Cancer Chemother Pharmacol (2008) 61:1–13
DOI 10.1007/s00280-007-0573-x

REVIEW

Third-line therapy for metastatic colorectal cancer

M. G. Gundgaard · J. B. Soerensen · E. Ehrnrooth

Received: 10 May 2007 / Accepted: 24 July 2007 / Published online: 5 September 2007

Abstract
Background The past years' therapy for colorectal cancer has evolved rapidly with the introduction of novel cytotoxic agents such as irinotecan, capecitabine and oxaliplatin. Further advances have been achieved with the integration of targeted agents such as bevacizumab, cetuximab and recently, panitumumab. As a result, third-line treatment is now a necessary step in the optimal treatment of patients with metastatic colorectal cancer (MCRC).
Materials and methods We conducted a literature review of English language publications on third-line therapy for MCRC from January 2000 to April 2007. Data on median overall survival (mOS), median time to progression (mTTP) and response rate were recorded.
Results We found 27 articles and 22 abstracts to fulfil the criteria. Patients who received regimens containing oxaliplatin and infusional 5-fluorouracil (5-FU) demonstrated mTTP up to 7 months and a mOS of 16 months. With irinotecan and 5-FU, mOS around 8 months were reported and with cetuximab combined with irinotecan, the highest mOS was 9.8 months.
Conclusion Third-line therapy in advanced colorectal cancer may improve mOS for patients with MCRC. Therefore, randomized studies should be conducted in the future.

Keywords Advanced · Colorectal cancer · Review · Third-line therapy

M. G. Gundgaard (✉) · J. B. Soerensen · E. Ehrnrooth
Department of Oncology, Rigshospitalet,
Blegdamsvej 9, 2100 Copenhagen, Denmark
e-mail: ggundgaard@hotmail.com

E. Ehrnrooth
Science and Development Projects,
NOVO Nordisk, Bagsvaerd, Denmark

Introduction

Every year one million patients worldwide are diagnosed with colorectal cancer and approximately 50% of them will relapse after curative intended surgery [1]. During the last four decades the first drug of choice for patients with metastatic colorectal cancer (MCRC) was the fluoropyrimidine 5-fluorouracil (5-FU) [2].

Major advances have occurred during the last years in the treatment of MCRC with the introduction of new treatment modalities. Thus, two randomized trials have established the role of irinotecan as second-line agent in patients who have failed on 5-FU based treatment [3, 4].

Oxaliplatin is a third-generation platinum, which has shown activity in patients with MCRC refractory to 5-FU and leucovorin (LV) [5]. The role of oxaliplatin combined with 5-FU (FOLFOX) as second-line treatment in MCRC was demonstrated in a randomized trial comparing FOLFOX4, oxaliplatin monotherapy and 5-FU plus LV. Treatment with FOLFOX4 showed superior response rate (RR) and time to progression [6].

Further progress in the treatment of MCRC has been made by years of translational research. Recently bevacizumab (avastin), a monoclonal antibody (mAb) against the vascular endothelial growth factor (VEGF) and cetuximab (erbitux), a mAb that targets the endothelial growth factor receptor (EGFR), have shown promising activity in patients with MCRC.

In a phase III study by Hurwitz et al., median survival was significantly increased from 15.6 months to 20.3 months with the addition of bevacizumab to irinotecan, 5-FU and LV for patients with previously untreated MCRC [7].

A randomized phase II study compared cetuximab with cetuximab plus irinotecan in the treatment of irinotecan refractory MCRC and showed improvements in RR in

favor of the combination, with RRs of 23% in the combination group compared to 11% in the group treated with cetuximab alone. Patients had been treated with one or more than three previous chemotherapy lines [8]. Cetuximab was approved by the FDA in 2004 and is indicated for patients with EGFR positive tumours who have failed irinotecan-based chemotherapy or as a single agent for patients who are intolerant to irinotecan-based treatment [9].

While there are a number of well-documented treatment options for first- and second-line treatments of MCRC, there are less data on the beneficial effect of systemic treatment used in third-line therapy. Therefore we reviewed the current literature on third-line treatment of MCRC.

Materials and methods

We conducted a literature review for English language publications on third-line therapy for MCRC from January 2000 to April 2007 using the search terms: colorectal cancer, advanced, metastatic, third line. The database Medline and abstracts from major meetings including the following were searched: American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), Annals of Oncology, Cancer Chemotherapy and Pharmacology and European Cancer Conference (ECCO).

For each trial the number of patients included and the numbers of previous treatments were recorded. The administered drugs were specified in the order of first-, second- or third-line treatment if this was specified, in order to examine any possible correlation between previous treatment and response to third-line therapy. Trials involving fewer than ten patients were considered too small and were not included. Furthermore, trials where the activity of third-line therapy was not clearly specified were excluded. Any kind of chemotherapy or targeted therapy was allowed as previous therapy. The clinical trials could be phase II or III. Retrospective trials were also considered.

Data on median overall survival (mOS), median time to progression (mTTP) and RR, that is complete and partial response, were recorded from each trial. Where progression-free survival (PFS) was reported, the result was referred to as the mTTP.

Any toxic death was presented in this review. Quality of life and adverse events were not clearly reported in all trials and the data are therefore not presented.

Results

A total of 27 published articles and 22 abstracts were identified to fulfil the search criteria. Two studies were randomized phase III trials [10, 11]. This section reports on the mTTP and mOS for selected trials whereas data on RR and confidence interval (CI) are reported in Tables 2, 3, 4, and 5. Table 1 shows RR and mTTP for the most common

Table 1 Most common chemotherapy regimens used in the first-line treatment of MCRC and the efficacy of each regimen

Regimen	Administration	Treatment with 5-FU (days)	Doses 5-FU (mg/m^2)	RR (%)	mTTP (months)
5-FU/LV					
De Gramont [64]	CI + B	d 1 + 2	400 B 600 CI	22.3	6.2
Mayo [73]	B	d 1–5	425 B	22.6	5.3
Modified de Gramont [74]	CI + B	d 1	400 B 2,800 CI	36	9.3
5-FU/irinotecan					
IFL (Saltz) [75]	B	W × 4	500 B	39	7
FOLFIRI [60]	CI + B	d 1	400 B 2,400–3,000 CI	56	8.5
OXALIPLATIN/5-FU					
FOLFOX 2 [76]	CI	d 1 + 2	1,500–2,000 CI	45.3	8.3
FOLFOX 3 [77][a]	CI	d 1 + 2	1,500 CI	20	6
FOLFOX4 [64]	CI + B	d 1 + 2	400 B 600 CI	50.7	9
FOLFOX6 [60]	CI + B	d 1	400 B 2,400–3,000 CI	54	8
FOLFOX7 [78][b]	CI	d 1	2,400 CI	59.2	8.7
FUFOX [73]	CI	W × 4	2,000 CI	48.3	7.9
XELOX [79]	PO	d1–d15	1,000 PO × 2	55	7.7

CI continuous infusion, *B* bolus, *d* day, *W* weekly, *PO* per oral, *LV* leucovorin, *FUFOX* oxaliplatin, folinic acid and 5-FU, *XELOX* xeloda (capecitabine) and oxaliplatin, *RR* response rate, *mTTP* median time to progression

[a] Second-line therapy

[b] Reinduction of FOLFOX7

chemotherapy regimens used in first-line treatment of MCRC. mOS and mTTP for each trial are illustrated in graphs as well.

5-FU + oxaliplatin based regimens

Table 2 summarizes the data in 13 studies from 644 patients, who received infusional 5-FU and oxaliplatin as third-line treatment.

