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Phase II Trial of Irinotecan and Raltitrexed in Chemotherapy-naive Advanced Colorectal Cancer

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Abstract. *Background: Irinotecan and raltitrexed are active agents in advanced colorectal cancer (ACC) and preclinical data suggest a remarkable synergistic activity. Phase I studies demonstrated that single-agent full dose of both drugs can be administered with moderate toxicity. The aim of this phase II trial was to assess the activity and tolerability of the combination in untreated ACC. Patients and Methods: Forty-eight patients entered the trial and received irinotecan 350 mg/m^2 d.1 and raltitrexed 3 mg/m^2 d.2, every three weeks. After recruitment of the first 16 patients, grade III-IV toxicity was observed in 6 patients (38%). Therefore, an amendment reduced by 15% the dose of both drugs (irinotecan 300 mg/m^2, raltitrexed 2.6 mg/m^2). Results: A total of 290 cycles were administered (range 1-18, median number 6). According to intention-to-treat analysis, the overall response rate was 27% (95% confidence interval 16%-42%), including 3 complete responses and 10 partial responses. The median duration of response was 10 months, while median progression-free survival and overall survival were 5 and 14 months, respectively. In the first 16 patients, the main toxicities were grade III-IV diarrhea in 25% and grade III-IV neutropenia in 13%. In the subsequent 32 patients, they were grade III-IV diarrhea in 34% and grade III neutropenia in 6%. Two toxic deaths occurred. Conclusion: The combination irinotecan-raltitrexed is an active regimen, but the significant incidence of side-effects requires accurate patient selection and, eventually, new schedules.*

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Historically, in the treatment of advanced colorectal cancer (ACC), 5-Fluorouracil (5-FU) has been the standard cytotoxic agent over the past 30 years. Attempts have been made to enhance its efficacy with new treatment combinations and schedules, in order to produce a higher response rate, with longer progression-free survival and overall survival of patients with advanced disease.

The efficacy of irinotecan (CPT-11) in combination with 5-FU as a first-line chemotherapy in ACC was demonstrated in two large randomized phase III trials, that included more than 1,000 patients. Saltz *et al*. (1) have published their experience using a combination regimen of CPT-11/5-FU-bolus administration/folinic acid (FA), compared with the Mayo Clinic schedule. Douillard *et al*. (2) evaluated the combination CPT-11/5-FU-infusional schedule/FA *versus* the same 5-FU-infusional /FA regimen. Both demonstrated that the combination CPT-11/5-FU/FA was superior in response rates, time to progression and survival.

However, there are some limitations to the use of 5-FU-based-regimens: the infusional administration requires a central line positioning that might affect the quality of life of a metastatic colorectal cancer patient and that might increase infective and thromboembolic risk. On the other hand, bolus 5-FU requires frequent hospital visits and seems to be aggravated by a higher toxicity rate, as investigated recently by Bouzid *et al*. (3). Moreover, it is widely known that the use of 5-FU is contraindicated in patients with concomitant ischaemic heart disease or low levels of dihydropyrimidine dehydrogenase (DPD), the initial and rate-limiting enzyme in the metabolism of 5-FU (4, 5).

Raltitrexed, a specific thymidilate synthase inhibitor, is a potential alternative to 5-FU. Its clinical activity is comparable to that of infusional or bolus 5-FU regimens, with a potential advantage in terms of patient convenience, since it is administered as a short intravenous infusion once every 3 weeks (6-8).

Because of the different mechanism of action and the clinical activity of irinotecan and raltitrexed as single agents,

pre-clinical studies have suggested a sequence-dependent synergy for the combination. The synergy was maximal when irinotecan was administered 24 hours before raltitrexed (9). Three recent phase I studies demonstrated that single-agent full-dose irinotecan and raltitrexed should be administered in patients with refractory colorectal cancer. The recommended dosages for phase II trials were 350 mg/m^2 for irinotecan and 3 mg/m^2 for raltitrexed, administered on the same day or sequentially on days 1 and 2 every 3 weeks (10-12).

