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Clinical efficacy of 'Tomudex' (raltitrexed) in advanced colorectal cancer

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Direct and specific thymidylate synthase inhibitors, such as raltitrexed ('Tomudex', formerly ZD1694), provide a promising new therapeutic approach to the treatment of advanced colorectal cancer. Two international phase III trials (studies 3 and 12) compared raltitrexed (3 mg/m²) with 5-fluorouracil plus low-dose leucovorin or plus high-dose leucovorin, respectively. Study 3 included a 15.5-month follow-up for efficacy and a 26-month follow-up for survival. Results of an interim analysis for study 12 are presented. Objective tumour response rates for each treatment group were comparable in both studies 3 ($P = 0.48$) and 12 ($P = 0.896$). The median time to progression was similar between treatments in study 3 ($P = 0.44$), but was significantly longer for 5-fluorouracil + leucovorin compared with raltitrexed in study 12 (5.1 versus 3.9 months, $P = 0.005$). The median survival (raltitrexed versus 5-fluorouracil + leucovorin) was comparable in both studies 3 (10.1 versus 10.2 months, $P = 0.42$) and 12 (10.7 versus 11.8 months, $P = 0.36$). Palliative benefits were similar between treatments in both studies. A third phase III trial (study 10), carried out in North America, demonstrated a statistically significantly longer median survival for 5-fluorouracil + leucovorin compared with raltitrexed (12.7 months versus 9.7 months; $P = 0.01$). However, the possible unfamiliarity of the clinicians with raltitrexed and the early discontinuation of a 4 mg/m² raltitrexed arm due to toxicity may have led to an unconscious investigator bias in this trial, leading to a non-protocol-led withdrawal of patients from the study. Overall, raltitrexed is comparable with standard 5-fluorouracil + leucovorin therapy in terms of response rates and overall survival, and has a more convenient dose schedule.

Keywords: Advanced colorectal cancer, efficacy, 5-fluorouracil, raltitrexed, safety, tolerability, 'Tomudex'

Treatment of advanced colorectal cancer

Current standard therapy for advanced colorectal cancer involves combinations of 5-fluorouracil and leucovorin. The optimal treatment regimen for 5-fluorouracil + leucovorin combinations has still to be established: the Mayo (North Central Cancer Treatment Group) protocol of 5-fluorouracil combined with low-dose leucovorin has been described as an acceptable treatment for advanced colorectal cancer and is the only regimen to demonstrate a survival benefit over 5-fluorouracil alone, but other combination regimens, such as the Machover regimen of 5-fluorouracil with high-dose leucovorin, or continuous 5-fluorouracil infusions are also frequently used [1–5].

The inhibition of thymidylate synthase accounts for at least part of the cytotoxic efficacy of 5-fluorouracil + leucovorin, but toxicity may arise from the interaction of 5-fluorouracil metabolites with other cellular systems, such as RNA synthesis [6]. Administration of 5-fluorouracil + leucovorin requires frequent hospital visits. Effective drug therapy, available in a form which is more straightforward and convenient to administer than 5-fluorouracil + leucovorin, is required. Raltitrexed ('Tomudex', formerly ZD1694) is a direct, specific thymidylate synthase inhibitor which is currently being evaluated in a range of solid tumours [7]. This report compares the clinical efficacy of raltitrexed and 5-fluorouracil + leucovorin in patients with advanced colorectal cancer.

Phase III studies

A phase II study [8], carried out in Europe in 176 patients with advanced colorectal cancer treated with 3 mg/m² raltitrexed, demonstrated an overall objective response rate of 26% (95% confidence interval 19–33%), and a median survival of 11.2 months (95% confidence interval 9.6–13.1 months). On the basis of this study, two large, randomized comparative international phase III trials were conducted in a number of European countries, South Africa and Australia. In study 3, 3 mg/m² raltitrexed given as a 15-min infusion once every 3 weeks was compared with the Mayo regimen [9] of 5-fluorouracil (425 mg/m²) and low-dose leucovorin (20 mg/m²), in 439 patients. In study 12, 3 mg/m² raltitrexed was compared with the Machover regimen [1] of 5-fluorouracil (400 mg/m²) plus leucovorin (200 mg/m²), in a total of 495 patients.

