Treatment of Colorectal Cancer with and without Bevacizumab: A Phase III Study

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Key Words

Bevacizumab • Colorectal cancer

Abstract

Objective: The objective of this phase III trial was to compare chemotherapy combined with bevacizumab versus chemotherapy alone in the treatment of patients with advanced colorectal cancer. **Methods:** From September 2004 till September 2008, 222 treatment-naïve patients were enrolled and divided into 2 arms: 114 arm A patients were treated with leucovorin, 5-fluorouracil plus irinotecan in combination with bevacizumab, and 108 arm B patients were treated as above without bevacizumab. All patients were stage IV with histologically confirmed adenocarcinoma. **Results:** The median overall survival of arm A patients was 22.0 months (95% CI: 18.1–25.9) and 25.0 months (CI: 18.1–31.9) for arm B patients. There was no statistically significant difference between the 2 arms ($p = 0.1391$). No statistically significant difference between the 2 arms regarding the response rate was observed: partial response, 42 patients (36.8%) and 38 patients (35.2%) for arms A and B, respectively. Hematologic toxicity did not differ in the comparison of the 2 arms. Non-hematologic toxicity in arm A involved hypertension in 23 (20.2%) of the patients and proteinuria in 7 (6.1%); 3 patients experienced hemorrhage and 1 patient intestinal perfora-

tion. None of these side effects was observed in arm B patients. **Conclusion:** No statistically significant difference in median overall survival in patients with advanced colorectal cancer treated with bevacizumab plus a combination therapy (arm A) and those treated with the combination only, without bevacizumab (arm B), was observed.

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Introduction

Over the last years, new agents have been introduced for the treatment of metastatic colorectal cancer, the main objective being to prolong patient survival. One of these agents is bevacizumab (Avastin; Genetech Inc.), a monoclonal antibody, a diffusible endothelial-specific mitogen and an antibody to vascular endothelial growth factor (VEGF). VEGF is a secreted ligand that binds to specific receptors expressed by angioblasts and endothelial cells [1]. The VEGF receptor (VEGFR) family ligands, VEGF-1 and VEGF-2, are biologically related to angiogenesis, and VEGF-c and D-VEGFR-3 are associated with lymphangiogenesis. Tumor angiogenesis is complex in that many cell types and factors are involved: i.e. such as platelet-derived growth factor, b-fibroblast growth factor, VEGFA, HGF, TGF α and EGF [2]. The characteristics of

the tumor and its environment promote VEGF expression [3]. VEGF is overexpressed in a good number of human malignancies and it is considered to be an important regulator of physiologic and pathologic angiogenesis [4]. There are preclinical studies that have shown inhibition of human xenografts by this bevacizumab antibody. There are also clinical trials which have shown prolonged survival when bevacizumab is combined with chemotherapy [5] versus chemotherapy without bevacizumab. Bevacizumab decreases tumor size, improves chemotherapy delivery, suppresses new vessel growth and suppresses regrowth via the vessels' 'scaffolds' [6, 7]. Small tumors (1–2 mm) may be avascular (dormant), whereas large tumors are vascular with metastatic potential [8]. After a single infusion of bevacizumab alone, significant reductions (80%) in tumor vascular volume and density have been observed in clinical and preclinical models [6, 9]. In a number of published studies before bevacizumab was applied, the results of median survival were varied and this was attributed to the different cytotoxic agents used [10–18]. It is quite possible that the effectiveness of an antiangiogenic agent may not produce a response in every patient with metastatic disease but it may in certain subgroups which have a different profile based on wild-type or mutated genes. A retrospective trial showed the effectiveness of bevacizumab by subgrouping colorectal cancer testing K-ras, b-raf and p-53 wild-type or mutant genes [19]. Research has been done on antiangiogenic therapy biomarkers and their efficacy [5, 20–23].

The aim of the present study was to compare 2 groups of patients with advanced colorectal cancer, treated with chemotherapy plus bevacizumab (arm A) and without bevacizumab (arm B). The primary objective of the study was to determine survival and the secondary objective the response rate and toxicity.

