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# ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

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## Abstract

Colorectal cancer (CRC) is one of the commonest malignancies in Western countries. Over the last 20 years, and the last decade in particular, the clinical outcome for patients with metastatic CRC (mCRC) has improved greatly due not only to an increase in the number of patients being referred for and undergoing surgical resection of their localised metastatic disease but also to a more strategic approach to the delivery of systemic therapy and an expansion in the use of ablative techniques. This reflects the increase in the number of patients that are being managed within a multidisciplinary team environment and specialist cancer centres, and the emergence over the same time period not only of improved imaging techniques but also prognostic and predictive molecular markers. Treatment decisions for patients with mCRC must be evidence based. Thus, these ESMO consensus guidelines have been developed based on the current available evidence to provide a series of evidence-based recommendations to assist in the treatment and management of patients with mCRC in this rapidly evolving treatment setting.

## Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Europe and a leading cause of death both in Europe and worldwide [1, 2]. In 2012 there were 447,000 new cases of CRC in Europe with 215,000 deaths and worldwide there were 1.4 million new cases with 694,000 deaths. Over the last decade in particular, the clinical outcome for patients with metastatic CRC (mCRC) has improved. Today, the median overall survival (OS) for patients with mCRC being treated both in phase III trials and in large observational series or registries, is about 30 months and more than double that of 20 years ago.

However, it is unclear which improvements and strategic changes in the treatment and management of patients with mCRC in recent years have been responsible for the improved treatment outcomes for these patients. Factors which may have contributed are:

a) Changes in the clinical presentation of patients, prior to the commencement of treatment, due to closer follow-up after resection of the primary tumour and earlier detection of metastatic disease

b) Improvements in the efficacy of systemic therapies in terms of regimens used, sequence of administration, number of lines of therapy administered and biomarker-based patient selection

c) An increase in the number of patients being treated with a view to facilitating resection of their metastases, offering an increased number of patients the chance of cure and/or durable relapse-free survival and, more recently, the utilisation of other ablative therapy techniques with the aim of achieving the same outcome

d) Implementation of “continuum of care” treatment strategies coupled with the early integration of optimal supportive care measures.

These ESMO Consensus Guidelines therefore aim to reflect the diagnostic, therapeutic and strategic improvements which have contributed to the current “state-of-the-art” treatment approaches and to provide guidance for the comprehensive management of patients with mCRC going forward.

### Methodology

In 2014, the ESMO Guidelines Committee decided to update the clinical recommendations for mCRC using a consensus conference approach. An international panel of experts in the management of patients with CRC, from a range of diagnostic and therapeutic disciplines, was convened in Zurich in December 2014 to update the existing ESMO Consensus Guidelines for the management of patients with colon and rectal cancer [3]. A set of pre-formulated topics was prepared and three working groups convened in the areas of:

a) Molecular pathology and biomarkers

b) Local and ablative treatment [LAT] (including surgery and the management of patients with oligometastatic disease [OMD])

c) The treatment of metastatic disease.

Each panel member was assigned to one of the above working groups. Three consensus conference chairs (E Van Cutsem, A Cervantes, and D Arnold) were also appointed. Prior to the consensus conference clinically-relevant questions were identified for each working group. Each working group was responsible for reviewing relevant literature in order to draft preliminary recommendations relating to each of their assigned questions. No systematic literature search was undertaken. The experts in each group were invited to submit their recommendations in advance to structure the on-site discussions. During the conference, in parallel sessions, the three working groups discussed and reached agreement on recommendations relating to each of their assigned questions. Recommendations from each group were then presented to the entire panel of experts, where they were discussed and modified as required until consensus was reached.

An adapted version of the 'Infectious Diseases Society of America-United States Public Health Service Grading System' was used (**Table 1,** [4]) to define the level of evidence and strength of each recommendation proposed by the group, as for all of the ESMO Consensus and ESMO Clinical Practice Guidelines, and are given in the text in square brackets. Statements made based on expert opinion were also considered to be justified standard clinical practice by the experts and the ESMO faculty. These ESMO Consensus Guidelines follow on from those published in 2012 [3] and should be used to support the 2014 ESMO Clinical Practice Guidelines [5].

## Molecular pathology and biomarkers

A clinical or biological suspicion that a patient may have mCRC should always be confirmed by adequate radiological imaging, and the histology of the primary tumour or metastases, as appropriate, conducted prior to the commencement of systemic therapy, as described previously [5]. Tissue samples will typically range from large tumour samples to smaller biopsy/endoscopy samples. Whenever possible, any diagnostic biopsy or tissue sampling procedure should aim to maximise the number of samples collected (ideally n = 10 biopsies). In addition to samples taken for embedding, additional frozen material should be collected to provide the opportunity for future 'new' tests to be conducted on frozen tissue if required. It is also essential that all tissue and biopsy samples are handled appropriately in order to facilitate meaningful and accurate molecular testing.

### Tissue handling

Standardisation of tissue processing for patients with mCRC still remains a challenge. The time from tissue sampling to fixation should be minimised to only a few minutes if possible, to prevent any degradation of proteins and nucleic acids that might occur during cold ischaemia [6, 7]. Fixation in 10% neutral buffered formalin (4% formaldehyde solution), which is widely available, is generally compatible with any procedure for protein, RNA and/or DNA biomarker analysis. The fixation time should be between 6 and 48 hours [8]. Longer or shorter fixation times may adversely affect biomarker testing, whilst under-fixation is also associated with poor tissue morphology [9]. Acidic fixatives (e.g. Bouin) are not recommended since they lead to the rapid degradation of nucleic acids [10]. Similarly, accelerated fixation with heated formalin is discouraged as it degrades tissue morphology and affects the results of molecular studies [11]. Biomarker analyses should be carried out within 4–6 weeks of the sections being cut, as ageing of formalin-fixed, paraffin-embedded tissue sections causes the degradation of both epitopes and DNA [12].

*Recommendation 1: Tissue handling*

- Fixation with 10% neutral buffered formalin (4% formaldehyde) is recommended [V, A].
- Fixation time should be no less than 6 hours, and no greater than 48 hours in duration. In the case of microwave-enhanced fixation the quality of both nucleic acids and proteins must be verified [IV, A].
- Sections for biomarker testing should ideally be cut immediately prior to analysis [IV, A].

### Selection of specimens for biomarker testing

The pathologist plays a central role in biomarker testing and can either perform the biomarker tests at his/her laboratory if it has been accredited for biomarker testing, or send the tissue block to an accredited reference laboratory for external testing. In both instances, the primary pathologist should review the available material for each patient and choose the most appropriate block to be used for testing. The pathologist should also ensure that the tissue block selected for biomarker analysis contains a sufficient quantity of neoplastic cells for the analysis [13]. This is particularly crucial for DNA- or RNA-based biomarker

testing, such as *RAS* mutation analysis, because a low fraction of neoplastic cells can lead to dilution of mutant alleles and false negative results [14, 15]. To evaluate the tumour content of the sample, it is recommended that the pathologist assesses a haematoxylin and eosin-stained section of the paraffin block designated for DNA extraction and mutation analysis prior to DNA extraction. The minimum fraction of tumour versus non-tumour cells required will depend on the genotyping method. It has been demonstrated that a tumour cell content of 30% or less might lead to false negative results when a technique with low sensitivity such as Sanger sequencing is used for testing [16, 17]. A neoplastic cell content of at least 50% is therefore recommended when using a technique with low sensitivity. Sections of tissue with high tumour content may be used directly. In samples with a low tumour cell content, and where feasible, suitable areas identified by the pathologist may be scraped (manual macro-dissection) from the tissue slide(s) in order to enrich the tumour cell content. Laser capture micro-dissection can also be used, but this technology is not widely available, and requires the skills of a pathologist, additional work and, therefore, high costs.

*Recommendation 2: Selection of specimens for biomarker testing*

- The primary pathologist should review all available tumour specimens to select those that are most suitable for biomarker analyses [IV, A].
- Enrichment of samples by macro-dissection to maximise tumour cell content (>50%) prior to DNA extraction is recommended [III, A].

**Tissue selection for biomarker testing**

Most patients undergo surgery of their primary tumour, although in some cases only an endoscopic biopsy of the primary is performed. Thus, archival samples of primary tumour tissue are usually available for biomarker testing for the majority of patients with advanced or mCRC. However, for the approximately 20% of patients who present with metastatic disease, archival material from their primary tumour will not always be available. For these patients, biomarker testing is usually performed using specimens obtained from primary tumour biopsies or the metastatic tumour, for example from resected liver metastases or positive lymph nodes. For some patients, both the primary tumour and metastatic tissue specimens may be available for mutation testing. Indeed, a number of studies have addressed the concordance in *KRAS* mutation status between primary colorectal tumours and their metastases with conflicting results. While some studies have failed to find any difference in *KRAS* mutation status between the primary tumours and their metastases [18-22], others have reported discordant results in 4%–32% of the patients [23-35]. However, many of these studies involved the analysis of small numbers of samples, involving heterogeneous metastatic sites and the use of techniques with low sensitivity that might have led to false negative results if adequate enrichment of the tumour cells was not performed. In a large study of 305 matched primary colorectal tumours and liver metastases, the discordance rate was 3.6% [36]. When these data are pooled with results from different previous small studies, the overall rate of discordance is approximately 5% for liver metastases. In contrast, a discordance rate of 25% has been described for lymph node metastases. Although these data are limited to *KRAS* exon 2 mutations, they can be extrapolated to situations where expanded *RAS* analysis has been conducted (see below), for which no information is available. Based on this evidence, tissue from either a patient's primary tumour or a liver metastasis may be used for *RAS* mutation testing. Lymph node metastases do not seem to be suitable for the determination of the *RAS* mutation status of colorectal tumours. In patients for whom both primary tumour and metastases are available, testing of a sample from either site is sufficient.

*Recommendation 3: Tissue selection*

- Tissue from either the primary tumour or a liver metastasis may be used for *RAS* mutation testing [III, A].
- Other metastatic sites such as lymph node or lung metastases may be used only if primary tumour or liver metastases samples are not available [II, B].

**Definition and validation of biomarkers**

Biomarkers can be diagnostic, predictive or prognostic. Ideally a biomarker should only serve one of these purposes, but there are good and clinically relevant examples of prognostic biomarkers that predict a response to a specific therapy, for example human epidermal growth factor receptor 2 (HER2) in breast cancer and *BRAF* (strongly prognostic and, to a lesser extent, predictive) in CRC [37-39]. It is also essential to follow strict rules for the development and validation of biomarkers that are specific to the purpose and sometimes also specific to the nature of each biomarker. Establishing clinical utility in the appropriate clinical setting is essential [40].

***RAS* testing**

*Evidence that tumour RAS mutational status is predictive*

Retrospective analyses of pivotal clinical trials for the epidermal growth factor receptor (EGFR) monoclonal antibodies, cetuximab and panitumumab, have shown that patients with mCRC whose tumours contain activating mutations in *KRAS* exon 2 (codons 12/13), do not derive a benefit from EGFR monoclonal antibody therapy [41-47]. Furthermore, recent evidence from the PRIME study with panitumumab [48], from the CRYSTAL study with cetuximab [49] and from other studies of EGFR monoclonal antibody therapies has shown that mutations other than those in *KRAS* exon 2 (i.e. exons 3 and 4 of *KRAS* and exons 2, 3 and 4 of *NRAS* [expanded *RAS* analysis]) also predict a lack of response to EGFR-targeting monoclonal antibodies and that these therapies may in fact have a detrimental effect in patients with *RAS*-mutant disease, specifically when combined with an oxaliplatin-based cytotoxic backbone [48-54].

In the PRIME study, in which patients were randomised to receive panitumumab plus FOLFOX4 (infusional 5-fluorouracil [5-FU], leucovorin, oxaliplatin) versus FOLFOX4 alone first-line, additional *RAS* mutations were detected in the tumours of 17% of patients with mCRC originally classified as *KRAS* exon 2 wild-type. These patients also failed to benefit from panitumumab therapy, and had inferior progression-free survival (PFS) and OS times compared with those treated with FOLFOX4 alone (not statistically significant). In fact this study was the first to hint at a detrimental effect of panitumumab in patients whose tumours carried *RAS* mutations at sites other than *KRAS* exon 2 [48].

Conversely, those patients whose tumours did not have *RAS* mutations at the tested sites had significantly better outcomes from the addition of panitumumab to FOLFOX4 than those patients whose tumours contained *RAS* mutations. The phase II PEAK study that evaluated FOLFOX6 plus panitumumab versus FOLFOX6 plus bevacizumab in untreated patients with *KRAS* exon 2 wild-type mCRC, supported these findings. Patients with *KRAS* and *NRAS* exon 2, 3 and 4 wild-type mCRC treated with FOLFOX6 plus panitumumab achieved a better PFS than those treated with FOLFOX6 plus bevacizumab and a trend towards improved OS was also observed [53]. Using next-generation sequencing [NGS] techniques, investigators analysed tumour samples previously assessed for *KRAS* exon 2 codon 12 and 13 mutations from patients enrolled in the phase III 20020408 trial of panitumumab in patients with chemorefractory mCRC [52] for additional *RAS*-activating mutations. Patients with *RAS* wild-type tumours achieved an overall response rate (ORR) with panitumumab of 15% compared with 1% for those patients with *RAS*-mutant tumours.

These findings with panitumumab have been upheld by trials evaluating cetuximab. Using sensitive BEAMing (Beads, Emulsions, Amplification, and Magnetics) technology, *KRAS* exon 2 wild-type tumours from the pivotal CRYSTAL and OPUS studies were retrospectively evaluated for mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2, 3 and 4 [49, 50]. In the phase III CRYSTAL study, which randomised patients to receive first-line FOLFIRI (infusional 5-FU, leucovorin, irinotecan) with or without cetuximab, other *RAS* mutations were detected in nearly 15% of evaluable patients previously assessed to be *KRAS* exon 2 wild-type. Similarly, in the phase II OPUS study, which randomised patients to receive first-line FOLFOX4 with

or without cetuximab, mutations at other *RAS* loci were detected in 31% of evaluable tumours previously assessed to be *KRAS* exon 2 wild-type. In patients with *RAS* wild-type tumours (according to the expanded *RAS* analysis), the addition of cetuximab to FOLFIRI or FOLFOX4 was associated with improved treatment outcomes across all efficacy endpoints. Conversely, in patients with *RAS* mutant tumours, no benefit from the addition of cetuximab to FOLFIRI versus FOLFIRI alone was observed [49]. In the OPUS study the addition of cetuximab to FOLFOX4 was associated with a non-significant improvement in PFS and OS in patients with *RAS* wild-type tumours; it seemed to be detrimental in patients whose tumours carried *RAS* mutations.

Data from the phase III FIRE-3 trial also underscore the importance of expanded *RAS* mutational analysis in the selection of patients for treatment with cetuximab. Previously untreated patients, with *KRAS* exon 2 wild-type mCRC, were randomised to receive FOLFIRI with either cetuximab or bevacizumab. Additional *RAS* mutations were identified in the tumours of 16% of assessable patients, with an improvement in OS (median 33.1 vs 28.7 months) observed for patients with *RAS* wild-type tumours treated with cetuximab compared with those with *KRAS* exon 2 wild-type tumours treated with cetuximab [55].

Confirmation of these observations was provided by a systematic review and meta-analysis of randomised controlled trials evaluating EGFR antibody therapy [56]. The analysis showed that across nine trials involving 5948 patients, patients with tumours without any *RAS* mutations were found to have a significantly better treatment outcome with EGFR monoclonal antibody therapy than those whose tumours harboured *RAS* mutations [56].

In summary, the cumulative data clearly show that patients whose tumours harbour any *RAS* mutation are unlikely to benefit from EGFR antibody therapy, confirming the presence of a *RAS* mutation (according to expanded *RAS* analysis) as a *negative predictive marker* of treatment outcome in patients with mCRC who might be under consideration for EGFR monoclonal antibody therapy. Thus, cetuximab and panitumumab should only be considered for the treatment of patients with *RAS* wild-type mCRC. Expanded *RAS* analyses should be conducted on all patients eligible/being considered for EGFR antibody therapy.

*Timing of testing*

Wong et al. (2014) [57] discuss whether *RAS* testing of CRC is better practised as a 'reflex' or an 'on-demand' process. However, the general consensus of the expert panel was that patients should be assessed for their tumour *RAS* mutation status at the time of diagnosis of their metastatic disease, to facilitate strategic treatment decisions within a multidisciplinary team [MDT] environment, local reimbursement regulations permitting. However, it should also be noted that an external quality assessment has uncovered differences in the quality of *RAS* testing for EGFR antibody therapy [58] and that, to date, the exact cut-off for clinically relevant *RAS* mutant allele frequencies has not been determined.

Investigation of cost estimates and the economic implications of expanded *RAS* testing in patients with mCRC showed the increased societal cost of expanded *RAS* testing versus *KRAS* exon 2 testing to be inconsequential when compared with the amount of money saved by not treating the additional up to 18% of patients who harbour additional *RAS* mutations (beyond those in *KRAS* exon 2) with EGFR antibody therapies [59].

*Recommendation 4: RAS testing*

- *RAS* mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A].
    - *RAS* testing should be performed on all patients at the time of diagnosis of mCRC [I, A ]
- *RAS* testing is mandatory prior to treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A].

- A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC.
- Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*).
- *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).
- Turnaround time for *RAS* testing (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.
- Validation (or verification, where more applicable) of *RAS* testing assays should be performed and recorded prior to implementation in clinical use. Laboratory audit mechanisms should be in place.
- Laboratories providing *RAS* testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited.