There were nine clinical phase II studies and one phase III study. The number of patients per study varied from 11 to 126. mTTP ranged from 4.4 to 8 months and mOS from 5.9+ to 16 months [12–20].

One phase III study investigated the sequence of therapy by randomizing patients between treatment with FOLFOX4 and irinotecan after previous second-line therapy with the opposite [10]. The primary goal of the trial was to investigate efficacy of FOLFOX4 and irinotecan as second-line therapy after first-line exposure to 5-FU. Patients were allocated to third-line therapy with the opposite agent when failure of second-line treatment in a non-random fashion. The mTTP was 5 months, when FOLFOX4 was administered after irinotecan and 2.7 months, when irinotecan was administered after FOLFOX4. For the FOLFOX-treated group, the mOS was 10 months compared to 8.7 months for the irinotecan-treated group. The difference was not reported to be statistically significant. There was more gastrointestinal toxicity in the irinotecan-treated group and more neutropenia and paresthesia in the FOLFOX4 treated patients.

One randomized phase II study compared the de Gramont regimen with FOLFOX4 after therapy with fluoropyrimidine/capecitabine and irinotecan in different combinations. The majority of patients had previously received sequential fluoropyrimidine and irinotecan, and the study showed a significantly greater mTTP (4.8 months vs. 2.4 months) in favor of the FOLFOX4 regimen [12]. However, the FOLFOX4 exposed patients did not demonstrate any improvement in mOS (9.9 months vs. 11.4 months). Sixty-nine percent of patients from the de Gramont arm crossed over to FOLFOX4 due to treatment failure, besides mOS was not a primary end point.

Trials investigating different FOLFOX regimens were found including FOLFOX2, 3 and 4. One study compared FOLFOX2 with FOLFOX4 [18] and showed higher mTTP, 7 months vs. 5 months, and higher mOS, 9 months vs. 7+ months, in favor of FOLFOX2 regimen.

The study reporting the highest mOS of 16 months and the highest mTTP of 8 months included 78 patients. In this study, patients had chronomodulated oxaliplatin and 5-FU plus LV. Previous therapy was not reported but the patients were pre-treated with 2–7 lines [20].

One trial reported one toxic death because of neutropenia and sepsis [15]. The study by Kemeny et al. [12] reported three toxic deaths in the FOLFOX4 arm. Two patients had small bowel obstruction and a third patient had respiratory failure.

5-FU + irinotecan based regimens

Four phase II trials with a total of 119 patients included used irinotecan as third-line treatment (Table 3). The number of patients varied from 13 to 61. mTTP ranged from 2.3 to 5.7 months and mOS from 7 months to 8.7 months [24–27]. mOS were not reported in two trials. In one trial, previous irinotecan had been given [24] and all studies reported previous treatment with oxaliplatin. Irinotecan was administered with infusional 5-FU (FOLFIRI) in 106 patients [24–26] and in one study irinotecan was delivered weekly with high-dose 5-FU plus LV [27]. No toxic deaths were reported in any of these trials.

Regimens with miscellaneous agents

In 479 patients the treatment with third-line therapy consisted of agents or regimens not previously mentioned in this review (Table 4). Sixteen studies were phase II studies and included from 15 to 77 patients. The mTTP for the different regimens ranged from 2.3 months to 5.6 months and mOS from 5 to 14.2 months [28–43].

Oxaliplatin was re-induced in one retrospective trial and delivered as hepatic arterial infusion (HAI) preceded by treatment with 5-FU, oxaliplatin and irinotecan in two or three palliative lines. mTTP was found to be 4 months and the mOS was reported to be 13 months [44].

In one trial, the oral agent S-1, a combination of tegafur, gimeracil and oteracil potassium, was investigated. The mTTP was found to be 3 months and mOS 13.8 months [33].

Irinotecan was given to 77 patients as chronomodulated therapy together with oxaliplatin and 5-FU. mTTP was reported to be 5.5 months and mOS was 14.2 months, the highest observed among these trials [41]. Two patients were alive without any detectable disease after a median follow-up of 38 months. These patients had subsequently been surgically treated and had postoperative received further chronotherapy.

Two trials reported one toxic death each because of neutropenic sepsis [42, 43]. In the study by Gubanski et al. [29], one patient died, probably due to one episode of febrile neutropenia.

Regimens with targeted therapies including antibodies and growth factors

Table 5 summarizes the studies performed with patients receiving targeted therapy as third line. In total 1,033

Table 2 Third-line infusional 5-FU + oxaliplatin in MCRC

Reference	*n*	Previous treatment (line)	Treatment regimen	RR *n* (%)	Median (months)	
					TTP	OS
Rowland et al. [10], phase III	126	5-FU, *n* = 126: irinotecan (a) vs. *n* = 94: FOLFOX4 (b)	FOLFOX4 (a), irinotecan (b)	(a): 20 (16), (b): 4 (4)	(a): 5, (b): 2.7	(a) 10, (b) 8.7
Kemeny et al. [12], phase II	110	5-FU ± LV, irinotecan, capecitabine	FOLFOX4 (*n* = 110) OR De Gramont (*n* = 104)	FOLFOX4: 14 (13), 95%CI (7.1–20.5), De Gramont: 2 (2), 95%CI (0.2–6.8)	FOLFOX4: 4.8, 95%CI (4–5.5), De Gramont: 2.4, 95%CI (1.5–2.9)	FOLFOX4: 9.9, 95%CI (8.3–11.5), De Gramont: 11.4, 95%CI (9.8–13.3)
Salek [13], phase II	11	5-FU/LV, irinotecan	Oxaliplatin, bolus 5-FU/LV	No response	NR	6+, range 1.9–12.4
Chau et al. [14], phase II	22	5-FU, irinotecan	Oxaliplatin, PVI 5-FU	6 (27.3)	NR	6
Abon et al. [15], phase II	23	Bolus 5-FU/LV (1), irinotecan (2)	5-FU/LV, oxaliplatin	2 (8.7)	NR	8, range 0.23–15.6+
Luppi et al. [16], phase II	28	5-FU, irinotecan 46%	FOLFOX2	9 (32)	6, range 2–11	7.5, range 1.9–17
Martoni et al. [17], phase II	16	5-FU	Oxaliplatin, PVI 5-FU	1 (6.3)	NR	NR
Mosconi et al. [18], phase II	23	5-FU	FOLFOX2 (*n* = 6), FOLFOX4 (*n* = 17)	FOLFOX2: 1 (16.7), FOLFOX4: 4 (23.5)	FOLFOX2: 7, FOLFOX4: 5	FOLFOX2: 9, FOLFOX4: 7+
Kallen et al. [19], phase II	11	Bolus 5-FU/FA (1), Inf. 5-FU/FA (2)	5-FU/FA, oxaliplatin	NR	6, range 0–6.5	11, range 7–20
Giacchetti et al. [20], phase II	78	NR	5-FU/LV, oxaliplatin, chronomod	28 (36)	8, range 6–10	16, range 12–19
Croles et al. [21], retrospective review	25	5-FU, irinotecan	FOLFOX3	4 (14), 95%CI (4–33)	5.8, 95%CI (4.8–6.7)	8.5, 95%CI (6.4–10.5)
Moehler et al. [22], retrospective review	13	5-FU/FA (1), irinotecan (2)	FUFOX	2 (15)	4.4, range 0.7–9.1	10, range 1.2–15.2
Bensmaine et al. [23], statistical analysis	158	5-FU	Oxaliplatin, 5-FU/FA	26 (16.5)	4.6	9.1
Total *n*	644					

n number of patients, *OS* overall survival, *NR* not reported, *FA* folinic acid, *RR* response rate (complete and partial response), *TTP* time to progression, *PVI* protracted venous infusion

