CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

Efficacy of second-line chemotherapy after a first-line triplet in patients with metastatic colorectal cancer

S. Bazarbashi MBBS,* A.M. Hakoun MBBS,† A.M. Gad MD,*‡ M.A. Elshenawy MD,*§ A. Aljubran MD,* A.M. Alzahrani MD,* and A. Eldali MSc#

ABSTRACT

Background Exposing patients with metastatic colorectal cancer (mCRC) to all three active chemotherapeutic agents (oxaliplatin, irinotecan, fluorouracil) has improved survival. The benefit of second-line chemotherapy after a first-line triplet is not clearly defined. We evaluated the efficacy of second-line chemotherapy in patients who had received first-line triplet therapy.

Methods The medical records of patients treated on a prospective trial of first-line triplet therapy were reviewed for second-line treatment. Univariate and multivariate analyses were performed to establish factors of prognostic significance.

Results Of the 53 patients who received first-line triplet therapy, 28 (53%) received second-line chemotherapy [13 men; 8 with a colon primary; mutant *KRAS* in 10, wild-type in 15, and unknown status in 3; Eastern Cooperative Oncology Group performance status (PS) of 1 in 16 patients, PS 2 in 3, PS 3 in 2, and unknown in 7; involved organs: liver in 17 patients, lung in 16, and peritoneum in 8]. Second-line chemotherapy consisted of XELOX or FOLFOX in 13 patients, XELIRI or FOLFIRI in 12, and single-agent irinotecan in 3. Concurrent bevacizumab was given in 16 patients (57%), and cetuximab, in 2 (7%). Median survival was 28.0 months [95% confidence interval (CI): 22.8 months to 33.2 months] for patients receiving second-line therapy and 23.0 months (95% CI: 13.2 months to 32.8 months) for those not receiving it. Best response was partial in 6 patients (21%), stable disease in 11 (39%), and progressive disease in 11 (39%). Median progression-free survival was 4.8 months (95% CI: 2.4 months to 9.6 months), and overall survival was 15 months (95% CI: 9.6 months to 20.4 months).

Conclusions Second-line chemotherapy after first-line triplet therapy in mCRC is feasible and suggests efficacy comparable to that reported for second-line therapy after a doublet, regardless of the agent used.

Key Words Colorectal cancer, metastatic; second-line treatments; triplet chemotherapy; systemic therapy

Curr Oncol. **2019 Feb;26(1):e24-e29** **www.current-oncology.com**

INTRODUCTION

The treatment of metastatic colorectal cancer (mCRC) had changed considerably since the early 2000s. The most important milestones were the introduction of irinotecan[1], oxaliplatin[2], bevacizumab[3], and monoclonal antibodies against the epidermal growth factor receptors[4,5]. Doublet chemotherapy regimens using either oxaliplatin or irinotecan—FOLFOX (leucovorin, fluorouracil, oxaliplatin), FOLFIRI (leucovorin, fluorouracil, irinotecan)—are considered standard-of-care options for the first-line treatment of mCRC[6].

Compared with doublet chemotherapy regimens, triplet regimens have been associated with improved progression-free survival (PFS) and overall survival (OS) by some investigators[7–10]. Second-line therapy after failure of a first-line single-agent or doublet regimen has shown efficacy, with improved survival[11–13]. The benefit of second-line chemotherapy after failure of a triplet regimen has been less extensively investigated[14,15].

Correspondence to: Shouki Bazarbashi, Oncology Center, King Faisal Specialist Hospital and Research Center, PO Box 3354, Riyadh 11211 Saudi Arabia. E-mail: Bazarbashi@kfshrc.edu.sa ■ **DOI:** https://doi.org/10.3747/co.26.4217

We previously published the results of our phase I/II trial of a triplet consisting of capecitabine, oxaliplatin, and irinotecan with bevacizumab (XELOXIRIA) in patients with advanced CRC[16]. In that study, 53 patients received XELOXIRIA, with 4% achieving a complete response, and 60% achieving a partial response. Median PFS was 16 months, and median OS was 28 months. Toxicity was high, with grades 3 and 4 toxicity rates of 36% for diarrhea, 21% for vomiting, and 17% for fatigue. Here, we report the efficacy of second-line chemotherapy in patients for whom the first-line triplet regimen failed.

