British Journal of Cancer (2007) 96, 439–444

www.bjcancer.com

Clinical Studies

Uracil/ftorafur/leucovorin combined with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) as first-line treatment for metastatic colorectal cancer patients: results of randomised phase II study

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This randomised phase II study evaluates the safety and efficacy profile of uracil/tegafur/leucovorin combined with irinotecan (TEGAFIRI) or with oxaliplatin (TEGAFOX). One hundred and forty-three patients with measurable, non-resectable metastatic colorectal cancer were randomised in a multicentre study to receive TEGAFIRI (UFT 250 mg m^{-2} day days 1–14, LV 90 mg day days 1–14, irinotecan 240 mg m^{-2} day 1; q21) or TEGAFOX (UFT 250 mg m^{-2} day days 1–14, LV 90 mg day days 1–14, oxaliplatin 120 mg m^{-2} day 1; q21). Among 143 randomised patients, 141 were analysed (68 received TEGAFIRI and 73 TEGAFOX). The main characteristics of the two arms were well balanced. The most common grade 3–4 treatment-related adverse events were neutropenia (13% of cases with TEGAFIRI; 1% in the TEGAFOX group). Diarrhoea was prevalent in the TEGAFIRI arm (16%) *vs* TEGAFOX (4%). Six complete remission (CR) and 19 partial remission (PR) were recorded in the TEGAFIRI arm (odds ratio (OR): 41.7; 95% confidence limit (CL), 29.1–55.1%), and six CR and 22 PR were recorded in the TEGAFOX group, (OR: 38.9; 95% CL, 27.6–51.1). At a median time follow-up of 17 months (intequartile (IQ) range 12–23), a median survival probability of 20 and 19 months was obtained in the TEGAFIRI and TEGAFOX groups, respectively. Median time to progression was 8 months for both groups. TEGAFIRI and TEGAFOX are both effective and tolerable first-line therapies in MCRC patients. The employment of UFT/LV given in doublet combination is interesting and the presented data appear comparable to equivalent infusion regimens described in the literature. The safety profile of the two combinations also allows an evaluation with other biological agents such as monoclonal antibodies.
British Journal of Cancer (2007) **96,** 439–444. doi:10.1038/sj.bjc.6603493 www.bjcancer.com
Published online 23 January 2007

Keywords: UFT; irinotecan; oxaliplatin; metastatic colorectal cancer

Up until the mid-1990s, best supportive care was still a valid treatment option in the treatment of advanced metastatic colorectal cancer and 5-fluorouracil (5-FU) represented the mainstay chemotherapy. In the last decade, irinotecan (CPT-11), oral fluoropyrimidines, oxaliplatin (L-OHP) and monoclonal anti-

options. This, of course, presents a challenge. Fluorouracil infusion in association with CPT-11 or L-OHP has shown a good activity and tolerability profile in metastatic colorectal cancer; therefore, FOLFIRI or FOLFOX are now considered the first-line options (de Gramont *et al*, 2000; Douillard *et al*, 2000; Saltz *et al*, 2000; Mayer,

our and of UFT m 5-FU wing the to only about half, and drug levels in normal mucosa were maintained at least 48 h after the final dose (Sadahiro *et al*, 2001). However 5-FU concentrations in the normal mucosa were approximately one-third of those measured in tumour tissue. Three phase III studies have been conducted to compare the efficacy and toxicity of UFT and bolus 5-FU, both modulated by leucovorin (LV) (Carmichael *et al*, 2002; Douillard *et al*, 2002; Lembersky *et al*, 2006). The results documented that they are equivalent in efficacy and that UFT/LV has a more favourable toxicity profile, with less neutropenia, diarrhoea, nausea, vomiting and mucositis. Given the *in vitro* synergy between L-OHP and UFT in the HT29 cell xenograft model, and between CPT-11 and 5-FU, some phase I studies have been conducted to define the recommended dose (Louvet *et al*, 2000; Prince and Hill, 2000; Alonso *et al*, 2001). Therefore, in the light of the above, it is to be expected that the combination of UFT/LV with CPT-11 (TEGAFIRI) or L-OHP (TEGAFOX) will be at least as effective as the corresponding infusion regimen.