The development of raltitrexed in North America followed a different path, beginning with a phase I dose-finding study and then progressing directly to a phase III comparative trial (study 10), in which raltitrexed was compared with the Mayo regimen of 5-fluorouracil + leucovorin. Study 10 differed in design from the other phase III studies by originally including a 4 mg/m² raltitrexed arm. The use of a higher dose was based on the results of a phase I study in North America, which suggested

Table 1. Objective response rates in phase III trials

	Study 3		Study 10		Study 12	
	Raltitrexed (n=223)	5-FU+LV (L) (n=216)	Raltitrexed (n=217)	5-FU+LV (L) (n=210)	Raltitrexed (n=247)	5-FU+LV (H) (n=248)
Complete response (%)	3.6	3.7	2.8	1.4	3.2	3.6
Partial response (%)	15.7	13.0	11.5	13.8	15.4	14.5
Overall response rate						
Complete + partial (%)	19.3	16.7	14.3	15.2	18.6	18.1
Stable disease (%)	35.0	32.4	33.2	40.0	51.4	52.4

Raltitrexed was given at a dose of 3 mg/m² every 3 weeks. 5-FU+LV (L), 5-fluorouracil at 425 mg/m² per day plus leucovorin at 20 mg/m² per day for 5 days every 4–5 weeks (Mayo regimen); 5-FU+LV (H), 5-fluorouracil at 400 mg/m² per day plus leucovorin at 200 mg/m² per day for 5 days every 4 weeks (Machover regimen). Odds ratios (95% confidence intervals) and significance values for differences between treatments in overall response rate: study 3: 1.2 (0.73–1.97), P=0.48; study 10: 0.86 (0.50–1.49), P=0.597; study 12: 1.03 (0.65–1.63), P=0.896.

that the maximum tolerated dose of raltitrexed was 4.5 mg/m² [10]. However, unacceptable toxicity in patients randomized to the 4 mg/m² dose of raltitrexed caused a temporary suspension of the trial, which continued as a two-arm trial in 427 patients, following notification of investigators and discontinuation of the 4 mg/m² arm. Subsequent analysis was based on the two-arm study.

The doses of 5-fluorouracil + leucovorin used in all three trials were selected as those which had demonstrated optimal efficacy in published studies. In each case, the two drugs were given as rapid injections once a day for 5 days, repeated once every 4 or 5 weeks. The minimum follow-up for an objective response was 15.5 months in study 3 and 12 months in study 10; for study 12 a 9-month interim analysis is presented. Follow-up for survival was 26 months in study 3, 12 months in study 10 and 9 months in study 12 (interim analysis). All analyses were performed on an intent-to-treat basis and the treatment groups were well balanced demographically.

Objective response

Objective responses occurring in the phase III studies are shown in Table 1. The proportion of patients achieving a complete response to treatment in study 3 was 3.6% for raltitrexed and 3.7% for 5-fluorouracil + leucovorin. Similar results were obtained in study 10, where 2.8% of raltitrexed patients and 1.4% of 5-fluorouracil + leucovorin patients achieved a complete response, and in study 12, where complete responses occurred in 3.2% of raltitrexed patients versus 3.6% of 5-fluorouracil + leucovorin patients. Partial responses to treatment followed a similar pattern, occurring in 15.7% of raltitrexed patients versus 13.0% of 5-fluorouracil + leucovorin patients in study 3, 11.5% versus 13.8% of patients in study 10 and in 15.4% of raltitrexed patients versus 14.5% of 5-fluorouracil + leucovorin patients in study 12. The overall response rates were 19.3 versus 16.7% in study 3 (P=0.48), 14.3 versus 15.2% in study 10 (P=0.597) and 18.6 versus 18.1% in study 12 (P=0.896) for raltitrexed and 5-fluorouracil + leucovorin treatments, respectively.

In study 3, the disease remained stable in 35.0 and 32.4% of patients randomized to raltitrexed and 5-fluorouracil + leucovorin, respectively (Table 1). Similar proportions of patients with stable disease were seen in the raltitrexed (33.2%) and 5-fluorouracil + leucovorin groups (40.0%) in study 10. The proportion of patients with stable disease in study 12 was higher overall, but did not differ between the raltitrexed and 5-fluorouracil + leucovorin groups (51.4 and 52.4%, respectively).

