

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

E. Van Cutsem^{1*}, A. Cervantes², R. Adam³, A. Sobrero⁴, J. H. Van Krieken⁵, D. Aderka⁶, E. Aranda Aguilar⁷, A. Bardelli⁸, A. Benson⁹, G. Bodoky¹⁰, F. Ciardiello¹¹, A. D'Hoore¹², E. Diaz-Rubio¹³, J.-Y. Douillard¹⁴, M. Ducreux¹⁵, A. Falcone^{16,17}, A. Grothey¹⁸, T. Gruenberger¹⁹, K. Haustermans²⁰, V. Heinemann²¹, P. Hoff²², C.-H. Köhne²³, R. Labianca²⁴, P. Laurent-Puig²⁵, B. Ma²⁶, T. Maughan²⁷, K. Muro²⁸, N. Normanno²⁹, P. Österlund^{30,31}, W. J. G. Oyen³², D. Papamichael³³, G. Pentheroudakis³⁴, P. Pfeiffer³⁵, T. J. Price³⁶, C. Punt³⁷, J. Ricke³⁸, A. Roth³⁹, R. Salazar⁴⁰, W. Scheithauer⁴¹, H. J. Schmoll⁴², J. Tabernero⁴³, J. Taïeb²⁵, S. Tejpar¹, H. Wasan⁴⁴, T. Yoshino⁴⁵, A. Zaanan²⁵ & D. Arnold⁴⁶

¹Digestive Oncology, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium; ²Medical Oncology Department, INCLIVA University of Valencia, Valencia, Spain; ³Hepato-Biliary Centre, Paul Brousse Hospital, Villejuif, France; ⁴Medical Oncology, IRCCS San Martino Hospital, Genova, Italy; ⁵Research Institute for Oncology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; ⁶Division of Oncology, Sheba Medical Center, Tel Aviv University, Tel Aviv, Israel; ⁷Medical Oncology Department, University Hospital Reina Sofia, Cordoba, Spain; ⁸School of Medicine, University of Turin, Turin, Italy; ⁹Division of Hematology/Oncology, Northwestern Medical Group, Chicago, USA; ¹⁰Department of Oncology, St László Hospital, Budapest, Hungary; ¹¹Division of Medical Oncology, Seconda Università di Napoli, Naples, Italy; ¹²Abdominal Surgery, University Hospitals Gasthuisberg Leuven and KU Leuven, Leuven, Belgium; ¹³Medical Oncology Department, Hospital Clínico San Carlos, Madrid, Spain; ¹⁴Medical Oncology, Institut de Cancérologie de l'Ouest (ICO), St Herblain; ¹⁵Department of Medical Oncology, Gustave Roussy, Université Paris-Saclay, Villejuif, France; ¹⁶Department of Medical Oncology, University of Pisa, Pisa, Italy; ¹⁷Division of Medical Oncology, Department of Oncology, University Hospital 'S. Chiara', Istituto Toscano Tumori, Pisa, Italy; ¹⁸Division of Medical Oncology, Mayo Clinic, Rochester, USA; ¹⁹Department of Surgery I, Rudolfstiftung Hospital, Vienna, Austria; ²⁰Department of Radiation Oncology, University Hospitals Gasthuisberg and KU Leuven, Leuven, Belgium; ²¹Comprehensive Cancer Center, University Clinic Munich, Munich, Germany; ²²Instituto do Câncer do Estado de São Paulo, University of São Paulo, São Paulo, Brazil; ²³Northwest German Cancer Center, University Campus Klinikum Oldenburg, Oldenburg, Germany; ²⁴Cancer Center, Ospedale Giovanni XXIII, Bergamo, Italy; ²⁵Digestive Oncology Department, European Hospital Georges Pompidou, Paris, France; ²⁶Department of Clinical Oncology, Prince of Wales Hospital, State Key Laboratory in Oncology in South China, Chinese University of Hong Kong, Shatin, Hong Kong; ²⁷CRUK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, University of Oxford, Oxford, UK; ²⁸Department of Clinical Oncology and Outpatient Treatment Center, Aichi Cancer Center Hospital, Nagoya, Japan; ²⁹Cell Biology and Biotherapy Unit, I.N.T. Fondazione G. Pascale, Napoli, Italy; ³⁰Helsinki University Central Hospital, Comprehensive Cancer Center, Helsinki, Finland; ³¹Department of Oncology, University of Helsinki, Helsinki, Finland; ³²The Institute of Cancer Research and The Royal Marsden Hospital, London, UK; ³³Department of Medical Oncology, Bank of Cyprus Oncology Centre, Nicosia, Cyprus; ³⁴Department of Medical Oncology, University of Ioannina, Ioannina, Greece; ³⁵Department of Oncology, Odense University Hospital, Odense, Denmark; ³⁶Haematology and Medical Oncology Unit, Queen Elizabeth Hospital, Woodville, Australia; ³⁷Department of Medical Oncology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; ³⁸Department of Radiology and Nuclear Medicine, University Clinic Magdeburg, Magdeburg, Germany; ³⁹Digestive Tumors Unit, Geneva University Hospitals (HUG), Geneva, Switzerland; ⁴⁰Catalan Institute of Oncology (ICO), Barcelona, Spain; ⁴¹Department of Internal Medicine I and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; ⁴²Department of Internal Medicine IV, University Clinic Halle, Martin-Luther-University Halle-Wittenberg, Halle, Germany; ⁴³Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (V.H.I.O.), Barcelona, Spain; ⁴⁴Department of Cancer Medicine, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; ⁴⁵Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan; ⁴⁶Instituto CUF de Oncologia (ICO), Lisbon, Portugal

Received 31 March 2016; revised 27 May 2016; accepted 31 May 2016

Colorectal cancer (CRC) is one of the most common 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

*Correspondence to: Prof. Eric Van Cutsem, ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganella-Lugano, Switzerland.
E-mail: clinicalguidelines@esmo.org

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.

Key words: colorectal cancer, ESMO, consensus, clinical practice guidelines

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 ~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:

- (i) changes in the clinical presentation of patients, before the commencement of treatment, due to closer follow-up after resection of the primary tumour and earlier detection of metastatic disease;
- (ii) 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;
- (iii) 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;
- (iv) 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:

- (i) molecular pathology and biomarkers;

- (ii) local and ablative treatment (LAT) [including surgery and the management of patients with oligometastatic disease (OMD)];
- (iii) the treatment of metastatic disease.

Each panel member was assigned to one of the above working groups. Three consensus conference chairs (EVC, AC and DA) were also appointed. Before 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 before 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

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

^aBy permission of the Infectious Diseases Society of America.

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 h [8]. Longer or shorter fixation times may adversely affect biomarker testing, while 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 h, and no greater than 48 h 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 before 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 before 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%) before 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 carried out. Thus, archival samples of primary tumour tissue are usually available for biomarker testing for the majority of patients

with advanced or mCRC. However, for ~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 carried out 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 carried out. 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 ~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 a response rate (RR) 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 end points. 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 versus 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. [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 carried out on all patients at the time of diagnosis of mCRC [I, A].
- *RAS* testing is mandatory before 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 carried out and recorded before 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 before 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 an 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].

MSI testing

Tumours with MSI retain their chromosomal numbers intact but contain microsatellite repeats, which vary in length due to 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 an 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 an 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 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: MSI 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 in the treatment of patients with mCRC [II, B].

biomarkers of chemotherapy sensitivity or toxicity

dihydropyrimidine dehydrogenase. Dihydropyrimidine dehydrogenase (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 before 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 before 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. UDP glucuronosyltransferase 1 family, polypeptide A1 (*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. The function of the excision repair cross-complementation group 1 (*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 *ERCC1* 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 *ERCC1* 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. Thymidylate synthase (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) lead to higher TS expression and activity. TS activity and CRC sensitivity to 5-FU seem 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 carried out in patients with a suspicion of *UGT1A1* deficiency as reflected by low conjugated bilirubin and in patients where an irinotecan dose of >180 mg/m² 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- α (TGF- α), 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, and 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]. However, 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 1.13–3.40; 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 TGF- 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 and colleagues 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 carried out 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. [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 TGF- 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 ablative treatment (LAT), including surgery, and management of patients with OMD

the role of MDTs 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 an 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. 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, an 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 one or two 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 subgroup 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.

Subcharacterisation 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 those 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 TS 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

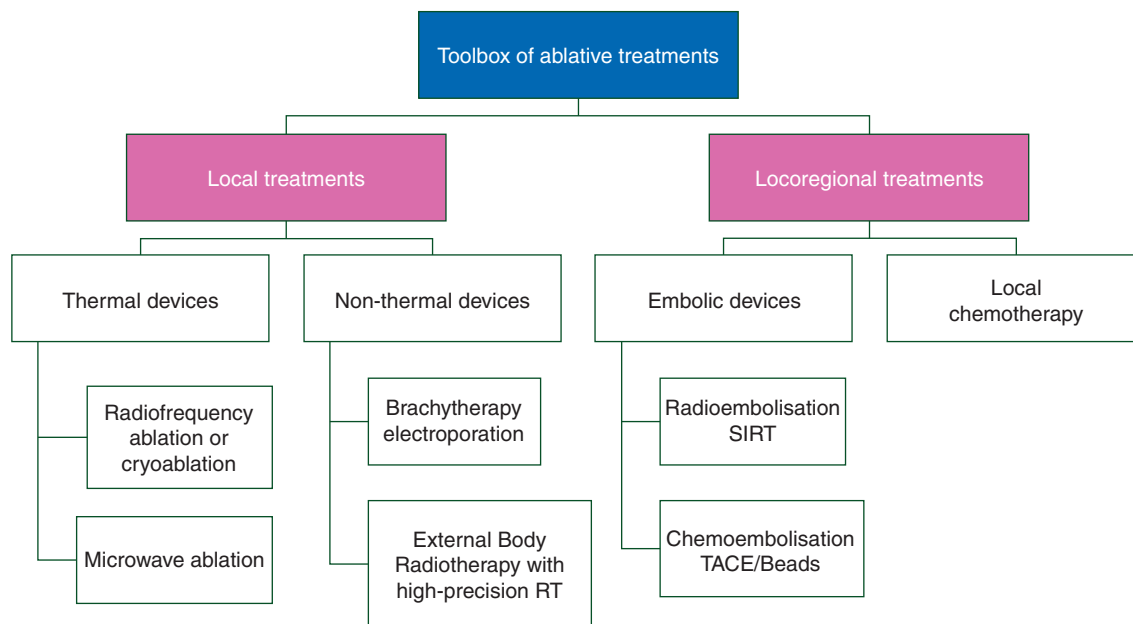


Figure 1. Toolbox of ablative treatments. SIRT, selective internal radiation therapy; RT, radiation therapy; TACE, transarterial chemoembolisation.

should be considered technically resectable as long as complete macroscopic resection is feasible, while 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 3 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 one-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

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

Category	Contraindication
Technical (A)	
1. Absolute	Impossibility of R0 resection with ≥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 All methods, including radiofrequency ablation.	

