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SPECIAL ARTICLE

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

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Available online 25 October 2022

Key words: metastatic colorectal cancer, Clinical Practice Guidelines, diagnosis, treatment, follow-up

INCIDENCE AND EPIDEMIOLOGY

Colorectal cancer (CRC) is the third most common cancer worldwide, with 1.1 million new cases per year, and is the second leading cause of cancer death.[1] CRC occurs more frequently in middle- to high-income countries with an eightfold variation in incidence across the world. This rise may be associated with known risk factors, including alcohol intake, tobacco use, obesity, sedentariness and dietary patterns (diets low in fruits, vegetables and unrefined plant food, and high in red meat, processed foods and fat).[1,2]

In Europe in 2018, CRC accounted for the second highest number of cancer deaths. However, mortality has declined since 2012.[2] In middle- to high-income countries this reflects screening and early detection programmes, better therapeutic approaches (systemic therapies, biomarker-guided integration of biologicals, resection of metastases and local ablative therapies), allowing more patients the opportunity of prolonged disease control, and even cure.

Approximately 15%-30% of patients present with metastases, and 20%-50% of patients with initially localised disease will develop metastases. The most common location of metastases being liver, then lung, peritoneum and distant lymph nodes.

This European Society for Medical Oncology (ESMO) Guideline describes improvements in diagnosis, staging and treatment of metastatic CRC (mCRC) patients, which have contributed to the current 'state-of-the-art' treatment approaches, and provides guidance for the comprehensive management of patients with mCRC.

DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

A clinical or biological suspicion of mCRC should always be confirmed by adequate radiological imaging and histology of the primary tumour or metastases before the administration of any therapy.

Tissue handling procedures should be optimised to allow biomarker testing. Fixation with 10% neutral buffered formalin (4% formaldehyde) for no less than 6 h and no more than 48 h is recommended. The primary pathologist should review all available tumour specimens and enrich samples by macro-dissection to maximise tumour cell content (>20%) before DNA extraction.

Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, describes biomarkers and molecular targets for precision medicines and corresponding ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) scores. Testing for mismatch repair (MMR) status and *KRAS*, *NRAS* exon 2, 3 and 4 as well as *BRAF* mutations is recommended in all patients at the time of mCRC

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☆Note: Approved by the ESMO Guidelines Committee: April 2002, last update November 2002. This publication supersedes the previously published version—*Ann Oncol.* 2014;25(suppl 3):iii1-iii9.

diagnosis, due to its relevance in selecting first-line therapy. This can be carried out on either the primary tumour or any metastatic site, with a suggested turnaround of ≤10 days. As these mutations are negative predictive factors for the use of anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs), *RAS* testing is mandatory before this treatment is initiated.[3-5] Laboratories providing *RAS* testing should demonstrate successful participation in a relevant external quality assessment scheme. In situations where adequate tissue is not available, exclusion of a RAS mutation status can be conducted by analysing plasma-derived cell-free DNA.[6-8]

BRAF V600E mutation is a strong negative prognostic factor in mCRC. *BRAF* mutation status should be assessed simultaneously with *RAS* testing for prognostication. Additionally, treatment with cetuximab—encorafenib has shown better response, progression-free survival (PFS) and overall survival (OS) than treatment with irinotecan—cetuximab in *BRAF* V600E-mutant mCRC in second- and third-line treatment.[9] Non-V600E class III *BRAF* mutations are not associated with a worse prognosis, while the role of class II mutations remains unclear.[10]

Deficient mismatch repair (dMMR)/microsatellite instability (MSI) testing in mCRC can assist clinicians with genetic counselling, including for identification of Lynch syndrome, and should be done to select patients for immune checkpoint inhibition (ICI) as part of the initial molecular work-up.[11-13]

Identification of human epidermal growth factor receptor 2 (HER2) amplification by immunohistochemistry (IHC) or FISH is recommended in *RAS* wild-type (wt) patients to detect those who may benefit from HER2 blockade.[14] For practical reasons, this could be done with the initial molecular tests, but anti-HER2 inhibition is only recommended in second and further lines. Therefore, the HER2 amplification will only influence a treatment plan after at least first-line progression.

Testing of other biomarkers including *ALK* and *ROS1* gene fusions, mutations of *PIK3CA* and HER2 activating mutations is not (yet) recommended outside clinical trials. *NTRK* fusions are extremely uncommon in mCRC with an incidence of <0.5%; however, testing is recommended when feasible. Screening for NTRK fusions can be carried out by IHC, followed by confirmation with next generation sequencing. Most *NTRK*-rearranged tumours are located in the right colon and are frequently MSI-high (MSI-H). *NTRK* testing could be done at any time but will only influence treatment decisions after progression on at least two lines of treatment. In the rare event of an *NTRK* fusion detected after a comprehensive genomic analysis, including RNA, treatment with larotrectinib or entrectinib is recommended.[15-18]

As fluoropyrimidines [e.g. 5-fluorouracil (5-FU) and capecitabine] are utilised in most mCRC patients, testing for dihydropyrimidine dehydrogenase (DPD) deficiency should be conducted before initiating these drugs; please refer to the ESMO Clinical Practice Guideline (CPG) on localised colon cancer for further guidance.[19] For trifluridine—tipiracil, DPD testing is not required.

Recommendations

- For biomarker testing, fixation with 10% neutral buffered formalin (4% formaldehyde) for no less than 6 h and no more than 48 h is recommended [V, A].
- The primary pathologist should review all available tumour specimens and enrich samples by macrodissection to maximise tumour cell content (>20%) before DNA extraction [IV, A].
- Testing for MMR status and *KRAS*, *NRAS* exon 2, 3 and 4 and *BRAF* mutations is recommended in all patients at the time of mCRC diagnosis [I, A].
- *RAS* testing is mandatory before treatment with anti-EGFR mAbs and can be carried out on either the primary tumour or other metastatic sites [III, A].
- *BRAF* mutation status should be assessed simultaneously with the evaluation of *RAS*, for prognostic assessment [I, B] and for the option of treatment with cetuximab—encorafenib [I, A].
- dMMR/MSI testing in mCRC can assist in genetic counselling for Lynch syndrome [II, B].
- dMMR/MSI status is also recommended as the initial molecular work-up in metastatic disease for its predictive value for the use of ICIs [I, A].
- Identification of HER2 amplification by IHC or FISH is recommended in *RAS*-wt patients to detect those who may benefit from HER2 blockade [III, B].
- Testing of other biomarkers including *ALK* and *ROS1* gene fusions, mutations of *PIK3CA* and HER2 activating mutations is not recommended outside clinical trials [IV, D].
- In the rare event that an *NTRK* fusion is detected by IHC and/or comprehensive genomic analysis, treatment with larotrectinib or entrectinib is recommended [III, A].
- Testing for DPD deficiency has to be conducted before initiating 5-FU-based chemotherapy (ChT) [III, A].

STAGING AND RISK ASSESSMENT

After diagnosis of mCRC, apart from a complete medical history and physical examination, a complete blood count and biochemical laboratory testing should be carried out, including carcinoembryonic antigen (CEA) and, optionally, carbohydrate antigen (CA 19-9) levels.

Staging is carried out primarily with imaging techniques, usually contrast-enhanced computed tomography (CT) of the thorax, abdomen and pelvis. Valuable additions are abdominopelvic ultrasonography, preferably with specific contrast enhancers, or magnetic resonance imaging (MRI). MRI is the preferred choice in case of colorectal liver metastases (CRLMs) amenable to local treatment (LT), to accurately define the number and location of metastases.[20] The same radiological technique should be used at baseline and for response assessment after therapy. An [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography (FDG—PET) scan can be useful, particularly in patients with increased tumour markers without evidence of metastatic disease, or to define the extent of metastatic disease on potentially resectable metastases.

At mCRC diagnosis different risk factors should be considered. Patients with a higher Eastern Cooperative Oncology Group performance status (PS) have worse prognosis, which can be due to advanced disease stage at diagnosis and/or because they are unfit for active treatment.[21]

Proximal colon tumours located before the splenic flexure have different embryological origins and patterns of molecular characteristics compared with distal tumours.[22] Proximal tumours are more frequently mucinous, associated with an inflammatory response, with dMMR/MSI-H and hypermutated, with a higher frequency of *KRAS* and *BRAF* mutations.[23] In contrast, distal colon tumours more frequently have chromosomal alterations, amplification of *EGFR* and HER2 genes and aberrant EGFR signalling. In mCRC, patients with proximal colon tumours have a worse prognosis, independently of the applied treatments.

Resection of the primary tumour is sometimes necessary because of obstructive symptoms or bleeding; however, when asymptomatic it is not recommended in unresectable metastatic disease. Although data from retrospective studies recommend resection of the primary tumour,[24-26] randomised trials specifically addressing this could not confirm survival advantage in patients with synchronous unresectable metastases.[27,28]

The role of multidisciplinary teams and tumour boards in the assessment of mCRC patients

Improved clinical outcomes are seen when treatment approaches for individual mCRC patients are discussed within a multidisciplinary team (MDT) of experts who meet regularly to review mCRC cases.[29] The core MDT should include representation from medical oncology, pathology, diagnostic radiology, radiation oncology, colorectal and hepatobiliary surgery, gastroenterology and stomatherapy (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.10.003). Further expertise may be required from surgeons with peritoneal metastasis expertise, thoracic surgeons, interventional radiologists and nuclear medicine specialists. If not available in a local MDT, an established referral route should exist with a specialised cancer centre (virtual MDTs) to ensure equity of access to optimal care.[30]

The MDT has an ongoing role throughout the mCRC patient pathway, initially to review the diagnostic work-up to define whether or not a patient has clearly resectable or unresectable metastatic disease and to consider management of the primary tumour.[31,32] Patients defined as initially unresectable could have a second reassessment of resectability, preferably within 2-3 months of starting therapy, as proposed by an expert consensus.[33] Conversely, when disease is deemed 'never to be resectable', subsequent discussions may be managed by the treating medical oncologist and patient regarding pros and cons of various approaches and sequences, based on the perceived aims.

Recommendations

- Staging is carried out primarily with imaging techniques, such as a contrast-enhanced CT of the thorax, abdomen and pelvis [IV, A].
- A liver MRI is recommended to characterise non-typical liver lesions on CT scans or when liver metastases seem resectable or potentially resectable [IV, A].
- An FDG—PET scan can be useful, particularly in patients with increased tumour markers without evidence of metastatic disease, or to define the extent of metastatic disease on potentially resectable metastases [IV, B].
- Resection of an asymptomatic primary tumour in patients with unresectable metastatic disease cannot be recommended as standard of care [I, D].

MANAGEMENT OF RESECTABLE/POTENTIALLY RESECTABLE DISEASE

Treatment of potentially resectable mCRC

Surgical resection of R0-resectable (resectable, leaving no tumour at the margin) CRLMs is a potentially curative treatment, with reported 5-year survival rates of 20%-45%. The criteria for R0-resectability of CRLMs depend on technical and oncological (prognostic) criteria and on the experience of the MDT.

Technically, resectability is not limited by number, size or bilobar metastatic involvement, if tumours may be resected leaving sufficient remnant organ (e.g. $\geq$30% remnant liver). Other ablative techniques, such as thermal ablation (TA) or stereotactic body radiotherapy (SBRT), may be added to surgery to achieve a complete treatment or provide an alternative to resection if inoperable due to frailty or poor anatomical location for resection.