### ***BRAF* testing**

*BRAF* mutations (nearly always V600E) are found in the tumours of between 8% and 12% of patients with mCRC included in clinical trials and are almost exclusively non-overlapping with *RAS* mutations [38, 60, 61]. A retrospective analysis of patients with mCRC demonstrated that two thirds of *BRAF* mutant patients' primary lesions were located on the right side of the colon and associated with an increased incidence of peritoneal and distant lymph node metastases, but fewer pulmonary metastases [60]. Just under one third of *BRAF* mutant tumours also had microsatellite instability (MSI), and the same proportion of tumours with MSI contained *BRAF* mutations.

*BRAF* mutations are a significant negative prognostic marker for patients with mCRC. Tran et al. [60] reported a median survival for patients with *BRAF* mutant mCRC of 10.4 months compared with 34.7 months for patients with *BRAF* wild-type tumours. In a multivariate analysis the hazard ratio (HR) for survival was 10.662 ($p$ <0.001) [60]. This particularly poor prognosis for patients with *BRAF* mutant tumours is supported by a number of randomised studies with specific chemotherapy regimens [38, 44, 48, 61-63]. Although the evidence of *BRAF* mutations as a negative predictive biomarker for EGFR antibody therapy in later lines is accumulating [64, 65], its role in earlier lines in combination studies with chemotherapy has not been ascertained [44]. Indeed, two meta-analyses [66, 67] showed the efficacy benefit of EGFR antibody therapies to be greater in patients with *RAS* wild-type/*BRAF* wild-type tumours than in those with *RAS* wild-type/*BRAF* mutant tumours. In the meta-analysis that included two second-line trials and two trials involving chemorefractory patients [66], the lack of the conferral of a significant efficacy benefit by EGFR-antibody therapies over standard chemotherapy alone in patients with *BRAF* mutant tumours was considered to support the assessment of tumour *BRAF* mutation status prior to the initiation of EGFR-antibody therapy. Conversely, authors of the second meta-analysis [67], concluded that there was insufficient evidence to exclude EGFR antibody therapy from patients with *RAS* wild-type/*BRAF* mutant disease. However, in a small subgroup analysis (n = 28) of the TRIBE study, the cohort of patients with *BRAF* mutant tumours treated with the chemotherapy triplet FOLFOXIRI plus bevacizumab showed a non-statistically significant increase in OS compared with those treated with FOLFIRI plus bevacizumab [68].

Also, *BRAF* V600E-mutated melanomas are sensitive to the *BRAF* mutant inhibitor vemurafenib [69], but *BRAF* mutated CRCs are not as sensitive [70, 71]. Feedback reactivation of EGFR in CRC could explain why CRCs generally have a lower response to *BRAF* inhibitors [37, 71]. Clinical trials are ongoing to test targeted therapies in patients with metastatic *BRAF* (V600E) mutant CRC, using combinations of *BRAF* mutant inhibitors (dabrafenib, vemurafenib or encorafenib) in combination with MEK and EGFR inhibition, and in some cases conventional cytotoxic therapy. Early results are promising [72, 73].

Furthermore, somatic *BRAF* V600E mutations have been associated with sporadic cases of DNA mismatch repair deficiency (dMMR) showing a MSI phenotype [74]. However, *BRAF* V600E mutation is not associated with the MSI phenotype due to a germline MMR mutation (Lynch Syndrome) [75, 76]. *BRAF* V600E mutation testing has therefore been proposed as a means to exclude Lynch Syndrome. Recently, however patients with *BRAF* mutant tumours with mutations in codons 594 and 596 were shown to exhibit microsatellite stability (MSS) and markedly longer OS when compared with patients with BRAF V600E mutant disease [77].

Tumour *BRAF* mutation status should be determined for every case of CRC, ideally at the time of diagnosis, as this represents a different biological subtype, and in combination with testing for dMMR, can assist in the identification of a germline versus somatic cause of dMMR. In patients with mCRC, *BRAF* mutation status should be assessed at the same time as *RAS* mutational status for prognostic assessment (and/or potential selection for clinical trials).

*Recommendation 5: BRAF testing*

- Tumour *BRAF* mutation status should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B].

**Microsatellite instability testing**

Tumours with MSI retain their chromosomal numbers intact but contain microsatellite repeats, which vary in length due to a deficiency in their MMR system (dMMR), and are thought to contribute to the early steps of tumourigenesis in patients with CRC. Tumours with MSI represent only 4%–8% of tumours in patients with mCRC. Data are currently scarce on the prognostic and predictive values of a MSI phenotype in the metastatic disease setting [78-80]. A recent retrospective analysis demonstrated that the median age was a bit younger (67 years), poor differentiation was more frequent (58%), and that 45% of patients whose tumours had a MSI phenotype had stage IV disease at presentation. *BRAF* V600E mutations were present in 30% of patients with MSI [79]. In mCRC, some data have suggested that MSI tumours tend to have lower disease control rates when treated with oxaliplatin-based first-line therapy [81], although most studies show MSI status to be not relevant as a single predictive marker for response to irinotecan- or oxaliplatin-based chemotherapy regimens and not predictive for the effect of chemotherapy more generally in these patients [78, 82, 83].

In a pooled analysis of four phase III studies in the first-line treatment of mCRC (CAIRO, CAIRO2, COIN, and FOCUS) *BRAF* mutations have been shown to be more frequent in patients whose tumours exhibit MSI than in those whose tumours exhibit MSS [62]. The same pooled analysis showed PFS and OS to be significantly worse for patients with tumours with MSI when compared with those with tumours showing MSS (HR, 1.33; 95% confidence interval [CI], 1.12-1.57 and HR, 1.35; 95% CI, 1.13-1.61, respectively), and for patients with *BRAF* mutant tumours when compared with those with *BRAF* wild-type tumours (HR, 1.34; 95% CI, 1.17-1.54 and HR, 1.91; 95% CI, 1.66-2.19, respectively) [62]. Emerging data have shown MMR status to predict the clinical benefit of immune checkpoint blockade with pembrolizumab in patients with mCRC. The immune-related objective response rate (RR) and immune-related 6-month PFS rate were 40% (4 out of 10 patients) and 78% (7 out of 9 patients), respectively, for patients with dMMR CRC and 0% and 11% for those with MMR proficient CRC, with excellent median PFS and survival (not reached) in the cohort with dMMR CRCs versus 2.2 and 5.0 months respectively in the cohort with MMR proficient tumours [84].

Thus, the prevalence of MSI and *BRAF* mutations in the tumours of patients with mCRC is low. Both biomarkers confer an inferior prognosis, which in the case of patients with tumours with MSI may be driven by the presence of *BRAF* mutations. These conclusions are supported by the data from other studies which show the presence of a *BRAF* V600E mutation to be as poor a prognostic factor in patients with tumours with MSI as it is in other patients with mCRC [60].

*Recommendation 6: Microsatellite instability testing*

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B].
- MSI testing has strong predictive value for the use of immune check-point inhibitors (pembrolizumab) in the treatment of patients with mCRC [II, B].

**Biomarkers of chemotherapy sensitivity or toxicity**

*Dihydropyrimidine dehydrogenase (*DPD)*:* DPD is a key enzyme in the metabolic catabolism of 5-FU and capecitabine. About 85% of 5-FU is eliminated through a catabolic process involving DPD. Numerous genetic mutations have been identified in the DPD gene locus (*DPYD*), with a few key variants having functional consequences for enzymatic activity. Deficiencies in DPD activity have been shown to cause 5-FU-treated cancer patients to experience severe drug-related toxicities [85], and DPD activity is a predictive biomarker of potential toxicity when using 5-FU and capecitabine [86]. Polymorphism has been documented mainly on the *DPYD*2A* gene at a frequency of 2%–3% with geographical variation.

Several methods are available to detect DPD deficiency such as the functional dihydrouracil/uracil ratio in plasma, the uracil breath test or *DPYD*2* mutations. Patients with known partial DPD deficiency benefit from dose adaptation of their 5-FU/capecitabine therapy to avoid severe toxicity. In patients with complete DPD deficiency, fluoropyrimidines should not be used and an alternative treatment offered.

DPD deficiency is generally not assessed in routine practice prior to 5-FU administration. There is no recommended standardised assessment technique although several methods are available (see above). None of the current strategies are adequate to mandate routine DPD testing prior to starting fluoropyrimidine-based therapy [II, C].

Testing for DPD deficiency however, remains an option. In the case of patients who experience severe 5-FU toxicity, DPD levels should be tested before 5-FU is re-introduced.

*UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*):* UGT1A1 is an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble, excretable metabolites. The gene is part of a complex locus that encodes several UDP-glucuronosyltransferases. Polymorphism may be associated with increased toxicity to irinotecan. UGT1A1 is responsible for bilirubin glucuronidation as well as glucuronidation of SN-38, the active metabolite of irinotecan.

Genetic variations within the *UGT1A1* gene have also been associated with the development of certain drug toxicities. The *UGT1A1**28 variant, the allele behind many cases of Gilbert syndrome, has been associated with an increased risk for neutropaenia in patients receiving irinotecan [87, 88], and the United States Food and Drug Administration recommends on the irinotecan drug label that patients with the *28/*28 genotype should receive a lower starting dose of irinotecan [89]. The *28 allele has also been shown to be associated with an increased risk of developing diarrhoea in patients receiving irinotecan [87, 88]. The *UGT1A1**6 variant, more common in Asian populations than the *28 variant, has also been associated with the development of irinotecan-related toxicities. Patients who are heterozygous or homozygous for the *6 allele may have a higher risk of developing neutropaenia and diarrhoea than those with the *UGT1A1**1/*1 genotype.

Thus, *UGT1A1* gene polymorphisms are predictive of irinotecan-related side effects including diarrhoea, neutropaenia and vomiting. However, in everyday practice, UGT1A1/*UGT1A1* status is rarely used as a predictive biomarker of irinotecan toxicity. Attention should be paid to bilirubin levels especially in patients where conjugated bilirubin is <20% of total bilirubin.

*Excision repair cross-complementation group 1 (*ERCC1*):* The function of the ERCC1 protein is predominantly in the nucleotide excision repair of damaged DNA. Nucleotide excision repair is the primary DNA repair mechanism involved in the removal of therapeutic platinum-DNA adducts from tumour DNA. A variety of methods can be used to measure the level of ERCC1 activity, namely immunohistochemistry

(IHC) for protein expression, reverse transcription polymerase chain reaction (RT-PCR) for mRNA expression and DNA single nucleotide polymorphism (SNP) for genotyping. High ERCC1 levels have been shown to be a negative predictive marker for platinum-based therapy in patients with lung cancer [90, 91]. In CRC, depending on the techniques used, high ERRC1 expression levels have been shown to be associated with poor prognosis and to be predictive of a poor outcome in patients receiving oxaliplatin-based therapy (RT-PCR mRNA evaluation). A meta-analysis showed *ERCC1*-C118T polymorphisms to predict clinical outcome in patients with CRC receiving oxaliplatin-based therapy [92]. More specifically PFS and OS were significantly shorter in patients with T/T or T/C genotypes of *ERCC1*-C118T when compared with those with the C/C genotype. Thus, high *ERCC1* gene expression seems to confer oxaliplatin resistance, while *ERCC1*-C118T polymorphisms are predictive of treatment outcome in patients receiving oxaliplatin-based therapy [92]. Recently it has been proposed that ERRC1 induction after exposure to oxaliplatin may be dependent on *KRAS* mutational status [93].

At the present time, the use of ERCC1 protein levels cannot be recommended for treatment decisions involving the use of oxaliplatin in routine practice. Clinical trials have not been able to demonstrate a predictive role for ERCC1 status for treatment with oxaliplatin.

*Thymidylate synthase* (TS): TS is the primary target for 5-FU. 5-FU is an inhibitor of TS. Experimentally, it has been shown that low levels of TS expression lead to a better response to 5-FU and improved survival of colon cancer patients [94]. The TS gene *(TYMS)* is under the control of a promoter acting as an enhancer (*TSER*). Earlier studies have shown that higher numbers of *TSER* repeats (*TSER2*, TSER3** or higher) leads to higher TS expression and activity. TS activity and CRC sensitivity to 5-FU seems to correlate with *TSER* polymorphisms. These correlations, however, need to be confirmed in a larger randomised study.

*Recommendation 7: Biomarkers of chemotherapy sensitivity and toxicity*

- DPD testing before 5-FU administration remains an option but is not routinely recommended [II, D].
- UGT1A1 phenotyping remains an option and should be performed in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin and in patients where an irinotecan dose of >180 mg/m$^2$ per administration is planned [95] [III, C].
- ERCC1 expression cannot be recommended for use as a biomarker for treatment decisions involving the use of oxaliplatin in routine clinical practice, but could be included prospectively in clinical trials [III, D].
- TS activity and *TSER* genotyping are not recommended for use in clinical practice [II, D].

**Emerging biomarkers**

A list of biomarkers beyond *RAS* mutational status is emerging which may impact on the response to all classes of targeted agents, and specifically the current perspective of EGFR-antibody therapies. These include *HER2*, *MET* and *KRAS* gene amplification, ligands such as transforming growth factor alpha (TGFα), amphiregulin and epiregulin, *EGFR* mutations and alterations/mutations in *HER3*, *PI3KCA* and *PTEN*.

Mutations in *KRAS*, *NRAS*, and *BRAF* and amplification of *HER2* and *MET* drive primary (de novo) resistance to anti-EGFR treatment. Recently, the emergence of alterations in these genes was detected in patients who responded to EGFR blockade and then relapsed. Molecular heterogeneity impairs the efficacy of EGFR-antibody therapy in patients with mCRC by fuelling *de novo* and acquired resistance [96]. With the exception of *EGFR* mutations, which are described only in the acquired setting, all of the genetic alterations defined as a mechanism of *de novo* resistance are also responsible for acquired resistance. Differences can be found in the frequency of individual genetic alterations, such as *KRAS* and *NRAS* exon 3 mutations, which occur more frequently in the acquired rather than in the *de novo* setting. Acquired resistance to EGFR-antibody therapy is driven by the selection of cell clones that carry *RAS* or *RAF*

mutations but account for only 0.4%–17% of tumour cells. Mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2, 3, 4, as well as amplification of *KRAS*, *HER2* and *MET* [96-99] account for around 20% of mCRC patients who do not benefit from anti-EGFR treatment, although initially selected for anti-EGFR treatment based on *KRAS* exon 2 wild type status [48, 52-54, 97, 100-104]. The prognostic role of *PIK3CA* mutations is uncertain [105], but a *PIK3CA* exon 20 mutation may predict resistance to EGFR-antibody therapy [106-110], although the correlation is not strong enough to be applied as a negative predictive marker [111]. *PIK3CA* and PTEN alterations often co-occur with *KRAS* or *BRAF* mutations [107, 112], but there is insufficient evidence for their use as biomarkers of resistance to EGFR-antibody therapy. There is no clear evidence for HER3 overexpression and *HER3* mutations*,* mesenchymal-epidermal transition *(*MET)/*MET* alterations (overexpression or gene amplification) or *KRAS* amplification, *EGFR* mutations (tyrosine kinase [TK] or ligand-binding domains) or amplification in the resistance to EGFR antibody therapies. Emerging data indicate that *HER2* activating mutations or *HER2* amplification may mediate in some instances resistance to EGFR antibodies [100, 113]. A phase II clinical trial also showed that *HER2* amplification is predictive of response to HER2 dual inhibition with trastuzumab and lapatinib in a cohort of CRC patients failing EGFR antibody therapy [114].

Thus, although CRC is primarily considered to be a genetic disease, characterised by the sequential accumulation of genetic alterations, there is growing evidence that epigenetic alterations add an additional layer of complexity to its pathogenesis and characterise a subgroup of CRCs with a distinct aetiology and prognosis. A systematic review and meta-analysis of the prognostic value of the CpG island methylator phenotype (CIMP) in patients with CRC showed the CIMP to be independently associated with a significantly worse prognosis [115]. Whilst, epigenetic DNA hypermethylation inactivation of the *SRBC* gene, the product of which interacts with the product of the *BRCA1* gene, predicted a shorter PFS, particularly in oxaliplatin-treated patients with mCRC for whom metastasectomy was not indicated (HR, 1.96; 95% CI, 1.13 to 3.40; log-rank *P* = 0.01). *SRBC* hypermethylation was also associated with a shorter PFS (HR, 1.90; log-rank *P* = 0.045), in a validation cohort of unresectable colorectal tumours treated with oxaliplatin [116].

*Recommendation 8: Emerging biomarkers not recommended for routine patient management outside of a clinical trial setting:*

- Detection of mutations in *PIK3CA*, exon 20 [II, D]
- Evaluation of PTEN loss by IHC [V, D]Evaluation of the levels of the EGFR ligands amphiregulin, epiregulin and transforming growth factor-α [II, D]
- Evaluation of levels of EGFR protein expression [II, E]
- Evaluation of *EGFR* amplification and copy number and *EGFR* ectodomain mutations [IV, D]
- Evaluation of *HER2* amplification or *HER2* activating mutations
- Evaluation of HER3, and MET receptor overexpression [IV, D].

**Emerging technologies**

A number of novel tools for the assessment of diagnostic, prognostic and/or predictive biomarkers in patients with mCRC have been proposed, with an increasing interest in liquid biopsies involving the analysis of either circulating tumour cells (CTCs) or circulating tumour DNA (ctDNA). Although the levels of CTCs as assessed (mostly using the CellSearch system) have been shown to correlate with prognosis in patients with mCRC [117], the clinical utility of CTC assessments in patients with mCRC has hardly been explored.