The aims of this multicentre randomised non-comparative phase II study are to evaluate the safety profile of TEGAFIRI or TEGAFOX as first-line treatment and to determine the therapeutic efficacy in terms of response rate, duration of response, time to progression and overall survival.

MATERIALS AND METHODS

Patient eligibility

Patients with metastatic colorectal cancer, previously untreated by chemotherapy for advanced disease, were eligible for this study. Adjuvant chemotherapy, if administered, must have been completed at least 6 months before enrolment in the study. Histological confirmation of colorectal adenocarcinoma and the presence of at least one unidimensionally measurable lesion was requested. The patients had to be 18–75 years of age, with ECOG performance status 0–2. Other eligibility criteria were: absolute neutrophil count $\geqslant 2.0 \times 10^9 l^{-1}$ at least; platelets $\geqslant 100 \times 10^9 l^{-1}$ or more, haemoglobin $\geqslant 10\,g\,dl^{-1}$; lactic deydrogenase (LDH) $\leqslant 1500\,U\,l^{-1}$; serum creatinine $\leqslant 1.25\,mg\,dl^{-1}$; serum bilirubin $\leqslant 1 \times$ upper normal limit (UNL), alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) or alkaline phosphatase $< 2.5 \times$ UNL. However, level of up to five times the UNL for alkaline phosphates, ALAT and ASAT were allowed in patients with liver metastases. The study was conducted according to the Good Clinical Practices and Declaration of Helsinki. Written informed consent was required. The study and all current amendments were approved by the Ethics Committees of all of the participating centres.

Study design and treatment

This was an open-label, multicentre, randomised non-comparative Phase II study, conducted by the Italian Trials in Medical Oncology (ITMO) group and coordinated by Medical Oncology Unit 2. Patients who fulfilled the selection criteria were stratified by centre and by previous adjuvant chemotherapy and centrally randomised by the ITMO Scientific Office. TEGAFIRI consisted of UFT: $250\,mg\,m^{-2}$ day and LV: 90 mg total dose daily, given for 14 days, combined with a 1-h infusion of CPT-11: $240\,mg\,m^{-2}$ on day 1. TEGAFOX was administered as UFT: $250\,mg\,m^{-2}$ day and LV: $90\,mg\,total\,dose^{-1}$ daily, given for 14 days, combined with a 3-h infusion of L-OHP: $120\,mg\,m^{-2}$ on day 1. The total daily UFT dose was divided to be given every 8 h; if the dose could not be equally divided, the greatest dose was administered in the morning. The treatment was given for a maximum of six cycles in presence of disease stabilisation or eight cycles in case of objective responses, as shown in Figure 1. The therapy was interrupted for unacceptable toxicity or consent withdrawal.

Safety and efficacy analyses

Safety analyses included all patients who received at least one dose of the study medication. The analysis also included clinical assessments of adverse event reactions. Complete blood counts were obtained before every cycle and 21 days after the last day of chemotherapy.

The intensity of clinical adverse events was graded according to the NCI-CTC grading system (version 3.0). Adverse events not listed on the NCI-CTC grading system were graded as mild (grade 1), moderate (grade 2), severe (grade3) or life-threatening (grade 4). Hand–foot syndrome (palmar–plantar erythrodysesthesia-HFS) was classified as 3 grades: grade 1 (numbness, dysesthesia, painless swelling or erythema not disrupting normal activity); grade 2 (painful erythema with swelling affecting daily living activities); grade 3 (desquamation, ulceration, blistering or severe pain or any symptoms leading to an inability to work or perform daily living activities).

All cases who had received at least three cycles of study treatment and had at least one tumour assessment were considered evaluable for activity. Patients who failed to follow-up or who refused therapy were also included. Basal evaluation was performed within 28 days before starting treatment. Tumour dimensions that had a minimum size of at least one diameter of 10 mm were assessed using computerised tomography scans and magnetic resonance imaging. Figure 1 shows the treatment plan and the planned disease revaluation. All responses were confirmed and complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) were defined according to the response definitions of the RECIST criteria (Therasse *et al*, 2000).

