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# How to select the optimal treatment for first line metastatic colorectal cancer

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## Abstract

Choice of first line treatment for patients with metastatic colorectal cancer (mCRC) is based on tumour and patient related factors and molecular information for determination of individual treatment aim and thus treatment intensity. Recent advances (*e.g.*, extended *RAS* testing) enable tailored patient assignment to the most beneficial treatment approach. Besides fluoropyrimidines, irinotecan and oxaliplatin, a broad variety of molecular targeting agents are currently available, *e.g.*, anti-angiogenic agents (bevacizumab) and epidermal growth factor receptor (EGFR) antibodies (cetuximab, panitumumab) for first line treatment of mCRC. Although some combinations should be avoided (*e.g.*, oral or bolus fluoropyrimidines, oxaliplatin and EGFR antibodies), treatment options range from single agent to highly effective four-drug regimen. Preliminary data comparing EGFR antibodies and bevacizumab, both with chemotherapy, seem to favour EGFR antibodies in *RAS* wildtype disease. However, choosing the most appropriate treatment approach for mCRC patients remains a complex issue, with numerous open questions.



**Key words:** Colorectal cancer; Metastatic; Induction chemotherapy; Epidermal growth factor receptor

**Core tip:** Selection of the optimal first line treatment for metastatic colorectal cancer is a complex issue influencing course of disease and most likely survival of the individual patient. Available data will be analyzed to allow for a patient and disease specific, molecularly stratified treatment approach, applying systemic treatment (chemotherapy and antibodies) and locally ablative measures (surgery and radiofrequency ablation).

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## INTRODUCTION

After lung (1.61 million cases) and breast cancer (1.38 million), colorectal cancer (CRC, 1.23 million) is one of the most commonly diagnosed malignancies worldwide[1]. Moreover, after lung cancer, CRC is the second most common cause of cancer deaths[2]. Around one quarter of patients with CRC present with metastatic disease at time of diagnosis (synchronous disease), and up to 40% of patients will develop metastases during the course of their disease, resulting in a relatively high overall mortality rate associated with CRC.

As a result of recent advances in the treatment of

**Table 1 Prognostic scores/health assessments**

| Score | Risk category | Factors |
|---|---|---|
| "Kohne" score[13] | Low risk | ECOG 0/1 and only one tumour site |
| | Intermediate risk | ECOG 0/1, ALP < 300 U/L and more than one tumour site or ECOG > 1 and WBC < 1 × $10^{10}$/L and only one tumour site |
| | High risk | ECOG 0/1 and more than one tumour site and ALP ⩾ 300 U/L or ECOG > 1 and more than one tumour site or ECOG > 1 and WBC > 1 × $10^{10}$/L |
| FOCUS 2[15] | Comprehensive health assessment at baseline limited health | Weight change<br>Timed 20 metre walk<br>MMSE<br>CCI |
| | Assessment during course of treatment (excluding MMSE and CCI) | Patient completed questionnaire (social activity, physical fitness, symptoms, overall quality of life and depression) |

ECOG: Eastern collaborative oncology group performance status; ALP: Alkaline phosphatase; WBC: White blood cells; MMSE: Mini mental state examination; CCI: Charlson comorbidity index.

metastatic colorectal cancer (mCRC), median overall survival (OS) can now be as long as 30 mo in selected patient groups and up to 70% of patients will receive at least two lines of treatment[3-7]. Several drugs as single agent or in various combinations are available for mCRC, including fluoropyrimidines (5FU, capecitabine), irinotecan, oxaliplatin, the vascular endothelial growth factor (VEGF) antibody bevacizumab, the epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab for *RAS* wildtype patients, the VEGF receptors 1 and 2 fusion protein aflibercept and the multitarget tyrosine kinase inhibitor regorafenib. Moreover, secondary resection and/or ablation *e.g.*, by surgery or radiofrequency may contribute to long-term survival and even cure, or at least allow a relevant chemotherapy free interval[8,9].