METHODS

Medical records and case report forms for patients with MCRC treated with first-line XELOXIRIA in a prospective clinical trial (NCT01311050 at http://ClinicalTrials.gov/) were reviewed for second-line chemotherapy. All patients received first-line XELOXIRIA, which consisted of oral capecitabine at a dose of 1000 mg/m^2 twice daily for 14 days, intravenous oxaliplatin 130 mg/m^2 over 2 hours on day 1, intravenous irinotecan 150 mg/m^2 over 90 minutes on day 1, and intravenous bevacizumab 7.5 mg per kilogram body weight over 30 minutes on day 1. Cycles were repeated every 21 days. After the first 30 patients, the dose of capecitabine was reduced to 800 mg/m^2 twice daily for 14 days because of excessive toxicity. After 5–8 cycles, patients achieving a response or stable disease were maintained on capecitabine and bevacizumab until progression, undue toxicity, or death.

Data collected for patients who received second-line chemotherapy included performance status at the start of second-line chemotherapy, complete blood count, serum carcinoembryonic antigen (CEA) and alkaline phosphatase (ALP), number and location of metastatic sites, response to first-line chemotherapy, PFS on first-line chemotherapy, *KRAS* status (*NRAS* was not available), chemotherapy-free interval (CFI) before second-line therapy, and second-line regimen (number of cycles, response, PFS, and OS).

Survival Analysis and Statistics

For all patients receiving second-line therapy, imaging was reviewed for assessment of response according to RECIST (Response Evaluation Criteria in Solid Tumours), version 1.1[17]. Measurement of PFS began at the start date of second-line chemotherapy and ended at the date of first documented disease progression or death from any cause. Measurement of OS began at the start date of second-line chemotherapy and ended at the date of death from any cause. If a patient was not known to have died, survival was censored at the date of last contact. Tabulation and statistics were performed in the SAS statistical software application (version 9.4: SAS Institute, Cary, NC, U.S.A.). The Kaplan–Meier method was used to calculate PFS and OS. Calculation of p values used the log-rank test, and results were considered statistically significant if equal to or less than 0.05.

Univariate and multivariate Cox regression analyses were performed for PFS and OS, including factors that might have an impact (age, sex, performance status, serum CEA, serum ALP, *KRAS* status, tumour site, liver involvement, number of organs involved, response to first-line therapy, PFS for first-line therapy, CFI before second-line therapy, and type of second-line chemotherapy).

Ethics Considerations

This retrospective study was approved by the hospital's institutional review board with waiver of consent, given that most of the patients had died by the time of the study. Patient confidentiality was maintained throughout the study.

RESULTS

Patient Characteristics

The first-line triplet trial of XELOXIRIA enrolled 53 patients with MCRC. Results have been reported[16]. Of those patients, 28 (53%) received second-line therapy. The most common reasons for not proceeding to second-line chemotherapy were either no progression or poor performance status. A small proportion did not proceed because of toxicity from first-line chemotherapy or withdrawal of consent. Table I summarizes the characteristics of the patients who received second-line chemotherapy.

Efficacy of Second-Line Chemotherapy

Of the 28 patients receiving second-line chemotherapy, 6 (21%) achieved a partial response, and 11 (39%) achieved stable disease, for a disease control rate of 61%. The remaining patients experienced disease progression. No patient achieved a complete response. At a median follow-up of 28 months, median PFS was 4.8 months [95% confidence interval (CI): 2.4 months to 9.6 months] and OS was 15 months (95% CI: 9.6 months to 20.4 months; Figure 1). Median OS was 28 months (95% CI: 22.8 months to 33.2 months) for patients who received second-line chemotherapy and 23 months (95% CI: 13.2 months to 32.8 months) for those who did not receive second-line chemotherapy (log-rank p = 0.69, Figure 2). Irinotecan-based chemotherapy was given to 15 patients, and oxaliplatin-based chemotherapy, to 13 patients. The PFS and OS for irinotecan-based second-line therapy were 3.6 months (95% CI: 1.2 months to 8.4 months) and 18 months (95% CI: 1.2 months to 21.6 months); for oxaliplatin-based chemotherapy, they were 8.4 months (95% CI: 2.4 months to 12 months) and 14.4 months (95% CI: 12 months to not reached).