Conversely, analysis of ctDNA is emerging as a new tool for molecular profiling that has more possibilities for translation into the clinic than CTCs. The seminal work of Bardelli et al has shown very promising results from ctDNA liquid biopsies [118, 119]. In addition to the seminal papers from Bardelli and colleagues and Montagut et al. [120], a number of tumour-blood concordance studies are currently being conducted that

will undoubtedly validate the clinical utility of these technologies for identifying tumour mutations in the blood of patients. Currently, its use as a monitoring tool for secondary resistance to EGFR antibody therapies is under investigation. It can be anticipated that liquid biopsies will be used therapeutically in the near future as more and better drugs are developed against mutant clones (or those with other molecular alterations e.g. amplifications, etc.) that emerge upon exposure to EGFR-targeted therapies [40, 118, 120-135].

Similarly, increasing evidence suggests that micro RNA (miRNA) is involved in the pathogenesis and progression of mCRC [136]. However, the prognostic and predictive role of miRNA needs to be demonstrated in a randomised clinical trial setting. Finally, NGS can provide important information on tumour heterogeneity and clonal evolution. NGS has already been published as a reliable technology for use in patients with mCRC and has the potential to screen for larger cancer gene panels in clinical trials [137].

*Recommendation 9: Emerging technologies*

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].
- Whole genome, whole exome and whole transcriptome analysis should be performed only in a research setting [V, D].

### View on how molecular classification should be developed going forward

CRC is a heterogeneous disease with heterogeneous outcomes and drug responses. To date, pathological staging and gene expression signatures have failed to accurately predict disease recurrence and prognosis. In an attempt to identify biologically homogeneous subtypes of CRC, many independent groups, have reported the results of gene expression-based subtyping, with Marisa et al. (2013) [138], the first to present a robust transcriptome-based classification of colon cancer. Subsequently, an international consortium dedicated to large-scale data sharing and analytics has recently provided a robust and unified classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable, with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signalling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor β activation, stromal invasion, and angiogenesis [139]. This effort provides the most robust and reproducible classification system currently available for CRC and may form the basis for future clinical trials.

## Local and ablative treatment, including surgery and the management of patients with oligometastatic disease

### The role of multidisciplinary teams and tumour boards

The optimal treatment strategies for patients with mCRC are evolving rapidly with improved clinical outcomes being achieved when the treatment approaches for individual patients are discussed within a MDT of experts who meet regularly as a tumour board to review mCRC cases [140, 141]. An ideal MDT should include access to both a colorectal surgeon (preferably with expertise in peritoneal approaches) and a specialist hepatobiliary and/or, lung surgeon as necessary, with the obligatory inclusion of a pathologist and a diagnostic radiologist, as well as radiation and medical oncologists, as standard. An interventional radiologist/nuclear physician may also be included as appropriate, as the role of ablative treatments gains increasing importance (see below). Ideally patients should be treated either in specialist cancer centres or, alternatively, where this is not possible, as part of a network of individuals dedicated to the management of

CRC with an established referral route between their site or centre and a specialist cancer centre (virtual MDTs). Wherever possible, MDTs should provide the opportunity to register patients for the local and/or national registries with extreme/unusual patients' details just noted, to provide information on the diversity of patients seen. Several (observational) studies have shown improved clinical outcomes, including improved OS, when patients with CRC are managed by MDTs [141, 142].

The role of the MDT is to define the initial diagnostic workup and then the treatment focus, based on the best diagnostic and therapeutic decision-making available [3]. Furthermore, a MDT-managed treatment strategy has to be maintained for the duration of a patient's treatment, to allow the refinement of treatment strategies according to on-treatment information (e.g. response to a selected treatment) and evaluation of the potential need for the integration of ablative treatments (such as secondary surgery and LAT strategies, see below).

The first step in the process is for the MDT members to critically define whether or not a patient has initially clearly resectable or initially unresectable metastatic disease and to define the status of the resection of the primary tumour when considering the management of both synchronous and/or oligometastatic CRC, and the first-line treatment of patients with metastatic disease. Conversely, for patients whose disease is deemed "never to be resectable", the discussion may be left to the treating medical oncologist (after discussion with the MDT) and patient as to the pros and cons of various approaches and sequences based on the perceived aims (e.g. duration of disease control versus quality of life [QoL], and toxicity profiles, etc.).

**Oligometastatic disease**

OMD is characterised by the localisation of the disease to a few sites and lesions and is associated with the option to use LAT approaches in patient treatment strategies with a view to improving disease control and therefore clinical outcome in these patients.

Generally, OMD may be characterised by the existence of metastases at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, predominantly visceral and occasionally lymphonodal. Typically these are the primary, and other involved sites such as the liver, lung, peritoneum, nodes, and ovary. Patients with disease at other sites, such as multiple lesions in the bones and the brain, may also be treated using a local ablative approach, but as these patients are associated with an unfavourable prognosis, local ablative treatment strategies are only used to prevent immediate complications. This latter group of patients should be excluded from a classification of OMD. On the other hand, a patient with 1 or 2 resectable liver metastases, and a single bone lesion, should be classified as having OMD, because for a patient with this disease profile locally ablative treatment strategies could be used and meaningfully contribute to their prognosis.

Thus, treatment strategies for patients with OMD should be based on the possibility of achieving complete ablation of all tumour masses, using surgical R0 resection (complete resection with clear resection margins and no evidence of microscopic residual tumour) and/or LAT, either initially or possibly after induction treatment with systemic therapy, for both the primary tumour and metastases.

For patients with OMD confined to a single organ (most frequently the liver), or a few organs (pre-dominantly visceral metastases, e.g. lung), a potentially curative approach exists. Numerous case series have shown that in this setting long term survival or even cure can be attained in 20%–50% of patients who undergo complete R0 resection of their metastases [143]. Even in the absence of randomised trials comparing surgical with non-surgical disease management, surgery has become the standard treatment approach for patients with resectable OMD.

For patients with more extensive OMD involving more sites or lesions e.g. primary, liver, lung, peritoneum, nodes, bones, brain, ovary and >4 organs, the value of a surgical approach is controversial. In these patients surgery may contribute to long-term survival but is rarely curative [143]. For this group of patients,

the consideration of localised interventions (LAT) becomes relevant, in combination with systemic therapy (as part of a multimodal therapy approach), following a careful MDT discussion and assessment. The goal for this group of patients is to achieve long-term disease control, potentially contributing to OS (and, although unlikely, potentially cure), with well-controlled sites of metastases, but without continued systemic therapy. Liver-directed therapy is probably the best established of the LAT interventions, however, the increasing use of the appropriate ablative treatment strategy from a "toolbox" of options, including for example stereotactic ablative body radiotherapy (SBRT) and radiofrequency ablation (RFA) for visceral or nodal involvement, peritonectomy with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal disease, and nodal dissection, sees the management of this sub-group of patients becoming increasingly complex (Figure 1). Furthermore, the potential still exists for isolated bone, pancreatic, and brain metastases, but these are rare and likely to not have a defined treatment pathway.

Sub-characterisation of OMD according to site also impacts on the treatment options and the timing of treatment. Patients with liver and lung metastases have a much better prognosis than patients with other metastatic disease locations. In fact, because lung involvement is associated with better outcomes, it may be appropriate to "watch and wait" or at least employ a sequential approach [144, 145]. The data showing different outcomes depending on the site(s) of OMD are likely to reflect molecular differences. For example, patients whose mCRC is associated with *RAS and BRAF* mutations have worse clinical outcomes, with *RAS* mutations shown to be associated with an increased incidence of lung, bone and brain metastases [146]. Moreover there are data to suggest that tumour T*S* expression levels and *RAS* mutation status are altered by site of metastasis compared with the primary [23-36, 147].

*Recommendation 10: OMD*

- For patients with OMD, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions, see below).
- The best local treatment should be selected from a "toolbox" of procedures according to disease localisation, treatment goal ("the more curative the more surgery"/higher importance of local/complete control), treatment-related morbidity and patient-related factors such as comorbidity/ies and age [IV, B].

**Liver metastases and surgical resection**

For patients with colorectal liver metastases (CLM) the treatment strategy should be directed towards complete resection whenever possible, with both "oncological" (prognostic) and "technical" (surgical) criteria being considered when evaluating patients for surgery [148]. However, prospective evaluations do not exist either for "oncological" or for "technical" criteria, and for many of these, there is no (international) consensus.

The "technical" definitions of resectable CLM have evolved over time, with the current consensus proposing that disease should be considered technically resectable as long as complete macroscopic resection is feasible, whilst maintaining at least a 30% future liver remnant (FLR) or a remnant liver to body weight ratio >0.5 (e.g. >350 g of liver per 70 kg patient) [149-151]. However, the concern remains that not all patients with technically resectable liver-limited metastases benefit from surgery, with approximately half developing widespread systemic disease within three years of resection [152].

The "oncological" criteria provide prognostic information that predict a longer disease-free survival (DFS) or a higher likelihood of cure. These include, as strong parameters, the number of lesions, the presence (or suspicion) of extrahepatic disease, and the criteria used in numerous retrospective evaluations and in the FONG score [153]. Thus, for some patients neoadjuvant chemotherapy may be a better option than upfront surgery.

In practice patients can be categorised into groups based on technological and oncological criteria as outlined in **Figure 2** and according to the new system for deciding whether or not a patient is eligible for resection proposed by Adam et al. [148], and described in **Table 2**.

### Imaging in the identification of resectable/unresectable disease

Computed tomography (CT) scans are routinely used for primary staging and disease surveillance in patients with CRC. Although practice varies between treatment centres, the evidence suggests that the best methods for detection of liver metastases from CRC are CT and magnetic resonance imaging (MRI) [154]. However many teams alternate liver ultrasonography (US) and CT for detection of disease to decrease the exposure of patients to the radiation resulting from repeated CT scans. For the characterisation of focal liver lesions, CT, contrast-enhanced US (CEUS) and MRI can be used [155]. For lesions <10 mm in diameter MRI is a more sensitive modality than CT [156] and specifically hepatobiliary MRI with specific contrast enhancers (such as Gadoxetate) which is associated with a higher accuracy of lesion detection [157].

For the detection of extrahepatic metastases and local recurrence at the site of the initial colorectal surgery, CT and positron emission tomography **(**PET)/CT scans are used [158]. A prospective randomised trial evaluating high-quality CT and PET imaging involving 263 patients showed only a 7.6% change in management following PET [159], while a retrospective analysis reported a change in intended curative therapy to palliative therapy or vice versa in a third of patients [160]. Also, a recently published meta-analysis of studies evaluating PET and PET/CT in patients with liver metastases reported PET findings to result in changes in the management of a mean of 24% of patients, with a mean incidence of PET-based extrahepatic disease of 32% [161]. However, although PET may provide additional information, mainly in patients with a high risk of extrahepatic disease, there is currently no consensus as to the patient population with the most to gain. The current evidence is not considered strong enough to recommend the use of PET in all patients.

*Recommendation 11: Imaging in the identification and management of disease*

- Imaging should comprise firstly an abdominal/pelvic and thoracic CT scan and, in the case of doubt, a second method such as US (CEUS), MRI or PET/CT scan depending on the localisation of the metastases. US may be helpful to characterise liver metastases, MRI liver, peritoneal or pelvic metastases and PET/CT extrahepatic disease [IV, B].
- A stepwise imaging approach is the recommended policy, in relation to the therapeutic possibilities, rather than the use of all imaging modalities in all patients [V, B].

### Liver metastases that are technically resectable up front

The primary goal for patients who present with technically resectable liver metastases is clearly cure, with the primary goal R0 resection although it should be noted that a 10-year follow up is required for confirmation of this [162]. In the management of these patients imaging is used to determine the nature and true extent of their disease.

In patients with “favourable oncological” criteria (i.e. >50% likelihood of cure based on various factors including long-term metachronous disease), and “favourable surgical” criteria (no massive disease infiltration), both upfront surgery (R0 resection/no evidence of disease [NED]) and perioperative chemotherapy are options. The panel expressed no clear preference for one option over the other, since the 5-year OS rate reported for the EPOC study with perioperative chemotherapy, 51% (95% CI, 45-58) in the perioperative chemotherapy group versus 48% (95% CI, 40-55) in the surgery-only group, is not convincing, despite the fact that that the DFS in eligible patients was significantly improved [163].

However, in patients with disease that is technically easy to resect but where the prognostic situation is unclear or likely not to be “excellent”, perioperative chemotherapy should be the treatment approach of choice (**Figure 2**). Perioperative chemotherapy in this group should comprise 3 months chemotherapy prior to surgery and 3 months chemotherapy post-surgery, only. The preferred treatment in this setting should be FOLFOX (or alternatively capecitabine with oxaliplatin [CAPOX]) as reported for the EPOC trial [163, 164]. EGFR-targeting monoclonal antibodies (cetuximab and panitumumab) are not to be used in this setting, based on the data from the New EPOC trial [165]. No data with bevacizumab are available for this specific patient group, therefore bevacizumab should not be used [V, consensus >75%].

In patients with disease that is technically easy to resect but with one or more unfavourable prognostic features, resulting in a relatively low chance of ‘cure’, there is uncertainty regarding the best treatment strategy. Either FOLFOX alone, as used in the EPOC study, or a highly active regimen such as a chemotherapy doublet plus monoclonal antibody therapy or FOLFOXIRI either alone or in combination with bevacizumab, should be considered preoperatively [V, consensus >75%].

In the case of patients with good oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [166]. However, the experience of Kemeny et al. (2009) indicates that patients with unfavourable prognostic criteria (e.g. by FONG score) may benefit from adjuvant treatment [167]. However, the expert opinion is that if patients have not received any previous chemotherapy for metastatic disease, then chemotherapy is recommended [low level of evidence – expert opinion], with the recommendations being FOLFOX or CAPOX, unless patients were previously recently (<6–12 months) exposed to oxaliplatin-based adjuvant chemotherapy for stage II or III CRC.

*Recommendation 12: Perioperative treatment*

- Both, technical criteria for resection and prognostic considerations define the need for systemic perioperative therapy [IV, B].
- In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [I, C; consensus >75%].
- In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (FOLFOX or CAPOX) should be administered [I, B; consensus >75%].
- Targeted agents should not be used in resectable patients where the indication for perioperative treatment is prognostic in nature [II, E].
- In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [IV, B] (Figure 2). Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.
- In patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from adjuvant treatment [III, B].
- In patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX or CAPOX is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy) [IV, B].
- Decision-making should include patients’ characteristics and preferences [IV, B].

**Unresectable CLM with “conversion" as a strategic treatment goal**

Any patient with limited liver and/or lung metastases should be considered a candidate for potential secondary resection as currently there are no criteria that allow us to distinguish between those patients for whom purely palliative treatment and those for whom potentially curative treatment is appropriate.

Systemic therapy given with a view to rendering technically unresectable colorectal metastases resectable is called *conversion therapy*, and offers the best means of 'converting' patients with unresectable metastatic disease to resectability [168]. Also, although survival times are slightly shorter for those patients with mCRC who undergo conversion therapy followed by surgery than for those patients with initially resectable metastatic disease, they are far better than if resection was not performed at all [168, 169].

In patients receiving conversion therapy, response to systemic therapy is a strong prognostic indicator but is also unpredictable. With the increasing efficacy of systemic therapy regimens, it is recommended that resectability is first evaluated after (only) 2 months of optimal treatment and again after 4 months, when the maximal tumour shrinkage is deemed to have occurred in most patients, so that the opportunity for resection is not missed in patients who *a priori* have a low chance of further resection [148]. However, due to the limitations of RECIST (1.1; potentially 2.0) [170], radiologists should be advised to pay special attention to the treatment effects if the vascular endothelial growth factor (VEGF)-targeting antibody bevacizumab is a component of the therapy regimen.

As reported previously [5], up to 75% of these patients will suffer a relapse following resection of their hepatic metastases, with the majority occurring in the liver. There is no role for partial palliative resection of metastases, but other ablative techniques, such as RFA or SBRT, may be used as an adjunct to surgery to achieve a situation where there is NED. They may also provide an alternative to resection in the case of patients with poor anatomical localisation of their metastases for resection, and in order to retain sufficient FLR. Resection of resectable lung metastases offers 25%–35% 5-year survival rates in carefully selected patients. Although resection of lung metastases is less well studied, R0 resection of lung metastases can also be recommended [5].

In addition approximately 20%–30% of newly diagnosed patients with mCRC present with synchronous metastases. There is no standard of care for treating patients with synchronous CRC liver metastases, although in this potentially curative setting treatment typically involves a two-stage resection. However, sometimes surgery is not the first step for these patients who may also require systemic therapy. The majority opinion was that patients presenting with synchronous metastatic disease should be treated more aggressively, with the recommendation that preoperative chemotherapy should be used.

**Conversion treatment**

The observation that patients with initially unresectable CLM whose metastases are rendered resectable after responding to chemotherapy have a better long-term outcome than patients treated with chemotherapy alone has led to the introduction of conversion chemotherapy into clinical practice [148, 171-174].

Resection rates have been shown to be correlated with tumour response rates to systemic therapy [175]. However, these correlations may be biased by other factors such as the year of the trial (in later years with more active systemic regimens, resection is more frequently integrated into the therapeutic algorithms), as well as patient selection and criteria for resection. Furthermore, only a few of the trials specifically designed to investigate conversion chemotherapy as a treatment strategy in patients with initially unresectable CLM (**Table 3**) were randomised controlled trials, making it difficult to reach any decision regarding the "best" regimen to use in this clinical setting.

