogenase deficiency is recommended before initiating 5-fluorouracil (5-FU)-, capecitabine- or tegafur—gimeracil—oteracil (S-1)-based therapies [III, A].

STAGING AND INITIAL ASSESSMENT

Key recommendations regarding staging and initial assessment for mCRC are provided below. Supporting data for these recommendations are described in Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2026.03.005.

Recommendations

- Contrast-enhanced (CE) computed tomography (CT) of the thorax, abdomen and pelvis is recommended for staging [IV, A].
- CE CT should be carried out in line with imaging protocols developed by the European Organisation for Research and Treatment of Cancer, the European Society of Oncologic Imaging and the European Society of Gastrointestinal and Abdominal Radiology [IV, A].
- Liver CE magnetic resonance imaging (MRI) with hepatobiliary agents is recommended in all patients eligible for locoregional therapy based on CE CT imaging or to characterise nontypical lesions [II, A].
- Staging laparoscopy can be recommended in case of peritoneal metastasis (PM) eligible for surgical resection to assess the extent of disease and reduce the risk of futile surgery [III, B].
- [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography can be recommended for selected patients with increased tumour markers without evidence of metastatic disease or to define the extent of extrahepatic metastatic disease in patients potentially eligible for locoregional therapy or liver transplantation [IV, B].
- All patients should be evaluated by an organ-specific multidisciplinary team (MDT) at diagnosis to define the treatment plan, integrating all necessary clinical, radiological and biological information for decision making [IV, A].
- For potentially resectable disease, resectability should be defined at baseline [referring to recent (<4 weeks) high-quality imaging, including a detailed morphological description of tumour burden], every 2-3 months during first-line treatment and rediscussed in further lines in patients with a very good response [IV, A].

ROLE OF LOCAL AND LOCOREGIONAL TREATMENTS AND PROCEDURES

Details regarding primary tumour care in synchronous mCRC and considerations around oligometastatic disease (OMD) are provided in Supplementary Material Section 4, available at https://doi.org/10.1016/j.annonc.2026.03.005.

Locoregional therapy and strategy

Locoregional therapy is most often indicated in patients with OMD with the goal of complete macroscopic treatment of all metastatic sites, either initially or after systemic therapy, within one or multiple steps. Locoregional therapy may offer a chance of cure, depending on clinical scenarios and prognostic factors.

Upfront locoregional therapy (without preceding systemic therapy) is possible in favourable prognostic situations with limited metastatic spread according to the number and site of metastatic organs, number of lesions, prognostic scores, carcinoembryonic antigen (CEA) levels, locoregional lymph node (LN) status, time to metastasis and *BRAF* status. In most cases, initial systemic therapy is appropriate, followed by MDT reassessment for locoregional therapy in case of disease stabilisation. Locoregional therapy should be offered as soon as is safely feasible and should not be delayed to attempt further lesion shrinkage. An algorithm for the management of mCRC potentially amenable to locoregional therapy is provided in Figure 1.

Several scoring systems combining clinicopathological factors have been developed to identify patients who most benefit from locoregional therapy after curative-intent resection;[1-3] however, their utility in the general population is inconsistent,[4] and no strategies with curative intent should be withheld based on these models.

Additional applications of locoregional therapy include the treatment of oligoprogression (i.e. an isolated progressing metastatic lesion in overall controlled disease) and salvage therapy in patients with liver-dominant disease, in which intra-arterial therapies can be considered.

Management of specific metastatic sites

Details regarding the management of colorectal liver metastasis (CRLM), lung metastases, PMs and other

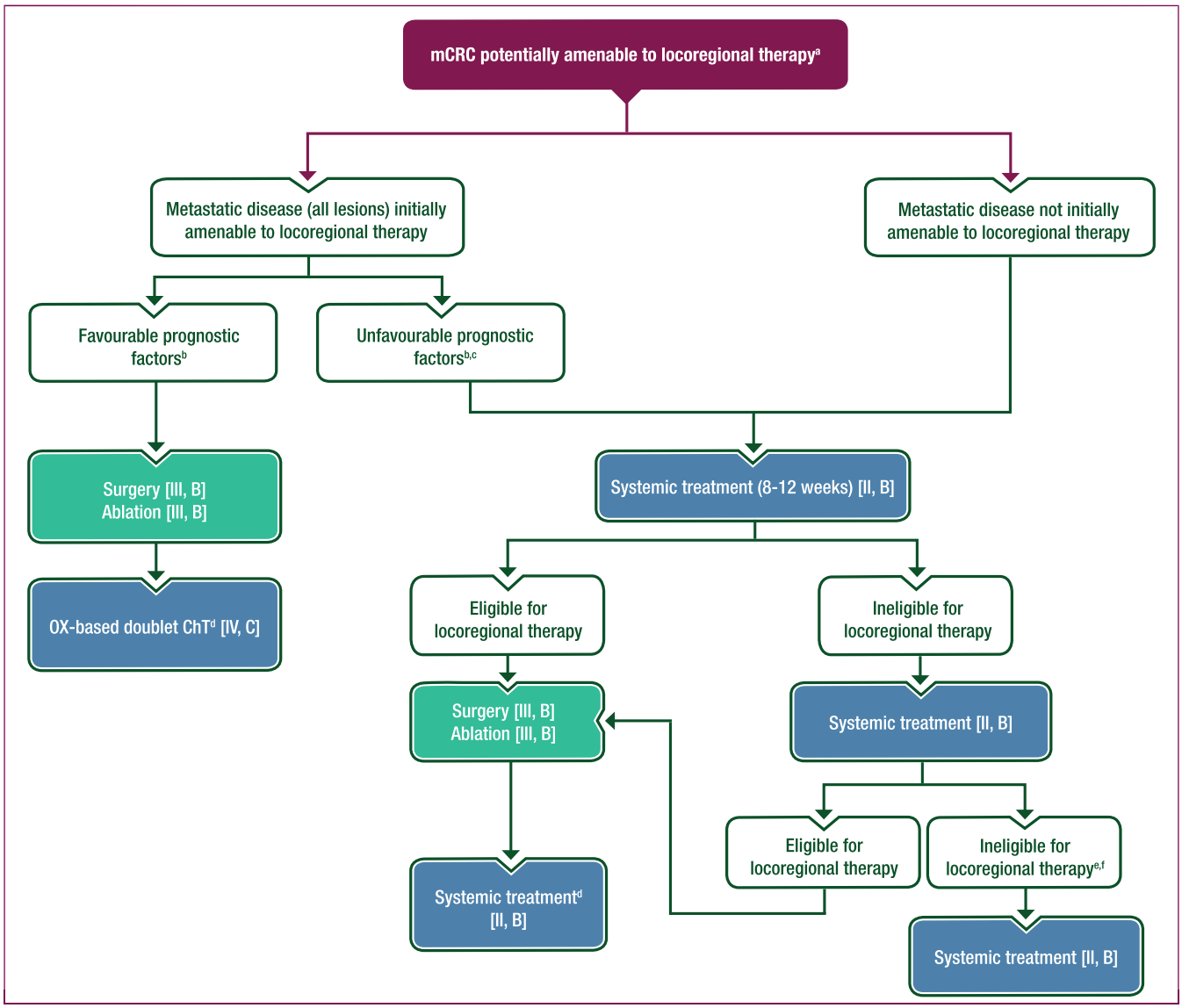

Figure 1. Management of mCRC potentially amenable to locoregional therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects.
CEA, carcinoembryonic antigen; ChT, chemotherapy; CRLM, colorectal liver metastasis; dMMR, MMR-deficient; ECOG, Eastern Cooperative Oncology Group; mCRC, metastatic colorectal cancer; MDT, multidisciplinary team; MMR, mismatch repair; OMD, oligometastatic disease; OX, oxaliplatin; PS, performance status; wt, wild-type.
[a]Treatment for all patients with OMD should be discussed within an MDT [IV, A].
[b]Factors to be considered: number of involved organs, number of lesions, prognostic scores, time to metastases, *BRAF* status, MMR status, CEA levels, pathological lymph nodes [IV, B]. Locoregional treatments can still be offered as an option to patients with resectable *BRAF*^{V600E}-mutated and/or dMMR mCRC, where upfront systemic therapies are generally indicated [IV, B].
[c]In the presence of multiple negative prognostic factors, the best available systemic treatment, including ChT plus targeted therapies, can be recommended [III, B].
[d]The overall duration of pre- and post-operative systemic therapy should generally be 6 months [II, B].
[e]Liver transplantation plus ChT is recommended as a curative-intent option for highly selected patients with liver-only permanently unresectable CRLM, provided that strict selection criteria [*BRAF*-wt, CEA $<$80 ng/ml, sustained response to systemic therapy (disease stabilisation for $\geq$3 months, no later than the third line of therapy), no extrahepatic disease during the entire disease history, resected primary tumour, ECOG PS $<$2, age 18-65 years] and organ policy prioritisation are met [II, A].
[f]See main text for recommendations for specific metastatic sites.

metastatic sites are provided in Supplementary Material Section 4.