'Oncological' criteria concern prognostic factors that impact disease-free survival (DFS) or the likelihood of cure. Characteristics including onset of metastatic disease (synchronous versus metachronous), clinical aggressiveness of the tumour as well as concomitant extrahepatic disease could lead to the recommendation of a neoadjuvant strategy instead of upfront surgery to get 'the proof of time' for a well-controlled disease and are seen as relevant factors. Indeed, up to 55%-80% of patients will experience relapse following metastatic resection, the majority occurring in the resected organ. Biological determinants including *RAS, BRAF* or dMMR/MSI mutational status may also influence treatment strategy. Despite the recognised poor prognosis in some cohorts, patients with *BRAF*-mutant mCRC who underwent R0 resection of all metastatic lesions had comparable outcomes to their *BRAF*-wt counterparts. Despite limited evidence, the exclusion of these patients from a potentially curative approach does not seem justified.

With very favourable prognostic criteria and a good technical resectability, perioperative systemic treatment may not be needed. Conversely, unfavourable criteria mandate the use of 'best systemic treatment' options. In patients with an unclear prognostic situation, systemic

treatment should be initiated to gain more prognostic insights by observation. The use of perioperative leucovorin (LV)—5-FU—oxaliplatin (FOLFOX) ChT, 3 months pre- and post-operatively in patients with technically 'easy-to-resect' resectable CRLMs but with negative prognostic factors, has been positively proven and can be considered as a standard of care in this circumstance (EORTC 40983 trial).[34,35]

Most patients have metastatic disease that is not initially suitable for potentially curative resection. It is, however, important to select patients with resectable metastases and those with initially unresectable disease in whom resection may be possible after a major response with systemic therapy. The aim of treatment here should be to convert initially unresectable disease to resectable. Median survival rates after resection are two- to threefold higher than in patients treated with systemic therapy alone, with a potential of cure.[32]

Resection of lung metastases offers 25%-35% 5-year survival rates in carefully selected patients. Resection of lung metastases in conjunction with resection of CRLMs has also shown survival benefit.[34,36]

In selected patients with limited peritoneal metastasis, complete cytoreductive surgery and hyperthermic intraperitoneal ChT (HIPEC) may provide prolonged survival when carried out in experienced high-volume centres (in view of the relatively high morbidity associated with the procedure).[37-39] This observation, however, has not been confirmed in randomised, phase III trials and therefore cannot be recommended as standard of care. A recent phase III trial (PRODIGE 7) has failed to show the added value of an oxaliplatin-based HIPEC on cytoreductive surgery. Indeed, the PRODIGE 7 trial reported the absence of an OS benefit after adding HIPEC to cytoreductive surgery and more frequent post-operative late complications with this combination, in patients with colorectal peritoneal metastases.[40] There are ongoing trials to see if other HIPEC regimens (using mitomycin and different HIPEC procedures) may possibly lead to better outcomes.

Ovariectomy, lymphadenectomy and resection of selected other single metastases have also shown survival benefit in patient series.[32]

Primarily technically R0-resectable CRLMs. In patients with 'favourable' oncological criteria (e.g. metachronous lesions, fewer metastases, unilobar disease, no extrahepatic disease), upfront resection should be done. The only phase III trial (dedicated to CRLMs) conducted in this situation showed a benefit in DFS but a non-significant improvement in OS if perioperative treatment with FOLFOX is administered.[34,41]

In patients with 'unfavourable' oncological criteria (synchronous lesions, more than three metastases, bilobar disease, limited extrahepatic disease) and 'favourable surgical' criteria (e.g. no vascular infiltration), perioperative ChT, preferably with any fluoropyrimidine and oxaliplatin, should be proposed.

Attention should be paid to the presence of small metastases (10-15 mm), which may disappear while on systemic therapy, with the risk of being missed during surgery while still active in terms of presence of tumour cells. In this situation, neoadjuvant ChT should not exceed 2 months if indicated; upfront surgery or other interventional approaches such as a percutaneous destruction should also be discussed with the MDT. For patients in whom the metastases have disappeared on standard imaging, microscopic disease is often still present and an MDT discussion of the optimal strategy is required.

Post-operative ChT can be delivered, but the randomised evidence to support this is scarce and therefore it cannot be considered as standard of care. Fluoropyrimidine—oxaliplatin-based ChT for 6 months after resection of metastases may improve outcomes unless patients failed a prior adjuvant treatment (oxaliplatin-based) for stage II or III disease within 12 months. Targeted agents are not recommended during perioperative therapy in patients with upfront resectable metastases.[35,42] Perioperative or post-operative adjuvant treatment strategy decisions may be influenced by 'biology of the disease', the timing of onset of metastases (synchronous versus metachronous), technical criteria for resectability (or ablation) and/or the number and size of metastases.

For patients who relapse within 6 months after oxaliplatin-based adjuvant therapy (potentially resistant to this treatment and often with a persistent sensitive neuropathy), an MDT discussion of the optimal individual strategy is required. If a preoperative strategy is chosen, treatment selection should reflect this situation and the 'best available systemic treatment' should be used.

Potentially resectable metastatic disease, conversion therapy. The addition of a targeted agent to a cytotoxic doublet or triplet is the most effective treatment in mCRC. For efficacy assessment, overall response rate (ORR) seems to be the best parameter in direct and cross-trial comparisons.

Anti-EGFR mAbs in *RAS*-wt patients with left-sided primary tumours are more effective than bevacizumab-based combinations.[43,44]

According to cross-trial comparisons, LV—5-FU—oxaliplatin—irinotecan (FOLFOXIRI) with and without bevacizumab also resulted in high ORRs.[45-47]

In patients with *RAS*-mutant disease, a cytotoxic triplet—bevacizumab and, to a lesser extent, a cytotoxic doublet—bevacizumab are considered the best choice in patients who may tolerate this intensive approach.

Resection of the metastases should be carried out 3-4 weeks from the previous administration of ChT alone or ChT—anti-EGFR mAbs, or at least 5 weeks after ChT—bevacizumab (if bevacizumab has not been omitted from the last cycle). It should be carried out as soon as the metastases, as a result of size reduction, are technically resectable, since unnecessarily prolonged administration of ChT may lead to increased liver toxicity and thus, higher post-operative morbidity.[36]

Surgery following systemic treatment could be more challenging than for initially resectable patients. Specific

techniques, such as portal embolisation, resection combined with radiofrequency ablation (RFA)/microwave ablation (MWA) or two-stage hepatectomy, may be applied further. Also, patients unresponsive to first-line ChT should not be denied liver resection since the outcome of resected patients after second-line ChT could also be favourable. This approach needs frequent assessment of response to indicate surgery at the right moment. Intra-arterial ChT could be an option in such patients, to both recover a response and to achieve liver resection.[48,49] The management of these patients requires a particular dedication and expertise within the team.[50,51]

After surgery, re-uptake of the previous systemic treatment—with the same regimen—can be considered, specifically if pathological response has occurred, but there is no evidence from randomised studies to support this approach. Generally, the total treatment duration should not exceed 6 months. New approaches, such as intra-arterial post-operative adjuvant treatments, are currently under investigation in randomised studies.[52]

LTs in management of patients with oligometastatic disease

Management of oligometastatic disease. The definition of oligometastatic disease (OMD) is important as treatment strategies should be based on the possibility of achieving eradication of all metastases and/or a 'no evidence of disease' (NED) status, either initially or after systemic therapy.

Generally, a traditional clinical definition of OMD is:

- One to five metastatic lesions, occasionally more if complete eradication is possible
- Up to two metastatic sites
- Controlled primary tumour (optionally resected)
- All metastatic sites must be safely treatable by LT

OMD status has therefore been established by radiological appearances and clinical judgment. Currently, biological factors do not contribute to this definition, but this may change considering, for example, molecular subtypes with specific prognostic background and/or treatment implications. Notably, OMD status can occur in multiple clinical scenarios in the continuum of care, e.g. during different treatment lines. Therefore, careful and continuous reassessment is recommended.

Consideration should be given to relevant factors in the OMD setting:

- Disease-related factors, e.g. size, number and localisation of metastatic sites, status of primary tumour, previous treatment-free intervals, previous treatments and their respective outcome, overall prognosis
- Surgery and other LT-related factors, e.g. technical ability to treat and/or to achieve a locally complete eradication. This must be discussed versus potential toxicity and the invasiveness of the technique and the alternatives (mostly, continuation or initiation of systemic treatment)
- Patient-related factors, e.g. PS, frailty and comorbidity, fitness for systemic treatment and LT, individual treatment goals and preferences

Assessment for LT of OMD must include an optimal imaging strategy before LT: generally, a contrast-enhanced CT scan, with MRI, ultrasound, PET and others. Specialist MDT input and thorough patient assessment and counselling are warranted.

The selection of the best LT for OMD differs according to:

- The size, number and localisation of the metastases
- The expected likelihood of complete eradication
- The invasiveness of the chosen technique
- The local expertise with regard to the use of a particular LT method
- Consideration of patient frailty, life expectancy and preferences

The integration of LT into the therapeutic continuum of care can be:

- As a definitive eradication in limited disease. Usually, surgery will be used for this goal, but a nonsurgical LT only if tumour characteristics (e.g. localisation) and/or patient factors would limit the surgical approach.
- As a replacement for surgery; mostly in prognostically unclear situations or after response to systemic treatment in more widespread disease.
- As a primary or metastasis-specific treatment to halt further dissemination. This could delay (or even eliminate) the need for systemic treatment. This can be used as an initial treatment for slowly progressing tumours.
- As a consolidative treatment, following systemic therapy to delay or pause further treatment.

OMD should be considered a specific situation in mCRC treatment. OMD management will, generally, in most cases start with induction ChT treatment, with response (or at least disease stabilisation) being a strong predictor for a favourable prognosis, justifying the enhanced local control by LT. However, in favourable prognostic situations with limited metastatic spread, upfront LT (without preceding systemic therapy) is a standard of care. LT is an option in oligo-progressive disease (i.e. very limited recurrence/non-response in a patient receiving systemic treatment). Such OMD could be construed as a result of intra-tumour heterogeneity. The aim of LT here is to eliminate the cell clones no longer responding to treatment and to enable the continuation of the systemic therapy.

Intent of treatment and choice of LT

Curative treatment approaches. A complete eradication of tumour can be obtained using surgical R0 resection and/or A0 ablation (evidence of ablation margins and NED at follow-up imaging). For patients with OMD confined to a single organ (most frequently liver or lung), or a few organs or sites (pre-dominantly visceral metastases, e.g. liver and lung), a potentially curative approach exists. In this setting, long-term survival or even cure can be attained in 20%-45% of patients who undergo complete R0 resection or complete A0 TA of their metastases.[53-55]

In the absence of randomised trials comparing surgical with nonsurgical disease management, surgery has remained the standard treatment approach for patients with resectable OMD. However, TA and radiotherapy achieve high rates of complete tumour eradication of small metastases and can be seen as alternatives if a widely invasive surgical approach is required.[55-58]

Patients with liver and lung metastases have a better prognosis than those with other metastatic disease locations. For example, as limited lung metastases are associated with slower growth and prolonged survival, a 'watch and wait' strategy with regular surveillance imaging may also be appropriate.[59,60] The data showing different outcomes depending on the site(s) of OMD are likely to reflect molecular differences. Selection of the best 'situation-adapted' treatment strategy should consider all of these factors as part of an MDT treatment decision before the start of systemic treatment and at the time of best response.