Based on the results of these preliminary studies, we investigated the tolerability and activity of the combination at the maximum tolerated dose (MTD) suggested in phase I studies, on a 2-day schedule of administration. The regimen was administered as first-line treatment in patients with advanced or metastatic colorectal cancer.

Patients and Methods

Patient population. Patients with histologically confirmed metastatic colorectal cancer, untreated with chemotherapy for advanced disease, were eligible for the study. The required wash-out period from previous adjuvant chemotherapy was a minimum of 12 months. Additional eligibility criteria included: ECOG performance status (PS) ≤2; age ≥18 years; a life expectancy of at least 3 months; measurable metastatic lesions that had not been previously irradiated; and adequate bone marrow, renal and hepatic function [neutrophil count ≥1,500/mm^3, platelet count >100,000/mm^3, serum creatinine ≤1.5 mg/dl, serum bilirubin ≤1.5 upper limit of normal (ULN), transaminase levels ≤2.5 ULN in the absence of liver metastases or ≤5 ULN in the presence of liver metastases]. Patients were ineligible for study entry if there was a history of serious concomitant disease, prior malignancy (except adequately treated basal cell skin cancer or *in situ* carcinoma of the uterine cervix), presence of central nervous system metastases, pregnancy, breast-feeding and inadequate contraceptive precautions.

The protocol was submitted and approved by the local ethical committee and written informed consent for the study was necessary before patient registration onto the study.

Treatment schedule. Irinotecan was administered intravenously on day 1, at a dose of 350 mg/m^2, over 30 minutes; raltitrexed was administered 24 hours later at a dose of 3 mg/m^2, in a 15-minute intravenous infusion. Courses were repeated every 21 days until progression of disease, patient's refusal or unacceptable toxicity. Specific antiemetic prophylaxis was based on 5-HT$_3$ receptor antagonists. All patients were given Atropine 0.25 mg subcutaneously before the CPT-11 administration, to prevent cholinergic syndrome.

Treatment evaluation. Baseline evaluation included assessment of hepatic, hematopoietic and renal functions, CEA and CA 19-9 levels, ECG, chest X-ray/computerized tomography (CT) and abdominal-pelvic CT scan. After 3 cycles of treatment, assessment of tumor response was performed by adequate instrumental examination consistent with the baseline evaluation. Disease response was evaluated according to WHO criteria (13).

Table I. *Patients' characteristics: median age 63 (range 46-77 years).*

Characteristic	N° of patients	%
Sex		
Male	32	67
Female	16	33
Performance status		
0	25	52
1	17	36
2	6	12
Primary tumor site		
Colon	32	67
Rectum	16	33
Prior treatment		
Surgery	48	100
Adjuvant CT	20	42
Relapse-free interval		
Absent	22	46
Present	26	54
Site of disease		
Liver	33	69
Nodes	9	19
Lung	14	29
Pelvis	6	13
Peritoneum	4	8
Local relapse	4	8
Other	2	4
Liver disease only	20	42
No. of metastatic sites		
Single	30	62.5
Multiple (2)	12	25
Multiple (≥3)	6	12.5

Physical examination, assessment of toxicity and evaluation of hepatic, renal and hematopoietic function were performed at the beginning of each course. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0) (14). In case of any grade II toxicity, the treatment was delayed for one week, while in case of grade III hematological or gastrointestinal toxicity, a 20% dose reduction of both drugs was applied after complete recovery from the side-effects. In case of any grade IV toxicity, the dose reduction was 50%.

Delayed-onset diarrhea was managed with the conventional high-dose loperamide schedule (15). Patients were consistently rehydrated. Patients with severe or refractory diarrhea, or with diarrhea and concomitant fever or dehydration, and those with febrile neutropenia, were hospitalized for supportive therapy.