According to recent data, choice of first line treatment seems to be relevant for further course of disease, despite available efficacious second, third and if applicable fourth line regimen and the cross over use of all available drugs in later lines. The aim of this article is to review the available data on choice of first line treatment in mCRC. Pertinent data from published trials and reports and abstracts presented at selected oncology association meetings [American Society of Clinical Oncology and European Society for Medical Oncology (ESMO)/European cancer organisation] until September 2013 were reviewed.

## PROGNOSTIC FACTORS FOR PATIENT STRATIFICATION

Prognosis of mCRC depends on several patient related (*e.g.*, age, performance status, co-morbidity), tumour related (*e.g.*, spread of disease, growth dynamics, symptoms, localization in particular liver and/or extrahepatic metastases), biochemical (*e.g.*, baseline values of carcinoembryonic antigen, lactate dehydrogenase, platelets, leucocytes, haemoglobin, alkaline phosphatase, albumine) or molecular factors (*e.g.*, *KRAS* or *NRAS* mutations, *BRAF* mutation)[10]. Whereas *BRAF* mutation is associated with shorter survival, prognostic value of *KRAS* mutation is not clarified yet[11,12]. Some factors are combined to scores, which might be useful for stratification of patients within clinical trials and in daily clinical practise (Table 1)[13-15]. Determination of patients' individual prognoses might be useful for choice of treatment, particularly in regard of intensity of systemic treatment and integration of local ablation into the overall therapeutic concept.

Besides the above-mentioned factors prognostic information can be derived from a broad variety of tissue or blood markers, *e.g.*, circulating tumour cells, levels of growth factor receptor-ligands, mutations or amplifications within the relevant signalling pathways or receptors, or epigenetic alterations[16,17]. These prognostic factors might gain relevance in the future, but are currently neither broadly available nor relevant for clinical decisions[10].

## PREDICTIVE FACTORS FOR TREATMENT EFFICACY OR TOXICITY

Despite tremendous efforts in searching for predictive markers in mCRC, only *RAS* mutation have been established, precluding treatment with EGFR antibodies. Initially *KRAS* mutations in exon 2 (codon 12 and 13) have been found to be predictive for non-response to cetuximab or panitumumab[18,19]. Although data are conflicting, *KRAS* codon G13D mutation (16% of *KRAS* mutated tumours) seems not to preclude efficacy of cetuximab in patients with *KRAS* mutations[20,21]. However, neither in the COIN trial, combining oxaliplatin with different fluoropyrimidine schedules and cetuximab, nor in the available panitumumab trials *KRAS* G13D mutated tumours seem to derive relevant benefit from anti-EGFR treatment[22-24].

Recently, retrospective analyses of the PRIME study demonstrated the negative predictive value of *KRAS* mutation in exon 3 and 4 and *NRAS* mutations in exon 2,3 and 4 for treatment with 5FU/leucovorin and oxaliplatin (FOLFOX) and panitumumab[25]. In patients with any RAS mutation the addition of panitumumab to FOLFOX had a detrimental effect on progression free survival (PFS) (HR = 1.31; 95%CI: 1.07-1.60) and OS (HR = 1.21; 95%CI: 1.01-1.45). In contrast, median OS was 25.8 mo *vs* 20.2 mo (HR = 0.77; 95%CI: 0.64-0.94, $P$ = 0.009) in the all *RAS* wild-type population in favour of the combination of panitumumab and FOLFOX. Although data from the cetuximab containing trials (CRYSTAL, OPUS) are not yet available, *RAS* mutational status will likely be of similar impact for cetuximab treatment[26].