Liver transplantation for unresectable or unablatable CRLM. Liver transplantation can be discussed for patients with unresectable but liver-limited, *BRAF*-wild-type (wt) mCRC whose primary tumour was previously resected and who experienced sustained ($>$3 months) disease control with systemic treatment. Information on liver transplantation is provided in Supplementary Material Section 4.

Recommendations

- Treatment for all patients with OMD should be discussed within an MDT [IV, A].
- Primary resection cannot be recommended for patients with an asymptomatic primary tumour and unresectable synchronous metastatic disease [I, D].
- Upfront resection or ablation can be recommended for patients with easily resectable or ablatable metastases and favourable prognostic criteria [III, B].

- If metastases are not easily resectable or ablatable, and/or in the presence of ≥1 poor prognostic criterion, upfront systemic treatment for 8-12 weeks can be recommended, followed by locoregional therapy if feasible [II, B].
- The factors to be considered for the selection of treatment include number of involved organs, number of lesions, prognostic scores, time to metastases, *BRAF* status, MMR status, CEA levels and pathological LNs [IV, B].
  - o Locoregional treatments can still be offered as an option to patients with resectable *BRAF*^{V600E}-mutated and/or dMMR mCRC, for which upfront systemic therapies are generally indicated [IV, B].
- In the presence of multiple negative prognostic factors, the best available systemic treatment, including chemotherapy (ChT) plus targeted therapies, can be recommended [III, B].
- Postoperative oxaliplatin-based doublet ChT may be considered for patients who did not receive preoperative treatment [IV, C].
- Postoperative systemic treatment can be administered in patients who have received preoperative treatment [II, B].
- The overall duration of pre- and postoperative systemic therapy should generally be 6 months [II, B].

CRLM

- Thermal ablation can be recommended over liver resection to treat small CRLMs (<3 cm) [II, B].
- Ablation by high conformal radiotherapy [e.g. stereotactic body radiotherapy (SBRT) or high-dose rate brachytherapy] can be recommended for unresectable CRLMs not eligible for thermal ablation [III, B].
- Resection and/or local ablation can be recommended for recurrent disease after surgical resection or ablation for CRLM [IV, B].
- Liver transplantation plus ChT is recommended as a curative-intent option for highly selected patients with liver-only permanently unresectable CRLM, provided that strict selection criteria [*BRAF*-wt, CEA <80 ng/ml, sustained response to systemic therapy (disease stabilisation for ≥3 months, no later than the third line of therapy), no extrahepatic disease during the entire disease history, resected primary tumour, Eastern Cooperative Oncology Group (ECOG) performance status (PS) <2, age 18-65 years] and organ policy prioritisation are met [II, A].
- In patients with liver-dominant disease, intra-arterial treatment with transarterial chemoembolisation, transarterial radioembolisation, selective internal radiotherapy or hepatic artery infusion may be considered as intensification or salvage treatments [III, C].

Other metastatic sites

- In patients with lung-only metastases or OMD including lung lesions, ablation or SBRT can be recommended alongside or as an alternative to resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity and other factors [III, B].
- In case of PM only, complete cytoreductive surgery is recommended [II, A]. Hyperthermic intraperitoneal ChT cannot be recommended outside of clinical trials [II, D].
- Surgical resection of ovarian metastases can be recommended as they are frequently chemoresistant and may lead to complications, including obstruction [IV, B].
- Surgical removal of retroperitoneal LN metastases may be considered in selected patients to obtain 'no evidence of disease' status in an OMD setting [IV, C]. SBRT may also be considered [IV, C].

SYSTEMIC THERAPY

First-line therapy

A hierarchical approach is applied for first-line treatment of mCRC, with dMMR and/or MSI-H status considered the first decision driver. For patients with MMR-proficient (pMMR) or microsatellite stable (MSS) tumours, treatment choice is mainly driven by ECOG PS, primary tumour location, *RAS* and *BRAF* mutational status and individual preference.[5-11] An algorithm for the first-line treatment of mCRC is provided in Figure 2.

dMMR or MSI-H tumours. Patients with dMMR or MSI-H tumours with no contraindication for immunotherapy should receive nivolumab—ipilimumab or pembrolizumab.[12] While anti-programmed cell death protein 1 antibodies should be continued for up to 2 years, clinical trials aimed at optimising the duration of first-line immunotherapy are awaited. A comparison of nivolumab—ipilimumab and nivolumab alone demonstrated that double checkpoint inhibition provides superior efficacy compared with monotherapy without a major increase in toxicity.[13] There is no evidence to support the combination of ChT with ICIs. Patients with dMMR or MSI-H and *BRAF*^{V600E}-mutated tumours should also receive first-line immunotherapy, since subgroup analyses of pivotal trials demonstrated a similar magnitude of benefit from ICIs in this subgroup.

ChT agents, biological drugs and combinations.

General principles. Fluoropyrimidines are the backbone of most treatment regimens in mCRC. Infusional 5-FU and oral capecitabine are considered equal. In case of intolerance to classic 5-FU or capecitabine in terms of cardiotoxicity or hand-foot syndrome, S-1 can be used.[14] Doublet regimens with differential toxicity profiles and comparable efficacy derive from the addition of oxaliplatin or irinotecan to fluoropyrimidines.[15] While oxaliplatin can be combined with both infusional and oral fluoropyrimidines [leucovorin (LV)—5-FU—oxaliplatin (FOLFOX) or capecitabine—oxaliplatin (CAPOX)], irinotecan-based regimens usually consist of infusional drugs [LV—5-FU—irinotecan (FOLFIRI)] to avoid overlapping toxicities of irinotecan and capecitabine, although a dose-adjusted combination of capecitabine—irinotecan seems feasible.[16] LV—5-FU—oxaliplatin—irinotecan (FOLFOXIRI) demonstrated greater