Use of LT with non-curative intent. For patients with more extensive disease, the value of an LT may contribute to long-term survival or a prolonged PFS, but is rarely curative.[61] Here, LT is part of a multimodal therapy approach to provide well-controlled sites of metastases with optional discontinuation of systemic therapy, with the goal of long-term disease control and potentially improved OS. For example, the reported median ChT-free survival after TA of lung metastases from CRC was 12.2 months in the overall population and 20.9 months in lung-only metastases patients.[62]

Modalities for LT in OMD. Modalities for LT are summarised in Figure 1. Management of OMD is outlined in Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.10.003.

Surgery. Treatment should aim to achieve complete resection of all tumour masses, using surgical resection and/or nonsurgical interventions.

For patients with resectable OMD confined to a single organ (most frequently liver or lung) and/or a few organs (and even localised peritoneal spread), surgery remains the standard and best (potentially) curative treatment approach. Operative resection of metastases must be seen in the context of prognostic information and technical limitations.

Local ablation techniques. *Thermal ablation.* TA such as RFA has a limitation inherent to size range of maximum 2-3 cm.[63] Safety margin of ablation is a strong predictor of complete eradication.[55,64] In the randomised phase II CLOCC trial (ChT plus RFA ± surgical resection versus ChT alone, for patients with a median of four CRLMs), an improvement in PFS and in OS was reported.[65]

Data on the use of TA in combination with liver resection in an effort to obtain NED demonstrate improved perioperative outcomes without compromising long-term survival compared with bilateral resection.[36,66] Data on TAs other than RFA are limited, but outcome appears similar between RFA and MWA, with ablative margins predictive for complete eradication of the targeted disease with both technologies, and a possible better control of perivascular tumours with MWA.[55]

A meta-analysis supports surgery to provide better local control and longer OS for CRLMs.[67] Reported differences were due to limitations of TA technologies, operator experience and insufficient safety margins applied, or subject to possible patient selection bias. TA applied to patients who previously benefitted from surgery improves liver-specific PFS,[65] leading to the utilisation of RFA as a valid treatment option for recurrent disease after surgical

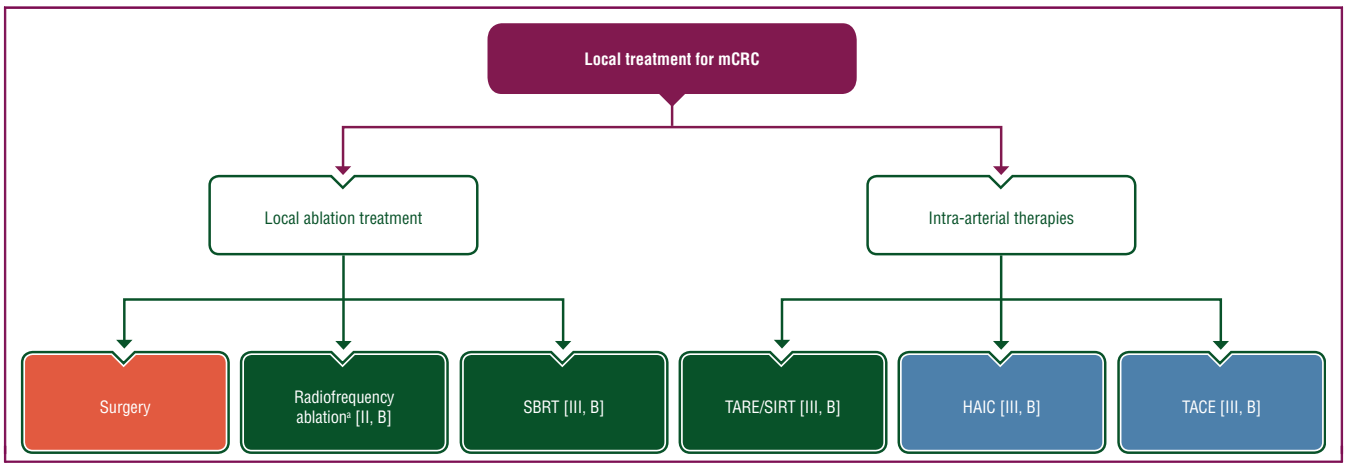

Figure 1. Local treatment of CRC metastases. Purple: general categories or stratification; red: surgery; dark green: radiotherapy; blue: systemic anticancer therapy; white: other aspects of management.

CRC, colorectal cancer; CRLM, colorectal liver metastasis; HAIC, hepatic arterial infusion chemotherapy; mCRC, metastatic colorectal cancer; OMD, oligometastatic disease; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TA, thermal ablation; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

[a]In patients with unresectable CRLMs only, or OMD in the liver, TA can be considered for small metastases [III, B]. In patients with lung-only metastases or OMD including lung lesions, TA may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity or other factors [III, B].

resection in small CRLMs.[68-71] Randomised clinical trials are ongoing to accurately assess surgery versus TA in CRLMs (COLLISION study).

TA techniques also have proven efficacy in the ablation of lung metastases: local control rates of 88%-94% at 1 year and 77%-90% at 3 years have been reported.[54,56,72,73] Similarly, margins and volume of ablation are more predictive of complete tumour eradication than type of TA used.[74] Mortality and major complication rates may be as low as 1%.[75] A systematic review concluded that a firm conclusion could not be drawn with regard to the use of surgery or RFA.[76]

SBRT. High conformal hypo-fractionated SBRT of metastases has been reported with a large range of local control rates of 31%-90% after 2 years, including 80% for liver and lung metastases, but also for lymph nodes.[57,58] The risk of failure correlates with tumour size as well as biologically effective dose and motion management both for lung and CRLMs.[77-79] Across several series, no grade $\geq$3 events were recorded. SBRT is considered an effective and safe ablative treatment, but with no large prospective study available. Therefore, with the benefit of short treatment time, lack of a need for recovery and favourable overall toxicity profile, SBRT is a treatment option, although it is yet unclear which patients benefit most. The OLIVER trial (NCT03296839) aims to evaluate the impact of SBRT versus ChT alone, while another randomised trial aims to compare MWA and SBRT for inoperable CRLMs (NCT02820194).

Intra-arterial therapies. *Transarterial chemoembolisation.* The data on transarterial chemoembolisation (TACE) for CRLMs are mostly related to the use of irinotecan-based drug-eluting microspheres (DEBIRI), including two randomised studies. Despite significant limitations in design and analysis of both, DEBIRI compared with LV—5-FU—irinotecan (FOLFIRI) resulted in statistically significant improved OS and PFS,[80] whereas FOLFOX—bevacizumab—DEBIRI (FOLFOX—DEBIRI) reported improved response rate (RR), downsizing to resection and PFS compared with FOLFOX—bevacizumab.[81] In the neoadjuvant setting, DEBIRI is reported as safe and feasible, yielding pathological major or complete response in >77% of targeted lesions.[82] A review of DEBIRI data, including 850 patients reported ORR of 56.2% and median PFS and OS of 8.1 and 16.8 months, respectively.[83] In the chemorefractory setting, a new microspheres/irinotecan formulation demonstrated an ORR of 83% and median OS (mOS) of 14 months.[84]

Transarterial radioembolisation/selective internal radiation therapy. Transarterial radioembolisation (TARE)/selective internal radiation therapy (SIRT) typically involves a single delivery of a radionuclide [yttrium (Y)-90, or holmium-166],[85,86] connected to either resin or glass particles, or bio-resorbable poly (L-lactic acid) microspheres as a delivery platform into the hepatic artery with the therapeutic effect essentially limited to irradiation.

For patients with liver-limited metastases failing the available chemotherapeutic options, TARE with Y-90 resin microspheres has prolonged time to tumour progression and time to liver progression, in a small, randomised study.[87]

However, aggregated data of >1000 patients treated within three randomised studies failed to show a benefit in OS,[88] when TARE was added to the first cycle of an investigator-determined 'best systemic treatment'. A randomised phase III study of TARE with resin microspheres failed to show an overall PFS (as primary endpoint) benefit, whilst a significantly better 'liver-specific-PFS' was documented.[89] In this trial, 45% of patients had the primary tumour in place and 40% had extrahepatic disease, suggesting that TARE may be most beneficial in patients with liver-limited or liver-predominant disease. Another potential subgroup with a distinct benefit is patients with right-sided primary tumour.[88,90]

A recent further phase III trial compared second-line ChT alone with second-line ChT plus transarterial Y-90 glass microspheres in 428 patients with liver-dominant or liver-only disease (EPOCH trial). A significant improvement in PFS (as primary endpoint) was documented and ORRs were 21.1% and 34.0% for ChT alone and ChT plus TARE, respectively. A subgroup analysis suggested PFS benefit may be more dominant in patients with fewer than three lesions, resected primary tumour, lower tumour burden, left primary tumour location (PTL) and a *KRAS* mutation.

Hepatic arterial infusion ChT. Hepatic arterial infusion ChT (HAIC) is carried out through intra-arterial ports or pumps placed surgically or percutaneously.[91] The most commonly used drugs are floxuridine (FUDR) and oxaliplatin, infused through ports. The European experience is mostly linked with intra-arterial oxaliplatin over 2 h and systemic 5-FU—LV delivered over 48 h. HAIC with oxaliplatin demonstrated 62% ORR in heavily pre-treated patients with more than ninefold higher complete pathological response than systemic therapy.[92,93] The phase II OPTILIV study with HAIC with irinotecan—oxaliplatin—5-FU combined with intravenous (i.v.) cetuximab met its primary endpoint of conversion to R0-R1 (microscopic tumour at the margin) hepatectomy in 29.7% of 64 *RAS*-wt pre-treated patients bearing a median of 10 CRLMs involving six segments of the liver.[49]

Recommendations

Treatment of potentially resectable mCRC

- In patients with resectable metastases and with favourable prognostic criteria and a good surgical approach, perioperative systemic treatment may not be needed [III, B].
- In patients with resectable metastases, the use of perioperative oxaliplatin-based ChT is recommended where the prognostic situation is unclear [II, B].
- Anti-EGFR mAbs in left-sided *RAS*-wt patients should be used as conversion therapy, when complete resection is the aim [II, A].
- In patients with right-sided and *RAS*-mutant disease, FOLFOXIRI—bevacizumab and, to a lesser extent, a

cytotoxic doublet—bevacizumab should be considered the best choice depending on patients' ability to tolerate triplet ChT [II, A].
- Patients unresponsive to first-line ChT should not be denied resection or ablation of metastases since the outcome of resected patients after second-line treatment could be also favourable. Intra-arterial ChT could be an option in such patients, not only to recover a response but also to achieve liver resection [III, C].
- In case of a peritoneal metastasis only, complete cytoreductive surgery should be carried out [II, A]. The addition of HIPEC can be considered as an experimental procedure, still to be validated in clinical trials. Therefore, its use cannot be recommended outside of this setting [II, D].

Intent and choice of local treatment

- Treatment approaches for all patients with mCRC should be discussed within an MDT of experts (especially in LT) who meet regularly to review OMD cases [V, A].
- LT can be used as a primary or metastasis-specific treatment to halt further dissemination, and/or following systemic therapy as a consolidation treatment, to delay or pause further treatment [III, C].
- Frequent radiological re-evaluations of the potential applicability of surgery or other LT techniques should be carried out, generally every 8-12 weeks [IV, A].