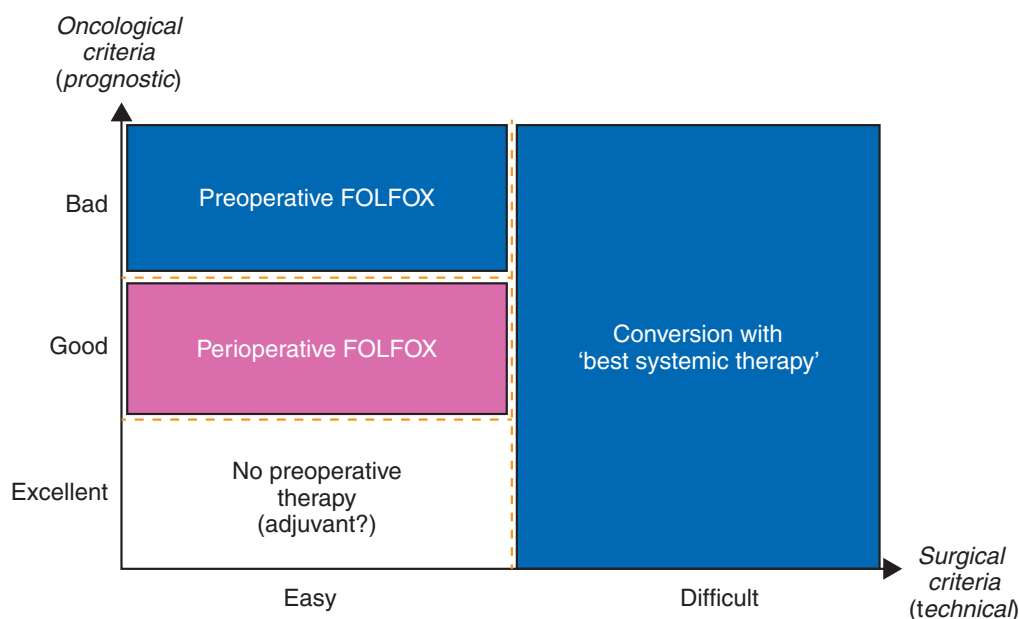


Figure 2. Categorisation of patients according to technical and oncological criteria. FOLFOX, infusional 5-fluorouracil, leucovorin, oxaliplatin.

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 first 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 meta-chronous 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 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 before 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. [167] indicates that patients with unfavourable prognostic criteria (e.g. by FONG score) may benefit from adjuvant treatment. 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 carried out 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 ~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 pre-operative 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 response 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 RR of 62% was achieved for all patients and 70% in patients with *KRAS* exon 2 wild-type disease. An encouraging 33% 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 in patients with unresectable disease have shown treatment intensification to lead to increased RRs 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 RR 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

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.

either treatment arm undergoing hepatic resection had a longer median survival time than those who did not [46.4 versus 25.7 months for the cetuximab arm ($P = 0.007$) and 36.0 versus 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 RRs 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 RR [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, while 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 RR (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 RRs 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 RRs 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 to characterise the response, but may also be useful 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 with 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 RRs. In the FIRE-3 and PEARL 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 ~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 RRs 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 RRs 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 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 bevacizumab or FOLFOXIRI plus 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.

metastases at unfavourable/uncommon sites and role of ablative treatment with or 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;

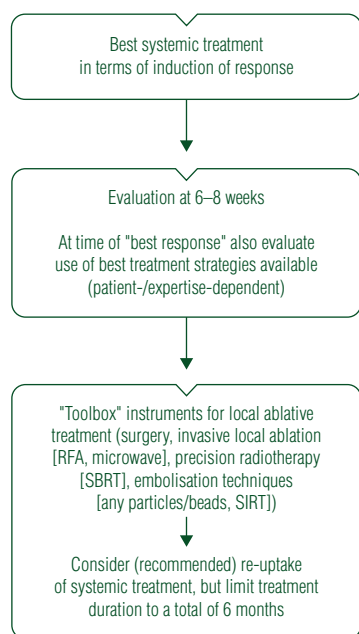


Figure 3. Standard treatment algorithm for patients with oligometastatic disease. RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy.

- 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 an MDT treatment decision before 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 OMD (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 LATs

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 ~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 two-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].

stereotactic ablative body radiotherapy

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 an 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 end point

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 HIPEC for patients with peritoneal metastases

In selected patients with peritoneal metastasis, complete cytoreductive surgery and HIPEC may provide prolonged survival when carried out 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

Table 4. Drivers for first-line treatment

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

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

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, socioeconomic 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 ~30 months as the result of an 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 four 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 in 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 RRs 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 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

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 B) Impending clinical threat, impending organ dysfunction and severe (disease-related) symptoms Treatment biomarker driven: <i>RAS</i> wt, <i>RAS</i> mt, <i>BRAF</i> mt patient subgroups	Asymptomatic patients No impending clinical threat Resection not an option Treatment biomarker driven: <i>RAS</i> wt, <i>RAS</i> mt, <i>BRAF</i> mt patient subgroups	Best supportive care
Treatment goal	A) Cytoreduction, followed by R0 resection; NED achieved by LAT 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.

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 5000 patients where no difference was detected [253, 254].

FOLFOXIRI in combination with bevacizumab has also been shown to enhance RR 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 carried out 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 [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, in contrast, the addition of EGFR antibodies to oxaliplatin-based regimens where non-infusional fluoropyrimidines were used (e.g. bolus administration, FLOX; capecitabine, CAPOX) has 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 an 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 with 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 1000 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, although 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 (as was done in the pivotal trials examining FOLFOXIRI).
- 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 *BEYYP* 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, a similar OS benefit has been 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 carried out 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, 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.

- Trifluridine/tipiracil is recommended 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

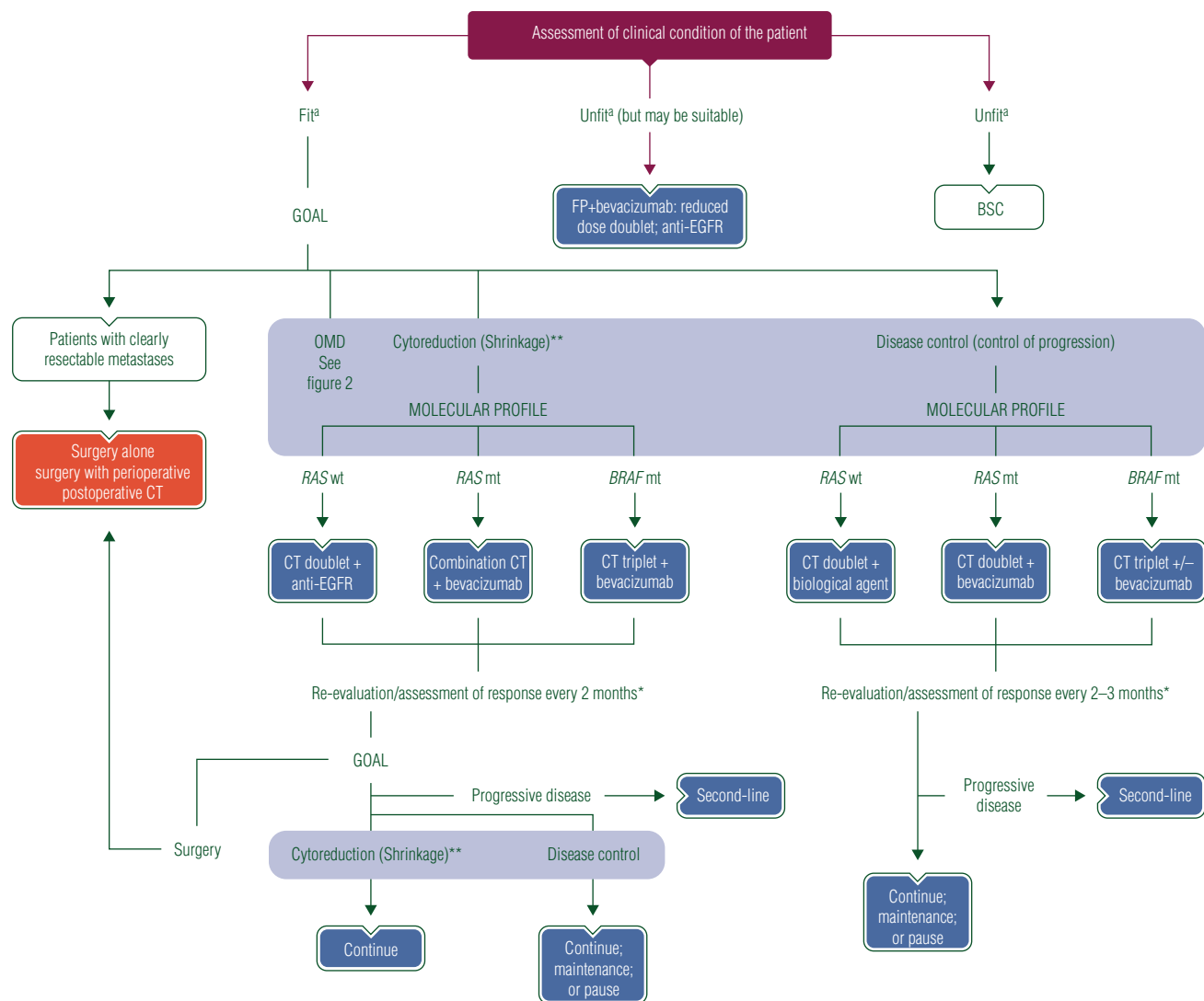


Figure 4. Zurich treatment algorithm. BSC, best supportive care; CT, chemotherapy; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; mt, mutant, NED, no evidence of disease; OMD, oligometastatic disease; wt, wild-type. ^aPatients assessed as fit or unfit according to medical condition not due to malignant disease. *After two re-evaluations, consider maintenance. **(A) Includes two 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.

