Evidence Tables

Citation: Aparicio J, Vincent JM, Maestu I, Bosch C, Galan A (2005) First line treatment with Irinotecan and raltitrexed in metastatic colorectal cancer. Mature results of a multicentre phase II study. *Oncology* 68;1:58-63

Design: Multicentre phase II non-randomised study

Country: Spain

Setting:

Aim: to assess the efficacy and toxicity of irinotecan and raltitrexed as first line treatment

Inclusion criteria
Histological confirmation of colorectal cancer with metastatic disease not amenable for curative surgical resection
No previous chemotherapy for advanced disease
Adjuvant 5FU based chemotherapy and/or pelvic radiotherapy to be completed more than 6 months before study entry
WHO performance status of 0-2
Life expectancy of at least 3 months
Age more than 18 years
At least one bidimensionally measurable lesion
Satisfactory bone marrow, renal and liver functions

Exclusion criteria
Prior exposure to irinotecan or raltitrexed
Metastatic involvement of >50% of the liver
Chronic enterpathy or unresolved bowel obstruction
Breast feeding or pregnancy
Previous malignant disease other than carcinoma *in situ* of the cervix or basal cell skin carcinoma
Cerebral metastases or leptomeningeal carcinomatosis
Severe or uncompensated concomitant medical conditions.

Sample Size
60 evaluable patients to better estimate efficacy (standard error of 5% for an expected 35-40% overall response rate).

Randomisation Method
N/A

Population
N=62

Study Duration
12 month recruitment period
Median potential follow up was 37 months

Interventions
Irinotecan plus raltitrexed

Irinotecan 350mg/m^2 was given as a 60 min infusion followed 1 hour later by raltitrexed 3mg/m^2 administered as a 15 min infusion, both in a thrice weekly schedule.

Salvage treatment was given at disease progression according to the investigator centres guidelines, but oxaliplatin based chemotherapy was recommended.

Outcomes
Analysis of tumour response
Toxicity

Time to disease progression
Overall survival

Results

331 courses of irinotecan plus raltitrexed were delivered (median: 5/patient; range 1-16); 6 patients received only 1 cycle and 9 patients received only 2 cycles.
Reasons for early discontinuation were treatment related toxicities in 5 patients, patients refusal in 4 cases, need for urgent surgery in 4 cases and disease progression in 2 cases.
32% (n=20) of patients needed dose reduction and 14% of cycles (n=48) were delayed
The main adverse events were diarrhoea, asthenia and emesis
5% (n=3) of patients died as a result of treatment related toxicities (grade III-IV diarrhoea and concomitant neutropenia leading to sepsis and hydroelectrolyte imbalance).

Response was assessed in 56 patients with measurable disease who received at least 2 cycles of treatment.
27% (n=17) achieved partial response and 3% (n=2) achieved a complete response for an overall intention to treat response rate of 30% (95% CI, 18-44%) in all 62 enrolled patients.
37% of patients showed stable disease and 23% did not respond at all (unclear but presume this relates to progressive disease).

66% of patients received any one form of therapy after first line treatment failure, primarily oxaliplatin based chemotherapy.
37 cases received a second line, 18 a third line and 4 a fourth line treatment.
7 patients were treated with salvage surgery at any time point and 3 patients were treated with palliative irradiation.

As of November 2003, 84% of patients (n=52) had died and the median potential follow-up was 37 months (31-42).
Actuarial median survival was 12.2 months (95% CI, 9.2-15.1) and median time to disease progression was 6.3 (95% CI, 4.0-8.6).

Citation: Chiara S, Nobile MT, Tomasello L, Acquati M (2005) Phase II trial of irinotecan and raltitrexed in chemotherapy-naive advanced colorectal cancer *Anticancer Research* 25;2B:1391-1396

Design: Phase II non-randomised trial

Country: Italy

Setting: Hospital

Aim: To assess the activity and tolerability of combined raltitrexed and irinotecan in patients with advanced colorectal cancer

Inclusion criteria
Patients with histologically confirmed metastatic colorectal cancer, untreated with chemotherapy for advanced disease.
Previous adjuvant chemotherapy completed 12 months prior to study
ECOG performance status ≤2
Age ≥18 years
Life expectancy of at least three months
Measurable metastatic lesions that had not been previously irradiated and adequate bone marrow, renal and hepatic function

Exclusion criteria
History of serious concomitant disease, prior malignancy apart from adequately treated basal cell skin cancer or *in situ* cervical carcinoma.
Presence of central nervous system metastases
Pregnancy, breast feeding or inadequate contraceptive precautions

Sample Size
A sample of 24 patients was required in the first stage; if 6/24 patients experienced a clinical response, a further 21 patients were enrolled in the second stage and up to three more patients could be accrued to correct for attrition.
The treatment under investigation could be deemed interesting for further trials if more than 14 clinical responses were observed out of the total number of enrolled patients.

Randomisation Method

Population
N=48

Study Duration

Interventions
Irinotecan plus Raltitrexed

Irinotecan 350mg/m^2 was administered intravenously over 30 minutes on day 1
Raltitrexed was administered 24 hours later at a dose of 3mg/m^2 in a 15 minute intravenous infusion
Courses were repeated every 21 days until disease progression, patient refusal or unacceptable toxicity.

Outcomes
Toxicity
Activity
Survival

Results
Median Age was 63 years (range 46-77) and median ECOG performance status was 0 (range 0-2)
46% (n=22) of patients had synchronous metastatic disease, 26 patients had metastatic disease and 4 patients presented local relapse associated with distant metastases.
30 patients had a single involved site and 18 patients had multiple metastatic sites.
41.6% (n=20) of patients had undergone prior adjuvant chemotherapy consisting of 5-FU/FA combination regimens in 17 cases and methotrexate/5FU/FA regimens in 3 cases.

