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Metastatic Colorectal Cancer (mCRC): French Intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR)

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Abstract

Introduction: This document is a summary of the French Intergroup guidelines regarding the management of metastatic colorectal cancer (mCRC) published in January 2019, and available on the French Society of Gastroenterology website (SNFGE) (www.tncc.org).

Methods: This collaborative work was realized by all French medical and surgical societies involved in the management of mCRC. Recommendations are graded in three categories (A, B and C), according to the level of evidence found in the literature, up until December 2018.

Results: The management of metastatic colorectal cancer has become complex because of increasing available medical, radiological and surgical treatments alone or in combination. The therapeutic strategy should be defined before the first-line treatment, mostly depending on the presentation of the disease (resectability of the metastases, symptomatic and/or threatening disease), of the patient's condition (ECOG PS, comorbidities), and tumor biology (RAS, BRAF, MSI). The sequence of targeted therapies also seems to have an impact on the outcome (angiogenesis inhibition beyond progression). Surgical resection of metastases was the only curative intent treatment to date, joined recently by percutaneous tumor ablation tools (radiofrequency, microwave). Localized therapies such as hepatic intra-arterial infusion, radioembolization and hyperthermic intraperitoneal chemotherapy, also have seen their indications specified (liver-dominant disease and resectable peritoneal carcinomatosis). New treatments have been developed in heavily pretreated patients, increasing overall survival and preserving quality of life (regorafenib and trifluridine/tipiracil). Finally, immune checkpoint inhibitors have demonstrated high efficacy in MSI mCRC.

Conclusion: French guidelines for mCRC management are put together to help offer the best personalized therapeutic strategy in daily clinical practice, as the mCRC therapeutic landscape is complexifying. These recommendations are permanently being reviewed and updated. Each individual case must be discussed within a multidisciplinary team (MDT).

Running Title: French clinical practice guidelines for metastatic colorectal cancer

Keywords: French Clinical Practice Guidelines, Metastatic ColoRectal Cancer, Chemotherapy, Hepatic Metastases Surgery, Targeted therapy, Therapeutic strategy.

I- Introduction

The present article is a summary of the French intergroup guidelines published in January 2019 on the SNFGE society website: www.tncd.org [1]. These guidelines are a collaborative work written by a multidisciplinary committee originating from 8 medical societies (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR) comprising several experts from different specialties involved in the management of mCRC (digestive and thoracic surgeons, pathologists, radiation oncologists, medical oncologists, gastroenterologists and radiologists). The initial document was reviewed and modified after further evaluation by a review committee, and the last version received final validation from the steering committee of the participating National Societies. These guidelines are an up-to-date comprehensive overview of pre-therapeutic exams, medico-surgical therapeutic strategies, the best chemotherapies and targeted therapy choices according to patients' and tumors' characteristics, somatic molecular alterations, the site of localized therapies and new drugs available. Recommendations based on the level of evidence were scored in 3 categories graded A, B and C), with only expert opinion (agreement or not, grade D) when no scientific evidence was validated [Table 1].

II- Pre-therapeutic assessment

Ila- RECOMMENDATIONS

Pre-therapy assessment typically begins by evaluating the patient's overall status, performance status, co-morbidities, tumor extension and results of molecular diagnostic tests from primary tumor tissue or metastases, focusing on:

- . RAS status (KRAS, NRAS) as a predictor of EGFRi (Epidermal Growth Factor Receptor Inhibitor) resistance (**recommendation: grade A**);
- . BRAF V600E status as a poor prognosis factor (**recommendation: grade B**);
- . MSI phenotyping (by immunochemistry of MMR proteins or microsatellite testing on tumor DNA) as a poor prognosis factor and predictor of immune checkpoint inhibitors' efficacy in mCRC (**recommendation: grade C**);
- . DPD phenotyping (by measuring plasma uracil concentration): fluoropyrimidine dose adjustment in case of partial DPD deficiency and fluoropyrimidine contraindication in case of complete DPD deficiency (**expert agreement**);
- . Thoraco-abdominopelvic CT scan at baseline +/- liver MRI to assess for resectability of liver metastases.

Iib- OPTIONS

- . UGT1A1 genotyping (for irinotecan dose adjustment in case of Gilbert's syndrome);

- . DPYD Genotyping in patients with abnormal plasma uracil concentration (**expert agreement**);
- . TEP-Scan when surgery of metastases (especially in the liver) is considered (**recommendation: grade B**).