In the CELIM trial, one of the first of these trials to be conducted, patients with technically unresectable and/or ≥5 liver metastases treated with either FOLFOX plus cetuximab or FOLFIRI plus cetuximab, were evaluated for resectability every 2 months [176]. A tumour response rate of 62% was achieved for all patients and 70% in patients with *KRAS* exon 2 wild-type disease. An encouraging 34% of patients across the two treatment arms underwent R0 resection of their liver metastases. However, as this trial involved randomisation between two different chemotherapy regimens, both in combination with cetuximab, no conclusion can be drawn regarding either the benefit of different treatment intensities or the benefit of any specific drug used.

More importantly, two randomised phase II trials have shown treatment intensification to lead to increased response rates with a consequential increase in the rates of R0 resection and therefore improved prognosis [177, 178]. The first of these was a prospective, randomised, Chinese trial in 138 patients with *KRAS* exon 2 wild-type liver-limited disease where an increased response rate in the cetuximab-containing combination chemotherapy (FOLFIRI/mFOLFOX6) arm was associated with an increase in R0 resection rate [177]. Twenty patients (29%) in the cetuximab-containing arm and nine (13%) in the chemotherapy alone arm became eligible for resection. Overall, 18 patients (26%) in the cetuximab arm and five (7%) in the chemotherapy alone arm underwent an R0 resection. Significantly, patients in either treatment arm undergoing hepatic resection had a longer median survival time than those who did not (46.4 vs 25.7 months for the cetuximab arm [$P$ = 0.007] and 36.0 vs 19.6 months for the chemotherapy alone arm [$P$ = 0.004]).

The second trial was the European, multinational, open-label, phase II OLIVIA trial in which patients with unresectable liver metastases were randomised to receive bevacizumab plus either FOLFOXIRI ($n$=41) or mFOLFOX6 ($n$=39) [178]. The overall resection rates were 61% and 49%, respectively and the R0 resection rates were 49% and 23%, respectively. The corresponding tumour response rates were 81% and 62%, respectively. In this trial FOLFOXIRI plus bevacizumab was associated with higher response and resection rates than mFOLFOX6 plus bevacizumab in patients with initially unresectable CLM. However, as bevacizumab was included in both arms and the intensification was set by the addition of a third chemotherapy compound, the relative value of bevacizumab in this setting remains unclear, as FOLFOXIRI alone is known to achieve a high ORR [179]. Also, consideration of the other available data from these studies [176, 177, 180], clearly shows both FOLFOX and FOLFIRI to be active in combination with EGFR inhibitors in patients with *RAS* wild-type disease in this treatment setting, whilst FOLFOXIRI plus (or minus) bevacizumab has been shown to be superior to the corresponding FOLFOX or FOLFIRI regimens and its activity to be independent of tumour *RAS and BRAF* mutation status [68, 178, 181, 182].

Studies involving the retrospective analysis of ORR (specifically in patients with liver-limited disease) and the corresponding R0 resection rates provide additional information [44, 46, 183, 184], but need to be regarded with caution. However, it seems clear that regimens that achieve high ORRs are beneficial and are associated with higher R0 resection rates. Thus, the standard chemotherapy regimens used in the CRYSTAL, PRIME and OPUS trials with EGFR-targeting monoclonal antibodies versus chemotherapy alone in patients with *RAS* wild-type disease, and FOLFOXIRI plus bevacizumab versus the doublet mFOLFOX6 plus bevacizumab should be regarded as standard treatment options. Moreover data from the FIRE-3 [55] and CALGB [185] studies, show that a cytotoxic doublet plus cetuximab in *RAS* wild-type patients is associated with higher response rates compared with bevacizumab, although this did not translate into higher resection rates in either of these studies.

**Role of other efficacy (response) parameters**

The new metric response parameters early tumour shrinkage (ETS) and depth of response (DpR) are emerging as predictors of long-term outcome in patients with mCRC [186], and in particular those receiving EGFR-antibody therapy [187-189], although recent data have also shown this for a triplet compared to a doublet of cytotoxics in combination with bevacizumab [68, 190]. In trials investigating treatment intensification [44, 46, 182, 191, 192], the more intensive therapy arms had higher DpR and ETS rates, and higher ORRs. In the FIRE-3 and PEAK trials, the DpR and ETS rates were higher for the EGFR-inhibitor containing combinations (cetuximab and panitumumab, respectively) than for the bevacizumab-containing regimen [193, 194].

The pathological response after preoperative chemotherapy also provides strong prognostic information and could serve in the future as a stratification parameter for further treatment decisions. To date, no prospective pathological response data from randomised trials are available and therefore pathological response should not yet be used as a decision-making factor.

The time to maximum response is typically about 12–16 weeks (FIRE-3 trial DpR analysis) [193] in patients with disease that is borderline in terms of resectability and who are receiving perioperative therapy (**Figure 2**). According to the expert consensus discussion, the total therapy duration pre- and post-surgery should not exceed 6 months.

The role of continued systemic treatment, post conversion treatment and surgery, is unclear. It is also unclear whether the monoclonal antibody therapies should be continued post resection. Intra-arterial chemotherapy and chemoembolisation have been shown to achieve high ORRs and R0 resection rates in small series [195-197] and may be used to shrink a larger tumour so that it can be removed by surgery, but the data on chemoembolisation for liver metastases from CRC are exploratory.

*Recommendation 13: Conversion therapy*

- In potentially resectable patients (if conversion is the goal), a regimen leading to high response rates and/or a large tumour size reduction (shrinkage) is recommended [II, A].
- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:
    - In patients with *RAS* wild type disease a cytotoxic doublet plus an anti-EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus or minus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A]
    - In patients with *RAS* mutant disease: a cytotoxic doublet plus or minus bevacizumab or FOLFOXIRI plus or minus bevacizumab [II, A].
- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

**Surgery at uncommon sites plus ablative techniques with/without surgery**

Patients with a limited number of lesions and involved sites and who therefore do not belong to the group of patients with limited CLM should be regarded as having OMD and be treated according to the standard treatment algorithm presented in **Figure 3**.

In these patients the use of local ablation therapies such as RFA or cryoablation has been shown to be feasible, as well as precision radiotherapy (SBRT) and, to a lesser extent, chemoembolisation.

The selection of the best instruments from the “toolbox” of ablative therapies (**Figure 3**) for use in this setting differs according to:

- The size and localisation of the metastases – and therefore access with regard to the use of the best treatment method
- The rates of local control achieved (with the local control greater for surgery than for the other options)
- The invasiveness of the technique
- The non-tumour related prognostic considerations and patient factors as well as patient preferences
- The local expertise with regard to the use of a particular ablative treatment method
- Consideration of patient frailty and life expectancy.

Selection of the best 'situation-adapted' treatment strategy should consider all of these factors as part of a MDT treatment decision prior to the start of systemic treatment and at the time of best response. Adoption of the treatment approach outlined in **Figure 3** requires repeated MDT discussions for the duration of an individual patient's treatment pathway.

**Use of local and ablative therapy in patients with oligometastatic disease (with non-curative intent)**

A treatment goal of ablation is a relatively new concept for patients with mCRC and involves an attempt to eradicate all visible metastatic lesions using the best instrument from the toolbox of LATs, in combination with systemic therapy. The overall goal of this strategy is not necessarily to cure the patient, as the prognosis for these patients is generally poor due to the unfavourable localisation of their metastases and the number of involved organs coupled with the limitations of local ablative treatments, compared with surgical resection.

However, full ablation of all visible sites may allow discontinuation of the standard of care, systemic therapy, with the possibility of a (relevant) relapse-/disease-free interval. The CLOCC trial, a prematurely terminated randomised phase II trial, has shown that the combined approach with surgery and RFA of unresectable metastases plus systemic therapy may be associated with a significant improvement in OS [198].

*Recommendation 14: Ablative techniques*

- Despite the lack of more available prospective data, this strategic treatment approach should be evaluated and pursued further in suitable patients [II, B].

**Toolbox of local and ablative treatments**

The most important discriminator for the usage of different toolbox instruments is, after tumour location, the type of energy administered. Current technologies comprise invasive thermal ablation with distinct size limitations (e.g. RFA and others), conformal radiation techniques which are directed against isolated lesions, and chemoembolisation or radioembolisation with yttrium-labelled microspheres, both of which are limited to the liver for use in the management of CLM that are rather diffuse.

**Thermal ablation**

In patients with advanced CLM, thermal ablation such as RFA often cannot be used due to the inherent size limitation of about 3 cm [199]. However, in the phase II CLOCC trial (chemotherapy plus or minus RFA) [200] RFA combined with surgical resection for the treatment of patients with CLM suggested an improvement in both PFS and OS [198]. A considerable amount of data are available on the use of thermal ablation in combination with liver resection for the treatment of patients with CLM either as part of a 2-stage approach or intraoperatively using ultrasound guidance [201].

Thermal ablation techniques also have proven efficacy in the ablation of lung metastases from CRC. Local control rates of 88%–92% at 1 year, and 77% at 3 years have been reported for RFA of lung metastases [202, 203]. Mortality and major complication rates may be as low as 1%, whereas grade 1 and 2 events occur in up to 33% of treatments [204, 205]. However, a recent meta-analysis of four RFA patient series and 23 surgical patient series demonstrated that the data currently available for lung metastases from CRC do not allow a firm conclusion to be drawn with regard to the use of surgery or RFA, although most evidence supports surgery as the most effective treatment option [205].

**SBRT**

High conformal hypofractionated irradiation (e.g. SBRT, high-dose rate [HDR]-brachytherapy) of CLM has been reported to achieve high local control rates. The risk of recurrence correlates with increasing tumour size as well as the applied dose regimen [206, 207].

SBRT and HDR-brachytherapy achieve similar results to RFA, with local tumour control >80% at 12 months depending on size [208-212]. Also, although grade 2 toxicity may be as high as 70%, grade ≥3 events have not been recorded across several series. Support for the use of SBRT in the liver is growing with data reported for five retrospective studies [213-215] and eight prospective studies [216-222] of SBRT in the treatment of liver metastases from various primaries. SBRT has also been used successfully in patients with unresectable visceral pulmonary or hepatic metastases [223]. Prospective trials will validate which patients benefit most from SBRT with its short treatment time course, lack of a need for recovery, and favourable overall toxicity profile. The use of SBRT together with systemic therapy should also be investigated prospectively.

*Recommendation 15: Local ablation techniques*

- In patients with unresectable liver metastases only, or OMD, local ablation techniques such as thermal ablation or high conformal radiation techniques (e.g. SBRT, HDR-brachytherapy) can be considered. The decision should be taken by a MDT based on local experience, tumour characteristics, and patient preference [IV, B].
- In patients with lung only or OMD of the lung, ablative high conformal radiation or thermal ablation may be considered if resection is limited by comorbidity, the extent of lung parenchyma resection, or other factors [IV, B].
- SBRT is a safe and feasible alternative treatment for oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [IV, B].
- RFA can be used in addition to surgery with the goal of eradicating all visible metastatic sites [II, B].

**Chemoembolisation**

To date, the data on chemoembolisation for liver metastases from CRC are mostly observational series in various treatment situations [195-197]. Comparative data are limited to irinotecan-based drug eluting beads in a small phase II cohort in previously-treated patients showing a benefit versus systemic chemotherapy [224], and the role of intra-arterial irinotecan in patients pre-exposed to intravenous irinotecan is unclear. Numerous trials with chemotherapy-loaded particles (beads) are ongoing, also in combination with systemic treatment and in the neoadjuvant setting.

**Radioembolisation**

Radioembolisation (selective internal radiation therapy [SIRT]) typically involves a single delivery of yttrium-90 connected to either resin or glass particles into the hepatic artery with the therapeutic effect essentially limited to irradiation.

For patients with liver-limited metastases failing the available chemotherapeutic options, radioembolisation with yttrium-90 resin microspheres has been shown to prolong the time to tumour progression in the liver, based on a small randomised phase III study [225].

Recently, a randomised phase III study of SIRT with resin microspheres as an adjunct to chemotherapy in the first-line treatment setting failed to show an overall PFS benefit (as primary endpoint of the study) and the OS data are not yet available (SIRFLOX study) [226]. However, a (potentially relevant) improved time to liver progression has been shown for patients treated with chemotherapy plus radioembolisation. In this

trial around 45% of patients had the primary tumour in place and around 40% had extrahepatic disease, suggesting that radioembolisation may be most beneficial in patients with liver-limited disease.

Yttrium-90 labelled particles may also currently be a good alternative in patients who are potential candidates for resection, but display a small FLR volume. A matched-pair analysis comparing yttrium-90 labelled particles with portal vein embolisation showed a lesser, but still pronounced benefit of yttrium-90 labelled particles with regard to contralateral liver hypertrophy, following simultaneous treatment of the ipsilateral tumour load with yttrium-90 labelled particles [227].

*Recommendation 16: Embolisation*

- For patients with liver-limited disease failing the available chemotherapeutic options
    - Radioembolisation with yttrium-90 microspheres should be considered [II, B]
    - Chemoembolisation may be also considered as a treatment option [IV, B].
- Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as “consolidation treatment” but should be limited to clinical trials.

**Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for patients with peritoneal metastases**

In selected patients with peritoneal metastasis, complete cytoreductive surgery and HIPEC may provide prolonged survival when performed in experienced high-volume centres (in view of the relatively high morbidity associated with the procedure) [228-230]. The efficacy of this multimodality treatment depends on the extent of peritoneal dissemination and is scored using the peritoneal cancer index (PCI), which is the main prognostic factor [231]. Involvement of the lower ileum is a negative prognostic factor. Cytoreductive surgery is particularly effective in patients with low-volume peritoneal disease (a PCI <12 is often suggested) and no evidence of systemic disease. With recommendations on standardising the delivery of HIPEC in patients with CRC [232] and evaluation of oxaliplatin versus mitomycin C for HIPEC [233], cytoreductive surgery and HIPEC is on the verge of becoming the accepted standard treatment approach for patients with peritoneal metastases from a colorectal primary.

*Recommendation 17: Cytoreductive surgery and HIPEC*

- Complete cytoreductive surgery and HIPEC can be considered for patients with limited peritoneal metastases in centres which are very experienced in the use of HIPEC [III, B].

## Treatment of metastatic disease

The definition of a (potential) treatment aim and strategy is important for both the upfront integration of a multimodal treatment approach and for the choice of a systemic treatment strategy (first-line and later-line) as part of a ‘continuum of care’.

Relevant factors for determination of the treatment goal are:

- Tumour- and disease-related characteristics, such as clinical presentation and patterns of tumour biology (e.g. metastases limited to the liver and/or lung, the dynamics of progression, symptoms and prognostic molecular or biochemical markers)
- Patient-related factors (co-morbidity, socio-economic factors and expectations of the patient)
- Treatment-related factors such as toxicity (**Table 4**).

A patient with classical mCRC may typically achieve an OS of about 30 months as the result of a MDT-managed “continuum of care”. An example of a typical “continuum of care” treatment sequence is outlined below:

- Approximately 4–6 months of first-line “induction” therapy
- 4–6 (-8) months of “maintenance” therapy – or no treatment after resection and/or ablation following first-line treatment
- About 3 months re-introduction (or treatment beyond progression)
- 5–7 months of second-line therapy
- A treatment break before initiation of a further line
- Approximately 3 months of third-line therapy
- Potentially a fourth line (in patients with *RAS* wild-type disease)
- A few months of re-challenge of initial induction or first-line therapy
- A few months best supportive care only.

**Determination of the therapeutic strategy**

The optimal therapeutic strategy for each patient is determined following a clinical examination, blood counts, determination of liver and renal function parameters, measurement of tumour marker (the most relevant being carcinoembryonic antigen [CEA]) levels, an abdominal and thoracic CT/MRI scan and an assessment of the patient’s general clinical condition (health), independent of their malignant disease.

The general condition and performance status of a patient are strong prognostic and predictive factors for chemotherapy. Whether a patient is classified as ‘fit’ or ‘unfit’ is now used to determine whether or not they will be assigned to a more intensive (combination of 2 or 3 cytotoxics with a biological) or less intensive treatment approach with the classical drivers of treatment choice being tumour, patient and treatment characteristics as outlined in **Table 4**. Historically, ‘fit’ patients with mCRC were categorised according to the previous ESMO consensus guidelines into 4 groups (0, 1, 2, and 3) to determine the strategic treatment approaches (**Table 5**) [3, 5].

The decision as to whether a patient has initially resectable or initially unresectable metastatic disease should be made at the first meeting of the MDT. Patients with initially resectable metastatic disease should be referred for immediate resection or perioperative chemotherapy with the goal being to achieve complete R0 resection and/or a situation where the patient can be treated with another ablative treatment (LAT). In the case of patients with OMD the goal would be the creation of a situation where the patient has NED as described previously.

However, in the case of fit patients with mCRC, whose metastases are not initially resectable, it is becoming increasingly obvious that the original ESMO groups 1 and 2 are becoming less clearly delineated and the treatment strategies less strict (see shading **Table 5**).

Indeed, two clinically relevant categories are evolving for the systemic treatment of ‘fit’ patients with CRC whose metastatic disease is not resectable at presentation:

A)

1. Those for whom intensive treatment is appropriate with the goal of cytoreduction (tumour shrinkage) and conversion to resectable disease

   OR

2. Those who need intensive treatment, although they will never make it to resection or LAT, since they need a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, or severe symptoms.