Table 3 Third-line 5-FU + irinotecan in MCRC

Reference	*n*	Previous treatment (line)	Treatment regimen	RR *n* (%)	Median (months)	
					TTP	OS
Gervais et al. [24], phase II	16	Irinotecan + 5-FU/ZD9331, FOLFOX	Folfiri3	3 (19)	4.1	NR
Kim et al. [25], phase II	29	Oxaliplatin (2)	Folfiri	6 (20.7)	5.7, 95%CI (3.8–7.6)	8.7, 95%CI (7.8–9.5)
Maindrault et al. [26], phase II	61	De Gramont (1), FOLFOX (2)	Folfiri	3 (5)	2.3	NR
Stickel et al. [27], phase II	13	AIO (1), AIO + oxaliplatin (2)	AIO + irinotecan	2 (15) 95%CI (2–45)	3.9, range 3–6	7, range 2–18
Total *n*	119					

RR = response rate (complete and partial response), *TTP* time to progression, *OS* overall survival, *NR* not reported, *AIO* folinic acid (500 mg/m^2) as a 1 to 2-h infusion day 1; followed by 5-FU (2.000 mg/m^2) intravenous (IV) administered as a 24-h infusion once weekly, *ZD9331* antifolate inhibitor of thymidylate synthase

patients were treated. One phase III and 13 phase II trials were found. According to the phase II trials, the number of patients included ranged from 10 to 346 [45–56]. mTTP varied from 1.4 months to 4.7 months and mOS from 5.5–9.8 months, though only reported in half of the studies.

Panitumumab, a mAb targeting the EGFR, benefited patients with MCRC in a multicentre phase III trial. A total of 463 patients were randomized between best supportive care (BSC) ($n = 232$) alone or BSC and panitumumab ($n = 231$) [11]. One patient included did not receive the treatment as third- or fourth-line therapy. The primary end point was PFS. The mTTP for the panitumumab treated group (1.9 months) was significantly prolonged compared to mTTP in the BSC group (1.7 months). No differences were found in mOS. Seventy-six percent of the patients in the BSC group crossed over to panitumumab after treatment failure. There was a good safety profile. In two smaller trials, mTTP were shown to be 2 and 3 months, respectively, for treatment with panitumumab single-agent. mOS were not reported [55, 56].

In three trials cetuximab monotherapy was used as the targeted agent after treatment with oxaliplatin, irinotecan and for some patients 5-FU. The mTTP was demonstrated to be between 1.4 and 2.4 months and mOS between 6.6 and 7 months [45–47].

Treatment with cetuximab was well tolerated with minimal toxicity. In the study by Chen et al. [51] bevacizumab toxicity was similar to that seen in other trials with hypertension and bowel perforation among others. Two deaths reported were of unknown aetiology. Data on adverse events was reported for 338 patients enrolled and not specified for the current 100 patients assessable. Besides, no toxic deaths were reported in any of the trials.

Discussion

Randomized studies reporting efficacy after failing second-line treatment for MCRC have been limited, and at this time there is no standard third-line therapy for MCRC according to NCI [59].

The integration of oxaliplatin and irinotecan at the end of the 1990s definitely improved mOS for patients in the first-line treatment of MCRC [60]. Unfortunately the prognosis for these patients is still dismal with 5-year survival less than 10% [61]. In view of these figures, and increased survival after first- and second-line treatment, there is a need for treatment options for fit patients in third line.

Current evidence supports the combination of fluoropyrimidine with either irinotecan or oxaliplatin as first-line therapy [62] and treatment with the other combination as second-line therapy [63]. Today, the vast majority of patients have already received these three drugs, when they become candidates for third-line therapy.

In this review, all clinical studies were conducted as phase II trials except for two phase III trials [10, 11]. Though small, the phase II studies may be directing for a rational design of a confirmatory phase III trial. Level of evidence for the phase III trial by Van Cutsem [11] was 1b. For the trial by Rowland et al. [10], level of evidence was 1c. According to the phase II trials, level of evidence was 2a or 2b.

When considering the clinical trials using combinations of 5-FU + oxaliplatin in third line, the results were in general encouraging. In the intergroup N9841 phase III trial by Rowland et al. [10] the sequence of FOLFOX4 and irinotecan in 5-FU refractory patients was investigated in a cross-over trial of second and third-line therapy. In third line, FOLFOX4 was associated with an improved mTTP

Table 4 Miscellaneous agents in third-line treatment of MCRC

Reference	*n*	Previous treatment (line)	Treatment	RR *n* (%)	Median (months)	
					TTP	OS
Ardavanis et al. [28], phase II	28	5-FU/LV, oxaliplatin, irinotecan	Capecitabine	2 (7)	4, range 2–7	6
Gubanski et al. [29], phase II	20	Irinotecan + 5-FU/LV, FOLFOX4	Capecitabine	No response	2.8	6.1
Lim et al. [30], phase II	19	5-FU/FA + irinotecan, 5-FU/FA + oxaliplatin	Capecitabine, MMC	1 (4.8)	2.6, 95%CI (2.5–2.7)	6.8, 95%CI (0.9–12.7)
Harba et al. [31], phase II	20	Oxaliplatin, irinotecan, 5-FU/LV	Capecitabine, MMC	2 (10)	3.7, range 0.5–10	7.75, range 1.5–22
Chong et al. [32], phase II	33	5-FU, irinotecan	Capecitabine, MMC	5 (15.2), 95%CI (6.8–40.7)	5.4, 95%CI (4.6–6.2)	9.3, 95%CI (6.9–11.7)
Jeung et al. [33], phase II	26	Oxaliplatin, irinotecan	S-1	4 (14.3), 95%CI (0.4–28.1)	3	13.8
Tsavaris et al. [34], phase II	20	5-FU/LV (1), irinotecan (2), 5-FU (3)	Tomudex	No response	4.8, range 2.2–7	7.4, range 6–7.8
Garcia et al. [35], phase II	23	5-FU, oxaliplatin, irinotecan	Irinotecan, Tomudex	No response	3	NR
Rosati et al. [36], phase II	16	5-FU, oxaliplatin, irinotecan	Tomudex, MMC	No response	2.3, 95%CI (1.7–3)	5, 95%CI (2.5–7.5)
Lonardi et al. [37], phase II	19	5-FU, irinotecan, oxaliplatin	Gemcitabine	Disease control: 50% for $\geq$3 line, $P = 0.78$	NR	NR
Pachon et al. [38], phase I/II	18	Oxaliplatin, irinotecan	Gemcitabine, 5-FU	No response	3.7, range 1.5–13.2	9.9, range 1.9–19
Hartmann et al. [39], phase II	45	Bolus 5-FU/FA (1), Cont. inf. 5-FU/FA (2)	Irinotecan	6 (13.3), 95%CI (5.1–26.8)	5.6, 95%CI (4.2–6.3)	7.9, 95%CI (6.1–11.1)
Benavides et al. [40], phase II	15	5-FU	Irinotecan	2 (13.3)	5.3	7.7
Gholam et al. [41], phase II	77	FLO, IFL	Chronomodulated irinotecan, oxaliplatin, 5-FU/LV	2 (3)	5.5, 95%CI (3.7–6)	14.2, 95%CI (9.8–17.3)
Polus et al. [42], phase II	46	Folfiri (1), FOLFOX (2) OR FOLFOX (1), Folfiri (2)	Irinotecan, MMC	3 (6.5)	NR	Not reached
Schulz et al. [43], phase II	44	5-FU (1), irinotecan (2)	ZD9331	2 (4.5)	2.8, 95%CI (1.9–3.3)	NR
Gollasch et al. [44], retrospective review	10	5-FU, irinotecan, oxaliplatin	HAI oxaliplatin, 5-FU/capecitabine	3 (30)	4, range 1–8	13, range 2–15+
Total *n*	479					