III- Operability, resectability criteria and medico-surgical approaches

This section mainly concerns liver metastases (see Annex 1).

Surgical resection must systematically be discussed during MDT meetings, including at least one surgeon and one radiologist with experience in liver metastases.

The main criteria for the surgical decision are:

- Patient's condition: feasibility of anesthesia and resection?
- Tumor: possibility of R0 resection?
- Anatomy: expected healthy residual liver volume >25%-40%, depending on the presence or absence of another liver pathology

Once the assessment is completed, complexity levels are defined in 3 classes (see Annex 2).

IIIa- Resectable liver metastases

IIIa1- RECOMMENDATIONS

- . In case of class 1 resectability: Simplified FOLFOX 4: 6 pre-operative + 6 post-operative cycles [2, 3] (**recommendation: grade C**). Up front liver surgery: if pathological examination is required or if small (<2cm) and limited number of metastases and are likely to disappear after chemotherapy (**recommendation: grade C**)
- . In case of liver metastasis disappearance on imaging after chemotherapy: Hepatic resection should remove the site of missing lesions because pathologic complete response (pCR) is obtained in less than 20% of cases [4] (**recommendation: grade C**)
- . Synchronous primary tumor and metastases: If metastases are identified pre-operatively and accessible to minor resection (class 1), one-stage liver metastases and primary tumor resections may be considered. In other cases, liver-first approach (reverse strategy) should be considered.
- . Class 2 resectability: Surgery needs to be performed in a center specialized in hepatic surgery (**expert agreement**) and up-front chemotherapy is recommended (**expert agreement**).

. In case of hepatic pedicle and celiac lymph nodes: Surgery is therefore not indicated in case of class 2 resectability (**recommendation: grade C**)

IIIa2- OPTIONS

. Pre-operative right portal vein embolization (+/- right portal branch ligation) [5] in case of right hepatectomy with remaining left-side liver volume <25% (if between 25 to 40%, embolization should be discussed according to the hepatic function).

. Two-stage hepatectomy [6, 7]

. Radiofrequency ablation or stereotaxic radiotherapy [8]

. Post-operative chemotherapy (**recommendation: grade B**): LV5FU2 [9, 10] or simplified FOLFOX4 regimen for 6 months if no pre-operative chemotherapy; or using the induction chemotherapy which enabled resectability for a total duration of 6 months (pre- and post-operative) [11] (**expert agreement**). For the post-operative regimen, maintenance of the pre-operative targeted therapy should be discontinued as its benefit is not demonstrated in this setting (**expert agreement**).

. In case of liver metastasis disappearance after chemotherapy: If the site of the missing metastases is not resected, adjuvant hepatic intra-arterial chemotherapy may be considered as it could decrease recurrence rates based on retrospective series [12] (**expert agreement**).

IIIb- Resectable extra-hepatic metastases

IIIb1- RECOMMENDATIONS

. Lung metastases: as hepatic metastases, surgery is indicated only if complete resection is possible (**recommendation: grade B**)

. Peritoneal carcinomatosis: complete resection +/- hyperthermic intraperitoneal chemotherapy (HIPEC) [13, 14, 15] should be discussed in a specialized center in case of isolated carcinomatosis with moderate extension (**recommendation: grade B**). As for hepatic metastases, perioperative chemotherapy is indicated for a total duration not exceeding 6 months (**expert agreement**). In case of HIPEC expected morbidity must be low and mitomycin should be the preferred agent (not oxaliplatin) (**expert agreement**).

. Resection +/- HIPEC is proposed if the following criteria are met [16]:

- . age < 65-70
- . WHO performance status <2
- . no extra-peritoneal metastasis (or <3 hepatic metastases)
- . complete resection of all lesion >2 mm is possible
- . no progression under chemotherapy
- . peritoneal carcinomatosis index (PCI) <17

Peritoneal carcinomatosis discovered at laparotomy: the procedure is stopped after PCI calculation and the case must be discussed during a MDT meeting (**expert agreement**).

IIIb2- OPTIONS

. Lung metastases: percutaneous radiofrequency ablation or microwave ablation or stereotactic radiotherapy (**expert agreement**).

IIIc- Borderline resectable metastases (or potentially resectable metastases)

IIIc1- RECOMMENDATIONS

. A chemotherapy regimen with a high response rate (objective responses as per RECIST1.1 criteria) should be performed in order to allow secondary resection [11]: triplet chemotherapy +/- targeted therapy or doublet chemotherapy +/- targeted therapy (anti-EGFR are preferred in RAS wild-type tumors) [17, 18]. Resectability should be reassessed after 4 to 6 cycles (**expert agreement**).