Treatment modifications

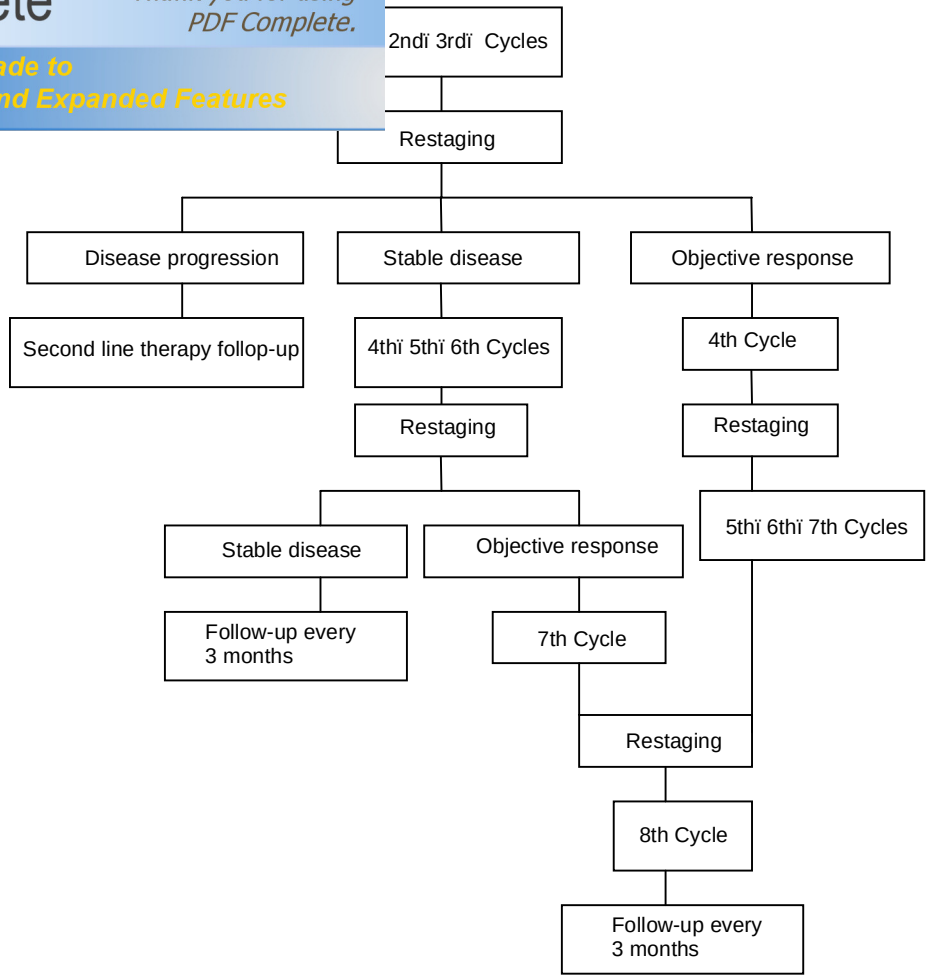

Figure 1 Study design.

In the presence of grade 2–4 diarrhoea, the UFT/LV administration was interrupted until recovery. The drug was then restarted with a reduction in dose by 25% in presence of grade 3–4 toxicity or with the second appearance of grade 2 diarrhoea. If grade $\geqslant 2$ HFS and/or mucositis occurred, the UFT administration was immediately stopped.

To ensure that the patient has been complying adequately with their medication regimen, at each visit the returned medication was checked and counted and the amount returned recorded in the drug dispensing log. If the patient stopped treatment, for any other reason other than side effects, for more than 1 week, he or she was withdrawn from the trial for non-compliance.

Statistical analysis

toxicity and was checked by simulation assuming an increase in the toxicity rate above 40% and/or a reduction of the response rate below 35%.

