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How we treat metastatic colorectal cancer

Vincenzo De Falco ,[1] Stefania Napolitano,[1] Susana Roselló,[2] Marisol Huerta,[2] Andrés Cervantes ,[2] Fortunato Ciardiello,[1] Teresa Troiani[1]

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VDF and SN contributed equally.

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[1]Medical Oncology, Department of Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Campania, Italy
[2]Department of Medical Oncology, INCLIVA Biomedical Research institute, University of Valencia, Valencia, Comunitat Valenciana, Spain

Correspondence to
Dr Teresa Troiani;
troiani.teresa@yahoo.it

ABSTRACT

Colorectal cancer is the second leading cause of cancer-related death worldwide. About 20% of patients suffer from metastatic disease at diagnosis, while about one-third of patients treated with curative intent relapsed. In these patients, an accurate staging allows to plan a treatment strategy within a multidisciplinary team in order to achieve predefined goals. Patient's clinical features, tumour characteristics and molecular profile (*RAS/BRAF* and microsatellite instability (MSI) status) should be considered during the treatment choice. Combination of chemotherapy (fluoropyrimidines, oxaliplatin and irinotecan) plus biological agents (antiepidermal growth factor receptor or antiangiogenic drugs) in addition to surgery, could give a chance of cure in resectable or potentially resectable tumours. However, in never resectable tumours, disease control and prolonging survival should be the goal to achieve simultaneously with control of symptoms. In addition to standard therapies, especially in case of unresectable oligometastatic disease, several local ablative treatment are available. In later lines, when improving quality of life become predominant, regorafenib and trifluridine/tipiracil demonstrated survival benefit, while re-challenge therapies represent an option only in selected patients. In patients with *BRAFV600E*-mutant tumour or with MSI, new therapies showed survival gain and probably will be a new piece in the treatment algorithm.

INTRODUCTION

Colorectal cancer (CRC) is considered the third most commonly diagnosed cancer in males and the second in females worldwide, with an estimated 1.8 million new cases in 2018. In the same year, CRC was responsible for 881 000 deaths, making it the second leading cause of cancer-related death in men and women.[1] The largest proportion of CRC occurs in the rectum and sigmoid colon, while a smaller proportion occurs in caecum and ascending colon. About 20% of patients have synchronous metastases at diagnosis, frequently in the liver, and about 35% of patients develop metastases after a curative intent treatment.[2] In the past decade, the increasing number of effective drugs, the improvement of surgical procedures and the availability of different local ablative treatment (LAT), led to a significant increase in overall survival (OS) of metastatic CRC (mCRC) patients which is now ~30 months.

DIAGNOSIS, STAGING AND TREATMENT PLANNING

After histological diagnosis of CRC, physical examination, blood count, and renal and liver function can help to define the clinical status of the patient. Thoracoabdominal CT scan is the best option to identify distant metastases, while MRI is more sensitive to detect malignant liver lesions. PET scan is useful only in case of lesions of uncertain significance.[3]

In order to optimise treatment strategy, the institution of a multidisciplinary team (MDT) is crucial to determine the goal to achieve. In fact, treatment algorithm has been tailored according to three major points: (1) patient characteristics (performance status (PS), comorbidities, age and previous adjuvant treatment) and preferences (quality of life (QoL), acceptance of toxicities and expectations); (2) tumour features (tumour burden, pattern of progression, sites of metastasis, potential resectable metastases and primary tumour location); (3) molecular profile (*RAS/BRAF* status, microsatellite instability (MSI), and—eventually—human epidermal growth factor receptor (HER2 overexpression and *NTRK* (neurotrophic tyrosine receptor kinase) rearrangement) (figure 1).

