

Treatment of Metastatic Colorectal Cancer: Standard of Care and Future Perspectives

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Summary

Palliative chemotherapy for metastatic colorectal cancer has undergone substantial changes in recent years. The implementation of modern biologicals in the treatment has substantially improved overall survival up to 30 months. With the increasing number of therapeutic options, the question of optimal treatment sequence arises, which is addressed in current studies like FIRE 4 or STRATEGIC-1. Furthermore, clinical and molecular biomarkers to predict efficacy and tolerability are urgently needed. Today, the detection of activating RAS mutations is the only validated biomarker which precludes patients from anti-EGFR treatment. The detection of BRAF mutation V600E is associated with a very poor prognosis corresponding to a survival of 9–12 months. Prospective trials evaluating an optimal approach to this subgroup are still missing. First results from strategies targeting the aberrant signal transduction are promising and require further validation. Despite the advances so far, life expectancy unfortunately continues to be limited in the majority of patients with metastatic colorectal cancer. New strategies are needed to improve the prognosis. To this end, the identification of Her2/neu as a potential target and first experiences with checkpoint inhibition in patients with mismatch repair-deficient tumors are promising and also require further validation.

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Introduction

Colorectal cancer is the third most frequent type of cancer in Germany with expected 61,000 newly diagnosed cases in 2016 [1]. The median age at diagnosis is about 70 years. Approximately 25% of the patients show synchronous metastases and 25% develop metastases during the course of the disease [2]. Metastatic colorectal cancer (mCRC) has a critical prognosis with a 5-year survival rate of less than 10% [3]. In Germany, mCRC leads to 26,000 deaths per year [1]. Treatment of mCRC has undergone substantial changes in the last 20 years. New therapeutics and combination regimens have led to marked improvements in both response rate (RR) and overall survival (OS). This article provides an overview of the current standard of care and future perspectives in the systemic treatment of mCRC.

Choice of First-Line Treatment

General Aspects

In general, the choice of first-line treatment should be influenced by the tolerability of the medication as well as the patient's comorbidities, biological age, and preferences. It is important to emphasize that decisions regarding the first-line treatment are crucial for the patient's outcome: first-line treatment has a significantly higher overall response rate (ORR) and longer progression-free survival (PFS) than consecutive treatment lines [4]. Furthermore, the fraction of patients receiving chemotherapy decreases with each treatment line [5]. Finally, the choice of first-line treatment defines the possible consecutive regimens.

Therapeutics and Regimens

Standard of care for the majority of patients is the combination of 5-fluorouracil (FU)/leucovorin (LV) with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) together with a monoclonal

Table 1. Summary of important clinical trials in the authors' view (according to [4])

Study	Phase	Treatment	n	ORR, %	PFS, months	HR	OS, months	HR
<i>First-line studies</i>								
Falcone et al. [8]	III	FOLFIRI	122	34	6.9		16.7	
		FOLFOXIRI	122	60	9.8	0.63	22.6	0.70
Tournigand et al. [7]	III	FOLFIRI	109	56	8.5		21.5	
		FOLFOX	111	54	8.1	–	20.6	–
CRYSTAL ^a [14]	III	FOLFIRI	350	39.7	8.4		20.0	
		FOLFIRI + cetuximab	316	57.3	9.9	0.696	23.5	0.796 ^c
OPUS ^a [15]	II	FOLFOX	97	34.0	7.2		18.5	
		FOLFOX + cetuximab	82	57.3	8.3	0.567	22.8	0.855 ^c
PRIME ^b [16]	III	FOLFOX	253	–	7.9		20.2	
		FOLFOX + panitumumab	259	–	10.1	0.72	25.28	0.77
NO16966 [10]	III	FOLFOX/XELOX	701	38.0	8.0		21.3	
		FOLFOX/XELOX + bevacizumab	699	38.0	9.4	0.83	19.9	0.89 ^c
Hurwitz et al. [17]	III	IFL + placebo	411	34.8	6.2		15.6	
		IFL + bevacizumab	402	44.8	10.6	0.62	20.3	0.66
FIRE-3 ^b [45, 46]	III	FOLFIRI + cetuximab	171	66	10.4		33.1	
		FOLFIRI + bevacizumab	171	60	10.2	0.97 ^c	25.6	0.697
CALGB-80405 ^{b*} [47]	III	chemotherapy + cetuximab	270	68.6	11.4		32.0	
		chemotherapy + bevacizumab	256	53.8	11.3	1.1 ^c	31.2	0.9 ^c
PEAK ^b [48]	II	FOLFOX + panitumumab	88	63	13.0		41.3	
		FOLFOX + bevacizumab	82	60	9.5	0.65	28.9	0.63 ^c
TRIBE [9]	III	FOLFIRI + bevacizumab	256	54	9.7		25.8	
		FOLFOXIRI + bevacizumab	252	65	12.3	0.77	29.8	0.80
AVEX [13]	III	capecitabine	140	10	5.1		16.8	
		capecitabine + bevacizumab	140	19	9.1	0.53	20.7	0.79 ^c
<i>Second and further line studies</i>								
E3200 [30]	III	FOLFOX	291	8.6	4.7		10.8	
		FOLFOX + bevacizumab	286	22.7	7.3	0.61	12.9	0.75
TML [31]	III	chemotherapy	411	4	4.1		9.8	
		chemotherapy + bevacizumab	409	5	5.7	0.68	11.2	0.81
VELOUR [32]	III	FOLFIRI	614	11.1	4.7		12.1	
		FOLFIRI + aflibercept	612	19.8	6.9	0.76	13.5	0.82
RAISE [33]	III	FOLFIRI + placebo	536	72	4.5		11.7	
		FOLFIRI + ramucirumab	536	67	5.7	0.793	13.3	0.844
CORRECT [35]	III	placebo + BSC	255	0.4	1.7		6.4	
		regorafenib + BSC	505	1.0	1.9	0.49	5.0	0.77
^a KRAS wild-type population. ^b RAS wild-type population. ^c Non-significant. *Only data from 526 patients available. Presented hazard ratios are all significant if not otherwise indicated. Primary study end points are presented in italics. BSC = Best supportive care; ORR = overall response rate; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.								