B) Those for whom intensive treatment is not necessary and where the goal is disease control.

The application of LAT within the context of OMD and the sequence of induction chemotherapy followed by LAT (without further systemic treatment) may also need to be considered as a pre-defined treatment sequence. Such patients should be considered as belonging to group A1 above.

For patients in both categories, knowledge of the *RAS and BRAF* mutational status of their disease, is used to further refine treatment strategies (**Table 6**).

**The systemic therapy options in the first-line treatment setting**

The typical first-line chemotherapy backbone comprises a fluoropyrimidine (intravenous 5-FU or oral capecitabine) used in various combinations and schedules with irinotecan or oxaliplatin [5]. Combination chemotherapy with a fluoropyrimidine plus oxaliplatin or irinotecan (FOLFOX or FOLFIRI) provides higher response rates and better progression-free and (partly) OS times than a fluoropyrimidine (5-FU/leucovorin) alone [I, B] [234, 235]. Infusional regimens of 5-FU/leucovorin [234, 235] are generally less toxic than bolus regimens [236, 237] and should be used in preference. The oral fluoropyrimidine capecitabine can be used as an alternative to 5-FU/leucovorin alone [238] and in combination with oxaliplatin [239]. Capecitabine is less frequently used in combination with irinotecan due to early concerns that it was more toxic than FOLFIRI [240, 241]. However, the results are controversial [242, 243]. The monoclonal antibodies bevacizumab (anti-VEGF) and cetuximab and panitumumab (anti-EGFR) have been shown to improve the clinical outcome of patients with mCRC when combined with combination chemotherapy regimens in the first-line setting [I, B] [43-46, 48-50, 101, 244, 245].

The triplet combination chemotherapy regimen FOLFOXIRI has been demonstrated to be superior to FOLFIRI in an Italian study [181]. FOLFOXIRI plus bevacizumab has also been shown to be superior to both FOLFIRI plus bevacizumab and FOLFOX6 plus bevacizumab [68, 178, 182]. However, the superiority of the cytotoxic triplet over a cytotoxic doublet has not been demonstrated in all studies [246]. The contribution of bevacizumab in the triplet combination is also uncertain.

Thus, the chemotherapy options for the treatment of patients with mCRC in the first-line setting are typically (for most patients) a cytotoxic doublet such as FOLFOX, CAPOX or FOLFIRI or, possibly, in very selected patients the cytotoxic triplet FOLFOXIRI or fluoropyrimidine monotherapy in selected patients with asymptomatic primarily unresectable metastases that are likely to be eligible for multiple lines of treatment and who are not candidates for a combination chemotherapy.

*Anti-VEGF therapy* – The monoclonal antibody bevacizumab, which binds circulating VEGF-A, has been recommended in previous ESMO Guidelines [5] and has been shown to increase the activity (either RR, PFS and/or OS) in combination with bolus 5-FU/leucovorin/irinotecan and in combination with 5-FU/leucovorin or capecitabine alone in the first-line treatment setting [I, B] [244, 247-249]. Bevacizumab in combination with a fluoropyrimidine plus oxaliplatin has been shown to increase PFS but not RR or OS in the first-line setting in a large phase III study [I, B] [245]. However, in smaller randomised trials evaluating the addition of bevacizumab to FOLFOX or FOLFIRI failed to demonstrate an improved outcome [250, 251] which is somewhat at odds with the randomised trial comparisons of both chemotherapy backbones plus bevacizumab versus each other [242, 252], data from the CALGB 80405 trial where investigator-based selection did not lead to a difference between chemotherapy backbones [185], and the data from large observational trials with nearly 5,000 patients where no difference was detected [253, 254].

FOLFOXIRI in combination with bevacizumab has also been shown to enhance response rate and PFS compared with FOLFIRI plus bevacizumab [68] and to produce one of the longest median OS recorded in this clinical setting, but is limited to very selected patients. The contribution of bevacizumab to the cytotoxic regimens in both arms of this study is uncertain as it was not investigated.

Bevacizumab is usually continued in combination with any cytotoxic agent or any combination of cytotoxic agents until disease progression or unacceptable toxicity [5]. Currently, there is no validated predictive marker for bevacizumab.

*Anti-EGFR therapy* – The EGFR antibodies cetuximab and panitumumab are active in various combinations with their activity, either alone or in combination with cytotoxics, limited to those patients whose tumours do not harbour a *RAS* mutation. It has been shown that expanding *RAS* mutational analysis of tumours to include detection of mutations in exons 3 and 4 of *KRAS* and exons 2, 3 and 4 of *NRAS* is superior to *KRAS* exon 2 analysis in predicting which patients are unlikely to respond (negative predictive factor) or in whom EGFR antibody therapy may be detrimental. Thus, a tumour *RAS* mutation is a negative predictive marker for treatment outcome with the EGFR monoclonal antibody therapies [II, B], and as stated previously (*Recommendation 4*), knowledge of the expanded *RAS* mutational status of a patient's tumour is therefore a prerequisite for the use of cetuximab or panitumumab as mandated by the European Medicines Agency (EMA) [255, 256].

Expanded *RAS* analysis should be performed at diagnosis in order to determine whether EGFR antibody therapies are likely to be of clinical benefit. Moreover, the evidence is increasing that a *BRAF* mutation is predictive for a lack of benefit from EGFR-targeting monoclonal antibodies administered as monotherapy in later lines [64, 65. However its role in combination with cytotoxic agents has not been ascertained {Van Cutsem, 2011 #54]However, its role in combination with cytotoxic agents has not been ascertained [44].

Cetuximab has been shown to improve the RR and median PFS and OS rates in first-line in combination with FOLFIRI when compared with FOLFIRI alone in mCRC patients with *RAS* wild-type tumours [43, 44, 49] [I, B]. Both cetuximab and panitumumab also increase the activity of the cytotoxic doublet FOLFOX in mCRC patients with *RAS* wild-type tumours [38, 45, 46, 48, 50, 183]. However, by contrast, the addition of EGFR antibodies to oxaliplatin-based regimens where non-infusional fluoropyrimidines were used (e.g. bolus administration, FLOX; capecitabine, CAPOX) have not resulted in any benefit [38, 61].

Biologicals are generally indicated for the first-line treatment of patients with mCRC unless contraindicated due to, for example, reduced organ function, poor performance status or cardiovascular insufficiency. Capecitabine-based therapy should not be used in combination with EGFR antibody therapies [38].

*Recommendation 18: First-line systemic therapy combinations according to targeted agent used*

- Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [I, A].
- The VEGF antibody bevacizumab should be used in combination with:
    - The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI
    - The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal - and potentially also in fit patients with tumour *BRAF* mutations [II, B]
    - Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [I, B].
- EGFR antibodies should be used in combination with:
    - FOLFOX/FOLFIRI [I, A]
    - Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [I, E].

Consideration also needs to be given to the clear evidence that patients should receive all three available cytotoxic agents (fluoropyrimidine, oxaliplatin and irinotecan) and all targeted treatments (anti-VEGF and, if *RAS* wild-type, anti-EGFR) during the course of their treatment whenever possible [257, 258], although the optimal sequence remains to be elucidated.

To date, there is no unequivocal evidence for the superiority of one class of biological over another (bevacizumab versus the EGFR antibody therapies) in the first-line treatment of patients with *RAS* wild-type mCRC although the combination with an EGFR antibody led to an improved RR in both phase III trials and to an improved OS in the FIRE 3 study, but not in the CALGB study. The PFS was identical for bevacizumab- and cetuximab-containing combinations in both phase III studies [55, 193, 259, 260].

Also, although the treatment goal is a moving target, depending on the course of the disease, the aim should be for 70%–80% of 'fit' patients to receive second-line therapy and 50%–60% of 'fit' patients, third-line therapy.

**Discontinuation of treatment and the concept of maintenance therapy**

Historically, continuing patients on chemotherapy until disease progression or unacceptable toxicity has been routine in clinical trials. However, clinical trials using this approach as well as clinical observations made during routine practice have indicated the dangers of continuing cytotoxic therapy, specifically oxaliplatin-containing therapy, as cumulative toxicity often occurs before clinical progression. As a result, discontinuation and/or intermittent combination chemotherapy/maintenance strategies have been investigated in a number of clinical trials with the result that these approaches provide an attractive treatment option for patients with a response or stable disease.

The early UK MRC CR06 trial randomised patients with either an objective response or stable disease following 3 months of single-agent fluoropyrimidine therapy to continue on chemotherapy or take a treatment break with further chemotherapy reserved for disease progression [261]. No clear difference in OS was observed between the two treatment arms with a HR of 0.87 favouring intermittent therapy.

Since then the administration of intermittent combination chemotherapy has been investigated in a number of clinical trials. The GISCAD study showed that intermittent treatment with FOLFIRI compared to continued treatment did not diminish the efficacy of treatment [262]. The OPTIMOX-1 trial randomised patients to receive FOLFOX4 until progression (or unacceptable toxicity) or FOLFOX7 (using a higher dose of oxaliplatin) for six cycles after which patients whose disease responded continued on maintenance 5-FU with the reintroduction of oxaliplatin only at disease progression [263]. No difference in PFS or OS time was noted and was taken as an indication that oxaliplatin-free intervals did not shorten survival time. The randomised OPTIMOX-2 and UK MRC COIN trials subsequently investigated treatment breaks without maintenance 5-FU [264, 265]. In both studies, a detrimental effect with inferior outcomes due to treatment-free intervals could not be excluded, but was small probably due to the short 'induction' phase of chemotherapy.

More recently, the concept of treatment discontinuation has been refined further. Randomised trials involving more than 1,000 patients have investigated the concept of "maintenance" treatment as a separate phase in the treatment strategy and continuum of care [266-270]. The data from these randomised phase II/III trials comparing maintenance therapy with biologicals plus or minus chemotherapy with a chemotherapy-free interval [265, 269-271] show any fluoropyrimidine plus bevacizumab to have the best activity in terms of interval PFS and a trend towards an improved survival. Also, athough a study from the Nordic group did not show a benefit from the combination of bevacizumab and erlotinib [272], the DREAM study showed a significant OS advantage for a maintenance strategy with bevacizumab plus erlotinib [266]. However, this combination is not considered as a standard treatment because of the relatively small size of the DREAM study and the lack of activity of erlotinib in mCRC [266]. Currently, the integration of

approaches other than de-escalation as maintenance strategies [266, 272], should be reserved for clinical trials.

Thus, after 'induction' treatment, an active maintenance treatment is seen as a possible option especially in patients treated with oxaliplatin-based chemotherapy, as it allows an early and upfront pre-planned discontinuation of the initially chosen systemic therapy combination. The optimal maintenance treatment following induction with fluoropyrimidine/oxaliplatin and bevacizumab is a combination of a fluoropyrimidine (capecitabine) plus bevacizumab as demonstrated in the CAIRO3 and AIO 0207 trials [268, 270] [I, B], and may also be considered for patients following initial FOLFOXIRI plus or minus bevacizumab therapy [182, 273]. However, the future challenge is to determine in which patients' treatment should be deescalated and in which patients it can be stopped completely. Very limited and preliminary data exist on maintenance strategies involving EGFR-antibody therapies, which do not allow any conclusion to be drawn [61, 266, 267, 274]

For patients receiving FOLFIRI first-line, the optimum duration of induction therapy is unclear and continuation of FOLFIRI induction therapy is recommended for at least as long as tumour shrinkage continues or disease stabilisation is maintained and the treatment remains tolerable.

Individualisation of the treatment approach after discussion with the patient is an essential component of this process and should include discussions of projected survival time, time free from cancer symptoms, time free from the side effects and constraints of treatment, and impact on career and family life (social and financial).

It is important to acknowledge that the discussion on maintenance treatment raises the question of a pre-planned abbreviation and shortening of the time on first-line therapy, followed by a well-defined treatment algorithm.

However, "treatment holidays" per se, in the meaning of a prolonged pausing of any treatment for a limited time, can be discussed for any patient with indolent and asymptomatic presentation of their disease.

In any patient, re-introduction of an initially successful induction regimen should be considered as a treatment option either following the ´maintenance` strategy or at a later stage in the therapeutic pathway.

*Recommendation 19: Maintenance therapy*

- Patients receiving FOLFOX or CAPOX plus bevacizumab-based therapy as induction therapy, should be considered for maintenance therapy after 6 cycles of CAPOX and 8 cycles of FOLFOX. The optimal maintenance treatment is a combination of a fluoropyrimidine plus bevacizumab. Bevacizumab as monotherapy is not recommended [I, B].
- Patients receiving FOLFIRI can continue on induction therapy – at a minimum – for as long as tumour shrinkage continues and the treatment is tolerable [V, B].
- For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy despite the lack of clinical data.
- For patients receiving initial therapy with a single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [V, A].
- Individualisation and discussion with the patient is essential [V, A].
- Initial induction therapy or a second-line therapy have to be reintroduced at radiological or first signs of symptomatic progression. If a second-line therapy is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no relevant residual toxicity is present [III, B].

**Second-line**

Second-line therapy describes the therapy received from the time that the first-line chemotherapy backbone has to be changed, mostly after failure of a first-line strategy, and should be offered to as many patients as possible. Second-line therapy is normally proposed for patients with good performance status and adequate organ function, and is dependent on the first-line therapy choice. Second-line therapy with oxaliplatin and irinotecan is known to be superior to best supportive care and 5-FU [275-277].

In patients in whom the initial chemotherapy backbone has failed, the chemotherapy backbone should be changed [5]. Following failure on 5-FU/leucovorin, patients who can tolerate it should be switched to an irinotecan or oxaliplatin-containing combination chemotherapy regimen such as FOLFIRI, FOLFOX or possibly irinotecan/oxaliplatin [278-280]. Patients who receive FOLFIRI up front should receive FOLFOX and those patients who receive FOLFOX up front should receive an irinotecan-containing regimen, preferably FOLFIRI, with early evidence of the efficacy of this strategy provided by the trial of Tournigand et al. [281].

Also, as stated previously, treatment with all three cytotoxics (fluoropyrimidine, irinotecan and oxaliplatin) during the course of a patient's treatment is associated with longer survival [257, 258]. However, when considering current treatment strategies, biologicals and predictive markers (e.g.: tumour *RAS* mutation status for EGFR antibody therapy) need to be added to the mix which makes the decision making more complex.

If bevacizumab was not used as the biological first-line, it should be considered in second-line, as FOLFOX plus bevacizumab was shown to improve OS compared with FOLFOX alone in a phase III trial [282] and confirmed in subsequent studies [283-285]. Data from the randomised phase III TML study [283], and from the *BEBYP* study [286], showed continuation of bevacizumab treatment with second-line chemotherapy to benefit patients previously treated with bevacizumab, suggesting that patients treated first-line with bevacizumab can benefit from subsequent therapies that target VEGF. The anti-angiogenic fusion protein aflibercept has been shown to confer a survival advantage when added to FOLFIRI in patients previously progressing on a prior oxaliplatin-containing regimen compared with FOLFIRI plus placebo [287]. A benefit has also been reported for patients treated with aflibercept who had received prior bevacizumab therapy [288]. Recently, an OS benefit was also reported for the anti-VEGFR2 antibody ramucirumab, also in combination with FOLFIRI, as second-line treatment following first-line treatment with a fluoropyrimidine, oxaliplatin and bevacizumab [289]. In total, four trials have reported a gain in OS by the addition of an antiangiogenic compound, irrespective of the various first-line regimens [282, 283, 287, 289].

Both EGFR antibodies, cetuximab and panitumumab, have been shown to increase RR and PFS, but not OS when combined with irinotecan-containing therapy in the second-line treatment setting [47, 65, 290] and can be considered if not used previously in the treatment of patients with *RAS* wild-type disease. However, generally, there is a similar relative benefit when cetuximab (and panitumumab) is used in later lines compared with second line, which was confirmed in a recent randomised trial [291].

No randomised phase III studies have been performed which compare the different biologicals available, specifically in patients who are fast progressors (PFS <3-4 months) on a first-line bevacizumab-containing regimen. In view of the inclusion criteria of the bevacizumab, aflibercept and ramucirumab trials [283, 287, 289], aflibercept and ramucirumab may be considered for the treatment of patients with *RAS* mutant or unclassified tumours, and EGFR inhibitors for patients with *RAS* wild-type disease, especially when a higher RR is desired. The toxicity profiles of bevacizumab, aflibercept, ramucirumab and cetuximab/panitumumab also need to be considered. A randomised phase II trial, however, suggested no difference in OS or in PFS between bevacizumab and panitumumab when combined with FOLFIRI [292]. This trial does not influence the recommendations, because it is a randomised phase II trial and also in view of the previously mentioned data on the similar relative benefit of EGFR antibodies in later lines compared with second line.

*Recommendation 20: Second-line combinations with targeted agents*

- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].
- Patients who received bevacizumab first-line should be considered for treatment with:
    - Bevacizumab post-continuation strategy [I, A]
    - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A]
    - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with *RAS* wild-type *(BRAF* wild-type) disease
        - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [II, A].
- Patients who are fast progressors on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and - in the case of patients with *RAS* wild-type disease and no pre-treatment with anti-EGFR therapy - EGFR antibody therapy, preferably in combination with chemotherapy [II, B].