RR response rate (complete and partial response), *TTP* time to progression, *OS* overall survival, *NR* not reported, *FA* folinic acid, *MMC* mitomycin C, *S-1* tegafur/gimeracil/oteracil potassium, *ZD9331* antifolate inhibitor of thymidylate synthase, *HAI* hepatic arterial infusion

Table 5 Monoclonal antibodies alone or in combination with chemotherapy in MCRC

Reference	*n*	Previous treatment (line)	Treatment regimen	RR *n* (%)	Median (months)	
					TTP	OS
Mirtsching et al. [45], phase II	28	5-FU, irinotecan, oxaliplatin	Cetuximab	3 (11)	2.4, range 0.2–6.2	NR
Lenz et al. [46], phase II	346	5-FU, oxaliplatin, irinotecan	Cetuximab	43 (12.4), 95%CI (9.1–16.4)	1.4, 95%CI (1.4–2.1)	6.6, 95%CI (5.6–7.6)
Mirtsching et al. [47], phase II	38	Oxaliplatin, irinotecan	Cetuximab	3 (8)	1.6, 95%CI (1–2.2)	7, 95%CI (5.8–8.2)
Vincenzi et al. [48], phase II	55	Oxaliplatin (1), irinotecan (2)	Cetuximab, irinotecan	14 (25), 95%CI (21.7–39.6)	4.7, 95%CI (2.5–7.1)	9.8, 95%CI (3.9–10.1)
Gebbia et al. [57], retrospective review	60	Oxaliplatin (1), irinotecan (2)	Cetuximab, irinotecan	12 (20), 95%CI (11–32)	3.1, range 1.2–9	6, range 2–13
Grande et al. [49], phase II	23	5-FU/capecitabine, oxaliplatin, irinotecan	Cetuximab, irinotecan	3 (13), 95%CI (3–34)	3.5, range 1–10+	7.3, range 1.5–12+
Grothe et al. ONGOING [50], phase II	15	5-FU, oxaliplatin, irinotecan, MMC (4 pts), Gefitinib (4 pts)	Cetuximab, oxaliplatin, capecitabine	4 (27)	2.5, range 0.25+–9.6	5.5+, range 0.6–10.9+
Levi et al. [58], retrospective review	33	5-FU, irinotecan, oxaliplatin	Cetuximab/cetuximab, irinotecan, 5-FU/LV ± oxaliplatin/cetuximab, oxaliplatin, 5-FU/LV	11 (33)	NR	NR
Chen et al. [51], phase II	100	Irinotecan, oxaliplatin	Bevacizumab, 5-FU/LV	4 (4), 95%CI (1.1–9.9)	3.5, 95%CI (2.1–4.7)	9, 95%CI (7.2–10.2)
Emmanouilides et al. ONGOING [52], phase II	19	Irinotecan, oxaliplatin	Bevacizumab, 5-FU/LV	No response	3.7	5.5+
Peinert et al. ONGOING [53], phase II	13	Cetuximab	Bevacizumab, capecitabine, MMC	1 (7.7)	NR	NR
Dorligschaw et al. [54], phase II	10	5-FU/LV/capecitabine, oxaliplatin, irinotecan	Gefitinib alone or combined with irinotecan, oxaliplatin, capecitabine, MMC	No response	NR	NR
Van Cutsem et al. [11], phase III	231	5-FU, irinotecan, oxaliplatin	Panitumumab, BSC (a), BSC (b)	(a) 23 (10), (b) No response	(a) 1.9, 95%CI (1.8–2); (b) 1.7, 95%CI (1.7–1.8)	NR
Hecht et al. [55], phase II	23	5-FU, irinotecan, oxaliplatin	Panitumumab	3 (13)	2, 95%CI (1.6–5.4)	NR
Berlin et al. [56], phase II	39	5-FU, irinotecan, oxaliplatin	Panitumumab	3 (8)	3	NR
Total *n*	1,098					

RR response rate (complete and partial), *TTP* time to progression, *OS* overall survival, *NR* not reported, *MMC* mitomycin C, *BSC* best supportive care

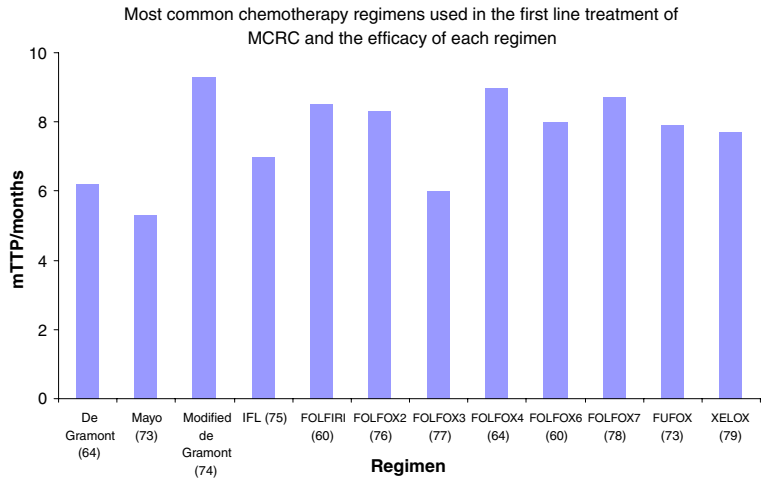
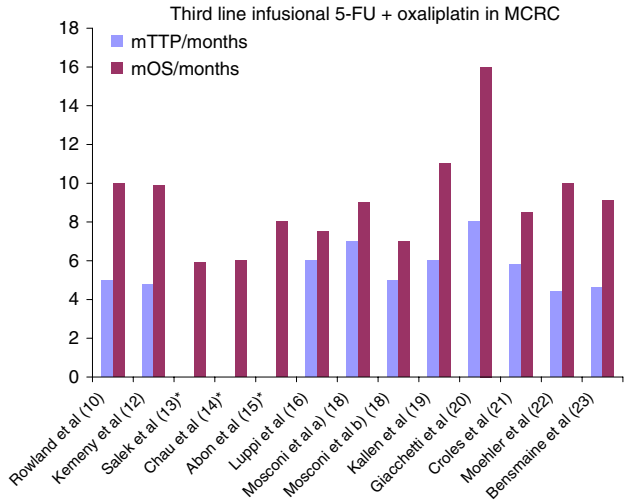
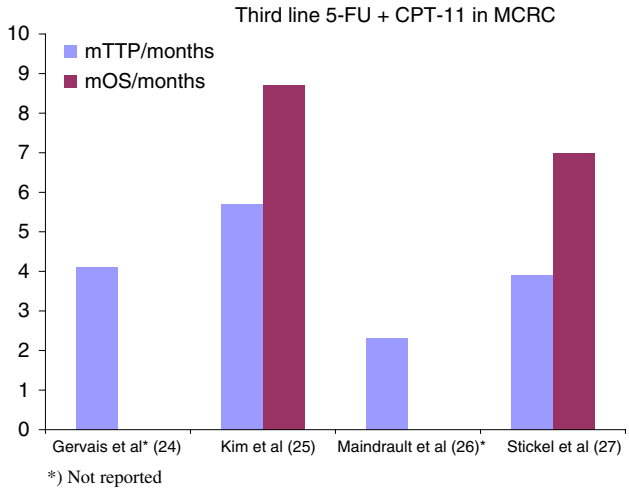


Fig. 1 Most common chemotherapy regimens used in the first-line treatment of MCRC and the efficacy of each regimen



*) Not reported

Fig. 2 Third-line infusional 5-FU + oxaliplatin in MCRC



*) Not reported

Fig. 3 Third-line 5-FU + irinotecan in MCRC

and mOS. The study showed activity for both agents after failure of 5-FU and the complementary regimen. The question of the optimal use of oxaliplatin and irinotecan based regimens after first-and second-line therapy is not solved and needs further investigation.

