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Assessing the role of combination therapy in mCRC

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ABSTRACT

Doublet chemotherapy regimens (i.e. FOLFOX and FOLFIRI) have been shown to improve objective response rate and progression-free survival compared with fluoropyrimidine monotherapy, and may also improve overall survival (OS) in patients with metastatic colorectal carcinoma (mCRC). Further improvements in efficacy parameters can be achieved by the addition of a third cytotoxic agent, such as in FOLFOXIRI, or a targeted agent (e.g. bevacizumab or cetuximab) to doublet chemotherapy. Data suggests that two groups of patients, defined by clinical characteristics, may be particularly appropriate for aggressive combination treatment: patients at risk of rapid disease progression, and those with liver metastases, which may become resectable following such therapy. Furthermore, theoretical considerations suggest that use of combination regimens first-line increases the number of patients who are able to benefit from exposure to multiple agents, enabling improvement of overall survival for all patient groups.

First-line combination therapy can be envisaged as the first phase in a programme of treatment consisting of intensive induction therapy given for a limited period, followed by less intensive maintenance therapy given until disease progression. On disease progression, intensive therapy with either the induction regimen or another regimen may be considered to regain disease control. While accumulating data have established the efficacy of aggressive induction therapy, further research is required to determine the value and feasibility of maintenance therapy and post-progression reinduction therapy, together with the identification of the most appropriate agents to use in these settings.

1. Introduction

The benefits of combination chemotherapy over monotherapy in the first-line treatment of metastatic colorectal cancer (mCRC) have been demonstrated in numerous studies.[1–6] However, as the range of treatment options grows, with both chemotherapy and targeted agents to be considered, and an increasing number of patients are able to receive second- and third-line therapies, the question of how best to use these agents now needs to be addressed.

2. Efficacy of combination therapy

Large phase III key studies have clearly demonstrated the value of combination chemotherapy in the first-line setting (Table 1). Three studies comparing irinotecan-based combination regimens with 5-fluorouracil/folinic acid (5-FU/FA) monotherapy have demonstrated significant improvements in progression-free survival (PFS) with combination therapy.[1–3] Significant increases in overall survival (OS) were also seen in two of the studies. Similar

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Table 1 – Improved objective response rate (ORR), progression-free survival (PFS) or time to progression (TTP), and overall survival (OS) with the addition of irinotecan or oxaliplatin to 5-FU monotherapy

Study	N	ORR, %		PFS/TTP, months		OS, months	
		5-FU	Combination therapy	5-FU	Combination therapy	5-FU	Combination therapy
Irinotecan studies							
Saltz 2000 [1]	683	21	39, p < 0.001	4.3	7.0, p = 0.004	12.6	14.8, p = 0.04
Douillard 2000 [2]	387	31	49, p < 0.001	4.4	6.7, p < 0.001	14.1	17.4, p = 0.031
Kohne 2005 [3]	430	34	62, p < 0.0001	6.4	8.5, p < 0.0001	16.9	20.1, p = 0.2779
Oxaliplatin studies							
Giacchetti 2000 [4]	200	16	53, p < 0.001	6.1	8.7, p = 0.048	19.9	19.4
de Gramont 2000 [5]	420	22	51, p = 0.0001	6.2	9.0, p = 0.0003	14.7	16.2, p = 0.12
AIO trial [6]	242	23	48, p < 0.0001	5.2	7.8, p = 0.001	16.1	19.7, p = 0.19

improvements in PFS have been reported for oxaliplatin-based combination regimens over 5-FU monotherapy. [4–6] Differences in OS were, however, not statistically significant, due to the influence of salvage therapy on this outcome. All studies showed significant improvements in response rate for combination therapy.