Despite the strong adverse prognostic effect of *BRAF* mutation (8% of *RAS* wild-type patients), the predictive value for treatment with EGFR antibodies is still unclear, with some analysis indicating a lack of benefit, particularly in advanced treatment situations[24,26,27], whereas data from first line trials (CRYSTAL, PRIME and OPUS) show

**Table 2 European Society for Medical Oncology clinical groups for first line treatment stratification[10]**

| ESMO group | Clinical presentation | Treatment aim | Treatment intensity |
|---|---|---|---|
| 0 | Clearly R0-resectable liver and/or lung metastases | Decrease risk of or delay relapse | FOLFOX |
| 1 | Liver and/or lung metastases only which: Might become resectable after induction chemotherapy | Maximum tumour shrinkage | Three or four drug combination |
| 2 | Multiple metastases/sites, with: Rapid progression and/or Tumour-related symptoms/risk of rapid deterioration | Immediate clinically relevant response or at least tumour control | Three or four drug combination |
| 3 | Multiple metastases/sites without option for resection and no major symptoms or severe comorbidity | Abrogation of further progression Tumour shrinkage less relevant Low toxicity essential | Consider sequential approach: start with Single agent, or Doublet with low toxicity |

ESMO: European Society for Medical Oncology.

some benefit[25,28].

There is no baseline predictive marker for the available anti-angiogenic drugs *e.g.*, bevacizumab or aflibercept. Changes in levels of angiogenic factors (*e.g.*, basic fibroblast, placental, or hepatocyte growth factor) during treatment with bevacizumab might indicate development of resistance and predict progression[29,30]. However, as recently shown in two randomized phase Ⅲ trials resistance to chemotherapy occurs before resistance to bevacizumab[31,32].

Beside the prediction of treatment toxicity (dihydropyrimidine-dehydrogenase deficiency for fluoropyrimidines or uridine-glucuronosyltransferase (UGT1A1) polymorphism for irinotecan), drug efficacy (*e.g.*, by topoisomerase-1 overexpression for irinotecan, or excision repair cross-complementing gene 1 polymorphisms for oxaliplatin) cannot be reliably predicted[33-37].

Current research focuses on distinct subsets of CRC patients defined by gene arrays, epigenetic alterations, or cancer stem cells, which might allow for a better treatment stratification[38-42]. Moreover, liquid biopsies (either by analysis of circulating DNA or tumour cells) obtained during course of treatment might give insights into tumour changes and development of resistance[43-46].

## STRATIFICATION OF FIRST LINE MANAGEMENT FOR MCRC

Decision of treatment intensity for first line treatment should be based on clinical presentation at diagnosis, considering factors like patients' characteristics independent from the malignant disease, (if given) tumour-related symptoms, patients´ preferences, localisations of metastases, and the general treatment aim. Current ESMO guidelines stratify patients according to these factors in clinical groups with different treatment intensities (Table 2)[10]. Four groups are defined: ESMO group 0 comprising patients with clearly resectable liver metastases, group 1 with potentially resectable disease after achieving tumour response, group 2 symptomatic patients or high tumour load with risk of rapid deterioration and finally group 3 with asymptomatic, low tumour burden and severe co-morbidity.

For ESMO group 0 patients with clearly R0 resectable colorectal liver metastases surgery is the treatment of choice due to the proven chance of cure, whereas the sequence and intensity of perioperative chemotherapy is controversial. Based on the current ESMO consensus these patients should be managed preferably by perioperative FOLFOX for 3 mo before and 3 mo after resection[10,47,48]. Alternatively upfront resection with or without postoperative chemotherapy might be applied, particularly in metachronous, small and single liver metastasis[10]. Although intensification of perioperative treatment with antibodies has shown feasibility in single arm phase Ⅱ trials (*e.g.*, for bevacizumab), recently reported preliminary results of the New EPOC trial, evaluating chemotherapy and cetuximab in the perioperative setting, have raised strong scepticism[49,50]. Therefore, FOLFOX currently remains the standard treatment for clearly resectable liver metastases.