Time to progression

Objective disease progression was assigned by a computer algorithm following an increase of 25% from the smallest sum of lesions, or the appearance of a new lesion. Also, patients who died without documented progression were included in the analysis as progression events.

Disease progression occurred in over 90% of patients in study 3. The median time to progression was 4.8 months in raltitrexed patients and 3.6 months in 5-fluorouracil + leucovorin patients. The hazard ratio for the difference between treatments was 1.08 (95% confidence interval 0.89–1.31), and there was no significant difference in time to progression between treatments (P = 0.44).

In study 10, disease progression also occurred in more than 90% of patients in either group. The median time to progression in this study was 3.1 months in the raltitrexed group, and 5.3 months in the 5-fluorouracil + leucovorin group, with a hazard ratio of 1.55 (95% confidence interval 1.26–1.90), indicating a significantly longer time to progression in the 5-fluorouracil + leucovorin group (P < 0.0001).

In study 12, over 75% of patients had progressed, or died without documented disease progression, and median times to progression were 3.9 months in raltitrexed patients and 5.1 months in 5-fluorouracil + leucovorin patients. The hazard ratio for the difference between treatments in this trial was 1.33 (95% confidence interval 1.09–

Table 2. Survival in international phase III trials

Trial	Arm	Median survival (months)	Death (%)	Hazard ratio (95% CI)	*P* value
3	Raltitrexed (n=223)	10.1	89	1.09 (0.89–1.33)	0.42
	5-FU+LV (n=216)	10.2	85		
10	Raltitrexed (n=217)	9.7	75	1.35 (1.07–1.71)	0.01
	5-FU+LV (n=210)	12.7	65		
12	Raltitrexed (n=247)	10.7	50	1.13 (0.87–1.45)	0.36
	5-FU+LV (n=248)	11.8	48		

5-FU, 5-fluorouracil; LV, leucovorin.

Table 3. Palliative effects in phase III trials

	Study 3		Study 10		Study 12	
	Raltitrexed	5-FU + LV	Raltitrexed	5-FU + LV	Raltitrexed	5-FU + LV
All patients (no.)	223	216	199	179	230	222
Weight gain of at least 5% (%)	16.6	15.7	21.1	27.4	13.0	18.9
PS ≥1 on entry (no. patients)	121	128	115	103	123	132
PS score improvement (%)	36.4	29.7	39.1	40.8	38.2	31.1
Disease symptoms on entry (no. patients)	NA	NA	NA	NA	115	124
Symptom improvement (%)	NA	NA	NA	NA	86.1	83.1

5-FU, 5-fluorouracil; LV, leucovorin; PS, performance status; NA, not assessed.

1.62), indicating a significant difference in time to progression in favour of 5-fluorouracil + leucovorin (P = 0.005).

There is statistical evidence that in study 12 the raltitrexed patients were assessed for progression significantly earlier than the 5-fluorouracil + leucovorin patients, partly because the first protocolled assessment visit at week 6 coincided with the raltitrexed dose, whereas in study 3, the first assessment for progression occurred at 12 weeks. Furthermore, in study 12, survival postprogression was greater in raltitrexed patients than 5-fluorouracil + leucovorin patients (7.1 versus 6.4 months) regardless of whether or not second-line therapy was given, indicating that the time to progression results may have been influenced by the study design.

Survival

In study 3, 89 and 85% of patients randomized to raltitrexed and 5-fluorouracil + leucovorin, respectively, died during follow-up (Table 2); in study 10, the corresponding figures were 75 and 65%, while in study 12, 50% of raltitrexed and 48% of 5-fluorouracil + leucovorin patients died. Median survival in the two groups was 10.1 and 10.2 months in study 3, 9.7 and 12.7 months in study 10, and 10.7 and 11.8 months in study 12, respectively (Table 2). The hazard ratios for treatment differences, 1.09 (95% confidence interval 0.89–1.33) in study 3 (P = 0.42) and 1.13 (95% confidence interval 0.87–1.45) in study 12 (P = 0.36), indicated that the duration of survival did not differ significantly between treatments in either trial. However, in study 10, the hazard ratio for treatment differences was 1.35 (95% confidence interval 1.07–1.71), indicating a significant difference in survival in favour of 5-fluorouracil + leucovorin.