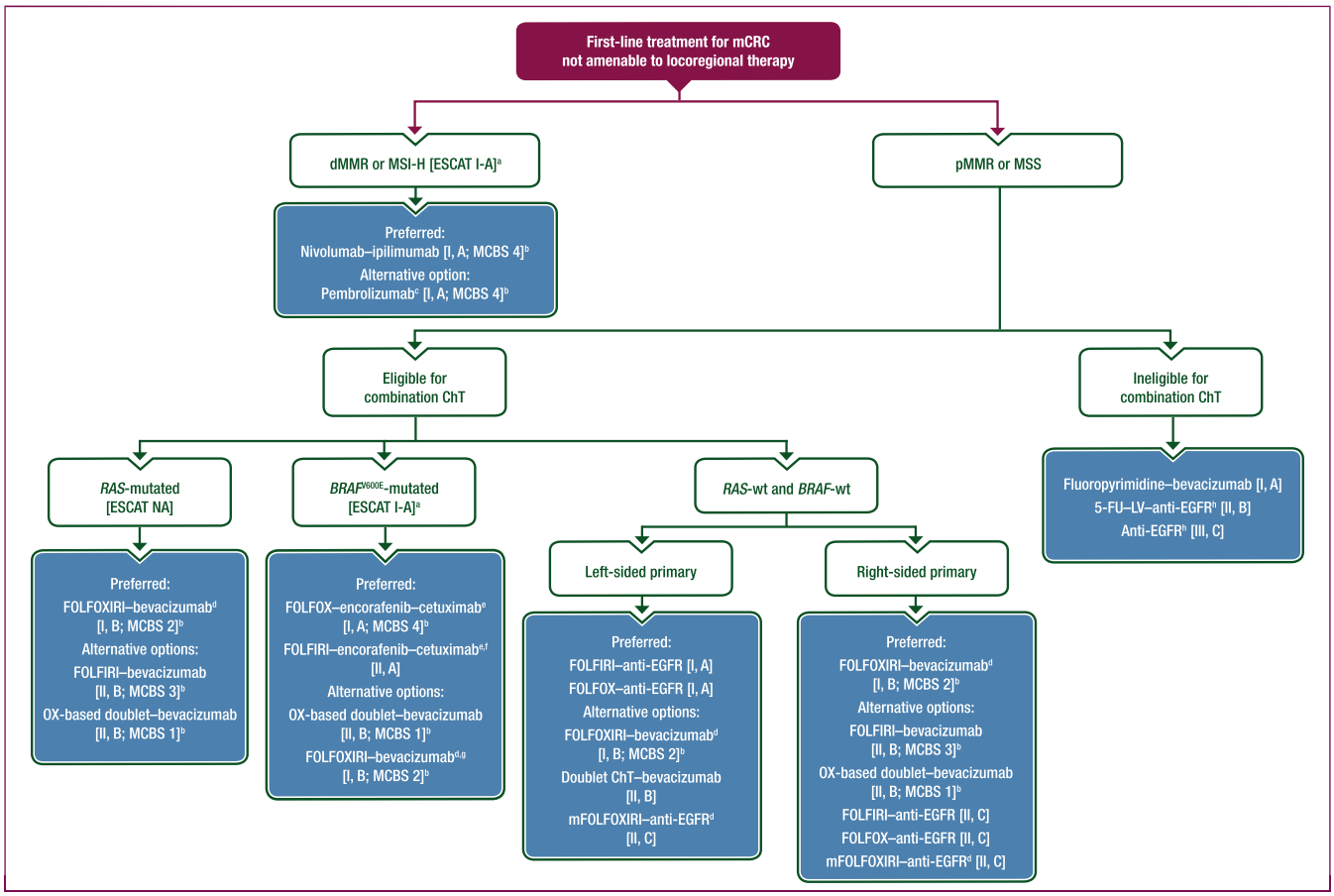

Figure 2. First-line treatment for mCRC not amenable to locoregional therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
5-FU, 5-fluorouracil; ChT, chemotherapy; dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; FOLFOXIRI, leucovorin—5-fluorouracil—oxaliplatin—irinotecan; ICI, immune checkpoint inhibitor; LV, leucovorin; MCBS, Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mFOLFOXIRI, modified leucovorin—5-fluorouracil—oxaliplatin—irinotecan; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NA, not applicable; OX, oxaliplatin; pMMR, mismatch repair-proficient; PS, performance status; wt, wild-type.
[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[94]
[b]ESMO-MCBS v2.0[95] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[c]If ICI doublet therapy is not possible.
[d]FOLFOXIRI can only be recommended for patients aged <70 years with ECOG PS 0-2 or 71-75 years with ECOG PS 0 [I, B].
[e]FDA approved, not EMA approved.
[f]Particularly for patients previously treated with OX-based adjuvant regimens or with contraindications to OX.
[g]For patients with right-sided primaries.
[h]For patients with *RAS*-wt and *BRAF*-wt disease with left-sided primaries.

efficacy than FOLFIRI and FOLFOX at the price of a higher rate of gastrointestinal and haematological adverse events (AEs)[17,18] and can be used in selected fit patients without significant comorbidities.

Bevacizumab is the only vascular endothelial growth factor (VEGF)-targeted agent used for first-line treatment of mCRC. All ChT backbones are established in combination with bevacizumab.

Anti-EGFR agents can be combined with FOLFOX or FOLFIRI, with both options considered equally active. The combination of an anti-EGFR agent with dose-modified FOLFOXIRI is feasible, but conflicting results concerning the improvement in efficacy limit the generalisability of this regimen to an all-comer population.[19-22] Combinations of anti-EGFR agents and oral fluoropyrimidines or bolus 5-FU-based regimens have demonstrated unfavourable efficacy and should be avoided, although the reason for the potential negative interaction is not clear.

Patients with pMMR or MSS tumours eligible for combination ChT. Patients with *RAS*-mutated tumours have not been evaluated as a prespecified population in trials of current regimens, but data from a pooled analysis of five studies comparing triplet ChT—bevacizumab and doublet ChT—bevacizumab suggested that FOLFOXIRI provided benefit in these patients.[18] Consistent with this finding, in

patients with initially unresectable liver-limited right-sided and/or *RAS*- or *BRAF*^{V600E}-mutated mCRC, FOLFOXIRI—bevacizumab was associated with greater initial efficacy than doublet ChT—bevacizumab.[23]

In the phase III BREAKWATER trial, FOLFOX—encorafenib—cetuximab demonstrated significant improvements in dual primary endpoints [objective response rate (ORR) and progression-free survival (PFS)] as well as overall survival (OS; secondary endpoint) compared with FOLFOX, CAPOX or FOLFOXIRI with or without bevacizumab in patients with *BRAF*^{V600E}-mutated tumours (but not other *BRAF* mutations).[24,25] The safety profile was consistent with that expected based on each drug's known AEs. FOLFIRI—encorafenib—cetuximab also demonstrated a good safety profile and improved efficacy when compared with FOLFIRI—bevacizumab[26] and might provide a valuable option, especially in patients progressing after oxaliplatin-based adjuvant regimens or those with a contraindication to oxaliplatin. If not available, doublet or triplet ChT—bevacizumab can be considered an option.[27]

The use of anti-EGFR mAbs is restricted to patients with *RAS*-wt and *BRAF*-wt tumours and is preferred in those with a left-sided primary tumour [i.e. between the splenic flexure and rectum (both included)]. In retrospective and prospective cohorts, head-to-head comparisons of anti-EGFR mAbs versus bevacizumab (each combined with doublet ChT) in the first-line treatment of left-sided *RAS*-wt mCRC have demonstrated that anti-EGFR agents are associated with a clinically relevant OS advantage, although the magnitude of benefit varies between trials.[28,29] The preferred treatment for patients with *RAS*-wt and *BRAF*-wt mCRC with a left-sided primary tumour is therefore doublet ChT—anti-EGFR. A modified schedule of FOLFOXIRI (mFOLFOXIRI)—anti-EGFR provided longer OS than FOLFOX—anti-EGFR in a randomised trial at the price of higher toxicity; thus, the regimen requires careful patient selection.[22] FOLFOXIRI—bevacizumab can be considered an alternative. No comparison of doublet ChT—anti-EGFR versus FOLFOXIRI—bevacizumab has been carried out in large prospective randomised trials.

Patients with *RAS*-wt and *BRAF*-wt mCRC with right-sided primary tumours do not benefit from anti-EGFR therapy in the same way as patients with left-sided primaries.[28,29] Although ORR benefits have been reported, long-term outcomes do not support the use of anti-EGFR mAbs but do support the use of bevacizumab, pointing to FOLFOXIRI—bevacizumab as a potential strategy. If an anti-EGFR mAb is considered for patients with right-sided primary tumours, extended molecular profiling (including *PTEN*, *AKT*, *MEK1* and *EGFR* ectodomain mutations, *HER2* and *MET* amplifications and *ALK*, *RET* and *NTRK1-3* fusions) might help to identify patients who are most likely to benefit[30] and to overcome the surrogate information provided by primary tumour location.

Patients with pMMR or MSS tumours not eligible for combination ChT. Patients who are unable or unwilling to receive full-dose ChT combination regimens (due to PS, age and/or comorbidities) may receive less intensive regimens. For patients with pMMR or MSS, *RAS*-wt and *BRAF*-wt left-sided tumours, single-agent ChT with infusional 5-FU—LV plus an anti-EGFR agent can be considered based on the results of the phase II randomised noncomparative PANDA trial, which reported promising results in elderly patients who were not optimal candidates for combination ChT.[31] Anti-EGFR mAbs can also be administered alone, although the level of evidence is lower.[32,33]

For all other patients, the combination of a fluoropyrimidine (either infusional or oral capecitabine) with bevacizumab might be a preferred option, with demonstrated efficacy in several trials that included both unselected patients and cohorts comprising predominantly elderly patients.[34,35] The choice of infusional or oral fluoropyrimidine should be based on patient preference and should consider the specific requirements for oral drug use and the expected side-effects.

Dose-reduced (80%) oxaliplatin-based combination ChT with or without bevacizumab was better tolerated and more efficient than full-dose single S-1 in older adult patients who were ineligible for full-dose combination ChT.[36]

Maintenance therapy in patients who are ineligible for local therapies

Maintenance therapy aims to reduce treatment burden without compromising clinical outcomes. When compared with complete treatment breaks after induction ChT, maintenance therapies improve PFS; however, the impact on OS is unclear.[37] A complete treatment break at the cost of a numerically small disadvantage in OS is, therefore, an option to be discussed with patients.[38,39] An algorithm for maintenance treatment in mCRC is provided in Figure 3.