Statistical analysis. The expected number of patients to be accrued was calculated with the minimax Simon's design, with a two-step recruitment scheme (16). Having set α error=0.05 (probability to accept an inactive treatment), β error=0.01 (probability to refuse an active treatment) and δ=20%, the combination was not considered effective if the response rate was less than or equal to 20%, while it was considered interesting for further clinical use if

Table II. *Toxicities per patient of 16 patients who received CPT-11/raltitrexed at 350/3 mg/m^2 (maximum NCI-CCT grade) in 102 courses overall.*

	G1 no.	G2 no.	G3 no.	G4 no.
Diarrhea	4	4	3	1
N/V	4	6	2	
Weight loss	1			
Mucositis	3	2		
Fever	4			
Anemia			1	
Neutropenia	1	2	1*	1
Thombocytopenia	1	1		
Asthenia	2	3	1	
TOTAL	20	18	8	2

*neutropenic fever

Table III. *Toxicities per patient of 32 patients who received CPT-11/raltitrexed at 300/2.6 mg/m^2 (maximum NCI-CCT grade) in 188 courses overall.*

	G1 no.	G2 no.	G3 no.	G4 no.
Diarrhea	6	1	9	2
N/V	8	6	7	
Weight loss	2	1		
Mucositis	2	1	1	1
Fever	5	2		
Anemia	1	2		
Neutropenia	1		2	
Hepatic toxicity*	1	4	2	
Asthenia	5	5	2	
TOTAL	31	22	23	3

* increase of SGOT and SGPT

the response rate was at least 40%. A sample of 24 patients was required in the first stage. If 6 out of 24 patients experienced a clinical response, a further 21 patients were enrolled in the second step and up to 3 more patients could be accrued to correct for attrition. The treatment under investigation could be considered interesting for further trials if more than 14 clinical responses were observed out of the total number of enrolled patients.

Analyses were conducted according to the intention-to-treat method.

Results

Between August 2000 and April 2002, 48 consecutive patients were entered into the trial. The patient characteristics are listed in Table I. The median age was 63 years (range 46-77) and median ECOG Performance Status was 0 (range 0-2). Twenty-two patients (46%) had synchronous metastases, 26 had metastatic disease and 4 patients presented local relapse associated with distant metastases. Thirty patients had a single involved site, while 18 patients presented multiple metastatic sites. A total of 20 out of 48 patients had undergone prior adjuvant chemotherapy consisting of 5-FU/FA combination regimens in 17 cases, and methotrexate/5-FU/FA regimen in 3 patients. After recruitment of the first 16 patients, toxicity grade III-IV was observed in 6 patients (Table II). Therefore, an amendment of the protocol was proposed to the ethical committee for a reduction of 15% of the total dose of both drugs of the combination (irinotecan 300 mg/m^2 and raltitrexed 2.6 mg/m^2) for the subsequent patients entering the trial.

Overall, 290 cycles of irinotecan and raltitrexed were administered. The median number of treatment courses per patient was 6 (range 1-18). Twenty-three patients required 20% dose reductions, corresponding to 79/290 (27.2 %) of overall courses. In 2 patients, 50% dose reduction was necessary. Overall, 13 cycles (4.5 %) were delayed for 1 week and 6 courses (2 %) for 2 weeks to allow for toxicity recovery. Overall, the median dose-intensity was 0.90 (0.58-1.00) for irinotecan and 0.91 (0.54-1.00) for raltitrexed.

As salvage treatment, 21 patients received combination chemotherapy including oxaliplatin + 5-FU/FA and 4 patients received 5-FU/FA schedules.

Toxicity. Table II reports the toxicity observed in the first 16 patients treated with irinotecan 350 mg/m^2 + raltitrexed 3 mg/m^2 (worst toxicity in 102 courses). Six/16 patients experienced severe toxicity as follows: grade III diarrhea in 2 patients after the 3rd and 7th course, respectively, grade III diarrhea and neutropenic fever in one patient after the 7th course, grade IV diarrhea and neutropenia in one patient after the 4th cycle; 3/6 patients required hospitalization due to diarrhea and/or

neutropenia. In total, 3/16 patients interrupted the chemotherapy: 2 patients having experienced grade III-IV toxicity at the 4th and the 7th cycle, while 1 patient refused further therapy after the 5th cycle, in which grade II toxicity was recorded.

