

Raltitrexed: current clinical status and future directions

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Raltitrexed ('Tomudex') monotherapy is a conveniently administered alternative to 5-fluorouracil (5-FU) in the first-line treatment of advanced colorectal cancer (CRC), and has single-agent activity in a variety of advanced solid tumours. Although both raltitrexed and 5-FU are thymidylate synthase inhibitors, raltitrexed has a specific mode of action and a toxicity profile distinct from 5-FU. The mechanism of action of raltitrexed is also completely different from that of oxaliplatin, irinotecan and other drugs with which it has been combined. These properties, together with preclinical data, suggested that combinations of raltitrexed with 5-FU, other chemotherapeutic agents, or radiotherapy could result in improved therapies for a variety of advanced solid tumours, including advanced CRC. This review outlines the appropriate management of patients treated with raltitrexed, whether as monotherapy or in combination, and discusses the preliminary results of combination studies with raltitrexed in a range of tumour types including advanced CRC, malignant mesothelioma, gastric, pancreatic, head and neck, and non-small-cell lung cancers. Of particular interest is the combination of raltitrexed and oxaliplatin, which has shown promising antitumour effects in first-line treatment of advanced CRC and malignant mesothelioma, a disease that is refractory to chemotherapy.

Key words: colorectal cancer, 5-fluorouracil, mesothelioma, oxaliplatin, raltitrexed

Introduction

Raltitrexed ('Tomudex') is a specific inhibitor of thymidylate synthase (TS). It predominantly enters the cell via the reduced folate carrier and then undergoes polyglutamation. The polyglutamated form is more potent than the parent compound. It is retained in the cell and prevents TS from binding to its folate cofactor. 5-fluorouracil (5-FU) is also an inhibitor of TS. However, it is metabolised into several active agents, including the TS inhibitor fluorodeoxyuridine monophosphate, which binds to the pyrimidine binding site of the enzyme [1]. Other 5-FU metabolites have multiple effects such as nonspecific disruption of RNA and DNA synthesis [2].

Although 5-FU has been the basis of standard treatment for advanced colorectal cancer (CRC), tumour responses are often disappointing. In addition, the optimum treatment regimen remains unclear despite extensive investigation of i.v.- and bolus-dosing schedules, and combination with a variety of modulating agents, particularly leucovorin (LV) [3]. Bolus and infusional 5-FU–LV regimens are still used as standard in many areas, but the current standard therapy for advanced

CRC is generally a combination of 5-FU–LV with either oxaliplatin or irinotecan [4–7]. However, toxicity continues to be problematic in some 5-FU treatment schedules and alternative agents are needed for use in monotherapy and combination regimens.

Raltitrexed is an alternative to standard 5-FU–LV-based regimens for the first-line treatment of advanced CRC. In three out of four phase III randomised studies, median survival with raltitrexed (9.7–10.9 months) was comparable to that of bolus or infusional 5-FU–LV (10.0–12.7 months) [8–11]. Response rates with raltitrexed were equivalent to those of either bolus or infusional 5-FU-based regimens in all four studies. However, in two of the four trials the additional protocol end point, of time to progression, was significantly shorter in the group of patients receiving raltitrexed than the group treated with 5-FU–LV [9, 10]. The tolerability of raltitrexed has also been well defined in trials in more than 1000 patients with advanced CRC. While it has an acceptable and manageable toxicity profile if administered appropriately, like other cytotoxic agents, such as 5-FU, it is associated with systemic, gastrointestinal and haematological side effects [12]. However, there is a significantly lower incidence of both severe leucopenia and mucositis with raltitrexed compared with bolus 5-FU–LV regimens. Although raltitrexed is associated with a statistically significant higher incidence of severe increases in liver transaminases than bolus 5-FU–LV regimens,

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such changes are usually asymptomatic and self-limiting when not associated with disease progression. Also, reduced incidences of diarrhoea have been recorded during treatment with raltitrexed compared with 5-FU regimens [9, 10].

Combinations of raltitrexed with other active antitumour agents, with different mechanisms of action and distinct tolerability profiles, may be expected to offer improved efficacy whilst maintaining acceptable toxicity. Based on these properties, possible combinations with raltitrexed include 5-FU, irinotecan, platinum-based agents (e.g. cisplatin and oxaliplatin) and radiotherapy. This review summarises raltitrexed combination therapy studies in advanced CRC and other solid tumour types for which treatment prospects are emerging. Furthermore, recommendations are provided for the appropriate management of patients receiving raltitrexed treatment, whether as monotherapy or in combination, based on extensive clinical experience.

Safety and patient management

As expected with cytotoxic therapy, life-threatening toxicity has been reported with raltitrexed in all of the large phase III studies. Most of the treatment-related deaths (3.8% raltitrexed compared with 2.6% 5-FU-LV) appeared to be due to a combination of gastrointestinal toxicity (mainly diarrhoea) and myelosuppression, usually with infection or sepsis [12]. Many occurred in the absence of appropriate dose reductions as specified in the 'prescribing information'. When patients were excluded who did not receive appropriate dose reductions or delays, or who were not treated according to the 'prescribing information', the incidence of treatment-related deaths was 1.3% during treatment with raltitrexed, compared with 1.7% during treatment with bolus 5-FU-LV [12]. Qualitatively similar events were observed in a large multicentre trial, designed to compare raltitrexed in the adjuvant setting with the standard regimen of 5-FU plus folinic acid. The trial was ended when the number of drug-related deaths in the raltitrexed group (1.9%) was double that in the control group (0.8%). However,

Table 1. Raltitrexed dose reduction criteria based on creatinine clearance

Creatinine clearance (ml/min)	Dose (% of 3.0 mg/m ²)	Dosing interval
>65	100	3-weekly
55–65	75	4-weekly
25–54	50	4-weekly
<25	No therapy or stop therapy	

the majority of deaths in the raltitrexed group (65%) were due to serious deviations from the trial protocol, including failure to modify the dose of raltitrexed based on creatinine clearance calculations [13].