Prior oxaliplatin-based therapy with or without bevacizumab. Maintenance with a fluoropyrimidine has a good safety profile and does not impair the long-term outcomes of patients who have received fluoropyrimidine—oxaliplatin (i.e. FOLFOX or CAPOX). This approach was later adopted for patients who had received 4-6 months of induction therapy with oxaliplatin-based regimens combined with bevacizumab.[40,41] Although the clinical significance of effects on OS remain unclear, active maintenance therapy consistently provides improvements in PFS. Based on the available options, maintenance with fluoropyrimidine—bevacizumab is preferred after induction therapy with fluoropyrimidines, oxaliplatin and bevacizumab. Since the largest of the randomised trials in this context proposed the reintroduction of the initial oxaliplatin-containing therapy after maintenance therapy, this strategy should be adopted in clinical practice while taking persisting toxicities into account. Similar considerations apply to patients who have received FOLFOXIRI—bevacizumab; based on randomised clinical trial data, optimal treatment duration is 4 months, followed by maintenance therapy with 5-FU—LV—bevacizumab and then reintroduction of the same regimen (FOLFOXIRI) or a

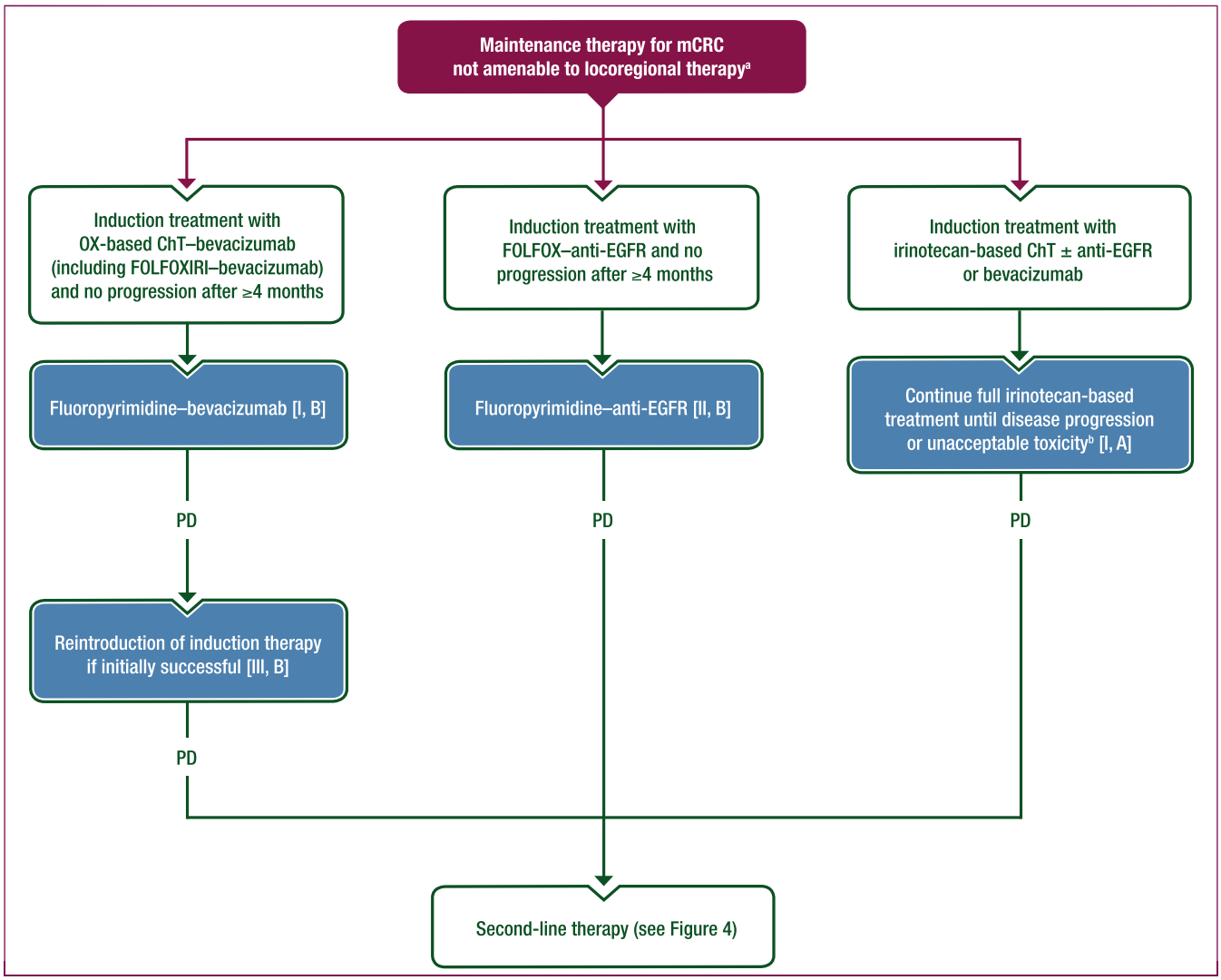

Figure 3. Maintenance therapy for mCRC not amenable to locoregional therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; FOLFOXIRI, leucovorin—5-fluorouracil—oxaliplatin—irinotecan; mCRC, metastatic colorectal cancer; OS, overall survival; OX, oxaliplatin; PD, progressive disease.
[a]Treatment breaks can be recommended instead of maintenance therapy in good responders on an individual basis and with the knowledge that there may be a small disadvantage in OS [III, B].
[b]Discussion of maintenance options based on clinical scenario and patient preference can be recommended [III, B].

deintensified version (i.e. FOLFOX or FOLFIRI) in case of disease progression.[9]

Prior oxaliplatin-based therapy with an anti-EGFR mAb. Several maintenance strategies to be applied after FOLFOX—anti-EGFR have been explored.[42-45] Consistent with observations after bevacizumab-based induction therapy, 5-FU—LV—anti-EGFR may provide the most favourable efficacy, without demonstrating a clear OS advantage.[46] In contrast to other scenarios, there is no evidence of benefit with reintroduction of the same ChT—anti-EGFR regimen after progression. If maintenance therapy includes anti-EGFR mAbs and 5-FU, a classic second-line regimen should be started in case of disease progression during this maintenance treatment.

Prior irinotecan-based regimen. Unlike oxaliplatin, irinotecan does not regularly induce dose-limiting toxicities; therefore, there is less evidence available regarding de-escalation of irinotecan-based regimens. Patients can receive irinotecan-based regimens until disease progression or unacceptable toxicity. In case of toxicities, maintenance therapy with 5-FU with or without a biological agent may be considered.

Second-line therapy

For fit patients, second-line options depend on molecular profile and the initial treatment regimen. An algorithm for the second-line treatment of mCRC is provided in Figure 4. Reintroduction of the induction therapy is a valid choice, especially when disease progression occurs after a bevacizumab-based maintenance therapy or a ChT break. In the case of oligo-progression, locoregional therapy can be considered while continuing the same systemic therapy.

