

# Factors influencing choice of chemotherapy in metastatic colorectal cancer (mCRC)

Luigi Rossi  
Foteini Vakiarou  
Federica Zoratto  
Loredana Bianchi  
Anselmo Papa  
Enrico Basso  
Monica Verrico  
Giuseppe Lo Russo  
Salvatore Evangelista  
Guilia Rinaldi  
Francesca Perrone-Congedi  
Gian Paolo Spinelli  
Valeria Stati  
Davide Caruso  
Alessandra Prete  
Silverio Tomao

Department of Medico-Surgical Sciences and Biotechnologies, "Sapienza" University of Rome, Rome, Italy; Oncology Unit, ICOT, Latina, Italy

Correspondence: Luigi Rossi  
Oncology Unit, ICOT, Franco Faggiana Street, 1668, Latina, 04100, LT, Italy  
Tel +39 349 564 3418  
Email dr.rossi@ymail.com

**Abstract:** Management of metastatic colorectal cancer requires a multimodal approach and must be performed by an experienced, multidisciplinary expert team. The optimal choice of the individual treatment modality, according to disease localization and extent, tumor biology, and patient clinical characteristics, will be one that can maintain quality of life and long-term survival, and even cure selected patients. This review is an overview of the different therapeutic approaches available in metastatic colorectal cancer, for the purpose of defining personalized therapeutic algorithms according to tumor biology and patient clinical features.

**Keywords:** metastatic colorectal cancer, patient clinical features, tumor biology, multidisciplinary approach

## Introduction

Approximately 20% of patients affected by colorectal cancer (CRC) present metastatic disease in early diagnosis, while 35% of patients, treated with curative intent, will develop advanced disease over time.<sup>1</sup> The prognosis of these patients is poor and the aims of chemotherapy are care (only in selected cases), survival prolongation, disease progression delay, quality of life improvement, tumor size reduction, or symptom palliation. Through available multidisciplinary therapeutic strategies (surgery, chemotherapy, biological agents, radiotherapy), the clinical approach to unresectable metastatic CRC (mCRC) should be potentially curative or palliative. Moreover, knowledge of both tumor biology and patient clinical features has allowed for the identification of four different patient classes, which correspond to four different therapeutic options, respectively: (1) patients with minimal disease that is immediately resectable (R0-resectable liver with/without lung metastases [group 0]); (2) patients with extensive disease that is not immediately resectable (potentially resectable metastatic disease after conversion chemotherapy [group 1]); (3) never-resectable metastatic disease in symptomatic patients whose quality of life and survival are compromised due to disease extension (palliation therapy [group 2]); and (4) never-resectable metastatic disease in asymptomatic patients (palliation therapy, continuum care [group 3]).<sup>2</sup> The purpose of this review is to summarize the different therapeutic approaches to adopt according to patient clinical characteristics and tumor biomolecular features (Table 1 shows the groups mentioned above and related treatments) and to explain current therapeutic options available in mCRC.

**Table 1** First-line treatment options according to tumor biology and patient clinical features

Group	Clinical presentation	Treatment aim	Treatment intensity	KRAS wild-type	KRAS mutated
0	R0-resectable liver and/or lung metastases	– Cure – Decrease risk of relapse	– Nothing – Moderate (FOLFOX)	–	–
1	Not R0-resectable liver or lung metastases but might become resectable after conversion CT	Maximum tumor shrinkage	Upfront most active combination regimen	FOLFIRI+cet FOLFOX+pan/cet FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI	FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI
2	Multiple metastases sites, with rapid progression and symptomatic patients	– Clinically relevant tumor shrinkage if possible – At least achieve control of DP	Upfront active combination: at least doublet	FOLFIRI+cet FOLFOX+pan/cet FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI	FOLFOX/XELOX+bev FOLFOXIRI FOLFIRI/XELIRI+bev FOLFOX/XELOX FOLFIRI/XELIRI
3	Multiple metastases sites, asymptomatic patients	– Abrogation of further progression – Tumor shrinkage less relevant	Sequential approach	5-FU/LV Cape 5-FU/LV+bev Cape+bev XELOX/FOLFOX FOLFIRI/XELIRI cet/pan watchful waiting triplets (±bev or cet/pan)	5-FU/LV Cape 5-FU/LV+bev Cape+bev XELOX/FOLFOX FOLFIRI/XELIRI FOLFOXIRI/Bev

**Abbreviations:** 5-FU, 5-fluorouracil; bev, bevacizumab; cape, capecitabine; cet, cetuximab; LV, leucovorin; FOLFIRI, infusional 5-FU/bolus folinic acid/irinotecan; FOLFOX, infusional 5-FU/bolus folinic acid/oxaliplatin; FOLFOXIRI, infusional 5-FU/bolus folinic acid/irinotecan/oxaliplatin; pan, panitumumab; DP, disease progression; XELOX, capecitabine/oxaliplatin; XELIRI, cape/irinotecan; CT, chemotherapy.