After recruitment of the first 16 patient, grade III-IV toxicity was observed in 6 patients resulting in a reduction of the total dose of both drugs by 15% for subsequent patients entering the trial (Irinotecan 300mg/m^2 and raltitrexed 2.6 mg/m^2).

290 cycles of irinotecan and raltitrexed were administered; the median number of treatment courses per patients was 6 (range 1-18).
23 patients required a dose reduction of 20% and in 2 patients a 50% dose reduction was necessary
4.5% of cycles were delayed by 1 week and 2% of cycles were delayed by 2 weeks to allow recovery from toxicity.
Median dose intensity was 0.90(0.58-1.00) for irinotecan and 0.91 (0.54-1.00) for raltitrexed.
21 patients received combination chemotherapy including oxaliplatin + 5FU/FA and 4 patients received 5-FU/FA schedules.

Toxicity
For the first group of patients recruited, 6/16 patients experienced severe toxicity; Grade III Diarrhoea in 2 patients (3^{rd} and 7^{th} cycles respectively), grade III diarrhoa and neutropenic fever in 1 patient (7^{th} cycle), grade IV diarrhoea and neutropenia in one patient (4^{th} cycle).
3/6 patients required hospitalisation due to diarrhoea and/or neutropenia.

17/32 patients treated with the initial dose of irinotecan 300mg/m^2 and raltitrexed 2.6mg/m^2 experienced grade III and grade IV toxicities.
Toxicities consisted mainly of diarrhoea, nausea/vomiting, neutropenia, transaminase elevation, asthenia and stomatitis.
Hospitalisation of 3 patients was required due to grade III hepatic toxicity, grade III diarrhoea and grade IV mucositis
One patients required 50% dose reduction for grade IV mucositis and grade III neutropenia
Two toxic deaths occurred; one due to dehydration from grade IV diarrhoea associated with grade III emesis and one related to grade III diarrhoea and grade II emesis after the 2^{nd} course of chemotherapy (at 20% dose reduction).
Five patients interrupted chemotherapy due to combined grade III-IV toxicity after a median of 3 courses (range 1-6) and one patient refused therapy after the 6^{th} course of chemotherapy not associated with toxicity.

Activity and Survival
43/48 patients were evaluable for response; 2 patients discontinued chemotherapy after the 1^{st} course and 3 patients discontinued after the 2^{nd} course due to grade III-IV toxicities (including toxic deaths).

According to intention to treat analysis, overall response rate was 27% (95% CI 16%-42%) including complete response in 6.3% and partial response in 20.8%. 29.2% of patients had stable disease and 33.3% of patients had disease progression.
31% of patients (5/16) receiving the initial dose of oxaliplatin/raltitrexed achieved objective response and 25% of patients (8/32) receiving the lower dose achieved objective response.

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

Citation: Cortinovis D, Bajetta E, Di Bartolomeo M, Dogini G (2004) Raltitrexed plus oxaliplatin in the treatment of metastatic colorectal cancer *Tumori* 90;2:186-191

Design: Single Arm Phase II Study

Country: Italy

Setting:

Aim: To study the antitumoral activity and safety of the combined use of raltitrexed and oxaliplatin in patients with advanced colorectal cancer.

Inclusion criteria
Patients with cyto-histologically confirmed metastatic colorectal cancer and bidimensionally measured disease defined as the presence of at least one lesion with the longest diameter of ≥15mm with no radiotherapy allowed in the case of a single lesion.
Prior chemotherapy must have been completed at least four weeks prior to study entry
Age ≥18 years
ECOG performance status of 0-1
Life expectancy of >3 months
Adequate bone marrow reserve
Normal liver and renal function tests

Exclusion criteria
Brain metastases
History of other malignancies with the exception of excised cervical cancer and basal skin/squamous cell carcinoma.

Sample Size
Planned sample size of 33 patients, subsequently increased to 51 patients as interim analysis revealed the feasibility and activity of the regimen and because of the absence of any other chemotherapy program for this subset of patients available at the Institute.

Randomisation Method
N/A

Population
N=51

Study Duration
Median Follow up was 16 months (range: 8-24 months)

Interventions
Raltitrexed (TOM) + Oxaliplatin (L-OHP)

15 min iv infusion of TOM (2.5mg/m^2) followed by a 3 hour infusion of L-OHP (100mg/m^2) both administered on day 1 every 3 weeks for a maximum of six cycles.

Outcomes
Primary
Response rate
(complete response (CR) defined as complete disappearance of all objective signs of disease on two occasions separated by at least 4 weeks; partial response (PR) was defined as a ≥50% reduction in the sum of the products of the greatest perpendicular dimensions of measurable bidimensional lesions without a CR and the absence of a >25% increase in any lesion without the appearance of any new lesion, confirmed on two occasions separated by at least 4 weeks; progressive disease (PD) was defined as the growth of any existing measurable lesion by at least 25% or the appearance of any new lesion; stable disease (SD) was defined as any measurement not fulfilling the criteria for CR, PR or PD)
Treatment safety and toxicity

Secondary
Time to progression (measured and date of start of chemotherapy to date of documented progressive disease)
Overall Survival (measured from the beginning of treatment to date of death from any cause)

Results
51 patients were enrolled in the study, of which 28 were considered 'elderly' (≥65 years).
25 patients had metastatic disease at the time of diagnosis; 33 patients had one metastatic site
20 patients had previously received chemotherapy for advanced disease with bolus FU plus leucovorin or infusional FU and 22 patients were chemotherapy naive.