**Third-line**

Both cetuximab and panitumumab have shown efficacy in the third-line/salvage-therapy setting in patients with *RAS* wild-type tumours [293-295], and are equally active as single agents [296]. The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [293]. Any activity in patients with *BRAF* mutant tumours, if active at all, seems to be limited to patients with chemorefractory mCRC [64, 65]. There is no unequivocal evidence to support administration of the alternative EGFR antibody, if a patient is refractory to the other.

The multi-targeted kinase inhibitor regorafenib has reported activity versus placebo plus best supportive care in two phase III trials [297, 298]. Regorafenib has demonstrated a significant improvement in OS (and maintenance of QoL over time) in patients pre-treated with all available cytotoxics and bevacizumab and EGFR antibodies [297], and can be proposed as a standard treatment in this setting [I, B]. However some concerns over safety have raised some doubt as to whether the labelled dose (160 mg/day day 1-21 q4 weeks) is the optimal dose. In reality it seems that in some regions many physicians start with a lower dose and then increase the dose to the approved dose if no toxicity is observed. Frequent and close monitoring for regorafenib toxicity is recommended.

Recently TAS-102, an oral agent that combines trifluridine and tipiracil hydrochloride, has been shown to be effective in the treatment of patients with refractory mCRC, leading to a significant survival benefit that is similar to that of regorafenib, but with limited toxicity and is therefore a potential new option [299, 300].

*Recommendation 21: Third-line therapy*

- In *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
    - Cetuximab and panitumumab are equally active as single agents [I, A]
    - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
    - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies [I, C].

- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B]
    - Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.
- TAS-102 (trifluridine/tipiracil) is a new option for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B].

## Consensus recommendations on the use of cytotoxics and biologicals in the first- and subsequent-line treatment of patients with mCRC

Within the expert panel the consensus was that the initial categorisation of patients with mCRC for treatment should be made according to whether they were clinically 'fit' or 'unfit' and subsequently according to treatment goal. There was also the recognition that there may be an intermediate category of patients who are 'unfit' but may benefit from treatment. It was also recognised that all treatment decisions involving patients categorised as being clinically fit must be made at a tumour board meeting by a MDT, informed by the appropriate molecular analyses. The appropriate molecular analyses are to be performed at the time of initial diagnosis of mCRC and should comprise a full analysis of tumour *RAS* mutational status (*KRAS*: exon 2, 3 and 4 and *NRAS*: exon 2, 3 and 4) with a simultaneous analysis of tumour *BRAF* mutational status, conducted in a validated laboratory/testing centre, to facilitate the best diagnostic and prognostic decision making possible. All patients considered for systemic therapy should be stratified according to whether their tumours were *RAS* wild-type, *RAS* mutant or *BRAF* mutant.

The expert panel consensus outlined below led to the generation of the Zurich treatment algorithm (**Figure 4**)**.**

**Allocation to first-line treatment**

**1. Fit patients with resectable metastatic disease**

The assignment of 'fit' patients to surgery is dependent on surgical evaluation within a MDT according to technical and prognostic criteria, as described above, and consideration of any contraindications for resection; as outlined in **Table 2**.

In the case of 'fit' patients with initially resectable metastatic disease the recommendation is (*Recommendation 12 this document)* that they can either be referred immediately for potentially curative surgery or for perioperative chemotherapy (FOLFOX) [163, 164], dependent on the available prognostic information and surgical considerations.

**2. Fit patients with unresectable metastatic disease**

For fit patients with unresectable metastatic disease the treatment goals are either cytoreduction (A) or disease control and hence prolongation of survival (**Figure 4** and **Table 6**).

*A. Cytoreduction*

1. For those patients with potentially resectable mCRC for whom cytoreduction and conversion to resectable disease and/or for patients with OMD the integration of local or ablative methods after response to systemic therapy are the goals, intensive treatment (cytotoxics in combination with biologicals) should be the treatment of choice for first-line induction therapy.

   However, uncertainty remains as to which is the best combination to use for patients stratified according to the molecular profile of their disease, with the treatment recommendations of the panel presented in **Figure 4** and below, with the alternative options presented in **Table 7**.

*Consensus recommendation for patients where cytoreduction with 'conversion' and/or the integration of local ablative treatment is the goal*

- A1a. For those patients who have *RAS* wild-type disease, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice.
- A1b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab or cytotoxic triplet plus bevacizumab are the preferred options.
- A1c. Patients should be revaluated for their disease status every 2 months in order to ensure that resectable patients are not over treated.
- A1d. If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage patients should be recommended for either potentially curative surgery or the most suitable LAT strategy - with a view to eliminating all evidence of disease (i.e.: R0 resection, NED).
- A1e. If no response is evident at first evaluation it is suggested that the cytotoxic doublet is changed in order to maximise the chance of resection [5].
- A1f. Where there is evidence for cytoreduction but the patients are not suitable for surgery, they should continue on combination chemotherapy plus the appropriate biological dependent on *RAS* and *BRAF* mutation status as indicated in **Figure 4**.
- A1g. Where there is evidence of disease progression, patients should continue to second-line therapy (**Figure 5**).
- A1h. Toxicity might also require a change to an alternative regimen.

2. A specific group of patients who need an intensive treatment, although neither resection nor LAT of metastases are a treatment goal: are patients in need of a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction and severe disease-related symptoms. In these patients a similar strategy can be proposed, although the consensus on the preferred treatment of choice was less strong.

*Consensus recommendation for patients where cytoreduction is needed because of aggressive biology and/or risk of developing or existing severe symptoms*

- A2a. For those patients who have RAS wild-type disease, a cytotoxic doublet plus an EGFR antibody is a preferred option, although a cytotoxic doublet plus bevacizumab is an equally valid alternative. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.
- A2b. For those patients with RAS mutant disease, a cytotoxic doublet plus bevacizumab is the preferred option. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.
- A2c. Patients should be revaluated for their disease status every 2 months.
- A2d. Treatment should not be changed in patients without tumour progression and not suffering from major toxicity.

*B. Disease control*

The recommendation for fit patients, for whom surgery or induction therapy plus LAT are not options and, where the treatment goal is long-term disease control without symptomatic toxicity, is that they should receive chemotherapy (usually a doublet) plus bevacizumab or a cytotoxic doublet plus EGFR antibody therapy as an alternative option for patients with *RAS* wild-type disease.

Patients should be re-evaluated every 2–3 months. Where there is evidence of good disease control, patients should continue on therapy and if after two re-evaluations, a patient has achieved a good response/disease control, active maintenance therapy with chemotherapy might be considered *(see Recommendation 19)*. Patients with progressive disease or excessive toxicity should progress to second-line therapy (See **Figure 5 and Table 7**).

*Consensus recommendation for patients where disease control is the goal*

- B1a. For these patients, a cytotoxic doublet in combination with bevacizumab or in patients with *RAS* wild-type tumours a cytotoxic doublet plus an EGFR antibody are recommended.
- B1b. Patients should be revaluated for their disease status every 2–3 months.
- B1c. In patients with a good response or at least disease control, active maintenance therapy should be considered. A fluoropyrimidine plus bevacizumab is the preferred option if they started with a cytotoxic doublet plus bevacizumab.
- B1d. Where there is evidence of disease progression patients should continue to second-line therapy (**Figure 5**).
- B1e. Toxicity might also require a change to second-line therapy.

### 3. Unfit patients

Patients with mCRC who are assessed as being unfit for any treatment should receive best supportive care. For the other patients in this group who are unfit, but may be suitable for treatment, physician experience should guide treatment choice with potential treatment options being capecitabine plus bevacizumab or a reduced-dose doublet of cytotoxics.

In the case of unfit patients with *RAS* wild-type disease where there is the fear that they may be receiving their last line of treatment, anti-EGFR therapy can be considered (**Figure 4**).

### 4. Treatment of elderly patients with mCRC

Fit older patients should be treated with systemic combination chemotherapy plus targeted agents as they derive the same benefit as younger patients [301]. For older patients unfit for standard combination chemotherapy (with or without targeted agents), less intensive therapies including capecitabine plus bevacizumab or reduced dose fluoropyrimidine plus oxaliplatin or irinotecan are appropriate first line options [301].



## Conflict of interest

Prof Adam has reported: honoraria from Amgen, Merck-Serono, Sanofi, Roche. Dr Aranda Aguilar has reported: advisory role for Amgen, Bayer, Celgene, Merck, Roche, Sanofi. Prof Arnold has reported: honoraria/consultancy for Roche, Merck-Serono, Bayer, Amgen; research funding from Roche. Prof Bardelli has reported: advisory boards for Horizon Discovery, Trovagene and Biocartis; stock holder for Horizon Discovery. Dr Benson has reported: research support directly to institution from Amgen, Genentech, Astellas/Aveo, Gilead, Bayer; scientific consultancy for Genentech, Lilly/ImClone, Sanofi, Bayer, Bristol-Myers Squibb; no stock and no speakers' bureau. Prof Bodoky has reported: research grants from Bayer, Celgene, Lilly, Roche, Abbvie; speaker for Roche, Bayer, Lilly, Amgen, Janssen, Taiho, Pfizer, Novartis. Dr Cervantes has reported: member of speaker's bureau for Roche and Merck-Serono; advisory

boards for Merck-Serono, Roche, Amgen, Bayer and Lilly. Prof Ciardiello has reported: consultancy/advisory roles for Bayer, Roche, Merck Serono, Sanofi, Lilly, Astra Zeneca. Dr Diaz-Rubio has reported: advisory boards for Roche, Merck-Serono, Sanofi, Bayer, Amgen; research grants from Roche, Merck-Serono, Amgen. Prof Douillard has reported: advisory boards, symposia, lectures for Amgen, Roche, Merck-Serono, Sanofi, Bayer. Prof Ducreux has reported: advisory boards for Celgene, Merck Serono, Roche, Amgen, Novartis, Sanofi; symposia lectures for Merck Serono, Roche, Novartis, Celgene; research funding from Roche, Pfizer, Chugai. Prof Falcone has reported: honoraria for advisory role, speaker at symposia and research funding from Amgen, Bayer, Merck-Serono, Roche, Sanofi and Lilly. Dr Grothey has reported: research fundings and honoraria for consultancy activities from Genentech, Roche, Eisai, Bayer, Amgen. Prof Gruenberger has reported: speakers' bureau member and research funding from Roche, Merck-Serono, Amgen, Sanofi-Aventis, Bayer. Prof Heinemann has reported: research funding from Merck-Serono, Roche, Sanofi, Amgen, Lilly; speaker's honoraria and advisory boards for Merck-Serono, Roche, Sanofi, Amgen and Lilly. Prof Koehne has reported: speakers' honoraria and advisory boards for Amgen, Merck, Pfizer, Sanofi; research grants from Novartis, Roche, Celgene. Prof Labianca has reported: advisory boards for Merck, Roche, Sanofi, Amgen. Dr Laurent-Puig has reported: honoraria for conferences and consulting from Amgen, Sanofi, Merck-Serono, Boehringer Ingenheim, Astra Zeneca, Roche, Lilly, Integragen. Prof Ma has reported: research grants from Merck Serono, Hoffmann La Roche; consultancy/advisory board for Bayer, Boehringer-Ingelheim, Novartis. Prof Maughan has reported: research funding from Astra-Zenecca, Glaxo-Smith-Kline and Almac Diagnostics. Dr Muro has reported: member of speaker's bureau for Merck Serono, Taiho, Chugai and Takeda. Dr Osterlund has reported: honoraria for lectures, advisory boards or travel grants from Amgen, Bayer, Celgene, Merck-Serono, Nordic Drugs, Roche, Sanofi Oncology, Prime Oncology, and Finnish medical associations. Dr Papamichael has reported: advisory boards and lectures for Roche, Merck-Serono, Amgen. Dr Pentheroudakis has reported: research grants from Roche, Sanofi, Amgen. Dr Pfeiffer has reported: advisory boards, symposia, lectures for Amgen, Bayer, Celgene, Merck-Serono, Merck Sharp & Dohme, Nordic Drugs, Roche, Sanofi, Taiho. Prpf Price has reported: advisory boards for Amgen, Roche, Merck. Prof Punt has reported: advisory role for Merck-Serono, Roche, Bayer, Nordic Pharma, Amgen. Prof Dr Ricke has reported: research funding, speaker fees, advisory board member for: Bayer, Simtex, Merck-Serono. Dr Salazar has reported: member of advisory board and speaker's bureau for Merck-Serono and Amgen; research funding from Roche, Amgen and Merck-Serono. Dr Scheithauer has reported: research funding and honoraria for consultancy activities from Roche, Merck, Bayer, Amgen. Prof Schmoll has reported: support for clinical trials from Roche; advisory boards for Amgen, Roche and Bayer. Prof Sobrero has reported: advisory boards and satellite symposia for Roche, Merck-Serono, Amgen, Takeda, Bayer, Sanofi, Lilly, Celgene. Dr Tabernero has reported: consultancy/advisory role for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck-Serono, Novartis, Roche, Sanofi, Symphogen, Taiho and Takeda. Prof Taieb has reported: advisory, research grants, speaker for Roche, Merck, Amgen, Sanofi, Bayer. Prof Van Cutsem has reported: research grants Bayer, Boehringer, Amgen, Celgene, Ipsen, Lilly, Merck, Novartis, Roche, Sanofi. Prof van Krieken has reported: research funding from Amgen and Merck-Serono. Dr Wasan has reported: advisory boards and speakers' bureau for Sanofi, Bayer, Roche, Merck, Sirtex Medical, Lilly. Dr Yoshino has reported: research funding from Pfizer, Eli Lilly, Sumitomo Dainippon, Taiho, Yakult and Daiichi Sankyo.

Prof Aderka, Prof D'Hoore, Dr Haustermans, Dr Hoff, Dr Normanno, Prof Oyen, Dr Roth, Dr Tejpar and Dr Zaanan have reported no potential conflicts of interest.

**Table 1.** Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America – United States Public Health Coding System[a] [4]).

| | |
|---|---|
| **Levels of evidence** | |
| I | Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity |
| II | Small randomised trials or large randomised trials with a suspicion of bias (low methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies of case-control studies |
| V | Studies without control group, case reports, experts opinions |
| **Grades of recommendation** | |
| A | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C | Insufficient evidence for efficacy or benefit does not outweigh the risk of the disadvantages (adverse events, costs, …) optional |
| D | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome, never recommended |

[a]By permission of the Infectious Diseases Society of America.

**Table 2.** Contraindications to hepatic resection in patients with CRC liver metastases (adapted from Adam et al. 2012) [148]

| Category | Contraindication |
|---|---|
| Technical (A) | |
| 1. Absolute | Impossibility of R0 resection with ≥25–30% liver remnant |
| | Presence of unresectable extrahepatic disease |
| 2. Relative | R0 resection possible only with complex procedure (portal vein embolisation, two-stage hepatectomy, hepatectomy combined with ablation[a]) |
| | R1 resection |
| Oncological (B) | |
| 1. | Concomitant extrahepatic disease (unresectable) |
| 2. | Number of lesions ≥5 |
| 3. | Tumour progression |

Patients should be categorised as A1 or A2/B1, B2, or B3.
[a]Includes all methods, including radiofrequency ablation.