. BRAF V600E mutation is not predictive of resistance to anti-EGFR but provides a poor prognosis. Treatment intensification is indicated (triplet chemotherapy plus bevacizumab is recommended if possible) (**recommendation: grade B**).

. Recommendations regarding initially unresectable metastases showing response to chemotherapy for potential secondary resection:

- Surgery should be performed as soon as the metastases become resectable, with a maximum of 4 months of chemotherapy;
- Wait 4-6 weeks after chemotherapy before surgery [19, 20]

. Hepatic intra-arterial chemotherapy (HIA) has shown high response rates in phase II trials (HIA oxaliplatin + IV chemotherapy LV5FU2 +/- targeted therapy) and may be considered as an alternative to IV chemotherapy alone (**recommendation: grade C**) or as a salvage treatment (**expert agreement**).

. For patients with resection of metastases:

- A total of 6 months of peri-operative chemotherapy is recommended (**expert agreement**).
- No evidence in the literature supports the post-operative continuation of targeted therapy when previously used with the pre-operative regimen (**expert agreement**).

IIIc2- OPTIONS

. Pre-operative bevacizumab treatment must be stopped at least 5-6 weeks before surgery (expert consensus). There is no evidence supporting targeted therapy continuation following resection surgery (**expert agreement**).

. FOLFIRI (or FOLFOX) + cetuximab/panitumumab (RAS WT) [21, 22, 23, 24, 25, 26, 27] (**recommendation: grade B**)

. FOLFOXIRI or FOLFIRINOX [28, 29, 30, 31, 32] + bevacizumab (**recommendation: grade B**) in patients with few comorbidities. This regimen is preferred for patients with BRAF-mutated tumors.

. FOLFIRI or FOLFOX (XELOX) + bevacizumab [33, 34, 35, 36, 37, 38] (**recommendation: grade C**)

. FOLFOXIRI (or FOLFIRINOX) + cetuximab/panitumumab (RAS WT) [39, 40] (**recommendation: grade C**)

. FOLFOX 4 simplified or FOLFIRI [41, 42, 43] (**recommendation: grade C**)

. HIA with oxaliplatin + LV5FU2 IV +/- targeted therapy [44] (**recommendation: grade C**) for liver metastases only and in specialized centres.

IIIId- Unresectable metastases

Unresectability is defined by the MDT, with a focus on:

- comorbidities impairing the surgical procedure;
- profile of the metastatic disease (site, number and lymph nodes involvement)

Palliative chemotherapy aims at maintaining patients' quality of life and prolonging survival (**recommendation: grade B**)

Concerning chemotherapy there are two main options:

- up-front polychemotherapy (doublet or triplet +/- targeted therapy)
- monotherapy (LV5FU2 or capecitabine +/- targeted therapy)

These strategies have been compared (without targeted therapy) in four phase III trials, which have shown similar results. That is to say, median overall survivals of about 16 months for both groups, explained by the inclusion of elderly patients with polymetastatic CRC and poor performance status [45, 46, 47, 48]. Moreover, the 2001-02 FFCD trial showed no superiority of a doublet chemotherapy (FOLFIRI) over monotherapy (LV5FU2) in elderly patients aged 75 years or older [49].

If a poor performance status is observed as a result of tumor aggressivity, a doublet +/- targeted therapy is indicated, if possible. When the deterioration results from patient frailty or comorbidities, first-line monotherapy is preferred [50].

. Response assessment is based on the same radiological technique, after 2 to 3 months of therapy (CT-scan is the gold-standard)

- if major response: surgery should be discussed
- if response or stability: chemotherapy is continued or paused until new progression; with a reassessment every 2 months. In case of initial doublet or triplet chemotherapy, maintenance therapy may be proposed. A major response may justify a break in chemotherapy (**recommendation: grade C**) [51, 52]. 5FU/capecitabine is the best maintenance treatment option +/- combined with bevacizumab (**recommendation: grade B**). During maintenance therapy or chemotherapy break, a stable response does not justify resuming induction chemotherapy. In case of progression after maintenance/chemotherapy break, chemotherapy +/- targeted therapy that initially induced disease control may be re-introduced.