Since renal excretion (extrapolated to infinity) accounts for 40–50% of the total raltitrexed dose in patients with normal renal function [14], impaired renal function (creatinine clearance <65 ml/min) may result in plasma accumulation, leading to increased toxicity [15]. Indeed, poor toxicity outcomes have been associated with impaired renal function without appropriate dose modification. To ensure that patients receive a dose suitable for their renal status, serum creatinine measurements must be made prior to the start of treatment and before each subsequent treatment. If an abnormal serum creatinine level is detected, creatinine clearance should be calculated or measured and the raltitrexed dose modified accordingly (Table 1). In addition, serum creatinine may not correlate well with creatinine clearance, for example, if the patient is elderly or has undergone a sudden weight loss. In this case, creatinine clearance should also be calculated or measured and the dose of raltitrexed modified if appropriate.

Dose modifications or delays are also necessary following the occurrence of gastrointestinal and/or haematological toxicities. It is recommended that treatment with raltitrexed is postponed until all signs of gastrointestinal or haematological events have resolved, and then treatment resumed at a reduced dose or stopped as appropriate, depending on the severity of toxicity (Table 2). Once the dose has been reduced, all sub-

Table 2. Raltitrexed dose reduction criteria based on the worst grade of gastrointestinal and haematological toxicity in the previous cycle

Haematological toxicity ^a	Gastrointestinal toxicity ^b				
	Grade 0 (%) ^c	Grade 1 (%) ^c	Grade 2 (%) ^c	Grade 3 (%) ^c	Grade 4
Grade 0	100	100	75	50	Stop treatment
Grade 1	100	100	75	50	Stop treatment
Grade 2	100	100	75	50	Stop treatment
Grade 3	75	75	75	50	Stop treatment
Grade 4	50	50	50	Stop treatment	Stop treatment

^aWHO toxicity grades of leucopenia, neutropenia or thrombocytopenia.

^bWHO toxicity grades of diarrhoea or mucositis.

^cDose as percentage of 3.0 mg/m².

sequent doses should be given at the reduced dose. Although dose modifications may prevent the development of further toxicities, it is paramount that any side effects are treated promptly, particularly diarrhoea, vomiting, fever, infections or stomatitis. Patients experiencing diarrhoea and vomiting should be carefully monitored to ensure that the resulting dehydration is managed promptly. Those with severe gastrointestinal and haematological toxicity should receive rehydration and appropriate antibiotic support and possibly cytokine support if indicated. A recent preclinical study has suggested that folate rescue with LV may be beneficial in the small minority of patients who present with severe antiproliferative toxicities [16]. Another option for patient management is to use supportive drugs prophylactically, to reduce the incidence of side effects following treatment with raltitrexed. 5-HT₃ inhibitors, such as ondansetron, seem to reduce the severity of nausea and vomiting [17, 18]. Nystatin may reduce the severity of stomatitis, and dexamethasone may reduce fever in the small number of patients who present with these effects [17]. Indeed, in a study of 58 patients treated prophylactically with a combination of ondansetron, dexamethasone, ranitidine and nystatin, no patients reported grade 3 or 4 gastrointestinal toxicity [17].

These recommendations for patient management have been based on clinical experience with patients receiving raltitrexed monotherapy for advanced CRC. However, they are equally applicable to combination studies in a range of tumour types. It could be expected that a combination of raltitrexed with another cytotoxic agent would lead to additive toxicity. However, results from the following, albeit relatively small, phase I and II studies do not suggest that this is the case. Indeed, in many of these studies raltitrexed could be combined with another chemotherapeutic agent, often almost at its recommended dose for single-agent use.

Raltitrexed combination studies

Advanced colorectal cancer

The recent introduction of new drugs with single-agent activity against advanced CRC but with distinct mechanisms of action has enabled the investigation of combination regimens. In two phase III studies of oxaliplatin in combination with infusional 5-FU and calcium folinate, the response rate and progression-free survival were better than with just 5-FU and calcium folinate [4, 5]. However, these studies did not show survival benefits. Another phase III study, primarily conducted in Europe, compared irinotecan combined with 5-FU–LV, and 5-FU–LV alone, as first-line therapy for metastatic CRC [6]. The results showed that progression-free survival (median 6.7 compared with 4.4 months, $P < 0.001$) and objective response rate (35% compared with 22%, $P < 0.005$) were significantly improved with the triple-drug therapy compared with the two-drug therapy. These results were complemented by an American phase III study, which com-

pared the combination irinotecan–5-FU–LV with bolus doses of 5-FU–LV [7]. The irinotecan–5-FU–LV combination consistently provided significantly higher response rates (33% compared with 18%, $P < 0.001$) and median time to treatment failure (5.0 compared with 3.8 months, $P < 0.05$). Moreover, irinotecan–5-FU–LV is the only treatment to show a survival advantage in metastatic CRC over high-dose continuous infusion 5-FU–LV.

The results of these studies into combination chemotherapy as first-line treatment for CRC have clearly shown that it is more active than monotherapy. However, there are still opportunities for improvement and this provides the rationale for investigations into combination therapy with raltitrexed.

Raltitrexed–5-FU combination

Although raltitrexed and 5-FU are both inhibitors of TS, they act via different mechanisms, occupy different binding sites and have different specificities for the enzyme. A metabolite of 5-FU, F-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), binds to the pyrimidine binding site of TS, leading to depletion of dTTP and reducing the rate of DNA synthesis.

Preclinical observations using *in vitro* human carcinoma cell lines consistently showed sequence-specific additive or synergistic cytotoxicity [19]. In the case of the HCT-8 cell line, raltitrexed leads to an increase of intracellular phosphoribosyl pyrophosphate (PRPD), which suggests that the cytotoxic effects of raltitrexed combined with 5-FU may be due to the increased formation of 5-FU nucleotides. This in turn leads to enhanced incorporation of 5-FU nucleotides into RNA and increased cell killing. Whether this factor is responsible for the synergistic activity in this cell line, or if this observation extends to other cell lines, is unknown. Because of their different cellular pharmacology, raltitrexed and 5-FU present several different sites for interaction that may be very complex.

A summary of phase I and II trials in which a combination of raltitrexed and 5-FU (bolus, infusion or oral fluoropyrimidines) has been used as first- or second-line therapy is given in Table 3. It was observed that the two agents can be combined almost at their respective recommended doses as single agents. Manageable tolerability and favourable response rates have resulted from such combinations. Further promising response rates have been obtained with triple combinations that include these two agents [20].