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

Category	Fit patients ^b						Unfit ^b	
	Cytoreduction (tumour shrinkage)			Disease control (control of progression)			May be unfit	Unfit
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 ^{c,d}	CT doublet + bevacizumab	FOLFOXIRI + bevacizumab	CT doublet + bevacizumab or CT doublet + EGFR antibody ^c	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 ^e	FP + bevacizumab	FP + bevacizumab	FP + bevacizumab ^e	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 ^{c,f} 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 ^{c,f} or irinotecan + cetuximab ^f	Regorafenib or trifluridine/ tipiracil	Regorafenib or trifluridine/ tipiracil	CT doublet + EGFR antibody ^c or irinotecan + cetuximab	Regorafenib or trifluridine/tipiracil	Regorafenib or trifluridine/tipiracil		—
Second choice	EGFR antibody monotherapy ^f			EGFR antibody monotherapy ^f				—
Third choice	Regorafenib or trifluridine/ tipiracil			Regorafenib or trifluridine/ tipiracil				—

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

^aCross references to Figure 4.

^bPatients assessed as fit or unfit according to medical condition not due to malignant disease.

^cEGFR antibodies: cetuximab and panitumumab.

^dIn patients in need of a rapid reduction in 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.

^eIn patients where a bevacizumab-containing regimen was started. In patients where a cetuximab-containing combination was started: pause or less intensive regimen.

^fIf not yet pretreated with an EGFR antibody.

categorised as being clinically fit must be made at a tumour board meeting by an MDT, informed by the appropriate molecular analyses. The appropriate molecular analyses are to be carried out 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 an 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

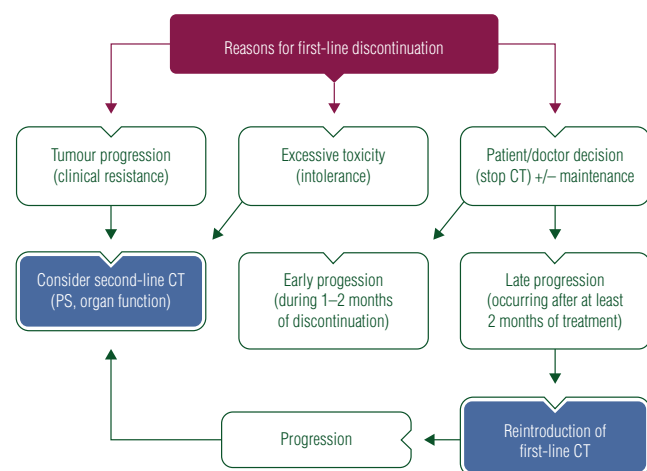


Figure 5. Maintenance and second-line treatment options. CT, chemotherapy; PS, performance status.

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 reevaluated 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 in 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

Table 8. Summary of recommendations

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

Recommendation 1: Tissue handling

- Fixation with 10% neutral buffered formalin (4% formaldehyde) is recommended [V, A]
- Fixation time should be no less than 6 h, and no greater than 48 h 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 before analysis [IV, A]

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%) before DNA extraction is recommended [III, A]

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]

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 carried out on all patients at the time of diagnosis of mCRC [I, A]
- RAS testing is mandatory before 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 carried out and recorded before 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.

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 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 carried out in patients with a suspicion of UGT1A1 deficiency as reflected by low conjugated bilirubin and in patients where an irinotecan dose of >180 mg/m² 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 carried out only in a research setting [V, D]

Continued

Table 8. *Continued*

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 first 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 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 bevacizumab or FOLFOXIRI plus 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 an 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

Continued

Table 8. Continued

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

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 (as was done in the pivotal trials examining FOLFOXIRI)
- 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.
- 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

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 reevaluated 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)

Continued

Table 8. *Continued*

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

- 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 reevaluated 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 reevaluated 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.

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 reevaluated 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 reevaluated 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].

note

A summary of recommendations is provided in Table 8.

funding

All costs relating to the consensus conference were covered from the European Society for Medical Oncology central funds. There was no external funding of the event or manuscript production.

disclosure

RA has reported honoraria from Amgen, Merck-Serono, Sanofi, Roche. EAA has reported advisory role for Amgen, Bayer, Celgene, Merck, Roche, Sanofi. DAr has reported honoraria/consultancy for Roche, Merck-Serono, Bayer, Amgen; research funding from Roche. ABa has reported advisory boards for Horizon Discovery, Trovagen and Biocartis; stock holder for Horizon Discovery. ABe 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. GB has reported research grants from Bayer, Celgene, Lilly, Roche, Abbvie; speaker for Roche, Bayer, Lilly, Amgen, Janssen, Taiho, Pfizer, Novartis. AC has reported member of speaker's bureau for Roche and Merck-Serono; advisory boards for Merck-Serono, Roche, Amgen, Bayer and Lilly. FC has reported consultancy/advisory roles for Bayer, Roche, Merck-Serono, Sanofi, Lilly, Astra Zeneca. ED-R has reported advisory boards for Roche, Merck-Serono, Sanofi, Bayer, Amgen; research grants from Roche, Merck-Serono, Amgen. J-YD has reported advisory boards, symposia, lectures for Amgen, Roche, Merck-Serono, Sanofi, Bayer. MD 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. AF has reported honoraria for advisory role, speaker at symposia and research funding from Amgen, Bayer, Merck-Serono, Roche, Sanofi and Lilly. AG has reported research fundings and honoraria for consultancy activities from Genentech, Roche, Eisai, Bayer, Amgen. TG has reported speakers' bureau member and research funding from Roche, Merck-Serono, Amgen, Sanofi-Aventis, Bayer. VH 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. C-HK has reported speakers' honoraria and advisory boards for Amgen, Merck, Pfizer, Sanofi; research grants from Novartis, Roche, Celgene. RL has reported advisory boards for Merck, Roche, Sanofi, Amgen. PL-P has reported honoraria for conferences and consulting from Amgen, Sanofi, Merck-Serono, Boehringer Ingelheim, Astra Zeneca, Roche, Lilly, Integragen. BM has reported research grants from Merck Serono, Hoffmann La Roche; consultancy/advisory board for Bayer, Boehringer-Ingelheim, Novartis. TM has reported research funding from Astra Zeneca, GlaxoSmithKline and Almac Diagnostics. KM

has reported member of speaker's bureau for Merck-Serono, Taiho, Chugai and Takeda. PO 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. DP has reported advisory boards and lectures for Roche, Merck-Serono, Amgen. GP has reported research grants from Roche, Sanofi, Amgen. PP has reported advisory boards, symposia, lectures for Amgen, Bayer, Celgene, Merck-Serono, Merck Sharp & Dohme, Nordic Drugs, Roche, Sanofi, Taiho. TJP has reported advisory boards for Amgen, Roche, Merck. CP has reported advisory role for Merck-Serono, Roche, Bayer, Nordic Pharma, Amgen. JR has reported research funding, speaker fees, advisory board member for Bayer, Simtex, Merck-Serono. RS has reported member of advisory board and speaker's bureau for Merck-Serono and Amgen; research funding from Roche, Amgen and Merck-Serono. WS has reported research funding and honoraria for consultancy activities from Roche, Merck, Bayer, Amgen. HJS has reported support for clinical trials from Roche; advisory boards for Amgen, Roche and Bayer. AS has reported advisory boards and satellite symposia for Roche, Merck-Serono, Amgen, Takeda, Bayer, Sanofi, Lilly, Celgene. JTab has reported consultancy/advisory role for Amgen, Bayer, Boehringer Ingelheim, Celgene, Chugai, Lilly, MSD, Merck-Serono, Novartis, Roche, Sanofi, Symphogen, Taiho and Takeda. JTai has reported advisory, research grants, speaker for Roche, Merck, Amgen, Sanofi, Bayer. EVC has reported research grants Bayer, Boehringer, Amgen, Celgene, Ipsen, Lilly, Merck, Novartis, Roche, Sanofi. JHVK has reported research funding from Amgen and Merck-Serono. HW has reported advisory boards and speakers' bureau for Sanofi, Bayer, Roche, Merck, Sirtex Medical, Lilly. TY has reported research funding from Pfizer, Eli Lilly, Sumitomo Dainippon, Taiho, Yakult and Daiichi Sankyo. DAd, ADH, KH, PH, NN, WJGO, AR, ST and AZ have reported no potential conflicts of interest.

references

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49: 1374–1403.
2. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136: E359–E386.
3. Schmol HJ, Van Cutsem E, Stein A et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. *Ann Oncol* 2012; 23: 2479–2516.
4. Dykewicz CA, Centers for Disease Control and Prevention, Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144.
5. Van Cutsem E, Cervantes A, Nordlinger B et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014; 25(Suppl 3): iii1–iii9.
6. Neumeister VM, Anagnostou V, Siddiqui S et al. Quantitative assessment of effect of preanalytic cold ischemic time on protein expression in breast cancer tissues. *J Natl Cancer Inst* 2012; 104: 1815–1824.
7. Portier BP, Wang Z, Downs-Kelly E et al. Delay to formalin fixation 'cold ischemia time': effect on ERBB2 detection by in-situ hybridization and immunohistochemistry. *Mod Pathol* 2013; 26: 1–9.