A total of 215 courses of chemotherapy were administered for a median of 6 cycles per patient (range: 1-6.
24 patients completed the treatment plan and only 5 patients received less than three cycles; one patient received 3 cycles but was not re-evaluated due to sudden death for an unknown cause.

Safety Analysis
The most frequent, non-haematological toxicity was transient transaminitis: Grade I-II in 28% of patients and Grade III-IV in 31% of patients.
Grade III diarrhoea occurred in 12% of patients, nausea/vomiting in 6% and asthenia in 2% of patients
Grade IV nausea/vomiting occurred in one patient
Grade I neurotoxicity occurred in 51% of patients and Grade II in 2% of patients
Grade III neutropenia was observed in 2% of patients.
Chemotherapy was discontinued because of toxicity in 6% (n=3) of patients
15 patients required per protocol 25% reductions of L-OHP and/or TOM dose

Analysis of the 28 elderly patients showed that the adverse event profile was similar to that observed in patients aged <65 years. The main toxicities were diarrhoea (grade III in 18%) and transaminitis (grade III-IV in 21%).

Efficacy Analysis
The overall response rate in the 45 assessable patients was 31% (PR in 12 patients and CR in 2 patients).
Median time to response was 3.5 months (range: 2-6 months).
51% of patients had SD and 18% had PD.
The activity of the regimen was similar in the subset of elderly patients (n=24) with a 25% response rate and 58% of patients with AD.

After median follow-up the median time to progression was 7 months (range 6-9 months)
24/51 (47%) eligible patients were still alive at last follow-up contact, with a median overall survival of 15 months (range 8-28 months).

Citation: Feliu J, Castanon C, Salud A, Mel JR, Escudero P, Pelegrin A, Lopez-Gomez L, Ruiz M, Gonzalez E, Juarez F, Lizon J, Castro J,, Gonzalez-Baron M (2005) Phase II randomised trial of raltitrexed-oxaliplatin versus raltitrexed-irinotecan as first line treatment in advanced colorectal cancer

Design: Phase II Randomised Trial

Country: Spain

Setting:

Aim: To determine which of the two schemes offered better activity and less toxicity in patients with advanced colorectal cancer

Inclusion criteria
Patients with at least one histologically confirmed adenocarcinoma
Patients who had received prior adjuvant 5FU-based chemotherapy if they had remained disease free for at 6 months after completion
ECOG Performance status ≤2
Life expectancy of at least 3 months
Adequate bone marrow function
Peripheral neuropathy ≤1
Adequate hepatic and renal function

Exclusion criteria
Patients with operable metastatic disease
Patients with prior chemotherapy for advanced disease, brain or meningeal metastases
History of malignancy apart from basal cell carcinoma or in-situ cervical carcinoma

Sample Size
An accrual of 38 patients per arm was deemed to give a 90% chance of selecting the better treatment schedule if the difference in response rate is at least 15% and the smaller response rate is assumed to be 35%.
10% was added to the figures to allow for losses.

Randomisation Method
Not specified

Population
N=94 patients with recurrent or metastatic colorectal cancer
48 randomised to raltitrexed + oxaliplatin and 46 randomised to raltitrexed + irinotecan

Study Duration

Interventions
Ralitrexed + Oxaliplatin: Median dose intensity was 41mg/m^2/week for oxaliplatin and 0.95mg/m^2 for raltitrexed representing 95% of the scheduled doses for both oxaliplatin and raltitrexed.

Raltitrexed + Irinotecan: Median dose intensity was 114mg/m^2/week for irinotecan and 0.97mg/m^2/week for raltitrexed representing 98% of the scheduled irinotecan dose and 97% of the scheduled raltitrexed dose

Outcomes
Response Rate
Time to Progression
Toxicity

Results
Tumour Response and Survival
According to intention to treat analysis there was no significant difference in overall response rate for either treatment (p>0.05); the overall response rate was 46% (95% CI 29.5%-57.7%) for raltitrexed+oxaliplatin and 34% (95% CI 19.8%-48.4%) for raltitrexed+irinotecan.

In per protocol analysis the overall response rate was 49% (95% CI 33.3%-62.9%) in the raltitrexed+oxaliplatin group and 37% (95% CI 21.2%-51.3%) in the raltitrexed+irinotecan group.

Median duration of response was 7.9 months in the raltitrexed+oxaliplatin group and 9.2 months in the raltitrexed+irinotecan group (log rank p=0.696).

Control of disease (CR, PR and SD) was achieved in 69% of patients receiving raltitrexed+oxaliplatin and in 67% of patients receiving raltitrexed+irinotecan.

At the time of analysis, 77% of patients receiving raltitrexed+oxaliplatin and 74% of patients receiving raltitrexed+irinotecan had progressed.
Median time to progression (TTP) was 8.2 months for patients in the raltitrexed+oxaliplatin arm and 8.8 months for patients in the raltitrexed+irinotecan arm (log rank p=0.656).

After median follow-up of 14 months, 69% of patients in the raltitrexed+oxaliplatin group were still alive and 59% of patients in the raltitrexed+irinotecan arm were still alive

Second line chemotherapy was administered to 65% of patients who progressed in the raltitrexed+oxaliplatin arm and in 68% of patients who progressed in the raltitrexed+irinotecan arm.