In Table III, the toxicity in the 32 patients treated with the initial dose of irinotecan 300 mg/m^2 and raltitrexed 2.6 mg/m^2 is reported. Seventeen/32 patients experienced grade III-IV toxicity: grade IV toxicity was observed in 2 patients (6%); grade III significant toxicity was registered in 23 cases and consisted mainly of diarrhea, nausea/vomiting, neutropenia, transaminase elevation, asthenia and stomatitis. Hospitalization of 3 patients was required due to grade III hepatic toxicity, grade III diarrhea and grade IV mucositis. In 1 patient, 50% dose reduction was employed for grade IV mucositis and grade III neutropenia. Two toxic deaths occurred: in one case as a consequence of dehydration due to grade IV diarrhea associated with grade III emesis; in the other patient, it was correlated with grade III diarrhea and grade II emesis after the 2nd course of chemotherapy (at 20% dose reduction). Five patients interrupted chemotherapy due to combined grade III-IV toxicity after a median of 3 courses (range 1-6) and 1 patient refused therapy after the 6th course, not associated with toxicity; in 2 cases, patients had achieved an objective response (1 complete response + 1 partial response).

Activity and survival. Forty-three/48 patients were evaluable for response. The reasons for non-evaluability were chemotherapy discontinuation in 2 patients after the first course due to grade III-IV toxicity and in 3 patients after the second cycle, due to grade III-IV side-effects (including 2 toxic deaths).

According to intention-to-treat analyses, the overall response rate was 27% (95% C.I. 16%-42%), including 3 complete responses (6.3%) and 10 partial responses (20.8%). Fourteen patients (29.2%) had stable disease and 16 patients (33.3%) progressed. We observed 5/16 objective responses (31%) in patients receiving an initial dose of irinotecan 350 mg/m^2 and raltitrexed 3 mg/m^2 and 8/32 objective responses (25%) in patients treated with irinotecan 300 mg/m^2 and raltitrexed 2.6 mg/m^2.

The median progression-free-survival was 5 months and overall survival was 14 months. The median duration of response was 11 months for patients in complete response (range: 4-23+) and 10 months (range: 3-24) for patients in partial response.

Discussion

The availability of several active drugs in recent years has improved the prognosis of patients with ACC, which nevertheless remains one of the major causes of cancer deaths in Western countries.

First-line chemotherapy with irinotecan in addition to bolus or infusional 5-FU demonstrated its efficacy in terms of response rate, time to progression and overall survival. To overcome the limitations arising with 5-FU, different agents have been evaluated in combination with irinotecan.

The use of 5-FU, in fact, requires caution in patients with DPD deficiency, which is estimated to be as high as 3% in the general population, since it results in an approximately 33% mortality rate. Moreover, the drug is often contraindicated in case of ischaemic heart disease (4, 5). Furthermore, in case of infusional 5-FU, there may be specific contraindications or even refusal to the implantation of a central venous catheter. Indeed, the combination of CPT-11/5-FU bolus /FA has been reported to be associated with a high rate of early death related to gastrointestinal syndrome and ischaemic events, suggesting that an increased awareness is needed among health care providers (17).

The use of the irinotecan-raltitrexed combination is justified based on at least three distinct considerations: the different mechanism of action of the two drugs documented by preclinical data resulting in a synergistic cell kill; the non-overlapping specific toxicity of the two drugs; the feasible schedule administration on an out-patient basis (9-12).

The present study confirmed the activity of the combination of irinotecan and raltitrexed, achieving 27% (95% CI 16%-42%) objective response rate, 30% stable disease and a median duration of response and overall survival of 10 and 14 months, respectively. However, unexpectedly, the toxicity profile of the regimen was significant in the subset of patients treated with the dosage suggested by phase I trials. The dose reduction performed in the subsequent set of patients, allowed the administration of an adequate dose-intensity of both drugs and an appropriate median number of courses/patient. Nevertheless, the tolerability of the combination regimen did not significantly improve: in fact, important gastrointestinal toxicity was observed in 40% of the patients (grade III and IV diarrhea in 11 patients and grade II and IV mucositis in 2 patients) and 2 toxic deaths occurred. Moreover hepatic toxicity, diarrhea and mucositis required hospitalization in 3 cases. However, myelosuppression was less frequent and manageable on an outpatient basis, compared to toxicity recorded in the 16 patients treated with full doses.