Prognostic Factors

Table II shows the PFS and OS durations for patient subgroups by potential prognostic factors. Despite a trend toward better results for patients who were female, who had elevated serum ALP, who had wild-type *KRAS,* who achieved a partial response on first-line chemotherapy, or who received oxaliplatin-based rather than irinotecan-based chemotherapy, no difference in PFS or OS reached statistical significance. Only normal serum CEA (compared with elevated CEA) and CFI greater than 3 months (compared with 3 months or less) at the time of second-line chemotherapy were associated with significantly longer PFS and OS in univariate analysis. Cox regression analysis showed that elevated ALP was an independent prognostic factor for improved PFS. On the other hand, female sex was the only independent prognostic factor for improved OS;

TABLE I Characteristics of 28 patients receiving second-line chemotherapy

Characteristic	Value
Age (years)	
Median	52.5
Range	35–67
Sex [*n* (%)]	
Men	13 (46.4)
Women	15 (53.6)
ECOG PS [*n* (%)]	
0	16 (57.1)
1	3 (10.7)
2	2 (7.2)
Unknown	7 (25)
Primary tumour site [*n* (%)]	
Colon	8 (28.57)
Rectum	20 (71.43)
Adenocarcinoma histology [*n* (%)]	
Moderately differentiated	23 (89.3)
Poorly differentiated	1 (3.6)
Mucinous	2 (7.1)
Organ involvement [*n* (%)]	
Liver	17 (60.7)
Lung	16 (57.1)
Peritoneum	8 (28.6)
Node or nodes	11 (39.3)
Involved organs *(n)*	
Median	2
Range	1–5
KRAS status [*n* (%)]	
Mutant	10 (35.7)
Wild type	15 (53.6)
Unknown	3 (10.7)
First-line response [*n* (%)]	
Partial	18 (64.3)
Stable disease	10 (35.7)
PFS in first line (months)	
Median	9.1
Range	3–26.9
Second-line regimen [*n* (%)]	
XELOX or FOLFOX	13 (46.4)
XELIRI or FOLFIRI	12 (42.9)
Irinotecan ± cetuximab	3 (10.7)
Concurrent targeted therapy [*n* (%)]	
Bevacizumab	16 (57.1)
Cetuximab	2 (7.1)

ECOG PS = Eastern Cooperative Oncology Group performance status; PFS = progression-free survival; XELOX = capecitabine–oxaliplatin; FOLFOX = 5-fluorouracil–leucovorin–oxaliplatin; XELIRI = capecitabine–irinotecan; FOLFIRI = 5-fluorouracil–leucovorin–irinotecan.

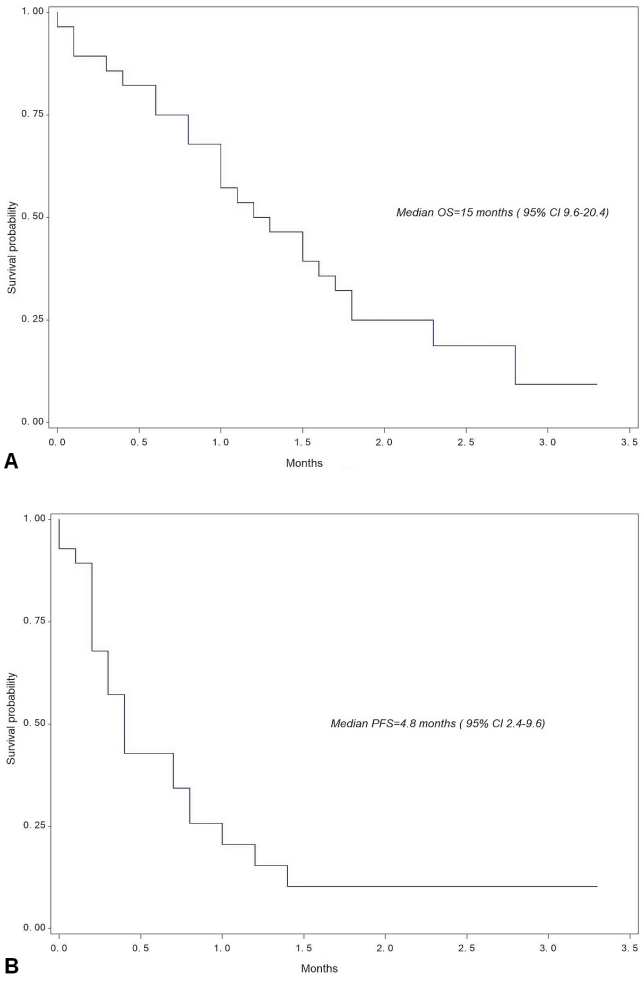

FIGURE 1 Kaplan–Meier plots of (A) overall survival (OS) and (B) progression-free survival (PFS) in patients treated with second-line chemotherapy after first-line triplet chemotherapy. CI= confidence interval.

elevated ALP approached statistical significance ($p = 0.06$, Tables III and IV).