Summarising the data from large randomised studies of fluoropyrimidine-based therapy in mCRC indicates a median OS for fluoropyrimidine monotherapy of approximately 12–14 months, [7–9] increasing to 14–20 months with doublet chemotherapy regimens (FOLFOX or FOLFIRI). [1–6,10,11]

Other approaches for combination therapy have also been shown to be effective, although for some strategies the evidence is less clear cut. Triple-agent chemotherapy may be a useful option for some patients, as studies suggest that it can further increase the response rate, PFS and OS over doublet chemotherapy. Two Phase III studies have reported numerical increases in objective response rate, PFS and OS with FOLFOXIRI compared with FOLFIRI as first-line therapy in patients with unresectable mCRC. [12,13] However, the results only reached statistical significance in one study, [12] and tolerability was generally worse with the triple regimen than with the doublets, suggesting that the place of this approach in treating mCRC has yet to be established.

With the development and approval of targeted agents, such as bevacizumab and cetuximab, a further option is the addition of such an agent to chemotherapy. Comparative phase III studies have shown advantages for the addition of a targeted agent to irinotecan- or oxaliplatin-based chemotherapy in both the first-line setting [14–16] and in patients refractory to irinotecan and/or oxaliplatin (Table 2). [17,18] Most notable has been the 28-month overall survival seen with FOLFIRI in combination with bevacizumab – a significant improvement upon the 23.1 months seen with FOLFIRI alone. [19,20] The degree of improvement in these trials, however, varied between the different combinations, indicating that further studies are needed to determine the optimal strategies for this approach.

The use of two targeted therapies, with or without chemotherapy has also been investigated, but appears to offer no advantage over currently approved regimens. In the CAIRO2 study, adding cetuximab to capecitabine/oxaliplatin/bevacizumab did not lead to improvements in response rates, PFS or median OS. [21] Similarly, the addition of panitumumab, another EGFR antibody, to a FOLFOX-bevacizumab or a FOLFIRI-bevacizumab backbone did not result in superior outcomes (Table 2). [22,23]

Further analyses have highlighted the role of molecular markers in identifying patients most likely to respond to these targeted treatment regimens. In the CRYSTAL study, the addition of cetuximab to infusional 5-FU/FA/irinotecan (FOLFIRI) showed a significant improvement in PFS compared with FOLFIRI alone in patients with wild-type *KRAS* (HR = 0.68, p = 0.0167), but no significant benefit for those with mutated *KRAS* (HR = 1.07, p = 0.75). [24] Similarly, in the phase II OPUS trial, cetuximab addition to a FOLFOX regimen was associated with significantly greater response rates (61% vs. 37%, p = 0.01) and median PFS (7.7 vs. 7.2 months, p = 0.02) compared with FOLFOX alone in patients with wild-type *KRAS*. [25] In patients with mutated *KRAS* in the OPUS trial, these outcome measures were actually better with FOLFOX alone than with FOLFOX plus cetuximab (response rate: 49% vs. 33%, p = 0.11; PFS: 8.6 vs. 5.5 months, p = 0.02), raising the possibility that cetuximab may have a negative effect in this patient group. The CAIRO2 study produced similar findings, with a significantly shorter PFS observed when cetuximab was added to the bevacizumab-containing regimen than without it in patients with mutated KRAS, but no significant difference observed between the treatment groups in wild-type *KRAS* patients. [21] Molecular markers, such as *KRAS*, are likely to play an increasing role in tailoring the treatment strategy for each individual patient.

3. Additional advantages of first-line combination therapy

Beyond the traditional endpoints of overall and progression-free survival in first-line, it is also useful to consider

Table 2 – Randomised phase III studies assessing the activity of targeted therapies added to chemotherapy in the management of mCRC