Studies that define the optimal FOLFOX regimen with or without targeted agents in third line are still lacking. Oxaliplatin has demonstrated synergism with 5-FU with significantly higher anti-tumour activity than for 5-FU alone in first line [64]. One trial confirmed higher efficacy of a FOLFOX regimen compared to de Gramont also in third line [11], but the study did not give information on a possible advantage of re-induction of FOLFOX. However, the results supported the strategy of offering all five active drugs in advanced colorectal cancer [63].

When looking at trials with irinotecan and infusional 5-FU in third line, the results were satisfactory, however the trials were not randomized and with a limited number of patients. None of the studies used bolus 5-FU in combination with irinotecan (IFL). Reports on severe toxicities especially diarrhoea for the use of IFL came from an independent panel of CRC experts in 2001 [65].

In the trials using miscellaneous drugs, the third-line treatment modality differed widely as regards both the drugs and the schedules. When capecitabine was combined with MMC, the mTTP and mOS differed widely between the studies. Due to the small number of patients and different pre-treatment modalities, the possible antitumour activity with this combination cannot be established.

Tomudex (raltitrexed) was used alone or in combination with irinotecan or MMC [34–36]. There was no response for the combinations or for the single agent. Despite a possible role in first line demonstrated in one large phase III trial [66], the palliative effect of tomudex as a third-line agent in MCRC has not been confirmed.

5-fluorouracil was administered in first- or second-line setting in almost every trial (Tables 2, 3, 4), and previous data suggest a benefit from re-induction of 5-FU [67]. The

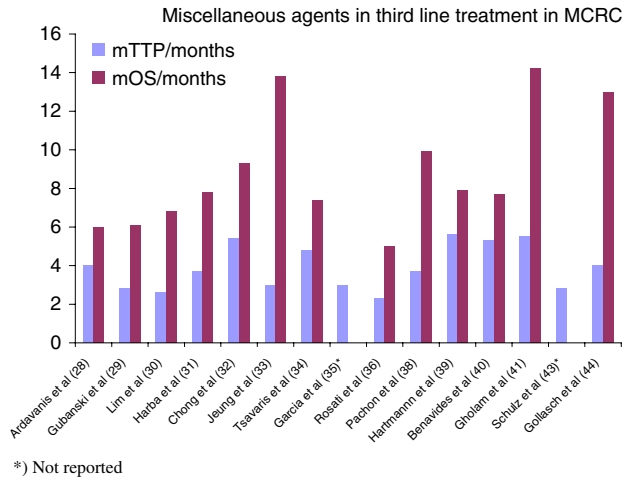


Fig. 4 Miscellaneous agents in third-line treatment in MCRC

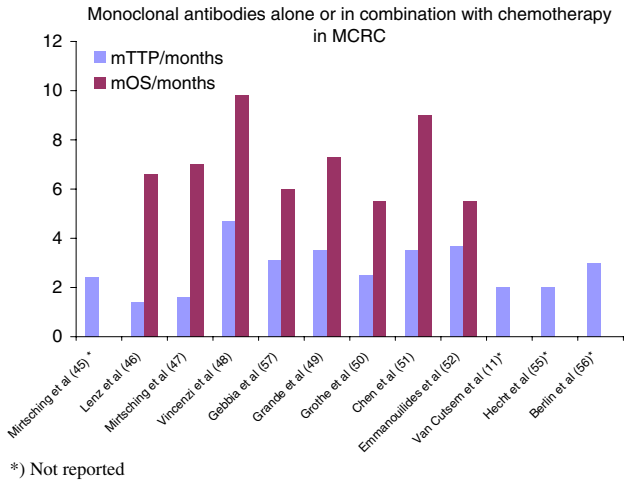


Fig. 5 Monoclonal antibodies alone or in combination with chemotherapy in MCRC

number of patients was, however, too small in order to establish a possible benefit of re-induction of 5-FU.

Targeted therapies are now in focus in combination with chemotherapy however, clinical trials on third line targeted therapy are still few. The efficacy of cetuximab in combination with irinotecan in patients with irinotecan-refractory MCRC was established by Cunningham et al. [8]. The combination demonstrated an advantage over single-agent cetuximab in regard to mOS and mTTP in both second- and third-line therapy. The efficacy of cetuximab plus irinotecan was clearly shown in three studies [48, 49, 57]. In a recent press release from Merck the results from the NCIC-CO.17 trial of cetuximab vs. BSC in third-line patients were reported. The trial met its primary efficacy end point showing a statistically significant improvement in OS. This is the first data of an EGFR targeted mAb to demonstrate such efficacy (data presented at ASCO 2007) [68].

When added to FOLFOX, bevacizumab has shown improvements in mOS compared to FOLFOX alone for patients previously treated with irinotecan-based chemotherapy [69].

Recent data from a phase II trial (BONDII) has shown a benefit of combining bevacizumab and cetuximab in previously treated MCRC [70] and any additive efficacy from this combination needs to be confirmed in phase III trials.

In two studies by Chen et al. and by Emmanouilides et al., the RRs were surprisingly low for bevacizumab in combination with 5-FU and LV [51, 52]. The studies are ongoing and final results are still pending. Whether there is a benefit in continuing therapy with bevacizumab for patients progressing on a bevacizumab-containing regimen still needs to be investigated. Thus, the role of bevacizumab in third line is still unclear.

Significant improvement of mTTP was shown for treatment with panitumumab in a phase III study in patients with chemo refractory colorectal cancer [11]. In a large phase II study the efficacy of panitumumab for patients failing standard chemotherapy was shown in year 2004 [71]. The patients had failed previously therapy with fluoropyrimidine and irinotecan or oxaliplatin or both. In September 2006 panitumumab granted approval from FDA for patients with EGFR expressing metastatic CRC who progressed on or following regimens containing fluoropyrimidine, irinotecan and oxaliplatin [9].

The best combination and sequence of chemotherapeutic agents and mAb's is an unanswered question. Selecting the right patients for therapy with the VEGF-inhibiting bevazicumab and the EGFR-inhibiting cetuximab and panitumumab is an issue. Evaluating the molecular and biochemical markers for tumour response is a must to optimize the possibility for the right treatment choice.

In general, searching for literature resulted in the finding of clinical trials, which were small (10–346 patients). We found wide variations in the results of third-line treatment both with respect to the RR, the mTTP and the mOS. The differences can be related to the selection of patients, stochastic variations due to low number of patients and the actual or previous treatment regimen. Information on all efficacy parameters needed to draw conclusions on the activity are missing in many trials. Whether third-line treatment for patients with MCRC can improve the mOS still needs to be confirmed in randomized trials.

Conclusions

Big challenges in designing the third-line trials exist. With the great abundance of treatment modalities available, the therapeutic goals are more likely to be achieved by exposing the patients to every possible treatment in a continuum

of care instead of practising successive lines of therapy with treatment till disease progression within the same line. This must be regarded as a paradigm shift in the treatment strategy of MCRC. The patients are treated individually in regard to minimize toxicity and improve quality of life and mOS. The treatment strategy has changed from the "line treatment" to different concepts, i.e. the use of shifting therapy prior to progression, intermittent therapy, maintenance of therapy and use of stop/go fashion with reintroducing a drug after a planned interruption. The individualized planning yet delays the performing of randomized clinical trials and the ultimate treatment sequence and combination of chemotherapy with targeted therapy still remains unknown. Especially the outcome of mOS for the different modalities is difficult to conclude [72].

