

Bevacizumab in Association With de Gramont 5-Fluorouracil/Folinic Acid in Patients With Oxaliplatin-, Irinotecan-, and Cetuximab-Refractory Colorectal Cancer

A Single-Center Phase 2 Trial

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BACKGROUND: The aim of the current study was the investigation of the value of bevacizumab + 5-fluorouracil(5-FU)/folinic acid in patients with advanced colorectal cancers who have exhausted standard chemotherapy options. **METHODS:** The authors included 48 heavily pretreated patients (colon:rectum, 33:15; men:women, 23:25; median age, 63 years; range, 27-79 years) whose disease had progressed during or within an oxaliplatin-based first-line chemotherapy, an irinotecan-based second-line regimen, and a third-line treatment with cetuximab plus weekly irinotecan. Bevacizumab was given at a dose of 5 mg/kg. 5-FU/folinic acid was administered according to the de Gramont schedule. **RESULTS:** The response rate was 6.25%, and 30.4% of patients demonstrated stable disease as the best response. The median time to disease progression was 3.5 months (95% confidence interval [95% CI], 2.3-6.9 months), and the median survival time was 7.7 months (95% CI, 3.9-11.9 months). The most common grade 3 to 4 side toxicities (graded according to the National Cancer Institute Common Toxicity Criteria [version 2.0]) were: diarrhea (20.8%), fatigue (14.5%), and stomatitis (12.5%). Grade 3 to 4 hemorrhage occurred in 8 patients (16.6%), including 4 cases of bleeding in the gastrointestinal tract. Other relatively common adverse events such as hypertension, thrombosis, and bowel perforation were reported in 50%, 18.7%, and 4.16%, of patients respectively. **CONCLUSIONS:** The data from the current study suggest a modest but significant clinical benefit of bevacizumab + de Gramont schedule in heavily pretreated colorectal cancer patients. **Cancer 2009;115: 000-000. © 2009 American Cancer Society.**

KEY WORDS: bevacizumab, de Gramont, colorectal cancer, 5-fluorouracil, folinic acid.

Bevacizumab is a humanized immunoglobulin G1 murine antibody directed against all isoforms of vascular endothelial growth factor (VEGF)-A.¹ To our knowledge to date, it is the most clinically advanced

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monoclonal antibody (MoAb) targeting the VEGF signaling pathway and the only 1 currently approved for use in the treatment of metastatic colorectal cancer (MCRC).

A randomized phase 2 trial (AVF0780) investigated the safety and efficacy of 2 dose levels of bevacizumab in combination with 5-fluorouracil (5-FU)/leucovorin in patients with MCRC.²

The 2 treatment arms that included bevacizumab (at doses of 5 mg/kg or 10 mg/kg, respectively) resulted in higher risk ratios (40% and 24%, respectively) and a longer median time to disease progression (9 months and 7.2 months, respectively) and median overall survival (OS) (21.5 months and 16.1 months, respectively) compared with the control arm comprised of 5-FU/leucovorin alone (5.2 months and 13.6 months, respectively).

However, because higher clinical efficacy was noted in the 5-mg/kg arm compared with the 10-mg/kg arm, the 5-mg/kg dose of bevacizumab was chosen for further clinical study. Although bevacizumab was generally well tolerated, this trial identified several important safety signals, including an increased incidence of thromboembolic complications, hypertension, proteinuria, bleeding complications in the form of epistaxis, headache, fever, and rash. In general, however, these adverse events were either clinically insignificant or were easily managed.

Some phase 3 trials have confirmed the preliminary efficacy data published by Kabbinavar et al.²

In a pivotal randomized phase 3 study, previously untreated patients with advanced colorectal cancer (CRC) who received bevacizumab and weekly irinotecan plus bolus 5-fluorouracil/leucovorin (IFL) regimen had longer progression-free survival (PFS) (10.6 months vs 6.2 months; $P < .00001$) and survived significantly longer (20.3 months vs 15.6 months; $P = .00003$) than those receiving IFL chemotherapy alone plus placebo.³ The only adverse event that occurred with greater frequency with the anti-VEGF regimen was grade 3 (graded according to the National Cancer Institute Common Toxicity Criteria [version 2.0]) hypertension, which was managed effectively with oral medications.