Raltitrexed–oxaliplatin combination

Oxaliplatin is a platinum derivative, which is active as a single-agent as a first-line treatment for patients with advanced CRC [21, 22] and *in vitro* studies have demonstrated an additive effect with raltitrexed [23]. Platinum-based agents largely act by forming intrastrand DNA–platinum adducts/crosslinks, between two adjacent guanine:guanine or guanine:adenine base pairs, leading to DNA strand breaks and p53-dependent apoptosis. Excision- or mismatch-repair processes may repair

Table 3. Raltitrexed combination studies with 5-FU in patients with advanced or metastatic CRC.

Study	Schedule	1st or 2nd line	No. of patients	Phase	Main DLT	RD (mg/m ²)	Response rate (95% CI)
Raltitrexed–infusional 5-FU [49]	Raltitrexed (15 min inf) on days 8 and 22 + 5-FU (24 h inf) weekly ×5 for 5 weeks, q 6 weeks	1st	43	I	Neutropenia, thrombocytopenia, diarrhoea	2.6/2600	46% (28% to 65%)
Raltitrexed–UFT [50]	Raltitrexed (15 min inf) on days 1 and 22 + UFT (tid orally) on days 1–28, q 6 weeks	1st	32	I/II	Diarrhoea	Not yet defined Current dose: 3.5 ^a /300	39%
Raltitrexed–bolus 5-FU [51]	Raltitrexed (15 min inf) on day 1 + 5-FU (bolus) on day 2, q 3 weeks	1st and 2nd	63	I	Neutropenia	5.5 ^a /1200	14%
Raltitrexed–HCFU [52]	Raltitrexed (15 min inf) on day 1 + HCFU (orally) on days 2–14, q 3 weeks	1st and 2nd	28	I/II	Diarrhoea, fatigue	3.0/300	1st line: 50% (29% to 71%)
Raltitrexed–HCFU [18]	Raltitrexed (15 min inf) on day 1 + HCFU (orally) on days 2–14, q 3 weeks	1st and 2nd	31	II	na	3.0/300	1st line: 42%; 2nd line: 12.5%
Raltitrexed–bolus 5-FU + LFA [53]	Raltitrexed (15 min inf) on day 1 + LFA 250 mg/m ² fixed dose (2 h inf) + 5-FU (bolus) on day 2, q 2 weeks	2nd	41	I	Neutropenia	3.0/1050	15% (6% to 30%)
Raltitrexed–5-FU–oxaliplatin [20]	Oxaliplatin (2 h inf) followed by raltitrexed (15 min inf) on day 1 + LFA 250 mg/m ² fixed dose (2 h inf) + 5-FU (bolus) on day 2, q 2 weeks	2nd	52	I	Neutropenia	3.0/1050/130	26% (14% to 41%)

^a>recommended dose of 3.0 mg/m² once every 3 weeks for monotherapy.

CI, confidence interval; DLT, dose-limiting toxicity; HCFU, carmofur; inf, infusion; LFA, levofolinic acid; na, not available; RD, recommended dose; UFT, tegafur.

these breaks provided deoxyribonucleotides are available. It has been hypothesised that the synergistic effects of combination with raltitrexed are due to depletion of dTTP and subsequent interference with the repair process. Thus, the combination of raltitrexed and oxaliplatin is an attractive proposition, with simple and concomitant administration of both drugs, distinct mechanisms of action resulting in different toxicity profiles and the potential for at least additive antitumour activity.

A phase I study first demonstrated promising activity for this combination, with stable disease lasting for at least 3 months in six out of 11 heavily pretreated patients, with progressive advanced CRC before inclusion [24]. The recommended dose was determined as raltitrexed 3.0 mg/m² with oxaliplatin 130 mg/m², and dose-limiting toxicities (DLTs) were asthenia, nausea and vomiting. The efficacy of this combination as a first-line treatment for advanced CRC was subsequently confirmed in two phase II studies (Table 4) with objective response rates of 46% [25] and 60% [26] and disease progression in only 4% and 8% of patients, respectively (Figure 1).

The response rates with raltitrexed–oxaliplatin are comparable to those with oxaliplatin–5-FU–LV and irinotecan–5-FU–LV. In phase III trials, the combination of oxaliplatin–5-FU–LV resulted in response rates of 53% [4] and 51% [5]. Similarly, the combination of irinotecan–5-FU–LV resulted in confirmed response rates of 39–41% in phase III studies [6, 7]. Median survival was 14.9 months with the raltitrexed–oxali-

platin combination (Table 4), which was comparable to that obtained with oxaliplatin–5-FU–LV and irinotecan–5-FU–LV combinations.

The promising phase I and preliminary phase II data with the raltitrexed–oxaliplatin combination as a first-line treatment, prompted the initiation of a phase II study of this combination as a second-line therapy in patients with advanced CRC. This showed a promising activity; the reported response rate was 16% [27].

Raltitrexed–irinotecan combination

Irinotecan is a DNA topoisomerase I inhibitor that inhibits cell division. It is approved as a single agent for the treatment of 5-FU-refractory CRC. Furthermore, the addition of irinotecan to 5-FU–LV, as first-line treatment for metastatic CRC, significantly increased median survival compared with just 5-FU–LV [6, 7]. *In vitro* studies have demonstrated synergistic cytotoxicity with a short-term exposure to SN38, the active metabolite of irinotecan, followed by raltitrexed [28]. It was observed, however, that the reverse sequence, longer exposure or co-exposure had an antagonistic effect, which led to the hypothesis that raltitrexed reduces the rate of DNA synthesis. This, in turn, reduces the rate at which the topoisomerase I–SN38 cleavable complex is converted into DNA strand breaks.

A phase I study has demonstrated that the combination of raltitrexed and irinotecan has activity, with manageable toxic-

Table 4. Phase II results of raltitrexed–oxaliplatin combination studies in patients with advanced CRC.