8. Engel KB, Moore HM. Effects of preanalytical variables on the detection of proteins by immunohistochemistry in formalin-fixed, paraffin-embedded tissue. *Arch Pathol Lab Med* 2011; 135: 537–543.
9. Arber DA. Effect of prolonged formalin fixation on the immunohistochemical reactivity of breast markers. *Appl Immunohistochem Mol Morphol* 2002; 10: 183–186.
10. Babic A, Loftin IR, Stanislaw S et al. The impact of pre-analytical processing on staining quality for H&E, dual hapten, dual color in situ hybridization and fluorescent in situ hybridization assays. *Methods* 2010; 52: 287–300.
11. Chafin D, Theiss A, Roberts E et al. Rapid two-temperature formalin fixation. *PLoS One* 2013; 8: e54138.
12. Kerr KM, Bubendorf L, Edelman MJ et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014; 25: 1681–1690.
13. van Krieken JH, Jung A, Kirchner T et al. KRAS mutation testing for predicting response to anti-EGFR therapy for colorectal carcinoma: proposal for an European quality assurance program. *Virchows Arch* 2008; 453: 417–431.
14. Dijkstra JR, Heideman DA, Meijer GA et al. KRAS mutation analysis on low percentage of colon cancer cells: the importance of quality assurance. *Virchows Arch* 2013; 462: 39–46.
15. Tsiatis AC, Norris-Kirby A, Rich RG et al. Comparison of Sanger sequencing, pyrosequencing, and melting curve analysis for the detection of KRAS mutations: diagnostic and clinical implications. *J Mol Diagn* 2010; 12: 425–432.
16. Carotenuto P, Roma C, Rachiglio AM et al. Detection of KRAS mutations in colorectal carcinoma patients with an integrated PCR/sequencing and real-time PCR approach. *Pharmacogenomics* 2010; 11: 1169–1179.
17. Tol J, Dijkstra JR, Vink-Borger ME et al. High sensitivity of both sequencing and real-time PCR analysis of KRAS mutations in colorectal cancer tissue. *J Cell Mol Med* 2010; 14: 2122–2131.
18. Etienne-Grimaldi MC, Formento JL, Francoual M et al. K-Ras mutations and treatment outcome in colorectal cancer patients receiving exclusive fluoropyrimidine therapy. *Clin Cancer Res* 2008; 14: 4830–4835.
19. Losi L, Benhattar J, Costa J. Stability of K-ras mutations throughout the natural history of human colorectal cancer. *Eur J Cancer* 1992; 28A: 1115–1120.
20. Suchy B, Zietz C, Rabes HM. K-ras point mutations in human colorectal carcinomas: relation to aneuploidy and metastasis. *Int J Cancer* 1992; 52: 30–33.
21. Weber JC, Meyer N, Pencreach E et al. Allelotyping analyses of synchronous primary and metastasis CIN colon cancers identified different subtypes. *Int J Cancer* 2007; 120: 524–532.
22. Zauber P, Sabbath-Solitare M, Marotta SP, Bishop DT. Molecular changes in the Ki-ras and APC genes in primary colorectal carcinoma and synchronous metastases compared with the findings in accompanying adenomas. *Mol Pathol* 2003; 56: 137–140.
23. Oudejans JJ, Slebos RJ, Zoetmulder FA et al. Differential activation of ras genes by point mutation in human colon cancer with metastases to either lung or liver. *Int J Cancer* 1991; 49: 875–879.
24. Al-Mulla F, Going JJ, Sowden ET et al. Heterogeneity of mutant versus wild-type Ki-ras in primary and metastatic colorectal carcinomas, and association of codon-12 valine with early mortality. *J Pathol* 1998; 185: 130–138.
25. Albanese I, Scibetta AG, Migliavacca M et al. Heterogeneity within and between primary colorectal carcinomas and matched metastases as revealed by analysis of Ki-ras and p53 mutations. *Biochem Biophys Res Commun* 2004; 325: 784–791.
26. Oliveira C, Velho S, Moutinho C et al. KRAS and BRAF oncogenic mutations in MSS colorectal carcinoma progression. *Oncogene* 2007; 26: 158–163.
27. Artale S, Sartore-Bianchi A, Veronese SM et al. Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. *J Clin Oncol* 2008; 26: 4217–4219.
28. Santini D, Loupakis F, Vincenzi B et al. High concordance of KRAS status between primary colorectal tumors and related metastatic sites: implications for clinical practice. *Oncologist* 2008; 13: 1270–1275.
29. Cejas P, Lopez-Gomez M, Aguayo C et al. KRAS mutations in primary colorectal cancer tumors and related metastases: a potential role in prediction of lung metastasis. *PLoS One* 2009; 4: e8199.
30. Garm Spindler KL, Pallisgaard N, Rasmussen AA et al. The importance of KRAS mutations and EGF61A>G polymorphism to the effect of cetuximab and irinotecan in metastatic colorectal cancer. *Ann Oncol* 2009; 20: 879–884.
31. Loupakis F, Pollina L, Stasi I et al. PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer. *J Clin Oncol* 2009; 27: 2622–2629.
32. Molinari F, Martin V, Saletti P et al. Differing deregulation of EGFR and downstream proteins in primary colorectal cancer and related metastatic sites may be clinically relevant. *Br J Cancer* 2009; 100: 1087–1094.
33. Perrone F, Lampis A, Orsenigo M et al. PI3KCA/PTEN deregulation contributes to impaired responses to cetuximab in metastatic colorectal cancer patients. *Ann Oncol* 2009; 20: 84–90.
34. Baldus SE, Schaefer KL, Engers R et al. Prevalence and heterogeneity of KRAS, BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases. *Clin Cancer Res* 2010; 16: 790–799.
35. Italiano A, Hostein I, Soubeyran I et al. KRAS and BRAF mutational status in primary colorectal tumors and related metastatic sites: biological and clinical implications. *Ann Surg Oncol* 2010; 17: 1429–1434.
36. Knijn N, Mekenkamp LJ, Klomp M et al. KRAS mutation analysis: a comparison between primary tumours and matched liver metastases in 305 colorectal cancer patients. *Br J Cancer* 2011; 104: 1020–1026.
37. Corcoran RB, Ebi H, Turke AB et al. EGFR-mediated re-activation of MAPK signaling contributes to insensitivity of BRAF mutant colorectal cancers to RAF inhibition with vemurafenib. *Cancer Discov* 2012; 2: 227–235.
38. Maughan TS, Adams RA, Smith CG et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 2011; 377: 2103–2114.
39. Swain SM, Baselga J, Kim SB et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372: 724–734.
40. Dancey JE, Dobbin KK, Groshen S et al. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res* 2010; 16: 1745–1755.
41. Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 1626–1634.
42. Karapatis CS, Khambata-Ford S, Jonker DJ et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008; 359: 1757–1765.
43. Van Cutsem E, Kohne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009; 360: 1408–1417.
44. Van Cutsem E, Kohne CH, Lang I et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 2011; 29: 2011–2019.
45. Bokemeyer C, Bondarenko I, Makhson A et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009; 27: 663–671.
46. Bokemeyer C, Bondarenko I, Hartmann JT et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 2011; 22: 1535–1546.
47. Peeters M, Price TJ, Cervantes A et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010; 28: 4706–4713.
48. Douillard JY, Oliner KS, Siena S et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *N Engl J Med* 2013; 369: 1023–1034.
49. Van Cutsem E, Lenz HJ, Kohne CH et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 2015; 33: 692–700.
50. Bokemeyer C, Kohne CH, Ciardiello F et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. *Eur J Cancer* 2015; 51: 1243–1252.