In addition to being combined with either 5-FU/leucovorin or the bolus weekly IFL schedule, bevacizumab has been studied with oxaliplatin-based chemotherapy in the second-line setting. In the study published by Giantonio et al, patients with advanced CRC, who were previously treated with 5-FU-based therapy and irinotecan

for advanced or recurrent disease after adjuvant chemotherapy, were randomized to 1 of 3 treatment arms, including FOLFOX-4, FOLFOX-4 and bevacizumab, and bevacizumab alone.⁴

The results of this trial demonstrated that the addition of bevacizumab to oxaliplatin, 5-FU, and leucovorin improves the duration of survival for patients with previously treated MCRC that was refractory to irinotecan-based chemotherapy. In contrast to the randomized first-line trial, Chen et al failed to demonstrate any benefit in terms of response rate, finding that the association of bevacizumab and 5-FU/leucovorin was associated with rare objective responses.⁵

The main purpose of the current study was to evaluate the efficacy and safety of the association of bevacizumab and 5-FU/folinic acid in an extremely pretreated but homogeneous population of CRC patients.

MATERIALS AND METHODS

Patients

We considered patients eligible if they were aged >18 years and had stage IV, histologically confirmed, colorectal adenocarcinoma (grading determined according to the American Joint Committee on Cancer staging system).

Other criteria for eligibility were: an Eastern Collaborative Oncology Group (ECOG) performance status of <2 and adequate hematologic function (hemoglobin of >9 g/dL, neutrophil count of $>1500/\text{mm}^3$, and platelet count of $>100,000/\text{mm}^3$), renal function (serum creatinine <1.5 times the upper limit of normal), and liver function (total bilirubin <1.5 times the upper limit of normal range; aspartate aminotransferase and alanine aminotransferase <5 times the upper limit of normal).

To be eligible, patients must also have previously received 1 oxaliplatin-based chemotherapy regimen (capecitabine + oxaliplatin or FOLFOX IV regimen) and 1 irinotecan-based chemotherapy (leucovorin, 5-FU, and irinotecan [FOLFIRI] regimen or irinotecan alone) for at least 2 months. All patients were included if progression of disease was documented during receipt of these regimens or within 3 months thereafter.

The capecitabine plus oxaliplatin (XELOX) regimen was administered as follows: oxaliplatin at a dose of $70 \text{ mg}/\text{m}^2$ as continuous infusion for 12 hours (8:00 AM to 8:00 PM) on Days 1 and 8 plus chronomodulated

capecitabine at a dose of 1750 mg/m²/day orally (8:00 AM: 25% of total dose; 6:00 PM: 25% of total dose; and 11:00 PM: 50% of total dose) on Days 1 through 14 every 21 days.⁶

FOLFOX IV consisted of leucovorin (200 mg/m²/d) followed by a 5-FU bolus (400 mg/m²/d) and 22-hour infusion (600 mg/m²/d) for 2 consecutive days every 2 weeks with oxaliplatin at a dose of 85 mg/m² as a 2-hour infusion on Day 1.⁷

FOLFIRI consisted of irinotecan at a dose of 180 mg/m² as a 90-minute infusion on Day 1 and leucovorin at a dose of 400 mg/m² as a 2-hour infusion during irinotecan therapy, immediately followed by a 5-FU bolus of 400 mg/m² and 46-hour continuous infusion of 2.4 to 3 g/m² every 2 weeks.⁸

Three-weekly irinotecan was comprised of irinotecan at a dose of 350 mg/m². Finally, after progression to and an oxaliplatin-based and irinotecan-based chemotherapy, all patients were treated with cetuximab plus weekly irinotecan according to the following schedule: cetuximab was given at an initial dose of 400 mg/m², followed by weekly infusions of 250 mg/m², and irinotecan was administered weekly at the dose of 90 mg/m².⁹

Disease progression was documented by computed tomography (CT) or magnetic resonance imaging (MRI). At least 1 unidimensionally measurable lesion was required. Epidermal growth factor receptor (EGFR) expression in the primary tumor or in at least 1 metastatic lesion was performed. All the patients signed a consent form.