Study	Douillard et al. [26]	Scheithauer et al. [25]
Treatment	Raltitrexed 3 mg/m ² (15-min inf) + oxaliplatin 130 mg/m ² (2-h inf) ^a , q 3 weeks	Raltitrexed 3 mg/m ² (15-min inf) + oxaliplatin 130 mg/m ² (2-h inf) ^a , q 3 weeks
Phase	II	I/II
Patients entered	71 patients with advanced CRC (all first-line)	69 patients with advanced CRC (all first-line)
Response rate (95% CI)	60% (47% to 71%)	46% (31% to 61%) ^a
Complete response	1 in 63 patients (2%)	1 in 48 patients (2%)
Partial response	37 patients (59%)	21 patients (44%)
Stable disease	20 patients (32%)	24 patients (50%)
Progressive disease	5 patients (8%)	2 patients (4%)
Median survival (range)	14.9 months (0.4–21+)	Not yet reached after a median follow-up of 13 months
Median response duration (range)	9.4 months (2.3–21+)	na
Median time to progression (range)	6.4 months (0.5–21+)	na
Grade 3 or 4 adverse events in ≥10% of patients		
Neutropenia	28 patients	21 patients
Elevated transaminases	23 patients	12 patients
Diarrhoea	17 patients	na
Leucopenia	16 patients	na
Vomiting	14 patients	na
Nausea	13 patients	na

^aAt recommended dose.

CI, confidence interval; inf, infusion; na, not available

ity, in 5-FU pretreated patients with advanced gastrointestinal cancer [29]. Of 30 evaluable patients, six (20%) had a partial response. The recommended dose was irinotecan 350 mg/m² (30 min infusion), followed after 30 min with raltitrexed 3 mg/m² (15 min infusion), on a 3-weekly schedule. DLTs were lethargy and diarrhoea. A further phase I study is ongoing to

determine the recommended dose of a triple combination of raltitrexed, irinotecan and 5-FU (Maroun, Canada).

Raltitrexed–radiotherapy combination

A number of studies have demonstrated benefits of combining preoperative or postoperative 5-FU with radiotherapy, compared with radiotherapy alone, in patients with rectal cancer [30]. Like 5-FU, raltitrexed has radiosensitising effects and has been shown in preclinical studies to be at least equivalent to 5-FU in inhibiting tumour cell survival and tumour xenograft growth in irradiation studies [31]. Therefore, a series of trials have been initiated to investigate combinations of raltitrexed with radiotherapy.

Phase I studies have defined the recommended doses of raltitrexed in combination with preoperative [32] and postoperative [33] radiotherapy, and in patients with advanced inoperable/recurrent rectal cancer [34] (Table 5). An encouraging response rate of 73% (eight of 11 patients, including three complete responses, assessed according to WHO criteria) was observed in the preoperative study. An ongoing phase II study will further evaluate this combination in the preoperative setting and two ongoing phase II trials are assessing the efficacy of raltitrexed and radiotherapy in patients with advanced inoperable or recurrent rectal cancer.

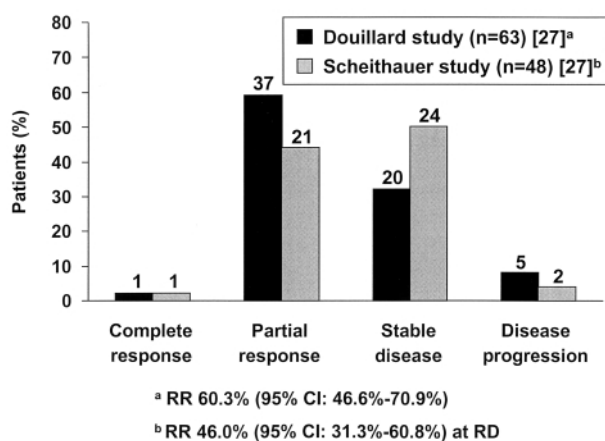


Figure 1. Objective responses in raltitrexed–oxaliplatin combination studies in patients with advanced CRC. CI, confidence interval; RD, recommended dose; RR, response rate.

Table 5. Phase I raltitrexed chemoradiation studies in patients with rectal cancer.

Study	Schedule	Patients	DLTs	RD (mg/m ²)	Response rate
Preoperative [32]	45 Gy radiotherapy in 1.8 Gy daily fractions 5× per week for 5 weeks followed by a 5.4 Gy boost on day 38. Raltitrexed (15-min inf) 1 h prior to radiotherapy on days 1, 19 and 38. Surgery + intraoperative 10 Gy radiotherapy following 6–8 weeks rest	14 patients with TNM stage II/III resectable adenocarcinoma of the extraperitoneal rectum with no distant metastases	Leucopenia	3.0	73% of 11 patients
Postoperative [33]	Surgery followed by 4–6 weeks rest. 50.4 Gy radiotherapy in 1.8 Gy daily fractions 5× per week for 5–6 weeks. Raltitrexed (15-min inf) 1 h prior to radiotherapy on days 1 and 22	22 patients with Dukes' stage B or C adenocarcinoma of the rectum who had curative resections	Diarrhoea, elevated transaminase levels, leucopenia, neutropenia	2.6	Not evaluated
Advanced [34]	50 Gy radiotherapy in 2.0 Gy daily fractions 5× per week for 5 weeks. Raltitrexed (15-min inf) 1 h prior to radiotherapy on days 1 and 22	19 patients with advanced inoperable/recurrent rectal cancer	Diarrhoea, neutropenia, anaemia, leucopenia	2.6	Not evaluated

Other developments may include shorter dosing intervals of raltitrexed to potentially increase radiosensitising effects, and combination with other drugs such as oxaliplatin to further enhance chemoradiation efficacy. Indeed, a phase I study of raltitrexed–oxaliplatin and radiotherapy is ongoing [35]. Chemoradiotherapy with raltitrexed is also being investigated in patients with pancreatic or head and neck cancer.

In general, results from trials in advanced CRC have been encouraging and support the continued investigation of all the combinations investigated to date. Preliminary data also indicate that such combinations may be beneficial in patients with other solid tumours.

Malignant mesothelioma

Patients with malignant mesothelioma, a tumour of the pleura or peritoneum, have a poor prognosis, with median survival generally ranging from 4 months for extensive malignant disease to 18 months for malignant local pleural disease [36]. Malignant mesothelioma is relatively refractory to chemotherapy and, as there is no standard therapy, patients with malignant mesothelioma are routinely proposed for entry into trials assessing new drugs and combinations.

Encouraging initial results using a combination of raltitrexed–oxaliplatin in patients with malignant mesothelioma prompted the enrolment of such patients, with a range of advanced solid tumours, into a phase I/II trial. Ultimately, interesting antitumour activity was observed, with six objective partial responses among 17 assessable patients (35%, 95% confidence interval 14% to 59%). These included four patients who were considered to be cisplatin-refractory as defined by disease progression (Table 6). This result supported the initiation of a phase II trial [37]. Preliminary results are again promising, with a response rate of 25% among 56 evaluable patients (Figure 2), indicating that this combination warrants further investigation in phase III studies in patients with malignant mesothelioma.