**Table 3.** Conversion chemotherapy approach in patients with liver-limited disease

| Study | CTx | Controlled study | *n* | RR, % | Liver resection rate, % |
|---|---|---|---|---|---|
| Vie-LM-Bev [302] | CAPOX + bevacizumab | No | 56 | 73 | 93 |
| CELIM [176] | FOLFOX6/FOLFIRI + cetuximab | No | 106 | 70 | 33 |
| GONO [179] | FOLFOXIRI + bevacizumab | No | 30 | 80 | 40 |
| POCHER [303] | Chrono-IFLO + cetuximab | No | 43 | 79 | 60 |
| BOXER [304] | CAPOX + bevacizumab | No | 45 | 78 | 40 |
| OLIVIA [178] | FOLFOXIRI + bevacizumab versus FOLFOX + bevacizumab | Yes | 80 | 81 versus 62 | 49 versus 23 (R0) |
| Ye et al. [177] | FOLFIRI/FOLFOX ± cetuximab | Yes | 116 | 57 versus 29 | 26 versus 7 (R0) |

CAPOX (XELOX), capecitabine and oxaliplatin; Chrono-IFLO; chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin; CTx, chemotherapy; FOLFIRI, infusional 5-fluorouracil, leucovorin and irinotecan; FOLFOX, infusional 5-fluorouracil, leucovorin and oxaliplatin; FOLFOXIRI, infusional 5-fluorouracil, leucovorin, irinotecan and oxaliplatin; RR, response rate

**Table 4.** Drivers for first-line treatment

| Tumour characteristics | Patient characteristics | Treatment characteristics |
|---|---|---|
| Clinical presentation:<br>Tumour burden<br>Tumour localisation | Age | Toxicity profile |
| Tumour biology | Performance status | Flexibility of treatment administration |
| *RAS* mutation status | Organ function | Socio-economic factors |
| *BRAF* mutation status | Comorbidities, patient attitude, expectation and preference | Quality of life |

**Table 5.** Historical ESMO groups for treatment stratification of fit patients with metastatic CRC [3]

| | **Group 0**<br>**Resectable** | **Group 1**<br>**Potentially resectable** | **Group 2**<br>**Not resectable** | **Group 3**<br>**Not resectable** |
|---|---|---|---|---|
| **Clinical presentation** | Clearly resectable<br>R0 liver and/or lung disease | Unresectable liver/lung limited disease which might become resectable after response to conversion therapy | Multiple metastases/sites<br>Tumour-related symptoms<br>Able to withstand intensive therapy | Asymptomatic<br>Multiple metastases<br>Never able to undergo resection<br>Unsuitable for intensive therapy<br>Frail with co-morbidities |
| **Treatment goal** | Cure (NED) | Maximum tumour shrinkage | Clinically relevant tumour shrinkage<br>Disease control | Halt/slow tumour progression<br>Tumour shrinkage less relevant<br>Tolerability most relevant |
| **Treatment intensity** | ***Surgery***<br>Immediate surgery with no prior chemotherapy<br>or<br>moderate (FOLFOX) perioperative chemotherapy | ***Intensive treatment approach***<br>Upfront most active combination regimen | ***Intensive treatment approach***<br>Upfront active combination (at least a chemotherapy doublet) | ***Less intensive treatment approach***<br>Treatment selected according to patient preference<br>Sequential approach (start with single agent or doublet with low toxicity)<br>FOLFOX an exception |

CRC, colorectal cancer; FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin; NED, no evidence of disease

**Table 6.** Revised ESMO groups for treatment stratification of patients according to whether patients are 'fit' or 'unfit'

| **Patient's classification** | **'Fit' patients** | | **'Unfit' patients** |
|---|---|---|---|
| | Group 1 | Group 2 | |
| **Clinical presentation** | A. Conversion and achievement of NED<br>B. Impending clinical threat, impending organ dysfunction and severe (disease-related symptoms)<br><br>Treatment biomarker driven: *RAS* wt, *RAS* mt, *BRAF* mt patient subgroups | Asymptomatic patients<br>No impending clinical threat<br>Resection not an option<br><br>Treatment biomarker driven: *RAS* wt, *RAS* mt, *BRAF* mt patient subgroups | Best supportive care |
| **Treatment goal** | A. Cytoreduction, followed by R0 resection; NED achieved by LAT<br>B. Improvement of symptoms and hence avoidance of rapid evolution and prolonged survival | Disease control and hence prolonged survival | Palliative |

LAT, local and ablative therapy; mt, mutant; NED, no evidence of disease; wt, wild-type

**Table 7.** Systemic therapy choices according to the Zurich treatment algorithm for patients with unresectable metastatic disease (excluding those with oligometastatic disease)*

| **Category** | **Fit patients[a]** | | | | | | **Unfit[a]** **May be unfit** | **Unfit** |
|---|---|---|---|---|---|---|---|---|
| Treatment goal | **Cytoreduction (tumour shrinkage)** | | | **Disease control (control of progression)** | | | **Palliation** | |
| Molecular profile | *RAS* wt | *RAS* mt | *BRAF* mt | *RAS* wt | *RAS* mt | *BRAF* mt | Any | Any |
| First-line | | | | | | | | |
| Preferred choice (s) | CT doublet + EGFR antibody[b, c] | CT doublet + bevacizumab | FOLFOXIRI + bevacizumab | CT doublet + bevacizumab or CT doublet + EGFR antibody[b] | CT doublet + bevacizumab | FOLFOXIRI +/- bevacizumab | FP + bevacizumab | BSC |
| Second choice | FOLFOXIRI +/- bevacizumab | FOLFOXIRI + bevacizumab | CT doublet + bevacizumab | FP + bevacizumab | | CT doublet + bevacizumab | Reduced-dose CT doublet | _ |
| Third choice | CT doublet + bevacizumab | FOLFOXIRI | FOLFOXIRI | | | | If *RAS* wt may consider EGFR antibody therapy | _ |
| Maintenance | | | | | | | | |
| Preferred choice | FP + bevacizumab[d] | FP + bevacizumab | FP + bevacizumab | FP + bevacizumab[d] | FP + bevacizumab | FP + bevacizumab | FP + bevacizumab | _ |
| Second choice | Pause | Pause | Pause | Pause | Pause | Pause | FP | - |
| Second-line | | | | | | | | |
| Preferred choice(s) | CT doublet + bevacizumab | CT doublet + bevacizumab | CT doublet + bevacizumab | CT doublet + bevacizumab or CT doublet + EGFR antibody | CT doublet + bevacizumab | CT doublet + bevacizumab | | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Second choice | CT doublet + EGFR antibody[b,e] or FOLFIRI + aflibercept/ ramucirumab | FOLFIRI + aflibercept/ ramucirumab | FOLFIRI + aflibercept/ ramucirumab | FOLFIRI + aflibercept/ ramucirumab | FOLFIRI + aflibercept/ ramucirumab | FOLFIRI + aflibercept/ ramucirumab | - |
| Third-line | | | | | | | |
| Preferred choice (s) | CT doublet + EGFR antibody[b, e] or Irinotecan + cetuximab[e] | Regorafenib | Regorafenib | CT doublet + EGFR antibody[b] or Irinotecan + cetuximab | Regorafenib | Regorafenib | - |
| Second choice | EGFR antibody monotherapy[e] | TAS102 | TAS102 | EGFR antibody monotherapy[e] | TAS102 | TAS102 | - |
| Third choice | Regorafenib | | | Regorafenib | | | - |

BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrmidine; FOLFOXIRI, infusional 5fluorouracil, leucovorin, irinotecan and oxaliplatin; mt, mutant; wt, wild-type.

*Cross references to Figure 4.

[a]Patients assessed as fit or unfit according to medical condition not due to malignant disease.

[b]EGFR antibodies: cetuximab and panitumumab.

[c]In patients in need of a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction and severe disease-related symptoms a similar strategy can be proposed, although the consensus on the preferred treatment of choice was less strong. For those patients who have *RAS* wild-type disease, a cytotoxic doublet plus an EGFR antibody is a preferred option, although a cytotoxic doublet plus bevacizumab is an equally valid alternative. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients.

[d]In patients where a bevacizumab-containing regimen was started. In patients where a cetuximab-containing combination was started: pause or less intensive regimen.

[e]If not yet pretreated with an EGFR antibody

**Table 8.** Summary of recommendations

| **Molecular pathology and biomarkers** |
|---|
| Recommendation 1: Tissue handling<br>● Fixation with 10% neutral buffered formalin (4% formaldehyde) is recommended [V, A].<br>● Fixation time should be no less than 6 hours, and no greater than 48 hours in duration. In the case of microwave-enhanced fixation the quality of both nucleic acids and proteins must be verified [IV, A].<br>● Sections for biomarker testing should ideally be cut immediately prior to analysis [IV, A].<br><br>*Recommendation 2: Selection of specimens for biomarker testing*<br>• The primary pathologist should review all available tumour specimens to select those that are most suitable for biomarker analyses [IV, A].<br>• Enrichment of samples by macro-dissection to maximise tumour cell content (>50%) prior to DNA extraction is recommended [III, A].<br><br>*Recommendation 3: Tissue selection*<br>• Tissue from either the primary tumour or a liver metastasis may be used for *RAS* mutation testing [III, A].<br>• Other metastatic sites such as lymph node or lung metastases may be used only if primary tumour or liver metastases samples are not available [II, B].<br><br>*Recommendation 4: RAS testing*<br>• *RAS* mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in the metastatic disease setting [I, A].<br>o *RAS* testing should be performed on all patients at the time of diagnosis of mCRC [I, A ]<br>• *RAS* testing is mandatory prior to treatment with the EGFR-targeted monoclonal antibodies cetuximab and panitumumab [I, A].<br>• A network of arrangements should be established to ensure the rapid and robust transit of tissue samples from referral centres to testing laboratories, to minimise the turnaround time and avoid delays in having this information available for all patients with mCRC.<br>• Primary or metastatic colorectal tumour tissue can be used for *RAS* testing (see also *Recommendation 3*).<br>• *RAS* analysis should include at least *KRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61, 117 and 146) and *NRAS* exons 2, 3 and 4 (codons 12, 13, 59, 61 and 117).<br>• Turnaround time for *RAS* testing (expanded *RAS* analysis) should be ≤7 working days from the time of receipt of the specimen by the testing laboratory to the time of issuing of the final report, for >90% of specimens.<br>• Validation (or verification, where more applicable) of *RAS* testing assays should be performed and recorded prior to implementation in clinical use. Laboratory audit mechanisms should be in place.<br>• Laboratories providing *RAS* testing of colorectal tumours should demonstrate their successful participation in a relevant external quality assessment scheme, and be appropriately accredited. |

*Recommendation 5: BRAF testing*

- Tumour *BRAF* mutation status should be assessed alongside the assessment of tumour *RAS* mutational status for prognostic assessment (and/or potential selection for clinical trials) [I, B].

*Recommendation 6: Microsatellite instability testing*

- MSI testing in the metastatic disease setting can assist clinicians in genetic counselling [II, B].
- MSI testing has strong predictive value for the use of immune check-point inhibitors (pembrolizumab) in the treatment of patients with mCRC [II, B].

*Recommendation 7: Biomarkers of chemotherapy sensitivity and toxicity*

- DPD testing before 5-FU administration remains an option but is not routinely recommended [II, D].
- UGT1A1 phenotyping remains an option and should be performed in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin and in patients where an irinotecan dose of >180 mg/m$^2$ per administration is planned [95] [III, C].
- ERCC1 expression cannot be recommended for use as a biomarker for treatment decisions involving the use of oxaliplatin in routine clinical practice, but could be included prospectively in clinical trials [III, D].
- TS activity and *TSER* genotyping are not recommended for use in clinical practice [II, D].

*Recommendation 8: Emerging biomarkers not recommended for routine patient management outside of a clinical trial setting:*

- Detection of mutations in *PIK3CA* exon 20 [II, D]
- Evaluation of PTEN loss by IHC [V, D]
- Evaluation of the levels of the EGFR ligands amphiregulin, epiregulin and transforming growth factor-α [II, D]
- Evaluation of levels of EGFR protein expression [II, E]
- Evaluation of *EGFR* amplification and copy number and *EGFR* ectodomain mutations [IV, D]
- Evaluation of *HER2* amplification or *HER2* activating mutations
- Evaluation of HER3, and MET receptor overexpression [IV, D].

*Recommendation 9: Emerging technologies*

- Although CTC number correlates with prognosis in patients with mCRC, the clinical utility of CTC assessments is not yet clear and therefore cannot be recommended [IV, D].
- The utility of liquid ctDNA biopsies to guide treatment decisions is currently under investigation in clinical trials, but cannot yet be recommended in routine practice [V, D].
- Whole genome, whole exome and whole transcriptome analysis should be performed only in a research setting [V, D].

**LAT (including surgery and the management of patients with OMD)**

*Recommendation 10: OMD*

- For patients with OMD, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions, see below).
- The best local treatment should be selected from a "toolbox" of procedures according to disease localisation, treatment goal ("the more curative the more surgery"/higher importance of local/complete control), treatment-related morbidity and patient-related factors such as comorbidity/ies and age [IV, B].

*Recommendation 11: Imaging in the identification and management of disease*

- Imaging should comprise firstly an abdominal/pelvic and thoracic CT scan and, in the case of doubt, a second method such as US (CEUS), MRI or PET/CT scan depending on the localisation of the metastases. US may be helpful to characterise liver metastases, MRI liver, peritoneal or pelvic metastases and PET/CT extrahepatic disease [IV, B].
- A stepwise imaging approach is the recommended policy, in relation to the therapeutic possibilities, rather than the use of all imaging modalities in all patients [V, B].

*Recommendation 12: Perioperative treatment*

- Both, technical criteria for resection and prognostic considerations define the need for systemic perioperative therapy [IV, B].
- In patients with clearly resectable disease and favourable prognostic criteria, perioperative treatment may not be necessary and upfront resection is justified [I, C; consensus >75%].
- In patients with technically resectable disease where the prognosis is unclear or probably unfavourable, perioperative combination chemotherapy (FOLFOX or CAPOX) should be administered [I, B; consensus >75%].
- Targeted agents should not be used in resectable patients where the indication for perioperative treatment is prognostic in nature [II, E].
- In situations where the criteria for prognosis and resectability are not sharply defined, perioperative therapy should be considered (as part of a continuum of treatment option) [IV, B] (Figure 2). Patients with synchronous onset of metastases should be allocated to this group and therapeutic pathway.
- In patients with favourable oncological and technical (surgical) criteria, who have not received perioperative chemotherapy, there is no strong evidence to support the use of adjuvant chemotherapy [II, C], whereas patients with unfavourable criteria may benefit from adjuvant treatment [III, B].
- In patients who have not received any previous chemotherapy, adjuvant treatment with FOLFOX or CAPOX is recommended (unless patients were previously recently exposed to oxaliplatin-based adjuvant chemotherapy) [IV, B].
- Decision-making should include patients' characteristics and preferences [IV, B].

*Recommendation 13: Conversion therapy*

- In potentially resectable patients (if conversion is the goal), a regimen leading to high response rates and/or a large tumour size reduction (shrinkage) is recommended [II, A].
- There is uncertainty surrounding the best combination to use as only few trials have addressed this specifically:

- In patients with *RAS* wild type disease a cytotoxic doublet plus an EGFR antibody seems to have the best benefit risk/ratio, although the combination of FOLFOXIRI plus or minus bevacizumab may also be considered and, to a lesser extent, a cytotoxic doublet plus bevacizumab [II, A]
- In patients with *RAS* mutant disease: a cytotoxic doublet plus or minus bevacizumab or FOLFOXIRI plus or minus bevacizumab [II, A].

- Patients must be re-evaluated regularly in order to prevent the overtreatment of resectable patients as the maximal response is expected to be achieved after 12–16 weeks of therapy in most patients.

*Recommendation 14: Ablative techniques*

- Despite the lack of more available prospective data, this strategic treatment approach should be evaluated and pursued further in suitable patients [II, B].

*Recommendation 15: Local ablation techniques*

- In patients with unresectable liver metastases only, or OMD, local ablation techniques such as thermal ablation or high conformal radiation techniques (e.g. SBRT, HDR-brachytherapy) can be considered. The decision should be taken by a MDT based on local experience, tumour characteristics, and patient preference [IV, B].
- In patients with lung only or OMD of the lung, ablative high conformal radiation or thermal ablation may be considered if resection is limited by comorbidity, the extent of lung parenchyma resection, or other factors [IV, B].
- SBRT is a safe and feasible alternative treatment for oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments [IV, B].
- RFA can be used in addition to surgery with the goal of eradicating all visible metastatic sites [II, B].

*Recommendation 16: Embolisation*

- For patients with liver-limited disease failing the available chemotherapeutic options
  - Radioembolisation with yttrium-90 microspheres should be considered [II, B]
  - Chemoembolisation may be also considered as a treatment option [IV, B].
- Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as “consolidation treatment” but should be limited to clinical trials.

*Recommendation 17: Cytoreductive surgery and HIPEC*

- Complete cytoreductive surgery and HIPEC can be considered for patients with limited peritoneal metastases in centres which are very experienced in the use of HIPEC [III, B].

**Treatment of metastatic disease**

*Recommendation 18: First-line systemic therapy combinations according to targeted agent used*

- Biologicals (targeted agents) are indicated in the first-line treatment of most patients unless contraindicated [I, A].
- The VEGF antibody bevacizumab should be used in combination with:
    - The cytotoxic doublets FOLFOX/CAPOX/FOLFIRI
    - The cytotoxic triplet FOLFOXIRI in selected fit and motivated patients where cytoreduction (tumour shrinkage) is the goal - and potentially also in fit patients with tumour BRAF mutations [II, B]
    - Fluoropyrimidine monotherapy in patients unable to tolerate aggressive treatment [I, B].
- EGFR antibodies should be used in combination with:
    - FOLFOX/FOLFIRI [I, A]
    - Capecitabine-based and bolus 5-FU based regimens should not be combined with EGFR antibodies [I, E].

*Recommendation 19: Maintenance therapy*

- Patients receiving FOLFOX or CAPOX plus bevacizumab-based therapy as induction therapy, should be considered for maintenance therapy after 6 cycles of CAPOX or 8 cycles of FOLFOX. The optimal maintenance treatment is a combination of a fluoropyrimidine (plus bevacizumab). Bevacizumab as monotherapy is not recommended [I, B].
- Patients receiving FOLFIRI can continue on induction therapy – at a minimum – for as long as tumour shrinkage continues and the treatment is tolerable [V, B].
- For patients receiving initial therapy with FOLFOXIRI plus or minus bevacizumab a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy despite the lack of clinical data.
- For patients receiving initial therapy with single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained [V, A].Individualisation and discussion with the patient is essential [V, A].
- Initial induction therapy or a second-line therapy have to be reintroduced at radiological or first signs of symptomatic progression. If a second-line therapy is chosen, re-introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no residual toxicity is present [III, B].

*Recommendation 20: Second-line combinations with targeted agents*

- Patients who are bevacizumab naïve should be considered for treatment with an antiangiogenic (bevacizumab or aflibercept) second-line [I, A]. The use of aflibercept should be restricted to combination with FOLFIRI for patients progressing on an oxaliplatin-containing regimen [I, A].
- Patients who received bevacizumab first-line should be considered for treatment with:
    - Bevacizumab post-continuation strategy [I, A]
    - Aflibercept or ramucirumab (in combination with FOLFIRI) when treated in first line with oxaliplatin [I, A]
    - EGFR antibodies in combination with FOLFIRI/irinotecan for patients with *RAS* wild-type *(BRAF* wild-type) disease
        - Relative benefit of EGFR antibodies is similar in later lines compared with second-line [II, A].

- Patients who are fast progressors on first-line bevacizumab-containing regimens, should be considered for treatment with aflibercept or ramucirumab (only in combination with FOLFIRI) [II, B], and - in the case of patients with *RAS* wild-type disease and no pre-treatment with anti-EGFR therapy - EGFR antibody therapy, preferably in combination with chemotherapy [II, B].