Study Design and Treatment

The current study was a single-center, phase 2 trial conducted from March 2004 to February 2006. Bevacizumab was given at the dose of 5 mg/kg. De Gramont chemotherapy was comprised of folinic acid (200 mg/m²/d) followed by a 5-FU bolus (400 mg/m²/d) and 22-hour infusion (600 mg/m²/d) for 2 consecutive days every 2 weeks.

Dexamethasone was given at the dose of 16 mg before each course. A standard antiemetic drug was always given in the premedication and in the following days, at the physician's discretion. All the patients were to be treated until disease progression or unacceptable toxic

effects occurred. In the case of disease progression, further anticancer treatments were allowed.

Tumor response was evaluated every 8 weeks with the use of consistent imaging techniques (CT or MRI). Assessment was performed by the investigators, who used Response Evaluation Criteria in Solid Tumors (RECIST).¹⁰

Toxic effects were assessed according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Modifications of bevacizumab dose were not planned, and the drug was stopped if grade 3 to 4 adverse events possibly related to bevacizumab were recorded. Modifications in the doses of the de Gramont regimen were made in cases of hematologic or nonhematologic toxic effects.

The present trial was approved by the institutional review board of our institution, and written informed consent was obtained from all participating patients.

Statistical Plan and Analysis

This study used Simon's Minimax 2-stage design¹¹ to test the null hypothesis that the true overall response rate was $\leq 5\%$ (which would not be clinically meaningful), as opposed to the alternative hypothesis that the true overall response rate was $\geq 10\%$. Up to 33 patients were planned for each cohort to assess the overall response rate with 85% power and $\alpha = .05$. If ≥ 2 objective tumor responses were observed in the cohort, an additional 15 patients would be enrolled onto that cohort in stage 2.

The primary endpoint was the rate of confirmed radiologic tumor response, as assessed by a local committee, in the intent-to-treat population. Secondary endpoints were the evaluation of time to disease progression, OS, safety profile, and the median time to response. All analyses were performed following an intent-to-treat analysis method. The time to disease progression was calculated as the period from the date of the initiation of treatment to the first observation of disease progression or to death from any cause within 60 days after the initiation of treatment or the most recent tumor assessment. The OS time was calculated as the period from the date treatment was initiated until death from any cause or until the date of the last follow-up, at which point data were censored. Time to disease progression and OS were both

determined by the Kaplan-Meier product-limit method.¹²

The difference in terms of time to disease progression and OS according to anticancer treatment delays or termination was evaluated by the log-rank test.¹³

The cutoff point for survival data was July 2007; for safety data, it was July 2006. SPSS statistical software (version 14.00; SPSS, Chicago, Ill) was used for statistical analysis. A *P* value of <.05 was considered to indicate statistical significance.

RESULTS

Between March 2004 and February 2006, 48 consecutive patients were enrolled in this single-center phase 2 trial. The main characteristics of the patient population are summarized in Table 1. The median number of courses administered was 5 (range, 2-13 courses). Forty-six patients were evaluated for the declared study efficacy endpoints and 48 for the safety analysis.