. If targeted therapy is used:

- The choice of targeted therapy for first-line treatment is based on RAS, BRAF and MSI status.
- Right versus left colon cancer: studies have shown that cancer sidedness is a prognosis factor regardless of mutational status in mCRC, with poor prognosis for right-sided colon cancers [53, 54]. Current data on the impact of tumor side (right/left colon) on therapeutic options suggest that left-sided colon cancer could be a predictor of EGFRi efficacy, and conversely, right-sided colon cancer is rather a predictor of bevacizumab efficacy [55, 56, 57]. The level of evidence remains too weak however to use tumor site as a main criterion to select the targeted therapy (EGFRi vs VEGFi) (**expert agreement**).

IIIId1- RECOMMENDATIONS for patients with non life threatening metastases, BRAF wild-type tumor, low tumor load and good performance status:

. Treatment escalation starting with mono-chemotherapy (5FU/capecitabine) +/- bevacizumab. Response is evaluated every 2 months. In case of progression, subsequent lines of treatment are proposed (**recommendation: grade A**).

. Polychemotherapy +/- targeted therapy to facilitate chemotherapy break (**recommendation: grade A**), or maintenance chemotherapy with 5FU/capecitabine +/- bevacizumab (**recommendation: grade B**) (Optimox 1 or CAIRO 3 strategies) [58, 59].

IIIId2- OPTIONS for patients with non life threatening metastases, BRAF wild-type tumor, low tumor load and good performance status:

. In case of an objective response or stability after 4 to 6 months of chemotherapy: chemotherapy break should be discussed with tumor reassessment every 2 months until progression [60, 61, 62, 63]. Predictive factors of slow progression during chemotherapy break or maintenance therapy are:

- partial or complete response, normal LDH and alkaline phosphatases, WHO performance status 0-1, initial normal platelet count, one or two metastatic sites, normalization or high decrease of CEA [62, 64] (**recommendation: grade C**).
- MSI tumors: anti-PD-1 or anti-PDL-1 treatment should be considered in a clinical trial pending marketing authorization (**expert agreement**).
- BRAF mutation: chemotherapy intensification with triplet +/- targeted therapy, preferably bevacizumab (**expert agreement**) [65, 39].

IIIId3- RECOMMENDATIONS for patients with life threatening metastases, BRAF mutated tumor, rapid tumor growth, high tumor load and/or poor performance status (WHO 2) due to tumor aggressiveness:

. High-response doublet or triplet therapy +/- targeted therapy is recommended, according to performance status and comorbidities (**expert agreement**).

IIIId4- OPTIONS for patients with life threatening metastases, BRAF mutated tumor, fast tumor progression, high tumor load and/or poor performance status (WHO 2) due to tumor aggressiveness:

- . Doublet +/- cetuximab or panitumumab (RAS WT) (**recommendation: grade B**)
- . Triplet (FOLFOXIRI or FOLFOXIRINOX) +/- bevacizumab (**recommendation: grade B**)
- . BRAF mutation: triplet +/- bevacizumab (grade B) or triplet +/- anti-EGFR (cetuximab or panitumumab) (**recommendation: grade C**) [65, 39]
- . Doublet +/- bevacizumab (**recommendation: grade C**)
- . Triplet + cetuximab or panitumumab (RAS WT) (**expert agreement**)

IIIId5- RECOMMENDATIONS for patients with non life threatening unresectable metastases, aged, frail, with severe comorbidity-related and/or with poor performance status (WHO 2):

- . Mono-chemotherapy (5FU/capecitabine) +/- bevacizumab is recommended

(**recommendation: grade A**) or mono-chemotherapy +/- EGFRi if RAS WT (**expert agreement**) [66]. Doublet +/- EGFRi if RAS WT or bevacizumab with adjusted cytotoxic chemotherapy dosage (and/or 5FU bolus suppression) can be considered.

III d6- OPTIONS for patients with non life threatening unresectable metastases, aged, frail, with severe comorbidity-related and/or with poor performance status (WHO 2):

- . 5FU/capecitabine +/- bevacizumab (**recommendation: grade A**)
- . Doublet chemotherapy +/- cetuximab or panitumumab (RAS WT) (**recommendation: grade B**)
- . Doublet chemotherapy +/- bevacizumab (**recommendation: grade C**)

IV- What to do after a first-line chemotherapy?