Material and Methods

Patient Eligibility for Treatment with or without Bevacizumab

Eligibility for the study required histologically confirmed colorectal cancer classified as stage IV, including patients with single or multiple metastases. All patients had undergone prior surgery and the primary tumor was excised. Patients who had bidimensionally measurable disease on physical examination, X-rays, computed tomography, WHO performance status of 0–2, expected survival ≥ 12 weeks, adequate bone marrow reserves (leukocyte count $\geq 3,500 \mu\text{L}^{-1}$, platelet count $\geq 100,000 \mu\text{L}^{-1}$ and hemoglobin $\geq 10 \text{ g/dL}^{-1}$), adequate renal function (serum creatinine $\leq 1.5 \text{ mg/dL}^{-1}$) and liver function (serum bilirubin $\leq 1.5 \text{ mg/dL}^{-1}$) and serum transaminases ≤ 3 times of the upper limit of normal or ≤ 5 times the upper limit of normal in cases of liver

metastases and age ≥ 18 years were eligible. Patients with a second malignancy were also excluded. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines [24] and was approved by the hospital's institutional ethics review board. All patients gave their informed consent before entering the study.

Study Design

The study was designed as a single-center phase III randomized trial. It was powered to detect a difference in response rate and survival between the 2 arms. The sample size was initially planned to include 200 patients (100 in each arm) with an increase in the number of patients if a statistical difference of 5% between the 2 arms, with regard to response rate and to median survival, was not reached.

Treatment Plan

The patients were randomly assigned to arm A or arm B. Arm A patients were to be treated with leucovorin 200 mg/m^2 , 5-fluorouracil 500 mg/m^2 plus irinotecan 135 mg/m^2 and additionally bevacizumab 7.5 mg per kilogram of body weight, every 3 weeks. Arm B patients received the same treatment without bevacizumab. The treatment was given on day 1 within 4 h for the cytotoxic agents, plus 90 min for bevacizumab in arm A patients. The premedication included ondasetron 8 mg i.v. and dexamethasone 8 mg i.v. half an hour before the beginning of the treatment and repeated after the end of chemotherapy. The number of planned cycles was 8 and patients who achieved response or stable disease remained without treatment until disease progression. For patients with disease progression, irinotecan was replaced by oxaliplatin 135 mg/m^2 ; in both arms, the same percentage of patients with progressive disease was changed from irinotecan to oxaliplatin. Course delays of 1 week, due to adverse reactions, were permitted. Concomitant supportive therapies, such as granulocyte colony-stimulating factors or blood transfusions, antibiotics and erythropoietic agents were allowed according to the guidelines of the American Association of Clinical Oncology [25].

Baseline and Treatment Assessment and Evaluation

Before study entry, all patients underwent the following evaluations: medical history, physical examination, tumor measurement or evaluation, WHO performance status, ECG, full blood count, liver and kidney function tests and urinalysis. Staging was determined by chest and abdominal computed tomography, bone scan and occasionally magnetic resonance imaging. Blood count, blood urea and serum creatinine were measured before each treatment administration and 7 days after each course. During the treatment period, radiologic tests were conducted after 6 courses or at the end of the study and after any course if the clinical signs were indicative of disease progression. The disease status was determined according to the response evaluation criteria in solid cancer tumors. All patients in both arms were assessed for toxicity according to the National Cancer Institute Common Toxicity Criteria, version 2.0 [25]. A complete response was considered to be the disappearance of all measurable disease confirmed at 8 weeks at the earliest and a partial response a 30% decrease in all measurable disease, also confirmed at 8 weeks at the earliest. In stable disease, neither the partial response nor the progressive disease criteria were met; progressive disease was considered to be a 20% increase in tumor burden and no complete response, partial

Table 1. Patients' characteristics

	Arm A	Arm B
Patients	114	108
Age, years		
Median	67	62
Range	45–82	30–87
Gender		
Male	73 (64.0)	68 (63.0)
Female	41 (36.0)	40 (37.0)
Disease stage IV	114	108
Histology		
Adenocarcinoma	114	108
Moderate differentiation	109 (95.6)	105 (97.2)
Performance status		
0–1	85 (74.6)	78 (72.2)
2	29 (25.4)	30 (27.8)
Site of metastases		
Liver only	53 (46.5)	51 (47.2)
Lung only	12 (10.5)	8 (7.4)
Abdominal only	6 (5.3)	4 (3.7)
Multiple	43 (37.7)	45 (41.7)

Figures in parentheses are percentages.

Table 2. Response rate

	Arm A	Arm B
Total number of patients	114 (100)	108 (100)
Complete response	–	–
Partial response	42 (36.8)	38 (35.2)
Stable disease	50 (43.9)	50 (46.3)
Progressive disease	22 (19.3)	20 (18.5)

Figures in parentheses are percentages.

response or stable disease documented before increased disease [26]. A 2-step deterioration in performance status, a >10% loss of pretreatment weight or increasing symptoms did not by themselves constitute disease progression. However, the appearance of these complaints was followed by a new evaluation of the extent of the disease. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists and oncologists.