Toxicity
65% of patients receiving raltitrexed+oxaliplatin and 70% of patients receiving raltitrexed+irinotecan experienced some toxicity.
The main toxicities were gastrointestinal and haematologic and in general both regimens were well tolerated.
The most common toxicity was hepatic: transaminase elevation was detected in 60% of patients receiving raltitrexed+oxaliplatin and in 62% of patients receiving raltitrexed+irinotecan, with 4 patients in each group experiencing grades 3-4 toxicity.
Significantly more diarrhoea was observed in the raltitrexed+irinotecan arm (52%) compared with the raltitrexed+oxaliplatin arm (31%); $p<0.05$. The difference is due to the higher rates of grade 1-2 diarrhoea in the raltitrexed+irinotecan arm (39%) and the percentage of patients with grade 3-4 diarrhoea was similar in both groups.

Asthenia was detected in 35% of patients in the raltitrexed+oxaliplatin group and in 52% of patients in the raltitrexed+irinotecan group.
Neurological toxicity was observed was observed in 64% of patients in the raltitrexed+oxaliplatin group, of which 10% was grade 3-4.
Cholinergic syndrome was detected in 19% of patients in the raltitrexed+irinotecan group.
One toxic death occurred in the raltitrexed+oxaliplatin group and 3 in the raltitrexed+irinotecan group.

Citation: Feliu J, Salud A, Escudero P, Lopez-Gomez L (2004) Irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study *British Journal of Cancer* 90;8:1502-1507

Design: Phase II (single arm)

Country: Spain

Setting:

Aim: To evaluate the efficacy and toxicity of irinotecan (CPT-11) in combination with raltitrexed as first line treatment of advanced colorectal cancer

Inclusion criteria
Patients with recurrent or metastatic colorectal cancer with at least one legion histologically confirmed as adenocarcinoma
Patients that had received prior 5-FU based chemotherapy were eligible if they had remained disease free for at least six months after completion of adjuvant chemotherapy
ECOG performance status ≤2
Life expectancy of at least 3 months
Adequate haematological parameters
Adequate hepatic function
Adequate renal function

Exclusion criteria
Patients with operable metastatic disease
Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases or a history of any other malignancy except cases of basal cell carcinoma or in situ cervical carcinoma adequately treated.

Sample Size
A planned sample of 90 patients was chosen to better estimate efficacy; 20% maximum width of the 95% confidence interval for an expected 35% overall response rate.

Randomisation Method
N/A

Population
N=91

Study Duration

Interventions
CPT-11 350mg/m^2 in a 30 minute infusion on day 1 followed after 30 minutes by a 15-minute infusion of raltitrexed 3mg/m^2

Outcomes
Response Rate
Clinical Benefit
Survival
Time to Progression

Results
Patient Characteristics
A total of 487 cycles were given with a median of five cycles per patient (range 1-14).
16 patients (18%) received less than 3 cycles, eight due to disease progression, four due to patient refusal, two moved to a different city and two due to death.

Tumour Response and Survival
Complete response was observed in 5 patients and partial response in 23 for an overall response rate of 34% (95% CI, 25.9-46.5%).
36 patients remained with a stable disease and 19 patients showed a progression
Progression free survival was 11.1 months
Median survival was 15.6 months

Actuarial 1 year survival was 58%
No relationship was observed between response rate and site of metastases, number of metastatic sites, previous adjuvant chemotherapy, ECOG performance, age or sex.
Progression free survival was longer in patients with ECOG 0 compared with patients with ECOG 1-2 status (13.3 vs. 7.9 months; p<0.002).
Overall survival was longer in patients with ECOG 0 compared with patients with ECOG 1-2 status (21.4 months vs. 8.3 months; p<0.0001).

Toxicity
70% of patients (n=64) suffered some toxicity, usually grade 1-2 though 18% (n=16) of patients developed grade 3-4 side effects
Primary reported toxicities were gastrointestinal and haematological
13 patients developed diarrhoea, 4 had nausea and vomiting, 2 had stomatitis, 3 febrile neutropenia, 5 anaemia, and 3 asthenia.
One patient suffered an episode of atrial fibrillation during the fourth cycle which was terminated using medical treatment.
There were 4 treatment related hospital admissions reported
No toxic deaths occurred
No relationship was observed between the occurrence of grade 3-4 toxicity and patients ECOG status, age or sex.

Citation: Laudani A, Gebbia V, Leonardi V, Savio G (2004) Activity and Toxicity of oxaliplatin plus raltitrexed in 5 fluorouracil refractory metastatic colorectal adenocarcinoma *Anti-Cancer Research* 24;2C:1139-1142

Design: Randomised Phase II Trial

Country: Italy

Setting:

Aim: to evaluate the anti tumour efficacy and safety of a novel oxaliplatin/raltitrexed combination in pretreated advanced colorectal cancer patients.