IVa- RECOMMENDATIONS

. Recent data indicate that the L1-L2 therapy sequence may impact treatment efficacy. Given the relevance of continuous angiogenesis blockade in 3 phase III trials [11, 68, 69] and biological rationale [70], the work group recommends:

- o Maintaining angiogenesis blockade in L2 when bevacizumab was used in L1, including cases of RAS WT tumors (**Expert agreement**); as phase II and retrospective data indicate a non-optimal efficacy of EGFRi in L2 following bevacizumab treatment [71, 72]
- o Conversely, in case of L1 with EGFRi therapy, an antiangiogenic should be prescribed in L2.

. Progression and/or intolerance during cytotoxic chemotherapy (5FU, irinotecan and oxaliplatin), EGFRi antibodies (if RAS WT) therapy and VEGFi antibodies therapies:

- o 2 systemic treatments are available for patients with good performance status (0-1): regorafenib and trifluridine/tipiracil (**recommendation: grade A**).
- o SIR-Spheres® (Y-90 resin microspheres) in case of exclusive or predominant liver metastases with maintained liver function (**recommendation: grade B**) [73, 74]
- o Palliative care (ECOG PS>2) or clinical trial (**expert agreement**)

IVb- OPTIONS

- . Oxaliplatin re-introduction [75] if no previous progression on oxaliplatin-based

chemotherapy and/or if the neurotoxicity that justified interruption has regressed (**recommendation: grade C**)

. Re-introduction of EGFRi if no previous progression on EGFRi-based chemotherapy, the toxicities that justified interruption has regressed and for patients who underwent an interval chemotherapy without anti-EGFR and no evidence of RAS mutation when re-introduced (**expert agreement**)

. Hepatic intra-arterial chemotherapy (oxaliplatin + LV5FU2) (**recommendation: grade C**) in experienced care centers

V- **Intra-arterial therapies for patients with liver exclusive or predominant disease**

Va- **RECOMMENDATIONS**

. SIR-Spheres® (Y-90 resin microspheres) when hepatic function is maintained (bilirubine <1.5N) and metastases are liver-limited/live-predominant and chemorefractory to systemic treatment (**recommendation: grade B**) [73, 74]

Vb- **OPTIONS For exclusive or liver-predominant metastases**

. HIAC (Hepatic Intra Arterial Chemotherapy):

- Post-operative HIAC in combination with systemic chemotherapy in patients with suspected missing metastases or with a high risk of recurrence (**recommendation: grade C**)
- Pre-operative HIAC in combination with systemic chemotherapy if first-line systemic chemotherapy did not bring sufficient downstaging, or is not likely to induce sufficient downstaging for allowing secondary surgery (**recommendation: grade C**)
- Palliative HIAC, in case of resistance to all systemic chemotherapies (**recommendation: grade C**)

. DEBIRI: in palliative care setting for patients resistant to all systemic chemotherapies (**recommendation: grade B**) [76]

VI- **Local ablative treatments for liver-exclusive or predominant metastases**

Results are optimal when metastases are small (<3cm), few (<5), and distant from vascular and biliary structures [77].

. Resectable liver metastases:

- When surgery is contraindicated

- When metastases are small, with limited number of lesions and their localization would need extensive liver resection
- When liver metastases are likely to disappear under chemotherapy, focal ablation or localization by hepatic coil before chemotherapy may be considered.

. Unresectable liver metastases:

- When resection is not possible due to insufficient expected liver residual volume and/or high risk of post-operative liver failure, a combination of resection and local ablative techniques may be considered if it allows R0/R1 surgery [78]. (**recommendation: grade B**)

Via- RECOMMENDATIONS

[none]

Vib- OPTIONS

. Radiofrequency (**expert agreement**)

. Microwave (**expert agreement**)

. Stereotactic radiotherapy (**expert agreement**)

. Contraindications regarding radiofrequency and microwave therapy (and therefore potential indications of stereotactic radiotherapy): ascites, severe non-curable hemostasis disorder, sub-capsular localization, intra-hepatic biliary duct dilatation, metastases in contact with digestive, biliary or vascular structures, lesion with diameter >30mm.

. Main limits to stereotaxic radiotherapy are target volume, number of lesions and remaining healthy liver percentage.