RESULTS

Between July 2002 and November 2004, 143 patients were randomised by 14 Italian Institutions. Two patients were not analysed because they were never treated (rapidly progressive disease and ineligibility criteria); 68 patients were assigned to TEGAFIRI and 73 to TEGAFOX. Table 1 shows the main demographic and baseline characteristics that were comparable between treatment arms. Most patients had received no prior

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the TEGAFIRI arm, and no deaths were recorded in the TEGAFOX arm. Regarding dose reduction, TEGAFIRI cycles were administered with only a UFT reduction in 44 cycles (12%) and with a CPT-11 reduction in 11 (3%), whereas 37 (10%) cycles were administered with reduction in the dose of both drugs. TEGAFOX cycles were administered with only a reduced dose of UFT in 59 cycles (13%) and with only a reduced dose of L-OHP in 9 (2%), whereas 16 (4%) cycles were administered with both drugs at reduced doses. Most of these reductions consisted of 75% of the initial dose.

Table 1 Main basal characteristics

	No. of pts (%)	
	TEGAFIRI (No. 68 pts)	**TEGAFOX (No. 73 pts)**
Age (years)		
Median (range)	61 (36–74)	62 (23–73)
< 70	61 (89.7)	66 (90.4)
⩾70	7 (10.3)	7 (9.6)
M/F:	40 (58.8)/28 (41.1)	39 (53.4)/34 (46.5)
PS (ECOG)		
0–1	58 (85.3)–10 (14.7)	66 (90.4)–5 (6.9)
2	—	2 (2.7)
Site of primary lesion		
Colon dx	15 (22.1)	15 (20.6)
Colon sn	34 (50)	40 (54.7)
Rectum	19 (27.9)	18 (24.7)
No. of metastatic sites		
1	31 (45.6)	43 (58.9)
2	26 (38.2)	15 (20.5)
⩾3	11 (16.2)	15 (20.5)
Adjuvant chemotherapy		
Yes	13 (19.1)	14 (19.2)
Altered LDH value	27 (40)	15 (20)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH, lactic deydrogenase; pts, patients; PS.

Table 2 shows the adverse events reported during the treatment with TEGAFIRI and TEGAFOX. The most common grade 3–4 treatment-related adverse events were neutropenia, which was reported in 13% of cases with TEGAFIRI and in 1% in the TEGAFOX group. Diarrhoea was prevalent in the TEGAFIRI arm (16%) *vs* TEGAFOX (4%). No HFS was reported in the TEGAFIRI group whereas grade 1–2 HFS was evident in 10% of the TEGAFOX group. Abdominal pain, allergic reactions, infection, liver toxicity and infection with fever were recorded as other toxicity. However, the overall incidence of any type grade 3–4 side effects was reported in 37–21% of TEGAFIRI and TEGAFOX patients, respectively.

Sequential grade 3–4 toxicity (as defined in the Materials and methods section) was recorded in four (5.9, 95% CL, from 1.6 to 14.4%) TEGAFIRI patients and three (4.1, 95% CL, from 0.9 to 11.5%) TEGAFOX patients.

Efficacy analysis

Eight patients in the TEGAFIRI group and one in the TEGAFOX group interrupted therapy soon after the first cycle, owing to side effects with no clinical benefit, and they were excluded. Thus, a total of 60 TEGAFIRI cases and 72 TEGAFOX patients were evaluable for efficacy analysis. Among these excluded cases, all except two were more than 65 years old. Table 3 shows study results on the best overall response rates. Six CR and 19 PR were recorded in the TEGAFIRI arm, for an overall response rate of 41.7% (95% CL, from 29.1 to 55.1%). In the TEGAFOX arm, six CR and 22 PR were recorded, corresponding to an overall response rate of 38.9% (95% CL, from 27.6 to 51.1).

The median duration of response was 6 (range: 3–15) for TEGAFIRI and 6 months (range: 3–23) for TEGAFOX group.