Study	Regimens	Setting	Phase, n	Outcomes [a]
Bevacizumab				
Hurwitz 2004 [14]	Bolus 5-FU/irinotecan +/– bevacizumab	1st line	Phase III, n = 813	Advantage for addition of bevacizumab: OS: 20.3 vs. 15.6 months, p < 0.001 PFS: 10.6 vs. 6.2 months, p < 0.001
NO16966 [16]	XELOX/FOLFOX +/– bevacizumab	1st line	Phase III, n = 1401	Advantage for addition of bevacizumab: PFS: 9.4 vs. 8.0 months, p = 0.0023
ECOG3200 [17]	FOLFOX +/– bevacizumab vs. bevacizumab monotherapy	Previously irinotecan/5FU/FA-treated patients	Phase III, n = 829	Advantage for addition of bevacizumab to FOLFOX: OS: 12.9 vs. 10.8 months, p = 0.0011 PFS: 7.3 vs. 4.7 months, p < 0.0001 RR: 22.7 vs. 8.6%, p < 0.0001 Bevacizumab monotherapy inferior to combination therapy: OS: 10.2 months PFS: 2.7 months ORR: 3.3%
BICC-C [19,20]	mIFL/FOLFIRI +/– bevacizumab	1st line	Phase III, n = 117 (period 2)	Advantage for addition of bevacizumab to FOLFIRI: OS: 28.0 vs. 23.1 months (Period 1) PFS: 11.2 vs. 7.6 months (Period 1) Advantage for FOLFIRI over mIFL (plus bevacizumab): OS: 28.0 vs. 19.2 months, p = 0.037 PFS: 11.2 vs. 8.3 months for mIFL, p = 0.004
Cetuximab				
CRYSTAL [15,24]	FOLFIRI +/– cetuximab	1st line	Phase III, n = 1217	Advantage for addition of cetuximab, All patients: OS: 19.9 vs. 18.6, p = 0.30 PFS: 8.9 vs. 8 months, p = 0.036 ORR: 46.9% vs. 38.7%, p = 0.005; KRAS wild-type cohort (n = 348): OS: 24.9 vs. 21.0, p = 0.22 PFS: 9.9 vs. 8.7, p = 0.017 ORR: 59.3% vs. 43.2%, p = 0.0025
EPIC [18]	Irinotecan +/– cetuximab	2nd/3rd line, Oxaliplatin-refractory patients	Phase III n = 1298	Advantage for addition of cetuximab (all patients): PFS: 4.0 vs. 2.6 months, p < 0.001 ORR: 16.4% vs. 4.2%, p < 0.001
Two targeted agents				
CAIRO2 [21]	Capecitabine/oxaliplatin/ bevacizumab +/– cetuximab	1st line	Phase III, n = 755	No benefit in OS and RR, and shorter PFS for addition of cetuximab: OS: 20.3 vs. 20.4 months, p = 0.21 PFS: 9.8 vs 10.7 months, p = 0.019 RR: 43.9 vs. 40.6%, p = 0.44
PACCE [22,23]	Chemotherapy (FOLFOX or FOLFIRI) + bevacizumab +/– panitumumab	1st line	Phase III	Shorter PFS for addition of panitumumab to FOLFOX-bevacizumab. With FOLFIRI, no benefit in PFS, but higher response rate for the addition of panitumumab

[a] PFS and OS figures represent median values reported.

the additional advantages combination therapy can have on broader treatment goals, such as rates of resection, in patients for whom surgery was not previously an option.

Enabling a patient to undergo resection significantly impacts on therapeutic outcome. Approximately 60% of patients with mCRC will develop liver metastases, for which surgical resection is the only chance of cure. The 5-year survival rate in patients with untreated liver metastases is virtually zero – this compares with a 20–35% chance of cure (10-year survival) in patients following resection. [26] Surgery is, however, a viable option for only about 15% of patients by time of diagnosis.