Currently, the combination of raltitrexed and cisplatin, compared with cisplatin alone, is being investigated in a phase III

study in patients with malignant mesothelioma (European Organisation for Research and Treatment of Cancer). The recommended dose for this study was determined in a phase I study in patients with non-small-cell lung cancer (NSCLC) (see below). The results of this phase III study are eagerly awaited.

Non-small-cell lung cancer

NSCLC is the most commonly occurring form of lung cancer. Although no standard chemotherapy regimen exists for the treatment of metastatic NSCLC, cisplatin-based combination chemotherapy is commonly used [38]. A phase I trial of raltitrexed with cisplatin in metastatic NSCLC established the maximum tolerated doses of the 3-weekly combination to be raltitrexed 3.5 mg/m² and cisplatin 80 mg/m², and determined that the recommended dose for further study was raltitrexed 3.0 mg/m² and cisplatin 80 mg/m². The toxicity was predictable and manageable, and was similar to that frequently observed with cisplatin alone or in combination. Toxicity solely related to raltitrexed included diarrhoea [39].

Advanced gastric cancer

The prognosis for patients with advanced gastric cancer is poor. However, combination chemotherapy has resulted in significant survival advantages compared with best supportive care alone. At present, many of the active regimens in advanced gastric cancer include 5-FU infusion in combination with cisplatin, and often also a third agent, such as an anthracycline. High response rates have been obtained, in particular with the use of protracted venous infusional 5-FU, cisplatin and epirubicin (ECF regimen) [40]. However, this regimen uses an indwelling central venous catheter, with significant morbidity. The option of replacing the infusional 5-FU with raltitrexed has therefore been investigated.

Promising efficacy results were obtained in the phase I dose-finding study, in patients with inoperable advanced gastro-oesophageal cancer who received a regimen including

Table 6. Raltitrexed combination studies in patients with a range of advanced solid tumours

Tumour type	Study	Schedule	Patients	Phase	Results
Malignant mesothelioma	Raltitrexed–oxaliplatin [24]	Raltitrexed (15-min inf) followed 45 min later by oxaliplatin (2-h inf), q 3 weeks	48 patients (9 chemo-naive) with advanced solid tumours, 17 of whom had malignant mesothelioma	I	RD: raltitrexed 3 mg/m ² –oxaliplatin 130 mg/m ² ; DLT: asthenia, vomiting, nausea, anorexia, visual neurotoxicity, thrombocytopenia, diarrhoea, peripheral neuropathy, pain; RR: 35% (95% CI 14% to 59%) of 17 patients with malignant mesothelioma
	Raltitrexed–oxaliplatin [37]	Raltitrexed 3 mg/m ² (15-min inf) followed 45 min later by oxaliplatin 130 mg/m ² (2-h inf), q 3 weeks	72 patients (56 chemo-naive)	II	RR: 25% (95% CI 15% to 37%) of 56 patients; Median survival of chemo-naive patients: 189 days (95% CI 147 to 222 days) from start of treatment, 309 days (95% CI 259 to 439 days) from diagnosis; Grade 3 or 4 adverse events in ≥10% of patients: asthenia (21%), anorexia (13%), elevated transaminase levels (13%)
NSCLC	Raltitrexed–cisplatin [39]	Raltitrexed (15-min inf) followed by cisplatin (1–2 h inf), q 3 weeks	21 patients with metastatic NSCLC (all chemo-naive)	I	RD: raltitrexed 3.0 mg/m ² –cisplatin 80 mg/m ² ; DLT: diarrhoea, asthenia, anaemia, neutropenia, thrombocytopenia, elevated bilirubin levels; RR: 16% (95% CI 8% to 33%) of 19 patients
Advanced gastric cancer	Raltitrexed–cisplatin–epirubicin [41]	Raltitrexed (15-min inf) followed by cisplatin 60 mg/m ² (4-h inf) + epirubicin 50 mg/m ² (bolus)	24 patients with inoperable gastro-oesophageal adenocarcinoma (all first-line)	I	RD: raltitrexed 2.5 mg/m ² –cisplatin 60 mg/m ² –epirubicin 50 mg/m ² ; DLT: neutropenia, diarrhoea, stomatitis; RR: 45% of 20 patients
	Raltitrexed–cisplatin–epirubicin [42]	Raltitrexed 2.5 mg/m ² (15-min inf) followed by cisplatin 60 mg/m ² (4-h inf) + epirubicin 50 mg/m ² (bolus)	21 patients with inoperable gastro-oesophageal adenocarcinoma (all first-line)	II	RR: 29% (95% CI 11% to 52%) of 21 patients entered; Median survival: 18 weeks from the start of chemotherapy; Grade 3 or 4 adverse events: neutropenia (45%), leucopenia (35%), fatigue (20%), diarrhoea (15%), nausea and vomiting (10%); three treatment-related deaths
	Raltitrexed–doxorubicin [54]	Raltitrexed (15-min inf) followed by doxorubicin (20-min inf), q 3 weeks	25 inoperable patients with metastatic cancer, 20 of whom had gastric cancer (all first-line)	I	RD: raltitrexed 3.5 mg/m ² –doxorubicin 60 mg/m ² ; DLT: febrile neutropenia, granulocytopenia; RR: 29% (95% CI 8% to 58%) of 20 patients
Pancreatic	Raltitrexed–gemcitabine [45]	Raltitrexed (15-min inf) on day 1 followed 15 min later by gemcitabine (30-min inf) on days 1 and 8, q 3 weeks	31 patients (20 chemo-naive) with advanced incurable solid tumours	I	RD: raltitrexed 3.5 mg/m ² –gemcitabine 800 mg/m ² ; DLT: thrombocytopenia, granulocytopenia, diarrhoea, hyperglycaemia, shortness of breath; RR: 8% (1 CR unconfirmed) of 26 patients (14 patients had SD, including the two entered patients with pancreatic cancer)
Head and neck cancer	Raltitrexed–5-FU–LFA [53]	Raltitrexed (15-min inf) on day 1 + LFA 250 mg/m ² (2-h inf) and 5-FU (bolus) on day 2, q 2 weeks	58 patients (42 second-line) including 17 with advanced head and neck cancer	I	RD: raltitrexed 3.0 mg/m ² –LFA 250 mg/m ² –5-FU 1050 mg/m ² ; DLT: neutropenia, renal toxicity; RR: 35% (95% CI 14% to 62%) of 17 patients with head and neck cancer
	Raltitrexed–cisplatin–5-FU–LFA [47]	Cisplatin (1-h inf) and raltitrexed (15-min inf) on day 1, LFA 250 mg/m ² (2-h inf) and 5-FU (bolus) on day 2, q 2 weeks	45 patients with locally advanced/metastatic head and neck cancer (all first-line)	I/II	RD: cisplatin 60 mg/m ² –raltitrexed 2.5 mg/m ² –LFA 250 mg/m ² –5-FU 900 mg/m ² ; DLT: neutropenia, fatigue; RR: 67% (95% CI 51% to 80%) of 45 patients; 100% of 15 patients treated at RD
	Raltitrexed–cisplatin [48]	Raltitrexed (15-min inf) followed by cisplatin 100 mg/m ² (4-h inf) on day 1, q 3 weeks	14 patients with locally advanced/metastatic head and neck cancer (all first-line)	I/II	RD: raltitrexed 3.0 mg/m ² –cisplatin 80 mg/m ² ; DLT: neutropenia, diarrhoea, thrombocytopenia, lethargy, elevated transaminases; RR: 69% of 13 evaluable patients