After a median time follow-up of 17 months (IQ range 12–23), a median survival probability of 20 (IQ range 14–31) and 19 (IQ range: 11–29) months was obtained in the TEGAFIRI and TEGAFOX group, respectively. Median time to progression reported was 8 months (IQ range 5–11) for TEGAFIRI and 8 months (IQ range: 5–14) for TEGAFOX patients. The overall survival and time to progression are shown in Figures 2 and 3 respectively.

Table 2 Frequency of patients reporting adverse events

	% pts							
	TEGAFIRI (No. 68 pts)				**TEGAFOX (No. 73 pts)**			
Grade NCI CTC	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**

		No.
Complete response	6 (10.0)	6 (8.3)
Partial response	19 (31.7)	22 (30.6)
Stable disease	23 (38.3)	25 (34.7)
Treatment failure	12 (20.0)	19 (26.4)
Objective response	25 (41.7) (95% CL, 29.1–55.1%)	28 (38.9) (95% CL, 27.6–51.%1)

Abbreviation: CL = confidence limit.

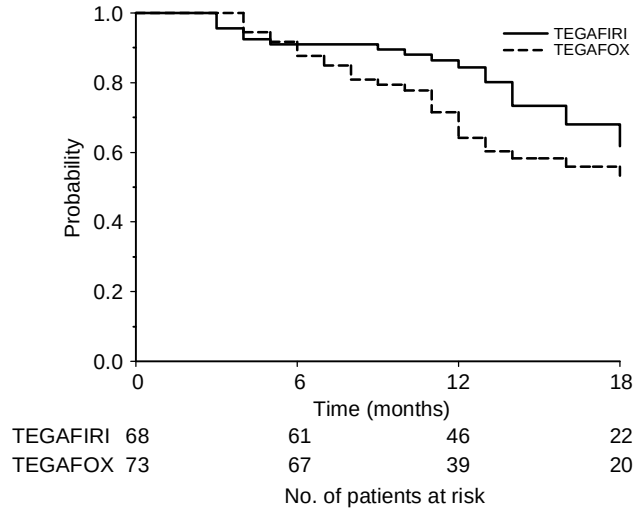

Figure 2 Overall survival by treatment.

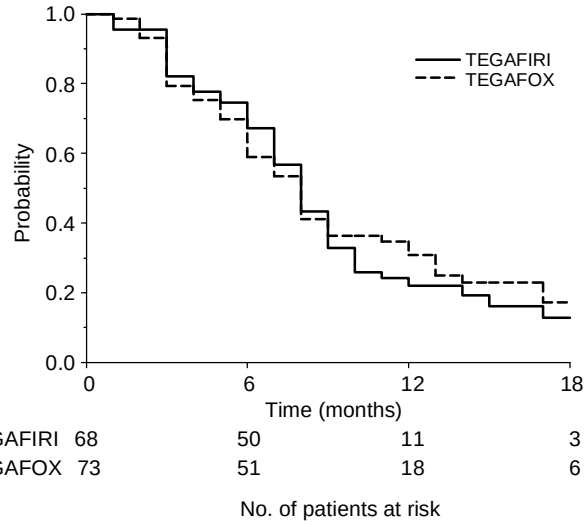

Figure 3 Time to progression by treatment in analysed patients.

DISCUSSION

The introduction in clinical practice of combination therapies such as FOLFIRI or FOLFOX has been an important development in colorectal cancer patient treatment. But, at the same time, it also creates some disadvantages such as the requirement of central venous catheters (CVC), infusion pumps or repeated intravenous administrations that are uncomfortable for the patients. Moreover, positioning of CVC could be complicated by pneumothorax, local infection, thrombosis and the frequent ambulatory visits that may have a negative impact on quality of life.