## Surgical treatment of advanced disease

Surgery is feasible even in advanced disease. It is important to establish, in patients with unresectable mCRC and in whom the primary tumor has not been removed, whether or not the primary tumor is symptomatic; in fact, if the primary tumor is symptomatic (bleeding, bowel obstruction, bowel perforation), surgery is immediately necessary. Liver, lung, and ovarian metastases and primary site of disease should be evaluated for surgery, and surgery should be considered in all patients who have had an important tumoral mass reduction through chemotherapy. The chemotherapy should be discontinued as soon as the disease becomes resectable, because continuation of treatment exposes patients to liver toxicity and surgery risks. R0-resectable liver metastases represents the only curative option available,<sup>3</sup> while R1-resectable liver metastases is an acceptable strategy if it produces a significant benefit to patients.<sup>4</sup> Currently, patients diagnosed with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation, to assess resectability status.

## Management of patients with minimal disease (R0-resectable liver and/or lung metastases [group 0])

Before explaining the therapeutic approach to be taken in this patient group (group 0), it is necessary to clarify resectability criteria. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve (>30%).<sup>4</sup> It should be noted that metastasis number or size, bilobar extension disease, and vascular structure involvement are not contraindicative to resection of the tumor and its metastases. Patients with a single small (<2 cm) liver metastasis may be considered for upfront surgery and for postoperative chemotherapy with an infusional 5-fluorouracil (5-FU)/bolus 5-FU/leucovorin (LV)/oxaliplatin (FOLFOX)-based regimen for an overall treatment of 6 months.<sup>5</sup> For patients with up to four liver metastases, perioperative chemotherapy (3 months pre-chemotherapy and 3 months post-chemotherapy with FOLFOX regimen) should be applied. The European Organisation for Research and Treatment of Cancer 40983 trial has demonstrated an advantage in

progression-free survival (PFS) in patients undergoing resection plus chemotherapy versus resection alone (18.7 vs 11.7 months, respectively) and a rate of PFS at 3 years from 33.2% to 42.4% (hazard ratio [HR] 0.73;  $P = 0.025$ ) in patients who underwent surgery after perioperative chemotherapy.<sup>6</sup> Furthermore, a recent meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic perioperative therapy with 642 evaluable patients with CRC liver metastases. The pooled analysis showed a benefit of chemotherapy in PFS (HR 0.75;  $P = 0.003$ ) and disease-free survival (HR 0.71;  $P = 0.001$ ), but not in overall survival (OS) (HR 0.74;  $P = 0.088$ ).<sup>7</sup> This approach represents the current standard for patients with minimal and resectable disease.<sup>7</sup> Pre- and postoperative chemotherapy versus postoperative chemotherapy alone, as well as the addition of biological agents, are being investigated in ongoing trials. In the new Early Presentation Of Cancer Project (EPOC) study, 272 patients with *KRAS* wild-type (wt) tumor operable liver metastases were randomized to receive FOLFOX plus or minus cetuximab for 12 weeks before, then 12 weeks following, surgery. The new EPOC study was stopped when the futility analysis was predefined by a protocol. With 45.3% of the expected events observed, PFS was significantly worse in the cetuximab arm (14.8 vs 24.2 months; HR 1.50;  $P < 0.048$ ).<sup>8</sup> In clinical practice, postoperative adjuvant chemotherapy with FOLFOX/ capecitabine/ oxaliplatin (XELOX) or FOLFOX/XELOX plus bevacizumab is administered for an overall treatment of 6 months, despite lack of data favoring this approach and an unspecified chemotherapy duration (6 months).<sup>9</sup> As regards treatment of lung-only metastases, the issue is similar to liver metastases.<sup>10</sup> Results from a retrospective analysis of 795 previously untreated mCRC patients randomized in a Phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that patients with lung-only metastases (two out of 24 patients) were able to undergo curative resection after treatment. The median OS in these patients was 42.4 months.<sup>11</sup> Despite the lack of data from prospective trials regarding perioperative treatment, an approach similar to management of resectable liver metastases should be considered. Alternatively, an initial resection followed by postoperative adjuvant treatment with fluoropyrimidine with or without oxaliplatin for 6 months can be performed.<sup>10</sup>

### Management of patients with extensive disease (potentially resectable metastatic disease after conversion chemotherapy [group I])

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with

liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, chemotherapy is being increasingly considered in highly selected cases in an attempt to down-size colorectal metastases and convert them to a resectable status. Usually, a doublet chemotherapy plus monoclonal antibody or a triplet chemotherapy is used for conversion chemotherapy.