Patients with unresectable disease (ESMO groups 1, 2 or 3) should receive upfront systemic chemotherapy, apart from the small group of asymptomatic patients with low tumour burden eligible for and complying with a watch and wait approach[51,52]. Whereas groups 1 and 2 patients urge for intensive upfront chemotherapy to either ensure secondary resectability or allow for rapid symptom control, group 3 could be treated with a sequential treatment approach, starting with a low toxic single agent or two-drug combination regimen. Patients with asymptomatic, but surely unresectable disease due to location or overall extent and without relevant co-morbidity may not be ideally stratified in ESMO group 3, but rather treated with upfront intensive chemotherapy. Moreover, current available phase Ⅲ trials included patients irrespective of ESMO grouping, thus limiting the potential prognostic or predictive value of upfront patient stratification. Although grouping patients might be helpful for guidance of treatment strategy beyond induction treatment, *e.g.*, secondary resection, main systemic treatment options are either intensive three to four drug regimens or "sequential" one to two drugs regimens (Table 3).

## SELECTION OF AN INTENSIVE FIRST LINE REGIMEN FOR MCRC

With respect to the increasing awareness of secondary surgery and developments in surgical and locally ablative measures, there is a growing group of patients that might

**Table 3 Available treatment regimens for first-line metastatic colorectal cancer**

| Treatment intensity | Molecular factor | Regimens |
|---|---|---|
| Single agent | | 5FU/LV |
| | | Capecitabin |
| Two-drug | | Capecitabin/bevacizumab |
| | | FOLFOX/XELOX |
| | | FOLFIRI/XELIRI |
| Three-drug | *RAS* wt | FOLFOX + panitumumab |
| | | FOLFIRI + cetuximab |
| | Independent of RAS status | FOLFOX/XELOX + bevacizumab |
| | | FOLFIRI/XELIRI + bevacizumab |
| | | FOLFOXIRI |
| Four-drug | | FOLFOXIRI + bevacizumab |

Combination chemotherapy with 5-fluorouracil, folinic acid (5FU/LV), and oxaliplatin (FOLFOX), or irinotecan (FOLFIRI) or both (FOLFOXIRI), or capecitabine and oxaliplatin (XELOX) or irinotecan (XELIRI).

be converted to resectability or at least achieve a "no evidence of disease" status after integration of other ablative techniques, and thus benefit from intensive upfront treatment. Therefore, either a chemotherapy doublet in combination with the VEGF antibody (bevacizumab) or an EGFR antibody [only *RAS* wild-type patients], or a chemo triplet (FOLFOXIRI) and more recently the highly active four drug regimen [FOLFOXIRI and bevacizumab or similar combinations (*e.g.*, FOLFIRINOX with a 5FU Bolus and slightly different doses) with EGFR antibodies] are available treatment options in this situation[4,22,53-59]. Comparative quantity, quality and celerity of response of these regimens are a matter of debate and currently only limited randomized data are available.

Preliminary data of the phase Ⅱ PEAK study comparing FOLFOX in combination with either panitumumab or bevacizumab in 285 previously untreated, *KRAS* wild-type mCRC patients indicated similar overall response rate (ORR)[60]. In the all *RAS* wildtype (*KRAS*/*NRAS* exon 2, 3 and 4) population panitumumab and FOLFOX significantly prolonged PFS (13.1 mo *vs* 9.5 mo, HR = 0.63; 95%CI: 0.43-0.94, $P = 0.02$) and showed a favourable trend in OS (HR = 0.55; $P = 0.06$) compared to bevacizumab and FOLFOX[61]. Similarly, early results from the phase Ⅲ AIO KRK-0306 (FIRE 3) study comparing FOLFIRI with either bevacizumab or cetuximab in 592 *KRAS* wildtype patients demonstrated a significantly prolonged OS (28.7 mo *vs* 25 mo, HR = 0.77; 95%CI: 0.62-0.96, $P = 0.017$) besides similar ORR (62% *vs* 58%, $P = 0.183$) and PFS (10 mo *vs* 10.3 mo, HR = 1.06; 95%CI: 0.88-1.26, $P = 0.547$) for cetuximab *vs* bevacizumab based chemotherapy, respectively[3]. Recent analyses demonstrated a pronounced OS benefit in *RAS* wildtype patients (33.1 mo *vs* 25.9 mo, $P = 0.01$) in favour of the cetuximab combination[62]. Subsequent treatments were balanced in regard of use of second line oxaliplatin and the cross over to the other antibody (46.6% receiving bevacizumab after cetuximab and 41.4% receiving EGFR antibody after bevacizumab). Interestingly, treatment in the cetuximab arm was shorter with a median duration of 4.8 mo *vs* 5.3 mo for all drugs and 6.8 mo *vs* 8 mo for any drug compared to the bevacizumab arm respectively. Although the primary endpoint of the FIRE 3 trial (ORR) was not reached and results of both trials are not fully published, the similar trend in the FIRE 3 and the PEAK study suggest a beneficial impact for EGFR antibodies and chemotherapy in first line *RAS* wildtype mCRC. Further data will soon be available from the large Intergroup trial (CALGB/SWOG 80405).

