Systemic Treatment: Maintenance Compared with Holiday

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OVERVIEW

With the currently available cytotoxic and targeted drugs, metastatic colorectal cancer (mCRC) may be controlled by systemic treatment for a substantial period of time. However, many questions remain about the optimal use of drugs and duration of treatment. The feasibility of chemotherapy-free intervals has been studied in patients with mCRC treated with chemotherapy alone, but the results are conflicting. Current data show that oxaliplatin may be safely interrupted, but they do not allow a firm conclusion on the safety of a full treatment break of chemotherapy. For targeted therapy, continuous inhibition of intracellular signaling by prolonged administration would theoretically be beneficial for efficacy of treatment. Recent data support the use of maintenance treatment with chemotherapy and bevacizumab. No data on the optimal duration of treatment with anti-epidermal growth factor receptor (EGFR) agents are currently available.

Colorectal cancer is the second most common cause of cancer deaths worldwide, and its incidence is still increasing. Approximately 50% of the patients will eventually develop distant metastases, which may be treated with surgical resection and/or systemic treatment. The systemic treatment for mCRC has changed substantially over the past 20 years. Currently available drugs with proven efficacy can be classified as cytotoxic (i.e., classic chemotherapy) and targeted drugs (e.g., antibodies, small molecules). A large number of patients respond well to treatment, and many patients often ask for drug holidays. If this would not compromise survival, a drug holiday could increase quality of life (QoL) and would reduce health care costs. This paper will review the data on the optimal duration of treatment.[1]

CHEMOTHERAPY

Effective cytotoxic drugs in mCRC include the fluoropyrimidines, irinotecan, and oxaliplatin. These drugs are the backbone of systemic treatment of mCRC. There is no outright preference for either oxaliplatin or irinotecan in first-line combination schedules.[2] Retrospective studies have shown that the exposure to these three cytotoxics during the course of disease appears more important than their up-front combined use.[3-5] This has been confirmed by the results of subsequent prospective studies, of which the results showed no benefit for up-front combination treatment over sequential treatment starting with fluoropyrimidine monotherapy.[6,7] The choice between combination or sequential therapy may depend on several factors, such as tumor-related symptoms, potential resectability of metastases, and performance status.[8] As a result of the improved outcome of treatment, an increasing number of patients continue to do well on chemotherapy. Objective responses are usually achieved within the first 4 to 6 months of treatment.

Optimal Duration of Chemotherapy

The optimal duration of treatment is still a matter of debate, with no consensus on whether chemotherapy should be continued until disease progression or that a chemotherapy break is justified after the maximum response has been achieved. Furthermore, in case of intermittent treatment, it is unknown whether treatment should be resumed after a predefined interval or at disease progression. The feasibility of chemotherapy-free intervals has been studied, but the results are conflicting. In a Medical Research Council study, patients with stable disease or better after initial 12 weeks of chemotherapy were randomly selected to receive continuous or intermittent treatment, with resumption of the initial treatment on progression.[9] No survival difference was observed between the continuous and intermittent treatment arm. However, a large number of eligible patients refused to be randomly assigned or received unplanned treatment on progression. The availability of oxaliplatin introduced the problem of handling its most relevant toxic effect: the sensory neuropathy. The question arose whether intermittent treatment with oxaliplatin could reduce neurotoxicity without a detrimental effect on efficacy. The OPTIMOX1 study randomly selected previously untreated patients with mCRC to receive oxaliplatin in combination with 5-fluorouracil (5-FU)/leucovorin (LV; FOLFOX4) until progression or six cycles of FOLFOX7, followed by maintenance treatment with

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5-FU/LV for 12 cycles and then reintroduction of FOLFOX7 until progression.[10] There was no significant difference in median progression-free survival (9.0 vs. 8.7 months, hazard ratio [HR] 1.06, p = 0.47) or overall survival (19.3 vs. 21.2 months, HR 0.93, p = 0.49). In the intermittent treatment arm, a decreased incidence of toxicity was observed. Oxaliplatin was reintroduced in this treatment arm in 40% of the patients, in whom disease control was achieved in 70%. The authors concluded that oxaliplatin can be safely discontinued after six cycles. Next, the OPTIMOX2 trial was conducted to evaluate the strategy of discontinuation of all oxaliplatin-based chemotherapy compared with maintenance with 5-FU/LV after induction treatment with FOLFOX7.[11] In both arms, FOLFOX was reintroduced on disease progression, which, different from RECIST criteria, was defined as the time point at which tumors had regained their initial pretreatment size. The median progression-free survival was significantly prolonged in the maintenance arm as compared to the chemotherapy-free interval arm (8.6 vs. 6.6 months, respectively; HR 0.61, p = 0.017), but there was no significant difference in median overall survival (23.8 vs. 19.5 months; HR 0.88, p = 0.42). However, the trial was discontinued early because of the registration of bevacizumab, and therefore, no definite conclusions could be drawn. QoL was not evaluated in either OPTIMOX1 or OPTIMOX2.