FIRST-LINE TREATMENT

Effective first-line therapy is a key determinant of successful treatment in mCRC (table 1A). Many different factors influence the choice of upfront treatment, including patient characteristics, tumour features and molecular profile. Indeed, it is important to evaluate the comorbidities and age of the patient that can affect the possibility of using a more intensive approach: in particular, patients will be assessed as fit or unfit according to medical condition not due to malignant disease. In the case of unfit patients, physician experience should drive treatment decision with potential treatment

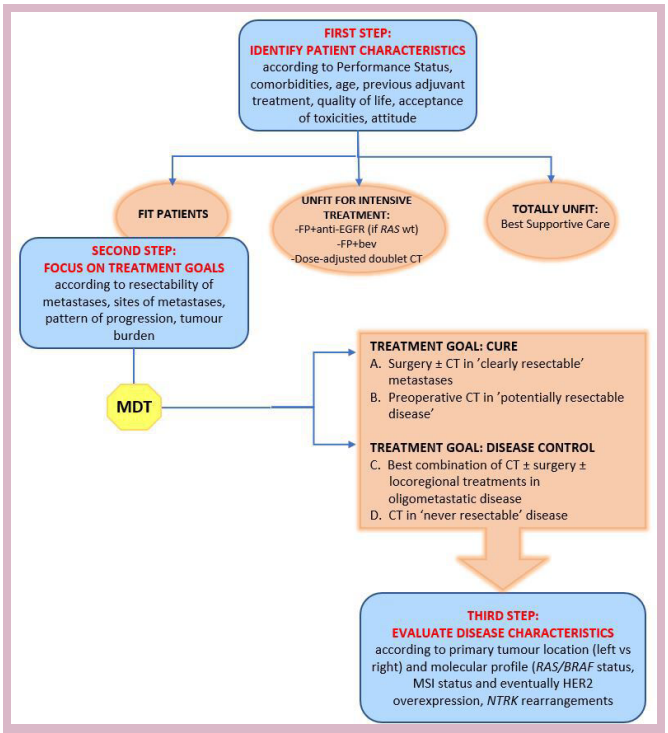

Figure 1 Algorithm for the treatment of mCRC. Bev, bevacizumab; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor; FP, fluoropyrimidine; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; MDT, multidisciplinary team; MSI, microsatellite instability; *NTRK*, neurotrophic tyrosine receptor kinase; *RAS*, rat sarcoma viral oncogene homolog; wt, wild-type.

options: capecitabine+bevacizumab or a dose-adjusted doublet chemotherapy.[4 5] In the case of unfit *RAS* wild-type (WT) patients, if there is the possibility that they may be receiving further treatments, anti-EGFR therapy can be considered.

In presence of fit patient, the best diagnostic and subsequent therapeutic decision-making available are managed by MDT: it should establish achievable goals and coordinate the different specialists to reach them through the four possible scenarios:

1. **Clearly resectable metastases:** In patients with technically easily resectable disease (ensuring a surgical procedure with adequate safety margins) and favourable prognostic criteria, upfront resection is recommended. In those patients where the prognosis is unclear or unfavourable,[6] perioperative chemotherapy (overall 6 months with FOLFOX or CAPOX) is mandatory. No indication for the use of target agents in this setting is available.[7] Moreover, in patients who have not received any prior systemic chemotherapy, adjuvant treatments with FOLFOX or CAPOX is recommended.
2. **Potentially curable with a conversion therapy:** In patients for whom the goal is tumour shrinkage or cytoreduction, intensive systemic treatment with the aim of conversion therapy is necessary. Before planning the treatment strategy, it is essential to consider molecular profile (*RAS* and *BRAF* status), tumour location (left versus right) and patient characteristic. For those patients who have left-sided *RAS* WT disease, cytotoxic doublet plus an anti-EGFR antibody should be treatment of choice.[8] For the ones with right-sided *RAS* WT disease, cytotoxic triplet+bevacizumab should be the treatment of choice, but cytotoxic doublet plus an anti-EGFR treatment can be another option for patients with any contraindication.[9] For those patients with *RAS* or *BRAF*-mutant disease, a cytotoxic doublet+bevacizumab or cytotoxic triplet+bevacizumab (in fit and suitable patients) are the preferred options.[10] After starting these 'conversion therapies', patients must be re-evaluated every 8 to 12 weeks with a maximum of 6 months to achieve the maximal response and to avoid overtreatment. Complete resection of the liver metastases is feasible, maintaining at least 30% of liver remnant; data of retrospective studies show a 5-year OS rates ranging from 25% to 58%.[11] Surgery R0 resection can be curative also with pulmonary metastasis, providing tumour-free margins.[12]
3. **Oligometastatic disease:** It defines a subgroup of patients with better prognosis characterised by few sites of metastases (up to three different sites, with five or more lesions). The treatment strategy is based on the possibility of achieving complete ablation of all tumour masses using surgery R0 resection and/or LATs (thermal ablation techniques, conformal radiation techniques and embolisation techniques), either initially or possibly after induction treatment with systemic therapy.[13]
4. **Never resectable disease:** In case of metastases not completely resectable with surgery, treatment goal is disease control rate and intensive protocols is not necessary. In this setting, a doublet chemotherapy plus a biologic agent is the standard of care, according to tumour molecular profile and 'sideness'. In particular, for those patients who have left-sided *RAS* WT disease, cytotoxic doublet plus an anti-EGFR antibody should be the treatment of choice. For the ones with right-sided *RAS* WT disease or *RAS* mutated, cytotoxic doublet+bevacizumab is the preferred option. The choice of a triplet chemotherapy is justified only with intent of cytoreduction in case of symptomatic disease, or in *BRAF*-mutant tumours due to their negative prognosis.[6]