Doublet chemotherapy regimens comprising infusional 5-FU/bolus 5-FU/LV/irinotecan (FOLFIRI) or FOLFOX have reported that a significant portion (32.5% and 40%, respectively) of the patients with initially unresectable liver metastases undergo liver resection.<sup>12,13</sup> Data emerging from randomized trials suggest that the addition of a targeted agent to a doublet chemotherapy might be more effective in treatment of liver-limited disease. In the CELIM Phase II trial, patients were randomized to receive cetuximab with either FOLFOX or FOLFIRI.<sup>14</sup> Retrospective analysis showed that, in both treatment arms, combined resectability increased from 32% to 60% after chemotherapy in patients with *KRAS* wt tumor ( $P < 0.0001$ ) with the addition of cetuximab. A recent meta-analysis of four randomized controlled trials concluded that the addition of monoclonal antibody anti-epidermal growth factor receptor (EGFR) to chemotherapy significantly increased the resection rate (RR) ([R0] from 11% to 18%; odds ratio [OR] 1.59;  $P = 0.04$ ), and PFS, but not OS in patients with *KRAS* wt tumor.<sup>15</sup> Also, bevacizumab was analyzed in this setting. Data seem to suggest that the combination of bevacizumab with an irinotecan-based regimen modestly improves the RR (<2%).<sup>16</sup> On the other hand, the association of FOLFOX with bevacizumab showed no benefit in RR and tumor reduction compared with chemotherapy alone (8.4% vs 6.1%, respectively).<sup>17</sup> However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable. In addition, infusional 5-FU/LV/oxaliplatin/irinotecan (FOLFOXIRI) has been compared with FOLFIRI in unresectable patients.<sup>18</sup> FOLFOXIRI led to an increase in R0 secondary RRs, from 6% to 15% ( $P = 0.033$ ). In a follow-up study of the Gruppo Oncologico Nord Ovest (GONO) trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs 8%), with a median OS of 23.4 versus 16.7 months ( $P = 0.026$ ).<sup>19</sup> There are no available data regarding effectiveness comparisons between doublet chemotherapy plus bevacizumab versus doublet chemotherapy plus cetuximab or panitumumab in *KRAS* wt patients, but, at the same time, FOLFIRI or FOLFOX plus anti-EGFR antibodies appears to be more effective in terms of major tumor shrinkage and secondary resectability

than bevacizumab-based combination in potentially resectable patients with extensive disease. FOLFOXIRI plus bevacizumab is very effective, but data about liver metastases R0 are not yet available.<sup>20</sup>

## First-line treatment of advanced disease

The current first-line management of disseminated mCRC involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. The association of 5-FU/LV revealed an advantage in terms of RR without any impact on OS.<sup>21</sup> The doublet chemotherapy FOLFIRI and FOLFOX led to a considerable increase in RR and prolonged OS, and similar RR and PFS times were obtained when these regimens were used as first-line therapy.<sup>22,23</sup> XELOX is comparable to FOLFOX in terms of activity and efficacy, while capecitabine/irinotecan (XELIRI) is burdened by severe gastrointestinal toxicity.<sup>24,25</sup> FOLFOXIRI is more effective than FOLFIRI in terms of PFS (9.8 vs 6.9 months; HR 0.63;  $P=0.0006$ ) and OS (22.6 vs 16.7 months; HR 0.70;  $P=0.032$ ), although this regimen has to be reserved for patients with appropriate conditions and without relevant comorbidities.<sup>18</sup> Currently, conventional first-line therapy of mCRC is based on the association of conventional chemotherapy regimens and biological drugs that include bevacizumab, cetuximab, or panitumumab; in fact, clinical trials have shown that targeted agents increase the efficacy of conventional chemotherapy regimens.<sup>16,17,26,28-30</sup> Bevacizumab has been shown to increase RR and PFS in association with all chemotherapy regimens. OS, however, appears to differ between the various combinations of treatment; specifically, OS is greater in FOLFIRI plus bevacizumab regimen than FOLFOX plus bevacizumab.<sup>16,17</sup> Recently, the TRIPlet chemotherapy plus BEvacizumab (TRIBE) randomized, Phase III trial has proven a statistically significant advantage in FOLFOXIRI plus bevacizumab treatment group versus FOLFIRI plus bevacizumab in terms of PFS and objective response rate (ORR).<sup>20</sup>

Literature has shown that tumors with a mutation in codon 12 or 13 (exon 2) of the *KRAS* gene are essentially insensitive to EGFR inhibitors such as cetuximab or panitumumab;<sup>26,27</sup> it has also recently emerged that both rare *KRAS* mutations (exon 3) and *NRAS* mutations could invalidate the efficacy of panitumumab treatment.<sup>28</sup>