Efficacy Analysis

For the intent-to-treat analysis, 46 patients were evaluated for efficacy (2 patients were removed from the study early because the patients refused to continue anticancer therapy and were not evaluable for both time to disease progression and OS). The best objective responses were achieved as follows: 0 (0%) complete responses, 3 (6.5%; 95% confidence interval [95% CI], 1.9-6.5%) partial responses, 14 (30.4%; 95% CI, 22.5-41.7%) cases of stable disease, and 30 (65.2%; 95% CI, 44.7-71.8%) instances of disease progression. Therefore, the overall response rate was 6.5% (95% CI, 4.3-10.4%), and the disease control rate (partial response + stable disease) was 36.9% (95% CI, 25.8-44.8%). The median time to disease progression was 3.5 months (95% CI, 2.3-6.9 months), and the median OS time was 7.7 months (95% CI, 3.9-11.9 months).

No patients received any further anticancer treatment after they withdrew from therapy for disease progression.

Comparing patients with an ECOG performance status of 2 (25% of the total study population) with the others revealed no differences in terms of response rate. However, a slight but significant difference in terms of

Table 1. Baseline Characteristics of the Patients

Patient Characteristics	No. of Patients
Total	48 (100%)
Men/women	23/25 (47.2%/52.08%)
Age, y	
Median	68
Range	31-74
ECOG performance status	
0	19 (39.5%)
1	17 (35.4%)
2	12 (25%)
Primary tumor site	
Colon	33 (68.7%)
Rectum	15 (31.2%)
No. of metastatic sites	
1	12 (25%)
2	23 (47.9%)
≥3	13 (27.08%)
First-line regimen	
XELOX	26 (54.1%)
FOLFOX	22 (45.8%)
Second-line regimen	
FOLFIRI	38 (79.1%)
Three-weekly irinotecan	10 (20.8%)
Third-line regimen	
Cetuximab plus weekly irinotecan	48 (100%)

ECOG indicates Eastern Cooperative Oncology Group; XELOX, capecitabine plus oxaliplatin; FOLFOX, leucovorin followed by a 5-fluorouracil bolus; FOLFIRI, leucovorin, 5-fluorouracil, and irinotecan.

time to disease progression (2.6 months vs 3.8 months; *P* = .03) and OS (6.0 months vs 8.9 months; *P* = .007) was noted.

Moreover, we compared patients defined as responders to at least 1 (first-line, second-line, or third-line) anticancer treatment (39 patients) with nonresponders (7 patients), and did not identify any differences with regard to response rate, time to disease progression, or OS (data not shown).

Adverse Events

All patients were evaluated for safety analysis. Leukopenia and neutropenia were the most common hematologic toxicities, with an incidence of 54.1% and 64.5%, respectively. However, grade 3 to 4 neutropenia was recorded only in 6 patients (12.5%), and it did not cause any dose reductions or treatment discontinuation. No patients

Table 2. Adverse Events Related to Treatment Recorded in 48 Patients*

Side Effects	No. of Patients With Toxicity	
	All Grades	Grade 3-4
Hematologic		
Anemia	12 (25%)	5 (10.4%)
Leukopenia	26 (54.1%)	2 (4.1%)
Neutropenic	31 (64.5%)	6 (12.5%)
Thrombocytopenia	13 (27.08%)	3 (6.2%)
Nonhematologic		
Diarrhea	29 (60.4%)	10 (20.8%)
Fatigue	28 (58.3%)	7 (14.5%)
Oral mucositis	18 (37.5%)	6 (12.5%)
Nausea/vomiting	6 (12.5%)	0 (0%)
Liver toxicity	8 (16.6%)	2 (4.1%)
Hypersensitivity reaction	1 (2.08%)	0 (0%)

*Toxicity was according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

required the administration of granulocyte–colony-stimulating factor to recover after a neutropenic event. In 2 patients, neutropenic fever required hospitalization and infusion of antibiotics.

The most common nonhematologic toxicities were diarrhea (grade 3-4 in 20.8% of patients), fatigue (grade 3-4 in 14.5% of patients), and oral mucositis (grade 3-4 in 12.5% of patients). Safety results are summarized in Table 2.