All fit patients should be exposed to the five to six active agents at some time point during their disease progression. The exposure of patients to five to seven different drugs must be balanced with minimizing toxicities and quality of life. Patients who have already received these agents may benefit from reintroduction of some of the drugs or new strategies like sequential use/stop and go or being enrolled into phase I and II trials of novel agents. Fig. 1, 2, 3, 4, 5

References

1. Cunningham D, Findlay M (1993) The chemotherapy of colon cancer can no longer be ignored. Eur J Cancer 29A(15):2077–2079
2. de Gramont A, Bosset J-F, Milan C, Rougier P, Bouché O, Etienne P-L, Marvan F, Louvet C, Guillot T, François E, Bedenne L (1997) Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 15(2):808–815
3. Cunningham D, Pyrhönen S, James RD, Punt CJA, Hickish TF, Heikkila R, Johannesen TB, Starkhammer H, Topham CA, Awad L, Jacques C, Herait P (1998) Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352(9138):1413–1418
4. Rougier P, Van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques C (1998) Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352(9138):1407–1412
5. de Gramont A, Vignoud J, Tournigand C, Louvet C, André T, Varette C, Raymond E, Moreau S, Le Bail N, Krulik M (1997) Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. Eur J Cancer 33(2):214–219
6. Rothenberg ML, Oza AM, Bigelowe RH, Berlin JD, Marshall JL, Ramanathan RK, Hart LL, Gupta S, Garay CA, Burger BG, Le Bail N, Haller DG (2003) Superiority of oxaliplatin and fluorouracil–leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil–leucovorin: interim results of a phase III trial. J Clin Oncol 21(11):2059–2069
7. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350(23):2335–2342
8. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 351(4):337–345
9. US Food and Drug Administration. www.FDA.gov
10. Rowland KM, Pitot HC, Sargent DJ, Philip PA, Mitchell EP, Mailliard JA, Goldberg RM, Alberts SR (2005) Results of 3rd line therapy on N9841: a randomized phase III trial of oxaliplatin/5-fluorouracil (5FU)/leucovorin (FOLFOX4) versus irinotecan (CPT-11) in patients (pts) with advanced colorectal cancer (CRC) previously treated with prior 5FU chemotherapy. Proc ASCO, annual meeting, abstract no 3519
11. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, Canon JL, Van Laethem JL, Maurel J, Richardson G, Wolf M, Amado RG (2007) 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 25(13):1658–1664
12. Kemeny N, Garay CA, Gurtler J, Hochster H, Kennedy P, Benson A, Brandt DS, Polikoff J, Wertheim M, Shumaker G, Hallman D, Burger B, Gupta S (2004) Randomized multicenter phase II trial of bolus plus infusional fluorouracil/leucovorin compared with fluorouracil/leucovorin plus oxaliplatin as third-line treatment of patients with advanced colorectal cancer. J Clin Oncol 22(23):4753–4761
13. Salek T (2005) Oxaliplatin, bolus 5-fluorouracil (5-FU) and leucovorin (LV/b-FOL) in heavily pretreated patients with metastatic colorectal cancer. National Cancer Institute Slovakia, the first "b-FOL" experience. ESMO, abstract no 70
14. Chau I, Webb A, Cunningham D, Hill M, Waters JS, Norman A, Massey A (2001) Oxaliplatin and protracted venous infusion of 5-fluorouracil in patients with advanced or relapsed 5-fluorouracil pretreated colorectal cancer. Br J Cancer 85(9):1258–1264
15. Abón G, Muñoz A, Rubio I, Manel MJ, Ferreiro J, Fernández R, Fuente N, López AG, Barceló R, López VG (2000) Third line oxaliplatin with leucovorin (LV) and continuous infusion 5-fluorouracil (5FU) in metastatic colorectal cancer. ESMO, abstract no 211P
16. Luppi G, Zanelli F, Di Stasi A, Bertolini F, Pifferi M (2002) Folfox 2 regimen in heavily pretreated patients with advanced colorectal cancer. Tumori 88(4):270–272
17. Martoni A, Mini E, Pinto C, Nobili S, Gentile AL, Dentico P, Angelelli B, Scicolone S, Piana E, Mazzei T (2001) Oxaliplatin and protracted continuous 5-fluorouracil infusion in patients with pretreated advanced colorectal carcinoma. Ann Oncol 12(4):519–524
18. Mosconi S, Cascinu S, Zaniboni A, Catalano V, Giordani P, Beretta GD, Martignoni G, Pancera G, Baldelli AM, Poletti P, Curti C, Labianca R (2000) The value of oxaliplatin in combination with continuous infusion ± bolus 5-fluorouracil and levo-folinic acid in metastatic colorectal cancer progressing after 5FU-based chemotherapy: a GISCAD (Italian Group for the study of digestive tract) cancer phase II trial. Tumori 86(6):465–469
19. Kallen K-J, Hofmann MAK, Timm A, Gödderz W, Galle PR, Heike M (2000) Weekly oxaliplatin, high-dose infusional 5-fluorouracil and folinic acid as palliative third-line therapy of advanced colorectal carcinoma. Z Gastroenterol 38:153–157
20. Giacchetti S, Zidani R, Chollet P, Dogliotti L, Kunstlinger F, Le Rol A, Garufi C, Brienza S, Focan C, Bertheault-Cvitkovic F, Misset J, Lévi F (2000) Chronotherapy of metastatic colorectal cancer (MCC) with 5-fluorouracil (5-FU)-leucovorin (LV)-oxaliplatin