Inclusion criteria
Patients with histologically proven metastatic or locally recurrent colorectal adenocarcinoma and bidimensionally measurable disease according to the WHO criteria.
Patients that developed progressive disease after palliative fluorouropyrimidine based chemotherapy or within 3 months of adjuvant chemotherapy completion
Age 19-75 years
ECOG performance status 0-2
Life expectancy of at least 3 months
Adequate bone marrow function, renal function and hepatic functions
Geographic accessibility to ensure close follow-up

Exclusion criteria
Patients with central nervous system metastases
Serious or uncontrolled concurrent medical illness
Peripheral neuropathy
History of other tumours with the exception of adequately excised uterine cervical of basal skin carcinomas

Sample Size
No details given

Randomisation Method
N/A

Population
N=45

Study Duration
Recruitment was between February 2000 and May 2002
No details were given on follow-up

Interventions
Raltitrexed plus Oxaliplatin

Raltitrexed 30mg/m^2 as a 15 minute intravenous infusion followed 45 minutes later by
Oxaliplatin 130 mg/m^2 intravenous infusion as a 2 hour venous infusion on day 1 every three weeks

Outcomes
Response Rate (according to WHO criteria and analysis of side effects recorded according to the NCI Common Toxicity Criteria)

Duration of Response (measured from onset of the best response to date of disease progression)
Progression Free Survival (calculated from the starting date of treatment to the time of progression or relapse)
Overall Survival

Results
All patients had previous surgery for primary disease and 5 patients also had liver surgery for metastatic disease.
Previous treatments included adjuvant radiotherapy (29%) and adjuvant chemotherapy (40%)
93% of patients had received previous front line 5FU based chemotherapy and 18% (n=8) also had second line chemotherapeutic treatment.
31/45 patients had multiple metastases involving 2 or more organ systems; sites of metastases included liver, ling, pelvic region, node, pleura, peritoneum, bone, and adrenals.

A total of 178 courses of chemotherapy were administered to the 40 patients with a median number of 4 cycles/patient (range 1-10).

Response
93% (n=42) patients had adequate follow-up and were fully assessable for response and toxicity.
Overall response rate was 29% (95% CI 16-44%) including one complete response and 12 partial responses.
16% (n=6) patients showed stable disease.

Median time to progression was 4 months (range 1-12+)
Median overall survival was 9 months (range 1-29+)

Toxicity
Haematological toxicity was generally mild to moderate and fully reversible within one week in all patients.
Grade III anaemia occurred in one patient and grade I leukopenia occurred in 2 patients.
Grade III nausea/vomiting was observed in 3 patients and grade II in 10 patients
Grade III diarrhoea was observed in 3 patients and grade II in 3 patients
Transient grade I-II transaminitis occurred in 5 patients
Asthenia was severe in 5 patients
Oxaliplatin induced peripheral neurosensory toxicity in 5 patients but only two experienced moderate to severe neuropathy.
Minor side effects included fever, abdominal pain, renal toxicity, hypotension and stomatitis.

Citation: Maroun JA, Jonker D, Seymour L, Goel R, Vincent (2006) Phase I/II study of irinotecan (camptosar), oxaliplatin and raltitrexed (tomudex) (COT) in patients with advanced colorectal cancer

Design: Non-randomised Phase I/II study

Country: Canada

Setting: Academic Cancer Centres (Canada)

Aim: to determine the recommended doses of irinotecan followed by raltitrexed then oxaliplatin.

Inclusion criteria
Histologically proven advanced or metastatic carcinoma of the colon or rectum with measurable lesions
Age ≥18 years
ECOG performance status ≤2
No prior chemotherapy for metastatic disease
Adequate haematological and biochemical functions
Prior adjuvant chemotherapy with or without radiotherapy
Prior radiation completed >4 weeks prior to enrolment and affecting ≤ of marrow reserve

Exclusion criteria
Prior adjuvant irinotecan or oxaliplatin
Patients receiving concurrent treatment with other experimental drugs or anti-cancer agents
Patients with documented brain metastases or neuropathy ≥2 and serious medical conditions

Sample Size
Three cohorts of 3 patients accrued at each dose level with dose escalation between cohorts.

Randomisation Method
N/A

Population
N=31 in 5 cohorts

Study Duration

Interventions
Irinotecan + Raltitrexed + Oxaliplatin

Outcomes
Complete Response
Partial Response
Response Duration
Stable Disease
Stable Disease Duration
Progressive Disease

Results
A total of 257 cycles were administered with a range of 1-18 cycles.
Actual dose intensity of each drug per cohort varied between 78% and 100% of the planned dose.
15 patients discontinued the protocol therapy due to progressive disease, two patients with symptomatic disease progression and four patients were taken off the study due to toxicity. Two patients were censored and removed from the study due to becoming eligible for surgery. Five patients refused further treatment further therapy after prolonged treatment. One patient was taken off the study

Toxicity

- 30 patients were evaluable for haematological toxicity.
- Grade IV granulocytopenia occurred in 50% of patients in cohort 4 and 13% of patients in cohort 5.
- Grade 3 thrombocytopenia occurred in 25% of patients in cohort 3 and 13% of patients in cohort 5 (overall incidence = 10%).
- Febrile neutropenia occurred in one patient.
- Although significant incidence and severity of haematological toxicity were reported, it was not considered to

be dose-limiting as per protocol.

- Due to neutropenia in cohorts 2-6 there were delays in dose administration and some dose reductions.
- The magnitude of dose-adjustments seemed related mostly to the dose level of irinotecan

Non-haematologic toxicity
Non-haematologic toxicity was common and dose-limiting, with the most common reported toxicities being gastro-intestinal (diarrhoea, nausea, vomiting and anorexia).
42% (n=13) patients reported grade I-II early onset diarrhoea
Late onset diarrhoea occurred in 93% of patients and was dose limiting; 78% reported grade I-II and 16% reported grade III diarrhoea.
Grade I-II nausea was reported in 80% of patients and grade III in 19% nausea of patients; grade I-II vomiting occurred in 61% of patients and grade III in 26% of patients.
Grade I-II anorexia was reported in 68% of patients and grade III anorexia was reported in 16%.
Stomatitis was infrequent (grade I-II in 16%).
Fatigue was a common side effect and contributed in some cases to patients declining further protocol treatment.
One patient on dose level 3 died following the first dose of treatment though it was concluded that the main cause of death was due to complications from disease progression and bowel obstruction.
Sensory neurotoxicity was common with oxaliplatin; neuromotor symptoms occurred in 33% of patients (n=10), neurosensory symptoms Neurosensory symptoms occurred in 81% of patients (n=25) and were grades I-II in severity. Typically these symptoms are worse on cold exposure and increased in severity and duration in subsequent cycles.