After an induction therapy of 3 to 6 months, chiefly after an oxaliplatin-based chemotherapy, a maintenance treatment is possible to improve QoL. In particular, after FOLFOX/FOLFOXIRI+bevacizumab first-line therapy, maintenance with fluoropyrimidine+bevacizumab is preferred rather than bevacizumab alone.[14] Instead, subsequently a first-line with an anti-EGFR and a maintenance therapy with anti-EGFR+5-FU seems to be the best options but several trials are ongoing to address this question.[15 16]

Table 1 Main clinical trials in (A) first-line, (B) second-line and (C) further lines for mCRC

Clinical trial	Population	Treatment	mOS		mPFS		ORR	
(A) First-line chemotherapy treatment								
Hurwitz, NEJM 2004	Unselected mCRC	IFL+bev IFL+placebo	20.3 m 15.6 m	HR 0.66 p<0.001	10.6 m 6.2 m	HR 0.54 p<0.001	44.8% 34.8%	p=0.004
Saltz, JCO 2008	Unselected mCRC	XELOX/FOLFOX+bev XELOX/FOLFOX+placebo	21.3 m 19.9 m	HR 0.89 p=0.077	9.4 m 8.0 m	HR 0.83 p=0.0023	47% 49%	p=0.31
OPUS trial Bokmeyer, JCO 2009 (update Ann Onc 2015)	Unselected mCRC (analysis for *KRAS* exon 2 wt subgroup in brackets)	FOLFOX+cet FOLFOX	22.8 m (19.8 m) 18.5 m (17.8 m)	HR 0.86 (0.94) p=0.39 (0.80)	8.3 m (12.0 m) 7.2 m (5.8 m)	HR 0.57 (0.53) p=0.0064 (0.0615)	57% (58%) 34% (29%)	p=0.0027 (0.0084)
CRYSTAL trial Van Cutsem, NEJM2009, update JCO 2015	Unselected mCRC (analysis for *KRAS* exon 2 wt subgroup in brackets)	FOLFIRI+cet FOLFIRI	23.5 m (28.4 m) 20.0 m (20.2 m)	HR 0.80 (0.69) p=0.0093 (0.0024)	9.9 m (11.4 m) 8.4 m (8.4 m)	HR 0.70 (0.56) p=0.0012 (<0.001)	57.3% (66.3) 39.7% (38.6)	p<0.001 (<0.001)
PRIME trial Douillard, JCO 2010	Unselected mCRC, analysis only for *KRAS* exon 2 wt subgroup	FOLFOX+pan FOLFOX	23.9 m 19.7 m	HR 0.83 p=0.072	9.6 m 8.0 m	HR 0.80 p=0.02	55% 48%	p=0.068
Kohne, J Cancer Res Clin Oncol 2012	Unselected mCRC, single-arm trial (analysis for *KRAS* exon 2 wt versus mut subgroups in brackets)	FOLFIRI+pan	/	/	7.6 m (8.9 m in RASwt, 7.2 m in RASmut)	HR 0.5	49% (56% in RASwt, 39% in RASmut)	
FIRE-3 trial Stintzing, Lancet 2016	*KRAS* exon 2 wt mCRC (analysis for *KRAS*/*NRAS* exons 2 to 4 wt subgroup in brackets)	FOLFIRI+cet FOLFIRI+bev	28.7 m (33.1 m) 25.0 m (25.0 m)	HR 0.77 (0.70) p=0.017 (0.0059)	10.0 m (10.3 m) 10.3 m (10.2 m)	HR 1.06 (0.97) p=0.55 (0.77)	62% (65.3) 58% (58.7)	p=0.18 (0.18)
CALGB/SWOG 80405 trial Venook, JAMA 2017	*KRAS* exon 2 wt mCRC (extended *RAS* wt subgroup in brackets)	FOLFOX/FOLFIRI+cet FOLFOX/FOLFIRI+bev	30.0 m (31.5 m) 29.0 m (33.3 m)	HR 0.88 (0.91) p=0.08 (0.459)	10.5 m (10.9) 10.6 m (11.1 m)	HR 0.95 (0.90) p=0.45 (0.359)	59.6% 55.2%	p=0.13
PEAK trial Schwartzberg, JCO 2014	*KRAS* exon 2 wt mCRC (extended *RAS* wt subgroup in brackets)	FOLFOX+pan FOLFOX+bev	34.2 m (41.3 m) 24.3 m (28.9 m)	HR 0.62 (0.63) p=0.009 (0.058)	10.9 m (13.0 m) 10.1 m (9.5 m)	HR 0.87 (0.65) p=0.353 (0.029)	57.8% (63.6) 53.5% (60.5)	/
TRIBE trial Loupakis, Cremolini, NEJM 2014, Lancet 2015[9 10]	Unselected mCRC	FOLFOXIRI+bev FOLFIRI+bev	29.8 m 25.8 m	HR 0.80 p=0.03	12.3 m 9.7 m	HR 0.77 p=0.006	65% 54%	p=0.013
(B) Second-line chemotherapy treatment								