Overall, 21 patients experienced a delay or change in dosing (of 5-FU) as a result of adverse events during the study. In particular, treatment was delayed in 10 patients because of bevacizumab-related toxicities, and the 5-FU dose was reduced or treatment delayed in 11 patients because of 5-FU-related toxicities.

Because of nonhematologic toxicities, the 5-FU dose was reduced (25% dose reduction) in 9 patients (18.7%). Because of the persistence of diarrhea in 2 of the 9 patients, 5-FU was discontinued, and treatment was continued with bevacizumab only. In only 2 patients, the 5-FU dose was reduced for neutropenic fever.

Grade 3 to 4 hemorrhage was reported in 8 patients (16.6%), with 4 events (8.3%) occurring in the gastrointestinal tract. The rate of venous thrombosis was 18.7%, with 3 (6.2%) cases of pulmonary thromboembolism reported; in all 3 cases, hospitalization was required with-

Table 3. Adverse Events Possibly Related to Bevacizumab Recorded in 48 Patients*

Side Effects	No. of Patients With Toxicity	
	All Grades	Grade 3-4
Hemorrhage		
Gastrointestinal	8 (16.6%)	4 (8.3%)
Nose	13 (27%)	3 (6.2%)
Other	4 (8.3%)	1 (2%)
Cardiovascular events		
Hypertension	24 (50%)	6 (12.5%)
Thrombosis/embolism	9 (18.7%)	3 (6.2%)
Arterial events		
Cardiac ischemia	0 (0%)	0 (0%)
Cerebral vascular events	1 (2%)	1 (2%)
Other adverse events		
Gastrointestinal perforation	2 (4.1%)	2 (4.1%)
Gastrointestinal fistula	5 (10.4%)	3 (6.2%)

*Toxicity was according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

out a fatal event. Data regarding adverse events possibly related to bevacizumab are summarized in Table 3.

Bowel perforation was rare (2 patients). In 1 patient, bowel perforation was diagnosed by a leak of oral contrast into the pelvis after a standard CT scan performed to restage disease after 2 months of treatment, but the perforation appeared to be contained and treated with intravenous antibiotics. In 3 cases, grade 3 to 4 fistulas were identified, with 1 fatal outcome after a surgical procedure needed to evacuate a local abdominal abscess (because of the urgency of the intervention, the interval between the last bevacizumab administration and surgery was inadequate: only 2 weeks). In the other 2 cases, surgery for the drainage of a pelvic abscess was required, with complete resolution of the clinical presentation after 35 days and 45 days, respectively.

Other than the previously mentioned 2 patients who decided to withdraw from therapy, only 4 patients were excluded from the study because of toxicity (the 2 patients who developed bowel perforations and 2 patients who developed fistulas).

Comparing patients with an ECOG performance status of 2 (25% of our total population) with the remaining patient population revealed no significant differences with regard to the incidence of adverse events.

Table 4. Influence of Treatment Delay or Change in Dosing on Disease Control*

Disease Control	PR+SD/Total (%)	P
No treatment delay or change in dosing	13/25 (52%)	.046
Treatment delay or change in dosing	4/21 (19.04%)	
TTP, median mo (95% CI)		
No treatment delay or change in dosing	4.00 (3.6-6.7)	.03
Treatment delay or change in dosing	2.00 (1.3-3.4)	
OS, median mo (95% CI)		
No treatment delay or change in dosing	9.0 (8.3-10.5)	.07
Treatment delay or change in dosing	4.5 (4.0-9.1)	

PR indicates partial response; SD, stable disease; TTP, time to disease progression; 95% CI, 95% confidence interval; OS, overall survival.

* Efficacy evaluated in 46 patients.