The COIN trial also investigated intermittent compared with continuous chemotherapy.[12] Patients were randomly assigned to continuous oxaliplatin plus 5-FU/LV (FOLFOX) or capecitabine (CAPOX) or the same regimen given for 12 weeks with resumption of treatment on disease progression. Patients on intermittent treatment did spend less time on treatment, had substantially less toxicity, and scored better on several QoL symptom scales (but not on QoL global scales). Median overall survival in the continuous and the intermittent group was 15.8 and 14.4 months, respectively (HR 1.08, p = 0.60). Patients with elevated baseline platelet counts did perform poorly on intermittent treatment. The authors concluded that although noninferiority was not shown for intermittent treatment, chemotherapy-free intervals may be a treatment option for selected patients.

For irinotecan-based chemotherapy, two studies investigated whether continuous treatment was superior to a defined period of treatment. In a study by Lal et al, patients with stable disease or better after eight cycles of irinotecan in second line were randomly assigned to continuation or discontinuation of irinotecan until disease progression.[13] Only 17% of the patients who received second-line irinotecan were eligible for randomization, leaving 55 evaluable patients. There was no difference in median progression-free survival or overall survival between the two treatment arms. Furthermore, QoL was comparable in both arms. Although these results suggest that irinotecan can be safely discontinued after eight cycles, this study was underpowered. In the GISCAD study,[14] a total of 337 patients were randomly selected to receive intermittent treatment with FOLFIRI given in a 2-months-on 2-months-off schedule or continuous treatment with FOLFIRI—both until disease progression. The intermittent schedule was not inferior to continuous treatment for the primary endpoint of overall survival nor for progression-free survival or response rate. Furthermore, toxicity profiles were comparable, which is not surprising, as the toxicities of irinotecan are usually not cumulative. QoL was not evaluated in this study. The authors concluded that the intermittent use of FOLFIRI does not decrease its efficacy compared to its continued use.

These data show that QoL has been investigated in only a few studies that address the benefit of intermittent compared with continuous treatment. Although palliative chemotherapy by definition should primarily strive for the relief or the delay of symptoms, it has been shown that patients' main incentive to accept palliative chemotherapy in advanced CRC trials is prolongation of life rather than improvement of QoL.[15,16] With the observed small or absent differences between the treatment strategies in the aforementioned trials, data on QoL would therefore be helpful to discuss these strategies with patients.

KEY POINTS

- Maintenance treatment with capecitabine plus bevacizumab is effective.
- Current data do not support the use of bevacizumab monotherapy.
- The optimal treatment duration of anti-EGFR therapy is unknown.
- For chemotherapy, current data do not allow a firm conclusion on the safety of a full treatment break.
- Oxaliplatin can be safely discontinued and re-introduced at progression of disease.

TARGETED THERAPY

Targeted drugs with efficacy in mCRC include bevacizumab—an antibody against vascular endothelial growth factor A (VEGF)—and cetuximab and panitumumab—antibodies against the EGFR.[17] More recently, aflibercept—a recombinant fusion protein that blocks the activity of VEGF and placental growth factor[18]—and regorafenib—a multikinase inhibitor that blocks the activity of several protein kinases involved in tumor angiogenesis, oncogenesis, and the tumor microenvironment—have shown efficacy in patients with mCRC.[19] Bevacizumab and aflibercept are used in combination with chemotherapy, and the anti-EGFR antibodies may also be used as monotherapy. The currently available data support use of regorafenib only as monotherapy. Bevacizumab has shown survival benefits with fluoropyrimidine-containing chemotherapy and is currently considered as a standard first-line treatment option for patients with mCRC.[20-24] In second line, bevacizumab also improved progression-free survival and overall survival in combination with FOLFOX chemotherapy.[25] This latter study showed no benefit for bevacizumab monotherapy. The benefit of the anti-EGFR antibodies panitumumab and cetuximab is restricted to patients with a *RAS* wild-type tumor.[26] These antibodies have shown survival benefits with chemotherapy in first line[27-29] and