Statistical Design

The main endpoint for sample size determination was the survival rate. In order to detect a $\pm$ difference at a 3-year time point, 200 patients were needed so as to have 80% power at the 5% significance level. The study was designed as a group sequential trial. An interim analysis based on the O'Brien/Fleming boundary

Fig. 1. Kaplan-Meier survival distribution curve.

values was performed when 50% of the endpoint had been reached (100 deaths). The study would have ended prematurely if a significant difference in survival had been detected. The randomization of patients was performed according to the method of random permuted blocks within strata. Dynamic balancing was performed by the hospital. Pearson's χ^2 test was used for comparisons of categorical variables, or Fisher's exact test, when appropriate. The nonparametric Mann-Whitney test was applied for the comparison of continuous variables. Time-to-event analyses were performed where survival distribution was estimated by the Kaplan-Meier curve (fig. 1), and treatment comparison was made using the Log-rank test. All reported p values are 2-sided. A p value of <0.05 was considered significant.

Results

From September 2004 till September 2008, 222 patients were enrolled in this single-center trial. All patients (114 in arm A and 108 in arm B) were evaluable for survival, response rate and toxicity. The patients' characteristics are shown in table 1, which indicates gender, age, disease stage, histology, performance status and the site of metastases.

Response Evaluation

The response rate is shown in table 2. There were no complete responses in either of the 2 arms. In arm A, partial remission was achieved in 42/114 patients (36.8%) and in arm B in 38/108 patients (35.2%). With regard to stable disease, there was no statistically significant difference

between the 2 arms: 43.9 and 46.3% in arms A and B, respectively. No statistically significant difference was found between the 2 arms with respect to disease progression and response duration.

Survival Time

The median follow-up period was 36 months and the range 12–72 months. The survival time for arm A patients was 22 months (95% CI: 18.1–25.9) and of arm B patients 25.0 months (95% CI: 18.1–31.9) (table 3). No statistically significant difference was determined (Log-rank test p value = 0.1391).

Toxicity

The toxicity results are shown in table 4. Hematologic toxicity (leukopenia, anemia and thrombocytopenia) was observed and was similar in patients of both arms; one third of the patients had leukopenia and anemia. Thrombocytopenia was quite rare (4/114, 3.5%, and 5/108, 4.6%, in arms A and B, respectively). Nonhematologic toxicity differed between the 2 arms with regard to 4 side effects: hypertension was detected in 23/114 (20.2%) of the arm A patients treated with the combination with bevacizumab, proteinuria in 7/114 patients (6.1%) and hemorrhage in 3/114 (2.6%); 1 patient with abdominal spread of the disease and intestinal infiltration died from enteric perforation. Nausea/vomiting, diarrhea and asthenia were similar in both arms.

Discussion

The present study has shown no statistically significant difference in survival between the 2 arms. It is worth mentioning that no patient in arm A continued bevacizumab treatment after cytotoxic treatment had been stopped. In other words, no bevacizumab maintenance treatment was given. According to another trial, the overall survival was 25.1 months and the median survival of the group treated with bevacizumab beyond progression was 31.8 months, while in the group without bevacizumab beyond progression the median survival was 19.9 months [23]. Maintenance treatment is still under investigation. It is questionable whether an agent without a cytotoxic effect may prolong survival. It has been pointed out [27] that a high response rate would have suggested that bevacizumab is a chemotherapy-sensitizing agent through multiple lines of chemotherapy. By contrast, no increase in response rate accompanied by a prolonged overall survival may determine that this agent is cyto-

Table 3. Survival time (months), Log-rank test p value = 0.1391

Treatment	Patients	Median	95% CI
Arm A (chemotherapy with bevacizumab)	114	22.0	18.1–25.9
Arm B (chemotherapy without bevacizumab)	108	25.0	18.1–31.9
Total sample	222	24.0	20.4–27.6