Influence of Dose Reduction/Delay of Treatment on Anticancer Efficacy

As stated earlier, a reduction of dose or a delay was required in 21 patients during treatment. We analyzed the efficacy of treatment in this subgroup, comparing it with the efficacy in the group of patients who better tolerated treatment. The response rate in the group with a treatment delay or change in dosing was lower than in the group without (19.04% vs 50%, respectively). This difference was statistically significant, with a *P* value of .046. Furthermore, a statistically significant difference also was recorded in terms of time to disease progression, with a median time to disease progression in the group of patients who required a treatment delay or change in dosing of 2 months versus 4 months in the group that did not (*P* = .03) (Table 4).

DISCUSSION

The efficacy of oncology drug regimens traditionally has been assessed by their potency to shrink existing tumors and, ideally, to prolong PFS and OS. Tumor response can be easily evaluated in small trials, and data from small trials may provide early evidence that an investigational agent warrants further testing. In clinical practice, the observation of a tumor response reassures the patient and the oncologist that the selected therapy is active in the malignant disease. The common use of tumor response criteria as a measure of efficacy in CRC has persisted despite multiple analyses demonstrating a weak correlation between tumor response and OS.¹⁴

This concept is supported even more by the introduction into oncology of novel drugs without intrinsic direct cytotoxic activity, such as antiangiogenic agents, suggesting that tumor response could be re-evaluated as a key marker of efficacy in patients with CRC.¹⁵

This theory is supported by the recent article by Grothey et al,¹⁵ in which the authors evaluated the survival benefit, both in terms of PFS and OS, associated with tumor response in 2 clinical trials, 1 containing bevacizumab in the experimental arm³ and 1 that did not.¹⁶

By this analysis, the authors clearly demonstrated that even patients with advanced CRC who did not achieve a response according to traditional criteria significantly benefited from being treated with the superior regimen and had the same magnitude of benefit as responders, regardless of whether this regimen was chemotherapy alone or included the antiangiogenic agent bevacizumab.

All these data support the hypothesis that disease control may be translated into survival benefit, even if patients in an experimental arm do not demonstrate an increase in response rate.

The data presented in the current trial indicate that treating heavily resistant CRC patients may be possible without severe toxicities, even if some secondary effects possibly related to bevacizumab have been recorded. This result is very interesting in particular because, to the best of our knowledge, the current study is the first to be performed in a population of patients treated with irinotecan-based, oxaliplatin-based, and cetuximab-based anticancer agents. Moreover, the identification of a disease

control rate of 36.9% appears to suggest some anticancer activity in this very heavily pretreated population. However, we must note that, to the best of our knowledge, no data from randomized clinical trials are actually available regarding the potential role of bevacizumab-based anticancer therapy in such a population and, most likely even more important, there are no data regarding quality of life in patients receiving this treatment versus patients who do not.

The key finding in this trial is that introducing a bevacizumab-based therapy in a very late phase of therapy in CRC patients may yet play a role in contributing to tumor control.

Moreover, the use of bevacizumab plus the de Gramont schedule as fourth-line therapy (as first bevacizumab use) could be reserved for patients for whom antiangiogenic therapy has previously been contraindicated for different reasons (such as instable blood hypertension, a recent episode of arterial thromboembolism, recent episode of bleeding, or recent bowel perforation). Once these contraindications have been resolved or stabilized, these patients may yet benefit from bevacizumab-based therapy. Moreover, there is a substantial difference reported by Chen et al⁵; in the current study, all patients had been previously treated with an additional third-line therapy (cetuximab-based therapy). This is a clear demonstration that bevacizumab-based therapy can produce an interesting rate of disease control, time to disease progression, and OS when administered to patients refractory to anti-EGFR MoAb therapy.