A recent study retrospectively analysed data from all published and presented trials reporting the objective response rate and rate of resection of metastases in patients with mCRC who were treated with systemic chemotherapy, showing that there seems to be a direct correlation between the objective response rate to first-line chemotherapy and the rate of resection. [27] Analysis of data for studies involving patients with metastases confined to the liver showed a strong and highly significant correlation between rates of liver resection and tumour response to chemotherapy ($r = 0.96$, $p = 0.002$). A weaker but also significant correlation between response rate and resection rate ($r = 0.74$, $p < 0.001$) was reported for studies involving nonselected patients (i.e. patients may have had other metastases). Since combination therapy achieves significantly higher response rates than fluoropyrimidine monotherapy, this is a convincing argument in favour of using aggressive combination chemotherapy in first-line. Interestingly, the correlation between higher response rates and a greater number of liver metastases resections was also seen with the addition of cetuximab to chemotherapy [15,28] and with triple chemotherapy compared with FOLFIRI. [12,13]

Another group of patients who are less likely to receive combination therapy are those with a poor performance status, related to tumour symptoms. Such patients are often excluded from clinical studies, but account for approximately one third of patients in clinical practice. However, a meta-analysis of data from nine phase III studies involving 6,286 patients reported that patients with a performance status (PS) of 2 benefited to a greater extent with combination therapy than with monotherapy, although these patients, when compared with those with good performance status (PS 0–1) had an inferior PFS (4.9 vs. 7.6 months, $p < 0.0001$) and OS (8.5 months vs. 17.3 months, $p < 0.0001$). [29] A further analysis of data from five Phase III studies comparing monotherapy with combination therapy showed that the benefit of combination therapy in terms of improved PFS and OS was similar for PS 2 and PS 0–1 patients (hazard ratio for monotherapy vs. combination therapy: PFS 0.78 (PS 2) vs. 0.72 (PS 0–1); OS 0.88 for PS 2 and PS 0–1, although severe (grade 3/4) gastrointestinal toxicity was significantly more frequent in poor PS patients. These data indicate that poor performance status patients can benefit from first-line combination therapy and should be considered for such treatment. However, this needs to be balanced against the potential for reduced tolerability in these patients. To date, there are few quality of life data available comparing monotherapy and combination therapy, particularly for patients with poor PS. In the FOCUS2 trial, which enrolled elderly and/or frail patients, approximately 30% of whom were PS 2, a significantly higher proportion of patients experienced improved quality of life over the first 12 weeks of treatment with monotherapy than with combination therapy. [30] Interestingly, however, the incidence of any grade 3 toxicity over this period did not differ significantly between the two treatment approaches. These findings, however, are perhaps not surprising, and it should be remembered that any gain in quality of life at the start of therapy may be forfeited upon tumour progression, when more intensive treatment may be required.

Using combination therapy first-line also provides access to multiple agents to a greater proportion of patients, since currently 30–40% of patients do not receive further therapy on disease progression. [31,32] Patients who are least likely to receive second-line therapy are those who do not respond to first-line therapy, and the likelihood of this is distinctly greater where monotherapy rather than combination therapy is used first-line. For example, in a phase III study comparing 5-FU monotherapy with 5-FU/irinotecan or 5-FU/oxaliplatin in first-line, 37% of patients receiving monotherapy failed to achieve tumour control compared with 22–25% for combination therapy, [31] while in a phase III study comparing first-line capecitabine with capecitabine/irinotecan, only 13% failed to achieve tumour control with combination therapy compared with 26% for monotherapy. [32] Thus, using combination therapy first-line increases the chances that an individual patient will be able to proceed to second-line therapy.

Receiving second-line therapy is important, as evidence suggests that overall survival is improved in patients who receive oxaliplatin, irinotecan and fluoropyrimidine during the course of their treatment. An analysis of major phase III studies has shown a significant correlation between median OS and the percentage of patients who received oxaliplatin, irinotecan and fluoropyrimidine during the course of their treatment, but not the percentage receiving any second-line therapy. [33] Thus increasing the proportion of patients treated second-line increases the likelihood that a patient will receive all three drugs. Trials examining sequential approaches versus combination treatment have shown the former do not lead to statistically inferior OS in the selected patient cohorts. It could be hypothesised, therefore, that the existing trend to lower OS may be related to the reduced proportion of patients receiving all three active drugs, rather than to the specific sequencing of therapy.