Local ablation treatment

- In patients with unresectable CRLMs only, or OMD in the liver, TA can be considered for small metastases [III, B].
- TA is a valid treatment option for recurrent disease after surgical resection for small CRLMs [II, B].
- In patients with lung-only metastases or OMD including lung lesions, TA may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity or other factors [III, B].
- SBRT is a treatment option, although it is yet unclear which patients benefit most [III, B].

Intra-arterial therapies

- TACE, TARE/SIRT and HAIC may be also considered as treatment options with non-curative intent [III, B].
- SIRT, HAIC and chemoembolisation of CRLMs in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials [V, D].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE WITHOUT POTENTIAL CONVERSION

An MDT discussion would be advisable to decide the best treatment approach for each individual patient, taking into consideration several factors that were established in the 2016 ESMO Consensus guideline (see Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.10.003), such as clinical presentation (impending symptoms at diagnosis, PTL), histology and molecular biology of the tumour, the patient characteristics (age, PS, comorbidities, socioeconomic factors), the goal of treatment and treatment-related issues [toxicity, quality of life (QoL), etc.].[94] When considering the best treatment option for patients with mCRC, all of the above-mentioned factors and medical history must be taken into consideration.

Frail patients will not tolerate combination therapies with potential side-effects. In these patients, the main treatment goal is maintaining QoL and improving symptoms. These patients could instead receive lower toxicity therapies, such as fluoropyrimidine as monotherapy or combined with bevacizumab, or anti-EGFR mAbs in left-sided *RAS*-wt tumours. The 2016 ESMO consensus guideline established that the initial consideration for treatment stratification was whether patients were 'fit' or 'unfit'.[94]

Age alone is not a contraindication of combined therapy, for a patient with good fitness, organ function and without significant comorbidities. A complete geriatric assessment to consider all the factors that can affect treatment tolerance and compliance is advisable.[95,96]

Tumour characteristics are critical, for both prognosis and predicted response to the available treatments. The tumour burden, location of the metastases (involving one or more organs) and the primary tumour, or impending symptoms related to the primary tumour (haemorrhage or intestinal obstruction), will guide the treatment strategy.

The PTL and mutational status of the tumour is key to decide the best treatment approach, as described above. The location of the primary tumour proximal to the splenic flexure also has prognostic implications, with a shorter survival related both to the nature of the tumour, metastatic sites, and to a poor response to treatment with ChT and mAbs. It must be stressed that those right colon tumours, in general, benefit less in terms of PFS and OS from treatment with anti-EGFR mAbs, compared with tumours located distal to the splenic flexure.[22] Nevertheless, RRs are similar for both tumour locations.

The historical ESMO classification of patients in four groups according to the treatment goals has evolved (see Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2022.10.003).[97] Treatment goals for fit patients differ according to different scenarios (see Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2022.10.003): (i) cure, generally achieved through surgery, in those cases of OMD localised to liver, lung and other solitary organs, (ii) to achieve a good response and downstaging with ChT, allowing treatment with curative intent in initially unresectable disease and (iii) improving tumour-related symptoms, delaying progression and prolonging survival in metastatic disease not amenable to definitive surgical treatment or LTs despite response and all while maintaining QoL. In the third group of patients, the continuum of care concept demonstrates that sequencing of all the different treatment options results in prolonged disease control and improved survival.[98] Liver transplantation is emerging as an experimental option for patients with CRLMs but results of randomised studies are still pending.

First-line treatment

Proposed first-line treatment strategies are shown in Figure 2.

Cytotoxic agents. 5-FU is the backbone of mCRC treatment. Most first- and second-line clinical trials have explored different combinations based on fluoropyrimidines, both i.v. 5-FU (as bolus or as continuous infusion, with a different toxicity profile) or oral capecitabine; these are considered equivalent.[99,100] S-1 (tegafur—gimeracil—oteracil) is an alternative fluoropyrimidine when i.v. 5-FU or capecitabine-based ChT cannot be used due to cardiotoxicity and/or hand-foot syndrome.[101]

The addition of oxaliplatin and/or irinotecan to a fluoropyrimidine improves RR and survival.[102,103] Both doublets, FOLFOX and FOLFIRI, are considered to be equally effective and the selection in the first-line can be guided by their different toxicity profiles and the biological added to enhance efficacy. Capecitabine is more frequently combined with oxaliplatin (CAPOX) and less frequently with irinotecan (CAPIRI) because CAPIRI has a more toxic profile than FOLFIRI.[104] A dose-modified CAPIRI schedule showed a more favourable toxicity profile.[105] The triplet FOLFOXIRI has improved RRs and survival compared with FOLFIRI, but side-effects limit its applicability to selected fit patients without significant comorbidities.[45]

Several trials have explored delivering treatment with fluoropyrimidines, oxaliplatin and irinotecan either sequentially or in combination in first or later lines of treatment, showing that both strategies achieved similar OS.[106-108] This observation confirmed that first-line treatment with a fluoropyrimidine, as a single

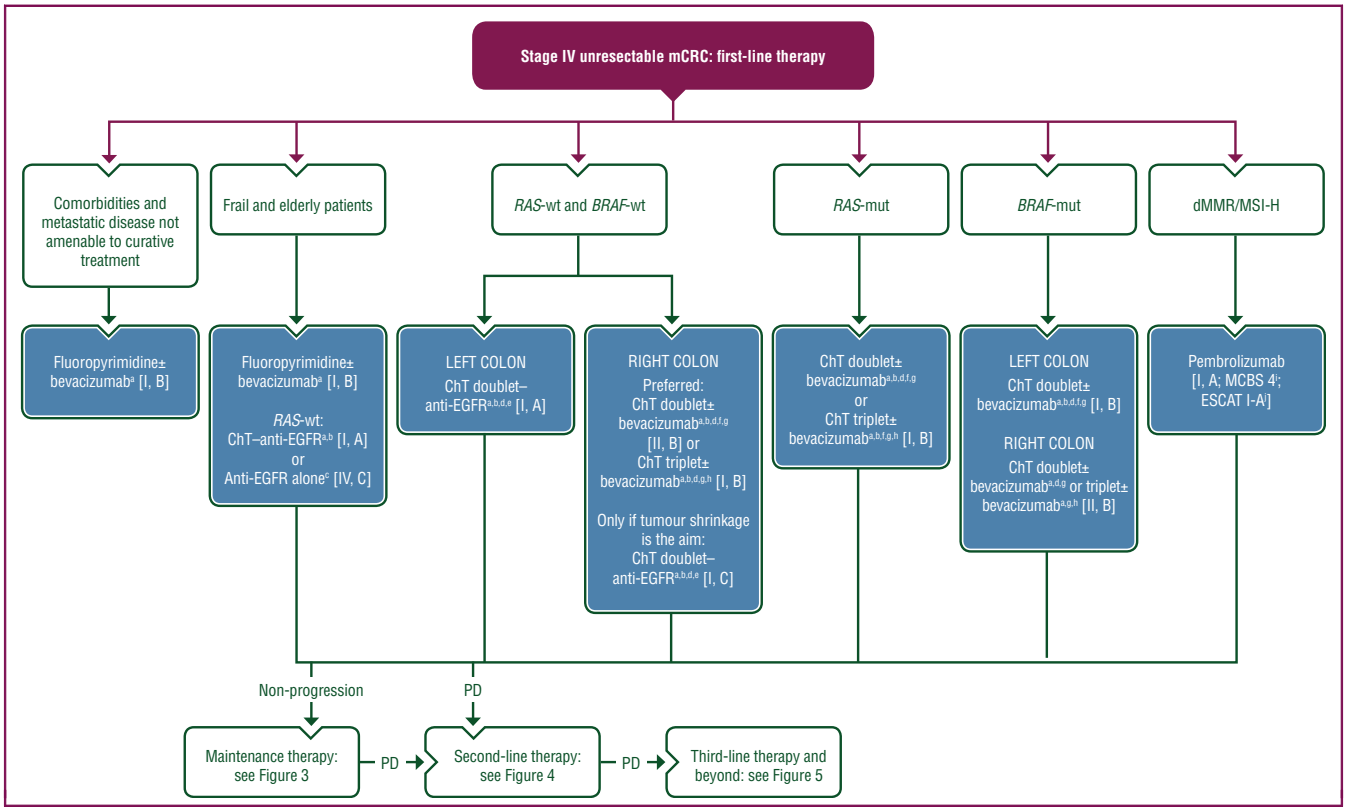

Figure 2. Management of stage IV unresectable mCRC in first-line therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, 5-fluorouracil; ChT, chemotherapy; dMMR, deficient mismatch repair; 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; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PS, performance status; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]Additional details on treatments and drug combinations can be found under the section 'Management of advanced and metastatic disease without potential conversion' (subsections 'First-line treatment' and 'Second-line treatment').

[c]In frail or elderly patients unable to tolerate ChT whose tumours are left-sided and RAS-wt.

[d]FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4; FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; mFOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3.[i]

[e]FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; modified FOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3; for FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4.[i]

[f]In a very selected population.

[g]CAPOX— or FOLFOX4—bevacizumab ESMO-MCBS v1.1 score: 1.[i]

[h]A triplet with FOLFOXIRI plus bevacizumab is an option for selected patients with good PS and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2].[i]

[i]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[j]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

agent, is a reasonable option, particularly in frail patients.

Biological targeted agents. Several targeted agents against EGFR (cetuximab and panitumumab) or against the vascular endothelial growth factor (VEGF) pathway (bevacizumab and ramucirumab, or the protein aflibercept) have demonstrated improved outcomes when combined with ChT, or as a monotherapy in the case of anti-EGFR mAbs.

Anti-EGFR. Two different anti-EGFR mAbs have demonstrated activity in mCRC as monotherapy or combined with ChT. Cetuximab is a chimeric anti-EGFR mAb, which has demonstrated effectiveness in different lines of treatment, as has panitumumab, a humanised anti-EGFR mAb.[109,110] Both treatments can produce characteristic skin toxicity, which must be properly managed with antibiotics and topical corticosteroids.[111]

The presence of *RAS* mutations is associated with resistance to anti-EGFR mAbs and knowing the expanded *RAS* mutational status is mandatory for use of both cetuximab and panitumumab, avoiding anti-EGFR mAb treatment when a *RAS* mutation is confirmed.[112,113]

In the first-line setting, FOLFIRI—cetuximab was studied in a non-selected population of mCRC patients.[114] A retrospective analysis demonstrated that only those patients without *KRAS* exon 2 mutations had a significantly reduced risk of disease progression, improved OS and increased RR, compared with those who received FOLFIRI alone, and a *RAS* expanded analysis confirmed the benefit in RR and survival.[115]

A combination of FOLFOX with or without panitumumab was similarly studied in an initially non-selected population of mCRC, although analysis of the mutational status was completed in >90% of the patients. In the *KRAS*-wt population, a statistically significant improvement in PFS and OS was observed with FOLFOX4—panitumumab.[116] An expanded *RAS* analysis, including mutations in *KRAS* exons 2, 3 and 4, *NRAS* exons 2, 3 and 4 and *BRAF* V600E, also confirmed the efficacy of FOLFOX—panitumumab in the *RAS*-wt population.[112]

Cetuximab—oxaliplatin in the first-line setting was also explored, showing a better RR and a trend toward an improvement in PFS and OS in the *RAS*-wt population in a randomised phase II study and better ORR, PFS and OS in a Chinese phase III study.[113,117]

When a CAPOX combination was explored in addition to cetuximab in the COIN trial, no significant benefit in terms of PFS or OS was observed, with the exception of an increased RR in the *RAS*-wt population treated with cetuximab.[118] Moreover, the addition of cetuximab to capecitabine-based therapy resulted in more diarrhoea and skin toxicity, leading to a dose reduction/discontinuation of the ChT schedule and a reduced exposure to fluoropyrimidines. Combination with anti-EGFR mAb—capecitabine-based ChT is not recommended. FLOX (LV—bolus 5-FU—oxaliplatin)—cetuximab also failed to show any benefit. Therefore, anti-EGFR—bolus 5-FU-based ChT is not recommended.[119]

Tumour location is an important factor when deciding the use of anti-EGFR mAbs in *RAS*-wt tumours. As mentioned previously, the benefit of anti-EGFR mAbs is very relevant in left-sided tumours, with a significant increase in RR and relevant prolongation of PFS and OS.[22] In right-sided tumours no benefit is observed for PFS and OS by the addition of cetuximab or panitumumab, except an increase in RRs. For this reason, a doublet or a triplet with bevacizumab is the preferred option for patients with right-sided tumours independently of the *RAS* mutational status. Only in right-sided *RAS*-wt tumours, in which a good response is needed, i.e. for conversion therapy, a doublet with an anti-EGFR mAb can be selected. In frail or elderly patients, unable to tolerate ChT, whose tumours are left-sided and *RAS*-wt, monotherapy with anti-EGFR mAbs may be an option.[120] Combination of anti-EGFR mAb with ChT cannot be recommended in *BRAF*-mutant tumours.