Dose limiting toxicity and maximum tolerated dose
There were no DLT's in the first two dose levels; at the third dose level 2 patients experienced dose limiting gastro-intestinal toxicity; there were no DLT's at the fourth dose level; there were 2 DLT's in the fifth cohort.

Efficacy
30 patients were evaluable for response and objective responses were documented at each dose level.
Partial remissions were recorded in 15 patients for an overall response rate of 45% (95% CI: 31-68%).
Nine patients had stable disease as best response.
Median time to progression was 7.3 months (95% CI 6.51-9.2) and overall median survival was 16.6 months (95% CI: 13.5-21.3)
6/16 patients treated at the recommend phase II dose (220 CPT-11, 2.75 tomudex and 100 oxaliplatin) had a partial response for a response rate of 56.3% (95% CI: 29.9-80.2).

General comments
Magnitude of escalation of each drug was dependent on the analysis of toxicity occurring during the previous cohort of patients and on a decision of which drug to escalate and to what extent.
If one of three patients exhibited dose limiting toxicity (DLT), three more patients were entered into the cohort. If less than 2/6 patients experienced DLT, accrual was initiated at the next dose level. If 2 or more patients exhibited DLT, the dose level was declared to be the maximum tolerated dose (MTD).

Citation: Popov I, Carrato A, Sobrero A, Vincent M, Kerr D (2008) Raltitrexed (Tomudex) versus standard leucovorin modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in adjuvant colon cancer 01 (PETACC-1) *European Journal of Cancer* 44;15:2204-2211

Design: Randomised Trial

Country: Multiple

Setting: Unclear

Aim: to assess if raltitrexed (tomudex) is non-inferior to 5FU/LV for relapse free survival (RFS) and overall survival (OS) in adjuvant stage III colon cancer

Inclusion criteria
Patients with stage III (T1-4, N1-2, M0) colon cancer and had previously undergone potentially curative surgical resection with no evidence of residual disease within 56 days before ramdomisation.
Age ≥18
WHO performance status 0-1

Exclusion criteria
None given

Sample Size
The non-inferiority hypothesis required that the HR for raltitrexed versus 5FU/LV be significantly less than 1.25 at the one-sided 0.05 significance level for both RFS and OS.

For 90% power, assuming two years of recruitment and three more years of follow-up and 10% loss on follow-up the study was estimated to require 2765 patients (703 events).

Randomisation Method
Randomisation was done at national data centres and was stratified by institution.
Patients were randomised in a 1:1 ratio
No details were given on method of randomisation

Population
N=1921 (after study recruitment was stopped by the sponsors)

Study Duration

Interventions
Ratlitrexed versus 5FU/LV

Raltitrexed 3mg/m^2 administered as a 15 min infusion on day 1, repeated on day 22 and so on for eight cycles (i.e. every three weeks for a total of 24 weeks).
Leucovorin (LV) 20mg/m^2 administered as an iv bolus followed by a 370-425mg/m^2 iv bolus of 5-fluorouracil (5FU). Both drugs given on days 1-5, repeated on days 29-33 and so on for six cycles (i.e. every four weeks for a total of 24 weeks).

Outcomes
Primary
Relapse free survival (RFS) (counted from randomisation to the date of either radiologically proven recurrence or death, whichever occurred first).
Overall survival (OS) (counted from randomisation to the date of death from any cause)

Secondary
To compare safety profiles of raltitrexed and 5FU/LV using the NCIC-CTC scoring scales.

Results
An unscheduled analysis of the first 647 patients showed a greater treatment completion rate in the control arm and more withdrawals due to serious adverse events in the raltitrexed arm, this resulted in the sponsor deciding to stop patient inclusion.

The intention to treat population included all patients treated according to the regimen to which they were randomised (n=1921).
The per protocol population included all patients who were eligible, randomised before Jan 16, 1999 and had received at least one dose of study drug (n=993).

A total of 1921 patients were randomised prior to trial closure (969 to 5FU/LV and 952 to raltitrexed); 34 patients were not eligible, 25 patients received non-protocol treatments and treatment data were unavailable for 40. All the patients were kept in the ITT population.

Median follow-up was 49 months

Both groups received a median of 6 cycles of chemotherapy; the planned number of cycles was received by 83.9% (n=786) of patients on the 5FU/LV arm and by 42.4% (n=389) of patients on the raltitrexed arm.
When the study closed prematurely, 28.5% (n=271) patients discontinued raltitrexed treatment while almost all patients continued with 5FU/LV treatment.

Median relative dose intensity of 5-FU was 97% (0.1-134%), whilst the median relative dose intensity of raltitrexed was 104% (9-150%).

Neutropenia, diarrhoea and stomatitis were the most commonly reported grade III-IV adverse effects for patients treated with 5FU/LV.

Adverse Effect	5FU/LV	Raltitrexed
Grade III-IV Neutropenia*	27%	7.9%
Grade III-IV Diarrhoea	14.9% (n=139)	5.4% (n=49)
Grade III-IV Stomatitis	12.4% (n=116)	0.9% (n=8)
Alopecia	13.6% (n=127)	4.9% (n=45)
Grade III-IV transaminase elevation	0.6% (n=6)	20.5% (n=188)

*Grade III-IV neutropenia and was complicated by fever or infection in 4% of cases in the 5FU/LV group and in 2.2% of cases in the raltitrexed group.