Continued

Table 1 Continued

Clinical trial	Population	Treatment	mOS		mPFS		ORR	
ECOG E3200 trial Giantonio, JCO 2007[18]	mCRC previously treated with a fluoropyrimidine and irinotecan	FOLFOX+bev FOLFOX	12.9m 10.8m	HR 0.75 p=0.0011	7.3m 4.7m	HR 0.61 p<0.0001	22.7% 8.6%	p<0.0001
Cao, Med Oncol 2015[20]	mCRC previously treated with oxaliplatin-based CT	FOLFIRI+bev FOLFIRI	15.2m 11.3m	/	8.5m 5.1m	/	47.7% 28.5%	p=0.001
ML18147 trial Bennouna, Lancet Oncol 2013[21]	mCRC previously treated with CT+bev	CT+bev CT	11.2m 9.8m	HR 0.83 p=0.0211	5.7m 4.1m	HR 0.68 p<0.0001	5% 4%	/
BEBYP trial Masi, Ann Oncol 2015[19]	mCRC previously treated with CT+bev	CT+bev CT	14.1m 15.5m	HR 0.77 p=0.043	6.8m 5.0m	HR 0.70 p=0.010	21% 17%	p=0.573
VELOUR trial Van Cutsem, JCO 2012[22]	mCRC previously treated with oxaliplatin, including patients who received prior bevacizumab	FOLFIRI+aflib FOLFIRI	13.5m 12.06m	HR 0.817 p=0.0032	6.9m 4.67m	HR 0.758 p<0.0001	19.8% 11.1%	p<0.001
EPIC trial Sobrero JCO 2008[24]	Unselected mCRC previously treated with oxaliplatin and fluoropyrimidine	Irinotecan+cet Irinotecan	10.7m 10.0m	HR 0.975 p=0.71	4.0m 2.6m	HR 0.692 p≤0.0001	16.4% 4.2%	p<0.0001
Peeters JCO 2010[25]	Unselected mCRC previously treated without irinotecan or anti-EGFR. Analysis only for *KRAS* exon 2 wt subgroup	FOLFIRI+pan FOLFIRI	14.5m 12.5m	HR 0.85 p=0.12	5.9m 3.9m	HR 0.73 p=0.004	35% 10%	p<0.001
RAISE trial Tabernero, Lancet Oncol 2015[23]	mCRC previously treated with oxaliplatin-based CT+bev	FOLFIRI+ram FOLFIRI	13.3m 11.7m	HR 0.844 p=0.0219	5.7m 4.5m	HR 0.793 p<0.0005	13.4% 12.5%	p=0.63
(C) Further lines								
CORRECT trial Grothey, Lancet 2013[26]	Unselected mCRC progressed after all standard therapies	Regorafenib Placebo	6.4m 5.0m	HR 0.77 p=0.0052	1.9m 1.7m	HR 0.49 p<0.0001	1% 0.4%	p=0.19
RECOURSE trial Mayer, NEJM 2015	Unselected mCRC progressed after all standard therapies	Trifluridine/tipiracil Placebo	7.1m 5.3m	HR 0.68 p<0.001	2.0m 1.7m	HR 0.48 p<0.001	1.6% 0.4%	p=0.29