Anti-VEGF. In the first-line setting of mCRC, the only anti-angiogenic that has shown better outcomes in combination with ChT is bevacizumab, a selective VEGF-A inhibitor. This antiangiogenic has characteristic class-related side-effects including increase in blood pressure and proteinuria and, less frequently, arterial thrombosis, and an increased risk of bleeding, intestinal perforation and wound healing delay, which can be decreased with proper patient selection. There are currently no biomarkers to identify which patients may benefit more from this treatment.

The addition of bevacizumab to capecitabine increased PFS compared with capecitabine monotherapy and this benefit on PFS was confirmed in patients ≥70 years old in the AVEX phase III trial.[121,122] No significant differences in OS were observed.

The addition of bevacizumab to an irinotecan—bolus 5-FU—LV (IFL) showed an improvement in OS, PFS and RR, compared with IFL—placebo.[123] In the NO16966 phase III trial, a 2 × 2 factorial design compared any fluoropyrimidine—oxaliplatin combination (CAPOX or FOLFOX4) with or without bevacizumab or placebo, showing an improvement in outcome, limited to PFS.[124]

The TRICOLORE phase III trial compared mFOLFOX6 or CAPOX and bevacizumab with irinotecan—S-1 (IRIS)—bevacizumab,[125] concluding that IRIS—bevacizumab is non-inferior to mFOLFOX6— or CAPOX—bevacizumab with respect to PFS, with comparable OS.[126]

Anti-EGFR or anti-VEGF strategy in *RAS*-wt mCRC patients. To address which targeted therapy would offer the greatest benefit when combined with ChT in the first-line setting, the FIRE-3 trial compared FOLFIRI—bevacizumab with FOLFIRI—cetuximab, in *KRAS* (exon 2)-wt mCRC. No differences in the primary endpoint of ORR or in PFS were observed. However, an OS improvement was observed with cetuximab. A *post hoc* analysis showed a significant proportion of patients achieved a better objective response, early tumour shrinkage and median depth of response in the extended *RAS*-wt population receiving FOLFIRI—cetuximab.[43]

A combined analysis of the FIRE-3 and CRYSTAL trials confirmed the benefit in OS on left-sided tumours treated with FOLFIRI—cetuximab.[127]

The CALGB/SWOG 80405 trial also compared cetuximab with bevacizumab, in combination with an investigator's choice ChT doublet (FOLFOX or FOLFIRI), in *KRAS* (exon 2)-wt mCRC. No differences in the primary endpoint of OS were observed between the study arms, suggesting that both treatment strategies were equally effective in the first-line setting on *KRAS*-wt mCRC. The expanded *RAS* analyses showed no differences in OS or PFS but an increased RR with cetuximab.[44]

A subsequent exploratory retrospective analysis of CALGB/SWOG 80405 trial examined the impact of PTL. Patients with left-sided *KRAS*-wt tumours treated with cetuximab had an increased OS and PFS; conversely, patients with right-sided tumours treated with bevacizumab had an increased OS, confirming the limited benefit of anti-EGFR therapies on right-sided tumours.[128]

An exploratory phase II trial compared mFOLFOX6 with panitumumab versus bevacizumab in patients with *KRAS* exon 2-wt mCRC.[129] The final results confirmed a benefit in PFS in the extended *RAS*-wt population treated with FOLFOX—panitumumab, with no significant differences in OS.[129] A phase III randomised trial (PARADIGM) comparing both options resulted in a significant benefit in OS for the FOLFOX—panitumumab arm in left-sided tumours, as well as the whole population. The mOS was >36 months, confirming the benefit of this therapy in the first-line setting, although most of the benefit is driven by left-sided tumours.[130]

Combining anti-VEGF plus anti-EGFR mAbs is not superior to ChT—anti-VEGF alone in terms of PFS, OS and RR. Furthermore, it increases grade 3 and 4 adverse event rates, and is therefore not recommended.[131]

Triplets. The strategy of combining the three active ChT agents 5-FU, oxaliplatin and irinotecan (FOLFOXIRI) has been explored in mCRC, with the main purpose of improving tumour shrinkage (shown by RR), thus allowing a complete resection of metastases, but increasing potential toxicities.[107,132] A phase III trial showed increased RRs and greater R0 resection rates of metastases with the triplet among patients with CRLMs only (36% versus 12%). Moreover, PFS and OS were both significantly improved with FOLFOXIRI. These findings were not confirmed in a similar Greek phase III trial, which included PS2 patients.[132]

The addition to bevacizumab in both arms of the TRIBE phase III trial confirmed the higher efficacy of triple ChT backbone, with an improvement in PFS (median: 12.1 months in the triplet—bevacizumab group and 9.7 months with FOLFIRI—bevacizumab) and in the ORR (65% versus 53%).[46] Updated results confirmed a benefit in mOS.[133] Within molecular subtypes, the largest mOS was 37.1 months in the *RAS* and *BRAF* V600E-wt subgroup, while the *BRAF*-mutated group had the shortest survival with 13.4 months. Since no prospective trial has included comparison with an arm with FOLFOXIRI without bevacizumab, the contribution of bevacizumab is considered uncertain.

The TRIBE2 phase III study compared an upfront triplet (FOLFOXIRI) followed by a planned maintenance plus the reintroduction of the same regimen after disease progression, versus a sequence of mFOLFOX6 and FOLFIRI doublets, each of the ChT regimens in combination with bevacizumab. This approach favoured the triplet/maintenance/reintroduction strategy over sequential use for PFS2 (the interval between randomisation and the date of second progression). No interaction was observed between treatment effect and *RAS* and *BRAF* V600E mutational status as shown by the *post hoc* subgroup analyses of the TRIBE trial.[134]

Triplets including FOLFOXIRI should not be used in patients >75 years old, with PS2 or in patients with significant comorbidities. No phase III evidence supports the use of anti-EGFR mAbs in combination with triplets, as shown in the TRIPLETE trial,[135] despite the initial benefit in ORR in the VOLFI phase II trial.[136]

First-line therapy in dMMR/MSI-H disease. The activity of anti-programmed cell death protein 1 (PD-1) blockade immunotherapy has been demonstrated on mCRC patients with dMMR/MSI-H status. Phase II trials of nivolumab and pembrolizumab, PD-1 ICIs, in dMMR/MSI-H mCRC patients demonstrated benefit in this small patient subgroup.[137,138]

In a pivotal phase III trial, 307 previously untreated dMMR/MSI-H mCRC patients were randomised to receive pembrolizumab (administered until progression or up to a maximum of 2 years) or standard therapy (ChT plus targeted agents, according to investigator's choice). Pembrolizumab demonstrated improvement in the primary endpoint of PFS.[12] Although no significant differences in OS were observed, this may be due to the high percentage of crossover in the ChT arm (60% of patients progressing received an ICI). Treatment-related adverse events of grade ≥3 occurred less frequently with pembrolizumab (22%), compared with the ChT arm (66%). The QoL analysis also favoured the use of pembrolizumab.[139]

Maintenance therapy

The concept of maintenance treatment has significance for patients with disease not amenable for surgery or LT (see Figure 3). This describes de-escalation of treatment intensity, resulting in improved side-effects and QoL, without relevantly compromising therapeutic efficacy and disease control. This concept evolved from the need to limit the cumulative dose of oxaliplatin cycles, with accumulative neurotoxicity; at that point, the question arose of whether to maintain the remainder or some of the drugs, or completely stop therapy. Patient discussion is essential, explaining the benefits and risks of a maintenance approach.

Studies of maintenance strategies with continuation of fluoropyrimidines after induction ChT, or a complete ChT-free interval, showed contradictory results. In the MRC COIN trial, a combination of continuous oxaliplatin—fluoropyrimidine was compared with the same treatment followed by a ChT-free interval until progressive disease.[118,134] This trial failed to show non-inferiority of the intermittent ChT approach. The OPTIMOX1 trial suggested that a maintenance strategy with