second line,[30] as well as monotherapy in late line.[31,32] Bevacizumab should not be combined with an anti-EGFR antibody.[33,34] In patients with *RAS* wild-type tumors, there appears no outright benefit for either bevacizumab or anti-EGFR antibody treatment in combination with first-line chemotherapy, although some studies show a yet unexplained survival benefit for starting with anti-EGFR treatment.[35-37] Aflibercept has shown efficacy in combination with FOLFIRI for patients with mCRC previously treated with an oxaliplatin-containing regimen, with or without bevacizumab.[18] For patients with mCRC whose disease progressed on these standard therapies, regorafenib increased overall survival compared with best supportive care.[19]

Optimal Duration of Targeted Therapy

Targeted therapy is characterized by the inhibition of intracellular signal transduction pathways that are relevant for tumor growth. RECIST criteria appear to be less suitable to evaluate its effects.[38,39] Theoretically, discontinuation of a drug that inhibits growth signals could result in tumor regrowth. This would favor its prolonged administration, which is, however, associated with a higher risk for toxicity and increased health care costs. The first data that supported the prolonged use of bevacizumab came from the NO16966 study.[22] In this study, first-line bevacizumab in combination with oxaliplatin-based chemotherapy showed only a modest increase in the primary endpoint of progression-free survival compared to chemotherapy alone (9.4 vs. 8.0 months; HR 0.83, $p = 0.0023$). However, compared to the initial registration study,[20] in the NO16966 study, a much lower percentage of patients received bevacizumab until disease progression or death. The relevance of this was shown by the results of a planned subset analysis of NO16966, taking into account only progression or death events occurring within 28 days from the last dose of any component of the study. In this analysis, the results of the chemotherapy-alone treatment were comparable with the overall analysis, but the median progression-free survival for chemotherapy plus bevacizumab was increased (HR 0.63). Further support for the benefit of prolonged use of bevacizumab comes from observational studies in which investigators could decide whether or not to continue bevacizumab after disease progression on first-line treatment, with a switch in the chemotherapy regimen.[40] Patients who continued bevacizumab beyond progression had increased overall survival. In an experimental model, bevacizumab beyond progression resulted in measurable changes in the tumor proliferation and microenvironment compared to discontinuation of bevacizumab.[41] The clinical observation was confirmed, albeit with a smaller benefit, in a prospective randomized study.[42] In this study, patients with mCRC with disease progression up to 3 months after discontinuing first-line chemotherapy plus bevacizumab were randomly assigned to second-line chemotherapy with or without bevacizumab. Median overall survival (primary endpoint) was significantly better in patients treated with bevacizumab (HR 0.81, $p = 0.0062$). The MACRO trial prospectively investigated the use of maintenance treatment of bevacizumab monotherapy in first line.[43] After six cycles of capecitabine, oxaliplatin, and bevacizumab, patients were randomly selected to receive either the continuous administration of this schedule or bevacizumab monotherapy. Noninferiority was not confirmed. The primary endpoint—median progression-free survival—was 10.4 compared with 9.7 months for the continuous and the monotherapy bevacizumab arm, respectively (HR 1.10, $p = 0.38$). Of note, patients were randomly selected at the start of first-line treatment, and therefore, the inclusion of patients who did not complete the first six cycles of induction therapy may have influenced the outcome. Furthermore, the efficacy of bevacizumab monotherapy may be questioned.[25,44] The SAKK 41/06 study assessed the efficacy of continuing treatment with single-agent bevacizumab after induction therapy with chemotherapy and bevacizumab.[45] In this phase III trial, patients with mCRC without disease progression after 4 to 6 months of standard first-line chemotherapy plus bevacizumab were randomly assigned to bevacizumab monotherapy or observation. Noninferiority of the primary endpoint time to progression (TTP) could not be demonstrated for treatment holidays compared with continuation of bevacizumab. Median TTP was 4.1 months for bevacizumab continuation compared with 2.9 months for no continuation (HR 0.74; 95% CI, 0.58 to 0.96). There was no difference in median OS between the treatment arms (HR 0.83, $p = 0.2$).