To decrease the level of these complications, new oral 5-FU prodrugs were introduced into the clinical practice. These agents such as UFT and capecitabine have demonstrated a relevant antitumour activity in preclinical trials and the pharmacokinetic profile of these drugs is equivalent to infusion 5-FU (Ishikawa *et al*, 1998). The role of oral fuoropyrimidines as a backbone of TEGAFIRI group and grade 3–4 neurotoxicity (6%), grade 3 diarrhoea (4%) and grade 3 neutropenia (1%) in the TEGAFOX patients. Moreover, during the treatment, two sequentially occurring grade 3–4 toxicities were reported in only 6% of TEGAFIRI cases and 4% of TEGAFOX patients. It means that a good safety profile has been obtained by a slight dose reduction (25%) of the two combinations.

Regarding any type toxicity, the TEGAFIRI regimen (grade 3–4: 37%) shows an increase in incidence with respect to the TEGAFOX regimen (grade 3–4: 21%). Twelve percent of TEGAFIRI patients and 1% of the TEGAFOX group stopped treatment for side effects soon after the first cycle; in the TEGAFIRI group, all cases were more than 65 years old. This means that the TEGAFOX regimen could be considered more suitable for older patients.

Other phase II trials have investigated the use of these two combinations. The toxicity profile observed with TEGAFOX and TEGAFIRI in the present study compares favourably with that reported in other phase II trials (Feliu *et al*, 2004, (Mendez *et al*, 2005; Bennouna *et al*, 2006). In particular, the rate of TEGAFOX grade 3–4 neurotoxicity was around 14–15% in Bennouna and Feliu studies as compared with 6% in our study. This probably correlated with the maximum number of administered cycles according to the study design reported in our study. Regarding TEGAFIRI, the toxicity rates of neutropenia and diarrhoea were comparable with those reported by Mendez.

However, these toxicity profiles correspond to those reported combining capecitabine and CPT11 or L-OHP with the exception of the greater rate of HFS that is reported in 20% of patients treated with capecitabine (Bajetta *et al*, 2004; Reddy, 2005; Twelves

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ACKNOWLEDGEMENTS

We thank Mrs Susanna Maggi, Paola Crippa and the Scientific Service of the ITMO group for editorial assistance.

REFERENCES

Alonso V, Escudero P, Zorrilla M, Isla MD, herrero A, Mayordomo JI, Martines-Trufero J, Saenz A, tres A, Anton A (2001) Phase I trial of weeekly irinotecan combined with UFT as second-line treatment for advanced colorectal cancer. *Eur J Cancer* **37:** 2385–2391

Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, Pinotti G, Bonetti A, Carreca I, Biasco G, Bonaglia L, Marini G, Iannelli A, Cortinovis D, Ferrario E, Beretta E, Lambiase A, Buzzoni R (2004) Randomized multicenter phase II trial of two different schedules of irinotecan combined to capecitabine as first line treatment in metastatic colorectal cancer. *Cancer* **100:** 279–287

Bennouna J, Perrier H, Paillot B, Priou F (2006) A phase II study of oral uracil/ftorafur (UFT) plus leucovorin combinae with oxaliplatin(TEGAFOX) as first-line treatment in patients with metastatic colorectal cancer. *Br J Cancer* **94:** 69–73

Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A, Skovsgaard T, Munier S, Martin C (2002) Randomized comparative study of tegafur/uracil and oral leucovorin *vs* parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* **20:** 3617–3627

Colucci G, Gebbia V, Paletti GC, Giuliani F, Caruso M, Gebbia N, Carteni G, Agostara B, Pezzella G, Manzione L, Borsellino N, Misino A, Romito S, Durini E, Cordio S, Di Seri M, Lopez M, Maiello E, Montemurro S, Cramarossa A, Lorusso V, Di Bisceglie M, Chiarenza M, Valerio MR, Guida T, Leonardi V, Pisconti S, Rosati G, Carrozza F, Nettis G, Valdesi M, Filippelli G, Fortunato S, Mancarella S, Brunetti C, Gruppo Oncologico Dell'Italia Meridionale (2005) Phase III randomized trial of FOLFIRI *vs* FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico dell'Italia Meridionale (GOIM). *J Clin Oncol* **23:** 4866–4875