DISCUSSION

The benefit of exposing patients with CRC to all three active chemotherapeutic agents (oxaliplatin, irinotecan, fluorouracil) has been shown to improve survival[18]. Accordingly, the value of second-line chemotherapy with any of those agents in patients who receive all three drugs in the first line has been less clear. Because many of our patients did not receive second-line chemotherapy (for a number of reasons), it is difficult to prove directly in this study that second-line chemotherapy improves survival in patients who previously received triplets. However, at least indirectly, it appears that second-line chemotherapy is as effective in this patient population as it is in patients who receive second-line chemotherapy after initial doublet therapy[6].

In the present study, the PFS and OS for patients unselected for *RAS* status receiving second-line chemotherapy

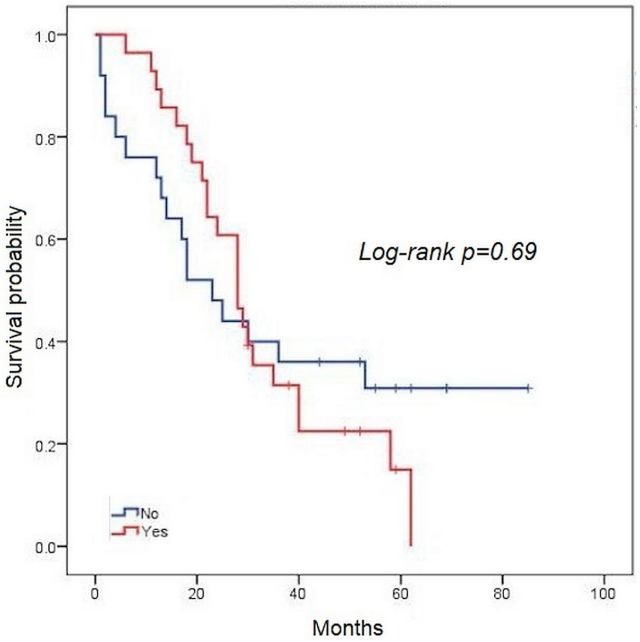

FIGURE 2 Kaplan–Meier plot of overall survival in patients treated with and without second-line chemotherapy.

after triplet therapy were 4.8 months (95% CI: 2.4 months to 9.6 months) and 15 months (95% CI: 9.6 months to 20.4 months) respectively. Those results are very similar to results in many contemporary trials of second-line therapy after doublet chemotherapy. In the VELOUR trial, the PFS was 4.6 months in the standard arm and 6.9 months in the aflibercept arm. Similarly, OS was 12.1 months in the standard arm and 13.5 months in the aflibercept arm[19]. In the TML trial (bevacizumab after progression), PFS was 4.1 months in the standard arm and 5.7 months in the bevacizumab arm; OS was 9.8 months and 11.2 months respectively[20].

Many other trials have also reported results of second-line chemotherapy[11,12,21,22]. The outcome of second-line chemotherapy after a first-line triplet has also been reported by GONO (Italy's Gruppo Oncologico Nord Ovest)[14,15]. In their report, second-line chemotherapy after FOLFOXIRI in 136 patients resulted in an overall response rate of 23%. Median PFS and OS were 5.9 months and 13.2 months respectively—a result similar to that reported here. In an exploratory subgroup analysis, re-treatment with FOLFOXIRI compared with a second-line doublet was associated with longer PFS (8.2 months vs. 6.3 months, $p = 0.003$; hazard ratio: 0.61) and OS (19.3 months vs. 14.0 months, $p = 0.02$; hazard ratio: 0.57). Compared with FOLFOXIRI or a doublet, single-agent chemotherapy or fluoropyrimidine plus mitomycin C was associated with a significantly lower response

TABLE II Univariate analysis of progression-free (PFS) and overall survival by prognostic subgroup