The CAIRO3 study of the Dutch Colorectal Cancer Group provided prospectively collected data on the optimal duration of treatment with chemotherapy and bevacizumab.[46] This study randomly selected patients with stable disease or better after six cycles of initial therapy to receive capecitabine, oxaliplatin, and bevacizumab and observation or maintenance therapy with continuous low-dose capecitabine and bevacizumab. Maintenance treatment significantly improved the first TTP (HR 0.43, $p < 0.0001$), the second TTP (primary endpoint) after reintroduction of capecitabine, oxaliplatin, and bevacizumab (HR 0.67, $p < 0.0001$), and the second TTP after any treatment following first progression (HR 0.68, $p < 0.001$). Toxicity of maintenance treatment was acceptable, and QoL did not deteriorate. Median overall survival was also improved by 3.5 months with maintenance treatment, but this was not statistically significant (HR 0.83, $p = 0.06$). However, the trial was not powered to demonstrate a benefit in overall survival. Notable survival benefits were observed in selected patient subgroups (e.g., patients with a complete or partial response as best response to induction treatment, and patients with synchronous metastatic disease and resected primary tumor). The main conclusion of CAIRO3 is that maintenance treatment with capecitabine plus bevacizumab is effective. The AIO 207 trial compared (1) maintenance treatment with a fluoropyrimidine plus bevacizumab, (2) bevacizumab alone, and (3) observation after induction treatment of 6 months with a fluoropyrimidine, oxaliplatin, and bevacizumab.[47] Maintenance treatment with bevacizumab alone was noninferior compared to chemotherapy plus bevacizumab for the primary endpoint: time to failure of treatment strategy. Noninferiority could not be demonstrated for no treatment. The main characteristics of

TABLE 1. Main Differences in Design of CAIRO3 and AIO 207 Trials

	CAIRO3	AIO 207
Patients	556	476
Design	Two-arm superiority	Three-arm noninferiority
Primary Endpoint	PFS2	TFS
Treatment Period Prior to Randomization	4.5 mo	6 mo
Exclusion of Patients Who Did Not Tolerate (Part of) Induction Treatment	Yes	No
Reintroduction of Oxaliplatin (%)	47%-60%	21%-45%

Abbreviations: PFS2, progression-free survival as measured by disease progression or death after reintroduction of capecitabine, oxaliplatin, and bevacizumab following either maintenance treatment with capecitabine plus bevacizumab or observation; TFS, time to failure of strategy, progression, or death after reintroduction of fluoropyrimidine, oxaliplatin, and bevacizumab following either maintenance treatment with fluoropyrimidine plus bevacizumab, bevacizumab alone, or observation.

CAIRO3 and AIO 207 are shown in Table 1. Although the design of AIO 207 was less straightforward than CAIRO3, the AIO 207 data support the use of fluoropyrimidine plus bevacizumab maintenance treatment.

For anti-EGFR treatment, only data from the NORDIC trial provide some insight on its optimal duration of treatment. This trial investigated treatment with first-line cetuximab with continuous or intermittent chemotherapy (fluorouracil, leucovorin, and oxaliplatin [FLOX]) compared with FLOX alone.[48] Cetuximab did not add a notable benefit to FLOX chemotherapy, neither given continuously nor given intermittently. No difference was found within subsets of patients with *KRAS* wild-type or mutant tumors; however, the study was not sufficiently powered for these subgroup analyses. The GERCOR DREAM study showed positive results for maintenance treatment with erlotinib—an EGFR tyrosine kinase inhibitor—in combination with bevacizumab.[49] After initial treatment with chemotherapy (FOLFOX, CAPOX, or FOLFIRI) and bevacizumab, patients with mCRC were randomly assigned to maintenance treatment with bevacizumab with or without erlotinib. The primary endpoint was progression-free survival on maintenance treatment, which was significantly better for patients treated with both drugs. However, the absolute benefit in median progression-free survival was only 1.1 month (HR 0.76, p = 0.010). Median OS was also significantly better for patients treated with maintenance treatment with bevacizumab plus erlotinib compared to bevacizumab monotherapy, 24.9 compared with 22.1 months, respectively (HR 0.79, p = 0.035). The NORDIC ACT trial had a similar design, randomly selecting patients to receive maintenance treatment with bevacizumab with or without erlotinib after induction treatment with chemotherapy (CAPIRI, CAPOX, FOLFIRI, OR FOLFOX).[50] The primary endpoint progression-free survival was not significantly different between the two arms, 5.7 compared with 4.2 months, respectively (HR 0.79, p = 0.12). Also median overall survival was comparable in both arms (HR 0.88, p = 0.51). Given the fact that the value of erlotinib has not been demonstrated in mCRC and that the efficacy of bevacizumab monotherapy is not supported by results of other trials, the implications of the DREAM and NORDIC ACT trial results for general practice are difficult to assess.