VII- Overview of RECOMMENDATIONS based on RAS status

See annex 4, 5

VIII- Treatment selection strategies (chemo/bio) based on initial therapy

See annex 6

Conflict of interest

- JM Phelip: Roche, Merck, Amgen, Bayer, Sanofi, Servier, Pierre Fabre
- D Tougeron: Roche, Merck, Amgen, Bayer, Sanofi, Servier, MSD, BMS, Astra Zeneca, BTG
- B Rousseau : Roche, Servier, Bayer, Novartis
- O. Bouché: Roche, Merck, Amgen, Servier, Pierre Fabre, Bayer

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References :

- 1- Phelip JM, Benhaim L, Bouché O, et al. «Cancer colorectal métastatique». Thésaurus National de Cancérologie Digestive, Janvier 2019, [En ligne] [<http://www.tncd.org>]
- 2- 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;371:1007-16
- 3- 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;14:1208-15
- 4- Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006;24:3939-45
- 5- Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. *Ann Surg* 2008;24:451-5
- 6- Chun YS, Vauthey JN, Ribero D, et al. Systemic chemotherapy and two-stage hepatectomy for extensive bilateral colorectal liver metastases: perioperative safety and survival. *J Gastrointest Surg.* 2007;11:1498-504
- 7- Wicherts DA, Miller R, de Haas RJ, Bitsakou G, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann Surg* 2008;248:994-1005
- 8- Pawlik TM, Izzo F, Cohen DS, et al. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. *Ann Surg Oncol* 2003;10:1059-69
- 9- Portier G, Elias D, Bouché O, et al. Multicenter randomized trial of adjuvant systemic chemotherapy using 5-Fluorouracil and folinic acid versus observation after resection of liver metastases of colorectal origin. Results of an intergroup phase III study (FFCD-ACHBTH-AURC 9002 trial). *J Clin Oncol* 2006;24 :4976-82.
- 10- Mitry 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;26:4906-11
- 11- Kopetz S, Chang GJ, Overman MJ. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009;27:3677-83
- 12- Elias D, Goere D, Boige V, et al. Outcome of posthepatectomy-missing colorectal liver metastases after complete response to chemotherapy: impact of adjuvant intra-arterial hepatic oxaliplatin. *Ann Surg Oncol* 2007;14:3188-94
- 13- Glockzin G, Zeman F, Croner RS, et al. Perioperative Systemic Chemotherapy, Cytoreductive Surgery, and Hyperthermic Intraperitoneal

- Chemotherapy in Patients With Colorectal Peritoneal Metastasis: Results of the Prospective Multicenter Phase 2 COMBATAC Trial. *Clin Colorectal Cancer* 2018;18:30223-8.
- 14- Gelli M, Huguenin JFL, de Baere T, et al. Peritoneal and extraperitoneal relapse after previous curative treatment of peritoneal metastases from colorectal cancer: What survival can we expect? *Eur J Cancer* 2018;100:94-103
 - 15- Goéré D, Sourrouille I, Gelli M, et al. Peritoneal Metastases from Colorectal Cancer: Treatment Principles and Perspectives. *Surg Oncol Clin N Am* 2018;27:563-583
 - 16- Goéré D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. *Ann Surg Oncol* 2015;22:2958-64
 - 17- Alonso V, Escudero P, Fernández-Martos C, et al. Coexpression of p-IGF-1R and MMP-7 Modulates Panitumumab and Cetuximab Efficacy in RAS Wild-Type Metastatic Colorectal Cancer Patients. *Neoplasia* 2018;20:678-686
 - 18- Iwamoto S, Ooki A, Morita S, et al. A prospective Phase II study to examine the relationship between quality of life and adverse events of first-line chemotherapy plus cetuximab in patients with KRAS wild-type unresectable metastatic colorectal cancer: QUACK trial. *Cancer Med*. 2018;7:4217-27
 - 19- Bergeat D, Rayar M, Mouchel Y, et al. Preoperative bevacizumab and surgery for colorectal liver metastases: a propensity score analysis. *Langenbecks Arch Surg* 2017;402:57-67
 - 20- Soubrane O, Brouquet A, Zalinski S, et al. Predicting high grade lesions of sinusoidal obstruction syndrome related to oxaliplatin based chemotherapy for colorectal liver metastases: correlation with post-hepatectomy outcome. *Ann Surg* 2010;251:454-60
 - 21- 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;27:663-71
 - 22- Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-17
 - 23- 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 .
 - 24- 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;28:4697-705.