Table 4. Toxicity

	Arm A	Arm B
Hematologic		
Leukopenia	39 (34.2)	39 (36.1)
Anemia	36 (31.6)	36 (33.3)
Thrombocytopenia	4 (3.5)	5 (4.6)
Nonhematologic		
Nausea/vomiting	40 (35.1)	36 (33.3)
Diarrhea	17 (15.0)	19 (17.6)
Asthenia	29 (25.4)	30 (27.8)
Cardiotoxicity	–	–
Nephrotoxicity	–	–
Neuropathy	–	–
Hypertension	23 (20.2)	–
Proteinuria	7 (6.1)	–
Enteric perforation	1 (0.9)	–
Hemorrhage	3 (2.6)	–
Congestive cardiac failure	–	–
Arterial thrombosis	–	–

Figures in parentheses are percentages.

static [28]. In addition, there is no evidence that bevacizumab as a single agent is effective in patients with metastatic colorectal cancer, especially in refractory tumors [20]. Certain controversies have been observed in the data of previous studies with respect to median overall survival. A recently published study of 1,401 patients divided into subgroups, given bevacizumab in combination with oxaliplatin-based chemotherapy or oxaliplatin-based chemotherapy combined with a placebo, showed no statistically significant difference and no superiority of the group that received bevacizumab, $p = 0.077$ [21]. Only the progression-free survival of 9.4 months for the group that had bevacizumab versus 8 months for the group that had the placebo showed a statistically significant difference ($p = 0.0023$). Two other trials, by comparison, have shown the statistical superiority of the bevacizumab arm [5, 29].

In our study the median survival of the arm which received bevacizumab was 22 months and this is similar to one of the aforementioned studies [21] where the median overall survival was 21.3 months. There is another difference between our study and the one just mentioned, a difference that concerns the median overall survival of patients treated only with cytotoxic chemotherapy: our median survival of the arm which did not receive bevacizumab was 25 months, while in the aforementioned study it was 19.9 months. In another study, 19.8 months was also achieved for the median overall survival in patients treated with XELOX and 19.6 months in another group treated with FOLFOX-4 [30]. The longer survival rate observed in our trial was also reported in another study of 342 patients. The median overall survival was also 25 months. The responders of that study had a median survival of 30 months and the patients with stable disease 19 months [31]. In other words, the median survival of the patients with stable disease in the latter study is the same

as was the overall median survival of other previously mentioned studies. With reference to stable disease and not progressive disease, this stability may take place while patients are on treatment or when they are without any treatment. Can this condition of stable disease be interpreted that there is no neoangiogenesis taking place for bevacizumab to have effectiveness? This condition of disease stability could be classified as a dormant tumor [8]. The study that examined such biomarkers as K-ras, b-raf and p-53 in relation to the treatment effect, with or without bevacizumab [19], concluded that the survival benefit with the addition of bevacizumab in the treatment of metastatic colorectal cancer is independent of the status of the aforementioned biomarkers.

No statistically significant difference was observed in median overall survival in patients with advanced colorectal cancer treated with bevacizumab plus a combination therapy (arm A) and those treated with the combination only, without bevacizumab (arm B).

References

- Ferrara N, Davis-Smyth T: The biology of vascular endothelial growth factor. *Endocr Rev* 1997;19:4–25.
- Ferrara N, Kerbel RS: Angiogenesis as a therapeutic target. *Nature* 2005;438:967–974.
- Presta LG, Chen H, O'Connor SJ, Chisholm VY, Meng G: 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.
- Jubb AM, Pham TQ, Handy AM, Frantz GD, Peale FV, Wu TD, Koeppen HW, Hillan KJ: Expression of vascular endothelial growth factor, hypoxia-inducible factor 1 α and carbonic anhydrase IX in human tumours. *J Clin Pathol* 2004;57:504–512.
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hamsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.
- Willet CG, Boucher Y, di Tomaso E, Duda DG, Munn LL, Tong RT, Chung DC, Sahani DV, Kalva SP, Kozin SV, Mino M, Cohen KS, Scadden DP, Hartford AC, Fischman AG, Clark JW, Ryan DP, Zhu AX, Blaszkowsky LS, Chen HX, Shellito PC, Lauwers GY, Jain RK: Direct evidence that VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Natl Med* 2004;10:145–147.
- Gerber HP, Ferrara N: A specific approach to VEGF inhibition. *Cancer Res* 2005;65:671–680.
- Berger MM: Fluorescent inhibitors for IspF. *Nature* 2002;418:785–789.
- Yuan Y, Sherman DR, Barry CE: Exploring drug-induced alteration in gene expression. *Proc Natl Acad Sci USA* 2002;14321–14326.
- Rougier P, van Cutsem E, Bajetta E, Niederle N, Possinger K, Labianca R, Navarro M, Morant R, Bleiberg H, Wils J, Awad L, Herait P, Jacques P: Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;352:1407–1412.
- Cunningham D, Pyrhonen S, James RD, Punt CJ, Hickish TF, Heikkila R, Johannesen TB, Starkhammar H, Topham CA, Awad L, Jacques C, Herait P: Randomized trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;352:1413–1418.
- Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggivolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL, Levi F: Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as a first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;18:136–147.
- Stathopoulos GP, Stergiou GS, Golematis B, Thalassinou N, Fillipakis M: Effects of adriamycin 5-fluorouracil and mitomycin-C combination chemotherapy in advanced colorectal cancer. *Oncology* 1995;54:306–309.
- De Grammont A, Bosset JF, Milan C, Rougier F, Bouche O, Etienne P-L, Morvan F, Louvet C, Guillot T, Francois E, Bedenne L: Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus infusion for advanced colorectal cancer: a French Intergroup study. *J Clin Oncol* 1997;15:808–815.
- Douillard J-Y, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandi KP, Iveson T, Carmichael J, Alaki M, Gruia G, Awad L, Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicenter randomized trial. *Lancet* 2000;355:1041–1047.
- De Gramont A, Figer A, Seymour M, Hommerin F, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F, Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;18:2938–2947.