CONCLUSION

For the palliative treatment of patients with mCRC with chemotherapy alone, current data do not allow a firm conclusion on the safety of a full treatment break. The benefit of a drug holiday with a possible detrimental effect on outcome must be weighed against the toxicity and possibly decreased QoL that is associated with continuous treatment. In case of the use of combination chemotherapy with oxaliplatin, the chemotherapy may be reduced to fluoropyrimidine monotherapy during the maintenance phase, with reintroduction of oxaliplatin on progression. As to the use of targeted therapy, current data do not support the use of maintenance treatment with bevacizumab monotherapy. No data are available on the optimal duration of anti-EGFR antibody treatment. Data from the CAIRO3 and AIO 207 study support the use of maintenance treatment with chemotherapy and bevacizumab. Therefore, with bevacizumab being part of standard first-line treatment schedules, current data support the use of maintenance treatment with bevacizumab in combination with chemotherapy. Further studies should provide data on specific subgroups in which maintenance treatment is most effective.

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Relationships are considered self-held and compensated unless otherwise noted. Relationships marked "L" indicate leadership positions. Relationships marked "I" are those held by an immediate family member; those marked "B" are held by the author and an immediate family member. Institutional relationships are marked "Inst." Relationships marked "U" are uncompensated.

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References

1. Simkens LH, Koopman M, Punt CJ. Optimal duration of systemic treatment in metastatic colorectal cancer. *Curr Opin Oncol.* 2014;26:448-453.
2. Punt CJ. Irinotecan or oxaliplatin for first-line treatment of advanced colorectal cancer? *Ann Oncol.* 2005;16:845-846.
3. Grothey A, Sargent D, Goldberg RM, et al. 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;22:1209-1214.
4. Grothey A, Sargent D. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line. *J Clin Oncol.* 2005;23:9441-9442.
5. Koopman M, Punt CJ. Chemotherapy, which drugs and when. *Eur J Cancer.* 2009;45 Suppl 1:50-56.
6. 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;370:135-142.
7. 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;370:143-152.
8. Koopman M, Seymour MT, Punt CJ. The CAIRO and FOCUS studies: which lesson is to be learned? *Oncologist.* 2009;14:192-193.
9. Maughan TS, James RD, Kerr DJ, et al. Comparison of intermittent and continuous palliative chemotherapy for advanced colorectal cancer: a multicentre randomised trial. *Lancet.* 2003;361:457-464.
10. 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;24:394-400.
11. Chibaudel B, Maindrault-Goebel F, Lledo G, et al. Can chemotherapy be discontinued in unresectable metastatic colorectal cancer? The GERCOR OPTIMOX2 Study. *J Clin Oncol.* 2009;27:5727-5733.
12. Adams RA, Meade AM, Seymour MT, et al. Intermittent versus continuous oxaliplatin and fluoropyrimidine combination chemotherapy for first-line treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet Oncol.* 2011;12:642-653.
13. Lal R, Dickson J, Cunningham D, et al. A randomized trial comparing defined-duration with continuous irinotecan until disease progression in fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer. *J Clin Oncol.* 2004;22:3023-3031.
14. Labianca R, Sobrero A, Isa L, et al. Intermittent versus continuous chemotherapy in advanced colorectal cancer: a randomised 'GISCAD' trial. *Ann Oncol.* 2011;22:1236-1242.
15. de Kort SJ, Willemse PH, Habraken JM, et al. Quality of life versus prolongation of life in patients treated with chemotherapy in advanced colorectal cancer: a review of randomized controlled clinical trials. *Eur J Cancer.* 2006;42:835-845.
16. Koedoot CG, de Haan RJ, Stiggelbout AM, et al. Palliative chemotherapy or best supportive care? A prospective study explaining patients' treatment preference and choice. *Br J Cancer.* 2003;89:2219-2226.
17. Cunningham D, Atkin W, Lenz HJ, et al. Colorectal cancer. *Lancet.* 2010;375:1030-1047.
18. 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;30:3499-3506.
19. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381:303-312.
20. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335-2342.
21. Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol.* 2005;23:3706-3712.
22. Saltz LB, Clarke S, az-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol.* 2008;26:2013-2019.
23. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. *Lancet Oncol.* 2013;14:1077-1085.
24. Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. *J Clin Oncol.* 2010;28:3191-3198.
25. 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;25:1539-1544.
26. Douillard JY, Rong A, Sidhu R. RAS mutations in colorectal cancer. *N Engl J Med.* 2013;369:2159-2160.
27. Van Cutsem E, Peeters M, Siena S, et al. 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.* 2007;25:1658-1664.
28. 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;28:4697-4705.
29. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol.* 2009;27:663-671.
30. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol.* 2010;28:4706-4713.
31. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med.* 2008;359:1757-1765.
32. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol.* 2008;26:1626-1634.
33. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med.* 2009;360:563-572.
34. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol.* 2009;27:672-680.