- 25- Van Cutsem E, Köhne 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 RAS and BRAF mutation status. *J Clin Oncol* 2011;29:2011-9.
- 26- 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;377:2103-14
- 27- Poston G, Adam R, Xu J, et al. The role of cetuximab in converting initially unresectable colorectal cancer liver metastases for resection. *Eur J Surg Oncol* 2017;43:2001-2011
- 28- 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
- 29- Masi G, Cupini S, Marcucci L, et al. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. *Ann Surg Oncol* 2006;13:58-65
- 30- 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;25:1670-6
- 31- Tomasello G, Petrelli F, Ghidini M, et al. FOLFOXIRI Plus Bevacizumab as Conversion Therapy for Patients With Initially Unresectable Metastatic Colorectal Cancer: A Systematic Review and Pooled Analysis. *JAMA Oncol*. 2017;13:3(7)e170278
- 32- Cremolini C, Loupakis F, Masi G, et al. FOLFOXIRI or FOLFOXIRI plus bevacizumab as first-line treatment of metastatic colorectal cancer: a propensity score-adjusted analysis from two randomized clinical trials. *Ann Oncol* 2016;27:843-9
- 33- Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335-42
- 34- Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. *J Clin Oncol* 2008;26:3523-9
- 35- Fuchs C, 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;25:4779-86

- 36- Saltz LB, Clarke S, Díaz-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;26:2013-9
- 37- Schmiegel WH, Reinacher-Schick A, Freier W, et al. Comparable safety and response rate with bevacizumab in combination with capecitabine/oxaliplatin (CapOx/Bev) versus capecitabine/irinotecan (CapIri/Bev) in advanced CRC (mCRC): A randomized phase II study of the AIO GI tumor study group. *J Clin Oncol* 2007;25(Suppl 18S):4034a
- 38- Ducreux M, Adenis A, Pignon JP, et al. Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: final results from a randomised phase II study of bevacizumab plus FOLFIRI versus bevacizumab plus XELIRI (FNCLCC ACCORD 13/0503 study). *Eur J Cancer* 2013;49:1236-45
- 39- Geissler M, Martens UM, Knorrnschild R et al. mFOLFOXIRI + panitumumab versus FOLFOXIRI as first-line treatment in patients with RAS wild-type metastatic colorectal cancer m(CRC): A randomized phase II VOLFI trial of the AIO (AIO-KRK0109). *Annals of Oncology* 2017; 28 (suppl_5): v158-v208
- 40- Ychou M, Rivoire M, Thezenas S, et al. FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: a phase II randomized study – Prodigé 14 – ACCORD 21 (METHEP-2), a unicancer GI trial. *J Clin Oncol* 2016;34:abstr 3512
- 41- Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;355:1041-7
- 42- Tournigand C, Cervantes A, Figuer 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
- 43- Grothey A, Hart LL, Rowland KM, et al. Intermittent oxaliplatin (oxali) administration and time-to-treatment-failure (TTF) in metastatic colorectal cancer (mCRC): Final results of the phase III CONcePT trial (abstract). *J Clin Oncol* 2008;26(Suppl15S):4010
- 44- Ducreux M, Ychou M, Laplanche A, et al. Hepatic arterial oxaliplatin infusion plus intravenous chemotherapy in colorectal cancer with inoperable hepatic metastases: a trial of the gastrointestinal group of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 2005;23:4881-7
- 45- 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;370:143-52
- 46- Ducreux M, Malka D, Mendiboure J, et al. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000-05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011;12:1032-1044

- 47- 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;370:135-42
- 48- Cunningham D, Sirohi B, Pluzanska A et al. Two different first-line 5-fluorouracil regimens with or without oxaliplatin in patients with metastatic colorectal cancer *Ann Oncol* 2009;20 :244-5
- 49- Aparicio T, Lavau-Denes S, Phelip JM et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). *Ann Oncol* 2016.27:121-7
- 50- Sargent DJ, Köhne CH, Sanoff HK, et al. Pooled safety and efficacy analysis examining the effect of performance status on outcomes in nine first-line treatment trials using individual data from patients with metastatic colorectal cancer. *J Clin Oncol* 2009;27:1948-55
- 51- 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;385:1843-52
- 52- Berry SR, Cosby R, Asmis T, et al. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 2015;26:477-85
- 53- Petrelli F, Tomasello G, Borgonovo K, et al. Prognostic Survival Associated With Left-Sided vs Right-Sided Colon Cancer: A Systematic Review and Meta-analysis. *JAMA Oncol* 2017;3(2):211-219
- 54- Boeckx N, Koukakis R, Op de Beeck K et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. *Ann Oncol* 2017;28:1862-1868
- 55- Venook A, Niedzwiecki D, Innocenti F et al. Impact of primary (1^o) tumor location on overall survival (OS) and progression-free survival (PFS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB/SWOG 80405 (Alliance). *J Clin Oncol* 34, 2016 (suppl; abstr 3504)
- 56- Heinemann V, Dominik Modest DP, Von Weikersthal LF et al. Gender and tumor location as predictors for efficacy: Influence on endpoints in first-line treatment with FOLFIRI in combination with cetuximab or bevacizumab in the AIO KRK 0306 (FIRE3) trial. *J Clin Oncol* 32:5s, 2014 (suppl; abstr 3600)
- 57- Holch, J.W, Ricard, I, Stintzing, S, et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur J Cancer*. 2017;70:87-98
- 58- 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;385:1843-52