- 17 Scheithauer W, Kornek GV, Raderer M, Schüll B, Schmid K, Kovats E, Schneeweiss B, Lang F, Lenaver A, Depisch D: Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2003;21:1307–1312.
- 18 Souglakos J, Mavroudis D, Kakolyris S, Kouroussis CH, Vardakis N, Androulakis N, Angelaki S, Kalbakis K, Tsetis D, Athanasiadis N, Samonis G, Georgoulas V: Triplet combination with irinotecan plus oxaliplatin plus continuous-infusion fluorouracil and leucovorin as first-line treatment in metastatic colorectal cancer: a multicenter phase II trial. *J Clin Oncol* 2002;20:2651–2657.
- 19 Ince WL, Jubb AM, Holden SN, Holmgren EB, Tobin P, Sridhar M, Hurwitz H, Kabbinavar F, Novotny WF, Hillan KJ, Koeppe H: Association of K-ras, b-raf and p-53 status with the treatment effect of bevacizumab. *J Natl Cancer Inst* 2005;97;13:981–989.
- 20 Giantonio Bruce J, Katalano PJ, Meropol NJ, O' Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AIB III: Bevacizumab in combination with oxaliplatin, fluorouracil and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group study E 3200. *J Clin Oncol* 2007;25: 1539–1544.
- 21 Saltz LA, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang T-S, Rivera F, Couture F, Sirzén F, Cassidy J: 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.
- 22 Sandler A, Herbst R: Combining targeted agents: blocking the epidermal growth factor and vascular endothelial growth factor pathways. *Clin Cancer Res* 2006;12:4221s–4425s.
- 23 Grothey A, Sugrue MM, Pardie DM, Dong W, Sergeant D, Hedrick E, Kozloff M: 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.
- 24 ICH Efficacy EG (R1) Good Clinical Practice Consolidated Guidelines. <http://ich.org/cache/compo/475–175.html>.
- 25 Arbus SG, Ivy SP, Setser A: The Revised Common Toxicity Criteria: Version 2.0. <http://ctep.info.nih.gov>.
- 26 Therasse P, Arbus SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, Van Oosterom AT, Christian MC, Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors, European Organisation for Research and Treatment of Cancer, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
- 27 Carmeliet P: VEGF as a key mediator of angiogenesis in cancer. *Oncology* 2005;69 (suppl 3):4–10.
- 28 Ellis LM, Haller DG: Bevacizumab beyond progression: does this make sense? Editorial. *J Clin Oncol* 2009;3:1–3.
- 29 Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E: Phase II, randomized trial comparing bevacizumab plus fluorouracil (5-fluorouracil)/leucovorin (LV) with 5-fluorouracil/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;21:60–65.
- 30 Cassidy J, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang T-S, Rivera F, Couture F, Sirzén F, Saltz L: Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;26:2006–2012.
- 31 Stathopoulos GP, Rigatos SK, Malamos NA, Stathopoulos JG, Thallasinou P, Papazachariou E, Antoniou F, Kondopodis E, Xyntroulas G: Long-term survival of patients with advanced colorectal cancer may not be due to the response to chemotherapy. *Oncology Rep* 2004;12:1295–1300.