51. Peeters M, Oliner KS, Price TJ et al. Analysis of KRAS/NRAS mutations in a Phase III Study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015; 21: 5469–5479.
52. Poulin-Costello M, Azoulay L, Van Cutsem E et al. An analysis of the treatment effect of panitumumab on overall survival from a phase 3, randomized, controlled, multicenter trial (20020408) in patients with chemotherapy refractory metastatic colorectal cancer. *Target Oncol* 2013; 8: 127–136.
53. Schwartzberg LS, Rivera F, Karthaus M et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol* 2014; 32: 2240–2247.
54. Stintzing S, Jung A, Rossius L et al. Mutations within the EGFR signaling pathway: influence on efficacy in FIRE-3—a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. *J Clin Oncol* 2014; 32(3 Suppl): abstr 445.
55. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2014; 15: 1065–1075.
56. Sorich MJ, Wiese MD, Rowland A et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. *Ann Oncol* 2015; 26: 13–21.
57. Wong NA, Gonzalez D, Salto-Tellez M et al. RAS testing of colorectal carcinoma—a guidance document from the Association of Clinical Pathologists Molecular Pathology and Diagnostics Group. *J Clin Pathol* 2014; 67: 751–757.
58. Tack V, Ligtenberg MJ, Tembuysen L et al. External quality assessment unravels interlaboratory differences in quality of RAS testing for anti-EGFR therapy in colorectal cancer. *Oncologist* 2015; 20: 257–262.
59. Kircher SM, Mohindra N, Nimeiri H. Cost estimates and economic implications of expanded RAS testing in metastatic colorectal cancer. *Oncologist* 2015; 20: 14–18.
60. Tran B, Kopetz S, Tie J et al. Impact of BRAF mutation and microsatellite instability on the pattern of metastatic spread and prognosis in metastatic colorectal cancer. *Cancer* 2011; 117: 4623–4632.
61. Tveit KM, Guren T, Glimelius B et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 2012; 30: 1755–1762.
62. Venderbosch S, Nagtegaal ID, Maughan TS et al. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. *Clin Cancer Res* 2014; 20: 5322–5330.
63. Tol J, Nagtegaal ID, Punt CJ. BRAF mutation in metastatic colorectal cancer. *N Engl J Med* 2009; 361: 98–99.
64. Peeters M, Oliner KS, Parker A et al. Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res* 2013; 19: 1902–1912.
65. Seymour MT, Brown SR, Middleton G et al. Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol* 2013; 14: 749–759.
66. Pietrantonio F, Petrelli F, Coiu A et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. *Eur J Cancer* 2015; 51: 587–594.
67. Rowland A, Dias MM, Wiese MD et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. *Br J Cancer* 2015; 112: 1888–1894.
68. Cremolini C, Loupakis F, Antoniotti C et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol* 2015; 16: 1306–1315.
69. Sosman JA, Kim KB, Schuchter L et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med* 2012; 366: 707–714.
70. Kopetz S, Desai J, Chan E et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J Clin Oncol* 2015; 33: 4032–4038.
71. Prahallad A, Sun C, Huang S et al. Unresponsiveness of colon cancer to BRAF (V600E) inhibition through feedback activation of EGFR. *Nature* 2012; 483: 100–103.
72. Corcoran RB, Atreya CE, Falchook GS et al. Combined BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600-mutant colorectal cancer. *J Clin Oncol* 2015; 33: 4023–4031.
73. Hyman DM, Puzanov I, Subbiah V et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med* 2015; 373: 726–736.
74. Bettstetter M, Dechant S, Ruemmele P et al. Distinction of hereditary nonpolyposis colorectal cancer and sporadic microsatellite-unstable colorectal cancer through quantification of MLH1 methylation by real-time PCR. *Clin Cancer Res* 2007; 13: 3221–3228.
75. Domingo E, Niessen RC, Oliveira C et al. BRAF-V600E is not involved in the colorectal tumorigenesis of HNPCC in patients with functional MLH1 and MSH2 genes. *Oncogene* 2005; 24: 3995–3998.
76. Loughrey MB, Waring PM, Tan A et al. Incorporation of somatic BRAF mutation testing into an algorithm for the investigation of hereditary non-polyposis colorectal cancer. *Fam Cancer* 2007; 6: 301–310.
77. Cremolini C, Di Bartolomeo M, Amatu A et al. BRAF codons 594 and 596 mutations identify a new molecular subtype of metastatic colorectal cancer at favorable prognosis. *Ann Oncol* 2015; 26: 2092–2097.
78. Des Guetz G, Uzzan B, Nicolas P et al. Microsatellite instability: a predictive marker in metastatic colorectal cancer? *Target Oncol* 2009; 4: 57–62.
79. Goldstein J, Tran B, Ensor J et al. Multicenter retrospective analysis of metastatic colorectal cancer (CRC) with high-level microsatellite instability (MSI-H). *Ann Oncol* 2014; 25: 1032–1038.
80. Muller CI, Schulmann K, Reinacher-Schick A et al. Predictive and prognostic value of microsatellite instability in patients with advanced colorectal cancer treated with a fluoropyrimidine and oxaliplatin containing first-line chemotherapy. A report of the AIO Colorectal Study Group. *Int J Colorectal Dis* 2008; 23: 1033–1039.
81. Nopel-Dunnebacke S, Schulmann K, Reinacher-Schick A et al. Prognostic value of microsatellite instability and p53 expression in metastatic colorectal cancer treated with oxaliplatin and fluoropyrimidine-based chemotherapy. *Z Gastroenterol* 2014; 52: 1394–1401.
82. des Guetz G, Mariani P, Cucherousset J et al. Microsatellite instability and sensitivity to FOLFOX treatment in metastatic colorectal cancer. *Anticancer Res* 2007; 27: 2715–2719.
83. Kim JE, Hong YS, Ryu MH et al. Association between deficient mismatch repair system and efficacy to irinotecan-containing chemotherapy in metastatic colon cancer. *Cancer Sci* 2011; 102: 1706–1711.
84. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015; 372: 2509–2520.
85. Sanoff HK, McLeod HL. Predictive factors for response and toxicity in chemotherapy: pharmacogenomics. *Semin Colon Rectal Surg* 2008; 19: 226–230.
86. Meulendijks D, Henricks LM, Sonke GS et al. Clinical relevance of DPYD variants c.1679T>G, c.1236G>A/HapB3, and c.1601G>A as predictors of severe fluoropyrimidine-associated toxicity: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; 16: 1639–1650.
87. Marsh S, Hoskins JM. Irinotecan pharmacogenomics. *Pharmacogenomics* 2010; 11: 1003–1010.
88. Barbarino JM, Haidar CE, Klein TE, Altman RB. PharmGKB summary: very important pharmacogene information for UGT1A1. *Pharmacogenet Genomics* 2014; 24: 177–183.
89. Camptosar prescribing information. <http://labeling.pfizer.com/ShowLabeling.aspx?id=533>. 2014.

90. Olausson KA, Mountzios G, Soria JC. ERCC1 as a risk stratifier in platinum-based chemotherapy for nonsmall-cell lung cancer. *Curr Opin Pulm Med* 2007; 13: 284–289.
91. Soria JC. ERCC1-tailored chemotherapy in lung cancer: the first prospective randomized trial. *J Clin Oncol* 2007; 25: 2648–2649.
92. Qian YY, Liu XY, Wu Q et al. The ERCC1 C118T polymorphism predicts clinical outcomes of colorectal cancer patients receiving oxaliplatin-based chemotherapy: a meta-analysis based on 22 studies. *Asian Pac J Cancer Prev* 2014; 15: 8383–8390.
93. Orlandi A, Di Salvatore M, Bagala C et al. ERCC1 induction after oxaliplatin exposure may depend on KRAS mutational status in colorectal cancer cell line: in vitro veritas. *J Cancer* 2015; 6: 70–81.
94. Peters GJ, Backus HH, Freemantle S et al. Induction of thymidylate synthase as a 5-fluorouracil resistance mechanism. *Biochim Biophys Acta* 2002; 1587: 194–205.
95. Hoskins JM, Goldberg RM, Qu P et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007; 99: 1290–1295.
96. Misale S, Di Nicolantonio F, Sartore-Bianchi A et al. Resistance to anti-EGFR therapy in colorectal cancer: from heterogeneity to convergent evolution. *Cancer Discov* 2014; 4: 1269–1280.
97. Bardelli A, Siena S. Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. *J Clin Oncol* 2010; 28: 1254–1261.
98. Mohan S, Heitzer E, Ulz P et al. Changes in colorectal carcinoma genomes under anti-EGFR therapy identified by whole-genome plasma DNA sequencing. *PLoS Genet* 2014; 10: e1004271.
99. Yonesaka K, Zejnullahu K, Okamoto I et al. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Sci Transl Med* 2011; 3: 99ra86.
100. Bertotti A, Migliardi G, Galimi F et al. A molecularly annotated platform of patient-derived xenografts ('xenopatiens') identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. *Cancer Discov* 2011; 1: 508–523.
101. Douillard JY, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010; 28: 4697–4705.
102. Stintzing S, Jung AS, Rossius L et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3. *Eur J Cancer* 2013; 49(Suppl 3): abstr LBA17.
103. Valtorta E, Misale S, Sartore-Bianchi A et al. KRAS gene amplification in colorectal cancer and impact on response to EGFR-targeted therapy. *Int J Cancer* 2013; 133: 1259–1265.
104. Vaughn CP, Zobell SD, Furtado LV et al. Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. *Genes Chromosomes Cancer* 2011; 50: 307–312.
105. Ogino S, Lochhead P, Giovannucci E et al. Discovery of colorectal cancer PIK3CA mutation as potential predictive biomarker: power and promise of molecular pathological epidemiology. *Oncogene* 2014; 33: 2949–2955.
106. Jhawer M, Goel S, Wilson AJ et al. PIK3CA mutation/PTEN expression status predicts response of colon cancer cells to the epidermal growth factor receptor inhibitor cetuximab. *Cancer Res* 2008; 68: 1953–1961.
107. Karapetis CS, Jonker D, Daneshmand M et al. PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer—results from NCIC CTG/AGITG CO.17. *Clin Cancer Res* 2014; 20: 744–753.
108. Prenen H, De Schutter J, Jacobs B et al. PIK3CA mutations are not a major determinant of resistance to the epidermal growth factor receptor inhibitor cetuximab in metastatic colorectal cancer. *Clin Cancer Res* 2009; 15: 3184–3188.
109. Sartore-Bianchi A, Martini M, Molinari F et al. PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies. *Cancer Res* 2009; 69: 1851–1857.
110. Tian S, Simon I, Moreno V et al. A combined oncogenic pathway signature of BRAF, KRAS and PIK3CA mutation improves colorectal cancer classification and cetuximab treatment prediction. *Gut* 2013; 62: 540–549.
111. Misale S, Yaeger R, Hobor S et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature* 2012; 486: 532–536.
112. Laurent-Puig P, Cayre A, Manceau G et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. *J Clin Oncol* 2009; 27: 5924–5930.
113. Kavuri SM, Jain N, Galimi F et al. HER2 activating mutations are targets for colorectal cancer treatment. *Cancer Discov* 2015; 5: 832–841.
114. Siena S, Sartore-Bianchi A, Lonardi S et al. Trastuzumab and lapatinib in HER2-amplified metastatic colorectal cancer patients (mCRC): the HERACLES trial. *J Clin Oncol* 2015; 33(15 Suppl): abstr 3508.
115. Juo YY, Johnston FM, Zhang DY et al. Prognostic value of CpG island methylator phenotype among colorectal cancer patients: a systematic review and meta-analysis. *Ann Oncol* 2014; 25: 2314–2327.
116. Moutinho C, Martinez-Cardus A, Santos C et al. Epigenetic inactivation of the BRCA1 interactor SRBC and resistance to oxaliplatin in colorectal cancer. *J Natl Cancer Inst* 2014; 106: djt322.
117. Cohen SJ, Punt CJ, Iannotti N et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 3213–3221.
118. Diaz LA, Jr., Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol* 2014; 32: 579–586.
119. Siravegna G, Bardelli A. Genotyping cell-free tumor DNA in the blood to detect residual disease and drug resistance. *Genome Biol* 2014; 15: 449.
120. Montagut C, Dalmases A, Bellosillo B et al. Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. *Nat Med* 2012; 18: 221–223.
121. Aung KL, Board RE, Ellison G et al. Current status and future potential of somatic mutation testing from circulating free DNA in patients with solid tumours. *Hugo J* 2010; 4: 11–21.
122. Bettegowda C, Sausen M, Leary RJ et al. Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med* 2014; 6: 224ra224.
123. Dawson SJ, Tsui DW, Murtaza M et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *N Engl J Med* 2013; 368: 1199–1209.
124. De Mattos-Arruda L, Weigelt B, Cortes J et al. Capturing intra-tumor genetic heterogeneity by de novo mutation profiling of circulating cell-free tumor DNA: a proof-of-principle. *Ann Oncol* 2014; 25: 1729–1735.
125. Diaz LA, Jr., Williams RT, Wu J et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature* 2012; 486: 537–540.
126. Forshew T, Murtaza M, Parkinson C et al. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. *Sci Transl Med* 2012; 4: 136ra168.
127. Gormally E, Caboux E, Vineis P, Hainaut P. Circulating free DNA in plasma or serum as biomarker of carcinogenesis: practical aspects and biological significance. *Mutat Res* 2007; 635: 105–117.
128. Higgins MJ, Jelovac D, Barnathan E et al. Detection of tumor PIK3CA status in metastatic breast cancer using peripheral blood. *Clin Cancer Res* 2012; 18: 3462–3469.
129. Murtaza M, Dawson SJ, Tsui DW et al. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature* 2013; 497: 108–112.
130. Newman AM, Bratman SV, To J et al. An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med* 2014; 20: 548–554.
131. Punnoose EA, Atwal S, Liu W et al. Evaluation of circulating tumor cells and circulating tumor DNA in non-small cell lung cancer: association with clinical endpoints in a phase II clinical trial of pertuzumab and erlotinib. *Clin Cancer Res* 2012; 18: 2391–2401.
132. Schwarzenbach H, Hoon DS, Pantel K. Cell-free nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer* 2011; 11: 426–437.