^a>recommended dose, of 3.0 mg/m² once every 3 weeks, for monotherapy.

CI, confidence interval; CR, complete response; DLT, dose-limiting toxicity; LFA, levofofolic acid; NSCLC, non-small-cell lung cancer; RD, recommended dose; RR, response rate; SD, stable disease.

raltitrexed, cisplatin and epirubicin (Table 6). Of 20 evaluable patients, nine (45%) responded to therapy [41], prompting a phase II study. Initial results showed a response rate of 29%. However, concerns resulting from treatment-related deaths during the trial due to neutropenic sepsis (one patient) and cardiorespiratory complications of chemotherapy-induced

enteritis (one patient), and one death considered to be possibly treatment-related due to myocardial infarction, led to premature termination of this trial [42]. A phase I study has also determined the recommended doses for a combination of raltitrexed and the anthracycline doxorubicin as treatment for advanced or metastatic gastric cancer (Table 6).

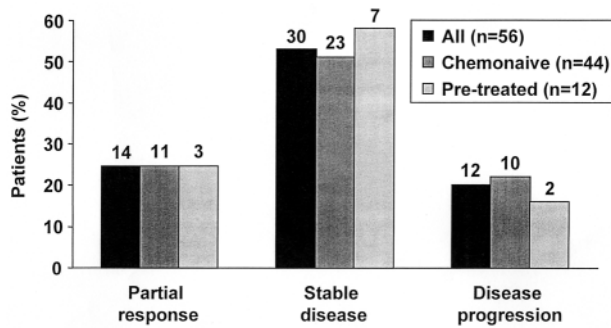


Figure 2. Objective responses in raltitrexed–oxaliplatin combination studies in patients with malignant mesothelioma.

Pancreatic cancer

The prognosis is extremely poor for patients with pancreatic cancer, due to difficulties in diagnosis, the aggressiveness of pancreatic cancers and the lack of effective systemic therapies. Patients with locally advanced disease and a reasonable performance status are commonly treated with 5-FU-based chemoradiotherapy. However, the limited therapeutic options and modest impact of such treatment on survival warrants the investigation of new therapies in patients with locally advanced disease. A phase II trial of raltitrexed with radiotherapy is ongoing in patients with locally advanced, inoperable but non-metastatic pancreatic cancer (Price, UK).

Similarly, most studies of single-agent or combination chemotherapy in patients with advanced pancreatic cancer have resulted in low response rates and little reproducible effect on survival or quality of life. 5-FU remains the most extensively studied agent for pancreatic cancer; however, in a randomised comparison, gemcitabine treatment resulted in a significantly higher clinical benefit response (24% compared with 5%) and median survival, although this was still only 6 months [43]. Raltitrexed monotherapy also has modest activity in patients with advanced pancreatic cancer: a response rate of 5% was obtained in a phase II study. However, the majority of these patients had been pretreated [44].

A combination of raltitrexed and gemcitabine is currently being investigated in phase II trials in patients with advanced or metastatic pancreatic cancer (Sleeboom, Holland; Borner, Switzerland) and advanced pancreatic and biliary tract cancer (van Laethem, Belgium). The recommended dose for these studies was determined in a phase I study in patients with a range of tumour types in which two patients with pancreatic cancer had disease stabilisation (Table 6) [45].

Head and neck cancer

The median survival for patients with locally advanced or metastatic head and neck cancer is 6 months, a figure that has not been improved by chemotherapy. Therefore, such patients are candidates for trials of new agents and combinations [46]. The most active single agents include methotrexate, cisplatin

and 5-FU. Standard treatment is a combination chemotherapy regimen, most commonly cisplatin with infusional 5-FU.

A phase I study of raltitrexed–5-FU with levofolinic acid (LFA) has demonstrated an encouraging response rate (35%) in patients with locally advanced or metastatic head and neck cancer [47]. However, rather than continue with this regimen in phase II studies, the investigators decided to add cisplatin, the most active single-agent in head and neck cancer, to the combination. The ensuing phase I/II study demonstrated that it is possible to combine cisplatin, raltitrexed and 5-FU at doses close to their single-agent doses with an encouraging response rate (67%) in patients receiving first-line therapy for the treatment of locally advanced or metastatic squamous cell carcinoma of the head and neck. Furthermore, all of the 15 patients treated at the recommended dose achieved an objective response. A randomised phase II trial comparing cisplatin–raltitrexed–5-FU–LFA with cisplatin–methotrexate–5-FU–LFA is ongoing. A phase I/II trial has also defined the recommended dose for the combination of raltitrexed and cisplatin [48].

Summary and future perspectives

Raltitrexed is established in the first-line treatment of advanced CRC. It has a convenient administration schedule, and an acceptable and manageable toxicity if given appropriately. However, as with other cytotoxic agents, careful management of patients is required to avoid serious toxicity. Combinations of raltitrexed with a broad range of cytotoxic agents have been shown to be feasible in colorectal, lung, gastric, and head and neck cancers. Schedules have been established for combination with 5-FU, oxaliplatin, irinotecan, cisplatin, doxorubicin, gemcitabine and radiotherapy. Promising results have been obtained with combination chemotherapy in patients with advanced CRC (with first-line response rates ranging from 39 to 60%) and other advanced solid tumours, especially malignant mesothelioma. Ongoing studies should further establish a role for raltitrexed as a component of combination therapies in a variety of advanced solid tumours.