Serious adverse events were reported for 18.3% (n=177) of patients in the 5FU/LV group and for 16.3% (n=155) of patients in the raltitrexed group.
Death related to treatment was reported for 0.9% (n=8) patients in the 5FU/LV group and for 2.2% (n=20) of patients in the raltitrexed group.
Overall 60 day mortality was not significantly different between the two arms, with a substantial number of the deaths in the raltitrexed arm occurring after 60 days.
Of the deaths attributed to raltitrexed, 11 were associated with major protocol deviation and the majority of toxic deaths were reported from one Cooperative Group.

Survival
In the intention to treat population, 26.1% of patients had died in the 5FU/LV group compared with 26.5% in the raltitrexed group (HR: 1.04; 90% CI 0.9-1.21)
5-year survival rate was 62.3% (95% CI 58.4-66.1) in the 5FU/LV group and 61.9% (95% CI 55.4-66.1) in the raltitrexed group.

In the per protocol population, 30% of patients in the 5FU group died compared with 29.4% in the raltitrexed group (HR 1.01; 90% CI 0.84-1.23).
5-year survival rate was 60.9% (95% CI 55.5%-65.8%) in the 5FU/LV group and 62.6% (95% CI 57.1-67.7) in the raltitrexed group.

Recurrence
In the intention to treat population 35.8% of patients in the 5FU/LV group had relapsed or dies compared with 38.9% of patients in the raltitrexed group (HR 1.14, 90% CI 1.01-1.29).
5-year recurrence free survival rate was 50.9% (95% CI, 46.6-54.9) on 5FU/LV and 46.7% (95% CI, 42.2-51) on raltitrexed.

In the per protocol population, 39.6% of patients had relapsed or died in the 5FU/LV group compared with 43.1% in the raltitrexed group.
5-year recurrence free survival rate was 50.3% (95% CI 44.8-55.6) in the 5FU/LV group and 47.8% (95% CI 42.3-

53) in the raltitrexed group.
General comments The study's independent data monitoring committee reviewed all trial data accumulated as of June 30, 1999 (1838/2765 patients had been recruited) and recommended suspension of recruitment for 2 months because of the number of drug related deaths in the raltitrexed arm was 17 (1.9%) of 911 patients which was considered unacceptable in the adjuvant setting.

Citation: Santini D, Massacesi C, D'Angelillo RM, Marcucci M (2004) Raltitrexed plus weekly oxaliplation as first line chemotherapy in metastatic colorectal cancer: a multi centre non-randomised phase II study *Medical Oncology* 21;1:59-66

Design: Phase II Trial (non-randomised)

Country: Italy

Setting: Multi-centre

Aim: to evaluate the activity and toxicity of a new raltitrexed and oxaliplatin based regimen as a first line chemotherapy in patients with metastatic colorectal cancer

Inclusion criteria
Patients with pathologically confirmed, metastatic or locally recurrent colorectal cancer
ECOG performance status 0-1
Age 18-75 years
No pulmonary or cardiovascular contraindications
Adequate haematological, hepatic and renal functions
Prior adjuvant chemotherapy completed for at least 6 months

Exclusion criteria
Serum creatinine concentration >1.5mg/dl and creatinine clearance <50ml/min

Sample Size
A planned sample size of 55 patients was chosen to better estimate efficacy; 25% maximum width of the 95% confidence interval for an expected overall 40% response rate.

Randomisation Method
N/A

Population
N=44

Study Duration
Median follow-up was 14 months (range 6-18 months)

Interventions
Raltitrexed plus oxaliplatin

Raltitrexed 3mg/m^2 given as 15 min intravenous infusion on day 1
Oxaliplatin 70mg/m^2 given as 2 hour infusion on day 1 and day 8
The cycle was repeated every 21 days.

Outcomes
Analysis of tumour response and feasibility

Time to disease progression (TTP) (Measured from the date of registration to the date of documented progressive disease or death)
Overall Survival (OS) (measured from time of registration to the date of death from any cause)
Median time to response (calculated from the date of response registration to the date of disease progression or death).

Results
8/44 patients had previously received 5-FU-based adjuvant chemotherapy
In this study, 241 chemotherapy courses were administered; 5 patients received less than three cycles, 19 patients six to eight cycles and 5 patients received nine cycles.

Response
In 5 patients persistent toxicity resulted in early discontinuation of treatment before first evaluation.

For intention to treat analysis 44 patients were evaluated for efficacy; 4 complete responses, 16 partial responses, 18 stable disease and 6 failures.

Overall response rate was 45.5% (95% CI: 30.1-54.1%)
Tumour control rate (response + stable) was 86.4% (95% CI 45.1-91.1%
Median time of response duration was 4.8 months (range: 1.4-16)
Of the four patients who achieved complete response one had liver and bladders metastases 5 months after chemotherapy discontinuation, two had peritoneal metastases 9 and 8 months after chemotherapy discontinuation and one had abdominal lymph node metastases 4 months after chemotherapy discontinuation.

Follow-up and Survival
Median overall survival for eligible patients was more than 14.8 months (not reached the time of analysis; range 3-23 months) (95% CI; 11.2-18.4)
72.7% (32/44) of patients were still alive and 12 patients died of for progressive disease.
Median time to disease progression was 6 months (95% CI; 4.4-7.6 months)
Second line chemotherapy was performed in 27 patients (CPT-II + 5FU in 15 patients and prolonged infusional 5FU in 8 patients and oxaliplatin plus 5FU in 4 patients)
Two patients with partial response and metastatic disease confined to the lung and spleen, respectively, were submitted to radical surgery of the residual disease after discontinuation of first line chemotherapy and then treated with second line anticancer treatments.