4. Combination therapy as part of a planned treatment strategy

While combination therapy may be an appropriate first-line therapy for most patients, this does not mean that it should necessarily be given for as long as the patient can tolerate such therapy or the tumour progresses. Rather, aggressive combination therapy can be envisaged as a form of “induction” therapy, given for a limited

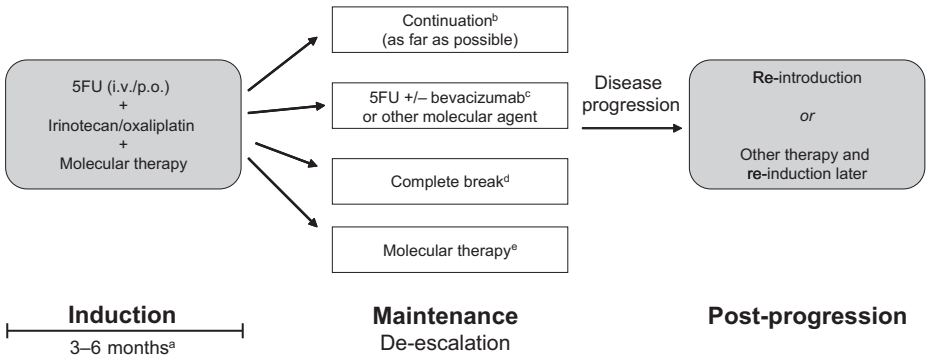

Fig. 1 – Suggested phases in the management of mCRC following initiation with aggressive induction therapy. Notes: (a) Three months treatment duration in the OPTIMOX trials; [31] **6 month (pre-planned) in the FOLFOXIRI trials;** [12,13] **6 months were also the median treatment duration in the Hurwitz, CRYSTAL and NO16966 trials.** [14–16] **(b) Standard option. (c) Proven strategies in retrospective analyses (bevacizumab) or in the OPTIMOX trials.** [33,34] **(d) Experimental approach. (e) In clinical trials.**

period with the aim of achieving disease control and/or maintaining the option for resection of metastases. According to this paradigm, induction therapy would be followed by less intensive "maintenance" therapy; more aggressive therapy could then be considered again on disease progression (Figure 1).

Induction therapy is likely to involve doublet chemotherapy (FOLFOX or FOLFIRI), possibly combined with a targeted agent, or triple-agent chemotherapy. As the optimal duration of induction therapy has not yet been defined and the question of whether further intensification is appropriate where a patient has failed to respond to the initial combination regimen remains unanswered, patients should be evaluated following the initial treatment and resection or ablation can then be performed if permissible. If these treatments are not an option, maintenance therapy or even a complete break from therapy could be considered.

The option for a pre-planned treatment de-escalation was demonstrated in the OPTIMOX-1 trial.[34] The role of a therapy break or a period of less intensive "maintenance" therapy after aggressive induction therapy has been investigated in the OPTIMOX2 study.[35] In this phase II study (n = 202), all patients received induction therapy with FOLFOX7. Patients then received either 5-FU/FA monotherapy followed by the reintroduction of FOLFOX7 on disease progression, or a therapy break and reintroduction of FOLFOX7 on progression. Maintenance therapy with 5-FU was found to be beneficial in comparison with having a chemotherapy-free interval, but the findings of this trial are likely to be influenced by the unusual criteria for reintroduction "at baseline tumour size". According to this management approach, a patient would continue with maintenance therapy with 5-FU until disease progression. At this stage, re-induction of aggressive therapy is needed. Such post-progression therapy could consist of either the same therapy used in the induction phase (which was stopped without progression) or an alternative combination regimen, if tolerated by the patient. The findings from the OPTIMOX2 study suggest that the use of maintenance therapy now warrants further investigation in phase III studies. The role of both cetuximab and bevacizumab in induction and/or maintenance therapy also warrants further exploration.