Recently, three phase II studies have been published confirming the efficacy of the combination of irinotecan and raltitrexed in patients with ACC. Carnaghi *et al*. (18) showed that this regimen was active at the dose of irinotecan 350 mg/m^2 and raltitrexed 2.6 mg/m^2, obtaining 46% overall response rate. The administration of a full dose of irinotecan, the most active drug in the combination, could explain the higher response rate compared to the present study. However, toxicity data demonstrated 'not negligible'

side-effects, mainly gastrointestinal and hematological. In particular, grade III-IV diarrhea (26% of patients) compared well with our toxicity data (34%), while neutropenia was significantly superior (20% *vs.* 6%). Other authors have investigated the tolerability and activity of the sequence of CPT-11 and raltitrexed both administered on day 1. In a large series of untreated patients, Feliu *et al.* (19) achieved 30% overall response rate and observed mild toxicity with 15% grade III-IV diarrhea and 3% neutropenic fever. The same regimen had been tested by Aparicio *et al.* among pretreated metastatic patients. An encouraging response rate (15.4%) associated with only moderate toxicity was reported (20).

It should be underlined that the schedule designed to optimize the maximum synergism between the two drugs (24-h interval) resulted in a moderate advantage in response rate, at the expense of a considerable toxicity. The safety profile in our experience is that of a somewhat high toxicity.

Manageable toxicity was recently reported by Garcia *et al.* (21) with a bi-weekly schedule of irinotecan 200 mg/m^2 and raltitrexed 2 mg/m^2. In a series of 95 patients, an objective response rate of 32% was achieved and side-effects consisted of grade III-IV diarrhea and neutropenia in 18% and 11%, respectively. A weekly low-dose irinotecan schedule could be investigated to improve tolerability in association with biological agents (22, 23). These data suggest that alternative drug combinations should ameliorate the combination regimen, offering the opportunity to deliver an adequate dosage of drugs.

References

1 Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL and Miller LL: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. N Eng J Med *343*: 905-912, 2000.

2 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L and Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. Lancet *355*: 1041-1047, 2000.

3 Bouzid K, Khalfallah S, Tujakowski J, Piko B, Purkalne G, Plate S, Padrik P, Serafy M, Pshevloutsky EM and Boussard B: Irinotecan Study Group: A randomized phase II trial of irinotecan in combination with infusional or two different bolus 5-fluorouracil and folinic acid regimens as first-line therapy for advanced colorectal cancer. Ann Oncol *14*: 1106-1114, 2003.

4 Anand AJ: Fluorouracil cardiotoxicity. Ann Pharmacother *28*: 374-378, 1994.

5 Lu Z, Zhang R and Diasio RB: DPD activity in human peripheral blood mononuclear cells and liver: population characteristics, newly identified deficient patients, and clinical implication in 5-FU chemotherapy. Cancer Res *53*: 5433-5438, 1993.

6 Cunningham D, Zalcberg JR, Rath U, Olver I, Van Cutsem E, Svensson C, Seitz JF, Harper P, Kerr D, Perez-Manga G *et al*: "Tomudex" (ZD1694): results of a randomized trial in advanced colorectal cancer demonstrate efficacy and reduced mucositis and leucopenia. Eur J Cancer *31*: 1945-1954, 1995.

7 Feliu J, Mel JR, Camps C, Escudero P, Aparicio J, Menendez D, Garcia Giron C, Rodriguez MR, Sanchez JJ and Gonzalez Baron M: Oncopaz Cooperative Group Associated Hospitals: Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen. Eur J Cancer *38*: 1204-1211, 2002.

8 Kohne CH, Thuss-Patience P, Friedrich M, Daniel PT, Kretzschmar A, Benter T, Bauer B, Dietz R and Dorken B: Raltitrexed (Tomudex): an alternative drug for patients with colorectal cancer and 5-fluorouracil associated cardiotoxicity. Br J Cancer *77*: 973-977, 1998.