Variable	Comparator	Progression-free survival (months)			Overall survival (months)		
		Median	95% CI	*p* Value	Median	95% CI	*p* Value
Age	≤65 Years	4.8	2.4 to 9.6	0.47	16.8	9.6 to 21.6	0.14
	>65 Years	4.8	0 to 9.6		7.8	1.2 to 14.4	
Sex	Men	4.8	2.4 to 16.8	0.58	14.4	3.6 to 27.6	0.72
	Women	4.8	2.4 to 8.4		18	9.6 to 21.6	
Alkaline phosphatase	Normal	3.6	2.4 to 8.4	0.22	13.8	7.2 to 21.6	0.59
	Elevated	9.6	3.6 to 16.8		18	4.8 to NR	
Carcinoembryonic antigen	Normal	NR	0 to NR	0.01	33.6	1.2 to NR	0.0074
	Elevated	3.6	2.4 to 4.8		12	7.2 to 18	
KRAS status	Wild type	8.4	2.4 to 16.8	0.11	18	7.2 to 27.6	0.35
	Mutated	4.2	2.4 to 8.4		12	3.6 to 20.4	
Primary location	Colon	4.2	0 to NR	0.35	10.8	1.2 to NR	0.75
	Rectum	3	1.2 to 8.4		10.2	1.2 to 33.6	
Liver involvement	Present	4.8	2.4 to 14.4	0.23	15.6	9.6 to 21.6	0.97
	Absent	4.8	1.2 to 9.6		14.4	1.2 to 33.6	
Organs involved	1	6	0 to NR	0.52	13.2	0 to NR	0.90
	>1	4.8	2.4 to 8.4		16.8	9.6 to 21.6	
Response to first-line CTx	Partial	8.4	2.4 to 12	0.34	15	4.8 to 21.6	0.72
	Stable disease	4.2	2.4 to 4.8		15.6	7.2 to 21.6	
PFS duration on first-line therapy	≤6 Months	3.6	1.2 to 8.4	0.28	20.4	1.2 to 27.6	0.87
	>6 Months	4.8	2.4 to 12		13.2	9.6 to 18	
CTx-free interval	≤3 Months	4.8	2.4 to 8.4	0.01	13.2	9.6 to 19.2	0.0184
	>3 Months	NR	NR to NR		NR	NR to NR	
Second-line CTx	Irinotecan	3.6	1.2 to 8.4	0.28	18	1.2 to 21.6	0.33
	Oxaliplatin	8.4	2.4 to 12		14.4	12 to NR	

CI = confidence interval; NR = not reached; CTx = chemotherapy.

TABLE III Multivariate analysis of factors with possible prognostic significance for progression-free survival

Factor	HR	95% CI	*p* Value
Age	0.94	0.87 to 1.02	0.18
Sex	0.46	0.11 to 1.89	0.29
Alkaline phosphatase	0.03	0.03 to 0.84	0.02
Elevated CEA	3.1	0.69 to 13.9	0.14
CTx-free interval	0.54	0.25 to 1.16	0.12
KRAS status	1.93	0.65 to 5.73	0.23

HR = hazard ratio; CI = confidence interval; CEA= carcinoembryonic antigen; CTx = chemotherapy.

TABLE IV Multivariate analysis of factors with possible prognostic significance for overall survival

Parameter	HR	95% CI	*p* Value
Age	0.98	0.92 to 1.06	0.75
Sex	0.13	0.02 to 0.82	0.03
Alkaline phosphatase	0.14	0.18 to 1.08	0.06
Elevated CEA	2.01	0.59 to 6.9	0.26
CTx-free interval	0.60	0.32 to 1.13	0.011
KRAS status	1.56	0.53 to 4.55	0.41

HR = hazard ratio; CI = confidence interval; CEA= carcinoembryonic antigen; CTx = chemotherapy.

rate (8%), PFS (3.0 months), and OS (8.7 months). None of our patients had triplet re-introduction. All but 2 patients in our series received doublet chemotherapy.

The univariate subgroup analysis suggested lower efficacy for second-line chemotherapy in patients with a CFI of less than 3 months. That finding is similar to results reported by the GONO group and likely represents patients who are truly chemotherapy-refractory, which is probably why CFI did not remain significant in the multivariate analysis. In the GONO report, the OS for patients with a CFI of 3 months or less was 5.9 months, compared with 13.4 months for patients with a CFI of 3–6 months[15]. Interestingly, elevated ALP and female sex emerged as factors of prognostic significance for PFS and OS respectively. Although women have fared slightly better than men in most second-line trials[23–26], the difference has not reached statistical significance, and it was not considered by the GONO group. We believe that a pooled analysis of individual patient data from similar trials might provide an answer.

Limitations of our study include the small number of patients and the retrospective nature of the analysis. On the other hand, our study is the only one outside the Italian experience to address the issue of second-line chemotherapy after triplet chemotherapy.