133. Taly V, Pekin D, Benhaim L et al. Multiplex picodroplet digital PCR to detect KRAS mutations in circulating DNA from the plasma of colorectal cancer patients. *Clin Chem* 2013; 59: 1722–1731.
134. Taniguchi K, Uchida J, Nishino K et al. Quantitative detection of EGFR mutations in circulating tumor DNA derived from lung adenocarcinomas. *Clin Cancer Res* 2011; 17: 7808–7815.
135. Thierry AR, Mouliere F, El Messaoudi S et al. Clinical validation of the detection of KRAS and BRAF mutations from circulating tumor DNA. *Nat Med* 2014; 20: 430–435.
136. Li J, Mansmann UR. A microRNA molecular modeling extension for prediction of colorectal cancer treatment. *BMC Cancer* 2015; 15: 472.
137. Ciardiello F, Normanno N, Maiello E et al. Clinical activity of FOLFIRI plus cetuximab according to extended gene mutation status by next-generation sequencing: findings from the CAPRI-GOIM trial. *Ann Oncol* 2014; 25: 1756–1761.
138. Marisa L, de Reynies A, Duval A et al. Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value. *PLoS Med* 2013; 10: e1001453.
139. Guinney J, Dienstmann R, Wang B et al. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015; 21: 1350–1356.
140. Prades J, Borrás JM. Shifting sands: adapting the multidisciplinary team model to technological and organizational innovations in cancer care. *Future Oncol* 2014; 10: 1995–1998.
141. Shah S, Arora S, Atkin G et al. Decision-making in Colorectal Cancer Tumor Board meetings: results of a prospective observational assessment. *Surg Endosc* 2014; 28: 2783–2788.
142. Prades J, Remue E, van Hoof E, Borrás JM. Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes. *Health Policy* 2015; 119: 464–474.
143. Weiser MR, Jarnagin WR, Saltz LB. Colorectal cancer patients with oligometastatic liver disease: what is the optimal approach? *Oncology (Williston Park)* 2013; 27: 1074–1078.
144. Khattak MA, Martin HL, Beeke C et al. Survival differences in patients with metastatic colorectal cancer and with single site metastatic disease at initial presentation: results from South Australian clinical registry for advanced colorectal cancer. *Clin Colorectal Cancer* 2012; 11: 247–254.
145. Price TJ, Townsend AR, Beeke C et al. 'Watchful waiting' for metastatic colorectal cancer, antediluvian or an option to be considered again? *Asia Pac J Clin Oncol* 2012; 8: 10–13.
146. Yaeger R, Cercek A, Chou JF et al. BRAF mutation predicts for poor outcomes after metastasectomy in patients with metastatic colorectal cancer. *Cancer* 2014; 120: 2316–2324.
147. Ohrling K, Edler D, Hallstrom M, Ragnhammar P. Expression of thymidylate synthase in liver and lung metastases of colorectal cancer and their matched primary tumours. *Anticancer Res* 2008; 28: 1741–1747.
148. Adam R, De Gramont A, Figueras J et al. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 2012; 17: 1225–1239.
149. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007; 356: 1545–1559.
150. Zorzi D, Laurent A, Pawlik TM et al. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007; 94: 274–286.
151. Jones RP, Stattner S, Sutton P et al. Controversies in the oncosurgical management of liver limited stage IV colorectal cancer. *Surg Oncol* 2014; 23: 53–60.
152. Kanas GP, Taylor A, Primrose JN et al. Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors. *Clin Epidemiol* 2012; 4: 283–301.
153. Fong Y, Fortner J, Sun RL et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999; 230: 309–318; discussion 318–321.
154. Floriani I, Torri V, Rulli E et al. Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J Magn Reson Imaging* 2010; 31: 19–31.
155. Bartolotta TV, Taibbi A, Midiri M et al. Characterisation of focal liver lesions undetermined at grey-scale US: contrast-enhanced US versus 64-row MDCT and MRI with liver-specific contrast agent. *Radiol Med* 2010; 115: 714–731.
156. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010; 257: 674–684.
157. Zech CJ, Korpphongs P, Huppertz A et al. Randomized multicentre trial of gadoxetic acid-enhanced MRI versus conventional MRI or CT in the staging of colorectal cancer liver metastases. *Br J Surg* 2014; 101: 613–621.
158. Hendlisz A, Gollinopoulos V, Garcia C et al. Serial FDG-PET/CT for early outcome prediction in patients with metastatic colorectal cancer undergoing chemotherapy. *Ann Oncol* 2012; 23: 1687–1693.
159. Moulton C, Levine MN, Law C et al. An Ontario Clinical Oncology Group (COG) randomized controlled trial (RCT) assessing FDG PET/CT in resectable liver colorectal adenocarcinoma metastases (CAM). *J Clin Oncol* 2011; 29(Suppl): abstr 3520.
160. Petersen RK, Hess S, Alavi A, Hoiland-Carlson PF. Clinical impact of FDG-PET/CT on colorectal cancer staging and treatment strategy. *Am J Nucl Med Mol Imaging* 2014; 4: 471–482.
161. Maffione AM, Lopci E, Bluemel C et al. Diagnostic accuracy and impact on management of (18)F-FDG PET and PET/CT in colorectal liver metastasis: a meta-analysis and systematic review. *Eur J Nucl Med Mol Imaging* 2015; 42: 152–163.
162. Tomlinson JS, Jarnagin WR, DeMatteo RP et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007; 25: 4575–4580.
163. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2013; 14: 1208–1215.
164. Nordlinger B, Sorbye H, Glimelius B et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008; 371: 1007–1016.
165. Primrose J, Falk S, Finch-Jones M et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. *Lancet Oncol* 2014; 15: 601–611.
166. Mityr E, Fields AL, Bleiberg H et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol* 2008; 26: 4906–4911.
167. Kemeny N, Capanu M, D'Angelica M et al. Phase I trial of adjuvant hepatic arterial infusion (HAI) with floxuridine (FUDR) and dexamethasone plus systemic oxaliplatin, 5-fluorouracil and leucovorin in patients with resected liver metastases from colorectal cancer. *Ann Oncol* 2009; 20: 1236–1241.
168. Adam R, Delvart V, Pascal G et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004; 240: 644–657; discussion 657–658.
169. Adam R, Barroso E, Laurent C et al. Impact of the type and modalities of preoperative chemotherapy on the outcome of liver resection for colorectal metastases. *J Clin Oncol* 2011; 29(15 Suppl): abstr 3519.
170. Chun YS, Vauthey JN, Boonsirikamchai P et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA* 2009; 302: 2338–2344.
171. Adam R, Bhangui P, Poston G et al. Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases? *Ann Surg* 2010; 252: 774–787.
172. Nordlinger B, Van Cutsem E, Gruenberger T et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann Oncol* 2009; 20: 985–992.
173. Nordlinger B, Van Cutsem E, Rougier P et al. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur J Cancer* 2007; 43: 2037–2045.