De Gramont A, Figer A, Seymour M, Homerin M, 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 (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* **18:** 2938–2947

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

Douillard JY, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, Vincent MD, Lembersky BC, Thompson S, Maniero A, Benner SE (2002) Multicenter phase iii study of uracil/tegafur and oral leuocovorin *vs* fluorouacil and Leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* **20:** 3605–3616

Feliu J, Vicent JM, Garcia-Giron C, Constela M, Fonseca E, Aparicio J, Lomas M, Anton-Aparicio L, Dorta FJ, Gonzales-Baron M (2004) Phase II study of UFT and oxaliplatin in first-line treatment of advanced colorectal cancer. *Br J Cancer* **91:** 1758–1762

Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR (2004) A randomized continuous 5-fluorouracil infusion and oral uracil plus N1-(2-tetrahydrofuryl)-5-fluorouracil. *Clin. Cancer Res* **4:** 2085–2088

Ishikawa T, Sekiguchi F, Fukase Y, Sawada N, Ishitsuka H (1998) Positive correlation between the efficacy of capecitabine and doxifluoridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumour in human cancer xenografts. *Cancer Res* **58:** 685–690

Lembersky BC, Wieand HS, Petrelli NJ, O'Connell MJ, Colangelo LH, Smith RE, Seay TE, Giguere JK, Marshall ME, Jacobs AD, Colman LK, Soran A, Yothers G, Wolmark N (2006) Oral uracil and tegafur plus leucovorin compared with intravenous fluorouracil and leucovorin in stage ii and iii carcinoma of the colon: results from national surgical adjuvant breast and bowel project protocol C-06. *J Clin Oncol* **24:** 2059–2064

Louvet C, Coudray AM, Tourningand C, Prevost S, Raymond E, de Gramont A, Chazard M, Gespach C (2000) Synergistic antitumoral activity of combined UFT, folinic acid and oxaliplatin against human colorectal HT29 cell xenografts in athymic nude mice. *Anti Cancer Drugs* **11:** 7

Mayer RJ (2004) Two steps forward in the treatment of colorectal cancer. *N Engl J Med* **350**(23)**:** 2406–2408

Mendez M, Alfonso PG, Pujol E, Ganzales E, Castanon C, Cerezuela P, Lopez-Mateos Y, Cruz JJ (2005) Weekly irinotecan plus UFT and leucovorin as first-line chemotherapy of patients with advanced colorectal cancer. *Invest New Drugs* **23**(3)**:** 243–251

Milano G, Ferrero JM, Franciois E (2004) Comparative pharmacology of oral fluoropyrimidines: a focus on pharmacokinetics, pharmacodynamics and pharmacomodulation. *Br J Cancer* **91:** 613–617

Prince T, Hill M (2000) UFT/leucovorin plus irinotecan in advanced or metastatic colorectal cancer. *Oncology* **14**(Suppl)**:** 28–31

Reddy GK (2005) Capecitabine/oxaliplatin combinations in advanced colorectal cancer: summary of recent randomized studies. *Clin Colorectal Cancer* **5:** 242–244

Sadahiro S, Suzuki T, Kameya T, Iwase H, Tajima T, Makuchi H (2001) A pharmacological study of weekday-on/weekend-off oral UFT schedule in colorectal cancer patients. *Cancer Chemother Pharmacol* **47:** 457–460

Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* **343:** 905–914

Thall PF, Simon RM, Estey EH (1995) Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Stat Med* **14:** 357–379

Therasse P, Arbuck SG, Eisenhauer EA (2000) New guidelines to evaluate the response to treatment in solid tumor. *J Natl Cancer Inst* **92:** 205–216

Tournigand C, Andrè T, Achille E, Lledo G, Flesh M, Mery-Mignard D, Quinaux E, Couteau C, Buyse M, Ganem G, Landi B, Colin P, Louvet C, de Gramont A (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomised GERCOR study. *J Clin Oncol* **22:** 229–237

Twelves CJ, Butts CA, Cassidy J, Conroy T, Braud F, Diaz-Rubio E,