(L-OHP) as second to seventh line treatment. Proc ASCO, annual meeting, abstract no 1255
21. Croles N, Smorenburg CH, van Groeningen CJ, Giaccone G, Boven E (2004) FOLFOX3 in heavily pretreated patients with metastatic colorectal cancer. Neth J Med 62(7/8):242–245
22. Moehler M, Hoffmann T, Hildner K, Siebler J, Galle PR, Heike M (2002) Weekly oxaliplatin, high-dose folinic acid and 24h-5-fluorouracil (FUFOX) as salvage therapy in metastatic colorectal cancer patients pretreated with irinotecan and folinic acid/5-fluorouracil regimens. Z Gastroenterol 40:957–964
23. Bensmaïne MA, Marty M, de Gramont A, Brienza S, Lévi F, Ducreux M, François E, Gamelin E, Bleiberg H, Cvitkovic E (2001) Factors predicting efficacy of oxaliplatin in combination with 5-fluorouracil (5-FU) ± folinic acid in a compassionate-use cohort of 481 5-FU-resistant advanced colorectal cancer patients. Br J Cancer 85(4):509–517
24. Gervais H, Artru P, Louvet C, Tournigand C, Maindrault F, Garcia M-L, de Gramont A (2002) Reintroduction of irinotecan in pretreated patients with metastatic colorectal cancer. Proc ASCO, annual meeting, abstract no 688
25. Kim HJ, Kwon HC, Kim SH, Kim JS (2003) Irinotecan with biweekly, low-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for oxaliplatin pretreated metastatic colorectal cancer. Proc ASCO, annual meeting, abstract no 1196
26. Maindrault F, Louvet C, André T, Gilles V, Artru P, Tournigand C, Garcia M, Gervais H, Carola E, Krulik M, de Gramont A (2001) Time to disease control (TDC) to evaluate the impact on survival of three chemotherapy lines in metastatic colorectal cancer (MRC) based on 5-fluorouracil, oxaliplatin and irinotecan (GERCOR) Proc ASCO, annual meeting, abstract no 581
27. Stickel F, Jüngert B, Brueckl V, Schirner I, Brueckl WM, Männlein G, Hegewald J, Mühldorfer S, Bittorf B, Hohenberger W, Hahn EG, Wein A (2003) Weekly high-dose 5-fluorouracil as 24-h infusion and folinic acid (AIO) plus irinotecan as second- and third-line treatment in patients with colorectal cancer pre-treated with AIO plus oxaliplatin. Anticancer Drugs 14(9):745–749
28. Ardavanis AS, Ioannidis GN, Orphanos GS, Rigatos GA (2006) Salvage treatment with single-agent capecitabine in patients with heavily pretreated advanced colorectal cancer. Anticancer Res 26(2B):1669–1672
29. Gubanski M, Naucler G, Almerud A, Lidestahl A, Lind P ARM (2005) Capecitabine as third line therapy in patients with advanced colorectal cancer. Acta Oncol 44(3):236–239
30. Lim DH, Park YS, Park BB, Ji SH, Lee J, Park KW, Kang JH, Lee SH, Park JO, Kim K, Kim WS, Jung CW, Im YH, Kang WK, Park K (2005) Mitomycin-C and capecitabine as third-line chemotherapy in patients with advanced colorectal cancer: a phase II study. Cancer Chemother Pharmacol 56(1):10–14
31. Harba A, Jordan K, Kegel I, Behrens R, Grothey A, Schmoll HJ (2003) Capecitabine/mitomycin C as salvage therapy in oxaliplatin and CPT11 refractory advanced colorectal carcinoma (ACRC). Proc ASCO, annual meeting, abstract no 1335
32. Chong G, Dickson JLB, Cunningham D, Norman RA, Rao S, Hill ME, Price TJ, Oates J, Tebbutt N (2005) Capecitabine and mitomycin C as a 3rd line therapy for patients with metastatic colorectal cancer resistant to fluorouracil and irinotecan. Br J Cancer 93(5):510–514
33. Jeung HC, Rha SY, Cho BC, Yoo NC, Roh JK, Roh WJ, Chung HC, Ahn JB (2006) A phase II trial of oral S-1 monotherapy in metastatic colorectal cancer after failure of irinotecan-and oxaliplatin containing regimens. Br J Cancer 95(12):1637–1641
34. Tsavaris N, Kosmas C, Vadiaka M, Kontos A, Fotia M, Angelopoulou A, Vrizidis N, Soulla M, Sougioultzis S, Koufos Ch (2002) Raltitrexed (Tomudex) administration in patients failing multiple prior chemotherapy regimens in advanced colorectal cancer: a pilot study. Invest New Drugs 20:133–136
35. Garcia M, Gilles V, Louvet C, Defrance R, Tournigand C, Artru P, Maindrault-Goebel F, de Gramont A, Krulik M (2000) Bi-weekly irinotecan (CPT-11) combined with raltitrexed ("Tomudex") treatment in heavily pre-treated patients with advanced colorectal cancer: a feasibility study. Proc ASCO, annual meeting, abstract no 987
36. Rosati G, Rossi A, Germano D, Reggiardo G, Manzione L (2003) Raltitrexed and mitomycin-C as third-line chemotherapy for colorectal cancer after combination regimens including 5-fluorouracil, irinotecan and oxaliplatin: a phase II study. Anticancer Res 23(3C):2981–2985
37. Lonardi S, Paris MK, Stefani M, Caroti C, D'Amico M, Jirillo A, Pronzato P, Gallo L, Monfardini S, Aschele C (2004) Gemcitabine (GEM) as salvage therapy in patients (pts) with advanced colorectal cancer (CRC) refractory to 5-fluorouracil (FU), irinotecan (IRI) and oxaliplatin (OXA). Proc ASCO, annual meeting, abstract no 3577
38. Pachon V, Garcia-Alfonso P, Iglesias L, Siso I, Abad G, Khosravi P, Diaz V, Perez-Manga G (2005) Gemcitabine plus continuous infusion of 5-FU for heavily pretreated advanced colorectal cancer patients. Phase I/II study. Proc ASCO, annual meeting, abstract no 3735
39. Hartmann JT, Oechsle K, Jäger E, Reis HE, Haag C, Niederle N, Wilke H-J, Pflüger K-H, Batran SAl, Büchele T, Hofheinz RD, Kanz L, Bokemeyer C (2004) Prospective multicenter phase II study of irinotecan as third line therapy in metastatic colorectal cancer and progression after bolus and infusional 5-fluorouracil. Anticancer Drugs 15(5):473–477
40. Benavides M, García-Alfonso P, Cobo M, Muňoz-Martín A, Gil-Calle S, Carabantes F, Villar E, Graupera J, Balcells M, Pérez-Manga G (2004) Weekly irinotecan (CPT-11) in 5-FU heavily pretreated and poor-performance-status patients with advanced colorectal cancer. Med Oncol 21(3):255–262
41. Gholam D, Giacchetti S, Brezault Bonnet C, Bouchahda M, Hauteville D, Adam R, Decot B, Ghémard O, Kustlinger F, Jasmin C, Levi F (2006) Chronomodulated irinotecan, oxaliplatin, and leucovorin-modulated 5-fluorouracil as ambulatory salvage therapy in patients with irinotecan-and oxaliplatin-resistant metastatic colorectal cancer. Oncologist 11(10):1072–1080
42. Polus M, Peeters M, Baert F, Vergauwe P, Kalantari H, Hendrickx K, Collignon J, van Maele P, Vandeputte L, van Laethem JL (2004) CPT-11 and mitomycin-C in heavily pre-treated patients with metastatic colorectal cancer: a Belgian multicentre phase II study. Proc ASCO, annual meeting, abstract no 3716
43. Schulz J, Keller A, Canfield V, Parker G, Douglass E (2004) ZD9331 as second- or third-line therapy in patients with advanced colorectal cancer: a phase II multicenter trial. Am J Clin Oncol 27(4):337–342
44. Gollasch H, Gebauer B, Sturm I, Thuss-Patience P, Pink D, Stroszczynski C, Kretzschmar A (2004) Hepatic artery infusion (HAI) of oxaliplatin (Ox) as third and fourth-line therapy for patients with hepatic metastases (M) from colorectal cancer (CRC) pretreated with systemic Ox. Proc ASCO, annual meeting, abstract no 3695
45. Mirtsching B, Headlee C, Beasley S, Teel C, Jackson D (2004) Cetuximab single-agent activity in refractory metastatic colorectal cancer: single-center experience. Proc ASCO, annual meeting, abstract no 3703
46. Lenz HJ, Van Cutsem E, Khambata-Ford S, Mayer RJ, Gold P, Stella P, Mirtsching B, Cohn AL, Pippas AW, Azarnia N, Tsuchihashi Z, Mauro DJ, Rowinsky EK (2006) Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. J Clin Oncol 24(30):4914–4921
47. Mirtsching BC, Cichon J, Beasly S, Teel C, Jackson D, Headlee C (2005) Cetuximab in refractory metastatic colorectal cancer: analysis