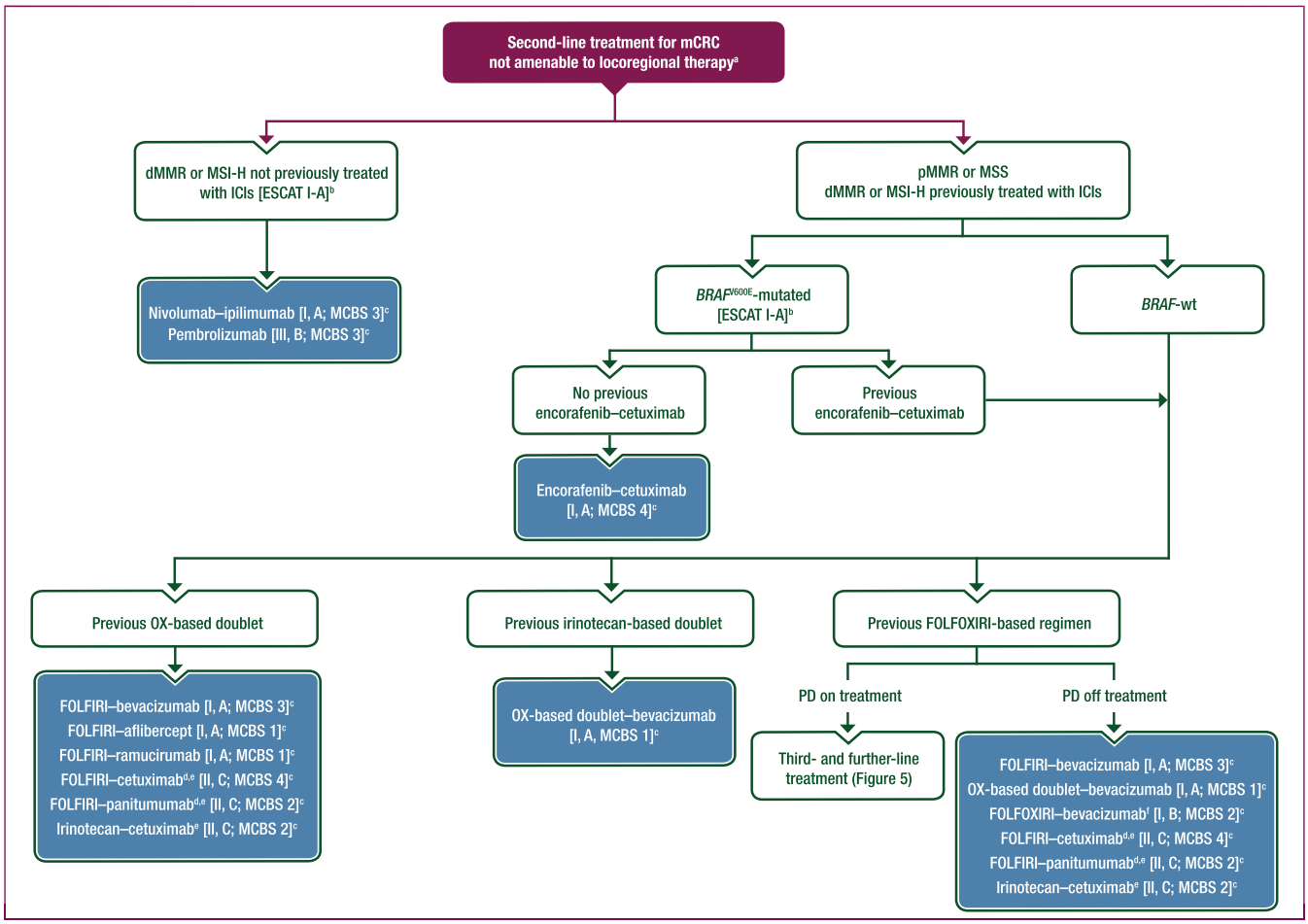

Figure 4. Second-line treatment for mCRC not amenable to locoregional therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FOLFIRI, leucovorin—5-fluorouracil—irinotecan; FOLFOXIRI, leucovorin—5-fluorouracil—oxaliplatin—irinotecan; ICI, immune checkpoint inhibitor; MCBS, Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OX, oxaliplatin; PD, progressive disease; pMMR, mismatch repair-proficient; PS, performance status; wt, wild-type.
[a]Reintroducing the same induction treatment can be recommended, especially following maintenance with fluoropyrimidine—bevacizumab or treatment breaks [III, B].
[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[94]
[c]ESMO-MCBS v2.0[95] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[d]EMA approved, not FDA approved.
[e]If left-sided primary, *RAS*-wt, *BRAF*-wt, and no previous anti-EGFR therapy.
[f]If ECOG PS 0, prior RECIST response to FOLFOXIRI—bevacizumab and progression after an OX- and irinotecan-free interval of ≥4 months.

dMMR or MSI-H tumours. The phase II KEYNOTE-164 study demonstrated efficacy with pembrolizumab in dMMR or MSI-H mCRC previously treated with ≥1 prior line of therapy.[47] In the multicohort phase II CheckMate 142 study, robust and durable clinical benefit was reported with nivolumab—ipilimumab in previously treated dMMR or MSI-H mCRC, with a manageable safety profile.[48] More recently, CheckMate 8HW demonstrated better outcomes with nivolumab—ipilimumab than with nivolumab alone across all lines of therapy (43% of enrolled patients had received ≥1 prior regimen).[13]

Patients progressing on an ICI-based first-line strategy are eligible for second-line treatment based on the clinical situation and *RAS* and *BRAF* mutational status. There is no evidence to support continuation or switching of immunotherapy after progression.

pMMR, MSS, *BRAF*^{V600E}-mutated tumours. The standard treatment for patients with *BRAF*^{V600E}-mutated tumours who have not previously received BRAF-targeted therapy is based on the phase III BEACON trial, in which encorafenib—cetuximab resulted in improved OS with no worsening in quality of life or increase in grade 3 AEs compared with irinotecan-based ChT—cetuximab.[49] Patients previously treated with first-line FOLFOX—encorafenib—cetuximab may benefit from FOLFIRI combined with an anti-angiogenic agent (e.g. bevacizumab, aflibercept or ramucirumab).

pMMR, MSS, *BRAF*-wt tumours.

Choice of ChT. The ChT backbone depends mainly on the first-line treatment. After first-line oxaliplatin-based therapy, second-line treatment with fluoropyrimidine—irinotecan or irinotecan monotherapy is an option. Conversely, patients treated with first-line irinotecan-based therapy can receive second-line oxaliplatin-based ChT (FOLFOX or CAPOX) if there are no contraindications. After first-line FOLFOXIRI—bevacizumab, second-line treatment is based on the timing of progression. Patients who experience progression during treatment with FOLFOXIRI must be considered for potential later-line therapy according to the clinical situation. Patients who experience progression during an off-treatment period or during maintenance therapy (which is usually advised because the duration of induction should be $\leq$4 months) might benefit from reintroduction of FOLFOXIRI—bevacizumab or doublet ChT-based therapies, depending on clinical status and molecular profile.

Choice of combined targeted agent. In patients previously treated with bevacizumab, maintaining bevacizumab in combination with second-line ChT (oxaliplatin- or irinotecan-based, depending on first-line treatment) improves PFS and OS compared with ChT alone.[50] In the phase III VELOUR trial, ORR, PFS and OS were improved with FOLFIRI—aflibercept versus FOLFIRI in patients previously treated with oxaliplatin, including a subgroup of patients previously treated with bevacizumab.[51] In the phase III RAISE study, OS and PFS benefits were observed with FOLFIRI—ramucirumab versus FOLFIRI in patients with disease progression during or after first-line fluoropyrimidine—oxaliplatin—bevacizumab.[52] Each of these antiangiogenics in combination with ChT has demonstrated improved OS in the second-line setting, irrespective of first-line treatment. In case of *RAS*-mutated tumours with rapid progression while receiving first-line bevacizumab, second-line ChT—aflibercept or ChT—ramucirumab can be considered, as both studies included patients with rapid progression during first-line bevacizumab.[51,52] In patients previously treated with irinotecan—fluoropyrimidine-based ChT alone, FOLFOX—bevacizumab demonstrated improved OS and PFS compared with FOLFOX4 in a phase III trial.[53]

In patients with *RAS*-wt and *BRAF*-wt tumours, cetuximab and panitumumab demonstrated activity in the second or later line as single agents and in combination with ChT. In the phase III EPIC trial, second-line irinotecan—cetuximab improved PFS and ORR compared with irinotecan alone in patients refractory to first-line oxaliplatin- and fluoropyrimidine-based treatment, but OS was not increased.[54] Similarly, in patients with *KRAS*-wt tumours, the addition of panitumumab to irinotecan or FOLFIRI significantly improved ORR and PFS with no OS benefit.[55] In a randomised phase II study, a switch to panitumumab or cetuximab showed no benefit over continued doublet ChT—bevacizumab;[56] therefore, in patients with *RAS*-wt and *BRAF*-wt tumours who were previously treated with bevacizumab, second-line treatment with ChT—antiangiogenics is a good option. ChT—anti-EGFR can increase ORR, albeit in the absence of a demonstrated OS gain, and the benefit might be greater in left-sided tumours and in later-line treatment. The safety profile should also be considered in this decision.

Third- and further-line therapy

Several options are available for patients who are fit and motivated to receive further-line therapy, including targeted drugs against rare molecular alterations. Thorough molecular characterisation is, therefore, encouraged before third-line treatment. Locoregional therapy in the context of OMD is still possible and should be considered. It is important to integrate best supportive care (BSC) alongside systemic therapy, while some patients are best managed by BSC alone. An algorithm for the third- and further-line treatment of mCRC is provided in Figure 5.

Molecularly unselected patients.