Preclinical studies have demonstrated that a murine MoAb against VEGF can inhibit the growth of human tumor xenografts when given alone or with chemotherapy.^{17,18} A humanized variant of this antibody (bevacizumab) has clinical activity in human cancer and increases survival when added to standard chemotherapy in patients with MCRC.³

Mice who received active antibody demonstrated a 90% reduction in tumor volume at the highest dose. These findings correspond well with the paradigm that tumors require neovascularization for growth.¹⁹

A consequence of this biologic action of VEGF in vivo could be that the blockage of VEGF-dependent angiogenesis leads to prolonged disease control in cancers of different histologies. On this basis, we found the rationale to propose to our heavily treated patients a palliative

therapy containing bevacizumab. Clearly, we understand that such treatment may be related to a significant increase in cost in this patient population. Therefore, a detailed cost analysis of bevacizumab-based anticancer treatment in heavily pretreated CRC patients could be very useful for understanding the economic impact of this treatment. Moreover, the safety profile also needs to be considered. The incidence of grade 3 to 4 hypertension in the phase 3 study of patients receiving bevacizumab plus chemotherapy as first-line anticancer therapy for advanced CRC by Hurwitz et al was 11%.³ Consequently, the incidence of this side effect overlapped the incidence reported in previous first-line clinical trials. The incidence of grade 3 to 4 hemorrhage was noted in 16% of patients in the current study versus 5% for the study by Chen et al⁵; this discrepancy could be, at least partially, ascribed to the finding that patients in the current study were more heavily pretreated.

One of the main concerns in this trial is represented by the percentage of patients who went on to receive fourth-line chemotherapy. According the results of the Medical Research Council FOCUS trial, approximately 24% to 27% of patients with metastatic CRC receive third or further lines of chemotherapy.²⁰ Considering the relatively recent introduction of biologic agents in the treatment of this patient population, this percentage is destined to increase in the coming years.

In conclusion, to our knowledge, the current study is the first to demonstrate some anticancer activity of bevacizumab + de Gramont schedule in patients who had received all other anticancer drugs available for the treatment of MCRC, with an acceptable safety profile.

Conflict of Interest Disclosures

The authors made no disclosures.

References

1. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res.* 1997;57:4593-4599.
2. Kabbinavar FF, Schulz J, McCleod M, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol.* 2005;23:3697-3705.
3. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for

- metastatic colorectal cancer. *N Engl J Med.* 2004;350:2335-2342.
4. 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.
 5. Chen HX, Mooney M, Boron M, et al. 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.* 2006;24:3354-3360.
 6. Santini D, Vincenzi B, La Cesa A, et al. Continuous infusion of oxaliplatin plus chronomodulated capecitabine in 5-fluorouracil- and irinotecan-resistant advanced colorectal cancer patients. *Oncology.* 2005;69:27-34.
 7. Andre T, Bensmaine MA, Louvet C, et al. Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. *J Clin Oncol.* 1999;17:3560-3568.
 8. 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;343:905-914.
 9. Vincenzi B, Santini D, Rabitti C, et al. Cetuximab and irinotecan as third-line therapy in advanced colorectal cancer patients: a single centre phase II trial. *Br J Cancer.* 2006;94:792-797.
 10. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92:205-216.
 11. Simon R. Optimal 2-stage designs for phase II clinical trials. *Control Clin Trials.* 1989;10:1-10.
 12. Kaplan E, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
 13. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer.* 1977;35:1-39.
 14. Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Re: A model to select chemotherapy regimens for phase III trials for extensive-stage small-cell lung cancer. *J Natl Cancer Inst.* 2001;93:399-401.
 15. Grothey A, Hedrick EE, Mass RD, et al. Response-independent survival benefit in metastatic colorectal cancer: a comparative analysis of N9741 and AVF2107. *J Clin Oncol.* 2008;26:183-189.
 16. 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;22:23-30.
 17. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med.* 2003;9:669-676.
 18. Dickson PV, Hamner JB, Sims TL, et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res.* 2007;13:3942-3950.
 19. Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med.* 1971;285:1182-1186.
 20. Seymour MT, Maughan TS, Ledermann JA, et al. Colorectal Clinical Studies Group. 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.