Continued

Table 1 Continued

Clinical trial	Population	Treatment	mOS		mPFS		ORR	
CO.17 trial Karapetis, NEJM 2008[33]	*KRAS* wt exon 2 mCRC progressed after all standard CT (w/o anti-EGFR)	Cetuximab Placebo	9.5m 4.8m	HR 0.55 p<0.001	3.7m 1.9m	HR 0.40 p<0.001	12.8% 1.2%	/
Van Cutsem JCO 2007[34]	Unselected mCRC progressed after all standard CT	Panitumumab Placebo	No difference	HR 1 p=0.81	8.0w 7.3w	HR 0.54 p<0.0001	10% 0%	p<0.0001

/, not reported; aflib, aflibercept; cet, cetuximab; FOLFIRI, irinotecan, leucovorin and 5-fluorouracil; FOLFOX, oxaliplatin, leucovorin, 5-fluorouracil; IFL, irinotecan, leucovorin, 5-fluorouracil; m, months; mCRC, metastatic colorectal cancer; mut, mutant; ORR, overall response rate; OS, overall survival; pan, panitumumab; PFS, progression-free survival; ram, ramucirumab; w, weeks; WT, wild type; XELOX, oxaliplatin and capecitabine.

SECOND-LINE TREATMENT

Second-line regimen choice depends on the systemic therapies given in first line. About two-thirds of mCRC patients received a second-line therapy. Typical second-line chemotherapy options include FOLFIRI or FOLFOX depending on the systemic therapy given in the first-line setting.[17] (table 1B) Furthermore, the addition of bevacizumab, in naïve-patients or 'beyond-progression', has demonstrated a benefit compared with chemotherapy alone.[18–21] Other two antiangiogenic drugs are available in second line in association with FOLFIRI: aflibercept, a fusion protein, improved OS in patients progressed to previously oxaliplatin-based chemotherapy even in those pretreated with bevacizumab;[22] ramucirumab, a monoclonal antibody against VEGFR2, also showed a gain in OS after a first line with FOLFOX+bevacizumab.[23] Cetuximab or panitumumab within an irinotecan-based therapy, can be both considered in second line in *RAS* WT tumours that haven't received any anti-EGFR, although the benefit is only in progression-free survival (PFS) and overall response rate (ORR) but not in OS.[24 25]

FURTHER LINES

In later lines, treatment goals must be QoL and PS maintenance, other than disease control. In this setting, regorafenib[26–28] (a multitargeted kinase inhibitor) and trifluridine/tipiracil[29] (an antimetabolite) have demonstrated similar OS benefit against placebo in chemorefractory mCRC patients (table 1C). In the absence of head-to-head comparative trials, choice of the sequence between the two drugs should be made according to patient's characteristics and comorbidity, considering the different toxicity profile.[30] In fact, trifluridine/tipiracil seems more manageable but with higher prevalence of neutropaenia. For regorafenib, dose is an issue and an escalating dose could permit a greater efficacy without affecting QoL, as described in several recent trials.[31 32] Furthermore, in *RAS* WT patients not previously treated with any anti-EGFR therapy, cetuximab or panitumumab have demonstrated similar survival benefit as third-line treatment.[33–35] Finally, re-challenge with previous drugs to which the tumour has already developed resistance, is an option in later lines, particularly if there was an adequate time interval. Few trials that addressed this topic with either oxaliplatin, irinotecan or anti-EGFR (in *RAS* WT tumours) did not demonstrate a clear benefit.[36 37] Therefore, differences in mechanisms of action and, more importantly, the safety profile of available third and further lines, including re-challenge treatments, may guide treatment selection for individual patients when QoL is the main goal.