*Recommendation 21: Third-line therapy*

- In *RAS* wild-type and *BRAF* wild-type patients not previously treated with EGFR antibodies cetuximab or panitumumab therapy should be considered
    - Cetuximab and panitumumab are equally active as single agents [I, A]
    - The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients [II, B]
    - There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies [I, C].
- Regorafenib is recommended in patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B]
    - Regorafenib is superior to placebo in terms of OS although there are toxicity concerns in frail patients.
- TAS-102 (trifluridine/tipiracil) is al new option for patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies [I, B].

**Consensus recommendations on the use of cytotoxics and biologicals in the first- and subsequent-line treatment of patients with mCRC**

*Consensus recommendation for patients where cytoreduction with 'conversion' and/or the integration of local ablative treatment is the goal*

- A1a. For those patients who have *RAS* wild-type disease, a cytotoxic doublet plus an EGFR antibody should be the treatment of choice.
- A1b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab or cytotoxic triplet plus bevacizumab are the preferred options.
- A1c. Patients should be revaluated for their disease status every 2 months in order to ensure that resectable patients are not over treated.
- A1d. If, after the first re-evaluation at 2 months, there is evidence of tumour shrinkage patients should be recommended for either potentially curative surgery or the most suitable LAT strategy - with a view to eliminating all evidence of disease (i.e.: R0 resection, NED).
- A1e. If no response is evident at first evaluation it is suggested that the cytotoxic doublet is changed in order to maximise the chance of resection [5].
- A1f. Where there is evidence for cytoreduction but the patients are not suitable for surgery, they should continue on combination chemotherapy plus the appropriate biological dependent on *RAS* and *BRAF* mutation status as indicated in **Figure 4**.
- A1g. Where there is evidence of disease progression, patients should continue to second-line therapy (**Figure 5**).
- A1h. Toxicity might also require a change to an alternative regimen.

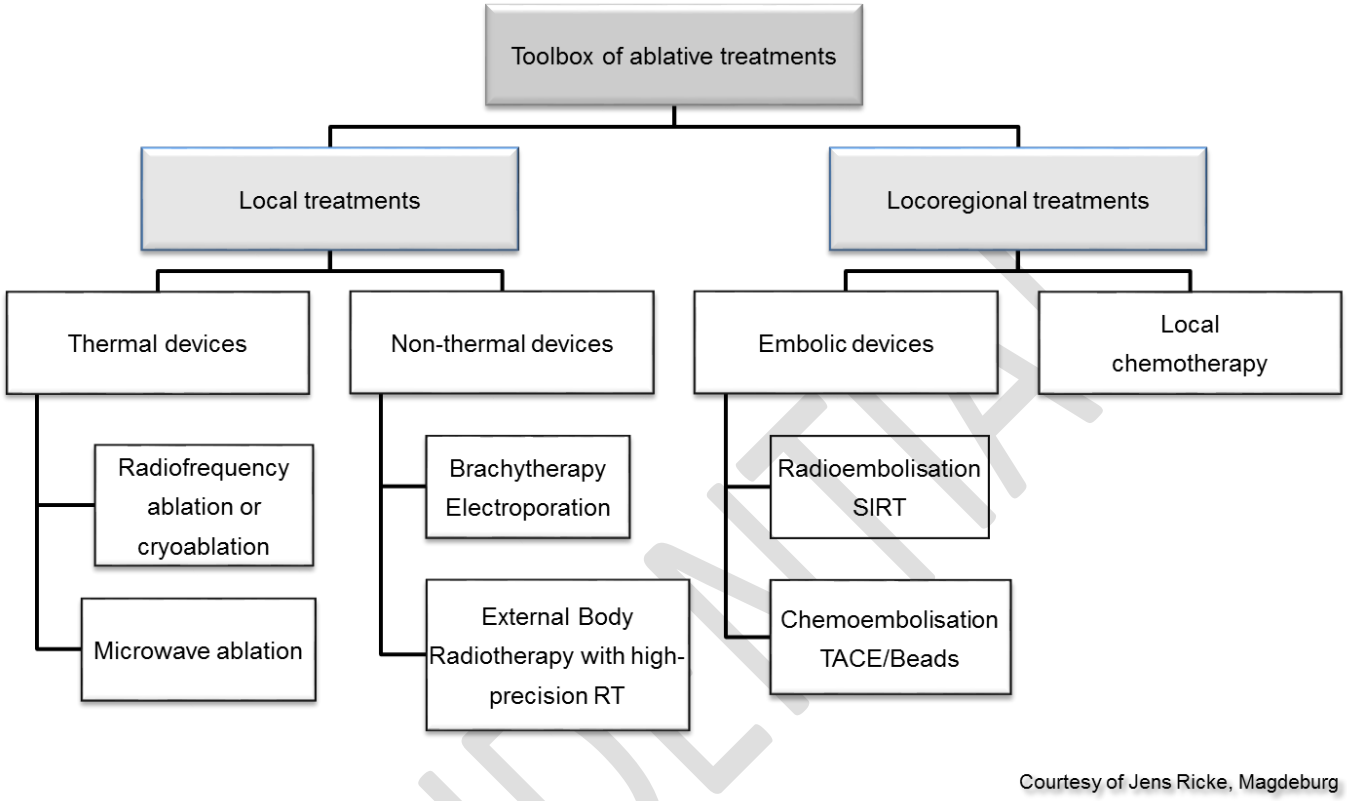
*Consensus recommendation for patients where cytoreduction is needed because of aggressive biology and/or risk of developing or existing severe symptoms*

- A2a. For those patients who have *RAS* wild-type disease, a cytotoxic doublet plus an EGFR antibody is a preferred option, although a cytotoxic doublet plus bevacizumab is an equally valid alternative. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients
- A2b. For those patients with *RAS* mutant disease, a cytotoxic doublet plus bevacizumab is the preferred option. A cytotoxic triplet plus or minus bevacizumab may be an alternative for selected, very fit and motivated patients
- A2c. Patients should be revaluated for their disease status every 2 months
- A2d. Treatment should not be changed in patients without tumour progression and not suffering from major toxicity.

*Consensus recommendation for patients where disease control is the goal*

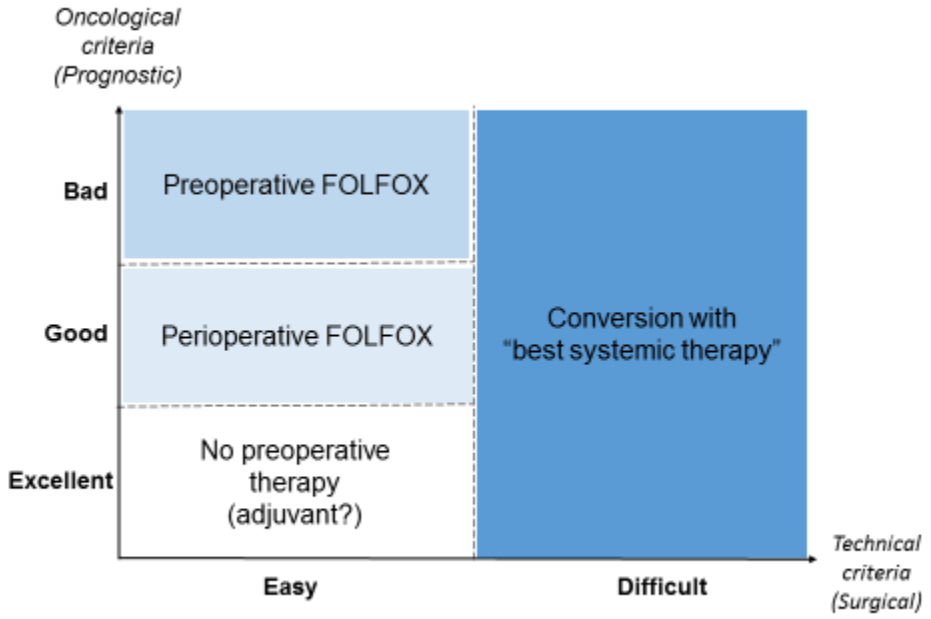
- B1a. For these patients, a cytotoxic doublet in combination with bevacizumab or in patients with *RAS* wild-type tumours a cytotoxic doublet plus an EGFR antibody are recommended.
- B1b. Patients should be revaluated for their disease status every 2–3 months.
- B1c. In patients with a good response or at least disease control, active maintenance therapy should be considered. A fluoropyrimidine plus bevacizumab is the preferred option if they started their treatment with a cytotoxic doublet plus bevacizumab.
- B1d. Where there is evidence of disease progression patients should continue to second-line therapy (**Figure 5**).
- B1e. Toxicity might also require a change to second-line therapy.

**Figure 1.** Toolbox of ablative treatments



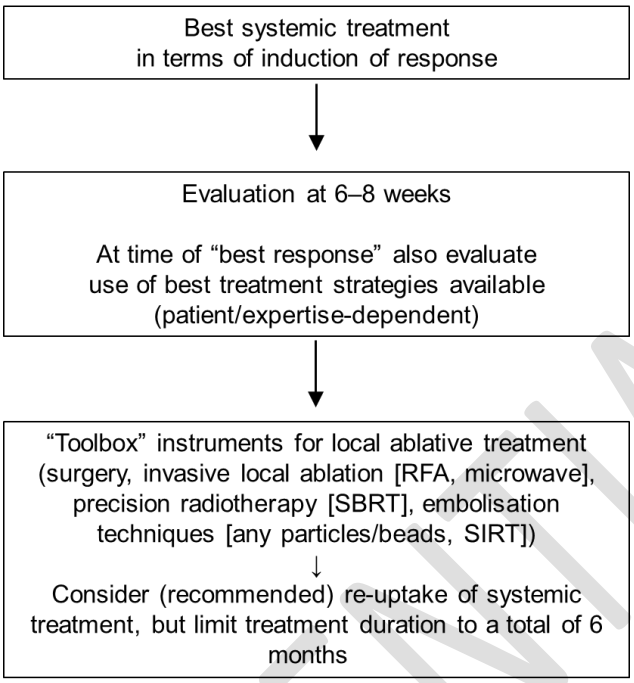

SIRT, selective internal radiation therapy; RT, radiation therapy; TACE, Transarterial chemoembolisation.

**Figure 2.** Categorisation of patients according to technical and oncological criteria



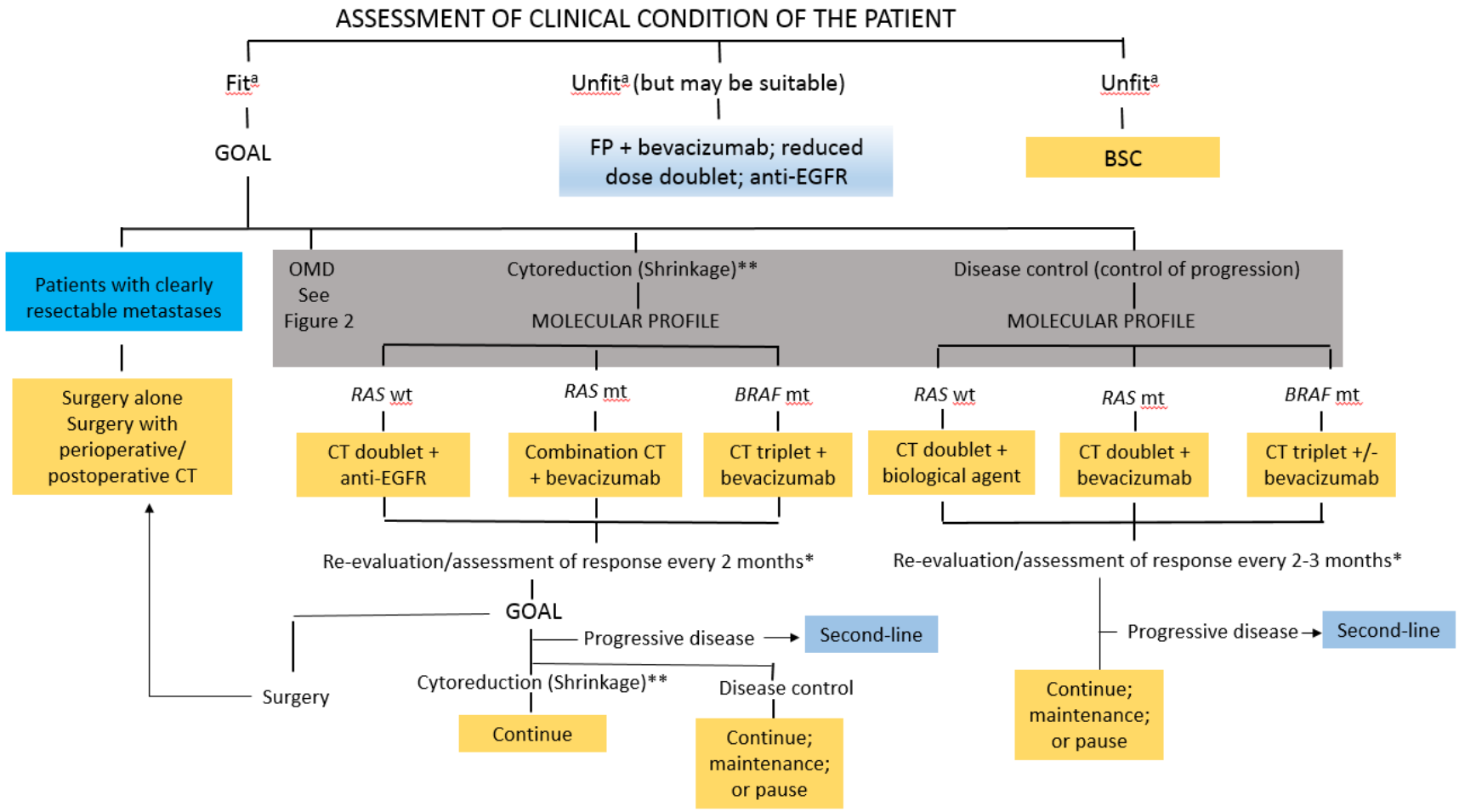

FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin

**Figure 3.** Standard treatment algorithm for patients with OMD




OMD, oligometastatic disease; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy.

**Figure 4.** Zurich treatment algorithm



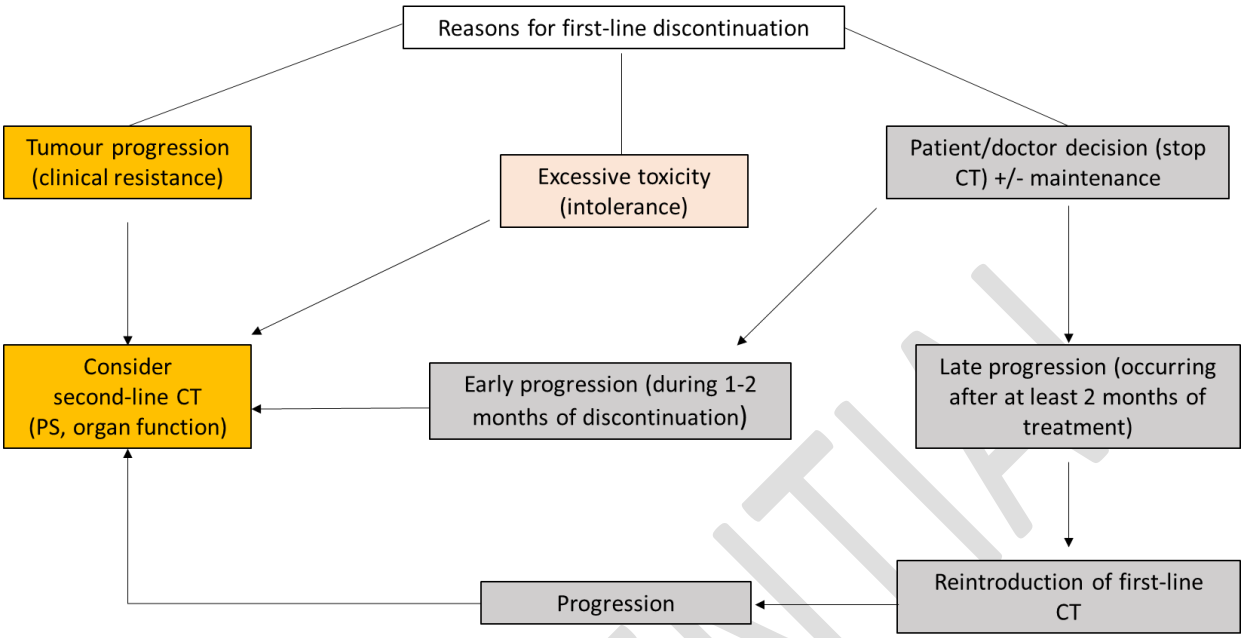

BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrmidine; mt, mutant, NED, no evidence of disease; OMD, oligometastatic disease; wt, wild-type.

aPatients assessed as fit or unfit according to medical condition not due to malignant disease

*After 2 re-evaluations, consider maintenance

** A) Includes 2 subgroups: 1. Those for whom intensive treatment is appropriate with the goal of cytoreduction (tumour shrinkage) and conversion to resectable disease; 2. Those who need an intensive treatment, although they will never make it to resection or LAT, since they need a rapid reduction of tumour burden because of impending clinical threat, impending organ dysfunction, severe symptoms.

**Figure 5.** Maintenance and second-line treatment options




CT, chemotherapy; PS, performance status

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