- 59- Berry SR, Cosby R, Asmis T, et al. Continuous versus intermittent chemotherapy strategies in metastatic colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 2015;26:477-85
- 60- Maughan TS, James RD, Kerr DJ, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicenter randomised trial. *Lancet* 2003;361:457-64
- 61- Labianca R, Sobrero A, Isa L, et al. Italian Group for the Study of Gastrointestinal Cancer-GISCAD. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol* 2011;22:1236-42.
- 62- Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX 2 Study. *J Clin Oncol* 2009;27:5727-33
- 63- 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;12:642-53
- 64- Chibaudel B, Tournigand C, Artru P, et al. FOLFOX in patients with metastatic colorectal cancer and high alkaline phosphatase level: an exploratory cohort of the GERCOR OPTIMOX1 study. *Ann Oncol* 2009;20:1383-6
- 65- Loupakis F, Cremolini C, Masi G et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609-18
- 66- Cunningham D, Lang I, Marcuello E, et al. AVEX study investigators. 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;14:1077-85
- 67- Lesniewski-Kmak K, Moiseenko V, Saunders M et al. Phase II study evaluating trifluridine/tipiracil + bevacizumab and capecitabine + bevacizumab in first-line unresectable metastatic colorectal cancer (mCRC) patients who are non-eligible for intensive therapy (TASCO1): Results of the primary analysis. *Annals of Oncology* 2018;29, Issue suppl_5
- 68- 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
- 69- 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
- 70- Wainberg, Z.A., Drakaki, A. The importance of optimal drug sequencing in metastatic colorectal cancer: biological rationales for the observed survival benefit conferred by first-line treatment with EGFR inhibitors. *Expert Opin Biol Ther.* 2015;15:1205–1220. *Expert Opin Biol Ther* 2015;15:1205–20
- 71- Hiret S, Borg C, Bertaut A et al. Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (Prodige 18

- UNICANCER GI). *J Clin Oncol* 2016;34, no. 15_suppl:3514-3514
- 72- Taniguchi H, Komori A, Narita Y et al. A short interval between bevacizumab and anti-epithelial growth factor receptor therapy interferes with efficacy of subsequent anti-EGFR therapy for refractory colorectal cancer. *Japanese J of Clin Oncol* 2016;46:228-233
- 73- 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;28:3687-94.
- 74- Bester L, Meteling B, Pocock N, et al. Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *J Vasc Interv Radiol.* 2012;23:96-105
- 75- Maindrault-Goebel F, Tournigand C, Andre T, et al. Oxaliplatin reintroduction in patients previously treated with leucovorin, fluorouracil and oxaliplatin for metastatic colorectal cancer. *Ann Oncol* 2004;15:1210-4
- 76- 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;32:1387-95
- 77- Gillams A, Goldberg N, Ahmed M, et al. Thermal ablation of colorectal liver metastases: a position paper by an international panel of ablation experts, The Interventional Oncology Sans Frontieres meeting 2013. *Eur Radiol* 2015;25:3438-54.
- 78- Evrard S, Rivoire M, Arnaud J, et al. Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection. *Br J Surg* 2012;99:558-65

Table 1 - Grade of recommendations

Grade	Quality of evidence	Definition
A	High	Strongly recommended based on robust scientific evidence (<i>e.g.</i> , several randomized controlled trials/meta-analyses) Further research is very unlikely to change our confidence in the estimate of effect
B	Moderate	Usually recommended based on scientific presumption (<i>e.g.</i> , one randomized controlled trial) Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C	Low	Option based on weak scientific evidence (<i>e.g.</i> , one or several non-randomized trials) Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
D	Very low	Expert opinion (agreement or not) Any estimate of effect is very uncertain