Cetuximab in first-line chemotherapy has shown a benefit in terms of PFS in patients with k-ras wt tumor; a retrospective analysis in this subgroup also demonstrated that cetuximab plus FOLFIRI gave a greater benefit in terms of

OS than FOLFIRI alone.<sup>26</sup> Analogously, panitumumab plus FOLFOX showed a statistically significant advantage in all RAS wt patients in terms of PFS and OS.<sup>28,29</sup> Table 2 shows RR, PFS, and OS data of main mCRC first-line treatment clinical trials. Finally, FIRE-3 study results were presented during the 13th ASCO annual meeting.<sup>31</sup> In this Phase III trial, 592 patients with *KRAS* wt tumor were randomized to receive FOLFIRI plus cetuximab or FOLFIRI plus bevacizumab. The median duration of treatment was 4.7 months versus 5.3 months, respectively. The primary end point was RR, but the study did not meet this end point because RR was comparable in the two groups (62% vs 57%, OR 1.249); median PFS was nearly identical (10.3 vs 10.4 months; HR 1.04;  $P=0.69$ ); however, OS showed a significantly better outcome in the FOLFIRI plus cetuximab group (28.8 vs 25.0 months; HR 0.77;  $P=0.0164$ ). This study has several methodological limitations, therefore it does not decisively solve the riddle of which biological agent should be used in the first-line treatment of mCRC RAS wt patients.<sup>31</sup> We must await the results of a Phase III study conducted by the CALGB group in order to have solid data about cetuximab versus bevacizumab in mCRC first-line treatment.<sup>32</sup>

In conclusion, the choice of which therapeutic regimen to use in mCRC first-line treatment is based on consideration of the goals of therapy and the differing toxicity profiles of the constituent drugs.

## Management of never-resectable and symptomatic patients (palliation therapy [group 2])

The treatment aim in group 2 is rapid tumor size reduction to resolve symptoms related to disease extension. Either triplet or doublet chemotherapy can be the first choice because each provides the chance of fast and major response (Tables 1 and 2). There is no clear preference for triplet or doublet chemotherapy; rather, the decision is based on tumor symptoms, dynamics, tumor biology, and clinical patient characteristics.

## Management of never-resectable and asymptomatic patients (continuum care [group 3])

For those patients without present or imminent symptoms and limited risk for rapid deterioration, the aim is prevention of tumor progression with symptom disappearance and prolongation of life with minimal treatment, thus ensuring continuum care. Treatment is based on a single agent or doublet chemotherapy with low toxicity. Of great importance is the data of the AVEX trial, a Phase III study conducted on

**Table 2** RR, PFS, and OS data of main clinical trials about mCRC first-line treatment

Author	Phase study	Treatment	Population	OS (months)	HR P-value	PFS (months)	HR P-value	RR (%)	OR P-value
Hurwitz et al <sup>16</sup>	III	IFL/placebo	923	15.6	0.66 <i>P</i> < 0.001	6.2	0.54 <i>P</i> < 0.001	34.8	<i>P</i> = 0.004
		IFL/BV		20.3		10.6		44.8	
		5-FU/FA/BV		18.3		8.8		40	
Saltz et al <sup>17</sup>	III	XELOX/FOLFOX4	1,400	19.9	0.89 <i>P</i> = 0.0769	8.0	0.83 <i>P</i> = 0.0023	49	0.90 <i>P</i> = 0.31
		XELOX/FOLFOX+BV		21.3		9.4		47	
Falcone et al <sup>20</sup>	III	FOLFOXIRI+BV	508	31.0 <sup>a</sup>	0.83 <i>P</i> = 0.125 <sup>a</sup>	12.2	0.77 <i>P</i> = 0.006	65	<i>P</i> = 0.006
		FOLFIRI+BV		25.8 <sup>a</sup>		9.7		53	
Van Cutsem et al <sup>26</sup>	III	FOLFIRI+C	348 (wt KRAS pts)	23.5	<i>P</i> = 0.093	8.9	0.85 <i>P</i> = 0.048	46.9	1.40 <i>P</i> = 0.004
		FOLFIRI		20.0		8.0		38.7	
Bokemeyer et al <sup>30</sup>	II	FOLFOX+C	134 (wt KRAS pts)	22.8	0.85 <i>P</i> = 0.39	7.7	0.57 <i>P</i> = 0.016	61	2.54 <i>P</i> = 0.19
		FOLFOX		18.5		7.2		37	
Douillard et al <sup>29</sup>	III	FOLFOX+P	656 (wt KRAS pts)	23.9	0.83 <i>P</i> = 0.072	9.6	0.80 <i>P</i> = 0.02	55	1.35 <i>P</i> = 0.068
		FOLFOX		19.7		8.0		48	
Oliner et al <sup>28</sup>	III	FOLFOX+P	259 (all wt RAS pts)	26.0	0.78 <i>P</i> = 0.04	10.1	0.72 <i>P</i> < 0.01	NR	NR
		FOLFOX		20.0		7.9		NR	