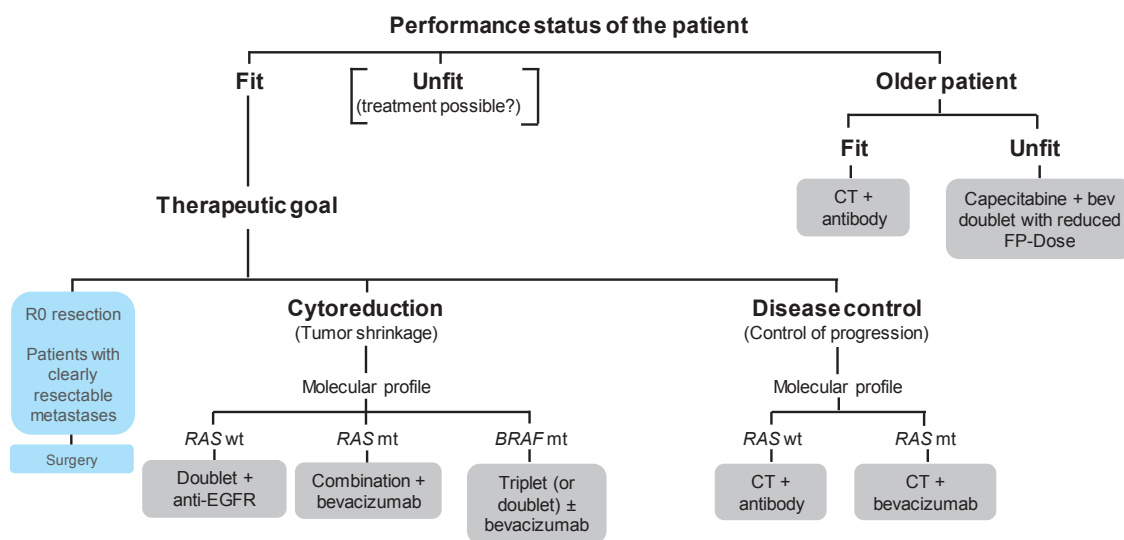
antibody (moAb) against either vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) [6]. Bevacizumab is a moAb against VEGF, whereas cetuximab and panitumumab are directed against EGFR. All three are approved for first-line treatment in mCRC.

FOLFOX and FOLFIRI show a comparable efficacy regarding OS [7]. For clinically fit patients, a higher ORR and a longer OS can be achieved with the triple combination of FOLFOXIRI alone [8] or in combination with bevacizumab [9]. Intravenous 5-FU can

be replaced by the oral fluoropyrimidine capecitabine either in combination with oxaliplatin (CapOx) [10] or irinotecan (CapIri) [11]. In general, capecitabine should not be combined with cetuximab due to negative results obtained in the COIN study [12]. Especially for elderly patients, the combination of capecitabine and bevacizumab is effective and well tolerated [13].

Cetuximab and panitumumab are both approved for first-line treatment with either FOLFIRI or FOLFOX [14–16]. The approval of bevacizumab in the first-line setting is based on a phase III trial

Fig. 1. Possible approach to choose first-line treatment for patients with mCRC (adapted according to the ESMO Pocket Guidelines 2015 Lower Gastrointestinal Cancer, Section metastatic colorectal cancer). FP = Fluoropyrimidin; CT = chemotherapy.



using an irinotecan-containing combination (IFL), which is no longer common due to toxicity [17, 18]. A study evaluating bevacizumab first-line in combination with oxaliplatin-based regimens could only demonstrate a benefit regarding PFS, while it was minor and non-significant concerning OS [10]. The optimal sequence of anti-EGFR and anti-VEGF strategy in patients without corresponding contraindications is still under debate and warrants further investigation. Key studies of this review are summarized in table 1.