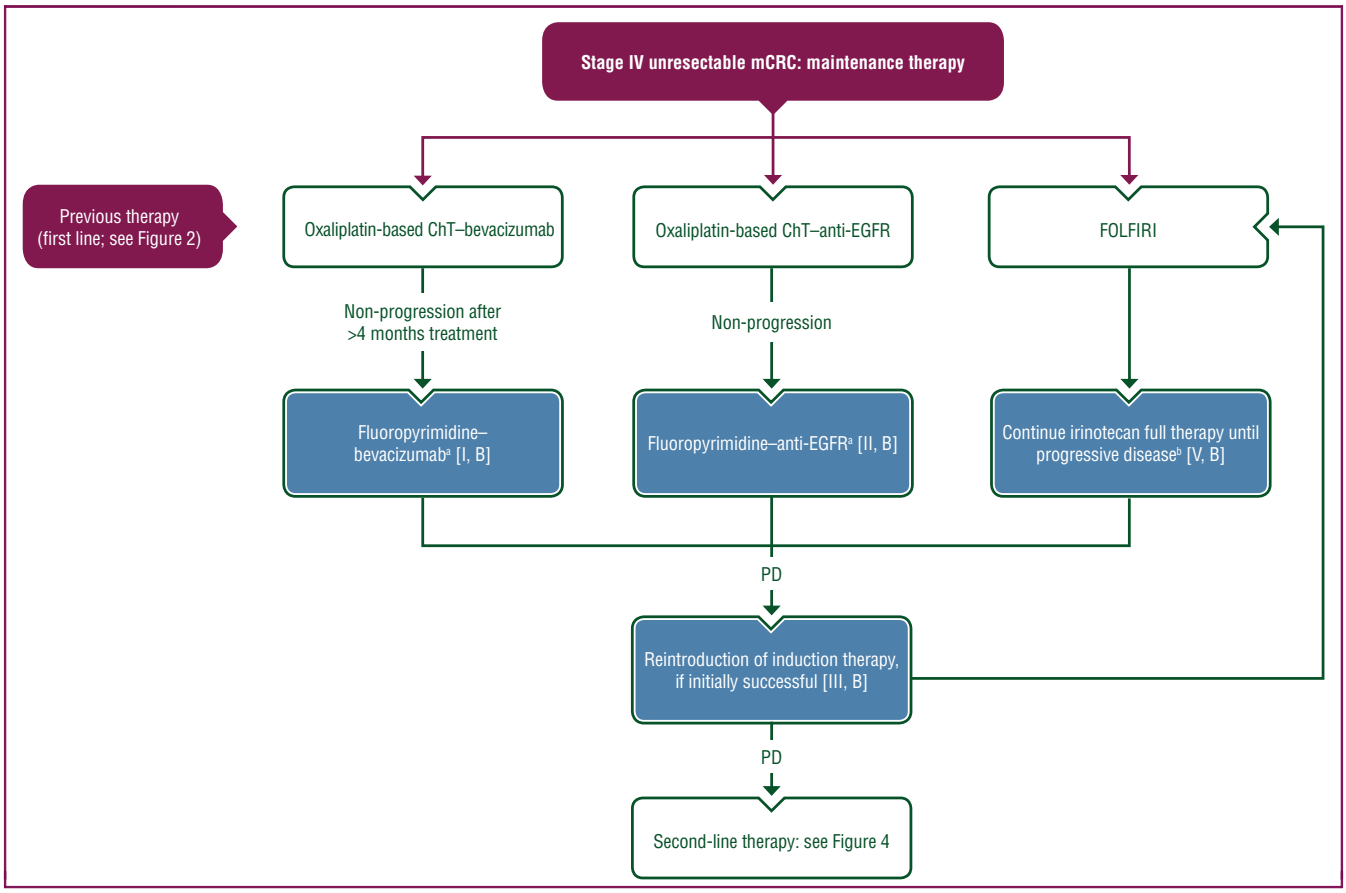

Figure 3. Management of stage IV unresectable mCRC with maintenance therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
5-FU, fluorouracil; ChT, chemotherapy; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin—5-fluorouracil—irinotecan, mCRC, metastatic colorectal cancer; PD, progressive disease; S-1, tegafur—gimeracil—oteracil.
[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
[b]Due to the lack of a cumulative toxicity of FOLFIRI.

fluoropyrimidines could be considered after induction ChT with FOLFOX. However, the OPTIMOX2 trial explored short induction FOLFOX7, followed by a maintenance strategy with 5-FU—LV or a ChT-free interval, confirming the negative impact of the ChT-free interval on the median duration of disease control and survival.[140]

The role of biologicals in maintenance strategies was tested. Bevacizumab maintenance was explored after first-line induction ChT—bevacizumab in the SAKK 41/06 and PRODIGE 9 phase III trials showing no differences in disease control duration, concluding that single-agent bevacizumab has no meaningful therapeutic value.[141,142] In the CAIRO3 study, maintenance treatment with capecitabine—bevacizumab was compared with a complete break, showing an improvement in the primary endpoint of PFS2.[143] In the AIO 0207 trial, after first-line induction with oxaliplatin-based ChT—bevacizumab, patients were randomly assigned to either maintenance with fluoropyrimidines—bevacizumab, bevacizumab alone or observation. The primary endpoint was to show non-inferiority for time to strategy failure with bevacizumab alone compared with fluoropyrimidine—bevacizumab.[144] Its results support fluoropyrimidine—bevacizumab as the preferable option. There are no phase III data to support maintenance treatment with anti-EGFR mAbs, although two phase II randomised trials have shown that maintenance with 5-FU—anti-EGFR is better than 5-FU or anti-EGFR alone.[145,146]

Second-line treatment

The benefit of delivering second-line treatment to fit patients with no significant comorbidities has been demonstrated in multiple trials. Proposed treatment strategies in the second line are shown in Figure 4. The ChT backbone depends mainly on the first-line treatment received. With first-line oxaliplatin-based therapy, second-line treatment with irinotecan with fluoropyrimidine or monotherapy would be advisable. Conversely, those treated with first-line irinotecan-based could receive oxaliplatin-based treatment (FOLFOX or CAPOX) in second line if no contraindications.

Anti-EGFR. The anti-EGFR mAbs cetuximab and panitumumab have demonstrated activity in the second-line (or later-line) treatment of mCRC in *RAS*-wt tumours, as single agents and in combination with ChT. The EPIC phase III trial

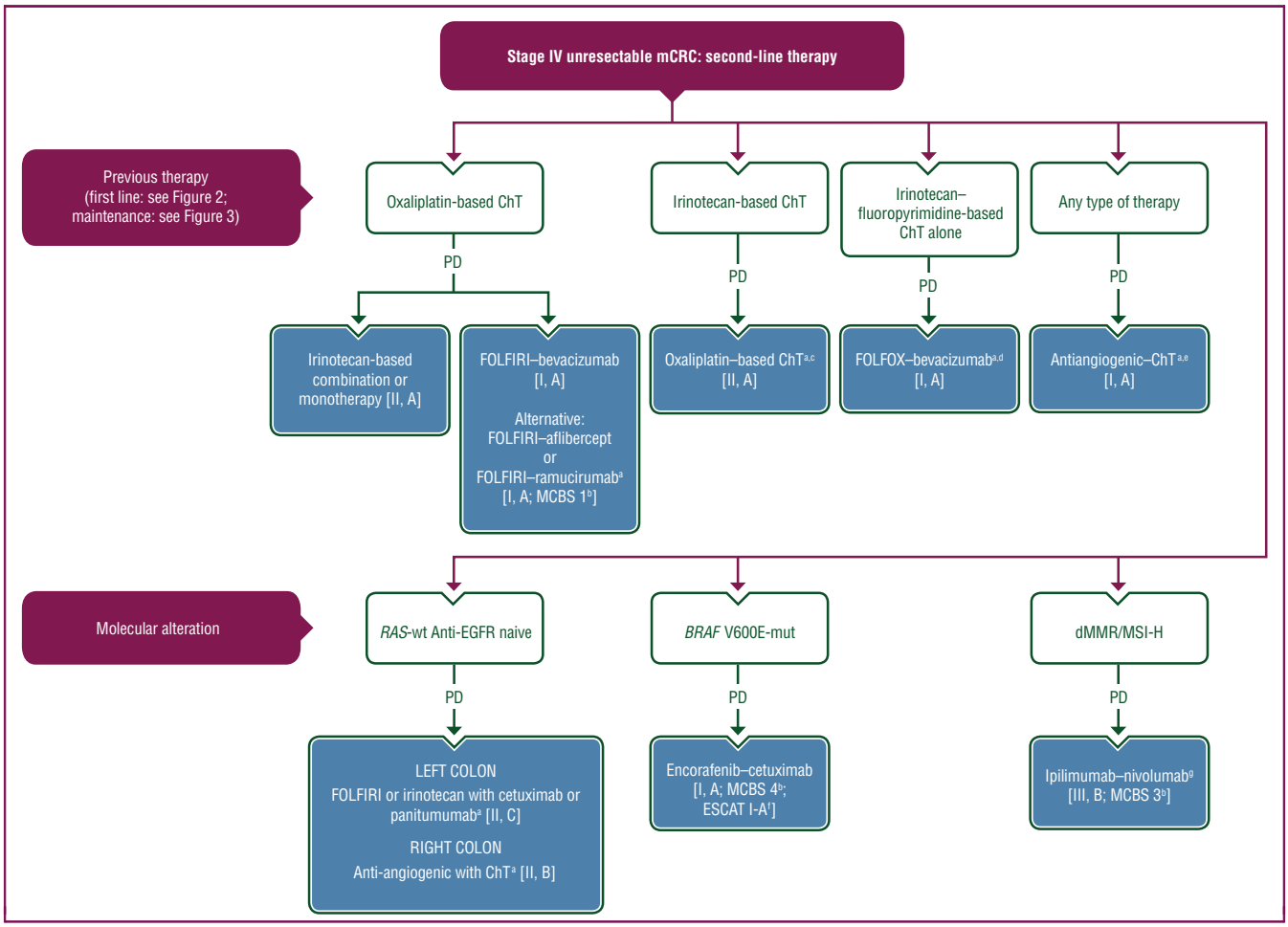

Figure 4. Management of stage IV unresectable mCRC in the second line. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

5-FU, fluorouracil; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; dMMR, deficient mismatch repair; 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; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; mut, mutant; PD, progressive disease; PTL, primary tumour location; S-1, tegafur—gimeracil—oteracil; wt, wild-type.

[a]In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].

[b]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

[c]FOLFOX or CAPOX, if no contraindications.

[d]Bevacizumab can be combined with ChT doublet (a fluoropyrimidine with oxaliplatin or irinotecan, depending on the first-line ChT backbone delivered) [I, A; ESMO-MCBS v1.1 score: 1].

[e]With or without previous first-line treatment with bevacizumab and independently of *RAS* mutational status and the PTL.

[f]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.

[g]Indicated for immunotherapy-naive patients.

explored second-line treatment with irinotecan, with or without cetuximab, in patients refractory to first-line oxaliplatin—fluoropyrimidine-based treatment.[147] While OS was not increased, almost half of the control arm received cetuximab post-progression and this addition of cetuximab improved PFS and RR.[147]

Second-line FOLFIRI with or without panitumumab was tested in a phase III trial.[148] In *KRAS*-wt patients, panitumumab significantly improved RR and PFS with a non-significant trend toward longer OS.

Anti-VEGF. In patients previously treated with irinotecan—fluoropyrimidine-based ChT alone, a combination of FOLFOX—bevacizumab demonstrated improved OS and PFS in a phase III trial in comparison with FOLFOX4.[149]

In patients previously treated with bevacizumab (in the first-line setting), maintaining bevacizumab in combination with second-line ChT (oxaliplatin or irinotecan-based, switching depending on the first-line treatment delivered) demonstrated improvement in the primary endpoint of OS.[150]

Aflibercept is a recombinant fusion protein that blocks the activity of VEGF-A and B, as well as placental growth factor, by acting as a high-affinity ligand trap. The VELOUR phase III trial reported improvement in OS and PFS with aflibercept in combination with FOLFIRI, in

mCRC patients previously treated with oxaliplatin, including the subgroup of patients previously treated with bevacizumab.[151]

The RAISE phase III trial tested ramucirumab, a human mAb that targets the extracellular domain of VEGF receptor 2, in combination with FOLFIRI in mCRC patients with disease progression during or after first-line therapy with bevacizumab—oxaliplatin—fluoropyrimidines.[152] A benefit in both OS and PFS was observed.

Each of these antiangiogenics in combination with ChT has demonstrated improved OS in the second-line treatment of mCRC, irrespective of the first-line treatment. In case of *RAS*-mutated tumours with a rapid progression while on bevacizumab first-line treatment, second-line therapy with ChT combined with aflibercept or ramucirumab could be considered, as those trials included patients with a rapid progression while on first-line treatment with bevacizumab.