174. Van Cutsem E, Nordlinger B, Adam R et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006; 42: 2212–2221.
175. Folprecht G, Grothey A, Alberts S et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005; 16: 1311–1319.
176. Folprecht G, Gruenberger T, Bechstein WO et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. *Lancet Oncol* 2010; 11: 38–47.
177. Ye LC, Liu TS, Ren L et al. Randomized controlled trial of cetuximab plus chemotherapy for patients with KRAS wild-type unresectable colorectal liver-limited metastases. *J Clin Oncol* 2013; 31: 1931–1938.
178. Gruenberger T, Bridgewater J, Chau I et al. Bevacizumab plus mFOLFOX-6 or FOLFOXIRI in patients with initially unresectable liver metastases from colorectal cancer: the OLIVIA multinational randomised phase II trial. *Ann Oncol* 2014; 26: 702–708.
179. Masi G, Loupakis F, Salvatore L et al. Bevacizumab with FOLFOXIRI (irinotecan, oxaliplatin, fluorouracil, and folinate) as first-line treatment for metastatic colorectal cancer: a phase 2 trial. *Lancet Oncol* 2010; 11: 845–852.
180. Folprecht G, Gruenberger T, Bechstein W et al. Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann Oncol* 2014; 25: 1018–1025.
181. Falcone A, Ricci S, Brunetti I et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007; 25: 1670–1676.
182. Loupakis F, Cremolini C, Masi G et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014; 371: 1609–1618.
183. Douillard JY, Siena S, Cassidy J et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014; 25: 1346–1355.
184. Okines A, Puerto OD, Cunningham D et al. Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *Br J Cancer* 2009; 101: 1033–1038.
185. Venook A, Niedzwiecki D, Lenz HJ et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). *J Clin Oncol* 2014; 32(15 Suppl): abstr LBA 3.
186. Piessevaux H, Buyse M, Schlichting M et al. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol* 2013; 31: 3764–3775.
187. Mansmann UR, Laubender RP, Giessen CA et al. Validating the prognostic relevance of initial change in tumor size using a series of therapeutic regimens for patients with metastatic colorectal cancer (mCRC). *J Clin Oncol* 2012; 30 (Suppl 4): abstr 580.
188. Mansmann UR, Laubender RP, Sartorius U et al. Improved early prediction of individual prognosis for patients with mCRC: joint modeling of tumor shrinkage with volume data for PFS and OS. *J Clin Oncol* 2012; 30(Suppl 15): abstr 3603.
189. Piessevaux H, Buyse M, De Roock W et al. Radiological tumor size decrease at week 6 is a potent predictor of outcome in chemorefractory metastatic colorectal cancer treated with cetuximab (BOND trial). *Ann Oncol* 2009; 20: 1375–1382.
190. Cremolini C, Loupakis F, Antoniotti C et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol* 2015; 26: 1188–1194.
191. Cremolini C, Loupakis F, Falcone A. FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2015; 372: 291–292.
192. Cremolini C, Loupakis F, Masi G et al. FOLFOXIRI/bevacizumab versus FOLFIRI/bevacizumab as first-line treatment in unresectable metastatic colorectal cancer: results of phase III TRIBE trial by GONO Group. *Ann Oncol* 2014; 24(Suppl 4): abstr O-0026.
193. Stintzing S, Modest DP, Fischer von Weikersthal L et al. Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306) in the final RAS evaluable population. *Ann Oncol* 2014; 25(Suppl 5): abstr LBA11.
194. Rivera F, Karthaus M, Hecht JR et al. First-line treatment with modified FOLFOX6 (mFOLFOX6) + panitumumab or bevacizumab in patients with RAS/BRAF wild-type (WT) metastatic colorectal carcinoma (mCRC). *Ann Oncol* 2015; 26(Suppl 4): abstr PD-014.
195. Bhutiani N, Akinwande O, Martin RC, 2nd. Efficacy and toxicity of hepatic intra-arterial drug-eluting (irinotecan) bead (DEBIR) therapy in irinotecan-refractory unresectable colorectal liver metastases. *World J Surg* 2015.
196. Liu DM, Thakor AS, Baerlocher M et al. A review of conventional and drug-eluting chemoembolization in the treatment of colorectal liver metastases: principles and proof. *Future Oncol* 2015; 11: 1421–1428.
197. Martin RC, 2nd, Scoggins CR, Schreeder M et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. *Cancer* 2015; 121: 3649–3658.
198. Ruers T, Punt C, Van Coevorden F et al. Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC). *J Clin Oncol* 2015; 33 (15 Suppl): abstr 3501.
199. Tanis E, Nordlinger B, Mauer M et al. Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983. *Eur J Cancer* 2014; 50: 912–919.
200. Ruers T, Punt C, Van Coevorden F et al. Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004). *Ann Oncol* 2012; 23: 2619–2626.
201. Evrard S, Poston G, Kissmeyer-Nielsen P et al. Combined ablation and resection (CARE) as an effective parenchymal sparing treatment for extensive colorectal liver metastases. *PLoS One* 2014; 9: e114404.
202. Lencioni R, Crocetti L, Cioni R et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008; 9: 621–628.
203. Petre EN, Jia X, Thornton RH et al. Treatment of pulmonary colorectal metastases by radiofrequency ablation. *Clin Colorectal Cancer* 2013; 12: 37–44.
204. Kashima M, Yamakado K, Takaki H et al. Complications after 1000 lung radiofrequency ablation sessions in 420 patients: a single center's experiences. *Am J Roentgenol* 2011; 197: W576–W580.
205. Schlijper RC, Grutters JP, Houben R et al. What to choose as radical local treatment for lung metastases from colo-rectal cancer: surgery or radiofrequency ablation? *Cancer Treat Rev* 2014; 40: 60–67.
206. Ricke J, Mohnike K, Pech M et al. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys* 2010; 78: 479–485.
207. Sterzing F, Brunner TB, Ernst I et al. Stereotactic body radiotherapy for liver tumors: principles and practical guidelines of the DEGRO Working Group on Stereotactic Radiotherapy. *Strahlenther Onkol* 2014; 190: 872–881.
208. Colletini F, Schnapauff D, Poellinger A et al. Percutaneous CT-guided high-dose brachytherapy (CT-HDRBT) ablation of primary and metastatic lung tumors in nonsurgical candidates. *Rofo* 2012; 184: 316–323.
209. Comito T, Cozzi L, Clerici E et al. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. *BMC Cancer* 2014; 14: 619.
210. Filippi AR, Badellino S, Guarneri A et al. Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases. *Technol Cancer Res Treat* 2014; 13: 37–45.

211. Tselis N, Ferentinos K, Kolotas C et al. Computed tomography-guided interstitial high-dose-rate brachytherapy in the local treatment of primary and secondary intrathoracic malignancies. *J Thorac Oncol* 2011; 6: 545–552.
212. Peters N, Wieners G, Pech M et al. CT-guided interstitial brachytherapy of primary and secondary lung malignancies: results of a prospective phase II trial. *Strahlenther Onkol* 2008; 184: 296–301.
213. Blomgren H, Lax I, Naslund I, Svanstrom R. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. *Acta Oncol* 1995; 34: 861–870.
214. Wada H, Takai Y, Nemoto K, Yamada S. Univariate analysis of factors correlated with tumor control probability of three-dimensional conformal hypofractionated high-dose radiotherapy for small pulmonary or hepatic tumors. *Int J Radiat Oncol Biol Phys* 2004; 58: 1114–1120.
215. Wulf J, Guckenberger M, Haedinger U et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. *Acta Oncol* 2006; 45: 838–847.
216. Ambrosino G, Polistina F, Costantin G et al. Image-guided robotic stereotactic radiosurgery for unresectable liver metastases: preliminary results. *Anticancer Res* 2009; 29: 3381–3384.
217. Goodman KA, Wiegner EA, Maturen KE et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys* 2010; 78: 486–493.
218. Hoyer M, Roed H, Traberg Hansen A et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. *Acta Oncol* 2006; 45: 823–830.
219. Lee MT, Kim JJ, Dinniwel R et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. *J Clin Oncol* 2009; 27: 1585–1591.
220. Mendez Romero A, Wunderink W, Hussain SM et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: a single institution phase i-ii study. *Acta Oncol* 2006; 45: 831–837.
221. Rusthoven KE, Kavanagh BD, Cardenes H et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009; 27: 1572–1578.
222. Scorsetti M, Arcangeli S, Tozzi A et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. *Int J Radiat Oncol Biol Phys* 2013; 86: 336–342.
223. Fumagalli I, Bibault JE, Dewas S et al. A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases. *Radiat Oncol* 2012; 7: 164.
224. Fiorentini G, Aliberti C, Tilli M et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. *Anticancer Res* 2012; 32: 1387–1395.
225. Hendlisz A, Van den Eynde M, Peeters M et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol* 2010; 28: 3687–3694.
226. van Hazel GA, Heinemann V, Sharma NK et al. SIRFLOX: randomized phase iii trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. *J Clin Oncol* 2016; 34: 1723–1731.
227. Garlipp B, de Baere T, Damm R et al. Left-liver hypertrophy after therapeutic right-liver radioembolization is substantial but less than after portal vein embolization. *Hepatology* 2014; 59: 1864–1873.
228. Cao C, Yan TD, Black D, Morris DL. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2009; 16: 2152–2165.
229. Cotte E, Passot G, Mohamed F et al. Management of peritoneal carcinomatosis from colorectal cancer: current state of practice. *Cancer J* 2009; 15: 243–248.
230. Elias D, Lefevre JH, Chevalier J et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol* 2009; 27: 681–685.
231. Elias D, Mariani A, Cloutier AS et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. *Eur J Surg Oncol* 2014; 40: 1467–1473.
232. Turaga K, Levine E, Barone R et al. Consensus guidelines from The American Society of Peritoneal Surface Malignancies on standardizing the delivery of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer patients in the United States. *Ann Surg Oncol* 2014; 21: 1501–1505.
233. Prada-Villaverde A, Esquivel J, Lowy AM et al. The American Society of Peritoneal Surface Malignancies evaluation of HIPEC with mitomycin C versus oxaliplatin in 539 patients with colon cancer undergoing a complete cytoreductive surgery. *J Surg Oncol* 2014; 110: 779–785.
234. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18: 2938–2947.
235. Douillard JY, Group VS. Irinotecan and high-dose fluorouracil/leucovorin for metastatic colorectal cancer. *Oncology (Williston Park)* 2000; 14: 51–55.
236. de Gramont A, Bosset JF, Milan C et al. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997; 15: 808–815.
237. Meta-Analysis Group in CancerLevy E, Piedbois P et al. Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. *J Clin Oncol* 1998; 16: 3537–3541.
238. Van Cutsem E, Hoff PM, Harper P et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Br J Cancer* 2004; 90: 1190–1197.
239. Cassidy J, Clarke S, Diaz-Rubio E et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2006–2012.
240. Fuchs CS, Marshall J, Mitchell E et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007; 25: 4779–4786.
241. Kohne CH, De Greve J, Hartmann JT et al. Irinotecan combined with infusional 5-fluorouracil/folinic acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. *EORTC study 40015*. *Ann Oncol* 2008; 19: 920–926.
242. Schmiegel W, Reinacher-Schick A, Arnold D et al. Capecitabine/irinotecan or capecitabine/oxaliplatin in combination with bevacizumab is effective and safe as first-line therapy for metastatic colorectal cancer: a randomized phase II study of the AIO colorectal study group. *Ann Oncol* 2013; 24: 1580–1587.
243. Moosmann N, von Weikersthal LF, Vehling-Kaiser U et al. Cetuximab plus capecitabine and irinotecan compared with cetuximab plus capecitabine and oxaliplatin as first-line treatment for patients with metastatic colorectal cancer: AIO KRK-0104—a randomized trial of the German AIO CRC study group. *J Clin Oncol* 2011; 29: 1050–1058.
244. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–2342.
245. Saltz LB, Clarke S, Diaz-Rubio E et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; 26: 2013–2019.
246. Souglakos J, Androulakis N, Syrigos K et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006; 94: 798–805.
247. Cunningham D, Lang I, Marcuello E et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol* 2013; 14: 1077–1085.
248. Kabbinar F, Irl C, Zurlo A, Hurwitz H. Bevacizumab improves the overall and progression-free survival of patients with metastatic colorectal cancer treated with 5-fluorouracil-based regimens irrespective of baseline risk. *Oncology* 2008; 75: 215–223.