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‘Tomudex’ is a trade mark of the AstraZeneca group of companies.

References

1. Jackman AL, Kimbell R, Ford HE. Combination of raltitrexed with other cytotoxic agents: rationale and preclinical observations. *Eur J Cancer* 1999; 35 (Suppl 1): S3–S8.
2. Thomas DM, Zalcberg JR. 5-fluorouracil: a pharmacological paradigm in the use of cytotoxics. *Clin Exp Pharmacol Physiol* 1998; 25: 887–895.

3. Vincent M, Labianca R, Harper P. Which 5-fluorouracil regimen?—the great debate. *Anticancer Drugs* 1999; 10: 337–354.
4. Giacchetti S, Perpoint B, Zidani R et al. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000; 18: 136–147.
5. de Gramont A, Figer A, Seymour M et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000; 18: 2938–2947.
6. Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355: 1041–1047.
7. Saltz LB, Cox JV, Blanke C et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000; 343: 905–914.
8. Cunningham D, Zalcberg JR, Rath U et al. Final results of a randomised trial comparing ‘Tomudex’ (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. ‘Tomudex’ Colorectal Cancer Study Group. *Ann Oncol* 1996; 7: 961–965.
9. Pazdur R, Vincent M. Raltitrexed (Tomudex®) versus 5-fluorouracil and leucovorin (5-FU + LV) in patients with advanced colorectal cancer (ACC): results of a randomized, multicenter, North American trial. *Proc Am Soc Clin Oncol* 1997; 16: (Abstr 801).
10. Cocconi G, Cunningham D, Van Cutsem E et al. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. *J Clin Oncol* 1998; 16: 2943–2952.
11. Maughan TS, James RD, Kerr D et al. Preliminary results of a multicentre randomised trial comparing 3 chemotherapy regimens (de Gramont, Lokich and raltitrexed) in metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1999; 18: 262a (Abstr 1007).
12. Zalcberg J. Overview of the tolerability of ‘Tomudex’ (raltitrexed): collective clinical experience in advanced colorectal cancer. *Anticancer Drugs* 1997; 8 (Suppl 2): S17–S22.
13. Drug-company decision to end cancer trial [editorial]. *Lancet* 1999; 354: 1045.
14. Beale P, Judson I, Hanwell J et al. Metabolism, excretion and pharmacokinetics of a single dose of [¹⁴C]-raltitrexed in cancer patients. *Cancer Chemother Pharmacol* 1998; 42: 71–76.
15. Judson I, Maughan T, Beale P et al. Effects of impaired renal function on the pharmacokinetics of raltitrexed (Tomudex ZD1694). *Br J Cancer* 1998; 78: 1188–1193.
16. Farrugia DC, Aherne GW, Brunton L et al. Leucovorin rescue from raltitrexed (Tomudex)-induced antiproliferative effects: in vitro cell line and in vivo mouse studies. *Clin Cancer Res* 2000; 6: 3646–3656.
17. Thomas R. Optimising the side effects of raltitrexed with appropriate supportive drugs. A prospective community hospital study. *Proc Am Soc Clin Oncol* 2000; 19: 308a (Abstr 1217).
18. Österlund P, Elomaa I, Virkkunen P et al. A Phase II study of raltitrexed (‘Tomudex’) combined with capecitabine in metastatic CRC. *Proc Am Soc Clin Oncol* 2000; 19: 282a (Abstr 1104).
19. Longo GS, Izzo J, Chang YM et al. Pretreatment of colon carcinoma cells with Tomudex enhances 5-fluorouracil cytotoxicity. *Clin Cancer Res* 1998; 4: 469–473.
20. Comella P, De Vita F, De Lucia L et al. Oxaliplatin and raltitrexed combined with leucovorin-modulated 5-fluorouracil i.v. bolus every two weeks: a dose finding study in advanced previously treated colorectal carcinoma. Southern Italy Cooperative Oncology Group. *Ann Oncol* 2000; 11: 461–468.
21. Becouarn Y, Ychou M, Ducreux M et al. Phase II trial of oxaliplatin as first-line chemotherapy in metastatic colorectal cancer patients. Digestive Group of French Federation of Cancer Centers. *J Clin Oncol* 1998; 16: 2739–2744.
22. Diaz-Rubio E, Sastre J, Zaniboni A et al. Oxaliplatin as single agent in previously untreated colorectal carcinoma patients: a phase II multicentric study. *Ann Oncol* 1998; 9: 105–108.
23. Raymond E, Djelloul S, Buquet-Fagot C et al. Oxaliplatin (I-OHP) and cisplatin (CDDP) in combination with 5-FU, specific thymidylate synthase (TS) inhibitors (AG337, ZD1694), and topoisomerase I (TOPO-I) inhibitors (SN38, CPT-11) in human colonic, ovarian and breast cancers. *Proc Annu Meet Am Assoc Cancer Res* 1996; 37: (Abstr 291).
24. Fizazi K, Ducreux M, Ruffié P et al. Phase I, dose-finding and pharmacokinetic study of raltitrexed combined with oxaliplatin in patients with advanced cancer. *J Clin Oncol* 2000; 18: 2293–2300.
25. Scheithauer W, Kornek G, Ulrich-Pur H et al. Promising therapeutic potential of oxaliplatin + raltitrexed in patients with advanced colorectal cancer (ACC): results of a Phase I/II trial. *Proc Am Soc Clin Oncol* 2000; 19: 257a (Abstr 997).
26. Douillard JY, Michel P, Gamelin E et al. Raltitrexed (‘Tomudex’) plus oxaliplatin: an active combination for first-line chemotherapy in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 2000; 19: 250a (Abstr 971).
27. Van Cutsem E, Van Laethem JL, Dirix L et al. Phase II study of raltitrexed in combination with oxaliplatin as second line treatment in refractory advanced colorectal cancer. *Eur J Cancer* 2001; 37 (Suppl 6): 273 (Abstr 1008).
28. Aschele C, Baldo C, Sobrero AF et al. Schedule-dependent synergism between raltitrexed and irinotecan in human colon cancer cells in vitro. *Clin Cancer Res* 1998; 4: 1323–1330.
29. Ford HE, Cunningham D, Ross PJ et al. Phase I study of irinotecan and raltitrexed in patients with advanced gastrointestinal tract adenocarcinoma. *Br J Cancer* 2000; 83: 146–152.
30. Minsky BD. The role of adjuvant radiation therapy in the treatment of colorectal cancer. *Hematol Oncol Clin North Am* 1997; 11: 679–697.
31. Teicher BA, Ara G, Chen YN et al. Interaction of tomudex with radiation in vitro and in vivo. *Int J Oncol* 1998; 13: 437–442.
32. Valentini V, Morganti AG, Fiorentino G et al. Chemoradiation with raltitrexed (‘Tomudex’) and concomitant preoperative radiotherapy has potential in the treatment of stage II/III resectable rectal cancer. *Proc Am Soc Clin Oncol* 1999; 18: 257a (Abstr 987).
33. Botwood N, James R, Vernon C, Price P. Raltitrexed (‘Tomudex’) and radiotherapy can be combined as postoperative treatment for rectal cancer. *Ann Oncol* 2000; 11: 1023–1028.
34. James RD, Price P, Smith M. Raltitrexed (‘Tomudex’) plus radiotherapy is well tolerated and warrants further investigation in patients with advanced inoperable/recurrent rectal cancer. *Proc Am Soc Clin Oncol* 1999; 18: 288a (Abstr 1105).
35. Valentini V, Morganti AG, Luzi S et al. Chemoradiation with raltitrexed (‘Tomudex’) and oxaliplatin in pre-operative treatment of stage II/III resectable rectal cancer: A dose-finding study. *Proc Am Soc Clin Oncol* 2001; 20: 520a (Abstr).
36. Antman KH, Schiff PB, Pass HI. Benign and malignant mesothelioma. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology*, 5th edition. New York, NY: Lippincott-Raven 1997; 1853–1878.
37. Fizazi K, Doubre H, Viala J et al. The combination of raltitrexed (‘Tomudex’) and oxaliplatin is an active regimen in malignant meso-