Trifluridine—tipiracil with or without bevacizumab. Trifluridine—tipiracil (FTD—TPI) demonstrated improved OS and PFS compared with placebo in patients who had previously received or were unable to tolerate treatments containing a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and (if *RAS*-wt) cetuximab or panitumumab, although ORR was only 1.6%.[57] The SUNLIGHT study was the first randomised trial to test a new treatment strategy against an efficacious compound in the chemorefractory setting; addition of bevacizumab to FTD—TPI in the third line was associated with clinically and statistically significant improvements in OS and PFS and a modest impact on ORR (6% versus 1% with FTD—TPI).[58]

Regorafenib. Regorafenib improved OS and PFS compared with placebo in patients who had previously received or were unable to tolerate treatments containing a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and (if *RAS*-wt) cetuximab or panitumumab.[59,60] The most frequent grade $\geq$3 AEs were hand-foot syndrome, hypertension, fatigue and diarrhoea. Alternative dosing schedules have been evaluated, which improve treatment tolerability.[61,62]

Fruquintinib. In the phase III FRESCO-1 study, fruquintinib improved OS and PFS compared with placebo; however, only 30% and 14% of patients had previously received an anti-VEGF or anti-EGFR agent, respectively.[63] In the international FRESCO-2 trial, fruquintinib improved OS and PFS compared with BSC in patients previously treated with fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab (if *RAS*-wt), FTD—TPI and/or regorafenib.[64]

Rechallenge with ChT. Re-use of ChT in the third line and beyond is considered rechallenge or reintroduction, depending on whether progression previously occurred while receiving that agent. Reintroduction of the initial induction therapy can be considered in patients who previously derived clinical benefit without progression, although the level of evidence is low; however, there is no evidence for the re-use of agents

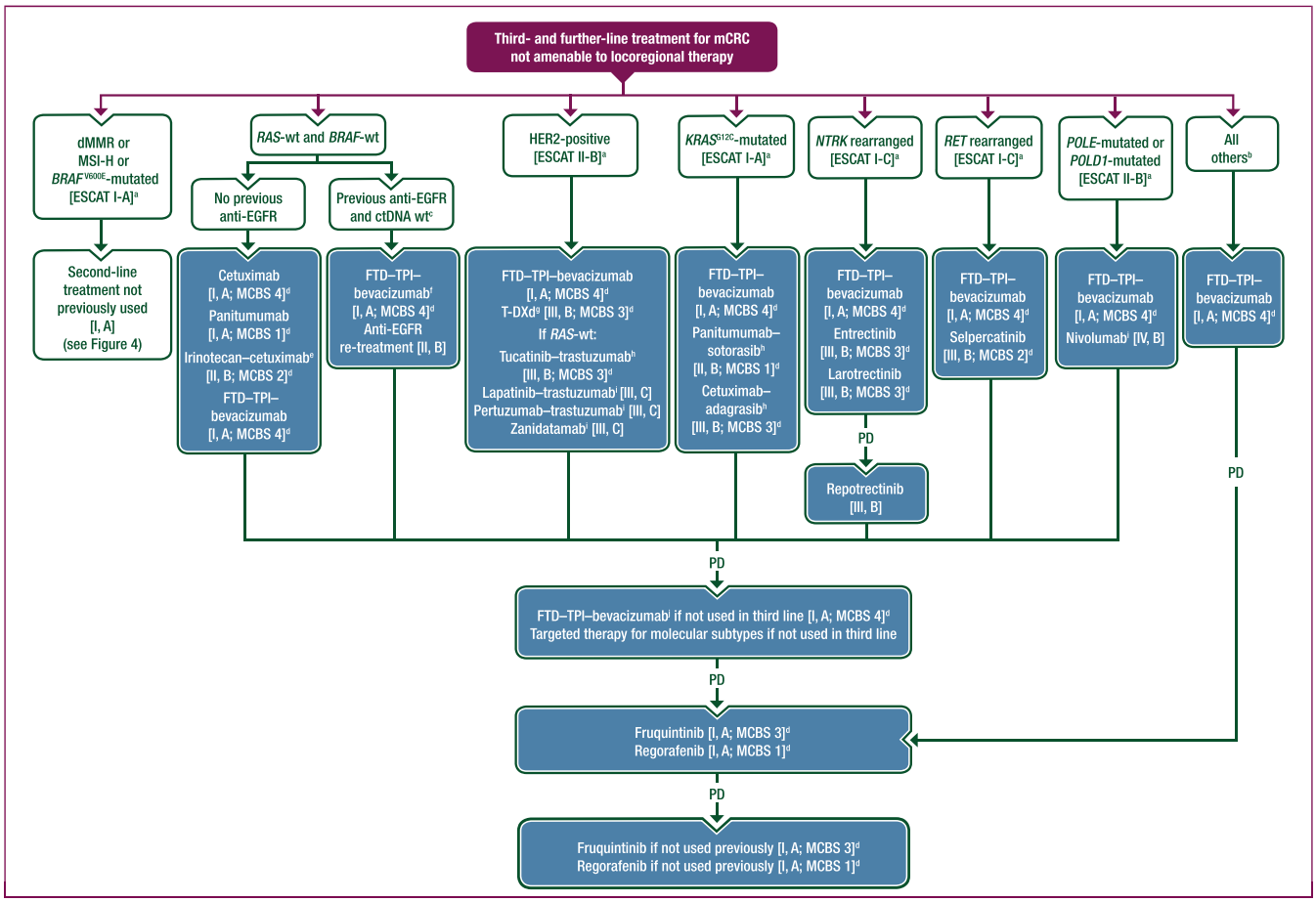

Figure 5. Third- and further-line treatment for mCRC not amenable to locoregional therapy.
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
ChT, chemotherapy; ctDNA, circulating tumour DNA; dMMR, mismatch repair-deficient; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; FTD—TPI, trifluridine—tipiracil; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MCBS, Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; PD, progressive disease; T-DXd, trastuzumab deruxtecan; wt, wild-type.
[a]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[94]
[b]Reintroduction of the initial induction therapy may be optionally recommended after second-line therapy for patients who derived clinical benefit during first-line ChT and progressed while off treatment [IV, C].
[c]*RAS*, *BRAF* and preferably *EGFR* ectodomain mutations should be assessed.
[d]ESMO-MCBS v2.0[95] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]Recommended over cetuximab monotherapy for irinotecan-refractory patients.
[f]For patients who are not candidates for or have a contraindication to anti-EGFR therapy.
[g]FDA approved for HER2 IHC 3+ tumours, not EMA approved; also suitable for patients previously treated with anti-HER2 strategies.
[h]FDA approved, not EMA approved.
[i]Not EMA or FDA approved.
[j]FTD—TPI is recommended for patients with contraindications to bevacizumab [I, A; ESMO-MCBS v2.0 score: 3].

on which disease progression has occurred or for salvage ChT (e.g. mitomycin C, capecitabine, raltitrexed or gemcitabine).

Molecularly stratified patients.

Anti-EGFR mAbs in patients with RAS-wt, BRAF-wt, anti-EGFR-naïve or anti-EGFR-pretreated tumours. Anti-EGFR agents are typically used in earlier lines of therapy for patients with *RAS*-wt left-sided tumours. If a patient has not previously received anti-EGFR mAbs, cetuximab or panitumumab, either as monotherapy or in combination with irinotecan, are options in the third line regardless of primary tumour location.

Several phase II trials have investigated cetuximab or panitumumab retreatment, either alone or in combination with ChT.[65-68] In most trials, patients were included based on clinical criteria (i.e. previous benefit from anti-EGFR agents, duration of anti-EGFR wash-out period) and baseline ctDNA was analysed *post hoc*. A meta-analysis of four trials including 114 patients with *RAS*-wt and *BRAF*-wt ctDNA reported an ORR of 18%, median PFS of 4 months and median OS of 13 months with anti-EGFR

retreatment.[69] In three recent randomised trials, ctDNA was used to prospectively select patients, showing comparable ORR and PFS results[70-72] and better outcomes when compared with regorafenib;[70] therefore, liquid biopsy-driven rechallenge with anti-EGFR agents may be an option for selected patients in the refractory setting. Patients with ctDNA *RAS*, *BRAF* and/or *EGFR* ectodomain mutations, as well as other determinants of anti-EGFR resistance whenever available (i.e. *MET* amplification, *MEK1* mutations) should receive alternative options.[70,73]

ICIs. Patients with dMMR or MSI-H tumours typically receive first-line ICIs; however, data support the use of ICIs in the third line if not previously used.[74] There is no evidence to support rechallenge with immunotherapy after progression during treatment, but other treatment options can be selected based on molecular subtype. The efficacy of FTD—TPI—bevacizumab seems independent of MMR status.[58]

BRAF inhibitors and anti-EGFR agents. BRAF inhibitors are typically used in the first or second line. For patients who have not previously received BRAF inhibitors, use of encorafenib—cetuximab in the third or later line is supported by the phase III BEACON trial.[75] There is no evidence to support rechallenge with encorafenib—cetuximab after previous exposure.