Palliative effects

Palliative effects of treatment on weight gain, performance status and disease symptoms are shown in Table 3. A gain in body weight of at least 5% was observed in 16.6% of patients in the raltitrexed group and 15.7% of patients in the 5-fluorouracil + leucovorin group in study 3. In study 10, 21.1% of raltitrexed patients and 27.4% of 5-fluorouracil + leucovorin patients gained at least 5% of their baseline body weight during treatment, while in study 12, the corresponding figures were 13.0 and 18.9%.

More than half of the patients in each study had a performance status score of one or more. Improvements in performance status score were seen after treatment in 36.4% of raltitrexed patients and 29.7% of 5-fluorouracil + leucovorin patients in study 3, in 39.1% of raltitrexed patients and 40.8% of 5-fluorouracil + leucovorin patients in study 10, and in 38.2% of raltitrexed patients and 31.1% of 5-fluorouracil + leucovorin patients in study 12. More than 80% of patients with disease symptoms at the time of entry to study 12 reported improvements in symptoms after treatment with either drug. The results demonstrate the quality-of-life benefits that can be achieved with chemotherapy in a significant number of patients. These palliative improvements were more likely to occur in patients who responded to treatment or whose disease at

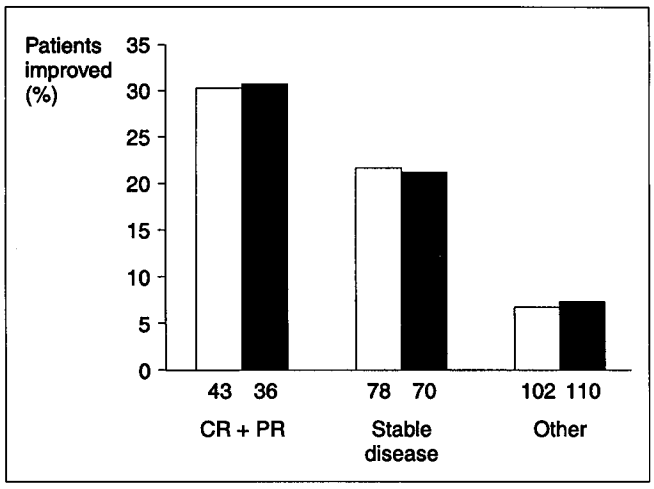

Fig. 1. Percentage of patients with an improvement in weight of at least 5% during study 3. Figures under columns denote numbers of patients. CR, complete response; PR, partial response; open bars, raltitrexed; closed bars, 5-fluorouracil + leucovorin.

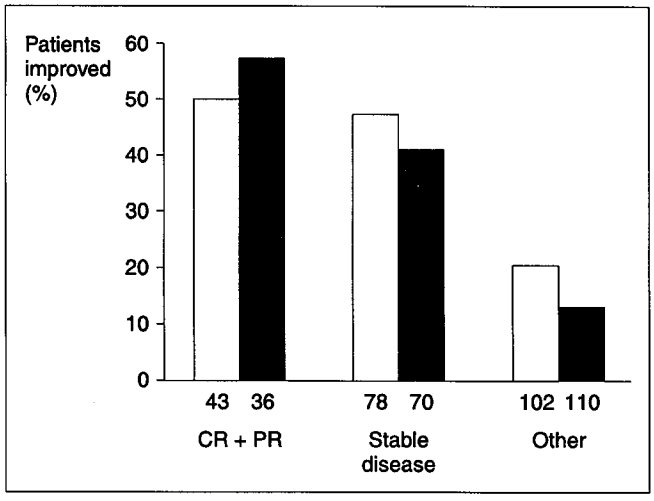

Fig. 2. Percentage of patients with an improvement in World Health Organization (WHO) performance status during study 3 (patients with a score of ≥1 at baseline). Figures under columns denote numbers of patients. CR, complete response; PR, partial response; open bars, raltitrexed; closed bars, 5-fluorouracil + leucovorin.

least remained stable during trial therapy, compared with patients who progressed. For example, in study 3 responders to treatment were more likely to gain weight (Fig. 1) or achieve an improvement in performance status (Fig. 2), compared with patients who did not achieve these treatment outcomes. These data suggest a substantial clinical benefit for patients with stable disease in addition to those who respond to treatment.