**Note:** <sup>a</sup>Immature data.

**Abbreviations:** 5-FU, 5-fluorouracil; BV, bevacizumab; C, cetuximab; P, panitumumab; FA, folinic acid; FOLFIRI, infusional 5-FU/bolus folinic acid/irinotecan; FOLFOX4, infusional 5-FU/bolus FA/oxaliplatin; FOLFOXIRI, infusional 5-FU/bolus FA/irinotecan/oxaliplatin; HR, hazard ratio; IFL, bolus 5-FU/FA/irinotecan; mCRC, metastatic colorectal cancer; NR, not reported; OR, odds ratio; OS, overall survival; PFS, progression-free survival; pts, patients; RR, response rate; wt, wild-type; XELOX, capecitabine/oxaliplatin.

elderly mCRC patients that showed how the combination of fluoropyrimidines with bevacizumab is superior to fluoropyrimidines alone.<sup>33</sup> Initial therapy guidelines recommend a choice of five chemotherapy regimens: FOLFOX; FOLFIRI; XELOX, infusional 5-FU/LV; or capecitabine, plus or minus the association with a biological agent (Tables 1 and 2).<sup>16,17,26,28,29</sup>

## Maintenance treatment strategies

There are several maintenance strategies that are used in mCRC after effective first-line chemotherapy in order to reduce disease progression and treatment toxicity.

The OPTIMOX1 study showed that a stop-and-go approach using oxaliplatin-free intervals resulted in decreased neurotoxicity, but did not affect OS, in patients receiving FOLFOX as initial therapy for metastatic disease.<sup>34</sup> Therefore, adjusting the schedule and timing of the administration of this drug can limit this adverse effect. From OPTIMOX1 trial results is derived another therapeutic strategy: reintroduction of a chemotherapeutic agent and residual sensitivity. In the investigational arm of the OPTIMOX1 study, oxaliplatin was reintroduced in 40% of patients and achieved a disease control rate of 69%. Thus, reintroduction of oxaliplatin should be considered in patients who have an initial benefit from FOLFOX or XELOX and who can tolerate it.

Another study, the CONcePT trial, evaluated alternating oxaliplatin administration according to the following

schedule: eight doses of FOLFOX plus bevacizumab followed by eight maintenance doses of 5-FU/LV plus bevacizumab, alternating the two regimens until disease progression. Through this stop-and-go strategy, PFS of 12 months and a low toxicity profile were obtained.<sup>35</sup>

In addition to conventional chemotherapeutic drugs, biologic agents have also been tested in mCRC maintenance therapy; in particular, bevacizumab has been analyzed more in this setting than cetuximab.

The anti-EGFR monoclonal antibody was investigated as a maintenance single-agent in the NORDIC VII trial, but results were not encouraging.<sup>36</sup>

Diaz-Rubio et al, in a Phase III trial, suggested that maintenance therapy with single-agent bevacizumab represented an appropriate option after XELOX plus bevacizumab chemotherapy induction, on the basis of noninferiority results in terms of PFS obtained in a bevacizumab maintenance group versus a XELOX plus bevacizumab maintenance group (10.4 vs 9.7 months, respectively).<sup>37</sup> At the ASCO 13th annual meeting, two other clinical trials<sup>38,39</sup> about the use of bevacizumab in first-line treatment until progression were presented but having, in the control arm, exclusively observation. The CAIRO3 study was designed to investigate the efficacy of observation versus maintenance treatment with capecitabine plus bevacizumab after induction treatment with six cycles of XELOX plus bevacizumab. Maintenance treatment with XELOX plus bevacizumab is feasible and significantly prolongs PFS; there is also a



significant difference in OS in adjustment analysis.<sup>38</sup> In the noninferiority Phase III SAKK 41/06 trial, noninferiority of maintenance treatment with bevacizumab alone versus observation arm, after 4–6 months of first-line chemotherapy plus bevacizumab was investigated. The noninferiority in time to progression could not be demonstrated, although advantageous data for PFS were shown (9.5 months in bevacizumab group vs 8.5 in the observation group;  $P = 0.02$ ); no difference in OS was observed in the two arms.<sup>39</sup> At present, there are no clear data on the use of bevacizumab in the maintenance setting. In order to attain precise indications, it is necessary to wait for data from the Phase III AIO KRK 0207 trial, which compares maintenance therapy with bevacizumab alone versus bevacizumab plus fluoropyrimidines versus observation.<sup>40</sup>