Anti-HER2 strategies. Trials of HER2 blockade in refractory mCRC have mainly been single arm, with notable differences in patient selection and HER2-positivity definitions. Promising results were initially reported with trastuzumab—lapatinib.[76] More recently, trastuzumab plus the highly selective HER2 tyrosine kinase inhibitor (TKI) tucatinib showed encouraging ORR, PFS and OS in patients with treatment-refractory, HER2-positive, *RAS*-wt mCRC.[77] Similarly, the antibody—drug conjugate trastuzumab deruxtecan (T-DXd) showed convincing activity in patients with immunohistochemistry (IHC)3+ or IHC2+ and *in situ* hybridisation (ISH)-positive disease but not among patients with IHC2+ ISH-negative or IHC1+ tumours.[78] Interstitial lung disease and pneumonitis occurred in 10% of patients. A lower dose was associated with a higher ORR and fewer serious AEs than the original dose.[79] Responses were also observed in patients with *RAS*-mutated tumours and in those who had previously received other HER2-directed therapies. Benefit was more pronounced in the IHC3+ subgroup, consistent with the current Food and Drug Administration (FDA) tumour-agnostic approval.[80] Consistent results were recently reported with the bispecific mAb zanidatamab.[81] The only randomised trial (SWOG S1613) did not demonstrate significant benefit with trastuzumab—pertuzumab compared with irinotecan—cetuximab.[82]

KRAS^{G12C} inhibitors plus anti-EGFR agents. *KRAS*^{G12C} mutation is present in 3% of mCRCs. Although KRAS^{G12C} inhibitors showed disappointing results as single agents,[83] combination with anti-EGFR mAbs improved their efficacy.[84] Promising results were reported with cetuximab—adagrasib in a single-arm study.[85] Panitumumab—sotorasib was compared with investigator's choice (FTD—TPI or regorafenib) in 160 patients with *KRAS*^{G12C}-mutated mCRC previously exposed to fluoropyrimidine, oxaliplatin and irinotecan.[86] Panitumumab—sotorasib was associated with improvements in PFS and ORR, with no significant difference in OS (secondary endpoint). Of note, >30% of the control group subsequently received a KRAS^{G12C} inhibitor.[87]

ICIs in POLE or POLD1 proofreading mutated tumours. Mutations in *POLE* or *POLD1* occur in ~1% of mCRCs. They are considered highly immunogenic with an ultra-mutated phenotype and high tumour mutational burden and are proposed biomarkers for ICI sensitivity. Nivolumab activity was observed in a trial of patients with MSS *POLE*-mutated solid tumours.[88] In a retrospective international case series of patients with mCRC with a *POLE* or *POLD1* proofreading domain mutation receiving ICIs, ORR was 89% compared with 54% in MSI-H patients.[89]

Agnostic treatments against NTRK and RET fusions. A small proportion of mCRCs (<1%) harbour *NTRK1-3* fusions or *RET* rearrangements, for which there are tumour-agnostic drug approvals. It is highly challenging to conduct mCRC-specific trials in these populations; however, basket trials evaluating TKIs targeting neurotrophic tyrosine receptor kinase (NTRK; larotrectinib, entrectinib and repotrectinib) or rearranged during transfection (RET; selpercatinib) included patients with mCRC.[90-93] Repotrectinib also provided benefit in patients who were previously treated with an NTRK inhibitor.[93]

Optimal sequencing of agents in the third line and beyond. With several strategies now available in further lines, the sequence of treatments is important; however, at this stage in the treatment continuum, many patients are not fit to progress to further therapies.

Most trials do not provide direct comparisons between options, and subgroup analyses from pivotal phase III trials in molecularly unselected patients did not point to subgroups who may derive more benefit from one treatment over another. Selection and sequencing of agents in later lines of therapy thus requires consideration of molecular status, burden of disease, requirement for response, benefit in previous lines and consideration of ongoing toxicity.

For most molecularly unselected patients, FTP—TPI—bevacizumab is the best-evidenced third-line treatment. TKIs are mainly used in subsequent lines, with fruquintinib demonstrating fourth-line activity in patients who had largely previously received FTP—TPI, although it might also be used in the fifth line following progression on regorafenib.

For patients with an actionable molecular alteration, targeted therapy is the preferred choice when there is an available agent and testing, if not previously exposed to that agent, especially when a response is required (e.g. in case of high tumour burden). Similar considerations can be applied to the choice of liquid biopsy-driven anti-EGFR retreatment. FTD—TPI—bevacizumab is still an option

based on robust data from a phase III clinical trial in molecularly unselected patients, with demonstrated benefit across molecular subgroups.[58]

Recommendations

First-line therapy

- For patients with dMMR or MSI-H mCRC, nivolumab—ipilimumab is recommended [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v2.0 score: 4]. Pembrolizumab is recommended if ICI doublet therapy is not possible [I, A; ESMO-MCBS v2.0 score: 4].
- For patients with pMMR, MSS, *RAS*-mutated mCRC, FOLFOXIRI—bevacizumab can be recommended [I, B; ESMO-MCBS v2.0 score: 2]. FOLFOXIRI can only be recommended for patients aged <70 years with ECOG PS 0-2 or aged 71-75 years with ECOG PS 0 [I, B].
  - o Doublet ChT—bevacizumab [e.g. FOLFIRI—bevacizumab (ESMO-MCBS v2.0 score: 3) or oxaliplatin-based doublet—bevacizumab (ESMO-MCBS v2.0 score: 1)] can also be recommended to a lesser extent [II, B].
- For patients with pMMR, MSS, $BRAF^{V600E}$-mutated mCRC, FOLFOX—encorafenib—cetuximab is recommended [I, A; ESMO-MCBS v2.0 score: 4; FDA approved, not European Medicines Agency (EMA) approved].
  - o FOLFIRI—encorafenib—cetuximab is recommended, particularly for patients previously treated with oxaliplatin-based adjuvant regimens or with contraindications to oxaliplatin [II, A; FDA approved, not EMA approved].
  - o Oxaliplatin-based doublet—bevacizumab can be recommended if FOLFOX—encorafenib—cetuximab is not available [II, B; ESMO-MCBS v2.0 score: 1].
  - o FOLFOXIRI—bevacizumab can be recommended in selected patients with right-sided tumours if FOLFOX—encorafenib—cetuximab is not available [I, B; ESMO-MCBS v2.0 score: 2].
- For patients with pMMR, MSS, *RAS*-wt, *BRAF*-wt mCRC with left-sided primaries, FOLFIRI—anti-EGFR or FOLFOX—anti-EGFR are recommended [I, A].
  - o FOLFOXIRI—bevacizumab [I, B; ESMO-MCBS v2.0 score: 2] or doublet ChT—bevacizumab [II, B] can also be recommended.
  - o mFOLFOXIRI—anti-EGFR may also be considered [II, C].
- For patients with pMMR, MSS, *RAS*-wt, *BRAF*-wt mCRC with right-sided primaries, FOLFOXIRI—bevacizumab can be recommended [I, B; ESMO-MCBS v2.0 score: 2].
  - o FOLFIRI—bevacizumab (ESMO-MCBS v2.0 score: 3) or oxaliplatin-based doublet—bevacizumab (ESMO-MCBS v2.0 score: 1) can also be recommended [II, B].
  - o FOLFIRI—anti-EGFR, FOLFOX—anti-EGFR or mFOLFOXIRI—anti-EGFR may also be considered [II, C].
- For patients with pMMR or MSS mCRC who are unfit to receive the ChT regimens listed above, fluoropyrimidine—bevacizumab is recommended [I, A].
  - o For patients with *RAS*-wt, *BRAF*-wt disease with left-sided primaries, 5-FU—LV—anti-EGFR can be recommended [II, B] and anti-EGFR alone can be considered [III, C].