Discussion

Raltitrexed has now been studied in three large randomized clinical trials, incorporating 1393 patients with advanced colorectal cancer, representing a uniquely large database. The trials involved comparison of raltitrexed with standard 5-fluorouracil + leucovorin regimens, with a minimum follow-up for efficacy of between 9 and 15.5 months, and a minimum follow-up for survival of between 9 and 26 months.

Objective response rates were similar in the raltitrexed and 5-fluorouracil + leucovorin arms in all the comparative studies to date, and are consistent with the results of published studies [11–14]. Although slight but statistically significant increases in time to progression were seen in studies 10 and 12, the median survival did not differ significantly between groups for either study 3 or study 12, and only the North American study 10 demonstrated a statistically significant difference in overall survival in favour of 5-fluorouracil + leucovorin. It is interesting that in this study, which was not preceded by a phase II study in North America, the duration of treatment with 5-fluorouracil + leucovorin was almost twice that of raltitrexed. Problems associated with excess toxicity in the 4 mg/m^2 raltitrexed arm may have heightened awareness in investigators, which led to a lower relative threshold of continuation of raltitrexed therapy. Overall, the European/South African/Australian phase III studies demonstrate that the effects of raltitrexed on survival are comparable with those of 5-fluorouracil + leucovorin. The survival of patients receiving best supportive care alone is 5–6 months [15,16]. Survival in patients treated with raltitrexed ranged from 9.7 months to 11.2 months across the phase II and III studies, which is clearly longer than in patients given best supportive care alone. The median durations of survival with raltitrexed in randomized phase III studies (9.7–10.7 months) are consistent with the range of estimates of survival from published randomized studies [3,9,17–21] in patients treated with bolus 5-fluorouracil combined with either low-dose leucovorin (9.3–12.7 months) or high-dose leucovorin (8.0–13.5 months).

Active treatment with raltitrexed was associated with considerable palliative benefits, such as weight gain, improvement in performance status and improvement in disease symptoms in all three of the phase III studies. These palliative benefits were also comparable to those seen in the 5-fluorouracil + leucovorin groups. It is clear that for either treatment, the greatest palliative benefits are seen in patients who achieve a complete or partial response to treatment or stabilization of their disease (45–70% of all patients). The tolerability of raltitrexed in the phase III trials is discussed elsewhere in this supplement [22].

Conclusions

Four large trials incorporating 1570 patients have evaluated raltitrexed as treatment for advanced colorectal cancer. Three comparative phase III studies have shown that response rates with raltitrexed are comparable with those gained using standard 5-fluorouracil + leucovorin regimens. Survival in patients treated with raltitrexed is comparable to that described for 5-fluorouracil + leucovorin regimens in the literature, with two out of three large phase III studies confirming comparable survival in patients treated with raltitrexed and 5-fluorouracil + leucovorin. Raltitrexed also provides similar palliative benefits compared with 5-fluorouracil + leucovorin. The activity of raltitrexed, combined with a simpler and more convenient dosing schedule, thus represents a step forward in the treatment of advanced colorectal cancer.