35. Venook AP, Niedzwiecki D, Lenz HJ, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX) with bevacizumab (BV) or cetuximab (CET) for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum. *J Clin Oncol.* 2014;32:5s (suppl; abstr LBA3).

36. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:1065-1075.

37. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. *J Clin Oncol.* 2014;32:2240-2247.

38. Jain RK, Duda DG, Willett CG, et al. Biomarkers of response and resistance to antiangiogenic therapy. *Nat Rev Clin Oncol.* 2009;6:327-338.

39. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA.* 2009;302:2338-2344.

40. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: Results from a large observational cohort study (BRiTE). *J Clin Oncol.* 2008;26:5326-5334.

41. Heijmen L, Punt CJ, Ter Voert EG, et al. Monitoring the effects of bevacizumab beyond progression in a murine colorectal cancer model: a functional imaging approach. *Invest New Drugs.* 2013;31:881-890.

42. Bennouna J, Sastre J, Arnold D, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol.* 2013;14:29-37.

43. Diaz-Rubio E, Gomez-Espana A, Massuti B, et al. First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: the phase III MACRO TTD study. *Oncologist.* 2012;17:15-25.

44. Strickler JH, Hurwitz HI. Maintenance therapy for first-line metastatic colorectal cancer: activity and sustainability. *Oncologist.* 2012;17:9-10.

45. Koeberle D, Betticher DC, von Moos R, et al. Bevacizumab continuation versus no continuation after first-line chemotherapy plus bevacizumab in patients with metastatic colorectal cancer: a randomized phase III non-inferiority trial (SAKK 41/06). *Ann Oncol.* Epub 2015 Jan 20.

46. Simkens LH, Van Tinteren H, May A, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer, the phase 3 CAIRO3 study of the Dutch Colorectal Cancer Group (DCCG). *Lancet.* In press.

47. Arnold D, Graeven U, Lerchenmuller C, et al. Maintenance strategy with fluoropyrimidines (FP) plus bevacizumab (Bev), Bev alone, or no treatment, following a standard combination of FP, oxaliplatin (Ox), and Bev as first-line treatment for patients with metastastic colorectal cancer (mCRC): a phase III non-inferiority trial (AIO KRK 0207). *J Clin Oncol.* 2014;32:5s (suppl; abstr 3503).

48. Tveit KM, Guren T, Glimelius B, et al. Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol.* 2012;30:1755-1762.

49. Tournigand C, Chibaudel B, Samson B, et al. Maintenance therapy with bevacizumab with or without erlotinib in metastatic colorectal cancer according to KRAS: results of the GERCOR DREAM phase III trial. *J Clin Oncol.* 2013;31 (suppl; abstr 3515).

50. Johnsson A, Hagman H, Frodin JE, et al. A randomized phase III trial on maintenance treatment with bevacizumab alone or in combination with erlotinib after chemotherapy and bevacizumab in metastatic colorectal cancer: the Nordic ACT Trial. *Ann Oncol.* 2013;24:2335-2341.