Further research is required to determine the optimum combinations and regimens to use at each stage in the management of patients with mCRC. Available data support the use of aggressive combination therapy as first-line therapy for mCRC, but there are few data to indicate the best options for maintenance and post-progression therapy, including molecular targeted agents. However, the availability of an increasing number of active agents should help improve the outlook for patients at all stages in their treatment, and the onus is on researchers to determine the best way to combine and use the powerful agents now available.

Recent findings suggest that molecular markers will play an increasingly important role in tailoring therapy, including treatment intensity, for individual patients.[36] Greater evaluation of changes in biomarkers may aid in monitoring disease progression and identifying the most appropriate course of treatment approach.

5. Conclusions

Accumulating data indicate that combination therapy may offer significant advantages over monotherapy in the management of mCRC. The increased response rate and duration of PFS seen with two or more agents in combination has been shown to lead to improved outcomes for patients who can tolerate more aggressive therapy. Use of combination therapy first-line as induction therapy, with the aim of bringing the tumour under control, is likely to be particularly appropriate for patients with symptomatic disease who are at risk of rapid deterioration. Combination therapy should, however, be considered as part of a planned treatment programme; some evidence suggests that maintenance treatment with fluoropyrimidine monotherapy could

form part of the treatment schedule following initial combination therapy. While the role of aggressive combination therapy as first-line induction therapy is becoming increasingly clear, the best treatment strategies following induction and on disease progression are yet to be established and warrant further investigation.

Conflicts of interest statement

Professor Arnold has received honoraria from Pfizer, and has been a speaker for Roche and sanofi-aventis and has received research funding and acted as a speaker for Amgen and Merck.

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References

1. Saltz LB, Cox JV, Blanke C, Rosen LS, *et al*. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;**343**(13):905-14.
2. Douillard JY, Cunningham D, Roth AD, *et al*. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;**355**(9209):1041-7.
3. Kohne CH, van Cutsem E, Wils J, *et al*. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol* 2005;**23**(22):4856-65.
4. Giacchetti S, Perpoint B, Zidani R, *et al*. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;**18**(1):136-47.
5. 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**(16):2938-47.
6. Grothey A, Deschler B, Kroening H, *et al*. Phase III study of bolus 5-fluorouracil (5-FU)/folinic acid (FA) (Mayo) versus weekly high-dose 24h 5-FU infusion/ FA + Oxaliplatin (OXA) (FUFOX) in advanced colorectal cancer (ACRC). *Proc Am Soc Clin Oncol* 2002;**21**:129a (abstract 512).
7. The Meta-Analysis Group In Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998;16(1):301-8.
8. Van Cutsem E, Twelves C, Cassidy J, *et al*. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large Phase III study. *J Clin Oncol* 2001;**19**(21):4097-106.
9. Hoff PM, Ansari R, Batist G, *et al*. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized Phase III study. *J Clin Oncol* 2001;**19**(8):2282-92.
10. 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**(2):229-37.
11. Goldberg RM, Sargent DJ, Morton RF, *et al*. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;**22**(1):23-30.
12. Falcone A, Ricci S, Brunetti I, *et al*. 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**(13):1670-6.
13. Souglakos J, Androulakis N, Syrigos K, *et al*. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised Phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006;**94**(6):798-805.
14. Hurwitz H, Fehrenbacher L, Novotny W, *et al*. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**(23):2335-42.
15. Van Cutsem E, Nowacki M, Lang I, *et al*. Randomized Phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. *J Clin Oncol* 2007;**25**(18S): abstract 4000.
16. Saltz LB, Clarke S, Diaz-Rubio E, *et al*. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/NO16966, a randomized Phase III trial in first-line metastatic colorectal cancer. *J Clin Oncol* 2007;**25**(18S): abstract 4028.
17. Giantonio BJ, Catalano PJ, Meropol NJ, *et al*. 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* 2007;**25**(12):1539-44.
18. Sobrero AF, Maurel J, Fehrenbacher L, *et al*. EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;**26**(14):2311-9.
19. Fuchs CS, Marshall J, Mitchell E, *et al*. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007;**25**:4779-4786.
20. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of