Maintenance therapy

- Fluoropyrimidine—bevacizumab can be recommended as maintenance therapy following oxaliplatin-based ChT—bevacizumab induction therapy, including FOLFOXIRI—bevacizumab, if there is no disease progression after ≥4 months [I, B].
- Fluoropyrimidine—anti-EGFR can be recommended as maintenance therapy following FOLFOX—anti-EGFR induction therapy if there is no disease progression after ≥4 months [II, B].
- No specific maintenance therapies are indicated following irinotecan-based regimens; therefore, continuation of the full irinotecan-based regimen is recommended until disease progression or unacceptable toxicity [I, A]. Discussion of maintenance options based on clinical scenario and patient preference can be recommended [III, B].
- Treatment breaks can be recommended instead of maintenance therapy in good responders on an individual basis and with the knowledge that there may be a small disadvantage in OS [III, B].

Second-line therapy

- For patients with dMMR or MSI-H mCRC who have not previously received ICIs, nivolumab—ipilimumab is recommended [I, A; ESMO-MCBS v2.0 score: 3]. Pembrolizumab can also be recommended [III, B; ESMO-MCBS v2.0 score: 3].
- For patients with $BRAF^{V600E}$-mutated mCRC (pMMR or MSS, or dMMR or MSI-H previously treated with ICIs), encorafenib—cetuximab is recommended if not previously used [I, A; ESMO-MCBS v2.0 score: 4].
- Regardless of primary tumour location and *RAS* and *BRAF* mutational status, FOLFIRI—bevacizumab (for patients with disease progression on a prior oxaliplatin-based regimen; ESMO-MCBS v2.0 score: 3) or oxaliplatin-based doublet—bevacizumab (for patients with disease progression on a prior irinotecan-based regimen; ESMO-MCBS v2.0 score: 1) is recommended [I, A].
  - o FOLFIRI—aflibercept [I, A; ESMO-MCBS v2.0 score: 1] and FOLFIRI—ramucirumab [I, A; ESMO-MCBS v2.0 score: 1] are also recommended for patients previously treated with oxaliplatin-based regimens.
- Reintroducing the original induction treatment can be recommended, especially following maintenance with fluoropyrimidine—bevacizumab or treatment breaks [III, B].
- After first-line FOLFOXIRI—bevacizumab, FOLFIRI—bevacizumab (ESMO-MCBS v2.0 score: 3) or oxaliplatin-based doublet—bevacizumab (ESMO-MCBS v2.0 score: 1) is recommended [I, A].
  - o Reintroduction of FOLFOXIRI—bevacizumab can be recommended for patients with ECOG PS 0, prior RECIST response to FOLFOXIRI—bevacizumab and progression after an oxaliplatin- and irinotecan-free interval of ≥4 months [I, B; ESMO-MCBS v2.0 score: 2].

- For patients with left-sided *RAS*-wt and *BRAF*-wt tumours who previously received oxaliplatin-based doublet ChT or FOLFOXIRI—bevacizumab and have not been treated with anti-EGFR agents, FOLFIRI—cetuximab (ESMO-MCBS v2.0 score: 4; EMA approved, not FDA approved), FOLFIRI—panitumumab (ESMO-MCBS v2.0 score: 2; EMA approved, not FDA approved) or irinotecan—cetuximab (ESMO-MCBS v2.0 score: 2) may be considered, noting that no OS benefit has been demonstrated [II, C].

Third- and further-line therapy

Molecularly unselected patients.

- FTD—TPI—bevacizumab, if available, is recommended for patients who have previously received fluoropyrimidines, oxaliplatin, irinotecan and biologics [I, A; ESMO-MCBS v2.0 score: 4].
- Regorafenib is recommended after FTD—TPI—bevacizumab due to the better efficacy of the latter in the third line [I, A; ESMO-MCBS v2.0 score: 1].
- Fruquintinib is recommended for patients who have previously received fluoropyrimidines, oxaliplatin, irinotecan and biologics, after progressing while receiving FTD—TPI or regorafenib [I, A; ESMO-MCBS v2.0 score: 3].
- Reintroduction of the initial induction therapy may be optionally recommended after second-line therapy for patients who derived clinical benefit during first-line ChT (often oxaliplatin) and progressed while off treatment [IV, C].
- Salvage ChT cannot be recommended [IV, D].

Molecularly stratified patients.

- For patients with dMMR or MSI-H or *BRAF*^{V600E}-mutated disease, second-line options that have not been used previously are recommended [I, A].
- The recommendations above for molecularly unselected patients also apply to each subgroup below, with FTD—TPI—bevacizumab being a recommended third-line option across all subgroups [I, A; ESMO-MCBS v2.0 score: 4]. In later lines, FTD—TPI is recommended for patients with contraindications to bevacizumab [I, A; ESMO-MCBS v2.0 score: 3].
- For patients with *RAS*-wt and *BRAF*-wt tumours who have not previously received anti-EGFR mAbs, cetuximab (ESMO-MCBS v2.0 score: 4) or panitumumab (ESMO-MCBS v2.0 score: 1) are recommended, regardless of primary tumour location [I, A].
  - Cetuximab—irinotecan can be recommended over cetuximab alone for irinotecan-refractory patients [II, B; ESMO-MCBS v2.0 score: 2].
- For patients with *RAS*-wt, *BRAF*-wt (and preferably also *EGFR* ectodomain-wt) ctDNA who have previously received anti-EGFR mAbs, retreatment with anti-EGFR mAbs can be considered [II, B].
- For patients with HER2-positive, *RAS*-wt disease who have previously received fluoropyrimidines, oxaliplatin and irinotecan, tucatinib—trastuzumab can be recommended [III, B; ESMO-MCBS v2.0 score 3; FDA approved, not EMA approved]. Alternative options include lapatinib—trastuzumab, pertuzumab—trastuzumab or zanidatamab [III, C; none of these options are EMA or FDA approved].
- For patients with HER2-positive disease (IHC3+), regardless of *RAS* status, who have previously received fluoropyrimidines, oxaliplatin and irinotecan and/or have previously received anti-HER2 agents, T-DXd can be recommended [III, B; ESMO-MCBS v2.0 score 3; FDA approved, not EMA approved].
- For patients with *KRAS*^{G12C}-mutated disease who have received fluoropyrimidines, oxaliplatin and irinotecan in previous lines, panitumumab—sotorasib [II, B; ESMO-MCBS v2.0 score: 1; FDA approved, not EMA approved] or cetuximab—adagrasib [III, B; ESMO-MCBS v2.0 score: 3; FDA approved, not EMA approved] can be recommended.
- For *NTRK*-rearranged mCRC, entrectinib [III, B; ESMO-MCBS v2.0 score: 3] or larotrectinib [III, B; ESMO-MCBS v2.0 score: 3] can be recommended for third- or further-line treatment.
  - Repotrectinib can be recommended following progression while receiving entrectinib or larotrectinib [III, B].
- For *RET*-rearranged mCRC, selpercatinib can be recommended for third- or further-line treatment [III, B; ESMO-MCBS v2.0 score: 2].
- For *POLE*- or *POLD1*-mutated mCRC, nivolumab can be recommended for third- or further-line treatment [IV, B; not EMA or FDA approved].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Information on follow-up, long-term implications and survivorship is provided in Supplementary Material Section 5, available at https://doi.org/10.1016/j.annonc.2026.03.005.

Recommendations

- During active treatment, disease reassessments are recommended every 8-12 weeks, including (in most cases) CT or MRI, as well as CEA measurements [III, A].
- Patients with radically resected metastatic disease with a realistic potential for cure can undergo intensive surveillance, including CT (or MRI when indicated) and CEA measurements every 3-6 months during the first 2 years and then every 6-12 months up to 5 years [III, B].
- Patients who have undergone liver transplantation should undergo intensive surveillance, including CT (or MRI when indicated) and CEA measurements every 3-6 months during the first 2 years and then every 6-12 months up to 5 years [I, A].
- Patients with dMMR or MSI-H tumours with ongoing response or stable disease after 2 years of ICIs with no serious AEs should undergo CEA and radiological assessments every 3-6 months [I, A].

- Supportive care and nutritional management can be recommended as part of the follow-up of all patients [III, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/guidelines/esmo-guidelines-methodology). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Precision Oncology Task Force.[94] ESMO-MCBS v2.0[95] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/guidelines/esmo-mcbs). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The ESMO-MCBS scores included in this CPG are correct at the time of publication. For the most up-to-date scores, please refer to the scorecards linked in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2026.03.005. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2026.03.005.[96] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/esmo-clinical-practice-guideline-metastatic-colorectal-cancer.

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