INNOVATIVE STRATEGIES AND NEW TARGETS

Additional encouraging strategies have been studied in several subsets of patients in the past years. In particular, practice-changing results derived from BEACON trial. The trial has been conducted in patients with *BRAFV600E*

mutation pretreated with at least one prior line of treatment. In this setting, the combination of encorafenib and cetuximab±binimetinib demonstrated a significant survival benefit compared with irinotecan+cetuximab or FOLFIRI+cetuximab: this led to the FDA (Food and Drug Administration) approval of encorafenib+cetuximab in *BRAFV600E*-mutant mCRC after prior therapy (European Medicines Agency approval is going to follow).[38] Open questions remain: (1) the addition of binimetinib has not improve OS compared with encorafenib+cetuximab alone; (2) this therapy could be effective also in first line (results of ANCHOR trial are expected in the next months).

Furthermore, although immunotherapy revolutionised the oncology landscape in the last 10 years, this success did not involve mCRC therapy. Different trials evaluating immunotherapy alone or in combination failed to demonstrate any efficacy in unselected population.[39] Nevertheless, in patients with deficient mismatch repair (dMMR)/MSI-H phenotype, which represents 4% to 5% of mCRC, results are very promising. Recently, pembrolizumab showed impressive results in this population in first line compared with standard chemotherapy in terms of median PFS (16.5 vs 8.2 months; HR 0.60; p=0.0002), ORR (43.8% vs 33.1%) and duration of response: this study will probably change the scenarios in this setting by becoming the new standard of care, making the assessment of MSI mandatory at diagnosis.[40] Furthermore, a recent update of the first-line CheckMate 142 trial, mCRC patients treated with 3 mg/kg nivolumab and 1 mg/kg ipilimumab showed an ORR of 69%, and a 24-month PFS and OS rates of 74% and 79%, respectively.[41] Previously, in MSI-H heavily pretreated patients, pembrolizumab and nivolumab have already demonstrated a good efficacy in terms of ORR and PFS.[42 43]

Finally, approximately 3% to 4% of mCRC patients harboured HER2 amplifications. HERACLES-A, a multicentre clinical trial, showed that a dual blockade of HER2 is effective in mCRC patients with amplification of this oncogene, providing ORR as high as 30% with the combination of trastuzumab and lapatinib.[44] Similar results have been obtained in this subgroup of patients with the combination of pertuzumab and trastuzumab (MyPathway phase II trial), that achieved a 32% ORR in heavily pretreated patients.[45] Recently, in the phase II DESTINY-CRC01 trial, trastuzumab deruxtecan, an antibody-drug conjugate, demonstrated remarkable activity in pretreated HER2-expressing mCRC, being careful of interstitial lung disease as critical toxicity.[46]

Ultimately, larotrectinib and entrectinib in tumours harbouring rearrangements of the *NTRK*1, *NTRK*2 or *NTRK*3 gene showed good efficacy in heavily pretreated mCRC.[47 48]

CONCLUSION

CRC is an heterogeneous entity for which therapeutic algorithm need to be chosen upfront by a multidisciplinary tumour board in order to ensure the 'continuum of care' for the patients. Finally, the advent of genomic analysis has generated new possibilities for evaluating off-label targeted therapies in refractory cancers and for enrolment in clinical trial with matched targeted therapeutics. Above all, physicians should personalise the treatment, considering several factors, including molecular profile, tumour location, achievable goals, patient characteristics and preference.

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ORCID iDs
Vincenzo De Falco http://orcid.org/0000-0003-0261-0382
Andrés Cervantes http://orcid.org/0000-0003-3806-3691

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