Feasibility and efficacy of a maximum intensive treatment with a four-drug regimen has been preliminarily shown in the phase Ⅲ TRIBE trial comparing FOLFIRI/bevacizumab and FOLFOXIRI/bevaciumab[7]. Overall response rate 53% *vs* 65% ($P = 0.006$), PFS 9.7 mo *vs* 12.1 mo (HR = 0.75; 95%CI: 0.62-0.90, $P = 0.003$) and OS 25.8 mo *vs* 31.0 mo (HR = 0.79; 95%CI: 0.63-1.00, $P = 0.054$) favoured the FOLFOXIRI and bevacizumab arm. Secondary surgery was applied at similar rates in both arms (12% *vs* 15% with the four-drug regimen). Treatment was generally well tolerated. Although rates of distinct grade 3/4 toxicity, particular, diarrhoea (11% *vs* 19%), stomatitis (4% *vs* 9%) and neutropenia (20% *vs* 50%) were significantly higher with the four-drug regimen, rates of febrile neutropenia, severe adverse events and treatment related death were similar. Efficacy of FOLFOXIRI and bevacizumab was independent of *KRAS* mutational status. Interestingly, patients with BRAF mutations seem to have better outcome with the four-drug regimen, despite their poor prognosis. In regard of similar outcomes in non-randomized phase Ⅱ trials FOLFOXIRI/bevacizumab should be considered for BRAF mutated patients[63,64].

According to the most recently presented preliminary trial results, the choice of first line regimen, *e.g.*, FOLFIRI + cetuximab (or FOLFOX + panitumumab) for *RAS* wildtype patients or FOLFOXIRI + bevacizumab for patients with good performance status seems to be relevant for the achievement of an OS of about 2.5 years[3,7]. Available treatment options are summarized in Table 4.

## SELECTION OF A NON-INTENSE OR SEQUENTIAL TREATMENT APPROACH FOR MCRC

An increasingly ageing population with related co-morbidity which might not be amenable for a secondary curative approach (ESMO group 3) urge for comprehensive assessments focusing on toxicity and outcome prediction and well tolerated regimens for these patients (*e.g.*, single agent or two drug combinations)[15,65]. In the recently reported phase Ⅲ AVEX trial the addition of bevacizumab to capecitabine prolonged PFS from 5.1 to 9.1 mo (HR = 0.53; 95%CI: 0.41-0.69, $P < 0.0001$) and showed a strong trend in OS with an acceptable tolerability profile in patients with at least 70 years of age[66]. Alternatively, upfront combination with fluoropyrimidines and oxaliplatin seems to be feasible in elderly patients and prefer-

**Table 4 Efficacy and tolerability of three to four drug first line regimen**

| Regimen | Efficacy | | | | Tolerability | | |
|---|---|---|---|---|---|---|---|
| | PFS | | OS | | Grade 3/4 AE | SAE | Fatal AEs |
| | RAS wt | RAS mut | RAS wt | RAS mut | | | |
| FOLFOX + panitumumab[25] | 10.1 | 7.3[1] | 25.8 | 15.5[1] | 84% | 40% | 5% |
| FOLFIRI + cetuximab[4,62] | 10.5 | NR[1] | 33.1 | NR[1] | 71%-79% | 26% | NR |
| | 9.9 (KRAS exon 2) | | 23.5 (KRAS exon 2) | | | | |
| FOLFOX/XELOX + bevacizumab[56] | 9.4 | | 21.3 | | 80% | NR | 2% |
| FOLFIRI + bevacizumab[7,62] | 10.4 | NR | 25.9 | NR | NR | 20% | 3.5% |
| | 9.7 | | 25.8 | | | | |
| FOLFOXIRI + bevacizumab[7] | 12.1 | | 31.0 | | NR | 20% | 2.8% |