metastatic colorectal cancer: updated results from the BICC-C Study. *J Clin Oncol* 2008;**26**(4):689-90.
21. Punt CJ, Tol J, Rodenburg CJ, *et al*. Randomized Phase III study of capecitabine, oxaliplatin, and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). *J Clin Oncol* 2008;**26**(May 20 suppl): abstract LBA4011.
22. Hecht JR, Mitchell E, Chidiac T, *et al*. An updated analysis of safety and efficacy of oxaliplatin (Ox)/ bevacizumab (bev) +/– panitumumab (pmab) for first-line treatment (tx) of metastatic colorectal cancer (mCRC) from a randomized, controlled trial (PACCE). ASCO GI Cancer Symposium 2008: abstract 273.
23. Hecht JR, Mitchell E, Chidiac T, *et al*. Interim results from PACCE: Irinotecan (Iri)/bevacizumab (bev) ± panitumumab (pmab) as first-line treatment (tx) for metastatic colorectal cancer (mCRC). ASCO GI Cancer Symposium 2008: abstract 279.
24. Van Cutsem E, Lang I, D'Haens G, *et al*. KRAS status and efficacy in the CRYSTAL study: First-line treatment of patients with metastatic colorectal cancer (mCRC) receiving FOLFIRI with or without cetuximab. *Ann Oncol* 2008;**19**(8S): abstract 710.
25. Bokemeyer C, Bondarenko I, Hartmann JT, *et al*. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience. *J Clin Oncol* 2008;**26**(May 20 suppl): abstract 4000.
26. Tomlinson JS, Jarnagin WR, DeMatteo RP, *et al*. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007;**25**(29):4575-80.
27. Folprecht G, Grothey A, Alberts S, Raab HR, Kohne CH. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;**16**(8):1311-9.
28. Bokemeyer C, Bondarenko I, Makhson A, *et al*. Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study. *J Clin Oncol* 2007:**25**(18S): abstract 4035.
29. Goldberg RM, Kohne CH, Seymour M, *et al*. A pooled safety and efficacy analysis examining the effect of performance status (PS) on outcomes in nine first-line treatment (rx) trials (cts) of 6,286 patients (pts) with metastatic colorectal cancer (MCRC). *J Clin Oncol* 2007;**25**(18S): abstract 4011.
30. Seymour MT, Maughan TS, Wasan HS, *et al*. Capecitabine (Cap) and oxaliplatin (Ox) in elderly and/or frail patients with metastatic colorectal cancer: The FOCUS2 trial. *J Clin Oncol* 2007;**25**(18S): abstract 9030.
31. Seymour MT, Maughan TS, Ledermann JA, *et al*. Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;**370**(9582):143-52.
32. 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**(9582):135-42.
33. 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**(7):1209-14.
34. Tournigand C, Cervantes A, Figer A, *et al*. OPTIMOX1: a randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;**24**(3):394-400.
35. Maindrault-Goebel F, Lledo G, Chibaudel B, *et al*. Final results of OPTIMOX2, a large randomized phase II study of maintenance therapy or chemotherapy-free intervals (CFI) after FOLFOX in patients with metastatic colorectal cancer (MRC): a GERCOR study. *J Clin Oncol* 2007;**25**(18S): abstract 4013.
36. Braun MS, Richman SD, Quirke P, *et al*. Predictive biomarkers of chemotherapy efficacy in colorectal cancer: results from the UK MRC FOCUS trial. *J Clin Oncol* 2008;**26**(16):2690-8.