249. Tebbutt NC, Wilson K, GebSKI VJ et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol* 2010; 28: 3191–3198.
250. Passardi A, Nanni O, Tassinari D et al. Effectiveness of bevacizumab added to standard chemotherapy in metastatic colorectal cancer: final results for first-line treatment from the ITACa randomized clinical trial. *Ann Oncol* 2015; 26: 1201–1207.
251. Souglakos J, Ziras N, Kakolyris S et al. Randomised phase-II trial of CAPIRI (capecitabine, irinotecan) plus bevacizumab vs FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus bevacizumab as first-line treatment of patients with unresectable/metastatic colorectal cancer (mCRC). *Br J Cancer* 2012; 106: 453–459.
252. Yamazaki K, Nagase M, Tamagawa H et al. A randomized phase III trial of mFOLFOX6 plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment for metastatic colorectal cancer: West Japan Oncology Group study 4407G (WJOG4407G). *J Clin Oncol* 2014; 32(15 Suppl): abstr 3534.
253. Kozloff M, Yood MU, Berlin J et al. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: the BRITe observational cohort study. *Oncologist* 2009; 14: 862–870.
254. Van Cutsem E, Rivera F, Berry S et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. *Ann Oncol* 2009; 20: 1842–1847.
255. European Medicines Agency. CHMP summary of opinion—erbitux. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000558/WC500155463.pdf (6 January 2015, date last accessed).
256. European Medicines Agency. CHMP summary of opinion—vectibix. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000741/WC500144827.pdf (6 January 2015, date last accessed).
257. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004; 22: 1209–1214.
258. Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol* 2005; 23: 9441–9442.
259. Heinemann V, Modest DP, Fischer von Weikersthal L et al. Independent radiological evaluation of objective response, early tumor shrinkage, and depth of response in FIRE-3 (AIO KRK-0306). *Ann Oncol* 2014; 25(Suppl 2): abstr 0-0030.
260. Lenz HJ, Niedzwiecki D, Innocenti F et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded RAS analyses untreated metastatic adenocarcinoma of the colon or rectum (mCRC). *Ann Oncol* 2014; 25(Suppl 5): abstr 5010.
261. Maughan TS, James RD, Kerr DJ et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet* 2003; 361: 457–464.
262. Labianca R, Sobrero A, Isa L et al. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol* 2011; 22: 1236–1242.
263. Tournigand C, Cervantes A, Figer A et al. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer—a GERCOR study. *J Clin Oncol* 2006; 24: 394–400.
264. Adams RA, Meade AM, Seymour MT et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet Oncol* 2011; 12: 642–653.
265. Chibaudel B, Maindrault-Goebel F, Lledo G et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol* 2009; 27: 5727–5733.
266. Tournigand C, Chibaudel B, Samson B et al. Bevacizumab with or without erlotinib as maintenance therapy in patients with metastatic colorectal cancer (GERCOR DREAM; OPTIMOX3): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2015; 16: 1493–1505.
267. Diaz-Rubio E, Gomez-Espana A, Massuti B et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist* 2012; 17: 15–25.
268. Hegewisch-Becker S, Graeven U, Lerchenmuller CA et al. Maintenance strategies after first-line oxaliplatin plus fluoropyrimidine plus bevacizumab for patients with metastatic colorectal cancer (AIO 0207): a randomised, non-inferiority, open-label, phase 3 trial. *Lancet Oncol* 2015; 16: 1355–1369.
269. Koeberle D, Betticher DC, von Moos R et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). *Ann Oncol* 2015; 26: 709–714.
270. Simkens LH, van Tinteren H, May A et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. *Lancet* 2015; 385: 1843–1852.
271. Wasan H, Meade AM, Adams R et al. Intermittent chemotherapy plus either intermittent or continuous cetuximab for first-line treatment of patients with KRAS wild-type advanced colorectal cancer (COIN-B): a randomised phase 2 trial. *Lancet Oncol* 2014; 15: 631–639.
272. Johnsson A, Hagman H, Frodin JE et al. A randomized phase III trial on maintenance treatment with bevacizumab alone or in combination with erlotinib after chemotherapy and bevacizumab in metastatic colorectal cancer: the Nordic ACT Trial. *Ann Oncol* 2013; 24: 2335–2341.
273. Stein A, Atanackovic D, Hildebrandt B et al. Upfront FOLFOXIRI+bevacizumab followed by fluoropyrimidin and bevacizumab maintenance in patients with molecularly unselected metastatic colorectal cancer. *Br J Cancer* 2015; 113: 872–877.
274. Garcia Alfonso P, Benavides M, Sanchez Ruiz A et al. Phase II study of first-line mFOLFOX plus cetuximab (C) for 8 cycles followed by mFOLFOX plus C or single agent (S/A) C as maintenance therapy in patients (P) with metastatic colorectal cancer (mCRC): The MACRO-2 trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). *Ann Oncol* 2014; 25(Suppl 4): abstr 4990.
275. Cunningham D, Pyrhonen S, James RD et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998; 352: 1413–1418.
276. Rougier P, Lepille D, Bennouna J et al. Antitumour activity of three second-line treatment combinations in patients with metastatic colorectal cancer after optimal 5-FU regimen failure: a randomised, multicentre phase II study. *Ann Oncol* 2002; 13: 1558–1567.
277. Rougier P, Van Cutsem E, Bajetta E et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998; 352: 1407–1412.
278. Haller DG, Rothenberg ML, Wong AO et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single-agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *J Clin Oncol* 2008; 26: 4544–4550.
279. Koopman M, Antonini NF, Douma J et al. Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007; 370: 135–142.
280. Seymour MT, Maughan TS, Ledermann JA et al. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007; 370: 143–152.
281. Tournigand C, Andre T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004; 22: 229–237.
282. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007; 25: 1539–1544.
283. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 29–37.

284. Beretta GD, Petrelli F, Stinco S et al. FOLFIRI + bevacizumab as second-line therapy for metastatic colorectal cancer pretreated with oxaliplatin: a pooled analysis of published trials. *Med Oncol* 2013; 30: 486.
285. Lievre A, Samalin E, Mitry E et al. Bevacizumab plus FOLFIRI or FOLFOX in chemotherapy-refractory patients with metastatic colorectal cancer: a retrospective study. *BMC Cancer* 2009; 9: 347.
286. Masi G, Salvatore L, Boni L et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Ann Oncol* 2015; 26: 724–730.
287. Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012; 30: 3499–3506.
288. Tabernero J, Van Cutsem E, Lakomy R et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer* 2014; 50: 320–331.
289. Tabernero J, Yoshino T, Cohn AL et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015; 16: 499–508.
290. Sobrero AF, Maurel J, Fehrenbacher L et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 2311–2319.
291. Cascinu S, Lonardi S, Rosati G et al. A phase III multicenter trial comparing two different sequences of second/third line therapy (cetuximab/irinotecan followed by FOLFOX versus FOLFOX followed by cetuximab/irinotecan) in metastatic KRAS wt colorectal cancer (mCC) patients, refractory to FOLFIRI/Bevacizumab. *Eur J Cancer* 2015; 51(Suppl S3): abstr 2006.
292. Hecht JR, Cohn A, Dakhil S et al. SPIRITT: a randomized, multicenter, phase II study of panitumumab with FOLFIRI and bevacizumab with FOLFIRI as second-line treatment in patients with unresectable wild type KRAS metastatic colorectal cancer. *Clin Colorectal Cancer* 2015; 14: 72–80.
293. Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; 351: 337–345.
294. Geva R, Vecchione L, Tejpar S et al. Bevacizumab plus chemotherapy as salvage treatment in chemorefractory patients with metastatic colorectal cancer. *Onco Targets Ther* 2013; 6: 53–58.
295. Hecht JR, Patnaik A, Berlin J et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. *Cancer* 2007; 110: 980–988.
296. Price TJ, Peeters M, Kim TW et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. *Lancet Oncol* 2014; 15: 569–579.
297. Grothey A, Van Cutsem E, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; 381: 303–312.
298. Li J, Qin S, Xu R et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015; 16: 619–629.
299. Mayer RJ, Van Cutsem E, Falcone A et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med* 2015; 372: 1909–1919.
300. Yoshino T, Mizunuma N, Yamazaki K et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2012; 13: 993–1001.
301. Papamichael D, Audisio RA, Glimelius B et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. *Ann Oncol* 2015; 26: 463–476.
302. Gruenberger B, Tamandl D, Schueller J et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008; 26: 1830–1835.
303. Garufi C, Torsello A, Tumolo S et al. Cetuximab plus chronomodulated irinotecan, 5-fluorouracil, leucovorin and oxaliplatin as neoadjuvant chemotherapy in colorectal liver metastases: POCHER trial. *Br J Cancer* 2010; 103: 1542–1547.
304. Wong R, Cunningham D, Barbachano Y et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. *Ann Oncol* 2011; 22: 2042–2048.