Toxicity
Neutropenia was the most common haematological side effect: Grade III in 15.9% of patients.
Grade IV thrombocytopenia requiring hospitalisation was required in 2 patients
Transient transaminitis, neurotoxicity, asthenia and diarrhoea were the most common non-haematological side effects.
Grade III transaminitis was reported in 36.4% (n=16), neurotoxicity in 9.1% (n=4) and asthensia 9.1% (n=4) patients.
Severity of neurotoxicity was appeared related to the cumulative dose of oxaliplatin: patients with grade 0 neurotoxicity received a mean cumulative dose of 560 mg/m^2; patients with grade I received a mean cumulative dose of 723 mg/m^2; patients with grade II and III received a mean cumulative dose of 900 mg/m^2. No patients developed grade III neurotoxicity before a total cumulative dose of 530mg/m^2.
6.8% (n=3) patients experienced a grade IV non-haematological toxicity (diarrhoea).
Treatment was discontinued in 29.5% (n=13) patients due to toxicity; treatment was discontinued in 5 patients before the third cycle, before the sixth cycle in 6 patients and before the 9th cycle in 2 patients
According to the treatment plan, 4 patients had a 25% dose reduction of both cytotoxic agents due to grade III transaminitis, diarrhoea or thrombocytopenia.
In 7 patients raltitrexed dosage was modified due to a declining creatinine clearance.
Treatment was delayed at least once for 27 patients due to liver toxicity, thrombocytopenia, neutropenia, fever, anaemia, and atrial fibrillation.

Citation: Vyzula R, Kocakova I, Demlova R, Kiss I (2006) Raltitrexed plus oxaliplatin in the second line treatment of metastatic colorectal cancer *Neoplasma* 53;2:119-127

Design: Phase II study

Country: Czech Republic

Setting: Hospital

Aim: to evaluate the efficacy of combined chemotherapy with raltitrexed plus oxaliplatin (TOMOX) as second line treatment in patients with metastatic colorectal cancer.

Inclusion criteria
Patients aged between 18 and 70 years with histologically confirmed metastatic, non-resectable colorectal adenocarcinoma, progressing after first line palliative chemotherapy with the last chemotherapy treatment to have been ≥4 weeks prior to study entry.
Performance status 0-2
Life expectancy of ≥3 months
At least one measurable metastatic lesion by CT
Adequate haematological parameters, liver function and renal function

Exclusion criteria
Patients who had received >1 line of chemotherapy
Patients with symptomatic central nervous system metastases, bone metastases alone, carcinomatous leptomeninigitis, infection or previous cancer history apart from resolved cervical cancer or basal cutaneous carcinoma
Pregnant or lactating women
Patients with paraesthesia greater than NCI-CTC grade 1
Patients in whom raltitrexed or oxaliplatin were contraindicated.

Sample Size

Randomisation Method
N/A

Population
N=51

Study Duration
Median follow-up time was 48.9 weeks (range 16.7-128 weeks)

Interventions
Raltitrexed plus Oxaliplatin

Raltitrexed 3mg/m^2 given as a 15 minute intravenous (IV) infusion followed 45 minutes later by oxaliplatin 130mg/m^2 IV as 2 hour infusion on day 1, repeated every 3 weeks until disease progression.

Outcomes
Primary
Efficacy (Objective Response Rate)

Secondary
Overall Survival
Time to Progression
Toxicity

Results
17 patients had received prior adjuvant chemotherapy
Most patients (78.3%) had received irinotecan as first line, either as monotherapy or in combination with an IV bolus or continuous 5FU/FA regimen.
The most common site of metastases was the liver (76.5%)
47.1% of patients had more than one site of metastatic disease

Patients received a median of 6 cycles of TOMOX (range 1-11 cycles) with a total of 260 cycles administered.
Median duration of TOMOX treatment was 18 weeks (range 3.3-35 weeks).
Reasons for discontinuing treatment included progressive disease in 35 patients (68.6%), toxicity in 8 patients (15.7%) and a combination of both in one patient (2%).

Efficacy, time to progression and survival
47/51 patients were evaluable.
17% (n=8) experienced partial response, 59.6% (n=28) experienced stable disease and 23.4% (n=11) experienced progressive disease after 3 cycles of chemotherapy, there were no complete responses observed.
In the 29 patients that had received six cycles of chemotherapy at the time of analysis, 3.5% (n=1) experienced a partial response, 44.8% (n=13) experienced stable disease and 51.7% (n=15) experienced progressive disease.
Median time to progression was 18 weeks (range 4-37 weeks)
Median overall survival was 54.4 weeks with 25 percentage overall survival 90.5 weeks and 75 percentage overall survival 34.2.

Toxicity
No grade 4 toxicity was observed and the only grade 3 toxicities were leukopenia and diarrhoea

General comments
First line treatment included:
FOLFIRI or weekly modifications of FOLFIRI in patients with good performance status and no contraindications to Irinotecan.
In patients whose PS deteriorated following surgery and/or patients at risk of obstructive ileus, 5FU/FA Mayo or deGramont regimens were administered.
Monotherapy with irinotecan was administered to patients with disseminated disease and to patients with possible resistance to 5FU and to patients experiencing 5FU intolerance.