In *RAS*-wt patients treated upfront with bevacizumab, second-line treatment with antiangiogenics or anti-EGFR mAbs combined with ChT are good options. Treatment with anti-EGFR mAbs can increase the RR, although the benefit is more extensive in left-sided tumours. In right-sided tumours a combination with ChT and an anti-VEGF could be a better option. The side-effects profile should also be considered in this decision. In dMMR/MSI-H tumours progressing after first-line ChT, the European Medicines Agency (EMA) approved the use of ipilimumab—nivolumab.[153]

BRAF V600E-mutated mCRC. As described, the presence of *BRAF* mutations is associated with a poor prognosis in mCRC, and current therapies have demonstrated less effectiveness in these patients. New strategies blocking the *BRAF* signalling pathway have shown preliminary activity.[154,155] A phase III study in *BRAF*-mutant patients progressing after first- or second-line treatment tested the combination of encorafenib (an oral *BRAF* V600E inhibitor), with binimetinib and cetuximab.[156] Patients were randomly assigned (1 : 1 : 1) to receive encorafenib—cetuximab with or without binimetinib (doublet or triplet) versus ChT (FOLFIRI or irinotecan) plus cetuximab. OS was significantly superior in the experimental arms, either doublet or triplet, compared with standard of care. The mOS was 9.3 months in the experimental arms and 5.9 months in the control group. A confirmed significantly better ORR was reported as 26.8% in the triplet arm, 19.5% in the doublet, versus 1.8% in the control group. The QoL was not deteriorated in the experimental arm and grade $\geq$3 adverse events reported were higher in the standard arm (61%) compared with the doublet (50%) or triplet treatment (58%). This study led to the approval of encorafenib—cetuximab for *BRAF* V600E pre-treated mCRC; further studies are ongoing to test this combination in early phases of metastatic disease. Patients with *BRAF*-mutant tumours and MSI-H status, who are receiving first-line immunotherapy, could also benefit from encorafenib—cetuximab upon progression.

Third- and further-line treatment

Proposed treatment strategies for third and further lines are shown in Figure 5.

Reintroduction of the initial induction therapy can be considered after second-line therapy, in patients who did not progress during the course of first-line ChT.

Anti-EGFRs. Both cetuximab and panitumumab as single agents have demonstrated activity in mCRC after previous treatment with standard ChT. In comparison with best supportive care (BSC), cetuximab monotherapy improved OS and PFS, whilst preserving QoL with less deterioration in physical function and global health status scores.[110] Panitumumab was also compared with BSC in mCRC patients who had been previously treated with standard ChT, showing an increase in PFS and ORR. No difference in OS was observed, probably due to crossover.[109] This benefit in PFS as well as in OS was observed only in the *KRAS*-wt population for both cetuximab and panitumumab.[3,4] In *RAS*-wt patients not previously treated with anti-EGFR mAbs, in the third or further lines, a combination of irinotecan—cetuximab was superior to cetuximab monotherapy in ORR and PFS, but not in OS. Therefore, a combination of irinotecan—cetuximab can be used in this setting.[157] Similarly, rechallenge with anti-EGFR mAbs has shown initial good outcomes in *RAS*-wt patients according to liquid biopsy testing in small non-randomised studies.[158,159]

Regorafenib. Regorafenib is an oral multikinase inhibitor that demonstrated activity in refractory mCRC in a phase III placebo-controlled trial, showing an increase in mOS and PFS over BSC.[160] Another phase III trial confirmed a benefit on OS with regorafenib in comparison with placebo. The most common grade $\geq$3 adverse events were hand-foot syndrome, hypertension, fatigue, diarrhoea, hyperbilirubinaemia, increased liver enzymes and rash.[161] This treatment could be a possibility in fit patients with refractory disease after standard ChT with 5-FU—irinotecan—oxaliplatin, with or without anti-VEGF therapies or anti-EGFR mAbs.

Trifluridine—tipiracil (TAS-102). TAS-102 is an oral agent that combines trifluridine, a thymidine-based nucleoside analogue, with tipiracil hydrochloride, a novel thymidine phosphorylase inhibitor that improves the bioavailability of trifluridine. TAS-102 has demonstrated improved PFS and OS in refractory mCRC in a phase III trial.[162] The most frequently observed adverse events are neutropaenia and leukopaenia and, much less frequently, febrile neutropaenia. A similar phase III trial confirmed a longer mOS and a lower risk of death for those patients treated with TAS-102 compared with placebo.[163]

HER2-positive mCRC. Amplification of HER2 is a rare condition in mCRC. Therapies with HER2 blockade have shown significant antitumour activity: a dual blockade of HER2 with a combination of trastuzumab, an anti-HER2 mAb and the tyrosine kinase inhibitor lapatinib, in a population of patients with *KRAS* exon 2-wt and HER2-positive mCRC

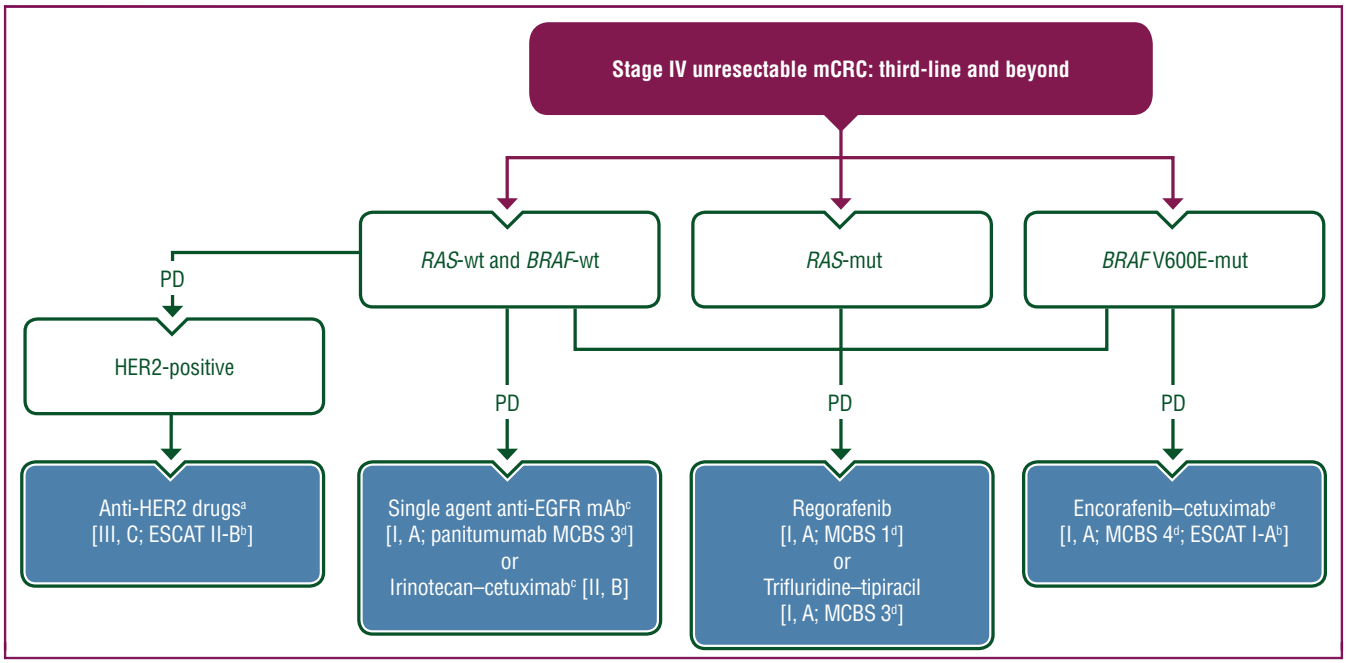

Figure 5. Management of stage IV unresectable mCRC in third-line therapy and beyond. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.
EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mCRC, metastatic colorectal cancer; mut, mutant; PD, progressive disease; wt, wild-type.
[a]For a summary of recommended anti-HER2 regimens for mCRC see Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.10.003.
[b]ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] See Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003, for more information on ESCAT scores.
[c]In *RAS*-wt patients not previously treated with anti-EGFR monoclonal antibodies.
[d]ESMO-MCBS v1.1[165] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[e]Treatment for *BRAF*-mut patients if not used in the second line.

refractory to standard of care, led to an ORR (partial or complete) of 30%, and disease stability in an additional 44% of patients.[14] A summary of HER2 blockade studies is provided in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2022.10.003.

Recommendations

First-line therapy

- Determining the *RAS* mutational status on a tumour biopsy [I, A] (or through a liquid biopsy in case no tumour sample is available [II, B]) is mandatory to guide the best treatment decision.
- Delivering a biological therapy in combination with ChT in the first-line setting is recommended, unless contraindicated [I, A].
- In the majority of patients, first-line treatment will consist of a doublet of ChT (FOLFOX, FOLFIRI, CAPOX) that can be combined with an anti-VEGF or anti-EGFR mAb [I, B; for FOLFIRI—cetuximab ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 4; FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; modified FOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3].
- In *RAS*-wt and *BRAF*-wt left-sided tumours, doublet ChT plus an anti-EGFR mAb is the preferred option [I, A]. Due to increased side-effects and lack of efficacy, combination with cetuximab—capecitabine or bolus 5-FU-based ChT is not recommended [I, E].
- In *RAS*-wt right-sided tumours, ChT ± bevacizumab is the preferred option [II, B]; although in cases in which a higher response is needed for conversion therapy, a doublet with cetuximab or panitumumab can be used [II, C].
- Anti-EGFR mAbs can be combined with the doublets FOLFOX or FOLFIRI [I, A; FOLFOX4—panitumumab ESMO-MCBS v1.1 score: 4; modified FOLFOX6—panitumumab ESMO-MCBS v1.1 score: 3; for FOLFIRI—cetuximab ESMO-MCBS v1.1 score: 4].
- Bevacizumab can be combined with single fluoropyrimidines, irinotecan or oxaliplatin-based doublet of ChT (FOLFOX, CAPOX, FOLFIRI) or triplets (FOLOXIRI) [I, B].
- Combining anti-VEGF plus anti-EGFR mAbs is not recommended [I, E].
- A triplet with FOLFOXIRI plus bevacizumab could also be an option for selective patients with good PS and without comorbidities [I, B; ESMO-MCBS v1.1 score: 2]. Triplets including FOLFOXIRI should not be used in patients >75 years old, with PS2 or in patients with significant comorbidities [IV, E].
- In selected cases, when downstaging is the objective or in right-sided colon cancer with *BRAF* V600E mutations,

a triplet (FOLFOXIRI), which can be combined with bevacizumab, should be considered, but a doublet plus bevacizumab could provide similar outcomes [II, B].
- Triplets with FOLFOXIRI and anti-EGFR mAbs are not recommended [I, D].
- In patients with comorbidities, older age or with metastatic disease not amenable to a curative treatment strategy and no significant disease-related symptoms, monotherapy with a fluoropyrimidine ± bevacizumab can be used [I, B]. In frail or elderly patients unable to tolerate ChT, whose tumours are left-sided and *RAS*-wt, monotherapy with anti-EGFR mAbs can be considered [IV, C].
- In patients presenting with cardiotoxicity and/or hand-foot syndrome on 5-FU or capecitabine-based ChT, S-1 may be used as an alternative [III, B].
- Patients should receive all available treatments during the course of the disease [I, B].
- In dMMR/MSI-H mCRC patients, the ICI pembrolizumab has demonstrated benefit over standard ChT and targeted agents, in the first-line setting and it is recommended as standard of care [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].

Maintenance therapy

- After first-line therapy with ChT based on oxaliplatin—bevacizumab, maintenance therapy with a fluoropyrimidine and bevacizumab could be considered in non-progressive patients after at least 4 months of treatment [I, B].
- After first-line therapy with ChT based on oxaliplatin plus anti-EGFR mAbs, maintenance therapy with a fluoropyrimidine plus anti-EGFR mAbs could be considered in non-progressive patients [II, B].
- When FOLFIRI is used in first-line treatment, due to the lack of a cumulative toxicity, we should continue irinotecan full therapy until progressive disease [V, B].
- Reintroduction of an initial successful induction therapy should be done after progressive disease while on maintenance therapy [III, B].