Associations between targeted agents have also been investigated in maintenance treatment: the GERCOR-DREAM trial evaluated bevacizumab combined with erlotinib after first-line oxaliplatin- or irinotecan-based chemotherapy. After 31 months of follow-up, median PFS was 4.6 months in the bevacizumab group versus 5.8 months in the bevacizumab plus erlotinib group (HR 0.73;  $P = 0.005$ ).<sup>41</sup>

As the maintenance strategy we reported treatment-free interval, which was investigated in two trials, OPTIMOX2 and COIN.<sup>42, 43</sup>

In the Phase II OPTIMOX2 trial,<sup>42</sup> patients were randomized to receive either an OPTIMOX1 approach or an induction FOLFOX regimen followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX. Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, preplanned, chemotherapy-free interval (OS 23.8 vs 19.5 months;  $P = 0.42$ ). However, the median duration of disease control, which was the primary end point of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval ( $P = 0.046$ ).

The MRC COIN study<sup>43</sup> compared continuous oxaliplatin-based chemotherapy until disease progression and treatment holiday after 3 months of induction treatment, followed by chemotherapy reintroduction, on disease progression. Although this trial did not show noninferiority of intermittent compared with continuous chemotherapy in terms of OS, chemotherapy-free intervals remain a treatment option for some patients with advanced colorectal cancer, offering

reduced time on chemotherapy, reduced cumulative toxic effects, and improved quality of life.

## Second-line chemotherapy after first disease progression and further treatment lines

Second and further chemotherapy lines in mCRC depend on previous therapies. Particularly, based on clinical evidence, there are four different chemotherapeutic modalities to use after first-line disease progression. For patients who received an oxaliplatin-based regimen for initial therapy, FOLFIRI or irinotecan alone are recommended options. Usually in patients with *KRAS* wt tumor, irinotecan-based chemotherapy can be combined with cetuximab or panitumumab,<sup>44,45</sup> while in patients with *KRAS* mutant tumor can be combined with bevacizumab<sup>46,47</sup> or aflibercept.<sup>48</sup> Anti-vascular endothelial growth factor treatment use beyond first-line bevacizumab-based chemotherapy progression has been analyzed by the TML and VELOUR trials, which observed patients continuing on bevacizumab or aflibercept having a modest improvement in OS.<sup>47,48</sup>

For mCRC patients who received an irinotecan-based regimen as initial treatment, FOLFOX or XELOX alone or with bevacizumab,<sup>46</sup> cetuximab or panitumumab plus irinotecan, or single-agent cetuximab or panitumumab are recommended options.<sup>44,45,49,50</sup> In patients treated with 5-FU/LV or capecitabine as initial therapy, options after first progression include FOLFOX, XELOX, FOLFIRI, single-agent irinotecan, or irinotecan plus oxaliplatin. These can varyingly be combined with bevacizumab or aflibercept.<sup>46,47</sup> Finally, for patients who received FOLFOXIRI as initial therapy, cetuximab or panitumumab plus irinotecan or cetuximab or panitumumab alone are recommended options for those with *KRAS* wt tumor.<sup>44,45,49,50</sup> However, regarding later chemotherapy lines, the possible options for patients with *KRAS* wt not previously treated with anti-EGFR antibodies are cetuximab with or without irinotecan and panitumumab with or without FOLFIRI.<sup>44,45,49,50</sup> In patients who are refractory to 5-FU, oxaliplatin, irinotecan, anti-EGFR antibodies (*KRAS* wt tumor only), bevacizumab, and regorafenib, treatment with fluoropyrimidines and mitomycin or reintroduction of oxaliplatin (and irinotecan) results in very limited improvement in some patients treated as last line. However, despite poor results in the data, this might be justified in some patients. Finally, regorafenib demonstrated an advantage in terms of OS versus placebo in last-line salvage treatment.<sup>51</sup>