Predictive and Prognostic Factors

So far, the only established predictive biomarker in the treatment of mCRC is the detection of activating mutations in KRAS (Kirsten RAS) or NRAS (neuroblastoma RAS) oncogene. These mutations occur in about 50% of mCRC and affect exons 2–4 in both genes [16]. Activated RAS can bypass the antiproliferative effects of anti-EGFR antibodies and patients with RAS mutation do not profit from such treatment [16, 19]. In combination with oxaliplatin, anti-EGFR treatment could even harm these patients [16]. Hence, testing the patient's tumor samples for RAS mutation is obligatory [6]. Cetuximab and panitumumab are contraindicated if a RAS mutation is detected. This also includes KRAS p.G13D mutation since more recent evidence indicates that also this subgroup does not benefit from the addition of cetuximab to chemotherapy [20, 21].

Besides testing for RAS mutation, the expected ESMO Clinical Practice Guidelines (initial presentation at the ECC conference 2015) will also advise to test for BRAF mutation V600E in patients with mCRC. This mutation can be found in 8–10% of patients and is associated with a poor prognosis [16, 22].

Treatment of Patients with RAS-Mutated Tumors

Patients with RAS-mutated tumor have fewer treatment options because anti-EGFR strategies are contraindicated. While optimal treatment of this subgroup is unclear, chemotherapy is mostly combined with bevacizumab in the first-line setting. Taking into account the results of the TML trial, the continuation of treatment with bevacizumab beyond first progression leads to a moderate but

statistically significant prolongation of OS irrespective of KRAS mutation status [23].

Treatment of Patients with RAS Wild-Type Tumors

For patients without RAS mutation all approved first-line options are available. Whether optimal first-line treatment should contain an anti-EGFR or an anti-VEGF agent has recently been the focus of a controversial debate. Altogether, three trials address this question: FIRE-3, CALGB-80405, and PEAK (for details see table 1). A meta-analysis taking the three trials into account shows superior ORR and OS with first-line anti-EGFR therapy compared with anti-VEGF therapy. According to these results, it seems reasonable to initiate treatment of RAS wild-type patients with an anti-EGFR strategy [4], especially if tumor shrinkage is the primary aim [24].

Treatment of Patients with BRAF Mutation

The prognosis of patients with BRAF mutation is very poor with a median OS of 9–14 months [9, 15, 22]. In this subgroup, the TRIBE study comparing bevacizumab plus either FOLFIRI or FOLFOXIRI revealed a profound benefit for the more intensive regimen and should be considered in these patients [9].

Treatment of Patients with Resectable Metastases

For patients with primarily resectable liver or lung metastases, upfront resection is an option, especially if metastases are limited in number and size [6]. In the EPOC study, perioperative chemotherapy with FOLFOX has increased PFS (primary end point) without significant impact on OS [25]. The approach to these patients should ideally be defined in a multidisciplinary team taking the individual patient's context into account [4]. After complete resection of colorectal metastases, some evidence suggests an additive 5-FU-based chemotherapy [26]. According to the results of the recent New EPOC study, patients with resectable liver metastases should not be treated with cetuximab plus chemotherapy [27].

Figure 1 indicates a possible approach to choose first-line treatment for patients with mCRC.

FIRE-4 (AIO KRK-0114)

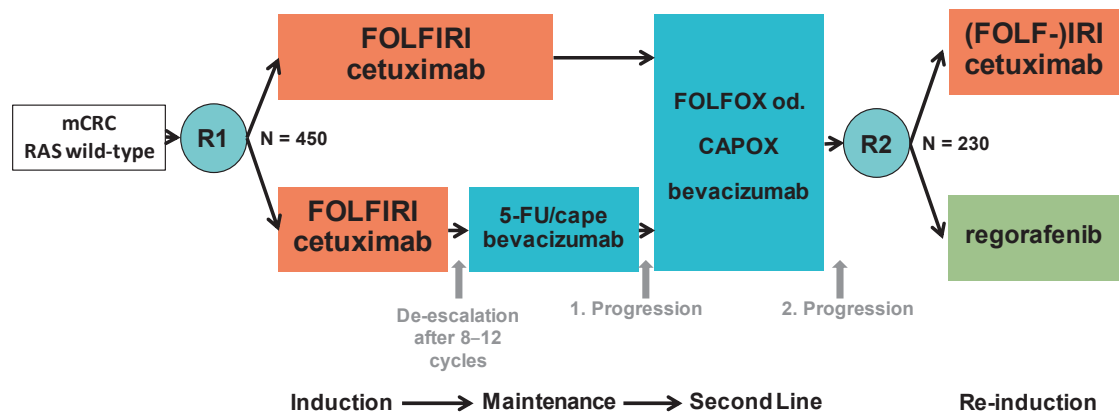


Fig. 2. Study design of the FIRE-4 (AIO KRK-0114) trial.