CONCLUSIONS

Our data support the feasibility of second-line chemotherapy in patients for whom a first-line triplet regimen has failed. Efficacy with the second-line chemotherapy in that situation is similar to the efficacy seen after a first-line doublet.

ACKNOWLEDGMENTS

The authors acknowledge the review and editorial support of Danial Haller MD.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Oncology Center, King Faisal Specialist Hospital and Research Center, and †Research Office, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia; ‡Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Ain Shams University, Cairo, and §Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Menoufia University, Shebin Elkom, Egypt; ‖Department of Biostatistics, Epidemiology and Scientific Computing, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia.

REFERENCES

1. Saltz LB, Cox JV, Blanke C, *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;343:905–14.
2. de Gramont A, Figer A, Seymour M, *et al.* Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938–47.
3. Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–42.
4. Douillard JY, Siena S, Cassidy J, *et al.* Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–705.
5. Van Cutsem E, Kohne CH, Lang I, *et al.* Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor *KRAS* and *BRAF* mutation status. *J Clin Oncol* 2011;29:2011–19.
6. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Colon Cancer.* Ver. 2.2018. Fort Washington, PA: NCCN; 2018. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf (free registration required); cited 20 May 2018]
7. Falcone A, Ricci S, Brunetti I, *et al.* on behalf of the Gruppo Oncologico Nord Ovest. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;25:1670–6.
8. Loupakis F, Cremolini C, Masi G, *et al.* Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609–18.
9. Fornaro L, Masi G, Loupakis F, Vasile E, Falcone A. Palliative treatment of unresectable metastatic colorectal cancer. *Expert Opin Pharmacother* 2010;11:63–77.
10. Ychou M, Rivoire M, Thezenas S, *et al.* A randomized phase II trial of three intensified chemotherapy regimens in first-line treatment of colorectal cancer patients with initially unresectable or not optimally resectable liver metastases. The METHEP trial. *Ann Surg Oncol* 2013;20:4289–97.
11. Mitry E, Ducreux M, Rougier P. Second-line irinotecan chemotherapy in the treatment of metastatic colorectal cancers: phase III trials [French]. *Bull Cancer* 1998;spec no:38–42.

12. Tournigand C, Andre T, Achille E, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229–37.
13. Cunningham D, Pyrhonen S, James RD, *et al.* Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413–18.
14. Fornaro L, Vasile E, Masi G, *et al.* Outcome of second-line treatment after first-line chemotherapy with the GONO FOLFOXIRI regimen. *Clin Colorectal Cancer* 2012;11:71–6.
15. Masi G, Marcucci L, Loupakis F, *et al.* First-line 5-fluorouracil/folinic acid, oxaliplatin and irinotecan (FOLFOXIRI) does not impair the feasibility and the activity of second-line treatments in metastatic colorectal cancer. *Ann Oncol* 2006;17:1249–54.
16. Bazarbashi S, Aljubran A, Alzahrani A, Mohieldin A, Soudy H, Shoukri M. Phase I/II trial of capecitabine, oxaliplatin, and irinotecan in combination with bevacizumab in first-line treatment of metastatic colorectal cancer. *Cancer Med* 2015;4:1505–13.
17. Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
18. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. 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* 2004;22:1209–14.
19. Van Cutsem E, Tabernero J, Lakomy R, *et al.* Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 2012;30:3499–506.
20. Bennouna J, Sastre J, Arnold D, *et al.* on behalf of the ML18147 study investigators. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29–37.
21. Koopman M, Antonini NF, Douma J, *et al.* Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. *Lancet* 2007;370:135–42.
22. Ducreux M, Malka D, Mendiboure J, *et al.* on behalf of the Fédération Francophone de Cancérologie Digestive (FFCD) 2000–05 collaborative group. Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011;12:1032–44.
23. Peeters M, Price TJ, Cervantes A, *et al.* Final results from a randomized phase 3 study of FOLFIRI ± panitumumab for second-line treatment of metastatic colorectal cancer. *Ann Oncol* 2014;25:107–16.
24. Tabernero J, Yoshino T, Cohn AL, *et al.* on behalf of the RAISE study investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol* 2015;16:499–508. [Erratum in: *Lancet Oncol* 2015;16:e262]
25. Tabernero J, Van Cutsem E, Lakomy R, *et al.* Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer* 2014;50:320–31.
26. Masi G, Salvatore L, Boni L, *et al.* Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Ann Oncol* 2015;26:724–30.