References

1. Machover D, Goldschmidt E, Chollet P, *et al.*: **Treatment of advanced colorectal and gastric adenocarcinoma with 5-fluorouracil and high dose folinic acid.** *J Clin Oncol* 1986, **4**:685–696.
2. Doroshow JH, Multhauf P, Leang L, *et al.*: **Prospective randomized comparison of fluorouracil versus fluorouracil and high-dose continuous infusion leucovorin calcium for the treatment of advanced measurable colorectal cancer in patients previously unexposed to chemotherapy.** *J Clin Oncol* 1990, **8**:491–501.
3. Labianca R, Pancera G, Aitini E, *et al.*: **Folinic acid + 5-fluorouracil (5-FU) versus equidose 5-FU in advanced colorectal cancer. Phase III study of 'GISCAD' (Italian Group for the Study of Digestive Tract Cancer).** *Ann Oncol* 1991, **2**:673–679.
4. Moertel CG: **Chemotherapy for colorectal cancer.** *N Engl J Med* 1994, **330**:1136–1141.
5. Caudry M, Bonnel C, Floquet A, *et al.*: **A randomized study of bolus fluorouracil plus folinic acid versus 21-day fluorouracil infusion alone or in association with cyclophosphamide and mitomycin C in advanced colorectal carcinoma.** *Am J Clin Oncol* 1995, **18**:118–125.
6. Jackman AL, Farrugia DC, Gibson W, *et al.*: **ZD1694 ('Tomudex'): a new thymidylate synthase inhibitor with activity in colorectal cancer.** *Eur J Cancer* 1995, **31A**:1277–1282.
7. Cunningham D, Zalcberg J, Smith IE, *et al.*: **'Tomudex', a novel, specific thymidylate synthase inhibitor with clinical antitumour activity in a range of solid tumours [abstract 0904].** *Ann Oncol* 1994, **5** (suppl 8):179.
8. Zalcberg JR, Cunningham D, Van Cutsem E, *et al.*: **ZD1694: a novel thymidylate synthase inhibitor with substantial activity in the treatment of patients with advanced colorectal cancer.** *J Clin Oncol* 1996, **14**:716–721.
9. Poon MA, O'Connell MJ, Wieand HS, *et al.*: **Biochemical modulation of fluorouracil: evidence of significant improvement in survival and quality of life in patients with advanced colorectal carcinoma.** *J Clin Oncol* 1989, **7**:1407–1418.
10. Judson IR: **'Tomudex' (raltitrexed) development: preclinical, phase I and II studies.** *Anticancer Drugs* 1997, **8** (suppl 2):S5–S9.
11. Valone FH, Friedman MA, Wittlinger PS, *et al.*: **Treatment of patients with advanced colorectal carcinomas with fluorouracil alone, high dose leucovorin plus fluorouracil or sequential methotrexate, fluorouracil and leucovorin: a randomized trial of the Northern California Oncology Group.** *J Clin Oncol* 1989, **7**:1427–1436.
12. Kochwa W: **5-fluorouracil (5-FU) plus interferon 2-alpha (Roferon-A) versus 5-FU plus leucovorin (LV) in metastatic colorectal cancer: results of a multicentre multinational phase III study [abstract].** *Am Soc Clin Oncol* 1993, **12**:562.
13. Scheithauer W, Depisch D, Kornek G, *et al.*: **Randomized comparison of fluorouracil and leucovorin therapy versus fluorouracil, leucovorin and cisplatin therapy in patients with advanced colorectal cancer.** *Cancer* 1994, **73**:1562–1568.
14. Valsecchi R, Labianca R, Cascinu S, *et al.*: **High dose (HD) versus low dose (LD) L-leucovorin (LLV) as a modulator of 5-days 5-fluorouracil in advanced CRC: a GISCAD phase III study.** *Proc Am Soc Clin Oncol* 1995, **14**:457.
15. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D: **Randomized comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer.** *BMJ* 1993, **306**:752–755.
16. Smyth JF, Hardcastle JD, Denton G, *et al.*: **Two phase III trials of tauromustine (TCNU) in advanced colorectal cancer.** *Ann Oncol* 1995, **6**:948–949.
17. Poon MA, O'Connell MJ, Wieand HS, *et al.*: **Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer.** *J Clin Oncol* 1991, **9**:1967–1972.
18. Bobbio-Pallavicini E, Porta C, Moroni M, *et al.*: **Folinic acid does improve 5-fluorouracil activity *in vivo*: results of a phase III study comparing 5-fluorouracil to 5-fluorouracil and folinic acid in advanced colon cancer patients.** *J Chemother* 1993, **5**:52–55.
19. Buroker TR, O'Connell MJ, Wieand HS, *et al.*: **Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer.** *J Clin Oncol* 1994, **12**:14–20.
20. Corfu Study Group: **Phase III randomized study of two fluorouracil combinations with either interferon alfa-2a or leucovorin for advanced colorectal cancer.** *J Clin Oncol* 1995, **13**:921–928.
21. Recchia F, Nuzzo A, Lalli A, *et al.*: **Randomized trial of 5-fluorouracil and high-dose folinic acid with or without alpha-2B interferon in advanced colorectal cancer.** *Am J Clin Oncol* 1996, **19**:301–304.
22. Zalcberg J: **Overview of the tolerability of 'Tomudex' (raltitrexed): collective clinical experience in advanced colorectal cancer.** *Anticancer Drugs* 1997, **8** (suppl 2):S17–S22.