Second-line treatment

- In patients treated with first-line oxaliplatin-based therapy, second-line treatment with irinotecan-based or monotherapy is recommended. On the contrary, those patients treated with irinotecan-based in first line could receive an oxaliplatin-based treatment (FOLFOX or CAPOX) in second line if no contraindications [II, A].
- In *RAS*-wt patients not previously treated with an anti-EGFR mAb, treatment with ChT (FOLFIRI or irinotecan) and cetuximab or panitumumab could be considered for left-sided colon tumours [II, C]. For right-sided tumours, second-line therapy with an anti-angiogenic combined with ChT is recommended [II, B].
- In patients previously treated with irinotecan—fluoropyrimidine-based ChT alone, a combination of FOLFOX—bevacizumab is recommended [I, A].
- A second-line treatment with an antiangiogenic combined with ChT, regardless of whether the first-line treatment included bevacizumab or not, should be used, independently of the *RAS* mutational status and the PTL [I, A].
- Bevacizumab can be combined with a fluoropyrimidine-doublet with oxaliplatin or irinotecan, depending on the first-line ChT backbone delivered [I, A; ESMO-MCBS v1.1 score: 1].
- Aflibercept or ramucirumab in combination with FOLFIRI could be used as an alternative to bevacizumab with FOLFIRI in patients progressing on first-line treatment with oxaliplatin-based ChT [I, A; ESMO-MCBS v1.1 score: 1].
- For *BRAF* V600E-mutated, pre-treated mCRC patients, encorafenib—cetuximab is recommended as the best option in second line [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- For dMMR/MSI-H tumours progressing after first-line ChT, ipilimumab—nivolumab is recommended [III, B; ESMO-MCBS v1.1 score 3].

Third- and further-line treatment

- Reintroduction of the initial induction therapy can be considered after second-line therapy, as long as the patient did not progress during the induction course of first-line ChT [III, B].
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals [I, A, ESMO-MCBS v1.1 score: 1].
- Trifluridine—tipiracil is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan and biologics, if available, or in earlier lines of therapy following oxaliplatin and irinotecan regimen failure, depending on local approvals [I, A; ESMO-MCBS v1.1 score: 3].
- For *BRAF* V600E-mutated, pre-treated mCRC patients, encorafenib—cetuximab is recommended as the best option in third line [I, A; ESMO-MCBS v1.1 score: 4; ESCAT: I-A].
- In *RAS*-wt and *BRAF*-wt patients not previously treated with EGFR antibodies, cetuximab and panitumumab are recommended as single agents [I, A; panitumumab ESMO-MCBS v1.1 score: 3].
- In irinotecan-refractory patients, cetuximab—irinotecan is recommended over cetuximab alone [II, B].
- Administering an alternative anti-EGFR antibody, if a patient is refractory to one of the other anti-EGFR antibodies, is not recommended [I, E].
- In patients maintaining *RAS*-wt status, rechallenge with anti-EGFR mAbs may be an option in selected patients [III, C].
- In HER2-positive patients with mCRC, treatment with HER2 dual blockade is optionally recommended, especially in *RAS*-wt tumours [III, C; ESCAT: II-B].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

The survivorship goals include physical evaluation and management of the long-term toxicities related to surgery, LTs, ChT, targeted agents or immunotherapy. If the patient is receiving an active treatment, radiological evaluation should be carried out every 8-12 weeks, including (in most cases) CT scan or MRI, as well as the measurement of CEA levels. Patients with a radically resected metastatic disease with potential for cure may initially merit more intense monitoring with radiological assessment with CT (or MRI) and measurement of CEA levels every 3 months during the first 2 years and every 6 months thereafter.[19]

Recommendations

- For patients receiving active treatment, radiological evaluation should be carried out every 8-12 weeks, including (in most cases) CT scan or MRI, as well as the measurement of CEA levels [IV, B].
- Patients with a radically resected metastatic disease with potential for cure merit more intense monitoring initially with radiological assessment with CT (or MRI) and measurement of CEA levels every 3 months during the first 2 years and every 6 months thereafter [I, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.10.003. ESCAT scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[164] A table of ESMO-MCBS scores is included in Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2022.10.003. ESMO-MCBS v1.1[165] was used to calculate scores for new therapies/indications approved by the EMA or the Food and Drug Administration (FDA) (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2022.10.003.[166,167] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/gastrointestinal-cancers/metastatic-colorectal-cancer.

ACKNOWLEDGEMENTS

Manuscript editing support was provided by Claire Bramley, Catherine Evans and Richard Lutz (ESMO Guidelines staff). Nathan Cherny, Chair of the ESMO-MCBS Working Group, Urania Dafni and Giota Zygoura of Frontier Science Foundation Hellas provided review and validation of the ESMO-MCBS scores. Nicola Latino (ESMO Scientific Affairs staff) provided coordination and support of the ESMO-MCBS scores and Angela Corstorphine of Kstorfin Medical Communications Ltd. provided medical writing and editing support in the preparation of the ESMO-MCBS table; this support was funded by ESMO. Dr Benedikt Westphalen and Dr Noelia Tarazona (members of the ESMO Translational Research and Precision Medicine Working Group) and Dr Svetlana Jezdic (ESMO Medical Affairs Advisor) provided validation support for ESCAT scores.

FUNDING

No external funding has been received for the preparation of this guideline. Production costs have been covered by ESMO from central funds.

DISCLOSURE

AC reports fees paid to his institution as an invited speaker from Amgen, Foundation Medicine, Merck Serono and Roche; fees paid to his institution for advisory board membership from Amgen, AnHeart Therapeutics, Merck Serono, Roche and Transgene; personal fees for editorial roles as Associate Editor for Annals of Oncology and ESMO Open and as Editor for Cancer Treatment Reviews; institutional funding as principal investigator (PI) from Actuate Therapeutic, Adaptimmune, Amcure, Amgen, Astellas, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb (BMS), FibroGen, Genentech, Lilly, MedImmune, Merck Serono, Merck Sharp & Dohme (MSD), Natera, Novartis, Servier, Sierra Oncology and Takeda; he reports a non-remunerated role as General and Scientific Director of INCLIVA Biomedical Research Institute. RA reports personal fees as an invited speaker from Merck Serono and Sanofi. SR reports personal fees as an invited speaker from Amgen, MSD and Servier; personal fees for advisory board membership from Amgen, Servier and Sirtex; institutional funding as a local PI from Ability Pharmaceuticals, Astellas, G1 Therapeutics, Hutchinson, Menarini, Mirati, Novartis, Pfizer, Pierre Fabre, Roche and Seagen. DA reports personal fees as an invited speaker from Amgen, AstraZeneca, Boston Scientific, BMS, Ipsen, Merck Serono, MSD, Pierre Fabre, Roche, Samsung Bioepis, Sanofi (Genzyme), Servier and Terumo; personal fees as an invited speaker and continued medical education (CME) provider from ACE Oncology, Aptitude Health, Art Tempi Media, Clinical Care Options, From Research to Practice, Imedex, MedAhead (Austria), PRMA Consulting, Streamitup (Germany), Tactic MD LLC, WebMD Health Corp; personal fees for advisory board membership from AstraZeneca, Boston Scientific, BMS, CRA International, Ketchum, MSD, Pierre Fabre, Samsung Bioepis, Sanofi (Genzyme) and

Terumo; personal fees for advisory board membership, CME provider and App producer from onkowissen; personal fees for editorial roles as an Associate Editor for Annals of Oncology, ESMO Open and Clinical Colorectal Cancer; institutional funding from AbbVie and as a local PI from BMS and Pierre Fabre, as a coordinating PI from OncoLytics and as a Steering Committee member from Roche; he reports fees paid to his institution as Chair of the Data Safety Monitoring Board from Sanofi (Genzyme); non-remunerated activities as a project lead with OncoLytics, member of the American Society of Clinical Oncology (ASCO), the Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO), European School of Oncology (ESO) and a leadership role and Steering Committee membership with the Arbeitsgemeinschaft Internistische Onkologie in der Deutschen Krebsgesellschaft (AIO) and European Organisation for Research and Treatment of Cancer (EORTC) gastrointestinal group. NN reports personal fees as an invited speaker from Eli Lilly, Illumina, Merck, MSD and Thermo Fisher; personal fees for advisory board membership from Amgen, AstraZeneca, Bayer, Biocartis, Incyte, Novartis and Roche; institutional funding from AstraZeneca, Biocartis, Blueprint, Illumina, Incyte, Merck, Qiagen, Roche and Thermo Fisher; and non-remunerated activities as President of International Quality Network of Pathology (IQN Path) and President of the Società Italiana di Cancerologia (SIC). JT reports personal fees as an invited speaker and for advisory board membership from Amgen, BMS, Merck, MSD, Novartis, Pierre Fabre, Roche and Servier; non-remunerated activities as Chair of the Aide et Recherche en Cancérologie Digestive (ARCAD) Foundation pancreas research group, president of the scientific committee for the ARCAD foundation and as member of the administrative council, scientific committee, executive board responsible for international relationships/partnerships for the Federation Francophone de Cancerologie Digestive (FFCD) in the PRODIGE Intergroup for the FFCD. JS reports personal fees as an invited speaker from Merck Serono, Pierre Fabre and Servier; personal fees for advisory board membership from Pierre Fabre, Ventana and Zentalis; personal fees for consultancy and review of guidelines from Roche Diagnostics; personal fees for CME activities from GI Connect; personal fees for expert testimony from Seagen; personal fees for travel expenses from BMS and Servier; institutional funding from Pierre Fabre. TDB reports personal fees as an invited speaker from Boston Scientific and GE Healthcare; personal fees for advisory board membership from Guerbet, Quantum Surgical and Terumo; institutional funding from Quantum Surgical and Terumo. PO reports personal fees as an invited speaker from BMS Eisai, Fresenius Kabi, Nordic Drugs, Novartis, Nutricia, Roche and Servier; personal feels for advisory board membership from Amgen, AstraZeneca, Bayer, Daiichi Sankyo (in collaboration with AstraZeneca), Eisai, Incyte, Merck, MSD, Pierre Fabre, Roche, Sanofi and Sobi; and personal fees for expert testimony for the Finnish Medicines Agency from BMS; she reports institutional funding for research grants from Amgen and Servier; as a local PI from Incyte and as a coordinating PI from Pfizer and Roche; she reports non-remunerated activities as a member of the Colores patient advocacy group and as a Board Member of the Finnish Cancer Society. TY reports personal fees as an invited speaker from Bayer, Chugai, Merck Biopharma, MSD and Ono; institutional funding from Amgen, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Genomedia, MSD, Ono, Sysmex and Taiho and as a local PI from Chugai, Daiichi Sankyo, Ono, Pfizer and Sanofi. EM reports personal fees as an invited speaker from Bayer, ESMO, Incyte, Merck S.p.A., Merck Serono, Pierre Fabre, Roche and Servier; personal fees for writing engagements from AstraZeneca, Incyte, MSD, Pierre Fabre, Roche and Servier; personal fees for advisory board membership from Amgen, Incyte, MSD, Pierre Fabre, Roche and Servier.

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