- thelioma: results of a Phase II study. *Proc Am Soc Clin Oncol* 2000; 19: 578a (Abstr 2276).
38. Nicum S, Cullen MH. Chemotherapy versus palliative care in non-small cell lung cancer. *Anticancer Drugs* 2000; 11: 603–607.
 39. Manegold C, Buchholz E, Kloeppel R et al. Raltitrexed ('Tomudex') and cisplatin in metastatic non-small cell lung cancer (NSCLC): preliminary results of a Phase I dose-escalation study. *Eur J Cancer* 1999; 35 (Suppl 4): S253 (Abstr 1002).
 40. Webb A, Cunningham D, Scarffe JH et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol* 1997; 15: 261–267.
 41. Eatock MM, Anthony DA, El-Abassi M et al. A dose-finding study of raltitrexed (tomudex) with cisplatin and epirubicin in advanced gastroesophageal adenocarcinoma. *Br J Cancer* 2000; 82: 1925–1931.
 42. Mackay H, McInnes A, Paul J et al. A Phase II study of raltitrexed ('Tomudex') in combination with epirubicin and cisplatin in patients with advanced oesophageal and gastric adenocarcinoma. *Ann Oncol* 2000; 11 (Suppl 4): 64 (Poster 282).
 43. Burris HA 3rd, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403–2413.
 44. Pazdur R, Meropol NJ, Casper ES et al. Phase II trial of ZD1694 (Tomudex) in patients with advanced pancreatic cancer. *Invest New Drugs* 1996; 13: 355–358.
 45. Cripps C, Batist G, Dahrouge S et al. A Phase I study of raltitrexed ('Tomudex') and gemcitabine in advanced cancer. *Eur J Cancer* 1999; 35 (Suppl 4): S288 (Abstr 1158).
 46. Schantz SP, Harrison LB, Forastiere AA. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and Practice of Oncology*, 5th edition. New York, NY: Lippincott-Raven 1997; 791–801.
 47. Caponigro F, Comella P, Rivellini F et al. Cisplatin, raltitrexed, levofolinic acid and 5-fluorouracil in locally advanced or metastatic squamous cell carcinoma of the head and neck: a phase I-II trial of the Southern Italy Cooperative Oncology Group (SICOG). *Ann Oncol* 2000; 11: 575–580.
 48. ten Bokkel Huinink D, Tesselaar ME, Batenburg de Jong RJ et al. A Phase I study of a fixed dose of cisplatin with increasing doses of raltitrexed (Tomudex) in the treatment of patients with locally advanced or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol* 2001; 12: 357–363.
 49. Mayer S, Vanhoefer U, Hilger R et al. Extended Phase I study of raltitrexed and infusional 5-FU in patients with metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 2000; 19: 299a (Abstr 1169).
 50. Vazquez S, Vieitez JM, Garcia Alfonso P et al. Raltitrexed (Tomudex) combined with UFT: a phase I/II dose-escalation study in metastatic colorectal cancer. *Ann Oncol* 2000; 11 (Suppl 4): 52 (Abstr 229).
 51. Schwartz G, Bertino J, Kemeny N et al. Phase I trial of sequential raltitrexed ('Tomudex') followed by 5-FU in patients with advanced colorectal cancer. *Proc Am Soc Clin Oncol* 2000; 19: 252a (Abstr 977).
 52. Elomaa P, Österlund P, Virkkunen P et al. A Phase I/II dose escalation and tolerability study of raltitrexed combined with capecitabine in metastatic colorectal cancer. *Proc Am Soc Clin Oncol* 1999; 18: 243a (Abstr 932).
 53. Caponigro F, Avallone A, McLeod H et al. Phase I and pharmacokinetic study of tomudex combined with 5-fluorouracil plus levofolinic acid in advanced head and neck cancer and colorectal cancer. *Clin Cancer Res* 1999; 5: 3948–3955.
 54. Bjarnason G, Charpentier D, Wong R et al. NCIC CTG IND 98: a Phase I dose-escalation study of raltitrexed ('Tomudex') plus doxorubicin in patients with advanced cancer. *Eur J Cancer* 1999; 35 (Suppl 4): S290 (Abstr 1164).