**Table 3** RR, PFS, and OS data of main clinical trials about mCRC non-first-line treatment

Author	Phase study	Line treatment	Treatment	Population	OS (months)	HR P-value	PFS (months)	HR P-value	RR (%)	OR P-value
Giantonio et al <sup>46</sup>	III	II	FOLFOX4	823	12.9	0.75 <i>P</i> = 0.0011	7.3	0.61 <i>P</i> < 0.0001	22.7	<i>P</i> < 0.001
			FOLFOX4+BV		10.8		4.7		8.6	
			BV		10.2		2.7		3.3	
Bennouna et al <sup>47</sup>	III	II	CT+BV	820	11.2	0.81 <i>P</i> = 0.0062	5.7	0.68 <i>P</i> < 0.0001	6	NR
			CT		9.8		4.1		4	
Van Cutsem et al <sup>48</sup>	III	II	FOLFIRI+A	1226	13.5	0.758 <i>P</i> = 0.0032	6.9	0.758 <i>P</i> < 0.0001	19.8	<i>P</i> = 0.0001
			FOLFIRI		12.06		4.67		11.1	
Sobrero et al <sup>45</sup>	III	II	CPT-11+C	1298	10.7	0.975 <i>P</i> = 0.71	4.0	0.692 <i>P</i> < 0.0001	16.4	<i>P</i> < 0.0001
			CPT-11		10.0		2.6		4.2	
Peeters et al <sup>44</sup>	III	II	FOLFIRI+P	1186	14.5	0.85 <i>P</i> = 0.12	5.9	0.73 <i>P</i> = 0.004	35	NR
			FOLFIRI		12.5		3.9		10	
Cunningham et al <sup>49</sup>	III	Further lines	CPT-11+C	329	8.6	0.91 <i>P</i> = 0.48	4.1	0.54 <i>P</i> < 0.001	22.9	<i>P</i> = 0.007
			C		6.9		1.5		10.8	
Van Cutsem et al <sup>50</sup>	III	Further lines	P	463	NR	1.00, <i>P</i> = 0.81	8.0 <sup>a</sup>	0.61 <i>P</i> < 0.0001	10	<i>P</i> < 0.001
			BSC		NR		7.3 <sup>a</sup>		0	
Grothey et al <sup>51</sup>	III	Further lines	R	760	6.4	0.77 <i>P</i> = 0.0052	1.9	0.49 <i>P</i> < 0.0001	1.0	<i>P</i> = 0.19
			BSC		5.0		1.7		0.4	

**Note:** <sup>a</sup>Weeks.

**Abbreviations:** A, aflibercept; BSC, basic supportive care; BV, bevacizumab; C, cetuximab; CPT-11, irinotecan; CT, chemotherapy; FOLFIRI, infusional 5-fluorouracil/bolus folinic acid/irinotecan; FOLFOX4, infusional 5-fluorouracil/bolus folinic acid/oxaliplatin; HR, hazard ratio; mCRC, metastatic colorectal cancer; NR, not reported; OR, odds ratio; OS, overall survival; P, panitumumab; PFS, progression-free survival; R, regorafenib; RR, response rate.

Table 3 illustrates RR, PFS, and OS data of main clinical trials evaluating mCRC second- and further-line treatments.

## Conclusion

Treatment of mCRC involves the use of active cytotoxic drugs and biological agents, either in combination or as single agents. Until recently, the only biological agent with proven first-line efficacy was bevacizumab, but options have expanded from the data generated with anti-EGFR monoclonal antibodies. Anti-EGFR agents can be added to first-line FOLFIRI or FOLFOX in patients whose tumors express RAS wt. These agents may improve outcomes when added to chemotherapy, particularly in PFS and, in the case of cetuximab, OS and ORR. The selection of first-line therapy should be based on the individual treatment goals after considering the efficacy and tolerability of each regimen. For patients with metastases confined to the liver, surgical resection offers a potentially curative approach. For initially unresectable lesions, treatment regimens offering high response rates may produce sufficient tumor shrinkage to permit complete resection. Regimens with high response rates are also preferable for patients requiring symptom relief or for those with large tumor burdens. The choice between intensive and nonintensive management also depends on other factors, including the patient's functional status, comorbidities, and

desires. A sequential single-agent strategy or an intermittent approach (combination therapy followed by maintenance) may minimize toxicity and be appropriate for patients who are not surgical candidates, irrespective of treatment response. Finally, the choice of second or further chemotherapy lines is closely related to the drugs used in prior-line treatment and has been shown to improve both PFS and OS.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Malvezzi M, Arfé A, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2011. *Ann Oncol*. 2011;22:947–956.
- Schmoll 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.
- Folprecht G, Grothey A, Alberts S, Raab HR, Köhne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol*. 2005;16:1311–1319.
- Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am*. 2003;12:165–192.
- Nordlinger B, Van Cutsem E, Gruenberger T, et al; European Colorectal Metastases Treatment Group; Sixth International Colorectal Liver Metastases Workshop. 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(6):985–992.