Strategy after Initial Treatment

Maintenance Therapy

Especially in the context of oxaliplatin-containing regimens, the duration is frequently limited due to cumulative neurotoxicity. Hence, several studies have examined a strategy with de-escalation after an initial treatment phase followed by a maintenance therapy with re-escalation in the case of progressive disease. For 5-FU/LV/oxaliplatin combinations with bevacizumab, two phase III trials have demonstrated that an active maintenance therapy (with fluoropyrimidine and bevacizumab) moderately prolongs PFS without significantly improving OS [28, 29]. In regard of the results of the CAIRO 3 trial, 4.5 months should be regarded as the optimum duration of induction therapy [29].

Later-Line Therapy

Second-line treatment depends on the combination of chemotherapy and biological in the first-line setting and should counteract an occurred resistance. This includes switching oxaliplatin-based to irinotecan-based treatment as well as anti-EGFR to anti-VEGF biological or vice versa. For example, FOLFOX plus bevacizumab yields a significant benefit regarding OS [30]. Of note, the continuation of bevacizumab after first progression has shown a significant benefit regarding OS [31]. Furthermore, the antiangiogenic fusion protein aflibercept in combination with FOLFIRI can prolong OS after progression upon an oxaliplatin-containing chemotherapy irrespective of previous bevacizumab usage [32]. With ramucirumab, an anti-VEGFR-2 antibody, the Food and Drug Administration has recently approved another beneficial second-line option in combination with FOLFIRI [33]. If not previously given, cetuximab and panitumumab are active as single agents in chemorefractory patients with comparable clinical activity [34]. After failure of the standard treatment options, the multi-

target tyrosine kinase inhibitor regorafenib has shown a significant prolongation of OS in the last-line setting [35]. Due to a decision of the pharmaceutical company Bayer AG, regorafenib is no longer available in Germany as of April 15, 2016.

In later treatment lines, a rechallenge with cetuximab can be discussed if patients had achieved a good objective response during first-line treatment with this moAb [36]. The current phase III trial FIRE-4 investigates this strategy prospectively. A maintenance strategy is also incorporated into the innovative study design (fig. 2). Another study which also addresses optimal treatment sequence is the STRATEGIC-1 trial [37].

Future Perspectives

Patients with BRAF Mutation

Patients with activating BRAF mutation have a dismal prognosis even if treated with intensive chemotherapy. Hence, new strategies are urgently needed. First results from targeting the aberrant signal transduction are promising, albeit the usage of a single BRAF inhibitor has no beneficial effect due to positive feedback activation of EGFR [38, 39]. To overcome this, a pilot study examined the feasibility and efficacy of BRAF inhibitor vemurafenib combined with panitumumab [40]. Toxicity was manageable with less cutaneous side effects than would be expected with either agent. Clinical activity was moderate with an ORR of 17%. This could be augmented by further combining BRAF inhibitor dabrafenib with panitumumab and MEK inhibitor trametinib in a phase I/II study leading to an ORR of 26% with a median PFS of 4.1 months in heavily pretreated patients [41]. With this combination, no grade IV toxicity was observed. These promising results need to be validated in further trials.

Checkpoint Inhibition

Inhibition of the immune checkpoint PD-1 revealed disappointing results in patients with mCRC [42]. In contrast, patients whose tumor showed a mismatch repair deficiency (MMD) derived a clinical benefit from PD-1 blockade with pembrolizumab in a phase II trial [43]. Median PFS and OS were not reached in patients suffering from mCRC with MMD but were 2.2 and 5.0 months, respectively, in the cohort comprising mCRC without MMD (hazard ratio 0.1 ($p < 0.001$) and 0.22 ($p = 0.05$), respectively). In this study, MMD status was associated with a high somatic mutation load, which could serve as predictive biomarker for checkpoint inhibition, irrespective of the underlying tumor entity.

Her2/neu

About 5% of mCRC show an overexpression of Her2/neu. A phase II trial evaluated the treatment with trastuzumab and lapatinib in this subgroup and found a considerable clinical efficacy in

heavily pretreated patients [44]. The primary end point was met with an ORR of 34.7%. Disease control rate was 78%. Treatment was well tolerated with no grade 4–5 toxicity. These results deserve further clinical assessment to validate Her2/neu as a predictive factor for the corresponding targeted therapy.

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