[1]These fields only informative (epidermal growth factor receptor antibodies not licensed for *RAS* mutated tumours). Combination chemotherapy with 5-fluorouracil, folinic acid, and oxaliplatin (FOLFOX), or irinotecan (FOLFIRI) or both (FOLFOXIRI), or capecitabine and oxaliplatin (XELOX). PFS: Progression free survival; OS: Overall survival; AE: Adverse events; SAE: Severe adverse events; NR: Not reported.

ably, if applied with dose reductions, compared to singe agent fluoropyrimidine alone[15,67]. However, for elderly patients a tolerable and efficacious first line regimen seem to be particulary relevant, with less than 50% of patients receiving second line treatment.

Sequential treatment strategies were evaluated independent of age in first line mCRC[66,68-70]. Although sequential treatment did not seem to be inferior to upfront two-drug combination in trials of the chemotherapy only era (only fluoropyrimidines, irinotecan and oxaliplatin), it is questionable whether these results can be transferred into the current treatment situation (including molecular targeting agents)[68-70].

## LIMITATIONS FOR CHEMOTHERAPY AND ANTIBODY COMBINATIONS

Besides very few limitations antibodies can be combined with fluoropyrimidines, oxaliplatin and/or irinotecan in several combinations. EGFR antibodies and bevacizumab should not be combined[71,72]. If EGFR antibodies are combined with an oxaliplatin based chemotherapy backbone, infusional 5FU (FOLFOX) should be chosen instead of an oral or bolus fluoropyrimidine regimen (XELOX or FLOX) according to clinical data from the COIN and NORDIC VII studies showing no benefit for the addition of cetuximab to these regimen[22,73].

The combination of capecitabin and irinotecan (with or without oxaliplatin or bevacizumab) requires dose reductions for both drugs[74-76]. Similarly, FOLFOXIRI needs to be dose reduced in combination with EGFR antibodies[58,59].

## ADDITION OF UPFRONT LOCAL TREATMENT IN UNRESECTABLE MCRC PATIENTS

Integration of secondary resection after response to induction chemotherapy is a well-established treatment approach[8,77]. The randomized CLOCC trial furthermore showed that upfront local ablation by radiofrequency with or without liver surgery followed by chemotherapy in patients with unresectable liver metastases was beneficial in terms of PFS (16.8 mo *vs* 9.9 mo, $P = 0.025$) compared to chemotherapy alone[78]. Comparative data comparing upfront with post-induction local ablation are not available. However, post-induction ablation likely offers a more stratified approach adapting for the individual patient and tumour biology and might thus be preferred.

## CONCLUSION

Treatment of mCRC is complex and highly individualized taking into account disease and patient characteristics, molecular and biochemical markers and thus enabling a personalized management in terms of selecting the most appropriate measures and sequences of systemic and local treatment.

In regard of the current data unresectable patients with *RAS* wildtype should receive an EGFR antibody based chemotherapy, whereas patients with *RAS* mutation should receive two or three drug chemotherapy in combination with bevacizumab, if an intensive treatment approach is chosen. For patients with a non-intense or sequential approach fluoropyrimidine and bevacizumab seems to be an efficacious and low toxic treatment option.

Future research might help to further tailor anti EGFR treatment, excluding patients deriving no benefit from EGFR inhibition. Moreover, close meshed and timely information (*e.g.*, acquired by liquid biopsies) about the current molecular tumour situation and potentially developing resistance might be helpful to guide treatment during the course of disease.

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