6. Nordlinger B, Sorbye H, Glimelius B, et al; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomized controlled trial. *Lancet*. 2008;371:1007–1016.
7. Ciliberto D, Prati U, Roveda L, et al. Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. *Oncol Rep*. 2012;27:1849–1856.
8. Primrose JN, Falk S, Finch-Jones M, et al. A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: the new EPOC study. Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013; 31(Suppl):abstract 3504.
9. Bilchik AJ, Poston G, Adam R, Choti MA. Prognostic variables for resection of colorectal cancer hepatic metastases: an evolving paradigm. *J Clin Oncol*. 2008;26:5320–5321.
10. Limmer S, Unger L. Optimal management of pulmonary metastases from colorectal cancer. *Expert Rev Anticancer Ther*. 2011;11(10): 1567–1575.
11. Delaunoit T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol*. 2005;16:425–429.
12. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol*. 2004;15: 933–939.
13. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol*. 2005;23:9243–9249.
14. 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.
15. Petrelli F, Barni S. Resectability and outcome with anti-EGFR agents in patients with KRAS wild-type colorectal liver-limited metastases: a meta-analysis. *Int J Colorectal Dis*. 2012;27:997–1004.
16. 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.
17. 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.
18. 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.
19. Masi G, Vasile E, Loupakis F, et al. Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis. *J Natl Cancer Inst*. 2011;103:21–30.
20. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab (bev) versus FOLFIRI/bev as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients (pts): Results of the phase III TRIBE trial by GONO group. Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013;31(Suppl):abstract 3505.
21. [No authors listed]. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol*. 1992;10(6):896–903.
22. Tournigand C, André 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.
23. Colucci G, Gebbia V, Paoletti G, et al; Gruppo Oncologico Dell'Italia Meridionale. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol*. 2005;23:4866–4875.
24. Diaz-Rubio E, Taberero J, Gomez-Espana A, et al. Phase III study of capecitabine plus oxaliplatin versus continuous-infusion fluorouracil plus oxaliplatin as first line therapy in metastatic colorectal cancer. *J Clin Oncol*. 2007;25(27):4224–4230.
25. Köhne 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.
26. Van Cutsem E, Köhne CH, Láng 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.
27. 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(10):1626–1634.
28. Oliner KS, Douillard JY, Siena S, et al. Analysis of KRAS/NRAS and BRAF mutations in the phase III PRIME study of panitumumab (pmab) plus FOLFOX versus FOLFOX as first-line treatment (tx) for metastatic colorectal cancer (mCRC). Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013;31(Suppl):abstract 3511.
29. 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.
30. 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.
31. Heinemann V, von Weikersthal LF, Decker T, et al. Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013;31(Suppl):abstract LBA3506.
32. Cancer and Leukemia Group B. Cetuximab and/or Bevacizumab Combined With Combination Chemotherapy in Treating Patients With Metastatic Colorectal Cancer. Available from: <http://clinicaltrials.gov/show/NCT00265850>. ClinicalTrials.gov Identifier: NCT00265850. Accessed October 24, 2013.
33. Cunningham D, Lang I, Lorusso V, et al. Bevacizumab (bev) in combination with capecitabine (cape) for the first-line treatment of elderly patients with metastatic colorectal cancer (mCRC): results of a randomized international phase III trial (AVEX). Proceedings of the Gastrointestinal Cancer Symposium ASCO GI; January 24–26, 2013; San Francisco, CA. *J Clin Oncol*. 2013;30(Suppl 34):abstract 337.
34. 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.
35. Grothey A, Hart L, Rowland K, et al. Intermittent oxaliplatin administration improves time-to-treatment failure in metastatic colorectal cancer: final results of the phase III of the CONCEPT Trial. *J Clin Oncol*. 2008;26(Suppl):4010.
36. Tveit K, 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.



37. Díaz-Rubio E, Gómez-España A, Massutí B, et al; Spanish Cooperative Group for the Treatment of Digestive Tumors. 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(1):15–25.
38. Koopman M, Simkens LKJ, Ten Tije AJ, et al. Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC): the phase III CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG). Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013;31(Suppl):abstract 3502.
39. Koeberle D, Betticher DC, Von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemo-bevacizumab therapy in patients with metastatic colorectal cancer: a randomized phase III noninferiority trial (SAKK 41/06). Proceedings of the 13th ASCO annual meeting; May 31–June 4, 2013; Chicago, IL. *J Clin Oncol*. 2013;31(Suppl):abstract 3503.
40. AIO-Studien-gmbH. Optimal Maintenance Therapy With Bevacizumab After Induction in Metastatic Colorectal Cancer (CRC). Available from: <http://clinicaltrials.gov/show/NCT00973609>. ClinicalTrials.gov Identifier: NCT00973609. Accessed October 24, 2013.
41. Tournigand C, Samson B, Scheithauer W, et al. Bevacizumab (Bev) with or without erlotinib as maintenance therapy, following induction first-line chemotherapy plus Bev, in patients (pts) with metastatic colorectal cancer (mCRC): efficacy and safety results of the International GERCOR DREAM phase III trial. Proceedings of the 12th ASCO annual meeting; Chicago; 1–5 June 2012. *J Clin Oncol*. 2012;30(Suppl 18):abstract LBA3500.
42. 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.
43. 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.
44. 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.
45. 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.
46. Giantonio BJ, Catalano PJ, Meropol NJ, et al; Eastern Cooperative Oncology Group Study E3200. 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*. 2009;25:1539–1544.
47. Bennouna J, Sastre J, Arnold, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol*. 2013;14(1):29–37.
48. 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.
49. 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.
50. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*. 2007;25:1658–1664.
51. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303–312.

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