9 Aschele C, Baldo C, Sobrero AF, Debernardis D, Bornmann WG and Bertino JR: Schedule-dependent synergism between raltitrexed and irinotecan in human colon cancer cells *in vitro*. Clin Cancer Res *4*: 1323-1330, 1998.

10 Ford HE, Cunningham D, Ross PJ, Rao S, Aherne GW, Benepal TS, Price T, Massey A, Vernillet L and Gruia G: Phase I study of irinotecan and raltitrexed in patients with advanced gastrointestinal tract adenocarcinoma. Br J Cancer *83*: 146-152, 2000.

11 Stevenson JP, Redlinger M, Kluijtmans LA, Sun W, Algazy K, Giantonio B, Haller DG, Hardy C, Whitehead AS and O'Dwyer PJ: Phase I clinical and pharmacogenetic trial of irinotecan and raltitrexed administered every 21 days to patients with cancer. J Clin Oncol *19*: 4081-4087, 2001.

12 Aparicio J, de las Penas R, Vicent JM, Garcera S, Llorca C, Maestu I, Yuste AL and Farres J: Multicenter phase I study: irinotecan plus raltitrexed in patients with 5-fluorouracil-refractory advanced colorectal cancer. Oncology *63*: 42-47, 2002.

13 Cancer Therapy Evaluation Program. Common Toxicity Criteria, Version 2.0 Bethesda, MD: National Cancer Institute, 1998.

14 Miller AB, Hoogstraten B, Staquet M and Winkler A: Reporting results of cancer treatment. Cancer *47*: 207-214, 1981.

15 Wadler S, Benson AB 3rd, Engelking C, Catalano R, Field M, Kornblau SM, Mitchell E, Rubin J, Trotta P and Vokes E: Recommended guidelines for the treatment of chemotherapy-induced diarrhea. J Clin Oncol *16*: 3169-3178, 1998.

16 Simon R: Optimal two-stage designs for phase II clinical trials. Control Clin Trials *10*: 1-10, 1989.

17 Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E and Wadler S: Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol *19*: 3801-3807, 2001.

18 Carnaghi C, Rimassa L, Garassino I, Zucali PA, Masci G, Fallini M, Morenghi E and Santoro A: Irinotecan and raltitrexed: an active combination in advanced colorectal cancer. Ann Oncol *13*: 1424-1429, 2002.

19 Feliu J, Salud A, Escudero P, Lopez-Gomez L, Pericay C, Castanon C, de Tejada MR, Rodriguez-Garcia JM, Martinez MP, Martin MS, Sanchez JJ and Baron MG: Oncopaz Cooperative Group and Associated Hospitals: irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study. Br J Cancer *90*: 1502-1507, 2004.

20 Aparicio J, Vicent JM, Maestu I, Garcera S, Busquier I, Bosch C, Llorca C, Diaz R, Fernandez-Martos C and Galan A: Multicenter phase II trial evaluating a three-weekly schedule of irinotecan plus raltitrexed in patients with 5-fluorouracil-refractory advanced colorectal cancer. Ann Oncol *14*: 1121-1125, 2003.

21 Garcıa Giron C, Salut A, Sanchez-Rovira P, Benavides M, Gonzalez E, Jiménez E, Arizcun A, Murias A, Moreno AL and Balcells M: Phase II trial of irinotecan (IRI) and raltitrexed (RTD) administered every two weeks in chemotherapy naive advanced colorectal cancer (ACRC) patients. Proc Am Soc Clin Oncol *21*: 172a (abstract 685).

22 Cerea G, Vaghi M, Ardizzoia A, Villa S, Bucovec R, Mengo S, Gardani G, Tancini G and Lissoni P: Biomodulation of cancer chemotherapy for metastatic colorectal cancer: a randomized study of weekly low-dose irinotecan alone *versus* irinotecan plus the oncostatic pineal hormone melatonin in metastatic colorectal cancer patients progressing on 5-fluorouracil-containing combinations. Anticancer Res *23*: 1951-4, 2003.

23 Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I and Van Cutsem E: Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med *351*: 337-45, 2004.

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