of efficacy and response by patient and disease variables. Proc ASCO, gastrointestinal symposium, abstract no 205
48. Vincenzi B, Santini D, Rabitti C, Coppola R, Beomonte Zobel B, Trodella L, Tonini G (2006) Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: a single centre phase II trial. Br J Cancer 94(6):792–797
49. Grande C, Mel JR, Salgado M, Reboredo M, Candamio S, Fernandez I, Quintero G, Huidobro G, Firvida JL, Valladares M (2006) Multicenter phase II study of cetuximab and irinotecan as third line chemotherapy in patients (pts) with metastatic colorectal cancer (MCRC) previously treated with both irinotecan and oxaliplatin regimens. Proc ASCO, annual meeting, abstract no 13551
50. Grothe W, Arnold D, Peinert S, Voigt W, Mantovani Loeffler L, Siewczynski R, Steps G, Boehme J, Graeven U, Schmoll H (2005) Cetuximab with oxaliplatin and capecitabine (CAPOX) in patients with metastatic colorectal cancer (mCRC) refractory to standard chemotherapy. Proc ASCO, annual meeting, abstract no 3669
51. Chen HX, Mooney M, Boron M, Vena D, Mosby K, Grochow L, Jaffe C, Rubinstein L, Zwiebel J, Kaplan RS (2006) Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI treatment referral center trial TRC-0301. J Clin Oncol 24(21):3354–3360
52. Emmanouilides C, Pegram M, Robinson R, Hecht R, Kabbinavar F, Isacoff W (2004) Anti-VEGF antibody bevacizumab (Avastin) with 5FU/LV as third line treatment for colorectal cancer. Tech Coloproctol 8(Suppl 1):50–52
53. Peinert S, Arnold D, Grothe W, Lesske J, Siewczynski R, Schädlich B, Kegel T, Behrmann C, Schmoll H-J (2005) Salvage therapy with bevacizumab, capecitabin, and mitomycin C (BECAM) for patients with metastatic colorectal or gastric cancer refractory to 5fluorouracil, oxaliplatin, irinotecan, and cetuximab. ECCO abstract no 793
54. Dorligschaw O, Kegel T, Jordan K, Harba A, Grothey A, Schmoll H-J (2003) ZD1839 (Iressa)-based treatment as last-line therapy in patients with advanced colorectal cancer (ACRC). Proc ASCO, annual meeting, abstract no 1494
55. Hecht J, Mitchell E, Baranda J, Malik I, Richards D, Navale L, D'Avirro P, Amado R (2006) Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing low (1–9%) or negative (<1%) levels of epidermal growth factor receptor (EGFr). Proc ASCO, annual meeting, abstract no 3547
56. Berlin J, Neubauer M, Swanson P, Harker G, Burris H, Hecht JR, Navale L (2006) Panitumumab antitumor activity in patients (pts) with metastatic colorectal cancer (mCRC) expressing $\geq$10% epidermal growth factor receptor (EGFr). Proc ASCO, annual meeting, abstract no 3548
57. Gebbia V, Del Prete S, Borsellino N, Ferraù F, Tralongo P, Verderame F, Leonardi V, Capasso E, Maiello E, Bordonaro R, Stinco S, Aqostara B, Barone C (2006) Efficacy and safety of cetuximab/irinotecan in chemotherapy-refractory metastatic colorectal adenocarcinomas: a clinical practice setting, multicenter experience. Clin Colorectal Cancer 5(6):422–428
58. Levi F, Karaboue A, Jasmin C, Innominto P, Machover D, Kunstlinger F, Castagne V, Adam R, Guettier C, Bouchahda M (2005) Cetuximab reversal of chemotherapy resistance in patients with extensively pretreated metastatic colorectal cancer treated at Paul-Brousse hospital. ECCO abstract no 710
59. NCI 2007. www.cancer.gov. Health professional version
60. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomised GERCOR study. J Clin Oncol 22(2):229–237
61. Adjei AA (1999) A review of the pharmacology and clinical activity of new chemotherapy agents for the treatment of colorectal cancer. Br J Clin Pharmacol 48(3):265–277
62. Goetz MP, Grothey A (2004) Developments in combination chemotherapy for colorectal cancer. Expert Rev Anticancer Ther 4(4):627–637
63. Grothey A, Sargent D, Goldberg RM, Schmoll H-J (2004) Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil–leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol 22(7):1209–1214
64. de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18(16):2938–2947
65. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19(18):3801–3807
66. Cocconi G, Cunningham D, Van Cutsem E, Francois E, Gustavsson B, van Hazel G, Kerr D, Possinger K, Hietschold SM (1998) Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex colorectal cancer study group. J Clin Oncol 16(9):2943–2952
67. Hejna M, Kornek GV, Raderer M, Depisch D, Brodowicz T, Fiebiger WC, Scheithauer W (1998) Reinduction therapy with the same cytostatic regimen in patients with advanced colorectal cancer. Br J Cancer 78(6):760–764
68. www.Merck.de. 2006
69. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer J, Mitchell P, Alberts SR, Schwartz MA, Benson AB, Eastern Cooperative Oncology Group Study E3200 (2007) 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 25(12):1539–1544
70. Saltz LB, Lenz H, Kindler H, Hochster H, Wadler S, Hoff P, Kemeny N, Hollywood E, Gonen M, Chen H (2005) Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer. Proc ASCO, Gastrointestinal Cancers Symposium, abstract no 169b
71. Hecht JR, Patnaik A, Malik I Venook A, Berlin J, Croghan G, Wiens BL, Visonneau S, Jerian S, Meropol NJ (2004) ABX-EGF monotherapy in patients (pts) with metastatic colorectal cancer (mCRC): an updated analysis. Proc ASCO, annual meeting, abstract no 3511
72. Goldberg RM, Rothenberg ML, Van Cutsem E, Benson AB, Blanke CD, Diasio RB, Grothey A, Lenz H-J, Meropol NJ, Ramanathan RK, Becerra CHR, Wickham R, Armstrong D, Viele C (2007) The continuum of care: a paradigm for the management of metastatic colorectal cancer. Oncologist 12(1):38–50
73. Grothey A, Deschler B, Kroening H, Ridwelski K, Reichardt P, Kretzscmar A, Clemens M, Hirschmann W, Lorenz M, Asperger W, Buechele T, Schmoll H-J (2002) Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (MAYO) vs. weekly high-dose 24h 5-FU infusion/FA + oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). Proc ASCO, annual meeting, abstract no 512
74. Cheeseman SL, Joel SP, Chester JD, Wilson G, Dent JT, Richards FJ, Seymour MT (2002) A "modified de Gramont" regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 87(4):393–399
75. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan study group. N Engl J Med 343(13):905–914

76. Giacchetti S, Bjarnason G, Garufi C, Genet D, Iacobelli S, Tampellini M, Smaaland R, Focan C, Coudert B, Humblet Y, Canon JL, Adenis A, Lo Re G, Carvalho C, Schueller J, Anciaux N, Lentz MA, Baron B, Gorlia T, Levi F (2006) Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: the European Organisation for Research and Treatment of Cancer Chronotherapy Group. J Clin Oncol 24(22):3562–3569
77. Maindrault-Goebel F, de Gramont A, Louvet C, Andre T, Carola E, Gilles V, Lotz JP, Tournigand C, Mabro M, Molitor JL, Artru P, Izrael V, Krulik M (2000) Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. Oncology Multidisciplinary Research Group (GERCOR). Ann Oncol 11(11):1477–1483
78. Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, Antré T, Tabah-Fisch I, de Gramont A (2006) OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-GO fashion advanced colorectal cancer–a GERCOR study. J Clin Oncol 24(3):394–400
79. Cassidy J, Tabernero J, Twelves C, Brunet R, Butts C, Conroy T, Debraud F, Figer A, Grossmann J, Sawada N, Schöffski P, Sobrero A, Van Cutsem E, Díaz-Rubio E (2004) XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 22(11):2084–2091